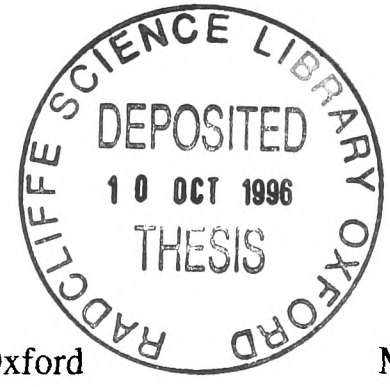
# Monophosphines in Asymmetric Catalysis

Thesis submitted in partial
fulfilment of the reqirements for
the degree of Doctor of Philosophy

by

John Christopher Pettigrew Laing




Linacre College, Oxford Michaelmas 1995

# Abstract

## Monophosphines in Asymmetric Catalysis

John Christopher Pettigrew Laing, Linacre College, DPhil, Michaelmas 1995

This thesis described investigations into the synthesis and reactions of chiral monophosphines, in five chapters. Chapter 1 introduces asymmetric catalysis, Chapter 2 and 3 describe the synthesis of enantiomerically pure monophosphine *via* an oxide and borane route respectively. Chapter 4 describes the organometallic reactions of these monophosphines and Chapter 5 contains experimental details of the reactions.

**Chapter 1** describes the importance of chirality and significant asymmetric processes. The literature methods of producing homochiral monophosphines are detailed.

**Chapter 2** describes the synthesis of enantiomerically enriched monophosphine oxides. Diastereomerically pure (2R, 4S, 5R)-2-chloro-5-phenyl-3,4-dimethyl-1,3,2-oxazaphospholidine was prepared from $PCl_3$ and (-)-ephedrine. This compound was reacted with 2-adamantyl magnesium bromide to afford (2R, 4S, 5R) and (2S, 4S, 5R)-3,4-dimethyl-2-2-adamantyl-5-phenyl-1,3,2-oxazaphospholidin-2-oxide after oxidation with $^tBuOOH$. An X-ray crystal structure was obtained of the $R_P$ diastereoisomer and a detailed NMR study carried out on the $S_P$ diastereoisomer. The $R_P$ diastereoisomer was reacted with 2-methoxyphenylmagnesium bromide to give $R_P$-N-methyl-N-(1S,2S)-(1-methyl-2-hydroxy-2-phenyl)-ethyl-P-(2-methoxyphenyl)-P-(2-adamantyl)phosphinamide in 68% yield and 95% d.e.. The ephedrinyl residue was replaced by O-methyl under acid catalysis with inversion of configuration and with >85% e.e.. Displacement of the methoxy group using phenyl lithium occurred with inversion of configuration to give the corresponding phosphine oxide in 65% e.e., which could be reduced under forcing conditions using polymethylhydrosiloxane in the presence of $Ti(O^iPr)_4$.

**Chapter 3** describes the synthesis of enantiomerically enriched monophosphines via phosphine borane complexes. Diastereomerically pure (2R, 4S, 5R)-2,5-diphenyl-3,4-dimethyl-1,3,2-oxazaphospholidine borane was prepared directly from $PhPCl_2$ and (-)-ephedrine, followed by oxidation with $BH_3.Me_2S$. This compound reacted regiospecifically with *ortho*-anisyl lithium to afford the product formed by P-O cleavage with >96% d.e. and with retention of configuration at phosphorus. The ephedrinyl residue was replaced by O-methyl under acid conditions with inversion of configuration and with >98% e.e.. Ferrocenyl, 1-adamantyl and *tert*-butyl lithium reagents displaced the methoxy group with inversion of configuration and with >92% e.e., as determined by $^1H$ NMR methods. The phosphine borane complexes were then reduced quantitatively with $Et_2NH$ with retention of configuration and with >98% e.e..

**Chapter 4** describes the synthesis of iridium and rhodium complexes of (S)-*t*-butyl-(2-methoxyphenyl)-phenyl phosphine and (S)-ferrocenyl-(2-methoxyphenyl)-phenyl phosphine. The iridium complexes are shown to reduce a range of prochiral olefins, including Z-methyl-2-acetylamino-3-phenylpropenoate (MAC) in up to 19% e.e.. The di-(R,R)-(ferrocenyl-(2-methoxyphenyl)-phenyl phosphine) rhodium complex is more selective, reducing MAC in 54% e.e., while the rhodium complex of (S)-*t*-butyl-(2-methoxyphenyl)-phenyl phosphine reduces MAC in 24% e.e..

For Mother, Father and the
Goose, B.A.

## Acknowledgements

I would like to thank my supervisior, Dr. John M. Brown, for his enthusiam, dedication and considerable patience over the past years. This work would not have been possible without his considerable input.

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John Christopher Pettigrew Laing, Oxford, 1995

Opus ante hos octo annus coeptum coronat finis

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# Abbreviations

| | |
|---|---|
| Me | Methyl |
| Et | Ethyl |
| Pr | Propyl |
| Bu | Butyl |
| Ph | Phenyl |
| Ar | Aryl |
| Fc | Ferrocenyl |
| COD | Cyclooctadiene |
| cat | Catalyst |
| acac | Acetylacetone |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| thf | Tetrahydrofuran |
| RT | Room Temperature |
| e.e. | Enantiomeric excess |
| d.e. | Diastereotopic excess |
| i | iso |
| t | tertiary |
| min | Minutes |
| h | Hour(s) |
| d | Days(s) |
| NMR | Nuclear Magnetic Reasonance |
| ppm | parts per million |
| J | Coupling Constant |
| tlc | Thin Layer Chromatography |
| Temp. | Temperature |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| CHIRAPHOS | 2,3-bis(diphenylphosphino)butane |
| Fc | Ferrocenyl |
| FAB | Fast atom bombardment |

# Chapter 1

Introduction

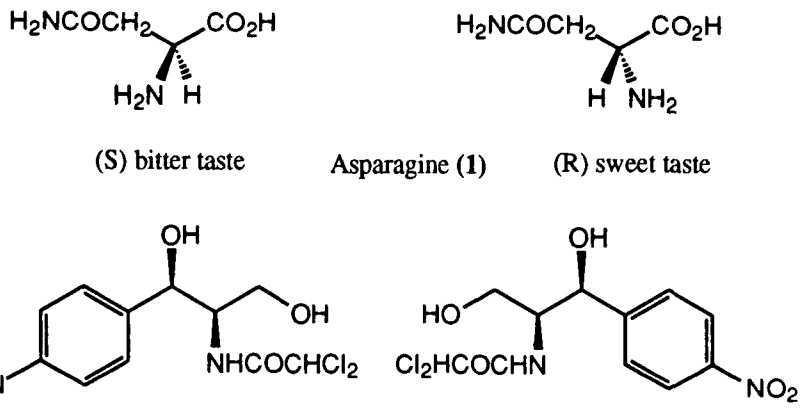
# Chapter 1. Introduction

## 1.1. Chirality

Biological systems, in most cases, recognise a pair of enantiomers as different substances, and the two enantiomers will elicit different responses. The manufacture of chemical products applied either for medicinal or agrochemical purposes is now increasingly concerned with enantiomeric purity, that is, the ability to produce molecules as single enantiomers. In addition to biological activity being normally associated only with a single enantiomer, the reasons for producing enantiomerically pure materials include;

- opposite enantiomers may exhibit harmful properties reducing or eliminating the benefit of the desired enantiomer;
- the unwanted isomer is at best 'isomeric ballast' needlessly applied to the environment;
- the required enantiomer may be more than twice as active as the racemate[1] due to antagonism;
- the physical characteristics of enantiomers compared to racemates may confer processing or formulation advantages.

Examples of enantiomeric pairs, **1** and **2**, exhibiting different properties are given in Scheme 1.




Scheme 1

Although the existence of optical activity has been known since the early 19th century[2], and resolution of enantiomers had been achieved by the middle of the 19th century[3], it is only since the 1960's that enantiomerically pure molecules have been produced selectively in any significant amount.

Modern techniques for the synthesis of enantiomerically pure molecules include;

- synthesis *via* a readily available enantiopure[4] compound, often from a natural source, that may be incorporated as a building block; the so called 'chiral pool' approach[5];
- synthesis using reagents or reactants that contain a stereogenic auxiliary, a group in the vicinity of the reaction site that controls the stereochemistry of the synthetic transformation, and may be easily removed afterwards[6,7];
- use of an enantiomerically pure catalyst, which may be an enzyme or a synthetic product[8].

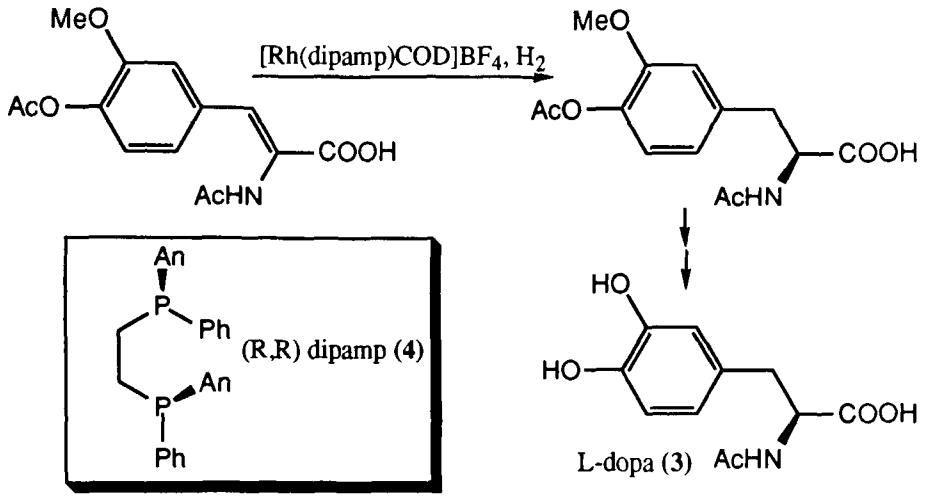
The principle advantage of the enantiomerically pure catalytic method over the 'chiral pool' and stereogenic auxiliary methods is that a relatively large amount of enantiomerically enriched product may be produced from a relatively small amount of enantiopure catalyst, while the other methods are, in principle, stoichiometric (although stereogenic auxiliaries may be recovered and recycled).

Examples of successful catalytic stereogenic synthetic reactions include hydrogenation[9,10], hydrosilylation[11,12], cyclopropanation[13,14], oxidation[15,16,17], carbonylation[18] and hydroboration[19].

In designing successful catalytic stereogenic synthesis, catalyst structure is of crucial importance. Synthetic catalysts are often based on a central metal atom with stereogenic ligands attached. Therefore, the structure of the ligand is of crucial importance since it controls the path of the reactants, *via* steric and electronic effects, through the metal, and thus the enantioselectivity of the reaction.

## 1.2. Asymmetric catalysis

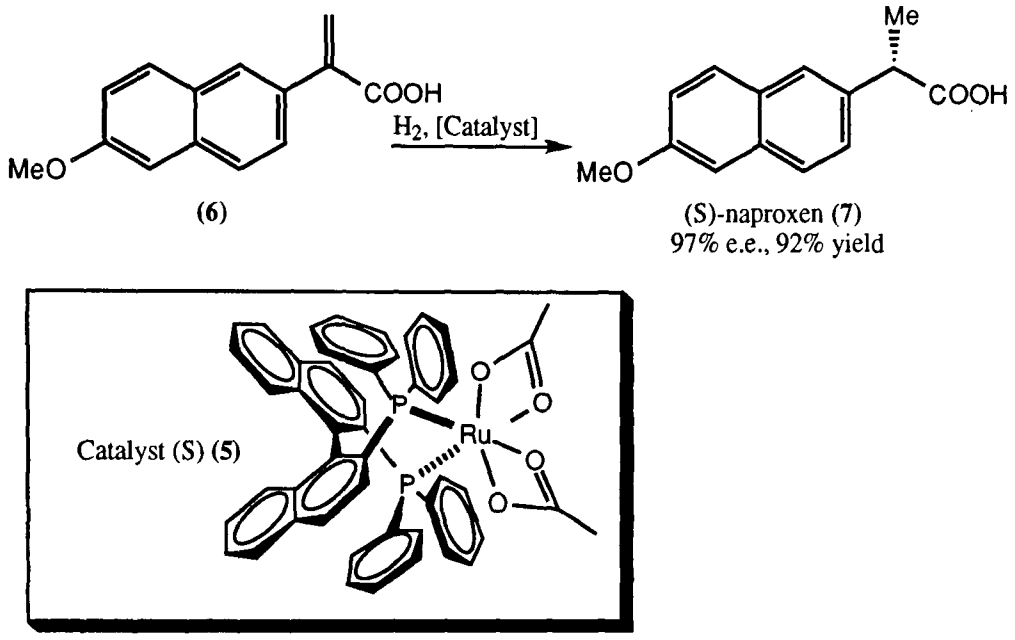
The first commercial application of synthetic catalysts was in the early 1970's, and involved a stereogenic hydrogenation reaction using a soluble Wilkinson[20] type catalyst modified with stereogenic ligands. The process, developed by Monsanto, for the production of L-dopa **3**, Scheme 2, was a landmark in stereogenic synthesis[21], as it showed that synthetic catalysts could successfully be used in the synthesis of enantiomerically enriched compounds, and was thus a spur for a huge amount of additional research.




Scheme 2

The ligand **4** used in the Monsanto process is unusual as it contains the stereogenicity at phosphorus, whereas most phosphine ligands used in catalysis contain the stereogenicity in the backbone.

Various ligands possessing heteroatoms other than phosphorus have been successfully used in stereogenic synthesis,[22,23,24] but those with chelating phosphorus atoms are by far the most common and successful. Most of these chelating phosphines possess chirality in the backbone, and this is in part due to the difficulties of creating chirality at phosphorus. An important diphosphine that has found substantial uses in asymmetric catalysis is BINAP[21], which possesses an axis of axial chirality. For example, a ruthenium complex of BINAP **5** reduces the itaconic acid derivative[25] **6** to produce (S)-naproxen **7**, a useful anti-inflammatory agent[26], Scheme 3.

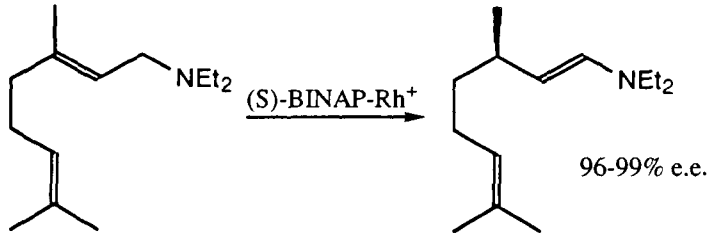



(6)

(S)-naproxen (7)
97% e.e., 92% yield

Scheme 3

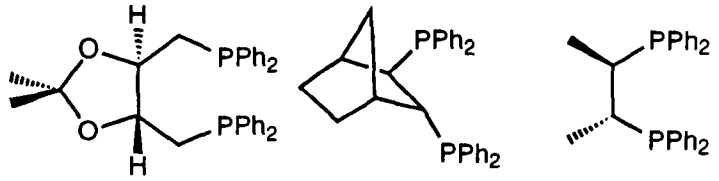
BINAP has also successfully been used in rhodium catalysed reactions, such as the isomerisation of the allyl amine, diethylgeranyenamine **8**, to give the chiral enamine, citronellal diethylenamine **9**, Scheme 4. This is an important step of the Takasago process for the synthesis of (-)-menthol[27].




(8) (9)

Scheme 4

Examples of other successful diphosphines include DIOP[28] **10**, NORPHOS[29] **11** and CHIRAPHOS[30] **12**, all of which possess chirality in the backbone, Scheme 5.




(R,R)-DIOP (10) NORPHOS (11) (R,R)-CHIRAPHOS (12)

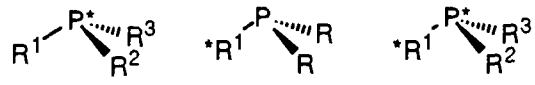
Scheme 5

### 1.3. Chiral monophosphines

Although less well known and less frequently used, chiral monophosphines have also found applications in asymmetric catalysis. Monophosphines fall into three main categories:

- those possessing a stereogenic phosphorus atom;
- those possessing chirality on a side chain;
- those possessing both an asymmetric phosphorus atom and a chiral side chain.

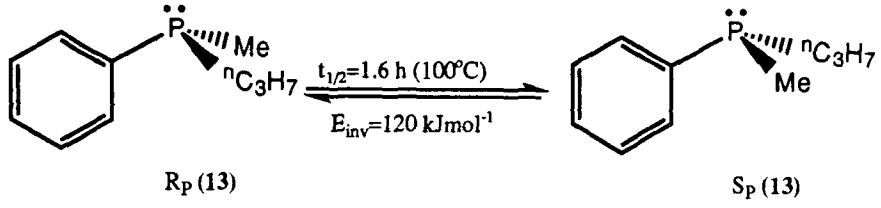
These are illustrated in Scheme 6.




* indicates chirality

Scheme 6

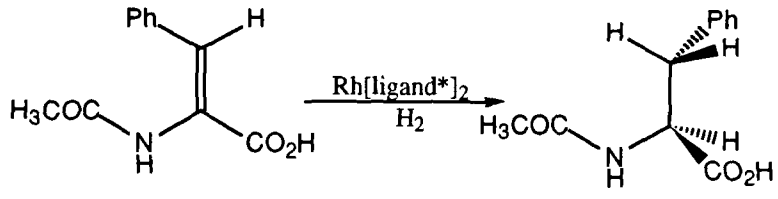
Phosphines that possess a stereogenic phosphorus atom do not racemise at room temperature providing the substituents on phosphorus are strongly bound. For example, enantiomerically pure methyl(n-propyl)phenylphosphine[31] **13** has a half-life ($t_{1/2}$) of 1.6 h at 100°C, Scheme 7.

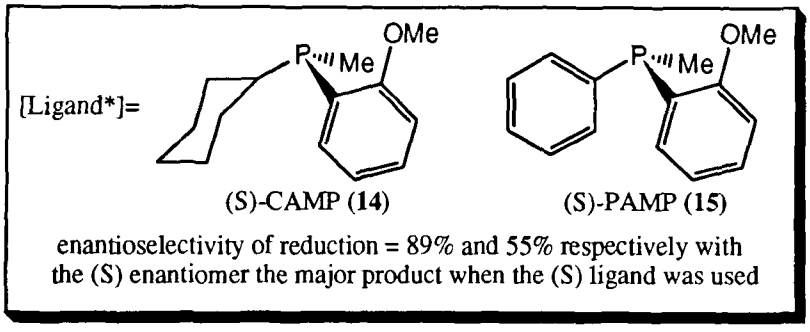



$R_P$ (13) $S_P$ (13)

Scheme 7

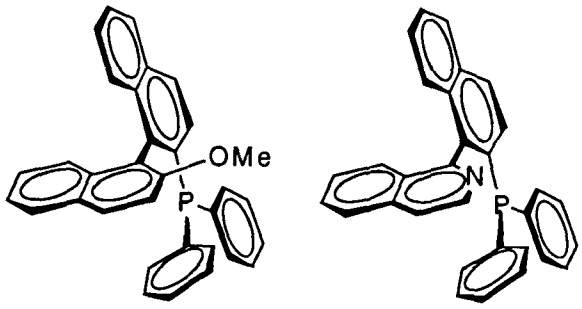
An example of where monophosphines have successfully been used in asymmetric catalysis is in the reduction of dehydroamino-acids, Scheme 8. Both CAMP[32] **14** and PAMP[33] **15** reduced (Z)-α-acetamidocinnamic acid[34] with good enantioselectivity and in high chemical yield.




Scheme 8

Other monophosphines successfully used in enantioselective catalysis include the MOP ligands **16**, developed by Hayashi,[35,36] and the QUINAP ligand **17**, developed by Brown[37], which have been successfully used in catalytic hydroboration reactions. These ligands are illustrated in Scheme 9.



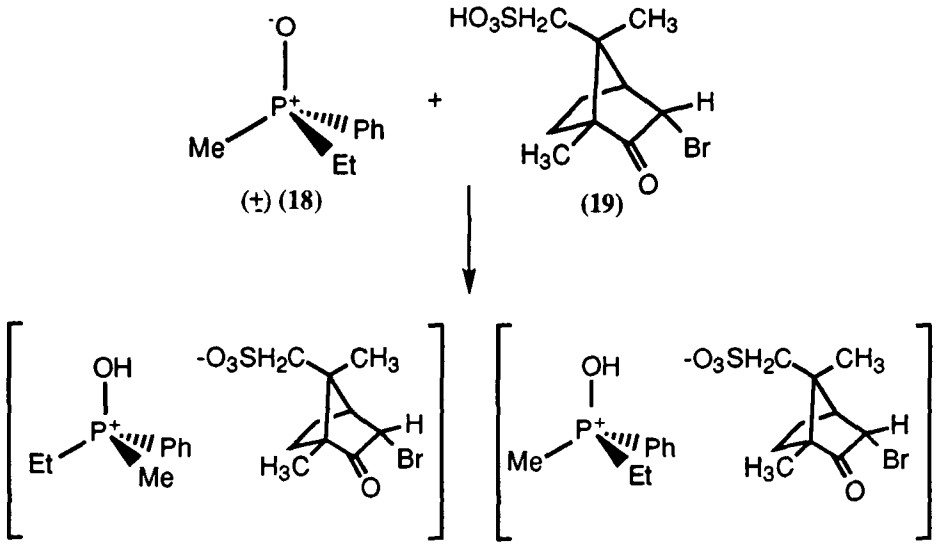

MeO-MOP **(16)** QUINAP **(17)**

Scheme 9

These monophosphines are typical in that their synthesis in an enantiomerically pure form involves a resolution and that their chirality derives from the backbone. This is the situation for the majority of chiral monophosphines. The methods used to produce P-chiral phosphines are detailed below.

## 1.4. Resolution of racemates by crystallisation

A full description of the resolution methods used to obtain homochiral monophosphines is given by Pietrusiewicz and Zablocka[38] and thus only the significant highlights are included here. The first phosphorus compound to be obtained in enantiomeric excess was ethylmethylphenylphosphine oxide[39] **18**, which was obtained using (+)-bromocamphorsulphonic acid **19** as a resolving agent, Scheme 10.

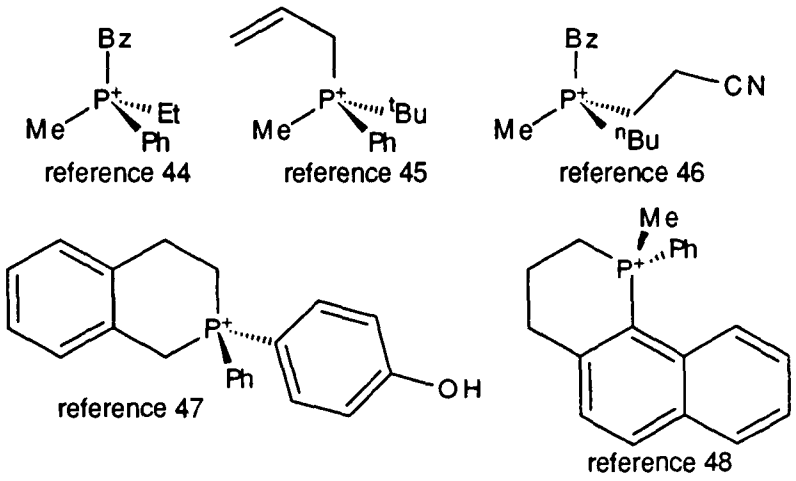



Separable by fractional crystalisation from ethyl acetate/ether over 15 years to give both enantiomers of ethylmethylphenylphosphine oxide with good enantiomeric purity

Scheme 10

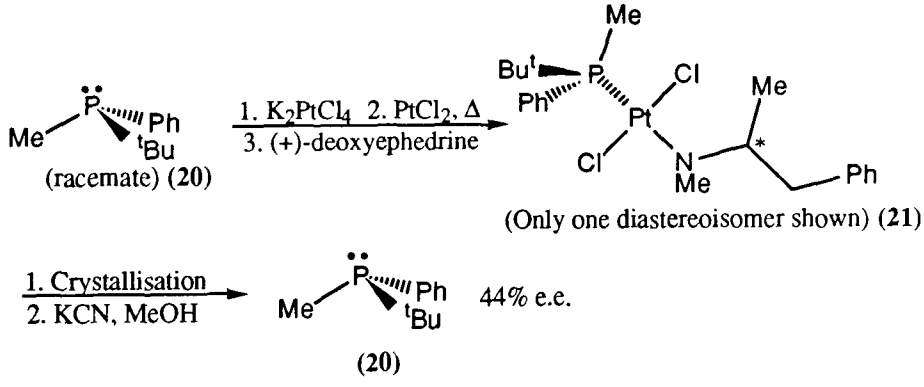
The two diastereoisomeric salts formed were fractionally crystallised from ethyl acetate and ether to give, after separation of the resolving agent, both enantiomers in high enantioselective excess[40]. This resolution method relies on the protonation of the weakly basic phosphoryl oxygen and thus, although reproducible, is not very effective and has been used to resolve very few other phosphine oxides[41]. However, this method of oxygen protonation can be useful for the resolution of diphosphine oxides such as the oxides of BINAP[42] and NORPHOS[43].

The resolution of P-chiral phosphonium salts was first reported in 1959 by McEwan and co-workers[44] who used silver dibenzoyl tartrate as a resolving agent to separate the enantiomers of benzylethylmethylphenylphosphonium iodide. A large number of P-chiral phosphonium salts have been resolved this way[45,46] and this method has also been used for the resolution of cyclic P-chiral monophosphines[47,48], Scheme 11.




Scheme 11

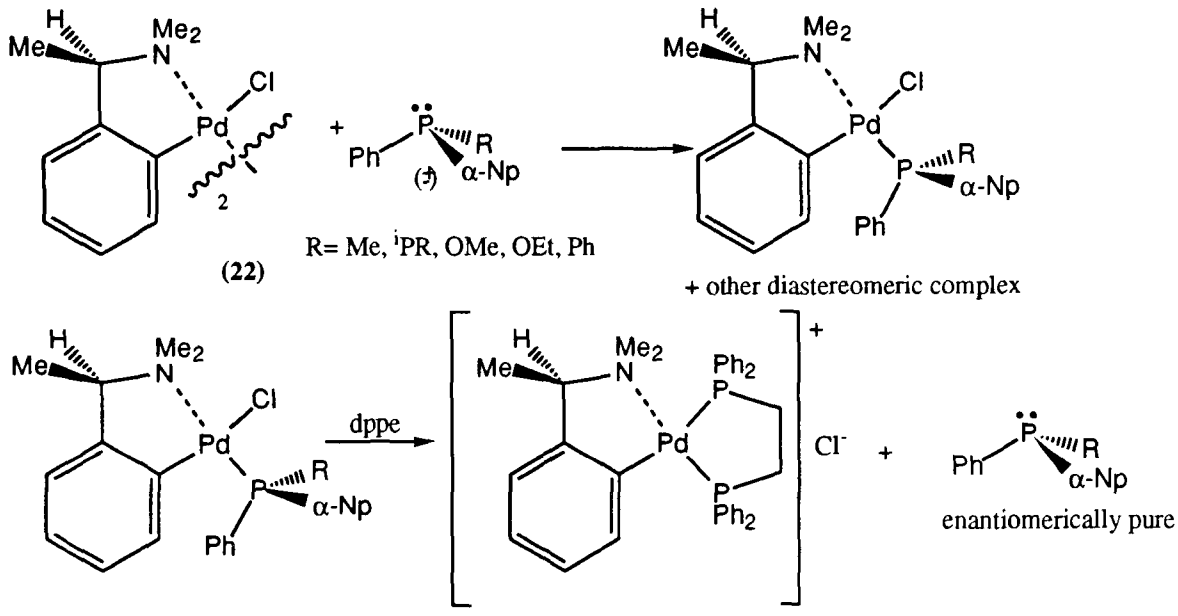
Following the discovery that reductive cleavage of the resolved salts did not lead to racemisation[49], this method was used for the synthesis of scalemic phosphines in gram quantities. However, it had earlier been discovered that 'phosphines' could be resolved in oxidation state 3. Chan[50] partially resolved *tert*-butyl-methylphenylphosphine **20** by the formation of platinum complex **21**, which exists as a diastereomeric pair, Scheme 12.




Scheme 12

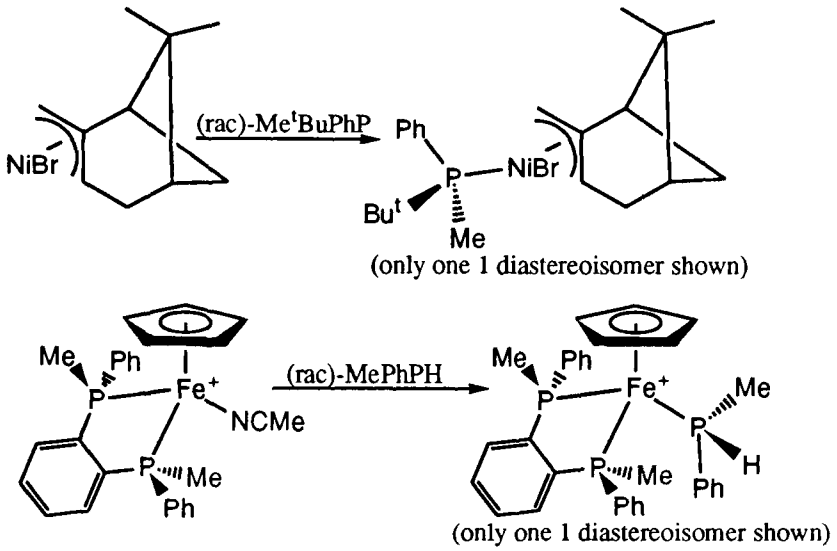
A major advance in resolution techniques was the introduction of palladium as the complexing metal. Many researchers, including Otsuka[51] and Wild[52], succeeded in completely resolving scalemic phosphines in high chemical yield. Some of the phosphines resolved are illustrated in Scheme 13

along with one of the most successful resolving agents, (-)-di-μ-chlorobis{2-[1-(dimethylamino)ethyl] phenyl-C,N}dipalladium **22**.



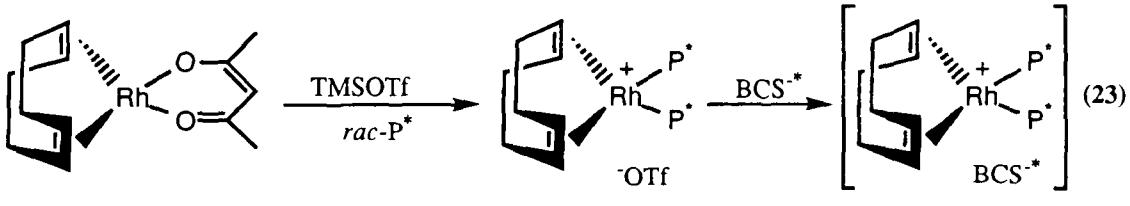

Scheme 13

Although palladium is the metal of choice for most resolutions, other metals have been used. Diastereomeric nickel[53] and iron[54] complexes may be formed and separated by fractional crystallisation, Scheme 14.




Scheme 14

Rhodium complexes[55] have also been used and this method has the advantage that the phosphine, when resolved, is already on a suitable metal for asymmetric catalysis. A rhodium cyclo-octadiene complex **23** of α-bromocamphor-π-sulphonate and two phosphine units is synthesised and the least soluble diastereoisomer precipitates out, Scheme 15. The chiral anion is then exchanged with a chloride or hexafluorophosphate anion to give a rhodium phosphine complex that may be used in asymmetric catalysis.



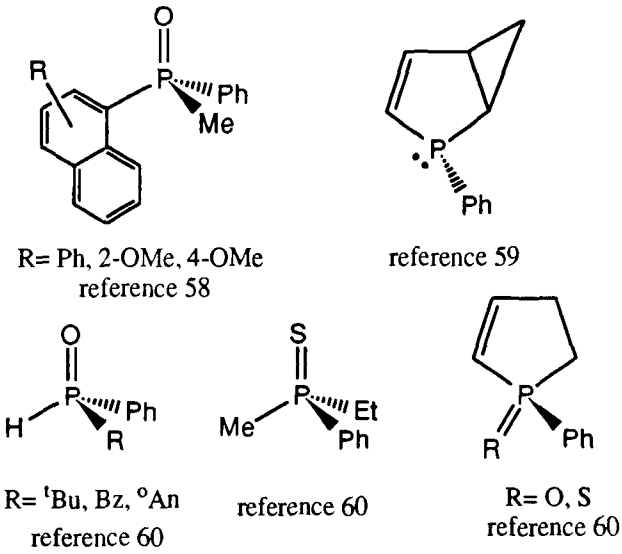

BCS$^-$ is α-bromocamphor-π-sulphonate

Diastereomeric complexes separable by fractional crystallisation from ether

Scheme 15

## 1.5. Resolution of racemates by chromatography

Following the development of chiral chromatography columns, several workers have succeeded in isolating chiral phosphines with high enantiomeric excess. Initial attempts[56,57] focused on phosphine oxides and depended upon interaction with the weak P=O dipole. Most of initial resolutions that were successful contained aromatic moieties, although recent work has seen a wide range[58,59] of chiral phosphine oxides, sulphides and phosphines resolved, Scheme 16.

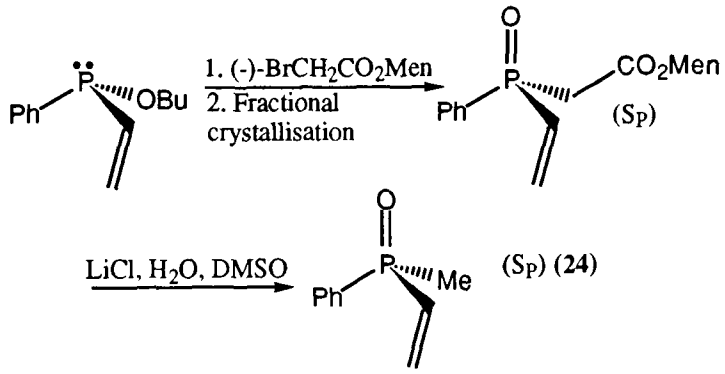



Scheme 16

As chromatographic enantiomer separation improves, it seems likely that the range of phosphine derivatives that may be separated will continue to increase and that chromatographic separations will become more common-place. A limitation that exists at present is that only small quantities of homochiral phosphine compounds have been isolated and therefore a major challenge is to increase the scale of these separations. Another method used to resolve chiral phosphines is to produce diastereotopic derivatives and resolve the diastereoisomers, usually by fractional crystallisation but also by chromatography.

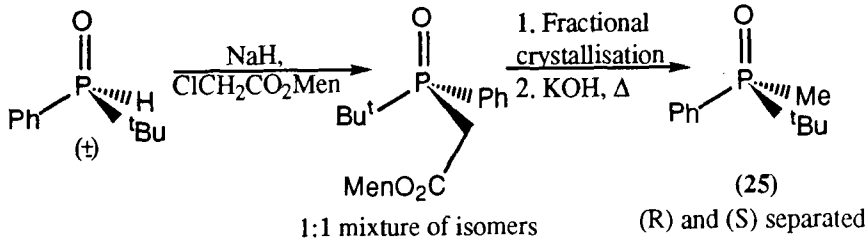
## 1.6. Resolution *via* synthesis of diastereoisomers

It is often possible to design synthetic schemes so that a chiral moiety is introduced into the phosphorus compound and then removed at a later stage, after resolution by crystallisation. Such methodology was used in the synthesis of the enantiomerically pure phosphine oxide **24** by Pietrusiewicz and co-workers[60], Scheme 17.



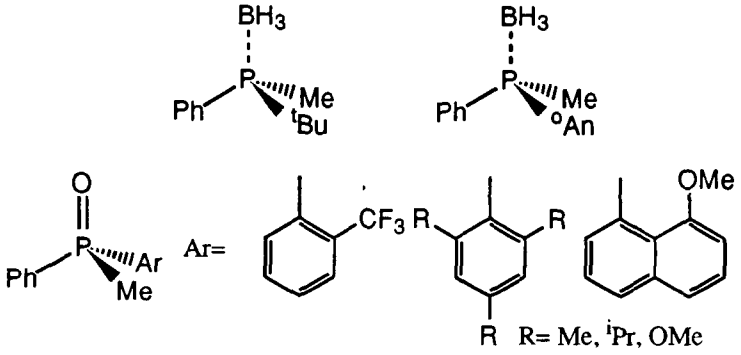

Scheme 17

In this example, the Sp **24** diastereoisomer precipitates out of the reaction mixture upon cooling and the chiral auxiliary is then removed by a simple decarboxylation procedure to afford the phosphine oxide in high enantiomeric excess. This method of synthesising enantiomerically pure phosphorus compounds often involves a Michaelis-Becker reaction of secondary phosphine oxides, Scheme 18.



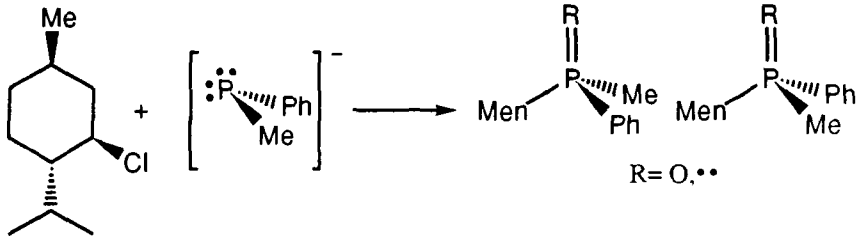

Scheme 18

In this example[61], both enantiomers of *tert*-butylmethyl phenylphosphine oxide **25** were produced in gram quantities. A wide variety of phosphine complexes[59] have been produced in this manner, including borane complexes[62], Scheme 19.




Scheme 19

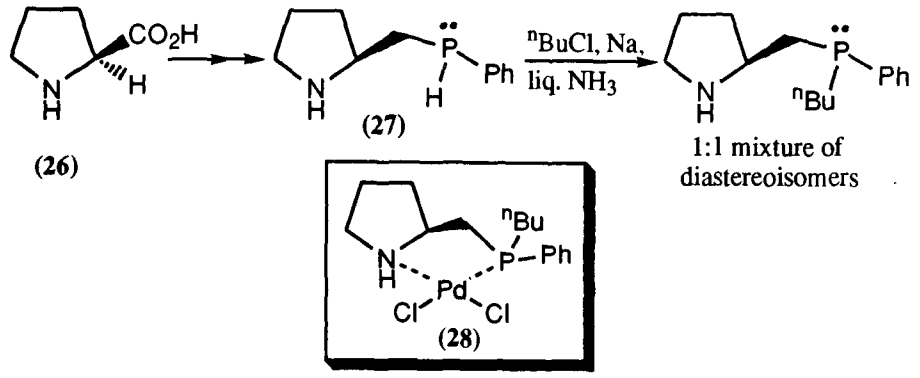
Many synthetic targets require additional chirality, usually on carbon atoms. In this case, diastereoisomers are produced and these are usually resolved by simple crystallisation. An example of such a situation is Fisher and Mosher's synthesis[63] of two menthylphosphines (and their oxides after treatment with hydrogen peroxide), Scheme 20.




Scheme 20

These diastereoisomers were isolated by crystallisation to yield gram quantities of diastereomerically pure material[64].

