New Bisphosphine Ligands for Asymmetric Catalysis

A thesis submitted in partial
fulfilment of the requirements
for the degree of Doctor of Philosophy

by

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September 1991

Acknowledgements

I would like to express my gratitude to Dr. John M. Brown for his supervision and enthusiasm throughout this work.

I am grateful to my Industrial supervisor, Dr. Michael J. Russell for his continued interest during this project.

I would also like to thank my College tutors, Dr. John H. Jones and Dr. David Logan for their help, advice and encouragement during my time at Balliol.

For determining the crystal structures of (2*S*, 4*S*, 5*R*)-(**50**), (2*S*, 4*S*, 5*R*)-(**51**) and (2*R*, 4*S*, 5*R*)-(**52**) and their collaborative research I am grateful to Dr's Carl Schwalbe and Sally Freeman at the University of Aston. For help in determining the structure of (2*R*, 4*S*, 5*R*)-(**49**) I am grateful to Dr. Keith Prout and the staff of the Chemical Crystallography Department at Oxford. I would also like to thank Dr. Alison Edwards for her help in solving the structure of (*R*p)-(**71**).

I am indebted to the technical and support staff within the Dyson Perrins Laboratory, especially Mrs Elizabeth McGuinness for her generous advice and running many of the n.m.r. spectra.

For proof reading this thesis and supplying the phosphine that didn't quite work I would like to thank Peter Scott of the Inorganic Chemistry Laboratory.

Of my colleagues within the Dyson Perrins Laboratory I would particularly like to acknowledge the help, advice and friendship of Carl Garland. Thanks also go to Simon Woodward, Kevin Matthews and Neil Cooley for their technical advice and friendship and to Tim Cheeseright for valuable proof reading.

For memorable (and not so memorable) 'Team' adventures and keeping a sense of proportion on 'Life' (except Wayne) I would like to thank to thank Carl, Scruff, McAlastair, Wayne and Ronald.

For their love and encouragement I am grateful to my family and *h*Ammy.

Finally, I would like to thank Johnson Matthey for full funding of this work in the form of an industrial sptudentship. I am also grateful to Balliol College for financial help.

Aslib Abstract

New Bisphosphine Ligands for Asymmetric Catalysis

J.V. Carey B.Sc, G.R.S.C. Balliol College. D.Phil. Michaelmas 1991.

The success of homogeneous asymmetric catalysis has been attributed to the structure and stereochemistry of the coordinated ligand(s). The most effective ligands are C_2-symmetrical bisphosphines containing either a rigid chiral backbone linking two PPh_2 units or a bisphosphine, DIPAMP containing two chiral phosphine units linked by an achiral backbone. The synthesis of P-chiral ligands of this type has been severely hindered by the lack of a general synthetic route allowing the incorporation of phosphorus chirality without the need for separation of diastereomeric precursors or resolution of intermediate enantiomers. The objective of this work was to develop a general synthetic route to homochiral bulky arylphosphines with substantial flexibility in the groups at phosphorus and extend the approach to new P-chiral bisphosphines.

In one approach, diastereomerically pure (2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine was prepared directly from $PhPCl_2$ using *l*-ephedrine as a chiral auxiliary. Stereospecific oxidation using Bu^tOOH gave the corresponding P-oxide which was shown to have *R*-stereochemistry at phosphorus by single-crystal X-ray diffraction studies. The compound reacted regiospecifically with *ortho*-anisylmagnesium bromide to afford the product formed by P-O bond cleavage with >96% d.e. and with retention of configuration at phosphorus as demonstrated by single-crystal X-ray diffraction studies. The *l*-ephedrine residue was replaced by O-methyl under acid-catalysis with inversion of configuration and with >95% e.e., the reaction was monitored by ^1H n.m.r. spectroscopy which gave $t_{1/2}$ of *ca.* 30 min. Attempts to incorporate *para*-fluorophenol using similar conditions led to the isolation of the pyrophosphinate in low yield. The OMe residue in the methyl (*ortho*-anisyl)phenylphosphinate was readily displaced by aliphatic Grignard reagents giving the corresponding phosphine oxides with inversion of configuration and with >95% e.e.. Displacement of methoxy using aryl magnesium bromides showed similar enantioselectivity but in lower chemical yield, however the corresponding arylmagnesium chlorides were more efficient.

In a second approach, diastereomerically pure (2*R*, 4*S*, 5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine was prepared from PCl_3 and *l*-ephedrine. The compound underwent diastereoselective P-Cl cleavage with aryl Grignard and aryllithium reagents with net retention of configuration at phosphorus and with 90% d.e.. Oxidation of the *ortho*-anisyl derivative afforded (2*R*, 4*S*, 5*R*)-2-(*ortho*-anisyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide which was subsequently reacted with a range of bulky aryl Grignard reagents to afford the corresponding biarylphosphinamides with retention of configuration at phosphorus. Subsequent acid-catalysed methanolysis and displacement of the methoxy residue with PhMgCl afforded a range of bulky arylphosphine oxides with defined configuration at phosphorus with >95% e.e. as determined by ^1H n.m.r. methods.

(*S*)-*ortho*-anisyl (*meta*-anisyl)phenylphosphine oxide underwent regiospecific *ortho*-lithiation on the *meta*-anisyl ring which on quenching with D_2O afforded the corresponding 2-deuteride in 80% yield. The 2-iodo analogue was also prepared although in low chemical purity and is a key precursor to new axially dissymmetric bisphosphines containing chiral phosphorus centres. Other approaches to P-chiral ferrocenyl ligands and biaryl ligands are also described and modifications for further development are implicated.

An X-ray crystallographic study of six aryl-oxazaphospholidines is also presented and demonstrates the influence of the substituents at phosphorus in determining the conformation of the 1,3,2-oxazaphospholidine ring. A comparison with solution ^1H n.m.r. data showed, in some cases, good correlation between the P-O-C-H dihedral angle and the corresponding solid state torsion angle.

The following publications have resulted from the work presented in this thesis:

THE NUCLEOPHILIC DISPLACEMENT ROUTE TO HOMOCHIRAL ARYLPHOSPHINE OXIDES.

By John. M. Brown, Joseph. V. Carey and Michael J.H. Russell.

in *Tetrahedron*, **46** (1990) 4877.

also

SOLID STATE CONFORMATIONS OF SIX 1,3,2-OXAZAPHOSPHOLIDINES DERIVED FROM (-)-EPHEDRINE: X-RAY CRYSTAL STRUCTURES OF THE 2-PHENOXY-2-OXO, 2-PHENYL-2-OXO AND 2-PHENYL-2-THIO ANALOGUES.

By Carl H. Schwalbe, Geetanjlee Chopra, Sally Freeman, John M. Brown and Joseph V. Carey.

accepted for publication in *J. Chem. Soc., Perkin Trans II.*, (1991).

Abbreviations

Ac	Acetyl
n-But	Butyl
t-But	*tert*-Butyl
Bn	Benzyl
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
COD	Cyclooctadiene
c.m.	Centimetre
C.I.	Chemical Ionisation
CS_2	Carbon disulphide
DMF	Dimethylformamide
E.I.	Electron Impact
Et	Ethyl
EtOAc	Ethylacetate
Et_2O	Diethyl Ether
e.s.d.'s	Estimated standard deviations
F.A.B.	Fast Atom Bombardment
HCl	Hydrochloric acid
h	hours
i.r.	infra red
L	Ligand
LDA	Lithiumdiisopropylamine
Me	Methyl
MeOH	Methanol
m	Minute
ml	mililitre
n.m.r.	nuclear magnetic resonance
Nu	Nucleophilile
THF	Tetrahydrofuran
TMEDA	*N,N,N'N'*-Tetramethylethylenediamine
*	Chiral centre

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Chapter 1. Introduction.

1.1. Homogeneous Asymmetric Catalysis.

The importance of enantiomerically pure compounds stems from the central role of enantiomer recognition in living systems[1]. Of the methods available to introduce enantioselectivity in chemical synthesis[2] the most efficient is the use of an enantiomerically pure catalyst, where a small amount of chiral material can transfer chirality to a large amount of substrate. This type of process is referred to as 'Asymmetric Catalysis'.

The most extensively studied area in asymmetric catalysis is the hydrogenation of carbon-carbon or heteroatom-carbon multiple bonds[3,4,5] giving access to one or more asymmetric centres. Such hydrogenations can be subdivided according to the nature of chirality generation (Figure 1): Case A - If the substrate already contains an asymmetric centre then the use of an achiral catalyst produces diastereoisomers and is stoichiometric in the sense that a new asymmetric centre is formed through the influence of the existing one; Case B - if the catalyst is chiral then the double bond may be hydrogenated stereoselectively and is a substoichiometric process; Case C - kinetic resolution involves the hydrogenation of racemic substrate where the complexed substrates react at different rates[6]. In such cases the optical purity of the product decreases with time, while that of the starting material increases at the same rate and usually it is optically pure substrate which is required.

The pioneering work in homogeneous catalysis is due to Wilkinson and co-workers[7] who introduced chlorotris(triphenylphosphine)rhodium(I); an efficient, benzene-soluble, hydrogenation catalyst. Its success initiated the growth of asymmetric catalysis both in terms of the generation of new ligands and mechanistic studies on their transition-metal complexes[2,3,5]. The subsequent development of asymmetric catalysis has depended upon the identification of the factors responsible for governing enantioselectivity. By modifying such control elements as ligand-metal binding, substrate-metal binding and ligand-substrate binding, enantioselectivities comparable to those of biological systems are possible. Of these, the structure and stereochemistry of ligand(s) attached to the metal template is the most crucial since this controls the flow of information from the catalyst to the substrate, allowing discrimination between possible reaction pathways.

Although successful asymmetric syntheses have been achieved using ligands containing amine, amide, sulphoxide and cyclopentadienyl functionalities, tertiary phosphines have been used most extensively because of their versatility, and because their electronic and steric properties can be predicted[8].

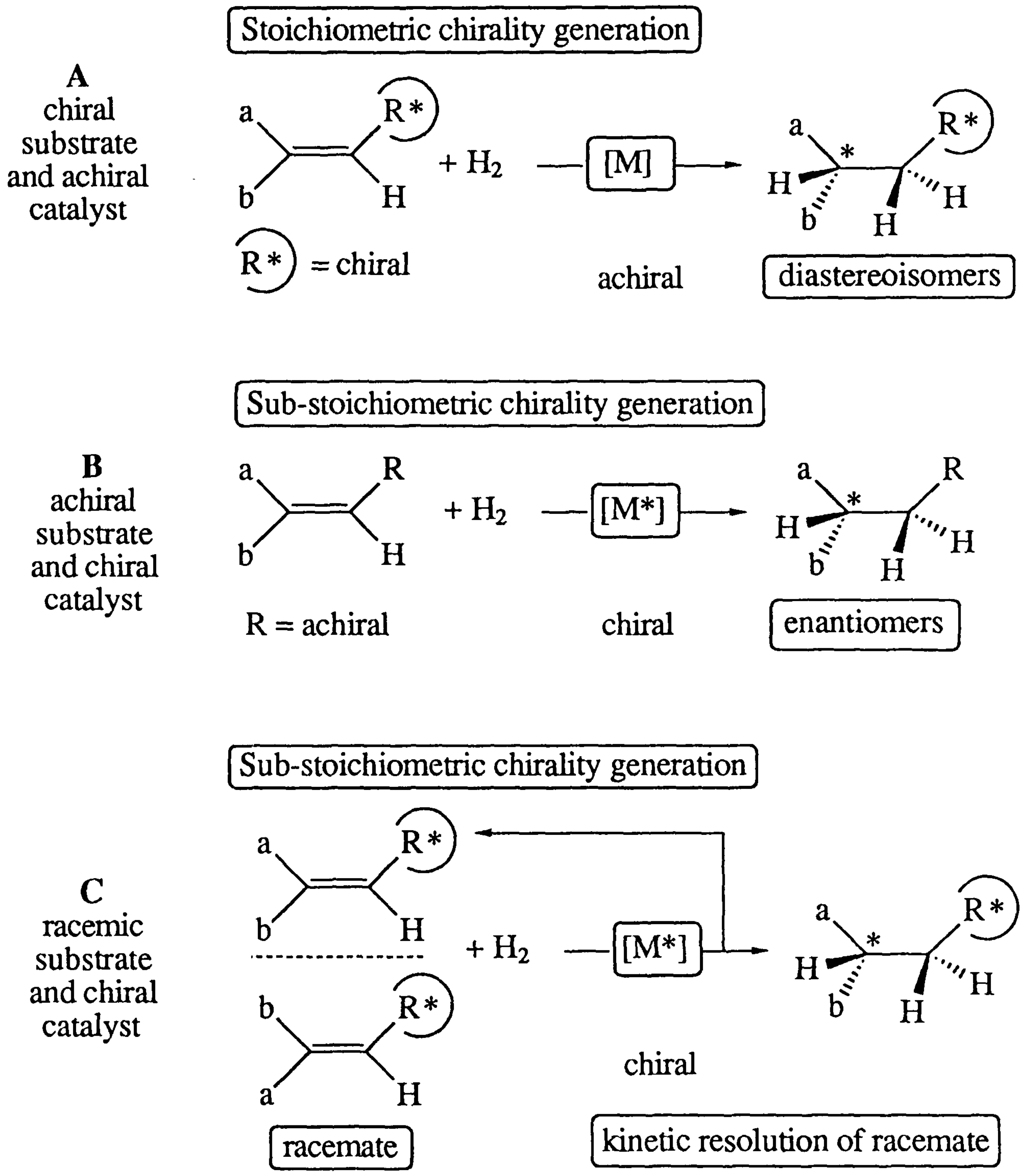
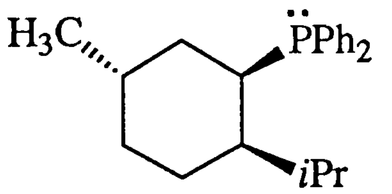


Figure 1. The nature of chirality generation for homogeneous catalysis.

Historically, Morrison *et al.*[9] were responsible for developing enantioselective hydrogenations using a phosphine ligand achiral at phosphorus but bearing a chiral substituent (**1**). Knowles *et al.*[10] introduced the homochiral phosphines PAMP-(**2**) and CAMP-(**3**). The rhodium complexes of (*S*)-(**2**) and (*S*)-(**3**) catalysed the reaction in Figure 2 with 55% and 89% e.e. respectively (Table 1).



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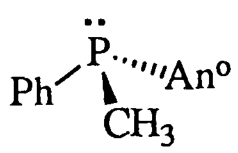

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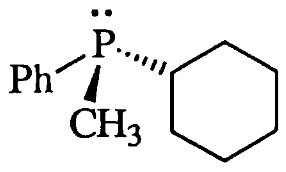

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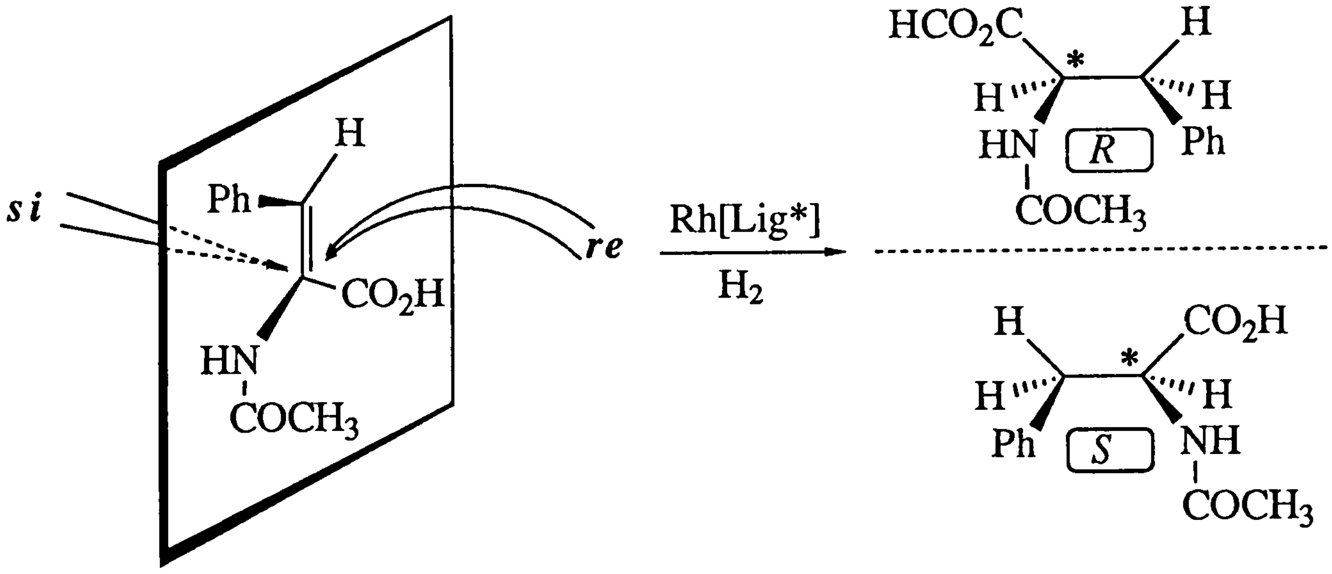
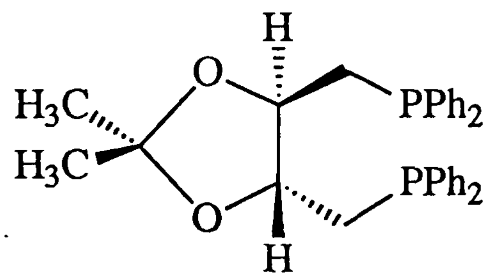


Figure 2. Catalytic hydrogenation of (Z)-α-acetamidocinnamic acid.

1.2. Bisphosphine ligands containing chiral backbones.

Kagan *et al.*[11] discovered that bisphosphines were more selective ligands for catalytic hydrogenations than monophosphines (where each rotamer is a separate catalytic species with individual *R*/*S* selectivity relative to the metal-phosphorus bond). In the Rh(I) complex of (*R*,*R*)-[(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis-(diphenylphosphine)]-(**4**) [(*R*,*R*)-(-)-DIOP-(**4**)], there is restricted rotation about the metal-phosphorus bond due to ring formation. The Rh(I) complex of (*R*,*R*)-(-)-(**4**) catalyses the reaction in Figure 2 with 81% e.e.[12] (Table 1). Since the chirality is three bonds removed from the complexed metal this suggests that it is the relative rigidity of the 7-membered chelate ring imposed by the ligand backbone which is responsible for controlling the orientation of the phenyl rings and enabling them to interact enantioselectively. This was substantiated by the observation that the rhodium complex of (**5**) gave poor enantioselectivities in the reduction of enamides[13].



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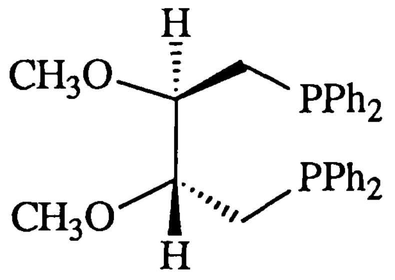

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Table 1. Catalytic Hydrogenation of (Z)-α-acetamidocinnamic acid.

Ligand	%e.e.	Config.	Ref.
(*S*)-PAMP-(**2**)	55	S	10
(*S*)-CAMP-(**3**)	89	S	10
(*R*,*R*)-(-)-DIOP-(**4**)	81	R	12
(*S*)-(-)-BINAP-(**6**)	84	R	25
(*S*,*S*)-(-)-BPPFA-(**10**)	93	S	38
(*R*,*R*)-(-)-DIPAMP-(**11**)	94	S	44
(*S*,*S*)-(-)-(**12**)	94	R	45
(*R*,*R*)-(-)-(**15**)	79	S	49

Due to the mild reaction conditions employed in homogeneous catalysis and the ability to prepare optically pure amino acids[5] the development of rhodium-bisphosphine catalysis was rapid. The majority of the bisphosphines developed contain two PPh_2 units linked by a chiral backbone of varying complexity providing the 'scaffold' for inducing asymmetry into the reactant. The area has been extensively reviewed by Halpern[4], Kagan[14], Nógrádi[15], Brunner[16] and more recently Scharf *et al.*[17], and thus this chapter attempts only to highlight the most successful examples and implications for further development. Mechanistic aspects of homogeneous asymmetric catalysis have also been thoroughly reviewed by the aforementioned authors and will not be addressed here.

The vast majority of bisphosphines form five- or seven-membered chelate rings. The geometry of these highly skewed structures (Figure 3) determines the disposition of the phenyl rings on the phosphorus atoms; two phenyls are orientated in axial and two in equatorial directions. The equatorial phenyls exert a profound steric influence on the equatorial coordination sites of the chelated metal. A five-membered-ring rhodium chelate complex may take up either a δ- or λ-conformation depending on the nature of the coordinated ligand (Figure 3). Analogously, seven-membered chelate rings in the chair form may adopt a chair-δ- or a chair-λ-conformation, again depending on the nature of the coordinated ligand. For bis(diphenylphosphine)rhodium complexes with a C_2 symmetrical axis and containing a five or seven-membered ring, the conformations depicted in Figure 3 illustrate the likely stereochemical course.

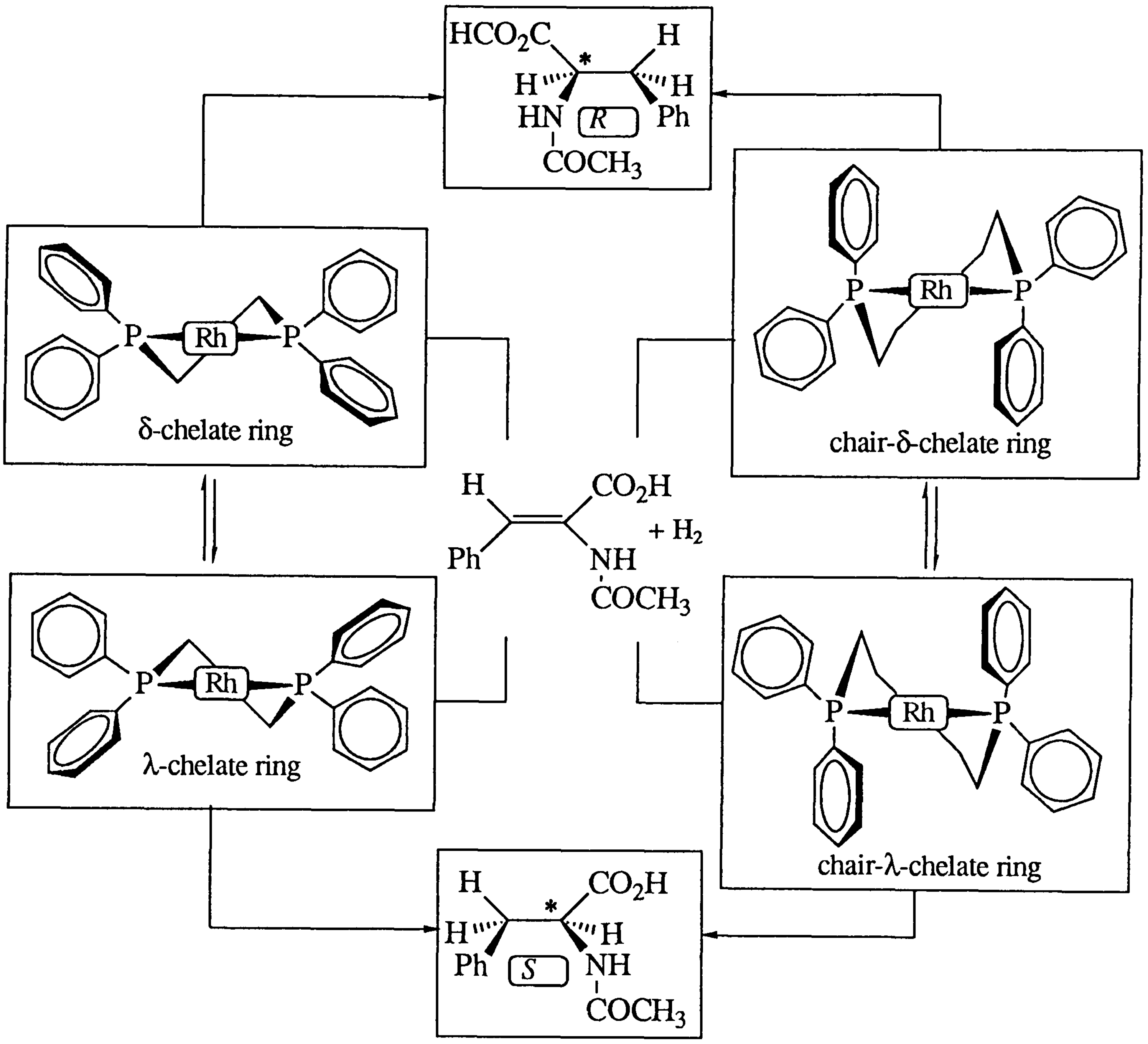
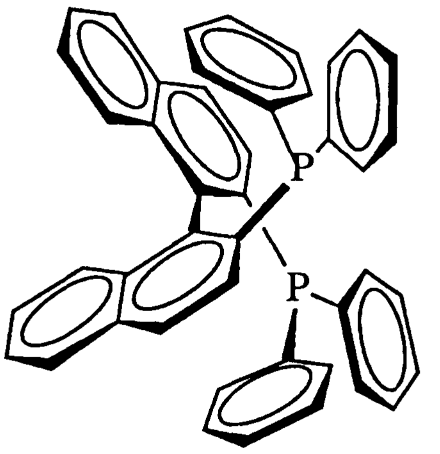


Figure 3. Conformations of Rh five- and seven-membered chelates.

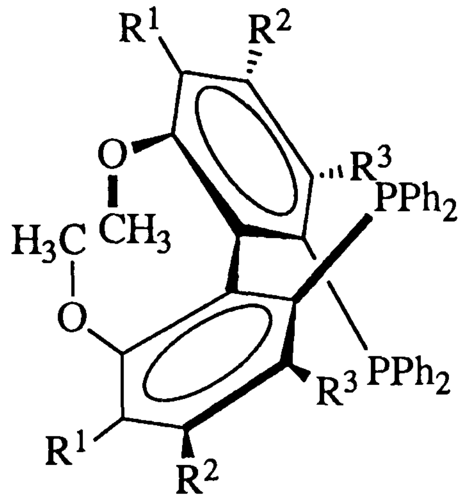
According to Kagan *et al.*[11], and reiterated by Pavlov *et al.*[18] and Nagel[19] (*vide infra*) five-membered chelates with λ-conformation and seven-membered chelates with chair-λ-conformation give an (*S*)-configuration in the product. In contrast, chelate rings with δ-conformation and chair-δ-conformation lead to the (*R*)-configuration in the product. Further insight into configurational conformations was provided by Brown *et al.*[20] (*vide infra*).

A breakthrough in ligand selectivity came when 2,2'-bis(biphenylphosphino)-1,1'-binaphthyl-(**6**), [(BINAP (**6**)], a rigid, bulky ligand containing an axially dissymmetric binaphthyl backbone was introduced by Noyori *et al.*[21,22].



(*S*)-(-)-BINAP **6**

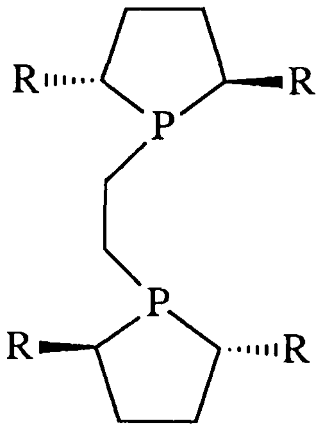
Although BINAP-(**6**) is the most rigid of all bisphosphines, it can accommodate a wide variety of transition metals by rotation about the C(1)-C(1') pivot and C(2 or 2')-P bonds without a serious increase in torsional strain. The dissymmetry of the (*S*)-(-)-BINAP-(**6**) ligand fixes the δ conformation of the seven membered chelate ring containing the bisphosphine, as indicated by the single-crystal X-ray analysis of its octahedral Ru(II) complexes[23] and square-planar Rh(I) complexes[24]. Its rhodium complex catalyses the reaction in Figure 2 with 84% e.e.[25] (Table 1). Ruthenium complexes of BINAP-(**6**) show very high reactivities and enantioselectivities under mild conditions for an extensive range of substrates[26,27]. The scope and mechanism of asymmetric catalysis using BINAP-(**6**) complexes is currently under intensive study[28]. Based on the successes of BINAP-(**6**) Schmid *et al.*[29,30] have developed a range of axially dissymmetric bisphosphines (**7**).



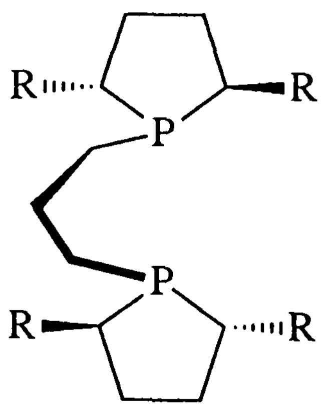
7a[29] $R^1 = R^2 = R^3 = H$
7b[29] $R^1 = OCH_3$; $R^2 = R^3 = H$
7c[29] $R^1 = R^2 = OCH_3$; $R^3 = H$
7d[30] $R^1 = R^2 = H$; $R^3 = OCH_3$

Like BINAP-(**6**) they have a two-fold symmetry axis and form stable chelate complexes with many metals. The absolute configuration of the palladium complex of (+)-(*R*)-(**7a**) has been determined by single-crystal X-ray crystallography[29]. Preliminary results of catalytic hydrogenation using the corresponding rhodium and ruthenium complexes show enantioselectivities as good as those obtained with BINAP-(**6**) in the hydrogenation of allylic alcohols[31]. The 6,6'-dimethyl analogue of (**7a**) has also been prepared by Schmid *et al.*[32] and shows excellent enantioselectivity in the Rh(I) catalysed allylamine-to-enamine isomerisations and in Ru(II)-catalysed hydrogenations of allylic alcohols and *β*-keto esters.

Burk *et al.*[33] have prepared a range of electron-rich 2,5-disubstituted phospholanes-(**8a-c**). The structure of the rhodium complex, [(COD)Rh(*R*,*R*)-(**8a**)]$^+$SbF$_6^-$ has been determined by single-crystal X-ray diffraction studies[34]. The ligand has a C_2-symmetrical environment and an angle of 24.0° between the P-Rh-P plane, indicating a highly asymmetric environment which strongly influences π-facial selectivity during binding of prochiral unsaturated substrates. Similar distortions are also seen in the related Rh[BINAP-(**6**)] complex[35].



8a; R = CH_3
8b; R = CH_2CH_3
8c; R = $CH_2CH_2CH_3$



9a; R = CH_3
9b; R = CH_2CH_3
9c; R = $CH_2CH_2CH_3$

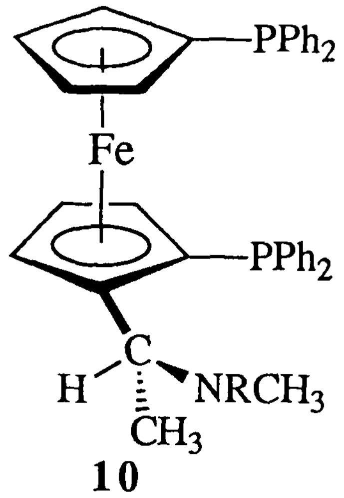
The corresponding methylene homologues (**9a-c**) have also been prepared and the structure of the rhodium complex of the propyl derivative, [(COD)Rh(*R*,*R*)-(**8c**)]$^+$SbF$_6^-$ has been determined by single-crystal X-ray diffraction studies[36]. The structure shows a slightly larger angle of 24.6° between the P-Rh-P plane. Selected enantioselectivities of these complexes for the hydrogenation of methyl acetamidocinnamate are compared in

Table 2. The differences in selectivities between the rhodium complexes of (**8**) and (**9**) were explained as being due to the larger flexibility of the propane backbone of (**9**) relative to the ethane backbone of (**8**).

Table 2. Hydrogenation of Methyl Acetamidocinnamate

Ligand	%e.e.	Config.
(*R*,*R*)-(**8a**)	85	R
(*S*,*S*)-(**8a**)	85	S
(*R*,*R*)-(**9a**)	60	R
(*S*,*S*)-(**9b**)	40	S

A unique approach to ligand synthesis, encompassing ligand-substrate binding together with potential ligand-metal binding control elements was introduced by Hayashi *et al.*[37]. They have studied the enantioselectivities of a number of 1,1'-ferrocene-bis(diphenylphosphino)-(**10**), [(BPPF)-(**10**)] ligands which because of their bite angle behave similarly to 1,4-bisphosphines. Rh[(*S*$_c$)-(*R*$_{Fe}$)-(BPPFA) (**10**; R = CH_3)] catalyses the reaction in Figure 2 with 93% e.e.[38] (Table 1).



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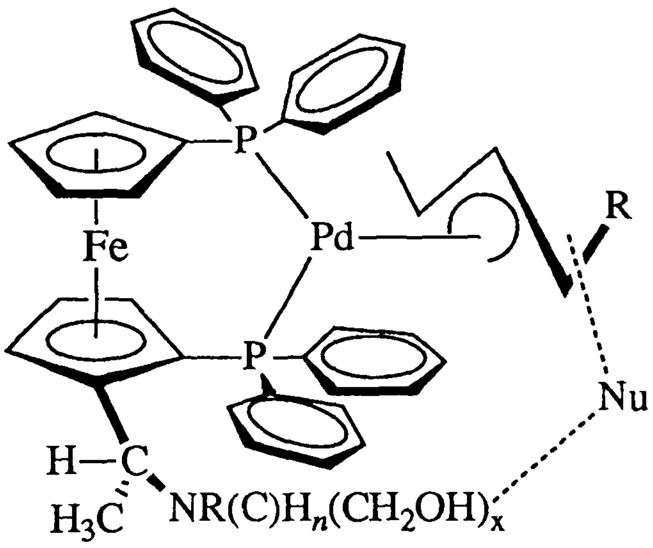
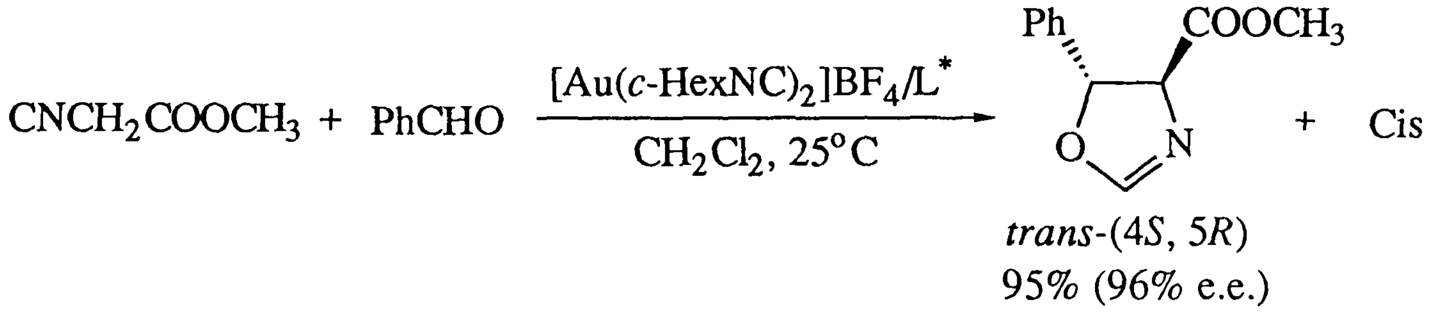
The palladium complex of 1,1'-bis(diphenylphosphino)ferrocene is an efficient cross-coupling catalyst for alkenyl-aryl coupling. The mechanistic pathway of such reactions have been elucidated by Brown *et al.*[39]. Kumada and co-workers[40] have investigated the effect of the stereogenic carbon atom of (**10**) on the disatereo- and enantio-selectivity of transition metal-catalysed Grignard cross-coupling reactions. They showed that the planar chirality plays the dominant role in product configuration

A range of chiral (BPPF)-(**10**) ligands bearing a polar functional group on a pendant side chain have also been developed (Scheme 1). The hydroxy functionality on the chiral side chain directs the incoming nucleophile preferentially to one of the two diastereotopic carbon atoms of the allylic intermediate. Optical yields of up to 96% have been obtained in allylation reactions of 1,3-diphenyl-2-propenyl acetate[41] using the ligand $n = 0$; $x = 3$ (Scheme 1).



Scheme 1

The reaction of benzaldehyde with methyl isocyanoacetate was catalysed by bis(cyclohexylisocyanoate)gold(I) tetrafluoroborate in the presence of the chiral ferrocenylamine ligand (L*, Scheme 2), (*R*)-*N*-methyl-*N*-[2-(1-piperidino)ethyl]-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine [(*R*)-(*S*)-(**10**; R = $CH_2CH_2NR'_2$; R' = 2-piperidino)] afforded *trans*-dihydrooxazole with 96% e.e.[42] (Scheme 2).



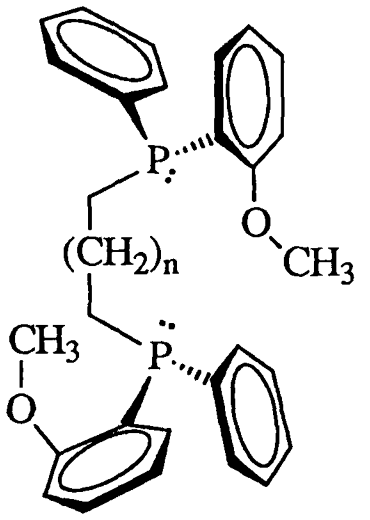
Scheme 2

Detailed mechanistic studies on these systems have been carried out by Tongi and Pastor[43] who have shown that the product stereochemistry is dependent on both the central and planar chirality in the ferrocenylphosphine catalyst (chiral cooperativity).

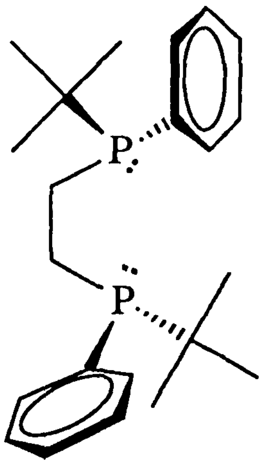
Highest enantio- and diastereo-selectivities were obtained in the gold(I)-catalysed aldol reaction when the central and planar chirality in the chiral ferrocenyl ligand are opposite, specifically, product selectivities were dependent upon the steric and electronic properties of the pendant side-chain substituents.

1.3. P-Chiral bisphosphine ligands.

(*R*,*R*)-1,2-ethanediylbis[(*ortho*-anisyl)phenylphosphine]-(**11**) [(*R*,*R*)-DIPAMP-(**11**)], introduced by Knowles and co-workers[44] is a 1,2-bisphosphine containing chirality at the phosphorus centres, the methylene[45] (**12**) and ethylene[46] (**13**) homologues have also been prepared as has the *tert*-butyl analogue (**14**)[46].



11; n = 0
12; n = 1
13; n = 2



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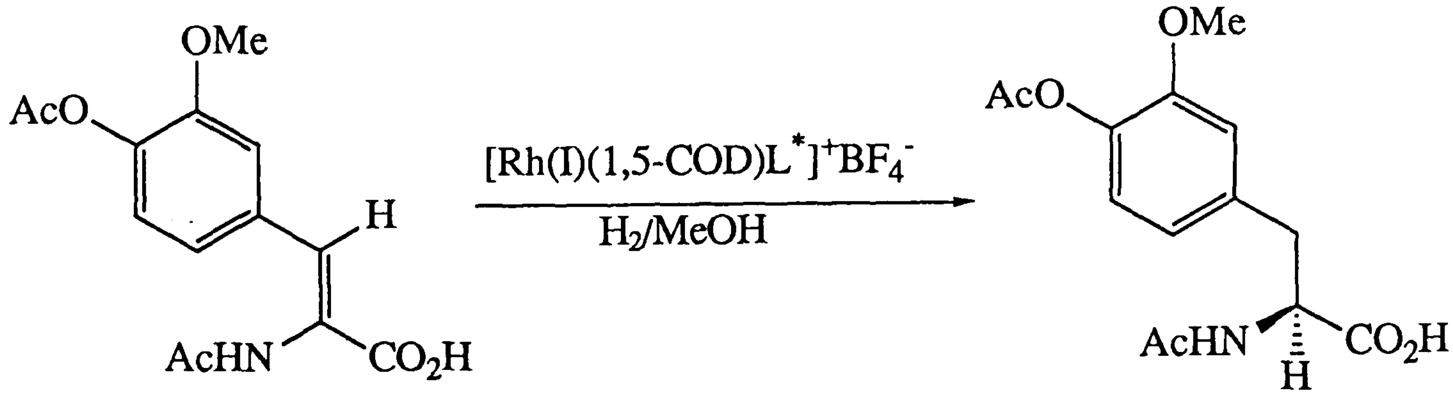
The Rh(I) complexes of ligands (**11** & **12**) both catalyse the reaction in Figure 2 with 94% e.e. (Table 1), the corresponding complexes of (**13**) and (**14**) have not been studied.

The catalyst [(1,5-COD)Rh(DIPAMP-(**11**)]$^+$ BF_4^- offers the advantage over catalysts containing ligands possessing chiral backbones in that the enantioselectivity is, in many cases higher, (*c.f.* Table 1). This catalyst is also used in the commercial Monsanto synthesis of L-Dopa[47] (Scheme 3), a drug used in the treatment of Parkinson's disease. The above tetrafluoroborate complex is also stable to air and moisture which allows it to be handled easily.



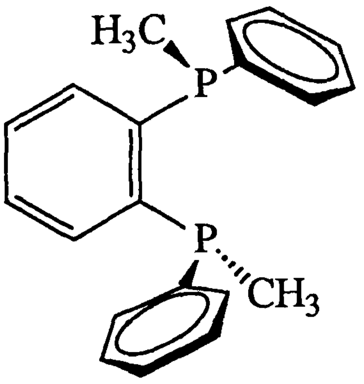
L^* = (*R*, *R*)-(DIPAMP)-**11**

L-Dopa 95% e.e

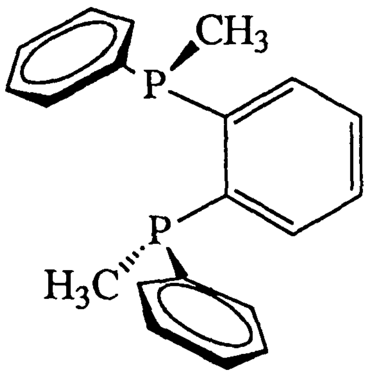
Scheme 3

The structure of the [(COD)Rh(I)(*R*,*R*)-DIPAMP)-(**11**)] complex has been determined by single-crystal diffraction studies[44]. The square-planar complex has a P-Rh-P angle of 83° with the rest of the angles of the five-membered ring close to tetrahedral. The four phenyl groups are arranged around the metal in an alternating edge-face manner with the bulkier *ortho*-anisyl groups occupying a facial orientation and serve to block any pseudorotation of the five-membered ring. Knowles[44] assumed the edge-face arrangement was responsible for the observed stereochemical control, however subsequent molecular graphics analysis by Brown and Evans[20] showed this phenomenon was due to a weak interaction between P-axial *ortho*-hydrogens and the metal. This leads to a slight Rh-P-C angle difference between axial and equatorial rings and explains the observed edge-face arrangement.

Wild and Roberts[48] have prepared a pair of isostructural cationic rhodium(I) complexes of (*R*,*R*)-(+)- and (*S*,*S*)-(-)-1,2-phenylenebis(methylphenylphosphine)-(**15**). Both ligands form rigid dissymmetric five-membered chelate rings in which the chirality is due to a pair of equivalent asymmetric tertiary phosphorus atoms. The (*R*,*R*)-(+)-complex catalysed the reaction in Figure 2 with 79 % e.e.[49] (Table 1).

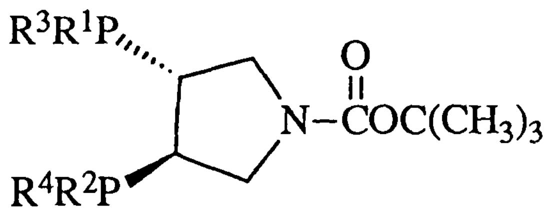


(*R*,*R*)-**15**



(*S*,*S*)-**15**

Similarly, Negel *et al.*[50] have prepared a range of diastereomeric ligands with one alkyl and one phenyl group at each phosphorus atom (**16b-e**), these represent the only ligands containing both carbon and phosphorus stereocentres. In order to correlate chirality at phosphorus with enantioselectivity they prepared the corresponding rhodium complexes of (**16a-e**) with defined stereochemistry at phosphorus. In contrast to complexes of 1,2-phenylenebis(methylphenylphosphine)-(**15**), the chiral backbone of these ligands fixes the chiral array in the δ-conformation (Figure 3) which in turn defines the orientation of the phosphorus substituents. The Rh complexes of (**16c-e**) therefore have all possible arrangements of two methylphosphino groups, enabling the ensuing chirality of the metal to determine the enantioselectivity.



(3*R*,4*R*,)	**16a**: $R^1 = R^2 = Ph$;	$R^3 = R^4 = Ph$
(P*R*,3*R*,4*R*,P'*S*)	**16b**: $R^1 = R^2 = CH_2Ph$;	$R^3 = R^4 = Ph$
(P*S*,3*R*,4*R*,P'*S*)	**16c**: $R^1 = R^4 = CH_3$;	$R^2 = R^3 = Ph$
(P*R*,3*R*,4*R*,P'*R*)	**16d**: $R^1 = R^4 = Ph$;	$R^2 = R^3 = CH_3$
(P*R*,3*R*,4*R*,P'*S*)	**16e**: $R^1 = R^2 = CH_3$;	$R^3 = R^4 = Ph$

From the selectivities obtained in the hydrogenation of α-(acetylamino)cinnamic acids and methyl esters under various reaction conditions (substrate/catalyst ratio, pressure and temperature) they found diverse catalytic properties[19]. Although the selectivities were highest for the symmetrical PPh_2 - derived ligand (98% e.e.), the P-chiral ligand which bears the phenyl groups axial and the methyl groups equatorial (**16c**) showed higher enantioselectivity (62% e.e.) than its counterpart (**16d**) with the methyl groups axial and the phenyl groups equatorial (26.4% e.e.). They conclude that the nature of functionality at the axial position is responsible for enantioselectivity. However, if the skeleton of the ligand is rigid, this is no longer crucial.

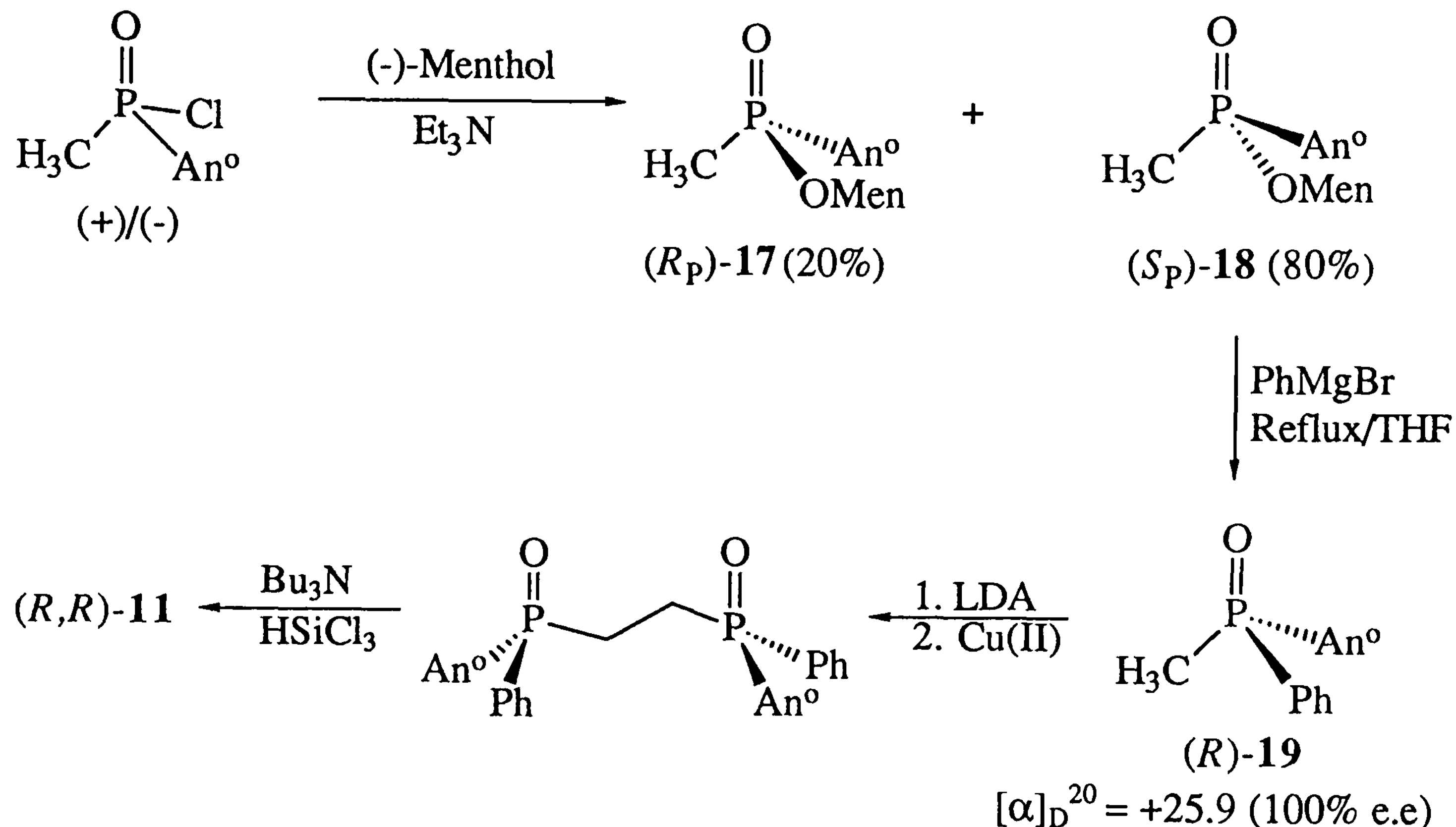
1.4. Summary of the origins of enantioselectivity.

Of the attempts made to correlate ligand structure and enantioselectivity the following points have been established: (1) Bisphosphine ligands are far superior to monophosphines; (2) Chirality at phosphorus is not a necessity for enantioselectivity, but has shown to be highly effective in the rhodium chemistry of DIPAMP-(**11**); (3) Generally, an increase in the conformational flexibility of the complex is accompanied by a decrease in enantioselectivity; (4) The rigidity of the backbone is critical, in BINAP-(**6**) the rigid binaphthyl backbone disposes the two PPh_2 groups to interact enantioselectively. (5) For P-chiral bisphosphines containing non-rigid backbones the nature of the axial substituent affects enantioselectivity. The more bulky the axial substituent then the higher the enantioselectivity.

DIPAMP-(**11**) owes its success in rhodium chemistry to the optical activity at the phosphorus centres, since having the chirality in such close proximity to the reactant enables more efficient transfer of the 'chiral information'. However, the synthesis of P-chiral ligands of this type had stagnated due to the difficulty in introducing chirality at the phosphorus centres; the early synthetic routes described in the following section serving to illustrate this point.

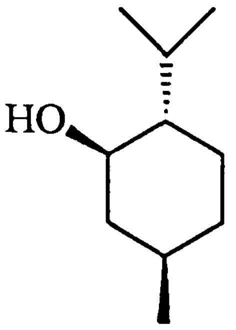
1.5. Synthetic routes to DIPAMP-(11).

The original published[44] synthesis of DIPAMP-(**11**) is based on the resolution of a pair of intermediate methyl (1*R*, 2*S*, 5*R*)-menthyl(phenyl)phosphinates first prepared by Mislow[51] (*vide infra*). However the desired ester, *i.e.* the one with *R* configuration at phosphorus, is the minor product. This route can only be overcome by the use of synthetic (and expensive) (1*S*, 2*R*, 5*S*)-(+)-menthol. Knowles[47] later improved this route using methyl menthyl(*ortho*-anisyl)phosphinates-(**17** & **18** Scheme 4), in this case the (R_P)-(**17**) diastereoisomer is less soluble. Nucleophilic displacement of (-)-menthol in (S_P)-(**17**) using phenylmagnesium bromide under somewhat forcing conditions proceeds with inversion of configuration to yield (*R*)-methyl (*ortho*-anisyl)phenylphosphine oxide-(**19**), abbreviated (*R*)-PAMP oxide-(**19**). Formation of the anion and Cu(II) promoted oxidative coupling gives bisphosphine oxide which was reduced by $HSiCl_3$ in the presence of base to yield (*R*,*R*)-DIPAMP-(**11**) with inversion of configuration at phosphorus. The small amount of the the *meso* isomer formed was removed by recrystallisation.



Scheme 4

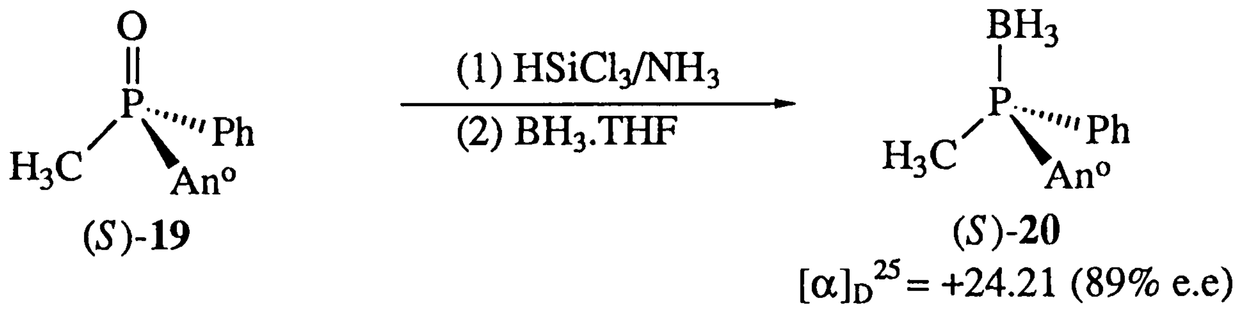
Where appropriate, (-)-Menthol (abbreviated; -OMen) refers to natural (1*R*, 2*S*, 5*R*)-(-)-menthol shown below.



(1*R*, 2*S*, 5*R*)-(-)-Menthol

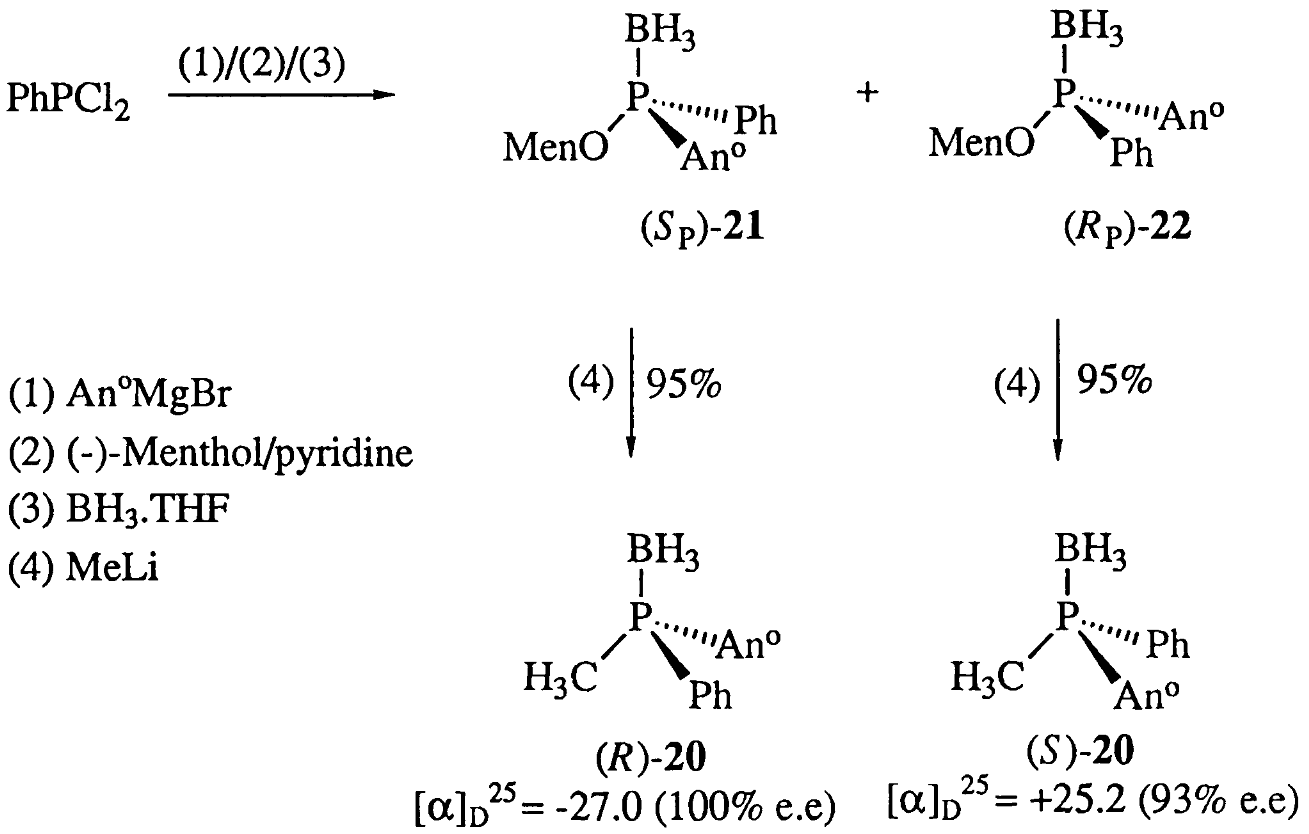
Imamoto and co-workers[52] have recently improved the menthoxy displacement step in Scheme 4 using one-electron reducing agents. Optimum results were obtained using lithium 4,4'-di-*tert*-butylbiphenylide, subsequent treatment with alkyl halides gives access to the corresponding alkylphosphine oxide with 67% yield and 95% e.e. However, the limitations of this route to alkyl halides renders it little scope.

A number of groups have attempted to improve the synthesis of DIPAMP-(**11**). Imamoto *et al.*[46] have utilised phosphine boranes, based on the work of Schmidbaur *et al.*[53] who have shown that the methyl group adjacent to the phosphine-borane moiety is activated. The boranato group also serves as a protecting group for phosphorus and can be easily removed by ligand-transfer using amines. (*S*)-methyl (*ortho*-anisyl)phenylphosphine borane-(**20**) was prepared by reduction of the corresponding (*S*)-PAMP oxide-(**19**) and addition of BH_3.THF complex (Scheme 5).



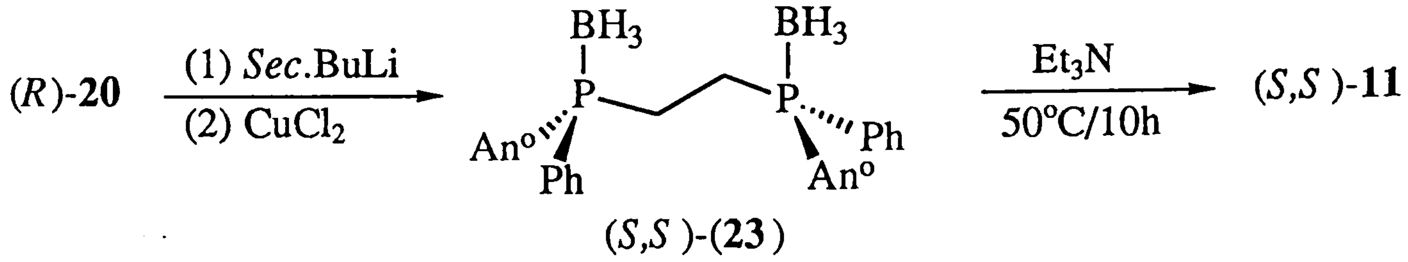
Scheme 5

Alternatively[46] (*S*)- and (*R*)-(**20**) were synthesised *via ortho*-anisyl (menthyloxy)phenylphosphine boranes-(**21** & **22**, Scheme 6), prepared as a diastereomeric mixture in a one pot synthesis. Separation of the two diastereoisomers by recrystallisation and treatment with MeLi afforded (*R*)- and (*S*)-(**20**) in 100% and 93% e.e. respectively.



Scheme 6

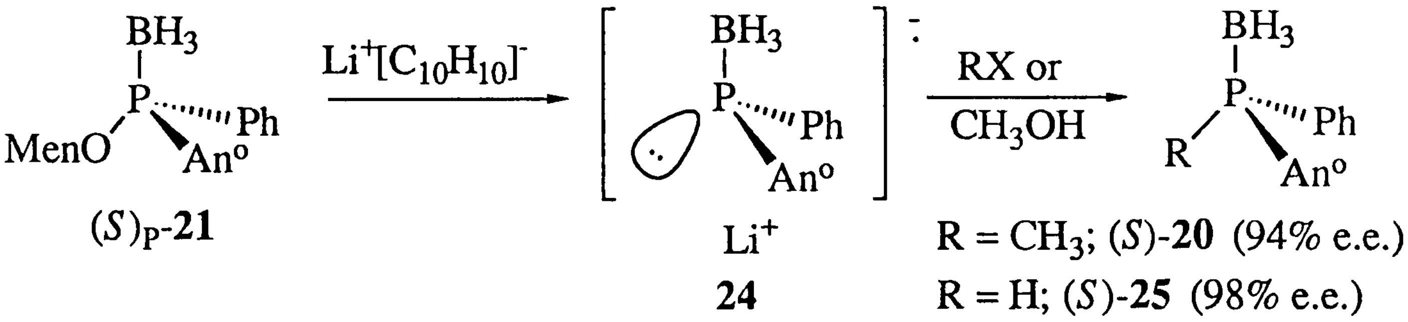
Cu(II) promoted oxidative coupling of (*R*)-(**20**) yielded the (*S*,*S*)-bisphosphine-borane-(**23**, Scheme 7) which was deprotected with retention of configuration at phosphorus, to yield (*S*,*S*)-DIPAMP-(**11**) in 84% yield and 89% e.e..



Scheme 7

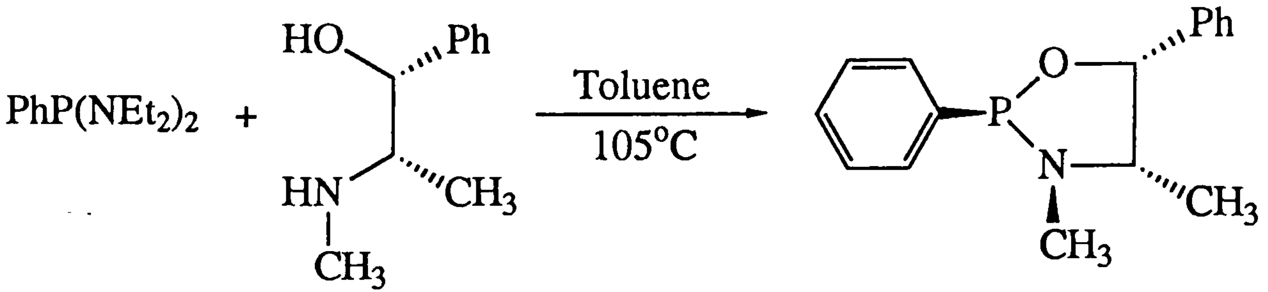
Using similar routes (S,S)-1,4-bis(*ortho*-anisylphenylphosphino) butane-(**13**) and (R,R)-1,2-bis(*tert*-butyl-phenylphosphino) ethane-(**14**) were also prepared[46].

Imamoto and co-workers[54] have also recently improved the menthoxy displacement step in Scheme 2 using one-electron reducing agents (Scheme 8). Optimum results were obtained using lithium naphthalenide. Subsequent treatment of the intermediate anion-(**24**) with alkyl halides gave access to the corresponding alkyl(aryl)phosphine borane in quantitative yield, and with almost complete retention of configuration at phosphorus. The synthesis of optically active (S)-*ortho*-anisyl(phenyl)phosphine borane-(**25**) by this route (Scheme 8) is particularly noteworthy, and is more general than for the corresponding menthol cleavage from methyl menthyl(aryl)phosphinates-(**17** & **18**)[52] described earlier.



Scheme 8

The synthesis of the (R, R)-DIPAMP-(**11**) precursor, (R)-PAMP oxide-(**19**) was further developed by Jugé *et al.*[55], whose first approach was based on the previously observed[56] diastereoselectivity in the Michaelis-Arbuzov rearrangement of oxazaphospholidine-(**26**, Scheme 9), prepared from bis(diethylamino)phenylphosphine using *l*-ephedrine as a chiral auxiliary .

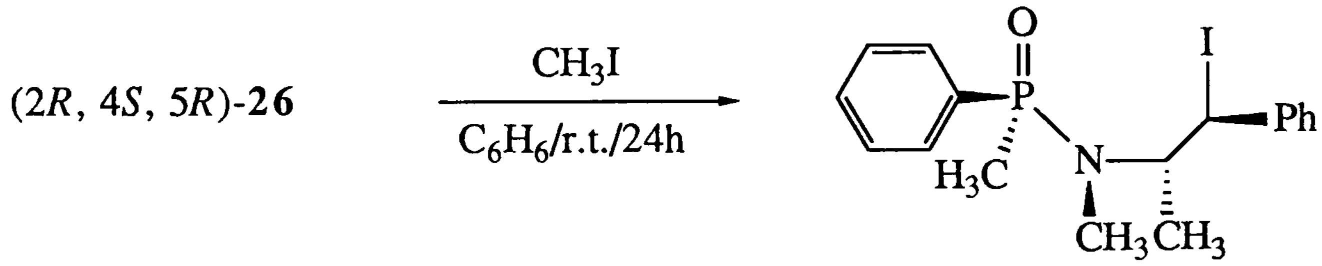


l-Ephedrine

(2*R*, 4*S*, 5*R*)-**26**

Scheme 9

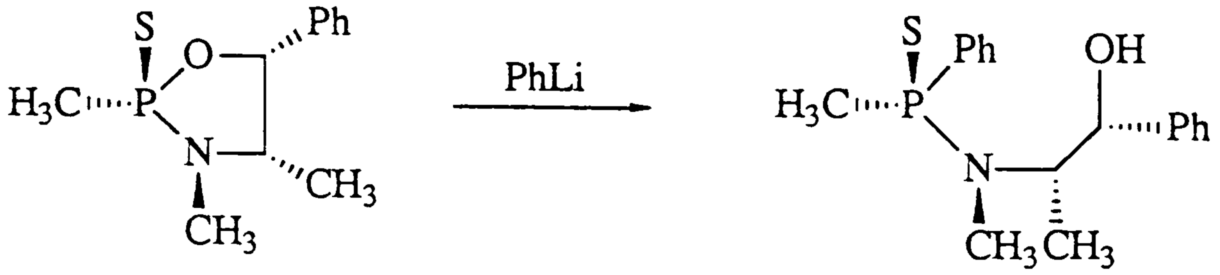
(2*R*, 4*S*, 5*R*)-2,5-Diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-(**26**) underwent diastereoselective P-O bond cleavage on reaction with methyl iodide to afford (*R*P)-methyl(phenyl)phosphinamide-(**27**, Scheme 10) with 85% d.e.[57].



(*R*P)-**27** (85% d.e.)

Scheme 10

Inch and co-workers[58] had previously demonstrated diastereoselectivity in the P-O cleavage of (2*R*, 4*S*, 5*R*)-2,3,4-trimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-thione-(**28**) using phenyllithium which proceeded with retention of configuration at phosphorus to yield (*R*P)-methyl(phenyl)thiophosphinamide-(**29**) with 98% d.e. (Scheme 11).

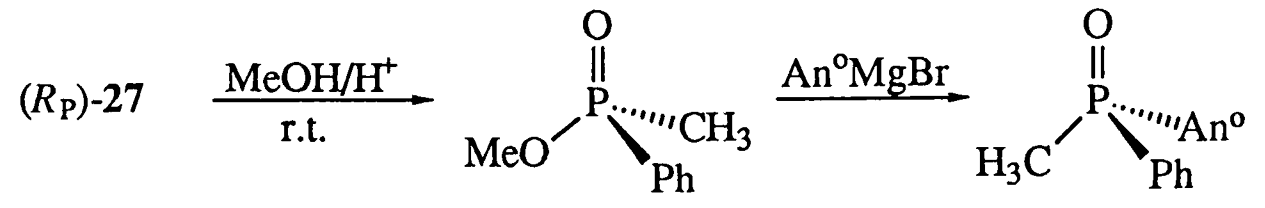


(2*R*, 4*S*, 5*R*)-**28**

(*R*P)-**29** (98% d.e.)

Scheme 11

Separation of (*R*P)-(**27**) from its diastereoisomer followed by acid catalysed methanolysis yielded the corresponding (*S*)-(+)-methyl methyl(phenyl)phosphinate-(**30**) with inversion of configuration at phosphorus with 95% d.e. and in 85% yield (Scheme 12). Nucleophilic displacement of the methoxy residue with *ortho*-anisylmagnesium bromide yielded (*R*)-(**19**) with 95% e.e. with inversion of configuration at phosphorus.

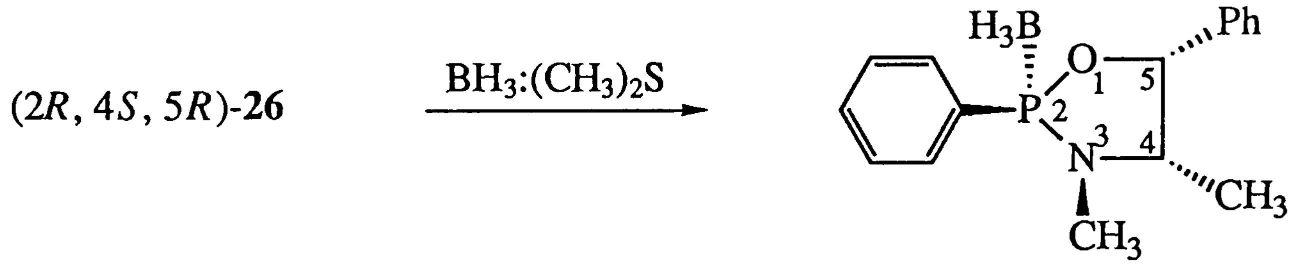


(*S*)-**30**
$[\alpha]_D = +57$ (95% e.e)

(*R*)-**19** 95% e.e.

Scheme 12

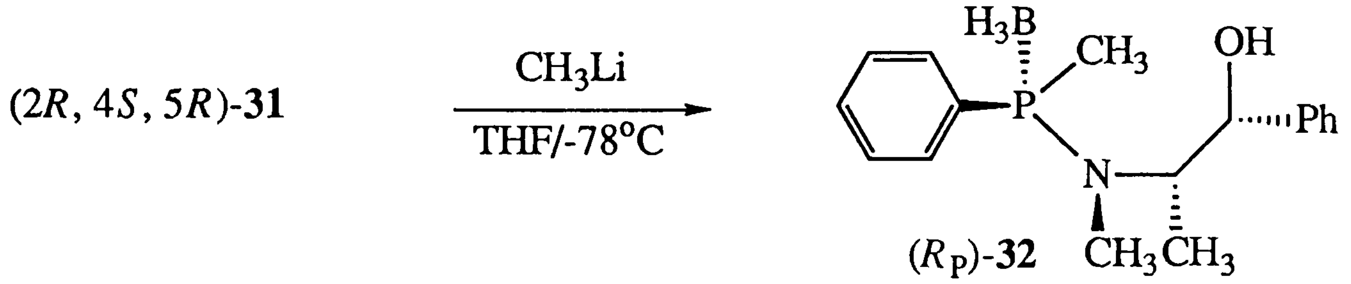
Diastereoselectivity in the P-O ring opening step was further improved by Jugé *et al.* *via* the corresponding boranato complex. Diastereomerically pure (2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-borane-(**31**, Scheme 13) was prepared in one step from (2*R*, 4*S*, 5*R*)-(**26**) and was isolated as a white, air-stable, crystalline solid[59,60].



(2*R*, 4*S*, 5*R*)-**31**

Scheme 13

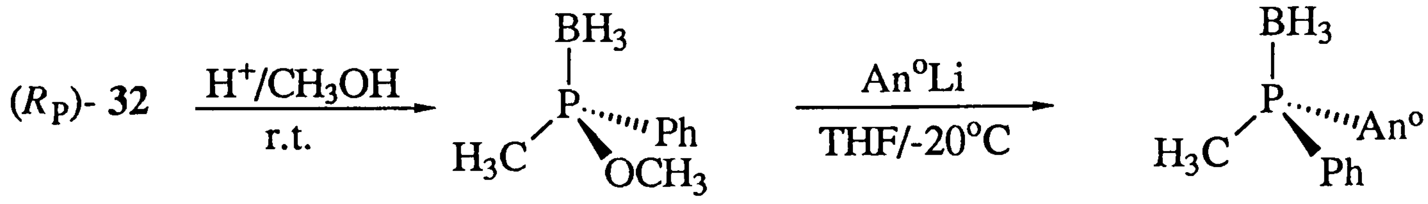
As will be described later in this thesis, (2*R*, 4*S*, 5*R*)-(**31**) underwent nucleophilic P-O bond cleavage with arylmagnesium bromides with poor diastereoselectivity. Conversely, Jugé *et al.*[60] reacted methyllithium with (**31**) to afford the corresponding (*R*P)-methyl (phenyl)phosphine borane-(**32**, Scheme 14) with complete diastereoselectivity, he also confirmed the poor diastereoselectivity obtained with the corresponding aryl Grignard reagents[61].



(*R*P)-**32**

Scheme 14

Acid-catalysed methanolysis of (*R*P)-(**32**) yielded the corresponding (*S*)-phosphinate-(**33**, Scheme 15) with inversion of stereochemistry at phosphorus.



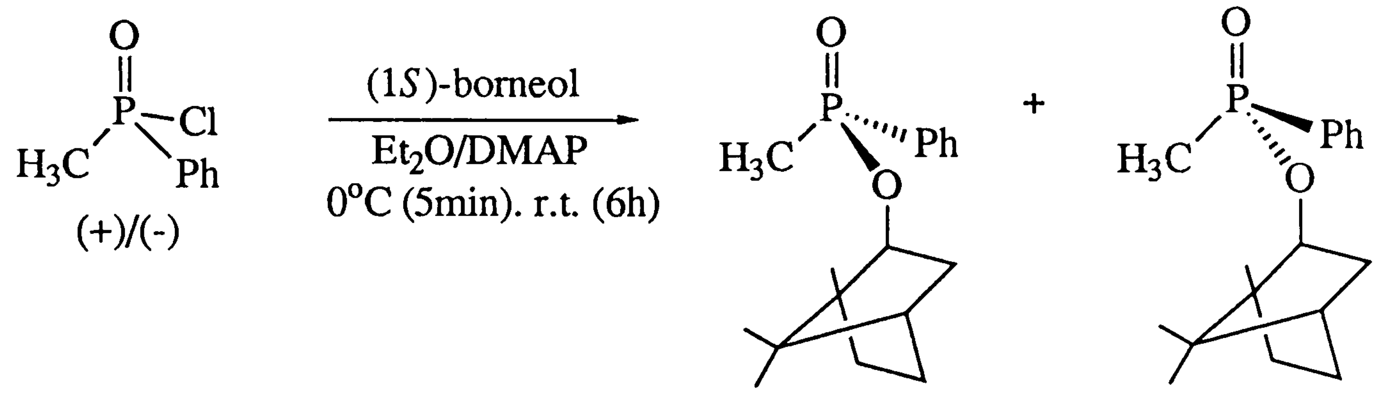
(*S*)-**33**

(*R*)-**20**
$[\alpha]_D^{25}$ = -26.0 (98% e.e.)

Scheme 15

Nucleophilic displacement of the methoxy residue with *ortho*-anisyl lithium yielded (*R*)-(-)-PAMP borane-(**20**, Scheme 15) with inversion of configuration at phosphorus. The subsequent route to DIPAMP-(**11**) is in accordance with Imamoto's work (Scheme 7).

Schmidt *et al.*[62] have recently published a new route to (*R*, *R*)-DIAMP-(**11**) based on a modification of the synthesis described by Knowles and co-workers[44] (Scheme 16 *c.f.* Scheme 4). The route involves the synthesis of the (1*S*)-bornyl phosphinate esters-(**34** & **35**) which are formed in a *ca.* 4:1 [(*R*P):(*S*P)] mixture from (1*S*)-borneol and dimethylaminopyridine (DMAP) in diethyl ether. Chromatographic separation afforded the desired (1*S*)-bornyl (*R*P)-methyl(phenyl)phosphinate-(**34**, Scheme 16) in 77% yield as a single diastereoisomer. The reaction does not suffer from the difficulties found in the Knowles route using (-)-menthol (Scheme 4). Reaction of (*R*P)-(**34**) with *ortho*-anisylmagnesium bromide furnished (*R*)-(**19**) in 83% yield and 97% e.e.. The subsequent reactions to (*R*, *R*)-DIPAMP-(**11**) are in accordance with the work of Imamoto *et al.*[46] (Schemes 5 & 7).

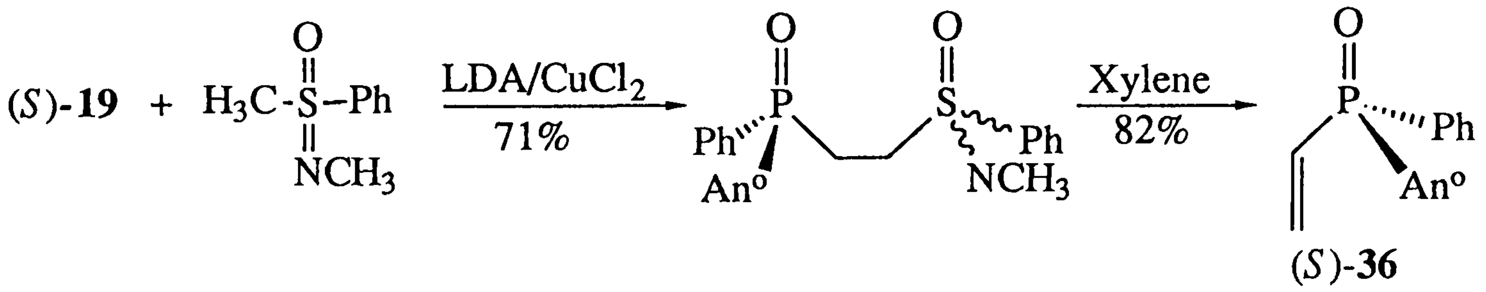


(*R*P)-**34** (77%)

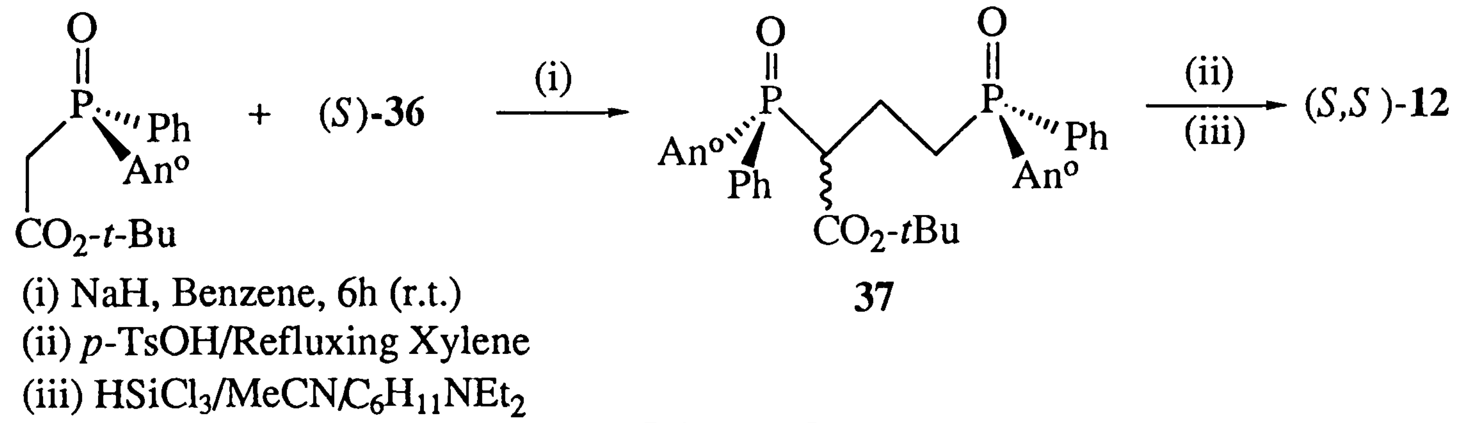
(*S*P)-**35** (19%)

Scheme 16

The methylene homologue of DIPAMP-(**11**), (*S*, *S*)-1,3-propanebis(*ortho*-anisyl)phenylphosphine-(**12**), has also been prepared by Johnson and Imamoto[45] *via* a modification of the DIPAMP route. Homochiral *ortho*-anisyl (phenyl)vinylphosphine oxide-(**36** Scheme 17) was prepared *via* oxidative coupling of (*S*)-(**19**) with *N*-*S*-dimethyl-*S*-phenylsulfoxmine. (*S*)-(**36**) was then coupled to (*S*)-[(*tert*-butoxycarbonyl)methyl](*ortho*-anisyl)phenylphosphine oxide (Scheme 18), prepared from the lithium anion of (*S*)-(**19**) and di-*tert*-butyl dicarbonate. This afforded (**37**) which upon hydrolysis and reduction yielded (*S*,*S*)-(**12**).



