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Analogues of Acetyl Acetate As Nucleophiles & Ligands

by

Christopher J. Martin

A Doctoral Thesis

submitted in partial fulfilment of the requirements

for the award


DOCTOR OF PHILOSOPHY

of

Loughborough University

1997

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Abstract

This thesis contains the synthesis of a series of novel ligands that include the enantiomerically pure 2-oxazoline moiety. The thesis also considers the application of new nucleophiles for the palladium catalysed allylic substitution reaction. The synthesis of enantiomerically enriched analogues of γ -amino butyric acid (GABA) is presented.

The first series of ligands are designed as analogues of acetyl acetonate (acac). The ligands include the enantiomerically pure 2-oxazoline ring and a carbonyl moiety. The ligands are available in good yield in two steps. The second series of ligands include a ligating sulfur atom. The synthesis of novel oxazoline-sulfide ligands is detailed. The diastereoselective oxidation of these ligands is considered. Diastereomerically pure oxazoline-sulfoxide ligands are prepared in good yield.

New nucleophiles are applied to the palladium catalysed allylic substitution reaction. The substitution products are available in good yield and with excellent stereoselectivity. The synthesis of analogues of GABA is considered. The preparation of enantiomerically enriched α -substituted- γ -amino butyric acids is presented. The stereocentre is introduced in the first step of the synthesis. The analogues are subsequently isolated in good yield after six steps.

Keywords

oxazoline	ligands	acetyl acetonate	acac	sulfur	sulfoxide
palladium	catalysis	nucleophiles	γ -amino butyric acids	GABA	

Acknowledgements

Let us fling to the winds all moping and madness,
Play us a jig in the spirit of gladness
On the creaky, old squeaky strings of the fiddle.

The why of the world is an answerless riddle
Puzzlesome, tiresome, hard to unriddle
To the seventeen devils with sapient sadness:
Tra la, tra la.

James Joyce

c. 1900

Firstly I would like to thank Jonathan Williams for his support, encouragement and enthusiasm over the past three years. I must acknowledge David Rawson's continuing interest in the research and his contributions to the project throughout, not to mention his excellent hospitality. Also I would like to thank Russ Bowman for his support in the last six months of the thesis.

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For technical support I wish to thank John Kershaw, Alistair Daley, John Greenfield, Linda Sands, Paul Hartopp, Alex Slawin, John Spray, Simon Riggott and the EPSRC mass spectrometry service at Swansea. I would also like to thank Graham Beck for the use of his 'phone and as a source of invaluable information regarding academic bureaucracy.

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I must thank my Mum, Dad, Nicky and the rest of the family for their unswerving support and for their belief in me.

Finally I wish to dedicate this thesis to Louise and Sparkle. I am forever indebted to them for their love.

Abbreviations

Acac	Acetyl acetate
Bn	Benzyl
Bu	Butyl
BMPD	(<i>R,R</i>)-Bis-(2-methylferrocenyl)-propane-1,3-dione
cat.	Catalyst
Cbz	Benzyl chloroformate
GC	Gas chromatography
d.e.	Diastereoisomeric excess
DET	Diethyl tartrate
DIBAH	Diisobutylaluminium hydride
dpm	Dipivaloylmethane
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
e.e.	Enantiomeric excess
hfc	D-3-heptafluorobutyrylcamphorate
hplc	High performance liquid chromatography
Im	Imidazole
IPA	<i>Iso</i> -propyl alcohol
iPr	<i>Iso</i> -propyl
LDA	Lithium diisopropylamide
mCPBA	<i>m</i> -Chloroperbenzoic acid
Me	Methyl
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
py	Pyridine
TFA	Trifluoroacetic acid

TFAA	Trifluoroacetic anhydride
TBAF	Tetrabutylammonium fluoride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
tlc	Thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -Tetramethylethylenediamine
<i>p</i> -Tol	<i>para</i> -Tolyl

Contents

Chapter 1	The Application of the Enantiomerically Pure 2-Oxazoline Moiety in Ligands for Asymmetric Catalysis	1
1.1	Introduction	2
1.2	Ligand Synthesis	3
1.2.1	C ₂ -Symmetric Ligands	4
1.2.2	Asymmetric Ligands	8
1.3	Applications in Asymmetric Synthesis	13
1.3.1	Asymmetric Hydrosilylation of Ketones	13
1.3.2	Cyclopropanation and Aziridination of Alkenes	15
1.3.3	Palladium Catalysed Allylic Substitution	17
1.3.4	Diels-Alder Reaction	19
1.3.5	Miscellaneous Applications	22
1.4	Conclusion	30
Chapter 2	Enantiomerically Pure Analogues of Acetyl Acetonoate as Ligands	31
2.1	Introduction	32
2.1.1	Nickel-Acac Complexes	32
2.1.2	Copper-Acac Complexes	34
2.1.3	Cobalt-Acac Complexes	34
2.1.4	Zirconium-Acac Complexes	35
2.1.5	Manganese-Acac Complexes	35
2.1.6	Oxidation and Reduction Chemistry	36
2.1.7	Enantiomerically Pure Diketone Complexes	38
2.2	Design and Synthesis of Ligands	41
2.2.1	Ligand Design	41
2.2.2	Synthesis of the Ligands	43
2.3	Asymmetric Hetero Diels-Alder Reaction	55
2.4	Conclusion	58

Chapter 3	Oxazoline Ligands Including Sulfur as a Ligating Atom	59
3.1	Introduction	60
3.1.1	Chiral Ligands Including a Ligating Sulfur Atom	60
3.1.2	Copper Catalysed Conjugate Addition to Unsaturated Ketones	62
3.1.3	Palladium Catalysed Allylic Substitution	64
3.2	Sulfur-Oxazoline Ligands	65
3.2.1	Ligand Synthesis	67
3.2.2	Palladium Catalysed Allylic Substitution Reaction	68
3.3	Sulfoxide-Oxazoline Ligands	72
3.3.1	Directed Oxidations at Sulfur with Achiral Oxidants	72
3.3.2	Oxazoline Directed Oxidations	75
3.3.3	Oxidation of the Sulfide Substrates to Sulfoxides	77
3.3.4	Direct Synthesis of the Sulfoxide-Oxazoline Ligands	79
3.4	Conclusion	83
Chapter 4	Analogues of Acetyl Acetate as Nucleophiles	84
4.1	Introduction	85
4.1.1	Important Aspects of the Reaction Mechanism	85
4.1.2	Stereocontrol and Phosphine-Oxazoline Ligands	89
4.1.3	Nucleophiles and Substrates	91
4.2	Palladium Catalysed Nucleophilic Substitution Reaction	92
4.2.1	Results of the Nucleophilic Substitution Reactions	92
4.2.2	Source of Enantioselectivity and Diastereoselectivity	94
4.3	Approaches to Atropine	96
4.4	γ -Amino Butyric Acid	101
4.4.1	Enantiomerically Enriched Analogues of GABA	102
4.4.2	Nucleophilic Substitution Reactions	103
4.4.3	Source of Stereocontrol	106
4.4.4	Synthesis of Substituted Analogues of GABA	107
4.5	Conclusion	110

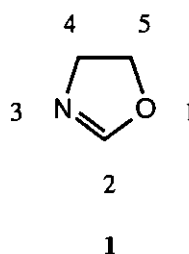
Chapter 5	Experimental	111
5.1	General Information	112
5.2	Experimental for Chapter 2	113
5.3	Experimental for Chapter 3	118
5.4	Experimental for Chapter 4	131
Chapter 6	X-Ray Structure Report	148
6.1	Experimental	149
6.1.1	Data Reduction	150
6.1.2	Structure Solution and Refinement	150
6.1.3	References	151
6.1.4	Experimental Details	152
Chapter 7	References	160

Chapter One

The Application of the Enantiomerically Pure 2-Oxazoline Moiety in Ligands for Asymmetric Catalysis

1.1 Introduction

The 2-oxazoline **1** is a naturally occurring heterocycle which has been known in the literature for over one hundred years.¹ In 1994 Gant and Meyers published a comprehensive review of the literature concerning the chemistry of the 2-oxazoline.² In the review Gant and Meyers discussed the chemistry of the 2-oxazoline in some depth but they only briefly touched upon the use of the enantiomerically pure 2-oxazoline in asymmetric catalysis. It is our intention to consider this topic in more detail.



2-oxazoline

Figure 1

In 1974 Meyers and co-workers published two papers that reported the application of the oxazoline as a recoverable ligand.³ The complexes **2** and **3** were realised by mixing the appropriate reductant with a hydroxyoxazoline to form the chiral reducing agents. In both cases the ligands were used in stoichiometric quantities to facilitate the reduction of prochiral ketones. The oxazoline was subsequently used successfully as an efficient chiral auxiliary by Meyers *et al.*⁴

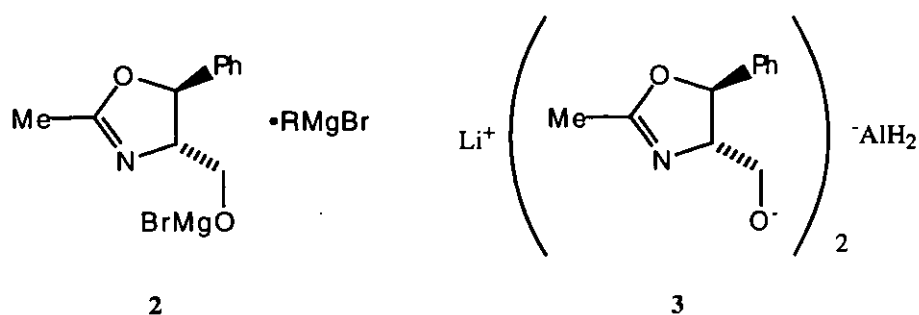


Figure 2

In 1986 Pfaltz and co-workers presented copper-semicorrin complexes as catalysts for the cyclopropanation of alkenes.⁵ The C₂-symmetric semicorrins **4** were shown to be efficient

ligands that readily bound to copper and afforded a complex capable of introducing high levels of enantioselectivity.

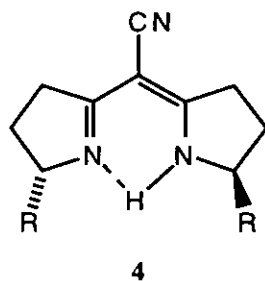


Figure 3

In 1990 Masamune and co-workers presented the bis-oxazoline **5** as a C_2 -symmetric ligand for the copper catalysed cyclopropanation reaction.⁶ Consideration of the reaction conditions allowed the researchers to achieve enantioselectivities of up to 98% e.e.

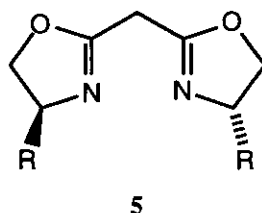


Figure 4

These initial results demonstrated the utility of ligands derived from the skeleton of the semicorrin or bis-oxazoline. The bis-oxazoline has since been reported to form catalytic complexes with a host of metals and these complexes have been used in a variety of useful synthetic processes.⁷

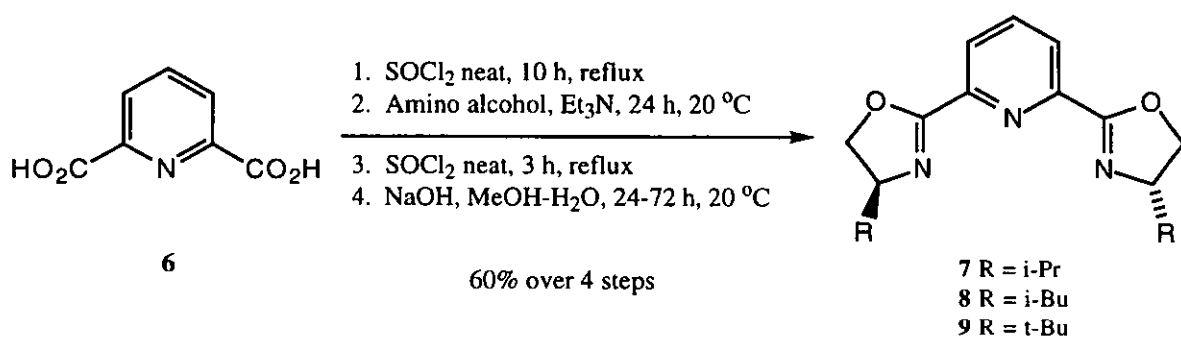
1.2 Ligand Synthesis

Asymmetric ligands for synthesis that include the enantiomerically pure 2-oxazoline moiety are now common in the literature. The ligands are generally straight forward to prepare from enantiomerically pure amino alcohols. The amino alcohols are available from the racemisation free reduction of the appropriate amino acid.⁸ Hence the ligands are derived from a common, versatile skeleton that allows various substitution patterns to be explored

easily. In this way a ligand may be quickly optimised for a particular catalytic process. The ligands fall into two groups those that are asymmetric and those that are C₂-symmetric.

1.2.1 C₂-Symmetric Ligands

The C₂-symmetric group of bis-oxazoline ligands were first introduced by Nishiyama *et al.* in 1989.⁹ The researchers synthesised pyridine, bis(oxazoliny) ligands **7-9** as a new class of chiral ligand for asymmetric catalysis in *ca.* 60% over 4 steps. These ligands, which came to be known as "pybox", were prepared from pyridine-2,6-dicarboxylic acid **6** and an appropriate amino alcohol.



Scheme 1

The bulky alkyl groups on the oxazoline ring were spread over the catalytic site. They directly influenced the geometry of the catalyst and consequently affected the reagents and resultant stereoselectivity of rhodium catalysed hydrosilylation reactions.

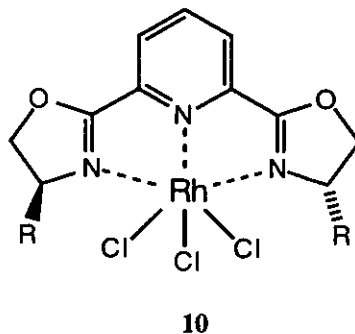
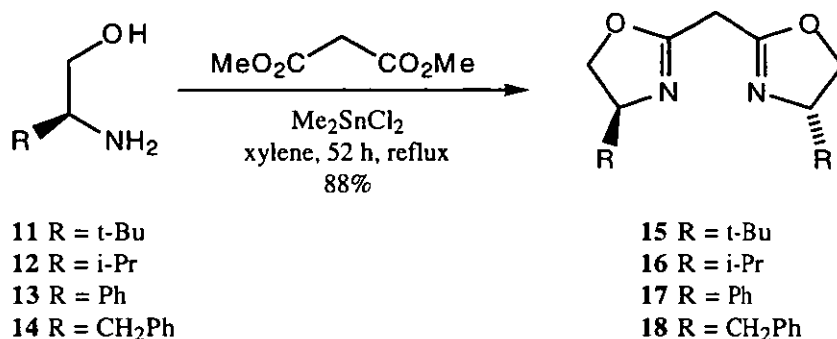


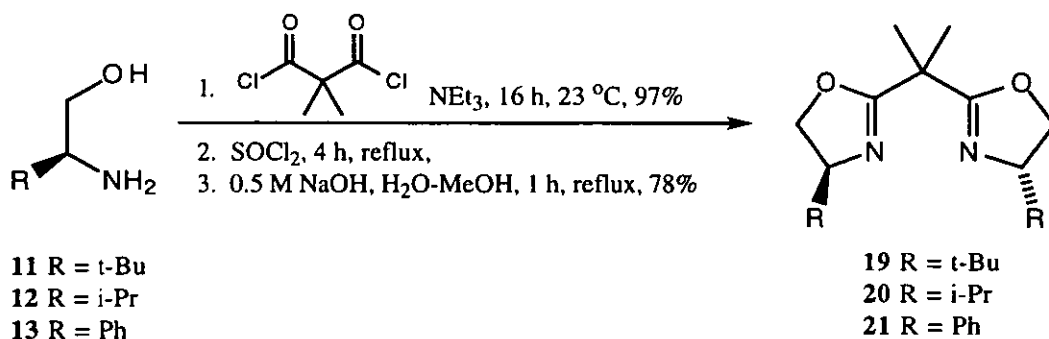
Figure 5

The strengths of the ligand design were apparent and other C₂-symmetric oxazoline ligands quickly followed. Notably Masamune and co-workers published a paper in 1990 that attracted a lot of attention.⁶ The bis-oxazoline ligands **15-18** were prepared directly from dimethyl malonate and a corresponding amino alcohol in good yield.



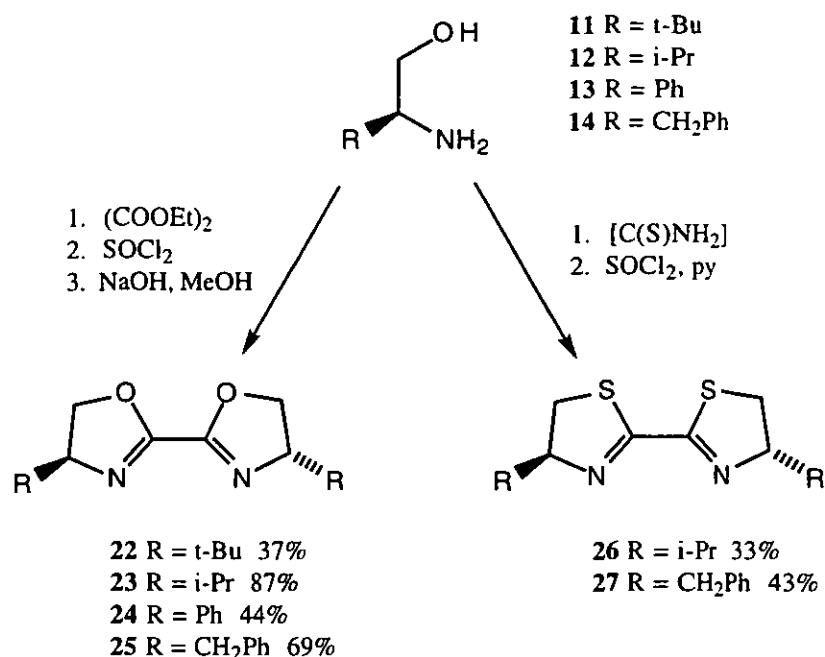
Scheme 2

It was found that the methylene protons of the bridgehead were labile and the ligand tended to form tautomers. It was common for the ligand to be found as its anion. The research groups of both Corey^{10b} and Evans^{10c} synthesised a similar series of ligands **19-21**, in good chemical yield, that included a dimethyl substituted bridgehead. The absence of labile protons prevented any tautomerisation and consequently the ligand remained neutral.



Scheme 3

In 1991 Helmchen and co-workers synthesised C₂-symmetric bis-oxazolines **22-25** and bithiazolines **26-27** that lacked the bridgehead carbon completely.¹¹ The researchers used a similar approach as Corey and Evans to prepare their ligands. Initial formation of an amide, or thioamide, followed by sequential chlorination and cyclisation.



Scheme 4

The ligands **22-27** were able to form 5-membered complexes with metals compared with the 6-membered complexes of the previous bis-oxazolines. Recently several groups have discussed the application of ligands that form a 7-membered chelate.¹² The size of the chelate directly affects the geometry of the metal-ligand complex and hence effects the enantioselectivity of the catalysed reaction. To date the six membered chelates **29** have been studied most extensively. They currently appear to be superior ligands, acting as the most efficient relays of stereochemical information.

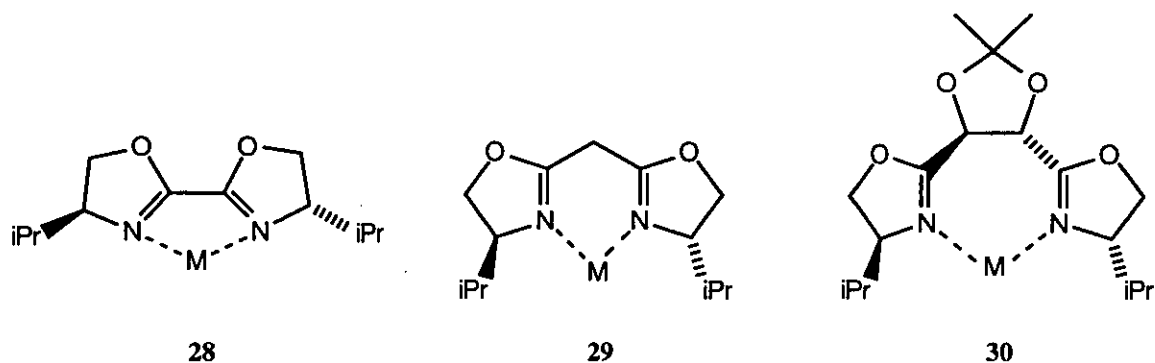
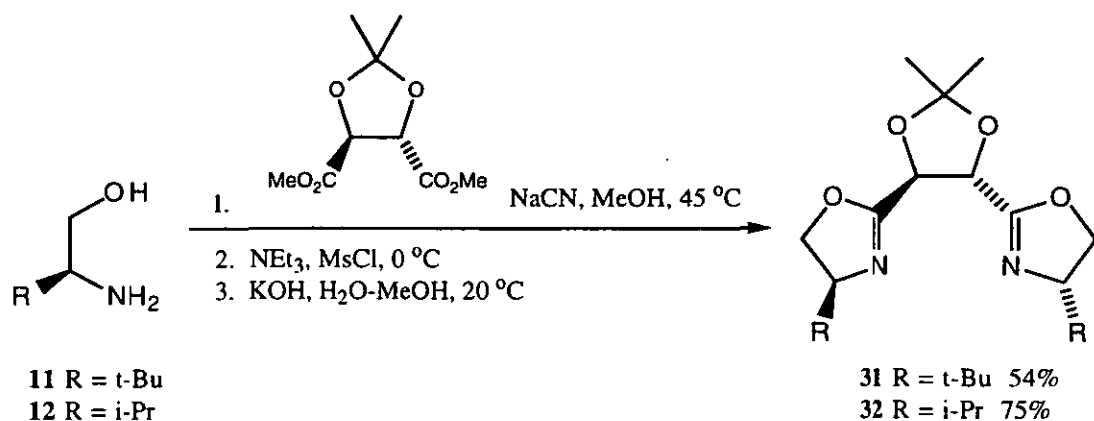


Figure 6

The latest bis-oxazoline ligands are derived from a tartrate skeleton. In the synthesis of these ligands the alcohol is activated to act as a leaving group by the formation of a mesylate

ester.¹³ This results in an efficient synthesis using milder conditions than those previously employed.



Scheme 5

In 1996 the research groups of Ikeda¹⁴ and Hayashi¹⁵ both published novel C₂-symmetric ligands that included the enantiomerically pure 2-oxazoline moiety and another C₂-symmetric unit. The ligand synthesised by Hayashi and co-workers combined the C₂-symmetry of the binaphthyl moiety with the carbon centred chirality of the oxazoline. Both diastereomers were synthesised and separated to provide each diastereomer in an isolated yield of over 70%.

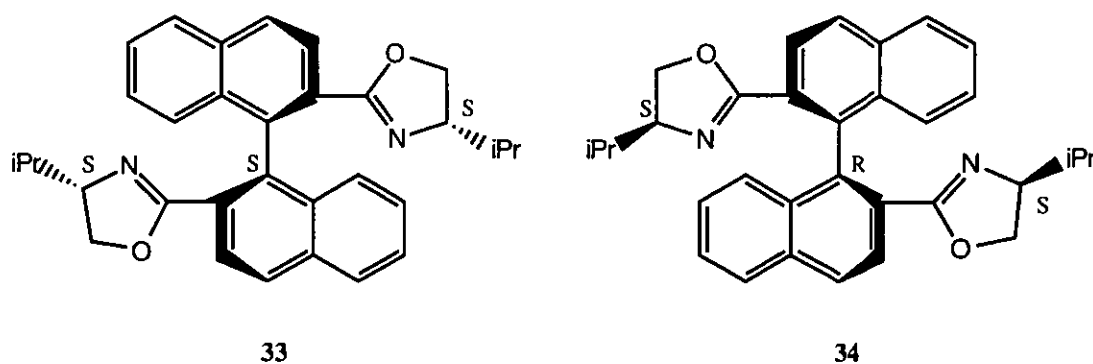
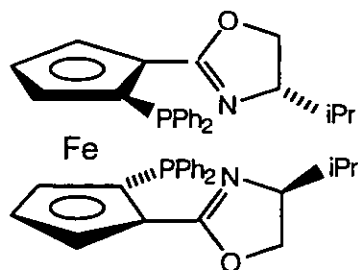


Figure 7

Ikeda's ligands were obtained from the highly diastereoselective *ortho*-lithiation of 1,1'-bis(oxazoliny)ferrocenes. The ligand 35 was isolated as the major product in good chemical yield.



35

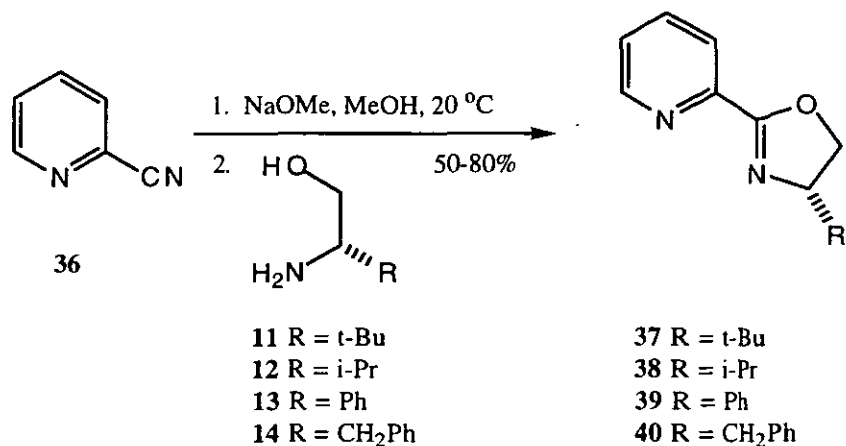
Figure 8

The utility of the ligands detailed above and the following asymmetric ligands shall be discussed in due course. They have found application in a wide range of catalytic processes. The success of these ligands is partly due to their ease of preparation and the flexibility of the syntheses which allows researchers to readily access a range of analogues and tune a ligand for a particular reaction.

1.2.2 Asymmetric Ligands

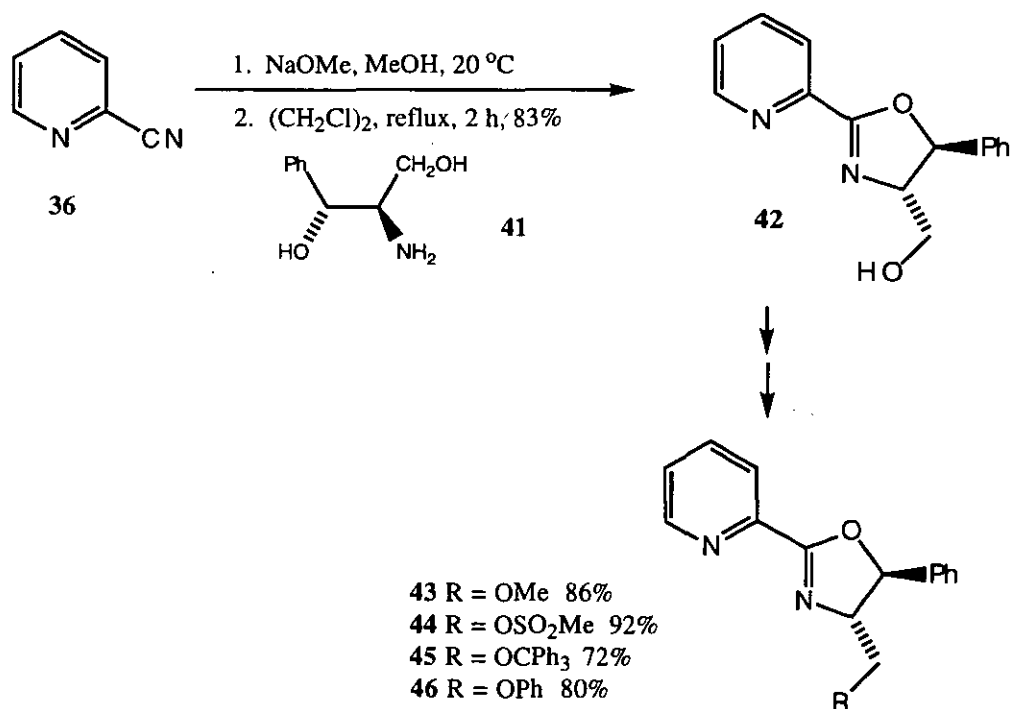
In addition to the successful C_2 -symmetric ligands there have been several ligand systems that lack this symmetry. The asymmetric ligands are characterised by an enantiomerically pure 2-oxazoline moiety tethered to an auxiliary donor atom. Several hetero-atoms have been used as the second chelating atom including phosphorus,¹⁹⁻²¹ sulfur,²² nitrogen,²⁴ oxygen^{22b} and selenium.²³ The resultant bidentate ligands have been shown to be efficient ligands in a variety of catalytic processes.

In 1989 Brunner and Obermann synthesised 2-(2-pyridinyl)-2-oxazolines **37-40** as ligands for rhodium.¹⁶ These simple, readily available ligands proved to be efficient sources of stereocontrol in the rhodium catalysed hydrosilylation of acetophenone.



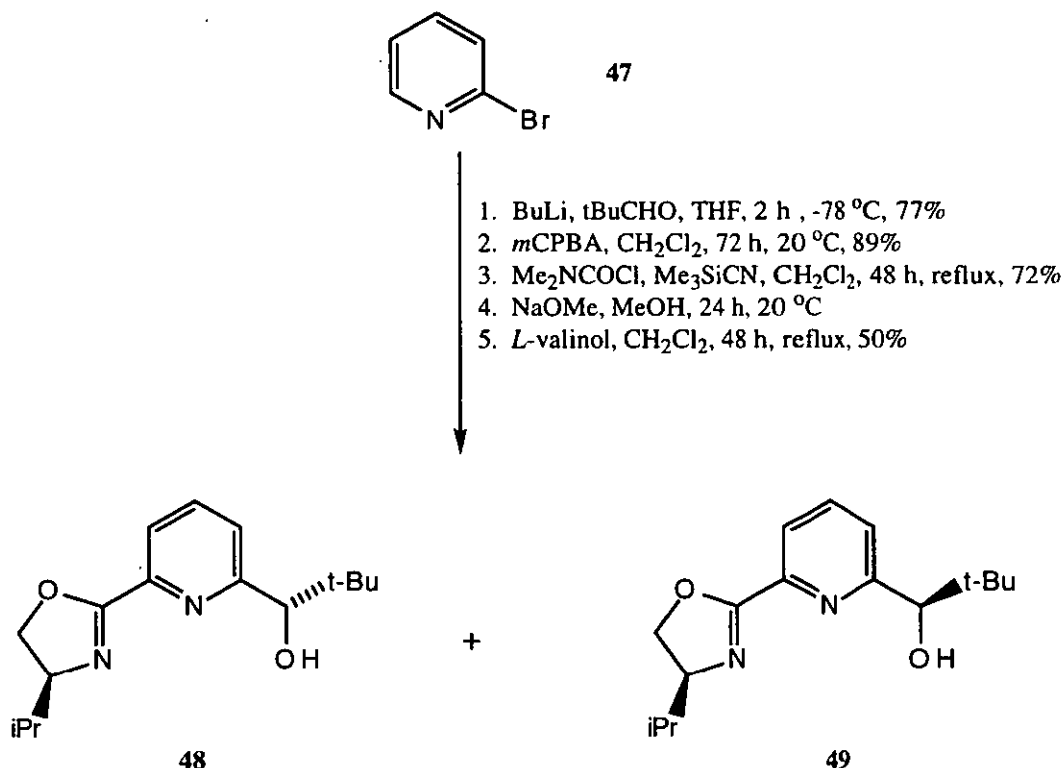
Scheme 6

Balavoine *et al.* synthesised similar ligands **42-46** in 1989.¹⁷ The ligands were generally tridentate with the extra chelating moiety attached to the 4 position of the oxazoline ring. The ligands were prepared from a common starting material, (4*S*,5*S*)-4-hydroxymethyl-5-phenyl-2-(2-pyridinyl)-1,2-oxazoline **42** which is available on a hundred gram scale. The hydroxy functionality allowed the researchers to elaborate the intermediate ligand and access a variety of pendant groups.



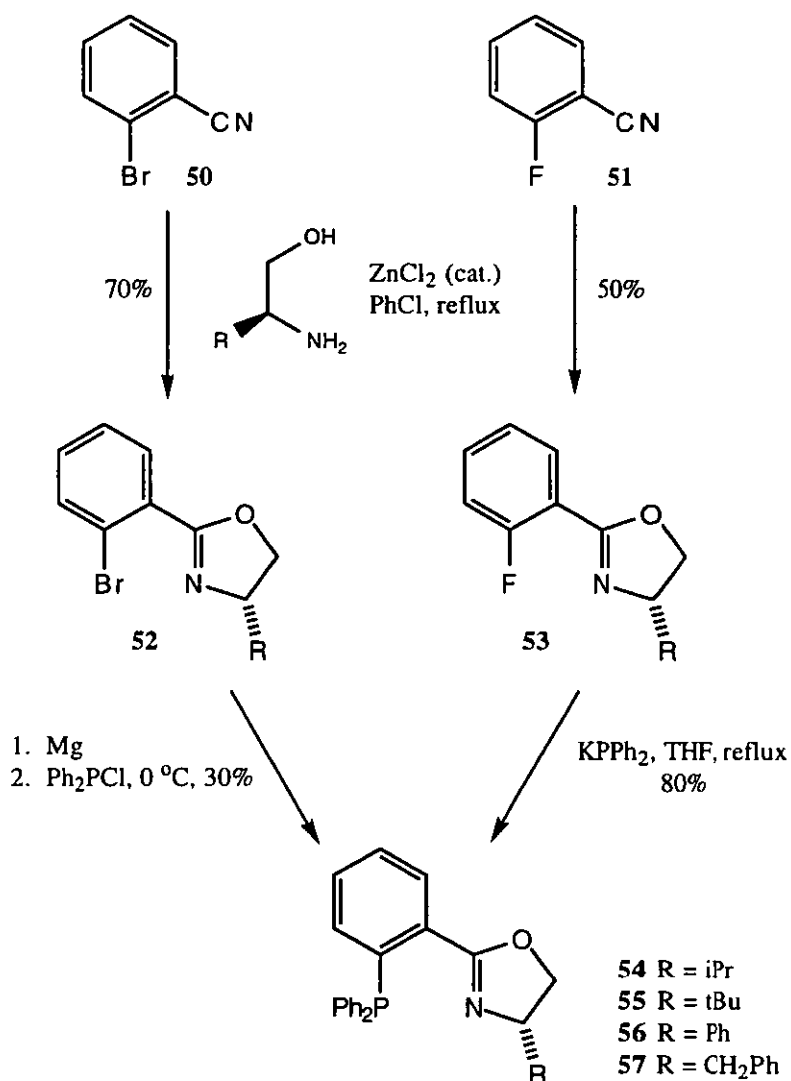
Scheme 7

Recently Macedo and Moberg have applied a similar ligand to the enantioselective addition of diethyl zinc to aldehydes.¹⁸ The ligands were synthesised in five steps as a mixture of diastereomers before being separated to provide **48** and **49** as individual isomers in moderate yield.



Scheme 8

In 1993 Helmchen,¹⁹ Pfaltz²⁰ and Williams²¹ independently published synthetic routes to chiral arylphosphine-oxazolines **54-57** as novel ligands for the palladium catalysed allylic substitution reaction. These ligands have subsequently been very successful in this and other reactions which will be detailed later. The synthetic approaches to these ligands are similar, all providing the desired ligands in good chemical yield. Pfaltz and Helmchen favour the reaction of a Grignard reagent formed from **52** with chlorodiphenyl phosphine or chloro-(1-naphthyl)-phenyl phosphine to produce the air stable ligands. Williams and co-workers alternatively use potassium diphenylphosphide to introduce phosphorus into the ligand.



Scheme 9

In addition Williams,²² Helmchen²³ and Fujisawa²⁴ have used this chemistry to develop a series of ligands where nitrogen, selenium, sulfur or oxygen are the chelating hetero-atom. A selection of these ligands is illustrated below.

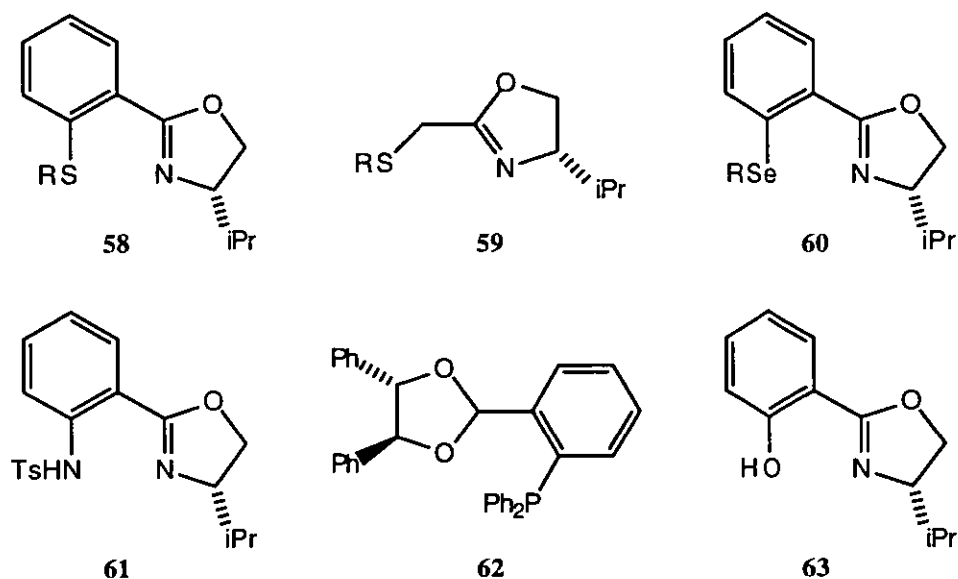


Figure 9

Recently Evans and Brandt have published a novel ligand **64** for palladium catalysed allylic substitution.²⁵ The ligand includes an oxazoline moiety which derives its stereochemistry from (-)- β -pinene. The ligand illustrated below is clearly related to ligand **54** and consequently behaves in a similar manner in the substitution reaction.

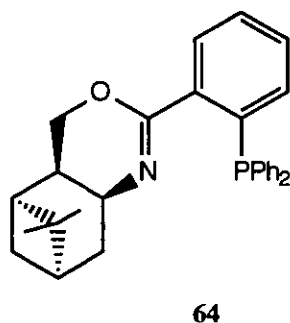


Figure 10

In conclusion, the enantiomerically pure 2-oxazoline moiety has become an important part of many modern ligands for asymmetric catalysis. The oxazoline is simple to prepare and analogues are easily accessible from commercially available starting materials. This ligand system has been successful in a variety of catalytic processes which are detailed below.

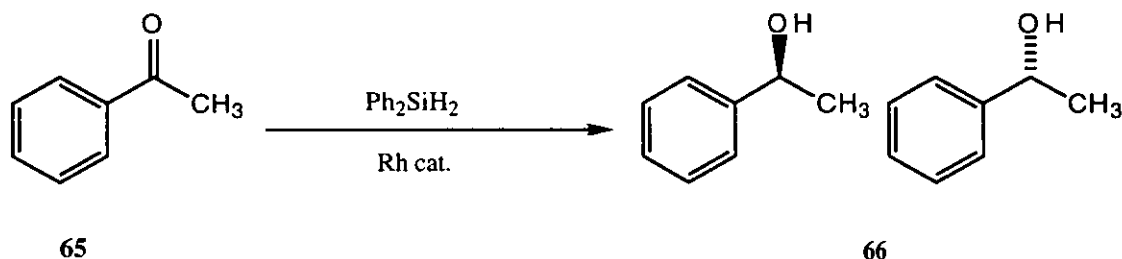
1.3 Applications in Asymmetric Synthesis

The ligands detailed above have proved themselves to be effective relays of stereochemical information in a variety of synthetic processes. The ligands form stable complexes with a variety of metals and these complexes are able to catalyse a host of reactions. A survey of these results is presented below.

1.3.1 Asymmetric Hydrosilylation of Ketones

Several of the ligands that we have considered have been applied to the asymmetric hydrosilylation of ketones.²⁶ In particular "pybox"²⁷ **7-9** but also 2-(2-pyridinyl)-2-oxazoline **37-40** and its analogues **42-46**,^{16,17} the bisoxazolines **22-25** and bithiazolines **26-27**,¹¹ phosphine-oxazoline ligands^{22c,23} **54-57** and tartrate based ligands **31-32**.¹⁴

The reduction of acetophenone with diphenylsilane in the presence of a rhodium catalyst is generally used as a comparative test for the efficacy of a new ligand.



Scheme 10

Brunner and Obermann studied hydrosilylation in the presence of 2-(2-pyridinyl)-2-oxazolines **42-46** and found they could achieve reasonable levels of enantiocontrol in the right conditions.¹⁶ The best combination of conditions produced a chemical yield of 90% and 83% e.e. This result was dependent on the particularly bulky ligand **37** and the solvent. In addition the ratios of substrate, diphenylsilane, rhodium and ligand were also found to be important. The levels of stereoselectivity fell away quickly as the size of the alkyl substituent decreased. The solvent of choice was carbon tetrachloride, the use of other

solvents eroded the enantioselectivity. The optimum ratio of reagents was: rhodium:ligand 1:10; rhodium:acetophenone 1:50 and acetophenone:diphenylsilane 1:0.25.

Following on from this work, Balavoine and co-workers published their studies of hydrosilylation in the presence of the pyridine ligands **42-46**.¹⁷ The researchers performed the reaction under similar conditions to Brunner and Obermann. The most successful ligand was **45** where the pendant group is a bulky trityl ether. They found that the use of α -naphthyl phenylsilane as the reducing agent raised the stereoselectivity from 63% e.e. to 80% e.e. in excellent chemical yield. Balavoine believed that the significant factors in introducing high levels of stereoselectivity were the sheer bulk of the ligand and the silane reagent. The additional chelating moiety they had included in their ligand seemed to be of little benefit.

Nishiyama *et al.* found that the reduction of acetophenone and other prochiral ketones proceeded with excellent enantioselectivity in the presence of rhodium-pybox complexes.^{27a} The highest levels of selectivity and reactivity were obtained using **7** where the bulky substituent is *iso*-propyl. The use of smaller groups and the bulkier *t*-butyl all resulted in a less efficient catalyst. The pybox-RhCl₃ complex was found to be a poor catalyst until the addition of a small quantity of silver salts initialised the reaction. The reaction then proceeded smoothly to produce (*S*)-phenylethanol in 91% yield and 94% e.e. The reduction of other prochiral ketones resulted in a variety of alcohols in good to excellent levels of enantioselectivity, 60-99% e.e. In later work the researchers found that electron-withdrawing substituents on the "pybox" ligand increased the rate of hydrosilylation.^{27b} The change in overall electron density on the complex did not significantly affect the levels of enantioselectivity.

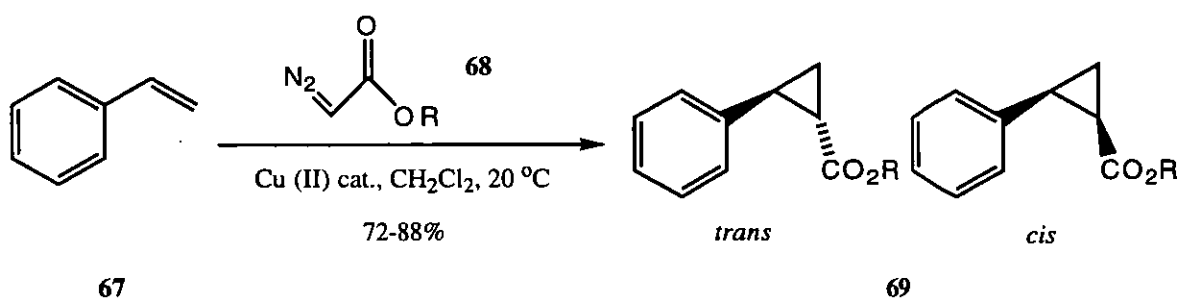
In 1991 Helmchen and co-workers tested their new bisoxazoline **22-25** and bithiazoline **26-27** ligands in the rhodium catalysed hydrosilylation of prochiral ketones.¹¹ Unfortunately the reaction generally proceeded with mediocre results but enantioselectivities of 70% and 84% e.e. were achieved. Likewise Ikeda and co-workers recently applied their novel tartrate based bisoxazoline ligands to this reaction.¹⁴ Their results demonstrated the potential of this class

of ligand but the results showed inconsistent levels of enantioselectivity below 70% e.e. Helmchen²³ and Williams^{22c} both reported using **54-57** as ligands for rhodium. Williams and co-workers achieved their best results when the reactions were run at -78 °C, producing **66** in an isolated yield of 86% and 82% e.e. It was found that the use of naphthyl phenylsilane compared with diphenylsilane increased the enantioselectivity to 86% e.e. Helmchen and co-workers also reported an increase in selectivity due to the use of the more bulky silane. In addition they screened several different ligands for optimum characteristics. Ligand **54** was found to be more effective than ligands with smaller or bulkier substituents. Helmchen and co-workers were able to isolate the product alcohol in 95% yield and 82% e.e. It was found that changes in the phosphorus moiety were either detrimental to the results or produced only small changes of *ca.* 3-4% e.e. The phosphine-oxazoline ligands were shown to be consistently good ligands for rhodium but the levels of enantioselectivity achieved were never excellent.

The stereoselective hydrosilylation and reduction of prochiral ketones is a challenging area of research. Nonetheless several ligand systems that include the enantiomerically pure 2-oxazoline moiety have displayed consistently high levels of stereocontrol in this reaction.

1.3.2 Cyclopropanation and Aziridination of Alkenes

In 1990 Masamune presented the bisoxazolines **15-18** as new ligands for the copper catalysed cyclopropanation of alkenes.⁶ The researchers studied the cyclopropanation of styrene with ethyl diazoacetate.



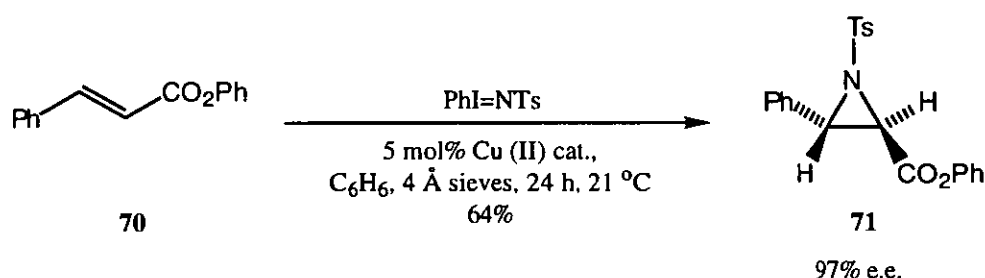
Scheme 11

In this instance the most effective ligand was **15** where the particularly bulky *t*-butyl is present. A *trans:cis* ratio of 3:1 was achieved but more importantly the levels of enantioselectivity were also high 90% and 77% e.e. respectively. These results were further enhanced by the selection of the appropriate diazo reagent. The use of chiral menthyl esters raised the levels of stereoselectivity. In particular the use of a *l*-(-)-menthyl diazo ester resulted in a *trans:cis* ratio of 84:14 and 98% and 96% e.e. respectively. These results were then shown to be consistent across a range of prochiral alkenes. Masamune and co-workers went on to investigate a series of bisoxazoline ligands and different alkene systems.^{10a} They found that the *trans:cis* ratio depended almost exclusively on the structure of the alkene and the structure of the diazo ester. The highest levels of enantioselectivity were the result of using particularly bulky ligands.

Independently Evans and co-workers published a similar study early in 1991.^{10c} Not surprisingly they also found that the *trans:cis* ratio was directly related to the structure of the diazo ester. The researchers were able to increase the selectivity for the *trans* isomer to 94:6 with the *trans* isomer having an enantiomeric excess of 99%. The most successful conditions included the bulky ligand **15** with the diazoacetic acid ester derived from 2,6-di-*tert*-butyl-4-methylphenol. Evidently such bulky reagents provide for a sterically demanding environment in the catalytic cycle resulting in excellent levels of stereocontrol.

Several other research groups have applied their ligands to asymmetric cyclopropanation with mixed results. The binaphthyl ligands **33-34** of Hayashi and co-workers performed well in the reaction. The highest levels of stereoselectivity were a *trans:cis* ratio of 68:32 including enantiomeric excesses of 95% and 97% respectively. Unfortunately these results were not consistent but they demonstrated the continuing importance of bulky ligands to achieve good results. Andersson and Knight independently applied their tartrate based bisoxazoline ligands **31-32** to copper catalysed asymmetric cyclopropanation.^{12a,12c} The results were varied but careful selection of the reaction conditions allowed the researchers to access levels of stereoselectivity of up to a *trans:cis* ratio of 77:23 and enantioselectivities of 98% and 93% respectively.

Many of the research groups mentioned above have also considered asymmetric aziridination alongside their investigations into asymmetric cyclopropanation. Evans²⁸ and Masamune^{10a} both briefly discussed aziridination whilst presenting results for asymmetric cyclopropanation. Their best results were 61% e.e. and 88% e.e. respectively. Evans and co-workers took these initial results further and reached levels of stereoselectivity of 94-97% e.e. with several prochiral alkenes. On this occasion ligand **17** was found to be the most appropriate ligand. The more bulky **15** was found to be less efficient under the reaction conditions. In addition a more sterically demanding alkene facilitated greater levels of stereocontrol.



Scheme 12

Knight and co-workers found that their ligands **31-32** provided for only mediocre levels of stereoselectivity in the asymmetric aziridination reaction although the products were available in good chemical yield.³⁰ Enantioselectivities ranged from 2%-18% e.e. with isolated yields of up to 85%.

