Chiral Oxime Ethers: Applications in Synthesis

by

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Abstract

Chapter One reviews the literature, discussing the role of nucleophilic additions to oximes and their derivatives. This introduction is primarily concerned with the formation of new carbon-carbon bonds, this is achieved by the addition of organometallic reagents to the carbon-nitrogen double bond functionality of oximes and their derivatives.

Chapter Two concentrates on the use of novel oxime ethers in the asymmetric synthesis of amine derivatives. Formation of the novel oxime ethers, with a chiral group attached to the oxygen atom, and their reactions with organometallic reagents is discussed. The work is primarily concerned with the diastereoselectivity imparted by the chiral auxiliary attached to oxygen, in particular, the effect of the geometry about the carbon-nitrogen double on the observed diastereoselectivity. This chapter also discusses the steps taken to increase diastereoselectivity obtained to synthetically useful levels by optimisation of the chiral auxiliary.

The methodology developed in Chapter Two is applied to the asymmetric synthesis of the hemlock alkaloids (-)-coniine and (+)-*pseudo*conhydrine. The synthesis of the alkaloids involving the extremely diastereoselective addition of a Grignard reagent to a chiral oxime ether is discussed in Chapter Three.

Chapter Four studies the use of chiral oxime ethers in the synthesis of chirally pure amino acids. This is achieved by the highly diastereoselective addition of organometallic reagents to the chiral oxime ethers followed by oxidative cleavage of a suitable carboxylic acid precursor.

Acknowledgements

The work contained in this thesis and its preparation would not have been possible without the help of a number of exceptional people. My supervisor, Christopher J. Moody, deserves much thanks for constantly providing me with challenges, encouragement and help over the last three years. I would like to thank my friends and colleagues at the Lilly Research Centre where I spent an enjoyable and enlightening three months. In particular, thanks goes Peter Gallagher, my industrial supervisor, and Andy Williams, not only for useful discussions, but for their obtuse sense of humour. Elizabeth 'dizzy lizzy' Swann who provided much of the ground work for this project and has an infectious sense of humour deserves special thanks.

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Special thanks has to go to Sarah whose constant belief in me has driven me on. The stability to my life she supplies with her love is a constant source of amazement to me.

I reserve my deepest gratitude for my parents for their never ending support, encouragement and love in everything I have done. Without this devotion I would not be where I am today and I dedicate this thesis to them.

A.P.L.
September 1996

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The Synthesis of Amino Acids

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Life without chemistry is like a broken pencil.....

.....Pointless

Abbreviations

Ac	acetyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
9-BBN	9-borabicyclo[3:3:1]nonane
Bn	benzyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
DCM	dichloromethane
d.e.	diastereomeric excess
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
DMF	dimethylformamide
e.e.	enantiomeric excess
Et	ethyl
LDA	lithium diisopropylamine
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MOM	methoxymethyl
Ms	methanesulphonyl
Ph	phenyl
i-Pr	*iso*-propyl
pTSA	*para*-toluenesulphonic acid
py	pyridine
RAMP	(R)-1-amino-2-(methoxymethyl)pyrrolidine
r.t.	room temperature
SAMP	(S)-1-amino-2-(methoxymethyl)pyrrolidine
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

To
Mum and Dad

Chapter One

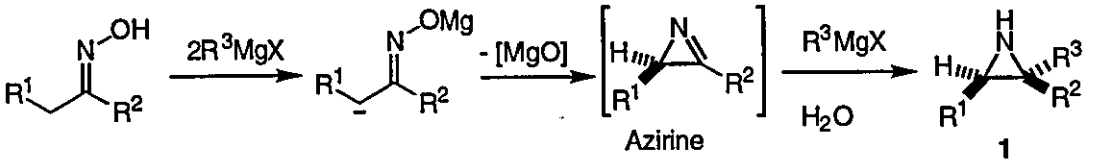
The Addition of Organometallic Reagents to Oximes and Oxime Ethers

1.1. Introduction

The chemistry of alkenes and carbonyl compounds is fundamental to much of organic synthesis, although too numerous to detail here, the reactions of *C=C* and *C=O* bond are a recurring theme in a comprehensive treatise.[1] The chemistry of the *C=N* bond in contrast has been less well studied, with the exception of imines whose chemistry has been widely exploited.

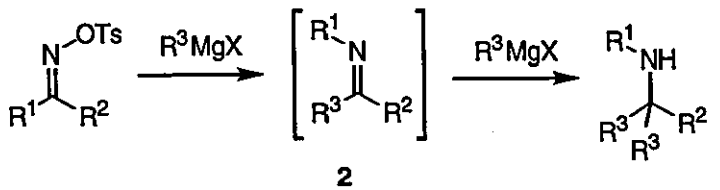
The chemistry of oximes is well known and certain reactions have been text book material for years, and of these some constitute satisfactory methods in synthesis. Among these are the hydrolysis to ketones, reduction to amines or hydroxylamines, oxidation to nitro compounds, and perhaps the best known reactions of oximes the Beckmann and Neber rearrangements.[2-4]

Treatment of oximes and their derivatives with organometallic reagents can lead to a number of products, these reactions appear to be very sensitive to the nature of the medium. Hoch and Campbell reported that aziridines **1** were formed in moderate yields when ketoximes, containing α-hydrogens, were treated with Grignard reagents in boiling toluene.[5,6] The mechanism is thought to be similar to that of the Neber rearrangement, involving an azirine intermediate **(Scheme 1)**. The stereochemistry observed is due to the addition of the Grignard reagent to the azirine on the opposite face to the other substituent.



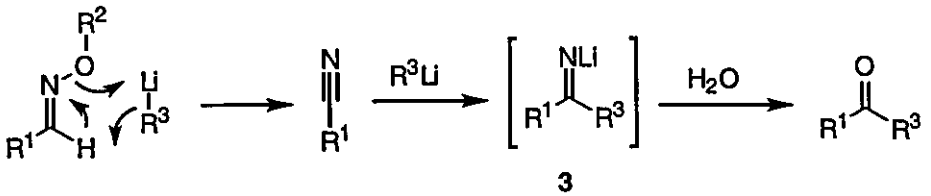
Scheme 1

Grignard reagents or alkylaluminium reagents can also be used to initiate the Beckmann rearrangement of oxime tosylates in toluene at low temperature (-78-0°C).[2] The resulting imine **2** can be further reacted with the organometallic reagent and so constitutes a synthesis of secondary amines **(Scheme 2)**.[10]



Scheme 2

Aldoximes can be dehydrated to nitriles by a large number of dehydrating reagents, of which acetic anhydride is the most common.[7] Itsuno has reported the use of organolithium reagents to achieve this transformation with aldoxime ethers in THF at 0°C **(Scheme 3).**[8] The organolithium removes the aldoxime proton and lithium alkoxide is expelled, and the corresponding nitrile is produced. Under the reaction conditions the nitrile reacts further to give the lithiated imine **3**, which on workup gives the ketone in high yield. This constitutes an excellent procedure for the synthesis of ketones from aldehydes.



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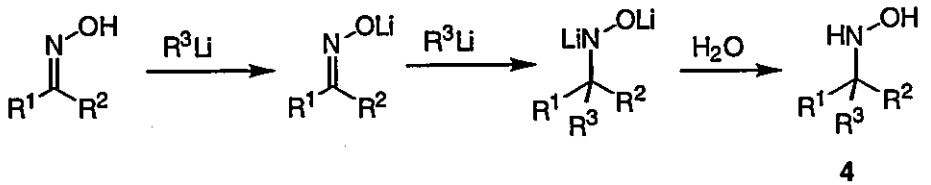
Scheme 3

Ketoximes or *O*-alkyl oximes with α-hydrogens can also react with organolithium compounds which results in the formation of an enamine equivalent, that can be alkylated on carbon with high regioselectivity.[9]

1.2. Additions of Organometallic Reagents to Oximes

Richey was first to achieve the addition of organolithium reagents to oximes in 1976.[10] The hydroxylamines **4** were produced in good yield if α-hydrogens were not present **(Scheme 4).**



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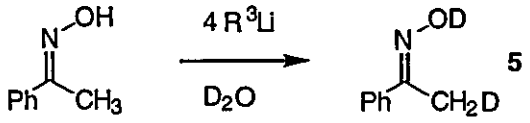
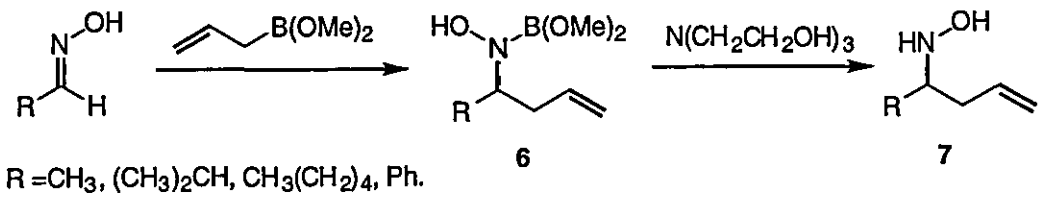
Scheme 4

The lower yields were attributed to deprotonation α to the *C=N* bond. For example, acetophenone oxime was treated with four equivalents of *n*-butyllithium at room temperature in light petroleum and after work up with water, starting material only was recovered. The reaction was worked up with D_2O and α-deuterioacetophenone oxime **5** was isolated **(Scheme 5).**



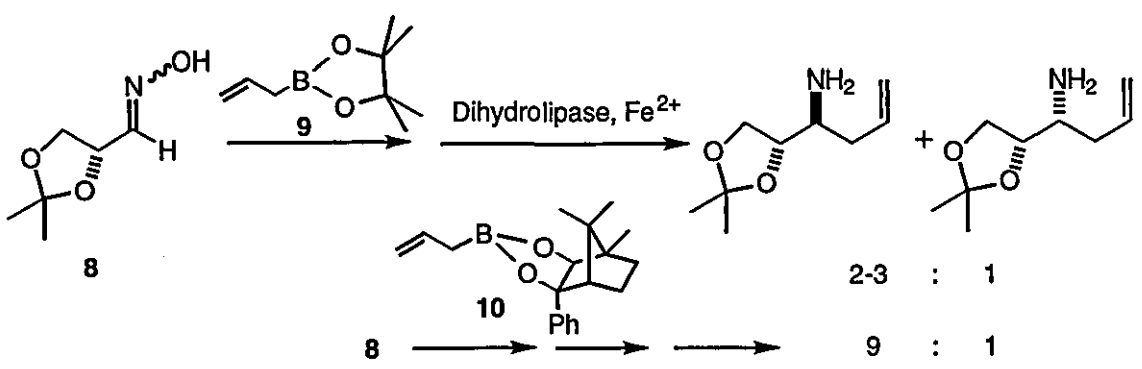
Scheme 5

Following his work on the additions of allylboron compounds to imines, Hoffmann studied the addition of allylboronates to oximes extensively during the 1980s.[11] Treatment of a mixture of *E* and *Z*-oximes with allyl dimethoxyboronate in boiling 1,2-dichloroethane for 72 hours gave the product hydroxylamine **6**, with boron still attached. The boron was removed by treatment with triethanolamine to yield the hydroxylamines **7** in 70-90% **(Scheme 6).**



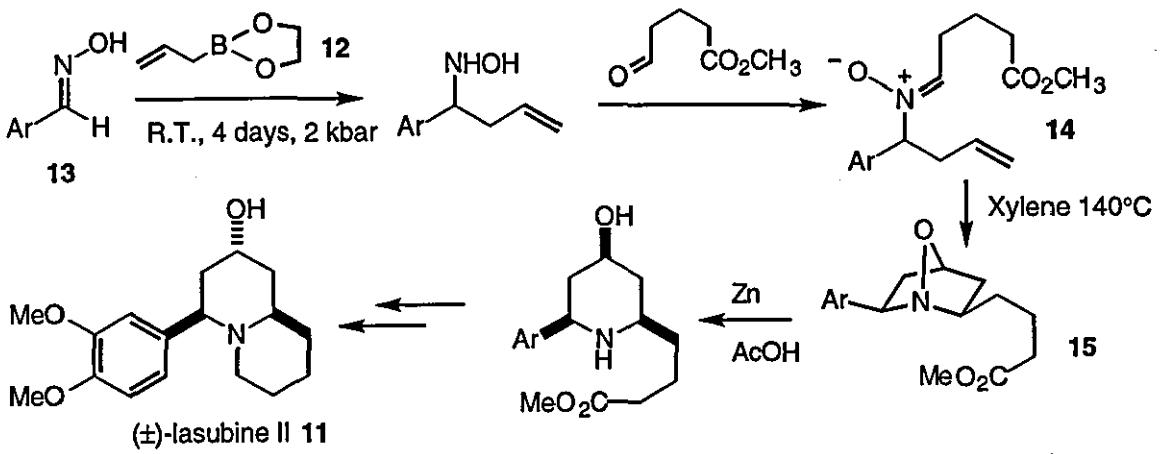
Scheme 6

Yields of the reaction were higher than for the corresponding Grignard and organolithium reagents. The basicity of the allylboronates is thought to be less than for its magnesium and lithium counterparts and hence α-deprotonation does not occur. In an attempt to synthesise chirally pure amines, Hoffmann prepared the oxime from glyceraldehyde **8**. Addition of the pinacol derived allylboronate **9** in boiling carbon tetrachloride gave a good yield, although poor diastereoselectivity (2-3:1), of the hydroxylamine. The dihydrolipase was used to reduce the *N-O* bond to produce the free amines. Use of the chiral allylboronate derived from camphor **10** gave the addition products with 9:1 diastereoselectivity as a result of matched stereodifferentiation **(Scheme 7).**



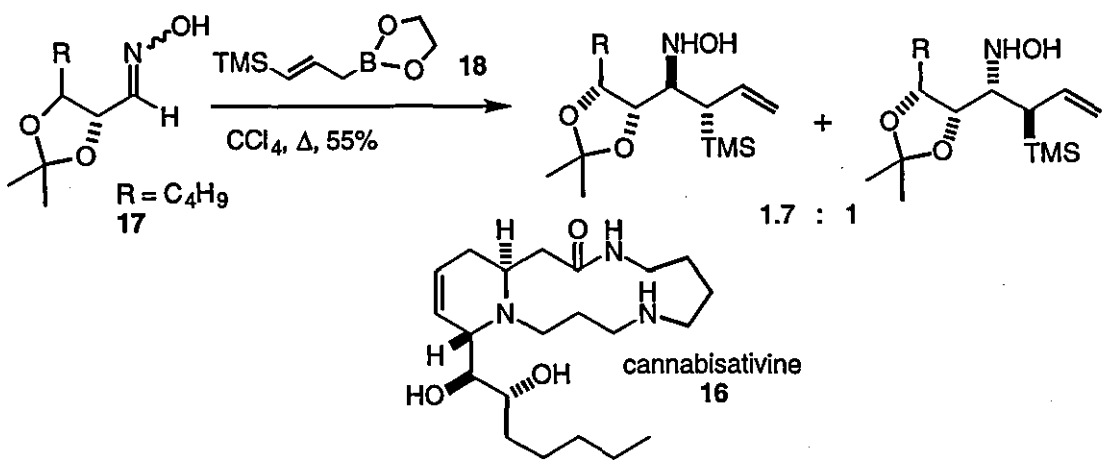
Scheme 7

This methodology has been applied to the synthesis of lasubine II **11** by Hoffmann and Endesfelder.[12] Addition of allylboronate **12** to the oxime **13** produces the hydroxylamine which on treatment with an aldehyde gave the nitrone **14.** Heating **14** to 140°C gave the cycloaddition product **15**, and *N-O* bond cleavage of this adduct furnishes the all *cis* 2,6-disubstituted-4-piperidinol which can be further manipulated to the natural product **(Scheme 8).**



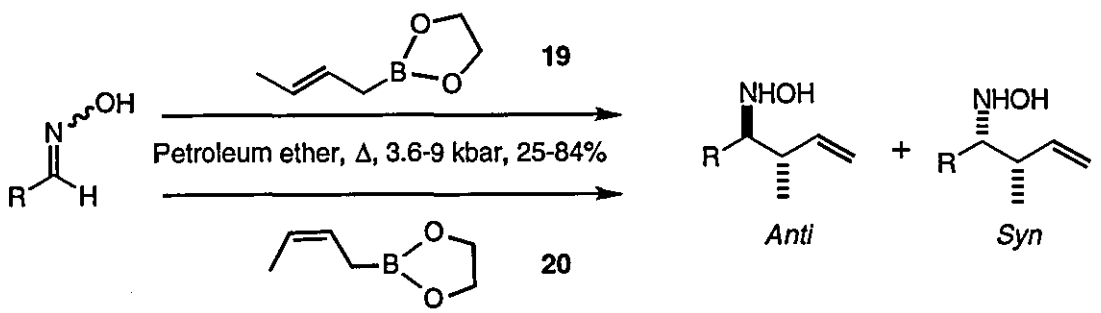
Scheme 8

Wuts and Jung have also used this methodology in the diastereoselective synthesis of the skeleton of cannabisativine **16.**[13] Reaction of oxime **17** with the silyl allylboronate **18** gave a mixture (1.7:1) of the two 3,4-*anti* products, the *syn* products were produced as a minor event and were not isolated. Following the previous methodolgy of nitrone formation and cycloaddition the skeleton of the natural product was prepared **(Scheme 9).**



Scheme 9

In his continuing study of boronates and oximes Hoffmann undertook a study of the diastereoselective addition of crotylboronates to oximes involving the addition of *E* and *Z*-isomers of the crotylboronate.[14] A mixture of *syn* and *anti* aldoximes was treated with ethanediol-*E*-crotylboronate **19** to produce a mixture of *syn* and *anti* hydroxylamines, with reasonable selectivity for the *anti* diastereomer. The reactions were carried out at high pressures (9 kbar), again indicating the low reactivity of the *C=N* bond of oximes. The oximes were also treated with the *Z*-crotylboronate **20** to give moderate yields of the hydroxylamines, again as a mixture of diastereomers but this time the *syn* isomer predominated **(Scheme 10)**. The results obtained are summarised in **Table 1**. The sense of diastereoselection of the crotyl boronates is the same as for aldehydes, which has been well documented.

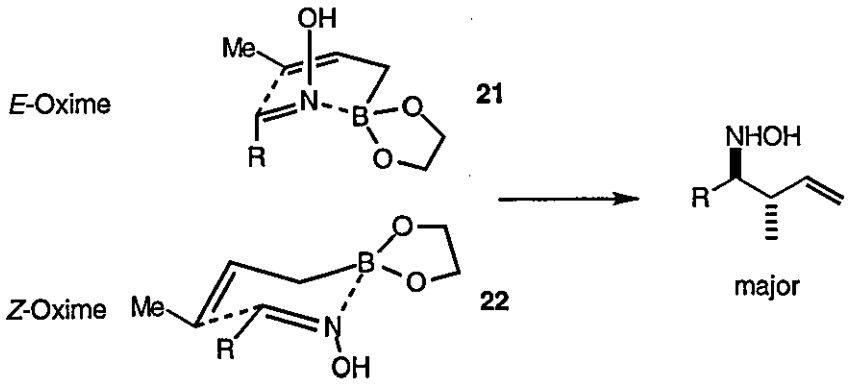


Scheme 10

Crotylboronate	*Oxime (R)*	*Anti:Syn*
E	Ph	95:5
	i-Pr	81:19
	$CH_3(CH_2)_3$	75:25
Z	Ph	12:88
	i-Pr	3:97
	$CH_3(CH_2)_3$	6:94

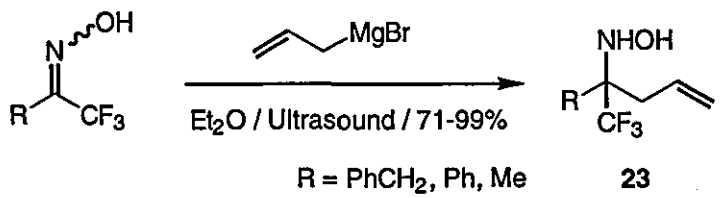
Table 1

If the starting oxime has the *E*-geometry, then based on the standard cyclic transition state the boron must co-ordinate to the *Z*-position of the nitrogen, this then leads to a boatlike transition state **21**. However, if the oxime has a *Z*-geometry then the boron must co-ordinate to the *E*-position, this type of co-ordination leads to a chair transition state **22** as shown in **Scheme 11**, the same argument applies to the *Z*-crotonate. The diastereoselectivity observed for the additions obviously involves a delicate competition between the two transition states.



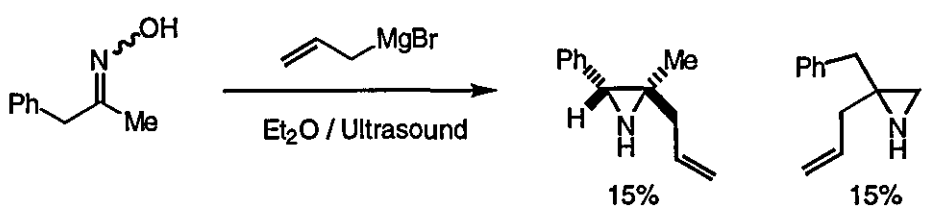
Scheme 11

In a study involving alkyl and allyl Grignard reagents Mison has studied the effect of these reagents on trifluoromethyl oximes.[15] Simple alkyl Grignard reagents in ether or THF at room temperature under ultrasound conditions gave the corresponding aziridines, as expected. However, allyl magnesium bromide under the same conditions gave 71-99% yields of the corresponding hydroxylamines **23 (Scheme 12)**, indicating again the unique reactivity of the allyl group.



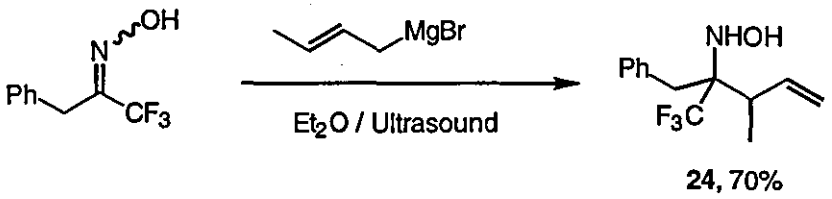
Scheme 12

The reactions generality is due to the presence of both the trifuoromethyl group and the allyl substituent of the Grignard reagent. If the trifluoromethyl group was not present then aziridines were formed as illustrated by reacting allylmagnesium bromide with phenylacetone oxime **(Scheme 13)**. Thus the trifluoromethyl group increases the electrophilicity of the *C=N* bond rather than the acidity of the α-hydrogens, which constitute the first step in aziridine synthesis.



Scheme 13

The addition of crotylmagnesium bromide was performed, which gave the rearranged product **24** in 70% yield **(Scheme 14)**. This is generally explained by the cyclic transition state of allylic additions as described by Hoffmann **(Scheme 11)**, and accounts for the reluctance of ethylmagnesium bromide to add to the oximes.



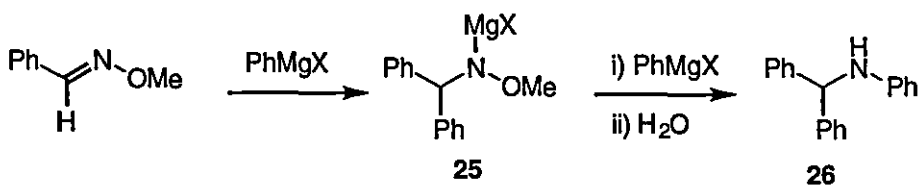
24, 70%

Scheme 14

1.3. Additions of Organometallic Reagents to Oxime Ethers

The electrophilicity of the *C=N* bond in oxime ethers is greatly reduced compared to that of imines and as a consequence of this, the conditions required to achieve addition are relatively harsh. The problem of α-deprotonation is also apparent with more basic organometallics, such as Grignard reagents.

The *C=N* bond of oxime ethers have a greater reactivity towards nucleophiles in comparison to oximes as indicated by the work of Busch and Hobein.[16] They first reported the addition of organometallic reagents to the *C=N* bond of oxime ethers in 1907. Treatment of *O*-methyl benzaldoxime with phenylmagnesium bromide gave the magnesium amide species **25**, it is then thought that a further molecule of Grignard reagent attacks the nitrogen atom with concomitant loss of methoxide. Quenching the anion with water gave the corresponding *N*-arylated species **26** in modest yield **(Scheme 15)**.

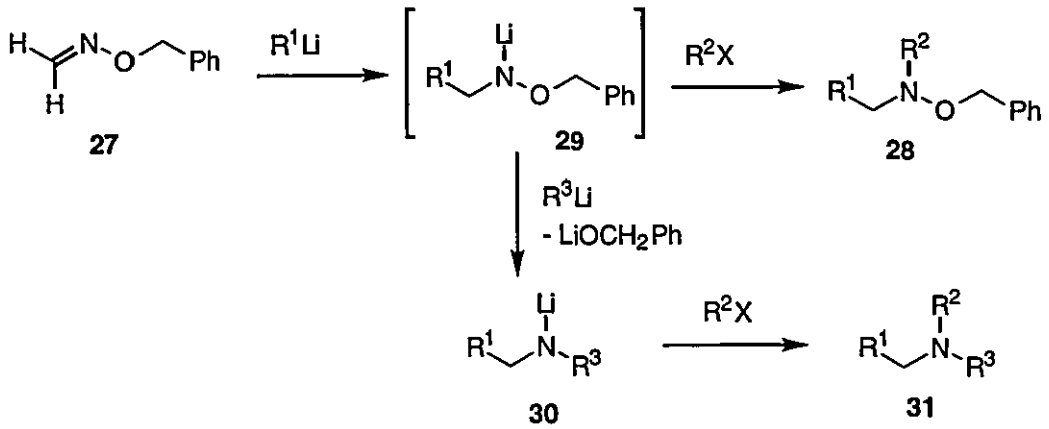


25 **26**

Scheme 15

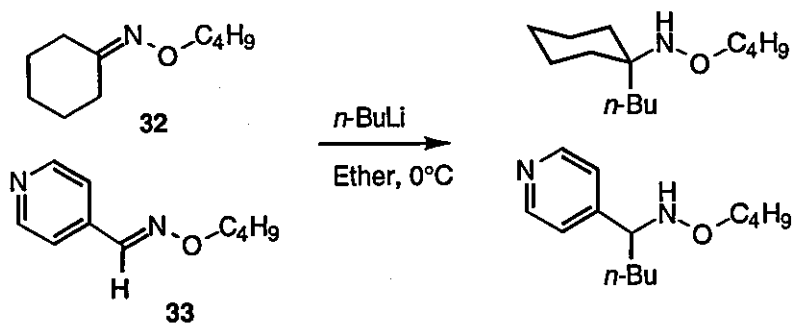
This reaction was exploited by Basha and Brooks in 1987.[17] *O*-Benzyl formaldoxime was used as a "+CH-NH+" synthon, making use of the *N*-alkylation procedure of Busch and Hobein. Treatment of the oxime **27** in THF at -40°C with an organolithium reagent gave, after quenching with water, benzyl bromide or acyl chlorides, the corresponding substituted hydroxylamines **28**. However, if the intermediate **29** is not quenched, but

is treated with a further equivalent of organolithium, addition at the nitrogen occurs with cleavage of the *N-O* bond. The lithium amide **30** can then be quenched by a series of electrophiles to produce *tert*-amines or *sec*-amides in good overall yield (25-70%) **(Scheme 16)**.



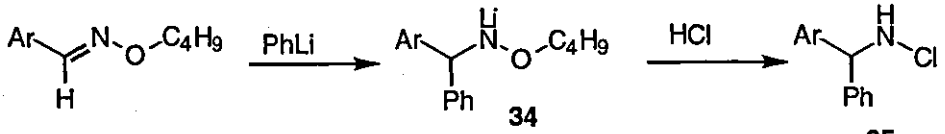
Scheme 16

In 1908 Marxer and Horvath extended the methodology of Busch and Hobein by adding organolithium reagents to *O*-butyl oxime ethers.[18] Treatment of *O*-butyl cyclohexanone oxime ether **32**, and the *iso*-nicotinaldehyde derivative **33** with *n*-butyllithium in ether at 0°C gave the addition products in moderate yields **(Scheme 17)**.



Scheme 17

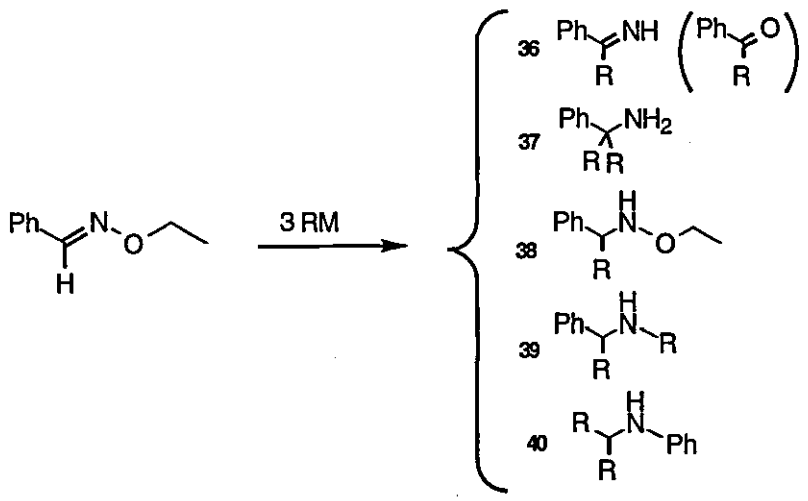
However, treatment of substituted benzaldoximes under the same conditions lead to a quantity of *N*-alkylated product. If the initial product **34** of the addition of phenyllithium is treated with concentrated HCl, then the product obtained is the chloramine **35**, presumably obtained from the direct displacement of butoxide by chloride ion on the nitrogen atom **(Scheme 18)**.



Ar = *p*-methoxyphenyl, *o,p*-dichlorophenyl

Scheme 18

A systematic study of the reaction of organometallic reagents with oxime ethers was undertaken by Pornet and Miginiac.[19] These researchers studied the reaction of alkyl, aryl and allylic organometallic reagents with oxime ethers. Treatment of *O*-ethyl benzaldoxime with a series of organometallic reagents showed that five major products were isolable from the reaction mixtures **(Scheme 19).**



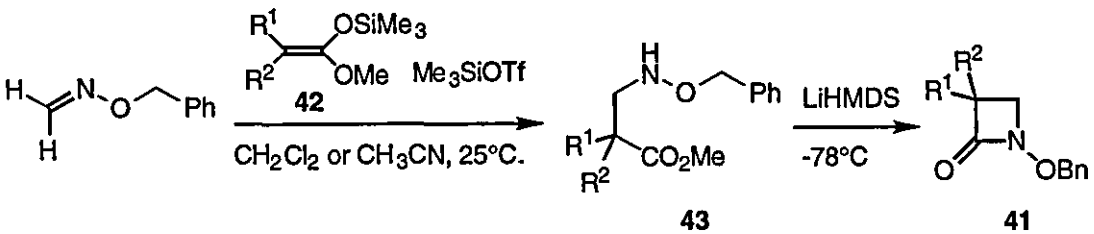
Scheme 19

The ratio of products were found to be a function of the reaction conditions and on the nature of the organometallic reagent. The products could be explained as follows; **36,** dehydration of the oxime and addition to the corresponding nitrile as described by Itsuno. **37,** Addition to the imine **36. 38,** Standard addition to the *C=N* bond without *N-O* bond cleavage. **39,** Addition to the *C=N* bond with *N*-alkylation as described by Basha and Brooks. **40,** A Beckmann type rearrangement.

At 20°C in ether the lithium derivatives were found to convert the starting material into products much more readily than the corresponding Grignard reagents, for example *n*-butyllithium gave the rearranged products **36,37,39** and **40** while *n*-butylmagnesium bromide gave mainly starting material. Allylic lithium, magnesium and zinc reagents all gave complete consumption of starting material. The zinc and lithium derivatives both gave the addition product **38,** though in moderate yields (60 and 10% respectively). However allylmagnesium bromide gave exclusively the Beckmann

rearranged product **40**. Heating the reactions under reflux increased the conversion to products but also increased the tendancy for them to rearrange, with **40** being the most abundant product. However, cooling the reaction of *n*-butyllithium with the oxime to -10°C in pentane gave predominantly the addition product **38**.

From the study by Pornet and Miginiac it was clear that the *C=N* bond is unreactive and requires activation to give good yields of the corresponding hydroxylamines. Ikeda noted this and has reported a procedure for the preparation of *N*-benzyloxy-β-lactams **41** by the reaction of ketene silyl acetals **42** with oxime ethers and trimethylsilyl triflate as a catalyst **(Scheme 20)**.[20] *N*-Benzyloxy-β-lactams were prepared because they were viewed as precursors to *N*-hydroxylated-β-lactams which have been identified as interesting monobactams. These compounds have recieved attention as chemotherapeutics because of their activity against a broad spectrum of Gram-negative bacteria.



Scheme 20

O-Benzyl formaldoxime or the acetaldoxime were treated with the silyl acetal at room temperature in DCM in the presence of a catalytic amount of TMS triflate. The yields of the reactions are generally good (42-93%). Ring closure of the β-benzyloxyaminocarboxylates **43** to the corresponding β-lactams **41** is achieved by treatment with lithium *bis*(trimethylsilyl) amide at -78°C in THF. The mechanism of addition has been postulated as involving a silylated *N*-benzyloxyiminium salt as shown in **Figure 1**, which has the effect of increasing the electrophilicity of the imine carbon.

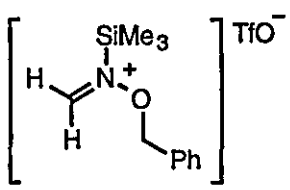
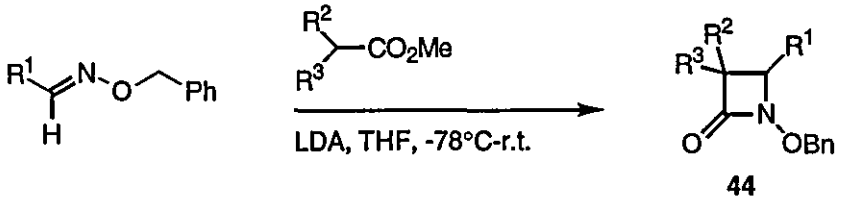


Figure 1

Ikeda has also achieved the addition of ester enolates to oxime ethers and has prepared a series of *N*-benzyloxy-β-lactams **44 (Scheme 21).**[21] The use of ester enolates with the corresponding imine derivatives was limited in that the imine to enamine isomerization occurred readily under the reaction conditions. Oxime ethers were found to undergo the imine to enamine transformation less readily due to the deactivation of the imine bond by the lone pairs on the oxygen atom. The results of the addition of ester enolates to oxime ethers are summarised in **Table 2.**



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Scheme 21

R1	*R2*	*R3*	*Yield (%)*
H	Me	Me	67
H	Ph	Et	82
H	cyclohexyl		65
H	cyclopentyl		49
Me	Me	Me	48
Et	Me	Me	40

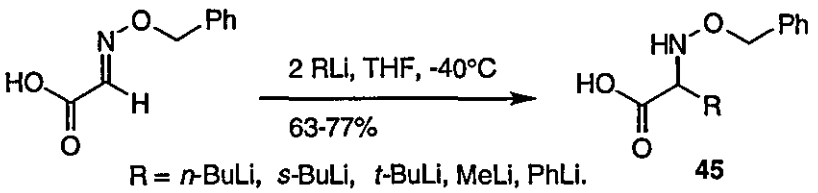
Table 2

Miller *et al* also identified the need to activate the *C=N* bond and has combined this with the potential of oxime ethers derived from glyoxylate and pyruvate to be amino acid precursors **(Scheme 22).**[22] The activation of the *C=N* bond comes from the electron withdrawing abilities of the carboxylate group.

Scheme 22

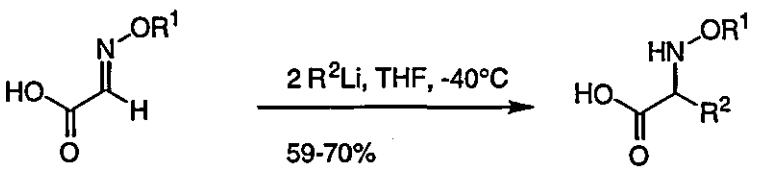
Clearly the addition of nucleophiles to the substrates could occur at two possible sites; the carbonyl of the carboxylate and the desired addition to the *C=N* bond. The free

carboxylic acid function acted as sufficient protection of the carbonyl moiety. The addition of two equivalents of organolithium reagent in THF at -40°C to the *O*-benzyl oxime ether of glyoxylate gave the desired products **45** in good yields as shown in **Scheme 23.** The carboxyl group increases the electrophilicity of the oxime carbon atom, thus rendering it more susceptible to nucleophilic attack. Despite this magnesium and zinc reagents were ineffective.



Scheme 23

In an attempt to induce stereoselectivity, Miller incorporated a series of chiral auxiliaries on the oxygen atom of the oxime **(Scheme 24).** (±)-1-Phenylethanol was employed as the chiral auxiliary with only modest results **46a**, the addition of *t*-butyllithium gave a 30-40% diastereomeric excess, while *n*-butyllithium failed to give any diastereoselectivity possibly due to the smaller size of the nucleophile. Further attempts also led to disappointing results; the addition of *n*-butyllithium to the oxime incorporating a THP group on oxygen **46b** led to only 30% diastereomeric excess. Marginally better results were obtained by the use of 2-methoxy-1-phenylethanol as the chiral auxiliary **46c.** The addition of *n*-butyllithium to this oxime ether gave the addition product in 33% diastereomeric excess. The results of these addition reactions are summarised in **Table 3.**

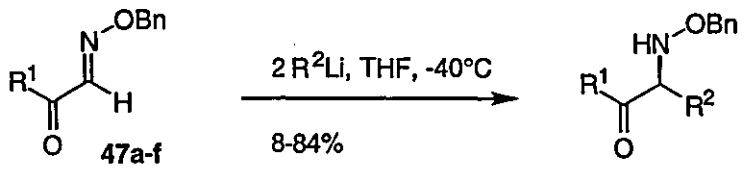


Scheme 24

Oxime	*R1*	*R2*	*Yield (%)*	*d.e. (%)*
46a	(±)-CH(Me)Ph	*n*-BuLi	70	0
46a	(±)-CH(Me)Ph	*t*-BuLi	69	30-40
46b	(±)-THP	*n*-BuLi	65	30
46c	(R)-CHPh(CH_2OMe)	*n*-BuLi	59	33

Table 3

Miller then turned his attention to asymmetric induction by the action of a chiral group attached at the carbonyl carbon. Clearly esters were unemployable, as direct attack on the carbonyl carbon would result, but chiral amides appeared to be tolerated **(Scheme 25)**. A series of chiral amides **47a-f** derived from chiral amines and amino acids were prepared and a range of organolithium reagents were added to the *C=N* bond. The best result, in terms of diastereomeric excess, was obtained by the addition of *t*-butyllithium to the chiral amide derived from α-methyl benzylamine **47a**. This reaction gave a diastereomeric excess of 47%. The results for this study are summarised in **Table 4.**



Scheme 25

Oxime	*R1*	*R2Li*	*Yield (%)*	*d.e. (%)*
47a	(D)-NHCH(Me)Ph	*n*-BuLi	79	30
47a	(D)-NHCH(Me)Ph	*t*-BuLi	79	47
47b	(R,S)-NHCH(Me)CH(OR)Ph			
	R = H	*n*-BuLi	54	0
	R = H	*t*-BuLi	84	0
47c	R = Me	*n*-BuLi	68	33
47d	(S)-Prolinol	*n*-BuLi	9	-
47e	(S)-*O*-Methylprolinol	*n*-BuLi	8	-
47f	(S)-NHCH(*i*-Pr)COOH	*n*-BuLi	64	0
47f	(S)-NHCH(*i*-Pr)COOH	*t*-BuLi	53	20

Table 4

Further to Millers findings, Yamamoto discovered that allylic zinc and boron reagents added to glyoxylate derived oxime ethers.[23] The idea of chiral induction at the carbonyl carbon was also employed, although Yamamoto discovered that the ester group was stable to the allyl metal species. The auxiliary chosen was 8-phenylmenthol, which has frequently exhibited high levels of enantioface selectivity. It can be seen that the phenyl group effectively shields the *re* face allowing attack to come solely from the *si* face **(Figure 2).**

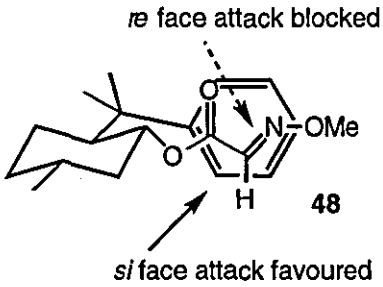
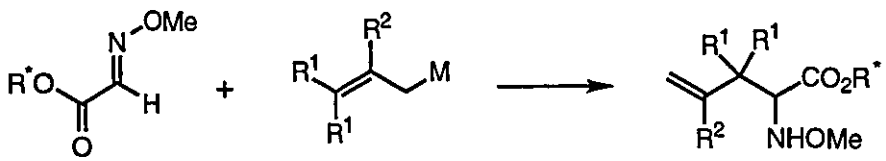


Figure 2

Treatment of the oxime ether **48** with allyl boron reagents gave poor yields (<40%). However, the corresponding allyl zinc reagents gave better yields (>50%) as shown in **Scheme 26.** The difference in yields is attributed to the difference in co-ordination of the corresponding heteroatoms. Poor electrophilicity of the oxime nitrogen may diminish co-ordination of the boron atom and hence decrease the yield. Zinc however, does not require co-ordination to the nitrogen atom to induce the allylation reaction. The results of the allylation reactions are summarised in **Table 5.**



Scheme 26

R1	*R2*	*M*	*Yield (%)*	*d.e. (%)*
H	H	B	39	20
H	H	$B(OMe)_2$	29	6
H	H	ZnBr	52	74
Me	Me	ZnBr	55	98

Table 5

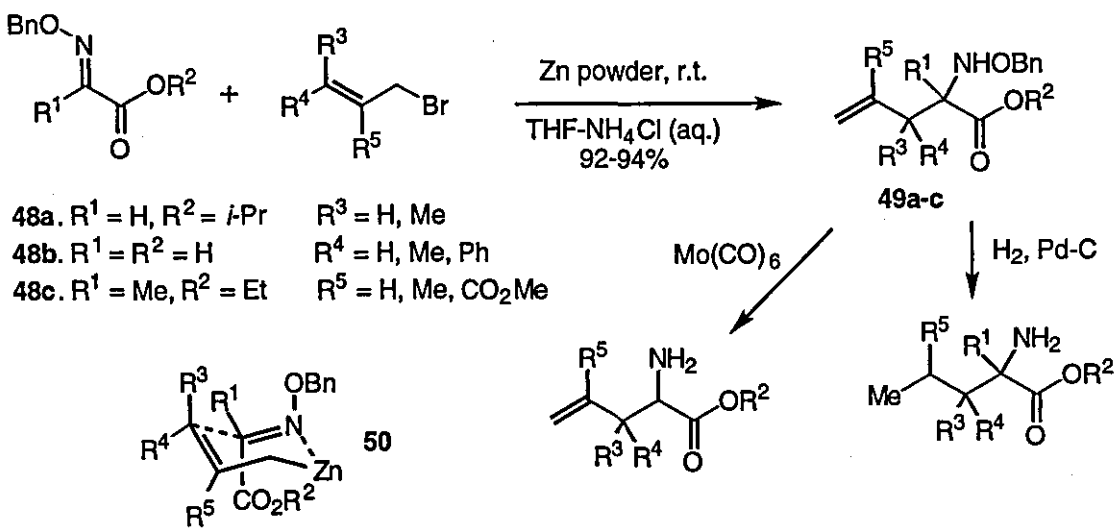
The diastereoselectivity was also found to be dependent on the metal used. Allyl zinc reagents were discovered to give high levels of asymmetric induction (74-98% d.e.), whereas the boron reagents gave poorer results (<20% d.e.). This is again attributed to the poor co-ordination of the boron atom to the oxime nitrogen. The 8-phenylmenthol group was found to induce the (S)-chirality at the newly formed chiral centre. The allyl zinc reagents probably attack the oxime from the *si* face as the *re* face is shielded by the phenyl group. The induction of this chirality implies that the

metal chelation occurs in the *syn* form rather than the *anti* form, **(Scheme 27)**. The same tendancy has been observed with the reaction of 8-phenylmenthol glyoxylate with allylic tin reagents and boron trifluoride.

syn form *anti* form

Scheme 27

Recently, further to the results obtained from Yamamoto, Hanessian has reported the action of allylic zinc reagents on *O*-benzyl glyoxylic acid oxime derivatives **48a-c** in aqueous media to give the corresponding hydroxylamines **49a-c**.[24] The hydroxylamines are reduced to the amines by the action of molybdenum hexacarbonyl or by hydrogenolysis **(Scheme 28)**. The reactions of the allylic reagents are highly regioselective and react through the γ-position. The reactions are thought to proceed through a cyclic transition state **50**, with the zinc atom co-ordinating to the nitrogen of the oxime ether.



48a. R^1 = H, R^2 = *i*-Pr R^3 = H, Me
48b. R^1 = R^2 = H R^4 = H, Me, Ph
48c. R^1 = Me, R^2 = Et R^5 = H, Me, CO_2Me

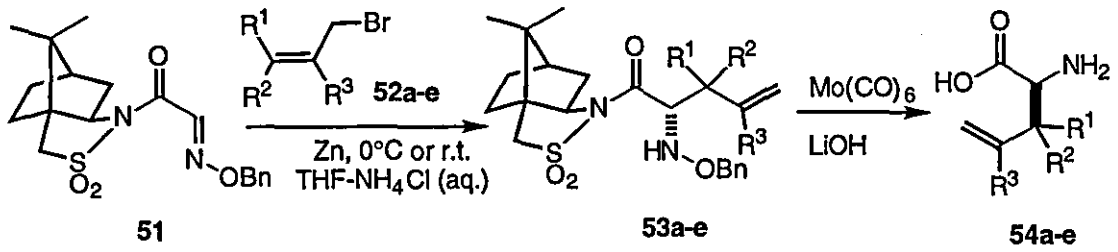
49a-c

50

Scheme 28

Hanessian has also induced asymmetry in this reaction by utilising Oppolzers camphorsultam auxiliary. The chiral amide derived from glyoxylic acid oxime **51** was treated with a series of allyl bromides **52a-e** in the presence of zinc powder **(Scheme 29)**. The addition took place through the γ-position as described above and the yields of the addition products **53a-e** were generally excellent (88-99%) with the diastereoselectivity ranging from 99:1 to 81:19 **(Table 6)**. The *N-O* bond was

selectively cleaved by $Mo(CO)_6$ and the auxiliary removed with lithium hydroxide in good yields to provide the free allylglycines **54a-e.**



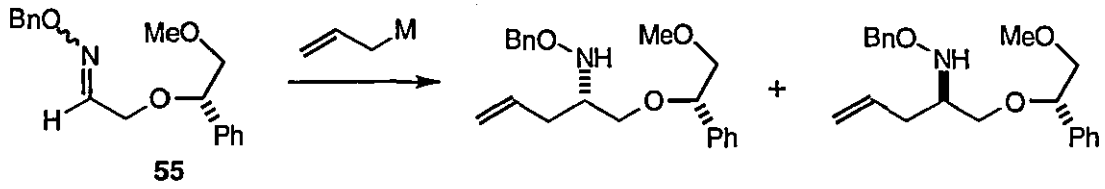
Scheme 29

Allyl bromide	*R^1*	*R^2*	*R^3*	*Temp. (°C)*	*Yield of **53** (%)*	*d.e. (%)*
52a	H	H	H	r.t.	95	82
52a	H	H	H	0	94	84
52b	Me	Me	H	r.t.	90	98
52c	H	H	Me	0	93	62
52d	H	H	CO_2Me	0	99	68
52e	H	Ph	H	r.t.	88	98

Table 6

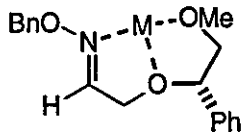
It was now understood that the addition of allylic reagents to oxime ethers occurs readily, provided that activation of some description was present, and that the co-ordination of the metal to the nitrogen of the oxime was crucial. Fujisawa and co-workers discovered that the addition of allylic metal reagents to chiral oxime ethers, with two heteroatoms in the chiral oxime side chain, could produce either enantiomer of the chiral hydroxylamine depending on the nature of the metal used.[25] This has also been illustrated by the addition of allylic metallic reagents to chiral ketones.[26]

The chiral oxime ether **55** was prepared from 2-methoxy-1-phenylethanol as a 1:1 mixture of *E* and *Z*-isomers. Addition of allylmagnesium bromide to the mixture of *E* and *Z*-isomers gave a 1:1 mixture of diastereomers. The addition of a solution of allyl Grignard pretreated with cerium trichloride gave a reasonable diastereomeric ratio (4:1) with 45% recovered starting material, predominantly the *Z*-isomer. Treatment of the oximes with allyl lithium gave the addition product with a diastereomeric ratio of 1:5 **(Scheme 30).** The absolute stereochemistry was found to be reversed by the action of lithium compared to the corresponding magnesium/cerium reagent.