Scheme 17



(i) NaH, Benzene, 6h (r.t.)
(ii) *p*-TsOH/Refluxing Xylene
(iii) $HSiCl_3/MeCN/C_6H_{11}NEt_2$

Scheme 18

1.6. Project Objectives.

At the commencement of this project, synthetic routes to enantiomerically pure P-chiral phosphine oxides and phosphines involved resolution. The aim of this work was to develop a general synthetic route to these compounds avoiding any resolutions. The initial criteria was the synthesis of the DIPAMP precursor, (*R*)-PAMP oxide-(**19**) where the configuration at phosphorus and optical purity were already defined. The extension of this route to the preparation of any P-chiral phosphine, with flexibility in the groups at phosphorus was also desired, since bulky chiral monophosphines have much potential in iridium chemistry.

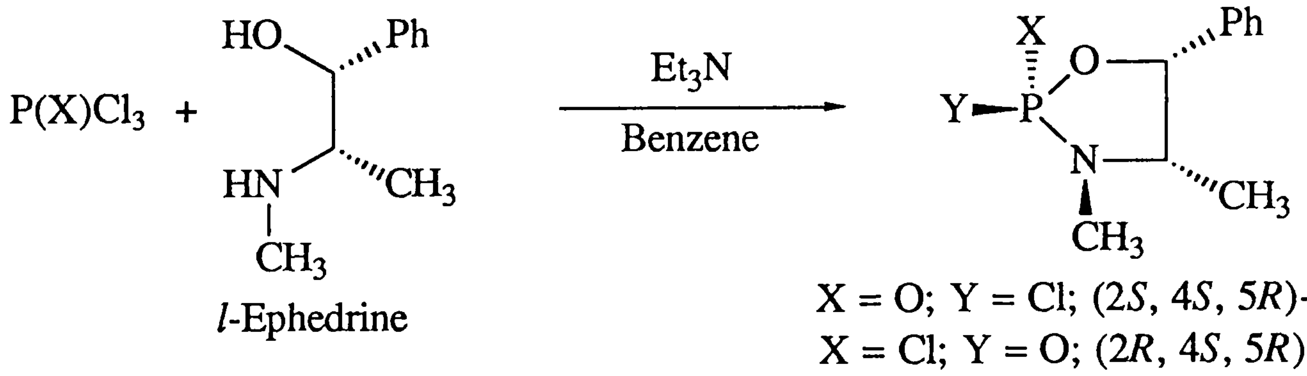
Another aim of this work was the synthesis new chiral bisphosphines with substantial flexibility both in the groups at phosphorus and in the carbon backbone. New ligands of this type have much potential in rhodium and ruthenium homogeneous asymmetric catalysis already described.

The synthesis of a range of aryl-oxazaphospholidines is described in the next chapter together with their structural characterisation by ^1H n.m.r. and single-crystal X-ray diffraction studies. The effectiveness of these compounds as precursors to homochiral phosphines is described in subsequent chapters. As this work progressed, complementary procedures to Imamoto's and Juge's work were developed.

Chapter 2. Synthesis and structure of *l*-ephedrine-derived 1,3,2-oxazaphospholidines.

2.1. Synthesis of *l*-ephedrine-derived 1,3,2-oxazaphospholidines.

Devillers and Nevech[63] first demonstrated the effectiveness of *l*-ephedrine as a chiral auxiliary in the formation of diastereomeric mixtures of (4*S*, 5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxides-(**38** & **39**) and -2-thiones-(**40** & **41**) from $P(X)Cl_3$ (X = O or S) in the presence of triethylamine (Scheme 19).

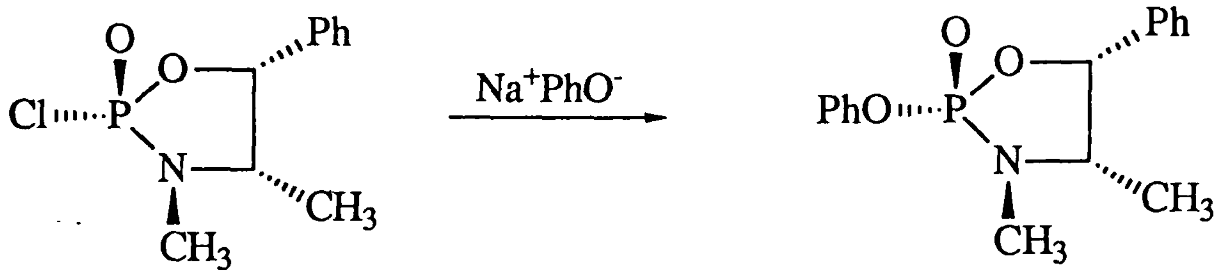


X = O; Y = Cl; (2*S*, 4*S*, 5*R*)-**38**
X = Cl; Y = O; (2*R*, 4*S*, 5*R*)-**39**
X = S; Y = Cl; (2*S*, 4*S*, 5*R*)-**40**
X = Cl; Y = S; (2*R*, 4*S*, 5*R*)-**41**

Scheme 19

Inch and co-workers[64] later optimised the reactions in Scheme 19 and separated the diastereoisomers by chromatography. The ratio of diastereoisomers was found to be 10:1 with the (2*R*)-diastereoisomer assigned as the major product on the basis of ^1H n.m.r. data. The 2-chloro-oxazaphospholidines shown in Scheme 19 have been used as derivatising agents for assaying the enantiomeric purity of 1° and 2° alcohols by ^{31}P n.m.r. spectroscopy[65]. The structures of (2*R*)- and (2*S*, 4*S*, 5*S*)-(**40** & **41**) have also been confirmed by single-crystal X-ray diffraction studies (*vide infra*)[66,67].

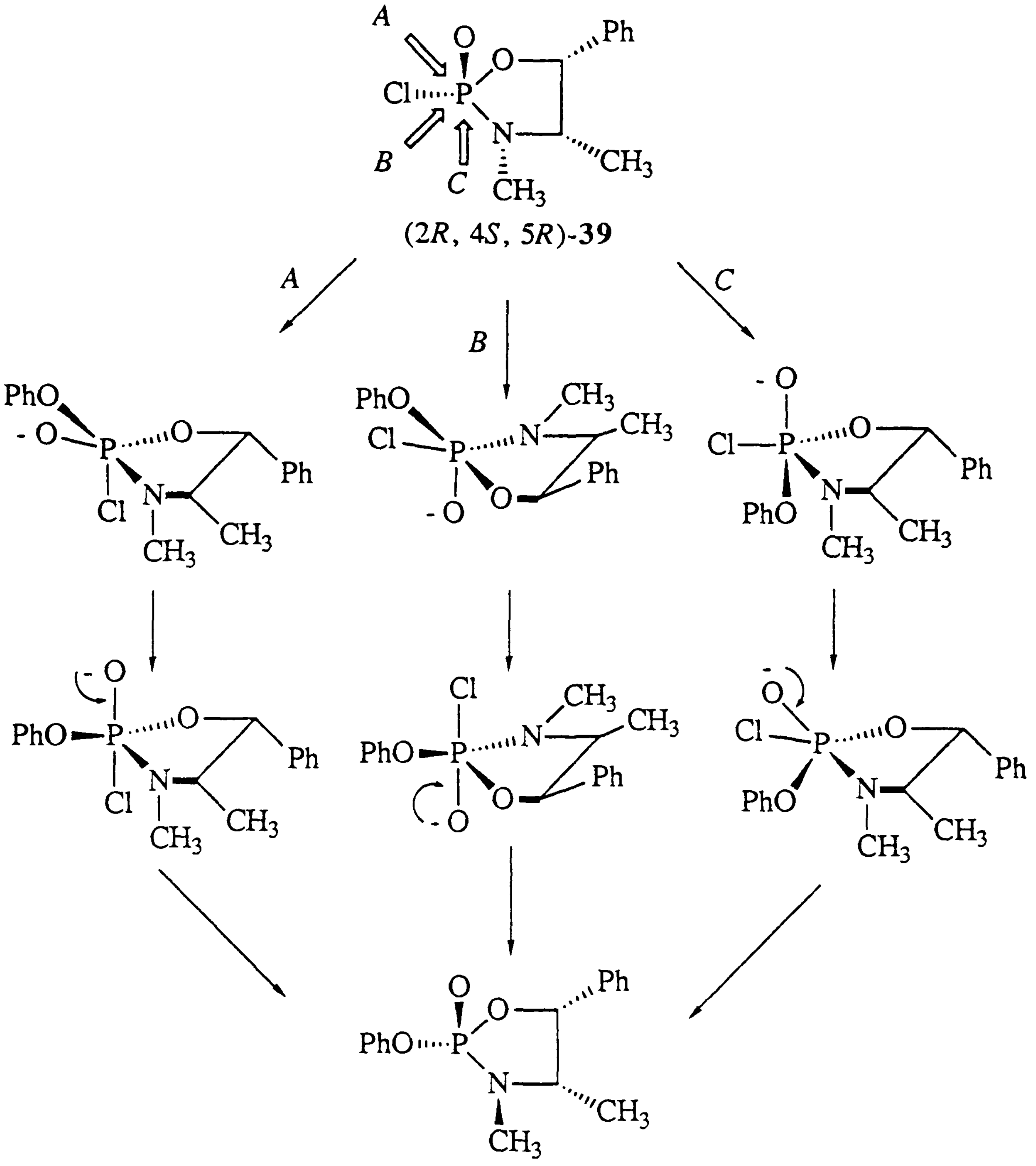
Inch and co-workers[64] extended the above methodology and prepared a range of 2-substituted-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxides, -2-thiones and -2-selones. For example, (2*R*, 4*S*, 5*R*)-(**39**) reacted with sodium phenoxide to afford (2*R*, 4*S*, 5*R*)-2-phenoxy-3,4,-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(**42**) as a single diastereoisomer in 83% yield with retention of configuration at phosphorus (Scheme 20). The structure of (2*R*, 4*S*, 5*R*)-(**42**) has been confirmed by single-crystal X-ray diffraction studies (*vide infra*).



(2*R*, 4*S*, 5*R*)-**39** (2*R*, 4*S*, 5*R*)-**42** (83%)

Scheme 20

In proposing a mechanism for such displacements the general rules are that nucleophilic attack and leaving group departure occur at apical positions. Furthermore a pseudorotation of the trigonal bipyramidal intermediate occurs prior to departure of the leaving group.



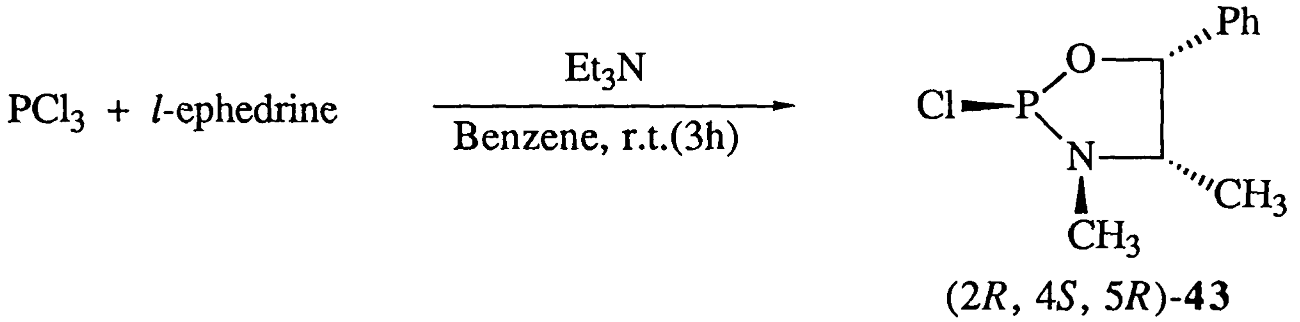
(2*R*, 4*S*, 5*R*)-**39**

(2*R*, 4*S*, 5*R*)-**42**

Scheme 21

Scheme 21 shows that providing these rules are observed then retention of configuration is the result, irrespective of whether attack occurs opposite nitrogen (Pathway *A*), or endo- or exo-cyclic oxygen (Pathways *B* and *C*). However, the accepted pathway[64], consistent with similar systems[68], is attack opposite endocyclic oxygen (pathway B) to form the trigonal bipyramidal intermediate followed by pseudorotation prior to departure of chloride ion.

Diastereochemically pure 2-substituted-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-thione and -2-selone derivatives were alternatively prepared by addition of sulfur or selenium to the appropriate cyclic trivalent oxazaphospholidine, prepared from $RPCl_2$ and *l*-ephedrine[64]. More significantly, Inch and co-workers[64] showed that reaction of trichlorophosphine with *l*-ephedrine in the presence of triethylamine afforded (2*R*, 4*S*, 5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(**43**) as a single diastereoisomer (Scheme 22).

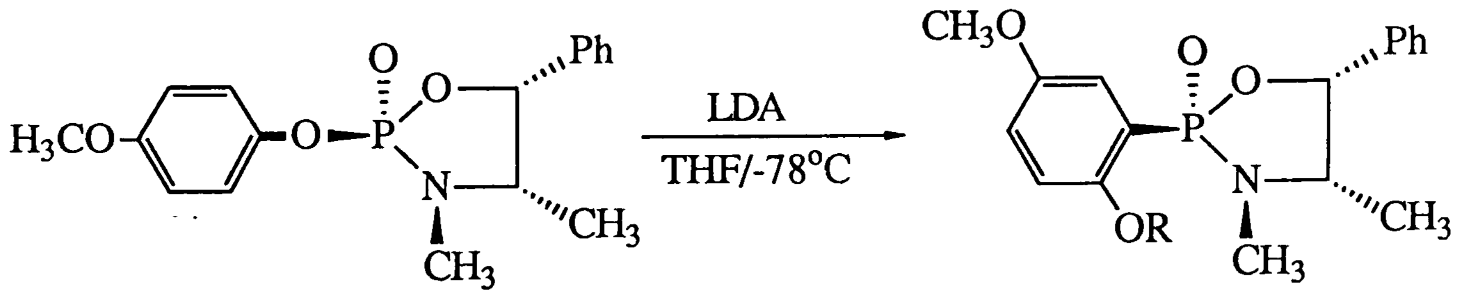


(2*R*, 4*S*, 5*R*)-**43**

Scheme 22

Similarly, other authors have prepared 2-substituted-3,4-dimethyl-1,3,2-oxazaphospholidine-2-oxides as intermediates in the stereospecific synthesis of ^{16}O-, ^{17}O-, and ^{18}O-labelled phosphates, thiophosphates[69] and labelled aryl phosphates[70].

Welch and co-workers[71] have studied the stereochemistry of the base-induced rearrangement of 2-aryloxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxides. Base-induced (LDA) rearrangement of (2*R*, 4*S*, 5*R*)-2-(4-methoxyphenoxy)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(**44**) afforded (2*R*, 4*S*, 5*R*)-2-(2-hydroxy-5-methoxybenzene)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(**45**) as a single diastereoisomer in 85% yield (Scheme 23). The P-O to P-C rearrangement appears to be stereochemically unencumbered by the ring substituents and proceeds with retention of configuration at phosphorus.



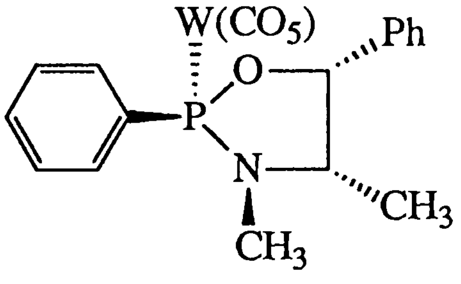
(2*R*, 4*S*, 5*R*)-**44**

R = H; (2*R*, 4*S*, 5*R*)-**45** (85%)
R = CH_3; (2*R*, 4*S*, 5*R*)-**46** (50%)

Scheme 23

Methylation of (2*R*, 4*S*, 5*R*)-(**45**) afforded (2*R*, 4*S*, 5*R*)-2-(2,5-dimethoxybenzene)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(**46**) in 50% yield (Scheme 23).

Richter[56] had demonstrated the diastereoselectivity in the reaction of *l*-ephedrine with bis(diethylamine)phenylphosphine which yielded (2*R*, 4*S*, 5*R*)-2,5-dimethyl-3,4-dimethyl-1,3,2-oxazaphospholidine-(**26**) in 90% d.e.. Diastereomerically pure (2*R*, 4*S*, 5*R*)-(**26**) was subsequently prepared by Jugé *et al.*[55] (Scheme 9), and as described in the previous chapter, demonstrated its diastereoselective Michaelis-Arbuzov rearrangement in the synthesis of homochiral phosphine oxides. However, the loss of diastereoselectivity in the M-A step continued the search for a suitable intermediate to these compounds. Its tungsten complex, (2*R*, 4*S*, 5*R*)-(**47**) was also used by Jugé and co-workers[72] to prepare monophosphines with 50% e.e. using similar methodology as that shown in Schemes 10 & 12.

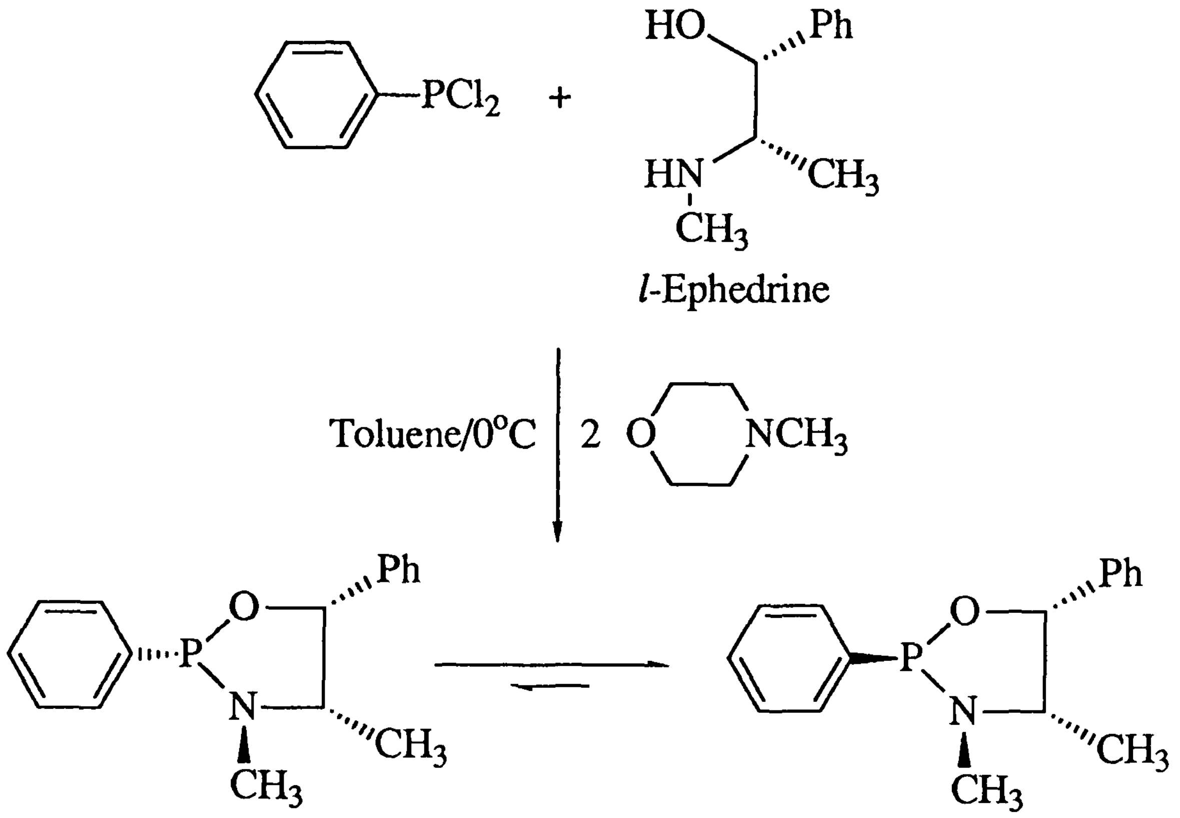


(2*R*, 4*S*, 5*R*)-**47**

2.2. Strategy and Results.

Based on the diastereoselectivity demonstrated above in the formation of (2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-(**26**) the chemistry of this compound was investigated.

Diastereomerically pure (2*R*, 4*S*, 5*R*)-(**26**) was prepared conveniently from dichlorophenylphosphine and *l*-ephedrine in the presence of two equivalents of *N*-methylmorpholine at 0°C under an argon atmosphere (Scheme 24). The reaction was monitored by ^{31}P n.m.r. spectroscopy which showed the initial formation of two diastereoisomers in *ca.* 50 : 50 ratio (δP = 152.9, 139.3 p.p.m.). However after stirring for one day at ambient temperature the lower field signal essentially disappeared, presumably through the operation of thermodynamic control.

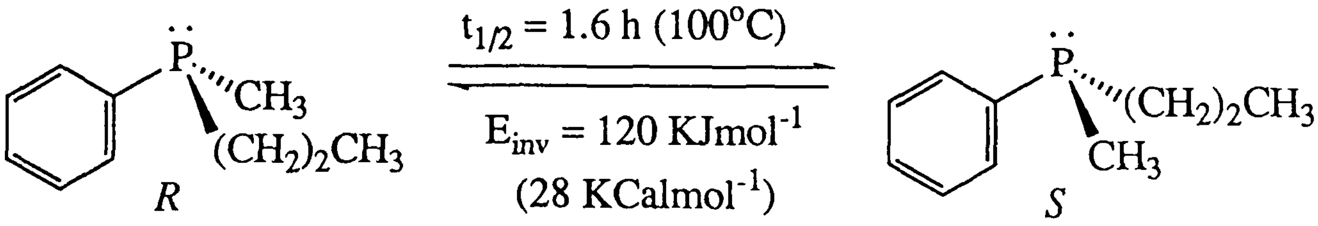


δ_P = 152.9
(2*S*, 4*S*, 5*R*)-**48**

δ_P = 139.3
(2*R*, 4*S*, 5*R*)-**26**

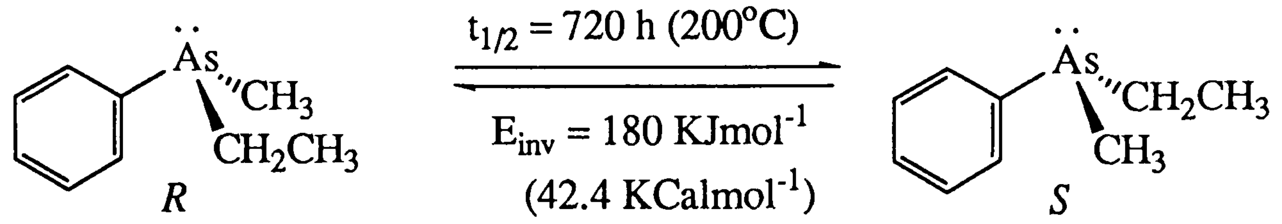
Scheme 24

An insight into the mechanism for the equilibrium shown in Scheme 24 may be found by considering the energetics of inversion at phosphorus (E_{inv}), which has been measured as 120 KJmol^{-1} (28 KCal mol^{-1}) for methyl (*n*-propyl)phenylphosphine, and has a half-life ($t_{1/2}$) of 1.6 h at 100°C (Scheme 25)[73].



Scheme 25

The rate of inversion is fast relative to methyl (ethyl)phenylarsenate for which E_{inv} = 180 $KJmol^{-1}$ (42.4 $KCalmol^{-1}$) and $t_{1/2}$ = 720 h at 200°C (Scheme 26)[74], due to a higher energy-of-rotation barrier for the equilibrium in this case (Scheme 26).

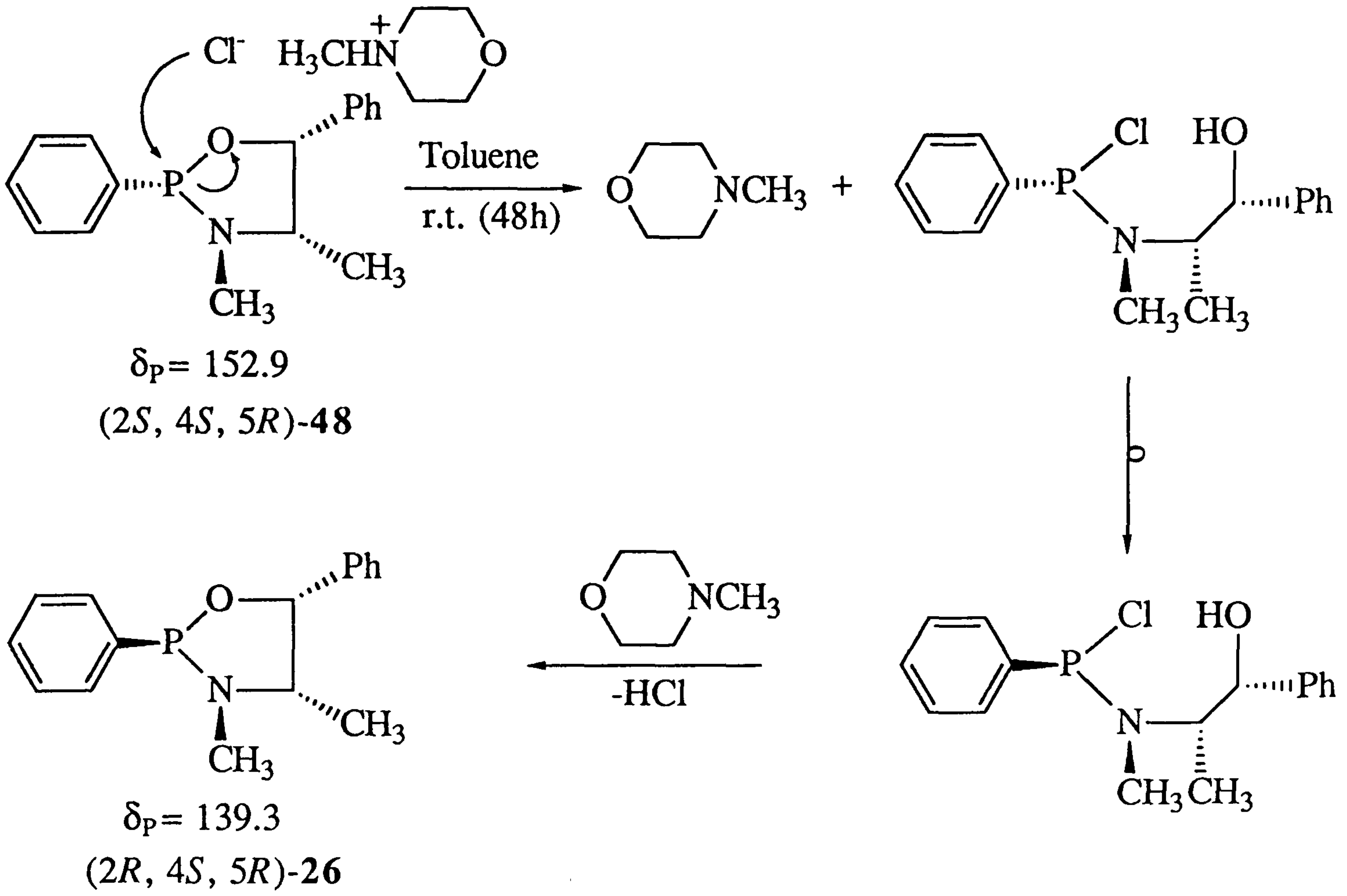


Scheme 26

E_{inv} for the oxazaphospholidine equilibrium shown in Scheme 24, although not precisely measured, is somewhat greater than for methyl (*n*-propyl)phenylphosphine in Scheme 25, and a secondary factor must therefore be in operation. Formation of the (2*R*, 4*S*, 5*R*)-(**26**) diastereoisomer would be thermodynamically favoured since the phenyl rings in the five-membered ring are arranged *trans*. This affords greater conformational stability compared to the (2*S*, 4*S*, 5*R*)-(**48**) diastereoisomer in which the phenyl rings are arranged in a *cis* configuration, although this alone would not be expected to be responsible for the facile equilibrium observed in Scheme 24.

Repeating the reaction under the same conditions and immediate removal of the precipitated *N*-methylmorpholine hydrochloride salt afforded a clear solution. Analysis by ^{31}P n.m.r. spectroscopy showed the same (50:50) ratio of diastereoisomers as previously observed after *c.a.* 10 minutes (Scheme 24), however after monitoring the reaction for a further 48h only a negligible increase in the (2*R*, 4*S*, 5*R*)-(**26**) diastereoisomer was observed.

Thus the increase in the rate of equilibrium was therefore due to catalysis by the *N*-methylmorpholine hydrochloride, a possible mechanism for which is presented in Scheme 27. Attack of phosphorus by chloride ion causes P-O ring cleavage to afford the ring opened species and regeneration of *N*-methylmorpholine, the ring-opened intermediate undergoes pseudorotation followed by ring closure affording the *trans*-diastereoisomer, (2*R*, 4*S*, 5*R*)-(**26**, Scheme 27).

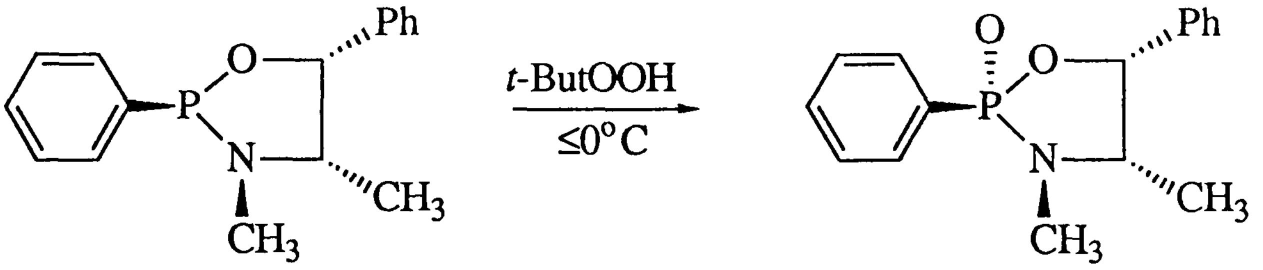


δ_P= 152.9
(2*S*, 4*S*, 5*R*)-**48**

δ_P= 139.3
(2*R*, 4*S*, 5*R*)-**26**

Scheme 27

After the equilibration shown in Scheme 24 was complete (24h) the reaction mixture was separated from the precipitated *N*-methylmoropholine hydrochloride and oxidized with one-equivalent of *tert*-butyl hydroperoxide at ≤0°C. This occurred stereospecifically to yield diastereomerically pure (2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-oxide-(**49**) as a white air-stable, crystalline solid (Scheme 28) in 39% yield. Its structure was determined by single-crystal X-ray diffraction studies in order to confirm the absolute configuration at phosphorus as *R* (*vide infra*)[59].



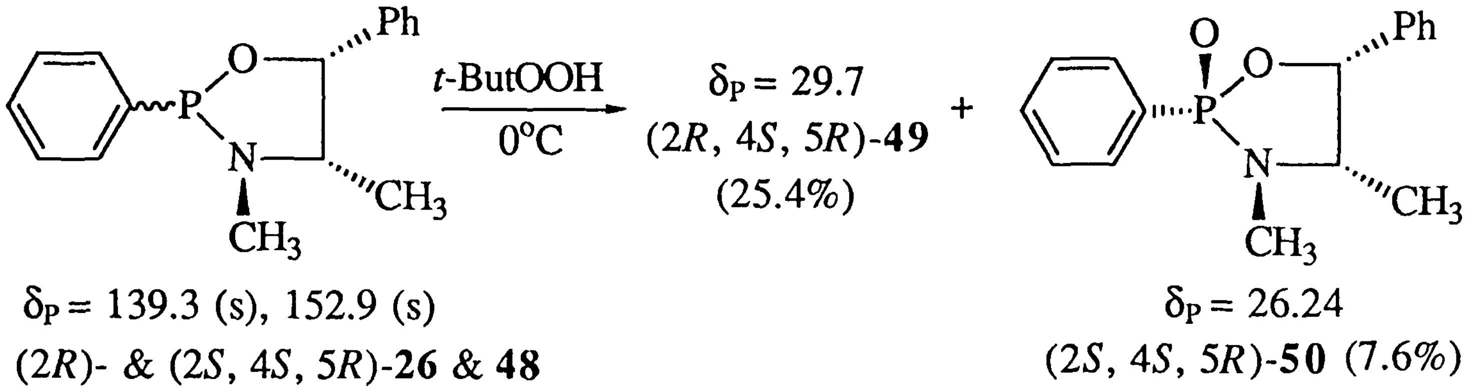
δ_P= 139.3
(2*R*, 4*S*, 5*R*)-**26**

δ_P= 29.7
(2*R*, 4*S*, 5*R*)-**49**

Scheme 28

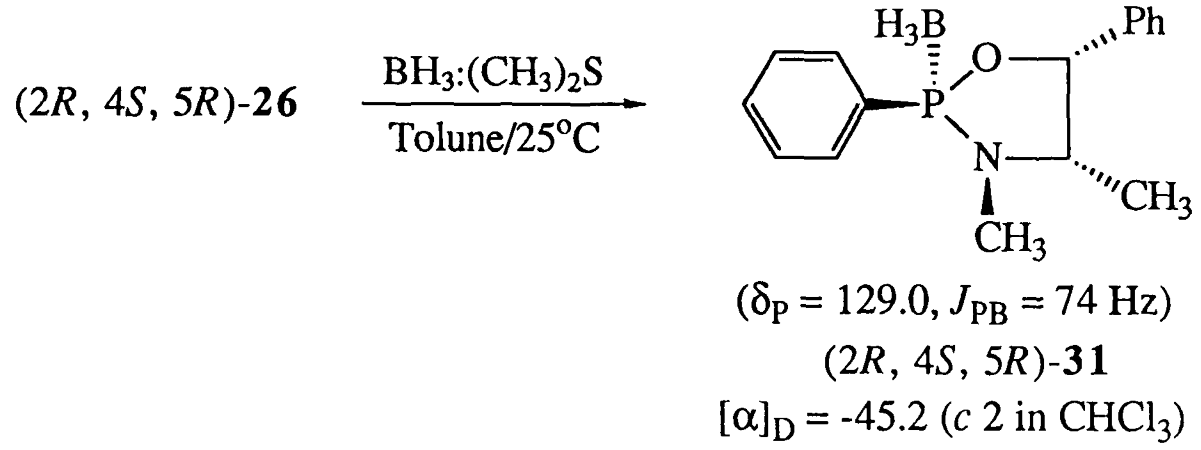
Although the yield of (2*R*, 4*S*, 5*R*)-(**49**) was relatively small (39%) this compound was routinely prepared on a 25g scale from commercially available $PhPCl_2$ using standard laboratory apparatus. The yield of 70% for (2*R*, 4*S*, 5*R*)-(**26**) reported by Jugé *et al.*[55] was based on using $PhP(NCH_3)_2$ as the precursor, itself prepared from $PhPCl_2$ and dimethylamine. Inch and co-workers[64] showed that (2*R*, 4*S*, 5*R*)-(**49**) was the major diastereoisomer formed in the reaction of $PhP(O)Cl_2$ with *l*-ephedrine hydrochloride where the diastereomeric ratio was 1.2:1 (2*R* : 2*S*).

The minor, (2*S*, 4*S*, 5*R*)-(**50**) diastereoisomer was prepared by the premature oxidation of the diastereomeric mixture before the equilibration shown in Scheme 24 was complete. The (2*R*)- and (2*S*, 4*S*, 5*S*)-(**49** & **50**) diastereoisomers were isolated in a 3.3:1 (*R*:*S*) ratio (Scheme 29) and were easily separated by flash column chromatography. The absolute configuration of the minor, (2*S*, 4*S*, 5*S*)-(**50**) diastereoisomer was also confirmed as *S* by single-crystal X-ray diffraction studies (*vide infra*).



Scheme 29

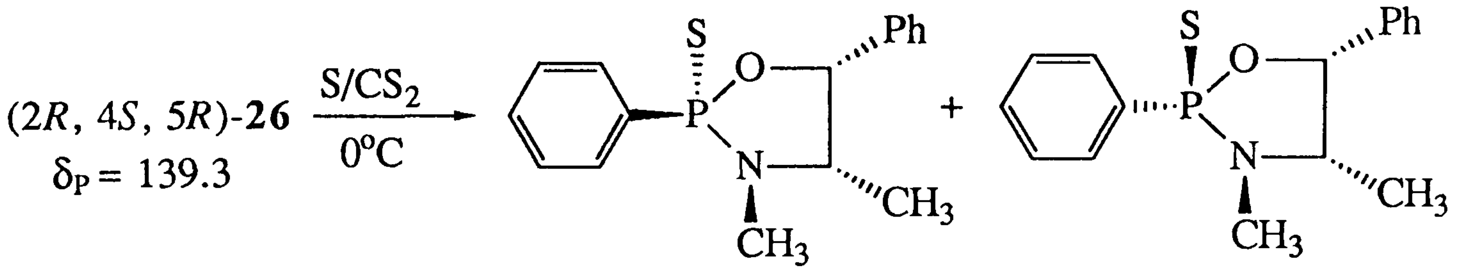
The crude (2*R*, 4*S*, 5*R*)-oxazaphopholidine-(**26**) was reacted with $BH_3{:}(CH_3)_2S$ complex at ambient temperature to produce a crystalline borane complex (**31**, Scheme 30) as a single diastereoisomer in 34% overall yield.



Scheme 30

After publication of the above results[59], Jugé *et al.*[60] prepared (2*R*, 4*S*, 5*R*)-(**31**, Scheme 13) as an intermediate to homochiral monophosphines (Schemes 14 & 15). However, the optical rotation was reported as +4.5 (*c* 4 in $CHCl_3$) by Jugé *et al.*[60], compared to -45.2 (*c* 2 in $CHCl_3$) recorded in this study, the melting points are within experimental error; 105°C (this study) and 107°C (Jugé *et al.*[60]). Careful analysis by ^{31}P, ^{11}B, ^{1}H and ^{13}C n.m.r. spectroscopy confirmed the purity of the diastereoisomer prepared here as >99%.

The first attempt to prepare the -2-thione analogue by addition of molecular sulfur to (2*R*, 4*S*, 5*R*)-oxazaphospholidine-(**26**) resulted in the isolation of a 2:1 (2*S* : 2*R*) mixture of (2*S*)- and (2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-thiones-(**51** & **52**). Optimum results were obtained using sulfur dissolved in CS_2 which produced a 9:1 (2*S* : 2*R*) mixture of 2-thione diastereoisomers-(**51** & **52**, Scheme 31), although these were easily separable by flash column chromatography. The absolute configurations of both diastereoisomers were also confirmed by single-crystal X-ray diffraction studies (*vide infra*).



$\delta_P = 90.27$ $\delta_P = 91.66$

(2*S*, 4*S*, 5*R*)-**51** (31.8%) (2*R*, 4*S*, 5*R*)-**52** (3.2%)

Scheme 31

Alternatively, (2*S*)- and (2*R*, 4*S*, 5*R*)-(**51** & **52**) were prepared from phenylthiophosphoryldichloride and *l*-ephedrine as described by Inch and co-workers[64] in which the ratio of the diastereoisomers was determined to be 2:1 (2*S* : 2*R*) by ^{1}H and ^{31}P n.m.r. spectroscopy (Scheme 32).

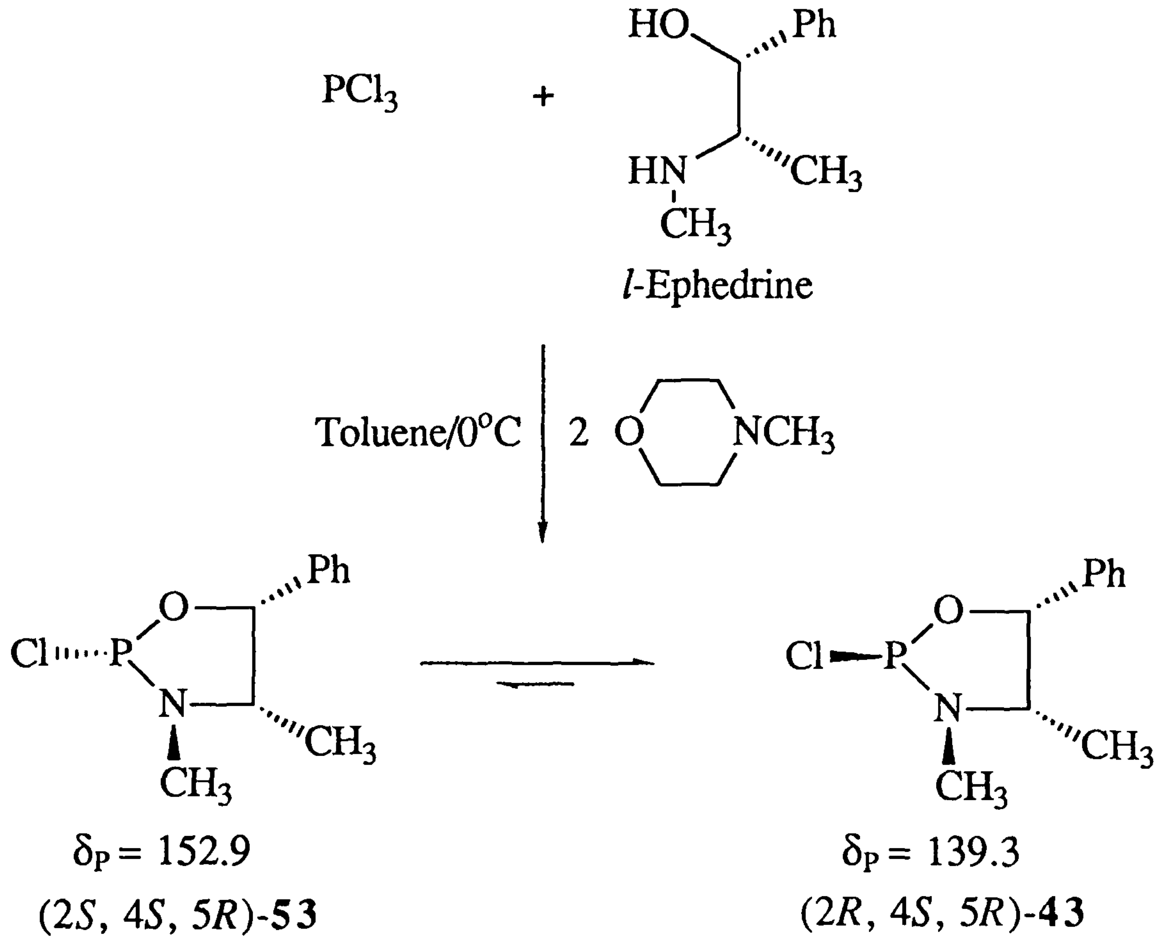
$$PhP(S)Cl_2 + l\text{-Ephedrine} \xrightarrow[THF]{Et_3N} \underset{(2S,\,4S,\,5R)\text{-}\mathbf{51}}{\delta_P = 90.27} + \underset{(2R,\,4S,\,5R)\text{-}\mathbf{52}}{\delta_P = 91.66}$$

2 : 1

Scheme 32

Up to this point (2*R*, 4*S*, 5*R*)-oxazaphospholidine-(**26**) was a useful precursor to diastereomerically pure (2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-oxide-(**49**) and -2-borane-(**31**). In order to extend the range to other 2-aryl-substituents the chemistry of (2*R*, 4*S*, 5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(**43**, Scheme 22) was investigated.

Diastereomerically pure (2*R*, 4*S*, 5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(**43**) was prepared from trichlorophosphine and *l*-ephedrine by a modification of the method used by Inch and co-workers^{64}. The reaction was monitored by ^{31}P n.m.r. spectroscopy (Scheme 33) which initially showed the presence of two diastereoisomers (δP = 167.70, δP = 169.15 in THF), however after four hours the lower field signal essentially disappeared, presumably through the operation of thermodynamic control. A similar observation had been found for the formation of the 2-phenyl analogue, (2*R*, 4*S*, 5*R*)-(**26**, Schemes 24 & 27).

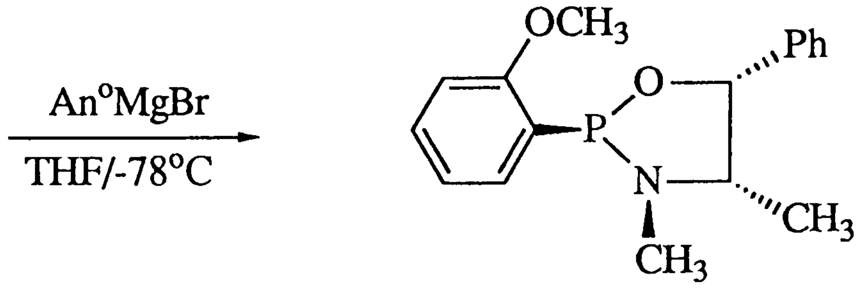


Scheme 33

Kugelrohr distillation of the crude product under anhydrous conditions afforded (2*R*, 4*S*, 5*R*)-(**43**) as a white, air and moisture-sensitive solid. Analysis by ^{1}H and ^{31}P n.m.r. spectroscopy conformed its purity as >99%, with none of the minor diastereoisomer observed. The solid could be stored for several days under an inert atmosphere but readily degraded in THF or toluene solutions.

Reaction of (2*R*, 4*S*, 5*R*)-(**43**) with *ortho*-anisylmagnesium bromide yielded (2*R*, 4*S*, 5*R*)-2-(*ortho*-anisyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(**54**) in 90% d.e. (Scheme 34). Precedent for net retention of configuration in such reactions originates form Inch's work[64] who had previously prepared (2*R*, 4*S*, 5*R*)-2-methoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine from (2*R*, 4*S*, 5*R*)-(**43**) and methanol. The -2-selone derivative was subsequently isolated in 7% yield (based on PCl_3).

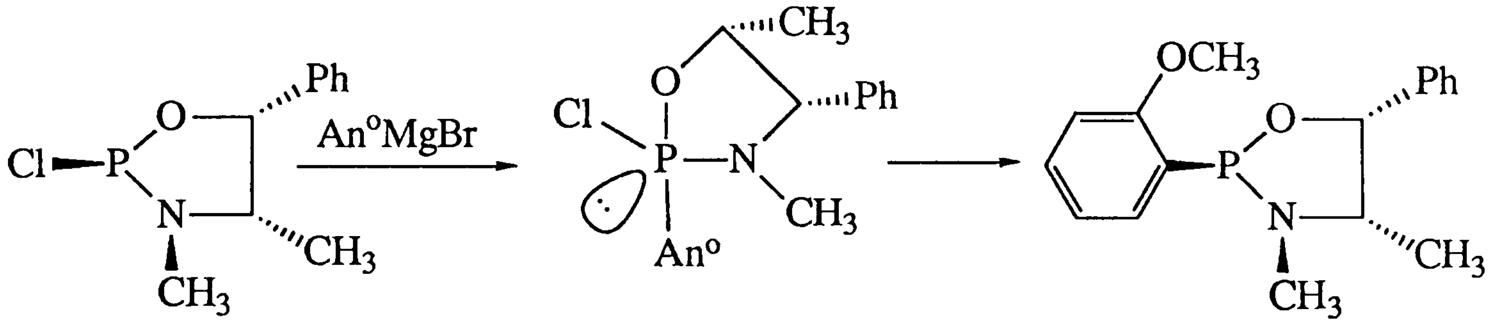
δ_P = 139.3
(2*R*, 4*S*, 5*R*)-**43**



δ_P = 135.2 90% d.e.
(2*R*, 4*S*, 5*R*)-**54**

Scheme 34

The mechanism of P-Cl cleavage would be in accordance with nucleophilic attack opposite oxygen to generate a trigonal bipyramidal intermediate followed by pseudorotation (Scheme 35). The mechanism is analogous to that for the P(V) oxide (Scheme 21) with the lone electron pair on phosphorus occupying the vacant coordination site in (2*R*, 4*S*, 5*R*)-(**43**, Scheme 35).

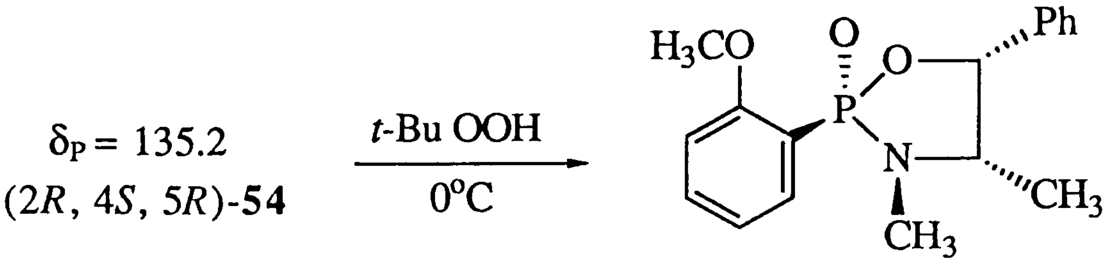


(2*R*, 4*S*, 5*R*)-**43** (2*R*, 4*S*, 5*R*)-**54**

Scheme 35

Oxidation of (2*R*, 4*S*, 5*R*)-(**54**) *in situ* using *tert*-butylhydroperoxide afforded (2*R*, 4*S*, 5*R*)-2-(*ortho*-anisyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-

(**55**), with 95% d.e. (Scheme 36). This was easily purified by column chromatography and isolated as a white, air-stable crystalline solid, it was shown to be diastereochemically pure by ^{1}H n.m.r. spectroscopy. Isolation of the minor diastereoisomer of (2*R*, 4*S*, 5*R*)-(**55**) proved to be difficult by chromatography due to a co-eluting impurity. Its tentative assignment was made only on the basis of ^{1}H n.m.r. spectroscopy. Since this is a non-descriptive preparation it has been excluded from the Experimental Chapter.



δ_P = 135.2
(2*R*, 4*S*, 5*R*)-**54**

δ_P = 27.7
(2*R*, 4*S*, 5*R*)-**55**

Scheme 36

2.3. Summary.

The diastereospecific synthesis of (2*R*, 4*S*, 5*R*)-(**26**) from $PhPCl_2$ had been achieved using *l*-ephedrine as a chiral auxiliary by a modification of an established procedure. The diastereospecific synthesis of the novel -2-oxide-(**49**) and -2-borane-(**31**) derivatives had also been demonstrated, while the analogous (2*S*, 4*S*, 5*R*)-(**51**) -2-thione analogue had been prepared in 90% d.e.. These results are summarised in Table 3.

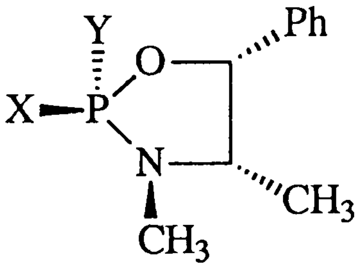


Table 3. P(V) 2-aryl-oxazaphospholidines prepared in this study.

Compound	X	Y	%Yield	[α]$_D$	m.p.(°C)
(2*R*, 4*S*, 5*R*)-(**31**)	Ph	BH_3	34.0	-45.5	105
(2*R*, 4*S*, 5*R*)-(**49**)	Ph	O	39.3	-37.5	159-161
(2*S*, 4*S*, 5*R*)-(**50**)	O	Ph	7.6	-52.0	146-147
(2*S*, 4*S*, 5*R*)-(**51**)	Ph	S	31.8	-139.3	99-100
(2*R*, 4*S*, 5*R*)-(**52**)	S	Ph	3.2	+29.5	147-148
(2*R*, 4*S*, 5*R*)-(**55**)	An°	O	60.2	-44.1	156-157

The corresponding P(III) chloro-oxazaphospholidine-(**43**) gave access to aryl-oxazaphospholidines by nucleophilic cleavage of chloride from (2*R*, 4*S*, 5*R*)-(**55**) using aryl Grignard reagents. The reaction proceeded with a net retention of configuration at phosphorus and represented a versatile route to new aryl-oxazaphospholidines of known configuration at phosphorus. Further evidence for this stereochemical assignment was provided by a derivitisation experiment supported by crystallographic data (*vide infra*).

2.4. Structure and solid state conformations of *l*-ephedrine-derived oxazaphospholidines.

The saturated ring of 1,3,2-oxazaphospholidines can exist in several conformations on the cyclopentane pseudorotation pathway[75], including half-chairs and envelopes as well as intermediate structures (Figure 4)[64,66,67,76-79]. The conformation adopted depends on the substituents both at phosphorus and on the ring. In order to investigate this observation the solid state conformations of the five membered ring of 1,3,2-oxazaphospholidines derived from (-)-ephedrine were analysed (Table 4).

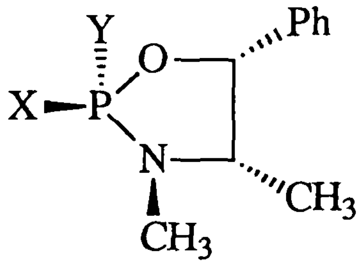


Table 4. Crystal structures for *l*-ephedrine-derived 1,3,2-oxazaphospholidines.

Structure	X	Y	Reference
(2*R*, 4*S*, 5*R*)-(**31**)	Ph	BH_3	79
(2*S*, 4*S*, 5*R*)-(**40**)	Cl	S	66
(2*R*, 4*S*, 5*R*)-(**41**)	S	Cl	67
(2*S*, 4*S*, 5*R*)-(**56**)	PhO	O	80
(2*R*, 4*S*, 5*R*)-(**42**)	O	PhO	80
(2*R*, 4*S*, 5*R*)-(**49**)	Ph	O	This work
(2*S*, 4*S*, 5*R*)-(**50**)	O	Ph	This work
(2*S*, 4*S*, 5*R*)-(**51**)	Ph	S	This work
(2*R*, 4*S*, 5*R*)-(**52**)	S	Ph	This work
(2*R*, 4*S*, 5*R*)-(**57**)	CH_3	O	70
(2*R*, 4*S*, 5*R*)-(**58**)	O	SCH_3	81
(2*R*, 4*S*, 5*R*)-(**59**)	S	NHPh	82

Knowles and co-workers[70] had previously determined the structure of (2*R*, 4*S*, 5*R*)-2,3,4-trimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-oxide-(**57**), for which the configuration at phosphorus was required to assign the chirality of [^{16}O,^{17}O,^{18}O] phosphonopyruvate. The conformation resembles an envelope with C4 below the C5-O1-P2-N3 plane. In contrast, (2*R*, 4*S*, 5*R*)-2-thiomethyl-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(**58**) most resembles a half-chair with C4 above and C5 below the O1-P2-N3 plane[81]. Three 2-thio structures have also been published, (2*R*, 4*S*, 5*R*)-(**41**), (2*S*, 4*S*, 5*R*)-(**40**) and (2*R*, 4*S*, 5*R*)-(**59**), and these most closely adopt an N3-C4 half-chair, a C4 envelope and a P2 envelope, respectively[66,67,82]. More recently, X-ray crystallography of the 2-borane analogue (2*R*, 4*S*, 5*R*)-(**31**) shows that this most closely resembles a C4-N3 half chair[69]. In an attempt to rationalise the conformations adopted, the crystal structures of three pairs of diastereoisomeric 1,3,2-oxazaphospholidines were determined by single-crystal X-ray diffraction studies in a collaborative effort with Dr's Freeman and Schwalbe at the University of Aston. As part of this study they prepared (2*R*, 4*S*, 5*R*)- and (2*S*, 4*S*, 5*R*)-2-phenoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-oxides-(**42** & **56**) which were of interest because of their role in the synthesis of chiral phenyl (^{16}O,^{17}O,^{18}O)-phosphate[83]. The structure of the major, (2*R*, 4*S*, 5*R*)-(**42**) diastereoisomer was solved by single-crystal X-ray diffraction studies. The PLUTO plot[84] (Figure 5) shows that the phenyl rings are indeed arranged *syn* within the 5-membered ring. This assignment is in agreement with that made by Inch *et al.*[64] who proposed that the major, (2*R*, 4*S*, 5*R*)-(**42**) diastereoisomer had an *R* configuration at phosphorus. Examination of molecular models (CHEM-X) revealed an absence of serious non-bonded interactions involving the phenoxy group; therefore it is reasonable that steric constraints do not dictate the diastereoisomeric ratio of the products. For comparison of the ring conformations, the crystal structure of the minor, (2*S*, 4*S*, 5*R*)-(**56**) diastereoisomer was also solved. The PLUTO plot[84] is shown in Figure 6. After completion of the refinement, Setzer and co-workers[78] reported the crystal structure of (2*R*, 4*S*, 5*R*)-(**42**), however the quality of their crystal was poor (R = 10.3%). This structure determined in this study is in broad agreement with that proposed by Setzer *et al.*[78] however their standard deviations on atomic coordinates, bond lengths and bond

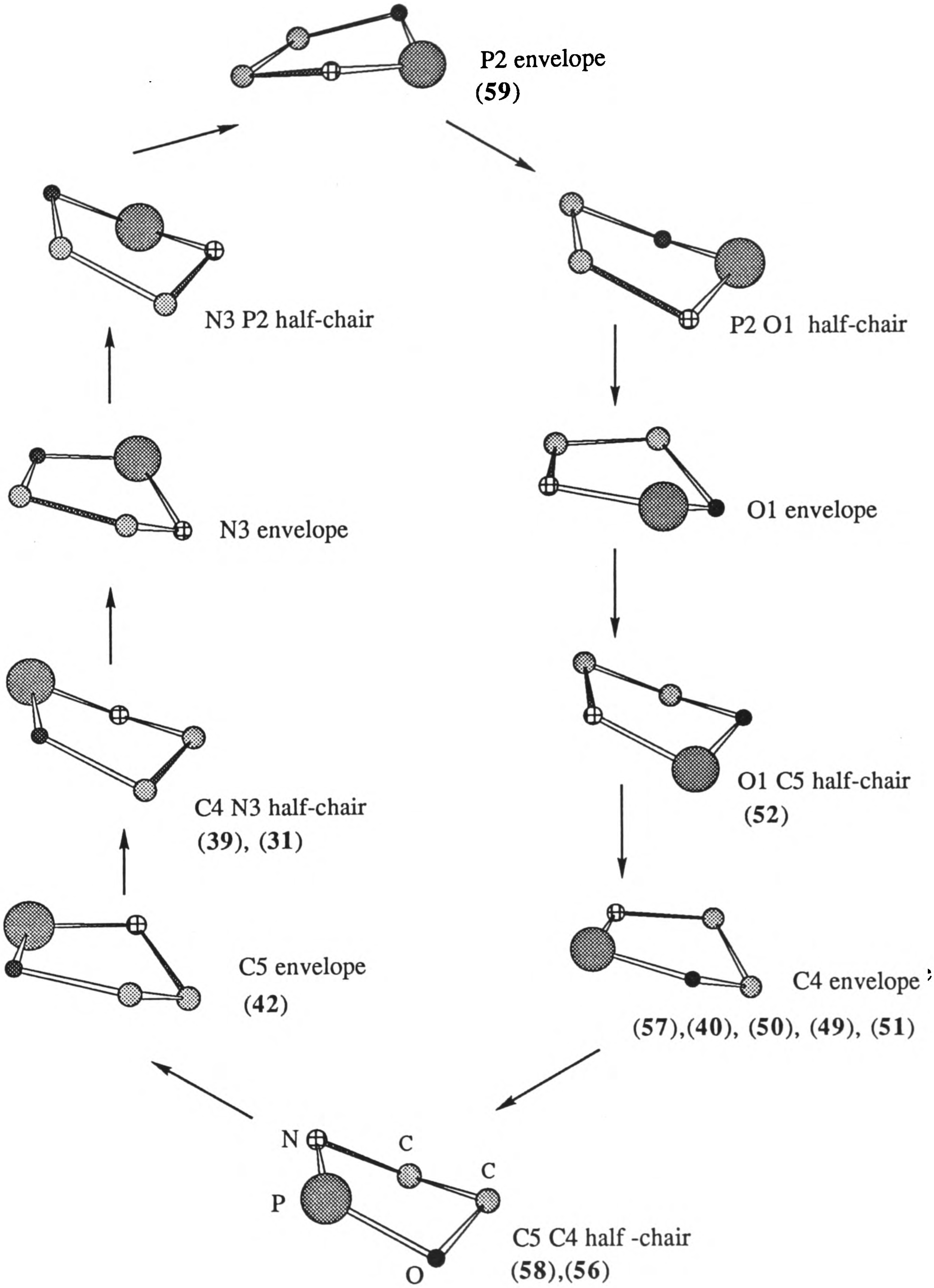


Figure 4. Pseudorotation itinerary for oxazaphospholidines; the closest approximation of X-ray structures to conformers is indicated. Atom shadings are indicated on the bottom structure.

angles are much higher. More seriously, some values do not agree; for example, the length of the P(2)-O(1) bond is 0.034 Å (3σ) longer and the O(1)-P(2)-N(3) angle 1.9^{o} (3σ) smaller than reported by Setzer *et al.*[78].

Both diastereoisomers of 2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidin-2-oxides-(**49** & **50**) were fully characterised and the ^{1}H NMR data are summarised in Table 5. The structure of the minor, (2*S*, 4*S*, 5*R*)-(**50**) diastereoisomer was solved by X-ray crystallography and was confirmed to have the *S* configuration at phosphorus. The PLUTO plot[84] is shown in Figure 7. The structure of the major, (2*R*, 4*S*, 5*R*)-(**49**) diastereoisomer was also solved by X-ray crystallography, the PLUTO plot[84] is shown in Figure 8.

The structures of the (2*R*, 4*S*, 5*R*)-(**52**) and (2*S*, 4*S*, 5*R*)-(**51**) thio analogues were similarily determined by single-crystal X-ray diffraction studies. The minor, (2*R*, 4*S*, 5*R*)-(**52**) first eluted diastereoisomer was confirmed to have the *R* configuration at phosphorus. The PLUTO plot[84] is shown in Figure 9. For the major, (2*S*, 4*S*, 5*R*)-(**51**) diastereoisomer the PLUTO plot[84] is shown in Figure 10.

For the six structures, the crystal data summarised in Table 20 (Chapter 6) shows that the coordinates are of good quality with R values between 2.90 and 5.30 %. All crystals occupy the space group $P2_12_12_1$, except for (2*S*, 4*S*, 5*R*)-(**51**) which is $P2_1$. Selected bond lengths are given in Table 6, bond angles in Table 7, and torsion angles in Table 8, and are directly compared in Figure 11. The endocyclic bond lengths and bond angles for the six structures are similar to those reported for other analogues[66,67,70,81,82]. The P-N bonds in the compounds with a PhO group are ~ 0.02 Å shorter than the corresponding analogues with a Ph group. This is likely to be attributable to the anomeric effect[85], as the lone pair of electrons in the p orbital on the planar nitrogen overlaps better with the anti-bonding orbitals on phosphorus when the electronegative phenoxy group is the substituent at phosphorus. The anomeric effect may also be operating further in structures (2*R*, 4*S*, 5*R*)-(**42**)- and (2*S*, 4*S*, 5*R*)-(**56**), as in each case the phenoxy group resides over the five membered ring, allowing the lone pairs of electrons on the oxygen of the phenoxy group to be antiperiplanar to both the P-N and P-O ring bonds facilitating orbital overlap.

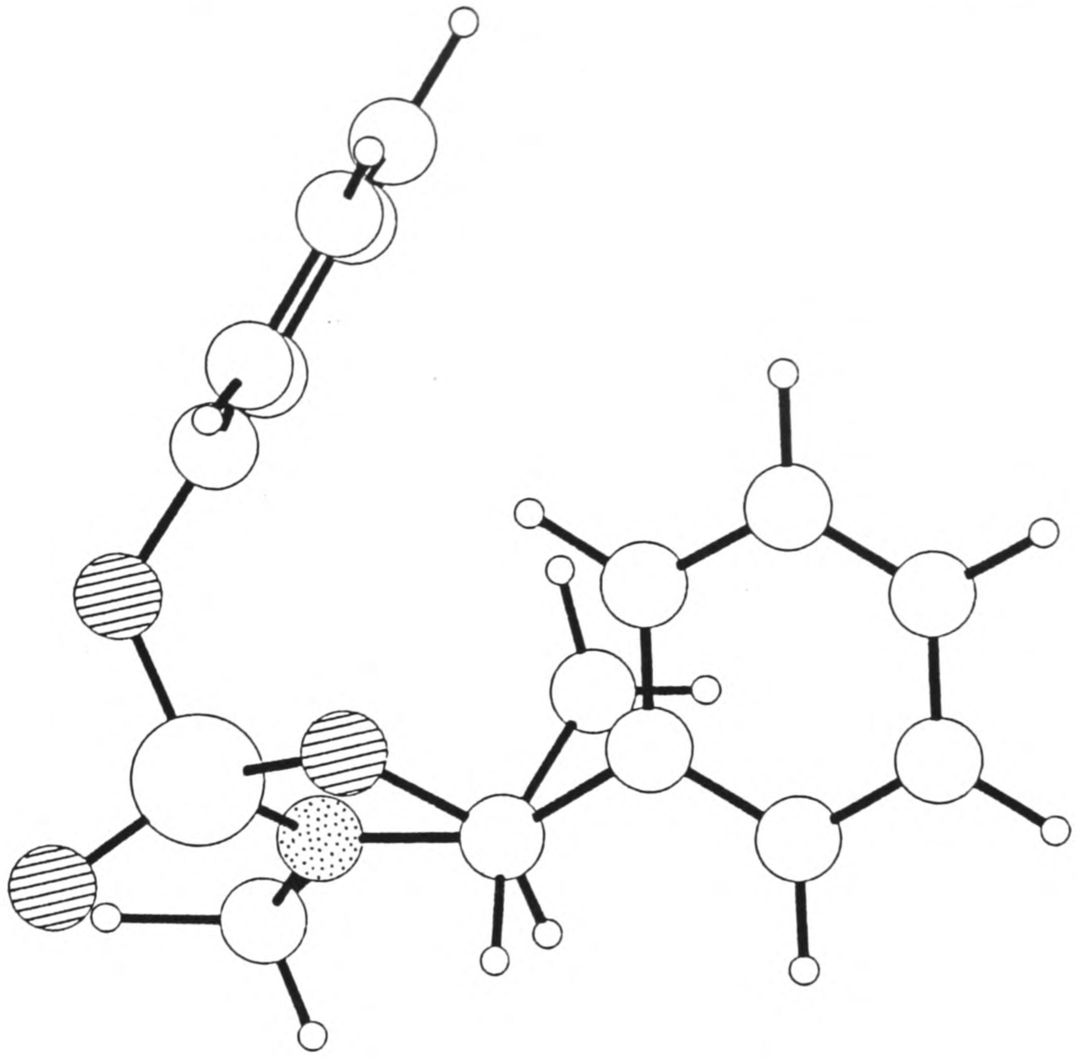


Figure 5. PLUTO plot of (2*R*, 4*S*, 5*R*)-2-phenoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(**42**) viewed down the C4-C5 bond.

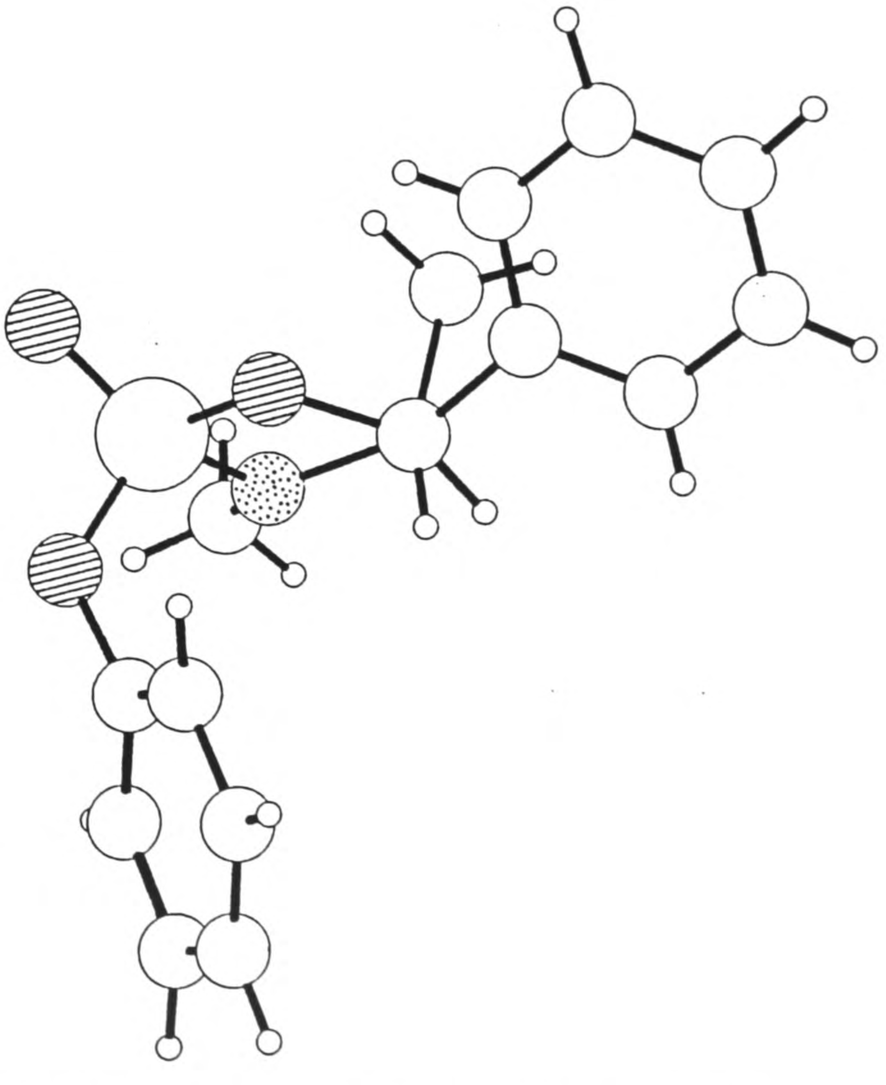


Figure 6. PLUTO plot of (2*S*, 4*S*, 5*R*)-2-phenoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(**56**) viewed down the C4-C5 bond.

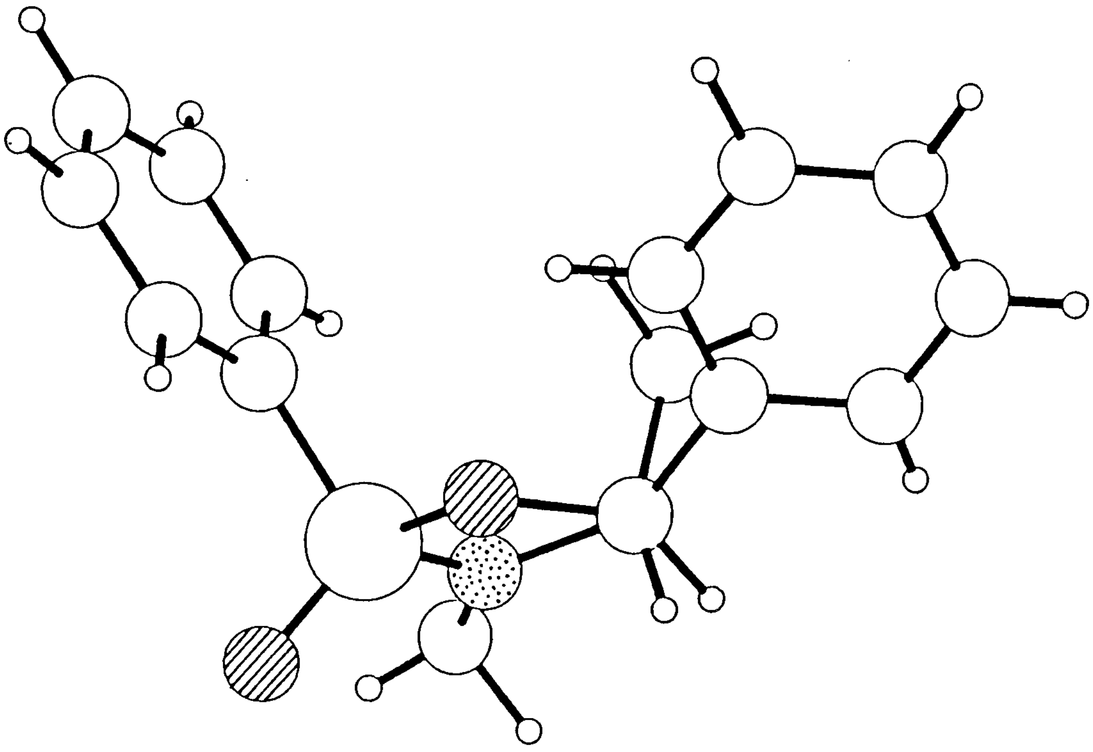


Figure 7. PLUTO plot of (2*S*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-oxide-(**50**) viewed down the C4-C5 bond.

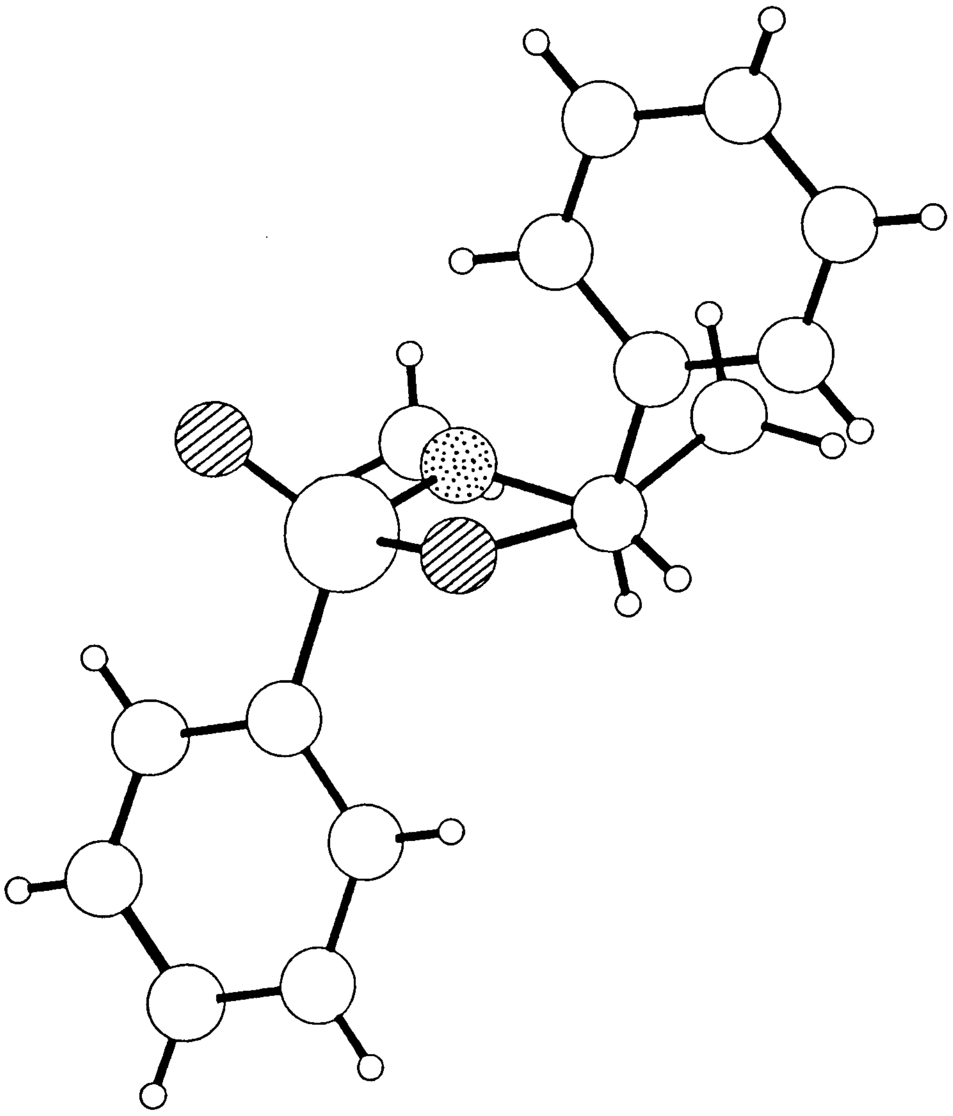


Figure 8. PLUTO plot of (2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-oxide-(**49**) viewed down the C4-C5 bond.

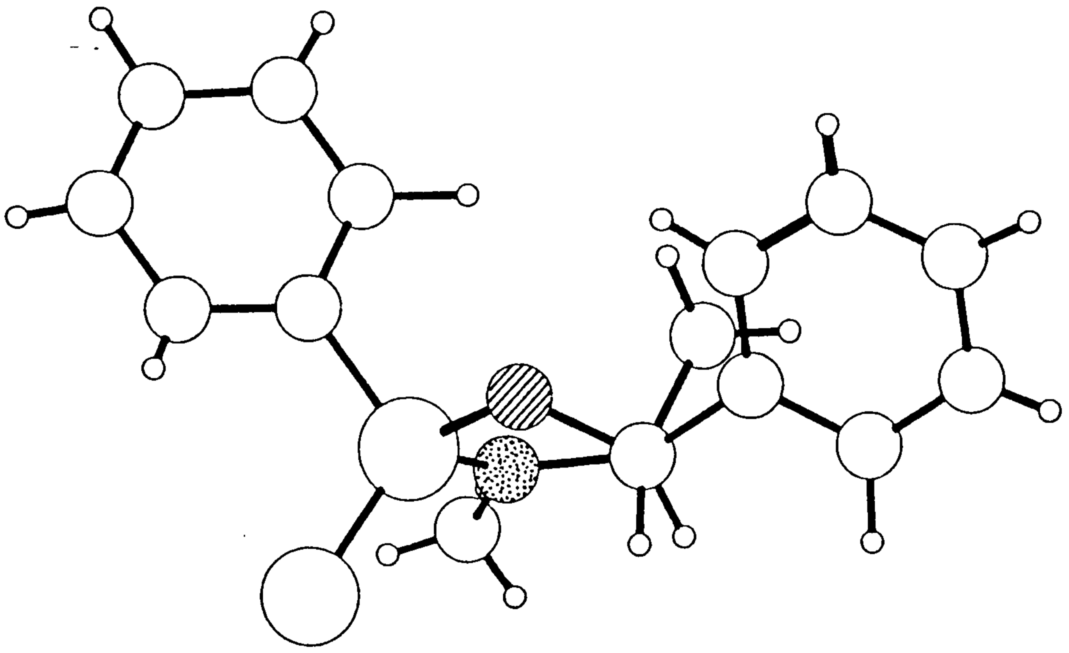


Figure 9. PLUTO plot of (2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-thione-(**52**) viewed down the C4-C5 bond.

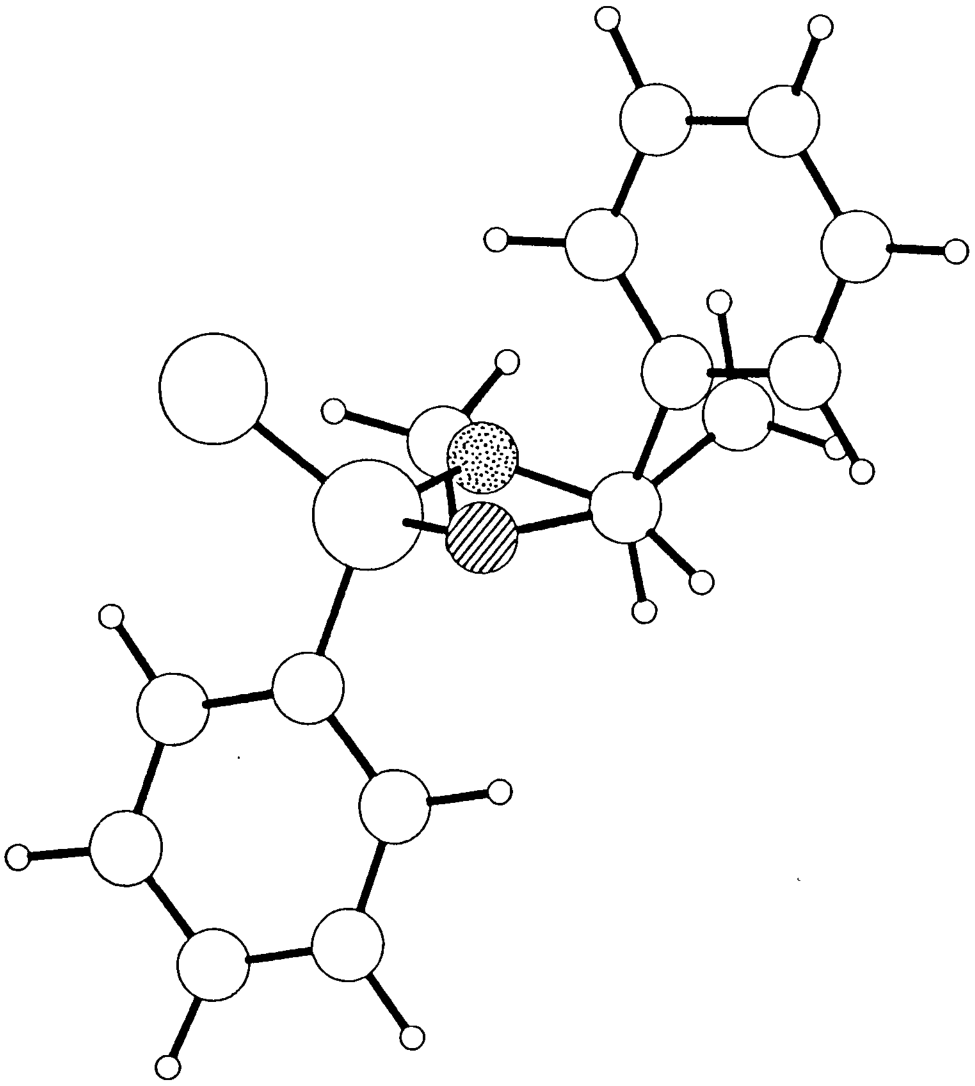
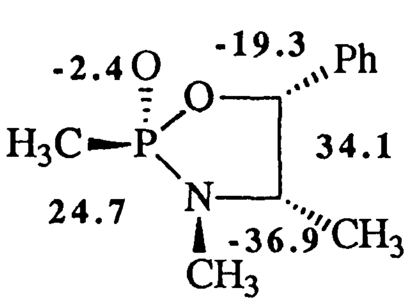
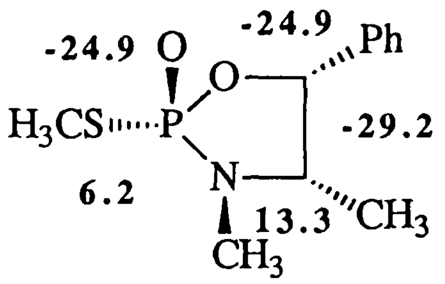


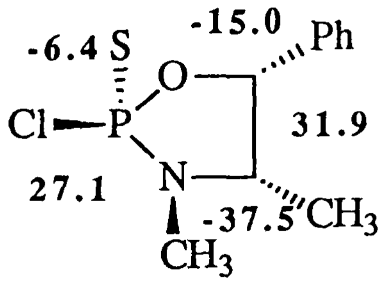
Figure 10. PLUTO plot of (2*S*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-thione-(**51**) viewed down the C4-C5 bond.