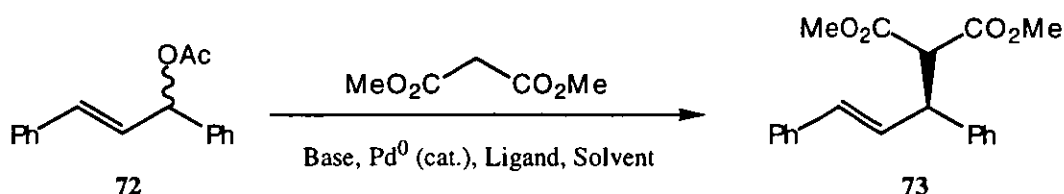
The ligands under consideration have been shown to provide high levels of stereocontrol in cyclopropanation and aziridination reactions. They form efficient catalytic complexes with copper and are able to relay stereochemical information under a variety of conditions.

1.3.3 Palladium Catalysed Allylic Substitution

There has been intense interest in the palladium catalysed allylic substitution reaction over the past few years. Several research groups, notably those of Helmchen¹⁹, Pfaltz²⁰ and Williams²¹, have applied significant research efforts to this reaction using oxazoline ligands.

The main areas of interest have been the development of novel ligands, the investigation of suitable nucleophiles³¹ and the elaboration of the substitution products into simple natural products.³²

The palladium catalysed reaction of diphenylpropenylacetate **72** with dimethylmalonate has become established as the standard reaction in which to test the efficacy of new ligands. The reaction proceeds smoothly to generally yield the substitution product **73** in good chemical yield. The level of enantioselectivity may be determined directly from **73** either by using chiral shift ¹H-NMR techniques or by chiral hplc analysis.



Scheme 13

Several ligand systems have been applied to this reaction under a variety of conditions of base, solvent and temperature. In 1991 Pfaltz published a preliminary result where **73** was isolated in 86% yield and 77% e.e.³³ In this case the bisoxazoline ligand **25** provided the stereocontrol.

In 1993 several research groups^{19,20,21} independently synthesised ligands **54-57** which provided for excellent levels of stereocontrol. The results ranged from yields of 85-98% and good to excellent levels of enantioselectivity, 85%-98% e.e. There was a clear correlation between the substituents on the oxazoline ring and the level of stereocontrol. The enantiomeric excesses increased as the size of the substituent increased. The results peaked at *iso*-propyl with *tert*-butyl being found to be too bulky, 98% e.e. compared with 95% e.e. Other subsequent analogues of **54** have met with mixed results. The exchange of phosphorus for sulfur as the second donor atom lead to an extensive series of ligands.³⁴ These ligands **58-59** provided for excellent yields and very high levels of stereocontrol but they were unable

to match the phosphine-oxazoline ligands. Representative results include almost quantitative yields and levels of selectivity up to 92% e.e.

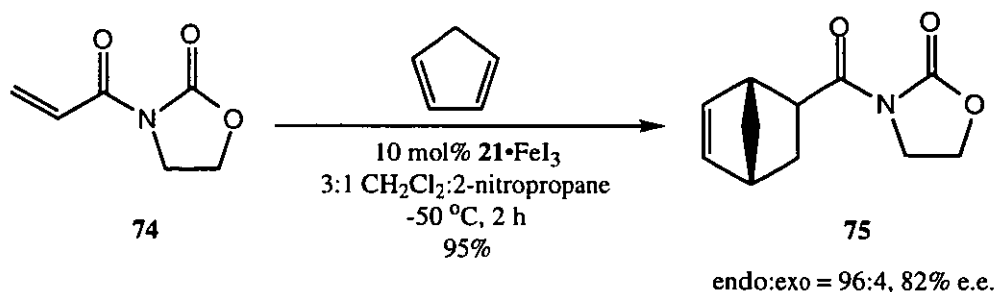
Ikeda and co-workers recently achieved excellent levels of stereocontrol, comparable to the phosphine-oxazoline ligands, with their ferrocene based C₂-symmetric ligands **35**.¹⁴ The isolated chemical yields were over 90% and enantiomeric excesses were consistently between 93% and 99% e.e.

The reliability of this reaction, its consistently high chemical yields and excellent levels of stereocontrol have prompted several researchers to use the substitution products as starting materials in asymmetric synthesis. For instance the substitution products have been elaborated into β -amino acids,^{32a} succinic acids and γ -lactones.^{32b}

1.3.4 The Diels-Alder Reaction

Metal complexes with bis-oxazoline ligands **19-21** and "pybox" ligands **7-9** have been found to be efficient catalysts for both the Diels-Alder reaction and the hetero Diels-Alder reaction.

In 1991 Corey and co-workers used a complex of bis-oxazoline **21** and iron (III) to catalyse the reaction of dienophile **74** and cyclopentadiene to realise the product **75** in 82% e.e. and endo:exo selectivity of 96:4.^{10b}



Scheme 14

The researchers rationalised that an octahedral complex of **74** and the ligand **21** around the Fe(III) atom would activate **74** to reaction with cyclopentadiene at low temperatures. The

geometry of the product being determined by the stereochemical environment around the catalyst.

Corey and Ishihara also studied a similar system where a magnesium complex **76** was the catalyst.³⁵ The researchers were interested in the tetrahedral geometry of such a complex in comparison to the octahedral complex previously reported. In fact the results were very similar for both systems.

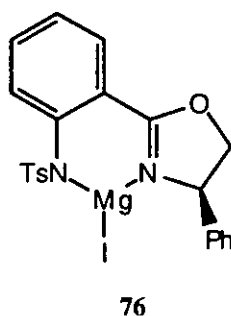
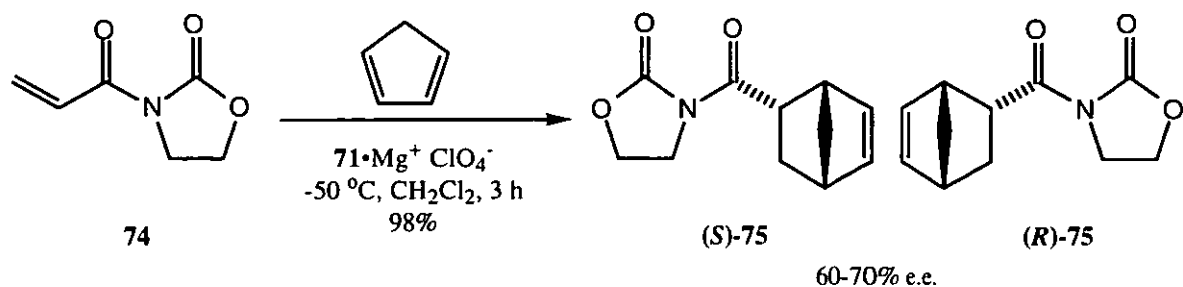


Figure 11

The research groups of Fujisawa²⁴ and Desimoni³⁶ have also applied magnesium based catalysts to the Diels-Alder reaction. Fujisawa and co-workers found that the use of **76** as a catalyst required relatively high concentrations of the complex but the desired product **75** was isolated in a yield of 81% and 91% e.e.

Desimoni and co-workers found that they could isolate either enantiomer of **75** in excess by the selecting the appropriate of reaction conditions. Initially the reaction had produced (*S*)-**75** in excellent yield and moderate stereoselectivity, 68%-70% e.e. The addition of 2 equivalents of water resulted in the opposite enantiomer (*R*)-**75** being formed in excess, 59%-65% e.e. The researchers proposed that the addition of water to the complex **76** changed the co-ordination geometry around the magnesium. The water molecules were believed to co-ordinate axially to the magnesium resulting in a change from tetrahedral to octahedral geometry. Consequently a different steric environment was presented to the incoming reagents. The most accessible face of the complex had changed, the result was the other enantiomer being formed in excess.



Scheme 15

It has been demonstrated that the best levels of stereocontrol in the Diels-Alder reaction involving oxazoline ligands are achieved in the presence of copper. Ghosh *et al.* showed that the bulky ligand **77** was most effective in relaying stereochemical information in association with copper (99% e.e.) rather than iron (65% e.e.) or magnesium (65% e.e.).³⁷

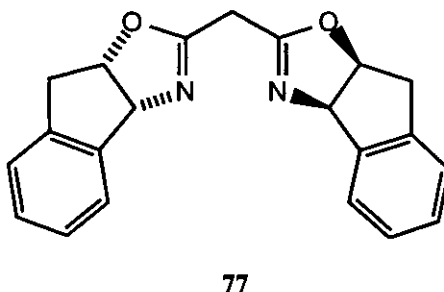


Figure 12

Evans *et al.* successfully used ligands **19-21** to introduce high levels of enantioselectivity into a copper catalysed Diels-Alder reaction in 1993.³⁸ The results showed a clear relationship between the structure of the bisoxazoline ligand and the level of enantioselectivity. Where previously the substitution on the oxazoline had been phenyl **21**, the best ligand **19** now included the large *tert*-butyl group. The enantioselectivities were seen to rise from 30% e.e. to >98% e.e. The ligand was then shown to display consistently excellent levels of stereocontrol in the reaction of the various dienophiles with cyclopentadiene, the products were isolated in high yields 82-93% and 90-98% e.e.

The researchers investigated copper-pybox **78** complex as a catalyst in the Diels-Alder reaction.^{38b} They found that the rate of reaction and extent of conversion were strongly dependent on the nature of the counter ion. Where the counter ion was $^- \text{OTf}$ the reaction

required 120 h to go to completion, compared with just 8 h when SbF_6^- was the counter ion. The best results from this study allowed the researchers to isolate the product in 85% yield and 99% e.e. The other results were also consistently high for a series of dienes and dienophiles, demonstrating the flexibility of the catalyst.

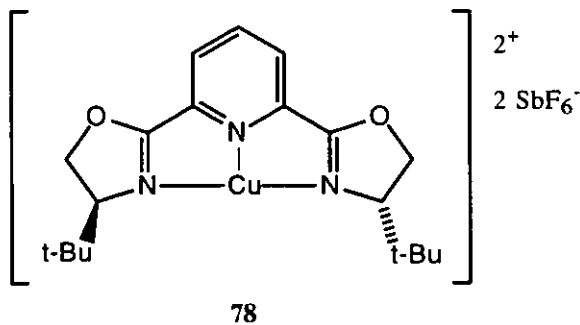


Figure 13

Evans and co-workers also assessed zinc-bisoxazoline complexes as catalysts for the Diels-Alder reaction.^{38c} They found that the zinc complexes were efficient catalysts but the copper analogues were still superior as shown by a reaction time of 8 h vs. 4 h and enantioselectivities of 92% e.e. vs. >98% e.e.

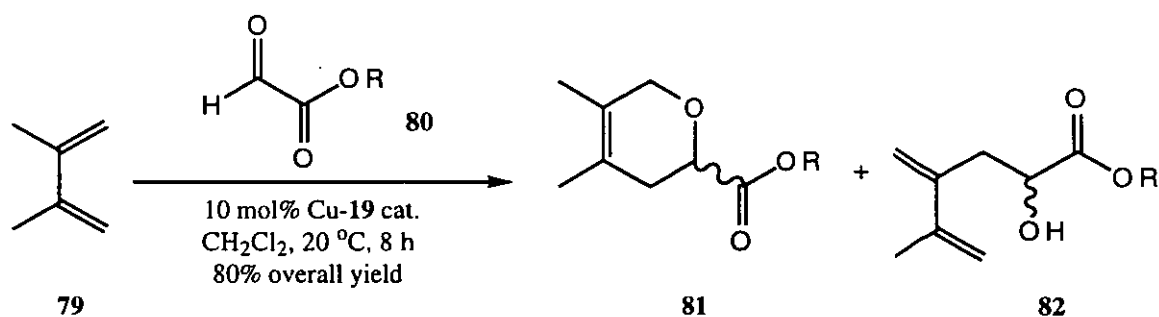
The oxazoline moiety has made a significant contribution to the efficacy of ligands for the Diels-Alder reaction. It is able to provide for very high levels of stereocontrol in this powerful and important synthetic tool.

1.3.5 Miscellaneous Applications

In addition to the major areas of research discussed previously there are several areas of chemistry where the oxazoline has only made a brief appearance to date.

1.3.5.1 Asymmetric Hetero Diels-Alder and Ene Reactions

Johannsen and Jorgensen used a copper complex of bisoxazoline **19** to catalyse the reaction of glyoxylate esters with dienes to produce hetero Diels-Alder products.³⁹

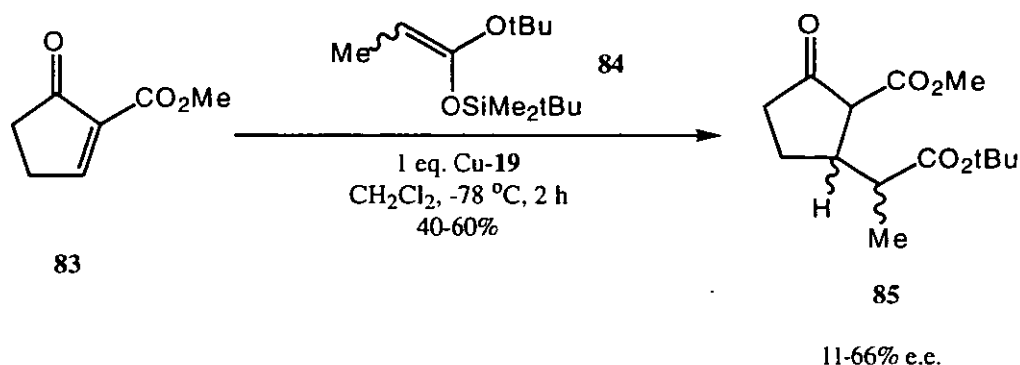


Scheme 16

The researchers found that they constantly produced a mixture of **81** and **82**. The ratio of **81**:**82** was directly affected by the substitution on the glyoxylate ester. The bulky *iso*-propyl ester encouraged the formation of the Diels-Alder product, whereas smaller substituents favoured the acyclic product. It was noted that the size of the ester had little or no influence on the level of enantioselectivity. The levels of enantioselectivity generally ranged between 80% and 90% e.e. although chemical yields were often mediocre. The highest levels of stereocontrol occurred at lower temperatures at the expense of the isolated yield. Nonetheless useful levels of stereocontrol have been achieved in this reaction.

1.3.5.2 Mukaiyama-Michael Reactions

Scolastico and co-workers have used a copper complex including ligand **19** to promote and catalyse the enantioselective conjugate addition of enol silanes to activated double bonds.⁴⁰



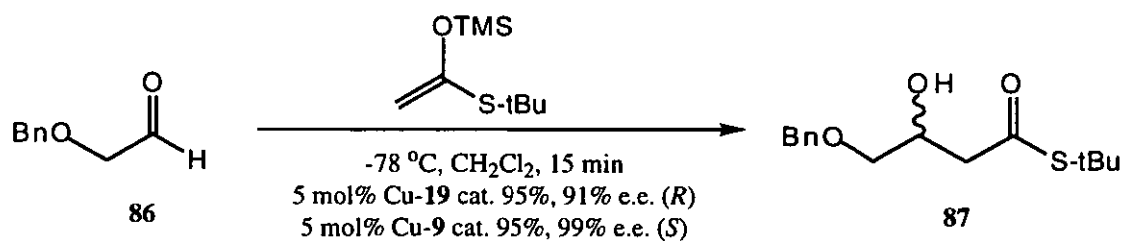
Scheme 17

The copper complex of **19** was initially used in stoichiometric quantities to promote the reaction. Once the researchers had established the optimum conditions for their study they reduced the quantity of the complex to catalytic levels. The product of the catalytic system was available in poor yield initially but with a reasonable level of stereocontrol.

Improvement in the catalytic conditions, including the choice of a less polar solvent, provided for the isolation of **85** in 65% yield, 63% e.e. and 72% d.e. The best stoichiometric result was a 63% yield, 66% e.e. and 80% d.e. The catalytic process was eventually only slightly less selective than the stoichiometric reaction.

1.3.5.3 The Mukaiyama-Aldol Reaction

Evans and co-workers have applied complexes Cu-**9** and Cu-**19** to the question of selective aldol reactions in addition to the Diels-Alder work presented above.⁴¹ They found the copper complexes to be efficient catalysts for this reaction and achieved excellent levels of stereocontrol.

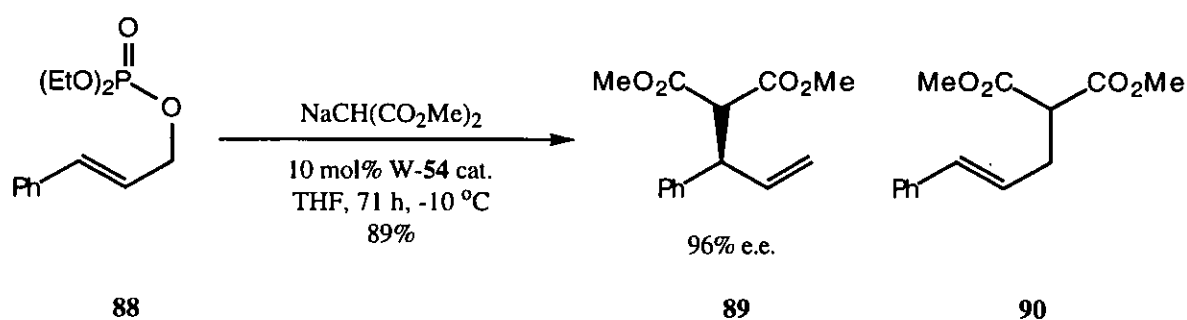


Scheme 18

The researchers were able to isolate (*R*)-**87** in 91% e.e. when using the bisoxazoline complex Cu-**19** or (*S*)-**87** in 99% e.e. when the reaction was catalysed by "pybox" complex Cu-**9**. Complex Cu-**9** was used to catalyse a series of reactions demonstrating the utility and versatility of the process. All the products were available in high isolated yields, 90-99%, and excellent enantioselectivities, 92-99% e.e. In a similar study Evans *et al.* compared and contrasted copper and zinc complexes with "pybox" **9** as catalysts for the Mukaiyama-Aldol reaction.^{38c} The copper complex was clearly superior to the zinc complex. For instance the copper complex provided the product in 99% e.e. in 15 min compared with a reaction time of 4 h and 78% e.e. for the zinc complex. The copper complex displays the advantage of maintaining a well-defined substrate-catalyst geometry throughout the reaction, in addition to a stronger Lewis acidic character. Consistently making it a more efficient catalyst than its zinc analogue.

1.3.5.4 Tungsten Catalysed Allylic Substitution

Lloyd-Jones and Pfaltz studied the successful phosphine-oxazoline ligand **54** in the tungsten catalysed allylic substitution reaction.⁴² The initial results of this work were discouraging but careful consideration of the reaction conditions allowed the researchers to isolate **89** in 68% yield and 96% e.e.



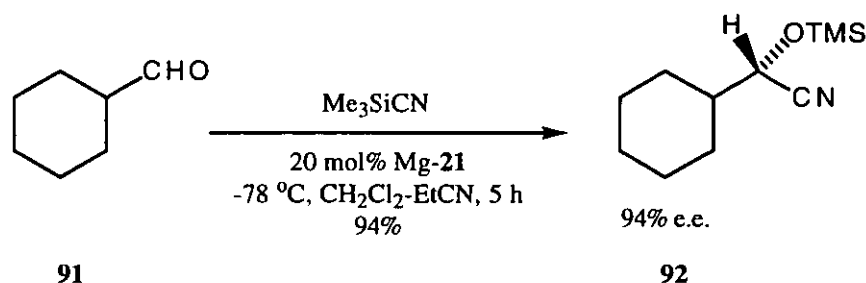
Scheme 19

The most successful conditions required the pre-association of $[\text{W}(\text{CO})_3(\text{CH}_3\text{CN})_3]$ with ligand **54** before the addition of the nucleophile and then the phosphonate **88** under an inert atmosphere. The reaction was then shown to be consistently high yielding and highly

selective with several analogues of **88**. It was also noted that the more bulky substituents on ligand **54** eroded the levels of stereoselectivity. Nonetheless these results further illustrate the utility of the phosphine-oxazoline ligands **54-57**.

1.3.5.5 Additions to Aldehydes

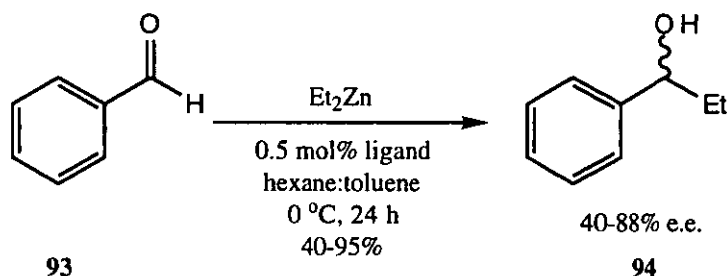
Corey and Wang catalysed the addition of trimethylsilyl cyanide to cyclohexane carboxyaldehyde with a magnesium complex with **21**.⁴³



Scheme 20

Initially **92** was isolated in 85% yield and 65% e.e. It was found that the addition of 12 mol% of **21** as a co-catalyst increased the stereoselectivity to 94% e.e. and a chemical yield of 94%. The enantioselective cyanohydrin synthesis was found to be consistent for a range of non-conjugated aldehydes, 84-95% e.e., although the reduction of benzaldehyde and certain α,β -unsaturated aldehydes was only achieved with moderate levels of stereoselectivity.

Williams and Moberg have both reported the use of oxazolines in the addition of diethylzinc to aldehydes.^{18,22b}



Scheme 21

Allen and Williams used oxazolines **63** to catalyse the reaction and achieved enantioselectivities of up to 67% e.e. Macedo and Moberg found that the pyridyloxazolines **48-49** were able to catalyse the addition of diethylzinc to realise the product alcohol in 95% yield and 88% e.e. Both research groups found that their results were sensitive to the substitution pattern on the aldehyde as well as the bulk of the ligand. Electron donating groups on the benzene ring provided for less reactive aldehydes and greater levels of stereoselectivity.

1.3.5.6 Allylzincation

The research groups of Hanessian⁴⁴ and Nakamura⁴⁵ have both used zinc-oxazoline complexes **95** to enantioselectively introduce an allyl moiety.

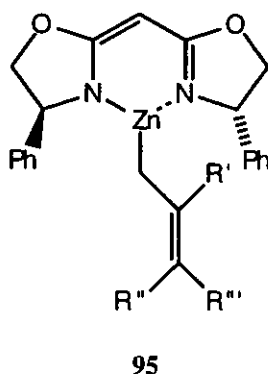
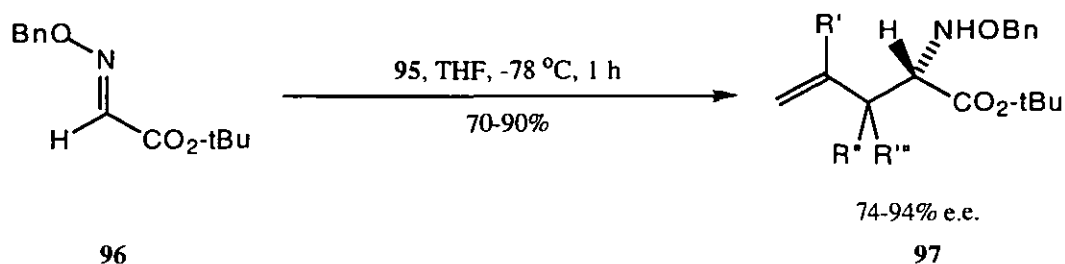


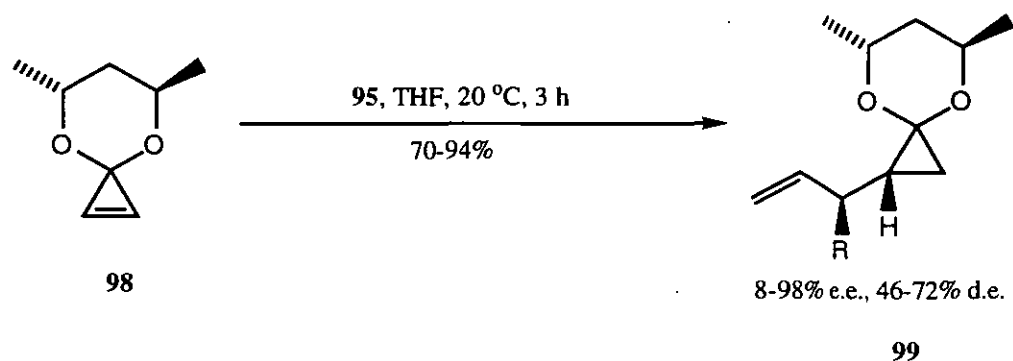
Figure 14

Hanessian and Yang used enantioselective allylation in the synthesis of allylglycines and allylalanine. They found that they could isolate the product **97** in good yield, 70-90%, and high enantioselectivity, 74-94% e.e. The researchers found that the *tert*-butyl and benzyl analogues of **95** were unable to introduce any noteworthy level of stereocontrol.



Scheme 22

Nakamura and co-workers have studied the enantioselective addition of allylzinc to both carbon-carbon double bonds^{45a} and carbon-nitrogen double bonds.^{45b} The addition of allylzinc to cyclopropenone acetals proceeded in high yield, 70%-94%, and good levels of diastereoselectivity and enantioselectivity, 72% d.e. and 98% e.e.



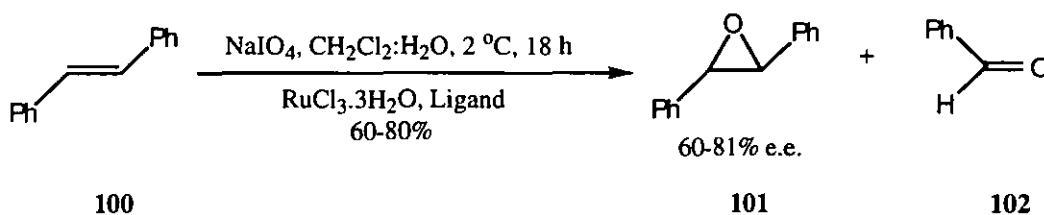
Scheme 23

Nakamura and co-workers also obtained excellent results for the addition of allylzinc to a series of carbon-nitrogen double bonds. The levels of stereoselectivity ranged from 30-99% e.e., more often in over 85% e.e. with isolated yields over 75%. Once more the *t*-butyl analogue of **95** was found to be too bulky and levels of selectivity were poorer and the reaction less efficient than the example using **95**, 25% yield and 88% e.e., compared with 72% yield and 95% e.e.

1.3.5.7 Oxidation Chemistry

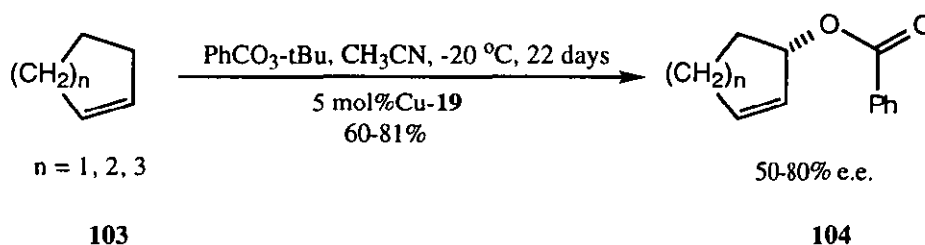
Oxazolines have been associated with several oxidation procedures including catalytic epoxidation⁴⁶ and allylic oxidation.⁴⁷ Waegell and co-workers used ruthenium complexes to

catalyse the epoxidation of *trans*-stilbene **100**. In addition to the formation of the desired oxidation product **101**, the researchers isolated benzaldehyde **102** as a product from the oxidative cleavage of the alkene. Stilbene oxide **101** was isolated in good yields and good to high levels of stereoselectivity, 60-81% e.e. The pyridyloxazolines **37-40** were found to be more effective ligands for ruthenium than other oxazolines and "pybox" **7-9**.



Scheme 24

The research groups of Pfaltz^{47a} and Andrus^{47b} have both used copper-bisoxazoline complexes to catalyse allylic oxidations.

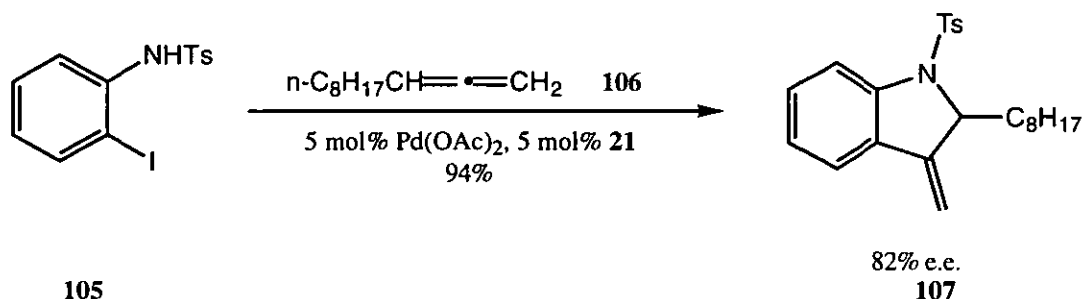


Scheme 25

Both groups screened several cyclic alkenes and found little discrimination associated with ring size. Isolated yields were moderate to good and levels of enantioselectivity were generally over 50% e.e., increasing to 80% e.e. under the right conditions. Variation of the substitution on the bis-oxazoline was found to have little influence on the level of stereoselectivity which was found to be more susceptible to changes in solvent and temperature. Acetonitrile was found to be the solvent of choice and a reduction in the reaction temperature facilitated an increase in enantioselectivity although at the cost of an increased reaction time.

1.3.5.8 Heck Reactions

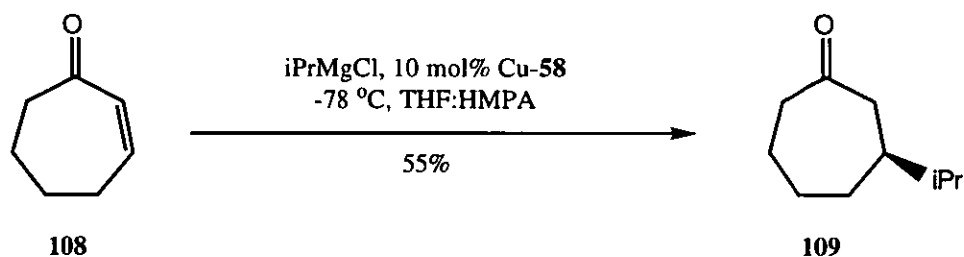
Larock has performed Heck reactions with the functionalised substituted aryl iodide **105** and the allene **106** to give the enantiomerically enriched cyclised product **107** when used in conjunction with a catalytic quantity of the bis-oxazoline **21**.⁴⁸



Scheme 26

1.3.5.8 Conjugate Additions

Zhou and Pfaltz have used copper in association with **58** to provide asymmetric induction in the addition of *iso*-propyl magnesium chloride to 2-cycloheptenone **108** which affords the substitution product **109**.⁴⁹



Scheme 27

1.4 Conclusion

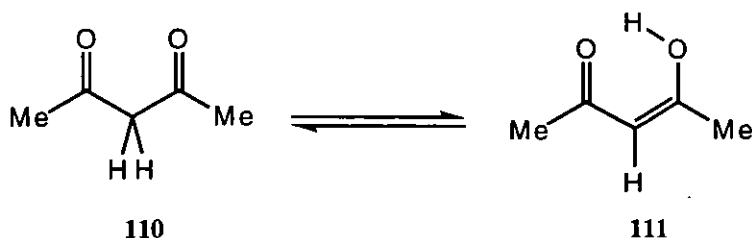
The enantiomerically pure 2-oxazoline has made a significant contribution to the field of asymmetric catalysis over the past decade. No doubt this small but effective ligand will be successfully applied to new areas of research in the future.

Chapter Two

Enantiomerically Pure Analogues of Acetyl Acetonoate as Ligands

2.1 Introduction

2,4-Pentanedione or acetyl acetone is a simple yet common 1,3-diketone ligand. Acetyl acetone is weakly acidic, $pK_a \approx 9$, and exists as a solvent dependent mixture of tautomers. The keto form **110** predominates in protic solvents whereas the enol form **111** favours aprotic solvents and is stabilised by internal hydrogen bonding.⁵⁰



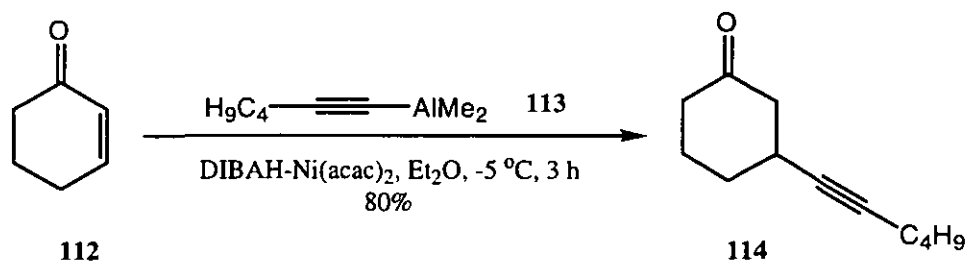
Scheme 27

The deprotonation of acetyl acetone forms the powerful chelating species acetyl acetonate (acac). The ligand is able to form complexes with virtually every transition and main group metal. The subsequent compounds are appreciably more robust than those involving simple ketones. Transition metal complexes that include a simple ketone as a ligand tend to be labile, whereas the proclivity of acac to form chelates allows even alkali metal complexes to be isolated.

The stability and availability of metal-acac complexes has promoted the wider application of these compounds. Many research groups have found that metal-acac complexes are able to catalyse useful synthetic transformations. A brief survey of metal-acac complexes as catalysts is presented below.

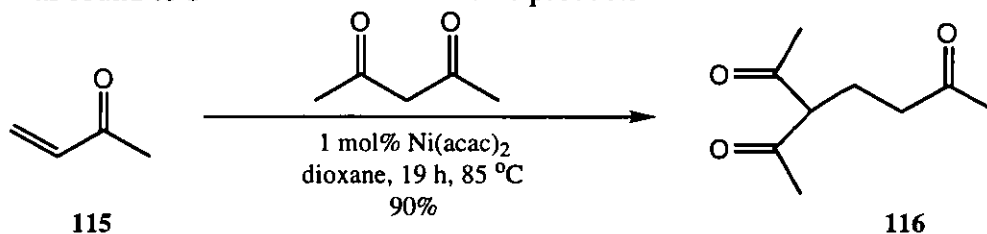
2.1.1 Nickel-Acac Complexes

Bis(2,4-pentanedionato)nickel(II) has been reported as a mild and efficient catalyst by several research groups. For example Schwartz and co-workers found that a mixture of $Ni(acac)_2$ and DIBAH smoothly catalysed the conjugate addition of organoaluminium acetylides to α,β -unsaturated ketones.⁵¹ The procedure was reported as the first method by which *trans* enones could be readily alkynylated in good yield.



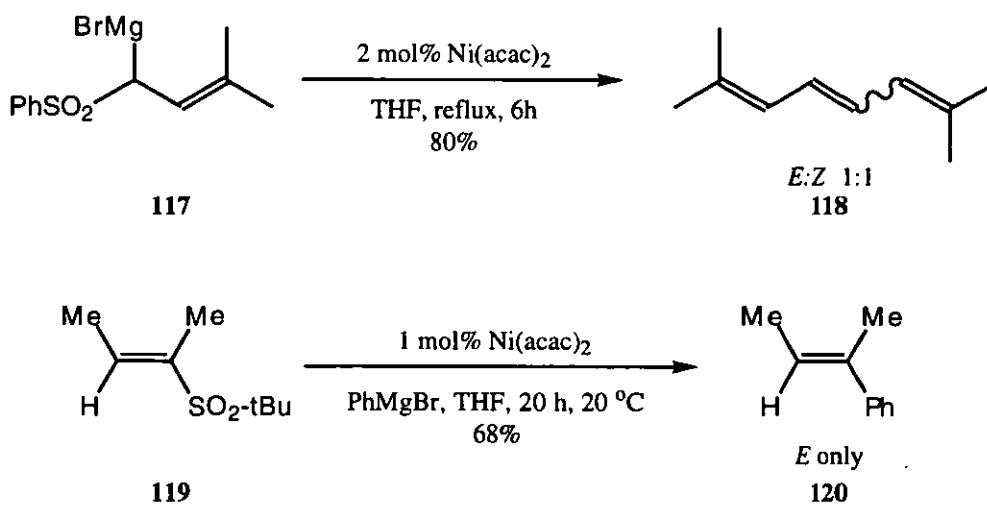
Scheme 28

Nelson *et al.* found that Ni(acac)₂ would catalyse the conjugate addition of 2,4-pentanedione to α,β -unsaturated ketones. The researchers were able to improve significantly upon the previous reported yield of 45%, isolating the product in up to 90% yield.⁵² In addition the reaction was found to be cleaner with fewer side products.



Scheme 29

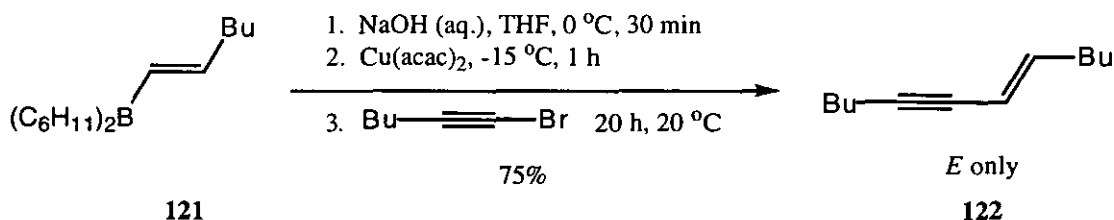
Julia and co-workers reported that Ni(acac)₂ facilitated the cross-coupling of alkenes.⁵³ The reaction was high yielding but lacked any stereocontrol. The researchers also found that both Ni(acac)₂ and Fe(acac)₃ would catalyse the reaction of vinylic sulfones and Grignard reagents.⁵⁴ In this case the product was exclusively the *E* isomer in good yield.



Scheme 30

2.1.2 Copper-Acac Complexes

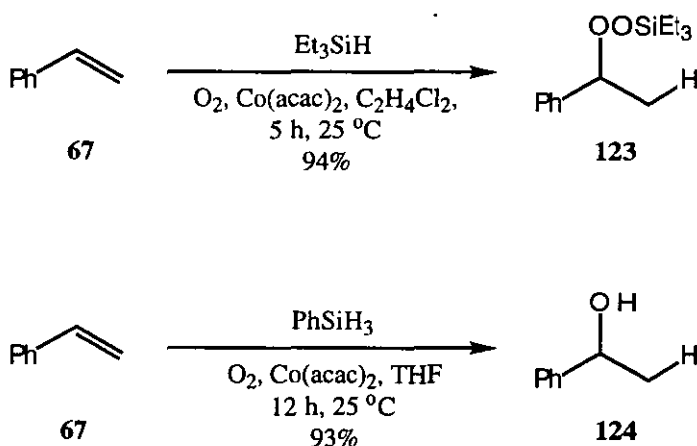
It has been reported by Arase and co-workers that $\text{Cu}(\text{acac})_2$ will catalyse cross coupling reactions. The researchers reported that the coupling of alkenyldicyclohexylborane **121** with 1-bromo-alkyne in the presence of $\text{Cu}(\text{acac})_2$ would afford only the *E* isomer with no observed *Z* isomer contamination.⁵⁵



Scheme 31

2.1.3 Cobalt-Acac Complexes

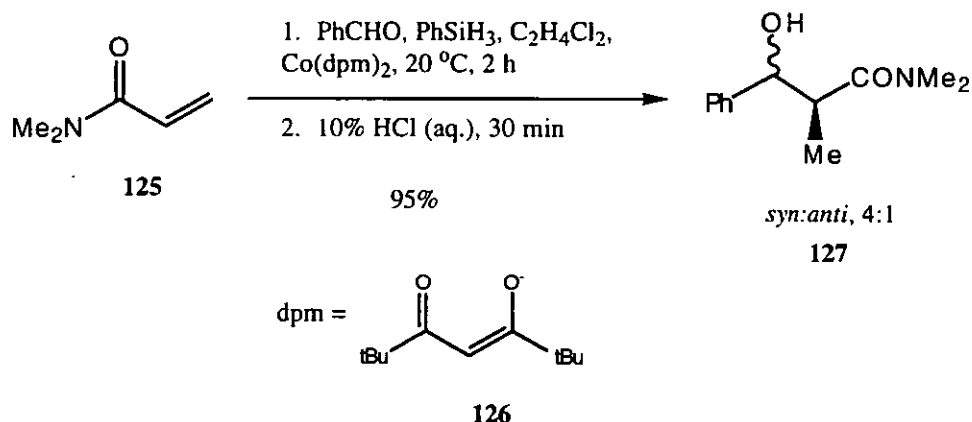
Complexes of cobalt with a selection of diketone ligands have been reported as catalysts by Isayama and Mukaiyama.⁵⁶ The researchers initially showed that $\text{Co}(\text{acac})_2$ catalysed the reduction of alkenes with triethylsilane and molecular oxygen to produce silyl peroxides **123**. Interestingly, the same reaction run in the presence of phenylsilane proceeds directly to the alcohol **124**.



Scheme 32

Isayama and Mukaiyama went on to use cobalt catalysts in the condensation of alkenes and aldehydes. They found $\text{Co}(\text{acac})_2$ to be an adequate catalyst but improved results were

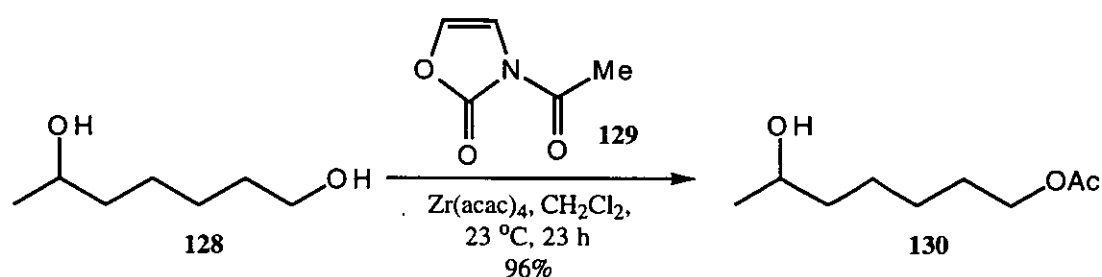
obtained with Co(dpm)_2 . The reaction afforded the product in 95% yield with stereoselectivity of *syn:anti*, 4:1.



Scheme 33

2.1.4 Zirconium-Acac Complexes

Kunieda *et al.* detailed the selective acylation of polyalcohols in 1985.⁵⁷ Zirconium acetylacetonate selectively catalysed the monoacylation of primary alcohols under mild conditions. The diol **128** was treated with an excess of 3-acetyl-2-oxazolone **129** and a catalytic amount Zr(acac)_4 to provide the monoacetate **130** in 96% yield and a 92:8 selectivity over the diacetate.

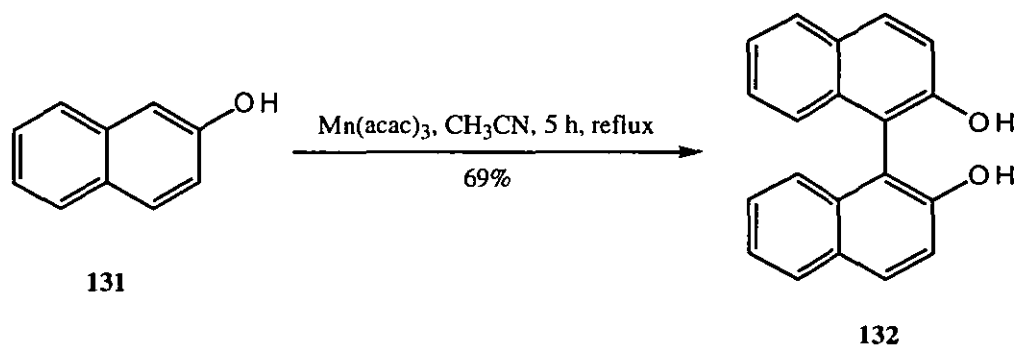


Scheme 34

2.1.5 Manganese-Acac Complexes

Dewar and Nakaya applied manganic tris(acetylacetonate) to the oxidative coupling of phenols to give biphenols exclusively.⁵⁸ The particular advantages of this system were the

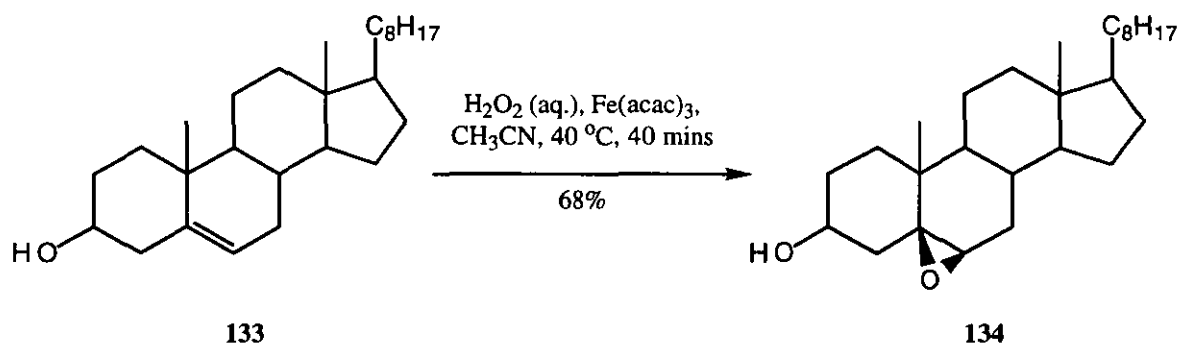
mild reaction conditions compared with previous methods and the availability of biphenols in good yield without being oxidised to quinones.



Scheme 35

2.1.6 Oxidation and Reduction Chemistry

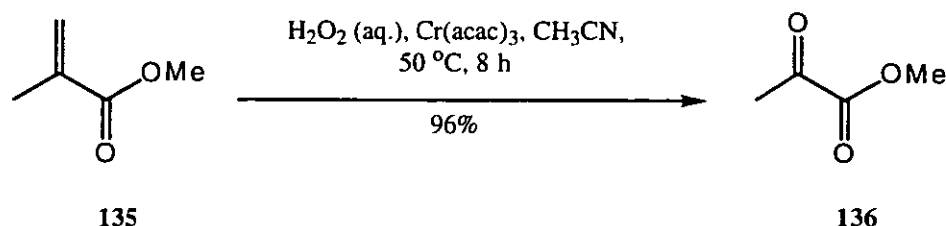
Tohma *et al.* found that ferric acetylacetonate would catalyse the epoxidation of cholesterol **133** with hydrogen peroxide.⁵⁹ The procedure was a mild method that provided for the sterically hindered β -epoxide in high yield. Previous oxidations had favoured the formation of the α -epoxide and direct β -epoxidation had not been possible.



Scheme 36

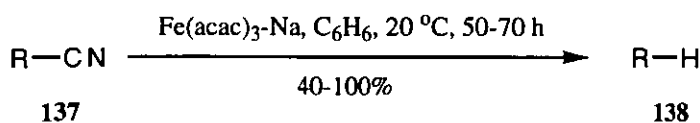
Inoue and co-workers reported the oxidation of methacrylic esters with hydrogen peroxide in the presence of chromium compounds including Cr(acac)_3 .⁶⁰ The oxidation of the alkene with strong peracids had only provided for the epoxide, oxidation to the ketone had not been achieved. The oxidation of methacrylic acid esters **135** to pyruvic acid esters **136** was found to proceed smoothly in the presence of hydrogen peroxide and a number of chromium

compounds. In particular $\text{Cr}(\text{acac})_3$ facilitated a high conversion of starting material, 96%, and a good isolated yield of 74%.



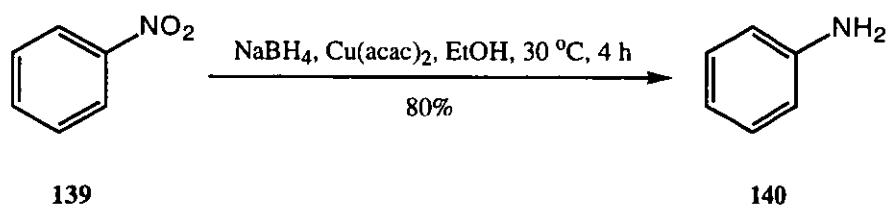
Scheme 37

Metal-acac complexes have also been shown to catalyse reducing systems. Tamelen and co-workers found that a series of alkyl nitriles were smoothly decyanated in the presence of $\text{Fe}(\text{acac})_3$.⁶¹



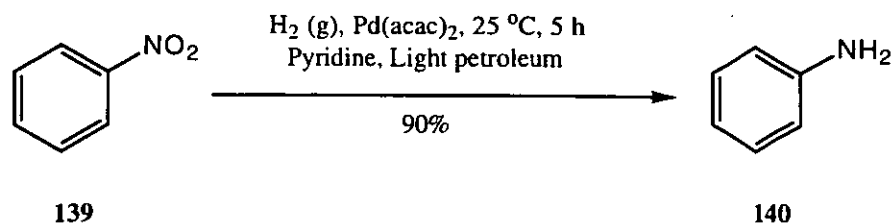
Scheme 38

The reduction of aromatic nitro compounds to the analogous amines has been achieved with copper (II) acetylacetonate⁶² and palladium (II) acetylacetonate.⁶³ Hanaya *et al.* found that $\text{Cu}(\text{acac})_2$ and sodium borohydride in an alcoholic solution reduced a variety of substituted nitrobenzenes to substituted anilines.



Scheme 39

Datta *et al.* reported the facile reduction of nitrobenzene to aniline by hydrogenation in the presence of palladium (II) acetylacetonate and pyridine. The reduction proceeded smoothly in a few hours and the catalyst could be simply regenerated and applied to the reduction of fresh nitrobenzene.