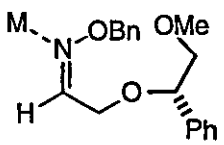


Scheme 30

Separation of the *E* and *Z*-oxime ethers and treatment of the two isomers with the organometallic reagents was performed to quantify the effect of each isomer on the observed diastereomeric ratio. Addition of the three organometallic reagents to the *Z*-oxime ether ***Z*-55** led to poor diastereoselectivity (<36% d.e.), however the additions to the *E*-isomer ***E*-55** showed promising results. The addition of the magnesium/cerium reagent gave a 6:1 ratio of diastereomers while the lithium derivative gave a ratio of 1:11 of the opposite diastereomer. It was concluded from these results that the co-ordination of the oxime nitrogen and the two oxygens atoms was crucial for diastereofacial discrimination. The *E*-isomer ***E*-55** can readily form the chelated structure **(Figure 3)**, whereas the *Z*-isomer ***Z*-55** clearly cannot form this type of chelate. This may account for the activation of the *C=N* bond and the diasterofacial discrimination that is observed. The formation of each diastereomer is attributed to the different co-ordination properties of the metal used.



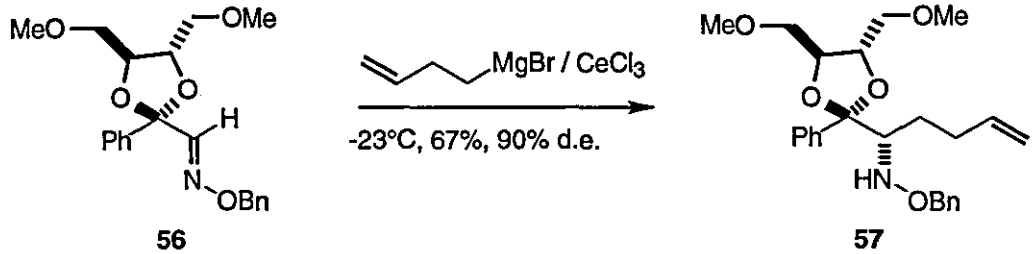
E-Isomer
***E*-55**



Z-Isomer
***Z*-55**

Figure 3

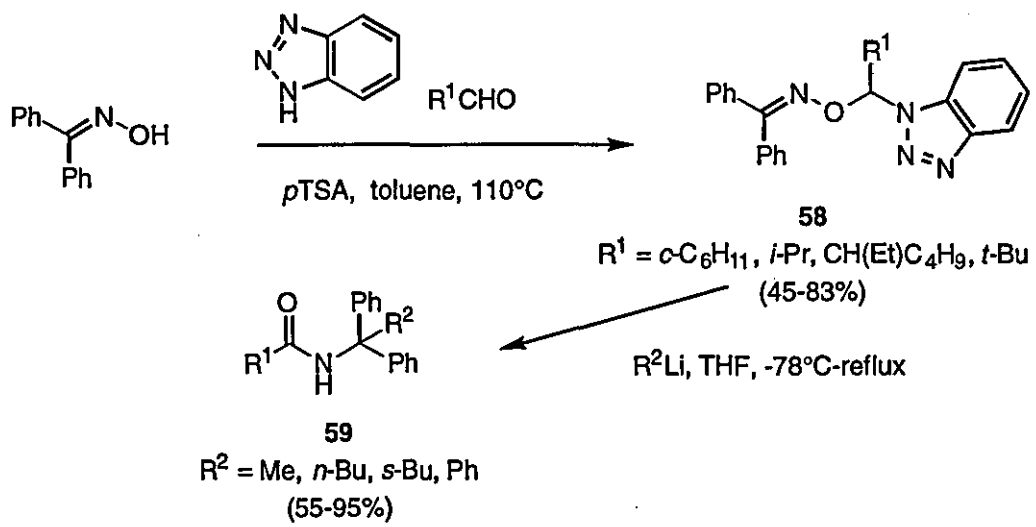
Fujioka *et al* have also reported the use of cerium reagents in the addition to oxime ethers.[27] The reagent, derived from butenylmagnesium bromide and cerium trichloride was added to the oxime ether acetal **56** in THF at -23°C **(Scheme 31)**. It would appear that the cerium co-ordinates to the oxime nitrogen to activate the *C=N* bond towards addition. The product **57** was obtained in 67% yield and 90% d.e., the sense of asymmetric induction was explained in terms of a chelation model with the chiral acetal. The organocerium reagents gave higher yields and stereoselectivities than the corresponding Grignard and organolithium reagents, where starting material was recovered.



56 57

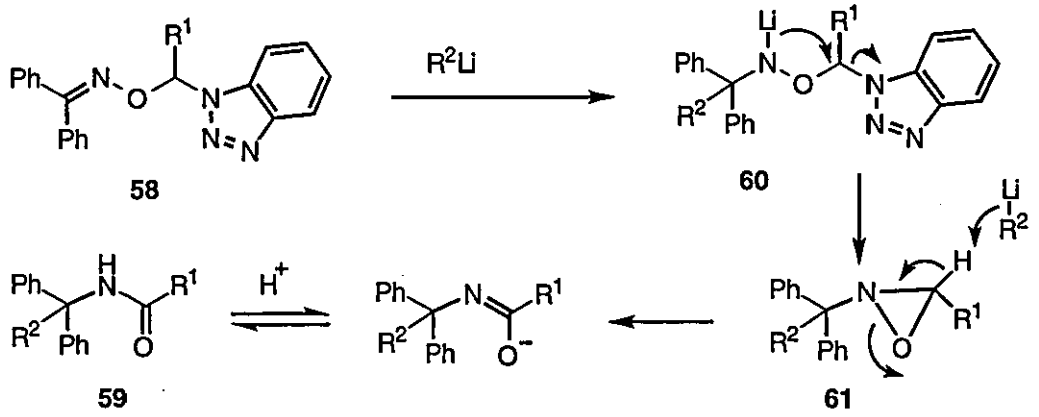
Scheme 31

Previously it has been reported that organolithium reagents add to oxime ethers in only poor yields when not activated. However, Katritzky reported a procedure involving the addition of alkyl organolithium reagents and phenyllithium to an unactivated *C=N* bond of an oxime ether.[28] The procedure involves a method for the non-oxidative transformation of aldehydes into *N*-monosubstituted amides. The formation of the oxime ethers involves the Mannich reaction of an aldehyde, oxime and benzotriazole in which the oxime ethers **58** were produced in good yields. Treatment of **58** with two equivalents of organolithium reagent in THF, initially at -78°C then heating to reflux, led to the rearrangement to yield the *N*-monosubstituted amides **59 (Scheme 32).**



Scheme 32

The mechanism for this conversion involves the addition of the organolithium reagent to the *C=N* of the bond of the oximes **58** to produce the lithium amide **60.** Ring closure with the subsequent loss of benzotriazole gave the oxaziridines **61.** The second equivalent of organolithium removes the oxaziridine proton providing ring opening to give the primary amides **59 (Scheme 33).**



Scheme 33

1.4. Additions of Organometallic Reagents to Oxime Ethers Mediated by Boron Trifluoride Etherate

Clearly the scope of the addition of organometallic reagents to oximes was limited. However, precomplexation of a Lewis acid and the oxime has provided a series of greatly improved results. The Lewis acid is thought to bind to the nitrogen of the oxime, thus rendering the oxime carbon more electrophilic and therefore more susceptible to nucleophilic attack. The Lewis acid that has provided the best results to date is boron trifluoride etherate. The complex, shown in **Figure 5**, postulated by Uno and Suzuki is thought to be the reactive species.[29]

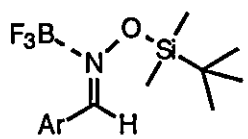
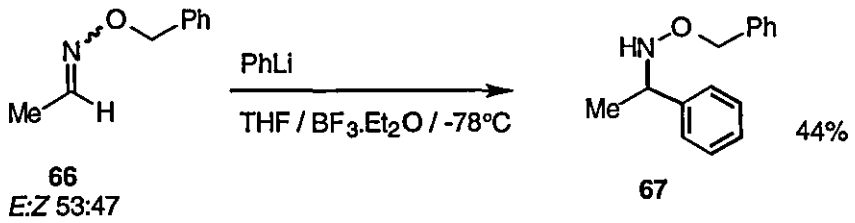


Figure 5

Prompted by the addition of organometallic reagents to imines mediated by boron trifluoride,[30] Volkmann and Weeks undertook a study of the addition of penicillin derived Grignard reagents to oxime ethers in the presence of boron trifluoride etherate.[31] The 6-amino methyl substituent on a penicillin nucleus has been shown to infer potent β-lactamase inhibitory activity. The methods for synthesis previously have been lengthy and therefore Volkmann and Weeks reasoned that the addition of a penicillin derived Grignard reagent **62** to a formaldehyde imine equivalent would give a more direct route to this framework. Ethyl formaldoxime was found to be stable, unlike the corresponding imine, and studies into its reactivity were carried out with the dibromopenicillin sulfone **62 (Scheme 34)**.

Previously it has been reported that the treatment of oximes, with abstractable α-hydrogens, with nonstabilized organometallic reagents led to hydroxylamines in poor yields and aziridines. Rodrigues reported that the attempted addition of phenyllithium to *O*-benzyl acetaldoxime **66** in THF was unsuccessful and that the recovered starting material was consistent with α-hydrogen abstraction.[32] However, the addition of one equivalent of boron trifluoride etherate to the phenyllithium prior to addition gave the hydroxylamine **67** in 44% yield **(Scheme 36).**

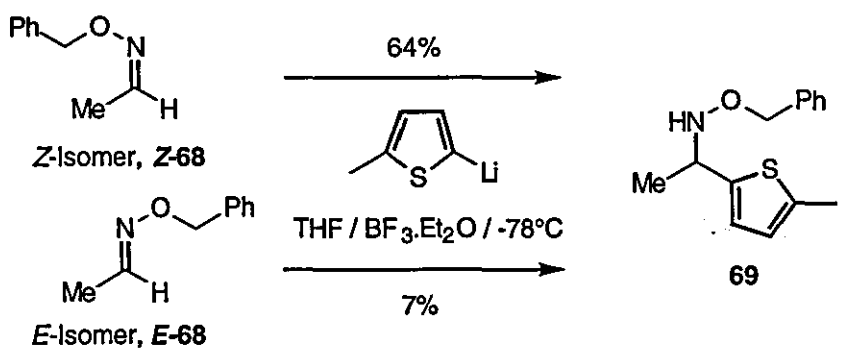


66
E:*Z* 53:47

67

Scheme 36

Aryl, acetylenic and vinyl lithium reagents added smoothly to produce the desired product, however alkyllithium derivatives failed to yield hydroxylamines in THF. The addition of other Lewis acids and varying the amounts of boron trifluoride gave a reduction in yields. Treatment of the oximes containing a high proportion of the *E*-isomer gave poor yields of the hydroxylamine, and the recovered starting material was found to be exclusively the *E*-isomer. The *E*-oxime ***E*-68** was reacted under the boron trifluoride conditions with 2-thienyllithium and only 7% of addition product **69** was detected. The *Z*-isomer ***Z*-68** was reacted under the same conditions and gave a 64% yield of the hydroxylamine **69**. These results suggest that the *Z*-isomer of oxime ethers generally reacts preferentially under these conditions **(Scheme 37).**



Z-Isomer, ***Z*-68**

E-Isomer, ***E*-68**

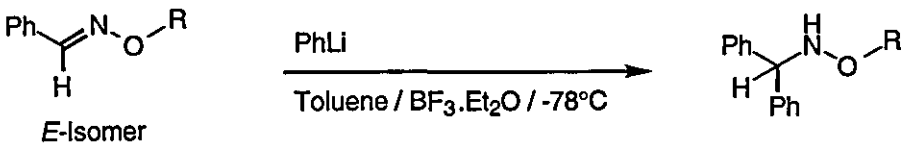
69

Scheme 37

Complementing the work of Rodrigues and co-workers, Uno and Suzuki have reported the addition of aryl, allyl and alkyl lithium reagents to oxime ethers.[29] The conditions used were similar to that of Rodrigues, except that THF was replaced by

toluene. Several different combinations of organolithium and oxime ethers were examined and the following conclusions could be drawn.

(i) The co-ordination of the oxime nitrogen to the boron trifluoride is essential for success of the reaction, the presence of oxygen atoms at sites away from the nitrogen greatly reduced the yield of the reaction **(Scheme 38).**



E-Isomer

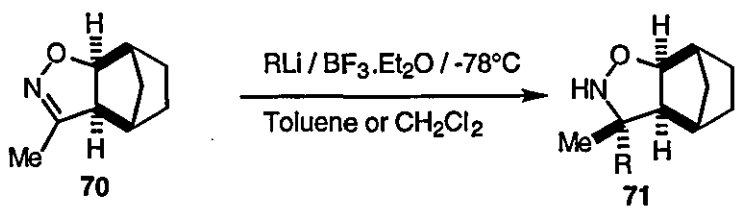
R = $PhCH_2$ (59%)
MOM (31%)
$MeOCH_2CH_2$ (13%)

Scheme 38

(ii) As the reaction depends on the co-ordination of the oxime nitrogen with the Lewis acid, the use of co-ordinating solvents, such as THF, also decreases the yield of addition.

(iii) Lower reactivity of the *E*-isomer was also observed, as recovered starting material was usually enriched in the *E*-isomer.

Uno and Suzuki have also studied the reaction of organolithium reagents on cyclic oxime ethers (isoxazolines) mediated by boron trifluoride etherate **(Scheme 39).**[33] The produced *N*-unsubstituted isoxazolidines **71** are generally difficult to synthesise from the traditional method of reaction of a nitrone with an olefin. The isoxazolines **70** were prepared by the action of a nitrile oxide on an olefin.



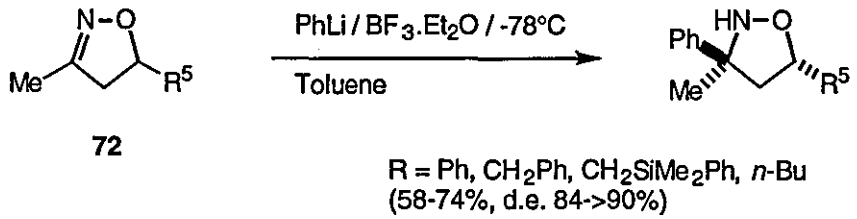
70 **71**

R = Me, Ph, *n*-Bu, $n\text{-}C_6F_{13}$ (14-92% as single diastereomers)

Scheme 39

In most examples addition to the 4,5-disubstituted isoxazolines **70** occurs in good yields and excellent diastereoselectivity. The major diastereomer is produced from the

addition of the organolithium reagent to the face opposite to the C-4 substituent. Similar selectivities are observed for C-5 monosubstituted isoxazolines **72 (Scheme 40).**

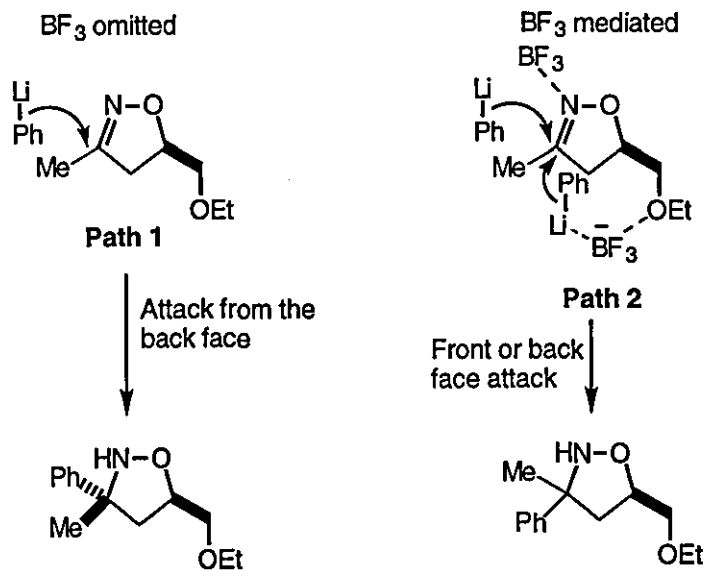


72

R = Ph, CH_2Ph, CH_2SiMe_2Ph, *n*-Bu
(58-74%, d.e. 84->90%)

Scheme 40

Results worthy of note however, involve the presence of oxygen in the C-5 side chain. When $R^5 = CH_2OEt$ then the addition gives an essentially 1:1 mixture of diastereomers in the presence of boron trifluoride, but if boron trifluoride is omitted then the diasteromeric ratio increases to 10:1. The proposed rationale for this is shown in **Scheme 41.**

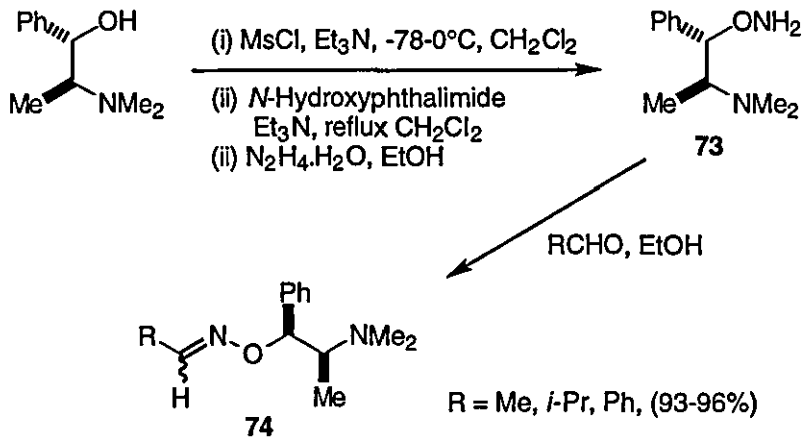


Scheme 41

Path 1 indicates attack from the least hindered bottom face as expected. However, **Path 2** shows there maybe some chelation between the *OEt* of the side chain, the boron trifluoride and the incoming aryllithium, thus directing attack on the top face. As well as this face selectivity the expected back face addition may occur to give rise to poor diastereoselectivity.

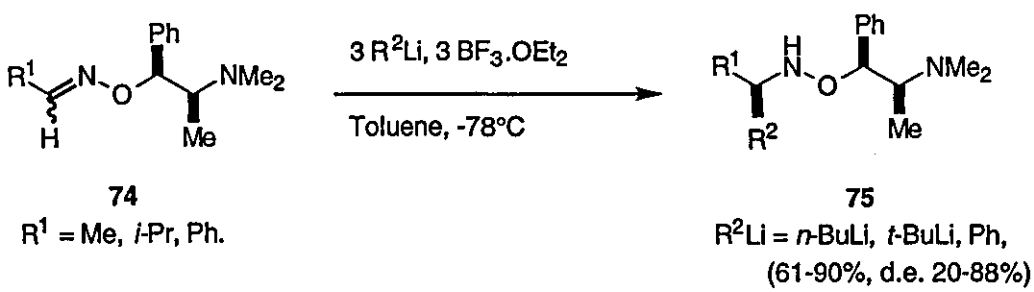
Perhaps the most pioneering work in this area has come from Dieter and Datar, who have previously reported a procedure for effecting regio and stereoselective

substitution of the benzyl hydroxyl group in ephedrine derivatives.[34] This methodology has been utilised in the synthesis of chirally pure hydroxylamine **73**.[35] A series of aldehydes were treated with **73** which gave the corresponding oxime ethers **74** in excellent yields as mixtures of *E* and *Z*-isomers **(Scheme 42).**



Scheme 42

Treatment of the oxime ethers **74** with organolithium reagents in the presence of boron trifluoride etherate gave the hydroxylamines **75** in good yields. Grignard reagents alone or in the presence of zinc bromide or lithium perchlorate in THF, ether or toluene failed to give the desired products. Three equivalents of both organolithium reagent and boron trifluoride etherate in toluene were found to be the optimum conditions **(Scheme 43)**. The three equivalents are thought to be required as alkyllithium reagents attack boron trifluoride at low temperatures to give alkylidifluoroboranes, alkylfluoroborates and tetraalkylborates.



74
R^1 = Me, *i*-Pr, Ph.

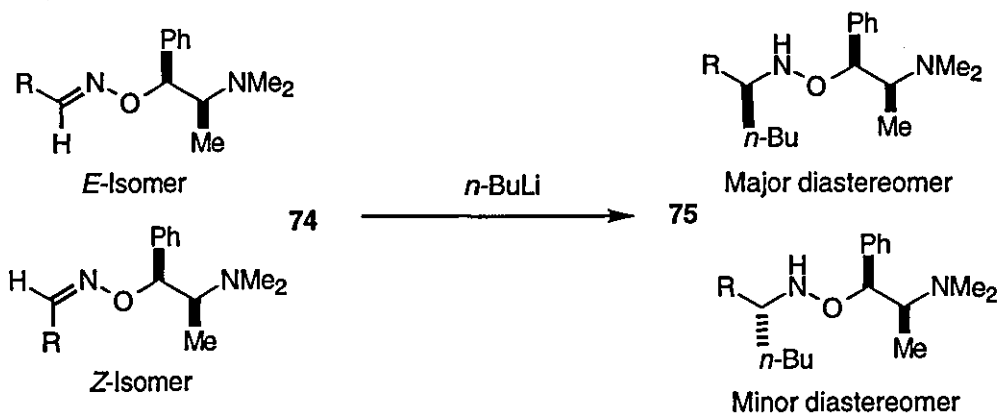
75
R^2Li = *n*-BuLi, *t*-BuLi, Ph,
(61-90%, d.e. 20-88%)

Scheme 43

The addition of organolithium reagents to oxime ethers **74** provided two interesting points:

(i) The oxime ether rich in the *Z*-isomer gave greater conversion to the hydroxylamine than the corresponding addition to the oxime rich in the *E*-isomer in accordance with the results obtained by Rodrigues.

(ii) The addition products **75** diastereomeric excesses mirror closely the ratio of *E* and *Z*-isomers of the starting oximes **74 (Scheme 44).**



R = Me, *E*:*Z* = 63:37, diasteromeric ratio = 60:40

i-Pr, *E*:*Z* = 92:8, diastereomeric ratio = 90:10

Ph, *E*:*Z* = 94:6, diastereomeric ratio = 89:11

Scheme 44

The absolute configuration of the stereogenic centre created in these reactions can be understood in terms of a chairlike conformation **(Figure 6).** The observed absolute configuration of the major enantiomer (S) derives from attack of the organolithium from the bottom face of the chair conformation on the *E*-isomer. The minor enantiomer arises from attack again from the lower face but from the *Z*-isomer.

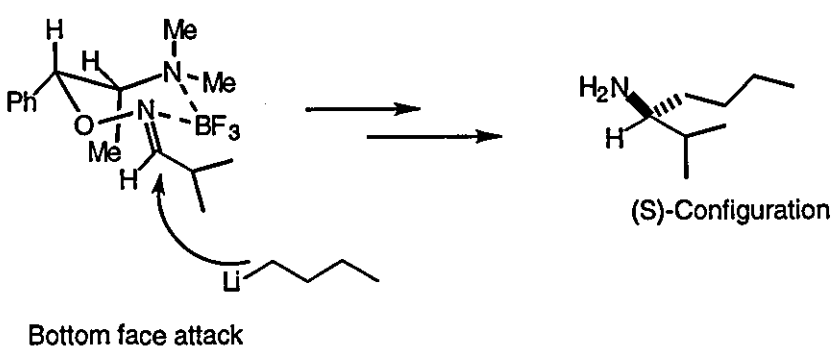
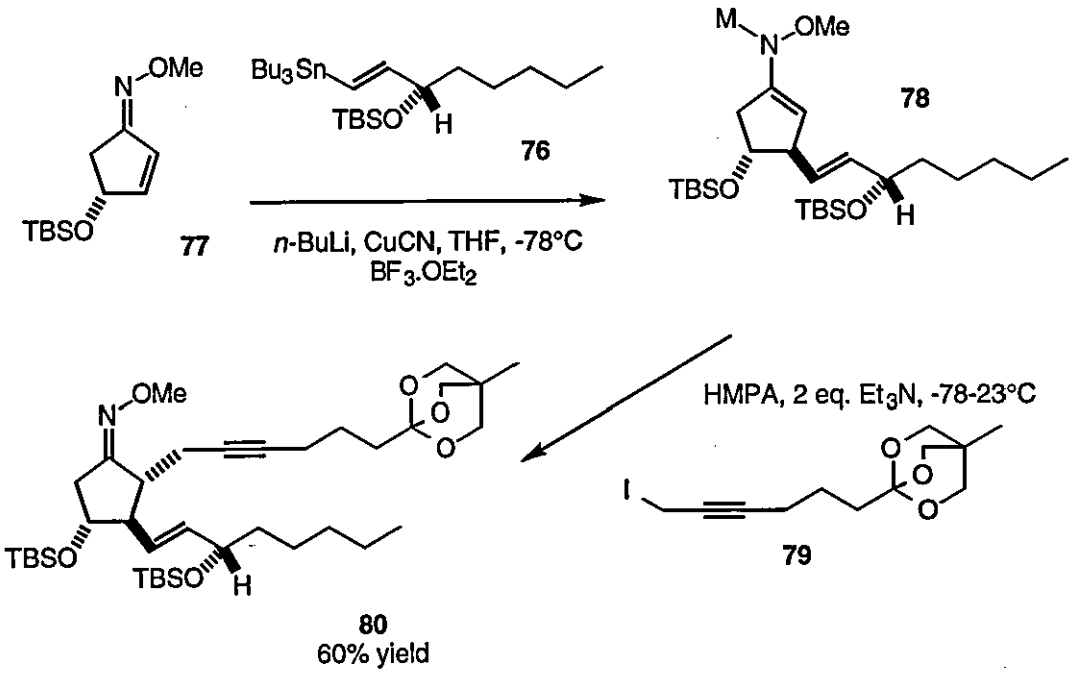


Figure 6

Molecular model studies have shown that the axial methyl substituent of the *N,N*-dimethyl group of the auxiliary provides much of the steric hindrance to the top face, which is required for the observed stereochemistry.

Not only have oxime ethers been reported to undergo 1,2 addition but Corey has reported the 1,4 addition of a cuprate **76** to an α,β-unsaturated oxime ether **77**.[36] The cuprate **76** was prepared and treated with a solution of the oxime ether **77** and boron trifluoride etherate at -78°C. The resulting enolate equivalent **78** was trapped with the iodide **79** *in situ* to yield the desired prostanoid **80** in 60% yield **(Scheme 45)**. The stereochemistry is set up by the addition of the cuprate on the opposite side of the ring to the bulky silylated alcohol.



Scheme 45

1.5. Summary

The addition of organometallic reagents to oximes and oxime ethers is a poorly studied area, but nonetheless several interesting results have been obtained in terms of yields and diastereoselectively. Below is a summary of the main points of this review.

(i) The addition of chiral allylboronates to oximes has been shown to give moderate levels of asymmetric induction, but harsh conditions are required to obtain good yields.

(ii) The addition of nucleophiles to oxime ethers has been shown to require activation of some description to ensure high yields. The methods of activation include the use of allyl metallic reagents or activation of the *C=N* bond by Lewis acids or electron withdrawing groups such as the carboxylate functionality

(iii) Boron trifluoride etherate has been shown to be the superior Lewis acid for the addition of organolithium or Grignard reagents to oxime ethers.

(iv) The highest levels of diastereoselectivity have been obtained by Dieter with the addition of organolithium reagents to an oxime ether with *N*-methylephedrine as a chiral auxiliary on oxygen.

(v) The results obtained by Dieter are good, upto 88% d.e., but for a synthesis of chirally pure amines, the diastereoselectivity needs to be improved.

Chapter Two

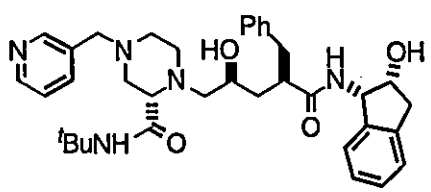
The Addition of Organometallic Reagents to Novel Chiral Oxime Ethers

2.1. Introduction

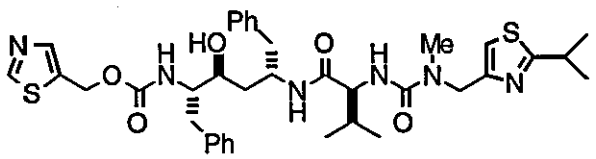
The pharmaceutical and agricultural industries have, over the past ten years, become increasingly aware of the need to prepare enantiomerically pure compounds.[37] Since the tragedy of Thalidomide®, where the effect of one enantiomer was radically different from the other, the quest for enantiomerically pure compounds has begun in earnest.[38]

Resolution aside, there are really only two methods for the formation of chirally pure compounds; the incorporation of a removable chiral entity into the molecule to induce chirality (chiral auxiliary), or more efficiently the use of a chiral ligand that may well be used in sub-stoichiometric amounts. Despite the overwhelming amount of research into the chiral modification of carbonyl compounds to chiral alcohols and of olefins to chiral saturated carbon derivatives,[39,40] the azomethine (*C=N*) moiety remains relatively understudied.

The preparation of chiral amine derivatives has a major impact on both the pharmaceutical and agricultural industries since many of the lead compounds contain this functionality. Drug candidates requiring the synthesis of a chiral amine group are exemplified by the Merck compound *Crixivan* **81** and the Abbott compound *Norvir* **82** **(Scheme 46).**



***Crixivan*, 81**



***Norvir*, 82**

Scheme 46

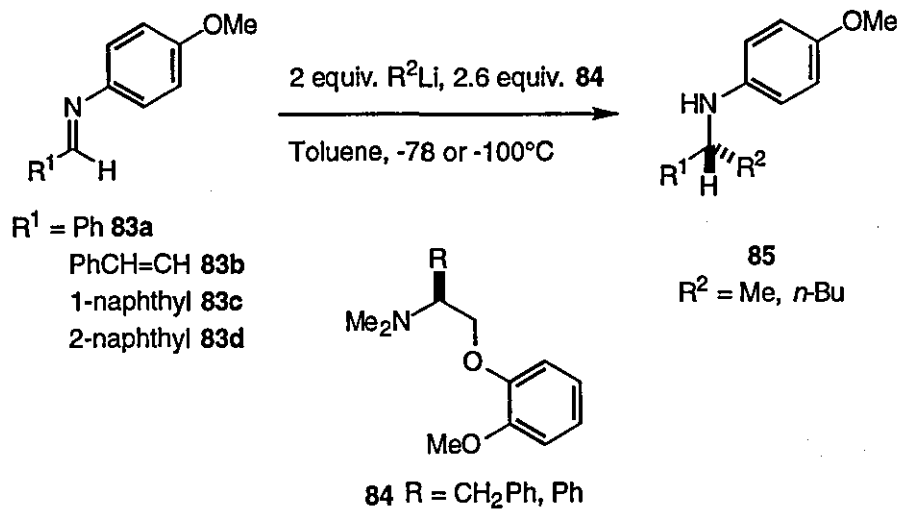
2.1.1. Ligand Mediated Addition of Organometallic Reagents to the Azomethine Functionality

Addition of Organolithium Reagents

The addition of certain nucleophiles to unsaturated functionality has been reported not to occur unless an external ligand is added. The ligand activates the substrates in such a way that addition may now be achieved, and if the ligand is chiral then there may be some asymmetric induction at the newly formed centre. The scope of this introduction

is to give a brief overview of the development of methods for the synthesis of chiral amines from the addition of organometallic reagents to the azomethine functionality.[41]

Tomioka was first to study the action of methyllithium and *n*-butyllithium on *N*-aryl imines **83** in the presence of a chiral mediator **84**.[42] The conditions of choice were found to utilise toluene as solvent and -78 or -100°C as the optimum temperature with 2.6 equivalents of external chiral mediator **84** and 2 equivalents of organometallic reagent **(Scheme 47)**.[43]



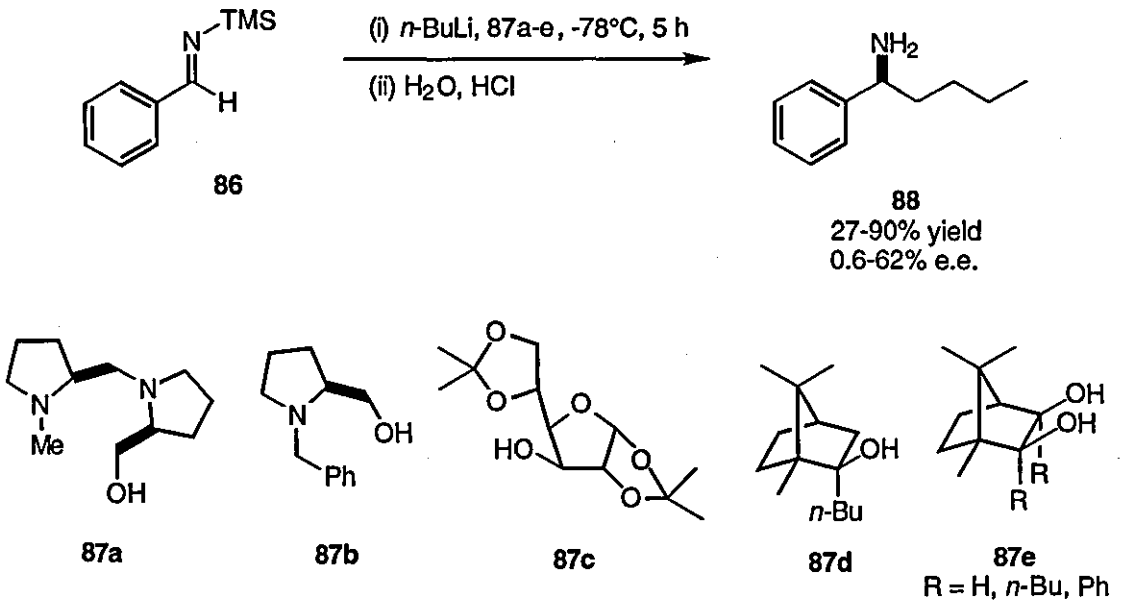
Scheme 47

The isolated yields of the secondary amines **85** were very good, up to 98% and the observed enantiomeric excesses were found only to be moderate (48-75% e.e.). The highest e.e. was obtained by the addition of methyllithium to the imine derived from naphthalenecarboxaldehyde **83c.** Worthy of note is that the solvent plays an important role, the secondary amines were recovered in nearly racemic form when THF was employed as the solvent. The chiral mediators **84** could be recovered in excellent yield. The *N*-aryl group could be removed successfully by Cbz protection of the nitrogen and oxidation with ceric ammonium nitrate to give the *N*-protected primary amines.

Tomioka has made further studies and found that the substituents on the aryl ring had a profound effect on the enantioselectivity, for example changing the 4-methoxyphenyl group for 4-methoxy-2-methylaniline gave the secondary amines in up to 90% e.e..[44] Further to these findings the same group discovered that the chiral ligands **84** could be used in sub-stoichiometric amounts.[45] The additions of methyllithium and *n*-butyllithium to the imines **83a-d** were again studied with 0.05-0.5 equivalents of chiral

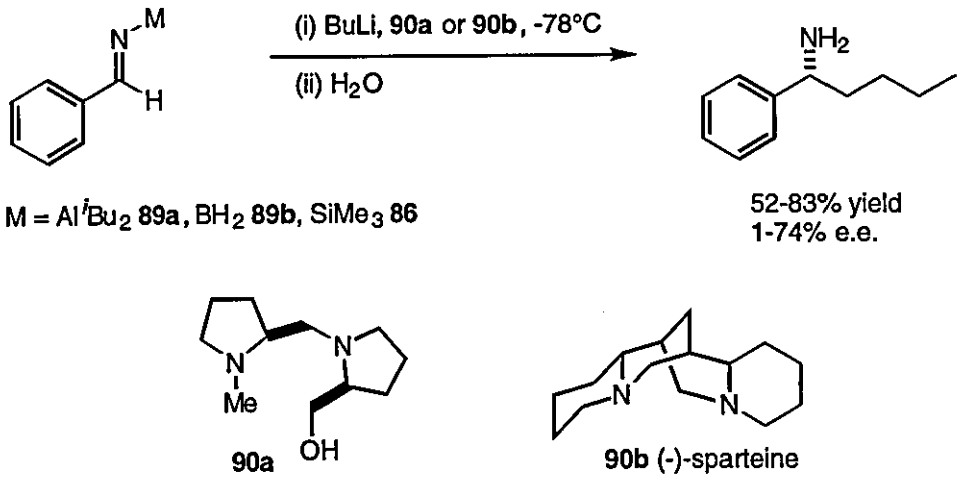
ligand. The yields were found to be uniformly high (81-99%) with the naphthaldehyde derivative **83c** again showing significant values of asymmetric induction (50-59%) with 0.3 equivalents of ligand.

Moving away from the *N*-aryl imines, Itsuno studied the addition of *n*-butyllithium to the *N*-trimethylsilyl imine **86** derived from benzaldehyde in the presence of various chiral alcohols **(Scheme 48)**.[46] The chiral amines were isolated in good yields and moderate enantiomeric excess (0.6-62%) depending on the solvent and chiral promoter used. The solvent used for the addition of *n*-butyllithium to the imines was found to have a crucial effect on the yields, enantioselectivity and even the configuration of the chiral amine. The ligand **87c** was found to give the most favourable results with 62% e.e. favouring the S-enantiomer. The TMS imines **86** have the advantage over the *N*-aryl imines **83** in that the produced amines **88** can be deprotected easily by the action of dilute HCl.



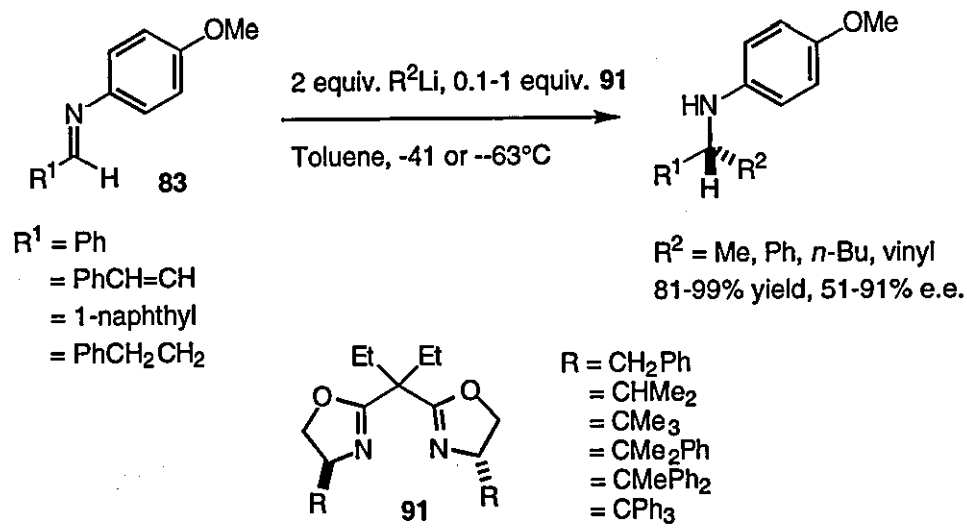
Scheme 48

In keeping with the theme of an easily removable group on nitrogen, Itsuno turned his attention to *N*-metallo imines **89**.[47] The group examined the effect of various chiral ligands **90** in the addition of *n*-butyllithium to an *N*-alumino imine **89a**, *N*-boryl imine **89b** and an *N*-silyl imine **86** derived from benzaldehyde **(Scheme 49)**. The best result (70% yield, 74% e.e.) was obtained by the action of a preformed *n*-butyllithium:(-)-sparteine **90b** complex on the *N*-diisobutylalumino imine **89b** at -78°C in pentane.



Scheme 49

Returning to the *N*-aryl imines **83**, Denmark has shown that the use of C_2 symmetric bisoxazolines **91** as ligands can provide useful levels of asymmetric induction (51-91% e.e.) and high yields (81-99%).[48,49] Methyllithium was again found to give the highest enantiomeric excess and diisopropyl ether was found to be the best solvent **(Scheme 50)**.

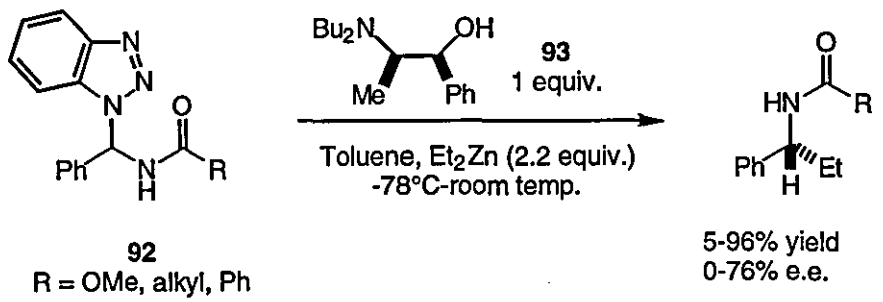


Scheme 50

Addition of Dialkylzinc Reagents

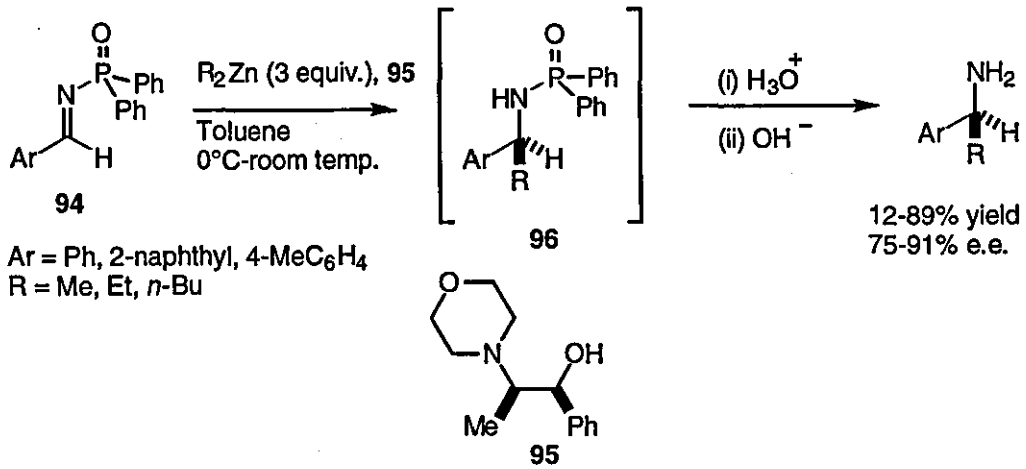
Following the success of the addition of dialkylzinc reagents to aldehydes in the presence of chiral promoters, Itsuno attempted to achieve this addition with the *N*-silyl imines **86**, however this was unsuccessful.[46] It was concluded that imines were too

unreactive and that activated imines were required such as *N*-acyl or *N*-phosphinoyl imines. Katritzky and co-workers developed a system in which an *N*-(amidobenzyl)benzotriazole **92** was used as a masked *N*-acyl imine **(Scheme 51).**[50] The use of *N,N*-dibutylnorephedrine **93** as a chiral mediator led to the corresponding amines being produced with a range of yields (5-96%) and only modest enantioselectivity.



Scheme 51

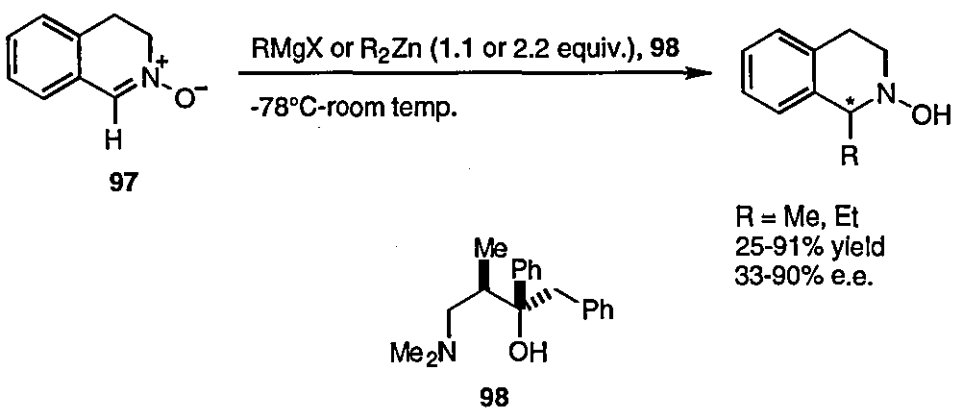
Shortly after this publication Soai and co-workers showed that *N*-diphenylphosphinoyl imines **94** could also undergo addition of dialkylzinc reagents, the phosphinoyl moiety creates the required activation of the azomethine function **(Scheme 52).**[51] The use of a stoichiometric amount of chiral β-amino alcohol **95** gave good yields and high enantioselectivity (90% e.e.) of the corresponding phosphinamide **96.** Hydrolysis of **96** gave the primary amines in good yields. However, decreasing the chiral promoter to sub-stoichiometric amounts led to a substantial drop in yields but the enantioselectivity remained high.



Scheme 52

Addition to Nitrones with RMgX and R_2Zn

An interesting piece of work by Ukaji, Inomata and co-workers has shown that the oxygen of the nitrone is capable of co-ordinating strongly to a metal, thus creating a chiral environment in the presence of a chiral promoter.[52] The mediator used was Chirald® **98**, which is a chiral amino alcohol commercially available from the Aldrich Chemical Company. The additions were attempted with alkyl metals such as methyl and ethylmagnesium bromide, dimethyl and diethyl zinc. The addition of ethylmagnesium bromide in dimethoxyethane to the nitrone **97** with magnesium bromide as an additive gave the corresponding (S)-hydroxylamine in 90% e.e. **(Scheme 53)**. In contrast the addition of diethyl zinc gave a reversal of enantioselectivity with the (R)-hydroxylamine being isolated in 74% yield and 57% e.e. This reversal of configuration depending upon the metallic reagent used is remarkable and worthy of note.

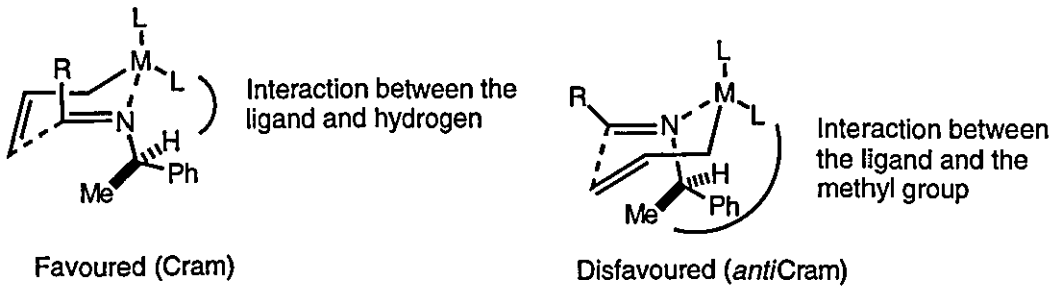


Scheme 53

2.1.2. Addition of Organometallic Reagents to the Azomethine Functionality Containing Chiral Auxiliaries

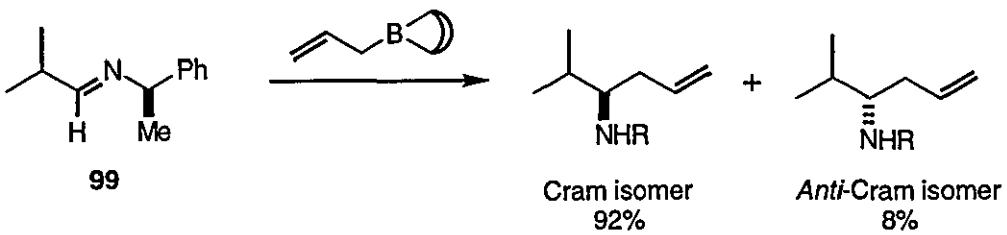
Additions to Imines

Of all the compounds containing the azomethine functional group, imines have been examined the most thoroughly. Yamamoto has studied the addition of allylic metal reagents to chiral imines derived from 1-phenylethylamine.[53] The ratio of diastereomers is normally high and has been found to depend on the metal used and the associated ligands. A cyclic transition state has been postulated in which the ligands on the metal can be seen to exert an influence on face selectivity **(Scheme 54)**.