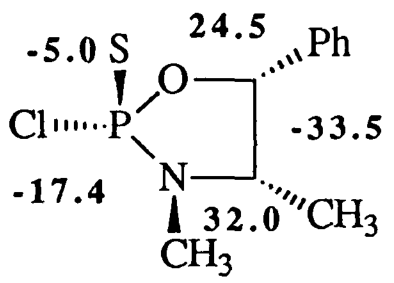
(2*R*, 4*S*, 5*R*)-(**57**)



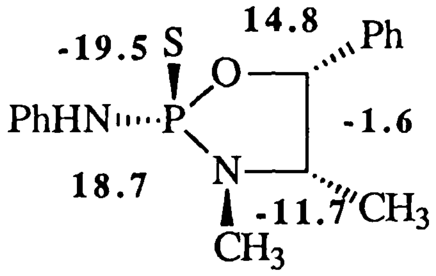
(2*R*, 4*S*, 5*R*)-(**58**)



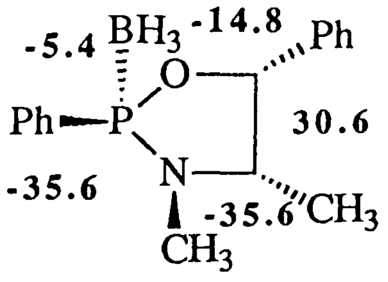
(2*S*, 4*S*, 5*R*)-(**40**)



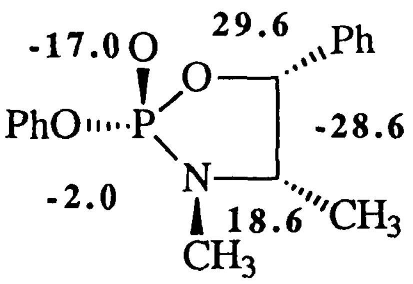
(2*R*, 4*S*, 5*R*)-(**41**)



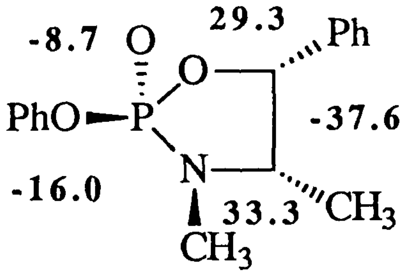
(2*R*, 4*S*, 5*R*)-(**59**)



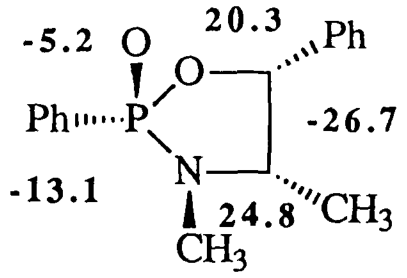
(2*R*, 4*S*, 5*R*)-(**31**)



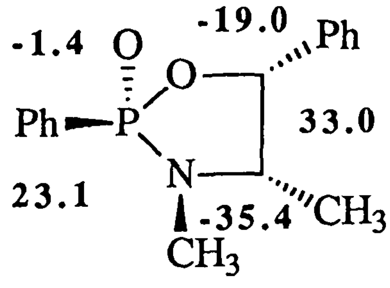
(2*R*, 4*S*, 5*R*)-(**42**)



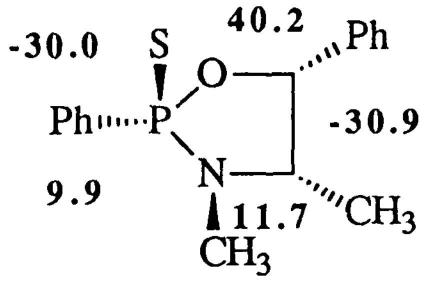
(2*S*, 4*S*, 5*R*)-(**56**)



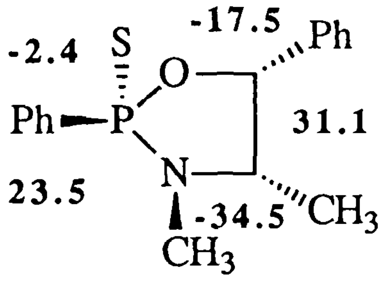
(2*S*, 4*S*, 5*R*)-(**50**)



(2*R*, 4*S*, 5*R*)-(**49**)



(2*R*, 4*S*, 5*R*)-(**52**)



(2*S*, 4*S*, 5*R*)-(**51**)

Figure 11. Ring torsion angles for oxazaphospholidine structures.

The P=O bond lengths range between 1.453 and 1.466 Å and are typical for phosphoryl P=O double bonds. For the six crystal structures (Figures 5-10), the sum of angles at N(3) [P(2)-N(3)-C(4) + P(2)-N(3)-C(13) + C(4)-N(3)-C(13)] are 358.8, 353.4, 359.9, 351.6, 358.0 and 350.2°, consistent with almost trigonal planar geometry at nitrogen[86]. In all structures, the O(1)-P(2)-X(6) and N(3)-P(2)-X(6) angles are greater than normal tetrahedral angles, presumably to separate the electronegative heteroatoms. The C(5)-C(4)-C(14) and C(4)-C(5)-C(15) angles are also greater than tetrahedral and the plane of the C(5)-phenyl ring is always perpendicular to the oxazaphospholidine ring, both factors minimising steric clashes between the C(4)-methyl and C(5)-phenyl substituents.

2.5. Calculation of asymmetry parameters for oxazaphospholidines.

Five-membered rings are highly fluctional and capable of adopting a range of non-planar conformations separated by very small energy barriers in solution[75]. In the solid state, depending on the effects of substituents and crystal packing, a single conformation may result. With the availability of a number of closely related structures based on the oxazaphospholidine ring system, it was of interest to see if systematic trends could be identified. Since the endocyclic P-N and P-O bonds are somewhat longer than other endocyclic bonds (Table 6) and the geometry at N is best approximated as sp^2, there is an inbuilt preference for conformations in the region of the C4 and C5 envelopes on the pseudorotation pathway (Figure 4). This is reinforced by a need to avoid eclipsing of the substituents on C4 and C5.

The asymmetry parameters were calculated to establish whether the rings adopt an envelope (ΔC_S) or half chair (ΔC_2) conformation[87]. The smaller the value, the closer the structure approaches the ideal envelope or half chair. The deviations of the flap atom from the appropriate four-atom plane were calculated to give further information on the envelope conformations; and for the half chairs, the deviation of the atoms from the three-atom plane were determined. The results are summarised in Table 9.

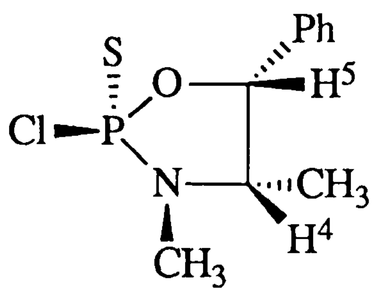
The (2*R*, 4*S*, 5*R*)-2-phenoxy-oxazaphospholidine-2-oxide-(**42**) adopts an envelope conformation in which C5 is below the O1-P2-N3-C4 plane. The ring C4-methyl is pseudoaxial and the C5-phenyl pseudoequatorial which minimises the steric interactions with the phenoxy ring (Figure 5). In contrast, the (2*S*, 4*S*, 5*R*)-(**56**) diastereoisomer exists as a half chair, with C4-Me above and C5-Ph below the O1-P2-N3 plane, with C4-Me in a pseudoaxial position and C5-Ph pseudoequatorial (Figure 6). The 2-phenyl-2-oxide-(**49** & **50**) diastereoisomers both exist as C4 envelopes. Where the two phenyl groups are *syn* in (2*S*, 4*S*, 5*R*)-(**50**), the C4 flap is above the C5-O1-P2-N3 plane, which puts the C4-methyl group pseudoaxial and the C5-phenyl group pseudoequatorial (Figure 7). For the *anti* isomer (2*R*, 4*S*, 5*R*)-(**49**), the C4 flap is below the C5-O1-P2-N3 plane, with the C5-phenyl pseudoaxial and the C4-methyl pseudoequatorial (Figure 8). The *anti* 2-phenyl-2-thio-(**51**) analogue adopts an identical C4 envelope to (2*R*, 4*S*, 5*R*)-(**49**, Figure 8), the torsion angles of these structures showing remarkable similarity. The *syn* 2-phenyl-2-thio isomer (2*R*, 4*S*, 5*R*)-(**52**) exists as an O1-C5 half chair, with O1 above and C5 below the P2-N3-C4 plane, placing C5-phenyl pseudoequatorial and C4-methyl pseudoaxial (Figure 10).

2.6. Solution conformations of *l*-ephedrine-derived oxazaphospholidines.

Some information on the solution conformation may be obtained from the relevant $^3J_{P\text{-}H5}$ coupling constants (assumed to be positive over the torsion angle range), and these have been the subject of analysis by three independent groups[64,76,63]. Inch and co-workers[64] had reported a $J_{P\text{-}H5}$ coupling constant of 1 Hz for (2*R*, 4*S*, 5*R*)-(**41**) which for other *syn*-2-substituted oxazaphospholidines prepared in this study had been unobserved. The ^1H n.m.r. spectrum was therefore re-examined at 500 MHz and no $J_{P\text{-}H5}$ coupling was observed (Table 5). For the compounds where the substituent on phosphorus is *syn* to the ring methyl and phenyl groups, the $^3J_{P\text{-}H5}$ value at H5 is < 1 Hz (Table 5), consistent only with an averaged P-O-C-H torsion angle close to 90°. From similar results, Inch and co-workers[64] proposed that these rings adopt an envelope conformation, with O1 out of the plane of the other four atoms. In contrast, Navech[76] proposed half chairs, with C4 and C5 out of plane of the other three atoms, and Setzer[77] proposed a twist envelope conformation, in which the aromatic substituent on phosphorus is pseudoaxial. For the *syn* structures the POCH torsion angles are -98, -87 and -96° in the crystals, consistent with the small $^3J_{P\text{-}H5}$ coupling constants. For these molecules, the envelope conformations observed in the crystals may reflect the conformations adopted in solution and they are in broad agreement with those proposed by Setzer[77]. In contrast, Inch's proposal of an O1 envelope, which would cause eclipsing of the C4-Me and C5-Ph groups, is not supported by the X-ray data. The conformations of the *syn* compounds (2*R*, 4*S*, 5*R*)-(**58**) and (2*R*, 4*S*, 5*R*)-(**52**) appears to support the claim of Navech[76] that these compounds adopt half-chair conformations, however the POCH torsion angles of -66 and -73° are inconsistent with a small $^3J_{P\text{-}H5}$ coupling constant of less than 1 Hz, therefore the conformation in solution must be different than that observed in the solid state.

For the *anti* compounds (2*R*, 4*S*, 5*R*)-(**57**), (2*R*, 4*S*, 5*R*)-(**40**), (2*R*, 4*S*, 5*R*)-(**31**), (2*S*, 4*S*, 5*R*)-(**56**), (2*R*, 4*S*, 5*R*)-(**49**) and (2*S*, 4*S*, 5*R*)-(**51**) the $^3J_{P\text{-}H5}$ values of 3 to 6.5 Hz are observed, so that the torsion angle is removed from orthogonality here. For structures (2*R*, 4*S*, 5*R*)-(**57**), (2*R*, 4*S*, 5*R*)-(**49**) and (2*S*, 4*S*, 5*R*)-(**51**), all of which adopt C4 envelopes with C4 below the plane of the ring, the POCH torsion angles of -136, -139 and -139° are consistent with the observed $^3J_{P\text{-}H5}$ coupling constants and the conformations adopted in solution could be similar to those observed in the solid state. In contrast, compound (2*S*, 4*S*, 5*R*)-(**56**), with a POCH torsion angle of -89° is incompatible with the ^1H NMR data, and the half-chair adopted in the solid state is unlikely to be a major conformer in solution.

The $^3J_{P\text{-}H4}$ values do not display any evident trend although they are all much larger (in the range 10.6 to 18 Hz) implying that the torsion angle P-N-C-H is well removed from orthogonal in the average structure. For (2*R*, 4*S*, 5*R*)-(**41**) the H-4 region of its 1H n.m.r. spectrum (500 MHz) is reproduced in Figure 12b, together with its 5-H decoupled and H_3C-decoupled spectra in Figures 12c and 12a respectively.



(2*R*, 4*S*, 5*R*)-**41**

$J_{H\text{-}CH3}$ = 6.8 Hz
$J_{P\text{-}H4}$ = 28.9 Hz
J_{HH} = 6.4 Hz

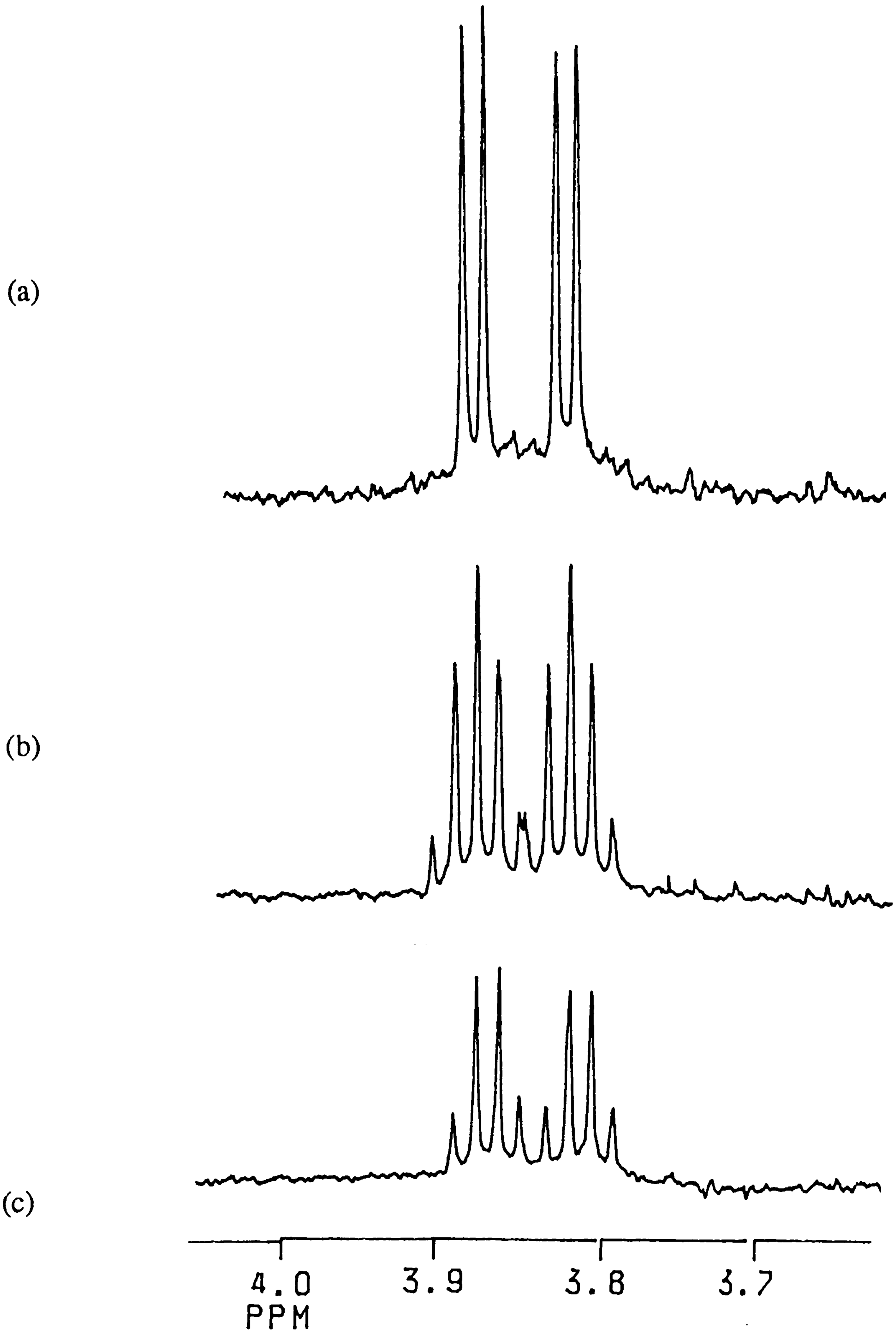


Figure 12. ^1H n.m.r. Spectrum (500 MHz; $CDCl_3$) of H-4 region of (2*R*, 4*S*, 5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-thione-(**41**); (a): CH_3-decoupled, (b): normal and (c) H-5-decoupled spectra.

Table 5. ^1H n.m.r. ($CDCl_3$) data for (4*S*, 5*R*)-1,3,2-Oxazaphospholidnes.

Structure	MHz	CH_3(3H, d)		NCH_3(3H,d)		H-4(1H, ddq)				H-5(1H)				Reference
		δ	J_{HH}	δ	J_{PH}	δ	J_{PH}	J_{HH}	J_{HH}	δ	m	J_{HH}	J_{PH}	
(2*S*)-(**50**)	500	0.85	6.5	2.83	10.0	3.68	9.8	6.1	6.5	5.92	d	6.1		This work
(2*R*)-(**49**)	500	0.93	6.6	2.78	10.3	3.58	17.0	6.4	6.6	5.60	dd	6.4	3.5	This work
(2*R*)-(**52**)	500	0.82	6.6	2.76	9.3	3.80	10.6	6.3	6.6	5.96	d	6.3		This work
(2*S*)-(**51**)	500	0.92	6.5	2.63	10.1	3.80	14.0	6.2	6.5	5.60	dd	6.2	4.9	This work
(2*R*)-(**42**)	300	0.6	6.7	2.77	11.9	3.80	18	6.2	6.7	5.74	d	6.2		80
(2*S*)-(**56**)	300	0.78	6.5	2.66	12.5	3.80	12	6.3	6.5	5.34	dd	6.3	3.75	80
(2*R*)-(**31**)	500	0.85	6.5	2.69	10.9	3.90	9.0	6.1	6.5	5.59	dd	6.1	3.0	This work
(2*R*)-(**57**)	250	0.82	6.5	2.68	10.0	3.56	14.3	6.0	6.5	5.41	dd	6.0	4.6	70
(2*R*)-(**41**)	100	0.87		2.85	15	3.85	29.5			5.81	dd	6.5	1.0	64
(2*S*)-(**40**)	100	0.78		2.72	17.5	3.73	13.0			5.59	dd	7.25	6.5	64
(2*R*)-(**41**)	500	0.89	6.8	2.93	14.7	3.85	28.9	6.4	6.8	5.83	d	6.4		This work

Table 6. Selected bond lengths (Å) with e.s.d.'s in parentheses for 1,3,2-oxazaphospholidines

	(2*R*)-(**42**)	(2*S*)-(**56**)	(2*S*)-(**50**)	(2*R*)-(**49**)	(2*R*)-(**52**)	(2*S*)-(**51**)
O(1)-P(2)	1.581(2)	1.588(2)	1.591(2)	1.581(2)	1.602(3)	1.594(4)
O(1)-C(5)	1.465(3)	1.458(4)	1.452(3)	1.463(4)	1.457(5)	1.444(8)
P(2)-N(3)	1.613(2)	1.623(3)	1.635(2)	1.641(3)	1.643(3)	1.640(6)
P(2)-O(6)	1.457(2)	1.453(3)	1.466(2)	1.463(3)		
P(2)-S(6)					1.931(1)	1.915(3)
N(3)-C(4)	1.473(3)	1.468(4)	1.474(4)	1.465(5)	1.456(5)	1.462(8)
N(3)-C(13)	1.455(4)	1.463(5)	1.455(4)	1.450(4)	1.447(6)	1.479(8)
P(2)-O(21)	1.593(2)	1.583(2)				
O(21)-C(7)	1.399(3)	1.398(4)				
P(2)-C(7)			1.794(3)	1.790(3)	1.800(5)	1.793(6)

Table 7. Selected bond angles (°) with e.s.d.'s in parentheses for 1,3,2-oxazaphospholidines

	(2*R*)-(**42**)	(2*S*)-(**56**)	(2*S*)-(**50**)	(2*R*)-(**49**)	(2*R*)-(**52**)	(2*S*)-(**51**)
P(2)-O(1)-C(5)	111.7(1)	111.4(2)	114.0(2)	113.4(2)	109.5(2)	114.0(4)
O(1)-P(2)-N(3)	96.7(1)	96.4(1)	95.6(1)	96.1(1)	94.2(2)	94.6(2)
O(1)-P(2)-O(6)	119.4(1)	116.1(1)	115.9(1)	117.4(2)		
O(1)-P(2)-S(6)					116.9(1)	118.1(2)
N(3)-P(2)-O(6)	117.4(1)	120.7(2)	117.6(1)	115.3(2)		
N(3)-P(2)-S(6)					118.3(1)	115.3(2)
P(2)-N(3)-C(4)	113.6(2)	110.9(2)	113.6(2)	109.7(2)	113.9(3)	111.6(4)
P(2)-N(3)-C(13)	125.3(2)	122.1(3)	125.9(2)	121.7(3)	123.3(4)	120.8(4)
C(4)-N(3)-C(13)	119.9(2)	120.4(3)	120.4(3)	120.2(3)	120.8(4)	117.8(6)
N(3)-C(4)-C(5)	103.4(2)	102.0(2)	102.6(2)	103.3(3)	103.5(3)	101.9(5)
N(3)-C(4)-C(14)	111.7(2)	113.3(3)	112.7(3)	113.4(3)	112.2(4)	112.4(5)
C(7)-P(2)-O(1)			104.8(1)	104.8(1)	104.3(1)	104.2(1)
C(7)-P(2)-O(6)					109.9(1)	110.5(2)
C(7)-P(2)-S(6)					112.1(2)	111.7(2)
C(7)-P(2)-N(3)			111.7(1)	111.6(1)	109.1(2)	111.4(3)
C(8)-C(7)-P(2)			122.1(2)	118.9(3)	120.2(3)	120.2(4)
C(12)-C(7)-P(2)			119.8(2)	122.4(3)	121.5(4)	121.3(4)

Table 8. Selected torsion angles (°) for 1,3,2-oxazaphospholidines

	(2*R*)-(**42**)	(2*S*)-(**56**)	(2*S*)-(**50**)	(2*R*)-(**49**)	(2*R*)-(**52**)	(2*S*)-(**51**)
P(2)-O(1)-C(5)-C(4)	29.6	29.3	20.3	-19.0	40.2	-17.5
P(2)-O(1)-C(5)-C(15)	154.7	155.3	146.3	106.9	165.9	108.7
C(5)-O(1)-P(2)-N(3)	-17.0	-8.7	-5.2	-1.4	-30.0	-2.4
C(5)-O(1)-P(2)-O(6)	109.7	-137.6	119.3	-124.0		
C(5)-O(1)-P(2)-S(6)					94.7	-124.4
O(1)-P(2)-N(3)-C(4)	-2.0	-16.0	-13.1	23.1	9.9	23.5
O(1)-P(2)-N(3)-C(13)	165.0	-167.4	170.4	171.0	173.6	168.4
O(6)-P(2)-N(3)-C(4)	-130.1	109.6	-136.2	147.2		
P(2)-N(3)-C(4)-C(5)	18.6	33.3	24.8	-35.4	11.7	-34.5
P(2)-N(3)-C(4)-C(14)	-106.8	-89.9	-99.3	-159.6	-112.4	-157.4
C(13)-N(3)-C(4)-C(5)	-149.2	-174.7	-158.4	176.0	-152.4	179.3
N(3)-C(4)-C(5)-O(1)	-28.6	-37.6	-26.7	33.0	-30.9	31.1
N(3)-C(4)-C(5)-C(15)	-149.9	-159.8	-148.5	-89.2	-152.6	-92.3
C(14)-C(4)-C(5)-O(1)	94.0	84.9	96.0	156.6	91.5	152.6
C(14)-C(4)-C(5)-C(15)	-27.3	-37.2	-25.8	34.4	-30.2	29.2
O(1)-P(2)-O(21)-C(7)	37.3	-50.2				
P(2)-O(21)-C(7)-C(8)	97.0	-107.6				
P(2)-O(21)-C(7)-C(12)	-85.9	77.9				
C(5)-O(1)-P(2)-O(21)	-133.0	104.0				
O(21)-P(2)-N(3)-C(4)	106.3	-127.2				
O(1)-P(2)-C(7)-C(8)			111.5	162.5	57.7	152.9
O(1)-P(2)-C(7)-C(12)			-69.4	-19.5	-124.5	-27.8
C(5)-O(1)-P(2)-C(7)			-119.4	112.9	-141.0	111.0
C(7)-P(2)-N(3)-C(4)			95.3	-85.5	116.7	-83.8
P(2)-O(1)-C(5)-H(2)	-87	-89	-96	-139	-73	-139

Table 9. Conformational Details of Oxazaphospholidines

	(2*R*)-(**42**)	(2*S*)-(**56**)	(2*S*)-(**50**)	(2*R*)-(**49**)	(2*R*)-(**52**)	(2*S*)-(**51**)
ΔC_s	1.33, C5	9.88, C4	5.27, C4	3.36,C4	14.50,C5	4.88,C4
ΔC_2	13.15,C4-C5	5.89,C4-C5	6.43,C4-C5	14.28,C4-N3	1.39,O1-C5	11.95,N3-C4
4-Atom plane	O1-P2-N3-C4	C5-O1-P2-N3	C5-O1-P2-N3	C5-O1-P2-N3	O1-P2-N3-C4	C5-O1-P2-N3
Deviations	C5,-0.433	C4,0.529	C4,0.394	C4,-0.517	C5,-0.531	C4,-0.502
from it (Å)	C15,0.128	C15,0.637	C15,0.816	C15,1.347	C15,-0.154	C15,1.326
3-Atom plane	O1-P2-N3	O1-P2-N3	O1-P2-N3	C5-O1-P2	P2-N3-C4	C5-O1-P2
Deviations	C4,0.047	C4,0.378	C4,0.306	N3,0.041	O1,0.276	N3,0.069
from it (Å)	C5,-0.399	C5,-0.206	C5,-0.119	C4,-0.484	C5,-0.303	C4,-0.445
	C15,0.180	C15,0.375	C15,0.670	C15,1.352	C15,0.227	C15,1.335

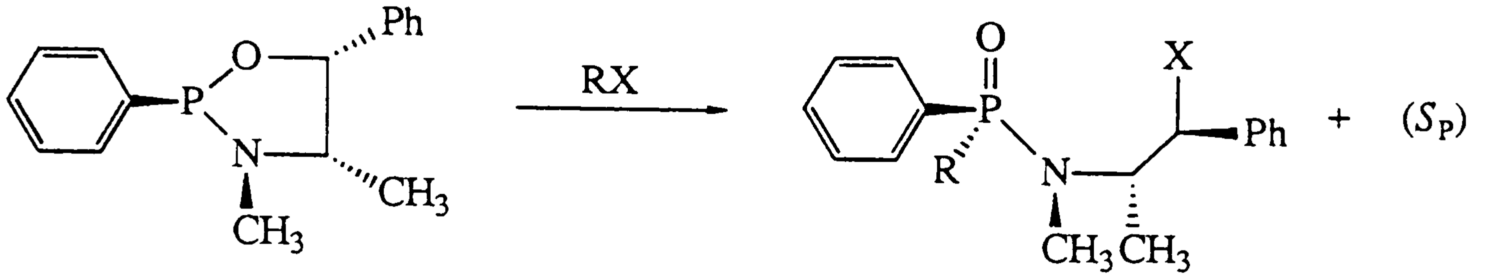
2.7. Summary.

It is not possible to make generalisations by comparison of NMR and X-ray data. The crystal structures fall into a defined region of the pseudorotation pathway between the N3-C4 half-chair and the C5-O1 half-chair, with a small preponderance of C4 or C5 envelopes (Figure 4). In contrast, the solution n.m.r. seem to indicate that the averaged conformations of *syn*-isomers (2*R*, 4*S*, 5*R*)-(**42**), (2*S*, 4*S*, 5*R*)-(**50**) and (2*R*, 4*S*, 5*R*)-(**52**) are in one region, probably close to the C4 envelope. The *anti*-isomers (2*S*, 4*S*, 5*R*)-(**56**), (2*R*, 4*S*, 5*R*)-(**49**) and (2*S*, 4*S*, 5*R*)-(**51**) fit into a related but slightly distinct conformational pattern. In a broad sense, the results are consistent with the suggestions of Setzer[77,78] and those of Devillers and Navech[76], but inconsistent with the proposal of Inch *et al.*[64] that compounds in this class adopt O1 envelope conformations.

Chapter 3. Diastereoselective P-O bond cleavage of aryl-oxazaphospholidines.

3.1. Arbuzov approaches.

The Michaelis-Arbuzov rearrangement of (2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-(**26**) on reaction with alkyl halides was described in Chapter 1 as a route to optically active phosphine oxides (Schemes 10 & 12). Jugé *et al.*[55] demonstrated that (2*R*, 4*S*, 5*R*)-(**26**) underwent diastereoselective P-O bond cleavage on reaction with alkyl halides to give the corresponding (R_P)-phenyl(alkyl)phosphinamides with a net retention of configuration at phosphorus (Scheme 37 & Table 10).



(2*R*, 4*S*, 5*R*)-**26**

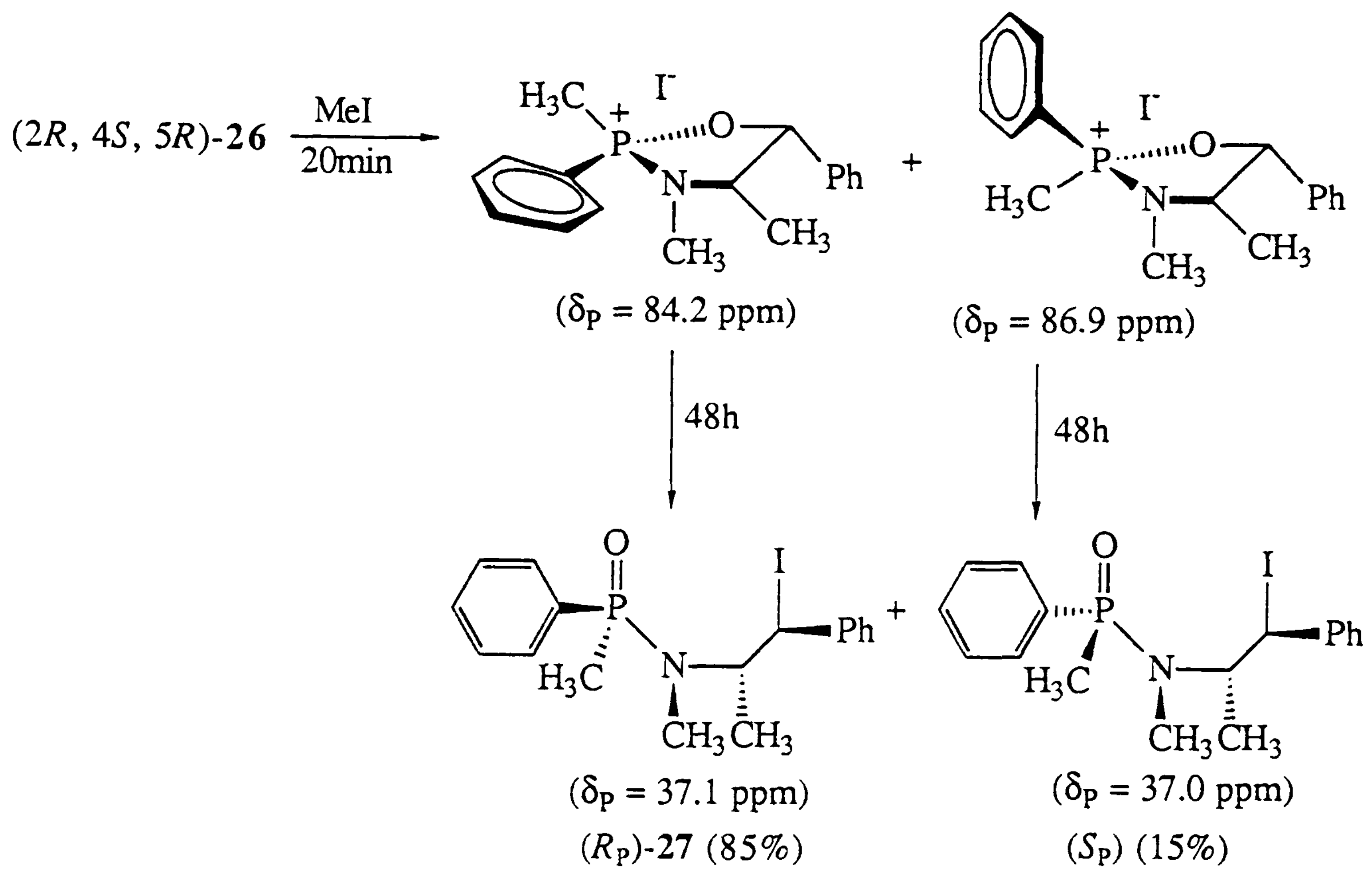
(R_P)

Scheme 37

Table 10. Diastreoselectivity for Scheme 37.

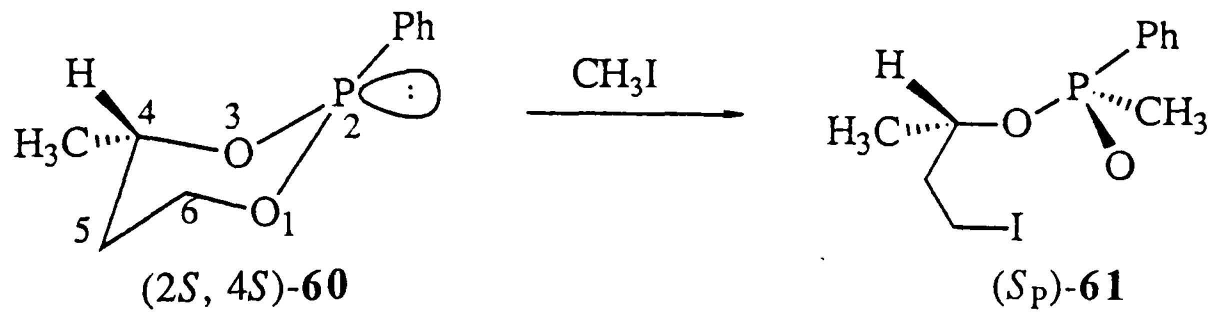
RX	Conditions	d.e.% (R_P)
MeI	24h/C_6H_6/RT	85
EtI	14min/80°C	70
PrI	24h/CH_2CH_2/RT	80
BnBr	1h/110°C	0
BnBr	72h/C_6H_6/RT	40
BnCl	30min/100°C	60

The loss of stereoselectivity in the phosphonium step was investigated by the same group using ^{31}P n.m.r. spectroscopy[57]. Arbuzov rearrangement of (2*R*, 4*S*, 5*R*)-(**26**) with methyl iodide resulted in the initial formation of a phosphonium species in a *c.a.* 4:1 (2*R* : 2*S*) ratio (Scheme 38). After two days at 25°C the phenyl(methyl)phosphinamides-(**27**, Schemes 10 & 38) were observed in the same ratio, thus the loss of diastereoselectivity does not occur in the second step. The loss of diastereoselectivity was reported to be due to the steric factors imposed by the oxazaphospholidine ring in (2*R*, 4*S*, 5*R*)-(**26**) which result in permutations of the methyl and phenyl groups in the transition state. The authors also drew comparisons with the borane complex-(2*R*, 4*S*, 5*R*)-(**31**, Scheme 13) in which the geometry of the O-P-N and C-P-N bond angles are nearly 90° and 120° respectively[79], however the solution conformation of (2*R*, 4*S*, 5*R*)-(**26**) would be considerably more flexible.



Scheme 38

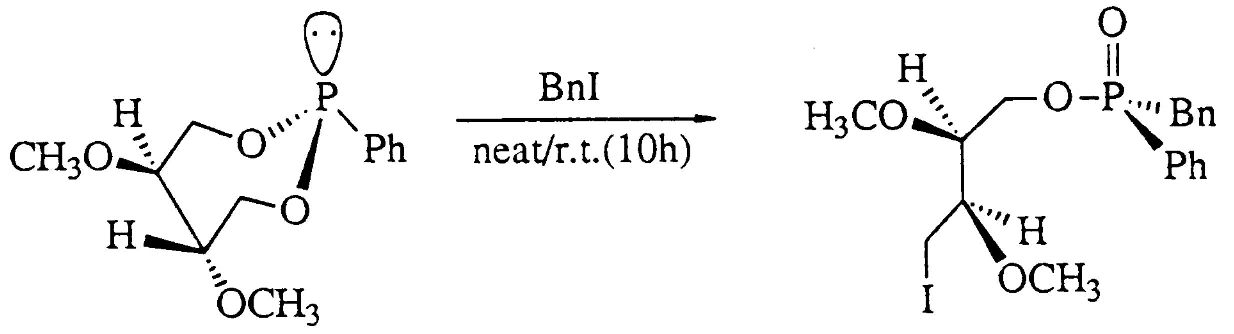
Other approaches using Arbuzov chemistry have also been adopted using chiral auxiliaries. Suga and co-workers[88] have utilized the diastereoselectivity in the ring opening of (2*S*, 4*S*)-4-methyl-2-phenyl-1,3,2-dioxaphosphorinane-(**60**, Scheme 39), prepared from dichlorophenylphosphine and (*S*)-1,3-butanediol.



Scheme 39

Arbuzov reaction of (S_P)-(**60**) with various alkyl halides yielded the P-O ring opened (S_P)-phenyl(alkyl)phosphinate-(**61**) diastereospecifically with retention of configuration at phosphorus (Scheme 39).

The same authors also studied the corresponding reactions with the (5*S*, 6*S*)-dimethoxy-2-phenyl-1,3,2-dioxaphosphacycloheptane-(**62**)[89] (Scheme 40), which under similar conditions gave poor diastereoselectivity for the ring-opened product (S_P)-(**63**) in the Arbuzov step. This was reportedly due to formation of a long-lived phosphonium ion intermediate allowing thermodynamic equilibrium, however the flexibility of the ring could be the dominant factor, as observed in the previously observed Arbuzov rearrangement of (2*R*, 4*S*, 5*R*)-(**26**) by Jugé *et al.*[57] (Scheme 38).



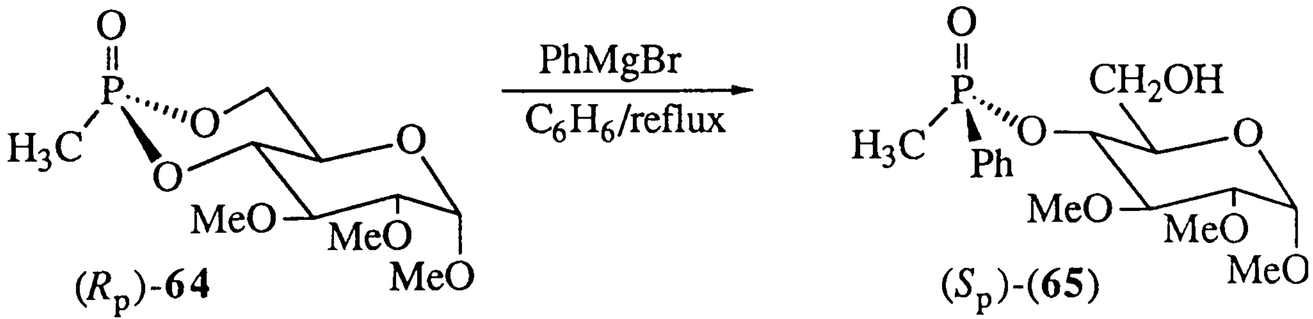
(5*S*, 6*S*)-**62**

(S_p)-(**63**)

Scheme 40

3.2. Nucleophilic displacement approaches.

Inch and co-workers[90] first demonstrated nucleophilic displacement from a resolved phosphinoglycoside-(**64**, Scheme 41) prepared from methylphosphonic difluoride and 2,3-di-*O*-methyl-α-D-glucopyranoside. P-O ring opening of (R_P)-(**64**) using phenylmagnesium bromide gave the corresponding (*S*)-methyl(phenyl)phosphonate-(**65**).



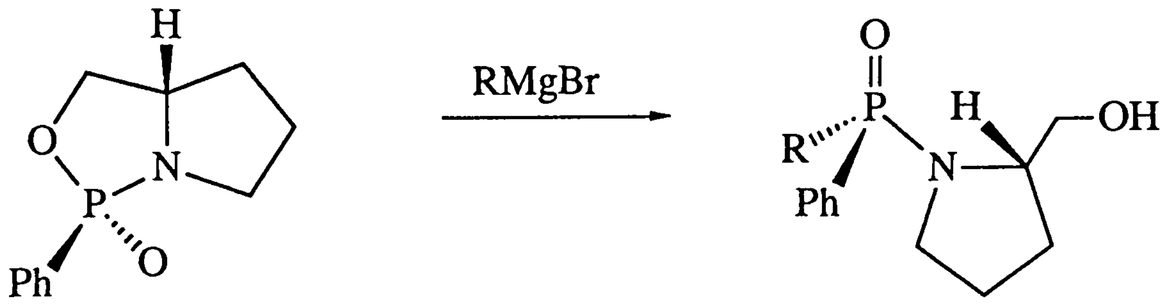
(R_p)-**64**

(S_p)-(**65**)

Scheme 41

Koizumi *et al.*[91] have utilized the diastereoselectivity in the ring opening of bicyclic oxazaphospholes derived from pyrrolidine and phenylphosphonic dichloride[92].

Resolved (*R*p)-2-phenyl-tetrahydropyrrolo-1,3,2-oxaphosphole-2-oxide-(**66**) reacted with alkyl and arylmagnesium bromides to afford the corresponding (*S*p)-amidate as a result of P-O bond cleavage with inversion of configuration at phosphorus (Scheme 42).



(*R*)-**66**

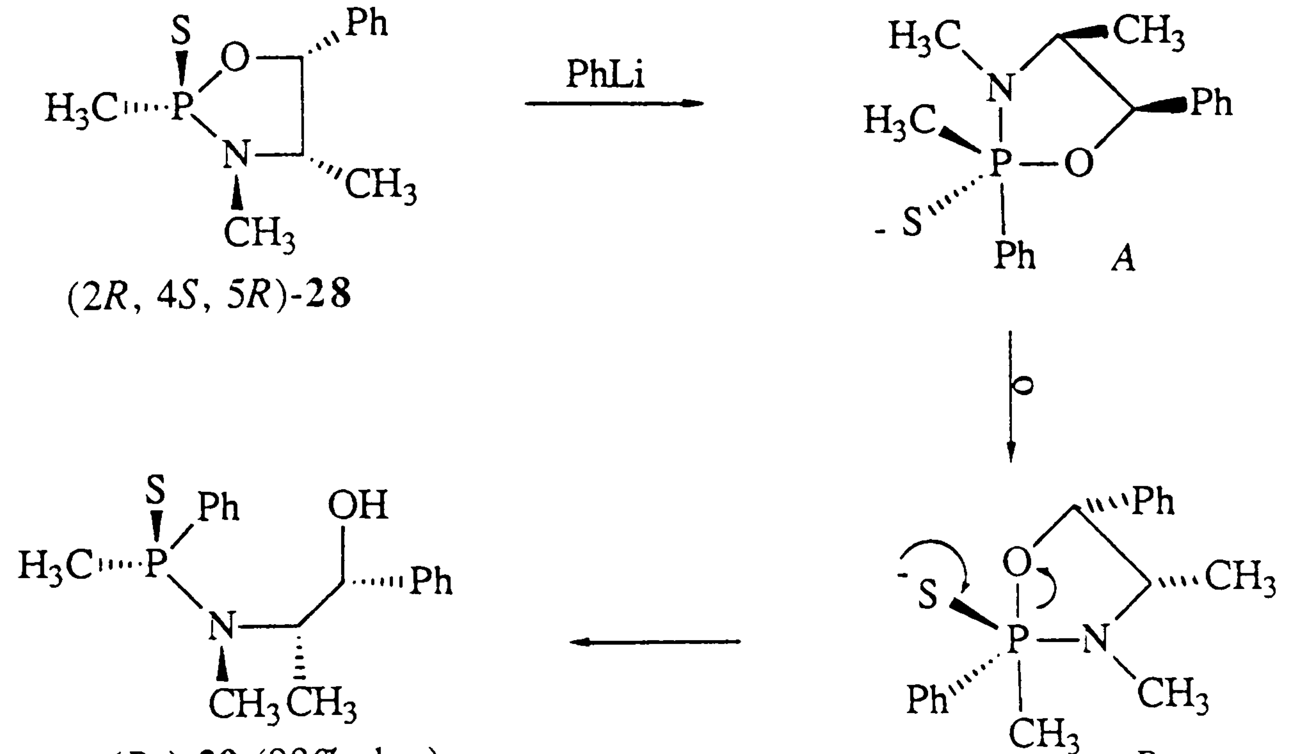
(*S*p)-**67**

Scheme 42

3.3. Nucleophilic P-O bond cleavage of oxazaphospholidines.

3.3.1. 2-Substituted-oxazaphospholidine-2-thiones.

As described in chapter 1, Inch and co-workers[58] demonstrated diastereoselectivity in the P-O cleavage of (2*R*, 4*S*, 5*R*)-2,3,4-trimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-thione-(**28**, Scheme 11) using phenyl lithium which proceeded with net retention of configuration at phosphorus to yield (*R*p)-methyl (phenyl)thiophosphinamide-(**29**) with 98% d.e.. The mechanism proposed for this reaction by Inch and co-workers[58] was attack of phenyl lithium opposite nitrogen to generate the trigonal bipyramidal intermediate (*A*, Scheme 43) which then pseudorotates to *B* followed by apical P-O bond cleavage to generate (*R*p)-(**29**).

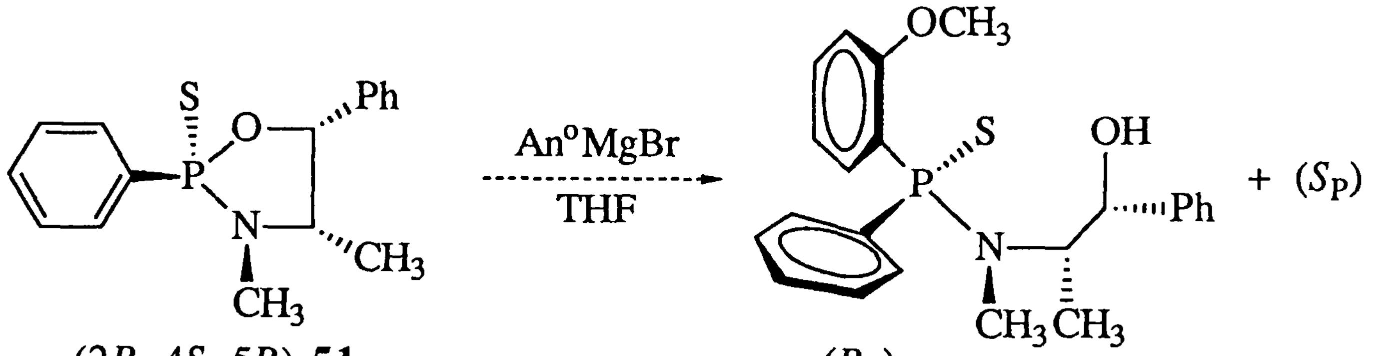


(2*R*, 4*S*, 5*R*)-**28**

(*R*p)-**29** (98% d.e.)

Scheme 43

Nucleophilic P-O bond cleavage of the phenyl analogue, (2*S*, 4*S*, 5*R*)-(**51**) prepared in this study was attempted under milder conditions than used by Inch and co-workers[63]. Reaction of diastereomerically pure (2*S*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphopholidine-2-thione-(**51**) with *ortho*-anisylmagnesium bromide in THF at -30°C, followed by stirring overnight at ambient temperature, resulted in the isolation of starting material (scheme 44).



(2*R*, 4*S*, 5*R*)-**51**

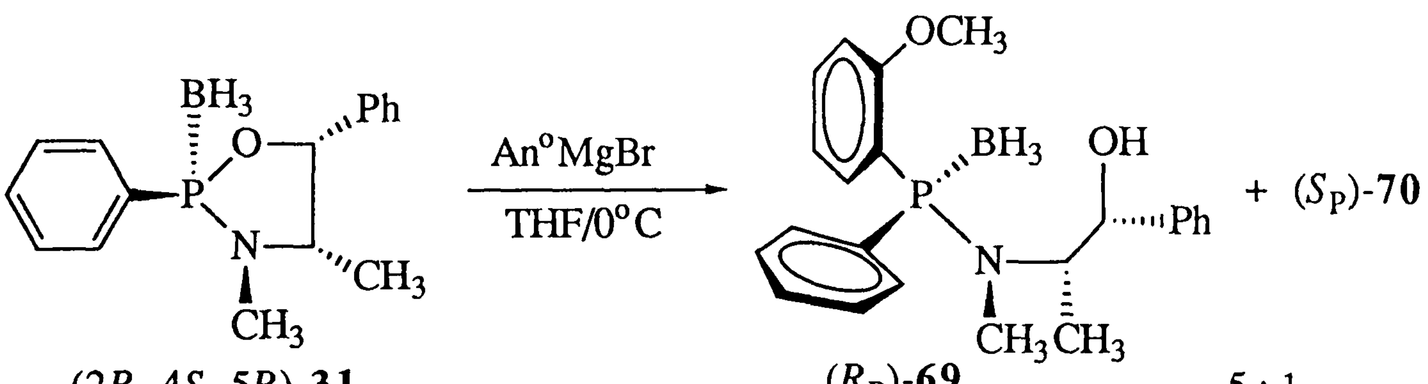
(R_P)

Scheme 44

Even after extensive optimisation of reaction conditions (concentration, solvent and temperature) none of the ring-opened product-(**68**) was formed. Since diastereomerically pure (2*S*, 4*S*, 5*R*)-(**51**) could only be isolated after chromatographic separation the aryl lithium route used by Inch and co-workers[58] was avoided.

3.3.2. 2-phenyl-oxazaphospholidine-2-borane-(31).

Reaction of *ortho*-anisylmagnesium bromide with diastereomerically pure (2*R*, 4*S*, 5*R*)-oxazaphospholidine-2-borane-(**31**) afforded a *ca.* 5:1 mixture of (R_P) and (S_P)-*ortho*-anisyl(phenyl)phosphine boranes-(**69** & **70**, Scheme 45). The ratio of diastereoisomers was determined by ^{1}H n.m.r. spectroscopy (200 MHz) and direct comparison of this data with later work (*vide infra*).



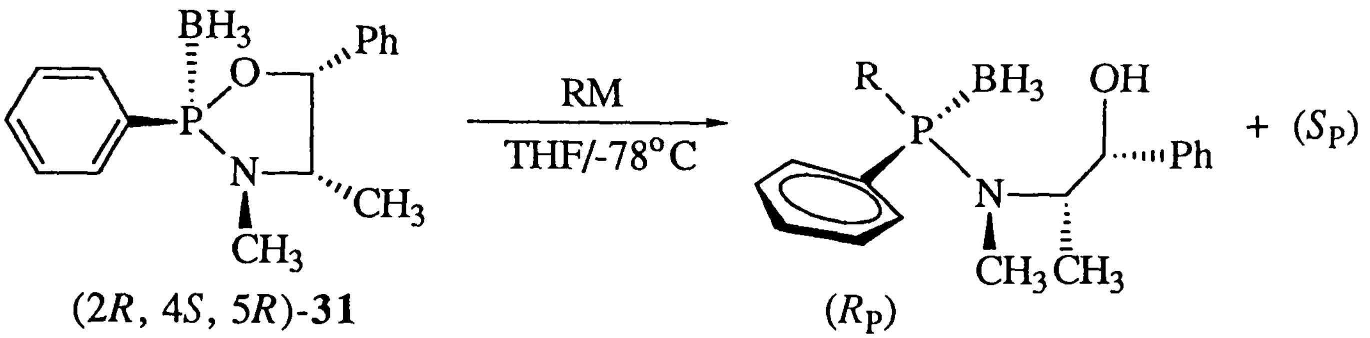
(2*R*, 4*S*, 5*R*)-**31**

(R_P)-**69**

5 : 1

Scheme 45

After this preliminary work was published[59] Jugé *et al.*[60] published similar results confirming the poor diastereoselectivity in the nucleophilic P-O cleavage of (2*R*, 4*S*, 5*R*)-(**31**), in view of this no attempt was made to separate the diastereomeric mixture. These authors improved upon this diastereoselectivity using alkyl and aryllithium reagents which reacted with (2*R*, 4*S*, 5*R*)-oxazaphospholidine-2-borane-(**31**) to afford the corresponding (*R*P)-phenyl(aryl or alkyl)phosphine boranes-(Scheme 46) with complete diastereoselectivity (Table 11).



(2*R*, 4*S*, 5*R*)-**31**

(R_P)

Scheme 46

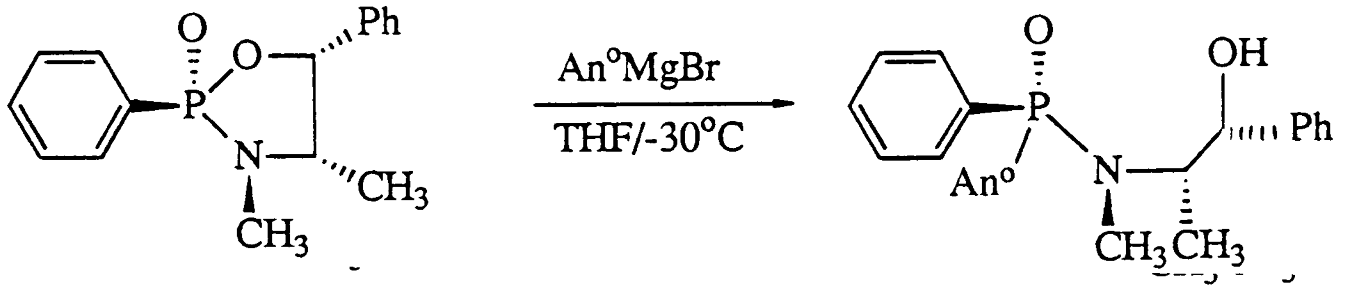
Table 11. Ring opening of (2*R*, 4*S*, 5*R*)-(**31**) with RM.

RM	%Yield	%d.e.(R_P)
MeLi	95	100
MeMgI	90	100
n-ButLi	95	100
An^{o}MgBr	30	40
An^{o}Li	95	100
2-NaphLi	95	100

3.3.3. 2-Aryl-oxazaphospholidine-2-oxides.

Reaction of diastereochemically pure (2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-oxide-(**49**) with a 1.4 molar equivalent of *ortho*-anisylmagnesium bromide in THF at -30°C for 2 h and then ambient temperature for 18 h afforded, after aqueous work-up, a white solid. Analysis of this crude product by ^1H n.m.r. spectroscopy (200MHz) showed that regiospecific P-O bond cleavage had occurred to generate (R_P)-*ortho*-anisyl(phenyl)phosphinamide-(**71**) with none of the minor diastereoisomer detected. Despite this, in view of the accuracy of the n.m.r.

spectrometer the diastereomeric excess can only be quoted as ≥96% (Scheme 47). The compound was easily purified by recrystallisation from THF which afforded diastereochemically pure (*R*P)-(**71**) as a white crystalline solid in 70% yield.



(2*R*, 4*S*, 5*R*)-**49**

(*R*P)-**71** (96% d.e.)

Scheme 47

This observation has precedents from the work of Inch[58] in the reaction of (2*R*, 4*S*, 5*R*)-(**28**) with phenyl lithium which occurred with retention of configuration (Scheme 43), and Koizumi's work[91] on the reaction of the bicyclic oxazaphosphole-(**66**) with organo-magnesium reagents which proceeded with inversion of configuration (Scheme 42).

In view of these contrasting results, the structure of (*R*P)-(**71**) was determined by single-crystal X-ray diffraction studies. Selected bond lengths are given in Table 12, bond angles in Table 13. The molecular structures of (2*R*, 4*S*, 5*R*)-(**49**) and (*R*P)-(**71**) (Figure 13) show clearly that the nucleophilic P-O cleavage occurs with retention of configuration at phosphorus. This confirms the configurational assignment made by Inch and co-workers[58] but in contrast to that proposed by Koizumi *et al.*[91], furthermore the stereochemical course here is opposite to that for the open-chained phosphinates prepared by Mislow[51]. The structure of (*R*P)-(**71**) also shows no hydrogen-bonding between the OH moiety and the oxygen residing on phosphorus although there is free rotation about the P-N and N-C(8) bonds. Full experimental details of the data collection and refinement are presented in Chapter 6, together with with complete structure factor, bond angle and bond length tables in the Appendix.

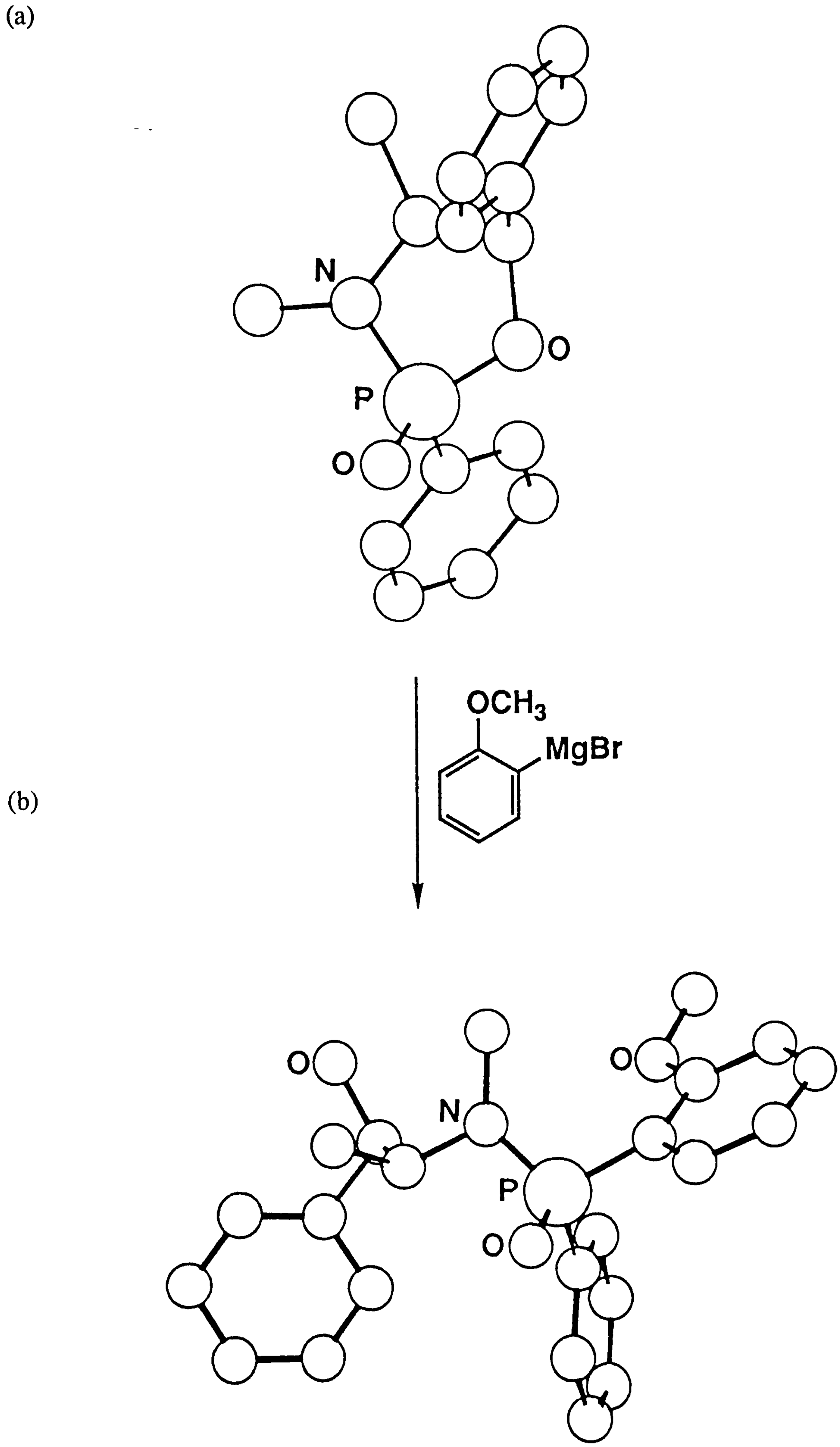


Figure 13. X-Ray crystal structures of (a): (2*R*, 4*S*, 5*R*)-(**49**) and (b): (R_{P})-(**71**) demonstrating retention of configuration in the nucleophilic P-O ring-opening step.

Table 12. Selected bond lengths (Å) with e.s.d.'s in parentheses for (*R*P)-(**71**).

Atom	Bond lengths (A)
P(1)-O(2)	1.490(5)
P(1)-N(1)	1.632(7)
P(1)-C(17)	1.40(1)
O(1)-C(7)	1.791(8)
O(1)-H(26)	1.01
O(3)-C(22)	1.36(1)
O(3)-C(23)	1.40(1)
N(1)-C(8)	1.47(1)
N(1)-C(10)	1.49(1)

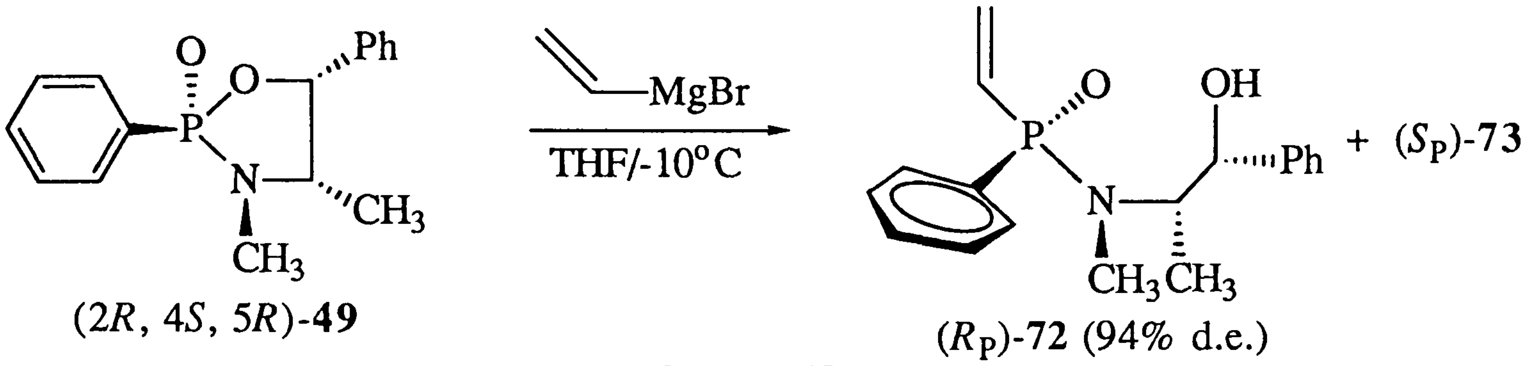
Table 13. Selected bond angles (°) with e.s.d.'s in parentheses for (*R*P)-(**71**).

Atoms	Bond angles (°)
N(1)-P(1)-O(2)	115.0(4)
C(11)-P(1)-O(2)	107.2(4)
C(11)-P(1)-N(1)	105.7(4)
C(17)-P(1)-O(2)	110.3(4)
C(17)-P(1)-N(1)	110.3(4)
C(17)-P(1)-C(11)	108.0(4)
H(26)-O(1)-C(7)	97.8(5)
C(23)-O(3)-C(22)	118.8(8)
C(8)-N(1)-P(1)	113.8(6)
C(10)-N(1)-P(1)	123.4(6)
C(10)-N(1)-C(8)	118.2(7)

After the above results were published[59] Jugé *et al.*[61] described a crystallographic study of the stereochemistry of the borane route (Scheme 47). The structure of the (2*R*, 4*S*, 5*R*)-2-phenyl-oxazaphospholidine-2-borane-(**31**) complex[79] was discussed in Chapter 2, although the coordinates of the ring-opened product-(*R*P)-(**69**) have not been published.

The scope of the nucleophilic P-O ring cleavage in the phenyl-oxazaphospholidine-2-oxide series was further extended by reaction of (2*R*, 4*S*, 5*R*)-(**49**) with a 1.2 molar equivalent of vinylmagnesium bromide. Analysis of the crude ^{1}H n.m.r.

spectrum showed that (*R*P)-phenyl(vinyl)phosphinamide-(**72**) had been formed also as a result of stereoselective P-O bond cleavage with 94% d.e. (Scheme 48). The minor (*S*P)-(**73**) diastereoisomer was easily removed by recrystallisation from THF to afford the major, (*R*P)-(**72**) as a single diastereoisomer in 80% yield.



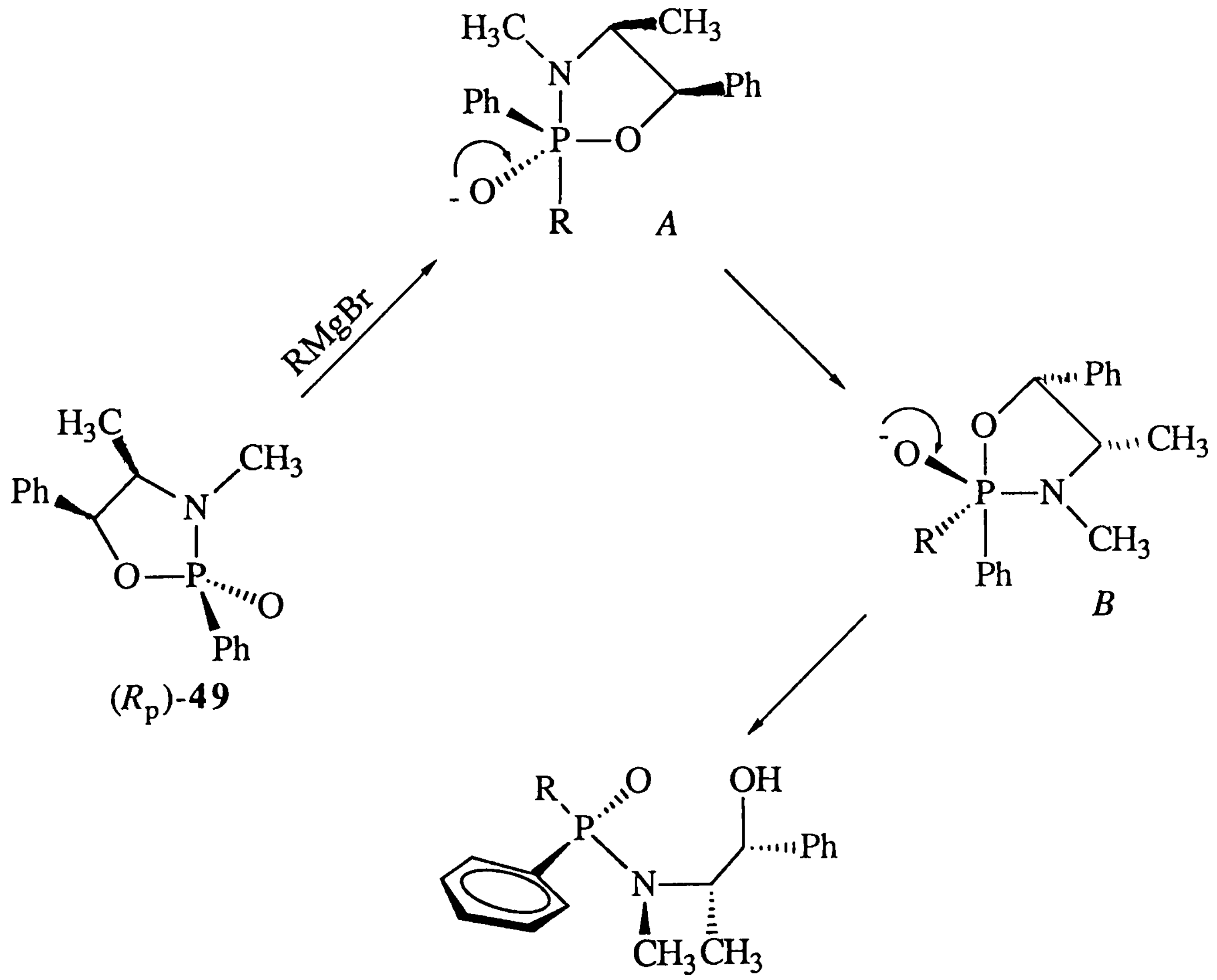
(2*R*, 4*S*, 5*R*)-**49**

(*R*P)-72 (94% d.e.)

Scheme 48

It was found for the reaction in Scheme 48 that the temperature was critical since the vinyl moiety in (*R*P)-(**72**) was susceptible to nucleophilic attack, performing the reaction <-10°C gave the desired compound regiospecifically.

A possible mechanism for the observed stereochemical course in Schemes 47 and 48 is presented in Scheme 49.



Scheme 49

Nucleophilic attack opposite nitrogen to generate the trigonal bipyramidal intermediate *A* , which then pseudorotates to *B*, apical P-O bond cleavage then occurs to generates the phosphinamide with retention of configuration at phosphorus. This has precedent in Inch's work on the P-O bond cleavage of (2*R*, 4*S*, 5*R*)-(**28**, Scheme 43).

The oxazaphospholidine-2-oxide-(**49**) reacts with organomagnesium reagents in opposite stereochemical sense to the open-chain examples of Mislow. The reasons for this stereochemical divergence are not well understood but both pathways involve a trigonal bipyramidal intermediate, however in the ring-opened derivatives there is no opportunity for pseudorotation and hence the stereochemistry proceeds with inversion of configuration at phosphorus (Figure 50).

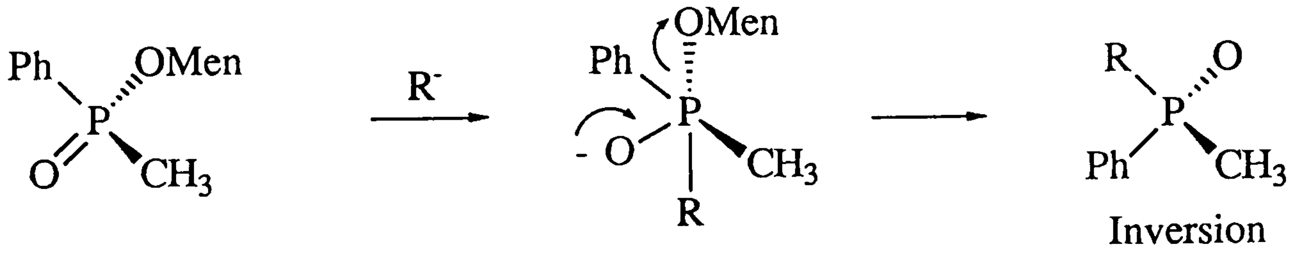
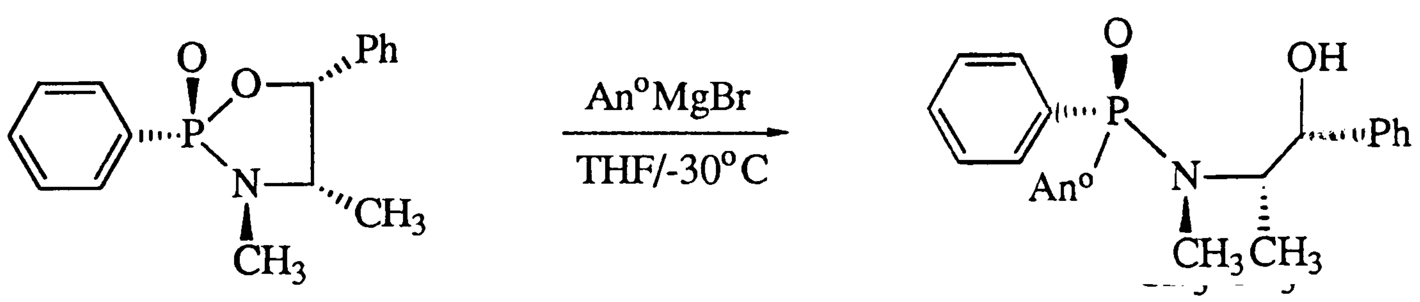


Figure 50

The above mechanisms are consistent with the generally assumed view[58] that bond making and bond breaking processes at P(V) occur at apical positions of the trigonal bipyramidal intermediate. Reactions which proceed with retention of configuration involve a pseudorotation while inversion processes do not. Moreover the various processes involved are clearly a function of the substituents at phosphorus and are insufficiently understood for confident predictions to be made concerning the stereochemical outcome of substitution reactions at phosphorus.

Reaction of the minor, (2*S*, 4*S*, 5*R*)-(**50**) diastereoisomer with *ortho*-anisylmagnesium bromide, under identical conditions to the major diastereoisomer, afforded the corresponding (S_P)-(**73**) diastereoisomer as a result of regiospecific P-O bond cleavage in 80% yield and with >96% d.e. (Scheme 51).

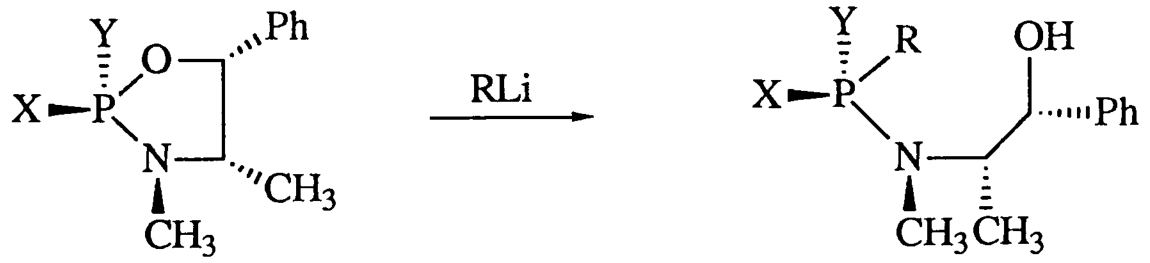


(2*S*, 4*S*, 5*R*)-**40**

(*S*P)-**53** (>98% d.e.)

Scheme 51

This contrasts with Inch's results for the ring opening of (2*S*, 4*S*, 5*R*)-2,3,4-trimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-thione-(**74**) with phenyl lithium which gave only 70% of the retention product, (*S*P)-methyl phenylthiophosphinate (Scheme 52 & Table 14).



X = CH_3 : Y = S: (2*S*, 4*S*, 5*R*)-**74**
X = S : Y = CH_3: (2*R*, 4*S*, 5*R*)-**28**

Scheme 52

More surprisingly, reaction of (2*S*, 4*S*, 5*R*)-(**74**) with alkyl lithium reagents proceeds with predominant inversion of configuration at phosphorus, while the corresponding reactions with (2*R*, 4*S*, 5*R*)-(**28**) occur with almost complete retention of configuration (Table 14).

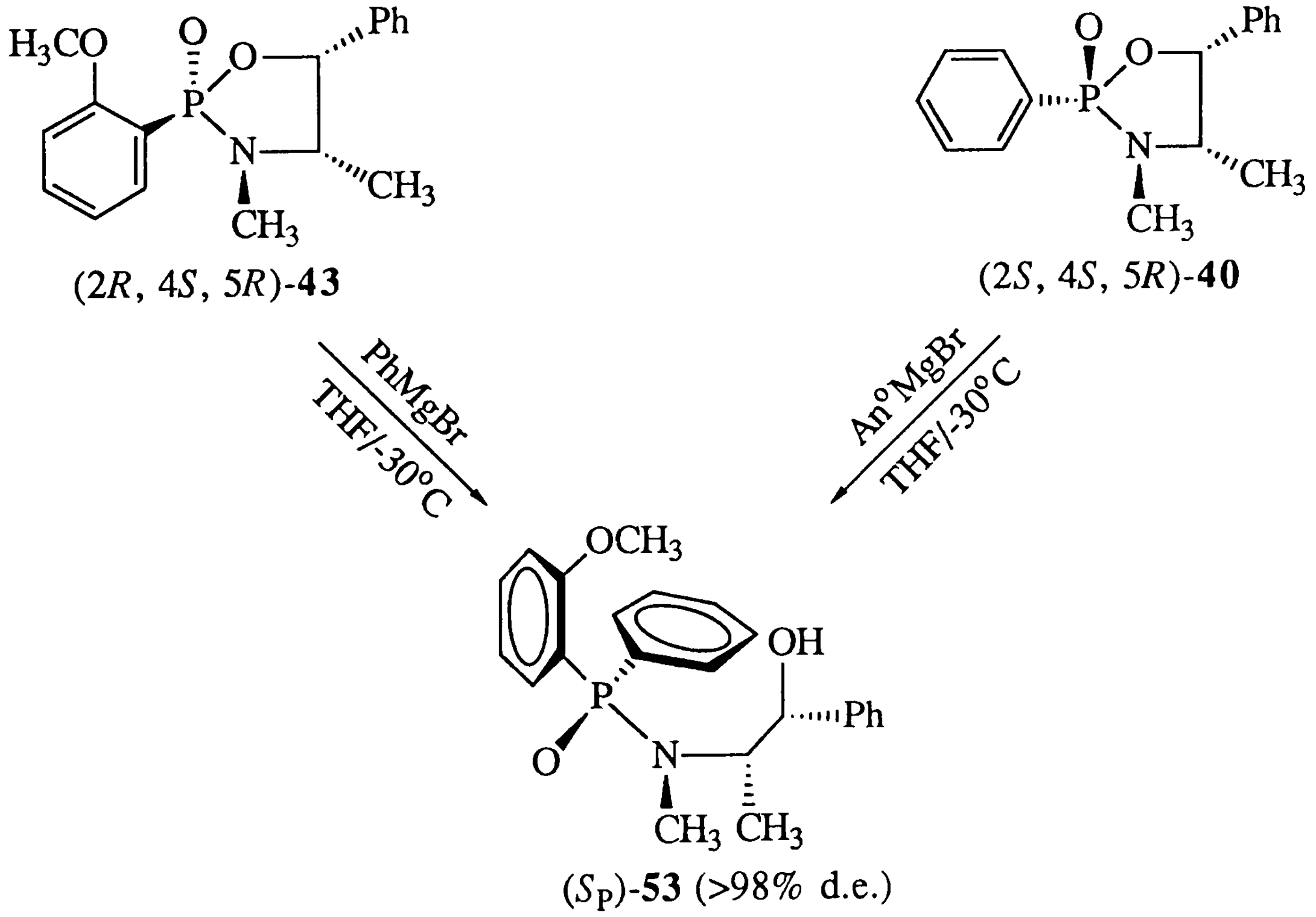
Table 14. Stereochemistry for the reactions in Scheme 52.

Starting Material	Reactants		
	PhLi Product ratio (*R*P):(*S*P)-(**24**)	*n*-BuLi Product ratio (*R*P):(*S*P)	EtLi Product ratio (*R*P):(*S*P)
(2*R*, 4*S*, 5*R*)-(**23**)	98:2	95:5	95:5
(2*S*, 4*S*, 5*R*)-(**23**)	30:70	70:30	75:25

No explanation was provided for these results, however a steric effect is probably in operation in the case of the (2*S*, 4*S*, 5*R*)-(**28**) diastereoisomer in which the conformation of the methyl-oxazaphospholidine ring must be considerably different to its phenyl analogue, the structure of which was confirmed by single-crystal X-ray diffraction studies (Figure 10).

Up to this point the nucleophilic P-O cleavage of (2*R*, 4*S*, 5*R*)-(**49**) had provided precursors to homochiral phosphine oxides with two of the three P-C bonds in place with defined stereochemistry at phosphorus. In order to extend the scope of this procedure to the synthesis of other biarylphosphinamides the chemistry of (2*R*, 4*R*, 5*S*)-2-(*ortho*-anisyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(**55**) was investigated.

Treatment of (2*R*, 4*S*, 5*R*)-(**55**) with phenylmagnesium bromide in THF at -30°C (2h) then stirring overnight afforded (*S*P)-(**73**, Scheme 53) which was the product of the reaction between (2*S*, 4*R*, 5*S*)-(**50**) and *ortho*-anisylmagnesium bromide (Scheme 50). The reaction also proceeded with >96% d.e. and the product was purified by recrystallisation to afford (*S*P)-(**73**) in 96% yield. This served to confirm the configurational assignment of (2*S*, 4*R*, 5*S*)-(**43**), and its precursor since the absolute configuration of (*R*P)-(**71**) had been determined by single-crystal X-ray diffraction studies (Figure 13).