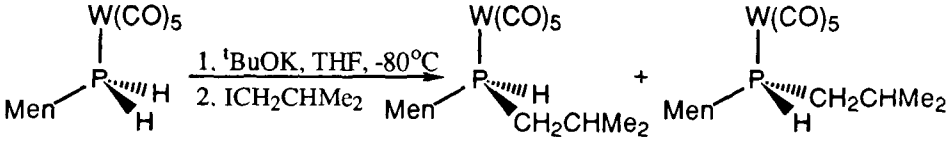
Kinoshita and co-workers[65] used proline **26** to derive an aminophosphine **27** that was resolved by the formation of the palladium salt **28**, Scheme 21.




Scheme 21

The crystallisation from chloroform-ethanol gave two different types of crystals, blocks and needles, which were separated by hand picking and the X-ray crystal structures subsequently obtained.

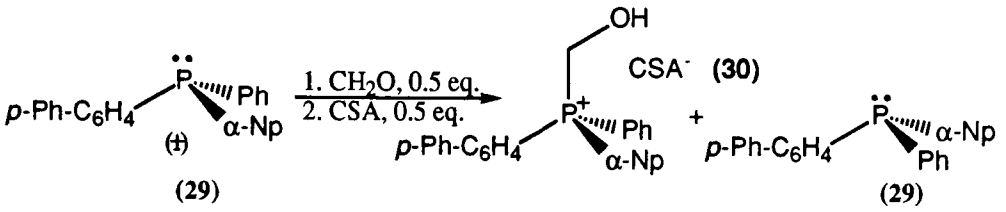
Mathey and co-workers[66] reported that primary and secondary phosphines co-ordinated to tungsten react in a stereoselective manner to give unequal mixtures of diastereoisomers, Scheme 22.




Scheme 22

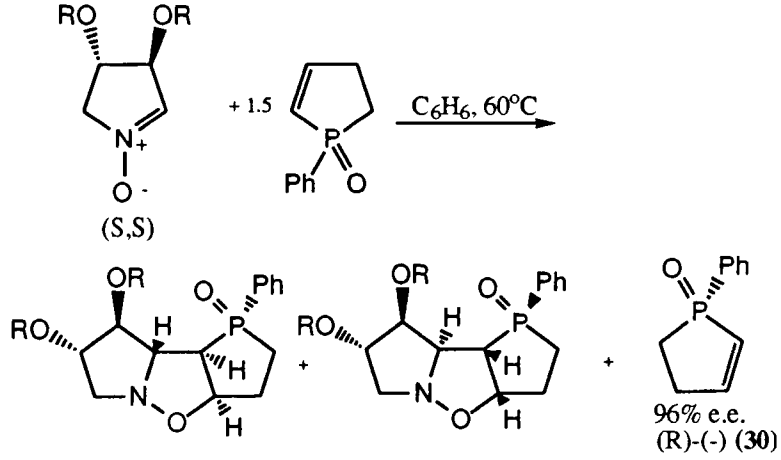
The two diastereoisomers were obtained in a ratio of 7:3 or 3:7 depending upon the reaction temperature. Further alkylation of these secondary phosphine complexes is possible, using similar conditions to afford tertiary phosphine complexes, the reaction again occurring with a high degree of stereospecificity.

If only half an equivalent of electrophile is used, kinetic resolution occurs. Wittig and co-workers[67] were the first to show this when they partially resolved *p*-biphenylyl-1-naphthyl phenylphosphine **29** by the use of (+)-camphor-10-sulphonic acid **30** in a quarternization reaction, Scheme 23.




Scheme 23

The unreacted half of the phosphine was enriched in the (-) enantiomer while the reacted half, which was liberated with triethylamine, was enriched with the (+) enantiomer. It was later revealed[68] that the enantiomeric excesses were low but this represented the first time kinetic resolution had been used to resolve a pair of phosphine enantiomers. Many other workers[69,70,71] have attempted to use kinetic resolution but enantiomeric excesses obtained have been low. One notable exception is the 1,3-dipolar cycloaddition reaction developed by Brandi and co-workers where (R)-1-phenyl-2-phospholene-1-oxide **31** was obtained from its racemate in 96% enantiomeric excess, Scheme 24.

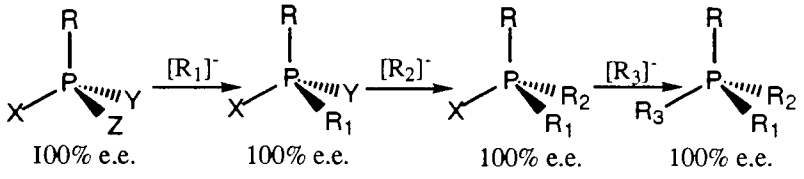



Scheme 24

The major limitation of all reaction pathways that involve resolution is that the chemical yields are small as even perfect separation leads to a yield of 50%, and this is rarely obtained. Therefore, considerable emphasis has been placed on the stereoselective synthesis of P-chiral phosphines.

## 1.7. Stereoselective synthesis

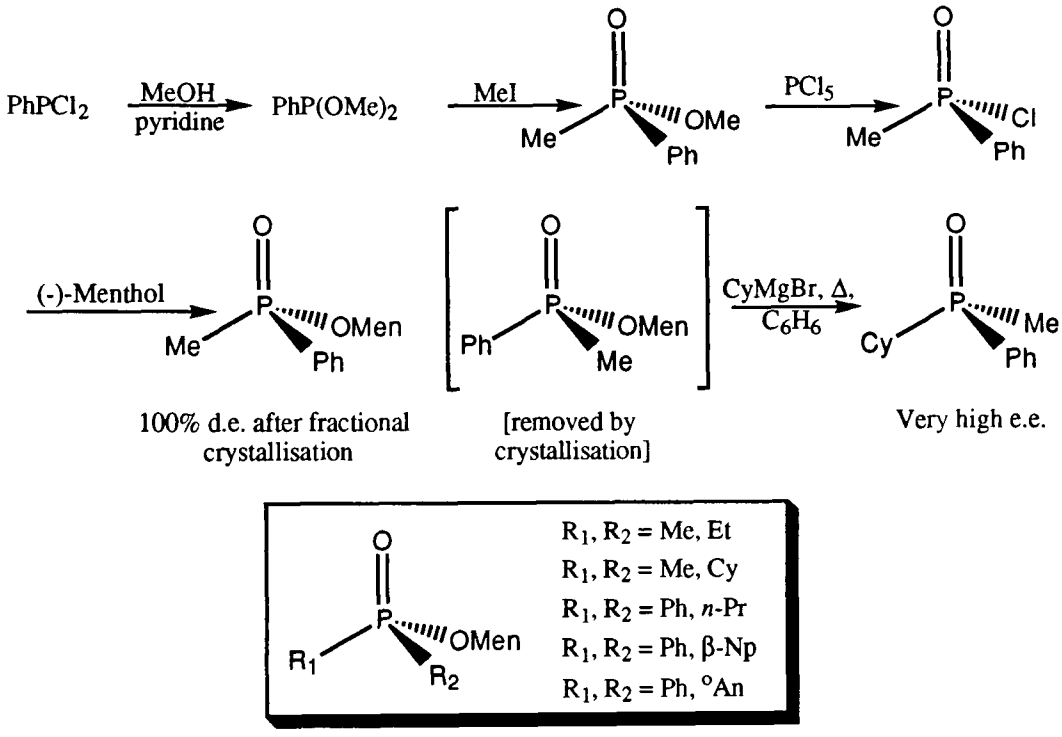
The above methods are only applicable for a narrow range of molecules, and are thus not generally useful. The desire for general methods of producing chiral monophosphines focused attention on stereoselective routes. Such a route requires a resolved phosphorus precursor possessing one or more leaving groups that may be cleaved in a stereoselective manner, Scheme 25.




R = lone pair or some cleavable moiety (e.g. oxide, sulphide, borane etc.)
Each reaction idealy occurs with complete retention (as shown) or complete inversion of configuration.

Scheme 25

The first workers to demonstrate that this was possible were the groups of Nudelman/Cram[72] and Mislow[73] who demonstrated that menthylphosphinates could be separated into diastereoisomers and that the chiral leaving group could be cleaved with a high degree of stereospecificity. A typical Mislow reaction is shown in Scheme 26, along with some of the menthylphosphinates[74,75] that have since been synthesised.

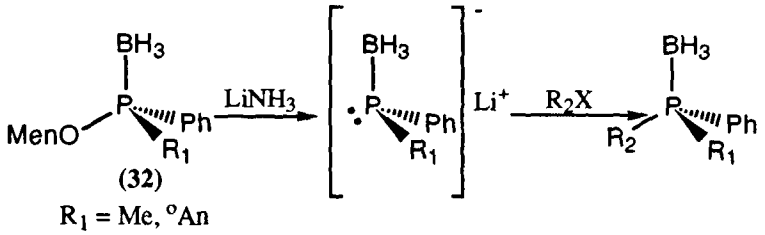



Scheme 26

This route was used for the synthesis of the historically important Monsanto synthesis of DIPAMP[76] which was prepared in large quantities.

Most of the early displacements were effected with Grignard displacements but organolithium reagents have also been used with success[73]. Organolithium reagents often succeed in displacing the leaving group under milder conditions and in higher chemical yield, although the degree of stereoselectivity is sometimes lower.

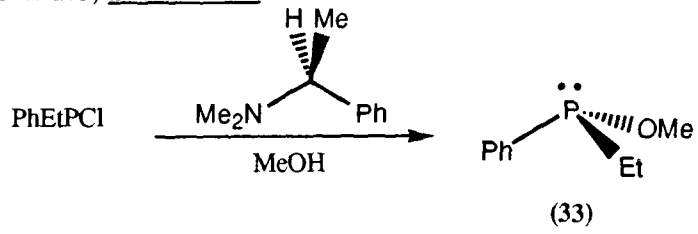
Imamoto and co-workers[77] performed a stereoselective reductive cleavage of the ester P-O bond in menthyl phosphinates **32** using one-electron reducing agents such as lithium amide. The cleavage of the menthyl group was found to take place with almost no loss of configuration at phosphorus, Scheme 27.




Scheme 27

The cleavage process takes place with retention of configuration, and is thus complementary to the Mislow procedure which occurs with inversion of configuration. It is therefore possible to produce both enantiomers of a phosphine derivative from a single diastereoisomer of phosphinate.

The synthesis of homochiral phosphines directly from phosphine intermediates (oxidation state 3) by substitution reactions was attempted after Benschop[78] and co-workers had shown that P-resolved esters of phosphorus acids were configurationally stable. Mikolajczyk[79] synthesised several partially resolved alkyl phosphinites **33** and thiophosphinites *via* an asymmetric route, Scheme 28.

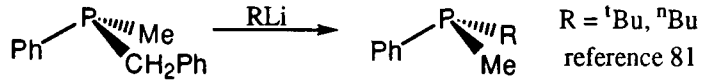



Scheme 28

This route produced the first simple phosphinites that could be used to study the stereochemistry of displacement of ester groups in trivalent phosphorus compounds. Use of phosphinites revealed that the substitution of the phosphinite ester by organolithium reagents occurs with high stereoselectivity and inversion of configuration. Following this work, other workers including Chodkiewicz[80] and Kyba[81], produced scalemic monophosphines from phosphine intermediates, Scheme 29.

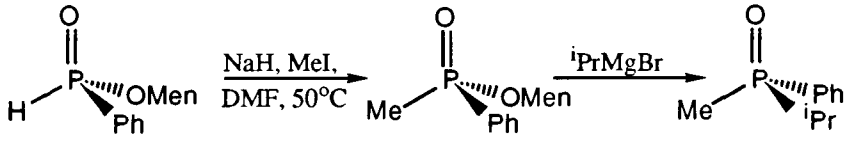



reference 80 R, $R_1$ = Me, °An; R, $R_1$ = Me, Bz; R, $R_1$ = Me, α-Np; R, $R_1$ = Me, °Tol; R, $R_1$ = Bz, *i*Pr; R, $R_1$ = Bz, °Tol




Scheme 29

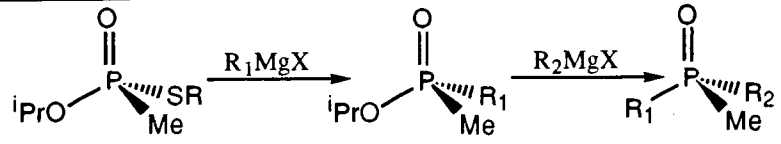
All the early displacement chemistry involved only one nucleophilic displacement and thus the chemistry was of limited scope. In order to broaden the scope of the displacement reactions, Mislow developed a procedure[82] that allowed two sequential displacement reactions on phosphorus, Scheme 30.




Scheme 30

The other enantiomer of the target oxide could be obtained by reversing the order of the introduction of the two substituents. However, this method did not find wide use due to the difficulty of resolving the chiral precursor.

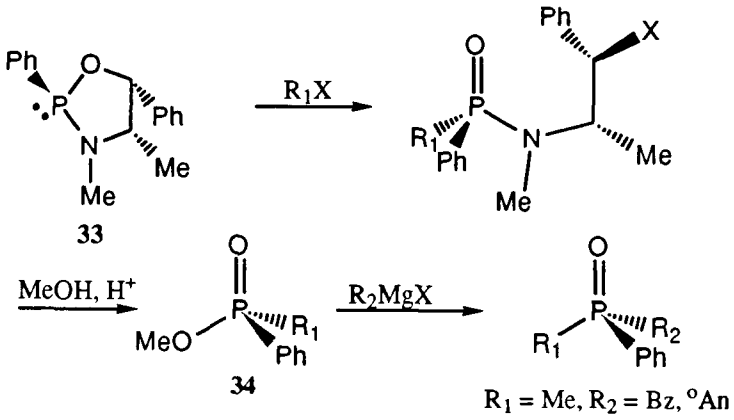
Moriyama and Bentrude[83] and later Corey[84] in a route to DIPAMP were able to exploit the leaving group differences in oxygen and sulphur and thus introduce two carbon groups at phosphorus. Moriyama and Bentrude started from resolved thiophosphonates and involved the addition of two Grignard reagents, Scheme 31.




$R_1$, $R_2$ = Bz, nPr;
$R_1$, $R_2$ = Bz, Ph

Scheme 31

Exploiting the difference in leaving group potential, and following on from the pioneering work of Inch[85], Jugé and Genet[86] developed a similar route using oxygen and nitrogen moieties as the leaving group. Diastereomerically pure oxazaphospholidine **33** was used as the P resolved substrate and underwent two nucleophilic displacement reactions, Scheme 32.



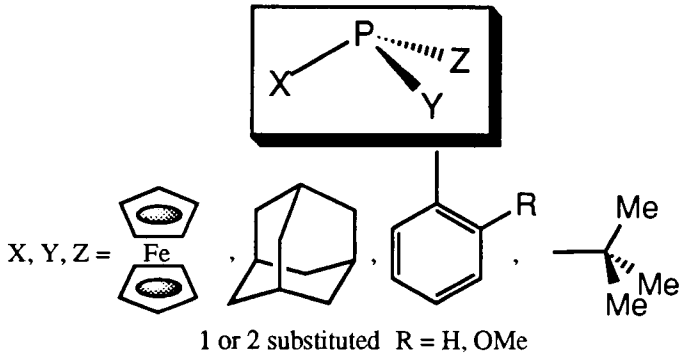

Scheme 32

Reaction of the oxazaphospholidine **33** occurred with retention of configuration but did result in a small loss of chirality (4%) at phosphorus. After recrystallisation, methanolysis produced the methyl phosphinate **34** in 96% e.e. which was subsequently converted to a phosphine oxide by the reaction of a further Grignard reaction in 92-95% e.e. Additional work by the same group[87] revealed that borane complexes could also be used to provide monophosphorus borane complexes in very high enantiomeric excess.

Following on from the approach of Inch[85], Brown and co-workers[88] carried this route forward and developed a route which involved three sequential displacements at phosphorus. Brown started with a diastereomerically pure chloro-oxazaphospholidine by the reaction between (-)-ephedrine and phosphorus trichloride which provided a chiral environment around phosphorus. Use of this route lead to the synthesis of a number of triaryl phosphine oxides in high enantiomeric excess.

## 1.8. Project objectives

Although the groups of Jugé/Genet and Brown had succeeded in producing a wide range of chiral monophosphine derivatives in high enantiomeric excess, the vast majority of these compounds involved small or medium sized moieties. The aim of this work was to extend the scope of these reactions to produce some bulky monophosphines in high enantiomeric excess, and to test their application in an asymmetric catalytic reaction. The hypothesis was that sterically crowded, electron rich phosphines would provide a very precise environment that would facilitate reactions of very high enantioselectivity. The initial target molecule was to contain large entities such as adamantyl, *tert*-butyl and ferrocenyl in addition to medium sized groups such as *ortho*-anisyl and phenyl, Scheme 33.




Scheme 33

The synthesis of a range of novel monophosphines is described in the following chapters in addition to asymmetric hydrogenations using these novel ligands. Characterisation by detailed high field NMR analysis is included, and conclusions as to the suitability of this route are made.

# Chapter 2

The phosphine oxide route to enantiomerically pure phosphines

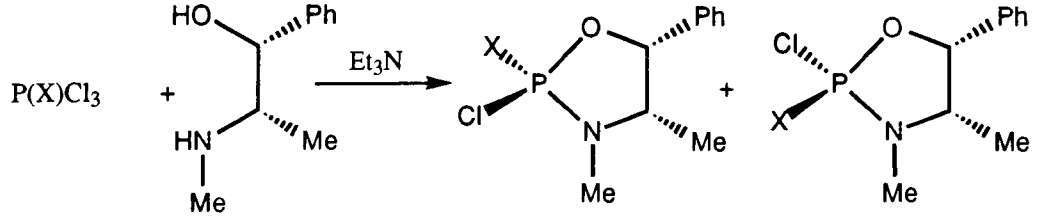
# Chapter 2. The phosphine oxide route to enantiomerically pure phosphines

## Introduction

Precedents[87] had shown that 1,3,2-oxazaphospholidinone oxides underwent three successive nucleophilic displacements to afford tri-substituted phosphine oxides in high enantiomeric excess. Moderate to high chemical yields had been obtained in substitution reactions when the nucleophiles where small aryl groups, with the displacements occurring in a highly stereoselective manner. It was therefore of interest to see if this methodology could be extended to the synthesis of bulky monophosphines. Phosphine oxides, being polar compounds, tend to be crystalline and this is of value as recrystallisation procedures are often an important part of the purification process for the intermediates.

## 2.1 Synthesis of oxazaphospholidinone oxides

(-)-Ephedrine, a cheap and readily available amino alcohol, was used by Devillers and Nevech[89] in the synthesis of a diastereotopic mixture of (4S,5R)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxides or -2-thiones, **35**, Scheme 31.

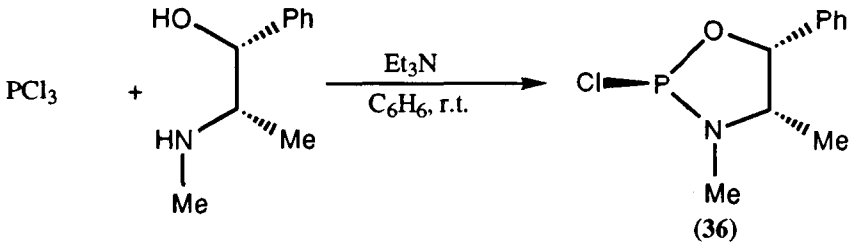



X = O, S
(35)

Scheme 31

The seperate diastereoisomers were later isolated by chromatography[90] in a ratio of 10:1, with the (2R) diastereoisomer dominant. Inch and co-workers extended the range of 1,3,2-oxazaphospholidines to include selones and phenoxides, and also

developed a route to (2R,4S,5R)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine as a single diastereoisomer, **36**, Scheme 32.



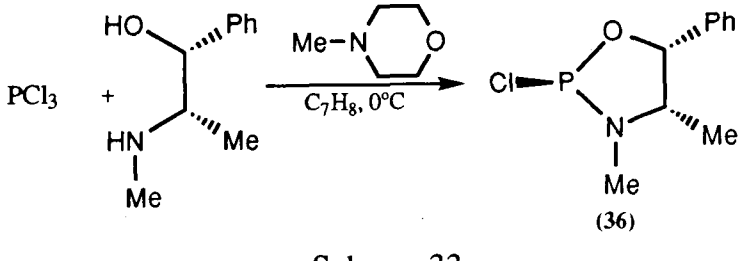

(36)

Scheme 32

Compound **36** had been successfully used by Brown and Carey[91] among others as a starting material for the synthesis of homochiral aryl monophosphine oxides, and was chosen as the principal starting material for the chemistry in this work. Compound **36** is particularly suitable as:

- it is readily synthesised in multigram quantities *via* a one pot reaction;
- it may be stored for several months if kept under argon in the dark at -10°C;
- it contains a phosphorus atom in a chiral environment surrounded by three different leaving groups.

Halide **36** was prepared by a modification of Inch's method[92], in which N-methyl morpholine replaced triethylamine as the base and toluene replaced benzene as the solvent. Isolated yields of up to 85% were obtained, which compare favourably with those of Inch[92] and Carey[91], by ensuring the solvents and reactants used were thoroughly degassed and that the reaction mixture was vigorously stirred throughout, Scheme 33.

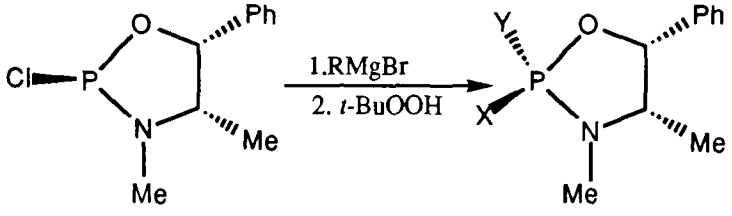



(36)

Scheme 33

Chloride displacement by various nucleophiles has been successfully demonstrated by a number of workers, including Brown[91] and Knowles[105], to give aryl and alkyl oxazaphospholidinones which were subsequently oxidised before isolation, Table 1. Diastereoisomeric mixtures of aryl and alkyl oxazaphospholidinones were obtained and were isolated as single diastereoisomers by fractional crystallisation or chromatography.

Table 1. Examples of oxazaphospholidinone-2-oxides in the literature.




| Structure | X | Y | Reference |
|---|---|---|---|
| (2R,4S,5R)-(37) | Ph | O | 91 |
| (2S,4S,5R)-(37) | Ph | O | 91 |
| (2R,4S,5R)-(38) | $^{o}$An | O | 91 |
| (2R,4S,5R)-(39) | Me | O | 93 |
| (2S,4S,5R)-(40) | PhO | O | 93 |
| (2R,4S,5R)-(40) | O | PhO | 93 |

## 2.2 Strategy and results

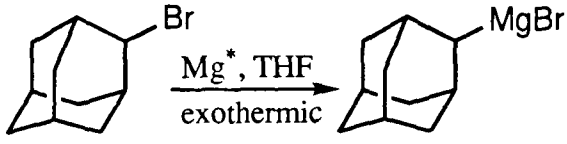
Following the literature[85], attempts were made to synthesis a series of bulky aryl and alkyl 1,3,2-oxazaphospholidines. Ferrocenyl and 1- or 2-adamantyl were selected as desirable moieties for potential monophosphine ligands because of their electronic and steric properties.

**Adamantyl-1,3,2-oxazaphospholidine-2-oxide**

Synthesis of the adamantyl derivative of compound **37** required a reliable method for the production of adamantyl Grignard reagents. Although two potential adamantyl structures exist, 2-adamantyl and 1-adamantyl, the 2-adamantyl moiety was favoured due to synthetic accessibility of the anion, although considerable attempts were made to incorporate the 1-adamantyl moiety.

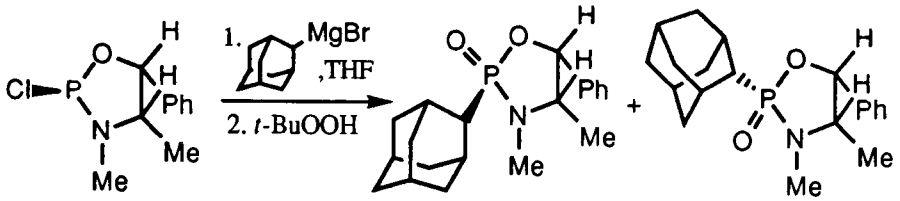
*2-Adamantyl chemistry*

Grignard reagents are effective in the nucleophilic displacement step; thus 2-adamantylmagnesium bromide was synthesised from 2-adamantyl bromide and activated magnesium, Scheme 34.



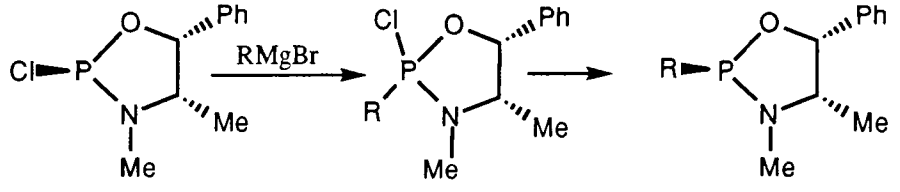

Scheme 34

Subsequent reaction of the Grignard reagent with halide **36** affords both diastereoisomers of (4S,5R)-2-2-adamantyl-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide, (R)-**41** and (S)-**41**, after oxidation, Scheme 35.




Scheme 35

Uniquely, it was possible to obtain the inversion ($S_P$) (P-inverted) isomer as the major product by performing the reaction under kinetic control. The stereoselectivity of this reaction, performed under kinetic conditions, is different to the reactions of both Inch and Carey with net inversion of configuration at phosphorus as opposed to retention. Inch had prepared (2R,4S,5R)-2-methoxy-3,4-dimethyl-5-phenyl-1,3,2-oxaza-phospholidine from the reaction of methanol with halide **36**. The mechanism of P-Cl cleavage was believed to involve nucleophilic attack trans to oxygen, creating a trigonal bipyramidal intermediate followed by pseudorotation, Scheme 36.




Scheme 36

As the kinetic diastereoisomer may be produced as the major product, the above proposed mechanism cannot be operating in the adamantyl case. It was possible to obtain the thermodynamic diastereoisomer in up to 60% diastereomeric excess by using longer reaction times, however.

The diastereoisomers were separated by column chromatography using ethyl acetate as the eluent, although fractional crystallisation from ethyl acetate led to pure ($R_P$) diastereoisomer. The structures of both $R_P$ and $S_P$ diastereoisomers of compound **41** were established by spectroscopic methods and the absolute

configuration of compound (2R)-**41** confirmed by X-ray diffraction studies.

**Spectroscopic analysis**

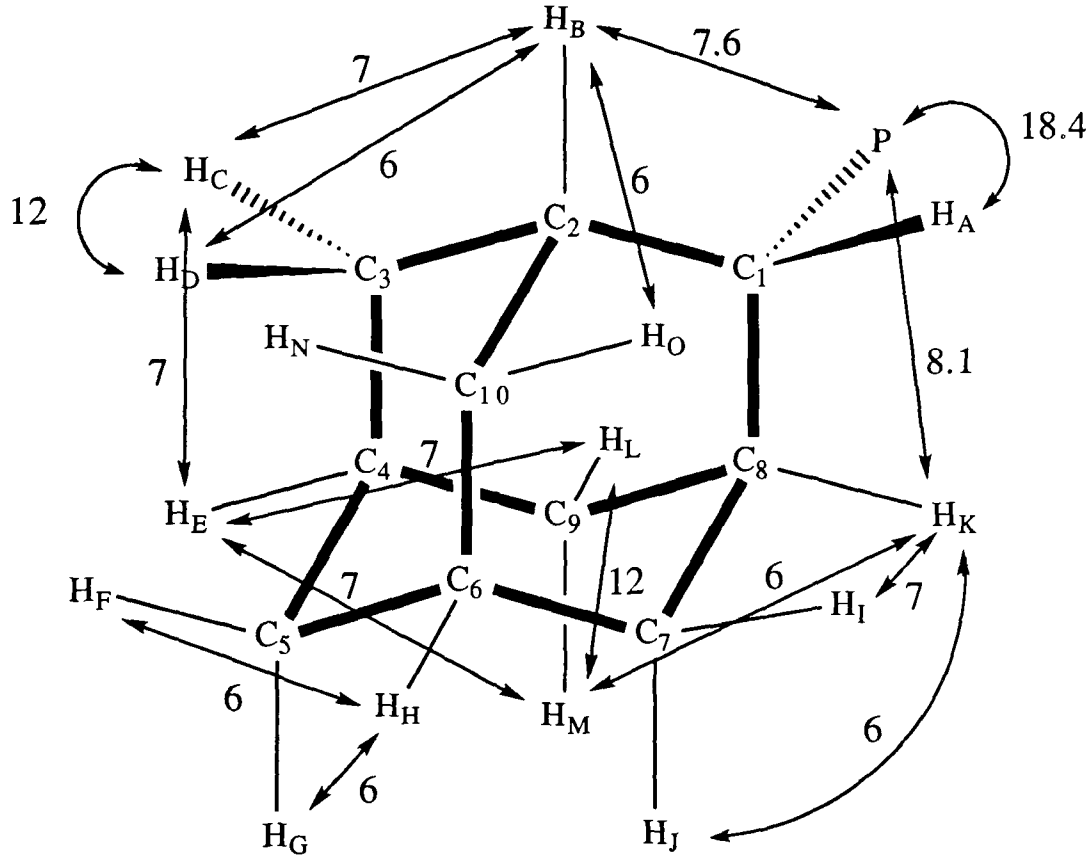
A considerable number of aryl-1,3,2-oxazaphospholidine-2-oxide crystal structures exist in the literature[93], and thus comparison of $^{1}H$ and $^{13}C$ NMR spectra provides information as to the absolute configuration at phosphorus. Due to the considerable bulk of the adamantyl group, configurational correlation is unreliable since the solution conformation maybe different. The key $^{1}H$ NMR resonances around the oxazaphospholidinone ring are given in Table 2.

Table 2. Selected $^{1}H$ NMR data for ($R_P$)-**41**, ($S_P$)-**41** and ($R_P$)-**37**, ($S_P$)-**37**.

| Structure | ($R_P$)-**41** | ($S_P$)-**41** | ($R_P$)-**37** | ($S_P$)-**37** |
|---|---|---|---|---|
| Reference | This work | This work | 91 | 91 |
| $CCH_3$ δ (ppm) | 0.71 | 0.84 | 0.92 | 0.82 |
| $J_H$ | 6.7 | 6.5 | 6.5 | 6.6 |
| $NCH_3$ δ (ppm) | 2.83 | 2.71 | 2.76 | 2.76 |
| $J_P$ | 8.8 | 9.5 | 10.1 | 9.3 |
| H-4 δ (ppm) | 3.64 | 3.62 | 3.78 | 3.85 |
| $J_P$ | 0.0 | 15.8 | 14.1 | 10.6 |
| $J_H$ | 6.1 | 6.2 | 6.2 | 6.3 |
| $J_{CH3}$ | 6.6 | 6.5 | 6.5 | 6.6 |
| H-5 δ (ppm) | 5.82 | 5.41 | 5.60 | 5.96 |
| $J_P$ | 0.0 | 3.7 | 4.8 | 0.0 |
| $J_H$ | 6.1 | 6.2 | 6.2 | 6.3 |

A detailed $^{1}H$ NMR study was carried out on compound ($S_P$)-**41**, resulting in a large number of the adamantyl couplings identified, as shown in Scheme 37. In order to identify the resonances belonging to the adamantyl proton and carbon atoms, it was necessary to perform COSY, NOESY and DEPT analysis, and $^{13}C$-$^{13}C$ correlation spectroscopy. Most of the coupling constants are derived from 2-D spectra with significant line broadening and thus cannot be quoted to better than one significant figure, with the remainder (two significant figures) being calculated from 1-D high field spectroscopy.

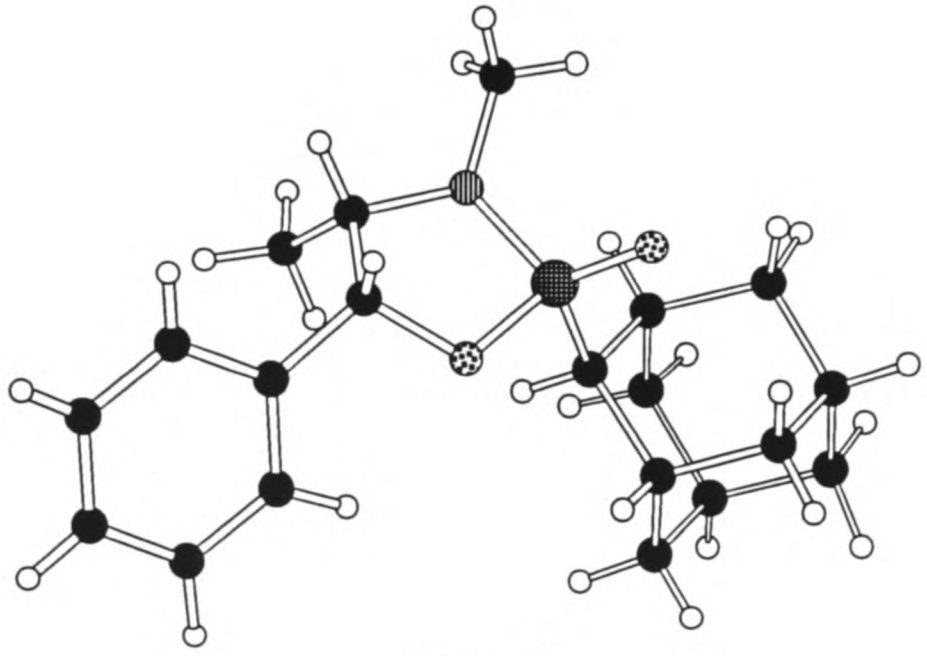
$^{1}H$, $^{13}C$ and $^{31}P$ NMR data ($CDCl_3$) for compound ($S_P$)-**41**
("W" couplings omitted for clarity, coupling constants in Hertz)



| $^1$H NMR | ppm | $^1$H / $^{31}$P | ppm | $^{13}$C NMR | ppm |
|---|---|---|---|---|---|
| $H_A$ | 2.397 | $H_K$ | 2.227 | $C_1$ | 44.86 |
| $H_B$ | 2.475 | $H_L$ | 2.280 | $C_2$ | 28.44 |
| $H_C$ | 2.249 | $H_M$ | 1.613 | $C_3$ | 33.39 |
| $H_D$ | 1.697 | $H_N$ | 1.916 | $C_4$ | 27.32 |
| $H_E$ | 1.911 | $H_O$ | 1.819 | $C_5$ | 37.43 |
| $H_F$ | 1.780 | | | $C_6$ | 27.87 |
| $H_G$ | 1.780 | P | 47.12 | $C_7$ | 39.71 |
| $H_H$ | 1.958 | | | $C_8$ | 28.44 |
| $H_I$ | 1.777 | | | $C_9$ | 32.93 |
| $H_J$ | 1.899 | | | $C_{10}$ | 39.41 |

Scheme 37

Despite the considerable amount of spectroscopic information on compound ($S_P$)-**41**, it was not possible to determine configuration and thus a X-ray diffraction study was required. Crystals of compound ($S_P$)-**41** were unsuitable for X-ray studies (very fine needles) and thus attention was focused upon compound ($R_P$)-**41**. It was possible to obtain suitable crystals of compound ($R_P$)-**41** from a wet methanol solution and the X-ray structure was determined, Scheme 38.



Scheme 38

Analysis of the bond lengths and angles revealed that the molecule had a very similar conformation to ($R_P$)-**37** and ($R_P$)-**40**, and that the bulky adamantyl moiety did not interfer with the 5-membered ring.

Table 3. Selected bond lengths (Å) for ($R_P$)-**41** with literature structures for comparison, with e.s.d.'s in parentheses.

| Molecule | ($R_P$)-**41** | ($R_P$)-**37** | ($R_P$)-**40** |
|---|---|---|---|
| Atoms | length(Å) | length(Å) | length(Å) |
| P2-O6 (oxide) | 1.467(2) | 1.463(3) | 1.457(2) |
| P2-N3 | 1.643(2) | 1.641(3) | 1.613(2) |
| P2-O1 | 1.597(2) | 1.581(2) | 1.581(2) |
| P2-substituent | 1.809(3) | 1.790(3) | 1.593(2) |
| N3-C7 | 1.448(4) | 1.450(4) | 1.455(4) |
| N3-C4 | 1.462(3) | 1.465(5) | 1.473(3) |
| C5-C9 (Ph) | 1.489(3) | 1.505(4) | 1.500(3) |
| C5-O1 | 1.461(3) | 1.463(4) | 1.465(3) |
| C4-C5 | 1.545(3) | 1.536(4) | 1.539(3) |
| C4-C8 (methyl) | 1.511(3) | 1.519(4) | 1.516(4) |

Table 4. Selected bond angles (°) for ($R_P$)-**41** with literature structures for comparison, with e.s.d.'s in parentheses.

| Molecule | ($R_P$)-**41** | ($R_P$)-**37** | ($R_P$)-**40** |
|---|---|---|---|
| Atoms | bond angle | bond angle | bond angle |
| O6-P2-O1 | 177.52(12) | 177.4(2) | 199.4(1) |
| O1-P2-N3 | 95.04(10) | 96.1(1) | 96.7(1) |
| sub-P2-O1 | 101.09(10) | 104.8(1) | 103.9(1) |
| O6-P2-N3 | 115.16(12) | 115.3(2) | 117.4(1) |
| O6-P2-sub | 114.08(12) | 110.2(2) | 105.7(1) |
| N3-P2-sub | 111.50(13) | 111.6(1) | 113.2(1) |
| C5-O1-P2 | 112.62(14) | 113.4(2) | 111.7(1) |
| C4-N3-P2 | 114.0(2) | 109.7(2) | 113.6(2) |
| N3-C4-C5 | 103.2(2) | 103.3(3) | 103.4(2) |
| O1-C5-C9 | 109.5(2) | 110.2(3) | 109.5(2) |
| C9-C5-C4 | 116.5(2) | 116.1(2) | 115.4(2) |
| C7-N3-P2 | 124.2(2) | 121.7(3) | 125.3(2) |
| N3-C4-C8 | 112.4(2) | 133.4(3) | 111.7(2) |
| C8-C4-C5 | 114.7(2) | 114.2(3) | 115.9(2) |
| O1-C5-C4 | 105.6(2) | 105.2(3) | 105.9(2) |
| C7-N3-C4 | 121.1(3) | 120.2(3) | 119.9(2) |

Table 5. Selected torsion angles (°) for ($R_P$)-**41** with literature structures for comparison, with e.s.d.'s in parentheses.

| Molecule | ($R_P$)-**41** | ($R_P$)-**37** | ($R_P$)-**40** |
|---|---|---|---|
| Atoms | torsion angle | torsion angle | torsion angle |
| O6-P2-N3-C7 | 41.6(3) | N/A | N/A |
| C15-P2-N3-C7 | -90.5(3) | N/A | N/A |
| O1-P2-N3-C4 | -5.1(2) | 23.1 | -2.0 |
| C7-N3-C4-C8 | 87.2(4) | N/A | N/A |
| C7-N3-C4-C5 | -148.7(3) | 176.0 | -149.2 |
| N3-C4-C5-O1 | -30.7(2) | 33.0 | -28.6 |
| N3-C4-C5-C9 | -152.5(2) | -89.2 | -149.9 |
| C9-C5-O1-P2 | 156.3(2) | 106.9 | 154.7 |
| O6-P2-O1-C5 | 106.2(2) | -124.0 | 109.7 |
| C15-P2-O1-C5 | -128.8(2) | 112.9 | -133.0 |
| O1-P2-N3-C7 | 165.2(3) | 171.0 | 165.0 |
| O6-P2-N3-C4 | -128.7(2) | 147.2 | -130.1 |
| C15-P2-N3-C4 | 99.3(2) | -85.5 | 106.3 |
| P2-N3-C4-C8 | -102.2(2) | -159.6 | -106.8 |
| P2-N3-C4-C5 | 21.9(2) | -35.4 | 18.6 |
| C8-C4-C5-O1 | 91.9(3) | 156.6 | 94.0 |
| C8-C4-C5-C9 | -29.9(3) | 34.4 | -27.3 |
| C4-C5-O1-P2 | 30.0(2) | -19.0 | 29.6 |
| N3-P2-O1-C5 | -15.6(2) | -1.4 | -17.0 |

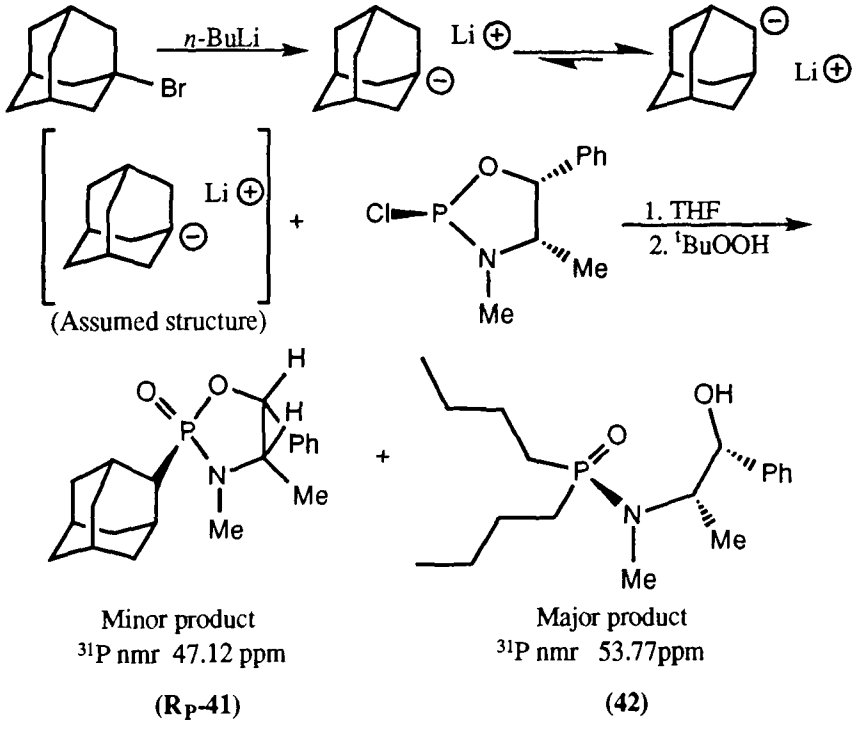
Having developed a good route to both diastereoisomers of compound **41**, it was desirable to synthesise the 1-adamantyl analogues.