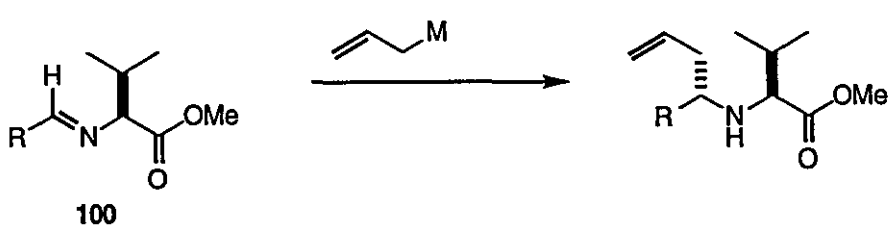
Scheme 54

Allyl-9-BBN has been shown to add to the imine **99** to give a 92:8 diastereomeric ratio in favour of the Cram isomer **(Scheme 55).**[54] Allylstannanes require the addition of Lewis acids and the diastereoselectivity of these reactions was found to be dependent on the Lewis acid used. For example, a ratio of 82:18 was obtained from a $TiCl_4$ mediated reaction, whereas $BF_3.OEt_2$ gave a 67:33 ratio. The addition of methylcopper and dimethylcuprate has also been achieved with Cram:*anti*-Cram ratios up to 90:10. In all cases the Cram product was favoured.



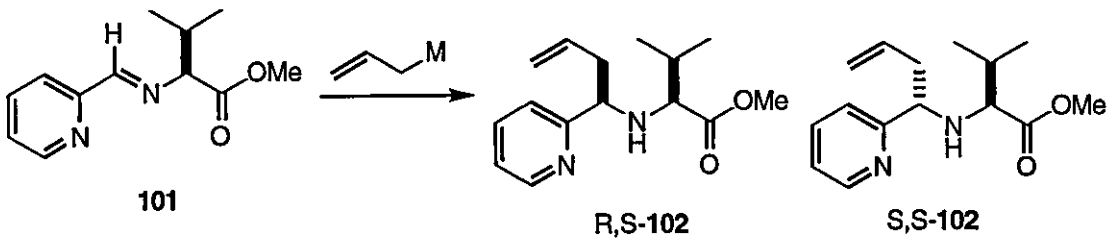
Scheme 55

Allylic metal reagents were added to imines derived from valine methyl ester **100.** The metal couples of Al/Ti and Mg/Cu gave excellent diastereoselectivity (95-98% d.e.) and the auxiliary can be removed easily by electrolysis to give the amines in high yields **(Scheme 56).**[55] A cyclic chelated transition state has been postulated between the nitrogen and the ester to account for the observed stereochemistry.



Scheme 56

The addition of allylic metal reagents to imine **101** derived from pyridine-2-carboxaldehyde and valine has recently been studied by Alvaro and Savoia.[56] It has been found that the configuration of the newly formed stereocentre can be reversed with high levels of diastereoselectivity by changing the metallic species **(Scheme 57)**. The use of an allylic lead complex gave a 92% diastereomeric excess in favour of the product S,S-**102**. Whereas an allylic tin species gave a diastereomeric excess of 94% in favour of the product R,S-**102**. The rationale for this is due to the differing co-ordination properties of the metals.



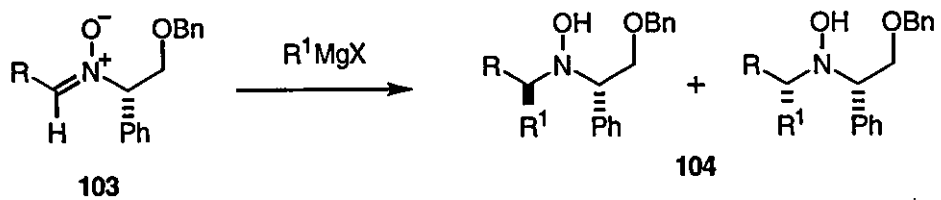
101 R,S-**102** S,S-**102**

AllylPbBr.MgBrCl, 98% yield, 4:96 (R,S:S,S)
$AllylSnICl_2$, 90% yield, 97:3 (R,S:S,S)

Scheme 57

Additions to Nitrones

To complement the work on imines, Chang and Coates added Grignard reagents to chiral nitrones **103**, which are the *N*-oxidised derivatives of imines.[57] Treatment of the nitrone with alkyl and phenylmagnesium halides gave the corresponding hydroxylamines **104** in good yields and diastereoselectivity (60-98% d.e.) **(Scheme 58)**.



103 **104**

R = Ph, R^1 = *i*-Pr, X = Cl	94	6
R = Ph, R^1 = *t*-Bu, X = Cl	95	5
R = 4-MeOPh, R^1 = Ph, X = Br	2	98
R = *n*-pentyl, R^1 = Me, X = Br	10	90
R = *n*-pentyl, R^1 = *t*-Bu, X = Cl	99	1

Scheme 58

The observed diastereoselectivity was rationalised by a cyclic transition state in which the oxygen atoms of the auxiliary and nitrone both co-ordinate magnesium. This transition state has two sterically different faces as shown in **Figure 7**, where attack by the nucleophile comes from the face bearing the hydrogen.

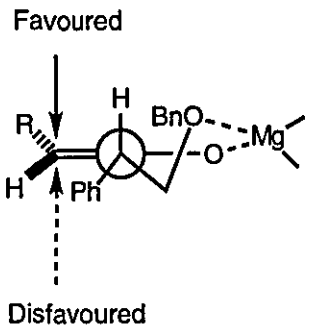
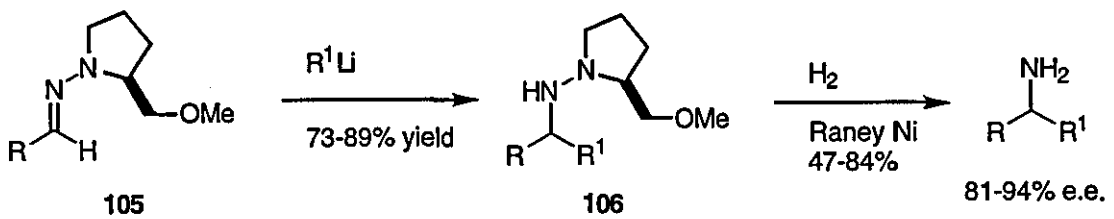


Figure 7

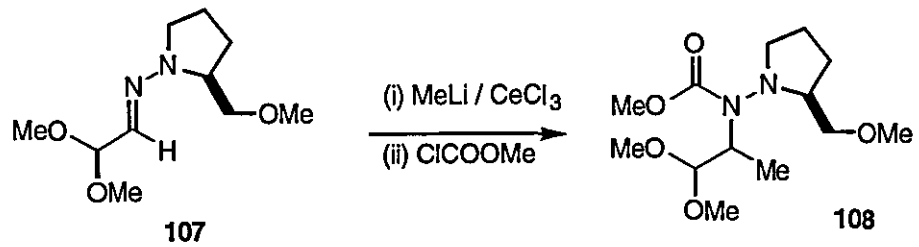
Additions to Hydrazones

The pioneering work by Enders is perhaps the most well known and predictable method of producing chiral amines from nucleophilic additions to the azomethine function.[58] The addition of organolithium reagents to SAMP hydrazones **105** provided the corresponding hydrazines **106** with excellent diastereoselectivity (81-94% d.e.). The *N-N* bond was cleaved with Raney nickel to provide the primary amines **(Scheme 59)**.



Scheme 59

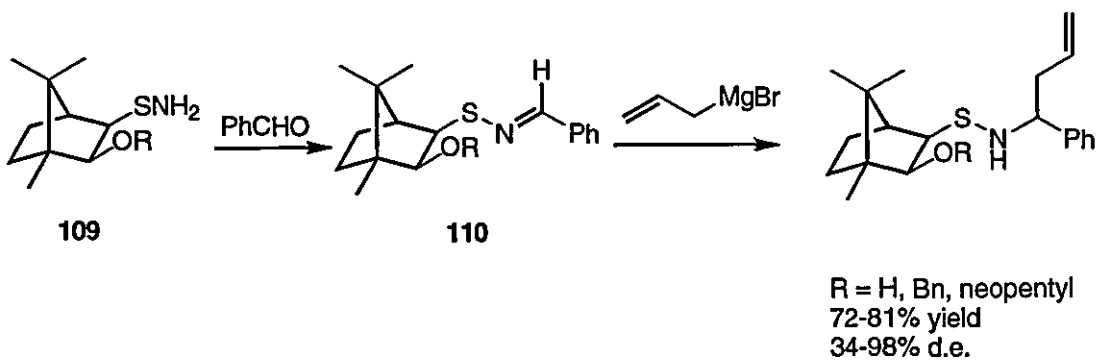
Denmark has also studied this process and has shown that utilising organocerium reagents the diastereoselectivity of the additions to SAMP hydrazones **107** could be further increased **(Scheme 60)**.[60] The hydrazines produced were protected *in situ* as their corresponding methyl or benzyl carbamates **108** since the free hydrazines were air sensitive. The *N-N* bond was again cleaved by the action of Raney nickel.



Scheme 60

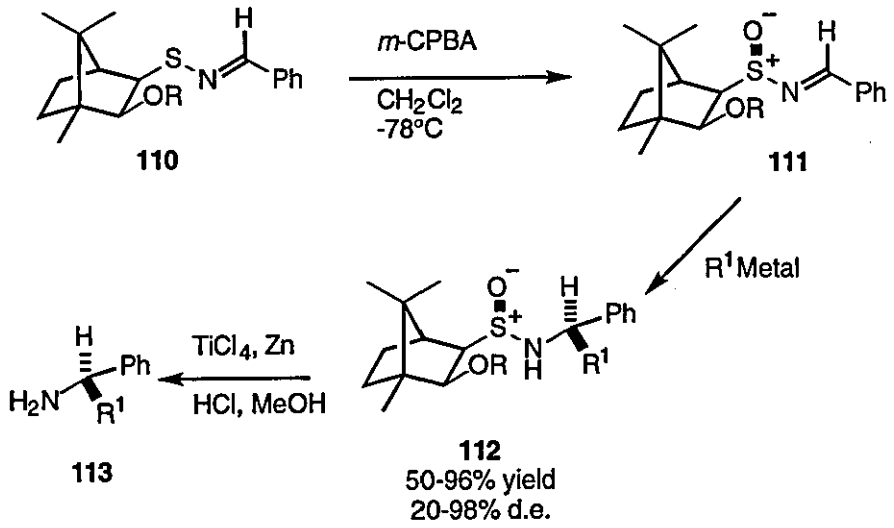
Additions to Sulfinimines and Sulfenimines

Two major problems of the previous additions to the azomethine function exist: the harsh conditions required for *N-N* bond cleavage of the SAMP hydrazones and the fact that some chiral auxiliaries are destroyed on removal. This prompted Yang and co-workers to study the additions to chiral sulfenimines and sulfinimines where he has shown that the removal of the auxiliary is facile and the auxiliary is recyclable.[60] The camphor derived auxiliary **109** has been attached to benzaldehyde to produce the corresponding sulfenimines **110**. Addition of allylmagnesium bromide to this species gave poor to excellent diastereoselectivity (34-98% d.e.) **(Scheme 61).**



Scheme 61

The sulfenimines **110** could be oxidised with high diastereoselectivity by the action of *m*-CPBA to the corresponding sulfinimines **111**. Addition of allyl Grignard reagents provided the sulfenamides **112** in excellent yields and diastereoselectivity, other alkyl Grignard reagents gave lower diastereoselectivity **(Scheme 62)**. A cyclic transition state for both the additions to sulfenimines and sulfinimines has been postulated. The auxiliary could be removed and the primary amines **113** isolated by the action of $TiCl_4$, Zn and HCl in methanol.

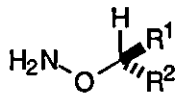


Scheme 62

Although the strategy of employing chiral hydrazones, imines, nitrones and sulfinimines has provided an impressive repertoire in the transformations of aldehydes and ketones into optically enriched amines, the problem of diastereoselective addition to oxime ethers remains largely unsolved. As described in Chapter 1, the additions to chiral *O*-alkyl oxime ethers has been achieved but only in modest diastereomeric excess and warrants further investigation.

2.2. Design and Synthesis of Chiral Oxime Ethers

Our interests lay in the design and synthesis of enantiopure *O*-alkyl hydroxylamines **114** **(Figure 8)** which could be reacted with a series of carbonyl compounds to produce chiral oxime ethers.



114

Figure 8

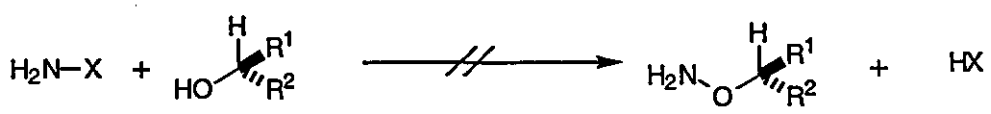
Chiral *O*-alkyl hydroxylamines offer the opportunity to be excellent auxiliaries because of their potential ease of synthesis from commercially available alcohols. We wished to exploit the stereocontrolling properties of the chiral moiety on the oxygen atom in a variety of reactions at the *C=N* centre.

The criteria for the synthesis and general applicability of the hydroxylamines **114** are outlined below:

(i) The chiral moiety should be cheap and readily available as either enantiomer,

(ii) The chiral hydroxylamine should be readily attached to aldehydes and ketones and should render the two enantiotopic faces of the *C=N* bond inequivalent.

In the planning of the synthesis of enantiopure hydroxylamines **114** two major strategies may be employed. One such possibility would be the formation of the *N-O* bond in which alcohols derived from the chiral pool could be aminated on oxygen by the action of an electrophilic amine source **115 (Scheme 63)**.[61]

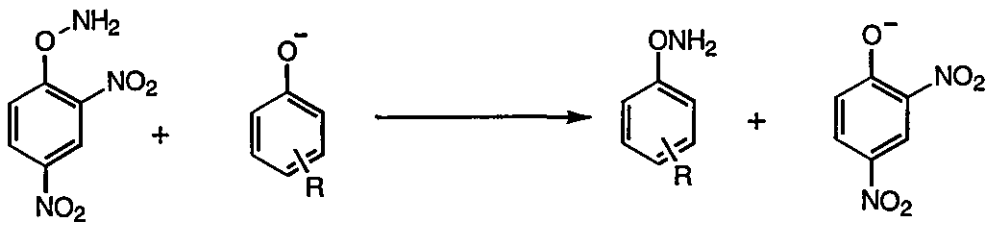


115a-c
X = Cl, OSO_3H, 2,4-dinitrophenoxy

114

Scheme 63

Many species containing an electrophilic nitrogen source are reported in the literature, however direct amination of oxygen is rare. In 1956 Thielacker published the results of the use of chloramine, NH_2Cl, as an aminating agent of alkoxides, in particular menthol.[62] This method was attempted in our laboratory by the formation of an anhydrous solution of chloramine in ether from aqueous sodium hypochlorite and ammonium hydroxide,[63] followed by the addition of sodium menthoxide. However, menthol was recovered quantitatively after several attempts. Rapoport has shown that the use of hydroxylamine **115c** has resulted in the amination of phenols **(Scheme 64)**.[64] Unfortunately the reaction with simple alkoxides failed. Failure is attributed to the increased basicity of alkoxides in comparison with phenols.

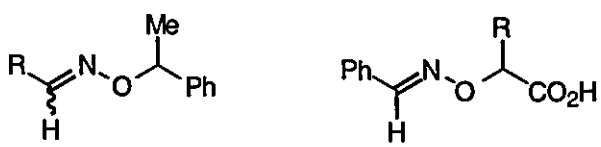


115c

Scheme 64

The second strategy, in which the *N-O* bond is already installed was examined. *N*-Hydroxyphthalimide and *N*-hydroxysuccinimde are both reported to undergo alkylation on the oxygen atom under a variety of conditions.[65] Unmasking of the amine whilst maintaining the *N-O* bond is also prevalent in the literature,[66] and consequently this method was employed.

The derivatives chosen for study were the simple *O*-(1-phenylethyl) aldoximes **116** and the carboxylic acid derivatives **117 (Figure 9).**



116 **117**

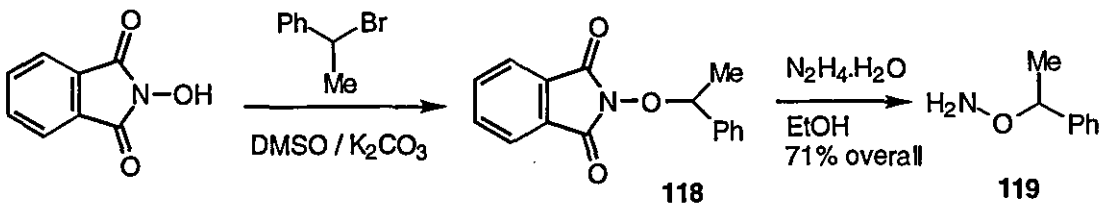
Figure 9

The simple *O*-1-phenylethyl auxiliary was chosen on the basis of the well documented reactions of α-methylbenzylamine where the small (H), medium (Me) and large (Ph) groups have such a profound effect on stereoselectivity.[54] The carboxylic acid

derivatives **117** were chosen to incorporate a group to which the incoming nucleophile could be chelated and hence promote a face selective approach.

Synthesis of Chiral Oxime Ethers

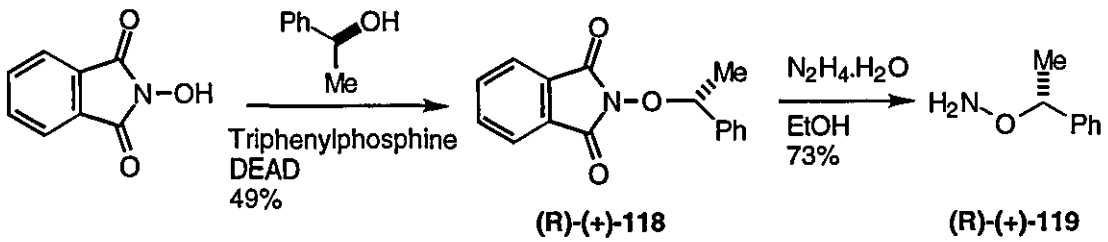
The starting material for the aldoximes **116** was *O*-(1-phenylethyl) hydroxylamine **119.** This was initially prepared by alkylation of *N*-hydroxyphthalimide with racemic (1-phenylethyl)bromide in DMSO with potassium carbonate as base which gave the alkoxyphthalimide **118.** This was followed by cleavage of the phthaloyl unit with hydrazine hydrate **(Scheme 65).**



Scheme 65

After stirring the phthalimide and bromide at room temperature for 12 hours, water was added to the mixture and a white precipitate was observed. Filtration provided the alkoxyphthalimide **118** in sufficient purity to be used in the next step. An analytically pure sample was obtained by recrystallisation from ethanol. The alkoxyphthalimide **118** was then treated with hydrazine hydrate in ethanol at 50°C to cleave the phthaloyl group. The reaction could be monitored by the appearance of the phthaloyl byproduct as a white precipitate as the solution was allowed to cool. Aqueous work up and column chromatography afforded the desired racemic hydroxylamine **119** as a volatile oil.

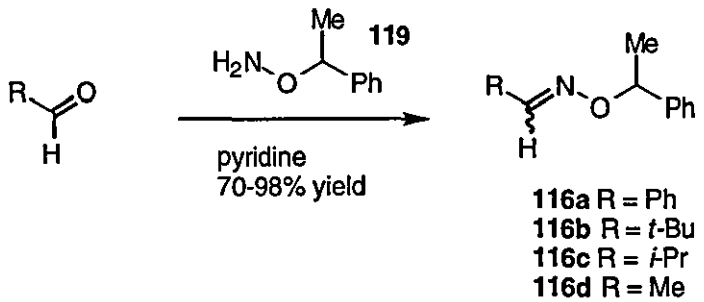
The optically pure hydroxylamine **(R)-(+)-119** was prepared by the Mitsunobu reaction of (S)-(-)-1-phenylethanol and *N*-hydroxyphthalimde.[67] *N*-Hydroxyphthalimde and the chiral alcohol were treated with triphenylphosphine and diethyl azodicarboxylate (DEAD) in THF at room temperature. The reaction was allowed to stand for 24 hours, evaporation of the solvent and column chromatography of the residue gave the chirally pure alkoxyphthalimide **(R)-(+)-118** in 49% yield **(Scheme 66).** Subsequent cleavage of the phthaloyl unit with hydrazine hydrate gave the (R)-(+)-hydroxylamine **(R)-(+)-119** in 36% overall yield.



Scheme 66

The enantiomeric excess of **(R)-(+)-118** was determined by ^1H NMR spectroscopy employing $Eu(hfc)_3$ as a chiral shift reagent. This indicated that the alkoxyphthalimide was formed in greater than 95% enantiomeric excess.

The synthesis of the oxime ethers **116** was achieved by the condensation of **119** with a series of aldehydes. The aldehydes were cooled to 0°C in pyridine and the hydroxylamine **119** added, the solution was stirred for 1 hour and aqueous work up gave the virtually pure oximes in high yield **(Scheme 67).**



Scheme 67

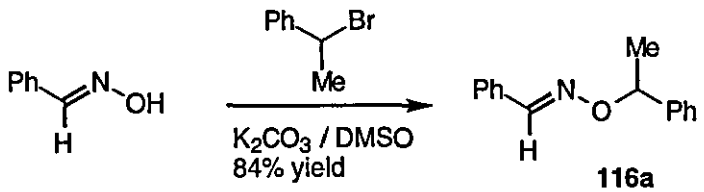
The oximes **116a** and **116b** were obtained as single geometrical isomers (*E*), while the oximes **116c** and **116d** were obtained as a mixture of *E* and *Z*-isomers **(Table 7).** The ratio of geometrical isomers is dependent on the size of the substituent of the aldehyde, for example, where R is large (*t*-Bu) then solely the *E*-isomer is produced. However, a decrease in the size of the substituent (R = Me) gave a virtually 1:1 ratio of the *E* and *Z*-isomers.

R[1]	*Product*	*E:Z*	*Yield (%)*
Ph	**116a**	100:0	70
t-Bu	**116b**	100:0	83
i-Pr	**116c**	76:24	97
Me	**116d**	46:54	98

Table 7

The ratio of geometrical isomers was determined by proton and carbon NMR spectroscopy. In the proton NMR for the oxime **116d** the former aldehyde proton (*HC=N*) for the *E*-isomer appears at 7.5 ppm but at 6.8 ppm for the *Z*-isomer, and integration of the peaks gives the *E:Z* ratio directly. The carbon NMR of **116c** also shows a similar trend in which the carbon atom α to the *C=N* bond in the *E*-isomer appears at 29.3 ppm and the same atom in the *Z*-isomer is shifted upfield by 4.2 ppm.

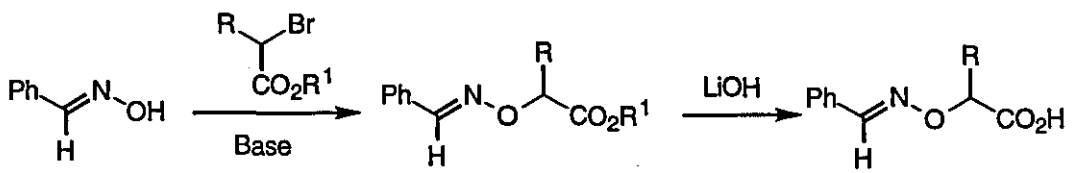
Oxime ether **116a** was also prepared in racemic form by the alkylation of *syn*-benzaldoxime with (1-phenylethyl)bromide in DMSO with potassium carbonate as base. Column chromatography afforded the oxime ether in good yield **(Scheme 68).**



116a

Scheme 68

Oxime ethers **120a** and **120b** were initially prepared by Dr Elizabeth Swann by alkylation of *syn*-benzaldoxime with the appropriate α-bromoester in DMF with sodium hydride. Oxime ether **120c** could not be prepared under these conditions which led to the decomposition of the α-bromoester; similarly treatment with potassium *tert*-butoxide in *tert*-butanol at elevated temperature also led to decomposition. However, the same system at room temperature gave **120c** in moderate yield **(Scheme 69).** Hydrolysis of the ester groups with lithium hydroxide in aqueous THF afforded the oxime acids **117a-c** in good yields (52-98%) as colourless solids.



120a R = Me, R^1 = Et, 76%
120b R = *i*-Pr, R^1 = Et, 60%
120c R = Ph, R^1 = Me, 58%

117a R = Me, 52%
117b R = *i*-Pr, 98%
117c R = Ph, 68%

Scheme 69

The acids **117a** and **117c** and the ester **120c** provided crystals suitable for *X*-ray crystallography **(Figures 10-12).** Oxime acid **117c** crystallised as the monomer whereas **117a** crystallised as the carboxylic dimer. The crystal structures show that

although the chiral centre renders the two faces of the oxime *C=N* bond inequivalent, in the solid state at least, the auxiliary is a substantial distance away from the electrophilic carbon of the oxime *C=N* bond.[68]

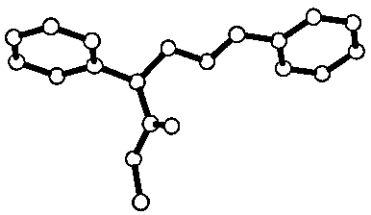


Figure 10.
X-ray crystal structure of *O*-(1-methoxycarbonylbenzyl) benzaldoxime **120c**.

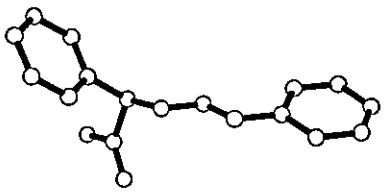


Figure 11.
X-ray crystal structure of *O*-(1-carboxybenzyl) benzaldoxime **117c**.

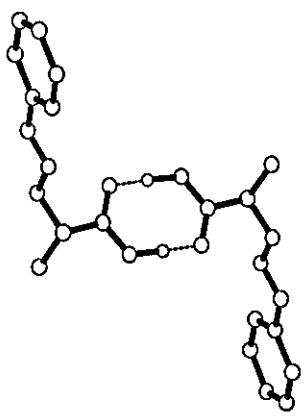
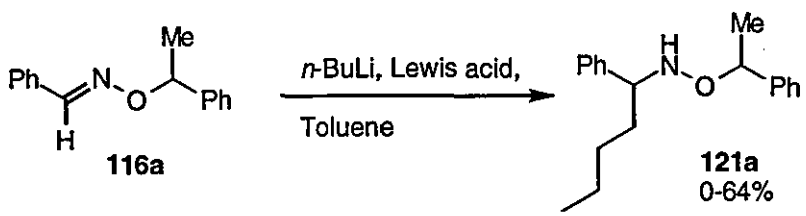


Figure 12.
X-ray crystal structure of *O*-(carboxyethyl)benzaldoxime **117a** (as carboxylic acid dimer).

2.3. Addition of Organometallic Reagents to Oxime Ethers

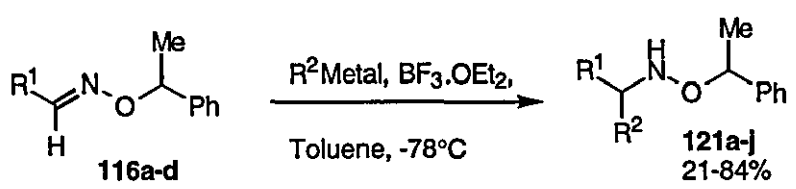
The reactivity of the *C=N* bond of oxime ethers is less than that of the corresponding imine derivatives as described in Chapter 1. Additions of organometallic reagents is possible with the aid of a Lewis acid. The optimised conditions based on those reported by Dieter were found to be three equivalents of organometallic reagent added to a solution of the oxime ether and three equivalents of boron trifluoride etherate at -78°C in toluene.[35] If less than three equivalents of Lewis acid and organometallic reagent were used then a quantity of unconsumed starting material was recovered. Several other Lewis acids were tried on a standard reaction of *n*-butyllithium with oxime ether **116a**, but only zinc chloride and boron trifluoride etherate afforded addition products **(Scheme 70)**.



Scheme 70

Titanium(IV), iron(III) and tin(IV) chloride caused decomposition of the oxime ether and produced (1-chloroethyl)benzene as a byproduct resulting from displacement of the auxiliary by chloride ion. With titanium(IV) *iso*propoxide as the additive no reaction occurred. The zinc chloride mediated addition reaction proceeded in only 13% yield, and less than 10% diastereomeric excess, with the remainder being unconsumed starting material. The addition of *n*-butyllithium to oxime ether **116a** at 0°C resulted in low yield (30%) and diastereomeric excess (30% d.e.).

A series of organometallic reagents were added to the oxime ethers **116a-d** under the conditions described by Dieter.[41] Three equivalents of organometallic reagent were added dropwise to a cooled solution of the oxime ether and boron trifluoride etherate in toluene **(Scheme 71).** The results of the addition reactions are summarised in **Table 8**.

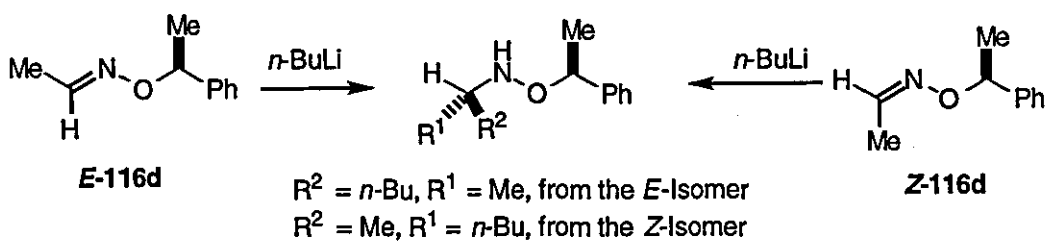


Scheme 71

Oxime ether	R^1	R^2*Metal*	*Product*	*Yield (%)*	*d.e. (%)*
116a	Ph	*n*-BuLi	**121a**	64	71
116a	Ph	*t*-BuLi	**121b**	54	38
116a	Ph	H_2C=$CHCH_2MgBr$	**121c**	70	69
116a	Ph	*i*-PrMgCl	**121d**	30	74
116b	*t*-Bu	*n*-BuLi	**121e**	84	74
116b	*t*-Bu	H_2C=$CHCH_2MgBr$	**121f**	62	44
116b	*t*-Bu	PhLi	**121b**	21	95
116c	*i*-Pr	*n*-BuLi	**121g**	83	77
116c	*i*-Pr	H_2C=$CHCH_2MgBr$	**121h**	70	59
116d	Me	*n*-BuLi	**121i**	70	5
116d	Me	H_2C=$CHCH_2MgBr$	**121j**	58	14

Table 8

n-Butyllithium added to the *C=N* bond of the oximes **116a-d** smoothly in under 15 minutes to give the corresponding hydroxylamines **121a, e, g** and **i** in good yields (64-84%). Examination of the crude NMR showed that the product in most cases was produced in greater than 90% purity, however initial problems of purification led to the decreased yields. The diastereoselectivity of the *n*-butyllithium additions was good, 71% and 74% d.e. for the oximes **116a** (*E:Z* 100:0) and **116b** (*E:Z* 100:0) respectively. The fact that an 8:1 diastereomeric ratio (77% d.e.) was obtained from the addition of *n*-butyllithium to oxime ether **116c** which has a *E:Z* ratio of only 3:1 seems at first glance to be anomalous. However, if we consider that the addition occurs with the *E*-isomer and only a small amount with the *Z*-isomer then the diastereomeric ratio obtained is feasible, indeed a small amount of the *Z*-oxime ether was recovered. The oxime ether **116d** gave only poor diastereomeric excess, this is presumably due to the fact that the oxime **116d** was present as a mixture of *E* and *Z*-isomers in an essentially 1:1 ratio. The addition of *n*-butyllithium to the *E*-isomer of oxime **116d** would lead to the opposite diastereomer to that produced from the addition to the *Z*-isomer **(Scheme 72).**



***E*-116d** **R^2 = *n*-Bu, R^1 = Me, from the *E*-Isomer**
R^2 = Me, R^1 = *n*-Bu, from the *Z*-Isomer ***Z*-116d**

Scheme 72

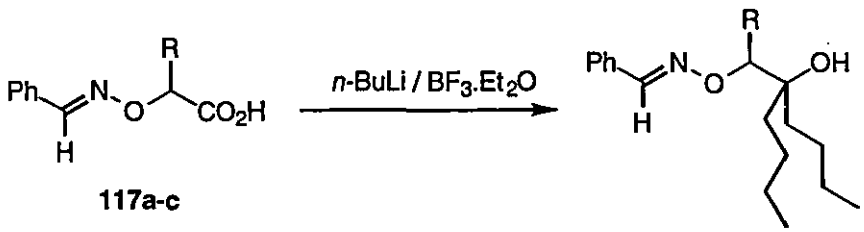
Allylmagnesium bromide added successfully to the oxime ethers **116a-d**, however the yields were slightly less than for the corresponding *n*-butyllithium addition (58-70%). The hydroxylamines were also accompanied by varying amounts of impurities, including 1-phenylethanol resulting from *N-O* bond cleavage. This is probably as a result of the slightly longer reaction times needed for allylmagnesium bromide addition. The diastereoselectivity was also in accordance with the findings for the addition of *n*-butyllithium. Oxime ether **116a** (*E:Z* 100:0) gave the highest diastereomeric excess (69% d.e.), however **116b** (*E:Z* 100:0) gave a disappointingly poor diastereomeric excess (44% d.e.) and a poor yield (62%). Oxime ethers **116c** (*E:Z* 3:1) and **116d** (*E:Z* 1:1.2) gave the hydroxylamines **121h** and **121j** in diastereomeric ratios in accordance with their *E:Z* ratios, 59% d.e. and 14% d.e. respectively.

The use of organometallic reagents with branching in the α-position were found to produce the corresponding hydroxylamines in poor yield. For example, treatment of oxime ether **116a** with *t*-butyllithium gave the addition product in only 54% yield, the remainder of the material was found to contain decomposition products. The diastereoselectivity of this addition was also poor (38% d.e.). The addition of *iso*-propylmagnesium chloride to oxime ether **116a** also gave a poor yield (30%) with recovered starting material making up an almost quantitative mass balance, the diastereoselectivity was found to be good (74% d.e.). It would appear that the addition of secondary or tertiary organometallic reagents occurs more slowly than the corresponding primary reagents possibly due to steric factors. The fact that *t*-butyllithium gave decomposition products and *iso*-propylmagnesium chloride gave recovered starting material is probably due to the nature of the organometallic reagents. The addition of phenyllithium to the oxime ether **116b** gave the addition product in poor yield (21%) but excellent diastereomeric excess (95% d.e.). This reaction provided the opposite major diastereomer to that obtained from the addition of *t*-butyllithium to **116a** which proved useful in our assignments of the diastereomeric excesses. The diastereomeric excesses were determined by examining the proton and the carbon NMR spectra, the diastereomeric ratios derived from the proton or the carbon spectra rarely differed by more than 5%. *t*-Butylmagnesium bromide and diethylzinc failed to add to oxime ether **116a**.

From these initial experiments it can be concluded that the addition of primary organolithium and Grignard reagents add to the oxime ethers smoothly to give the hydroxylamines, whereas secondary, tertiary and aryl organometallic reagents gave poorer yields. Also the diastereomeric ratio of the hydroxylamines has been found to mirror the *E:Z* ratio of the oxime ethers. It would appear that reagents such as *t*-

butylmagnesium bromide and diethylzinc are not nucleophilic enough in character to add to the oxime ethers.

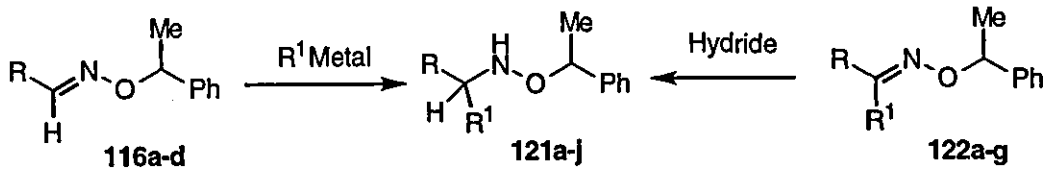
Turning our attention towards the oxime ethers **117a-c**, where it is hoped that the carboxylic acid function will co-ordinate to the incoming nucleophile, we added a solution of *n*-butyllithium under the standard conditions to the oxime ethers **117a-c** in the presence of boron trifluoride etherate at -78°C **(Scheme 73).** However, the attempted addition to the oxime ethers resulted only in the addition at the carboxylic acid centre to produce the corresponding tertiary alcohol, with the *C=N* bond remaining intact.



117a-c

Scheme 73

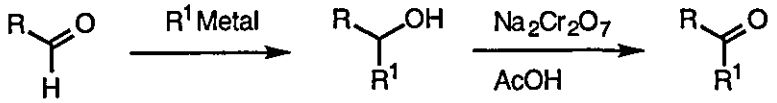
In order to confirm our NMR assignments in the determination of the diastereomeric ratio a 1:1 mixture of diastereomers was synthesised. The reduction of the corresponding ketoxime ethers was identified as a possible route to the hydroxylamines **121a-j (Scheme 74).**



116a-d **121a-j** **122a-g**

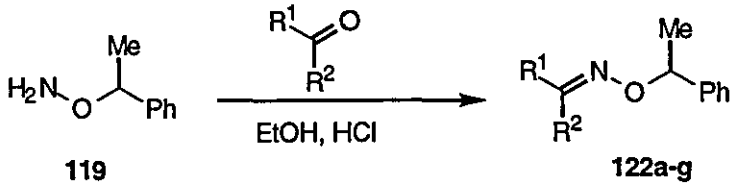
Scheme 74

The reaction of the hydroxylamine **119** with a series of ketones would provide the reduction precursors. The use of the hydroxylamine **119** also allows us to study the diastereoselectivity of the reductions. The ketones which were to be coupled to the hydroxylamine **119** were either commercially available or synthesised as shown in **Scheme 75.** *n*-Butyllithium or allylmagnesium bromide were added to the corresponding aldehydes affording the secondary alcohols. The alcohols were oxidised to the ketones by chromic acid in good overall yields in accordance with the literature protocol.[69]



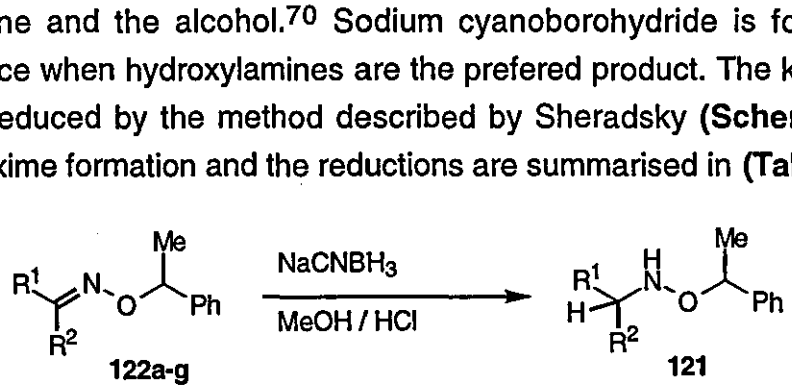
Scheme 75

The ketoxime ethers **122a-g** were prepared by condensing the racemic hydroxylamine **119** with the ketones. The reactions of **119** with aldehydes proceeded smoothly with aldehydes in pyridine, however the reaction with ketones did not occur. The condensation was carried out in ethanol with a catalytic amount of protic acid (HCl). The reaction does not proceed if the acid is omitted, presumably it is required to protonate the intermediate and drive the reaction to completion. The ketoxime ethers **122a-g** were formed in good yields and as a mixture of geometrical isomers with the *E*-isomer predominating **(Scheme 76)**.



Scheme 76

Reduction of ketoxime ethers is possible with a wide range of reagents, however diborane is too harsh as a reducing agent and results in cleavage of the *N-O* bond to afford the amine and the alcohol.[70] Sodium cyanoborohydride is found to be the reagent of choice when hydroxylamines are the prefered product. The ketoxime ethers **122a-g** were reduced by the method described by Sheradsky **(Scheme 77)**.[71] The results of the oxime formation and the reductions are summarised in **(Table 9)**.[72]



Scheme 77

R^1	R^2	*Ketoxime*	*E : Z*	*Yield (%)*	*Hydroxylamine*	*Yield (%)*	*d.e.(%)*
Ph	Bu	**122a**	100 : 0	96	**121a**	53	19
Ph	allyl	**122b**	100 : 0	89	**121c**	45	12
t-Bu	Bu	**122c**	100 : 0	50	**121e**	60	<5
t-Bu	allyl	**122d**	100 : 0	97	**121f**	65	<5
i-Pr	Bu	**122e**	76 : 24	99	**121g**	61	<5
i-Pr	allyl	**122f**	79 :21	79	**121h**	53	<5
Me	Bu	**122g**	60 :40	86	**121i**	58	<5

Table 9

A solution of the oxime ether **122** and sodium cyanoborohydride in methanol were stirred with bromocresol green as an indicator. The reaction does not proceed at neutral pH, methanolic HCl was added dropwise as the reaction proceeded to keep the pH less than 2. The reaction, monitored by TLC, was usually complete within 1 hour. If starting material remained after this time more reducing agent could be added to drive the reaction to completion. The reactions proceeded smoothly to give the clean hydroxylamines. However the less reactive phenyl oximes **122a,b**, furnished a substantial amount of starting material. The diastereomeric excesses of the reductions was found in all cases to be poor, possibly due to small size of the nucleophile. The essentially 1:1 mixture of diastereomers confirmed the NMR assignments of the organometallic addition reactions. The slight stereochemical bias was found to produce the opposite diastereomer to that obtained from the organometallic additions. This is most probably due to the chiral group directing the nucleophile (hydride) to the same side of the *C=N* bond as it did for the organometallic reagent and hence affording opposite diastereomers.

2.4. Stereochemical Outcome and Rationale of the Additions

The diastereomeric excesses of the addition of organometallic reagents to oxime ethers **116a-d** was found to be moderately good, it remained to determine the relative stereochemical outcome of the addition reactions. This was addressed in two ways; *X*-ray crystallography and chemical degradation to known compounds.

The hydrochloride salt of hydroxylamine **121c.HCl** was formed by treatment of the crude addition product with HCl in ether, The white gummy solid was filtered and recrystallised from light petroleum and ether. The recrystallised solid, obtained in 42% yield, proved to be a single diastereomer and provided crystals suitable for *X*-ray

analysis. The structure is shown in **Figure 13**, and shows that both stereocentres have the same configuration.

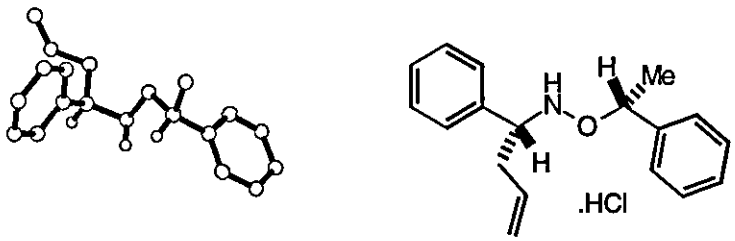
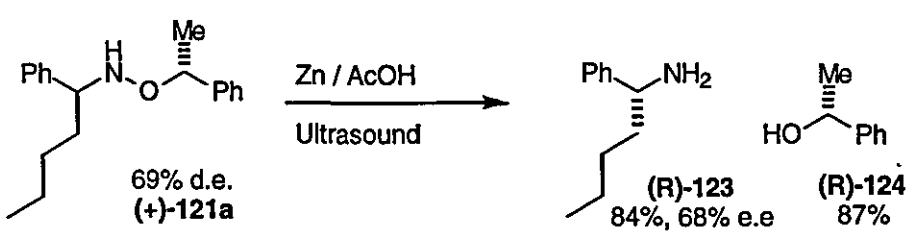


Figure 13. *X*-ray crystal structure of hydroxylamine **121c.HCl**.

Chemical degradation of an optically enriched product to known compounds and the optical rotations of which could be compared to the literature values. This would give the absolute configuration of the chiral centres directly. The reaction sequence was repeated using optically pure materials. Benzaldehyde was condensed with optically pure hydroxylamine **(R)-(+)-119** to afford the oxime ether **(R)-(+)-116a**, addition of *n*-butyllithium gave the substituted hydroxylamine **(+)-121a** with 69% d.e.. The cleavage of *N-O* bonds is well described in the literature and lithium aluminium hydride (LAH) is reported to cleave hydoxylamines derived from oxime ethers to give the corresponding amines and alcohols.[35,25] However, in our hands this method was unsuccessful and led to the recovery of starting material. The substrates described in the literature have pendant Lewis basic groups to which the LAH could bind and then deliver hydride intramolecularly, our compounds do not possess such groups. Enders has reported the use of an ultrasound bath in the zinc and acetic acid reduction reaction, and this method was employed and is shown in **Scheme 78**.[73]



Scheme 78

Zinc powder was added to a solution of the hydroxylamine **(+)-121a** in a 1:1 mixture of acetic acid and water, the mixture was then placed in an ultrasound bath for 2 hours.

The surface area of the reaction was found to be important, if a small flask is used then the reaction proceeds slowly, however if a large flask is used the reaction is complete in a short space of time. The amine and alcohol could be separated from the reaction mixture by washing the acidic aqueous solution with ether, these fractions contain the relatively pure 1-phenylethanol **124** in 87% yield. The aqueous layer is then basified and washed with dichloromethane to provide 1-phenylpentylamine **123** in 84% yield. The alcohol was found to possess a positive optical rotation, $[\alpha]_D$ = +42° (c=0.83, MeOH), confirming it to be the (R)-enantiomer [authentic (R)-1-phenylethanol has $[\alpha]_D$ = +45° (c=0.87, MeOH)]. The starting alcohol, 1-phenylethanol **124**, had a negative optical rotation and thus the Mitsunobu reaction inverted the alcohols configuration. Comparison of the optical rotation of the amine with $[\alpha]_D$ = +8.7° (c=20.1, $CDCl_3$) with the literature values for material with 85% e.e.,[74] $[\alpha]_D$ = +14.1° (neat), and with 92% e.e.,[75] $[\alpha]_D$ = +11.7° (c=1, $CHCl_3$) strongly suggest that the stereochemistry of the hydroxylamine **(+)-121a** was R,R.

Although the exact conformation of the oxime ethers **116a-d** in solution is unknown we assume that due to appreciable conjugation of the oxygen lone pair they are effectively planar. The almost planar structure of oximes is supported by *X*-ray studies,[76] which also show that the sp^2-carbon and the substituent on oxygen are *trans* about the *N-O* bond in the solid state. The stereochemical outcome of these reactions is thought to be brought about as a result of the oxime-boron trifluoride complex depicted in **Figure 14.**

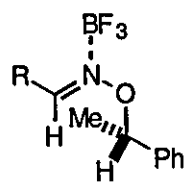


Figure 14

This hypothesis was rationalised by the knowledge that the nitrogen of the oxime ether is the most nucleophilic centre, and hence will probably be the centre to which the boron trifluoride binds. Assuming minimum steric interactions, *i.e.* the A-1,2 strain that would exist between the *N-BF3* bond and the *O-C* bond would be minimised by the two groups adopting a *trans* relationship. As a result of this the chiral centre is pushed closer in space to the *C=N* bond. Attack of the *C=N* bond by the nucleophile on the least hindered face gives the configuration of the newly formed sp^3-centre.

2.5. Modified Chiral Auxiliaries

In order to increase the viability of the methodology described above, the diastereoselectivity must be increased. As a consequence of this, new auxiliaries would have to be prepared. Returning to the postulated reactive species, it was proposed that the phenyl group shields the front face of the *C=N* bond as shown in **Figure 15**.

