Novel enantiopure ligands for asymmetric catalysis

Novel Enantiopure Ligands For Asymmetric Catalysis

by

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Abstract

The scope of the palladium catalysed allylic substitution reaction is reviewed with particular reference to stereocontrol The use of enantiopure oxazolines and acetals in asymmetric synthesis is briefly outlined

The work presented is concerned with the design and construction of enantiopure ligands which are able to impart very high levels of enantioselectivity in the aforementioned palladium catalysed allylic substitution reaction The ligands exploit the stereochemistry-controlling properties of the oxazoline moiety, whilst incorporating a secondary donor atom. The ligands rely upon an electronic disparity between these two atoms to direct nucleophilic addition.

The performance of the ligands was examined in the reaction of racemic 1,3–diphenyl–3–acetoxy–1–propene with the sodium salt of dimethyl malonate. The yield and enantioselectivity of the process varied depending upon which ligand was employed in the process. By increasing the π–accepting ability of the auxiliary donor, the enantioselectivity of nucleophilic addition is observed to increase

It was discovered that enantiopure phosphine containing oxazolines were the most effective ligands, the substitution product being obtained in quantitative yield with very high enantioselectivity (>95% ee) and short reaction times. The origin of enantioselectivity using the enantiopure oxazoline ligands is discussed

The use of enantiopure acetals as ligands examined the incorporation of other heteroatoms into the design of the ligand, whilst generating a similar topology. Again, the enantioselectivity was found to be highly dependent upon the nature of the auxiliary ligand.

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I gratefully acknowledge the support of the Science and Engineering Research Council (as was) for the provision of a quota studentship.

To my parents and family, I will be eternally grateful for their support and encouragement without which I would not be in the position I am today I reserve the deepest and most sincere words of gratitude for Mandy, my wife For her unfailing love and support I dedicate this work.

Christopher Gregory Frost
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Contents

Abbreviations

*n*BuLi	*n*–Butyllithium
*t*Bu	*tert*–Butyl
BSA	N,O-bis(trimethylsilyl)acetamide
cat	Catalytic
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
DCM	Dichloromethane
de	Diastereomeric excess
DIOP	2,3–O–Isopropylidene–2,3–dihydroxy–1,4–bis(diphenylphosphino)butane
DMAP	4–Dimethylaminopyridine
DMF	N,N–Dimethylformamide
ee	Enantiomeric excess
$Eu(hfc)_3$	Tris[3–(heptafluoropropylhydroxymethylene) camphorato], europium (III)
GC	Gas chromatography
mins	Minutes
NMR	Nuclear Magnetic Resonance
OTf	Trifluoromethanesulfonate (Triflate)
Ph	Phenyl
*i*Pr	Isopropyl
py	Pyridine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	N,N,N',N'–Tetramethylethylenediamine
Tr	Trityl (CPh_3)

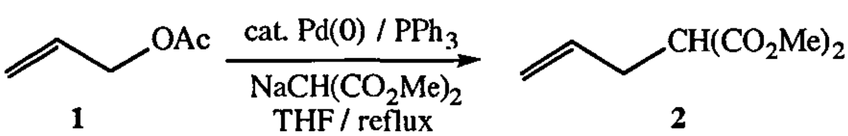
Chapter One

Scope Of Palladium Catalysed Allylic Substitution

1.1 Introduction

Transition metal based catalysts have found widespread use in many synthetically useful processes, frequently achieving high levels of chemo- and stereoselectivity.[1] Palladium catalysed reactions are of particular importance both in the laboratory and on an industrial scale Examples of these include Stille couplings[2], Heck reactions[3], Wacker oxidation[4] and allylic substitution reactions [5]

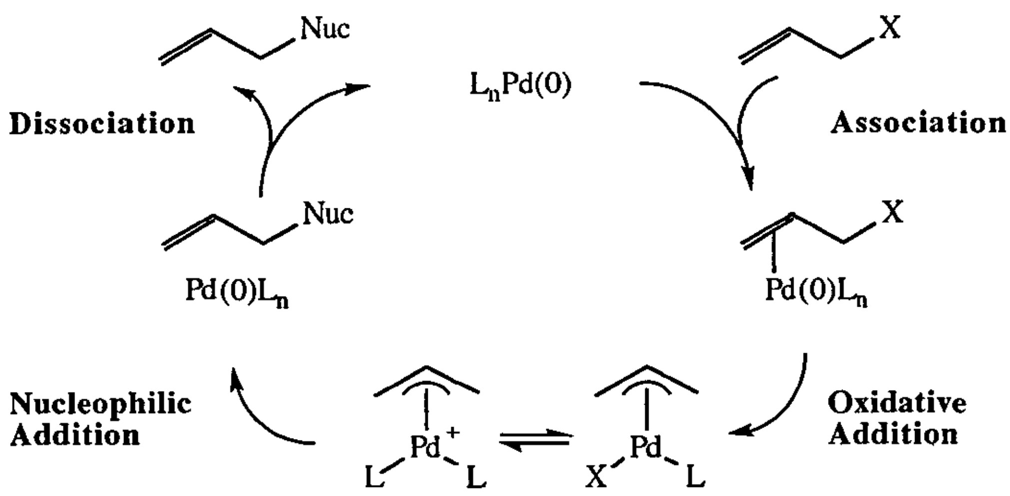
The palladium catalysed nucleophilic substitution of allylic compounds is an established, efficient and reliable process, and has become an important tool for the synthetic organic chemist The first η^3-allylpalladium complexes were isolated and characterised by Shaw over 30 years ago, synthesised by the reaction of dienes with palladium(II) salts.[6] In 1965, Tsuji *et al*[7] reported on the stoichiometric reaction of π-allylpalladium complexes with nucleophiles, effecting an overall allylic substitution Later, in the early 1970's the groups of Walker[8] and Hata[9] discovered that the allylic displacement of acetate with a variety of nucleophiles required only a catalytic amount of palladium. These findings opened the door to a vast area of further studies and applications Since the mid–1970's the palladium catalysed allylic substitution reaction has evolved into a very mild, efficient process illustrated by the reaction of allyl acetate **1** with the sodium salt of dimethyl malonate in the presence of catalytic amounts of triphenylphosphine and palladium(0).[10] Such reactions are typically conducted in a polar solvent such as THF to afford the substitution product **2** in good yield and with a high number of turnovers (**Scheme 1**).



Scheme 1

1.2 Mechanism of palladium catalysed allylic substitution

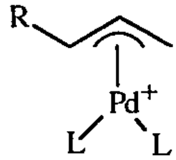
The generally accepted mechanism of palladium catalysed substitution involves the initial co-ordination of palladium(0) to the alkene followed by oxidative addition to afford an intermediate η^3–allyl complex In the presence of triphenylphosphine, or other π-accepting ligands, an equilibrium between a neutral and cationic complex results. The use of bidentate ligands favours formation of the cationic complex Nucleophilic addition to the cationic complex is favoured, and occurs at one of the allylic termini to furnish the palladium(0) complex of the product Dissociation of the palladium(0) catalyst liberates the product, and regenerates the active palladium catalyst, as shown in **Scheme 2**.[11]



Scheme 2

For a mono-substituted allyl complex, there are two geometrical isomers which may be adopted, the *syn* isomer **3**, and the *anti* isomer **4** The preferred geometry is *syn*, **3** for obvious steric reasons. Likewise the disubstituted allyl complexes favour the *syn*, *syn* geometry **5**

syn
Favoured



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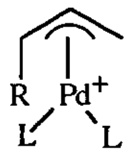
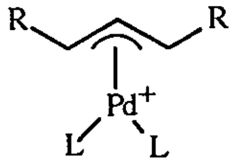


4

anti
Disfavoured

syn, syn
Favoured



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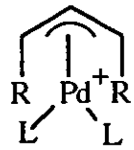
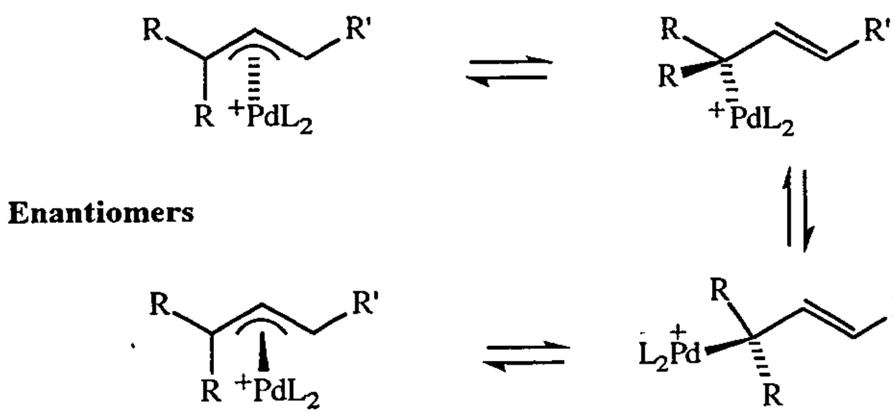


6

anti, anti
Disfavoured

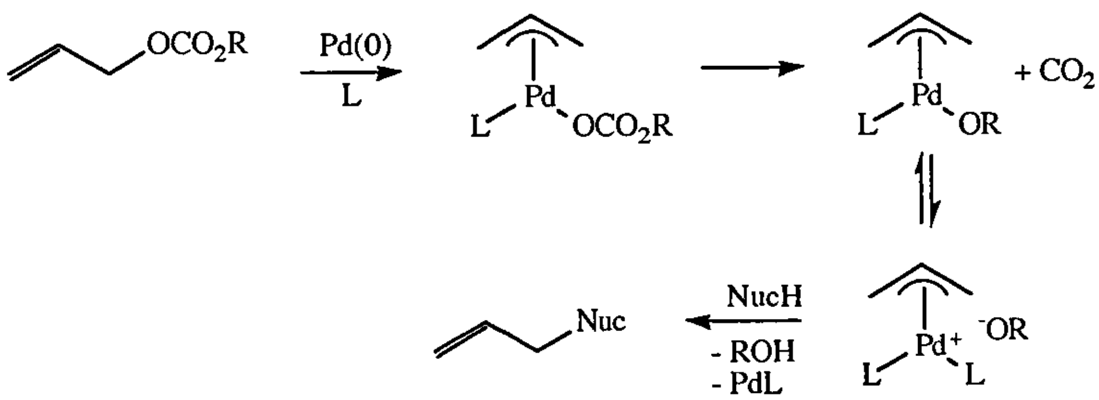
For more highly substituted allyl complexes, a similar geometrical preference based on the steric requirements of the substituents involved occurs. The isomeric forms are able to equilibrate by a π-σ-π mechanism, and when one terminus of the allyl unit contains two identical groups, this process can occur rapidly.[12] The enantiomeric forms of such a complex are in equilibrium as demonstrated in **Scheme 3**. The importance of enantioface inversion is that the stereochemistry of the starting substrate is lost during the isomerisation process and enantioselection is then determined by the stereochemistry of the palladium complex intermediate, since there is no memory of the original stereochemistry provided by the starting material.



Scheme 3

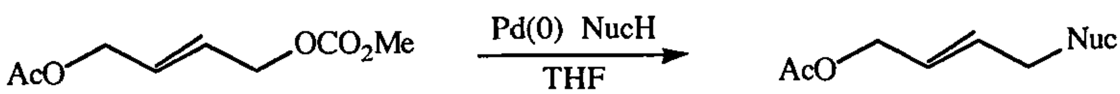
1.3 Range of substrates and nucleophiles

Whilst allylic acetates remain the most frequently employed substrates for palladium catalysed allylic substitution, a range of other leaving groups will also function perfectly well These include halides,[13] sulfones,[14] carbonates,[15] epoxides[16] and phosphates [17] Tsuji and Minami[18] applied the carbonate class of leaving group in 1985. In this process palladium(0) initially co-ordinates to the allylic substrate displacing the carbonate group which loses carbon dioxide generating an alkoxide The alkoxide is sufficiently basic to deprotonate many of the nucleophile precursors employed in these reactions The mechanism is outlined in **Scheme 4**



Scheme 4

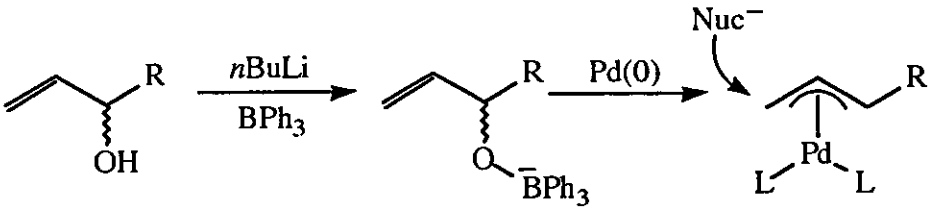
For the allylic substrate **7**, containing both carbonate and acetate functionalities, the carbonate functions as a better leaving group than the acetate, thereby affording the substitution product **8** in good yield (**Scheme 5**).



7 **8**

Scheme 5

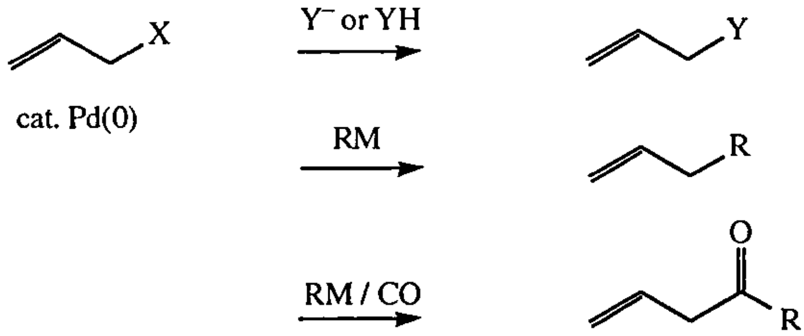
Although related derivatives of allylic alcohols have frequently been used as substrates, the parent alcohols themselves are generally much less reactive This apparently stems from the poor capability of a non–activated hydroxyl to serve as a leaving group Recently Kocovsky *et al* have developed a method which allows palladium catalysed allylic substitution to occur between allylic alcohols and anionic carbon nucleophiles.[19] The alkoxide is first generated from **9** by means of *n*-butyllithium in THF and then converted *in situ* into an activated intermediate **10** by adding triphenylboron. Addition of palladium(0) generates the η^3-complex **11**, nucleophilic addition to which rapidly occurs, as shown in **Scheme 6**



9 **10** **11**

Scheme 6

The nucleophiles which are most commonly employed for the palladium catalysed allylic substitution reaction are the 'soft' stabilised carbanions such as dimethyl malonate, but under suitable conditions, a variety of other nucleophiles have been used including nitrogen based nucleophiles,[20] sulfur nucleophiles,[21] oxygen nucleophiles,[22] phosphorus nucleophiles,[23] silicon nucleophiles,[24] vinyl boranes,[25] hydrides[26], tetraphenylborate[27] and organometallics. [28] In the presence of carbon monoxide and suitable nucleophiles, carbonylation reactions have also been achieved, as shown in **Scheme 7** [29]



Scheme 7

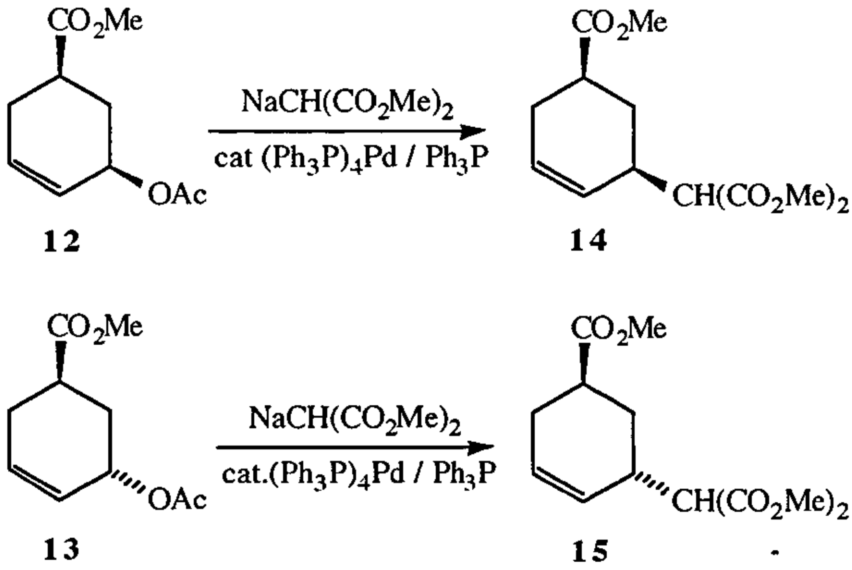
1.4 Mechanistic aspects of stereochemistry

As with a number of transition-metal catalysed reactions, palladium catalysed allylic substitution is known to occur *via* a stepwise process.[30] Two important steps have been identified

(1) The reaction of the palladium catalyst with the substrate to produce the π-allyl intermediate.

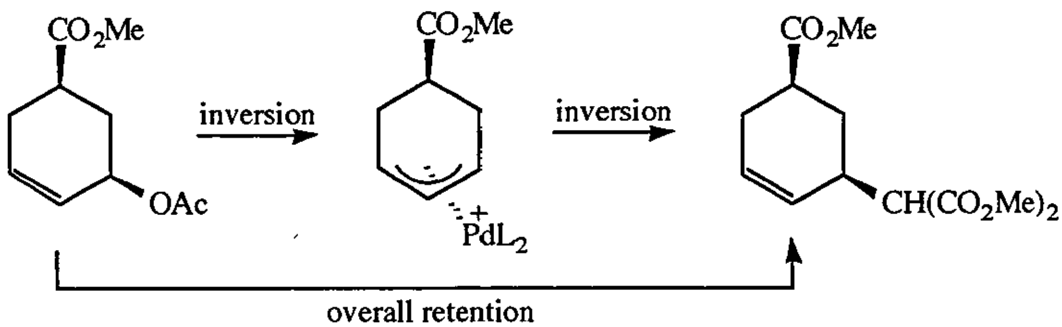
(2) The displacement of the palladium by a nucleophile to give the product *via* an intermediate olefin complex.

In the absence of isomerisation processes, the overall stereochemistry of the reaction will be dependent upon the stereochemistry of the individual steps Trost *et al* investigated the stereochemistry of alkylation reactions using substituted cyclic substrates, and soft nucleophiles, which gave rise to diastereomeric products.[31] Reaction of the *cis*-substituted compound **12** affords the *cis*-substituted product **14**, whereas the *trans*-substituted compound **13** affords the *trans*-substituted product **15 (Scheme 8)**.



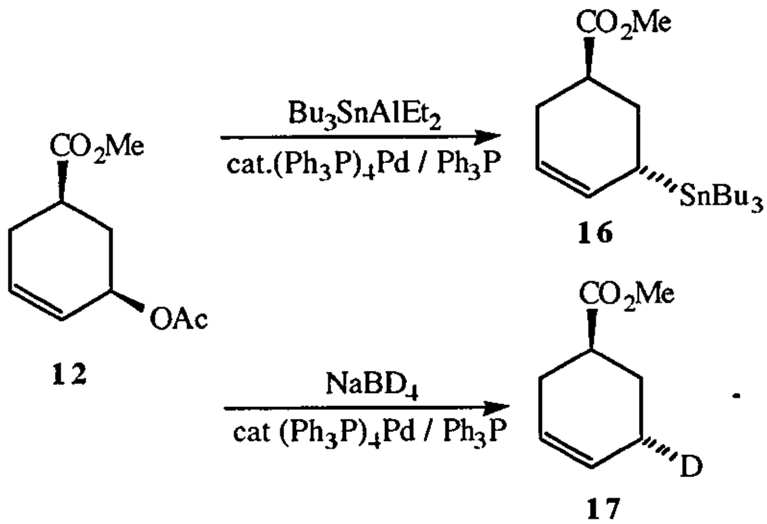
Scheme 8

Net retention of configuration was demonstrated to be the result of two steps that proceed with inversion of configuration. The palladium displaces the leaving group with inversion, followed by nucleophilic attack from the *exo* face, again with inversion, as shown in **Scheme 9**



Scheme 9

In contrast, it was discovered that many nucleophiles do not afford retention of stereochemistry. For example, Trost *et al* demonstrated that the nucleophile $Bu_3SnAlEt_2$ furnishes the allylstannane **16** with clean inversion,[32] and Keinan *et al* have shown on the same system that sodium borodeuteride also affords inversion of stereochemistry, to afford **17 (Scheme 10)**.[33] Likewise, Negishi *et al* have shown that other hard nucleophiles undergo the reaction with overall inversion[34] This can be rationalised by assuming the hard nucleophile first attacks the metal centre and then migrates to the allyl ligand[35]



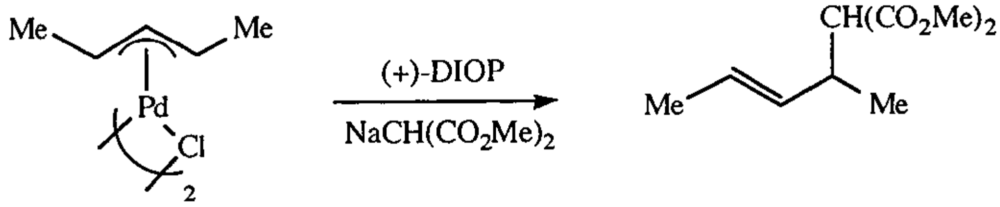
Scheme 10

A classification of nucleophiles exists based on their ability to substitute sterically hindered allylic acetates.[36] In such cases, only nucleophiles which attack *via* prior co-ordination to the metal are effective, since nucleophiles are sterically blocked from approaching the complex from the *exo* face. As a rough guide, nucleophiles with a pKa > 20 attack *via* the metal, whereas nucleophiles with a pKa < 20 attack the allyl ligand directly.

1.5 Enantiocontrol of reactions

(i) Background

In 1973, Trost and Dietsche showed that the stoichiometric reaction of palladium chloride dimer **18** with $NaCH(CO_2Me)_2$ and enantiopure phosphine ligands, such as (+)-DIOP afforded the substitution product **19**, achieving an enantiomeric excess of up to 23% (**Scheme 11**)[37]

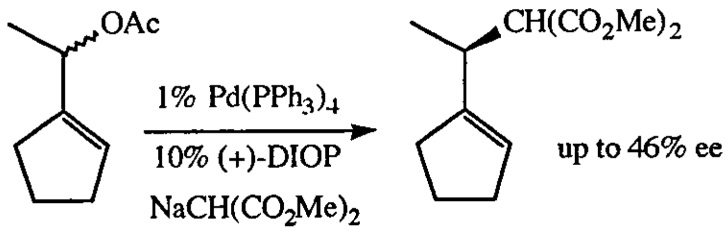


18

19

Scheme 11

The first reported example of a catalytic, asymmetric palladium catalysed allylic substitution reaction was the conversion of racemic allyl acetate **20** to the enantiomerically enriched product **21**, however only a modest enantioselectivity of up to 46% ee was achieved (**Scheme 12**)



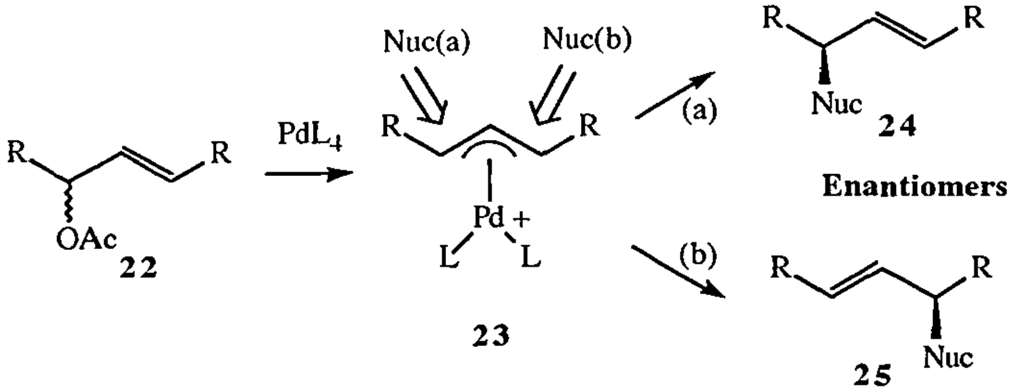
20

21

Scheme 12

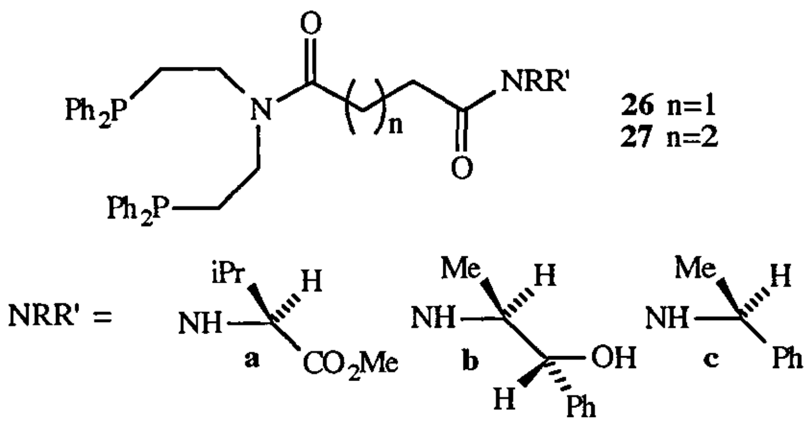
(ii) Asymmetric induction via secondary interactions

Most of the reported asymmetric palladium catalysed allylic substitution processes[38] start from a racemic allylic component **22**, which in the absence of enantiopure ligands, forms an intermediate *meso* complex **23** with palladium(0). Since a nucleophile may attack at either terminus of the allylic component, the enantiomers **24** and **25** are formed (**Scheme 13**) The degree of the enantioselectivity of a reaction depends on the ability of the enantiopure ligand to promote attack of the nucleophile to one terminus of the allylic component in preference to the other



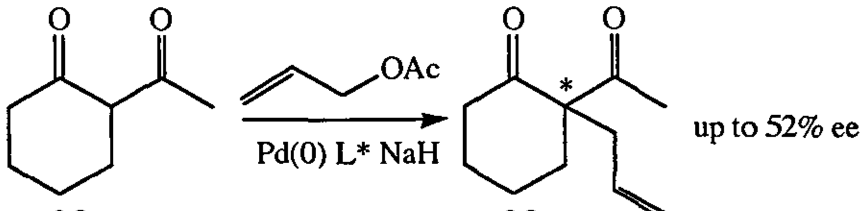
Scheme 13

The problem of achieving high levels of asymmetric induction results from the fact that a soft nucleophile attacks complex **23** from the opposite side to the ligand, and as a result, the distance between the reaction centre and the chirality-controlling centre is large On the basis of this mechanism Hayashi *et al* designed ligands to interact with the reacting substrates by means of secondary interactions[39] between functional groups on the enantiopure ligands and substrates.[40]



Phosphine ligands **26** and **27** were examined for stereoselectivity in the palladium catalysed reaction of sodium enolate of 2-acetylcyclohexanone **28** with allyl acetate The reaction with **26a** at –50°C gives the alkylation product **29** in the highest enantiomeric excess of 52% ee for the cases tested **(Scheme 14)**

The enantioselectivities are remarkable in view of how remote the existing stereocentre is from the newly created stereocentre



Scheme 14

The co-ordinative interaction between the enantiopure functional groups and the sodium enolate has been proposed for the origin of the observed stereoselectivity as illustrated in **Figure 1** The low selectivity (15% ee) with **27c** which has 1-phenylethyl as the chirality controlling group supports the proposed chelation The importance of linker chain length is shown by lower selectivity of **27a** compared with **26a**

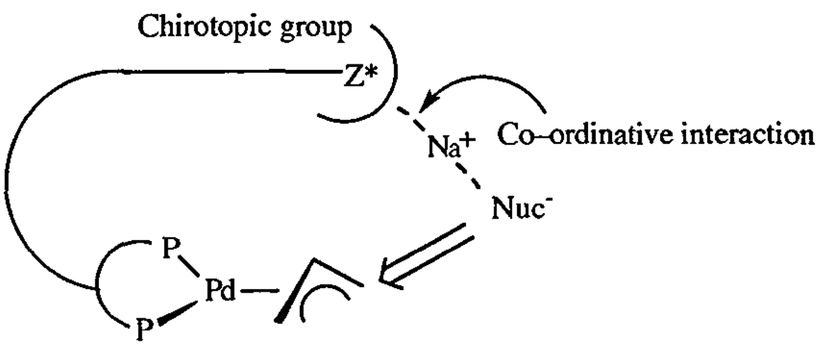
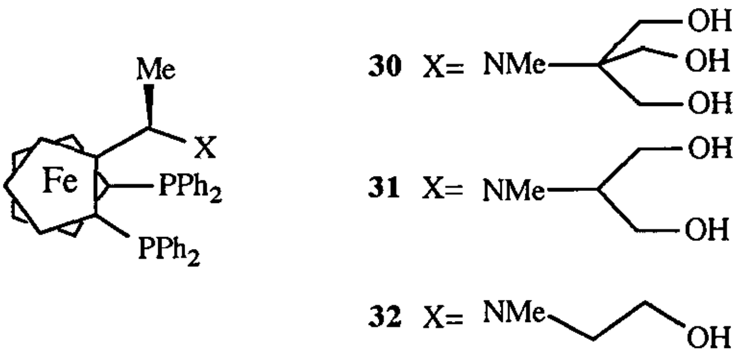


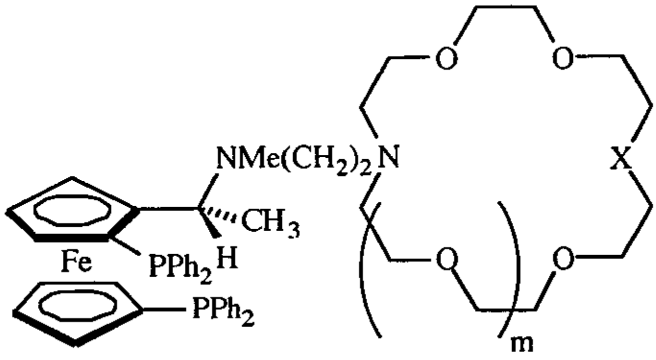
Figure 1

Hayashi *et al* have also devised a family of enantiopure ligands **30-32** with similar side chain modifications, prepared from (R)-1-[(S)-1, 2-bis(diphenylphosphino)-ferrocenyl]ethyl acetate [41] In a similar fashion to above, ligands **30-32** were used in the same palladium catalysed allylic alkylation. The palladium catalyst bearing ferrocenylphosphine **32** which contains one hydroxyl group on the terminal position of the pendant chain, is the most catalytically active and stereoselective, giving the alkylation product **29** in 73% yield and in 81% ee at –60°C.