*1-Adamantyl chemistry*

Three routes for the synthesis of 1-adamantyl oxazaphospholidinone-2-oxides were identified and involved both nucleophilic and electrophilic approaches:

- *via* 1-adamantylmagnesium bromide;
- *via* dichloro-1-adamantylphosphine;
- *via* direct lithiation of 1-adamantyl bromide.

Of these, only direct lithiation gave isolable products, Scheme 38.




Minor product
$^{31}$P nmr 47.12 ppm
**($R_P$-41)**

Major product
$^{31}$P nmr 53.77ppm
**(42)**

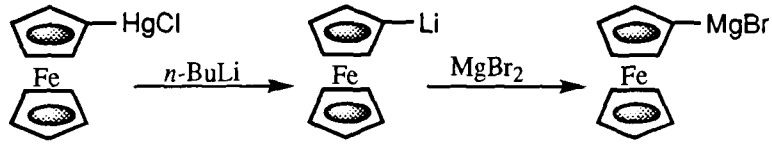
Scheme 38

The major product from the reaction, N-methyl-N-(1S,2S)-(1-methyl-2-hydroxy-2-phenyl)ethyl-P-(dibutyl)phosphinamide **42**, precipitated from methanol as large eight sided crystals and contains two diastereotopic butyl groups. Interestingly, despite being six bonds away from the nearest chiral centre, the terminal methyl groups of the butyl moieties are clearly separate in the high field $^1$H NMR. As no trace of the desired 1-adamantyl compound was

detected, the focus was switched towards the incorporation of a ferrocenyl moiety.

**Ferrocenyl-1,3,2-oxazaphospholidine-2-oxide**

Synthesis of the ferrocenyl analogue required a reliable method for the production of a ferrocenyl magnesium halide. Lithiation of ferrocene with *t*-butyl lithium, as described by Kagan[94], followed by transmetalation with magnesium bromide afforded only traces of the required Grignard reagent, which was unsuitable for the planned reaction with compound **36**, because it contained a considerable amount of excess *t*-butyl lithium which reacted preferentially at phosphorus. Efforts focussed on the more reliable metal exchange reaction involving chloromercuriferrocene[95] as the source of ferrocene. A small excess of *n*-butyl lithium was used to replace the chloro-mercurio group with lithium, which was then successfully replaced by magnesium, Scheme 39.




Scheme 39

Trial reactions of this Grignard reagent with compound **36** were found to be successful, with fair yields of (2R,4S,5R)-2-ferrocenyl-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide (**$R_P$)-43** being obtained after oxidation and workup. However, due to the toxicity of organomercury compounds, and the possible formation of volatile dibutylmercury, this method was deemed unsuitable for large scale reactions, and thus an alternative was sought.

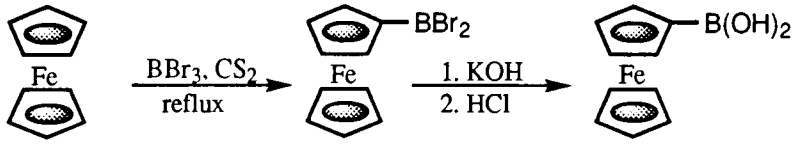
Ferrocenylmagnesium bromide may be readily synthesised from the corresponding halide using standard Grignard techniques. A literature search revealed that the optimum method for the synthesis of ferrocenyl halide involved the reaction of ferrocenylboronic acid

with the appropiate copper halide[96], and subsequent experiment showed that this procedure was extremely effective.

Two procedures exist for the synthesis of ferrocenyl boronic acid;

- reaction of ferrocene with an excess of *n*-butyl lithium followed by *n*-butyl borate[97];
- reaction of ferrocene with boron tribromide followed by aqueous alkaline hydrolysis[98].

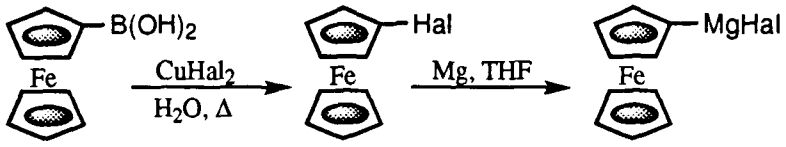
The first method is flawed in that it depends upon an unreliable lithiation of ferrocene and affords mixtures of mono- and di- substituted ferrocenylboronic acid which are difficult to separate. However, Epton's procedure[98] for the synthesis of mono-boronic acid is effective and allows for the preparation of multi-gram quantities, Scheme 40.




Scheme 40

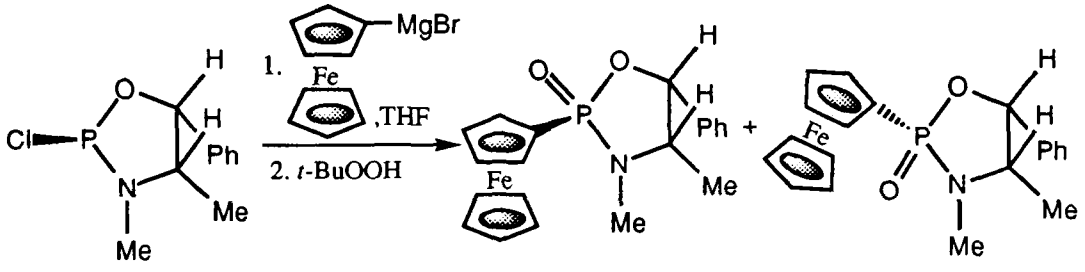
Epton's experimental omits to caution that over-acidification of the boronic acid during the work-up procedure results in de-boronation[99], resulting in ferrocene being obtained. This is of key importance in obtaining high yields as careless acidification substantially reduces chemical yield. Also significant is the use of carbon disulphide which, unlike many other reactions, may not be replaced by the less toxic dichloromethane.

Ferrocenyl bromide and chloride may then be synthesised in 68-78% yield respectively by steam distillation with the corresponding copper halide, and then, after isolation, converted quantativily to the required Grignard reagent, Scheme 41.




Scheme 41

Reaction of the Grignard reagent with compound **36** proceeds smoothly to afford both diastereoisomers of compound **43** after oxidation, Scheme 42.




**(Rp)-43** **(Sp)-43**

Scheme 42

Diastereomeric excesses of up to 95% were obtained when the reaction was performed under thermodynamic control, with good chemical yields obtained. Compound (2R)-**43** predominates although substantial quantities of the minor (2S) diastereoisomer were obtained at shorter reaction times. The ferrocenyl-phosphines were converted to phosphine oxides by oxidation with *t*-butyl hydroperoxide and separated as orange crystalline solids by flash chromatography. Analysis by high field $^1$H NMR and subsequent comparison with the both diastereoisomers of (4S,5R)-3,4-dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine-2-oxide revealed strong similarities in solution structure.

Table 6. Selected $^1H$ NMR data for the ferrocenyl and phenyl 1,3,2-oxazaphospholidinone-2-oxides

| Structure | (2R)-**43** | (2S)-**43** | (2R)-**37** | (2S)-**37** |
|---|---|---|---|---|
| Reference | This work | This work | 91 | 91 |
| $CCH_3$ δ (ppm) | 0.85 | 0.73 | 0.92 | 0.82 |
| $J_H$ | 6.5 | 6.6 | 6.5 | 6.6 |
| $NCH_3$ δ (ppm) | 2.58 | 2.71 | 2.76 | 2.76 |
| $J_P$ | 10.3 | 9.3 | 10.1 | 9.3 |
| δ (ppm) | 3.61 | 3.57 | 3.78 | 3.85 |
| $J_P$ | 11.4 | 0.0 | 14.1 | 10.6 |
| $J_H$ | 6.5 | 6.1 | 6.2 | 6.3 |
| $J_{CH3}$ | 6.4 | 6.6 | 6.5 | 6.6 |
| δ (ppm) | 5.49 | 5.89 | 5.60 | 5.96 |
| $J_P$ | 6.5 | 0.0 | 4.8 | 0.0 |
| $J_H$ | 6.5 | 6.1 | 6.2 | 6.3 |

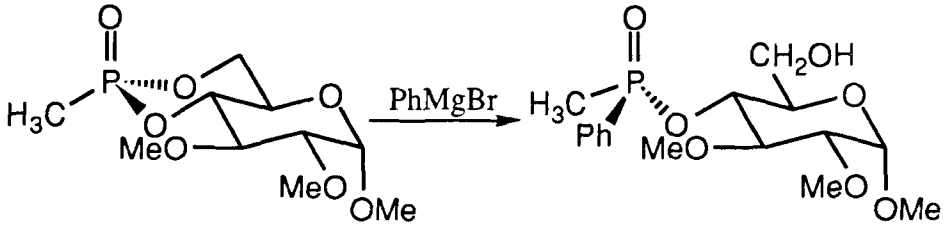
## Diastereoselective ring opening reactions of aryl and alkyl 1,3,2-oxazaphospholidinone-2-oxides

The 1,3,2-oxazaphospholidinones produced above have been converted to oxides prior to cleavage of the P-O bond for four principal reasons;

- the oxides are air (oxygen) stable and thus subsequent experimental procedure is greatly simplified;
- the phosphine oxides produced are crystalline solids and thus resolvable by fractional crystallisation, whereas the phosphines tend to be viscous liquids;
- a high degree of stereoselectivity had been obtained in similar literature reactions;

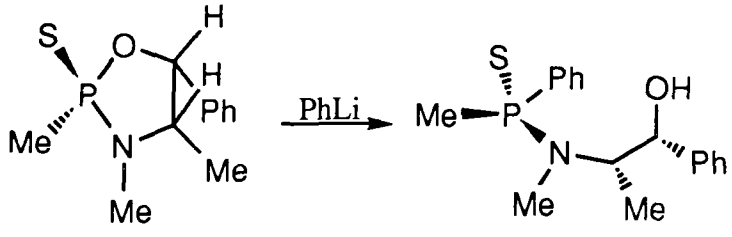
Michaelis-Arbuzov rearrangements[100] of the phosphine are only likely to be successful with small electrophiles, such as methyl iodide, and thus this route to phosphine oxides offers few prospects for a high yielding reaction; hence the attraction of using phosphines is greatly reduced.

Inch and co-workers[101] first demonstrated nucleophilic displacement from a resolved phosphinoglycoside prepared from the reaction of methylphosphonic difluoride with 2,3-di-O-methyl-α-D-glucopyranoside, Scheme 43.




Scheme 43

Inch[102] later demonstrated that diastereoselective P-O bond cleavage could be achieved in 1,3,2-oxazaphospholidinone systems by the reaction of phenyl lithium with an 1,3,2-oxazaphospholidinone-2-thione, Scheme 44, which occurred with a diastereomeric excess of 98%.

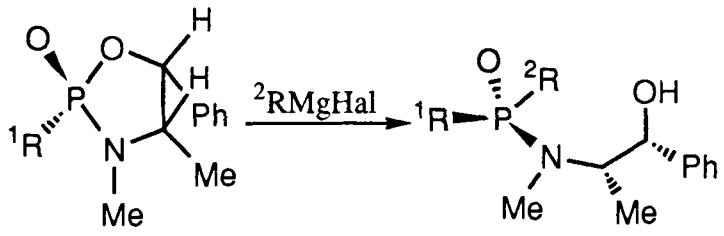



Scheme 44

The route using thiones suffers from the limited number of moieties that may be attached to phosphorus. Carey[103] attempted ring opening of the phenyl analogue with 2-methoxyphenyl magnesium halides but detected no ring opened product despite a wide variety of reaction conditions. In reactions of 1,3,2-

oxazaphospholidinone-2-oxides, P-O bond cleavage occurred with a high degree of stereoselectivity, however, Table 7.

Table 7. Nucleophilic P-O cleavage reactions of 1,3,2-oxazaphospholidinone-2-oxides.




| Precursor chirality | 1R | 2R | Yield (%) | D.E. (Sp) | D.E. (Rp) |
|---|---|---|---|---|---|
| $R_P$ | Ph | $^{o}$An | 70 | < 4 | > 96 |
| $R_P$ | Ph | $CH_2CH$ | 80 | > 94 | < 6 |
| $S_P$ | Ph | $^{o}$An | 80 | > 96 | < 4 |
| $R_P$ | $^{o}$An | Ph | 96 | > 96 | < 4 |
| $R_P$ | $^{o}$An | $CH_2CH$ | 80 | > 94 | < 6 |
| $R_P$ | $^{o}$An | 2-Np | 81 | > 96 | < 4 |
| $R_P$ | $^{o}$An | $^{p}$An | 82 | > 96 | < 4 |
| $R_P$ | $^{o}$An | $^{m}$An | 76 | > 96 | < 4 |

Following the success of Carey's ring opening reactions, organomagnesium halides were employed to cleave the P-O bond in the 2-adamantyl and ferrocenyl series of 1,3,2-oxazaphospholidinone-2-oxides.

## 2-Adamantyl-1,3,2-oxazaphospholidine-2-oxides

Reactions of 2-adamantylmagnesium halide with (2R,4S,5R)-2-methoxyphenyl-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide were unsuccessful, despite a wide variety of reaction conditions. However, the 'reverse' reaction of diastereomerically pure (2S)-41 and (2R)-41 with a variety of organomagnesium halides led to both diastereoisomers of the ring opened product, Table 8A. In the cases where ring opening occurred, reactions with the (2R) diastereoisomer consistently occurred with a greater degree of stereoselectivity. The major product from these reactions was the diastereoisomer formed with retention of configuration at phosphorus.

Table 8A. Ring opening reactions of both diastereoisomers of compound **41**.

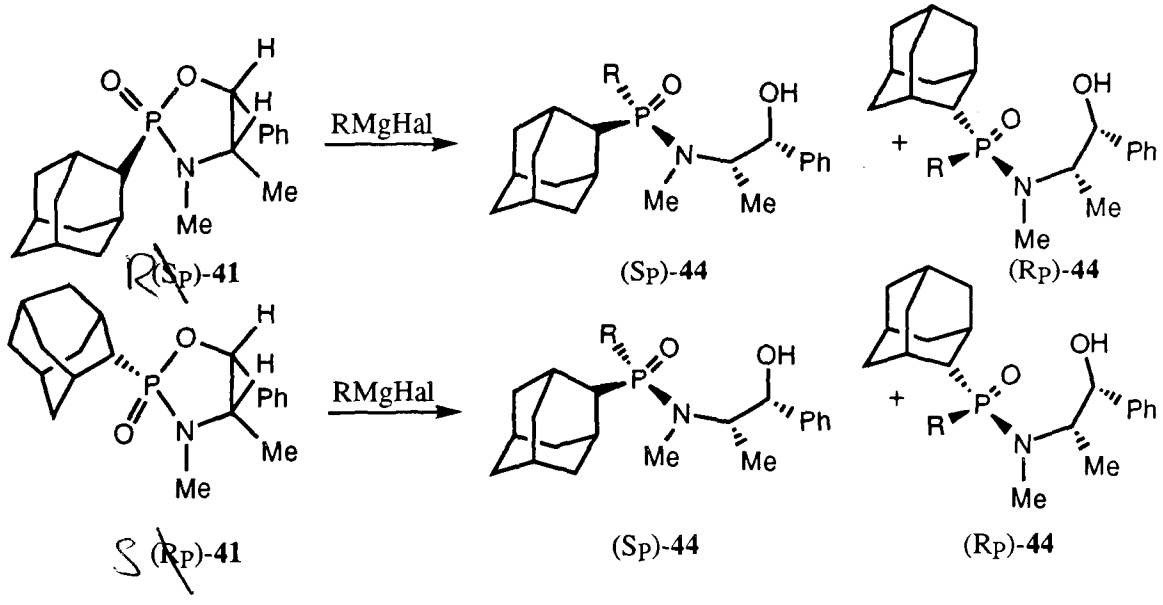
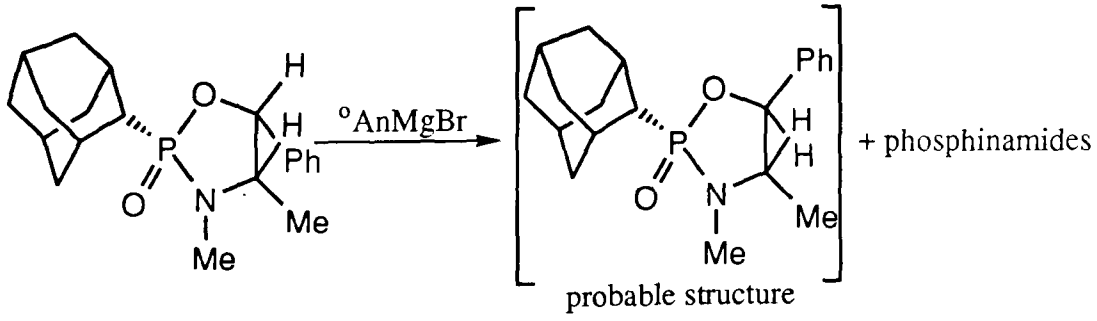


Table 8A.

| Run | Isomer | MHal | Solvent | Temp | Yield % | Stereochemistry | % |
|---|---|---|---|---|---|---|---|
| 1 | S | °AnMgCl | THF | 65 | 24 | $S_P$ | 53 |
| 2 | R | °AnMgCl | THF | 65 | 42 | $R_P$ | >95 |
| 3 | S | °AnMgBr | Toluene | 46 | 0 | - | - |
| 4 | R | °AnMgBr | Toluene | 46 | 0 | - | - |
| 5 | S | °AnMgBr | Toluene | 102 | 13 | $S_P$ | 32 |
| 6 | R | °AnMgBr | Toluene | 102 | <10 | $R_P$ | >98 |
| 7 | S | °AnMgBr | THF | 65 | 48 | $S_P$ | 55 |
| 8 | R | °AnMgBr | THF | 65 | 43 | $R_P$ | 95 |
| 9 | S | FcMgBr | THF | 65 | 0 | - | - |
| 10 | R | FcMgBr | THF | 65 | 0 | - | - |

Although forcing conditions and relatively long times are required to bring about reaction, in contrast to the P-O cleavage reactions of (2R,4S,5R)-3,4-dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine-2-oxide (which occur in a couple of hours at temperatures as low as -30°C), the reaction with the (2R)-**41** occurs with a high degree of stereoselectivity.

In run 7, an unusual side product in up to 5% yield is obtained, Scheme 45, which is a 2-2-adamantyl-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide, although with different configuration to the starting material in the ephedrine backbone. Interestingly, this diastereoisomer is extremely resistant to reaction at phosphorus by 2-methoxyphenylmagnesium halide, being unchanged after several days at reflux with an excess of organomagnesium halide.




Scheme 45

Evidence to support this structure includes a M/S fragmentation pattern very similar to compound **41**, and a *trans* coupling between the protons on C-4 and C-5 on the 5-membered ring.

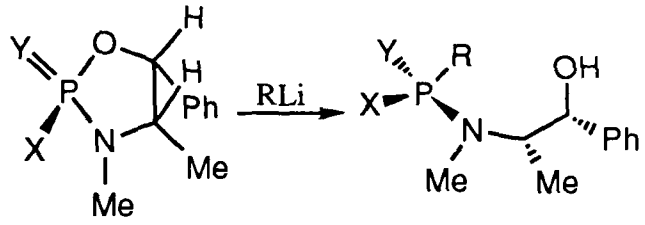
Although lithium reagents had been of little success in previous reactions of 1,3,2-oxazaphospholidinone-2-oxides, they potentially offered an improvement over Grignard reagents in the P-O cleavage reaction. The results of these reactions, summarised in Table 8B indicate that they do not in fact offer any improvement and that Grignard reagents appear to be optimum.

Table 8B. Ring opening reactions with organolithium reagents of both diastereoisomers of compound **41**.

| Run | Isomer | MHal | Solvent | Temp | Yield % | Stereochemistry | % |
|---|---|---|---|---|---|---|---|
| 11 | R | Li | $Et_2O$ | 39 | 25 | $R_P$ | 60 |
| 12 | S | Li | $Et_2O$ | 39 | 44 | $S_P$ | >95 |
| 13 | R | Li.TMEDA | THF | 55 | 0 | - | - |
| 14 | S | Li.TMEDA | THF | 55 | 0 | - | - |
| 15 | R | Li | THF | r.t. | 0 | - | - |
| 16 | S | Li | THF | r.t. | <10 | $S_P$ | 50 |

These results, and those of the Grignard reagents, are stereochemically consistent with the ring opening reactions of phenyl- and 2-methoxyphenyl-1,3,2-oxazaphospholidine-2-oxide in that they occur with retention of configuration. However, in the phenyl and 2-methoxyphenyl examples, both diastereoisomers react with approximately the same degree of stereoselectivity, Table 7, while in the 2-adamantyl reaction, there is a considerable difference in diastereoselectivity. This difference in stereoselectivity, as well as being intuitively expected, has precedence in the work of Inch[103], Table 9.

Table 9. Stereochemical outcome of reaction of both diastereoisomers of (4S,5R)-2,3,4-trimethyl-5-phenyl-1,3,2-oxazaphospholidinone-2-thione with organolithium reagents.




| | Organolithium | | |
|---|---|---|---|
| Precursor | PhLi | n-BuLi | EtLi |
| | Product ratio $R_P$:$S_P$ | | |
| Y=$CH_3$ | 98:2 | 95:5 | 95:5 |
| X=$CH_3$, Y=S | 30:70 | 70:30 | 75:25 |

The two diastereoisomers of N-methyl-N-(1S,2S)-(1-methyl-2-hydroxy-2-phenyl)-ethyl-P(2-methoxyphenyl)-P(2-adamantyl) phosphinamide have very similar $R_f$ values and are thus not easily separated by chromatography. However, fractional crystallisation from ethyl acetate afforded the $S_P$ diastereoisomer as white crystals.

**Spectroscopic analysis and physical characterisations**

Both diastereoisomers possess complex proton and carbon NMR spectra. By comparison with (2S)-**41**, most signals were assignable from 1-D spectra, with selected characteristic signals shown in Table 10. In contrast to ($S_P$) and ($R_P$)-N-(1S,2R)-2-hydroxy-1-methyl-2-phenylethyl-N-methyl-P(2-methoxyphenyl)-P-phenylphosphinamide the proton spectra of the 2 diastereoisomers of compound **44** are very different, possibly due to the considerable difference in steric bulk of 2-adamantyl and 2-methoxyphenyl moieties, compared with the relatively similar size of phenyl and 2-methoxyphenyl.

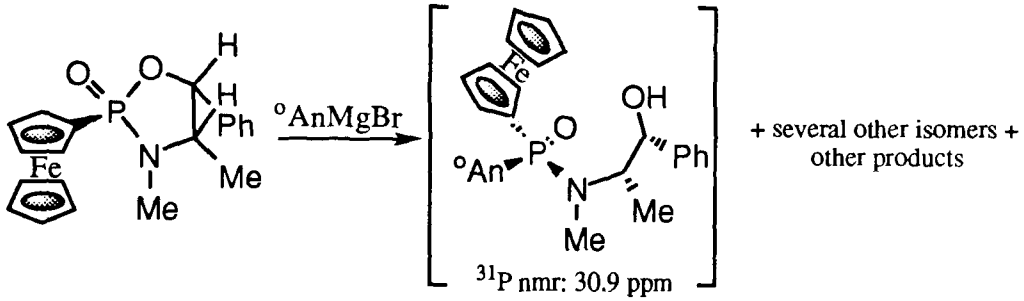
Table 10. Selected $^1H$ NMR data for ($R_P$)-**41**, ($S_P$)-**41**, ($R_P$)-**37**, ($S_P$)-**37**.

| Structure | ($R_P$)-**41** | ($S_P$)-**41** | ($R_P$)-**37** | ($S_P$)-**37** |
|---|---|---|---|---|
| Reference | This work | This work | 91 | 91 |
| $CHCH_3$ δ (ppm) | 1.016 | 0.962 | 1.17 | 1.21 |
| $J_H$ | 7.2 | 7.2 | 7.1 | 7.1 |
| $NCH_3$ δ (ppm) | 2.614 | 2.003 | 2.28 | 2.38 |
| $J_P$ | 8.8 | 9.4 | 10.8 | 10.5 |
| $CHCH_3$ δ (ppm) | 3.536 | 3.756 | 3.77 | 3.70 |
| $J_P$ | 14.4 | 9.6 | 10.5 | 12.0 |
| $J_H$ | 0.0 | 2.4 | 2.9 | 2.9 |
| $J_{OH}$ | 1.7 | 0.0 | 0.0 | 0.0 |
| $J_{CH3}$ | 7.2 | 7.2 | 7.1 | 7.1 |
| CHPh δ (ppm) | 4.882 | 4.463 | 4.8 | 4.8 |
| $J_{OH}$ | 0.0 | 6.3 | 4.9 | 4.9 |
| $J_H$ | 0.0 | 2.4 | 2.9 | 2.9 |

The 2-methoxyphenyl signals were determined by correlation to known systems and are very characteristic of a 2-methoxyphenyl-phosphorus systems.

**Ferrocenyl-1,3,2-oxazaphospholidine-2-oxides**

Reactions of ferrocenylmagnesium bromide with (2R,4S,5R)-2-methoxyphenyl-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine -2-oxide were unsuccessful, despite a wide variety of reaction conditions. However, the 'reverse' reaction of (2R)-**43** with a 2-methoxyphenyl magnesium bromide leads to a variety of products, including a diastereoisomer of the ring opened product, compound **45**, albeit in very low yield, Scheme 46.

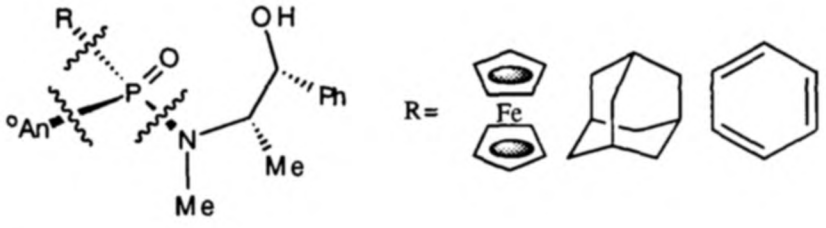



**45**

Scheme 46

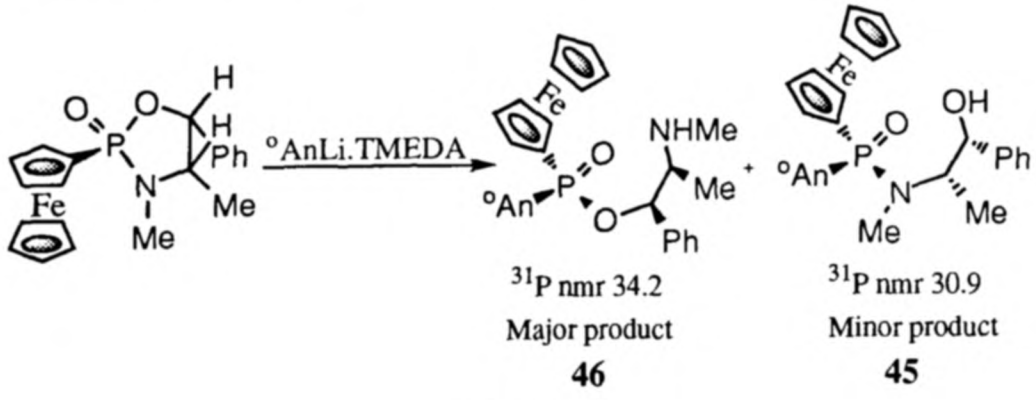
The wide variety of ferrocenyl compounds produced in this reaction may be separated by thin layer chromatography, using ethyl acetate/pentane mixtures as the eluent. Characterisation of the phosphinamide, which is incomplete, is based upon $^{1}$H and $^{31}$P NMR and mass spectrometric evidence. Comparison of fragmentation patterns with 2-adamantyl and phenyl analogues confirm the phosphinamide structure, Table 11.

Table 11. Selected phosphinamide mass spectrometry fragmentation patterns.




| Compound | (Sp)-Fc°An | | (Rp)-2-Ad°An | | (Rp)-Ph°An | |
|---|---|---|---|---|---|---|
| Reference | This work | | This work | | 91 | |
| Conditions | FAB + | | $CI^+(NH_3)$ | | $CI^+(NH_3)$ | |
| | Mass signal, percentage of maximum (%) | | | | | |
| M+1 | 504 | 45% | 454 | 100% | 396 | 100% |
| R | 186 | 18% | 135 | 5% | | - |
| M-R | 318 | 0% | 320 | 3% | | - |
| M-ephedrine | 339 | 100% | 289 | 10% | 231 | 35% |
| M-anisyl | 396 | 20% | 346 | 40% | 288 | 75% |

Due to the low yields of phosphinamide **45**, alternative synthetic methods were sought. Organolithium reagents were used but gave even poorer yields of the desired phosphinamide, although the major product, albeit in low yield, was a P-N cleaved phosphinester **46**, Scheme 47.




$^{31}P$ nmr 34.2
Major product
**46**

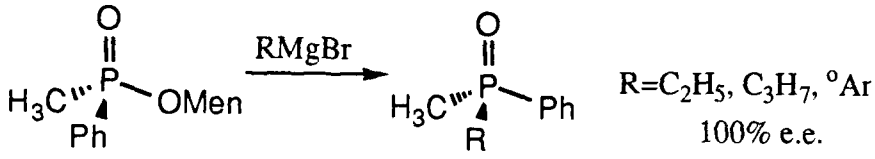
$^{31}P$ nmr 30.9
Minor product
**45**

Scheme 47

Attention was redirected towards 2-adamantyl chemistry as yields of phosphinamide **45** were low and isolation difficult and unsuitable for large scale reactions.

## 2.3 Synthesis of chiral monophosphine oxides

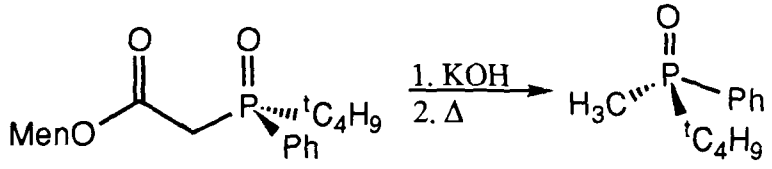
Mislow and co-workers[104] developed Arbuzov methods for the synthesis of homochiral monophosphines using (-)-menthol as a chiral auxiliary, Scheme 48.




Scheme 48

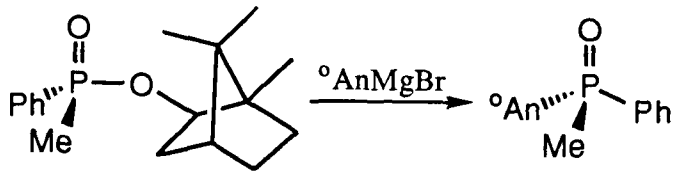
In a similar manner, Knowles and co-workers[105] reacted methyl-menthyl(2-methoxyphenyl)phosphinate with phenyl magnesium chloride to give PAMP, the precursor of DIPAMP.

Imamoto and co-workers[106] synthesised enantiomerically pure alkyl and aryl-(menthoxycarbonyl)-phenylphosphine oxides as intermediates to homochiral phosphine oxides through a decarboxylation reaction, Scheme 49.



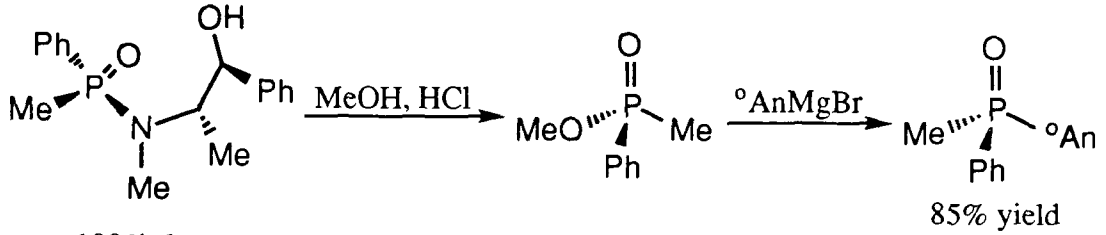

Scheme 49

Schmidt and co-workers[107] used (-)-borneol as a chiral auxiliary in the synthesis of monophosphines. This route was superior to that of Knowles because the desired ($R_P$) phosphinate was obtained in higher yield, Scheme 50.




Scheme 50

Jugé[100] had shown that optimum yields of monophosphine oxides were obtained by the incorporation of an additional step before the final nucleophilic displacement. Acid catalysed methanoylsis of the phosphinamide leads to almost quantitative yields of methylphosphinate, which is then reacted with a Grignard reagent to give a monophosphine oxide in high enantiomeric excess, Scheme 51.




100% d.e.

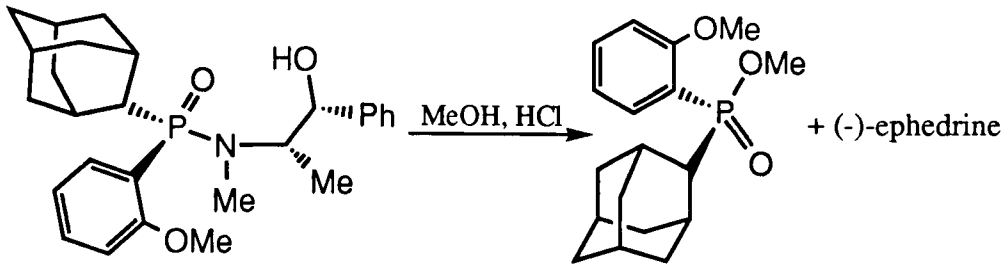
85% yield
95% e.e.

Scheme 51

Brown and co-workers[91] had shown this two step approach to be suitable for a wide variety of phosphinates, and thus this was the method adopted.

**Acid catalysed methanolysis**

Methanolysis of phosphinamide ($R_P$)-**44** required considerably higher temperatures and longer reaction times than the less sterically congested systems of Brown[91]. The reaction, which may be monitored by $^1H$ NMR by using DCl and $CD_3OD$, only proceeds at temperatures at or above 25°C, Scheme 52.




($R_P$)-**44** **47**

Scheme 52

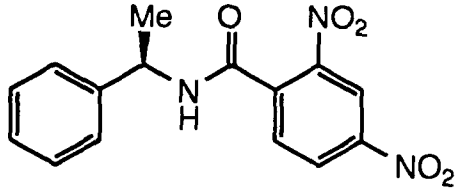
A series of experiments were run in order to determine the optimum conditions for methanoylsis, Table 12. Brown had experienced a small amount of 'leakage' of chirality during anhydrous methanolysis but obtained almost quantitative chemical yields. However, during similar reactions in this study, loss of chirality was a significant problem and yields ranged from poor to moderate. The highest enantiomeric excess was obtained with the lowest temperature (run 3) while higher chemical yields were obtained by heating in concentrated acid (runs 2,5).

Table 12. Optimisation of acid catalysed methanolysis of (2R,4S,5R)-2-2-adamantyl-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide.

| Run | Temp | Volume (MeOH) | [HCl] | Yield (%) | E.E. (%) |
|---|---|---|---|---|---|
| 1 | 63 | 2.5 | 0.25 | 57 | 64 |
| 2 | 45 | 2.5 | 0.25 | 68 | 77 |
| 3 | r.t. | 2.5 | 0.25 | 50 | 88 |
| 4 | 63 | 2.5 | 0.05 | 38 | 49 |
| 5 | 63 | 20 | 0.25 | 69 | 73 |

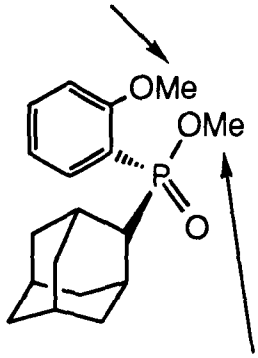
As the yields are poor compared to literature precedents, aqueous hydrochloric acid was used as an alternative to anhydrous acid. However, under these more polar conditions, yields did not improve and thus efforts concentrated on using anhydrous acid.

In order to determine the enantiomeric excess of the product, chiral shift experiments were performed using Kagan's reagent[108], Scheme 53. Baseline separation of methoxy peaks was obtained and thus the enantiomeric excess of the methyl phosphinate was calculated.