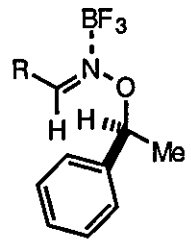
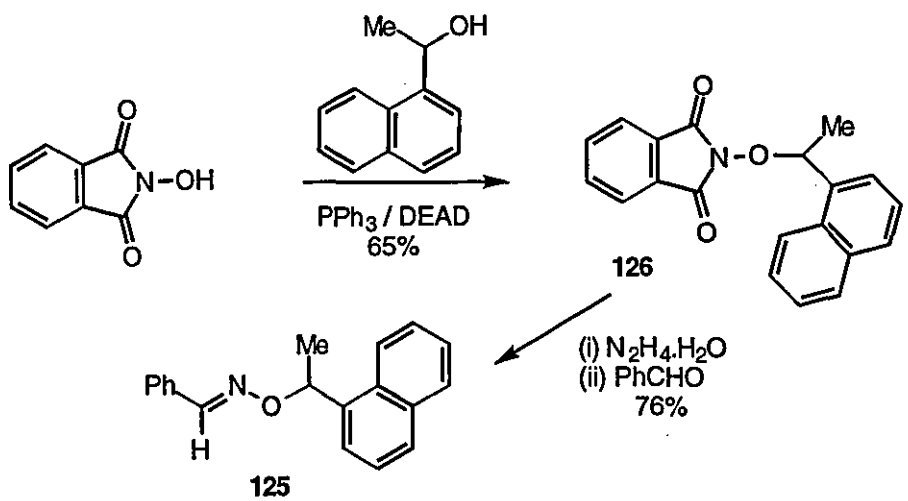


Figure 15

Thus, it was rationalised that if the size of the aromatic group was increased then the diastereoselectivity would similarly increase. The α-methylnaphthyl oxime ether **125** was prepared as shown in **Scheme 79**.

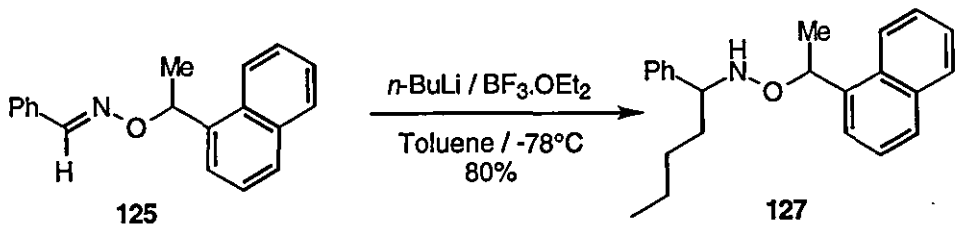


Scheme 79

Mitsunobu reaction of *N*-hydroxyphthalimide with racemic 1-naphthylethanol gave the alkoxyphthalimide **126** as a colourless solid in good yield. Subsequent cleavage of the phthaloyl group and condensation of the hydroxylamine *in situ* with benzaldehyde provided the oxime ether **125** in excellent yield as the *E*-isomer. The *in situ* cleavage and condensation was chosen as a convenient one pot procedure and obviated the need to isolate the volatile *O*-substituted hydroxylamine. The work up of the oxime ether

involved evaporation of the ethanol, addition of a chlorinated solvent and a drying agent ($MgSO_4$). The chlorinated solvent facilitates the precipitation of the phthaloyl derivatives. Filtration and evaporation yields the crude oxime ether, column chromatography readily affords the pure oxime ether **125.**

The addition of *n*-butyllithium under the standard conditions to the oxime ether **125** gave after work up a good yield of the corresponding hydroxylamine **127 (Scheme 80).** However, the diastereoselectivity of the reaction was markedly less for the naphthyl auxiliary (55% d.e.) than for the corresponding phenyl auxiliary (71% d.e.).



Scheme 80

From this result it could be concluded that the aromatic group on the chiral directing group does not directly participate in shielding of the *C=N* bond. Re-examination of the stereochemical model led us to believe that the alkyl substituent on the auxiliary plays an important role in the shielding of the *C=N* bond, and the aryl group may provide an 'anchor' to hold the conformation **(Figure 16).** The hydrogen attached to the oxime carbon sits in between the small (H) and the medium sized (R) groups to minimise steric interactions.

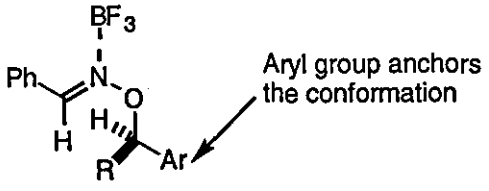
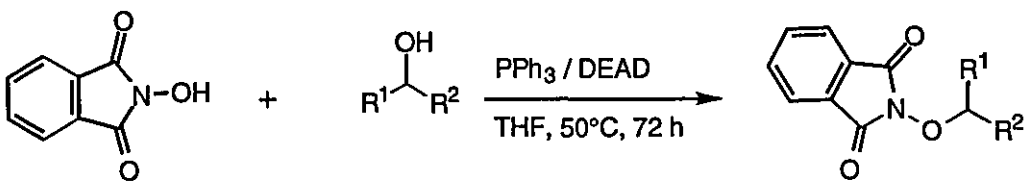


Figure 16

In order to gain evidence to support this hypothesis a series of auxiliaries were synthesised in which the simple methyl group of the auxiliary was homologated and the phenyl group was retained as the aryl portion. The chiral alcohols which constitute the chiral directing moiety were either commercially available or prepared in racemic form in almost quantitative yield by reduction of the corresponding ketones with sodium borohydride.

Mitsunobu reaction of *N*-hydroxyphthalimide with the secondary alcohols produced the alkoxyphthalimides **128a-e** in moderate to good yields under optimised conditions **(Scheme 81)**. The Mitsunobu conditions were optimised by the use of two equivalents of *N*-hydroxyphthalimide, triphenylphosphine and DEAD. The resulting THF solution was heated at 50°C for three days, the yields in most cases were higher than for the unoptimised conditions. The yields vary in accordance with the relative bulk of the alkyl substituents, for example the yield of the Mitsunobu reaction for 1-phenylbutanol which gave alkoxyphthalimide **128b** is 87% but the isomeric 2-methyl-1-phenylpropanol gave only 32% of **128c** under optimised conditions and 7% under unoptimised conditions. Not surprisingly the severely hindered alcohol, 2,2-dimethyl-1-phenylpropanol did not undergo the Mitsunobu reaction. The results are summarised in **Table 10.**



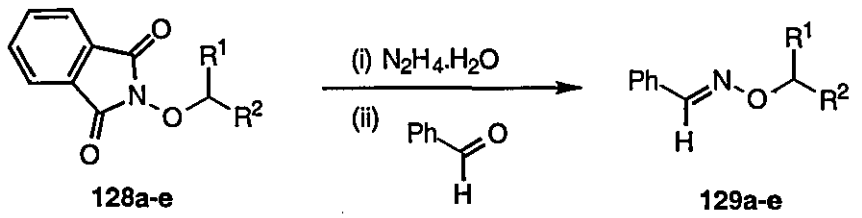
128a-e

Scheme 81

Phthalimide	*R1*	*R2*	*Yield (%)*
128a	Et	Ph	65
128b	*n*-Pr	Ph	87
128c	*i*-Pr	Ph	32
128d	*n*-Bu	Ph	36
128e	Me	Et	95

Table 10

The alkoxyphthalimides **128a-e** were cleaved with hydrazine hydrate in ethanol at 50°C and the resulting hydroxylamines were condensed with benzaldehyde at room temperature *in situ* to produce the corresponding oxime ethers **129a-e** as solely their *E*-isomers which were isolated by column chromatography as colourless oils **(Scheme 82)**. The results of the alkoxyphthalimide to oxime transformation are summarised in **Table 11.**

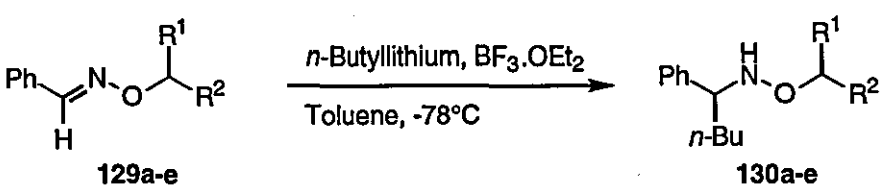


Scheme 82

Oxime ether	*R^1*	*R^2*	*Yield (%)*
129a	Et	Ph	87
129b	*n*-Pr	Ph	91
129c	*i*-Pr	Ph	91
129d	*n*-Bu	Ph	93
129e	Me	Et	90

Table 11

The benzaldoxime ethers **129** with the different chiral auxiliaries attached were now prepared and so the study into the efficacy of the auxiliaries was begun. The standard test reaction was the addition of 3 equivalents of *n*-butyllithium to the oxime ethers at -78°C in the presence of 3 equivalents of boron trifluoride etherate in toluene. This reaction produced the corresponding substituted hydroxylamines **130a-e (Scheme 83).** The diastereoselectivity of the reactions could be readily determined by integration of the benzylic protons in the proton NMR spectra or from the peak heights in the carbon NMR spectra, the two values obtained from the different methods were again found to be in agreement (±5%). The results were found to be as expected, increasing the size of the alkyl group on the auxiliary did indeed increase the diastereoselectivity of the addition reactions, the results are summarised in **Table 12.**



Scheme 83

Oxime ether	R^1	R^2	*Hydroxylamine*	*Yield (%)*	*d.e. (%)*
129a	Et	Ph	**130a**	91	93
129b	*n*-Pr	Ph	**130b**	87	90
129c	*i*-Pr	Ph	**130c**	74	>95
129d	*n*-Bu	Ph	**130d**	80	90
129e	Me	Et	**130e**	70	10

Table 12

Increasing the size of the alkyl group from methyl to ethyl afforded a dramatic increase in selectivity from 71% d.e. for the former and 92% d.e. for the latter. Addition to the *iso*-propyl oxime ether **129c** gave the best result in which the other diastereomer was barely visible in the proton NMR. Unfortunately the alcohol required for this auxiliary, 2-methyl-1-phenylpropanol, was not commercially available in enantiomerically pure form. A slight decrease in diastereoselectivity (5% d.e.) was observed when changing from *iso*-propyl to *n*-propyl. However, the alcohol required for the synthesis of the *n*-propyl auxiliary, 1-phenylbutanol, is commercially available as both enantiomers. The auxiliary derived from *sec*-butanol afforded a very poor d.e. (10%), this is in keeping with the postulate that an aromatic ring is required to lock the configuration of the reactive species. The auxiliaries derived from 1-phenylbutanol, (S)-*O*-1-phenylbutyl hydroxylamine (SOPHy) and its enantiomer ROPHy were chosen for further studies in the reaction of organometallic reagents with chiral oxime ethers because both enantiomers are cheap and readily available in high enantiomeric purity. The revised postulated reacting species is shown in **Figure 17.** The boron trifluoride binds to the oxime nitrogen thus forcing the *O-C* bond *trans* to the *N-BF3* bond to reduce A-1,2 strain. The hydrogen on the oxime *C=N* bond sits in between the hydrogen and the *n*-propyl group of the auxiliary, and the phenyl ring locks this conformation. From this model it is clearly visible why the large values of diastereoselectivity are observed, the *n*-propyl group effectively shields the front face of the *C=N* bond.

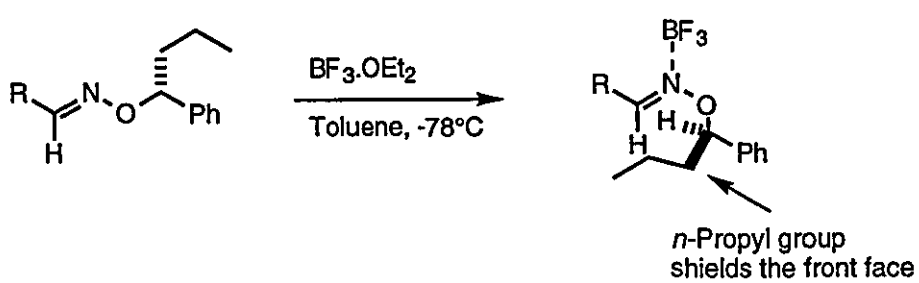


Figure 17

2.6. Summary

(i) A method for the synthesis of chirally pure *O*-1-(phenylethyl) hydroxylamine was devised using *N*-hydroxyphthalimide in the Mitsunobu reaction. This reaction was found to be general for several secondary alcohols.

(ii) A one pot procedure has been developed for the transformation of alkoxyphthalimides to oxime ethers, which obviated the need to isolate the volatile *O*-alkyl hydroxylamines.

(iii) The addition of organometallic species to the *C=N* bond of the *O*-1-(phenylethyl) oxime ethers was found to be facile and good yields and diastereoselectivities were observed.

(iv) A study of the reaction conditions and known reactions of oximes led to the proposal of a theoretical reacting species which accounts for the stereochemical outcome of the addition reactions.

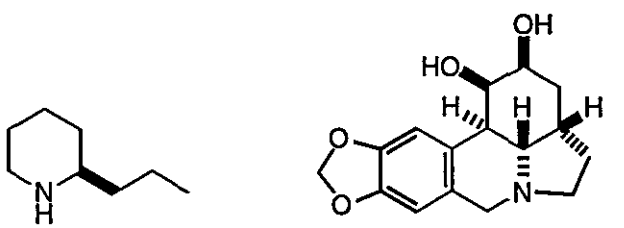
(v) Rationalisation of the reacting species allowed the formation of a range of new and improved chiral auxiliaries, of which the reactions of (R) and (S)-*O*-1-(phenylbutyl) hydroxylamine (ROPHy and SOPHy) were studied in greater detail (Chapters 3 and 4).

Chapter Three

The Synthesis of Piperidine Alkaloids

3.1. Introduction

Piperidine alkaloids are biologically potent natural products which can be obtained from various sources in the plant and animal kingdoms.[77] They have a variety of structures, but all have the six membered nitrogen containing piperidine ring. These alkaloids have provided the organic chemist with many challenging problems and several excellent solutions have emerged. Ladenburg synthesised coniine in 1886, which was the first ever alkaloid synthesis. Coniine **131** is one of the simplest alkaloids and consists of a 2-propyl substituted piperidine ring as shown in **Figure 18**. Complex piperidine alkaloids have also been synthesised by many groups around the world, such as Oppolzer's synthesis of (+)-trianthine.[78]



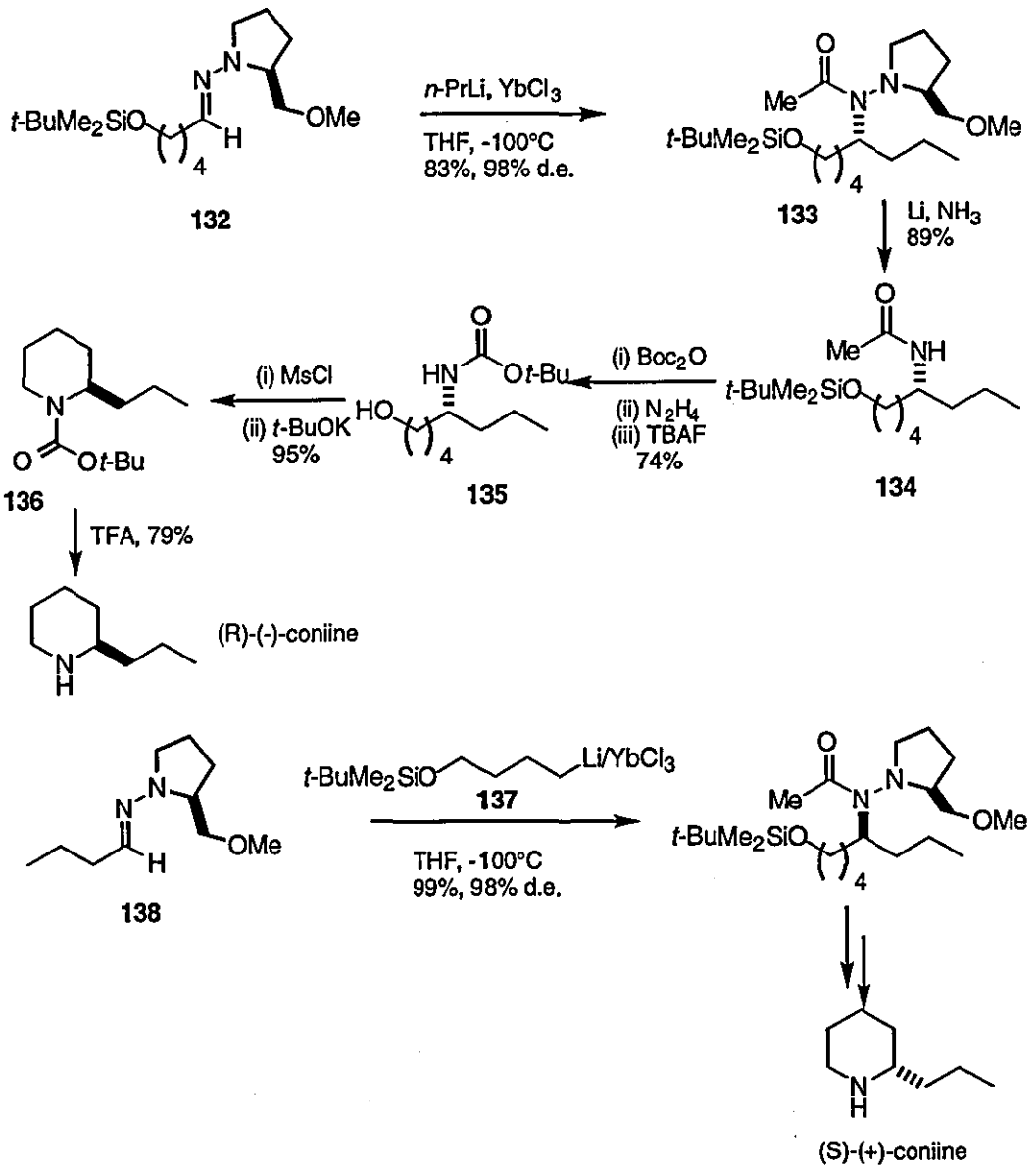
131 (R)-(-)-coniine (+)-trianthine

Figure 18

Coniine is obtained from the Hemlock species *Conium maculatum* and has been a synthetic target for many groups since its first synthesis.[79] This molecule is ideally suited for proving the efficacy of new methodology because it is small in size and fully characterised. Several syntheses of note have emerged over the last 5 years. Of particular interest are those reported by Enders and Oppolzer which are outlined below.

The development of the SAMP and RAMP hydrazone methodology has facilitated the synthesis of many chiral amine derivatives in almost enantiomeric purity. Enders has reported the synthesis of both isomers of coniine by the addition of organoytterbium reagents to the *C=N* bond of SAMP hydrazones **(Scheme 84)**.[79h] The addition of *n*-propyllithium to the hydrazone **132** in the presence of ytterbium chloride followed by *in situ* acetylation provided the hydrazide **133** in excellent yields and diastereoselectivity. *N-N* bond cleavage with lithium in ammonia recycled the chiral auxiliary and gave the acetamide **134** in 89% yield. Changing the *N*-protecting groups and removing the silyl protection on the alcohol gave the Boc protected amino alcohol **135** in good yield. Mesylation of the alcohol and treatment with base gave the Boc protected coniine **136** which was deprotected with trifluoroacetic acid to provide

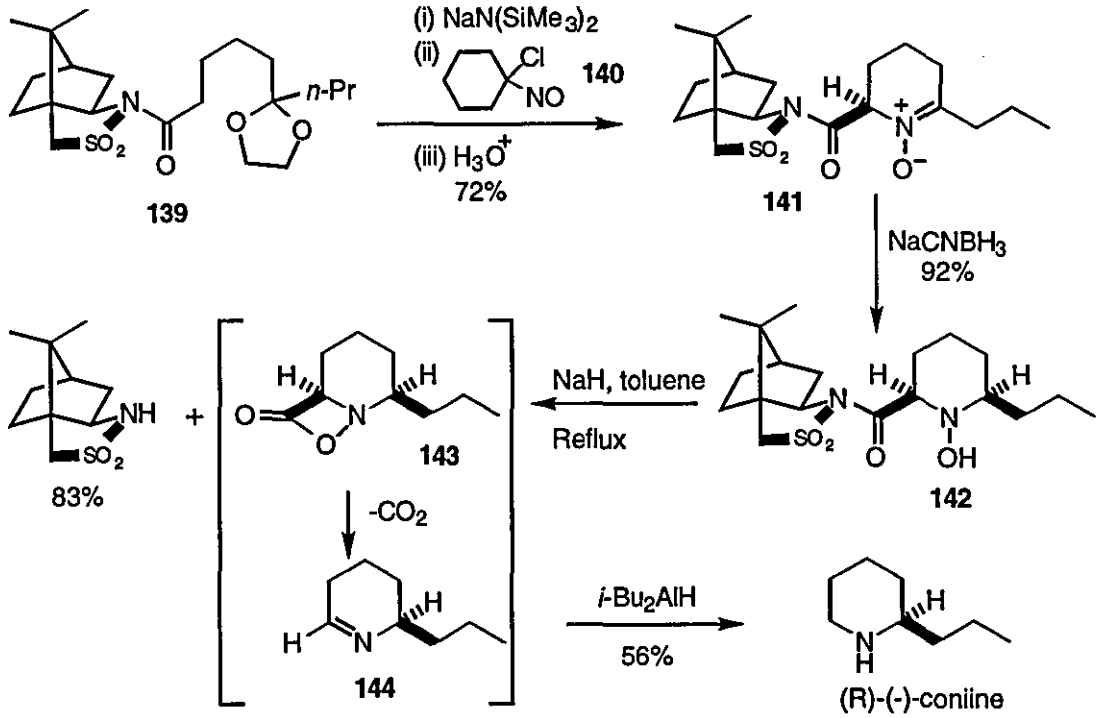
(R)-(-)-coniine in 98% e.e.. (S)-(+)-Coniine was prepared in the same way but involved the addition of the silyl protected butoxylithium derivative **137** to the SAMP hydrazone **138**. The (S)-(+)-isomer of coniine was obtained by this procedure in 98% e.e..



Scheme 84

Oppolzer's method also relied on the use of a chiral auxiliary in the formation of a cyclic nitrone.[79c] The main strategy for the synthesis involved the asymmetric reduction of the cyclic nitrone and removal of the chiral auxiliary by transesterification **(Scheme 85)**. The acylated camphor sultam **139** was treated with base and the anion quenched with the hydroxyaminating agent **140**. The resulting ketal, isolated in almost complete optical purity, was cleaved with aqueous acid and the ketone

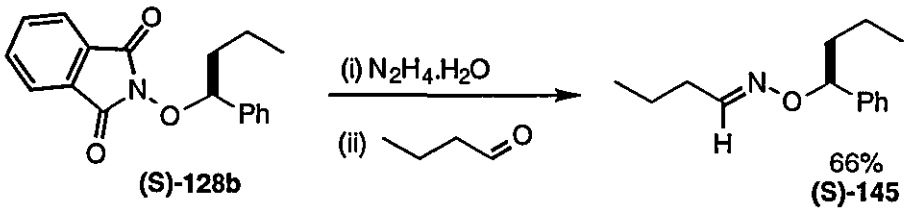
condensed intramolecularly with the hydroxylamine *in situ* to produce the cyclic nitrone **141**. Reduction of the nitrone double bond with $NaCNBH_3$ produced the *cis*-2-propyl-5-acyl piperidine **142** with complete stereocontrol. Removal of the auxiliary was found to be trivial and was achieved by heating the sodium derivative of the hydroxylamine in toluene. Internal transesterification occurred and the resulting oxazetidinone **143** spontaneously decarboxylated to give the cyclic imine **144**. The imine was reduced *in situ* with DIBAL to provide optically pure (R)-(-)-coniine.



Scheme 85

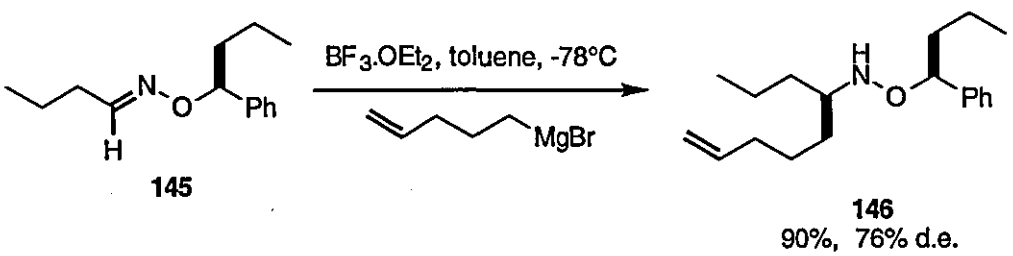
3.2. Piperidine Alkaloid Synthesis

In our synthesis it was proposed that we take advantage of the highly diastereoselective nucleophilic addition of organometallic reagents to SOPHy derived oximes. The oxime to commence the synthesis was prepared *via* the one pot procedure from the alkoxyphthalimide **(S)-128b** and *n*-butyraldehyde **(Scheme 86)**. The alkoxyphthalimide was treated with hydrazine hydrate at 50°C the solution was allowed to cool to room temperature, and then *n*-butyraldehyde was added. The corresponding oxime ether **145** was obtained as a 2:1 mixture of geometrical isomers with the more stable *E*-isomer predominating. This isomer was separated from the *Z*-isomer by column chromatography in 66% yield. The ratio of geometrical isomers was obtained by integration of the peaks in the proton NMR corresponding to the proton attached to the *C=N* bond.



Scheme 86

A suitable organometallic reagent which could be added to the *C=N* bond of the oxime ether was sought. The desired organometallic reagent must contain the relevant functionality to enable a cyclisation reaction to form the piperidine skeleton, also the functionality must be stable to the reaction conditions. Pent-4-enylmagnesium bromide was chosen, as the double bond is stable to the action of boron trifluoride etherate and has been shown to be amenable to cyclisation reactions.[80] The Grignard reagent was formed as a 2 M solution in ether from 4-pentenyl bromide and magnesium turnings. Three equivalents of the Grignard reagent were added *via* a syringe to a mixture of oxime ether **145** and boron trifluoride etherate in toluene at -78°C under an atmosphere of nitrogen. The reaction mixture was left for 30 minutes at this temperature and then water was added. The mixture was allowed to warm to room temperature and an extractive work up followed by column chromatography gave the addition product **146** in 90% yield **(Scheme 87)**. However, the corresponding diastereomeric excess was found to be only 76%. In order to produce a feasible route to chirally pure piperidines the diastereoselectivity had to be improved.



Scheme 87

It was thought that by lowering the bath temperature to -100°C the diastereomeric excess could be improved. The rationale for this was based on the postulated reacting species **(Figure 19)**. It is thought that the boron trifluoride is bound to the oxime nitrogen and therefore forces the chiral auxiliary towards the reacting sp^2 centre. However, it may be possible that under the reaction conditions the boron becomes unco-ordinated which would allow free rotation about the *N-O* bond. As a consequence of this the chiral auxiliary would move away from the sp^2 centre and the

diastereomeric excess would be lowered. Lowering the temperature to -100°C may improve the co-ordination of the boron to nitrogen resulting in an improved diastereomeric excess. From **Figure 19** it can be seen that the *n*-propyl group effectively shields the back face of the *C=N* bond and the addition of the Grignard reagent would occur on the top face.

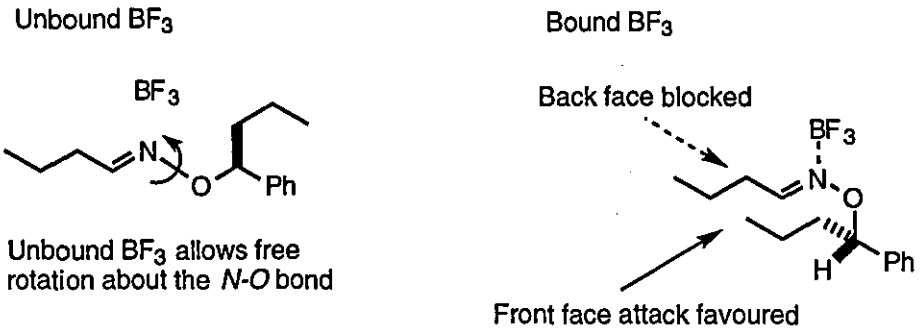
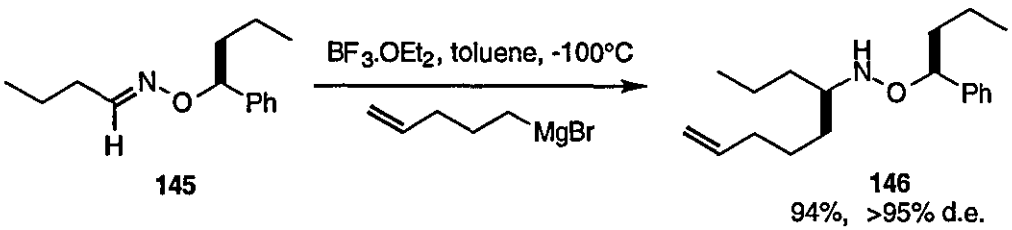


Figure 19

The reaction was repeated at -100°C and provided the addition product **146** in 94% yield **(Scheme 88).** The diastereoselectivity of this reaction was estimated at 95% d.e. as only one diastereomer was observed in the proton and carbon NMR spectra. The configuration of the newly formed chiral centre was assigned as R on the basis of our model of the reactive species for the addition reactions, and by the subsequent conversion of **146** in (R)-(-)-coniine.

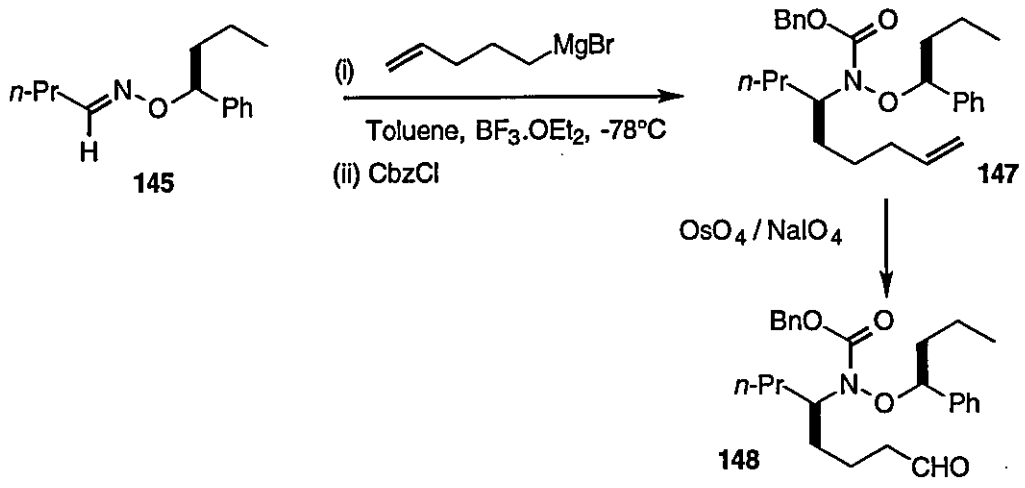


145 **146**
94%, >95% d.e.

Scheme 88

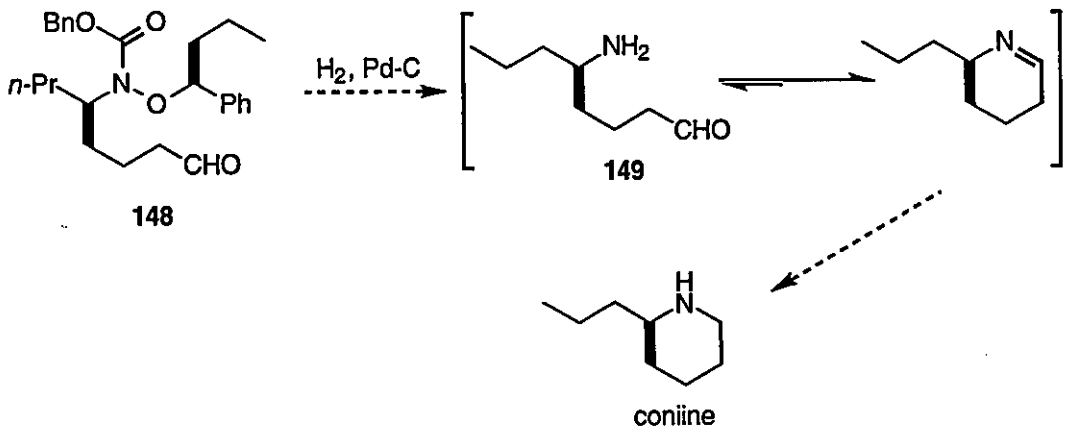
Isolation of the addition product **146** had the drawback that further steps are required to cleave the N-O bond and protect the nitrogen functionality. An alternative to that was to protect the nitrogen at an earlier stage with the *N-O* bond still intact. This was achieved *in situ* by the addition of benzyl chloroformate to the reaction mixture after the addition of the Grignard reagent to the *C=N* bond **(Scheme 89).** The *N*-protected compound **147** was treated with osmium tetroxide under the Johnson-Lemieux conditions to cleave the double bond to the aldehyde **148.**[81] Osmium tetroxide attacks the double bond to form the standard osmate ester which then breaks down to

produce two moles of aldehyde from one mole of the olefin. Sodium periodate reoxidises the osmium back to osmium tetroxide. These conditions selectively cleave olefins to aldehydes without further oxidation to the corresponding carboxylic acids, and are used as an alternative to ozonolysis. The oxidation proceeded well and gave a good yield of the aldehyde **148** after column chromatography.



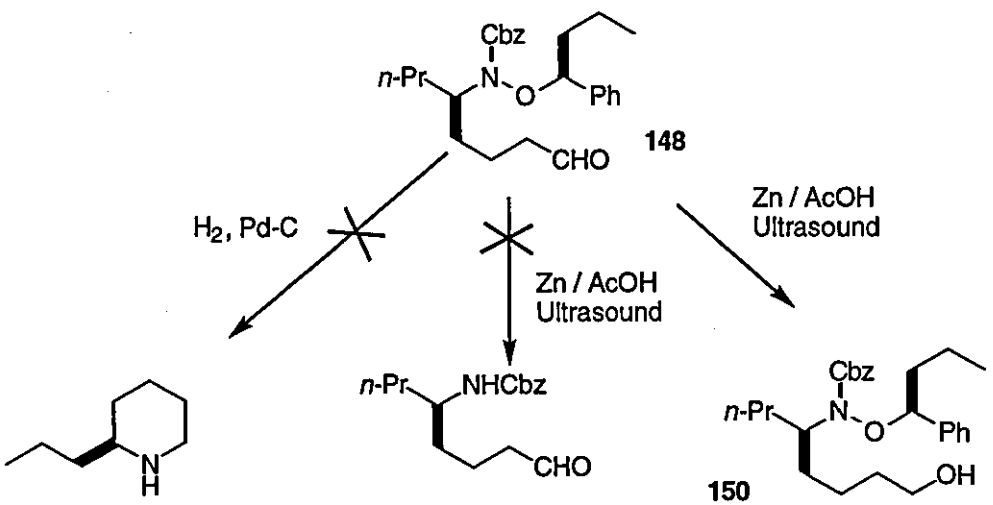
Scheme 89

It is well known that the *N-O* bond can be cleaved and the Cbz group removed by catalytic hydrogenation. Removal of the nitrogen protection in this way may cause the free amine **149** to condense with the aldehyde to produce the cyclic imine, which under the reaction conditions would be reduced to the natural product **(Scheme 90)**.



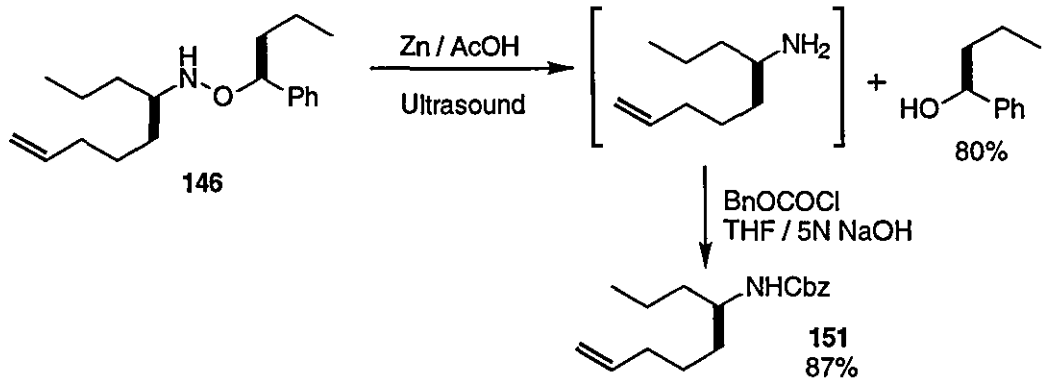
Scheme 90

However, the attempts at cyclisation by hydrogenation failed, with the proton NMR showing no evidence of the natural product. At this stage it was thought that the removal of the chiral auxiliary by cleavage of the *N-O* bond may be advantageous to the synthesis. The Cbz protected hydroxylamine **148** was treated with zinc in acetic acid with sonication as described in the previous Chapter.[73] Unfortunately, this method failed to cleave the *N-O* bond but not surprisingly reduced the aldehyde to a hydroxy group **150.** This procedure was abandoned at this point as the reactions gave complex mixtures and the yields were poor **(Scheme 91).**



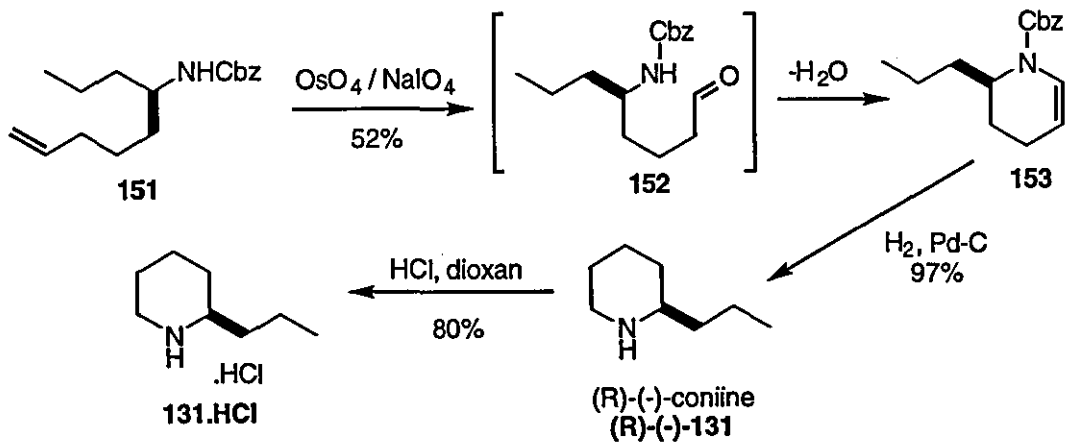
Scheme 91

It was concluded that the *in situ* protection of the nitrogen atom after the addition of the Grignard reagent was not practical in terms of the subsequent conversions. Thus it was deemed more elegant to remove and recover the chiral auxiliary immediately after the addition of the Grignard reagent **(Scheme 92).** The *N-O* bond of **146** was cleaved using the zinc and acetic acid with ultrasound protocol. The hydroxylamine **146** was dissolved in a 1:1 mixture of acetic acid and water, zinc dust was added and the mixture was sonicated for 2 hours at 40°C. The crude reaction mixture was filtered and basified with aqueous sodium hydroxide to pH 14 and THF added. The mixture was cooled to 0°C and benzyl chloroformate was added and the resulting solution was stirred overnight. Aqueous work up and column chromatography of the resulting oily residue gave the benzyl carbamate of the primary amine **151** in 87% yield as a colourless solid. The chiral auxiliary, 1-phenylbutanol was recovered in good yield without racemisation, as determined by optical rotation.



Scheme 92

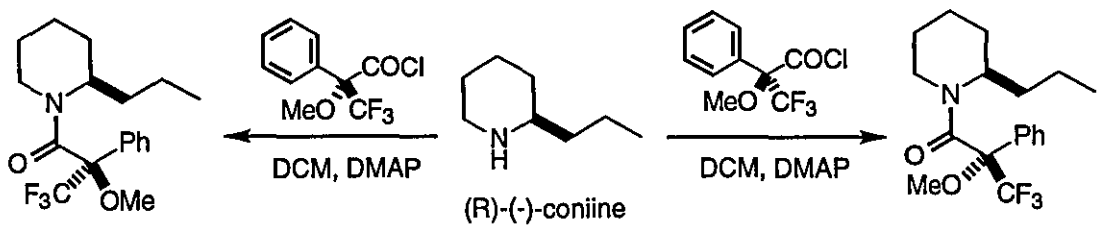
The protected amine **151** was treated with a catalytic amount of osmium tetroxide and sodium periodate under the Johnson-Lemieux conditions to cleave the *C=C* bond. The resulting aldehyde **152** cyclised and dehydrated *in situ* to provide the cyclic enecarbamate **153** in a modest 52% yield **(Scheme 93)**. Removal of the protecting group and reduction of the double bond by catalytic hydrogenation gave (R)-(-)-coniine **(R)-(-)-131** in 97% yield as a volatile oil. The absolute stereochemistry of coniine was assigned as R on the basis of optical rotation, $[\alpha]_D$ -8.1° (*c*=2, $CHCl_3$) [lit.,[79h] $[\alpha]_D$ -7.9° (*c*=1, $CHCl_3$)]. For ease of handling and to facilitate purification the hydrochloride salt was made by treatment of coniine with HCl in dioxane which yielded the salt **131.HCl** in 80% yield.[79h]



Scheme 93

In order to quantify the enantiomeric excess of the synthetic coniine, the Moshers amides were prepared **(Scheme 94)**. Coniine was dissolved in dichloromethane and the (S)-(+)-Moshers acid chloride was added, to this solution was added DMAP and the reaction was stirred overnight at room temperature. Aqueous work up gave a

poor yield of the corresponding amide **(R,S)-154**.[79a] Integration of the proton NMR spectrum indicated that the diastereomeric excess was 91%, although with the presence of rotamers the assignment of the major and minor diastereomeric peaks was not as clear as would be desired. As a consequence of this, the opposite diastereomer **(R,R)-154** was prepared by the action of (R)-(-)-Moshers acid chloride on coniine. The peaks observed for this diastereomer were in full agreement with the opposite diastereomer and the enantiomeric excess of coniine was assigned as 91%.

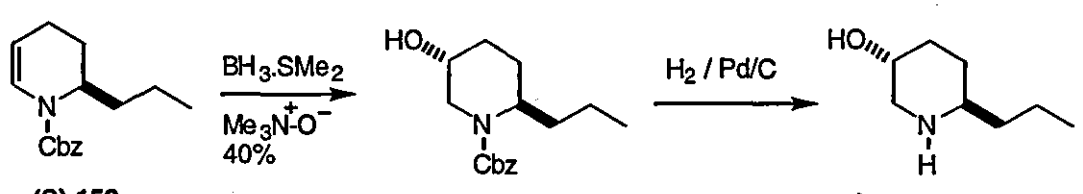


(R,R)-154
91% d.e.

(R,S)-154
91% d.e.

Scheme 94

This methodology was further developed to incorporate the synthesis of another hemlock alkaloid, (S)-(+)-*pseudo*conhydrine **155**.[82] The starting point for the synthesis was the enecarbamate **(S)-153** which was previously prepared by cyclodehydration. The enecarbamate has a handle to introduce further functionality in the 5- and 6-positions in the form of a double bond. Hydroboration of the double bond with borane followed by oxidation with trimethylammonium *N*-oxide gave the alcohol **156** in a modest 58% yield.[83] The hydroboration was totally regioselective giving only the 5-substituted piperidine. However, the corresponding alcohols were produced as a 2:1 mixture of *trans* and *cis* diastereomers, with the more stable *trans* isomer predominating. Column chromatography of the mixture led to a simple separation of the diastereomers to produce the *trans* form in 40% yield **(Scheme 95)**. Removal of the Cbz protecting group by catalytic hydrogenation gave the alkaloid (S)-(+)-*pseudo*conhydrine **155** in 98% yield.



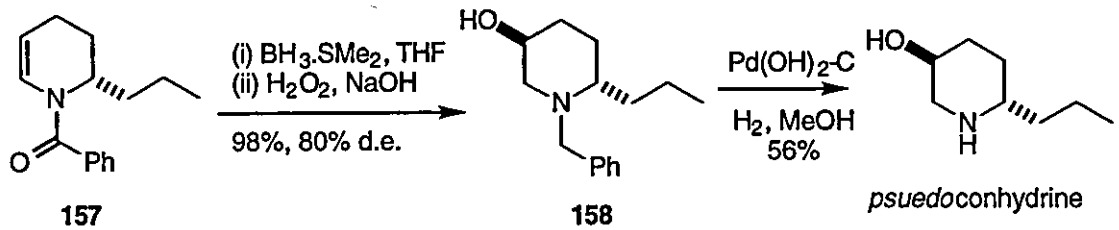
(S)-153

156
Also *cis* isomer 18%

155
*pseudo*conhydrine

Scheme 95

*Pseudo*conhydrine has also been synthesised by Oppolzer,[84] who found that changing the protecting group on the nitrogen had a profound effect on the *trans:cis* ratio of the hydroboration/oxidation reactions. Oppolzer found that the use of the Cbz group gave a similar selectivity and yield to those we found (46% yield, 3:1 *trans:cis*). However, using the benzoyl group **157** and lowering the temperature gave much improved results, the yield increased to 98% and the diastereoselectivity also increased to 9:1 in favour of the *trans* isomer **(Scheme 96)**. The borane conditions also reduce the amide to the benzyl amine **158** which was removed by hydrogenolysis in moderate yield to give the natural product.



Scheme 96

The reason for the increase in yield and selectivity has been postulated as being due to the increased double bond character of the amide *N-C* bond. This has the effect of forcing the C-2 substituent (*n*-Pr) into an axial position to minimise A-1,3 strain, which increases the face shielding by the *n*-propyl group. As a consequence of this the hydroboration occurs on the top face to give predominantly the *trans* diastereomer **(Figure 20)**.

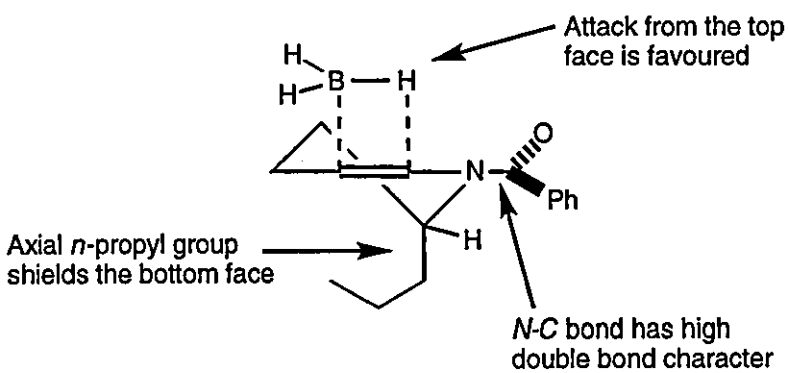


Figure 20

3.3. Summary

(i) We have achieved the addition of an alkyl Grignard reagent to the *C=N* bond of the SOPHy oxime derived from *n*-butyraldehyde **145**. The addition reaction gave the highest diastereomeric excess reported for the addition of an alkylmetal reagent to any oxime (> 95% d.e.).

(ii) The reduction of the *N-O* bond and subsequent protection of the amine to give the carbamate **151** occurred in good yields without loss of stereochemical integrity. The chiral alcohol was also recovered in good yield without loss of optical purity.

(iii) Cleavage of the double bond under the Johnson-Lemieux conditions gave the aldehyde which spontaneously cyclised and dehydrated to give the cyclic enecarbamate **153** in moderate yield.

(iv) Hydroboration and oxidation of the cyclic enecarbamate **153** proceeded with excellent regiochemistry but poor stereoselectivity, nevertheless this provided the piperidinol framework **156** for *pseudo*conhydrine.

(v) Catalytic hydrogenation of the cyclic enecarbamate **153** and the piperidinol **156** provided the natural products in excellent yields.