It is noteworthy that the catalysts that show the highest levels of stereoselectivity are more catalytically active in general. Hayashi has proposed that a secondary interaction between the enantiopure ferrocenylphosphine ligands and the nucleophile accelerates the alkylation by drawing the nucleophile up to the π-allyl complex. In this case, hydrogen bonding between the hydroxyl group and enolate anion is more probably the secondary interaction involved, rather than co-ordination to the sodium of the enolate The evidence for this lies in the fact that replacement of the terminal hydroxyl group with an amino or a methoxy group resulted in the formation of alkylation product with opposite configuration and low enantioselectivity.

A further series of enantiopure ferrocenylphosphine ligands have been recently developed by Ito *et al* The incorporation of monoaza or diaza crown ethers of varying ring sizes and linker chain lengths furnishes ligands **33a-c** and **34**. These ligands were designed to interact with the nucleophile through formation of an inclusion complex with the crown ether.[42]

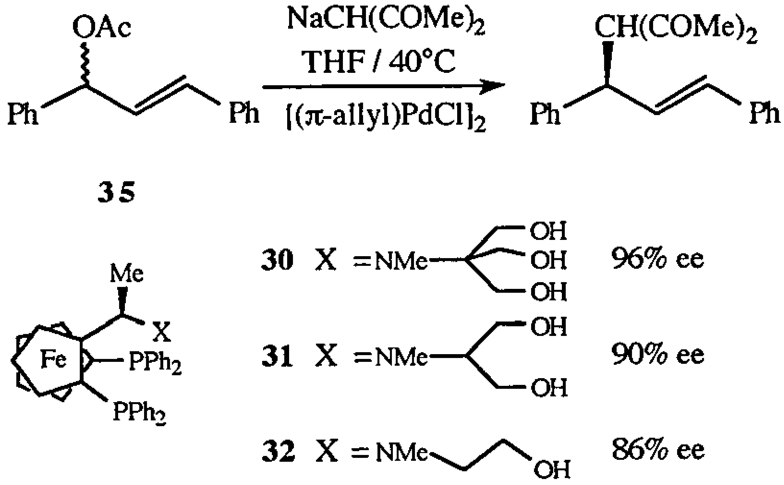


33a	m=-1	X=O
33b	m=1	X=O
33c	m=2	X=O
34	m=1	X=NMe

The crown ether modified ligands were examined for enantioselectivity and catalytic activity in the asymmetric alkylation of **28** using potassium fluoride as a base with mesitylene as solvent As expected from the complementarity between hole size of crown ether and ionic radius of a guest cation, ligand **33b** with monoaza-18-crown-6 moiety significantly accelerates the alkylation with increased enantioselectivity (60% ee) compared with the ferrocenylphosphine ligand lacking the crown ether moiety (22% ee). Ligands **33a** and **33c** were found to retard the reaction, giving the alkylation product in low yield with reduced enantioselectivity. The highest enantioselectivity of 75% was obtained at –40°C with **34**

Interestingly, the sense of asymmetric induction achieved by use of the crown ether modified ligands is always opposite to that of Hayashi's hydroxylated ligand **32**. This is deemed to originate from the fact that rather than directing nucleophilic attack through non-covalent bonding the sterically bulky crown ether moiety blocks the approach of the enolate to one terminus of the π-allyl moiety, providing a chiral pocket for nucleophilic attack at the other.

The enantiopure hydroxylated ferrocenylphosphines **30-32** previously applied to the asymmetric allylation of β-diketones have also been used to attain asymmetric induction at symmetrically substituted allylic substrates. Hayashi *et al* have achieved extremely high enantioselectivities in the palladium catalysed allylic alkylation of 1,3-disubstituted allylic acetates with sodium acetylacetonate and related stabilised carbon nucleophiles (**Scheme 15**).[43] The enantioselectivity in the reaction of 1,3-diphenyl-3-acetoxy-1-propene **35** with sodium acetylacetonate increases as the number of hydroxyl groups on the pendant side of the enantiopure ligand increases



Scheme 15

The X-ray crystal structure of the π-allylpalladium complex bearing hydroxylated ligand **32** has been published.[44] The pendant hydroxyl group is shown to reach over to the *exo* face of the π-allyl group and is located in close proximity to one of the π-allyl carbon atoms. Hayashi proposes a hypothetical transition state model where hydrogen bonding between the hydroxyl group and enolate anion causes preferential attack of the enolate to one terminus of the π-allyl moiety, as illustrated in **Figure 2**

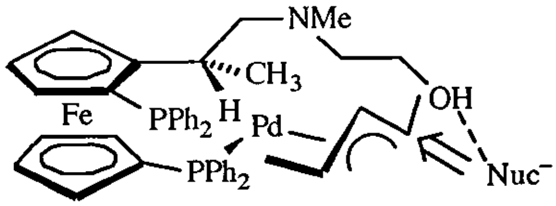
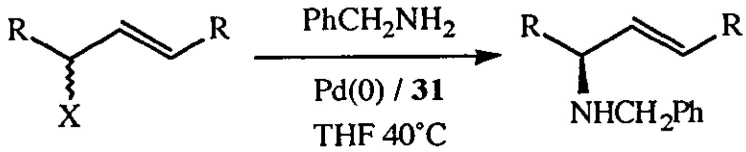


Figure 2

Palladium catalysed allylic amination with benzylamine or its derivatives occurs with increased stereoselectivity compared to allylic alkylation using dihydroxylated ligand **31** as shown in **Scheme 16**[45]



R=Ph	X=OCO_2Et	96% ee
R=Me	X=$OPOPh_2$	73% ee
R=iPr	X=OCO_2Et	96% ee

Scheme 16

^{31}P NMR of a π-allyl complex bearing 1,3-diphenyl π-allyl group and enantiopure ligand **31** indicates that the complex exists as an equilibrium mixture of two isomeric forms in a ratio of 20 1, which are tentatively assigned to 'W' form and 'M' form, respectively, as shown in **Figure 3**. An addition of an excess of benzylamine to the equilibrium mixture gave allylic amine product in up to 96% ee

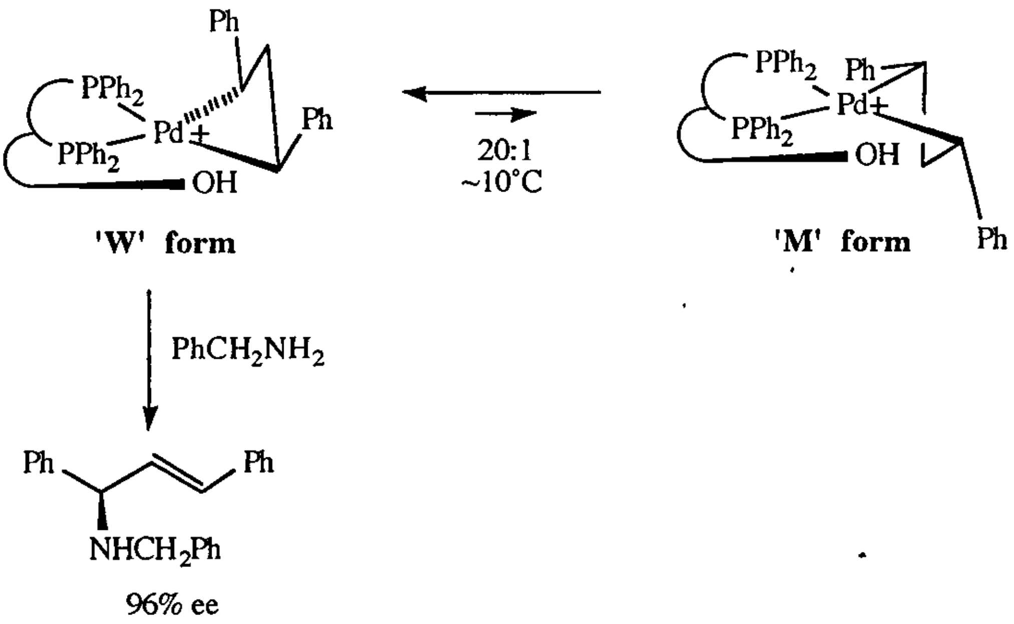
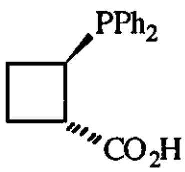


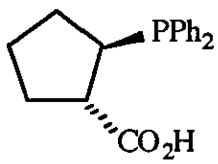
Figure 3

On the other hand a 2 1 equilibrating mixture of 1,3-diphenyl π-allylpalladium complex bearing an enantiopure ferrocenylphosphine ligand lacking the hydroxyl pendant, gave the amination product of lower enantiomeric purity (62% ee) on treatment with an excess of benzylamine.

Minami *et al* have synthesized a series of enantiopure monodentate phosphine ligands, which have a carboxylic acid functionality and a cyclobutane or cyclopentane backbone **36** and **37**.



36a



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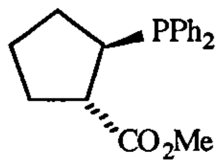

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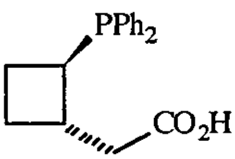
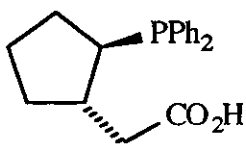


37a



37b

The ligands have been applied successfully to the asymmetric alkylation of 1,3-diphenyl-3-acetoxy-1-propene **35** with triethyl sodiophosphonoacetate **39** and dimethyl malonate (**Table 1**).[46]

Table 1

Nuc	*Ligand*	*% ee*	*Nuc*	*Ligand*	*% ee*
39	**36a**	79	$CH_2(CO_2Me)_2$	**36b**	85
39	**36b**	83	$CH_2(CO_2Me)_2$	**37a**	2
39	**37a**	2	$CH_2(CO_2Me)_2$	**37b**	7
39	**37b**	48	$CH_2(CO_2Me)_2$	**38**	37
$CH_2(CO_2Me)_2$	**36a**	77			

Although high enantioselectivity of around 80% ee is obtained in the reaction with both nucleophiles in the presence of enantiopure ligands **36b** and its cyclobutane analogue **36a**, a drastic decrease in the stereoselectivity is caused by the use of enantiopure ligands whose carboxyl group is connected to the cycloalkane backbone *via* a methylene group **37a** and **37b**. This indicates that the position of the carboxyl substituent is important for the stereoselective allylic alkylation. The importance of the carboxyl group is further supported by the decrease in enantioselectivity observed for the reaction using ligand **38** which is the ester analogue of **36b**. It has been proposed that the high enantioselectivities observed with ligands **36a** and **36b** is caused by an electronic repulsion between the carboxylate anion on the ligands and the negative charge of the incoming nucleophiles, which directs the nucleophilic attack onto one of the π-allyl carbons, as illustrated in **Figure 4**

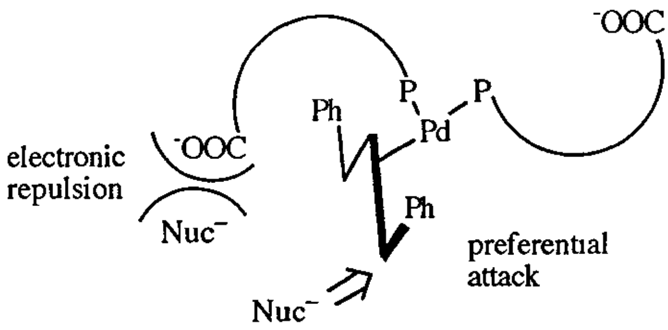
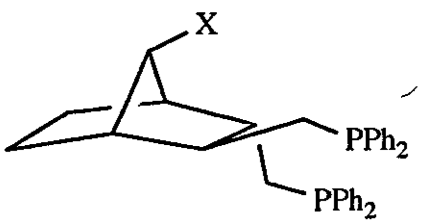


Figure 4

Novel enantiopure diphosphine ligands bearing hetero-functional groups have been prepared in eleven steps by Achiwa *et al.*[47] The ligands **40** were designed so that the hetero-functional group would extend over the diphenylphosphine substituents to interact with the incoming nucleophile The ligands were examined for stereoselectivity in the reaction of 1,3-diphenyl-3-acetoxy-1-propene **35** with the sodium salt of dimethyl malonate in the presence of palladium complexes Ligand **40a** produced only racemic alkylation product whereas ligand **40f** possessing a pendant carboxyl group achieved an enantioselectivity of 49% ee Again this lends support to the idea of secondary interactions occurring between functional group on the ligand and the approaching nucleophile.

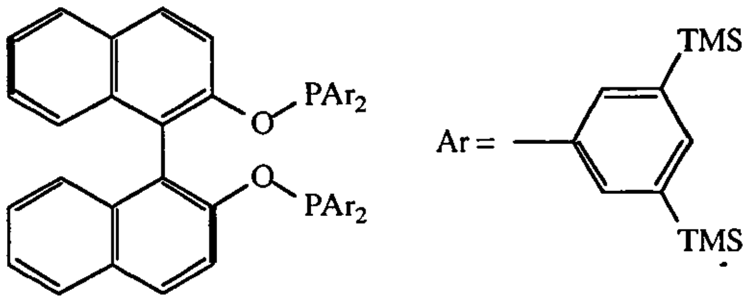


X=H	**40a**
X=OCH_2OCH_3	**40b**
X=OH	**40c**
X=OCH_2CH_2OH	**40d**
X=OCH_2CO_2tBu	**40e**
X=OCH_2COOH	**40f**

up to 49% ee with **35**

In a similar fashion to the enantiopure crown ether modified ferrocenylphosphines **33** and **34**, Trost *et al* have developed the sterically bulky ligand **41**, which is able to sterically block the approach of a nucleophile to one of the allylic termini [48]

The large ring size formed in the bidentate phosphine-palladium complex forces the 'arms' of the ligand around the allyl moiety and leads to increased enantioselectivity Reactions proceeding *via* a *meso* complex have been achieved with up to 69% ee employing this ligand



41

(iii) Asymmetric induction via steric effects

Many ligands which are able to impart impressive levels of asymmetric induction are not able to reach around to the *exo* face of the allyl group and direct or block the incoming nucleophile. In these cases it seems that the effect may be caused by an electronic bias in the symmetry of the allyl unit The steric effects of the ligand could force the allyl group away at one terminus, and thereby presumably generate an enhanced centre for nucleophilic addition, since it should carry more positive charge character, as represented in **Figure 5**

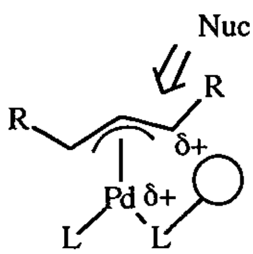
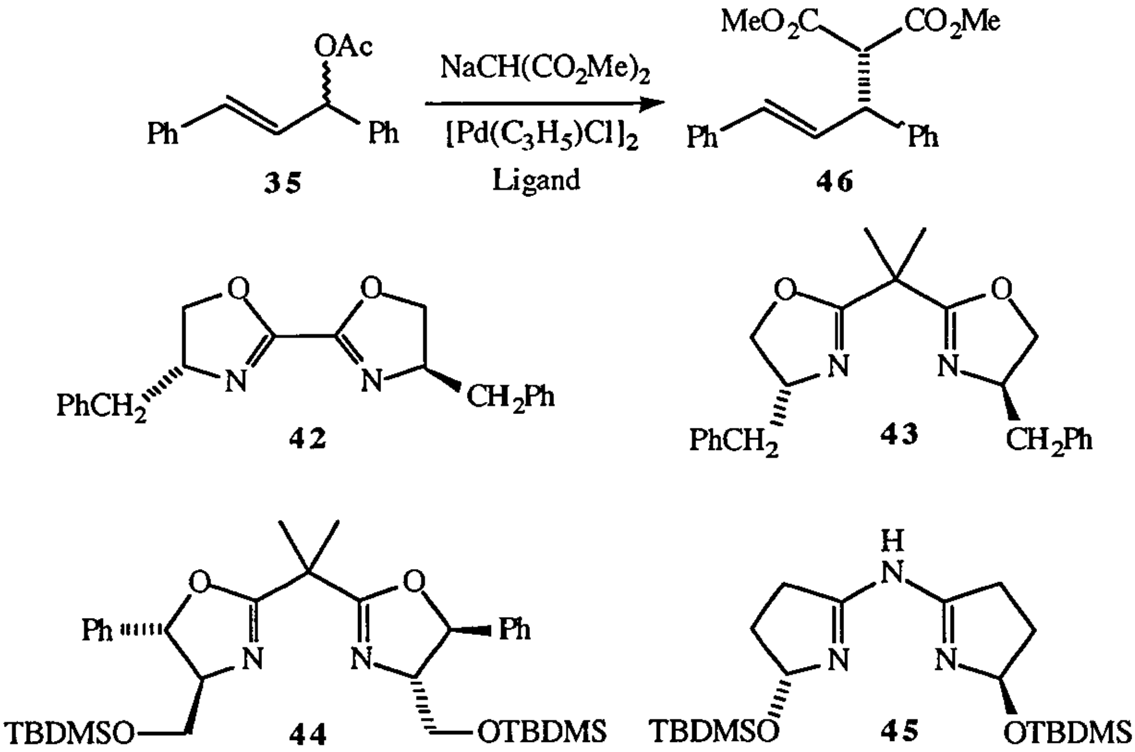


Figure 5

Ligands which may be considered in this category include the *bis*–oxazolines **42-44** and 5-azasemicorrins **45** employed by Pfaltz *et al*[49] Initial experiments were performed with palladium complexes of enantiopure ligand **42** in the reaction of racemic 1,3-diphenyl-3-acetoxy-1-propene **35** with the sodium salt of dimethyl malonate. The alkylation product **46** was obtained in good chemical yield with an enantiomeric excess of 77% (**Scheme 17**)



Scheme 17

Replacement of the benzyl groups in **42** by more bulky *iso*propyl or *tert*-butyl substituents resulted in loss of catalytic activity. Surprisingly, the *bis*–oxazoline **42** and the corresponding methylene *bis*–oxazoline **43** gave essentially identical results, despite their different coordination geometries (5- vs 6-membered chelate ring) and different electronic properties (**42** is a better π-acceptor than **43**) (see **Table 2**) The selectivities and reaction rates were found to be solvent-dependent The best results were obtained in polar media using a mixture of dimethyl malonate and N,O-bis(trimethylsilyl)acetamide, according to a procedure described by Trost *et al*[50] The catalytic procedure is smoothly initiated by the addition of a catalytic amount of potassium acetate Under these conditions, in the presence of 1-2 mol% of catalyst the reaction proceeded smoothly at room temperature to give the desired alkylation product **46** in very high enantiomeric purity and essentially quantitative yield The most effective ligands were found to be the azasemicorrin **45** and the methylene bisoxazoline **44** which both carry silyloxymethyl groups at the stereogenic centre adjacent to the co-ordination site

Table 2

Ligand	*Nucleophile*	*Solvent*	*%Yield*	*% ee*
42	$NaCH(CO_2Me)_2$	THF	86	77 (R)
43	$NaCH(CO_2Me)_2$	THF	85	76 (R)
43	$CH_2(CO_2Me)_2$	CH_2Cl_2	97	88 (R)
44	$CH_2(CO_2Me)_2$	CH_2Cl_2	97	97 (R)
45	$CH_2(CO_2Me)_2$	CH_2Cl_2	99	95 (S)

Evidence for the concept of regioselective steric activation of one of the Pd-C bonds is provided by the crystal structures of two π-allypalladium complexes with enantiopure ligand **43**. The important features of the two structures are depicted in **Figure 6** as reported by Pfaltz.[51]

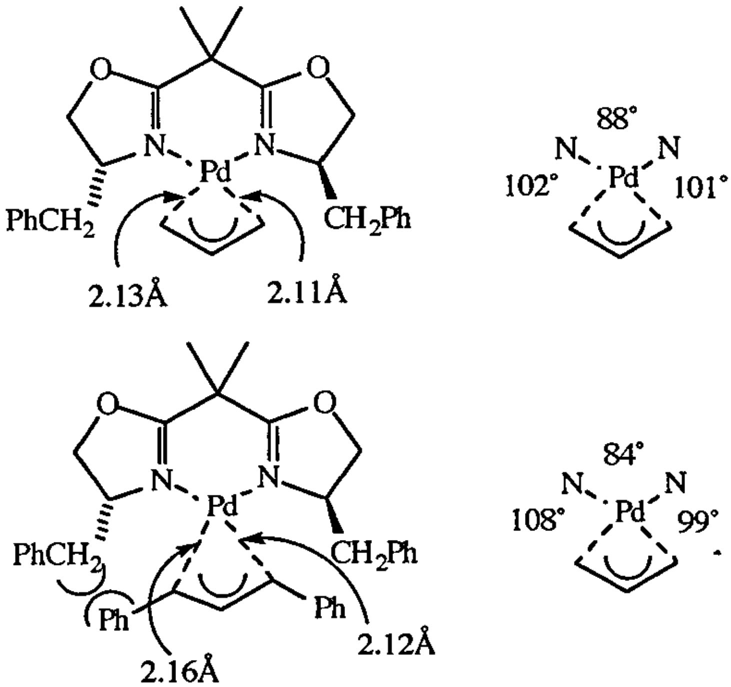
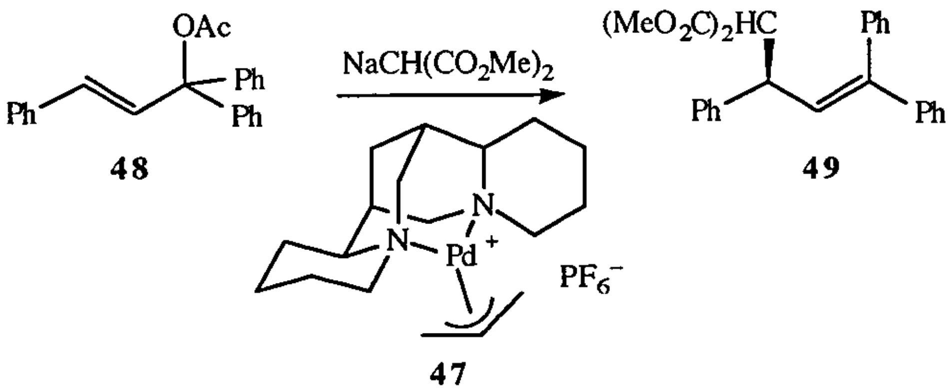


Figure 6

The complex with the unsubstituted allyl ligand was found to adopt the expected square planar co-ordination geometry of Pd(II) and an almost planar conformation of the methylene *bis*–oxazoline ligand framework. The structure of the corresponding (1,3-diphenylallyl)Pd complex, which is the actual intermediate in the catalytic reaction, was found to be strikingly different As a consequence of the steric repulsion between the allylic phenyl group and the adjacent benzyl substituent of the enantiopure ligand, the methylene *bis*–oxazoline ring system adopts a strongly distorted, non-planar conformation. The repulsive interaction between the enantiopure ligand and one of the allylic termini is also reflected in the bond lengths and angles of the $[PdC_3N_2]$ core. The longer, more strained Pd–C bond carries more positive charge character at carbon From the absolute configuration of the product it is known that the nucleophile preferentially attacks this terminus, this is a major factor in the enantioselection process.

It should be made clear that other oxazoline containing ligands have been prepared by ourselves, and other groups These will be discussed in subsequent chapters

Another ligand which achieves appreciable levels of enantioselectivity presumably by the distortion of the symmetrical allyl unit by steric forces is the naturally occuring alkaloid (-)-sparteine. Despite early reports of only mediocre enantioselectivities, Togni tested palladium complexes of sparteine **47** in the asymmetric alkylation of **48** by stabilised anions and was able to produce the product **49** with up to 85% ee **(Scheme 18)** [52]

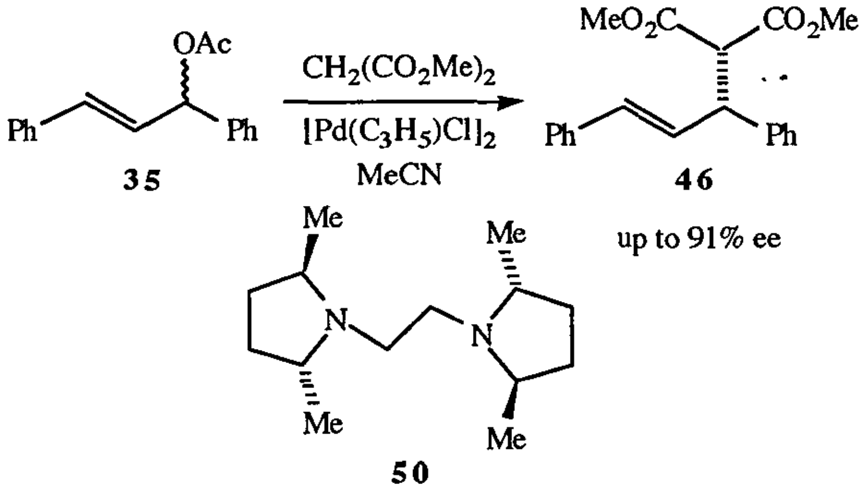


Scheme 18

This reaction does not proceed *via* a *meso* intermediate, but the diastereomeric allyl complexes are in rapid equilibrium An X-ray crystal structure of the proposed intermediate has been solved, and the observed diastereomer is consistent with the stereochemical outcome of the reaction. Various 2D ^{1}H NMR techniques indicate that the structure of the complex in solution remains essentially unchanged More recently Togni *et al* have successfully applied *iso*sparteine to the asymmetric alkylation reaction.[53]

Koga *et al* reports the development of a simple diamine ligand **50** for use in palladium catalysed asymmetric alkylation of 1,3-diphenyl-3-acetoxy-1-propene

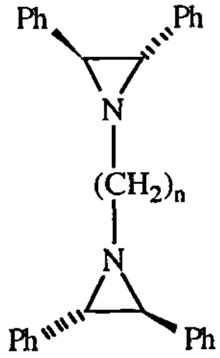
35 with dimethyl malonate according to the procedure described by Trost and Pfaltz [54] The product **46** was obtained in high yields and high enantiomeric excesses. Little solvent effect on enantioselectivity was observed In diethyl ether, THF, benzene, or 1,2-dichloroethane, the enantioselectivity was almost unchanged (87-88% ee). Interestingly, in polar solvents such as acetonitrile or DMF, the reaction proceeded smoothly without diminishing enantioselectivity **(Scheme 19)**



Scheme 19

The mechanism of enantioselection was investigated by X-ray diffraction and NMR studies As a result of the analysis, the asymmetric induction was found to be caused by the repulsive interaction between the enantiopure ligand and the substrate, which affected the electronic character of the two allylic termini, in complete agreement with the explanation given by Pfaltz.

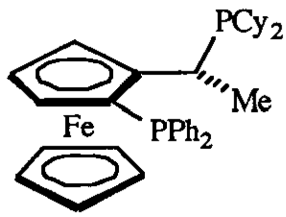
In a related approach, Tanner *et al* have explored the use of enantiopure aziridines for palladium catalysed allylic substitution.[55] The readily available *bis*–aziridines **51**, effect an enantioselective nucleophilic substitution of allylic acetate **35** furnishing the addition product with >99% ee.



>99% ee with **35** (n=2)

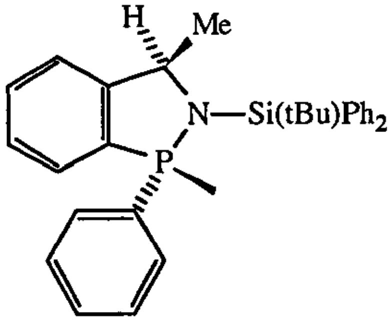
51

Lately, other enantiopure ligands have been used successfully for asymmetric palladium catalysed alkylations, these include the ferrocenyldiphosphine **52** synthesised by Togni *et al*,[56] and the monodentate phosphorus-based ligand **53**, devised by Wills *et al* [57]



52

Up to 93% ee with **35**



53

Up to 91.5% ee with **35**

Recently, Trost *et al* have reported the nature of the ion pair as nucleophile being critical in determining the enantioselectivity in allylic alkylation of 3–(acyloxy)cycloalkenes [58] Using tetrahexylammonium as counterion gave the best results, excellent enantioselectivities (up to 98% ee) have been obtained with both a carbon and a nitrogen nucleophile and with varying ring sizes of the allylic acetate.

Chapter Two

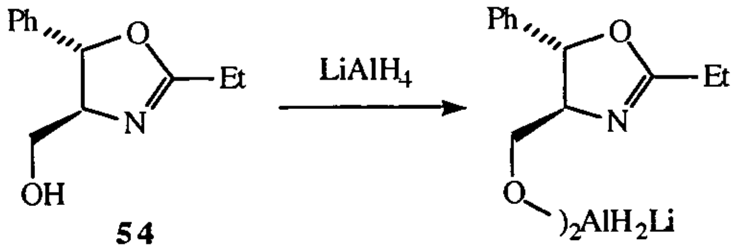
Enantiopure Oxazolines as Ligands

2.1 *Introduction*

The naturally occurring 2-oxazoline ring system, a simple cyclic imino ester was first identified over a century ago[59] Since then, the synthetic utility of 2-oxazolines has been demonstrated to provide novel, efficient routes to various organic molecules.[60] A number of reliable synthetic routes towards 2-oxazolines exist, the majority of which have been covered in a number of excellent reviews[61] One worthy of particular note is a recent, comprehensive report on the chemistry of 2-oxazolines by Meyers[62]

Since their introduction in 1974 by Meyers,[63] enantiopure 2-oxazolines have been extensively used as valuable auxiliaries in asymmetric synthesis.[64] They can effect efficient chirality transfer from the heterocycle to newly formed bonds, thereby generating new centres of chirality with high asymmetric induction Oxazolines have been found in many microbial metal chelators such as vibriobactin,[65] mycobactin[66] and parabactin[67] In these cases they are incorporated into multidentate metal complexes, illustrating the high chelating ability of this moiety. Based on these properties, enantiopure oxazolines have been used as ligands for transition metals in asymmetric catalysis.