(2*R*, 4*S*, 5*R*)-**43**

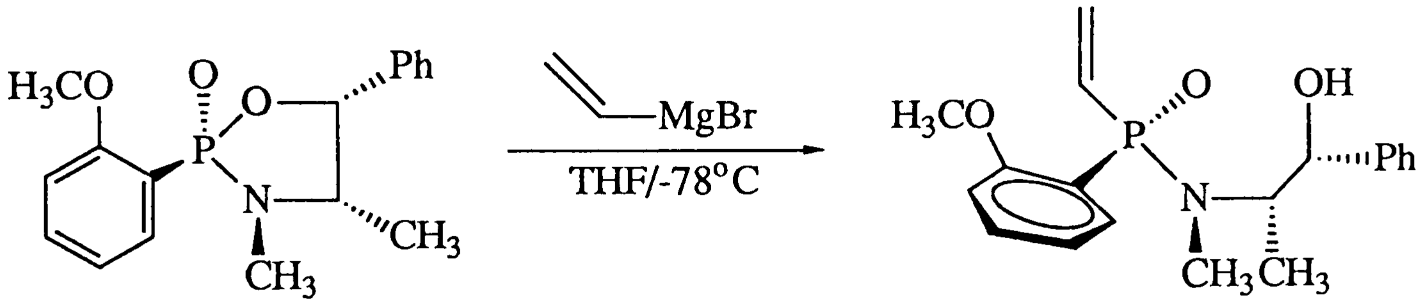
(2*S*, 4*S*, 5*R*)-**40**

(*S*P)-**53** (>98% d.e.)

Scheme 53

A similar reactivity pattern for (R_P)-(**55**) emerged for the stereoselective P-O bond cleavage using other Grignard reagents under milder condition than used by Inch and Jugé.

Reaction of (2*R*, 4*S*, 5*R*)-(**55**) with a 1.2 molar equivalent of vinylmagnesium bromide afforded (S_P)-*ortho*-anisyl(vinyl)phosphinamide-(**75**) with 94% d.e. (Scheme 54). Recrystallisation of the crude product from THF gave (R_P)-(**75**) as a white crystalline solid in 80% yield.

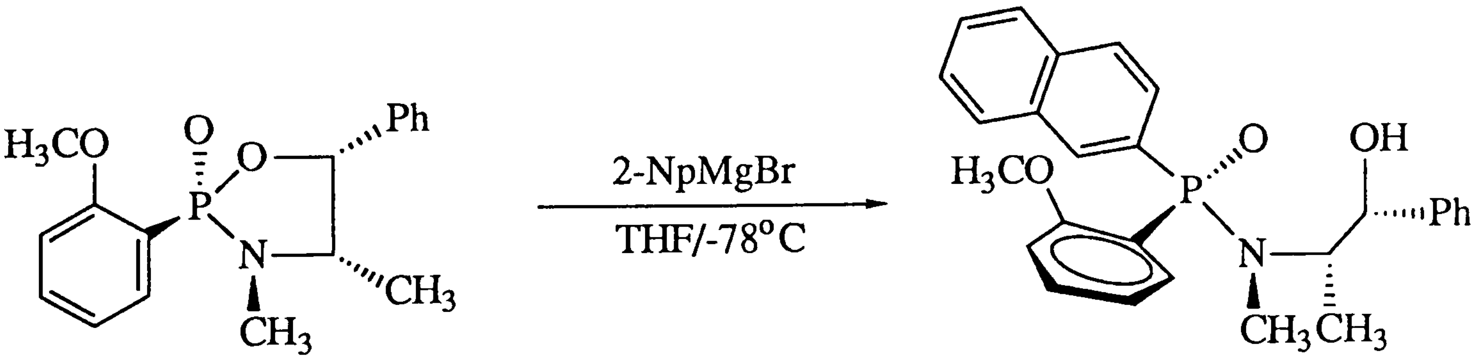


(2*R*, 4*S*, 5*R*)-**55**

(S_P)-**75** (94% d.e.)

Scheme 54

P-O bond cleavage of (2*R*, 4*S*, 5*R*)-(**55**) using 2-naphthylmagnesium bromide required a 2.2 molar equivalence of the Grignard reagent for complete conversion. Analysis of the crude product by ^{1}H n.m.r. spectroscopy showed (R_P)-(**76**) had formed essentially as a single diastereoisomer with >96% d.e. (Scheme 55). The product was recrystallised from THF to afford (R_P)-(**76**) as a white crystalline solid in 81% yield.

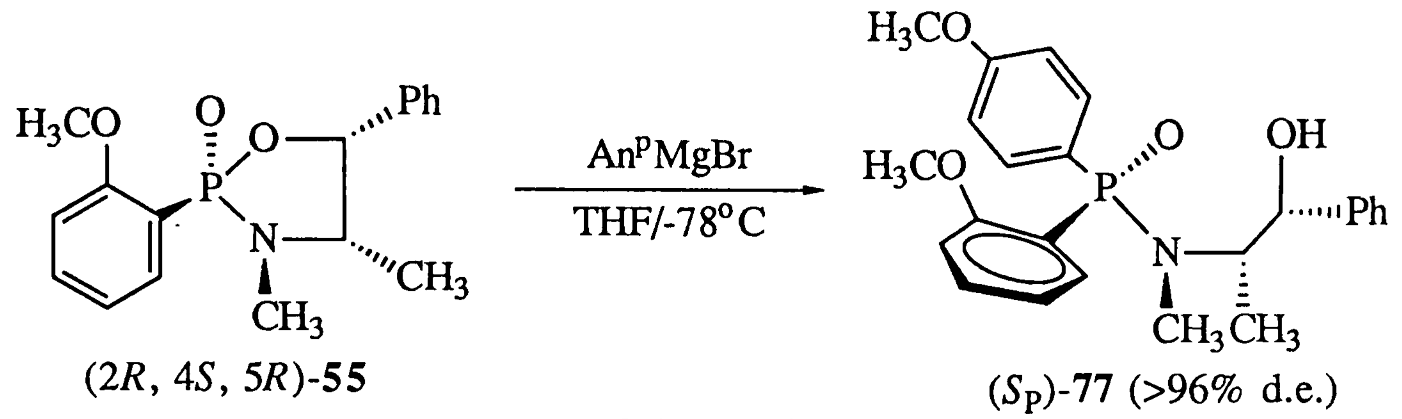


(2*R*, 4*S*, 5*R*)-**55**

(S_P)-**76** (>96% d.e.)

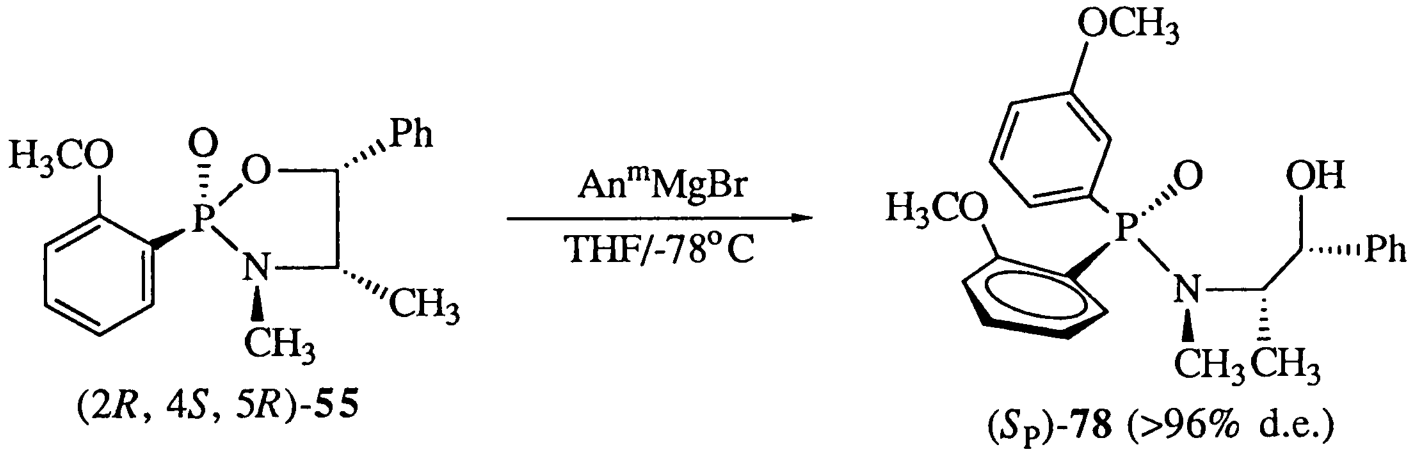
Scheme 55

Reaction of (2*R*, 4*S*, 5*R*)-(**55**) with a 1.2 molar equivalent of *para*-anisylmagnesium bromide afforded (R_P)-*ortho*-anisyl(*para*-anisyl)phosphinamide-(**77**) with >96% d.e., as determined by 200MHz ^{1}H n.m.r. spectroscopy (Scheme 56). Recrystallisation of the crude product from THF gave (R_P)-(**77**) as a white crystalline solid in 82% yield.



Scheme 56

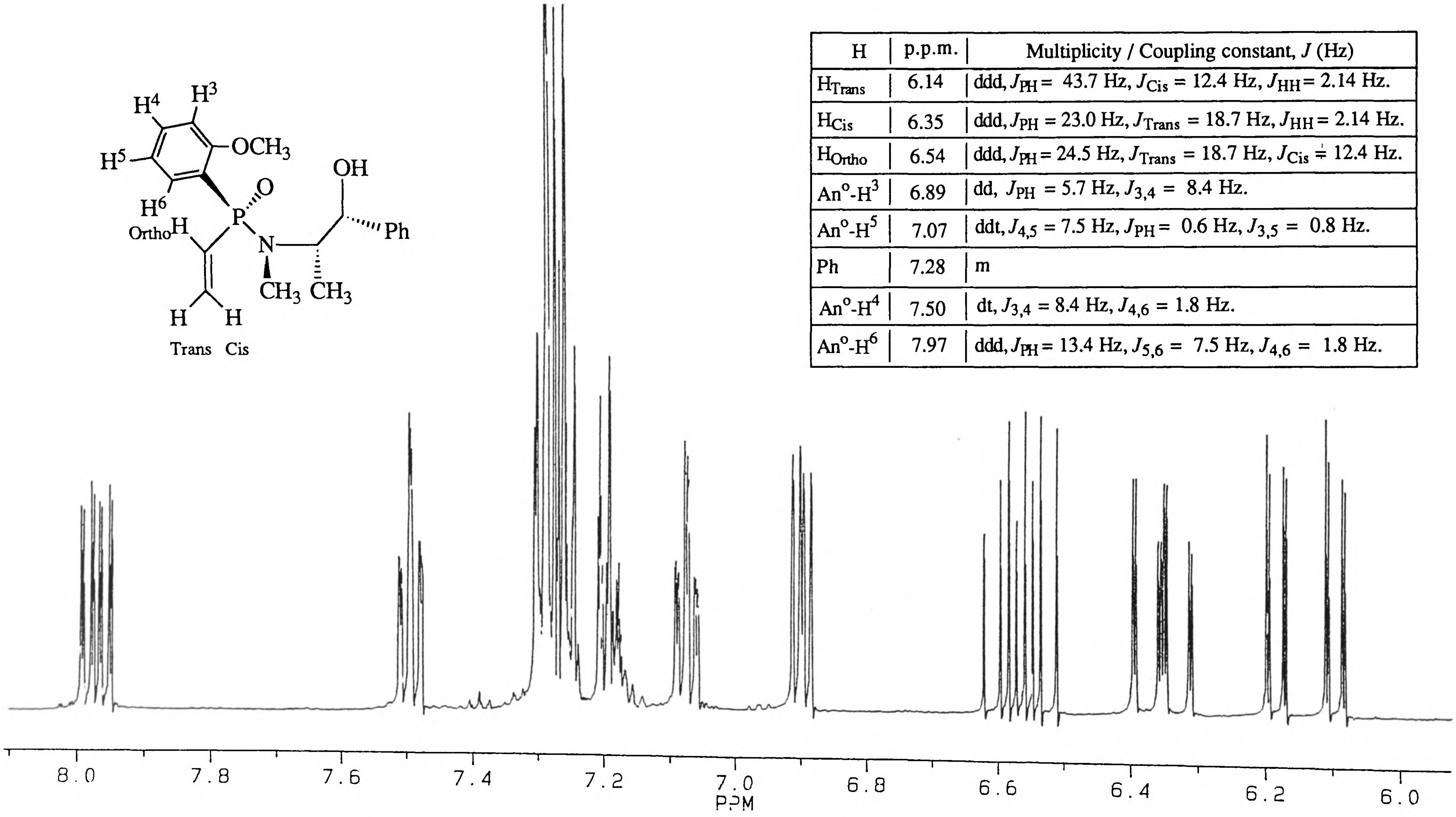
Similarly, reaction of (2*R*, 4*S*, 5*R*)-(**55**) with a 1.1 molar equivalent of *meta*-anisylmagnesium bromide afforded (*R*P)-*ortho*-anisyl(*meta*-anisyl)phosphinamide-(**78**) with >96% d.e., as determined by ^{1}H n.m.r. spectroscopy (Scheme 57). Recrystallisation of the crude product from THF gave (*R*P)-(**78**) as a white crystalline solid in 76% yield.



Scheme 57

3.4. ^{1}H n.m.r. characterisation of arylphosphinamides.

The ^{1}H n.m.r. spectrum (500 MHz; CDCl$_3$) of (*S*P)-(**75**) is reproduced in Figure 14 between 6.0 and 8.2 p.p.m.. The vinyl proton resonances are centered between 6.0 and 6.7 p.p.m. and can be regarded as an ABX splitting pattern, the ddd splitting pattern for each of the three distinct proton environments were assigned from their ^{31}P-^{1}H and ^{1}H-^{1}H$_{Trans}$ coupling constants. Where appropriate the ^{1}H n.m.r. spectra for other arylphosphinamides were assigned by correlation with this data and/or by COSY techniques.



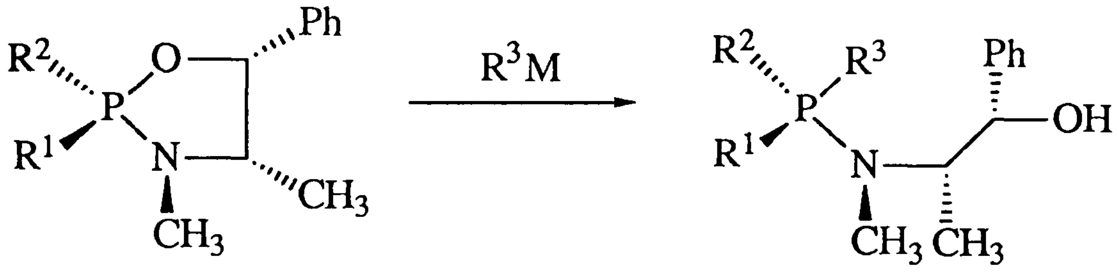
H	p.p.m.	Multiplicity / Coupling constant, J (Hz)
H_{Trans}	6.14	ddd, J_{PH} = 43.7 Hz, J_{Cis} = 12.4 Hz, J_{HH} = 2.14 Hz.
H_{Cis}	6.35	ddd, J_{PH} = 23.0 Hz, J_{Trans} = 18.7 Hz, J_{HH} = 2.14 Hz.
H_{Ortho}	6.54	ddd, J_{PH} = 24.5 Hz, J_{Trans} = 18.7 Hz, J_{Cis} = 12.4 Hz.
An°-H^3	6.89	dd, J_{PH} = 5.7 Hz, $J_{3,4}$ = 8.4 Hz.
An°-H^5	7.07	ddt, $J_{4,5}$ = 7.5 Hz, J_{PH} = 0.6 Hz, $J_{3,5}$ = 0.8 Hz.
Ph	7.28	m
An°-H^4	7.50	dt, $J_{3,4}$ = 8.4 Hz, $J_{4,6}$ = 1.8 Hz.
An°-H^6	7.97	ddd, J_{PH} = 13.4 Hz, $J_{5,6}$ = 7.5 Hz, $J_{4,6}$ = 1.8 Hz.

Figure 14. ^1H n.m.r. spectrum (500 MHz; $CDCl_3$) of (S_P)-*ortho*-anisyl(vinyl)phosphinamide-(**75**).

3.5. Conclusion.

Up to this point a range of novel phenyl(aryl)- biaryl- and aryl(vinyl)-phosphinamides had been prepared by nucleophilic P-O bond cleavage of aryl-oxazaphospholidine-2-oxides. The displacement is regiospecific and highly stereoselective, with >98% d.e. observed in all cases. The compounds were all subsequently obtained diastereomerically pure as white, air-stable crystalline solids. The stereochemical assignments were made on the basis of X-ray crystallography from which correlation of n.m.r. data was used to assign new compounds. The phosphinamides prepared in this study are collated in Table 15.

Table 15. Summary of nucleophilic P-O bond cleavage of oxazaphospholidines.



Precursor	R^1	R^2	R^3M	%Yield	Product ratio (d.e.)		Reference
					(S_P)	(R_P)	
(R_P)-(**28**)	CH_3	S	PhLi	-	2	98	58
(S_P)-(**74**)	S	CH_3	PhLi	-	30	70	58
(S_P)-(**51**)	Ph	S	An^{o}MgBr	0	0	0	This work
(R_P)-(**31**)	Ph	BH_3	An^{o}MgBr	60	17	83	This work
(R_P)-(**31**)	Ph	BH_3	An^{o}Li	-	0	100	60
(R_P)-(**49**)	Ph	O	An^{o}MgBr	70	< 4	> 96	This work
(R_P)-(**49**)	Ph	O	$CH_2CHMgBr$	80	< 6	> 94	This work
(S_P)-(**50**)	O	Ph	An^{o}MgBr	80	> 96	<4	This work
(R_P)-(**55**)	An^o	O	PhMgBr	96	> 96	< 4	This work
(R_P)-(**55**)	An^o	O	$CH_2CHMgBr$	80	> 94	< 6	This work
(R_P)-(**55**)	An^o	O	2-NpMgBr	81	> 96	< 4	This work
(R_P)-(**55**)	An^o	O	An^{p}MgBr	82	> 96	< 4	This work
(R_P)-(**55**)	An^o	O	An^{m}MgBr	76	> 96	< 4	This work

The diastereoselectivities in the P-O bond cleavage of the oxazaphospholidines in Table 15 are a consequence of the different electronic and steric effects imposed by these substituents and the nature of the nucleophile. For the oxazaphospholidine-2-oxides P-O bond cleavage is most efficiently carried out using milder Grignard reagents whereas for the corresponding borane-(**31**) and thiones-(**28** & **74**) analogues this is best effected using organolithium reagents. This might be rationalised in terms of coordination of magnesium to oxygen in the former case prior to nucleophilic attack which is inoperative in the latter two cases.

Chapter 4. Synthesis of homochiral arylphosphine oxides.

4.1. Introduction.

Prior to the synthesis of the highly effective homogeneous hydrogenation catalyst, $[Rh(1,5\text{-}COD)(R,R)\text{-}(DIPAMP)\text{-}(\mathbf{11})]^+BF_4^-$ homochiral monophosphine complexes had enjoyed some success in asymmetric synthesis. For example, the rhodium(I) complex of (*S*)-CAMP-(**3**) catalysed the reaction in Figure 2 with 89% e.e. (Table 1). It was also used in the first commercial synthesis of L-DOPA (Scheme 3)[93]. The development of new homochiral arylphosphines is particularly important as far as iridium catalysis is concerned, since the most efficient iridium catalysts for olefin reduction are cationic bulky monophosphine complexes[94].

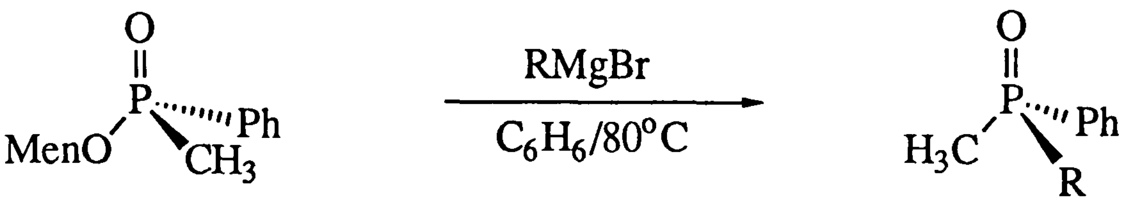
However, almost without exception, the synthesis of homochiral monophosphines has been carried out in eventual pursuit of enatiomerically pure bisphosphines, especially (*R*, *R*)-DIPAMP-(**11**). The synthetic sequence, described in Chapter 1.5 involved Cu(II) promoted oxidative coupling of homochiral monophosphine oxides (Scheme 4) to afford the corresponding bisphosphine oxide which can be stereoselectively reduced. The aim of this work was to develop a general synthetic route to homochiral monophosphines and develop methodology to new bisphosphine ligands.

This chapter describes the synthesis of a range of homochiral arylphosphine oxides in high chemical and optical purity using the diastereomerically pure arylphosphinamides prepared in Chapter 3, a brief summary of previous work follows.

4.2. Arbuzov approaches.

Many of the early approaches to homochiral arylphosphine oxides involved Arbuzov chemistry using (-)-menthol as a chiral auxiliary, this was followed by exocyclic P-O bond cleavage under somewhat forcing conditions, resulting in some cases with a loss in enantioselectivity. However, the most major drawback of this route has been the separation of diastereomeric mixtures, resulting in overall poor yield.

Mislow and co-workers[51] were the pioneers of the Arbuzov approach to the synthesis of homochiral alkyl- and arylphosphine oxides using resolved (S_P)-methyl menthyl (phenyl)phosphinate-(**79**, Scheme 58 & Table 16).



(S_P)-**79**

(S)-**19** : R = An°
(R)-**80** : R = C_2H_5
(R)-**81** : R = Bn
(R)-**82** : R = n-C_3H_7

Scheme 58

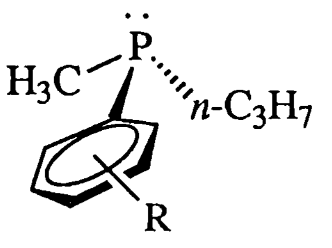
The route to (R)-(**19**, Scheme 58) was subsequently improved upon by Knowles in his first approach[44] to (R, R)-DIPAMP-(**11**). Reaction of resolved (R)-(**79**) with *ortho*-anisylmagnesium bromide afforded homochiral (R)-(**19**, Table 16). In a later approach[47] to the commercial synthesis of (R, R)-DIPAMP-(**11**), Knowles used methyl menthyl(*ortho*-anisyl)phosphinates-(**17** & **18** Scheme 4) from which the desired (Sp)-(**18**) diastereoisomer was obtained more readily by recrystallisation relative to the corresponding phenyl analogue-(Sp)-(**79**, Scheme 58), this was reported to be due to the poor solubility of the (Rp)-(**17**) diastereoisomer in Scheme 4. Since many of the routes to arylphosphine oxides have included the synthesis of several key compounds their enantioselectivities are directly compared in Table 16.

Table 16. Optical and chemical purities of (R)-alkyl- and aryl(methyl)phenylphosphine oxides; $CH_3R(Ph)P{=}O$.

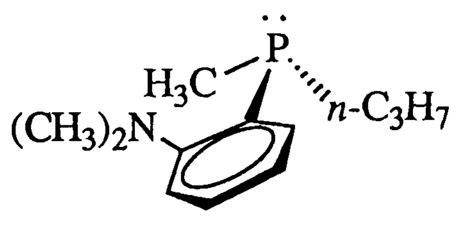
Product	R =	Precursor	%Yield	$[\alpha]_D$	%e.e.	Reference
80	C_2H_5	(Sp)-**79**	a	+23.0	100	51
80	C_2H_5	(Sp)-**79**	a	+15.5	70	51
80	C_2H_5	(Sp)-**65**	10	+21.0	a	90
81	Bn	(Sp)-**79**	a	+51.0	100	51
81	Bn	(Sp)-**61**	33	+34.6	77	88
81	Bn	(Sp)-**63**	80	+23.0	45	89
81	Bn	(S)-**30**	a	+39.2	77	55
82	n-C_3H_7	(Sp)-**79**	a	+17.0	100	51
82	n-C_3H_7	(Sp)-**61**	22	+14.8	76	88
19	An°	(Rp)-**79**	a	+25.9	100	44
19	An°	(S)-**30**	a	a	95	55
19	An°	(Sp)-**34**	83	+24.5	97	62
19	An°	(S)-**89**	97	+24.6	94	This work

a: This data was not given in the publication cited.

Horner and Schlotthauer[95] also utilized the Arbuzov approach in the synthesis of homochiral dialkylarylphosphines-(**83**) and aminophosphines-(**84**). The rhodium complex of (*R*)-(+)-methyl (*n*-propyl)*ortho*-dimethylaminophenylphosphine-(**84**) co-catalysed the reaction in Figure 2 with 80% e.e., the dimethylamino substituent acting as the second legating centre.

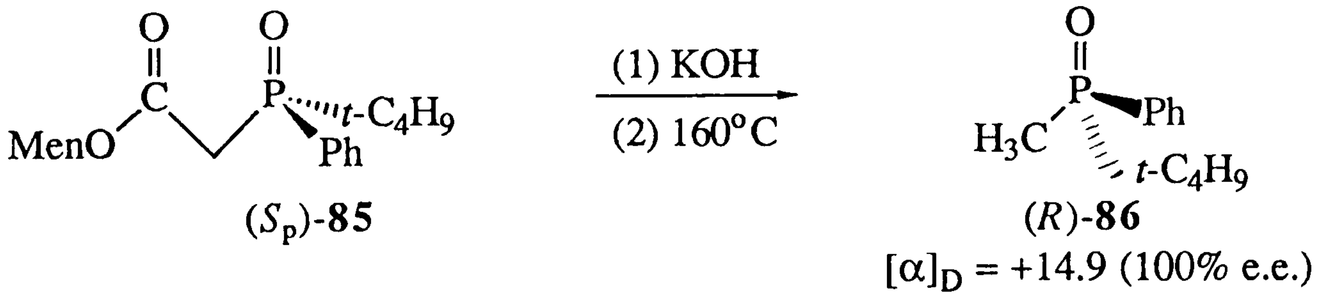


83



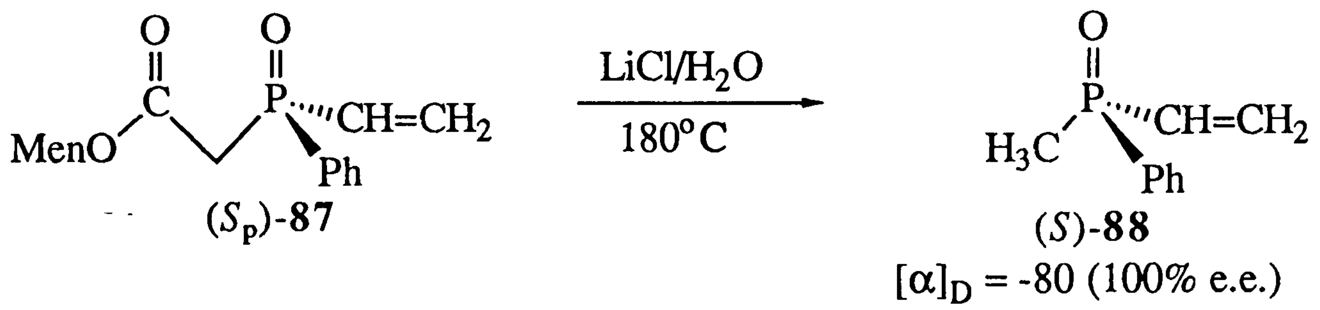
(*R*)-(+)-(**84**)

Imamoto *et al.*[96] have used resolved alkyl- and aryl-(menthoxycarbonyl)-phenylphosphine oxides in the synthesis of homochiral phosphine oxides (Scheme 59). Hydrolysis of the menthoxy residue from (*S*P)-(**85**) gave the acid which was subsequently decarboxylated to afford (*R*)-*tert*-butyl (methyl)phenylphosphine oxide-(**86**) in 89% yield and with 100% e.e. (Scheme 59).



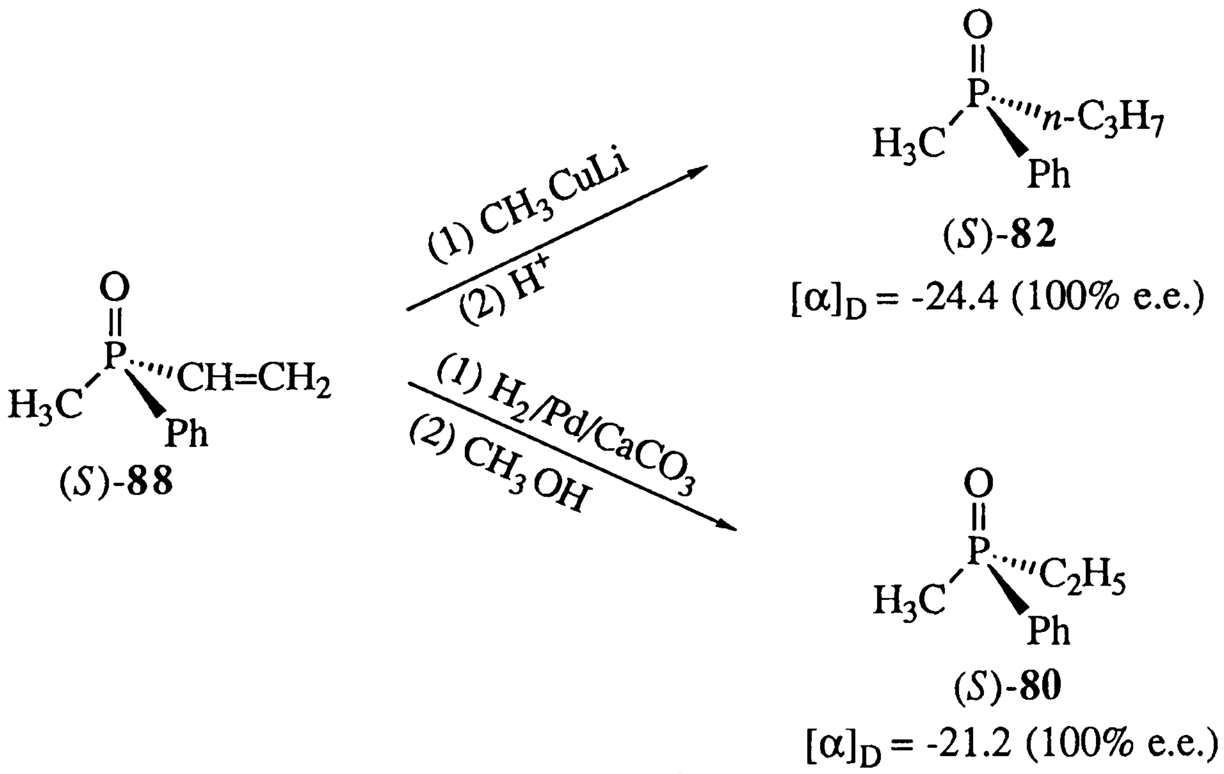
Scheme 59

Using a similar approach Pietrusiewicz *et al.*[97] have prepared a diastereomeric mixture of [(menthoxycarbonyl)methyl]phenyl(vinyl)phosphine oxides from butyl phenyl(vinyl)phosphonite and (-)-menthyl bromoacetate. The (*S*P)-(**87**) diastereoisomer was isolated by fractional crystallisation and methylated to yield enantiomerically pure (*S*)-methyl (phenyl)vinylphosphine oxide-(**88**, Scheme 60) in 60% yield, the absolute configuration of which has been recently confirmed by single-crystal X-ray diffraction studies[98].



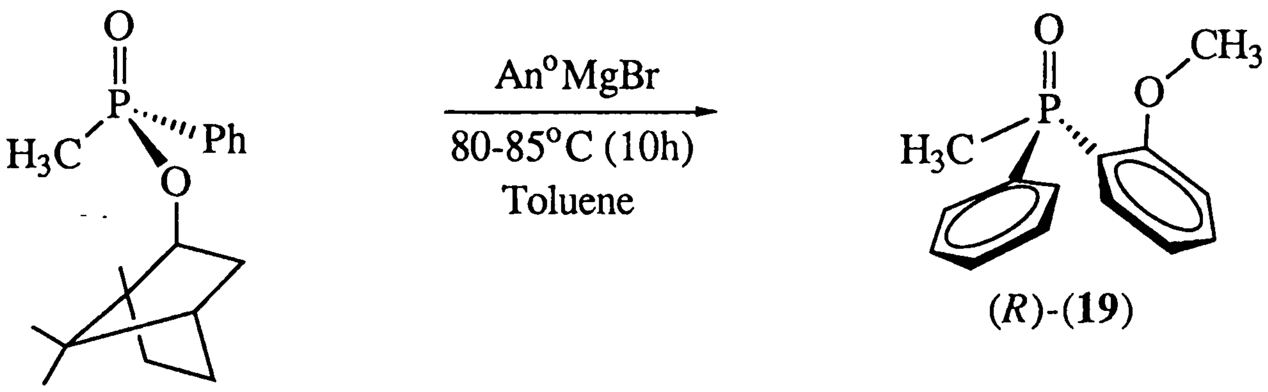
Scheme 60

Hydrogenation of (S)-(**88**) yielded enantiomerically pure (S)-(**80**) in 54% yield, while Michael addition at the vinyl substituent yielded diastereomerically pure (S)-(**82**) in 64% yield (Scheme 61). The optical purities were assigned on the basis of optical rotation data for (S)-(**80**) and (S)-(**82**) which were prepared independently from (-)-(R_P)-ethyl-[(methoxycarbonyl)methyl]phenylphosphine oxide.



Scheme 61

Schmidt *et al.*[62] recently demonstrated the effectiveness of (-)-borneol in this basic approach using (1S)-bornyl methyl(phenyl)phosphinates-(**34** & **35**, Scheme 16). The procedure offers distinct advantages over the Knowles route since the desired (1S)-bornyl-(R_P)-methyl(phenyl)phosphinate-(**34**) was obtained as the major diastereoisomer in 83% yield and was easily purified by column chromatography. Reaction of (R_P)-(**34**) with *ortho*-anisylmagnesium bromide in refluxing toluene (10h) afforded (R)-(**19**) with 97% e.e. and in 83% yield (Scheme 62).

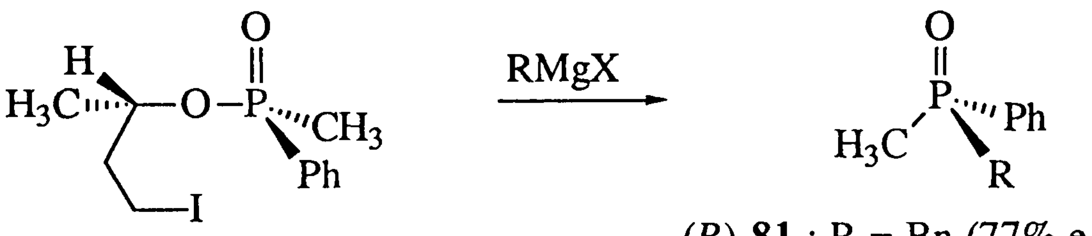


(R_P)-**34**

(R)-(**19**)

Scheme 62

Other approaches using Arbuzov chemistry have also been adopted using chiral auxiliaries. Suga *et al.*[88] have utilized the diastereoselectivity in the second P-O bond cleavage of (S_P)-(**61**, Scheme 39) using alkylmagnesium halides which proceeded with inversion of configuration at phosphorus, giving access to (R)-dialkyl(phenyl)phosphine oxides-(**81** & **82**) with >76% e.e. and in 33% and 22% yield respectively (Scheme 63, Table 16).



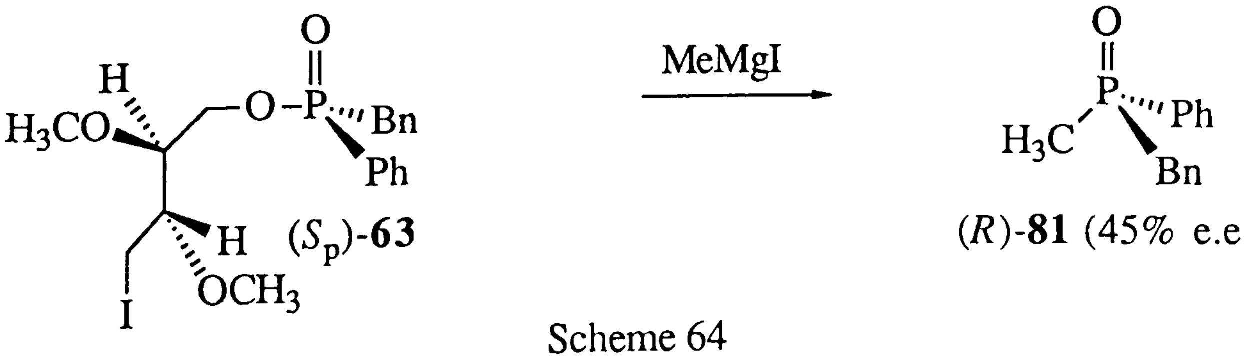
(S_P)-**61**

(R)-**81** : R = Bn (77% e.e.)

(R)-**82** : R = n-C_3H_7 (76% e.e.)

Scheme 63

The same authors[89] also studied the corresponding reactions with the second P-O bond cleavage of (S_P)-(**63**), prepared by nucleophilic P-O bond cleavage of (5S, 6S)-dimethoxy-2-phenyl-1,3,2-dioxaphosphacycloheptane-(**62**, Scheme 40). Reaction of (S_P)-(**63**) with methylmagnesium iodide yielded (R)-(**81**, Scheme 64) with inversion of configuration of phosphorus with 45% e.e. and in 80% yield (Table 16).

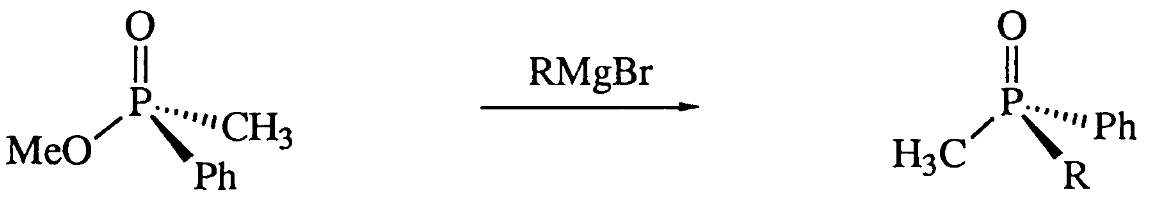


(S_p)-**63**

(R)-**81** (45% e.e.)

Scheme 64

As was described in Section 1.5, the most successful example in this area is due to Jugé *et al.*[55] who prepared (*R*P)-alkyl(phenyl)phosphinamides by Michaelis-Arbuzov rearrangement of (2*R*, 4*S*, 5*R*)-2-phenyl-oxazaphospholidine-(**26**, Scheme 37 & Table 10). Thus (*R*P)-methyl(phenyl)phosphinamide-(**27**) was prepared with 85% d.e. (Scheme 38) which, after separation from its minor diastereoisomer was subjected to acid-catalysed methanolysis to afford (*S*)-methyl methyl(phenyl)phosphinate-(**30**, Scheme 12) with 95% e.e. and 85% yield. Subsequent reaction with *ortho*-anisylmagnesium bromide gave (*R*)-(**19**) with 95% e.e., while the corresponding reaction with benzylmagnesium bromide afforded (*R*)-(**81**) with 77% e.e. (Scheme 65 & Table 16).



(*S*)-**30**

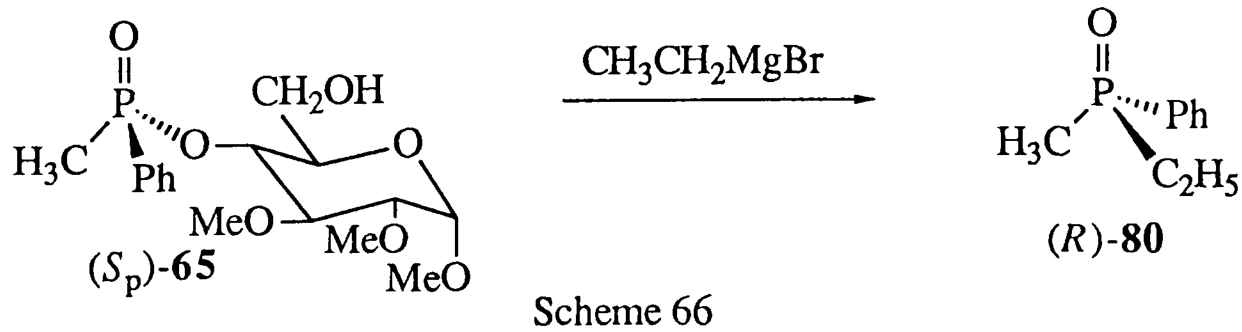
(*R*)-**81** : R = Bn (77% e.e.)

(*R*)-**19** : R = An° (95% e.e.)

Scheme 65

4.3. Nucleophilic displacement approaches.

Inch and co-workers[90] demonstrated that (*S*P)-methyl (phenyl)phosphonate-(**65**) prepared from a resolved (*R*P)-phosphinoglycoside-(**64**, Scheme 41) underwent a second P-O cleavage with ethylmagnesium bromide to yield homochiral (-)-(*R*)-ethyl (methyl)phenylphosphine oxide-(**80**) in 10% overall yield (Scheme 66 & Table 16).

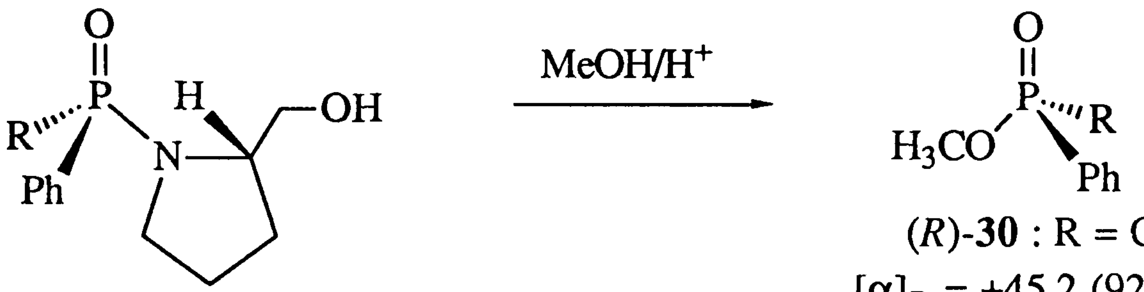


(S_P)-**65**

(*R*)-**80**

Scheme 66

Koizumi *et al.*[91] perported that (*S*P)-amidate-(**67**), was the regiospecific inversion product from from nucleophilic endocyclic P-O bond cleavage of (*R*P)-2-phenyl-tetrahydropyrrolo-1,3,2-oxaphosphole-2-oxide-(**66**, Scheme 42) which subsequently underwent acid-catalysed methanolysis also with inversion of configuration, to yield the corresponding (*R*)-phosphinates (*R*)-(**30**) with 92% e.e. and 32% yield, together with (*R*)-(**89**) in 44% yield (Scheme 67).



(S_P)-**67**

(*R*)-**30** : R = CH_3

$[\alpha]_D = +45.2$ (92% e.e.)

(*R*)-**89** : R = An°

$[\alpha]_D = -8.3$

Scheme 67

The rotation of (*R*)-(**30**, Scheme 67) was reported as $[\alpha]_D = +45.2$ (*c* 3.7 in CH_3OH) by Koizumi[91] which contrasts with Jugé's measurement of $[\alpha]_D = +57$ (*c* 4 in CH_3OH)[55] for the (*S*)-(**30**) antipode (Scheme 12). Jugé's result is supported by Harger's[99] measurement of $[\alpha]_D = +58$ also for the (*S*)-(**30**) antipode. Furthermore, the rotation for (*R*)-(**89**) of $[\alpha]_D = -8.3$ reported by Koizumi contrasts with results obtained in this study which, for the (*S*)-(**89**) antipode was measured as $[\alpha]_D = -23.01$ (*vide infra*). Providing the signs of the rotations reported by Koizumi are correct then the antipodes have been incorrectly assigned which has far reaching consequences for Koizumi's stereochemical assignment for the P-O cleavage shown in Scheme 42.

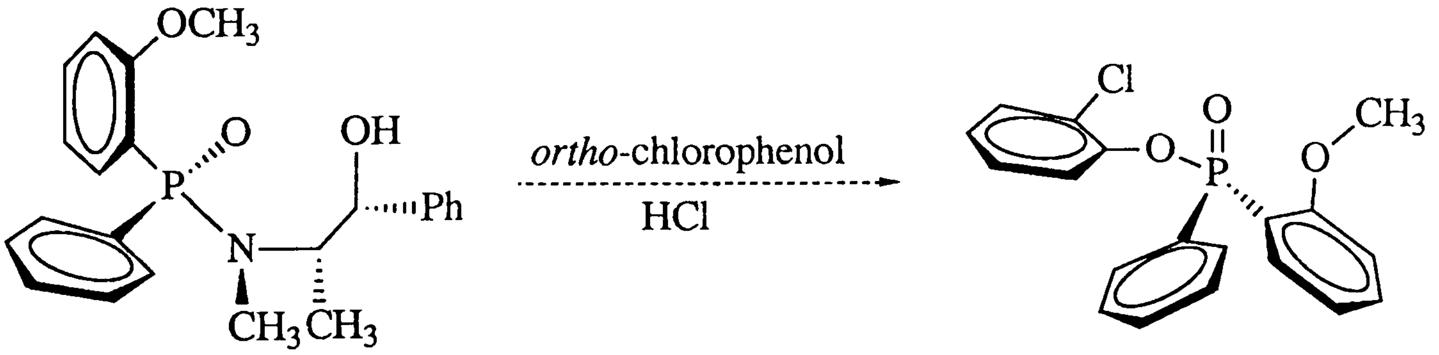
Further support that the stereochemical assignment for the ring-opened amidate proposed by Kozumi is incorrect comes from X-ray data obtained in this study for the endocyclic P-O ring cleavage of (2*R*, 4*S*, 5*R*)-2-phenyl-oxazaphospholidine-2-oxide-(**49**), which was shown to proceed with retention of configuration at phosphorus, in agreement with the ring opening of the corresponding thione and borane analogues observed by Inch and Jugé respectively. The corresponding oxaphosphole-2-thione analogues of (**51**) were also perported by Koizumi *et al.*[91] to undergo nucleophilic P-O bond cleavage with inversion of configuration at phosphorus, in contrast to Inch's[58] findings for the corresponding (2*R*, 4*S*, 5*R*)-2-methyl-oxazaphospholidine-2-thione (Scheme 44).

4.4. Strategy and Results.

Chapter 3 described the preparation of a range of novel phenyl(aryl)-, biaryl- and aryl-(vinyl)phosphinamides (Section 3.4, Table 15) with high diastereoselectivity and defined configuration at phosphorus. The next step involved removal of the *l*-ephedrine residue, however to make this third replacement a better nucleofugal leaving group than the P-N moiety was required. There is literature precedent for acid-catalysed cleavage of P-N bonds with inversion of configuration in the presence of alcohols from the work of Jugé[55], Inch[100] and Chodkiewicz[101]. Initial efforts centred on applying this route to the introduction of phenols such as *ortho*-chlorophenol and *para*-fluorophenol.

4.4.1. Acid-catalysed alcoholysis of arylphosphinamides.

Reaction of (*R*P)-(**71**) with *ortho*-chlorophenol in the presence of a catalytic amount of HCl under varying conditions (solvent and temperature) were unsuccessful with none of the desired *ortho*-chlorophenoxy (*ortho*-anisyl)phenylphosphinate-(**90**, Scheme 68) formed, only starting material or pyrolysis products were isolated.

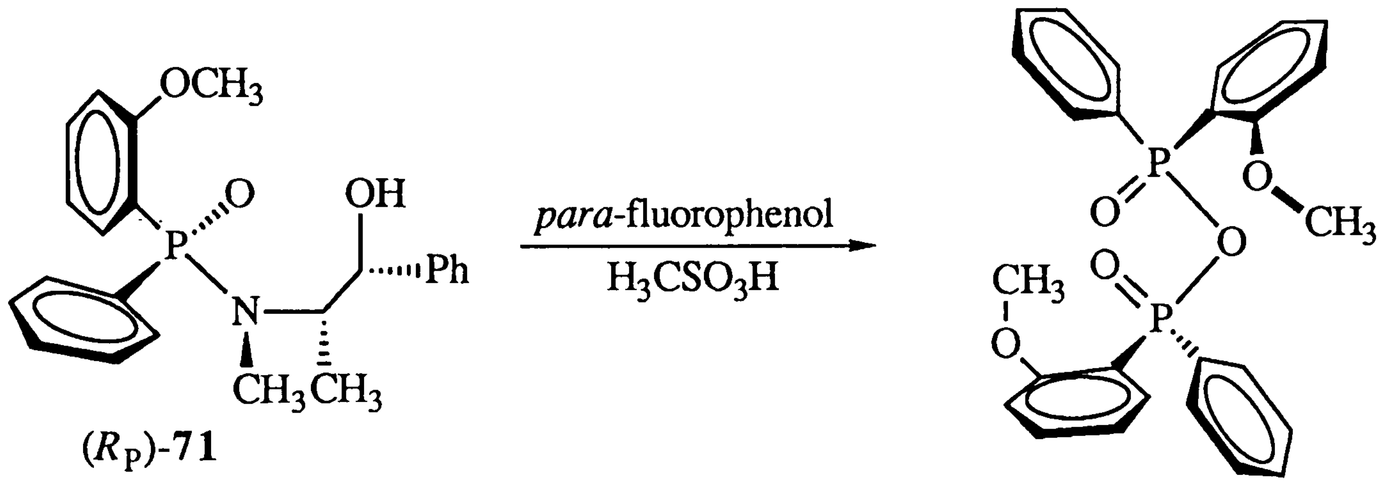


(*R*P)-**71**

90

Scheme 68

The corresponding reaction of (*R*P)-(**71**) with a six-fold excess of *para*-fluorophenol and a two-molar ratio of methylsulphonic acid yielded a white solid in *ca.* 10% yield. Its mass spectrum (C.I.) showed the molecular ion $(M+1, 100)^+$ at 479 Daltons and a further ion at 249 Daltons (35), while its infrared spectrum showed a characteristic P=O stretching at 1240 cm^{-1} and a further broad stretching at 960-979 cm^{-1} indicative of a P-O-P stretch in a pyrophosphinate (**91**, Scheme 69)[102].



(R_P)-**71**

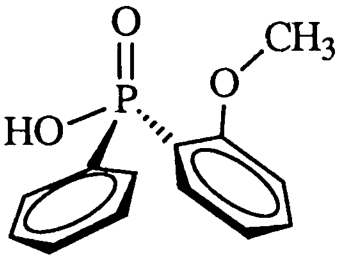
$R_{mm} = 478.4$

91

Scheme 69

(stereochemistry undefined)

Further analysis by ^{1}H and ^{31}P n.m.r. spectroscopy, together with elemental analysis supported its assignment as the dimerised product (**91**, Scheme 69), the other observable peak in the mass spectrum corresponding to the parent ion of the acid (**92**).



$R_{mm} = 248.2$

92

Acid-catalysed alcoholysis of (R_P)-(**71**) was initially investigated using d_4-methanol and a two-molar ratio of DCl in CD_2Cl_2 (Figure 15). The reaction was monitored directly by ^{1}H n.m.r. spectroscopy (200 MHz) which showed the immediate formation of (S)-d_3-methyl (*ortho*-anisyl)phenylphosphinate-(**93**) and ephedrine-(**94**), with $t_{1/2}$ of *ca.* 30 minutes (Figure 15).

Acid-catalysed methanolysis of (R_P)-(**71**) was carried out using a two-molar equivalence of a standardised HCl/methanol solution prepared from acetyl chloride and dry methanol under anhydrous conditions. The temperature of the reaction shown in Scheme 70 was maintained at 0°C for 5h and then left to stir at ambient temperature overnight, the mixture was then quenched with dilute sodium hydroxide and after several washes with water was extracted into dichloromethane from which (S)-methyl (*ortho*-anisyl)phenylphosphinate-(**89**) was isolated as a colourless oil in 93% yield (Scheme 70).

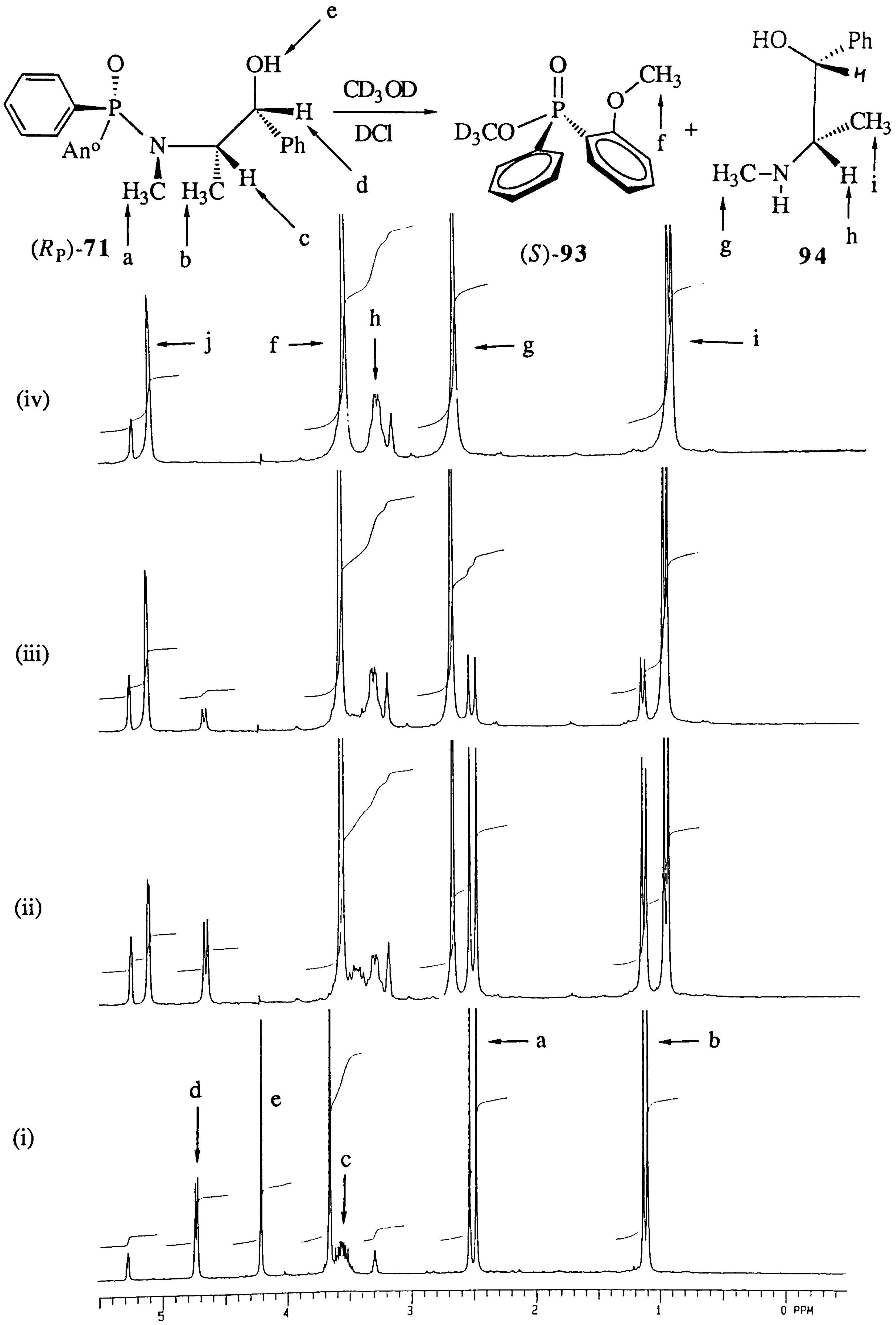
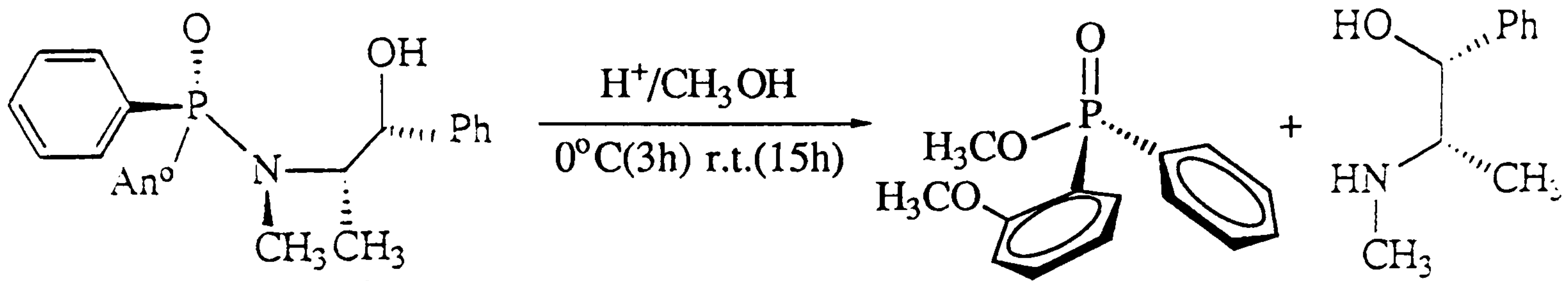


Figure 15: DCl-Catalysed d_4-alcoholysis of (R_P)-(**71**) at 25°C in CD_3OD/CD_2Cl_2; monitored by ^1H n.m.r. (200 MHz; CD_2Cl_2): (i) S.M. (ii) after 30 min (iii) after 2 h (iv) after 18 h.

The aqueous layer was made basic (pH > 12) from which ephedrine-(**94**) was isolated as a white crystalline solid[103] (Scheme 70), in contrast to the aziridine proposed by Jugé[57].



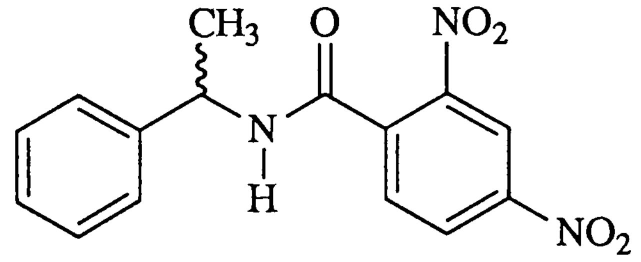
(R_P)-**71**

$[\alpha]_D$ = -23.02
(*S*)-**89**

l-Ephedrine
94

Scheme 70

The synthesis of (**89**) was previously described by Koizumi (Scheme 67) *via* acid-catalysed methanolysis of (S_P)-(**67**) in 45% yield, although the incorrect configuration was assigned to the final phosphinate. Allowing for this error, the unquantified optical rotation of $[\alpha]_D$ = -8.3 reported by Koizumi for (*S*)-(**89**, Scheme 67) is much lower than $[\alpha]_D$ = -23.02 recorded in this study. In order to quantify the enantioselectivity of (*S*)-(**89**) its optical purity was determined using the optically pure chiral-shift reagent, (*S*)-(+) or (*R*)-(-)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine-(**95**), introduced by Kagan and co-workers[104].

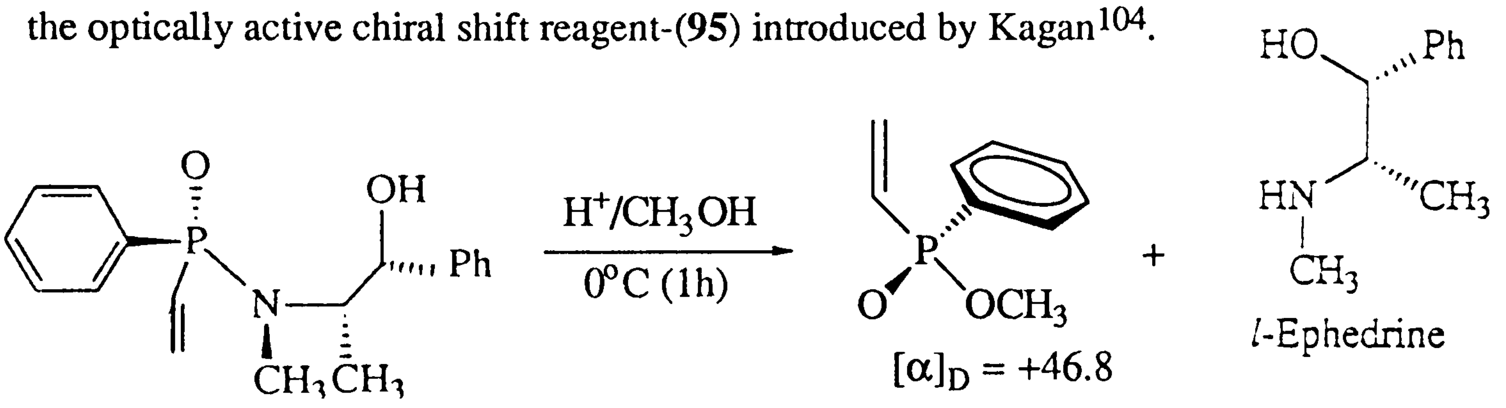


(*R*)-(-) or (*S*)-(+)-**95**

Typically, the phosphinate or phosphine oxide was prepared as a stock solution (0.08 M in $CDCl_3$) and an aliquot (0.25 ml, 0.019 mmol) was transferred using a precision syringe to a 5 mm n.m.r. tube to which was added aliqouts of a stock solution of (*R*)-(-) or (*S*)-(+)-(**95**) (0.0635 M in $CDCl_3$) and the 500 MHz ^1H n.m.r. spectrum recorded for both antipodes of the chiral shift reagent with expansion of the methyl and/or methoxy region(s). Optimum results were obtained using a 1.6:1 equivalence (0.50 ml, 0.032 mmol) of (*R*)-(-)- or (*S*)-(+)-(**95**):P=O. Application of this technique to (*S*)-(+)-

(**89**) and expansion of the methyoxy doublet at 3.75 p.p.m. (J_{PH} = 11.4 Hz) shows two smaller doublets (Figure 16a) which shifted in the opposite direction when the (*S*)-(+)-antipode of the chiral shift reagent was used (Figure 16b). Integration of these peaks gave the proportion of antipodes present from which an e.e. for (*S*)-(**89**) was calculated to be 96%.

Acid-catalysed methanolysis of (*R*P)-phenyl (vinyl)phosphinate-(**72**, Scheme 48) using a two-molar ratio of HCl/methanol at 0°C (1h) under anhydrous conditions afforded, after aqueous work-up, (*S*)-methyl (phenyl)vinylphosphinate-(**96**) in 93% yield as a colourless oil (Scheme 71). The optical purity was determined to be 95% e.e. using the optically active chiral shift reagent-(**95**) introduced by Kagan[104].



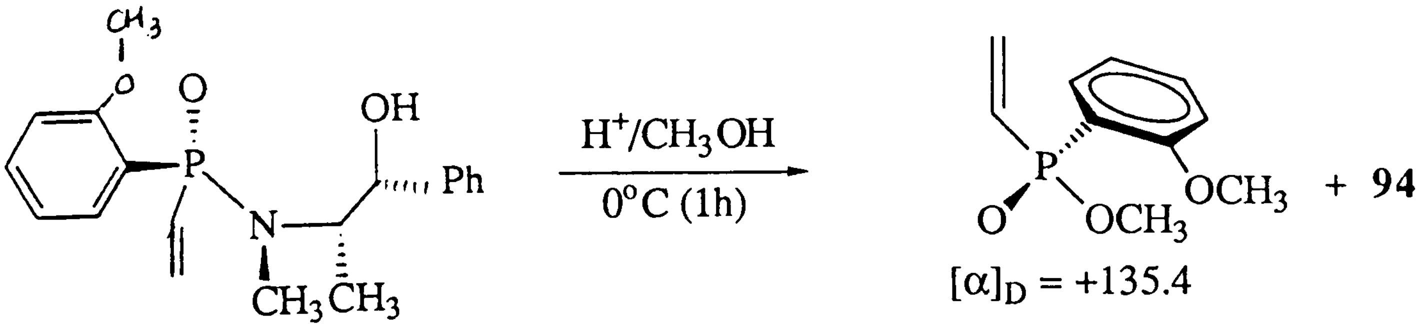
(*R*P)-**72**

[α]D = +46.8
(*S*)-**96** (95% e.e.)

l-Ephedrine
94

Scheme 71

The *ortho*-anisyl analogue, (*S*P)-(**75**, Scheme 54) was treated similarly and afforded the corresponding (*S*)-methyl (*ortho*-anisyl)vinylphosphinate-(**97**, Scheme 72) with inversion of configuration at phosphorus with 95% e.e.. The compound was isolated as a colourless oil in 99% yield.



(*S*P)-75

[α]D = +135.4
(*R*)-**97** (95% e.e.)

Scheme 72

The range of *ortho*-anisyl(aryl)phosphinamides prepared in this study showed similar enantioselectivity in the acid-catalysed methanolysis of the P-N ephedrine fragment.

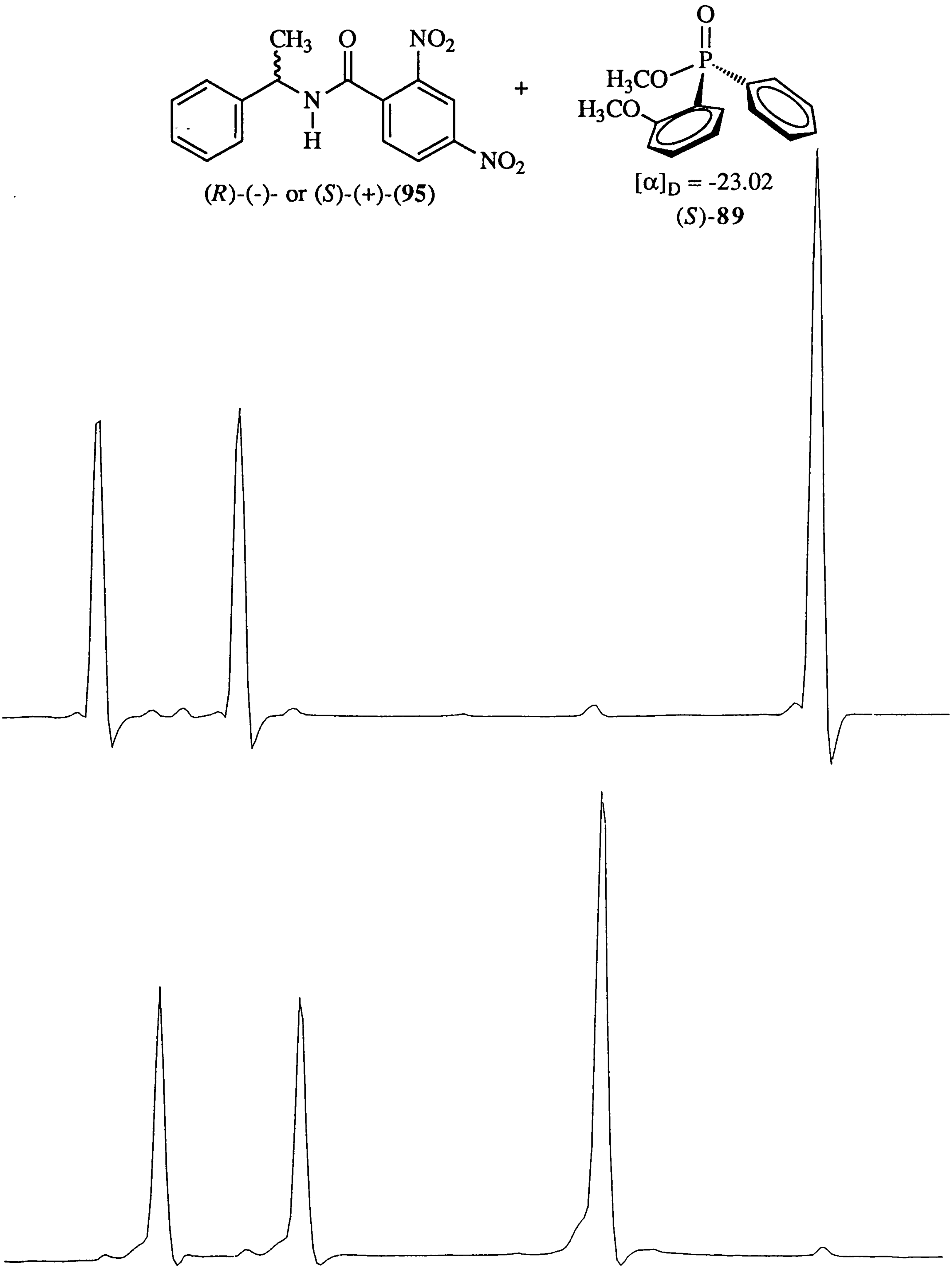
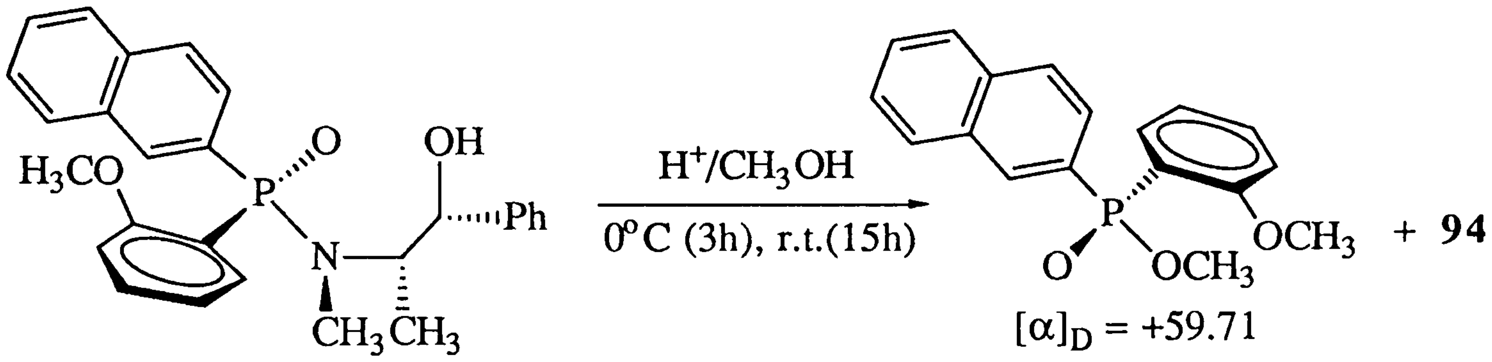


Figure 16: Determination of optical purity of (*R*)-(+)-(**89**) by 500 MHz ^{1}H n.m.r. using the Kagan shift reagent, (a): (*R*)-(-) and (b): (*S*)-(+)-(**95**).

HCl-catalysed methanolysis of (SP)-methyl (*ortho*-anisyl)-2-naphthylphosphinamide-(**76**, Scheme 55) under conditions shown in Scheme 73 afforded, after aqueous work-up, the corresponding (R)-methyl (*ortho*-anisyl)-2-naphthylphosphinate-(**98**) as a white crystalline solid. The enantiomeric excess for this reaction was determined to be >95% e.e. using the chiral shift reagent-(**95**) previously described. The white solid was easily purified by recrystallisation from hot toluene to afford enantiomerically pure (R)-(**98**) as a white crystalline solid in 77% yield.



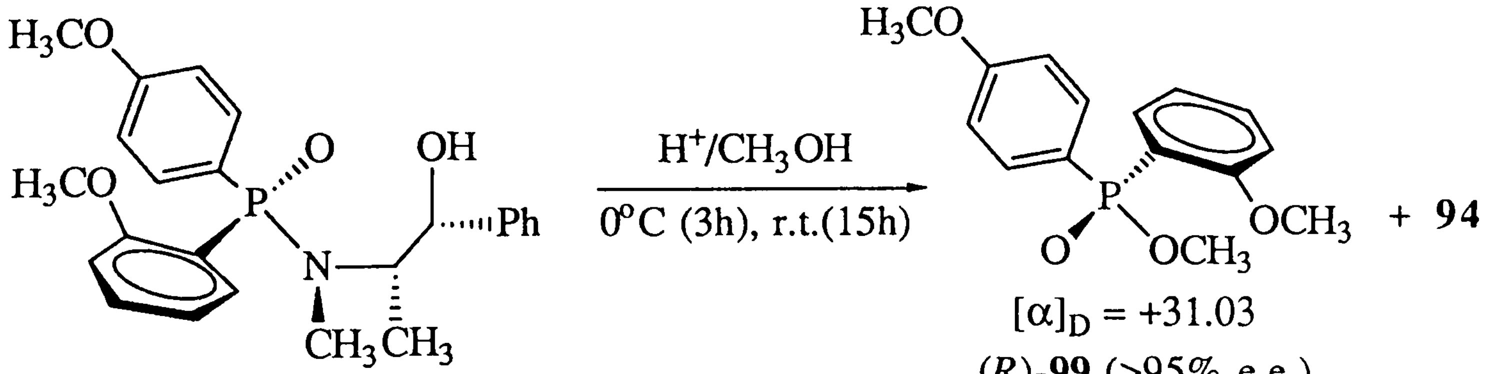
(SP)-**76**

$[\alpha]_D = +59.71$

(R)-**98** (>95% e.e.)

Scheme 73

Similarly, HCl-catalysed methanolysis of (SP)-*ortho*-anisyl (*para*-anisyl)phosphinamide-(**77**, Scheme 56) under conditions shown in Scheme 74 afforded, after aqueous work-up, (R)-methyl (*ortho*-anisyl)*para*-anisylphosphinate-(**99**) with >95% e.e. as determined by ^1H n.m.r. using the chiral shift reagent described above. The solid was purified by recrystallisation from hot toluene to afford enantiomerically pure (R)-(**99**) in 95% yield.



(SP)-**77**

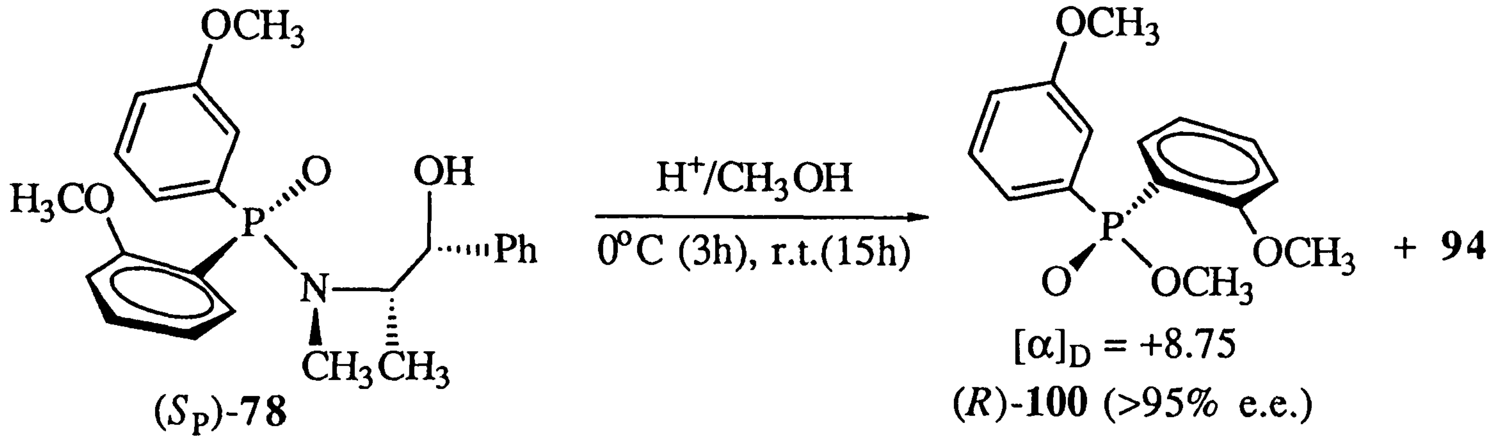
$[\alpha]_D = +31.03$

(R)-**99** (>95% e.e.)

Scheme 74

Reaction of (SP)-*ortho*-anisyl (*meta*-anisyl)phosphinamide-(**78**, Scheme 57) with a two-molar equivalence of a standardised HCl/methanol solution under conditions shown in Scheme 75 afforded, after aqueous work-up, (R)-methyl (*ortho*-anisyl)*meta*-

anisylphosphinate-(**100**) with >95% e.e. as determined by ^1H n.m.r. using the chiral shift reagent described above. The solid was purified by recrystallisation from hot toluene to afford enantiomerically pure (*R*)-(**100**) in 99% yield.



Scheme 75

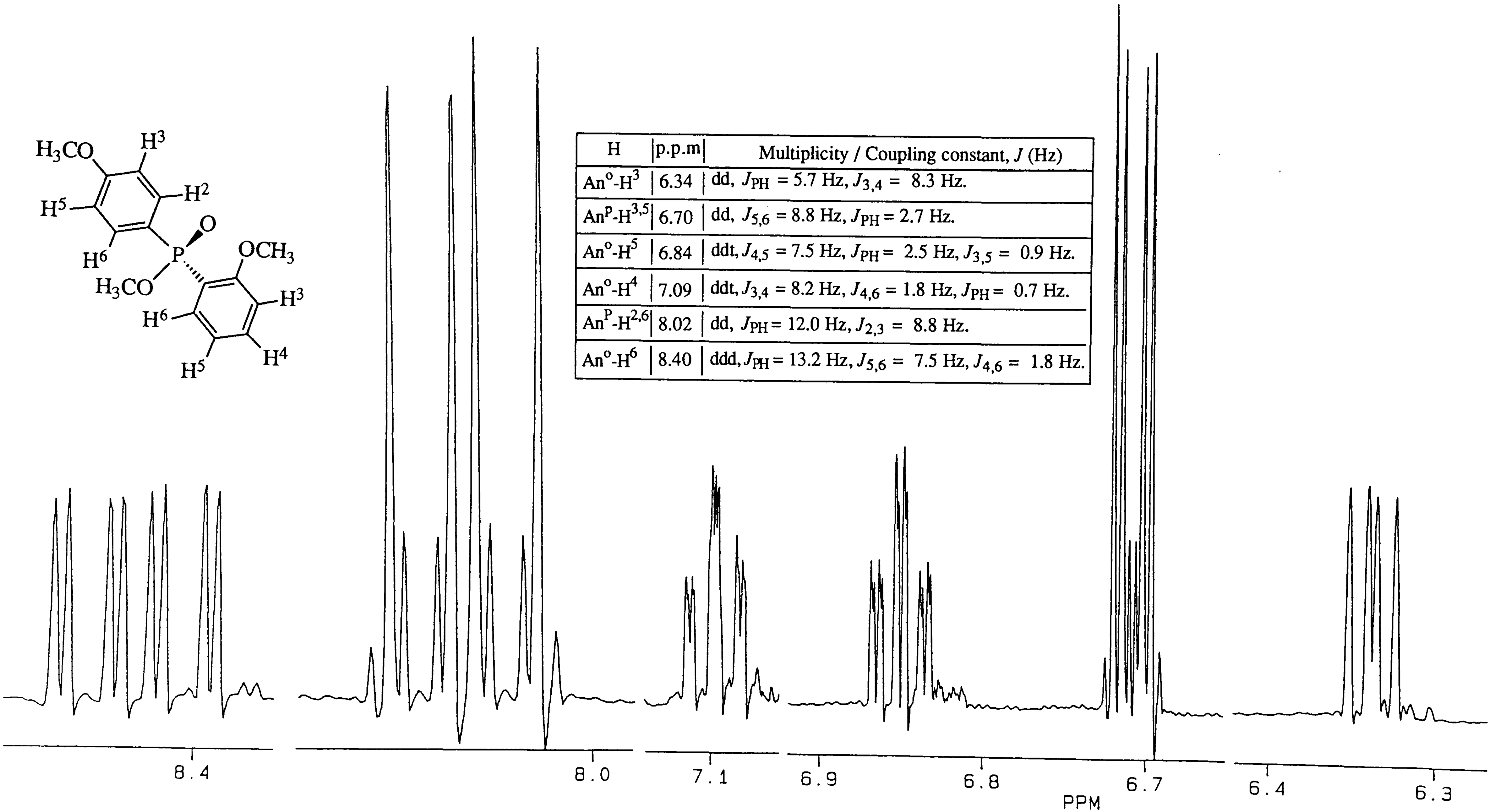
The optical and chemical purities for the reactions shown in Schemes 70-75 are collated in Table 17.

Table 17. Optical and chemical purities of aryl- and vinyl-(aryl')phosphinamides prepared in this study: $R^1R^2P(O)OCH_3$.

Precursor	R^1	R^2	Product	%Yield	$[\alpha]_D$	%e.e.
(R_P)-(**71**)	Ph	An^o	(*S*)-(**89**)	93	-23.02	96
(R_P)-(**72**)	Ph	C_2H_3	(*S*)-(**96**)	93	+46.80	95
(S_P)-(**75**)	C_2H_3	An^o	(*R*)-(**97**)	99	+135.4	95
(S_P)-(**76**)	2-Np	An^o	(*R*)-(**98**)	77	+59.71	>95
(S_P)-(**77**)	An^p	An^o	(*R*)-(**99**)	95	+31.03	>95
(S_P)-(**78**)	An^m	An^o	(*R*)-(**100**)	99	+8.75	>95

4.4.2. ^1H n.m.r. Characterisation of arylphosphinates.

The ^1H n.m.r. spectrum (500 MHz; $CDCl_3$) for the aromatic region of (*R*)-methyl (*ortho*-anisyl)*para*-anisylphosphinate-(**99**) is reproduced in Figure 17. The complete assignment of the spectrum was made by correlation with similar compounds prepared in this study and correlation of the coupling contrasts with literature values[102].



H	p.p.m	Multiplicity / Coupling constant, J (Hz)
An^{o}-H^{3}	6.34	dd, J_{PH} = 5.7 Hz, $J_{3,4}$ = 8.3 Hz.
An^{p}-H^{3,5}	6.70	dd, $J_{5,6}$ = 8.8 Hz, J_{PH} = 2.7 Hz.
An^{o}-H^{5}	6.84	ddt, $J_{4,5}$ = 7.5 Hz, J_{PH} = 2.5 Hz, $J_{3,5}$ = 0.9 Hz.
An^{o}-H^{4}	7.09	ddt, $J_{3,4}$ = 8.2 Hz, $J_{4,6}$ = 1.8 Hz, J_{PH} = 0.7 Hz.
An^{P}-H^{2,6}	8.02	dd, J_{PH} = 12.0 Hz, $J_{2,3}$ = 8.8 Hz.
An^{o}-H^{6}	8.40	ddd, J_{PH} = 13.2 Hz, $J_{5,6}$ = 7.5 Hz, $J_{4,6}$ = 1.8 Hz.