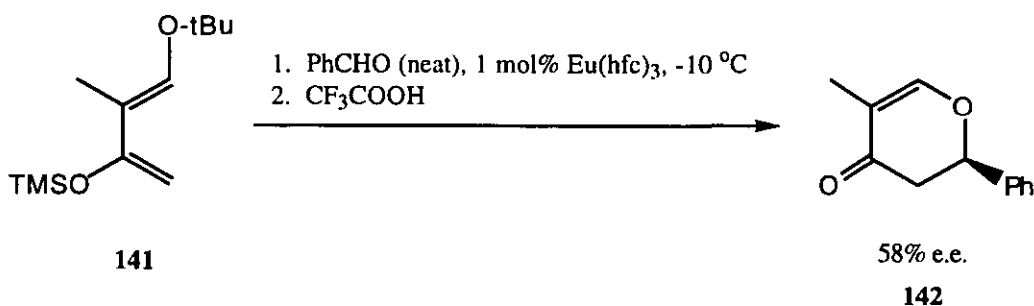


Scheme 40

2.1.7 Enantiomerically Pure Diketone Complexes

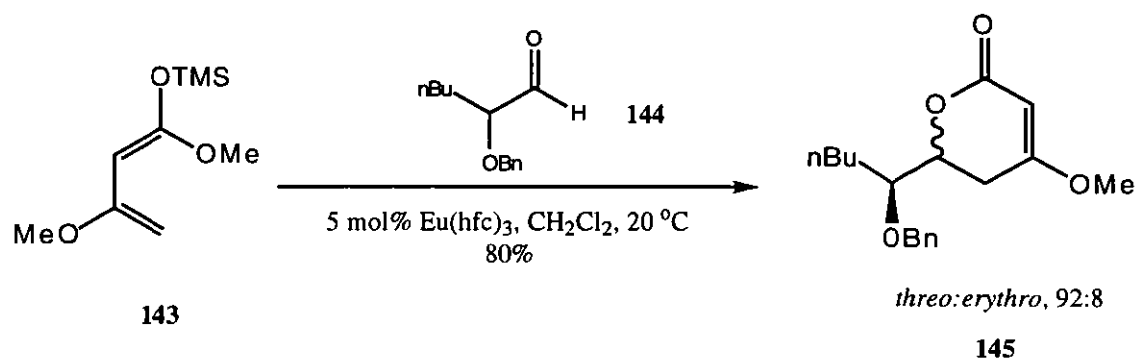
The major disadvantage of the acac ligand is that it is inherently achiral. The stereochemical course of the reactions catalysed by its complexes is not determined by the nature of the ligand. Only a few enantiomerically pure diketone ligands have been reported. These ligands are generally derived from camphor and have only exhibited good levels of stereoselectivity in a few synthetic applications. The most extensive application of diketone ligands has been chiral lanthanide shift reagents. Whitesides⁶⁴ and Goering⁶⁵ introduced shift reagents in 1974 as an analytical tool for directly determining enantiomeric excess in $^1\text{H-NMR}$. Since then chiral shift reagents have also been used as catalysts in asymmetric synthesis.

In 1983 Danishefsky and co-workers used Eu(hfc)_3 to catalyse the cyclocondensation of aldehydes with siloxydienes.⁶⁶ Generally the levels of stereoselectivity were poor but the researchers found that by careful choice of reagents and conditions they could isolate **142** in up to 58% e.e.



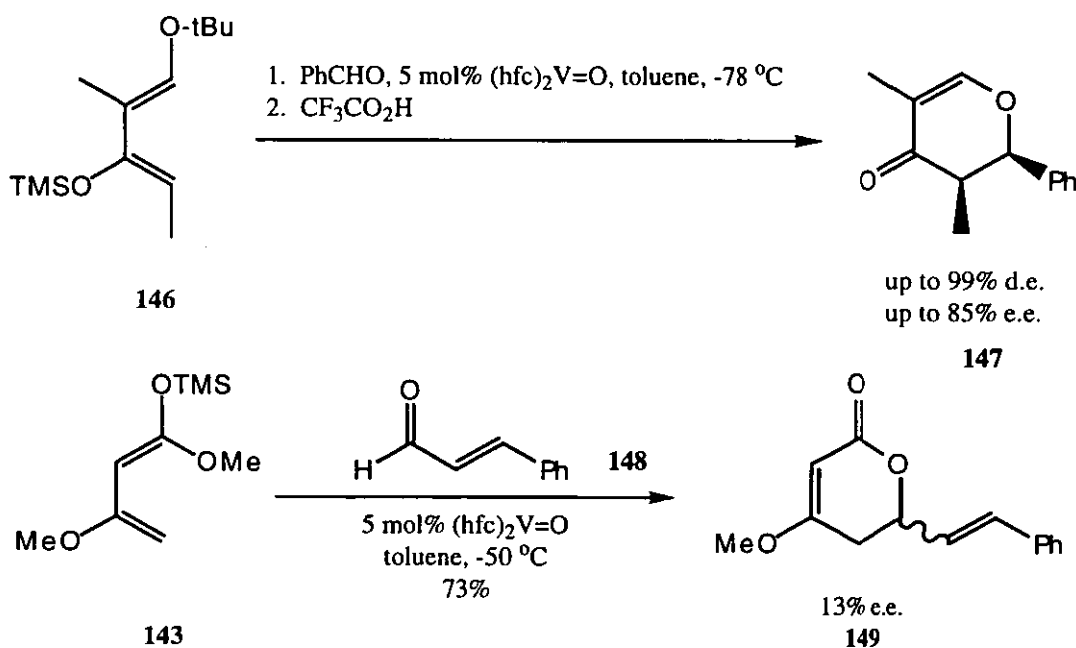
Scheme 41

Midland and Koops reported the use of $\text{Eu}(\text{hfc})_3$ in the cyclocondensation of alkoxyaldehydes **144** and Brassard's diene **143**.⁶⁷ They found that the levels of stereoselectivity were directly related to the size of the alkyl side chain and the alkoxy protecting group. The best levels of selectivity were achieved when the small side chain and protecting group promoted chelation of the reagents with the catalyst. The product **145** was isolated in 80% yield and a *threo:erythro* ratio of 92:8.



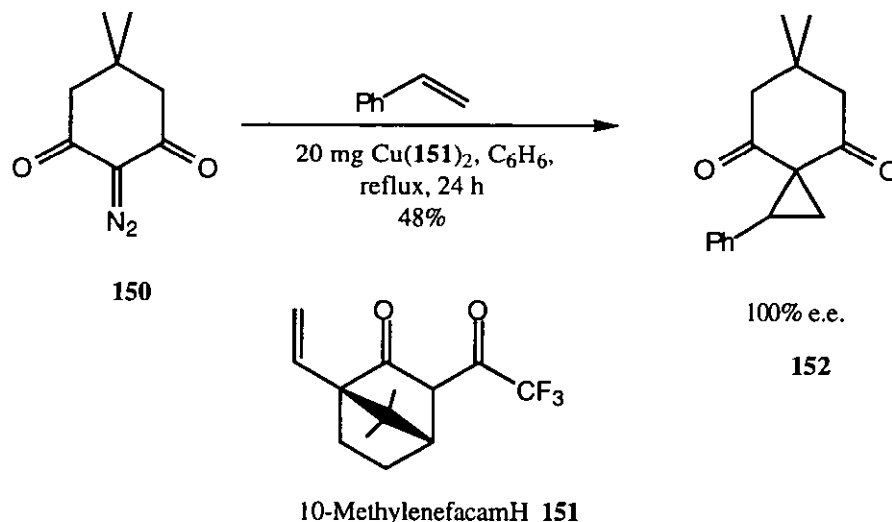
Scheme 42

Togni and co-workers applied a vanadium oxide catalyst to the hetero Diels-Alder reaction and were able to isolate the cycloadduct **147** in up to 99% d.e. and 85% e.e.⁶⁸ The reaction of Brassard's diene **143** with α,β -unsaturated aldehydes proceeded smoothly but with poor levels of stereocontrol. The product **149** was available in 73% yield but only 13% e.e.



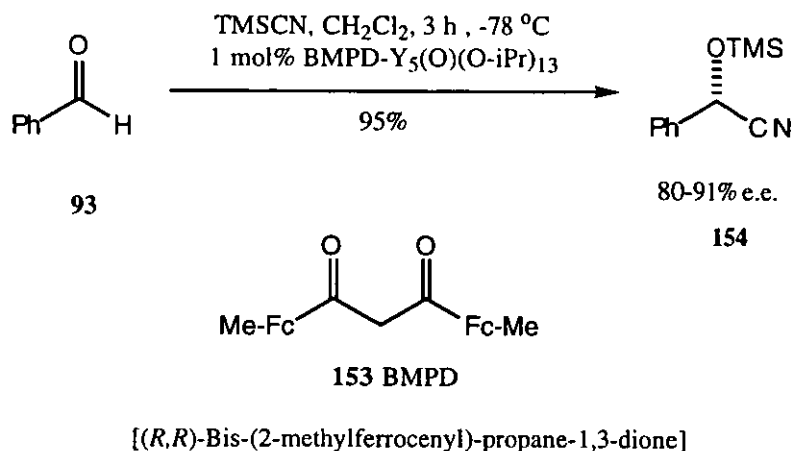
Scheme 43

Matlin and co-workers found that they could achieve high levels of stereoselectivity in the copper catalysed cyclopropanation of styrene.⁶⁹ Initially Cu(acac)₂ provided for racemic **152**, but the use of enantiomerically pure β -diketone ligands such as **151** led to high enantiomeric excesses. The cyclopropanation product was available in 48% yield and 100% e.e. after 24 h.



Scheme 44

Recently Abiko and Wang have disclosed a novel β -diketone ligand that derives its stereochemistry from ferrocene.⁷⁰ The researchers found that the complex between BMPD **153** and yttrium isopropoxide was an efficient catalyst for asymmetric silylcyanation. A series of aldehydes was treated with trimethylsilyl cyanide in the presence of the 1 mol% of the catalyst. Enantiomeric excesses over 80% e.e. and reaching up to 91% e.e. were achieved with consistently excellent chemical yields.



Scheme 45

1,3-Diketone ligands have been shown to be effective in a range of catalytic systems. In addition enantiomerically pure diketones have provided significant levels of stereocontrol in some interesting synthetic processes. This area of asymmetric catalysis shows potential for further investigation and development.

2.2 *Design and Synthesis of the Ligands*

It was anticipated that a ligand that included the structural features of both acetyl acetone and the 2-oxazoline would effectively bind to a metal and subsequently relay stereochemical information in a catalytic system.

2.2.1 *Ligand Design*

When considering the design and synthesis of a novel ligand we determined that the ligand should meet several criteria:

- to be enantiomerically pure
- to be analogous to acac and other 1,3-diketones
- to include a moiety to introduce stereochemical control
- to possess methylene protons of low pK_a to allow for easy enolisation
- to require only a short synthesis from commercially available starting materials.

We believed that an enantiomerically pure, well-defined stereocentre was crucial for the efficacy of the ligand. Any discrepancy would erode subsequent levels of stereocontrol. It was deemed important to maintain the strong binding characteristics of acac and other diketones as part of the overall design. Hence the desire to include labile protons which would allow the ligand to mimic the chemical properties of the 1,3-diketones. A short, direct synthesis was considered important to allow flexibility in the structure of the ligand and the facile synthesis of analogues.

We concluded that ligands based around the keto-oxazoline structure illustrated below would satisfy our design criteria.

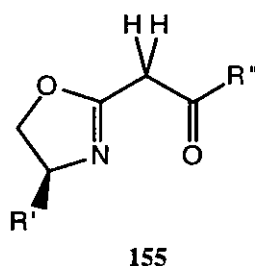
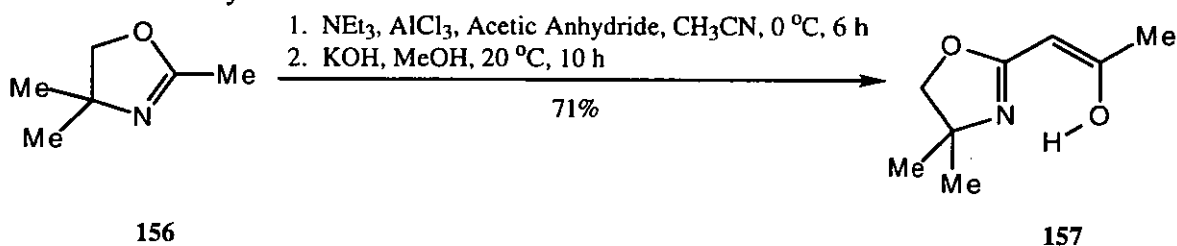


Figure 15

Compounds of this type have been reported in the literature. Tohda *et al.* detailed the Claisen condensation of 2-alkyl-2-oxazolines with alkanolic anhydrides in the presence of aluminium chloride and triethylamine.⁷¹



Scheme 46

The keto-oxazoline products were available in 31-71% yield as a mixture of tautomers. The researchers found that the enol form predominated in deuterated chloroform as would be expected for an aprotic organic solvent.

Huche and Lhommet similarly reported tautomeric mixtures of oxazoline-esters.⁷² They found that the ratio of "keto" **158** and enol **159** forms was related to the substitution around the oxazoline.

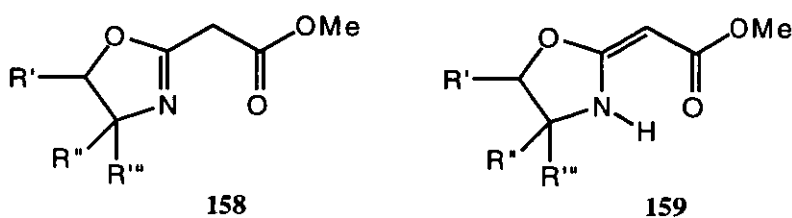


Figure 16

In a deuterated chloroform solution the "keto" form **158** was detected exclusively when R', R'' and R''' = H and when R' = Me. An alkyl group at the 4 position on the ring resulted in the formation of the enol isomer **159**. The percentage of enol was 30% in the case where R'' = R''' = Me. Comparatively Tohda and co-workers found the enol **157** to be present in up to 94%. Indicating that an electron withdrawing carbonyl moiety favoured the formation of the enol tautomer. These results suggest that ligands of this type may mimic the physical chemistry of 1,3-diketones and consequently have similar binding characteristics.

2.2.2 *Synthesis of the Ligands*

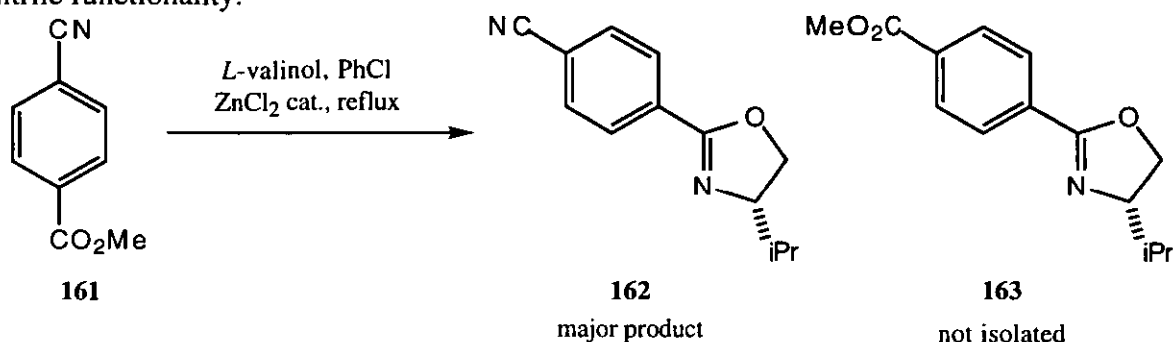
There are numerous methods available for the synthesis of the oxazoline ring.² We elected to initially consider the direct synthesis of the ring. Bolm and co-workers showed that the 2-oxazoline is available in one step by the condensation of an amino alcohol and a nitrile in the presence of a catalytic quantity of zinc chloride.⁷³ The proposed mechanism for the condensation is illustrated below. Initially the nitrile co-ordinates to the zinc chloride which encourages the nucleophilic addition of the amine. Intramolecular nucleophilic attack by the hydroxyl moiety followed by the loss of ammonia and regeneration of the zinc chloride catalyst gives the oxazoline.



Scheme 48

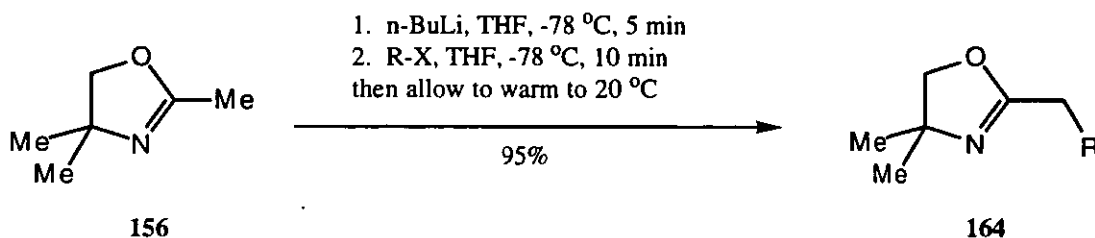
The zinc chloride catalyst was melted under reduced pressure and cooled under a nitrogen atmosphere. The remaining reagents were all added to the reaction flask and the reaction was heated at reflux under an inert atmosphere. Analysis of the reaction by tlc showed there to be a complex mixture of products present. Subsequent work-up of the reaction and column chromatography failed to provide the desired product. This reaction was repeated several times but with no success. It is possible that the ester moiety was involved in side reactions and hence the complex mixture of products from the reaction.

This result may be explained by an unpublished result from our group.⁷⁴ A similar reaction where *L*-valinol was condensed with methyl 4-cyanobenzoate **161** in the presence of a catalytic quantity of zinc chloride resulted in the formation of **162** rather than **163**. The product **162** being the result of the oxazoline ring forming at the ester moiety rather than the nitrile functionality.



Scheme 49

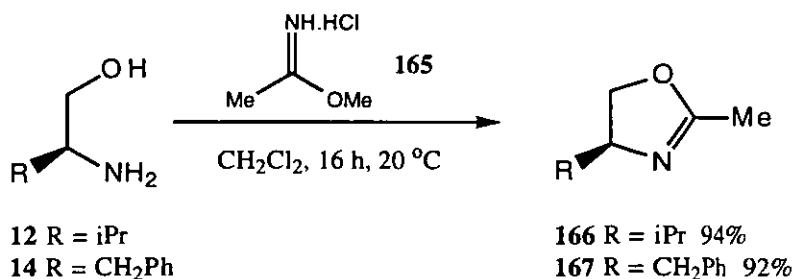
Meyers and co-workers have demonstrated that the oxazoline may be deprotonated and the resultant anion quenched with an electrophile.⁷⁵ The researchers formed the lithio salt of 2,4,4-trimethyl-2-oxazoline **156** and reacted it with alkyl halides to afford 2-alkyloxazolines which were hydrolysed to provide carboxylic acids.



Scheme 50

We chose to synthesise (*S*)-4-*iso*-propyl-2-methyloxazoline **166** as a precursor to the desired ligands. The methyloxazoline **166** could then be treated with a suitable base to form the anion which could be quenched with an appropriate electrophile.

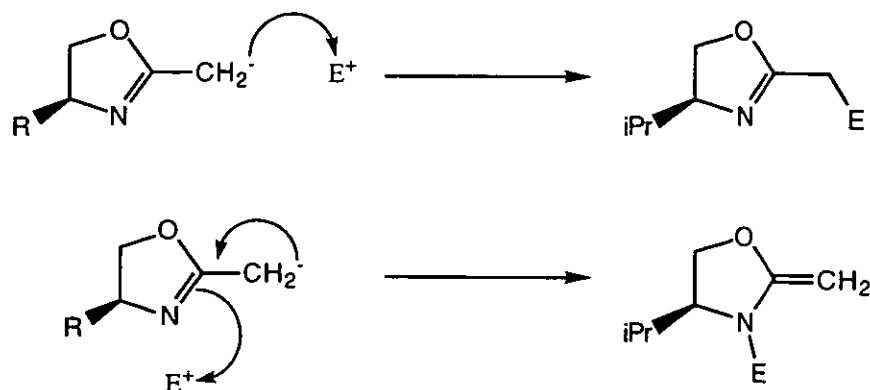
The methyloxazolines **166** and **167** were readily available on a multi-gram scale from the condensation of an amino alcohol with methyl acetimidate **165**. The products were isolated as colourless oils with a distinctive odour.



Scheme 51

Initial yields for this reaction were poor but it quickly became apparent to us that the volatile products were being lost on the rotary evaporator. Once this had been established we were able to achieve yields of over 90% consistently. The formation of the oxazoline ring was confirmed through NMR data and IR spectroscopy. The peak associated with the C=N stretch of the oxazoline near 1675 cm⁻¹ is characteristic of these compounds. Likewise the signal near 164 ppm in the ¹³C-NMR which correlates with the quaternary carbon of the oxazoline ring. The product was of sufficient purity, as determined by ¹H-NMR, to carry through to the next step without further purification.

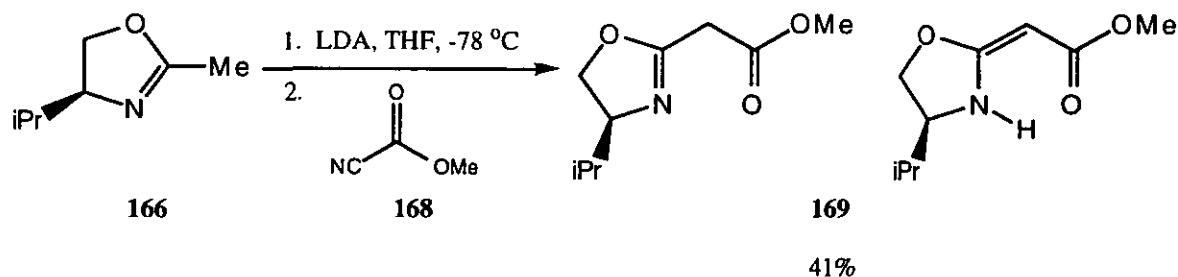
The issue of selective alkylation was one that needed to be addressed. It was unclear whether *N*-alkylation competing with *C*-alkylation would be a significant problem. We rationalised that a "soft" electrophile would favour *C*-alkylation where a "hard" electrophile would promote *N*-alkylation.



Scheme 52

We required a "soft" electrophile that was sufficiently reactive to provide the desired product smoothly but without being too reactive. An electrophile that reacted too quickly with the anion was likely to form unwanted *N*-alkylated products. In addition we hoped to directly introduce a carbonyl moiety and hence produce the ligand without resorting to any further synthetic steps. Consequently we selected Manders reagent, methyl cyanoformate **168**, as an appropriate electrophile. Methyl cyanoformate has previously been demonstrated as a mild and selective alkylating agent.⁷⁶

The lithiation of the 2-methyloxazoline **166** required rigorously anhydrous conditions. Lithium diisopropylamide was chosen as a strong, non-nucleophilic base. The anion was formed at $-78\text{ }^{\circ}\text{C}$ before being quenched by Manders reagent. After isolation and purification the product **169** was available as a yellow oil in 41% yield.



Scheme 53

The IR spectrum of the product included the distinctive $\text{C}=\text{N}$ stretch at 1673 cm^{-1} and a peak associated with the ester moiety at 1748 cm^{-1} . The ^1H -NMR initially looked confused until

it was appreciated that the CDCl_3 solution included a mixture of the "keto" and enol forms of the ligand. A small peak at 7.93 ppm was assigned as being the signal from the enol proton. The protons associated with the methoxy moiety had separate and distinctive signals at 3.74 ppm and 3.65 ppm. Likewise two signals in the ^{13}C -NMR at 62.3 ppm and 60.8 ppm were considered to represent the different environments of the linker carbon. The characteristic quaternary carbon was present at 160.5 ppm as were the pairs of doublets associated with the *iso*-propyl group at 0.9 ppm in the ^1H -NMR spectrum.

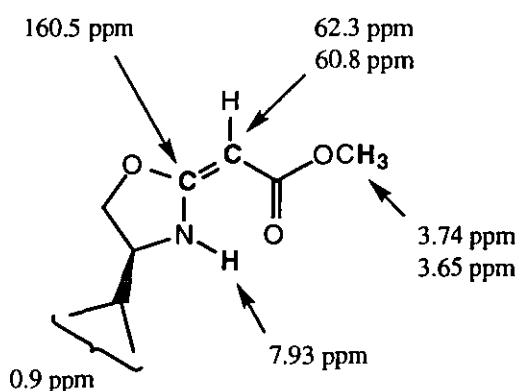
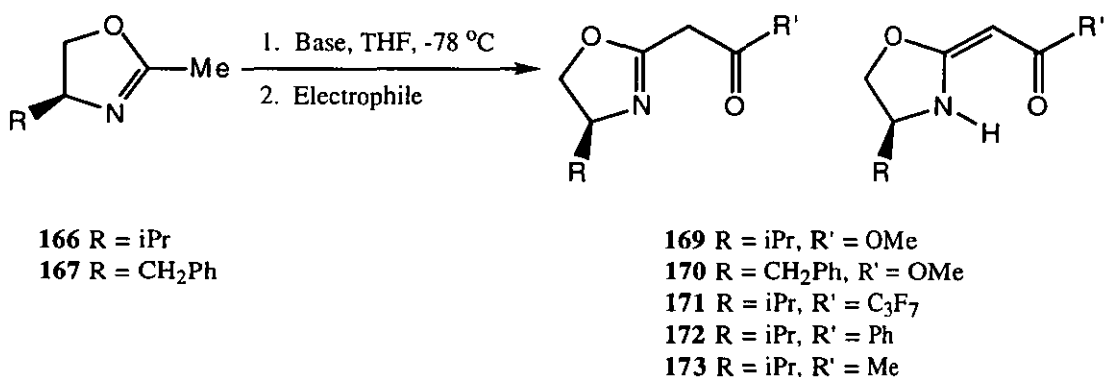
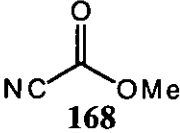
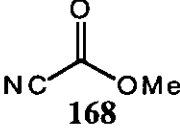
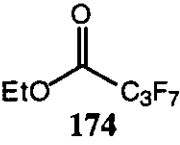
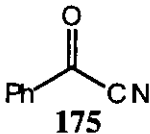
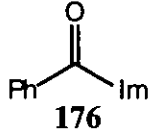
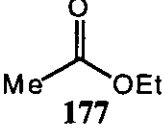
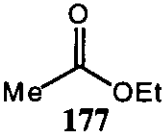
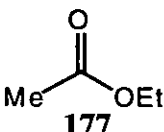


Figure 17

With this methodology in hand we synthesised several analogues of the first ligand. In each case the anion was formed in a similar manner and subsequently quenched with an appropriate electrophile to furnish us with the desired products.



Scheme 54

Entry	Conditions	Electrophile	Ligand	Yield (%)
1	1.1 eq. LDA, THF, -78 °C	 168	169	41
2	1.1 eq. LDA, THF, -78 °C	 168	170	16
3	1.1 eq. LDA, THF, -78 °C	 174	171	49
4	1.1 eq. LDA, THF, -78 °C	 175	172	25
5	1.1 eq. LDA, THF, -78 °C	 176	172	28
6	1.1 eq. n-BuLi, THF, -78 °C	 177	173	41
7	1.1 eq. t-BuLi, THF, -78 °C	 177	173	33
8	1.1 eq. t-BuLi, TMEDA, THF, -78 °C	 177	173	10

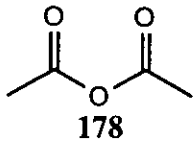
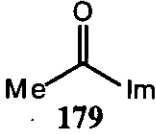
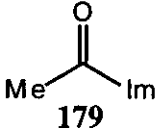
9	1.2 eq. n-BuLi, THF, -78 °C	 178	173	38
10	2.2 eq. LDA, THF, -78 °C, 6 h	 179	173	9
11	2.2 eq. LDA, THF, -78 °C, 30 min	 179	173	58

Table 1

When analysing the spectroscopic data several key features were looked for. Firstly that the IR spectrum included the appropriate peaks for the C=N stretch and the desired carbonyl moiety. That the ^{13}C -NMR confirmed that the oxazoline ring was intact by the presence of the distinctive quaternary peak near 160 ppm. That the ^1H -NMR included the signature signals of the oxazoline ring. These include the signals associated with the *iso*-propyl group at 0.9 ppm and 1.8 ppm and the ring protons. The ring protons display clear coupling patterns that are indicative of this system. In addition the ^1H -NMR spectrum was also seen to include a broad, high field signal as a result of the formation of the enol. The ratio of enol to "keto" forms varied between samples and compounds. Qualitatively, the more electron withdrawing carbonyl moieties such as the fluorinated ketone **171** tended to favour the enol form. The ester-oxazoline **169** preferred the "keto" form and only a small percentage of enol was usually seen.

The fluorinated ketone **171** was available by deprotonating **166** with LDA and quenching the anion with ethyl heptafluorobutyrate **174** to provide the ligand in 49% yield. The ^1H -NMR suggested that the ligand existed solely as the enol in deuterated chloroform. This was also confirmed by the IR spectrum which showed a particularly broad peak at 3252 cm^{-1} . It was anticipated that the fluorinated moiety would influence the chemical properties of the ligand.

The electron withdrawing group would lower the pKa of the ligand and promote enol formation. The fluorobutyl group would also increase the solubility characteristics of the ligand and any subsequent complexes. In addition it was suggested that the electron withdrawing nature of the ligand would affect the electron density of a metal. The removal of electron density would result in the metal being more electropositive and possibly more active as a catalyst.

The keto-oxazolines were synthesised to include a methyl ketone **173** and a phenyl ketone **172**. The significance of the phenyl ketone was to introduce a group that was UV active and hence act as a traceable label for the ligand in further investigations. The yields for the phenylketo-oxazoline **172** were low, only reaching 28% at best. Two different electrophiles were used to see if the nature of the leaving group affected the overall yield. Firstly the anion of **166** was quenched with benzoyl cyanide **175** to produce **172** in a yield of 25%. Secondly benzoyl imidazole **176** was used as the electrophile but with essentially no change in the overall yield. These reactions were repeated several times but the isolated yields did not improve. The product was isolated as an off-white solid after column chromatography. The IR spectrum included a broad peak at 3256 cm^{-1} which is associated with the formation of the enol. The ^{13}C -NMR included signals for the quaternary carbons at 187.4 ppm and 170.5 ppm which were assigned to the carbonyl carbon and the quaternary ring carbon of the oxazoline respectively. The ^1H -NMR included the requisite signals for the *iso*-propyl oxazoline. In addition a singlet at 5.59 ppm was assigned as an olefinic proton associated with the enol of **172**. The product was crystalline which enabled us to study the structure of the compound by x-ray analysis. A representation of the structure is illustrated below. Details of the x-ray structure may be found in the Chapter 6.

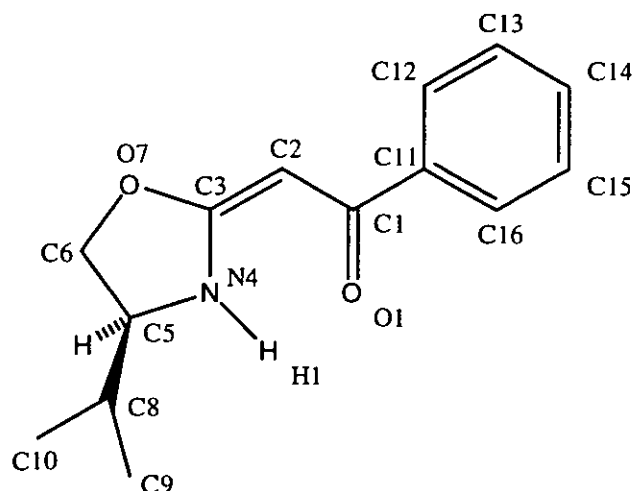


Figure 18

The crystal structure showed that in the solid state the ligand exists preferentially as the enol. It was determined that the region N4-C3-C2-C1-O1 is essentially planar due to the delocalisation associated with enol formation. Facts that support the illustrated structure are that:

- the bond length C3-N4 is 1.316(3) Å which is longer than would be expected for a C=N bond
- the bond length C3-C2 is 1.363(4) Å which is more akin with a C=C bond rather than a C-C bond
- the bond length C1-C2 is 1.408(4) Å which is longer than C3-C2 and is indicative of the position of the C=C bond
- the bond length C1-O1 is 1.250(3) Å which is appropriate for a C=O bond.

The product of these measurements indicates that the enol structure **180** is favoured rather than the isomer **181**.

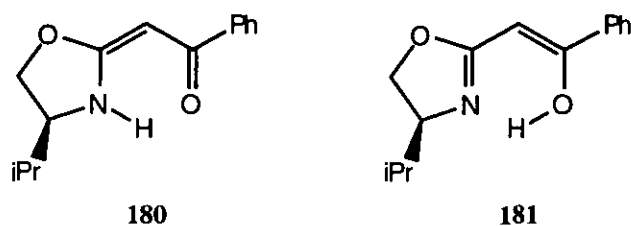
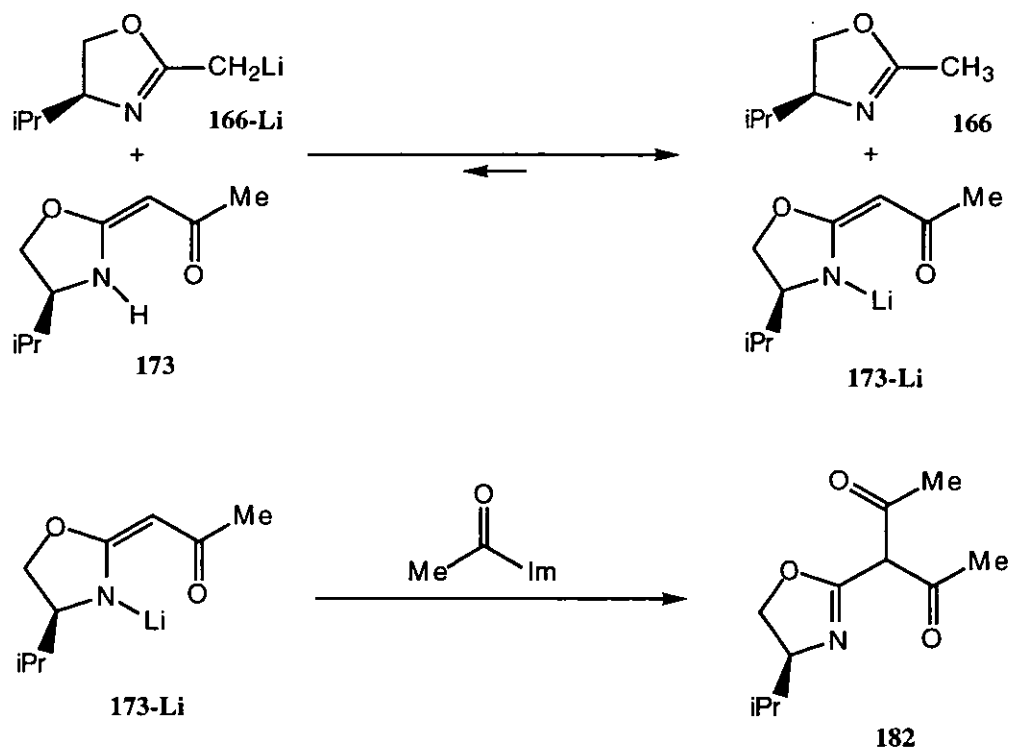


Figure 19

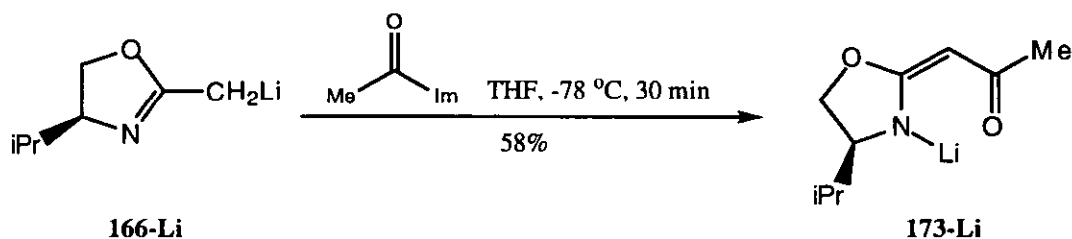
Initial approaches to the methylketo-oxazoline **173** were low yielding. We wished to be able to access the ligand on a multi-gram scale. We varied both the nature of the base and the electrophile in an attempt to optimise the reaction conditions. We chose to use the strong base *n*-BuLi to deprotonate **166**. The resultant anion was quenched with ethyl acetate **177** and the product was available after purification by flash chromatography in 41% yield. This was the best yield at this point and encouraged us to vary the conditions further. The use of *t*-BuLi resulted in a slightly lower yield of 33% and the addition of TMEDA produced **173** in a poor yield of 10%. A return to *n*-BuLi as the base and a change to acetic anhydride **178** as the electrophile returned the yield to a reasonable 38% but no higher.

We were able to synthesise **173** on a multigram scale by using 2.2 equivalents of LDA as the base and *N*-acetyl imidazole **179** as the electrophile. The first application of these conditions only provided the product in 9% after 6 h. It was believed that the problem was one of significant dialkylation. Once formed the product, by design, includes protons of low pKa. In the basic reaction conditions the removal of one of these protons is facile and the second alkylation proceeds quickly. In addition there may be competition between the anion of **166** and the monoalkylated product. It is reasonable to anticipate that the lithiated species **166-Li** deprotonates the product and consequently stops the desired reaction. In fact the dialkylated product **182** is now favoured.



Scheme 55

To reduce the quantity of dialkylated product **182** and promote the yield of the monoalkylated product **173** we shortened the reaction time. The methyl oxazoline **166** was deprotonated with 2.2 equivalents of LDA. The first equivalent was to perform the expected deprotonation, the second was added to deprotonate the product. This way we could ensure that the lithiated species **166-Li** was not quenched by its own product **173**. The drawback to maintaining a high concentration of **173-Li** was that the product was already lithiated and free to form the dialkylated product. It was anticipated that the second alkylation would be slower than the first alkylation, hence a reaction time of 30 minutes. Sufficient time to allow monoalkylation to proceed but hopefully too little time for dialkylation to occur.



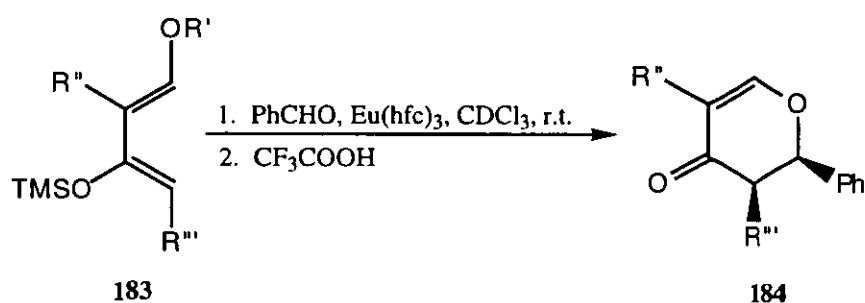
Scheme 56

The success of this approach is born out by the relatively high isolated yield of 58%. The spectral data for this compound included the characteristic signals for these ligands. The ^1H -NMR indicated that the ligand the favoured enol form almost exclusively.

With these ligands in hand we considered their application to synthetically useful reactions. We wished to determine the efficacy of these compounds as ligands for asymmetric catalysis.

2.3 Asymmetric Hetero Diels-Alder Reaction

In 1983 Danishefsky and co-workers introduced the chiral lanthanide shift reagents as mild Lewis acid catalysts.⁶⁶ The researchers used $\text{Eu}(\text{hfc})_3$ **185** to introduce modest levels of stereocontrol into the cyclocondensation of aldehydes and siloxydienes.



Scheme 57

It was demonstrated that the substitution around the siloxydiene directly influenced the level of stereoselectivity. The reaction conditions were then optimised with little affect on the enantioselectivity. Danishefsky concluded that the source of the stereocontrol was in the catalytic process and was not a general medium effect. The most significant features were the bulk of R' and the inclusion of a methyl substituent at R'''.

Entry	Conditions	R'	R''	R'''	e.e. (%)
1	CDCl ₃ , r.t.	Me	H	H	18
2	CDCl ₃ , r.t.	iPr	H	H	28
3	CDCl ₃ , r.t.	tBu	H	H	38
4	CDCl ₃ , r.t.	Me	Me	H	15
5	CDCl ₃ , r.t.	tBu	Me	H	39
6	CDCl ₃ , r.t.	Me	Me	Me	36
7	CDCl ₃ , r.t.	tBu	Me	Me	42
8	neat, -10 °C	tBu	Me	H	58
9	neat, -10 °C	tBu	Me	Me	55

Table 2

The condensation of benzaldehyde with Danishefsky's diene **141**, entry **1**, resulted in the product being isolated in only 18% e.e. It is proposed that a more effective ligand than the camphor derived hfc would provide for higher levels of stereocontrol. The chiral moiety of hfc **185** is relatively remote from the catalytic face of the metal. It has been demonstrated that the geometry of the oxazoline moiety **186** places the substituent at the 4 position close to the metal centre. We hoped that a catalyst involving an europium complex such as **186** would be a selective and mild Lewis acid catalyst.

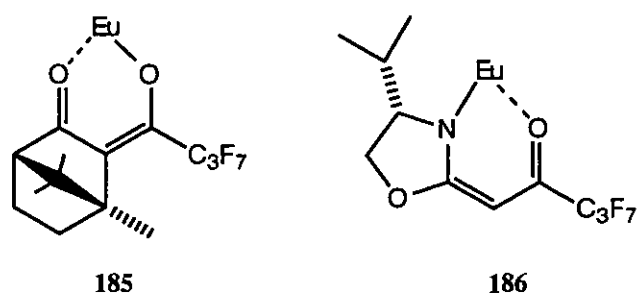
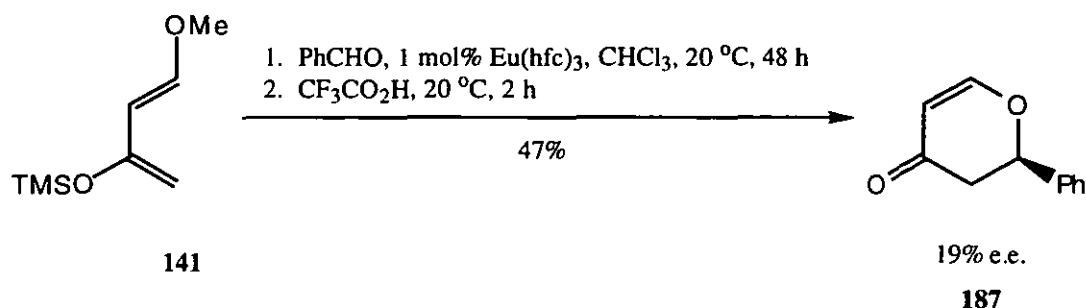


Figure 20

We initially repeated the published work to establish a reference point for the research.

Trans-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene **141**, Danishefsky's diene, is

commercially available and so seemed a suitable siloxydiene to begin with. A solution of the siloxydiene **141**, benzaldehyde and 1 mol% of Eu(hfc)₃ in chloroform was stirred for 48 h at ambient temperature. The resultant mixture was treated with trifluoroacetic acid before being worked-up and purified by flash chromatography to yield the product as a yellow oil in 47%.



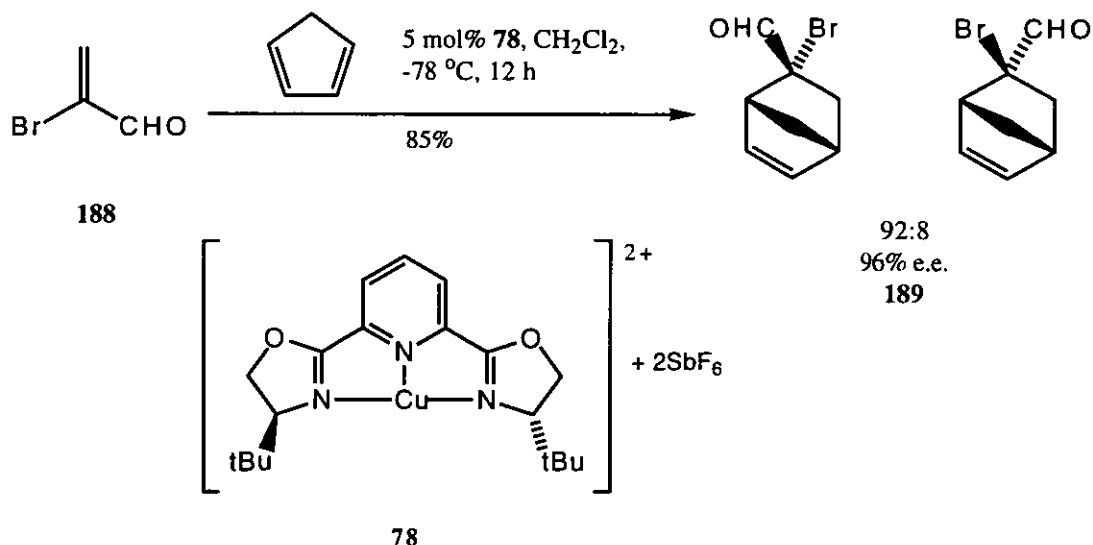
Scheme 58

The IR spectrum for the product included peaks associated with an α,β -unsaturated ketone at 1681 cm⁻¹ and 1595 cm⁻¹. The ¹H-NMR showed signals assigned as representing an alkene proton at 5.53 ppm and a benzylic proton at 5.42 ppm. In addition the enantioselectivity of the reaction was analysed by chiral HPLC. A sample was analysed on a Chiralcel OD column, eluted by a mixture of 1% IPA and 99% hexane at 1 mL/min. The product was shown to have an enantiomeric excess of 19% e.e. which is in agreement with Danishefsky's published result.

We then attempted to improve upon Danishefsky's result. We mimicked Danishefsky's initial conditions but varied the specifics. We used both Eu(NO₃)₃·5H₂O and EuCl₃·6H₂O as a source of europium. We chose to use ligands **169** and **171** for this investigation. The proportions of metal salt to ligand and reagents were varied. In some cases the ligand was deprotonated with sodium hydride, prior to the reaction, to promote co-ordination with the metal. The reactions were run without solvent and in chloroform, THF and acetone in various concentrations.

The product was readily available in good isolated yield but subsequent analysis by chiral HPLC indicated that the product was racemic. The presence of our ligands was unfortunately not influencing the stereochemical course of the reaction.

In 1995 Evans^{38b} and Keck⁷⁷ both published the results of Diels-Alder reactions catalysed by chiral complexes. Evans and co-workers used a chiral Cu-pybox **78** complex to catalyse the condensation of unsaturated aldehydes with cyclopentadiene. The researchers were able to isolate the cycloaddition products in up to 96% e.e. and an *exo:endo* ratio of 92:8.



Scheme 59

Keck and co-workers catalysed the reaction of Danishefsky's diene **141** and an aldehyde with a BINOL/Ti(O-*i*Pr)₄ derived Lewis acid. They were able to isolate **187** in moderate yield and excellent levels of stereoselectivity up to 97% e.e.

The publication of these two papers coincided with our own work in this area. We were not achieving comparable results and considered it prudent to apply our research efforts elsewhere.

2.4 Conclusion

We have developed an effective synthesis of a novel series of keto-oxazoline ligands. Unfortunately we were unable to achieve good levels of stereocontrol in the asymmetric hetero Diels-Alder reaction.

Chapter Three

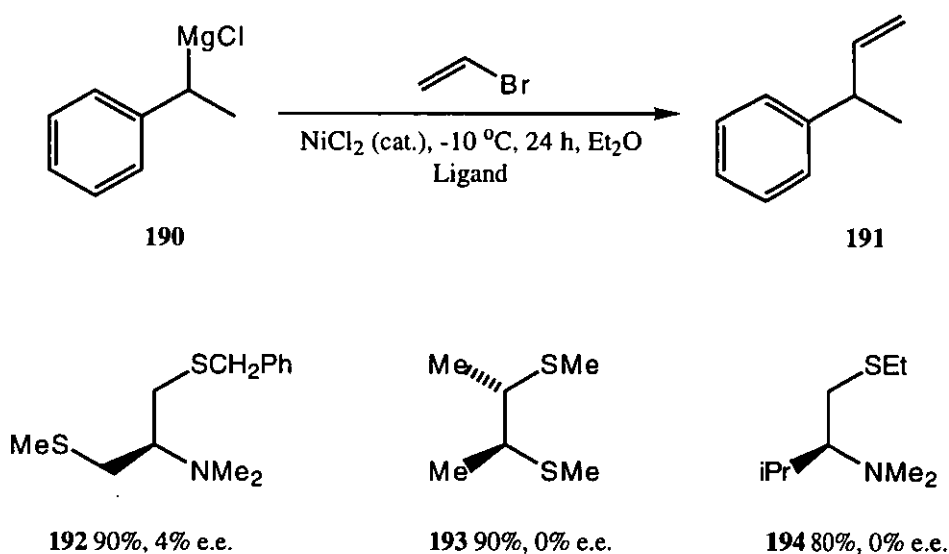
Oxazoline Ligands Including Sulfur as a Ligating Atom

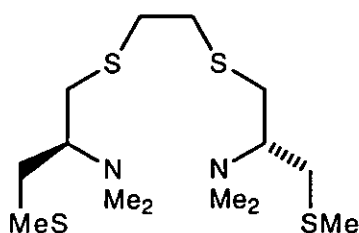
3.1 Introduction

Enantiomerically pure ligands that include a ligating sulfur moiety are relatively rare. In 1992 Blaser published a comprehensive review entitled "The Chiral Pool as a Source of Enantioselective Catalysts and Auxiliaries".⁷⁸ The review considered the design, synthesis and application of over one hundred ligands. Only one compound with a ligating sulfur atom was cited. But since that review ligands and chiral auxiliaries⁷⁹ that include a sulfur atom have become more common.

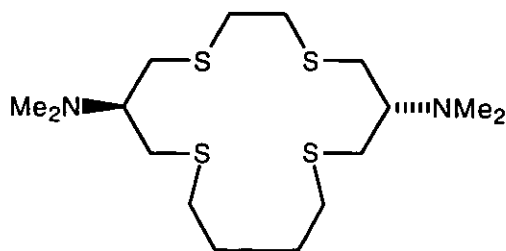
3.1.1 Chiral Ligands Including a Ligating Sulfur Atom

Kellogg and co-workers have used sulfur containing macrocycles as ligands for nickel.⁸⁰ The ligands promoted the nickel catalysed cross-coupling of a Grignard reagent with vinyl bromide. The levels of stereoselectivity achieved were generally low but the chemical yields were high and the reaction proceeded more quickly in the presence of the ligand. A selection of the ligands is illustrated below including the chemical yield for the reaction and the level of enantioselectivity reached.