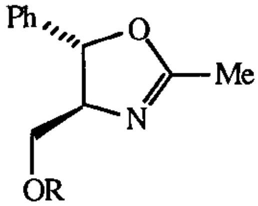
The first reported examples of enantiopure oxazolines as ligands facilitating asymmetric synthesis were by the group of Meyers in 1974 It was shown that enantiopure 4-hydroxymethyloxazoline **54** treated with 0 5 equivalents of lithium aluminum hydride was effective in the asymmetric reduction of ketones in up to 65% ee **(Scheme 20)**.[68]



54

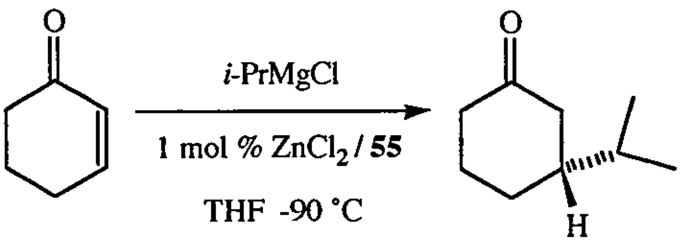
Scheme 20

Similarly, oxazolines **55** and **56** after treatment with one equivalent of Grignard reagent would add to various prochiral ketones furnishing enantiomerically enriched alcohols with up to 25% ee [69]



R = H **55**
Me **56**

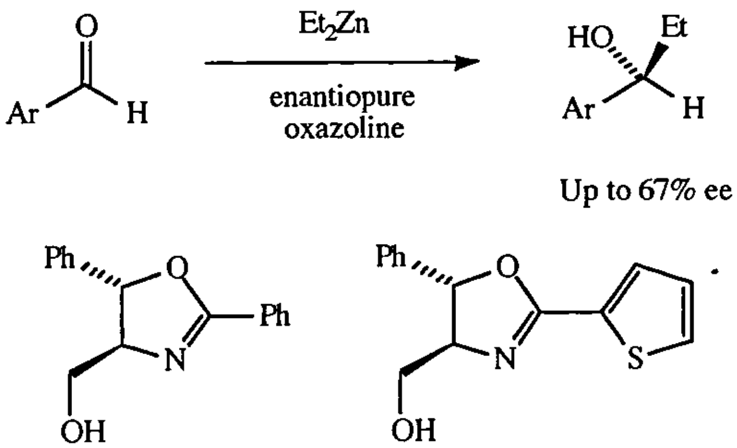
The same family of enantiopure oxazolines proved to be competent ligands for the Zn(II) catalyzed asymmetric addition of Grignard reagents to α,β-unsaturated ketones [70] A feature of the asymmetric transformation shown in **Scheme 21** using the Zn(II) complex derived from oxazoline **55** was high chemical yield (92%) and high regioselectivity (1,4 *versus* 1,2 addition gave a ratio of 165:1) The enantioselectivity however was rather modest at 16% ee.



16% ee

Scheme 21

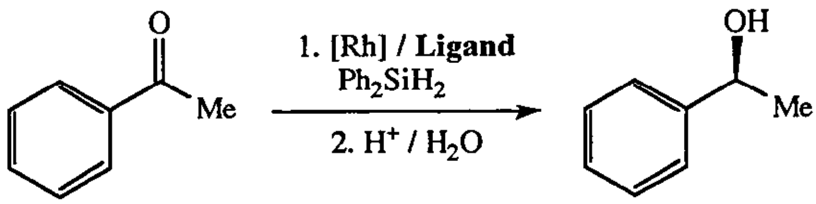
Oxazoline **55** and structurally related oxazolines **57** and **58** have enjoyed further success in the enantioselective addition of diethylzinc to various aromatic aldehydes yielding the enantiomerically enriched benzyl alcohols in up to 67% ee, as recently disclosed by Allen and Williams (**Scheme 22**) [71]



57 **58**

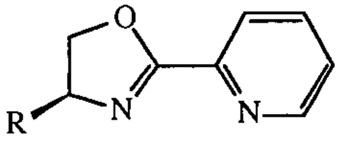
Scheme 22

In 1989, Brunner and Obermann introduced novel, enantiopure 2-(2-pyridinyl)oxazoline **59** which was used together with $[Rh(COD)Cl]_2$, to form homogeneous *in situ* catalysts for the enantioselective hydrosilylation of prochiral ketones using diphenylsilane [72] After hydrolysis, 1-phenylethanol **62** is produced in up to 84% ee from acetophenone **61**, as illustrated in **Scheme 23** (**59**, R=*t*Bu). Much lower selectivity was obtained using tridentate mono-oxazoline **60**.



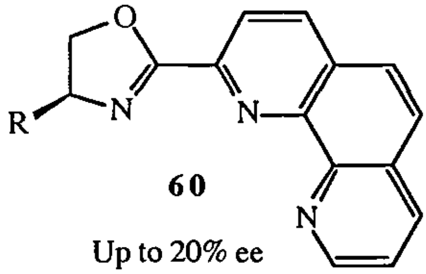
61 **62**

Scheme 23



59

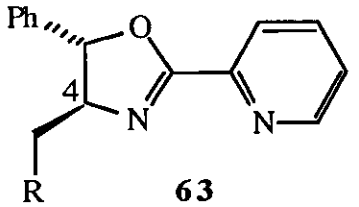
Up to 84% ee



60

Up to 20% ee

Structurally similar enantiopure 2-(2-pyridinyl)oxazolines **63** were prepared by Balavoine and Clinet, for use in the enantioselective hydrosilylation reaction.[73] The efficiency of these new chelating ligands was tested in the reaction of acetophenone **61** with α-naphthylphenylsilane.



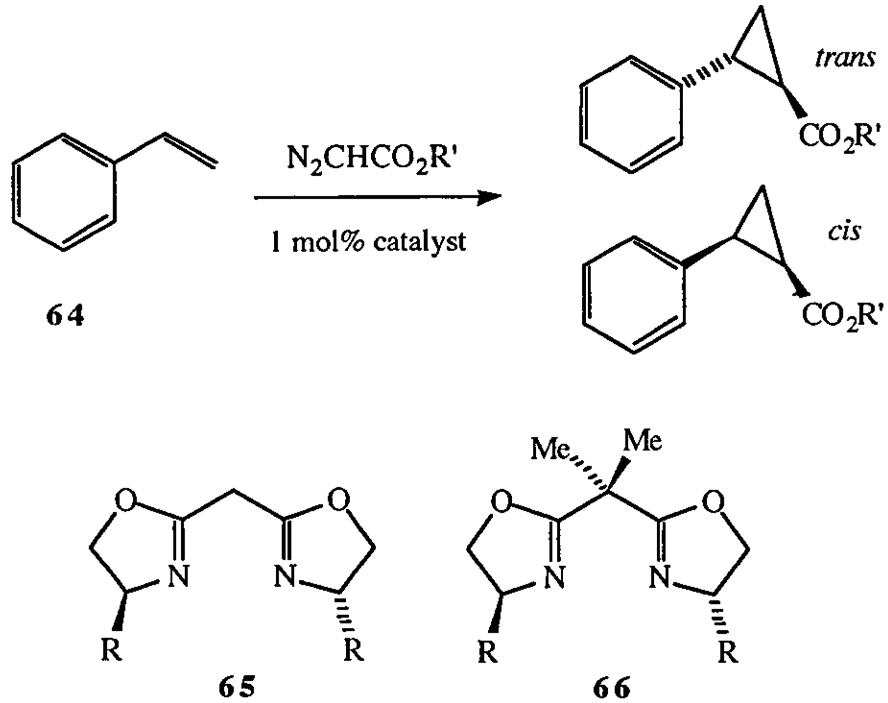
63

R= OH
OMe
OPh
$OCPh_3$
SH
SPh

Up to 80% ee

It was discovered that the enantioselectivity was highly dependent on both the steric and electronic properties of the substituent located at the 4-position on the oxazoline ring When the co-ordinating properties were similar, there was a clear correlation between the enantioselectivity and the size of the 4-substituent The highest level of enantioselection, (80% ee), was achieved in quantitative yield with the bulky trityl ether.

Significant advances in the levels of asymmetric induction occurred with the introduction of the C_2-symmetric *bis*-oxazolines by Masamune *et al.*[74] The catalytic enantioselective cyclopropanation of styrene **64** with ethyl diazoacetate in the presence of copper complexes of **65** as catalysts was found to occur in good yields and with high levels of enantioselectivity **(Scheme 24)** Two diastereomeric products are formed in a *trans* *cis* ratio of 2 5:1 The enantiomeric excess of the two enantiomers is strongly dependent on the substituents R on the ligand. The best results were obtained when the ligand **65** bears bulky substituents such as the *tert*-butyl group (*trans*, 90% ee ; *cis*, 77% ee)

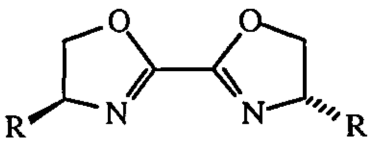


Scheme 24

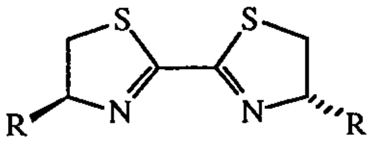
Independently, Evans *et al* reported that copper complexes of a similar family of *bis*-oxazolines **66** increase the enantioselectivity still further.[75] The geminal dimethyl groups prevent enolisation of the ligand, which therefore reacts in neutral form with copper (I) triflate to give a catalytically active complex In this case, the cyclopropanation of mono- and 1,1-disubstituted olefins using achiral diazoesters affords very high optical yields (up to 99% ee for styrene) and excellent *trans* : *cis* ratios (up to 94 6 for styrene). The reaction can be carried out at room temperature and 0.1 to 1 mol % of the complex is sufficient for efficient catalysis Further to this Evans *et al* have also recently revealed that the copper (I) triflate complex of **66** is a highly effective catalyst for aziridination of olefins[76] affording both aziridines and α-amino-β-hydroxy esters in very high enantiomeric excess

Pfaltz *et al* have also investigated the effectiveness of *bis*-oxazolines **65** in enantioselective catalysis [77] The results obtained for the asymmetric cyclopropanation of olefins with copper complexes of *bis*-oxazolines **65** are in agreement with the results described by Masamune and Evans Further to this, Pfaltz has employed oxazoline **65** in the iridium catalysed hydrogenation of ketones, affording excellent levels of enantioselection

The family of *bis*-oxazolines have been successfully applied to the enantioselective hydrosilylation of prochiral ketones with diphenylsilane Helmchen revealed respectable levels of enantioselectivity (up to 84% ee in the reduction of acetophenone **61**) using ligand **65** whilst **67** and **68** surprisingly gave poor results.[78]

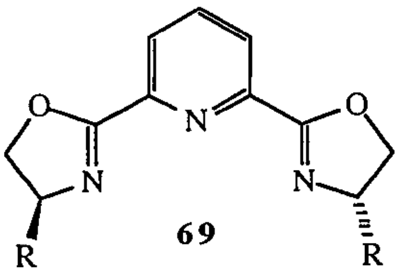


67



68

The enantiopure C_2-symmetric *bis*-oxazoline **69**, a tridentate ligand[79] and the related tetradentate ligand[80] **70** devised by Nishiyama have proved highly successful, giving up to 94% ee in the rhodium catalysed reduction of acetophenone **61**. Nishiyama *et al* have recently developed a powerful ruthenium catalyst derived from **69** for the efficient asymmetric cyclopropanation of olefins with diazoacetates.[81]



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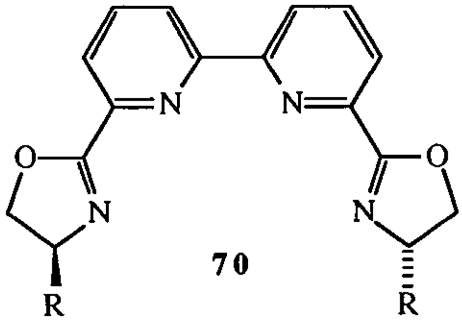
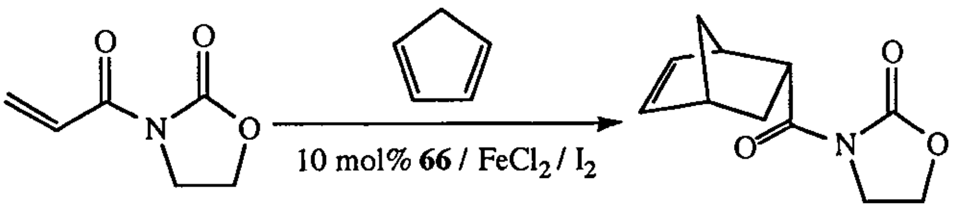


70

Corey has applied ligand **66** in conjunction with Lewis acidic catalysts to the Diels-Alder cycloaddition between cyclopentadiene and acryloyl oxazolidinone **71**, shown in **Scheme 25** resulting in formation of the *endo* cycloaddition product **72** with an enantioselectivity of 86% (*endo* : *exo*, 99 :1) [82]



71

72

Up to 86% ee

Scheme 25

The use of *bis*-oxazolines as enantiopure catalysts for the enantioselective Diels–Alder reaction has also been reported by Evans *et al.*[83] In an extensive study, Evans expands the scope of utilisable dienophiles and rationalises the sense of asymmetric induction for the cycloaddition process.

A new enantioselective method for the synthesis of enantiomerically enriched cyanohydrins from aldehydes has recently been reported by Corey and Wang [84] A pair of synergistic enantiopure *bis*-oxazolines, **65** (R=Ph) and **73** are used, one to activate the aldehyde and the other to provide an equivalent of enantiopure cyanide ion (**Figure 7**) High enantioselectivities, up to 95% ee, were obtained for aliphatic, non-conjugated aldehydes

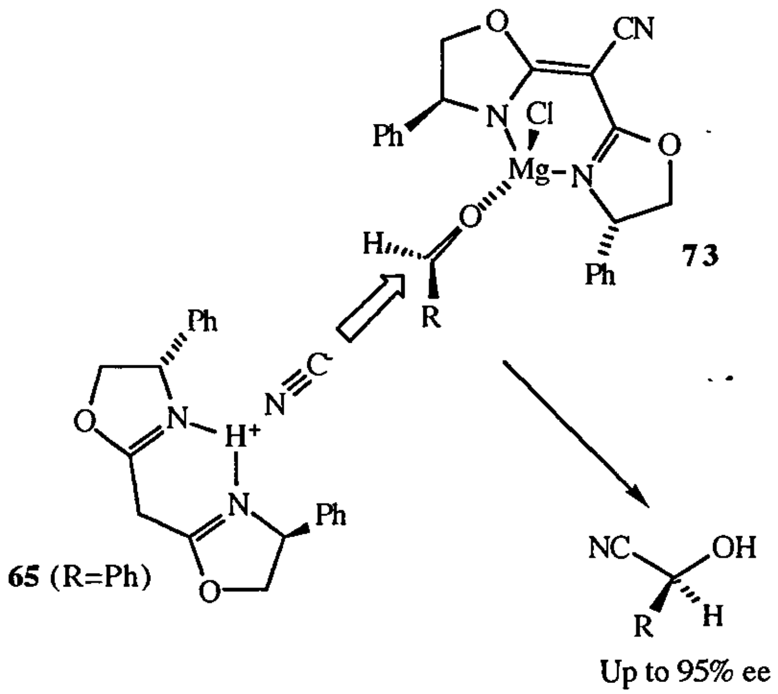
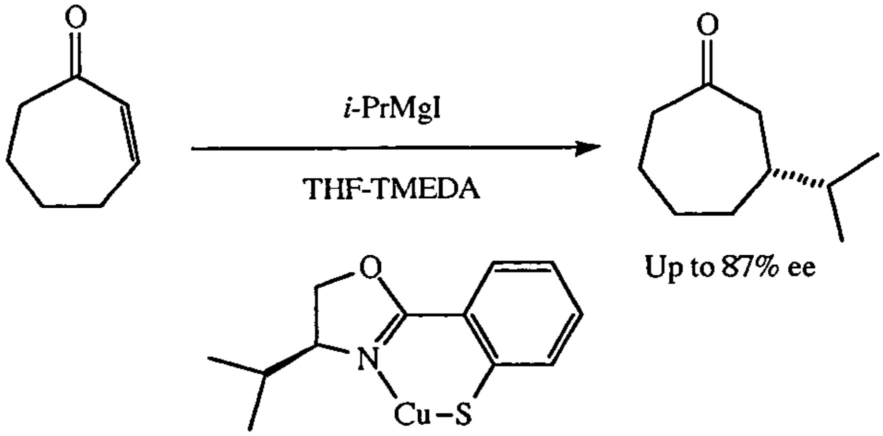


Figure 7

The high affinity of sulfur ligands for copper is exploited by Pfaltz and Zhou in the development of enantiopure heterocuprate complexes for enantioselective copper catalysed conjugate addition [85] Modified mono-oxazoline **74** proved to be an effective ligand for the catalytic, conjugate addition of Grignard reagents to cyclic α,β-unsaturated ketones, furnishing the addition product in up to 87% ee as illustrated in **Scheme 26**



74

Scheme 26

The synthesis of highly isotactic polymers with main chain chirality has been achieved using palladium (II) catalysts based on C_2–symmetric *bis*–oxazolines.[86]

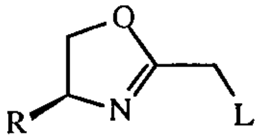
2.2 Ligand design

Enantiomerically pure oxazolines have been shown to be effective ligands for a variety of catalytic, asymmetric reactions The success of oxazolines as enantiopure ligands can be attributed to the fact that stereochemical information is directed towards the substrate bound to the metal catalyst.

The majority of successful oxazoline catalysts have relied upon a C_2-symmetrical nature to reduce the number of possible stereochemical outcomes within the catalytic cycle, thereby affording high levels of enantiocontrol. Although this strategy has proved very effective in an impressive repertoire of catalytic, asymmetric transformations, a problem has been the enantioselective palladium catalysed allylic substitution reaction

Our interests lay in the design of enantiopure ligands which exploit the stereochemistry-controlling properties of the oxazoline moiety, whilst incorporating a secondary donor atom, as shown in **Figure 8**.

Stereochemistry controlling oxazoline



Auxiliary donor ligand

Figure 8

The secondary donor atom could be tailored to the catalytic system to provide;

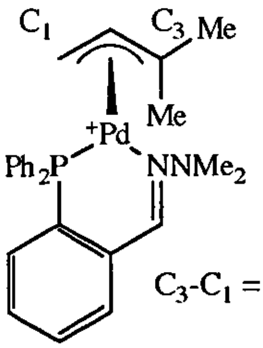
i) Modified binding properties

ii) Different steric environments

iii) Non-equivalent electronic behaviour of the donor atoms

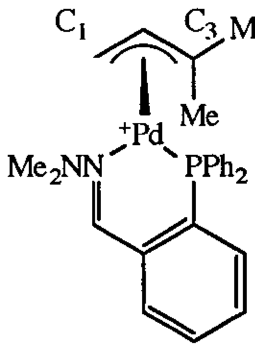
Electronic bias of this nature has been observed by Åkermark *et al* on allyl ligands bound to palladium [87] Specifically, it was noted that the rates and regioselectivity in the stoichiometric addition of nucleophiles to the η^3-(3-methylbutenyl)palladium(II) system were proportional to the total and relative charge of the η^3-allyl unit. Ligands with π-acceptor properties were found to produce reactive complexes which reacted preferentially at the more substituted η^3-allyl terminus and display large downfield ^{13}C NMR shifts for this terminus On the other hand, ligands not possessing π-acceptor properties gave less reactive complexes which reacted preferentially at the less substituted terminus The ^{13}C downfield shifts for these complexes were found to be small, as is also true for the shift difference between the two η^3-allyl termini

This can be seen clearly by considering complexes **75** and **76**. The two methyl groups allow for the development of more positive charge on the C_3 carbon. For the bidentate phosphorus/nitrogen ligand used in **75** and **76**, a dramatic effect was observed



C_3-C_1 = 78 ppm

75



C_3-C_1 = 8 ppm

76

When the phosphorus is *trans* to the C_3 position, a substantial C_3-C_1 shift difference is observed. However, when the nitrogen is *trans* to the C_3 position, the C_3-C_1 shift difference is dramatically reduced to just 8 ppm. Nucleophilic addition to complex **75** occurs mainly at the C_3 position, despite the steric constraints, due to the electronic properties of the ligand

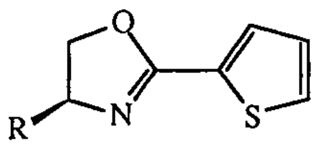
Whilst phosphorus and nitrogen both function as good σ-donors, only the phosphorus functioned as a π-acceptor, thereby reducing the electron density on the *trans* carbon atom, rendering it more electrophilic and hence, more susceptible to nucleophilic attack

It has been shown previously that good levels of stereocontrol are achievable by the use of enantiopure ligands that are able to either interact with the incoming nucleophile or sterically hinder the approach of the nucleophile, directing to one end of the allyl moiety. Alternatively, similarly high levels of stereocontrol have been achieved utilising enantiopure ligands which distort the symmetry of the allyl moiety by steric forces, thus, generating a more electrophilic centre for preferential nucleophilic attack.

The designed enantiopure oxazoline ligands should be able to exert steric and electronic control over the palladium catalysed allylic substitution process, by creating an asymmetric environment and introducing an electronic bias into the intermediate palladium allyl species *via* the differing *trans* effects of the two donor atoms in the ligand

2.3 Preparation of enantiopure thienyl oxazolines

We wished to prepare enantiopure oxazoline ligands which contained a secondary donor atom One such possibility would be a sulfur donor contained within a thiophene ring, providing a family of bidentate, electronically non-equivalent ligands **77**.



77

Thiophenes have only occasionally been employed as ligands, although there are reports of thiophene functioning as either an η^1 or η^5 ligand.[88] In order to act as a bidentate ligand, we are assuming that an η^1 binding mode would be more plausible. In support of this, Maitlis *et al* has reported spectroscopic evidence for the complexation of two tetramethylthiophene ligands to a cationic palladium allyl moiety in an η1 binding mode, this is illustrated in **Figure 9** [89]

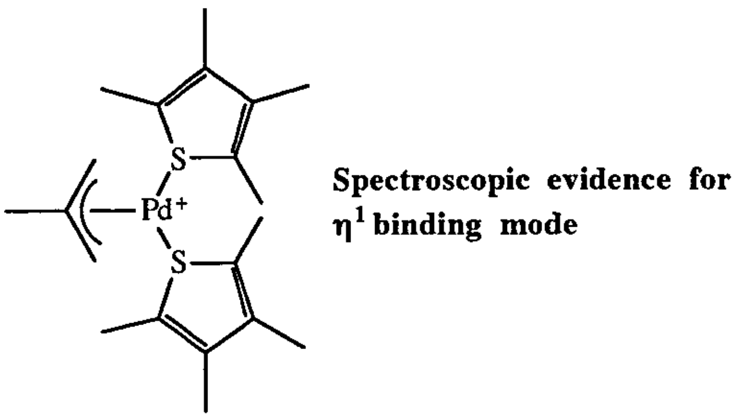
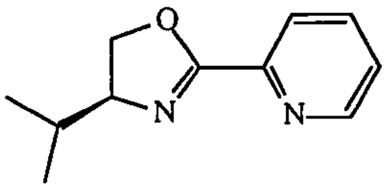
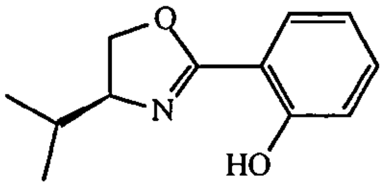


Figure 9

In 1974 Witte and Seeliger reported a procedure for the preparation of mono- and *bis*-oxazolines by direct reaction of nitriles with amino alcohols in the presence of catalytic amounts of metal salts.[90] By a reinvestigation of this procedure, Bolm *et al* demonstrated that a variety of substituted, optically active *bis*-oxazoline derivatives could readily be prepared under mild conditions [91] Using a slightly modified procedure Bolm prepared known mono-oxazolines **59** (R=*i*Pr) and **78**, from 2-cyanopyridine and 2-hydroxybenzonitrile respectively, in high yields

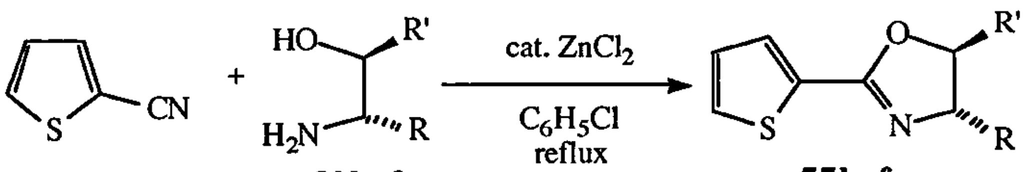


59 (R=*i*Pr)



78

We decided to adopt this mode of oxazoline synthesis in preference to other literature methods [92] Thus, the thienyl oxazolines **77b-f** were prepared in one step from commercially available thiophene carbonitrile **79** and enantiopure amino alcohols **80b-f (Scheme 27)**, which were either commercially available or easily obtained by reduction of the corresponding amino acids [93]



79 **80b–f** **77b–f**

Scheme 27

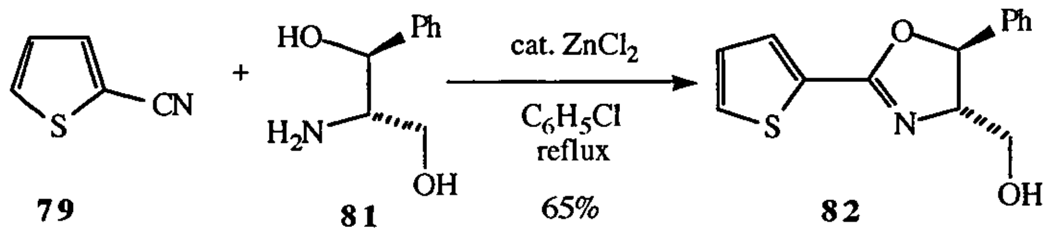
The procedure entails heating a solution of the thiophene carbonitrile with an excess of the appropriate enantiopure amino alcohol in chlorobenzene in the presence of a catalytic amount of zinc dichloride. Aqueous work-up followed by column chromatography furnishes the desired ligands in good yields (**Table 3**)

All of the thienyl oxazoline ligands have been satisfactorily characterised by both spectroscopic and analytical techniques. Strong evidence in favour of oxazoline formation can be found in the ^1H NMR spectra where a characteristic splitting pattern associated with the protons of the oxazoline ring is revealed In the case of ligands **77d** and **77e**, a ^1H–^{13}C correlation spectrum was required to distinguish between the C$\underline{H_2}$–O and C$\underline{H}$–N protons of the oxazoline ring Further confirmation of oxazoline formation can be found in the infra-red spectrum where a C=N stretching band at ~1650cm^{-1} is observed.

Table 3

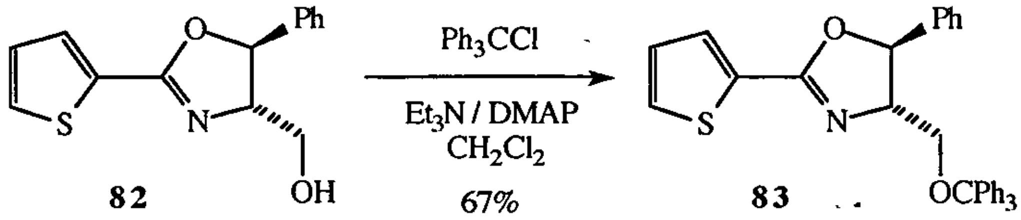
Amino alcohol	*R*	*R'*	*Oxazoline*	*Yield (%)*
80b	$PhCH_2$	H	**77b**	73
80c	^{i}Pr	H	**77c**	88
80d	Ph	H	**77d**	79
80e	^{t}Bu	H	**77e**	74
80f	Me	Ph	**77f**	91

A similar strategy was employed in the preparation of ligand **82**, from thiophene carbonitrile **79** and the cheap, commercially available enantiopure diol, (1S, 2S)-(+)-1-phenyl-2-amino-1,3-propanediol **81 (Scheme 28)** Accompanying the formation of **82** is a small quantity (<10%) of the isomeric oxazoline This can be conveniently removed by recrystallisation



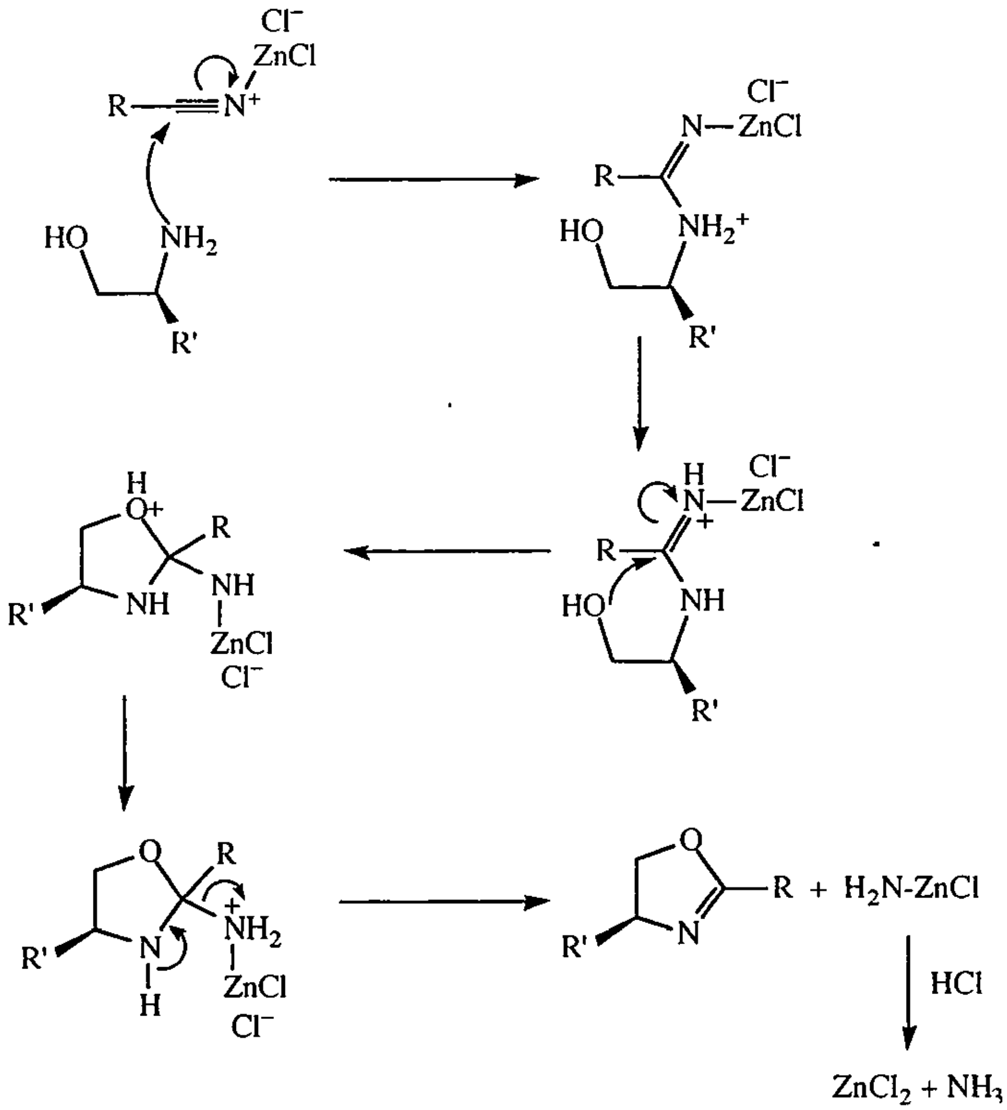
Scheme 28

The pendant hydroxyl group in **82** is useful in two ways; Firstly, as a ligand **82** could be used to probe the effects of secondary interactions between ligand and nucleophile on enantioselectivity Also, further elaboration of **82** would provide ligands with different steric properties Upon treatment with triethylamine and trityl chloride, **82** is converted to the bulky trityl ether **83** (**Scheme 29**).



