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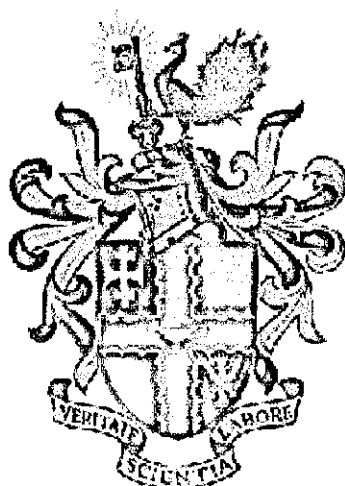
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Asymmetric Synthesis.
Approaches via Enantiomerically Pure Acetal and
Oxazoline Ligands.



by

Louise M. Newman

A Doctoral Thesis
submitted in partial fulfilment of the requirements
for the award

DOCTOR OF PHILOSOPHY
of
Loughborough University
1999

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Abstract

This thesis describes the synthesis of novel ligands that include enantiomerically pure acetal and oxazoline moieties. These ligands are utilised in a number of metal-mediated asymmetric syntheses.

All asymmetric acetals and pyridine based acetals are synthesised in good yield in a single step from their corresponding enantiomerically pure diols. C_2 symmetric bisacetals are investigated as ligands in the organolithium and Grignard additions to benzaldehyde with promising results. C_2 symmetric bisacetals and pyridine based acetals are tested for their ability to induce asymmetry in copper(I) catalysed cyclopropanation of styrene using ethyl diazoacetate and the lanthanide(III) catalysed Diels–Alder cycloaddition involving Danishefsky's diene with little success.

Enantiomerically pure phosphinooxazoline ligands are available in good yield in two steps from their corresponding enantiomerically pure aminoalcohols.

Enantiomerically pure acetal substituted pyridines and phosphinooxazoline ligands are considered in the rhodium (I) catalysed hydrosilylation of ketones. Reaction conditions for the more successful phosphinooxazoline ligands are optimised. Using these ligands a range of enantiomerically enriched alcohols is presented in good yield and enantiomeric excess.

Novel phosphinoxazoline ligands are applied to the palladium(0) catalysed allylic substitution reaction with excellent enantioselectivities of the substitution product.

Keywords

acetal, acetalisation, asymmetric, catalysis, cyclopropanation, Diels-Alder, diol, enantiomeric excess, Grignard, hydrosilylation, ligand, oxazoline, palladium allylic substitution, 1-phenylethanol, rhodium.

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'You will do foolish things, but do them with enthusiasm.'

Colette (1873-1954)

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Contents

Section		Page
	Abbreviations	i
Chapter 1	Introduction to the advances in catalytic asymmetric synthesis	1
1.1	Introduction	2
1.2	Significant advances in catalytic asymmetric synthesis	2
1.2.1	Epoxidation	2
1.2.2	Dihydroxylation	6
1.2.3	Aminohydroxylation	10
1.2.4	Hydrogenation	11
1.2.5	Additional chiral reductions	14
Chapter 2	Ligand precedent and synthesis	16
2.1	Introduction	17
2.2	Known applications of enantiomerically pure acetals	19
2.2.1	Reactions of silicon based nucleophiles	21
2.2.1.1	Allylic silanes	21
2.2.1.2	Cyanotrimethylsilane	23
2.2.1.3	Silyl enolates	24
2.2.2	Reduction by hydrides	25
2.2.3	Organometallics	27
2.2.4	Reactions without acetal ring cleavage	28
2.2.4.1	Acetal auxiliaries on the electrophile	29
2.2.4.2	Cyclopropanation reactions	29
2.2.4.3	Cyclisation Reactions	30
2.2.4.4	Acetal auxiliaries on the nucleophile	30
2.2.5	Other uses of acetals	31
2.3	Ligand design	32

2.4	Ligand synthesis	34
2.4.1	Bisacetal ligands	39
2.4.2	Acetal/Pyridine based ligands	44
2.4.3	Phosphinoacetal ligands	46
2.4.4	Phosphorous/Oxazoline based ligands	48
2.4.4.1	Aryl phosphine oxazoline ligands	48
2.4.4.2	Alkyl phosphine oxazoline ligands	58
2.4.5	Attempted developments into expansion of chiral ligands	60
2.5	Conclusion	65
Chapter 3	Organometallic additions to benzaldehyde	66
3.1	Introduction	67
3.1.1	Grignard additions	67
3.1.1.1	Nature of the Grignard reagent	68
3.1.1.2	Reaction mechanism	69
3.1.1.3	Asymmetric Grignard systems	71
3.1.2	Organolithium additions	74
3.1.2.1	Asymmetric organolithium systems	75
3.2	Results and discussion	78
3.2.1	Grignard additions	80
3.2.1.1	Ligand effects	80
3.2.1.2	Solvent effects	82
3.2.1.3	Grignard reagent effects	85
3.2.2	Organolithium additions	86
3.3	Conclusions	88
Chapter 4	Cyclopropanation	89
4.1	Introduction	90
4.1.1	Semicorrin-copper catalysts	92
4.1.2	Bisoxazoline-copper catalysts	94

4.1.3	Bis(oxazoliny)pyridine–metal catalysts	98
4.2	Results and discussion	99
4.3	Conclusion	104
Chapter 5	Diels-Alder Reaction	105
5.1	Introduction	106
5.1.1	Homo Diels–Alder reactions	107
5.1.2	Hetero Diels–Alder reactions	111
5.2	Results and discussion	116
5.3	Conclusion	122
Chapter 6	Hydrosilylation	123
6.1	Introduction	124
6.1.1	Mechanistic proposals	125
6.2	Applications of asymmetric ligands	129
6.2.1	Enantiomerically pure phosphorus based ligands	129
6.2.2	Enantiomerically pure nitrogen based ligands	130
6.2.3	Enantiomerically pure nitrogen/phosphorus bidentate ligands	136
6.3	Results and discussion	138
6.3.1	Pyridylacetal ligands	138
6.3.2	Phosphinooxazoline ligands and analogues	140
6.3.2.1	Solvent effects	142
6.3.2.2	Initial ligand comparisons	143
6.3.2.3	Effects on ligand metal complexation over time	146
6.3.2.4	Temperature Effects	147
6.3.2.5	Effects of Diphenylsilane Concentration	148
6.3.2.6	Effects of Ligand/catalyst Complex Concentration	150
6.3.2.7	Other factors	151

6.3.2.8	Summary of optimisation conditions	153
6.3.2.9	Substrate effects	155
6.4	Conclusions	157
Chapter 7	Palladium Catalysed Allylic Substitution	158
7.1	Introduction	159
7.1.1	Mechanism	159
7.1.2	η^3 -Allyl complex geometry and isomerisation	160
7.1.3	Stereochemistry in the palladium catalysed allylic substitution	162
7.1.4	Stereocontrol using enantiopure phosphine-nitrogen ligands	164
7.1.4.1	Electronic factors	165
7.1.4.2	Steric factors	166
7.1.5	Phosphine-oxazoline ligands	168
7.2	Application of novel phosphine-oxazoline ligands	171
7.2.1	Substrate synthesis	171
7.2.2	Aryl phosphine-oxazoline ligands	173
7.2.3	Alkyl phosphine-oxazoline ligands	174
7.2.4	Additional phosphorus-nitrogen ligands	175
7.3	Conclusion	178
Chapter 8	Experimental	179
	References	212
Appendix 1	X-ray structure report for compound [70]	
Appendix 2	X-ray structure report for compound [71]	
Appendix 3	X-ray structure report for compound [72]	

Abbreviations

AA	asymmetric aminohydroxylation
AD	asymmetric dihydroxylation
AD-mix	a commercially available mixture of compounds which is used to perform the Sharpless asymmetric dihydroxylation
Ar	aryl
BSA	<i>N,O</i> ,bis(trimethylsilyl)acetamide
<i>m</i> CPBA	<i>m</i> -chloroperoxybenzoic acid
DHQ	dihydroquinine
DHQD	dihydroquinidine
DMAP	4-dimethylaminopyridine
IPA	<i>iso</i> -propyl alcohol
L-DOPA	L-dopamine
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
<i>p</i> TSA	<i>p</i> -toluene sulfonic acid
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine

Chapter 1 Introduction to the advances in catalytic asymmetric synthesis

- 1.1 Introduction
- 1.2 Significant advances in catalytic asymmetric synthesis
 - 1.2.1 Epoxidation
 - 1.2.2 Dihydroxylation
 - 1.2.3 Aminohydroxylation
 - 1.2.4 Hydrogenation
 - 1.2.5 Additional chiral reductions

1.1 Introduction

In this brief introduction are highlighted some of the significant advances in the ever increasing field that is asymmetric catalysis. This is a very large topic of chemistry and so only a few examples, in particular those systems which have successfully utilised enantiomerically pure ligands for their asymmetric induction are discussed. The use of enantiomerically pure ligands has become significant in recent years in controlling the enantioselectivity of many transformations in organic chemistry. This has a particular impact in industry where absolute control over producing enantiomerically pure centres is paramount especially in the production of many pharmaceuticals. Combinations of asymmetric ligands and metal centres enable control of asymmetric inductions which may have previously been unobtainable. In advanced systems ligand–metal chelates can be used in catalytic quantities thus reducing overall cost and purification difficulties.

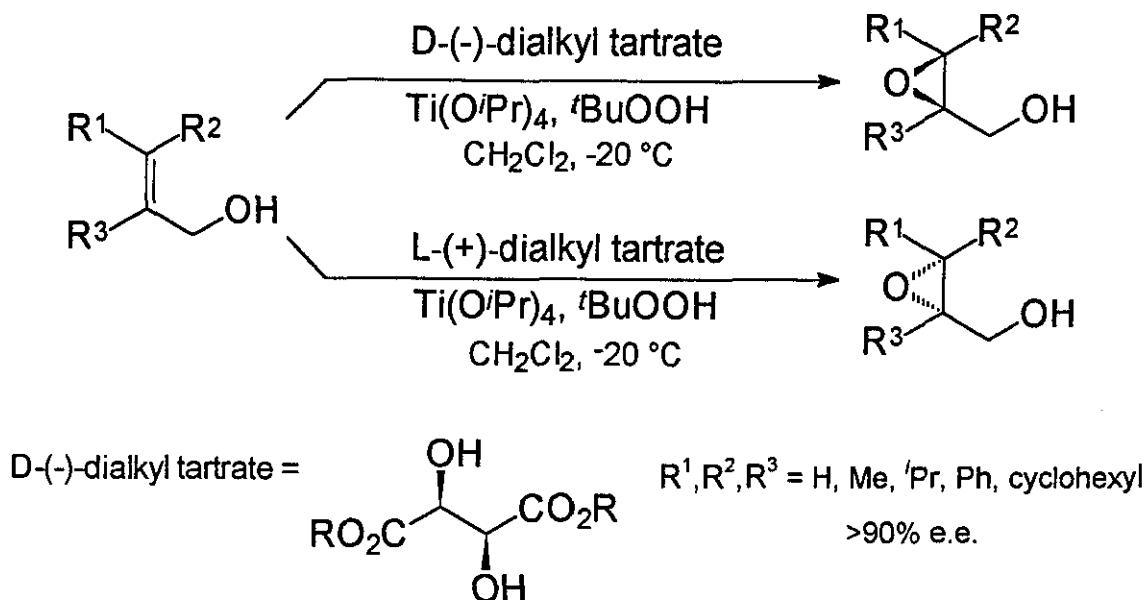
1.2 Significant Advances in Catalytic Asymmetric Synthesis

1.2.1 Epoxidation

One of the first and most extensively used methods for enantioselective alkene epoxidation was developed by Sharpless in 1980.¹ High levels of enantioselectivity have been achieved using the *tert*-butyl hydroperoxide–titanium *tetraiso*-propoxide–diethyl tartrate mixture on a variety of primary allylic alcohols (**Scheme 1**).²

¹ T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, 102, 5974.

² Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, 109, 5765.



Scheme 1

This system has the advantage of being catalytic and highly stereoselectively and regioselectively predictable.³ However the system is limited to substrates containing a co-ordination site (usually hydroxy) with which to bind the catalyst.

The efficient epoxidation of electron deficient alkenes (especially chalcones) has been studied by Enders using stoichiometric quantities of chirally modified zinc alkyl peroxides.^{4,5} Thus being the first group to introduce modified peroxides acting as nucleophilic oxidants, rather than the known electrophilic oxidants used by Sharpless. Jackson and co-workers have subsequently employed nucleophilic, chirally modified, metal alkyl *tert*-butylperoxides based on lithium or magnesium and diethyl tartrate in the same system with excellent results, 81–94% e.e.⁶

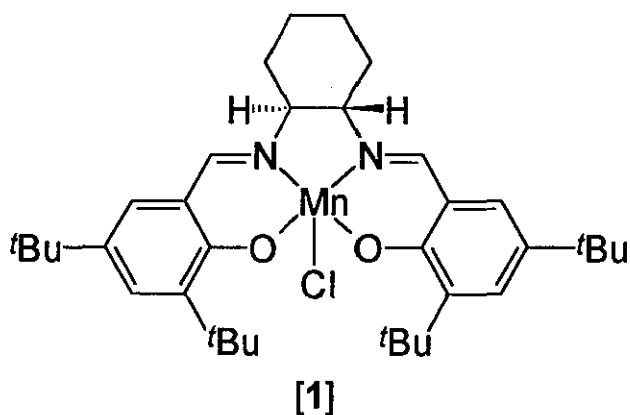
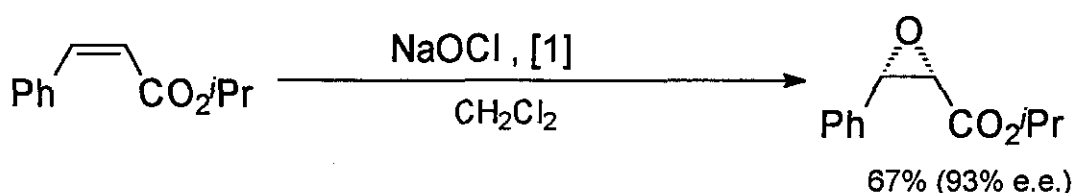
³ K. B. Sharpless in *Comprehensive Organic Synthesis*, Pergamon, Oxford, 1991, vol. 7, 389.

⁴ D. Enders, J. Zhu, G. Raabe, *Angew. Chem.*, 1996, 108, 1827.

⁵ D. Enders, J. Zhu, G. Raabe, *Angew. Chem. Int. Ed. Engl.*, 1996, 35, 1725.

⁶ C. L. Elson, R. F. W. Jackson, S. J. F. MacDonald, P. J. Murray, *Angew. Chem., Int. Ed. Engl.*, 1997, 36, 410.

The asymmetric epoxidation of alkenes containing no other binding groups has also been investigated. The most successful of these involve catalysts based on manganese(III) complexes of enantiopure C_2 -symmetric salen ligands [1, 2], although chromium salen derived catalysts are also known to be effective.⁷ Jacobsen and co-workers have shown good enantioselectivities in the epoxidation of cinnamate esters using catalyst [1] and sodium hypochlorite as the oxidant (Scheme 2).⁸



Scheme 2

The highest product stereoselectivities are restricted to *cis*-alkene substrates, increasing with the size of the substituents. The related manganese complex [2] has been reported to carry out the asymmetric epoxidation of styrene [3] using the oxidising system *m*CPBA/NMO at low temperature.⁹ The depleted temperature

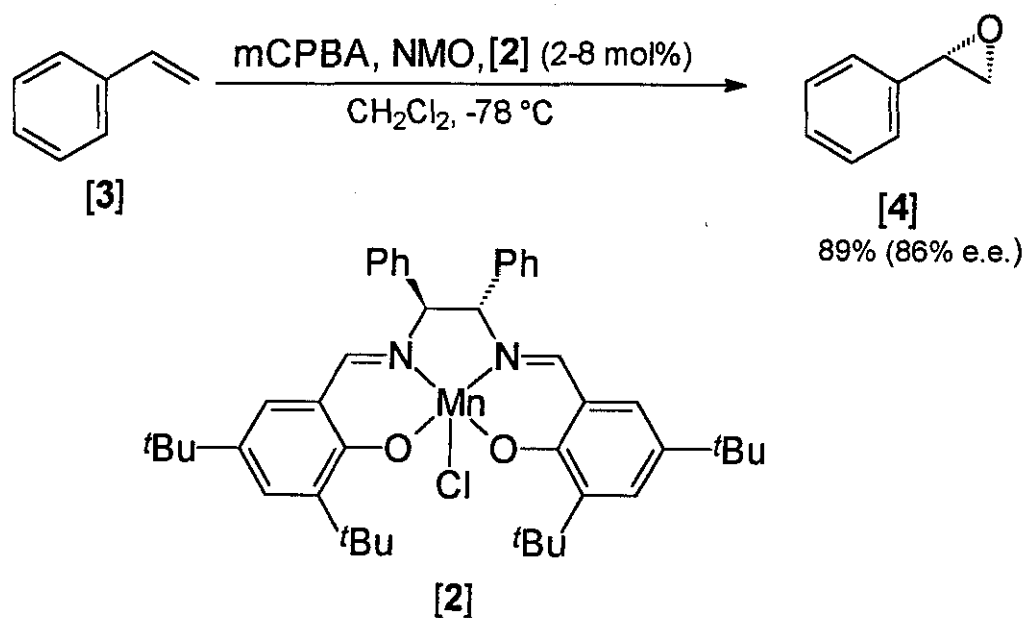
⁷ C. Bousquet, D. G. Gilheany, *Tetrahedron Lett.*, 1995, 36, 7739.

⁸ E. N. Jacobsen, L. Deng, Y. Furukawa, L. E. Martinez, *Tetrahedron*, 1994, 50, 4323.

⁹ M. Palucki, G. J. McCormick, E. N. Jacobsen, *Tetrahedron Lett.*, 1995, 36, 5457.

benefitted the enantioselectivity affording the styrene oxide [4] in 86% e.e. (**Scheme**

3).



Scheme 3

Tri-substituted alkenes¹⁰ and tetra-substituted alkenes¹¹ have also been successfully asymmetrically epoxidised using the catalysts **[1, 2]** and with other related Mn–salen complexes.¹²

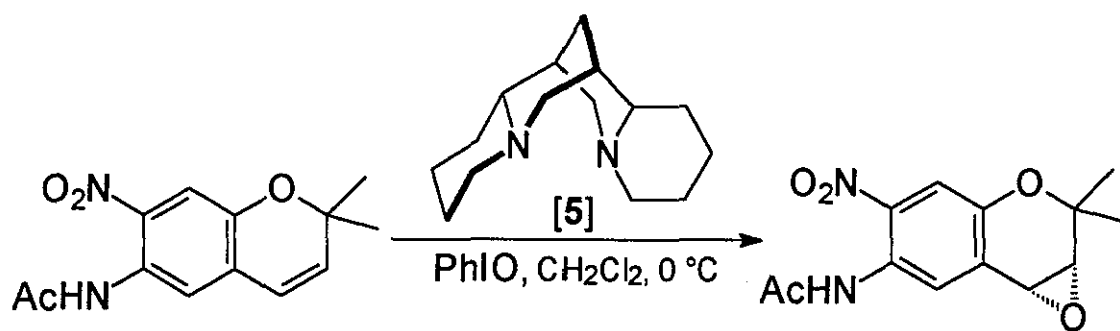
Recently published preliminary results show moderate enantioselectivities in epoxidation reactions catalysed by a combination of achiral manganese–salen complexes and chiral diamines.¹³ The diamines were considered to co-ordinate to manganese in the axial position thus forcing the Mn–salen complex into a single conformational isomer. Enantiopure sparteine **[5]** proved the most successful diamine when used in conjunction with the cationic complex **[6]** (**Scheme 4**).

¹⁰ B. D. Brandes, E. N. Jacobsen, *J. Org. Chem.*, 1994, 59, 4378.

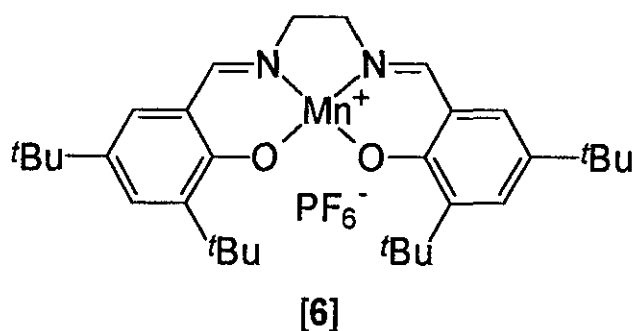
¹¹ B. D. Brandes, E. N. Jacobsen, *Tetrahedron Lett.*, 1995, 36, 5123.

¹² T. Fukuda, R. Irie, T. Katsuki, *Synlett*, 1995, 197.

¹³ T. Hashihayata, Y. Ito, T. Katsuki, *Tetrahedron*, 1997, 53, 9541.



60% e.e.

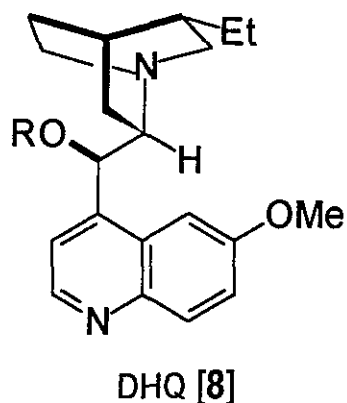
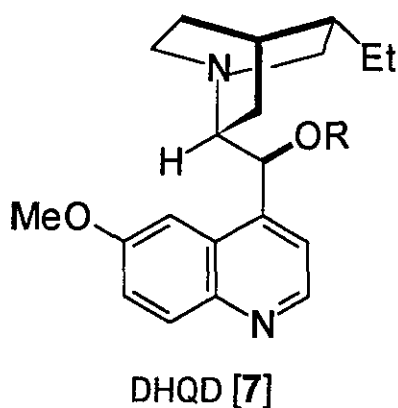


Scheme 4

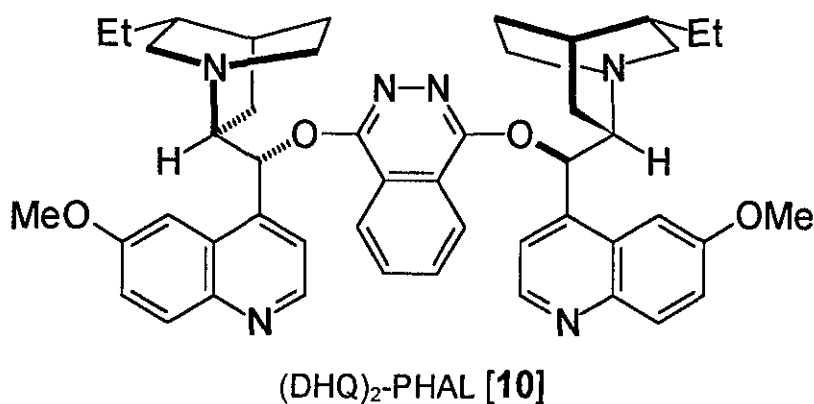
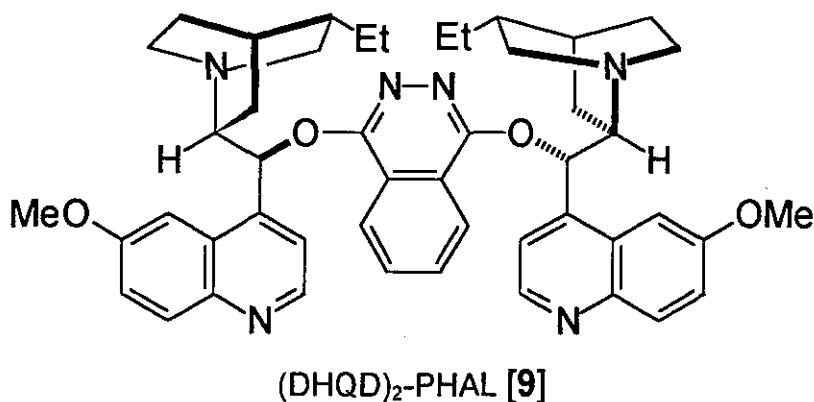
Enantioselectivities were further enhanced by the addition of water although this led to depleted chemical yields.

1.2.2 Dihydroxylation

The asymmetric dihydroxylation (AD) of alkenes has been developed into a highly synthetically useful tool due to its extensive generality and excellent stereoselectivity. Sharpless has dominated the field by the introduction of the osmate ligand based system incorporating enantiomerically pure derivatives of dihydroquinidine (DHQD) [7] or dihydroquinine (DHQ) [8].



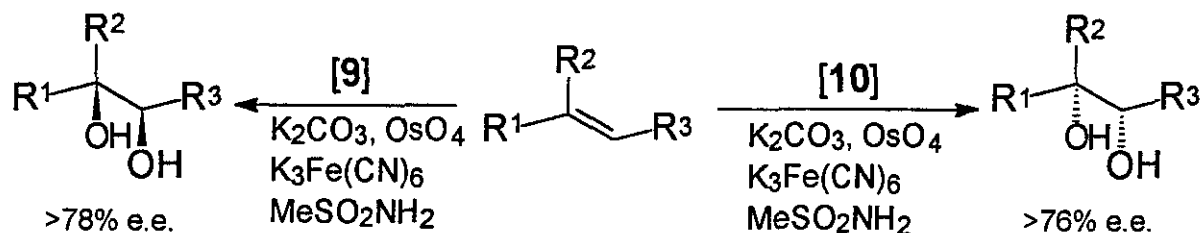
The ligands (DHQD)₂PHAL [9] and (DHQ)₂PHAL [10] are easily prepared from DHQD [7] and DHQ [8] by reaction with 1,4-dichlorophthalazine.¹⁴



In the presence of potassium osmate, potassium carbonate, methane sulfonamide and stoichiometric quantities of the oxidant, potassium ferricyanide, a range of alkenes undergo enantioselective dihydroxylation. Osmium tetroxide produced *in*

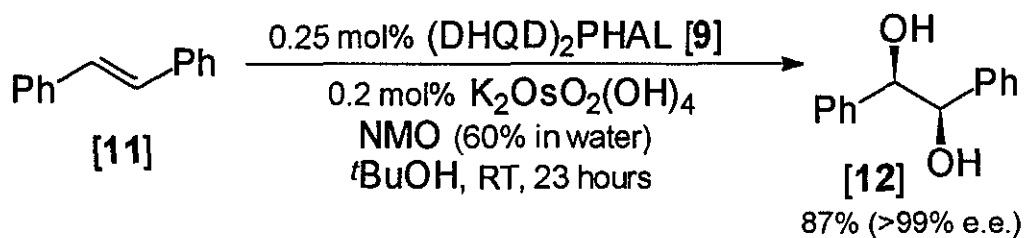
¹⁴ W. Amberg, Y. Bennani, R. Chada, G. Crispino, W. Davis, J. Hartung, K. Jenong, Y. Ogino, T. Shibita, K. B. Sharpless, *J. Org. Chem.*, 1993, 58, 844.

situ, complexes with the ligand and forms the enantioselective osmate ester, which on hydrolysis (accelerated by methane sulfonamide) provides the enantiomerically enriched diol. The two ligands shown produce opposite enantiomers with excellent selectivities (**Scheme 5**).¹⁵



Scheme 5

Indeed the enantioselectivity for the epoxidation of styrene has been shown to be >99% even on an adapted kilogram scale (**Scheme 6**).¹⁶



Scheme 6

¹⁵ K. B. Sharpless, W. Amberg, Y. Bennani, G. Crispino, J. Hartung, K. Jeong, H. Kwong, K. Morikawa, K. Wang, D. Xwu, *J. Org. Chem.*, 1992, 57, 2768.

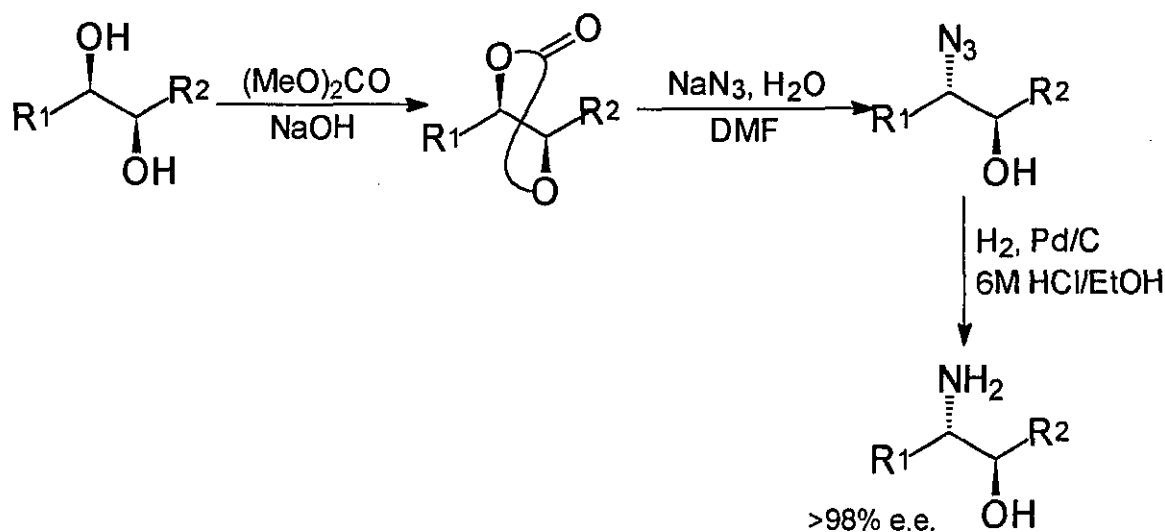
¹⁶ Z. Wang, K. B. Sharpless, *J. Org. Chem.*, 1994, 59, 8302.

The scope of the AD reaction has been extended to include several classes of alkene,

- *trans*-1,2-disubstituted allylic halides¹⁷
- alkenes containing sulfur functionality (does not oxidise sulfur)¹⁸
- *cis*-allylic alcohols (with less success *cis*-1,2-disubstituted alkenes)¹⁹
- cyclic *cis*-disubstituted conjugated alkenes (can give variable results)²⁰

The huge impact of asymmetric dihydroxylation within enantioselective synthesis is enhanced by the versatility of the enantiopure 1,2-diol functionality (see Chapter 2).

In a recent publication Sharpless and co-workers took their own technology a step further to generate enantiomerically pure 1,2-aminoalcohols from the corresponding 1,2-diols.²¹ This involved a simple three step sequence of transesterification, stereoselective ring opening by sodium azide and palladium hydrogenation of the resulting azido alcohol (**Scheme 7**). In all cases the enantiomeric excesses were 98% or greater.



Scheme 7

¹⁷ K. P. M. Vanhessche, Z. Wang, K. M. Sharpless, *Tetrahedron Lett.*, 1994, 35, 3469.

¹⁸ P. J. Walsh, P. T. Ho, S. B. King, K. B. Sharpless, *Tetrahedron Lett.*, 1994, 35, 5129.

¹⁹ M. S. Vannieuwenhze, K. B. Sharpless, *Tetrahedron Lett.*, 1994, 35, 843.

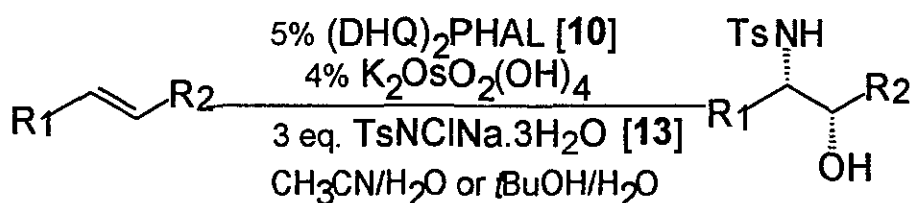
²⁰ Z. M. Wang, K. Kakiuchi, K. B. Sharpless, *J. Org. Chem.*, 1994, 59, 6895.

²¹ HT. Chang, K. B. Sharpless, *Tetrahedron Lett.*, 1996, 37, 3219.

The details of the asymmetric dihydroxylation mechanistic pathway are still under debate, however similarly rationalised intermediates have been proposed by Corey²² and Sharpless²³ supported by kinetic²⁴ and molecular modelling studies.²⁵

1.2.3 Aminohydroxylation (AA)

In an attempt to generate the synthetically useful enantiomerically pure β -hydroxyamino units Sharpless has ingeniously adapted the osmium technology, more widely used in the dihydroxylation of alkenes. Thus many alkenes have been converted into their tosyl protected β -hydroxyamino derivatives in modest to good enantiomeric excess (36-81%) using the following method (Scheme 8).²⁶



Scheme 8

Fortuitously many of the product were highly crystalline and thus the enantiomeric purity could be enhanced by recrystallisation. Subsequently this process was further developed to enhance both enantio- and regio-selectivity.^{27,28} This was achieved by manipulation of the sulfonamide derived chloramine salt [13] to a similar structure bearing only a methyl group on the sulfur (resulting in e.e. up to 95%). They then

²² E. J. Corey, M. C. Noe, S. Sarshar, *Tetrahedron Lett.*, 1994, 35, 2861.

²³ H. Becker, P. T. Ho, H. C. Kolb, S. Loren, P. O. Norrby, K. B. Sharpless, *Tetrahedron Lett.*, 1994, 35, 7315.

²⁴ H. C. Kolb, P. G. Andersson, K. B. Sharpless, *J. Am. Chem. Soc.*, 1994, 116, 1278.

²⁵ P. O. Norrby, H. C. Kolb, K. B. Sharpless, *J. Am. Chem. Soc.*, 1994, 116, 8470.

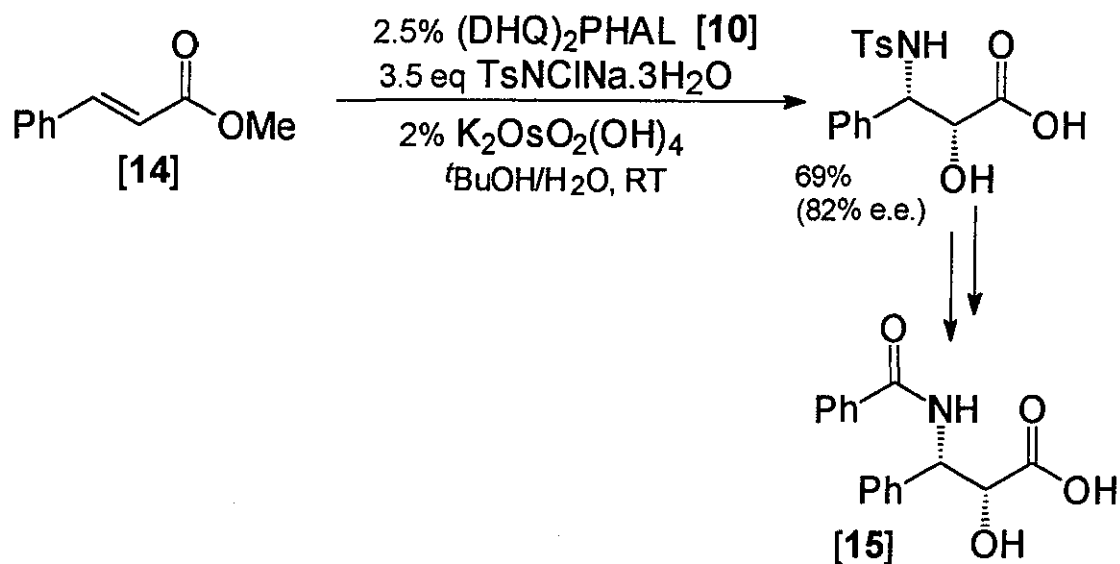
²⁶ G. Li, H. T. Chang, K. B. Sharpless, *Angew. Chem. Int., Ed. Engl.*, 1996, 35, 451.

²⁷ J. Rudolph, P. C. Sennhenn, C. P. Vlaar, K. B. Sharpless, *Angew. Chem. Int., Ed. Engl.*, 1996, 35, 2810.

²⁸ G. Li, H. H. Angert, K. B. Sharpless, *Angew. Chem. Int., Ed. Engl.*, 1996, 35, 2813.

took this approach further to replace the sulfonamide with alkyl carbamates. The optimum of which was the ethyl derivative.

The Sharpless group reported using the AA (as well as the AD)²⁹ technology in the synthesis of the taxol side chain [15] from the methyl cinnamate [14] (Scheme 9).³⁰



Scheme 9

1.2.4 Hydrogenation

Many chiral non-racemic phosphine based ligands are documented to facilitate asymmetric hydrogenation of olefins with good success. Commonly these are used in conjunction with rhodium(I) or ruthenium(II), although other metals are also known.^{31,32} A sample of these ligands, all of which have exhibited >90% e.e. with the appropriate substrate, is shown (Figure 1), along with their acronyms.

²⁹ Z. Wang, H. C. Kolb, K. B. Sharpless, *J. Org. Chem.*, 1994, 59, 5104.

³⁰ G. Li, K. B. Sharpless, *Acta. Chem. Scand.*, 1996, 50, 649.

³¹ For a review of developments prior to 1990 see R. Noyori, *Chem. Soc. Rev.*, 1989, 18, 187.

³² For an overview of this topic see, R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley and Son or G. Procter, *Asymmetric Catalysis*, Oxford University Press, Great Britain, 1998, 62.

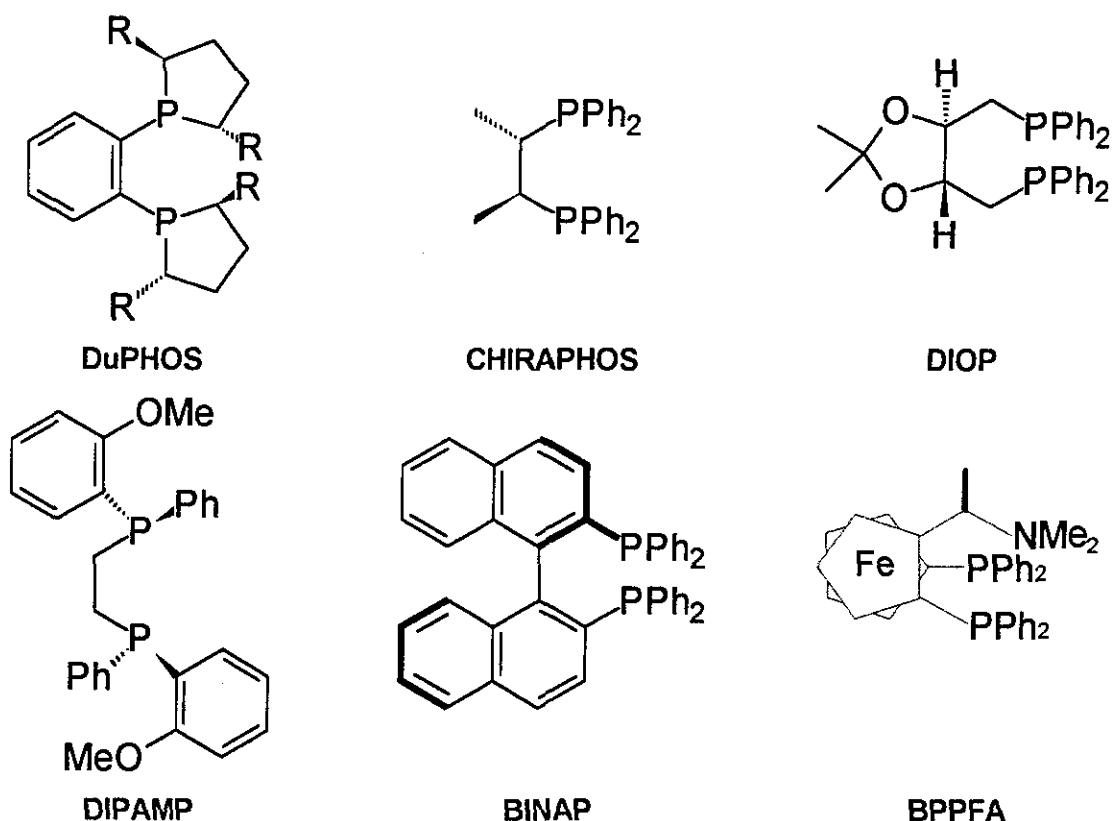
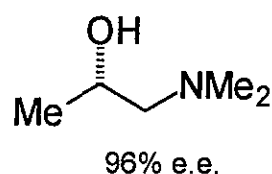
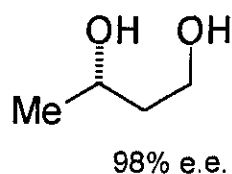


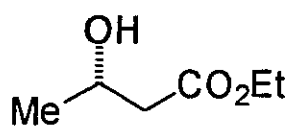
Figure 1

Recent advances have generated a plethora of new ligands, with success being dependant on the substrate and its additional available chelating groups.

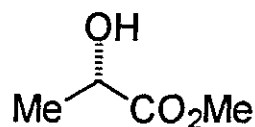
Complexes formed by the combination of BINAP and ruthenium(II) have been shown to facilitate enantioselectivity in the hydrogenation of ketones which contain a further chelating moiety.³³ The complex binds to both the ketone oxygen and the additional moiety to generate either a five or six membered chelate ring, which is then elaborated into the alcohol in excellent enantiomeric excess. Examples of formed products are shown in Figure 2.



³³ M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya and R. Noyori, *J. Am. Chem. Soc.*, 1988, 110, 629.



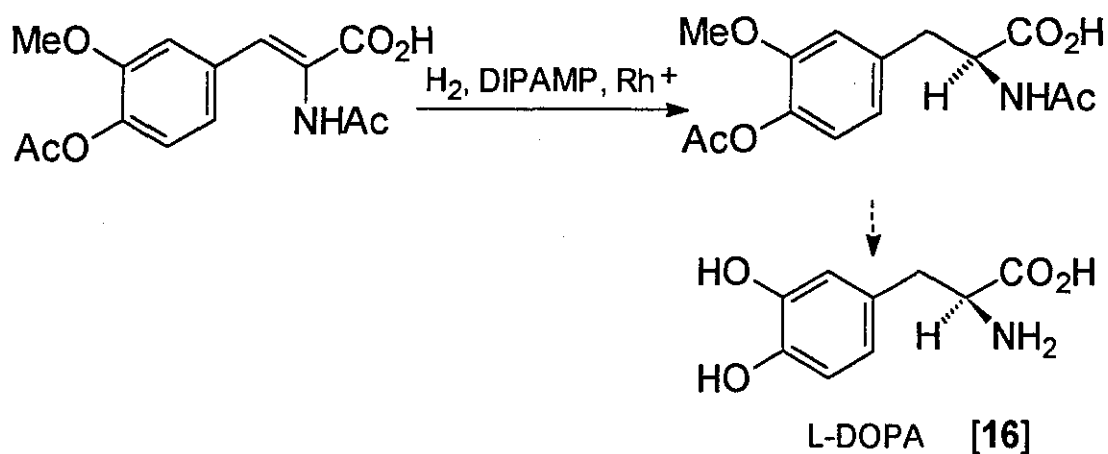
>99% e.e.



83% e.e.

Figure 2

Cationic complexes of DIPAMP are particularly successful for generating enantiomerically enriched amino acids from the parent dehydro- α -acylamino acids which can then be developed in the commercial synthesis of L-DOPA [16] (Scheme 10).³⁴

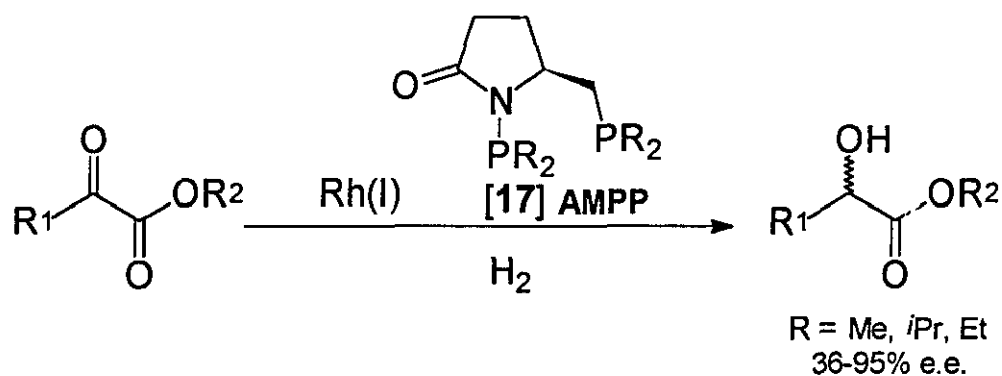


Scheme 10

Amidophosphine-phosphinite ligand (AMPP) [17] catalyses the asymmetric reduction of alkyl α -keto acid derivatives in moderate to good enantiomeric excess (36-95%) (Scheme 11).³⁵

³⁴ Stereoselectivity in Organic Synthesis, G. Procter, Oxford University Press, 1998, 65.

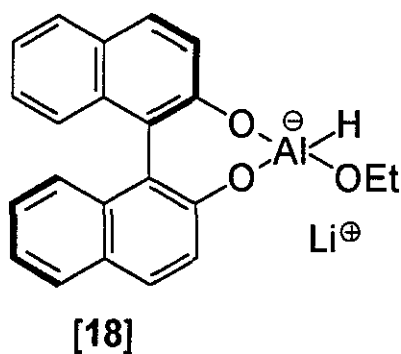
³⁵ J. F. Carpentier, A. Mortreux, *Tetrahedron Asymmetry*, 1997, 8, 1083.



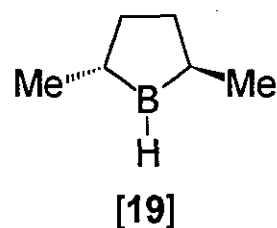
Scheme 11

1.2.5 Additional Chiral Reductions

A wide range of success has been obtained from the enantioselective reduction of prochiral ketones. In particular the reduction of prochiral ketones facilitated by modified versions of hydrides [18] or boranes [19].³⁶



catalysed the reaction in 94% e.e.



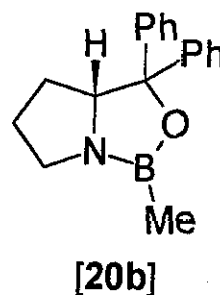
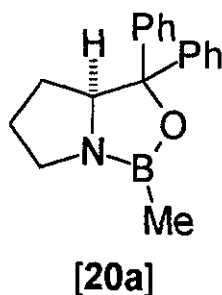
catalysed the reaction in >99% e.e

However these chiral species were necessary in at least stoichiometric quantities and were thus superseded as more adaptable enantiomeric catalysts emerged. The most useful examples of these new catalysts being the boron based compounds developed by Corey, Bakshi and Shibata.³⁷ They utilise the appropriate ligand type

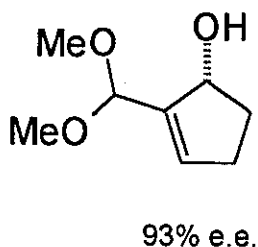
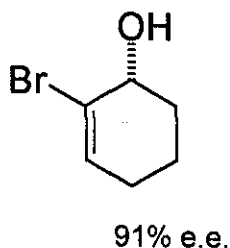
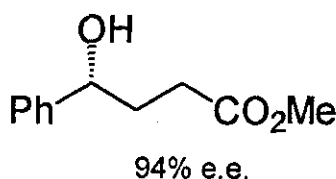
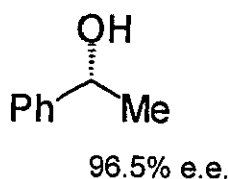
³⁶ S. Masamune, R. M. Kennedy, J. S. Petersen, K. N. Houk and Y.-D. Wu, *J. Am. Chem. Soc.*, 1986, **108**, 7404.

³⁷ E. J. Corey, O. J. Link, *Tetrahedron Lett.*, 1992, **33**, 4141; and references cited therein.

[20a-b] and stoichiometric quantities of borane to reduce both acyclic and cyclic ketones.



For high enantioselectivity the groups either side of the initial substrate carbonyl have to show a reasonable size difference and the catalyst must be present in approximately 10 mol%. A number of examples of alcohols are shown having been derived from their parent ketones *via* this reduction.



This method is very powerful as it enables high enantiomeric excesses to be achieved whilst the mild conditions leave other functional groups intact.

Additional methods of reducing prochiral ketones are discussed in chapters 2, 3 and 6.

Each subsequent chapter in this tome will contain its own introduction to the relevant literature and thus will present each piece of novel work in context as it emerges.

Chapter 2 Ligand Precedent and Synthesis

- 2.1 Introduction
- 2.2 Known applications of enantiomerically pure acetals
 - 2.2.1 Reactions of silicon based nucleophiles
 - 2.2.1.1 Allylic silanes
 - 2.2.1.2 Cyanotrimethylsilane
 - 2.2.1.3 Silyl enolates
 - 2.2.2 Reduction by hydrides
 - 2.2.3 Organometallics
 - 2.2.4 Reactions without acetal ring cleavage
 - 2.2.4.1 Acetal auxiliaries on the electrophile
 - 2.2.4.2 Cyclopropanation reactions
 - 2.2.4.3 Cyclisation Reactions
 - 2.2.4.4 Acetal auxiliaries on the nucleophile
 - 2.2.5 Other uses of acetals
- 2.3 Ligand design
- 2.4 Ligand synthesis
 - 2.4.1 Bisacetal ligands
 - 2.4.2 Acetal/Pyridine based ligands
 - 2.4.3 Phosphinoacetal ligands
 - 2.4.4 Phosphorous/Oxazoline based ligands
 - 2.4.4.1 Aryl phosphine oxazoline ligands
 - 2.4.4.2 Alkyl phosphine oxazoline ligands
 - 2.4.5 Attempted developments into expansion of chiral ligands
- 2.5 Conclusion

2.1 Introduction

In recent years the field of asymmetric synthesis using enantiomerically pure ligands has expanded rapidly. The scope of ligands available demonstrate that a wide range of hetero atoms (P, N, S and O) can be used to chelate to metal centres. We considered that whilst there were already many species of ligand in the literature they often were highly complex or only available after a multi-step synthesis. We felt that this distracted from the main task of using ligands in asymmetric synthesis which is to make cheap and user-friendly ligands which give high e.e.s within their processes. As the aim of designing such ligands is that they eventually be used in an industrial process, they must be robust and commercially viable.

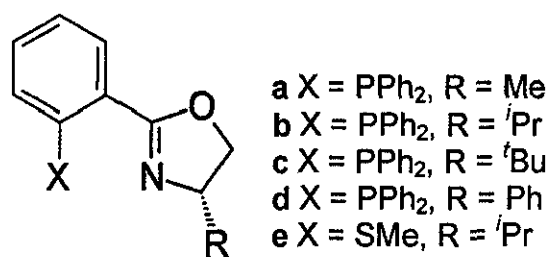
We wished to devise a simple, novel family of ligands which could be utilised in conjunction with a number of metals to induce asymmetry. In doing so we wished to comply with the following criteria for these ligands;

- Enantiomerically pure species
- Made from commercially available starting materials
- Short and simple synthesis
- Enantiomerically pure centre next to the chelating moiety

It was considered that these criteria would lead to an efficient synthesis of the ligands and the required enantiomerically pure centre close to the site of asymmetric induction.

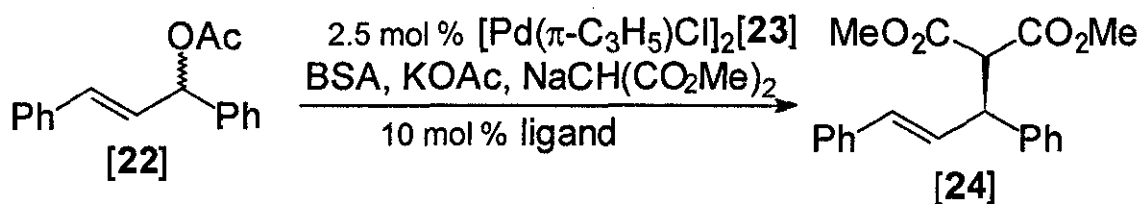
Assessment of the available literature led us to consider analogues of enantiomerically pure oxazoline ligands. Within our research group there was

already experience of such chiral moieties, commonly as one half of bidentate ligands of type [21].³⁸

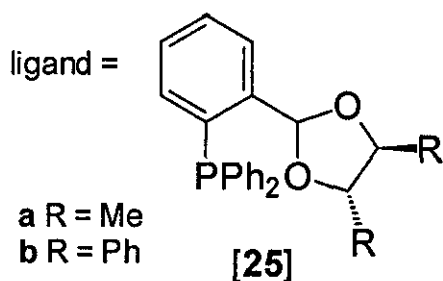


[21]

Development within our group had led to some preliminary work based on the acetal derivatives of these ligands with good success (Scheme 12).³⁹



68–88% e.e.



Scheme 12

Our interest in further work using acetal based ligands was thus initiated.

It was noted that ligands of type [25a-b], were the only literature examples of acetal moieties used in asymmetric synthesis.⁴⁰

³⁸ J. V. Allen, S. J. Coote, G. J. Dawson, C. G. Frost, C. J. Martin, J. M. J. Williams, *J. Chem. Soc., Perkin Trans. 1.*, 1994, 1.

³⁹ C. J. Frost, J. M. J. Williams, *Synlett.*, 1994, 551.

⁴⁰ See reference 39 for derivatives including acetal/sulfur ligands in the same system.

However acetals (in particular those derived from diols having a C_2 axis of symmetry) have been used in several diastereoselective reactions.^{41,42} Here acetals have been shown to undergo cleavage reactions of the acetal ring or be used to control both the reactivity and stereoselectivity due to their proximity to a prochiral centre.

2.2 Known Applications of Enantiomerically Pure Acetals

Acetals and ketals are commonly used as protecting groups for aldehydes and ketones. However under certain conditions, particularly in the presence of strong Lewis acids, they are susceptible to both nucleophilic attack and electrophilic substitution.

Chiral acetals of both butane-2,3-diol and pentane-2,4-diol have been cleaved diastereoselectively by a number of nucleophiles in the presence of Lewis acids. Low temperature NMR spectroscopic studies have shown that the Lewis acid complexes to the acetal without cleavage of the ring.⁴³ In doing so one of the C–O bonds lengthens, creating a pseudo-oxocarbenium ion. This is most apparent in the more rigid dioxane ring formed from (S,S)-pentane-2,4-diol. Uncomplexed cyclic acetals of this type exist largely in the chair conformation **A** (Figure 3) which suffers the less sterically hindering 1,3 diaxial interactions. Whereas conformation **B** is destabilised by the 1,3 diaxial interaction between the bulky R and Me groups.

⁴¹ J. K. Whitesell, *Chem. Rev.*, 1989, 89, 1581.

⁴² A. Alexakis, P. Mangeney, *Tetrahedron: Asymmetry*, 1990, 8, 477.

⁴³ S. E. Denmark, T. M. Willson, N. G. Almstead, *J. Am. Chem. Soc.*, 1983, 111, 9258.

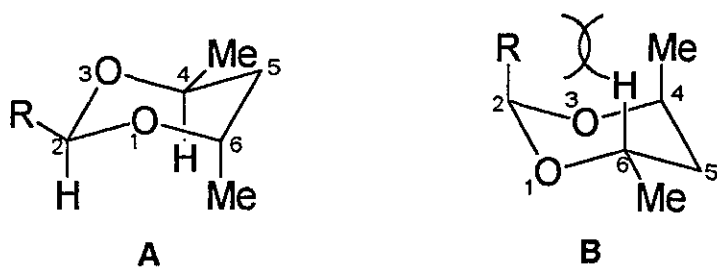


Figure 3

Chelation of the acetal conformation **A** with a Lewis acid occurs at the O¹ thus elongating the C²-O¹ bond and conversely shortening the C²-O³ bond. This increases the steric favourability of the conformation as H² is drawn away from the methyl group at position 6, lowering the steric hindrance between these two groups (Figure 4).

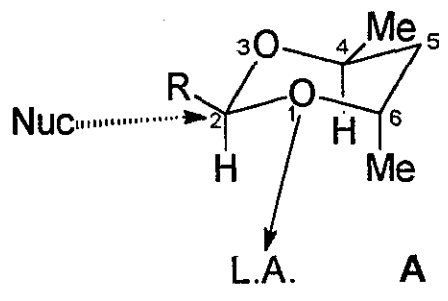


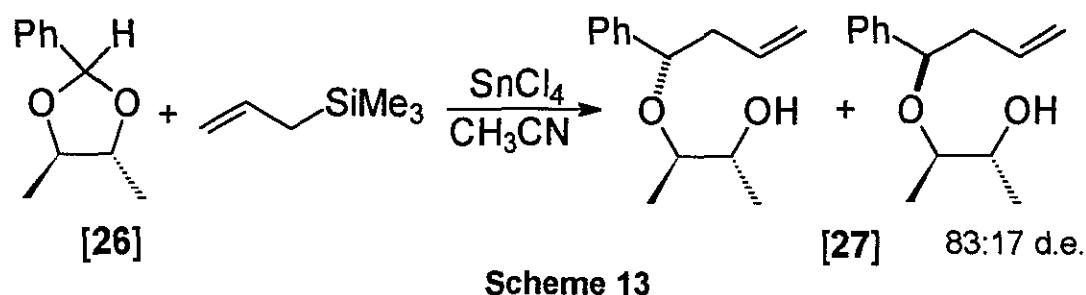
Figure 4

Recent stereochemical and NMR spectroscopic investigations on these acetals indicate that on co-ordination to the Lewis acid, the geometry around the O¹ alters from sp³ to more sp² in nature, giving a planar or weak pyramidal complex. On formation of the complex the nucleophile is free to attack *anti* to the weakened C-O bond in an S_N2 fashion.

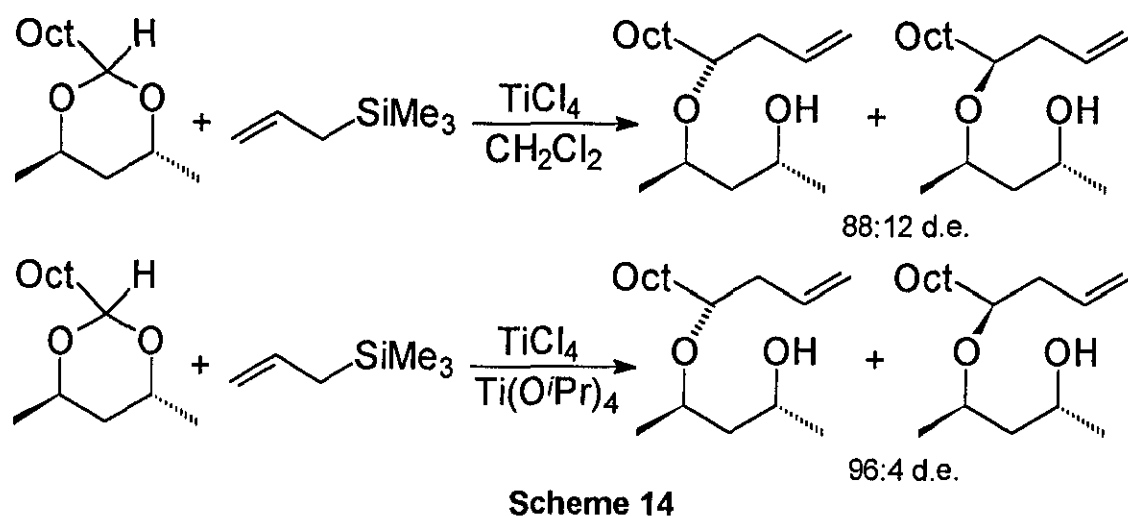
2.2.1 Reactions of Silicon based Nucleophiles

2.2.1.1 Allylic Silanes

The reactions of chiral acetals with allylic silanes in the presence of a Lewis acid were initially documented in 1982 by McNamara and Kishi.⁴⁴ The reaction of benzaldehyde/butane-2,3-diol acetal [26] with allyltrimethylsilane and SnCl₄ as the Lewis acid, afforded a diastereomeric ratio of 83:17 for the free alcohol [27] (Scheme 13).



This was improved upon shortly afterwards by Johnson *et al* who utilized TiCl₄ and TiCl₄/Ti(OⁱPr)₄ as the Lewis acid (Scheme 14).⁴⁵

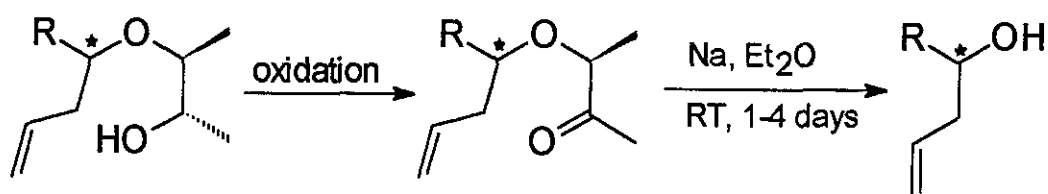


⁴⁴ J. M. McNamara, Y. Kishi, *J. Am. Chem. Soc.*, 1982, 104, 7371.

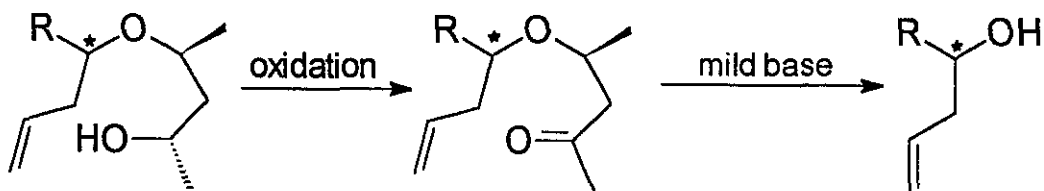
⁴⁵ P. A. Bartlett, W. S. Johnson, J. D. Elliot, *J. Am. Chem. Soc.*, 1983, 105, 2088.

Johnson also improved the ease of the reaction by using acetals of pentane-2,4-diol origin.⁴⁶ These acetals once cleaved can be oxidised and β -eliminated (as opposed to the harsh α -elimination procedure) to obtain the required enantiomerically enriched alcohol. This was performed using milder reaction conditions than had been previously used (**Scheme 15**).

α -elimination



β -elimination

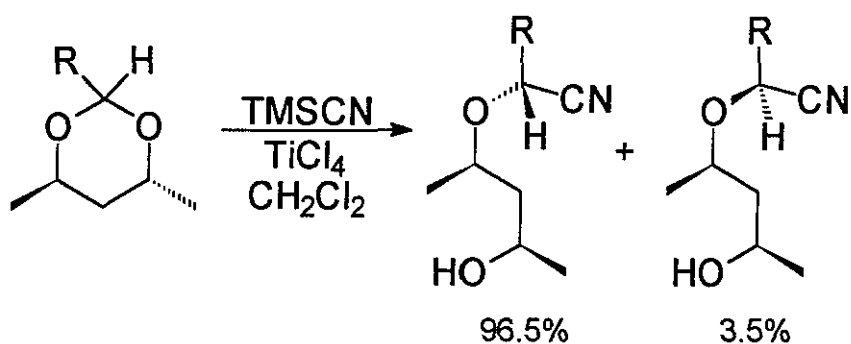


Scheme 15

⁴⁶ P. A. Bartlett, W. S. Johnson, J. D. Elliot, *J. Am. Chem. Soc.*, 1984, 106, 3951.

2.2.1.2 Cyanotrimethylsilane

In the same way as allylic silanes, cyanotrimethylsilane may be employed as a nucleophile leading to cyanohydrin ethers (**Scheme 16**).

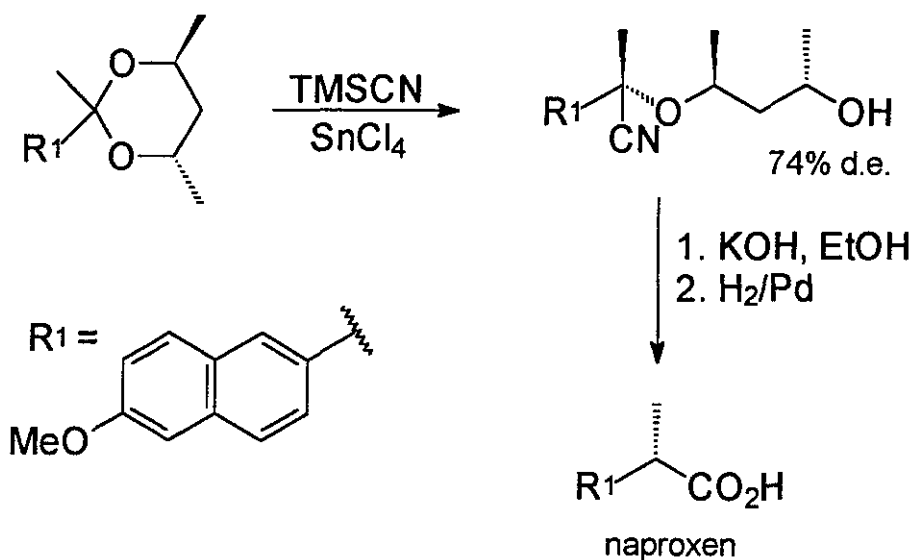


Scheme 16

This method can also be applied to ketals to obtain chiral cyanohydrins which may then subsequently be converted to α -hydroxyacids, aldehydes or amines.

Alternatively the acetal, once cleaved, may be removed by hydrogenolysis to afford a carboxylic acid, as in the synthesis of naproxen (**Scheme 17**).⁴⁷ This being one of the few examples of an industrial scale asymmetric synthesis.

⁴⁷ T. Hiyama, K. Saito, K. I. Sato, N. Wakasa, M. Inone, *Chem. Lett.*, 1986, 1471.



Scheme 17

2.2.1.3 Silyl Enolates

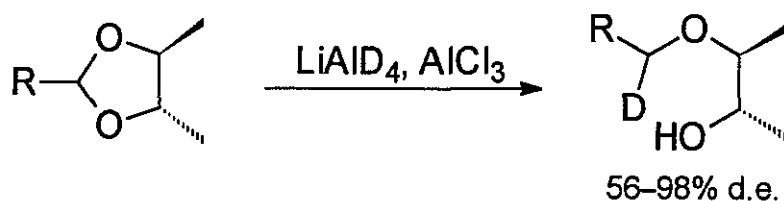
Silyl enolates, either as enol ethers or α -silyl carbonyl compounds, are also known to cleave acetals in the presence of Lewis acids.⁴⁸ Recently zinc enolates, particularly the Reformatsky reagent, with TiCl_4 as the Lewis acid, have also been shown to cleave acetals. The best diastereoselectivities obtained were with C_2 symmetrical pentane-2,4-diol derived acetals.⁴⁹

⁴⁸ H. Sekizaki, M. Jung, J. M. Mc Namara, Y. Kishi, *J. Am. Chem. Soc.*, 1982, 104, 7372.