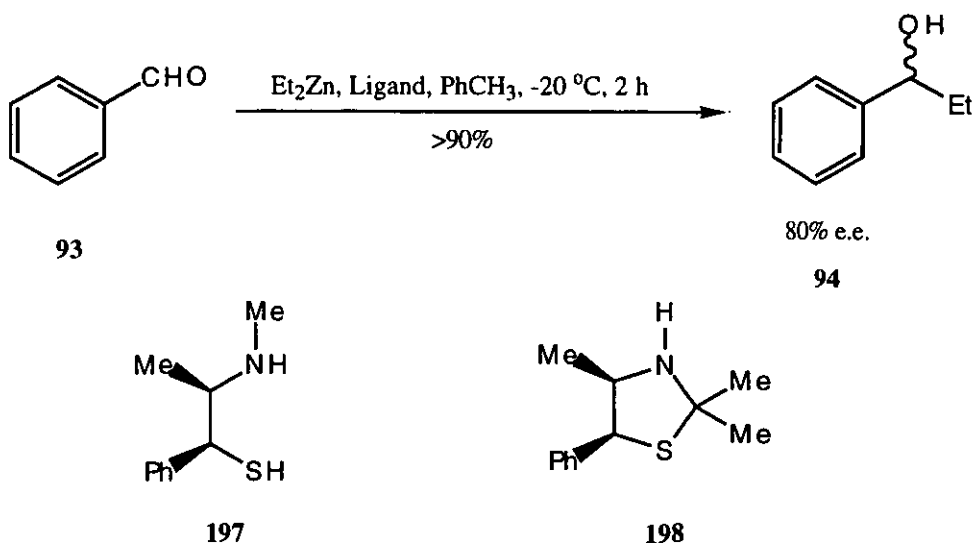
195 78%, 8% e.e.



196 50%, 46% e.e.

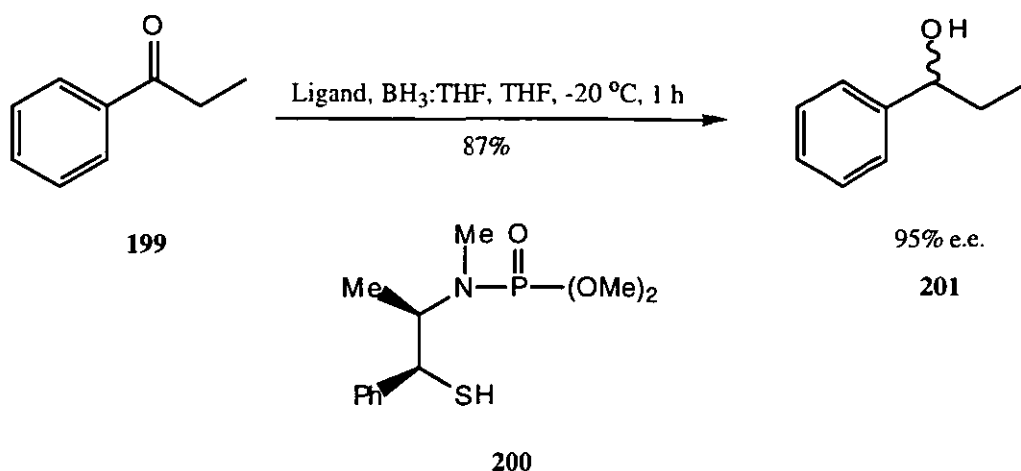
Scheme 60

More recently Kellogg and co-workers have developed novel ligands for reduction chemistry. Ligands **197** and **198** were successful in the reduction of benzaldehyde with diethylzinc.⁸¹ The product **94** was available in excellent yield and up to 80% e.e.



Scheme 61

In addition the researchers considered the borane mediated reduction of prochiral ketones.⁸² The reduced product **201** was isolated in up to 87% yield and 95% e.e.



Scheme 62

Montenegro *et al.* and Gladiali and co-workers have independently synthesised novel ligands that contain ligating sulfur atoms.⁸³ Ligand **202** derives its chirality from camphor whereas **203** utilises the C_2 -symmetry of the bulky binaphthyl moiety. The efficacy of **202** and **203** has yet to be tested.

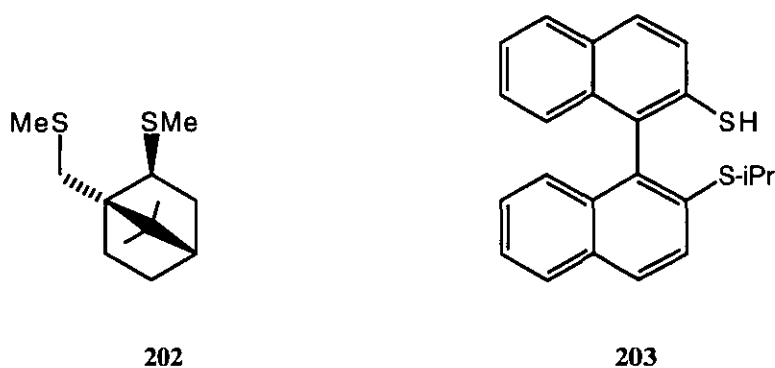
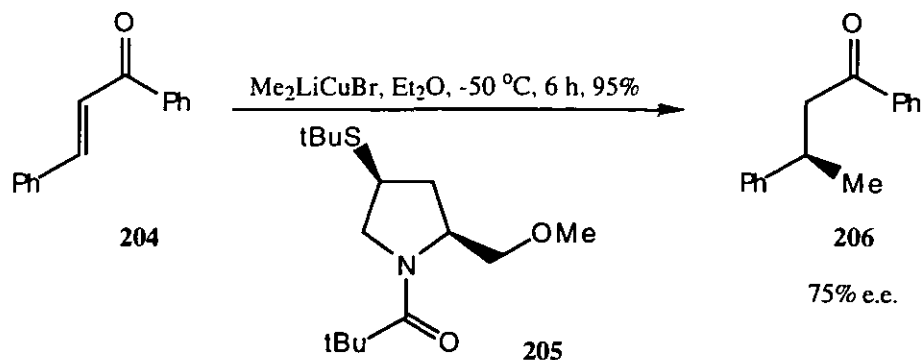


Figure 21

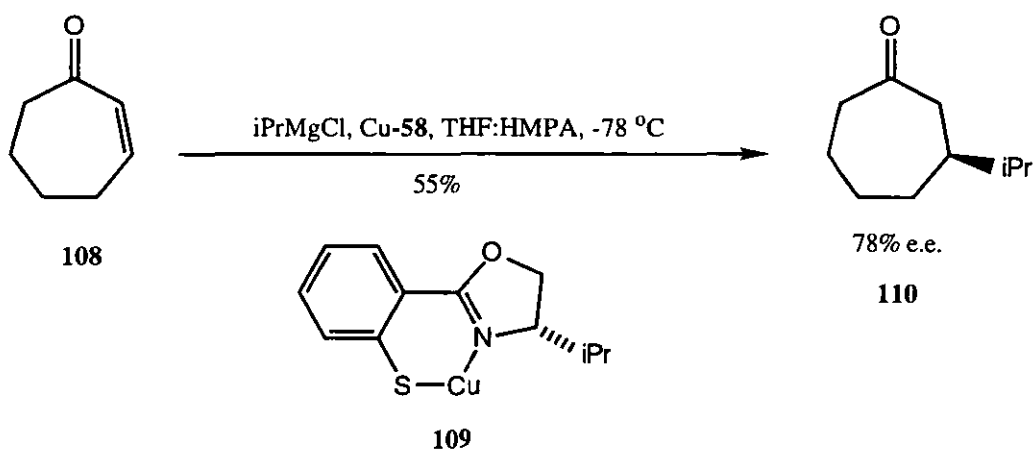
3.1.2 Copper Catalysed Conjugate Addition to Unsaturated Ketones

Leyendecker and Laucher synthesised **205** from (2*S*,4*R*)-hydroxyproline as a ligand for copper.⁸⁴ The researchers introduced a sulfur moiety at the 4 position on the pyrrolidine ring because of its well established affinity for copper. The efficacy of the ligand was tested in the asymmetric methylation of chalcone **204**. The substituted product **206** was available in excellent yield and up to 75% e.e.



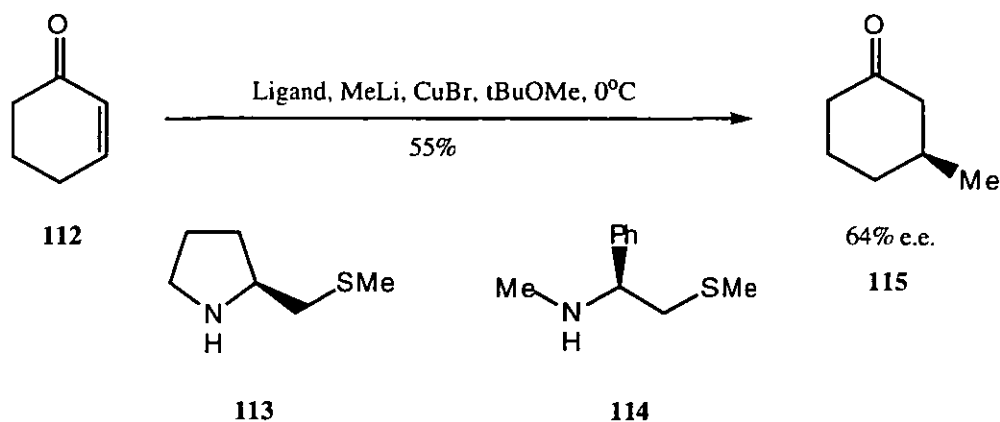
Scheme 63

Pfaltz and Zhou have used complex **109** in the copper catalysed conjugate addition of a Grignard reagent to an α,β -unsaturated ketone.⁴⁹ They were able to isolate the product **110** in up to 78% e.e.



Scheme 64

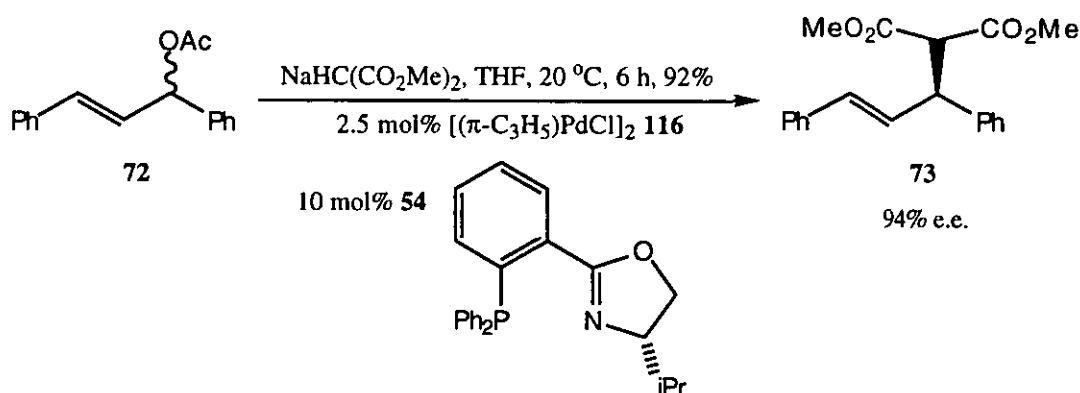
Kennedy and co-workers have also synthesised ligands for enantioselective conjugate additions.⁸⁵ The researchers developed ligands derived from *L*-proline and (*S*)-phenyl glycine. The ligands were then used in stoichiometric quantities to direct the addition of methylcuprate to 2-cyclohex-1-one. The addition products were available in up to 55% yield and 64% e.e.



Scheme 65

3.1.3 Palladium Catalysed Allylic Substitution

In 1993 several research groups introduced the phosphine-oxazolines **54-57** as efficient ligands for the palladium catalysed allylic substitution reaction.^{19,20,21} The rationale behind the design of these ligands was two-fold. Firstly the oxazoline moiety was to provide stereocontrol through the influence of the bulky alkyl group at the 4 position on the ring. The 2-oxazoline has already been shown to directly influence the topology of a variety of catalysts. Secondly the different electronic properties of the ligating phosphorus and nitrogen atoms were intended to induce electrostatic differences between the carbon atoms of the η^3 -allyl intermediate. The ligands were shown to be very effective and the substitution product **73** was available in excellent yield and enantioselectivity.



Scheme 66

There has been further interest in developing novel and different ligands for this reaction. In particular the nature of the auxiliary donor atom and the source of enantioselectivity have been varied. It had been established that a π -accepting ligating atom was important to the success of the ligand. Consequently sulfur was chosen to replace phosphorus as the second donor atom in some of the new ligands.

Chelucci and Cabras synthesised the bicyclic ligand **207** and found that they could achieve up to 83% e.e. in the substitution product **73**.⁸⁶ Bryce and co-worker had limited success with their tetrathiafulvalene based ligands.⁸⁷ Realising the product in yields below 30% and enantioselectivities around 20% e.e.

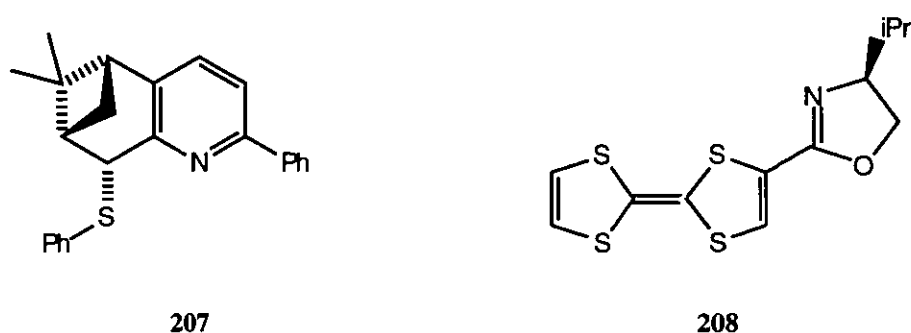
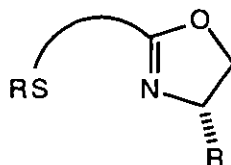


Figure 22

The details of the chemistry of the palladium catalysed allylic substitution reaction, its mechanism and the source of stereocontrol will be discussed in the next chapter, section 4.1.1.

3.2 Sulfur-Oxazoline Ligands

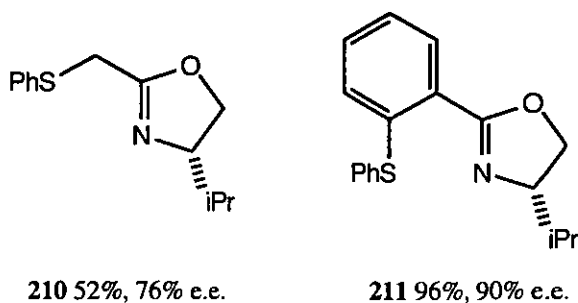
The Williams group synthesised ligands that included a ligating sulfur atom and derived their stereocontrol from the oxazoline moiety. The sulfur moiety was tethered to the oxazoline ring at the 2 position by either alkyl or aryl linkers.



209

Figure 23

Two of the ligands are illustrated below along with their result for the palladium catalysed allylic substitution reaction.^{22a} The sulfur-oxazoline ligands were effective ligands for palladium although the levels of stereocontrol were lower than for the phosphine-oxazoline ligands **54-57**.

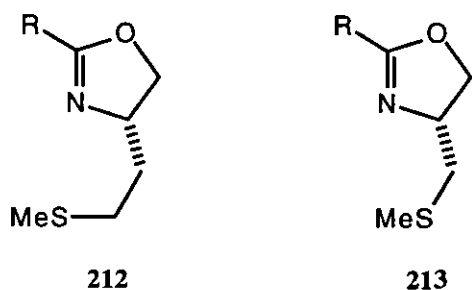


210 52%, 76% e.e.

211 96%, 90% e.e.

Figure 24

We wished to synthesise sulfur-oxazoline ligands derived from the sulfur containing amino acids *S*-methyl-*L*-cysteine **212** and *L*-methionine **213**. In this case the sulfur moiety would be tethered to the 4 position of the oxazoline ring. We were interested to see how this would subsequently affect the behaviour of the ligand in the allylic substitution reaction.



212

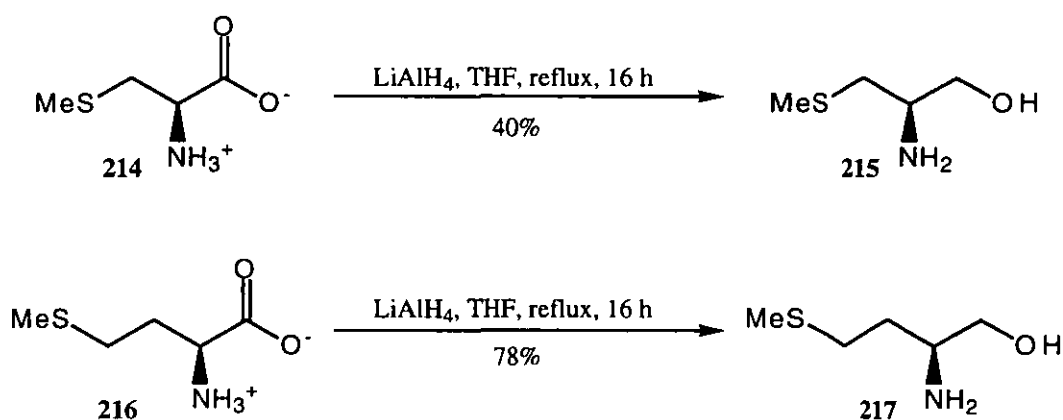
213

Figure 25

3.2.1 Ligand Synthesis

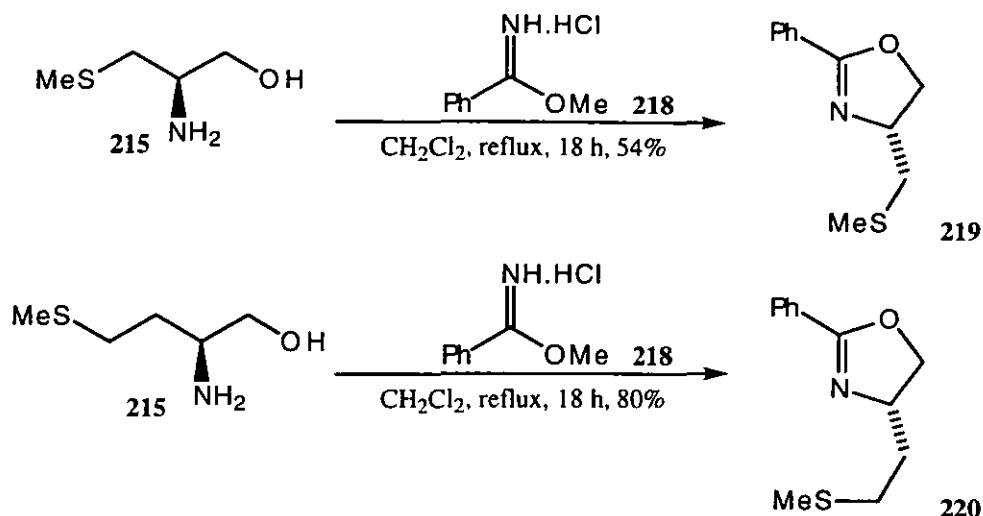
It was necessary to reduce the amino acids **214** and **216** to their corresponding amino alcohols **215** and **217** before the formation of the oxazoline ring. This transformation was smoothly achieved with lithium aluminium hydride. The amino acid **214** was reduced to the corresponding amino alcohol **215**. Amino alcohol **217** was readily available from the reduction of methionine **216**. The products were purified by short path distillation to provide the desired amino alcohols as colourless oils.

The ^1H -NMR of **215** showed new signals at 3.42 ppm and 3.64 ppm which were assigned to the protons adjacent to the hydroxyl moiety. The ^1H -NMR of **217** included similar signals. The IR spectrum for both compounds lacked a peak in the carbonyl stretch region indicating the reduction of the acid functionality.



Scheme 67

Once in hand the amino alcohols were condensed with methyl benzimidate **218** in dichloromethane at reflux. The structure of the ligands was confirmed by ^1H -NMR, ^{13}C -NMR and IR spectroscopy.⁸⁸ The IR spectrum included a peak at 1650 cm⁻¹ which is indicative of a C=N bond. The ^{13}C -NMR included a signal at 165 ppm for **219** and 163 ppm for **220** which was assigned to the quaternary ring carbon. The ^1H -NMR included the distinctive signals of the oxazoline ring protons and the singlet associated with the SCH₃ moiety.



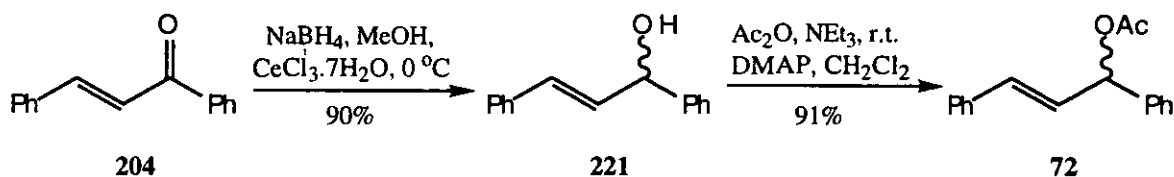
Scheme 68

The efficacy of the ligands was tested in the palladium catalysed allylic substitution reaction.

3.2.2 Palladium Catalysed Allylic Substitution Reaction

The racemic acetate **72** is available in excellent yield in two steps. Firstly chalcone **204** is reduced to the alcohol **221** under Luche conditions.⁸⁹ The reaction proceeds smoothly and the alcohol is carried through to the next step without further purification. The alcohol was acylated with acetic anhydride to provide the acetate **72**.

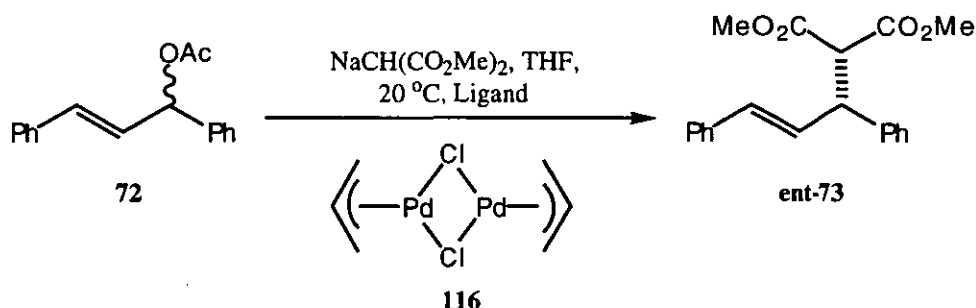
The formation of the alcohol was confirmed by IR spectroscopy. Likewise the lack of an alcohol peak and presence of an ester peak in the spectrum at 1740 cm^{-1} indicated a successful esterification. The $^1\text{H-NMR}$ included signals associated with olefinic protons confirming that the alkene had not been reduced during the first step.



Scheme 69

In brief, the palladium catalysed allylic substitution reaction involves the initial loss of the acetate moiety through oxidative addition of the palladium to form an intermediate η^3 -allyl complex. The intermediate is attacked directly by the nucleophile, and the substitution product is formed by a reductive elimination mechanism. The geometry and steric environment of the intermediate complex may be directly influenced by the ligands chelating the palladium. The details of this reaction shall be considered further in section 4.1.1.

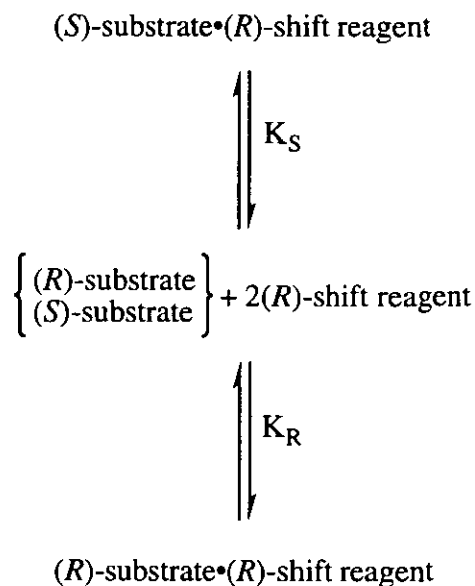
The procedure for the palladium catalysed allylic substitution reaction is well established. The sodium salt of dimethyl malonate as a solution in THF was added to a stirring mixture of acetate **72**, palladium **116** and ligand under an inert atmosphere. The product **73** could be isolated in good yield. The ^1H -NMR showed signals at 3.74 ppm associated with the methyl esters and a doublet at 4.00 ppm from the methine proton separating the ester groups.



Scheme 70

The isolated product was assayed for enantiomeric excess by employing the enantiopure shift reagent $\text{Eu}(\text{hfc})_3$ in ^1H -NMR. The use of enantiopure lanthanide shift reagents is a simple widely used technique for the determination of enantiomeric purities by NMR spectroscopy.^{64,65} Under normal conditions the equilibrium between the substrate and the lanthanide shift reagent is rapid on the NMR time scale. This results in a time-averaged spectrum arriving from the average of complexed and uncomplexed substrate molecules. Rapidly equilibrating complexes are formed by an enantiopure lanthanide shift reagent binding to each of the two enantiomers. These complexes are diastereomeric and can have different chemical shifts. The difference in shifts may have at least two causes. Firstly, the equilibrium constants (K_R , K_S), may be different for diastereomeric complexes, thereby causing larger shifts for the complex having the larger binding constant. Also, the two

diastereomeric complexes formed may differ in their geometry which may cause a difference in the induced shift for corresponding signals in the two complexes.



Scheme 71

The results of the substitution reaction are summarised below.

Ligand	Yield (%)	E.e. (%)
219	86	56
220	79	88

Table 3

The ligands were shown to be effective in relaying stereochemical information to the substitution product. Interestingly the optical rotation data showed the substitution product to be predominately the (*R*)-(+)-enantiomer. Previously it had been demonstrated that the absolute stereochemistry of the major isomer was the (*S*)-(-)-enantiomer, using ligands derived from *L*-amino acids.^{22a} This result may be rationalised by considering the organisation in the η^3 -allyl intermediate.

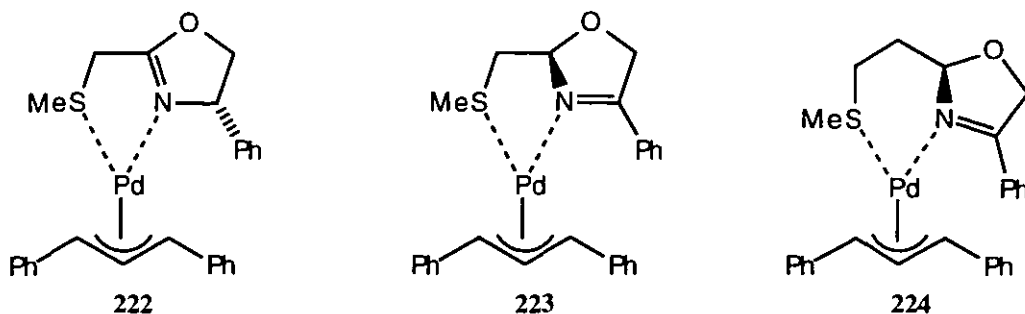


Figure 26

The ligand illustrated in **222** provides the substitution product **73** in 67% yield and 60% e.e.^{22a} In comparison the use of ligand **219** produces **ent-73** in 56% e.e. and 86% isolated yield. The levels of stereoselectivity are similar but in **222** the (*S*)-(-)-enantiomer is the major stereo isomer, whereas in **223** the (*R*)-(+)-enantiomer predominates. The structures may be seen to be quasi-enantiomeric, hence providing for different enantiomers in the product. The configuration of the ligand and subsequent complex with palladium has directly influenced the configuration of the product. It is of note that the amino acids from which both these ligands are derived are of the same configuration. Nonetheless each is able to provide for a different enantiomer in excess in the substitution product.

Furthermore ligand **220** provides the product in an isolated yield of 79% and 88% e.e., once more with the (*R*)-(+)-enantiomer in excess. The longer tether of **220** compared with **219** has increased the size of the chelate formed. Consequently the asymmetric environment is placed closer to the allyl moiety complexed with the palladium. This results in an overall increase in the level of stereocontrol.

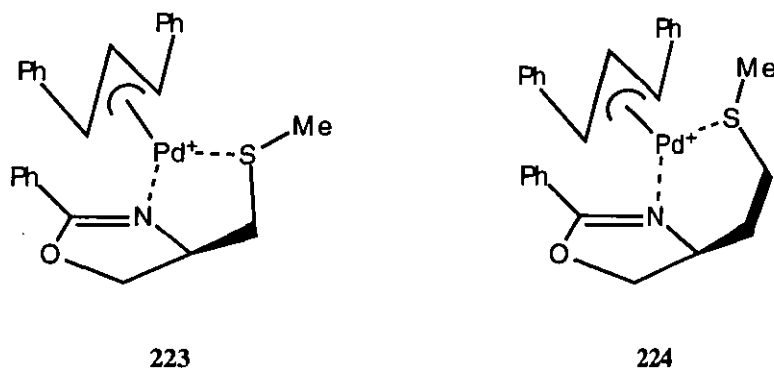


Figure 27

The ligands **219** and **220** have been demonstrated to be effective in the palladium catalysed allylic substitution reaction. The chiral substitution product **ent-73** is available in high yield and moderate to good enantiomeric excess.

3.3 Sulfoxide-Oxazoline Ligands

As a natural extension to the use of sulfur-oxazoline ligands we considered the application of sulfoxide-oxazoline ligands. Sulfoxides have been used both as chiral auxiliaries⁹⁰ and as chiral ligands in asymmetric catalysis.⁹¹ It has been demonstrated that an enantiomerically pure sulfoxide may efficiently induce stereoselectivity in a variety of asymmetric reactions, including Diels-Alder reactions,⁹² aldol reactions⁹³ and other carbon-carbon bond forming processes.⁹⁴

It was envisaged that oxazoline-sulfoxides may also behave as analogues of acetyl acetone. The ligand illustrated below includes all the structural features that were discussed in Section 2.2.1. In addition to the labile methylene protons and the enantiomerically pure oxazoline moiety the ligand would include a chiral sulfoxide moiety. Since these potential ligands possess two chirality centres, it would be possible to have matched and mismatched pairs between the *4S* centre of the oxazoline ring and the *S_S* and *R_S* isomers of the sulfoxide.

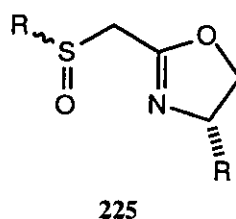


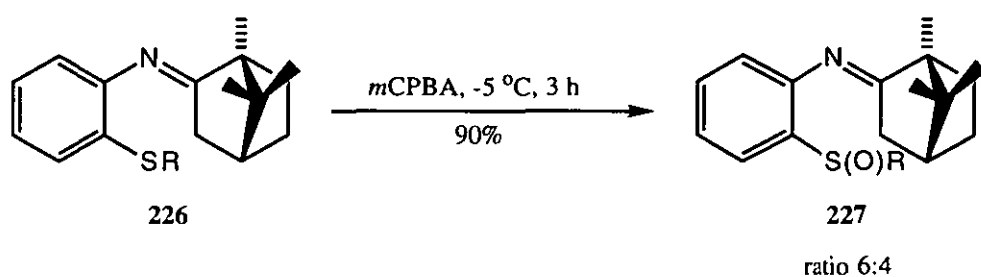
Figure 28

3.3.1 Directed Oxidations at Sulfur with Achiral Oxidants

A significant amount of research effort has considered enantioselective and diastereoselective oxidation of sulfur moieties.⁹⁵ There is extensive methodology available for enantioselective oxidation at sulfur using chiral oxidants. Also several research groups have investigated the

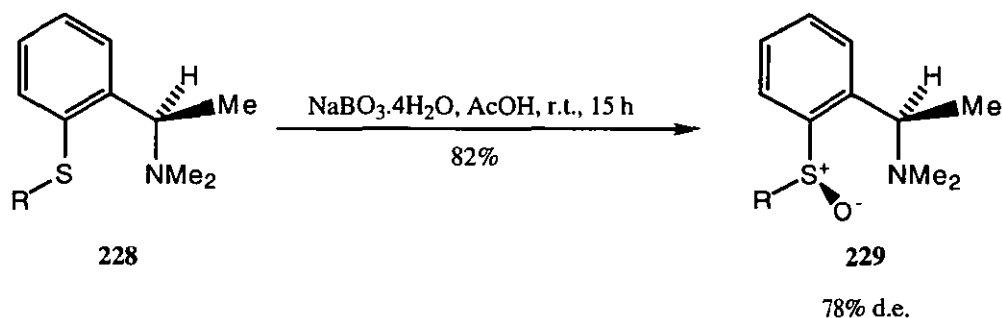
diastereoselective oxidation of chiral sulfides using achiral oxidants.⁹⁶ The proximity of a defined chirality centre has been exploited to relay stereochemistry to the newly formed sulfoxide.

De Lucchi and co-workers used chirality derived from camphor to introduce diastereoselectivity into the oxidation of sulfur by *m*CPBA.^{96d} They achieved a 6:4 ratio of diastereomeric sulfoxides consistently. In one case the researchers varied the reaction conditions including solvent, reaction temperature and achiral oxidant but found no change in the level of stereoselectivity.



Scheme 72

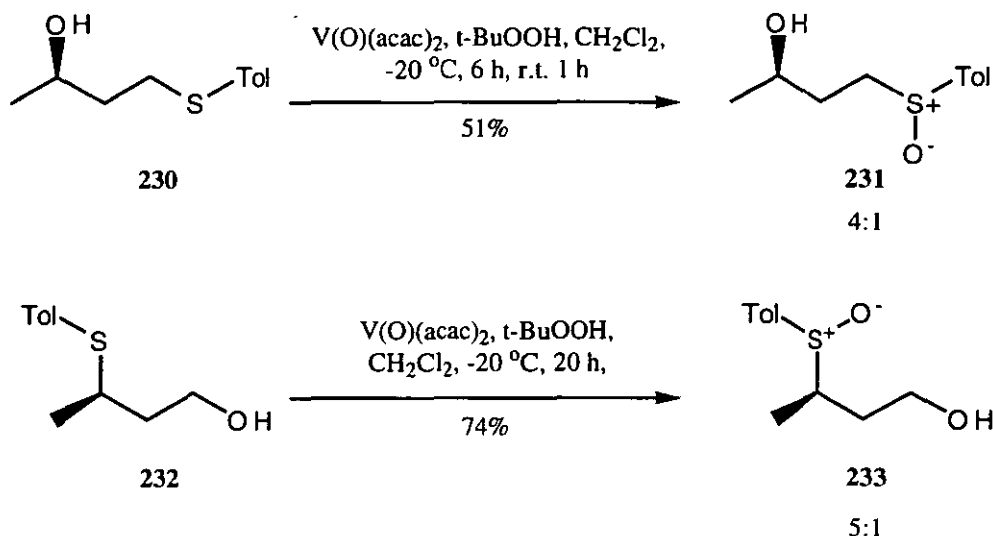
Ohta and co-workers used a chiral moiety *ortho* to the sulfide to direct the approach of an achiral oxidant.^{96e} They found organic peracids to be ineffective for the diastereoselective oxidation. Sodium perborate was found to be the most efficient oxidant. The products were available in excellent chemical yield and up to 78% d.e.



Scheme 73

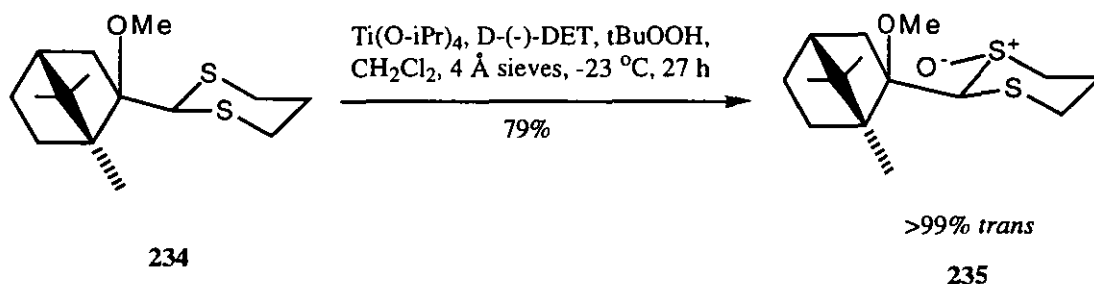
Breitschuh and Seebach reported that the combination of chirality α to the sulfur atom and a pendant hydroxyl moiety provided for levels of diastereocontrol up to 5:1. The researchers

oxidised the sulfide **230** to its sulfoxide **231** with *tert*-butyl hydroperoxide, catalysed by the addition of $V(O)(acac)_2$. They suggested that the hydroxyl moiety was co-ordinated to the vanadium and assisted the approach of the oxidant. The presence of the methyl group α to the sulfur in **232** was responsible for the selectivity.



Scheme 74

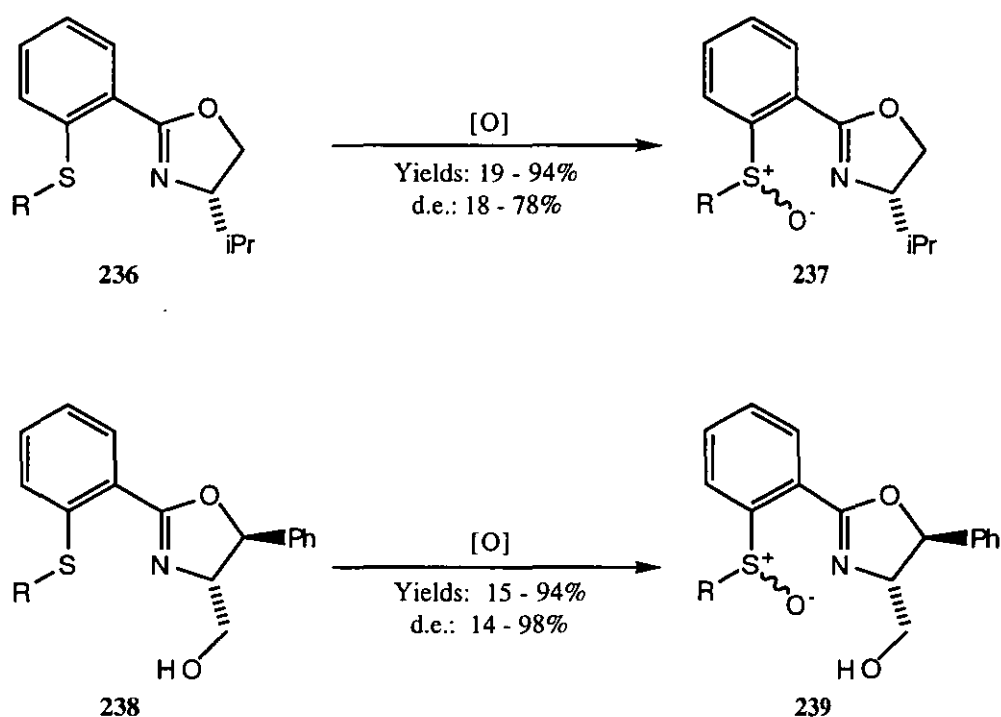
Page and co-workers have achieved excellent levels of stereocontrol in the enantioselective oxidation of substituted 1,3-dithianes.⁹⁷ The researchers determined that the level of stereocontrol was directly influenced by the substituent at the 2 position of the dithiane. Toru and co-workers subsequently considered the asymmetric oxidation of dithianes that included a chiral auxiliary.⁹⁸ After careful consideration of the reaction conditions and appropriate chiral auxiliaries the researchers were able to isolate **235** in good yield and essentially as one isomer.



Scheme 75

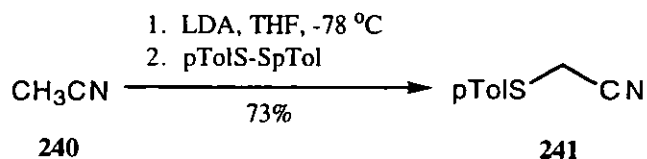
3.3.2 Oxazoline Directed Oxidations

In association with Justin Bower we investigated the opportunities for approaching the desired ligands by the selective oxidation of sulfide-oxazoline ligands. Justin Bower demonstrated that the enantiomerically pure oxazoline moiety could directly influence the stereochemical oxidation of a prochiral sulfur centre.⁹⁹



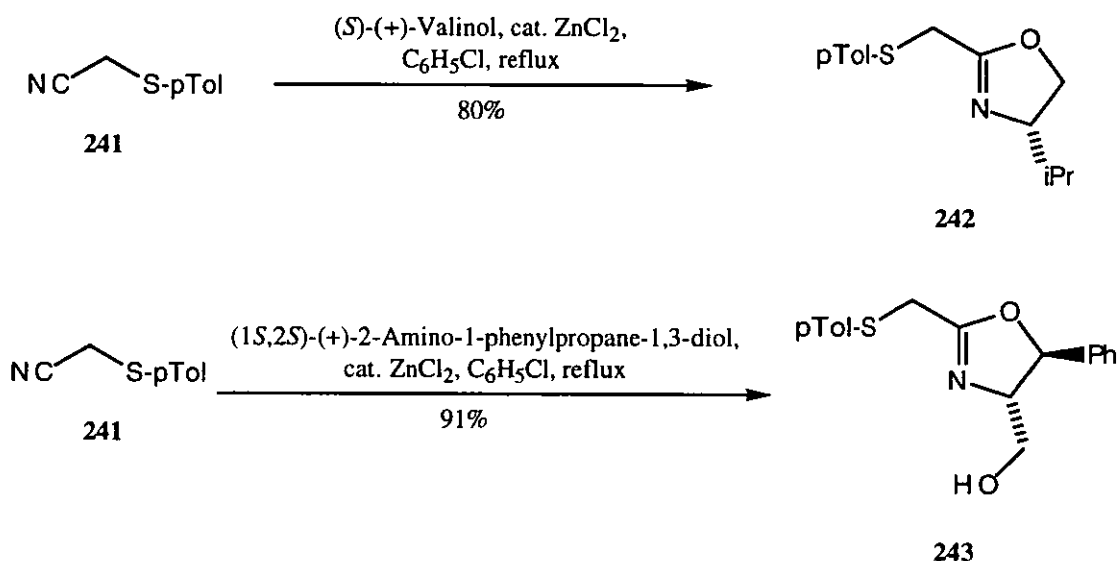
Scheme 76

Initially we synthesised three sulfides to act as oxidation substrates **242**, **243** and **244**. The preparation of the sulfides was straightforward. We chose to prepare *para*-tolylsulfides to ensure consistency in later results, as will become apparent in due course. Consequently it was necessary to prepare [4-(methylphenyl)sulfanyl]acetonitrile **241**. A solution of acetonitrile in THF was lithiated with LDA and the subsequent anion was quenched with di-*p*-tolyl sulfide. After work-up and purification by column chromatography the product **241** was isolated as an oil in 73%. The IR spectrum included a peak associated with a nitrile moiety at 2261 cm⁻¹ and the ¹H-NMR included a signal at 3.51 ppm which was assigned to the methylene protons.



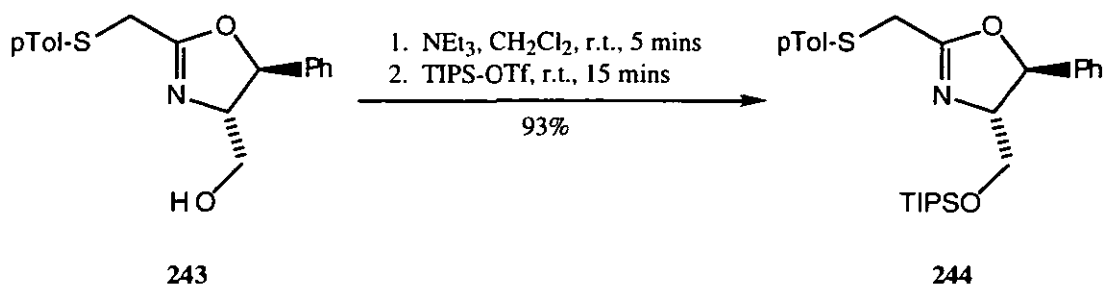
Scheme 77

The synthesis of the oxazoline ring was achieved by using zinc chloride catalysed condensation of **241** with an amino alcohol. The condensation required the reagents to be heated at reflux in chlorobenzene until analysis by tlc showed that all of the nitrile had been consumed. After work-up and purification the ligands were available in good yield. The spectroscopic data was consistent with the formation of the oxazoline ring. Key features included the quaternary carbon at 163.8 ppm for **242** and 168.2 ppm for **243**, characteristic signals of the oxazoline ring. Also the IR spectrum included peaks at 1665 cm^{-1} and 1651 cm^{-1} respectively associated with the C=N stretch.



Scheme 78

The hydroxyl moiety of **243** was subsequently protected as its TIPS silyl ether. The alcohol was treated sequentially with triethylamine and triisopropylsilyl trifluoromethanesulfonate for 15 mins at ambient temperature. The product **244** was isolated as an oil in 93% yield. The ^1H -NMR included a multiplet of signals between 1.13 and 0.99 ppm which were assigned to the isopropyl groups of the TIPS ether.

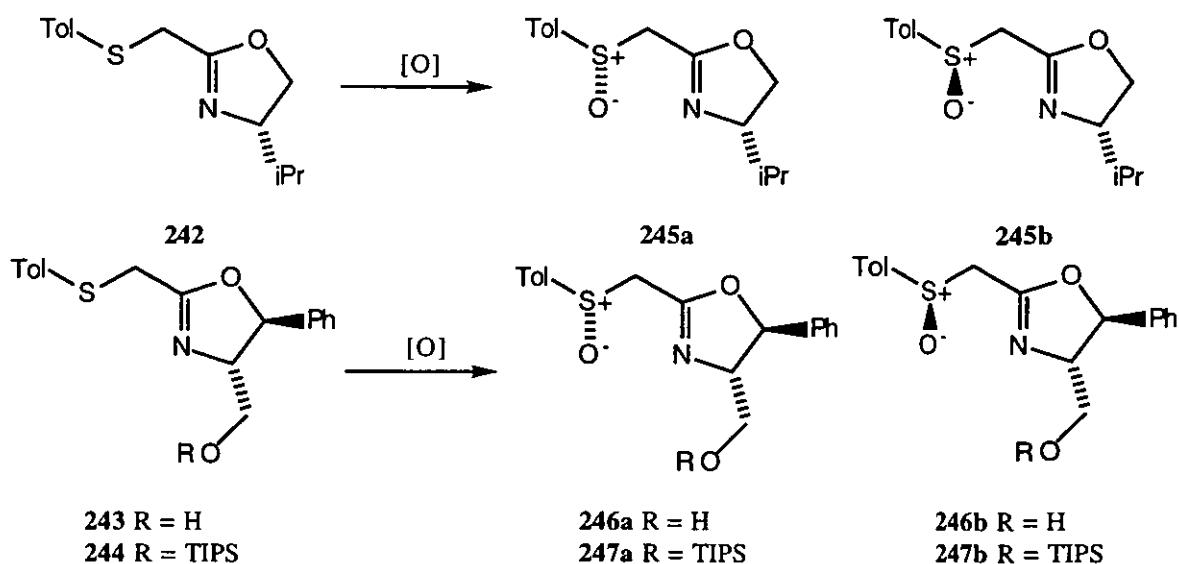


Scheme 79

With the three substrate sulfides in hand we proceeded to consider their oxidation to chiral sulfoxides.

3.3.3 Oxidation of the Sulfide Substrates to Sulfoxides

The sulfides **242**, **243** and **244** were oxidised with *m*CPBA to afford the sulfoxides **245a:245b**, **246a:246b** and **247a:247b** respectively.¹⁰⁰ The isolated yields for the sulfoxides were generally low, 11-48%. The identity of the sulfoxides was confirmed by spectroscopic data. The IR spectrum included a peak at approximately 1050 cm^{-1} due to the stretching of the S=O bond. The ^{13}C -NMR data showed that the signal from the CH_2 adjacent to the sulfur atom had moved downfield which would be consistent with the more electron withdrawing nature of the sulfoxide moiety compared with a simple sulfide.



Scheme 80

The diastereomeric ratios were determined by inspection of the ^1H -NMR. The isolated yields and diastereomeric ratios are summarised in below.

Sulfide	Conditions	Product	Ratio	Yield (%)
242	<i>m</i> CPBA, CHCl_3 , -78 $^\circ\text{C}$, 1 h	245a:245b	37:63	27
242	<i>m</i> CPBA, CHCl_3 -MeOH, -78 $^\circ\text{C}$, 1 h	245a:245b	37:63	26
242	<i>m</i> CPBA, CHCl_3 -hexane, -78 $^\circ\text{C}$, 1 h	245a:245b	26:74	48
243	<i>m</i> CPBA, CHCl_3 , -78 $^\circ\text{C}$, 1 h	246a:246b	88:12	11
243	<i>m</i> CPBA, CHCl_3 -MeOH, -78 $^\circ\text{C}$, 1 h	246a:246b	91:9	16
243	<i>m</i> CPBA, CHCl_3 -hexane, -78 $^\circ\text{C}$, 1 h	246a:246b	96:4	34
244	<i>m</i> CPBA, CHCl_3 , -78 $^\circ\text{C}$, 1 h	247a:247b	16:84	14
244	<i>m</i> CPBA, CHCl_3 -MeOH, -78 $^\circ\text{C}$, 1 h	247a:247b	42:58	15
244	<i>m</i> CPBA, CHCl_3 -hexane, -78 $^\circ\text{C}$, 1 h	247a:247b	31:69	24

Table 4

The level of influence displayed by the *iso*-propyl moiety in the oxidation of **242** to **245a:245b** was seen to be relatively small. Nonetheless it can be seen that the favoured diastereomer occurs when the oxidant approaches the sulfur atom from the face *anti* to the *iso*-propyl group. The affect of steric hindrance is reinforced by the oxidation of **244** to **247a:247b**. In this case the favoured diastereomer is the isomer generated when the oxidant approaches the sulfide *anti* to the TIPS silyl ether. Furthermore the sense of stereoinduction is seen to be opposite to that for the oxidation of **243** where the hydroxyl moiety is not protected.

Interestingly the oxidation of **243** to produce **246a:246b** proceeds with the favoured diastereomer occurring where the oxidant approaches the sulfur atom from the same face as the hydroxyl moiety. In addition the levels of stereocontrol are seen to increase to a ratio of 96:4 which equates to 92% d.e. It is suggested that the hydroxyl moiety and the nitrogen atom of the oxazoline ring co-ordinate with the incoming oxidant. The result is a more

organised intermediate structure which facilitates a higher level of stereocontrol in the oxidation process.