Chapter Four

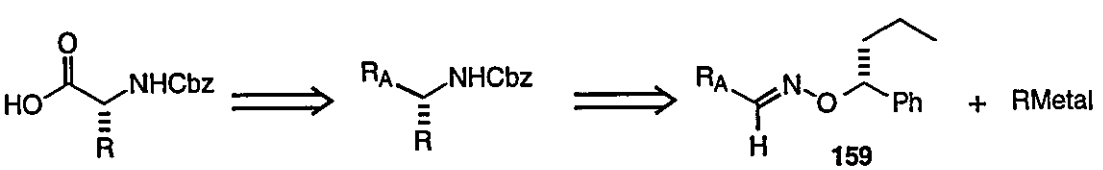
The Synthesis of Amino Acids

4.1. Introduction

Many of the activities within the body are controlled by enzymes which are made up of proteins, the proteins themselves are polymers of α-amino acids.[85] The nucleic acids are responsible for the sequence of amino acids in the polymer (polypeptide). In nature there are 20 naturally occurring amino acids all having the L-stereochemistry. The α-amino acids that make up proteins are called proteinogenic, and many are produced on an industrial scale by fermentation and chemical synthesis. However, the synthesis of α-amino acids in the laboratory is still an active area because of the demand for unusual, non-proteinogenic amino acids which have interesting biological properties. Peptide and peptidomimetic therapeutics constitute an area of considerable interest and hence non-proteinogenic α-amino acids are continually required.

4.2. Design and Synthesis of α-Amino Acids

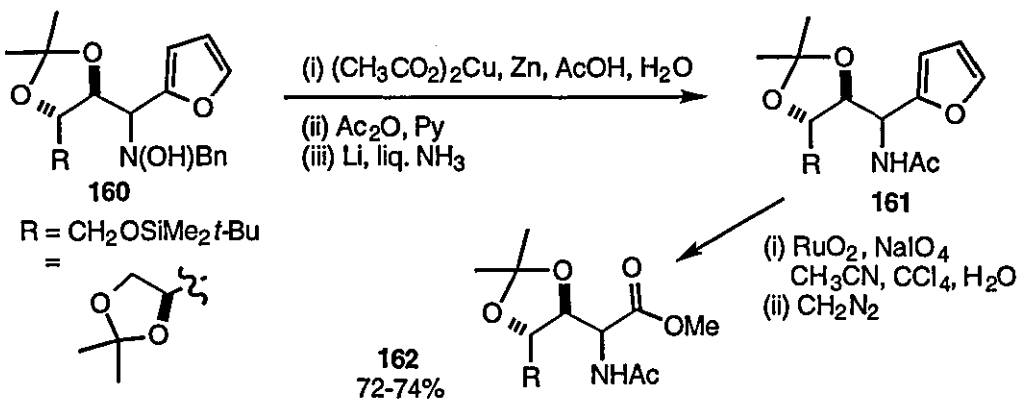
As was shown in the previous two Chapters we have developed a method for the preparation of primary amines in almost enantiomerically pure form. We wished to extend this methodology to the synthesis of α-amino acids. With the methodology in hand to add nucleophiles to the azomethine functionality of chiral oxime ethers, it was deemed possible that a group attached to the oxime may act as a carboxylic acid precursor. Retrosynthetic analysis of an amino acid is shown in **Scheme 97**. The carboxylic acid function can come from a suitable precursor (R_A) and the side chain can take the form of a nucleophile adding to the *C=N* bond of a chiral oxime ether. The oxime ether **159** would be obtained from the condensation of an aldehyde (R_ACHO) and the corresponding hydroxylamine. This would not only provide the necessary chiral centre at the α-position in enantiomerically pure form, but would also allow us to control the absolute stereochemistry depending on the chiral auxiliary used (SOPHy or ROPHy).



Scheme 97

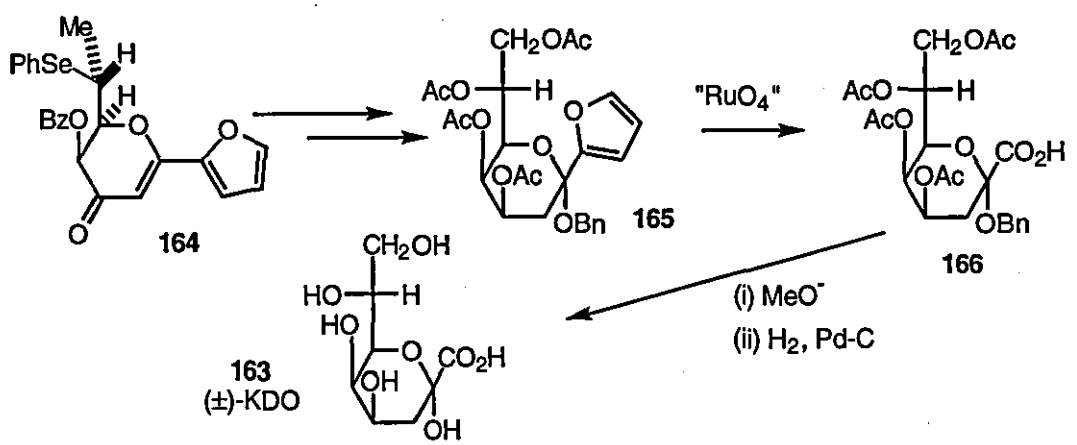
The group R_A that was initially chosen for study was the furan group, which has a long history of being a carboxylic acid synthon. Oxidation of the furan ring with a whole

range of reagents has been reported to give the carboxylic acid[86]. Notably the work by Dondoni to prepare non-proteogenic amino acids utilises this methodology **(Scheme 98)**.[87] The derivative **160** was obtained from the addition of lithiofuran to the corresponding nitrone. Cleavage of the *N-O* bond, protection of the nitrogen as its acetate and removal of the benzyl protecting group gave the oxidation precursor **161**. Treatment of **161** with ruthenium tetroxide prepared *in situ* gave the α-amino acid **162** in good yield isolated as the methyl ester after treatment with diazomethane.



Scheme 98

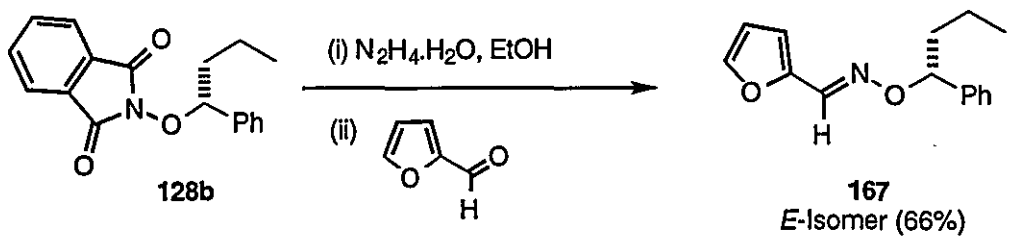
Danishefsky has also utilised this methodology in the synthesis of (±)-3-deoxy-D-*manno*-2-octulopyranosate (KDO) **163 (Scheme 99)**.[88] The pyran ring **164** was prepared by a hetero-Diels-Alder reaction attaching the furan ring at an early stage in the synthesis. Manipulation of this pyran produced the highly oxygenated pyran **165**. Oxidation with a catalytic amount of ruthenium tetroxide cleaved the furan ring to the carboxylic acid **166**. Removal of the benzyl protecting group by hydrogenolysis and methanolysis of the acetate groups gave the racemic natural product **163**.



Scheme 99

Synthesis of the Furan Derivatives

The synthesis of the furan derived oximes was facile and amenable to large scale synthesis. The one pot procedure described previously in Chapter 2 was used to convert the chiral alkoxyphthalimide **128b** into the corresponding furan oxime ether **167 (Scheme 100).** A solution of the (R)-phthalimide in ethanol was treated with hydrazine hydrate at 50°C. The solution was then allowed to cool, 2-furanaldehyde (furfural) was added and the resulting solution was stirred overnight. Work up involving the addition of carbon tetrachloride to precipitate the phthaloyl residues and column chromatography gave the pure (R)-*E*-oxime ether **167** in 66% yield as a colourless oil. The *Z*-isomer was also isolated in 32% yield.

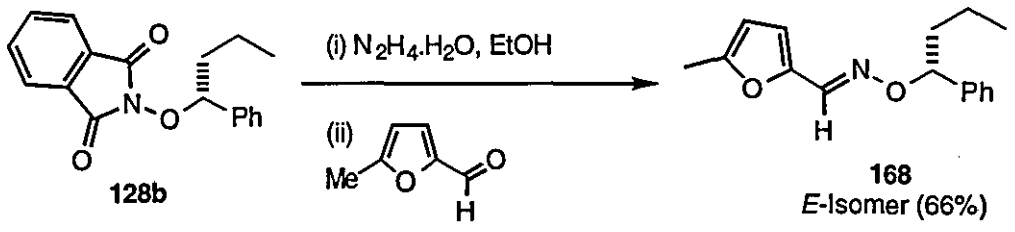


128b **167** *E*-Isomer (66%)

Scheme 100

However, on standing overnight the clear oil began to darken in colour and after a few days very little of the oxime remained which made characterisation and handling difficult. Placing the oxime in a freezer and out of the light seemed to slow down the process of decomposition. The decomposition products were not identified but were probably polymers of some description. Unfortunately as one of the primary aims of the project was to prepare reagents that could be stored for long periods of time, these criteria was clearly not met by the furan oxime **167.**

Furan rings are well known for their reactions which occur in the 2- and 5-positions, clearly the 2-position of furfural is blocked but the 5-position is still capable of reaction. We reasoned that this is the site at which decomposition or polymerisation may occur. Thus, if this site is blocked then decomposition/polymerisation may be prevented. The oxime derived from 5-methylfurfural was prepared in the same way as the furfural oxime, from the (R)-alkoxyphthalimide **128b** and the aldehyde in ethanol. The pure (R)-*E*-isomer **168** was isolated in 66% yield by column chromatography as a colourless oil **(Scheme 101).**

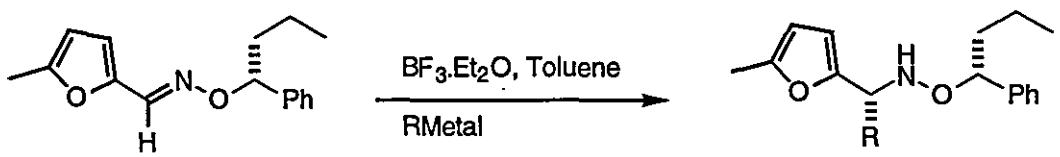


Scheme 101

This compound was found to be stable and readily characterised. The oxime ether **168** was allowed to stand in an open topped vial at room temperature for three months without any detectable decomposition.

Addition of Organometallic Reagents to the Furan Oxime Ethers

The oxime ether **168** was subjected to the same addition protocol as described in the previous Chapter. The furan oxime ether **168** and boron trifluoride etherate were stirred at -78°C in toluene under a nitrogen atmosphere. Three equivalents of the organometallic reagent was then added dropwise over 30 minutes *via* a syringe. The reactions were left for 30 minutes at -78°C, water was added and the reaction mixtures were allowed to warm to room temperature. An extractive work up led to the isolation of the substituted hydroxylamines **169a-c** in good overall yields **(Scheme 102).** The yields and diastereomeric ratios of the additions are summarised in **Table 13.**



Scheme 102

Organometallic	*Hydroxylamine*	*Yield (%)*	*d.e. (%)*
MeLi	**169a**	77	83
n-BuLi	**169b**	87	81
CH_2=$CHCH_2MgBr$	**169c**	56	59

Table 13

The diastereoselectivity of the addition reactions could be determined from the crude proton NMR spectra. The peaks corresponding to the benzylic proton of the auxiliary at 6 ppm or the furan protons at 5.5 ppm could be integrated to give the diastereotopic ratio directly. **Figure 21** shows the diasteromeric ratio for the hydroxylamine **169b.** The benzylic proton H_1 and furyl protons H_2 are shown.

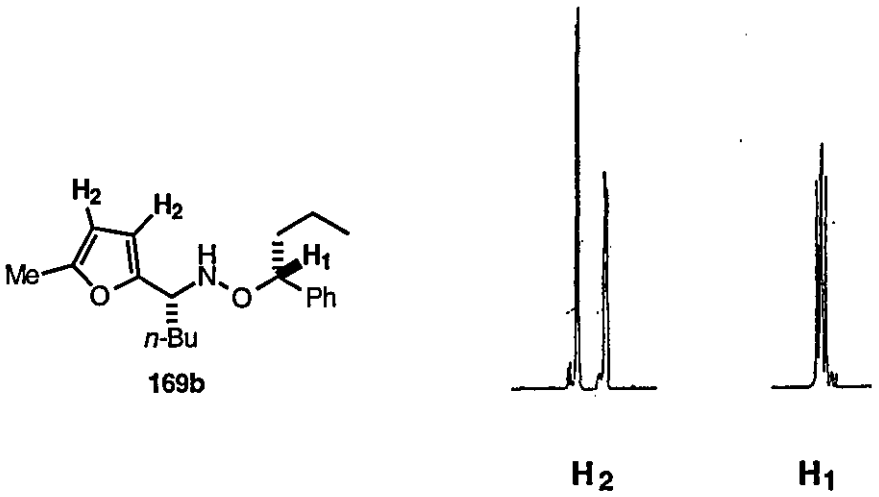


Figure 21.
The diastereomeric ratio (81% d.e.) of the hydroxylamine **169b**

The reactions of the furan oximes **168** were found to be rapid in most cases, even at -78°C. The crude NMR spectra of hydroxylamines **169a** and **169b**, derived from the addition of methyllithium and *n*-butyllithium respectively, were found to be essentially homogeneous with very few impurities. The crude proton NMR of hydroxylamine **169c** derived from the addition of allylmagnesium bromide was found to contain several unidentified impurities. The reaction of phenylmagnesium bromide with the oxime ether **168** was attempted and addition appeared to take place to some extent, however this material could not be separated from the remaining starting material. The diastereoselectivities of the addition reactions to give hydroxylamines **169a-c** were found to be disappointing; the best diastereomeric excess obtained was that for the methyllithium addition, 83% d.e., with *n*-butyllithium giving a similar result (81% d.e.). Allylmagnesium bromide however, gave poorer selectivity (59% d.e.). These results indicate that organolithium reagents are the reagents of choice for this procedure both in terms of purity of the products and diastereoselectivity.

The sense of addition was assumed to be the same as described earlier, based on our model for the selectivity **(Figure 22).** The hydrogen of the oxime sits in between the small (H) and the medium (propyl) groups of the auxiliary when the oxime nitrogen

is chelated to boron trifluoride etherate. The propyl group shields the top face and attack must come from the lower face.

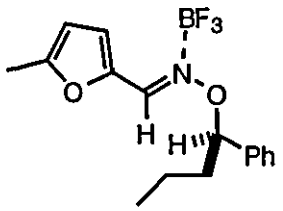
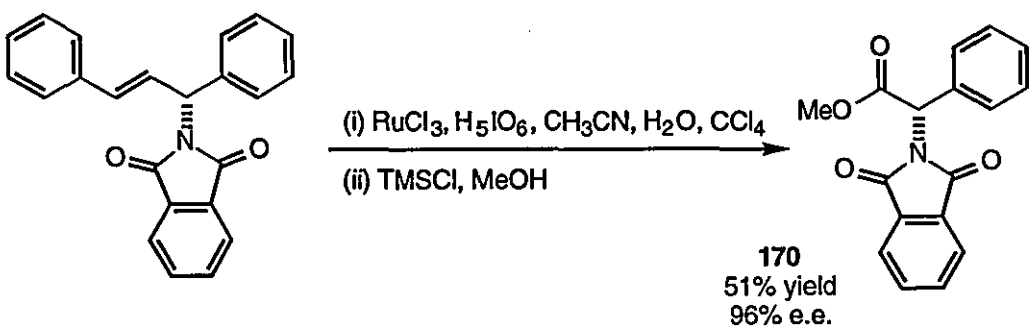


Figure 22

Perhaps the most surprising result is the addition of methyllithium to the oxime ether **168**. Dieter has reported that methyllithium did not add at all to his ephedrine derived oxime ethers,[35] not only did it add to our oximes but also gave the best result. However, these results are not suitable for an amino acid synthesis as the diastereomeric excesses of the additions are too low. The low values for the diastereoselectivity may be attributed to the furan oxime so clearly a different oxime was required for an amino acid synthesis.

Synthesis of Cinnamaldehyde Oxime Ethers

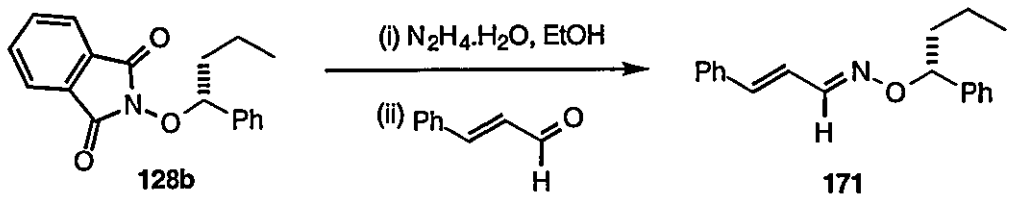
Oxidative cleavage of carbon-carbon double bonds has been at the centre of organic chemistry for years.[86] Ozonolysis is one such well known example of the reaction with many advantages. Sharpless has developed an alternative procedure using a catalytic amount of ruthenium tetroxide to oxidatively cleave *C=C* bonds to the corresponding carboxylic acid derivatives,[89] it was this reaction we wished to explore. Williams and Jumnah have recently synthesised protected phenylglycine **170** utilising the oxidative cleavage of the double bond to unmask the carboxylate functionality **(Scheme 103)**.[90] The cleavage of the cinnamyl function gave good yields of the carboxylic acid, which was isolated as its methyl ester.



170
51% yield
96% e.e.

Scheme 103

The design of a new oxime ether to complement the oxidative cleavage methodology led us away from the furan ring and towards a derivative with a double bond as the masked carboxylate function. The oxime ether derived from cinnamaldehyde was the first derivative we chose to study and was found to be quite satisfactory. The usual one pot procedure for the phthalimide to oxime ether transformation was used and column chromatography gave the pure *E*-oxime ether **171** in 76% yield as a colourless solid, the *Z*-isomer was also recovered in 23% yield as a colourless oil **(Scheme 104).**



128b **171**

Scheme 104

The *E*-cinnamaldehyde oxime was the first oxime we had obtained as a solid and recrystallisation from light petroleum gave analytically pure crystals suitable for *X*-ray crystallography.[68] **Figure 23** shows the crystal structure of the oxime. It is worthy of note that the *C=C, C=N* and *N-O* bonds are all in the same plane.

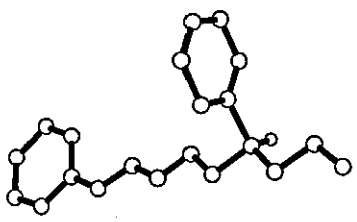
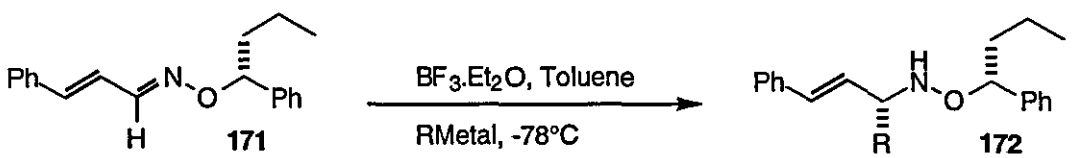


Figure 23. The cinnamaldehyde oxime ether **171**

For this synthesis of amino acids to be of value, certain criteria must be reached; the yield of the hydroxylamine **171** from the addition of the organometallic reagent to the cinnamaldehyde oxime ether **172** must be high, also the chiral auxiliary should direct the attack of the nucleophile to give rise to a single diastereomer.

The addition of organometallic reagents to the cinnamaldehyde oxime ether took place utilising the usual addition protocol **(Scheme 105)**. The oxime ether was cooled to -78°C in toluene under a nitrogen atmosphere and 3 equivalents of boron trifluoride etherate was added. The solution was allowed to equilibrate for 15 minutes after which time 3 equivalents of the organometallic reagent were added dropwise over 20 minutes. The solutions were monitored by TLC and when all the starting material had been consumed, usually less than 30 minutes, water was added and an extractive work up followed. The results of the addition reactions are summarised in **Table 14.**

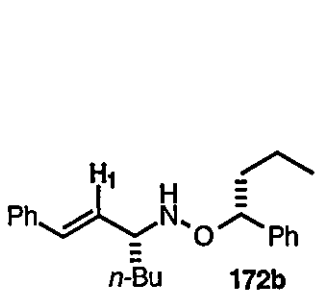


Scheme 105

Entry	*Organometallic*	*Hydroxylamine*	*Yield (%)*	*d.e. (%)*
1	MeLi	**172a**	95	92
2	*n*-BuLi	**172b**	92	93
3	*i*-BuLi	**172c**	93	92
4	PhLi	**172d**	76	90
5	MeMgBr	**172e**	41	73
6	EtMgBr	**172f**	91	71
7	*n*-BuMgBr	**172g**	89	78
8	$PhCH_2MgBr$	**172h**	34	72
9	PhMgBr	**172i**	69	80
10	*i*-PrMgBr	**172j**	<10	-
11	*t*-BuMgBr	**172k**	<10	-
12	*t*-BuLi	**172l**	<10	-

Table 14

Several regions of the proton NMR spectra of the addition products were diagnostic. The peak corresponding to the oxime *HC=N* at 8 ppm disappears and the olefinic protons gave a distinctive doublet and double doublet pattern. The diastereomeric excesses were usually obtained from the integration of the olefinic peak corresponding to proton $\mathbf{H_1}$ at 6 ppm as it was usually clearly different for the two diastereomers, this is illustrated in **Figure 24.**



172b

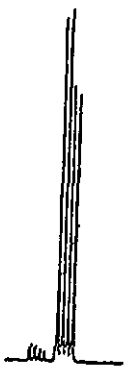


Figure 24. Diastereomeric ratio (93% d.e.) of hydroxylamine **172b**

Generally primary organolithium reagents gave better results than the corresponding Grignard reagents both in terms of yield and diastereomeric excess. It would appear that the counter ion has a profound effect on the stereoselectivity, however this has not been studied in great detail. It is important to note that the lithium and the magnesium reagents both give the same major diastereomer. Organometallic reagents with branching at the α-position such as *t*-Bu and *i*-Pr gave complex reaction mixtures and a yield of the hydroxylamine of less than 10%. In these cases the counter ion, lithium or magnesium made little difference as exemplified by entries 11 and 12 **(Table 14).**

n-Butyllithium gave the best result with a diastereomeric excess of 93% (entry 2), which is significantly better than that obtained for the addition to the furan oxime (81% d.e.). Also methyllithium gave an excellent result (95% yield, 92% d.e., entry 1) which is again better than that gained from the furan oxime (83% d.e.). Phenyllithium previously has given poor yields but high diastereoselectivity in additions to the oxime ether **116b** containing the 1-phenylethyl auxiliary (Chapter 1). This was also found to be true for the cinnamaldehyde oxime **171**, however if the number of equivalents of phenyllithium is decreased from 3 to 1.5 then the yield of isolated hydroxylamine **172d** increases dramatically up to 76% with a good diastereomeric excess (90% d.e.). Therefore it can be concluded that the excess phenyllithium reacts further with the hydroxylamine product to facilitate its decomposition. The organolithium compounds used were bought from the Aldrich Chemical Company, however we wished to make the naturally occurring amino acid norleucine which has an *iso*-butyl

side chain and the corresponding organolithium reagent was not available. Thus *iso*-butyllithium was made according to the procedure described by Wakefield.[91] Finely divided lithium wire was slurried in ether at 0°C and *iso*-butyl bromide was added dropwise. Care was taken not to allow the temperature to increase above 0°C to eliminate Wurtz type couplings. *iso*-Butyllithium added to the cinnamaldehyde oxime **171** smoothly in accordance with the commercially available organolithium reagents to give an excellent yield (93%) and d.e. (92%) of the hydroxylamine **172c**.

A whole range of commercially available Grignard reagents were added to the cinnamaldehyde oxime **172** but unfortunately the results were not as good as the corresponding organolithium reagents in terms of yield and diastereoselectivity (**Table 8**, entries 5-11). For example, *n*-butyllithium gave 93% d.e. and 92% yield, but the Grignard reagent, *n*-butylmagnesium bromide, gave only 78% d.e. and 89% yield. The products from the Grignard additions were accompanied by side products which were not present in the organolithium reactions. Some results are worthy of note, the additions of phenyl, ethyl and *n*-butylmagnesium bromides gave good yields of the hydroxylamines, 69, 91 and 89% respectively and reasonable diastereoselectivity (PhMgBr 80% d.e., Et 71% d.e., *n*-Bu 78% d.e.).

Methyl and benzylmagnesium bromide both gave the addition products **172e,h**, however a substantial amount of starting material was recovered. The benzylmagnesium bromide was commercially available only as a solution in THF and it is thought that the THF co-ordinates to the boron trifluoride etherate under the reaction conditions rather than the oxime nitrogen. This would then render the oxime *C=N* bond less susceptible to nucleophilic attack and hence account for the recovered starting material. The other Grignard reagents were available as solutions in diethyl ether which is a much poorer ligand than THF and hence does not compete for the co-ordination to the boron trifluoride.

Stereochemical Rationale for the Addition Reactions

The model for the stereochemical outcome was the same as has been discussed previously in Chapter 2 and for the furan derived oximes. This theory of facial selectivity was borne out by the subsequent conversion of the hydroxylamines **172a-d** into the corresponding amino acids and comparing the optical rotations with those described in the literature, as will be described later. The boron trifluoride binds to the oxime nitrogen forcing the *O-C* bond *trans* to the *N-BF_3* bond and the propyl group effectively shields the top face **(Figure 25).**

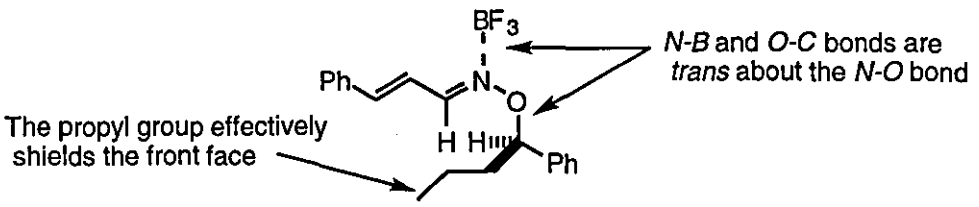
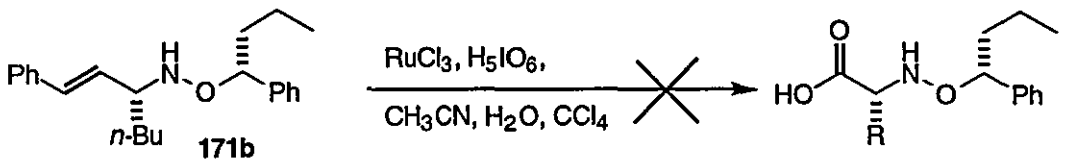


Figure 25

N-O Bond Cleavage and Nitrogen Protection

With the chiral centre in place with excellent optical purity we needed to cleave the *C=C* bond of the hydroxylamines **172a-d** to prepare the amino acids as described by Sharpless using ruthenium tetroxide. It was doubtful that the *N-O* bond would remain intact under the reaction conditions and the unprotected nitrogen would doubtless be oxidised to the *N*-oxide. However, in view of the short synthesis of amino acids that this protocol would provide the reaction was attempted **(Scheme 106)**.



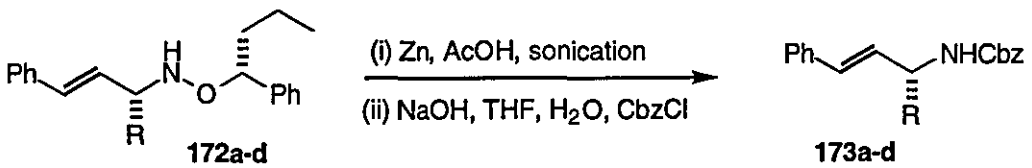
Scheme 106

The use of ruthenium tetroxide, which is prepared *in situ* from ruthenium trichloride or dioxide and an oxidative source, is a well established method for the cleavage of *C=C* bonds. The hydroxylamine **172b** was dissolved in a triphasic mixture of water, acetonitrile and carbon tetrachloride. The ratio of solvents was found by Sharpless to be critical, the best yields were obtained when the ratio of water, acetonitrile and carbon tetrachloride was 3:2:2. Periodic acid was added to the hydroxylamine in solution and the mixture stirred for 15 minutes. A catalytic amount of ruthenium trichloride was added and the mixture stirred for 24 hours. Aqueous work up gave a black tar which was analysed by TLC, ^{1}H NMR and IR and was shown to be a multicomponent mixture with no evidence of the required product.

It was clear that the chiral auxiliary would have to be removed, by *N-O* bond cleavage, and the free NH_2 protected. This is clearly a much more elegant synthesis as the chiral auxiliary can then be recovered and recycled. The protecting group chosen was the Cbz carbamate because of its ease of formation and it is reported to be stable

under the oxidative conditions.[87] We have already descibed a simple synthesis of the Cbz carbamates from the corresponding hydroxylamines, which we used with success in the synthesis of the piperidine alkaloids coniine and *pseudo*conhydrine (Chapter 3).

The hydroxylamines **172a-d** were dissolved in an acetic acid/water mixture (1:1) and zinc powder added, the mixture was then sonicated for 2-6 hours. The reactions did not proceed without sonication. This procedure cleaved the *N-O* bond efficiently with no evidence of byproducts, the free amines could be isolated at this stage but it was found to be more practical to protect the amines as their Cbz carbamates **173a-d (Scheme 107).**



172a-d **173a-d**

Scheme 107

When the *N-O* bond cleavage was complete the mixture was basified (pH 9) and extracted with dichloromethane. The combined dichloromethane extracts were evaporated and the residue dissolved in a THF/water mixture (1:1). The mixture was cooled to 0°C, benzyl chloroformate (CbzCl) was added and the solution was stirred overnight. Column chromatography gave the Cbz protected amines **173a-d** in 31-86% yields as colourless solids. The chiral alcohols were also recovered from each reaction in about 80% yield, comparison of the optical rotations with that of pure (R)-1-phenylbutanol showed that there was little or no racemisation of the alcohol on cleaving the *N-O* bond. The results of the hydroxylamine to Cbz carbamate transformations are summarised in **Table 15.**

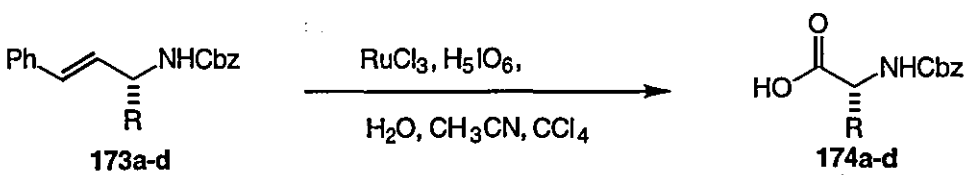
Hydroxylamine	*R*	*Carbamate*	*Yield (%)*
172a	Me	**173a**	31
172b	*n*-butyl	**173b**	83
172c	*i*-butyl	**173c**	86
172d	Ph	**173d**	66

Table 15

The yields for the cleavage and protection steps of hydroxylamines **172b-d** are unoptimised and satisfactory. The isolated yield of the carbamate **173a** is low, however this is a function of the unoptimised work up conditions and not of the reaction which appeared to proceed quantitatively. The carbamates were obtained as colourless solids and were readily characterised. The IR and proton NMR spectra were diagnostic, a band at 1697 cm^{-1} in the IR spectra indicates the presence of the carbamate carbonyl function. A broad singlet at about 5 ppm in the proton NMR indicates the presence of the benzyl group.

Cleavage of the Double Bond to Unmask the Carboxylic Acid

The *C=C* bond cleavage was attempted on the *N*-protected cinnamylamines **173a-d**, the standard protocol was employed, as described above **(Scheme 108).** Following the addition of periodic acid and ruthenium trichloride to the triphasic mixture the solution was warmed to 50°C for 24 hours. An extractive work up provided the *N*-protected amino acids **174a-d** in poor to moderate yields. The yields of the reaction for the substrates **173a-d** are summarised in **Table 16.**



Scheme 108

Carbamate	*R*	*Amino Acid*	*Yield (%)*	*Configuration*
173a	Me	**174a**	25	R
173b	*n*-butyl	**174b**	57	R
173c	*i*-butyl	**174c**	36	R
173d	Ph	**174d**	55	S

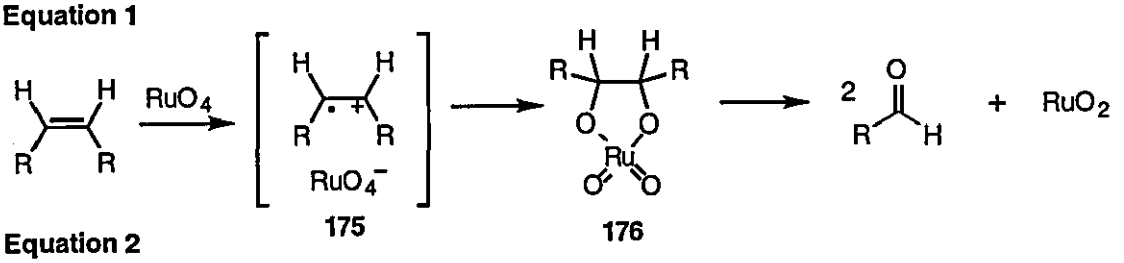
Table 16

The configurations of the amino acids were assigned on the basis of their optical rotations, in accordance with the literature values. The absolute configurations of the amino acids were found to be R, which is consistent with the model for the asymmetric induction. The absolute configuration of the amino acid **174d**, (S)-*N*-Cbz phenylglycine, is an artefact of the Cahn-Ingold-Prelog classification of the asymmetric

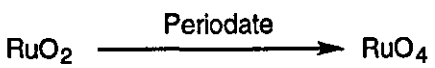
centre and not as a result of an anomaly in the face selectivity of the addition reaction to the *C=N* bond.

The transformation of olefin to carboxylic acid is reported to involve a direct electron transfer process. The reported mechanism of the catalytic oxidation is shown in **Scheme 109.**[92] Electron transfer from the olefin to the ruthenium tetroxide results in the formation of a radical cation-perruthenate complex **175.** Combination of the two species gives the ruthenate diester **176** which is similar to that postulated for the osmium tetroxide oxidations. The ruthenate diester **176** readily breaks down to produce two moles of aldehyde from one mole of the olefin **(Equation 1).** Ruthenium dioxide is the byproduct, and is reoxidised to ruthenium tetroxide by the action of the periodate species **(Equation 2).** The aldehydes are themselves transient species under the reaction conditions and are oxidised by the action of ruthenium tetroxide to the corresponding carboxylic acids **(Equation 3).** Finally the ruthenium dioxide is again reoxidised to ruthenium tetroxide by periodate to complete the catalytic cycle **(Equation 2).**

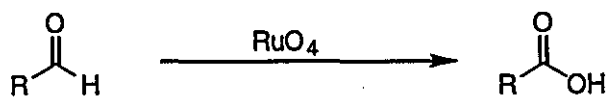
Equation 1



Equation 2



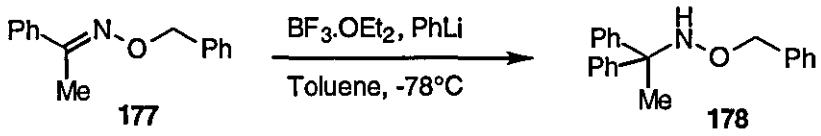
Equation 3



Scheme 109

4.3. Quaternary Amino Acids

The addition of organometallic reagents to ketoxime ethers has only once been reported in the literature and not in an asymmetric sense **(Scheme 110).**[29] Uno and Suzuki added phenyllithium to *O*-benzyl acetophenone oxime **177** to give a moderate yield of the corresponding hydroxylamine **178.**



Scheme 110

The hydroxylamine produced from the addition to ketoxime ethers has the possibility of containing a quaternary chiral centre. As a consequence of this, we wished to apply our ROPHy oxime methodology in order to prepare enantiomerically enriched quaternary chiral centres.[93] The derivative chosen for study was the ROPHy oxime of benzylidene acetone **179**, prepared by the usual one pot procedure from the (R)-alkoxyphthalimide **128b** and benzylidene acetone **(Figure 26).**

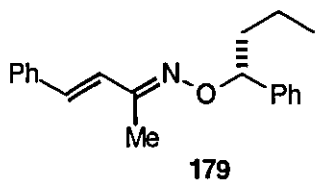
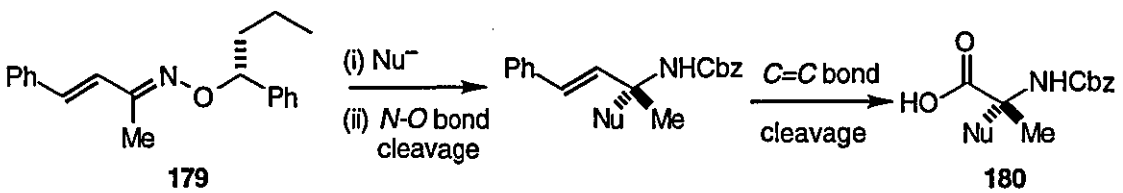


Figure 26

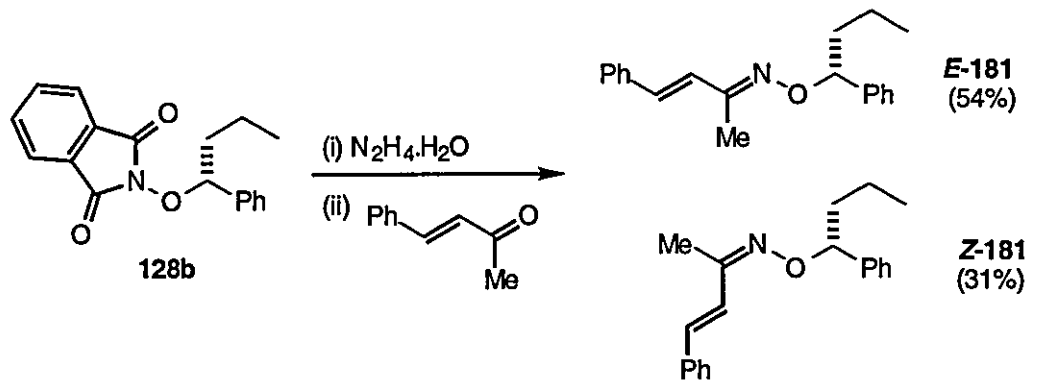
The reason this derivative was chosen was so that the *C=C* bond could be cleaved at some point in the same way as for the cinnamaldehyde oxime **171**. This time however, quaternary amino acids **180** would be synthesised as depicted in **Scheme 111.**



Scheme 111

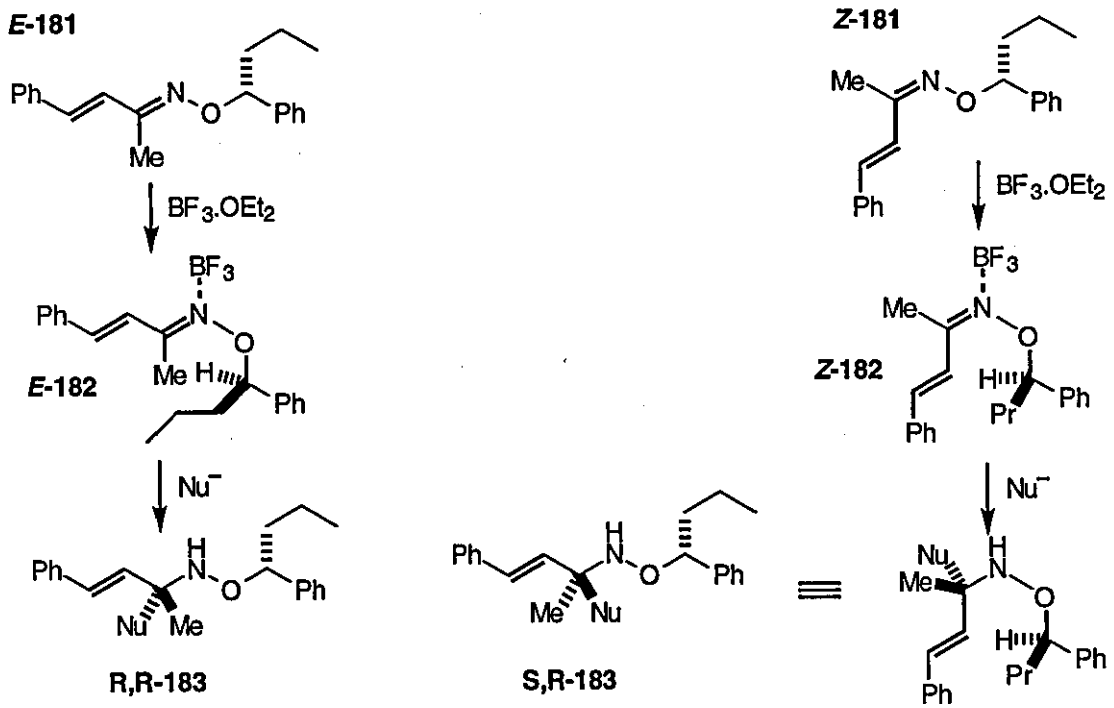
The chiral (R)-alkoxyphthalimide **128b** was treated with hydrazine hydrate in ethanol at 50°C to free the hydroxylamine (ROPHy) from the phthaloyl unit. This was followed by treatment with benzylidene acetone and a catalytic amount of protic acid (HCl). The reaction of ROPHy with a ketone does not occur unless acid is added, as described earlier (Chapter 2). The ethanolic solution was stirred overnight and evaporation of the solvent gave an amorphous residue. Column chromatography of the residue gave the *E* and *Z*-isomers in 54% and 31% yields respectively **(Scheme 112).** Both

isomers (***E*-181** and ***Z*-181**) were isolated as colourless solids and were recrystallised from light petroleum.



Scheme 112

We decided to study the effect of the geometry of the *C=N* bond on the diastereomeric outcome of the addition reactions. From analysing the proposed reactive conformations and the work done previously (Chapter 2) we would expect that the *E*-isomer would give the R,R-diastereomer, whereas the *Z*-isomer would give the diastereomer with the S,R configuration **(Scheme 113).**



Scheme 113

Co-ordination of the boron trifluoride to the oxime nitrogen gave the usual reactive species with the chiral centre being pushed closer to the reactive sp^2 centre to relieve the A-1,2 strain. The *E*-isomer gave rise to the species ***E*-182** which would be attacked from the back face by the nucleophile to give the R,R-diastereomer **(R,R)-183.** The *Z*-isomer gave rise to the species ***Z*-182** which is also attacked from the back face, and this gives rise to the S,R-diastereomer **(S,R)-183.** We would expect the diastereomeric excesses of the additions to the benzylidene acetone oximes to be less than for the corresponding cinnamaldehyde derived oxime because of the methyl group attached to the *C=N* bond. In the reactive species this methyl group will prevent the chiral auxiliary from getting as close to the reactive centre as it would for the cinnamaldehyde oxime **(Figure 27).**

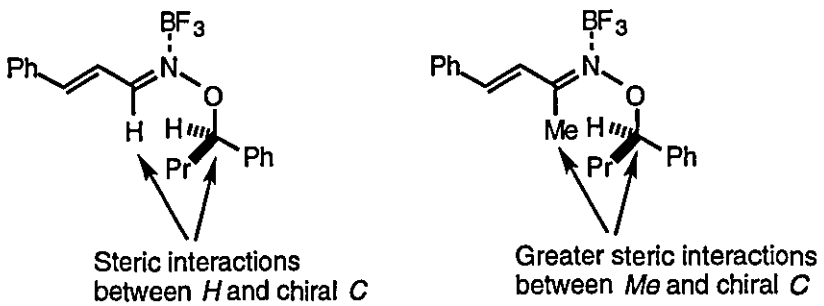


Figure 27

By the same token we would expect that the *Z*-isomer of the benzylidene acetone oxime ***Z*-181** would also give a lower diastereomeric ratio than the corresponding *E*-isomer ***E*-181** because the methyl group would give less steric hindrance than the cinnamyl group **(Figure 28).**

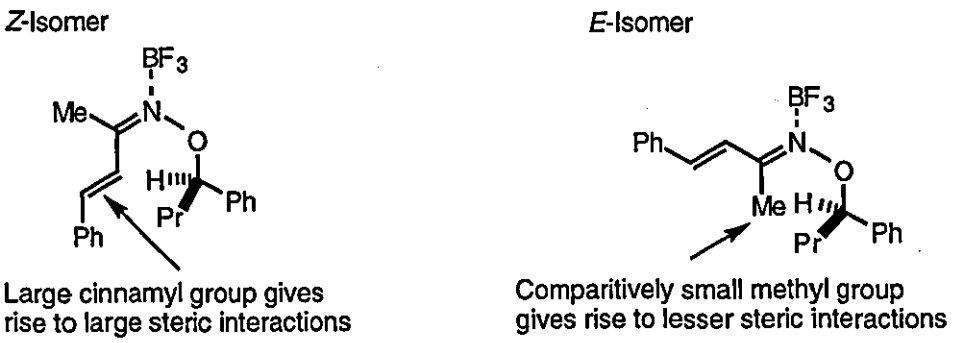
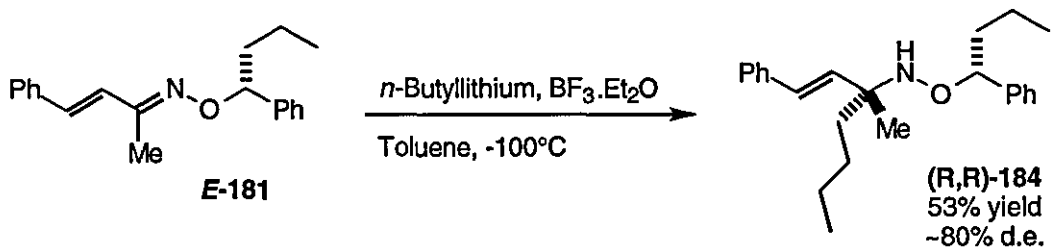


Figure 28

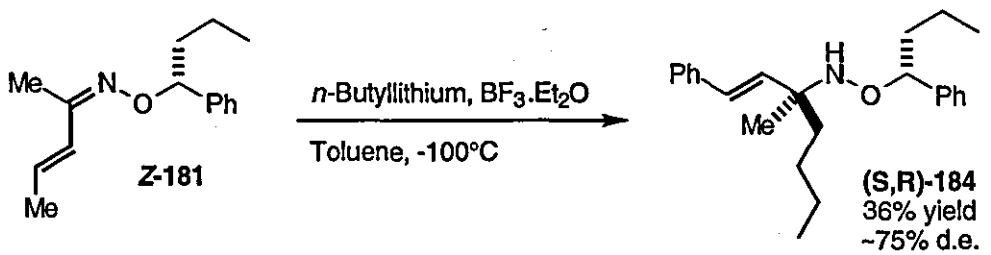
With these ideas in mind we studied the addition of *n*-butyllithium to each of the geometrical isomers in turn. Addition of 3 equivalents of the organometallic reagent to

the *E*-isomer ***E*-181** at -78°C gave the desired hydroxylamine **(R,R)-184** in only poor yield, with the remainder of the material being an intractable tar. Lowering of the bath temperature to -100°C and repeating the reaction gave the desired hydroxylamine **(RR)-184** in an improved 53% yield. The diastereomeric ratio was difficult to determine due to the peaks in the NMR spectrum overlapping to some extent for the major and minor diastereomers. A reasonable estimate for the diastereomeric excess was about 80% d.e. **(Scheme 114).**



Scheme 114

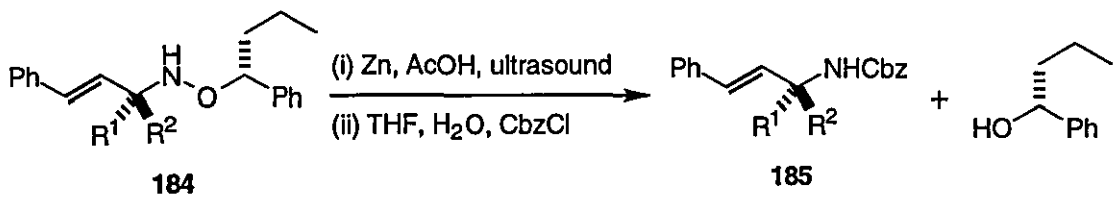
The addition of *n*-butyllithium to the *Z*-isomer ***Z*-181** at -100°C gave the addition product **(S,R)-184** in poor yield (36%) as a colourless oil **(Scheme 115)**. Two points of interest were noted, firstly from the proton NMR spectrum the opposite diastereomer was observed to that obtained from the addition to the *E*-isomer, as predicted. Secondly, in accordance with our theory, the diastereomeric excess estimated for the product obtained from the *Z*-isomer (75% d.e.) was less than that obtained from the addition to the *E*-isomer (80% d.e.).