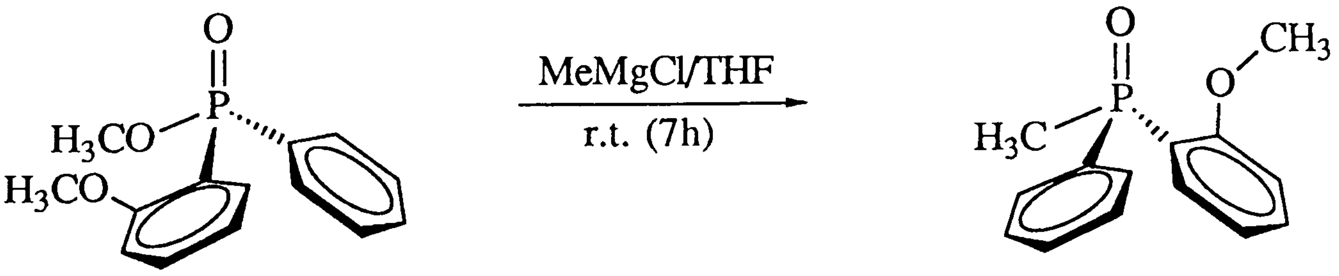
Figure 17. ^{1}H n.m.r. spectrum (500 MHz; CDCl3) of (*R*)-methyl (*ortho*-anisyl)*para*-anisylphosphinate-(**99**).

4.5. The third nucleophilic displacement step.

4.5.1. Synthesis of homochiral (R)-alkyl (ortho-anisyl)-phenylphosphine oxides.

As described in Section 1.5 the initial criteria for demonstrating an efficient route to homochiral arylphosphine oxides was the synthesis of the (*R*, *R*)-DIPAMP-(**11**) precursor, (*R*)-methyl (*ortho*-anisyl)phenylphosphine oxide-(**19**) for which the configuration at phosphorus and optical purity were already defined (Scheme 4 & Table 16).

Homochiral (*S*)-methyl (*ortho*-anisyl)phenylphosphinate-(**89**, Scheme 70) had been prepared with 96% e.e. and in high yield (93%) as a colourless oil. Initial efforts concentrated on displacement of the methoxy residue using alkyllithium and alkyl Grignard reagents which has precedent from Jugé's work (Scheme 12 & 15). Reaction of (*S*)-(**89**) with methyllithium under a variety of conditions (solvent, concentration and temperature) resulted in a mixture of the desired (*R*)-methyl (*ortho*-anisyl)phenylphosphine oxide-(**19**) and starting material. However the corresponding reaction with a two-molar equivalent of methylmagnesium chloride at ambient temperature in THF over 7h afforded, after aqueous work-up, (*R*)-methyl (*ortho*-anisyl)phenylphosphine oxide-(**19**, Scheme 76) as a single regioisomer in 97% yield. The compound was obtained as a white solid which was subjected to the ^{1}H n.m.r. chiral-shift experiment described above which showed the enantiomeric excess to be at least 94%, this was further confirmed by an optical rotation measurement of +24.6 (Table 16).



$[\alpha]_D = +24.5$

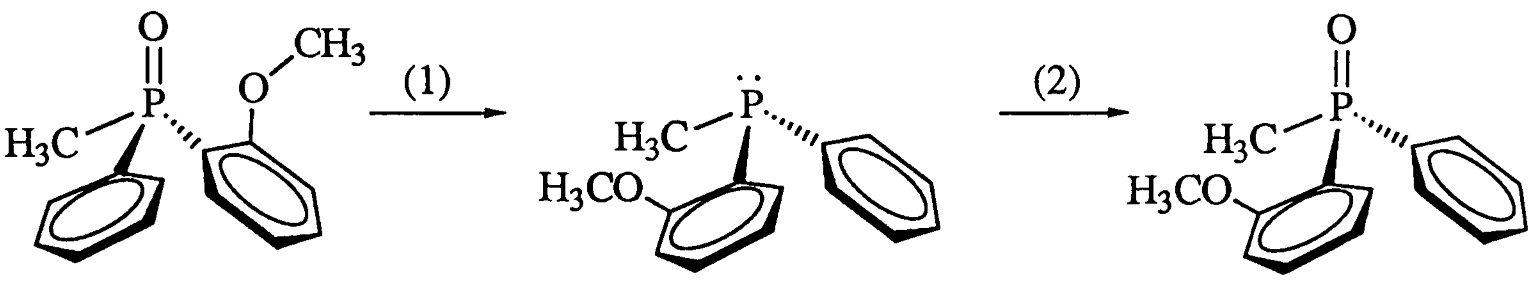
(*S*)-**89**

(*R*)-**19** (94% e.e.)

Scheme 76

(*S*)-Methyl (*ortho*-anisyl)phenylphosphine-(**2**), one of the first homochiral phosphines studied in asymmetric catalysis (Table 1), was prepared from (*R*)-(**19**) according to a literature procedure[44,47]. The synthetic sequence involved reduction of (*R*)-

(**19**) using trichlorosilane in the presence of triethylamine which proceeds with high stereoselectivity. The mechanism has been extensively studied by Mislow[105] and proceeds with inversion of configuration at phosphorus (Scheme 77).



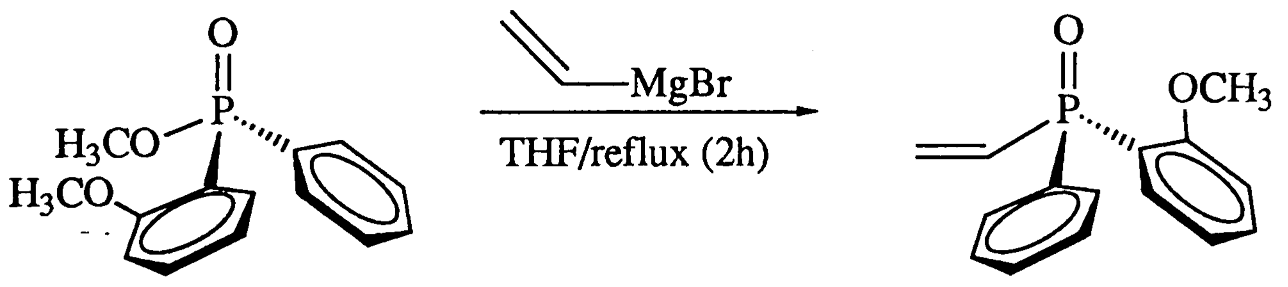
(*R*)-**19** (*S*)-**2** (*S*)-**19**

(1) $HSiCl_3/Et_3N$/r.t. (18h)
(2) *t*-ButOOH/r.t. (5min)

Scheme 77

Stereospecific oxidation of (*S*)-(**2**) using *tert*-butylhydroperoxide afforded (*S*)-(**19**) in almost quantitative yield. The compound was prepared on a 0.1 g scale and used to spike the ^1H n.m.r. chiral-shift experiment for the (*R*)-antipode, this enabled confirmation as to the assignment of the (*S*)-(**19**) antipode in the spectrum.

The synthesis of homochiral (*S*)-*ortho*-anisyl (phenyl)vinylphosphine oxide-(**36**, Scheme 17) was described in section 1.5 and was used by Johnson and Imamoto[45] as an intermediate in the synthesis of (*S*, *S*)-(**12**), the methylene homologue of DIPAMP-(**11**). Since (*S*)-PAMP oxide-(**19**) was used as the precursor to (*S*)-(**36**, Scheme 17) the direct synthesis of this compound from (*S*)-(**89**) was investigated. Reaction of (*S*)-(**89**) with vinylmagnesium bromide in THF at ambient temperature over 18h did not afford any of the desired product. Performing the reaction under reflux with a two-molar excess of vinylmagnesium bromide over 2h and analysis of the quenched product by ^1H n.m.r. spectroscopy (200 MHz) showed *ca.* 2% conversion to the desired product (Scheme 78). Further optimisation of the reaction conditions did not give any improved yield of (*R*)-(**36**).

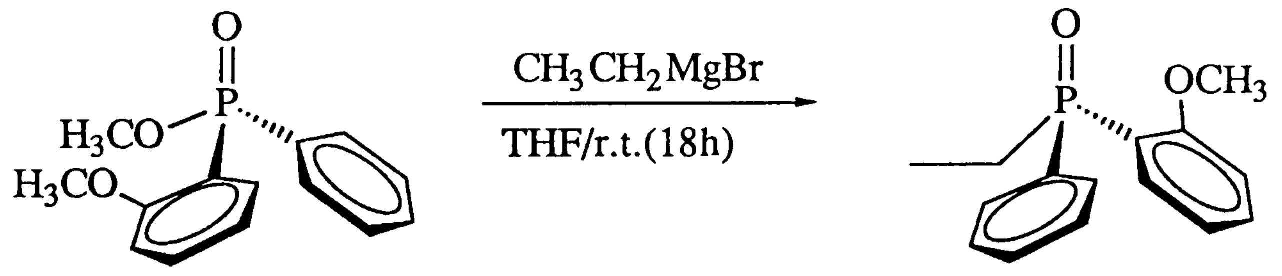


(*S*)-**89** (*R*)-**36**

Scheme 78

Nucleophilic displacement of the methoxy residue from (*S*)-(**89**) was investigated using other Grignard reagents.

Reaction of (*S*)-(**89**) with a 10% molar excess of ethylmagnesium chloride in THF at ambient temperature over 18h afforded, after aqueous work-up, (*R*)-ethyl (*ortho*-anisyl)phenylphosphine oxide-(**101**, Scheme 79) as a single, clean product. The optical purity of the crude colourless oil was determined to be 96% e.e. using the chiral shift reagent-(**95**) described previously. Evacuation (0.01 mm Hg) over 4 days produced crystals of (*R*)-(**101**) in 84% yield which did not require further purification.



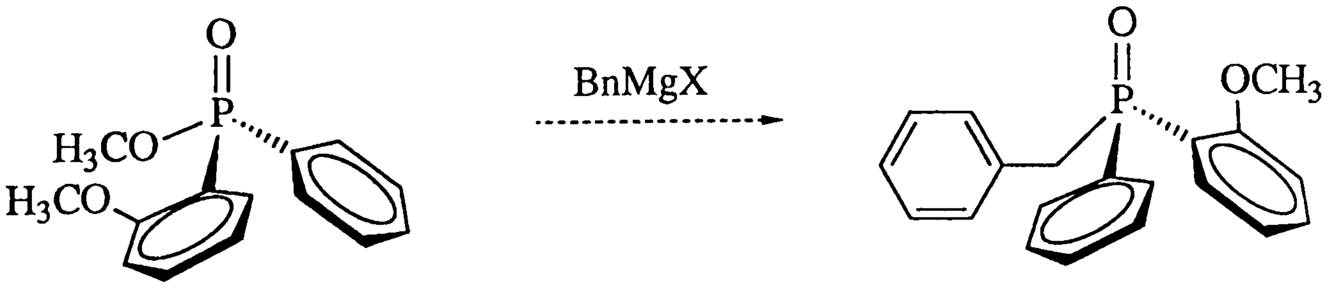
(*S*)-**89**

$[\alpha]_D = +29.1$

(*R*)-**101** (96% e.e.)

Scheme 79

Surprisingly, the corresponding reaction of (*S*)-(**89**) with either benzylmagnesium bromide or the corresponding chloride under a variety of conditions (solvent, temperature and concentration) did not afford any of the desired (*R*)-benzyl (*ortho*-anisyl)phenylphosphine oxide-(**102**, Scheme 80).



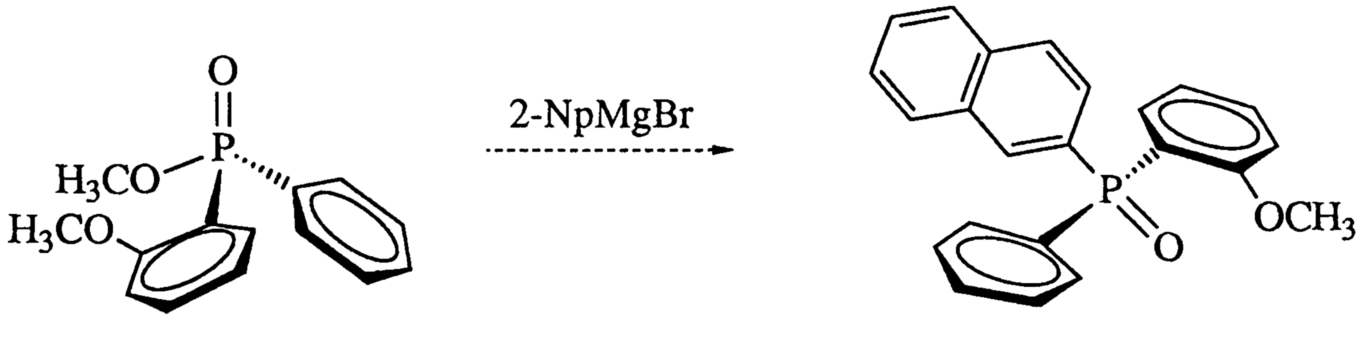
(*S*)-**89** X = Br or Cl (*R*)-**102**

Scheme 80

4.5.2. *Synthesis of homochiral triarylphosphine oxides.*

Up to this point (*S*)-(**89**) had shown to be a precursor to alkyl (*ortho*-anisyl)phenylphosphine oxides in high yield and with excellent optical purity. The nucleophilic displacement of the methoxy residue in (*S*)-(**89**) was next investigated using aryl Grignard reagents.

Reaction of (*S*)-(**89**) with 2-naphthylmagnesium bromide under a variety of conditions (solvent, temperature and concentration) did not afford any of the desired (*R*)-*ortho*-anisyl (2-naphthyl)phenylphosphine oxide-(**103**, Scheme 81).

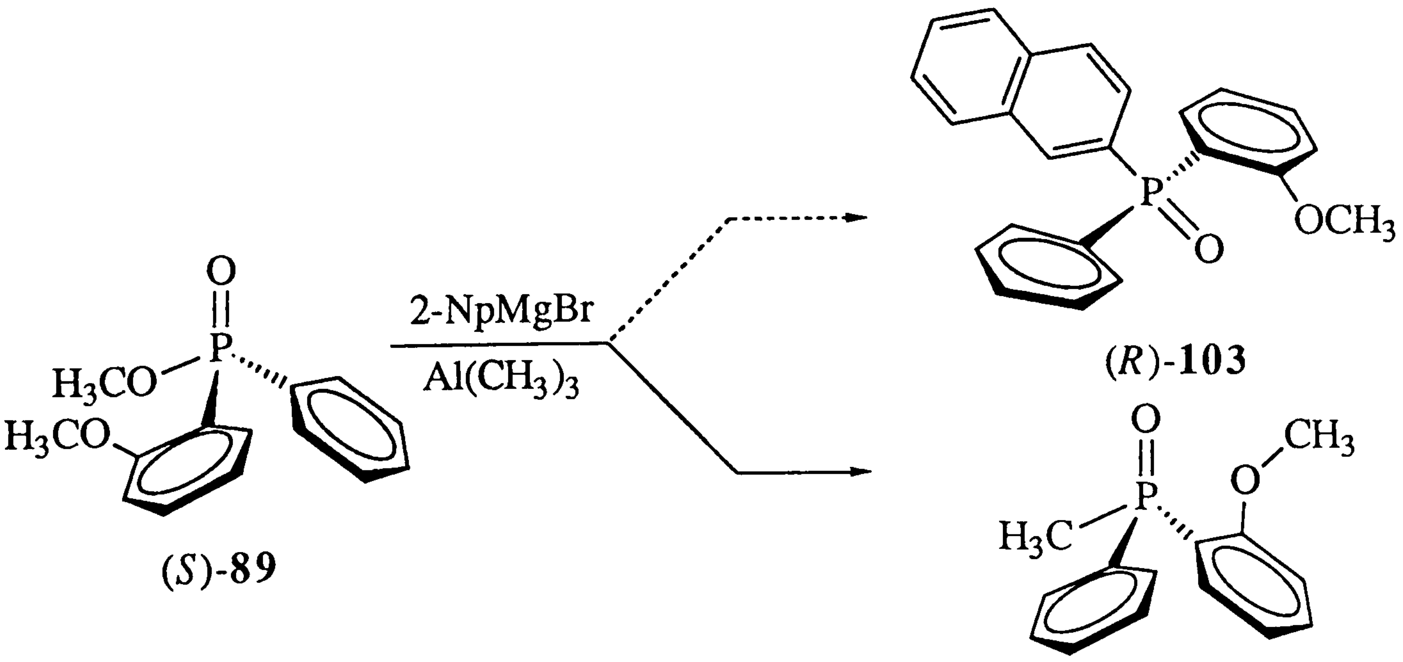


(*S*)-**89**

(*R*)-**103**

Scheme 81

Trimethylaluminium had previously been shown in this laboratory[106] and elsewhere[107] to be an effective catalyst for the coupling of homochiral vinylphosphine oxides to prochiral biarylphosphine oxides. Addition of a stoichiometric quantity of trimethylaluminium to (*S*)-(**89**) followed by an excess (10-100%) of 2-naphthylmagnesium bromide afforded the methylated product (*R*)-(**19**) and no (*R*)-(**103**, Scheme 82).



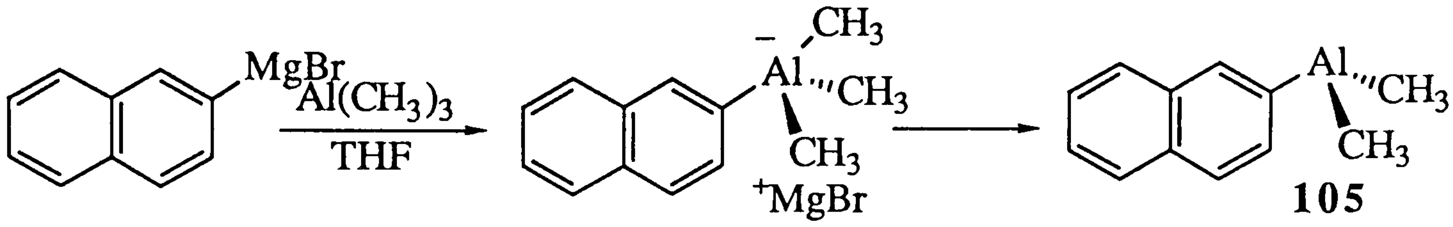
(*S*)-**89**

(*R*)-**103**

(*R*)-(**19**)

Scheme 82

The reason for methylation rather than substitution by 2-naphthyl is presumably due to *trans*-metalation resulting in the formation of the trimethyl-2-naphthylaluminium-(**104**) species (Scheme 83) which subsequently forms the more stable bimethyl-2-naphthylaluminium-(**105**) and generates methylmagnesium bromide. Either (**104**) or (**105**) may be responsible for nucleophilic substitution of the methoxy residue in (*S*)-(**89**, Scheme 83).



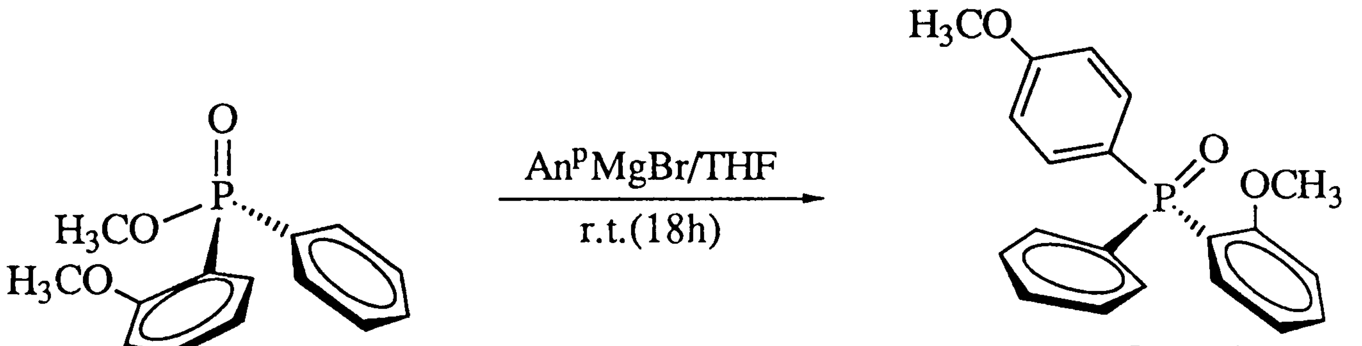
104

105

+ CH_3MgBr

Scheme 83

Reaction of (*S*)-(**89**) with a 10% molar excess of *para*-anisylmagnesium bromide in THF at ambient temperature over 18h afforded (*R*)-*ortho*-anisyl (*para*-anisyl)phenylphosphine oxide-(**106**, Scheme 84), together with an unidentified co-product. Chromatographic separation gave (*R*)-(**106**) as a colourless oil in 36% yield and with 95% e.e. as determined by ^1H n.m.r. using the chiral shift reagent-(**95**), described above. Attempts at optimisation of this reaction did not improve the purity of the crude product.



(*S*)-**89**

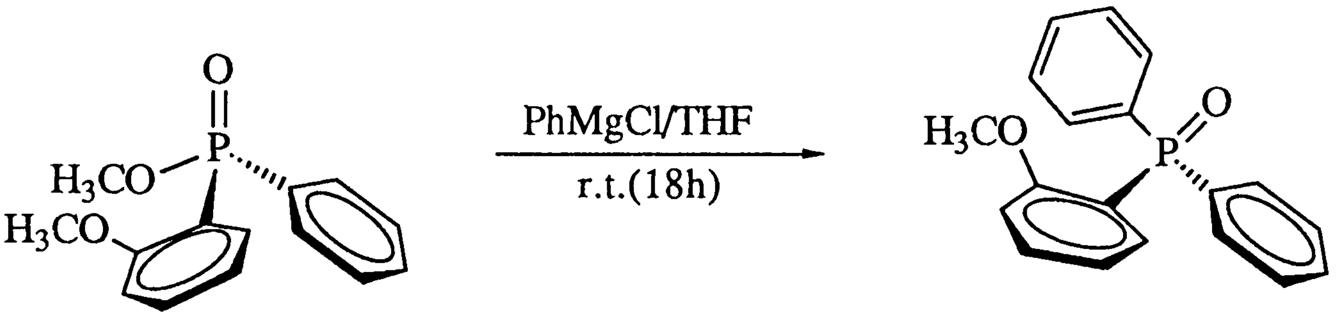
$[\alpha]_D = -3.5$

(*R*)-**106** (95% e.e.)

Scheme 84

Up to this point methoxy displacement from (*S*)-(**86**) had been shown to be most effective using alkylmagnesium chlorides rather than the corresponding bromides; the reactant is less reactive towards arylmagnesium bromides. Also its reaction with methyl lithium resulted in incomplete conversion to (*R*)-(**19**).

The reaction of (*S*)-(**89**) with a 3 molar excess of phenylmagnesium chloride in THF over 18h afforded, after aqueous work-up, *ortho*-anisyl(biphenyl)phosphine oxide-(**107**) in almost quantitative yield (Scheme 85). The quality of the crude product, as observed by ^{1}H n.m.r. spectroscopy, was found to be superior to the corresponding reaction with *para*-anisylmagnesium bromide in Scheme 84.



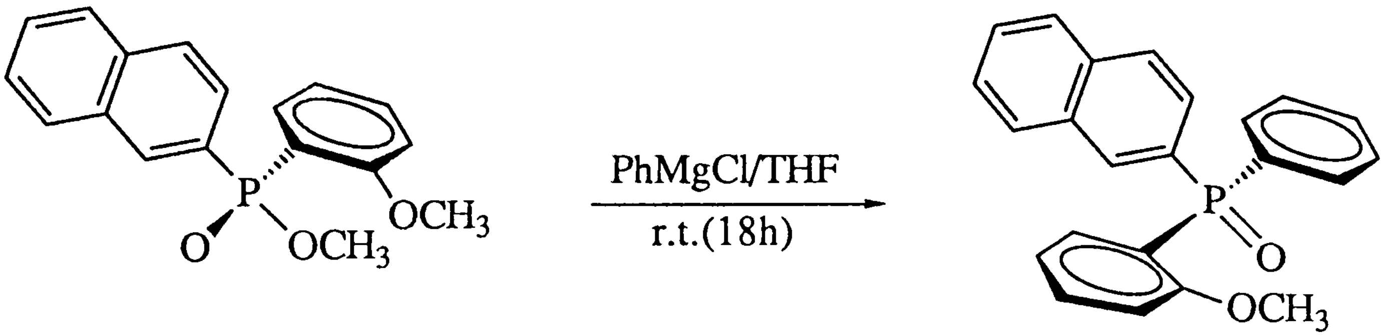
(*S*)-**89**

107

Scheme 85

In view of this, the synthesis of the (*S*)-antipodes of (**103**) and (**106**) were prepared *via* their respective (*R*)-methyl (*ortho*-anisyl)arylphosphinates using phenyl magnesium chloride in the final methoxy displacement step.

Reaction of (*R*)-methyl (*ortho*-anisyl)-2-naphthylphosphiante-(**98**, Scheme 73) with an eight-fold excess of phenylmagnesium chloride in THF at ambient temperature over 18h afforded, after aqueous work-up, (*S*)-methyl (*ortho*-anisyl)-2-naphthylphosphine oxide-(**103**, Scheme 86) as a colourless oil in 90% yield.



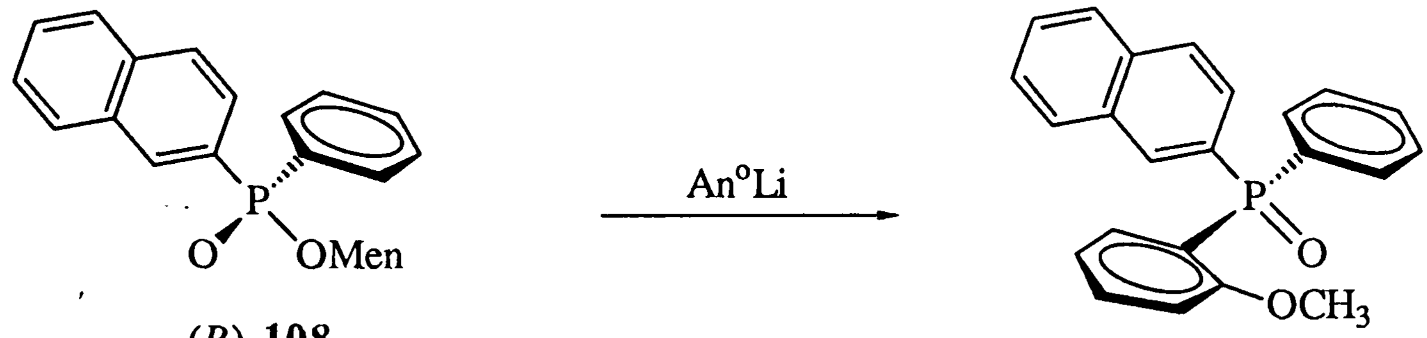
(*R*)-**98**

$[\alpha]_D = -7.6$

(*S*)-**103**

Scheme 86

(*S*)-(**103**) had previously been prepared by Mislow *et al.*[51] by nucleophilic displacement of menthyl from (R_P)-menthyl (2-naphthyl)phenylphosphine oxide-(**108**, Scheme 87) and *ortho*-anisyl lithium.



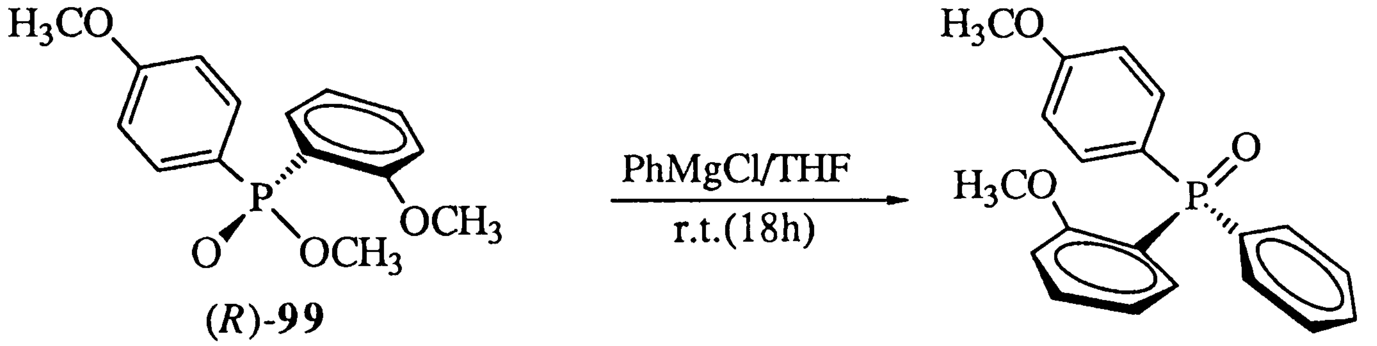
(*R*)-**108**

$[\alpha]_D = -1.8$
(*S*)-**103** (44% e.e.)

Scheme 87

Mislow reported a 44% e.e. for the reaction in Scheme 87 corresponding to a rotation of -1.8, for (*S*)-(**103**, Scheme 87), this compared to -7.6 recorded for the same compound prepared in this study (Scheme 86), the optical purity was therefore deemed to be >96% e.e. for the reaction in Scheme 86.

The corresponding reaction of (*R*)-methyl (*ortho*-anisyl)*para*-anisylphosphine oxide-(**99**, Scheme 74) with an eight molar excess of phenylmagnesium chloride in THF at ambient temperature over 18h afforded, after aqueous work-up, (*S*)-*ortho*-anisyl (*para*-anisyl)phenylphosphine oxide-(**106**, Scheme 88) as a colourless oil in 90% yield.

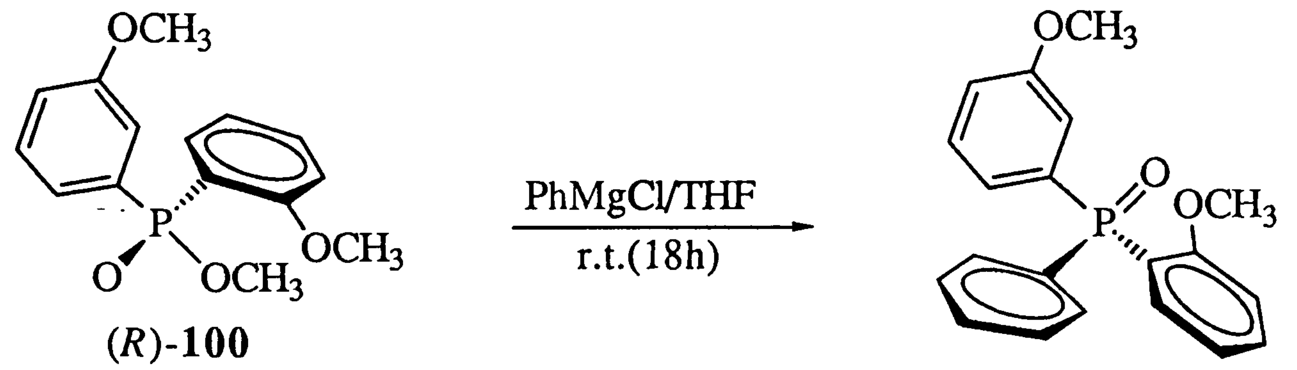


(*R*)-**99**

$[\alpha]_D = -2.07$
(*S*)-**106** (95% e.e.)

Scheme 88

Reaction of (*R*)-methyl (*ortho*-anisyl)*meta*-anisylphosphinate-(**100**, Scheme 75) with an eight-fold excess of phenylmagnesium chloride in THF over 18h afforded, after aqueous work-up, (*S*)-*ortho*-anisyl (*metal*-anisyl)phenylphosphine oxide-(**109**, Scheme 89) as a colourless oil. Purification by flash column chromatography and recrystallisation from diethyl ether gave (*S*)-(**109**) as a white crystalline solid in 77% yield. The optical purity was determined to be 96% by ^{1}H n.m.r. (500 MHz) using the chiral shift reagent-(**95**), described above.

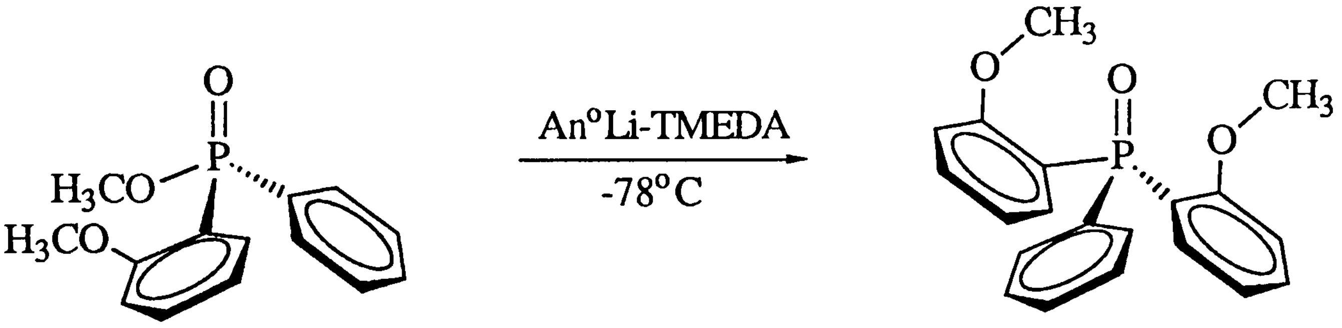


(*R*)-**100**

$[\alpha]_D$ = -9.54
(*S*)-**109** (96% e.e.)

Scheme 89

During work on the approach to new bisphosphines ligands it was discovered that aryllithium-TMEDA reagents were particularly efficient in the final methoxy displacement step. For example, bis(*ortho*-anisyl)phenylphosphine oxide-(**110**) was prepared from (*S*)-(**89**) by another worker in the group[108] (Scheme 90)



(*S*)-**89**

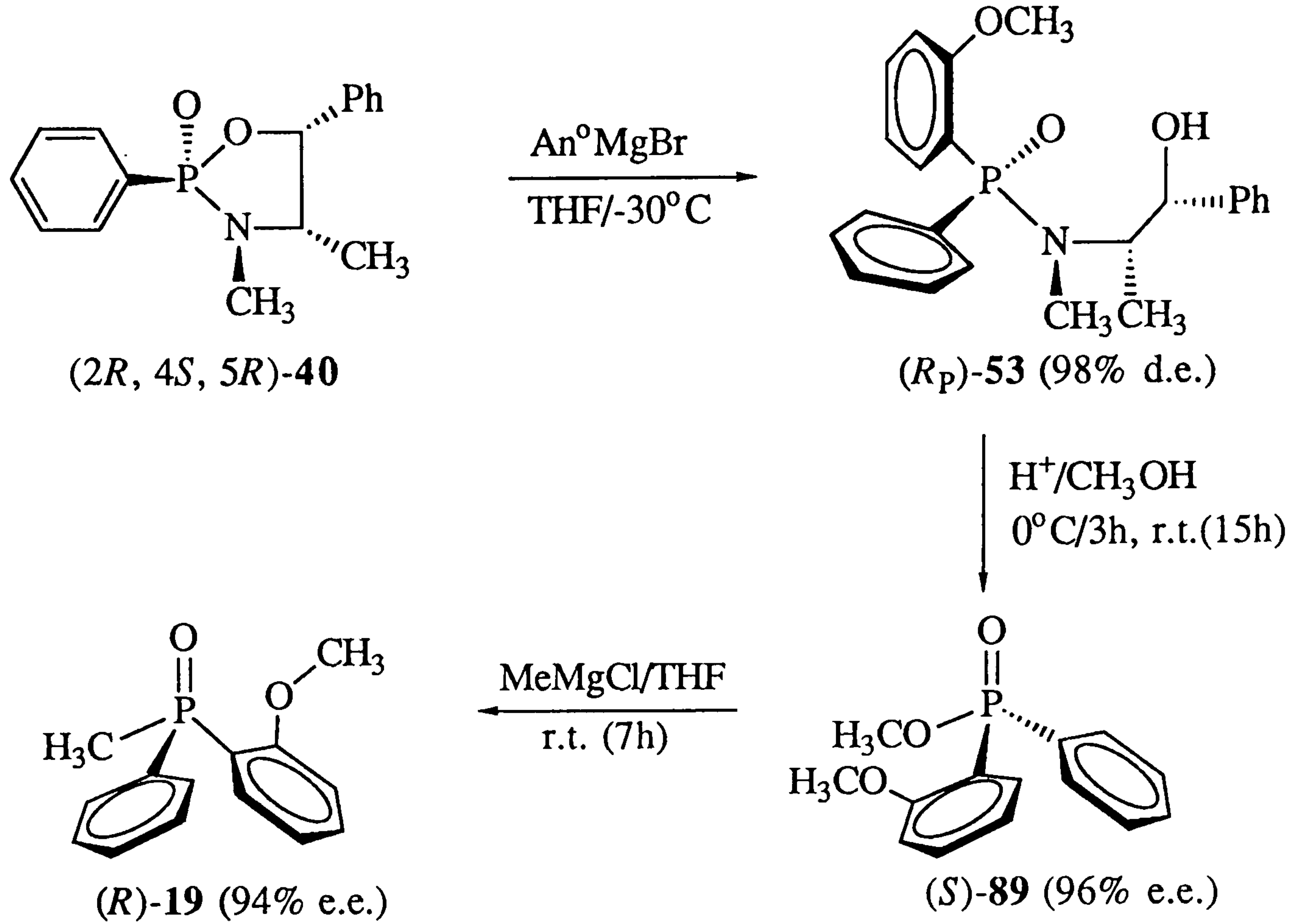
110

Scheme 90

4.6. Overview.

The synthesis of (*R*)-PAMP oxide-(**19**) with 94% e.e. had been effected by three successive nucleophilic displacements from (2*R*, 4*S*, 5*R*)-2-phenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-oxide-(**49**) under relatively mild reaction conditions. Stereoselective reduction to (*S*)-PAMP-(**2**) was carried out using an established procedure[105]. The diastereo- or enatio-selectivity at each of the nucleophilic displacement steps was shown to be very high, furthermore the stereochemistry of the intermediate phosphine oxides was defined. The overall synthetic sequence for the synthesis of homochiral (*R*)-(**19**) is shown in Scheme 91 and represents the first synthesis of this compound not requiring separation of diastereomeric mixtures.

In a second approach, starting from PCl_3 and forming diastereomerically pure (2*R*, 4*S*, 5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(**43**) the synthesis of homochiral triarylphosphine oxides had been achieved by three successive



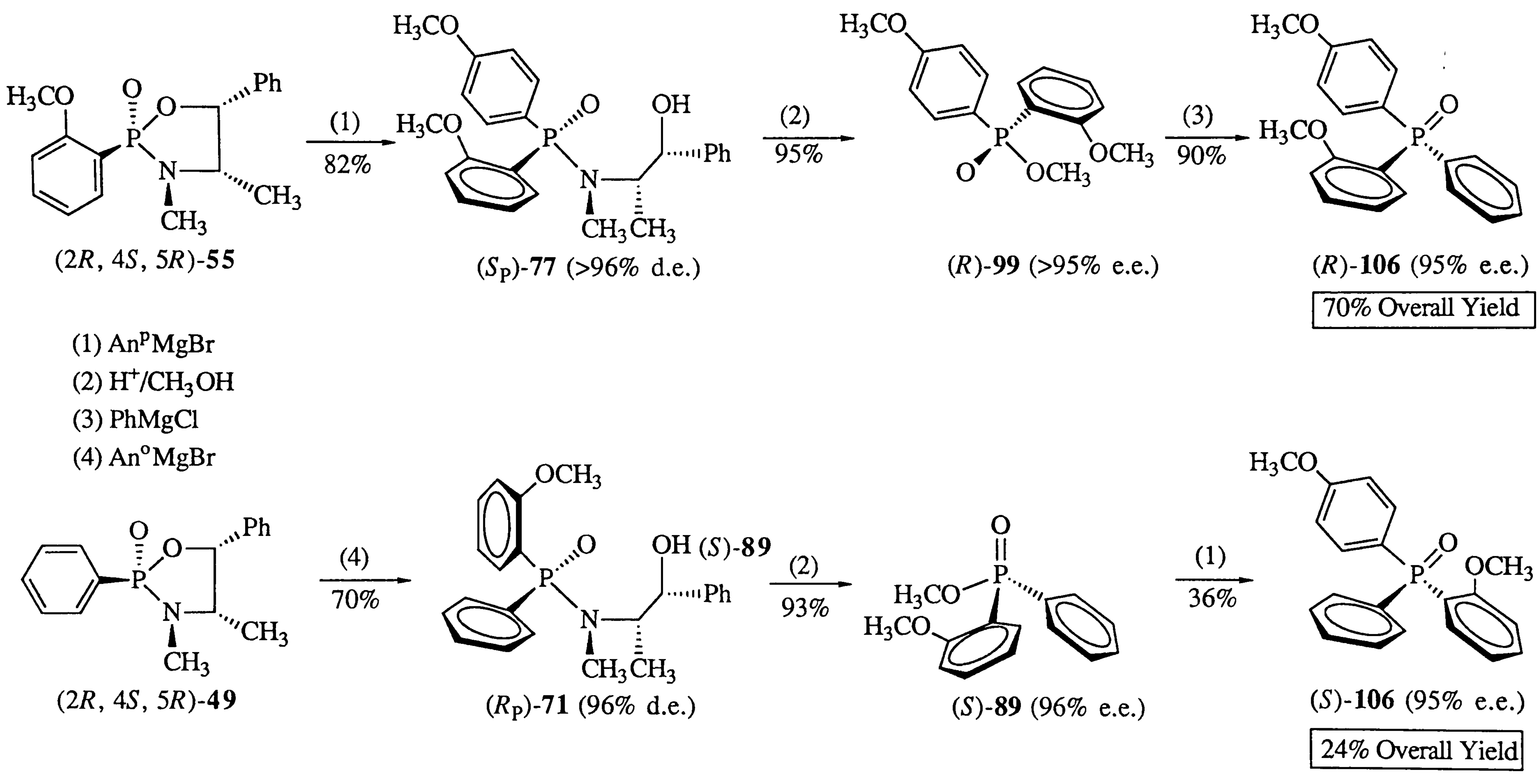
Scheme 91

nucleophilic displacement steps. This latter route was shown to be very general as demonstrated in the synthesis of the bulky, (*S*)-*ortho*-anisyl (2-naphthyl)phenylphosphine oxide-(**103**) in >96% e.e. (Table 18 & Scheme 86).

Table 18. Optical and chemical purities of arylphosphine oxides; An°(R)PhP=O prepared in this study.

Precursor	R	Product	%Yield	$[\alpha]_D$	%e.e.
(*S*)-(**89**)	CH_3	(*R*)-(**19**)	97	+23.5	94
(*S*)-(**89**)	C_2H_3	(*R*)-(**101**)	84	+29.1	96
(*S*)-(**89**)	An^P	(*R*)-(**106**)	36	-3.5	95
(*S*)-(**89**)	Ph	(**107**)	97	–	–
(*R*)-(**98**)	2-Np	(*S*)-(**103**)	90	-7.6	>96
(*R*)-(**99**)	An^P	(*R*)-(**106**)	90	-2.07	95
(*R*)-(**100**)	An^m	(*S*)-(**109**)	77	-9.54	96

Although in principle this route could be applied to the synthesis of any triarylphosphine oxide, it proved easier to incorporate a phenyl group in the final nucleophilic displacement step using PhMgCl which had shown to be more efficient than the corresponding ArMgBr reagents. The synthesis of the (*R*)- and (*S*)-antipodes of *ortho*-anisyl (*para*-anisyl)phenylphosphine oxide-(**109**) serves to illustrate this point (Scheme 92).



Scheme 92. Synthesis of homochiral (*R*)- and (*S*)-*ortho*-anisyl(*para*-anisyl)phenylphosphine oxide-(**106**).

Chapter 5. Approaches to New Bisphosphine Ligands.

5.1. Introduction.

The high enantioselectivities achieved in homogeneous catalysis using P-Chiral bisphosphine ligands was outlined in Chapter 1. The synthesis of the key ligand in this area, DIPAMP-(**11**) has been exclusively based on the Cu(II) promoted oxidative coupling of homochiral PAMP oxide-(**19**, Scheme 4) or PAMP borane-(**20**, Scheme 7).

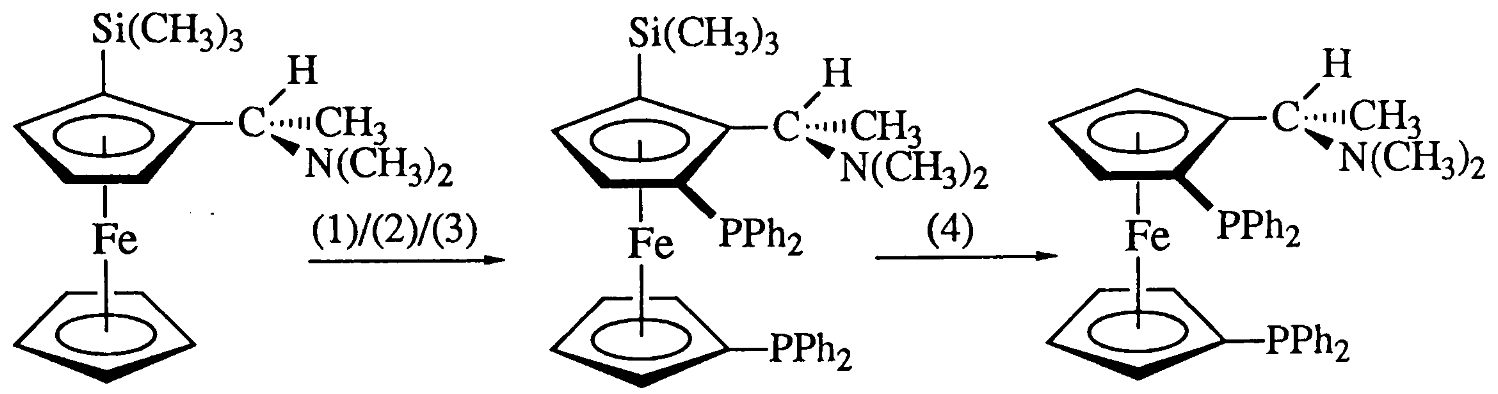
Having demonstrated the effectiveness of the nucleophilic displacement approach to homochiral triaryphosphines, the application of this route to homochiral bisphosphines was investigated. Of particular interest was the synthesis of P-chiral ligands containing either the ferrocenyl backbone or axially dissymmetric backbones; such ligands would encompass the structural characteristics which have, *hitherto* shown to be the most effective features for homogeneous catalysis.

This Chapter presents the preliminary work towards achieving these goals, so while several key compounds are presented, further development is required.

5.2. Approaches to P-Chiral Ferrocenyl ligands.

5.2.1. 1,1'-Bis(diphenylphosphino)ferrocene derivatives.

As described in Chapter 1, Ito and Hayashi have developed an extensive range of 1,1'-bis(diphenylphosphino)ferrocene ligands which contain both planar and central chirality[37,38,109,110]. The synthetic route to (S_C)-(S_{Fe})-*N*,*N*-dimethyl-1-[2,5-bis(diphenylphosphino)ferrocenyl]ethylamine-(**10**), abbreviated (S_C)-(S_{Fe})-BPPFA-(**10**) has recently been improved by Togni and Pastor[111]. The synthetic sequence involved the lithiation of *N*,*N*-dimethyl-1-ferrocenylethylamine which was sililylated to afford (S_C)-(R_{Fe})-(**111**), sequential lithiation at the 1,1'-positions (Scheme 93), and reaction with two moles of chlorodiphenylphosphine afforded (S_C)-(R_{Fe})-(**112**) in 80% yield and the corresponding diphenylphosphino-ferrocene in 20% yield. Separation of this mixture following desilylation gave (S_C)-(S_{Fe})-BPPFA-(**10**) in 25% overall yield from (S_C)-(R_{Fe})-(**111**, Scheme 93).

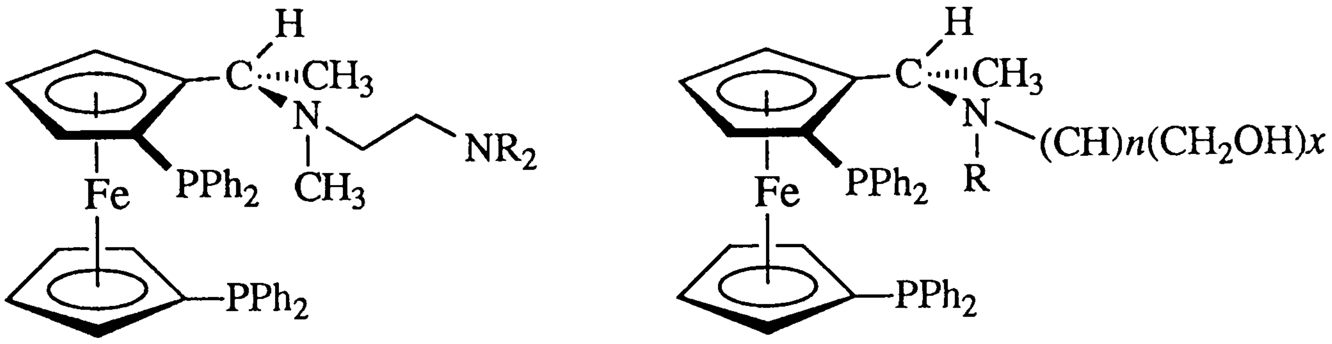


(S_C)-(R_{Fe})-**111** (S_C)-(R_{Fe})-**112** (S_C)-(S_{Fe})-**10**

(1) *n*-BuLi (3) $ClPPh_2$
(2) *n*-BuLi/TMEDA (4) *t*-BuOK/DMSO

Scheme 93

Although an efficient ligand in its own right, (S_C)-(S_{Fe})-BPPFA-(**10**) was the key intermediate in the synthesis of (S_C)-(S_{Fe})-(**113**) bearing a variety of tertiary amino substituents at the end of the pendant ferrocene side chain[109]. Using similar methodology this was also extended to side chains containing hydroxy functionalities (**114**)[37,109].



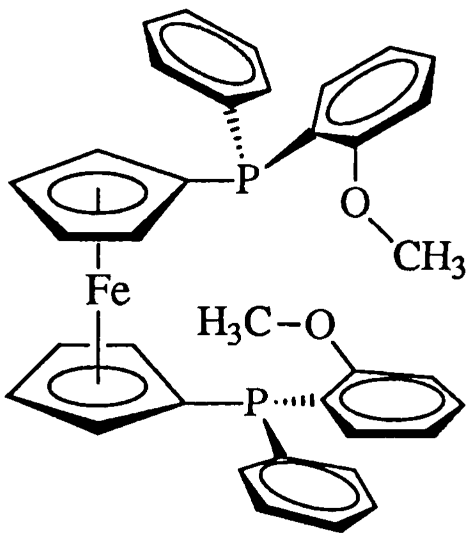
(S_C)-(S_{Fe})-**113** (S_C)-(R_{Fe})-**114**

Scheme 94

The enantioselectivities of both classes of ligands are directly related to the presence and position of the amino or hydroxy functionality on the pendant side chain which is believed to be involved in directing the incoming nucleophile during catalysis. Such ligand-substrate binding is an uncommon control element in homogeneous catalysis.

5.2.2. Strategy.

Two approaches to the P-chiral ferrocenylbisphosphine-(**115**) were attempted. The first involved nucleophilic displacement of methoxy from (*S*)-(**89**) using 1,1'-bis(metalated)ferrocene complexes. The second involved utilising diastereomerically pure (2*R*, 4*S*, 5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(**43**) from which two further nucleophilic displacements would be required.



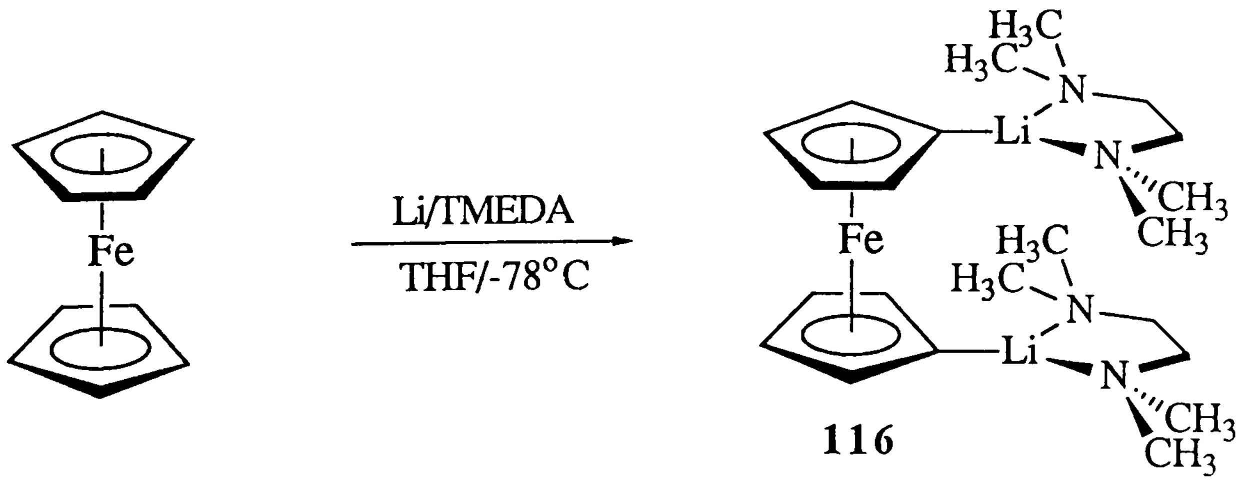
115

The first approach has precedents in the methoxy displacement from (*S*)-(**89**) and (*R*)-(**99**) using arylmagnesium halides (Scheme 92) or the corresponding aryl Li(TMEDA) complex (Scheme 90). The second approach has precedent in the P-Cl cleavage of $PhPCl_2$ using both the monolithioferrocene and its LiTMEDA complex as shown in Scheme 93.

In order to investigate this chemistry the appropriate metalated ferrocene backbones were required. It seemed appropriate to prepare both the 1,1'-bis(LiTMEDA) ferrocene complex and the corresponding 1,1'-bis(bromomagnesio)ferrocene complex as well as the monolithioferrocene complex.

5.2.3. Synthesis of mono- and 1,1'-bis-(metalated)ferrocene reagents.

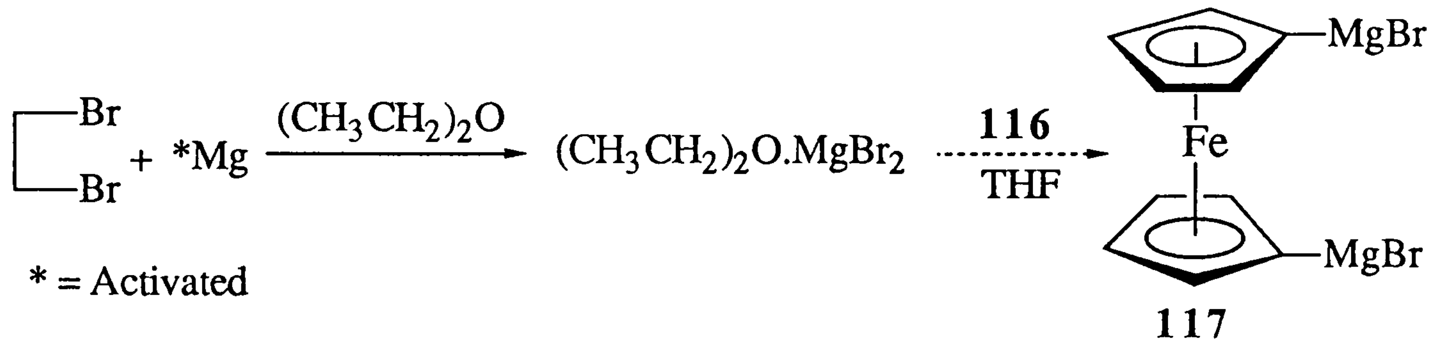
1,1'-Bis(lithium-*N,N,N,'N,'*-tetramethylethylenediamine)ferrocene-(**116**) was prepared *in situ* from ferrocene and lithium-*N,N,N,'N,'*-tetramethylethylenediamine (Scheme 95) according to a literature procedure[112].



Scheme 95

The complex was formed as a characteristic orange precipitate and used immediately after preparation.

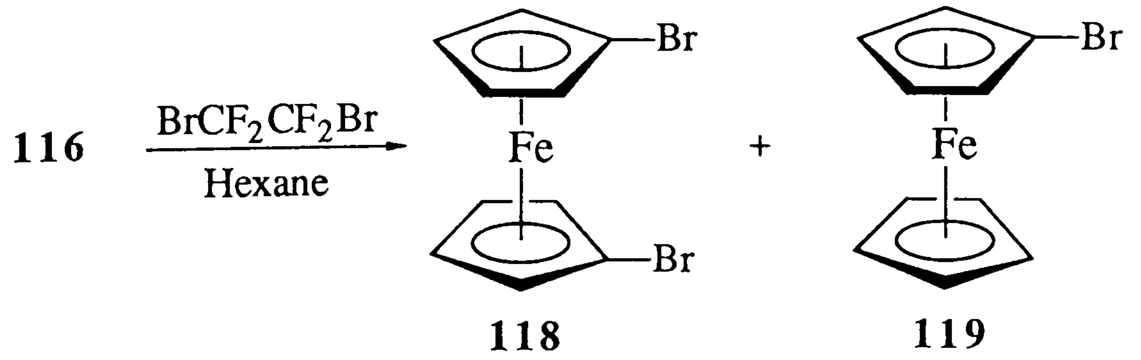
1,1'-Bis(bromomagnesio)ferrocene-(**117**) had previously been prepared *in situ* by Seyferth *et al.*[113] from 1,1'-bis(sodium)ferrocene and magnesium bromide etherate complex. Attempts to extend this metalation exchange using (**116**) and commercial grade magnesium bromide etherate was unsuccessful. A fresh solution of magnesium bromide etherate was prepared under anhydrous conditions from dry 1,2-dibromoethane and activated magnesium turnings[114] (Scheme 96), however on titration of this Grignard solution it was shown to be inactive.



Scheme 96

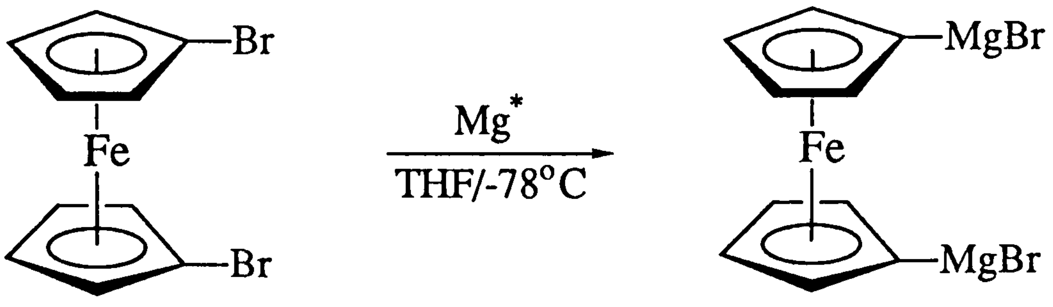
A further route to (**117**) *via* magnesiation of the 1,1'-dibromomoferrocene-(**118**) complex was therefore investigated.

Kovar *et al.*[115] have described the synthesis of 1,1'-dibromoferrocene-(**118**) from (**116**) and 1,2-dibromotetrafluoroethane in 78% yield. This reaction was repeated under identical conditions which afforded 1,1'-dibromoferrocene-(**118**) in 24% yield together with the monobromoferrocene-(**119**) in 15% yield (Scheme 97). Both complexes were isolated as orange crystalline solids after separation from ferrocene by sublimation and further purified by several recrystallisations from hot methanol in which the mother liquor became increasingly rich in (**119**).



Scheme 97

The subsequent preparation of 1,1'-bis(bromomagnesio)ferrocene-(**117**) was carried out using activated magnesium turnings prepared by rapid stirring under argon for 24h[114], followed by addition of a THF solution of (**118**, Scheme 98).

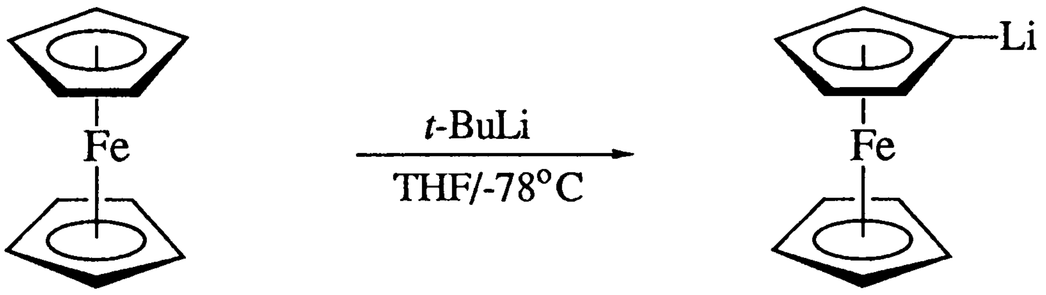


118 **117**

Scheme 98

The activity of the Grignard reagent (**117**) was determined by titration and the quenched product was confirmed as ferrocene by extraction into dichloromethane which afforded a yellow solid, shown to be ferrocene by ^{1}H n.m.r. spectroscopy.

Monolithioferrocene-(**120**) was prepared according to the method described by Kagan and co-workers[116] from ferrocene and *tert*-butyllithium in THF at -78°C (Scheme 99).



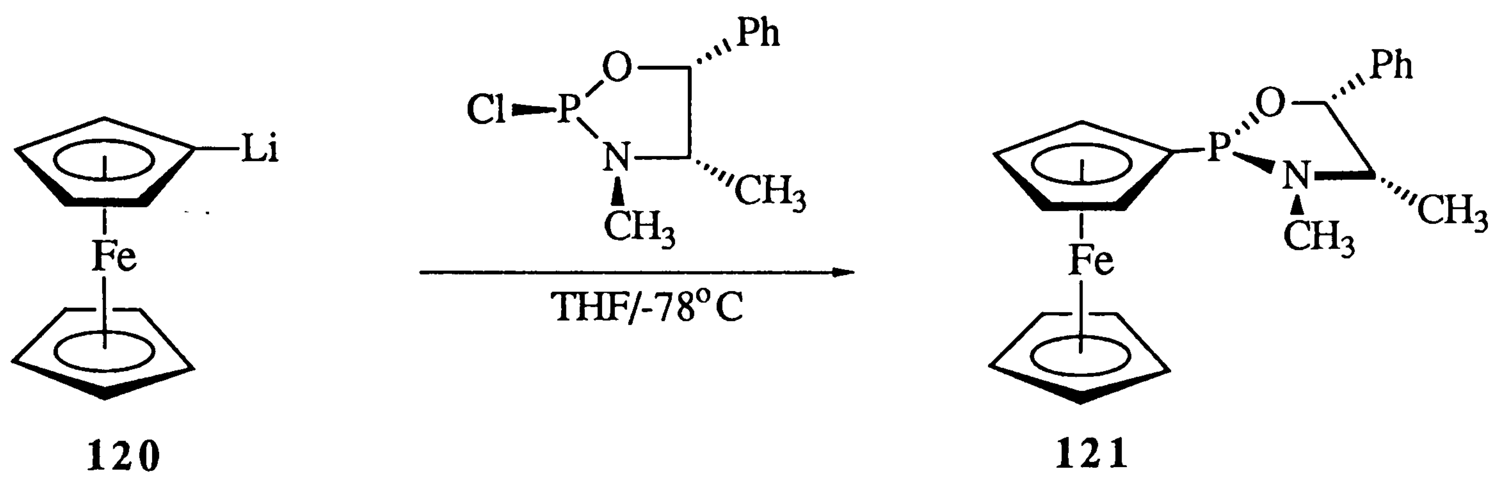
120

Scheme 99

5.2.4. Reactivity of mono- and 1,1'-bis-(metalated)ferrocene reagents.

Reaction of the 1,1'-bis(lithium-*N,N,N,'N,'*-tetramethylethylenediamine)-ferrocene-(**116**) complex with (*S*)-methyl (*ortho*-anisyl)phenylphosphinate-(**89**) under various reaction conditions (solvent, temperature and molar ratio) was unsuccessful.

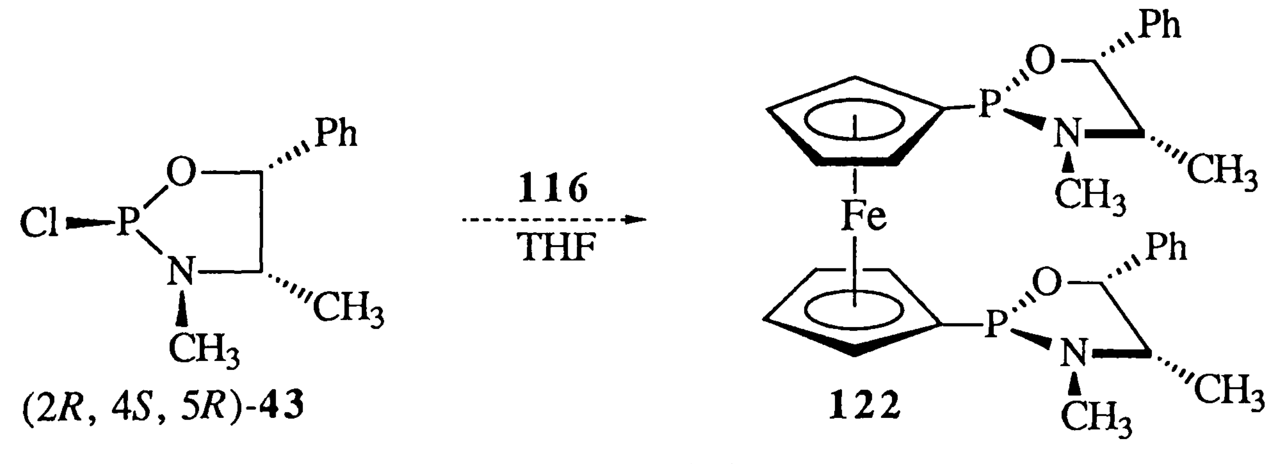
The reaction of monolithioferrocene-(**120**) with a molar equivalence of (2*R*, 4*S*, 5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphosphilidine-(**43**) afforded 2-(ferrocene)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(**121**) as a mixture of diastereoisomers at phosphorus (Scheme 100).



Scheme 100

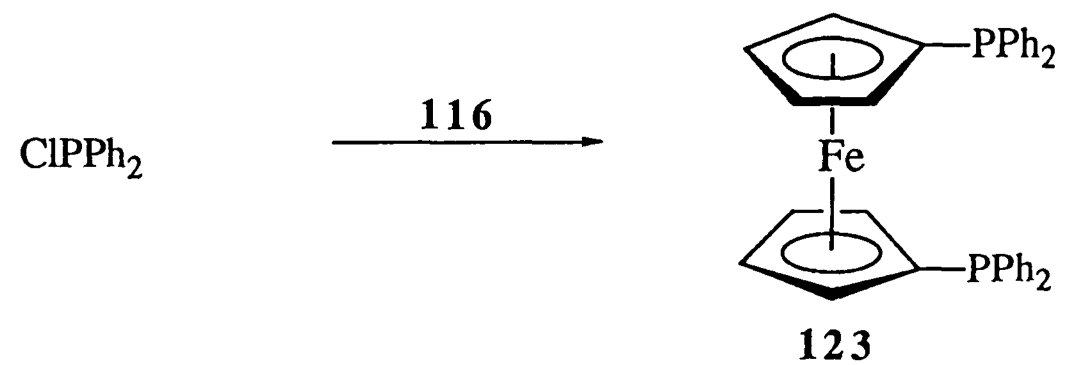
The crude reaction mixture was analysed by ^1H n.m.r. spectroscopy (200 MHz; $CDCl_3$) which showed the presence of two diastereoisomers in *ca.* 1.3:1 ratio. Purification by flash column chromatography afforded the diastereoisomers in a 3:1 ratio. From this point the synthesis of 1,1'-bis-2-(3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine)-ferrocene-(**122**) seemed a logical progression to the desired bisphosphine-(**115**).

Reaction of (**116**) with (2*R*, 4*S*, 5*R*)-(**43**) yielded a mixture of products from which the desired 1,1'-bis-2-(3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine)-1,1'-ferrocene-(**122**) could not be isolated even after extensive optimisation of reaction conditions (Scheme 101).



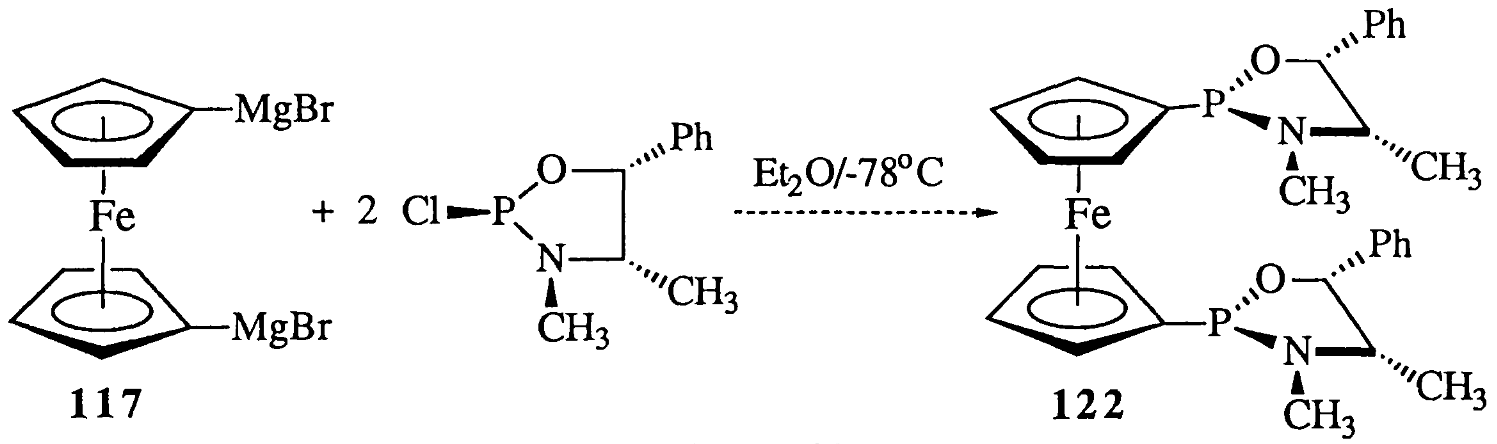
Scheme 101

For comparative purposes the synthesis of 1,1'-bis(diphenylphosphino)-ferrocene-(**123**) from chlorodiphenylphosphine *via* complex (**116**) was investigated. Reaction of chlorodiphenylphosphine with (**116**) according to a literature procedure[117] resulted in the isolation of 1,1'-bis(diphenylphosphino)ferrocene-(**123**, Scheme 102) as an orange crystalline solid in 50% yield.



Scheme 102

1,1'-Bis(bromomagnesio)ferrocene)-(**117**) was reacted with a two-molar excess of freshly prepared (2*R*, 4*S*, 5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(**43**) in diethyl ether under anhydrous conditions at -78°C. The reaction was monitored by analytical t.l.c. which showed the development of a new band. After 1h a portion of the reaction mixture was analysed by ^{1}H n.m.r. spectroscopy which showed a mixture of products. The desired 1,1'-bis-2-(3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine)-ferrocene-(**122**, Scheme 103) could not be observed.

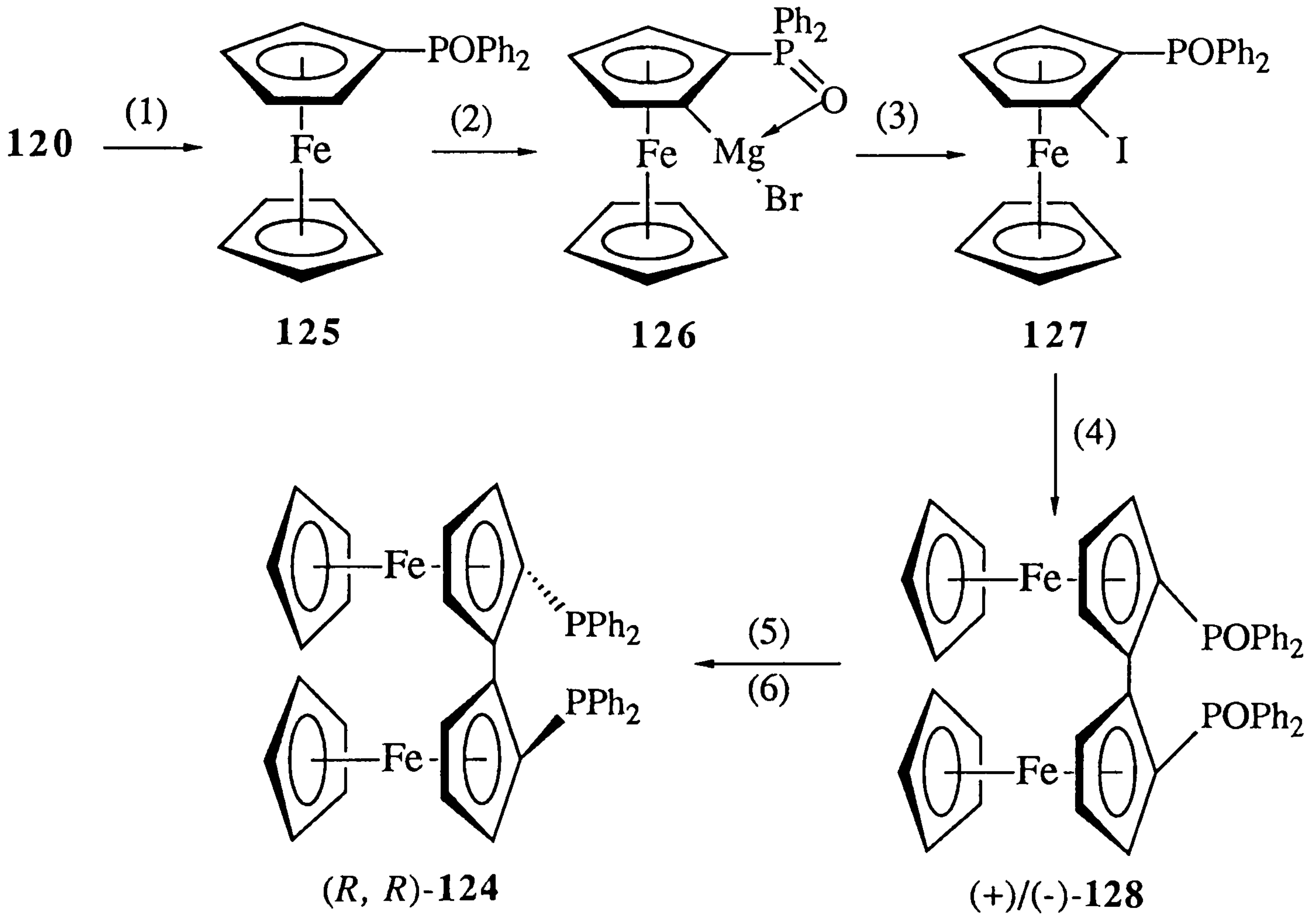


Scheme 103

Accordingly, the reaction conditions were optimised with variations in molar ratio of reagents, temperature and reaction time, however analysis of the crude product by ^{1}H n.m.r. (200 MHz) showed mixtures in all cases. Several attempts were made to isolate products from these reactions using dry and flash column chromatography, however it was apparent that the phosphine components were decomposing on the stationary support. Oxidation of the crude reaction mixtures using *tert*-butylhydroperoxide resulted in oxidation at the iron centre, as shown by the green iron(III) solutions obtained.

After this work was completed Ito and co-workers[118] published a synthetic route to new (*R*, *R*)- and (*S*, *S*)-2,2''-bis(diphenylphosphino)-1,1''-biferrocenes-(**124**, Scheme

104). The key reaction was the selective magnesiation of (diphenylphosphinyl)ferrocene-(**125**) prepared from monolithioferrocene-(**120**) and $ClPOPh_2$. The ferrocenylmagnesium bromide complex-(**126**) was iodinated to afford the iodoferrocene-(**127**) which underwent nickel(0) promoted coupling to yield (+)/(-)-biferrocenes-(**128**). These were optically resolved using (-)- and (+)-dibenzoyltartaric acid (DBTA) and reduced using trichlorosilane/triethylamine to afford (*R*, *R*)- and (*S*, *S*)-2,2''-bis(diphenylphosphino)-1,1''-biferrocene-(**124**, Scheme 104). This route provides enormous scope for developing 2-(ferrocene)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(**121**, Scheme 100) which would enable the synthesis of P-chiral ligands outlined in Scheme 104.

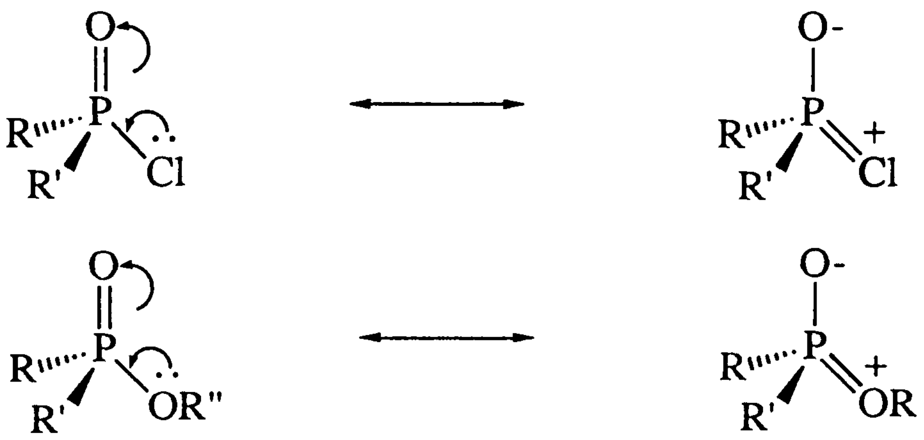


(1) $ClPOPh_2$ (61%) (4) $Ni(acac)_2$ /DIBAL (55%)
(2) i-Pr_2NMgBr-thf/0°C (5) (-)- (+)-DBTA (80%)
(3) I_2 /-30°C (6) $HSiCl_3$, Et_3N/100°C (95%)

Scheme 104

The difference in reactivity of (*S*)-(**96**) and (2*R*, 4*S*, 5*R*)-(**43**) towards nucleophilic attack is presumably due to electronic effects. Chlorine and oxygen have an electron-withdrawing inductive effect (-I) and an electron-donating mesomeric effect (+M)

(Scheme 105). For chlorine -I exerts more influence than the +M, resulting in a net electron-withdrawing effect. However for oxygen +M is greater than -I, resulting in a net electron donation. The consequence is that chlorine enhances its susceptibility to nucleophilic attack, whereas oxygen has the opposite effect, leading to the observed reactivity.



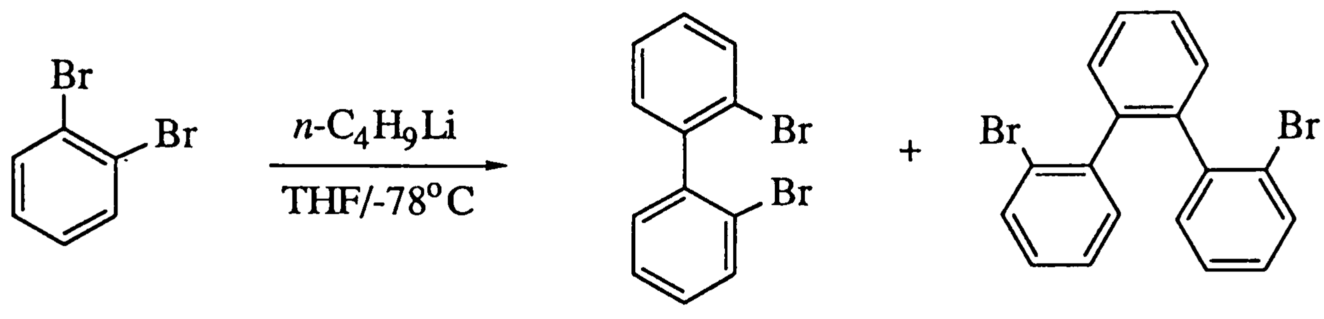
Scheme 105

5.3. Approaches to New P-Chiral Biarylphosphines.

5.3.1. Strategy and Results.

In order to establish the required methodology for a double nucleophilic displacement using di-Grignard or aryllithium reagents, the simpler biphenyl system was also investigated.