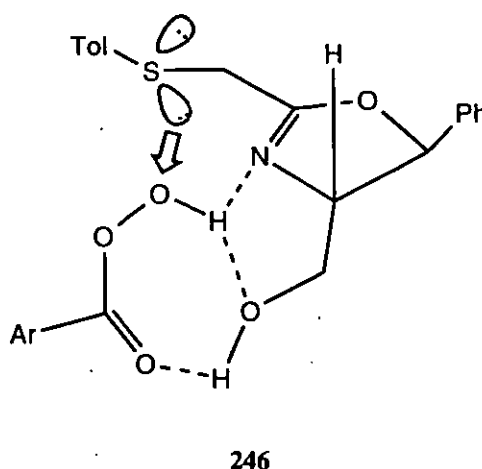
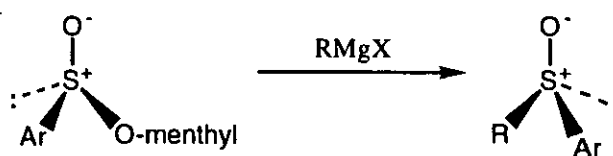


Figure 29

Overall though the isolated yields and levels of stereoselectivity were not sufficiently high or reliable to encourage us to use oxidation as a route to the desired ligands. It was felt that it was necessary to be able to access both diastereomers in good yield and excellent diastereoselectivity. A goal that was not realistically achievable through simple oxidation of the sulfide.

3.3.4 Direct Synthesis of the Sulfoxide-Oxazoline Ligands

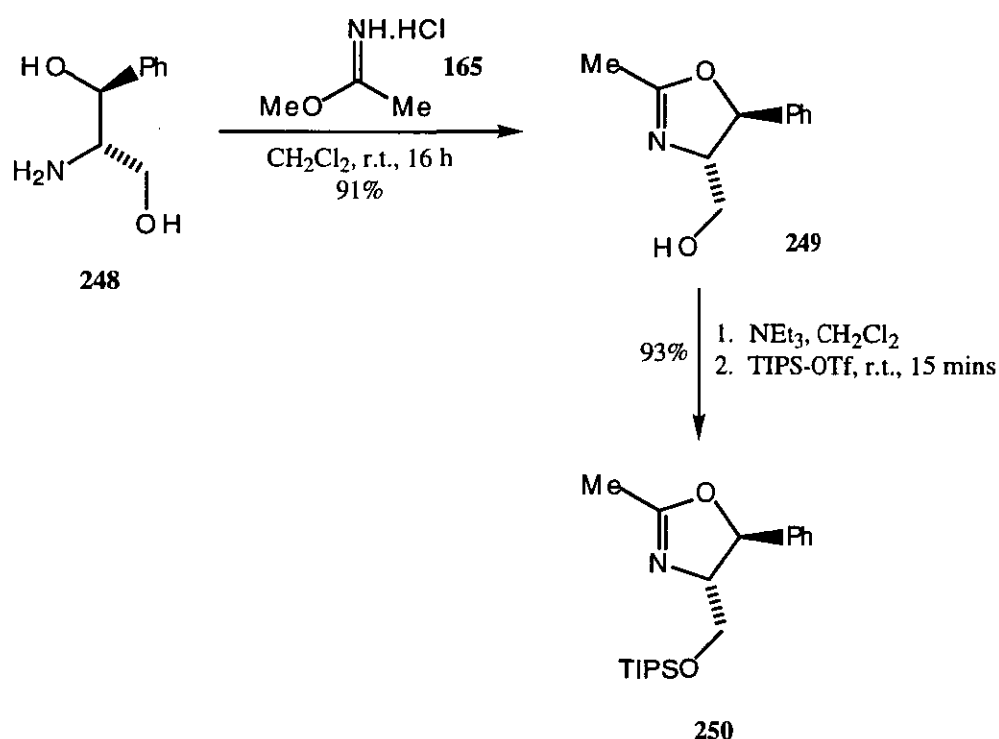
An alternative approach was to utilise technology first published by Andersen in 1964.¹⁰¹ Andersen and co-workers synthesised several sulfoxides by treating sulfinate esters with Grignard reagents. The researchers went on to demonstrate that the reaction proceeds through clean inversion of stereochemistry at the sulfur centre without loss of enantiomeric purity.



Scheme 81

We rationalised that we would be able to access the required ligands in excellent diastereomeric excess by application of this methodology. Both enantiomers of the sulfinate esters are available as single isomers. Generation of the anion of a 2-methyloxazoline followed by the addition of the appropriate sulfinate ester should furnish us with the desired diastereomer.

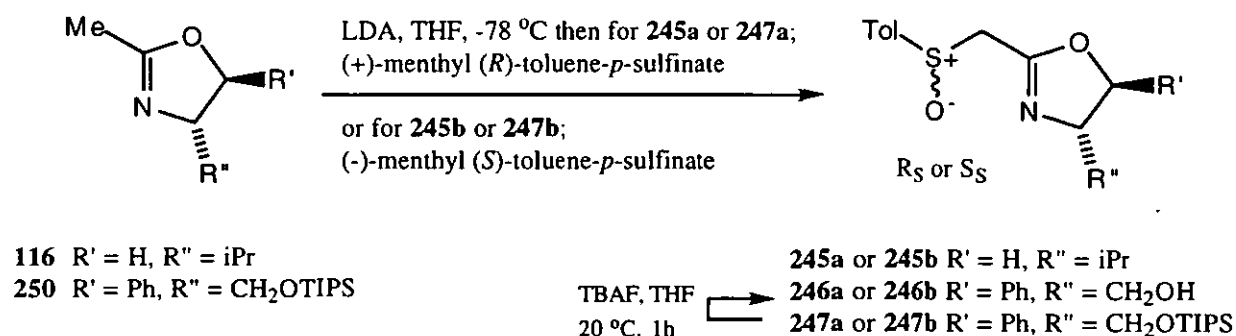
Methyl acetimidate **165** was condensed with (1*S*,2*S*)-(+)-2-amino-1-phenylpropane-1,3-diol **248** to provide for **249** in 91% yield. The alcohol was then treated with triethylamine followed by triisopropylsilyl trifluoromethanesulfonate to produce **250** in 93% after purification by flash chromatography. The IR spectrum of **250** included the characteristic peak at 1675 cm⁻¹. Likewise the ¹H-NMR included signals at 2.08 ppm and 1.16-1.04 ppm which were assigned to the protons of the 2-methyl moiety and the *iso*-propyl groups respectively.



Scheme 83

The 2-methyloxazolines **116** and **250** were deprotonated with LDA under rigorously anhydrous conditions. The anion was then quenched with an enantiomerically pure sulfinate ester to furnish us with the desired ligands. After work-up and purification by column

chromatography the ligands were available in good isolated yields. Ligands **247a** and **247b** were subsequently deprotected by TBAF to realise ligands **246a** and **246b** as the free alcohol in reasonable yield.



Scheme 83

Conditions	Ligand	R_S or S_S	Yield (%)
116, LDA, THF, -78 °C then (+)-menthyl (<i>R</i>)-toluene- <i>p</i> -sulfinate	245a	S_S	76
116, LDA, THF, -78 °C then (-)-menthyl (<i>S</i>)-toluene- <i>p</i> -sulfinate	245b	R_S	47
247a , TBAF, THF, 20 °C, 1 h	246a	S_S	29
247b , TBAF, THF, 20 °C, 1 h	246b	R_S	29
250, LDA, THF, -78 °C then (+)-menthyl (<i>R</i>)-toluene- <i>p</i> -sulfinate	247a	S_S	61
250, LDA, THF, -78 °C then (-)-menthyl (<i>S</i>)-toluene- <i>p</i> -sulfinate	247b	R_S	64

Table 5

The structure of the ligands was confirmed from the spectroscopic data. Importantly the integrity of the oxazoline ring was confirmed by IR spectroscopy which included the characteristic peak at 1650 cm⁻¹ due to the stretch of the C=N bond. Likewise the ¹³C-NMR spectrum included the quaternary carbon that is associated with the oxazoline ring. In addition comparison of the ¹³C-NMR spectroscopic data for the sulfides **242**, **243** and **244** with the analogous sulfoxides indicated the presence of the electron withdrawing sulfoxide moiety. The peaks had moved slightly downfield which would be consistent with the presence of the sulfoxide compared with the sulfide.

The relationship between the spectroscopic data of the synthesised sulfoxides and the oxidation products was apparent. The synthesised compounds showed only one set of signals whereas the oxidation products had shown a mixture of diastereomers. The configuration of the new compounds was known and allowed us to determine which diastereomers had been favoured in the oxidation process.

With diastereomerically pure ligands in hand we considered their application in the palladium catalysed allylic substitution reaction. Three ligands were chosen; the sulfide **242** and the corresponding sulfoxide ligands **245a** and **245b**. It had been demonstrated previously that the *iso*-propyl moiety provided for the highest levels of stereocontrol in this reaction.^{19,20,21} Hence the choice of these three ligands to be tested in the substitution reaction.

The reaction was run under similar conditions to those detailed previously in Section 3.2.2. The sulfide ligand **242** provided the substitution product **73** in 50% e.e. and reasonable yield. Analysis of the reactions including the sulfoxide ligands **245a** and **245b** showed that no substitution product was produced after several days reaction time. In our hands the ligands did not act as ligands for palladium and the substitution reaction did not proceed. The starting acetate **72** was recovered in effectively quantitative yield.

The poor result from the sulfoxide ligands may, in part, be due to the basicity of the sulfur atom. The sulfur atom in the sulfoxide moiety of **245** is less basic than the analogous atom in **242**. The electronegative oxygen atom affords the sulfur atom a relatively positive character compared to its lower oxidation state. Consequently the lone pair of electrons which were used to bind to the palladium atom are less available for co-ordination. The net result is that the sulfoxide ligands, in this case, are less effective ligands than their sulfide analogues.

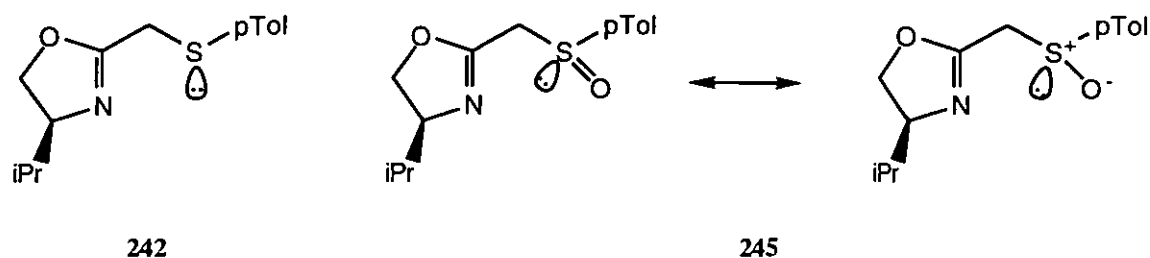


Figure 29

3.4 Conclusion

We have demonstrated that the enantiopure oxazoline moiety is able to influence the approach of an achiral oxidant to provide for a chiral sulfoxide moiety. This is an example of 1,5 and 1,6 asymmetric induction in the oxidation of sulfur. The level of stereocontrol in the oxidation step was generally low but under the right conditions stereoselectivity up to 92% d.e. was achieved.

We have synthesised a series of diastereomerically pure sulfoxide-oxazoline ligands in reasonable to good yield. These ligands have allowed us to determine the configuration of the oxidation products by comparison of the NMR data.

Chapter Four

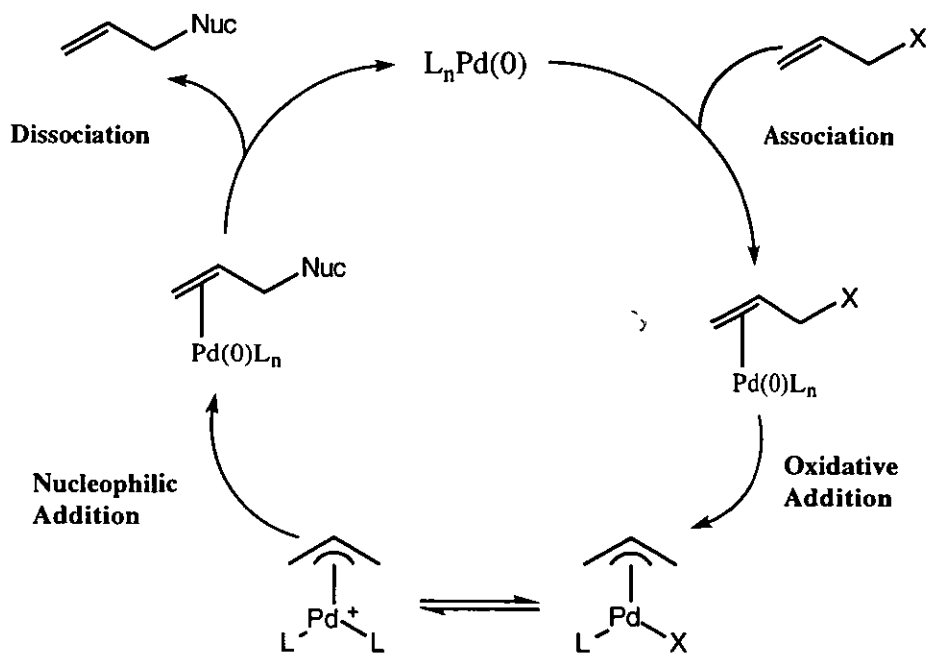
Analogues of Acetyl Acetate as Nucleophiles

4.1 Introduction

In recent years significant research efforts have been applied to the palladium catalysed allylic substitution reaction. Since Walker¹⁰² and Hata¹⁰³ demonstrated that the displacement of an allylic acetate by a variety of nucleophiles required only catalytic quantities of palladium, the palladium catalysed allylic substitution reaction has developed rapidly into a well defined and efficient process.

4.1.1 Important Aspects of the Reaction Mechanism

A lot of attention has been paid to refining the allylic substitution reaction as a regio- and stereoselective C-C bond forming process. Central to this work has been an understanding of the mechanism of the reaction. It is generally accepted that the reaction proceeds with initial co-ordination of palladium (0) to the alkene followed by an oxidative addition process to afford an intermediate η^3 -allyl complex. In the presence of π -accepting ligands such as triphenylphosphine an equilibrium between a neutral and cationic complex results. Bidentate ligands promote the formation of the cationic species. The cationic complex preferentially undergoes nucleophilic addition to afford the palladium (0) complex of the product. Dissociation of the palladium (0) liberates the product and regenerates the active palladium catalyst.¹⁰⁴



Scheme 84

The geometry of the η^3 -allyl intermediate tends to be determined by steric factors. Not surprisingly the complex adopts the least sterically demanding conformation. For a mono-substituted complex the *syn* conformation **251** is favoured to the *anti* arrangement **252**. Likewise a disubstituted complex prefers the *syn,syn* conformation **253** to the sterically demanding *anti,anti* conformation **254**. More highly substituted allyl complexes similarly prefer the least sterically demanding conformation available.¹⁰⁵

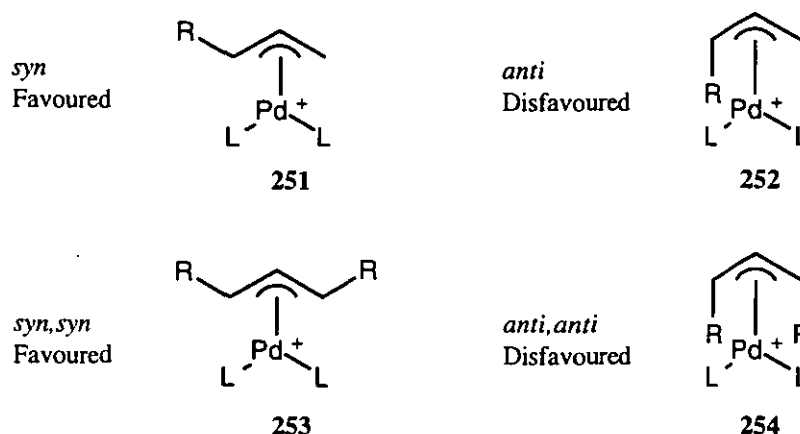
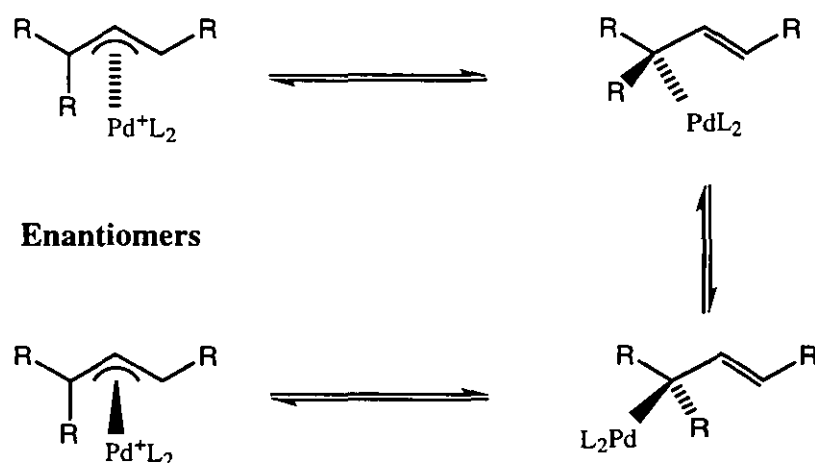


Figure 30

The isomerisation of η^3 -allyl complexes is well known. The complex is believed to change between isomeric forms by a π - σ - π mechanism. The complex exists as an equilibrium of enantiomeric forms, the result of which is the loss of any stereochemistry derived from the allyl precursor. Consequently the stereochemistry of the product is determined by the palladium complex intermediate.

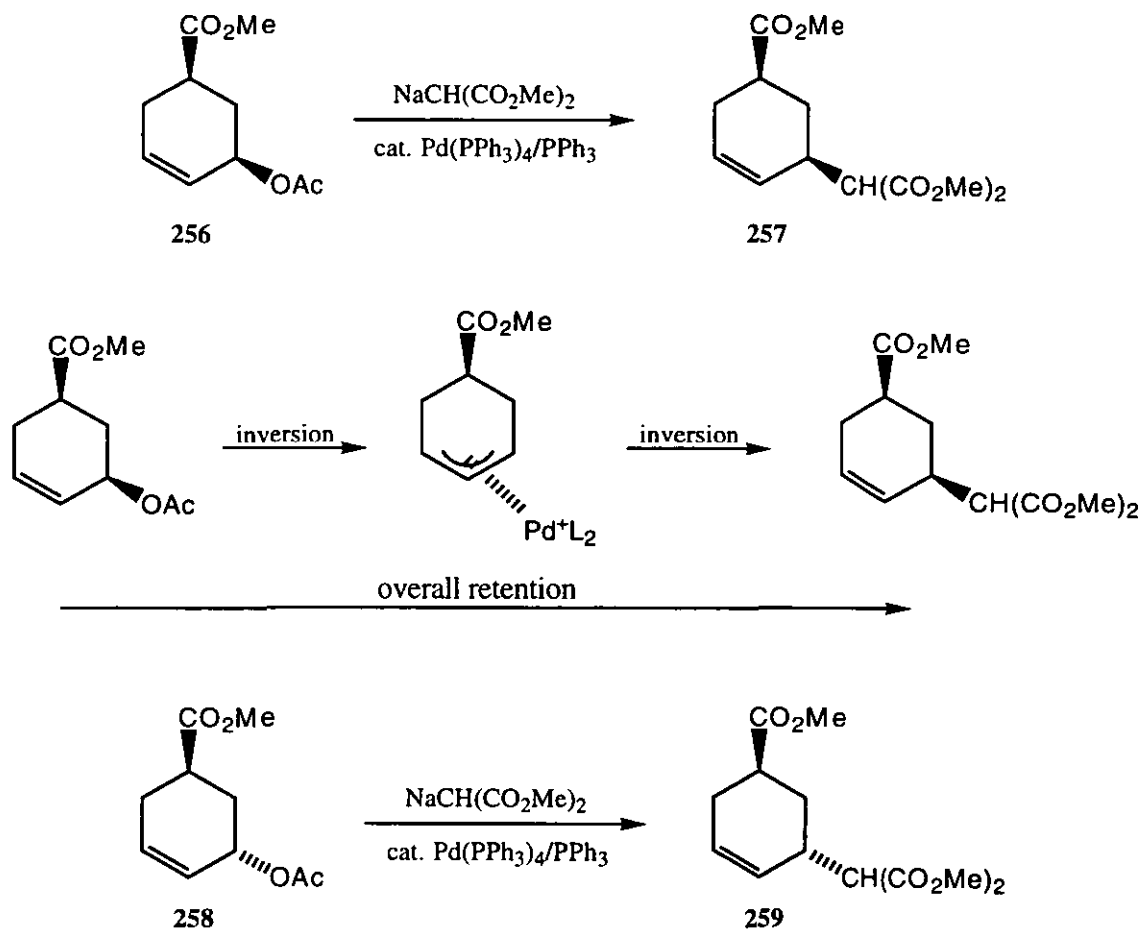


Scheme 85

In the absence of the isomerisation process the overall stereochemistry of the reaction will be determined by the individual steps of the reaction mechanism.¹⁰⁶ The two most significant stages are the initial formation of the π -allyl complex between the substrate and palladium catalyst and the subsequent displacement of the palladium by a nucleophile to give the product.

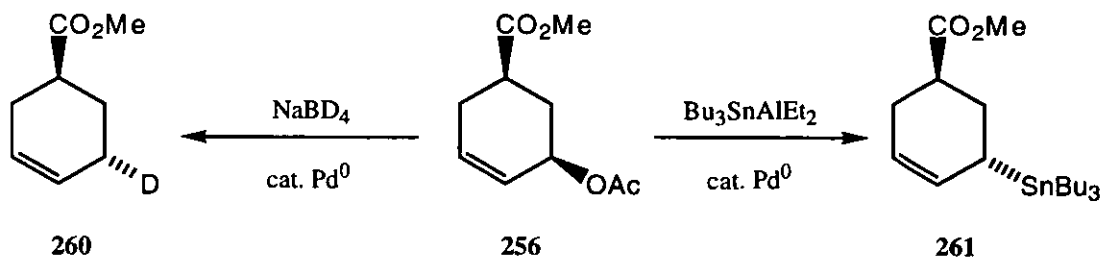
Studies by Trost and other researchers have shown that nucleophiles may react by either of two mechanisms.¹⁰⁷ The choice of mechanism ultimately determines the stereochemistry of the product. Nucleophiles with a $\text{pK}_\text{a} > 20$ have been found to attack at palladium followed by a rearrangement to give the product, whereas nucleophiles with a $\text{pK}_\text{a} < 20$ attack the allyl unit directly.¹⁰⁸

Trost and co-workers considered the attack of soft nucleophiles on cyclohexenyl acetates.^{107a} They found that the reaction of the *cis* compound **256** gave the *cis* substituted product **257** whilst the *trans* substituted compound **258** gave the *trans* substituted product **259**. The researchers proposed that the reaction proceeded through two consecutive inversion steps. Initially the palladium displaces the leaving group and forms the π -allyl complex with inversion of stereochemistry. Secondly the nucleophile attacks the *exo* face of the intermediate with inversion realising overall retention in the product.



Scheme 86

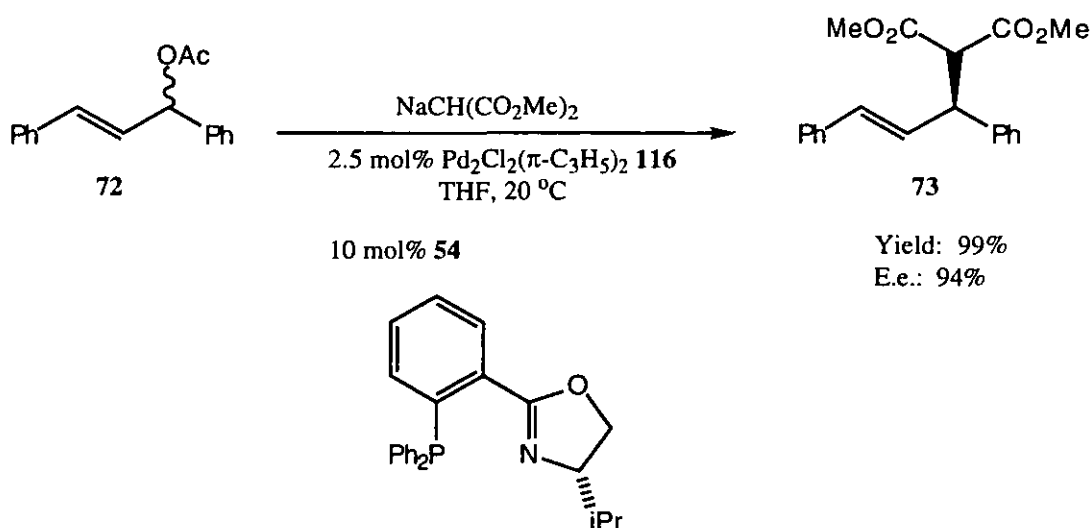
It is believed that hard nucleophiles initially attack the palladium centre and then migrate to the allyl moiety. The net result is an inversion of stereochemistry because the nucleophile attacks the allyl moiety from the same face as the palladium and hence the first inversion step determines the stereochemistry of the product. Trost demonstrated that the use of $\text{Bu}_3\text{SnAlEt}_2$ as a nucleophile provided for the allylstannane **261** with inversion.^{107b} Likewise Greenspoon and Keinan showed that reduction of the same system **256** with sodium borodeuteride afforded **260** with an inversion of stereochemistry.¹⁰⁹



Scheme 87

4.1.2 Stereocontrol and Phosphine-Oxazoline Ligands

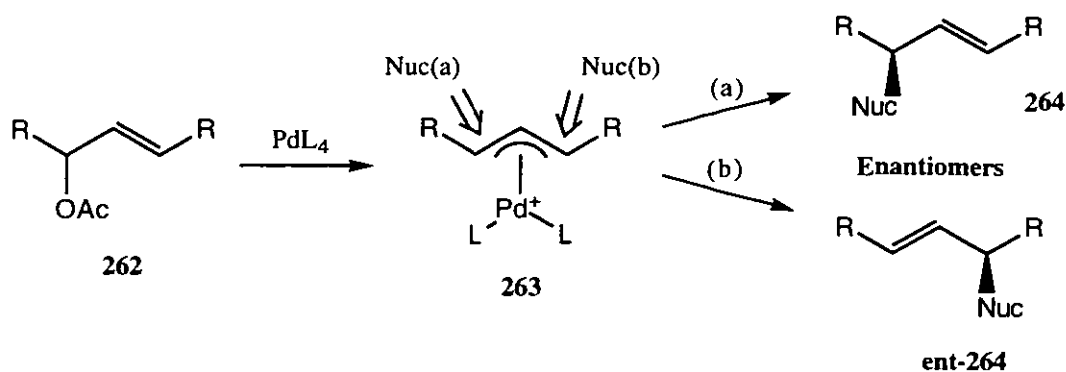
Enantiomerically pure ligands that include the 2-oxazoline moiety have been shown to be very effective relays of stereochemical information by several research groups. Notably the use of phosphine-oxazoline ligands for the palladium catalysed allylic substitution reaction has been particularly successful.^{19,20,21} The ligands consistently provide for very high chemical yields and excellent levels of stereocontrol.



Scheme 88

The high levels of stereocontrol are achieved by directly influencing the reactive intermediate. Through a combination of steric factors and electronic characteristics the ligand is able to promote the preferential formation of one enantiomer.

The η^3 -allyl intermediate of **263** is symmetrical. The nucleophile may attack either terminus resulting in the formation of the enantiomers **264** or **ent-264**. Consequently control of the reaction at this point would provide for the desired stereocontrol.



Scheme 89

It has been shown by Akermack and Vitagliano that bidentate nitrogen-phosphorus ligands perturb the electronic characteristics of a palladium allyl intermediate.¹¹⁰ Analysis of the ^{13}C -NMR data showed that when C_3 is *trans* to the ligating phosphorus atom its signal is found significantly downfield of the signal for C_1 . This suggests that C_3 has a more electropositive character than C_1 in complex 265. Consequently the allyl carbon *trans* to the π -accepting phosphorus atom is more electrophilic and hence more attractive to an incoming nucleophile. It is suggested that oxazoline-phosphine ligands are able to behave in a similar manner, encouraging nucleophilic attack *trans* to the phosphorus atom.

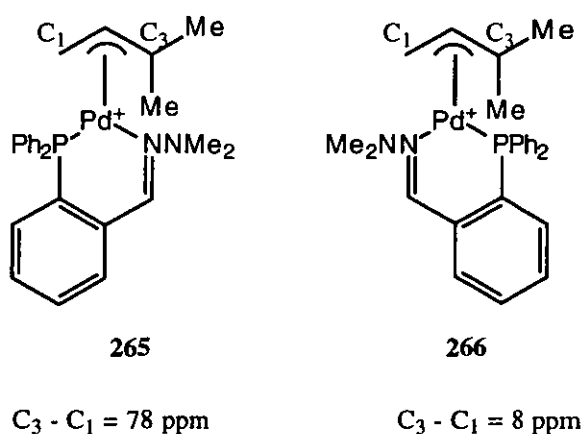
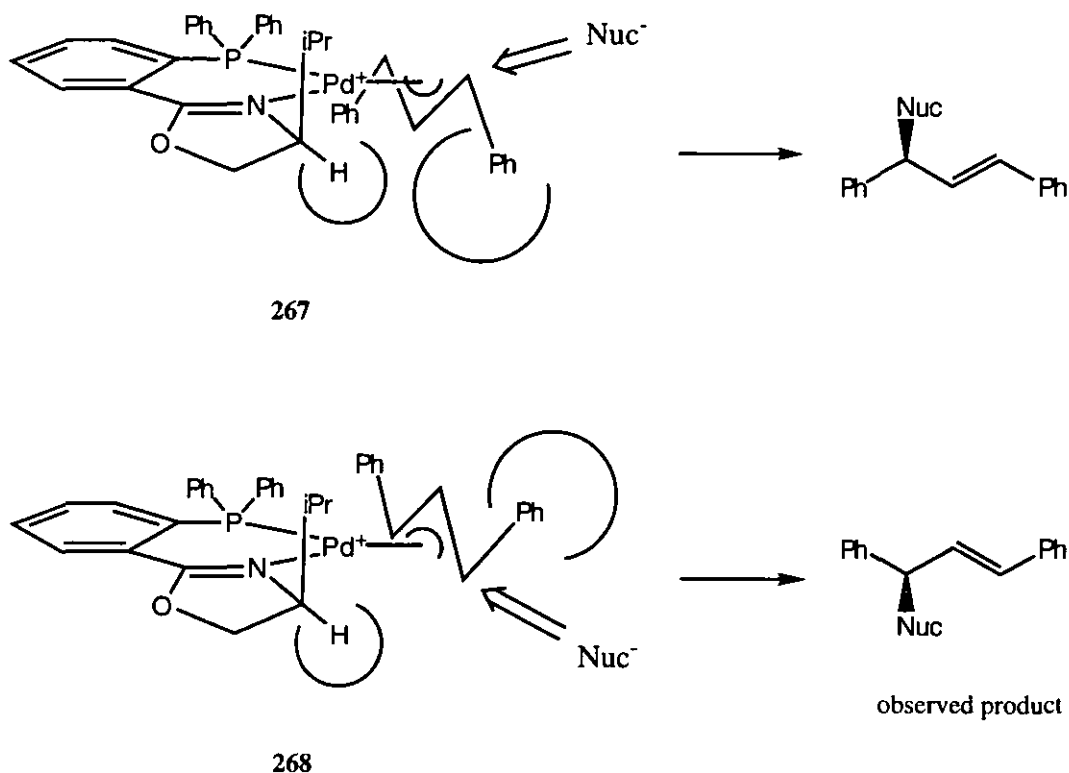


Figure 31

In addition to encouraging enantioselectivity through electronic factors the ligands also affect the reaction intermediates through steric hindrance. It can be envisaged that the palladium-allyl complex may adopt either of two conformations 267 and 268 and equilibrate between

these. The attack of either diastereomeric complex will lead to a different enantiomer in the product.



Scheme 90

Helmchen and co-workers have determined through x-ray crystallographic data and NMR studies that the preferred conformation is **268**, where the allyl moiety is considered to be in a W-shaped "up" arrangement.¹¹¹ The data shows that the *iso*-propyl group is pseudo-axial and in fact it is the hydrogen atom which interacts with the allyl moiety. To relieve the steric interactions the allyl moiety adopts the W-arrangement in preference to the "down" M-conformation. The nucleophile then attacks complex **268** *trans* to the phosphorus atom and proceeds to provide for the observed enantiomer in the product.

4.1.3 Nucleophiles and Substrates

A variety of allylic compounds has been shown to be good substrates for palladium catalysed substitution reactions.¹⁰⁵ The allylic acetates remain the most popular substrates but

halides,¹¹² alcohols,¹¹² phosphonates,¹¹³ sulfones,¹¹⁴ amines¹⁰² and epoxides¹¹⁵ have also been investigated.

Likewise a variety of nucleophiles has been applied to the reaction but stabilised soft carbanions are the most common. Nonetheless several heteroatom based nucleophiles including nitrogen,¹¹⁶ sulfur,¹¹⁷ oxygen,¹¹⁸ phosphorus,¹¹⁹ silicon,¹²⁰ boron¹²¹ and some organometallics¹²² function well as nucleophiles in this reaction.

The range of carbanion nucleophiles is extensive, essentially the only criterion required is that the conjugate acid of the anion has a pKa between 10 and 20. A whole series of functionality known to stabilise adjacent carbanions has been used in suitable nucleophiles including esters, ketones, sulfides, sulfoxides, sulfones, nitro and cyano groups.¹⁰⁵

4.2 *Palladium Catalysed Nucleophilic Substitution Reaction*

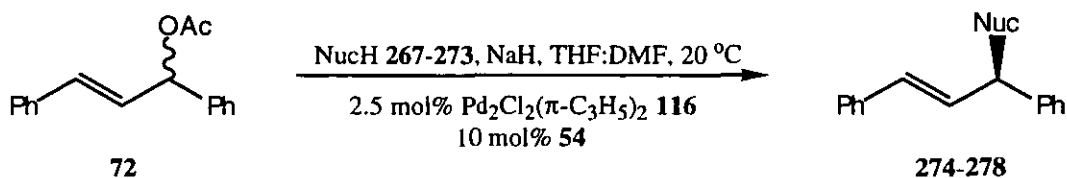
We were interested in using the palladium catalysed allylic substitution reaction as the first step in the synthesis of simple natural products. To this end we selected a few simple nucleophiles **269-273** and considered their application in the reaction.

The nucleophiles were chosen because they were all commercially available, they all had pKa's between 10 and 20 and they included a variety of functionality.¹⁰⁵ Initially we wished to introduce a range of functional groups and then consider which compounds would allow us to access simple natural products. Two factors were of particular importance, firstly the efficiency of the nucleophilic substitution reaction and secondly the level of stereocontrol that was possible.

4.2.1 *Results of the Nucleophilic Substitution Reactions*

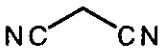
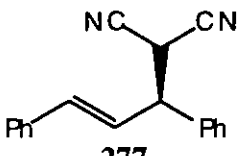
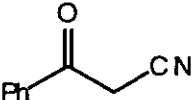
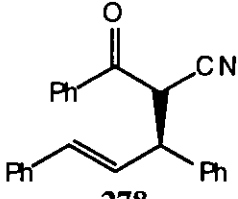
The procedure for a palladium catalysed allylic substitution reaction is reasonably straightforward. The sodium salt of the nucleophile, as a solution in an appropriate solvent,

is added to a stirring solution of palladium, ligand and allylic acetate. The solvent of choice is generally anhydrous THF and the reaction is found to proceed more quickly at high concentrations. We found that the sodium salts of our nucleophiles were not soluble in small volumes of THF. It was necessary to add a quantity of DMF to ensure complete solubility of the nucleophile and allow the reaction to proceed. Once the optimum reaction conditions had been established the reactions ran smoothly and consistently to give the desired products in good yield.



Scheme 91

NucH	pK _a ^a	Product	Yield (%)	E.e (%)	D.e.(%) ^c
<p>269</p>	14.2	<p>274</p>	>95	>98 ^b	8
<p>270</p>	12.5	<p>275</p>	76	96 ^b	27
<p>271</p>	13.1	<p>276</p>	73	92 ^d	10

 272	11.1	 277	93	86 ^e	n.a.
 273	10.2	 278	91	n.d. ^f	33

(a) see ref. 137. (b) Enantiomeric excess was determined by chiral shift $^1\text{H-NMR}$ using $\text{Eu}(\text{hfc})_3$. (c) Diastereomeric excesses were determined by inspection of the $^1\text{H-NMR}$. (d) Enantiomeric excess was determined by chiral HPLC: Chiralcel AD, 5% IPA:95% Hexane, 0.7 mL/min, 254 nm. (e) Enantiomeric excess was determined by chiral HPLC: Chiralcel OD-H, 20% IPA:80% Hexane, 1 mL/min, 254 nm. (f) No satisfactory method was found for determining the enantiomeric excess.

Table 6

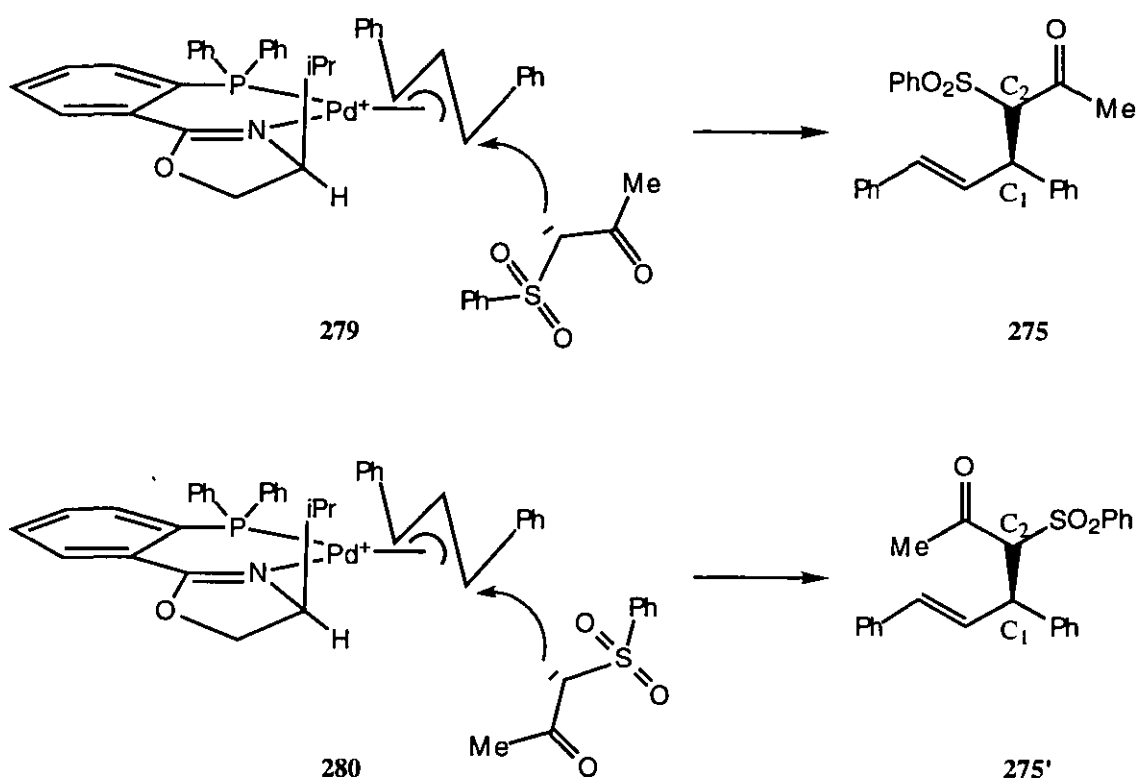
The products **274-278** all provided satisfactory spectroscopic and analytical data. The levels of stereocontrol were readily determined by $^1\text{H-NMR}$ or chiral HPLC. In the cases of **274** and **275** chiral shift $^1\text{H-NMR}$ showed enantiomeric excesses of >98% and 96% respectively. Likewise analysis of **276** and **277** by chiral HPLC determined the enantiomeric excesses to be 92% and 86% respectively. Both methods confirmed the measured diastereomeric excesses which had been determined by inspection of the $^1\text{H-NMR}$. In the case of **278** it was possible to measure the diastereomeric excess by inspection of the $^1\text{H-NMR}$ but no satisfactory method was found to determine the enantiomeric excess.

4.2.2 Source of Enantioselectivity and Diastereoselectivity

The levels of enantioselectivity achieved were high and in the case of **274** only one enantiomer was visible by chiral shift $^1\text{H-NMR}$. We believe the mechanism of the reaction to be consistent with that discussed previously and hence the enantioselectivity is the result of the chiral ligand influencing the intermediate step of the reaction. It is of interest to

consider the source of any diastereocontrol and the differences in enantioselectivity of the reaction as related to the nucleophile.

If we consider **275** which is isolated in good yield with 96% e.e. and 27% d.e. It is proposed that the excellent stereocontrol at C₁ is the result of the nucleophile predominantly attacking the "up" W-form of the π -allyl intermediate **268**. It is suggested that the stereocontrol at C₂ is the result of the orientation of the nucleophile relative to the π -allyl intermediate at the time of the formation of the bond between C₁ and C₂. It is believed that the chiral ligand **54** has no direct influence on the stereocontrol at C₂. Any diastereocontrol is the result of a kinetic preference for the reaction to proceed through one intermediate, either **279** or **280**.



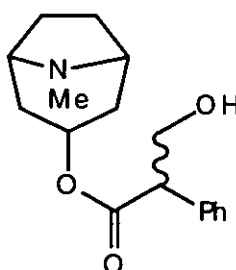
Scheme 92

It can be seen from **Table 6** that there may be some correlation between the nucleophile and the level of enantioselectivity. It is possible that two factors are causing the differences in selectivity. The pK_a of the nucleophile and the size of the nucleophile. It is not clear which factor is the dominant one. The level of enantioselectivity may be seen to decrease as the pK_a of the the nucleophile decreases. It may be that a reactive nucleophile facilitates high

levels of stereoselectivity. The trend is complicated when considering products **270** and **271**. Clearly pKa is not the only factor at work here. It is proposed that the size of the nucleophile also influences the level of enantioselectivity achieved. The interplay of several factors directly affects the final enantioselectivity of the reaction making prediction of the results difficult.

4.3 Approaches to Atropine

With the above results in hand we considered the synthesis of atropine **281**. Atropine is a naturally occurring compound that has been found to have useful pharmacological properties.¹²⁴ Pharmaceutical preparations of atropine are used to produce relaxation in the muscle wall of the intestine and relieve abdominal cramps, to dilate the pupil of the eye during optical examinations and as a bronchodilator for the relief of asthma attacks.



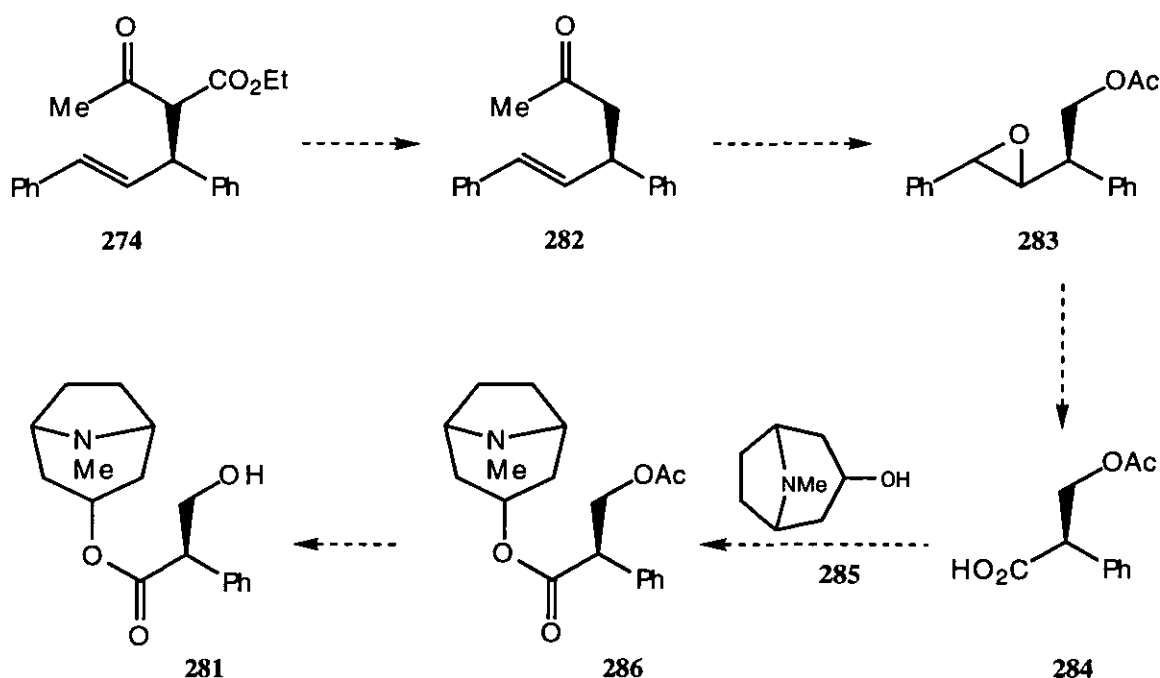
281

Figure 32

Atropine's marked physiological properties are believed to be predominantly due to (-)-atropine, although facile racemisation leads to an erosion of activity.¹²⁵ We were interested in developing a short synthesis of enantiomerically enriched atropine based on the methodology described above.

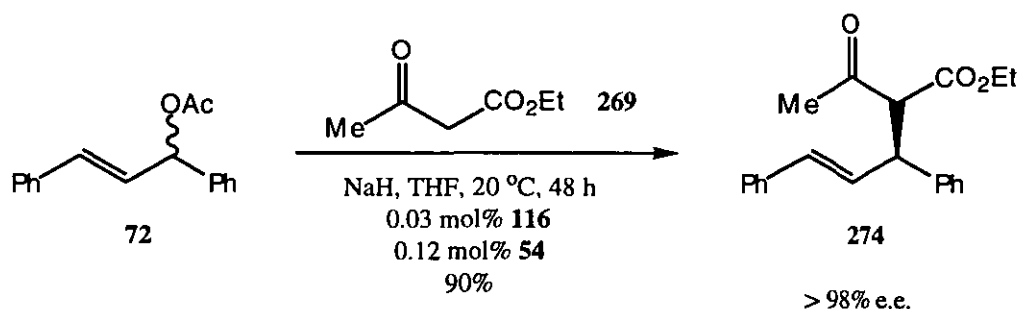
The proposed route is illustrated below. The starting point would be **274** which is available in good yield essentially as one enantiomer. Decarboxylation of **274** would provide for **282** followed by Baeyer-Villiger oxidation and concurrent epoxidation to yield **283**. Oxidative cleavage of the epoxide **283** would lead to the acid **284**. Coupling of the acid **284** with

commercially available tropine **285** would lead to **286** and subsequent deprotection of the ester would provide for atropine **281**.



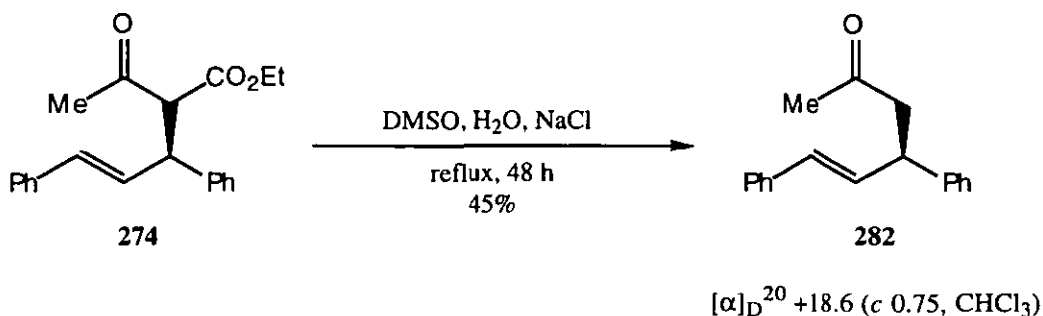
Scheme 93

It was considered important to be able to isolate **274** on a multi-gram scale without any loss of any stereo integrity. It was established that the complex formed from 5.5 mg of allyl palladium chloride dimer **116** and 23 mg of ligand **54** was able to catalyse the conversion of 9 g of racemic acetate **72** to 9 g of essentially enantiomerically pure **274**. It was not possible to visualise the minor enantiomer by chiral shift $^1\text{H-NMR}$. The efficiency of the first step is demonstrated by considering that the molar ratio of palladium atoms to acetate molecules is 1:1200. The only disadvantage was that the reaction was slower, taking 48 h to reach completion, as determined by tlc analysis.



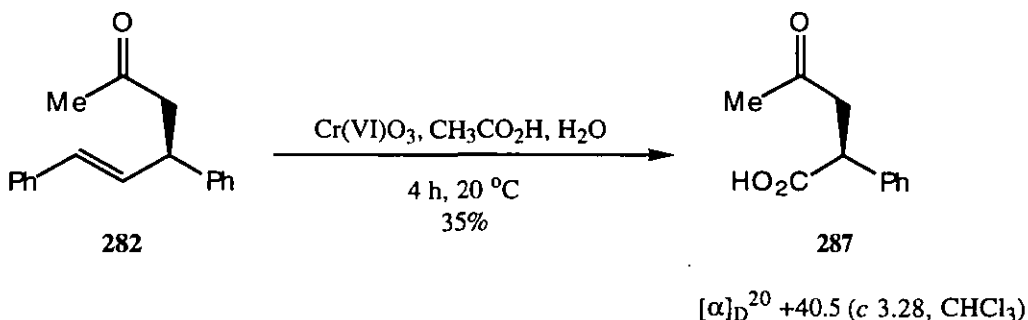
Scheme 94

The substitution product **274** was readily decarboxylated using a procedure published by Krapcho and co-workers.¹²⁶ The ketone **282** was isolated in reasonable yield after 48 h. The loss of the ester moiety was confirmed by ¹H-NMR which included a new signal at 2.95 ppm which was assigned to the methylene protons adjacent to the carbonyl moiety.