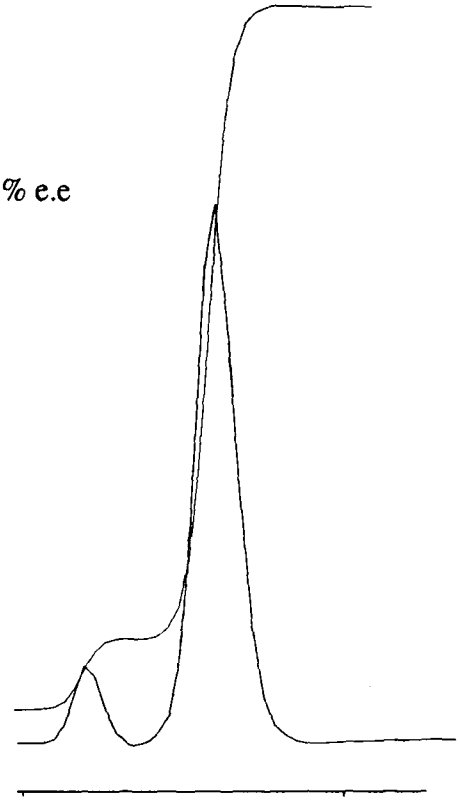

(S)-(+)-N-(3,5-dinitrobenzoyl)-
α-methylbenzylamine

singlet, baseline seperation
at 200 MHz (shown)




doublet, baseline separation
at 500MHz

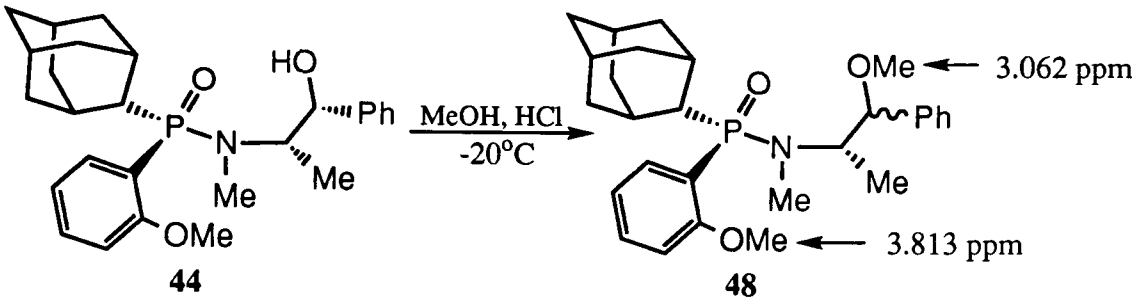
80% e.e



PPM

Scheme 53

Experimentation (Table 12) revealed that the highest optical yields of methyl-2-adamantyl-2-methoxyphenylphosphinate were obtained when low temperatures were used. Therefore, in an attempt to obtain compound **47** in very high enantiomer excess, acid catalysed methanoylsis was run at -20°C, Scheme 54. However, the major product in this reaction was the phosphinamide methoxyalated at the benzylic position, compound **48**.

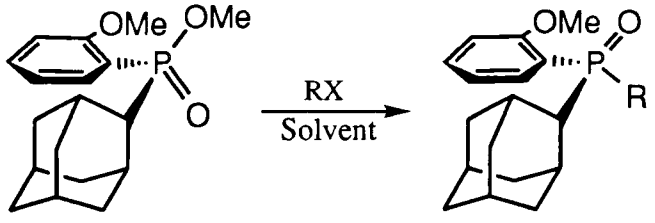



Scheme 54

**Methoxide displacement**

Mislow[104], Knowles[105], Schmidt[107], Suga[109] among others demonstrated that the Grignard reagents are very effective at displacing alkoxy groups. Therefore, a variety of Grignard and other organometallic reagents were reacted with phosphinate **47**, Table 14.

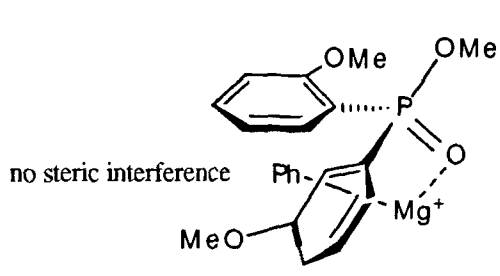
Table 14. Reaction of Grignard reagents with phosphinate **47**.



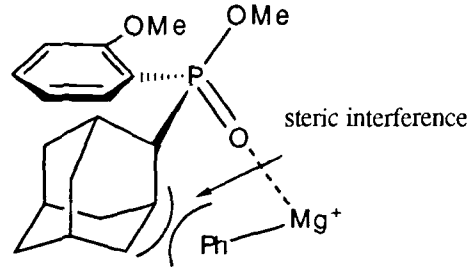

| Run | R | X | Temp (°C) | Solvent | Yield (%) |
|---|---|---|---|---|---|
| 1 | Me | MgCl | 60 | THF | 95 |
| 2 | Me | Al | r.t. | $C_7H_8$/THF | 0 |
| 3 | Me | MgBr | 40 | THF | 57 |
| 4 | Fc | MgCl | 65 | THF | >90[A] |
| 5 | Fc | MgBr | 65 | THF | >90[A] |
| 6 | Ph | MgCl | 65 | THF | 15 |
| 7 | Ph | Li | r.t. | $Et_2O$ | 99 |

A: Product is phosphonic acid rather than phosphine oxide

Reaction times varied from 48 hours (run 7) to 2 weeks (run 6), considerably longer than for less sterically demanding examples. Experiments 6 and 7 are in contrast to the findings of Brown and Carey[91] who found 'organolithium reagents much less effective then organomagnesium reagents in this methoxide displacement step'. The explanation for this behaviour is believed to lie in the differing Lewis acidity of the nucleophiles. The reaction is envisaged as occurring *via* an intermediate in which P=O-Mg co-ordination enhances the electrophilic character of phosphorus. When 2-adamantyl is present, it may sterically block the phenyl group from attacking if the magnesium is bound to the oxide oxygen, Scheme 55.




$S_N2$ displacement possible as phenyl can take up trajectory while magnesium atom activates phosphorus atom towards nucleophilic attack




$S_N2$ displacement not possible as adamantyl moiety prevents phenyl group taking up trajectory with magnesium atom activating phosphorus atom towards nucleophilic attack

Scheme 55

When organolithium reagents are used, the phenyl moiety is not 'tied' to the phosphine oxide oxygen and thus, although the phosphorus atom is not activated, reaction proceeds better than the Grignard case in sterically demanding environments.

Brown had found that displacement of methoxide occurred with negligible loss of enantiomeric purity. However, in the case of run 7 which has the mildest reaction conditions and the highest chemical yield, diarylalkylphosphine oxide of 65% e.e. is obtained if methyl phosphinate of 75% e.e. is used as starting material. (S)-N-(3,5-Dinitrobenzoyl)-α-methylbenzylamine is the chiral shift reagent in this case, although it is H-6 signal of the 2-methoxyphenyl moiety that splits to baseline and allows the enantiomer excess to be measured.

Although very high chemical yields may be obtained, enantiomeric excesses are poor. This loss of chirality supports the 'uncoordinated lithium' mechanism as the nucleophile has more reaction pathways to follow if it is not bound to oxygen. Due to the loss of chirality, mainly in the methanolysis step but also in the methoxide displacement step, a resolution step would be necessary before catalysis, and this would be best performed with trivalent phosphorus.

**Reduction of phosphine oxides**

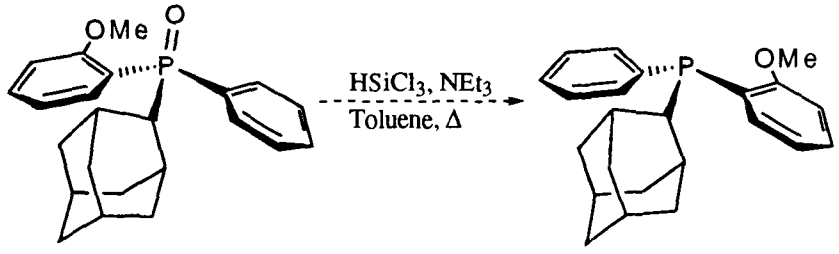
Many proceedures for the stereospecific reduction of phosphine oxides to phosphines have been developed[110,111,112], involving either complete retention or inversion of configuration. Silane based reducing agents are most commonly used, and depending upon the amine used, can produce phosphines with retention of configuration or inversion of configuration, Table 15.

Table 15. Silane reduction systems.

| Silane | Phosphine oxide | Stereochemistry | Reference |
|---|---|---|---|
| $HSiCl_3$ | BzPhMeP=O | Retention(100%) | 110,111 |
| $HSiCl_3$-pyridine | BzPhMeP=O | Retention(50%) | 110,111 |
| $HSiCl_3$-$NEt_3$ | BzPhMeP=O | Inversion(100%) | 110,111 |
| $PhSiH_3$ | BzPhMeP=O | Retention(100%) | 114 |
| $Si_2Cl_6$ | BzPhMeP=O | Inversion(98%) | 111 |
| $HSiCl_3$-$NEt_3$ | $^{o}$AnPhMeP=O | Inversion(97%) | 115 |
| $PhSiH_3$ | MenPhMeP=O | Retention(90%) | 116 |
| $Si_2Cl_6$ | MenPhMeP=O | Inversion(100%) | 115 |
| $HSiCl_3$-$NEt_3$ | MenPhMeP=O | Inversion(80%) | 115 |
| $PhSiH_3$ | *n*-PrPhMeP=O | Retention(100%) | 117 |
| $Si_2Cl_6$ | *n*-PrPhMeP=O | Inversion(100%) | 111 |

Although a high degree of stereoselectivity is usually achieved with these reagents, some loss of chirality is sometimes observed[113,114]. In general, maximum levels of stereospecificity are obtained by the use of low reaction temperatures and very short reaction times, in order to limit racemisation by 'flipping' and exposure to the reducing agent and unreacted phosphine oxide respectively.

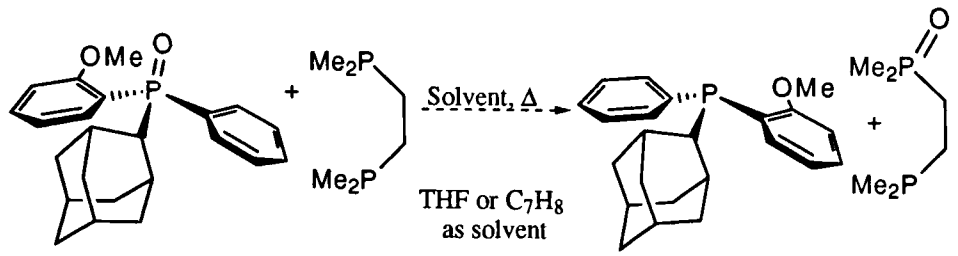
The trichlorosilane-triethylamine method was selected and attempts made to reduce (2-adamantyl)(phenyl)(2-methoxyphenyl) phosphine oxide, Scheme 56.




Scheme 56

However, despite using a ten-fold excess of reducing agent and refluxing in toluene for 17 hours, no reduction occurred. The inertness of 2-adamantyl-phenyl-2-methoxyphenyl phosphine oxide towards reduction is presumably due to steric crowding, and as no reduction had taken place, further experimentation with silane based systems was futile.

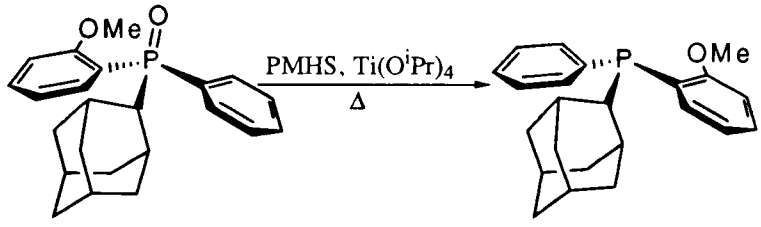
A theoretical limitation of all reduction methods is that oxygen transfer can occur between phosphine oxide and phosphine, resulting in loss of chirality in reactions that occur with inversion. However, it was suggested[115] that this oxygen transfer could be used advantageously if the phosphine oxide was reacted with a more nucleophilic phosphine, Scheme 57.




Scheme 57

However, heating the reaction solution at just below the reflux temperature in a sealed NMR tube for four weeks resulted in no reduction, and thus this method was abandoned.

Lawrence[116] recently published a phosphine oxide reduction method using polymethylhydrosiloxane (PMHS) as reducing agents in the presence of titanium isopropoxide. This method was used and found to successful, Scheme 58.

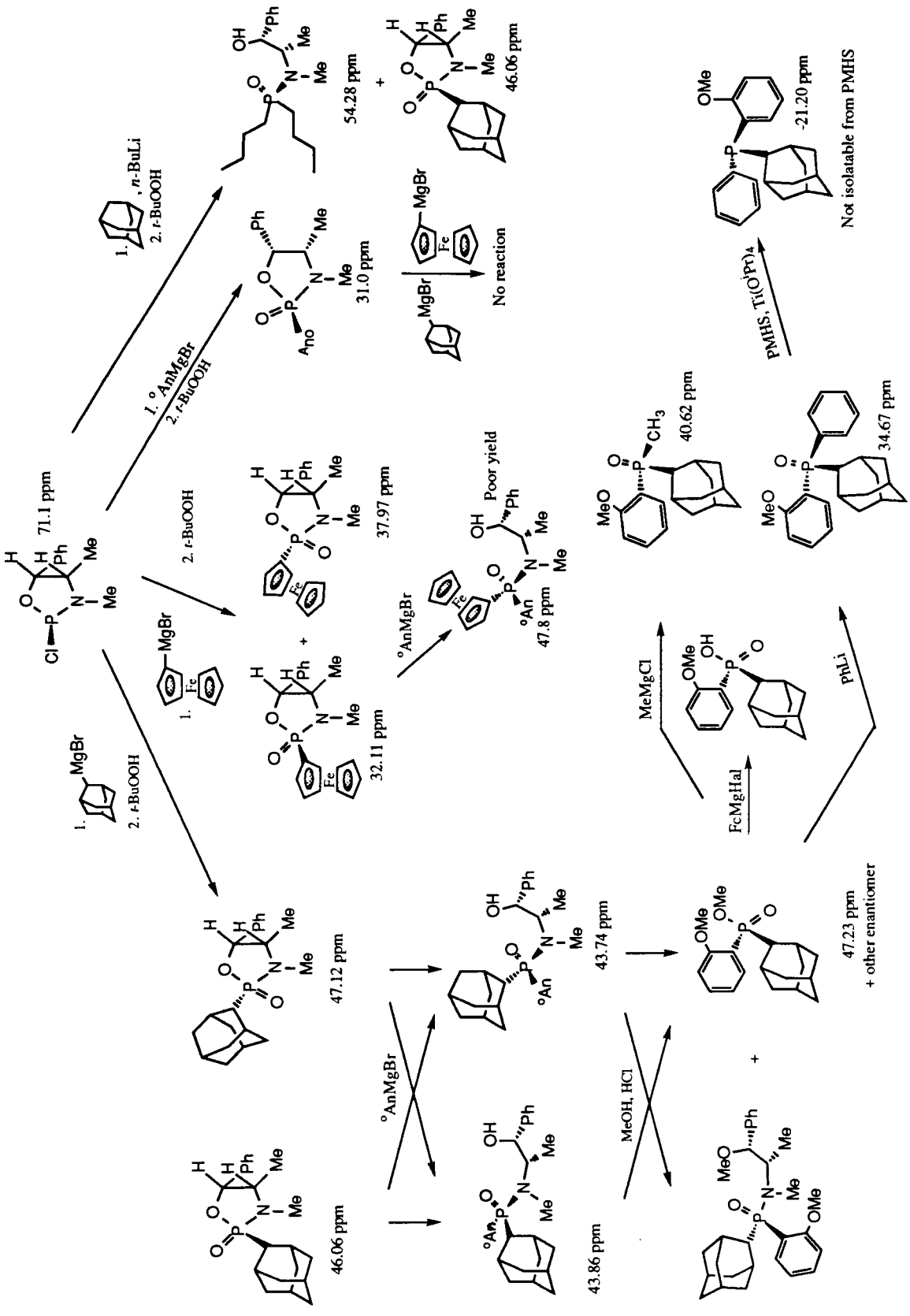



Scheme 58

The addition of titanium isopropoxide to the phosphine oxide in polymethylhydrosiloxane results in bubbles of silane gas being observed. The reaction solution, which was monitored by $^{31}P$ NMR, goes from colourless to a very dark blue, presumably the reduction of titanium$^{IV}$ to titanium$^{II}$. The reaction is judged by $^{31}P$ NMR to be complete after 70 hours.

However, despite successfully reducing the phosphine oxide, isolation from the polymer proved very difficult. Lawrence's formed quarternerly phosphonium salts by reacting the phosphine *in situ* with an alkyl halide, which he then isolated. This method was attempted with benzyl bromide but again it proved impossible to isolate the product from the polymer. Lawrence had also used triethoxysilane and titanium isopropoxide but this system failed to reduce the phosphine oxide, and was thus abandoned.

The principal reactions contained in Chapter 2 are summarised in Scheme 59.


71.1 ppm
1. MgBr
2. t-BuOOH
1. n-BuLi
2. t-BuOOH
1. oAnMgBr
2. t-BuOOH
54.28 ppm
46.06 ppm
31.0 ppm
No reaction
2. t-BuOOH
37.97 ppm
32.11 ppm
oAnMgBr
Poor yield
47.8 ppm
47.12 ppm
46.06 ppm
oAnMgBr
43.74 ppm
43.86 ppm
MeOH, HCl
MeMgCl
FcMgHal
PhLi
40.62 ppm
PMHS, Ti(OiPr)4
-21.20 ppm
Not isolatable from PMHS
34.67 ppm
47.23 ppm
+ other enantiomer

Scheme 59

# Chapter 3

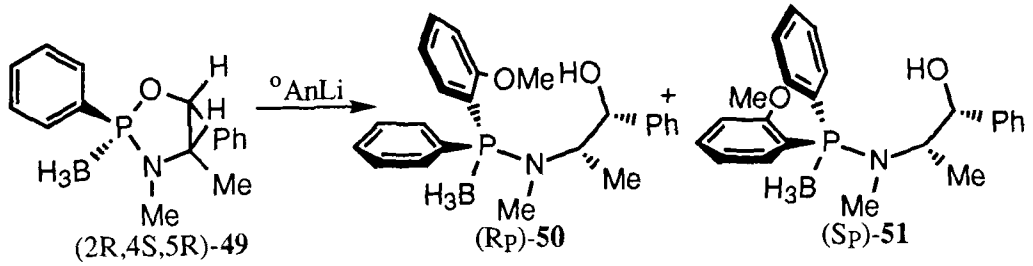
The phosphine borane route to homochiral monophosphines

# Chapter 3. The phosphine borane route to homochiral monophosphines

## Introduction

Chapter 2 demonstrated the generality of the phosphine oxide route and exposed severe limitations, both in terms of chemical and optical yields, for the synthesis of bulky homochiral monophosphines. However, the methodology of three sequential nucleophilic displacements has also been applied to phosphine borane systems, with considerable success with small and medium sized nucleophiles.

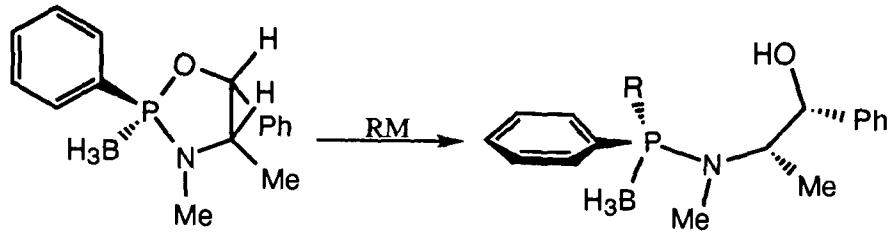
Brown[91], following the precedent of Juge[85], demonstrated that (2R,4S,5R)-phenyl-1,3,2-oxazaphospholidine-borane underwent a P-O cleavage in the presence of 2-methoxyphenylmagnesium bromide to afford a 5:1 mixture of ($R_P$) and ($S_P$) N-methyl-N-(1S,2S)-(1-methyl-2-hydroxy-2-phenyl)-ethyl-P(2-methoxyphenyl)-P-phenylphosphine borane, Scheme 60.




Scheme 60

Shortly after the publication of this result, Jugé[117] improved the selectivity of P-O cleavage by using organolithium reagents, Table 16.

Table 16. Ring openings of (2R,4S,5R)-**49** with RM



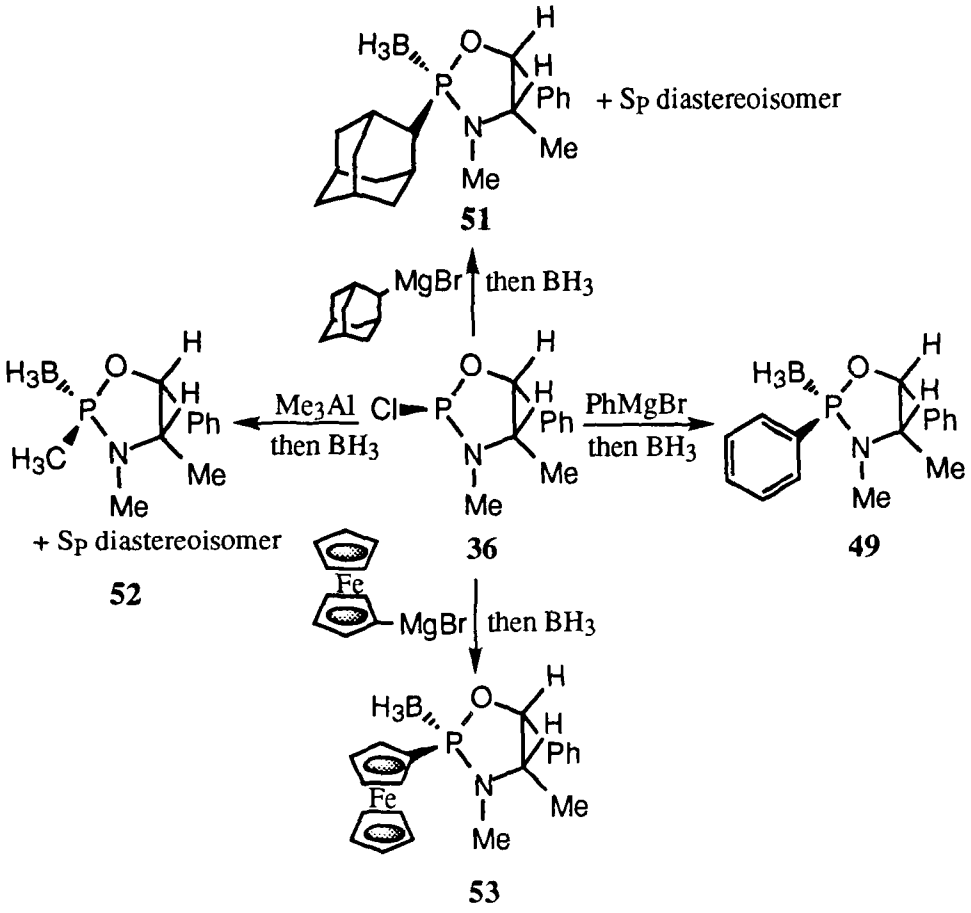

(2R,4S,5R)-**49**

| RM | Yield (%) | (%) |
|---|---|---|
| MeLi | 95 | 100 |
| MeMgI | 90 | 100 |
| *n*-BuLi | 95 | 100 |
| $^{o}$AnLi | 95 | 100 |
| 2-NapLi | 95 | 100 |

In order to see if this route was suitable for the synthesis of sterically bulky monophosphines, a series of oxazaphospholidinone boranes were required and these were synthesised in a similar mannar to the oxazaphospholidinone oxides.

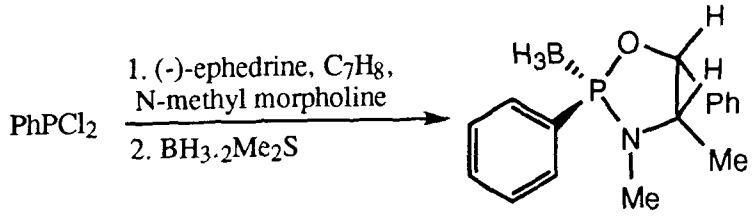
## 3.1 Synthesis of oxazaphospholidinone boranes

Reaction of compound **36** with a variety of organometallic reagents produced a variety of oxazaphospholidine-2-boranes after oxidation with $H_3B.SMe_2$, Scheme 61.




Scheme 61

The reactions producing compounds **51** and **53** were similar to the methods used to produce the oxide series, with $H_3B.SMe_2$ replacing $^tBuOOH$. The phenyl analogue was produced in an analogous method, using PhMgBr as the nucleophile. This compound, which was used in considerable quantities in this work, was also later synthesised directly from dichlorophenylphosphine and (-)-ephedrine, in a modification of the method described by Jugé[117].




Scheme 62

Synthesis of the diastereoisomers of (4S,5R)-2-chloro-2,3,4-trimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-borane **52** was not as straightforward as the other compounds in the series. Reaction of methyl lithium or methyl magnesium chloride with halide **36** provided a wide variety of compounds after boronation, including small amounts of the required compounds and some ring opened material. However, reaction with $Me_3Al$ was very clean with yields in excess of 90% by $^{31}P$ NMR, and a diastereomeric excess of 74%.

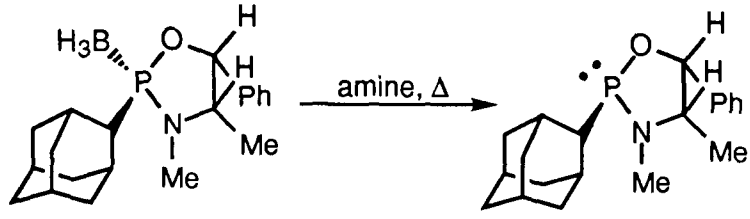
Some of the physical characteristics of the borane complexes differ considerably from their oxide analogues, while other characteristics are remarkably similar, Table 17.

Table 17. Selected characterisations for the $R_P$ diastereoisomers of the 2-adamantyl and ferrocenyl oxazaphospholidinone oxides and borane complexes.

| Compound | ($R_P$)-**41** | ($R_P$)-**51** | ($R_P$)-**43** | ($R_P$)-**53** |
|---|---|---|---|---|
| Physical Properties | | | | |
| Rotation | -70.9° | -17.3° | +81.3° | +22.5° |
| Melting pt. | 190-192°C | 152-154°C | 196-198°C | >230°C |
| NMR | | | | |
| $^{31}P$ (ppm) | 46.06 | 152.80 | 34.11 | 138.05 |
| $CCH_3$ δ(ppm) | 0.705 | 0.799 | 0.845 | 0.767 |
| $J_H$ | 6.7 | 6.6 | 6.5 | 6.5 |
| $NCH_3$ δ (ppm) | 2.830 | 2.712 | 2.575 | 2.550 |
| $J_P$ | 8.8 | 9.7 | 10.3 | 11.9 |
| H-4 δ (ppm) | 3.641 | 3.693 | 3.614 | 3.557 |
| $J_P$ | 0.0 | 0.0 | 11.4 | 0.0 |
| $J_H$ | 6.1 | 5.8 | 6.5 | 6.3 |
| $J_{CH3}$ | 6.6 | 6.6 | 6.4 | 6.5 |
| H-5 δ (ppm) | 5.819 | 5.498 | 5.488 | 5.516 |
| $J_P$ | 0.0 | 0.0 | 6.5 | 4.7 |
| $J_H$ | 6.1 | 5.8 | 6.5 | 6.3 |

## Deboronation of 2R and 2S-2-adamantyl-1,3,2-oxazaphospholidine-2-boranes

Alkyl 1,3,2-oxazaphospholidines have potential as ligands in asymmetric catalysis, and thus the stereoselective deboronation of compound **51** was attempted, Scheme 63. A wide variety of amines were employed as reducing agents and the general procedure followed that described by Imamoto[118].



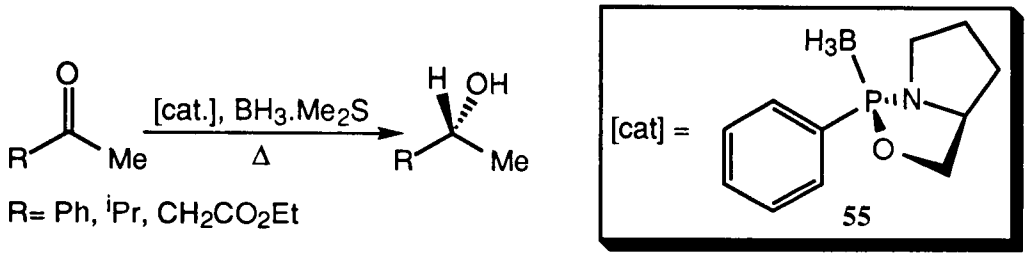

**51** **54**

Scheme 63

The amines employed were DBU, TEA, DMAP, N-methyl morpholine, diethylamine and pyridine, and although all deboronated compound **51** to a certain extent, DBU was found to be optimum. Ring opening occurred when the reaction was performed above 80°C, and thus to minimise reaction times, no solvent was used. Attempts to obtain pure phosphine **54** failed due to its high affinity for oxygen and problems removing the amine in work-up. As phosphine oxide always contaminated the purified product, these reactions were abandoned.

## Alkyl and aryl-1,3,2-oxazaphospholidine-2-boranes as enantioselective reducing agents

Buono[119] has shown that chiral oxazaphospholidine borane complexes may be used as a catalyst in the asymmetric reduction of ketones, Scheme 64.




Scheme 64

Buono demonstrated enantiomeric excesses upto 55% with 8 mol% of phosphine borane complex **55**, while stoichiometric amounts of the reducing agent afforded the alcohol with enantiomeric excesses of 99%.

A series of analogous experiments were performed with compounds **49** and **51** using a variety of ketones, including p-methoxyacetophenone and ethyl acetoacetate. However, despite reaction times of several days, no reduction was observed in stoichiometic experiments and no enantiomeric excess in catalytic experiments.

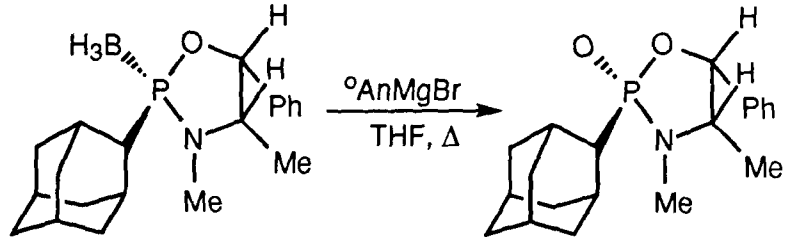
A possible reason for the failure of compound **51** to act as a reducing agent is the steric bulk of the 2-adamantyl moiety, and thus to investigate this, similar experiments were performed with compound **49**. Stoichiometric reactions with acetophenone and *p*-methoxyacetophenone gave no trace of alcohol and thus these reactions were abandoned.

## Diastereoselective ring opening reactions of aryl and alkyl 1,3,2-oxazaphospholidinone-2-boranes

Having synthesised a series of alkyl and aryl oxazaphospholidinones, attempts were made to cleave the P-O bond, in an analogous procedure to the phosphine oxide chemistry.

### (2S,4S,5R)-3,4-Dimethyl-2-adamantyl-5-phenyl-1,3,2-oxaza phospholidinone-2-borane

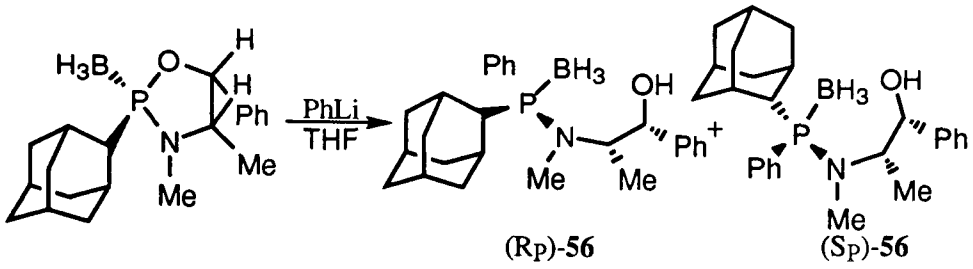
2-Methoxyphenyl magnesium bromide was found to be the optimum reagent in the ring opening of **41**, and thus was selected as the nucleophile for reaction with borane complex **51**. Although a clean reaction occured, the product was phosphine oxide **41** and not the desired ring opened product, Scheme 65. The reaction was not run under oxygen free conditions and thus the solvent is the source of the oxygen, with the Grignard reagent attacking at boron as opposed to phosphorus to first yield the trivalent phosphine.




**51** **41**

Scheme 65

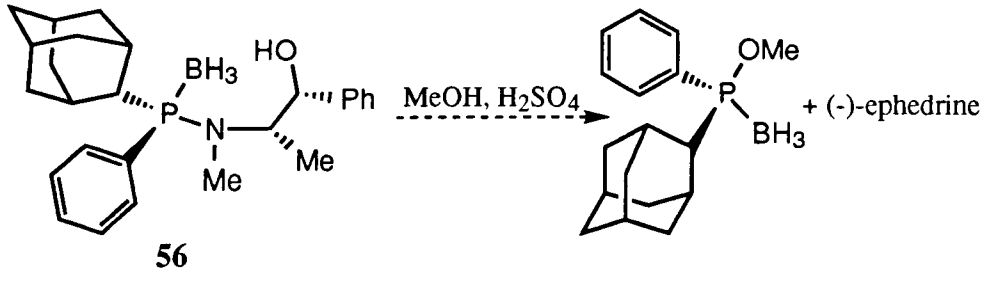
Juge[85] had demonstrated that aryl lithium reagents could be used in the ring opening reaction of compound **49**, and thus a similar reaction was attempted with compound **51**. This reagent attacked at phosphorus to afford the desired product, Scheme 66.




Scheme 66

The ring opened phosphorus borane complex is produced with 51% diastereomeric excess, and although it is unclear which diastereomer is predominating, it is assumed to be $R_P$ from analogy to the phosphine oxide example. These compounds could not be seperated by chromatography due to their similar Rf values, and fractional crystallisation was also unsuccessful.

Before considerable efforts were made to isolate each diastereomer, test reactions were performed to ensure that methanoylsis could be effected. Using the protocol described by Juge, the diastereomeric mixture of compound **56** was dissolved in acidic methanol, Scheme 67. Despite a variety of reaction conditions, no trace of the desired product could be detected and thus no further attempts were made to isolate the starting material as single diastereoisomers.



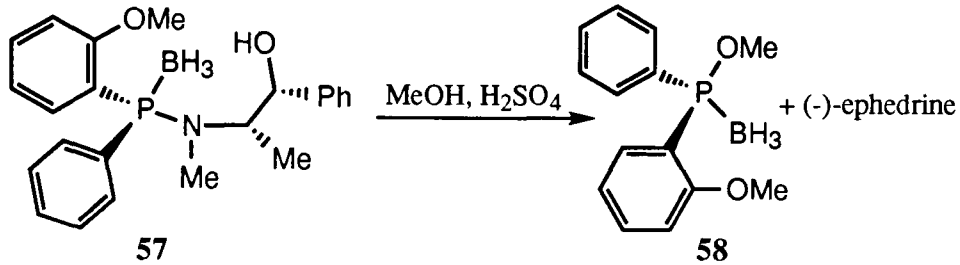

**56**

Scheme 67

As this route failed, the focus was shifted towards ring opening reactions of compound **49**.

**(2S,4S,5R)-3,4-Dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidinone-2-borane**

Juge had demonstrated that compound **57** could be produced in high yield (Scheme 60) and that methanolysis occured smoothly in acidic methanol with negligible loss of enantiomeric excess, Scheme 68.




**57** **58**

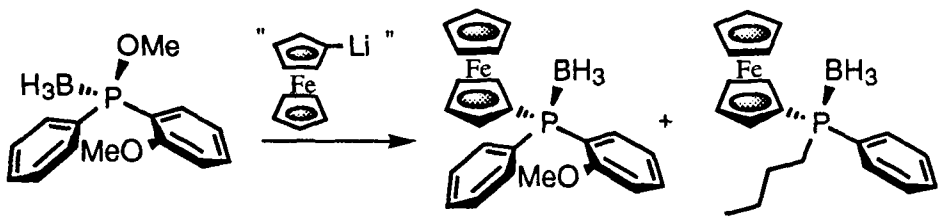
Scheme 68

Small nucleophilic reagents such as methyl lithium were shown to be successful in displacing the methoxide group. Bulky monophosphines could be produced if large moieties, such as ferrocenyl and adamantyl, were incorporated into the molecule.

## 3.2 Synthesis of monophosphine boranes

### Ferrocenyl phosphine borane complexes

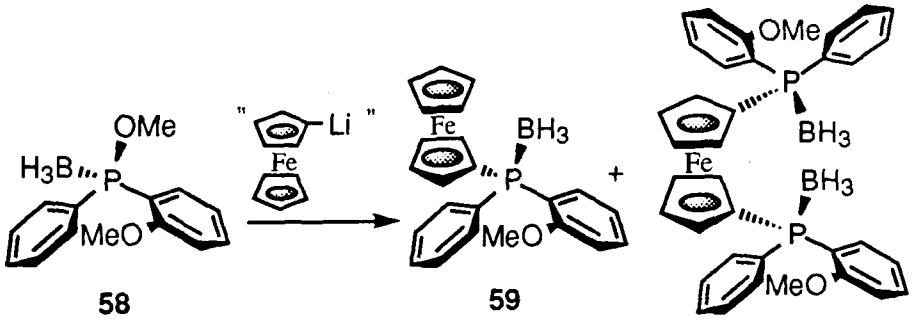
In order to synthesis a ferrocenyl phosphine borane complex, (R)-methyl-(2-methoxyphenyl)-phenylphosphite-P-borane was added to ferrocenyl lithium, synthesised from chloromercuriferrocene (Scheme 39), at -30°C. The reaction mixture, which was warmed to room temperature, contained three phosphorus compounds by $^{31}P$ NMR analysis after 40 hours, one of which was starting material. Isolation by chromotography and then fractional crystalisation resulted in the target material being obtained, with a small amount of a butyl analogue also isolated, Scheme 69.




**58** **59** **60**

Scheme 69

Due to the aforementioned toxicity of organo-mercury compounds, alternative methods for synthesising ferrocenyl lithium were sort. Despite poor results in earlier experiments, ferrocenyl lithium could be synthesised in good yield by the reaction of n-butyl lithium with ferrocene, and then reacted with the borane complex **58** to afford compound **59**, Scheme 70. In addition to the mono-substituted ferrocenylphosphine complex **59**, a small amount of the disubstituted complex was also synthesised and isolated.




**58** **59** **61**

Scheme 70

The structure of these ferrocenyl phosphine borane complexes was determined by NMR and confirmed by mass spectrometry, Table 18.

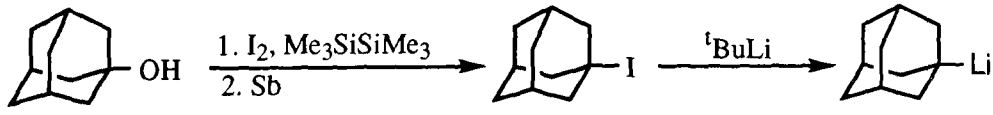
Table 18. Mass spectrometry fragmentation patterns for compounds **59**, **61**, **60**.

| Compound | $Fc^{o}AnPhPBH_3$ | | $F(^{o}AnPPBH_3)_2$ | | $Fc^{n}BuPhPBH_3$ | |
|---|---|---|---|---|---|---|
| Reference | This work | | This work | | This work | |
| Conditions | $EI^+$ | | $EI^+$ | | $EI^+$ | |
| $BH_3$ units (X) | 1 | | 2 | | 1 | |
| | Mass signal, percentage of maximum (%) | | | | | |
| M | 414 | 10% | - | | 364 | 5% |
| $M-(BH_3)_x$ | 400 | 100% | 614 | 30% | 350 | 70% |
| $M-(BH_3)_x$-Ph | 323 | 5% | 537 | 5% | 273 | 5% |
| Fc | 186 | 30% | 186 | 35% | 186 | 15% |

Having synthesised the ferrocenylphosphine borane complex **59**, attention was focused towards incorporating the adamantyl moiety.