⁴⁹ T. Basile, E. Tagliavini, C. Trombini, A. Umani-Rondu, *Synthesis*, 1990, 305.

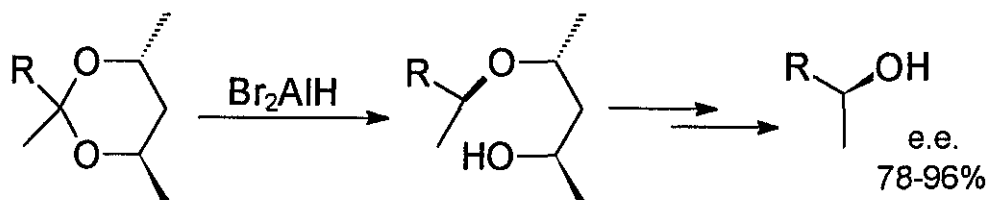
2.2.2 Reduction by Hydrides

Hydrides exhibiting Lewis acid character such as aluminium or boron hydrides can easily cleave acetals. C_2 symmetric acetals were first studied by Richter in 1981, with cleavage of butane-2,3-diol derived acetals using $LiAlD_4/AlCl_3$ reagent (**Scheme 18**).⁵⁰



Scheme 18

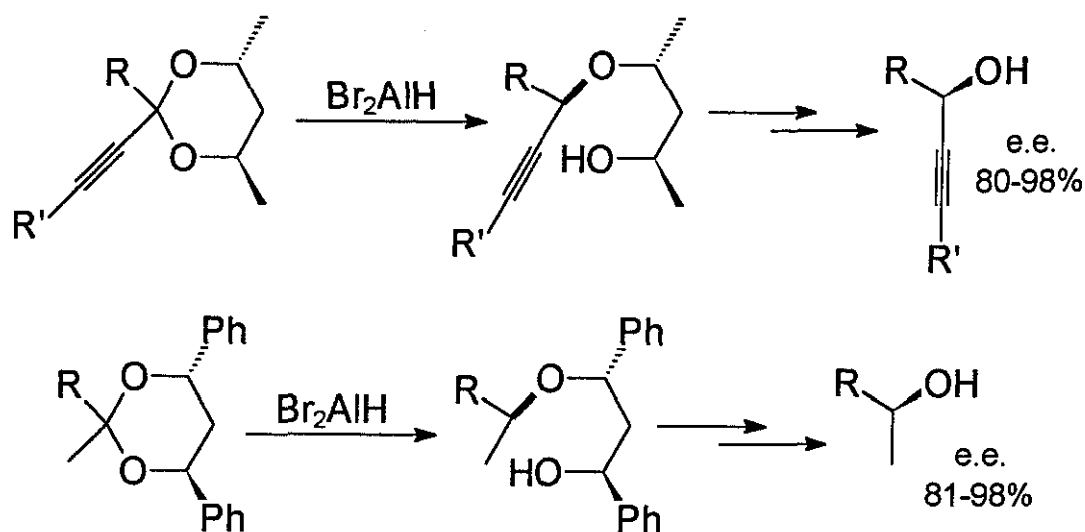
The diastereoselectivity obtained is greatly reduced when performing the reaction with ketal moieties. The possible two conformers of a ketal are much more energetically similar than those of the corresponding acetal and therefore the reaction is less stereoselective. However the reaction of pentane-2,4-diol derived ketals and dibromo-aluminium hydrides led to a number of secondary chiral alcohols with good enantiomeric excesses (**Scheme 19**).^{51, 52}



⁵⁰ W. J. Richter, *J. Org. Chem.*, 1981, 46, 5119.

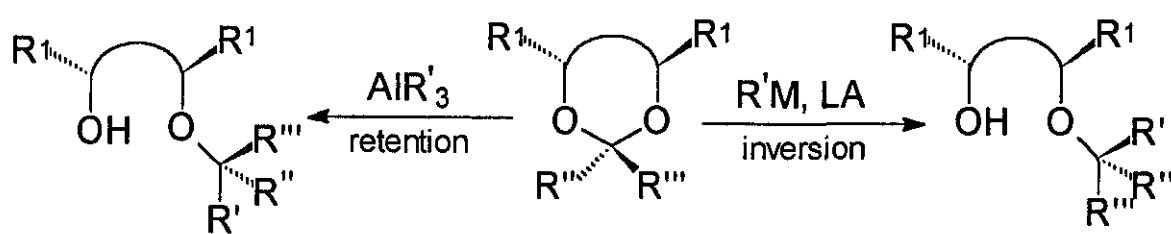
⁵¹ A. Mori, J. Fujiwara, K. Maruoka, H. Yamamoto, *Tetrahedron Lett.*, 1986, 26, 983.

⁵² K. Yamamoto, H. Ando, H. Chikematsu, *J. Chem. Soc., Chem. Commun.*, 1987, 334.



Scheme 19

Yamamoto has shown this system based on aluminium hydrides to be a retentive relationship between the incoming hydride and the departing oxygen atom, thus giving the opposite stereochemistry to the one expected.⁵² Systems involving the standard Lewis acid/nucleophile behave as expected in an inverse fashion (**Scheme 20**).



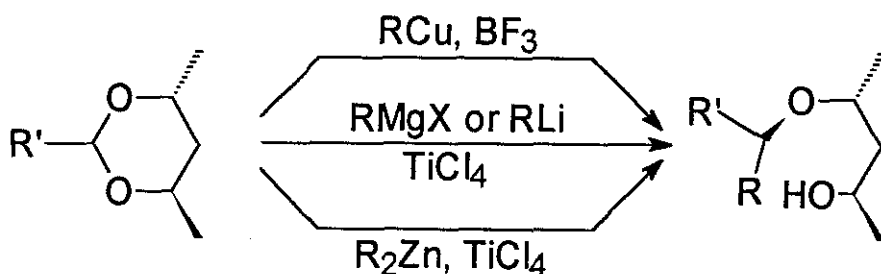
Scheme 20

To enable an alkyl addition to the *Re* face of the oxocarbenium ion (i.e. in a retentive fashion) Yamamoto developed a trialkylaluminium–pentafluorophenol complex which

affords up to 99% retention.⁵³ Small trialkyl aluminium reagents produce non-stereoselective results when used alone.

2.2.3 Organometallics

Organometallic reagents of lithium, magnesium, zinc and copper (with Lewis acid TiCl_4) cleave acetals (**Scheme 21**). Most successful are cyclic acetals derived from pentane-2,4-diol, giving up to 91% d.e., and acetals from aliphatic aldehydes/butane-2,3-diol, which afford >99%.^{54,55,56}



Scheme 21

In all cases the acetal cleavage occurs preferentially in the presence of a ketone or an ester.

Silicon and phosphorus derived acetals have also been cleaved using Grignard reagents to afford chiral silicon hydrides⁵⁷ and phosphine oxides respectively (**Scheme 22**).⁵⁸

⁵³ K. Ishihara, N. Hanaki, H. Yamamoto, *J. Am. Chem. Soc.*, 1993, 115, 10695.

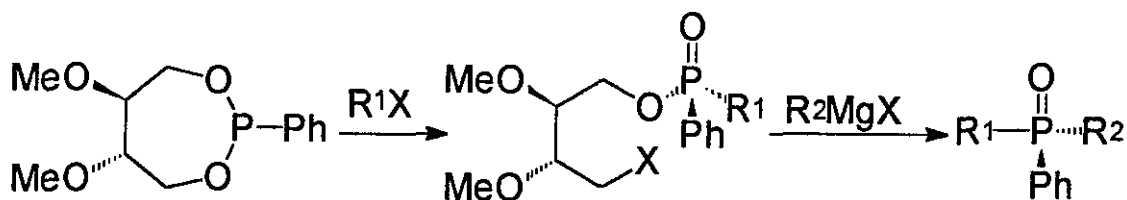
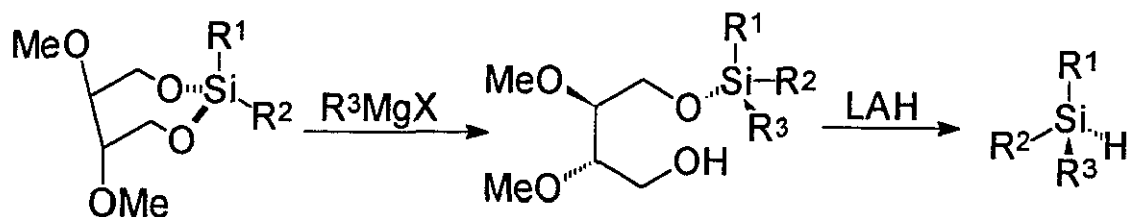
⁵⁴ A. Alexakis, P. Mangeney, A. Ghribi, I. Marek, R. Sedrani, C. Guir, J. Normant, *Pure Appl. Chem.*, 1988, 60, 49.

⁵⁵ S. D. Lindell, J. D. Elliot, W. S. Johnson, *Tetrahedron Lett.*, 1984, 25, 3947.

⁵⁶ A. Mori, K. Marueka, H. Yamamoto, *Tetrahedron Lett.*, 1984, 25, 3083.

⁵⁷ K. Kobayashi, T. Kato, S. Masuda, *Chem. Lett.*, 1987, 101.

⁵⁸ T. Kato, K. Kobayashi, S. Masuda, M. Segi, T. Nakajima, S. Suga, *Chem. Lett.*, 1987, 1915.



Scheme 22

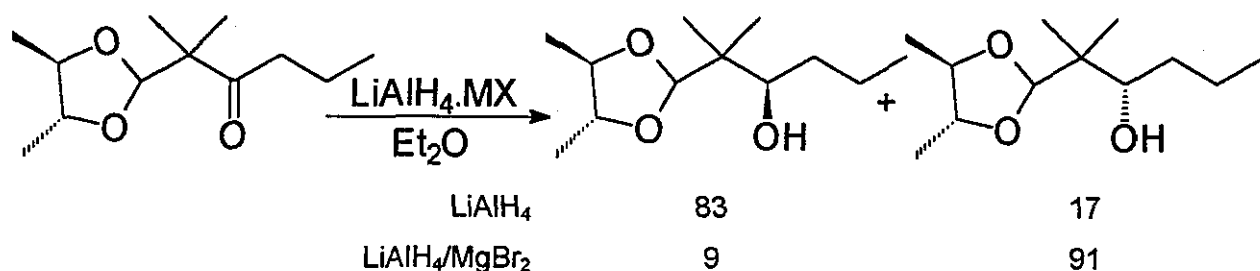
2.2.4 Reactions without Acetal Ring Cleavage

Cyclic chiral acetals may also be used as chiral auxiliaries in asymmetric synthesis.

The auxiliary may be either on the nucleophile or as part of the electrophile and may be positioned at various relative positions to the prochiral centre.

2.2.4.1 Acetal auxiliaries on the electrophile

The simplest system involving acetal occupying electrophiles contains a β -ketone to the acetal ring. Simple reduction of a β -ketone with LiAlH_4 affords one major diastereomer (66% d.e.). However addition of MgBr_2 gives the epimeric alcohol (82% d.e.) (**Scheme 23**).⁵⁹



Scheme 23

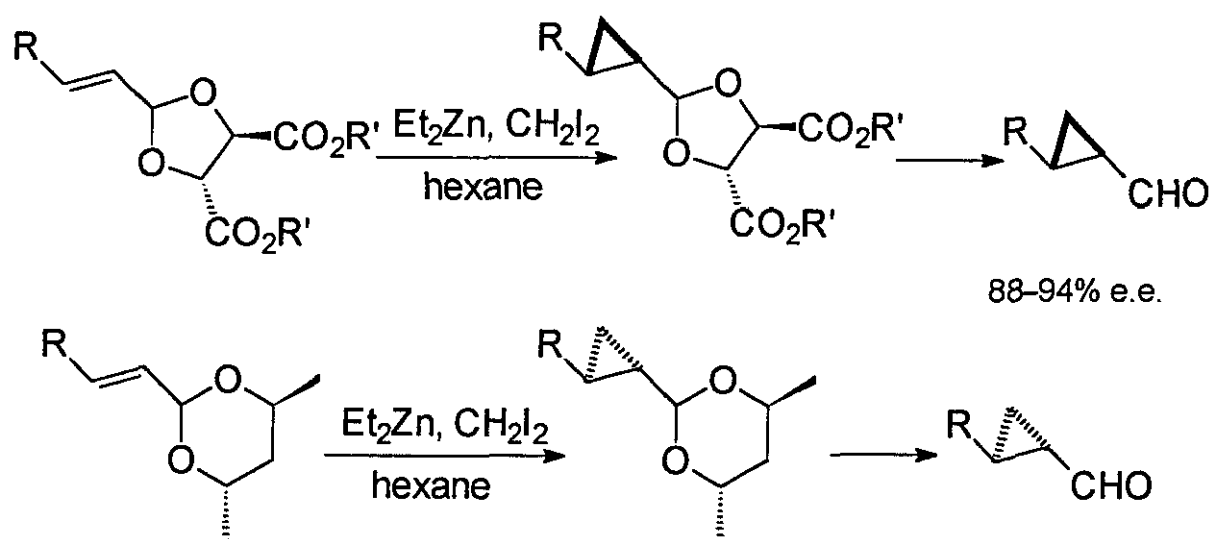
Acetals containing side chain heteroatoms protruding from the ring show an improved d.e. (up to 98%) due to the additional chelation of the metal which appears to direct the face selectivity.⁵⁹

2.2.4.2 Cyclopropanation reaction

Yamamoto *et al* reported good results in the asymmetric cyclopropanation of α,β -unsaturated acetals.⁶⁰ The acetals of pentane-2,4-diol and diethyl tartrate show opposite enantiomers of cyclopropane product (**Scheme 24**). Other cyclopropanation reaction conditions gave mostly racemic mixtures.

⁵⁹ K. Hasegawa, F. Matsuda, M. Yanaiya, T. Matsumoto, *Tetrahedron Lett.*, 1987, 28, 1671.

⁶⁰ I. Arai, A. Mori, H. Yamamoto, *J. Am. Chem. Soc.*, 1985, 105, 8254.



Scheme 24

2.2.4.3 Cyclisation Reactions

Diels–Alder reactions carried out on chiral acetals show only low to moderate selectivities. Better selectivities are observed when using α,β -unsaturated ketals in photochemical 2+2 additions (d.e. up to 84%) and rhodium(I) catalysed intramolecular cyclisations (e.e. up to 99%).^{61, 62}

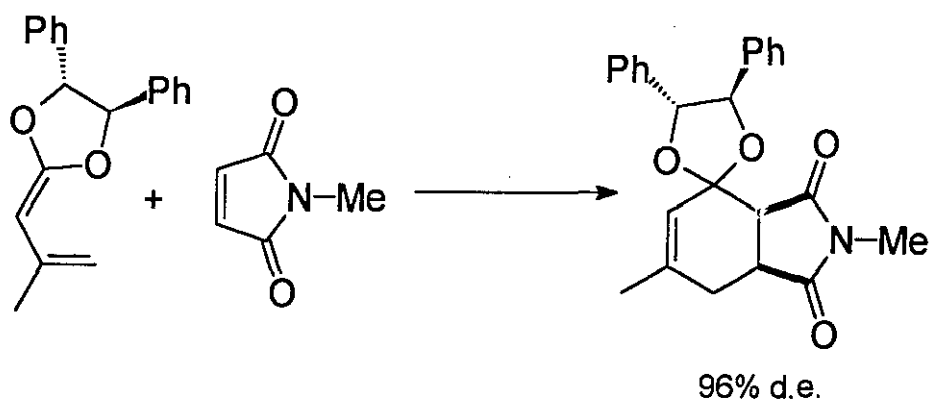
2.2.4.4 Acetal auxiliaries on the nucleophile

The number of chiral acetal containing nucleophiles is very limited. However the use of ketene acetals has been shown to be successful in cycloaddition reactions (Scheme 25).⁶³

⁶¹ G. L. Lange, C. P. Decicco, *Tetrahedron Lett.*, 1988, 29, 2613.

⁶² K. Funakaru, N. Togo, K. Sakai, *Tetrahedron Lett.*, 1989, 30, 2267.

⁶³ J. P. Konopelski, M. A. Boehler, *J. Am. Chem. Soc.*, 1989, 111, 4515.

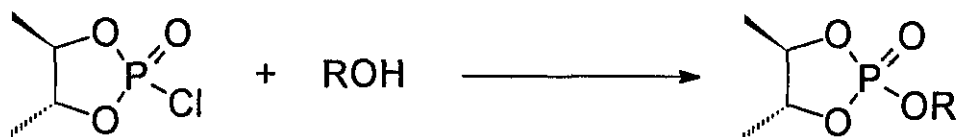


Scheme 25

2.2.5 Other uses of acetals

Acetals may also be used for other applications besides asymmetric induction. The resolution of ketones may be achieved by reaction with a chiral diol, to afford a diastereomeric ketal. The diastereomers once separated and purified (using standard procedures, *i.e.* crystallisation, chromatography) may then be cleaved to give back the original ketone in an optically pure state.

Another use of chiral acetals is in the determination of enantiomeric excess of chiral alcohols. This is performed by the formation of diastereomeric phosphates (**Scheme 26**) whose ratios may be measured by ^{31}P NMR spectroscopy with no interference from other nuclei.⁶⁴



Scheme 26

⁶⁴ R. C. Anderson, M. J. Shapiro, *J. Org. Chem.*, 1984, 49, 1304.

Overall it can be shown that acetals containing C_2 axis of symmetry have a diverse range of uses in synthetic and analytical chemistry.

2.3 Ligand Design

We decided to build on the potential of using acetals by investigating further the potential of the acetal moiety in controlling asymmetric synthesis. It was considered that the acetal group would be ideal for the criteria set for a novel set of ligands.

Whereas Frost and Williams had considered bidentate ligands based on the oxygen lone pair of an acetal moiety and phosphorus, this continued work initially focused bidentate ligands, derived from C_2 symmetrical diols, with both chelating atoms being the oxygen lone pairs of acetal groups (**Figure 5**).³⁹

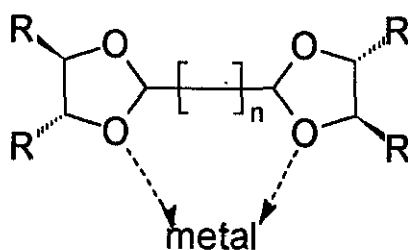


Figure 5

This was further developed throughout the research to include bi- and tri-dentate ligands based on a combination of acetal groups and pyridine (**Figure 6**).

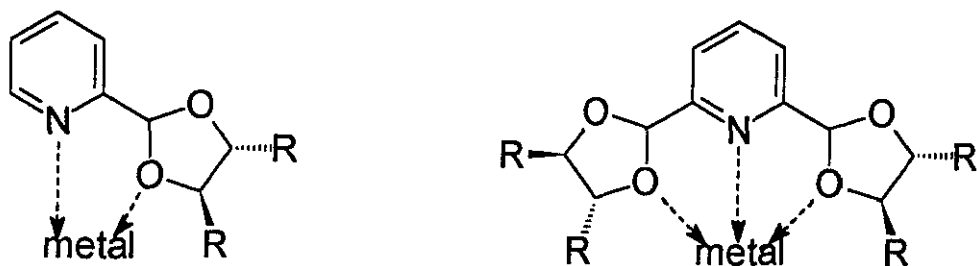
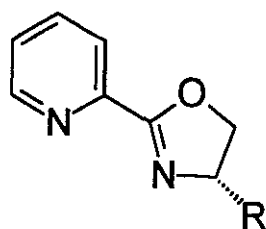
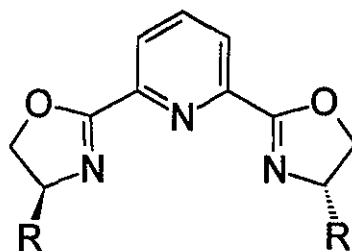


Figure 6

It was envisaged that these ligands would have enhanced coordinating capabilities due to the inclusion of the nitrogen moiety. They also exhibit similar topology to the known 'pymox' [23] and 'pybox' [24] ligands which show promising asymmetric induction in cyclopropanations (see Chapter 4) and hydrosilylations (see Chapter 6).

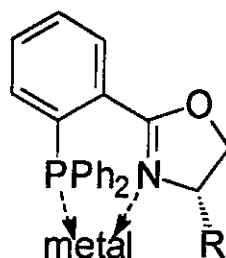
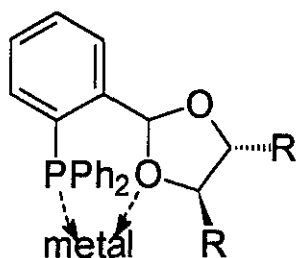


'pymox' [28]



'pybox' [29]

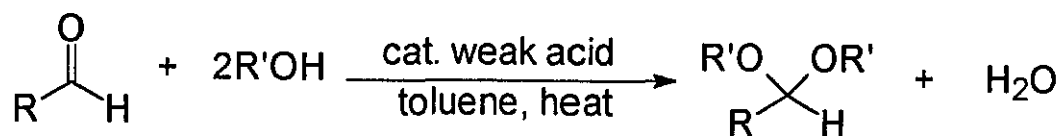
Later in our study, additional known acetal ligands [25a-b] were investigated in a novel asymmetric system (see Chapter 6), as were their oxazoline analogues [21a-d], including some novel phosphinooxazolines (see Chapters 6 and 7). Here examples are shown as the theorised metal chelates.



2.4 Ligand Synthesis

The success of enantiomerically pure acetals and oxazolines in asymmetric synthesis has led to the preparation of such compounds being well documented.^{65, 66} Here we have alluded to some of the numerous methods for synthesising both moieties and the methods employed in each case.

The common use of acetals as protecting groups for carbonyls in synthesis has led to the extensively utilised method of formation (method A). Acetals are formed by reaction of the corresponding carbonyl and alcohol, by heating in the presence of catalytic acid in toluene. The equilibrium is forced towards the product acetal by removal of water, either using drying agents or removal of the toluene/water azeotrope.



Method A

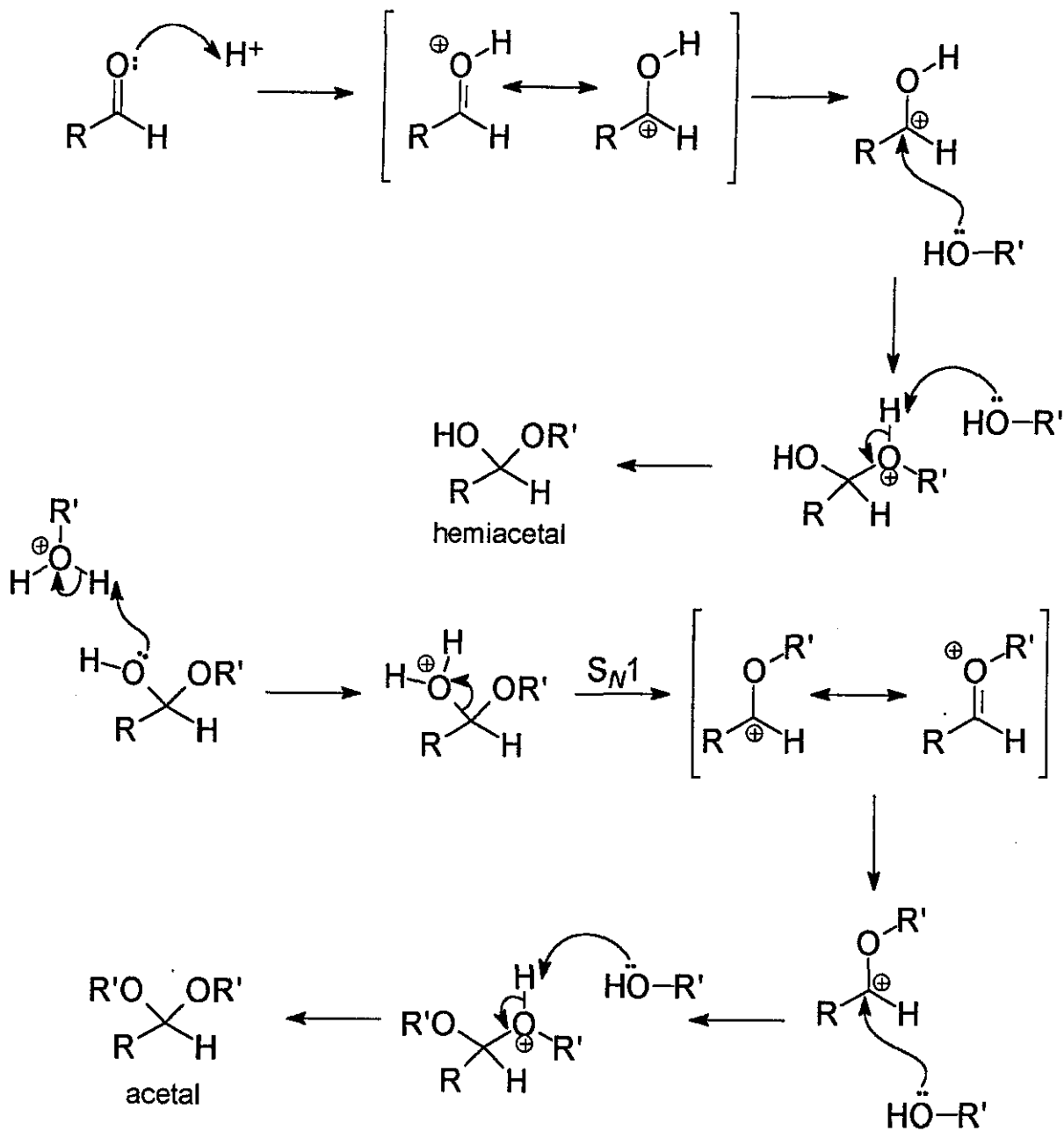
The scheme and mechanism shown here is of the more reactive aldehyde/alcohol combination. The mechanism is initiated by general acid catalysis with the rate-

⁶⁵ For a review on the preparation of acetals see, A. J. Meskins, *Synthesis*, 1981, 501.

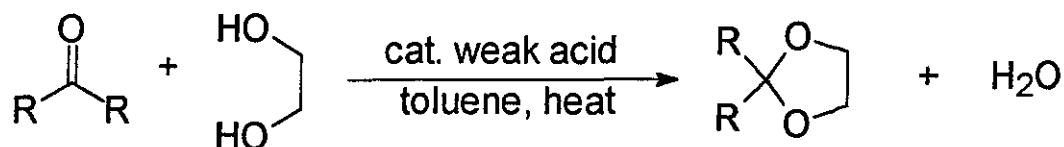
⁶⁶ T. G. Gant, A. I. Meyers, *Tetrahedron*, 1994, 50, 2297.

determining step being the loss of water from the protonated hemiacetal via an S_N1 mechanism.

Mechanism

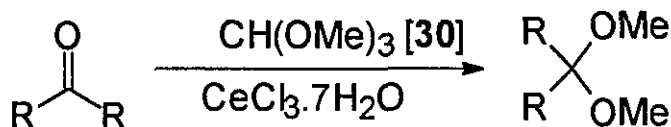


The reaction of ketones with alcohols does not normally take place easily under these conditions, but they can be made to react with 1,2-diols to form cyclic acetals (Scheme 27).



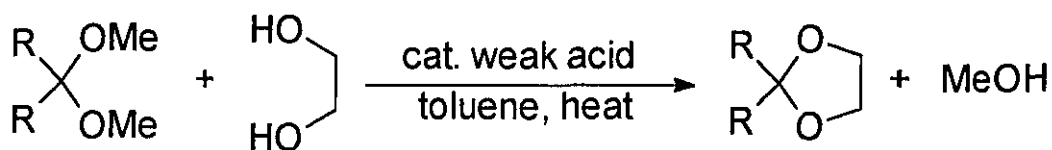
Scheme 27

Alternatively another method for the formation of acetals may be employed. Initially the carbonyl is converted into the dimethyl acetal upon treatment with trimethyl orthoformate [30] in methanol using cerium trichloride as a catalyst (Scheme 28).



Scheme 28

Subsequent transacetalisation with an alcohol/diol then affords the required acetal (method B).



Method B

In our efforts to synthesise bisacetal ligands we employed both methods **A** and **B**. We found no yield advantage of one system over another and so primarily adopted method **A** as this was a one step procedure. In the event of the appropriate aldehyde being unavailable we were able to acquire the dimethyl acetal derivative. In these cases we used the alternative transesterification method **B**.

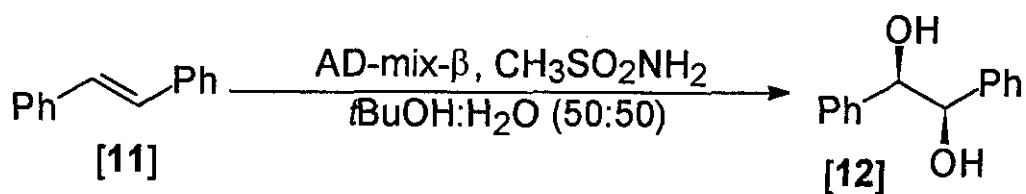
Commonly to the synthesis of all acetal ligands the aldehyde/dimethyl acetal starting materials were available from commercial sources. However, the corresponding diols were found to be expensive and so alternative arrangements had to be considered for the following;

(*R,R*)-butane-2,3-diol [32] . This was made available as a generous donation by Chiroscience *via* their asymmetric hydrogenation technology.

(*R,R*) and (*S,S*)-1,2-diphenyl ethanediol [12, 33]. These were made *via* the asymmetric dihydroxylation of *trans*-stilbene devised by Sharpless and co-workers.⁶⁷

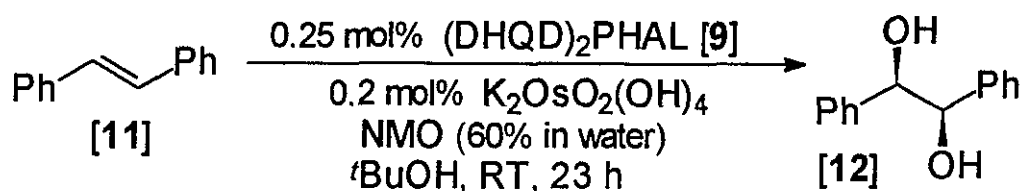
¹⁵ The mixture of compounds required to carry out the dihydroxylation is now available commercially available as AD-mix- α [containing (DHQ)₂PHAL)] and AD-mix- β [containing (DHQD)₂PHAL)]. These mixes in conjunction with methanesulfonamide and water/*tert*-butanol afford the diol products in *S,S* and *R,R* configurations respectively (**Scheme 29**).

⁶⁷ W. Amberg, Y. Bennani, R. Chada, G. Crispino, W. Davis, J. Hartung, K. Jenong, Y. Ogino, T. Shibita, K. B. Sharpless, *J. Org. Chem.*, 1993, 58, 844.



Scheme 29

As demand for the diol increased we turned to the modified kilogram scale preparation (**Scheme 30**).¹⁶

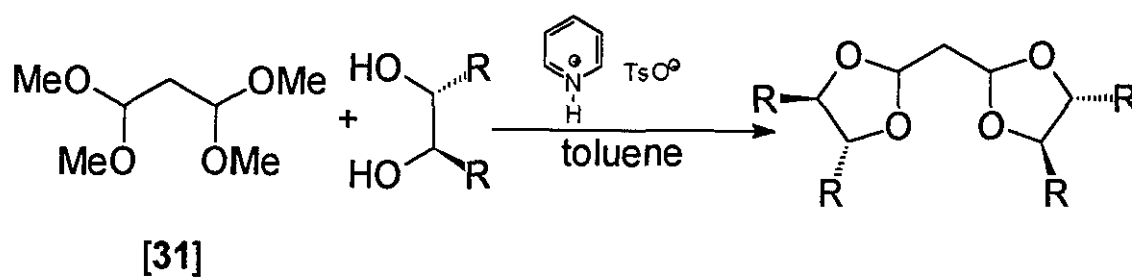


Scheme 30

We had a number of problems during our 50g scale up procedure. The reaction time stated in the literature was approximately 14 h; we quenched the reaction after 10 days with the reaction still not at completion. The mixture had then become solidified, required dilution and separating into portions to complete the work up. The product precipitated from solution as indicated in the paper but as an impure brown solid, not as white pure crystals. Batches of solid had to be taken up in ethyl acetate, washed with water and acid and evaporated to dryness under reduced pressure. The resulting light brown solid was recrystallised from ethyl acetate to produce the pure compound but in a much reduced yield, 39%.

2.4.1 Bisacetal Ligands

The common set of C_2 symmetric derived bisacetals [37–42] containing one CH_2 unit in between the acetal moieties was readily available from the transesterification (method **B**) of malonaldehyde bis-(dimethylacetal) [31], with the corresponding enantiomerically pure diol [12, 32–36] using pyridinium *p*-toluene sulfonate as a catalyst (**Scheme 31**). The generated methanol/toluene mix was removed using a Dean Stark apparatus in order to drive the reaction. The use of molecular sieves as a drying agent was found to be cumbersome as they disintegrated during the reaction and provided difficulty on work up.



Scheme 31

The preparation of these ligands is summarised in **Table 1**.

Table showing the target bisacetal ligands, including the enantiomerically pure diols from which each was synthesised and the yield.

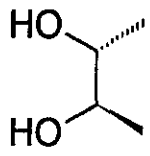
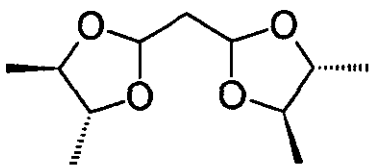
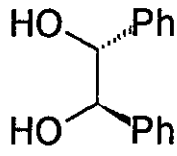
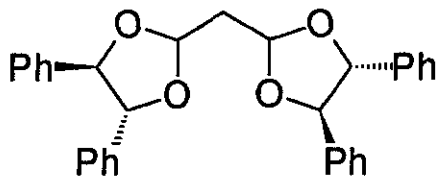
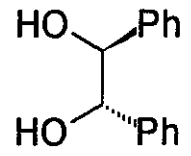
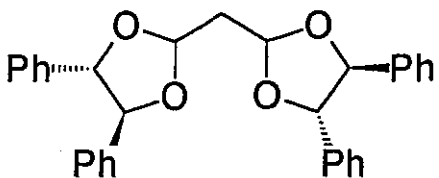
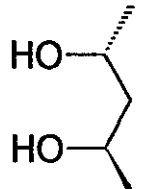
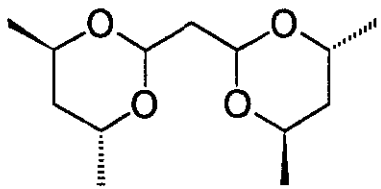
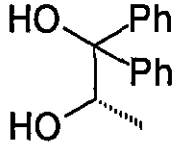
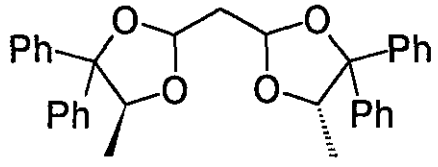
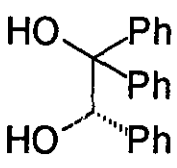
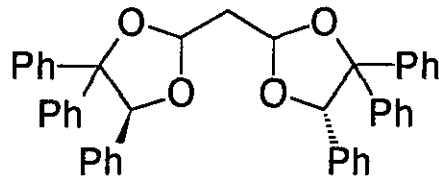
Diol	Yield (%)	Ligand
 <p>[32]</p>	95	 <p>[37]</p>
 <p>[12]</p>	71	 <p>[38]</p>
 <p>[33]</p>	66	 <p>[39]</p>
 <p>[34]</p>	32	 <p>[40]</p>
 <p>[35]</p>	66	 <p>[41]</p>

Table 1

Diol	Yield (%)	Ligand
 [36]	0	 [42]

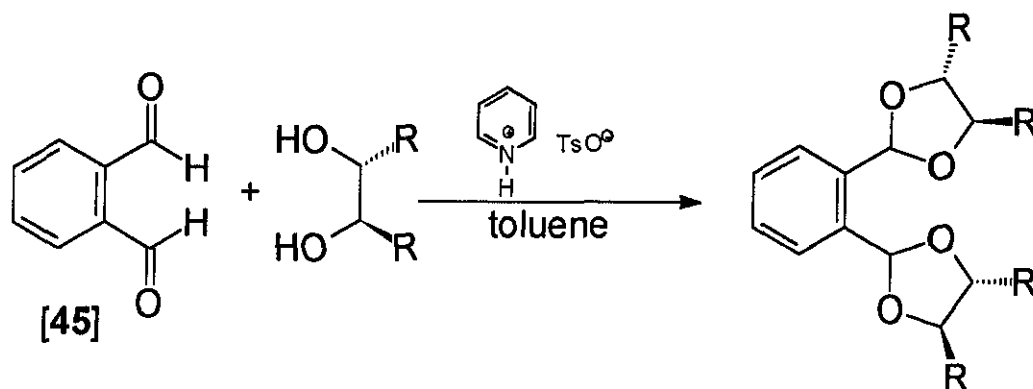
malonaldehyde bis-(dimethylacetal) [31] (1.17mmol), corresponding enantiomerically pure diol (2equivalents), pyridinium *p*-toluene sulfonate (0.01mmol) refluxed in 5cm³ toluene until reaction shown to be complete by tlc. e.e. determined by chiral shift NMR studies.

Table 1 (continued)

Unfortunately ligand [41] was synthesised as a crude mixture from which the pure product was inseparable and in poor yield, causing its use to be greatly limited.

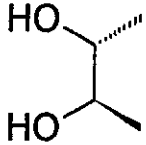
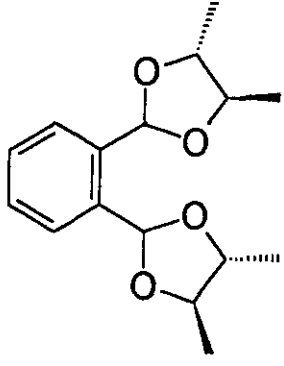
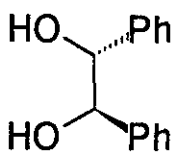
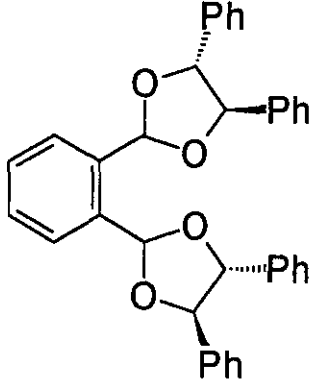
Attempts at making the more sterically hindered ligand [42] were completely unfruitful, presumably due to the bulk of the diol [36] (Table 1, entry 6).

The bisacetals [43, 44] containing the larger spacing unit of a phenyl ring between the acetal moieties were prepared *via* method A. In each case *o*-phthalic dicarboxaldehyde [45] was heated at reflux in toluene with the corresponding diol and pyridinium *p*-toluene sulfonate as a catalyst (Scheme 32). The water/toluene azeotrope was easily removed using a Dean Stark apparatus.



Scheme 32

Table 2 shows the ligands synthesised, with yields and the corresponding diol from which each was synthesised.

Diol	Yield (%)	Ligand
 <p>[32]</p>	54	 <p>[43]</p>
 <p>[12]</p>	78	 <p>[44]</p>

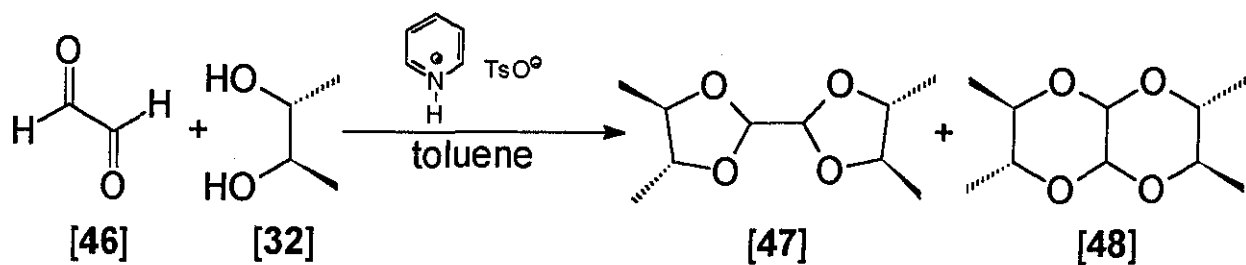
o-Phthalic dicarboxaldehyde [45] (1.17mmol), corresponding enantiomerically pure diol (2 equivalents), pyridinium *p*-toluene sulfonate (0.01mmol) refluxed in 5cm³ toluene until reaction shown to be complete by tlc. e.e. determined by chiral shift NMR studies.

Table 2

These constituted the bulkiest ligands, which on complexation with a metal should create a seven membered ring chelate.

Having generated two sets of bisacetal ligands with the capability of forming six and seven membered chelates to metals, we decided to make one other with a smaller bite angle. The known bisacetal [47] was obtained by the reflux of glyoxal [46] with

(*R,R*)-butane-2,3-diol [32] again using pyridinium *p*-toluene sulfonate as a catalyst (Scheme 33).⁶⁸



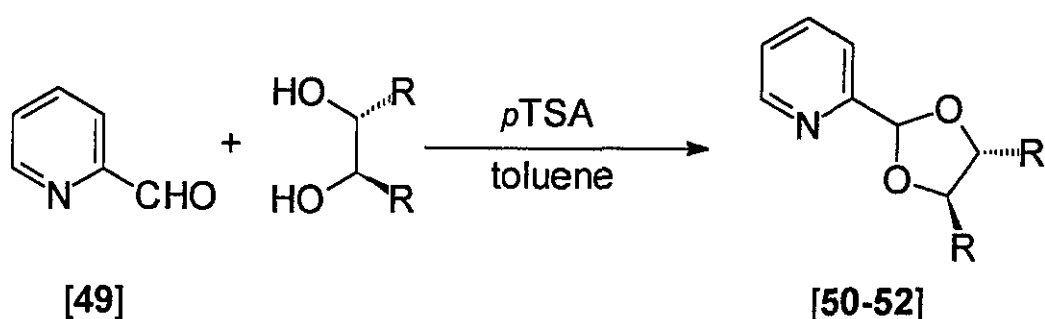
Scheme 33

Unfortunately this ligand has a known reaction by-product [48] which is inseparable. Fortunately we obtained the required product with only a 10% contamination (shown by NMR spectroscopy) and thus the ligand was used in subsequent asymmetric reactions as found. We were unable to qualify what effect, if any, this by-product had in the reactions in to which it was dispensed.

⁶⁸ P. P. Castro, S. Tihomirov, C. G. Gutierrez, *J. Org. Chem.*, 1988, 53, 5181.

2.4.2 Acetal/Pyridine Based Ligands

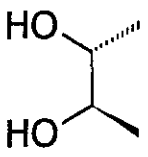
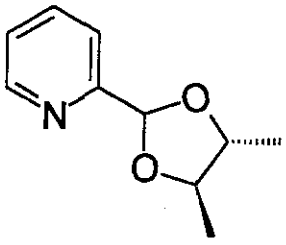
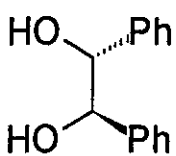
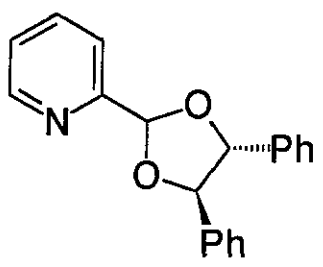
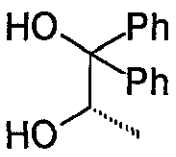
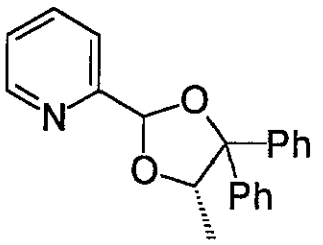
In much the same way as the bisacetals had been synthesised we pursued the synthesis of a range of ligands containing a pyridine ring with an acetal moiety at the 2-position. Pyridinium 2-carboxaldehyde [49] was refluxed in toluene with the corresponding diol and *p*-toluene sulfonic acid to afford the ligands [50–52] (Scheme 34).



Scheme 34

In this reaction we changed the acid catalyst to *p*-toluene sulfonic acid in an attempt to increase the rather disappointing yields. However, it appeared to be of little improvement over the previously used acid or over camphor sulfonic acid (the acid of choice by Frost).³⁹ The use of additional drying agents also did nothing to drive the reactions to completion.

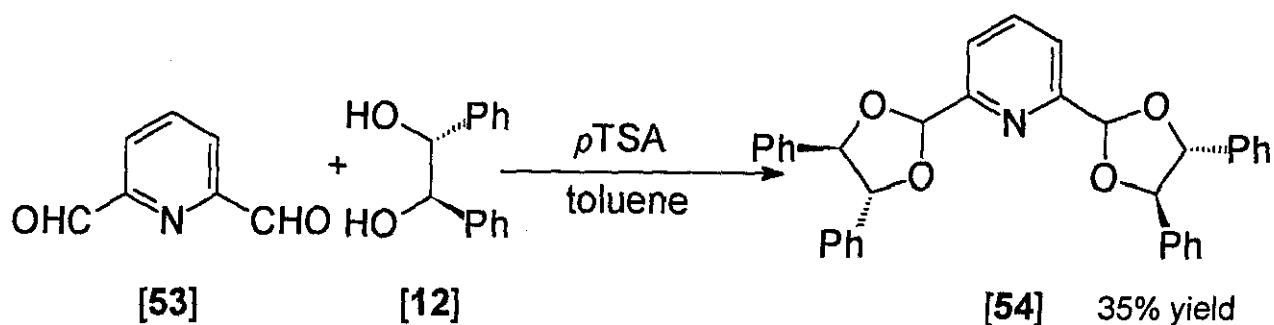
Table 3 showing the pyridine based ligands, the diols from which they were synthesised and the yields.

Diol	Yield (%)	Ligand
 <p>[32]</p>	51	 <p>[50]</p>
 <p>[12]</p>	48	 <p>[51]</p>
 <p>[35]</p>	27	 <p>[52]</p>

pyridinium-2-carboxaldehyde [49] (1.17mmol), corresponding enantiomerically pure diol (1 equivalent), pyridinium *p*-toluene sulfonate (0.05 equivalents) refluxed in 5cm³ toluene until reaction shown to be complete by tlc. e.e. determined by chiral shift NMR studies.

Table 3

A further example was produced (mimicking the 'pybox' ligands) [54], having acetal moieties at the 2- and 6-position of the pyridine ring. This ligand was synthesised in the same fashion using pyridinium-2,6-dicarboxaldehyde [53] and two equivalents of enantiomerically pure diol [12] (Scheme 35).

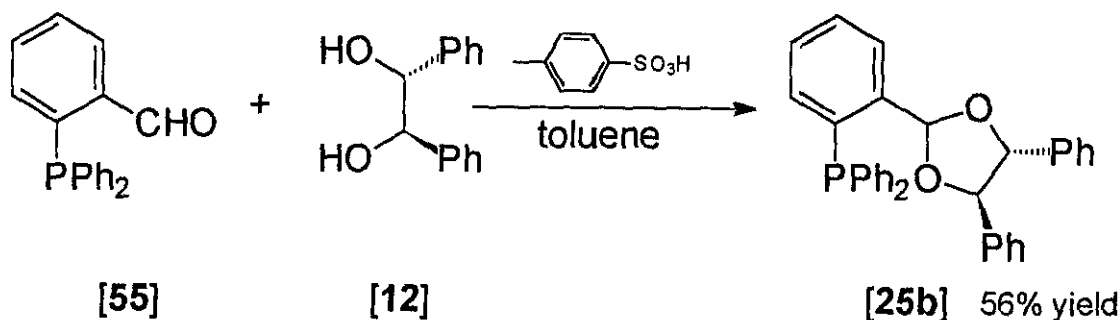


Scheme 35

In this case only the ligand produced from the phenyl derived diol was available. This was due to an untimely lack of (*R,R*)-butane-2,3-diol from the commercial suppliers.

2.4.3 Phosphinoacetal Ligands

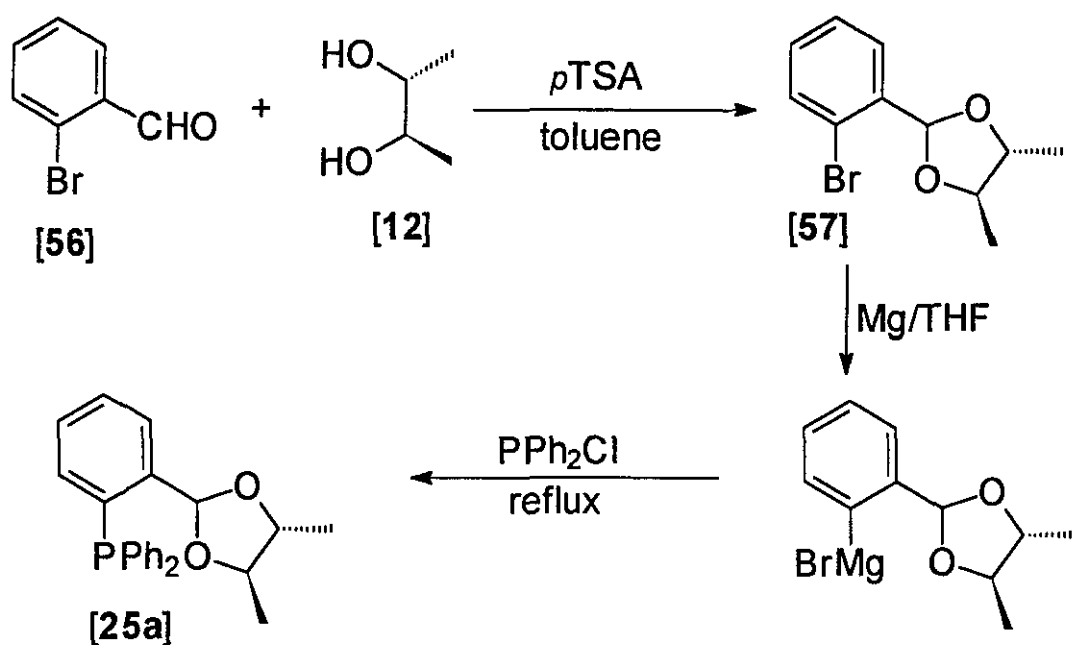
Towards the end of this research time (see Chapter 6) we considered it prudent to test the phosphino acetal ligand [25b] (first synthesised by Frost and Williams), as we were familiar with the procedure for synthesising it and considered that it would be successful in inducing enantioselectivity in the systems we were trying, based on its similarities to other successful ligands.³⁹ In order to do so we followed a modified version of the literature preparation. Based on the experience of our other acetal preparations, we went ahead with the quick one step acetalisation of diphenylphosphinophenyl-2-carboxaldehyde [55] with (*R,R*) diphenyl ethane-1,2-diol [12] (Scheme 36).



Scheme 36

The yield was much depleted from the literature preparation which uses the transacetalisation method **B**, from the dimethylacetal derivative of [55] but it was considered adequate for our needs at the time.

We also tried an alternative two step synthesis for the preparation of the analogous ligand [25a] (Scheme 37).



Scheme 37

Initially the bromocarboxaldehyde [56] was acetalised with (R,R) diphenyl ethane-1,2-diol [12] to form the bromo-arene [57] followed by the subsequent formation of the Grignard reagent. The organometallic species was then added to chlorodiphenylphosphine in solution and refluxed. Unfortunately the Grignard species was very difficult to form and appeared to quench itself almost immediately on activation. This was apparent as to some samples we added water or

benzaldehyde and no reaction occurred visibly or by TLC. Therefore addition to the phosphorus did not occur and the method was abandoned.

2.4.4 Phosphorus/Oxazoline Based Ligands

Phosphinooxazoline ligands (**Figure 7**) have been extensively documented and used in the literature and within our own research group. The particular emphasis of the asymmetric reactions in which they have been used is given in subsequent relevant chapters (6 and 7).

2.4.4.1 Aryl Phosphine Oxazoline Ligands

Here we are concentrating on the synthesis of known oxazoline ligands [**21a-c**] and novel oxazoline ligands [**70**, **71**], both of which were generated as part of this research.

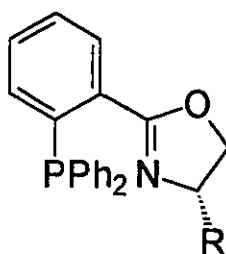


Figure 7

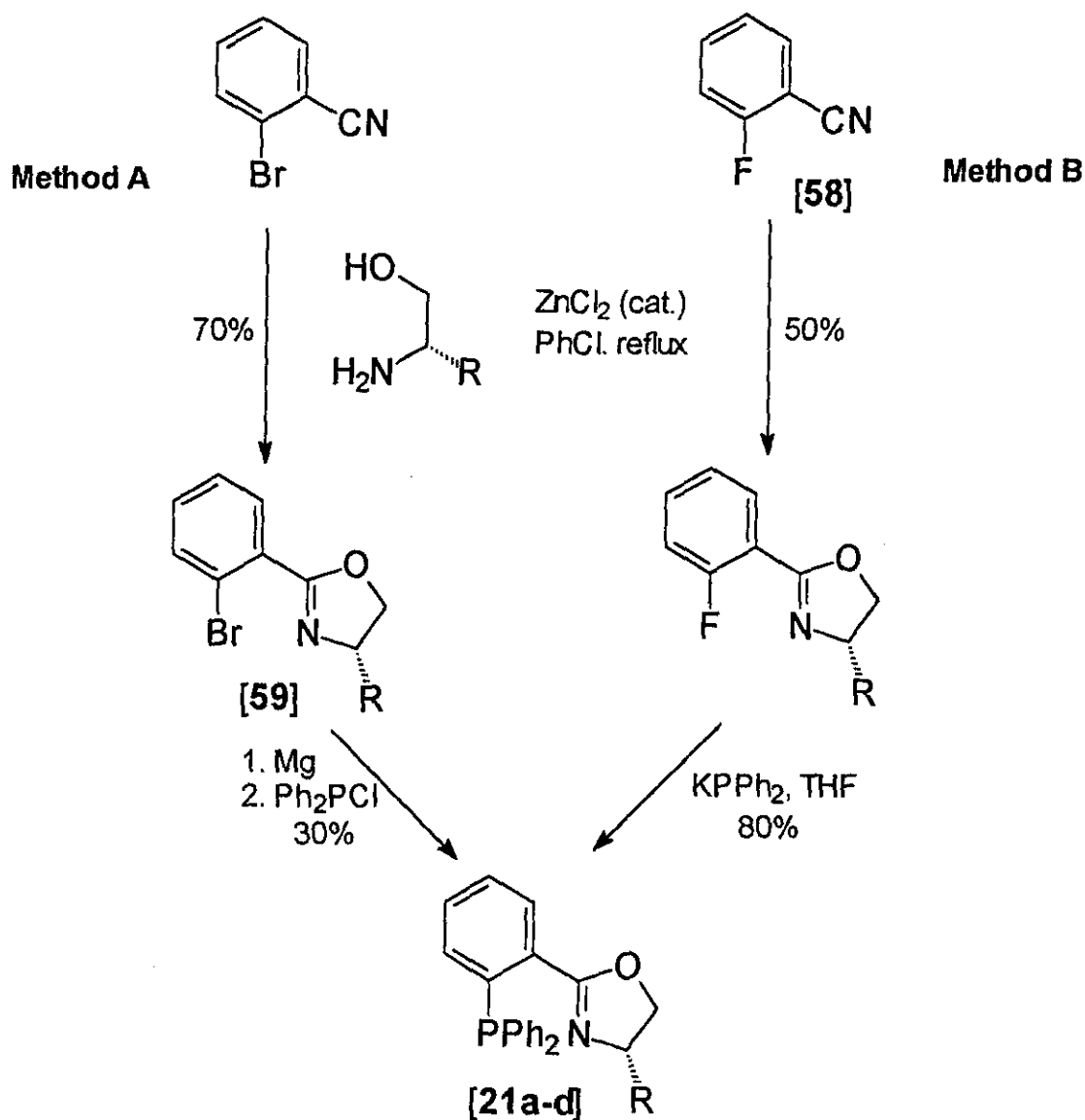
In 1993 Helmchen,⁶⁹ Pfaltz⁷⁰ and Williams⁷¹ independently published synthetic routes to chiral aryl-phosphine-oxazolines. The synthetic approaches to these ligands are similar, providing products in good chemical yield. All three groups synthesise the oxazoline ring from the reaction of a nitrile with the corresponding amino alcohol in the presence of zinc chloride as a catalyst.

⁶⁹ J. Sprinz, G. Helmchen, *Tetrahedron Lett.*, 1993, 34, 1769.

⁷⁰ P. von Matt, A. Pfaltz, *Angew. Chem. Int., Ed. Engl.*, 1993, 32, 566.

⁷¹ G. J. Dawson, C. G. Frost, J. M. J. Williams, S. J. Coote, *Tetrahedron Lett.*, 1993, 34, 3149.

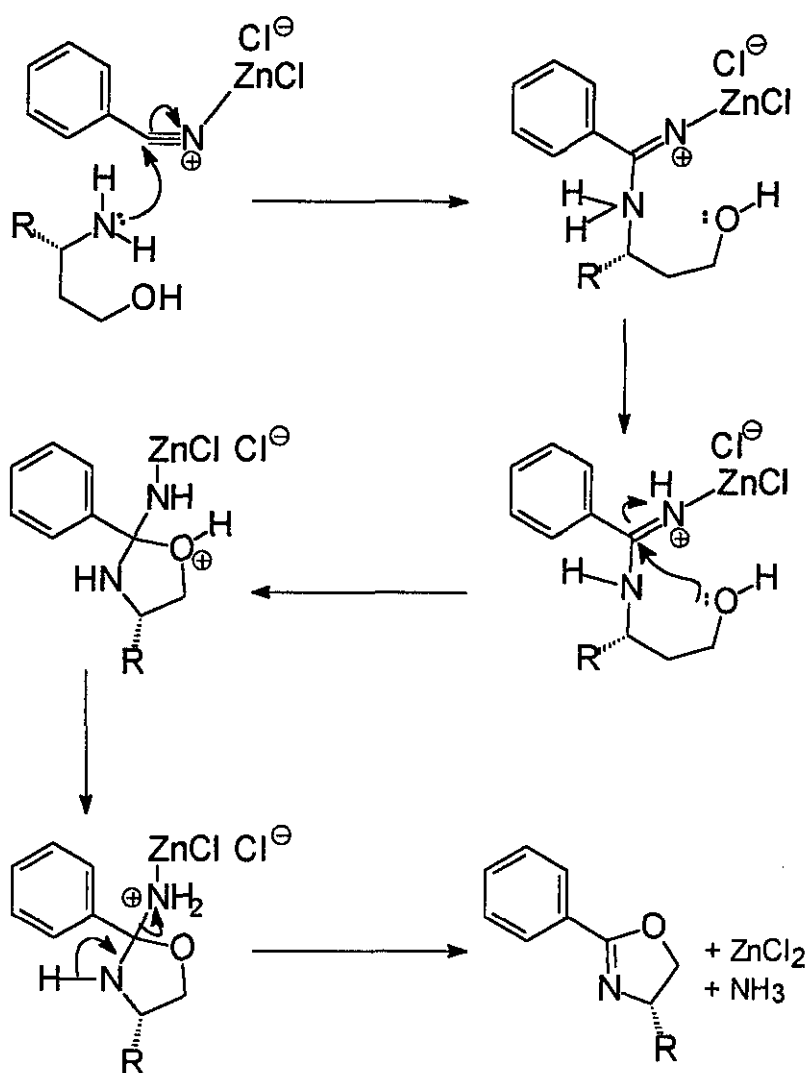
However the methods differ in the introduction of the phosphino group. Pfaltz and Helmchen both favour the reaction of a Grignard reagent formed from the bromoarene [59] with a chlorophosphine moiety (**method A**). Williams and co-workers alternatively use potassium diphenylphosphide to introduce the phosphine moiety (**method B**). Both methods are outlined in **Scheme 38**.



Scheme 38

We followed the typical 'in house' procedure, method **B**. With commercially available amino alcohols [60–64] and 2-fluorobenzonitrile [58] in hand we proceeded to effect

the condensation of these using a zinc chloride catalyst under reflux in chlorobenzene. The proposed mechanism of the ring formation reaction is illustrated in **Scheme 39**. 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 the regeneration of the zinc chloride catalyst affords the oxazoline.



Scheme 39

A summary of the 2-fluorophenyl oxazoline products [65–69] is given in Table 4.

Table showing the fluoro-oxazoline ligand precursors, the enantiomerically pure aminoalcohols from which each was synthesised and the yield in each case.

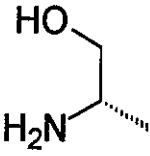
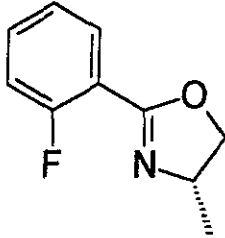
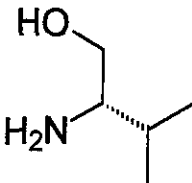
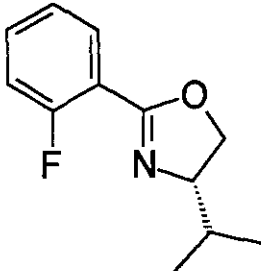
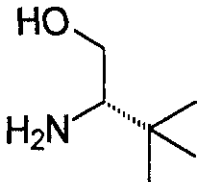
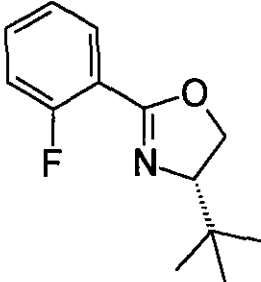
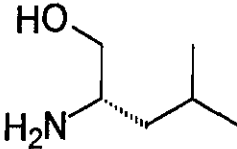
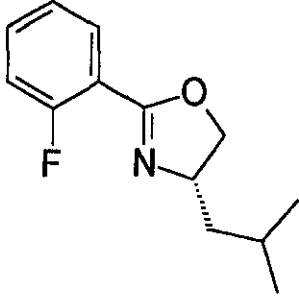
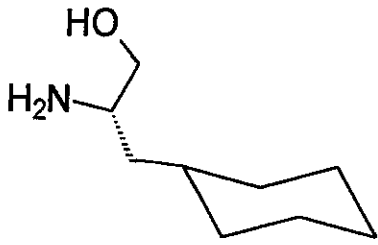
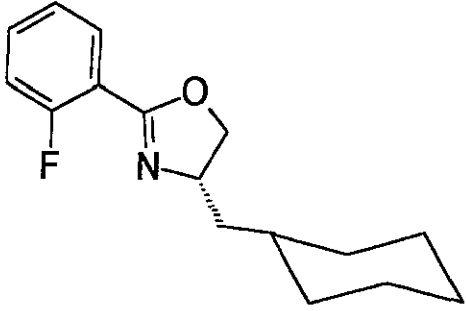
Amino alcohol	Yield (%)	Ligand intermediate
 <p>[60]</p>	34	 <p>[65]</p>
 <p>[61]</p>	39	 <p>[66]</p>
 <p>[62]</p>	24	 <p>[67]</p>
 <p>[63]</p>	69	 <p>[68]</p>

Table 4

Amino alcohol	Yield (%)	Ligand intermediate
 <p>[64]</p>	39	 <p>[69]</p>

fluorobenzonitrile [58] (26mmol), corresponding enantiomerically pure aminoalcohol (31mmol) and zinc chloride (1.1 ml (1M solution in Et₂O)) refluxed in chlorobenzene (8ml) under anhydrous conditions for 6 hours. e.e. confirmed by comparison of optical rotations to literature values.

Table 4 (continued)

The phosphine ligands [21a–c, 70, 71] were then prepared by the treatment of the fluoro-oxazoline intermediate with potassium diphenylphosphide in THF at reflux. In all cases the enantiomerically pure ligands were realised with no erosion of the asymmetric centres. Completed ligand syntheses are summarised in **Table 5**.

Table showing phosphino-oxazoline ligands and the fluoro precursors with corresponding yields.

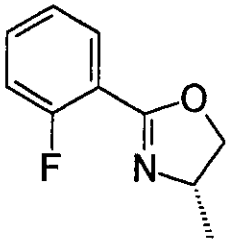
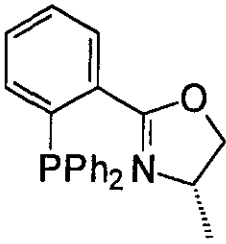
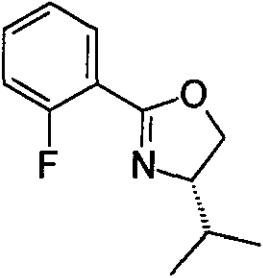
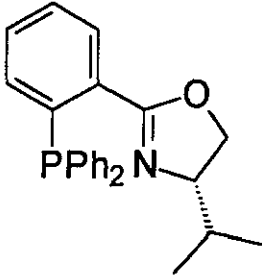
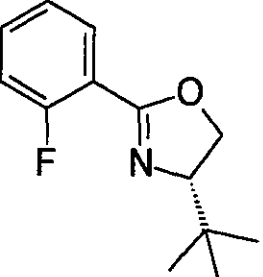
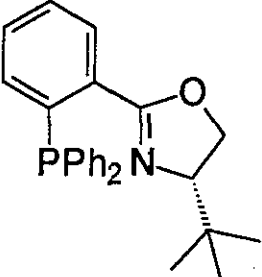
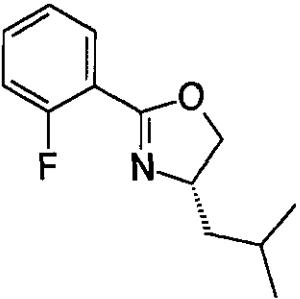
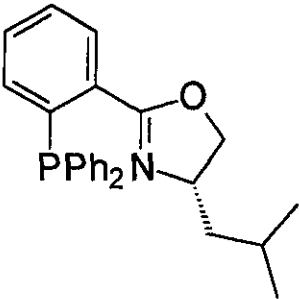
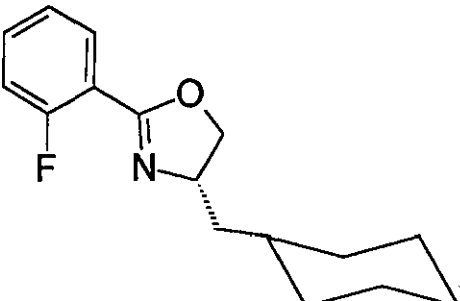
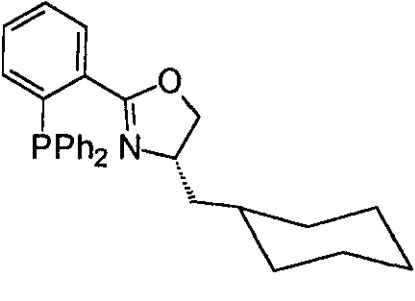
Fluoro-oxazoline intermediates	Yield (%)	Phosphine-oxazoline ligands
 <p>[65]</p>	33	 <p>[21a]</p>

Table 5

Fluoro-oxazoline intermediates	Yield (%)	Phosphine-oxazoline ligands
 <p data-bbox="368 614 430 654">[66]</p>	62	 <p data-bbox="1023 614 1115 654">[21b]</p>
 <p data-bbox="368 975 430 1015">[67]</p>	40	 <p data-bbox="1023 975 1115 1015">[21c]</p>
 <p data-bbox="368 1362 430 1402">[68]</p>	32	 <p data-bbox="1023 1362 1100 1402">[70]</p>
 <p data-bbox="368 1754 430 1793">[69]</p>	39	 <p data-bbox="1023 1754 1100 1793">[71]</p>

fluoro-oxazoline precursors (1mmol) was added dropwise to refluxing potassium diphenylphosphide (1.4mmol) in anhydrous THF. Reflux continued until all starting material reacted, shown by tlc. e. e. confirmed by comparison of optical rotations to literature values.