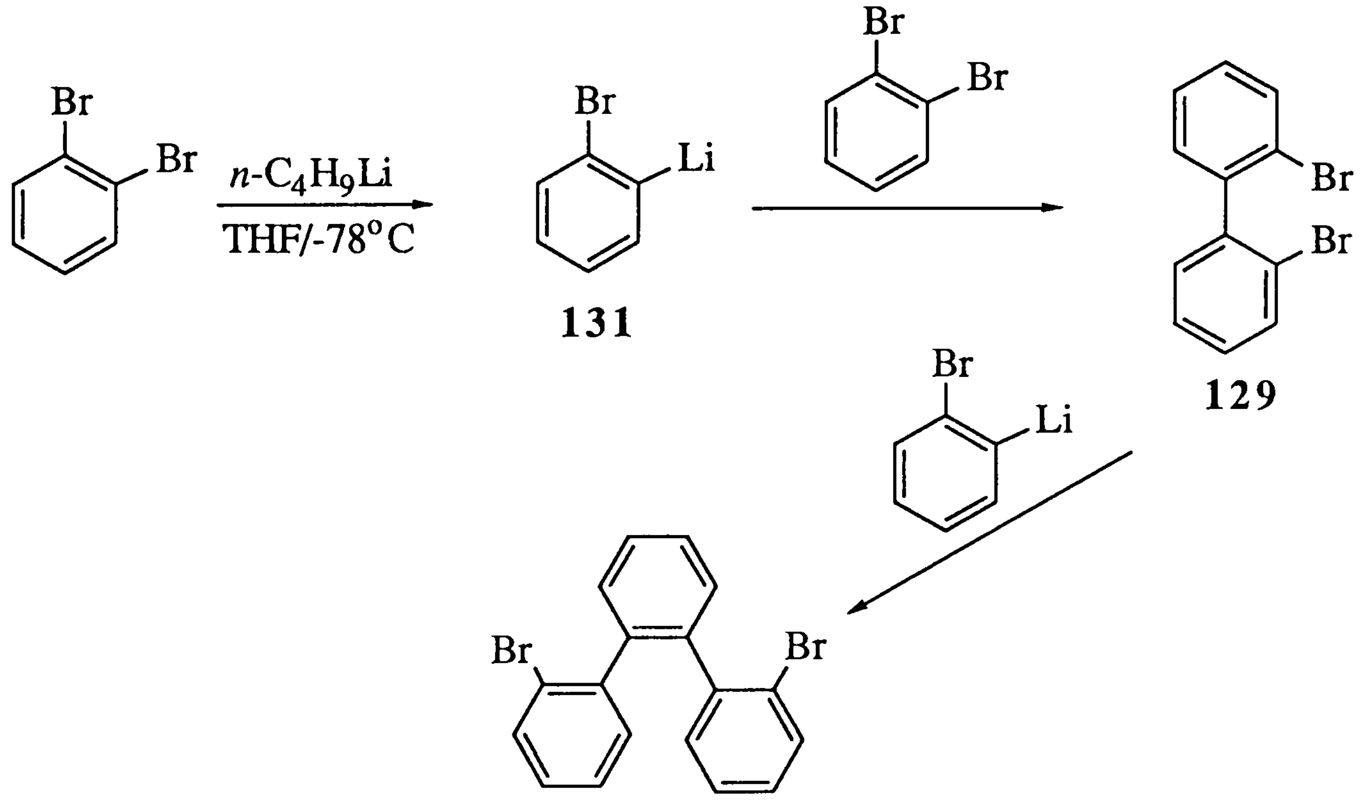
2,2'-Dibromobiphenyl-(**129**) was prepared by the method described by Gilman *et al.*[120] from two-mole equivalents of 1,2-dibromobenzene and *n*-butyllithium in THF at -78°C. The formation of a second product was also evident from ^1H n.m.r. analysis of the crude reaction mixture. 2,2'-Dibromobiphenyl-(**129**) was isolated as a white crystalline solid in *ca.* 14% yield after flash column chromatography, together with a colourless oil in *ca.* 5% yield. The mass spectrum (E.I.) of the oil showed the molecular ion peak at 388 (20) Daltons with a characteristic dibromide isotope pattern, together with a fragmentation peak at 228 (100) Daltons. This would be in accordance with 1,2-bis(*ortho*-bromophenyl)benzene-(**130**, Scheme 106) which has relative molar mass of 338.1, the debromination of which would account for the fragmentation peak at 228 Daltons (388-160). Further evidence in support of this assignment was obtained from ^1H n.m.r. spectroscopy and elemental analysis.



129 **130**

Scheme 106

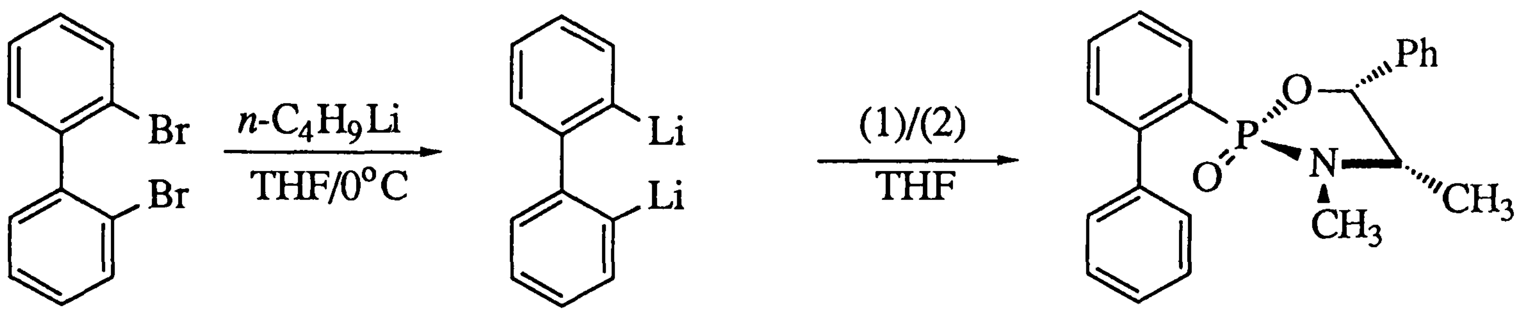
In the original publication[120] Gilman had also carried out the reaction in diethyl ether which resulted in the isolation of an unidentified colourless oil and no 1,2-dibromobiphenyl-(**129**). The mechanism proposed by Gilman, when THF is used as the solvent, involves *ortho*-bromophenyllithium-(**131**) as an intermediate formed *via* halogen-metal exchange of 1,2-dibromobenzene with *n*-butyllithium (Scheme 107). This in turn couples with *ortho*-dibromobenzene to afford 1,2-dibromobiphenyl-(**129**). The formation of the minor product, 1,2-bis(*ortho*-bromophenyl)benzene-(**130**) would be in accordance with this mechanism but with a second addition reaction with a molecule of *ortho*-bromophenyllithium-(**131**, Scheme 107).



Scheme 107

2,2'-Dilithiobiphenyl-(**132**) was prepared from 2,2'-dibromobiphenyl-(**129**) and *n*-butyllithium according to the method described by Rausch and co-workers[121].

Subsequent reaction with a two molar equivalent of (2*R*, 4*S*, 5*R*)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(**43**, Scheme 108) in THF afforded a yellow solid which was analysed directly by ^{31}P n.m.r. spectroscopy and showed two signals in the P(III) region at δP = 134.4 (major signal) and δP = 147.2 p.p.m. (minor signal), together with a peak in the P(V) region at δP = 54.7 p.p.m.



129 **132** **133**

(1) (2*R*, 4*S*, 5*R*)-**43** (-30°C)
(2) *t*-BtOOH (-10°C)

Scheme 108

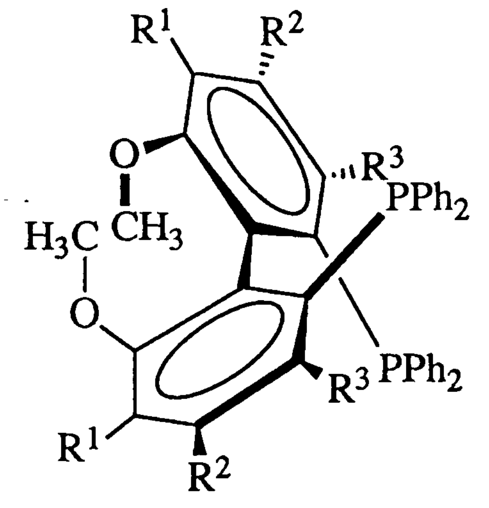
The mixture was oxidized *in situ* using *tert*-butylhydroperoxide and the yellow solid obtained was purified by flash column chromatography. Characterisation by mass spectrometry, ^{1}H and ^{31}P n.m.r. spectroscopy identified the major component as 2-biphenyl-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide)-(**133**, Scheme 108). Optimisation of the reaction conditions in Scheme 108 did not afford any of the desired 1,1'-biphenyl-bis-2-(3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide.

Attempts to prepare 2,2'-bis(magnesiumbromide)biphenyl from 2,2'-dibromobiphenyl-(**129**) were unsuccessful, since the Grignard appeared to decompose upon formation, as was similarly observed in the case of the 1,1'-ferrocene analogue (*vide supra*).

5.4. Approaches to axially dissymmetric P-Chiral bisphosphines.

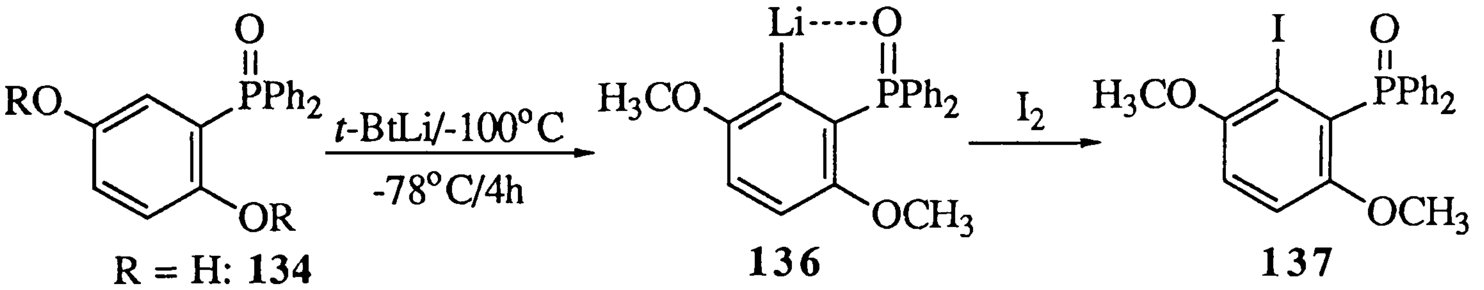
5.4.1. Introduction.

As described in Chapter 1, Schmid *et al.*[29,30] have developed a range of axially dissymmetric bisphosphines (**7a-c**), based on the success of BINAP-(**6**).



7a^{29} $R^1 = R^2 = R^3 = H$
7b^{29} $R^1 = OCH_3$; $R^2 = R^3 = H$
7c^{29} $R^1 = R^2 = OCH_3$; $R^3 = H$
7d^{30} $R^1 = R^2 = H$; $R^3 = OCH_3$

The bisphosphine oxide of (**7d**) was prepared by Dr. S. Woodward of this laboratory. Its synthesis involved the preparation of 2-(diphenylphosphinoyl)-quinhydrol-(**134**) by Michael addition of $Ph_2P(H)O$ to *para*-benzoquinone. Methylation of (**134**) afforded 2,5-dimethoxyphenyl(diphenyl)phosphine oxide-(**135**) which was selectively *ortho*-lithiated at the 6-position in the aryl ring-(**136**, Scheme 109). The anion-(**136**) reacted with molecular iodine to afford the 2-iodo derivative as a single regioisomer in 69% yield.



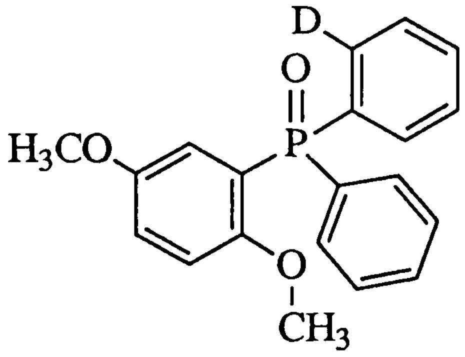
R = H: **134**
R = CH_3: **135**
136
137

Scheme 109

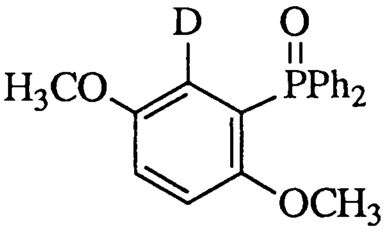
The synthetic use of the lithium carbocations derived from regioselective lithiation of alkyl groups adjacent to a biarylphosphinoyl substituent were previously described as intermediates in the synthesis of DIPAMP-(**11**, Scheme 4) and analogues. Other workers have utilised similar α-phosphorus-stabilised carbanions as chiral auxiliaries[122] in which the mechanism has been postulated to proceed through a common intermediate consistent with a low carbanion rotational barrier[123]. Surprisingly little work has been carried out on the directed lithiation of aromatics or heteroaromatics containing phosphinoyl substituents. Trippett[124] first demonstrated directed *ortho*-lithiation of diethyl phenylphosphonamide which was in turn reacted with a range of electrophiles.

Schlosser[125] showed that lithiation of triphenylphosphine oxide occurs selectively at the *ortho*-position in the synthesis of *ortho*-(1-hydroxyethyl)-phenyl-diphenylphosphine oxide. Only two other authors have used variations upon this approach[126,127], however neither have fully exploited its potential.

The regioselectivity in the lithiation of (**135**) was found by Brown and Woodward[30] to be time dependent by quenching the reaction mixture with D_2O (Table 20) and recording the ^1H n.m.r. spectrum. Initially, at -100°C lithiation is predominant at the *ortho*-phenyl sites to afford mostly (**138**), however upon equilibration at -78°C, proton-transfer occurs to the more activated 6-aryl site due to thermodynamic control facilitated by increased electron density provided by the two methoxy substituents. After four hours 2-^2H-3,6-dimethoxyphenyl-(diphenyl)phosphine oxide-(**139**) was obtained as a single regioisomer (Table 19).



138

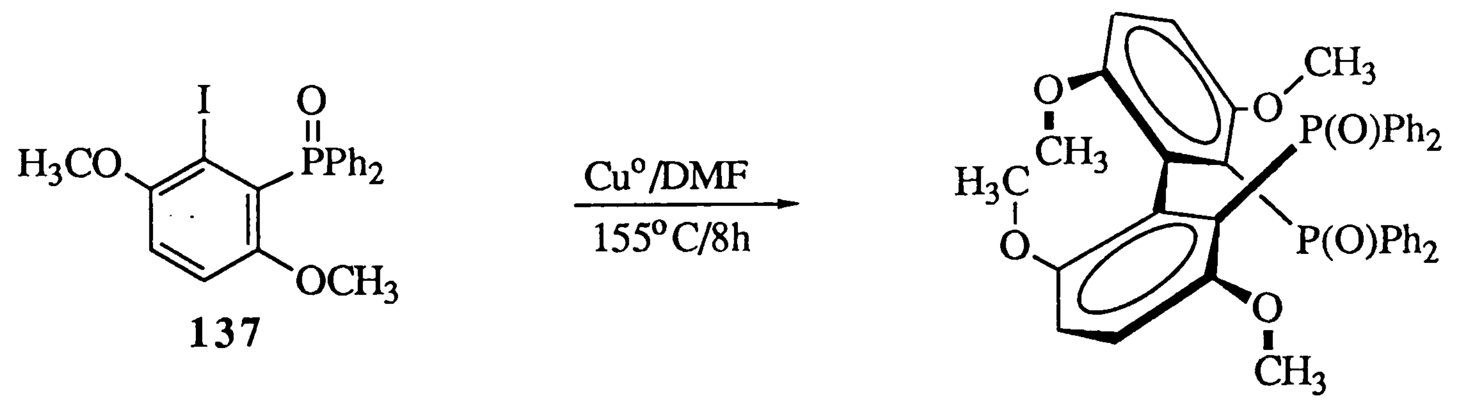


139

Table 19. Regioselectivity in the lithiation of (**135**).

Time	% (**138**)	% (**139**)
2 min	75	25
30 min	70	30
3 hr	20	80
4 hr	10	90

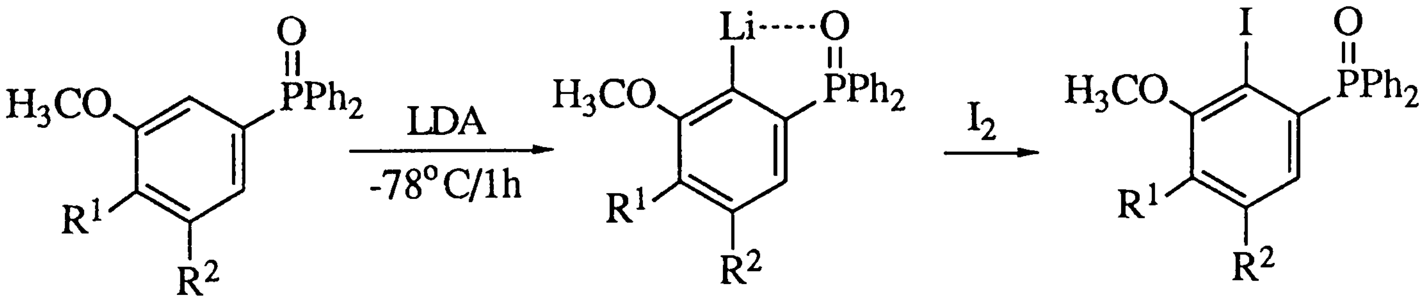
Quenching the mixture after four hours with various electrophiles yielded a variety of 2-substituted-3,6-dimethoxyphenyl(diphenyl)phosphine oxides, in particular iodination afforded 2-iodo-3,6-dimethyoxyphenyl(diphenyl)phosphine oxide-(**137**) regiospecifically (Scheme 109). Efficient Ullman coupling of (**137**) was effected using copper powder in refluxing DMF over 8 hours to afford a mixture of (+)- and (-)-2,2'-diphenylphosphinoyl-3,3',5,5'-tetramethoxybiphenyl-(**140**, Scheme 110).



137 **140**

Scheme 110

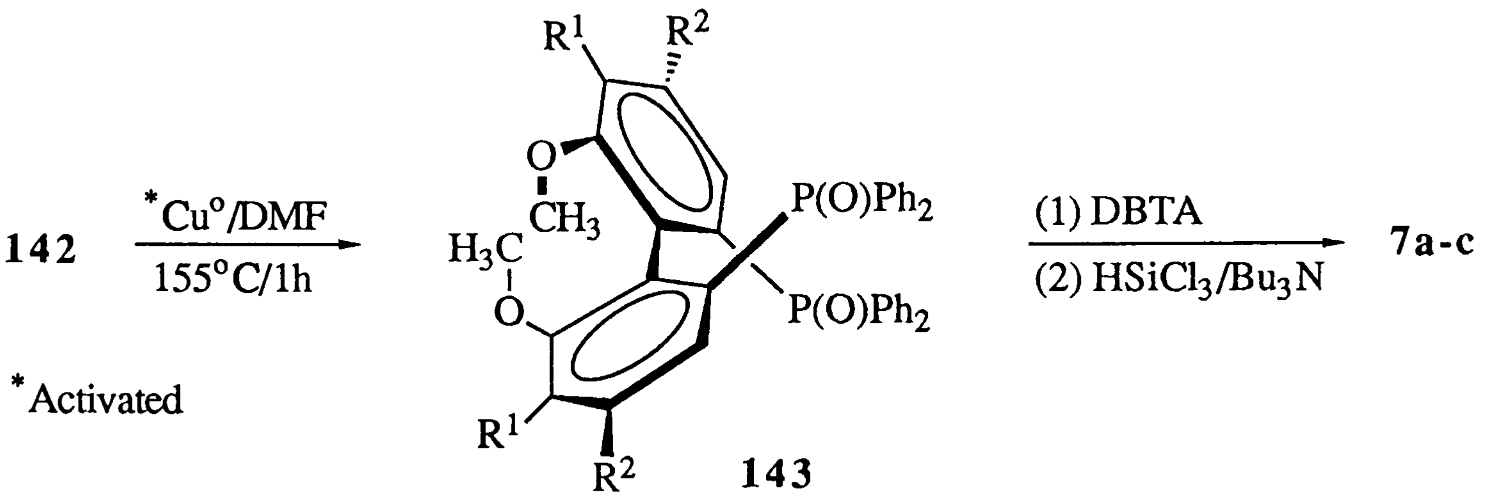
The subsequent reduction of the bisphosphine oxide-(**140**) to the bisphosphine-(**7b**) was only moderately successful using trichlorosilane in the presence of triethylamine, presumably due to steric effects imposed by the neighbouring 2-methoxy substituent. Similarly, Schmid *et al.*[29] prepared their range of axially-dissymmetric bisphosphines-(**7a-d**) by utilising the selective *ortho*-lithiation of (**141**) and Ullman coupling as demonstrated by Brown and Woodward above[30]. The former group chose to use LDA in preference to *tert*-butyllithium (Scheme 111) to form the carbanion at the 6-position of the arene ring. Upon iodination this resulted in isolation of only 80% of the iodinated products-(**142**) and 20% starting material, however these could be separated by crystallisation.



141 **142**

Scheme 111

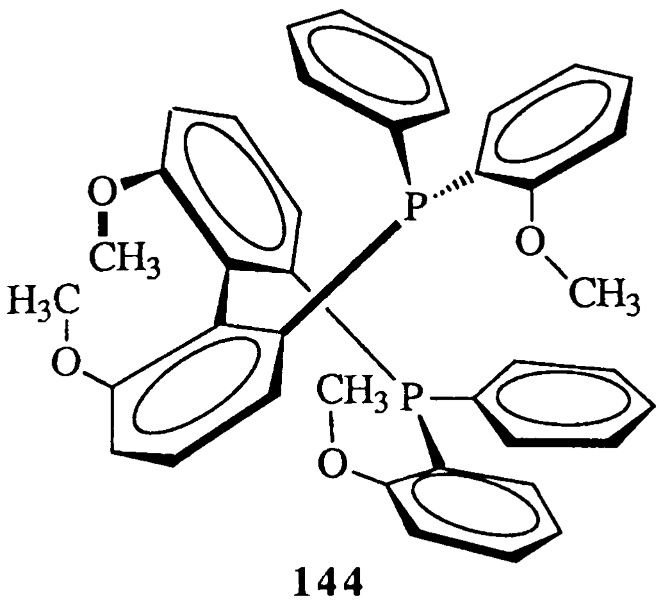
The 2-iodo-aryl(diphenyl)phosphine oxides-(**142**) underwent Ullman coupling under milder conditions than used by Brown and Woodward (Scheme 110) using activated copper bronze in refluxing DMF after only one hour (Scheme 112). The bisphosphine oxides-(**143**) were resolved using (-)-(2*R*, 3*R*)- and (+)-(2*S*, 3*S*)-2,3-*O*-dibenzoyltartaric acid [(-)- and (+)-DBTA , respectively] and, unlike the 2-methoxy analogue-(**140**), were efficiently reduced using trichlorosilane in the presence of tributylamine in refluxing xylene, to yield the corresponding phosphines-(7a-c). The molecular structure of the palladium complex of (+)-(*R*)-(**7a**) was determined by single-crystal X-ray diffraction studies which confirmed the absolute stereochemistry of the coordinated bisphosphine[29].



Scheme 112

5.4.2. The nucleophilc displacement route to P-chiral axially dissymmetric 1,4-bisphosphines.

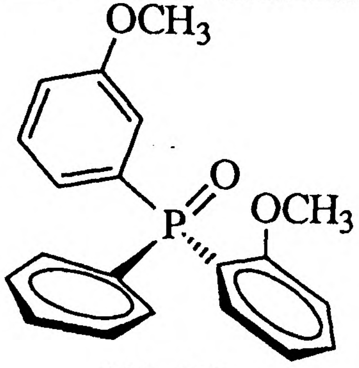
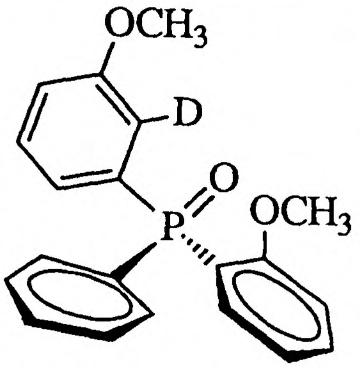
Based on the above results the synthesis of a homochiral biaryl(2-iodoaryl)phosphine oxide should allow the synthesis of a corresponding range of P-chiral axially dissymmetric 1,4-bisphosphines. Furthermore this methodology is only applicable to phosphine oxides since the corresponding phosphines do not undergo this reaction[29,30]. Interestingly the thione analogues undergo selective *para*-lithiation in the case of 2,5-dimethoxy(diphenyl)phosphine sulphide[29], presumably due to control by the methoxy substituents. In view of this it is unlikely that homochiral triarylphosphine boranes would undergo similar *ortho*-lithiation reactions, hence the nucleophilic displacement route provides a novel opportunity of accessing 1,4-bisphosphines of this type-(**144**).



144

As described in Chapter 4, the synthesis of (*S*)-*ortho*-anisyl (*meta*-anisyl)phenylphosphine oxide-(**109**) involves three successive nucleophilic displacements from (2*R*, 4*S*, 5*R*)-(**55**) with an overall yield of 57% (Scheme 113) and was deemed to be 96% e.e. by ^1H n.m.r. using the chiral shift reagent-(**95**). Since (*S*)-(**109**) contains both *meta*-anisyl- and *ortho*-anisyl arenes, competitive lithiation on the *ortho*-anisyl ring was considered a possibility. Brown[30] and Schmid[29] had used *tert*-butyllithium and lithiumdiisopropylamide respectively to effect selective *ortho*-lithiation (Schemes 109 & 111). Both of these routes, and modifications thereof, were used for the preparation of the anion of (**145**, Scheme 113) and screened by quenching the reaction mixtures with D_2O and observing the 6-H-*meta*-anisyl proton in the ^1H n.m.r. spectrum. Optimum results were obtained using *tert*-butyllithium and a reaction time of 6h at -78°C, which characteristically formed a straw-coloured solution. Measurement of the ^2H n.m.r. spectrum showed a single peak at δ = 24.61 p.p.m., indicating deuteration at only one site. More specifically, the ^1H n.m.r. spectrum (500 MHz; $CDCl_3$) showed 80% of 2-^2H-6-methoxyphenyl-*ortho*-anisyl(phenyl)phosphine oxide-(**146**) and no observed lithiation on the *ortho*-anisyl ring (Figure 18). The *meta*-anisyl-H-6-proton can be observed at 7.72 p.p.m. in (*S*)-(**109**) and compared directly in the *meta*-anisyl-^2H-2 analogue-(**146**).

The next step in the synthetic sequence involved the preparation of (*S*)-2-iodo-3-methoxyphenyl-(*ortho*-anisyl)phenylphosphine oxide-(**147**, Scheme 113). Quenching the anion-(**145**, Scheme 113) with molecular iodine, under optimum conditions described for the deuteration experiment, yielded a mixture of the desired compound together with starting material and impurities. The anisyl-methoxy signals in the ^1H n.m.r. spectrum served as a useful handle for monitoring optimisation of the iodination reaction. Varying the reaction conditions however resulted in formation of the iodide-(**147**) as an impure mixture, the other major component being starting material. This result contrasted with the ease of isolation of the corresponding deuteride-(**146**). Purification was partially effected using flash and dry column chromatography which resulted in the isolation of (*S*)-(**147**) in low yield and still containing some starting material, surprisingly this could not be purified further by flash or dry column chromatography, or recrystallisation.

		An^{o}-H-6	Ph-H-2,6	An^{m}-H-6	An^{m}-H-2
 (*S*)-**109**	Multiplicity	ddd	ddt	ddd	ddt
	δ / ppm	8.29	7.90	7.72	7.47
	$J_{P,H}$ (Hz)	13.2	12.3	13.5	12.0
	$J_{5,6}$ (Hz)	7.6	7.6	–	–
	$J_{4,6}$ (Hz)	1.8	1.5	1.2	–
	$J_{2,6}$ (Hz)	–	–	1.3	1.3
	$J_{2,3}$ (Hz)	–	–	–	7.5
 (*S*)-**146**	Multiplicity	ddd	ddt	–	ddd
	δ / ppm	8.26	7.90	–	7.45
	$J_{P,H}$ (Hz)	13.3	12.3	–	12.0
	$J_{5,6}$ (Hz)	7.6	7.7	–	–
	$J_{4,6}$ (Hz)	1.8	1.5	–	–
	$J_{2,4}$ (Hz)	–	–	–	1.0
	$J_{2,3}$ (Hz)	–	–	–	7.5

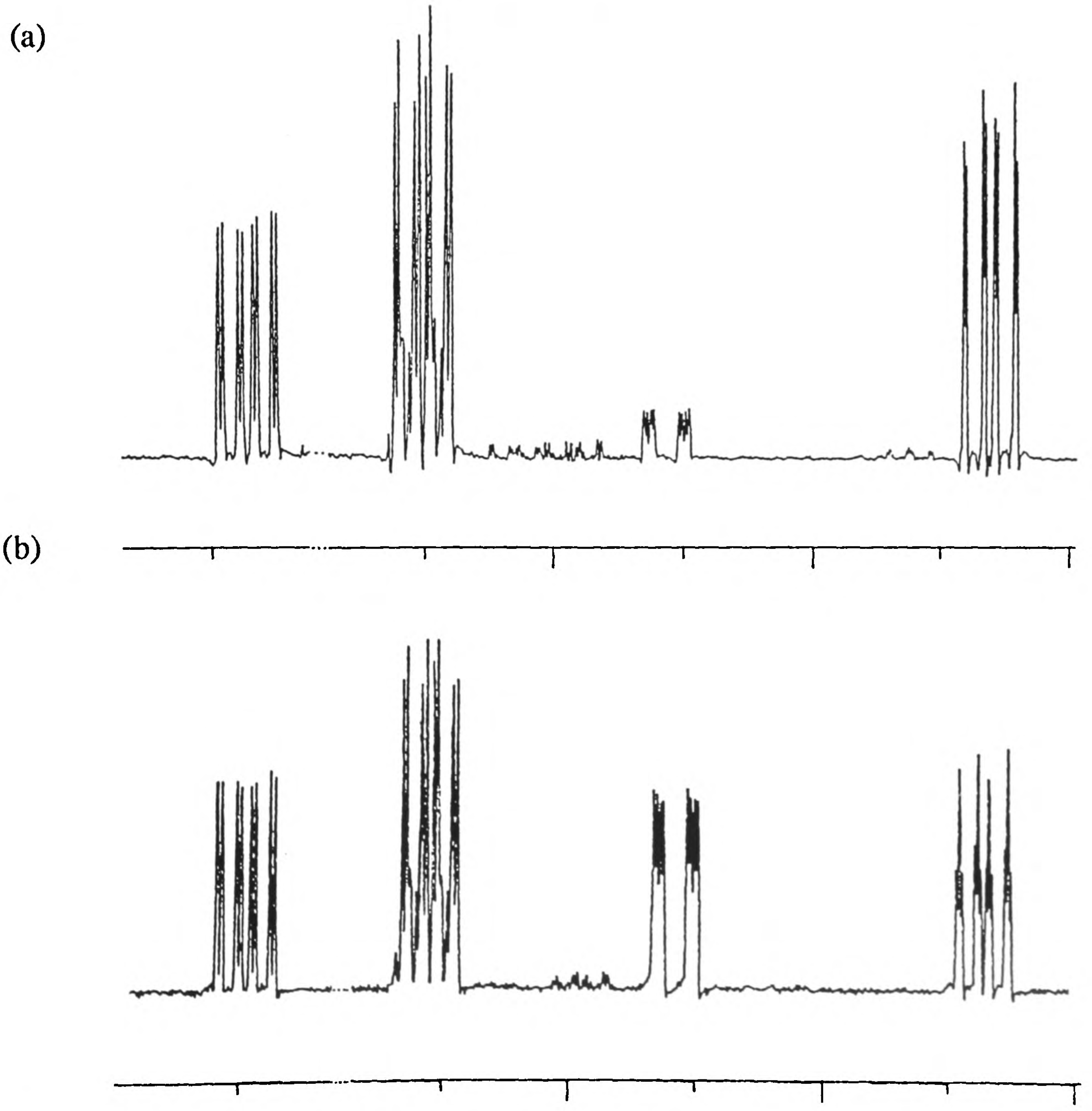
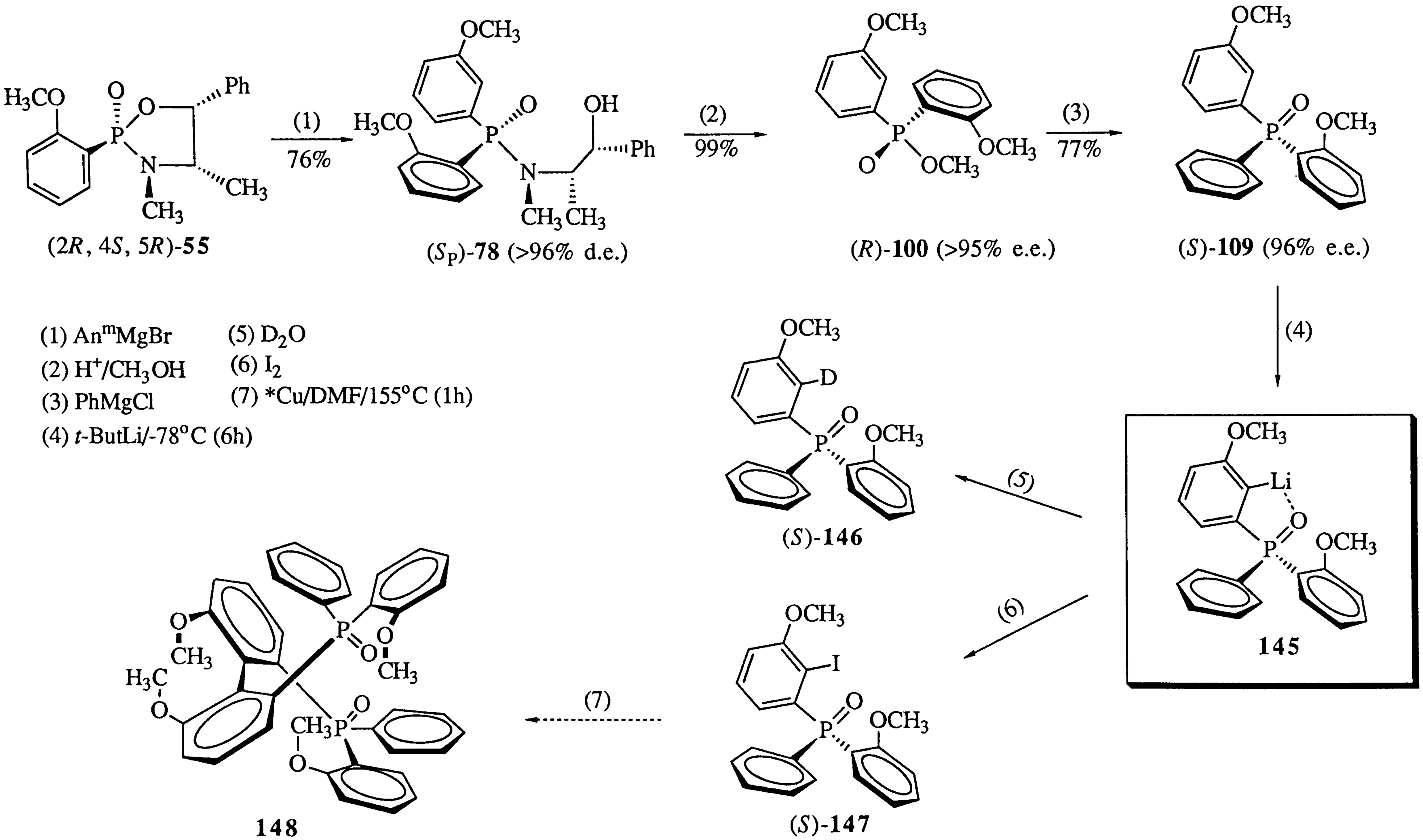


Figure 18: ^{1}H n.m.r. (500 MHz; C_6D_6) spectra of (a); (*S*)-(**109**) and (b); (*S*)-(**146**).



Scheme 113. Synthetic route to 2,2'-bis[*ortho*-anisyl(phenyl)phosphinoyl]biphenyl-(**148**)

For comparative purposes, 2-iodo-3,6-dimethoxyphenyl(diphenyl)phosphine oxide-(**137**) was prepared *via* the method described by Brown and Woodward[30] (Scheme 109). The most striking difference was that the anion-(**136**) precipitates from solution after *ca.* three hours, whereas the anion-(**145**, Scheme 113) under identical conditions was significantly more soluble. Furthermore, on iodination (**137**) was easily isolated as a white crystalline solid from the crude reaction mixture, the ^{1}H n.m.r. spectrum of which showed only the presence of a single regioisomer. This contrasted with the corresponding work-up of (**147**, Scheme 113).

The Ullman coupling of 2-iodo-3,6-dimethyoxyphenyl(diphenyl)phosphine oxide-(**137**) was effected using the method described by Schmid *et al.*[29] using copper bronze which had been pre-activated with iodine. In this way the reaction time was decreased by a factor of eight and the bisphosphine oxide-(**140**, Scheme 110) was obtained regiospecifically as a white crystalline solid.

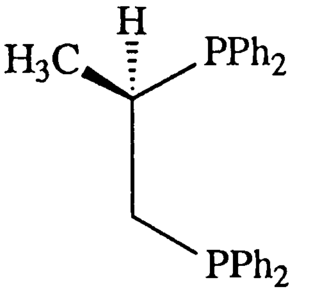
5.4.3. Summary.

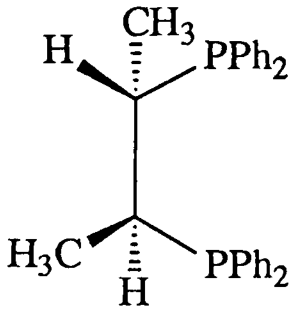
The preparation of homochiral (*S*)-2-iodo-3-methyoxyphenyl (*ortho*-anisyl)phenylphosphine oxide-(**147**) was effected by three successive nucleophilic displacements from diastereomerically pure (2*R*, 4*S*, 5*S*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(**43**) followed by selective *ortho*-iodination *via* the 2-lithio complex-(**145**, Scheme 113). The final iodination step requires further optimisation but represents a synthetically useful precursor to new axially dissymmetric bisphosphine ligands possessing chirality at the phosphorus centres.

5.5. Other Work.

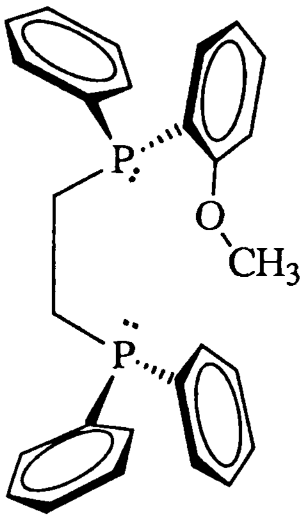
5.5.1. Approaches to 1,2-bisphosphines containing only one homochiral phosphorus centre.

Various structural modifications have been made to the DIPAMP-(**11**) ligand with the primary aim of extending the range of substrates available for homogeneous catalysis. These modifications have centred upon; increased bite-angle, exemplified by the methylene-(**12**) and ethylene-(**13**) homologues; and the nature of the substituents at phosphorus, for which the *tert*-butyl analogue-(**14**) is the only notable example. However, the necessity of having two chiral centres in DIPAMP-(**11**) has not been duely considered. This is rather surprising since the 1,2-bisphosphines, (*R*)-PROPHOS-(**149**) and (*S*, *S*)-CHIRAPHOS-(**150**) have chiral backbones containing one and two asymmetric centres respectively yet both catalyse the reaction in Figure 2 with *ca.* 90% e.e..


(*R*)-PROPHOS-**149**


(*S*, *S*)-CHIRAPHOS-**150**

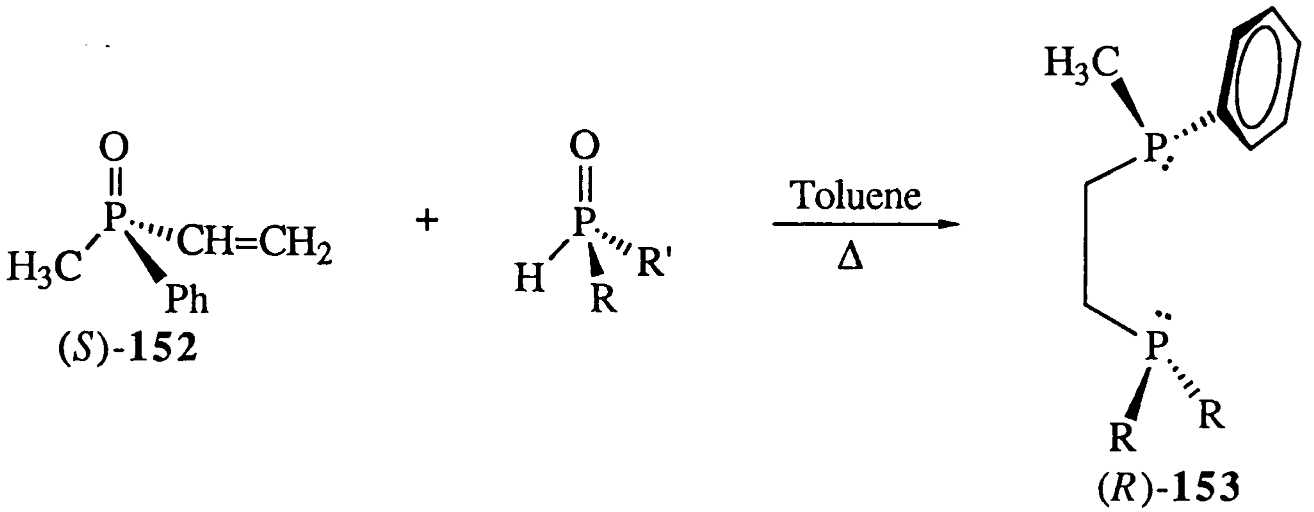
In order to address this question a synthetic route to 1-(diphenylphosphino)-2-(*R*)-[(*ortho*-anisyl)(phenyl)phosphino)]-1,2-ethane-(**151**) was required.


(*R*)-**151**

5.5.2. *Strategy.*

The starting point to the target compound-(**151**) centred upon coupling the previously described homochiral methyl phenyl(vinyl)phosphinates-(**96** & **97**, Chapter 4) and prochiral diphenylphosphine oxide. The work was carried out in collaboration with Mr G. Hill[106] and Mr M. Barker[108].

Prietrusiewicz *et al.*[128,129] had previously demonstrated this approach in the thermally-induced Michael addition of (*S*)-methyl phenyl(vinyl)phosphinate-(**152**) and bialkyl- and biarylphosphine oxides (Scheme 114). The reaction is slow and low-yielding and, in some cases, suffers from racemisation.



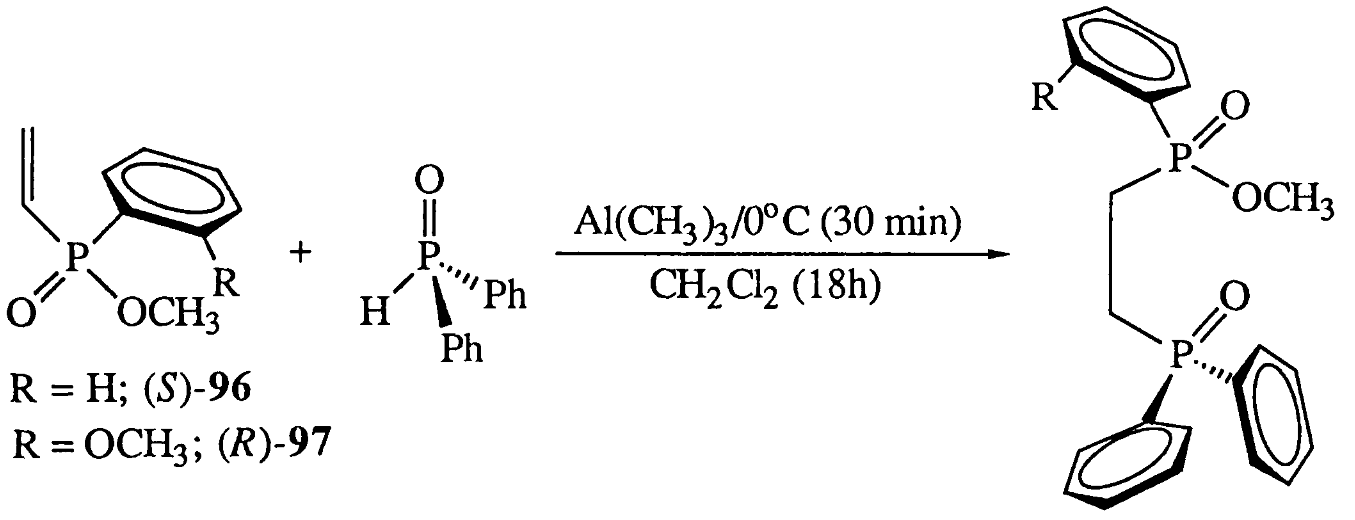
(*S*)-**152**

(*R*)-**153**

Scheme 114

An improvement upon this approach was made by using trimethylaluminium which has been shown by Green[107] to be highly effective in the addition of triarylphosphites to α-β-unsaturated carbonyl compounds.

The trimethylaluminium-catalysed Michael addition of (*S*)-methyl (phenyl)-vinylphosphiante-(**96**) and (*R*)-methyl (*ortho*-anisyl)vinylphosphinate-(**97**) with diphenylphosphine oxide was carried out as a stoichiometric reaction at 0°C in dichloromethane under anhydrous conditions according to Scheme 115.



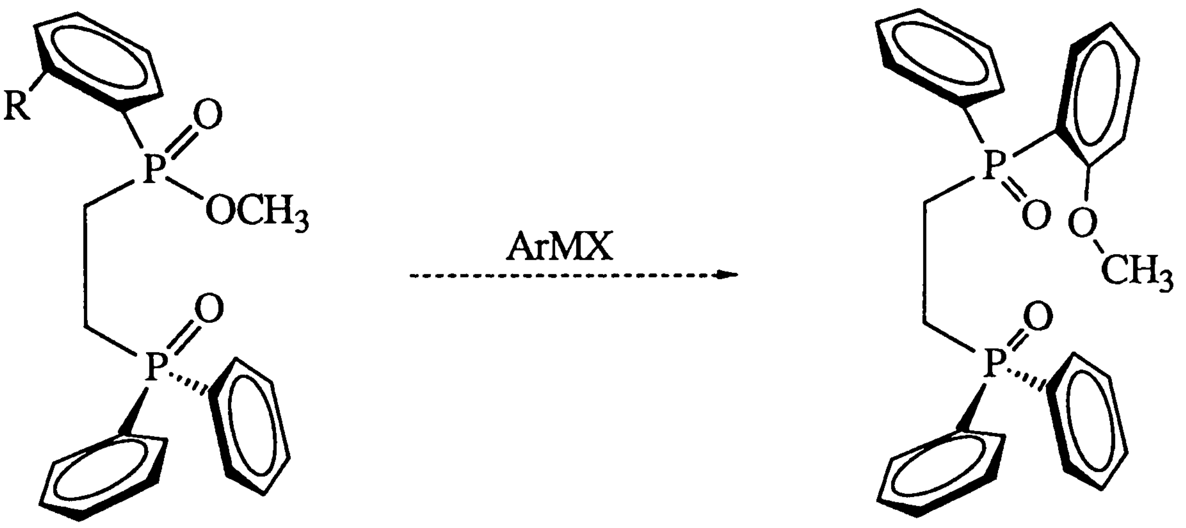
R = H; (*S*)-**96**
R = OCH_3; (*R*)-**97**

R = H; (*R*)-**154**
R = OCH_3; (*S*)-**155**

Scheme 115

Both 1-methoxy-1-phenylphosphino-2-diphenylphosphino-1,2-ethane-(**154**) and its *ortho*-anisyl analogue-(**155**) were isolated as a white powders in good yield. Their optical purities were determined to be >90% e.e. by ^1H n.m.r. spectroscopy using the chiral shift reagent-(**95**) described in Chapter 4.

The subsequent methoxy displacement from these compounds using arylmagnesium halides has precedent from the monophosphine work described in Chapter 4. However displacement of the methoxy residue could not be effected even under vigorous conditions using arylLi(TMEDA) complexes (Scheme 116, *c.f.* Scheme 90).



R = H; (*R*)-**154**
R = OCH_3; (*S*)-**155**

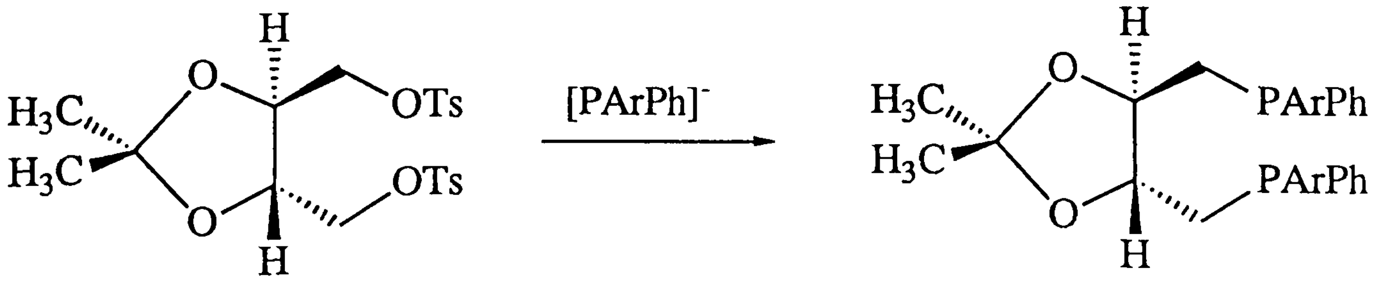
156

Scheme 116

Since the methoxy displacement step in compounds (*R*)-(**154**) and (*S*)-(**155**) proved opposite to that found for the methyl biarylphosphinates described in Chapter 4 the route was abandoned.

5.5.3. *New P-chiral DIOP-(4) analogues.*

Burgess *et al.*[130] have recently communicated their work concerning the synthesis of a range of ligands containing chirality at phosphorus and having the same backbone as DIOP-(**4**). The synthesis involved formation of the phosphide anions, $[PPhAr]^-$ prepared by reductive cleavage of biarylphenylphosphines followed by reaction with the electrophile, 1,4-ditosyl-2,3-*O*-isopropylidine-L-threitol (Scheme 117). The ligands were obtained after exhaustive separation of the diastereoisomers.



c.a. 1:2:1 mixture of diastereoisomers

Scheme 117

The DIPAMP-(**11**) analogue (Ar = *ortho*-anisyl) containing matched-(*S*,*S*)-configuration at phosphorus catalysed the reaction in Figure 2 with 70% e.e. of the *S*-amino acid, this being the highest enantioselectivity obtained with the ligands prepared. The result is somewhat surprising since both DIPAMP-(**11**) and DIOP-(**4**) give higher enantioselectivities (Table 1). Burgess explains this difference as being due to the difficulty in obtaining C_2 symmetry in the complexed chelate, furthermore his catalytic reactions were unoptimised.

The ligands prepared by Burgess form 7-membered chelates in which the DIOP-type backbone is relatively flexible which may account for the lower enatioselectivities, this gives further precedent to the development of P-chiral bisphosphines based on the biaryl and binaphthyl systems in which the added rigidity of the backbone should enhance the non-bonded interactions.

5.6. Project Overview.

The preparation of bulky triaryphosphines has, *hitherto*, required separation of diastereoisomers or enantiomer enrichment at some stage of the synthesis.

The work presented in this thesis has demonstrated: (1) Diastereoselectivity in the P-O bond cleavage of aryl-oxazaphosphilidine-oxides which proceeded with retention of configuration at phosphorus as shown by single-crystal X-ray studies; (2) The efficient removal of the chiral auxilliary to generate the corresponding methyl biarylphosphinates in almost quantitative yield and ≥95% e.e.; (3) The subsequent synthesis of homochiral triarylphosphine oxides in high yield and optical purity by efficient removal of the methoxy residue under mild conditions. Reduction to the corresponding phosphines has been established by Mislow[105] and was shown to proceed smoothly for (*R*)-(**19**). The application of the nucleophilic displacement route to these and other bulky ligands will be of use in iridium catalysis.

While many workers still successfully prepare new and interesting P-chiral bisphosphines for homogeneous asymmetric catalysis using chromatography or selective crystallisation to effect separation of diastereoisomers or enantiomers there is still a need for a more general and applied route to these compounds.

The work presented here has demonstrated the use of two key compounds in approaches to achieving this goal: (1) The diastereoselective P-Cl cleavage in (2*R*, 4*S*, 5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(**43**) using monolithioferrocene which gives precedent for the further development of P-chiral ferrocene ligands; (2) The regiospecific *ortho*-lithiation of the *meta*-anisyl ring in (*S*)-*ortho*-anisyl (*para*-anisyl)phenylphosphine oxide-(**109**) gave access to the corresponding iodo derivative which represents a key intermediate to new P-chiral axially dissymmetric bisphosphines.

Experimental.

6.1 General experimental techniques.

6.1.1. Instrumental.

Elemental microanalyses were performed by Mrs V. Lambourn within the Dyson Perrins Laboratory using a Carlo Erba 1106 elemental analyser.

Proton nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian Gemini 200 (200 MHz) or a Bruker AM 500 (500 MHz) spectrometer as indicated and are referenced to residual solvent protons ($C\mathit{H}Cl_3$, δ_H 7.27 or $C_6\mathit{H}_6$, δ_H 7.37). Where appropriate, multiplicities were determined using COSY or ^1H-^1H decoupling experiments. The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet).

Carbon-13 n.m.r. spectra were recorded on a Bruker AM 500 (126 MHz) or a Bruker AM 250 (62.9 MHz) spectrometer as indicated and are referenced to the residual solvent peaks ($\mathit{C}DCl_3$, δ_C 77.0 p.p.m. or C_6D_6, δ_C 128.0 p.p.m.). Where appropriate, multiplicities were determined using a DEPT (Distortionless Experiment by Polarisation Transfer) pulse sequence and recorded as either; s (singlet) or d (doublet).

Phosphorus-31 and boron-11 n.m.r. spectra were recorded on a Bruker AM 250 spectrometer operating at 101 MHz. Chemical shifts (δ) are given in p.p.m. downfield of 85% phosphoric acid (^{31}P) or BF_3 (^{11}B). Solvents and references are as indicated.

Infra-red (i.r.) spectra were recorded on a Perkin-Elmer 781 spectrometer with absorption maxima given in cm^{-1} with the following abbreviations: strong (s), medium (m), weak (w) and broad (br). Samples were prepared on NaCl plates as Nujol mulls, KBr discs or neat as indicated. Spectra were calibrated using the standard absorption frequency for polystyrene at 1601 cm^{-1}.

Mass spectra (*m*/*z*) were recorded by Dr. R.T. Aplin or Mr. R. Procter on a Varian MAT CH7, V.G Micromass 16F or ZAB-1F/16F spectrometers; values followed by the percentage abundance in parentheses, are given for the molecular ion peaks in Daltons. Ionisation techniques included; chemical ionisation (C.I.), electron impact (E.I.) and desorption chemical ionisation (D.C.I.) and are as indicated with ammonia used as the ionising source for C.I.

Optical rotations were measured on a thermostatted Perkin-Elmer 241 polarimeter using the 589.3 nm D line of sodium. Melting-points are uncorrected.

6.1.2. Experimental procedures.

All manipulations involving phosphines, Grignard and organo-lithium reagents were carried out under an argon atmosphere using standard vacuum line techniques[132] and all solvents were deoxygenated prior to use.

Flash chromatography was performed on Merck silica gel 60H, 230-300 mesh supplied by B.D.H and according to the method of Still[133]. When appropriate, components were identified by t.l.c in suitable solvents on Merck Kiesegel 60F 254 plastic plates coated with 0.2 mm of silica visualised by u.v. light. Dry flash chromatography was performed on Merck silica gel 60H using suction in place of head pressure according to the method of Harwood[134].

Solvents were purified according to the procedures described by Perrin *et al.*[135]. Toluene, triethylamine and *N*-methylmorpholine were freshly distiled from CaH_2. Methanol was freshly distiled from magnesium, dichloromethane from P_2O_5; tetrahydrofuran (THF), diethyl ether (Et_2O) were distiled from sodium benzophenone ketyl under nitrogen prior to use. All solvents were obtained from either B.D.H or Aldrich Chemical Co.. Dichlorophenylphosphine, [(1*R*, 2*S*)-(-)-α-(1-methylaminoethyl)benzyl alcohol], (*S*)-(+) or (*R*)-(-)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine-(**95**), *tert*-butylhydroperoxide (3.0 M in toluene), methylmagnesium chloride (1.0 M in THF) and ethylmagnesium chloride (1.0 M in THF), borane-methyl sulphide complex (10 M in BH_3), *t*-butyllithium (1.7 M in pentane) and *n*-butyllithium (1.4 M in hexane), 4-methylmorpholine, triethylamine, 4-fluorophenol, methylsulphonic acid and sulphur were obtained from the Aldrich Chemical Co and used without further purification. $CDCl_3$ and C_6D_6 were dried over 4-Å molecular sieves.

6.2. ^{1}H N.m.r. Shift Experiments.

Determination of the optical purity of phosphine oxides was carried out according to the method described by Kagan[104] *viz:* (*R*)-(-) or (*S*)-(+)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine-(**95**) (0.5 ml, 0.032 mmol, 0.064 M) in $CDCl_3$ was added to the phosphine oxide (0.25 ml, 0.019 mmol, 0.019 M) in $CDCl_3$ contained in a 5 mm n.m.r. tube. Its ^{1}H n.m.r spectrum (500 MHz) was then recorded and the procedure repeated for the opposite antipode of the chiral shift reagent.

6.3. Experimental for X-ray data collection.

The crystal structures of (2*R*, 4*S*, 5*R*)-(**42**), (2*S*, 4*S*, 5*R*)-(**56**), (2*S*, 4*S*, 5*R*)-(**50**), (2*R*, 4*S*, 5*R*)-(**52**) and (2*S*, 4*S*, 5*R*)-(**51**) were solved by Dr. C. Schwalbe at the University of Aston, while compound (2*R*,4*S*,5*R*)-(**49**) was solved with the help of Dr. C.K. Prout at The Chemical Crystallography Department (Oxford). Crystal data (Table 20) for the aryl-oxazaphospholidines were collected using Enraf-Nonius CAD4-F 4-circle diffractometers. Graphite monochromated X-radiation was used to collect reflected intensities by the ω-2θ scan technique, with Mo-Kα radiation (λ = 0.71069 Å) for (2*R*, 4*S*, 5*R*)-(**42**), (2*S*, 4*S*, 5*R*)-(**56**), (2*S*, 4*S*, 5*R*)-(**50**), (2*R*, 4*S*, 5*R*)-(**52**) and (2*S*, 4*S*, 5*R*)-(**51**) out to Bragg angles θ of 25, 26, 25, 25 and 25°, respectively, and with Cu-Kα (λ = 1.5418 Å) for (2*R*,4*S*,5*R*)-(**49**) to θ = 75°. The space group was determined unambiguously as a result of structure analysis. The unit cell parameters were obtained by least-squares refinement, the setting angles of 25 accurately centred reflections being used for this purpose. The ω scan angle was calculated from $[M + N(\tan\theta)]^o$, where M = 1.00, N = 0.35 for (2*R*, 4*S*, 5*R*)-(**42**), (2*S*, 4*S*, 5*R*)-(**56**), (2*S*, 4*S*, 5*R*)-(**50**), (2*R*, 4*S*, 5*R*)-(**52**) and (2*S*, 4*S*, 5*R*)-(**51**) and M = 1.10, N = 0.14 for (2*R*, 4*S*, 5*R*)-(**49**), and increased by 25% on each side for background determination. The scan speed was varied from 1.0 to 4.0, 0.8 to 3.3, 1.0 to 3.3, 1.0 to 6.7 , 1.0 to 3.3 and 0.6 to 2.5° min^{-1} depending upon the respective intensities. Several standard reflections were measured every hour during data collection and showed no appreciable variation with time. The data were corrected for Lorentz and polarisation effects[136]. An absorption correction was also applied to (2*R*, 4*S*, 5*R*)-(**49**) to obtain relative intensities. Calculations for (2*R*, 4*S*, 5*R*)-

Table 20. Crystal data for (4*S*, 5*R*)-1,3,2-oxazaphospholidines

	(2*R*)-(**42**)	(2*S*)-(**56**)	(2*S*)-(**50**)	(2*R*)-(**49**)	(2*R*)-(**52**)	(2*S*)-(**51**)
Molecular Formula	$C_{16}H_{18}NO_3P$	$C_{16}H_{18}NO_3P$	$C_{16}H_{18}NO_2P$	$C_{16}H_{18}NO_2P$	$C_{16}H_{18}OPS$	$C_{16}H_{18}OPS$
Molecular Weight	303.3	303.3	287.3	287.3	303.37	303.37
Melting Point/^{0}C	97-98	129-130.5	146-147	169-170	147-148	99-100
Lit m.p./^{0}C	93-94[7]		134-136[2]	159-161[2]		
Crystal Form	Colourless Prism	Colourless Hexagonal prism	Colourless Lath	Colourless prism	Colourless prism	Single colourless needle
Size / mm	0.4x0.6x0.9	0.75x0.38x0.25	0.6x0.3x0.15	0.4x0.6x0.8	0.6x0.3x0.2	0.8x0.3x0.2
Space Group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_1$
Cell dimensions						
a / Å	8.720(1)	9.674(2)	8.933(1)	6.844(1)	7.126(1)	10.328(3)
b / Å	10.883(1)	10.692(3)	10.392(1)	7.055(2)	13.937(1)	7.662(5)
c / Å	16.391(2)	15.267(4)	15.990(2)	31.170(4)	16.263(2)	10.554(3)
β/^{o}	-	-	-	-	-	108.64(2)
V / Å^3	1555.6	1579.1	1484.4	1505.0	1615.16	791.36
Z	4	4	4	4	4	2
d_{calcd} / g cm^{-3}	1.29	1.28	1.29	1.27	1.25	1.27
F(000) / e	640	640	608	608	640	320

continued..

Table 6. (continued). Crystal data for (4*S*, 5*R*)-1,3,2-oxazaphospholidines

	(2*R*)-(**42**)	(2*S*)-(**56**)	(2*S*)-(**50**)	(2*R*)-(**49**)	(2*R*)-(**52**)	(2*S*)-(**51**)
No. of unique reflections	1590	1781	1516	1751	1659	1508
No. of observed reflections	1488	1404	1330	1510	1333	1108
Absorption coeff/cm^{-1}	1.43	1.41	1.44	1.42	2.49	2.54
Final residuals						
R	0.030	0.034	0.029	0.053	0.038	0.048
R_w	0.041	0.036	0.034	0.062	0.0425	0.048
Weighting scheme $1/[\sigma^2(F)+nF^2]$, n=	0.000361	0.000159	0.000166	-	0.000741	0.001514
Largest diff peak /eÅ^{-3}	0.14	0.16	0.20	0.17	0.37	0.28
Largest diff hole / eÅ^{-3}-	0.21	-0.23	-0.16	-0.54	-0.29	-0.23
Extinction parameter*	0.00504	0.00376	0.00554	-	0.00338	-

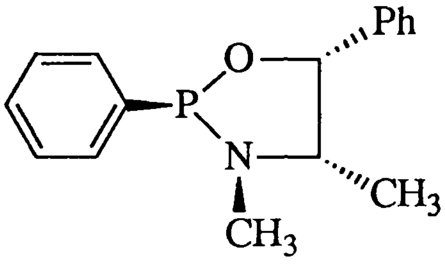
* The value of X in the correction factor [1-0.0001 $F_c{}^2X/(\sin\theta)$] to be applied to the calculated structure factor F_c.

(**42**), (2*S*, 4*S*, 5*R*)-(**56**), (2*S*, 4*S*, 5*R*)-(**50**), (2*R*, 4*S*, 5*R*)-(**52**) and (2*S*, 4*S*, 5*R*)-(**51**) were performed on a VAX8650 computer using SHELX,[137] and for (2*R*, 4*S*, 5*R*)-(**49**) on a VAX11/750 computer using the CRYSTALS[138] software package incorporating SHELXS[139] and MULTAN80[140]. Positional and thermal parameters for all hydrogen atoms of (2*R*, 4*S*, 5*R*)-(**42**), (2*S*, 4*S*, 5*R*)-(**56**), (2*S*, 4*S*, 5*R*)-(**50**) and (2*R*, 4*S*, 5*R*)-(**52**) were freely refined; H atoms of (2*R*, 4*S*, 5*R*)-(**49**) were assumed to ride on attached atoms and were placed in observed positions except H9 and H10 which were placed in calculated positions since they were not found on the difference map; H atoms of (2*S*, 4*S*, 5*R*)-(**51**) were placed in calculated positions with methyl groups treated as rotatable rigid bodies. The structures were refined by full-matrix [(2*R*, 4*S*, 5*R*)-(**42**), (2*S*, 4*S*, 5*R*)-(**56**), (2*S*, 4*S*, 5*R*)-(**50**), (2*R*, 4*S*, 5*R*)-(**52**) and (2*S*, 4*S*, 5*R*)-(**51**)]. or large-block [(2*R*, 4*S*,5*R*)-(**49**)], least-squares which included parameters for atomic coordinates, temperature factors (anisotropic for non-hydrogen atoms), an overall scale factor and an extinction parameter. Reflections for (2*R*, 4*S*, 5*R*)-(**42**), (2*S*, 4*S*, 5*R*)-(**56**), (2*S*, 4*S*, 5*R*)-(**50**), (2*R*, 4*S*, 5*R*)-(**52**) and (2*S*, 4*S*, 5*R*)-(**51**) were weighted according to $1/[\sigma^2(F_o) + nF_o^2]$, and for (2*R*, 4*S*, 5*R*)-(**49**) by applying a 3 term Chebychev series of the form $\omega = [1095.4t_o(X) + 1489.4t_1(X) + 441.5t_2(X)\}$ where $X = F_o/F_{max}$. Final Fourier series showed no significant residual electron density and there were no exceptional discrepancies between observed and calculated structure factors.

Crystal data for the X-ray structure analysis of (*R*$_P$)-(-)-*N*-methyl-*N*-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1*S*, 2*S*)-*P*-(2-methoxyphenyl)-*P*-phenylphosphinamide-(**71**) were measured using an Enfras-Nonius CAD-4 4-circle diffractometer. Graphite monochromated Cu-Kα X-radiation [(Cu-Kα)=1.518Å] using the ω/2θ scan technique was used to collect reflection intensities out to a Bragg angle of θ=75°. The space group was determined unambiguously as a result of the structure analysis. The unit cell parameters were determined by least-squares refinement, the setting angles of 25 accurately measured centred reflections being used for this purpose. The omega scan angle was calculated from [1.10+(0.14tanθ)]° and increased by 25% on each side for background determination. The scan speed was varied from 1.7 to 6.7° min^{-1} depending upon intensity. Several standard reflections were measured every hour during data collection and showed no appreciable variation with time. The data were corrected for Lorentz and polarisation effects. An absorption correction was also applied to obtain correct relative intensities. Crystal data for (*R*P)-(-)-*N*-methyl-*N*-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1*S*, 2*S*)-*P*-(2-methoxyphenyl)-*P*-phenylphosphinamide-(**71**): $C_{23}H_{26}NO_3P$, *M* 395.44, orthorhombic, space group $P2_12_12_1$, **a** 10.096(1), **b** 12.390(1), **c** 17.258(1), D_{calc} = 1.22 gcm^{-3}, Z = 4, μ(Cu-Kα) = 57.5 cm^{-1}. The crystal used for data collection was colourless and 1432 independent reflections were measured, with I>3o(I) 1200; R-factor = 0.071; weighted R-factor = 0.085. Calculations were performed on a VAX11/750 computer using the CRYSTALS[138] software package incorporating SHELXS[139] and MULTAN80[140]. Positional and thermal parameters for all hydrogen atoms were calculated except H(26) which was placed in its observed position.

6.4. Experimental for Chapter 2.

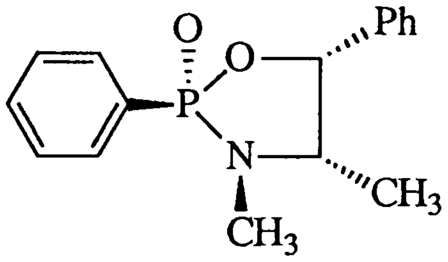
(2R, 4S, 5R)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-(26).



(2*R*, 4*S*, 5*R*)-(**26**) was prepared by modification of a literature procedure[56]. Dichlorophenylphosphine (32.84 ml, 0.24 mol) was added dropwise *via* cannula over 30 min to a cooled (0°C) and vigorously stirred solution of (1*R*, 2*S*)-(-)-ephedrine (40.0 g, 0.24 mol) and *N*-methylmorpholine (53.4 ml, 0.484 mol) in dry toluene (500 ml) under an argon atmosphere. Stirring was continued at this temperature for 1h after which the mixture was left to stir at ambient temperature for 18h. A portion (2 ml) was removed and its ^{31}P n.m.r. spectrum recorded. [δ_P (101 MHz; toluene; externally referenced to $CDCl_3$) 139.31 (1P, s)] which confirmed the presence of only one diastereoisomer. The solid *N*-methylmopholine hydrochloride was removed by standard Schlenk filtration and washed with dry toluene (3 x 30 ml). A portion was removed (2 ml) and the solvent removed *in vacuo* to yield (2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-

oxazaphospholidine-(**26**) as a white solid. δ_H (200 MHz; $CDCl_3$): 0.65 (3H, d, J_{HH} = 7 Hz; CCH_3), 2.6 (3H, d, J_{PH} = 14 Hz; NCH_3), 3.25 (1H, m; H-4), 5.55 (1H, d, J_{HH} = 7 Hz; H-5), 7.1-7.7 (10H, m; Ph). Lit[55]; δ_H (250 MHz; C_6D_6): 0.47 (3H,d, J = 7 Hz), 2.32 (3H, d, J = 14 Hz), 3.02 (1H, m), 5.35 (1H, d, J_1 = 7 Hz, J_2 = 3 Hz), 6.9-7.3 (8H, m), 7.45-7.6 (2H, m). δ_P (101 MHz; toluene): 139.31 (1P, s).

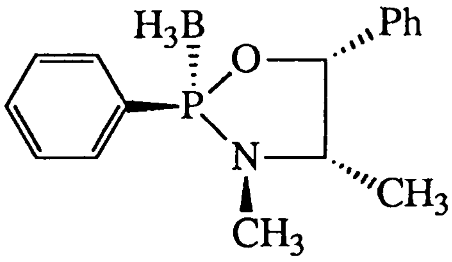
(2R, 4S, 5R)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-oxide-(49).



Diastereomerically pure (2*R*, 4*S*, 5*R*)-(**49**) was prepared by modification of a literature procedure[64]. The combined filtrate of (2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-(**26**) from above was cooled to -10°C and *tert*-butylhydroperoxide (80.66 ml, 0.24 mol, 3.0 M in toluene) was added with vigorous stirring at such a rate as to keep the temperature below 0°C. After being stirred for 1h the solution was left to stir at ambient temperature for 18h. White crystals were deposited which were collected by filtration. Concentration of the filtrate yielded a second crop which was treated similarly. Crystallisation from dry THF gave (-)-(2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-oxide-(**49**) (25.6 g, 39.3%) as white crystals, m.p. 169-170°C. Lit[64]; m.p. 159-161°C. (Found: C, 67.13; H, 6.30; N, 4.73; P, 10.83; M^+, 287. Calc for $C_{16}H_{18}NO_2P$: C 66.87; H, 6.31; N, 4.86; P, 10.87%; M, 287); $[\alpha]_D^{21}$ - 37.5 (c 1 in $CHCl_3$), Lit[64]; $[\alpha]_D^{21}$ -40.0 (c 1 in $CHCl_3$); ν_{max} (Nujol) 1 438 (s, P-Ph), 1 295 (s, P=O), 1 040 cm^{-1} (s, P-C-alkyl); δ_H (500 MHz; $CDCl_3$) 0.92 (3H, d, J_{HH} = 6.5 Hz; CCH_3), 2.76 (3H, d, J_{PH} = 10.1Hz; NCH_3), 3.75-3.80 (1H, ddq, J_{PH} = 14.1 Hz, J_{HH} = 6.2 Hz, J_{HH} = 6.5 Hz; H-4), 5.60 (1H, dd, J_{PH} = 4.8, J_{HH} = 6.2Hz; H-5), 7.31-7.39 (3 H, m, Ph-2,4,6), 7.43-7.45 (2 H, m, Ph-3,5), 7.45-7.51 (2 H, ddt, J_{PH} = 4.0 Hz, $J_{4,5}$ = 7.6 Hz; PPh-H-3,5), 7.53-7.56 (1 H, dt, $J_{4,5}$ = 7.6 Hz, $J_{4,6}$ = 1.5 Hz; PPh-H-4), 7.86-7.91 (2H, ddd, J_{PH} = 13.6 Hz, $J_{5,6}$ = 8.1 Hz,

$J_{4,6}$ = 1.5 Hz; PPh-H-2,6); Lit[64]; δ_H (200 MHz; $CDCl_3$) - (selected data) 3.79 (1H, ddq, J_{HP} = 14.4 Hz, J_{HH} = 6.3 Hz; H-4), 5.63 (1H, dd, J_{HP} = 4.7, J_{HH} = 6.3 Hz; H-5); δ_C (126 MHz; $CDCl_3$) 14.50 (s; 4-CH_3), 28.45 (d, J_{PC} = 5.6 Hz; NCH_3), 59.04 (d, J_{PC} = 10.1 Hz; C-4), 82.47 (s; C-5), 126.19 (s; Ph-C-2,6), 128.07 (s; Ph-C-4), 128.24 (s; Ph-C-3,5), 128.45 (d, J_{PC} = 14.7 Hz; PPh-C-2,6), 129.00 (d, J_{PC} = 170.7 Hz; Ph-C-1), 132.08 (s; PPh-C-4), 132.1 (d, J_{PC} = 10 Hz; PPh-C-3,5), 136.2 (s; Ph-C-1); δ_P (101 MHz; $CDCl_3$) 29.7 (1 P, s), Lit[64]; δ_P (81.015 MHz; $CDCl_3$) 29.16 (s); *m/z* (E.I): 287 (M, 45)$^+$, 272 (50), 196 (12), 181 (55), 146 (15), 104 (27), 77 (34).

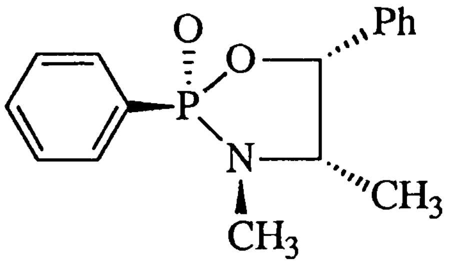
(2R, 4S, 5R)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-borane-(31).

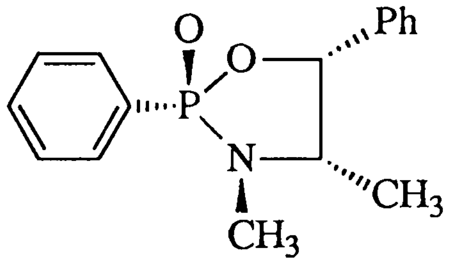


To the filtrate of (2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-(**26**) from the condensation step above carried out on a 30.5 mmolar scale was added borane-methyl sulphide complex (3.9 ml, 39.05 mmol, 10 M) with constant stirring under argon. After 18h the solution was concentrated under vacuum to yield a white solid which was collected by filtration and washed with cold toluene (10 ml). Crystallisation from toluene afforded *(2R, 4S, 5R)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-borane-(31)* (3.0 g, 34%) as a white crystalline solid, m.p. 105°C. Lit[60]; 107°C. (Found: C, 67.46; H, 7.57; N, 4.71; *M*$^+$, 284. $C_{16}H_{21}POBN$ requires: C, 67.40; H, 7.42; N, 4.91%; *M*, 285); $[\alpha]_D^{21}$ - 45.5 (*c* 2 in $CHCl_3$), Lit[60]; $[\alpha]_D$ +4.5 (*c* 4 in $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 0.84 (3 H, d, J_{HH} = 6.5Hz; 4-CH_3), 2.69 (3 H, d, J_{PH} = 10.9 Hz; NCH_3), 3.66-3.71 (1H, ddq, J_{PH} = 9.0 Hz, J_{HH} = 6.1 Hz, J_{HH} = 6.5 Hz; H-4), 5.59 (1H, dd, J_{PH} = 3.0, J_{HH} = 6.1Hz; H-5), 7.26-7.41 (5 H, m, Ph), 7.49-7.52 (2 H, td, J_{PH} = 2.1 Hz, $J_{4,5}$ = 7.7 Hz; PPh-H-3,5), 7.54-7.58 (1

H, td, $J_{4,5}$ = 7.3 Hz, $J_{4,6}$ = 1.5 Hz; PPh-H-4), 7.81-7.85 (2 H, ddt, J_{PH} = 10.2 Hz, $J_{5,6}$ = 8.4 Hz, $J_{4,6}$ = 1.5 Hz; PPh-H-2,6). Lit[60]; δ_H ($CDCl_3$) 0.2-1.7 (3 H, m, J_{BH} = 96 Hz; 0.83 (3 H, d, J = 8 Hz), 2.7 (3 H, d, J_{PH} = 11 Hz), 3.72 (1H, m), 5.65 (1H, dd, J_{HP} = 3 Hz, J_{HH} = 8 Hz), 7.3-7.8 (10 H, m). δ_C (126 MHz; $CDCl_3$) 13.56 (s; 4-CH_3), 29.46 (d, J_{PC} = 8.0 Hz; NCH_3), 59.16 (s; C-4), 84.1 (d, J_{PC} = 8.3 Hz; C-5), 126.64 (s; Ph-C-2,6), 128.36 (s; Ph-C-3,5), 128.60 (d; J_{PC} = 9.8 Hz; Ph-C-3,5), 130.90 (d, J_{PC} = 11.5 Hz; PPh-C-2,6), 132.33 (s; PPh-C-4), 136.20 (s; Ph-C-1); δ_P (101 Hz; CDC13) 129 (1 P, q, J_{BP} = 74 Hz); δ_B (80.18 Hz; $CDCl_3$) - 40.5 (1 B, d, J_{PB} = 74 Hz); *m/z* (C.I) 284 (M^+, 284)$^+$, 272 (100), 165 (35).

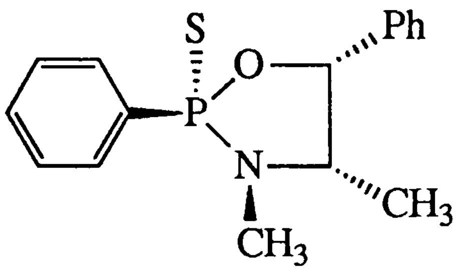
(2R, 4S, 5R) and (2S, 4S, 5R)-3,4-dimethyl-2,5-phenyl-1,3,2-oxazaphos-pholidine-2-oxides-(49 & 50).

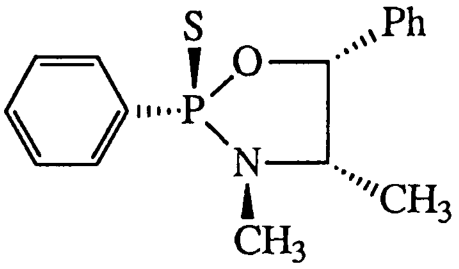




(2*R*, 4*S*, 5*R*)- and (2*S*, 4*S*, 5*R*)-(**49** & **50**) were prepared by modification of a literature method[64]. Dichlorophenylphosphine (36.51 ml, 0.269 mol) was added dropwise *via* cannula over 30min to a cooled (0°C) and vigorously stirred solution of (1*R*, 2*S*)-(-)-ephedrine (44.52 g, 0.269 mol) and *N*-methylmorpholine (59.25 ml, 0.54 mol) in dry toluene (600 ml) under an argon atmosphere. Stirring was continued at this temperature for 1h after which a portion (2 ml) was removed and its ^{31}P n.m.r. spectrum recorded. [δ_P (101 MHz; toluene; external standard $CDCl_3$) 152.9 (s, 1P), 139.31 (s, 1P)] which confirmed the presence of the two phenyl-oxazaphospholidine diastereoisomers. The solid *N*-methylmopholine hydrochloride was removed by standard Schlenk filtration and washed with dry toluene (3 x 30 ml). The combined filtrate was cooled to 0°C and *tert*-butylhydroperoxide (90 ml, 0.27 mol, 3.0 M in hexanes) was added with vigorous stirring. After being stirred for 1h the solution was left to stir at ambient temperature for 18h. White crystals were deposited which were collected by filtration and dried *in vacuo*. Concentration of the filtrate yielded a second crop which was treated similarly. Comparison of the ^{1}H n.m.r. spectrum with the pure (2*R*, 4*S*, 5*R*)-(**49**) diastereoisomer prepared stereospecifically showed a 3.3:1 ratio, with the (2*R*, 4*S*, 5*R*)-(**49**) diastereoisomer as the major product. T.l.c. in diethyl ether-dichloromethane (1:1, v/v) showed the two diastereoisomers of R*f* 0.38 (2*R*, 4*S*, 5*R*)-(**49**) and 0.14 (2*S*, 4*S*, 5*R*)-(**50**). These were separated by flash chromatography in diethylether-dichloromethane (1:1, v/v). The (2*R*, 4*S*, 5*R*)-(**49**) diastereoisomer was recrystallised from hot toluene (19.5 g, 25.4%) as white crystals. The (2*S*, 4*S*, 5*R*)-(**50**) diastereoisomer was similarly recrystallised from hot toluene (5.8 g, 7.6%) as white crystals. (2*R*, 4*S*, 5*R*)-(**49**): m.p. 169-170°C. Lit[64]; m.p. 159-161°C. Spectroscopic and analytical data were as described above. (2*S*, 4*S*, 5*R*)-(**50**): m.p. 146-147°C. Lit[64]; m.p. 134-135°C. (Found: C, 66.75; H, 6.26; N, 4.88; P, 11.09; M^+, 288. Calc for $C_{16}H_{18}NO_2P$: C, 66.87; H, 6.31; N, 4.86; P, 10.87%; *M*, 287); $[\alpha]_D^{21}$ -52.0 (*c* 1 in $CDCl_3$); Lit[64]; $[\alpha]_D$ -54 (*c* 1 in $CDCl_3$); ν_{max} (Nujol) 1 438 (s, P-Ph), 1 295 (s, P=O), 1 040 cm^{-1} (s, P-C-alkyl); δ_H (500 MHz; $CDCl_3$) 0.82 (3H, d, J_{HH} = 6.6 Hz; CH_3), 2.76 (3H, d, J_{HP} = 9.3Hz; NCH_3), 3.81-3.88 (1H, ddq, J_{PH} = 10.6 Hz, J_{HH} = 6.3 Hz, J_{HH} = 6.6 Hz; H-4), 5.96 (1H, dd, J_{HH} = 6.3Hz; H-5), 7.26-7.32 (3 H, m; Ph-2,4,6), 7.35-7.38 (2 H, m, Ph-3,5), 7.47-7.51 (2 H, ddt, J_{PH} = 4.0 Hz, $J_{4,5}$ = 7.3 Hz; PPh-H-3,5), 7.55-7.58 (1 H, dt, $J_{4,5}$ = 7.3 Hz, $J_{4,6}$ = 1.5 Hz; PPh-H-4), 7.89-7.94 (2H, ddd, J_{PH} = 13.7 Hz, $J_{5,6}$ = 8.1 Hz, $J_{4,6}$ = 1.5 Hz; PPh-H-2,6); Lit[64]; δ_H (200 MHz; $CDCl_3$) - (selected data) 3.86 (1H, ddq, J_{PH} = 10.7 Hz, J_{HH} = 6.5 Hz; H-4), 5.98 (1H, dd, J_{HP} = <0.2 Hz, J_{HH} = 5.98 Hz; H-5); δ_C (126 MHz; $CDCl_3$) 14.38 (s; 4-CH_3), 29.36 (d, J_{PC} = 6.3 Hz, NCH_3), 60.79 (d, *J* = 8.76 Hz; C-4), 80.3 (s; C-5), 125.62 (s; Ph-C-2,6), 128.01 (s; Ph-C-4), 128.4 (s; Ph-C-3,5), 128.5 (d, J_{PC} = 15.0 Hz; PPh-C-2,6), 130.0 (d, J_{PC} = 175 Hz; Ph-C-1), 132.1 (s; PPh-C-4), 132.4 (d, J_{PC} = 10.5 Hz; PPh-C-3,5), 136.1 (s; PPh-C-1); δ_P (101 MHz; toluene) 26.24 (1 P, s), Lit[64]; δ_P (81.015 MHz) 28.03 (s); *m/z* (C.I) 288 (M+1, 100)$^+$, 272 (15), 181 (15), 146 (5).