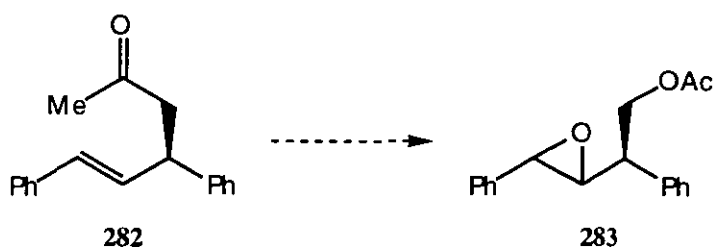
Scheme 95

At this point cleavage of the double bond was achieved using an aqueous solution of chromic acid to furnish us with the carboxylic acid **287** in a low yield.¹²⁷



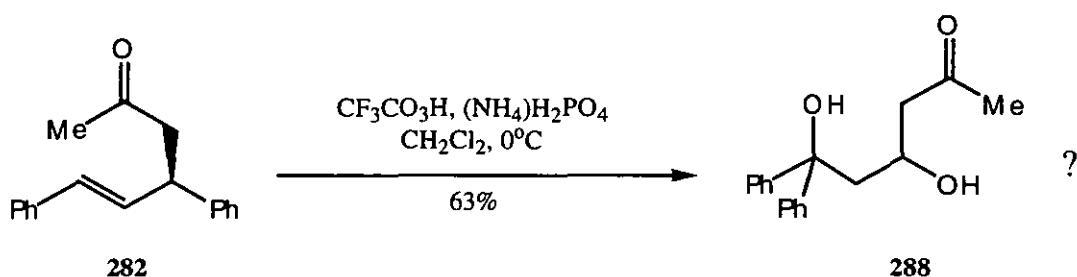
Scheme 96

The Baeyer-Villiger oxidation of **282** did not proceed as anticipated.¹²⁸ Many oxidation conditions were applied to the system to no avail. The oxidants included bis(trimethylsilyl) peroxide,¹²⁹ hydrogen peroxide in a basic solution,¹³⁰ urea-hydrogen peroxide,¹³¹ tetra-*n*-butyl ammonium oxone¹³² and pertrifluoroacetic acid.¹³³



Scheme 97

The only isolable product was obtained from the oxidation of **282** with pertrifluoroacetic acid. The product was isolated as a pale yellow oil in 63%, initial analysis showed that the product was not **283** but it wasn't recovered starting material either! It is suggested that the product may be **288**.



Scheme 98

The IR spectra included signals due to O-H and C=O stretching indicating that the Baeyer-Villiger rearrangement had not occurred but the starting material had been oxidised. This was confirmed by the ^1H -NMR which included a singlet at 2.15 ppm due to the methyl ketone. A methyl ester would be expected to generate a signal further downfield at approximately 3.5 ppm.

The ^{13}C -NMR suggested that the basic carbon framework had not changed but in association with the ^1H -NMR it was apparent that the substitution pattern was different. The connectivity of the molecule was unclear from either spectrum alone. Correlation spectra, ^1H - ^1H and ^1H - ^{13}C , provided more detailed information about the structure. Important points included; the phenyl groups were present, as was some new functionality - probably an alcohol. The ketone moiety was unchanged but the molecule now contained a quaternary

alkyl carbon and significantly no C=C bond. Interestingly there was also a short chain, XCH_2CHYCH_2Z , that showed complex coupling patterns in the 1H -NMR. The identity of X, Y and Z were important to elucidating the structure.

Probable components...2 x Ph, n x OH, no C=C plus

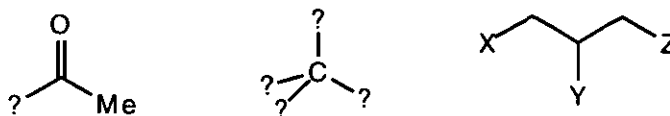


Figure 33

After some consideration the structure of **288** was proposed. The structure and spectroscopic data were in agreement with no anomalous signals. Furthermore analysis of the mass spectrum showed a peak at 284 units that would equate with $M+NH_4^+-H_2O$. It would be reasonable to expect a tertiary alcohol such as **288** to generate this ionised fragment. The 1H and ^{13}C -NMR data are presented below.

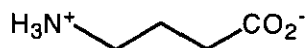
The 1H -NMR data: δ_H (250 MHz; $CDCl_3$) 7.43-7.21 (10H, m, Ar-H), 3.30 (1H, d, J 16.7, CHH'), 3.22-3.15 (2H, m, CHOH and C(O)CHH'), 3.08 (1H, d, J 16.7, CHH'), 2.90 (1H, dd, J 14.6 and 6.9, C(O)CHH') and 2.15 (3H, s, CH_3CO).

The ^{13}C -NMR data: δ_C (100.6 MHz; $CDCl_3$) 205.6 (\underline{CO}), 140.3, 137.4, 137.3, 128.8, 128.5, 127.9, 126.9, 126.7, 126.5 and 125.4 (arom. \underline{C}), 66.7 (\underline{CHOH}), 60.8 ($Ph_2\underline{COH}$), 47.3 ($\underline{CH_2OH}$), 35.6 ($\underline{CH_2CO}$) and 30.8 ($\underline{CH_3}$).

With the failure of this important transformation our initial route to atropine appeared to be at an end. Efforts were made to continue, using other nucleophiles at the beginning of the sequence to no avail. We could not establish a viable method to introduce the ester moiety and the synthesis was brought to a close.

4.4 γ -Amino Butyric Acid

4-Aminobutanoic acid (GABA) **289** is an important inhibitory neurotransmitter with several roles in the mammalian central nervous system.¹³⁴ Virtually all central neurones appear to be under the inhibitory control of GABA and a significant proportion utilise GABA as a neurotransmitter. GABA is involved in the control of hormone secretion,¹³⁵ cardiovascular function¹³⁶ and the synaptic mechanisms associated with anxiety¹³⁷ and aggressive behaviour.¹³⁸



289

Figure 34

Significantly GABA has been implicated in several neurological and neuropsychiatric disorders. These include epilepsy,¹³⁹ schizophrenia,¹⁴⁰ depression¹⁴¹ and Parkinson's disease to name a few.¹⁴² Consequently a lot of attention has been paid to the application of GABA analogues as clinically useful drugs.

GABA has been demonstrated to be a specific ligand for at least four different types of receptor and transport proteins.¹⁴³ Analogues of GABA have exhibited selectivity towards these proteins suggesting that the conformation of GABA is important when considering its activity. GABA receptors are classed as either GABA_A or GABA_B depending on their relative sensitivity to bicuculline **290**. GABA_A proteins are sensitive to the drug whereas GABA_B proteins are not. It has also been suggested that there is a third class, GABA_C, which has yet to be confirmed. Distinction between GABA carrier proteins has yet to be established.

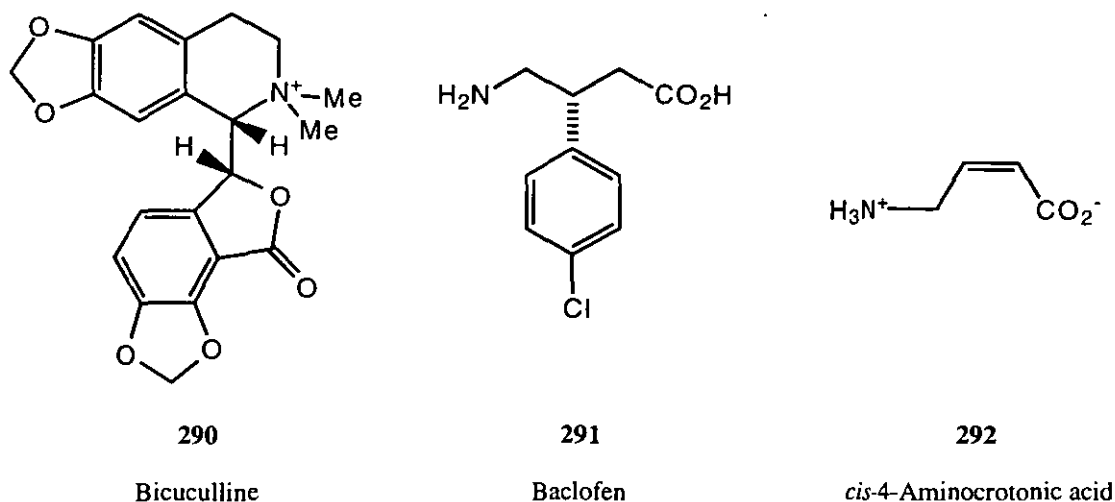
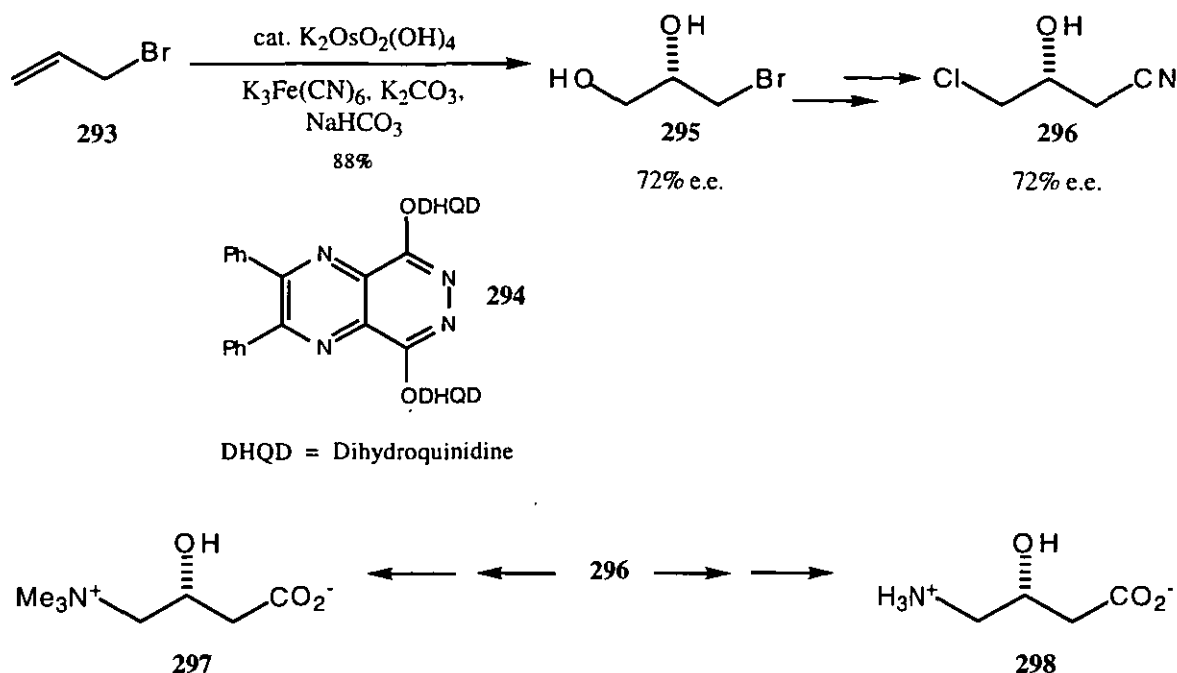


Figure 35

GABA_A is sensitive to **290** but GABA_B is not, a specific agonist for GABA_B is **291**. GABA_C is insensitive to both **290** and **291** but activated by **292**. This evidence demonstrates that drug action may be targeted at the appropriate protein by changing the conformation of the drug.

4.4.1 Enantiomerically Enriched Analogues of GABA

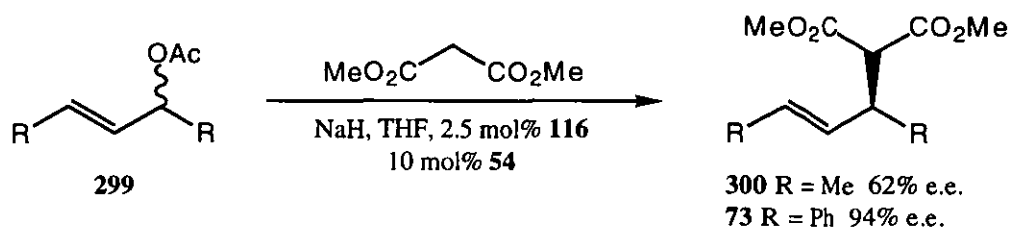
It became apparent to us that we could access novel analogues of GABA through the technology described previously. In addition we could confidently introduce a stereocentre adjacent to the carboxylic acid moiety. A short and efficient synthesis of enantiomerically enriched analogues of GABA could be of interest to the pharmaceutical industry. For instance, Sharpless and co-workers utilised their dihydroxylation technology in the synthesis of (*R*)-(-)-Carnitine **297** and (*R*)-(-)- γ -amino- β -hydroxybutyric acid (GABOB) **298**.¹⁴⁴ These two compounds have received a lot of attention for their pharmacological properties and a number of methods have been developed for their synthesis. Sharpless demonstrated that a catalytic asymmetric reaction could be used to generate an enantiomerically enriched intermediate **296**. Making the overall synthesis more efficient and suitable for further scale-up.



Scheme 99

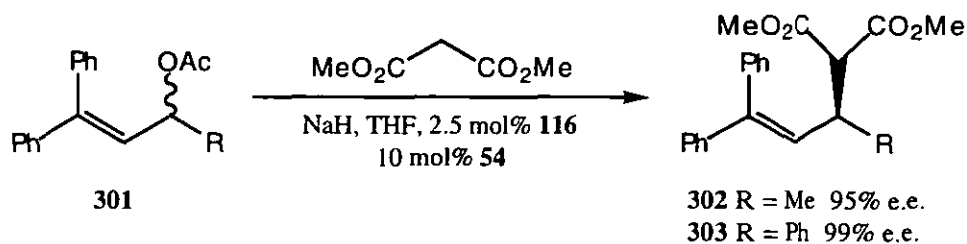
4.4.2 Nucleophilic Substitution Reactions

The major drawback of the allylic substitution reaction illustrated previously is that the level of stereocontrol is directly influenced by the terminal groups. If the groups are not bulky then the enantioselectivity falls away quickly. The example below illustrates this point. When the terminal groups are phenyl **73** then a good level of enantioselectivity is observed. When the terminal groups are methyl **300** then the stereoselectivity drops to 62% e.e.



Scheme 100

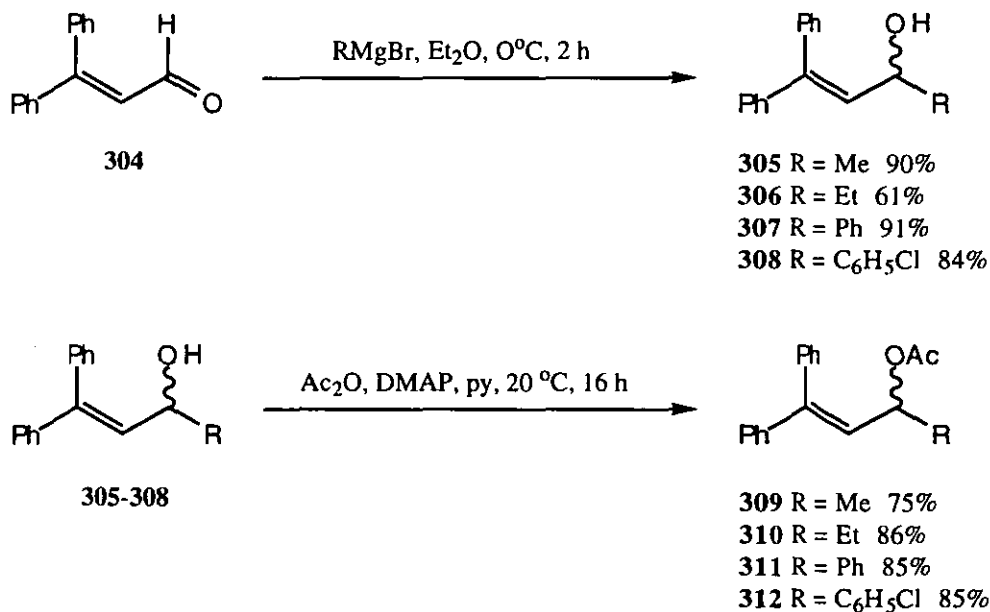
This problem has been addressed by developing the asymmetric allyl acetate **301** as a substrate for the palladium catalysed allylic substitution reaction. In this case the nature of R does not adversely affect the enantioselectivity.^{32a} Whether R equals methyl **302** or phenyl **303** the substitution product is consistently isolated in excellent enantiomeric excess.



Scheme 101

The flexibility in the synthesis of **301** results in a greater range of substrates and hence potentially more enantiomerically enriched products from a simple starting point. We chose to develop methyl cyanoacetate **271** as a nucleophile for this system. Elaboration of the substitution products would allow us to access substituted analogues of GABA.

Preparation of the allylic acetates was straightforward. Addition of the appropriate Grignard reagent to β -phenylcinnamaldehyde furnished us with the alcohols **305-308** in good yield. Examination of the ^1H -NMR spectrum confirmed the reduction of the aldehyde and the successful addition of the Grignard reagent. The alcohols were smoothly acylated with acetic anhydride to provide the allylic acetates in good yield. The ^1H -NMR showed a singlet at 2.0 ppm which was assigned to the methyl group, indicating the formation of the allylic acetate.

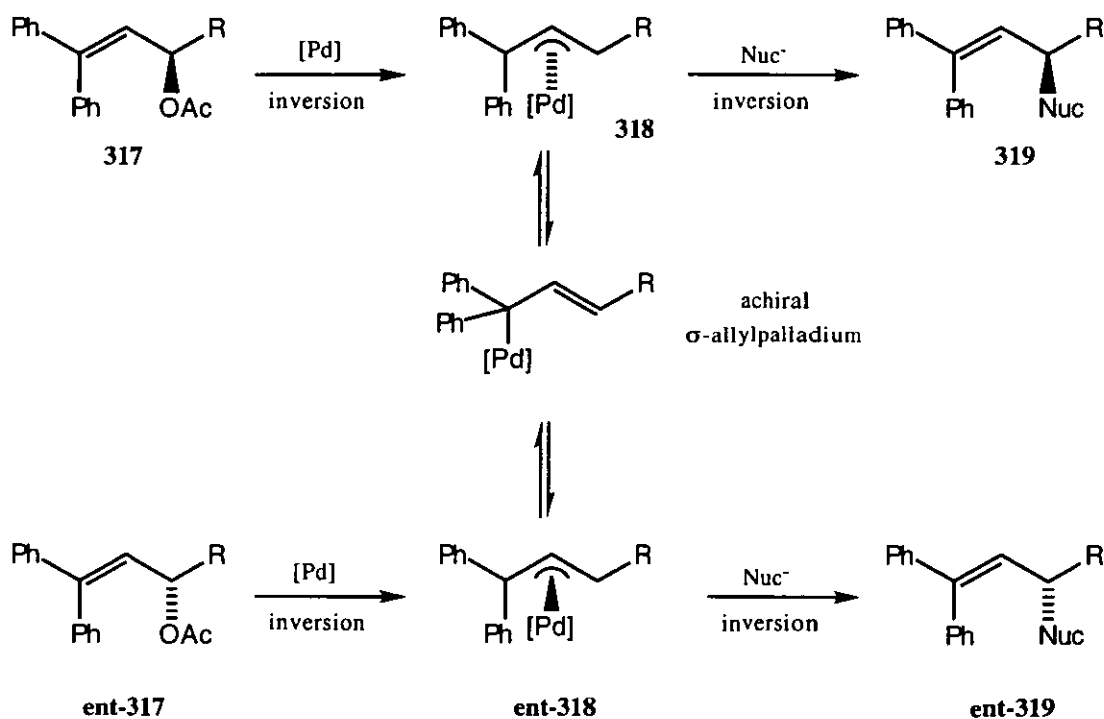


Scheme 102

4.4.3 Source of Stereocontrol

The stereoselectivity of the reaction is achieved in a similar fashion to the mechanism described above. It is maintained that the diastereoselectivity is not determined by the chiral ligand but is just the result of the orientation of the approaching nucleophile relative to the π -allyl complex. The source of enantioselectivity requires a little more consideration.

The allyl acetate does not proceed through a symmetrical intermediate as proposed earlier. In this case the π -allyl intermediates are derived from different enantiomers of starting material, consequently **318** and **ent-318** are diastereomeric when an enantiomerically pure ligand is used. However the π - σ - π mechanism allows for rapid equilibration between the two isomers.



Scheme 104

It seems reasonable that the chiral ligand encourages reaction through a preferred intermediate in a similar manner as the symmetrical intermediates **267** and **268**. A further complication arises when you consider that the allyl intermediate may orientate itself either *cis* or *trans* to the ligating phosphorus atom. Attack of the nucleophile on either **320** or **321** would result in the observed enantiomer in the product. It is suggested that the reaction proceeds through complex **321** where attack occurs *trans* to the phosphorus atom. This

would obviously require considerable steric crowding between the diphenylphosphine moiety and the diphenyl terminus of the substrate. This unfavourable congestion may explain the slower rate of addition to the unsymmetrical acetates.

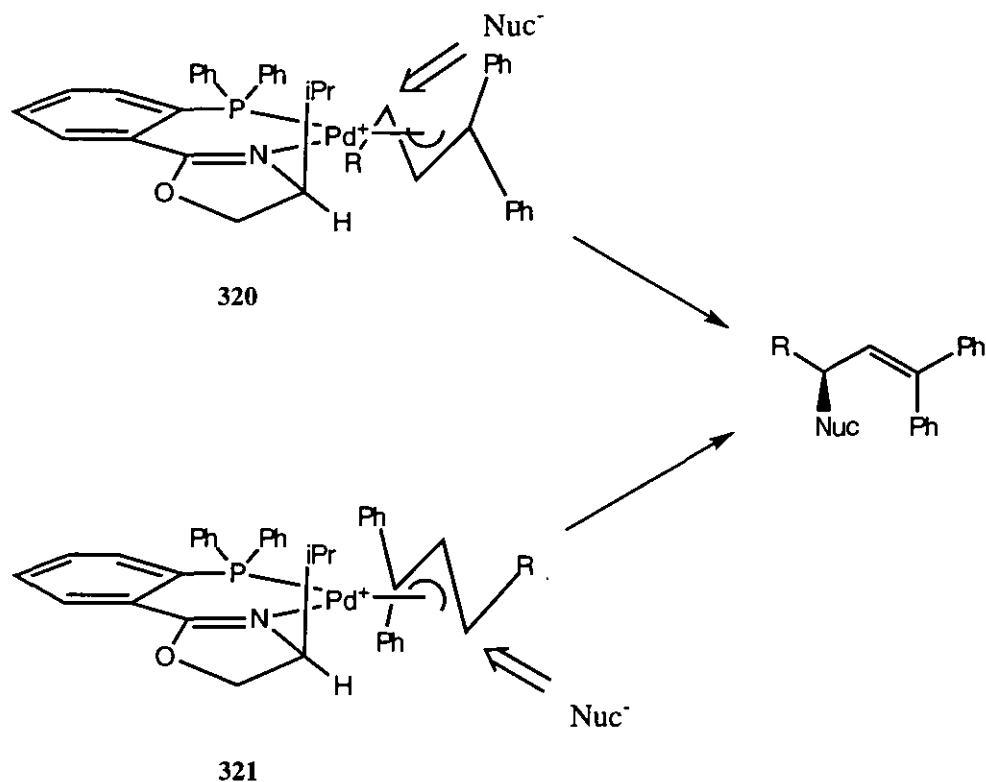
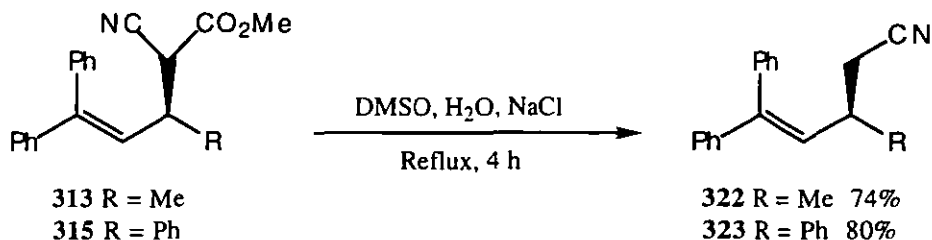


Figure 36

4.4.4 Synthesis of Substituted Analogues of GABA

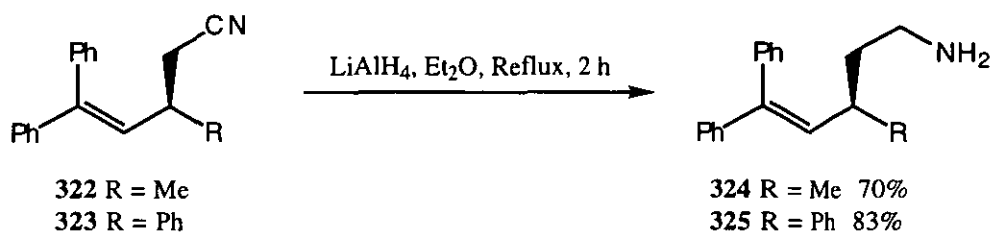
With the substitution products in hand we proceeded to synthesise the desired GABA analogues. We chose **313** to be carried through because the amino acid **331** is a known compound.¹⁴⁵ Also we found the synthesis of **315** on a multi-gram scale to be straightforward.

The first step was to remove the ester moiety by Krapcho decarboxylation.¹²⁶ The compounds were heated at reflux in "wet" DMSO until analysis by tlc showed complete conversion of the starting material to product. The decarboxylated products **322** and **323** were isolated in 74% and 80% respectively. The IR spectra of both compounds confirmed the absence of the ester moiety and its characteristic peak.



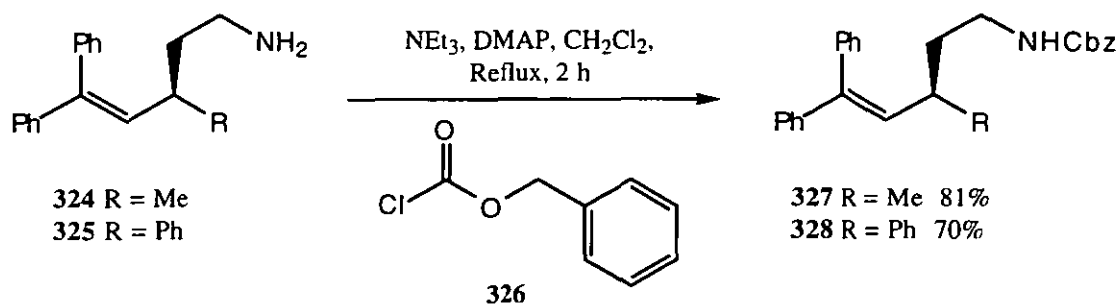
Scheme 105

The next step was to reduce the nitrile functionality to an amino group. This transformation was smoothly achieved in good yield using lithium aluminium hydride as the reducing agent. The ¹³C-NMR of **324** no longer included the quaternary carbon of the nitrile group which had been found at 118 ppm in the ¹³C-NMR spectra of **322**. Likewise the ¹H-NMR of **325** now included a broad singlet at 8.19 ppm which was assigned to the amine protons.



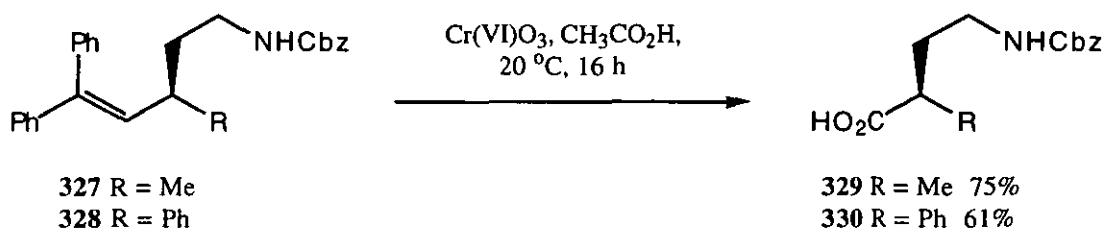
Scheme 106

It was now considered prudent to protect the amine functionality. We were concerned that without protection we would not be able to isolate our product from the acidic conditions used to cleave the C=C bond and form the carboxylic acid terminus. We elected to use benzyl chloroformate to protect the amine, anticipating facile cleavage of the carbamate and removal of the protecting group. The protection step was readily achieved and the desired products were quickly available in good yield. The ¹H-NMR of both products included the characteristic singlet at 5.0 ppm associated with the benzylic protons of the Cbz protecting group. In addition the IR spectra of both compounds included a peak due to the C=O bond in the carbonyl stretch region of the spectra.



Scheme 107

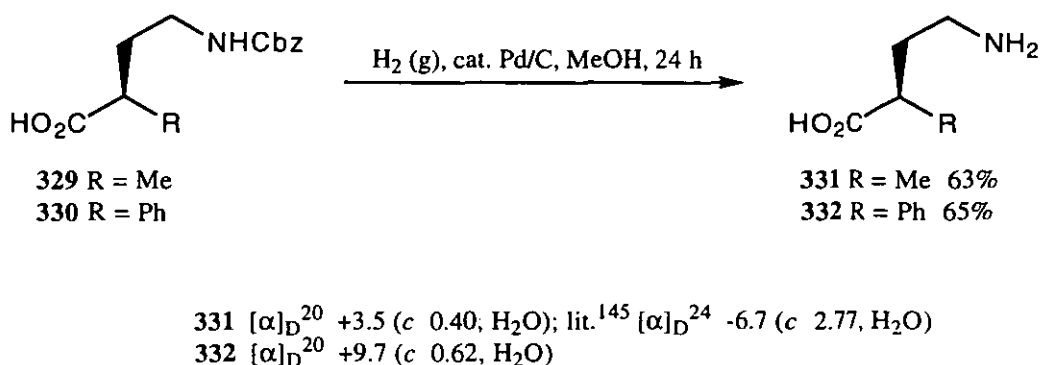
The penultimate step in the sequence was the oxidative cleavage of the C=C bond to furnish the carboxylic acid moiety. This transformation was readily achieved by a solution of chromium (VI) oxide in glacial acetic acid.^{32a} Isolation of the desired products required purification by flash chromatography using two different solvent systems. Firstly a mixture of dichloromethane and light petroleum (3:1) was used to elute any non-polar products. The column was then washed with a mixture of dichloromethane and methanol (9:1) to wash off the polar carboxylic acid. The acids **329** and **330** were available in 75% and 61% yield respectively.



Scheme 108

The final step in the synthesis was the removal of the nitrogen protection to realise the free amino acids. The cleavage of the carbamate by catalytic hydrogenation over palladium on carbon furnished us with the γ -amino acids **331** and **332** in good yield. The spectra for both compounds were satisfactory. The IR spectra included a stretch in the carbonyl region of the spectrum due to the carboxylic acid moiety. It was necessary to run the NMR spectra in D₂O because of solubility concerns. The ¹H-NMR clearly showed that the Cbz protecting group was no longer present. The ¹³C-NMR confirmed the structure of the carbon framework for

both **331** and **332**. The ^1H -NMR had included a broad peak due to HOD which had obscured some signals.



Scheme 109

Due to time constraints it was not possible to analyse the enantiomeric excess of the final products. Optical rotation data throughout the synthesis demonstrates that the compounds are chiral and enantiomerically enriched.

4.5 Conclusion

We have introduced several nucleophiles to the palladium catalysed allylic substitution reaction. The substitution products have been isolated in good yield and with excellent levels of stereocontrol.

We have successfully used the substitution reaction to introduce a well defined chiral centre at the beginning of a synthesis. This chirality has been carried through the synthesis of novel analogues of γ -amino butyric acid.

Chapter Five

Experimental

5.1 General Information

Solvents and Reagents - Commercially available solvents and reagents were used throughout without further purification, except for those detailed below which were purified as described. "Light petroleum" refers to the fraction of petroleum ether boiling between 40 °C and 60 °C. Light petroleum and ethyl acetate were distilled from anhydrous calcium chloride through a 36 cm Vigreux column before use. Dichloromethane was distilled from phosphorus pentoxide and methanol was distilled from magnesium turnings and iodine.

Chromatographic Procedures - Analytical thin layer chromatography was carried out using plastic backed plates coated with Merck Kieselgel 60 F₂₅₄. Plates were visualised under UV light (at 254 and/or 360 nm) or by exposure to an appropriate staining agent. Flash chromatography was carried out using Merck silica gel 60. Pressure was applied at the head of the column with hand bellows. Samples were applied pre-absorbed on silica or as a concentrated solution in an appropriate solvent.

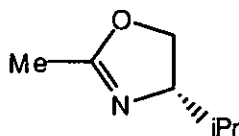
Spectroscopic Techniques - Infra red spectra were recorded in the range 4000-600 cm⁻¹ using either a Nicolet FT-205 spectrometer or a Perkin Elmer Paragon 1000, both with internal calibration. Spectra were recorded as thin films or as a Nujol mull. ¹H and ¹³C spectra were recorded using Bruker AC-250 and Bruker DPX-400 instruments. ¹H NMR spectra are referenced against residual undeuterated solvent, in the case of deuteriochloroform this is 7.260 ppm. Signals are described as singlets (s), doublets (d), double doublets (dd) *etc.* High and low resolution mass spectra were recorded on a Kratos MS80 instrument.

Other Data and Instrumentation - Melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected. Optical rotations were measured using either an Optical Activity AA 100 polarimeter or a PolAAr 2001 instrument and are given in 10⁻¹ deg cm² g⁻¹.

All of the following experimental reactions were carried out under an atmosphere of nitrogen except in cases where it was obviously unnecessary.

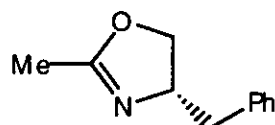
5.2 Experimental for Chapter 2

(4S)-4,5-Dihydro-4-isopropyl-2-methyl-1,3-oxazole **166**



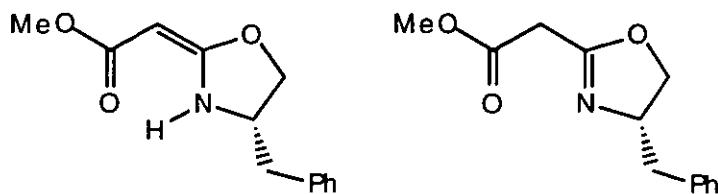
A solution of methyl acetimidate (1.27 g, 11.6 mmol) and *L*-valinol (1 g, 9.7 mmol) in dichloromethane (30 mL) was stirred for 16 h at ambient temperature. The reaction mixture was washed with a saturated solution of aqueous sodium hydrogencarbonate. The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo* to afford the *title compound* as a colourless oil (1.16 g, 94%). (found M^+ , 127.1069. $\text{C}_7\text{H}_{13}\text{NO}$ requires M^+ , 127.0997). $[\alpha]_{\text{D}}^{20}$ -86.2 (c 1.10, CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1677 ($\text{C}=\text{N}$). δ_{H} (250 MHz, CDCl_3) 4.23 (1 H, m, CHN), 3.85 (2 H, m, CH_2O), 1.98 (3 H, s, CH_3), 1.70 (1 H, m, $\text{CH}(\text{CH}_3)_2$), 0.96 (3 H, d, J 6.8, CHCH_3) and 0.87 (3 H, d, J 6.8, CHCH_3). δ_{C} (63 MHz, CDCl_3) 164.0 ($\text{C}=\text{N}$), 72.1 (CHN), 69.9 (CH_2O), 32.4 ($\text{CH}(\text{CH}_3)_2$), 18.5 (CHCH_3), 17.9 (CHCH_3) and 13.5 (CH_3).

(4S)-4,5-Dihydro-4-benzyl-2-methyl-1,3-oxazole **167**



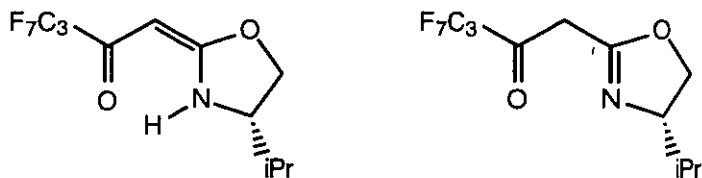
The above procedure was followed in the preparation of **167**. The product was isolated as a pale yellow oil (3.2 g, 92%). (found M^+ , 175.0997. $\text{C}_{11}\text{H}_{13}\text{NO}$ requires M^+ , 175.0997). $[\alpha]_{\text{D}}^{20}$ -43.1 (c 1.276, CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1675 ($\text{C}=\text{N}$). δ_{H} (250 MHz, CDCl_3) 7.32-7.17 (5H, m, Ar-H), 4.33 (1H, m, CHN), 4.15 (1H, t, J 8.4, $\text{CHH}'\text{O}$), 3.92 (1H, t, J 8.4, $\text{CHH}'\text{O}$), 3.07 (1H, dd, J 13.4 and 5.3, PhCHH'), 2.60 (1H, dd, J 13.4 and 8.4, PhCHH') and 1.96 (3H, s, CH_3). δ_{C} (63 MHz, CDCl_3) 164.5 ($\text{C}=\text{N}$), 137.9, 129.1, 128.4 and 126.4 (arom. C), 71.7 (CH_2O), 67.3 (CHN), 41.7 (PhCH_2) and 13.8 (CH_3).

(4S)-4-Benzyl-4,5-dihydro-2-ethylmethylacetate-1,3-oxazole **170**



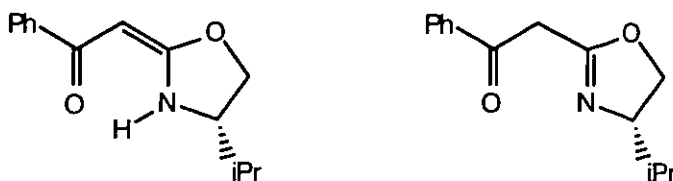
The product was isolated as a yellow oil (110 mg, 16%). (found M^+ , 233.1092. $C_{13}H_{15}NO_3$ requires M^+ , 233.1052). $[\alpha]_D^{20}$ -33.1 (c 0.302, $CHCl_3$). ν_{max}/cm^{-1} (neat) 3353 (enol OH), 1748 (CO_2Me), 1677 ($C=N$), 1613 ($C=C$) and 1092 ($C-O$). δ_H (250 MHz, $CDCl_3$) 9.29 (enol H), 7.38-7.16 (5H, m, Ar- H), 4.6 (1H, t, J 8.5, $CHH'O$), 4.39-4.24 (2H, m, CHN and $CHH'O$), 3.74 (3H, s, OCH_3) and 2.90 (2H, m, $PhCH_2$). δ_C (63 MHz, $CDCl_3$) 172.4 ($C=O$), 135.6 (enol $C=C$), 129.0, 128.8, 128.6, 128.4, 127.3 and 126.7 (arom. C), 73.3 (CH_2O), 56.2 (CHN), 51.2 (OCH_3) and 40.7 ($PhCH_2$).

(4S)-4,5-Dihydro-2-ethylfluorobutyrate-4-isopropyl-1,3-oxazole **171**



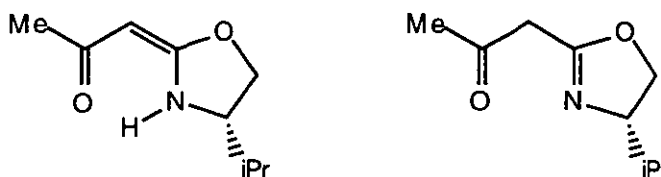
The product was isolated as a colourless solid (133 mg, 49%). M.p. 44-45 °C. (found M^+ , 323.0758. $C_{11}H_{12}F_7NO_2$ requires M^+ , 323.0756). $[\alpha]_D^{20}$ +70.4 (c 0.43, $CHCl_3$). ν_{max}/cm^{-1} (nujol) 3252 (enol OH), 1640 ($C=O$) and 1632 ($C=C$). δ_H (250 MHz, $CDCl_3$) 9.94 (1H, br. s, enol H), 5.29 (1H, s, $C=CH$), 4.58 (1H, t, J 9.1, $CHH'O$), 4.29 (1H, dd, J 9.1 and 6.2, $CHH'O$), 3.94 (1H, m, CHN), 1.85 (1H, m, $CH(CH_3)_2$) and 0.94 (6H, m, $CH(CH_3)_2$). δ_C (63 MHz, $CDCl_3$) 171.4 ($N-C=CH$), 74.1 ($N-C=CH$), 71.3 (CH_2O), 61.4 (CHN), 32.0 ($CH(CH_3)_2$), 17.8 and 17.5 ($CH(CH_3)_2$).

(4*S*)-4,5-Dihydro-2-ethylphenylketone-4-isopropyl-1,3-oxazole **172**



The product was isolated as an off-white solid (92 mg, 25%). M.p. 67-68 °C. (found M^+ , 231.1264. $C_{14}H_{17}NO_2$ requires M^+ , 231.1259). $[\alpha]_D^{20} +69.8$ (c 0.43, $CHCl_3$). ν_{max}/cm^{-1} (nujol) 3256 (enol OH), 1625 ($C=O$), 1582 ($C=C$) and 1000 ($C-O$). δ_H (250 MHz, $CDCl_3$) 7.89-7.85 (2H, m, Ar-H), 7.43-7.39 (3H, m, Ar-H), 5.59 (1H, s, $C=\underline{CH}$), 4.49 (1H, t, J 8.8, $\underline{CHH'O}$), 4.18 (1H, dd, J 8.8 and 6.5, $\underline{CHH'O}$), 3.84 (1H, m, \underline{CHN}), 1.79 (1H, m, $\underline{CH}(\underline{CH}_3)_2$), 1.01 (3H, d, J 6.8, \underline{CH}_3) and 0.94 (3H, d, J 6.8, \underline{CH}_3). δ_C (63 MHz, $CDCl_3$) 187.4 ($\underline{C=O}$), 170.5 ($\underline{C=N}$), 139.9 ($\underline{C=CH}$), 130.6, 128.2 and 126.8 (arom. \underline{C}), 73.7 ($C=\underline{CH}$), 70.8 (\underline{CH}_2O), 61.4 (\underline{CHN}), 32.4 ($\underline{CH}(\underline{CH}_3)_2$), 18.3 and 18.1 ($\underline{CH}(\underline{CH}_3)_2$).

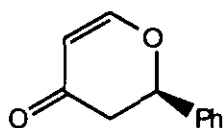
(4*S*)-Dihydro-4-isopropyl-2-(propan-2-one)-1,3-oxazole **173**



Lithium diisopropylamide (17.3 mL, 2 M solution in hexanes) was added slowly to a solution of (4*S*)-4,5-dihydro-4-benzyl-2-methyl-1,3-oxazole (2 g, 15.7 mmol) in dry THF (100 mL) at -78 °C whilst under an inert atmosphere. The resultant solution was stirred for 5 mins at -78 °C before the addition of *N*-acetyl imidazole (1.9 g, 17.3 mmol). The reaction was allowed to warm to ambient temperature and then quenched with a saturated ammonium chloride solution (100 mL). The aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organics were dried over $MgSO_4$ before being concentrated *in vacuo*. The crude product was purified by flash chromatography (ethyl acetate:light petroleum, 3:1) to afford the *title compound* as a pale yellow oil (1.53 g, 58%). (found M^+ , 169.1102. $C_9H_{15}NO_2$ requires M^+ , 169.1103). $[\alpha]_D^{20} +62.5$ (c 0.8, $CHCl_3$). ν_{max}/cm^{-1} (nujol) 3270

(enol OH), 1636 (C=O), 1545 (C=C) and 1024 (C-O). δ_{H} (250 MHz, CDCl_3) 4.89 (1H, s, C=CH), 4.42 (1H, t, J 8.6, CHH'O), 4.12 (1H, dd, J 8.6 and 6.4, CHH'O), 3.7 (1H, m, CHN), 2.04 (3H, s C(O)CH₃), 1.76 (1H, m, CH(CH₃)₂), 0.97 (3H, d, J 6.8, CHCH₃) and 0.87 (3H, d, J 6.8, CHCH₃). δ_{C} (63 MHz, CDCl_3) 76.4 (C=CH), 70.3 (CH₂O), 61.1 (CHN), 32.2 (CH(CH₃)₂), 28.6 (C(O)CH₃), 18.7 and 18.1 (CH(CH₃)₂).

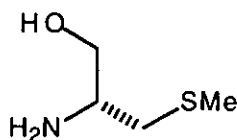
3-Dihydro-2-phenylpyran-4-one **187**



A solution of *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (861 mg, 5 mmol), benzaldehyde (584 mg, 5.5 mmol) and $\text{Eu}(\text{hfc})_3$ (60 mg, 50 μmol) in chloroform was stirred for 48 h at ambient temperature. Trifluoroacetic acid (0.5 mL) was added slowly to the solution and the resultant solution was stirred at ambient temperature for 2 h. The reaction was quenched by the slow addition of a solution of sodium hydrogen carbonate. The aqueous phase was extracted with diethyl ether (3 x 30 mL), dried over MgSO_4 and reduced *in vacuo*. The crude oil was purified by flash chromatography (diethyl ether:light petroleum, 1:3) to yield the *title compound* as a yellow oil (410 mg, 47%). $[\alpha]_{\text{D}}^{20}$ -15.4 (c 2.93, CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1681 (C=O), 1595 (C=C) and 1039 (C-O). δ_{H} (250 MHz, CDCl_3) 7.49-7.37 (6H, m, Ar-H and CH=CH-O), 5.53 (1H, d, J 7.0, CH=CH-O), 5.42 (1H, dd, J 14.3 and 4.1, PhCH), 2.91 (1H, dd, J 17.0 and 14.3, CHH'CHPh) and 2.64 (1H, dd, J 17.0 and 4.1, CHH'CHPh). δ_{C} (63 MHz, CDCl_3) 193.4 (C=O), 163.1 (CH=CH-O), 137.8, 128.9, 128.8 and 126.0 (arom. C), 107.3 (CH=CH-O), 81.0 (PhCH) and 43.3 (CH₂CHPh).

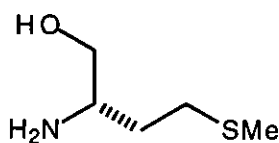
5.3 Experimental for Chapter 3

(S)-2-Amino-3-(methylthio)propan-1-ol 215



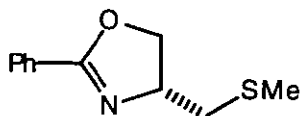
(S)-Methyl-*L*-cysteine (1.96 g, 14.5 mmol) was added slowly to a stirring slurry of lithium aluminium hydride (1.8 g, 48 mmol) in dry THF (30 mL). The resultant slurry was heated under reflux for 16 h whilst under an inert atmosphere. The reaction was quenched by the careful addition of water (2 mL), 15% sodium hydroxide (2 mL), water (6 mL) with stirring until the grey salts had decomposed to form a white precipitate. The solids were filtered and washed with diethyl ether. The organic fractions were dried over MgSO_4 and concentrated *in vacuo* to yield a yellow oil. The crude product was distilled (Kugelrohr air bath 120 °C at 7 mmHg) to yield the *title compound* as a colourless oil (686 mg, 40%). $\nu_{\text{max.}}/\text{cm}^{-1}$ (neat) 3350-3150 (OH and NH_2), 1600 (NH), 1400 (OH) and 1050 (C-O). δ_{H} (250 MHz, CDCl_3) 3.64 (1H, m, $\text{CHH}'\text{OH}$), 3.42 (1H, m, $\text{CHH}'\text{OH}$), 3.02 (1H, m, CHNH_2), 2.62 (1H, m, $\text{CHH}'\text{S}$), 2.42 (1H, m, $\text{CHH}'\text{S}$), 2.26 (3H, br. s, OH and NH_2) and 2.11 (3H, s, SCH_3).

(S)-2-Amino-4-(methylthio)butan-1-ol 217



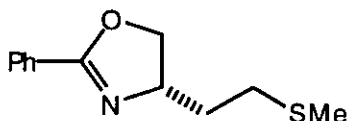
L-Methionine was similarly reduced to yield the *title compound* as a colourless oil (2.25 g, 78%). $\nu_{\text{max.}}/\text{cm}^{-1}$ (neat) 3350-3150 (OH and NH_2), 1600 (NH), 1400 (OH) and 1050 (C-O). δ_{H} (250 MHz, CDCl_3) 3.61 (1H, m, $\text{CHH}'\text{OH}$), 3.25 (1H, m, $\text{CHH}'\text{OH}$), 3.00 (1H, m, CHNH_2), 2.60 (2H, m, CH_2CHN), 2.12 (3H, s, SCH_3), 1.62-1.82 (4H, m, OH , NH_2 and SCHH') and 1.58 (SCHH').

(4S)-4,5-Dihydro-4-[2-(methylthio)methyl]-2-phenyl-1,3-oxazole 219

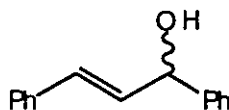


A solution of (*S*)-2-amino-3-(methylthio)propan-1-ol (700 mg, 6.3 mmol), DMAP (10 mg, 80 μ mol) and methyl benzimidate (1.19 g, 6.92 mmol) in dichloromethane (5 mL) was stirred for 48 h before being heated under reflux for 7 h. The reaction mixture was washed with water and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organics were dried over MgSO_4 and concentrated *in vacuo* to yield a yellow oil. The crude product was purified by flash chromatography (diethyl ether) to afford the *title compound* as a pale yellow oil (430 mg, 48%). (found M^+ , 207.0729. $\text{C}_{11}\text{H}_{13}\text{NOS}$ requires M^+ , 207.0718). $[\alpha]_{\text{D}}^{25}$ -11.1 (*c* 1.35, CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1650 (C=N), 1275 (SMe) and 1050 (C-O). δ_{H} (250 MHz, CDCl_3) 7.96-7.37 (5H, m, Ar-H), 4.55 (1H, m, CHN), 4.30 (2H, m, CH_2O), 2.97-2.63 (2H, m, CH_2S) and 2.19 (3H, s, SCH₃). δ_{C} (63 MHz, CDCl_3) 165 ($\text{C}=\text{N}$), 131.5-127.5 (arom. C), 72.0 (CH_2OH), 66.4 (CHN), 39.3 (CH_2S) and 16.1 (SCH₃).