Table 5 (continued)

Ligands [70] and [71] and their precursors are novel to this family of oxazolines. The yields stated are optimised, although relatively low in comparison with literature values of their analogues.

We considered that the success of the family of oxazoline based ligands in inducing asymmetry in metal catalysed systems was due to their metal binding ability. The distances between chelating atoms and thus the ligand and metal are imperative, especially in bringing the enantiomerically pure centre of the ligand into close proximity to the prochiral centre of the precursor, which is also bound to the metal.

We were fortunate to obtain X-ray crystallographic data for the two novel phosphinooxazoline ligands [70, 71], something which was not available for the other phosphorus-oxazoline in this series. We principally focussed our attention on the distance between the two chelating atoms in the ligands, *i.e.* phosphorus and nitrogen. For our ligands [70] and [71] the distances were concordant, at 2.85 Å and 2.86 Å respectively (Figure 8).

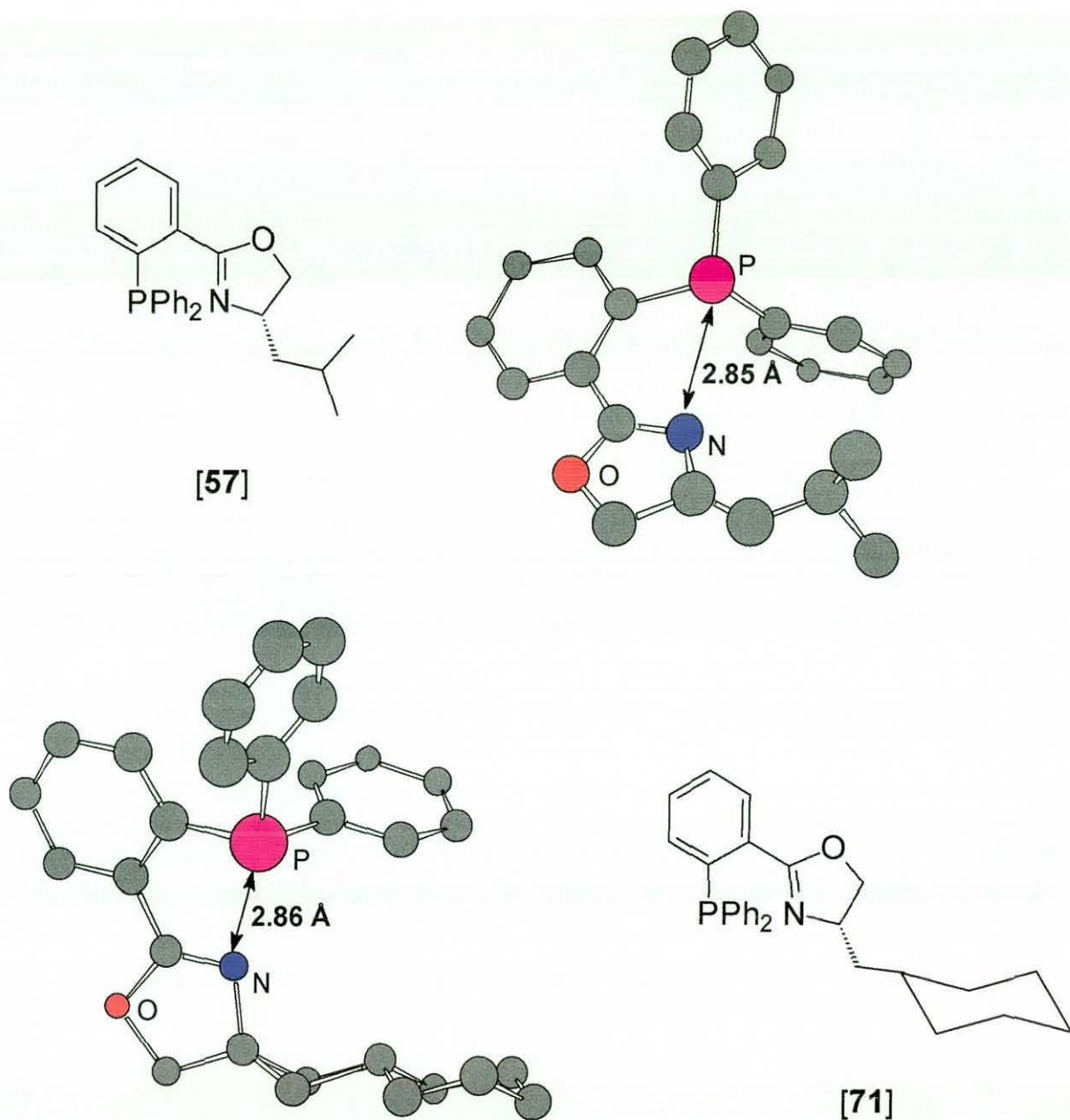
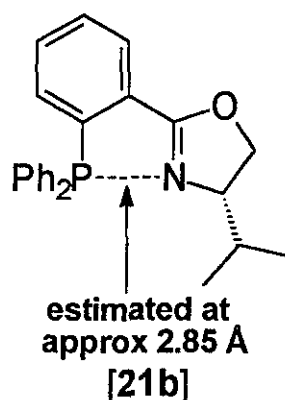
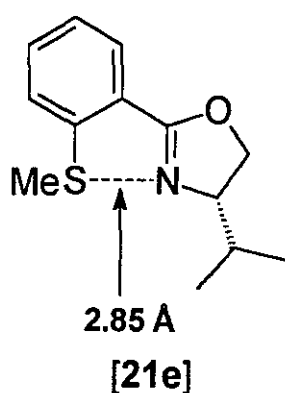


Figure 8

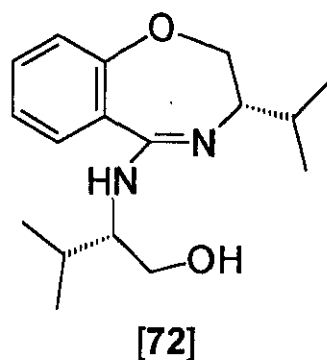
These atom distances were consistent with similar oxazoline ligands of this general structure containing a sulfur ligating atom [21e].⁷² Sulfur-oxazoline ligands are equally proficient at inducing asymmetry in palladium catalysed allylic substitution

⁷² J. Allen Ph.D. Thesis, Loughborough University, 1995.

reactions as their phosphorus analogues, although somewhat less reactive due to their lack of π -accepting behaviour.^{73, 74, 75}



Interestingly during the synthesis of ligand fluoro-precursor [66] a previously unreported by-product was observed. This by-product [72] appeared in up to 10% yield of the product, dependant on the time length of the oxazoline formation reaction. The longer the reaction time the more by-product was observed.



The by-product was detected as a white crystalline solid which precipitated from the product oil. It shows the inclusion of two amino-alcohol moieties to 2-fluorobenzonitrile, with one cyclising onto the ring with the expulsion of fluoride ion.

⁷³ G. J. Dawson, C. G. Frost, C. J. Martin, J. M. J. Williams, *Tetrahedron Lett.*, 1993, 34, 7793.

⁷⁴ J. V. Allen, G. J. Dawson, C. G. Frost, J. M. J. Williams, *Tetrahedron*, 1994, 50, 779.

⁷⁵ J. V. Allen, J. F. Bower, J. M. J. Williams, *Tetrahedron*, 1994, 5, 1895.

The structural identification of the crystalline solid was confirmed by the X-ray crystallographic data. This clearly shows the ring nitrogen having one single bond and one double to carbon, indicated by the bond lengths, 1.45 Å and 1.28 Å respectively (**Figure 9**). The *exo*-cyclic nitrogen shows only single bond lengths consistent with sp^3 hybridisation and is evidently bound to one residual hydrogen from the amino alcohol precursor.

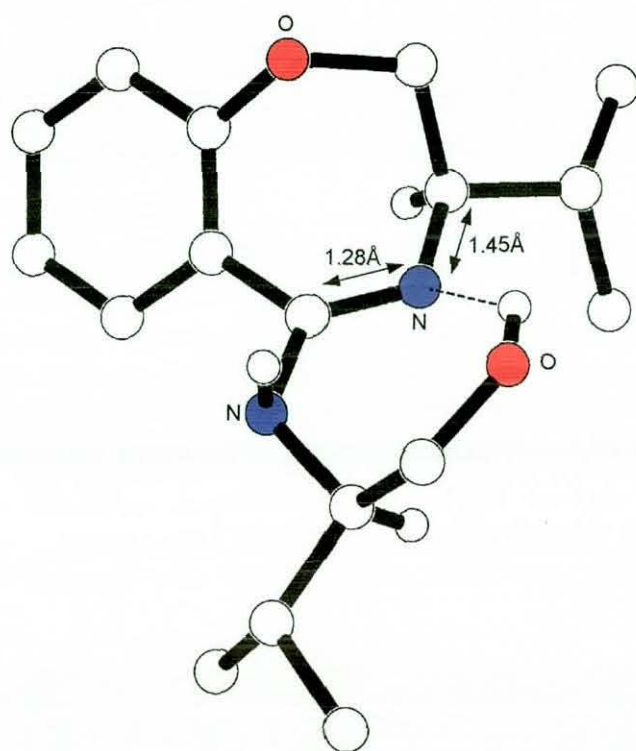
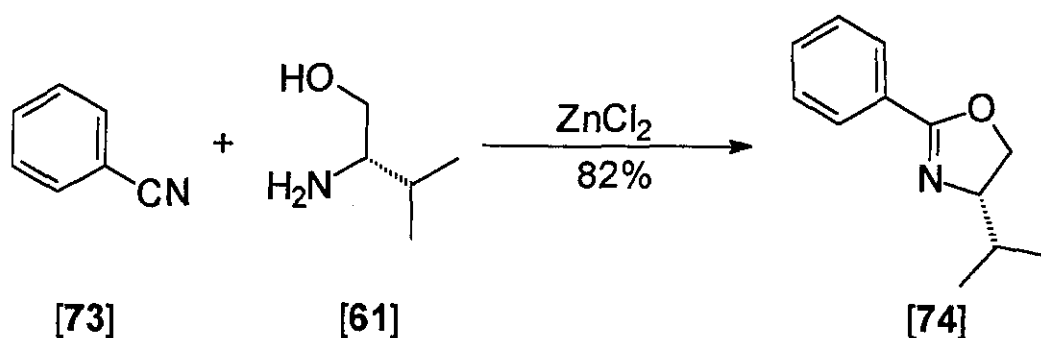


Figure 9

2.4.4.2. Alkyl Phosphine Oxazoline Ligands

Phosphorus oxazoline ligands incorporating aryl groups (normally phenyl) at the phosphorus are common due to their stability.⁷⁶ However we were unaware of any documentation of the corresponding alkyl derivatives. We took the opportunity of synthesising an example of an alkyl phosphinoxazoline ligand [75].

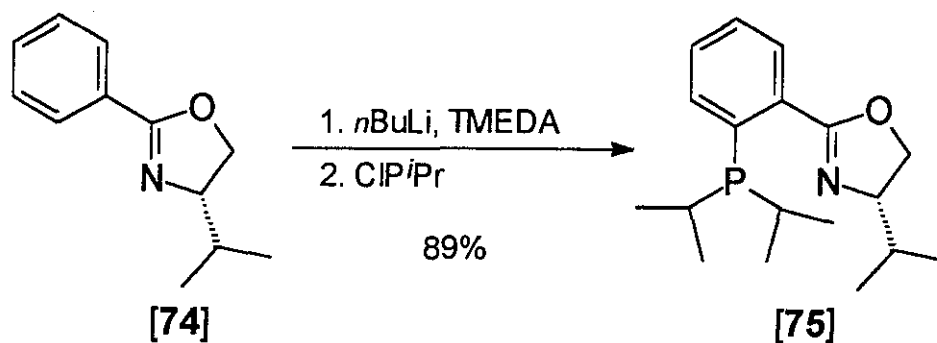
The oxazoline ring [74] was formed in the typical fashion from the condensation of benzonitrile [73] with (S)-valinol [61] in the presence of zinc chloride as a catalyst (Scheme 40).



Scheme 40

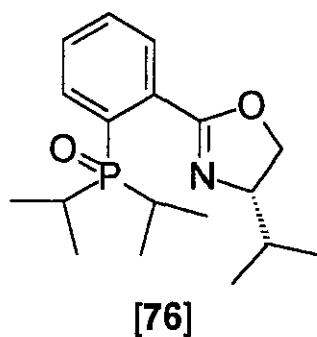
The diisopropylphosphine moiety was then introduced by standard deprotonation on the phenyl ring *ortho* to the oxazoline with *n*-butyllithium/TMEDA followed by quenching with chlorodiisopropylphosphine (Scheme 41).

⁷⁶ See all previous references to oxazoline ligands and M. Peer, J. C. de Jong, M. Kiefer, T. Langer, H. Rieck, H. Schell, P. Sennhenn, J. Sprinz, H. Steinhagen, B. Wiese, G. Helmchen, *Tetrahedron*, 1996, 52, 7547.



Scheme 41

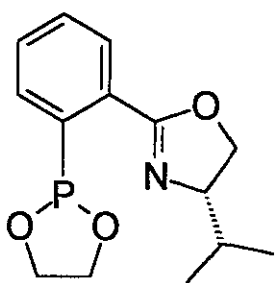
Rigorously dried Schlenk equipment was used in an overall attempt to exclude moisture from this reaction. However, some of the oxidised product [76] was observed as a small impurity in the ³¹P NMR spectrum. This was not surprising, as alkyl phosphorus moieties are known to be easily oxidised. Unfortunately the product could not be purified without creating more oxidised product and was used in asymmetric induction reactions crude (Chapter 7).



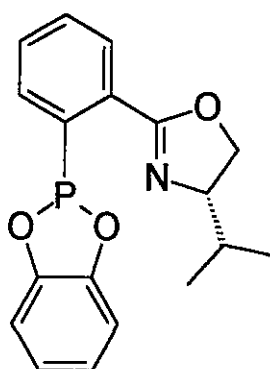
The ligand [75] was fully oxidised by stirring in air overnight and then characterized as the oxide derivative [76].

2.4.5 Attempted Developments into Expansion of Chiral Ligands

During the latter stages of this research we reached an impasse in which it was felt that the avenues of our research into purely acetal based ligand chemistry were exhausted. However we had acquired some good results with the known phosphine-oxazoline ligands [21a-c] (including our own novel ligands [70, 71] of the same ilk). We thus sought to combine the two structures. Here we wished to retain the oxazoline moiety, which had proven co-ordination qualities to metals and introduce the acetal moiety around the phosphorus atom. Initially we wished to observe the altered electronic effects on the chelating capability of the phosphorus by utilizing ligand [77] and [78] in palladium allyl substitution reactions (Chapter 7).

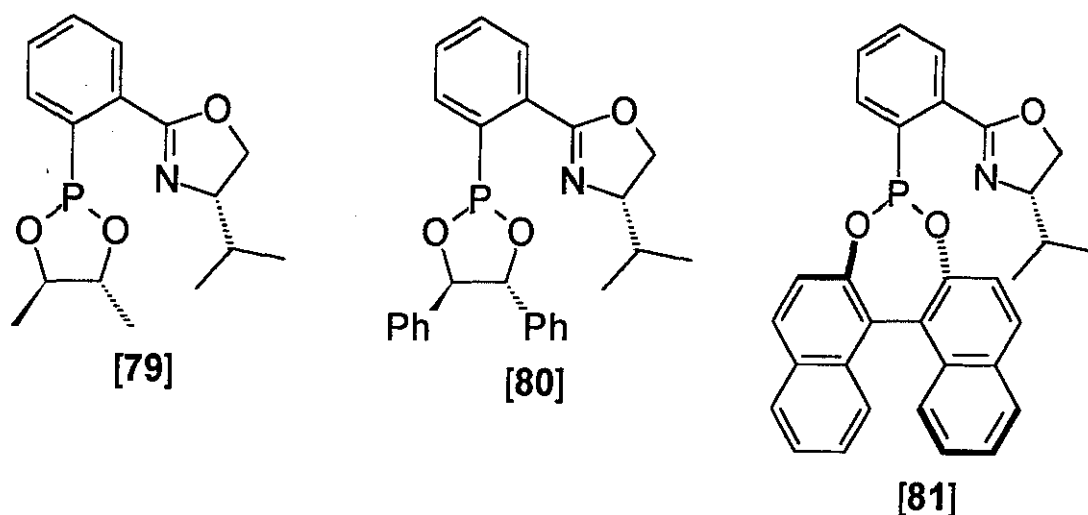


[77]



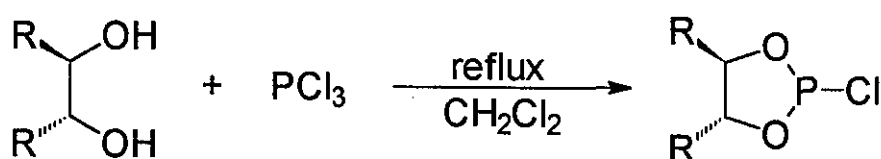
[78]

We then envisaged the introduction of chiral phosphorus-acetal rings, having either matched or mismatched arrangements to the oxazoline enantiomerically pure group [79-81].



The syntheses for each of these ligands had common approach. The oxazoline ring [74] was formed in the typical fashion from the condensation of benzonitrile [73] with (*S*)-valinol [61] in the presence of zinc chloride as a catalyst (**Scheme 40**).

Each of the phosphorus-acetal moieties was generated by the addition of the appropriate diol to a dry dichloromethane solution of phosphorus trichloride at a rate sufficient to maintain reflux (**Scheme 42**).⁷⁷



Scheme 42

The products were afforded by removal of solvent and excess phosphorus trichloride under reduced pressure. The generated products were very reactive and so were used directly in the subsequent step of the synthesis. It was also very difficult to identify if the products had indeed been formed. Only NMR spectroscopic techniques were available as a method of analysis, all others caused degradation. **Table 6**

⁷⁷ Except [77b] which was commercially available.

summarises the chlorophosphorus-acetal moieties thought to have been formed with apparent evidence.

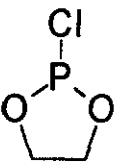
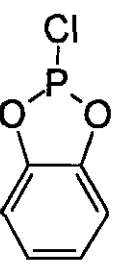
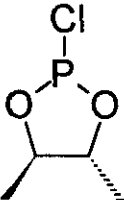
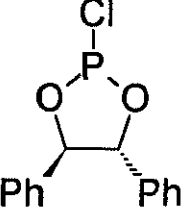
Chlorophosphine-acetal	Crude Yield(%)	Evidence of formation
 <p>[82]</p>	60	¹ H NMR spectrum shows no starting material and possible product, peaks at δ 4.25–4.45. ³¹ P NMR spectroscopy shows one predominant peak thought to be product (δ = 23).
 <p>[83]</p>	nd	Commercially available but arrived containing some oxide impurity by ³¹ P NMR
 <p>[84]</p>	93	¹ H NMR spectrum shows no starting material and possible product CH's at δ 4.44 and 3.93, methyl doublets at δ 1.44–1.54 ³¹ P NMR spectrum shows 2 equivalent peaks, one thought to be product and other the oxidised derivative (δ = 20.6 and 19.7)
 <p>[85]</p>	nd	¹ H NMR spectrum shows no clear product ³¹ P NMR spectrum shows 4 major peaks synthesis abandoned

Table 6

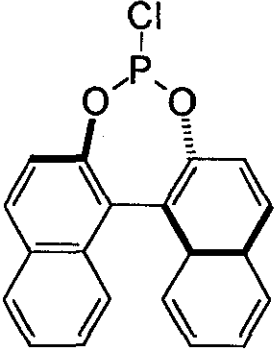
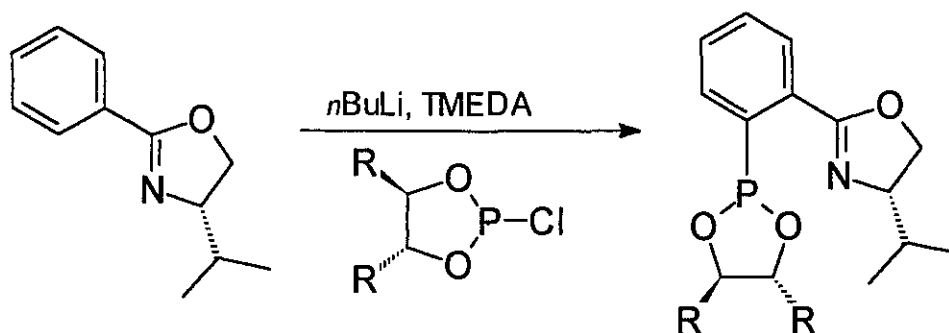
Chlorophosphine-acetal	Crude Yield(%)	Evidence of formation
 <p>[86]</p>	nd	¹ H NMR spectrum very complex showing no clear product ³¹ P NMR spectrum shows multiple major peaks Synthesis abandoned

Table 6 (continued)

The ligands [77–79] were then generated by standard deprotonation of [74] on the phenyl ring *ortho* to the oxazoline with *n*-butyl lithium/TMEDA followed by quenching with chlorophosphine-acetals moieties [82–84] (Scheme 43).



Scheme 43

Table 7 summarises the outcome from the attempted syntheses of the ligands. As presented in Table 7, the two ligands tentatively considered successfully synthesised [77, 79] were unable to be purified and thus were not fully characterised. Attempts to obtain their oxidised products for characterisation led to mixtures of

inseparable products. They were therefore tested in asymmetric reactions in a crude state (Chapter 6 and 7).

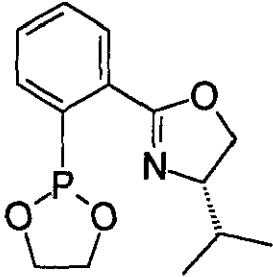
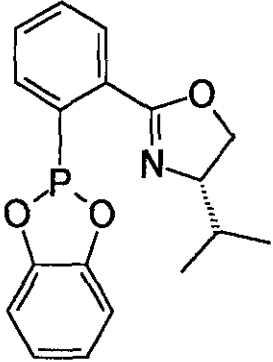
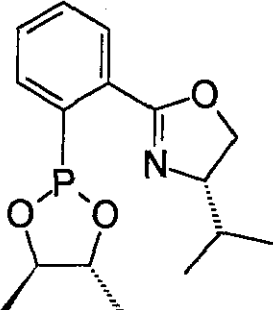
Ligand	Crude Yield (%)	Evidence of Formation and purification attempts
 <p>[77]</p>	56	<p>Crude ^1H NMR spectrum shows oxazoline protons plus additional proton peaks at δ 3.7–4.1 could be CH_2 from the acetal. ^{12}C NMR spectrum shows multiple CH_2 peaks. Crude material distilled. Clear oil not product by ^1H NMR spectroscopy but the residual material possible product and has one major peak by ^{31}P NMR spectroscopy. Still impure. No further characterisation due instability in air. Used as crude.</p>
 <p>[78]</p>	n/d	<p>^1H NMR spectrum of crude material is inconsistent with the required product due to a lack of aryl protons. On addition of water a very weak reaction occurred indicating that the phosphorus moiety had already degraded. Sample was discarded. Synthesis abandoned</p>
 <p>[79]</p>		<p>Crude ^1H NMR spectrum shows oxazoline protons plus additional proton peaks at δ 3.7–4.4 could be CH from the acetal. Also the Me groups from the oxazoline are more complex indicating phosphorus coupling. Crude material added to hexane, precipitate was not product, but crude material still shows favourable NMR spectrum peaks. Attempted aqueous wash caused additional degradation. No further characterisation due instability. Used as crude</p>

Table 7

2.5 Conclusion

Numerous novel and known enantiomerically pure ligands were synthesised for use in metal catalysed asymmetric reactions (see Chapters 3–8).

The ligands and their precursors successfully synthesised and characterised comprise of,

- Enantiomerically pure (*S,S*) diphenyl ethane-1,2-diol [12] obtained via dihydroxylation of *trans*-stilbene.
- Novel enantiomerically pure bisacetal ligands [37–41, 43, 44, 47] derived from enantiomerically pure diols, (plus attempted synthesis of ligand [42]).
- Novel enantiomerically pure pyridine/acetal ligands [50–52, 54], analogous to pymox and pybox ligands.
- Enantiomerically pure phosphinoacetal ligand [25b] derived from (*S,S*) diphenyl ethane-1,2-diol and diphenylphosphinophenyl-2-carboxaldehyde.
- Enantiomerically pure aryl phosphinooxazoline ligands [21a–c], including novel variants [70] and [71] and by-product [72] with X-ray crystallographic data.
- Novel enantiomerically pure alkyl phosphinooxazoline ligand [75] and its oxidised derivative [76].

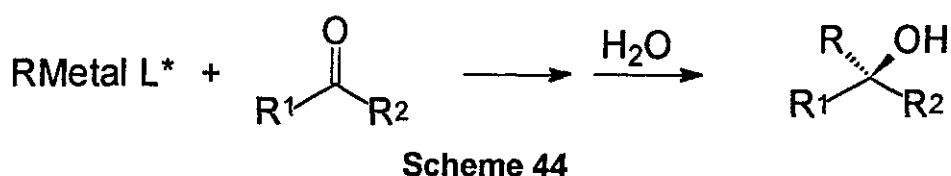
Also included are attempted syntheses of ligands [77–79] derived from enantiomerically pure phosphoranes [82–84] and phenyloxazoline [74], with successful (tentative) synthesis of enantiomerically pure ligands [77] and [79].

Chapter 3 Organometallic Additions to Benzaldehyde

- 3.1 Introduction
 - 3.1.1 Grignard additions
 - 3.1.1.1 Nature of the Grignard reagent
 - 3.1.1.2 Reaction mechanism
 - 3.1.1.3 Asymmetric Grignard systems
 - 3.1.2 Organolithium additions
 - 3.1.2.1 Asymmetric organolithium systems
- 3.2 Results and discussion
 - 3.2.1 Grignard additions
 - 3.2.1.1 Ligand effects
 - 3.2.1.2 Solvent effects
 - 3.2.1.3 Grignard reagent effects
 - 3.2.2 Organolithium additions
- 3.3 Conclusions

3.1 Introduction

The nucleophilic addition of organometallic reagents to carbonyl bonds which on quenching form 1°, 2° or 3° alcohols constitutes one of the most fundamental reactions in organic synthesis. Modifications of the organometallic compounds to include chiral, non-racemic auxiliaries or ligands offer an opportunity to create enantiomerically enriched alcohols (**Scheme 44**).



In particular the use of organomagnesium (Grignard) and organolithium reagents has prevailed due to their high generality and reactivity.

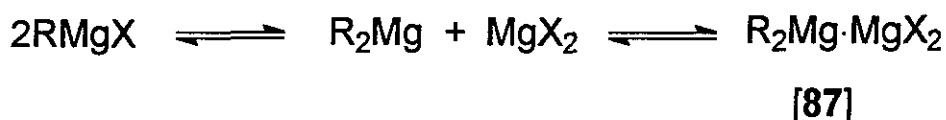
3.1.1 Grignard Additions

The addition of a Grignard reagent to an aldehyde or ketone is one of the most commonly used synthetic procedures to afford alcohols.⁷⁸ Since the proposition of the original simplistic formula, RMgX by Victor Grignard, there has been much conjecture about the mechanism of the Grignard reaction and the true nature of the organometallic species.

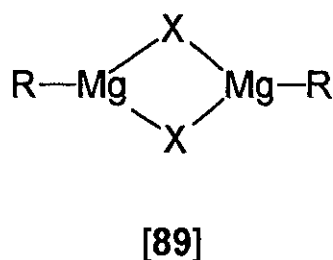
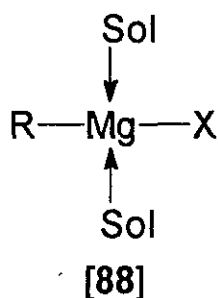
⁷⁸ For an excellent reference text; Handbook of Grignard Reagents, G. S. Silverman, Marcel Dekker, Inc, New York, 1996.

3.1.1.1 Nature of the Grignard Reagent

The actual structure of Grignard reagents in solution is now widely considered to be consistent with the following proposed equilibrium.



This 'Schlenk equilibrium' is highly dependent on the identity of R, X, concentration, temperature and most importantly solvent.^{79,80} It is well known that all of the above structures can co-ordinate with two molecules of diethyl ether. However, X-ray crystallographic studies of cooled ethereal and THF solutions showed exclusively the monomeric structure [88].^{81,82} The removal of the solvent drives the equilibrium to $\text{R}_2\text{Mg} + \text{MgX}_2$.



Grignard reagents in high concentration in diethyl ether contain dimers, trimers and higher polymers and so in this instance some of the complex [88] will be present,

⁷⁹ G. E. Parris, E. C. Ashby, *J. Am. Chem. Soc.*, 1971, 93, 1206.

⁸⁰ R. M. Salinger, H. S. Mosher, *J. Am. Chem. Soc.*, 1964, 86, 1782.

⁸¹ L. J. Guggenberger, R. E. Rundle, *J. Am. Chem. Soc.*, 1968, 90, 5375.

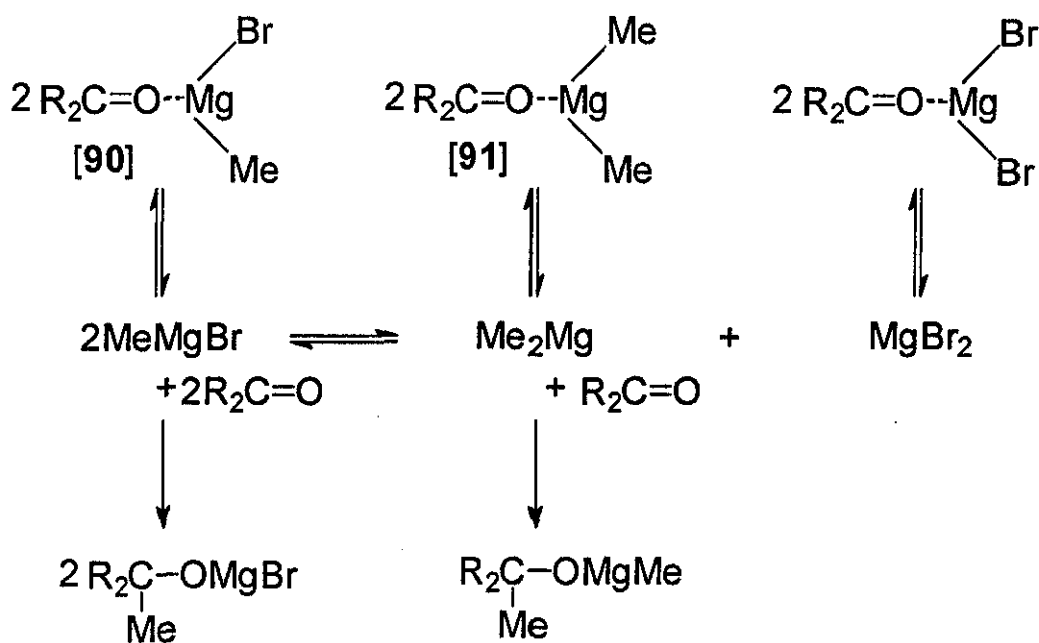
⁸² F. A. Schroder, *Chem. Ber.*, 1969, 102, 2035.

probably as the structure [89]. At low concentrations in diethyl ether and at all concentrations in THF the reagents are monomeric.⁸³

3.1.1.2 Reaction Mechanism

The mechanism of the Grignard reaction has been extensively discussed over the years with a number of highly plausible theories being offered. Problems can arise in studying the reaction since the solvated reagents (RMgX , R_2Mg and MgX_2) may all complex with the carbonyl substrate. Also trace amounts of impurities in the magnesium appear to have a great effect on the kinetics of the reaction.

Ashby and co-workers proposed a mechanism for the reaction between methylmagnesium bromide and 2-methylbenzophenone (Scheme 45).⁸⁴

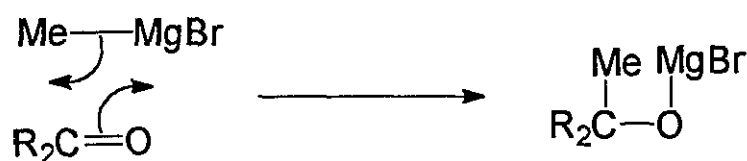


Scheme 45

⁸³ E. C. Ashby, M. B. Smith, *J. Am. Chem. Soc.*, 1964, 86, 4363.

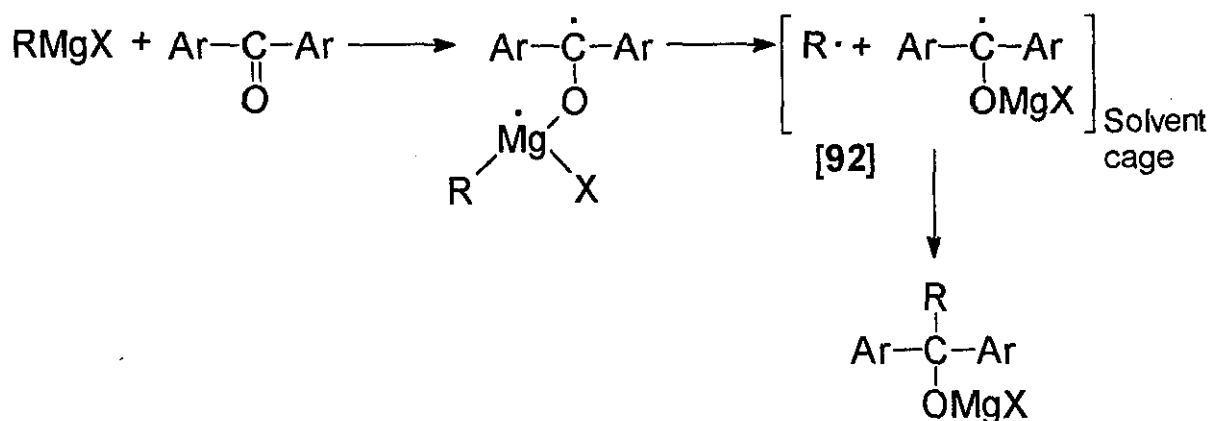
⁸⁴ E. C. Ashby, J. Laemmle, H. M. Neumann, *J. Am. Chem. Soc.*, 1972, 94, 5421.

When the Grignard reagent is present in excess, the mechanism is as shown, with product being formed from the initial intermediates [90] and [91]. If excess ketone is present the complexes [90] and [91] react further with each other and additional molecules of RMgX and ketone to give dimeric and trimeric species. On hydrolysis, these species are all converted to the alcohol product, R₂MeCOH. The actual MeMgBr or Me₂Mg reaction step with the substrate is not known but is postulated as a four centred cyclic transition state (Scheme 46).^{85,86}



Scheme 46

Another theory suggests that in some cases the reaction may, in part, go through a ketyl intermediate [92] (Scheme 47).^{87,88}



Scheme 47

⁸⁵ H. O. House, J. E. Oliver, *J. Org. Chem.*, 1968, 33, 929.

⁸⁶ E. C. Ashby, S. H. Yu, P. V. Roling, *J. Org. Chem.*, 1972, 37, 1918.

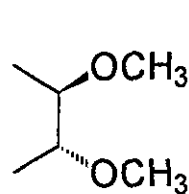
⁸⁷ C. Blomberg, H. S. Mosher, *J. Organomet. Chem.*, 1968, 13, 519.

⁸⁸ I. G. Lopp, J. D. Buhler, E. C. Ashby, *J. Am. Chem. Soc.*, 1975, 97, 4966.

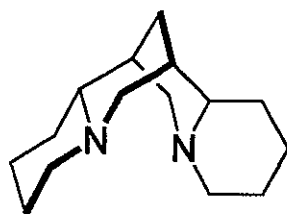
This pathway is called the 'single-electron-pathway' (SET) and is a more likely scenario for conjugated-aromatic aldehydes and ketones. It was envisaged that the addition of enantiopure moieties onto the magnesium would create a sterically hindered environment in the intermediate structure, which would facilitate the production of enantiomerically enriched alcohols via either mechanism.

3.1.1.3 Asymmetric Grignard Systems

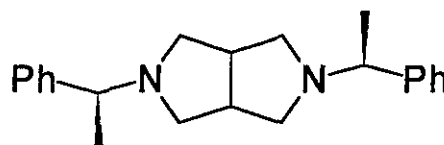
In 1953, Cohen and Wright first used (2*R*,3*R*)-dimethoxybutane [93] as a 'chiral solvent' to render Grignard additions enantioselective, albeit by only 5%.^{89, 90} Some years later (-)-sparteine [5] was observed to generate 22% e.e. in the reaction of benzaldehyde and ethylmagnesium bromide.^{91, 92}



[93]
5% e.e.



[5]
22% e.e.



[94]
8–42% e.e.

Small enhancements were made by using an alternative diamine [94].⁹³ In a fashion unusual to Grignard reactions, the ligand [94] showed a sharp decrease in enantiomeric excess as the temperature was lowered, with the optimum temperature for asymmetric induction being 35 °C. Significant progress was observed with the

⁸⁹ H. L. Cohen, G. F. Wright, *J. Org. Chem.*, 1953, 18, 432.

⁹⁰ For other examples of 'chiral solvents', T. D. Inch, G. J. Lewis, G. L. Sainsbury, D. J. Sellers, *Tetrahedron Lett.*, 1969, 41, 3657; D. Seebach, H. Dorr, B. Bastani, V. Ehrig, *Angew. Chem. Int., Ed. Engl.*, 1969, 8, 982; D. Seebach, W. Langer, *Helv. Chim. Acta.*, 1979, 62, 1701.

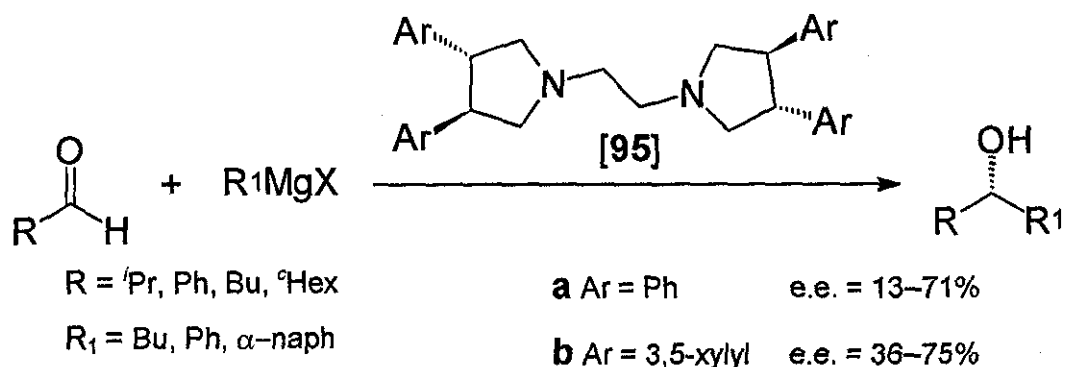
⁹¹ H. Nozaki, T. Aratani, T. Toraya, *Tetrahedron Lett.*, 1968, 4097.

⁹² H. Nozaki, T. Aratani, T. Toraya, *Tetrahedron*, 1971, 27, 905.

⁹³ I. E. Marko, A. Chesney, D. M. Hollinshead, *Tetrahedron: Asymmetry*, 1994, 5, 569.

introduction of novel chiral pyrrolidine based C₂-symmetric diamines [95a-b]

(Scheme 48).⁹⁴



Scheme 48

Here the conformational rigidity and steric bulk of the aryl groups create a well defined environment capable of enducing good enantioselectivities due to high enantiofacial differentiation of the carbonyl plane of the aldehydes (Figure 10).

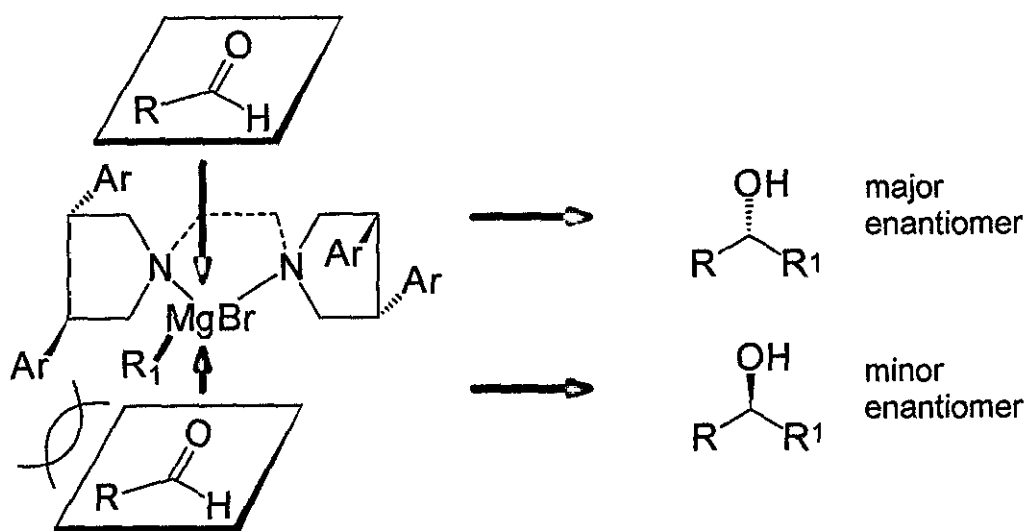
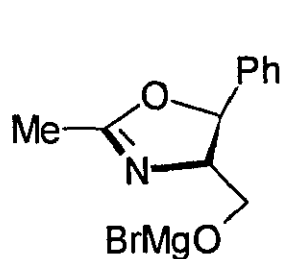


Figure 10

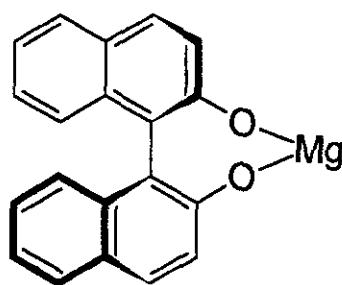
⁹⁴ M. Nakajima, K. Tomioka, K. Koga, *Tetrahedron*, 1993, 49, 9751.

An alternative approach by researchers was the use of magnesium/ligand auxiliaries as the stereoselective inducing agents in the reactions of achiral Grignard reagents and ketones/aldehydes.^{95,96,97,98} Whilst poorer results were obtained with the early complex [96],⁹⁵ the more recent developments of Noyori, [97]⁹⁶ and Seebach's Mg-TADDOLates [98a-b], have furnished some superlative results.^{97,98}



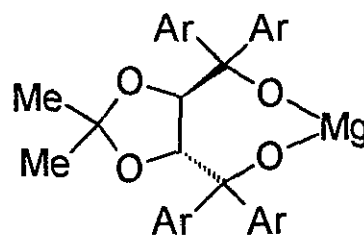
[96]

80% (25% e.e.)



[97]

>90% e.e.



[98a] Ar = Ph;

[98b] Ar = 2-naph
up to 98% e.e.

Enantiomeric excesses obtained for the reaction of acetophenone with a variety of Grignard reagents in the presence of the auxiliary [98a] gave essentially complete selectivities (Table 8). The scope of the ligands was extended to other aryl methyl ketones and heteroaryl methyl ketones with excellent success.

⁹⁵ A. I. Meyers, M. E. Ford, *Tetrahedron Lett.*, 1974, 14, 1341.

⁹⁶ R. Noyori, S. Suga, K. Kawai, S. Okada, M. Kitamura, *Pure Appl. Chem.*, 1988, 60, 1597.

⁹⁷ B. Weber, D. Seebach, *Angew. Chem., Int. Ed. Eng.*, 1992, 31, 84.

⁹⁸ B. Weber, D. Seebach, *Tetrahedron*, 1994, 50, 6117.

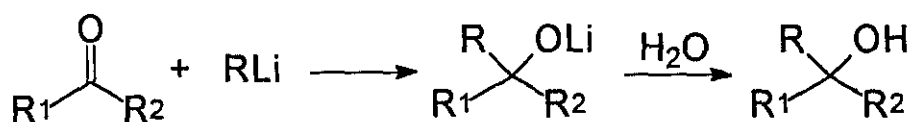
Table showing yields and enantiomeric excesses for the products from the reaction of ketones with specified Grignard reagents.

ketone	RMgBr	yield (%)	enantiomeric excess (%)
PhCOMe	EtMgBr	62	98
PhCOMe	PrMgBr	84	>98
PhCOMe	BuMgBr	75	>98
PhCOMe	OctMgBr	58	>98
PhCOMe	PhCH ₂ MgBr	14	70
2-naphCOMe	EtMgBr	75	98
2-pyridineCOMe	EtMgBr	51	96

Table 8

3.1.2 Organolithium Additions

The addition of organolithium reagents is also a powerful method for preparing alcohols from aldehydes or ketones in an analogous fashion to Grignard reagents (Scheme 49).

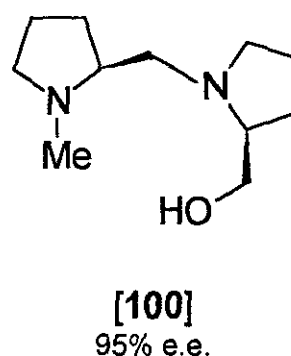
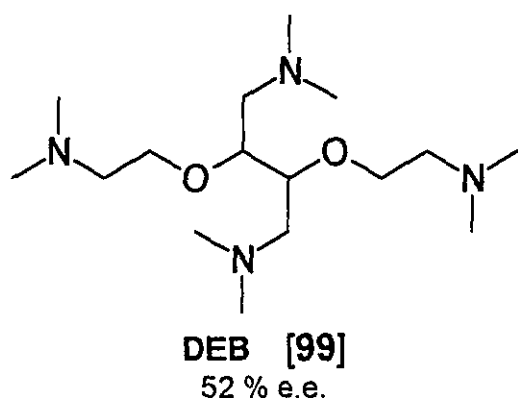


Scheme 49

The manipulation of these reaction systems to include enantiopure ligands and auxiliaries is also known to produce enantiomerically enriched products.

3.1.2.1 Asymmetric Organolithium Systems

The use of enantiomerically pure ligands containing oxygen and/or nitrogen chelating moieties has dominated the literature in this field. Seebach obtained some stereoselectivity in the reaction of butyllithium with benzaldehyde using the multidentate aminoether 'DEB' [99].⁹⁹



Alternative ligand structures based on aminoalcohols were observed to be far superior.¹⁰⁰ Here solvent effects were remarkable, with the best result of 95% enantiomeric excess obtained in a 1:1 mixture of dimethoxymethane and Me₂O at -123 °C using the hydroxy ligand [100]. The two pyrrolidine moieties and the lithiated hydroxymethyl group were proven to be necessary for asymmetric induction.¹⁰⁰

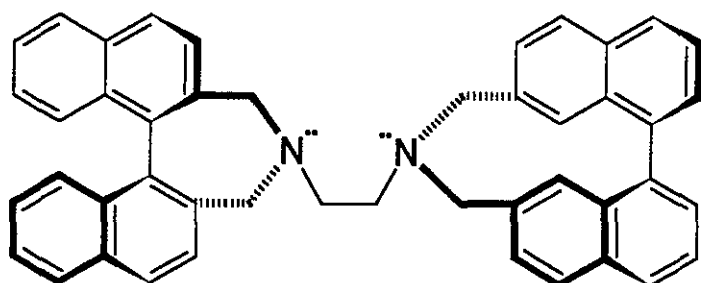
Exploitation of the known activation of organolithium reagents by complexation with tetramethylethylenediamine (TMEDA) led Mazaleyrat and Cram to construct C₂ symmetric enantiopure diamines [101] and [102].¹⁰¹ Application of these nitrogen

⁹⁹ D. Seebach, G. Crass, E. Wilka, D. Hilvert, E. Brunner, *Helv. Chim. Acta.*, 1979, 62, 2695.

¹⁰⁰ T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, K. Suzuki, *J. Am. Chem. Soc.*, 1979, 101, 1455.

¹⁰¹ J. P. Mazaleyrat, D. Cram, *J. Am. Chem. Soc.*, 1981, 103, 4585.

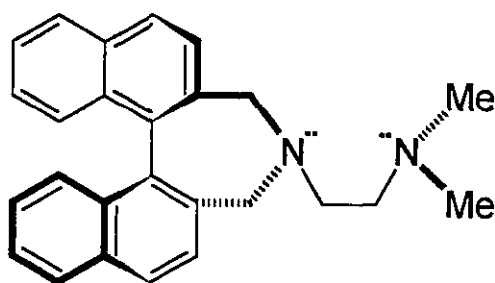
chelating species in the reactions of organolithium reagents with aldehydes led to mixed results, with the bulkier ligand **[101]** remaining consistently more effective.



[101]

e.e. = 55–89%

yields = 35–73%



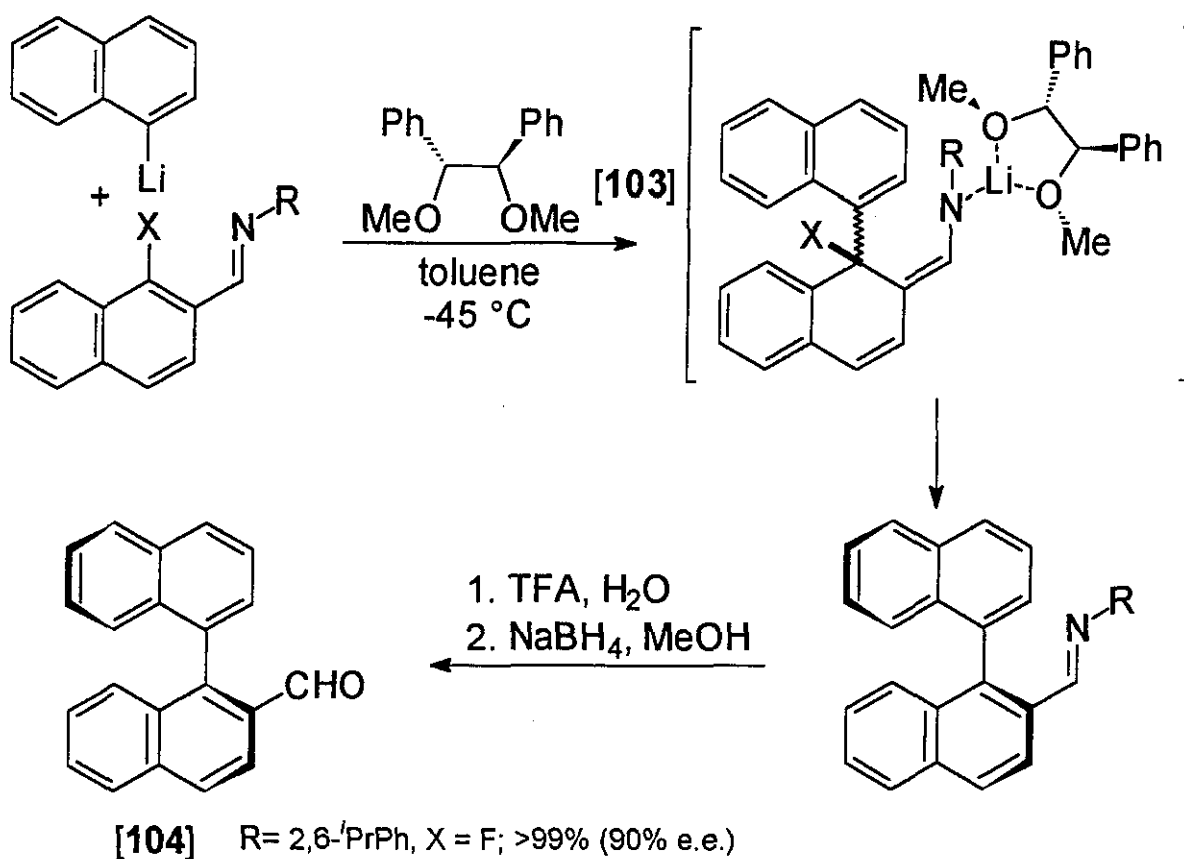
[102]

e.e. = 22–55%

yields = 65–75%

Alternative reactions also appear to be stereoselectively controlled by the presence of similarly chelating ligands. The use of stoichiometric quantities of the enantiopure ether **[103]** has been employed in asymmetric nucleophilic aromatic substitution leading to the enantiomerically enriched binaphthyl **[104]** (**Scheme 50**).¹⁰²

¹⁰² M. Shindo, K. Koga, K. Tomioka, *J. Am. Chem. Soc.*, 1992, 114, 8732.



Scheme 50

Repetition of this reaction using catalytic quantities of **[103]** is possible but to the detriment of the chemical yield. Subsequently the same researchers achieved good results by the use of catalytic ligand **[103]** in the enantioselective conjugate addition of aryllithiums to naphthalene BHA-esters.¹⁰³

Thus it has been shown that the application of enantiomerically pure ligands can affect the stereoselectivity of organometallic additions to prochiral carbonyl compounds to a reasonable level. In many cases the ligands employed are considered to chelate through lone pair interaction with the metal centre and the scope of this type of co-ordination has been observed to induce stereoselectivity in other organometallic reactions. There remains much scope for the further study of

¹⁰³ K. Tomioka, M. Shindo, K. Koga, *Tetrahedron Lett.*, 1993, 34, 681.

ligands pertaining in particular to the organomagnesium and organolithium additions to aldehydes/ketones.

3.2 Results and Discussion

We were primarily interested in the application of C_2 symmetric enantiomerically pure acetals as ligands in asymmetric synthesis. Although the C_2 symmetric bisacetals had no known precedent in the literature as ligands, it was envisaged that their use in inducing enantioselectivity in a metal mediated system would be possible. We considered the co-ordination of a bisacetal and a simple metal salt, e.g. $MgBr_2$. The proposed model of the complex formed shows a 3-ring fused system, which appears most favourable in the low energy *cis* conformation (**Figure 11**).

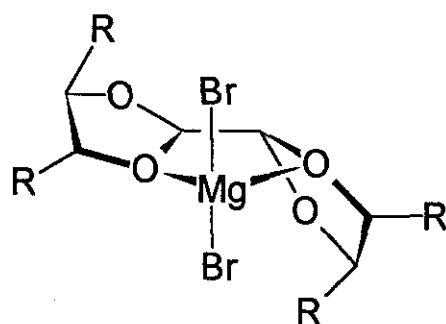
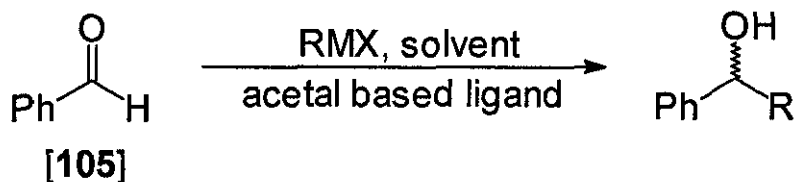


Figure 11

Thus two of the four quadrants of the complex are blocked, creating an excellent steric environment around the metal centre for asymmetric induction. In order to assess this potential we applied the novel ligands to the model reaction of organometallic nucleophilic attack on to benzaldehyde [105] (**Scheme 51**).



Scheme 51

It was postulated that the ligand/organometallic reagent/benzaldehyde intermediate would bind simultaneously to afford a structure open to nucleophilic attack at one face only, *i.e.* Figure 12.

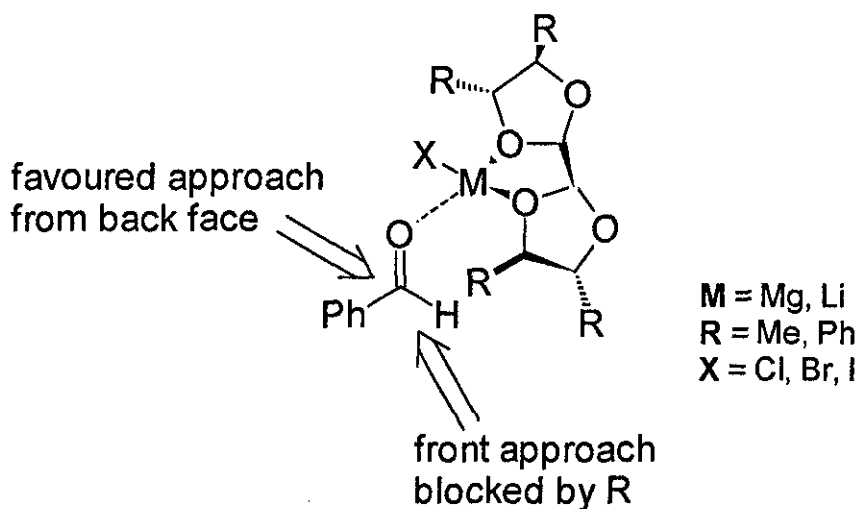


Figure 12

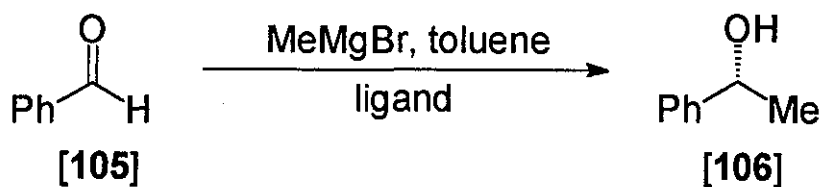
To assess the efficacy of the ligands we used Grignard and organolithium reagents as the nucleophiles in the addition to benzaldehyde.

3.2.1 Grignard Additions

The addition of Grignard reagents to benzaldehyde was carried out using stoichiometric quantities of bisacetal ligands [37, 38, 40, 43, 44, 47]. In all cases the appropriate acetal ligand was premixed with the Grignard reagent in diethyl ether, with the temperature kept below $-20\text{ }^{\circ}\text{C}$ to ensure that the acetal was not cleaved by the nucleophile. Adjustment of the solvent was carried out by removal of the diethyl ether under reduced pressure or using a stream of nitrogen followed by addition of the required solvent.

3.2.1.1 Ligand Effects

Preliminary experiments were carried out based on the addition of MeMgBr to benzaldehyde in the presence of the bisacetal ligands [37, 38, 40, 43, 44, 47] (Scheme 52). Each experiment was carried out in toluene containing small amounts of diethyl ether from the original Grignard solution.



Scheme 52

Table 9 shows the obtained enantiomeric excesses of product 1-phenylethanol, measured by chiral shift NMR spectroscopy.

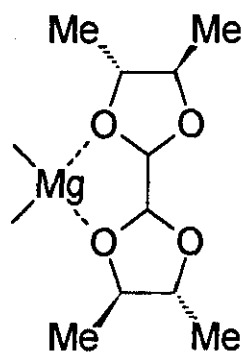
entry	ligand	yield of [98] (%)	enantiomeric excess of [98] (%)
1	[47]	55	7
2	[37]	55	35
3	[40] ¹⁰⁴	16	23
4	[38]	31	0
5	[43]	0	nd
6	[44]	30	0

Methyl magnesium bromide (2.16mmol) in Et₂O was premixed with appropriate ligand (2.16mmol) at -78°C. The solution was reduced using a stream of dry N₂ and benzaldehyde added (2.16mmol). Solution kept at -78°C for a further 60 min before warming to r.t. and working up in the usual way. e.e. determined by chiral shift NMR spectroscopy.

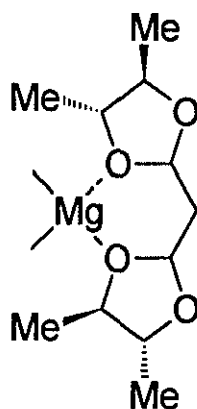
Table 9

The results clearly indicated the ligand [37] was involved in the reaction at the metal centre and achieved a promising level of stereoselectivity in the Grignard addition reaction. Ligands [47] and [40] also showed some promise, 7 and 23% e.e. respectively. Unfortunately the results obtained from the other ligands were disappointing and afforded racemic products. Comparison of the results from experiments using ligands [47], [37] and [43] showed a distinct advantage of the six-membered chelation to magnesium over that of five or seven membered chelation.

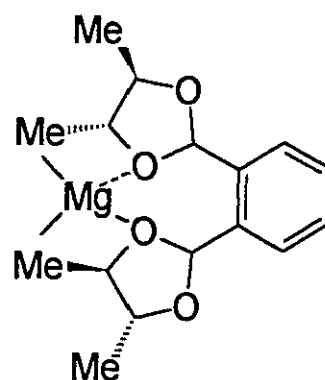
¹⁰⁴ This ligand was only available 18 months after the study and thus the enantiomeric excess it generated has been subsequently added here. The result is therefore not considered in the rationale for the rest of the study.



gives 7% ee



gives 35% ee



gives no reaction

It was also evident that the size of the asymmetric groups on the 'backbone' of the acetal ring were crucial to the stereoselectivity of the reaction. The introduction of phenyl moieties to the 'backbone' caused a complete loss of enantioselectivity (entries 4 and 6). It must be assumed that in the case of acetal [43], analogous to the successful smaller methyl derived ligand [37], the extra steric bulk of the phenyl groups hindered the chelation to the metal. Thus the ligand was excluded from participation within the reaction, rendering the product racemic.

Taking some encouragement from the 35% enantiomeric excess induced by the bisacetal ligand [37] we endeavoured to further optimise the reaction.

Note: Ligand [40] was only realised well after the completion of this study and although promising, will not be considered beyond this point.

3.2.1.2 Solvent Effects

On approaching the asymmetric addition reaction it occurred to us that the interactions between the oxygen lone pairs from the acetal ligands and the metal

centre were going to be rather weak. In order to prevent any hindrance to this co-ordination it was important to remove any other sources of ligation, i.e. co-ordinating solvents. Unfortunately the formation of Grignard reagents require the presence of a polar solvent with which the magnesium co-ordinates. We envisaged that the comparatively robust co-ordination of these solvents, i.e. diethyl ether, THF, would be in competition with our ligands, possibly preventing any ligand co-ordination. Therefore, the greater the co-ordinating ability of the solvent, the greater would be the inhibition of the enantioselectivity of the reaction. In order to investigate this we carried out parallel reactions between MeMgBr and benzaldehyde using ligand [37] in a series of solvents ranging from polar to non-polar (Table 10).

Table showing the yields and enantiomeric excesses of 1-phenyl ethanol synthesised under different solvent conditions.

solvent	yield of [106] (%)	enantiomeric excess of [106] (%)
tetrahydrofuran	43	0
diethyl ether	38	13.5
toluene–diethyl ether	55	35
hexane–diethyl ether	23	14

Methyl magnesium bromide (2.16mmol) in solvent was premixed with ligand [37] (2.16mmol) at -78°C. The solution was reduced using a stream of dry N₂ and benzaldehyde added (2.16mmol). Solution kept at -78°C for a further 60 min before warming to r.t. and working up in the usual way. e.e. determined by chiral shift NMR spectroscopy.

Table 10

As suspected the presence of the highly co-ordinating solvent THF appeared to completely inhibit the formation of any stereoselective ligand/metal intermediate and thus racemic product was formed. As the polarity of the solvent was decreased to

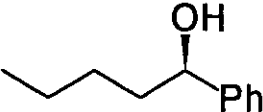
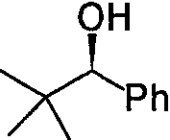
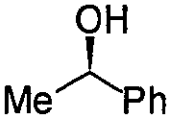
diethylether and then toluene (containing small amounts of diethyl ether) the enantiomeric purities of the product increased. This confirmed the theory of coordination competition and showed a trend which we hoped would continue as the polarity was dropped further. Regrettably the results for the reaction in hexane were poor. This may be attributed to the low solubility of the reagents, which would inhibit formation of the required complex, thus producing products with low enantiopurity. It was also noted that the chemical yield was scant. It was therefore concluded that the reaction in toluene was the most efficient. However the toluene solution still contained small amounts of diethyl ether which may have repressed the enantiomeric excess of the product. Removal of the diethyl ether under reduced pressure to dryness before addition of the toluene afforded no better results than leaving visible trace amounts. It must be concluded that the Grignard reagent maintains a solvent shell of diethyl ether on drying, with removal being highly unlikely. Solvent domination of the metal must be then disturbed in solution by the ligand.

In an endeavour to avoid the problems associated with the ligating solvents we attempted to generate MeMgI using a five-fold excess of ligand [37] as the solvent. This had the additional advantage of pre-co-ordinating the required Grignard reagent and ligand for direct use in the reaction. Inauspiciously the formation of MeMgI from MeI and Mg in ligand [37] solution did not occur. The addition of initiating agents, heat and co-solvents all proved futile.

3.2.1.3 Grignard Reagent Effects

An investigation into the influence of the Grignard reagent led us to consider the effective 'nucleophile' of the reagent, *i.e.* the R group in RMgX and the halo-counter ion, X. Initial experiments had been entirely concerned with the diminutive R group Me. We considered that the addition of larger nucleophiles to benzaldehyde may produce ameliorative enantiomeric excesses. Therefore reactions were carried out using *n*-butyl- and *t*-butyl-magnesium bromide in the standard fashion (Table 11).

Table showing the yields and enantiomeric excesses for the shown product alcohols which were synthesised by the addition of the specified Grignard reagent to benzaldehyde.

ligand	Grignard reagent	product	product yield (%)	product enantiomeric excess (%)
[37]	<i>n</i> -BuMgBr		nd*	14.5
[37]	<i>t</i> -BuMgBr		31	6
[37]	MeMgI		53	19

Grignard reagent (2.16mmol) in THF was premixed with ligand [37] (2.16mmol) at -78°C. The solution was reduced using a stream of dry N₂ and benzaldehyde added (2.16mmol). Solution kept at -78°C for a further 60 min before warming to r.t. and working up in the usual way. e.e. determined by chiral HPLC.