(2S, 4S, 5R)- and (2R, 4S, 5R)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-sulphides-(51 & 51).





(i) From dichlorophenylphosphine.

Dichlorophenylphosphine (3.86 ml, 0.028 mol) was added dropwise *via* cannula over 30min to a cooled (0°C) and vigorously stirred solution of (1*R*, 2*S*)-(-)-ephedrine (5.1 g, 0.028 mol) and triethylamine (7.93 ml, 0.056 mol) in dry toluene (200 ml) under an argon atmosphere. Stirring was continued at this temperature for 1h after which the mixture was left to stir at ambient temperature for 18h. A portion (2 ml) was removed and its ^{31}P n.m.r. spectrum recorded. [δ_P (101 MHz; toluene; external standard $CDCl_3$) 139.31 (1P, s)] which confirmed the presence of a single diastereoisomer. The solid triethylamine hydrochloride was removed by standard Schlenk filtration and washed with dry toluene (3 x 30 ml). The combined filtrate was cooled (0°C) and a saturated solution of sulphur in CS_2 was added with vigorous stirring. After being stirred for 1h the solution was left to stir at ambient temperature for 18h. Concentration of the filtrate yielded *(2S)- and (2R, 4S, 5R)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-sulfides-(51 & 52)* as a white crystalline solid. ^1H N.m.r. spectroscopy showed the presence of a pair of diastereoisomers in a 9:1 ratio. T.l.c. in 60-80 petroleum ether-dichloromethane (1:1, v/v) showed the two diastereoisomers of R_f 0.61 (2*R*, 4*S*, 5*R*)-(**52**) and 0.5 (2*S*, 4*S*, 5*R*)-(**51**). The pair of diastereoisomers were separated by flash column chromatography in 60-80 petroleum ether-dichloromethane (1:1, v/v). The minor, (2*R*, 4*S*, 5*R*)-(**52**) diastereoisomer was recrystallised from hot toluene (0.3 g, 3.2%) as white crystals and the (2*S*, 4*S*, 5*R*)-(**51**), major diastereoisomer was similarly recrystallised (2.7 g, 31.8%) also as white crystals. (2*S*, 4*S*, 5*R*)-(**51**): m.p. 99-100°C. (Found: C, 63.02; H, 5.87; N, 4.26; P, 9.13; M^+, 304. $C_{16}H_{18}NOPS$: requires C, 63.35; H, 5.98; N, 4.62; P, 10.21%; *M*, 303); $[\alpha]_D^{21}$ -139.3 (*c* 1 in $CDCl_3$): ν_{max} (Nujol) 890 (s, POCPh), 730 cm^{-1} (s, P=S); δ_H (500 MHz; $CDCl_3$) 0.94 (3H, d, J_{HH} = 6.6 Hz;

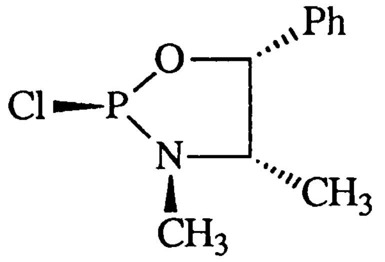
CCH_3), 2.66 (3H, d, J_{HP} = 12.5 Hz; NCH_3), 3.76-3.85 (1H, ddq, J_{PH} = 17.0 Hz, J_{HH} = 6.0 Hz, J_{HH} = 6.6 Hz; H-4), 5.66 (1H, dd, J_{PH} = 3.5 Hz, J_{HH} = 6.0Hz; H-5), 7.31-7.34 (1 H, tt, $J_{4,5}$ = 7.3 Hz, $J_{4,6}$ = 1.4 Hz; Ph-4), 7.36-7.40 (2 H,tt, $J_{5,6}$ = 7.5 Hz, $J_{4,6}$ = 1.6 Hz; Ph-2,6), 7.45-7.47 (2 H, m; Ph-H-3,5), 7.47-7.51 (2 H, ddt, J_{PH} = 4.0 Hz, $J_{4,5}$ = 7.5 Hz; PPh-H-3,5), 7.52-7.55 (1 H, ddt, J_{PH} = 2.1 Hz, $J_{4,5}$ = 7.5 Hz, $J_{4,6}$ = 1.7 Hz; PPh-H-4), 7.96-8.01 (2H, ddd, J_{PH} = 14.5 Hz, $J_{5,6}$ = 8.1 Hz, $J_{4,6}$ = 1.5 Hz; PPh-H-2,6); δ_C (126 MHz; $CDCl_3$) 14.52 (s; 4-CH_3), 29.26 (d, J_{PC} = 5 Hz; NCH_3), 60.10 (d, J_{PC} = 7.5 Hz; C-4), 83.57 (s; C-5), 126.48 (s; Ph-C-2,6), 128.37 (d, J_{PC} = 10.2 Hz; PPh-C-2,6), 128.5 (s; Ph-C-4), 131.20 (d, J_{PC} = 12.2 Hz; PPh-C-3,5), 132.07 (s; PPh-C-4), 135.00 (d, J_{PC} = 137 Hz; Ph-C-1), 136.27 (s; Ph-C-1); δ_P (101 MHz; $CDCl_3$) 90.27 (1 P, s); *m*/*z* (C.I) 304 (M+1, 100)$^+$, 256, (38), 224 (22), 192 (40), 160 (42) 96 (20), 64 (100).

(2*R*, 4*S*, 5*R*)-(**52**): m.p. 147-148°C. (Found: C, 63.81; H, 5.87; N, 4.26; P, 9.13; M^+, 304. $C_{16}H_{18}NOPS$ requires: C, 63.35; H, 5.98; N, 4.62; P, 10.21%; *M*, 303); $[\alpha]_D^{21}$ +29.55 (*c* 1 in $CDCl_3$); ν_{max} (Nujol) 880 (s, POCPh), 730 cm^{-1} (s, P=S); δ_H (500 MHz; $CDCl_3$) 0.85 (3H, d, J_{HH} = 6.6 Hz; CCH_3), 2.76 (3H, d, J_{HP} = 11.9 Hz; NCH_3), 3.75-83 (1 H, ddq, J_{PH} = 9.8 Hz, J_{HH} = 6.4 Hz, J_{HH} = 6.6 Hz; H-4), 5.92 (1 H, d, J_{HH} = 6.4 Hz; H-5), 7.2-7.33 (3H, m; Ph), 7.35-7.39 (2 H, m; Ph), 7.48-7.52 (2H, ddt, J_{PH} = 4.0 Hz, $J_{4,5}$ = 7.2 Hz; PPh-3,5), 7.54-7.57 (1H, ddt, J_{PH} = 2.8 Hz, $J_{4,5}$ = 7.5 Hz, $J_{4,6}$ = 1.1 Hz; PPh-4), (2H, ddt, J_{PH} = 14.9 Hz, $J_{5,6}$ = 8.1 Hz, $J_{4,6}$ = 1.1 Hz; PPh-2,6); δ_C (126 MHz; $CDCl_3$) 15.35 (s; 4-CH_3), 30.75 (d, J_{PC} = 6.1 Hz; NCH_3), 60.99 (d, J_{PC} = 7.0 Hz; C-4), 80.89 (s; C-5), 125.98 (s; Ph-C-2,6), 128.1 (d, J_{PC} = 10.1 Hz; PPh-C-2,6), 128.37 (s; Ph-C-3,5), 128.48 (s; Ph-C-4), 131.4 (d, J_{PC} = 13.0 Hz; PPh-C-3,5), 132.05 (s; PPh-C-4), 135.70 (d, J_{PC} = 133.3 Hz; Ph-C-1), 135.98 (s; Ph-C-1); δ_P (101 MHz; $CDCl_3$) 91.66 (1 P, s); *m*/*z* (C.I) 304 (M+1, 100)$^+$, 197 (40), 147 (40).

(ii) From phenylthiophosphoryl dichloride.

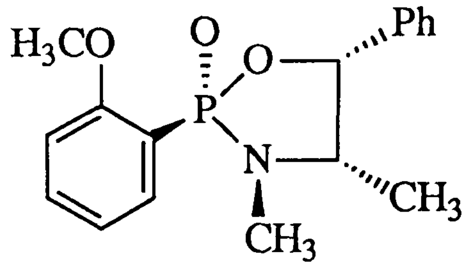
Phenylthiophosphoryl dichloride (0.76 ml, 4.91 mmol) was added dropwise *via* cannula to a vigorously stirred solution of (1*R*, 2*S*)-(-)-ephedrine (0.81 g, 4.9 mmol) and triethylamine (1.37 ml, 9.8 mmol) in dry toluene (10 ml). The mixture was stirred at ambient temperature for 15h after which the precipitated triethylamine hydrochloride was removed by filtration and washed with a portion (10 ml) of dry toluene. The organics were combined and concentrated to afford a 2:1 (2*S*: 2*R*) mixture (0.5 g, 34%) of (2*S*, 4*S*, 5*R*)-(**51**) and (2*R*, 4*S*, 5*R*)-(**52**) as determined by comparison with the previously prepared sample using ^{1}H n.m.r. spectroscopy. The solid was purified as described above and gave identical physical and chemical analysis.

(2R, 4S, 5R)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(43).



(2*R*, 4*S*, 5*R*)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(**43**) was prepared by modification of a literature procedure[64]. Trichlorophosphine (4.30 ml, 47.27 mmol) in dry toluene (10 ml) was added slowly (15 min) *via* cannula to a cooled and vigorously stirred solution of (1*R*, 2*S*)-(-)-ephedrine (8.14 g, 47.27 mmol) and *N*-methylmorpholine (10.40 ml, 94.54 mmol) in dry toluene (250 ml) under an argon atmosphere. Stirring was continued at this temperature for 1h after which the mixture was allowed to equilibrate to ambient temperature and stir overnight. The solid *N*-methylmorpholine hydrochloride was removed by standard Schlenk filtration and the solid washed with aliquots (3 x 20 ml) of dry toluene. The combined filtrate was stripped of toluene *in vacuo* to yield (2*R*, 4*S*, 5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(**43**) as a colourless oil which was purified by Kugelrohr distillation (0.1 mm Hg, 160°C) and isolated as a white solid (7.34 g, 68%) and stored under an argon atmosphere. δ_H (500 MHz; $CDCl_3$) 0.74 (3H, d, J_{HH} = 6.6 Hz; CCH_3), 2.73 (3H, d, J_{HP} = 16.2 Hz, NCH_3), 3.74-3.80 (1H, ddq, J_{PH} = 7.9 Hz, J_{HH} = 7.9 Hz, J_{HH} = 6.5 Hz; H-4), 5.92 (1H, dd, J_{PH} = 1.7, J_{HH} = 7.9 Hz; H-5), 7.34-7.43 (5 H, m, Ph). Lit[64]; δ_H (100 MHz; $CDCl_3$) - (selected data) 0.73 (3H, d, J_{HH} = 6 Hz; CCH_3) 2.73 (3H, d, J_{HP} = 16 Hz; NCH_3), 3.66 (1H, m), 5.84 (1H, dd, J_{HP} = 1.6, J_{HH} = 8 Hz; H-5); δ_P (101 MHz; toluene) 167 p.p.m.

(2R, 4S, 5R)-2-(2-Methoxyphenyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(55)



To (2*R*, 4*S*, 5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(**43**) (7.34 g, 31.96 mmol) in THF (200 ml) at -78°C was added 2-methoxyphenylmagnesium bromide (116 ml, 35.38 mmol, 0.305 M in THF) *via* cannula with vigorous stirring. The reaction mixture was allowed to equilibrate to ambient temperature over 5h after which a portion (2 ml) was removed and stripped of solvent i*n vacuo* to yield *(2R, 4S, 5R)-2-(2-methoxyphenyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(54)* as an off-white solid. δ_H (200 MHz; $CDCl_3$) 0.7 (3H, d, J_{HH} = 6.6 Hz; CCH_3), 2.65 (3H, d, J_{HP} = 16 Hz; NCH_3), 3.75 (1H, m; H-4), 3.9 (3 H, s; OCH_3), 5.52 (1H, d, J_{HH} = 6.6 Hz; H-5), 7.2-7.5 (9 H, m). δ_P (101 MHz, toluene) 135.2 p.p.m. To the solution was added *tert*-butylhydroperoxide (10.65 ml, 31.96 mmol) at 0°C with vigorous stirring. The mixture was allowed to equilibrate to ambient temperature and stirred for 2h and then was quenched with water (100 ml) and extracted into dichloromethane (3 x 150 ml) aliquots. The organics were combined, dried ($MgSO_4$) and the solvent removed by rotary evaporation to yield *(2R, 4S, 5R)-2-(2-methoxyphenyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(55)* as an off-white solid. Purification by flash column chromatography (CH_2Cl_2:Et_2O; 1:1 v/v) afforded (2*R*, 4*S*, 5*R*)-(**66**), (R_f = 0.6) as a white solid which was recrystallised further from hot toluene to afford white crystals (6.1 g, 60.2%), m.p. 156-157°C. (Found: C, 64.44; H, 6.36; N, 4.14; P, 10.03; M^+, 318. $C_{17}H_{20}NO_3P$ requires C, 64.35; H, 6.35; N, 4.41; P, 9.76%; *M*, 317); $[\alpha]_D^{21}$ -44.1 (*c* 1 in $CHCl_3$); ν_{max} (Nujol) 1 440 (s, P-Ph), 1 045 (s, POC), 1 300 cm^{-1} (s, P=O); δ_H (500 MHz; $CDCl_3$) 0.85 (3H, d, J_{HH} = 6.6 Hz; CCH_3), 2.62 (3H, d, J_{HP} = 10.2Hz, NCH_3), 3.85 (1H, ddq, J_{PH} = 9.7 Hz, J_{HH} = 7.1 Hz, J_{HH} = 6.6 Hz; H-4), 3.94 (3 H, s; OCH_3), 5.63 (1H, dd, J_{PH} = J_{HH} = 7.1 Hz; H-5), 6.96 (1 H dd, J_{PH} = 7.1 Hz, $J_{3,4}$ = 7.1 Hz; An^O-H-6), 7.04 (1 H, dt, J_{PH} = 3.0 Hz, $J_{5,6}$ = 7.5 Hz; An^O-H-5), 7.3-7.50 (6 H, m; Ph +

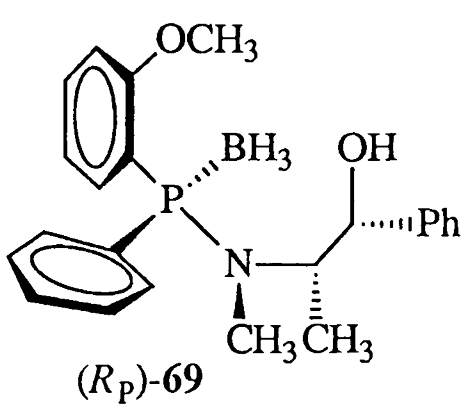
An^{O}-H-4), 8.0 (1 H ddd, J_{PH} = 14.7 Hz, $J_{5,6}$ = 7.5 Hz, $J_{4,6}$ = 1.8 Hz; An^{O}-H-6); δ_C (126 MHz; $CDCl_3$) 15.30 (s; 4-CH_3), 28.60 (d, J_{PC} = 6.0 Hz; NCH_3), 55.70 (s; OCH_3), 58.60 (d, J_{PC} = 12.0 Hz; C-4), 82.2 (s; C-5), 110.9 (d, J_{PC} = 8.1 Hz; An^{O}-C-5), 118.0 (d, J_{PC} = 120.0 Hz; An^{O}-C-1), 120.7 (d, J_{PC} = 13.8 Hz; An^{O}-C-6), 126.7 (s; Ph-C-3,5), 128.0 (s; Ph-C-4), 128.2 (s; Ph-C-2,6), 133.9 (s; An^{O}-C-4), 136.3 (d, J_{PC} = 6.1 Hz; An^{O}-C-3), 137.1 (s; PPh-C-1), 160.9 (s; An^{O}-C-2); δ_P (101 MHz; $CDCl_3$) +27.7 (1 P, s); m/z (C.I): 318 (M + 1, 100)$^+$.

6.5. Experimental for Chapter 3.

Preparation of 2-methoxy-, 3-methoxy-, 4-methoxy- and 2-naphthyl-magnesium bromide reagents.

The above Grignard reagents were prepared by addition of the appropriate arylbromide in THF to a suspension (THF) of magnesium turnings which had been activated by stirring under argon for 24h[114]. In most cases the addition of 1,2-dibromoethane was required to initiate reaction. After the reaction was complete the Grignard was titrated against a standard solution of HCl from which the mean of three titres (±0.05 ml) was taken and from which the molarity was calculated.

***(R*P)- and (*S*P)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-(2-methoxyphenyl)-P-phenylphosine boranes-(69 & 70).**

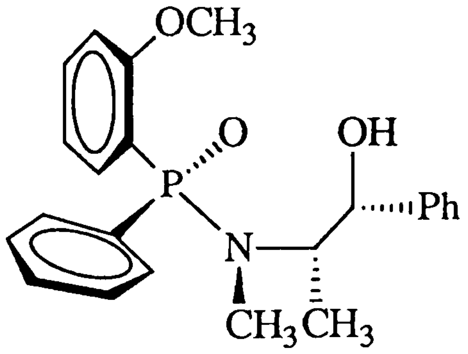


+ (*S*P)-**70**

(*R*P)-**69**

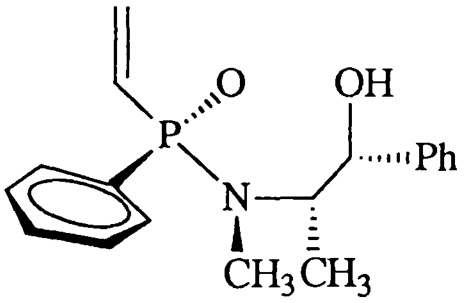
To a cooled (0°C) and stirred solution of (2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine-2-borane-(**31**) (1.56 g, 5.47 mmol) in dry THF (50 ml) was added, *via* cannula *ortho*-methoxyphenylmagnesium bromide (16.4 ml, 8.21 mmol). After stirring for 5h at ambient temperature the mixture was quenched with water (100 ml) and the mixture extracted with dichloromethane (2 x 100 ml). The organics were combined, dried ($MgSO_4$) and the solvent removed by rotary evaporation to yield *(R_P)- and (S_P)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-(2-methoxyphenyl)-P-phenylphosphine boranes-(69 & 70)* as an off-white solid. δ_H (200 MHz; $CDCl_3$) - R_P-(**69**): 0.7 (3 H, d, J_{HH} = 7.5 Hz; $CHCH_3$), 2.8 (3 H, d, J_{PH} = 10 Hz; $PNCH_3$), 3.7 (m), 3.8 (s; OCH_3), 5.7 (d, J_P = 7.5 Hz; CHPh), 6.8-8.0 (m, Ph). S_P-(**70**): 0.8 (3 H, d, J_{HH} = 7.5 Hz; $CHCH_3$), 2.7 (3 H, d, J_{PH} = 10 Hz; $PNCH_3$), 3.7 (m), 3.8 (s; OCH_3), 5.6 (1 H, dd, J_{PH} = 3 Hz, J_{HH} = 7.5 Hz; CHPh), 6.8-8.0 (m, Ph). δ_P (80.18 MHz; $CDCl_3$) 66.45 (q, $J_{B\text{-}P}$ = 96 Hz), 65.1 (q, $J_{B\text{-}P}$ = 96 Hz). Lit^{60}; ^{31}P ($CDCl_3$): 68.9 (R_P).

(R_p)-(-)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-(2-methoxy-phenyl)-P-phenyl phosphinamide-(71)



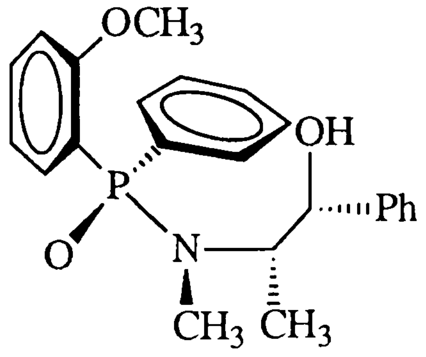
To a cooled (-30°C) and stirred solution of (-)-(2*R*, 4*S*, 5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxzaphospholidine-2-oxide-(**49**) (10.0 g, 34.8 mmol) in dry THF (150 ml) was added *via* cannula, under argon, a solution of 2-methoxyphenylmagnesium bromide (100 ml, 50 mmol, 0.5 M in THF). Stirring was continued at this temperature for 1h after which the solution was left to stir for 18h at ambient temperature. The excess Grignard reagent was quenched with water (100 ml) and the mixture extracted with dichloromethane (3 x 100 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated to yield *(R_p)-(-)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-(2-methoxyphenyl)-P-phenylphosphinamide-(71)* as a white solid. Crystallisation from toluene gave two crops of white needles (9.6 g, 70%), m.p. 195-197°C. (Found: C, 69.92; H, 6.81; N, 3.54; P, 7.56; M^+, 396. $C_{23}H_{26}NO_3P$ requires: C, 69.86; H, 6.63; N, 3.54; P, 7.82%; *M*, 395); $[\alpha]_D^{21}$ -14.8 (*c* 1 in CHCl$_3$); ν_{max} (Nujol) 3 250 (br, OH), 1 462 (s, P-Ph), 1 245 (m, P=O), 1035 cm^{-1}; δ_H (500 MHz; CDCl$_3$) 1.17 (3 H, d, J_{HH} = 7.1 Hz; CHCH_3), 2.28 (3 H, d, J_{PH} = 10.8 Hz; NCH_3), 3.75-3.79 (1 H, ddq, J_{PH} = 10.5 Hz, J_{HH} = 7.1 Hz, J_{HH} = 2.9 Hz; C*H*CH$_3$), 3.77 (3 H, s, OMe), 4.8 (1 H, dd, J_{HH} = 4.8 Hz, J_{HH} = 2.9 Hz; CHO*H*), 5.8 (1 H, d, J_{HH} = 4.9 Hz; C*H*Ph), 6.91-6.94 (1 H, dd, J_{PH} = 5.5 Hz, J_{HH} = 8.3 Hz; An^o-H-3), 7.00-7.03 (1 H, td, $J_{5,6}$ = 7.5 Hz, J_{PH} = 2.26 Hz, $J_{3,5}$ = 1.0 Hz; An^o-H-5), 7.20-7.23 (1 H, tt, $J_{4,5}$ = 7.3 Hz, $J_{4,6}$ = 2.0 Hz; Ph-H-4), 7.26-7.36 (4 H, m), 7.39-7.43 (2 H, td, $J_{4,5}$ = 7.7 Hz, J_{PH} = 3.3 Hz; PPh-H-3,5), 7.47-7.48 (1 H, dd, $J_{4,6}$ = 1.8 Hz, $J_{4,5}$ = 7.5 Hz; An^o-H-4), 7.49-7.53 (1 H, tt, $J_{4,5}$ = 8.3 Hz, J_{PH} = 1.0 Hz, $J_{4,6}$ = 1.8 Hz; PPh-H-4), 7.74-7.78 (2 H, ddt, J_{PH} = 12.1 Hz, $J_{5,6}$ = 7.9 Hz, $J_{4,6}$ = 1.5 Hz; PPh-H-2,6), 7.79-7.82 (1 H, ddd, J_{PH} = 13.6 Hz, $J_{5,6}$ = 7.6 Hz, $J_{4,6}$ = 1.8 Hz; An^o-H-6). δ_C (126 MHz; CDCl$_3$) 13.46 (s; C*C*H$_3$), 32.1 (d, J_{PC} = 5.4 Hz, N*C*H$_3$), 55.28 (s; O*C*H$_3$), 55.48 (s; *C*CH$_3$), 58.45 (s; *C*CH$_3$), 76.99 (s; *C*HPh), 110.90 (d, J_{PC} = 7.15 Hz; An^o-C-5), 118.90 (d, J_{PC} = 122 Hz; An^o-C-1), 121 (d, J_{PC} = 11.6 Hz; An^o-C-6), 126.75 (s; Ph-C-3,5), 126.93 (s; Ph-C-4), 127.84 (s; Ph-C-2,6), 128.1 (d, J_{PC} = 13.6 Hz; PPh-C-2,6), 132.05 (d, J_{PC} = 10.7 Hz; PPh-C-3,5), 133.5 (d, J_{PC} = 97.2 Hz; PPh-C-1), 134.04 (s; An^o-C-4), 136.05 (d, J_{PC} = 6.62 Hz; An^o-C-3), 142.47 (s; Ph-1), 160.85 (s, An^o-C-2); δ_P (101 Hz; CDCl$_3$) 30.98 (1 P, s); *m/z* (C.I) 396 (M+1, 100)$^+$, 378 (10), 288 (35), 248 (10), 148 (20).

(Rp)-(-)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-vinyl-P-phenylphosphinamide-(72).



To a cooled (-10^{o}C) and stirred solution of (2*R*, 4*S*, 5*R*)-3,4-dimethy-2,5-diphenyl-1,3,2-oxazaphospholidine-2-oxide-(**49**) (11.34 g, 39.5 mmol) in dry THF (250 ml) was added vinylmagnesium bromide (47.4 ml, 47.4 mmol, 1.0 M in THF). Stirring was continued at this temperature for 1h after which the mixture was allowed to stir at ambient temperature for 2h. The excess Grignard reagent was destroyed by quenching with water (100 ml) and the mixture extracted with dichloromethane (3 x 100 ml) aliquots. The organics were combined and concentrated to yield *(R_p)-(-)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-vinyl-P-phenylphosphinamide-(72)* as a white solid. Crystallisation from hot THF afforded white crystals (10.97 g; 88%), m.p. 128°C. (Found: C, 68.52; H, 7.29; N, 4.34; P, 10.08; M^+, 316. $C_{18}H_{22}NO_2P$ requires: C, 68.55; H, 7.03; N, 4.44; P, 9.82%; *M*, 315); $[\alpha]_D^{22}$ -68.9 (*c* 1 in $CHCl_3$); ν_{max} (KBr) 3 222 (br, OH), 1 138 (s, P=O); δ_H (500 MHz; $CDCl_3$) 1.18 (3H, d, J_{HH} = 7.0 Hz; CCH_3), 2.48 (3H, d, J_{HP} = 10.96 Hz, NCH_3), 3.67-3.71 (1H, ddq, J_{PH} = 4.3 Hz, J_{HH} = 7.0 Hz, J_{HH} =3.8 Hz; $CHCH_3$), 5.63 (1H, d, J_{HH} = 4.6 Hz; CHPh), 4.86 (1 H dd, J_{HH} = 4.3 Hz, J_{HH} = 4.3 Hz; CHOH), 6.07-6.17 (1 H, ddd, $J_{PH\text{-}Trans}$ = 40.8 Hz, J_{Cis} = 11.97 Hz, J_{HH} = 2.47 Hz; H-*Trans* to P), 6.18-6.21 (1 H, ddd, J_{PH} = 23.0 Hz, J_{Trans} = 18.5 Hz, J_{HH} = 2.47 Hz; H-*Cis* to P), 6.24-6.35 (1 H, ddd, J_{PH} = 23.0 Hz, J_{Trans} = 18.5 Hz, J_{Cis} = 11.9 Hz; H-*Ortho* to P), 7.22-7.29 (5 H, m), 7.37-7.41 (2 H, dt, $J_{5,6}$ = 7.7 Hz, J_{PH} = 3.2 Hz; H-3,5), 7.46-7.50 (1 H, dt, $J_{4,5}$ = 7.4 Hz; H-4), 7.55-7.59 (2 H, ddt, J_{PH} = 12.2 Hz, $J_{5,6}$ = 7.7Hz, $J_{4,6}$ = 1.4 Hz; H-2,6). δ_C (126 MHz; $CDCl_3$) 13.0 (s; C-CH_3), 30.54 (s; NCH_3), 58.26 (s, CCH_3), 76.89 (s; *C*-Ph), 126.4 (s, Ph-3,5), 128.0 (s; Ph-C-2,5), 128.4 (d, J_{PC} = 12.6 Hz; PPh-C-2,6), 130.0 (d, J_{PC} = 121.6 Hz; PPh-C-1), 131.9 (d, J_{PC} = 128.8 Hz; $PCHCH_2$), 131.7 (s, PPh-C-3,5), 131.7 (S, PPh-C-4), 134.7 (s, $PCHCH_2$), 142.8 (s, Ph-C-1); δ_P (101 MHz; $CDCl_3$) +30.5 (1 P, s); m/z (C.I): 316 (M + 1, 100)$^+$, 298 (25, M-OH), 288 (15, M-C_2H_3), 208 (95, M-C_8H_{11}).

(S_p)-(-)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-(2-methoxy-phenyl)-P-phenyl phosphinamide-(73).



(i) From (2*S*, 4*S*, 5*R*)-3,4-dimethy-2,5-diphenyl-1,3,2-oxazaphospholidine-2-oxide-(**50**):

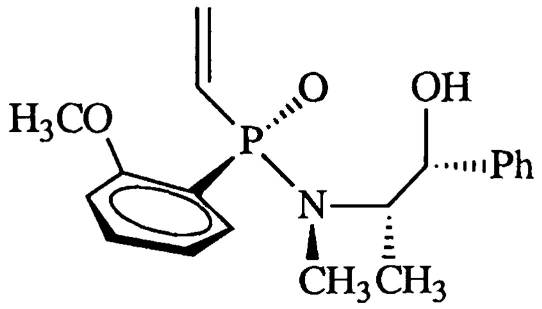
To a cooled (-30°C) and stirred solution of (2*R*, 4*S*, 5*R*)-3,4-dimethy-2,5-diphenyl-1,3,2-oxazaphospholidine-2-oxide-(**50**) (10.0 g, 34.8 mmol) in dry THF (150 ml) was added *via* cannula, a solution of 2-methoxyphenylmagnesium bromide (100 ml, 50 mmol, 0.5 M in THF). Stirring was continued at this temperature for 1h after which the solution was left to stir for 18h at ambient temperature. The excess Grignard reagent was quenched with water (100 ml) and the mixture extracted with dichloromethane (3 x 100 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated to yield *(Sp)-(-)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-(2-methoxyphenyl)-P-phenylphosphinamide-(73)* as a white solid. Crystallisation from toluene gave two crops of white needles (0.34 g, 96%), m.p. 153°C. (Found: C, 69.97; H, 6.80; N, 3.56. $C_{23}H_{26}NO_3P$ requires C, 69.86; H, 6.63; N, 3.54); $[\alpha]_D^{21}$ -30.65 (*c* 1 in $CHCl_3$); Spectroscopic data identical to (*R*p)-(-)-*N*-methyl-*N*-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-*P*-(2-methoxy-phenyl)-*P*-phenylphosphinamide-(**71**) prepared above.

(ii) From (2*R*, 4*S*, 5*R*)-2-(2-methoxyphenyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide (**55**).

To a cooled (-78°C) and stirred solution of (2*R*, 4*S*, 5*R*)-2-(2-methoxyphenyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(**55**) (0.5 g, 1.57 mmol) in dry THF (15 ml) was added *via* cannula, under argon, a solution of phenylmagnesium chloride (2.0 ml, 2.0 mmol, 2.0 M in THF). Stirring was continued at this temperature for 1h after which the solution was left to stir for 18h at ambient temperature. The excess Grignard reagent was quenched with water (20 ml) and the mixture extracted with dichloromethane (3 x 20 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated to yield (*S*p)-(-)-*N*-methyl-*N*-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-*P*-(2-methoxyphenyl)-*P*-phenylphosphinamide-(73) as a white solid. Crystallisation from toluene gave two crops of white needles (0.34 g, 96%), m.p. 153°C; $[\alpha]_D^{21}$ -29.80 (*c* 1 in $CHCl_3$); Spectroscopic data identical to (*R*p)-(-)-*N*-methyl-

N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-*P*-(2-methoxyphenyl)-*P*-phenylphosphinamide-(**71**) prepared above.

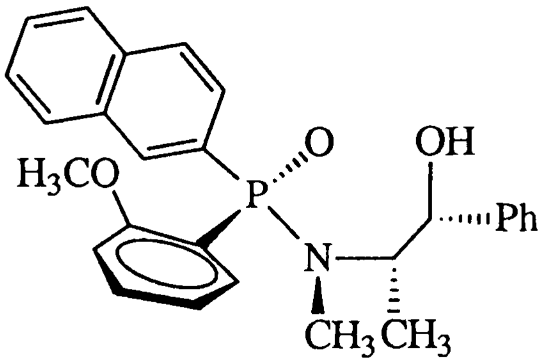
(S_p)-(-)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-(2-methoxyphenyl)-P-vinylphosphinamide-(75).



To a cooled (-78°C) solution of (2*R*, 4*S*, 5*R*)-2-(2-methoxyphenyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(**55**) (2.2 g, 6.93 mmol) in dry THF (150 ml) was added vinylmagnesium bromide (8.5 ml, 8.5 mmol, 1.0 M solution in THF) with vigorous stirring over 10 min. The mixture was left to stir at this temperature for 1 h after which Stirring was continued overnight at ambient temperature. The excess Grignard was quenched with water (100 ml) and extracted into dichloromethane (3 x 100 ml) aliquots. The organics were combined and dried ($MgSO_4$) and concentrated to yield *(S_p)-(-)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-(2-methoxyphenyl)-P-vinylphosphinamide-(75)* as a white solid. Crystallisation from hot THF yielded white crystals (1.9 g, 80%). m.p. 188-189°C. (Found: C, 66.35; H, 7.17; N, 4.04; P, 8.95; M^+, 346. $C_{19}H_{24}NO_3P$ requires: C, 66.07; H, 7.00; N, 4.05; P, 8.97%; *M*, 345); $[\alpha]_D^{22}$ -102.87 (*c* .041 in $CHCl_3$); ν_{max} (KBr) 3 222 (br, OH), 1 138 (s, P=O); δ_H (500 MHz; $CDCl_3$) 1.08 (3H, d, J_{HH} = 7.1 Hz; CCH_3), 2.44 (3H, d, J_{PH} = 10.6 Hz, NCH_3), 3.60-3.67 (1H, ddq, J_{PH} = 4.4 Hz, J_{HH} = 7.1 Hz, J_{HH} = 2.8 Hz; C*H*CH_3), 5.06 (1H, d, J_{HH} = 5.1 Hz; C*H*Ph), 4.81-4.83 (1 H dd, J_{HH} = 5.1 Hz, J_{HH} = 2.8 Hz; CHO*H*), 6.87-6.11 (1 H, ddd, $J_{PH\text{-}Trans}$ = 43.7 Hz, J_{Cis} = 12.4 Hz, J_{HH} = 2.14 Hz; H-*Trans* to P), 6.31-6.39 (1 H, ddd, J_{PH} = 23.0 Hz, J_{Trans} = 18.7 Hz, J_{HH} = 2.14 Hz; H-*Cis* to P), 6.52-6.63 (1 H, ddd, J_{PH} = 24.5 Hz, J_{Trans} = 18.7 Hz, J_{Cis} = 12.6 Hz; H-*Ortho* to P), 6.89 (1H, dd, J_{PH} = 5.7 Hz, $J_{3,4}$ = 8.4 Hz; H-5), 7.06-7.07 (1 H, ddt, J_{PH} = 0.6 Hz, $J_{3,5}$ = 0.75 Hz, $J_{5,6}$ = 7.5 Hz; H-5), 7.18-7.33 (5 H, m, Ph), 7.48-7.52 (1 H, dt, $J_{4,5}$ = 8.1

Hz;$J_{4,6}$ = 1.8 Hz, J_{PH} = 0.7 Hz; H-4), 7.95-7.99 (1 H, ddd, J_{PH} = 13.4 Hz, $J_{5,6}$ = 7.5 Hz, $J_{4,6}$ = 1.8 Hz; H-6). δ_C (126 MHz; $CDCl_3$) 12.39 (s; C-CH_3), 31.51 (s; NCH_3), 31.51 (s; OCH_3), 59.48 (s, CCH_3), 76.49 (s; *C*-Ph), 110.55 (s, An^o-C-5), 120.0 (d, J_{PC} = 127.1 Hz; An^o-C-1), 121.0 (d, J_{PC} = 11.5 Hz; An^o-C-6), 126.24 (s; Ph-C-3,5), 126.8 (s; Ph-C-4), 127.8 (s; Ph-C-2,6), 130.5 (d, J_{PC} = 124.1 Hz; P$CHCH_3$), 133.7 (s; An^o-C-4), 134.4 (s; CHCH_2), 135.1 (S, An^o-C-3), 142.6 (S, Ph-C-1), 160.2 (S, $COCH_3$); δ_P (101 MHz; $CDCl_3$) +27.7; *m/z* (C.I): 346 (M+1, 100)$^+$, 328 (12, M-OH), 238 (100, M-$C_{10}H_{14}$).

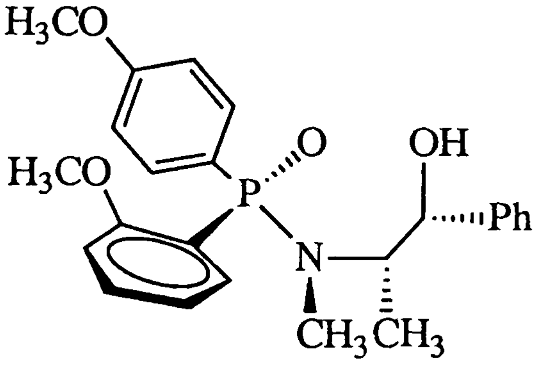
(S$_p$)-(-)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-(2-methoxyphenyl)-P-(2-naphthyl)phosphinamide-(76).



To a cooled (-78°C) and stirred solution of (2*R*, 4*S*, 5*R*)-2-(2-Methoxyphenyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(**55**) (2.0 g, 6.3 mmol) in dry THF (100 ml) was added, under an argon atmosphere, a solution of 2-naphthylmagnesium bromide (20 ml, 14.0 mmol, 0.7 M in THF). Stirring was continued at this temperature for 1h after which the mixture was allowed to stir at ambient temperature overnight. The excess Grignard reagent was quenched with water (100 ml) and the mixture extracted with dichloromethane (3 x 100 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated to yield a white solid. Crystallisation from hot THF afforded white crystals of *(S$_p$)-(-)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-(2-methoxyphenyl)-P-(2-naphthyl)phosphinamide-(76)* (2.26 g; 81%). m.p. 120°C. (Found: C, 72.55; H, 6.80; N, 2.84; P, 6.69; M^+, 446. $C_{27}H_{28}NO_3P$ requires: C, 72.79; H, 6.33; N, 3.14; P, 6.95%; *M*, 445); $[\alpha]_D^{19.5}$ = -18.81 (*c* 1.005 in $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 1.25 (3 H, d, J_{HH} = 7.1 Hz; CHCH_3), 2.40 (3 H, d, J_{PH} = 10.6 Hz; NCH_3), 3.71-3.79 (1 H, m; *CH*CH_3), 3.79 (3 H, s, An^{o}OMe), 4.87 (1 H, s; CHO*H*), 5.74

(1 H, s; C*H*Ph), 6.91-6.94 (1 H, dd, J_{HH} = 8.3 Hz, J_{PH} = 5.7 Hz; An^{o}-H-3), 7.04-7.08 (1 H, ddt, $J_{5,6}$ = 7.5 Hz, J_{PH} = 2.3 Hz, $J_{3,5}$ = 1.0 Hz; An^{o}-H-5), 7.21-7.69 (m), 8.34 (1 H, d, J_{PH} = 14.6 Hz; Np-H-7). δ_P (101 Hz; $CHCl_3$) 30.70 (1 P, s); *m/z* (C.I) 446 (M+1, 100)$^+$, 338 (95), 298 (15), 148 (50).

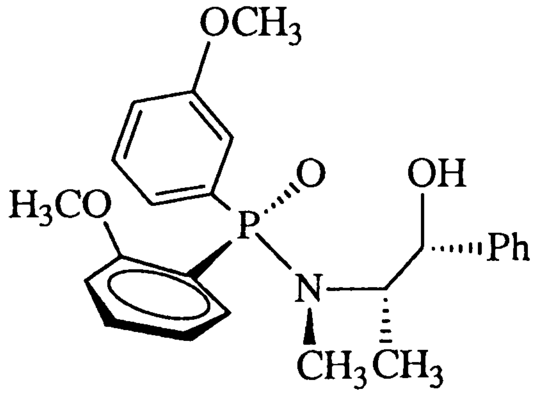
(S$_p$)-(-)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-(2-methoxyphenyl)-P-(4-methoxyphenyl)phosphinamide-(77).



To a cooled (-78°C) and stirred solution of (2*R*, 4*S*, 5*R*)-2-(2-Methoxyphenyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(**55**) (2.0 g, 6.3 mmol) in dry THF (100 ml) was added, a solution of 4-methoxyphenylmagnesium bromide (12.5 ml, 7.6 mmol, 0.6 M in THF). Stiring was continued at this temperature for 1h after which the mixture was allowed to stir at ambient temperature overnight. The excess Grignard reagent was quenched with water (100 ml) and the mixture extracted with dichloromethane (3 x 100 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated to yield a white solid. Crystallisation from hot THF afforded white crystals of *(S$_p$)-(-)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-(2-methoxyphenyl)-P-(4-methoxyphenyl)phosphinamide-(77)* (2.2 g; 82%). m.p. 190-191°C. (Found: C, 67.42; H, 6.69; N, 3.02; *M*$^+$, 293. $C_{24}H_{28}NO_4P$ requires C, 67.55; H, 6.63; N, 3.29; *M*, 292); $[\alpha]_D^{21}$ -26.08 (*c* 1.38 in $CHCl_3$); ν_{max} (Nujol) 3 220 (br, OH), 1 155 (m, P=O), 960 cm^{-1} (m, P-O-CPh); δ_H (500 MHz; $CDCl_3$) 1.19 (3 H, d, J_{HH} = 7.2 Hz; CHC*H$_3$*), 2.34 (3 H, d, J_{PH} = 10.5 Hz; NC*H$_3$*), 2.67 (1 H, m; C*H*CH$_3$), 3.81 (3 H, s, An^{o}OMe), 3.84 (3 H, s, An^{p}OCH$_3$), 4.84 (1 H, dd, J_{HH} = 5.0 Hz, J_{HH} = 2.7 Hz; CHO*H*), 5.85 (1 H, d, J_{HH} = 5.0 Hz; C*H*Ph), 6.89-6.92 (1 H, dd, J_{HH} = 8.7 Hz, J_{PH} = 5.8 Hz; An^{o}-H-3), 6.92-6.94 (2 H, dd, $J_{2,3}$ = 8.9 Hz, J_{PH} = 2.5 Hz; An^{p}-H-3,5), 7.03-

7.06 (1 H, ddt, $J_{5,6}$ = 7.5 Hz, J_{HP} = 2.3 Hz, $J_{3,5}$ = 0.7 Hz; An^{o}-H-5), 7.19-7.22 (1 H, tt, $J_{3,4}$ = 7.3 Hz, $J_{2,4}$ = 1.34 Hz; Ph-H-4), 7.26-7.29 (2 H, t, $J_{3,4}$ = 7.3 Hz; Ph-H-3,5), 7.38-7.40 (2 H, t, $J_{2,3}$ = 8.76 Hz; Ph-H-2,6), 7.48-7.51 (1 H, ddt, $J_{4,5}$ = 8.3 Hz, $J_{4,6}$ = 1.8 Hz, J_{PH} = 0.9 Hz; An^{o}-H-4), 7.65-7.70 (2 H, dd, J_{PH} = 12.1 Hz, $J_{5,6}$ = 8.8 Hz; An^{p}-H-2,6), 7.81-7.85 (1 H, ddd, J_{PH} = 13.9 Hz, $J_{5,6}$ = 7.6 Hz, $J_{4,6}$ = 1.8 Hz; An^{o}-H-6). δ_C (126 MHz; $CDCl_3$) 13.08 (s; CCH_3), 33.1 (d, J_{PC} = 5.4 Hz; NCH_3), 55.20 (s; 2 x AnOCH_3), 60.0 (s; CCH_3), 76.62 (s; CHPh), 110.90 (d, J_{PC} = 7.0 Hz; An^{o}-C-5), 113.7 (d, J_{PC} = 14.2 Hz; An^{p}-C-2,6), 120.0 (d, J_{PC} = ~122.0 Hz; An^{o}-C-1), 120.89 (d, J_{PC} = 12.5 Hz; An^{o}-C-6), 124.00 (d, J_{PC} = 138.5 Hz; An^{p}-C-1), 126.55 (s; Ph-3,5), 126.8 (s; Ph-C-4), 126.78 (s; Ph-C-2,6), 133.79 (s; An^{o}-C-4), 134.08 (d, J_{PC} = 11.8 Hz; An^{p}-C-3,5), 135.55 (d, J_{PC} = 6.7 Hz; An^{o}-C-3), 142.67 (s; Ph-C-1), 160.65 (s; An^{o}-C-2), 162.28 (s; An^{p}-C-4); δ_P (101 Hz; $CHCl_3$) 30.70 (1 P, s); *m/z* (C.I) 426 (M+1, 55)$^+$, 408 (5, M-H_2O), 318 (100), 278 (12), 261 (40), 229 (20).

(S_p)-(-)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-(2-methoxyphenyl)-P-(3-methoxyphenyl)phosphinamide-(78).

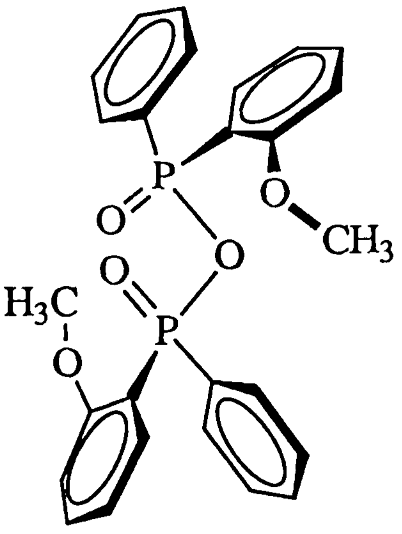


To a cooled (-78°C) and stirred solution of (2*R*, 4*S*, 5*R*)-2-(2-methoxyphenyl)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(**55**) (11.04 g, 34.80 mmol) in dry THF (350 ml) was added *via* cannula, a solution of 3-methoxyphenylmagnesium bromide (60 ml, 38.4 mmol, 0.64 M in THF) over a 20 min period. Stirring was continued at this temperature for 1h after which the mixture was allowed to stir at ambient temperature overnight. The excess Grignard reagent was quenched with water (200 ml) and the mixture extracted with dichloromethane (3 x 200 ml) aliquots. The organics were combined and concentrated to yield a white solid. crystallisation from hot

THF afforded *(S_p)-(-)-N-methyl-N-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1S, 2S)-P-(2-methoxyphenyl)-P-(3-methoxyphenyl)-phosphinamide-(78)* as white crystals of (11.2 g; 76%). m.p. 129°C. (Found: C, 67.99; H, 6.68; N, 3.35; P, 7.06; M^+, 426. $C_{24}H_{28}NO_4P$ requires: C, 67.55; H, 6.63; N, 3.29; P, 7.28%; *M*, 425); $[\alpha]_D^{21}$ -34.88 (*c*1.251 in $CHCl_3$); ν_{max} (Nujol) 3 250 (br, OH), 1 245 (m, P=O), 1035 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 1.21 (3 H, d, J_{HH} = 7.1 Hz; $CHCH_3$), 2.37 (3 H, d, J_{PH} = 10.6 Hz; NCH_3), 3.66-3.77 (1 H, m; $CHCH_3$), 3.80 (3 H, s, OMe), 3.81 (3 H, s, OMe), 4.86 (1 H, dd, J_{HH} = 4.9 Hz, J_{HH} = 2.8 Hz; CHO*H*), 5.63 (1 H, d, J_{HH} = 4.9 Hz; C*H*Ph), 6.90-6.93 (1 H, dd, J_{PH} = 5.5 Hz, J_{HH} = 8.3 Hz; An^o-H-3), 7.00-7.4 (m), 7.49-7.52 (1 H, ddt, $J_{4,6}$ = 1.6 Hz, J_{PH} = 0.6 Hz, $J_{4,5}$ = 8.3 Hz; An^o-H-4), 7.77-7.82 (1 H, ddd, J_{PH} = 13.9 Hz, $J_{5,6}$ = 7.6 Hz, $J_{4,6}$ = 1.6 Hz; An^o-H-6). δ_C (126 MHz; $CDCl_3$) 13.24 (s; CCH_3), 33.15 (s; NCH_3), 55.33 (s; $AnOCH_3$), 55.40 (s; $AnOCH_3$), 59.99 (s; CCH_3), 76.99 (s; *C*HPh), 111.13 (s; An^o-C-5), 117.2 (d, J_{PC} = 11.0 Hz; An^m-C-6), 117.8 (s; An^m-C-4), 118.5 (d, J_{PC} = ~130 Hz; An^o-C-1), 121.0 (d, J_{PC} = 12.1 Hz; An^o-C-6), 124.38 (s; An^m-C-3), 126.64 (s; Ph-C-3,5), 126.96 (s; Ph-C-4), 127.89 (s; Ph-C-2,6), 129.27 (d, J_{PC} = 14.5 Hz; An^m-C-2), 134.06 (s; An^o-C-4), 135.6 (s; An^o-C-3), 142.6 (s; Ph-C-1), 159.63 (s; An^o-C-2), 160.2 (s, An^p-C-3); δ_P (101 Hz; $CHCl_3$) 30.92 (1 P, s); *m/z* (C.I) 426 (M+1, 75)$^+$, 408 (10, M-H_2O), 318 (72), 278 (12), 261 (15), 148 (100).

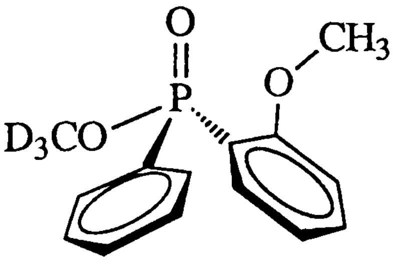
6.6. Experimental for Chapter 4.

Bis-(Phenyl-2-methoxyphenyl)-pyrophosphinate-(91).



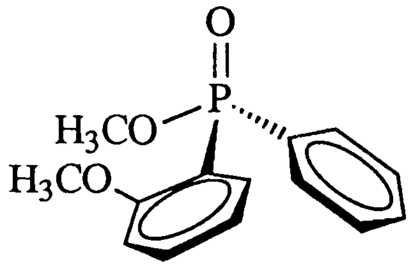
To (R_P)-(-)-*N*-methyl-*N*-(methyl-2-hydroxy-2 phenyl-2)-ethyl-(1*S*, 2*S*)-*P*-methyl-*P*-phenyl phosphinamide-(**71**) (2.0 g, 5.06 mmol) in dry dichloromethane (50 ml) was added a solution of 4-fluorophenol (3.4 g, 30 mmol) in dry dichloromethane (10 ml) followed by methanesulphonic acid (0.65 ml, 10.12 mmol) under argon with constant stirring. Stirring was continued at this temperature for 48 h after which the mixture was quenched with HCl (50 ml, 0.1 M) and the organic phase was decanted off. The organic phase was washed with NaOH (50 ml, 0.1 M), separated, dried ($MgSO_4$) and concentrated under vacuum to yield *bis-(Phenyl-2-methoxyphenyl)-pyrophosphinate-(91)* as a white solid. Recrystallisation from dichloromethane/hexane (1:1, v/v) yielded white crystals (0.2 g, 8.3%), m.p. 195°C (decomp.). (Found; C, 64.92; H, 5.06; P, 12.76; M^+, 479. $C_{26}H_{24}P_2O_5$ requires: C, 65.27; H, 5.06; P, 12.95%; *M*, 478); ν_{max} (Nujol) 1 440 (br, P-Ph), 1 240 (br, P=O), 960-979 (br, P-O-P); δ_H (500 MHz; $CDCl_3$) 3.56 (6H, s, OCH_3), 7.0-7.9 (18 H, m); δ_P (101 Hz; $CDCl_3$) 21.40 (1 P, s), 22.04 (1 P, s); *m/z* 479 $(M+1, 100)^+$, 249 (35).

(S)-d₃-Methyl (2-methoxyphenyl)phenylphosphinate-(93).



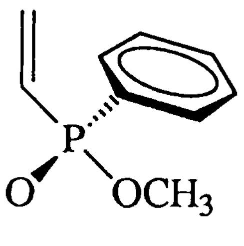
To a solution of (S_P)-(-)-*N*-methyl-*N*-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1*S*, 2*S*)-*P*-(2-methoxyphenyl)-*P*-phenyl phosphinamide-(**71**) (0.5 g, 1.26 mmol) in CD_2Cl_2 (5 g) was added d_3-methanol (5 g) contained in a Schlenk tube. A portion was removed and its ^1H n.m.r. spectrum recorded (Figure 15; t = 0). Deuterium chloride (1.88 ml, 2.5 mmol, 20% in D_2O) was added *via* precision syringe and the mixture stirred under an argon atmosphere and its ^1H n.m.r. spectrum monitored with time (Figure 15). After 24 h the mixture was quenched with dilute hydrochloric acid (100 ml; 0.1 M) and extracted into dichloromethane (2 x 100 ml). The organics were separated and washed with dilute sodium hydroxide solution (100 ml; 0.1 M) and after separation washed with water (100 ml). The organics were separated, dried ($MgSO_4$) and the solvent removed by rotary evaporation to yield *(S)-d_3-Methyl (2-methoxyphenyl)phenylphosphinate-(93)* as a colourless oil which was dried *in vacuo*. δ_H (500 MHz; $CDCl_3$) 3.70 (3 H, s; OMe), 6.80 (1 H, dd, $J_{3,4}$ = 8.4 Hz, J_{PH} = 5.6 Hz; An^o-H-3), 7.0-7.1 (1 H, ddt, $J_{5,6}$ = 7.5 Hz, J_{PH} = 2.5 Hz, $J_{3,5}$ = 0.9 Hz; An^o-H-5), 7.2-7.6 (4H, m, Ph-*m,p*, An^o-H-4), 7.75-7.9 (2H, ddd, $J_{5,6}$ = 7.4 Hz, J_{PH} = 9.6 Hz, $J_{4,6}$ = 1.0; Ph-H-2,6), 7.9-1.02 (1 H, ddd, J_{PH} = 13.1 Hz, $J_{5,6}$ = 7.5 Hz, $J_{4,6}$ = 1.8 Hz; An^o-H-6); δ_P (101 MHz; CD_2Cl_2:$CDCD_3$, 1:1 (v/v)) 28.64 (1 P, s).

(S)-(-)-Methyl (2-methoxyphenyl)phenylphosphinate-(89).



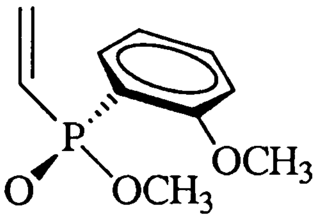
A standardised methanol solution of dry HCl (17.0 ml, 31.2 mmol, 1.845 M in methanol) was added dropwise to a vigorously stirred solution of (S_P)-(-)-*N*-methyl-*N*-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1*S*, 2*S*)-*P*-(2-methoxyphenyl)-*P*-phenyl phosphinamide-(**89**) (6.2 g, 15.6 mmol) in dry methanol (20 ml) at ambient temperature under argon. The reaction was left to stir for 18h after which it was poured into HCl (50 ml, 0.1 M) and extracted with dichloromethane (3 x 20 ml) aliquots. The organics were combined and washed with NaOH (50 ml, 0.1 M), they were then separated and the organics dried ($MgSO_4$) and concentrated to yield (-)-(*S*)-Methyl-(2-methoxyphenyl)phenylphosphinate-(**89**) as a yellow oil (3.8 g, 93%). The aqueous layer was made basic by the addition of sodium hydroxide (50 ml, 1.0M) and extracted with diethyl ether (2 x 100 ml) aliquots. The organics were separated and the solvent removed by rotary evaporation to yield the ephedrine-(**94**) as a white solid. (-)-(*S*)-(**89**); (Found: C, 64.30; H, 6.20; P, 11.65; M^+, 263. Calc for $C_{14}H_{15}PO_3$: C, 64.12; H, 5.76; P, 11.81%; *M*, 262); $[\alpha]_D^{21}$ -23.02 (*c* 1, $CHCl_3$); ν_{max} (Neat) 1 435 (br, P-Ph), 1 245 (s, P=O), 1 035 cm^{-1} (br, P-OMe); δ_H (500 MHz; C_6D_6) 3.71 (3 H, s; OMe), 3.75 (3 H, d, J_{PH} = 11.4 Hz, $POCH_3$), 6.29 (1 H, dd, $J_{3,4}$ = 8.35 Hz, J_{PH} = 5.6 Hz; An^o-H-3), 6.80-6.83 (1 H, ddt, $J_{5,6}$ = 7.54 Hz, J_{PH} = 2.5 Hz, $J_{3,5}$ = 0.87 Hz; An^o-H-5), 7.06-7.14 (4H, m, Ph-*m,p*, An^o-H-4), 8.02-8.06 (2H, ddd, $J_{5,6}$ = 7.4 Hz, J_{PH} = 9.6 Hz, $J_{4,6}$ = 1.0; Ph-H-2,6), 8.34-8.39 (1 H, ddd, J_{PH} = 13.13 Hz, $J_{5,6}$ = 7.54 Hz, $J_{4,6}$ = 1.84 Hz; An^o-H-6). δ_C (126 MHz; $CDCl_3$) 51.24 (s; P-OCH_3), 55.45 (s; OCH_3), 111.35 (d, J_{PC} = 6.9 Hz; An^o-C-5), 119.00 (d, J_{PC} = 135.0 Hz; An^o-C-1), 120.60 (d, J_{PC} = 12.0 Hz; An^o-C-6), 127.92 (d, J_{PC} = 13.5 Hz; Ph-C-2,6), 131.7 (d, J_{PC} = 11.0 Hz; Ph-C-3,5), 131.75 (s; Ph-C-4), 132.0 (d, J_{PC} = 142.0 Hz; Ph-C-1), 134.3 (s; An^o-C-4), 134.75 (d, J_{PC} = 5.2 Hz; An^o-C3), 161.03 (s; An^o-C-2); δ_P (101 MHz; $CDCl_3$) 26.04 (1 P, s); *m/z* (C.I); 263 (M+1, 100)$^+$.

(S)-(+)-Methyl (phenyl)vinylphosphinate-(96).



A standardised methanol solution of dry HCl (6.25 ml, 6.64 mmol, 1.063 M in methanol) was added dropwise to a vigorously stirred solution of (R_P)-(-)-*N*-methyl-*N*-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1*S*, 2*S*)-*P*-vinyl-*P*-phenylphosphinamide-(**72**) (1.05 g, 3.32 mmol) in dry methanol (50 ml). After 1 h the mixture was quenched with dilute HCl (50 ml, 0.1 M) and extracted into dichloromethane (3 x 100 ml) aliquots. The organics were separated and washed with dilute NaOH (50 ml, 0.1 M) and finally with water. The organics were separated and dried ($MgSO_4$) and the solvent removed by rotary evaporation to yield *(S_P)-(+)-Methyl (phenyl)vinylphosphinate-(**96**)* as a colourless oil (3.8 g, 93%) which was dried *in vacuo*.. (Found: C, 58.88; H, 6.45; P, 17.04; *M*+, 183. $C_9H_{11}PO_2$ requires: C, 59.34; H, 6.08; P, 17.00%; *M*, 182); $[\alpha]_D^{21}$ +46.8 (*c* 1, $CHCl_3$); ν_{max} (Neat) 1 224 (s, P=O); δ_H (500 MHz; $CDCl_3$) 3.68 (3 H, d, J_{PH} = 11.2 Hz, $POCH_3$), 6.08-6.20 (1 H, ddd, $J_{PH\text{-}Trans}$ = 45.1 Hz, J_{Cis} = 9.8 Hz, J_{HH} = 4.8 Hz; H-*Trans* to P), 6.28-6.30 (1 H, ddd, J_{PH} = 24.0 Hz, J_{Trans} = 18.0 Hz, J_{Cis} = 9.8 Hz; H-*Cis* to P), 6.23-6.30 (1 H, ddd, J_{PH} = 23.5 Hz, J_{Trans} = 18.0 Hz, J_{HH} = 4.87 Hz; H-*Ortho* to P), 7.44-7.48 (2 H, ddt, $J_{5,6}$ = 8.4 Hz, $J_{4,5}$ = 7.6 Hz, J_{PH} = 3.5 Hz; H-3,5), 7.51-7.56 (1 H, dt, $J_{4,5}$ = 7.4 Hz, $J_{4,6}$ = 1.5 Hz; H-4), 7.74-7.79 (2 H, ddt, J_{PH} = 12.2 Hz, $J_{5,6}$ = 8.4 Hz, $J_{4,6}$ = 1.5 Hz; H-2,6). δ_C (126 MHz; $CDCl_3$) 50.9 (d, J_{PC} = 6.4 Hz, P-OCH_3), 128.4 (d, J_{PC} = 13 Hz; C-2,6), 128.9 (d, J_{PC} = 133 Hz; $PCHCH_2$), 130.0 (d, J_{PC} = 100 Hz; C-1), 131.4 (d, J_{PC} = 11.0 Hz; C-3,5), 132.2 (s; $CHCH_2$), 134.6 (s; C-4); δ_P (101 MHz; $CDCl_3$) 30.1 (1 P, s); *m/z* (C.I); 183 (M+1, 100)$^+$, 155 (M - C_2H_3).

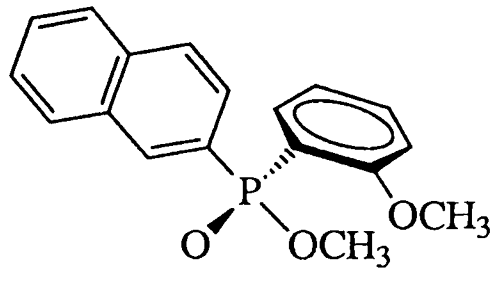
(R)-(+)-Methyl (2-methoxy-phenyl)vinylphosphinate-(97).



A standardised methanol solution of dry HCl (44.3 ml, 12.18 mmol, 0.275 M in methanol) was added dropwise to a vigorously stirred solution of (S_P)-(-)-*N*-methyl-*N*-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1*S*, 2*S*)-*P*-vinyl-*P*-(2-methoxy-phenyl)phosphinamide-(**75**) (2.10 g, 6.09 mmol) in dry methanol (50 ml). After 1h the mixture was quenched with dilute HCl (50 ml, 0.1 M) and extracted into dichloromethane (3 x 100 ml) aliquots. The organics were separated and washed with dilute NaOH (50 ml, 0.1 M) and finally with water. The organics were separated and dried ($MgSO_4$) and the solvent removed by rotary evaporation to yield (R_P)-(+)-Methyl

(2-methoxy-phenyl)vinylphosphinate-(**97**) as a colourless oil (1.4 g, 99%) which was dried *in vacuo*. $[\alpha]_D^{21}$ +135.4 (*c* 1, $CHCl_3$); ν_{max} (Neat) 1 235 cm^{-1} (s, P=O); δ_H (500 MHz; $CDCl_3$) 3.64 (3 H, d, J_{PH} = 11.6 Hz, $POCH_3$), 3.88 (s; OCH_3), 6.07-6.19 (1 H, ddd, $J_{PH\text{-}Trans}$ = 46.3 Hz, J_{Cis} = 12.3 Hz, J_{HH} = 2.3 Hz; H-*Trans* to P), 6.32-6.41 (1 H, ddd, J_{PH} = 24.0 Hz, J_{Trans} = 18.8 Hz, J_{HH} = 2.3 Hz; H-*Cis* to P), 6.43-6.54 (1 H, ddd, J_{PH} = 24.0 Hz, J_{Trans} = 18.8 Hz, J_{Cis} = 12.8 Hz; H-Ortho to P), 6.93 (1 H, ddt, J_{PH} = 5.9 Hz, $J_{3,4}$ = 8.4 Hz; H-3), 7.06 (1 H, dt, J_{PH} = 2.5 Hz, $J_{3,5}$ = 0.7 Hz $J_{5,6}$ = 7.5 Hz; H-5), 7.52 (1 H, ddt, $J_{4,6}$ = 1.8 Hz, $J_{4,5}$ = 7.9 Hz; H-4), 7.95 (1 H, ddd, $J_{4,6}$ = 1.8 Hz, $J_{5,6}$ = 7.5 Hz, J_{PH} = 13.4 Hz; H-6). δ_C (126 MHz; $CDCl_3$) 51.1(s; An^{o}OCH_3), 55.7 (s; $POCH_3$), 110.9 (s; C-5), 118.0 (d, J_{PC} = 120.0 Hz; C-1), 120.8 (d, J_{PC} = 12 Hz; C-6), 130.0 (d, J_{PC} = 134 Hz; $PCHCH_2$), 134.5 (s, $PCHCH_2$), 134.6 (s; C-4), 134.9 (s; C-3), 160.9 (s; C-2); *m/z* (C.I); 213 (M+1, 100)$^+$.

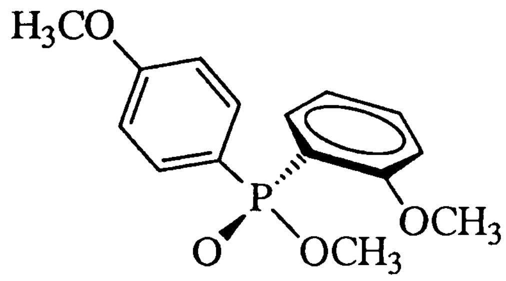
(R)-(+)-Methyl (2-Methoxyphenyl)-2-naphthylphosphinate-(98).



A standardised methanol solution of dry HCl (5.95 ml, 8.53 mmol, 1.433 M in methanol) was added dropwise to a vigorously stirred solution of (S_P)-(-)-*N*-methyl-*N*-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1*S*, 2*S*)-*P*-(2-methoxyphenyl)-*P*-2-naphthyl-phosphinamide-(**76**) (1.90 g, 4.3 mmol) in dry methanol (10 ml) at 0^{o}C under argon. The reaction was left to stir for 18h after which it was poured into HCl (50 ml, 0.5 M) and extracted with dichloromethane (3 x 100 ml) aliquots. The organics were combined and washed with NaOH (30 ml, 0.1 M), they were then separated and the organics dried ($MgSO_4$) and concentrated to yield *(R)-methyl-(2-methoxyphenyl)-2-naphthylphosphinate-(98)* as a white solid (1.03 g, 77.3%) which was further purified by recrystallisation from hot toluene and dried *in vacuo*. m.p. 150^{o}C. (Found: C, 69.40; H, 5.57; P, 9.86; M^+, 313. $C_{18}H_{17}O_3P$ requires: C, 69.22; H, 5.48; P, 9.92%; *M*, 312);

$[\alpha]_D^{19.5}$ +59.71 (*c*1.063 in $CHCl_3$); δ_H (500 MHz; C_6D_6) 3.70 (3 H, s; AnOMe), 3.80 (3 H, d, J_{PH} = 11.4 Hz; POC*H*$_3$), 6.25-6.28 (1 H, dd, $J_{3,4}$ = 8.3 Hz, J_{PH} = 5.8 Hz; An^o-H-3), 6.82-6.86 (1 H, ddt, $J_{4,5}$ = 7.5 Hz, J_{PH} = 2.5 Hz, $J_{3,5}$ = 0.9 Hz; An^o-H-5), 7.05-7.09 (1 H, ddt, $J_{4,5}$ = 7.5 Hz, $J_{4,6}$ = 2.5 Hz, J_{PH} = 0.9 Hz; An^o-H-4), 7.11-7.14 (2 H, dt, *J* = 6.8 Hz, $J_{4,6}$ = 1.3 Hz; Np), 7.17-7.20 (2 H, dt, *J* = 6.8 Hz, *J* = 1.4 Hz; Np), 7.54-7.56 (1 H, dd, $J_{1,2}$ = 8.4 Hz, J_{PH} = 3.7 Hz; Np-H-2), 8.04-8.08 (1 H, ddd, J_{PH} = 12.1 Hz, $J_{1,2}$ = 8.5 Hz, $J_{1,7}$ = 1.5 Hz; Np-H-1), 8.43-8.47 (1 H, ddd, J_{PH} = 12.1 Hz, $J_{5,6}$ = 7.5 Hz, $J_{4,6}$ = 1.5 Hz; An^o-H-6), 8.74 (1 H, d, J_{PH} = 14.5 Hz; Np-H-7). δ_C (126 MHz; C_6D_6) 51.35 (s; AnO*C*H$_3$), 55.52 (s; PO*C*H$_3$), 111.36 (d, J_{PC} = 7.4 Hz; An^o-C-3), 119.20 (d, J_{PC} = 136.3 Hz; An^o-C-1), 120.60 (d, J_{PC} = 12.3 Hz; An^o-C-6), 126.48 (s; Np), 126.87 (d, J_{PC} = 11.0 Hz; Np), 127.54 (s; Np), 127.75 (d, J_{PC} = 17.6 Hz; Np-C-2), 128.90 (s; Np), 129.50 (d, J_{PC} = 135.0 Hz; Np-C-1), 132.45 (d, J_{PC} = 14.6 Hz; Np-C-7), 133.75 (d, J_{PC} = 9.7 Hz; Np), 134.35 (An^o-C-5), 134.69 (d, J_{PC} = 6.2 Hz; An^o-C-5), 161.07 (s; An^o-C-2); δ_P (101 Hz; $CHCl_3$) 29.15 (1 P, s); *m*/*z* (C.I) 313 (M+1, 100)$^+$.

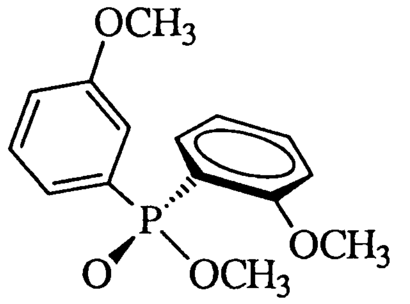
***(R)-(+)-Methyl (2-Methoxyphenyl)-4-methoxyphenylphosphinate-(99)*.**



A standardised methanol solution of dry HCl (4.65 ml, 4.7 mmol, 1.01 M in methanol) was added dropwise to a vigorously stirred solution of (S_P)-(-)-*N*-methyl-*N*-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1*S*, 2*S*)-*P*-(2-methoxyphenyl)-*P*-(4-methoxyphenyl)-phosphinamide-(**99**) (1.0 g, 2.35 mmol) in dry methanol (10 ml) at -3°C under argon. The reaction was left to stir for 18h after which it was poured into HCl (51 ml, 0.1 M) and extracted with dichloromethane (3 x 20 ml) aliquots. The organics were combined and washed with NaOH (15 ml, 0.1 M), they were then separated and the organics dried ($MgSO_4$) and concentrated to yield *(R)-(+)-methyl (2-methoxyphenyl)-4-methoxyphenyl-phosphinate-(**99**)* as a white solid (0.65 g, 95%) which was dried *in vacuo*. m.p. 68°C.

(Found: C, 61.54; H, 6.09; P, 10.04;*M*$^+$, 293. $C_{15}H_{17}NO_4P$ requires C, 61.64; H, 5.86; P, 10.60%; *M*, 292); $[\alpha]_D^{24}$ +31.03 (*c*1.115 in $CHCl_3$); δ_H (500 MHz; C_6D_6) 3.15 (3 H, s; An^{p}OMe), 3.17 (3 H, s; An^{o}OCH$_3$), 3.49 (3 H, d, J_{PH} = 11.4 Hz; POC*H*$_3$), 6.33-6.35 (1 H, dd, J_{PH} = 5.7 Hz, $J_{3,4}$ = 8.3 Hz; An^o-H-3), 6.68-6.71 (2 H, ddt, $J_{5,6}$ = 8.8 Hz, J_{PH} = 2.7 Hz, *J* = 2.0 Hz; An^p-H-3,5), 6.82-6.86 (1 H, ddt, $J_{4,5}$ = 7.5 Hz, J_{HP} = 2.5 Hz, $J_{3,5}$ = 0.9 Hz; An^o-H-5), 7.07-7.11 (1 H, ddt, $J_{3,4}$ = 8.2 Hz, $J_{4,6}$ = 1.8 Hz, J_{PH} = 0.7 Hz; An^p-H-4), 7.99-8.04 (2 H, ddt, J_{PH} = 12.0 H, $J_{2,3}$ = 8.8 Hz, *J* = 2.0 Hz; An^p-H-2,6), 8.38-8.42 (1 H, ddd, J_{PH} = 13.2 Hz, $J_{5,6}$ = 7.5 Hz, $J_{4,6}$ = 1.8 Hz; An^o-H-6). δ_C (126 MHz; C_6D_6) 50.63 (s; PO*C*H$_3$), 54.71 (s; AnO*C*H$_3$), 55.11 (s; AnO*C*H$_3$), 111.54 (s; An^o-C-5), 113.8 (d, J_{PC} = 14.2 Hz; An^p-C-2,6), 120.85 (d, J_{PC} = 11.9 Hz; An^o-C-6), 121.5 (d, J_{PC} = 133.9 Hz; An^o-C-1), 125.00 (d, J_{PC} = 148.5 Hz; An^p-C-1), 133.86 (s; An^o-C-4), 134.38 (d, J_{PC} = 11.6 Hz; An^p-C-3,5), 135.5 (s; An^o-C-3), 161.26 (s; An^o-C-2), 162.76 (s; An^p-C-4); δ_P (101 Hz; $CHCl_3$) 29.15 (1 P, s); *m/z* (C.I) 293 (M+1, 100)$^+$.

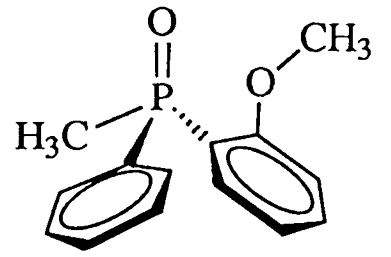
(R)-(+)-Methyl (2-Methoxyphenyl)-3-methoxyphenylphosphinate-(100).



A standardised methanol solution of dry HCl (51.6 ml, 52.78 mmol, 1.023 M in methanol) was added dropwise to a vigorously stirred solution of (S_P)-(-)-*N*-methyl-*N*-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1*S*, 2*S*)-*P*-(2-methoxyphenyl)-*P*-(3-methoxyphenyl)phosphinamide-(78) (11.23 g, 26.39 mmol) in dry methanol (150 ml) at -3°C under argon. The reaction was left to stir for 18h after which it was poured into HCl (50 ml, 0.1 M) and extracted with dichloromethane (3 x 20 ml) aliquots. The organics were combined and washed with NaOH (50 ml, 0.1 M), they were then separated and the organics dried ($MgSO_4$) and concentrated to yield *(R)-(+)-Methyl (2-*

Methoxyphenyl)-3-methoxyphenylphosphinate-(100) as a yellow oil (8 g, 100%) which was dried *in vacuo*. (Found: C, 59.58; H, 5.40; P, 10.14; *M*+, 293. $C_{15}H_{17}PO_4$ requires: C, 61.64; H, 5.86; P, 10.60%; *M*, 292); $[\alpha]_D^{20}$ +8.75 (*c* 0.41, $CHCl_3$); ν_{max} (Neat) 1245 (s, P=O), 1020 cm^{-1} (br, P-OMe); δ_H (500 MHz; C_6D_6) 3.71 (3 H, s; An^{m}OCH_3), 3.73 (3 H, d, J_{PH} = 11.4 Hz; POCH_3), 3.80 (3 H, s; An^{o}OCH_3), 6.84-6.87 (1 H, dd, $J_{3,4}$ = 8.3 Hz, J_{PH} = 6.0 Hz; An^o-H-3), 7.00-7.03 (1 H, m, $J_{3,4}$ = 8.3 Hz, $J_{2,4}$ = 2.6 Hz; An^m-H-4), 7.03-7.05 (1 H, m, $J_{5,6}$ = 7.6 Hz, J_{PH} = 2.6; An^o-H-5), 7.29-7.33 (1 H, dt, $J_{2,3}$ = 8.0 Hz, J_{PH} = 4.6; An^m-H-3), 7.36-7.41 (2 H, dt, J_{PH} = 13.0 Hz, $J_{2,3}$ = 8.0 Hz, $J_{2,4}$ = 2.7 Hz; An^m-H-2,6), 7.45-7.49 (1 H, dt, $J_{3,4}$ = 8.3 Hz, $J_{4,6}$ = 1.8; An^o-H-4), 7.91-7.96 (1 H, ddd, J_{PH} = 13.3 Hz, $J_{5,6}$ = 7.6 Hz, $J_{4,6}$ = 1.8 Hz; An^o-H-6). δ_C (126 MHz; $CDCl_3$) 51.24 (d, J_{PC} = 5.3Hz; POCH$_3$), 55.33 (s; AnOCH$_3$), 55.51 (s; AnOCH$_3$), 111.43 (d, J_{PC} = 7.4 Hz; An^o-C-5), 116.55 (d, J_{PC} = 11.7 Hz; An^m-C-6), 118.07 (s; An^m-C-4), 118.7 (d, J_{PC} = ~130 Hz; An^o-C-1), 120.6 (d, J_{PC} = 12.3 Hz; An^o-C-6), 124.00 (d, J_{PC} = 10.3 Hz; An^m-C-3), 129.1 (d; J_{PC} = 16.0 Hz; An^m-C-2), 133.0 (d, J_{PC} = 141.1 Hz; An^m-C-1), 134.3 (s; An^o-C-4), 134.73 (d, J_{PC} = 6.2 Hz; An^o-C-3), 159.25 (d, J_{PC} = 16.9 Hz; An^o-C-5), 161.08 (s, An^o-C-2); δ_P (101 MHz; $CHCl_3$) 29.45 (1 P, s); *m/z* (C.I); 293 (M+1, 100)$^+$, 274 (15), 261 (10), 242 (12), 229 (5), 214 (17).

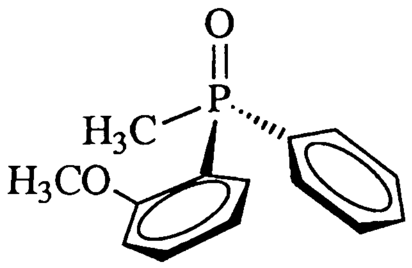
(R)-(+)-Methyl (2-methoxyphenyl)phenylphosphine oxide-(19).