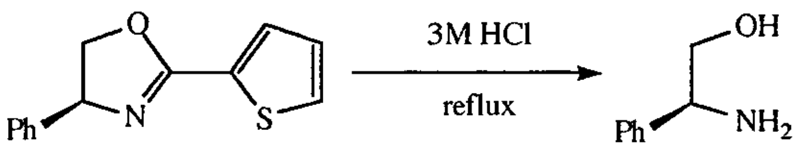
Scheme 29

The reasonable mechanism of oxazoline formation is illustrated in **Scheme 30** The nitrile functionality is able to co-ordinate to the zinc dichloride facilitating the initial nucleophilic addition of the amine The subsequent intermolecular nucleophilic attack by the hydroxyl group leads to the desired oxazoline with loss of ammonia and regeneration of the zinc dichloride catalyst .



Scheme 30

In order to ensure that no racemisation had occured during the zinc-catalysed ring formation, ligand **77d** was hydrolysed under acidic conditions liberating (S)-phenylglycinol, ($[\alpha]_D^{25}$=+32 0 (c=0 5, CH_2Cl_2)) (**Scheme 31**)



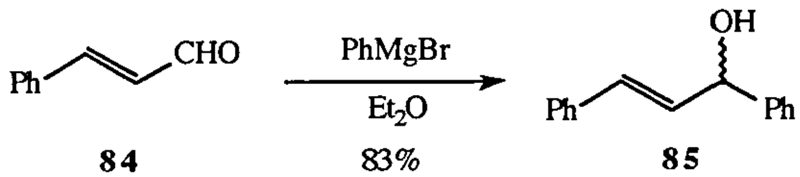
77d **80d**

Scheme 31

Comparison of the optical rotation with an authentic sample of (S)-phenylglycinol confirmed that there had been no loss of stereochemical integrity. Since the 4-phenyl substituted ligand was considered to be the most prone to potential racemisation, it is assumed that all of the other thienyl oxazoline ligands are likewise enantiomerically pure

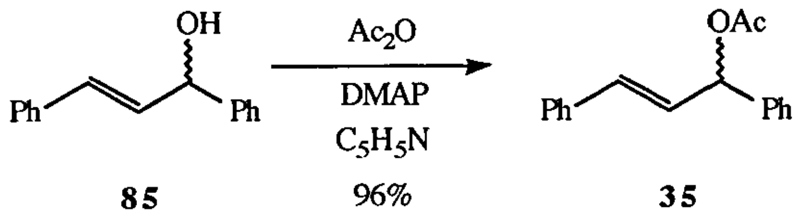
2.4 Results for palladium catalysed allylic substituition

With all of the enantiopure thienyl oxazoline ligands to hand, an investigation into the suitability of these ligands for asymmetric palladium catalysed allylic substitution began Thus, the allylic acetate **35** was prepared in two steps shown in **Schemes 32** and **33** The initial reaction of cinnamaldehyde with phenylmagnesium bromide in sodium dried ether at room temperature produced after work-up the allylic alcohol **85** as a low melting solid which could be used directly in the next step



Scheme 32

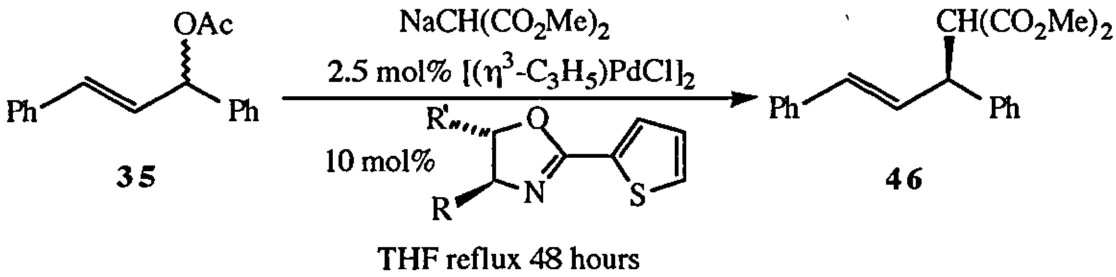
Treatment of **85** with an excess of acetic anhydride and a few crystals of DMAP in pyridine furnishes the desired allylic acetate **35** in excellent yield.



Scheme 33

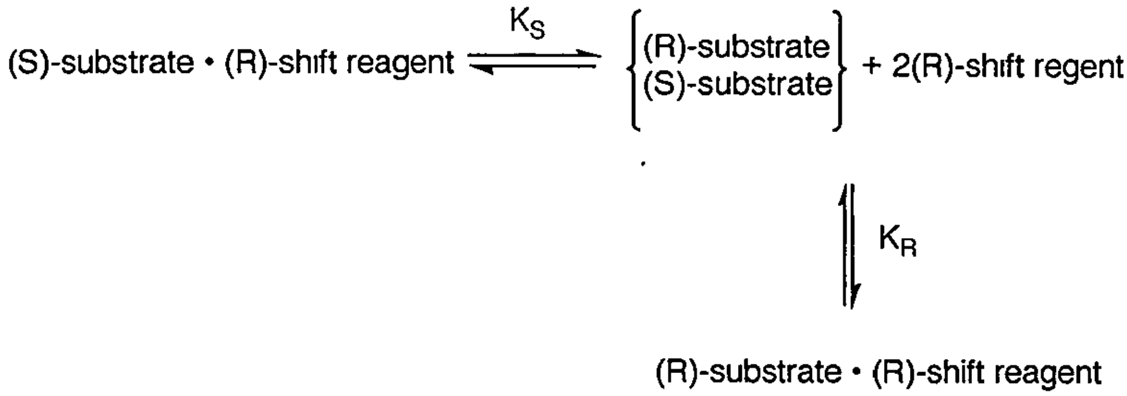
The reaction between allylic acetate **35** and sodiodimethylmalonate catalysed by 2.5 mol% of allyl palladium chloride dimer (equivalent to 5 mol% of palladium) and 10 mol% of one of the ligands **77b–f** was studied (**Scheme 34**). Initially, the catalytic reactions were carried out in dry THF and in all cases oxygen was excluded. The ligand and palladium catalyst were pre-mixed in the reaction solvent for 15 minutes prior to the reaction

After 48 hours at reflux, the reaction mixtures were quenched with water and were extracted with ether. The product was isolated by means of flash chromatography. The overall yields were modest, but as far as we could ascertain there are no detectable side products.



Scheme 34

The isolated product **46** was assayed for enantiomeric excess by employing the enantiopure shift reagent Eu(hfc)$_3$, in ^{1}H NMR. The use of enantiopure lanthanide shift reagents is a simple, widely used technique for the determinaton of enantiomeric purities by NMR spectroscopy[94] Under normal conditions the equilibrium between the substrate and the enantiopure lanthanide shift reagent is rapid on the NMR time scale:



Therefore only a single time-averaged spectrum results from the average of complexed and uncomplexed substrate molecules Rapidly equilibrating complexes are formed by an enantiopure lanthanide shift reagent binding to each of two enantiomers. These complexes are diastereomeric and can have different average chemical shifts This difference in shifts may have at least two causes. Firstly, the equilibrium constants (K_R, K_S) may be different for diastereomeric complexes, thereby causing larger shifts for the complex having the larger binding constant. Also, the two diastereomeric complexes formed may differ in their geometry which may cause a difference in the induced shift for corresponding signals in the two complexes

The shift experiment was carried out by preparing a solution of the substrate **46** in $CDCl_3$ The concentration of the substrate is kept as low as is compatible with having adequate signal strength Normally the more concentrated the sample, the broader will be the signals and therefore the poorer the resolution. For our purposes, 2 mg of the substrate **46** in 1 ml of solvent gave a perfectly acceptable spectrum Solid portions of the enantiopure shift reagent were then added incrementally to build up a series of spectra in which the molar ratio of enantiopure shift reagent is varied

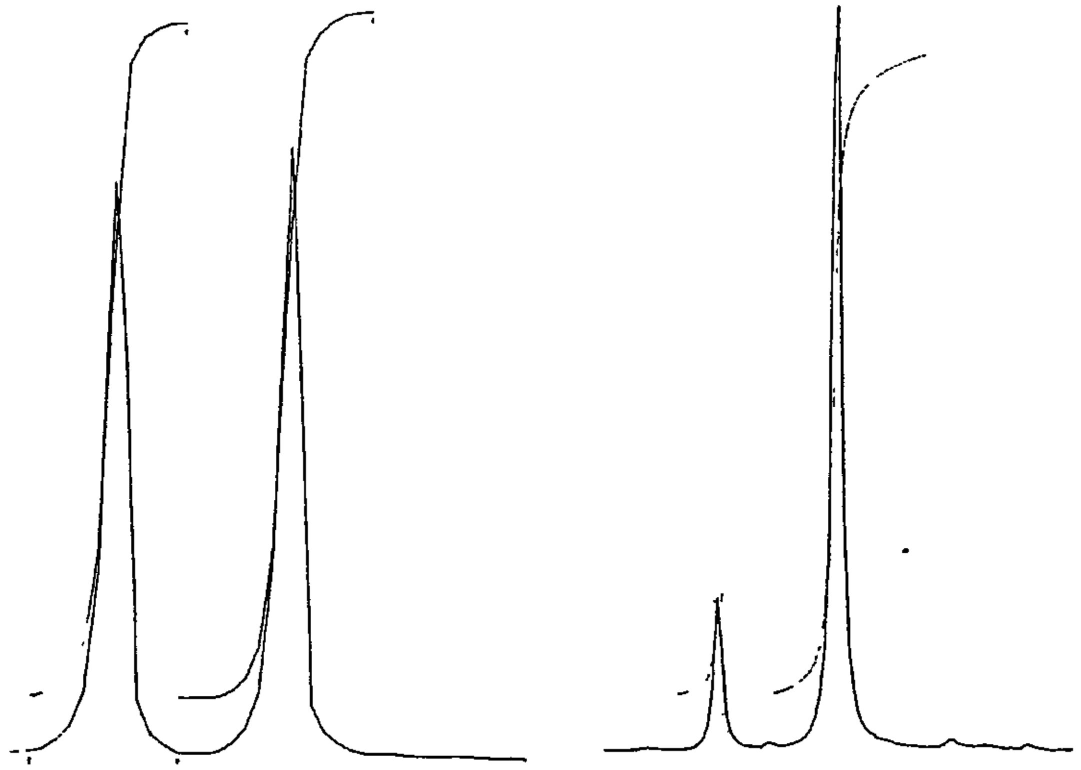


Figure 10

In our case a baseline separation of one of the signals due to a methyl ester was achieved using 0 8 equivalents of enantiopure shift reagent, this can be seen clearly in **Figure 10** where the chiral shift spectrum of the racemic mixture is compared with an enantiomerically enriched mixture ((S)-(-)-enantiomer in excess). In each case we obtained the (S)-(-)-enantiomer shown in excess, where the absolute configuration was determined by comparison of the optical rotation with literature values [95]

Good levels of enantiocontrol were obtained using ligand **77c** containing an *iso*-propyl group, but attempts to improve enantioselectivity by using ligands **77d** and

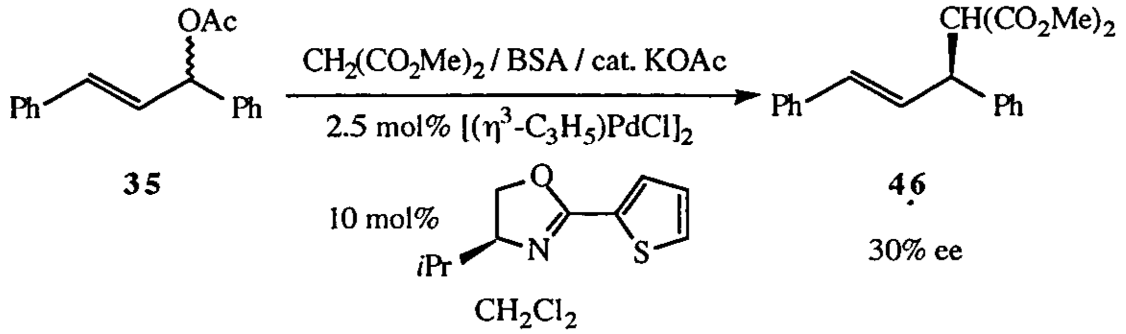
77e with the phenyl and *tert*-butyl groups afforded no reaction, presumably for steric reasons A similar lack of reactivity was observed employing ligand **83** containing the sterically cumbersome trityl ether After being heated under reflux for 120 hours no product was detected by TLC analysis or by examinaton of the crude NMR spectra (**Table 4**)

Table 4

Ligand	*Isolated yield (%)*	*Enantiomeric excess (%)*
77b	68	24
77c	63	68
77d	No reaction	–
77e	No reaction	–
77f	56	6

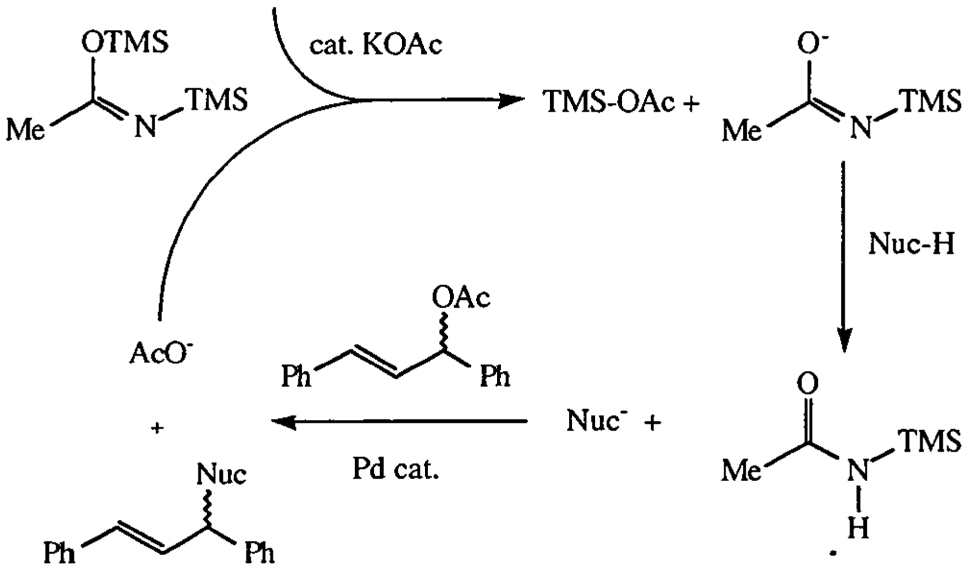
Remarkably, there was no observed enantiomeric excess when ligand **82** containing the pendant hydroxy component was used in the alkylation reaction though the product **46** was obtained in a respectable 65% yield This implies two things, Firstly, the hydroxy group does not impair the ligands role in the catalytic cycle. Second, there are no beneficial interactions with the incoming nucleophile that would enhance asymmetric induction

It should be noted that the observed enantioselectivity was very sensitive to the reaction solvent Performing the reaction in more co-ordinating solvents dramatically lowered the level of enantioselection For example, employing ligand **77c** in DMF under otherwise identical conditions to those in THF afforded the product **46** in enhanced yield (91%) but with diminished enantioselectivity (12% ee) The reaction in non-coordinating solvents gave problems due to the insolubility of the nucleophile However, the use of dimethyl malonate in the presence of *bis*-trimethylsilylacetamide[96] allowed the reaction to proceed in dichloromethane initiated by the addition of a catalytic amount of potassium acetate as illustrated in **Scheme 35**, but unfortunately with reduced yield (35%) and reduced enantiomeric excess (30% ee).



Scheme 35

The role of BSA in palladium catalysed allylic alkylations has not been clearly defined. No reaction occurs when the nucleophile is mixed with BSA in THF-d_8 over 48 hours as judged by the ^1H and ^{13}C NMR spectra, indicating that BSA is not involved in the direct silylation of the nucleophile [97] In addition, the reaction does not take place without added BSA or in the presence of triethylamine or 1,8-*bis*(dimethylamino)naphthalene The ability of BSA to promote the reaction may be due to desilylation of BSA by liberated acetate leading to deprotonation of the nucleophile *in situ*. Alkylation may then take place liberating more acetate as illustrated in **Scheme 36**.



Scheme 36

Under the standard conditions in dry THF, increasing the ratio of ligand **77c** to palladium was found to increase both the yield and enantioselectivity of the reaction **(Table 5)** These facts strongly suggest a low affinity between the ligand and the palladium allyl complexes, although association constants have not been determined.

Table 5

Palladium : Ligand	***Isolated yield (%)***	***Enantiomeric excess (%)***
1 : 1	23	34
1 : 2	63	68
1 : 4	85	76
1 : 10	89	81

The fact that the thienyl oxazolines do not bind strongly to palladium is further demonstrated by keeping the ligand **77c** to palladium ratio constant at 2:1 and varying the volume of solvent added to the reaction under otherwise standard conditions. At low concentrations of palladium ligand complex the resulting yields and enantioselectivities were diminished However, increasing the concentration of enantiopure catalyst led to higher selectivities and increased conversions (**Table 6**)

Table 6

Volume of added solvent (ml)	*Isolated yield (%)*	*Enantiomeric excess (%)*
0.5	85	80
2 0	63	68
20 0	39	40

2.5 Summary

(i) The thienyl oxazolines are easily prepared in one step from commercially available materials

(ii) The thienyl oxazolines succeed in their aim of controlling enantioselectivity through a combination of steric and electronic factors The question of increasing the levels of asymmetric induction has to be addressed

(iii) The thienyl oxazoline ligands do not bind strongly to the palladium allyl complexes. A symptom of this is their low reactivity.

Chapter Three

Sulfur and Phosphorus Containing Oxazolines

3.1 *Introduction*

We anticipated that the precise nature of the auxiliary donor ligand would have an influence on the electronic and steric environment around the metal. In order to examine such influences which directly relate to the rate of reaction and enantioselectivity, it was decided to synthesise enantiopure oxazoline ligands with auxiliary sulfide and diphenylphosphinophenyl donors, as shown in **Figure 11.**

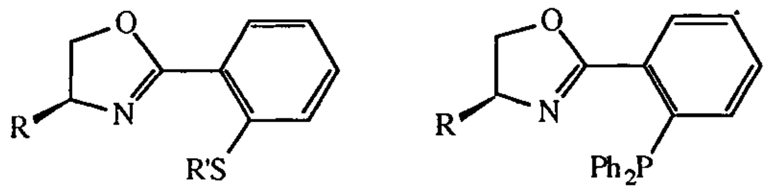
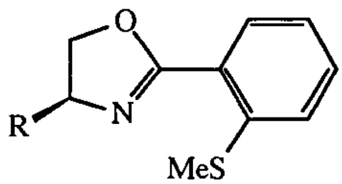


Figure 11

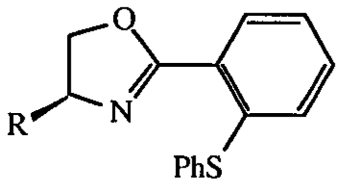
3.2 *Preparation of enantiopure aryl sulfide and phosphine containing oxazolines*

(i) Preparation of enantiopure aryl sulfide ligands

We wished to prepare enantiopure oxazoline ligands which contained a sulfide donor ligand. Although the possibilities are wide-ranging, we considered two electronically and sterically distinct ligand types **86** and **87**.

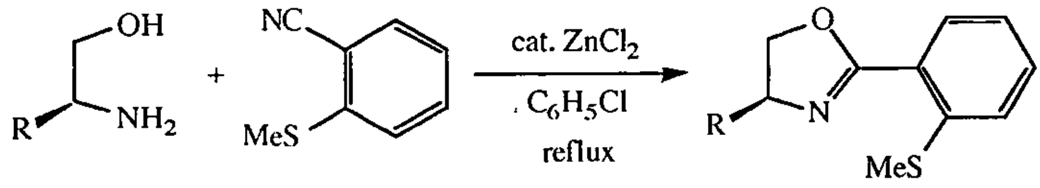


86



87

The family of enantiopure 2-((2-methylthio)phenyl)oxazolines **86a–e**, was prepared in one step from the commercially available 2-(methylthio)benzonitrile **88** and enantiopure amino alcohols as depicted in **Scheme 37**.



80a–e **88** **86a–e**

Scheme 37

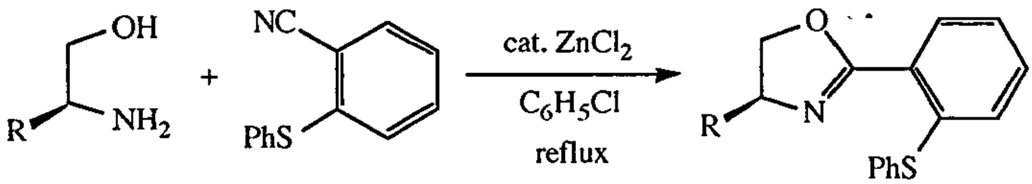
Thus, **88** was heated under reflux with the appropriate enantiopure amino alcohol **80a-e** in the presence of a catalytic amount of anhydrous zinc chloride in chlorobenzene for 48 hours. After aqueous work-up the ligands were readily purified by column chromatography affording the corresponding 2-((2-methylthio) phenyl)oxazolines **86a-e** in good yields **(Table 7)**

Table 7

Amino alcohol	*R*	*Oxazoline*	*Yield (%)*
80a	Me	**86a**	60
80b	CH_2Ph	**86b**	42
80c	^{i}Pr	**86c**	56
80d	Ph	**86d**	58
80e	^{t}Bu	**86e**	53

The family of 2-((2-methylthio)phenyl)oxazolines **86a-e** proved to be air-stable ligands and have all been fully characterised The formation of the oxazoline is easily demonstrated by ^{1}H NMR where the singlet due to the $SC\underline{H}_3$ of the 2-(methylthio)benzonitrile at δ 2 53 ppm disappears and is replaced by the heated under reflux for 24 hours whereupon a clear solution was obtained Aqueous work-up followed by flash chromatography afforded the desired 2-(phenylthio) benzonitrile **90** as a colourless crystalline solid.[100]

In an analogous fashion to the 2-((2-methylthio)phenyl)oxazolines, conversion of 2-(phenylthio)benzonitrile **90** to the oxazolines **87c** and **87e** was achieved by treatment with the corresponding enantiopure amino alcohols **80c** and **80e** under the standard zinc chloride catalysed conditions, as shown in **Scheme 39**



R=*i*Pr **80c**
*t*Bu **80e**

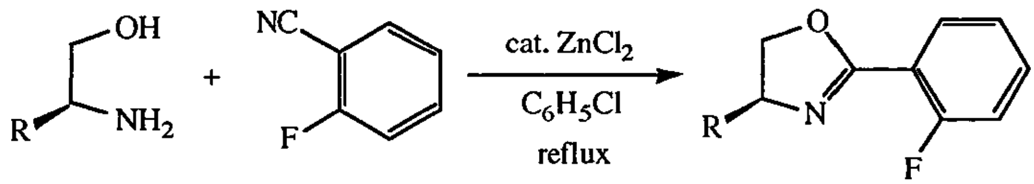
90

R=*i*Pr **87c** 73%
*t*Bu **87e** 62%

Scheme 39

(ii) Preparation of enantiopure phosphine ligands

The enantiopure 2-((2-diphenylphosphino)phenyl)oxazolines **91a-e** were prepared in collaboration with Graham J. Dawson The ligands were assembled by a two step process Initially, 2-fluorobenzonitrile **89** was converted into the corresponding oxazoline **92a-e** upon treatment with an enantiopure amino alcohol using the standard catalytic zinc chloride conditions, the reaction mixtures being heated under reflux in chlorobenzene for 24 hours (**Scheme 40**).



80a–e **89** **92a–e**

Scheme 40

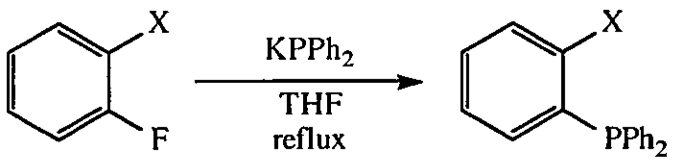
After work-up and purification the 2-(2-fluorophenyl)oxazolines **92a-e** were obtained in moderate yields (**Table 8**)

Table 8

Amino alcohol	*R*	*F-oxazoline*	*Yield (%)*
80a	Me	**92a**	47
80b	$PhCH_2$	**92b**	48
80c	^iPr	**92c**	46
80d	Ph	**92d**	49
80e	^tBu	**92e**	56

The experimental procedure was optimised for the case of **92c**. It became apparent that as the reaction time increased beyond 12 hours the yield of product diminished. It was also noted that decreasing the volume of chlorobenzene added to the reaction mixture enhanced the isolated yield of **92c**. The highest yields of **92c** were obtained when the 2-fluorobenzonitrile **89** and *L*-valinol **80c** were heated together with 10 mol% of zinc chloride in the absence of any solvent at 160°C for 2 hours. Aqueous work-up and flash chromatography afforded **92c** as colourless oil in 85% yield

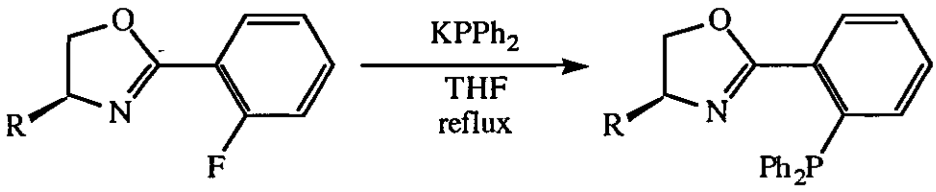
We have demonstrated that potassium diphenylphosphide may be employed to displace fluoride from 2-substituted aryl fluorides [101] Potassium diphenylphosphide may be conveniently purchased as a 0.5M solution in THF (Aldrich). Addition of the 2-substituted aryl fluoride to a solution of the phosphide at reflux affords the corresponding phosphines in good to excellent yields, as illustrated in **Scheme 41**.



X	*Yield (%)*
CHO	81
COMe	96
CN	89
OMe	75

Scheme 41

The same methodology could be applied to the synthesis of the 2-((2-diphenylphosphino)phenyl)oxazolines **91a-e**. Hence, the addition of a solution of the appropriate 2-(2-fluorophenyl)oxazoline **92a-e** in THF to a stirring solution of the diphenylphosphide at reflux afforded, after work-up and flash chromatography the corresponding 2-((2-diphenylphosphino)phenyl)oxazoline **91a-e** as shown in **Scheme 42.**



92a–e **91a–e**

Scheme 42

The potassium diphenylphosphide is a red solution in THF. When the solution is heated to reflux temperature, no loss of colour is observed Upon the addition of the 2-(2-fluorophenyl)oxazoline as a solution in THF the red solution associated with the diphenylphosphide rapidly fades to orange and then pale yellow. This provides a convenient method of monitoring the progress of the reaction because when the solution has changed to the yellow colour the transformation is complete. This occurs within one minute for all of the 2-(2-fluorophenyl) oxazolines **92a-e** affording the corresponding 2-((2-diphenylphosphino)phenyl) oxazolines **91a-e** in excellent yield (**Table 9**)

Table 9

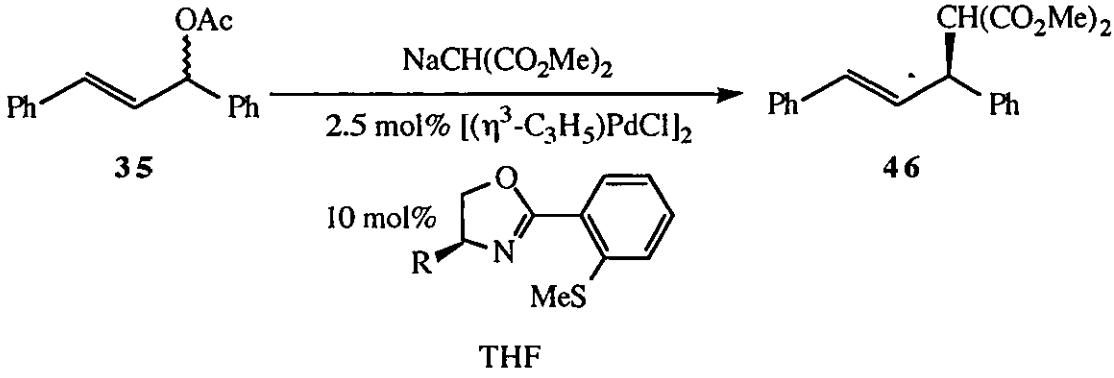
F-oxazoline	*R*	*P-oxazoline*	*Yield (%)*
92a	Me	**91a**	80
92b	$PhCH_2$	**91b**	76
92c	^{i}Pr	**91c**	76
92d	Ph	**91d**	84
92e	^{t}Bu	**91e**	92

All of the 2-((2-diphenylphosphino)phenyl)oxazolines **91a-e** were isolated as air-stable crystalline solids and all have been satisfactorily characterised Examination of the infra-red spectra and the ^{1}H NMR spectra clearly confirmed the presence of an oxazoline The mass specra complemented this information in all cases revealing the expected molecular ion. Indisputable evidence for the presence of the phosphine moiety was discovered in the ^{31}P NMR spectrum A singlet at –4 7 ppm is reported to be characteristic of a trivalent aryl phosphine.[102] It was discovered that on exposure to air in solution, slow oxidation to the corresponding phosphine oxides occurs over a period of several weeks. This could be seen quite clearly in the infra-red spectrum with the appearance of an absorption band at ~1250 cm^{-1} due to the P=O stretch of the phosphine oxide

3.3 *Results for palladium catalysed allylic substitution*

(i) Using enantiopure aryl sulfide ligands

With a facile ligand synthesis in hand, we investigated the suitability of the 2-((2-methylthio)phenyl)oxazoline ligands **86a-e** for asymmetric palladium catalysed allylic substitution (**Scheme 43**).



Scheme 43

Hence, the allylic acetate **35** was treated with a slight excess of the sodium salt of dimethyl malonate in THF at reflux in the presence of 2.5 mol% of [Pd(η^3-C_3H_5)Cl]$_2$ and 10 mol% of the ligand **86a-e** After 2 hours the reaction was complete in every case according to TLC analysis. After work-up, the substitution product **46** was isolated by flash chromatography in good yields and with reasonable levels of asymmetric induction (**Table 10**). In each case we observed the S-(-)-enantiomer predominating.