(4S)-4,5-Dihydro-4-[2-(methylthio)ethyl]-2-phenyl-1,3-oxazole 220

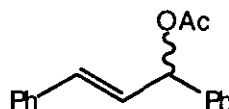


The previous procedure was followed to afford the *title compound* as a colourless oil (525 mg, 70%). $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1650 (C=N), 1275 (SMe) and 1050 (C-O). δ_{H} (250 MHz, CDCl_3) 7.47-7.37 (5H, m, Ar-H), 4.49 (2H, m, CH_2O), 4.06 (1H, m, CHN), 2.67 (2H, m, CH_2S), 2.14 (3H, s, SCH₃) and 1.98 (2H, m, CH_2CHN). δ_{C} (63 MHz, CDCl_3) 163 ($\text{C}=\text{N}$), 131.2-128.2 (arom. C), 72.3 (CH_2O), 65.7 (CHN), 35.4 (CH_2CHN), 30.7 (CH_2S) and 15.4 (SCH₃).



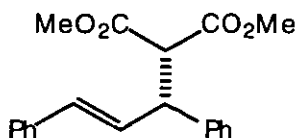
Sodium borohydride was carefully added to a stirred solution of chalcone (10 g, 48 mmol) and cerium (III) chloride heptahydrate (2 g, 50.8 mmol) in methanol (50 mL) at 0 °C. The reaction was stirred until analysis by tlc showed complete consumption of the starting material. Water was added to the reaction mixture (100 mL) which was subsequently extracted with dichloromethane (6 x 50 mL). The combined organics were dried (Na₂SO₄) and concentrated *in vacuo* to yield the *title compound* as a colourless solid (9.1 g, 90%) which was used directly in the next step. $\nu_{\text{max.}}/\text{cm}^{-1}$ (nujol) 3450 (OH). δ_{H} (250 MHz, CDCl₃) 7.44-7.22 (10 H, m, Ar-H), 6.54-6.32 (2H, m, PhCH=CH and PhCH=CH), 5.25 (1 H, d, *J* 5, PhCHOH) and 2.43 (1 H, br. s, OH).

1,3-Diphenylprop-2-enylacetate 72



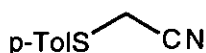
Acetic anhydride was slowly added to a solution of 1,3-diphenylprop-2-en-1-ol (9.1 g, 43.3 mmol) and DMAP (10 mg) in dichloromethane (50 mL). The resultant solution was stirred for 16 h before the excess solvent was removed *in vacuo*. The crude oil was purified by flash chromatography (ethyl acetate:light petroleum, 1:10) to yield the *title compound* as a pale yellow oil (9.8 g, 91%). $\nu_{\text{max.}}/\text{cm}^{-1}$ (neat) 1738 (C=O). δ_{H} (250 MHz, CDCl₃) 7.46-7.23 (10 H, m, Ar-H), 6.63 (1 H, *J* 15.6, PhCH=CH), 6.48 (1 H, dd, *J* 15.6 and 6.9, PhCH=CH), 6.35 (1 H, d, *J* 6.9, CHOAc) and 2.15 (3 H, s, C(O)CH₃). δ_{C} (63 MHz, CDCl₃) 170.1 (C=O), 139.2, 136.4, 132.5, 128.6, 128.5, 128.1, 128.0, 127.4, 127.0 and 126.6 (arom. C and C=C), 76.0 (CHOAc) and 21.2 (CH₃).

Dimethyl 1,3-diphenylprop-2-enylmalonate ent-73



Dimethyl malonate (159 mg, 1.2 mmol) was added to a slurry of sodium hydride (30 mg, 1.32 mmol) in dry THF (2 mL) under an inert atmosphere at 0 °C. In a separate flask under an inert atmosphere, a solution in dry THF (2 mL) of 1,3-diphenylprop-2-enylacetate, [(η^3 -C₃H₅)PdCl]₂ (2.5 mol%) and chiral ligand **L*** (10 mol%) was stirred for 15 mins at ambient temperature. Sodiodimethylmalonate was added dropwise to this solution and the resultant mixture was stirred for 48 h at ambient temperature. The reaction mixture was diluted with dichloromethane (50 mL) and washed with a saturated aqueous ammonium chloride solution (20 mL). The organic layer was separated, dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography (diethyl ether:light petroleum, 3:1) to yield the *title compound* as a pale yellow oil. Where **L*** = **219** (167 mg, 86%). Where **L*** = **220** (154 mg, 79%). $\nu_{\text{max.}}/\text{cm}^{-1}$ (neat) 1740 (C=O). δ_{H} (250 MHz, CDCl₃) 7.40-7.21 (10 H, m, Ar-H), 6.52 (1 H, d, *J* 15.7, PhCH=CH), 6.32 (1 H, dd, *J* 15.7 and 8.3, PhCH=CH), 4.30 (1 H, dd, *J* 10.9 and 8.3, PhCH), 4.00 (1 H, d, *J* 10.9, CH(CO₂Me)₂) and 3.74 (6 H, s, CO₂CH₃). δ_{C} (63 MHz, CDCl₃) 168.1 and 167.7 (C=O), 140.1, 136.8, 131.8, 129.1, 128.7, 128.4, 127.8, 127.5, 127.1 and 126.3 (arom. C and C=C), 57.6 (CH), 52.6 and 52.4 (CO₂CH₃) and 49.1 (CH).

(4-Methylphenyl)sulfanylacetonitrile 241



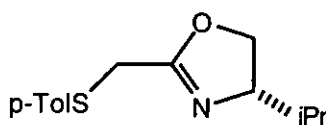
A solution of acetonitrile (0.2 g, 4.87 mmol) in THF (2 mL) was cooled to -78 °C under a nitrogen atmosphere. LDA (9.7 mL, 14.6 mmol as a 1.5 M solution in THF) was added dropwise to the flask and the mixture was stirred for 1 h at -78 °C. To this mixture was added *p*-tolylidissulfide (2.4 g, 9.7 mmol) as a solution in THF (3 mL) over a period of 5 mins.

The solution was stirred at -78 °C for 2 h before being allowed to warm to ambient temperature. The reaction mixture was washed with saturated ammonium chloride solution (20 mL) and the aqueous phase was washed with dichloromethane (5 x 30 mL). The combined organic phases were dried (Na₂SO₄) and concentrated *in vacuo* to leave an oily residue. This was purified by flash chromatography (light petroleum:diethyl ether, 4:1) to yield the *title compound* as a colourless oil (583 mg, 73%). (found M⁺, 163.0418. C₉H₉NS requires M⁺, 163.0456). $\nu_{\max}/\text{cm}^{-1}$ (neat) 2261 (CN). δ_{H} (250 MHz, CDCl₃) 7.49-7.18 (4 H, m, Ar-H), 3.51 (2 H, s, CH₂) and 2.36 (3 H, s, CH₃). δ_{C} (63 MHz, CDCl₃) 139.5, 133.1, 130.3 and 128.3 (arom. C), 116.6 (CN), 22.0 (CH₂) and 21.1 (CH₃).

General procedure for the formation of 4,5-dihydro-oxazoles using ZnCl₂ catalysis.

In a 50 mL Schlenk flask, zinc chloride (0.5 mmol) was melted under high vacuum and cooled under nitrogen to room temperature. Chlorobenzene (30 mL) was then added to the flask followed by the appropriate nitrile (10 mmol) and amino alcohol (15 mmol). The mixture was heated under reflux for 48 h after which time the solvent was removed under reduced pressure to give an oily residue, which was dissolved in dichloromethane (30 mL). The solution was washed with water (3 x 20 mL) and the aqueous phase back extracted with dichloromethane (30 mL). The combined organic phases were dried (Na₂SO₄) and then concentrated *in vacuo* to give an oily residue which was purified by flash chromatography to afford the product.

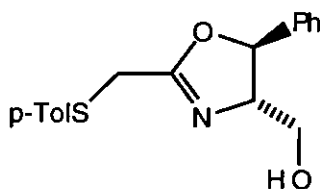
(4S)-4,5-Dihydro-4-isopropyl-2-[(4-methylphenyl) methylsulfanyl]-1,3-oxazole 242



(80%) as a pale yellow oil. (found M⁺, 249.1189. C₁₄H₁₉NOS requires M⁺, 249.1187). $[\alpha]_{\text{D}}^{20}$ -26.7 (*c* 0.37, CHCl₃). $\nu_{\max}/\text{cm}^{-1}$ (neat) 1665 (C=N). δ_{H} (250 MHz, CDCl₃) 7.36-7.08 (4 H, m, Ar-H), 4.25 (1 H, m, CHH'O), 4.00-3.72 (2 H, m, CHH'O and CHN), 3.60 (1 H, d, *J* 14.3, CHH'S), 3.53 (1 H, d, *J* 14.3, CHH'S), 2.31 (3 H, s, Ar-CH₃), 1.73-1.58 (1 H,

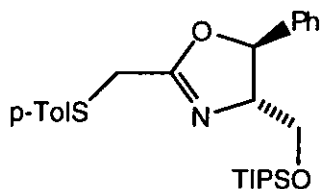
m, $\text{CH}(\text{CH}_3)_2$), 0.88 (3 H, d, J 6.7, $\text{CH}-\text{CH}_3$) and 0.81 (3 H, d, J 6.7, $\text{CH}-\text{CH}_3$). δ_{C} (63 MHz, CDCl_3) 163.8 ($\text{C}=\text{N}$), 137.2, 130.8 and 129.6 (arom. C), 72.3 (CHN), 70.6 (CH_2O), 32.4 ($\text{Ar}-\text{CH}_3$), 31.6 (CH_2S), 20.9 ($\text{CH}(\text{CH}_3)_2$), 18.6 ($\text{CH}-\text{CH}_3$) and 17.9 ($\text{CH}-\text{CH}_3$).

(4S,5S)-4,5-Dihydro-4-hydroxymethyl-5-phenyl-2-[(4-methylphenyl)methylsulfanyl]-methyl-1,3-oxazole 243



(91%) as a white solid. M.p. 111-112 °C. (found M^+ , 313.1101. $\text{C}_{18}\text{H}_{19}\text{NO}_2\text{S}$ requires M^+ , 313.1136). $[\alpha]_{\text{D}}^{20} +13.8$ (c 0.36, CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$ (nujol) 3373 (OH) and 1651 ($\text{C}=\text{N}$). δ_{H} (250 MHz, CDCl_3) 7.41-7.12 (9 H, m, Ar-H), 5.35 (1 H, d, J 7.5, CHO), 4.07-4.01 (1 H, m, CHN), 3.89-3.78 (3 H, m, $\text{CHH}'\text{OH}$ and CH_2S), 3.57 (1 H, dd, J 12.0 and 6.2, $\text{CHH}'\text{OH}$), 2.33 (3 H, s, $\text{Ar}-\text{CH}_3$) and 1.57 (1 H, br. s, OH). δ_{C} (63 MHz, CDCl_3) 168.2 ($\text{C}=\text{N}$), 139.2, 137.8, 131.4, 130.4, 129.9, 129.8, 129.2, 128.8, 128.6, 128.3, 127.6 and 125.8 (arom. C), 83.8 (CHO), 75.4 (CHN), 38.6 (CH_2OH), 31.6 (CH_2S) and 21.0 ($\text{Ar}-\text{CH}_3$).

(4S,5S)-4,5-Dihydro-4-hydroxymethyltriisopropylsilyl ether-5-phenyl-2-[(4-methylphenyl)methylsulfanyl]-1,3-oxazole 244



(4S,5S)-4,5-Dihydro-4-hydroxymethyl-5-phenyl-2-[(4-methylphenyl)methylsulfanyl]-methyl-1,3-oxazole (900 mg, 2.85 mmol) was dissolved in dichloromethane (30 mL). The solution was treated with triethylamine (348 mg, 3.44 mmol) and stirred for 5 mins at ambient temperature. Triisopropylsilyltrifluoromethane sulfonate (1.05 g, 3.44 mmol) was

added to the mixture in one portion and the solution was stirred for a further 15 mins at room temperature. The mixture was washed with a saturated ammonium chloride solution (50 mL) and the aqueous phase was washed with dichloromethane (3 x 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to produce an oily residue. This was purified by flash chromatography (light petroleum:diethyl ether, 2:1) to yield the *title compound* as a colourless oil (1.24 g, 93%). (found M^+ , 469.2472. $\text{C}_{27}\text{H}_{39}\text{NO}_2\text{SSi}$ requires M^+ , 469.2471). $[\alpha]_{\text{D}}^{20}$ -17.5 (c 0.29, CHCl_3). $\nu_{\text{max.}}/\text{cm}^{-1}$ (neat) 1654 ($\text{C}=\text{N}$). δ_{H} (250 MHz, CDCl_3) 7.40-7.09 (9 H, m, Ar-H), 5.48 (1 H, d, J 5.9, CH_O), 4.11 (1 H, m, CH_N), 4.00 (1 H, dd, J 9.9 and 3.9, $\text{CHH}'\text{O}$), 3.84 (1 H, d, J 14.5, $\text{CHH}'\text{S}$), 3.77 (1 H, d, J 14.5, $\text{CHH}'\text{S}$), 3.64 (1 H, m, $\text{CHH}'\text{O}$), 2.32 (3 H, s, Ar- CH_3) and 1.13-0.99 (21 H, m, 3 x $\text{CH}(\text{CH}_3)_2$). δ_{C} (63 MHz, CDCl_3) 164.6 ($\text{C}=\text{N}$), 141.1, 137.1, 136.1, 130.9, 128.6, 127.9, 127.3 and 125.4 (arom. C), 84.2 (CHO), 76.6 (CH_N), 65.3 (CH_2S), 31.8 (CH_2O), 21.1 (Ar- CH_3), 17.7 ($\text{CH}(\text{CH}_3)_2$) and 11.9 (CH).

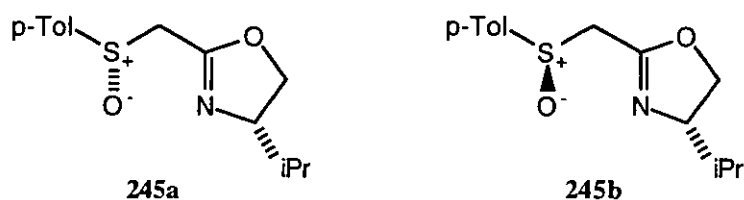
General procedure for the oxidation of (4S)-4,5-dihydro-4-isopropyl-2-[(4-methylphenyl)methylsulfanyl]-1,3-oxazole 242 by mCPBA.



A mixture of (4S)-4,5-dihydro-4-isopropyl-2-[(4-methylphenyl) methylsulfanyl]-1,3-oxazole (100 mg, 0.4 mmol) and 50% mCPBA (138 mg, 0.8 mmol) was stirred for 1 h in the appropriate solvent at -78 °C. The reaction mixture was washed with a concentrated solution of sodium hydrogen carbonate (20 mL). The aqueous layer was washed with dichloromethane (20 mL) and the combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was purified by flash chromatography (ethyl acetate) to yield (4S, S_s)-4,5-dihydro-4-isopropyl-2-[(4-methylphenyl)methylsulfinyl]-1,3-oxazole **245** as a pale yellow oil. Solvents: chloroform (yield 27%), chloroform:methanol, 1:1 (yield 26%) and chloroform:hexane, 1:1 (yield 48%). Diastereomeric ratios were determined by inspection of the ^1H NMR. All data was consistent with a mixture of (4S, S_s)-4,5-dihydro-4-

isopropyl-2-[(4-methylphenyl)methylsulfinyl]-1,3-oxazole **245a** and (4*S*,*R*_s)-4,5-dihydro-4-isopropyl-2-[(4-methylphenyl)methylsulfinyl]-1,3-oxazole **245b** which is detailed below.

*General procedure for the preparation of (4*S*,*R*_s)-4,5-dihydro-4-isopropyl-2-[(4-methylphenyl)methylsulfinyl]-1,3-oxazole **245a**, and (4*S*,*S*_s)-4,5-dihydro-4-isopropyl-2-[(4-methylphenyl)methylsulfinyl]-1,3-oxazole **245b**.*



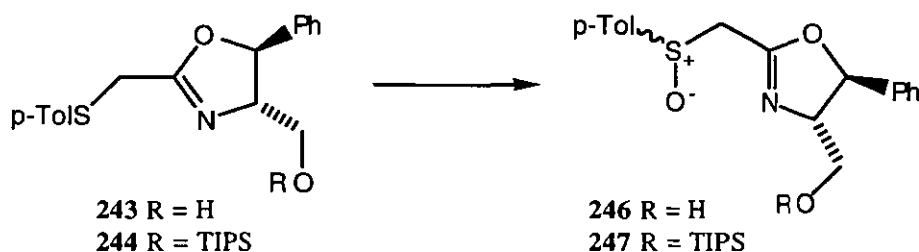
A 1.5 M solution of LDA (1.74 mL, 2.61 mmol) was added slowly to a solution of (4*S*)-4,5-dihydro-4-isopropyl-2-methyl-1,3-oxazole in dry tetrahydrofuran (5 mL) at -78 °C under an inert atmosphere. The resulting solution was stirred at -78 °C for 30 mins before the slow addition of the appropriate *p*-tolylmenthylsulfinates (384 mg, 1.3 mmol) in tetrahydrofuran (5 mL). The reaction was stirred for 2 h before being allowed to warm to ambient temperature and quenched with a saturated solution of aqueous ammonium chloride (20 mL). The mixture was diluted with diethyl ether (30 mL) and washed with a saturated solution of aqueous ammonium chloride (20 mL). The aqueous phase was washed with diethyl ether (2 x 20 mL) and the combined organics were dried (MgSO₄) and concentrated *in vacuo* to yield a dark yellow oil. The crude product was purified by flash chromatography (ethyl acetate) to afford the *title compound*.

*(4*S*,*R*_s)-4,5-Dihydro-4-isopropyl-2-[(4-methylphenyl) methylsulfinyl]-1,3-oxazole **245a*** (76%) as a pale yellow oil. (found *M*⁺, 265.1140. C₁₄H₁₉NO₂S requires *M*⁺, 265.1136). [α]_D²⁰ +100.0 (*c* 0.40, CHCl₃). ν_{max} /cm⁻¹ (neat) 1665 (C=N), 1053 (S=O). δ_{H} (250 MHz, CDCl₃) 7.57 (2 H, d, *J* 8.1, Ar-H), 7.32 (2H, d, *J* 8.1, Ar-H), 4.26 (1 H, m, CHN), 3.96-3.79 (3 H, m, CH2O and CHH'S(O)), 3.64 (1 H, d, *J* 14.3, CHH'S(O)), 2.42 (3 H, s, Ar-CH₃), 1.65 (1 H, m, CH(CH₃)₂), 0.91 (3 H, d, *J* 6.7, CH-CH₃) and 0.83 (3 H, d, *J* 6.7, CH-CH₃). δ_{C} (63 MHz, CDCl₃) 158.6 (C=N), 143.1, 140.0, 129.8 and 124.2 (arom. C), 72.5

($\underline{\text{CHN}}$), 70.8 ($\underline{\text{CH}_2\text{O}}$), 55.8 ($\underline{\text{CH}_2\text{S(O)}}$), 32.5 (Ar- $\underline{\text{CH}_3}$), 21.3 ($\underline{\text{CH}}(\text{CH}_3)_2$), 18.7 (CH- $\underline{\text{CH}_3}$) and 18.1 (CH- $\underline{\text{CH}_3}$).

(4*S,S*)-4,5-Dihydro-4-isopropyl-2-[(4-methylphenyl) methylsulfinyl]-1,3-oxazole **245b** (47%) as a pale yellow oil. (found M^+ , 265.1140. $\text{C}_{14}\text{H}_{19}\text{NO}_2\text{S}$ requires M^+ , 265.1136). $[\alpha]_{\text{D}}^{20}$ -222.2 (c 0.27, CHCl_3). $\nu_{\text{max.}}/\text{cm}^{-1}$ (neat) 1632 (C=N), 1034 (S=O). δ_{H} (250 MHz, CDCl_3) 7.58 (2 H, d, J 8.1, Ar- $\underline{\text{H}}$), 7.33 (2H, d, J 8.1, Ar- $\underline{\text{H}}$), 4.22 (1 H, m, $\underline{\text{CHN}}$), 3.96-3.83 (3 H, m, $\underline{\text{CH}_2\text{O}}$ and $\underline{\text{CHH}}'\text{S(O)}$), 3.60 (1 H, d, J 14.3, $\underline{\text{CHH}}'\text{S(O)}$), 2.42 (3 H, s, Ar- $\underline{\text{CH}_3}$), 1.64 (1 H, m, $\underline{\text{CH}}(\text{CH}_3)_2$), 0.89 (3 H, d, J 6.7, CH- $\underline{\text{CH}_3}$) and 0.84 (3 H, d, J 6.7, CH- $\underline{\text{CH}_3}$). δ_{C} (63 MHz, CDCl_3) 158.8 ($\underline{\text{C=N}}$), 142.8, 140.2, 129.9 and 124.3 (arom. $\underline{\text{C}}$), 72.4 ($\underline{\text{CHN}}$), 70.8 ($\underline{\text{CH}_2\text{O}}$), 56.0 ($\underline{\text{CH}_2\text{S(O)}}$), 32.4 (Ar- $\underline{\text{CH}_3}$), 21.4 ($\underline{\text{CH}}(\text{CH}_3)_2$), 18.6 (CH- $\underline{\text{CH}_3}$) and 18.1 (CH- $\underline{\text{CH}_3}$).

*General procedure for the oxidation of (4*S,S*)-4,5-dihydro-4-hydroxymethyl-5-phenyl-2-[(4-methylphenyl) methylsulfonyl]-methyl-1,3-oxazole **243**, and (4*S,S*)-4,5-dihydro-4-hydroxymethyltriisopropylsilylether-5-phenyl-2-[(4-methylphenyl)methylsulfonyl]-1,3-oxazole **244**, with mCPBA.*



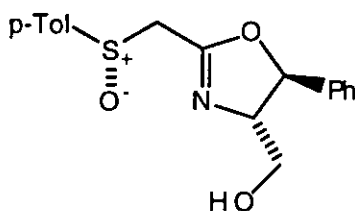
A mixture of sulfide (0.4 mmol) and 50% mCPBA (138 mg, 0.8 mmol) was stirred for 1 h in the appropriate solvent at -78 °C. The reaction mixture was washed with a concentrated solution of sodium hydrogen carbonate (20 mL). The aqueous layer was washed with dichloromethane (20 mL) and the combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was purified by flash chromatography (ethyl acetate) to yield the sulfoxide. **246a:246b** solvents: chloroform (yield 11%), chloroform:methanol, 1:1 (yield 16%) and chloroform:hexane, 1:1 (yield 34%). **247a:247b** solvents: chloroform (yield

14%), chloroform:methanol, 1:1 (yield 15%) and chloroform:hexane, 1:1 (yield 24%).

Diastereomeric ratios were determined by inspection of the ^1H NMR. All data was consistent with that expected for a mixture of diastereomers of **246a:246b** or **247a:247b**.

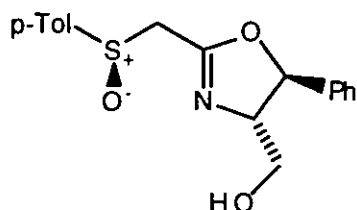
Data for the separate diastereomers is detailed below.

(4S,5S,S_s)-4,5-Dihydro-4-hydroxymethyl-5-phenyl-2-[(4-methylphenyl)methylsulfinyl]-methyl-1,3-oxazole 246a



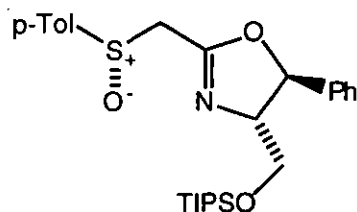
A solution of (4*S*,5*S*)-4,5-dihydro-4-hydroxymethyltriisopropylsilyl ether-5-phenyl-2-[(4-methylphenyl)methylsulfinyl]-1,3-oxazole (280 mg, 0.58 mmol) in THF (10 mL) was stirred with a 1 M solution of tetrabutylammonium fluoride (0.7 mL, 0.7 mmol) was stirred for an hour at ambient temperature. The reaction mixture was diluted with diethyl ether (30 mL) and washed with a saturated solution of aqueous ammonium chloride (30 mL). The organic phase was dried (MgSO_4) and concentrated *in vacuo*. The crude residue was purified by flash chromatography (ethyl acetate) to yield the *title compound* as a white solid (57 mg, 29%). M.p. 153-154 °C. (found M^+ , 329.0963. $\text{C}_{18}\text{H}_{19}\text{NO}_3\text{S}$ requires M^+ , 329.1086) $[\alpha]_{\text{D}}^{20}$ -200.5 (c 0.37, CHCl_3). $\nu_{\text{max.}}/\text{cm}^{-1}$ (nujol) 3360 (OH), 1666 (C=N) and 1050 (S=O). δ_{H} (250 MHz, CDCl_3) 7.60-7.16 (9 H, m, Ar-H), 5.34 (1 H, d, J 7.0, CH_2O), 4.12 (1 H, m, CH_2N), 3.96 (2 H, m, $\text{CHH}'\text{O}$ and $\text{CHH}'\text{S}(\text{O})$), 3.80 (1 H, d, J 14.3, $\text{CHH}'\text{S}(\text{O})$), 3.57 (1 H, m, $\text{CHH}'\text{O}$) and 2.42 (3 H, s, Ar- CH_3). δ_{C} (100.6 MHz, CDCl_3) 158.9 ($\text{C}=\text{N}$), 142.4, 141.0, 139.2, 138.6, 130.3, 130.1, 128.9, 128.6, 127.7 and 125.7 (arom. C), 83.2 (CHO), 74.0 (CHN), 63.5 ($\text{CH}_2\text{S}(\text{O})$) and 54.8 (CH_2O) and 22.2 (Ar- CH_3).

(4S,5S,R_S)-4,5-Dihydro-4-hydroxymethyl-5-phenyl-2-[(4-methylphenyl)methylsulfinyl]-methyl-1,3-oxazole 246b



The same procedure was used as detailed above. (29%) as a white solid. M.p. 156-157 °C. (found M^+ , 329.0956. $C_{18}H_{19}NO_3S$ requires M^+ , 329.1086). $[\alpha]_D^{20} +187.8$ (c 0.43, $CHCl_3$). ν_{max}/cm^{-1} (nujol) 3362 (OH), 1668 (C=N) and 1054 (S=O). δ_H (250 MHz, $CDCl_3$) 7.61-7.25 (9 H, m, Ar-H), 5.47 (1 H, d, J 7.3, CHO), 4.12 (1 H, m, CHN), 3.91 (2 H, m, CHH'O and CHH'S(O)), 3.76 (1 H, d, J 13.3, CHH'S(O)), 3.76 (1 H, m, CHH'O), 2.43 (3 H, s, Ar-CH₃) and 2.25 (1 H, br s, OH). δ_C (100.6 MHz, $CDCl_3$) 164.5 (C=N), 142.3, 141.2, 139.0, 138.7, 130.1, 129.8, 128.7, 128.6, 127.8 and 125.0 (arom. C), 84.4 (CHO), 74.3 (CHN), 64.2 (CH₂S(O)) 56.7 (CH₂O) and 22.4 (Ar-CH₃).

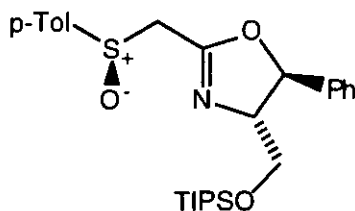
(4S,5S,S_S)-4,5-Dihydro-4-hydroxymethyltriisopropylsilylether-5-phenyl-2-[(4-methylphenyl)methylsulfinyl]-1,3-oxazole 247a



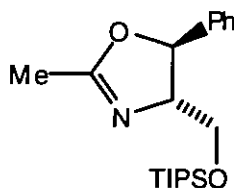
A solution of (4*S*,5*S*)-4,5-dihydro-4-hydroxymethyltriisopropylsilylether-2-methyl-5-phenyl-1,3-oxazole (500 mg, 1.44 mmol) in THF (5 mL) was cooled to -78 °C under an atmosphere of nitrogen. LDA (2.88 mL, 4.32 mmol as a 1.5 M solution in THF) was added dropwise to the flask and the mixture was stirred for 1 h at -78 °C. To this mixture was added (-)-menthyl-(*R*)-*p*-toluenesulfinate (847 mg, 2.88 mmol) in THF (5 mL) over a period of 5 mins. The solution was stirred at -78 °C for 2 h before being allowed to warm to ambient temperature. The reaction mixture was washed with saturated ammonium chloride solution

(20 mL) and the aqueous phase was washed with dichloromethane (5 x 30 mL). The combined organic phases were dried (Na₂SO₄) and concentrated *in vacuo* to leave an oily residue. This was purified by flash chromatography (light petroleum:ether, 1:2) to yield the *title compound* as a pale yellow oil (426 mg, 61%). (found M⁺, 485.2406. C₂₇H₃₉NO₃SSi requires M⁺, 485.2420). [α]_D²⁰ -145.3 (*c* 0.99, CHCl₃). ν_{max}./cm⁻¹ (neat) 1670 (C=N), 1046 (S=O). δ_H (250 MHz, CDCl₃) 7.64-7.19 (9 H, m, Ar-H), 5.45 (1 H, d, *J* 6.4, CHO), 4.05 (1 H, m, CHN), 3.93 (2 H, m, CHH'O and CHH'S(O)), 3.68 (1 H, d, *J* 13.3, CHH'S(O)), 3.59 (1 H, dd, *J* 9.9 and 7.2, CHH'O), 2.40 (3 H, s, Ar-CH₃) and 1.11-1.03 (21 H, m, 3 x CH(CH₃)₂). δ_C (63 MHz, CDCl₃) 159.1 (C=N), 142.3, 140.3, 129.9, 128.5, 128.0, 125.4 and 124.5 (arom. C), 84.4 (CHO), 76.6 (CHN), 65.1 (CH₂S(O)), 55.9 (CH₂O), 21.4 (Ar-CH₃), 17.7 (CH(CH₃)₂) and 11.8 (CH(CH₃)₂).

(4*S*,5*S*,*R*₅)-4,5-Dihydro-4-hydroxymethyltriisopropylsilylether-5-phenyl-2-[(4-methylphenyl)methylsulfinyl]-1,3-oxazole **247b**



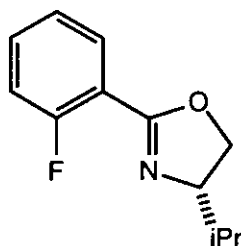
The same procedure was used as detailed above. (64%) as a pale yellow oil. (found M⁺, 485.2406. C₂₇H₃₉NO₃SSi requires M⁺, 485.2420). [α]_D²⁰ +47.6 (*c* 0.21, CHCl₃). ν_{max}./cm⁻¹ (neat) 1671 (C=N), 1047 (S=O). δ_H (250 MHz, CDCl₃) 7.60-7.27 (9 H, m, Ar-H), 5.45 (1 H, d, *J* 6.4, CHO), 4.03 (1 H, m, CHN), 3.94 (2 H, m, CHH'O and CHH'S(O)), 3.67 (1 H, d, *J* 13.3, CHH'S(O)), 3.59 (1 H, dd, *J* 9.9 and 7.2, CHH'O), 2.39 (3 H, s, Ar-CH₃) and 1.22-1.04 (21 H, m, 3 x CH(CH₃)₂). δ_C (63 MHz, CDCl₃) 159.5 (C=N), 142.1, 140.2, 129.9, 128.5, 128.0, 125.5 and 124.3 (arom. C), 84.5 (CHO), 76.4 (CHN), 65.1 (CH₂S(O)), 55.8 (CH₂O), 21.4 (Ar-CH₃), 17.9 (CH(CH₃)₂) and 11.8 (CH(CH₃)₂).



A solution of (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol (1.14 g, 6.85 mmol) and methyl acetimidate (0.5 g, 4.56 mmol) in dichloromethane (30 mL) was stirred for 16 h at ambient temperature. The mixture was washed with water (50 mL) and the aqueous phase washed with dichloromethane (3 x 30 mL). The combined organic phases were dried (Na₂SO₄) and concentrated *in vacuo* to yield the (4*S*,5*S*)-4,5-dihydro-4-hydroxymethyl-2-methyl-5-phenyl-1,3-oxazole as a colourless oil (0.79 g, 91%). A solution of (4*S*,5*S*)-4,5-dihydro-4-hydroxymethyl-2-methyl-5-phenyl-1,3-oxazole (200 mg, 1 mmol) in dichloromethane (25 mL) was treated with triethylamine (127 mg, 1.26 mmol) and stirred for 5 mins at room temperature. Triisopropylsilyltrifluoromethane sulfonate (385 mg, 1.26 mmol) was added to the mixture in one portion and the solution was stirred for a further 15 mins at room temperature. The mixture was washed with saturated ammonium chloride solution (50 mL) and the aqueous phase was washed with dichloromethane (3 x 50 mL). The combined organic phases were dried (Na₂SO₄) and concentrated *in vacuo* to produce an oily residue. This was purified by flash chromatography (light petroleum:ether, 1:1) to yield the *title compound* as a colourless oil (322 mg, 93 %). (found M^+ , 347.2278. C₂₀H₃₃NO₂Si requires M^+ , 347.2280). $[\alpha]_D^{20}$ -52.6 (c 0.57, CHCl₃). ν_{\max} /cm⁻¹ (neat) 1675 (C=N). δ_H (250 MHz, CDCl₃) 7.33-7.29 (5 H, m, Ar-H), 5.43 (1 H, d, J 5.8, CH₂O), 4.05 (2 H, m, CHN and CHH'O), 3.74 (1 H, dd, J 9.8 and 6.9, CHH'O), 2.08 (3 H, s, CH₃) and 1.16-1.04 (21 H, m, 3 x CH(CH₃)₂). δ_C (63 MHz, CDCl₃) 165.5 (C=N), 142.8, 128.5, 127.8 and 125.4 (arom. C), 83.5 (CHN), 76.4 (CHO), 65.4 (CH₂), 17.7 (CH(CH₃)₂), 13.9 (CH₃) and 11.7 (CH).

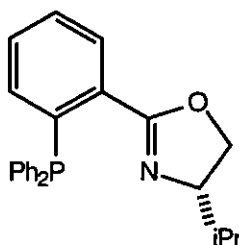
5.4 Experimental for Chapter 4

(4S)-4,5-Dihydro-2-(2-fluorophenyl)-4-isopropyl-1,3-oxazole 53



A catalytic quantity of zinc chloride (50 mg) in a flask was melted under vacuum and cooled under nitrogen. After cooling the flask was charged with chlorobenzene (20 mL), *L*-valinol (5 g, 48.5 mmol) and *o*-fluorobenzonitrile (8.8 g, 72.7 mmol). The solution was heated at reflux for 16 h. The solvent was removed under reduced pressure to give an oily residue which was dissolved in dichloromethane. The organic phase was washed with water (3 x 20 mL) before being dried (MgSO₄). The solvent was removed *in vacuo* to yield the crude product which was purified by flash chromatography (light petroleum:ethyl acetate, 7:1) to provide the *title compound* as a colourless oil (5.6 g, 56%). δ_{H} (400 MHz; CDCl₃) 7.89-7.12 (4H, m, Ar-H), 4.36 (1H, m, CHN), 4.16 (2H, m, CH₂O), 1.89 (1H, m, CH(CH₃)₂), 1.01 (3H, d, *J* 6.8, CHCH₃) and 0.92 (3H, d, *J* 6.8, CHCH₃). δ_{C} (100.6 MHz; CDCl₃) 162.9 (C=N), 132.0, 131.0, 123.7, 116.6 and 116.3 (arom. C), 71.2 (CH₂O), 69.2 (CHN), 31.0 (CH(CH₃)₂), 17.5 (CH₃) and 16.5 (CH₃).

(4S)-4,5-Dihydro-2-(2-Diphenylphosphinophenyl)-4-isopropyl-1,3-oxazole 54

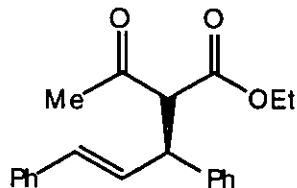


A flame dried flask was charged with potassium diphenylphosphide (29 mL as a 0.5M solution in THF, 14.5 mmol) under an inert atmosphere. The solution was heated to reflux

before the addition of (4*S*)-4,5-dihydro-2-(2-fluorophenyl)-4-isopropyl-1,3-oxazole (3 g, 14.5 mmol) as a solution in THF (5 mL). The mixture was heated at reflux for 6 h before the careful addition of water (20 mL). The aqueous layer was extracted with dichloromethane (5 x 20 mL). The combined organic phases were dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography (light petroleum:ethyl acetate, 5:1) to provide the *title compound* as a white solid. M.p. 82-83 °C. lit.²¹ 84-86 °C. $\nu_{\text{max}}/\text{cm}^{-1}$ (nujol) 1649 (C=N). δ_{H} (400 MHz; CDCl₃) 7.93 (1H, m, Ar-H), 7.69-7.22 (12H, m, Ar-H), 6.90 (1H, m, Ar-H), 4.11 (1H, m, CHN), 3.80 (2H, m, CH₂O), 1.51 (1H, m, CH(CH₃)₂), 0.81 (3H, d, *J* 6.7, CHCH₃) and 0.71 (3H, d, *J* 6.7, CHCH₃). δ_{C} (100.6 MHz; CDCl₃) 162.8 (C=N), 138.2-127.8 (arom. C), 72.7 (CHN), 69.7 (CH₂O), 32.9 (CH(CH₃)₂), 18.7 (CH₃) and 18.2 (CH₃).

Compounds **274**, **275**, **276**, **277**, and **278** were all prepared in a similar fashion. The method is detailed below.

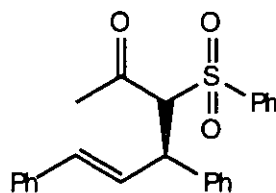
1,3-Diphenylhex-2-ene-4-ethylacetate-5-one **274**



Ethylacetoacetate (7.3 mL, 57.3 mmol) was slowly added to a slurry of sodium hydride (1.37 g, 57.3 mmol) in dry THF (20 mL) under an inert atmosphere at 0 °C. In a separate flask, under an inert atmosphere, a solution in dry THF (80 mL) of 1,3-diphenylprop-2-enylacetate (9.6 g, 38.2 mmol), [(η^3 -C₃H₅)PdCl]₂ (5.5 mg, 15 μ mol) and (4*S*)-4,5-dihydro-4-isopropyl-2-[2-(diphenylphosphino)phenyl]-1,3-oxazole (23 mg, 60 μ mol) was stirred for 15 mins at ambient temperature. Sodioethylacetoacetate was added dropwise onto this solution and the resultant mixture was stirred for 60 h at ambient temperature. The yellow slurry was diluted with dichloromethane (150 mL) and washed with a saturated aqueous ammonium chloride solution (200 mL). The organic layer was separated, dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography (ethyl acetate:light

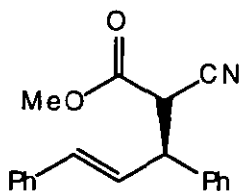
petroleum, 1:20) to yield the *title compound* as a colourless oil (11.1 g, 90%). (Found: M^+ , 322.1574. $C_{21}H_{22}O_3$ requires M^+ , 322.1569). $[\alpha]_D^{20}$ -17.2 (c 0.23, $CHCl_3$). ν_{max}/cm^{-1} (neat) 1743 (CO_2Et), 1717 ($C=O$), 1649 ($C=C$) and 1153 ($C-O$). δ_H (250 MHz; $CDCl_3$) 7.31-7.18 (10H, m, Ar-H), 6.47 (1H, d, J 9.2, PhHC=CH), minor diastereomer), 6.41 (1H, d, J 9.2, PhHC=CH, major diastereomer), 6.29 (1H, dd, J 12.6 and 8, PhHC=CH, major diastereomer), 6.24 (1H, dd, J 12.6 and 8, PhHC=CH, minor diastereomer), 4.30 (1H, d, J 8, $CH_3COCH, minor diastereomer), 4.26 (1H, d, J 8, $CH_3COCH, major diastereomer), 4.22-4.05 (3H, m, PhCH and OCH_2 , both diastereomers), 2.29 (3H, s, CH_3CO) and 1.28-1.18 (3H, m, OCH_2CH_3 , both diastereomers). δ_C (100.6 MHz; $CDCl_3$) 201.7 and 201.4 ($C=O$), 167.9 and 167.6 (CO_2Et), 140.2, 136.8, 131.8, 131.5, 129.5, 129.3, 128.9, 128.8, 128.5, 128.0, 127.9, 127.6, 127.5, 127.2, 126.4 and 126.3 (arom. C and $C=C$), 65.6 and 65.2 ($CHCO_2Et$), 61.6 and 61.4 (OCH_2), 48.9 and 48.7 (Ph-CH), 30.1 and 30.0 (CH_3O), 14.3 and 14.2 (CH_2CH_3).$$

1,3-Diphenyl-4-phenylsulfonylhex-2-ene-5-one **275**



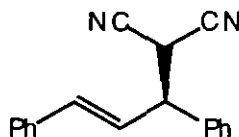
The nucleophile was sodiophenylsulphonylacetone (238 mg, 1.2 mmol). The *title compound* was isolated as a white solid (236 mg, 76%). M. p. 134-135 °C (Found: M^+ , 390.1297. $C_{24}H_{22}O_3S$ requires M^+ , 390.1290). $[\alpha]_D^{20}$ -58.9 (c 0.48, $CHCl_3$). ν_{max}/cm^{-1} (nujol) 1722 ($C=O$), 1598 ($C=C$), 1307 and 1144 (SO_2). δ_H (250 MHz; $CDCl_3$) 7.49-7.06 (15H, m, Ar-H), 6.41 (1H, d, J 15.4, Ph(H)C=CH), 6.09 (1H, dd, J 15.4 and 4.0, Ph(H)C=CH), 4.72 (1H, d, J 10.4, $CH_3COCH, minor diastereomer), 4.67 (1H, d, J 10.4, $CH_3COCH, major diastereomer), 4.33 (1H, t, J 9.5, PhCH) and 2.41 (3H, s, CH_3CO). δ_C (63 MHz; $CDCl_3$) 199.9 and 199.8 ($C=O$), 139.3, 136.5, 134.4, 134.0, 133.3, 132.9, 132.6, 129.7, 129.2, 128.8, 128.7, 128.6, 128.4, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 126.4 and 126.3 (arom. C and $C=C$), 79.7 and 79.3 ($CHCO$), 48.8 and 48.7 ((Ph-CH), 32.4 and 31.5 (CH_3O).$$

1,3-Diphenyl-4-methylacetatepent-2-enenitrile 276



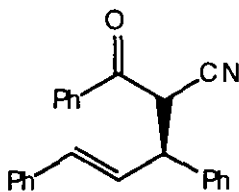
The nucleophile was sodiummethyl cyanoacetate (0.21 mL, 1.2 mmol). The *title compound* was isolated as a pale yellow oil (168 mg, 73%). (Found: M^+ , 291.1260. $C_{19}H_{17}NO_2$ requires M^+ , 291.1259). $[\alpha]_D^{20} +18.57$ (c 16.8, $CHCl_3$). ν_{max}/cm^{-1} (neat) 2250 (CN), 1747 (C=O), 1599 (C=C) and 1262 (C-O). δ_H (250 MHz; $CDCl_3$) for both diastereomers 7.41-7.24 (10H, m, Ar-H), 6.61-6.44 (2H, m, Ph(H)C=CH), 4.22 (1H, m, Ph-CH), 3.94 and 3.89 (1H, 2 x d, J 7.5, $CHCO_2Me$), 3.70 and 3.68 (3H, 2 x s, OCH_3). δ_C (63 MHz; $CDCl_3$) 165.6 and 165.3 ($\underline{C=O}$), 139.1, 134.3, 129.2, 129.1, 129.0, 128.8, 128.6, 128.5, 128.3, 128.1, 127.9, 127.8, 127.6, 126.7, 126.5 and 126.4 (arom. \underline{C} and $\underline{C=C}$), 115.2 (\underline{CN}), 53.2 (OCH_3), 49.8 and 49.5 (\underline{CHPh}), 45.3 and 44.9 (\underline{CHCN}).

2,4-Diphenyl-1,1-dicyanobut-3-ene 277



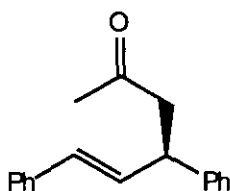
The nucleophile was sodiummalononitrile (0.15 mL, 2.4 mmol). The *title compound* was isolated as a colourless oil (190 mg, 93%). (Found: $M+NH_4^+$, 276.1501. $C_{18}H_{18}N_3$ requires M^+ , 276.1501). $[\alpha]_D^{20} +20.0$ (c 2.76, $CHCl_3$). ν_{max}/cm^{-1} (neat) 2360 (CN) and 1648 (C=C). δ_H (250 MHz; $CDCl_3$) 7.45-7.22 (10H, m, Ar-H), 6.68 (1H, d, J 15.7, PhCH=CH), 6.45 (1H, dd, J 15.7 and 7.4, PhCH=CH) and 4.12-4.03 (2H, m, NCCHCN and PhCH). δ_C (63 MHz; $CDCl_3$) 136.5, 135.8, 134.6, 129.4, 129.1, 128.9, 128.7, 128.6, 128.4, 127.9, 126.8 and 123.9 (arom. \underline{C} and $\underline{C=C}$), 111.7 (\underline{CN}), 49.7 (PhCH) and 30.2 (NCCHCN).

4-Benzoyl-1,3-diphenylpent-2-enenitrile 278



The nucleophile was sodiobenzoylacetonitrile (348 mg, 2.4 mmol). The *title compound* was isolated as a colourless oil (245 mg, 91%). (Found: M^+ , 337.1467. $C_{24}H_{19}NO$ requires M^+ , 337.1467). $[\alpha]_D^{20}$ -19.0 (c 2.80, $CHCl_3$). ν_{max}/cm^{-1} (neat) 2248 (CN) and 1693 (C=O). δ_H (250 MHz; $CDCl_3$) for both diastereomers 7.95-7.23 (15H, m, Ar-H), 6.54-6.35 (2H, m, $PhCH=CH$), 4.81 (1H, d, J 8.3, $CHCN$) and 4.32 (1H, dd, J 14.6 and 8.3, $PhCH$). δ_C (63 MHz; $CDCl_3$) 190.2 and 189.9 ($C=O$), 139.2, 134.2, 129.2, 129.1, 129.0, 128.7, 128.6, 128.5, 128.4, 128.1, 127.9, 127.8, 127.7, 126.6, 126.5 and 126.4 (arom. C and $C=C$), 116.2 (CN), 50.1 and 49.5 ($CHPh$), 46.3 and 45.9 ($CHCN$).

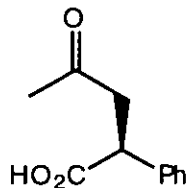
1,3-Diphenylhex-2-ene-5-one 282



A solution of 1,3-diphenylhex-2-ene-4-ethylacetate-5-one (9 g, 27.8 mmol), sodium chloride (2 g, 30.6 mmol), H_2O (1 mL) and DMSO (15 mL) was heated under reflux for 2 days. The resultant solution was diluted with brine (200 mL) and extracted with dichloromethane (6 x 50 mL). The combined organics were dried ($MgSO_4$) concentrated *in vacuo* and purified by flash chromatography (ethyl acetate:light petroleum, 1:10) to yield the *title compound* as a pale yellow oil (3.2 g, 45%). (Found: M^+ , 250.1360. $C_{18}H_{18}O$ requires M^+ , 250.1357). $[\alpha]_D^{20}$ +18.6 (c 0.75, $CHCl_3$). ν_{max}/cm^{-1} (neat) 1714 (C=O) and 1599 (C=C). δ_H (250 MHz; $CDCl_3$) 7.36-7.19 (10H, m, Ar-H), 6.35 (2H, m, $PhHC=CH$), 4.08, (1H, q, J 6.4, $PhCH$), 2.95 (2H, dd, J 6.4 and 1.7, CH_2CO) and 2.11 (3H, s, CH_3CO). δ_C (63 MHz;

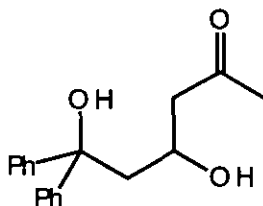
CDCl₃) 206.8 (CO), 142.9, 137.0, 130.8, 128.6, 128.4, 127.6, 127.2, 126.6, 126.2 and 125.9 (arom. C and C=C), 49.3 (CH₂), 43.9 (Ph-CH) and 33.3 (CH₃O).

4-Keto-2-phenylpentoic acid **287**



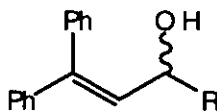
A solution of chromium (VI) oxide (177 mg, 1.77 mmol) in water (0.5 mL) and acetic acid (5 mL) was added dropwise with stirring to a solution of 1,3-diphenylhex-2-ene-5-one (150 mg, 0.59 mmol) in acetic acid (3 mL). The resultant darkly coloured solution was stirred at ambient temperature for 4 h before being poured onto water (20 mL). The aqueous mixture was extracted with ethyl acetate (3 x 15 mL), the combined organics were dried (MgSO₄) and concentrated *in vacuo* and purified by column chromatography (ethyl acetate:light petroleum, 1:6) to yield the *title compound* as a yellow oil (40 mg, 35%). (Found: M⁺, 192.0819. C₁₁H₁₂O₃ requires M⁺, 192.0786). [α]_D²⁰ +40.5 (*c* 3.28, CHCl₃). ν_{\max} /cm⁻¹ (neat) 3064 and 3030 (CO₂H), 1713 (CO₂H) and 1681 (C=O). δ_{H} (250 MHz; CDCl₃) 7.55-7.25 (5H, m, Ar-H), 5.00 (1H, dd, *J* 10.1 and 4.5, PhCH), 3.56 (1H, dd, *J* 15.0 and 10.1, CHH'), 2.95 (1H, dd, *J* 15.0 and 4.5, CHH') and 2.22 (3H, s, CH₃). δ_{C} (100.6 MHz; CDCl₃) 206.3 (CO), 171.6 (CO₂H), 130.3, 129.7, 129.3, 128.9, 128.5 and 128.3 (arom. C), 48.2 (CH), 46.7 (CH₂) and 29.6 (CH₃).