* product not separable from the ligand

Table 11

Contrary to our hypothesis, we observed a decline in enantiomeric excess as the nucleophile became more bulky. Considering this, in context with the observations noted about loss of enantioselectivity when employing bulkier ligands, it can be

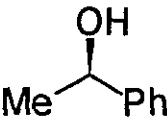
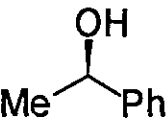
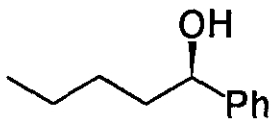
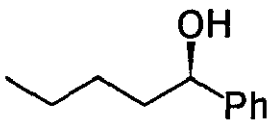
argued that the available area for binding around the metal centre is limited. Thus the weakly co-ordinating bisacetal may be unable to ligate to the metal sufficiently due to the bulk of the formally bonded R or X groups and the enantioselectivity is lost. Further evidence to support this theory was shown by the use of MeMgI in the standard reaction. Here the induced enantioselectivity was lower than that obtained by the bromine counter-part (MeMgBr, 35% e.e.), with iodine being a spatially bulkier moiety than bromine.

No advantage was indicated by manipulation of the Grignard reagent, with the use of MeMgBr remaining optimum.

3.2.2 Organolithium Additions

In an attempt to further optimise the asymmetric addition of nucleophiles to benzaldehyde we turned our attentions to considering the problem of metal–ligand binding. With magnesium having such a tenuous co-ordination with the bisacetal ligands it seemed prudent to assess alternative metal centres in their capacity to form more effective asymmetric intermediate complexes. We therefore studied analogous organolithium additions to benzaldehyde, again using ligand [37] (Table 12).

Table showing the yields and enantiomeric excesses for the shown product alcohols which were synthesised by the addition of the specified lithium reagent to benzaldehyde.

RLi reagent	solvent system	product	product yield (%)	product enantiomeric excess (%)
MeLi	toluene/diethyl ether		55	18
MeLi	hexane/diethyl ether		66	18
<i>n</i> -BuLi	toluene/hexane		nd	19
<i>n</i> -BuLi	hexane		nd	6

Lithium reagent (2.16mmol) in Et₂O was premixed with ligand [37] (2.16mmol) at -78°C. Benzaldehyde added (2.16mmol) dropwise. Solution kept at -78°C for a further 30 min before warming to r.t. and working up in the usual way. e.e. determined by chiral HPLC.

Table 12

A comparison of the additions of MeMgBr and MeLi to the aldehyde substrate showed much poorer results for the lithium adduct. This indicated that the lithium centre was less able to accommodate the acetals oxygen lone pairs than magnesium, possibly due to its reduced size, increasing steric 'crowding'.

One advantage of using organolithium reagents was the commercial availability of butyl lithium in non-polar solvents. Here we were able to study the reaction in the absence of competing solvent co-ordination. Initial studies in neat hexane proved disappointing due to a lack of solubility. Subsequent addition of a small quantity of

toluene afforded better results, an analogous increase in enantiomeric excess to that achieved by the magnesium adduct. Surprisingly the increase in steric bulk of the nucleophile (from methyl to butyl), in this case had no effect on the stereoselective outcome of the reaction. Organolithium reagents in conjunction with bisacetal ligand [37] gave some promising results but could not fulfil the potential shown by their organomagnesium analogues.

3.3 Conclusion

- Some encouraging results were obtained by the organolithium and Grignard reagent additions to benzaldehyde using the C_2 symmetric ligand [37] (35% e.e.) and later entry [40] (23% e.e.). All other bisacetal ligands induced little or no enantioselectivity in the reaction.
- The optimisation of the Grignard reaction clearly indicated the advantages of removing or avoiding co-ordinating solvents and using small nucleophile/counter ion reagents. Generally organolithium reagents generated lower enantioselectivities; these, however, were less reagent and solvent dependent.
- The accomplishment of obtaining 1-phenylethanol in 35% e.e. from the reaction of MeMgBr/ligand [37] with benzaldehyde in toluene/diethyl ether, lends some credence to our original proposed intermediate binding of a C_2 symmetric bisacetal to a metal, creating an appropriate environment for asymmetric reactions to take place.

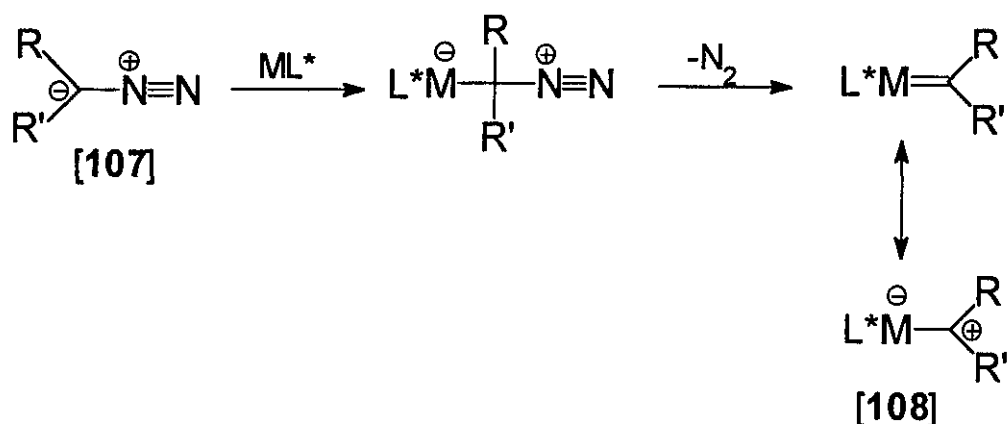
Further metal mediated reactions are observed in their ability to utilise the ligating potential of enantiopure acetals in subsequent chapters of this thesis.

Chapter 4 Cyclopropanation

- 4.1 Introduction
 - 4.1.1 Semicorrin–copper catalysts
 - 4.1.2 Bisoxazoline–copper catalysts
 - 4.1.3 Bis(oxazoliny)pyridine–metal catalysts
- 4.2 Results and discussion
- 4.3 Conclusion

4.1 Introduction

Cyclopropanations of alkenes by diazo compounds can be catalysed by metal complexes.¹⁰⁵ The reacting intermediate metal carbenoid [108] is formed from the decomposition of diazo compound [170] with a transition metal complex (Scheme 53).

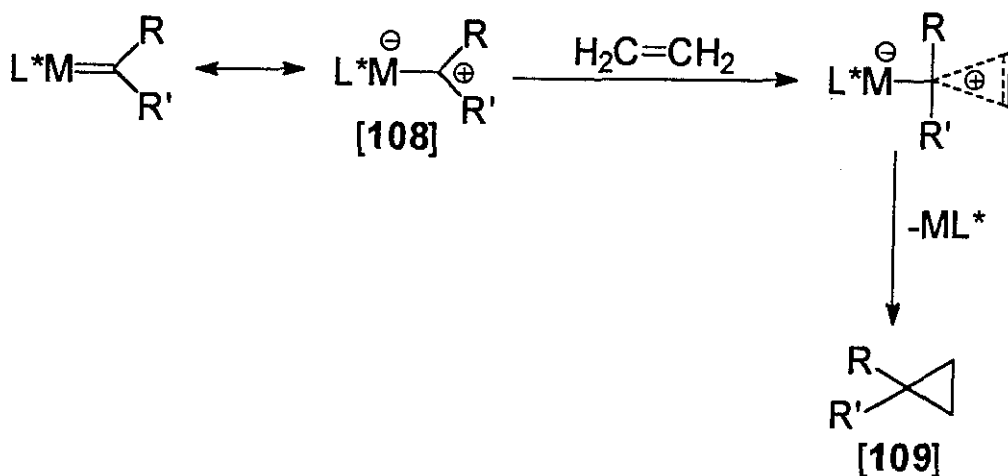


Scheme 53

The mechanism for this reaction, first suggested in 1952 by Yates,¹⁰⁶ shows nitrogen extrusion from the diazo species due to the diazo compound attack onto the metal complex. The metal aids in the stabilisation of the carbene [108], whose electrophilic carbon is attacked by the electron rich olefin, regenerating the metal catalyst (Scheme 54) and forming the cycloadduct [109].

¹⁰⁵ For an excellent review see, V. Singh, A. Gupta, G. Sekar, *Synthesis.*, 1997, 137.

¹⁰⁶ P. Yates, *J. Am. Chem. Soc.*, 1952, 74, 5376.



Scheme 54

The stereochemical outcome of the cyclopropanation is determined by the organic ligands attached to the metal centre. Generally these ligands are based around nitrogen chelation with adjacent asymmetric groups. A number of metal catalysts have been based on Rh,¹⁰⁷ Ru¹⁰⁸ and Co.¹⁰⁹ However the use of copper complexes has been studied much more extensively. One of the more prominent copper sources used is copper(I) triflate.¹¹⁰ The weak co-ordination of the triflate anion to the copper allows the metal to ionise easily, thus facilitating the co-ordination of additional ligands and the diazo compound. In each case the catalytic active species is based on Cu(I) and not Cu(II).

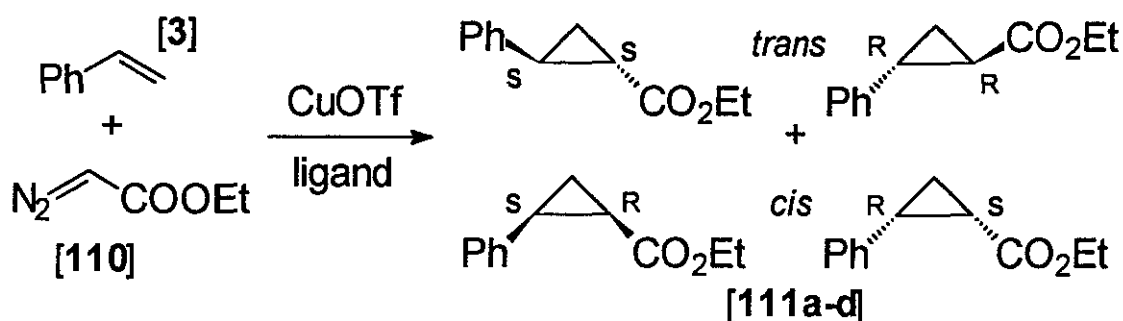
¹⁰⁷ M. Doyle, R. Austin, A. Bailey, M. Dwyer, A. Dyatkin, A. Kalinin, M. Kwan, S. Liras, C. Oalman, R. Pieters, M. Protopopova, C. Raab, G. Roos, Q. Zhou, S. Martin, *J. Am. Chem. Soc.*, 1995, **117**, 5763.

¹⁰⁸ S. Park, K. Murata, H. Matsumoto, H. Nishiyama, *Tetrahedron: Asymmetry.*, 1995, **6**, 2487.

¹⁰⁹ G. Jommi, R. Pagliarin, G. Rizzi, M. Sisti, *Synlett.*, 1993, 833.

¹¹⁰ R. Saloman, J. Kochi, *J. Am. Chem. Soc.*, 1973, **95**, 3300.

Many research groups have shown an interest in the development of chiral ligands to control the enantio and diastereoselectivities of cyclopropanations. The reaction most commonly used as a 'bench mark' for the assessment of each of these ligands is the cyclopropanation of styrene [3] with ethyldiazoacetate [110] to form the cyclopropanation products [111a-d] (Scheme 55).

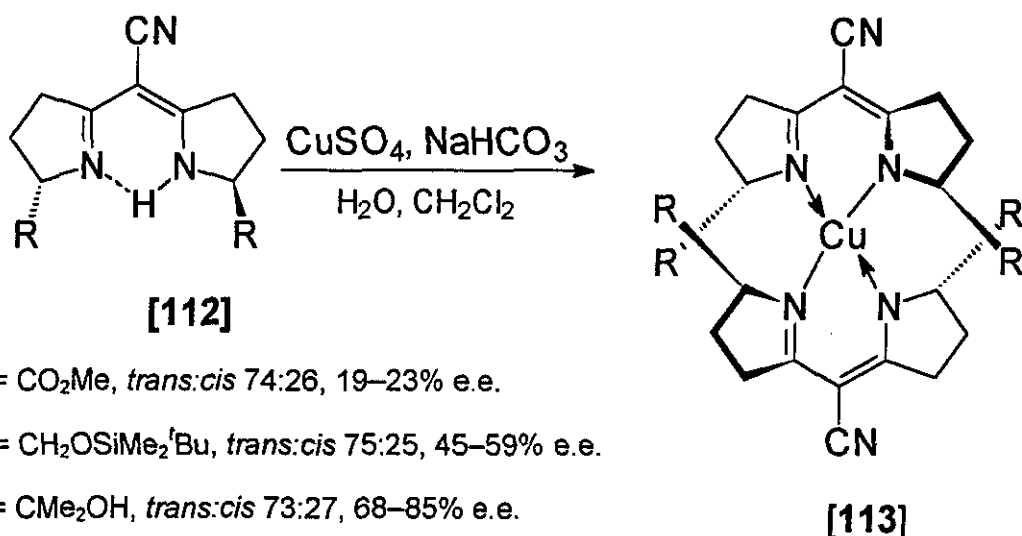


Scheme 55

4.1.1 Semicorrin-Copper Catalysts

One of the most significant developments in cyclopropanations catalysed by copper complexes came from Pfaltz and co-workers in 1986.¹¹¹ Here was the emergence of the first semicorrin type ligands [112a-c]. These C_2 symmetrical ligands were derived from commercially available (*S*) or (*R*)-pyroglutamic acid (Scheme 56).

¹¹¹ H. Fritschi, U. Leutenegger, A. Pfaltz, *Angew. Chem. Int. Ed. Engl.*, 1986, 25, 1005.



Scheme 56

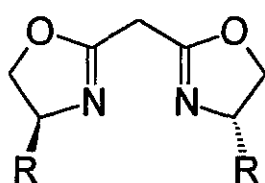
The Cu(II)–semicorrin complexes **[113a–c]** are reduced *in situ* to the active Cu(I) complexes by ethyl diazoacetate after either warming for a short time or by addition of phenylhydrazine. Both methods are common to literature systems.

Pfaltz discovered a correlation between high enantiomeric excesses in the *cis–trans* products and the bulkiness of the R-group on the ligand. However the *trans:cis* ratios were not outstanding and found to be substrate dependent. Modifications of the alkoxy group of the diazoacetate to larger moieties, such as *d*-menthyl, increased the ratio up to 82:18. Pfaltz also showed that the catalyst ligand **[113c]** was efficient for other terminal olefins, affording enantiomeric excesses in the range 92–97%.¹¹²

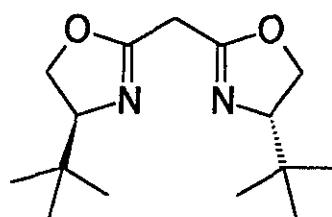
¹¹² H. Fritschi, U. Leutenegger, A. Pfaltz, *Helvetica Chimica Acta.*, 1988, 71, 1553.

4.1.2 Bisoxazoline-Copper Catalysts

As a natural progression from semicorrin ligands a number of groups continued to study cyclopropanation reactions using bisoxazoline ligands.^{113,114,115} The initial publication by Masamune in 1990 showed ligands bearing one chiral unit on each oxazoline ring [114a-d].¹¹³ These ligands gave comparative results to their semicorrin analogues in the model styrene reaction.



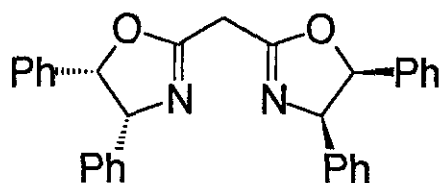
[114a] R = ^tPr
[114b] R = CH₂Ph
[114c] R = Ph



trans:cis 71:29
15–60% e.e.

[114d] *trans:cis* 75:25
cis 77% e.e., *trans* 90% e.e.

Masamune subsequently managed to overcome the limitations of the ligands in cyclopropanations of trisubstituted olefins by the addition of a further chiral moiety on each of the ligand oxazoline rings, e.g. [115].¹¹⁶



[115]

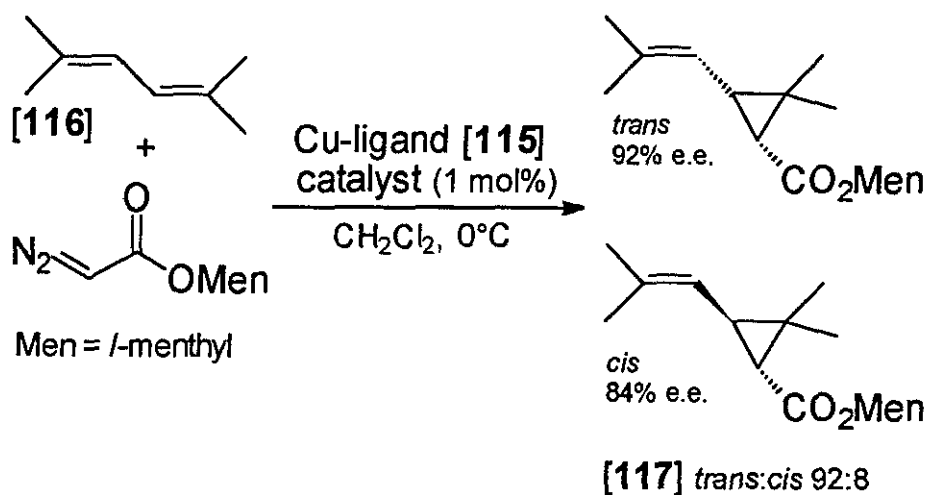
An illustration of this enhancement was apparent in the cyclopropanation of 2,5-dimethyl-2,4-hexadiene [116] to afford the chrysanthemates [117] (Scheme 57).

¹¹³ R. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Lett.*, 1990, 31, 6005.

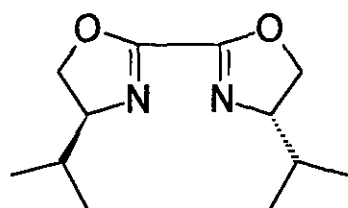
¹¹⁴ D. Evans, K. Woerpel, M. Hinman, M. Faul, *J. Am. Chem. Soc.*, 1991, 113, 726.

¹¹⁵ D. Muller, G. Umbricht, B. Weber, A. Pfaltz, *Helv. Chim. Acta.*, 1991, 74, 232.

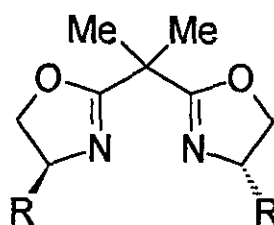
¹¹⁶ R. Lowenthal, S. Masamune, *Tetrahedron Lett.*, 1991, 32, 7373.



Here ligand **[115]** shows considerable increase in induced enantiomeric excess compared with the semicorrin ligand **[114a]** which afforded a *trans:cis* ratio of 84:16 and low enantiomeric excesses of 24% and 16% respectively. Independently Evans and co-workers published a similar study of ligands **[114a]**, **[114d]** and extended the range to include ligands **[118]**, **[119]**.¹¹⁴ Here the ligands complexed 1:1 with CuOTf were found to be superior to complexes with other Cu(I) and Cu(II) salts. The results also revealed that the five membered chelates were particularly poor for effective catalysis.



[118]
 <10% e.e.
trans:cis 66:36



[119a] R = ⁱPr *trans:cis* 69:31, 45–49% e.e.

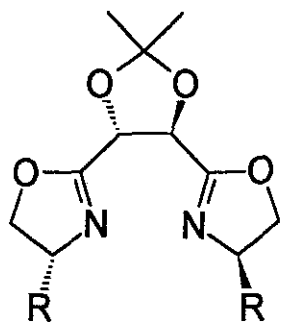
[119b] R = ^tBu *trans:cis* 73:27, 97–99% e.e.

[119c] R = CH₂Ph

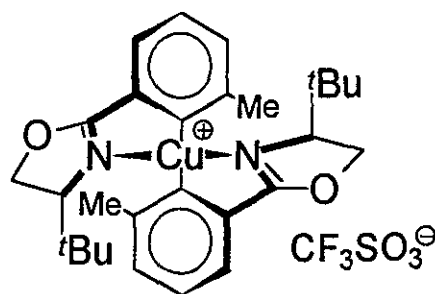
[119d] R = Ph

The neutral ligand [119b], containing geminal methyl groups to prevent enolisation, was found to be optimum in the standard cyclopropanation. Recently preliminary work has been published on the use of Cu(II)–ligand [119c–d] complexes exchanged in clay for cyclopropanation reactions with some success.¹¹⁷

Researchers have also investigated bisoxazoline ligands which complex as seven membered chelates to the metal centre.^{118,119} Andersson¹¹⁸ and Knight^{119,120} both presented bisoxazoline ligands based on a tartrate backbone [120]. Unfortunately these ligands were largely found to be inferior to ligands which form six membered chelates.



[120] R = *i*Pr, *t*Bu, CH₂Ph, Ph
2–80% e.e.



(*R, R, R*)

[121]

In 1995 Corey *et al* published the first enantioselective synthesis of sirenin using a then novel copper–bisoxazoline complex [121] to catalyse the cyclopropanation step.¹²¹ In the novel ligand the *ortho*-methyl groups were considered sufficiently bulky to prevent free rotation about the biphenyl bond and thus fix the conformation.

¹¹⁷ J. Fraile, J. Garcia, J. Mayoral, T. Tarnai, *Tetrahedron: Asymmetry.*, 1997, 8, 2089.

¹¹⁸ A. Bedekar, P. Andersson, *Tetrahedron Lett.*, 1996, 37, 4073.

¹¹⁹ A. Harm, J. Knight, G. Stemp, *Tetrahedron Lett.*, 1996, 37, 6189.

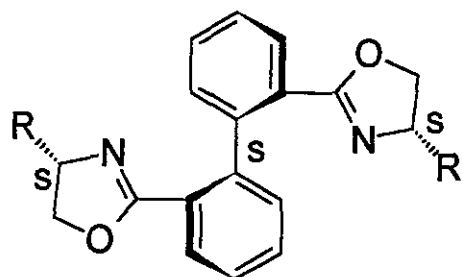
¹²⁰ A. Harm, J. Knight, G. Stemp, *Synlett.*, 1996, 677.

¹²¹ T. Gant, M. Noe, E. Corey, *Tetrahedron Lett.*, 1995, 36, 8745.

Complexation with CuOTf gave a nine membered chelate, which was much favoured over ligands showing the smaller bite angle of a lower order chelate.

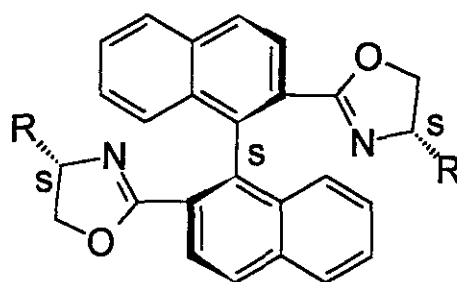
Ikeda and co-workers subsequently showed that the biphenyl bisoxazoline systems with no *ortho* substituent, once complexed with CuOTf, also only showed one configuration, assigned as (S, S, S).¹²⁴

Subsequently a number of other groups attempted the synthesis of analogous bicyclic bisoxazoline structures [122a–b, 123a–d, 124a–b].^{122,123,124}



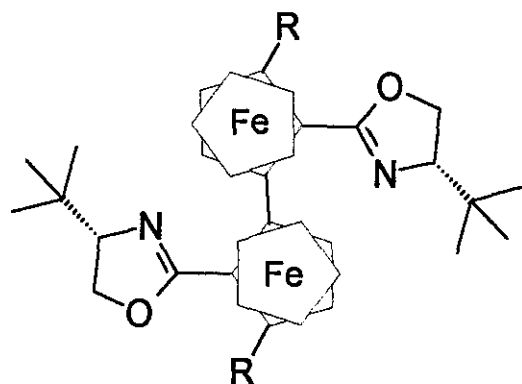
[122]

a R = ⁱPr *trans:cis* 74:36, 49–59% e.e.
b R = ^tBu *trans:cis* 68:32, 74–84% e.e.



[123]

a R = ⁱPr *trans:cis* 70:40, 61–62% e.e.
b R = ^tBu *trans:cis* 59:41, 86–87% e.e.
c R = Ph *trans:cis* 67:33, 55–57% e.e.
d R = CH₂Ph *trans:cis* 68:32, 8–16% e.e.



[124a] R = SiMe₃ *trans:cis* 66:34, 70–83% e.e.

[124b] R = SiEt₃ *trans:cis* 61:39, 62–74% e.e.

¹²² Y. Uozumi, H. Kyota, E. Kishi, K. Kitayama, T. Hayashi, *Tetrahedron: Asymmetry.*, 1996, 7, 1603.

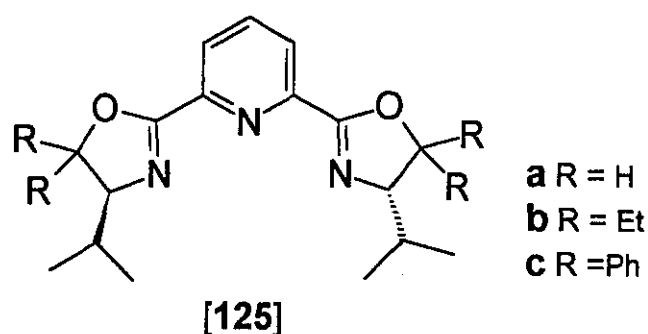
¹²³ S. Kim, C. Cho, K. Ahn, *Tetrahedron: Asymmetry.*, 1997, 8, 1023.

¹²⁴ Y. Imai, W. Zhang, T. Kid, Y. Nakatsuji, I. Ikeda, *Tetrahedron Lett.*, 1997, 38, 2681.

Each of these catalysts provided high enantiomeric excesses for the cyclopropanation of styrene with *l*-menthyl diazoester, but were disappointing as the alkoxy group was reduced in size.

4.1.3 Bis(oxazoliny)pyridine-Metal Catalysts

The 'pybox' type ligand [124a-b], developed by Nishiyama for the enantioselective hydrosilylation of ketones,¹²⁵ was shown to be excellent in the cyclopropanation of olefins when complexed with ruthenium.^{126,127}



In all cases the *trans*:*cis* ratios were higher than 9:1 and the enantiomeric purities ranged from 88–78% when using the ethyldiazoacetate, up to 96–84% upon using *l*-menthyldiazoacetate. Singh and co-workers have reported that 'pybox' ligands of type [125b–c] may also be used in conjunction with copper to catalyse the cyclopropanation of olefins.¹²⁸ However the enantioselectivities obtained during these reactions were found to be poor, <40%.

¹²⁵ H. Nishiyama, H. Sakaguchi, T. Nakamura, M. Horihata, M. Kondo, K Itoh, *Organometallics.*, 1989, **8**, 846.

¹²⁶ H. Nishiyama, Y. Itoh, H. Matsumoto, S. Park, K. Itoh, *J. Am. Chem. Soc.*, 1994, **116**, 2223.

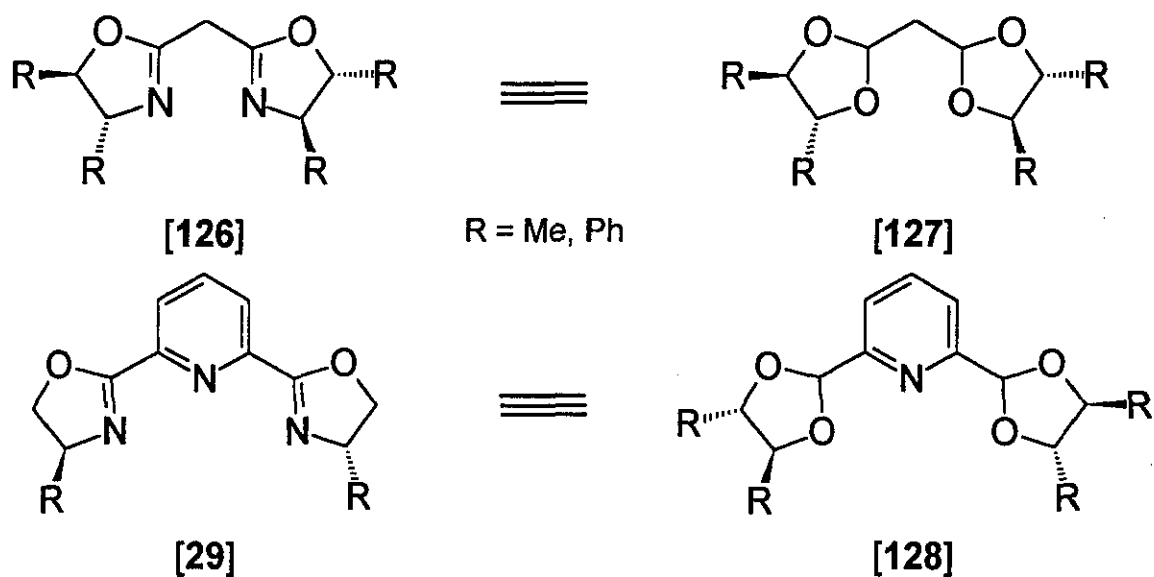
¹²⁷ S. Park, K. Murata, H. Matsumoto, H. Nishiyama, *Tetrahedron: Asymmetry.*, 1995, **6**, 2487.

¹²⁸ A. Gupta, D. Bhunjia, V. Singh, *Tetrahedron.*, 1994, **50**, 13725.

4.2 Results and Discussion

Having had some success with inducing asymmetry using enantiomerically pure acetal ligands we wished to extend the repertoire of these ligands. In searching for a new catalytic system for the ligands we became encouraged by the promising literature results obtained in the metal catalysed asymmetric cyclopropanation of alkenes using enantiomerically pure oxazoline ligands.

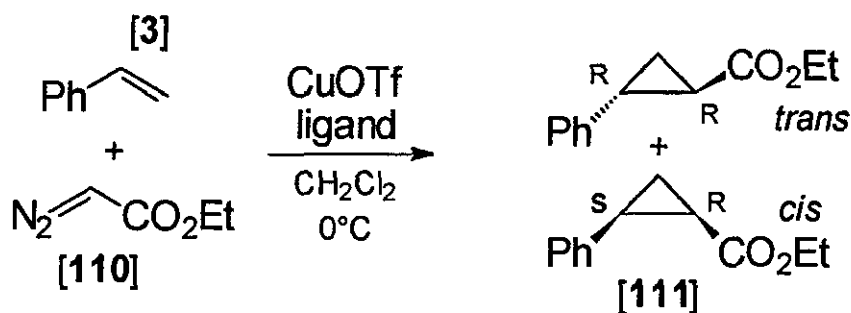
We envisaged that there would be significant structural and steric similarities between the precedented bisoxazoline ligands [29, 126] and the novel bisacetal ligands [127, 128] which could be exploited.



We therefore hypothesised that these common denominators should favour some positive results from the experimentation of the acetal ligands in analogous cyclopropanation reactions.

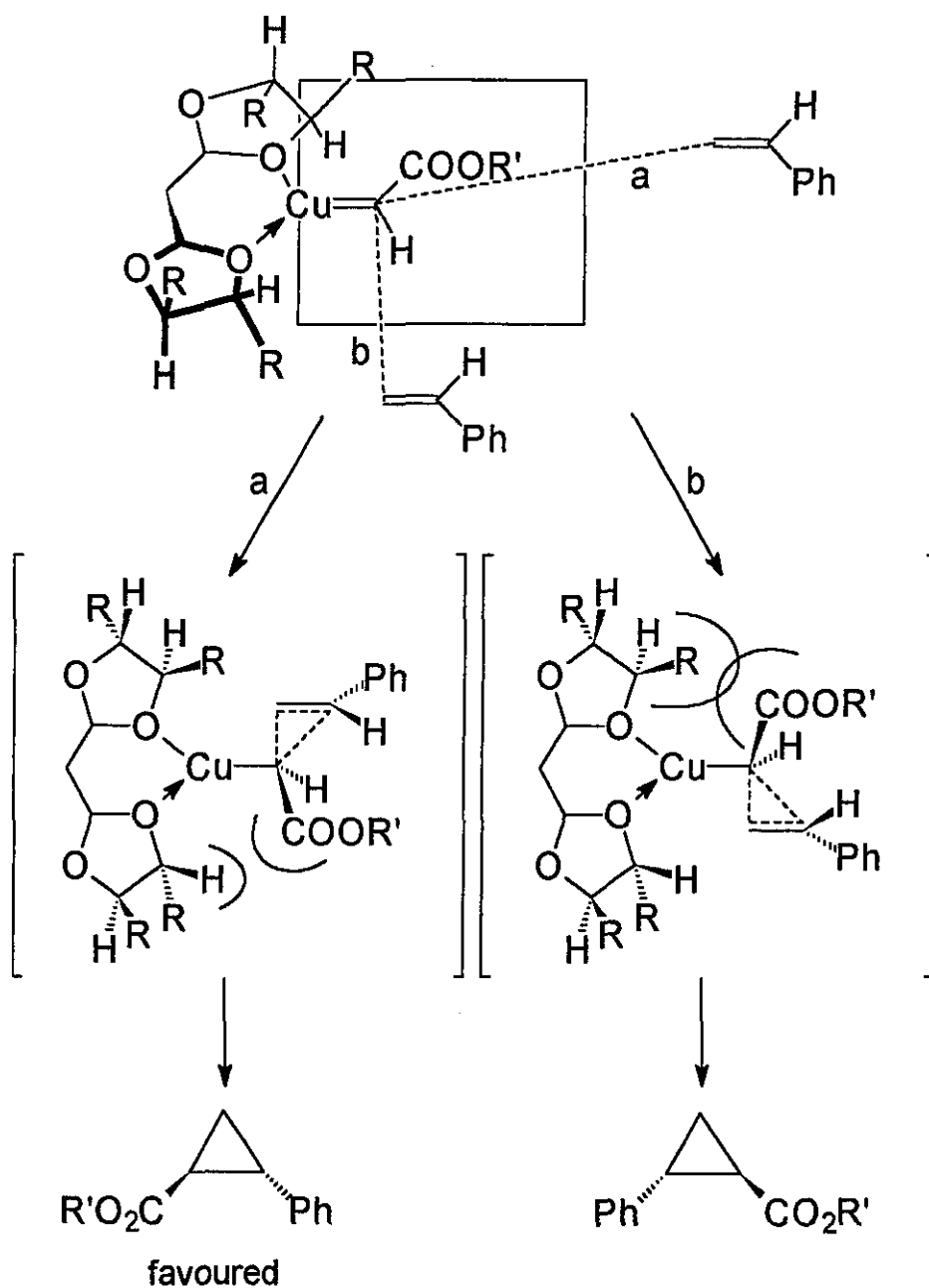
As a direct comparison to literature reactions we chose to study our available ligands in the copper catalysed cyclopropanation of styrene using ethyldiazoacetate

(Scheme 58).



Scheme 58

Our approach to forming copper(I) complexes of the ligands mimicked that of Evans, *i.e.* by direct addition of CuOTf to the ligand without need of further reduction of the metal.¹¹⁴ It was assumed that in solution the triflate anion would become dissociated from the metal centre, allowing co-ordination of the ligands through the lone pairs of oxygen and/or nitrogen moieties. We proposed a selective mechanism for the cyclopropanation based on the favourable six membered chelation of bisacetal ligand with copper (Scheme 59).



Scheme 59

Here the electrophilic carbon of the copper carbenoid is attacked by the more nucleophilic end of the olefin. Depending on the approach of the olefin to the carbenoid plane the ester group will be moved into or out of the plane. In pathway **b** the ester group has been forced into the plane. This causes an unfavourable

repulsive steric interaction between the bulky R-group on the ligand and the carboxy group-OR'. However in pathway **a** there appears to be no such repulsion as the ester group sterically interacts with a much smaller proton moiety. Thus pathway **a** is expected to be favoured over **b** affording either *cis* or *trans* (1*S*)-cyclopropanecarboxylate.

Bisacetal ligands [37] and [38] were each added to copper triflate and stirred for a sufficient time for the ligand–copper complex to form. The reaction then proceeded upon addition of styrene and ethyldiazoacetate and was left until all the starting materials had been consumed. Analysis by chiral GC showed that for each bisacetal ligand system no enantiomerically enriched *trans* or *cis*-products had been obtained (Table 13).

Table showing the e.e. and d.e. values for products [111] formed from the reaction of styrene with ethyldiazoacetate using specified ligands.

ligand	diastereoselective ratio <i>trans</i> : <i>cis</i>	enantiomeric excess (%) <i>trans</i>	enantiomeric excess (%) <i>cis</i>
[37]	68:32	0	0
[38]	62:38	0	0

Ligand (0.12 mol%) and CuOTf (0.06 mol%) in CH₂Cl₂ were stirred for 1 hour at r.t. Solution was cooled to 0°C and styrene (5.67 mmol) added, stirring for 30 mins. Ethyl diazoacetate (7.74 mmol) added over 5 hours, solution at 0°C throughout. Solution warmed to r.t. and left overnight.

Table 13

Further cyclopropanations were carried out using the pyridine based bisacetal ligands [50, 51, 54]. It was hoped that these would have increased success in binding to the metal centre due to the additional pyridine nitrogen chelation site. It

was also hoped that the eight membered chelation would be a favourable environment for asymmetric induction. However again no enantiomerically enriched products were produced (Table 14).

Table showing the e.e. and d.e. values for products [111] formed from the reaction of styrene with ethyldiazoacetate using specified ligands.

ligand	diastereoselective ratio <i>trans:cis</i>	enantiomeric excess (%) <i>trans</i>	enantiomeric excess (%) <i>cis</i>
[50]	68:32	0	0
[51]	60:40	0	0
[54]	67:33	0	0

Ligand (0.12 mol%) and CuOTf (0.06 mol%) in CH₂Cl₂ were stirred for 1 hour at r.t. Solution was cooled to 0°C and styrene (5.67 mmol) added, stirring for 30 mins. Ethyl diazoacetate (7.74 mmol) added over 5 hours, solution at 0°C throughout. Solution warmed to r.t. and left overnight.

Table 14

These disappointingly poor results can only be explained by the assumption that the enantiomerically pure acetal ligands had not successfully associated with the metal centre. Without the inclusion of the enantiopure ligands the copper (I) salt was able to proceed with the catalysis of the reaction in a purely racemic fashion. It may be considered possible to have predicted this lack of co-ordination due to the absence of a blue-green colouration on addition of the ligands to the CuOTf solution. This appearance of colour was indicative of copper–ligand complexation in Evans and other successful systems.¹¹⁴

In all systems the diastereomeric excesses obtained were poor but consistent with literature results. The small bias for the *trans* product is clearly favoured throughout.

This is evident upon consideration of the intermediate and can be exclusively attributed to the diazoacetate olefin interaction independent of the ligand.

Further extension of this work could involve an investigation of these novel ligands with other appropriate metals shown to facilitate the enantioselective cyclopropanations of olefins, *i.e.* ruthenium and rhodium.

4.3 Conclusion

Unfortunately we have shown that enantiomerically pure acetal based ligands exhibited no capacity to complex to copper(I). Thus we were unable to exert any level of stereocontrol in the asymmetric cyclopropanation of styrene. However some diastereoselectivity was noted, this being attributed to substrate interaction in line with literature values.

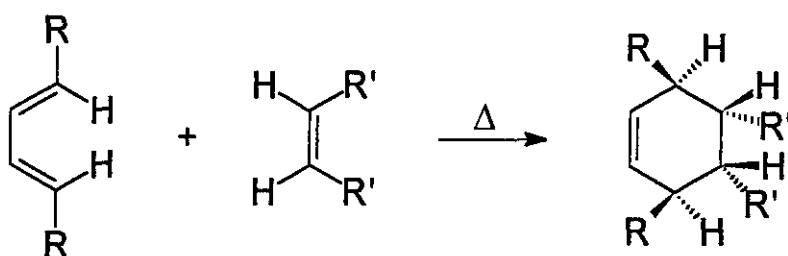
Chapter 5 Diels-Alder Reaction

- 5.1 Introduction
- 5.1.1 Homo Diels–Alder reactions
- 5.1.2 Hetero Diels–Alder reactions
- 5.2 Results and discussion
- 5.3 Conclusion

5.1 Introduction

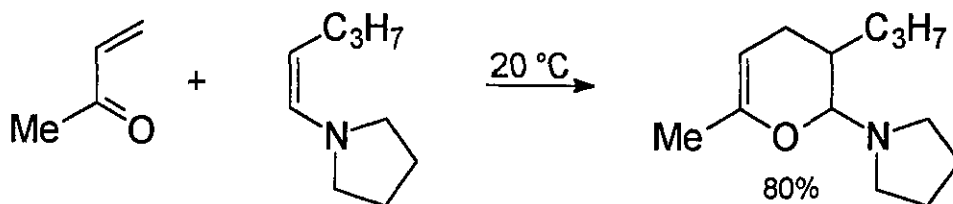
The Diels–Alder reaction is one of the fundamental reactions in organic chemistry due to the highly regio- and stereo-selective way it allows the formation of hetero- and carbo-cycles. The $[\pi 4_s + \pi 2_s]$ cycloaddition of a *cis*-1,3 diene and a dienophile affords a six membered adduct containing two new σ and one new π bond.

Substitution at the end termini of the diene or dienophile may result in the subsequent cyclic product having stereocentres (**Scheme 60**).



Scheme 60

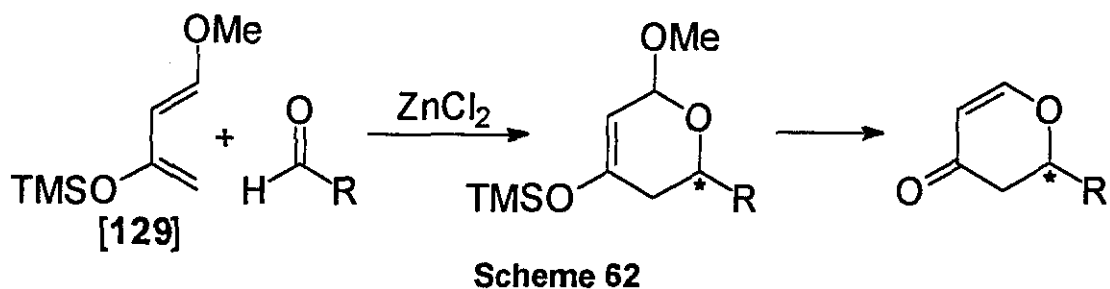
The introduction of a heteroatom into the conjugated diene or the dienophile allows under certain conditions the formation of a hetero cycloadduct. Although less common, the electron deficient heterodiene may react with an electron rich dienophile in an 'inverse electron demand' Diels–Alder reaction, e.g. **Scheme 61**.¹²⁹



Scheme 61

¹²⁹ R. Ireland, J. Daub, *J. Org. Chem.*, 1983, 48, 1303.

More evident in the literature is the presence of heterodienophiles. Here the reactivity of the dienophile is not greatly influenced by the inclusion of a heteroatom and may therefore react with a range of dienes in the 'normal electron demand' Diels–Alder cycloaddition.^{130,131}



The scope of this reaction is greatly increased in the presence of a Lewis acid (**Scheme 62**).^{132,133} Extensive research has been directed towards the use of asymmetric Lewis acids to further promote the stereospecificity in both the homo and hetero reaction.¹³⁴

5.1.1 Homo Diels–Alder Reactions

Chapuis was amongst the first to investigate the homo Diels–Alder reaction using asymmetric ligands containing diol functionality.¹³⁵ Cycloadditions of cyclopentadiene with dienophile [130] were carried out promoted by stoichiometric quantities of chiral Lewis acids. These were generated in situ from the addition of

¹³⁰ J. Jurczak, A. Zamojski, *Tetrahedron*, 1972, 28, 1505.

¹³¹ M. Chmielewski, J. Jurczak, *J. Org. Chem.*, 1981, 46, 2230.

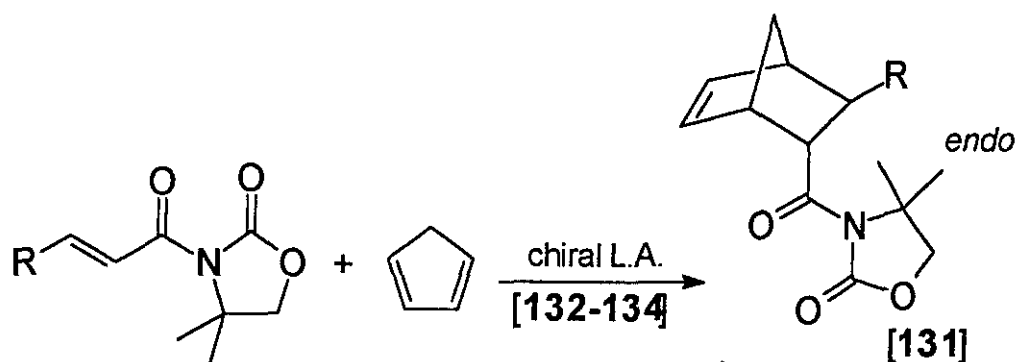
¹³² S. Danishefsky, J. Kerwin, S. Kobayashi, *J. Am. Chem. Soc.*, 1982, 104, 358.

¹³³ S. Danishefsky, J. Kerwin, S. Kobayashi, *J. Org. Chem.*, 1982, 47, 1981.

¹³⁴ For an excellent review, H. Kagan, O. Riant, *Chem. Rev.*, 1992, 92, 1007.

¹³⁵ C. Chapuis, J. Jurczak, *Helv. Chim. Acta.*, 1987, 70, 436.

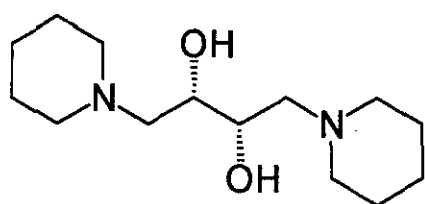
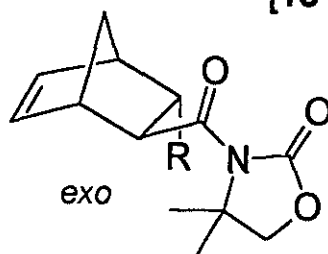
EtAlCl₂, Et₂AlCl or TiCl₄ to the respective enantiopure ligands [132–134] in a 2:1 ratio (Scheme 63).



[130]

a R = H

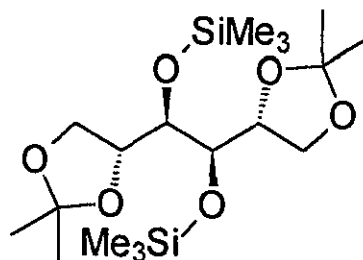
b R = Me



[132] + EtAlCl₂

endo:exo 73:23

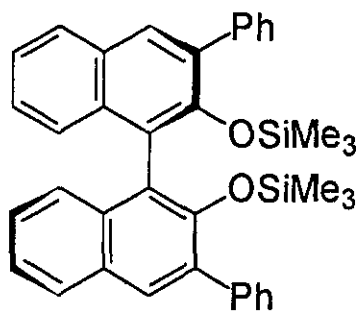
36% e.e.



[133] + TiCl₄

endo:exo 93:7

96% e.e.



[134] + TiCl₄

endo:exo 94:6

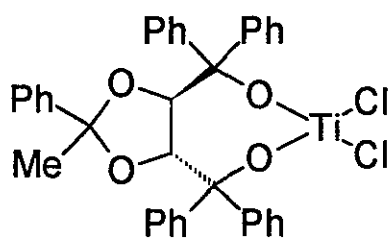
98% e.e.

Scheme 63

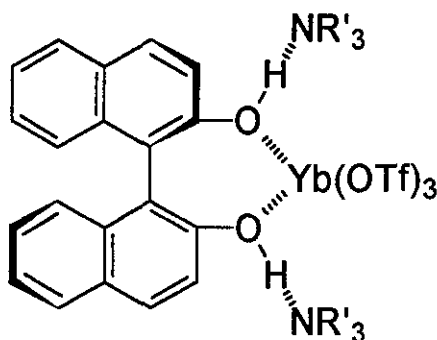
Here the careful selection of bidentate dienophile structure [130a–b] and ligands [132–134] led to excellent enantiomeric excesses of *endo* product [131] and high *endo:exo* ratios.

The most successful system for π face and *endo:exo* selectivity was proven to be that based on the binol backbone [134] and the use of a titanium metal centre.

Narasaka and co-workers continued the application of titanium Lewis acids to a similar reaction of cyclopentadiene with a modified dienophile having no geminal methyl groups.¹³⁶ The seven membered chelate [135] based on the 1,4-diol and dichlorodiisopropoxytitanium catalytically promoted the formation of good *endo:exo* ratio and the highest enantiomeric excess of *endo* product.



[135]
endo:exo 92:8
endo 91% e.e.



[136]
endo:exo 89:11
endo >95% e.e.

¹³⁶ K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, J. Sugimori, *J. Am. Chem. Soc.*, 1989, **111**, 5340.

Lanthanide based studies also revealed themselves to be applicable in Diels–Alder reactions. In early work Danishefsky found $\text{Yb}(\text{fod})_3$ to successfully catalyse cycloadditions requiring mild conditions.¹³⁷ By 1993 Kobayashi and co-workers had developed ytterbium/binol Lewis acids capable of inducing moderate to high enantioselectivities.^{138,139} Utilising the standard reaction of cyclopentadiene and dienophile [130a] as shown in **Scheme 63**, researchers conducted experiments, forming the asymmetric Lewis acid *in situ* from $\text{Yb}(\text{OTf})_3$, (*R*)-binaphthol and a range of tertiary amines (proposed theoretical intermediate [136]). The procuring of high enantioselectivities was found to be dependant on the amine employed and increased further on the addition of 4 Å mol sieves. The system containing the cyclic amine, *cis*-1,2,6-trimethylpiperidine was the most lucrative, affording the *endo* product [131] in 95% e.e.

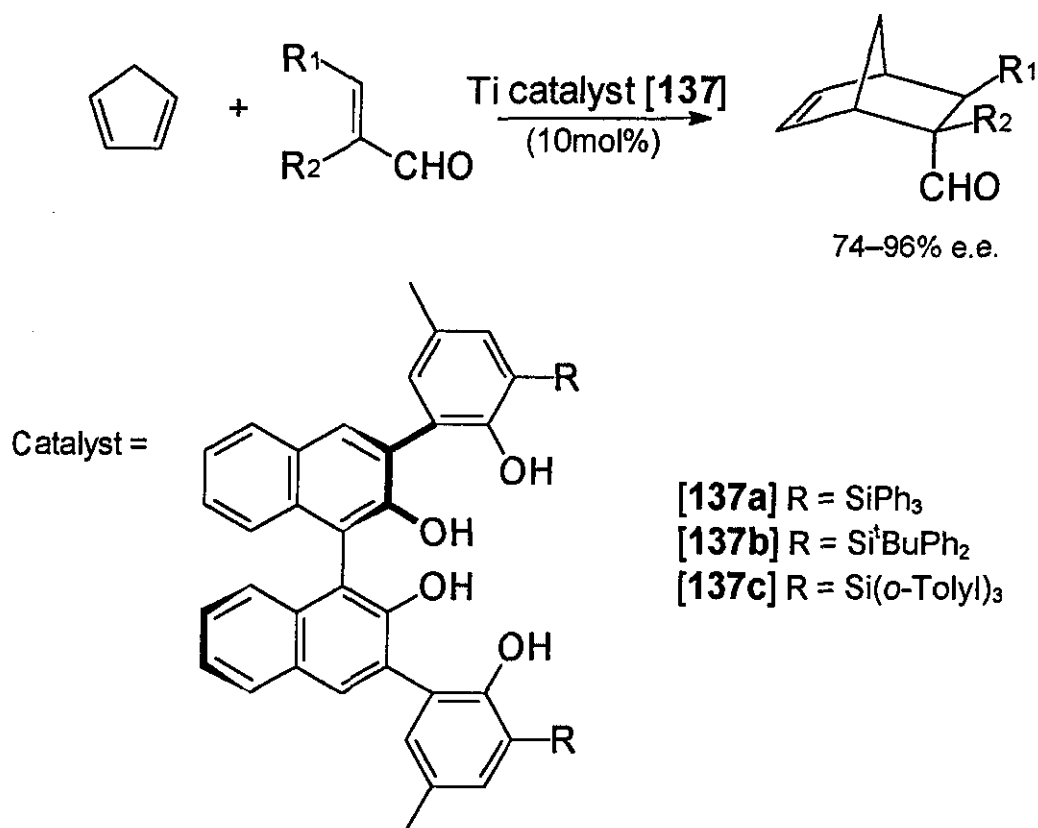
Helical asymmetric titanium reagents synthesised from $\text{Ti}(\text{O}^i\text{Pr})_4$ and ligands [137a–c] have been shown to catalyse the cycloaddition of cyclopentadiene with α , β -unsaturated aldehydes with consistently excellent results (**Scheme 64**).¹⁴⁰

¹³⁷ S. Danishefsky, M. Bednarski, *Tetrahedron Lett.*, 1985, 26, 2507.

¹³⁸ S. Kobayashi, I. Hachiya, H. Ishitani, M. Araki, *Tetrahedron Lett.*, 1993, 34, 4535.

¹³⁹ S. Kobayashi, H. Ishitani, *J. Am. Chem. Soc.*, 1994, 116, 4083.

¹⁴⁰ K. Maruoka, N. Murase, H. Yamamoto, *J. Org. Chem.*, 1993, 58, 2938.



Scheme 64

5.1.2 Hetero Diels–Alder Reactions

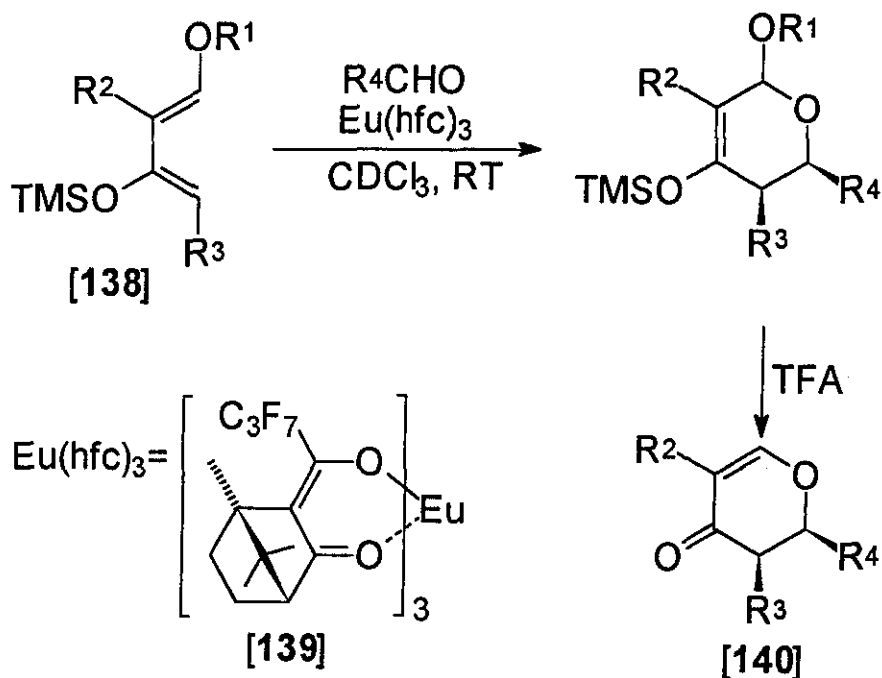
Pioneering work by Danishefsky into hetero Diels–Alder reactions introduced the use of the lanthanide shift reagents as mild asymmetric Lewis acid catalysts.^{141,142}

Modest levels of stereocontrol were achieved using Eu(hfc)₃ [139] in the cyclocondensation of aldehydes and siloxydienes [138] (Scheme 65).¹⁴³

¹⁴¹ M. Bednarski, S. Danishefsky, *J. Am. Chem. Soc.*, 1983, 105, 3716.

¹⁴² S. Danishefsky, M. Bednarski, *Tetrahedron Lett.*, 1984, 25, 721.

¹⁴³ M. Bednarski, C. Maring, S. Danishefsky, *Tetrahedron Lett.*, 1983, 24, 3451.



Scheme 65

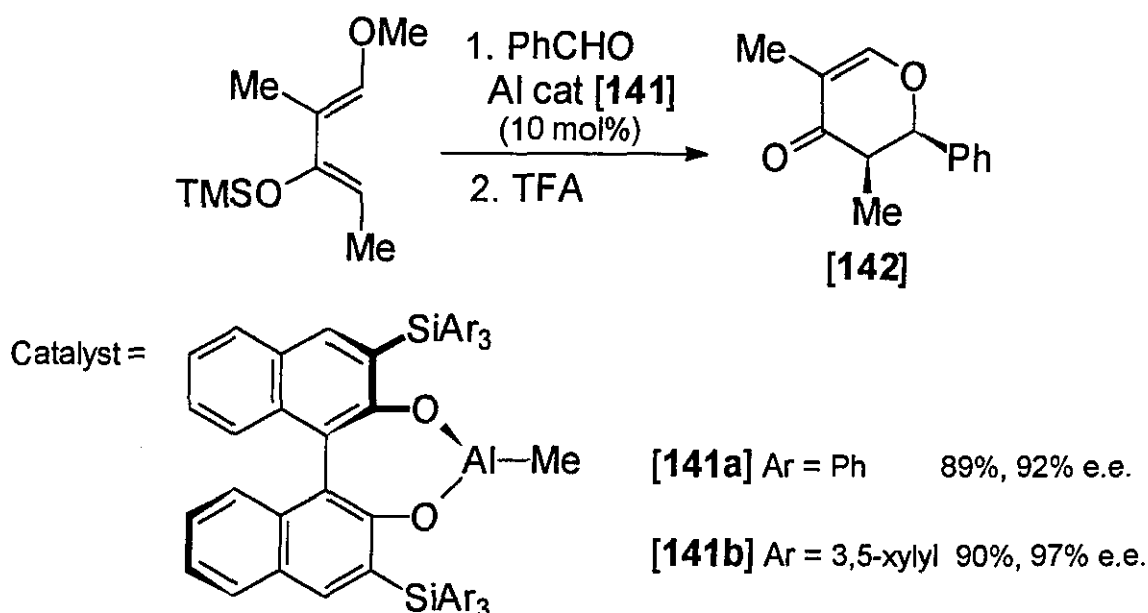
The stereoselectivity was demonstrated to be dependent largely on the substitution around the siloxydiene. The enantiomeric excess at the asymmetric centre α to the ring oxygen was increased with the bulk of R^1 and on the inclusion of a methyl substituent at R^3 (see Table 15). Optimum results were obtained at a lower temperature and reactions carried out in solvent free conditions (entry 7).

Table showing the e.e. values for the derivatives of product [140].

	conditions	R^1	R^2	R^3	e.e. (%)
1	$CDCl_3$, RT	Me	H	H	18
2	$CDCl_3$, RT	i Pr	H	H	28
3	$CDCl_3$, RT	t Bu	H	H	38
4	$CDCl_3$, RT	Me	Me	H	15
5	$CDCl_3$, RT	Me	Me	Me	36
6	$CDCl_3$, RT.	t Bu	Me	H	39
7	neat, $-10\text{ }^\circ\text{C}$	t Bu	Me	H	58

Table 15

The introduction by Yamamoto of bulky (R)-3,3'-bis(triarylsilyl)binaphthol aluminium catalysts [141a–b] to the Danishefsky reaction increased the optical induction dramatically (Scheme 66).¹⁴⁴

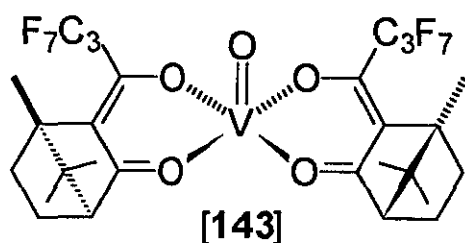


Scheme 66

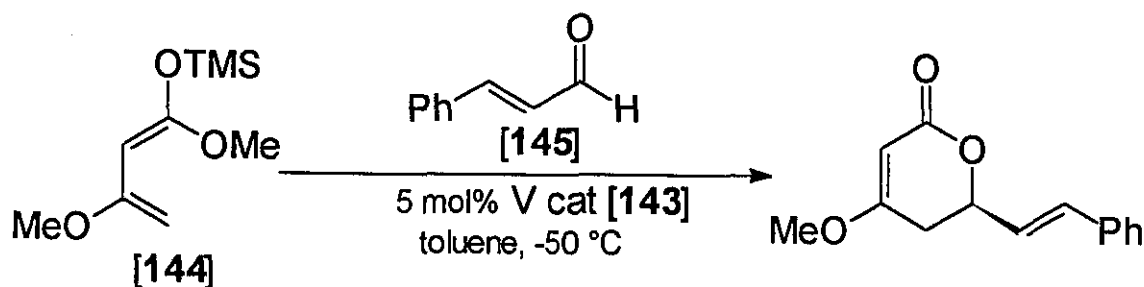
The stereoselectivities were dependent on the presence of steric congestion on the binaphthol but appeared independent of the catalytic quantities used. The observed enantioselectivities remained high for the cycloadditions of a range of siloxydienes and aldehydes, 67–95% e.e.

¹⁴⁴ K. Maruoka, T. Itoh, T. Shirasaka, H. Yamamoto, *J. Am. Chem. Soc.*, 1988, 110, 310.

Togni and co-workers applied vanadium(IV) catalysts [143] to the same system, isolating the cycloadduct [142] in up to 99% d.e. and 85% e.e.¹⁴⁵



This catalyst was extended to the reaction of Brassard's diene [144] and cinnamaldehyde [145] with some what less success, 73% yield but only 13% e.e. (Scheme 67).¹⁴⁶



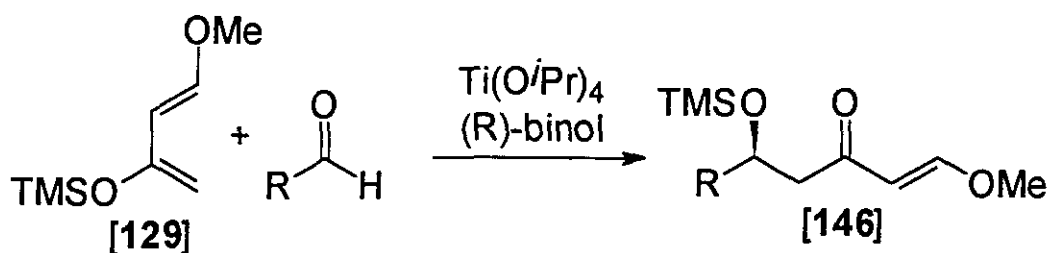
Scheme 67

Catalysts based on enantiopure titanium isopropoxide–binol complexes have also shown excellent success in the reaction of the unsubstituted Danishefsky's diene [129] with aldehydes.¹⁴⁷

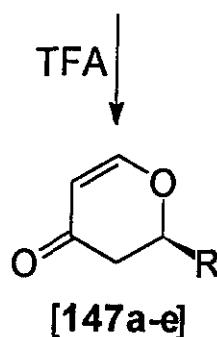
¹⁴⁵ A. Togni, *Organometallics*, 1990, 9, 3106.

¹⁴⁶ A. Togni, S. Pastor, *Chirality*, 1991, 3, 331.

¹⁴⁷ G. Keck, X. Li, D. Krishnamurthy, *J. Org. Chem.*, 1995, 60, 5998.



[147]	R =	e.e. (%)
a	Ph	75
b	CH_2OBn	97
c	furyl	97
d	$n\text{-C}_8\text{H}_{17}$	97
e	$\text{CH}_3\text{CH}=\text{CH}$	86



Scheme 68

Similar to a study by Corey *et al.*,¹⁴⁸ the Mukaiyama aldol product [146] was observed as the major component after the Lewis acid catalysed reaction, little of the product dihydropyranone [147a-e] was seen prior to cyclisation with TFA (Scheme 68).¹⁴⁹

The versatility of the asymmetric Diels-Alder cycloaddition has made it a very attractive tool in organic synthesis. Although some outstanding work has already been contributed in this field there remains potential for further investigation and development.

¹⁴⁸ E. Corey, C. Cywin, T. Roper, *Tetrahedron Lett.*, 1992, 33, 6907.

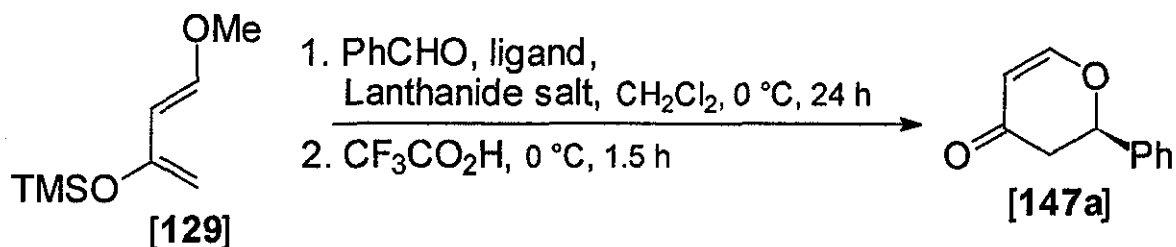
¹⁴⁹ similar observations have been made in non-asymmetric boron catalysed hetero Diels-Alders, E. Larson, S. Danishefsky, *J. Am. Chem. Soc.*, 1982, 104, 6458.

5.2 Results and Discussion

We had to date a batch of novel acetal ligands which had shown limited potential in magnesium and lithium reactions. In our hunt to find more applicable metal catalysed systems for these ligands we had been discouraged by results from copper and rhodium based reactions (**Chapter 6**). Therefore, we considered it prudent to reassess the potential binding capabilities of the oxygen lone pairs. We surmised that the problem might be a basic lack of ligand/metal orbital overlap. In forming a strategy to increase the potential for overlapping we turned our attentions to metals which have multiple binding sites. The most promising metals considered were those from the family of the Lanthanides. These particularly caught our attention as they can accommodate a high number of co-ordinations around the metal and facilitate reactions under mild conditions. There were also some promising NMR studies in the literature which speculated that lanthanide shift reagents could complex with cyclic ethers.¹⁵⁰ The ethers, which can be considered analogous to acetals, showed line broadening when added to lanthanide shift reagents. It was hoped that the ligands would facilitate similar co-ordination. We took some encouragement from the proposed transitional state complex put forward by Kobayashi, which suggests that $\text{Yb}(\text{OTf})_3$ binds to a lone pair on the oxygens of binol and not through formal bonds of the deprotonated diol (intermediate **[136]**).¹³⁹ It was considered that this, if correct, showed a precedent for our ligands also being successful in complexation to ytterbium and other lanthanides.

¹⁵⁰ M. M. Midland, R. W. Koops, *J. Org. Chem.*, 1990, 55, 4647.

We decided to use the cycloaddition of commercially available *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene) [129] with benzaldehyde as a known reaction in which we could compare our ligands to those published (Scheme 69).