The rate of the allylic substitution reaction with ligands **86a-e** is far greater than for the thienyl oxazoline ligands **77b-f** This rate difference may be attributed to the increased π-acceptor ability of a sulfur as a sulfide compared with a sulfur contained within an electron rich thiophene ring

Table 10

Ligand	*Isolated yield (%)*	*Enantiomeric excess (%)*
86a	91	40
86b	78	50
86c	93	55
86d	95	62
86e	92	68

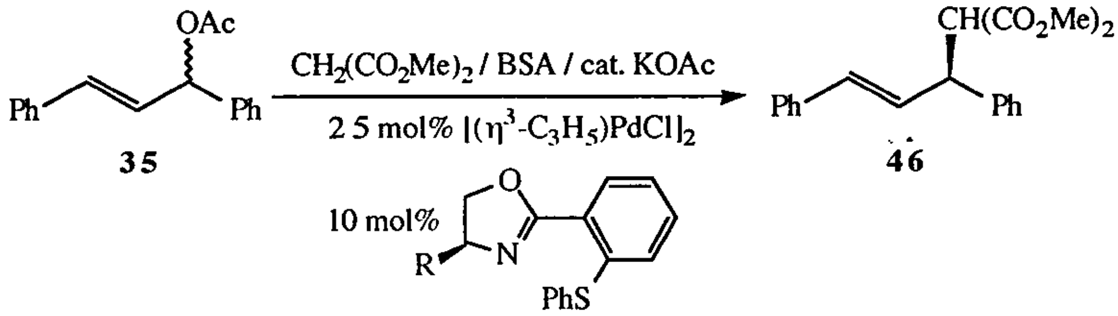
Encouraged by the increase in reactivity observed with the 2-((2-methylthio)phenyl)oxazolines **86a-e**, the substitution reactions were performed at room temperature It was found that the reactions proceeded to completion within 12 hours, and at the lower temperature the process was more enantioselective (**Table 11**).

Table 11

Ligand	*Isolated yield (%)*	*Enantiomeric excess (%)*
86b	90	52
86c	98	58
86d	84	66
86e	86	80

The level of enantioselectivity was observed to decrease when the alkylation reaction was performed under the standard BSA conditions in dichloromethane with ligand **86c**. After 24 hours at room temperature the product **46** was obtained in quantitative yield and an enantiomeric excess of 42% was detected.

In comparison with the corresponding 2-((2-methylthio)phenyl)oxazolines **86c** and **86e**, the 2-((2-phenylthio)phenyl)oxazolines **87c** and **87e** were employed as ligands for enantioselective palladium catalysed allylic substitution. The allylic acetate **35** was treated with dimethyl malonate and BSA in the presence of 2 5 mol% of the palladium chloride dimer catalyst and 10 mol% of the appropriate ligand as detailed in **Scheme 44**



Scheme 44

After stirring at room temperature the substitution product **46** was isolated in all cases enriched in the S-(-)-enantiomer as determined by comparison of the optical rotation with literature values The superior asymmetric induction achieved by changing from a methyl sulfide to a phenyl sulfide can be rationalised in terms of the obvious steric effects or the electronic effects as aromatic sulfides are better π-acceptors than aliphatic sulfides **(Table 12)**.[103]

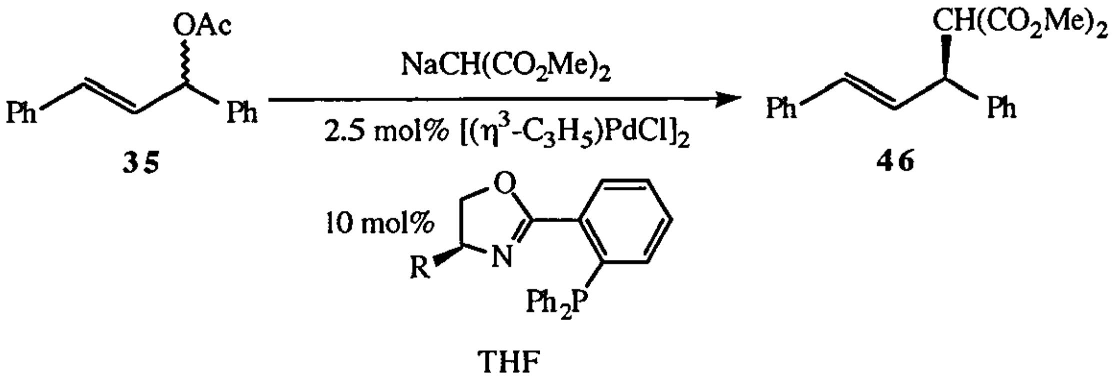
Table 12

Ligand	*Solvent*	*Time (hr)*	*Yield (%)*	*ee (%)*
87c	THF	36	91	78
87c	CH_2Cl_2	36	96	90
87e	THF	36	92	89
87e	CH_2Cl_2	48	67	>95
87e	CH_2Cl_2	96	92	>95

For those reactions using dichloromethane as solvent, enhanced enantioselectivity was observed This is likely to be due to the increased binding of the ligands in the non-coordinating solvent Excellent levels of enantioselection are achieved with ligand **87e**. However, there is a price to be paid; a feature of the asymmetric substitution involving **87e** in dichloromethane was lower reactivity of the catalytic complex

(ii) Using enantiopure phosphines

The readily accessible 2-((2-diphenylphosphino)phenyl)oxazolines **91a-e** were applied to the palladium catalysed allylic substitution reaction of allylic acetate **35** shown in **Scheme 45**, affording the substitution product **46** with very high levels of enantioselectivity **(Table 13)**.



Scheme 45

All of the ligands **91a-e** were seen to provide consistently high enantioselectivities All the complexes were found to induce the (S)-configuration of product. Surprisingly, there is only a small variation in the enantioselectivity observed when the size of the R group is varied considerably. Another remarkable feature of these ligands is the very short reaction times In all cases, essentially quantitative yields of the substitution product **46** were obtained in less than one hour!

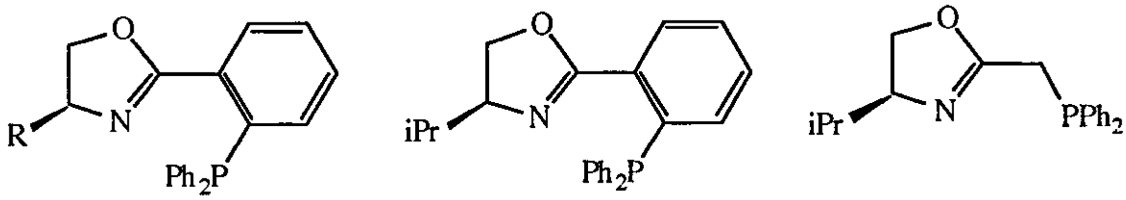
Table 13

Ligand	*R*	*Isolated Yield (%)*	*Enantiomeric excess (%)*
91a	Me	88	90
91b	$PhCH_2$	96	92
91c	^{i}Pr	>99	94
91d	Ph	96	92
91e	^{t}Bu	>99	90

Compared to the other oxazoline ligands **77a-e**, **86a-e**, **87c** and **87e** the 2-((2-diphenylphosphino)phenyl)oxazolines **91a-e** are less dependent on the choice of solvent and temperature. For example, in the presence of the palladium complex derived from ligand **91a**, the allylic acetate **35** is smoothly converted into the substitution product **46** in quantitative yield by treatment with the sodium salt of dimethyl malonate in THF at reflux temperature with no loss of enantioselectivity. When the reactions were run in dichloromethane under the standard BSA conditions employing ligand **91c**, conversion was found to be complete within one hour at room temperature affording the expected product **46** in quantitative yield with an enantioselectivity of >95% ee.

From these results the 2-((2-diphenylphosphino)phenyl)oxazolines **91a-e** are established as the most effective ligands for asymmetric palladium catalysed allylic substitution After this work was completed reports appeared in the literature from the laboratories of Pfaltz[104] and Helmchen[105] disclosing the synthesis and application of enantiopure phosphine containing oxazolines Both groups reported their use in palladium catalysed allylic substitution and achieved equally high enantioselectivities and reactivity (**Figure 12**).

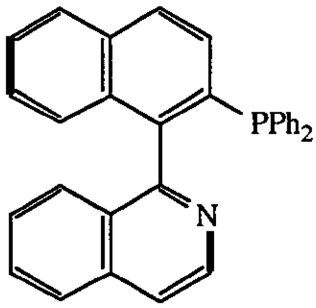
Pfaltz **Helmchen**



up to 99% ee with **35** | up to 98.5% ee with **35** | up to 73% ee with **35**

Figure 12

Very recently, Brown[106] has reported the use of chelating ligand **93** which contains two distinct donor atoms for asymmetric palladium catalysed allylic substitution.



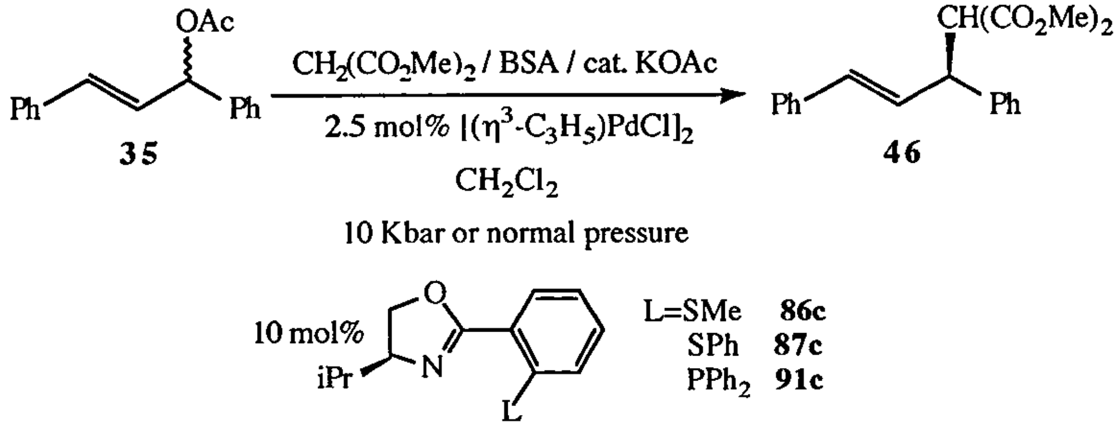
93

98% ee with **35**

3.4 The effect of pressure

It has been recognised that an important factor for the decrease in asymmetric induction in the palladium catalysed allylic substitution reaction is the dissociation of ligands from palladium. Therefore, the reaction of allylic acetate **35** with dimethyl malonate was investigated under high pressure conditions (10 Kbar) since it was anticipated that high pressure would enhance the binding of ligands to palladium.[107] This approach has been reported to be successful in the palladium catalysed coupling of 2,3-dihydrofuran and aryl compounds. At high pressure an increase in activity of the catalyst and an increase in enantioselectivity compared to normal pressure was observed [108]

Oxazolines **86c**, **87c** and **91c** were chosen to participate in this study due to their structural similarity but distinct binding properties To ensure a valid comparison, the reactions at normal and high pressure were performed on the same stock solution The components of the reaction mixture were added together at room temperature and pressure, the reaction was then initiated by the addition of a catalytic amount of potassium acetate The reaction mixture was then divided into two equal portions, one half of which was left standing for the requisite time, the other half was sealed in a teflon tube and subjected to a pressure of 10Kbar for the same amount of time (**Scheme 46**).



Scheme 46

After the allotted time, the reaction mixtures were filtered through a pad of silica and then analysed by capillary gas chromatography to compare their extent of conversion to desired product **46** The crude mixtures were further purified by flash chromatography to isolate the product **46**. The preferred assay to determine the enantiomeric excess was the use of the enantiopure shift reagent $Eu(hfc)_3$ in ^1H NMR.

Table 14

Ligand	*Pressure*	*Conversion (%)*	*Enantiomeric excess (%)*
86c	Normal	65	42
86c	10 Kbar	98	28
87c	Normal	58	82
87c	10 Kbar	97	70
91c	Normal	100	>95
91c	10 Kbar	100	86

The experiments were executed with 10 mol% of ligand and a palladium to ligand ratio of 1 to 2. After 4 hours it emerged that for oxazolines **86c** and **87c** the rate of reaction is significantly increased at higher pressures **(Table 14)** It was to be expected that no discernible increase in rate would be detected for the phosphine containing oxazoline **91c**, which is known from previous studies to reach completion within one hour at normal temperature and pressures However, in all cases enantioselectivity was diminished at high pressure compared with ambient pressure

3.5 Summary

(i) Both sulfide and phosphine containing oxazolines are effective in controlling the enantioselectivity of palladium catalysed allylic substitution.

(ii) The observed enantioselectivity was dependent on the nature of the auxiliary ligand and increased in the order (PPh_2 > SPh > SMe)

(iii) The reactivity of the phosphine containing oxazolines are exceptional even in comparison to triphenylphosphine as the supporting ligand

(iv) For the sulfide containing oxazolines, the observed enantioselectivities were dependent on the steric environment created by the 4-substituent on the oxazoline ring (^{t}Bu > Ph > ^{i}Pr > $PhCH_2$ > Me) The phosphine containing oxazolines were surprisingly insensitive to these changes

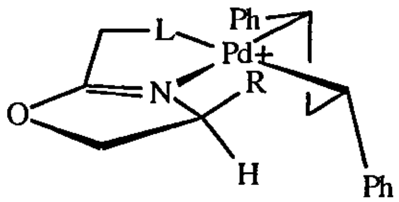
(v) High pressure (10 Kbar) reduces the observed enantioselectivity but increases the rate of reaction for palladium catalysed allylic substitution

Chapter Four

Origin Of Enantioselectivity Using Enantiopure Oxazoline Ligands

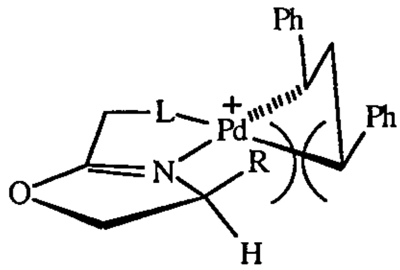
4.1 Introduction

The enantioselectivities obtained using the enantiopure oxazolines have demonstrated that the stategy we have adopted represents a fresh solution to the problem of asymmetric palladium catalysed allylic substitution The mechanistic rationale for the observed enantioselectivity is not obvious With the non-symmetrical enantiopure oxazolines, two diastereomeric allyl complexes are generated with palladium (0) Intuitively, it would be expected that complex **94**, the 'M' form would be sterically preferred over **95**, the 'W' form, due to the steric interactions between the R and the allyl moiety, and this was the reason for preparing these ligands In complex **94** this steric interaction appears not to be present, and therefore we assumed that the reaction would proceed *via* this complex.



94

Sterically favoured



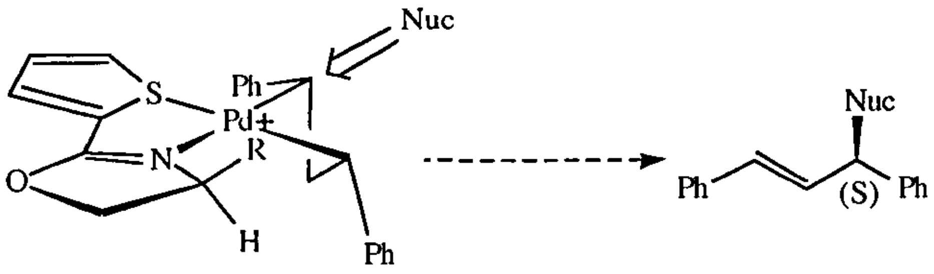
95

Sterically disfavoured

For enantioselection to be achieved the differing *trans* influences of the two donor atoms in the ligand would create an electronic bias in the intermediate palladium allyl species This would then be expected to direct nucleophilic addition to one terminus of the allyl group in preference to the other.

4.2 Using enantiopure thienyl oxazolines

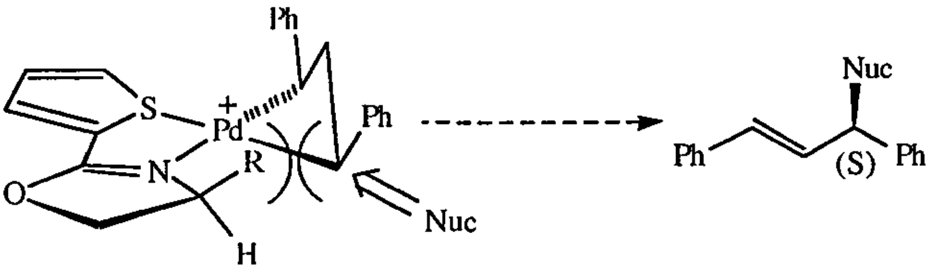
The thienyl oxazolines were successful in controlling the enantioselectivity of nucleophilic addition The experimental evidence suggests that the reaction proceeds *via* one of two possible diastereomeric transition states **96** or **97** in favour of the product with the (S)–configuration (**Figure 13**).



96

Sterically favoured

Observed enantiomerically enriched product



97

Sterically disfavoured

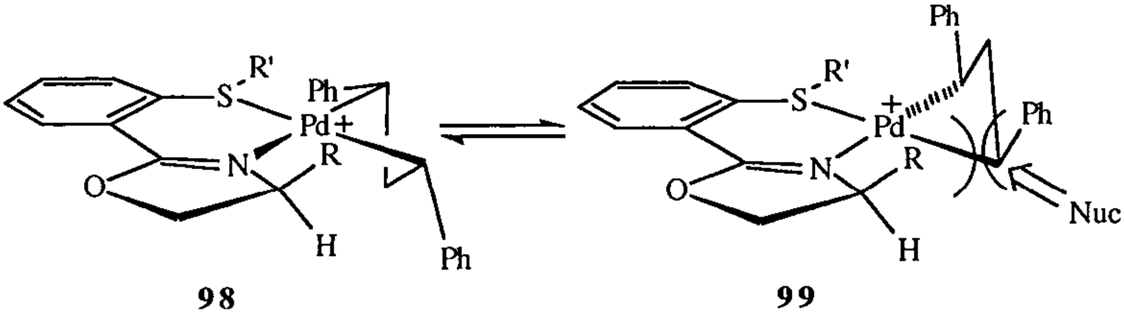
Figure 13

If the reaction proceeds *via* the sterically favoured complex **96** the nucleophile would have to attack *trans* to the nitrogen of the oxazoline ring. This would infer that the thiophene ring was not acting as a π-acceptor but was instead behaving more like a π-donating moiety. This might not be unexpected if the thiophene is viewed as a π-excessive aromatic Thus, electronic information would be relayed *via* the *trans* effect to the terminus *trans* to the sulfur. This terminus would be expected to possess a greater electron density, rendering the site less susceptible to nucleophilic attack

On the other hand, the reaction might proceed *via* the less favoured complex **97**. If this was the case, the nucleophile would have to attack the terminus *trans* to the thiophene ring. This would imply that a sulfur contained within a thiophene ring could act as a π-acceptor, which as a consequence would render the carbon *trans* to the sulfur more electrophilic. Whichever is the correct reaction pathway, the stereochemical outcome is being controlled by both the steric and electronic properties of the ligand

4.3 Using enantiopure sulfide containing oxazolines

All of the enantiopure sulfide containing oxazolines furnished the addition product enriched with the (S)-(–)-enantiomer This is analogous to the stereochemical outcome observed for the enantiopure thienyl oxazolines. In the case of the thienyl oxazolines it has been discussed that the thienyl group might function as a π-donor, and hence nucleophilic addition might occur *cis* to the sulfur However, for the sulfide containing oxazolines this argument is not valid, the nucleophile is only likely to approach the allyl terminus *trans* to the auxiliary sulfide ligand. Either the transition state is more distorted than represented here or the two diastereomeric allyl complexes are in rapid equilibrium as represented in **Scheme 47**. The reaction might then proceed through the less stable, but possibly more reactive, intermediate **99**

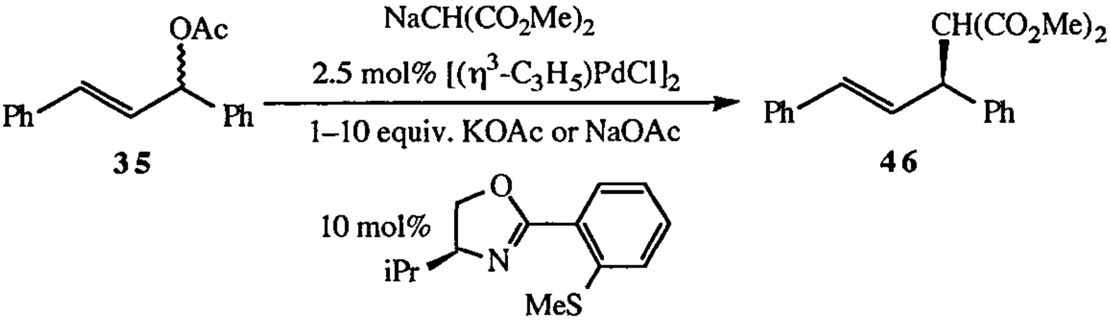


Sterically favoured **Sterically disfavoured**

More reactive?

Scheme 47

The rate at which such an equilibrium occurs would have an effect on the enantioselectivity of the reaction Since palladium allyl complexes are known to equilibrate in the presence of acetate[109], it was decided to examine the effect of adding acetate to the reaction Oxazoline **86c** was chosen to participate in this study, since the levels of enantioselectivity achieved with this ligand were modest and therefore either enhancement or reduction of the enantioselectivity would be easily detected (**Scheme 48**).



THF

Scheme 48

The reactions were performed under standard conditions at room temperature in THF. It was found that the addition of excess acetate to the reaction dramatically decreases the observed enantioselectivity of the product **46** (**Table 15**) This implies that the rate of equilibration of the two possible diastereomeric intermediates may be significant

Table 15

Added acetate	*Enantiomeric excess (%)*
None	58
1eq KOAc	48
10 eq KOAc	30
10 eq NaOAc	34

During the course of the reaction, the concentration of liberated acetate ion increases (in the absence of added acetate). In accord with the previous observations, the enantioselectivity of the reaction would be expected to decrease as the reaction progresses. This was investigated under the standard reaction conditions in THF at room temperature using ligand **86c**. At various time intervals aliquots were removed from the reaction and quenched with water After work–up the crude mixture was subjected to gas chromatography (SGE BP1 capillary column) to reveal the extent of conversion and analysis of the ^1H NMR spectrum in the presence of enantiopure shift reagent to determine the enantiomeric excess. Remarkably, no significant variation in the level of enantioselectivity was observed in relation to time and the extent of conversion **(Table 16)**

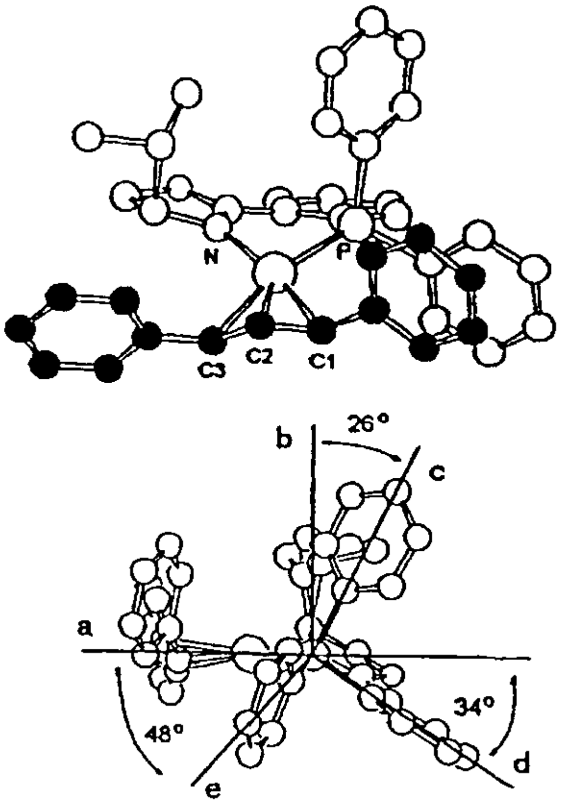
Table 16

Time (*hr*)	*Conversion* (*%*)	*Enantiomeric excess* (*%*)
0 5	12	44
2	64	46
5	85	44
8	100	48

4.4 Using enantiopure phosphine containing oxazolines

The enantiopure phosphine containing oxazolines have proved to be the most effective ligands for the palladium catalysed allylic substitution reactions studied In all cases, the reactions reached completion within one hour at room temperature, the enantioselectivities were consistently very high and furnished the product with the (S)–(–)–enantiomer predominating.

Very recently, Helmchen *et al* have obtained crystal and solution structures of an allylpalladium complex co-ordinated to a phosphine containing oxazoline ligand.[110] The results presented by Helmchen along with our own observations enable conclusions concerning the stereochemical course of allylic substitution to be drawn. The X–ray crystal structure of the allylpalladium complex derived from ligand **91c** is shown in **Figure 14**, the anions and hydrogen atoms have been omitted for clarity. Selected bond lengths and angles are given



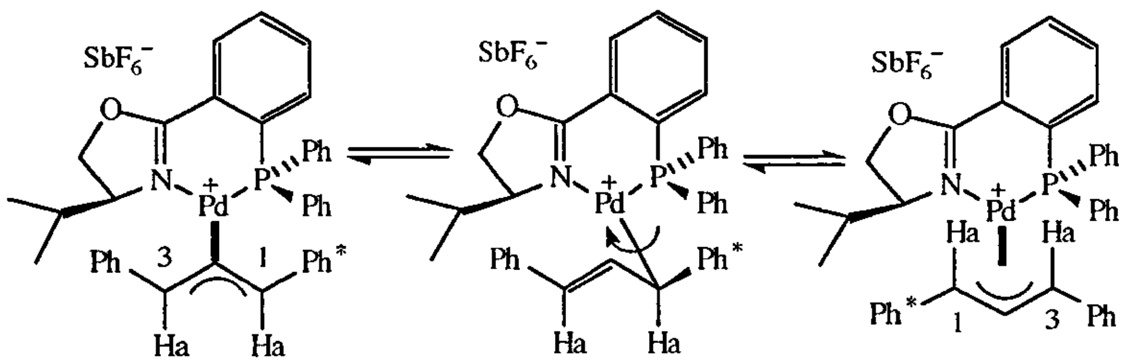
Distance (pm)		Angle (°)	
Pd–N	209.0	N–Pd–P	88 6
Pd–P	226.2	P–Pd–C1	100 4
Pd–C1	214 3	C1–Pd–C3	66 6
Pd–C2	217 9	C3–Pd–N	103 5
Pd–C3	226.3		

Figure 14

In the side view, the horizontal line (a) marks the co-ordination plane spanned by C1, C3, Pd, P, and N. The vertical line (b) is erected perpendicularly to the co-ordination plane at the P atom The angle between (a) and (d) is mainly determined by the necessity of bond angles near 90° at Pd and steric effects. Axial disposition of the *iso*–propyl group is a consequence of steric interactions of this group with ligands at Pd

Contrary to expectations, the 'W' form corresponding to the sterically disfavoured complex **100** was found in the crystal The disclosure by Helmchen that the Pd–C bond *trans* to phosphorus (226 ± 1 pm) is longer than the Pd–C bond *trans* to nitrogen (214 ± 1 pm) would be anticipated from the allylic complexes of other N–N and P–P chelate ligands [111] The revelation that **100** is the more stable complex may be remarkable in the light of the previous steric analysis, but there is a notable absence of any steric interactions between the 4–substituent on the oxazoline ring and the allylic phenyl group in the crystal structure (**Figure 14**)

NMR investigations were carried out by a variety of methods and revealed interesting results The palladium complex of **91c** with allylic acetate **35** displays an 8 : 1 ratio of the two diastereomeric allyl complexes **100** and **101**. This ratio was found to increase upon lowering of temperature The two complexes are able to interconvert *via* a Pd–C rotation mechanism, this is reported to proceed *via* the opening of the weaker (longer) Pd–C3 bond, as illustrated in **Scheme 49** However, Togni *et al* have recently disclosed an unusual, η^3–η^1 allyl isomerisation in allylpalladium complexes involving novel enantiopure chelating diphosphine ligands [112]

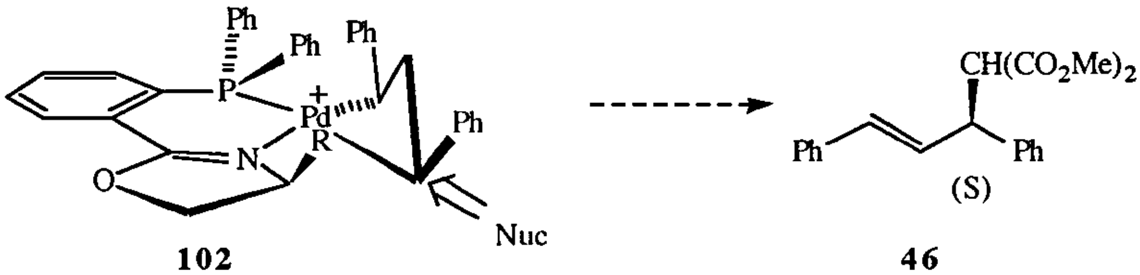


100 **101**

Scheme 49

The level of asymmetric induction achieved with the phosphine containing oxazoline **91c** was consistently above 95% ee (> 39 : 1), whilst the equilibrium diastereomer ratio of the two complexes **100** and **101** is only 8 . 1. This would infer that the control of enantioselectivity is a question of which diastereomer is the most reactive. Nucleophilic addition would 'funnel' through the more reactive diastereomer whilst equilibration of the two diastereomers was being maintained.

Nucleophilic addition at the allylic carbon with the weaker (longer) bond to palladium has previously been demonstrated by Pfaltz and co–workers with palladium complexes of C_2–symmetric *bis*–oxazoline ligands.[113] In line with this reasoning, the observed stereochemical outcome is consistent with complex **102** being the more reactive conformer, nucleophilic addition occuring mainly *trans* to the π-accepting phosphine ligand to afford principally the (S)–enantiomer of alkylation product **46**, as illustrated in **Figure 15** It is feasible that nucleophilic attack occurs at the minor diastereomer to a small extent This would be expected to take place mainly *trans* to the phosphorus furnishing the (R)–enantiomer of addition product.