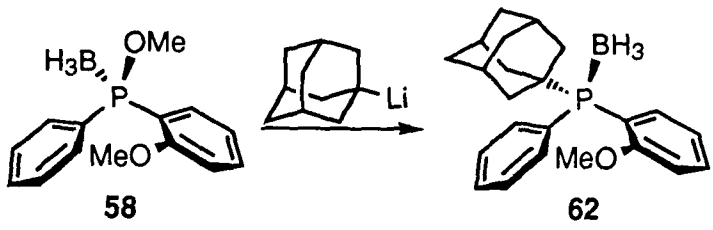
**Alkyl phosphine borane complexes**

West and coworkers[120] detailed a synthesis of 1-adamantyl lithium from 1-iodoadamantane, Scheme 71, which although proved unreliable, was found to give good yields of 1-adamantyl lithium on occasion.




Scheme 71

Reaction of this organolithium reagent with phosphine borane complex **58** resulted in (S)-(1-adamantyl)-(2-methoxyphenyl)-phenylphosphine borane **62** being produced in fair yield, Scheme 72.

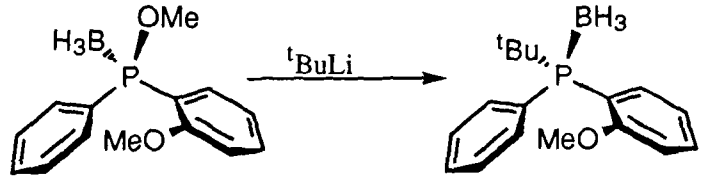



58 62

Scheme 72

Compound **62** was found to be free of any 2-substituted adamantyl compounds by NMR analysis, with the 1-adamantyl moiety having only three reasonances as opposed to the fifteen of the 2-adamantyl group.

As the synthesis of 1-adamantyl lithium was unrelaible and complex, attempts were made to incorporate a tertiary butyl group into the phosphine borane complex, Scheme 73.




58 63

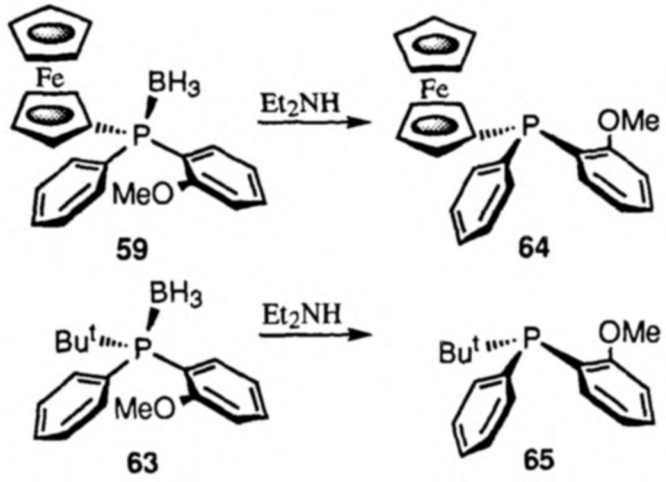
Scheme 73

The reaction proceeded smoothly to give good yields of the alkyl phosphine borane **63**. NMR analysis revealed that the protons on the butyl group coupled to phosphorus, resulting in a doublet being seen.

It was not possible to determine the enantiomeric excess of the phosphine borane complexes directly although they were found to be very high from subsequent experiments on compounds derived from the phosphine borane complexes.

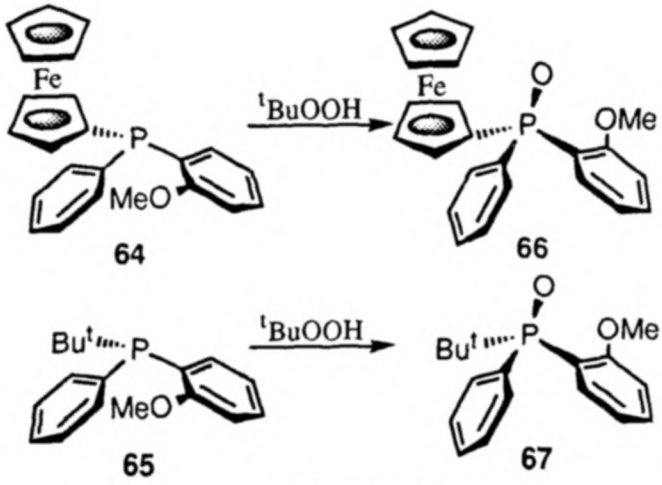
**Deboronation and the determination of enantiomeric excess**

The phosphine borane complexes **59** and **63** were reduced in essentially quantitive yields by heating under argon in diethylamine, Scheme 74.




Scheme 74

Although it is possible to determine the enantiomeric excess of phosphines by forming diastereomeric complexes with metals such as palladium, a simplier procedure was to oxidise the phosphines stereoselectivity and then perform chiral shift experiments with Kagan's reagent[108], Scheme 75. These NMR experiments revealed that phosphine **64** had been produced in at least 92% enantiomeric excess while phosphine **65** had been produced in at least 98% enantiomer excess.




Scheme 75

**Spectroscopic analysis and physical characterisations**

The change of substituent at phosphorus, from a borane group to a lone pair of electrons to an oxide group has a considerable effect on the molecules, Table 19, with the effect of the difference in electronegativilty between oxygen and borane clearly seen.

Table 19. Selected data for ferrocenyl compounds **59**,**64**,**66** and *tert*-butyl compounds **63**,**65**,**67**.

| Compound | **59** | **64** | **66** | **63** | **65** | **67** |
|---|---|---|---|---|---|---|
| Physical properties | | | | | | |
| Melting pt. | 150-152°C | 127-129°C | 163-165°C | 85-87°C | oil | 148-150°C |
| $^{31}$P NMR | | | | | | |
| $^{31}$P (ppm) | 15.02 | -26.40 | 28.20 | 36.74 | 7.60 | 43.40 |
| $^{1}$H NMR | | | | | | |
| $OCH_3$ δ (ppm) | 3.468 | 3.721 | 3.530 | 3.579 | 3.737 | 3.748 |
| $^{o}$An-H6 δ (ppm) | 7.790 | 7.295 | 7.983 | 7.987 | 7.450 | 8.166 |
| $J_P$ | 13.4 | 8.2 | 13.4 | 12.6 | 3.8 | 12.0 |
| $^{o}$An-$H_3$ δ (ppm) | 6.885 | 6.832 | 6.890 | 6.912 | 6.980 | 6.915 |
| $J_P$ | 3.7 | 4.5 | 5.3 | 3.4 | 4.4 | 5.1 |

Having produced two novel monophosphines in high enantiomeric excess, it was expedient to synthesis iridium and rhodium complexes to test the suitability of the ligands in asymmetric catalysis.

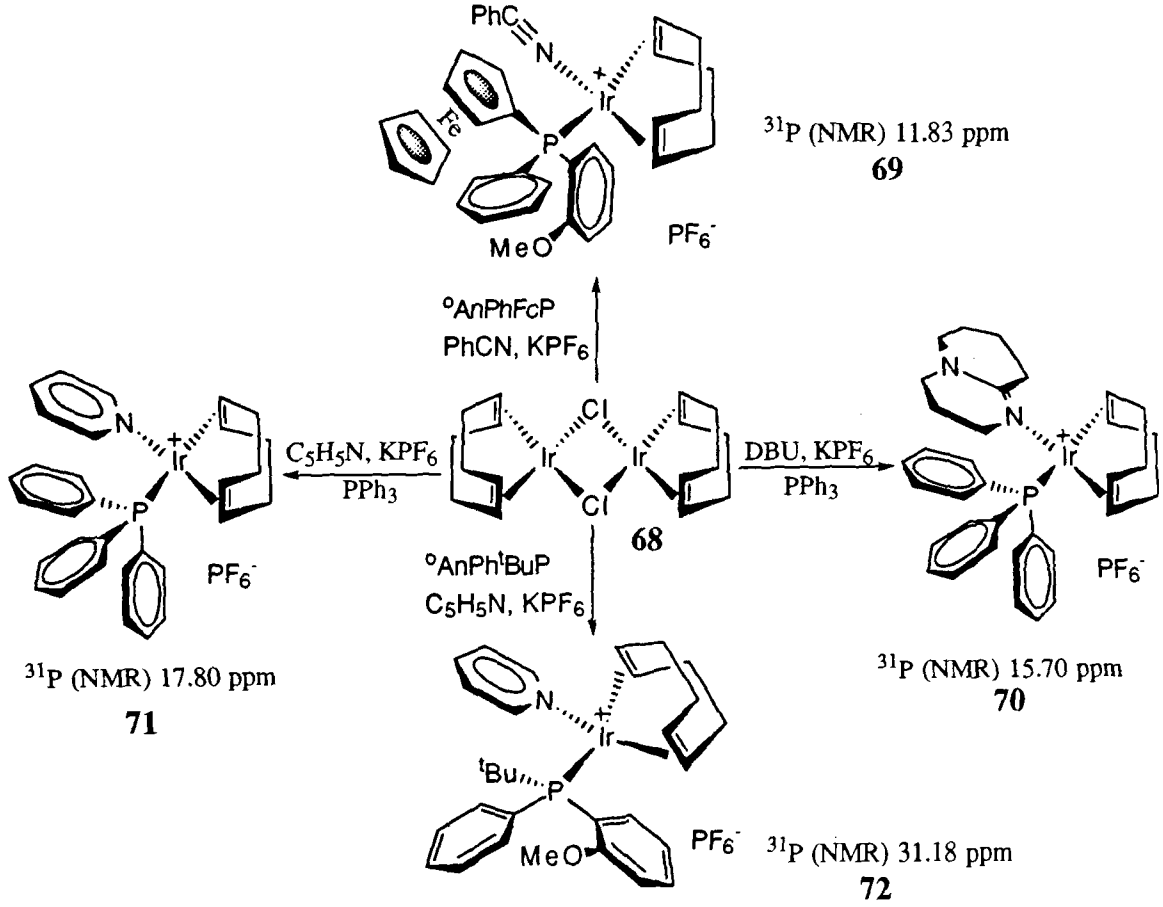
# Chapter 4

The synthesis and reactions of monophosphine iridium and rhodium complexes

# Chapter 4. The synthesis and reactions of monophosphine iridium and rhodium complexes

## 4.1 Iridium complexes

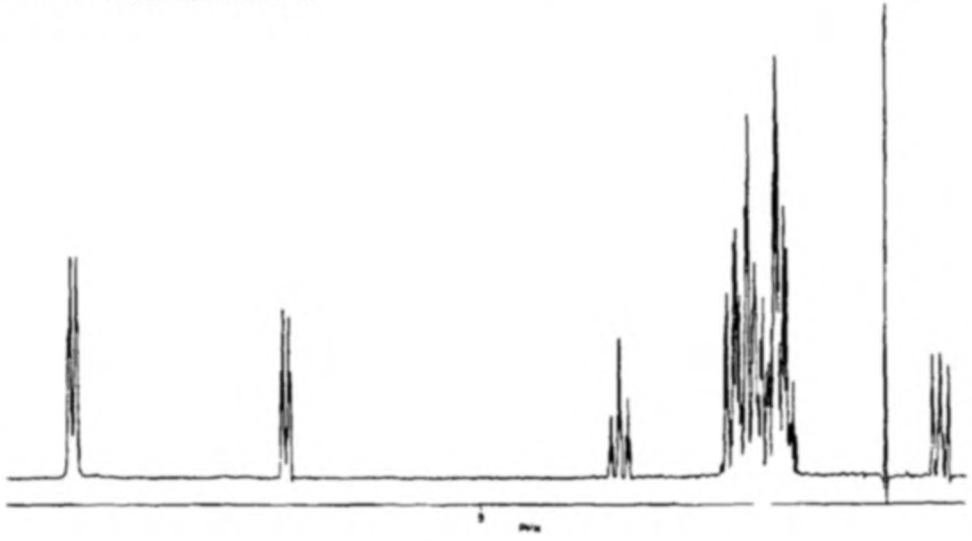
A variety of phosphine iridium complexes (**69** to **72**) were synthesised according to the proceedure of Crabtree[121], as shown in Scheme 76. All the iridium complexes, which are highly coloured and stable in the air at room temperature, were purified by recrystallisation to give good yields of the required complex.




Scheme 76

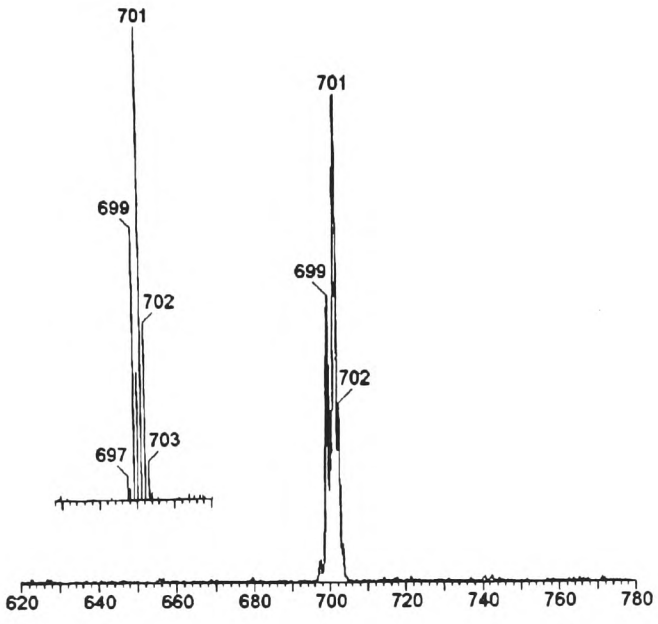
$^1$H NMR spectroscopy did not prove a satisfactory method for the characterisation of these iridium complexes due to the large number of protons and couplings. Some unusual reasonances were

observed, particularly with compound **71**. The five protons on the pyridine molecule gave rise to four signals, with the diastereotopic meta protons in different environments although the ortho protons are isochronous, Scheme 77.



Scheme 77

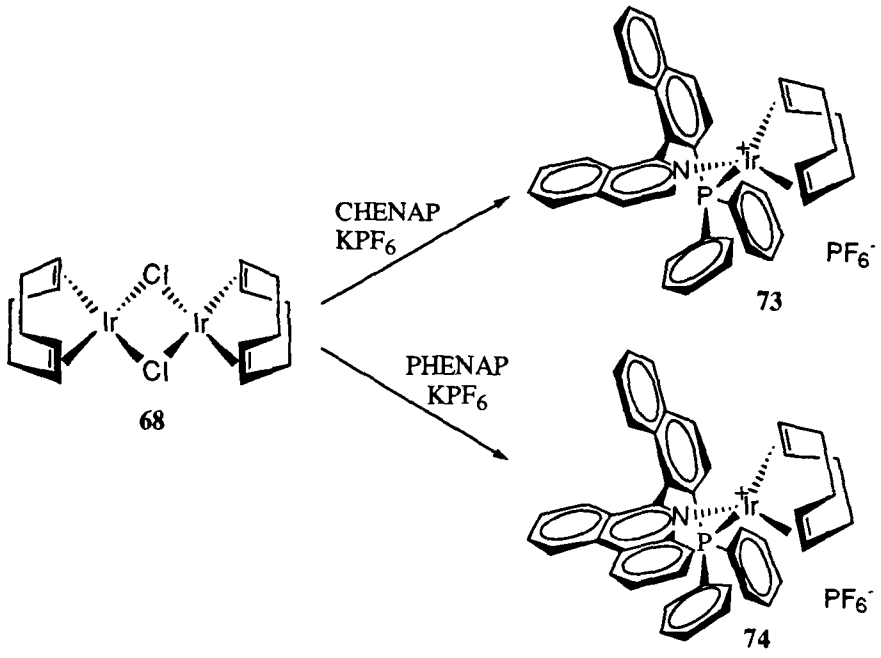
As $^{1}H$ NMR spectroscopy did not prove conclusive in identifying the structure of the phosphine iridium complexes, the isotope patterns generated by electrospray MS were examined, and clearly showed that the compounds formed had the correct empirical formula. For example, Scheme 78 contains the observed and calculated pattern for complex **69**, clearly indicating that the empirical formula of $C_{31}H_{33}OPIrFe$ is correct.




Scheme 78

In this and the other examples, the amine is only weakly bound to the iridium and is cleaved off by the reaction conditions, and thus the base ion peak corresponds to a phosphine-iridium-diene complex.

In addition to the iridium compounds produced in Scheme 76, two chelating monophosphine complexes were also synthesised, Scheme 79. The phosphines[122] iridium complexes were synthesised in a similar manner to Crabtree's procedure, except that it was no longer necessary to add additional amine.



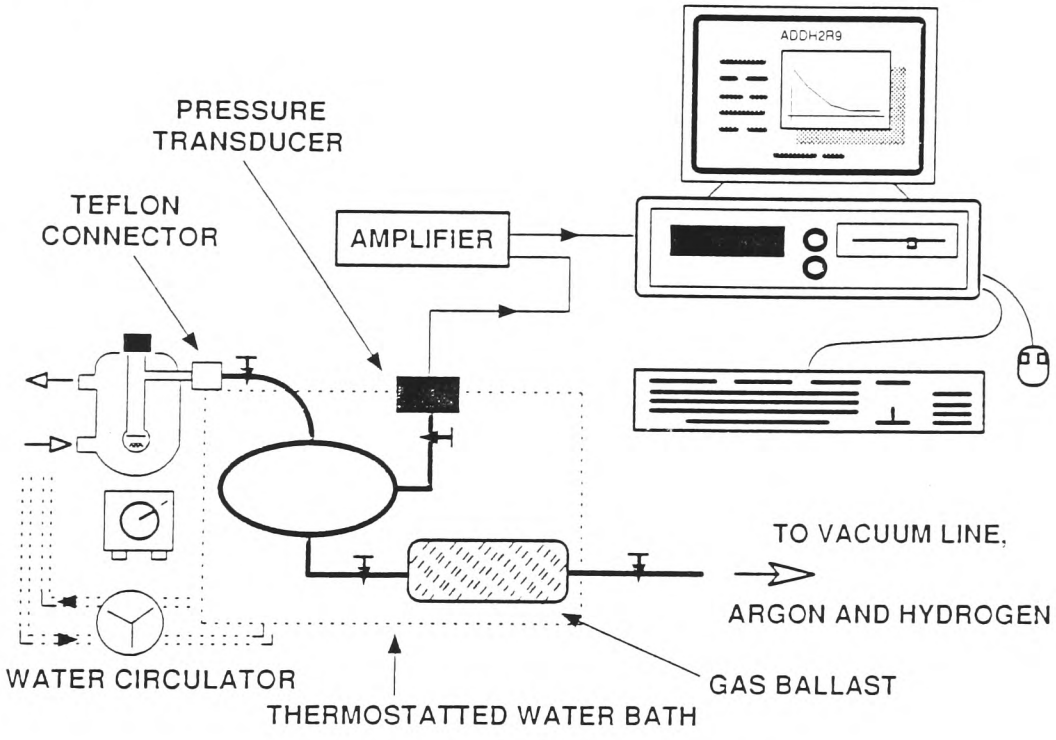

Scheme 79

Unlike the monodentate phosphine complexes (**69** to **72**) where the amine is weakly bound, there is no fragmentation in the electrospray mass spectrometry and the isotope patterns of the complete cationic species were thus recorded.

One of the most successful catalytic asymmetric reactions developed is hydrogenation, although iridium based catalytic systems have produced only modest results. In order to determine the effectiveness of the catalyst precursors synthesised, a series of hydrogenations were carried out.

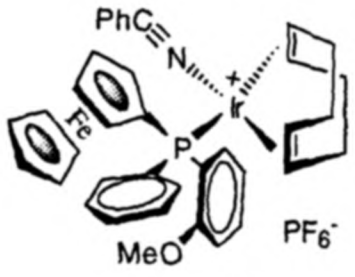
**Catalytic hydrogenation**

A range of olefins were hydrogenated with the iridium monophosphine complexes **69** to **74**. The general procedure involved adding the catalyst precursor to a degassed solution containing the hydrogenation substrate. The reaction mixture was then subjected to five freeze-thaw cycles to remove oxygen from the solution before being brought to the desired temperature and having hydrogen replace the argon atmosphere. The experiments were performed in a constant volume, constant temperature vessel, Scheme 80, with the rate of hydrogenation being calculated from examining the pressure of hydrogen in the vessel.

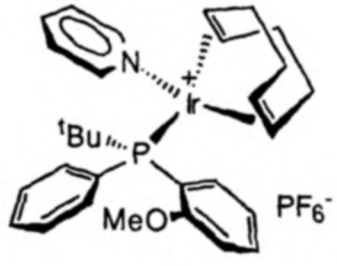



Scheme 80

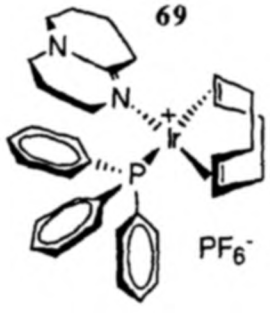
The catalyst percursors used and olefins reduced are shown in Scheme 81, with the results of the hydrogenations in Table 20.




**69**



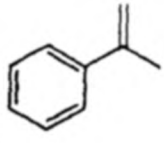

**72**



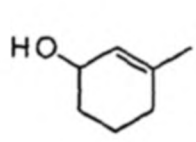

**70**



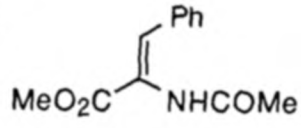

**71**



**75**



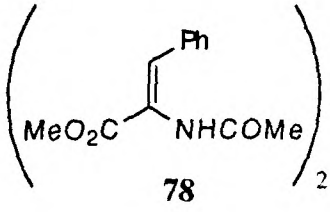

**76**




**77**

Scheme 80

In addition to using the catalyst precursors in Scheme 80, iridium complexes of Bu and Fc were synthesised *in situ* by the the iridium diolefin complex **78** with phosphines **64** and **65**, Scheme 81. Superior results were achieved when the catalytic species was synthesised in this manner.




**78**

$IrBF_4$ —Phosphine→ Phosphine-iridium catalyst

Phosphine = **64** or **65**

Scheme 81

Table 20. Selected results of the reduction of olefins **75**, **76**, **77** using iridium complexes **69**, **70**, **71** and **72**.

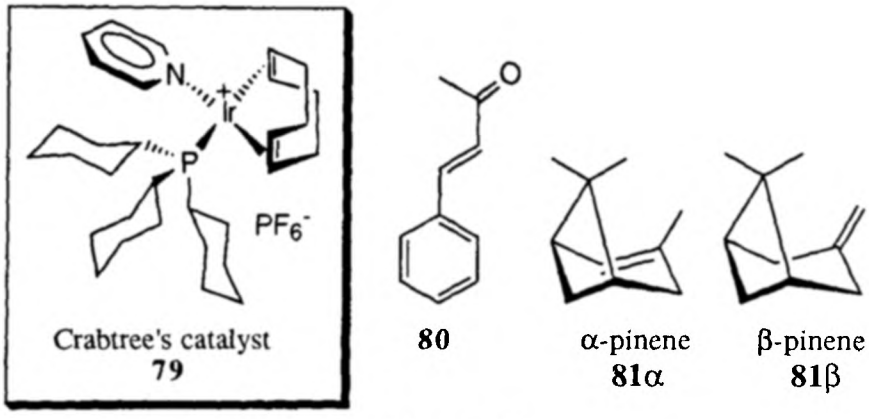
| Run | Catalyst precursor | Olefin | Catalyst mol% | Turn-overs | E.E. % (R/S) | Time[A] (s) |
|---|---|---|---|---|---|---|
| 1 | **71** | **75** | 1 | 100 | - | 500 |
| 2 | **71** | **75** | 0.1 | 106 | - | 1500 |
| 3 | **70** | **75** | 1.5 | 29 | - | 400 |
| 4[B] | **72** | **75** | 1 | 100 | - | 1200 |
| 5 | **71** | **76** | 5 | 0 | - | 1200 |
| 6 | **69**[C] | **77** | 7 | 5 | 16(R) | 1200 |
| 7[D] | **69**[C] | **77** | 10 | 10 | 13(R) | 1200 |
| 8 | **69** | **77** | 2 | trace | 18(R) | 9000 |
| 9[E] | **69**[C] | **77** | 3 | trace | 19(S) | 24 h |
| 10 | **72**[C] | **77** | 5 | 11 | 11(R) | 5000 |

Notes: A: Times given are when the hydrogenations were terminated or when the hydrogenator indicated that reaction had finished, whichever is the shorter;
B. Reaction solution turned black after a few minutes, and thus hydrogenation thought to be hetrogeneous;
C: Catalyst made in situ from iridium diolefin complex and phosphine, Scheme 81;
D: At 50°C;
E: In a Fischer Porter bottle at 66 psi.

As observed from runs 1 to 4, α-methylstyrene is readily reduced by monophosphine iridium complexes. In contrast, alcohol **76** could not be reduced by any of the complexes, and subsequent examination of the enantiomeric excess of the starting material revealed that no kinetic resolution had occured. However, the hydrogenation of olefin **77** did occur enantioselectivity, although sometimes in low yield (runs 8,9). The catalytic iridium species formed in these reactions are only stable for short periods of time, and thus some hetrogeneous hydrogenation also occurs, resulting in the observed enantiomeric excess being lower than actually obtained.

The enantiomeric excesses of the reduction product of olefin **77** experiments were determinded by chiral gas chromatography, using an amino acid column. The enantiomeric excesses measured were consistent to within 1% e.e. when enantiomeric excesses were determined several times, and thus the values given in Table 20 are to a high degree of accuracy.

As the enantiomeric excesses obtained were low, attention was switched to the chelating iridium complexes of QUINAP **73** and PHENAP **74**. A similar set of hydrogenations were also performed with Crabtree's catalyst in order to determine if the chelating structure provided superior results. The reaction protocol used was similar to that previously described, and the substrates hydrogenated, in addition to methyl styrene **82**, are as shown in Scheme 82.




Crabtree's catalyst **79** | **80** | α-pinene **81α** | β-pinene **81β**

Scheme 82

Table 21 contains selected hydrogenation results, performed in dichloroethane at 25°C and under 1.6 atmospheres of hydrogen, for these iridium complexes.

| Run | Catalyst precursor | Olefin | Catalyst mol % | Turn-overs | E.E. % | Time (S) |
|---|---|---|---|---|---|---|
| 1 | (*rac*)-**73** | **82** | 1 | 100 | - | 1000 |
| 2 | **79** | **82** | 1 | 45 | - | 200 |
| 3 | (S)-**74** | **82** | 3 | 0 | - | 2000 |
| 4[A] | (*rac*)-**73** | **82** | 0.2 | 500 | - | 6000 |
| 5 | **79** | **82** | 0.2 | 120 | - | 800 |
| 6 | (*rac*)-**73** | **82** | 0.1 | 560 | - | 15000 |
| 7 | **79** | **82** | 0.1 | 630 | - | 10000 |
| 8[A] | (*rac*)-**73** | **81β** | 0.05 | 2000 | - | 6000 |
| 9 | (*rac*)-**73** | **81α** | 2 | 50 | - | 1500 |
| 10 | **79** | **81α** | 2 | 50 | - | 400 |
| 11 | (*rac*)-**73** | **76** | 2 | 0 | - | 2000 |
| 12 | (*rac*)-**73** | **77** | 2 | 0 | - | 2000 |
| 13[C] | (S)-**73** | **77** | 5 | 0 | - | 2000 |
| 14 | (*rac*)-**73** | **80** | 1 | 0 | - | 5000 |
| 15 | **79** | **80** | 1 | 0 | - | 5000 |

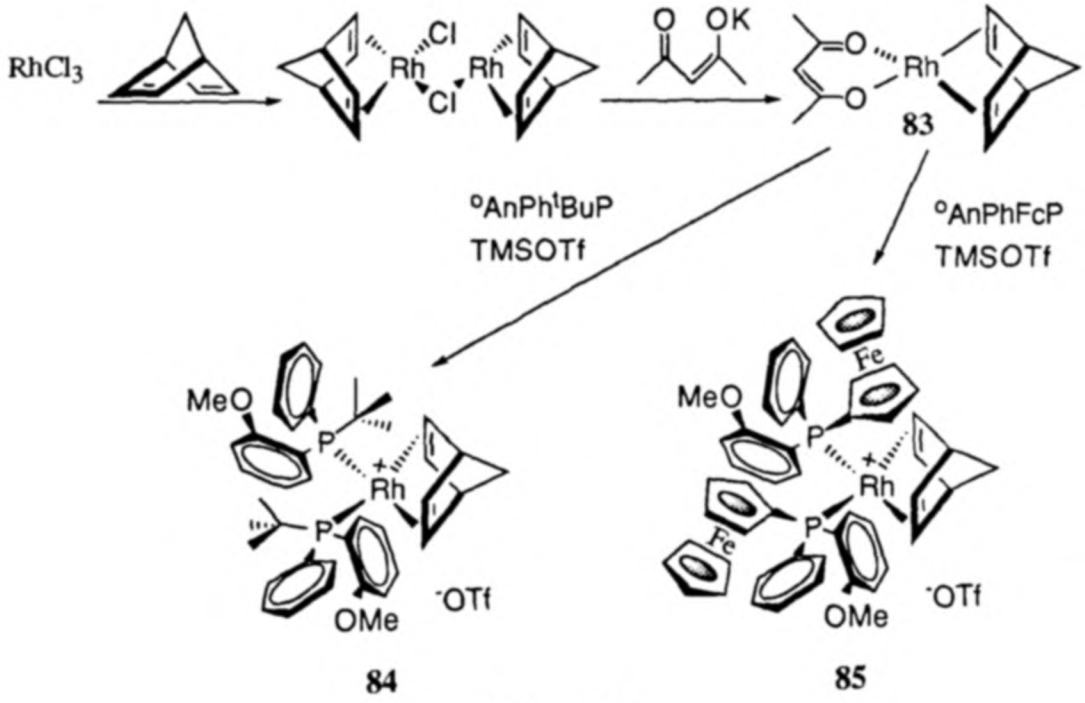
Notes: A. Dichloromethane used as solvent;
B: No kinetic resolution observed;
C: Catalyst made *in situ*, using the same procedure as Scheme 81;

α-Methylstyrene was rapidly reduced by complex **73** and complex **79** but not by complex **74**. Although Crabtree's catalyst turned over faster than complex **73**, it often failed to completely reduce the olefin (runs 1,3,5) while complex **73** completely reduced the olefin (runs 2,4). Complex **73** also completely reduced β-pinene (run 8) and the more sterically hindered α-pinene (run 9), although Crabtree's catalyst was again faster (run 10). In an attempted kinetic resolution of racemic α-pinene, no enantiomeric excess was detected in the starting material. Neither complex **73** or Crabtree's catalyst could reduce the prochiral olefins **76**, **77** or **80** (runs 11-15).

As only very modest enantiomeric excesses could be obtained using monodentate iridium complexes and the bidentate complexes performed poorly, attention was focused on the monodentate rhodium complexes.

## 4.2 Rhodium complexes

Phosphine rhodium complexes may be synthesised in a three step procedure from rhodium chloride, as described by Brown[123]. A norbornadiene rhodium chloride dimer is first prepared and isolated before reaction with potassium acetylacetonate to yield a stable yellow complex. Subsequent reaction of complex **83** with phosphine **64** and phosphine **65** resulted in the monophosphine rhodium complexes **84** and **85** being formed, Scheme 83.




Scheme 83

Complex **85** was obtained as dark red crystals and $^{31}P$ NMR analysis revealed a single doublet at 19.85 ppm ($J_{Rh}$ = 162 Hz) while complex **84** was obtained as a red oily solid with a single doublet at 42.2 ppm ($J_{Rh}$ = 166 Hz) in the $^{31}P$ NMR sprectra. As complex **84** did

not provide satisfactory mass spectrometric analysis, there is some uncertainty regarding its structure and thus its synthesis is not included in the experimental section.

Having formed two rhodium phosphine complexes, experiments were performed to determine their suitability as hydrogenation catalysts.

### 4.3 Catalytic hydrogenation

In a similar procedure to that identified above for iridium catalysis, olefin **77** was hydrogenated in methanol at 25°C under 1.6 atmospheres. The results of these hydrogenation are detailed in Table 22.

Table 22. Rhodium catalysed hydrogenations of olefin **77** (MAC).

| Run | Catalyst precursor | Catalyst mol% | Turnovers | E.E. % (R/S) | Time (H) |
|---|---|---|---|---|---|
| 1 | **84**[A] | 2.5 | 8 | 24 (R) | 24 |
| 2 | **85** | 4 | 25 | 42 (S) | 24 |
| 3 | **85**[A] | 5 | 20 | 54 (S) | 24 |

Notes: A. Catalyst made *in situ* by the reaction of 2 equivalents of phosphine with $(COD)_2RhOTf$

Catalysts produced in situ (runs 1,3) produced superior results to those made from preformed rhodium phosphine complexes (run 2), although complex **84** was not used due to handling difficulties. Although the enantiomeric excesses obtained were superior to those generated by the corresponding iridium complexes, they are still considerably below those obtained with many bisphosphines and PAMP.

# Chapter 5

Experimental

# EXPERIMENTAL

## 5.1 General Experimental Techniques

### 5.1.1 Instrumental

*Elemental microanalyses* were carried out by Mrs V. Lamburn in the Dyson Perrins Laboratory, using a Carlo Erba 1106 elemental analyser.

*NMR spectra:* $^{1}H$ NMR spectra were recorded on a Varian Gemini 200 (200 MHz), a Bruker AC 200 (200 MHz), a Bruker AM 250 (250 MHz), a Bruker WH 300 (300 MHz) or a Bruker AM 500 (500 MHz) spectrometer and are referenced to the residual solvent peak [$CHCl_3$ : δ 7.27; $CH_2Cl_2$ : δ 5.32; $C\underline{H}_3OH$ : δ 3.31; $(CH_3)_2CO$ : δ 2.05]. NOESY and COSY experiments were carried out by Mrs E. McGuinness and Dr. T. Claridge using a Bruker AMX 500 (500 MHz) spectrometer. $^{13}C$ NMR spectra were recorded on a Varian Gemini 200 (50.33 MHz), a Bruker AM 250 (62.83 MHz) and a Bruker AMX 500 (125.8 MHz) spectrometer and are referenced to the residual solvent peaks [$CDCl_3$ : δ 77.0; $CD_2Cl_2$ : δ 53.8; $CD_3OD$ : δ 49.0; $(\underline{C}D_3)_2CO$ : δ 29.8]. Where appropriate, multiplicities were determined using a DEPT (Distortionless Experiment by Polarisation Transfer) pulse sequence. $^{31}P$ NMR spectra were recorded on a Bruker AM 250 (101.23 MHz) spectrometer and are referenced externally to 85% phosphoric acid ($\delta_P$ = 0.0); $^{1}H\{^{31}P\}$ NMR spectra were recorded on a Bruker AMX 500 (500 MHz) spectrometer with a home-built heteronuclear decoupler trolley, using selective continuous wave phosphorus irradiation. These spectra were acquired on $^{1}H$ decoupler coils of a selective $^{31}P$ probe with the usual observation coil acting as the decoupler coil. $^{11}B$ NMR spectra were recorded on a Bruker AM 250 (80.2 MHz) spectrometer and are referenced externally to $BF_3.Et_2O$ ($\delta_{11B}$ = 0.0). Abbreviations used in the description of spectra are: δ

= chemical shift in parts per million, J = coupling constant in Hz, s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, dd = double doublet, ddd = doublet of double doublets, ddt = doublet of double triplets, dq = double quartet, m = multiplet, br = broad.

*Infra red spectra* were recorded on a Perkin Elmer 1750 Fourier Transform spectrometer. Samples were prepared on NaCl plates as nujol mulls, thin films or in KBr discs. Abbreviations used in the description of spectra are: w = weak, m = medium, s = strong, vs = very strong, br = broad, vbr = very broad.

*Mass spectra* were recorded by Mr R. Proctor on an Arain MAT CH7, VG Mircomass 16F or ZAB-1H 16F spectrometer. Electrospray and fast atom bombardment mass spectra were measured by Dr. R. T. Aplin on either a VG BIO Q Platform single quadrupole mass spectrometer or, a VG BIO Q triple quadrupole atmospheric pressure mass spectrometer equipped with a VG electrospray interface. Samples (10 µl) were injected into the electrospray source *via* a loop injector (Rheodyne 5717) as a solution, 40 pmol/µl, in water/acetonitrile (1:1) at a flow rate of 5µl/minute (Applied Biosystems model 140A dual syringe pump). Values are followed, in parentheses, by the intensity as a percentage of the base peak.

*Optical rotations*: all optical rotations were recorded on a thermostatted Perkin Elmer 241 polarimeter, using the 589.3 nmm D-line of sodium. Samples were prepared under argon as solutions in HPLC grade $CHCl_3$, $CH_2Cl_2$ and MeOH.

*Melting points* were recorded on a Reichert-Koffler block and are uncorrected.

*Chiral capillary gas chromatography* was carried out on a Fisons 8000 series machine, equipped with a Flame Ionisation Detector (FID) and a Hewlett Packard Intergrator, using a 25m permethylated β-cyclodexrerin in a BP10 stationary phase (Cydex-B$^{TM}$) column and a 50m XE-60-S-Val -S-A-PEA column. Retention times were quoted as $t_x$ where $t_x = t_{observed} - t_{solvent}$.

### 5.1.2 Experimental Procedures

All manipulations of oxygen and water sensitive materials were carried out under a dry argon atmosphere, using standard vacuum line and Schlenk techniques.[124] Solvents were deoxygenated by repeated freeze-thaw cycles, in which the solvent was frozen in liquid nitrogen, allowed to warm *in vacuo* and flushed with argon. Solid reagents were degassed as necessary by evacuation and flushing with argon at room temperature. Transfers and filtrations were carried out using stainless steel cannula wire.

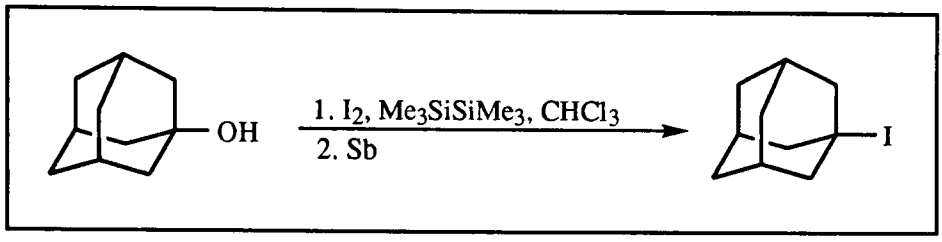
Solvents were purchased from Rhône-Poulenc Rorer, Fisons, Rathburns or the Aldrich Chemical Co., and were dried prior to use according to the procedures described by Perrin and Armarego.[125] All reagents were purchased from the Aldrich Chemical Co., Rose Chemicals, Sigma, Fluka or Lancaster. Precious metal salts were on loan from Johnson-Matthey.

Analytical thin layer chromatography (tlc) was performed on Merck plastic-backed plates precoated with 0.2 mm silica 60 $F_{254}$. Column chromatography was performed on Merck silica gel 60H, 230-300 mesh using the flash chromatographic method of Still. Preparative tlc was performed on glass plates coated with silica gel $HF_{254}$.

Z-methyl-2-acetylamino-3-phenylpropenoate and bis(1,5-cyclooctadiene) rhodium trifluoromethanesulphonate were a gift from Ms. U. Sharma.