Scheme 69

Lanthanides are known to have multiple possible geometries which are complex and often ill defined. However, we have tried to draw up a speculative working model of an intermediate for the reaction based on an octahedral framework (Figure 13).

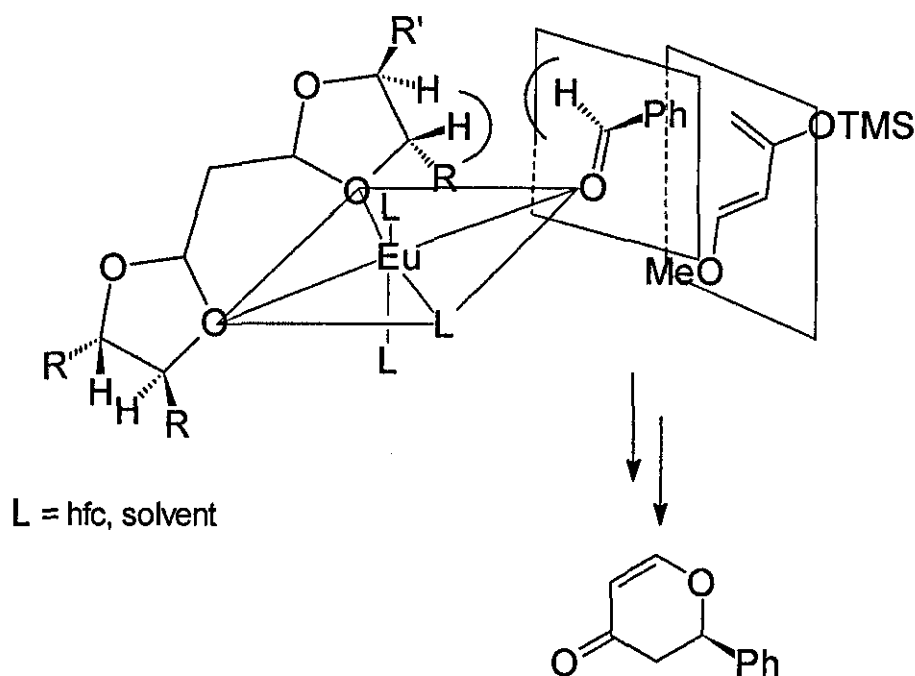


Figure 13

The co-ordinated prochiral aldehyde adopts a position creating the minimal steric hindrance to the ligand. The diene then approaches from the back face with the OTMS group furthest from the R' group on the ligand, creating upon reaction the R enantiomer of the product. As a reference point for the reaction we initially repeated published work by Danishefsky using $\text{Eu}(\text{hfc})_3$ as the catalyst in the absence of extra ligand sources.¹⁴³ The enantiomeric excess obtained was comparable with literature values (**Table 16**). We then proceeded to repeat the reaction adding the ligands which were available, those based on bisacetals [**37**, **38**, **44**], pyridylacetal [**51**] and phosphinoacetal [**25b**]. We aimed to add an excess of acetal ligand in order to displace one 'hfc' molecule from the $\text{Eu}(\text{hfc})_3$ and replace it with the ligand *in situ*.

A solution of the appropriate lanthanide compound (2 mol%) was premixed with an excess of the appropriate acetal ligand (10 mol%) to promote complexation with the metal. To this was added Danishefsky's diene [**129**] and benzaldehyde and stirred for 24 hours. The resultant mixture was treated with trifluoroacetic acid before work-up and purified by flash chromatography to afford the desired product [**147a**] as a yellow oil. In each case the samples were analysed by chiral HPLC.

Unfortunately the repetition of the reaction involving acetal ligands illustrated no enhancement of stereocontrol. This was somewhat predictable as the displacement of the 'hfc' moieties (attached to europium) by the asymmetric acetals was highly unlikely (**Table 16**). The 'hfc' moieties in $\text{Eu}(\text{hfc})_3$ are bonded through formal oxygen-metal bonds and although considered rather labile, the bonds must be

considered more stable than the lone pair interactions between europium and the oxygens in our ligands.

Table showing the yields and enantiomeric excesses for product [147a] synthesised with the specified combinations of Eu(hfc)₃ and ligands.

acetal ligand (10 mol%)	lanthanide compound (2 mol%)	enantiomeric excess (%)	yield (%)
none	Eu(hfc) ₃	16	52
[37]	Eu(hfc) ₃	17	nd
[38]	Eu(hfc) ₃	16	nd
[44]	Eu(hfc) ₃	19	10
[51]	Eu(hfc) ₃	16.5	17
[25b]	Eu(hfc) ₃	18	12

Ligand (0.05 mmol), benzaldehyde (0.5 mmol), Eu(hfc)₃ (0.01 mmol) were stirred in dry CH₂Cl₂ (0.5 ml) for 20 mins. The solution was cooled to 0°C and Danishefsky's diene (0.5 mmol) added dropwise. Solution was warmed to r.t. and stirred for 48 hours. Reaction mixture poured into 10% HCl and extracted into Et₂O. Solution cooled to 0°C, TFA added and left for 90 mins before work up.

Table 16

It was also noted that in all cases the presence of the acetal ligands in the reaction diminished the yield of product significantly, *i.e.* from 52% down to 17–10%.

A commercially available, alternative metal source are the triflate salts of lanthanides. These have shown to be highly dissociated in solution and thus it was expected that our ligands may have an opportunity to co-ordinate to the metal centre in these cases.

An ytterbium metal centre was selected as this had shown precedent in other reactions and allowed us to consider the effects of a lanthanide with a large atomic

radius.¹³⁹ The large size permits additional co-ordinations over the other metals chosen, commonly eight in total. It was conceived feasible that this system could contain single or multiple ligands bound to the metal, but a model of these was considered too complex to predict results.

Table showing the yields and enantiomeric excesses for product [147a] synthesised with the specified combinations of lanthanide compounds and ligands.

acetal ligand (10 mol%)	lanthanide compound (2 mol%)	enantiomeric excess (%)	yield (%)
none	Yb(OTf) ₃	0	28
[37]	Yb(OTf) ₃	7	n/d
[38]	Yb(OTf) ₃	0	n/d
[44]	Yb(OTf) ₃	0	32
[51]	Yb(OTf) ₃	0	13
[25b]	Yb(OTf) ₃	18	21
none	Sc(OTf) ₃	0	56
[37]	Sc(OTf) ₃	0	52
[38]	Sc(OTf) ₃	0	n/d
[44]	Sc(OTf) ₃	0	n/d
[51]	Sc(OTf) ₃	0	39
[25b]	Sc(OTf) ₃	0	n/d

Ligand (0.05 mmol), benzaldehyde (0.5 mmol), lanthanide compound (0.01 mmol) were stirred in dry CH₂Cl₂ (0.5 ml) for 20 mins. The solution was cooled to 0°C and Danishefsky's diene (0.5 mmol) added dropwise. Solution was warmed to r.t. and stirred for 48 hours. Reaction mixture poured into 10% HCl and extracted into Et₂O. Solution cooled to 0°C, TFA added and left for 90 mins before work up

Table 17

Unfortunately reactions catalysed by Yb(OTf)₃ and enantiomerically pure ligands [38, 44, 51, 25b] provided little or no stereocontrol in the reaction and thus racemic

product was largely obtained (**Table 17**). One exception to this was provided by the reaction involving the acetal ligand [37] and $\text{Yb}(\text{OTf})_3$ which afforded the product in a modest 7% e.e. This was interesting as the ligand, which sports methyl groups as the chiral moieties, was the same ligand which afforded the positive results in the additions of organometallic reagents to ketones (chapter 3).

Following the disappointment of these results we turned our attention to one final metal, scandium. This metal is often considered along side the lanthanides, having some of the same properties. The advantage of introducing scandium was that it contrasts with the other lanthanides we used by forming stronger complexes with less co-ordination sites. It was hoped that this simplified strengthened system would be more fruitful in obtaining enantiomerically pure products from the Diels–Alder reaction. However this appeared to be wishful thinking and again we obtained no enantioselectivity in the reaction using the combination of scandium and acetal ligands (**Table 17**).

We concluded that the acetal ligands either had no interaction with the metal or alternatively they were too labile to compete with the moieties already attached to the metal centres. We attempted to assess whether any ligand metal interaction had taken place by carrying out simple NMR studies. The NMR spectrum of ligand [37] was obtained and compared with the NMR spectrum of the same ligand containing $\text{Eu}(\text{hfc})_3$ (0.5–1 equivalents). No attributable line broadening was observed which is non-conclusive but indicated a lack of co-ordination.

We decided that there had been no significant progress in using enantiomerically pure acetal ligands as tools for inducing asymmetry in the Diels–Alder reaction using Danishefsky's diene. Therefore no further lanthanide metals were investigated.

5.3 Conclusion

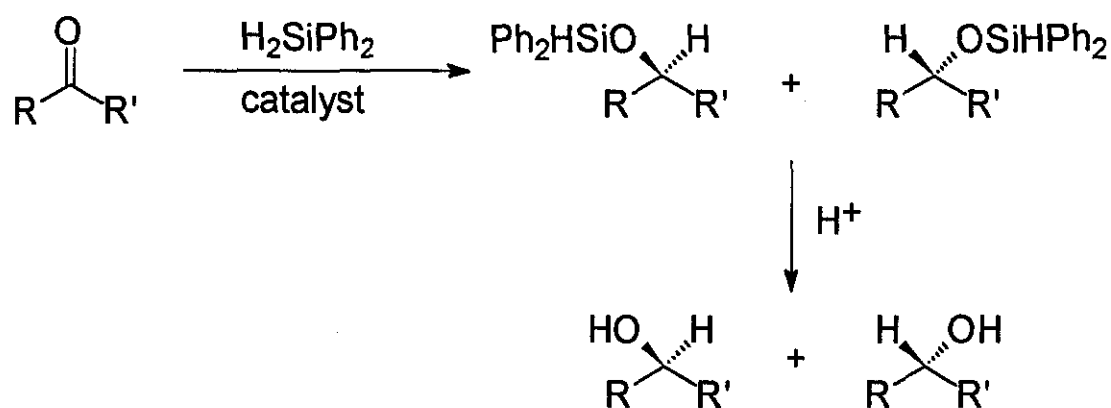
Unfortunately the use of acetal ligands failed to induce any stereocontrol in the asymmetric hetero Diels–Alder reaction. This observation implies a lack of metal–acetal ligand co-ordination within the system, thus achieving no chiral environment within the course of the reaction.

Chapter 6. Hydrosilylation

- 6.1 Introduction
 - 6.1.1 Mechanistic proposals
- 6.2 Applications of asymmetric ligands
 - 6.2.1 Enantiomerically pure phosphorus based ligands
 - 6.2.2 Enantiomerically pure nitrogen based ligands
 - 6.2.3 Enantiomerically pure nitrogen/phosphorus bidentate ligands
- 6.3 Results and discussion
 - 6.3.1 Pyridylacetal ligands
 - 6.3.2 Phosphinooxazoline ligands and analogues
 - 6.3.2.1 Solvent effects
 - 6.3.2.2 Initial ligand comparisons
 - 6.3.2.3 Effects on ligand metal complexation over time
 - 6.3.2.4 Temperature Effects
 - 6.3.2.5 Effects of Diphenylsilane Concentration
 - 6.3.2.6 Effects of Ligand/catalyst Complex Concentration
 - 6.3.2.7 Other factors
 - 6.3.2.8 Summary of optimisation conditions
 - 6.3.2.9 Substrate effects
- 6.4 Conclusions

6.1 Introduction

The asymmetric reduction of prochiral ketones to enantiomerically enriched alcohols is an important process in synthetic organic chemistry. One approach to this goal, which has been studied extensively over recent years, is the transition metal catalysed hydrosilylation of such ketones. Hydrosilylation is a method by which an organosilicon hydride is added across an unsaturated bond such as C=O, C=N or C=C. For our research purposes we wished to concentrate only on the hydrosilylation of carbonyl bonds. The addition of an organosilicon hydride across a carbonyl bond, catalysed by an asymmetric metal complex, affords a silyl ether, which may be subsequently hydrolysed to the corresponding alcohol (**Scheme 70**). Classically the transition metal catalyst used in the process is based on rhodium,¹⁵¹ although other metals including iridium based complexes are also known.¹⁵²

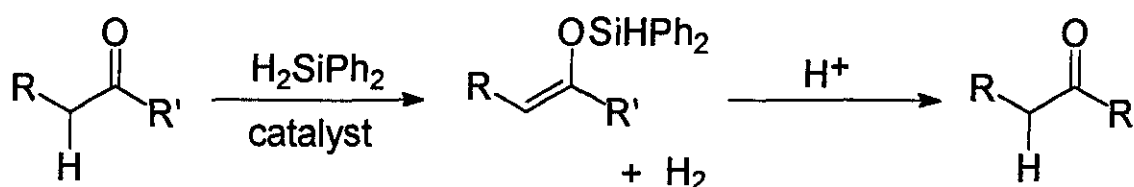


Scheme 70

¹⁵¹ I. Ojima, T. Kogure, M. Kumagai, *J. Org. Chem.*, 1977, 42, 1671.

¹⁵² Y. Nishibayashi, K. Segawa, H. Takada, K. Ohe, S. Uemura, *J. Chem. Soc., Chem. Commun.*, 1996, 847.

One limitation of the reaction will occur if the substrate contains a hydrogen in the α -position to the carbonyl group. Here dehydrogenative condensation may occur. This leads to an amount of silyl enol ether being formed, which on hydrolysis reforms as the original ketone (**Scheme 71**).¹⁵³ Fortunately the formation of the silyl enol ether appears to be minor (<5%) in most cases involving rhodium catalysts.



Scheme 71

The potential usefulness of this reduction arises from the mild reaction conditions and potential substrate functional groups tolerance, unlike a number of analogous methods, i.e. transfer hydrogenation, hydroboration.

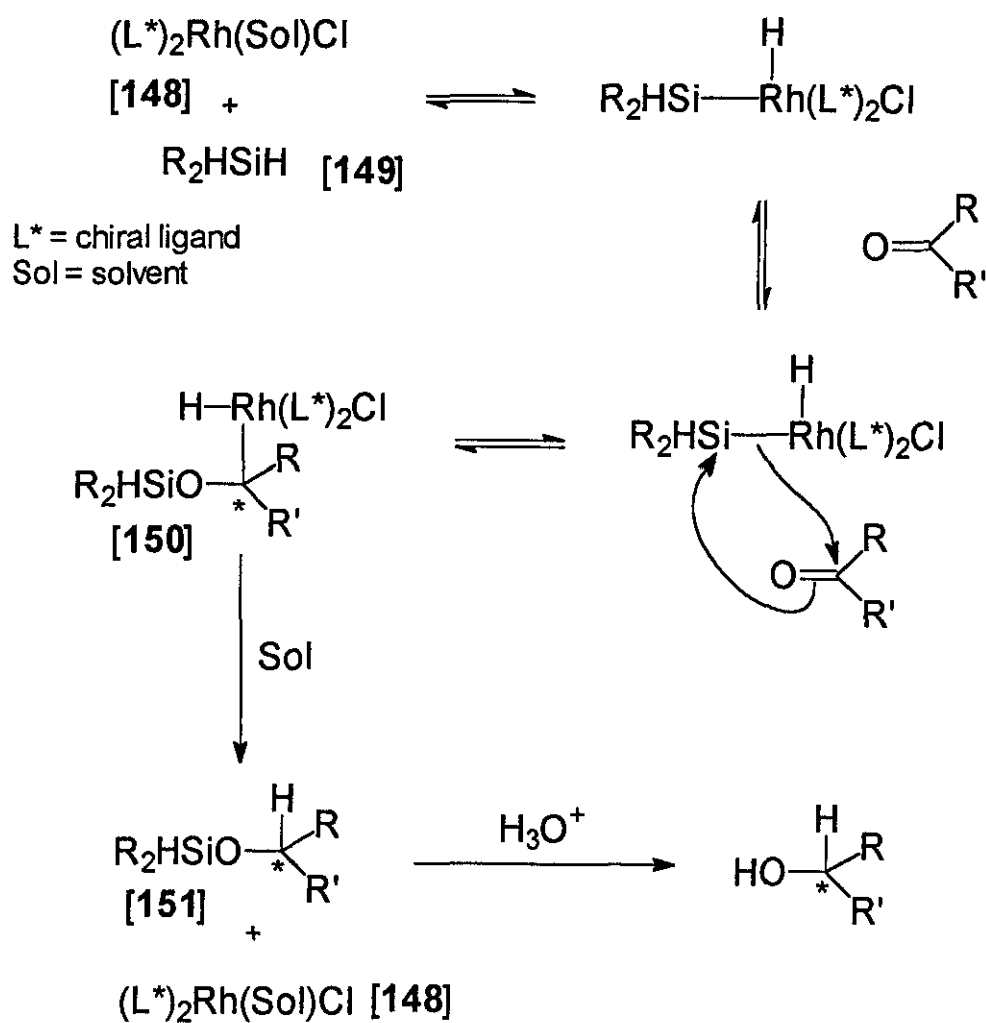
6.1.1 Mechanistic Proposals

The mechanism of the hydrosilylation of ketones has been a subject of much debate.¹⁵⁴ The most widely accepted theory, proposed by Ojima, states that the mechanism initiates with the oxidative addition of the hydrosilane [149] to the rhodium(I) complex [148]. The carbonyl then co-ordinates with the metal and inserts into the silicon-rhodium bond forming diastereomeric α -siloxyalkylrhodium hydride intermediates [150].

¹⁵³ O. Cervinka, *Enantioselective Reactions in Organic Chemistry*, Chap 10, Ellis Horwood, London, 1995.

¹⁵⁴ I. Ojima, *Asymmetric Synthesis*, Vol 5, Chap 4, Academic Press, New York, 1985 and papers cited therein.

It is at this insertion that the asymmetry can be induced due to the ligands coordinated at rhodium and the nature of the silane source. Reductive elimination with retention of configuration affords the enantiomerically enriched silyl ethers [151] and regenerates the catalyst [148]. The 'free' alcohols may then be obtained by normal acid hydrolysis (Scheme 72).



Scheme 72

A kinetic study of the hydrosilylation of *tert*-butyl phenyl ketone with diphenylsilane catalysed by $[(\text{-})\text{DIOP}]\text{Rh}(\text{COD})^+\text{ClO}_4^-$ has shown that the rate determining step is

the insertion of the ketone into the rhodium/silicon species.¹⁵⁵ A further consideration also has to be made when regarding the hydrosilylation mechanism of a substrate containing an additional carbonyl group, e.g. keto esters or diketones. In the case of moieties having more than one carbon unit between the two carbonyl groups Ojima suggests an attractive interaction of the second carbonyl to the metal centre (**Figure 14**).¹⁵¹ This additional interaction should induce greater rigidity in the transition state which may account for the considerable increase in the enantiomeric excesses obtained for the products of pyruvates compared to simple prochiral ketones.¹⁵⁶

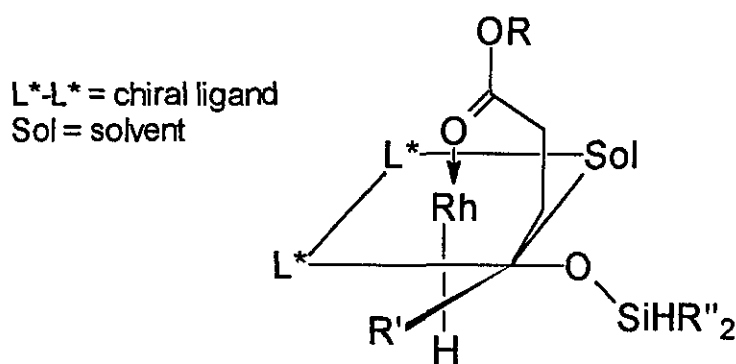


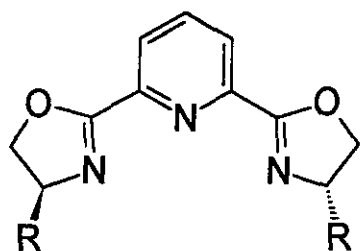
Figure 14

Another postulated mechanism pathway suggested by Nishiyama considers a concerted 1+2+2 [Rh^+ , C=O, H-Si] type mechanism.¹⁵⁷ The advantage of this system is that it predicts the results Nishiyama obtains whilst using the 'bipymox' [152] and 'pybox'-rhodium [29] catalysts.

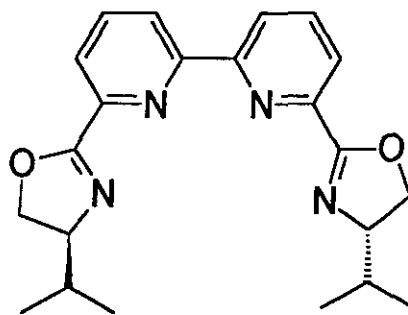
¹⁵⁵ I. Kolb and J. Hetflejs, *Coll. Czech. Chem. Comm.*, 1980, 45, 2224.

¹⁵⁶ I. Ojima, *Asymmetric Synthesis.*, Vol 5, Chap 4, page 114-120, Academic Press, New York, 1985 and papers cited therein.

¹⁵⁷ H. Nishiyama, S. Yamaguchi, S. Park, K. Itoh, *Tetrahedron: Asymmetry*, 1993, 4, 143.

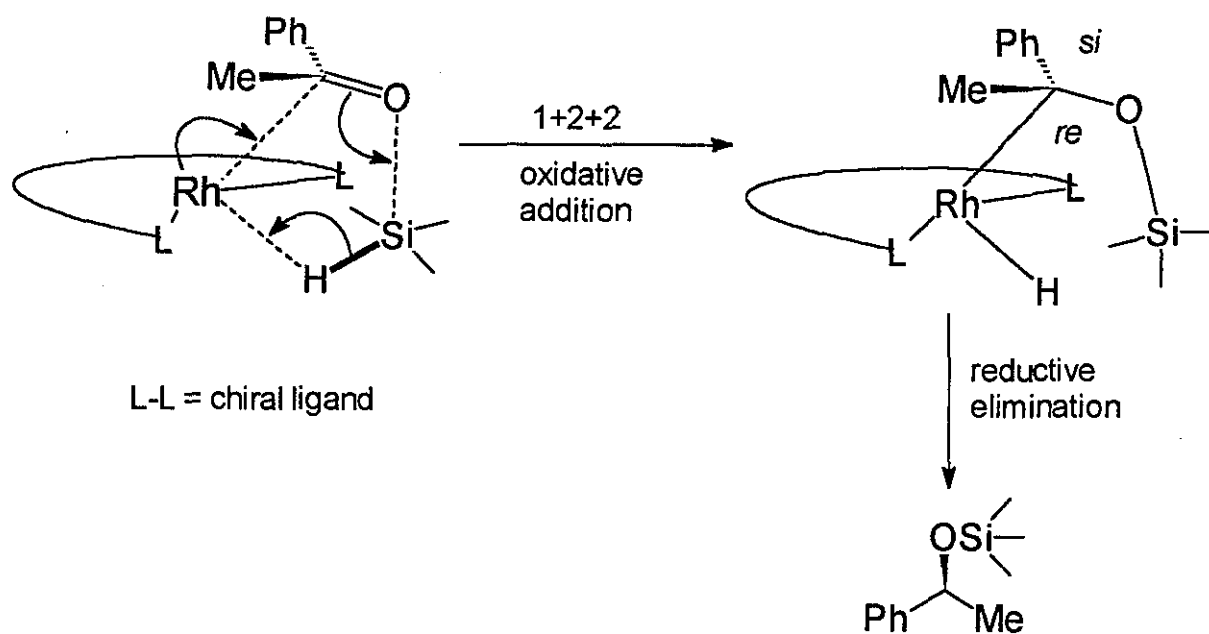


[29]
'pybox'



[152]
'bipymox'

Thus as he suggests the prochiral face selection of ketones in each case shows *re*-face selectivity to give the (*S*) alcohol (Scheme 73).¹⁵⁸



Scheme 73

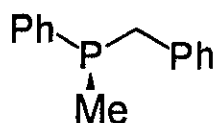
¹⁵⁸ H. Nishiyama, S. Yamaguchi, S. Park, K. Itoh, *Organometallics*, 1991, 10, 500.

6.2 Applications of Asymmetric Ligands

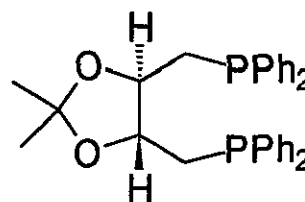
The enantiomerically pure ligands are based on a range of asymmetric structures predominantly concentrating on the chelation of phosphorus and/or nitrogen.

6.2.1 Enantiomerically Pure Phosphorus Based Ligands

Amongst the first chiral non-racemic ligands used in the asymmetric hydrosilylation of ketones were those based on phosphorus.¹⁵⁹ The most effective of these early catalysts was the Wilkinson compound $[\text{Rh}(\text{PPh}_3)_3\text{Cl}]$.¹⁶⁰ This literature precedent led to a plethora of new chiral phosphorus ligands, amongst the most popular BMPP [153] and DIOP [154]. However the enantiomeric excesses obtained from these preliminary hydrosilylations of simple ketones was only poor to moderate, 5–58%.



3–44% e.e.
R- BMPP [153]



5–58% e.e.
(*R,R*) DIOP [154]

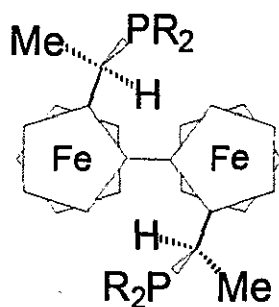
More recently Ito has developed a family of ligands based on a *trans*-chelating diphosphane moiety, 'nTRAP' [155].¹⁶¹ In a model system of diphenylsilane, $[\text{Rh}(\text{COD})_2]\text{BF}_4$ (1 mol%) and nTRAP, acetophenone was hydrosilylated in up to 92% enantiomeric excess and 89% yield. These excellent results were obtained

¹⁵⁹ K. Yamamoto, T. Hayashi, M. Kumada, *J. Organomet. Chem.*, 1972, 46, C65

¹⁶⁰ I. Ojima, M. Nihonyanagi, T. Kogure, M. Kumagai, S. Horiuchi, K. Nakatsugawa, *J. Organomet. Chem.*, 1975, 94, 449.

¹⁶¹ M. Sawamura, R. Kuwano, Y. Ito, *Angew. Chem. Int. Ed. Engl.*, 1994, 33, 111-113.

only using the *trans*-chelating ligands bearing primary alkyl groups, *n*PrTRAP [155a], and *n*BuTRAP [155b] the absence of which caused the enantiomeric excess to drop dramatically, *i.e.* 1% e.e. for *i*PrTRAP [155c].



[155]

*n*TRAP

a R = *n*Pr

b R = *n*Bu

c R = *i*Pr

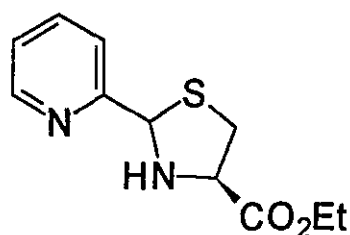
d R = Ph

6.2.2 Enantiomerically Pure Nitrogen Based Ligands

In order to exploit the asymmetric reduction of ketones by rhodium catalysed hydrosilylation a more efficient system of ligands needed to be introduced. It was discovered that enantiomerically pure nitrogen containing ligands could be synthesised relatively easily and inexpensively as they could be largely derived from readily available chiral pool material, *i.e.* 1° amines. The synthesis and use of nitrogen containing ligands was revealed initially by Brunner and co-workers.¹⁶² It was shown very early on that whilst the first nitrogen ligands, pyridine imines, were an improvement on phosphine ligands, an additional amount of conformational restriction was needed about the chiral centre. Brunner achieved this restriction by incorporating the asymmetric centre into a thiazolidine ring. In the model reaction of acetophenone with diphenylsilane, catalysed by [Rh(COD)Cl]₂ and pyridine

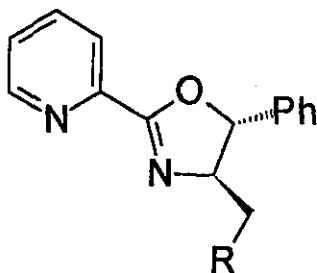
¹⁶² H. Brunner, *Angew. Chem., Int. Ed. Engl.*, 1983, 22, 897.

thiazolidine [156], the resulting alcohol obtained on hydrolysis gave a 97.6% enantiomeric excess.¹⁶³



[156]

97.6% e.e.



[157]

56–80% e.e.

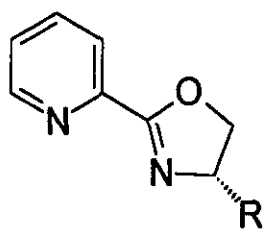
a R = OC(Ph)₃

b R = OCOCH=CHPh

c R = OPh

The theme of conformational restriction was continued into pyridinyloxazoline ligands by both Brunner¹⁶⁴ [28a-d, 158] and Balavoine¹⁶⁵ [157a-c].

'Pymox' ligands



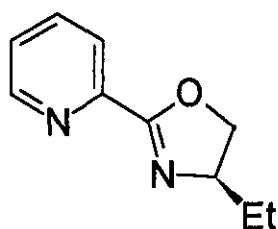
[28a] R = CH(Me)C₂H₅

[28b] R = ⁱPr

[28c] R = ⁱBu

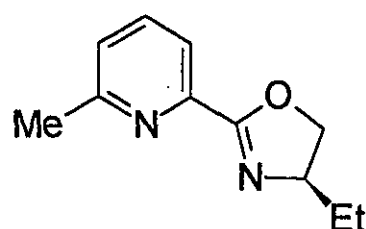
[28d] R = ⁱBu

52–83% e.e.



[158]

17–58% e.e.



[159]

30–48% e.e.

¹⁶³ H. Brunner, R. Becker, G. Riepl, *Organometallics*, 1984, 3, 1354.

¹⁶⁴ H. Brunner, U. Obermann, *Chem. Ber.*, 1989, 122, 499.

¹⁶⁵ G. Balavoine, J. Clinet, I. Lellouche, *Tetrahedron Lett.*, 1989, 30, 5141.

The extensive study of ligand [158] led to the observed enhanced effect on the enantiomeric excess when the reaction is performed in carbon tetrachloride (the 'CCl₄ effect').¹⁶⁴ This was a noticeable effect which was constant throughout the study of all the nitrogen chelating systems. It was also noted that in each system the ratios of pyridinyloxazoline ligand, acetophenone, diphenylsilane and rhodium catalyst were crucial. The following observations were made for ligand [158] based on the model reaction of the hydrosilylation of acetophenone in toluene using [Rh(COD)Cl]₂ and diphenylsilane, providing the S-enantiomer of 1-phenylethanol.

- enantioselectivity is enhanced by a low diphenylsilane:acetophenone ratio. Optimum = 0.25–0.5:1.
- low catalyst concentrations increase asymmetric induction. Optimum = 1–2 mol%.
- rhodium:diphenylsilane ratio of 1:50 induced higher enantiomeric excess than a ratio of 1:200.
- enantiomeric excess is enhanced by increase of ligand concentration, up to 5 mol%.
- high overall concentration enhances the optical activity of the product.

Brunner proposed an intermediate complex in the mechanism of the reaction to account for each of these observations (**Figure 15**).¹⁶⁶

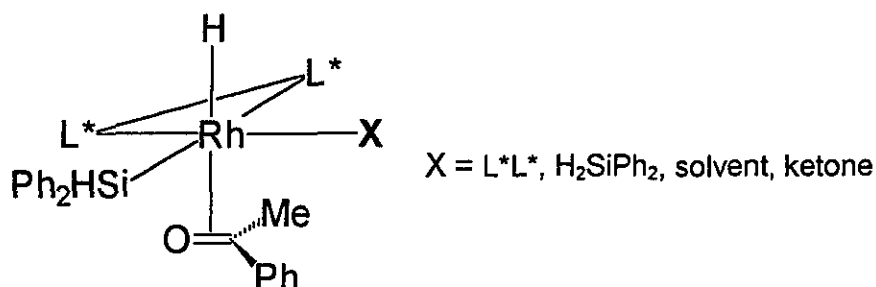


Figure 15

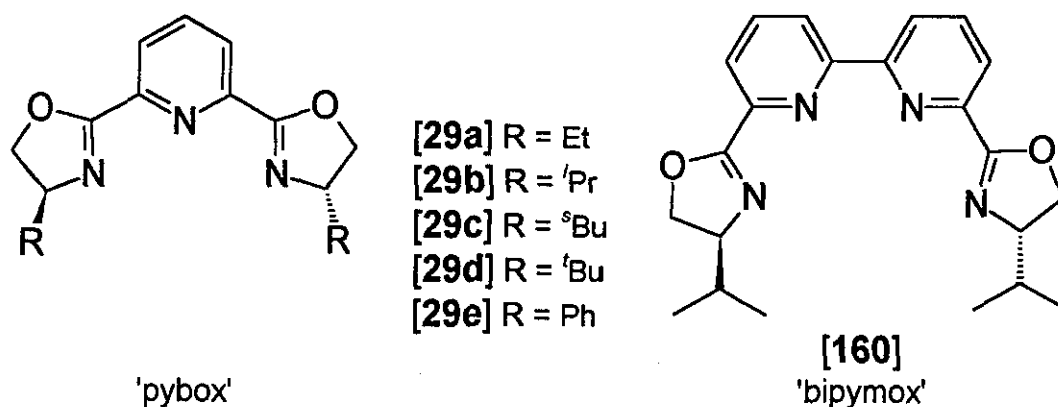
Here the co-ordination site **X** is in potential equilibria between each of the noted species. Only in the cases of **X** existing as ligand (bonded in a monodentate fashion) or ketone is there a co-ordination sphere in which the potential for alcohol selectivity is 'S'. This is shown experimentally, as the equilibrium is shifted towards one of these desired species by the addition of extra material (e.g. ketone or ligand) the enantiomeric excess of the alcohol increases. Intermediates based on **X** equalling diphenylsilane or solvent show a low potential for S selectivity in the alcohol. This is borne out in the experimental observations that further addition of silane or solvent diminishes the enantiomeric excess. The optimum result obtained using these pyridyloxazoline ligands [**28d**] was 90% yield (83% e.e.).^{164,167}

¹⁶⁶ H. Brunner, P. Brandel, *Tetrahedron: Asymmetry*, 1991, 2, 919.

¹⁶⁷ H. Brunner, C. Henrichs, *Tetrahedron: Asymmetry*, 1995, 6, 653.

Further ligands of this pyridyloxazoline series include the picolineoxazoline [159], which in identical reaction conditions to ligands [28] reverses the nature of the induced enantiomeric centre to afford the *R* enantiomer of 1-phenylethanol.¹⁶⁸

Nishiyama and co-workers have additionally highlighted the obvious effectiveness of using enantiomerically pure oxazolines as ligands. In this work Nishiyama has also considered pyridinyloxazoline ligands which he refers to as 'pymox' ligands [28], but concentrates more heavily on the C_2 symmetric bis-substituted analogues 'pybox'^{169,170} [29a–e] and 'bipymox'¹⁷¹ [160] ligands.



Both the pybox and bipymox ligands, although successful in creating good enantioselectivities, were very slow to complex with $[\text{Rh}(\text{COD})\text{Cl}]_2$, *i.e.* premixing over 24 hours was needed. A more efficient alternative procedure involved precomplexation of the ligands to rhodium trichloride. These trivalent rhodium complexes [161] and [162] were then used in the model hydrosilylation reaction of acetophenone with diphenylsilane. A catalytic amount of silver salts was needed to

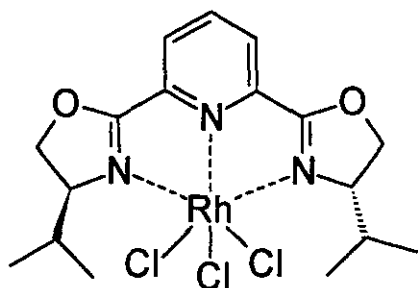
¹⁶⁸ H. Brunner, P. Brandel, *J. Organomet. Chem.*, 1990, 390, C81.

¹⁶⁹ H. Nishiyama, H. Sakaguchi, T. Nakamura, M. Horihata, M. Kondo, K Itoh, *Organometallics*, 1989, 8, 846.

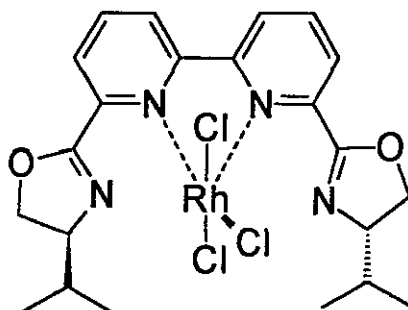
¹⁷⁰ H. Nishiyama, T. Nakamura, M. Kondo, K Itoh, *Organometallics*, 1991, 10, 500.

¹⁷¹ H. Nishiyama, S. Yamaguchi, S. Park, K. Itoh, *Tetrahedron: Asymmetry*, 1993, 4, 143.

initiate the reaction in each case and both systems were enhanced by additional uncomplexed ligand by up to 30% enantiomeric excess.

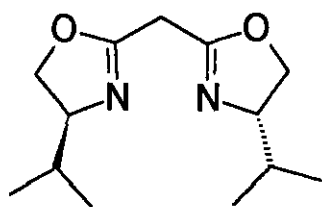


[161] 91%, 94% e.e.

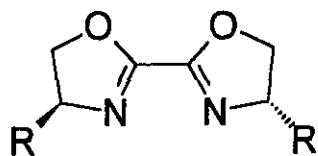


[162] 90% e.e.

A number of other prominent research groups have also presented results based on novel enantiomerically pure C_2 bis-oxazolines. Helmchen *et al* reported results based upon their new bisoxazoline **[163, 164a-d]** and bithiazoline **[165a-b]** ligands.¹⁷² Although they were able to achieve an optimum enantiomeric excess of 84% using ligand **[164b]**, the results for the other ligands were mainly disappointing, 0–55% e.e.



[163] 12% e.e.

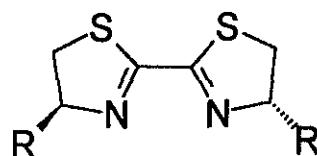


[164a] R = ^tPr 55% e.e.

[164b] R = CH₂Ph 84% e.e.

[164c] R = Ph 59% e.e.

[164d] R = ^tBu 0% e.e.

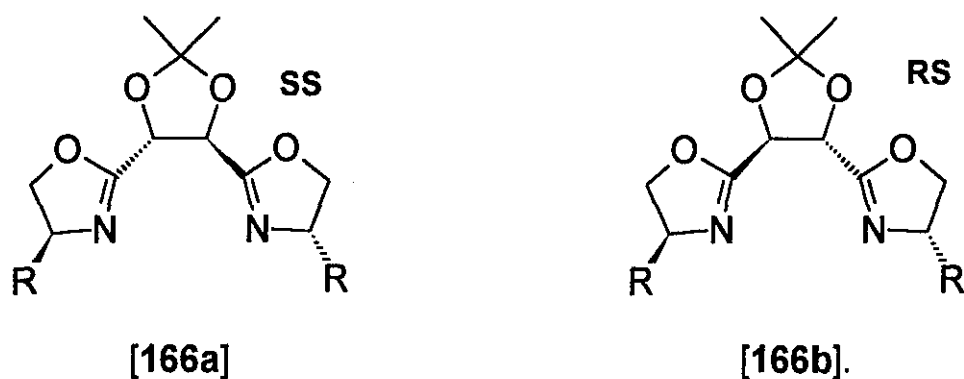


[165a] R = ^tPr 9% e.e.

[165b] R = CH₂Ph 50% e.e.

¹⁷² G. Helmchen, A. Krotz, K. Ganz, D. Hansen, *Synlett*, 1991, 257.

Similarly the tartrate based bisoxazolines [166] of Ikeda and co-workers showed largely unexceptional results of the order 25–65% e.e.¹⁷³ A matching of the configurations of the oxazoline (S,S) and the tartrate (S,S) [166a] consistently revealed higher enantiomeric excesses of 1-phenylethanol in the model reaction than unmatched counterpart [166b].



R = ⁱPr, ^tBu, Ph

6.2.3 Enantiomerically Pure Nitrogen/Phosphorus Bidentate Ligands

In each case that we have considered thus far, the mono-, di- or tri-dentate ligand donor atoms have been of a singular nature, *i.e.* all of one atom type. The advantages of modifying to a mixed donor atom system have been made apparent in some notable work by Ikeda,¹⁷⁴ Helmchen,¹⁷⁵ P. Evans,¹⁷⁶ Pfaltz,¹⁷⁷ Williams,³⁸ and Ahn.¹⁷⁸ Commonly these ligands incorporating two or more differing donor atoms concentrate on a phosphorus, nitrogen arrangement. Amongst the first to report this chelating system in hydrosilylation reactions were the groups of Uemura¹⁷⁹ and

¹⁷³ Y. Imai, W. Zhang, T. Kida, Y. Nakatsuji, I. Ikeda, *Tetrahedron: Asymmetry*, 1996, 7, 2453.

¹⁷⁴ W. Zhang, H. Toshikazu, I. Ikeda, *Tetrahedron Lett.*, 1996, 37, 4545.

¹⁷⁵ J. Sprinz, M. Kiefer, G. Helmchen, *Tetrahedron*, 1996, 52, 7547.

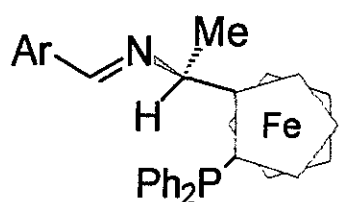
¹⁷⁶ P. A. Evans, T. Brandt, *Tetrahedron Lett.*, 1996, 37, 9143.

¹⁷⁷ P. von Matt, O. Loiseleur, G. Koch, A. Pfaltz, *Tetrahedron: Asymmetry*, 1996, 5, 573.

¹⁷⁸ K. Ahn, C. Cho, J. Park, S. Lee, *Tetrahedron: Asymmetry*, 1997, 8, 1179.

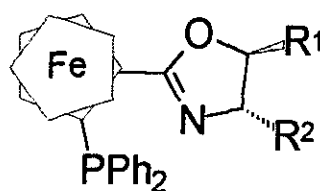
¹⁷⁹ Y. Nishibayashi, K. Segawa, K. Ohe, S. Uemura, *Organometallics*, 1995, 14, 5486.

Hayashi.¹⁸⁰ In both ligand systems each group has based the main body of the structure on a diphenylphosphine substituted ferrocene moiety.



[167]

- a** Ar = Ph
- b** Ar = *m*-CF₃C₆H₄
- c** Ar = *p*-CF₃C₆H₄
- d** Ar = C₆F₅



[168]

- a** R¹ = H, R² = Ph
- b** R¹ = H, R² = *i*Pr
- c** R¹ = Ph, R² = Ph (S-DIPOF)

Hayashi and co-workers opted for an imine secondary chelating site [167].

Examination of the results for these ligands in a model hydrosilylation reaction of acetophenone with diphenylsilane and [Rh(NBD)Cl]₂ revealed excellent results, 87–90% e.e. Of particular note are the ligands containing electron withdrawing groups on the aryl ring [167b–d]. These ligands have an incredibly increased reaction rate in comparison with single donor atom type systems and are able to complete the hydrosilylation of acetophenone within 10 minutes using 1 mol% rhodium catalyst. Reaction times for the majority of ligands range from 2 to 27 hours, with 14–18 hours being the most common period.

Uemura *et al* utilised the known efficiency of the oxazoline moiety in chelating to rhodium and inducing chirality to afford the secondary binding site in their novel ligands [168]. Excellent results were achieved using ligand [168c] (S-DIPOF), 91%

¹⁸⁰ T. Hayashi, C. Hayashi, Y. Uozumi, *Tetrahedron: Asymmetry*, 1995, 6, 2503.

e.e. of (*R*)-1-phenylethanol from a model reaction of acetophenone. Surprisingly the use of $[\text{Ir}(\text{COD})\text{Cl}]_2$ instead of $[\text{Rh}(\text{COD})\text{Cl}]_2$ affords the opposite enantiomer of 1-phenyl ethanol (*S*), which also shows high enantioselectivity (96 % e.e.).¹⁵⁴

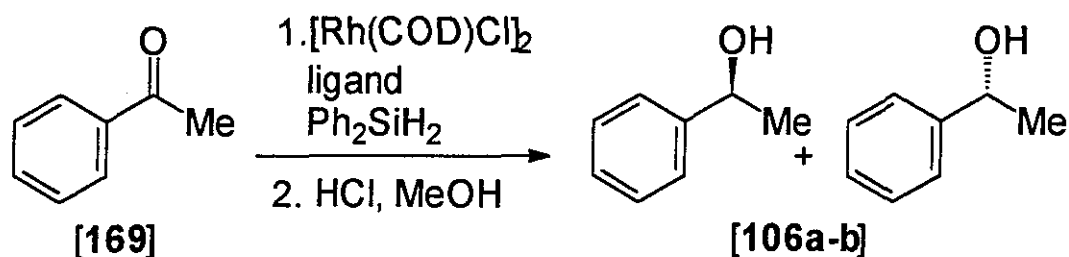
The highly enantioselective hydrosilylation of simple ketones appears to be a synthetic objective which has been fulfilled with reasonable efficiency by the available ligands in the literature. Nonetheless there remains scope for further study in this challenging and important area of research.

6.3 Results and Discussion

Here we would like to continue the preliminary investigations into the rhodium catalysed hydrosilylation of simple ketones. It is our intention to consider the ligand family of diphenylphosphinooxazolines [**21a–c**, **70**, **71**], analogous diphenylphosphinoacetal [**25b**] and pyridylacetal [**51**, **52**, **54**] ligands in such reactions and assess their efficacy in such a system.

6.3.1 Pyridylacetal Ligands

Our initial intention when carrying out this section of research was to devise a platform onto which we could introduce novel ligands based on bidentate or tridentate pyridine acetal moieties [**51**, **54**]. With the obvious structural similarities of our acetal ligands to the pybox [**29**] and pymox [**28**] systems it appeared logical to utilise the same model hydrosilylation reaction of acetophenone [**169**] (**Scheme 74**).



Scheme 74

Following a general procedure by Nishiyama and co-workers,¹⁷⁰ acetophenone, $[\text{Rh}(\text{COD})\text{Cl}]_2$ (0.25 mol%) and the appropriate ligand (2.5 mol%) were pre-complexed. It was proposed that a complex (**Figure 16**) would form, showing coordination of the rhodium to both the nitrogen of the pyridyl ring and the oxygen of the enantiopure acetal.

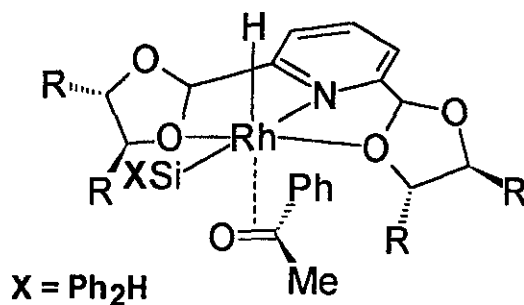


Figure 16

Insertion of the ketone into the rhodium–silicon bond and reductive elimination should then afford the *S* enantiomer of the alcohol. Assuming that the complex had formed, diphenylsilane was added and the reaction stirred until all the starting materials had been consumed before acid hydrolysis revealed the desired product, 1-phenylethanol. Chiral HPLC showed that no enantioselectivity had been achieved. In an attempt to rectify the situation, the reaction was repeated in carbon tetrachloride. The so called 'CCl₄ effect' had been shown to enhance the selectivity

of all the known hydrosilylation nitrogen chelating ligands.¹⁶⁴ In this case the effect was repeated, albeit in a disappointing fashion leading to a rise in the enantiomeric excess of 6%.

Despite considerable efforts using ligands [51] and [54], *i.e.* longer complexation times, variation of substrate:catalyst ratios, changes in temperature, no significant enantiomeric excesses could be obtained.

It became increasingly evident that the ligand–rhodium complexes necessary to sculpt a chiral environment for the hydrosilylation were not being formed during the course of the reaction. The failure of the oxygen lone pairs on the ligand to coordinate to the rhodium was the obvious underlying factor. The lack of exploitable leads for this system suggested that it was time to move to a more capable scenario involving a combination of phosphorus and nitrogen chelating atoms, namely phosphinooxazoline ligands.

6.3.2 Phosphinooxazoline Ligands and analogues

The family of 2-substituted phenyloxazolines has been the topic of much research in the academic literature. In particular the research groups of Pfaltz,⁷⁰ Helmchen,¹⁷⁵ and Williams³⁸ have shown these to be effective ligands for enantioselective palladium catalysed allylic substitutions. We wished to exploit what appeared to be an oversight and attempt to prove that these ligands had additional scope into the hydrosilylation of ketones. We envisaged that these ligands would bind *via* the P/N moieties (**Figure 17**), as these have proven to be effective in other systems.

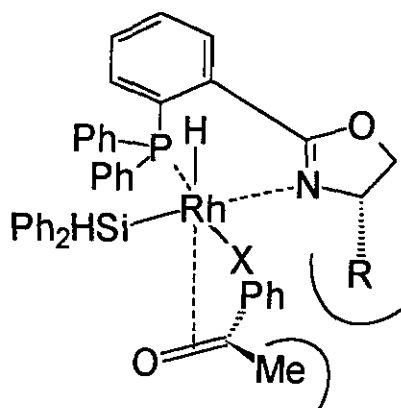


Figure 17

The ketone moiety is arranged so that the bulky phenyl group does not clash with the R group of the ligand. Some interaction was suspected between the smaller methyl group and the R group, but it was hoped that this would not interfere with the reaction enough to inhibit its completion. The X group is suspected to be either another acetophenone or diphenylsilane molecule as these are both present in great excess. This proposed intermediate affords the S enantiomer of product alcohol. Therefore a series of enantiomerically pure 2-diphenylphosphine oxazolines [21a-c, 70, 71] were synthesised for the purpose of using in the model hydrosilylation of acetophenone.¹⁸¹

Initially the conditions used for the reaction mimicked those used by Nishiyama.¹⁷⁰

The relevant quantities of the chemicals used in the model hydrosilylation of acetophenone were as follows;

[Rh(COD)Cl] ₂	ligand	acetophenone	Ph ₂ SiH ₂
0.01 mmol	0.1 mmol	4 mmol	4 mmol

¹⁸¹ L. Newman, J. Williams, *Tetrahedron: Asymmetry.*, 1996, 7, 1597.

With the ligands in hand we began to determine the effects each of the variables of the reaction sequentially. From these results we endeavoured to find an optimal set of reaction conditions.

6.3.2.1 Solvent Effects

In order to assess which solvent was most compatible with the new ligand systems preliminary reactions were carried out each at 0 °C. In each case the amount of solvent added was the same, 1 ml. These are shown in **Table 18**.

Table showing the enantiomeric excesses of 1-phenyl ethanol synthesised under the solvent and ligand conditions specified.

ligand	solvent	enantiomeric excess (%)
[21c]	none	26
[21c]	CCl ₄	14
[21b]	none	72
[21b]	CCl ₄	no reaction
[21b]	toluene	72
[21b]	THF	72

Acetophenone (8 mmol), [Rh(COD)Cl]₂ (0.04 mmol) and ligand (0.4 mmol) were stirred in desired solvent (2 ml) for 24 hours. The solution was then cooled to 0°C, diphenylsilane (8 mmol) added and stirred for 43 hours before work up.

Table 18

The results for both ligands [21b] and [21c] clearly show no advantage in using carbon tetrachloride, as Brunner had seen in his systems.¹⁶⁶ Indeed there appeared to be little need for solvent, as the obtained enantiomeric excesses for the isopropyl based ligand [21b] were not affected by adding any solvent. On this basis it seemed sensible not to include a solvent and thus remove the issue of the concentration

effects. However one potential problem which arose from the inclination to carry out further reactions in a solvent free system was made apparent when temperature studies were carried out. Any attempts to lower the temperature below $-40\text{ }^{\circ}\text{C}$ caused the solvent free system to freeze and therefore the reaction to be halted. The addition of an appropriate solvent prevented this and so allowed the assessment of the reaction at lower temperatures. These extra studies showed that THF appeared to be the most convenient and appropriate solvent to use in subsequent studies (Table 19).

Table showing the effects of solvent on the obtained enantiomeric excesses of 1-phenyl ethanol product.

ligand	solvent	temperature ($^{\circ}\text{C}$)	enantiomeric excess (%)
[21a]	THF	-78	55
[21a]	CH_2Cl_2	-78	48
[21b]	THF	-78	81
[21b]	toluene	-78	79

Acetophenone (8 mmol), $[\text{Rh}(\text{COD})\text{Cl}]_2$ (0.04 mmol) and ligand (0.4 mmol) were stirred in desired solvent (2 ml) for 24 hours. The solution was then cooled to appropriate temperature, diphenylsilane (8 mmol) added and stirred for 43 hours before work up.

Table 19

6.3.2.2 Ligand Comparisons

In order to establish the ligand of choice for the extensive study of this reaction some preliminary studies were carried out on the available phosphinooxazolines [21a-c, 70, 71] (Table 20).

Table showing the effects of different ligands on the enantiomeric excesses of the 1-phenyl ethanol product.

	ligand	chiral moiety	enantiomeric excess (%)	yield (%)
1	[21a]	Me	46	62
2	[21b]	^t Pr	72	40
3	[21c]	^t Bu	26	32
4	[70]	^t Bu	59	73
5	[71]	CH ₂ C ₆ H ₁₁	64	69

Acetophenone (8 mmol), [Rh(COD)Cl]₂ (0.04 mmol) and ligand (0.4 mmol) were stirred in THF (2 ml) for 24 hours. The solution was then cooled to -78°C, diphenylsilane (8 mmol) added and stirred for 43 hours before work up.

Table 20

This clearly indicated the isopropyl based oxazoline ligand as the most effective in terms of inducing enantioselectivity (entry 2). Of particular note is the observation by Williams *et al* that the same ligand was found to be the most capable of the series for the palladium catalysed allylic substitution model reaction.³⁸ Disappointingly any deviation of the asymmetric group from the isopropyl unit showed a drop in the enantioselectivity. The additional steric hinderance associated with the bulky *tert*-butyl group appeared to be detrimental (entry 3). The methyl group, clearly not sterically demanding enough, also gave mediocre results (entry 1). Ligands having a more extended chiral moiety (entries 4 and 5) although showing good results, imply that as the bulk of the asymmetric group becomes further from the asymmetric centre the induced enantioselectivity in the transition state and thus in the product falls.

In order to confirm the superiority of the phosphorus–nitrogen chelation to rhodium in the hydrosilylation of ketones, we carried out the standard reaction exchanging the ligand for **[21e]**¹⁸² and **[25b]** in turn. Ligand **[21e]** had a sulfur soft donor atom instead of the phosphino group of ligand **[21b]**. This was shown to be a vital donor site as the sulfur analogue failed to induce any activity in the hydrosilylation of acetophenone (**Table 21**).

Table showing the effects on the yield and enantiomeric excess of 1-phenyl ethanol on changing the ligand donor atoms used in the synthesis.

ligand	donor atoms	enantiomeric excess (%)	yield (%)
[21b]	P,N	72	40
[21e]	S,N	0	45
[25b]	P,O	30	80

Acetophenone (8 mmol), [Rh(COD)Cl]₂ (0.04 mmol) and ligand (0.4 mmol) were stirred in THF (2 ml) for 24 hours. The solution was then cooled to -78°C, diphenylsilane (8 mmol) added and stirred for 43 hours before work up.

Table 21

When further manipulating the donor atom to oxygen, as part of an acetal template, as in ligand **[25b]**, the effects of change were not as dramatic. With the rhodium metal bonding here through phosphorus and oxygen a reasonable enantiomeric excess was achieved, 30%. Overall these results verified the necessity of the P/N mixed donor system in order to co-ordinate successfully with the rhodium metal centre.

¹⁸² sample synthesised within the group.

Having proven conclusively that ligand **[21b]** was the most effective and efficient ligand, we set about optimising the other variables in the rhodium(I) catalysed hydrosilylation of acetophenone.

6.3.2.3 Effects on Ligand Metal Complexation over Time

For all of the original reactions carried out using these ligands we allowed an excessive time length for the metal/ligand/acetophenone complex to form. Prior to the addition of the diphenylsilane we allowed 24 hours for complexation. It was subsequently shown that this was not necessary (**Table 22**). Experimental results allude to the fact that the lowering of premixing time, even to as low as 20 mins, had no detrimental effect on the enantiomeric purity of the product alcohol.

Table showing the effect on the enantiomeric excess of 1-phenyl ethanol when changing the time allowed for complexation to take place.

ligand	time allowed for complexation	enantiomeric excess (%)
[21b]	24 hours	72
[21b]	2 hours	72
[21b]	20 mins	78

Acetophenone (8 mmol), $[\text{Rh}(\text{COD})\text{Cl}]_2$ (0.04 mmol) and ligand (0.4 mmol) were stirred in THF (2 ml) for specified time. The solution was then cooled to -78°C , diphenylsilane (8 mmol) added and stirred for 43 hours before work up.

Table 22

This observation appears logical as analogous ligands containing phosphorus moieties have shown high rates of reaction and therefore must have fast ligand/metal/substrate complexation times.¹⁸⁰ Although further rate studies were not carried out on this reaction the almost immediate appearance of a red/brown

colouration appears to indicate the possibility that complexation is instantaneous. In an endeavour to increase the efficiency all subsequent reactions were carried out with a 20 minute complexation time.

6.3.2.4 Temperature Effects

In order to complete the optimisation of the variable reaction conditions in the model hydrosilylation we embarked on some temperature studies. With the choice ligand [21b] in a solution of THF (1 ml), parallel reactions were carried out at the varying temperatures 0, -40 and -78 °C (Table 23).

Table showing the effect on the enantiomeric excess of 1-phenyl ethanol when changing the temperature at which the reaction takes place.

temperature (°C)	enantiomeric excess (%)
0	72
-40	77
-78	81

Acetophenone (8 mmol), [Rh(COD)Cl]₂ (0.04 mmol) and ligand (0.4 mmol) were stirred in THF (2 ml) for 20 mins. The solution was then cooled to -78°C, diphenylsilane (8 mmol) added and stirred for 43 hours before work up.

Table 23

Here we saw a small but significant increase in the enantiomeric excess of the product alcohol as the temperature was lowered. To our knowledge this was the first example of an enantioselective hydrosilylation of acetophenone to be carried out successfully below -20 °C. With attempts to lower the temperature further to -90 °C being unsuccessful, it was considered that the optimum reaction temperature be -78 °C. This temperature was therefore used in all ensuing reactions.

The following sections are concerned with the effect of changing the ratios of $[\text{Rh}(\text{COD})\text{Cl}]_2$:ligand, acetophenone and diphenylsilane. The variables which have already been fixed for each of these reactions are,

- temperature = $-78\text{ }^\circ\text{C}$
- solvent = THF (1 ml)
- complexation time = 20 mins
- ligand = [21b]

In addition;

- $[\text{Rh}(\text{COD})\text{Cl}]_2$:ligand ratio = 1:10
- Quantity of acetophenone = 1 mmol

6.3.2.5 Effects of Diphenylsilane Concentration

Normally in hydrosilylation reactions the diphenylsilane:acetophenone ratio of 1;1 is used. Thus far in our investigations this has been so. However Brunner had reported that for pyridineoxazoline ligands an increase in optical induction was noted at low diphenylsilane/acetophenone ratios, 0.25–0.5:1.¹⁶⁴ Preliminary results showed that there was no such enhancement of enantiomeric excess in our systems by the reduction of the relative amount of diphenylsilane (**Table 24**, entries 1 and 2).¹⁸³

¹⁸³ Catalyst and ligand quantities used were 1 mol% and 10 mol% respectively.

Table showing the effect on the enantiomeric excess of 1-phenyl ethanol when changing the acetophenone/diphenyl silane ratio.

	[Rh(COD)Cl] ₂ : ligand ratios (mol%)	acetophenone (mmol)	diphenyl silane (mmol)	enantiomeric excess (%)	yield (%)
1	1:10	1	0.5	82	30
2	1:10	1	1	86	33
3	1:10	1	2	85	41
4	1:10	1	4	82	86
5	1:10	1	6	79	69

Acetophenone (1 mmol), [Rh(COD)Cl]₂ (0.005 mmol) and ligand (0.05 mmol) were stirred in THF (1 ml) for 20 mins. The solution was then cooled to -78°C, diphenylsilane added and stirred for 43 hours before work up.

Table 24

However the chemical yields of the reaction were noticeably poor in both cases, 30–33%. Therefore we decided to focus predominantly on improving the yield by manipulating the diphenylsilane concentration further. In order to try to drive the reaction to completion we decided to increase the silane concentration 2,4 and 6 fold (**Table 24**, entries 3–5).¹⁸¹ The results clearly show a dramatic increase in the yield of the reaction corresponding to the rise in silane concentration. The most striking elevation in yield occurred at a four equivalent addition of diphenylsilane to acetophenone. There appears that there maybe a slight sacrifice in the obtained enantiomeric excess (up to 4%) in order to obtain such promising yield. Nonetheless this result of 82% e.e., 86% yield although not the highest e.e. obtained (86%), must be considered to be the most useful result. The advantage of an addition of a four-fold excess of silane was also appreciated in two sets of analogous experiments in which the rhodium catalyst and ligand concentrations had been lowered (**Table 25**).

Table showing the effects on the yield and enantiomeric excess of 1-phenyl ethanol when changing the acetophenone/diphenyl silane ratio.

[Rh(COD)Cl] ₂ : ligand ratios (mol%)	acetophenone (mmol)	diphenylsilane (mmol)	enantiomeric excess (%)	yield (%)
0.5:5	1	1	81	54
0.5:5	1	2	81	69
0.5:5	1	4	78	93
0.1:1	1	1	77	44
0.1:1	1	2	75	23
0.1:1	1	4	72	46

Acetophenone (1 mmol), [Rh(COD)Cl]₂ (0.005 mmol) and ligand (0.05 mmol) were stirred in THF (1 ml) for 20 mins. The solution was then cooled to -78°C, diphenylsilane added and stirred for 43 hours before work up.

Table 25

These additional experiments aided us in concluding that the optimum ratio of acetophenone to diphenylsilane was indeed 1 to 4.

6.3.2.6 Effects of Ligand/catalyst Complex Concentration

The concentration of catalyst/ligand to acetophenone remained the only outstanding variable to be resolved. Having all the other conditions and quantities set as in the previous chapter, along with the newly optimised ratio of acetophenone to diphenylsilane of 1:4, we embarked on the following experiments. In each case the ratio of ligand to rhodium catalyst was set at 1:10. The combination of these was then adjusted relative to the quantity of acetophenone, the values of which are shown in **Table 26**.¹⁸¹

Table showing the effects on the yield and enantiomeric excess of 1-phenyl ethanol when changing the acetophenone/diphenyl silane to rhodium/ligand ratio.

[Rh(COD)Cl] ₂ : ligand (mol%)	acetophenone: diphenylsilane (mmol)	enantiomeric excess (%)	yield (%)
0.1:1	1:4	72	46
0.5:5	1:4	78	93
1:10	1:4	82	86

Acetophenone (1 mmol), [Rh(COD)Cl]₂ and ligand were stirred in THF (1 ml) for 20 mins. The solution was then cooled to -78°C, diphenylsilane (4 mmol) added and stirred for 43 hours before work up.

Table 26

Both the 0.5:5 mol% and the 1:10 mol% combination show excellent results. Basing our choice of system on the optimisation of enantiomeric excess and on practical factors *i.e.* using 1 mol% of [Rh(COD)Cl]₂ (4.9 mg) rather than lesser amounts which become difficult to weigh accurately. We considered the [Rh(COD)Cl]₂:ligand quantities of 1:10 mol% to be the most appropriate in this reaction.

6.3.2.7 Other Factors

Several other isolated reactions were conducted on this model system. The first of which was to change the silane source. Nishiyama¹⁵⁸ and Balavoine¹⁶⁵ had both noted an increase in induced enantioselectivity when using the bulkier naphthylphenylsilane. In attempt to assess if this was true in our system we synthesised some naphthylphenylsilane but could not completely purify it.¹⁸⁴ Taking the crude silane and carrying out the reaction under standard conditions we did indeed see an increase in the enantiomeric excess of the product, 86% (yield =

¹⁸⁴ Prepared from PhSiCl₃ by treatment with (1-naphthyl)magnesium bromide and subsequent reduction with LiAlH₄ according to: T. Matsuda, J. Stille, *J. Am. Chem. Soc.*, 1978, 100, 268.

85%). However this was relatively small change (up 4% from 82%). As naphthylphenylsilane is difficult to synthesise, not commercially available and gives results only marginally better than for diphenylsilane it did not warrant further investigation.

We also investigated the possibility of using a cationic rhodium source as other researchers had found these to also catalyse the hydrosilylation reaction. Initially we used a commercially available catalyst $[\text{Rh}(\text{COD})_2]\text{BF}_4$, similar to $[\text{Rh}(\text{COD})\text{Cl}]_2$. Under standard conditions it produced both a poorer yield and enantiomeric excess than the standard $[\text{Rh}(\text{COD})\text{Cl}]_2$ (Table 27).¹⁸¹

Table showing the effects on the yield and enantiomeric excess of 1-phenyl ethanol when changing the catalyst.

catalyst	enantiomeric excess (%)	yield (%)
$[\text{Rh}(\text{COD})\text{Cl}]_2$	82	86
$[\text{Rh}(\text{COD})_2]\text{BF}_4$	67	40
$[\text{Rh}(\text{COD})\text{Cl}]_2 + \text{AgBF}_4$	81	10
$[\text{Ir}(\text{COD})\text{Cl}]_2$	10	41

Acetophenone (1 mmol), catalyst (1 mol%) and ligand (10 mol%) were stirred in THF (1 ml) for 20 mins. The solution was then cooled to -78°C , diphenylsilane (4 mmol) added and stirred for 43 hours before work up.

Table 27

We also tried the addition of silver salts to the standard reaction in order to produce an *in situ* cationic rhodium species. This also gave no improvement over the system of choice, as it showed exceptionally poor yields.

Following the lead of Uemura and co-workers¹⁵² we also looked at the iridium analogue of the cyclooctadiene catalyst, [Ir(COD)Cl]₂. Unfortunately unlike their systems we achieved only poor enantioselection of 10% and decided that we would continue, focusing only on the rhodium species.

6.3.2.8 Summary of Optimisation Conditions

The culmination of all the data from this topic of research allowed us to make the following judgements concerning the optimum condition and chemical quantities for the hydrosilylation of acetophenone using phosphinooxazoline ligands.