To a stirred solution of (*S*)-methyl (2-methoxyphenyl)phenylphosphinate-(89) (1.00 g, 3.81 mmol) in dry THF (50 ml) was added dropwise methylmagnesium chloride (3.05 ml, 7.62 mmol, 2.5 M in THF) at ambient temperature. After 7h the reaction was quenched with water (50 ml) and extracted with dichloromethane (3 x 50 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. A colourless oil was obtained, which after evacuation (0.01 mmHg) for 4 days yielded *(R)-(+)-methyl*

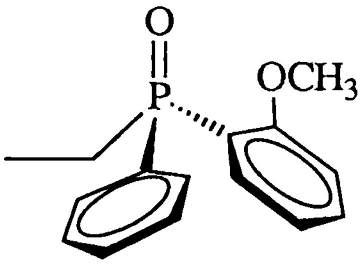
(2-Methoxyphenyl)phenylphosphine oxide-(19) (0.90 g, 97%) as a white solid, m.p. 80-81^{o}C; Lit[44]; m.p. 75-80^{o}C. (Found: C, 68.47; H, 6.08; P, 12.30; M^+, 247. Calc for $C_{14}H_{15}PO_2$: C, 68.27; H, 6.14; P, 12.58%; *M*, 246); $[\alpha]_D^{21}$ +24.6 (*c* 1.0, MeOH), Lit[8] $[\alpha]_D^{21}$ +25.9 (*c* 1, MeOH); δ_H (500 MHz; C_6D_6) 1.75 (3 H, d, J_{PH} = 74.9 Hz, PCH_3),) 2.98 (3 H, s; OMe), 6.28-6.31 (1 H, dd, $J_{3,4}$ = 8.2 Hz, J_{PH} = 5.2 Hz; An^o-H-3), 6.83-6.87 (1 H, ddt, $J_{4,5}$ = 7.38 Hz, J_{PH} =1.0, $J_{3,5}$ = 1.4 Hz; An^o-H-5), 7.05-7.19 (4H, m, Ph-*m,p*, An^o-H-4), 7.81-8.46 (2H, m; Ph-H-2,6), 8.41-8.46 (1 H, ddd, J_{PH} = 12.9 Hz, $J_{5,6}$ = 7.52 Hz, $J_{4,6}$ = 1.84 Hz; An^o-H-6). δ_C (126 MHz; $CDCl_3$) 16.20 (d, J_{PC} = 75.3 Hz, PCH_3), 55.20 (s; OCH_3), 110.94 (d, J_{PC} = 6.3 Hz; An^o-C-5), 120.98 (d, J_{PC} = 11.3 Hz; An^o-C-6), 121.70 (d, J_{PC} = 100.0 Hz; An^o-C-1), 128.05 (d, J_{PC} = 11.8 Hz; Ph-C-2,6) 130.18 (d, J_{PC} = 9.7 Hz; Ph-C-3,5), 131.10 (s; Ph-C-4), 133.75 (s; An^o-C-4), 133.90 (d, J_{PC} = 5.3 Hz; An^o-C-3), 135.20 (d, J_{PC} = 104.0 Hz; Ph-C-1), 159.91 (s; An^o-C-2); δ_P (101 MHz; $CDCl_3$) 25.48 (1 P, s). *m/z* (C.I); 247 (M+1, 100)$^+$.

(S)-methyl (2-Methoxyphenyl)phenylphosphine oxide-(19).



To a stirred solution of (*R*)-methyl (2-methoxyphenyl)phenylphosphine oxide-(**19**) (0.1 g, 0.41 mmol) and triethylamine (0.23 ml, 1.64 mmol) in dry benzene (8 ml) was added dropwise a solution of trichlorosilane (0.165 ml, 1.64 mmol) at ambient temperature under argon. After 18h the reaction was quenched with sodium hydroxide (25%) over a 5 min period and left to stir for a further 30 min. The organic phase was separated and the aqueous layer extracted with dichloromethane (3 x 25 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. to afford (*S*)-methyl (2-Methoxyphenyl)phenylphosphine-(**2**) as a colourless oil; δ_H (200 MHz; $CDCl_3$) 1.6 (3 H, d, J_{PH} = 3.9 Hz; PCH_3), 3.8 (3 H, s; OMe), 6.8-7.5 (9 H, m); δ_P (101 MHz; $CDCl_3$) -39.7 (1 P, s). The oil was redisolved in dichloromethane (10 ml) to which was added *tert*-butylhydroperoxide (0.55 ml, 1.64 mmol, 3.0 M in toluene) with constant stirring over 5 min. The mixture was quenched with water (10 ml) and the organic layer separated, dried ($MgSO_4$) and concentrated to yield a colourless liquid which after evacuation (0.01 mmHg) for 4 days to yield (*S*)-methyl (2-methoxyphenyl)phenylphosphine oxide-(**19**) (0.1 g) as a white solid, used directly in n.m.r. shift experiments. δ_H (500 MHz; C_6D_6) - identical to (*R*)-(**17**) described above.

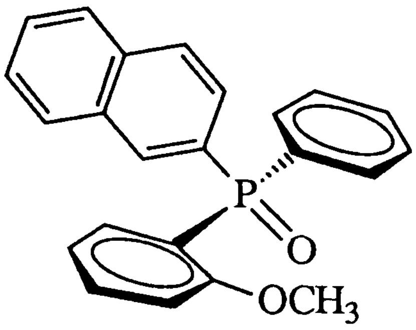
(R)-(+)-Ethyl (2-Methoxyphenyl)phenylphosphine oxide (101).



To a stirred solution of (*S*)-methyl (2-methoxyphenyl)phenylphosphinate-(**89**) (0.65 g, 2.48 mmol) in dry THF (50 ml) was added dropwise ethylmagnesium chloride (2.73 ml, 2.73 mmol, 1.0 M in THF) at ambient temperature. After 18h the reaction was quenched with water (50 ml) and extracted with dichloromethane (3 x 50 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. to afford *(R)-(+)-ethyl (2-methoxyphenyl)phenylphosphine oxide-(101)* as a colourless oil, which after evacuation (0.01 mmHg) for 4 days crystallised as a white solid, (0.54 g, 84%) m.p. 85-87^{o}C. (Found; C, 69.23; H, 6.72; P, 12.06; M^+, 261 $C_{15}H_{17}PO_2$ requires: C, 69.22; H, 6.58; P, 11.98%; *M*, 260); $[\alpha]_D^{21}$ +29.1 (*c* 1, in $CHCl_3$);ν_{max} (nujol) 1 445 (br, P-Ph), 1 245 cm^{-1} (br, P=O); δ_H (500 MHz; C_6D_6) 1.11-1.18 (3 H, dt, J_{PH} = 18.2 Hz, J_{HH} = 7.7 Hz; PCH_2CH_3) 2.14-2.45 (2 H, m; PCH_2CH_3), 3.74 (3H, OCH_3), 6.86-6.89 (1 H, dd, $J_{3,4}$ = 8.3 Hz, J_{PH} = 5.3 Hz; An^o-H-3), 7.27-7.37 (1 H, ddt, $J_{4,5}$ = 7.5 Hz, J_{PH} =1.9, $J_{3,5}$ = 1.0 Hz; An^o-H-5), 7.42-7.44 (1 H, ddt $J_{4,5}$ = 7.3 Hz, $J_{4,6}$ =1.8; An^o-H-4) ,7.46-7.49 (1 H, tt, $J_{4,5}$ = 8.2 Hz, $J_{4,6}$ =1.5 Hz; An^o-H-4), 7.74-7.78(2 H, ddt, J_{PH} = 11.7 Hz, $J_{5,6}$ =8.1, $J_{4,6}$ = 1.5 Hz; Ph-H-2,6), 7.97-8.01 (1 H, ddd, J_{PH} = 12.6 Hz, $J_{5,6}$ = 7.5 Hz, $J_{4,6}$ = 1.8 Hz; An^o-H-6); δ_C (126 MHz; C_6D_6) 5.55 (s; CH_2CH_3), 22.0 (d, J_{PC} = 74.3 Hz, P-CH_2CH_3), 55.17 (s; OCH_3), 110.7

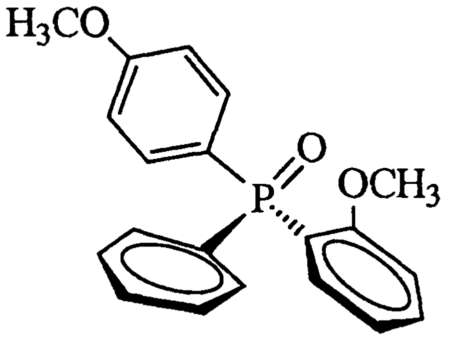
(d, 1 H, J_{PC} = 5.7 Hz; An^o-C-5), 120.9 (d, J_{PC} = ~100 Hz; An^o-C-1),121.1 (d, J_{PC} = 10.5 Hz; An^o-C-6), 120.9 (d, J_{PC} = ~130 Hz; An^o-C-1), 121.8 (d, J_{PC} = 11.5 Hz; Ph-C-2,6) 130.6 (s; Ph-C-3,5), 131.1 (s; An^o-C-4), 133.6 (s; Ph-C-4), 134.6 (s; Ph-C-3), 159.7 (s; An^o-C-2); δ_P (101 Hz; CDCl$_3$) 30.32 (1 P, s); *m/z* (C.I) 521 (20), 396 (25), 261 (M+1, 100)$^+$.

(S)-(-)-2-Methoxyphenyl (2-naphthyl)phenylphosphine oxide-(103).



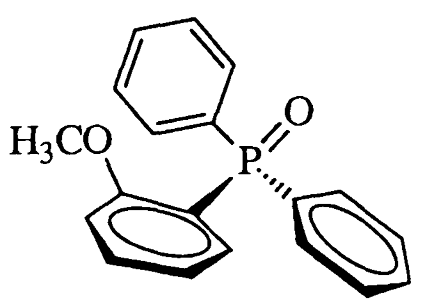
To a cooled (-78^{o}C) solution of (*R*)-methyl (2-naphthyl)-3-methoxyphenylphosphinate-(**98**) (0.2 g, 0.64 mmol) in THF (10 ml) was added phenylmagnesium chloride (2.6 ml, 5.2 mmol, 2.0 M in THF) over 30 min with vigorous stirring under an argon atmosphere. The mixture was left to stir overnight and equilibrate to ambient temperature unaided. The mixture was quenched with water (30 ml) and extracted into dichloromethane (3 x 20 ml) aliquots. The organics were combined, dried (MgSO$_4$) and concentrated to yield (*S*)-(-)-2-methoxyphenyl (2-naphthyl)phenylphosphine oxide-(**103**) as a colourless oil (0.21 g, 90%). (Found: C, 71.14; H, 5.56; P; M^+, 358 $C_{23}H_{19}PO_2$ requires C, 77.10; H, 5.34; P; *M*, 358); $[\alpha]_D^{23}$ -7.46 (*c* 0.925, CHCl3); δ_H (500 MHz; C$_6$D$_6$) 2.90 (3 H, s; An^{P}OMe), 6.32-6.35 (1 H, dd, $J_{3,4}$ = 8.3 Hz, J_{PH} = 5.3 Hz; An^o-H-3), 6.78-6.82 (1 H, ddt, $J_{4,5}$ = 7.4 Hz, J_{PH} = 2.6 Hz, $J_{3,5}$ = 0.6 Hz; An^o-H-5), 6.90-7.73 (9 H, m), 7.75-7.79 (2 H, ddt, J_{PH} = 12.1 Hz, $J_{5,6}$ = 8.0, $J_{4,6}$ = 1.5 Hz; PH-2,6), 7.81-7.86 (1 H, ddd, J_{PH} = 12.5 Hz, $J_{1,2}$ = 7.6 Hz, $J_{1,7}$ = 1.5 Hz; Np-H-1), 8.06-8.12 (1 H, ddd, J_{PH} = 13.4 Hz, $J_{5,6}$ = 7.6 Hz, $J_{4,6}$ = 1.8 Hz; An^o-H-6), 8.48-8.51 (1 H, d, J_{PH} = 14.1 Hz; Np-H-7). *m/z* (E.I.) 358 (m+1, 100), 340 (30), 327 (60), 267 (45).

(R)-2-Methoxyphenyl (4-methoxyphenyl)phenylphosphine oxide-(106).



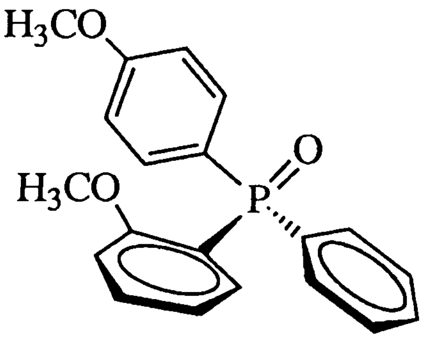
To a cooled (-20^{o}C) and stirred solution of (S_P)-methyl (2-methoxyphenyl)-phenylphosphinate-(**89**) (0.86 g, 3.28 mmol) in dry THF (70 ml) was added dropwise, 4-methoxyphenylmagnesium bromide (14.9 ml, 3.28 mmol, 0.22 M in THF), the mixture left to stir and equilibrate to ambient temperature unaided. After 18h the reaction was quenched with water (50 ml) and extracted with dichloromethane (3 x 50 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography (Flash silica, Et_2O/CH_2Cl_2; 60:40) yielded *2-methoxyphenyl (4-methoxyphenyl)phenylphosphine oxide-(**106**)* as a colourless oil (0.4 g, 36%). (Found; C,70.75; H, 5.74; M^+, 339. $C_{20}H_{19}PO_3$ requires: C, 71.00; H, 5.66%; M, 338); $[\alpha]_D^{21}$ -3.5 (c 0.5, MeOH); ν_{max} (nujol) 1 440 (br, P-Ph), 1 240 cm^{-1} (br, P=O); δ_H (500 MHz; C_6D_6) 2.96 (3 H, s; OCH_3), 3.20 (3 H, s; OCH_3), 6.34-6.36 (1 H, dd, $J_{3,4}$ = 8.1 Hz, J_{PH} = 5.5 Hz; An^{o}-H-3), 6.65-6.68 (2 H, dd, $J_{5,6}$ = 8.9 Hz, J_{PH} = 2.2 Hz; An^{p}-H-3,5), 6.82-6.86 (1 H, ddt, $J_{4,5}$ = 7.5 Hz, J_{PH} = 2.5 Hz, $J_{3,5}$ = 1.0 Hz; A^{n}o-H-5), 7.10-7.20 (4 H, m; Ph-H-3,4,5; An^{o}-H-4), 7.71-7.76 (2 H, ddt, J_{PH} = 11.9 Hz, $J_{5,6}$ = 8.8 Hz, $J_{4,6}$ = 2.1 Hz; An^{p}-H-2,6), 7.78-7.82 (2 H, ddt, J_{PH} = 12.5 Hz, $J_{5,6}$ = 7.0 Hz, $J_{4,6}$ = 1.7 Hz; Ph-H-2,6), 8.11-8.15 (1 H, ddd, J_{PH} = 13.2 Hz, $J_{5,6}$ = 7.6 Hz, $J_{4,6}$ = 1.8 Hz; A^{n}o-H-6).; δ_P (101 MHz; $CDCl_3$) 30.6 (1 P, s); m/z 339 (M+1, 100)$^+$.

2-Methoxyphenyl(diphenyl)phosphine oxide-(107).



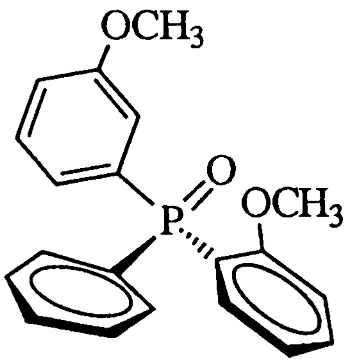
To a cooled (-20°C) and stirred solution of (S_P)-methyl (2-methoxyphenyl)-phenylphosphinate-(**89**) (0.14 g, 0.5 mmol) in dry THF (20 ml) was added dropwise, under argon, phenylmagnesium chloride (0.8 ml, 1.6 mmol, 2.0 M in THF), the mixture left to stir and equilibrate to ambient temperature unaided. After 18h the reaction was quenched with water (50 ml) and extracted with dichloromethane (3 x 50 ml) aliquots. The organics were combined, dried ($MgSO_4$) and the solvent removed by rotary evaporation to yield 2-methoxyphenyl(diphenyl)phosphine oxide-(**107**) (0.152 g, 97%). m.p. 178°C. δ_H (200 MHz; CDCl3) 3.55 (3 H, s; OCH_3), 6.8-8.0 (14 H, m).

(S)-2-Methoxyphenyl (4-methoxyphenyl)phenylphosphine oxide-(106).



To a cooled (-78°C) solution of (*R*)-methyl (2-methoxyphenyl)-4-methoxyphenylphosphinate-(**99**) (0.9 g, 3.1 mmol) in THF (10 ml) was added phenylmagnesium chloride (12.5 ml, 25 mmol, 2.0 M in THF) over 30 min with vigorous stirring under an argon atmosphere. The mixture was left to stir overnight and equilibrate to ambient temperature unaided. The mixture was quenched with water (30 ml) and extracted into dichloromethane (3 x 30 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated to yield a colourless oil which was purified by dry column chromatography eluted with diethyl ether-dichloromethane (1:1, *v/v*). *(S)-2-methoxyphenyl (3-methoxyphenyl)phenylphosphine oxide-(106)* was obtained as a colourless oil $R_f = 0.6$. (0.95 g, 90%). (Found: C, 71.14; H, 5.56; P. $C_{20}H_{19}PO_3$ requires C, 70.99; H, 5.66%); $[\alpha]_D^{23}$ -2.07 (*c* 1.16, CHCl3); Spectroscopic data identical to (*R*)-2-methoxyphenyl(4-methoxyphenyl)phenylphosphine oxide-(**106**).

(S)-(-)-2-Methoxyphenyl (3-methoxyphenyl)phenylphosphine oxide-(109).

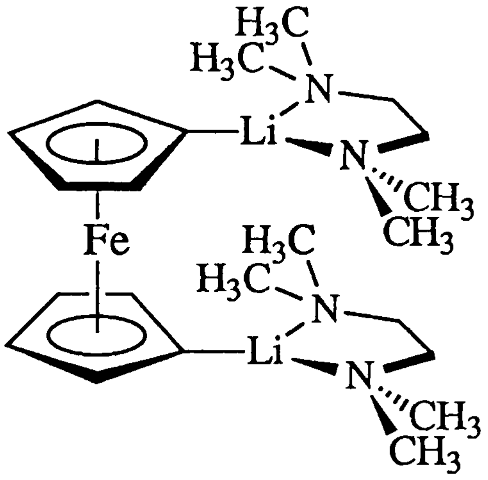


To a cooled (-78°C) solution of (*R*)-methyl (2-methoxyphenyl)-3-methoxyphenylphosphinate-(**100**) (8.1 g, 27.71 mmol) in THF (150 ml) was added phenylmagnesium chloride (45 ml, 90.0 mmol, 2.0 M in THF) over 30 min with vigorous stirring under an argon atmosphere. The mixture was left to stir overnight and equilibrate to ambient temperature unaided. The mixture was quenched with water (100 ml) and extracted into dichloromethane (3 x 100 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated to yield a colourless oil which was purified by flash column chromatography eluted with diethyl ether-tetrahydrofuran (1:1, *v*/*v*). A colourless oil was obtained at R*f* = 0.4 which was recrystallised from diethyl-ether to yield *(S)-(-)-2-methoxyphenyl(3-methoxyphenyl)phenylphosphine oxide-(**109**)* as white crystals (9.1 g, 97.3%). (Found: C, 70.89; H, 5.61; P, 9.18; M^+, 339 $C_{20}H_{19}PO_3$ requires C, 71.20; H, 5.38; P, 9.18%; *M*, 338); $[\alpha]_D^{24}$ -9.54 (*c* 0.985, $CHCl_3$); δ_H (500 MHz; C_6D_6) 2.93 (3 H, s; An^{m}OMe), 3.17 (3 H, s; An^{o}OCH$_3$), 6.31-6.34 (1 H, dd, J_{HH} = 8.3 Hz, J_{PH} = 5.2 Hz; An^o-H-3), 6.80-6.83 (2 H, m), 6.99-7.11 (5 H, m), 7.45-7.48 (1 H, ddt, J_{PH} = 12.0 Hz, $J_{2,3}$ = 7.5 Hz, $J_{2,6}$ = 1.2 Hz; An^m-H-2), 7.69-7.48 (1 H, ddd, J_{PH} = 13.5 Hz, $J_{2,6}$ = 1.3, $J_{4,6}$ = 1.23 Hz; An^m-H-6), 7.88-7.93 (2 H, ddd, J_{PH} = 12.3 Hz, $J_{5,6}$ = 7.6, $J_{4,6}$ = 1.5 Hz; Ph-H-2,6), 8.27-8.31 (1 H, ddd, J_{PH} = 13.2 Hz, $J_{5,6}$ = 7.6 Hz, $J_{4,6}$ = 1.8 Hz; An^o-H-6. δ_C (126 MHz; $CDCl_3$) 55.28 (s; AnO*C*H$_3$), 55.38 (s; AnO*C*H$_3$), 111.54 (d, J_{PC} = 6.0 Hz; An^o-C-5), 116.55 (d, J_{PC} = 10.5 Hz; An^m-C-6), 117.6 (s; An^m-C-4), 118.9 (d, J_{PC} = ~140 Hz; An^o-C-1), 120.9 (d, J_{PC} = 11.2 Hz; An^o-C-6), 124.1(d, J_{PC} = 9.6 Hz; An^m-C-3), 128.1 (d, J_{PC} = 12.2 Hz; Ph-C-2,6), 129.1 (d, J_{PC} = 14.4 Hz; An^m-C-2), 131.3 (d, J_{PC} = 9.7 Hz; Ph-C-3,5), 133.9 (d, J_{PC} = 107.3 Hz; Ph-C-1), 134.1 (s; An^o-C-4), 134.5 (d, J_{PC} = 107 Hz; An^o-C-1), 134.9 (s; An^o-C-3), 159.4 (s, An^m-C-

5), 161.02 (s, An^o-C-2); δ_P (101 MHz; $CHCl_3$) 24.61 (1 P, s); *m/z* (C.I); 339 (M+1, 100)$^+$, 320 (12), 217 (15), 168 (35), 154 (30), 94 (55).

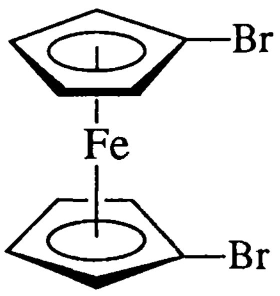
6.7. Experimental for Chapter 5.

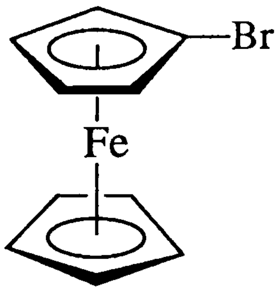
1,1'-Bis(lithium-N,N,N',N',-tetramethylethylenediamine)ferrocene-(116).



This complex was prepared according to an established literature procedure[112] from ferrocene which had been previously sublimed and recrystallised from methanol. The reagent was used immediately upon preparation.

1,1'-Dibromoferrocene-(118) and monobromoferrocene-(119).

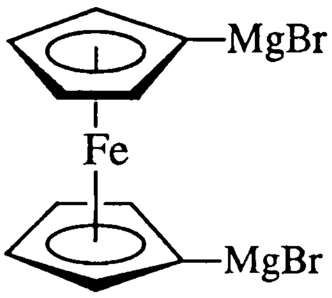




This complex was prepared from ferrocene (5.0 g, 0.03 mmol) according to a literature procedure[115]. The reaction residue was purified by sublimation and recrysatallisation from hot methanol to afford 1,1'-dibromoferrocene-(**118**) (2.5 g, 24.3%) and monobromoferrocene-(**119**) (1.2 g, 15%) both as orange crystalline solids. 1,1'-Dibromoferrocene-(**118**) m.p. 54°C; Lit[115] m.p. 55-56°C. (Found: C, 34.39%; H, 2.20%: *M*$^+$, 344. Calc for $C_{10}H_8Fe$: C, 34.93%; H, 2.34%: *M*, 343). δ_H (500 MHz; $CDCl_3$) 4.17 [4 H, t, J_{HH} = 3.8 Hz: (η^5-C_5H_5)], 4.43 [4 H, t, J_{HH} = 3.8 Hz; (η^5-C_5H_5)], δ_C (126 MHz; $CDCl_3$) 69.94 (s), 72.72 (s), 78.3 (s, C-1). *m/z* (E.I.) 344 (M+1, 40)$^+$, 128

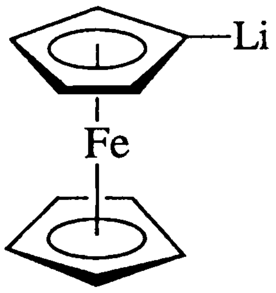
(100).. Monobromoferrocene-(**119**) δ_H (500 MHz; $CDCl_3$) 4.17 [5 H, s; (η^5-C_5H_4)], 4.43 [4 H, t, J_{HH} = 3.8 Hz; (η^5-C_5H_5)], δ_C (126 MHz; $CDCl_3$) 67.96 (s), 69.93 (s), 72.71 (s), 78.2 (s, C-1). *m/z* (E.I.) 263 (M+1, 10)$^+$.

1,1'-Bis(bromomagnesio)ferrocene-(117).



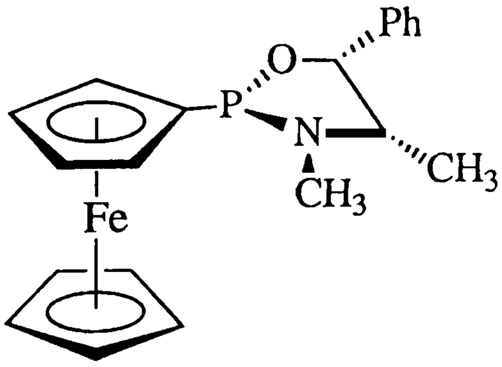
This complex was prepared by addition of 1,1'-dibromoferrocene-(**118**) (0.2 g, 0.44 mmol) in THF or Et2O (5 ml) to activated magnesium turnings (0.2 g, 8.3 mmol) in the appropriate solvent (2 ml) and 1,2-dibromoethane (1 drop). The reagent was used immediately upon preparation.

Monolithioferrocene-(120).



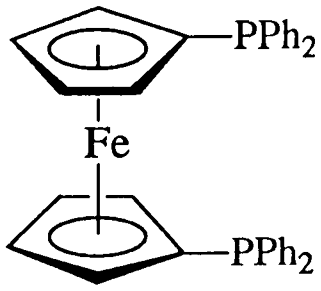
This complex was prepared from ferrocene according to an established literature procedure[116] and used immediately upon preparation.

2-(Ferrocene)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(121).



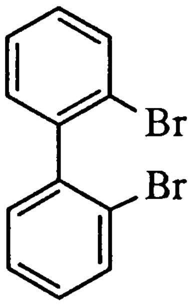
To a cooled (-78°C) solution of (2*R*, 4*S*, 5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(**43**) (2.3 g, 10.0 mmol) in THF (10 ml) was added *via* cannula, monolithioferrocene-(**120**) (8.4 mmol). The reaction was stirred for 2h at this temperature after which it was stirred for a further 18h at ambient temperature. The reaction mixture was quenched with water (50 ml) and extracted into dichloromethane (3 x 100 ml) aliquots. The organics were combined, dried ($MgSO_4$) and the solvent removed by rotary evaporation to afford a yellow residue. Purification by flash column chromatography (3:1 EtOAc: CH_2Cl_2) afforded an orange solid. δ_H (500 MHz; $CDCl_3$) - major diastereoisomer - 0.65 (3 H, d, J_{HH} = 6.4 Hz; CHC*H*$_3$), 2.70 (3 H, d, J_{PH} = 12.6 Hz; PNC*H*$_3$), 3.65 (1 H, m, C*H*CH$_3$), 4.2 (m), 4.6 (2 H, d, J_{PH} = 12.9 Hz; *o*-ferrocene protons), 5.75 (1 H, d, J_{HH} = 7.4 Hz; C*H*Ph), 6.6-6.8 (2 H, m), 7.4 (m). Minor diastereoisomer - 0.8 (3 H, d, J_{HH} = 6.7 Hz; CHC*H*$_3$), 2.85 (3 H, d, J_{PH} = 12.1 Hz; PNC*H*$_3$), 3.5 (1 H, m, C*H*CH$_3$), 4.2 (m), 4.4 (m), 5.5 (1 H, m, C*H*Ph), 6.65 (m), 7.4 (m).

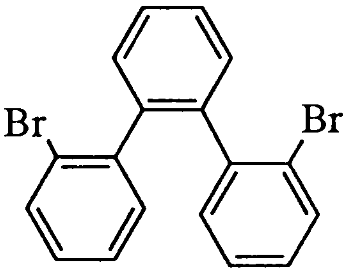
1,1'-Bis(diphenylphosphino)ferrocene-(123).



This complex was prepared from ferrocene (1.8 g, 10 mmol) according to an established literature procedure[117]. The reaction residue was purified by column chromatography and recrystallised from methanol to afford 1,1'-bis(diphenylphosphino)ferrocene-(**123**) as orange prisms (1.8 g, 50%); δ_H (200 MHz; $CDCl_3$) 4.11 [7 H, m, (η^5-C_5H_5)], 4.40 [2 H, m, (η^5-C_5H_5)], 7.36 (10 H, m, Ar-H); 31P (101 MHz; CH_2Cl_2) -19.58 (s). *m/z* (E.I.) 370 (M, 100)$^+$.

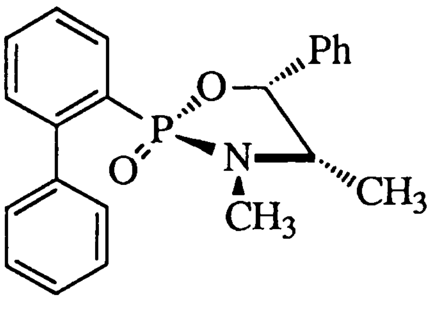
2,2'-Dibromobiphenyl-(129) and 1,2-bis(ortho-bromophenyl)benzene-(130).





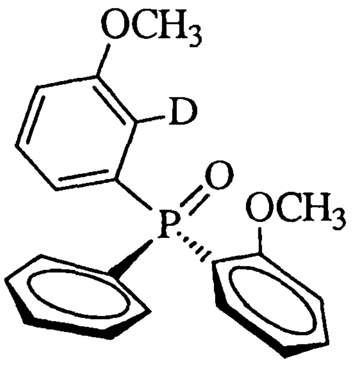
The above compounds were prepared by a literature procedure[120]. The yellow reaction residue was purified by flash column chromatography (1:1 v/v Et_2O-CH_2Cl_2) to afford 2,2-dibromobiphenyl-(**129**) (2.0 g, 14%) as a white crystalline solid and 1,2-bis(*ortho*-bromophenyl)benzene-(**130**) (1.5 g, 5%) as a colourless oil. 2,2'-Dibromobiphenyl-(**129**) was further purified by recrystallisation from absolute ethanol to afford white needles. m.p. 77°C. Lit[120] 79-80°C. (Found: C, 46.24%; H, 2.52%: M^+, 312. Calc for $C_{12}H_8Br_2$: C, 46.19%; H, 2.58%: *M*, 312). δ_H (500 MHz; CDC13) 7.27 (4 H, tt, J_{HH} = 7.6 Hz, J_{HH} = 1.3 Hz; H-3,4), 7.39 (1 H, dd, $J_{3,4}$ = 8 Hz, $J_{2,4}$ = 1.3 Hz; H-4). *m/z* (E.I.) 312 (M+, 40), 231 (25), 152 (100). 1,2-Bis(*ortho*-bromophenyl)benzene-(**130**) (Found: C, 55.42%; H, 3.31%: *M*+, 388. Calc for $C_{18}H_{12}Br_2$: C, 55.70%, H, 3.11%: *M*, 388). δ_H (200 MHz; $CDCl_3$) 6.9-7.2 (m), 7.25-7.7 (m). *m/z* (E.I.) 388 (*M*+, 20), 228 (100), 152 (17).

2-Biphenyl-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide-(133).



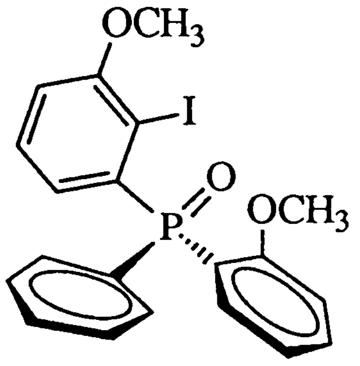
2,2-Dilithiobiphenyl-(**132**) was prepared from 2,2'-dibromobiphenyl-(**129**) (0.312 g, 1.0 mmol) in diethyl ether (3.2 ml) and *n*-butyllithium (1.0 ml, 2.0 mmol) at 0°C according to a literature procedure[121]. This solution was then cooled to -30°C to which (2*R*, 4*S*, 5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(**43**) (1.9 ml, 2.0 mmol, 1.0 M in THF) was added *via* syringe under an argon atmosphere. The mixture was left to stir at ambient temperature for 18h after which the reaction was quenched with water (50 ml) and extracted into dichloromethane (3 x 100 ml) aliquots. The organics were combined, dried ($MgSO_4$) and the solvent was removed by rotary evaporation to afford a yellow solid. This was dissolved in toluene (5 ml) to which was added *tert*-butylhydroperoxide (1.0 ml, 3 mmol) at 0°C and stirred for 1h. The mixture was quenched with water and processed as described above to yield a yellow solid. This was purified by flash column chromatography (1:1 v/v Et_2O-CH_2Cl_2).to yield *ca.* 5 mg of *2-biphenyl-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-(133)* as an off-white oil. δ_H (200 MHz; $CDCl_3$) 0.6 (3 H, d, J_{HH} = 6.6 Hz; CHCH_3), 2.4 (3 H, d, J_{PH} = 10.0 Hz; PNCH_3), 2.9 (1 H, m, C*H*Ph), 4.3 (1 H, m), 5..5 (1 H, m), 7.4 (m). *m/z* (C.I.) 364 (M^+, 100).

(S)-2-^{2}H-6-methoxyphenyl (2-methoxylphenyl)phenylphosphine oxide-(146).



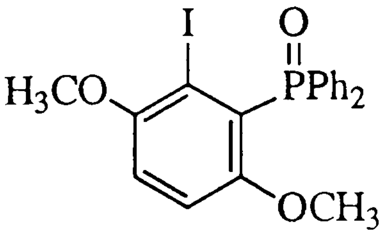
To a cooled (-78°C) solution of (*S*)-2-methoxyphenyl (3-methoxyphenyl)phenylphosphine oxide-(**109**) (0.1 g, 0.3 mmol) in THF (5 ml) was added *tert*-butyllithium (0.25 ml, 0.425 mmol, 1.7 M in pentane) over a 10 min period with vigorous stirring under an argon atmosphere. The mixture was left to stir at this temperature for 6h during which the colour of the solution changed to a straw yellow. The mixture was quenched with excess D_2O (0.4 ml, 0.4 g, 22.22 mmol) and extracted into dichloromethane (3 x 20 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated to yield a colourless oil which was recrystallised from diethyl-ether to yield *(S)-2-^{2}H-6-methoxypheyl (2-methoxylphenyl)phenylphosphine oxide-(146)* as a white powder (0.97 g, 97%). δ_H (500 MHz; C_6D_6) 2.93 (3 H, s; An^{m}OMe), 3.17 (3 H, s; An^{o}OCH$_3$), 6.31-6.34 (1 H, dd, J_{HH} = 8.3 Hz, J_{PH} = 5.2 Hz; An^o-H-3), 6.79-6.80 (2 H, m), 6.99-7.15 (5 H, m), 7.43-7.47 (1 H, ddd, J_{PH} = 12.0 Hz, $J_{2,3}$ = 7.5 Hz, $J_{2,6}$ = 1.0 Hz; An^{m}-H-2), 7.87-7.92 (2 H, ddd, J_{PH} = 12.3 Hz, $J_{2,3}$ = 7.7, $J_{2,4}$ = 1.5 Hz; Ph-H-2,6), 8.24-8.29 (1 H, ddd, J_{PH} = 13.3 Hz, $J_{5,6}$ = 7.6 Hz, $J_{4,6}$ = 1.8 Hz; An^{o}-H-6.

(S)-2-iodo-3-methoxyphenyl (2-methoxyphenyl)phenylphosphine oxide-(147).



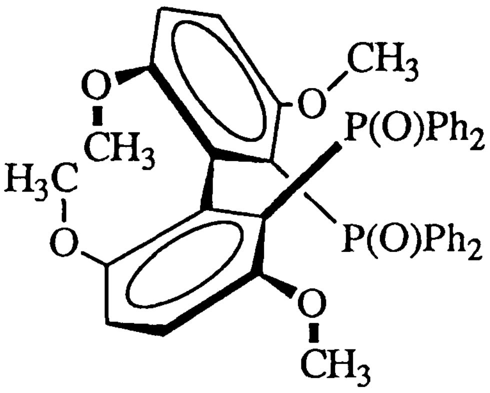
To a cooled (-100°C) solution of (*S*)-(-)-2-methoxyphenyl (3-methoxyphenyl)-phenylphosphine oxide-(**109**) (1.5 g, 4.45 mmol) in THF (50 ml) was added *t*-butyllithium (3.75 ml, 6.4 mmol) and left to stir for 30 min. The colour of the solution had changed from red to straw yellow. The solution was then left to stir for 5.5h at -78°C after which iodine (1.5 g, 6 mmol) was added and the mixture left to stir for a further 18h at ambient temperature. The mixture was quenched with water (50 ml) and extracted into dichloromethane (3 x 100 ml) aliquots. The organics were combined, dried ($MgSO_4$) and the solvent was removed by rotary evaporation to afford a yellow oil. Purification by flash column chromatography (3:1 60-80 petrol-MeOH) yielded *(S)-2-iodo-3-methoxyphenyl (2-methoxypheyl)phenylphosphine oxide-(147)* as a colourless oil (50 mg, 2.4 %). (Found: C, 51.27%; H, 3.75%: *M*+, 464. $C_{20}H_{18}PIO_3$ requires: C, 51.74%; H, 3.91%: *M*, 464). δ_H (200 MHz; $CDCl_3$) 2.8 (3 H, s, OCH_3), 3.18 (3 H, s, OCH_3), 6.9-7.6 (9 H, m), 8.2 (2 H, m; Ph-2,6), 8.4 (1 H, m, An^{o}-H-6). *m/z* (E.I.) 464 (*M*+, 70), 433 (35), 373 (100), 337 (80).

2-Iodo-3,6-dimethoxyphenyl(diphenyl)phosphine oxide-(137).



2-Iodo-3,6-dimethoxyphenyl(diphenyl)phosphine oxide-(**137**) was prepared by the method described by Brown and Woodward[30]. M.p. 216°C. Lit[30]; 212-213°C. δ_H (200 MHz; $CDCl_3$) 3.10 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 6.80 (1 H, m; H-4), 6.89 (1 H, d, $J_{4,5}$ = 9 Hz; 4-H), 7.40 (4 H, m), 7.47 (2 H, m), 7.68 (4 H, m).

2,2'-Diphenylphosphinoyl-3,3'-5,5'-tetramethoxybiphenyl-(140).



2,2'-Diphenylphosphinoyl-3,3'-5,5'-tetramethoxybiphenyl-(**140**) was prepared from 2-Iodo-3,6-dimethoxyphenyl(diphenyl)phosphine oxide-(**137**) by the method described by Schmid *et al.*[29]. M.p. >250°C. Lit[30]; >250°C. δ_H (200 MHz; $CDCl_3$) 3.10 (3 H, s, OCH3), 3.70 (3 H, s, OCH3), 6.80 (1 H, dd, $J_{4,5}$ = 9 Hz; H-4), 6.90 (1 H, d, $J_{4,5}$ = 9 Hz; H-5), 7.15 (4 H, m), 7.2-7.90 (m).

Appendix.

Atomic coordinates and (equivalent) isotropic temperature factors for (2*R*,4*S*,5*R*)-2-phenoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-oxide-(**42**) (x 10^4), except coordinates x10^5 for P and all parameters x 10^3 for H atoms.

Atom	x	y	z	Ueq
O(1)	6750(2)	6780(1)	4520(1)	531(9)
P(2)	64548(7)	81520(5)	42456(4)	499(3)
N(3)	4835(2)	7909(2)	3799(1)	538(11)
C(4)	4363(3)	6610(2)	3803(1)	483(13)
C(5)	5344(3)	6045(2)	4487(1)	470(12)
O(6)	6514(3)	9130(2)	4851(1)	711(11)
C(7)	8416(3)	7581(2)	3068(2)	540(13)
C(8)	7920(3)	7581(3)	2268(2)	665(17)
C(9)	8561(4)	6767(3)	1723(2)	768(18)
C(10)	9663(4)	5956(4)	1957(2)	783(20)
C(11)	10160(3)	5979(3)	2755(2)	791(20)
C(12)	9552(3)	6787(3)	3317(2)	659(16)
C(13)	3742(4)	8855(3)	3564(2)	741(20)
C(14)	4532(4)	6027(3)	2968(2)	609(16)
C(15)	5750(3)	4715(2)	4378(1)	517(13)
C(16)	7092(4)	4337(3)	4021(3)	809(21)
C(17)	7376(5)	3102(4)	3905(3)	944(25)
C(18)	6363(5)	2241(3)	4145(2)	853(22)
C(19)	5018(5)	2606(3)	4509(2)	797(21)
C(20)	4702(4)	3838(3)	4624(2)	636(16)
O(21)	7817(2)	8430(2)	3625(1)	669(11)
H(1)	338(4)	653(3)	397(2)	59(7)
H(2)	483(3)	617(2)	505(2)	51(7)
H(3)	719(4)	813(3)	215(2)	77(9)
H(4)	815(4)	682(4)	117(2)	90(11)
H(5)	1003(5)	514(4)	162(3)	131(15)
H(6)	1093(4)	535(3)	298(2)	94(12)
H(7)	980(3)	680(3)	384(2)	60(8)
H(8)	346(7)	859(5)	294(4)	166(21)
H(9)	435(5)	979(4)	371(2)	113(14)
H(10)	274(5)	874(4)	382(2)	94(12)
H(11)	555(4)	598(3)	274(2)	80(10)
H(12)	414(4)	526(3)	293(2)	76(9)
H(13)	396(4)	647(4)	255(2)	96(12)
H(14)	782(4)	484(4)	381(2)	85(11)
H(15)	807(5)	285(4)	365(3)	103(14)
H(16)	673(5)	130(4)	399(3)	117(14)
H(17)	420(7)	209(6)	449(4)	167(22)
H(18)	379(5)	407(4)	499(2)	103(12)

Atomic coordinates and (equivalent) isotropic temperature factors for (2*S*, 4*S*, 5*R*)-2-phenoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-oxide-(**56**) (x 10^4), except coordinates x 10^5 for P and all parameters x 10^3 for H atoms.

Atom	x	y	z	Ueq
O(1)	6656(2)	4478(2)	4494(2)	526(13)
P(2)	61382(9)	58518(7)	42755(6)	513(5)
N(3)	4512(3)	5504(2)	4183(2)	484(14)
C(4)	4322(3)	4148(3)	4086(2)	436(16)
C(5)	5498(3)	3632(3)	4642(2)	412(16)
O(6)	6860(3)	6493(2)	3572(2)	776(17)
C(7)	5924(3)	6355(3)	5966(2)	506(18)
C(8)	4824(4)	6978(3)	6325(3)	557(21)
C(9)	4422(5)	6755(4)	7166(3)	731(27)
C(10)	5136(7)	5895(5)	7644(3)	904(36)
C(11)	6245(7)	5274(5)	7296(4)	977(41)
C(12)	6662(5)	5503(4)	6448(4)	742(28)
C(13)	3508(6)	6374(4)	3806(4)	732(30)
C(14)	4345(5)	3717(4)	3143(3)	681(26)
C(15)	5926(3)	2305(3)	4457(2)	409(16)
C(16)	7031(3)	2012(3)	3931(2)	463(19)
C(17)	7380(4)	783(3)	3765(2)	568(20)
C(18)	6620(4)	-169(3)	4129(3)	605(22)
C(19)	5504(5)	109(3)	4650(3)	660(25)
C(20)	5177(4)	1349(3)	4820(2)	549(21)
O(21)	6361(2)	6680(2)	5124(2)	596(14)
H(1)	343(3)	392(3)	438(2)	37(7)
H(2)	529(3)	368(3)	523(2)	46(9)
H(3)	430(3)	750(3)	599(2)	44(9)
H(4)	364(4)	723(4)	745(3)	82(13)
H(5)	478(4)	577(4)	819(3)	79(13)
H(6)	674(4)	474(4)	754(3)	94(16)
H(7)	748(5)	511(4)	620(3)	86(14)
H(8)	388(5)	712(5)	404(3)	109(16)
H(9)	356(5)	632(4)	322(3)	108(18)
H(10)	262(6)	616(5)	397(4)	137(23)
H(11)	416(4)	284(4)	311(2)	75(11)
H(12)	522(4)	397(3)	291(2)	63(11)
H(13)	367(4)	412(4)	283(3)	89(13)
H(14)	749(3)	264(3)	369(2)	43(9)
H(15)	825(4)	65(3)	338(2)	75(11)
H(16)	686(4)	-103(3)	398(2)	63(10)
H(17)	493(4)	-50(4)	491(3)	79(12)
H(18)	449(3)	151(3)	520(2)	55(10)

Atomic coordinates and (equivalent) isotropic temperature factors for (2*S*,4*S*,5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidin-2-oxide-(**50**) (x 10^4), except coordinates x 10^5 for P and all parameters x 10^3 for H atoms.

Atom	x	y	z	Ueq
O(1)	2409(2)	3996(2)	7006(1)	426(11)
P(2)	16155(8)	51695(7)	65462(4)	367(3)
N(3)	228(3)	4325(2)	6168(2)	422(13)
C(4)	459(4)	2924(3)	6226(2)	419(16)
C(5)	1569(4)	2801(3)	6968(2)	381(15)
O(6)	1246(3)	6277(2)	7075(1)	520(13)
C(7)	2905(3)	5645(3)	5744(2)	382(15)
C(8)	2599(4)	5470(3)	4903(2)	546(20)
C(9)	3584(5)	5858(4)	4300(2)	681(24)
C(10)	4902(5)	6435(3)	4519(2)	648(24)
C(11)	5256(5)	6610(4)	5354(3)	686(25)
C(12)	4242(4)	6222(4)	5959(2)	570(21)
C(13)	-1100(4)	4841(4)	5761(3)	596(22)
C(14)	997(5)	2341(4)	5411(2)	580(22)
C(15)	2650(4)	1691(3)	6924(2)	377(15)
C(16)	2136(4)	449(3)	7053(2)	506(20)
C(17)	3083(4)	-588(3)	7006(2)	566(21)
C(18)	4568(4)	-397(4)	6845(2)	569(21)
C(19)	5117(4)	830(4)	6730(2)	534(20)
C(20)	4155(4)	1872(3)	6763(2)	468(19)
H(1)	-59(4)	251(3)	642(2)	48(8)
H(2)	103(3)	276(2)	747(2)	24(6)
H(3)	182(4)	510(3)	477(2)	56(10)
H(4)	333(3)	578(3)	370(2)	80(12)
H(5)	573(5)	670(4)	415(3)	75(11)
H(6)	637(5)	694(3)	552(2)	76(12)
H(7)	451(5)	635(4)	662(3)	96(13)
H(8)	-122(5)	463(4)	520(3)	88(14)
H(9)	-131(5)	569(4)	584(3)	88(14)
H(10)	-212(4)	446(3)	605(2)	69(11)
H(11)	223(5)	260(4)	526(3)	86(13)
H(12)	121(4)	146(4)	545(2)	67(11)
H(13)	33(4)	257(4)	499(3)	66(11)
H(14)	128(4)	40(3)	718(2)	45(10)
H(15)	258(5)	-142(4)	700(2)	67(11)
H(16)	529(5)	-112(4)	681(2)	80(12)
H(17)	630(5)	98(3)	660(2)	80(11)
H(18)	448(4)	272(3)	666(2)	66(11)

Atomic coordinates and (equivalent) isotropic temperature factors for (2*R*,4*S*,5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidin-2-oxide-(**49**) (x 10^4), except coordinates x 10^5 for P and all parameters x 10^3 for H atoms.

Atom	x	y	z	Ueq
O(1)	10690(3)	7331(3)	1019(1)	472(10)
P(2)	90400(10)	88890(10)	9792(20)	4850(37)
N(3)	10175(4)	10515(4)	1261(1)	484(17)
C(4)	12281(5)	10146(4)	1257(1)	469(13)
C(5)	12400(5)	7972(4)	1261(1)	441(13)
O(6)	7085(4)	8389(5)	1132(9)	706(17)
C(7)	8979(5)	9481(5)	421(1)	523(17)
C(8)	7339(7)	10419(6)	258(1)	693(20)
C(9)	7270(9)	10965(7)	-168(1)	810(33)
C(10)	8789(8)	10544(5)	-436(1)	719(30)
C(11)	10411(9)	9617(6)	-282(1)	733(27)
C(12)	10512(6)	9099(5)	149(1)	617(20)
C(13)	9455(8)	12444(5)	1287(1)	698(27)
C(14)	13369(6)	11097(6)	1623(1)	656(20)
C(15)	12443(5)	7047(4)	1696(1)	478(13)
C(16)	14223(6)	6410(6)	1857(1)	600(20)
C(17)	14324(7)	5559(7)	2256(1)	723(27)
C(18)	12652(9)	5349(7)	2500(1)	749(30)
C(19)	10887(7)	5970(7)	2343(1)	755(27)
C(20)	10780(6)	6798(6)	1940(1)	630(20)
H(1)	1284	1068	102	42
H(2)	1353	759	114	47
H(3)	632	1068	43	70
H(4)	622	1160	-27	90
H(5)	872	1088	-71	90
H(6)	1141	934	-46	120
H(7)	1158	851	25	80
H(8)	901	1271	153	120
H(9)	1051	1328	122	150
H(10)	845	1261	108	150
H(11)	1274	1086	189	80
H(12)	1481	1062	163	60
H(13)	1320	1263	157	110
H(14)	1532	655	170	49
H(15)	1548	515	236	80
H(16)	1273	481	276	70
H(17)	980	582	250	80
H(18)	962	718	184	60

Atomic coordinates and (equivalent) isotropic temperature factors for (2*R*,4*S*,5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidin-2-thione-(**52**) (x 10^4), except all parameters x 10^3 for H atoms.

Atom	x	y	z	Ueq
O(1)	4241(4)	7475(2)	6696(2)	582(16)
P(2)	3294(1)	6947(1)	7466(1)	564(5)
N(3)	1276(4)	7505(3)	7365(2)	646(19)
C(4)	1109(6)	8051(3)	6605(2)	643(24)
C(5)	2802(6)	7709(3)	6092(2)	545(22)
S(6)	3296(2)	5561(1)	7456(1)	952(9)
C(7)	4515(6)	7424(3)	8345(3)	575(23)
C(8)	4533(8)	8408(4)	8491(3)	757(27)
C(9)	5430(9)	8775(5)	9174(4)	901(38)
C(10)	6289(8)	8152(6)	9721(3)	930(38)
C(11)	6283(7)	7203(5)	9585(3)	890(37)
C(12)	5393(7)	6835(5)	8900(3)	720(30)
C(13)	-365(9)	7277(7)	7850(4)	1043(47)
C(14)	1049(10)	9129(4)	6760(4)	883(36)
C(15)	3556(6)	8407(3)	5479(2)	563(21)
C(16)	5146(8)	8935(3)	5625(3)	678(29)
C(17)	5772(11)	9582(4)	5042(4)	956(41)
C(18)	4855(12)	9718(4)	4338(4)	1038(45)
C(19)	3240(13)	9187(5)	4175(3)	979(42)
C(20)	2607(9)	8523(4)	4742(3)	754(29)
H(1)	-4(6)	783(3)	634(2)	60(12)
H(2)	245(6)	713(3)	583(2)	52(10)
H(3)	386(9)	889(4)	802(3)	104(16)
H(4)	562(10)	935(5)	916(4)	106(22)
H(5)	677(9)	847(5)	1023(4)	115(20)
H(6)	663(10)	678(5)	995(4)	105(20)
H(7)	537(5)	633(3)	880(2)	29(10)
H(8)	-30(10)	684(5)	823(4)	109(11)
H(9)	-132(9)	712(4)	754(4)	109(11)
H(10)	-88(10)	775(4)	807(4)	109(11)
H(11)	236(10)	934(4)	694(4)	101(10)
H(12)	5(9)	925(4)	716(3)	101(10)
H(13)	84(4)	947(4)	629(4)	101(10)
H(14)	574(7)	892(3)	611(3)	66(13)
H(15)	687(8)	990(4)	513(3)	89(18)
H(16)	527(9)	1012(4)	389(3)	99(17)
H(17)	247(14)	935(6)	377(5)	170(35)
H(18)	137(8)	808(4)	468(3)	82(15)

Atomic coordinates and (equivalent) isotropic temperature factors for (2*S*,4*S*,5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidin-2-thione-(**51**) (x 10^4), except all parameters x 10^3 for H atoms.

Atom	x	y	z	Ueq
O(1)	3827(4)	5342(7)	4941(3)	550(22)
P(2)	3156(1)	5368(-)	6108(1)	459(8)
N(3)	2251(5)	3592(8)	5601(5)	483(28)
C(4)	2844(6)	2491(9)	4798(6)	505(33)
C(5)	3432(6)	3859(9)	4056(6)	526(35)
S(6)	2134(2)	7390(4)	6278(2)	806(13)
C(7)	4562(5)	4976(7)	7598(6)	443(33)
C(8)	4527(6)	5602(10)	8818(6)	548(36)
C(9)	5601(7)	5269(13)	9988(6)	694(43)
C(10)	6708(8)	4350(11)	9924(7)	666(46)
C(11)	6768(7)	3729(10)	8720(8)	655(45)
C(12)	5703(6)	4030(9)	7565(7)	582(40)
C(13)	1561(7)	2718(11)	6458(7)	696(47)
C(14)	1798(8)	1264(10)	3882(8)	729(45)
C(15)	2488(6)	4407(8)	2704(6)	489(34)
C(16)	1299(6)	5353(12)	2592(6)	610(36)
C(17)	400(7)	5760(11)	1330(7)	679(47)
C(18)	688(7)	5243(14)	200(7)	720(44)
C(19)	1871(9)	4335(11)	311(7)	743(50)
C(20)	2765(7)	3912(10)	1564(6)	620(44)
H(1)	364	165	541	40(14)
H(2)	427	331	378	70(19)
H(3)	360	625	882	74(19)
H(4)	550	580	1090	111(27)
H(5)	755	423	1085	122(29)
H(6)	765	296	875	110(29)
H(7)	575	353	662	91(23)
H(8)	124	370	703	81(12)
H(9)	229	185	713	81(12)
H(10)	69	198	587	81(12)
H(11)	228	71	320	112(15)
H(12)	89	197	332	112(15)
H(13)	153	23	444	112(15)
H(14)	107	587	345	66(18)
H(15)	-60	629	122	112(28)
H(16)	4	567	-77	110(26)
H(17)	213	391	-55	75(20)
H(18)	368	316	167	78(22)

Table 12. Atomic coordinates and isotropic temperature factors for (*R*p)-(-)-*N*-methyl-*N*-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1*S*, 2*S*)-*P*-(2-methoxyphenyl)-*P*-phenylphosphinamide-(71) (x10^4).

Atom	x	y	z	Uiso
P(1)	1973(2)	949(2)	3339(1)	371
O(1)	-1455(6)	2481(5)	2094(4)	527
O(2)	2238(6)	-93(4)	2965(3)	378
O(3)	1217(7)	2553(5)	4633(4)	572
N(1)	528(7)	1429(5)	3091(4)	420
C(1)	448(9)	3078(7)	1254(6)	470(2)
C(2)	1780(1)	3416(8)	1187(6)	610(3)
C(3)	2280(1)	3687(9)	466(8)	860(4)
C(4)	1480(1)	3610(1)	-176(9)	950(4)
C(5)	200(1)	3240(1)	-131(8)	910(4)
C(6)	-290(1)	3012(9)	604(6)	700(3)
C(7)	-74(8)	2766(7)	2050(5)	370(2)
C(8)	373(9)	1592(7)	2255(5)	380(2)
C(9)	-530(1)	752(7)	1856(6)	570(3)
C(10)	-690(1)	1292(9)	3569(6)	700(3)
C(11)	3166(8)	1941(6)	3027(5)	370(2)
C(12)	3020(1)	3044(7)	3222(5)	530(2)
C(13)	4000(1)	3772(8)	2964(6)	580(3)
C(14)	5050(1)	3450(1)	2545(6)	660(3)
C(15)	5180(1)	2366(9)	2366(6)	670(3)
C(16)	4230(1)	1611(8)	2587(6)	570(3)
C(17)	2085(9)	834(7)	4371(4)	410(2)
C(18)	2670(1)	-120(8)	4640(6)	560(3)
C(19)	2860(1)	-296(9)	5435(7)	670(3)
C(20)	2490(1)	457(9)	5945(8)	760(3)
C(21)	1920(1)	1432(8)	5710(6)	650(3)
C(22)	1740(1)	1623(7)	4920(5)	490(2)
C(23)	740(1)	3330(1)	5152(7)	890(4)
H(1)	2360(1)	3464(8)	1658(6)	610(3)
H(2)	3220(1)	3932(9)	413(8)	860(4)
H(3)	1850(1)	3840(1)	-687(9)	950(4)
H(4)	-360(1)	3130(1)	-606(8)	910(4)
H(5)	-1240(1)	2790(9)	655(6)	700(3)
H(6)	198(8)	3325(7)	2437(5)	370(2)
H(7)	1295(9)	1469(7)	2063(5)	380(2)
H(8)	-590(1)	906(7)	1288(6)	570(3)
H(9)	-1430(1)	788(7)	2092(6)	570(3)
H(10)	-150(1)	15(7)	1937(6)	570(3)
H(11)	-1450(1)	1654(9)	3307(6)	700(3)
H(12)	-550(1)	1621(9)	4092(6)	700(3)
H(13)	-880(1)	504(9)	3628(6)	700(3)
H(14)	2250(1)	3301(7)	3534(5)	530(2)
H(15)	3910(1)	4553(8)	3099(6)	580(3)
H(16)	5720(1)	3990(1)	2365(6)	660(3)
H(17)	5980(1)	2118(9)	2076(6)	670(3)
H(18)	4320(1)	839(8)	2426(6)	570(3)
H(19)	2960(1)	-685(8)	4262(6)	560(3)
H(20)	3260(1)	-987(9)	5618(7)	670(3)
H(21)	2640(1)	320(9)	6509(8)	760(3)
H(22)	1660(1)	1984(8)	6104(6)	650(3)
H(23)	400(1)	3960(1)	4854(7)	890(4)
H(24)	1480(1)	3570(1)	5497(7)	890(4)
H(25)	10(1)	3020(1)	5473(7)	890(4)
H(26)	-1550(6)	2692(5)	2664(4)	516

Data deposited at the Cambridge crystallographic data base

Bond lengths (Å) with e.s.d.'s in parentheses for (2*R*,4*S*,5*R*)-2-phenoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-oxide-(**42**), (2*S*,4*S*,5*R*)-2-phenoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-oxide-(**56**), (2*S*,4*S*,5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidin-2-oxide-(**50**) and (2*R*,4*S*,5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidin-2-oxide-(**49**).

	(2*R*)-(**42**)	(2*S*)-(**56**)	(2*S*)-(**50**)	(2*R*)-(**49**)
O(1)-P(2)	1.581(2)	1.588(2)	1.591(2)	1.581(2)
O(1)-C(5)	1.465(3)	1.458(4)	1.452(3)	1.463(4)
P(2)-N(3)	1.613(2)	1.623(3)	1.635(2)	1.641(3)
P(2)-O(6)	1.457(2)	1.453(3)	1.466(2)	1.463(3)
N(3)-C(4)	1.473(3)	1.468(4)	1.474(4)	1.465(5)
N(3)-C(13)	1.455(4)	1.463(5)	1.455(4)	1.450(4)
C(4)-C(5)	1.539(3)	1.524(4)	1.552(4)	1.536(4)
C(4)-C(14)	1.516(4)	1.512(5)	1.516(4)	1.519(4)
C(5)-C(15)	1.500(3)	1.505(4)	1.505(4)	1.505(4)
C(7)-C(8)	1.381(4)	1.369(4)	1.384(4)	1.398(5)
C(7)-C(12)	1.377(4)	1.372(5)	1.380(4)	1.375(5)
C(8)-C(9)	1.377(4)	1.362(5)	1.367(5)	1.382(6)
C(9)-C(10)	1.360(5)	1.362(7)	1.367(6)	1.366(7)
C(10)-C(11)	1.377(5)	1.369(8)	1.384(6)	1.375(6)
C(11)-C(12)	1.379(5)	1.378(8)	1.385(5)	1.395(5)
C(15)-C(16)	1.372(4)	1.373(4)	1.386(4)	1.393(5)
C(15)-C(20)	1.381(4)	1.370(4)	1.382(5)	1.380(5)
C(16)-C(17)	1.381(5)	1.381(5)	1.372(4)	1.381(5)
C(17)-C(18)	1.346(6)	1.373(5)	1.366(5)	1.382(7)
C(18)-C(19)	1.374(6)	1.373(6)	1.378(5)	1.375(7)
C(19)-C(20)	1.382(4)	1.387(5)	1.384(5)	1.387(5)
P(2)-O(21)	1.593(2)	1.583(2)		
O(21)-C(7)	1.399(3)	1.398(4)		
P(2)-C(7)			1.794(3)	1.790(3)
C(4)-H(1)	0.90(3)	1.00(3)	1.07(3)	0.90
C(5)-H(2)	1.03(3)	0.91(3)	0.94(3)	0.90
C(8)-H(3)	0.90(4)	0.91(3)	0.82(3)	0.90
C(9)-H(4)	0.98(4)	1.01(4)	0.99(4)	0.90
C(10)-H(5)	1.09(5)	0.91(4)	0.99(4)	0.90
C(11)-H(6)	1.03(4)	0.83(5)	1.08(4)	0.90
C(12)-H(7)	0.88(3)	0.97(5)	1.09(4)	0.90
C(13)-H(8)	1.09(6)	0.95(5)	0.93(4)	0.83
C(13)-H(9)	1.17(5)	0.90(5)	0.91(4)	0.95
C(13)-H(10)	0.98(4)	0.92(6)	1.10(4)	0.95
C(14)-H(11)	0.97(4)	0.96(4)	1.16(4)	0.95
C(14)-H(12)	0.91(4)	0.96(4)	0.94(4)	1.04
C(14)-H(13)	0.98(4)	0.92(5)	0.93(4)	1.10
C(16)-H(14)	0.91(4)	0.88(3)	0.79(3)	0.90
C(17)-H(15)	0.79(5)	1.04(4)	0.98(4)	0.90
C(18)-H(16)	1.11(4)	0.98(4)	1.00(4)	0.90
C(19)-H(17)	0.91(6)	0.94(4)	1.09(4)	0.90
C(20)-H(18)	1.03(4)	0.89(3)	0.95(4)	0.90

Bond Angles (°) with e.s.d.'s in parentheses for (2*R*,4*S*,5*R*)-2-phenoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-oxide-(**42**), (2*S*,4*S*,5*R*)-2-phenoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-oxide-(**56**), (2*S*,4*S*,5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidin-2-oxide-(**50**) and (2*R*,4*S*,5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidin-2-oxide-(**49**).

	(2*R*)-(**42**)	(2*S*)-(**56**)	(2*S*)-(**50**)	(2*R*)-(**49**)
P(2)-O(1)-C(5)	111.7(1)	111.4(2)	114.0(2)	113.4(2)
O(1)-P(2)-N(3)	96.7(1)	96.4(1)	95.6(1)	96.1(1)
O(1)-P(2)-O(6)	119.4(1)	116.2(1)	115.9(1)	117.4(2)
N(3)-P(2)-O(6)	117.4(1)	120.7(2)	117.6(1)	115.3(2)
P(2)-N(3)-C(4)	113.6(2)	110.9(2)	113.6(2)	109.7(2)
P(2)-N(3)-C(13)	125.3(2)	122.1(3)	125.9(2)	121.7(3)
C(4)-N(3)-C(13)	119.9(2)	120.4(3)	120.4(3)	120.2(3)
N(3)-C(4)-C(5)	103.4(2)	102.0(2)	102.6(2)	103.3(3)
N(3)-C(4)-C(14)	111.7(2)	113.3(3)	112.7(3)	113.4(3)
C(5)-C(4)-C(14)	115.9(2)	114.2(3)	114.9(3)	114.2(3)
O(1)-C(5)-C(4)	105.9(2)	105.2(2)	107.0(2)	105.2(3)
O(1)-C(5)-C(15)	109.5(2)	110.1(2)	109.0(2)	110.2(3)
C(4)-C(5)-C(15)	115.4(2)	116.3(3)	115.9(2)	116.1(2)
C(8)-C(7)-C(12)	120.4(3)	120.9(4)	118.1(3)	118.7(3)
C(7)-C(8)-C(9)	119.3(3)	120.9(4)	121.3(4)	120.6(4)
C(8)-C(9)-C(10)	121.4(3)	118.6(5)	120.2(4)	120.0(5)
C(9)-C(10)-C(11)	118.6(3)	121.1(5)	120.1(4)	120.3(4)
C(10)-C(11)-C(12)	121.6(3)	120.5(5)	119.1(4)	120.0(4)
C(7)-C(12)-C(11)	118.6(3)	118.0(5)	121.2(3)	120.3(4)
C(5)-C(15)-C(16)	122.8(2)	122.6(3)	119.6(3)	118.9(3)
C(5)-C(15)-C(20)	118.4(2)	118.8(3)	121.9(3)	122.4(3)
C(16)-C(15)-C(20)	118.8(3)	118.6(3)	118.5(3)	118.7(3)
C(15)-C(16)-C(17)	120.3(4)	121.3(3)	121.3(3)	120.6(4)
C(16)-C(17)-C(18)	121.3(4)	120.1(3)	119.7(3)	120.1(4)
C(17)-C(18)-C(19)	119.1(3)	119.6(3)	120.4(3)	119.8(3)
C(18)-C(19)-C(20)	120.7(3)	119.7(4)	119.9(3)	120.2(4)
C(15)-C(20)-C(19)	119.9(3)	121.0(4)	120.3(3)	120.6(4)
O(1)-P(2)-O(21)	103.9(1)	107.6(1)		
N(3)-P(2)-O(21)	113.2(1)	109.3(1)		
O(6)-P(2)-O(21)	105.7(1)	106.0(1)		
P(2)-O(21)-C(7)	124.7(2)	124.9(2)		
O(21)-C(7)-C(8)	120.2(2)	118.8(3)		
O(21)-C(7)-C(12)	119.3(3)	120.1(3)		
C(7)-P(2)-O(1)			104.8(1)	104.8(1)
C(7)-P(2)-O(6)			109.9(1)	110.5(2)
C(7)-P(2)-N(3)			111.7(1)	111.6(1)
C(8)-C(7)-P(2)			122.1(2)	118.9(3)
C(12)-C(7)-P(2)			119.8(2)	122.4(3)
H(1)-C(4)-N(3)	110.9(19)	107.4(16)	106.9(15)	110.5
H(1)-C(4)-C(5)	105.3(19)	107.4(15)	107.8(16)	113.5
H(1)-C(4)-C(14)	109.3(19)	111.8(15)	111.2(16)	102.4
H(2)-C(5)-O(1)	104.8(14)	106.6(19)	105.5(15)	112.3
H(2)-C(5)-C(4)	110.7(15)	111.1(20)	109.6(15)	109.8
H(2)-C(5)-C(15)	109.9(14)	107.2(19)	109.4(15)	103.4
H(3)-C(8)-C(7)	115.0(22)	120.1(19)	118.2(24)	119.7
H(3)-C(8)-C(9)	125.7(22)	118.8(19)	120.4(24)	119.8
H(4)-C(9)-C(8)	114.7(23)	122.5(22)	119.9(23)	119.8
H(4)-C(9)-C(10)	123.9(23)	118.9(22)	119.8(23)	120.3
H(5)-C(10)-C(9)	126.4(24)	113.2(27)	127.5(23)	119.7
H(5)-C(10)-C(11)	113.5(24)	125.7(27)	112.1(23)	120.0
H(6)-C(11)-C(10)	122.6(21)	127.5(33)	118.8(20)	120.0
H(6)-C(11)-C(12)	115.5(21)	112.0(34)	121.7(20)	120.0

H(7)-C(12)-C(7)	116.8(20)	120.1(26)	118.8(25)	119.9
H(7)-C(12)-C(11)	124.5(20)	121.8(26)	120.0(25)	119.9
H(8)-C(13)-N(3)	101.7(31)	97.9(28)	116.1(26)	113.0
H(9)-C(13)-N(3)	105.5(20)	107.8(32)	117.8(28)	108.2
H(9)-C(13)-H(8)	121.6(35)	114.5(43)	109.4(35)	108.6
H(10)-C(13)-N(3)	112.0(22)	110.5(35)	110.8(18)	109.0
H(10)-C(13)-H(8)	100.0(39)	116.9(45)	103.5(34)	108.6
H(10)-C(13)-H(9)	115.3(30)	108.5(48)	96.5(34)	109.5
H(11)-C(14)-C(4)	117.3(20)	110.4(22)	113.0(20)	110.7
H(12)-C(14)-C(4)	114.7(21)	106.5(21)	113.5(21)	109.3
H(12)-C(14)-H(11)	105.6(30)	115.0(33)	92.7(31)	111.0
H(13)-C(14)-C(4)	112.6(22)	109.8(26)	108.4(24)	106.2
H(13)-C(14)-H(11)	103.3(27)	107.1(35)	113.3(32)	104.7
H(13)-C(14)-H(12)	101.6(29)	107.9(33)	115.4(32)	114.7
H(14)-C(16)-C(15)	125.5(23)	117.6(19)	114.4(25)	119.6
H(14)-C(16)-C(17)	114.1(23)	121.5(19)	124.2(25)	119.8
H(15)-C(17)-C(16)	123.0(34)	115.7(21)	114.4(24)	119.8
H(15)-C(17)-C(18)	115.2(33)	124.2(21)	125.1(23)	120.2
H(16)-C(18)-C(17)	112.7(25)	118.2(20)	122.2(23)	119.8
H(16)-C(18)-C(19)	128.1(25)	122.1(20)	117.4(24)	120.4
H(17)-C(19)-C(18)	118.4(39)	123.7(23)	120.0(20)	119.6
H(17)-C(19)-C(20)	116.6(40)	116.6(23)	120.1(20)	120.1
H(18)-C(20)-C(15)	120.7(22)	120.8(22)	117.1(23)	119.6
H(18)-C(20)-C(19)	118.2(22)	118.1(22)	122.5(23)	119.8

Bond lengths (Å) with e.s.d.'s in parentheses for (2*R*,4*S*,5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidin-2-thione-(**52**) and (2*S*,4*S*,5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidin-2-thione-(**51**).

	(2*R*)-(**52**)	(2*S*)-(**51**)
O(1)-P(2)	1.602(3)	1.594(4)
O(1)-C(5)	1.457(5)	1.444(8)
P(2)-N(3)	1.643(3)	1.640(6)
P(2)-S(6)	1.931(1)	1.915(3)
P(2)-C(7)	1.800(5)	1.793(6)
N(3)-C(4)	1.456(5)	1.462(8)
N(3)-C(13)	1.447(6)	1.479(8)
C(4)-C(5)	1.542(6)	1.545(8)
C(4)-C(14)	1.524(8)	1.522(9)
C(5)-C(15)	1.493(5)	1.508(8)
C(7)-C(8)	1.392(7)	1.385(8)
C(7)-C(12)	1.371(7)	1.393(8)
C(8)-C(9)	1.381(7)	1.394(8)
C(9)-C(10)	1.386(9)	1.363(10)
C(10)-C(11)	1.342(9)	1.376(10)
C(11)-C(12)	1.381(8)	1.375(9)
C(15)-C(16)	1.372(6)	1.398(9)
C(15)-C(20)	1.386(6)	1.375(8)
C(16)-C(17)	1.382(7)	1.393(9)
C(17)-C(18)	1.331(10)	1.377(10)
C(18)-C(19)	1.393(10)	1.378(11)
C(19)-C(20)	1.382(8)	1.388(10)
C(4)-H(1)	0.98(5)	1.08
C(5)-H(2)	0.95(4)	1.08
C(8)-H(3)	1.12(6)	1.08
C(9)-H(4)	0.81(6)	1.08
C(10)-H(5)	0.99(6)	1.08
C(11)-H(6)	0.87(7)	1.08

C(12)-H(7)	0.72(3)	1.08
C(13)-H(8)	0.87(6)	1.08
C(13)-H(9)	0.88(6)	1.08
C(13)-H(10)	0.83(6)	1.08
C(14)-H(11)	1.02(7)	1.08
C(14)-H(12)	0.98(6)	1.08
C(14)-H(13)	0.92(6)	1.08
C(16)-H(14)	0.90(5)	1.08
C(17)-H(15)	0.90(5)	1.08
C(18)-H(16)	0.97(6)	1.08
C(19)-H(17)	0.89(9)	1.08
C(20)-H(18)	1.08(6)	1.08

Bond Angles (°) with e.s.d.'s in parentheses for (2*R*,4*S*,5*R*)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidin-2-thione-(**52**) and (2*S*,4*S*,5*R*)-2,5-3,4-dimethyl-diphenyl-1,3,2-oxazaphospholidin-2-thione-(**51**).

	(2*R*)-(**52**)	(2*S*)-(**51**)
P(2)-O(1)-C(5)	109.5(2)	114.0(4)
O(1)-P(2)-N(3)	94.2(2)	94.6(2)
O(1)-P(2)-S(6)	116.9(1)	118.1(2)
N(3)-P(2)-S(6)	118.3(1)	115.3(2)
C(7)-P(2)-O(1)	104.3(1)	104.2(1)
C(7)-P(2)-S(6)	112.1(2)	111.7(2)
C(7)-P(2)-N(3)	109.1(2)	111.4(3)
P(2)-N(3)-C(4)	113.9(3)	111.6(4)
P(2)-N(3)-C(13)	123.3(4)	120.8(4)
C(4)-N(3)-C(13)	120.8(4)	117.8(6)
N(3)-C(4)-C(5)	103.5(3)	101.9(5)
N(3)-C(4)-C(14)	112.2(4)	112.4(5)
C(5)-C(4)-C(14)	114.6(4)	114.3(5)
O(1)-C(5)-C(4)	104.8(3)	106.4(4)
O(1)-C(5)-C(15)	110.1(3)	110.9(5)
C(4)-C(5)-C(15)	116.2(3)	115.4(5)
C(8)-C(7)-P(2)	120.2(3)	120.2(4)
C(12)-C(7)-P(2)	121.5(4)	121.3(4)
C(8)-C(7)-C(12)	118.3(5)	118.5(5)
C(7)-C(8)-C(9)	120.4(5)	120.6(6)
C(8)-C(9)-C(10)	119.3(6)	119.6(6)
C(9)-C(10)-C(11)	120.7(5)	120.6(6)
C(10)-C(11)-C(12)	120.1(5)	120.1(7)
C(7)-C(12)-C(11)	121.2(6)	120.5(6)
C(5)-C(15)-C(16)	122.1(4)	120.6(5)
C(5)-C(15)-C(20)	118.6(4)	119.9(6)
C(16)-C(15)-C(20)	119.3(4)	119.4(6)
C(15)-C(16)-C(17)	119.9(6)	119.7(6)
C(16)-C(17)-C(18)	121.6(7)	120.1(7)
C(17)-C(18)-C(19)	119.6(5)	120.2(6)
C(18)-C(19)-C(20)	119.8(6)	120.0(6)
C(15)-C(20)-C(19)	119.8(6)	120.5(7)
H(1)-C(4)-N(3)	106.2(24)	112.1
H(1)-C(4)-C(5)	108.1(24)	111.3
H(1)-C(4)-C(14)	111.7(25)	105.0
H(2)-C(5)-O(1)	107.2(23)	113.5
H(2)-C(5)-C(4)	107.2(24)	110.2
H(2)-C(5)-C(15)	110.9(21)	100.7
H(3)-C(8)-C(7)	117.9(27)	116.4

H(3)-C(8)-C(9)	121.6(28)	122.8
H(4)-C(9)-C(8)	114.9(45)	116.3
H(4)-C(9)-C(10)	124.1(47)	124.1
H(5)-C(10)-C(9)	114.1(38)	116.2
H(5)-C(10)-C(11)	125.0(37)	123.0
H(6)-C(11)-C(10)	123.9(41)	116.6
H(6)-C(11)-C(12)	115.0(42)	123.2
H(7)-C(12)-C(7)	115.5(31)	119.8
H(7)-C(12)-C(11)	123.3(31)	119.7
H(8)-C(13)-N(3)	119.8(46)	108.7
H(9)-C(13)-N(3)	111.7(39)	108.3
H(9)-C(13)-H(8)	105.8(58)	109.5
H(10)-C(13)-N(3)	114.4(52)	111.3
H(10)-C(13)-H(8)	106.4(62)	109.5
H(10)-C(13)-H(9)	95.8(57)	109.5
H(11)-C(14)-C(4)	107.9(33)	106.1
H(12)-C(14)-C(4)	107.6(34)	111.0
H(12)-C(14)-H(11)	115.4(46)	109.5
H(13)-C(14)-C(4)	112.4(36)	111.3
H(13)-C(14)-H(11)	103.5(54)	109.5
H(13)-C(14)-H(12)	110.2(49)	109.5
H(14)-C(16)-C(15)	121.5(30)	123.0
H(14)-C(16)-C(17)	118.4(30)	117.1
H(15)-C(17)-C(16)	119.3(36)	120.8
H(15)-C(17)-C(18)	118.9(34)	118.4
H(16)-C(18)-C(17)	125.7(35)	119.7
H(16)-C(18)-C(19)	114.4(35)	119.8
H(17)-C(19)-C(18)	121.1(59)	122.2
H(17)-C(19)-C(20)	117.7(61)	117.8
H(18)-C(20)-C(15)	114.6(24)	118.2
H(18)-C(20)-C(19)	125.6(24)	121.3

Bond Angles (°) with e.s.d.'s in parentheses for (R_{P})-(-)-*N*-methyl-*N*-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1*S*, 2*S*)-*P*-(2-methoxyphenyl)-*P*-phenylphosphinamide-(**71**).

N(1)-P(1)-O(2)	115.0(4)
C(11)-P(1)-O(2)	107.2(4)
C(11)-P(1)-N(1)	105.7(4)
C(17)-P(1)-O(2)	110.3(4)
C(17)-P(1)-N(1)	110.3(4)
C(17)-P(1)-C(11)	108.0(4)
H(1)-O(1)-C(7)	97.8(5)
C(23)-O(3)-C(22)	118.8(8)
C(8)-N(1)-P(1)	113.8(6)
C(10)-N(1)-P(1)	123.4(6)
C(10)-N(1)-C(8)	118.2(7)
C(6)-C(1)-C(2)	118(1)
C(7)-C(1)-C(2)	118.6(9)
C(7)-C(1)-C(6)	123.0(9)
C(3)-C(2)-C(1)	120(1)
C(4)-C(3)-C(2)	120(1)
C(5)-C(4)-C(3)	123(1)
C(6)-C(5)-C(4)	117(1)
C(5)-C(6)-C(1)	124(1)
C(1)-C(7)-O(1)	112.2(8)
C(8)-C(7)-O(1)	109.7(7)
C(8)-C(7)-C(1)	109.9(7)

C(7)-C(8)-N(1)	112.5(7)
C(9)-C(8)-N(1)	114.1(7)
C(9)-C(8)-C(7)	110.9(7)
C(12)-C(11)-P(1)	121.2(7)
C(16)-C(11)-P(1)	118.9(6)
C(16)-C(11)-C(12)	119.9(8)
C(13)-C(12)-C(11)	118.0(9)
C(14)-C(13)-C(12)	123(1)
C(15)-C(14)-C(13)	119(1)
C(16)-C(15)-C(14)	122(1)
C(15)-C(16)-C(11)	120.0(1)
C(18)-C(17)-P(1)	115.0(7)
C(22)-C(17)-P(1)	126.8(7)
C(22)-C(17)-C(18)	118.0(8)
C(19)-C(18)-C(17)	121(1)
C(20)-C(19)-C(18)	120(1)
C(21)-C(20)-C(19)	122(1)
C(22)-C(21)-C(20)	120(1)
C(17)-C(22)-O(3)	116.1(8)
C(21)-C(22)-O(3)	123.5(9)
C(21)-C(22)-C(17)	120.4(9)

Bond lengths (Å) with e.s.d.'s in parentheses for (RP)-(-)-*N*-methyl-*N*-(1-methyl-2-hydroxy-2-phenyl)-ethyl-(1*S*, 2*S*)-*P*-(2-methoxyphenyl)-*P*-phenylphosphinamide-(**71**).

P(1)-O(1)	1.490(5)
P(1)-N(1)	1.632(7)
P(1)-C(11)	1.803(8)
P(1)-C(17)	1.719(8)
O(1)-C(7)	1.40(1)
O(1)-H(1)	1.01
O(3)-C(22)	1.36(1)
O(3)-C(23)	1.40(1)
N(1)-C(8)	1.47(1)
N(1)-C(10)	1.49(1)
C(1)-C(2)	1.41(1)
C(1)-C(6)	1.35(1)
C(1)-C(7)	1.52(1)
C(2)-C(3)	1.38(1)
C(3)-C(4)	1.38(1)
C(4)-C(5)	1.38(2)
C(5)-C(6)	1.39(2)
C(7)-C(8)	1.56(1)
C(8)-C(9)	1.54(1)
C(11)-C(12)	1.41(1)
C(11)-C(16)	1.38(1)
C(12)-C(13)	1.41(1)
C(13)-C(14)	1.35(1)
C(14)-C(15)	1.38(2)
C(15)-C(16)	1.39(1)
C(17)-C(18)	1.40(1)
C(17)-C(22)	1.41(1)
C(18)-C(19)	1.40(1)
C(19)-C(20)	1.33(1)
C(20)-C(21)	1.40(1)
C(21)-C(22)	1.40(1)

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