102

Major diastereomer
More reactive complex

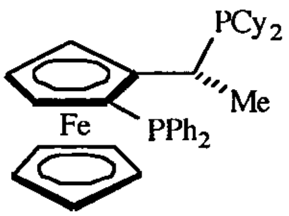
Nucleophile attacks trans to phosphine

46

Figure 15

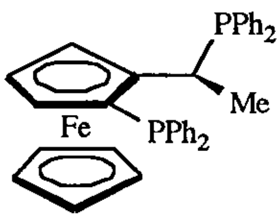
A similar conclusion was reached by Bosnich and co–workers in that the major diastereomer of their Pd–allyl complex, as defined by X–ray, was the one involved in the nucleophilic addition step [114] For the phosphine containing oxazolines the same concept was independently derived by Pfaltz [115] In a related paper Brown rationalises the sense of asymmetric induction for enantioselective alkylation with palladium complexes of 1–(2–diphenylphosphino–1–naphthyl)isoquinoline **93**.[116]

For the enantiopure oxazolines studied, the enantioselectivity was observed to decrease as the π-accepting capability of the ligand decreased (SMe < SPh < PPh_2) This could be attributed to increased nucleophilic attack at the allylic terminus *cis* to the auxiliary ligand in the more reactive diastereomer as the electronic disparity between the two allylic termini decreases. A recent paper by Togni *et al* lends support to this theory [117] For asymmetric allylic alkylation with palladium complexes of novel enantiopure ferrocenyldiphosphines, a decrease in enantioselectivity is observed utilising ligand **103** containing two electronically similar phosphine fragments compared with ligand **52** containing two electronically distinct phosphine groups



52

93% ee with **35**



103

66% ee with **35**

4.5 Summary

The recent crystallographic and NMR spectroscopic studies from the Helmchen and Pfaltz laboratories have shed some light on the pathway of asymmetric palladium catalysed allylic substitution with enantiopure P–N chelate ligands. It seems likely that the sulfur containing oxazolines function in a similar fashion However, as no X–ray or NMR studies have been conducted with the sulfur containing oxazoline ligands, any analogies with the phosphine analogues are hypothetical

(i) Two diastereomeric allylpalladium complexes are generated in the presence of enantiopure ligand The 'W' form predominates in the solid state and in solution

(ii) The ligands rely upon an electronic disparity between the two donor atoms to direct nucleophilic addition.

(iii) The 'W' form is the more reactive of two rapidly equilibrating diastereomers, attack occurs *trans* to the π–accepting auxiliary ligand to furnish in each case the (S)–(–)–enantiomer of product predominantly

(iv) By increasing the π–accepting ability of the auxiliary ligand the enantioselectivity of nucleophilic addition is observed to increase

Chapter Five

Enantiopure Acetals as Ligands

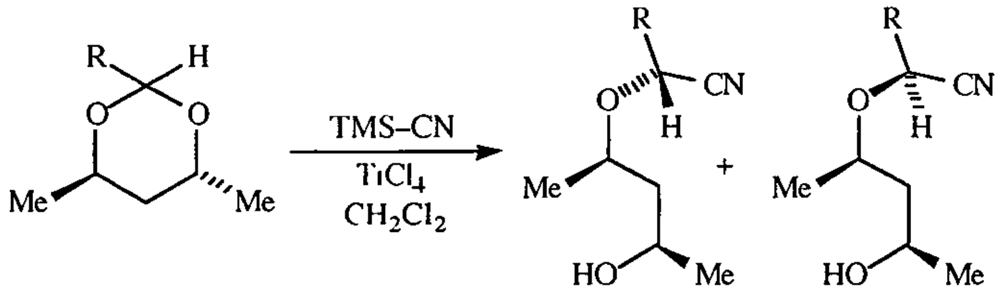
5.1 Introduction

In previous chapters it has been established that enantiopure oxazoline ligands provide high levels of asymmetric induction in palladium catalysed allylic substitution reactions The oxazolines incorporate an auxiliary donor ligand with distinct electronic properties, whilst providing an asymmetric environment adjacent to the chelated metal. We wished to examine the incorporation of other heteroatoms into the design of the ligand Enantiopure acetals would allow this whilst generating a similar topology (**Figure 16**).

Oxazoline ligands **Acetal ligands**

Figure 16

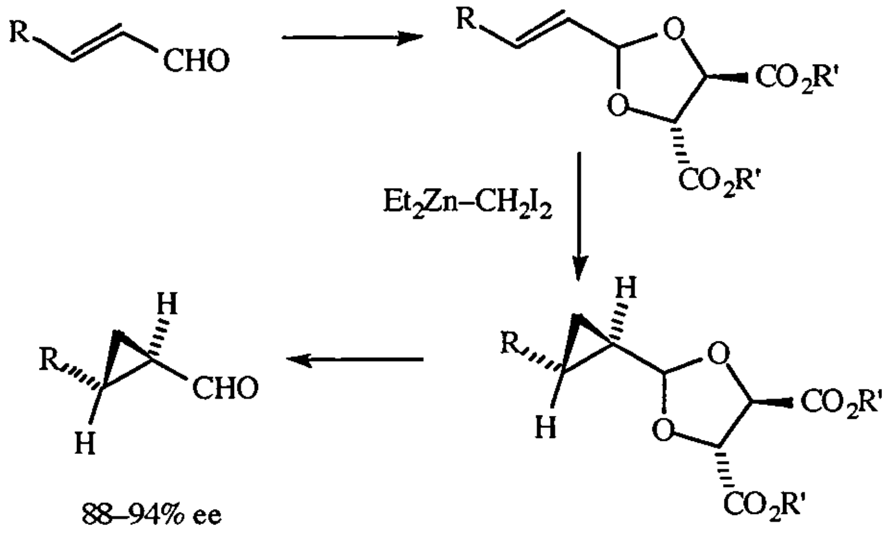
Enantiopure acetals have been successfully employed in diastereoselective reactions for over twenty years [118] A highly effective method for the synthesis of optically active alcohols was developed using enantiopure acetal protecting groups that are subjected to activation by electrophiles[119] or nucleophiles.[120] Johnson *et al* report the reaction of enantiopure acetals derived from (R,R)– and (S,S)–pentane–2,4–diol and cyanotrimethylsilane leading to the production of cyanohydrin ethers and derivatives thereof in high optical and chemical yields **(Scheme 50)**



R=Ph 96.5 3.5

Scheme 50

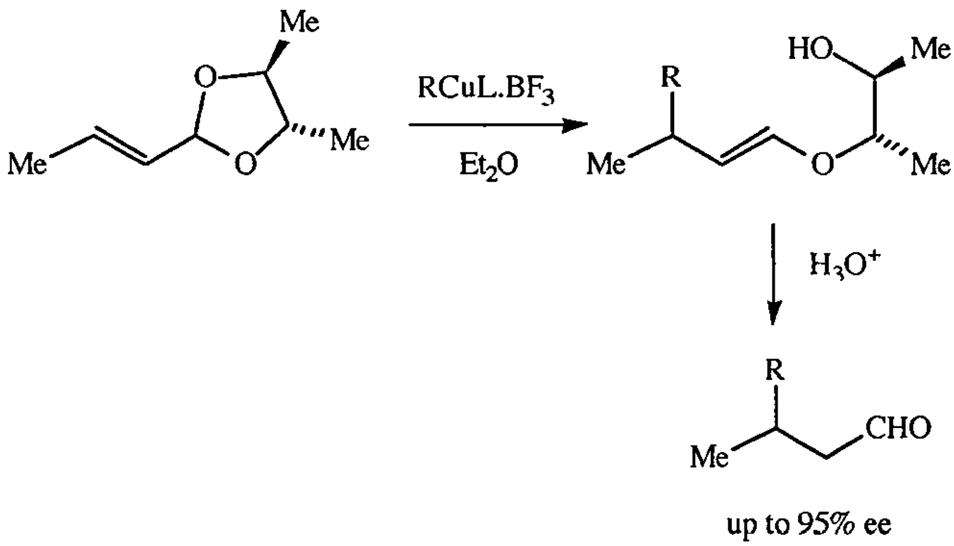
Yamamoto *et al* demonstrate the high efficiency of enantiopure α,β–unsaturated acetals in the asymmetric cyclopropanation reaction.[121] The process is outlined in **Scheme 51**, since both (R,R)– and (S,S)–tartaric acid esters are readily available in an enantiomerically pure form, this method allows the synthesis of both enantiomers of cyclopropanes from α,β–unsaturated aldehydes in a predictable manner.



Scheme 51

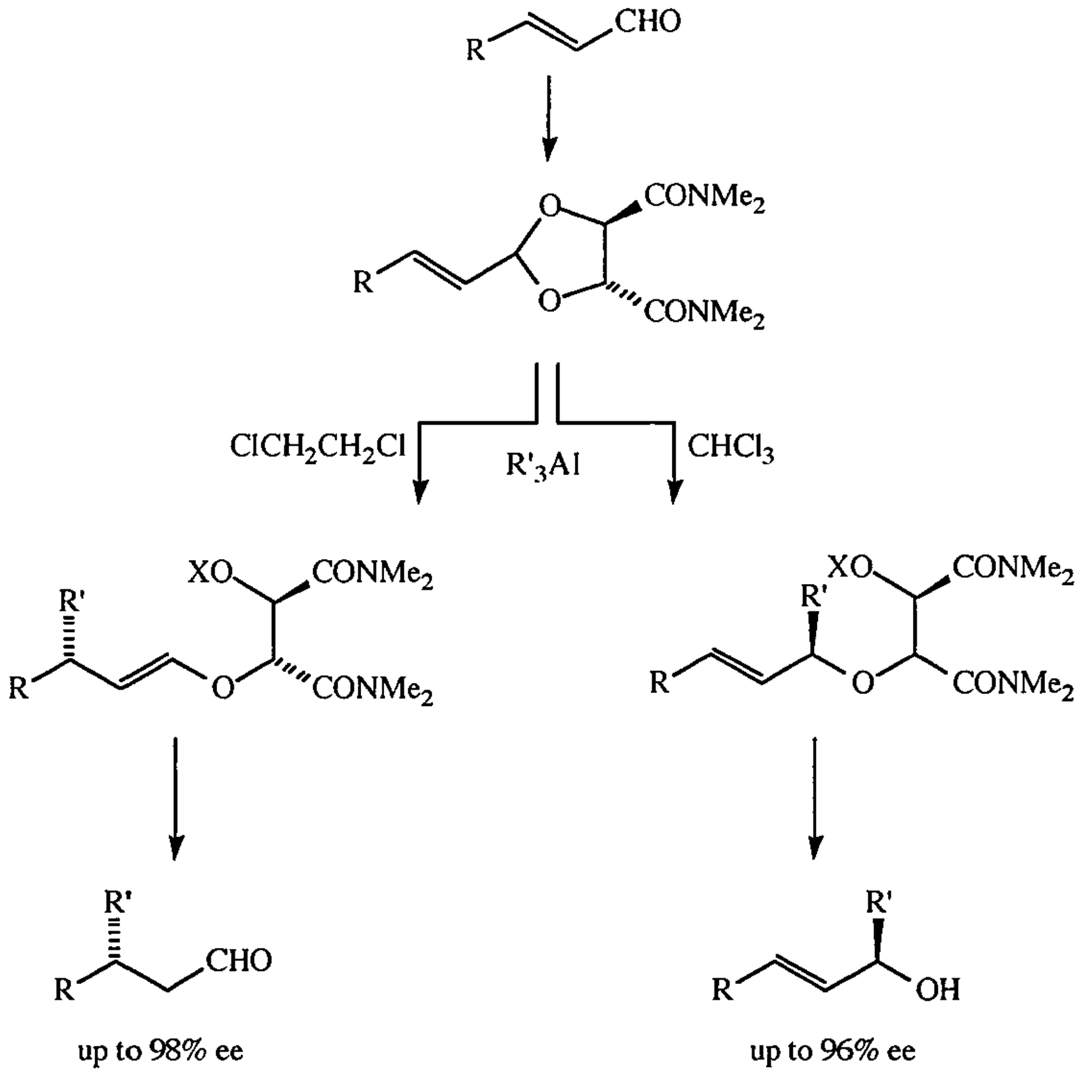
Alexakis *et al* have reported the diastereoselective conjugate addition of achiral organocopper reagents to enantiopure α,β–unsaturated acetals prepared from enantiopure C_2 symmetrical diols.[122] Aryl–, alkenyl– or vinylcopper with

BF_3 Et_2O react with vinylic acetals in an *anti* S_N2' reaction that results in a diastereoselective cleavage of the acetal ring The resulting enol ethers were easily hydrolysed to furnish enantiomerically enriched β–substituted aldehydes with the recovery of the enantiopure diol. (**Scheme 52**) Conjugate addition to enantiopure ketals has also been achieved with moderate stereoselectivity (up to 48% ee)



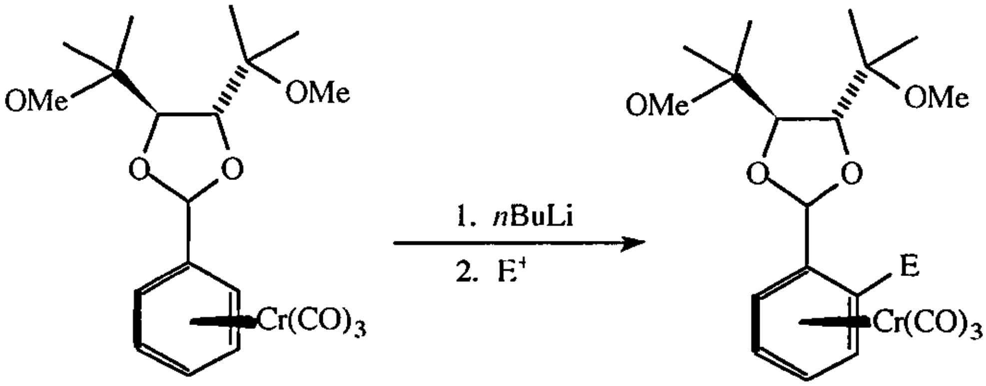
Scheme 52

In a related study, Yamamoto *et al* report the diastereoselective, nucleophilic1,4– or 1,2–addition of trimethylaluminium to enantiopure vinyl acetals derived from α,β–unsaturated aldehydes and (R,R)–(+)–N,N,N',N'–tetramethyltartaric acid diamide [123] Excellent levels of asymmetric induction are achieved, thus providing easy access to β–substituted aldehydes or allylic alcohols, as depicted in **Scheme 53**



Scheme 53

Tartrate derived aryl aldehyde acetals have been used successfully as enantiopure auxiliaries in the asymmetric metalation of chromium tricarbonyl arene complexes [124] Treatment of complex **104** with *n*BuLi followed by quenching with various electrophiles afforded products with high levels of diastereoselectivity (**Scheme 54**).



104

E= Me 92% de
PhS 92% de
Ph_2P >95% de

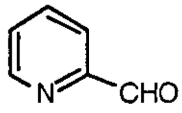
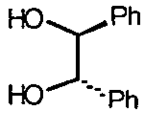
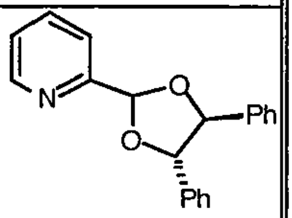
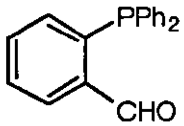
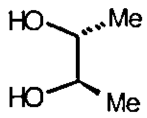
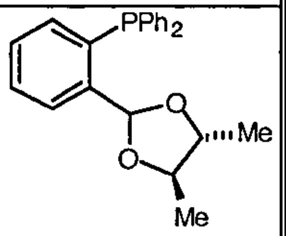
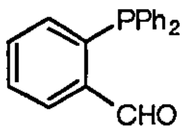
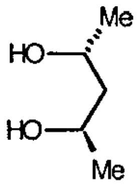
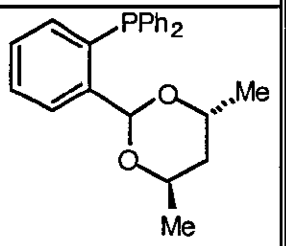
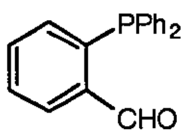
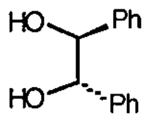
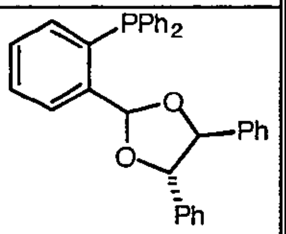
Scheme 54

Whilst enantiopure acetals have played an important role in auxiliary based asymmetric synthesis, their use as chelating ligands for asymmetric catalysis has not been reported There are however, numerous reported examples of ketal containing enantiopure ligands, for example, derived from tartaric acid or carbohydrates [125] Electronically similar, but synthetically complex, podand ionophores have also found applications in enantioselective complexation [126]

5.2 Preparation of enantiopure acetals

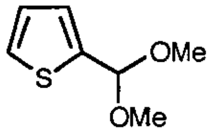
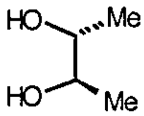
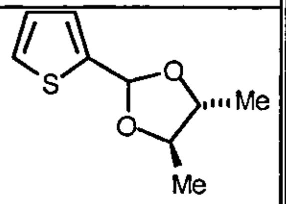
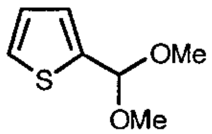
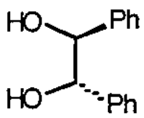
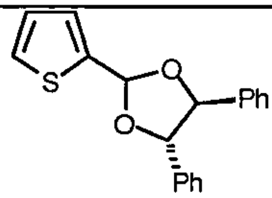
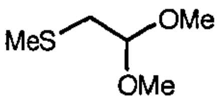
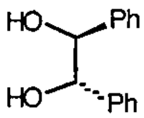
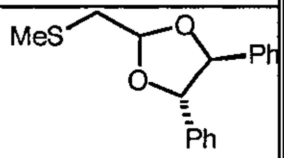
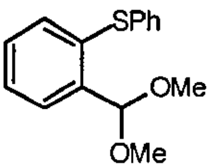
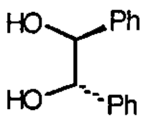
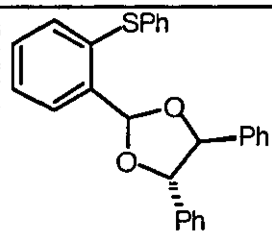
The success of acetals as enantiopure auxiliaries has led to the preparation of such compounds being well documented [127] The acetal ligands **105–108** were prepared by the reaction of the corresponding aldehyde with an enantiopure C_2–symmetric diol by heating in the presence of catalytic amounts of camphorsulfonic acid in toluene with removal of the toluene/water azeotrope All of the enantiopure acetal ligands have been satisfactorily characterised by both analytical and spectroscopic techniques The preparation of these ligands is summarised in **Table 17** The starting diols employed are (S,S)–1,2–diphenylethanediol, (R,R)–2,3–butanediol and (R,R)–2,4–pentanediol

Table 17

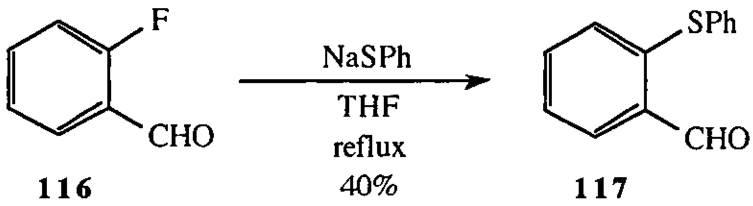
Aldehyde	*Diol*	*Yield (%)*	*Ligand*
		63	 **105**
		77	 **106**
		82	 **107**
		61	 **108**

Alternatively, the aldehyde was initially converted into the dimethyl acetal upon treatment with trimethyl orthoformate in methanol using cerium trichloride as a catalyst.[128] Subsequent transacetalisation with the diol in the presence of camphorsulfonic acid with the removal of the toluene/methanol azeotrope affords the desired ligands **112–115**, as summarised in **Table 18**

Table 18

Acetal	*Diol*	*Yield (%)*	*Ligand*
 **109**		92	 **112**
 **109**		77	 **113**
 **110**		52	 **114**
 **111**		64	 **115**

Aldehyde **117** is not commercially available, but is easily synthesised by the nucleophilic substitution of 2-fluorobenzaldehyde **116** with sodium benzenethiolate in an analogous procedure to the preparation of 2-(phenylthio)benzonitrile **90**, as illustrated in **Scheme 55**



Scheme 55

5.3 Results for palladium catalysed allylic substitution

The enantiopure acetal ligands were examined for their ability to provide asymmetric induction in palladium catalysed allylic substitution reactions The reaction of dimethyl malonate with the allylic acetates **35** and 2–acetoxypent–3–ene **118** were examined, in all cases 2.5 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 20 mol% of the ligand were used

Table 19

Ligand	*Substrate*	*Time (hr)*	*Product*	*Yield (%)*	*ee (%)*
105	**35**	96	**46**	70	32
112	**35**	48	**46**	59	<5
113	**35**	24	**46**	79	60
114	**35**	48	**46**	76	50
115	**35**	24	**46**	81	82
106	**35**	24	**46**	75	68
107	**35**	24	**46**	74	70
108	**35**	24	**46**	70	88
108	**118**	72	**19**	62	36

The alkylations were initially performed under standard BSA conditions in dichloromethane at room temperature However, for ligands **105**, **112** and **113**, these conditions failed to give any product In these cases, the alkylation reaction was accomplished with the sodium salt of dimethyl malonate in THF at 60°C. The enantiomeric excess was determined from the ^1H NMR spectrum in the presence of enantiopure shift reagent $Eu(hfc)_3$, and the results are detailed in **Table 19**. In each case the product **46** was formed with the (S)–(–)–enantiomer predominating, as determined from the sign of the optical rotation. This is surprising, since the absolute configuration of the ligand is opposite for the diphenyl–substituted acetals and the dimethyl–substituted acetals

It was noted that by increasing the π–accepting capability of the auxiliary ligand, the enantioselectivity of the isolated product **46** was observed to increase This is in accordance with the findings for the substitution reaction employing the enantiopure oxazoline ligands

In a similar way to our previous studies with oxazolines, where we have assumed that the incoming nucleophile approaches *trans* to the better π-acceptor, we assume that the same will be true for the acetal ligands. It is anticipated that the ligands bind in a chelating fashion as other allypalladium complexes have been reported containing P–O chelating ligands [129] It is less clear which lone pair of electrons on the acetal (all four are different from each other) is involved in binding to the palladium.

Upon binding to the palladium a new stereocentre is generated at the carbon between the two oxygen atoms of the acetal For steric reasons, it would be expected that the palladium binds to the lone pair *trans* to the adjacent Ph group of the acetal, this would then give rise to two possible isomers as illustrated in **Figure 17**.

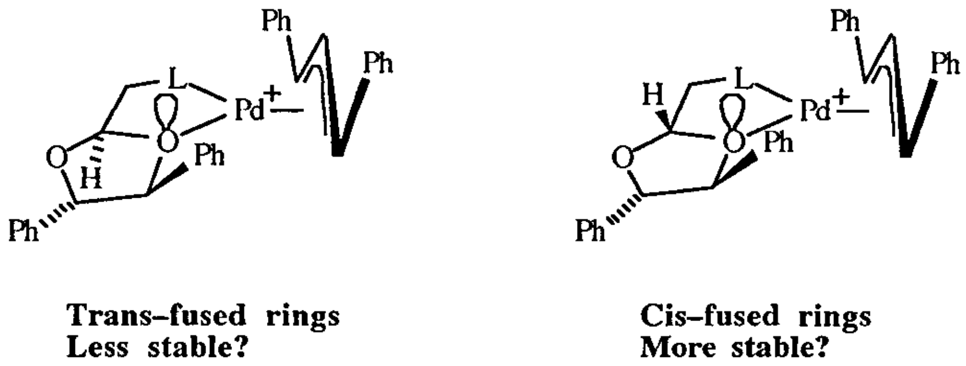


Figure 17

When the palladium is bound to the acetal ligand the complex could be considered analagous to a fused bicyclic system. When small rings are involved in such systems, the *cis*–fused isomer would be expected to be more stable than the corresponding *trans*–fused isomer.[130] Nucleophilic attack would then be expected to occur *trans* to the π–accepting auxiliary ligand furnishing the addition product **46** with the observed (S)–conformation, as depicted in **Figure 18**. The circumstances are more complex for the dimethyl–substituted acetal ligands, consequently an alternative interpretation is required.

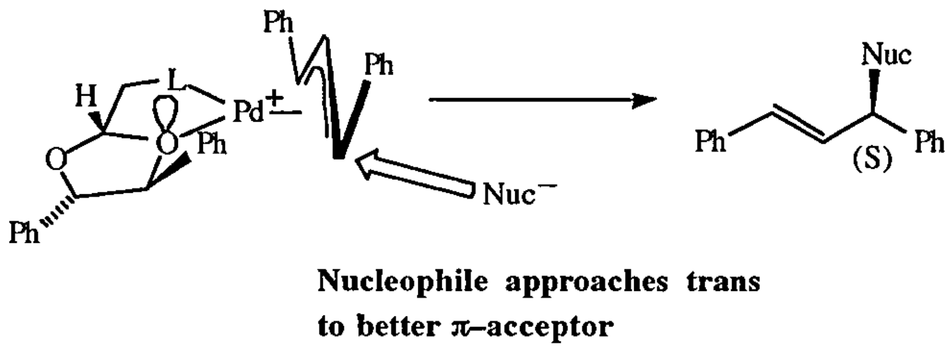


Figure 18

The rationale cited for the origin of enantioselectivity is purely conceptual and without the support of X–ray crystal structure data and NMR binding studies, no categorical conclusions can be reached

5.4 *Summary*

(i) Enantiopure acetals tethered to auxiliary donor ligands afford good levels of enantioselectivity in palladium catalysed allylic substitution

(ii) In comparison with enantiopure oxazoline ligands, the acetals exhibit lower levels of reactivity and asymmetric induction

(iii) The observed enantioselectivity was dependent on the nature of the auxiliary ligand and increased as the π-accepting capability of the ligand increased

Chapter Six

Experimental Section

6.1 General Information

Solvents and Reagents—Commercially available solvents and reagents were used throughout without further purification, except for those detailed below which were purified as described 'Light petroleum' refers to the fraction of petroleum ether boiling between 40°C and 60°C, and was distilled through a 36cm Vigreux column before use 'Ether' refers to diethyl ether, this was dried by standing over sodium wire for several days. THF was distilled from sodium benzophenone ketyl under nitrogen, prior to use Dichloromethane was distilled from phosphorus pentoxide DMF was dried by stirring over calcium hydride for 15h, decanted, and distilled under reduced pressure before storing over 4Å molecular sieves under nitrogen. Pyridine and triethylamine were distilled from, and stored over, potassium hydroxide pellets

Chromatographic Procedures—Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF_{254} Plates were visualised under UV light (at 254 and/or 360 nm) or by staining with phosphomolybdic acid reagent, followed by heating. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Sorbsil C 60 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

Spectroscopic Techniques—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 chloroform, thin films or as a nujol mull. Elemental analyses were carried out on a Perkin Elmer 2400 Elemental Analyser. ^{1}H and ^{13}C NMR spectra were recorded using Bruker AC-250 and Bruker WH-400 (SERC NMR Spectroscopy Centre, Warwick) instruments. ^{1}H NMR spectra are referenced against residual undeuterated solvent, in the case of removed *in vacuo* The residue was purified by flash chromatography (light petroleum/ether 3 1) to afford a clean product

(4S,5R)-4,5–Dihydro–4-methyl-5-phenyl-2-(2-thienyl)-1,3-oxazole **77f.** (91%) as a viscous, colourless oil B p 210–211°C at 0 5 mmHg (found MH+, 244 0796 $C_{14}H_{13}NOS$ requires MH+, 244 0796) $[\alpha]_D^{25}$ -553 6 (c 0.28, $CHCl_3$) υ_{max} /cm^{-1} 1651(C=N), 1445, 1093, 1056, 966, 847, 747 δ_H (400 MHz, $CDCl_3$) 0 87 (3H, d, J 7 0, C<u>H</u>3), 4 63 (1H, dq, J 7.0,6 8, C<u>H</u>CH3), 5 74 (1H, d, J 9.7, C<u>H</u>O), 7 11 (1H, m, thiophene C<u>H</u>), 7 23-7 37 (5H, m, aromatic C<u>H</u>), 7 49–7.69 (2H, m, thiophene C<u>H</u>) δ_C (100 Hz, $CDCl_3$) 17 6 (<u>C</u>H3), 65 5 (<u>C</u>HN), 84 3 (<u>C</u>HO), 126 0/ 127 5/ 127 8/ 128 2/ 129 8/ 130.3 (aromatic <u>C</u>H), 130 2/ 136 7 (aromatic <u>C</u>), 158.7 (<u>C</u>=N) *m/z* (EI) 244(MH+, 100%), 170(14), 137(32), 111(8)

(4S)-4-benzyl-4,5–Dihydro–2-(2-thienyl)-1,3-oxazole **77b.** (73%) as a colourless crystalline solid M p. 42–44°C. (found M+, 243.0725. $C_{14}H_{13}NOS$ requires M+, 243 0718). $[\alpha]_D^{25}$ +26 0 (c 0 5, $CHCl_3$). υ_{max} / cm^{-1} 1651(C=N), 1436, 1057, 709. δ_H (400 MHz, $CDCl_3$) 2 70 (1H, dd, J 9.1,13.7, C<u>H</u>H'Ph), 3 25 (1H, dd, J 4 8, 13 7, CH<u>H'</u>Ph), 4 13 (1H, dd, J 7 3, 8 7, C<u>H</u>H'O), 4.32 (1H, t, J 8 7, CH<u>H'</u>O), 4 52–4 60 (1H, m, C<u>H</u>N), 7 06-7 08 (1H, m, thiophene C<u>H</u>), 7 20–7 32 (5H, m, aromatic C<u>H</u>), 7.44-7.45 (1H, m, thiophene C<u>H</u>), 7.57-7 59 (1H, m, thiophene C<u>H</u>). δ_C (100 MHz, $CDCl_3$) 41 5 (<u>C</u>H2Ph), 67 9 (<u>C</u>HN), 72.1 (<u>C</u>H2O), 126.4/ 127 4/ 128 4/ 129 1/ 129 7/ 130 2 (aromatic <u>C</u>H), 137.7 (aromatic <u>C</u>), 159 6 (<u>C</u>=N) *m/z* (EI) 243(M+, 5%), 152(100), 124(14), 97(16), 69(12)

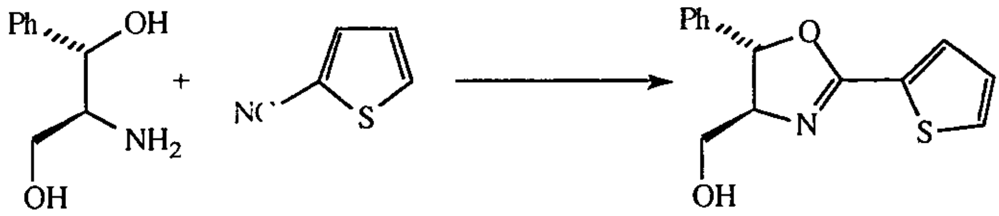
(4S)-4,5-Dihydro–4-isopropyl-2-(2-thienyl)-1,3-oxazole **77c.** (82%) as a colourless oil B p 125-126°C at 0.5 mmHg. (found M+, 195 0718. $C_{10}H_{13}NOS$ requires M+, 195 0718) $[\alpha]_D^{25}$ -89 3 (c 0 28, $CHCl_3$) υ_{max} / cm^{-1} 1651(C=N), 1433, 1060, 1021, 951, 853, 715. δ_H (400 MHz, $CDCl_3$) 0 90 (3H, d, J 6 8, C<u>H</u>3), 1 00 (3H, d, J 6 8, C<u>H</u>3), 1 84 (1H, m, C<u>H</u>(CH3)2), 4 05-4 15 (2H, m, C<u>H</u>2O),

4 34-4 41 (1H, m, CHN), 7.05 (1H, m, thiophene CH), 7 41 (1H, m, thiophene CH), 7 57 (1H, m, thiophene CH). δ_C (100 MHz, $CDCl_3$) 17.8 (CH_3), 18 8 (CH_3), 32 5 ($CH(CH_3)_2$), 70 2 (CH_2O), 72 6 (CHN), 127 4/ 129 4/ 129 9 (aromatic CH), 130 3 (aromatic C), 158 9 (C=N) *m/z* (EI) 195(M^+, 10%), 152(100), 124(47), 111(24), 97(52)

(4S)-4,5–Dihydro–4-phenyl-2-(2-thienyl)-1,3-oxazole **77d.** (79%) as a colourless crystalline solid. M p 78–79°C (Found C, 68 4 H, 4 9, N, 6 1. $C_{13}H_{11}NOS$ requires C, 68 1; H,4 8; N, 6.1%). $[\alpha]_D^{25}$ +18.33 (c 0 6, $CHCl_3$). υ_{max} / cm^{-1} 1644(C=N), 1434,1464. δ_H (250 MHz, $CDCl_3$) 4 26 (1H, t, J 8 1, CHH'O), 4 77 (1H, dd, J 8 2, 10 0, CHH'O), 5.36 (1H, dd, J 8 1, 10 0, CHN), 7 10 (1H, m, thiophene CH), 7 28 (m, 5H, aromatic CH), 7 47 (1H, m, thiophene CH), 7.68 (1H, m, thiophene CH) δ_C (63 MHz, $CDCl_3$) 70 3 (CHN), 75.2 (CH_2O), 126 8/ 127.7/ 128 8/ 130 1/ 130.7 (aromatic CH), 142.1(aromatic C), 160 2 (C=N) *m/z* (EI) 229(M^+, 75%), 199(100), 171(18), 151(19), 111(24), 96(39)

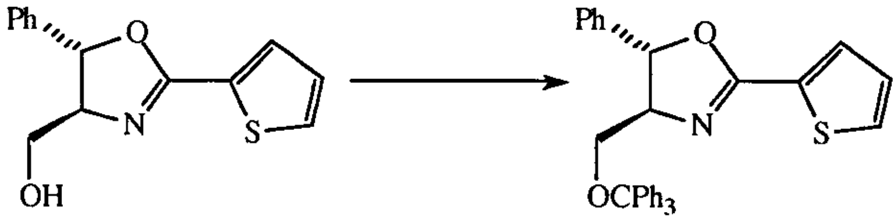
*(4S)-4,5–Dihydro–4-*tert*–butyl-2-(2-thienyl)-1,3-oxazole* **77e.** (74%) as a colourless crystalline solid M p 44–45°C (found M^+, 209 0868 $C_{11}H_{15}NOS$ requires M^+, 209 0874) $[\alpha]_D^{25}$ –76.5 (c 0.34, $CHCl_3$) υ_{max} / cm^{-1} 1654(C=N) δ_H (250 MHz, $CDCl_3$) 0.95 (9H, s, $C(CH_3)_3$), 4 03 (1H, dd, J 7.4, 10 0, CHN), 4.26 (2H, m, CH_2O), 7.06 (1H, m, thiophene CH), 7 43 (1H, m, thiophene CH), 7.59 (1H, m, thiophene CH). δ_C (63 MHz, $CDCl_3$) 25 9 (CH_3 x 3), 34.1 ($C(CH_3)_3$), 69.1 (CH_2O), 76 4 (CHN), 127 5/ 129 5/ 130 0 (aromatic CH), 130 2 (aromatic C), 159 1 (C=N). *m/z* (EI) 209(M^+, 5%), 152(100), 124(15), 111(15), 97(10).