Scheme 115

The diasteromeric excesses for these two reactions could not be determined directly from the proton NMR so a different method had to be devised. It was hoped that by converting the hydroxylamines **(R,R)-184** and **(S,R)-184** to their corresponding *N*-protected Cbz carbamates, by *N-O* bond cleavage, that chiral HPLC would determine their relative enantiomeric excesses. The hydroxylamines **(R,R)-184** and **(S,R)-184** were subjected to the ultrasound/zinc in acetic acid conditions to cleave the *N-O* bond.

The resulting free amines were not isolated but were treated with benzyl chloroformate, as described earlier, to provide the Cbz protected amines **185** as colourless solids in respectable yields **(Scheme 116)**. The chiral alcohol, (R)-1-phenylbutanol, was isolated in each case in good yield with no detectable racemisation.

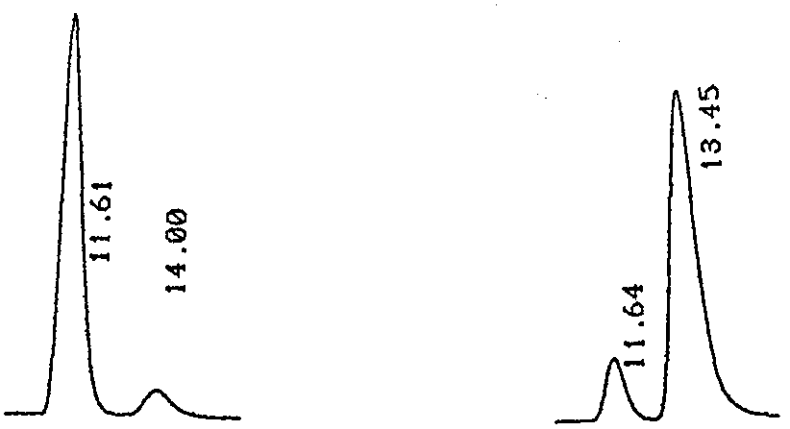


184 **185**

(S)-185 R^1 = Me, R^2 = *n*-Bu, 66%, 76% e.e.
(R)-185 R^1 = *n*-Bu, R^2 = Me, 70%, 82% e.e.

Scheme 116

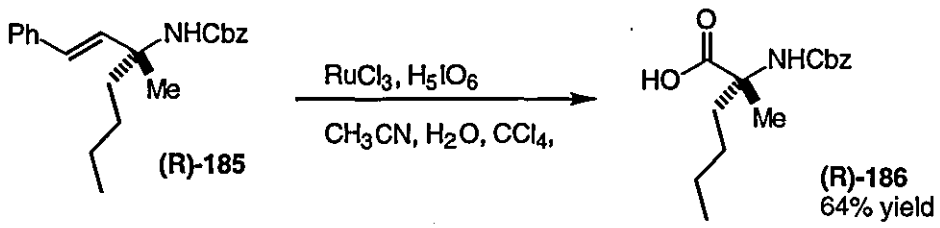
The two enantiomers of the Cbz carbamates were analysed by chiral HPLC in order to determine their relative enantiomeric excesses, the results are shown in **Figure 29**. The addition of *n*-butyllithium to the *E*-benzylidene acetone oxime ***E*-181** gave a diastereomeric excess of approximately 80%, this was quantified by the chiral HPLC of its Cbz carbamate **(R)-185** to give a value of 82% e.e.. The *Z*-oxime ***Z*-181** gave a diastereomeric excess of about 75% in the addition reaction. This value was borne out by chiral HPLC of the Cbz carbamate **(S)-185** which gave a value of 76% e.e..



82% e.e. of **(R)-185** 76% e.e. of **(S)-185**

Figure 29
Chiral HPLC results, showing the enantiomers of the protected amine **185**

To prepare the quaternary amino acid from the protected amine **(R)-185**, the standard ruthenium oxidation protocol was used. The amine was treated with periodic acid in the triphasic solvent system and the mixture stirred for 20 minutes until ruthenium trichloride was added. This mixture was stirred at 50°C for 24 hours, extractive work up and column chromatography gave the quaternary amino acid **(R)-186** in 64% yield **(Scheme 117)**.



Scheme 117

4.4. Summary

(i) The ROPHy oxime derived from 5-methylfurfural **168** gave only moderate diastereoselectivity of the corresponding hydroxylamines **169a-c**.

(ii) The corresponding cinnamyl oxime **171** is stable and crystalline and gave excellent levels of diastereoselectivity for the addition of organolithium reagents, but poorer values for Grignard reagents.

(iii) The *N-O* bond of the hydroxylamines **172a-d** were readily reduced and the free amines protected as their Cbz carbamates in good yields. The chiral auxiliary was also recovered in good yields.

(iv) The *C=C* bond of the cinnamyl group was oxidatively cleaved by ruthenium tetroxide to give the *N*-protected amino acids in moderate yields.

(v) Both enantiomers of the quaternary amino acid **185** could be prepared from the *E* and *Z*-isomers of the ROPHy oxime of benzylidene acetone.

Chapter Five

Experimental Details

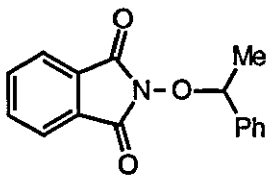
5.1. General Experimental Points

'Light petroleum' refers to the fraction boiling between 40°C and 60°C, and ether refers to diethyl ether; solvents were dried using standard methods according to procedures described in 'Purification of Laboratory Chemicals'.[ref] Commercially available compounds were generally used without further purification. Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under UV light (at 254 and/or 360 nm) or by staining with phosphomolybdic acid reagent, followed by heating. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60; samples were applied pre-adsorbed on silica or as a saturated solution in an appropriate solvent.

Infra red spectra were recorded in the range 4000-600 cm^{-1} using a Nicolet FT-205 or Perkin Elmer Paragon 1000 spectrometer, with internal calibration. Spectra were recorded neat or as Nujol mulls. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AC-250 or AC-400 instrument in deuteriochloroform as solvent. NMR chemical shifts are quoted in ppm relative to tetramethylsilane as internal standard. Coupling constants are reported in Hz. In reporting the NMR data for mixtures of diastereomers, signals arising from the major and minor isomers are reported separately if possible; the integration of signals is consistent within each isomer, *e.g.* a methyl group is reported as 3H for both isomers even though the peaks are unequal in area when the ratio of isomers is >1:1. Spectroscopic data is annotated with the following abbreviations: s - singlet; d - doublet; t - triplet; q - quartet. High and low resolution mass spectra were recorded on a Kratos MS80 instrument or on a VG Analytical ZAB-E instrument (EPSRC Mass Spectrometry Service Swansea). Compounds characterised by high resolution mass spectrometry were chromatographically homogeneous.

5.2. Experimental Details for Chapter 2

(±)-N-*(1-Phenylethoxy)phthalimide*

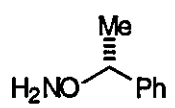


N-Hydroxyphthalimide (2.7 g, 1.6 mmol), (1-bromoethyl)benzene (9.18 g, 50 mmol), anhydrous potassium carbonate (6.8 g, 49 mmol) and DMSO (27 mL) were stirred together at 80°C. After 30 min, the mixture was poured into water (100 mL) and the solid filtered. The solid was dried at reduced pressure and recrystallised (ethanol) yielding the phthalimide (3.2 g, 73%) as a crystalline solid, m.p. 93-94°C, (Found: C, 71.88; H, 4.72; N, 5.23. $C_{16}H_{13}NO_3$ requires C, 71.90; H, 4.90; N, 5.24%); υ_{max} (Nujol)/cm^{-1} 2923, 1739, 1468, 1377; δ_H (250 MHz; $CDCl_3$) 7.72 (4H, m, ArH), 7.49 (2H, m, ArH), 7.33 (3H, m, ArH), 5.50 (1H, q, *J*=6.5 Hz, OCH), 1.72 (3H, d, *J*=6.5 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 163.6, 138.8, 134.3, 128.9, 128.8, 128.3, 127.6, 123.3, 85.1, 20.4; *m/z* (EI) 268 (MH^+, 36%), 267 (M^+, 3), 240 (9), 222 (5), 209 (5), 195 (4), 181 (13), 163 (100).

(R)-(+)-N-*(1-Phenylethoxy)phthalimide*

Diethyl azodicarboxylate (0.38 g, 2.2 mmol) was added to a solution of *N*-hydroxyphthalimide (0.33 g, 2 mmol), triphenylphosphine (0.52 g, 2 mmol) and (S)-(–)-1-phenylethyl alcohol (0.24 g, 2 mmol) in THF (20 mL) at room temperature. The resulting solution was allowed to stand for 24 h. The solution was evaporated to dryness and the residue chromatographed on silica gel (dichloromethane-light petroleum 1:1) to give the phthalimide, (0.26 g, 49%, e.e. >95%); $[\alpha]_D$ +222° (*c*=1, MeOH).

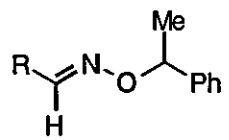
(R)-(+)-O-*(1-Phenylethyl)hydroxylamine* ***119***



Hydrazine hydrate (0.15 g, 4.6 mmol) was added to a solution of (+)-*N*-(1-phenylethoxy)phthalimide (0.91 g, 3.4 mmol) in absolute ethanol (5 mL) at room

temperature and the mixture was heated under reflux. After 10 min, the cooled mixture was filtered and the filtrate evaporated under reduced pressure yielding the hydroxylamine **119** (0.34 g, 73%) as a colourless oil, b.p. 80°C/1 mbar, (Found: M^+, 137.0839. $C_8H_{11}NO$ requires M, 137.0841); $[\alpha]_D$ +105° (*c*=1, MeOH); υ_{max} (film)/cm^{-1} 3317, 2976, 1585, 1495, 1452, 1074; δ_H (250 MHz; $CDCl_3$) 7.33 (5H, m, ArH), 5.17 (2H, broad s, NH_2), 4.65 (1H, q, *J*=6.5 Hz, OCH), 1.43 (3H, d, *J*=6.5 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 143.0, 128.6, 127.7, 126.3, 82.9, 21.9; *m/z* (EI) 105 (M^+ -ONH_2, 100%), 77 (18), 51 (9).

Preparation of *O*-(1-Phenylethyl) Oxime Ethers 116a-d



O-(1-Phenylethyl)hydroxylamine **119** (0.137 g, 1 mmol) and dry pyridine (10 mL) were added to a dry round bottomed flask at room temperature. Aldehyde (1 mmol) was added to it in a dropwise manner. The reaction mixture was stirred for 2 h. Water (20 mL) and dichloromethane (20 mL) were added and the layers separated. The aqueous layer was washed with dichloromethane (2 x 20 mL). The combined organic extracts were washed with water (2 x 20 mL) and HCl (2M; 20 mL), dried ($MgSO_4$) and filtered. Evaporation of the solvent *in vacuo* afforded the *title compound.*

(R)-(+)-O-*(1-Phenylethyl) benzaldoxime* ***116a***

(85%, *E:Z* 100:0) as a clear oil, b.p. 130°C/1 mbar, (Found: C, 80.01; H, 6.77; N, 6.20. $C_{15}H_{15}NO$ requires C, 79.96; H, 6.72; N, 6.22%); $[\alpha]_D$ +100° (*c*=1, MeOH); υ_{max} (film)/cm^{-1} 2978, 1575, 1448, 1083, 1072, 958; δ_H (250 MHz; $CDCl_3$) 8.12 (1H, s, CH=N), 7.23 (10H, m, ArH), 5.35 (1H, q, *J*=6.6 Hz, OCH), 1.61 (3H, d, *J*=6.6 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 148.6, 143.1, 132.5, 129.6, 128.6, 128.3, 127.5, 127.0, 126.4, 81.3, 21.9; *m/z* (EI) 226 (MH^+, 28%), 225 (M^+, 17), 122 (20), 105 (100).

(R)-(+)-O-*(1-Phenylethyl) trimethylacetaldehyde oxime* ***116b***

(83%, *E:Z* 100:0) as a clear oil, b.p. 130°C, (Found: MH^+, 206.1545. $C_{13}H_{19}NO$ requires MH, 206.1545); $[\alpha]_D$ +10° (*c*=1, MeOH); υ_{max} (film)/cm^{-1} 2968, 1601, 1454, 1366, 1084; δ_H (250 MHz; $CDCl_3$) 7.35 (6H, m, ArH, CH=N), 5.19 (1H, q, *J*=6.6 Hz,

OCH), 1.54 (3H, d, *J*=6.6 Hz, Me), 1.06 (9H, s, CMe_3); δ_C (62.9 MHz; $CDCl_3$) 158.3, 143.7, 128.1, 127.2, 126.4, 80.2, 33.5, 27.5, 21.6; *m/z* (CI) 206 (MH^+, 100%), 192 (10).

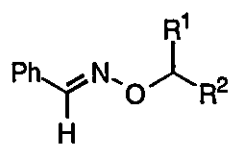
O-*(1-Phenylethyl) isobutyraldehyde oxime* ***116c***

(97%, *E:Z* 73:27) as a clear oil, b.p. 80°C/1 mbar, (Found: MH^+, 192.1388. $C_{12}H_{17}NO$ requires MH, 192.1388); υ_{max} (film)/cm^{-1} 2968, 1445, 1082; (*E*-isomer) δ_H (250 MHz; $CDCl_3$) 7.31 (6H, m, ArH, CH=N), 5.20 (1H, q, *J*=6.6 Hz, OCH), 2.46 (1H, septet, *J*=6.7 Hz, $CHMe_2$), 1.54 (3H, d, *J*=6.6 Hz, Me), 1.07 (3H, d, *J*=6.7 Hz, CHMeMe), 1.04 (3H, d, *J*=6.7 Hz, CHMeMe); δ_C (62.9 MHz; $CDCl_3$) 156.1, 143.2, 128.2, 127.3, 126.3, 80.3, 29.3, 21.9, 20.14, 20.11; (*Z*-isomer) δ_H (250 MHz; $CDCl_3$) 6.80 (1H, d, *J*=7.1 Hz, CH=N), 5.21 (1H, q, *J*=6.6 Hz, OCH), 3.25 (1H, septet, *J*=6.7 Hz, $CHMe_2$), 1.07 (3H, d, *J*=6.7 Hz, CHMeMe), 1.05 (3H, d, *J*=6.7 Hz, CHMeMe); δ_C (62.9 MHz; $CDCl_3$) 157.3, 143.6, 128.3, 126.0, 80.6, 25.1, 22.2, 19.7, 19.7; *m/z* (CI) 192 (MH^+, 100%), 164 (7), 122 (4).

O-*(1-Phenylethyl) acetaldoxime* ***116d***

(98%, *E:Z* 46:54) as a clear oil, b.p. 60°C/2 mbar, (Found: MH^+, 164.1075. $C_{10}H_{13}NO$ requires MH, 164.1075); υ_{max} (film)/cm^{-1} 2978, 1645; (*E*-isomer) δ_H (250 MHz; $CDCl_3$) 7.49 (1H, q, *J*=5.9 Hz, CH=N), 7.30 (5H, m, ArH), 5.20 (1H, q, *J*=6.5 Hz, OCH), 1.82 (3H, d, *J*=5.9 Hz, MeCH=N), 1.54 (3H, d, *J*=6.5 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 148.8, 146.8, 128.2, 127.2, 126.2, 80.3, 21.9, 12.0; (*Z*-isomer) δ_H (250 MHz; $CDCl_3$) 6.77 (1H, q, *J*=5.5 Hz, CH=N), 5.25 (1H, q, *J*=6.6 Hz, OCH), 1.91 (3H, d, *J*=5.5 Hz, MeCH=N), 1.56 (3H, d, *J*=6.6 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 143.6, 126.0, 80.6, 22.1, 15.2; *m/z* (EI) 105 (100%), 77 (24), 51 (15), 39 (5).

Preparation of *O*-Alkyl Benzaldoximes by Alkylation of *syn*-Benzaldoxime



(±)-O-*(1-Phenylethyl) benzaldoxime oxime* ***116a***

To a stirred solution of *syn*-benzaldoxime (1.25 g, 10 mmol) and anhydrous potassium carbonate (2.07 g, 15 mmol) in DMSO (50 mL) was added dropwise (1-bromoethyl)benzene (2.3 g, 12 mmol). The mixture was stirred overnight at room

temperature. Excess solvent was removed *in vacuo*. The residue was extracted with dichloromethane (20 mL) and washed with water (20 mL). The organic layer was dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography on silica gel using dichloromethane-light petroleum (1:2) as eluent yielding the oxime ether **116a** (1.95 g, 84%, *E:Z* 100:0) with identical spectroscopic properties to the (R)-(+)-enantiomer prepared above.

O-*(1-Ethoxycarbonylethyl) benzaldoxime* ***120a***

To a stirred solution of *syn*-benzaldoxime (0.12 g, 1 mmol) and potassium *t*-butoxide (0.13 g, 1.2 mmol) in *t*-butanol (10 mL) was added dropwise ethyl 2-bromopropionate (0.18 g, 1 mmol). The mixture was stirred overnight at room temperature. Excess solvent was removed under reduced pressure. The residue was extracted with ether (20 mL) and washed with water (2 x 10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the the crude ester which was purified by column chromatography on silica gel with dichloromethane-light petroleum (b.p. 40-60°C) (1:2) as eluent to furnish the title compound **120a** (1.6 g, 76%) as a yellow oil, (Found: M^+, 221.1051. $C_{12}H_{15}NO_3$ requires M, 221.1052); υ_{max} (film)/cm^{-1} 2932, 1750; δ_H (250 MHz; $CDCl_3$) 8.17 (1H, s, CH=N), 7.56 (2H, m, ArH), 7.36 (3H, m, ArH), 4.81 (1H, q, *J*=7.0 Hz, OCH), 4.42 (2H, q, *J*=7.2 Hz, CH_2Me), 1.53 (3H, d, *J*=7.0 Hz, Me), 1.29 (3H, t, *J*=7.2 Hz, CH_2Me); δ_C (62.9 MHz; $CDCl_3$) 175.1, 149.8, 132.6, 130.0, 128.7, 127.3, 77.8, 60.9, 17.0, 14.2; *m/z* (EI) 211 (M^+, 11%), 148 (9), 104 (100).

Similarly prepared were the following:-

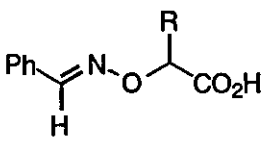
O-*(1-Ethoxycarbonyl-2-methylpropyl) benzaldoxime* ***120b***

Obtained from the alkylation of benzaldoxime with ethyl 2-bromo-3-methylbutanoate, (60%) as a colourless oil, (Found: C, 67.40; H, 7.70; N, 5.54. $C_{14}H_{19}NO_3$ requires C, 67.43; H, 7.69; N, 5.62%); υ_{max} (film)/cm^{-1} 2970, 2935, 1751; δ_H (250 MHz; $CDCl_3$) 8.20 (1H, s, CH=N), 7.56 (2H, m, ArH), 7.33 (3H, m, ArH), 4.50 (1H, d, *J*=6.1 Hz, OCH), 4.24 (2H, m, CH_2Me), 2.21 (1H, septet, *J*=6.8 Hz, $CHMe_2$) 1.28 (3H, t, *J*=7.1 Hz, CH_2Me), 1.05 (6H, 2d, *J*=6.8 Hz, $CHMe_2$); δ_C (62.9 MHz; $CDCl_3$) 171.8, 149.8, 131.9, 130.0, 128.6, 127.2, 86.9, 60.6, 30.4, 17.0, 18.6, 18.1, 14.3; *m/z* (EI) 249 (M^+, 6%), 176 (18), 104 (100).

O-*(1-Methoxycarbonylbenzyl) benzaldoxime* ***120c***

Obtained from the alkylation of benzaldoxime with methyl 2-bromo-2-phenylacetate, (58%) as a colourless solid, m.p. 50-60°C, (Found: C, 71.74; H, 5.90; N, 5.19. $C_{14}H_{19}NO_3$ requires C, 71.35; H, 5.62; N, 5.20%); υ_{max} ($CHCl_3$)/cm^{-1} 3030, 2956, 1752; δ_H (250 MHz; $CDCl_3$) 8.27 (1H, s, CH=N), 7.55 (4H, m, ArH), 7.39 (6H, m, ArH), 5.73 (1H, s, OCH), 3.76 (3H, s, CO_2Me); δ_C (62.9 MHz; $CDCl_3$) 170.9, 150.5, 134.5, 131.4, 130.1, 129.0, 128.6, 128.5, 127.6, 127.2, 83.6, 52.2; *m/z* (EI) 270 (MH^+, 4%), 269 (M^+, 12), 230 (8), 228 (8), 210 (100).

General Method for Hydrolysis of Oxime Esters 120a-c



A solution of oxime esters **120** (1 mmol), lithium hydroxide (5 mmol), water (5 mL) and THF (5 mL) was stirred for 2 h at room temperature. The mixture was acidified with HCl (6 M) and extracted with dichloromethane (3 x 10 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated to give a white solid, recrystallization (petroleum ether/ether) furnished the oxime acids.

O-*(1-Carboxyethyl) benzaldoxime* ***117a***

Obtained from the hydrolysis of the oxime ester **120a** (52%) as colourless crystals, m.p. 114-115°C, (Found: C, 62.13; H, 5.74; N, 7.14. $C_{10}H_{11}NO_3$ requires C, 62.17; H, 5.74; N, 7.25%); υ_{max} ($CHCl_3$)/cm^{-1} 3403, 3025, 2990, 1730; δ_H (250 MHz; $CDCl_3$) 8.19 (1H, s, CH=N), 7.51 (2H, m, ArH), 7.37 (3H, m, ArH), 4.86 (1H, q, *J*=7.1 Hz, OCH), 1.58 (3H, d, *J*=7.1 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 178.8, 150.3, 131.6, 130.2, 128.7, 128.6, 127.4, 77.3, 16.9; *m/z* (EI) 122 (MH^+, 75%), 105 (100), 77 (79).

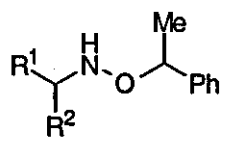
O-*(1-Carboxy-2-methylpropyl) benzaldoxime* ***117b***

Obtained from the hydrolysis of the oxime ester **120b** (98%) as colourless crystals, m.p. 64-66°C, (Found: M^+, 221.1056. $C_{12}H_{15}NO_3$ requires M, 221.1052); υ_{max} (Nujol)/cm^{-1} 3420, 3164, 2969, 1726; δ_H (250 MHz; $CDCl_3$) 9.70 (1H, broad s, CO_2H), 8.20 (1H, s, CH=N), 7.70 (2H, m, ArH), 7.36 (3H, m, ArH), 4.59 (1H, d, *J*=5.7 Hz, OCH), 2.25 (1H, septet, *J*=5.7 Hz, $CHMe_2$) 1.05 (6H, 2d, *J*=6.8 Hz, $CHMe_2$); δ_C (62.9 MHz; $CDCl_3$) 191.0, 163.5, 145.0, 143.5, 142.0, 140.7, 99.6, 43.8, 32.1, 31.1; *m/z* (EI) 222 (MH^+, 23%), 221 (M^+, 10), 176 (13), 138 (24), 104 (100).

O-*(1-Carboxybenzyl) benzaldoxime* ***117c***

Obtained from the hydrolysis of the oxime ester **120c** (68%) as colourless crystals, m.p. 99-100°C, (Found: C, 70.32; H, 5.14; N, 5.36. $C_{15}H_{13}NO_3$ requires C, 70.56; H, 5.14; N, 5.49%); υ_{max} ($CHCl_3$)/cm^{-1} 3068, 3014, 1724; δ_H (250 MHz; $CDCl_3$) 8.25 (1H, s, CH=N), 7.45 (11H, m, ArH, CO_2H) 5.73 (1H, s, OCH); δ_C (62.9 MHz; $CDCl_3$) 176.5, 151.0, 134.1, 131.3, 130.3, 129.3, 128.8, 128.7, 127.7, 127.4, 83.3; *m/z* (EI) 256 (MH^+, 100%), 255 (M^+, 17).

General Method for Addition of Organometallics to *O*-(1-Phenylethyl) Aldoximes



To a round bottomed flask fitted with a nitrogen inlet was added oxime ether **116** (1 mmol) and toluene (5 mL). The resulting solution was cooled to -78°C and boron trifluoride etherate (3 mmol) was added, the solution was stirred for 10 min. Organometallic reagent (3 mmol) was added dropwise over 10 min. After addition the solution was stirred at -78°C until all the starting material had been consumed, monitored by TLC (usually 1-12 h). The reaction was quenched at -78°C by the addition of water (1 mL), and then allowed to warm up to room temperature. The solvent was removed under reduced pressure and the residue partitioned between dichloromethane (20 mL) and water (20 mL). The layers were separated and the aqueous portion was washed with further portions of dichloromethane (2 x 20 mL). The combined organic extracts were washed with brine (10 mL) and then dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography on silica gel using dichloromethane-light petroleum (1:2) as eluent to give the *title compound.*

(R,R)-(+)-1-*Phenyl-N-(1-phenylethoxy)-1-pentylamine* ***121a***

Obtained by the addition of *n*-butyllithium to (+)-**116a** (64%, d.e. 71%) as a colourless oil, b.p. 100°C/1 mbar, (Found: M^+, 283.1945. $C_{19}H_{25}NO$ requires M, 283.1936); $[\alpha]_D$ +60° (*c*=1, MeOH); υ_{max} (film)/cm^{-1} 3270, 2957, 1604, 1454; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.26 (10H, m, ArH), 5.40 (1H, broad s, NH), 4.67 (1H, q, *J*=6.6 Hz, OCH), 3.95 (1H, dd, *J*=5.2, 8.7 Hz, CHN), 1.90 (1H, m, CH_2CHN), 1.65 (1H, m, CH_2CHN), 1.43 (3H, d, *J*=6.6 Hz, MeCHPh) 1.27 (4H, m, CH_2), 0.87 (3H,

t, *J*=6.9 Hz, $(CH_2)_3Me$); δ_C (62.9 MHz; $CDCl_3$) 143.5, 141.7, 128.3, 128.1, 127.8, 127.3, 126.3, 126.3, 80.9, 65.9, 33.5, 28.3, 22.7, 21.5, 14.0; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 4.51 (1H, q, J=6.6 Hz, OCH); δ_C (62.9 MHz; $CDCl_3$) 144.0, 142.7, 127.2, 81.0, 33.4, 29.8, 22.6, 21.7; *m/z* (EI) 284 (MH^+, 2%), 179 (22), 147 (16), 122 (41), 105 (100), 91 (53), 78 (30), 60 (11), 51 (15), 41 (20), 27 (15).

2,2-Dimethyl-1-phenyl-N-*(1-phenylethoxy) propylamine* ***121b***

Obtained by the addition of *tert*-butyllithium to (±)-**116a** (54%, d.e. 38%) as a colourless oil, (Found: M^+, 283.1926. $C_{19}H_{25}NO$ requires M, 283.1936); υ_{max} (film)/cm^{-1} 2973, 1454, 1365, 700; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.22 (10H, m, ArH), 5.68 (1H, broad s, NH), 4.65 (1H, q, *J*=6.6 Hz, OCH), 3.79 (1H, s, CHN), 1.41 (3H, d, *J*=6.6 Hz, Me), 0.90 (9H, s, CMe_3); δ_C (62.9 MHz; $CDCl_3$) 142.4, 140.3, 128.8, 128.1, 127.3, 127.3, 126.7, 126.5, 79.9, 74.0, 27.4, 20.7; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 4.58 (1H, q, *J*=6.6 Hz, OCH), 3.75 (1H, s, CHN), 1.11 (3H, d, *J*=6.6Hz, Me) 0.82 (9H, s, CMe_3); δ_C (62.9 MHz; $CDCl_3$) 143.8, 140.6, 128.9, 128.2, 127.2, 127.1, 126.6, 126.2, 81.0, 74.4, 27.2, 21.8; *m/z* (EI) 226 (14%), 122 (77), 105 (100), 91 (23), 77 (45), 57 (48), 41 (66), 27 (38).

2,2-Dimethyl-1-phenyl-N-*(1-phenylethoxy) propylamine* ***121b***

Obtained by the addition of phenyllithium to (±)-**116b** (21%, d.e. >95%) as a colourless oil, (Found: M^+, 283.1900. $C_{19}H_{25}NO$ requires M, 283.1936); υ_{max} (film)/cm^{-1} 2973, 1454, 1365, 700; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.33 (10H, m, ArH), 5.74 (1H, bs, NH), 4.52 (1H, q, *J*=6.6 Hz, OCH), 3.74 (1H, s, CHN), 1.11 (3H, d, *J*=6.6 Hz, Me), 0.82 (9H, s, CMe_3); δ_C (62.9 MHz; $CDCl_3$) 143.8, 140.6, 128.9, 128.2, 127.2, 127.1, 126.6, 126.3, 81.0, 74.4, 33.7, 27.2, 21.8; *m/z* (EI) 284 (MH^+, 24%), 226 (47), 147 (29), 122 (83), 105 (100), 91 (45), 77 (60), 57 (52), 41 (55), 27 (38).

1-Phenyl-N-*(1-phenylethoxy) but-3-enylamine* ***121c***

Obtained by the addition of allylmagnesium bromide to (±)-**116a** (70%, d.e. 69%) as a colourless oil, (Found: M^+, 267.1637. $C_{18}H_{21}NO$ requires M, 267.1623); υ_{max} (film)/cm^{-1} 2973, 1650, 1451; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.26 (10H, m, ArH), 5.72 (1H, m, CH=), 5.51 (1H, broad s, NH), 5.00 (2H, m, $=CH_2$), 4.65 (1H, q, *J*=6.5 Hz, OCH), 4.03 (1H, t, *J*=6.9 Hz, CHN), 2.66 (1H, m, $CH_2CH=CH_2$), 2.48 (1H, m, $CH_2CH=CH_2$), 1.43 (3H, d, *J*=6.5 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 143.2, 141.5, 135.0, 128.2, 128.1, 127.8, 127.3, 127.2, 126.3, 117.2, 80.9, 65.0, 38.4, 21.3; (minor

diastereomer) δ_H (250 MHz; $CDCl_3$) 4.51 (1H, q, *J*=6.5 Hz, OCH), 1.22 (3H, d, *J*=6.5 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 144.0, 142.2, 134.7, 128.3, 128.2, 127.7, 126.2, 117.5, 81.1, 64.9, 38.3, 21.7; *m/z* (EI) 268 (MH^+, 75%), 131 (62), 122 (80), 105 (100), 91 (61), 77 (67), 65 (16), 51 (47), 39 (54), 27 (27).

2-Methyl-1-phenyl-N-*(1-phenylethoxy) propylamine* ***121d***

Obtained by the addition of *iso*-propylmagnesium chloride to (±)-**116a** (30%, d.e. 74%) as a colourless oil, (Found: M^+, 269.1765. $C_{18}H_{23}NO$ requires M, 269.1776); υ_{max} (film)/cm^{-1} 3200, 2974, 1453, 700; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.25 (10H, m, ArH), 5.68 (1H, broad s, NH), 4.65 (1H, q, *J*=6.5 Hz, OCH), 3.74 (1H, d, *J*=7.0 Hz, CHN), 2.08 (1H, septet, *J*=6.8 Hz, $CHMe_2$), 1.41 (3H, d, *J*=6.5 Hz, Me), 0.98 (3H, d, *J*=6.8 Hz, CHMeMe), 0.77 (3H, d, *J*=6.8 Hz, CHMeMe); δ_C (62.9 MHz; $CDCl_3$) 144.4, 141.6, 128.3, 128.2, 127.8, 127.2, 127.0, 126.3, 81.6, 72.4, 31.6, 22.7, 21.0, 19.7; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 4.53 (1H, q, *J*=6.5 Hz, OCH), 3.65 (1H, d, *J*=7.0 Hz, CHN), 1.90 (1H, septet, *J*=6.8 Hz, $CHMe_2$), 1.17 (3H, d, *J*=6.5 Hz, Me), 0.91 (3H, d, *J*=6.8 Hz, CHMeMe), 0.68 (3H, d, *J*=6.8 Hz, CHMeMe); δ_C (62.9 MHz; $CDCl_3$) 145.3, 142.7, 127.1, 82.0, 72.8, 31.8, 22.3, 20.9, 20.1; *m/z* (EI) 270 (MH^+, 2), 165 (12), 133 (11), 226 (5), 165 (12), 133 (11), 122 (65), 105 (100), 91 (45), 77 (40), 65 (7), 51 (25), 27 (23).

2,2-Dimethyl-N-*(1-phenylethoxy)-3-heptylamine* ***121e***

Obtained by the addition of *n*-butyllithium to (+)-**116b** (84%, d.e. 74%) as a colourless oil, (Found: MH^+, 264.2327. $C_{17}H_{29}NO$ requires MH, 264.2327); $[\alpha]_D$ +69° (*c*=0.51, MeOH); υ_{max} (film)/cm^{-1} 3392, 2957, 1452, 1365; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.30 (5H, m, ArH), 4.74 (1H, q, *J*=6.6 Hz, OCH), 2.40 (1H, dd, *J*=3.0, 7.8 Hz, CHN), 1.37 (3H, d, *J*=6.6 Hz, Me), 1.35 (6H, m, $(CH_2)_3$), 0.92 (3H, t, *J*=6.9 Hz, $(CH_2)_3Me$), 0.90 (9H, s, CMe_3); δ_C (62.9 MHz; $CDCl_3$) 144.6, 128.2, 127.2, 126.2, 80.6, 69.6, 34.8, 30.4, 28.2, 27.4, 23.0, 22.1, 14.1; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 4.73 (1H, q, *J*=6.6 Hz, OCH); δ_C (62.9 MHz; $CDCl_3$) 144.2, 128.3, 127.1, 126.0, 80.3, 69.3, 34.4, 30.3, 27.9, 27.2, 22.8, 22.3, 14.1; *m/z* (CI) 264 (MH^+, 100%), 206 (44), 144 (10), 122 (10).

2,2-Dimethyl-N-*(1-phenylethoxy)-3-hex-5-enylamine* ***121f***

Obtained by the addition of allylmagnesium bromide to (±)-**121b** (62%, d.e. 44%) as a colourless oil, (Found: M^+, 247.1923. $C_{16}H_{25}NO$ requires M, 247.1936); υ_{max} (film)/cm^{-1} 2979, 1650, 1451, 1365; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.20

(5H, m, ArH), 5.87 (1H, m, CH=), 5.4 (1H, broad s, NH), 5.01 (2H, m, $=CH_2$), 4.74 (1H, q, *J*=6.6 Hz, OCH), 2.52 (1H, dd, *J*=5.0, 7.6 Hz, CHN), 2.34 (2H, m, $CH_2CH=CH_2$), 1.43 (3H, d, *J*=6.6 Hz, Me), 0.96 (9H, s, CMe_3); δ_C (62.9 MHz; $CDCl_3$) 144.0, 137.7, 128.2, 127.20, 126.2, 116.1, 80.14, 66.6, 34.5, 32.52, 27.6, 22.0; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 2.62 (1H, dd, *J*=5.0, 7.6 Hz, CHN), 1.41 (3H, d, *J*=6.6 Hz, Me), 0.99 (9H, s, CMe_3); δ_C (62.9 MHz; $CDCl_3$) 144.2, 137.5, 128.3, 127.2, 126.0, 116.9, 68.3, 34.7, 27.3, 22.4; *m/z* (EI) 248 (MH^+, 12%), 190 (20), 105 (100), 86 (77), 77 (23), 69 (11), 57 (25), 51 (11), 41 (49), 29 (21).

2-Methyl-N-*(1-phenylethoxy)-3-heptylamine* ***121g***

Obtained by the addition of *n*-butyllithium to **116c** (83%, d.e. 77%) as a colourless oil, b.p. 120°C/4 mbar, (Found: MH^+, 250.2171. $C_{16}H_{27}NO$ requires MH, 250.2171); υ_{max} (film)/cm^{-1} 2959, 1455; δ_H (250 MHz; $CDCl_3$) 7.30 (5H, m, ArH), 5.29 (1H, broad s, NH), 4.71 (1H, q, *J*=6.5 Hz, OCH), 2.64 (1H, m, CHN), 1.92 (1H, septet, *J*=6.7 Hz, $CHMe_2$), 1.43 (3H, d, *J*=6.6 Hz, Me) 1.34 (6H, m, $(CH_2)_3$), 0.96 (3H, t, *J*=6.9 Hz, $(CH_2)_3Me$), 0.91 (3H, d, *J*=6.7 Hz, CHMeMe), 0.84 (3H, d, *J*=6.7 Hz, CHMeMe); δ_C (62.9 MHz; $CDCl_3$) (major diastereomer) 143.9, 128.2, 127.2, 126.3, 80.5, 65.6, 29.0, 28.6, 27.7, 22.9, 21.8, 18.9, 17.8, 14.0; (minor diastereomer) δ_C (62.9 MHz; $CDCl_3$) 126.2, 80.8, 65.7, 29.1, 28.7, 22.9, 22.0, 17.7, 13.9; *m/z* (CI) 250 (MH^+, 26%), 234 (4), 130 (100), 86 (8).

2-Methyl-N-*(1-phenylethoxy)-3-hex-5-enylamine* ***121h***

Obtained by the addition of allylmagnesium bromide to **116c** (70%, d.e. 59%) as a colourless oil, (Found: MH^+, 234.1858. $C_{15}H_{23}NO$ requires MH, 234.1858); υ_{max} (film)/cm^{-1} 2975, 1650, 1454; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.18 (5H, m, ArH), 5.71 (1H, m, CH=), 5.1 (1H, broad s, NH), 4.97 (2H, m, $=CH_2$), 4.60 (1H, q, *J*=6.6 Hz, OCH), 2.56 (1H, m, CHN), 2.11 (2H, m, $CH_2CH=CH_2$), 1.76 (1H, septet, *J*=5.5 Hz, $CHMe_2$), 1.34 (3H, d, *J*=6.6 Hz, Me), 0.82 (3H, d, *J*=6.6 Hz, CHMeMe), 0.75 (3H, d, *J*=6.6 Hz, CHMeMe); δ_C (62.9 MHz; $CDCl_3$) 143.8, 136.3, 128.3, 127.3, 126.4, 116.7, 80.7, 65.1, 32.7, 28.5, 21.8, 19.1, 18.2; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 2.59 (1H, m, CHN), 1.32 (3H, d, *J*=6.6 Hz, Me), 0.83 (3H, d, *J*=6.6 Hz, CHMeMe), 0.76 (3H, d, *J*=6.6 Hz, CHMeMe); δ_C (62.9 MHz; $CDCl_3$) 143.9, 136.1, 128.3, 127.2, 126.1, 117.0, 80.8, 65.0, 32.0, 28.6, 21.0, 17.7; *m/z* (EI) 234 (MH^+, 100%), 192 (3), 122 (15), 114 (10).

N-*(1-Phenylethoxy)-2-hexylamine* ***121i***

Obtained by the addition of *n*-butyllithium to **116d** (70 %, d.e. <5%) as a colourless oil, b.p. 105°C/1 mbar, (Found: MH^+, 222.1858. $C_{14}H_{23}NO$ requires MH, 222.1858); υ_{max} (film)/cm^{-1} 2959, 1453, 1370; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.30 (5H, m, ArH), 4.71 (1H, q, *J*=6.6 Hz, OCH), 2.96 (1H, m, CHN), 1.43 (3H, d, *J*=6.6 Hz, Me) 1.24 (6H, m, $(CH_2)_3$), 1.01 (3H, d, *J*=6.2 Hz, MeCHN), 0.91 (3H, t, *J*=6.9 Hz, $(CH_2)_3Me$); δ_C (62.9 MHz; $CDCl_3$) 144.0, 128.4, 127.3, 126.3, 81.2, 56.1, 33.9, 28.2, 22.9, 22.0, 18.5, 14.1; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 1.09 (3H, d, *J*=6.2 Hz, MeCHN), 0.87 (3H, t, *J*=6.9 Hz, $(CH_2)_3Me$); δ_C (62.9 MHz; $CDCl_3$) 143.9, 126.2, 81.1, 56.1, 33.6, 22.0, 18.0, 14.0; *m/z* (EI) 222 (MH^+, 41%), 105 (100), 60 (58), 43 (49).

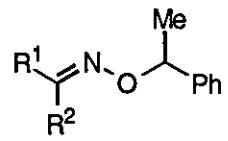
N-*(1-Phenylethoxy)-2-pent-4-enylamine* ***121j***

Obtained by the addition of allylmagnesium bromide to **116d** (58%, d.e. 14%) as a colourless oil, b.p. 120°C/0.5 mbar, (Found: MH^+, 206.1545. $C_{13}H_{19}NO$ requires MH, 206.1545); υ_{max} (film)/cm^{-1} 2975, 1645, 1452; (major diastereomer) δ_H (250 MHz; $CDCl_3$) 7.29 (5H, m, ArH), 5.79 (1H, m CH=), 5.08 (2H, m, $=CH_2$), 5.0 (1H, broad s, NH), 4.72 (1H, q, *J*=6.6 Hz, OCH), 3.07 (1H, m, CHN), 2.25 (2H, m, $CH_2CH=CH_2$), 1.43 (3H, d, *J*=6.6 Hz, Me), 1.01 (3H, d, *J*=6.6 Hz, MeCHNH); δ_C (62.9 MHz; $CDCl_3$) 143.8, 135.4, 128.3, 127.3, 126.2, 117.0, 81.2, 55.4, 38.5, 21.9, 17.5; (minor diastereomer) δ_H (250 MHz; $CDCl_3$) 4.73 (1H, q, *J*=6.6 Hz, OCH), 1.44 (3H, d, *J*=6.6 Hz, Me), 1.09 (3H, d, *J*=6.6 Hz, MeCHNH); δ_C (62.9 MHz; $CDCl_3$) 135.1, 126.2, 117.2, 81.1, 55.6, 38.2, 22.0, 18.0; *m/z* (EI) 206 (MH^+, 4%), 164 (10), 105 (100), 60 (68).

1-Phenyl-N-*(1-phenylethoxy) but-3-enylamine hydrochloride* ***121c.HCl***

To a solution of crude **121c** (1.12 g, 4.2 mmol) in ether (10 mL) was added HCl in ether (1M; 10 mL, 10 mmol). The precipitated gum was filtered and recrystallised (light petroleum-ether) to afford a single diastereomer of the *title compound* (0.47 g, 42%) as colourless crystals, m.p. 133-135°C, (Found: C, 71.23; H, 7.42; N, 4.85. $C_{18}H_{22}NOCl$ requires C, 71.25; H, 7.31; N, 4.62%); υ_{max} (Nujol)/cm^{-1} 2924, 2478, 1579, 1452; δ_H (250 MHz; $CDCl_3$) 11.9 (2H, broad s, NH_2), 7.37 (10H, m, ArH), 5.45 (1H, q, *J*=6.2 Hz, OCH), 5.40 (1H, m, CH=), 4.99 (2H, m, $=CH_2$), 4.20 (1H, dd, *J*=11.2, 4.5 Hz, CHN), 3.11 (1H, m, $CH_2CH=Me$), 2.96 (1H, m, $CH_2CH=CH_2$), 1.56 (3H, d, *J*=6.2 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 138.5, 132.1, 131.5, 129.6, 129.4, 128.9, 128.6, 128.6, 126.9, 119.2, 83.0, 65.4, 34.0, 21.3; *m/z* (EI) 226 (13%), 131 (16), 122 (58), 105 (100), 77 (55), 65 (10), 51 (34), 39 (27).

General Method for Preparation of *O*-(1-Phenylethyl) Ketoxime Ethers



To a round bottomed flask fitted with a nitrogen inlet were added ketone (3.65 mmol), HCl (3 drops) and ethanol (10 mL), the solution was then cooled to 0°C. (±)-*O*-(1-Phenylethyl)hydroxylamine **119** (0.50 g, 3.65 mmol) was then added dropwise. The solution was allowed to warm to room temperature and was stirred for 12 h. The ethanol was removed under reduced pressure and the residue partitioned between water (10 mL) and dichloromethane (10 mL). The mixture was separated and the aqueous portion was washed with dichloromethane (2 x 10 mL). The combined organic extracts were washed with water (20 mL) and dried ($MgSO_4$). Filtration and evaporation gave the *title compound.*

O-*(1-Phenylethyl) valerophenone oxime* ***122a***
(96%, *E:Z* 100:0) as a colourless oil, (Found: MH^+, 282.1858. $C_{19}H_{23}NO$ requires MH, 282.1858); υ_{max} (film)/cm^{-1} 2958, 1451; δ_H (250 MHz; $CDCl_3$) 7.60 (2H, m, ArH), 7.34 (8H, m, ArH), 5.36 (1H, q, *J*=6.6 Hz, OCH), 2.82 (2H, dd, *J*=7.0, 8.4 Hz, CH_2C=N), 1.62 (3H, d, *J*=6.6 Hz, Me), 1.50 (4H, m, $2CH_2$), 0.94 (3H, t, *J*=7.2 Hz $(CH_2)_3Me$); δ_C (62.9 MHz; $CDCl_3$) 158.5, 143.7, 136.9, 128.9, 128.3, 128.2, 127.3, 126.3, 126.3, 81.1, 28.7, 26.4, 22.9, 22.2, 13.9; *m/z* (CI) 282 (MH^+, 100), 162 (37), 122 (18), 105 (18).

1-Phenyl-O-(1-phenylethyl)-1-but-3-enone oxime ***122b***
(89%, *E:Z* 100:0) as a colourless oil, (Found MH^+, 266.1545. $C_{18}H_{19}NO$ requires MH, 266.1545); υ_{max} (film)/cm^{-1} 2978, 1645, 1445; δ_H (250 MHz; $CDCl_3$) 7.59 (2H, m, ArH), 7.34 (8H, m, ArH), 5.91 (1H, m, CH=), 5.38 (1H, q, *J*=6.6 Hz, OCH), 5.12 (2H, m, $=CH_2$) 3.57 (2H, m, CH_2C=N), 1.61 (3H, d, *J*=6.6 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 155.2, 143.6, 146.9, 132.5, 129.0, 128.3, 128.3, 127.3, 126.3, 126.3, 117.0, 81.3, 31.7, 22.2; *m/z* (CI) 266 (MH^+, 100%), 146 (23), 122 (16), 105 (8), 74 (9).

2,2-Dimethyl-O-(1-phenylethyl)-3-heptanone oxime ***122c***
(50%, *E:Z* 100:0) as a colourless oil, (Found: MH^+, 262.2171. $C_{17}H_{27}NO$ requires MH, 262.2171); υ_{max} (film)/cm^{-1} 2965, 1454, 1365; δ_H (250 MHz; $CDCl_3$) 7.35 (5H, m, ArH), 5.21 (1H, q, *J*=6.6 Hz, OCH), 2.60 (2H, m, CH_2C=N), 1.55 (3H, d, *J*=6.6 Hz, Me),

1,55 (2H, m, CH_2), 1.37 (2H, m, CH_2), 1.11 (9H, s, CMe_3), 0.98 (3H, t, *J*=7.2 Hz $(CH_2)_3Me$); δ_C (62.9 MHz; $CDCl_3$) 166.5, 144.2, 128.0, 126.7, 126.1, 80.0, 37.5, 28.9, 27.8, 26.1, 23.5, 22.1, 13.8; *m/z* (CI) 262 (MH^+, 100%), 248 (9), 142 (20), 122 (17), 105 (23).