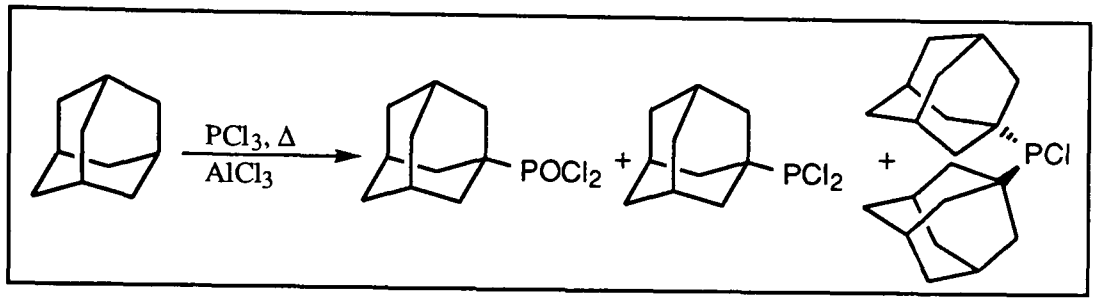
## 5.2 Phosphine synthesis

1-Iodoadamantane




Following the procedure of West *et al* (120), a solution of 1-adamantol (6.09 g, 40.0 mmol) in chloroform (30ml) and a solution of hexamethylsilane (8.44 ml, 41.2 mmol) in chloroform (15 ml) were slowly dripped onto a stirred chloroform solution of iodine (19.4 g, 76.4 mmol, 30 ml of chloroform) over a period of 1 h. After stirring for a further 5 h, antimony powder (8.74 g, 71.6 mmol) was added to the purple solution and the resulting suspension stirred overnight. A large amount of red-orange precipatate of antimony iodide was produced and this was removed by filtration of the suspension through a 2 inch bed of silica yielding a pale green solution. The precipitate was washed with chloroform (2 x 30 ml), the organic fractions combined and the solvent removed *in vacuo* yielding a pale red solid. This material was recrystalized from hot methanol to yield 1-iodoadamantane (8.73 g, 83%, 33.3 mmol) as white crystals, m.p. 77-79°C (lit 76-78°C). $\delta_H$ (200 MHz, $CDCl_3$) 2.64 (6H, d, J = 2.3, $ClCH_2$), 1.96 (3H, br, CH), 1.82 (6H, br, $CH_2$); $\delta_C$ (50.3 MHz, $CDCl_3$) 52.44 ($C_2$), 51.22 ($C_1$), 35.58 ($C_4$), 33.07 ($C_3$). $\upsilon_{max}$ (KBr) 2849 (s, C-H), 2672, 1451 (m, C-H), 1340, 1310, 1288, 1258, 1100, 1023, 942, 667 (s, C-I).

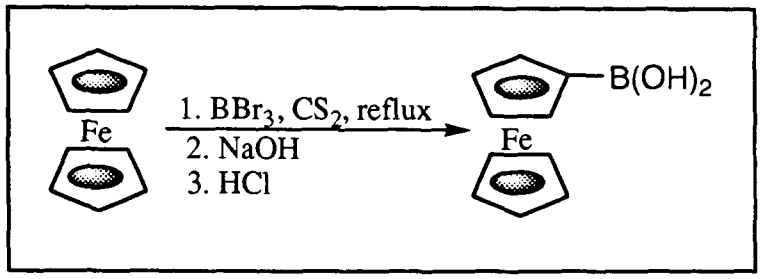
Synthesis of 1-adamantylphosphonic dichloride, dichloro-di-(1-adamantyl)phosphine and di-(1-adamantyl)phosphonic chloride




[126]

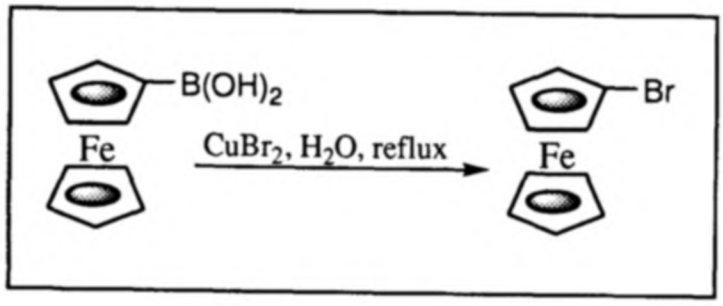
Following the method of Olah, phosphorus dichloride (0.96 ml) was slowly added to a suspension of adamantane (1.36 g, 10 mmol) and aluminium chloride (1.72 g, 13 mmol) in dichloromethane (25 ml) at 0°C. The mixture was then heated at reflux for 23 h before being cooled to rt. Hydrochloric acid (20 ml, 10%) was slowly added and the solution stirred for 30 min. The organics were then extracted with dichloromethane (3 x 10 ml), dried ($MgSO_4$) and solvent removed to give a mixture of 1-adamantylphosphonic dichloride, dichloro-(1-adamantyl)phosphine and di-(1-adamantyl)phosphonic chloride in a ratio of 1 : 2 : 8. Attempts to isolate these compounds were only partially successful by chromotography (flash silica, ethyl acetate / hexane : 9 /1) and only unreacted adamantane was obtained by distillation. Dichloro-(1-adamantyl)phosphine: $\delta_P$ (101.3 MHz, $CDCl_3$) 191.7; *m/z* ($CI^+$, $NH_3^+$) 237 ($M(^{35}Cl_2)$, 30%), 239 ($M(^{35}Cl, ^{37}Cl)$, 20), 241 ($M(^{37}Cl_2)$, 5), 152 (15) and 135 (Ad, 100); 1-Adamantylphosphonic dichloride: $\delta_P$ (101.3 MHz, $CDCl_3$) 64.9; *m/z* ($CI^+$, $NH_3^+$) 269 ($M(^{35}Cl_2)$, 55%), 271 ($M(^{35}Cl, ^{37}Cl)$, 30), 273 ($M(^{37}Cl_2)$, 5), 152 (15) amd 135 (Ad, 100); Di-(1-adamantyl)phosphonic chloride: $\delta_P$ (101.3 MHz, $CDCl_3$) 85.8; *m/z* ($CI^+$, $NH_3^+$) 352 ($M(^{35}Cl_2)$, 40%), 354 ($M(^{35}Cl, ^{37}Cl)$, 15), 152 (15) and 135 (Ad, 100).

## Ferrocenyl boronic acid




Following the procedure of Epton *et al*[127], boron tribromide (9.43 ml, 100 mmol) and ferrocene (15.5 g, 83 mmol) were added to carbon disulphide (125 ml) and heated under reflux for 24 h. After cooling to 0°C, the reaction mixture was filtered into 2M aqueous sodium hydroxide (175 ml). The basic solution was then extracted with diethyl ether (3 x 100 ml), filtered and cooled to 0°C. The aqueous solution was then acidified with 2M hydrochloric acid and a yellow precipatate was deposited. The precipatate was collected by filtration, washed with water (50 ml) and dried under vacuum to give ferrocenyl boronic acid (8.04 g, 42%) as a yellow solid m.p. 151-153°C (lit 143-148°C). $\delta_H$ (200 MHz, $CD_3COCD_3$) 4.46 (2H, m, BCC<u>H</u>), 4.29 (2H, m, BCCHC<u>H</u>), 4.08 (5H, s, $C_5H_5$); $\upsilon_{max}$ (KBr) 3248 (s) (O-H stretch), 1478, 1396 (s) (O-H bend), 1338 (s) (B-O), 1219, 1193, 1107, 1057, 1003; *m/z* ($EI^+$) 230 (M, 70), 212 (M-$H_2O$, 100%), 186 (M-$B(O_2H)$, 35) and 121 (M-$B(O_2H)$-$C_5H_5$, 65).

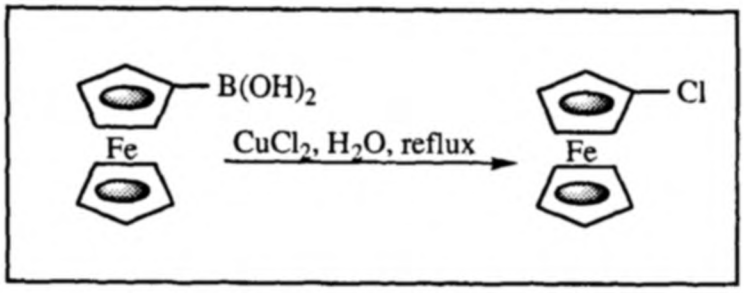
## Ferrocenyl bromide




[125]

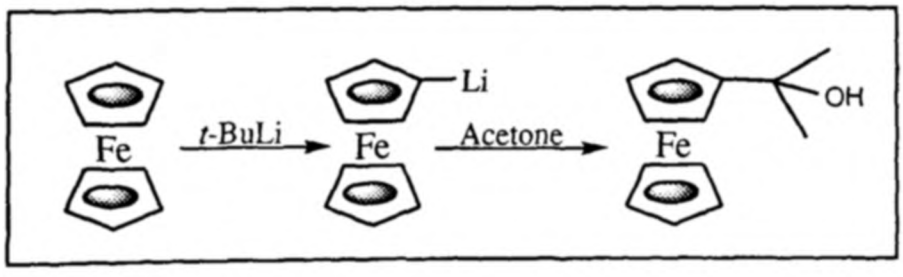
Following the procedure of Stanley *et al*, ferrocenyl boronic acid (0.23 g, 1 mmol) was added to a round bottomed flask containing an aqueous suspension of copper (II) bromide (0.22 g, 1 mmol, 50 ml of water). The reaction mixture was then heated and the aqueous distillate collected from a side arm. The organics were collected by ethereal extraction (3 x 50 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to afford ferrocenyl bromide as a bright orange solid (0.179 g, 68%), m.p. 32-34°C (lit 28-30°C). $\delta_H$ (200 MHz, $CDCl_3$) 4.46 (2H, dd, J 1.8, J 1.8, ortho H), 4.26 (5H, s, $C_5H_5$), 4.13 (2H, dd, J 1.8, J 1.8, meta H); $\delta_C$ (50.3 MHz, $CDCl_3$) 70.65 ($C_5H_5$), 67.96 and 67.12 (ortho and meta C). $\upsilon_{max}$ (KBr) 3094 (s) (C-H), 1634 (w) (C-H), 1408 (m), 1358 (m), 1167 (m), 1151 (m), 1105 (s), 1051 (m), 1019 (m), 1001 (s), 815 (s), 476 (s) (C-Br). *m/z* ($EI^+$) 264 ($M(^{79}Br)$, 55), 266 ($M(^{81}Br)$, 52), 186 (M-Br, 75), 184 (60), 129 ($C_5H_5$-$C_5H_4$, 55), 128 ($C_5H_4$=$C_5H_4$, 85), 121 ($FeC_5H_5$, 65) and 56 (Fe, 100%).

## Ferrocenyl chloride




In a similar procedure to the above, copper (II) chloride was used to yield ferrocenyl chloride as an orange powder (78%), m.p. 63-65°C. $\delta_H$ (200 MHz, $CDCl_3$) 4.39 (2H, dd, J 2.0, J 2.0, ortho H), 4.25 (5H, s, $C_5H_5$), 4.06 (2H, dd, J 2.0, J 2.0, meta H); $\delta_C$ (50.3 MHz, $CDCl_3$) 70.28 ($C_5H_5$), 67.92 (ortho/meta C) and 66.01 (ortho/meta C). $\upsilon_{max}$ (KBr) 3093 (s) (C-H), 1634 (w) (C-H), 1409 (m), 1383 (m), 1358 (m), 1345 (m), 1166 (m), 1105 (s), 1051 (m), 1019 (m), 1000 (s), 881 (s), 812 (s), 500 (s) (C-Cl), 477 (s). *m/z* ($EI^+$) 220 ($M(^{35}Cl)$, 100%), 222 ($M(^{37}Cl)$, 35), 186 (M-Cl, 90), 184 (55), 129 ($C_5H_5$-$C_5H_4$, 20), 128 ($C_5H_4$=$C_5H_4$, 85) and 56 (Fe, 72).

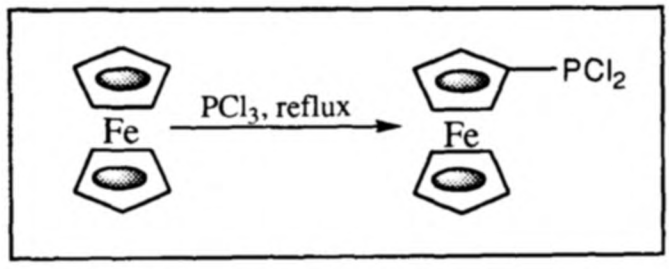
## 2-Ferrocenyl-propan-2-ol




*t*-Butyl lithium (2.95 ml, 1.7 M) was added to a stirred solution of ferrocene (1.10g) in THF (5 ml) at 0°C. After 20 min, acetone (0.19 ml) was added followed by water after a further 20 min. The organics were extracted into ether (3 x 10 ml) and dried ($MgSO_4$) to afford a yellow oil. The title material was purified by column chromatography

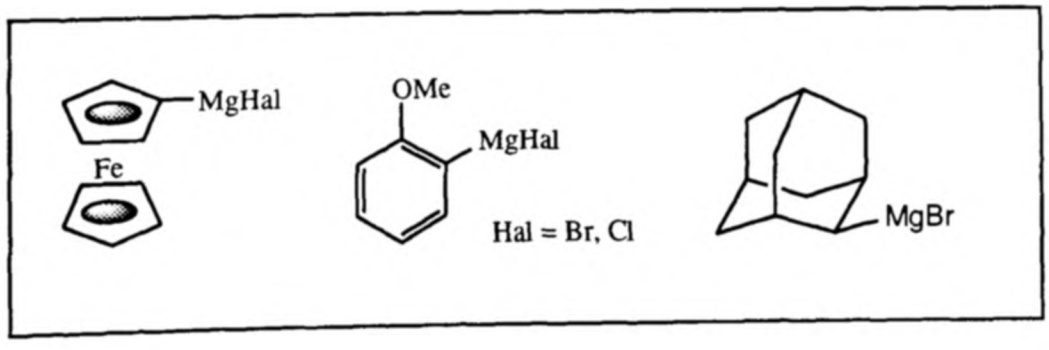
(flash silica, ethyl acetate/hexane 1:3, $R_f$ 0.5) and solvent removed under reduced pressure to yield a yellow solid (78 mg, 7%); m.p. 44-46°C. $\delta_H$ (200 MHz, $CDCl_3$) 4.22-4.19 (9H, m, Fc-H) and 1.51 (6H, s, $C(CH_3)_2$); $\delta_C$ (50.3 MHz, $CDCl_3$) 68.3 ('Fc-C), 67.7 (Fc-meta C), 65.6 (Fc-ortho C) and 30.9 ($C(CH_3)_2$); *m/z* ($EI^+$) 244 (M, 40%), 245 (10), 226 (M-$H_2O$, 100), 186 (Fc, 20), 161 (40), 121 (50) and 56 (50).

## Attempted synthesis of dichloroferocenyl phosphine




Phosphorus trichloride (1.74 ml, 20 mmol) was added to ferrocene (372 mg, 2 mmol) and the solution heated to reflux. The reaction was monitored by $^{31}P$ NMR and showed no trace of reaction after 48 h and was abandoned.

## Grignard reagents

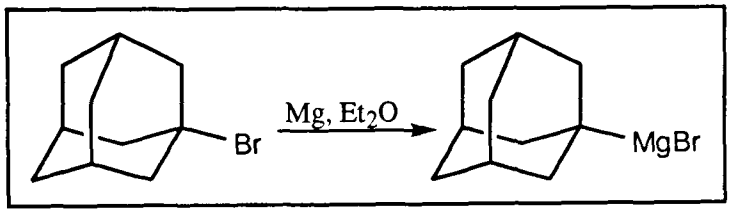



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Grignard reagents were made according to the general procedure of Brown, using mechanical stirring to activate the magnesium in each case. 1,2-Dibromoethane was also

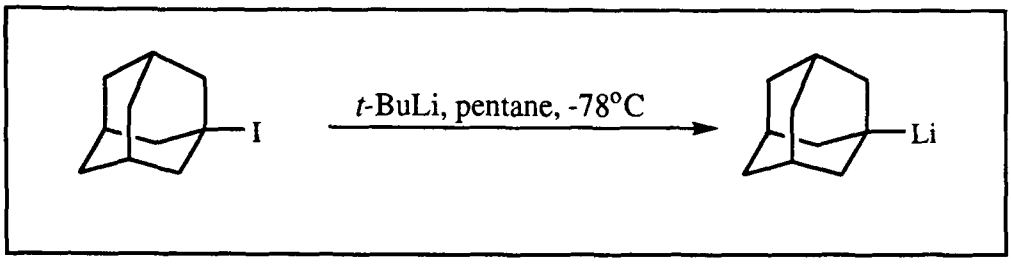
used in some cases. Solutions in THF or diethyl ether were produced in varying concentrations; ferrocenylmagnesium bromide (0.12M to 0.08M), ferrocenylmagnesium chloride (0.05M), 2-methoxyphenylmagnesium bromide (2.36M to 0.83M), 2-methoxyphenylmagnesium chloride (0.38M to 0.12M) and 2-adamantylmagnesium bromide (0.70M to 0.19M).

## Attempted synthesis of 1-adamantyl magnesium bromide




1,2-Dibromoethane (0.1 ml) was added to a solution of magnesium (1.82 g) in ether (32 ml) and stirred for 15 min. 1-Bromoadamantane (1.67 g) was then added and the solution stood at rt. Samples (1 ml) of the reaction solution were taken every 30 min and added to methylethyl ketone (1 ml) before being analysed by GC/MS. Only traces of the Grignard product were observed with most of the material being adamantane, diadamantane or unreacted 1-bromoadamantane and thus the reaction was abandoned after 4 h.

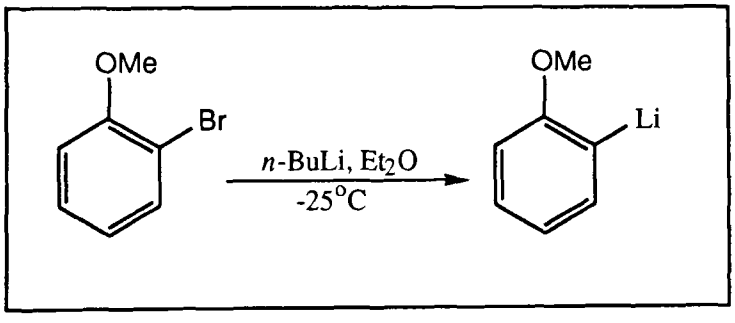
## 1-Adamantyl lithium




[28]

1-Adamantyl lithium was prepared by the method of West and was added to diethyl ether and then titrated against acid of known concentration. The material was used without any further purification.

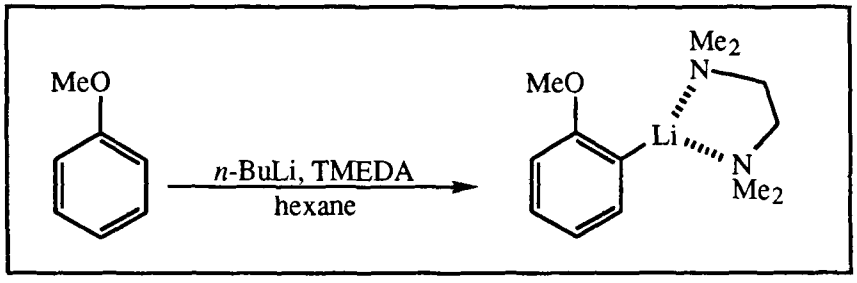
## 2-Methoxyphenyl lithium




[80]

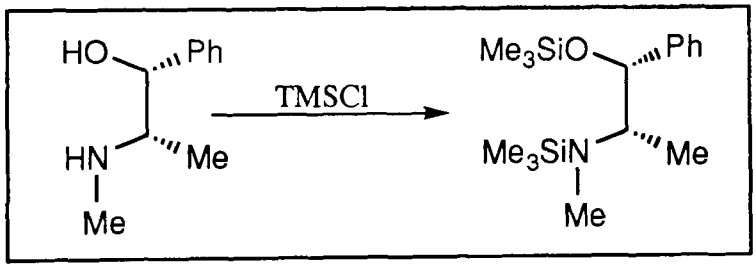
2-Methoxyphenyl lithium was prepared by the method of Brandsma as an ethereal solution and then titrated against acid of known concentration. The material was used without any further purification.

## 2-Methoxyphenyl lithium - TMEDA complex



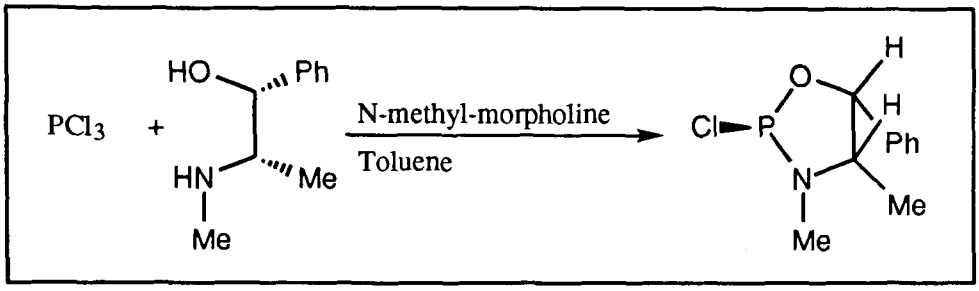

The TMEDA complex of 2-methoxyphenyl lithium was prepared according to Brandsma,[130] as a 0.4M solution in THF and was used without further purification.

## (2S,3R)-2-N-(Trimethylsilyl)-N-methylamino-3-phenyl-3-trimethylsilylether-propane



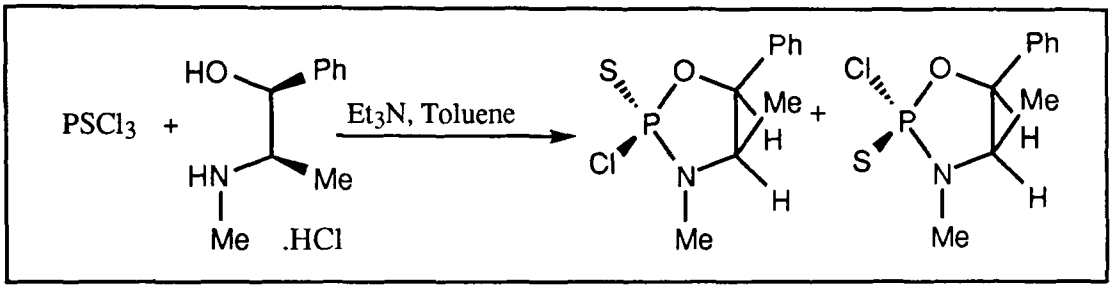

Bis(trimethylsilyl)acetamide (50 µl) was added to a solution of (1R,2S)-(-)-ephedrine (16.5 mg, 0.1 mmol) in deuteroacetonitrile (0.5 ml) in a 5 mm NMR tube. The solution was monitored and reaction was complete after 4 days to give (2S,3R)-2-N-(trimethylsilyl)-N-methylamino-3-phenyl-3-trimethylsilylether-propane which could not be isolated from the reaction mixture $\delta_H$ (200 MHz, $CD_3CN$) 7.32-7.17 (5H, m, Ph), 4.56 (1H, d, $J_{C\underline{H}CH3}$ 8.4, CHPh), 3.02 (1H, dq, $J_{CHPh}$ 8.4, $J_{CH3}$ 6.6, $C\underline{H}CH_3$), 2.46 (3H, s, $NCH_3$), 1.18 (3H, d, $J_{C\underline{H}CH3}$ 6.6, $CHC\underline{H}_3$), 0.07 (3H, s, $SiCH_3$) and -0.04 (3H, s, $SiCH_3$).

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



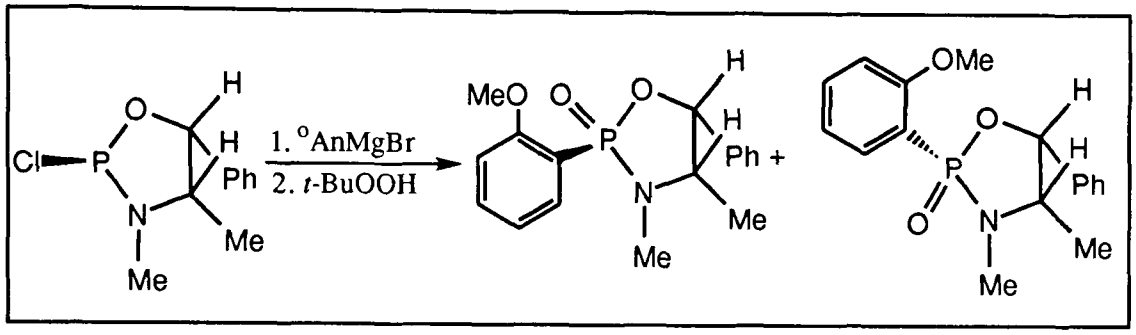

N-Methyl morpholine (13.91 ml, 100 mmol) was added to a stirred solution of (-)-ephedrine (8.26 g, 50 mmol) in toluene (300 ml) at -10°C. The solution was allowed to warm to 0°C and phosphorus trichloride (4.36 ml, 50 mmol) in toluene (10 ml) was slowly added. The mixture was allowed to warm to rt and stirred for 18 h. A pale yellow precipatate (N-methyl morpholine hydrochloride) was produced and this was removed *via* cannula filtration to afford a pale yellow solution. The toluene was removed under reduced pressure to give an orange oil which was purified by Kugelrohr distillation (155°C, 0.1 mmHg) to afford a white crystaline solid (9.72 g, 85 %); m.p. 80-82°C (Lit 82-85°C); $[\alpha]_D^{25}$ +56.7 (c 2.0, $CH_2Cl_2$); $\delta_H$ (500 MHz, $CDCl_3$) 7.43-7.34 (5H, m, Ph-H), 5.92 (1H, dd, $J_{H4}$ 7.9, $J_P$ 1.7, H-5), 3.71 (1H, ddq, $J_{H5}$ 7.9, $J_P$ 7.9, $J_{CH3}$ 6.5, H-4), 2.73 (3H, d, $J_P$ 16.2, $NCH_3$) and 0.74 (3H, d, $J_{H4}$ 6.5, $CHCH_3$); $\delta_P$ (101 MHz, $CDCl_3$) 71.1.

## (2R, 4R, 5S)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-sulphide and (2S, 4R, 5S)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-sulphide.



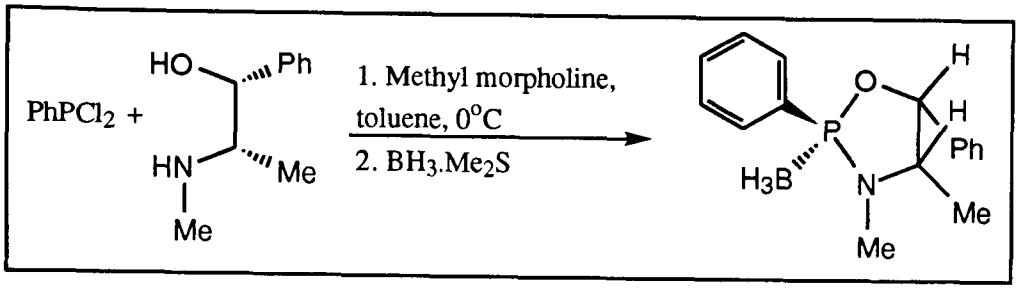

In a procedure similar to the method of Inch, a toluene (25 ml) solution of thiophosphoryltrichloride (6.90 g) was slowly added to a suspension of (+)-ephedrine in triethyl amine (34.4 ml) and toluene (150 ml). The mixture was stirred overnight and then slowly poured into water (100 ml). The aqueous layer was extracted with toluene (3 x 60 ml) and the combined organic extracts concentrated to give a thick oil. $^1$H NMR analysis revealed a mixture of 2 diastereoisomers in 55% diastereotopic excess which were seperated by column chromatography (chloroform / 40-60 pet. ether : 3 / 1, $R_f$ 0.5 (2R), $R_f$ 0.4 (2S)) to afford (2S, 4R, 5S)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphos pholidine-2-sulphide as a white solid (5.67 g, 70%); m.p. 127-129°C (Lit. 125-128°C); $\delta_H$ (200 MHz, $CDCl_3$) 7.44-7.28 (5H, m, Ph-H), 5.85 (1H, dd, $J_{H4}$ 6.5, $J_P$ 1.0, H-5), 3.87 (1H, ddq, $J_{H5}$ 6.5, $J_{CH3}$ 6.8, $J_P$ 29.0, H-4), 2.93 (3H, d, $J_P$ 14.8, $NCH_3$) and 0.90 (3H, d, $J_{H4}$ 6.8, $CCH_3$); $\delta_P$ (101.2 MHz, $CDCl_3$) 72.3; $\upsilon_{max}$ (KBr) 3422, 2982, 1603 (Ph-H vib.), 1493, 1455 ($CH_3$ deformations), 1425, 1384, 1330, 1210, 1189, 965, 943, 749 (P=S), 700 and 613. (2R, 4R, 5S)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-sulphide was obtained as an off white solid (0.81 g, 10%); m.p. 59-61°C (Lit. 58°C); $\delta_H$ (200 MHz, $CDCl_3$) 7.43-7.20 (5H, m, Ph-H), 5.62 (1H, dd, $J_{H4}$ 7.2, $J_P$ 7.2, H-5), 3.73 (1H, ddq, $J_{H5}$ 7.2, $J_{CH3}$ 6.4, $J_P$ 13.0, H-4), 2.75 (3H, d, $J_P$ 16.8, $NCH_3$) and 0.82 (3H, d, $J_{H4}$ 6.4, $CCH_3$); $\delta_P$ (101.2 MHz, $CDCl_3$) 77.0.

## (2R,4S,5R)-3,4-Dimethyl-2-(2-methoxyphenyl)-5-phenyl-1,3,2-oxazaphospholidine-2-oxide and (2S,4S,5R)-3,4-dimethyl-2-(2-methoxyphenyl)-5-phenyl-1,3,2-oxazaphospholidine-2-oxide



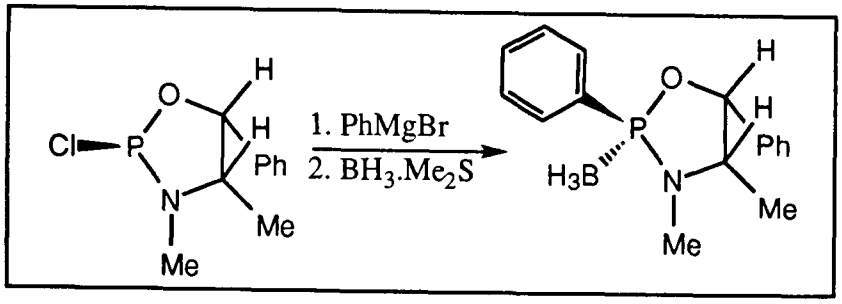

2-Methoxyphenylmagnesium bromide (34 ml, 0.77M, 26 mmol) was added to a stirred THF (150 ml) solution of (2R, 4S, 5R)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine (5.15 g, 22 mmol) at -78°C. The solution was stirred for 2 h and *t*-butyl hydroperoxide (7.5 ml, 3M in iso-octane, 22 mmol) was added. After allowing the solution to slowly come to rt, the reaction was quenched by the addition of water (250 ml) and the organics extracted with dichloromethane (3 x 100 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford a white solid which $^1H$ NMR analysis revealed as a mixture of two diastereoisomers in 64 % diastereoisomeric excess. (2R,4S,5R)-3,4-Dimethyl-2-(2-methoxyphenyl)-5-phenyl-1,3,2-oxazaphospholidine-2-oxide was isolated by column chromatography (flash silica, dichlromethane / ethyl acetate : 1 / 1, $R_f$ 0.5) as a white crystalline solid (4.67 g, 65%); m.p. 155-157°C (Lit· 156-157°C); $\delta_H$ (500 MHz, $CDCl_3$) 8.016 (1H, ddd, $J_{H4}$ 1.8, $J_{H5}$ 7.6, $J_P$ 14.7, °An-H6), 7.529-7.479 (3H, m, Ph-ortho/para H), 7.391 (2H, dd, $J_{ortho}$ 7.2, $J_{para}$ 7.2, meta-H), 7.324 (1H, ddd, $J_{H6}$ 1.8, $J_{H3}$ 6.9, $J_{H5}$ 6.9, °An-H4), 7.060 (1H, ddd, $J_{H6}$ 6.9, $J_{H4}$ 6.9, $J_P$ 3.0, °An-H5), 6.966 (1H, dd, $J_{H5}$ 6.9, $J_P$ 6.9, °An-H3), 5.637 (1H, dd, $J_P$ 6.9, $J_{H4}$ 6.9, H-5), 3.942 (3H, s, $OCH_3$), 3.843 (1H, ddq, $J_P$ 9.7, $J_{H5}$ 6.9, $J_{CH3}$ 6.6, H-4), 2.632 (3H, d, $J_P$ 10.2, $NCH_3$) and 0.858 (3H, d, $J_{H4}$ 6.6, $CCH_3$).

## (2R,4S,5R)-3,4-Dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine-2-borane



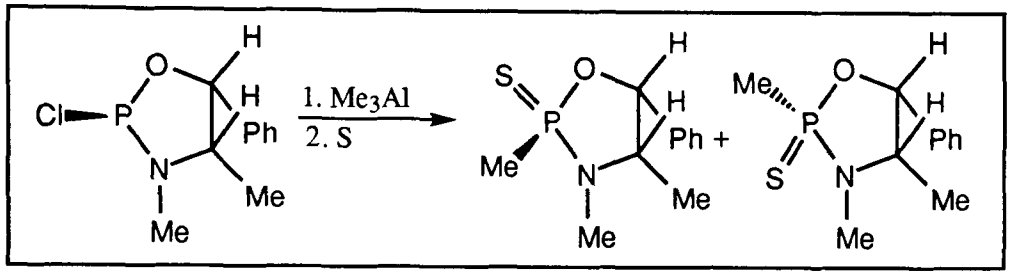

(-)-Ephedrine (4.125 g, 25 mmol) was dissolved in toluene (200 ml) and N-methyl morpholine (5.77 ml, 55 mmol) was slowly added. The solution was cooled to 0°C and phenyl dichlorophosphine (3.39 ml, 25 mmol) was carefully added. A cloudly white precipatate was instantly formed and the solution was stirred at rt for 48 h. Borane dimethyl sulphide complex (14 ml, 2M, 28 mmol) was added to the solution which was stirred for a further 48 h. Solvent was removed under reduced pressure to yield an oil which was purified by column chromatography (flash silica, ethyl acetate / 40-60 pet. ether : 1 / 1, $R_f$ 0.4) to yield a white solid. This solid was recrystallised from hot toluene to afford crystals of (2R,4S,5R)-3,4-dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidin-2-borane (4.63 g, 65%); m.p. 105-107°C (Lit. 107°C); $\delta_H$ (500 MHz, $CDCl_3$) 7.835 (2H, ddt, $J_P$ 10.2, $J_{H5}$ 8.4, $J_{H4}$ 1.5, PPh-ortho H), 7.554 (1H, dt, $J_{H5}$ 7.3, $J_{H6}$ 1.5, PPh-para H), 7.525 (2H, dt, $J_P$ 2.1, $J_{H4}$ 7.7, PPh-meta H), 7.397-7.345 (5H, m, CPh), 5.602 (1H, dd, $J_P$ 3.0, $J_{H4}$ 6.1, H-5), 3.690 (1H, ddq, $J_P$ 9.0, $J_{H5}$ 6.1, $J_{CH3}$ 6.5, H-4), 2.690 (3H, d, $J_P$ 10.9, $NCH_3$) and 0.835 (3H, d, $J_{H4}$ 6.5, $CCH_3$); $\delta_C$ (62.4 MHz, $CDCl_3$) 132.35 (PPh-para C), 130.93 (d, $J_P$ 15.0, PPh-ortho C), 128.57 (d, $J_P$ 12.4, PPh-meta C), 128.34 (CPh-ortho/meta C), 126.61 (CPh-ortho C), 84.15 (d, $J_P$ 7.4, C-5), 59.02 (C-4), 29.44 (d, $J_P$ 10.3, $NCH_3$) and 13.51 ($C\underline{C}H_3$); $\delta_P$ (101.3 MHz, $CDCl_3$) 129.0 (pseudo q, $J_B$ 74.0).

## (2R,4S,5R)-3,4-Dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine-2-borane




Phenylmagnesium bromide (2.2 ml, 1M, 2.2 mmol) was added to a stirred solution of (2R, 4S, 5R)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine (460 mg, 2 mmol) in THF (20 ml) at 0°C. The solution was heated to 50°C and stirred overnight. After cooling to 0°C, borane dimethyl sulphide complex (1.2 ml, 2M, 2.4 mmol) was added and the solution stirred for a further 4 h at rt before the reaction was quenched with water (30 ml). The organics were extracted into dichloromethane (3 x 20 ml) and dried ($MgSO_4$) to afford a white solid. This material was purified by column chromatography (flash silica, ethyl acetate / 40-60 pet. ether : 1 / 1, $R_f$ 0.4) to afford (2R,4S,5R)-3,4-dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine-2-borane as a white crystalline material (480 mg, 84%); m.p. 104-106°C; Spectroscopic data identical to an authentic sample.