- solvent = THF (1 ml) No enhanced effect using CCl₄, reactions can be as successful neat but not at low temperature.
- ligand = **[21b]** Enantiomeric excess drops dramatically with larger or much smaller asymmetric groups.
- time allowed for ligand/metal complex to form = 20 min Longer complexation times were found to be unnecessary, compatible with literature observations.
- temperature = -78 °C Enantioselectivity was found to increase steadily as the temperature was lowered from 0 °C to -78 °C.

- diphenylsilane equivalents to acetophenone = 4
1:1 ratios of ketone to silane showed excellent e.e.'s, but poor yields, high ratios of silane increased the yield dramatically to a peak at a ratio of 1:4.
- [Rh(COD)Cl]₂:ligand ratio = 1:10 mol%
Best obtained ratio overall, optimum e.e. Can obtain higher yield at lower concentration i.e. 0.5:5 mol% to the detriment of the e.e.
- acetophenone quantity = 1 mmol (concentration = 1 M)
Standard throughout

Observation of the reaction conditions clearly indicate a highly reactive and efficient ligand system which requires short reaction times, low temperature and mmol quantities of catalyst.

It should be noted at this point that in using (*S*)-ligands the alcohol product of the reaction, 1-phenylethanol is always formed in its '*R*' configuration. This is consistent with the findings for the analogous *S*-pyridyloxazoline ligands [28] (pymox).¹⁷¹

Interestingly work published by Helmchen and co-workers on a related hydrosilylation system (published simultaneously with our work) found that ligand [21b] also gave the highest levels of enantiomeric purity.¹⁸⁵

¹⁸⁵ T. Langer, J. Janssen, G. Helmchen, *Tetrahedron: Asymmetry*, 1996, 7, 1599.

Here it must be emphasised that each of these variables has been optimised independently. Thus the combination of the optimised variables does not necessarily constitute a complete optimisation of the reaction. It may be considered that alternative combinations of the variables could provide marginally enhanced results. However having carried out extensive research into the basic reaction, achieving excellent results (up to 86% e.e.), we decided to move on to the application of the reaction to alternative substrates.

6.3.2.9 Substrate Effects

With all the optimum conditions at hand we performed parallel hydrosilylation reactions, changing only the ketone substrate in each case. The results of these are shown in **Table 28**.

Table showing the yields and enantiomeric excesses of other alcohols synthesised using the optimised rhodium catalysed hydrosilylation reaction.

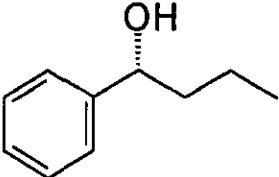
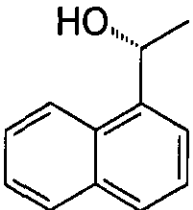
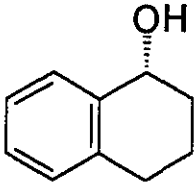
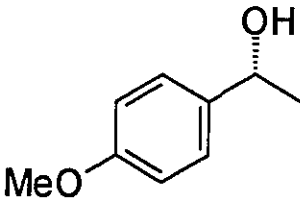
product alcohol	enantiomeric excess (%)	yield (%)
	81	90
	61	90

Table 28

product alcohol	enantiomeric excess (%)	yield (%)
	59	70
	28	38

Acetophenone (1 mmol), $[\text{Rh}(\text{COD})\text{Cl}]_2$ (0.005 mmol) and ligand (0.05 mmol) were stirred in THF (1 ml) for 20 mins. The solution was then cooled to -78°C , diphenylsilane added and stirred for 43 hours before work up. e.e. determined by chiral HPLC.

Table 28 (continued)

The reduction of valerophenone showed excellent results in both yield and optical purity, comparable with those obtained for the optimum acetophenone reaction. Good enantiomeric excesses were also recorded for the hydrosilylation of 1-acetonaphthone and α -tetralone. Somewhat poorer were the results for the reduction of the 4-methoxyacetophenone. This substrate was the only one to exhibit the significant formation of silylenol ether due to its propensity to enolise. This known factor reduces the yield as the hydrolysis of the enol ether leads back to starting ketone.¹⁵³ Overall the phosphinoxazoline rhodium complex catalysed enantioselective hydrosilylation of a variety ketones and gave moderate to good asymmetric induction.

6.4 Conclusions

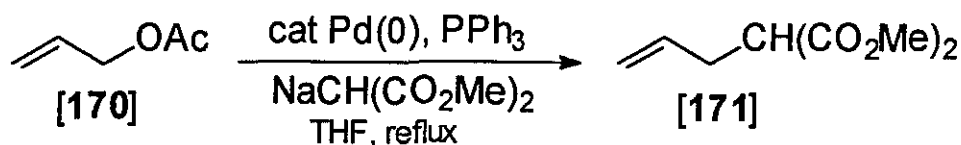
- We have demonstrated that enantiomerically pure phosphinoxazoline ligands are capable of enducing high enantioselectivities in the hydrosilylation of a range of ketones. They displayed high efficiency in the reaction.
- We have optimised the system for the hydrosilylation of acetophenone showing in particular the superiority of ligand [21b] in affording enantiomerically enriched 1-phenylethanol, yield = 86%, enantiomeric excess = 82%.
- Other ligands based on sulfuroxazolines, pyridyl and phosphinoacetals were found to be inferior.

Chapter 7 Palladium Catalysed Allylic Substitution

- 7.1 Introduction
 - 7.1.1 Mechanism
 - 7.1.2 η^3 -Allyl complex geometry and isomerisation
 - 7.1.3 Stereochemistry in the palladium catalysed allylic substitution
 - 7.1.4 Stereocontrol using enantiopure phosphine-nitrogen ligands
 - 7.1.4.1 Electronic factors
 - 7.1.4.2 Steric factors
 - 7.1.5 Phosphine-oxazoline ligands
- 7.2 Application of novel phosphine-oxazoline ligands
 - 7.2.1 Substrate synthesis
 - 7.2.2 Aryl phosphine-oxazoline ligands
 - 7.2.3 Alkyl phosphine-oxazoline ligands
 - 7.2.4 Additional phosphorus-nitrogen ligands
- 7.3 Conclusion

7.1 Introduction

The palladium catalysed allylic substitution reaction has attracted much attention over recent years. Since Walker¹⁸⁶ and Hata¹⁸⁷ demonstrated that the substitution of an acetate by a nucleophile in an allylic system required only catalytic quantities of palladium, the palladium catalysed allylic substitution reaction has been developed extensively into a highly efficient process. The simplest reaction system involves the reaction of allyl acetate [170] with the sodium salt of dimethyl malonate in the presence of catalytic quantities of phosphine ligands and palladium(0) to afford the substituted product [171] (Scheme 75).¹⁸⁸



Scheme 75

7.1.1 Mechanism

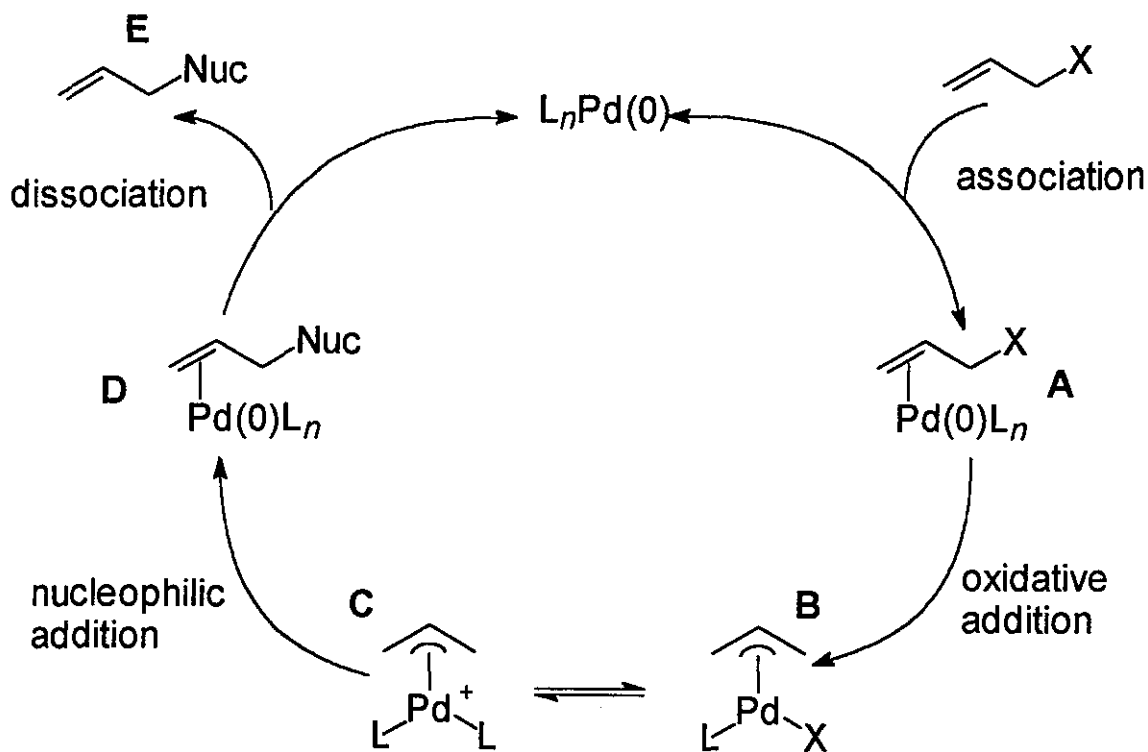
The creation of a new bond in the allylic substitution reaction may occur in a regio- or stereo-selective manner. Understanding the mechanism of this reaction allows us to predict such selection (Scheme 76). It is generally considered that the reaction begins with co-ordination of the palladium(0) to the alkene (A) followed by an oxidative addition process to afford an intermediate η^3 -allyl complex (B). In the presence of ligands containing π -accepting moieties such as triphenylphosphine, an equilibrium between a neutral and cationic complex results. The cationic species (C) preferentially undergoes nucleophilic addition to afford the palladium(0) complex of

¹⁸⁶ K. E. Atkins, W. E. Walker, R. M. Manyik, *Tetrahedron Lett.*, 1970, 3821.

¹⁸⁷ G. Hata, K. Takahashi, A. Miyake, *J. Chem. Soc., Chem. Commun.*, 1970, 1392.

¹⁸⁸ B. M. Trost, T. R. Verhoven, *J. Am. Chem. Soc.*, 1978, 100, 3435.

the product (D). The subsequent dissociation of the palladium(0) liberates the product (E) and regenerates the active palladium catalyst (Scheme 76).^{189,190}



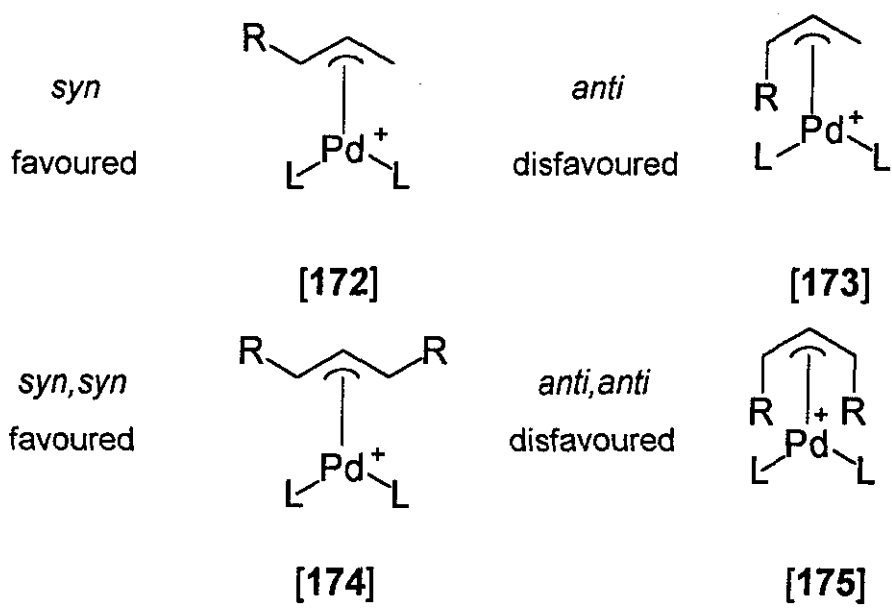
Scheme 76

7.1.2 η^3 -Allyl Complex Geometry and Isomerisation

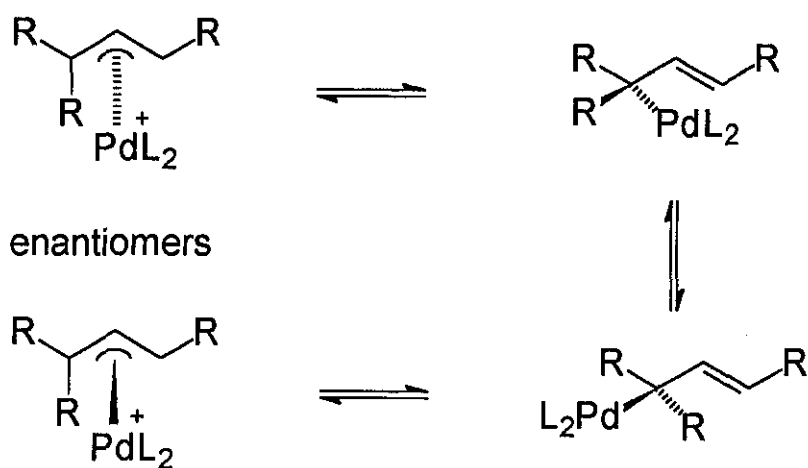
The geometry of the η^3 -allyl intermediates (B and C) relies heavily on steric factors and thus unsurprisingly forms the least sterically demanding conformation. Mono-substituted allyl complexes favour the *syn* conformation [172] over the *anti* conformation [173]. In a similar fashion disubstituted complexes prefer the *syn,syn* geometry [174] to the sterically demanding *anti,anti* geometry [175].

¹⁸⁹ T. Yamamoto, M. Akimoto, O. Saito, A. Yamamoto, *Organometallics*, 1986, 5, 1559.

¹⁹⁰ H. Kurosawa, *J. Organomet. Chem.*, 1987, 334, 243.



The isomerisation of η^3 -allyl complexes is well known and considered to occur rapidly *via* a π - σ - π mechanism (**Scheme 77**). The complex exists as an equilibrium of enantiomeric forms and thus any stereochemistry derived from the allyl precursor is lost. Consequentially any stereoselectivity in the reaction is determined by the palladium complex intermediate.

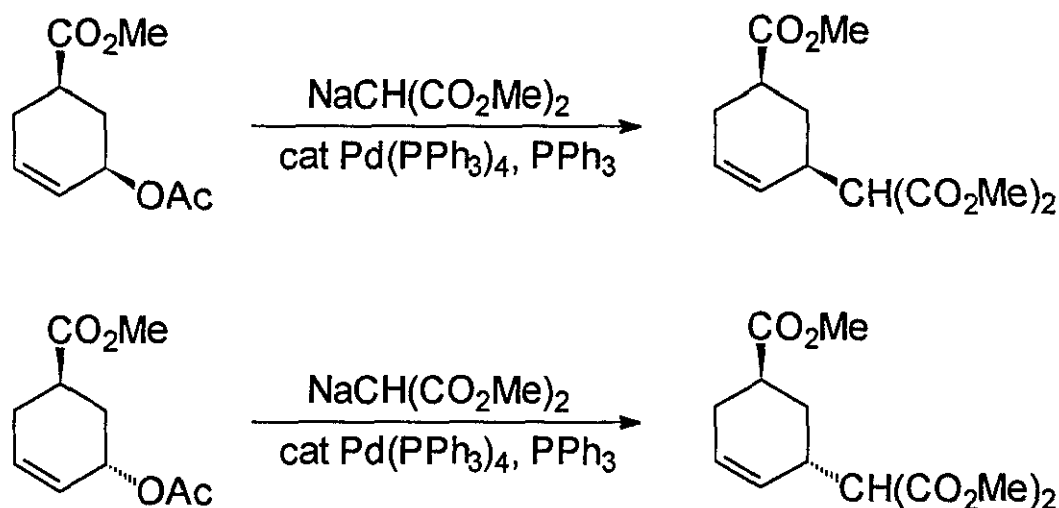


Scheme 77

7.1.3 Stereochemistry in the Palladium Catalysed Allylic Substitution

Studies by Trost and co-workers have shown that the mechanism of nucleophilic attack within the allylic substitution reaction may occur in one of two ways.^{191,192} The choice of this mechanism determines the stereochemical outcome of the product and may be controlled by the nature of the nucleophile. A nucleophile with a $pK_a > 20$ have been found to attack at palladium followed by a rearrangement to give the product, whereas nucleophiles of a lower $pK_a (< 20)$ attack the allyl moiety directly.¹⁹³

Trost *et al* considered the attack of soft nucleophiles on cyclohexenyl acetates (Scheme 78).¹⁹¹



Scheme 78

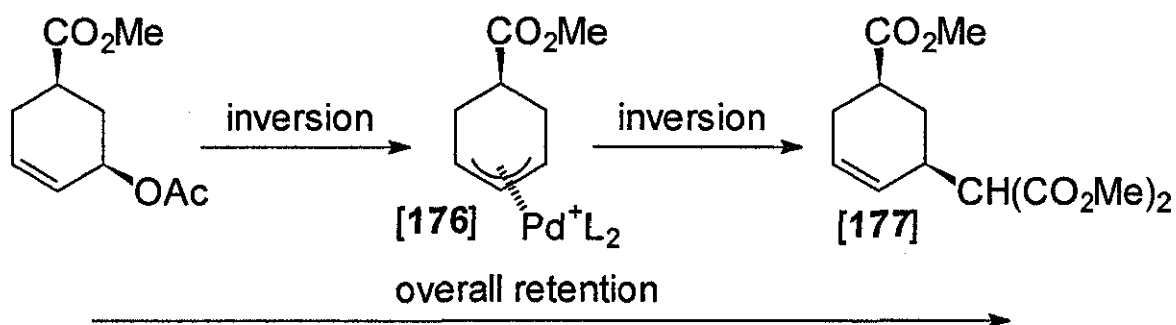
Researchers confirmed that retention of stereochemistry is obtained and proposed that the reaction proceeded through two consecutive inversion steps **Scheme 79**,

¹⁹¹ B. M. Trost, T. R. Verhoeven, *J. Org. Chem.*, 1976, 41, 3215.

¹⁹² B. M. Trost, J. W. Herndon, *J. Am. Chem. Soc.*, 1984, 106, 6835.

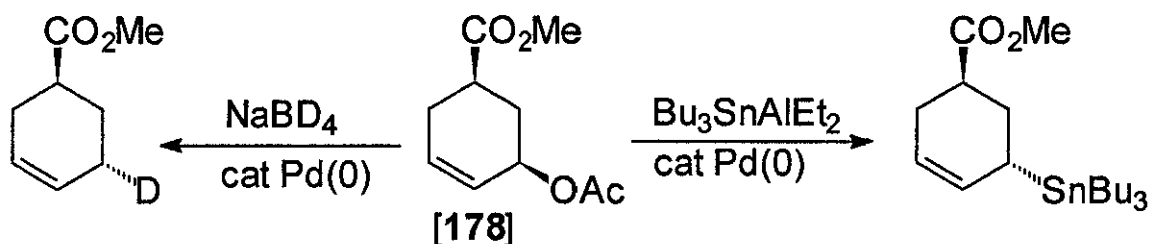
¹⁹³ J. C. Fiaud, J. Y. Legros, *J. Org. Chem.*, 1987, 52, 1907.

1. displacement of leaving group by palladium, formation of π -allyl complex with inversion of stereochemistry [176].
2. nucleophilic attack at the exo face of the intermediate with inversion [177].



Scheme 79

In a contrasting fashion it is believed that hard nucleophiles firstly attack the palladium centre and then migrate to the allyl moiety. The resultant stereochemistry is an inversion due to the nucleophile attacking the allyl from the same face as the palladium. A demonstration of this inversion was shown by Trost using $\text{Bu}_3\text{SnAlEt}_2$ as a nucleophile (Scheme 80).¹⁹² Greenspoon and Keinan presented the reduction of the same allyl precursor [178] with sodium borodeuteride with an inversion of stereochemistry.¹⁹⁴

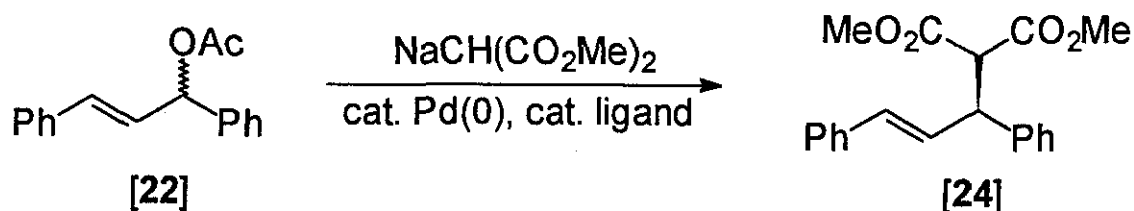


Scheme 80

¹⁹⁴ N. Greenspoon, E. Keinan, *J. Org. Chem.*, 1988, 53, 3723.

7.1.4 Stereocontrol using Enantiopure Ligands

Trost was one of the first to exploit the capability of enantiopure ligands in affecting the stereocontrol in the palladium catalysed allylic substitutions, with modest success.^{195,196} In recent years a multitude of other researchers have succeeded in producing ligands which are highly effective. The common reaction used for testing the efficacy of a particular ligand is the palladium catalysed allyl substitution of acetate [22] using the sodium salt of dimethyl malonate as a nucleophile (Scheme 81).

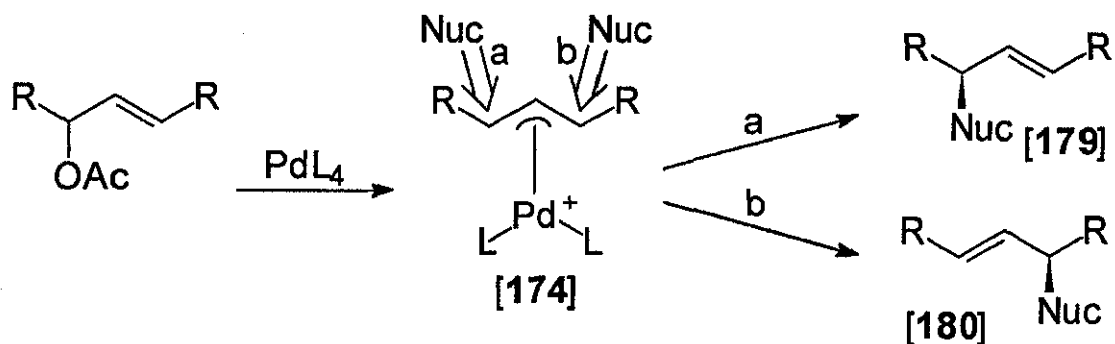


Scheme 81

The high levels of stereocontrol are achieved through a combination of the steric and electronic factors promoted by the ligand in affecting the η^3 -allyl intermediate. The reactive intermediate [174] in which the ligands on palladium are identical, is symmetrical and thus the nucleophile may attack at either terminus resulting in enantiomers [179] or [180] (Scheme 82).

¹⁹⁵ B. M. Trost, T. J. Dietsche, *J. Am. Chem. Soc.*, 1973, 95, 8200.

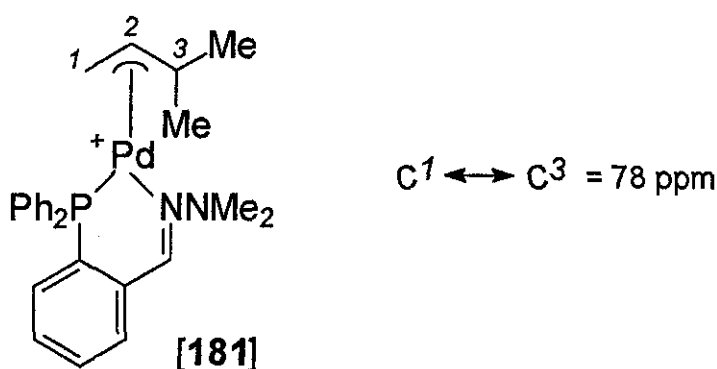
¹⁹⁶ B. M. Trost, P. E. Stege, *J. Am. Chem. Soc.*, 1977, 99, 1649.



Therefore, tailoring of the chelating moieties is necessary to induce a predilection for nucleophilic attack at only one centre.

7.1.4.1 Electronic Factors

The most documented examples of ligands inducing electronic biases in the η^3 -allyl intermediate are those based on bidentate nitrogen–phosphorus chelation. Akermark and Vitagliano published ^{13}C -NMR spectroscopic data for the complex [181].^{197,198}



Analysis of the ^{13}C shifts for C^1 and C^3 showed that when C^3 is *trans* to the ligating phosphorus atom, its signal is significantly downfield of the signal for C^1 . This

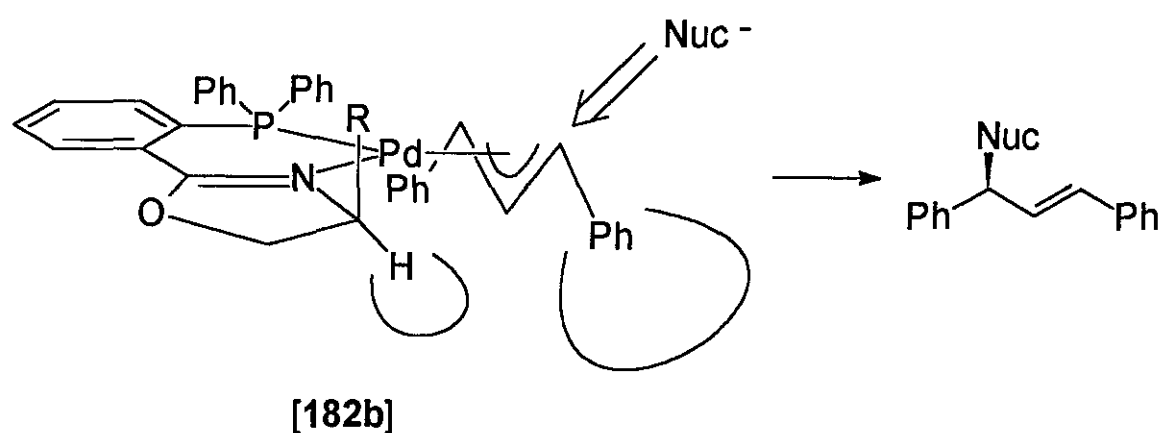
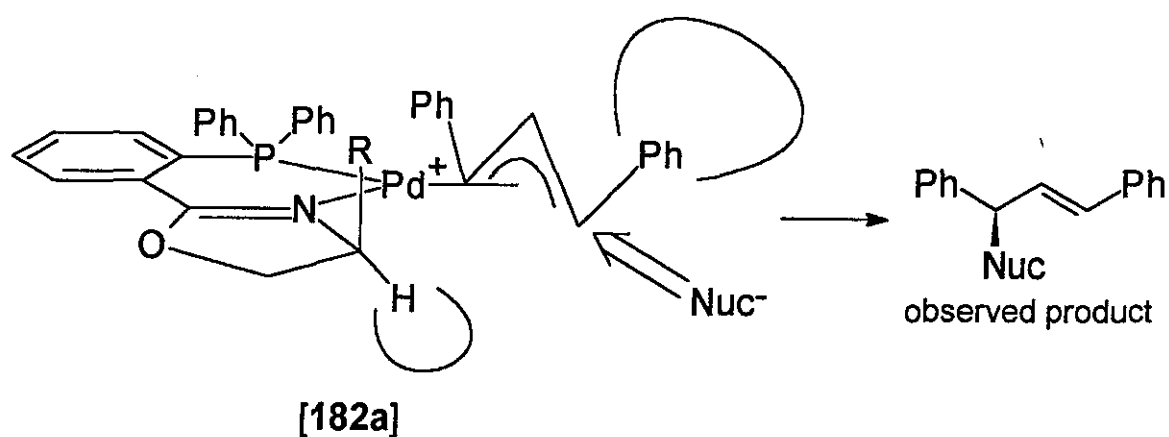
¹⁹⁷ B. Akermark, S. Hansson, B. Krakenberger, A. Vitagliano, K. Zetterberg, *Organometallics*, 1984, 3, 679.

¹⁹⁸ B. Akermark, B. Krakenberger, S. Hansson, A. Vitagliano, *Organometallics*, 1987, 6, 620.

suggests that C³ has a more electropositive character than C¹ and is therefore more attractive to the incoming nucleophile. This observation has been denoted the '*trans* effect' and establishes a predictable pathway of nucleophilic attack onto the palladium allyl system. This effect on the allyl carbon *trans* to the π -accepting phosphorus atom is also common to phosphine-oxazolines ligands.³⁸

7.1.4.2 Steric Factors

In addition to electronic factors, ligands also affect the η^3 -allyl intermediates through steric hindrance. When considering the phosphinooxazoline co-ordinated to the palladium allyl complex there is the possibility that either of two configurations may occur [182a] and [182b] (Scheme 83). Attack by the nucleophile on either of the diastereomeric complexes will give a different enantiomer in the product.



Scheme 83

Helmchen and co-workers have determined through X-ray crystallographic data and NMR spectroscopic studies that the preferred conformation is **[182a]** derived from the 'W-shaped' arrangement of the allyl moiety.¹⁹⁹ The data also showed that the R group is pseudo-axial and it is in fact the hydrogen atom which interacts with the allyl substrate. There is sufficient unfavourable steric hindrance between this hydrogen

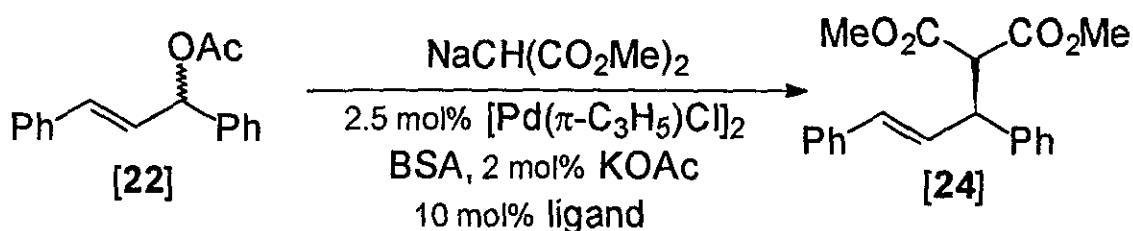
¹⁹⁹ J. Sprinz, M. Kiefer, G. Helmchen, M. Reggelin, G. Huttner, O. Walter, L. Zsoinai, *Tetrahedron Lett.*, 1994, 35, 1523.

atom and any substituents α to the allyl unit for the 'M-conformation' [182b] to be disfavoured.

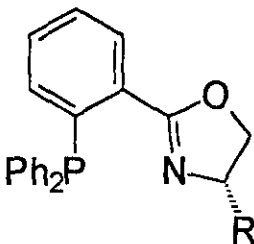
7.1.5 Phosphine–Oxazoline Ligands

Many different ligand systems have been reported in the literature to influence the palladium catalysed allylic substitution with good effect. Our particular interest lay with phosphorus–nitrogen based ligands, focussed around phosphinooxazolines.

In 1993 the research groups of Helmchen⁶⁹, Pfaltz⁷⁰ and Williams⁷¹ independently reported the synthesis of ligands [21a–d, 183]. These ligands showed good stereocontrol within the standard palladium catalysed substitution reaction of allyl acetate [22] with dimethyl malonate nucleophile (Scheme 84).



Scheme 84

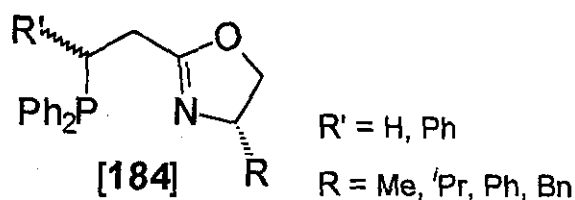
ligand = 

Ligand	R	Enantiomeric excess (%)
[21a]	Me	90
[21b]	ⁱ Pr	94
[21c]	^t Bu	90
[21d]	Ph	92
[183]	CH ₂ Ph	92

Ligand (10 mol%) and Pd catalyst (2.5 mol%) were stirred in dry CH₂Cl₂ for 15 mins. Acetate [22] (3 mmol), BSA (9 mmol), dimethyl malonate (9 mmol) and KOAc (8.8 mg) were added. Solution stirred at r.t. until completion shown by tlc.

Table 29

Each group showed a clear correlation between the substituents on the oxazoline ring and the obtained stereocontrol. The enantiomeric excesses of product [24] increased as the size of the substituent increased, peaking at 94% for the *iso*-propyl asymmetric moiety (Table 29). Further increases in bulk to *tert*-butyl showed a depreciation of stereocontrol, 90% e.e. Subsequently the system has been developed further to include other nucleophiles^{70,200,201} and the elaboration of the substitution products into simple natural products.^{202,203} Recently, analogous phosphorus-oxazoline ligands [184] have been synthesised. Here the extra free rotation shown in the ligand and the choice of solvent appear to be responsible for the mixed success obtained.²⁰⁴



14–100% yield, 11–97% e.e.

²⁰⁰ P. von Matt, O. Loiseleur, G. Koch, A. Pfaltz; C. Lefeber, T. Feucht, G. Helmchen, *Tetrahedron: Asymmetry*, 1994, 5, 573.

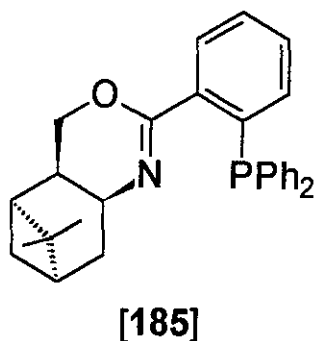
²⁰¹ I. C. Baldwin, J. M. J. Williams, *Tetrahedron: Asymmetry*, 1995, 6, 697.

²⁰² J. F. Bower, J. M. J. Williams, *Synlett*, 1996, 685.

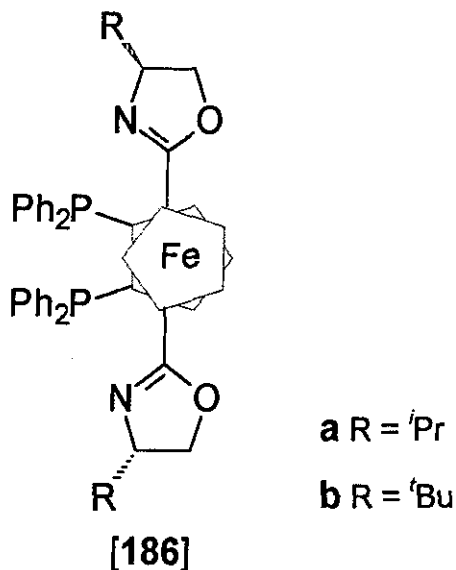
²⁰³ J. F. Bower, R. Jumnah, A. C. Williams, J. M. J. Williams, *J. Chem. Soc., Perkin Trans. 1.*, 1997, 1411.

²⁰⁴ S. R. Gilbertson, C. T. Chang, *J. Chem. Soc., Chem. Commun.*, 1997, 975.

Additional ligands based on β -pinene²⁰⁵ [185] and ferrocene^{206,207} [186a–b] have shown consistently excellent enantiomeric excesses and chemical yields.



>89% yield, >91% e.e.



>90% yield, 99% e.e.

Some enantioselectivity was lost when ferrocene ligand analogues containing only one phosphine group or one oxazoline group was used. Most significantly the ligands [186a–b] appear to be highly reactive and can complete the palladium catalysed allyl substitution model reaction in 10 minutes at 25 °C. It has been suggested from X-ray crystallography and ³¹P NMR spectroscopic studies that these ligands exist mainly as P,P-chelated species in the reaction.²⁰⁷

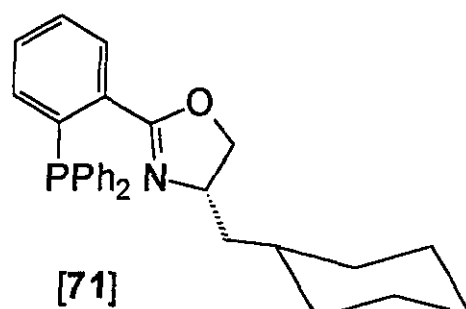
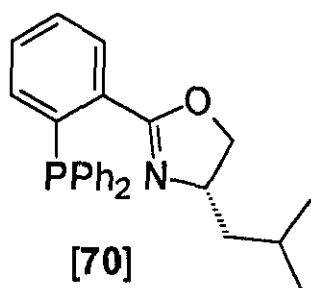
²⁰⁵ P. A. Evans, T. A. Brandt, *Tetrahedron Lett.*, 1996, 37, 9143.

²⁰⁶ W. Zhang, T. Hirao, I. Ikeda, *Tetrahedron Lett.*, 1996, 37, 4545.

²⁰⁷ K. H. Ahn, C. Cho, J. Park, S. Lee, *Tetrahedron: Asymmetry*, 1997, 8, 1179.

7.2 Application of Novel Phosphine–Oxazoline Ligands

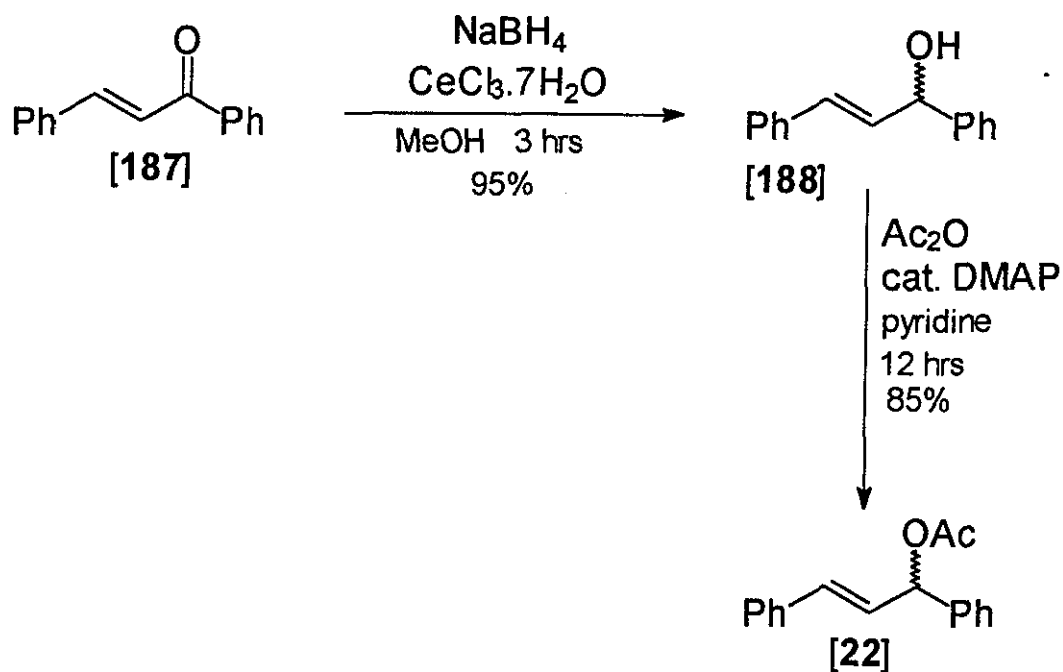
After carrying out research into the phosphinoxazoline–rhodium catalysed hydrosilylation of ketones, we found ourselves having synthesised two new ligands of the type [21]. Having experience within our group for the use of such ligands in the palladium catalysed allylic substitution reactions we considered it logical to confirm the efficacy of these novel ligands [70] and [71] within this system. It was considered that these ligands would behave in an analogous fashion to [21a–d] in effecting stereocontrol of the reaction *via*, the '*trans* effect' of the P–N chelation to the metal and sterically through the asymmetric substituent on the oxazoline ring.



7.2.1 Substrate Synthesis

In order to compare the effectiveness of these novel ligands with the known analogues we chose to apply them to the standard palladium catalysed substitution reaction of allyl acetate [22] with dimethyl malonate nucleophile (Scheme 84).

The substrate, *rac*-(*E*)-1,3-diphenylprop-2-enyl acetate [22] was obtained in two steps from commercially available chalcone [187] (Scheme 85).³⁸

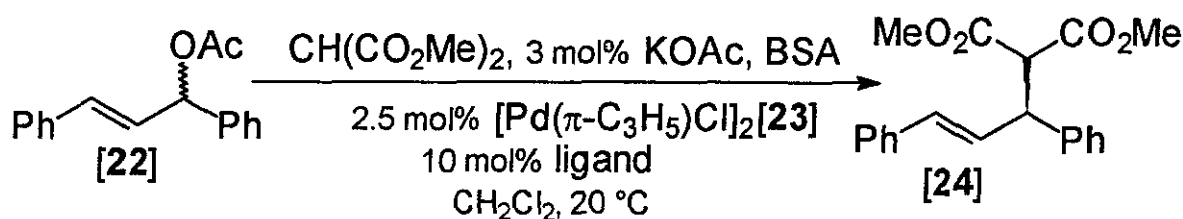


Scheme 85

Treatment of the methanol solution of chalcone [187] and cerium chloride heptahydrate with sodium borohydride resulted, after aqueous work up, in the crude alcohol [188]. ¹H NMR spectroscopic analysis of the crude alcohol confirmed that the product had formed, due to the appearance of a proton doublet at δ 5.4, corresponding to the hydrogen in the position α to the alcohol. Acetylation of the crude allyl alcohol [188] was achieved using acetic acid and catalytic quantities of DMAP in a solution of pyridine acting as base and solvent. The shift of the α -proton peak from δ 5.4 to δ 6.4 and the emergence of the three proton singlet at δ 2.1, corresponding to the acetoxy group, verified the product formation.

7.2.2 Aryl Phosphine Oxazoline Ligands

Following the established method of substitution on *rac*-(*E*)-1,3-diphenylprop-2-enyl acetate [22]²⁰⁸ with dimethyl malonate nucleophile (Scheme 86) we premixed a solution of the ligand (10 mol%) and palladium allyl chloride dimer (2.5 mol%) under an inert atmosphere.³⁸ To the resulting yellow solution was added the allyl acetate [22], *N,O*-bis(trimethylsilyl)acetamide (BSA), potassium acetate (3 mol%) and dimethyl malonate. Stirring was continued until conversion was confirmed by TLC analysis. The product was isolated by flash column chromatography in good yield and the enantiomeric excess measured by chiral HPLC.



Scheme 86

The ligands [70, 71] were found to follow the trend in being as effective in relaying stereochemical information to the substitution product [24] as their known analogues [21a–d] (Table 30, entries 1 and 2).

²⁰⁸ Acetate [22] was available within the group; for synthesis see reference 38.

Table showing the obtained yields and enantiomeric excesses of product [24] from using the specified ligands in the palladium catalysed allylic substitution reaction.

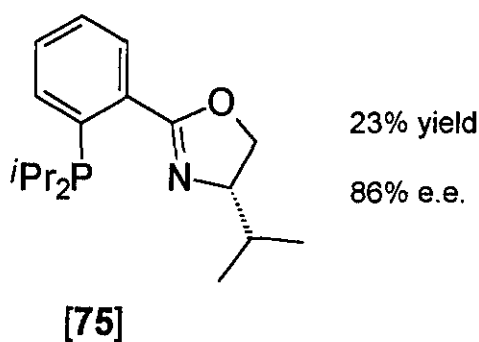
ligand	yield (%)	enantiomeric excess (%)
[70]	86	97
[71]	89	97
[75]	23	86

Ligand (10 mol%) and Pd catalyst (2.5 mol%) were stirred in dry CH₂Cl₂ for 15 mins. Acetate [22] (3 mmol), BSA (9 mmol), dimethyl malonate (9 mmol) and KOAc (8.8 mg) were added. Solution stirred at r.t. until completion shown by tlc

Table 30

7.2.3 Alkyl Phosphine Oxazoline Ligands

We also synthesised a ligand in which the substituents attached to phosphorus were alkyl moieties, [75]. Helmchen had researched the effect of ligands having a number of different aryl groups bound to phosphorus, *i.e.* biphenyl and naphthyl.⁷⁶ We wished to investigate further the implications involved in changing the environment around phosphorus.

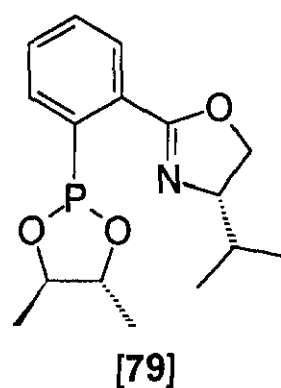
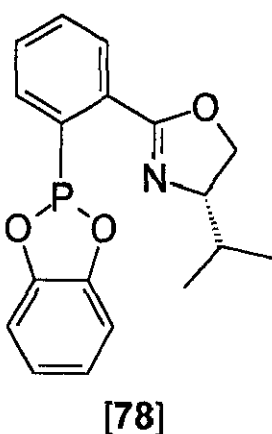
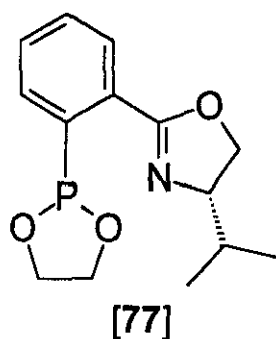


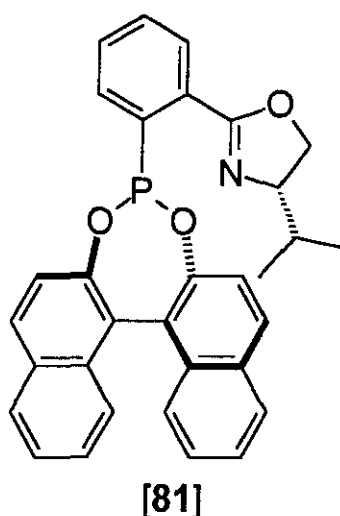
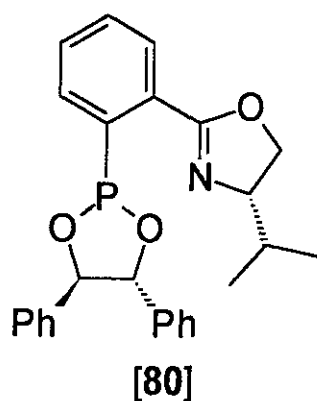
Phosphine moieties substituted with alkyl rather than aryl groups are known to be much more susceptible to oxidation. This was also the case for ligand [75] which could not be purified fully and was thus used in the standard substitution reaction

with oxide impurities. Again good enantiomeric excess was obtained, however there was a marked decrease in reactivity and the reaction could not be forced to completion, yielding only 23% product (**Table 30**, entry 3). The poor yield may, in part, be due to the ligand oxidising in the reaction and thus rendering itself unable to catalyse the reaction. This effect is also seen when using ligand **[21b]** which has been allowed to partially oxidise. An alternative explanation may be the lack of electron density on alkyl substituted phosphorus compared with aryl substituted phosphorus. This deficiency in electron density could hamper co-ordination with palladium in the intermediate and thus prevent the reaction proceeding efficiently.

7.2.4 Additional Phosphorus Nitrogen Ligands

In an attempt to incorporate the many facets of the ligands studied throughout this research into a singular idea, we envisaged the ligands **[77–81]**. The design of these novel ligands drew from the amalgamation of the highly successful phosphinooxazoline ligand **[21b]** and diols to form an acetal ring around the phosphorus atom.





Primarily we wished to establish the electron withdrawing effects of the oxygens on the phosphorus and the subsequent ability of the phosphorus to co-ordinate to palladium within the standard allylic substitution reaction using ligands [77, 78]. We also wished to investigate the potential advantages of placing chiral groups close to the chelating phosphorus as well as adjacent to the nitrogen of the oxazoline ring i.e. [79–81]. Here the opportunity for matched and mismatched asymmetric groups seem likely. Unfortunately difficulties arose in the syntheses generally based around difficult purification problems. Thus only ligands [77, 79] were produced, with the data to support the success of the synthetic goals as non-conclusive, showing only potential product in the crude form. However the ligands were used in the substitution of *rac*-(*E*)-1,3-diphenylprop-2-enyl acetate [22] with dimethyl malonate nucleophile with some success (Table 31).

Table showing the obtained yields and enantiomeric excesses of product [24] from using the specified ligands in the palladium catalysed allylic substitution reaction.

Crude Ligand	Yield (%)	Enantiomeric excess (%)
[77]	43	22
[79]	75	14

Ligand (10 mol%) and Pd catalyst (2.5 mol%) were stirred in dry CH₂Cl₂ for 15 mins. Acetate [22] (3 mmol), BSA (9 mmol), dimethyl malonate (9 mmol) and KOAc (8.8 mg) were added. Solution stirred at r.t. until completion shown by tlc

Table 31

The ligand [77], having a non-chiral environment around phosphorus shows a large drop in enantiomeric excess (22%) of the substitution product over analogous ligands [21b] (94%) and [75] (86%). This may be attributed to the adjusted electronic effect of the phosphorus which, would be predicted to have a depleted binding strength to the metal centre. However we cannot rule out the effects of the unknown contaminants in the ligand sample. These effects are at present unquantifiable.

Interestingly the ligand [79], having the additional enantiomerically pure centres around phosphorus showed no advantage in enantiomeric excess, 14% e.e. This may have been due to a mismatched environment with the oxazoline asymmetric centre. Unfortunately there was no available time to synthesis the other enantiomer of the acetal-phosphine to verify this theory.

Since the conclusion of the laboratory work for this thesis, Pfaltz and co-workers have published ligands similar to our ligands [77–81] for use within copper catalysed

1,4-additions of organozinc reagents to enones.²⁰⁹ In this paper they referred to an alternative publication in which the ligands syntheses and their use in palladium catalysed allylic substitution reactions are found. Unfortunately at this time the publication is still in press.²¹⁰

7.3 Conclusion

- We have expanded the range of known phosphorus–oxazoline ligands which co-catalyse the palladium catalysed allylic substitution reaction with excellent stereocontrol [70, 71], 97% e.e.
- We have demonstrated good results in the same reaction with alkyl substituted phosphorus oxazoline ligand [75] (86% e.e.), although this ligand demonstrates a lack of stability in metal binding.
- Novel, uncharacterised crude ligands [77, 79] also exhibited moderate success in the palladium catalysed allylic substitution reaction, 14–22% e.e. However the source of the drop in stereoselectivity remained unverified.

²⁰⁹ A. K. H. Knöbel, I. H. Escher, A. Pfaltz, *Synlett*, 1997, 1429.

²¹⁰ R. Pretot, A. Pfaltz, *Angew. Chem.*, in press.

Chapter 8 Experimental

General Experimental

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 boiling between 40–60°C, and was distilled through a 36 cm Vigreux column before use. Diethyl ether, xylene, benzene and toluene were dried where necessary by storage over sodium wire for several days. THF was distilled from sodium benzophenone ketyl under nitrogen, prior to use.

Dichloromethane was distilled from phosphorus pentoxide. Unless otherwise stated all starting materials used were obtained from commercially available sources.

Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF₂₅₄. Plates were visualised under UV light (at 254 nm) or by staining with phosphomolybdic acid or potassium permanganate solution, followed by heating. Flash chromatography was carried out using Merck Kieselgel 60 H silica gel. Pressure was applied at the column head with hand bellows.

Samples were applied pre-absorbed on silica or as a saturated solution in an appropriate solvent.

Infra red spectra were recorded in the range 4000-600 cm⁻¹ using a Nicolet FT-205 spectrometer, with internal calibration. Spectra were recorded as solutions in carbon tetrachloride, thin films or as a nujol mull. ¹H and ¹³C NMR spectra were recorded using a Bruker AC-250 MHz or 400 MHz instrument. High- and low-resolution mass spectra were recorded on a Kratos MS80 instrument or on a VG Analytical ZAB-E instrument (EPSRC mass spectrometry service, Swansea). GC-MS analyses were performed on Fisons GC-8000 with MD800 mass detection. Mp were measured on an Electrothermal digital melting point apparatus and are uncorrected. Optical rotations were measured on an Optical Activity AA 100 polarimeter.

Enantiomeric excesses of 1-phenyl ethanol were either calculated from; chiral shift NMR spectra obtained using in each case 1.5 mg of sample and 1.3 equivalents of the chiral shift reagent Tris [3-(heptafluoropropylhydroxymethylene)-(+)-camphorato], europium (III) derivative in CDCl_3 .

OR

chiral HPLC, Chiralcel OD column, flow rate = $1 \text{ cm}^3 \text{ min}^{-1}$, solvent mixture = 1% IPA–hexane, wavelength = 254 nm.

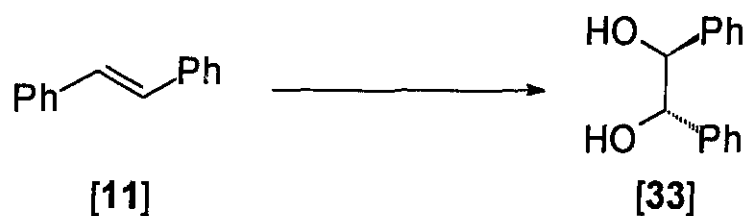
Unless otherwise stated the enantiomeric excesses all chiral products obtained from asymmetric reactions were measured by chiral HPLC, conditions as stated for 1-phenyl ethanol.

1,2 (*R,R*) diphenyl ethanediol



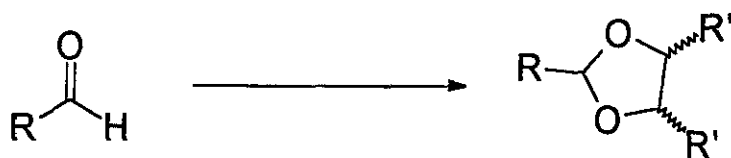
To a solution of *trans*-stilbene [11] (50 g, 280 mmol) in *tert*-butyl alcohol (112 ml) at 20 °C was added (DHQD)₂PHAL (549 mg, 0.25 mol%) and *N*-methylnmorpholine *N*-oxide [70 ml (60% in H₂O)]. Potassium osmate (VI) dihydrate (206 mg, 0.2 mol%) was then added and the solution stirred for 10 days at room temperature. 4,5-Dihydroxy 1,3-benzenedisulfonic acid disodium salt monohydrate (500 mg) was added and the reaction stirred for a further 4 hours. The reaction mixture was then poured into water (150 ml) and stirred for 3 hours. During this time the product precipitated out of solution and was then filtered and washed with water to give a light brown crude solid. Ethyl acetate (400 ml) was added to the solid, the solution washed with sulfuric acid (30 ml, 0.5 M) and dried over magnesium sulfate. The solvent was removed under reduced pressure. Pure product [12] (23.3 g, 39%) was obtained by recrystallisation from ethyl acetate; $[\alpha]_D^{22} +86$ (*c* 2.5 in C₂H₅OH) (lit. +94°); mp 146–148 °C (lit., 148–150 °C); δ_H (250 MHz; CDCl₃) 7.08- 7.25 (10H, m, ArH), 4.69 (2H, s, 2 x CH), 2.92 (2H, s, 2 x OH).¹⁵

1,2 (S,S) diphenyl ethanediol



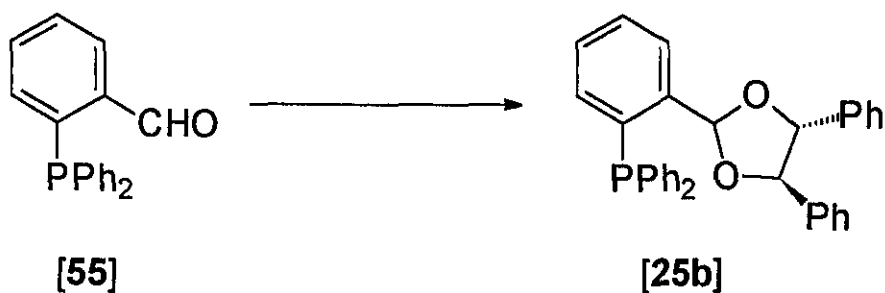
To a 1:1 solution of *tert*-butyl alcohol:water (50 ml) was added AD-mix- α (7 g, 1 equivalent to stilbene) and methanesulphonamide (0.475 g, 5 mmol). The solution was cooled to 0 °C and the *trans*-stilbene [11] (0.9 g, 5 mmol) added. The reaction mixture was stirred vigorously for 24 hours at 0 °C and then solid sodium sulphite (7.5 g, 59.5 mmol) added. The solution was allowed to warm to room temperature. The organic layer was extracted with ethyl acetate (3 x 30 ml), washed with potassium hydroxide (2 M, 2 x 40 ml) and dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure. The crude product was purified by flash chromatography (10% ethyl acetate–light petroleum) to give pure 1,2 (S,S) diphenyl ethanediol [33] (0.849 g, 79%); $[\alpha]_D^{22}$ -91 (c 2 in EtOH) (lit. -94°); mp 145–147 °C (lit. 148–150 °C); data as for compound previous enantiomer.¹⁶

General procedure for the preparation of acetals



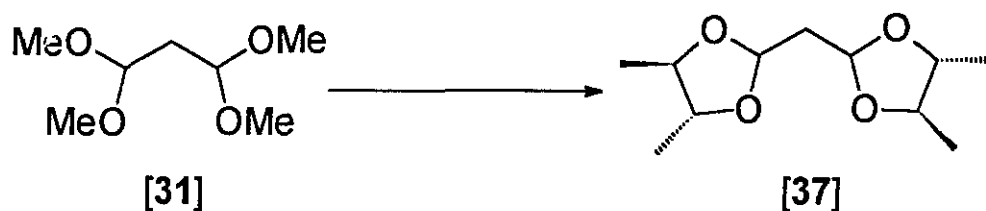
To a solution of the aldehyde or dimethylacetal (1.17 mmol) in toluene (5 ml) was added (*R,R*) diol (1.17 mmol) and pyridinium *p*-toluene sulphonate (25 mg, 0.01 mmol). The resulting suspension was heated under reflux conditions using Dean Stark apparatus until the reaction was complete as assessed by tlc. The solvent was removed under reduced pressure and diethyl ether (15 ml) added. The organic solution was then washed with saturated sodium bicarbonate solution (2 x 15 ml), followed by water (15 ml) and then saturated brine solution (15 ml). The organic extracts were dried over sodium sulfate and the solvent removed under reduced pressure. The obtained oils were purified by flash chromatography (10% ethyl acetate–light petroleum) to afford the title compounds.

{2-[(4*R*,5*R*)-4,5-diphenyl-1,3-dioxolan-2-yl]phenyl}(diphenyl)phosphine



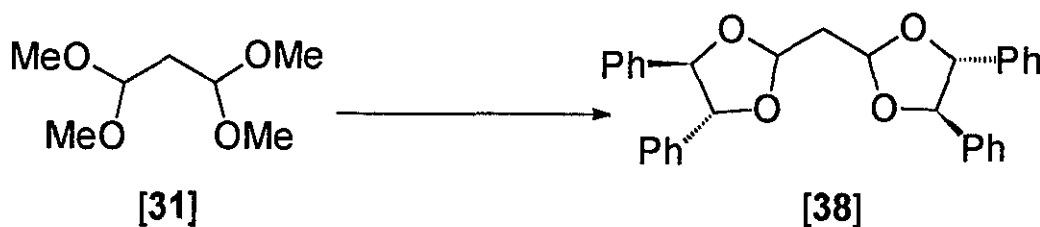
[25b] (56%) as a crystalline solid; mp 96–98 °C (lit., 94–95 °C); δ_{H} (250 MHz; CDCl_3) 7.71–7.10 (24H, m, ArCH), 6.96 (1H, s, $(\text{CH}(\text{OCHPh})_2)$), 4.76 (1H, d, J 7.8Hz, CHPh), 4.74 (1H, d, J 7.8Hz, CHPh).³⁹

(4R,5R)-2-[[[(4S,5S)-4,5-dimethyl-1,3-dioxolan-2-yl]methyl]-4,5-dimethyl-1,3-dioxolane



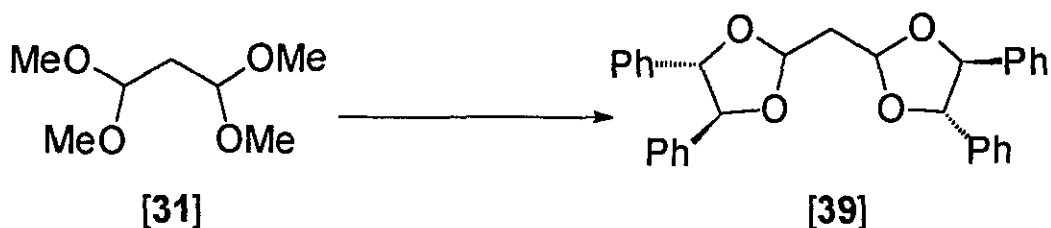
[37] (95%) as a colourless oil; $[\alpha]_D^{22} -22.5$ (c 2, CHCl_3); (Found 216.1362, $\text{C}_{11}\text{H}_{20}\text{O}_4$ requires 216.1362); ν_{max} . (neat) 2975, 1113 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 5.19 (2H, t, J 5.2 Hz, 2 x $\text{CH}_2\text{-CH}$), 3.58 (4H, m, 4 x CH-Me), 2.0 (2H, t, J 5.2 Hz, CH_2), 1.30 (6H, d, J 5.6 Hz, 2 x Me), 1.23 (6H, d, J 5.6 Hz, 2 x Me); δ_{C} (62.5 MHz; CDCl_3) 100.1 (2 x CH_2CH), 79.6 (2 x CHMe), 77.9 (2 x CHMe), 40.3 (CH_2), 17.1 (2 x Me), 16.9 (2 x Me); m/z , 217 ($\text{M}+\text{H}^+$, 41%), 215 (100), 101 (100), 73 (79), 55 (68).⁶⁸

(4R,5R)-2-[[[(4R,5R)-4,5-diphenyl-1,3-dioxolan-2-yl]methyl]-4,5-diphenyl-1,3-dioxolane



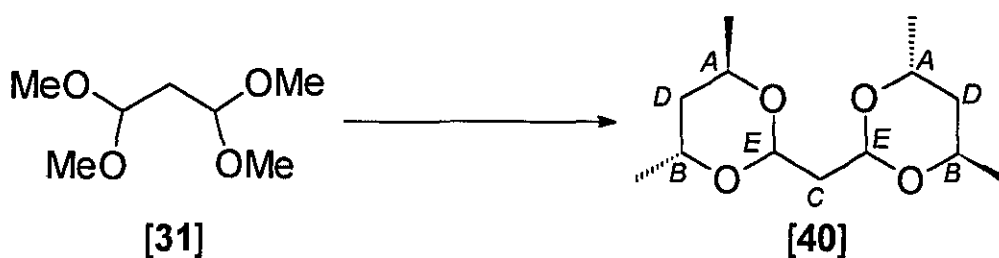
[38] (71%) as a colourless oil which solidified on standing over 4 days; $[\alpha]_D^{22} -10^\circ$ (c 2, CDCl_3); data as for ligand **[39]**.

(4S,5S)-2-[[[(4S,5S)-4,5-diphenyl-1,3-dioxolan-2-yl]methyl]-4,5-diphenyl-1,3-dioxolane



[39] (66%) as a colourless oil; $[\alpha]_D^{22} +10^\circ$ (c 2, CHCl₃); (Found 464.1988, C₃₁H₂₈O₄ requires 464.1988); ν_{\max} (CCl₄ solution) 3033, 2892, 1126, 1024, 788-761 cm⁻¹; δ_H (250MHz; CDCl₃) 7.34–7.28 (20H, m, ArH), 5.87 (2H, t, *J* 5.2 Hz, CH₂CH), 4.82 (4H, s, CHPh), 2.57 (2H, t, *J* 5.2 Hz, CH₂); δ_C (62.5 MHz; CDCl₃) 138.4 (2 x ArC), 136.7 (2 x ArC), 128.6–126.4 (20 x ArCH), 102.6 (2 x CH₂CH), 86.9 (2 x CHPh), 84.9 (2 x CHPh), 40.4 (CH₂); *m/z*, 464 (M⁺, 54%), 225 (66), 197 (54), 105 (100), 77 (52).