2,2-Dimethyl-O-(1-phenylethyl)-3-hex-5-enone oxime ***122d***

(97%, *E:Z* 100:0) as a colourless oil, b.p. 120°C/2 mbar, (Found: MH^+, 246.1858. $C_{16}H_{23}NO$ requires MH, 246.1858); υ_{max} (film)/cm^{-1} 2971, 1648, 1454, 1363; δ_H (250 MHz; $CDCl_3$) 7.27 (5H, m, ArH), 5.92 (1H, m, CH=), 5.17 (1H, q, *J*=6.6 Hz, OCH), 5.03 (2H, m, $=CH_2$), 3.09 (2H, m, $CH_2C=N$), 1.52 (3H, d, *J*=6.6 Hz, Me), 1.07 (9H, s, CMe_3); δ_C (62.9 MHz; $CDCl_3$) 163.2, 143.8, 133.7, 128.0, 127.0, 126.2, 116.1, 80.2, 37.6, 31.0, 27.9, 22.0; *m/z* (CI) 246 (MH^+, 100%), 105 (6).

2-Methyl-O-(1-phenylethyl)-3-heptanone oxime ***122e***

(99%, *E:Z* 76:24) as a colourless oil, (Found: MH^+, 248.2014. $C_{16}H_{25}NO$ requires MH, 248.2014); υ_{max} (film)/cm^{-1} 2964, 1467, 1365, 1084; (*E*-isomer) δ_H (250 MHz; $CDCl_3$) 7.24 (5H, m, ArH), 5.13 (1H, q, *J*=6.6 Hz, OCH), 2.41 (1H, septet, *J*=6.9 Hz, $CHMe_2$), 2.25 (2H, m, $CH_2C=N$), 1.47 (3H, d, *J*=6.6 Hz, Me), 1.37 (4H, m, $2CH_2$), 1.01 (3H, d, *J*=6.9 Hz, CHMeMe), 1.00 (3H, d, *J*=6.9 Hz, CHMeMe), 0.85 (3H, t, *J*=7.2 Hz $(CH_2)_3Me$); δ_C (62.9 MHz; $CDCl_3$) 165.1, 144.0, 128.0, 127.0, 126.1, 80.0, 33.6, 28.5, 26.7, 23.2, 22.2, 20.2, 13.8; (*Z*-isomer) δ_H (250 MHz; $CDCl_3$) 3.30 (1H, septet, *J*=6.9 Hz, $CHMe_2$), 2.07 (2H, m, $CH_2C=N$), 1.07 (3H, d, *J*=6.9 Hz, CHMeMe), 1.06 (3H, d, *J*=6.9 Hz, CHMeMe); δ_C (62.9 MHz; $CDCl_3$) 164.7, 30.3, 29.0, 27.4, 22.5, 19.1, 19.0; *m/z* (CI) 248 (MH^+, 100%), 128 (29), 122 (12), 105 (20).

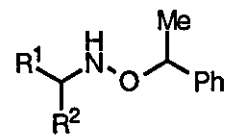
2-Methyl-O-(1-phenylethyl)-3-hex-5-enone oxime ***122f***

(79%, *E:Z* 79:21) as a colourless oil (Found: MH^+, 232.1701. $C_{16}H_{23}NO$ requires MH, 232.1701); υ_{max} (film)/cm^{-1} 2957, 1622, 1443; (*E*-isomer) δ_H (250 MHz; $CDCl_3$) 7.27 (5H, m, ArH), 5.88 (1H, m, CH=), 5.19 (1H, q, *J*=6.6 Hz, OCH), 5.07 (2H, m, $=CH_2$), 3.08 (2H, m, $CH_2C=N$), 2.48 (1H, septet, *J*=6.9 Hz, $CHMe_2$), 1.51 (3H, d, *J*=6.6 Hz, Me), 1.05 (3H, d, *J*=6.9 Hz, CHMeMe), 1.04 (3H, d, *J*=6.9 Hz, CHMeMe); δ_C (62.9 MHz; $CDCl_3$) 161.9, 134.9, 133.0, 128.1, 127.0, 126.1, 116.6, 80.2, 33.6, 31.8, 22.2, 20.1, 20.1; (*Z*-isomer) δ_H (250 MHz; $CDCl_3$) 3.36 (1H, septet, *J*=6.9 Hz, $CHMe_2$), 2.89 (2H, m, $CH_2C=N$), 1.09 (3H, d, *J*=6.9 Hz, CHMeMe), 1.07 (3H, d, *J*=6.9 Hz, CHMeMe); δ_C (62.9 MHz; $CDCl_3$) 128.1, 127.1, 126.2, 35.3, 27.6, 19.0, 19.0; *m/z* (CI) 232 (MH^+, 62%), 105 (100), 77 (4).

O-(1-Phenylethyl)-2-hexanone oxime ***122g***

(85%, *E:Z* 60:40) as a colourless oil, (Found: MH^+, 220.1701. $C_{14}H_{21}NO$ requires MH, 220.1701); υ_{max} (film)/cm^{-1} 2959, 1453; (*E*-isomer) δ_H (250 MHz; $CDCl_3$) 7.29 (5H, m, ArH), 5.21 (1H, q, *J*=6.6 Hz, OCH), 2.14 (2H, m, CH_2C=N), 1.90 (3H, s, MeC=N), 1.53 (3H, d, *J*=6.6 Hz, Me), 1.32 (4H, m, $2CH_2$), 0.88 (3H, t, *J*=7.2 Hz $(CH_2)_3Me$); δ_C (62.9 MHz; $CDCl_3$) 157.8, 144.3, 128.1, 127.1, 126.0, 80.0, 35.5, 28.6, 22.4, 22.2, 14.1, 13.8; (*Z*-isomer) δ_H (250 MHz; $CDCl_3$) 5.22 (1H, q, *J*=6.6 Hz, OCH), 2.42 (2H, m, CH_2C=N), 1.85 (3H, s, MeC=N), 1.54 (3H, d, *J*=6.6 Hz, Me), 1.45 (4H, m, $2CH_2$), 0.99 (3H, t, *J*=7.2 Hz $(CH_2)_3Me$); δ_C (62.9 MHz; $CDCl_3$) 158.3, 144.1, 127.0, 126.0, 80.0, 29.1, 27.8, 22.7, 22.4, 19.9, 13.9; *m/z* (CI) 220 (MH^+, 100%), 122 (12), 116 (8), 105 (19), 100 (39).

General Method for Reduction of *O*-(1-Phenylethyl) Ketoximes



To a dry round bottomed flask and pressure equalising dropping funnel were added ketoxime ether **122** (1 mmol), methanol (15 mL), bromocresol green (5 drops) and sodium cyanoborohydride (1.5 mmol). Methanolic HCl was added *via* the dropping funnel to keep the solution acidic. The reaction mixture was stirred at room temperature for 2 h and was monitored by TLC. If the starting material had not been consumed then more reducing agent (1.5 mmol) was added. The reaction was quenched with water (1 mL) and the solvent removed *in vacuo*. The residue was partitioned between water (10 mL) and dichloromethane (10 mL) and the layers separated. The aqueous portion was washed with dichloromethane (2 x 10 mL) and the combined organic extracts were washed with water (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude mixture was purified by column chromatography on silica gel with dichloromethane-light petroleum (1:2) as eluent to furnish the *title compound.*

1-Phenyl-N-*(1-phenylethoxy)-1-pentylamine* ***121a***

Obtained from the reduction of the ketoxime ether **122a** (53%, d.e. 19%) as a colourless oil with identical spectroscopic properties as the alkoxyamine **121a** prepared by the addition of *n*-butyllithium to the aldoxime **116a.**

2,2-Dimethyl-N-*(1-phenylethoxy)-3-heptylamine* ***121e***

Obtained from the reduction of ketoxime ether **122c** (65%, d.e. ~10%) as a colourless oil with identical spectroscopic properties as the alkoxyamine **121e** prepared by the addition of *n*-butyllithium to the aldoxime **116b.**

2-Methyl-N-*(1-phenylethoxy)-3-heptylamine* ***121g***

Obtained from the reduction of ketoxime ether **122e** (56%, d.e. ~10%) as a colourless oil with identical spectroscopic properties as the alkoxyamine **121g** prepared by the addition of *n*-butyllithium to the aldoxime **116c.**

N-*(1-Phenylethoxy)-2-hexylamine* ***121i***

Obtained from the reduction of the ketoxime ether **122g** (95%, d.e. ~5%) as a colourless oil with identical spectroscopic properties as the alkoxyamine **121i** prepared by the addition of *n*-butyllithium to the aldoxime **116d.**

1-Phenyl-N-*(1-phenylethoxy) but-3-enylamine****121c***

Obtained from the reduction of ketoxime ether **122b** (45%, d.e. 12%) as a colourless oil with identical spectroscopic properties as the alkoxyamine **121c** prepared by the addition of allylmagnesium bromide to the aldoxime **116a.**

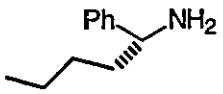
2,2-Dimethyl-N-*(1-phenylethoxy)-3-hex-5-enylamine* ***121f***

Obtained from the reduction of ketoxime ether **122d** (65%, d.e. <5%) as a colourless oil with identical spectroscopic properties as the alkoxyamine **121f** prepared by the addition of allylmagnesium bromide to the aldoxime **116b.**

2-Methyl-N-*(1-phenylethoxy)-3-hex-5-enylamine* ***121h***

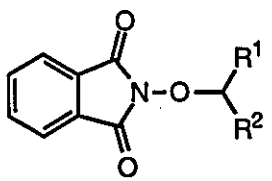
Obtained from the reduction of ketoxime ether **122f** (53%, d.e. <5%) as a colourless oil with identical spectroscopic properties as the alkoxyamine **121h** prepared by the addition of allylmagnesium bromide to the aldoxime **116c.**

1-Phenyl butylamine **(R)-(+)-*123***



Zinc powder (3.86 g, 59 mmol) was added to a solution of the alkoxyamine **121a** (0.84 g, 2.96 mmol) in acetic acid (8 mL) and water (7 mL). The solution was placed in a sonic bath for 2 h at 40°C. The mixture was extracted with ether (2 x 20 mL), the aqueous phase was basified (pH >13) with saturated sodium carbonate solution and extracted with dichloromethane (3 x 30 mL). The dichloromethane was dried (K_2CO_3), filtered and evaporated to furnish the title compound **(R)-(+)-123** (0.4 g, 84%, 68% e.e.) as a colourless oil, $[\alpha]_D$ +8.7° (*c*=20.15, $CDCl_3$) (lit.,[74,75] $[\alpha]_D$ +14.1° (neat) for material with 85% e.e.; $[\alpha]_D$= +11.7° (*c*=1, $CHCl_3$) for material with 92% e.e.). In order to recover the chiral alcohol, the ether extracts were washed, dried, and evaporated to give the crude 1-phenylethyl alcohol (87%), $[\alpha]_D$ = +42° (*c*=0.83, MeOH).

General Procedure for *N*-(Alkoxy)phthalimides



Diethyl azodicarboxylate (6.4 mL, 40.4 mmol) was added to a solution of *N*-hydroxyphthalimide (6 g, 37 mmol), triphenylphosphine (9.63 g, 37 mmol) and the substituted benzyl alcohol (18.5 mmol) in THF (200 mL) at 0°C. The resulting solution was warmed to 50°C and stirred for 3 days. The solution was evaporated and ether (200 mL) and saturated sodium carbonate solution (200 mL) were added and the layers separated. The ether layer was washed with further portions of sodium carbonate solution (2 x 100 mL) which were combined and back extracted with ether (2 x 100 mL). The combined ether portions were evaporated and the residue purified by column chromatography on silica gel with ether-light petroleum as eluent to furnish the *title compound.*

N-(*1-Phenylpropoxy)phthalimide* ***128a***

Obtained from the Mitsunobu reaction of 1-phenylpropanol with *N*-hydroxyphthalimide (65%) as a crystalline solid, m.p. 110-111°C; (Found: M+,

281.1052. $C_{17}H_{15}NO_3$ requires M, 281.1052); υ_{max} (Nujol)/cm^{-1} 2925, 1787, 1731, 1465, 1455, 703; δ_H (250 MHz; $CDCl_3$) 7.67 (4H, m, ArH), 7.46 (2H, m, ArH), 7.32 (3H, m, ArH), 5.26 (1H, t, *J*=6.9 Hz, OCH), 2.21 (1H, m, $\underline{CH_2}CH_3$), 1.96 (1H, m, $\underline{CH_2}CH_3$), 0.97 (3H, t, *J*=7.4 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 163.8, 137.9, 134.1, 128.8, 128.8, 128.2, 128.0, 123.2, 90.5, 77.5, 77.0, 76.5, 27.7, 10.0; *m/z* (EI) 282 (MH^+, 21%), 254 (10%), 164 (33%), 119 (100%), 91 (95%), 77 (27%).

(S)-(-)-N-(*1-Phenylbutoxy)phthalimide* ***128b***

Obtained from the Mitsunobu reaction of (R)-(+)-1-phenylbutanol with *N*-hydroxyphthalimide, (81%, >96% e.e., (-)-TFAE NMR) as a crystalline solid, m.p. 80-81°C; (Found: M^+, 295.1211. $C_{18}H_{17}NO_3$ requires M, 295.1208); $[\alpha]_D$ -185.1° (*c*=2, CH_2Cl_2); υ_{max} (Nujol)/cm^{-1} 2922, 1789, 1727, 698; δ_H (250 MHz; $CDCl_3$) 7.70 (4H, m, ArH), 7.45 (2H, m, ArH), 7.29 (3H, m, ArH), 5.34 (1H, t, *J*=7.0 Hz, OCH), 2.16 (1H, m, CH_2), 1.91 (1H, m, CH_2), 1.47 (2H, m, CH_2), 0.97 (3H, t, *J*=7.4 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 163.8, 137.9, 134.1, 128.8, 128.8, 128.2, 128.0, 123.2, 89.0, 36.8, 18.9, 13.8; *m/z* (EI) 163 (3%), 133 (52%), 117 (8%), 104 (9%), 91 (100%), 76 (11%).

N-(*2-Methyl-1-phenylpropoxy)phthalimide* ***128c***

Obtained from the Mitsunobu reaction of 2-methyl-1-phenylpropanol with *N*-hydroxyphthalimide, (32%) as a crystalline solid, m.p. 120-122°C; (Found: MH^+, 296.1287. $C_{18}H_{17}NO_3$ requires MH, 296.1287); υ_{max} (Nujol)/cm^{-1} 2959, 1786, 1729, 1465, 703; δ_H (250 MHz; $CDCl_3$) 7.66 (4H, m, ArH), 7.41 (2H, m, ArH), 7.30 (3H, m, ArH), 5.04 (1H, d, *J*=8.6 Hz, OCH), 2.32 (1H, sept *J*=6.7 Hz, $CH_3\underline{CH}CH_3$), 1.28 (3H, d, *J*=6.6 Hz, CH_3), 0.79 (3H, d, *J*=6.6 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 164.0, 137.7, 134.5, 129.3, 129.1, 129.0, 128.3, 123.6, 94.8, 33.4, 19.9, 19.4; *m/z* (EI) 133 (13%), 104 (40%), 91 (100%), 76 (38%), 41 (25%).

N-(*1-Phenylpentoxy)phthalimide* ***128d***

Obtained from the Mitsunobu reaction of 1-phenylpentanol with *N*-hydroxyphthalimide, (36%) as a crystalline solid, m.p. 72-75°C; (Found: M^+, 309.1351. $C_{19}H_{19}NO_3$ requires M, 309.1365); υ_{max} (Nujol)/cm^{-1} 2923, 1790, 1731, 696; δ_H (250 MHz; $CDCl_3$) 7.67 (4H, m, ArH), 7.46 (2H, m, ArH), 7.31 (3H, m, ArH), 5.33 (1H, t, *J*=7.1 Hz, OCH), 2.18 (1H, m, $\underline{CH_2}(C_3H_7)$, 1.91 (1H, m, $\underline{CH_2}(C_3H_7)$, 1.41 (4H, m, $2CH_2$), 0.89 (3H, t, *J*=6.7 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 164.0, 138.2, 134.1, 128.8, 128.8, 128.2, 128.0, 123.2, 89.2, 34.4, 27.7, 22.4, 13.9; *m/z* (EI) 310 (9%), 254 (11%), 164 (20%), 147 (97%), 117 (31%), 104 (43%), 91 (100%), 76 (29%).

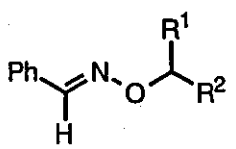
N-(*1-(1-Naphthylethoxy)phthalimide* ***126***

Obtained from the Mitsunobu reaction of 1-(1-naphthyl)ethanol with *N*-hydroxyphthalimide, (65%) as a crystalline solid, m.p. 118-120°C; (Found: M^+, 317.1052. $C_{20}H_{15}NO_3$ requires M, 317.1052); υ_{max} (Nujol)/cm^{-1} 2924, 1790, 1737, 702; δ_H (250 MHz; $CDCl_3$) 8.40 (1H, d, *J*=9.1 Hz, ArH), 7.86-7.86 (10H, m, ArH), 6.36 (1H, q, *J*=6.5 Hz, OCH), 1.85 (3H, d, *J*=6.5 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 164.2, 135.2, 134.3, 133.9, 131.7, 129.2, 128.9, 128.7, 126.4, 125.6, 125.3, 124.9, 123.3, 81.4, 20.2; *m/z* (EI) 317 (5%), 155 (100%), 127 (13%), 76 (14%).

N-(*2-Butoxy)phthalimide* ***128e***

Obtained from the Mitsunobu reaction of 2-butanol with *N*-hydroxyphthalimide, (95%) as a crystalline solid, m.p. 48-50°C; (Found: M^+, 219.0895. $C_{12}H_{13}NO_3$ requires M, 219.0895); υ_{max} (Nujol)/cm^{-1} 2923, 1785, 1739, 1465; δ_H (250 MHz; $CDCl_3$) 7.80 (4H, m, ArH), 4.32 (1H, m, OCH), 1.78 (1H, m, $\underline{CH_2}CH_3$), 1.63 (1H, m, $\underline{CH_2}CH_3$), 1.33 (3H, d, *J*=6.2 Hz, CH_3), 1.02 (3H, t, *J*=7.5 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 165.6, 135.4, 130.3, 124.7, 86.9, 29.0, 19.5, 10.8; *m/z* (EI) 220 (MH^+, 10%), 163 (100%), 146 (10%), 133 (24%), 104 (38%), 90 (22%), 76 (36%).

General Method for the Preparation *O*-Alkoxy Oxime Ethers



N-(Alkoxy)phthalimide (3.31 mmol) and ethanol (10 mL) were added to a round bottomed flask and the suspension heated until the phthalimide dissolves. Hydrazine hydrate (0.18 mL, 3.64 mmol) was added at this elevated temperature and the solution was allowed to cool to room temperature. Benzaldehyde (0.37 g, 3.5 mmol) was added and the mixture stirred overnight. The solvent was evaporated, carbon tetrachloride (30 mL) and magnesium sulfate were added to the residue. The resulting suspension was filtered and the filtrate evaporated, column chromatography of the residue on silica gel (dichloromethane-light petroleum 1:2) furnished the *title compound.*

O-*(1-Phenylpropyl) benzaldoxime* ***129a***

Obtained from the cleavage of *N*-(1-phenylpropoxy)phthalimide and subsequent condensation of the hydroxylamine with benzaldehyde (87%) as a colourless oil, (Found: M^+, 239.1309. $C_{16}H_{17}NO$ requires M, 239.1310); υ_{max} (film)/cm^{-1} 2968, 2935, 1494, 1448; δ_H (250 MHz; $CDCl_3$) 8.15 (1H, s, HC=N), 7.54 (2H, m, ArH), 7.33 (8H, m, ArH), 5.12 (1H, t, *J*=6.8 Hz, HCO), 2.04 (1H, m, CH_2), 1.90 (1H, m, CH_2), 0.96 (3H, t, *J*=7.4 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 148.6, 142.0, 132.5, 129.6, 128.8, 128.6, 128.2, 127.6, 127.2, 127.0, 86.9, 29.0, 10.0; *m/z* (EI) 239 (12%), 119 (100%), 91 (95%), 77 (44%), 65 (15%).

O-*(1-Phenylbutoxy) benzaldoxime* ***129b***

Obtained from the cleavage of *N*-(1-phenylbutoxy)phthalimide and subsequent condensation of the hydroxylamine with benzaldehyde, (91%) as a colourless oil, (Found: M^+, 253.1470. $C_{17}H_{19}NO$ requires M, 253.1467); υ_{max} (film)/cm^{-1} 2959, 2933, 1493, 1448; δ_H (250 MHz; $CDCl_3$) 8.17 (1H, s, HC=N), 7.56 (2H, m, ArH), 7.36 (8H, m, ArH), 5.23 (1H, t, *J*=6.8 Hz, HCO), 2.03 (1H, m, CH_2), 1.82 (1H, m, CH_2), 1.48 (2H, m, CH_2), 0.99 (3H, t, *J*=7.3 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 148.5, 142.4, 132.5, 129.6, 128.7, 128.2, 127.4, 127.0, 126.8, 85.5, 38.3, 18.9, 14.0; *m/z* (EI) 253 (7%), 212 (5%), 133 (92%), 117 (7%), 104 (22%), 91 (100%), 77 (35%).

O-*(2-Methyl-1-phenylpropoxy) benzaldoxime* ***129c***

Obtained from the cleavage of *N*-(2-methyl-1-phenylpropoxy)phthalimide and subsequent condensation of the hydroxylamine with benzaldehyde, (91%) as a colourless oil, (Found: M^+, 253.1465. $C_{17}H_{19}NO$ requires M, 253.1467); υ_{max} (film)/cm^{-1} 2961, 1493, 1448; δ_H (250 MHz; $CDCl_3$) 8.16 (1H, s, HC=N), 7.52 (2H, m, ArH), 7.32 (3H, m, ArH), 4.92 (1H, t, *J*=7.1 Hz, HCO), 2.19 (3H, sept, *J*=6.8 Hz, $CH(Me)_2$), 1.06 (3H, d, *J*=6.8 Hz, Me), 0.86 (3H, d, *J*=6.8, Me); δ_C (62.9 MHz; $CDCl_3$) 148.4, 141.3, 132.5, 129.5, 128.5, 128.3, 127.7, 127.4, 127.0, 90.8, 33.3, 18.8, 18.8; *m/z* (EI) 253 (5%), 133 (100%), 117 (12%), 104 (51%), 91 (87%), 77 (44%).

O-*(1-Phenylpentoxy) benzaldoxime* ***129d***

Obtained from the cleavage of *N*-(1-phenylpentoxy)phthalimide and subsequent condensation of the hydroxylamine with benzaldehyde, (93%) as a colourless oil, (Found: M^+, 267.1623. $C_{18}H_{21}NO$ requires M, 267.1623); υ_{max} (film)/cm^{-1} 2956, 2933, 1493, 1448; δ_H (250 MHz; $CDCl_3$) 8.22 (1H, s, HC=N), 7.60 (2H, m, ArH), 7.41 (3H, m, ArH), 5.27 (1H, t, *J*=6.8 Hz, HCO), 2.11 (1H, m, CH_2), 1.92 (1H, m, CH_2), 1.49

(4H, m, $2CH_2$), 0.99 (3H, t, *J*=6.9 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 148.5, 142.5, 132.6, 129.6, 128.5, 128.2, 127.4, 127.0, 126.6, 85.7, 35.9, 27.6, 22.7, 14.0; *m/z* (EI) 267 (4%), 147 (62%), 104 (14%), 91 (100%), 77 (22%), 69 (47%).

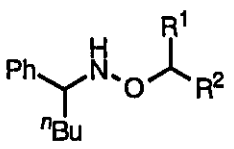
O-*(1-(1-Naphthylethoxy) benzaldoxime* ***125***

Obtained from the cleavage of *N*-(1-(1-naphthylethoxy)phthalimide and subsequent condensation of the hydroxylamine with benzaldehyde, (76%) as a colourless oil, (Found: M^+, 275.1307. $C_{19}H_{17}NO$ requires M, 275.1310); υ_{max} (film)/cm^{-1} 2979, 1597, 1511, 1447; δ_H (250 MHz; $CDCl_3$) 8.26 (1H, s, CH=N), 8.24 (1H, d, *J*=6.6 Hz, ArH), 7.94 (1H, d, *J*=6.6 Hz, ArH), 7.85 (1H, d, *J*=6.6 Hz, ArH), 7.61 (6H, m, ArH), 7.35 (3H, m, ArH), 6.19 (1H, q, *J*=6.6 Hz, OCH), 1.86 (3H, d, *J*=6.6 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 148.8, 138.5, 134.2, 132.2, 130.8, 129.7, 128.8, 128.6, 128.0, 127.0, 126.0, 125.4, 125.4, 123.6, 123.6, 78.5, 21.2; *m/z* (EI) 275 (5%), 155 (100%), 141 (7%), 128 (7%), 115 (4%), 103 (5%), 77 (8%).

O-*(2-Butoxy) benzaldoxime* ***129e***

Obtained from the cleavage of *N*-(2-butoxy)phthalimide and subsequent condensation of the hydroxylamine with benzaldehyde, (90%) as a colourless oil, (Found: M^+, 177.1154. $C_{11}H_{15}NO$ requires M, 177.1154); υ_{max} (film)/cm^{-1} 2970, 1447, 1374, 1333; δ_H (250 MHz; $CDCl_3$) 8.12 (1H, s, HC=N), 7.62 (2H, m, ArH), 7.40 (3H, m, ArH), 4.30 (1H, m, HCO), 1.78 (1H, m, CH_2), 1.64 (1H, m, CH_2), 1.34 (3H, d, *J*=6.4 Hz, Me), 1.02 (3H, t, *J*=7.5 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 147.7, 132.8, 129.4, 128.6, 126.8, 80.7, 28.4, 19.2, 9.7; *m/z* (EI) 177 (44%), 121 (100%), 104 (68%), 77 (77%), 57 (78%).

General Method for the Addition of *n*-Butyllithium to *O*-(Alkyl) Aldoximes



To a round bottomed flask fitted with a nitrogen inlet was added O-*(Alkyl) benzaldoxime* (1 mmol) and toluene (5 mL). The resulting solution was cooled to -78°C and boron trifluoride etherate (0.37 mL, 3 mmol) was added, the solution was stirred for 15 min. *n*-Butyllithium (1.6 M, 1.9 mL, 3 mmol) was added dropwise over 15 min. After addition the solution was stirred at -78°C for 1 h. The reaction mixture was quenched at -78°C by the addition of water (1 mL), and then allowed to warm to room

temperature. The solvent was removed under reduced pressure and the residue partitioned between dichloromethane (20 mL) and water (20 mL). The layers were separated and the aqueous layer was washed with further portions of dichloromethane (2 x 20 mL). The combined organic extracts were washed with brine and then dried ($MgSO_4$), filtered and evaporated. Column chromatography of the residue on silica gel (dichloromethane-light petroleum 1:2) furnished the *title compound.*

1-Phenyl-N-*(1-phenylpropoxy)-1-pentylamine* ***130a***

Obtained by the addition of *n*-butyllithium to oxime ether **129a** (91%, 93% d.e.) as a colourless oil, (Found: M^+, 297.2095. $C_{20}H_{27}NO$ requires M, 297.2093); υ_{max} (film)/cm^{-1} 2959, 2933, 1494, 1454, 699; δ_H (250 MHz; $CDCl_3$) 7.22 (10H, m, ArH), 5.25 (1H, br s, NH), 4.45 (1H, t, *J*=6.8 Hz, OCH), 3.93 (1H, dd, *J*=5.1, 8.8 Hz, NCH), 1.86 (2H, m, CH_2), 1.63 (2H, m, CH_2), 1.24 (4H, m, $2CH_2$), 0.87 (3H, t, *J*=7.5 Hz, Me), 0.84 (3H, t, *J*=7.2 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 142.9, 141.6, 128.1, 127.7, 127.2, 127.2, 126.7, 86.8, 65.7, 33.4, 29.0, 28.2, 22.7, 13.9, 10.4; *m/z* (EI) 298 (MH^+, 9%), 179 (40%), 147 (22%), 119 (71%), 91 (100%), 77 (16%).

1-Phenyl-N-*(1-phenylbutoxy)-1-pentylamine* ***130b***

Obtained by the addition of *n*-butyllithium to oxime ether **129b** (87%, 90% d.e.) as a colourless oil, (Found: M^+, 311.2249. $C_{21}H_{29}NO$ requires M, 311.2249); υ_{max} (film)/cm^{-1} 2957, 2932, 1494, 1455, 699; δ_H (250 MHz; $CDCl_3$) major diastereomer 7.29 (10H, m, ArH), 5.33 (1H, br s, NH), 4.57 (1H, t, *J*=7.3 Hz, OCH), 3.95 (1H, dd, *J*=5.1, 8.8 Hz, NCH), 2.00-1.16 (10H, m, CH_2), 0.92 (3H, t, *J*=7.3 Hz, Me), 0.90 (3H, t, *J*=7.3 Hz, Me), minor diastereomer 4.35 (1H, dd, *J*=5.1, 8.8 Hz, NCH); δ_C (62.9 MHz; $CDCl_3$) 143.4, 141.7, 128.1, 127.7, 127.2, 127.2, 126.6, 85.1, 65.7, 38.4, 33.4, 28.2, 22.7, 19.1, 14.0, 13.9; *m/z* (EI) 179 (23%), 147 (15%), 133 (31%), 104 (12%), 91 (100%), 77 (12%).

1-Phenyl-N-*(2-methyl-1-phenylpropoxy)-1-pentylamine* **130c**

Obtained by the addition of *n*-butyllithium to oxime ether **129c** (74%, 95% d.e.) as a colourless oil, (Found: M^+, 311.2247. $C_{21}H_{29}NO$ requires M, 311.2249); υ_{max} (film)/cm^{-1} 2957, 2931, 1494, 1455, 700; δ_H (250 MHz; $CDCl_3$) 7.23 (10H, m, ArH), 5.20 (1H, br s, NH), 4.25 (1H, d, *J*=7.8 Hz, OCH), 3.93 (1H, dd, *J*=5.0, 8.8 Hz, NCH), 1.94-1.02 (7H, m, $3CH_2$ and Me_2CH), 1.01 (3H, d, *J*=6.7 Hz, Me), 0.84 (3H, t, *J*=6.9 Hz, Me), 0.70 (3H, d, *J*=6.8 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 141.8, 141.6, 128.1, 127.7,

127.3, 127.2, 127.0, 90.7, 65.5, 33.5, 33.3, 28.2, 22.7, 19.3, 19.1, 13.9; *m/z* (EI) 179 (23%), 147 (20%), 133 (60%), 91 (100%), 77 (19%).

1-Phenyl-N-*(1-phenylpentoxy)-1-pentylamine* ***130d***

Obtained by the addition of *n*-butyllithium to oxime ether **129d** (80%, 90% d.e.) as a colourless oil, (Found: M^+, 325.2407. $C_{22}H_{31}NO$ requires M, 325.2406); υ_{max} (film)/cm^{-1} 2956, 2931, 1494, 1455, 699; δ_H (400 MHz; $CDCl_3$) major diastereomer 7.15 (10H, m, ArH), 5.25 (1H, br s, NH), 4.45 (1H, t, *J*=7.3 Hz, OCH), 3.84 (1H, dd, *J*=5.1, 8.8 Hz, NCH),1.84 (1H, m, CH_2), 1.71 (1H, m, CH_2), 1.50 (2H, m, CH_2), 1.19 (8H, m, $4CH_2$), 0.78 (3H, t, *J*=7.3 Hz, Me), 0.77 (3H, t, *J*=7.3 Hz, Me), minor diastereomer 4.30 (1H, dd, *J*=5.1, 8.8 Hz, NCH); δ_C (100 MHz; $CDCl_3$) major diastereomer 143.4, 142.1, 128.6, 128.2, 127.6, 127.1, 85.8, 66.2, 36.4, 33.9, 28.7, 28.5, 23.1, 23.1, 14.3, minor diastereomer 86.0, 66.3, 36.6, 34.0; *m/z* (EI) 179 (47%), 147 (70%), 122 (55%), 104 (52%), 91 (100%).

1-Phenyl-N-*(1-(1-naphthylethoxy)-1-pentylamine* ***127***

Obtained by the addition of *n*-butyllithium to oxime ether **125** (80%, 55% d.e.) as a colourless oil, (Found: M^+, 333.2094. $C_{23}H_{27}NO$ requires M, 333.2093); υ_{max} (film)/cm^{-1} 2956, 2930, 1454, 778; δ_H (250 MHz; $CDCl_3$) major diastereomer 7.83 (1H, d, *J*=7.4 Hz, ArH), 7.74 (1H, d, *J*=7.4 Hz, ArH), 7.64 (1H, d, *J*=7.4 Hz, ArH), 7.33 (4H, m, ArH), 7.18 (5H, m, ArH), 5.46 (1H, br s, NH), 5.36 (1H, q, *J*=6.5 Hz, OCH), 3.91 (1H, dd, *J*=6.0, 8.4 Hz, NCH), 1.83 (1H, m, CH_2), 1.56 (3H, d, *J*=6.6 Hz, Me), 1.52 (1H, m, CH_2), 1.17 (4H, m, $2CH_2$), 0.78 (3H, t, *J*=7.4 Hz, Me), minor diastereomer 7.98 (1H, d, *J*=7.4 Hz, ArH), 7.78 (1H, d, *J*=7.4 Hz, ArH), 7.67 (1H, d, *J*=7.4 Hz, ArH), 5.16 (1H, q, *J*=6.5 Hz, OCH), 3.89 (1H, dd, *J*=6.0, 8.4 Hz, NCH), 1.25 (3H, d, *J*=6.6 Hz, Me), 0.77 (3H, t, *J*=7.4 Hz, Me); δ_C (100 MHz; $CDCl_3$) major diastereomer 141.6, 138.9, 133.5, 130.6, 128.3, 127.9, 127.8, 127.4, 127.0, 125.4, 125.0, 125.0, 123.2, 122.8, 77.9, 65.6, 33.4, 28.0, 22.4, 20.8, 13.5, minor diastereomer 142.0, 139.5, 133.7, 130.9, 78.4, 65.7, 33.1, 28.7, 22.3, 21.2, 13.6; *m/z* (EI) 334 (MH^+, 10%), 155 (100%), 128 (13%), 104 (14%), 91 (33%), 77 (9%).

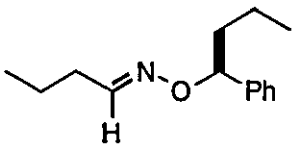
1-Phenyl-N-*(2-butoxy)-1-pentylamine* ***130e***

Obtained by the addition of *n*-butyllithium to oxime ether **129e** (70%, 10% d.e.) as a colourless oil, (Found: M^+, 235.1936. $C_{21}H_{29}NO$ requires M, 235.1936); υ_{max} (film)/cm^{-1} 2961, 2931, 1455, 1371, 699; δ_H (250 MHz; $CDCl_3$) major diastereomer 7.18 (5H, m, ArH), 5.29 (1H, br s, NH), 3.84 (1H, dd, *J*=5.1, 10.4 Hz, NCH), 3.42 (1H,

m, OCH), 1.77-1.03 (8H, m, $4CH_2$), 0.90 (3H, d, *J*=6.2 Hz), 0.80 (3H, t, *J*=7.3 Hz, Me), 0.78 (3H, t, *J*=7.3 Hz, Me), minor diastereomer 3.82 (1H, dd, *J*=5.1, 10.4 Hz, NCH), 3.40 (1H, m, HCO), 1.02 (3H, d, *J*=6.2 Hz), 0.79 (3H, t, Me), 0.59 (3H, t, *J*=7.4 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) major diastereomer 142.1, 80.2, 66.0, 33.3, 28.3, 28.0, 22.7, 18.5, 13.9, 9.8, minor diastereomer 142.2, 80.1, 33.5, 28.0, 18.7, 9.5; *m/z* (EI) 235 (10%), 178 (35%), 147 (38%), 122 (100%), 104 (14%), 91 (85%), 77 (10%).

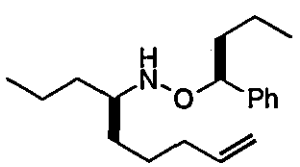
5.3. Experimental Details for Chapter Three

(S)-(-)-O-*(1-Phenylbutoxy) butyraldoxime* ***145***



Obtained from the cleavage of (S)-(-)-*N*-(1-phenylbutoxy)phthalimide **(S)-128b** and subsequent condensation of the hydroxylamine with butyraldehyde, (66%) as a colourless oil, (found: M^+, 219.1626. $C_{14}H_{21}NO$ requires M, 219.1623); $[\alpha]_D$ -4.6° (*c*=0.78, CH_2Cl_2); υ_{max} (film)/cm^{-1} 2959, 2934, 1454, 933; δ_H (250 MHz; $CDCl_3$) 7.42 (1H, t, *J*=6.2 Hz, HC=N), 7.31 (5H, m, ArH), 5.02 (1H, t, *J*=6.8 Hz, HCO), 2.10 (2H, dt, *J*=7.0, 14.2 Hz, CH_2), 1.90 (1H, m, CH_2), 1.70 (1H, m, CH_2), 1.40 (4H, m, $2CH_2$), 0.91 (3H, t, *J*=7.3 Hz, Me), 0.87 (3H, t, *J*=7.4 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 151.0, 142.9, 128.1, 127.1, 126.6, 84.4, 38.4, 31.3, 20.1, 18.8, 13.9, 13.4; *m/z* (EI) 220 (MH^+, 100%), 178 (74%), 133 (96%), 91 (94%), 43 (36%).

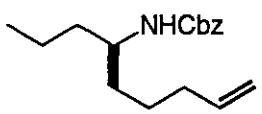
(6R, 1'S)-(-)-N-*(1-Phenylbutoxy)-6-non-1-enylamine* ***146***



To a round bottomed flask fitted with a nitrogen inlet and a condenser was added magnesium (1.22 g, 50 mmol), dry ether (25 mL) and a crystal of iodine. 5-Bromopent-1-ene (5.9 mL, 50 mmol) was added to the mixture and the ether began to boil as the Grignard reagent formed. The bromide was added at such a rate that the ether continued to reflux. When addition of the bromide was complete the Grignard solution was allowed to cool to room temperature. To a separate round bottomed flask fitted with nitrogen inlet was added the oxime ether **145** (2.62 g, 12 mmol) and dry toluene (40 mL). The resulting solution was cooled to -92°C and boron trifluoride etherate (4.43 mL, 36 mmol) was added, the solution was stirred for 15 min. The Grignard reagent (2M, 18 mL, 36 mmol) was added dropwise to the cooled toluene solution over 30 min. After addition the solution was stirred for 30 min at -92°C followed by the addition of water (1 mL). The mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. The residue was

partitioned between dichloromethane (50 mL) and water (50 mL). The layers were separated and the aqueous layer was washed with further portions of dichloromethane (2 x 50 mL). The combined organic extracts were washed with brine and then dried ($MgSO_4$), filtered and evaporated. Column chromatography of the residue on silica gel (ether-light petroleum 1:20) furnished the *title compound* (94%, 95% d.e.) as a colourless oil, (Found: M^+, 289.2404. $C_{19}H_{31}NO$ requires M, 289.2405); $[\alpha]_D$ -61.9° (*c*=0.62, CH_2Cl_2); υ_{max} (film)/cm^{-1} 2958, 2933, 1641, 1455, 910; δ_H (250 MHz; $CDCl_3$) 7.27 (5H, m, ArH), 5.78 (1H, m, $\underline{CH}$=CH_2), 5.04 (1H, broad s, NH), 4.96 (2H, m, CH=$\underline{CH_2}$), 4.52 (1H, dd, *J*=5.6, 7.5 Hz, OCH), 2.79 (1H, m, NCH), 2.04 (2H, m, $\underline{CH_2}$-CH=), 1.54 (12H, m, 6$\underline{CH_2}$), 0.91 (3H, t, *J*=7.2 Hz, CH_3), 0.85 (3H, t, *J*=7.1 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 143.4, 138.9, 128.2, 127.2, 126.5, 114.3, 85.1, 60.0, 38.7, 34.0, 33.9, 31.7, 25.0, 19.2, 14.2, 14.0; *m/z* (EI) 157 (12%), 133 (54%), 114 (21%), 91 (100%).

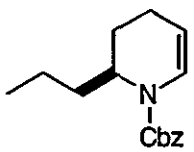
(R)-(-)-N-*(Benzyloxycarbonyl)-6-non-1-enylamine* ***151***



Zinc dust (28.5 g, 443 mmol) was added to a solution of chiral hydroxylamine **146** (3.2 g, 11.1 mmol) in acetic acid and water (20 mL 1:1). The mixture was placed in a sonic bath at 40°C for 2 h. The solution was filtered and ether (50 mL) and water (50 mL) were added, the layers were separated and the aqueous layer was washed with further portions of ether and dichloromethane. The combined organic extracts were evaporated and THF/water (100 mL 1:1) was added to the residue. Sodium carbonate (1.27 g, 12 mmol) was added and the mixture cooled to 0°C, benzylchloroformate (1.6 mL, 11.1 mmol) was then added dropwise and the mixture was allowed to warm to room temperature and was stirred for 2 h. The THF was removed *in vacuo* and ether (50 mL) added, the layers were separated and the aqueous layer washed with further portions of ether. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. Column chromatograpy of the residue on silica gel (ether-light petroleum 1:6) furnished the *title compound* (87%) as a colourless solid, m.p. 71-73°C; (Found: M^+, 275.1892. $C_{17}H_{25}NO_2$ requires M, 275.1885); $[\alpha]_D$ -1.5° (*c*=1, CH_2Cl_2); υ_{max} (film)/cm^{-1} 3312, 2925, 1687, 1547, 1462; δ_H (250 MHz; $CDCl_3$) 7.32 (5H, m, ArH), 5.70 (1H, m, $\underline{CH}$=CH_2), 5.08 (2H, s, CH_2Ph), 4.95 (2H, m, CH=$\underline{CH_2}$), 4.50 (1H, broad d, *J*=9 Hz, NH), 3.63 (1H, broad s, NCH), 2.04 (2H, m, $\underline{CH_2}$-CH=), 1.42 (8H, m, $\underline{CH_2}$), 0.90 (3H, broad t, *J*=6.9 Hz, CH_3); δ_C (62.9

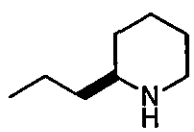
MHz; $CDCl_3$) 156.2, 138.5, 136.4, 128.4, 128.0, 128.0, 114.6, 66.4, 50.9, 37.6, 34.8, 33.5, 25.0, 18.9, 13.9; *m/z* (EI) 232 (10%), 162 (18%), 91 (100%).

(R)-(-)-1-*(Benzyloxycarbonyl)-2-propyl-1,2,3,4-tetrahydropyridine* ***153***



Osmium tetroxide (1 mol%, 14 mg, 0.06 mmol) was added to a solution of the alkene **151** (1.65 g, 6 mmol) in THF/water (40 mL, 3:1) and the mixture was stirred at room temperature for 5 min. The solution changed from colourless to brown and sodium periodate (2.35 g, 11 mmol) was then added portionwise over 20 min. The reaction was stirred for a further 20 min. Water (30 mL) and ether (50 mL) were added and the ether layer separated, the aqueous layer was washed with further portions of ether (4 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. Column chromatograpy of the residue on silica gel (dichoromethane) furnished the *title compound* (52%) as a colourless oil, (Found: M^+, 259.1579. $C_{16}H_{21}NO_2$ requires M, 259.1572); $[\alpha]_D$ -69.2° (*c*=0.5, CH_2Cl_2); υ_{max} (film)/cm^{-1} 2958, 2933, 1705, 1416, 1327; δ_H (250 MHz; $CDCl_3$) major rotamer 7.25 (5H, m, ArH), 6.67 (1H, br d, *J*=8 Hz, NC<u>H</u>=CH), 5.11 (2H, br s, CH_2Ph), 4.76 (1H, br m, NCH=C<u>H</u>), 4.26 (1H, br m, NCH), 2.01-1.24 (8H, m, $4CH_2$), 0.83 (3H, broad t, Me), minor rotamer 6.75 (1H, br d, *J*=8 Hz, NC<u>H</u>=CH), 4.80 (1H, br m, NCH=C<u>H</u>), 4.18 (1H, br m, NCH); δ_C (62.9 MHz; $CDCl_3$) major rotamer 153.4, 136.9, 128.9, 128.4, 128.4, 124.0, 106.3, 67.7, 50.7, 33.1, 24.4, 19.5, 18.0, 14.4; *m/z* (EI) 259 (M^+, 9%), 172 (20%), 91 (100%).

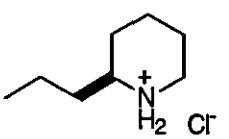
(R)-(-)-*2-Propylpiperidine* ***131***



Palladium on charcoal (70 mg, 10% on charcoal) was added to a solution of tetrahydropyridine **153** (1.68 g, 6.5 mmol) in methanol (20 mL), and the mixture was hydrogenated (41 psi H_2) for 12 h. The solution was filtered through celite and half the filtrate evaporated to furnish the *title compound* (0.4 g, 97%) as a colourless oil, $[\alpha]_D$ -8.1° (*c*=2, $CHCl_3$) (lit.,[79h] $[\alpha]_D$ -7.9° (*c*=1, $CHCl_3$); δ_H (250 MHz; $CDCl_3$) 2.98 (1H,

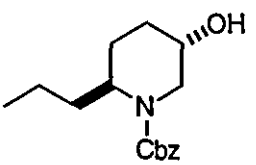
m, CHN), 2.55 (1H, dt, *J*=3.0, 11.7Hz, CHN (ax)), 2.37 (1H, m, CHN (eq)), 1.75-0.86 (11H, m, CH_2 NH), 0.84 (3H, t, *J*=6.6Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 56.5, 47.1, 39.6, 32.9, 26.6, 24.8, 18.9, 14.1.

(R)-(-)-*2-Propylpiperidine.HCl* ***131.HCl***



The methanolic solution of (R)-(-)-*2-propylpiperidine* **131** was treated with HCl in ether (6 mL, 6 mmol), the mixture was stirred for 5 min and the solvent was then evaporated *in vacuo*. The resulting residue was triturated with ether to provide the *title compound* (0.43 g, 80%) as a colourless solid, m.p. 212-213°C, (lit.,[79h] 217-218°C); $[\alpha]_D$ -7.6° (*c*=1, EtOH) (lit.,[79h] $[\alpha]_D$ -6.3° (*c*=0.62, EtOH); δ_H (400 MHz; $CDCl_3$) 9.51 (1H, broad s, NH), 9.21 (1H, broad s, NH), 3.49 (1H, m, CHN), 2.95 (1H, m, CHN) 2.83 (1H, m, CHN), 2.02-1.44 (10H, m, $5CH_2$), 0.97 (3H, t, *J*=7.3 Hz, Me); δ_C (100.6 MHz; $CDCl_3$) 57.6, 45.1, 35.7, 28.6, 22.8, 22.6, 19.0, 14.1.

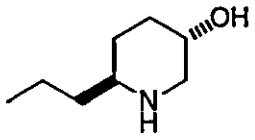
(2S, 5S)-(+)-N-*(Benzyloxycarbonyl)-2-Propyl-5-hydroxypiperidine* ***156***



(S)-(+)-1-(Benzyloxycarbonyl)-2-propyl-1,2,3,4-tetrahydropyridine **153** was treated with borane dimethyl sulphide complex in THF at -78°C, the mixture was allowed to warm to room temperature and stirred for 2 days. Trimethylamine N-oxide was added and the solution heated to reflux for 12 h. The solution was cooled and water (30 mL) and ether (30 mL) added, the layers were separated and the aqueous layer washed with ether (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. Column chromatography on silica gel with ethyl acetate / petroleum ether (2:1) as eluent afforded the pure *trans* isomer (40%) as a colourless oil, $[\alpha]_D$ +15.7° (*c*=1.4, MeOH) (lit.,[82] $[\alpha]_D$ +15.8° (*c*=1, $CHCl_3$); υ_{max} (film)/cm^{-1} 3434, 2942, 1693, 1429, 1243, 1151; δ_H (250 MHz; $CDCl_3$) 7.34 (5H, m, ArH), 5.13 (2H, dd, *J*=12.5, 15.8 Hz, CH_2Ph), 4.30 (1H, br m, C<u>H</u>OH), 4.10 (1H, br d, *J*=14.5 Hz, NCH_2),

3.91 (1H, br s, PrCHN), 3.03 (1H, dd, *J*=1.4, 14.3 Hz, NCH_2), 2.04 (2H, m, CH_2), 1.68 (2H, m, CH_2), 1.31 (4H, m, $2CH_2$), 0.90 (3H, t, *J*=7.1 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 155.0, 136.8, 128.4, 127.8, 127.7, 67.1, 64.5, 50.4, 44.8, 31.3, 25.4, 22.1, 19.4, 13.9.