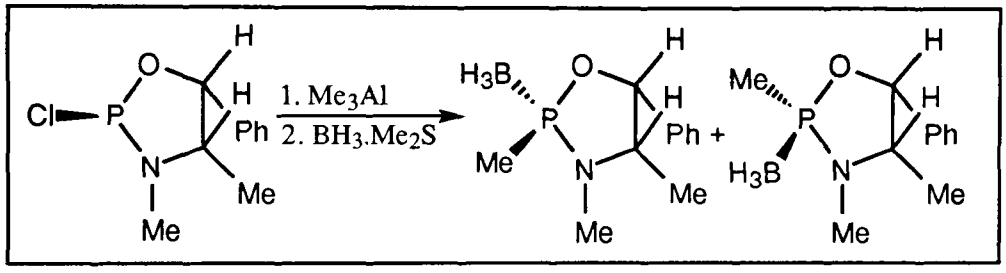
## (2R,4S,5R)-2,3,4-Trimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-sulphide and (2S,4S,5R)-2,3,4-trimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-sulphide




(2R, 4S, 5R)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine (460 mg, 2 mmol) was dissolved in THF (15 ml) and cooled to -78°C. Trimethyl aluminium (2.2 ml, 1.0 M, 2.2 mmol) was slowly added to the stirred solution which was allowed to warm to rt. After 6 h stirring, sulphur (96 mg, 3 mmol) in carbon disulphide (10 ml) was added and the reaction mixture stirred for 24 h. The reaction was quenched with water (20 ml) and the organics extracted with ether (3 x 30 ml) and dried ($MgSO_4$). After solvents were removed *in vacuo*, $^1H$ NMR analysis revealed the target materials had been made with a diastereotopic excess of 65%. The crude product was dissolved in dichloromethane and hexane was layered onto the dichloromethane layer. After 1 week, white needles of (2S, 4S, 5R)-2,3,4-trimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-thione crystallised out and were collected by filtration (136 mg, 28%); m.p. 90-92°C (Lit. 88-90°C); $\delta_H$ (200 MHz, $CDCl_3$) 7.45-7.28 (5H, m, Ph-H), 5.30 (1H, dd, $J_P$ 3.4, $J_{H4}$ 5.7, H-5), 3.64 (1H, ddq, $J_P$ 17.4, $J_{H5}$ 5.7, $J_{CH3}$ 6.6, H-4), 2.70 (3H, d, $J_P$ 12.6, $NCH_3$), 1.97 (3H, d, $J_P$ 34.1, $PCH_3$) and 0.84 (3H, d, $J_{H4}$ 6.6, $CCH_3$); $\delta_C$ (50.3 MHz, $CDCl_3$) 136.2 (d, $J_P$ 5.1, Ph-ispo C), 128.6 (Ph-ortho C), 128.4 (Ph-para C), 126.5 (Ph-meta C), 83.0 (d, $J_P$ 3.8, C-5), 59.9 (d, $J_P$ 6.7, C-4), 29.1 (d, $J_P$ 6.7, $NCH_3$), 23.5 (d, $J_P$ 93.0, $PCH_3$) and 12.8 ($CCH_3$); $\delta_H$ (101.3 MHz, $CDCl_3$) 98.9; $\upsilon_{max}$ (KBr) 2979, 2954, 2807 ($NCH_3$ bend), 1655, 1604 (Ph-H vib.), 1523, 1471, 1453, 1326, 1295, 1180, 1116, 1088, 985, 951,

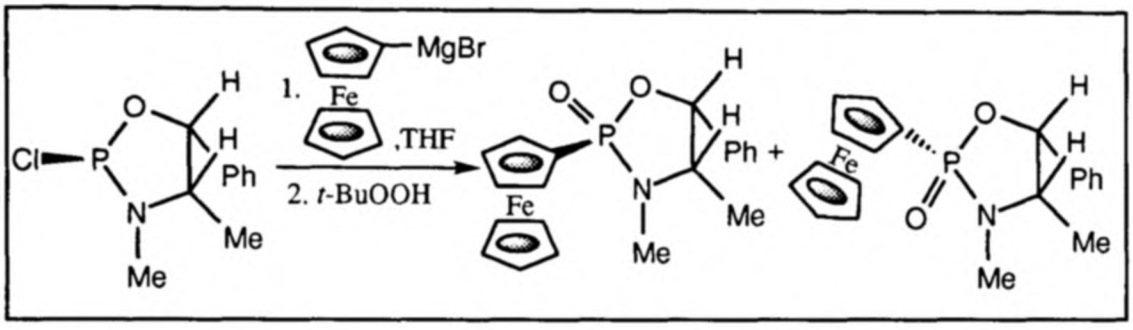
918, 908, 800, 768 (Ph-H out of plane bend), 758 (Ph-H out of plane bend), 726 and 703; *m/z* ($CI^+$, $NH_3$) 242 (M+1, 100%), 148 ($NCHCH_3CHPhO$, 20), 135 (15) and 120 (10). Despite a large number of attempts at chromatography and fractional crystallisation (2R, 4S, 5R)-2,3,4-trimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-thione could not be isolated.

## Attempted synthesis of (2R,4S,5R)-2,3,4-trimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-borane and (2S,4S,5R)-2,3,4-trimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-borane




(2R, 4S, 5R)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine (920 mg, 4 mmol) was dissolved in THF (25 ml) and cooled to -78°C. Trimethyl aluminium (4.5 ml, 1.0 M, 4.5 mmol) was slowly added to the stirred solution which was allowed to warm to rt. After 10 h stirring, borane dimethyl sulphide complex (3 ml, 2M, 6 mmol) was added and the reaction mixture stirred for 20 h. The reaction was analysed by $^{31}P$ NMR which revealed that the target materials had been made with a diastereotopic excess of 74%. The reaction was quenched with water (30 ml) and the organics extracted with ether (3 x 40 ml) and dried ($MgSO_4$). Solvents were removed *in vacuo* to afford a thick pungent smelling oil. $^1H$ NMR analysis revealed the target materials had been destroyed in the workup and the reaction was abandoned.

## (2R,4S,5R)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide and (2S,4S,5R)-3,4-dimethyl-2-ferrocenyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide

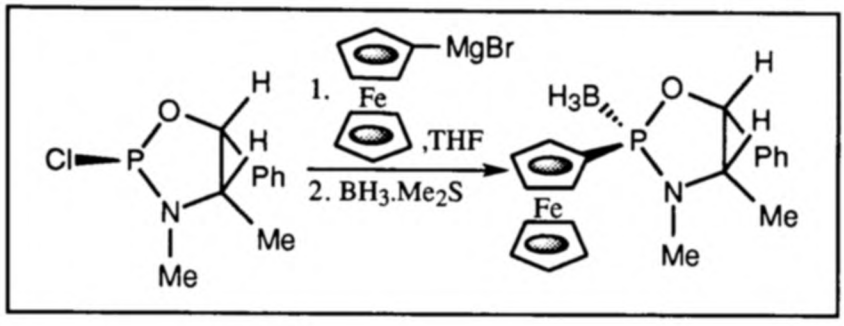



Ferrocenylmagnesium bromide solution (11.4 ml, 0.36 M, 4.1 mmol, 10 ml THF) was added to a stirred THF solution (40 ml) of (2R, 4S, 5R)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine (690 mg, 3.0 mmol) at -40°C. The reaction mixture was stirred for 2 h at -40°C and then allowed to warm up to rt over a period of 3 h. The phosphine was then oxidized by the addition of *t*-butyl hydroperoxide (1.0 ml, 3M in octane). After a further 2 h, the reaction was quenched with water (30 ml) and the organics extracted into ether (3 x 30 ml) and dried ($MgSO_4$). Solvent was removed under reduced pressure to afford a mixture of two diastereoisomers (95% d.e.) in 72% yield. The diastereoisomers were then seperated by column chromatography (flash silica, ethyl acetate, $R_f$ = 0.6 (2R) and $R_f$ = 0.1 (2S)) to give optically pure material. (2R,4S,5R)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide (838 mg, 71%) was obtained as orange crystals : m.p. 196-194°C , Found C 60.53; H 5.66 ; N 3.40 $C_{20}H_{22}NO_2P$ requires C 60.77; H 5.61; N 3.56%; $[\alpha]_D^{22}$ +81.3° (c 0.315, $CH_2Cl_2$); $\delta_H$ (500 MHz, $CDCl_3$) 7.498 (2H, d, $J_{meta}$ 7.4, ortho H), 7.417 (2H, dd, $J_{ortho}$ 7.4, $J_{para}$ 7.0, meta H), 7.351 (1H, d, $J_{meta}$ 7.0, para H), 5.488 (1H, dd, $J_{H4}$ 6.5, $J_P$ 6.5, $H_5$), 4.716 (1H, br s, Fc-$H_2$), 4.453 (2H, d, $J_P$ 4.9, Fc-$H_3$), 4.354 (5H, s, Fc'-H), 4.354 (1H, s, Fc-$H_2$), 3.614 (1H, ddq, $J_{H5}$ 6.5, $J_{CH3}$ 6.4, $J_P$ 11.4, C<u>H</u>$CH_3$), 2.575 (3H, d, $J_P$

10.3, $NCH_3$) and 0.845 (3H, d, $J_{H4}$ 6.5, $CHC\underline{H}_3$); $\delta_C$ (50.3 MHz, $CDCl_3$) 136.8 (Ph-ispo C), 128.5 (Ph-ortho C), 128.3 (Ph-para C), 126.8 (Ph-meta C), 82.5 ($\underline{C}HPh$), 73.7 (d, $J_P$ 15.3, Fc-$C_2$), 71.7 (d, $J_P$ 13.6, Fc-$C_3$), 71.3 (d, $J_P$ 13.3, Fc-$C_3$), 69.8 (Fc'-C), 69.8 (d, $J_P$ 15.0, Fc-$C_2$), 58.6 (d, $J_P$ 10.6, $\underline{C}HCH_3$), 28.6 (d, $J_P$ 5.5, $NCH_3$) and 14.3 (d, $J_P$ 4.3, $CH\underline{C}H_3$); $\delta_P$ (101.3 MHz, THF) 34.11; $\upsilon_{max}$ (KBr) 3074, 2966 ($CH_2$-H st.), 2824 ($NCH_2$-H st.), 1655, 1649, 1603 (Ar-H vib.), 1494, 1449 ($CH_2$-H deformations), 1390 (CH sym. deformations), 1373 (CH sym. deformations), 1351, 1342, 1242 (P=O), 1221, 1187, 1178, 1107, 1067, 1040 (P-O-alkyl), 983, 959, 918, 902, 885, 849, 826, 817, 747 (Ar-H out of plane bend), 708 and 700; *m/z* ($DCI^+$, $NH_3$) 396 (M+1, 100%), 397 (20), 395 (30), 394 (5), 265 (5), 248 (15), 148 ($NCHCH_3CHPhO$, 5) and 56 (10).

(2S,4S,5R)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide (15 mg, 1%) was obtained as an orange oil; Found C 60.75; H 5.42 ; N 3.40 ; $C_{20}H_{22}NO_2P$ requires C 60.77; H 5.61; N 3.56%; $[\alpha]_D^{25}$ -143.8° (c 0.80, $CH_2Cl_2$); $\delta_H$ (500 MHz, $CDCl_3$) 7.433 (2H, dd, $J_{ortho}$ 7.4, $J_{para}$ 7.4, meta H), 7.379-7.340 (3H, m, ortho/para H), 5.892 (1H, d, $J_{H4}$ 6.1, $H_5$), 4.742 (1H, br s, Fc-$H_2$), 4.640 (2H, br m, Fc-$H_3$), 4.418 (1H, m, Fc-$H_2$), 4.408 (5H, s, Fc'-H), 3.573 (1H, dq, $J_{H5}$ 6.1, $J_{CH3}$ 6.6, $C\underline{H}CH_3$), 2.714 (3H, d, $J_P$ 9.3, $NCH_3$) and 0.731 (3H, d, $J_{H4}$ 6.6, $CHC\underline{H}_3$); $\delta_C$ (50.3 MHz, $CDCl_3$) 136.5 (d, $J_P$ 10.0, Ph-ispo C), 128.4 (Ph-ortho C), 127.9 (Ph-para C), 125.5 (Ph-meta C), 79.9 ($\underline{C}HPh$), 74.3 (d, $J_P$ 16.6, Fc-$C_2$), 71.9 (d, $J_P$ 13.3, Fc-$C_3$), 71.4 (d, $J_P$ 14.4, Fc-$C_3$), 70.3 (d, $J_P$ 15.9, Fc-$C_2$), 69.9 (Fc'-C), 60.7 (d, $J_P$ 9.6, $\underline{C}HCH_3$), 29.1 (d, $J_P$ 6.6, $NCH_3$) and 13.8 ($CH\underline{C}H_3$); $\delta_P$ (101.3 MHz, $CDCl_3$) 37.97; $\upsilon_{max}$ (film, NaCl plates) 2976($CH_2$-H st.), 2485, 2231, 1672, 1495, 1453 ($CH_2$-H deformations), 1421, 1370 (CH sym. deformations), 1329, 1235 (P=O), 1186, 1108, 1061, 1030 (P-O-alkyl), 975, 824, 755 (Ph-H out of plane bend), 731, 705 and 629; *m/z* ($EI^+$) 396 (M+1, 10%), 395 (M, 50), 248 (100), 232 (FcPO, 10) and 184 (Fc, 15).

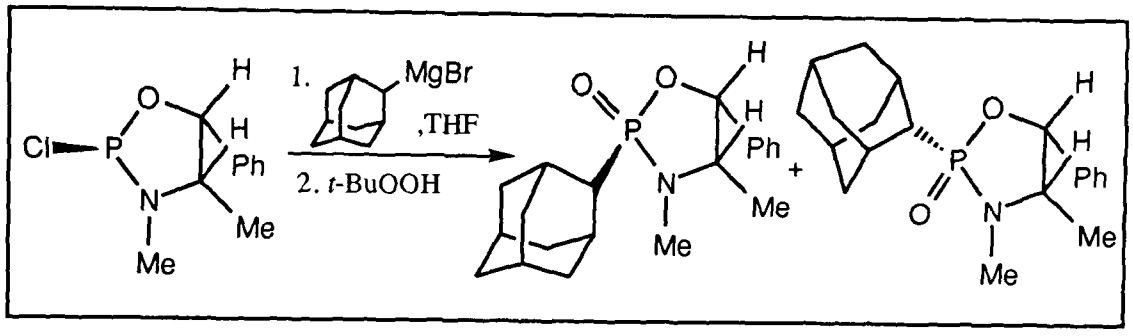
## (2R,4S,5R)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-1,3,2-oxazaphospholidine-2-borane




Ferrocenylmagnesium bromide solution (1.5 ml, 0.18 M, 0.27 mmol) was added to a stirred THF solution (5 ml, degassed) of (2R, 4S, 5R)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine (62 mg, 0.27 mmol) at -40°C. The reaction mixture was stirred for 2 h at -40°C and then allowed to warm up to rt over a period of 3 h. Borane dimethyl sulphide complex (0.15 ml, 2M) was then added to the reaction mixture which was stirred for 3 days. The reaction was quenched with water (10 ml) and the organics extracted into ether (3 x 10 ml) and dried ($MgSO_4$). Solvent was removed under reduced pressure to yield a mixture of compounds. The target material was seperated by column chromatography (flash silica, ethyl acetate / 40-60 pet. ether : 1 / 4, $R_f$ = 0.5) to give (2R,4S,5R)-3,4-dimethyl-2-ferrocenyl-5-phenyl-1,3,2-oxazaphospholidine-2-borane (69 mg, 65%) as orange crystals : m.p. >230°C $[\alpha]_D^{25}$ +22.5° (c 0.04, $CH_2Cl_2$); $\delta_H$ (500 MHz, $CDCl_3$) 7.435-7.338 (4H, m, Ph-ortho/meta H), 7.345 (1H, m,Ph-para H), 5.516 (1H, dd, $J_{H4}$ 6.3, $J_P$ 4.7, $H_5$), 4.605 (1H, dd, J 1.2, J 1.2, Fc-H), 4.495 (2H, dd, J 3.9, J 1.4, Fc-H), 4.350 (6H, s, Fc'-H, Fc-H), 3.557 (1H, dq, $J_{H5}$ 6.3, $J_{CH3}$ 6.5, C<u>H</u>$CH_3$), 2.550 (3H, d, $J_P$ 11.9, $NCH_3$) and 0.767 (3H, d, $J_{H4}$ 6.5, $CHC\underline{H}_3$); $\delta_C$ (125.8 MHz, $CDCl_3$) 136.8 (Ph-ispo C), 128.3 (Ph-ortho/para C), 127.1 (Ph-meta C), 84.6 (d, $J_P$ 7.7, <u>C</u>HPh), 74.0 (d, $J_P$ 17.9, Fc-C), 72.1 (d, $J_P$ 6.1, Fc-C), 71.8 (d, $J_P$ 8.6, Fc-C), 70.1 (Fc'-C), 69.7 (Fc-C), 58.3 ($\underline{C}HCH_3$), 29.4 (d, $J_P$ 6.2, $NCH_3$) and 13.9 ($CH\underline{C}H_3$); $\delta_P$

(101.3 MHz, $CDCl_3$) 138.05 ; *m/z* ($EI^+$) 393 (M, 15%), 394 (M, 3), 379 (M-$BH_3$, 70), 322 (5), 275 (15), 261 (15), 232 (10), 216 (FcP, 100), 186 (Fc, 10), 121 (40), 91 (20) and 56 (20).

## (2R,4S,5R)-3,4-Dimethyl-2-adamantyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide and (2S,4S,5R)-3,4-dimethyl-2-adamantyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide

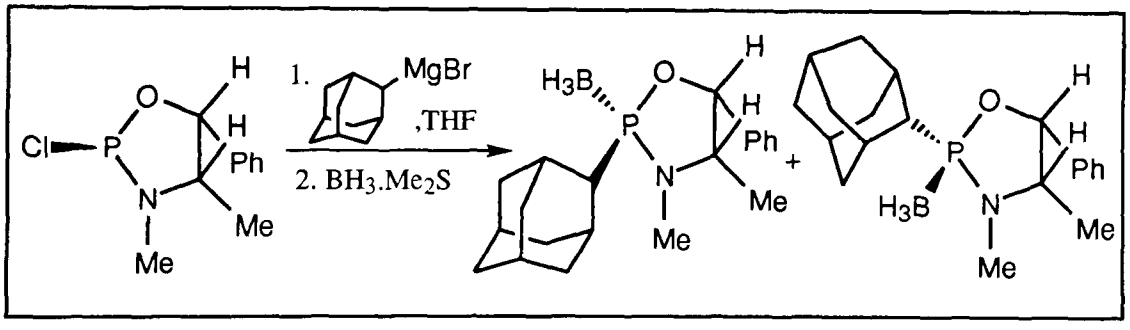



2-Adamantylmagnesium bromide (140 ml, 0.21 M in ether) was added to a stirred THF solution (20 ml) of (2R, 4S, 5R)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine (8.01 g, 35 mmol) at -78°C. The stirred reaction mixture was allowed to warm up to rt over a period of 4 h and was then oxidized by the addition of *t*-butyl hydroperoxide (12.8 ml, 3M in octane). After a further 2 h, the reaction was quenched with water (30 ml) and the organics were extracted into ether (3 x 60 ml) and dried ($MgSO_4$). Solvent was removed under reduced pressure to afford a mixture of two diastereoisomers in 87% yield. The diastereoisomers were then seperated by column chromatography (flash silica, ethyl acetate, $R_f$ = 0.5 (2R) and $R_f$ = 0.2 (2S)) to give optically pure material. (2S,4S,5R)-3,4-Dimethyl-2-adamantyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide (4.59 g, 38%) was obtained as white crystals : m.p. 220-222°C , Found C 69.50 (repeat 69.54); H 8.24 (8.13); N 3.82 (3.78). $C_{20}H_{28}NO_2P$ requires C 69.53; H 8.17; N 4.07%; $[\alpha]_D^{23}$ -37.7° (c 0.975, $CHCl_3$); $\delta_H$ (500 MHz,

$CDCl_3$) 7.424-7.361 (4H, m, ortho/meta H), 7.319 (1H, dd, $J_{meta}=J_{meta'}$ 6.9, para H), 5.405 (1H, dd, $J_{H4}$ 6.2, $J_P$ 3.7, CHPh), 3.617 (1H, ddq, $J_{H5}$ 6.2, $J_{CH3}$ 6.5, $J_P$ 15.8, C<u>H</u>$CH_3$), 2.708 (3H, d, $J_P$ 9.5, $NCH_3$), 2.475 (1H, br m, $J_P$ 7.6, $J_{HC}$ 7*, $J_{HD}=J_{HO}$ 6*, Ad-$H_B$), 2.397 (1H, br m, $J_P$ 18.4, $J_{HB}$ 7.6, $J_{HK}$ 8.1, Ad-$H_A$), 2.280 (1H, br m, $J_{HM}$ 12*, $J_{HE}$ 7*, Ad-$H_L$), 2.249 (1H, br m, $J_{HD}$ 12*, $J_{HB}=J_{HE}$ 7*, Ad-$H_C$), 2.227 (1H, br m, $J_P$ 8.1, $J_{HM}=J_{HJ}$ 6*, Ad-$H_K$), 1.958 (1H, br m, $J_{HG}=J_{HF}$ 6*, Ad-$H_H$), 1.916 (1H, br m, Ad-$H_N$), 1.911 (1H, br m, $J_{HM}=J_{HC}=J_{HL}$ 7*, Ad-$H_E$), 1.899 (1H, br m, $J_{HK}$ 6*, Ad-$H_J$), 1.819 (1H, br m, $J_{HB}$ 6*, Ad-$H_O$), 1.780 (2H,br m, $J_{HH}$ 6*, Ad-$H_F$,$H_G$), 1.777 (1H, br m, $J_{HK}$ 7*, Ad-$H_I$), 1.697 (1H, br m, $J_{HC}$ 12*, $J_{HB}$ 6*, Ad-$H_D$), 1.613 (1H, br m, $J_{HL}$ 12*, $J_{HK}$ 6*, $J_{HE}$ 7*, Ad-$H_M$) and 0.836 (3H, d, $J_{H4}$ 6.5, $CHCH_3$); $\delta_C$ (125 MHz, $CDCl_3$) 136.59 (d, $J_P$ 6.1, Ph-ispo C), 128.30 (Ph-ortho C), 128.01 (Ph-para C), 126.18 (Ph-meta C), 81.94 (<u>C</u>HPh), 58.68 (d, $J_P$ 8, N<u>C</u>$HCH_3$), 44.86 (d, $J_P$ 122, Ad-$C_1$), 39.71 (d, $J_P$ 16, Ad-$C_7$), 39.41 (d, $J_P$ 16, Ad-$H_{10}$), 37.43 (Ad-$C_5$), 33.39 (Ad-$C_3$), 32.93 (Ad-$C_9$), 29.02 (d, $J_P$ 4, $NCH_3$), 28.44 (Ad-$C_2$), 28.44 (Ad-$C_8$), 27.87 (Ad-$C_6$), 27.32 (Ad-$C_4$) and 13.98 ($CH$<u>C</u>$H_3$); $\delta_P$ (101.3 MHz, $CDCl_3$) 47.12; $\upsilon_{max}$ (KBr) 3066, 3035 (Ar-H st.), 2913 ($CH_2$ st), 2852 ($NCH_3$, C-H st), 2654, 2360, 2342, 1950, 1882, 1673, 1606 (Ph-H vib.), 1548, 1493 (Ph-H, vib.), 1470 ($CH_2$, C-H deformations), 1452 ($CH_2$, C-H deformations), 1381 ($CH_3$ symmetrical deformations), 1359, 1334, 1311, 1297 (P=O), 1236, 1213, 1178, 1128, 1112, 1102, 1086, 1062, 1031 (P-Oalkyl), 970, 912, 881, 848, 837, 758 (Ph-H out of plane bend), 710 (Ph-H out of plane bend) and 560; *m/z* ($CI^+$, $NH_3$) 346 (M+1, 100%), 347 (20), 228 (10), 148 ($NCHCH_3CHPhO$, 10) and 135 (Ad, 5). (2R,4S,5R)-3,4-Dimethyl-2-adamantyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide (5.61 g, 46%) was obtained as white crystals : m.p. 190-192°C , Found C 69.58 (repeat 69.53); H 8.46 (8.32); N 4.08 (4.08). $C_{20}H_{28}NO_2P$ requires C 69.53; H 8.17; N 4.07%; $[\alpha]_D^{23}$ -70.9° (c 1.11, $CHCl_3$); $\delta_H$ (500 MHz, $CDCl_3$) 7.424-7.242 (5H, m, Ar H), 5.819 (1H, d, $J_{H4}$ 6.1, CHPh), 3.641 (1H, ddq, $J_{H5}$ 6.1, $J_{CH3}$ 6.6, C<u>H</u>$CH_3$), 2.830 (3H, d, $J_P$ 8.8, $NCH_3$), 2.436-2.336 (5H, br m, Ad-$H_A$,$H_B$,$H_C$,$H_K$,$H_L$), 1.990-1.666 (10H, br m, Ad-$H_D$,$H_E$,$H_F$,$H_G$,$H_H$,$H_I$,$H_J$,$H_M$,$H_N$,$H_O$) and 0.705 (3H, d, $J_{H4}$ 6.7, $CHC$<u>H</u>$_3$); $\delta_C$ (62.9

MHz, $CDCl_3$) 136.42 (Ph-ispo C), 128.34 (Ph-ortho C), 127.86 (Ph-para C), 125.63 (Ph-meta C), 79.68 (CHPh), 61.25 (d, $J_P$ 6.1, $CHCH_3$), 46.10 (d, $J_P$ 124, Ad-$C_1$), 39.73 (d, $J_P$ 7.3 Ad-$C_{7/10}$), 39.55 (d, $J_P$ 7.4, Ad-$H_{7/10}$), 37.40 (Ad-$C_5$), 33.29 (Ad-$C_3$), 30.82 (d, $J_P$ 5.7, Ad-$C_9$), 28.73 ($NCH_3$), 28.44 (d, $J_P$ 3.5, Ad-$C_2$,$C_8$), 27.86 (Ad-$C_6$), 27.32 (Ad-$C_4$) and 14.56 ($CHCH_3$); $\delta_P$ (101.3 MHz, $CDCl_3$) 46.06; $\upsilon_{max}$ (KBr) 2900, 2864, 3849, 1607, 1497, 1453, 1380, 1356, 1330, 1246, 1221, 1212, 1191, 1112, 1100, 1082, 1062, 1035, 982, 957, 912, 582, 854, 839, 810 and 704; *m/z* ($CI^+$, $NH_3$) 346 (M+1, 100%), 347 (20), 148 ($NCHCH_3CHPhO$, 15), 135 (Ad, 10) and 58 (35).

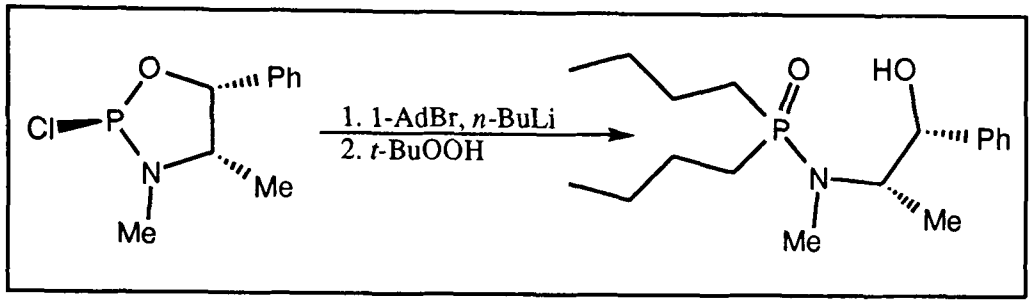
## (2S,4S,5R)-3,4-Dimethyl-2-adamantyl-5-phenyl-1,3,2-oxazaphospholidine-2-borane and (2R,4S,5R)-3,4-dimethyl-2-adamantyl-5-phenyl-1,3,2-oxazaphospholidine-2-borane




2-Adamantylmagnesium bromide (7.5 ml, 0.7 M in THF) was slowly added to a stirred THF solution (20 ml) of (2R, 4S, 5R)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine (1.15 g, 5 mmol) at -78°C. The stirred reaction mixture was allowed to warm up to rt over a period of 4 h and then stirred for a further 13 h. The reaction mixture was then oxidized by the addition of borane dimethyl sulphide complex (2.6 ml, 2M, 5.2 mmol). After a further 48 h, the reaction was quenched with water (30 ml) and the organics extracted into dichloromethane (3 x 30 ml) and dried ($MgSO_4$). Solvent was removed under reduced pressure to afford a mixture of two diastereoisomers in 68% yield.

(2R,4S,5R)-3,4-Dimethyl-2-adamantyl-5-phenyl-1,3,2-oxazaphospholidine-2-borane was then isolated by fractional crystallisation (ethyl acetate at -20°C) as white needles (650 mg, 38%): m.p. 152-154°C, Found C 69.88; H 9.40; N 3.82. $C_{20}H_{31}NOBP$ requires C 69.97; H 9.10; N 4.10%; $[\alpha]_D^{25}$ -17.3° (c 0.15, $CH_2Cl_2$); $\delta_H$ (500 MHz, $CDCl_3$) 7.401-7.351 (4H, m, Ph-ortho/meta H), 7.324 (1H, m, Ph-para H), 5.498 (1H, d, $J_{H4}$ 5.8, CHPh), 3.693 (1H, dq, $J_{H5}$ 5.8, $J_{CH3}$ 6.6, C<u>H</u>$CH_3$), 2.712 (3H, d, $J_P$ 9.7, $NCH_3$), 2.540 (1H, br, Ad-$H_B$), 2.366 (1H, br, Ad-$H_K$), 2.141-2.115 (2H, m, Ad-$H_C$,$H_L$), 2.027 (1H, br d, $J_P$ 5.7, Ad-$H_A$), 1.968-1.710 (8H, m, Ad-$H_E$,$H_F$,$H_G$,$H_H$,$H_I$,$H_J$,$H_N$,$H_O$), 1.622 (1H, br d, $J_{HC}$ 20.9, Ad-$H_D$), 1.475 (1H, br d, $J_{HL}$ 11.8, Ad-$H_M$), 0.820-0.350 (3H, br, $BH_3$) and 0.799 (3H, d, $J_{H4}$ 6.6, CHC<u>H</u>$_3$); $\delta_C$ (50.3 MHz, $CDCl_3$) 136.8 (Ph-ispo C), 128.5 (Ph-ortho C), 128.2 (Ph-para C), 126.4 (Ph-meta C), 84.0 (<u>C</u>HPh), 59.6 (<u>C</u>H$CH_3$), 49.0 (d, $J_P$ 22.9, Ad-$C_1$), 39.7 (d, $J_P$ 9.2 Ad-$C_7$), 39.3 (d, $J_P$ 13.2, Ad-$H_{10}$), 37.0 (Ad-$C_5$), 33.3 (Ad-$C_3$), 33.3 (Ad-$C_9$), 29.7 (d, $J_P$ 8.0, $NCH_3$), 27.9 (Ad-$C_{2/6/8}$), 27.7 (Ad-$C_{2/6/8}$), 27.6 (Ad-$C_{2/6/8}$), 27.1 (Ad-$C_4$) and 12.5 (CH<u>C</u>$H_3$); $\delta_P$ (101.3 MHz, $CDCl_3$) 152.8 (pseudo q, $J_B$ 75.7); $\delta_B$ (80.2 MHz, $CDCl_3$) -40.0 (dq, $J_P$ 75.7, $J_H$ 94.4); $\upsilon_{max}$ (KBr) 3446, 2976, 2959 (Ad-C-H st.), 2854 (Ad-C-H st.), 2824 ($NCH_3$ st.), 2400 ($BH_3$), 2375 ($BH_3$), 1606 (Ph-H vib.), 1559, 1496, 1451 ($CH_2$ deformations), 1381 ($CH_3$ symmetrical deformations), 1367, 1355, 1310, 1209, 1175, 1057, 1032 (P-Oalkyl), 964, 759, 737 (Ph-out of plane bending), 703 and 634; *m/z* ($EI^+$) 342 (M-1, 2%), 329 (35), 194 (100), 176 (25), 147 ($NCHCH_3CHPhO$, 15), 135 (Ad, 15), 91 (25), 79 (15), 67 (10) and 56 (10). (2R,4S,5R)-3,4-Dimethyl-2-adamantyl-5-phenyl-1,3,2-oxazaphospholidine-2-borane could not be isolated as a single diastereoisomer although samples up to 70% d.e. were obtained by fractional crystalisation.

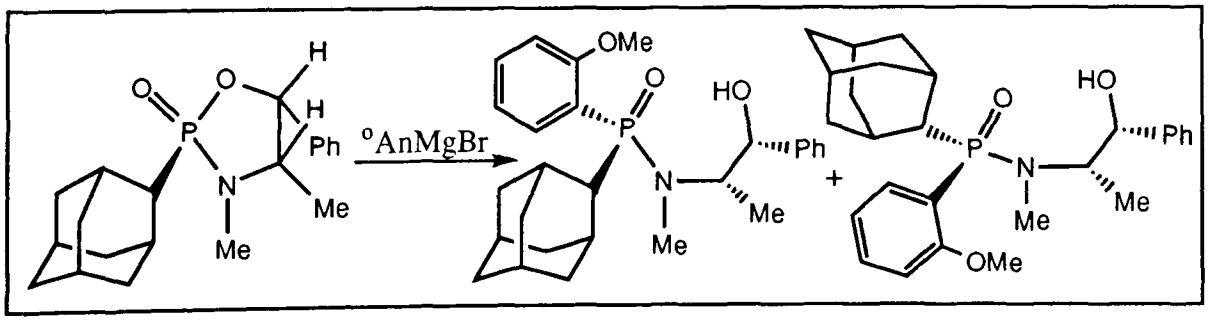
## Attempted synthesis of (4S,5R)-3,4-dimethyl-(1-adamantyl)-5-phenyl-1,3,2-oxazaphospholidine-2-oxide, actual synthesis of N-methyl-N-(1S, 2S)-(1-methyl-2-hydroxy-2-phenyl)ethyl-P-(dibutyl)phosphinamide




*n*-Butyl lithium (1.375 ml, 1.6 M in hexane, 2.20 mmol) was added to a solution of 1-adamantyl bromide (530 mg, 2.45 mmol, 15 ml THF) at -78 °C and stirred for 3 h. The resulting solution was subsequently added to a stirred THF solution of (2R, 4S, 5R)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine (230 mg, 1 mmol, 10 ml THF) at -78°C and allowed to slowly warm to rt. After a further 24 h stirring, *t*-butylhydroperoxide (0.35 ml, 3M, 1.05 mmol) was added and the mixture stirred for 16 h. Water (20 ml) was slowly added to quench the reaction and the organics were obtained by ethereal extraction (3 x 40 ml) and dried ($MgSO_4$) to give a mixture of products that were isolated *via* column chromatography (ethyl acetate as eluent). (2R,4S,5R)-3,4-Dimethyl-2-adamantyl-5-phenyl-1,3,2-oxazaphospholidin-2-oxide was obtained ($R_f$ 0.5, 14 mg, 4%) as a white crystaline material and gave identical spectroscopic data to an authentic sample. On washing the column with methanol, a methanolic solution of N-methyl-N-(1S, 2S)-(1-methyl-2-hydroxy-2-phenyl)ethyl-P-(dibutyl)phosphinamide was obtained. The solvent was removed under reduced pressure to yield the title compound as a white crystaline material (277 mg, 85%); m.p. 98-100°C. Found: C 66.40; H, 10.17; N, 4.06; $C_{18}H_{32}NO_2P$ requires C 66.43; H 9.91; N 4.30 %. $[\alpha]_D^{23}$ -34.3 (c 0.95, $CHCl_3$); $\delta_H$ (500 MHz, $CDCl_3$) 7.43 (2H, d, J 7.3, ortho H), 7.34 (2H, dd, J 7.3, J 7.3, meta H), 7.25 (1H, d, $J_{meta}$ 7.3, para H), 4.93 (1H, d, $J_{H5}$ 3.2, OH), 4.75 (1H, dd, $J_{H4}$ 3.3, $J_{OH}$

3.2, PhCH) 3.80 (1H, ddq, $J_{H5}$ 3.25, $J_{CH3}$ 7.1, $J_P$ 1.4, C<u>H</u>$CH_3$), 2.31 (3H, d, $J_P$ 9.5, $NCH_3$), 1.69-1.36 (12H, m, $CH_2$), 1.24 (3H, d, $J_{H4}$ 7.1, CHC<u>H</u>$_3$), 0.94 (3H, t, $J_{CH2}$ 7.2, C<u>H</u>$_3(CH_2)_3$) and 0.92 (3H, t, $J_{CH2}$ 7.0, C<u>H</u>$_3(CH_2)_3$); $\delta_C$ (62.8 MHz, $CDCl_3$) 142.7 (Ph-ispo C), 127.9 (Ph-meta C), 127.1 (Ph-para C), 126.8 (Ph-ortho C), 77.0 (PhCH), 57.5 (<u>C</u>H$CH_3$), 30.3 (d, $J_P$ 4.7, $NCH_3$), 28.3 (d, $J_P$ 16.3, $PCH_2$), 27.0 (d, $J_P$ 14.5, $PCH_2$), 24.1 (d, $J_P$ 5.7, $PCH_2$<u>C</u>$H_2$), 23.9 (d, $J_P$ 5.5, $PCH_2$<u>C</u>$H_2$), 23.6 ($PCH_2CH_2$<u>C</u>$H_2$), 23.5 ($PCH_2CH_2$<u>C</u>$H_2$), 13.9 (CH<u>C</u>$H_3$) and 13.6 (<u>C</u>$H_3(CH_2)_3P$); $\delta_P$ (101.3 MHz, $CDCl_3$) 54.28; $\upsilon_{max}$ (KBr) 3245 (O-H st), 3062, 3027 (Ar-H st), 2960 (C-H st), 2730 ($NCH_2$-H st), 1606 (Ar-H vib), 1496, 1456 (C-H deformations), 1405, 1376 ($CH_2$-H sym deformations), 1353, 1311, 1279 (P=O), 1263, 1181, 1094, 1045 (P-O-alkyl), 1028, 1011, 965, 901, 888, 805, 764 (Ar-H bend), 703 (Ar-H bend), 554, 513 and 476; *m/z* ($CI^+$, $NH_3$) 326 (M+1, 100%), 327 (25), 218 (55) and 58 (Ph, 40).