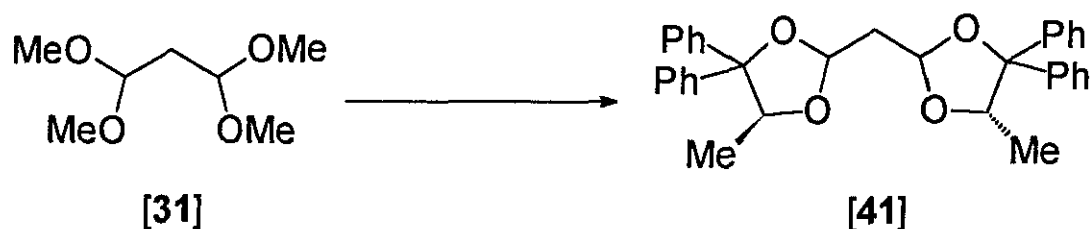
(4R,6R)-2-[[[(4R,6R)-4,6-dimethyl-1,3-dioxan-2-yl]methyl]-4,6-dimethyl-1,3-dioxane



[40] (66%) as a crystalline white solid; mp 44–47°C; $[\alpha]_D^{22} -36.6$ (c 2, CHCl₃); (Found 244.1674, C₁₃H₂₄O₄ requires 244.1675); ν_{\max} (CCl₄ solution) 2976, 1153, 1136 cm⁻¹; δ_H (200 MHz; CDCl₃) 4.98 (2H, t, *J* 5.6 Hz; 2 x E), 4.28 (2H, apparent quintet, *J* 6.7 Hz, 2 x A or B), 3.95 (2H, ddq, *J* 17.9 Hz, 12.2 Hz and 2.4 Hz, 2 x A or B), 1.85 (2H, t, 5.6 Hz, C), 1.84 (2H, m, 2 x D), 1.33 (2H, m, 2 x D), 1.34 (6H, d, *J* 6.9 Hz, 2 x Me),

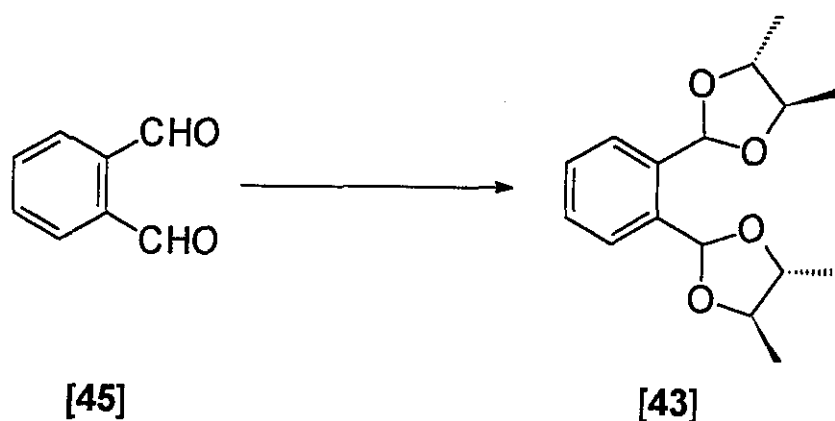
1.20 (6H, d, J 6.2 Hz, 2 x Me); δ_c (100 MHz; CDCl_3) 91.2 (2 x E), 67.8 (2 x B), 67.5 (2 x A), 40.7 (C), 36.7 (2 x D), 21.7 (2 x Me), 17.1 (2 x Me); m/z , 244 ($\text{M}+\text{H}^+$, 100%), 243 (86), 157 (62), 115 (100), 69 (83), 45 (36).⁶⁸

[41]



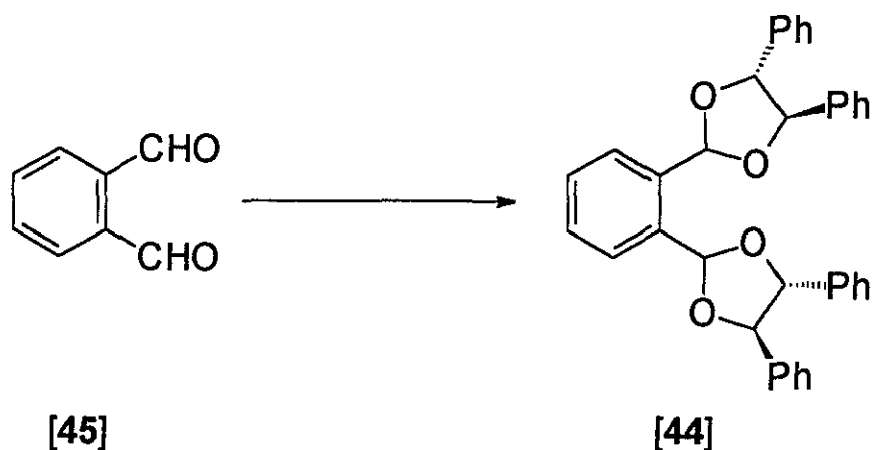
[41] (32%) as a white solid; mp 45–47 °C ; $[\alpha]_D^{22}$ -207.5 (c 2, CHCl_3); (Found 492.2300, $\text{C}_{33}\text{H}_{32}\text{O}_4$ requires 492.2300); ν_{max} (CCl_4 solution) 2980, 1127, 1013, 794–757 cm^{-1} ; δ_H (250 MHz; CDCl_3) 7.49–7.20 (20H, m, ArH), 5.26 (2H, t, J 5.4 Hz, 2 x CH_2CH), 4.76 (2H, q, J 6.3 Hz, 2 x CHMe), 2.58 (2H, t, J 5.4 Hz, CH_2), 1.04 (6H, d, J 6.3 Hz, 2 x Me); δ_c (62.5 MHz; CDCl_3) 143.8 (2 x ArC), 142.8 (2 x ArC), 128.2–126.5 (20 x ArCH), 99.3 (2 x CH_2CH), 80.9 (2 x CHMe), 58.7 (CH_2), 18.4 (2 x Me); m/z , 492 (M^+ , trace), 209 (100), 165 (43), 105 (57), 28 (42).

(4*R*,5*R*)-2-{2-[(4*R*,5*R*)-4,5-dimethyl-1,3-dioxolan-2-yl]phenyl}-4,5-dimethyl-1,3-dioxolane



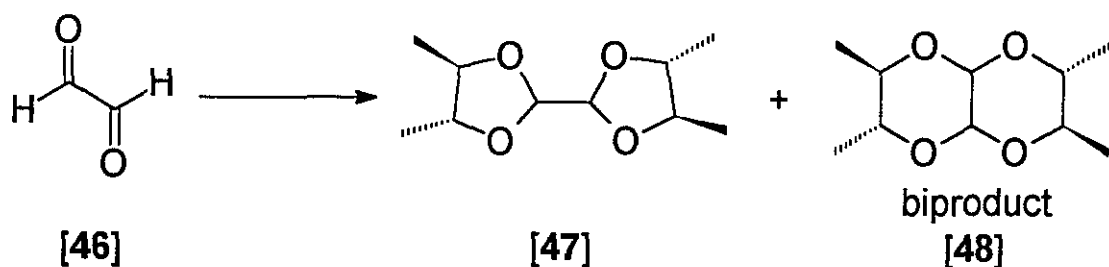
The solid was purified by flash chromatography (20% ethyl acetate–light petroleum) to afford [43] (54%) as a white solid; mp 72–75 °C; $[\alpha]_D^{22} -27.5$ (*c* 2, CHCl₃); (Found 278.1518, C₁₆H₂₂O₄ requires 278.1518); ν_{\max} (CCl₄ solution) 2975, 1114, 1083 cm⁻¹; δ_H (250 MHz; CDCl₃) 7.65 (2H, m, *ArH*), 7.36 (2H, m, *ArH*), 6.37 (2H, s, 2 x *CHPh*), 3.79 (4H, m, 4 x *CHMe*), 1.37 (6H, d, *J* 2.7 Hz, 2 x Me), 1.31 (6H, d, *J* 2.7 Hz, 2 x Me); δ_C (62.5 MHz; CDCl₃) 137.0 (2 x *ArC*), 128.8 (2 x *ArCH*), 126.1 (2 x *ArCH*), 99.4 (2 x *CHPh*), 80.2 (2 x *CHMe*), 78.3 (2 x *CHMe*), 17.1 (2 x Me), 16.8 (2 x Me); *m/z*, 278 (*M*⁺, trace), 205 (44), 133 (100), 56 (24), 55 (24).

(4*R*,5*R*)-2-{2-[(4*R*,5*R*)-4,5-diphenyl-1,3-dioxolan-2-yl]phenyl}-4,5-diphenyl-1,3-dioxolane



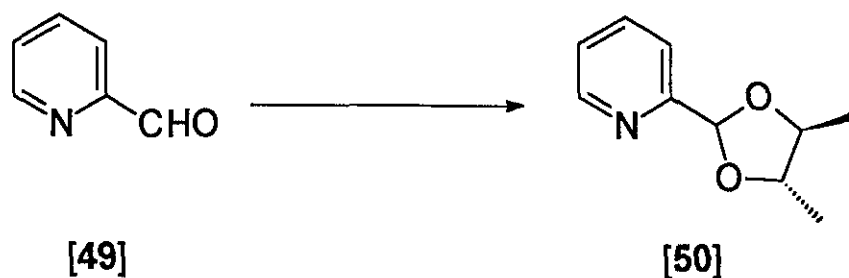
Recrystallization from hot ethyl acetate afforded [44] (78%) as a white solid; mp 139–141 °C; $[\alpha]_D^{22} -12.5$ (*c* 2, CHCl₃); (Found 526.2144, C₃₆H₃₀O₄ requires 526.2144); ν_{\max} (CCl₄ solution) 3035, 2889, 1124, 1061, 782–762 cm⁻¹; δ_H (250 MHz; CDCl₃) 7.97–7.93 (2H, m, ArH), 7.54–7.50 (2H, m, ArH), 7.38–7.27 (20H, m, ArH), 6.94 (2H, s, 2 x CH(OCHPh)₂), 4.98 (1H, d, *J* 7.5 Hz, CHPh), 4.95 (1H, d, *J* 7.5 Hz, CHPh); δ_C (62.5 MHz; CDCl₃) 138.4 (2 x ArC), 136.6 (4 x ArC), 129.3–126.4 (20 x ArCH), 102.1 (2 x CH(OCHPh)₂), 87.2 (2 x CHPh), 85.2 (2 x CHPh); *m/z*, 526 (M⁺, trace), 180 (100), 118 (24).

[47]



[47] (31%) as a colourless oil containing 10% of inseparable known biproduct (2*R*,3*R*,6*R*,7*R*)-2,3,6,7-tetramethylperhydro[1,4]dioxino[2,3-*b*][1,4]dioxine; δ_{H} (250 MHz; CDCl_3) 4.72 (2H, s, 2 x $\text{CH}(\text{O})_2$), 3.83 (2H, m, 2 x CHMe), 3.50 (2H, m, 2 x CHMe), 1.18 (6H, d, J 6.4 Hz, 2 x Me), 1.08 (6H, d, J 6.4 Hz, 2 x Me). Not fully characterised, used in asymmetric reactions as the mixture of product and biproduct.⁶⁸

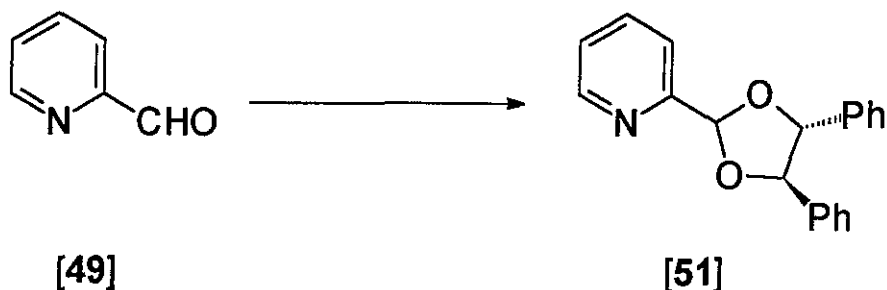
2-[[4*S*,5*S*]-4,5-dimethyl-1,3-dioxolan-2-yl]pyridine



[50] (51%) as a colourless oil ; $[\alpha]_{\text{D}}^{22} +32$ (c 1, CHCl_3); (Found (M^+) 178.0868, $\text{C}_{10}\text{H}_{12}\text{O}_2\text{N}$ requires 179.0868); ν_{max} (CCl_4 solution) 2974, 2875, 1438, 1378, 1106, 1086, 993, 779 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 8.62 (1H, m, pyH), 7.73 (1H, m, pyH), 7.58 (1H, m, pyH), 7.27 (1H, m, pyH), 5.98 (1H, s, py-CH), 3.90-3.81 (2H, m, 2 x CHMe), 1.40 (3H, d, J 5.5 Hz, Me), 1.35 (3H, d, J 5.5 Hz, Me); δ_{C} (62.5 MHz; CDCl_3) 155.0 (pyC), 149.2 (pyCH), 136.6 (pyCH), 123.7 (pyCH), 120.4 (pyCH), 102.5 ($\text{CH}(\text{O})_2$),

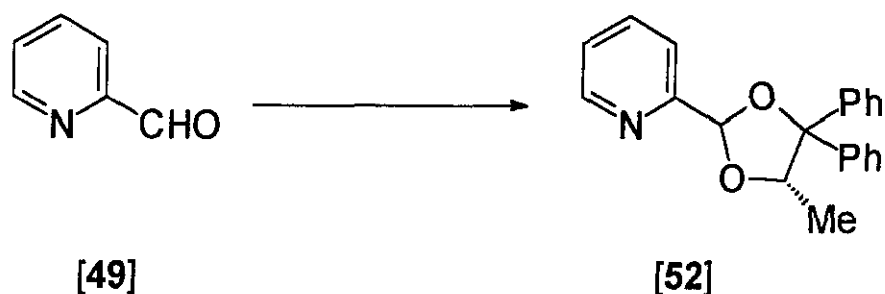
80.4 (CHMe), 78.8 (CHMe), 16.9 (Me), 16.7 (Me); m/z 179 (M^+ , trace), 178 (100), 174 (27), 170 (24).

2-[(4*R*,5*R*)-4,5-diphenyl-1,3-dioxolan-2-yl]pyridine



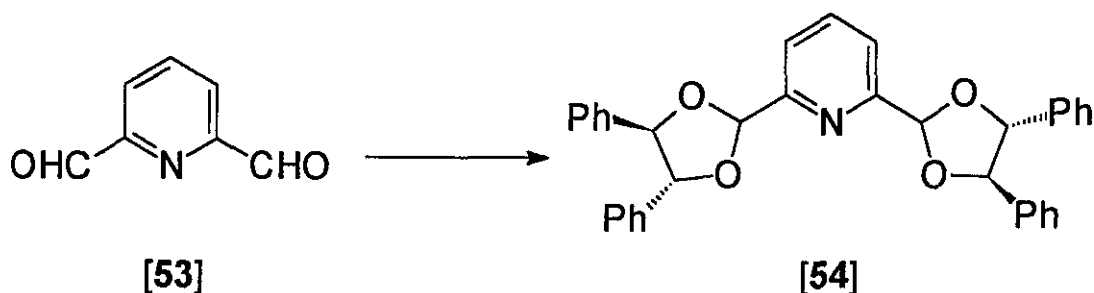
[51] (48%) as a white solid; mp 109–111 °C; $[\alpha]_D^{22} +15.0$ (c 2, CHCl_3); (Found 303.1259, $\text{C}_{20}\text{H}_{17}\text{O}_2\text{N}$ requires 303.1259); ν_{max} (CCl_4 solution) 2925, 1108, 767 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 8.70–8.67 (1H, m, pyH), 7.82–7.78 (3H, m, pyH), 7.38–7.26 (10H, m, ArH), 6.44 (1H, s, py-CH), 5.02 (1H, d, J 8.0 Hz, CHPh), 4.99 (1H, d, J 8.1 Hz, CHPh); δ_{C} (62.5 MHz; CDCl_3) 155.0 (pyC), 149.4 (pyCH), 137.5 (ArC), 136.9 (pyCH), 134.8 (ArC), 128.6–120.6 (10x ArCH and 2x pyCH), 104.6 ($\text{CH}(\text{OCHPh})_2$), 87.2 (CHPh), 85.4 (CHPh); m/z 303 (M^+ , trace), 197 (37), 168 (100), 89 (12).

[52]



[52] (27%) as an impure mixture; $[\alpha]_D^{22} +115.0$ (c 2, CCl_4); (Found 318.1494 ($\text{M}+\text{H}^+$). $\text{C}_{21}\text{H}_{20}\text{O}_2\text{N}$ requires 318.1494); ν_{max} . (neat) 2980, 1449, 1111 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 8.70 (1H, m, pyH), 7.85-7.83 (3H, m, pyH), 7.36-7.28 (10H, m, ArH), 5.88 (1H, s, $\text{CH}(\text{O})_2$), 5.02 (1H, q, J 6.3 Hz, CHMe), 1.14 (3H, d, J 6.3 Hz, Me); δ_{C} (62.5 MHz; CDCl_3) 156.2 (pyC), 149.3 (pyCH), 143.9 (ArC), 143.6 (ArC), 128.5-121.0 (10 x ArCH and 3 x pyCH), 102.8 (OCPH₂), 101.5 ($\text{CH}(\text{O})_2$), 81.0 (CHMe), 18.6 (Me); m/z , 317 (M^+ , trace), 273 (77), 244 (77), 167 (79), 165 (100), 79 (92).

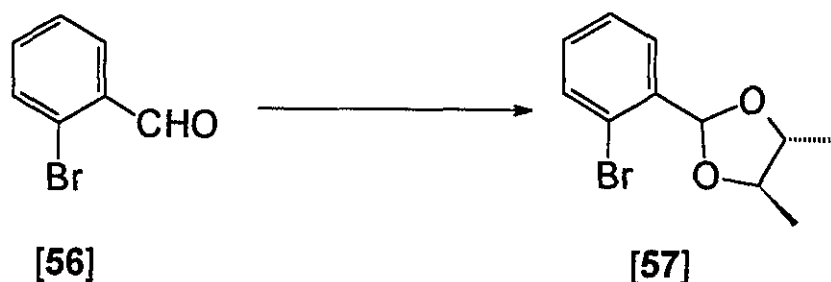
2,6-di[4*R*,5*R*]-4,5-diphenyl-1,3-dioxolan-2-yl]pyridine



[54] (35%) as a white solid; mp 54-56 °C; $[\alpha]_D^{22} +17.5$ (c 2, CHCl_3); (Found ($\text{M}+\text{H}^+$) 528.2175. $\text{C}_{35}\text{H}_{30}\text{O}_4\text{N}$ requires 528.2175); ν_{max} . (CCl_4 solution) 2923, 1460 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 8.02-7.83 (3H, m, pyH), 7.38-7.31 (20H, m, ArH), 6.51 (2H, s, 2 x $\text{CH}(\text{O})_2$), 5.06 (1H, d, J 8.0 Hz, CHPh), 4.99 (1H, d, J 8.0 Hz, CHPh); δ_{C} (62.5 MHz;

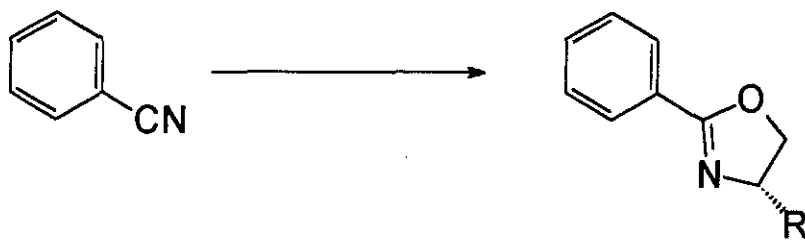
CDCl_3) 157.2 (2 x pyC), 138.1 (2 x pyCH), 137.9 (ArC), 137.7 (ArC), 136.3 (ArC), 128.8 (ArC), 128.7–121.4 (20 x ArCH and 1 x pyCH), 104.7 (2 x $\text{CH}(\text{O})_2$), 87.3 (2 x CHPh), 85.6 (2 x CHPh); m/z , 527 (M^+ , trace), 196 (15), 165 (17), 105 (73), 89 (72), 77 (100), 51 (62).

(4*R*,5*R*)-2-(2-bromophenyl)-4,5-dimethyl-1,3-dioxolane



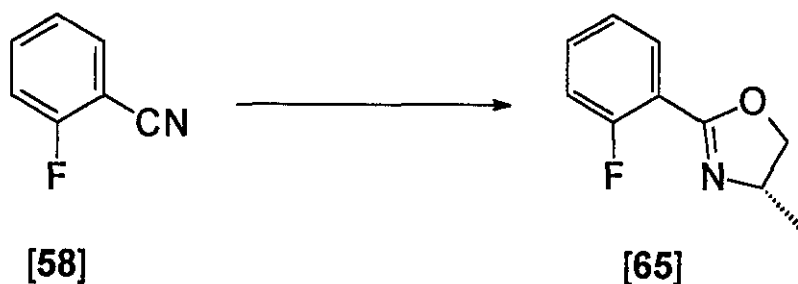
[57] (80%) as a colourless oil; $[\alpha]_{\text{D}}^{22} -10$ (c 2 in CHCl_3); (Found 256.0099, $\text{C}_{11}\text{H}_{13}\text{O}_2\text{Br}$ requires 256.0099); ν_{max} . (neat) 2975, 2870, 1441, 1264, 1095, 757 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 7.16–7.65 (4H, m, ArH), 6.23 (1H, s, ArCH), 3.82 (2H, m, 2 x CHMe), 1.39 (3H, d, J 5.9 Hz, Me), 1.33 (3H, d, J 5.6 Hz, Me); δ_{C} (100 MHz; CDCl_3) 139.3 (ArC), 132.6 (ArC), 130.4 (ArCH), 128.0 (ArCH), 127.4 (ArCH), 101.4 (Ar-CH), 80.4 (CHMe), 78.6 (CHMe), 17.0 (2 x Me); m/z , 257 ($\text{M}+\text{H}^+$, 57%), 255 (57), 185 (53), 183 (52), 133 (73), 101 (66), 89 (100), 55 (54), 43 (46).

General procedure for the preparation of the oxazoline ring



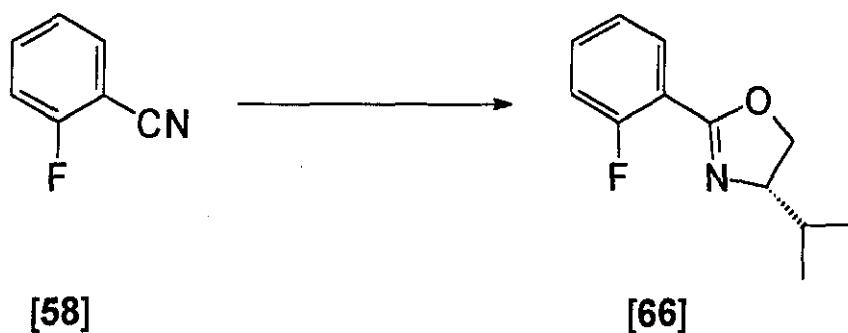
A mixture of the appropriate benzonitrile (4.7 g, 26 mmol), corresponding amino alcohol (3.198 g, 31 mmol) and zinc chloride [1.1 ml (1M solution in diethyl ether), 1.1 mmol] in chlorobenzene (8 ml) were heated to reflux under anhydrous conditions for 6 hours. The chlorobenzene was then removed under reduced pressure and the resulting oil purified directly by flash chromatography (10% ethyl acetate–light petroleum), to afford the desired products named below.

(4S)-2-(2-fluorophenyl)-4-methyl-4,5-dihydro-1,3-oxazole



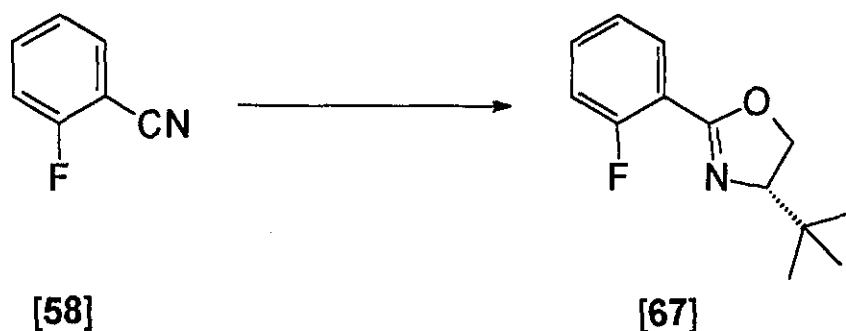
[65] (34%) as a colourless oil; $[\alpha]_D^{22} -65^\circ$ (c 1 in CHCl_3) (lit. -66°); δ_H (250 MHz; CDCl_3) 7.91–7.84 (1H, m, ArH), 7.49–7.10 (3H, m, ArH), 4.41 (2H, m, CH–N and CH–O), 3.95 (1H, t, J 7.3 Hz, CH–O), 1.37 (3H, d, J 6.4 Hz, Me).⁷⁴

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



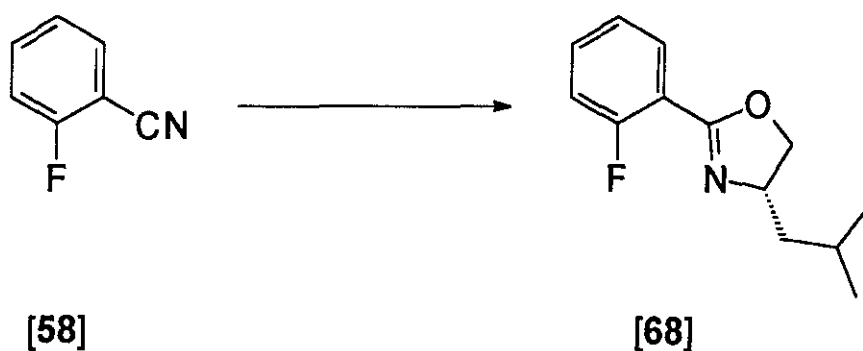
[66] (39%) as a colourless oil; $[\alpha]_D^{22} -60^\circ$ (c 1 in CHCl_3) (lit. -62°); δ_H (250 MHz; CDCl_3) 7.88–7.09 (4H, m, ArH), 4.38 (1H, m, CH–N), 4.12 (2H, m, $\text{CH}_2\text{--O}$), 1.89 (1H, m, CHMe_2), 1.00 (3H, d, J 6.8 Hz, Me), 0.91 (3H, d, J 6.8 Hz, Me).⁷⁴

(4S)-4-(tert-butyl)-2-(2-fluorophenyl)-4,5-dihydro-1,3-oxazole



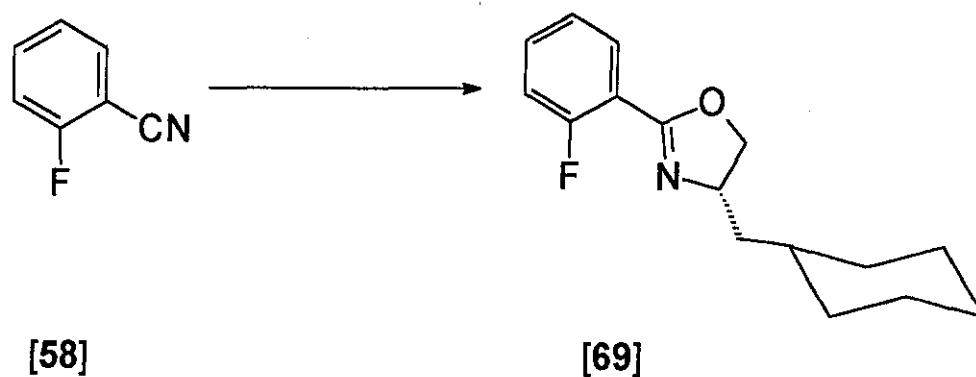
[67] (24%) as a colourless oil; $[\alpha]_D^{22} -66^\circ$ (c 0.6, CHCl_3) (lit. -69°); δ_H (250 MHz; CDCl_3) 7.86–7.14 (4H, m, ArH), 4.33 (1H, dd, J 8.2 Hz and 10.1 Hz, CH–O), 4.22 (1H, t, J 8.4 Hz, CH–N), 4.06 (1H, dd, J 7.7 Hz and 10.1 Hz, CH–O), 0.95 (9H, s, CMe_3).⁷⁴

[68]



[68] (69%) as a colourless oil; δ_{H} (400 MHz; CDCl_3) 7.88 (1H, m, ArH), 7.42 (1H, m, ArH), 7.28–7.08 (2H, m, ArH), 4.49 (1H, m, CH–O), 4.36 (1H, m, CH–O), 3.99 (1H, t, J 7.6 Hz, C=N–CH), 1.85–1.70 (2H, m, CH– CH_2CH), 1.40 (1H, m, CH_2CHMe_2), 0.99 (3H, d, J 3.5 Hz, CHMe), 0.96 (3H, d, J 3.5 Hz, CHMe). Not possible to purify, therefore this compound was not fully characterised. Purification occurred at the next step of the synthesis, see (4S)-2-[2-(1,1-diphenylphosphino)phenyl]-4-isobutyl-4,5-dihydro-1,3-oxazole [70].

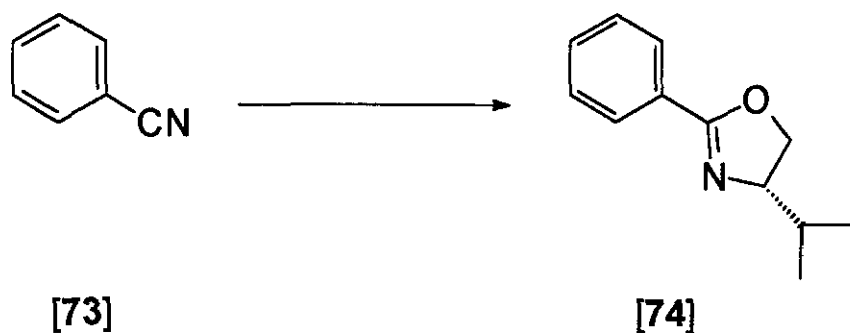
(4S)-4-(cyclohexylmethyl)-2-(2-fluorophenyl)-4,5-dihydro-1,3-oxazole



[69] (39%) as a colourless oil; δ_{H} (400 MHz; CDCl_3) 7.89 (1H, m, ArH), 7.43 (1H, m, ArH), 7.21–7.10 (2H, m, ArH), 4.48 (1H, m, CH–O), 4.39 (1H, m, CH–O), 3.99 (1H, t, J 7.0 Hz, C=NCH), 1.72–0.90 (13H, m, CH– CH_2CH and C_6H_{11}). Not possible to

purify, therefore this compound was not fully characterised. Purification occurred at the next step of the synthesis, see (4S)-4-(cyclohexylmethyl)-2-[2-(1,1-diphenylphosphino)phenyl]-4,5-dihydro-1,3-oxazole [71].

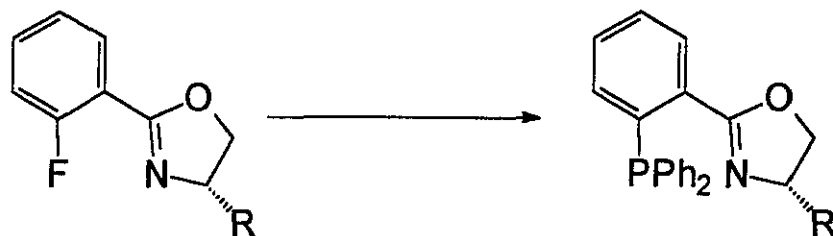
(4S)-4-isopropyl-2-phenyl-4,5-dihydro-1,3-oxazole



[74] (82%) as a colourless oil; δ_H (250 MHz; $CDCl_3$) 7.98–7.87 (2H, m, 2x *o*-ArH), 7.42–7.26 (3H, m, 2 x *m*-ArH and *p*-ArH), 4.37–4.24 (1H, m, O-CH), 4.08–4.05 (2H, m, O-CH and N-CH), 1.90–1.67 (1H, m, CHMe₂), 0.98–0.83 (6H, 2 x d, 2 x Me).²¹¹

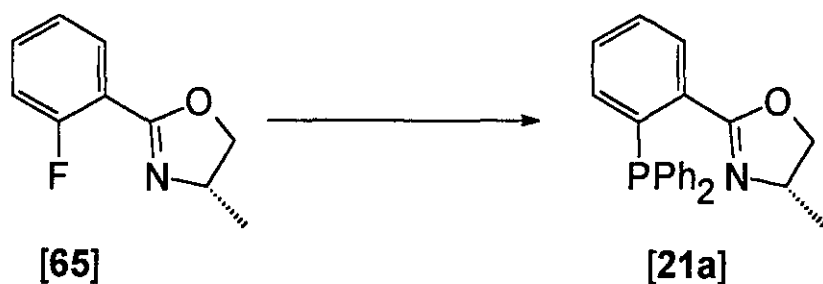
²¹¹ X. Guo, R. Schulz, *Polym. Int.*, 1994, 34(2), 229-233.

General Procedure for the preparation of (4S)-2-(2-diphenylphosphinophenyl)-4-substituted-4,5-dihydro-1,3-oxazoles



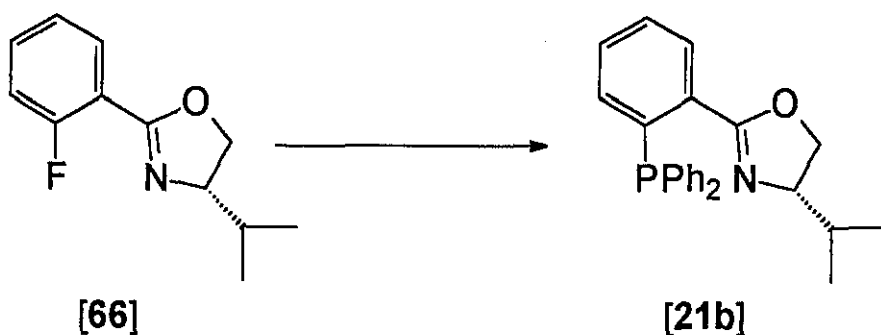
Under an inert atmosphere potassium diphenylphosphide (KPPH₂) (1.4mmol; 0.5M in THF) was heated to reflux. The corresponding (4S/R)- 4-substituted-2-(2-fluorophenyl)-4,5-dihydro-1,3-oxazole (1 mmol) was added to the refluxing potassium diphenylphosphide dropwise, as a solution in THF (1 ml). The reaction mixture was stirred under reflux until the reaction was complete, shown by the fading of the red phosphide solution to a pale yellow. The solvent (THF) was then removed under reduced pressure and the resulting oil dissolved in dichloromethane (10ml). The solution then washed with water (3 x 5ml), dried over sodium sulfate and the solvent removed under reduced pressure. The residue was purified by flash chromatography (8% ethyl acetate–light petroleum) to afford the title compounds.

(4S)-2-[2-(1,1-diphenylphosphino)phenyl]-4-methyl-4,5-dihydro-1,3-oxazole



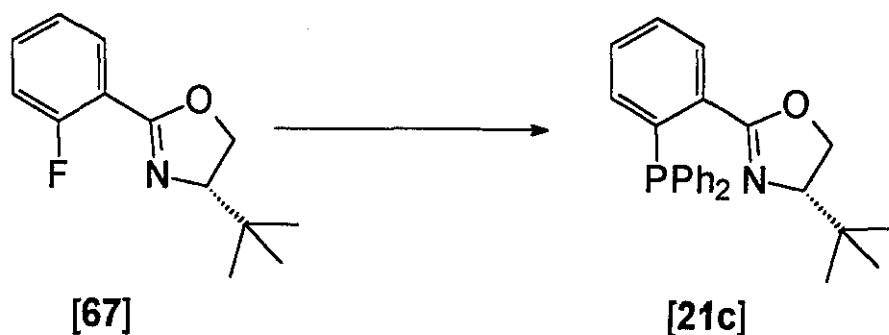
[21a] (33%) as a colourless solid; mp 91–94 °C (lit 93–95 °C); δ_{H} (250 MHz; CDCl_3) 7.90 (1H, m, ArH), 7.70–7.20 (12H, m, ArH), 6.84 (1H, m, ArH), 4.20–4.08 (2H, m, $\text{CH}_2\text{-O}$), 3.54 (1H, t, J 7.6 Hz, CH-N), 0.95 (3H, d, J 6.5 Hz, Me).⁷⁴

(4S)-2-[2-(1,1-diphenylphosphino)phenyl]-4-isopropyl-4,5-dihydro-1,3-oxazole



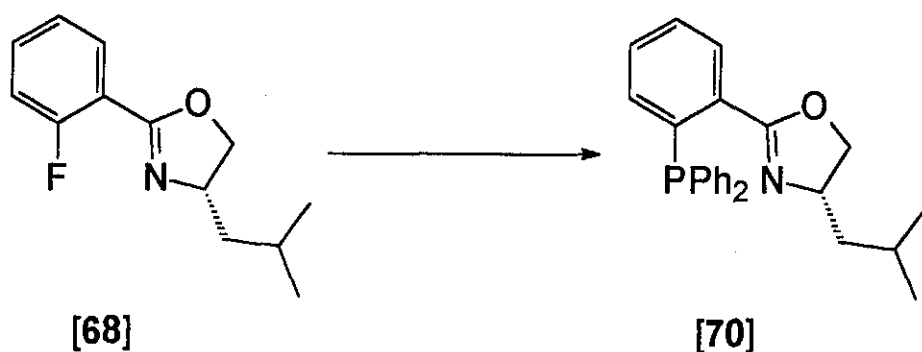
[21b] (62%) as an opaque solid; mp 85–88 °C (lit 84–86 °C); δ_{H} (250 MHz; CDCl_3) 7.92 (1H, m, ArH), 7.70–7.20 (12H, m, ArH), 6.89 (1H, m, ArH), 4.10 (1H, m, CH-O), 3.80 (2H, m, CH-N and CH-O), 1.52 (1H, m, CHMe_2), 0.80 (3H, d, J 6.7 Hz, Me), 0.69 (3H, d, J 6.7 Hz, Me).⁷⁴

(4S)-4-(tert-butyl)-2-[2-(1,1-diphenylphosphino)phenyl]-4,5-dihydro-1,3-oxazole



[21c] (40%) as a colourless solid; mp 110–114 °C (lit 114–116 °C); δ_{H} (250 MHz; CDCl_3) 7.94 (1H, m, ArH), 7.80–7.20 (12H, m, ArH), 6.90 (1H, m, ArH), 4.21–4.10 (2H, m, CH–N and CH–O), 3.99 (1H, t, J 8.3 Hz, CH–O), 0.72 (9H, s, CMe_3).⁷⁴

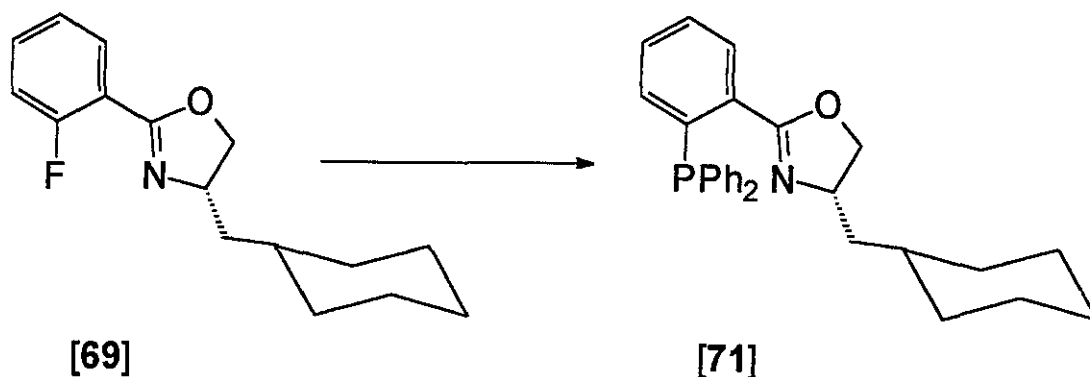
(4S)-2-[2-(1,1-diphenylphosphino)phenyl]-4-isobutyl-4,5-dihydro-1,3-oxazole



[70] (32%) as a colourless crystalline solid; mp 83–85 °C; $[\alpha]_{\text{D}}^{22}$ -18.2° (c 2, CHCl_3); (Found 387.1752, $\text{C}_{25}\text{H}_{26}\text{NOP}$ requires 387.1752); ν_{max} (CCl_4) 1651 cm^{-1} ; δ_{H} (400 MHz; CDCl_3) 7.48–7.25 (14H, m, ArH), 4.22 (1H, dd, J 8.0 and 8.8 Hz, CH–O), 4.09 (1H, m, CH–N), 3.63 (1H, t, J 8.0 Hz, CH–O), 1.57 (1H, m, CH–CHMe), 1.29 (1H, m, CH–CHMe), 0.93 (1H, m, CHMe_2), 0.85 (3H, d, J 6.4 Hz, Me), 0.82 (3H, d, J 6.4 Hz, Me); δ_{C} (100 MHz; CDCl_3) 163.0 (C=N), 139.3–138.0 (ArC), 134.5 (ArCH), 134.2 (ArCH), 133.9 (ArCH), 133.7 (ArCH), 133.6 (ArCH), 132.0 (ArC), 131.8 (ArC), 130.4–

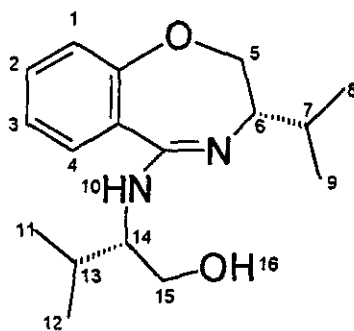
128.0 (9 x ArCH), 72.7 (CH₂-O), 65.1 (CH-N), 45.0 (CHCH₂CH), 25.2 (CHMe₂), 22.8 (Me), 22.5 (Me); *m/z*, 387 (M⁺, 17%), 287 (100), 183 (18).

(4S)-4-(cyclohexylmethyl)-2-[2-(1,1-diphenylphosphino)phenyl]-4,5-dihydro-1,3-oxazole



[71] (39%) as a colourless crystalline solid; mp 85–88 °C; $[\alpha]_D^{22} -15.0^\circ$ (*c* 0.4, CHCl₃); (Found 427.2065, C₂₈H₃₀NOP requires 427.2065); ν_{\max} . (CCl₄) 2923, 1651, 1434, 1043 cm⁻¹; δ_H (400 MHz; CDCl₃) 7.34–7.29 (14H, m, ArH), 4.21 (1H, dd, *J* 7.7 and 9.3 Hz, CH-O), 4.12 (1H, m, CH-O), 3.62 (1H, t, *J* 7.8 Hz, CH-N), 1.67–0.82 (13H, bm, CHCH₂CH and C₆H₁₁); δ_C (100 MHz; CDCl₃) 163.1 (C=N), 138.9–137.9 (4 x ArC), 134.4–128.0 (14 x ArCH), 72.8 (O-CH₂), 64.5 (C=N-CH), 43.7 (CH-CH₂CH), 34.5 (CH₂CH₂C₆H₁₁), 33.5, (CHCH₂CH₂), 33.1 (CHCH₂CH₂), 26.6 (CH₂CH₂CH₂), 26.2 (CH₂CH₂CH₂), 26.1 (CH₂CH₂CH₂); *m/z*, 427 (M⁺, 11%), 41 (27), 240 (25), 302 (100), 344 (36).

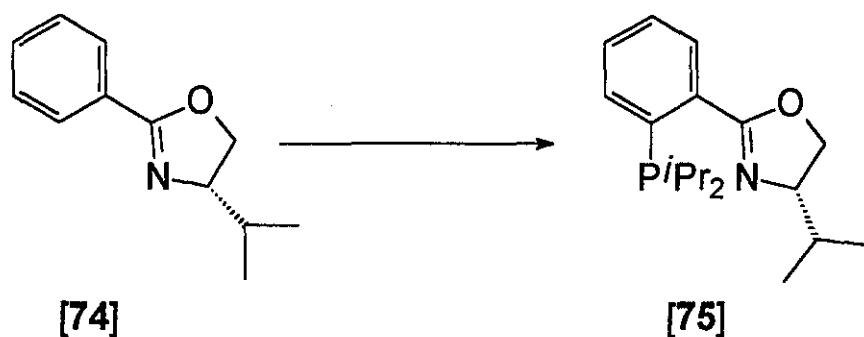
[72]



[72]

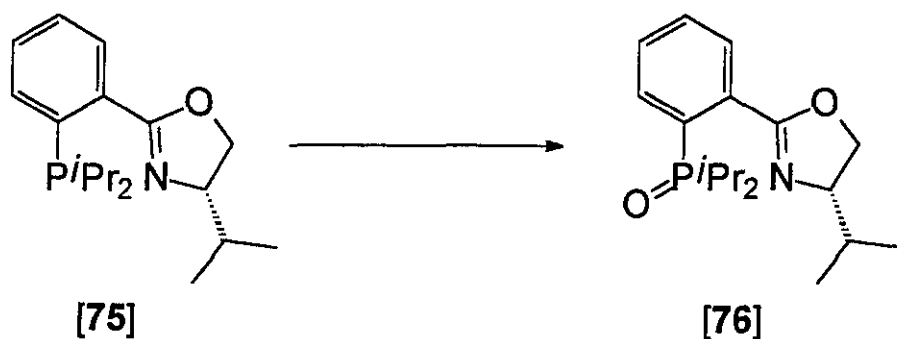
[72] was obtained as a crystalline solid biproduct of the reaction to produce [66]; δ_{H} (250 MHz; CDCl_3) 7.57 (1H, bs, 10), 7.44-7.36 (2H, m, 1 and 4), 7.19-7.03 (2H, m, 2 and 3), 4.52 (1H, bs, 16), 4.45-4.35 (2H, m, 5), 3.86-3.66 (3H, m, 14 and 15), 3.03-2.94 (1H, m, 7), 2.08-1.99 (1H, m, 13), 1.81-1.71 (1H, m, 6), 1.06-0.88 (12H, m, 8, 9, 11 and 12)

[75]



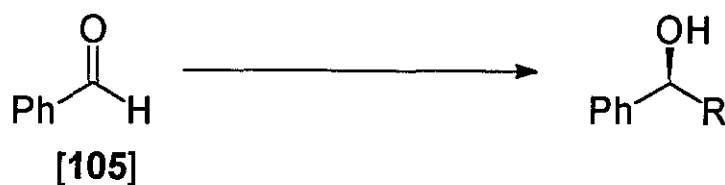
To a stirred solution of phenyl oxazoline [74] (945 mg, 5 mmol) in anhydrous diethyl ether (8 ml) under N_2 , was added *N,N,N,N*-tetramethylethylenediamine (1.74 g, 15 mmol) and the temperature lowered to $-78^\circ C$. *n*-Butyl lithium (2.2 ml, 5.5 mmol; 2.5M in hexane) was added and the solution was stirred for a further 2 hours. A solution of chlorodiisopropylphosphine (763 mg, 5 mmol) in anhydrous diethyl ether (20 ml) was added dropwise and the temperature maintained at $-78^\circ C$ for a further 60 min. After being allowed to warm to room temperature over 3 hours the solvent was removed under reduced pressure taking care to maintain anhydrous conditions and an inert atmosphere. On addition of heptane to the resulting yellow oil precipitation occurred and the inorganic solid was filtered using Schlenk apparatus. The yellow heptane solution containing product was dried under reduced pressure to afford crude product [75] (1.36 g, 89%). The instability of the phosphino moiety prevented this compound being purified. In all asymmetric reactions the ligand has been used in its crude state. Full characterisation has been obtained of the derived phosphine oxide [76].

**Diisopropyl{2-[(4S)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}phosphine
oxide**



Crude material containing the diisopropylphosphino oxazoline [75] was stirred in air for 48 hours. The oil was then purified by flash chromatography (50% ethyl acetate/light petroleum) to afford the phosphine oxide [76] (30%) as a viscous oil; $[\alpha]_D^{22} -4.0^\circ$ (*c* 0.6, CHCl_3); (Found 321.1857, $\text{C}_{18}\text{H}_{28}\text{O}_2\text{PN}$ requires 321.1857); ν_{max} (neat) 2959, 2869, 1652, 1244 1049 cm^{-1} ; δ_{H} (400 MHz; CDCl_3) 8.28 (1H, m, ArH), 7.87 (1H, m, ArH), 7.59–7.50 (2H, m, ArH), 4.44 (1H, m, CH–O), 4.06 (2H, m, CH–O and CH–N), 2.85 (1H, m, P–CHMe₂), 2.69 (1H, m, P–CHMe₂), 1.83 (1H, m, CH–CHMe₂), 1.33 (6H, m, P–CHMe₂), 1.06 (3H, d, CH–CHMe₂), 0.96 (3H, d, CH–CHMe₂), 0.95–0.86 (6H, m, P–CHMe₂); δ_{C} (100 MHz; CDCl_3) 163.0 (C=N), 135.0 (ArCH), 132.9 (ArC), 132.1 (ArC), 130.7–130.1 (3 x ArCH), 73.7 (CH–N), 70.4 (CH₂–O), 33.0 (CH–CHMe₂), 27.7–26.6 (2 x P–CHMe₂), 19.2 (CH–CHMe₂), 18.8 (CH–CHMe₂), 17.2–16.7 (4 x P–CHMe₂); δ_{P} (400 MHz; CDCl_3) 55.7 (1P, s, P=O); *m/z*, 321 (M^+ , 18%), 43 (34), 210 (27), 236 (100), 278 (57).

General procedure for reaction of benzaldehyde with a Grignard reagent

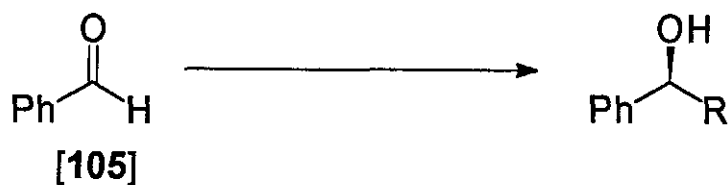


A diethyl ether (2 ml) solution of Grignard reagent (2.16 mmol)(3M solⁿ in Et₂O) was cooled to $-78\text{ }^{\circ}\text{C}$ and to it added appropriate ligand (2.16 mmol) in diethyl ether (2 ml). The mixture was then reduced to approx. 1 ml under a stream of dry N₂ and the anhydrous appropriate solvent (4 ml) added. The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1.5 hours and then benzaldehyde **[105]** (228 mg, 2.16 mmol) in the same solvent (1.5 ml) added dropwise maintaining the temperature during addition at $-78\text{ }^{\circ}\text{C}$ and for a further 60 minutes. The solution was warmed to room temperature, diluted with diethyl ether (10 ml) and washed with saturated ammonium chloride solution (2 x 10 ml). The organic extracts were then washed with saturated brine solution (10 ml) and dried over sodium sulfate. The solvent was removed under reduced pressure to afford the corresponding alcohol which was purified by flash chromatography (10% ethyl acetate–light petroleum), and the enantiomeric excess measured by chiral shift NMR and chiral HPLC. All alcohol data corresponds to literature values; 1-phenylethanol, 1-phenyl-pentan-1-ol,²¹² 2,2-dimethyl-1-phenyl-propan-1-ol.²¹³

²¹² A. J. M. Janssen, A. J. H. Klunder, B. Zwanenburg, *Tetrahedron*, 1991, 47, 7645-7662.

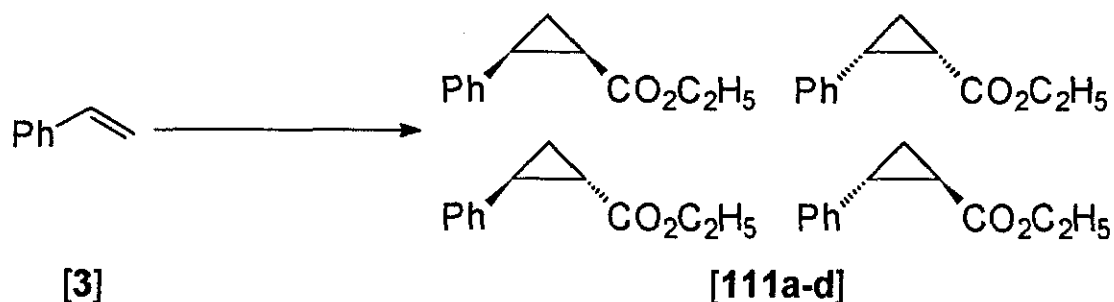
²¹³ A. Guijarro, D. J. Ramon, M. Yus, *Tetrahedron*, 1993, 49, 469-482.

General Procedure for reaction of benzaldehyde with organolithium species



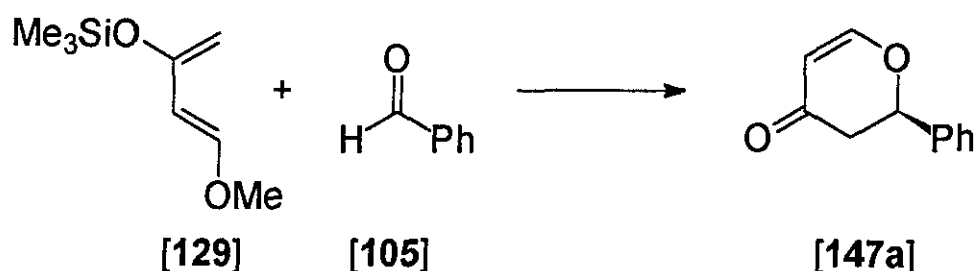
A diethyl ether (1 ml) solution of organolithium species (2.16 mmol; 1.4M in Et₂O) was cooled to -78 °C and to it added the ligand (2.16 mmol) in diethyl ether (1 ml). The solution was stirred at -78 °C for 1.75 hours and then benzaldehyde [105] (228 mg, 2.16 mmol) in diethyl ether (1 ml) added dropwise maintaining the temperature during addition at -78 °C and for a further 30 minutes. The solution was warmed to room temperature, diluted with diethyl ether (10 ml) and washed with saturated ammonium chloride solution (2 x 10 ml). The organic extracts were then washed with saturated brine solution (10 ml) and dried over sodium sulfate. The solvent was removed under reduced pressure to afford the corresponding alcohol, which was purified by flash chromatography (10% ethyl acetate–light petroleum), before being analysed by chiral HPLC. All alcohol data corresponds to literature values; 1-phenylethanol, 1-phenyl-pentan-1-ol.²¹²

General method for the copper (I) catalysed cyclopropanation of styrene using pyridine acetal ligands



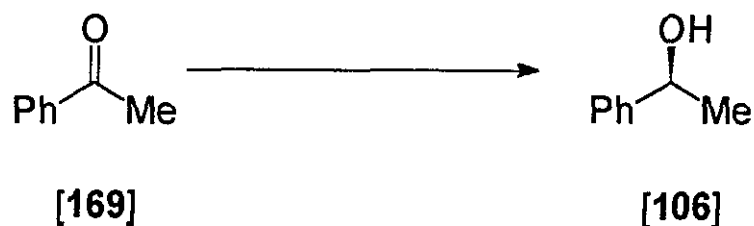
Acetal ligand (0.12 mol%) and copper(I) triflate.benzene complex (0.06 mol%) in dry dichloromethane (1.25 ml) were stirred at room temperature for 1 hour. The solution was then cooled to 0°C, the styrene [3] (590 mg, 5.67 mmol) added and the mixture stirred for 20 minutes to achieve equilibrium. A solution of ethyl diazoacetate (883 mg, 7.74 mmol) in dry dichloromethane (4 ml) was added to the cooled copper mixture over 5 hours, maintaining the temperature at 0 °C throughout. The reaction was then allowed to warm to room temperature and stirred for a further 16 hours. After this time the reaction was refluxed for 60 mins and then passed through a plug of silica. The solvent was removed under reduced pressure and the crude oil [111a-d] analysed by chiral GC; Cefadex B column (25 m), $H_2 = 0.7 \text{ kgcm}^{-2}$, carrier gas (He) = 0.9 kgcm^{-2} , air = 1.2 kgcm^{-2} , temperature = 125 °C, R_T trans = 62 and 65 mins, detector wavelength 254 nm, R_T cis = 74 and 77 mins; data corresponds with literature values for each set of diastereomers.¹¹²

General method for the Diels–Alder reaction using Lanthanide (III) catalysts and acetal ligands



To a stirred solution of acetal ligand (0.05 mmol) and benzaldehyde [105] (0.5 mmol) in dry dichloromethane (0.5 ml) was added the lanthanum(III) species (0.01 mmol). The mixture was stirred at room temperature for 20 minutes and then cooled to 0°C. Danishefsky's diene [129] (0.5 mmol) was then added dropwise, the reaction was allowed to warm to room temperature and stirred for a further 48 hours. After this time the reaction mixture was poured into 10% HCl (2 ml) and extracted into diethyl ether (8 ml). The solvent was removed under reduced pressure and then the oil was resolvated with dichloromethane (2 ml). The solution was again cooled to 0°C and TFA (0.6 mmol) added, stirring for a further 1.5 hours. The reaction was diluted with dichloromethane (5 ml), washed with saturated sodium bicarbonate solution (5 ml) and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude oil purified by flash chromatography (10% ethyl acetate–light petroleum) to afford the desired product [147a]; δ_{H} (250 MHz; CDCl₃) 7.49 (1H, d, *J* 6 Hz, CHCH–O), 7.41 (5H, s, ArH), 5.53 (1H, d, *J* 1.0 Hz, COCHCH), 5.43 (1H, dd, *J* 3.8 and 14.3 Hz), 2.92 (1H, dd, *J* 14.3 and 16.8 Hz, COCHCHPh), 2.66 (1H, dd, *J* 3.8 and 16.8 Hz, COCHCHPh).¹⁴³ Enantiomeric excesses were determined by chiral HPLC, Chiralcel OD column, solvent mixture = 1% IPA/hexane, flow rate = 1 cm³min⁻¹, detector wavelength 254 nm, R_T = 33 and 38 mins.

General method for hydrosilylation of acetophenone using [Rh(COD)Cl]₂ and pyridine acetal ligands



Acetophenone [169] (1 ml, 8 mmol), rhodium cyclooctadiene chloride dimer (10 mg, 0.04 mmol of Rh) and ligand were stirred together in the desired solvent (2 ml), at the appropriate temperature, for length of time stated in results section. The reaction mixture was then cooled to 0 °C and diphenylsilane added. The reaction was stirred at room temperature for a further 43 hours. After this time 10% HCl – acetone (2.5 ml) was added and the mixture stirred vigorously for 1.5 hours at 0 °C. The reaction was then diluted with diethyl ether (5 ml) and washed with saturated sodium bicarbonate (2x 5 ml), water (5 ml), saturated brine solution (5 ml) and dried over sodium sulfate. The solvent was removed under reduced pressure to afford a crude oil containing the required product, 1-phenyl ethanol [106]. The crude oil was purified by flash chromatography (10% ethyl acetate –light petroleum) prior to being analysed by chiral HPLC.

General method for hydrosilylation of ketones using [Rh(COD)Cl]₂ and oxazoline based ligands

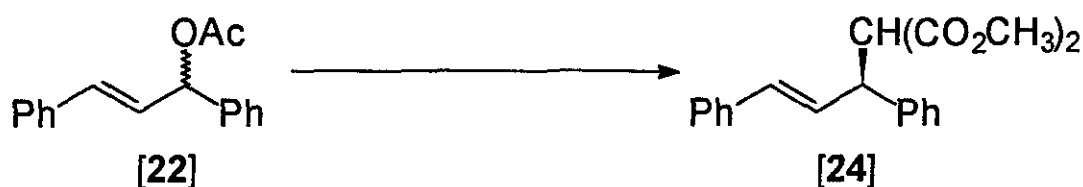


To a stirred solution of rhodium cyclooctadiene chloride dimer (0.01 mmol) and appropriate ligand (0.1 mmol) in dry THF (1ml) was added the desired ketone (1 mmol) under nitrogen. The solution was stirred at room temperature for 20 minutes before being cooled to the temperature stated. Diphenylsilane (4 mmol) was then added and the temperature maintained for 2 hours. The reaction was allowed to warm to room temperature and stirred for a further 24 hours. Upon cooling to 0 °C, methanol (2 ml) and 1M HCl (1.75 ml) were added and the solution stirred vigorously. After 2 hours, ethyl acetate (8 ml) was added and the solution washed with water (10 ml). The aqueous phase was re-extracted with ethyl acetate (2 x 8 ml), the organics combined and washed with saturated brine solution (10 ml). The solution was dried over sodium sulfate and the solvent removed under reduced pressure to afford a crude oil containing the required product stated below. The crude oil was purified by flash chromatography (10–20% ethyl acetate–light petroleum) prior to being analysed by chiral HPLC; Chiralcel OD column, flow rate = 1 cm³min⁻¹, solvent mixture = 1% IPA–hexane. In all cases data for the obtained alcohols corresponds to literature data; 1-phenylethanol, 1-phenylpentan-1-ol,²¹² 2,2-dimethyl-1-phenylpropan-1-ol,²¹³ 1-phenylbutan-1-ol,²¹² 1,2,3,4-tetrahydronaphthalen-1-ol,²¹⁴ 1-naphthalen-1-ylethanol,²¹⁵ 1-(4-methoxy-phenyl)ethanol.²¹²

²¹⁴ J. R. Hwu, Y. S. Wein, Y. Leu, *J. Org. Chem.*, 1996, 61, 1493-1499.

²¹⁵ P. D. Theisen, C. H. Heathcock, *J. Org. Chem.*, 1988, 53, 2374-2378.

General method for the palladium catalysed allylic alkylation of racemic-(*E*)-1,3-diphenylprop-2-enyl acetate with a dimethyl malonate nucleophile.³⁸



Appropriate ligand (10 mol%) and allyl palladium chloride dimer (27.4 mg, 2.5 mol%) were stirred in dry dichloromethane (5 ml) for 15 mins. The solution was then treated with racemic-(*E*)-1,3-diphenylprop-2-enyl acetate [22] (750 mg, 3 mmol), *N,O*-bis(trimethylsilyl)acetamide (BSA) (1.83 g, 9 mmol), dimethyl malonate (1.19 g, 9 mmol) and a catalytic amount of potassium acetate (8.8 mg). The reaction was stirred at room temperature for 17–41 hours until reaction was shown to be complete by tlc analysis and then diluted with diethyl ether (15 ml). The ether solution was then washed with ice cold saturated ammonium chloride solution (2 x 10 ml) and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the obtained oil was purified by flash chromatography (10% ethyl acetate–light petroleum) to afford the desired product, dimethyl-1,3-diphenylprop-2-enylmalonate [24]; δ_{H} (250 MHz; CDCl₃) 7.44–7.15 (10H, m, ArH), 6.48 (1H, d, *J* 15.0 Hz, PhCH=CH), 6.32 (1H, dd, *J* 8.1 and 15.0 Hz, PhCH=CH), 4.27 (1H, dd, *J* 8.1 and 11.0 Hz, PhCHCH=CH), 3.95 (1H, d, *J* 11.0 Hz, CH(CO₂Me)₂), 3.70 (3H, s, CO₂Me), 3.53 (3H, s, CO₂Me).³⁸ Enantiomeric excesses measured by chiral HPLC, Chiralcel AD column, solvent = 1% IPA–hexane, flow rate = 1 cm³min⁻¹, detector wavelength 254 nm.

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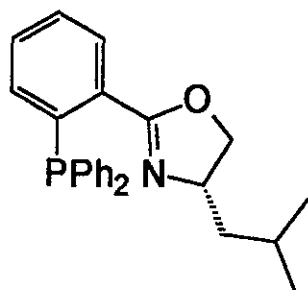
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Appendix 1

X-ray structure report for compound [70]



Experimental

Data Collection

A clear block crystal of $C_{25}H_{26}NOP$ having approximate dimensions of 0.10 x 0.10 x 0.23 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated $Cu-K\alpha$ radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 16 carefully centered reflections in the range $70.82 < 2\theta < 74.93^\circ$ corresponded to a primitive triclinic cell with dimensions:

$$\begin{aligned} a &= 9.797(4) \text{ \AA} & \alpha &= 91.70(3)^\circ \\ b &= 13.579(4) \text{ \AA} & \beta &= 100.38(3)^\circ \\ c &= 8.710(1) \text{ \AA} & \gamma &= 107.08(2)^\circ \\ V &= 1085.3(5) \text{ \AA}^3 \end{aligned}$$

For $Z = 2$ and $F.W. = 387.46$, the calculated density is 1.19 g/cm^3 . Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$$P\bar{1} (\#2)$$

The data were collected at a temperature of $20 \pm 1^\circ\text{C}$ using the ω scan technique to a maximum 2θ value of 120.6° . Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.29° with a take-off angle of 6.0° . Scans of $(1.05 + 0.35 \tan \theta)^\circ$ were made at a speed of $16.0^\circ/\text{min}$ (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).

Data Reduction

Of the 3443 reflections which were collected, 3223 were unique ($R_{int} = 0.078$). The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards decreased by 4.7%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ , for $Cu-K\alpha$ radiation is 12.1 cm^{-1} . An empirical absorption correction using the program DIFABS¹ was applied which resulted in transmission factors ranging from 0.70 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = $9.73025e-05$).

Structure Solution and Refinement

The structure was solved by direct methods² and expanded using Fourier techniques³. 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 1290 observed reflections ($I > 3.00\sigma(I)$) and 254 variable parameters and converged (largest parameter shift was 0.08 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.105$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)} = 0.065$$

The standard deviation of an observation of unit weight⁵ was 7.38. The weighting scheme was based on counting statistics and included a factor ($p = 0.001$) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin \theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.24 and -0.29 $e^-/\text{\AA}^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber⁶. Anomalous dispersion effects were included in Fcalc⁷; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley⁸. The values for the mass attenuation coefficients are those of Creagh and Hubbel⁹. All calculations were performed using the teXsan¹⁰ crystallographic software package of Molecular Structure Corporation.