(2S, 5S)-(+)-*2-Propyl-5-hydroxypiperidine (pseudoconhydrine)* ***155***



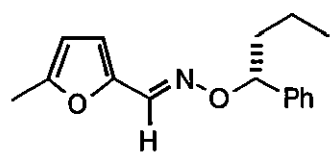
Palladium on charcoal (7 mg, 10 mol%, 10% on charcoal) was added to a solution of carbamate **156** (0.07 g, 0.25 mmol) in methanol (7 mL), and the mixture was hydrogenated (45 psi H_2) for 3 h. The solution was filtered through celite and the filtrate evaporated to furnish the *title compound* (98%) as a colourless solid, m.p. 102-103°C, (lit.,[82] 102-104); $[\alpha]_D$ +17.4° (*c*=0.62, $CHCl_3$) (lit.,[82] $[\alpha]_D$ +11.1° (*c*=1, EtOH); δ_H (250 MHz; $CDCl_3$) 3.60 (1H, m, C<u>H</u>OH), 3.18 (1H, m, PrCHN), 2.43 (1H, t, *J*=10.8 Hz, CH) 2.37 (1H, br s, OH), 2.06-1.69 (3H, m, NH, 2CH), 1.37-1.07 (7H, m, 7CH), 0.88 (3H, t, *J*=7.1 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 66.7, 53.6, 52.1, 36.7, 32.3, 29.4, 17.5, 12.3.

5.4. Experimental Details for Chapter Four

General Method for the Preparation of Oximes Ethers

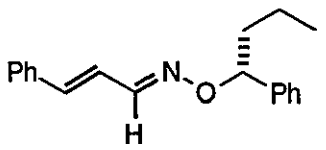
N-(1-Phenylbutoxy)phthalimide **128b** (4.65 g, 15.8 mmol) and ethanol (100 mL) were added to a round bottomed flask and the suspension heated until the phthalimide dissolves. Hydrazine hydrate (0.77 mL, 15.8 mmol) was added at this elevated temperature and the solution was allowed to cool to room temperature. Aldehyde or ketone (15.8 mmol) was added and the mixture stirred overnight. The solvent was evaporated, and carbon tetrachloride (30 mL) and magnesium sulfate were added to the residue. The resulting suspension was filtered and the filtrate evaporated, column chromatography of the residue on silica gel (diethyl ether-light petroleum 1:20) furnished the *title compound.*

E-*(R)-(+)*-O-*(1-Phenylbutyl)-5-methyl-2-furaldoxime* ***168.***



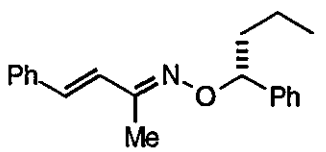
Obtained from the reaction of *N*-(R)-(+)-(1-phenylbutoxy)phthalimide **128b** with 5-methyl-2-furaldehyde, separated from the *Z*-isomer by column chromatography on silica gel (diethyl ether-light petroleum 1:20), (83%) as a colourless oil, (Found: M^+, 257.1416. $C_{16}H_{19}NO_2$ requires M, 257.1411); $[\alpha]_D$ +124.6° (*c*=1, CH_2Cl_2); υ_{max} (film)/cm^{-1} 2932, 1582, 1523, 1453, 1022; δ_H (250 MHz; $CDCl_3$) 7.97 (1H, s, CH=N), 6.45 (1H, d, *J*=3.3 Hz, furanH), 6.03 (1H, d, *J*=3.3 Hz, furanH), 5.25 (1H, t, *J*=6.9 Hz, OCH), 2.33 (3H, s, Me), 1.99 (1H, m, CH_2), 1.78 (1H, m, CH_2), 1.41 (2H, m, CH_2), 0.96 (3H, t, *J*=7.3 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 154.4, 145.9, 142.4, 139.2, 128.1, 127.3, 126.7, 114.3, 107.8, 85.4, 38.4, 18.8, 14.0, 13.8. *m/z* (EI) 133 (37%), 105 (39%), 91 (100%), 79 (48%).

E-*(R)-(+)*-O-*(1-Phenylbutyl) cinnamaldoxime* ***171***



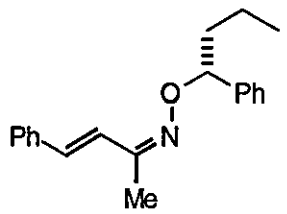
Obtained from the reaction of cinnamaldehyde with the phthalimide **128b** (80%) as a colourless solid, (recrystallised from light petroleum), m.p. 65-67°C; (Anal. calcd for $C_{19}H_{21}NO$: C, 81.67; H, 7.58; N, 5.02. Found: C, 81.58; H, 7.50; N, 4.90%); (Found: M^+, 279.1625. $C_{19}H_{21}NO$ requires M, 279.1623); $[\alpha]_D$ +48.1° (*c*=1, CH_2Cl_2); υ_{max} (film)/cm^{-1} 2931, 1455, 996, 972, 943; δ_H (250 MHz; $CDCl_3$) 7.97 (1H, dd, *J*=1.6, 7.6 Hz, HC=N), 7.32 (10H, m, ArH), 6.79 (2H, m, HC=CH), 5.14 (1H, dd, *J*=6.6, 7.1 Hz, HCO), 1.99 (1H, m, CH_2), 1.78 (1H, m, CH_2), 1.44 (2H, m, CH_2), 0.98 (3H, t, *J*=7.3 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 150.6, 142.4, 138.1, 136.5, 128.7, 128.5, 128.2, 127.4, 126.8, 126.6, 122.2, 85.4, 38.3, 18.8, 13.9; *m/z* (EI) 279 (14%), 133 (58%), 91 (100%), 77 (20%).

E-*(R)-(+)*-O-*(1-Phenylbutyl) benzylideneacetone ketoxime* ***E-181***



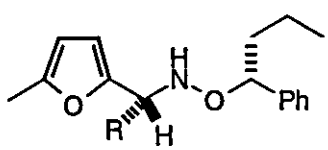
Obtained from the reaction of *N*-(R)-(+)-(1-phenylbutoxy)phthalimide **128b** with benzylidene acetone, separated from the *Z*-isomer by column chromatography on silica gel (diethyl ether-light petroleum 1:20), (51%) as a colourless solid (recrystallised from light petroleum), m.p. 49-50°C; (Found: M^+, 293.1780. $C_{20}H_{23}NO$ requires 293.1780); $[\alpha]_D$ +91.6° (*c*=2, CH_2Cl_2); υ_{max} (film)/cm^{-1} 2959, 1583, 1495, 1451, 960; δ_H (250 MHz; $CDCl_3$) 7.33 (10H, m, ArH), 6.83 (2H, s, PhCH=CH), 5.17 (1H, dd, *J*=6.3, 7.0 Hz, HCO), 2.18 (3H, s, MeC=N), 1.95 (1H, m, CH_2), 1.83 (1H, m, CH_2), 1.45 (2H, m, CH_2), 0.98 (3H, t, *J*=7.3 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 155.8, 143.1, 136.5, 132.4, 128.6, 128.2, 128.1, 127.2, 126.7, 126.4, 85.3, 38.7, 18.4, 14.0, 10.4; *m/z* (EI) 133 (14%), 105 (39%), 91 (100%), 77 (30%).

Z-(R)-(+)-O-(1-Phenylbutyl) benzylideneacetone ketoxime ***Z-181***



Obtained from the reaction of *N*-(R)-(+)-(1-phenylbutoxy)phthalimide **128b** with benzylidene acetone, separated from the *E*-isomer by column chromatography on silica gel (diethyl ether-light petroleum 1:20), (34%) as a colourless solid (recrystallised from light petroleum), m.p. 78-79°C; (Found: M^+, 293.1780. $C_{20}H_{23}NO$ requires 293.1780); $[\alpha]_D$ -378.7° (*c*=0.75, CH_2Cl_2); υ_{max} (film)/cm^{-1} 2959, 1621, 1494, 1454, 935; δ_H (250 MHz; $CDCl_3$) 7.63 (1H, d, *J*=16.6 Hz, PhCH=C<u>H</u>), 7.56 (2H, m, ArH), 7.33 (8H, m, ArH), 6.97 (1H, d, *J*=16.6 Hz, PhCH=), 5.17 (1H, dd, *J*=6.3, 6.8 Hz, HCO), 2.07 (3H, s, MeC=N), 1.97 (1H, m, CH_2), 1.73 (1H, m, CH_2), 1.45 (2H, m, CH_2), 0.97 (3H, t, *J*=7.3 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) 154.2, 145.0, 138.5, 137.7, 130.8, 130.7, 130.1, 129.9, 129.4, 128.5, 119.9, 87.0, 40.7, 20.9, 18.9, 16.0; *m/z* (EI) 293 (18%), 105 (22%), 91 (100%), 77 (24%).

Additions to the Furan Oxime 168.

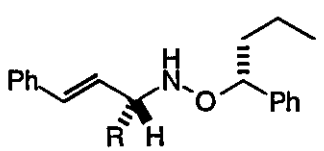


(1R, 1'R)-(+)-N-(1-phenylbutoxy)-5-(2-methylfuryl)-1-ethylamine **169a.**
Obtained from the addition of methyllithium to oxime **168**, (77%, 83% d.e.), as a colourless oil, (Found: MH^+, 274.1807. $C_{17}H_{24}NO2$ requires MH, 274.1807); $[\alpha]_D$ +87.5° (*c*=1, CH_2Cl_2); υ_{max} (film)/cm^{-1} 3030, 2958, 1566, 1454, 1019; δ_H (250 MHz; $CDCl_3$) major diastereomer 7.31 (5H, m, ArH), 6.05 (1H, d, *J*=3.1 Hz, furanH), 5.88 (1H, d, *J*=3.1 Hz, furanH), 5.43 (1H, broad s, NH), 4.58 (1H, dd, *J*=5.9, 7.3 Hz, OCH), 4.18 (1H, q, *J*=6.6 Hz, NCH), 2.25 (3H, s, furanMe), 1.82 (1H, m, CH_2), 1.62-1.27 (3H, m, CH_2), 1.44 (3H, d, *J*=6.6 Hz, Me), 0.93 (3H, t, *J*=7.4 Hz, Me), minor diastereomer 6.15 (1H, d, *J*=3.1 Hz, furanH), 5.91 (1H, d, *J*=3.1 Hz, furanH), 4.42 (1H, dd, *J*=5.9, 7.3 Hz, OCH), 2.30 (3H, s, furanMe); δ_C (62.9 MHz; $CDCl_3$) major diastereomer 153.4, 151.2, 143.2, 128.2, 127.2, 126.5, 107.2, 105.9, 85.3, 76.5, 54.0, 38.7, 19.1, 16.9, 14.0, 13.5, minor diastereomer 126.6, 107.0, 85.4, 38.5, 16.9; *m/z* (EI) 133 (16%), 109 (92%), 91 (100%), 77 (17%).

(1R, 1'R)-(+)-N-*(1-phenylbutoxy)-(5-(2-methylfuryl)-1-pentylamine* **169b.**
Obtained from the addition of *n*-butyllithium to oxime **168**, (87%, 81% d.e.), as a colourless oil, (Found: MH^+, 316.2277. $C_{20}H_{30}NO_2$ requires MH, 316.2277); $[\alpha]_D$ +90.3° (*c*=0.9, CH_2Cl_2); υ_{max} (film)/cm^{-1} 3030, 2957, 1565, 1454; δ_H (250 MHz; $CDCl_3$) major diastereomer 7.27 (5H, m, ArH), 6.02 (1H, d, *J*=3.0 Hz, furanH), 5.84 (1H, d, *J*=3.0 Hz, furanH), 5.35 (1H, broad s, NH), 4.51 (1H, dd, *J*=5.7, 7.6 Hz, OCH), 3.92 (1H, dd, *J*=5.6, 8.6 Hz, NCH), 2.23 (3H, s, furanMe), 1.79-1.21 (10H, m, $5CH_2$), 0.87 (6H, 2t, 2Me), minor diastereomer 6.07 (1H, d, *J*=3.0 Hz, furanH), 4.48 (1H, dd, *J*=5.7, 7.6 Hz, OCH), 2.27 (3H, s, furanMe); δ_C (62.9 MHz; $CDCl_3$) 152.3, 151.1, 143.8, 128.1, 127.1, 126.5, 107.9, 105.8, 85.0, 59.1, 38.6, 30.7, 28.3, 22.5, 19.1, 14.0, 13.9, 13.5. *m/z* (EI) 166 (88%), 151 (100%), 133 (12%), 110 (18%), 86 (34%).

(1R, 1'R)-(+)-N-*(1-phenylbutoxy)-(5-(2-methylfuryl)-1-but-3-enylamine* **169c.**
Obtained from the addition of allylmagnesium bromide to oxime **168**, (56%, 59% d.e.), as a colourless oil, (Found: MH^+, 300.1964. $C_{19}H_{26}NO_2$ requires MH, 300.1964); $[\alpha]_D$ +92.3° (*c*=1, CH_2Cl_2); υ_{max} (film)/cm^{-1} 3076, 2958, 1565, 1454, 1020; δ_H (250 MHz; $CDCl_3$) major diastereomer 7.32 (5H, m, ArH), 6.07 (1H, d, *J*=3.0 Hz, furanH), 5.88 (1H, d, *J*=3.0 Hz, furanH), 5.75 (1H, m, CH=), 5.46 (1H, broad s, NH), 5.06 (2H, m, $=CH_2$), 4.53 (1H, t, *J*=7.3 Hz, OCH), 4.03 (1H, t, *J*=6.8 Hz, NCH), 2.66 (1H, m, $\underline{CH_2}CH=$), 2.53 (1H, m, $\underline{CH_2}CH=$), 2.25 (3H, s, furanMe), 1.83-1.24 (4H, m, $2CH_2$), 0.90 (3H, t, *J*=7.2 Hz, Me), minor diastereomer 6.11 (1H, d, *J*=3.0 Hz, furanH), 5.92 (1H, d, *J*=3.0 Hz, furanH), 2.29 (3H, s, furanMe); δ_C (62.9 MHz; $CDCl_3$) major diastereomer 152.2, 150.9, 143.1, 134.8, 128.1, 127.2, 126.5, 117.2, 108.2, 105.9, 85.2, 55.6, 38.5, 35.4, 19.1, 14.0, 13.5, minor diastereomer 153.3, 134.5, 117.4, 107.8, 85.3, 58.5, 19.0; *m/z* (CI) 166 (80%), 150 (100%), 135 (100%), 110 (100%), 95 (58%), 58 (48%), 44 (52%).

General Procedure for the Addition of Organometallic Reagents to the Cinnamaldoxime 171.



The cinnamaldehyde derived oxime **171** (0.9 g, 3.22 mmol) in toluene (16 mL) was cooled to -78°C under nitrogen and boron trifluoride etherate (1.2 mL, 9.7 mmol) was added. The solution was stirred for 15 min, after this time the organometallic reagent

(9.7 mmol) was added dropwise over 15 min. The resulting clear solution was stirred for a further 30 min when water (10 mL) was added. The solution was allowed to warm to room temperature and ether (10 mL) was added. The two layers were separated and the aqueous layer was washed with further portions of ether (2 x 15 mL). The combined organic portions were dried (K_2CO_3), filtered and evaporated. Column chromatography (5% ether / light petroleum) afforded the *title compound.*

(3R, 1'R)-(+)-N-(1-Phenylbutoxy)-1-phenyl-3-but-1-enylamine ***172a***

Obtained by the addition of methyllithium to the cinnamaldoxime **171**, (95%, 92% d.e.) as a colourless oil, (Found: M^+, 295.1936. $C_{20}H_{25}NO$ requires M, 295.1933); $[\alpha]_D$ +87.4° (*c*=1, CH_2Cl_2); υ_{max} (film)/cm^{-1} 3252, 2959, 1494, 1454; δ_H (250 MHz; $CDCl_3$) major diastereomer 7.27 (10H, m, ArH), 6.47 (1H, d, *J*=16.1 Hz, PhCH=), 6.03 (1H, dd, *J*=7.1, 15.1 Hz, PhCH=C<u>H</u>), 5.18 (1H, br s, NH), 4.58 (1H, dd, *J*=5.8, 7.6 Hz, OCH), 3.75 (1H, m, NCH), 1.80 (1H, m, CH_2), 1.63-1.27 (3H, m, CH_2), 1.26 (3H, d, *J*=6.4 Hz, CH_3), 0.91 (3H, t, *J*=7.2 Hz, CH_3), minor diastereomer 6.51 (1H, d, *J*=16.1 Hz, PhCH=), 6.20 (1H, dd, *J*=7.1, 15.1 Hz, PhCH=C<u>H</u>), 1.15 (3H, d, *J*=6.4 Hz, CH_3), 0.81 (3H, t, *J*=7.2 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 143.6, 137.1, 131.2, 130.8, 128.4, 128.2, 127.4, 127.2, 126.6, 126.3, 85.4, 58.5, 38.7, 19.2, 18.6, 14.0; *m/z* (EI) 163 (22%), 131 (63%), 104 (15%), 91 (100%), 77 (15%).

(3R, 1'R)-(+)-N-(1-Phenylbutoxy)-1-phenyl-3-hept-1-enylamine ***172b***

Obtained by the addition of *n*-butyllithium to the cinnamaldoxime **171**, (95%, 92% d.e.) as a colourless solid (recystalliised from light petroleum), m.p. 47-49°C (Anal. calcd for $C_{23}H_{31}NO$: C, 81.82; H, 9.26; N, 4.15. Found: C, 81.61; H, 9.12; N, 4.00%); (Found: M^+, 337.2398. $C_{23}H_{31}NO$ requires M, 337.2406); $[\alpha]_D$ +57.3° (*c*=2, $CHCl_3$); υ_{max} (film)/cm^{-1} 3028, 2957, 1493, 1453; δ_H (250 MHz; $CDCl_3$) major diastereomer 7.25 (10H, m, ArH), 6.46 (1H, d, *J*=15.9 Hz, PhCH=), 5.96 (1H, dd, *J*=8.4, 15.9 Hz, PhCH=C<u>H</u>), 4.57 (1H, dd, *J*=5.9, 7.6 Hz, OCH), 3.54 (1H, m, NCH), 1.93-1.28 (10H, m, $5CH_2$) 0.89 (6H, 2t, 2Me), minor diastereomer 6.49 (1H, d, *J*=15.9 Hz, PhCH=), 6.12 (1H, dd, *J*=8.4, 15.9 Hz, PhCH=C<u>H</u>); δ_C (62.9 MHz; $CDCl_3$) 143.5, 137.0, 132.2, 130.1, 128.4, 128.2, 127.3, 127.2, 126.6, 126.3, 85.3, 63.7, 38.6, 32.2, 28.0, 22.7, 19.2, 14.0, 13.9; *m/z* (EI) 205 (23%), 173 (30%), 148 (15%), 133 (38%), 91 (100%), 77 (10%).

(3R, 1'R)-(+)-N-(1-Phenylbutoxy)-6-methyl-1-phenyl-3-hex-1-enylamine ***172c***
Obtained by the addition of *iso*-butyllithium to the cinnamaldoxime **171**, (93%, 92% d.e.) as a colourless solid, m.p. 61-63°C, (Found: MH+, 338.2484. $C_{23}H_{32}NO$ requires MH, 338.2484); $[\alpha]_D$ +43.6° (*c*=1.42, CH_2Cl_2); υ_{max} (film)/cm^{-1} 3030, 2956, 1494, 1454; δ_H (250 MHz; $CDCl_3$) major diastereomer 7.26 (10H, m, PhH), 6.49 (1H, d, *J*=16.0 Hz, PhCH=), 5.97 (1H, dd, *J*=8.3, 16.0 Hz, PhCH=CH), 5.15 (1H, broad s, NH), 4.57 (1H, t, *J*=7.4 Hz, OCH), 3.66 (1H, m, NCH), 1.81-1.12 (7H, m, CH, $3CH_2$), 0.91 (9H, m, 3Me), minor diastereomer 6.17 (1H, dd, *J*=8.3, 16.0 Hz, NCH); δ_C (62.9 MHz; $CDCl_3$) 143.2, 137.0, 132.1, 130.5, 128.4, 128.2, 127.4, 127.2, 126.7, 126.3; *m/z* (CI) 338 (12%), 188 (50%), 173 (62%), 149 (100%), 86 (71%).

(3S, 1'R)-(+)-N-(1-Phenylbutoxy)-1,3-diphenyl-3-prop-1-enylamine ***172d***
Obtained by the addition of phenyllithium to the cinnamaldoxime **171**, (76%, 90% d.e.) as a colourless oil, (Found: M+, 357.2097. $C_{25}H_{27}NO$ requires M, 357.2093); $[\alpha]_D$ +43.0° (*c*=2.58, $CDCl_3$); υ_{max} (film)/cm^{-1} 2957, 1600, 1494, 1453, 964; δ_H (250 MHz; $CDCl_3$) major diastereomer 7.40 (15H, m, PhH), 6.49 (1H, d, *J*=15.9 Hz, PhCH=), 6.23 (1H, dd, *J*=8.3, 15.9 Hz, PhCH=CH), 5.48 (1H, broad s, NH), 4.81 (1H, d, *J*=8.4 Hz, OCH), 4.48 (1H, dd, *J*=5.9, 7.6 Hz, NCH), 1.74-0.81 (4H, m, $2CH_2$), 0.73 (3H, t, *J*=8 Hz, Me), minor diastereomer 4.63 (1H, dd, *J*=8.3, 15.9 Hz, NCH); δ_C (62.9 MHz; $CDCl_3$) 143.1, 141.5, 136.9, 132.2, 128.9, 128.4, 128.3, 128.3, 127.8, 127.6, 127.4, 127.3, 126.7, 126.4, 85.3, 68.0, 38.5, 18.8, 13.8; *m/z* (EI) 357 (4%), 206 (13%), 193 (100%), 133 (74%), 115 (16%), 91 (86%), 77 (32%).

(3R, 1'R)-(+)-N-(1-Phenylbutoxy)-1-phenyl-3-but-1-enylamine ***172e***
Obtained by the addition of methylmagnesium bromide to the cinnamaldoxime, (41%, 73% d.e.) as a colourless solid, with identical spectroscopic properties as compound **172a**, $[\alpha]_D$ +64.3° (*c*=1, CH_2Cl_2).

(3R, 1'R)-(+)-N-(1-Phenylbutoxy)-1-phenyl-3-pent-1-enylamine ***172f***
Obtained by the addition of ethylmagnesium bromide to the cinnamaldoxime **171**, (91%, 71% d.e.) as a colourless solid, m.p. 56-57°C, (Found: MH+, 310.2171, $C_{21}H_{28}NO$ requires MH, 310.2171); $[\alpha]_D$ +42.6° (*c*=1.32, CH_2Cl_2); υ_{max} (film)/cm^{-1} 3250, 2960, 1599, 1493, 1454, 966; δ_H (250 MHz; $CDCl_3$) major diastereomer 7.31 (10H, m, ArH), 6.54 (1H, d, *J*=16.0 Hz, PhCH=), 6.00 (1H, dd, *J*=7.8, 16.0 Hz, PhCH=CH), 5.26 (1H, broad s, NH), 4.60 (1H, dd, *J*=6.0, 7.4 Hz, OCH), 3.50 (1H, m, NCH), 1.81 (2H, m, CH_2), 1.63-1.29 (4H, m, $2CH_2$), 0.94 (6H, 2t, *J*=7.4 Hz, 2Me),

minor diastereomer 6.55 (1H, d, *J*=16.0 Hz, PhCH=), 6.17 (1H, dd, *J*=7.8, 16.0 Hz, PhCH=CH), 0.87 (3H, t, *J*=7.4 Hz, Me); δ_C (62.9 MHz; $CDCl_3$) major diastereomer 143.0, 137.0, 132.5, 129.6, 128.4, 128.2, 127.4, 127.2, 126.6, 126.3, 85.5, 65.2, 38.6, 25.3, 19.2, 14.0, 10.2, minor diastereomer 132.0, 130.9, 85.5, 65.5, 38.7, 25.1, 19.1, 10.4; *m/z* (CI) 280 (15), 166 (37%), 149 (100%), 132 (50%), 58 (44%), 44 (67%).

(3R, 1'R)-(+)-N-*(1-Phenylbutoxy)-1-phenyl-3-hept-1-enylamine* ***172g***

Obtained by the addition of *n*-butylmagnesium bromide to the cinnamaldoxime **171**, (89%, 78% d.e.) as a colourless oil, possessing identical spectroscopic properties as compound **172b**, $[\alpha]_D$ +55.1° (*c*=1, CH_2Cl_2).

(3R, 1'R)-(+)-N-*(1-Phenylbutoxy)-1,4-diphenyl-3-but-1-enylamine* ***171h***

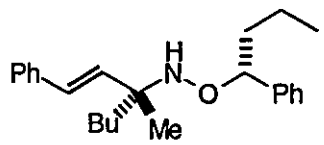
Obtained by the addition of benzylmagnesium bromide to the cinnamaldoxime **171**, (34%, 72% d.e.) as a colourless solid, m.p. 81-83°C, (Found: MH^+, 372.2327. $C_{26}H_{30}NO$ requires MH, 372.2327); $[\alpha]_D$ +45.7° (*c*=0.7, CH_2Cl_2); υ_{max} (film)/cm^{-1} 3028, 2958, 1494, 1454; δ_H (400 MHz; $CDCl_3$) major diastereomer 7.33 (15H, m, ArH), 6.45 (1H, d, *J*=16.0 Hz, PhCH=), 6.12 (1H, dd, *J*=7.7, 16.0 Hz, PhCH=CH), 5.40 (1H, broad s, NH), 4.65 (1H, dd, *J*=6.3, 7.4 Hz, OCH), 3.81 (1H, m, NCH), 3.17 (1H, dd, *J*=6.6, 13.4 Hz, CH_2Ph), 2.85 (1H, dd, *J*=6.6, 13.4 Hz, CH_2Ph), 1.89 (1H, m, CH_2), 1.64-1.32 (3H, m, $2CH_2$), 0.97 (3H, t, *J*=7.4 Hz, Me), minor diastereomer 6.50 (1H, d, *J*=16 Hz, PhCH=), 6.21 (1H, dd, *J*=7.7, 16.0 Hz, PhCH=CH), 0.91 (3H, t, *J*=7.4 Hz, Me); δ_C (400 MHz; $CDCl_3$) major diastereomer 143.3, 138.9, 137.4, 132.7, 130.0, 129.7, 128.8, 128.8, 128.7, 127.8, 127.0, 126.7, 126.6, 86.0, 65.1, 39.6, 39.0, 19.6, 14.4, minor diastereomer 132.4, 130.4, 65.1, 39.4, 14.5; *m/z* (CI) 372 (9%), 166 (44%), 149 (100%), 108 (54%), 58 (53%).

(3S, 1'R)-(+)-N-*(1-Phenylbutoxy)-1,3-diphenyl-3-prop-1-enylamine* ***172i***

Obtained by the addition of phenylmagnesium bromide to the cinnamaldoxime **171**, (69%, 80% d.e.) as a colourless oil, with identical spectroscopic properties as compound **172d**, $[\alpha]_D$ +39.0° (*c*=1, CH_2Cl_2).

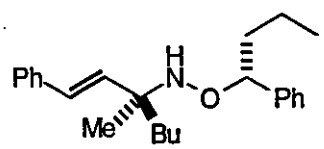
Additions to the Benzylidine Acetone Oximes 181

*(3R, 1'R)-(+)-*N*-(1-Phenylbutoxy)-3-methyl-1-phenyl-3-hept-1-enylamine* ***(R,R)-184***



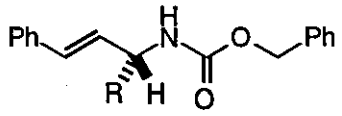
Obtained by the addition of *n*-butyllithium to *E*-benzylidine acetone oxime ***E*-181**, (53%, ~80% d.e.), as a colourless oil, (Found: MH^+, 352.2640. $C_{24}H_{34}NO$ requires MH, 352.2640); $[\alpha]_D$ +51.4° (*c*=1, CH_2Cl_2); υ_{max} (film)/cm^{-1} 3029, 2958, 1494, 1454; δ_H (250 MHz; $CDCl_3$) major diastereomer 7.32 (10H, m, ArH), 6.44 (1H, d, *J*=16.4 Hz, PhCH=), 6.21 (1H, d, *J*=16.4 Hz, PhCH=C<u>H</u>), 5.00 (1H, broad s, NH), 4.59 (1H, dd, *J*=5.2, 7.6 Hz, OCH), 1.76 (1H, m, CH_2), 1.56 (3H, m, CH_2), 1.34 (2H, m, CH_2), 1.30 (3H, s, Me), 0.92 (3H, t *J*=7.1 Hz, Me), minor diastereomer 6.30 (1H, d, *J*=16.4 Hz, PhCH=C<u>H</u>); δ_C (62.9 MHz; $CDCl_3$) major diastereomer 143.5, 137.5, 135.4, 128.5, 128.4, 128.2, 127.1, 126.5, 126.2, 85.4, 61.0, 39.0, 37.8, 26.0, 23.3, 22.2, 19.2, 14.0, minor diastereomer 22.4; *m/z* (CI) 352 (5%), 202 (95%), 187 (98%), 150 (100%), 100 (84%), 58 (23%).

*(3R, 1'R)-(+)-*N*-(1-Phenylbutoxy)-3-methyl-1-phenyl-3-hept-1-enylamine* ***(S,R)-184***



Obtained by the addition of *n*-butyllithium to *Z*-benzylidine acetone oxime ***Z*-181**, (36%, 77% d.e.), as a colourless oil, $[\alpha]_D$ +52.3° (*c*=1.84, CH_2Cl_2); υ_{max} (film)/cm^{-1} 3029, 2958, 1494, 1454; δ_H (250 MHz; $CDCl_3$) major diastereomer 7.32 (10H, m, ArH), 6.44 (1H, d, *J*=16.4 Hz, PhCH=), 6.28 (1H, d, *J*=16.4 Hz, PhCH=C<u>H</u>), 5.00 (1H, broad s, NH), 4.59 (1H, dd, *J*=5.2, 7.6 Hz, OCH), 1.76 (1H, m, CH_2), 1.56 (3H, m, CH_2), 1.34 (2H, m, CH_2), 1.30 (3H, s, Me), 0.92 (3H, t, *J*=7.1 Hz, Me), minor diastereomer 6.21 (1H, d, *J*=16.4 Hz, PhCH=C<u>H</u>); δ_C (62.9 MHz; $CDCl_3$) 143.7, 137.7, 135.5, 128.5, 128.4, 128.3, 127.2, 126.6, 126.3, 85.6, 61.2, 39.2, 37.9, 26.2, 23.4, 22.5, 19.3, 14.2.

General Method for *N*-Cbz Protected Amines by *N-O* Bond Cleavage.



Zinc dust (8 g, 122 mmol) was added to a solution of chiral hydroxylamine (3.1 mmol) in acetic acid and water (20 mL 1:1). The mixture was placed in a sonic bath at 40°C for 2 h. The solution was filtered and ether (50 mL) and water (50 mL) were added, the layers were separated and the aqueous layer was washed with further portions of ether and dichloromethane. The aqueous layer was basified with sodium hydroxide to pH 8 and further extracted with dichloromethane (2 x 30 mL). The combined organic extracts were evaporated and THF/water (100 mL 1:1) was added to the residue. Sodium carbonate (1.27 g, 12 mmol) was added and the mixture cooled to 0°C, benzylchloroformate (0.6 mL, 4 mmol) was then added dropwise and the mixture was allowed to warm to room temperature and was stirred for 12 h. The THF was removed in vacuo and ether (50 mL) added, the layers were separated and the aqueous layer washed with further portions of ether. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. Column chromatograpy of the residue on silica gel (ether-light petroleum 1:6) furnished the *title compound.*

(R)-(+)-N-*(Benzyloxycarbonyl)-1-phenyl-3-but-1-enylamine* ***173a***

Obtained from the cleavage of hydroxylamine **172a** and subsequent *N*-protection, (31%) as a colourless solid, m.p. 89-91°C, (Found: M^+, 281.1416. $C_{18}H_{19}NO_2$ requires M, 281.1416); $[\alpha]_D$ +48.8° (*c*=1, CH_2Cl_2); υ_{max} (film)/cm^{-1} 3309, 2974, 1681, 1538, 1269; δ_H (250 MHz; $CDCl_3$) 7.32 (10H, m, ArH), 6.53 (1H, d, *J*=15.8 Hz, PhCH=), 6.16 (1H, dd, *J*=15.8, 5.8 Hz, PhCH=$\underline{CH_2}$), 5.15 (2H, s, CH_2Ph), 4.50 (1H, broad s, NH), 4.50 (1H, broad m, NCH), 1.35 (3H, d, *J*=6.8 Hz, CH_3); δ_C (62.9 MHz; $CDCl_3$) 155.8, 136.6, 136.5, 131.1, 129.5, 128.5, 128.3, 128.0, 127.5, 126.6, 126.4, 66.7, 48.4, 21.0; *m/z* (EI) 282 (MH^+, 19%), 190 (77%), 178 (15%), 146 (53%), 129 (73%), 91 (100%), 42 (34%).

(R)-(+)-N-*(Benzyloxycarbonyl)-1-phenyl-3-hept-1-enylamine* ***173b***

Obtained from the cleavage of hydroxylamine **172b** and subsequent *N*-protection, (82%) as a colourless solid, m.p. 80-83°C, (Found: M^+, 323.1888, $C_{21}H_{25}NO_2$ requires M, 323.1885); $[\alpha]_D$ +39.0° (*c*=1, CH_2Cl_2); υ_{max} (film)/cm^{-1} 3313, 2955, 1682, 1539, 1255; δ_H (400 MHz; $CDCl_3$) 7.33 (10H, m, ArH), 6.59 (1H, d, *J*=15.7 Hz,

PhCH=), 6.13 (1H, dd, *J*=6.4, 15.9 Hz, PhCH=C<u>H</u>), 5.18 (2H, s, CH_2Ph), 4.85 (1H, broad s, NH), 4.38 (1H, broad s, CHN), 1.67 (2H, m, CH_2), 1.41 (4H, m, $2CH_2$), 0.95 (3H, t, *J*=6.7 Hz, Me); δ_C (400 MHz; $CDCl_3$) 156.2, 137.2, 137.0, 130.7, 128.9, 128.5, 127.9, 126.8, 67.1, 53.6, 35.7, 28.3, 22.9, 14.4; *m/z* (EI) 324 (MH^+, 4%), 266 (35%), 232 (80%), 188 (28%), 171 (37%), 130 (49%), 91 (100%), 65 (20%).

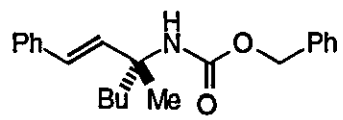
(R)-(+)-N-*(Benzyloxycarbonyl)-6-methyl-1-phenyl-3-hex-1-enylamine* ***173c***

Obtained from the cleavage of hydroxylamine **173c** and subsequent *N*-protection, (86%) as a colourless solid, m.p. 54-56°C, (Found: MH^+, 324.1964. $C_{21}H_{26}NO_2$ requires MH, 324.1964); $[\alpha]_D$ +34.8° (*c*=2, CH_2Cl_2); υ_{max} (film)/cm^{-1} 3320, 2956, 1694, 1504; δ_H (400 MHz; $CDCl_3$) 7.30 (10H, m, ArH), 6.54 (1H, d, *J*=16.0 Hz, PhCH=), 6.09 (1H, dd, *J*=6.1, 15.9 Hz, PhCH=C<u>H</u>), 5.15 (2H, s, CH_2Ph), 4.83 (1H, broad s, NH), 4.42 (1H, m, CHN), 1.71 (1H, m, Me_2CH), 1.48 (2H, m, CH_2), 0.96 (6H, m, 2Me); δ_C (100 MHz; $CDCl_3$) 156.2, 137.2, 131.0, 130.6, 129.5, 128.9, 1287, 128.5, 128.1, 127.1, 125.7, 67.1, 51.9, 45.2, 25.2, 23.1; *m/z* (CI) 324 (12%), 173 (100%), 108 (37%), 86 (53%).

(S)-(+)-N-*(Benzyloxycarbonyl)-1,3-diphenyl-3-prop-1-enylamine* ***173d***

Obtained from the cleavage of hydroxylamine **172d** and subsequent *N*-protection, (66%) as a colourless solid, m.p. 110-111°C, (Found: MH^+, 344.1651. $C_{23}H_{22}NO_2$ requires MH, 344.1651); $[\alpha]_D$ +8.0° (*c*=1, CH_2Cl_2); υ_{max} (film)/cm^{-1} 3317, 2955, 1689, 1531, 1241; δ_H (400 MHz; $CDCl_3$) 7.35 (15H, m, ArH), 6.64 (1H, d, *J*=15.9 Hz, PhCH=), 1H, dd, *J*=6.0, 15.9 Hz, PhCH=C<u>H</u>), 5.60 (1H, broad s, NCH), 5.32 (1H, broad s, NH), 5.19 (2H, dd, *J*=12.2, 16.4 Hz, CH_2Ph); δ_C (400 MHz; $CDCl_3$) 154.2, 139.6, 135.0, 129.9, 127.8, 127.4, 127.2, 127.1, 127.0, 126.7, 126.4, 126.3, 125.6, 125.2, 65.6, 55.5; *m/z* (CI) 344 (12%), 240 (13%), 208 (22%), 193 (100%), 106 (55%), 91 (31%).

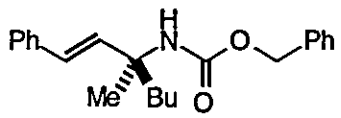
(R)-(+)-N-*(Benzyloxycarbonyl)-3-methyl-1-phenyl-3-hept-1-enylamine* ***(R)-185***



Obtained from the cleavage of hydroxylamine ***(R,R)-184*** and subsequent *N*-protection, (70%) as a colourless oil, (Found: MH^+, 338.2120. $C_{22}H_{28}NO_2$ requires

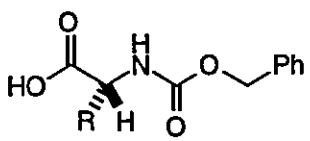
M, 338.2120); $[\alpha]_D$ +0.24° (*c*=6.6, CH_2Cl_2); υ_{max} (film)/cm^{-1} 3416, 3345, 2956, 1713, 1503, 1246; δ_H (400 MHz; $CDCl_3$) 7.36 (10H, m, ArH), 6.48 (1H, d, *J*=16.3 Hz, PhCH=), 6.36 (1H, d, *J*=16.3 Hz, PhCH=CH), 5.15 (2H (s, CH_2), 4.96 (1H, broad s, NH), 1.86 (2H, m, CH_2), 1.57 (3H, s, Me), 1.36 (4H, m, $2CH_2$), 0.96 (3H, t, *J*=6.7 Hz, Me); δ_C (100 MHz; $CDCl_3$) 155.0, 137.5, 137.2, 135.6, 129.2, 128.9. 128.5, 128.4, 128.1, 127.8, 126.9, 66.7, 56.8, 40.6, 26.5, 25.4, 23.4, 14.5; *m/z* (CI) 338 (19%), 187 (100%), 145 (34%), 108 (48%).

*(S)-(+)-*N*-(Benzyloxycarbonyl)-3-methyl-1-phenyl-3-hept-1-enylamine* ***(S)-185***



Obtained from the cleavage of hydroxylamine ***(S,R)-184*** and subsequent *N*-protection, (66%) as a colourless oil, possessing identical spectroscopic properties to its enantiomer ***(R)-185***, $[\alpha]_D$ +0.9° (*c*=0.8, CH_2Cl_2).

General Procedure for the Synthesis of Amino Acids by Oxidative Cleavage.



The protected amine (1.6 mmol) was stirred at room temperature in CCl_4 (2 mL), CH_3CN (2 mL) and water (3 mL) with periodic acid (6.6 mmol) for 10 mins. $RuCl_3.3H_2O$ (0.03 mmol) was added and the solution heated at 50°C for 24 hr. Water (20 mL) and dichloromethane (20 mL) were added and the layers separated, the aqueous layer was exhaustively extracted with dichloromethane (4 x 20 mL) and the organic layers were combined, dried filtered and evapoared. The residue was passed through a short silica gel column (ether-light petroleum (1:1) as eluent) to yield a clear oil. The oil was dissolved in saturated aqueous sodium bicarbonate solution (15 mL) which was washed with ether (2 x 10 mL), the aqueous layer was acidified (pH 1) with concentrated hydrochloric acid and extracted with dichloromethane (3 x 20 mL), the combined organic extracts were dried, filtered and evaporated to furnish the *title compound.*

(R)-(+)-N-*Cbz-alanine* ***174a***

Obtained from the double bond cleavage of protected amine **173a** as a colourless solid, (25%), m.p. 79-80°C, (lit.,[94] 82-83°C); $[\alpha]_D$ +12.8° (*c*=0.36, AcOH), (lit.,[94] $[\alpha]_D$ +14.5° (*c*=2, AcOH)); δ_H (400 MHz; $CDCl_3$) 9.08 (1H, broad s, COOH), 7.31 (5H, m, ArH), 5.39 (1H, broad d, *J*=6.7 Hz, NH), 5.13 (2H, s, CH_2Ph), 4.42 (1H, m, NCH), 1.46 (3H, d, *J*=7.2 Hz, Me).

(R)-(+)-N-*Cbz-norleucine* ***174b***

Obtained from the double bond cleavage of protected amine **173b** as a colourless solid, (57%), m.p. 51-52°C, (lit.,[94] 56-58°C); $[\alpha]_D$ +8.2° (*c*=1, MeOH), (lit.,[94] $[\alpha]_D$ +10.0° (*c*=1, MeOH)); δ_H (250 MHz; $CDCl_3$) 7.36 (5H, m, ArH), 5.25 (1H, broad d, *J*=6.7 Hz, NH), 5.13 (2H, s, CH_2Ph), 4.40 (1H, m, NCH), 1.87 (1H, m, CH_2), 1.70 (1H, m, CH_2), 1.35 (4H, m, $2CH_2$), 0.90 (3H, broad t, Me).

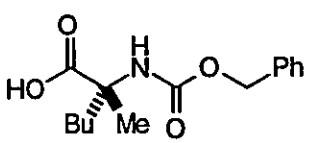
(R)-(+)-N-*Cbz-leucine* ***174c***

Obtained from the double bond cleavage of protected amine **173c** as a colourless oil, (36%); $[\alpha]_D$ +12.5° (*c*=1, EtOH), (lit.,[94] $[\alpha]_D$ +15.0° (*c*=2, EtOH)); δ_H (250 MHz; $CDCl_3$) 7.35 (5H, m, ArH), 5.19 (1H, broad d, *J*=6.7 Hz, NH), 5.12 (2H, s, CH_2Ph), 4.42 (1H, m, NCH), 1.62 (3H, m, CH, CH_2), 0.95 (6H, 2d, 2Me).

(R)-(+)-N-*Cbz-phenylglycine* ***174d***

Obtained from the double bond cleavage of protected amine **173d** as a colourless solid, (55%), m.p. 127-128°C, (lit.,[95] 128-131°C); $[\alpha]_D$ -110.0° (*c*=4, EtOH), (lit.,[95] $[\alpha]_D$ -116.5° (*c*=4, EtOH)); δ_H (250 MHz; $CDCl_3$) rotamers 7.34 (10H, m, ArH), 5.86 (1H, broad d, *J*=6.2 Hz, CH), 5.40 (1H, broad d, *J*=6.4 Hz, NH), 5.10 (2H, s, CH_2Ph).

(R)-(-)-N-*Cbz-2-carboxy-2-hexylamine* ***186***



Obtained from the double bond cleavage of protected amine **(R)-185** as a colourless oil (64%), (Found: M^+, 279.1476. $C_{15}H_{21}NO_4$ requires M, 279.1470); $[\alpha]_D$ -4.1° (*c*=1.6 EtOH); υ_{max} (film)/cm^{-1} 3346, 2959, 1713, 1505, 1455; δ_H (250 MHz; $CDCl_3$) 7.34

(5H, m, ArH), 5.63 (1H, broad s, NH), 5.10 (2H, d, *J*=7.1 Hz, CH_2Ph), 2.10 (1H, m, CH_2), 1.84 (1H, m, CH_2), 1.60 (3H, s, Me), 1.25 (4H, m, $2CH_2$), 0.87 (3H, t, *J*=6.6 Hz, Me) δ_C (62.9 MHz; $CDCl_3$) 179.5, 179.1, 128.5, 128.4, 127.9, 67.2, 66.5, 36.6, 26.0, 23.2, 22.5, 13.8; *m/z* (EI) 279 (M^+, 3%), 234 (10%), 190 (19%), 144 (11%), 108 (41%), 91 (100%), 42 (17%).

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Appendix

Selected *X*-Ray Crystallography Data

Crystal Data for Oxime Ether 120c.

Empiical Formula	$C_{16}H_{15}NO_3$
Formula Weight	269.299
Crystal Dimensions	1.2 x 0.8 x 0.6 mm
Crystal System	Monoclinic
Lattice Parameters	a = 6.24(1) Å
	b = 31.31(58.08) Å
	c = 8.08(1) Å
	V = 1435.1 $Å^3$
Space Group	$P2_1/c$
Z Value	4
D_{calc}	1.246 g/cm^3
μ(MoKα)	0.51 cm^{-1}

Crystal Data for Oxime Ether 117c.

Empiical Formula	$C_{15}H_{13}NO_3$
Formula Weight	255.272
Crystal Dimensions	1.2 x 1.0 x 0.4 mm
Crystal System	Monoclinic
Lattice Parameters	a = 29.13(20) Å
	b = 12.96(11) Å
	c = 7.82(1) Å
	V = 2634.6 $Å^3$
Space Group	C2/c
Z Value	8
D_{calc}	1.288 g/cm^3
μ(MoKα)	0.52 cm^{-1}

Crystal Data for Oxime Ether 117a.

Empiical Formula	$C_{10}H_{11}NO_3$
Formula Weight	193.08
Crystal Dimensions	0.8 x 0.3 x 0.3 mm
Crystal System	Monoclinic
Lattice Parameters	a = 8.27(1) Å
	b = 11.78(2) Å
	c = 12.20(2) Å
	V = 985.25 Å^3
Space Group	$P2_1/a$
Z Value	4
D_{calc}	1.301 g/cm^3
μ(MoKα)	0.59 cm^{-1}

Crystal Data for Hydroxylamine 121c.HCl.

Empiical Formula	$C_{18}H_{22}NOCl$
Formula Weight	303.83
Crystal Colour, Habit	clear, plate
Crystal Dimensions	0.24 x 0.35 x 0.67 mm
Crystal System	triclinic
Lattice Type	Primitive
Lattice Parameters	a = 9.53(2) Å
	b = 10.91(7) Å
	c = 8.61(6) Å
	V = 854.0 Å^3
Space Group	P1 (#2)
Z Value	2
D_{calc}	1.181 g/cm^3
μ(CuKα)	19.56 cm^{-1}

Crystal Data for Cinnamaldehyde Oxime Ether 171.

Empiical Formula	$C_{19}H_{21}ON$
Formula Weight	279.38
Crystal Colour, Habit	clear, needle
Crystal Dimensions	0.10 x 0.20 x 0.47 mm
Crystal System	orthorhombic
Lattice Type	Primitive
No. of Reflections used for Unit Cell Determination (2θ range)	19 (53.5-68.0°)
Omega Scan Peak Width at Half-height	0.35°
Lattice Parameters	a = 8.0(1) Å
	b = 36.8(1) Å
	c = 5.6(2) Å
	V = 1644(45) $Å^3$
Space Group	$P2_12_12_1$ (#19)
Z Value	4
D_{calc}	1.128 g/cm^3
F_{000}	600.00
μ(CuKα)	5.04 cm^{-1}