(4S,5S)-4,5-Dihydro-4-hydroxymethyl-5-phenyl-2-(2-thienyl)-1,3-oxazole **82.**



In a 50ml Schlenk flask, zinc chloride (68mg, 0 5 mmol) was melted under high vacuum and cooled under nitrogen After cooling to room temperature, chlorobenzene (30ml) was added followed by 2-thiophenecarbonitrile (1.1g, 10 mmol) and (1S, 2S)-(+)-1-phenyl-2-amino-1,3-propanediol (2 5g, 15 mmol) The mixture was heated under reflux for 48 hours The solvent was removed *in vacuo* to give an oily residue, which was dissolved in dichloromethane (30ml) The solution was extracted with water (3 x 20ml) and the aqueous phase with dichloromethane (3 x 30ml). The combined organic phases were dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give a crude solid which could be crystallised by dissolving in ether and cooling to –78°C to give the *title compound* (1 68g, 65%) as a colourless crystalline solid. M p. 160–162 °C (found C, 65 0, H, 5 0, N, 5 4 $C_{14}H_{13}NO_2S$ requires C, 64 9; H, 5.1; N, 5 4.) $[\alpha]_D^{25}$ +50 0 (c 1.02, $CHCl_3$). υ_{max} / cm^{-1} 1670(C=N). δ_H (400 MHz, $CDCl_3$) 3.75 (1H, dd, J 3 2, 11 9, CHH'OH), 4 02 (1H, br S, OH), 4 11 (1H, dd, J 3.2, 11 9, CHH'OH), 4 21 (1H, m, CHN), 5 60 (1H, d, J 8 1, CHO), 7.01 (1H, m, thiophene CH), 7 30-7 40 (5H, m, aromatic CH), 7 42–7.57 (1H, m, thiophene CH) δ_C (100 MHz, $CDCl_3$) 62 9 (CH_2OH), 76 7 (CHN), 83 0 (CHO), 125 8-130 9 (aromatic CH), 129 4/ 139 2 (aromatic C), 160 4 (C=N) *m/z* (EI) 260(MH^+, 100%), 230(27), 111(9)

(4S,5S)-4,5-Dihydro-5-phenyl-2-(2-thienyl)-4-triphenylmethoxymethyl-1,3-oxazole **83.**



To a stirring mixture of (4S,5S)-4,5-Dihydro-4-hydroxymethyl-5-phenyl-2-(2-thienyl)-1,3-oxazole **82** (0 50g, 1.9 mmol), triethylamine (0.59g, 5.7 mmol) and DMAP (1-2 crystals) in dichloromethane (20 ml) at room temperature was added trityl chloride (0 58g, 2 0 mmol) The mixture was allowed to stir overnight (12 hours), after which time TLC (light petroleum / ether 3:1) indicated that the starting material had been consumed The mixture was extracted with dichloromethane (3 x 30 ml) then the organic extracts washed with water (3 x 30 ml). The organic extracts were then dried (Na_2SO_4), filtered and the solvent removed *in vacuo.* The residue was purified by flash chromatography (light petroleum / ether 3.1) to afford the *title compound* (0 64g, 67%) as a colourless crystalline solid. M p. 126–127°C (found C, 79.5, H, 5.7, N, 2 8. $C_{33}H_{27}NO_2S$ requires C, 79 1; H, 5 4; N, 2.8.). $[\alpha]_D^{25}$ +35.7 (c 0 98, $CHCl_3$). υ_{max} / cm^{-1} 1643(C=N). δ_H (250 MHz, $CDCl_3$) 3.29 (1H, dd, J 7 3, 9 2, CHH'OTr), 3 55 (1H, dd, J 3 9, 9.2, CHH'OTr), 4 37 (1H, m, CHN), 5 46 (1H, d, J 6 3, CHO), 7.09-7.67 (23H, m, aromatic CH) δ_C (63 MHz, $CDCl_3$) 65 7 (CH_2OTr), 75 2 (CHN), 84 9 (CHO), 86 8 (CPh_3), 125 9–130 6 (aromatic CH), 140 8/ 143 8 (aromatic C), 159.9 (C=N) *m/z* (EI) 501(M^+, 5%), 320(10), 244(32), 228(100), 165(56), 111(25)

1,3-diphenylprop-2-en-1-ol **85.**

To a stirred solution of phenylmagnesium bromide, prepared from Mg (6 07g, 0 25mol) and bromobenzene (39 3g, 0 25mol) in sodium dried ether (50ml), was added dropwise to a solution of cinnamaldehyde (33g, 0 25mol) in sodium dried ether (50ml) over 15 min The mixture was allowed to stir for 3 hours at 25°C and then was quenched with saturated ammonium chloride The aqueous layer was extracted once with ether (30ml) and the combined ether extracts were washed with water (2 x 30ml), with brine (2 x 30ml), and dried ($MgSO_4$) Filtration followed by removal of the ether *in vacuo* afforded the *title compound* (43 6g, 83%) as a low melting solid which was used directly in the next step.

δ_H (250 MHz, $CDCl_3$) 2 39 (1H, s, O<u>H</u>), 5 25 (1H, d, J 6 8, C<u>H</u>OH), 6.32 (2H, m, <u>H</u>C=CH), 7.22-7.40 (10H, m, aromatic C<u>H</u>)

(E)-1,3-diphenyl-3-acetoxy-1-propene **35.**

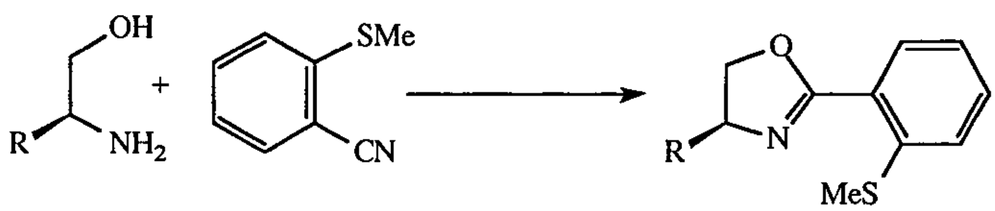
To a solution of 1,3-diphenylprop-2-en-1-ol **85** (25g, 0.12 mol) in acetic anhydride (12.4ml) and pyridine (50ml) was added DMAP(1-2 crystals) The mixture was then allowed to stir for 24 hours at room temperature The solvent was removed *in vacuo* and the residue diluted with water This was then extracted with ether (3 x 50ml). The combined ether extracts were washed with water (2 x 50ml) and then with brine (50ml) and then dried (Na_2SO_4) Filtration followed by removal of

To $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (4mg, 2 5 mol%) was added a solution of the ligand (10 mol%) in dry dichloromethane (1ml) The solution was allowed to stir for 15 mins at room temperature The resulting yellow solution was treated successively with a solution of *rac*-(E)-1,3-diphenyl-3-acetoxy-1-propene **35** (0 4 mmol) in dichloromethane (1ml), dimethyl malonate (1 2 mmol), N,O-bis(trimethylsilyl) acetamide (1.2 mmol), and anhydrous potassium acetate (3 mol%) The reaction mixture was stirred at room temperature for 12-96 hours, until conversion was complete according to TLC analysis. The reaction mixture was diluted with ether (25ml), transferred to a separatory funnel and washed with ice-cold saturated aqueous ammonium chloride (2 x 25ml) The organic phase was dried ($MgSO_4$), filtered then concentrated *in vacuo* The residue was purified by flash chromatography (light petroleum/ether 3 1)

Dimethyl–1,3–diphenylprop–2-enylmalonate **46.** υ_{max} / cm^{-1} 1765, 1740, 1605, 1500, 1460, 1440, 1325, 1265 δ_H (250 MHz, $CDCl_3$) 3 53 (3H, s, $CO_2C\underline{H}_3$), 3.70 (3H, s, $CO_2C\underline{H}_3$), 3 95 (1H, d, J 11, $C\underline{H}E_2$), 4 27 (1H, dd, J 11, 8, $PhC\underline{H}CE_2$), 6 32 (1H, dd, J 15, 8, $\underline{H}$C=CHPh), 6 48 (1H, d, J 15, HC=C$\underline{H}$Ph), 7.15-7.44 (10H, m, aromatic C$\underline{H}$) δ_C (63 MHz, $CDCl_3$) 49 1 ($\underline{C}$H), 52.4 ($\underline{C}H_3$), 52 6 ($\underline{C}H_3$), 57 6 ($\underline{C}$H), 126 3/ 127.1/ 127 5/ 127 8/ 128 4/ 128 7/ 129.1/ 131 8 (alkene/aromatic $\underline{C}$H), 136 8/ 140.1 (aromatic $\underline{C}$), 167 7/ 168 1($\underline{C}$=O)

6.3 Experimental for Chapter Three

General procedure for preparation of (4S)–4–substituted–4,5–Dihydro-2-[2–(methylsulfanyl)phenyl]–1,3–oxazoles



In a 50ml Schlenk flask, zinc chloride (68mg, 0 5 mmol) was melted under high vacuum and cooled under nitrogen. After cooling to room temperature, chlorobenzene (30ml) was added followed by (2-methylsulfanyl)benzonitrile (10 mmol) and the amino alcohol (13 mmol). The mixture was heated under reflux for 48 hours. The solvent was removed *in vacuo* to give an oily residue, which was dissolved in dichloromethane (30ml). The solution was extracted with water (3 x 20ml) and the aqueous phase with dichloromethane (3 x 30ml) The combined organic phases were dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography (light petroleum/ether 3 1)

(4S)-4,5–Dihydro–4–methyl–2–[2–(methylsulfanyl)phenyl]–1,3–oxazole **86a.** (60%) as a colourless oil B p. 180–185°C (Bath temperature) at 4mmHg (found M^+, 207.0718 $C_{11}H_{13}NOS$ requires M^+, 207.0718). $[\alpha]_D^{25}$ -21 4 (c 0 28, $CHCl_3$) υ_{max} / cm^{-1} 1645(C=N), 1472, 1434, 1354,1245,1034. δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, J 6.4, C<u>H</u>3CH), 2 44 (3H, s, SC<u>H</u>3), 3 91 (1H, m, C<u>H</u>H'O), 4.45 (1H, m, CH<u>H</u>'O), 4 49 (1H, m, C<u>H</u>N), 7.11-7.81 (4H, m, aromatic C<u>H</u>). δ_C (100 MHz, $CDCl_3$) 15 6 (S<u>C</u>H3), 21 5 (<u>C</u>H3CH), 62 6 (<u>C</u>HN), 73.0 (<u>C</u>H2O), 123 4/ 124.0/ 130.1/ 130 7 /124.9 (aromatic <u>C</u>H), 140 6 (aromatic <u>C</u>), 162 1 (<u>C</u>=N) *m/z* (EI) 207(M^+, 54%), 192(100), 152(31), 135(22), 51(21), 45(21)

(4S)-4-benzyl-4,5–Dihydro–2–[2–(methylsulfanyl)phenyl]–1,3–oxazole **86b.** (42%) as a colourless crystalline solid. M p. 68–69°C . (Found: C, 72 4; H, 5 9, N, 4 9 $C_{17}H_{17}NOS$ requires C, 72 1; H, 6 0, N, 4.9%). $[\alpha]_D^{25}$ +18 75 (c 0 16, $CHCl_3$). υ_{max} / cm^{-1} 1640(C=N) δ_H (400 MHz, $CDCl_3$) 2.47 (3H, s, S<u>C</u>H3), 2 74 (1H, dd, J 9 1, 13.7, PhC<u>H</u>H'), 3 31 (1H, dd, J 5.0, 13 7, PhCH<u>H</u>'), 4.10 (1H, dd, J 7.1, 8 4, C<u>H</u>H'O), 4 27 (1H, dd, J 8.4, 9.2, CH<u>H</u>'O), 4.69 (1H, m, C<u>H</u>N), 7.12-7 81 (9H, m, aromatic C<u>H</u>). δ_C (100 MHz, $CDCl_3$) 15 7 (S<u>C</u>H3), 41.7 (Ph<u>C</u>H2), 68 6

(<u>C</u>HN), 70 7 (<u>C</u>H_2O), 123 4/ 124 0/ 126 3/ 128 4/ 129.2/ 130.1/ 130 8 / 124 7 (aromatic <u>C</u>H), 137 9/ 140 8 (aromatic <u>C</u>), 162.7 (<u>C</u>=N) *m/z* (EI) 283(M^+, 35%), 268(23), 192(100), 137(24), 117(31), 91(31), 51(20).

(4S)-4,5-Dihydro-4-isopropyl-2-[2-(methylsulfanyl)phenyl]-1,3-oxazole **86c.** (56%) as a colourless oil B p 210°C (Bath temperature) at 2mmHg . (found M^+, 235 1030 $C_{13}H_{17}NOS$ requires M^+, 235 1030) $[\alpha]_D^{25}$ -72 22 (c 0.18, $CHCl_3$) ν_{max} / cm^{-1} 1649(C=N), 1471, 1436, 1352, 1244 δ_H (400 MHz, $CDCl_3$) 0 95 (3H, d, J 6 7, C<u>H</u>$_3$CH), 1 06 (3H, d, J 6 7, C<u>H</u>$_3$CH), 1 85 (1H, m, C<u>H</u>(CH_3)$_2$), 2 44 (3H, s, SC<u>H</u>$_3$), 4 09 (1H, t, J 7 8, C<u>H</u>H'O), 4 20 (1H, m, C<u>H</u>N), 4 35 (1H, dd, J 7 8, 9 5, CH<u>H'</u>O), 7 11-7 79 (4H, m, aromatic C<u>H</u>) δ_C (100 MHz, $CDCl_3$) 15 7 (S<u>C</u>H_3), 18 1 (<u>C</u>H_3CH), 18 8 (<u>C</u>H_3CH), 32 8 (<u>C</u>H(CH_3)$_2$), 69 3 (<u>C</u>H_2O), 73 3 (<u>C</u>HN), 123 3/ 124 0/ 129.9/ 130 6 (aromatic <u>C</u>H), 125.0/ 140.8 (aromatic <u>C</u>), 162.0 (<u>C</u>=N) *m/z* (EI) 235(M^+, 100%), 220(91), 192(73), 152(55), 137(49), 45(45)

(4S)-4,5-Dihydro-4-phenyl-2-[2-(methylsulfanyl)phenyl]-1,3-oxazole **86d.** (58%) as a colourless crystalline solid. M p 72–73°C . (Found: C, 71 5, H, 5 5; N, 5.2 $C_{16}H_{15}NOS$ requires C, 71 4, H, 5 6, N, 5 2%) $[\alpha]_D^{25}$ +100 0 (c 0.12, $CHCl_3$) ν_{max} / cm^{-1} 1638(C=N) δ_H (250 MHz, $CDCl_3$) 2 46 (3H, s, SC<u>H</u>$_3$), 4 20 (1H, t, J 8 2, C<u>H</u>N), 4 75 (1H, dd, J 10 1, 8 2, C<u>H</u>H'O), 5 51 (1H, dd, J 10.1, 8 2, CH<u>H'</u>O), 7 14-7.91 (9H, m, aromatic C<u>H</u>). δ_C (63 MHz, $CDCl_3$) 15 8 (S<u>C</u>H_3), 70.7 (Ph<u>C</u>H), 74 0 (<u>C</u>H_2O), 123 5/ 124 3/ 124 7/ 126 6/ 127.4/ 128 6/ 130 4/ 131 0 (aromatic <u>C</u>H), 137 0/ 142 0 (aromatic <u>C</u>), 159 5 (<u>C</u>=N). *m/z* (EI) 269(M^+, 50%), 254(58), 151(27), 120(28), 104(43), 51(39)

*(4S)-4,5-Dihydro-4-*tert*-butyl-2-[2-(methylsulfanyl)phenyl]-1,3-oxazole* **86e.** (53%) as a colourless crystalline solid M p. 67.5–68 5°C . (found M^+, 249 1187 $C_{14}H_{19}NOS$ requires M^+, 249 1187) $[\alpha]_D^{25}$ -121.05 (c 0 38, $CHCl_3$)

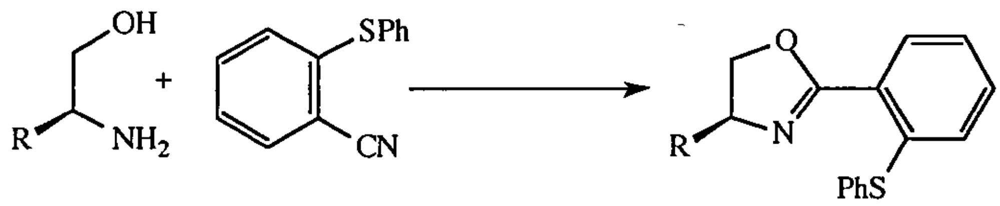
υ_{max} / cm^{-1} 1651(C=N) δ_H (400 MHz, $CDCl_3$) 0 98 (9H, s, C($C\underline{H}_3$)$_3$), 2 44 (3H, s, $SC\underline{H}_3$), 4 15 (1H, m, C$\underline{H}$N), 4 20 (1H, m, C$\underline{H}$H'O), 4 26 (1H, dd, J 7.7, 9 4, CH$\underline{H}$'O), 7 11-7.78 (4H, m, aromatic C$\underline{H}$) δ_C (100 MHz, $CDCl_3$) 15 8 ($S\underline{C}H_3$), 25 7 ($\underline{C}H_3$ x 3), 33 9 ($\underline{C}(CH_3)_3$), 67 7 ($\underline{C}H_2O$), 77 0 ($\underline{C}$HN), 123 3/ 124 0/ 129 0/ 130 6 (aromatic $\underline{C}$H), 125 0/ 141.0 (aromatic $\underline{C}$), 161 9 ($\underline{C}$=N) *m/z* (EI) 249(M$^+$, 45%), 234(28), 192(100), 151(30), 137(29), 41(29).

(2-phenylsulfanyl)benzonitrile **90.**

To a stirring mixture of sodium hydride (9 mmol) in THF (5ml) was added a solution of benzenethiol (9mmol) in THF (2ml) To the resulting white precipitate was added a solution of 2-fluorobenzonitrile (8 mmol) in THF (2ml) The mixture was allowed to stir under reflux for 48 hours whereupon the solution became clear. The reaction mixture was poured into dichloromethane (20ml), washed with 15% NaOH (20ml) then H_2O (20ml). The aqueous layers were extracted dichloromethane (2 x 50ml), the organic extracts were then combined, dried (Na_2SO_4), filtered and then concentrated *in vacuo.* The crude product was purified by flash chromatography (light petroleum/ether 3:1) to afford the *title compound* (93%) as a colourless crystalline solid. M p. 35–37 °C (lit 39–40 °C)[131]

υ_{max} / cm^{-1} 2220(CN) *m/z* (EI) 211(M$^+$, 100%), 109(60), 51(42)

General procedure for preparation of (4S)-4,5-Dihydro-2-[(2-phenylsulfanyl)phenyl]-4-substituted-1,3-oxazoles.



In a 50ml Schlenk flask, zinc chloride (68mg, 0.5 mmol) was melted under high vacuum and cooled under nitrogen After cooling to room temperature, chlorobenzene (30ml) was added followed by (2-phenylsulfanyl)benzonitrile **90** (10 mmol) and the amino alcohol (15 mmol) The mixture was heated under reflux for 48 hours The solvent was removed *in vacuo* to give an oily residue, which was dissolved in dichloromethane (30ml). The solution was extracted with water (3 x 20ml) and the aqueous phase with dichloromethane (3 x 30ml) The combined organic phases were dried (Na_2SO_4), filtered and the solvent removed *in vacuo* The residue was purified by flash chromatography (light petroleum/ether 3:1) to afford a clean product

(4S)-4,5-dihydro-4-isopropyl-2-[(2-phenylsulfanyl)phenyl]-1,3-oxazole **87c.** (73%) as a colourless oil (found M^+, 297.1187. $C_{18}H_{19}NOS$ requires M^+, 297.1187). $[\alpha]_D^{25}$ –42.5 (c 0 4, $CHCl_3$). υ_{max} / cm^{-1} 1650(C=N) δ_H (250 MHz, $CDCl_3$) 0 99 (3H, d, J 6.7, C<u>H</u>$_3$CH), 1.10 (3H, d, J 6.7, C<u>H</u>$_3$CH), 1.85 (1H, m, C<u>H</u>(CH_3)$_2$), 4.17 (2H, m, C<u>H</u>N and C<u>H</u>H'O), 4.43 (1H, dd, J 8 7, 7.1, CH<u>H</u>'O), 6.87-7.64 (9H, m, aromatic C<u>H</u>). δ_C (63 MHz, $CDCl_3$) 18 4 (<u>C</u>H$_3$CH), 18 9 (<u>C</u>H$_3$CH), 33.0 (<u>C</u>H(CH_3)$_2$), 69 8 (<u>C</u>H$_2$O), 73 4 (<u>C</u>HN), 124.4/ 126.4/ 127.6/ 128 6/ 128 8/ 129 9/ 132.9/ 133.6/ 134 9 (aromatic <u>C</u>H), 125 0/ 141.0/ 142.9 (aromatic <u>C</u>), 162.2 (<u>C</u>=N) *m/z* (EI) 297(M^+, 92%), 254(100), 220(53), 197(100), 137(29)

*(4S)-4,5-Dihydro-4-*tert*-butyl-2-[(2-phenylthio)phenyl]-1,3-oxazole* **87e.** (62%) as a colourless oil (found M+, 311 1344 $C_{19}H_{21}NOS$ requires M+, 311 1344) $[\alpha]_D^{25}$ -37.5 (c 0 24, $CHCl_3$) υ_{max} / cm^{-1} 1644(C=N) δ_H (250 MHz, $CDCl_3$) 1.03 (9H, s, C(C<u>H</u>$_3$)$_3$), 4 27 (3H, m, C<u>H</u>N and C<u>H</u>$_2$O), 6 83-7 81 (9H, m, aromatic C<u>H</u>) δ_C (63 MHz, $CDCl_3$) 25 9 (<u>C</u>H$_3$ x 3), 34.0 (<u>C</u>(CH$_3$)$_3$), 68.2 (<u>C</u>H$_2$O), 77 4 (<u>C</u>HN), 124 3/ 126 4/ 127 5/ 128 6/ 129 5/ 129.7/ 129.8/ 130 5/ 135.1 (aromatic <u>C</u>H), 125 0/ 130 0/ 141 0 (aromatic <u>C</u>), 162 4 (<u>C</u>=N) *m/z* (EI) 311(M+, 41%), 254(100), 197(32), 151(26), 109(19).

General Procedure For Preparation of 4–substituted (4S)–4,5–Dihydro–2–[–2–fluorophenyl]–1,3–oxazoles

In a 50ml Schlenk flask, zinc chloride (68mg, 0 5 mmol) was melted under high vacuum and cooled under nitrogen. After cooling to room temperature, chlorobenzene (30ml) was added followed by 2–fluorobenzonitrile (10 mmol) and the amino alcohol (15 mmol) The mixture was heated under reflux for 72 hours The solvent was removed *in vacuo* to give an oily residue, which was dissolved in dichloromethane (30ml). The solution was extracted with water (3 x 20ml) and the aqueous phase with dichloromethane (3 x 30ml). The combined organic phases were dried (Na_2SO_4), filtered and the solvent removed *in vacuo* The residue was purified by flash chromatography (light petroleum/ether 3 1) to afford a clean product.

(4S)–4,5–Dihydro–4–methyl–2–(2–fluorophenyl)–1,3–oxazole **92a.** (47%) as a colourless oil (found M^+, 179 0749. $C_{10}H_{10}FNO$ requires M^+, 179 0746). $[\alpha]_D^{25}$ –66 0 (c 0 8, $CHCl_3$) υ_{max} / cm^{-1} 1651 (C=N) δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, J 6 4, CH_3), 3 95 (1H, t, J 7 3, CHH'O), 4 41 (2H, m, CHN and CHH'O), 7.10–7 49 (3H, m, aromatic CH), 7 84–7 91 (1H, m, aromatic CH). δ_C (100 MHz, $CDCl_3$) 21 3 (CH_3), 62 1 (CHN), 73 5 (CH_2O), 116.3/ 116.5/ 123 6/ 131 0 (aromatic CH), 132 4/ 132 5 (aromatic C), 163 2 (C=N) *m/z* (EI) 179(M^+, 42%).

(4S)–4–benzyl–4,5–Dihydro–2–(2–fluorophenyl)–1,3–oxazole **92b.** (48%) as a colourless oil. (found M^+, 255 1064. $C_{16}H_{14}FNO$ requires M^+, 255 1059). $[\alpha]_D^{25}$ +6 0 (c 0 82, $CHCl_3$) υ_{max} / cm^{-1} 1649 (C=N) δ_H (400 MHz, $CDCl_3$) 2.74 (1H, dd, J 9 0 4 9, PhCHH'), 3 27 (1H, dd, J 9 0, 4 9, PhCHH'), 4 14 (1H, dd, J 7 4, 8 6, CHH'O), 4 32 (1H, dd, J 8 6, 9 4, CHH'O), 4 62 (1H, m, CHN), 7 11–7 87 (9H, m, aromatic CH). δ_C (100 MHz, $CDCl_3$) 41 5 (CH_2Ph), 67 9 (CHN), 71.2 (CH_2O). 116 4/ 116 6/ 123 7/ 123 8/ 126.3/ 128 4/ 129 1/ 130 9 (aromatic CH), 132 6/ 132 7/ 137.6 (aromatic C), 162 4 (C=N). *m/z* (EI) 255(M^+, 100%).