1,3-Dihydroxy-1,1-diphenylhexan-5-one **288**



A solution of peroxytrifluoroacetic acid was prepared by the careful addition of trifluoroacetic anhydride (0.11 mL, 1.6 mmol) to a stirred mixture of dichloromethane (3 mL) and hydrogen peroxide (5.7 mL, 27.5% aqueous solution) at 0 °C. The freshly prepared solution was then added slowly to a stirring solution of 1,3-diphenylhex-2-ene-5-one (200 mg, 0.79 mmol) and ammonium dihydrogenphosphate (271 mg, 2.36 mmol) in dichloromethane (3 mL) at 0 °C. The resultant mixture was stirred at ambient temperature for 16 h before being diluted with water (20 mL). Any remaining peroxide was destroyed by the careful addition of sodium thiosulfate. The resultant solution was extracted with diethyl ether (2 x 30 mL) and the combined organics were washed with a saturated solution of potassium carbonate (30 mL) before being dried over MgSO₄ and reduced *in vacuo* to yield the crude product as a yellow oil. The crude oil was purified by flash chromatography (ethyl acetate:light petroleum, 1:5) to yield the *title compound* as a pale yellow oil (142 mg, 63%). (Found: M+NH₄⁺-H₂O, 284.1651. C₁₈H₂₂NO₂ requires M+NH₄⁺-H₂O, 284.1650). ν_{max} /cm⁻¹ (neat) 3411 (OH), 1714 (C=O) and 1163 (C-O). δ_{H} (250 MHz; CDCl₃) 7.43-7.21 (10H, m, Ar-H), 3.30 (1H, d, *J* 16.7, CHH'), 3.22-3.15 (2H, m, CHOH and C(O)CHH'), 3.08 (1H, d, *J* 16.7, CHH'), 2.90 (1H, dd, *J* 14.6 and 6.9, C(O)CHH') and 2.15 (3H, s, CH₃CO). δ_{C} (100.6 MHz; CDCl₃) 205.6 (CO), 140.3, 137.4, 137.3, 128.8, 128.5, 127.9, 126.9, 126.7, 126.5 and 125.4 (arom. C), 66.7 (CHOH), 60.8 (Ph₂COH), 47.3 (CH₂OH), 35.6 (CH₂CO) and 30.8 (CH₃).

General Preparation of Alcohols 305-308



The preparation of alcohols 305-308 is typified by the preparation of alcohol 307.

Phenyl magnesium bromide (8 mL, 24 mmol, 3 M solution in diethyl ether) was added slowly to a stirring solution of β -phenylcinnamaldehyde (5 g, 24 mmol) in dry diethyl ether (50 mL) at 0 °C and under a nitrogen atmosphere. The resultant mixture was stirred at ambient temperature for 2 h before being quenched by the addition of a saturated ammonium chloride solution (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 30 mL)

and the combined organics were dried over MgSO_4 before being reduced *in vacuo* to give the crude alcohol. The crude alcohol was purified by flash chromatography (ethyl acetate:light petroleum, 1:10) to yield the desired alcohol.

1,1-Diphenyl-3-hydroxybut-2-ene 305

(90%) as a viscous oil. $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3333 (OH) and 1630 (C=C). δ_{H} (400 MHz; CDCl_3) 7.37-7.17 (10H, m, Ar-H), 6.07 (1H, d, J 9.1, $\text{Ph}_2\text{C}=\text{CH}$), 4.38 (1H, m, CHOH) and 1.32 (3H, d, J 6.1, CH_3). δ_{C} (100.6 MHz; CDCl_3) 141.7, 139.3, 132.3, 130.9, 129.9, 129.8, 129.4, 128.7, 128.2, 128.1, 127.6, 127.5, 127.4 and 127.2 (arom. C and $\text{C}=\text{C}$), 65.7 (CHOH) and 23.7 (CH_3).

1,1-Diphenyl-3-hydroxypent-2-ene 306

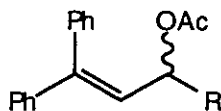
(61%) as a colourless oil. $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3333 (OH) and 1630 (C=C). δ_{H} (400 MHz; CDCl_3) 7.37-7.19 (10H, m, Ar-H), 6.04 (1H, d, J 9.2, $\text{Ph}_2\text{C}=\text{CH}$), 4.11 (1H, m, CHOH), 1.70-1.54 (3H, m, CH_2 and OH) and 0.91 (3H, t, J 7.5, CH_3). δ_{C} (100.6 MHz; CDCl_3) 143.8, 141.7, 139.1, 132.1, 130.9, 129.9, 129.5, 128.7, 128.3, 128.2, 127.6, 127.5, 127.4 and 127.1 (arom. C and $\text{C}=\text{C}$), 70.8 (CHOH), 30.6 (CH_2CH_3) and 9.8 (CH_2CH_3).

3-Hydroxy-1,1,3-triphenylprop-2-ene 307

(97%) as a colourless solid. $\nu_{\text{max}}/\text{cm}^{-1}$ (nujol) 3333 (OH) and 1630 (C=C). δ_{H} (250 MHz; CDCl_3) 7.41-7.23 (15H, m, Ar-H), 6.30 (1H, d, J 9.3, $\text{Ph}_2\text{C}=\text{CH}$), 5.31 (1H, d, J 9.3, CHOH) and 1.89 (1 H, br. s, OH). δ_{C} (63 MHz; CDCl_3) 143.2, 142.1, 137.9, 131.2, 129.7, 128.4, 127.8, 127.6, 127.5 and 116.8 (arom. C and $\text{C}=\text{C}$) and 71.4 (CHOH).

3-(4-Chlorophenyl)-1,1-diphenyl-3-hydroxyprop-2-ene 308

(84%) as a colourless oil. $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3333 (OH) and 1630 (C=C). δ_{H} (400 MHz; CDCl_3) 7.39-7.21 (15H, m, Ar-H), 6.23 (1H, d, J 9.4, $\text{Ph}_2\text{C}=\text{CH}$), 5.23 (1H, dd, J 9.4 and 3.3, CHOH) and 1.96 (1H, d, J 3.3, OH). δ_{C} (100.6 MHz; CDCl_3) 141.9, 141.3, 139.0, 133.3, 129.7, 129.6, 128.7, 128.5, 128.4, 127.9, 127.8, 127.6, 127.5 and 116.7 (arom. C and $\text{C}=\text{C}$) and 71.1 (CHOH).



The preparation of acetates **309-312** is typified by the preparation of acetate **311**.

Acetic anhydride (4.3 mL, 45.4 mmol) was added dropwise to a stirring solution of 1,1,3-triphenyl-3-hydroxyprop-1-ene (6.5 g, 22.7 mmol) and DMAP (10 mg, 82 μ mol) in pyridine (10 mL). The reaction was then stirred at ambient temperature for 16 h before being diluted with ethyl acetate (50 mL). The organic phase was washed with copper sulfate solution (6 x 30 mL) and then washed with water (50 mL). The organic phase was dried over MgSO_4 and reduced *in vacuo* to yield the crude product as an oil which was purified by flash chromatography (ethyl acetate:light petroleum, 1:20) to yield the desired acetate.

1,1-Diphenylbut-2-ene-3-acetate **309**

(75%) as a viscous oil. ν_{max} / cm^{-1} (neat) 1735 ($\text{C}=\text{O}$). δ_{H} (250 MHz; CDCl_3) 7.80-7.17 (10H, m, ArH), 6.03 (1H, d, J 9.0, $\text{Ph}_2\text{C}=\text{CH}$), 5.38 (1H, m, CHCH_3), 2.00 (3H, s, OAc) and 1.32 (3H, d, J 6.4, CHCH_3). δ_{C} (63 MHz; CDCl_3) 169.9 ($\text{C}=\text{O}$), 144.4, 140.3, 129.4, 128.8, 128.6, 128.3, 128.1, 127.9, 127.7, 127.6, 127.5, 127.3, 126.9 and 126.8 (arom. C and $\text{C}=\text{C}$), 69.2 (CHOAc), 21.2 ($\text{C}(\text{O})\text{CH}_3$) and 20.6 (CHCH_3).

1,1-Diphenylpent-2-ene-3-acetate **310**

(86%) as a colourless oil. (Found: M^+ , 280.1463. $\text{C}_{19}\text{H}_{20}\text{O}_2$ requires M^+ , 280.1463). ν_{max} / cm^{-1} (neat) 1735 ($\text{C}=\text{O}$). δ_{H} (250 MHz; CDCl_3) 7.42-7.20 (10H, m, Ar-H), 6.00 (1H, d, J 9.1, $\text{Ph}_2\text{C}=\text{CH}$), 5.26 (1H, m, CHOAc), 2.01 (3H, s, OAc), 1.67 (2H, m, CH_2CH_3) and 0.86 (3H, t, J 7.5, CH_2CH_3). δ_{C} (100.6 MHz; CDCl_3) 170.1 ($\text{C}=\text{O}$), 144.8, 141.7, 139.1, 129.6, 128.3, 128.2, 127.7, 127.5, 127.4 and 126.9 (arom. C and $\text{C}=\text{C}$), 74.0 (CHOAc), 28.1 (CH_2CH_3), 21.2 ($\text{C}(\text{O})\text{CH}_3$) and 9.5 (CH_2CH_3).

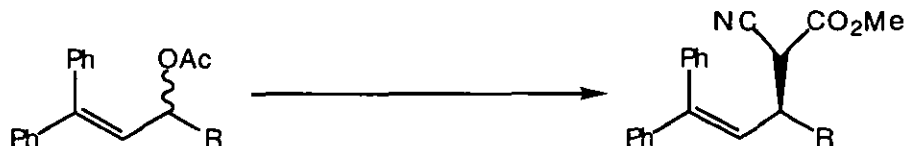
1,1,3-Triphenylprop-2-ene-3-acetate 311

(85%) as a colourless solid. ν_{\max} /cm⁻¹ (nujol) 1735 (C=O). δ_{H} (250 MHz; CDCl₃) 7.52-7.25 (15H, m, Ar-H), 6.28 (2H, m, Ph₂C=CH and CH₂OAc) and 2.02 (3H, s, OAc). δ_{C} (63 MHz; CDCl₃) 170.0 (C=O), 144.5, 141.2, 140.1, 129.4, 128.6, 128.5, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 126.8, 126.5 and 126.1 (arom. C and C=C), 74.0 (CH₂OAc) and 21.3 (C(O)CH₃).

3-(4-Chlorophenyl)-1,1-diphenylprop-2-ene-3-acetate 312

(85%) as a colourless oil. ν_{\max} /cm⁻¹ (neat) 1735 (C=O). δ_{H} (250 MHz; CDCl₃) 7.40-7.15 (14H, m, Ar-H), 6.25 (2H, m, Ph₂C=CH and CH₂OAc) and 2.05 (3H, s, OAc). δ_{C} (100.6 MHz; CDCl₃) 171.1 (C=O), 145.0, 141.1, 138.8, 138.7, 133.8, 129.5, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.5, 125.7 and 122.9 (arom. C and C=C), 73.5 (CH₂OAc) and 21.2 (C(O)CH₃).

General Procedure for the Palladium Catalysed Allylic Alkylation 313-316



The preparation of **313-316** is typified by the preparation of 1,1-diphenyl-3-ethyl-4-methylacetatepent-2-enenitrile **314**.

Methyl cyanoacetate (0.19 mL, 2.1 mmol) was added slowly to a slurry of sodium hydride (51 mg, 2.1 mmol) in dry THF (2 mL) and DMF (1 mL) at 0 °C whilst under a nitrogen atmosphere. The resultant anion was added to a solution of 1,1-diphenylpent-1-enyl-3-acetate (200 mg, 0.7 mmol), [(η³-C₃H₅)PdCl]₂ (7 mg, 19 μmol) and (4*S*)-4,5-dihydro-4-isopropyl-2-[2-(diphenylphosphino)phenyl]-1,3-oxazole (28 mg, 75 μmol) in dry THF (1 mL) and DMF (0.5 mL) which had been stirred under an inert atmosphere for 15 mins at ambient temperature. The reaction was monitored by tlc for the disappearance of acetate. Once all the acetate had been converted to product (36-48 h) the reaction was quenched with ammonium chloride solution. The aqueous phase was extracted with dichloromethane (3 x

30 mL), the combined organic phases were dried over MgSO_4 and concentrated *in vacuo* to give the crude product which was purified by flash chromatography (ethyl acetate:light petroleum, 1:10) to yield the desired product.

1,1-Diphenyl-3-methyl-4-methylacetatepent-2-enenitrile 313

(78%) as a viscous pale yellow solid. M.p. 69-70 °C. (Found: M^+ , 305.1416. $\text{C}_{20}\text{H}_{19}\text{NO}_2$ requires M^+ , 305.1416). $[\alpha]_{\text{D}}^{20}$ -67.4 (*c* 0.39, CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$ (nujol) 2252 (CN) and 1748 (C=O). δ_{H} (250 MHz; CDCl_3) 7.43-7.12 (10H, m, Ar-H), 6.02 and 5.96 (1H, d, *J* 10.5, $\text{Ph}_2\text{C}=\text{CH}$), 3.80 and 3.79 (3H, s, OCH_3), 3.45 (1H, d, *J* 6.0, CHCO_2Me), 3.17-3.06 (1H, m, CHCH_3) and 1.26 (3H, t, *J* 7.0, CHCH_3). δ_{C} (100.6 MHz; CDCl_3) 171.1 ($\text{C}=\text{O}$), 146.7, 141.3, 138.7, 138.3, 129.4, 129.3, 129.2, 129.1, 129.0, 128.6, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.5, 124.6 and 123.4 (arom. C and $\text{C}=\text{C}$), 115.1 and 115.0 (CN), 60.4 (OCH_3), 45.3 (CHCO_2Me), 45.1 (CHCH_3) and 44.8 and 44.7 (CHCH_3).

1,1-Diphenyl-3-ethyl-4-methylacetatepent-2-enenitrile 314

(90%) as a yellow solid. M.p. 97-98 °C. (Found: M^+ , 319.1572. $\text{C}_{21}\text{H}_{21}\text{NO}_2$ requires M^+ , 319.1572). $[\alpha]_{\text{D}}^{20}$ -10.3 (*c* 0.35, CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$ (nujol) 2252 (CN) and 1748 (C=O). δ_{H} (250 MHz; CDCl_3) 7.43-7.12 (10H, m, Ar-H), 5.97 and 5.90 (1H, d, *J* 10.7, $\text{Ph}_2\text{C}=\text{CH}$), 3.72 and 3.67 (3H, s, OCH_3), 3.56 and 3.50 (1H, d, *J* 4.6, CHCO_2Me), 2.98-2.86 (1H, m, CHCH_2), 1.72-1.59 (2H, m, CH_2CH_3) and 0.98-0.90 (3H, m, CH_2CH_3). δ_{C} (100.6 MHz; CDCl_3) 166.0 and 165.9 ($\text{C}=\text{O}$), 146.1, 146.0, 139.2, 129.5, 129.4, 128.5, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 126.8 and 126.1 (arom. C and $\text{C}=\text{C}$), 115.5 and 115.2 (CN), 60.3 (OCH_3), 43.2, 42.8, 41.4 and 41.2 (CHCO_2Me and CHCH_2), 27.0 and 25.6 (CH_2CH_3) and 11.7 and 11.5 (CH_2CH_3).

4-Methylacetate-1,1,3-triphenylpent-2-enenitrile 315

(74%) as a yellow solid. M.p. 115-116 °C. (Found: M^+ , 367.1572. $\text{C}_{21}\text{H}_{21}\text{NO}_2$ requires M^+ , 367.1572). $[\alpha]_{\text{D}}^{20}$ -121.9 (*c* 0.48, CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$ (nujol) 2252 (CN) and 1748 (C=O). δ_{H} (250 MHz; CDCl_3) 7.39-7.05 (15H, m, Ar-H), 6.50 and 6.43 (1H, d, *J* 10.6, $\text{Ph}_2\text{C}=\text{CH}$), 4.24-4.10 (1H, m, PhCH), 3.80 (1H, m, CHCO_2Me) and 3.63 (3H, s, OCH_3). δ_{C}

(63 MHz; CDCl₃) 165.2 and 165.0 (C=O), 146.2, 145.2, 141.1, 141.3, 129.4, 129.3, 129.1, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 125.2 and 123.9 (arom. C and C=C), 115.3 and 115.2 (CN), 53.3 and 53.2 (OCH₃), 45.7, 45.4, 45.3 and 44.9 (CHCO₂Me and CHPh).

3-(4-Chlorophenyl)-1,1-diphenyl-4-methylacetatepent-2-enenitrile **316**

(81%) as a pale yellow oil. (Found: M⁺, 401.1183. C₂₁H₂₁NO₂ requires M⁺, 401.1182). [α]_D²⁰ -139.3 (c 3.0, CHCl₃). ν_{max}/cm⁻¹ (neat) 2252 (CN) and 1748 (C=O). δ_H (250 MHz; CDCl₃) 7.39-6.99 (14H, m, Ar-H), 6.45 and 6.38 (1H, d, *J* 10.5, Ph₂C=CH), 4.22-4.07 (1H, m, CHC₆H₄Cl), 3.81-3.75 (1H, m, CHCO₂Me) and 3.66 and 3.64 (3H, s, OCH₃). δ_C (100.6 MHz; CDCl₃) 165.7 (C=O), 144.8, 141.5, 139.2, 139.0, 129.4, 129.2, 128.6, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3 and 127.0 (arom. C and C=C), 115.4 and 115.2 (CN), 53.4 and 53.2 (OCH₃), 44.4 and 44.0 (CHCO₂Me) and 35.1 and 35.0 (CHC₆H₄Cl).

Procedure for the Krapcho Decarboxylation **322** and **323**



A solution of 4-methylacetate-1,1,3-triphenylpent-2-enenitrile (90 mg, 0.24 mmol), sodium chloride (50 mg, 0.8 mmol) and water (20 mg, 1 mmol) in DMSO (5 mL) was heated under reflux for 4 h. The reaction was cooled to ambient temperature before being diluted with ethyl acetate (50 mL). The organic phase was washed with water (3 x 20 mL) and brine (3 x 20 mL) before being dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash chromatography (ethyl acetate:light petroleum, 1:6) to yield the desired product.

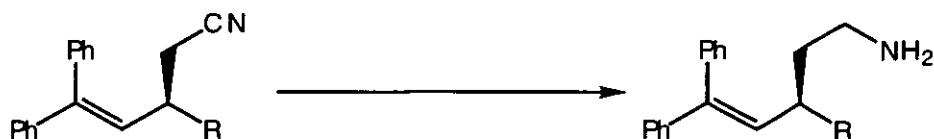
1,1-Diphenyl-3-methylpent-2-enenitrile 322

(74%) as a pale yellow oil. (Found: M^+ , 247.1361. $C_{18}H_{17}N$ requires M^+ , 247.1361). $[\alpha]_D^{20}$ -18.0 (c 0.60, $CHCl_3$). ν_{max}/cm^{-1} (neat) 2252 (CN) and 1599 (C=C). δ_H (250 MHz; $CDCl_3$) 7.43-7.16 (10H, m, Ar-H), 5.91 (1H, d, J 10.1, $Ph_2C=CH$), 2.78-2.67 (1H, m, $CHCH_3$), 2.32 (2H, d, J 6.3, CH_2CN) and 1.18 (3H, d, J 6.7, $CHCH_3$). δ_C (100.6 MHz; $CDCl_3$) 143.4, 141.5, 139.5, 130.5, 129.7, 129.4, 129.2, 128.9, 128.8, 128.7, 128.5, 128.2, 128.0, 127.9, 127.7, 127.5, 127.4 and 127.2 (arom. \underline{C} and $\underline{C=C}$), 118.3 (\underline{CN}), 34.1 ($\underline{CHCH_3}$), 25.0 ($\underline{CH_2CN}$) and 21.0 ($\underline{CHCH_3}$).

1,1,3-Triphenylpent-2-enenitrile 323

(80%) as a pale yellow solid. M.p. 81-82 °C. (Found: M^+ , 309.1517. $C_{18}H_{17}N$ requires M^+ , 309.1517). $[\alpha]_D^{20}$ -91.3 (c 0.46, $CHCl_3$). ν_{max}/cm^{-1} (nujol) 2252 (CN) and 1599 (C=C). δ_H (250 MHz; $CDCl_3$) 7.42-7.15 (15H, m, Ar-H), 6.29 (1H, d, J 10.4, $Ph_2C=CH$), 3.81 (1H, m, $PhCH$) and 2.71 (2H, d, J 6.9, CH_2CN). δ_C (100.6 MHz; $CDCl_3$) 144.3, 141.5, 141.4, 129.6, 129.1, 128.5, 128.2, 127.7, 127.6, 127.4, and 126.9 (arom. \underline{C} and $\underline{C=C}$), 118.1 (\underline{CN}), 41.5 ($PhCH$) and 25.3 ($\underline{CH_2CN}$).

Procedure for the Reduction with Lithium Aluminium Hydride 324 and 325



A solution of 1,1,3-triphenylpent-2-enenitrile (550 mg, 1.77 mmol) in dry diethyl ether (3 mL) was added slowly to a stirring slurry of lithium aluminium hydride (202 mg, 0.64 mmol) in diethyl ether (5 mL) at 0 °C whilst under a nitrogen atmosphere. The resultant solution was heated under reflux for 2 h before being cooled to 0 °C. The reaction was quenched by the careful addition of "wet" diethyl ether (20 mL). A 10% solution of sulfuric acid (10 mL) was added slowly to the white slurry and the mixture was stirred until all the precipitate had dissolved (15 mins). The aqueous phase was extracted with ethyl acetate (3 x 50 mL) and the

combined organics were dried over MgSO_4 before being reduced *in vacuo*. The crude product was purified by flash chromatography to yield the desired amine.

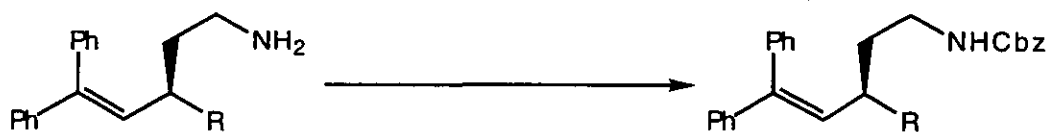
1,1-Diphenyl-3-methylpent-2-eneamine 324

(70%) as a colourless oil. (Found: M^+ , 251.1674. $\text{C}_{18}\text{H}_{21}\text{N}$ requires M^+ , 251.1674). $[\alpha]_{\text{D}}^{20}$ -86.0 (c 1.60, CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3405 (NH_2) and 1599 ($\text{C}=\text{C}$). δ_{H} (250 MHz; CDCl_3) 7.38-7.12 (10H, m, Ar-H), 5.82 (1H, d, J 10.3, $\text{Ph}_2\text{C}=\text{CH}$), 5.29 (2H, br. s, NH_2), 2.81-2.62 (2H, m, CH_2NH_2), 2.37-2.30 (1H, m, CHCH_3), 1.61 (2H, q, J 7.6, CHCH_2) and 1.02 (3H, d, J 6.6, CHCH_3). δ_{C} (100.6 MHz; CDCl_3) 142.0, 141.5, 140.1, 124.1, 129.8, 129.7, 129.6, 129.3, 129.2, 128.7, 128.6, 128.4, 128.1, 127.9, 127.3, 127.1 and 126.7 (arom. C and $\text{C}=\text{C}$), 39.4 (CH_2NH_2), 38.3 (CHCH_2), 30.8 (CHCH_3) and 21.4 (CHCH_3).

1,1,3-Triphenylpent-2-eneamine 325

(83%) as a white solid. M.p. 75-76 °C. (Found: M^+ , 313.1830. $\text{C}_{23}\text{H}_{23}\text{N}$ requires M^+ , 313.1830). $[\alpha]_{\text{D}}^{20}$ -89.7 (c 0.58, CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$ (nujol) 3405 (NH_2) and 1599 ($\text{C}=\text{C}$). δ_{H} (250 MHz; CDCl_3) 8.19 (2H, br. s, NH_2), 7.39-7.05 (15H, Ar-H), 6.17 (1H, d, J 10.4, $\text{Ph}_2\text{C}=\text{CH}$), 3.38 (1H, m, PhCH), 2.93-2.84 (1H, m, $\text{CHH}'\text{NH}_2$), 2.72-2.61 ($\text{CHH}'\text{NH}_2$) and 2.19-2.09 (2H, m, CHCH_2). δ_{C} (100.6 MHz; CDCl_3) 142.9, 142.8, 141.6, 139.4, 130.2, 129.6, 128.9, 128.5, 128.2, 127.4, 127.2, 127.1 and 126.8 (arom. C and $\text{C}=\text{C}$), 43.2 (PhCH), 38.5 (CH_2NH_2) and 34.5 (CHCH_2).

Procedure for N-Protection with Benzyl Chloroformate 327 and 328



Triethylamine (0.25 mL, 1.74 mmol) was added to a stirring solution of 1,1,3-triphenylpent-2-eneamine (500 mg, 1.59 mmol) and DMAP (10 mg, 82 μmol) in dichloromethane (10 mL). The resultant solution was stirred for 10 mins at ambient temperature before the dropwise addition of benzyl chloroformate (0.25 mL, 1.74 mmol). The reaction was then heated under

reflux for 2 h, cooled to ambient temperature and concentrated *in vacuo*. The crude product was purified by flash chromatography (ethyl acetate:light petroleum, 1:6) to yield the desired product.

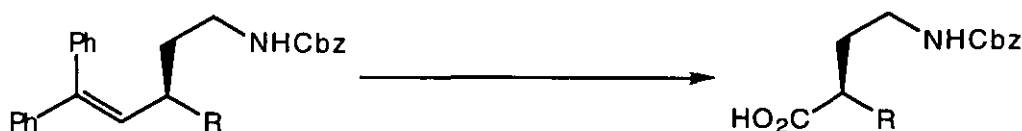
***N*-Benzyloxycarbonyl-1,1-diphenyl-3-pent-2-eneamine 327**

(81%) as a colourless oil. (Found: MH^+ , 386.2120. $C_{26}H_{28}NO_2$ requires MH^+ , 386.2137). $[\alpha]_D^{20}$ -41.0 (*c* 0.80, $CHCl_3$). ν_{max}/cm^{-1} (neat) 3424 and 3340 (NH), 1713 (C=O) and 1028 (C-O). δ_H (250 MHz; $CDCl_3$) 7.39-7.14 (15H, m, Ar-H), 5.84 (1H, d, *J* 10.3, $Ph_2C=CH$), 5.09 (2H, s, CH_2Ph), 4.48 (1H, br. s, $NHCbz$), 3.25-3.15 (1H, m, $CHH'NHCbz$), 3.07-2.99 (1H, m, $CHH'NHCbz$), 2.42-2.30 (1H, m, $CHCH_3$), 1.59-1.46 (2H, m, $CHCH_2$) and 1.05 (3H, d, *J* 6.6, $CHCH_3$). δ_C (100.6 MHz; $CDCl_3$) 156.2 ($C=O$), 142.2, 141.3, 140.2, 136.8, 134.6, 129.6, 128.7, 128.5, 128.4, 128.2, 128.0, 127.9, 127.1 and 127.0 (arom. C and $C=C$), 66.5 (CH_2Ph), 39.4 (CH_2NHCbz), 37.5 ($CHCH_2$), 31.6 ($CHCH_3$) and 21.4 ($CHCH_3$).

***N*-Benzyloxycarbonyl-1,1,3-triphenylpent-2-eneamine 328**

(70%) as a pale yellow oil. (Found: $M+NH_4^+$, 465.2542. $C_{31}H_{33}N_2O_2$ requires $M+NH_4^+$, 465.2542). $[\alpha]_D^{20}$ -82.6 (*c* 0.34, $CHCl_3$). ν_{max}/cm^{-1} (neat) 3424 and 3340 (NH), 1713 (C=O) and 1028 (C-O). δ_H (250 MHz; $CDCl_3$) 7.41-7.09 (20H, m, Ar-H), 6.21 (1H, d, *J* 10.5, $Ph_2C=CH$), 5.04 (2H, s, CH_2Ph), 4.51 (1H, br. s, NH), 3.50-3.40 (1H, m, $CHPh$), 3.25-3.01 (2H, m, CH_2NHCbz) and 1.93 (2H, q, *J* 7.2, $CHCH_2$). δ_C (100.6 MHz; $CDCl_3$) 156.2 (C=O), 144.3, 142.0, 141.9, 139.8, 136.6, 131.7, 131.0, 129.7, 128.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.3, 127.2 and 126.4 (arom. C and $C=C$), 66.5 (CH_2Ph), 42.9 ($CHPh$), 39.4 (CH_2NHCbz) and 37.1 ($CHCH_2$).

Procedure for the Oxidative Cleavage with Chromium Trioxide 329 and 330



A solution of chromium trioxide (1.27 g, 12.7 mmol) in glacial acetic acid (7 mL) was added slowly to a stirring solution of *N*-benzyloxycarbonyl-1,1,3-triphenylpent-2-eneamine (570

mg, 1.27 mmol) in glacial acetic acid (3 mL). The resultant solution was stirred for 16 h at ambient temperature before being poured onto water (50 mL). The aqueous phase was extracted with dichloromethane (6 x 20 mL) and the combined organics were dried over MgSO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (dichloromethane:light petroleum, 3:1 then dichloromethane:methanol, 9:1) to yield the desired acid.

***N*-Benzyloxycarbonyl-2-methyl-4-aminobutyric acid 329**

(75%) as a colourless oil. $[\alpha]_{\text{D}}^{20}$ -16.6 (*c* 0.29, CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3369 (CO_2H and NH), 1754 (CO_2H), 1722 ($\text{C}=\text{O}$). δ_{H} (400 MHz; CDCl_3) 7.57-7.16 (5H, m, ArH), 5.31 (2H, s, CH_2Ph), 3.85-3.79 (1H, m, $\text{CHH}'\text{NHCbz}$), 3.66-3.59 (1H, m, $\text{CHH}'\text{NHCbz}$), 2.56 (1H, m, CHCH_3), 2.23-2.15 (1H, m, CHCHH'), 1.66-1.61 (1H, m, CHCHH') and 1.22 (3H, d, *J* 7.0, CHCH_3). δ_{C} (100.6 MHz; CDCl_3) 176.4 (CO_2H), 151.7 ($\text{C}=\text{O}$), 128.9, 128.8, 128.5, 128.3, 128.2 and 128.0 (arom. C), 67.9 (CH_2Ph), 44.3 (CH_2NHCbz), 38.5 (CHCH_3), 26.5 (CHCH_2) and 15.3 (CHCH_3).

***N*-Benzyloxycarbonyl-2-phenyl-4-aminobutyric acid 330**

(61%) as a colourless oil. (Found: M^+ , 313.1314. $\text{C}_{18}\text{H}_{19}\text{NO}_4$ requires M^+ , 313.1314). $[\alpha]_{\text{D}}^{20}$ -15.8 (*c* 0.40, CHCl_3). $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3354 (CO_2H and NH), 1785 (CO_2H), 1717 ($\text{C}=\text{O}$). δ_{H} (250 MHz; CDCl_3) 7.60-7.20 (10H, m, Ar-H), 5.34-5.20 (3H, m, CHPh and CH_2Ph), 3.96-3.87 (1H, m, CHCHH'), 3.62-3.51 (1H, m, CHCHH') and 2.42 (2H, t, *J* 6.7, CH_2NHCbz). δ_{C} (100.6 MHz; CDCl_3) 197.5 (CO_2H), 153.7 ($\text{C}=\text{O}$), 133.4, 130.2, 129.3, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2 and 127.8 (arom. C), 67.9 (CH_2Ph), 52.7 (CHPh), 36.9 (CHCH_2) and 35.2 (CH_2NHCbz).



A solution of N-benzyloxycarbonyl-2-phenyl-4-aminobutyric acid (200 mg, 0.64 mmol) and 10% palladium on carbon powder (20 mg) in anhydrous methanol (5 mL) was stirred for 24 h under an atmosphere of hydrogen. The reaction mixture was filtered through celite[®], the celite[®] pad was washed with methanol (5 x 10 mL) and the filtrate was concentrated *in vacuo*. The resultant oil was dissolved in dichloromethane (20 mL) and the organic phase was extracted with water. The aqueous phase was then reduced *in vacuo* to yield the product.

2-Methyl-4-aminobutyric acid 331

(63%) as a white solid. M.p. 192-193 °C. lit.¹⁴⁵ 196-197 °C. (Found: M^+ , 117.0790. $C_5H_{11}NO_2$ requires M^+ , 117.0790). $[\alpha]_D^{20} +3.5$ (c 0.40, H_2O). lit.¹⁴⁵ $[\alpha]_D^{24} -6.7$ (c 2.77, H_2O). ν_{max}/cm^{-1} (KBr) 3290 (CO_2H and NH_2) and 1698 (CO_2H). δ_H (400 MHz; D_2O) 3.42-3.36 (2H, m, $\underline{CH_2NH_2}$), 2.63-2.57 (1H, m, $\underline{CHCH_3}$), 2.40 (1H, m, $\underline{CHCHH'}$), 1.87-1.78 (1H, m, $\underline{CHCHH''}$) and 1.20 (3H, d, J 6.9, $\underline{CHCH_3}$). δ_C (100.6 MHz; D_2O) 184.9 ($\underline{CO_2H}$), 40.3 ($\underline{CH_2NH_2}$), 36.6 ($\underline{CHCH_3}$), 29.3 ($\underline{CHCH_2}$) and 15.6 ($\underline{CHCH_3}$).

2-Phenyl-4-aminobutyric acid 332

(65%) as a white solid. M.p. 152-153 °C. (Found: $M-H^+$, 178.0868. $C_{10}H_{12}NO_2$ requires M^+ , 178.0868). $[\alpha]_D^{20} +9.7$ (c 0.62, H_2O). ν_{max}/cm^{-1} (KBr) 3288 (CO_2H and NH_2) and 1692 (CO_2H). δ_H (250 MHz; D_2O) 7.91-7.34 (5H, m, $\underline{Ar-H}$), 4.80 (D_2O peak obscuring \underline{CHPh}), 3.61-3.37 (2H, m, $\underline{CH_2NH_2}$) and 2.69-2.44 (2H, m, $\underline{CHCH_2}$). δ_C (100.6 MHz; D_2O) 179.7 ($\underline{CO_2H}$), 141.4, 131.8, 129.3, 128.8, 125.6 and 125.2 (arom. \underline{C}), 79.1 (\underline{CHPh}), 39.1 ($\underline{CH_2NH_2}$) and 38.2 ($\underline{CHCH_2}$).

Chapter Six

X-Ray Structure Report

6.1 Experimental

Data Collection

A clear block crystal of $C_{14}H_{17}NO_2$ having approximate dimensions of 0.28 x 0.32 x 0.46 mm was mounted on a glass fibre. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Cu-K α radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centred reflections in the range $70.48 < 2\theta < 74.38^\circ$ corresponded to a primitive orthorhombic cell with dimensions:

$$a = 11.990(2) \text{ \AA}$$

$$b = 14.566(2) \text{ \AA}$$

$$c = 7.379(4) \text{ \AA}$$

$$V = 1288.6(6) \text{ \AA}^3$$

For $Z = 4$ and F.W. = 231.29, the calculated density is 1.19 g/cm³. The systematic absences of:

$$h00: h \neq 2n$$

$$0k0: k \neq 2n$$

$$00l: l \neq 2n$$

uniquely determine the space group to be:

$$P2_12_12_1 (\#19)$$

The data was collected at a temperature of $20 \pm 1^\circ\text{C}$ using the ω scan technique to a maximum 2θ value of 120.1° . Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.30° with a take-off angle of 6.0° . Scans of $(1.26 + 0.35 \tan \theta)^\circ$ were made at a speed of 16.0 $^\circ$ /min (in omega). The weak reflections

($I < 15.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400 mm, the computer controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

6.1.1 Data Reduction

A total of 1157 reflections was collected. The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, μ , for Cu-K α radiation is 6.0 cm⁻¹. An empirical absorption correction factor using the program DIFABS¹ was applied which resulted in transmission factors ranging from 0.80 to 1.00. The data was corrected for Lorentz and polarisation effects. A correction for secondary extinction was applied (co-efficient = 2.30654e-06).

6.1.2 Structure Solution and Refinement

The structure was solved by direct methods² and expanded using Fourier techniques.³ The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement⁴ was based on 933 observed reflections ($I > 3.00\sigma(I)$) and 155 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of:

$$R = \sum \|F_o\| - \|F_c\| / \sum \|F_o\| = 0.033$$

$$R_w = \{ \sum w(F_o - F_c)^2 / \sum w F_o^2 \}^{1/2} = 0.028$$

The standard deviation of an observation of unit weight ⁵ was 3.75. The weighting scheme was based on counting statistics and included a factor ($p = 0.003$) to downweight the intense reflections. Plots of $\sum w(F_o - F_c)^2$ versus F_o , reflection order in data collection θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.07 and -0.08 e⁻/Å³, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.⁶ Anomalous dispersion effects were included in F_{calc} ;⁷ the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.⁸ The values for the mass attenuation co-efficients are those of Creagh and Hubbel.⁹ All calculations were performed using teXsan¹⁰ crystallographic software package of Molecular Structure Corporation.

6.1.3 References

1. DIFABS: Walker, N. & Stuart, Acta Cryst. A39, 158-166 (1983). An empirical absorption correction program.
2. SIR92: Altomare, A., Burla, M. C., Camalli, M., Cascarano, M., Giacovazzo, C., Guagliardi, A., Polidori, G. (1994). J. Appl. Cryst., in preparation.
3. DIRDIF92: Beurskens, P. T., Admiraal, G., Beurskens, G., Bosman, W. P., Garcia-Granda, S., Gould, R. O., Smits, J. M. M. and Smykalla, C. (1992). The DIRDIF program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.
4. Least-Squares:

Function minimised: $\sum w(F_o - F_c)^2$

where $w = \{\sigma^2(F_o)\}^{-1} = 4F_o^2 / \sigma^2(F_o^2)$

$\sigma^2(F_o^2) = s^2(C + R^2 B) + (pF_o^2)^2/Lp^2$

S = Scan rate

C = Total integrated peak count

R = Ratio of scan time to background counting time

B = Total background count

L_p = Lorentz-polarisation factor

p = p-factor

5. Standard deviation of an observation of unit weight:

$$\{\sum \omega(F_o - F_c)^2 / (N_o - N_v)\}^{1/2}$$

where: N_o = number of observations

N_v = number of variables

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6.1.4 Experimental Details

A. Crystal Data

Empirical Formula	$C_{14}H_{17}NO_2$
Formula Weight	231.29
Crystal Colour, Habit	clear, block
Crystal Dimensions	0.28 x 0.32 x 0.46 mm
Crystal System	orthorhombic
Lattice Type	Primitive
No. of Reflections Used for Unit	
Cell Determination (2θ range)	25 (70.5 - 74.4°)
Omega Scan Peak Width at Half Height	0.30°

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimised	$\Sigma w(F_o - F_c)^2$
Least Square Weights	$\{ \sigma^2(F_o) \}^{-1} = 4 F_o^2 / \sigma^2(F_o^2)$
p-factor	0.003
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I > 3.00 \sigma(I)$)	933
No. Variables	155
Reflection/Parameter Ratio	6.02
Residuals: R; Rw	0.033; 0.028
Goodness of Fit Indicator	3.75
Max Shift/Error in Final Cycle	0.01
Maximum peak in Final Diff. Map	$0.07 \text{ e}^- / \text{\AA}^3$
Minimum peak in Final Diff. Map	$-0.08 \text{ e}^- / \text{\AA}^3$

Table 1. Atomic co-ordinates and B_{iso} / B_{eq}

atom	x	y	z	B_{eq}
O(1)	0.7303(1)	0.1593	0.9794(4)	7.30(6)
O(7)	0.4666(2)	-0.0217(2)	0.9466(4)	8.23(7)
N(4)	0.6488(2)	-0.0095(2)	0.9483(4)	6.98(7)
C(1)	0.6319(2)	0.1873(2)	0.9909(5)	6.33(8)
C(2)	0.5395(2)	0.1277(2)	0.9845(6)	6.97(9)
C(3)	0.5540(2)	0.0357(2)	0.9606(5)	6.56(9)
C(5)	0.6343(2)	-0.1062(2)	0.9034(5)	6.66(9)
C(6)	0.5074(3)	-0.1147(2)	0.9283(6)	7.56(10)
C(8)	0.7025(2)	-0.1704(2)	1.0202(5)	6.99(9)
C(9)	0.8266(2)	-0.1487(2)	1.0037(5)	7.88(10)
C(10)	0.6788(3)	-0.2696(2)	0.9665(8)	10.9(1)

C(11)	0.6126(2)	0.2888(2)	1.0127(5)	6.28(8)
C(12)	0.5115(2)	0.3259(2)	1.0568(6)	6.87(9)
C(13)	0.4994(3)	0.4195(2)	1.0762(6)	7.9(1)
C(14)	0.5877(3)	0.4769(2)	1.0496(8)	9.1(1)
C(15)	0.6898(3)	0.4406(2)	1.0007(9)	10.2(1)
C(16)	0.7014(2)	0.3471(2)	0.9850(8)	9.0(1)
H(2)	0.4663	0.1519	0.9969	8.3650
H(4)	0.7232	0.0218	0.9519	11.6835
H(5)	0.6526	-0.1158	0.7796	7.9916
H(6a)	0.4907	-0.1492	1.0341	9.0752
H(6b)	0.4747	-0.1435	0.8258	9.0752
H(8)	0.6807	-0.1621	1.1429	8.3916
H(9b)	0.8501	-0.1587	0.8824	9.4529
H(9c)	0.8392	-0.0864	1.0357	9.4529
H(9a)	0.8676	-0.1875	1.0828	9.4529
H(10b)	0.7048	-0.2801	0.8467	13.1182
H(10c)	0.7161	-0.3099	1.0478	13.1182
H(10a)	0.6008	-0.2807	0.9717	13.1182
H(12)	0.4490	0.2869	1.0742	8.2470
H(13)	0.4288	0.4443	1.1084	9.5107
H(14)	0.5791	0.5413	1.0645	10.8989
H(15)	0.7514	0.4799	0.9781	12.2612
H(16)	0.7721	0.3222	0.9545	10.7866

$$B_{eq} = 8/3 \pi^2 (U_{11}(aa^*)^2 + U_{11}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^* \cos \gamma + 2U_{13}aa^*cc^* \cos \beta + 2U_{23}bb^*cc^* \cos \alpha)$$

Table 2. Anisotropic Displacement Parameters.

atom	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
O(1)	0.0498(9)	0.101(2)	0.127(2)	0.006(1)	-0.001(1)	0.008(2)
O(7)	0.061(1)	0.105(2)	0.147(2)	-0.006(1)	-0.003(2)	-0.014(2)
N(4)	0.055(1)	0.090(2)	0.120(2)	0.004(1)	0.000(2)	0.004(2)
C(1)	0.052(2)	0.101(2)	0.088(2)	0.003(2)	-0.003(2)	0.009(2)
C(2)	0.053(2)	0.092(2)	0.119(3)	0.004(2)	0.003(2)	-0.001(3)
C(3)	0.054(2)	0.103(2)	0.092(3)	-0.006(2)	-0.004(2)	-0.001(2)
C(5)	0.069(2)	0.097(2)	0.087(2)	-0.005(2)	-0.001(2)	-0.009(2)
C(6)	0.074(2)	0.104(3)	0.110(3)	-0.008(2)	-0.003(2)	-0.011(3)
C(8)	0.071(2)	0.087(2)	0.108(3)	0.002(2)	0.001(2)	0.001(2)
C(9)	0.080(2)	0.104(3)	0.116(3)	0.011(2)	0.000(2)	0.004(3)
C(10)	0.120(3)	0.085(3)	0.210(5)	-0.003(2)	-0.005(4)	-0.005(3)
C(11)	0.052(1)	0.093(2)	0.094(2)	-0.001(2)	-0.007(2)	0.010(2)
C(12)	0.061(2)	0.089(2)	0.111(3)	0.000(2)	0.005(2)	0.007(2)
C(13)	0.072(2)	0.101(3)	0.127(3)	0.008(2)	0.008(2)	0.005(3)
C(14)	0.087(2)	0.088(3)	0.171(4)	-0.007(2)	-0.005(3)	0.003(3)
C(15)	0.071(2)	0.107(3)	0.210(6)	-0.018(2)	-0.003(4)	0.015(4)
C(16)	0.055(2)	0.104(3)	0.183(5)	-0.005(2)	-0.006(3)	0.008(4)

The general temperature factor expression:

$$\exp(-2\pi^2(a^2U_{11}h^2 + b^2U_{22}k^2 + c^2U_{33}l^2 + 2a*b*U_{12}hk + 2a*c*U_{13}hl + 2b*c*U_{23}kl))$$

Table 3. Bond Lengths (Å)

atom	atom	distance	atom	atom	distance
O(1)	C(1)	1.250(3)	O(7)	C(3)	1.344(3)
O(7)	C(6)	1.446(3)	N(4)	C(3)	1.316(3)
N(4)	C(5)	1.459(3)	C(1)	C(2)	1.408(4)

C(1)	C(11)	1.505(3)	C(2)	C(3)	1.363(4)
C(5)	C(6)	1.538(4)	C(5)	C(8)	1.511(4)
C(8)	C(9)	1.526(4)	C(8)	C(10)	1.526(4)
C(11)	C(12)	1.367(4)	C(11)	C(16)	1.377(4)
C(12)	C(13)	1.378(4)	C(13)	C(14)	1.363(4)
C(14)	C(15)	1.382(5)	C(15)	C(16)	1.373(4)

Table 4. Bond Lengths (Å)

atom	atom	distance	atom	atom	distance
N(4)	H(4)	1.00	C(2)	H(2)	0.96
C(5)	H(5)	0.95	C(6)	H(6a)	0.95
C(6)	H(6b)	0.95	C(8)	H(8)	0.95
C(9)	H(9b)	0.95	C(9)	H(9c)	0.95
C(9)	H(9a)	0.95	C(10)	H(10b)	0.94
C(10)	H(10c)	0.95	C(10)	H(10a)	0.95
C(12)	H(12)	0.95	C(13)	H(13)	0.95
C(14)	H(14)	0.95	C(15)	H(15)	0.95
C(16)	H(16)	0.95			

Table 5. Bond Angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
C(3)	O(7)	C(6)	109.0(2)	C(3)	N(4)	C(5)	113.3(3)
O(1)	C(1)	C(2)	122.6(3)	O(1)	C(1)	C(11)	118.2(3)
C(2)	C(1)	C(11)	119.2(3)	C(1)	C(2)	C(3)	120.6(3)
O(7)	C(3)	N(4)	110.9(3)	O(7)	C(3)	C(2)	121.4(3)
N(4)	C(3)	C(2)	127.6(3)	N(4)	C(5)	C(6)	99.6(3)
N(4)	C(5)	C(8)	113.8(3)	C(6)	C(5)	C(8)	114.7(3)
O(7)	C(6)	C(5)	105.7(3)	C(5)	C(8)	C(9)	110.7(3)
C(5)	C(8)	C(10)	109.7(3)	C(9)	C(8)	C(10)	110.9(3)
C(1)	C(11)	C(12)	123.4(3)	C(1)	C(11)	C(16)	118.1(3)

C(12)	C(11)	C(16)	118.4(3)	C(11)	C(12)	C(13)	120.7(3)
C(12)	C(13)	C(14)	120.7(3)	C(13)	C(14)	C(15)	119.4(3)
C(14)	C(15)	C(16)	119.5(3)	C(11)	C(16)	C(15)	121.4(3)

Table 6. Bond Angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
C(3)	N(4)	H(4)	122.7	C(5)	N(4)	H(4)	123.5
C(1)	C(2)	H(2)	119.6	C(3)	C(2)	H(2)	119.8
N(4)	C(5)	H(5)	109.2	C(6)	C(5)	H(5)	109.3
C(8)	C(5)	H(5)	109.7	O(7)	C(6)	H(6a)	110.2
O(7)	C(6)	H(6b)	109.9	C(5)	C(6)	H(6a)	110.6
C(5)	C(6)	H(6b)	110.8	H(6a)	C(6)	H(6b)	109.6
C(5)	C(8)	H(8)	107.8	C(9)	C(8)	H(8)	108.3
C(10)	C(8)	H(8)	109.3	C(8)	C(9)	H(9b)	109.4
C(8)	C(9)	H(9c)	109.3	C(8)	C(9)	H(9a)	108.9
H(9b)	C(9)	H(9c)	109.8	H(9b)	C(9)	H(9a)	110.0
H(9c)	C(9)	H(9a)	109.3	C(8)	C(10)	H(10b)	109.5
C(8)	C(10)	H(10c)	108.3	C(8)	C(10)	H(10a)	108.9
H()	C(10)	H(10c)	110.1	H(10b)	C(10)	H(10a)	110.8
H()	C(10)	H(10a)	109.3	C(11)	C(12)	H(12)	120.4
C(13)	C(12)	H(12)	119.0	C(12)	C(13)	H(13)	119.9
C(14)	C(13)	H(13)	119.5	C(13)	C(14)	H(14)	120.3
C(15)	C(14)	H(14)	120.3	C(14)	C(15)	H(15)	119.9
C(16)	C(15)	H(15)	120.6	C(11)	C(16)	H(16)	119.4
C(15)	C(16)	H(16)	119.2				

Table 7. Non-bonded contacts out to 3.60 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
O(1)	C(12)	3.389(3)	55703	O(1)	C(13)	3.450(4)	55703
O(1)	C(8)	3.486(5)	65402	O(1)	C(9)	3.578(5)	65402

O(7) C(15) 3.545(4) 45703

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges *a*, *b* and *c*. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the *a*-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the co-ordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC of an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the co-ordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the *a* axis, +2 cell translations along the *b* axis, and 0 cell translations along the *c* axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	X	Y	Z	(2)	1/2-X	-Y	1/2+Z
(3)	1/2+X	1/2-Y	-Z	(4)	-X	1/2+Y	1/2-Z

Chapter Seven

References

7.1 References

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