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- (4) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

$$\text{where } w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

- (5) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

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(10) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{25}H_{26}NOP$
Formula Weight	387.46
Crystal Color, Habit	clear, block
Crystal Dimensions	0.10 X 0.10 X 0.23 mm
Crystal System	triclinic
Lattice Type	Primitive
No. of Reflections Used for Unit	
Cell Determination (2θ range)	16 (70.8 - 74.9°)
Omega Scan Peak Width	
at Half-height	0.29°
Lattice Parameters	$a = 9.797(4)\text{Å}$ $b = 13.579(4)\text{Å}$ $c = 8.710(1)\text{Å}$ $\alpha = 91.70(3)^\circ$ $\beta = 100.38(3)^\circ$ $\gamma = 107.08(2)^\circ$
	$V = 1085.3(5)\text{Å}^3$
Space Group	$P\bar{1}$ (#2)
Z value	2
D_{calc}	1.186 g/cm ³
F_{000}	412.00
$\mu(\text{CuK}\alpha)$	12.08 cm ⁻¹

B. Intensity Measurements

Diffractometer	Rigaku AFC7S
Radiation	CuK α ($\lambda = 1.54178 \text{ \AA}$) graphite monochromated
Attenuator	Ni foil (factor = 9.42)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal 13.0 mm vertical
Crystal to Detector Distance	400 mm
Voltage, Current	0kV, 0mA
Temperature	20.0°C
Scan Type	ω
Scan Rate	16.0°/min (in ω) (up to 4 scans)
Scan Width	(1.05 + 0.35 tan θ)°
$2\theta_{max}$	120.6°
No. of Reflections Measured	Total: 3443 Unique: 3223 ($R_{int} = 0.078$)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.7020 - 1.0000) Decay (4.72% decline) Secondary Extinction (coefficient: 9.73025e-05)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(F_o - F_c)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(F_o)} = [\sigma_c^2(F_o) + \frac{p^2}{4} F_o^2]^{-1}$
p-factor	0.0010
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I > 3.00\sigma(I)$)	1290

No. Variables	254
Reflection/Parameter Ratio	5.08
Residuals: R; Rw	0.105 ; 0.065
Goodness of Fit Indicator	7.38
Max Shift/Error in Final Cycle	0.08
Maximum peak in Final Diff. Map	$0.24 e^{-}/\text{\AA}^3$
Minimum peak in Final Diff. Map	$-0.29 e^{-}/\text{\AA}^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
P(7)	0.7541(4)	0.2351(2)	0.4154(3)	6.07(9)
O(1)	0.8901(9)	0.4909(5)	0.7954(7)	8.3(2)
N(3)	0.762(1)	0.4305(6)	0.5544(9)	8.3(3)
C(2)	0.819(1)	0.4089(8)	0.686(1)	7.3(4)
C(4)	0.802(2)	0.5436(8)	0.548(2)	11.3(5)
C(5)	0.887(1)	0.5851(7)	0.719(1)	9.9(4)
C(6)	0.812(1)	0.3095(7)	0.741(1)	6.8(4)
C(7)	0.765(1)	0.2166(7)	0.6340(9)	7.0(3)
C(8)	0.763(1)	0.1250(7)	0.686(1)	7.7(4)
C(9)	0.786(1)	0.1127(8)	0.846(1)	8.4(4)
C(10)	0.820(1)	0.200(1)	0.953(1)	8.7(4)
C(11)	0.829(1)	0.2965(9)	0.900(1)	9.4(5)
C(12)	0.562(1)	0.2216(8)	0.358(2)	6.4(4)
C(13)	0.454(2)	0.1786(8)	0.438(1)	7.0(4)
C(14)	0.308(2)	0.1627(7)	0.387(2)	8.3(5)
C(15)	0.268(2)	0.2004(9)	0.240(2)	8.0(4)
C(16)	0.375(2)	0.2460(9)	0.159(1)	8.0(5)
C(17)	0.517(2)	0.2561(7)	0.212(2)	7.4(4)
C(18)	0.760(1)	0.1088(7)	0.344(1)	6.4(3)
C(19)	0.891(1)	0.0915(7)	0.357(1)	7.2(4)
C(20)	0.905(1)	0.0016(8)	0.296(1)	8.2(4)
C(21)	0.789(2)	-0.0732(8)	0.210(1)	8.0(4)
C(22)	0.655(2)	-0.0578(7)	0.190(1)	8.6(4)
C(23)	0.640(1)	0.0317(7)	0.256(1)	6.5(3)

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
C(24)	0.761(3)	0.594(1)	0.444(2)	27.5(9)
C(25)	0.670(2)	0.5490(9)	0.284(2)	10.0(5)
C(26)	0.565(2)	0.606(1)	0.238(1)	14.7(7)
C(27)	0.778(2)	0.577(1)	0.161(2)	14.4(7)
H(4)	0.8890	0.5462	0.5115	13.6602
H(5a)	0.8407	0.6238	0.7721	12.3444
H(5b)	0.9822	0.6273	0.7131	12.3444
H(8)	0.7482	0.0691	0.6102	9.1050
H(9)	0.7743	0.0455	0.8807	9.8544
H(10)	0.8409	0.1914	1.0613	10.3846
H(11)	0.8421	0.3524	0.9752	11.3394
H(13)	0.4837	0.1582	0.5393	8.2832
H(14)	0.2385	0.1283	0.4468	9.7057
H(15)	0.1694	0.1937	0.1977	9.2222
H(16)	0.3485	0.2719	0.0621	9.4421
H(17)	0.5873	0.2884	0.1524	8.7890
H(19)	0.9761	0.1425	0.4132	8.5862
H(20)	0.9977	-0.0091	0.3108	9.6200
H(21)	0.8003	-0.1340	0.1644	9.4892
H(22)	0.5725	-0.1099	0.1325	10.4254
H(23)	0.5463	0.0409	0.2415	7.5822
H(24a)	0.7110	0.6345	0.4868	34.0279
H(24b)	0.8514	0.6378	0.4257	34.0279
H(25)	0.6235	0.4766	0.2769	11.8924

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(26c)	0.4917	0.5914	0.2996	17.4592
H(26a)	0.6157	0.6783	0.2520	17.4592
H(26b)	0.5210	0.5870	0.1307	17.4592
H(27a)	0.8493	0.5418	0.1846	18.0444
H(27b)	0.7283	0.5578	0.0552	18.0444
H(27c)	0.8251	0.6496	0.1745	18.0444
H(28)	0.7081	0.5394	0.5885	14.3088

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^* \cos \gamma + 2U_{13}aa^*cc^* \cos \beta + 2U_{23}bb^*cc^* \cos \alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
P(7)	0.099(3)	0.061(2)	0.079(2)	0.034(2)	0.020(2)	0.011(1)
O(1)	0.160(8)	0.071(4)	0.074(5)	0.043(5)	-0.014(5)	-0.013(4)
N(3)	0.16(1)	0.062(5)	0.084(7)	0.037(6)	-0.019(7)	-0.001(5)
C(2)	0.14(1)	0.085(7)	0.074(9)	0.065(8)	0.016(8)	0.010(7)
C(4)	0.20(2)	0.087(8)	0.13(1)	0.07(1)	-0.04(1)	-0.021(9)
C(5)	0.20(2)	0.072(7)	0.11(1)	0.062(9)	0.002(9)	0.004(7)
C(6)	0.09(1)	0.082(7)	0.089(9)	0.042(7)	0.010(7)	0.007(6)
C(7)	0.18(1)	0.067(6)	0.041(6)	0.061(8)	0.024(6)	0.024(5)
C(8)	0.15(1)	0.078(7)	0.071(8)	0.043(7)	0.021(7)	0.023(6)
C(9)	0.13(1)	0.073(7)	0.11(1)	0.018(7)	0.018(9)	0.025(7)
C(10)	0.14(1)	0.13(1)	0.057(8)	0.053(9)	-0.007(7)	0.015(8)
C(11)	0.20(2)	0.112(9)	0.056(8)	0.07(1)	0.004(8)	0.017(7)
C(12)	0.11(1)	0.065(6)	0.09(1)	0.045(8)	0.042(9)	0.005(6)
C(13)	0.09(1)	0.100(8)	0.080(9)	0.051(9)	0.00(1)	-0.007(7)
C(14)	0.10(1)	0.089(8)	0.15(1)	0.048(8)	0.042(9)	0.013(8)
C(15)	0.09(1)	0.077(8)	0.13(1)	0.039(9)	-0.03(1)	-0.009(7)
C(16)	0.13(2)	0.085(9)	0.09(1)	0.05(1)	0.01(1)	0.012(7)
C(17)	0.10(1)	0.087(7)	0.10(1)	0.047(8)	0.017(9)	0.009(7)
C(18)	0.12(1)	0.065(6)	0.053(7)	0.030(7)	0.009(7)	-0.003(5)
C(19)	0.10(1)	0.086(7)	0.096(8)	0.057(8)	0.012(7)	0.000(6)
C(20)	0.10(1)	0.091(8)	0.13(1)	0.049(8)	0.015(8)	0.000(7)
C(21)	0.14(1)	0.080(7)	0.105(9)	0.063(9)	0.025(9)	0.008(6)
C(22)	0.15(1)	0.072(7)	0.093(8)	0.046(8)	-0.010(8)	-0.023(6)
C(23)	0.09(1)	0.070(6)	0.097(8)	0.038(7)	0.030(7)	0.005(6)

Table 2. Anisotropic Displacement Parameters (continued)

atom	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
C(24)	0.69(5)	0.09(1)	0.12(1)	0.05(2)	-0.16(2)	0.031(9)
C(25)	0.16(2)	0.094(8)	0.12(1)	0.033(9)	0.00(1)	0.023(8)
C(26)	0.20(2)	0.19(1)	0.17(1)	0.07(1)	0.04(1)	0.00(1)
C(27)	0.14(2)	0.25(2)	0.19(1)	0.12(2)	0.00(1)	-0.01(1)

The general temperature factor expression:

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

Table 3. Bond Lengths(Å)

atom	atom	distance	atom	atom	distance
P(7)	C(7)	1.916(8)	P(7)	C(12)	1.81(1)
P(7)	C(18)	1.825(8)	O(1)	C(2)	1.37(1)
O(1)	C(5)	1.465(9)	N(3)	C(2)	1.26(1)
N(3)	C(4)	1.47(1)	C(2)	C(6)	1.43(1)
C(4)	C(5)	1.56(1)	C(4)	C(24)	1.23(1)
C(6)	C(7)	1.45(1)	C(6)	C(11)	1.39(1)
C(7)	C(8)	1.33(1)	C(8)	C(9)	1.40(1)
C(9)	C(10)	1.40(1)	C(10)	C(11)	1.38(1)
C(12)	C(13)	1.37(1)	C(12)	C(17)	1.40(1)
C(13)	C(14)	1.37(2)	C(14)	C(15)	1.43(1)
C(15)	C(16)	1.37(2)	C(16)	C(17)	1.35(2)
C(18)	C(19)	1.36(1)	C(18)	C(23)	1.40(1)
C(19)	C(20)	1.37(1)	C(20)	C(21)	1.36(1)
C(21)	C(22)	1.37(2)	C(22)	C(23)	1.39(1)
C(24)	C(25)	1.52(2)	C(25)	C(26)	1.47(2)
C(25)	C(27)	1.61(2)			

Table 4. Bond Lengths(\AA)

atom	atom	distance	atom	atom	distance
C(4)	H(4)	0.95	C(4)	H(28)	1.03
C(5)	H(5a)	0.95	C(5)	H(5b)	0.95
C(8)	H(8)	0.95	C(9)	H(9)	0.95
C(10)	H(10)	0.95	C(11)	H(11)	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
C(17)	H(17)	0.95	C(19)	H(19)	0.95
C(20)	H(20)	0.95	C(21)	H(21)	0.95
C(22)	H(22)	0.95	C(23)	H(23)	0.95
C(24)	H(24a)	0.95	C(24)	H(24b)	0.95
C(25)	H(25)	0.95	C(26)	H(26c)	0.95
C(26)	H(26a)	0.95	C(26)	H(26b)	0.95
C(27)	H(27a)	0.95	C(27)	H(27b)	0.95
C(27)	H(27c)	0.95			

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(7)	P(7)	C(12)	99.6(6)	C(7)	P(7)	C(18)	99.9(4)
C(12)	P(7)	C(18)	101.5(5)	C(2)	O(1)	C(5)	106.9(7)
C(2)	N(3)	C(4)	110.2(9)	O(1)	C(2)	N(3)	116.3(8)
O(1)	C(2)	C(6)	114.5(9)	N(3)	C(2)	C(6)	129(1)
N(3)	C(4)	C(5)	102.7(9)	N(3)	C(4)	C(24)	129(1)
C(5)	C(4)	C(24)	127(1)	O(1)	C(5)	C(4)	103.6(8)
C(2)	C(6)	C(7)	122(1)	C(2)	C(6)	C(11)	120.6(9)
C(7)	C(6)	C(11)	117.0(9)	P(7)	C(7)	C(6)	116.9(7)
P(7)	C(7)	C(8)	120.0(7)	C(6)	C(7)	C(8)	121.2(8)
C(7)	C(8)	C(9)	120.9(9)	C(8)	C(9)	C(10)	118.7(9)
C(9)	C(10)	C(11)	120.8(9)	C(6)	C(11)	C(10)	120.4(9)
P(7)	C(12)	C(13)	127(1)	P(7)	C(12)	C(17)	117(1)
C(13)	C(12)	C(17)	116(1)	C(12)	C(13)	C(14)	126(1)
C(13)	C(14)	C(15)	115(1)	C(14)	C(15)	C(16)	119(1)
C(15)	C(16)	C(17)	123(1)	C(12)	C(17)	C(16)	120(1)
P(7)	C(18)	C(19)	118.9(9)	P(7)	C(18)	C(23)	124.5(9)
C(19)	C(18)	C(23)	115.9(9)	C(18)	C(19)	C(20)	122(1)
C(19)	C(20)	C(21)	122(1)	C(20)	C(21)	C(22)	118(1)
C(21)	C(22)	C(23)	120(1)	C(18)	C(23)	C(22)	122(1)
C(4)	C(24)	C(25)	125(1)	C(24)	C(25)	C(26)	109(1)
C(24)	C(25)	C(27)	106(2)	C(26)	C(25)	C(27)	104(1)

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
N(3)	C(4)	H(4)	92.7	N(3)	C(4)	H(28)	86.4
C(5)	C(4)	H(4)	92.8	C(5)	C(4)	H(28)	87.0
C(24)	C(4)	H(4)	93.4	C(24)	C(4)	H(28)	87.5
H(4)	C(4)	H(28)	179.0	O(1)	C(5)	H(5a)	110.6
O(1)	C(5)	H(5b)	111.9	C(4)	C(5)	H(5a)	113.0
C(4)	C(5)	H(5b)	108.2	H(5a)	C(5)	H(5b)	109.5
C(7)	C(8)	H(8)	117.7	C(9)	C(8)	H(8)	121.4
C(8)	C(9)	H(9)	119.6	C(10)	C(9)	H(9)	121.6
C(9)	C(10)	H(10)	117.9	C(11)	C(10)	H(10)	121.3
C(6)	C(11)	H(11)	121.3	C(10)	C(11)	H(11)	118.2
C(12)	C(13)	H(13)	116.9	C(14)	C(13)	H(13)	117.0
C(13)	C(14)	H(14)	121.7	C(15)	C(14)	H(14)	122.9
C(14)	C(15)	H(15)	120.4	C(16)	C(15)	H(15)	120.4
C(15)	C(16)	H(16)	119.0	C(17)	C(16)	H(16)	118.1
C(12)	C(17)	H(17)	120.1	C(16)	C(17)	H(17)	119.9
C(18)	C(19)	H(19)	119.1	C(20)	C(19)	H(19)	118.9
C(19)	C(20)	H(20)	120.0	C(21)	C(20)	H(20)	118.0
C(20)	C(21)	H(21)	121.2	C(22)	C(21)	H(21)	121.0
C(21)	C(22)	H(22)	119.1	C(23)	C(22)	H(22)	120.6
C(18)	C(23)	H(23)	119.1	C(22)	C(23)	H(23)	119.2
C(4)	C(24)	H(24a)	107.5	C(4)	C(24)	H(24b)	101.9
C(25)	C(24)	H(24a)	105.9	C(25)	C(24)	H(24b)	106.1
H(24a)	C(24)	H(24b)	109.5	C(24)	C(25)	H(25)	113.9
C(26)	C(25)	H(25)	111.6	C(27)	C(25)	H(25)	110.9

Table 6. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
C(25)	C(26)	H(26c)	111.2	C(25)	C(26)	H(26a)	108.7
C(25)	C(26)	H(26b)	108.5	H(26c)	C(26)	H(26a)	109.5
H(26c)	C(26)	H(26b)	109.5	H(26a)	C(26)	H(26b)	109.5
C(25)	C(27)	H(27a)	108.2	C(25)	C(27)	H(27b)	112.3
C(25)	C(27)	H(27c)	107.8	H(27a)	C(27)	H(27b)	109.5
H(27a)	C(27)	H(27c)	109.5	H(27b)	C(27)	H(27c)	109.5

Table 7. Non-bonded Contacts out to 3.60 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
O(1)	C(27)	3.59(2)	76602				

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 coordinates 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 for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates 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.

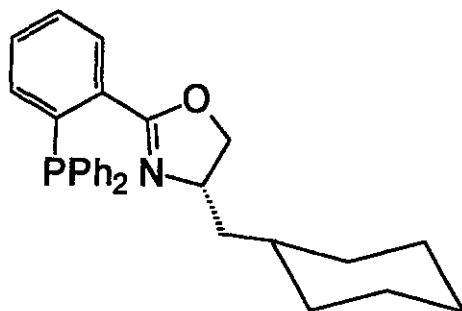
An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1) X, Y, Z (2) -X, -Y, -Z

Appendix 2

X-ray structure report for compound [71]



Experimental

Data Collection

A clear plate crystal of $C_{28}H_{30}NOP$ having approximate dimensions of 0.10 x 0.10 x 0.03 mm was mounted on a glass fiber. 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 15 carefully centered reflections in the range $28.82 < 2\theta < 40.63^\circ$ corresponded to a primitive triclinic cell with dimensions:

$$\begin{aligned} a &= 9.916(2) \text{ \AA} & \alpha &= 94.79(2)^\circ \\ b &= 13.636(3) \text{ \AA} & \beta &= 103.87(2)^\circ \\ c &= 9.831(3) \text{ \AA} & \gamma &= 108.29(2)^\circ \\ V &= 1206.9(5) \text{ \AA}^3 \end{aligned}$$

For $Z = 2$ and F.W. = 427.52, the calculated density is 1.18 g/cm³. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$$P\bar{1} (\#2)$$

The data were 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 0.07° with a take-off angle of 6.0° . Scans of $(1.21 + 0.35 \tan \theta)^\circ$ were made at a speed of $16.0^\circ/\text{min}$ (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).

Data Reduction

Of the 3609 reflections which were collected, 3368 were unique ($R_{int} = 0.120$). The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards increased by 1.1%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ , for Cu-K α radiation is 11.3 cm^{-1} . An empirical absorption correction using the program DIFABS¹ was applied which resulted in transmission factors ranging from 0.65 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = $5.33393e-05$).

Structure Solution and Refinement

The structure was solved by direct methods² and expanded using Fourier techniques³. 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 2657 observed reflections ($I > 3.00\sigma(I)$) and 290 variable parameters and converged (largest parameter shift was 0.08 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.077$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)} = 0.078$$

The standard deviation of an observation of unit weight⁵ was 5.08. The weighting scheme was based on counting statistics and included a factor ($p = 0.006$) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin \theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.24 and -0.28 $e^-/\text{\AA}^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber⁶. Anomalous dispersion effects were included in Fcalc⁷; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley⁸. The values for the mass attenuation coefficients are those of Creagh and Hubbel⁹. All calculations were performed using the teXsan¹⁰ crystallographic software package of Molecular Structure Corporation.

References

- (1) DIFABS: Walker, N. & Stuart, Acta Cryst. A39, 158-166 (1983). An empirical absorption correction program.
- (2) SIR92: Altomare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.
- (3) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.
- (4) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

$$\text{where } w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$$

$\sigma_c(Fo) = \text{e.s.d. based on counting statistics}$

$p = \text{p-factor}$

- (5) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(6) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(7) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(8) Creagh, D. C. & McAuley, W.J. ; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(9) Creagh, D. C. & Hubbell, J.H.; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(10) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	C ₂₃ H ₃₀ NOP
Formula Weight	427.52
Crystal Color, Habit	clear, plate
Crystal Dimensions	0.10 X 0.10 X 0.03 mm
Crystal System	triclinic
Lattice Type	Primitive
No. of Reflections Used for Unit	
Cell Determination (2 θ range)	15 (28.8 - 40.6°)
Omega Scan Peak Width	
at Half-height	0.07°
Lattice Parameters	a = 9.916(2) Å b = 13.636(3) Å c = 9.831(3) Å α = 94.79(2)° β = 103.87(2)° γ = 108.29(2)°
	V = 1206.9(5) Å ³
Space Group	P $\bar{1}$ (#2)
Z value	2
D _{calc}	1.176 g/cm ³
F ₀₀₀	456.00
μ (CuK α)	11.28 cm ⁻¹

B. Intensity Measurements

Diffractometer	Rigaku AFC7S
Radiation	CuK α ($\lambda = 1.54178 \text{ \AA}$) graphite monochromated
Attenuator	Ni foil (factor = 9.42)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal 13.0 mm vertical
Crystal to Detector Distance	400 mm
Voltage, Current	0kV, 0mA
Temperature	20.0°C
Scan Type	ω
Scan Rate	16.0°/min (in ω) (up to 4 scans)
Scan Width	(1.21 + 0.35 tan θ)°
$2\theta_{max}$	120.1°
No. of Reflections Measured	Total: 3609 Unique: 3368 ($R_{int} = 0.120$)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.6532 - 1.0000) Decay (1.05% increase) Secondary Extinction (coefficient: 5.33393e-05)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(Fo - Fc)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{r^2}{4} Fo^2]^{-1}$
p-factor	0.0060
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I > 3.00\sigma(I)$)	2657

No. Variables	290
Reflection/Parameter Ratio	9.16
Residuals: R; Rw	0.077 ; 0.078
Goodness of Fit Indicator	5.08
Max Shift/Error in Final Cycle	0.08
Maximum peak in Final Diff. Map	$0.24 e^{-}/\text{\AA}^3$
Minimum peak in Final Diff. Map	$-0.28 e^{-}/\text{\AA}^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq} and occupancy

atom	x	y	z	B_{eq}	occ
P(7)	0.2954(1)	0.24679(9)	0.5938(1)	4.55(3)	
O(1)	0.2566(4)	0.4285(3)	0.2364(4)	7.1(1)	
N(3)	0.2430(5)	0.4137(3)	0.4581(5)	6.6(1)	
C(2)	0.2369(5)	0.3688(4)	0.3396(5)	5.1(1)	
C(4)	0.276(1)	0.5267(5)	0.4520(7)	10.4(2)	
C(5)	0.2814(7)	0.5330(5)	0.3029(7)	8.2(2)	
C(6)	0.2122(4)	0.2581(4)	0.2992(5)	4.7(1)	
C(7)	0.2259(4)	0.1924(4)	0.4031(5)	4.6(1)	
C(8)	0.1963(5)	0.0871(4)	0.3528(5)	5.4(1)	
C(9)	0.1594(6)	0.0472(4)	0.2093(6)	6.4(1)	
C(10)	0.1478(6)	0.1124(5)	0.1114(5)	6.8(2)	
C(11)	0.1757(6)	0.2169(5)	0.1558(5)	6.2(1)	
C(12)	0.1271(4)	0.2439(3)	0.6409(5)	4.2(1)	
C(13)	-0.0154(5)	0.1881(4)	0.5537(5)	5.6(1)	
C(14)	-0.1380(5)	0.1882(4)	0.5967(6)	6.4(2)	
C(15)	-0.1227(6)	0.2429(5)	0.7230(7)	6.7(2)	
C(16)	0.0191(6)	0.3002(5)	0.8144(6)	6.6(2)	
C(17)	0.1404(5)	0.2986(4)	0.7682(5)	5.8(1)	
C(18)	0.3282(5)	0.1333(4)	0.6669(5)	4.8(1)	
C(19)	0.4569(6)	0.1169(5)	0.6576(6)	6.9(2)	
C(20)	0.4967(7)	0.0377(6)	0.7147(8)	8.6(2)	
C(21)	0.4149(8)	-0.0216(5)	0.7900(7)	8.0(2)	
C(22)	0.2874(8)	-0.0078(5)	0.8025(7)	8.4(2)	
C(23)	0.2432(6)	0.0698(4)	0.7385(6)	6.4(1)	

Table 1. Atomic coordinates and B_{iso}/B_{eq} and occupancy (continued)

atom	x	y	z	B_{eq}	occ
C(24)	0.235(2)	0.593(1)	0.530(1)	7.2(4)	1/2
C(24')	0.356(1)	0.594(1)	0.569(1)	7.0(3)	1/2
C(25)	0.2823(9)	0.5870(5)	0.6983(7)	8.6(2)	
C(26)	0.425(1)	0.637(1)	0.800(1)	16.9(5)	
C(27)	0.419(2)	0.633(1)	0.949(2)	19.1(6)	
C(28)	0.327(2)	0.6921(8)	0.9846(9)	13.9(4)	
C(29)	0.181(1)	0.650(1)	0.882(2)	17.9(5)	
C(30)	0.187(1)	0.6468(9)	0.734(1)	14.0(3)	
H(5a)	0.3751	0.5790	0.3015	9.7984	
H(5b)	0.2060	0.5573	0.2547	9.7984	
H(8)	0.2009	0.0409	0.4194	6.4256	
H(9)	0.1430	-0.0245	0.1789	7.6282	
H(10)	0.1200	0.0852	0.0126	8.1198	
H(11)	0.1696	0.2618	0.0873	7.3928	
H(13)	-0.0278	0.1497	0.4636	6.6719	
H(14)	-0.2342	0.1494	0.5361	7.6698	
H(15)	-0.2082	0.2429	0.7505	8.0497	
H(16)	0.0312	0.3382	0.9046	7.9691	
H(17)	0.2369	0.3375	0.8281	6.9196	
H(19)	0.5189	0.1616	0.6112	8.2962	
H(20)	0.5817	0.0242	0.7006	10.3360	
H(21)	0.4471	-0.0725	0.8351	9.5384	
H(22)	0.2293	-0.0508	0.8536	10.0134	
H(23)	0.1533	0.0786	0.7451	7.6403	

Table 1. Atomic coordinates and B_{iso}/B_{eq} and occupancy (continued)

atom	x	y	z	B_{eq}	occ
H(26a)	0.4909	0.6037	0.7819	20.0206	
H(26b)	0.4616	0.7090	0.7903	20.0206	
H(27a)	0.3775	0.5621	0.9590	22.7459	
H(27b)	0.5163	0.6630	1.0117	22.7459	
H(28a)	0.3180	0.6848	1.0775	16.7009	
H(28b)	0.3718	0.7639	0.9807	16.7009	
H(29a)	0.1322	0.5810	0.8953	21.5297	
H(29b)	0.1256	0.6933	0.8990	21.5297	
H(30a)	0.2250	0.7162	0.7176	16.8200	
H(30b)	0.0890	0.6132	0.6728	16.8200	

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^* \cos \gamma + 2U_{13}aa^*cc^* \cos \beta + 2U_{23}bb^*cc^* \cos \alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
P(7)	0.0405(7)	0.0628(8)	0.0587(7)	0.0112(5)	0.0038(5)	0.0074(6)
O(1)	0.118(3)	0.082(3)	0.074(2)	0.033(2)	0.029(2)	0.028(2)
N(3)	0.102(4)	0.076(3)	0.073(3)	0.032(3)	0.023(3)	0.017(2)
C(2)	0.052(3)	0.077(4)	0.061(3)	0.019(2)	0.006(2)	0.022(3)
C(4)	0.26(1)	0.067(4)	0.083(5)	0.058(5)	0.059(6)	0.029(4)
C(5)	0.129(6)	0.071(4)	0.106(5)	0.030(4)	0.025(4)	0.028(4)
C(6)	0.041(3)	0.071(3)	0.058(3)	0.014(2)	0.008(2)	0.010(2)
C(7)	0.041(3)	0.062(3)	0.063(3)	0.016(2)	0.006(2)	0.009(2)
C(8)	0.058(3)	0.070(3)	0.067(3)	0.020(2)	0.004(2)	0.004(3)
C(9)	0.075(4)	0.073(4)	0.077(4)	0.023(3)	0.002(3)	-0.008(3)
C(10)	0.090(4)	0.086(4)	0.061(3)	0.017(3)	0.006(3)	-0.005(3)
C(11)	0.076(4)	0.090(4)	0.060(3)	0.020(3)	0.016(3)	0.014(3)
C(12)	0.046(3)	0.051(3)	0.061(3)	0.017(2)	0.007(2)	0.011(2)
C(13)	0.053(3)	0.079(4)	0.076(3)	0.024(3)	0.010(2)	0.007(3)
C(14)	0.058(3)	0.089(4)	0.092(4)	0.026(3)	0.014(3)	0.012(3)
C(15)	0.060(4)	0.095(4)	0.114(5)	0.040(3)	0.031(3)	0.028(4)
C(16)	0.091(4)	0.098(4)	0.078(4)	0.048(3)	0.032(3)	0.015(3)
C(17)	0.063(3)	0.087(4)	0.068(3)	0.028(3)	0.011(3)	0.010(3)
C(18)	0.047(3)	0.069(3)	0.058(3)	0.019(2)	0.003(2)	0.005(2)
C(19)	0.053(3)	0.098(4)	0.109(4)	0.026(3)	0.012(3)	0.028(3)
C(20)	0.069(4)	0.121(6)	0.139(6)	0.051(4)	0.006(4)	0.026(5)
C(21)	0.105(5)	0.101(5)	0.096(5)	0.053(4)	0.001(4)	0.017(4)
C(22)	0.141(6)	0.091(5)	0.095(5)	0.042(4)	0.036(4)	0.039(4)
C(23)	0.081(4)	0.080(4)	0.089(4)	0.034(3)	0.026(3)	0.029(3)

Table 2. Anisotropic Displacement Parameters (continued)

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(24)	0.10(1)	0.083(9)	0.087(9)	0.041(8)	0.018(8)	0.012(7)
C(24')	0.082(9)	0.084(8)	0.083(8)	0.008(7)	0.028(7)	0.002(7)
C(25)	0.135(7)	0.091(5)	0.096(5)	0.028(4)	0.043(5)	0.003(4)
C(26)	0.123(8)	0.39(2)	0.167(9)	0.13(1)	0.057(8)	0.03(1)
C(27)	0.22(1)	0.32(2)	0.18(1)	0.17(1)	-0.05(1)	0.01(1)
C(28)	0.24(1)	0.163(9)	0.087(6)	0.034(9)	0.031(7)	-0.001(6)
C(29)	0.19(1)	0.36(2)	0.19(1)	0.13(1)	0.13(1)	0.03(1)
C(30)	0.105(7)	0.22(1)	0.169(9)	0.062(7)	-0.016(6)	-0.009(8)

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(\AA)

atom	atom	distance	atom	atom	distance
P(7)	C(7)	1.835(4)	P(7)	C(12)	1.826(4)
P(7)	C(18)	1.845(5)	O(1)	C(2)	1.365(5)
O(1)	C(5)	1.437(7)	N(3)	C(2)	1.248(6)
N(3)	C(4)	1.481(7)	C(2)	C(6)	1.454(7)
C(4)	C(5)	1.487(8)	C(4)	C(24)	1.36(1)
C(4)	C(24')	1.31(1)	C(6)	C(7)	1.424(6)
C(6)	C(11)	1.388(6)	C(7)	C(8)	1.392(6)
C(8)	C(9)	1.386(6)	C(9)	C(10)	1.372(7)
C(10)	C(11)	1.374(7)	C(12)	C(13)	1.394(6)
C(12)	C(17)	1.357(6)	C(13)	C(14)	1.380(7)
C(14)	C(15)	1.343(7)	C(15)	C(16)	1.408(7)
C(16)	C(17)	1.390(7)	C(18)	C(19)	1.385(7)
C(18)	C(23)	1.373(6)	C(19)	C(20)	1.380(8)
C(20)	C(21)	1.355(8)	C(21)	C(22)	1.367(9)
C(22)	C(23)	1.407(7)	C(24)	C(24')	1.17(2)
C(24)	C(25)	1.62(1)	C(24')	C(25)	1.61(1)
C(25)	C(26)	1.44(1)	C(25)	C(30)	1.51(1)
C(26)	C(27)	1.48(2)	C(27)	C(28)	1.48(2)
C(28)	C(29)	1.46(1)	C(29)	C(30)	1.47(1)

Table 4. Bond Lengths(\AA)

atom	atom	distance	atom	atom	distance
C(5)	H(5a)	0.95	C(5)	H(5b)	0.95
C(8)	H(8)	0.95	C(9)	H(9)	0.95
C(10)	H(10)	0.95	C(11)	H(11)	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
C(17)	H(17)	0.95	C(19)	H(19)	0.95
C(20)	H(20)	0.95	C(21)	H(21)	0.95
C(22)	H(22)	0.95	C(23)	H(23)	0.95
C(26)	H(26a)	0.95	C(26)	H(26b)	0.95
C(27)	H(27a)	0.95	C(27)	H(27b)	0.95
C(28)	H(28a)	0.95	C(28)	H(28b)	0.95
C(29)	H(29a)	0.95	C(29)	H(29b)	0.95
C(30)	H(30a)	0.94	C(30)	H(30b)	0.95

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(7)	P(7)	C(12)	102.7(2)	C(7)	P(7)	C(18)	100.5(2)
C(12)	P(7)	C(18)	101.0(2)	C(2)	O(1)	C(5)	104.8(4)
C(2)	N(3)	C(4)	107.7(5)	O(1)	C(2)	N(3)	117.7(5)
O(1)	C(2)	C(6)	115.6(5)	N(3)	C(2)	C(6)	126.7(5)
N(3)	C(4)	C(5)	103.3(5)	N(3)	C(4)	C(24)	124.8(8)
N(3)	C(4)	C(24')	118.0(8)	C(5)	C(4)	C(24)	123.9(8)
C(5)	C(4)	C(24')	129.0(8)	C(24)	C(4)	C(24')	51.8(7)
O(1)	C(5)	C(4)	106.4(5)	C(2)	C(6)	C(7)	121.4(4)
C(2)	C(6)	C(11)	118.7(5)	C(7)	C(6)	C(11)	119.9(5)
P(7)	C(7)	C(6)	121.2(3)	P(7)	C(7)	C(8)	121.8(4)
C(6)	C(7)	C(8)	116.8(4)	C(7)	C(8)	C(9)	122.5(5)
C(8)	C(9)	C(10)	119.5(5)	C(9)	C(10)	C(11)	120.1(5)
C(6)	C(11)	C(10)	121.1(5)	P(7)	C(12)	C(13)	123.8(4)
P(7)	C(12)	C(17)	118.5(3)	C(13)	C(12)	C(17)	117.8(4)
C(12)	C(13)	C(14)	120.7(5)	C(13)	C(14)	C(15)	120.7(5)
C(14)	C(15)	C(16)	120.4(5)	C(15)	C(16)	C(17)	117.6(5)
C(12)	C(17)	C(16)	122.8(5)	P(7)	C(18)	C(19)	116.1(4)
P(7)	C(18)	C(23)	125.9(4)	C(19)	C(18)	C(23)	117.8(5)
C(18)	C(19)	C(20)	121.3(5)	C(19)	C(20)	C(21)	120.1(6)
C(20)	C(21)	C(22)	120.4(6)	C(21)	C(22)	C(23)	119.4(6)
C(18)	C(23)	C(22)	120.8(5)	C(4)	C(24)	C(24')	62.0(9)
C(4)	C(24)	C(25)	111.9(9)	C(24')	C(24)	C(25)	68.5(9)
C(4)	C(24')	C(24)	66(1)	C(4)	C(24')	C(25)	115.1(9)
C(24)	C(24')	C(25)	69(1)	C(24)	C(25)	C(24')	42.4(6)

Table 5. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
C(24)	C(25)	C(26)	128.3(9)	C(24)	C(25)	C(30)	93.3(8)
C(24')	C(25)	C(26)	91.4(8)	C(24')	C(25)	C(30)	127.4(9)
C(26)	C(25)	C(30)	105.0(7)	C(25)	C(26)	C(27)	112.7(9)
C(26)	C(27)	C(28)	110(1)	C(27)	C(28)	C(29)	108.9(9)
C(28)	C(29)	C(30)	112.7(9)	C(25)	C(30)	C(29)	113.2(9)

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
O(1)	C(5)	H(5a)	110.3	O(1)	C(5)	H(5b)	110.1
C(4)	C(5)	H(5a)	110.3	C(4)	C(5)	H(5b)	110.1
H(5a)	C(5)	H(5b)	109.5	C(7)	C(8)	H(8)	118.7
C(9)	C(8)	H(8)	118.8	C(8)	C(9)	H(9)	120.3
C(10)	C(9)	H(9)	120.2	C(9)	C(10)	H(10)	119.9
C(11)	C(10)	H(10)	119.9	C(6)	C(11)	H(11)	119.3
C(10)	C(11)	H(11)	119.5	C(12)	C(13)	H(13)	119.4
C(14)	C(13)	H(13)	119.8	C(13)	C(14)	H(14)	119.6
C(15)	C(14)	H(14)	119.7	C(14)	C(15)	H(15)	119.7
C(16)	C(15)	H(15)	119.9	C(15)	C(16)	H(16)	121.1
C(17)	C(16)	H(16)	121.3	C(12)	C(17)	H(17)	118.5
C(16)	C(17)	H(17)	118.6	C(18)	C(19)	H(19)	119.0
C(20)	C(19)	H(19)	119.7	C(19)	C(20)	H(20)	119.9
C(21)	C(20)	H(20)	120.0	C(20)	C(21)	H(21)	119.6
C(22)	C(21)	H(21)	120.0	C(21)	C(22)	H(22)	119.9
C(23)	C(22)	H(22)	120.6	C(18)	C(23)	H(23)	119.5
C(22)	C(23)	H(23)	119.7	C(25)	C(26)	H(26a)	108.8
C(25)	C(26)	H(26b)	108.9	C(27)	C(26)	H(26a)	108.5
C(27)	C(26)	H(26b)	108.8	H(26a)	C(26)	H(26b)	109.1
C(26)	C(27)	H(27a)	109.6	C(26)	C(27)	H(27b)	109.7
C(28)	C(27)	H(27a)	109.2	C(28)	C(27)	H(27b)	108.8
H(27a)	C(27)	H(27b)	109.7	C(27)	C(28)	H(28a)	109.5
C(27)	C(28)	H(28b)	109.7	C(29)	C(28)	H(28a)	109.6
C(29)	C(28)	H(28b)	109.4	H(28a)	C(28)	H(28b)	109.7

Table 6. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
C(28)	C(29)	H(29a)	108.3	C(28)	C(29)	H(29b)	108.6
C(30)	C(29)	H(29a)	108.9	C(30)	C(29)	H(29b)	109.1
H(29a)	C(29)	H(29b)	109.4	C(25)	C(30)	H(30a)	109.1
C(25)	C(30)	H(30b)	108.3	C(29)	C(30)	H(30a)	108.5
C(29)	C(30)	H(30b)	108.0	H(30a)	C(30)	H(30b)	109.6

Table 7. Non-bonded Contacts out to 3.60 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
C(10)	C(10)	3.60(1)	2				

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 coordinates 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 for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates 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.

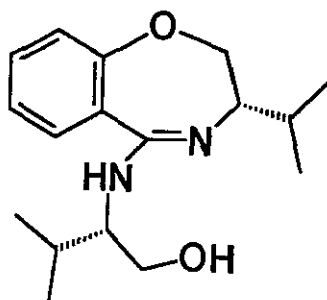
An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1) X, Y, Z (2) -X, -Y, -Z

Appendix 3

X-ray structure report for compound [72]



Experimental

Data Collection

A clear needle crystal of $C_{17}H_{26}N_2O_2$ having approximate dimensions of 0.10 x 0.10 x 0.30 mm was mounted on a glass fiber. 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 centered reflections in the range $56.48 < 2\theta < 73.48^\circ$ corresponded to a primitive triclinic cell with dimensions:

$$\begin{aligned} a &= 10.788(4) \text{ \AA} & \alpha &= 94.00(1)^\circ \\ b &= 12.498(2) \text{ \AA} & \beta &= 90.87(2)^\circ \\ c &= 6.315(1) \text{ \AA} & \gamma &= 77.73(2)^\circ \\ V &= 830.0(4) \text{ \AA}^3 \end{aligned}$$

For $Z = 2$ and F.W. = 290.40, the calculated density is 1.16 g/cm 3 . Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

P1 (#1)

The data were 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 0.13° with a take-off angle of 6.0° . Scans of $(1.05 + 0.35 \tan \theta)^\circ$ were made at a speed of $16.0^\circ/\text{min}$ (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 3 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).

Data Reduction

Of the 2614 reflections which were collected, 2461 were unique ($R_{int} = 0.070$). The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards decreased by 0.1%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ , for Cu-K α radiation is 6.0 cm^{-1} . An empirical absorption correction using the program DIFABS¹ was applied which resulted in transmission factors ranging from 0.61 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = $4.55327e-07$).

Structure Solution and Refinement

The structure was solved by direct methods² and expanded using Fourier techniques³. 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 1859 observed reflections ($I > 2.00\sigma(I)$) and 380 variable parameters and converged (largest parameter shift was 0.44 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.077$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2 / \Sigma w Fo^2)} = 0.057$$

The standard deviation of an observation of unit weight⁵ was 5.11. The weighting scheme was based on counting statistics and included a factor ($p = 0.001$) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin \theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.24 and $-0.25 e^-/\text{\AA}^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber⁶. Anomalous dispersion effects were included in F_{calc} ; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley⁸. The values for the mass attenuation coefficients are those of Creagh and Hubbel⁹. All calculations were performed using the teXsan¹⁰ crystallographic software package of Molecular Structure Corporation.

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) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(4) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

$$\text{where } w = \frac{1}{\sigma^2(Fo)} = \frac{4Fo^2}{\sigma^2(Fo^2)}$$

$$\sigma^2(Fo^2) = \frac{S^2(C+R^2B) + (pFo^2)^2}{Lp^2}$$

S = Scan rate

C = Total integrated peak count

R = Ratio of scan time to background counting time

B = Total background count

Lp = Lorentz-polarization factor

p = p-factor

(5) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|F_o| - |F_c|)^2 / (N_o - N_v)}$$

where: N_o = number of observations

N_v = number of variables

(6) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(7) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(8) Creagh, D. C. & McAuley, W.J. ; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(9) Creagh, D. C. & Hubbell, J.H.; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(10) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{17}H_{26}N_2O_2$
Formula Weight	290.40
Crystal Color, Habit	clear, needle
Crystal Dimensions	0.10 X 0.10 X 0.30 mm
Crystal System	triclinic
Lattice Type	Primitive
No. of Reflections Used for Unit	
Cell Determination (2θ range)	25 (56.5 - 73.5°)
Omega Scan Peak Width at Half-height	0.13°
Lattice Parameters	$a = 10.788(4) \text{ \AA}$ $b = 12.498(2) \text{ \AA}$ $c = 6.315(1) \text{ \AA}$ $\alpha = 94.00(1)^\circ$ $\beta = 90.87(2)^\circ$ $\gamma = 77.73(2)^\circ$
	$V = 830.0(4) \text{ \AA}^3$
Space Group	P1 (#1)
Z value	2
D_{calc}	1.162 g/cm ³
F_{000}	316.00
$\mu(\text{CuK}\alpha)$	6.03 cm ⁻¹

B. Intensity Measurements

Diffractometer	Rigaku AFC7S
Radiation	CuK α ($\lambda = 1.54178 \text{ \AA}$) graphite monochromated
Attenuator	Ni foil (factor = 9.42)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal 13.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	20.0°C
Scan Type	ω
Scan Rate	16.0°/min (in ω) (up to 3 scans)
Scan Width	(1.05 + 0.35 tan θ)°
$2\theta_{max}$	120.1°
No. of Reflections Measured	Total: 2614 Unique: 2461 ($R_{int} = 0.070$)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.6117 - 1.0000) Decay (0.11% decline) Secondary Extinction (coefficient: 4.55327e-07)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(F_o - F_c)^2$
Least Squares Weights	$\frac{1}{\sigma^2(F_o)} = \frac{4F_o^2}{\sigma^2(F\sigma^2)}$
p-factor	0.0010
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I > 2.00\sigma(I)$)	1859
No. Variables	380

Reflection/Parameter Ratio	4.89
Residuals: R; Rw	0.077 ; 0.057
Goodness of Fit Indicator	5.11
Max Shift/Error in Final Cycle	0.44
Maximum peak in Final Diff. Map	$0.24 e^{-}/\text{\AA}^3$
Minimum peak in Final Diff. Map	$-0.25 e^{-}/\text{\AA}^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
O(1)	0.1947(8)	0.5623(8)	0.653(1)	5.9(1)
O(15)	0.3553(8)	0.8570(8)	0.989(1)	5.6(1)
O(21)	0.5355(8)	1.1358(8)	1.471(1)	5.8(1)
O(35)	0.8599(8)	0.8420(7)	1.129(1)	5.8(1)
N(7)	0.1361(8)	0.7679(8)	1.165(1)	3.43(9)
N(8)	0.3166(8)	0.6493(8)	1.018(1)	3.60(9)
N(27)	0.5899(8)	0.9349(8)	0.947(1)	3.43(10)
N(28)	0.7121(8)	1.0420(8)	1.126(1)	3.65(9)
C(1)	0.1196(9)	0.5403(8)	0.806(2)	4.5(1)
C(2)	0.1143(9)	0.5925(8)	1.005(2)	3.9(1)
C(3)	0.0271(9)	0.5748(8)	1.148(1)	4.5(1)
C(4)	-0.0520(9)	0.5026(9)	1.087(2)	5.9(2)
C(5)	-0.0445(10)	0.4512(9)	0.888(2)	6.3(2)
C(6)	0.0388(10)	0.4713(9)	0.749(2)	6.0(2)
C(7)	0.1977(9)	0.6698(8)	1.060(1)	3.30(10)
C(9)	0.3679(9)	0.5409(9)	0.920(2)	4.2(1)
C(10)	0.3325(10)	0.5374(9)	0.682(2)	5.7(1)
C(11)	0.2065(8)	0.8446(8)	1.274(2)	3.5(1)
C(12)	0.1143(9)	0.9135(8)	1.438(1)	4.3(1)
C(13)	0.0746(9)	0.8404(9)	1.602(2)	6.3(2)
C(14)	0.1684(9)	1.0072(9)	1.555(2)	5.5(2)
C(15)	0.2578(9)	0.9168(8)	1.122(1)	4.7(1)
C(16)	0.5124(10)	0.5190(9)	0.928(2)	6.5(1)
C(17)	0.5497(10)	0.518(1)	1.167(2)	9.7(2)

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
C(18)	0.5759(10)	0.4110(10)	0.814(2)	8.2(2)
C(21)	0.4562(9)	1.1634(8)	1.300(2)	4.2(1)
C(22)	0.4836(9)	1.1073(8)	1.105(2)	3.7(1)
C(23)	0.3969(9)	1.1318(8)	0.948(1)	4.7(1)
C(24)	0.2841(9)	1.2160(9)	0.980(1)	6.1(2)
C(25)	0.2620(9)	1.2663(9)	1.184(2)	6.4(2)
C(26)	0.3510(10)	1.2399(9)	1.344(2)	5.9(2)
C(27)	0.6018(9)	1.0266(8)	1.065(1)	3.40(10)
C(29)	0.7154(9)	1.1482(8)	1.238(2)	3.71(10)
C(30)	0.6628(9)	1.1500(9)	1.461(2)	4.9(1)
C(31)	0.6967(9)	0.8556(8)	0.852(2)	3.3(1)
C(32)	0.6435(9)	0.7816(8)	0.680(2)	4.0(1)
C(33)	0.5610(10)	0.8494(9)	0.519(2)	6.0(2)
C(34)	0.7434(9)	0.6967(9)	0.567(2)	7.7(2)
C(35)	0.7813(9)	0.7846(8)	1.009(1)	4.5(1)
C(36)	0.8549(9)	1.1594(8)	1.257(2)	4.6(1)
C(37)	0.9110(10)	1.1495(10)	1.037(2)	7.6(2)
C(38)	0.871(1)	1.2646(9)	1.377(2)	6.9(2)
H(3)	0.0207	0.6196	1.2792	5.4643
H(4)	-0.1093	0.4950	1.1773	7.1194
H(5)	-0.0984	0.4128	0.8333	7.8307
H(6)	0.0430	0.4472	0.5988	7.0838
H(7)	0.1224	0.8069	1.0422	7.1679
H(9)	0.3393	0.4966	0.9805	5.0174

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(10b)	0.3642	0.5992	0.6039	6.4691
H(10a)	0.3632	0.4755	0.6105	6.4691
H(11)	0.2769	0.8121	1.3370	3.9301
H(12)	0.0405	0.9557	1.3530	5.0785
H(13a)	0.0128	0.8944	1.6847	7.4750
H(13b)	0.0402	0.7941	1.5203	7.4750
H(13c)	0.1468	0.8185	1.6717	7.4750
H(14a)	0.2424	0.9875	1.6235	6.3600
H(14b)	0.1918	1.0632	1.4429	6.3600
H(14c)	0.1069	1.0608	1.6379	6.3600
H(15b)	0.1893	0.9570	1.0243	5.6041
H(15a)	0.2878	0.9803	1.1933	5.6041
H(15o)	0.3776	0.7906	0.9362	7.1679
H(16)	0.5410	0.5872	0.8531	7.7922
H(17b)	0.6381	0.5228	1.1749	12.5711
H(17c)	0.5057	0.5948	1.2323	12.5711
H(17a)	0.5257	0.4679	1.2185	12.5711
H(18b)	0.5580	0.4229	0.6568	9.9146
H(18c)	0.6629	0.4073	0.8294	9.9146
H(18a)	0.5400	0.3643	0.8593	9.9146
H(23)	0.4095	1.1029	0.8000	5.4458
H(24)	0.2254	1.2494	0.8611	7.1473
H(25)	0.1862	1.3282	1.2058	7.2248
H(26)	0.3357	1.2856	1.4716	7.1532

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(27)	0.5025	0.8976	0.9729	7.1679
H(29)	0.6666	1.2179	1.1572	4.6817
H(30a)	0.6637	1.2283	1.5250	5.3672
H(30b)	0.7133	1.1023	1.5230	5.3672
H(31)	0.7474	0.9058	0.7774	3.9114
H(32)	0.5904	0.7542	0.7413	4.6037
H(33a)	0.6093	0.8995	0.4377	6.7694
H(33b)	0.5285	0.8105	0.4111	6.7694
H(33c)	0.4918	0.9074	0.5813	6.7694
H(34a)	0.7931	0.6628	0.6611	9.0098
H(34b)	0.7054	0.6607	0.4645	9.0098
H(34c)	0.7977	0.7407	0.4819	9.0098
H(35b)	0.7277	0.7700	1.0964	5.2728
H(35a)	0.8318	0.7351	0.9235	5.2728
H(35o)	0.8549	0.9407	1.0811	7.1679
H(36)	0.8988	1.1098	1.3234	5.3356
H(37b)	0.8690	1.2198	0.9527	9.6710
H(37c)	0.9991	1.1634	1.0435	9.6710
H(37a)	0.9042	1.0931	0.9585	9.6710
H(38b)	0.8273	1.3352	1.2956	8.2084
H(38c)	0.8412	1.2775	1.5069	8.2084
H(38a)	0.9601	1.2753	1.3702	8.2084

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^* \cos \gamma + 2U_{13}aa^*cc^* \cos \beta + 2U_{23}bb^*cc^* \cos \alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	0.085(3)	0.094(3)	0.039(2)	-0.009(3)	-0.012(2)	-0.005(2)
O(15)	0.077(3)	0.077(3)	0.063(3)	-0.034(2)	0.025(2)	-0.017(2)
O(21)	0.076(2)	0.099(3)	0.047(2)	-0.024(3)	0.003(2)	-0.004(2)
O(35)	0.053(2)	0.068(3)	0.087(3)	0.001(2)	-0.038(2)	-0.017(2)
N(7)	0.058(3)	0.044(2)	0.031(2)	-0.019(2)	-0.010(2)	0.000(2)
N(8)	0.043(2)	0.044(2)	0.047(3)	-0.004(2)	-0.004(2)	0.001(2)
N(27)	0.040(2)	0.044(2)	0.045(3)	-0.009(2)	-0.003(2)	-0.003(2)
N(28)	0.048(2)	0.048(2)	0.040(2)	-0.008(2)	-0.007(2)	-0.005(2)
C(1)	0.057(3)	0.050(3)	0.055(3)	0.006(2)	-0.017(2)	0.002(2)
C(2)	0.054(3)	0.045(3)	0.053(3)	-0.020(2)	-0.012(2)	0.010(2)
C(3)	0.040(3)	0.068(4)	0.066(4)	-0.014(3)	-0.015(2)	0.016(3)
C(4)	0.048(4)	0.060(4)	0.123(5)	-0.020(3)	-0.008(4)	0.026(3)
C(5)	0.070(4)	0.060(4)	0.121(5)	-0.035(4)	-0.048(3)	0.027(3)
C(6)	0.082(5)	0.067(4)	0.081(5)	-0.028(3)	-0.051(3)	-0.003(4)
C(7)	0.044(2)	0.047(3)	0.034(3)	-0.010(2)	-0.010(2)	0.003(2)
C(9)	0.048(2)	0.047(3)	0.059(3)	0.000(2)	-0.007(3)	-0.002(2)
C(10)	0.083(3)	0.077(4)	0.056(3)	-0.014(4)	0.008(3)	-0.009(3)
C(11)	0.037(3)	0.037(3)	0.053(3)	-0.001(2)	-0.006(2)	-0.006(2)
C(12)	0.048(3)	0.064(4)	0.045(3)	0.000(2)	-0.003(2)	-0.010(2)
C(13)	0.100(5)	0.094(5)	0.055(4)	-0.041(4)	0.026(3)	-0.001(3)
C(14)	0.094(5)	0.071(4)	0.045(3)	-0.029(3)	-0.001(3)	-0.020(3)
C(15)	0.076(4)	0.067(4)	0.037(3)	-0.021(3)	0.004(2)	0.002(2)
C(16)	0.049(2)	0.069(4)	0.123(5)	-0.010(3)	0.007(3)	-0.028(4)
C(17)	0.064(4)	0.144(7)	0.131(5)	0.010(5)	-0.038(4)	-0.073(6)

Table 2. Anisotropic Displacement Parameters (continued)

atom	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
C(18)	0.097(5)	0.076(5)	0.112(6)	0.029(4)	-0.015(4)	-0.027(4)
C(21)	0.062(3)	0.054(3)	0.047(2)	-0.019(2)	0.007(2)	-0.001(2)
C(22)	0.045(3)	0.053(3)	0.043(2)	-0.006(2)	0.001(2)	0.009(2)
C(23)	0.050(3)	0.077(4)	0.048(3)	-0.010(2)	-0.002(2)	0.002(3)
C(24)	0.051(3)	0.082(5)	0.094(4)	0.007(3)	-0.009(3)	0.031(3)
C(25)	0.062(4)	0.057(4)	0.115(4)	0.005(3)	0.015(3)	-0.007(4)
C(26)	0.079(4)	0.056(4)	0.084(4)	-0.004(3)	0.028(3)	-0.008(3)
C(27)	0.048(2)	0.043(3)	0.037(3)	-0.008(2)	-0.005(2)	0.006(2)
C(29)	0.050(2)	0.038(2)	0.054(3)	-0.009(3)	-0.002(2)	0.003(2)
C(30)	0.074(3)	0.063(4)	0.044(3)	-0.012(3)	-0.008(3)	-0.014(3)
C(31)	0.046(3)	0.038(3)	0.042(3)	-0.009(2)	-0.010(2)	0.000(2)
C(32)	0.066(3)	0.048(3)	0.041(3)	-0.025(2)	-0.015(2)	-0.001(2)
C(33)	0.078(4)	0.077(4)	0.061(4)	0.008(4)	-0.044(3)	-0.005(3)
C(34)	0.084(5)	0.084(5)	0.091(5)	0.035(4)	-0.031(4)	-0.048(4)
C(35)	0.047(3)	0.070(4)	0.048(3)	0.002(2)	-0.024(2)	0.002(3)
C(36)	0.051(3)	0.044(3)	0.083(3)	-0.014(3)	-0.010(3)	0.008(3)
C(37)	0.086(5)	0.120(6)	0.095(4)	-0.058(5)	0.032(4)	-0.023(5)
C(38)	0.126(6)	0.050(4)	0.096(5)	-0.046(4)	-0.005(4)	-0.005(3)

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)	1.35(1)	O(1)	C(10)	1.46(1)
O(15)	C(15)	1.41(1)	O(21)	C(21)	1.39(1)
O(21)	C(30)	1.42(1)	O(35)	C(35)	1.40(1)
N(7)	C(7)	1.39(1)	N(7)	C(11)	1.47(1)
N(8)	C(7)	1.28(1)	N(8)	C(9)	1.45(1)
N(27)	C(27)	1.35(1)	N(27)	C(31)	1.46(1)
N(28)	C(27)	1.29(1)	N(28)	C(29)	1.47(1)
C(1)	C(2)	1.37(1)	C(1)	C(6)	1.38(2)
C(2)	C(3)	1.38(1)	C(2)	C(7)	1.48(1)
C(3)	C(4)	1.40(2)	C(4)	C(5)	1.37(2)
C(5)	C(6)	1.34(2)	C(9)	C(10)	1.55(2)
C(9)	C(16)	1.53(2)	C(11)	C(12)	1.53(1)
C(11)	C(15)	1.55(2)	C(12)	C(13)	1.55(2)
C(12)	C(14)	1.55(2)	C(16)	C(17)	1.56(2)
C(16)	C(18)	1.51(2)	C(21)	C(22)	1.37(1)
C(21)	C(26)	1.34(2)	C(22)	C(23)	1.36(1)
C(22)	C(27)	1.46(1)	C(23)	C(24)	1.44(2)
C(24)	C(25)	1.40(2)	C(25)	C(26)	1.39(2)
C(29)	C(30)	1.53(1)	C(29)	C(36)	1.54(1)
C(31)	C(32)	1.56(1)	C(31)	C(35)	1.53(1)
C(32)	C(33)	1.52(2)	C(32)	C(34)	1.49(2)
C(36)	C(37)	1.51(2)	C(36)	C(38)	1.51(2)

Table 4. Bond Lengths(Å)

atom	atom	distance	atom	atom	distance
O(15)	H(15o)	0.86	N(7)	H(7)	0.94
N(27)	H(27)	1.16	C(3)	H(3)	0.96
C(4)	H(4)	0.87	C(5)	H(5)	0.88
C(6)	H(6)	0.97	C(9)	H(9)	0.81
C(10)	H(10b)	1.06	C(10)	H(10a)	0.87
C(11)	H(11)	0.88	C(12)	H(12)	1.02
C(13)	H(13a)	0.97	C(13)	H(13b)	0.89
C(13)	H(13c)	0.89	C(14)	H(14a)	0.90
C(14)	H(14b)	1.09	C(14)	H(14c)	0.97
C(15)	H(15b)	1.03	C(15)	H(15a)	1.00
C(16)	H(16)	1.10	C(17)	H(17b)	0.97
C(17)	H(17c)	1.03	C(17)	H(17a)	0.82
C(18)	H(18b)	1.02	C(18)	H(18c)	0.93
C(18)	H(18a)	0.83	C(23)	H(23)	0.98
C(24)	H(24)	1.03	C(25)	H(25)	1.00
C(26)	H(26)	0.95	C(29)	H(29)	1.07
C(30)	H(30a)	1.03	C(30)	H(30b)	0.83
C(31)	H(31)	1.05	C(32)	H(32)	0.84
C(33)	H(33a)	1.06	C(33)	H(33b)	0.92
C(33)	H(33c)	0.99	C(34)	H(34a)	0.87
C(34)	H(34b)	0.90	C(34)	H(34c)	1.06
C(35)	H(35b)	0.86	C(35)	H(35a)	0.89
C(36)	H(36)	0.83	C(37)	H(37b)	1.07
C(37)	H(37c)	1.00	C(37)	H(37a)	0.85

Table 4. Bond Lengths(\AA) (continued)

atom	atom	distance	atom	atom	distance
C(38)	H(38b)	1.07	C(38)	H(38c)	0.88
C(38)	H(38a)	1.00			

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(1)	O(1)	C(10)	119.7(9)	C(21)	O(21)	C(30)	118.4(9)
C(7)	N(7)	C(11)	121.9(9)	C(7)	N(8)	C(9)	115.5(9)
C(27)	N(27)	C(31)	123.7(9)	C(27)	N(28)	C(29)	116.5(9)
O(1)	C(1)	C(2)	121(1)	O(1)	C(1)	C(6)	117(1)
C(2)	C(1)	C(6)	120(1)	C(1)	C(2)	C(3)	119(1)
C(1)	C(2)	C(7)	120(1)	C(3)	C(2)	C(7)	120(1)
C(2)	C(3)	C(4)	118(1)	C(3)	C(4)	C(5)	121(1)
C(4)	C(5)	C(6)	119(1)	C(1)	C(6)	C(5)	120(1)
N(7)	C(7)	N(8)	122.3(10)	N(7)	C(7)	C(2)	114.0(10)
N(8)	C(7)	C(2)	123(1)	N(8)	C(9)	C(10)	109.5(9)
N(8)	C(9)	C(16)	109.2(10)	C(10)	C(9)	C(16)	105(1)
O(1)	C(10)	C(9)	110.9(10)	N(7)	C(11)	C(12)	105.5(9)
N(7)	C(11)	C(15)	113.6(9)	C(12)	C(11)	C(15)	112.0(9)
C(11)	C(12)	C(13)	111(1)	C(11)	C(12)	C(14)	112.8(10)
C(13)	C(12)	C(14)	109.7(10)	O(15)	C(15)	C(11)	113.2(10)
C(9)	C(16)	C(17)	106(1)	C(9)	C(16)	C(18)	113(1)
C(17)	C(16)	C(18)	109(1)	O(21)	C(21)	C(22)	119(1)
O(21)	C(21)	C(26)	115(1)	C(22)	C(21)	C(26)	124(1)
C(21)	C(22)	C(23)	117(1)	C(21)	C(22)	C(27)	122(1)
C(23)	C(22)	C(27)	120(1)	C(22)	C(23)	C(24)	121(1)
C(23)	C(24)	C(25)	117(1)	C(24)	C(25)	C(26)	120(1)
C(21)	C(26)	C(25)	118(1)	N(27)	C(27)	N(28)	120.9(10)
N(27)	C(27)	C(22)	115.1(10)	N(28)	C(27)	C(22)	123(1)
N(28)	C(29)	C(30)	108.8(9)	N(28)	C(29)	C(36)	108.5(9)

Table 5. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
C(30)	C(29)	C(36)	108.1(9)	O(21)	C(30)	C(29)	115.2(9)
N(27)	C(31)	C(32)	107.9(8)	N(27)	C(31)	C(35)	115.3(9)
C(32)	C(31)	C(35)	110.4(9)	C(31)	C(32)	C(33)	111.8(9)
C(31)	C(32)	C(34)	113.9(10)	C(33)	C(32)	C(34)	109(1)
O(35)	C(35)	C(31)	113.0(10)	C(29)	C(36)	C(37)	108(1)
C(29)	C(36)	C(38)	113(1)	C(37)	C(36)	C(38)	110(1)

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(15)	O(15)	H(15o)	136.2	C(7)	N(7)	H(7)	94.8
C(11)	N(7)	H(7)	93.7	C(27)	N(27)	H(27)	118.8
C(31)	N(27)	H(27)	113.0	C(2)	C(3)	H(3)	115.6
C(4)	C(3)	H(3)	125.5	C(3)	C(4)	H(4)	117.4
C(5)	C(4)	H(4)	121.3	C(4)	C(5)	H(5)	125.4
C(6)	C(5)	H(5)	114.5	C(1)	C(6)	H(6)	113.4
C(5)	C(6)	H(6)	125.3	N(8)	C(9)	H(9)	108.7
C(10)	C(9)	H(9)	110.9	C(16)	C(9)	H(9)	112.7
O(1)	C(10)	H(10b)	104.6	O(1)	C(10)	H(10a)	108.1
C(9)	C(10)	H(10b)	111.2	C(9)	C(10)	H(10a)	114.9
H(10b)	C(10)	H(10a)	106.5	N(7)	C(11)	H(11)	114.0
C(12)	C(11)	H(11)	110.2	C(15)	C(11)	H(11)	101.6
C(11)	C(12)	H(12)	106.1	C(13)	C(12)	H(12)	114.3
C(14)	C(12)	H(12)	102.5	C(12)	C(13)	H(13a)	100.6
C(12)	C(13)	H(13b)	102.0	C(12)	C(13)	H(13c)	101.9
H(13a)	C(13)	H(13b)	113.3	H(13a)	C(13)	H(13c)	113.1
H(13b)	C(13)	H(13c)	121.9	C(12)	C(14)	H(14a)	116.8
C(12)	C(14)	H(14b)	111.4	C(12)	C(14)	H(14c)	114.7
H(14a)	C(14)	H(14b)	101.7	H(14a)	C(14)	H(14c)	112.3
H(14b)	C(14)	H(14c)	97.3	O(15)	C(15)	H(15b)	106.4
O(15)	C(15)	H(15a)	108.3	C(11)	C(15)	H(15b)	113.0
C(11)	C(15)	H(15a)	114.7	H(15b)	C(15)	H(15a)	100.2
C(9)	C(16)	H(16)	106.9	C(17)	C(16)	H(16)	111.0
C(18)	C(16)	H(16)	109.5	C(16)	C(17)	H(17b)	106.6

Table 6. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
C(16)	C(17)	H(17c)	104.9	C(16)	C(17)	H(17a)	108.5
H(17b)	C(17)	H(17c)	101.8	H(17b)	C(17)	H(17a)	120.3
H(17c)	C(17)	H(17a)	113.4	C(16)	C(18)	H(18b)	104.2
C(16)	C(18)	H(18c)	105.4	C(16)	C(18)	H(18a)	105.3
H(18b)	C(18)	H(18c)	104.8	H(18b)	C(18)	H(18a)	112.9
H(18c)	C(18)	H(18a)	122.6	C(22)	C(23)	H(23)	124.6
C(24)	C(23)	H(23)	113.2	C(23)	C(24)	H(24)	125.1
C(25)	C(24)	H(24)	117.1	C(24)	C(25)	H(25)	117.8
C(26)	C(25)	H(25)	121.4	C(21)	C(26)	H(26)	125.5
C(25)	C(26)	H(26)	115.3	N(28)	C(29)	H(29)	114.3
C(30)	C(29)	H(29)	110.9	C(36)	C(29)	H(29)	106.1
O(21)	C(30)	H(30a)	107.4	O(21)	C(30)	H(30b)	112.3
C(29)	C(30)	H(30a)	103.6	C(29)	C(30)	H(30b)	106.1
H(30a)	C(30)	H(30b)	112.0	N(27)	C(31)	H(31)	102.6
C(32)	C(31)	H(31)	109.2	C(35)	C(31)	H(31)	111.2
C(31)	C(32)	H(32)	106.4	C(33)	C(32)	H(32)	101.9
C(34)	C(32)	H(32)	112.6	C(32)	C(33)	H(33a)	113.4
C(32)	C(33)	H(33b)	116.0	C(32)	C(33)	H(33c)	114.8
H(33a)	C(33)	H(33b)	103.3	H(33a)	C(33)	H(33c)	98.6
H(33b)	C(33)	H(33c)	108.9	C(32)	C(34)	H(34a)	108.0
C(32)	C(34)	H(34b)	108.2	C(32)	C(34)	H(34c)	105.7
H(34a)	C(34)	H(34b)	122.4	H(34a)	C(34)	H(34c)	107.0
H(34b)	C(34)	H(34c)	104.3	O(35)	C(35)	H(35b)	106.5
O(35)	C(35)	H(35a)	106.7	C(31)	C(35)	H(35b)	103.2

Table 6. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
C(31)	C(35)	H(35a)	102.5	H(35b)	C(35)	H(35a)	125.0
C(29)	C(36)	H(36)	112.2	C(37)	C(36)	H(36)	106.8
C(38)	C(36)	H(36)	104.5	C(36)	C(37)	H(37b)	110.1
C(36)	C(37)	H(37c)	110.6	C(36)	C(37)	H(37a)	116.6
H(37b)	C(37)	H(37c)	96.8	H(37b)	C(37)	H(37a)	107.1
H(37c)	C(37)	H(37a)	113.7	C(36)	C(38)	H(38b)	111.5
C(36)	C(38)	H(38c)	117.2	C(36)	C(38)	H(38a)	112.3
H(38b)	C(38)	H(38c)	105.1	H(38b)	C(38)	H(38a)	97.2
H(38c)	C(38)	H(38a)	111.5				

Table 7. Non-bonded Contacts out to 3.60 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
O(1)	C(13)	3.48(2)	55401	O(15)	N(27)	2.92(1)	1
O(15)	C(23)	3.58(2)	1	O(21)	C(23)	3.39(1)	55601
O(21)	C(33)	3.56(2)	55601	O(35)	N(7)	2.94(1)	65501
O(35)	C(3)	3.45(1)	65501	O(35)	C(12)	3.57(1)	65501
C(3)	C(35)	3.46(2)	45501	C(15)	C(23)	3.59(2)	1

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 coordinates 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 for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates 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