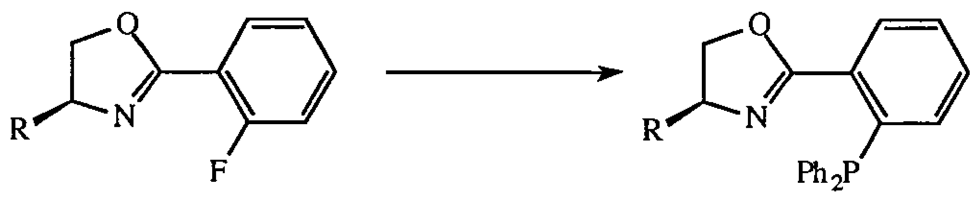
(4S)–4,5–Dihydro–4–isopropyl–2–(2–fluorophenyl)–1,3–oxazole **92c.** (46%) as a colourless oil (found M^+, 207 1059. $C_{12}H_{14}FNO$ requires M^+, 207 1058) $[\alpha]_D^{25}$ –62 (c 0 5, $CHCl_3$) υ_{max} / cm^{-1} 1651 (C=N) δ_H (400 MHz, $CDCl_3$) 0 91 (3H, d, J 6 8, $CHCH_3$), 1.01 (3H, d, J 6 8, $CHCH_3$), 1.89 (1H, m, $CH(CH_3)_2$), 4.14 (2H, m, CHH'O and CHN), 4 38 (1H, m, CHH'O), 7.09–7 88 (4H, m, aromatic CH) δ_C (100 MHz, $CDCl_3$) 16.6 (CH_3), 17.4 (CH_3), 31 0 ($CH(CH_3)_2$), 69 0 (CHN), 71 3 (CH_2O), 116 3/ 116 6/ 123.7 (aromatic CH), 131.0/ 132 0 (aromatic C), 163 0 (C=N) *m/z* (EI) 207(M^+, 22%).

(4S)–4,5–Dihydro–4–phenyl–2–(2–fluorophenyl)–1,3–oxazole **92d.** (49%) as a colourless oil. (found M^+, 241 0903 $C_{15}H_{12}FNO$ requires M^+, 241 0903). $[\alpha]_D^{25}$ –30 0 (c 0 5, $CHCl_3$) υ_{max} / cm^{-1} 1647(C=N) δ_H (250 MHz, $CDCl_3$) 4 27 (1H, t,

J 8 4, CHN), 4 35 (1H, dd, J 8 2, 8 4, CHH'O), 4.79 (1H, dd, J 8 2, 8 4, CHH'O), 7 13–8 00 (4H, m, aromatic CH). δ_C (63 MHz, $CDCl_3$) 70 0 (CHN), 74 5 (CH_2O), 123 9/ 124.0/ 124.7/ 124 8/ 126 6/ 127 6/ 128 5/ 128 7/ 131 3 (aromatic CH), 133 2/ 133 5/ 142 0 (aromatic C), 163 3 (C=N). *m/z* (EI) 241(M^+, 32%), 211(100), 123(27), 90(49) *m/z* (EI) 241(M^+, 75%)

*(4S)–4–*tert*–butyl–4,5–Dihydro–2–(2–fluorophenyl)–1,3–oxazole* **92e.** (56%) as a colourless oil. (found M^+, 221 1213 $C_{13}H_{16}FNO$ requires M^+, 221.1216) $[\alpha]_D^{25}$ –69 3 (c 1, $CHCl_3$) υ_{max} / cm^{-1} 1651 (C=N) δ_H (400 MHz, $CDCl_3$) 0.95 (9H, s, $C(CH_3)_3$), 4 06 (1H, dd, J 7.7, 10.2, CHH'O), 4 22 (1H, t, J 7.7 Hz, CHN), 4.33 (1H, dd, J 7.7, 10 2, CHH'O), 7 14–7.86 (4H, m, aromatic CH) δ_C (100 MHz, $CDCl_3$) 25 6 ($C(CH_3)_3$), 33 8 ($C(CH_3)_3$), 68 3 (CHN), 76 0 (CH_2O), 116 3/ 116 5/ 123.6/ 131.0 (aromatic CH), 132 4/ 132.5 (aromatic C), 162.9 (C=N). *m/z* (EI) 221(M^+, 62%)

General procedure preparation of 4–substituted (4S)–4,5–Dihydro–2–[2–(diphenylphosphino)phenyl]–1,3–oxazoles



To a 50ml two-necked flask, was added potassium diphenylphosphide (1mmol) (as a 0 5M solution in THF) *via* syringe. The solution was then heated to reflux and the 4–substituted (4S)–4,5–Dihydro–2–(2–fluorophenyl)–1,3–oxazole (1mmol) added as a solution in THF (2ml). The mixture was stirred under reflux for 2 hours, whereupon the red solution of the phosphide fades to a pale yellow The mixture is then canulated into a separating funnel and partioned between dichloromethane (20ml) and water (20ml) The dichloromethane layer is taken, dried (Na_2SO_4), filtered then the solvent removed *in vacuo* The residue is purified by dry flash chromatography with diethyl ether as eluant, to afford a clean product

(4S)–4,5–Dihydro–4–methyl–2–[2–(diphenylphosphino)phenyl]–1,3–oxazole **91a.** (80%) as a white solid M p 93–95°C . (found M+, 345.1303. $C_{22}H_{20}NOP$ requires M+, 345 1282). $[\alpha]_D^{25}$ –7 5 (c 2.0, $CHCl_3$) υ_{max} / cm^{-1} 1650 (C=N) δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, J 6 5, $C\underline{H}_3$), 3 54 (1H, m, C$\underline{H}$N), 4 08–4 21 (2H, m, $C\underline{H}_2O$), 6 84 (1H, m, aromatic C$\underline{H}$), 7 20–7 70 (13H, m, aromatic C$\underline{H}$) δ_C (100 MHz, $CDCl_3$) 20 6 ($\underline{C}H_3$), 61 7 ($\underline{C}$HN), 73 4 ($\underline{C}H_2O$), 127.7/ 128 1/ 128 2/ 128 3/ 128.5/ 128 6/ 128 8/ 130 2/ 130 4/ 130 6/ 132 3/ 133.2/ 133 6 (aromatic $\underline{C}$H), 133 8/ 133 9/ 134 0/ 134 3 (aromatic $\underline{C}$), 163 3 ($\underline{C}$=N). δ_P (162 MHz, $CDCl_3$) –4 7 (PPh_2) *m/z* (EI) 345(M+, 17%)

(4S)–4–benzyl–4,5–Dihydro–2–[2–(diphenylphosphino)phenyl]–1,3–oxazole **91b.** (76%) as a white solid M p. 106–108°C . (found M+, 421.1573. $C_{28}H_{24}NOP$ requires M+, 421.1595). $[\alpha]_D^{25}$ 14 0 (c 0.5, $CHCl_3$) υ_{max} / cm^{-1} 1649 (C=N) δ_H (400 MHz, $CDCl_3$) 2 12 (1H, dd, J 9.1, 13 8, C$\underline{H}$H'Ph), 2 92 (1H, dd, J 5 1, 13 8, CH$\underline{H'}$Ph), 3.75 (1H, t, J 8.2, C$\underline{H}$H'O), 4 01 (1H, t, J 8 2, CH$\underline{H'}$O), 4 33 (1H, m, C$\underline{H}$N), 6 86 (1H, m, aromatic C$\underline{H}$), 7.17–7.34 (17H, m, aromatic C$\underline{H}$), 7 85 (1H, m, aromatic C$\underline{H}$) δ_C (100 MHz, $CDCl_3$) 41 0 ($\underline{C}H_2Ph$), 67.8 ($\underline{C}$HN), 71 3 ($\underline{C}H_2O$), 126 3–138 1 (aromatic $\underline{C}$H and $\underline{C}$), 163.8 ($\underline{C}$=N). δ_P (162 MHz, $CDCl_3$) –4 9 (PPh_2) *m/z* (EI) 421(M+, 12%)

(4S)–4,5–Dihydro–4–isopropyl–2–[2–(diphenylphosphino)phenyl]–1,3–oxazole **91c.** (76%) as a white solid. M p 84–86°C (found M+, 373 1597. $C_{24}H_{24}NOP$ requires M+, 373 1595) $[\alpha]_D^{25}$ –40 (c 0 5, $CHCl_3$) υ_{max} / cm^{-1} 1651 (C=N) δ_H (400 MHz, $CDCl_3$) 0 69 (3H, d, J 6 7, $C\underline{H}_3$), 0 80 (3H, d, J 6.7, $C\underline{H}_3$), 1.52 (1H, m, $C\underline{H}(CH_3)_2$), 3.80 (2H, m, C$\underline{H}$N and C$\underline{H}$H'O), 4.10 (1H, m, CH$\underline{H'}$O), 6 89 (1H, m,

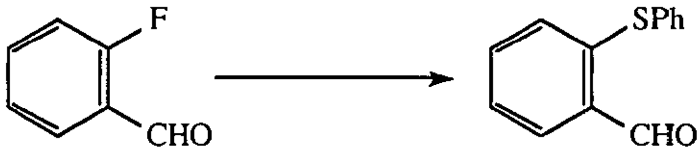
aromatic C*H*), 7 20–7.70 (12H, m, aromatic C*H*), 7 92 (1H, m, aromatic C*H*) δ_C (100 MHz, $CDCl_3$) 18 2 ($\underline{C}H_3$), 18 7 ($\underline{C}H_3$), 32 7 ($\underline{C}H(CH_3)_2$), 69 7 ($\underline{C}H_2O$), 72.9 ($\underline{C}$HN), 127 9 – 138.1 (aromatic $\underline{C}$H and $\underline{C}$) , 162 9 ($\underline{C}$=N) δ_P (162 MHz, $CDCl_3$) –4 6 (PPh_2) *m/z* (EI) 373(M^+, 26%).

(4S)–4,5–Dihydro–4–phenyl–2–[2–(diphenylphosphino)phenyl]–1,3–oxazole **91d.** (84%) as a colourless glassy solid M.p 57–58°C (found M^+, 407.1439. $C_{27}H_{22}NOP$ requires M^+, 407 1439). $[\alpha]_D^{25}$ +24 0 (c 0 25, $CHCl_3$) υ_{max} / cm^{-1} 1649 (C=N) δ_H (400 MHz, $CDCl_3$) 3 92 (1H. t, J 8.4, C$\underline{H}$H'O), 4 55 (1H, dd, J 8 4, 9.9, CH$\underline{H'}$O), 5 22 (1H, t, J 9 9, C$\underline{H}$N), 6 89–8 01 (19H, m, aromatic C$\underline{H}$). δ_C (100 MHz, $CDCl_3$) 70 0 ($\underline{C}$HN), 74 2 ($\underline{C}H_2O$) 126 5/ 127 0/ 127 9/ 128 3/ 128 4/ 128 6/ 130 2/ 130 5/ 131.4/ 133 6/ 133 8 (aromatic $\underline{C}$H), 134.1/ 134.3/ 134 3/ 137 7/ 141.9 (aromatic $\underline{C}$). δ_P (162 MHz, $CDCl_3$) –4 7 (PPh_2) *m/z* (EI) 407(M^+, 8%)

*(4S)–4,5–Dihydro–4–*tert*–butyl–2–[2–(diphenylphosphino)phenyl]–1,3–oxazole* **91e.** (92%) as a white solid. M p 114–116°C (found M^+, 387.1741. $C_{25}H_{26}NOP$ requires M^+, 387.1751). $[\alpha]_D^{25}$ –55 2 (c 0 6, $CHCl_3$). υ_{max} / cm^{-1} 1650 (C=N). δ_H (400 MHz, $CDCl_3$) 0.72 (9H. s, $C(C\underline{H}_3)_3$), 3.99 (1H, t, J 8 3, C$\underline{H}$N), 4.10 – 4 21 (2H, m, $C\underline{H}_2O$), 6 90 (1H. m, aromatic C$\underline{H}$), 7.20–7 80 (12H, m, aromatic C$\underline{H}$), 7 94 (1H, m, aromatic C$\underline{H}$) δ_C (100 MHz, $CDCl_3$) 25 7 ($C(\underline{C}H_3)_3$), 33 4 ($\underline{C}(CH_3)_3$), 68.1 ($\underline{C}$HN), 75 8 ($\underline{C}H_2O$), 127 9/ 128 0/ 128.1/ 128.2/ 128 3/ 128.4/ 129.7/ 130 2/ 130.6/ 131 1/ 131 6/ 131 7/ 133.3 (aromatic $\underline{C}$H), 133 5/ 134 0/ 134 2/ 138 5 (aromatic $\underline{C}$), 162 9 ($\underline{C}$=N). δ_P (162 MHz, $CDCl_3$) –4 7 (PPh_2) *m/z* (EI) 387(M^+, 11%).

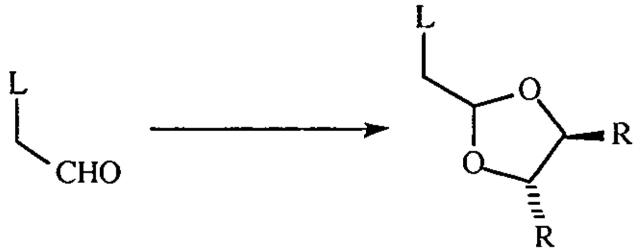
6.4 *Experimental for Chapter Five*

(2-phenylsulfanyl)benzaldehyde **117**



To a stirring mixture of sodium hydride (9 mmol) in THF (5ml) was added a solution of benzenethiol (9mmol) in THF (2ml) To the resulting white precipitate was added a solution of 2-fluorobenzaldehyde (8 mmol) in THF (2ml) The mixture was allowed to stir under reflux for 48 hours whereupon the solution became clear. The reaction mixture was poured into dichloromethane (20ml), washed with 15% NaOH (20ml) then H_2O (20ml) The aqueous layers were extracted with dichloromethane (2 x 50ml), the organic extracts were then combined, dried (Na_2SO_4), filtered then concentrated *in vacuo* The crude product was purified by flash chromatography (light petroleum/ether 3:1) to afford the *title compound* (40%) as a pale yellow oil (found M^+, 214 0436 $C_{13}H_{10}OS$ requires M^+, 214 0452) υ_{max} / cm^{-1} 1699, 1673 δ_H (250 MHz, $CDCl_3$) 7 10–7.91 (9H, m, aromatic C<u>H</u>), 10 40 (1H, s, C<u>H</u>O) δ_C (63 MHz, $CDCl_3$) 126 3/ 128 4/ 129 6/ 130 3/ 131 8/ 131 9/ 133 0/ 133 1/ 134.0 (aromatic <u>C</u>H), 137.1, 137 9 (aromatic <u>C</u>), 191 5 (<u>C</u>HO) *m/z* (EI) 214(M^+, 85%).

General procedure for the preparation of enantiopure acetal ligands from the aldehyde



A mixture of the aldehyde (1.6 mmol) , enantiopure diol (1 6 mmol) and (±)–10–camphorsulfonic acid (10 mol%) in toluene (10ml) was stirred under reflux for 2 hours The toluene/water azeotrope was then distilled off The residue was diluted with diethyl ether (30ml) and poured into a saturated solution of sodium hydrogencarbonate (50ml). The organic layer was washed with water (3 x 30ml), the organic extracts dried (Na_2SO_4), filtered and solvent removed *in vacuo* The crude solids were recrystallised from ethyl acetate to give a clean product.

(4S, 5S)–2–(2–pyridyl)–[4,5–Bis(phenyl)]–1,3–dioxolane **105.** (63%) as a colourless crystalline solid M. p. 105–107°C (found M^+, 303 1259. $C_{20}H_{17}NO_2$ requires M^+, 303 1259) $[\alpha]_D^{25}$ -24 8 (c 2.5, $CHCl_3$) υ_{max} / cm^{-1} 1029, 1044, 1074, 1108. δ_H (250 MHz, $CDCl_3$) 5 00 (1H, d, J 7.9, C<u>H</u>Ph), 5.02 (1H, d, J 7 9, C<u>H</u>Ph), 6 44 (1H, s, C<u>H</u>OO), 7.12–7.81 (14H, m, aromatic C<u>H</u>) δ_C (63 MHz, $CDCl_3$) 85 4 (<u>C</u>HPh), 87 2 (<u>C</u>HPh), 104 4 (<u>C</u>HOO), 120 8/ 124 2/ 126 4/ 126 9/ 127 8/ 128.0/ 128 3/ 138.5 (aromatic <u>C</u>H) 137 0/ 140 5/ 149 2 (aromatic <u>C</u>) *m/z* (EI) 303(M^+, 16%)

(4R, 5R)–2–((2–diphenylphosphino)phenyl)–[4,5–Bis(methyl)]–1,3–dioxolane **106.** (77%) as a colourless crystalline solid M. p 136–137°C (found M^+, 362 1588 $C_{23}H_{23}O_2P$ requires M^+, 362.1436) $[\alpha]_D^{25}$ -10 3 (c 3 5, $CHCl_3$)

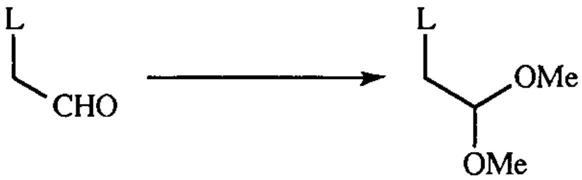
υ_{max} / cm^{-1} 1050, 1092, 1105. δ_H (250 MHz, $CDCl_3$) 1.02 (3H, d, J 5 6, C<u>H</u>$_3$) 1 18 (3H, d, J 5 6, C<u>H</u>$_3$), 3 60 (2H, m, 2 x C<u>H</u>CH_3), 6 59 (1H, s, C<u>H</u>OO), 7 17–7.87 (14H, m, aromatic C<u>H</u>) δ_C (63 MHz, $CDCl_3$) 16 8 (<u>C</u>H_3), 16 9 (<u>C</u>H_3), 78 5 (<u>C</u>HMe), 80 0 (<u>C</u>HMe), 98 9 (1C, d, J 5 1, <u>C</u>HOO), 128.1/ 128 2/ 128 3/ 128 4/ 131 6/ 131 8/ 131 9/ 132 1/ 132 2/ 133.1/ 133 3 (aromatic <u>C</u>H) 143 0 (aromatic <u>C</u>) *m/z* (EI) 362(M^+, 28%).

(4R, 6R)-2-((2-diphenylphosphino)phenyl)-[4, 6-Bis(methyl)]-1,3-dioxan **107.** (82%) as a colourless crystalline solid M p 141–142°C (found M^+, 376 1603 $C_{24}H_{25}O_2P$ requires M^+, 376 1592). $[\alpha]_D^{25}$ –40 0 (c 0 5, MeOH) υ_{max} / cm^{-1} 1118, 1128, 1186 δ_H (250 MHz, $CDCl_3$) 0 91 (3H, d, J 6 1, C<u>H</u>$_3$), 1 12 (3H, d, J 7 0, C<u>H</u>$_3$), 1 82 (2H, m, C<u>H</u>$_2$), 3 80 (2H, m, 2 x C<u>H</u>CH_3), 6 61 (1H, s, C<u>H</u>OO), 7 07–7 69 (14H, m, aromatic C<u>H</u>) δ_C (63 MHz, $CDCl_3$) 16 8 (<u>C</u>H_3), 21 4 (<u>C</u>H_3), 36 8 (<u>C</u>H_2), 68 0 (<u>C</u>HMe), 69 0 (<u>C</u>HMe), 91 1 (1C, d, J 5 6, <u>C</u>HOO), 127 8/ 128 1/ 128 2/ 128 4/ 131 6/ 131.9/ 132 0/ 132.1/ 132 5/ 132 9/ 133 1 (aromatic <u>C</u>H) 142 9 (aromatic <u>C</u>) *m/z* (EI) 376(M^+, 5%)

(4S, 5S)-2-((2-diphenylphosphino)phenyl)-[4, 5-Bis(phenyl)]-1,3-dioxolane **108.** (61%) as a colourless crystalline solid M p 94–95°C (found M^+ 486 2000. $C_{33}H_{27}O_2P$ requires M^+, 486 1749) $[\alpha]_D^{25}$ +14.0 (c 0 5, $CHCl_3$) υ_{max} / cm^{-1} 1026, 1057, 1090, 1101 δ_H (250 MHz, $CDCl_3$) 4 74 (1H, d, J 7 8, C<u>H</u>Ph), 4 76 (1H, d, J 7 8, C<u>H</u>Ph), 6 96 (1H, s, C<u>H</u>OO), 7 10–7.71 (24H, m, aromatic C<u>H</u>). δ_C (63 MHz, $CDCl_3$) 85.1 (<u>C</u>HPh), 87 0 (<u>C</u>HPh), 101.0 (1C, d, J 5.2, <u>C</u>HOO), 125 9/ 126 8/ 127 0/ 127.6/ 127.7/ 127.9/ 128 3/ 128 4/ 128 6/ 128 7/ 128 8/ 131.8/ 132 0/ 132 1/ 132 2/ 132 4/ 133.1/ 133 3 (aromatic <u>C</u>H) 136.7/ 138.7/ 142 4 (aromatic <u>C</u>) *m/z* (EI) 486(M^+, 11%)

Alternative procedure for preparation of enantiopure acetal ligands

Acetalisation



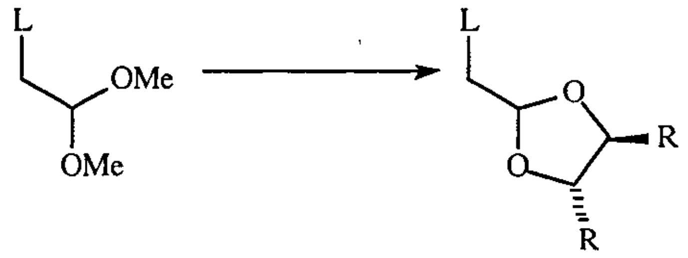
To a stirring mixture of the aldehyde (50 mmol) and cerium (III) chloride heptahydrate (2 6 mmol) in methanol (30ml) was added trimethyl orthoformate (75 mmol). The mixture was allowed to stir for 8 hours then concentrated *in vacuo* The residue was diluted with diethyl ether (30ml) then poured into sodium hydrogencarbonate solution (50ml) The aqueous layer is extracted with diethyl ether (2 x 50ml) The organic extracts are then washed with water (2 x 50ml), brine (50ml), dried (Na_2SO_4), filtered then the solvent is removed *in vacuo.* The residual oil is purified by distillation under reduced pressure to give a clean product

2–thiophene carboxaldehyde dimethyl acetal **109.** (86%) as a colourless oil. (found M^+, 158 0390. $C_7H_{10}O_2S$ requires M^+, 158 0401). υ_{max} / cm^{-1} 1095, 1075, 1054. δ_H (250 MHz, $CDCl_3$) 3 35 (6H, s, 2 x $OC\underline{H}_3$), 5 62 (1H, s, $C\underline{H}OMe$), 7.03 (3H, m, thiophene $C\underline{H}$). δ_C (63 MHz, $CDCl_3$) 52.4 (2 x $\underline{C}H_3$), 100 0 ($\underline{C}HOMe$), 125 4/ 125 6/ 126 6 (thiophene $\underline{C}H$) 141.5 (thiophene $\underline{C}$). *m/z* (EI) 158(M^+, 100%).

(2-phenylsulfanyl)benzaldehyde dimethyl acetal **111.** (96%) as a colourless oil (found M^+, 260 0873 $C_{14}H_{15}O_2S$ requires M^+, 260 0871). υ_{max} / cm^{-1} 1073, 10759. δ_H (250 MHz, $CDCl_3$) 3 34 (6H, s, 2 x $OC\underline{H}_3$), 5 72 (1H, s, $C\underline{H}OMe$), 7 23–7 29 (9H, m, aromatic $C\underline{H}$) δ_C (63 MHz, $CDCl_3$) 53.8 (2 x $\underline{C}H_3$), 101.7

(<u>C</u>HOMe), 126 9/ 127 0/ 127 2/ 129 2/ 130 8/ 132 5 (aromatic <u>C</u>H) 134 9/ 137 1/ 138 5 (aromatic <u>C</u>). *m/z* (EI) 260(M^+, 92%)

Transacetalisation



A mixture of the acetal (1 6 mmol) , enantiopure diol (1.6 mmol) and (±)–10–camphorsulfonic acid (10 mol%) in toluene (10ml) was stirred under reflux for 2 hours. The toluene/methanol azeotrope was then distilled off The residue was diluted with diethyl ether (30ml) and poured into a saturated solution of sodium hydrogencarbonate (50ml). The organic layer was washed with water (2 x 30ml), the organic extracts dried (Na_2SO_4), filtered and solvent removed *in vacuo* The crude solids were recrystallised from ethyl acetate to give a clean product

(4R, 5R)–2–(2–thienyl)–[4, 5–Bis(methyl)]–1,3–dioxolane **112.** (92%) as a colourless oil. (found M^+, 184.0566. $C_9H_{12}O_2S$ requires M^+, 184 0558). $[\alpha]_D^{25}$ -30 0 (c 1, $CHCl_3$) υ_{max} / cm^{-1} 1089, 1048, 1039 δ_H (250 MHz, $CDCl_3$) 1.31 (3H, d, J 4 0, $C\underline{H}_3$), 1 38 (3H, d, J 4 0, $C\underline{H}_3$), 3 80 (2H, m, 2 x $C\underline{H}CH_3$), 6 23 (1H, s, C<u>H</u>OO), 6 99 (1H, dd, J 5 0, 3 4, thiophene C<u>H</u>), 7.16 (1H, m, thiophene C<u>H</u>), 7.32 (1H, m, thiophene C<u>H</u>) δ_C (63 MHz, $CDCl_3$) 16 7 ($\underline{C}H_3$), 16 8 ($\underline{C}H_3$), 78 2 (<u>C</u>HMe), 80.2 (<u>C</u>HMe), 98 9 (<u>C</u>HOO), 125 9/ 126 2/ 126.5 (thiophene <u>C</u>H) 142 9 (thiophene <u>C</u>). *m/z* (EI) 184 (M^+, 21%)

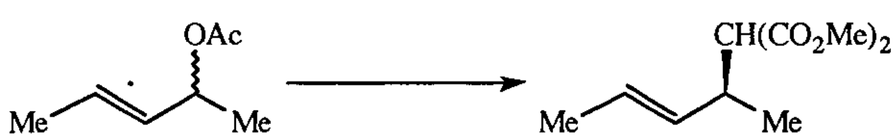
(4S, 5S)–2–(2–thienyl)–[4, 5–Bis(phenyl)]–1,3–dioxolane **113.** (77%) as a colourless crystalline solid M p 85–86°C. (Found C, 73 7, H, 5 1 $C_{19}H_{16}O_2S$

requires C, 74 0, H, 5 2%) $[\alpha]_D^{25}$ -21 0 (c 1.0, $CHCl_3$) υ_{max} / cm^{-1} 2933, 2895, 2830, 1093, 1056 δ_H (250 MHz, $CDCl_3$) 4 94 (1H, d, J 8 0, C<u>H</u>Ph), 4 96 (1H, d, J 8 0, C<u>H</u>Ph), 6 70 (1H, s, C<u>H</u>OO), 7 07 (1H, dd, J 5 0, 3 4, thiophene C<u>H</u>), 7 27-7.44 (12H, m, aromatic C<u>H</u>), δ_C (63 MHz, $CDCl_3$) 84 9 (<u>C</u>HPh), 87.1 (<u>C</u>HPh), 101 0 (<u>C</u>HOO) 126 5/ 126.6/ 126.7/ 126.9/ 128 3/ 128 5 (aromatic <u>C</u>H), 136 9/ 137.8/ 143 0 (aromatic <u>C</u>) *m/z* (EI) 308(M^+, 21%), 307(100)

(4S, 5S)–2–((2–methylsulfanyl)methyl)–[4, 5–Bis(phenyl)]–1,3–dioxolane **114.** (52%) as a colourless crystalline solid M p 41–42°C (found $M+NH_4^+$, 304 1371 $C_{17}H_{18}O_2S$ requires $M+NH_4^+$, 304 1371) $[\alpha]_D^{25}$ +31 0 (c 1 0, $CHCl_3$) υ_{max} / cm^{-1} 1043, 1078, 1035 δ_H (250 MHz, $CDCl_3$) 2 30 (3H, s, SC<u>H</u>$_3$), 2 97 (2H, d, J 4.3, C<u>H</u>$_2$$SCH_3$), 4 80 (2H, m, 2 x C<u>H</u>Ph), 5.71 (1H, t, J 4 3, C<u>H</u>OO), 7 21-7 36 (10H, m, aromatic C<u>H</u>), δ_C (63 MHz, $CDCl_3$) 16.9 (S<u>C</u>H$_3$), 38 3 (<u>C</u>H$_2$$SCH_3$), 85 1 (<u>C</u>HPh), 86 6 (<u>C</u>HPh), 105 3 (<u>C</u>HOO) 126 3/ 126 8/ 128 1/ 128 5 (aromatic <u>C</u>H), 137.2/ 137.7 (aromatic <u>C</u>) *m/z* (CI) 304($M+NH_4^+$, 100%)

(4S, 5S)–2–((2–phenylsulfanyl)phenyl)–[4, 5–Bis(phenyl)]–1,3–dioxolane **115.** (64%) as a colourless crystalline solid M. p 70–71°C (found M^+, 410.1333. $C_{27}H_{22}O_2S$ requires M^+, 410 1340). $[\alpha]_D^{25}$ +11.9 (c 0 9, $CHCl_3$) υ_{max} / cm^{-1} 1074, 1059, 1010. δ_H (250 MHz, $CDCl_3$) 5 09 (2H, m, 2 x C<u>H</u>Ph), 6 81 (1H, s, C<u>H</u>OO), 7.28-7.36 (19H, m, aromatic C<u>H</u>), δ_C (63 MHz, $CDCl_3$) 85 3 (<u>C</u>HPh), 87 4 (<u>C</u>HPh), 102 4 (<u>C</u>HOO) 126.2/ 126.5/ 126 9/ 127.0/ 127 6/ 127 8/ 128 1/ 128 6/ 128 7/ 129 2/ 129 7/ 130 1/ 130 8/ 133.1/ 134.9/ 136.7 (aromatic <u>C</u>H), 138 1/ 138 6/ 139 4/ 139 7 (aromatic <u>C</u>) *m/z* (EI) 410(M^+, 22%), 304(100)

Procedure for palladium catalysed allylic alkylation of 2-acetoxypent-3-ene **118.**



To the reaction flask was added $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (2 5 mol%) and ligand (10 mol%) in dichloromethane (2 ml) , the mixture was allowed to stir for 15 mins *rac*-2-acetoxypent-3-ene **118** (0 4 mmol) in dichloromethane (2 ml) was then added and stirring continued for a further 20 mins before adding dimethyl malonate (1.2 mmol), N,O-bis(trimethylsilyl)acetamide (1 2 mmol) in dichloromethane (1 ml) and a catalytic amount of sodium acetate (3 mol%) Stirring was continued until all the starting material had been consumed as shown by TLC (petroleum ether . ether (3 1)). The reaction mixture was diluted with diethyl ether (10 ml) and washed with saturated ammonium chloride soultion (10 ml) The separated organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography yielded **19** as a colourless oil [37] δ_H (250 MHz, $CDCl_3$) 1 28 (3H, d, J 6 2 , C<u>H</u>3), 1 68 (3H, d, J 6 8, C<u>H</u>3), 2 03 (3H, s, OC<u>H</u>3), 5 27 - 5 32 (1H m, C<u>H</u>), 5 43 - 5 53 (1H, m, C<u>H</u>), 5 65 - 5.76 (1H, m, C<u>H</u>)

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