## <u>($S_P$)-N-Methyl-N-(1S,2S)-(1-methyl-2-hydroxy-2-phenyl)-ethyl-P(2-methoxyphenyl)-P(2-adamantyl)phosphinamide and ($R_P$)-N-Methyl-N-(1S,2S)-(1-methyl-2-hydroxy-2-phenyl)-ethyl-P(2-methoxyphenyl)-P(2-adamantyl)phosphinamide</u>

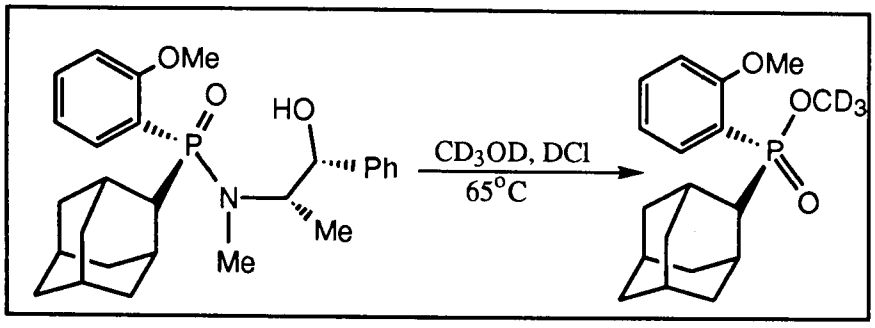



2-Methoxyphenylmagnesium bromide (40 ml, 1.6 M in THF) was added to a THF solution of (2R,4S,5R)-3,4-dimethyl-2-adamantyl-5-phenyl-1,3,2-oxazaphospholidin-2-oxide (4.50 g, 13.0 mmol) at rt. The reaction mixture was heated to 60°C and stirred for 10 days. Water (50 ml) was added and the organics extracted with ether (3 x 70 ml) to

yield a viscous oil. This material was purified by flash chromatography (flash silica, ethyl acetate / pentane : 1 / 1) to yield the title compounds. These were isolated by fractional crystallisation in ethyl acetate at -20°C and by TLC (ethyl acetate / pentane : 1 / 1 ) to give homochiral diastereoisomers. ($S_P$)-N-methyl-(1S,2S)-(1-methyl-2-hydroxy-2-phenyl)-ethyl-P(2-methoxyphenyl)-P(2-adamantyl)phosphinamide was obtained as a white powder (240 mg, 4 %); m.p. 162-164°C. Found: C 71.28; H, 8.22; N 3.15; $C_{27}H_{36}NO_3P$ requires C 71.49; H 7.99; N 3.10 %. $[\alpha]_D^{23}$ -18.8 (c 0.515, $CH_2Cl_2$); $\delta_H$ (500 MHz, $CDCl_3$) 8.050 (1H, ddd, $J_{H4}$ 1.8, $J_{H5}$ 7.5, $J_P$ 11.9, °An-H6), 7.460 (1H, ddd, $J_{H3}$ 8.2, $J_{H5}$ 7.9, $J_{H6}$ 1.8, °An-H4), 7.417 (2H, d, $J_{meta}$ 7.2, Ph-ortho H), 7.308 (2H, dd, $J_{para}$ 7.2, $J_{ortho}$ 7.3, Ph-meta H), 7.248 (1H, dd, $J_{meta}$ 7.2, $J_{meta'}$ 7.2, Ph-para H), 7.066 (1H, ddd, $J_{H4}$ 7.9, $J_{H6}$ 7.5, $J_P$ 0.6, °An-H5), 6.874 (1H, dd, $J_{H4}$ 8.2, $J_P$ 5.2, °An-H3), 6.437 (1H, d, $J_{H5}$ 6.3, PhCHOH), 4.463 (1H, dd, $J_{H4}$ 2.4, $J_{OH}$ 6.3, PhCH), 3.794 (3H, s, $OCH_3$), 3.756 (1H, ddq, $J_{H5}$ 2.4, $J_{Me}$ 7.2, $J_P$ 9.6, CHCH3) 3.003 (1H, br d, $J_P$ 12.7, Ad-$H_{A/B/K}$), 2.604 (1H, d, $J_P$ 11.3, Ad-$H_{A/B/K}$), 2.387 (2H, br m, Ad-$H_{A/B/K/C/L}$), 2.003 (3H, d, $J_P$ 9.4, $NCH_3$), 1.987-1.926 (3H, br m, Ad-$H_{C/L}$ and $2H_{E/H/I/J/N/O/P}$), 1.810-1.712 (5H, m, Ad-$H_{F/F/G/I/J/N/O/P}$), 1.647-1.597 (2H, br m, Ad-$H_D$, and Ad-$H_{F/G}$) and 1.418 (1H, br d, $J_{HL}$ 12.5, Ad-$H_M$) and 0.962 (3H, d, $J_{H4}$ 7.2, $CHCH_3$); $\delta_C$ (62.8 MHz, $CDCl_3$) 159.7 (°An-$C_2$), 142.1 (Ph-ispo C), 136.4 (d, $J_P$ 5.1, °An-$C_6$), 133.0 (°An-$C_4$), 127.5 (Ph-meta C), 127.2 (Ph-ortho C), 126.9 (Ph-para C), 120.9 (d, $J_P$ 9.1, °An-$C_5$), 120.8 (d, $J_P$ 107.0, °An-$C_1$), 109.9 (d, $J_P$ 6.2, °An-$C_3$), 76.4 (PhCH), 55.0 (d, $J_P$ 7.5, $CHCH_3$), 40.4 (d, $J_P$ 16.6, Ad-$C_{7/10}$), 39.8 (d, $J_P$ 14.5, Ad-$C_{7/10}$), 39.2 (d, $J_P$ 66.6, Ad-$C_1$) 37.5 (Ad-$C_5$), 32.9 (Ad-$C_{3/9}$), 32.2 (d, $J_P$ 5.7, Ad-$C_{3/9}$), 30.3 (d, $J_P$ 3.1, $NCH_3$), 28.4 (d, $J_P$ 9.3, Ad-$C_{2/8}$), 28.2 (d, $J_P$ 8.4, Ad-$C_{2/8}$), 27.1 (Ad-$C_4$, Ad-$C_4$) and 14.8 ($CHCH_3$); $\delta_P$ (101.3 MHz, $CDCl_3$) 43.74; $\upsilon_{max}$ (KBr) 3294 (O-H st.), 3063, 3027, 2904 (Ad-C-H st.), 2848 ($OCH_3$), 1590 (Ar-H vib), 1576 (Ar-H vib), 1477 (Ad-C-H deformations), 1451 (Ad-C-H deformations), 1431, 1273 (P=O), 1242, 1186, 1134, 1078, 1045, 1022, 835, 800, 759 (Ar-H bend), 701 (Ph-H bend), 682 and 541; *m/z* ($CI^+$, $NH_3$) 454 (M+1, 100%), 455 (M+2, 25), 346 (M-°An/PhCHOH, 55), 289 (M-

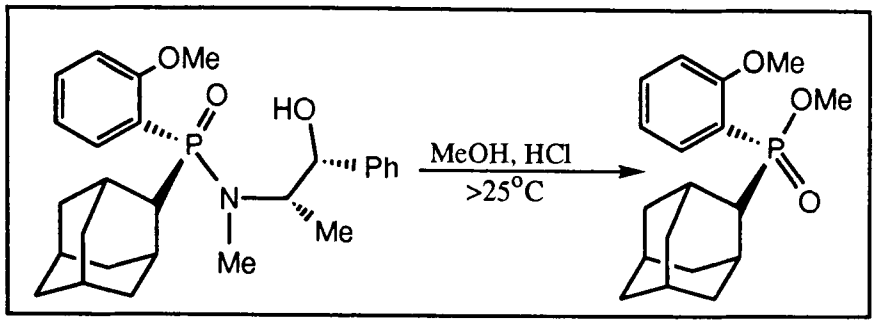
ephedrine, 15%) and 135 (Ad, 15). ($R_P$)-N-methyl-(1S,2S)-(1-methyl-2-hydroxy-2-phenyl)-ethyl-P(2-methoxyphenyl)-P(2-adamantyl)phosphinamide was obtained as a white powder (3.77 g, 68%); m.p. 214-216°C. Found: C 71.49; H, 8.41; N 3.06; $C_{27}H_{36}NO_3P$ requires C 71.49; H 7.99; N 3.10 %. $[\alpha]_D^{21}$ -23.6 (c 0.53, $CH_2Cl_2$); $\delta_H$ (500 MHz, $CDCl_3$) 8.101 (1H, ddd, $J_{H6}$ 1.8, $J_{H5}$ 7.5, $J_P$ 12.4, °An-H6), 7.477 (1H, ddd, $J_{H3}$ 8.3, $J_{H5}$ 7.3, $J_{H6}$ 1.8, °An-H4), 7.311 (2H, d, $J_{meta}$ 7.3, Ph-ortho H), 7.224 (2H, dd, $J_{para}$ 7.2, $J_{ortho}$ 7.3, Ph-meta H), 7.160 (1H, dd, $J_{meta}$ 7.2, $J_{meta'}$ 7.2, Ph-para H), 7.110 (1H, dd, $J_{H4}$ 7.3, $J_{H6}$ 7.5 °An-H5), 6.897 (1H, dd, $J_{H4}$ 8.3, $J_P$ 5.3, °An-H3), 6.067 (1H, d, $J_{H4}$ 1.7, PhCHOH), 4.882 (1H, s, PhCH), 3.861 (3H, s, $OCH_3$), 3.536 (1H, ddq, $J_{OH}$ 1.7, $J_{Me}$ 7.2, $J_P$ 14.4, CHCH3), 2.811 (1H, br d, $J_P$ 12.6, Ad-$H_{A/B/K}$), 2.693 (1H, d, $J_P$ 12.0, Ad-$H_{A/B/K}$), 2.614 (3H, d, $J_P$ 8.8, $NCH_3$), 2.412-2.387 (2H, m, Ad-$H_{A/B/K/C/L}$), 1.987-1.935 (3H, br m, Ad-$H_{C/L}$ and $2H_{E/H/I/J/N/O/P}$), 1.827-1.700 (4H, m, Ad-$H_{F/I/J/N/O/P}$), 1.672-1.646 (3H, m, Ad-$H_{D/F/G}$) and 1.419 (1H, br d, $J_{HL}$ 12.3, Ad-$H_M$) and 1.016 (3H, d, $J_{H4}$ 7.2, $CHCH_3$); $\delta_C$ (62.8 MHz, $CDCl_3$) 159.6 (°An-$C_2$), 142.8 (Ph-ispo C), 135.3 (d, $J_P$ 5.2, °An-$C_6$), 132.9 (°An-$C_4$), 127.8 (Ph-meta C), 126.7 (Ph-para C), 126.4 (Ph-ortho C), 121.2 (d, $J_P$ 9.0, °An-$C_5$), 110.2 (d, $J_P$ 7.3, °An-$C_3$), 63.6 (PhCH), 55.2 ($CHCH_3$), 41.7 (d, $J_P$ 88.8, Ad-$C_1$), 40.5 (d, $J_P$ 16.5, Ad-$C_{7/10}$), 40.3 (d, $J_P$ 14.7, Ad-$C_{7/10}$), 37.6 (Ad-$C_5$), 34.8 (d, $J_P$ 3.5, $NCH_3$), 33.2 (Ad-$C_{3/9}$), 32.4 (Ad-$C_{3/9}$), 28.3 (Ad-$C_{2/6/8}$), 28.3 (Ad-$C_{2/6/8}$), 28.1 (Ad-$C_{2/6/8}$), 27.2 (Ad-$C_4$) and 12.2 ($CHCH_3$); $\delta_P$ (101.3 MHz, $CDCl_3$) 43.86; $\upsilon_{max}$ (KBr) 3213 (O-H st.), 3062, 3028 (Ad-C-H st.), 2967, 2903, 2850 ($OCH_3$), 2673, 1933, 1815, 1589 (Ar-H vib), 1575 (Ar-H vib), 1474 (Ad-C-H deformations), 1429, 1387, 1370, 1343, 1268 (P=O), 1240, 1211, 1199, 1163, 1132, 1091, 1077, 1063, 1042, 1020, 994, 938, 769 (Ar-H bend), 757 (Ar-H bend), 712 (Ph-H bend), 700 (Ph-H bend), 682 (Ph-H bend), 566, 534 and 490; *m/z* ($CI^+$, $NH_3$) 454 (M+1, 100%), 455 (M+2, 25), 346 (M-°An/PhCHOH, 40), 289 (M-ephedrine, 10) and 135 (Ad, 5).

## (+)-(S)-$d_3$-Methyl-(2-methoxyphenyl)-(2-adamantyl)phosphinate




A 5 mm NMR tube was charged with ($R_P$)-N-methyl-(1S,2S)-(1-methyl-2-hydroxy-2-phenyl)-ethyl-P(2-methoxy phenyl)-P(2-adamantyl)phosphinamide (36 mg, 0.08 mmol) and dissolved in deutero-methanol (500 µl). Deuterium chloride (50 µl, 20% in deuterium oxide) was then added and the reaction mixture heated to 65°C. After 102 h heating, no starting materal was observed by $^1$H NMR and the reaction was thus complete. The reaction was quenched by the addition of water (5 ml) and the organics extracted into dichloromethane (3 x 20 ml). The organics were then purified by being passed down a short column (flash silica, ethyl acetate, $R_f$ 0.5) and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded (+)-(S)-d3-methyl-(2-methoxyphenyl)-(2-adamantyl)phosphinate as a white crystalline solid (22 mg, 86%): m.p. 108-110°C; $\delta_H$ (250 MHz, $CDCl_3$) 8.00 (1H, ddd, $J_{H4}$ 1.8, $J_{H5}$ 7.5, $J_P$ 12.4, °An-H6), 7.53 (1H, ddd, $J_{H3}$ 8.3, $J_{H5}$ 7.3, $J_{H6}$ 1.8, °An-H4), 7.09 (1H, ddd, $J_{H4}$ 7.3, $J_{H6}$ 7.5, $J_P$ 1.2, °An-H5), 6.94 (1H, dd, $J_{H4}$ 8.3, $J_P$ 5.4, °An-H3), 3.89 (3H, s, OMe), 2.66 (1H, br d, $J_{HD}$ 13.0, Ad-$H_C$), 2.58-2.51 (2H, m, Ad-$H_A$,$H_B$), 2.30 (1H, br d, $J_{HM}$ 12.7, Ad-$H_L$), 1.93-1.58 (10H, m, Ad-$H_D$,$H_E$,$H_F$,$H_G$,$H_H$,$H_I$,$H_J$,$H_K$,$H_N$ and $H_O$) and 1.47 (1H, br d, $J_{HL}$ 12.7, Ad-$H_M$); $\delta_P$ (101.3 MHz, $CDCl_3$) 47.08; *m/z* ($CI^+$, $NH_3$) 324 (M+1, 100%), 325 (20) and 292 (M-OMe, 20).

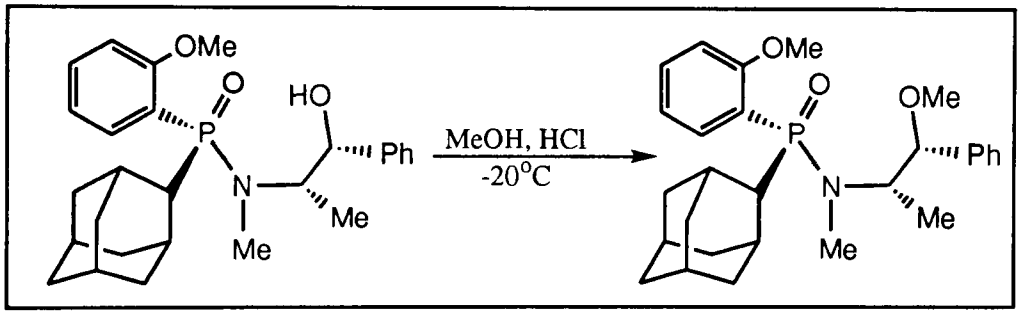
(+)-(S)-Methyl-(2-methoxyphenyl)-(2-adamantyl)phosphinate




($R_P$)-N-methyl-(1S,2S)-(1-methyl-2-hydroxy-2-phenyl)-ethyl-P(2-methoxyphenyl) -P(2-adamantyl)phosphinamide (316 mg, 0.70 mmol) was dissolved in acidic methanol (20 ml, O.18 M HCl in MeOH) and stirred at 55°C for 4 days. Solvent was removed *in vacuo* to yield a viscous oil which was dissolved in ethyl acetate. (-)-Ephedrine precipitates out and the title compound was purified by column chromatography (ethyl acetate as eluent, $R_f$ 0.6). (+)-(S)-Methyl-(2-methoxyphenyl)-(2-adamantyl)phosphinate was obtained as white crystals (120 mg, 54 %): m.p. 106-108°C , Found C 67.59; H 7.72. $C_{18}H_{25}O_3P$ requires C 67.49; H 7.86; $\delta_H$ (500 MHz, $CDCl_3$) 7.996 (1H, ddd, $J_{H4}$ 1.9, $J_{H5}$ 7.5, $J_P$ 12.3, °An-H6), 7.524 (1H, ddd, $J_{H3}$ 8.3, $J_{H5}$ 8.3, $J_{H6}$ 1.9, °An-H4), 7.087 (1H, dddd, $J_{H4}$ 8.3, $J_{H6}$ 7.5, $J_P$ 2.1, $J_{H3}$ 0.7, °An-H5), 6.935 (1H, dd, $J_{H4}$ 8.3, $J_P$ 5.3, °An-H3), 3.884 (3H, s, OMe), 3.542 (3H, d, $J_P$ 11.1, $POCH_3$), 2.656 (1H, br m, $J_{HD}$ 12.6, J 2.4, Ad-$H_C$), 2.540 (1H, br d, $J_P$ 16.0, Ad-$H_A$), 2.475 (1H, br m, Ad-$H_B$), 2.302 (1H, ddd, $J_{HM}$ 12.6, $J_{HF}$ 2.4, $J_{HI}$ 2.4, Ad-$H_L$), 1.921-1.873 (3H, br m, Ad-$H_H$,$H_E$ and $H_{I/J}$), 1.808-1.697 (5H, br m, Ad-$H_F$, $H_G$, $H_K$, $K_O$ and $H_{I/J}$), 1.676-1.619 (2H, br m, Ad-$H_D$, $H_N$) and 1.473 (1H, br d, $J_{HL}$ 12.6, Ad-$H_M$); $\delta_C$ (62.9 MHz, $CDCl_3$) 160.5 (°An-$C_2$), 136.6 (d, $J_P$ 5.9, °An-$C_6$), 134.0 (°An-$C_4$), 120.8 (d, $J_P$ 11.1, °An-$C_5$), 117.7 (d, $J_P$ 112.9, °An-$C_1$), 110.6 (d, $J_P$ 7.4, °An-$C_3$), 55.5 ($OCH_3$), 50.7 (d, $J_P$ 7.4, $POCH_3$), 44.4 (d, $J_P$ 101.7, Ad-$C_1$), 39.9 (Ad-$C_7$), 39.7 (d, $J_P$ 3.5, Ad-$H_{10}$), 37.5 (Ad-$C_5$), 33.2 (Ad-$C_3$), 32.8 (Ad-$C_9$), 28.1 (Ad-$C_{6/4}$), 27.8 (Ad-$C_2$, Ad-$C_8$) and 27.3 (Ad-$C_{6/4}$); $\delta_P$

(101.3 MHz, $CDCl_3$) 47.23; $\upsilon_{max}$ (KBr) 3008, 2905 ($CH_2$ st), 2848 (An-$OCH_3$, C-H st), 2360, 1593 (Ar-H vib.), 1479, 1471 ($CH_2$, C-H deformations), 1451 ($CH_2$, C-H deformations), 1432, 1275 (P=O), 1249, 1222, 1206, 1185, 1157, 1135, 1083, 1049 (P-OMe), 1030, 840, 804, 774, 691, 573 and 495; *m/z* ($CI^+$, $NH_3$) 321 (M+1, 100%), 322 (20) and 289 (M-OMe, 15).

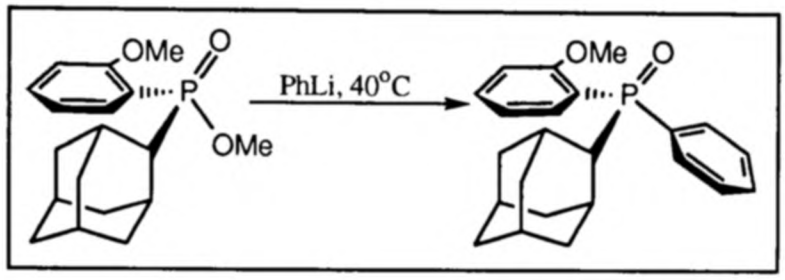
## ($S_P$)-N-Methyl-N-(1S,2S)-(1-methyl-2-methoxy-2-phenyl)-ethyl-P(2-methoxyphenyl)-P(2-adamantyl)phosphinamide and ($R_P$)-N-Methyl-N-(1S,2S)-(1-methyl-2-methoxy-2-phenyl)-ethyl-P(2-methoxyphenyl)-P(2-adamantyl)phosphinamide




($R_P$)-N-methyl-(1S,2S)-(1-methyl-2-hydroxy-2-phenyl)ethyl-P(2-methoxyphenyl)-P(2-adamantyl)phosphinamide (453 mg, 1.0 mmol) was dissolved in acidic methanol (20 ml, 0.5M HCl in MeOH) and stood at -20°C for 8 days. Solvent was removed *in vacuo* to yield a viscous oil which was dissolved in ethyl acetate. (-)-Ephedrine precipitates out and the title compound was purified by column chromatography (ethyl acetate as eluent, Rf 0.3). ($R_P$)-N-Methyl-N-(1S,2S)-(1-methyl-2-methoxy-2-phenyl)-ethyl-P(2-methoxy phenyl)-P(2-adamantyl)phosphinamide was obtained as an oil (184 mg, 38 %); $\delta_H$ (500 MHz, $CDCl_3$) 8.008 (1H, ddd, $J_{H4}$ 1.7, $J_{H5}$ 7.5, $J_P$ 12.1, An-H6), 7.424 (1H, ddd, $J_{H5}$ 7.9, $J_{H3}$ 8.1, $J_{H6}$ 1.7, An-H4), 7.199-7.117 (3H, m, Ph-H), 7.054 (1H, dd, $J_{H4}$ 7.9, $J_{H6}$ 7.5, An-H5), 7.039 (2H, m, Ph-H), 6.842 (1H, dd, $J_P$ 4.8, $J_{H4}$ 8.1, An-H3), 3.813 (3H, s, An-OMe), 3.062 (3H, s, HC-OMe), 2.732 (3H, d, $J_P$ 9.3, $NCH_3$), 2.60-1.20 (15H, br

m, Ad-H) and 1.081 (3H, d, $J_{CH}$ 6.8, $CHCH_3$); *m/z* ($CI^+$, $NH_3$) 468 (M+1, 100%), 469 (30), 436 (M-OMe, 10), 346 (AdAnP(O)NMeCHMe, 30), 259 (AdAnPO, 10) and 135 (Ad, 5).

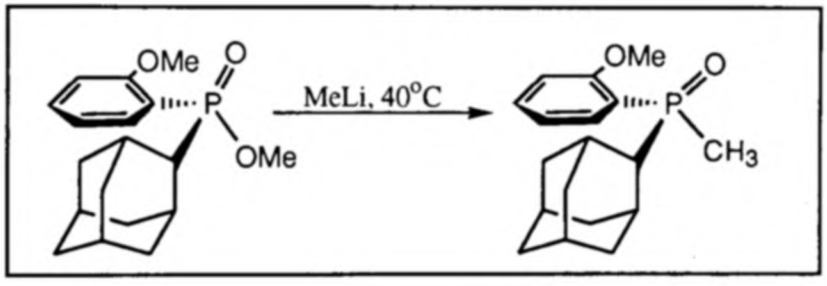
## (R)-2-Adamantyl-2-methoxyphenyl-phenyl-phosphine oxide




Phenyllithium (19 ml, 1.8 M in cyclohexane / ether : 70 / 30) was added to (+)-(S)-methyl adamantyl-2-methoxyphenyl-phosphinate (220 mg, 0.68 mmol) at rt and the solution was heated to 30°C and stirred overnight. The reaction was quenched by the addition of water (20 ml) and the organics extracted into ether (3 x 25 ml). The ethereal layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to afford a thick dark yellow oil which solidified on standing. This material was purified by flash chromatography (flash silica, ethyl acetate / hexane : 1 / 1) to yield, after solvent removal, a pale yellow oil which forms a white solid on standing (214 mg, 85 %); m.p. 157-159°C. Found: C 74.92; H, 7.39 $C_{23}H_{27}O_2P$ requires C 75.39; H 7.43 %; $\delta_H$ (500 MHz, $CDCl_3$) 8.156 (1H, ddd, $J_{H4}$ 1.8, $J_{H5}$ 7.6, $J_P$ 12.4, °An-H6), 7.941 (2H, ddd, $J_{meta}$ 7.7, $J_{para}$ 1.4, $J_P$ 10.6, Ph-ortho H), 7.466 (1H, ddd, $J_{H3}$ 8.2, $J_{H6}$ 1.8, $J_{H5}$ 7.4, °An-H4), 7.439-7.401 (3H, m, Ph-meta/para H), 7.121 (1H, dd, $J_{H4}$ 7.4, $J_{H6}$ 7.5, °An-H5), 6.872 (1H, dd, $J_{H4}$ 8.2, $J_P$ 5.1, °An-H3), 3.820 (3H, s, $OCH_3$) 2.981 (1H, d, $J_P$ 8.3, Ad-$H_{A/B/K}$), 2.791 (1H, d, $J_{HM}$ 12.6, Ad-$H_L$), 2.422 (1H, d, $J_{HD}$ 12.5, Ad-$H_C$), 2.253 (1H, br, Ad-$H_{A/B/K}$), 1.968-1.719 (9H, m, Ad-$H_{A/B/K}$, Ad-$H_E$, $H_F$, $K_G$, $H_H$, $H_I$, $H_J$, $H_N$ and $H_O$), 1.588 (1H, d, $J_{HL}$ 12.5, Ad-$H_D$) and 1.504 (1H, d, $J_{HL}$ 12.6, Ad-$H_M$); $\delta_C$ (62.8

MHz, $CDCl_3$) 159.0 ($^oAn$-$C_2$), 134.8 (d, $J_P$ 3.8, $^oAn$-$C_6$), 134.3 (d, $J_P$ 94.0, Ph-ispo C), 133.6 ($^oAn$-$C_4$), 131.1 (Ph-ortho), 130.9 (Ph-meta C), 130.7 (Ph-para C), 121.2 (d, $J_P$ 10.9, $^oAn$-$C_5$), 121.1 (d, $J_P$ 90.7, $^oAn$-$C_1$), 110.5 (d, $J_P$ 7.1, $^oAn$-$C_3$), 55.1 ($OCH_3$), 42.5 (d, $J_P$ 71.9, Ad-$C_1$), 40.2 (Ad-$C_{7/10}$), 40.0 (Ad-$H_{7/10}$), 37.4 (Ad-$C_5$), 33.1 (Ad-$C_{3/9}$), 33.0 (Ad-$C_{3/9}$), 28.8 (Ad-$C_6$), 28.2 (Ad-$C_{2/8}$), 28.1 (Ad-$C_{2/8}$), 27.2 (Ad-$C_4$) ; $\delta_P$ (101.3 MHz, $CDCl_3$) 34.67; $\upsilon_{max}$ (KBr) 2897, 2851 ($OCH_3$), 1589, 1577, 1478, 1459, 1432, 1275 (P=O), 1175, 1133, 1106, 1076, 1018, 692 and 563; *m/z* ($CI^+$, $NH_3$) 367 (M+1, 100%), 368 (M+2, 25), 335 (M-OMe+1, 20), 233 (5), 199 (5) and 91 (5).

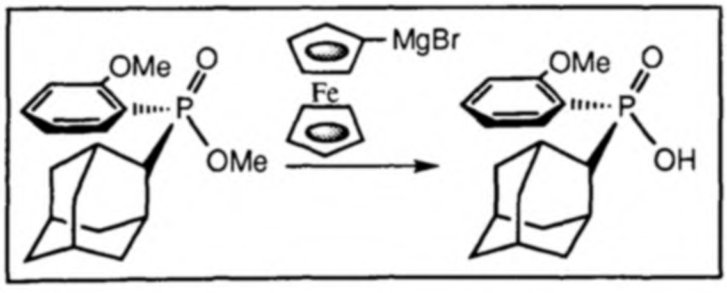
## (R)-2-Adamantyl-2-methoxyphenyl-methyl-phosphine oxide




Methyllithium (2.5 ml, 0.75 M in ether) was added to an ethereal solution of (+)-(S)-methyl adamantyl-2-methoxyphenyl-phosphinate (32 mg, 0.1 mmol, 3 ml of ether) at rt. After 2 days stirring at rt, the reaction was quenched with water (5 ml) and the organics extracted into ether (3 x 10 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford a thick oil which was purified by flash chromatography (ethyl acetate as eluent). After solvent removal, (R)-2-adamantyl-2-methoxyphenyl-methyl-phosphine oxide was obtained as white crystals : m.p. 133-135°C, Found C 70.82; H 8.21. $C_{18}H_{25}OP$ requires C 71.03; H 8.28; $\delta_H$ (500 MHz, $CDCl_3$) 8.034 (1H, ddd, $J_{H4}$ 1.8, $J_{H5}$ 7.4, $J_P$ 12.2, $^oAn$-H6), 7.576 (1H, dddd, $J_{H3}$ 8.1, $J_{H5}$ 7.3, $J_{H6}$ 1.8, $J_P$ 0.6, $^oAn$-H4), 7.132 (1H, dddd, $J_{H4}$ 7.3, $J_{H6}$ 7.4, $J_P$ 1.0, $J_{H3}$ 1.0, $^oAn$-H5), 6.907 (1H, dd, $J_{H4}$ 8.1, $J_P$ 4.8, $^oAn$-H3), 3.868 (3H, s, OMe), 2.738 (1H, br d, $J_{HD}$ 12.6, Ad-$H_C$), 2.478

(1H, br, Ad-$H_B$), 2.335-2.288 (2H, br m, Ad-$H_A$ and Ad-$H_L$), 2.075-1.930 (3H, br m, Ad-$H_H$,$H_E$ and $H_{I/J}$), 1.852-1.590 (7H, m, Ad-$H_F$, $H_G$, $H_K$, $K_O$, $H_D$, $H_N$ and $H_{I/J}$), 1.712 (3H, d, $J_P$ 13.0, $PCH_3$) and 1.431 (1H, br d, $J_{HL}$ 12.6, Ad-$H_M$); $\delta_C$ (62.9 MHz, $CDCl_3$) 159.1 (d, $J_P$ 3.5, °An-$C_2$), 135.0 (°An-$C_6$), 133.2 (°An-$C_4$), 121.1 (d, $J_P$ 11.2, °An-$C_5$), 110.2 (d, $J_P$ 7.5, °An-$C_3$), 55.2 ($OCH_3$), 45.1 (d, $J_P$ 70.3, Ad-$C_1$), 40.2 (d, $J_P$ 13.9, Ad-$C_7$), 40.0 (d, $J_P$ 11.2, Ad-$H_{10}$), 37.5 (Ad-$C_5$), 33.3 (Ad-$C_3$), 32.9 (Ad-$C_9$), 28.8 (Ad-$C_{2/4/6/8}$), 28.6 (Ad-$C_{2/4/6/8}$), 28.2 (Ad-$C_{2/4/6/8}$), 27.4 (Ad-$C_{2/4/6/8}$) and 15.3 (d, $J_P$ 70.3, $PCH_3$); $\delta_P$ (101.3 MHz, $CDCl_3$) 40.62; $\upsilon_{max}$ (KBr) 3437, 2904 ($CH_2$ st), 2849 ($OCH_3$, C-H st), 1591 (Ar-H vib.), 1577, 1478, 1451 ($CH_2$, C-H deformations), 1433 ($CH_2$, C-H deformations), 1343, 1274 (P=O), 1242, 1216, 1142, 1019, 889, 760 and 726; *m/z* ($CI^+$, $NH_3$) 305 (M+1, 100%), 306 (20) and 273 (M-OMe, 20).

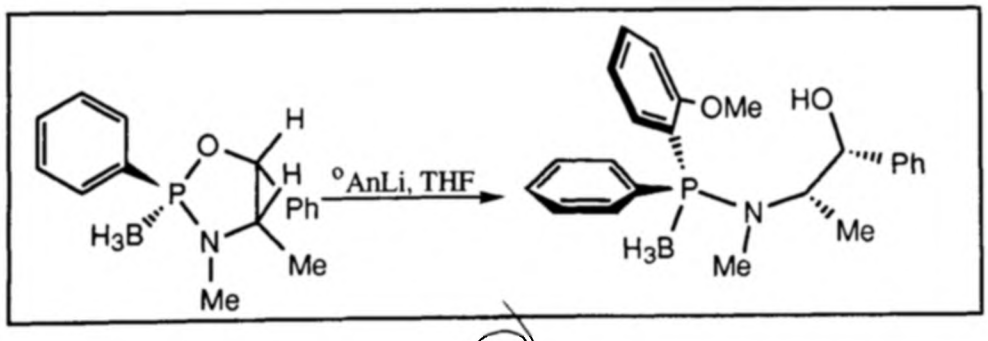
## Attempted synthesis of 2-adamantyl-ferrocenyl-2-methoxyphenyl-phosphine oxide, actual synthesis of 2-adamantyl-2-methoxyphenyl phosphonic acid




Ferrocenylmagnesium bromide (4 ml, 0.1 M, THF) was added to (S)-methyl-2-adamantyl-2-methoxyphenyl-phosphinate (26 mg, 0.08 mmol) and the solution heated to 65°C. After 96 h, the reaction was quenched by the addition of water (5 ml) and the organics extracted into ether (3 x 15 ml). The ethereal solution was dried ($MgSO_4$) and solvent removed under reduced pressure to yield ferrocene but no phosphorus containing compounds. The aqueous washings were acidified (HCl, 0.1M) to pH 1 and then extracted

with ether (3 x 20 ml). This solution was dried and solvent removed *in vacuo* to yield 2-adamantyl-2-methoxyphenyl phosphonic acid as an off white solid (20 mg, 81%); m.p. 208-211°C. $\delta_H$ (200 MHz, MeOD) 7.78 (1H, ddd, $J_{H5}$ 7.6, $J_{H3}$ 1.5, $J_P$ 12.6, An-H6), 7.56 (1H, ddd, $J_{H6}$ 1.5, $J_{H5}$ 6.9, $J_{H3}$ 6.9, An-H4), 7.11-7.03 (2H, m, An-H3, H5), 2.54 (1H, br d, J 16.2, Ad-H), 2.46-2.41 (2H, m, Ad-H), 2.10 (2H, br, Ad-H), 1.86-1.78 (8H, br m, Ad-H), 1.59-1.54 (2H, br m, Ad-H); $\upsilon_{max}$ (KBr) 2905 ($CH_2$ C-H st.), 2848 ($OCH_3$), 2354 ($BH_3$), 2654 (POO-H st.), 1656, 1593, 1579, 1480, 1462, 1450, 1429, 1278, 1246, 1194 (P=O), 1168, 1142, 1100, 1083, 1016, 949, 940, 803, 774, 734, 691 and 661; *m/z* ($EI^+$) 305 (M-1, 45%), 306 (M, 15), 307 (M+1, 5), 275 ($M-O_2$, 100%), 186 (20), 154 (30) and 135 (Ad, 20).

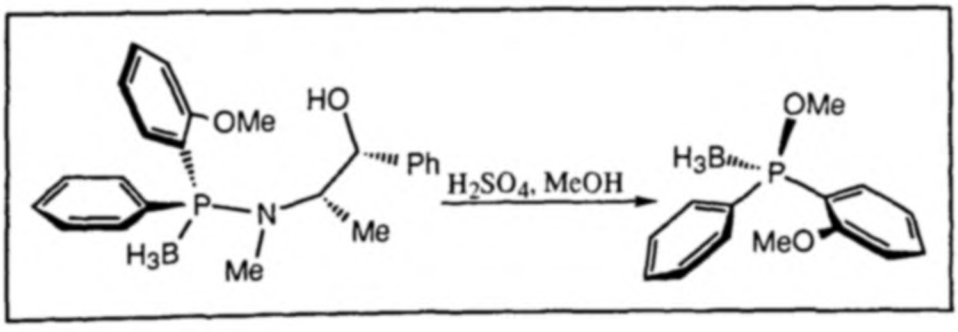
## ($S_P$)-N-Methyl-N-(1S,2S)-(1-methyl-2-hydroxy-2-phenyl)-ethyl-P-(2-methoxyphenyl)-P-(phenyl)phosphine-P-borane




In a method similar to that of Juge, 2-methoxyphenyllithium (500 ml, 0.3M, 150 mmol) was added to a stirred THF (300 ml) solution of (2R,4S,5R)-3,4-dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidin-2-borane (21.6 g, 76 mmol) at -78°C. The reaction was stirred for 4 h and then quenched by the addition of water (200 ml). The organics were extracted with ether (3 x 150 ml) and dried ($MgSO_4$) to yield an off white solid. This was purified by flash chromatography (flash silica, ethyl acetate / toluene : 1 / 20, $R_f$ 0.5) to yield ($S_P$)-N-methyl-N-(1S,2S)-(1-methyl-2-hydroxy-2-phenyl)-ethyl-P-(2-methoxy

phenyl)-P-(phenyl)phosphine-P-borane as white crystals (28.1 g, 95%); m.p. 108-110°C (Lit 111°C); $\delta_H$ (500 MHz, $CDCl_3$) 7.570 (1H, ddd, $J_{H4}$ 1.7, $J_{H5}$ 7.6, $J_P$ 12.7, An-H6), 7.466 (3H, m, J 7.2, PPh-ortho H, An-H4), 7.337 (2H, t, J 7.7, CPh-ortho-H), 7.297-7.249 (4H, m, PPh-meta/para H, CPh-para H), 7.177 (2H, t, J 7.1, CPh-meta H), 7.026 (1H, dddd, $J_{H3}$ 1.2, $J_{H4}$ 7.5, $J_{H6}$ 7.5, $J_P$ 1.2, An-H5), 6.918 (1H, dd, $J_{H4}$ 8.1, $J_P$ 4.0, An-H3), 4.924 (1H, dd, $J_{CHCH3}$ 4.6, $J_{OH}$ 4.6, PhCH), 4.344 (1H, dq, $J_{CH3}$ 6.8, $J_{PhCH}$ 4.6, $CHCH_3$), 3.594 (3H, s, $OCH_3$), 2.565 (3H, d, $J_P$ 8.1, $NCH_3$) and 1.229 (3H, d, $J_{CHCH3}$ 6.8, $CHCH_3$) (Lit.[Juge] 7.6-6.8 (14H, m), 4.84 (1H, d, J 7.5), 4.31 (1H, m), 3.52 (3H, s), 2.50 (3H, d, J 8.0), 1.19 (3H, d, J 7.5) and 1.7-0.2 (3H, m)); $\delta_C$ (125.8 MHz, $CDCl_3$) 161.2 (An-$C_2$), 142.6 (CPh-ipso C), 135.0 (An-$C_6$), 133.2 (An-$C_4$), 132.3 (d, $J_P$ 75.0, PPh-ipso C), 131.0 (d, $J_P$ 10.0, PPh-ortho C), 128.4 (CPh-meta C), 127.9 (CPh-para C), 127.6 (PPh-meta C), 126.5 (CPh-ortho C), 120.8 (An-$C_5$), 111.5 (An-$C_3$), 79.0 (PhCH), 58.1 ($CHCH_3$), 55.1 ($OCH_3$), 31.0 ($NCH_3$) and 12.5 ($CHCH_3$); $\delta_P$ (202.5 MHz, $CDCl_3$) 69.92 (br d, $J_B$ 87.2).

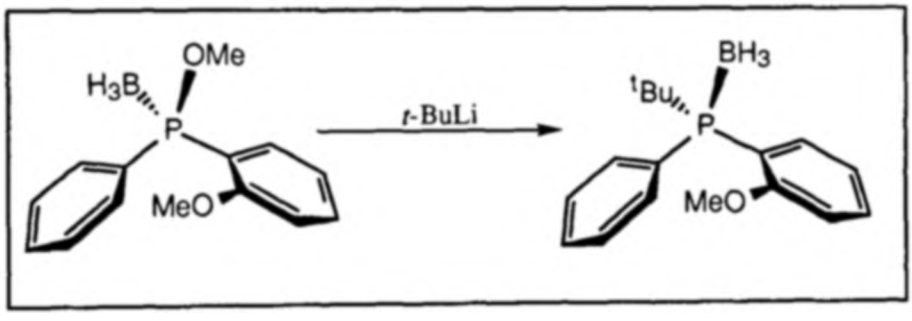
(+)-(R)-Methyl-(2-methoxyphenyl)-(phenyl)phosphite-P-borane




Methanol (1000 ml) was added to a Schlenk containing ($S_P$)-N-methyl-N-(1S,2S) (1-methyl-2-hydroxy-2-phenyl)-ethyl-P(2-methoxyphenyl)-P-(phenyl)phosphine-borane (29.9 g, 76 mmol) and the resulting solution stirred. Sulphuric acid (4.4 ml, 98%) was then added and the reaction mixture stirred overnight at rt. The methanol was then removed under reduced pressure and dichloromethane (200 ml) added to the residues. (-)-Ephedrine

was removed by filteration and the filterate was reduced *in vacuo*. The thick oil produced was passed through a short column (flash silica, ethyl acetate / toluene : 1 / 20) to afford, after solvent removal, (+)-(R)-methyl-(2-methoxyphenyl)-phenylphosphite-P-borane as a viscous oil (16.1 g, 81%); $\delta_H$ (500 MHz, $CDCl_3$) 7.812 (1H, ddd, $J_{H4}$ 1.7, $J_{H5}$ 7.6, $J_P$ 12.3, An-H6), 7.751 (2H, ddd, $J_{meta}$ 8.2, $J_{para}$ 1.3, $J_P$ 11.2, Ph-ortho), 7.508 (1H, dddd, $J_{H3}$ 8.0, $J_{H5}$ 9.3, $J_{H6}$ 1.7, $J_P$ 0.6, An-H4), 7.493 (1H, m, Ph-para H), 7.433 (2H, m, Ph-meta H), 7.083 (1H, dddd, $J_{H4}$ 9.3, $J_{H6}$ 7.5, $J_{H3}$ 1.0, $J_P$ 2.1, An-H5), 6.882 (1H, dd, $J_{H4}$ 8.0, $J_P$ 12.0, POMe), 3.663 (3H, s, OMe) and 1.350-0.750 (3H, br, $BH_3$) (Lit 7.8-6.8 (9H, m), 3.73 (3H, d, $J_P$ 12), 3.62 (3H, s), 1.7-0.3 (3H, m, $J_B$ 104).

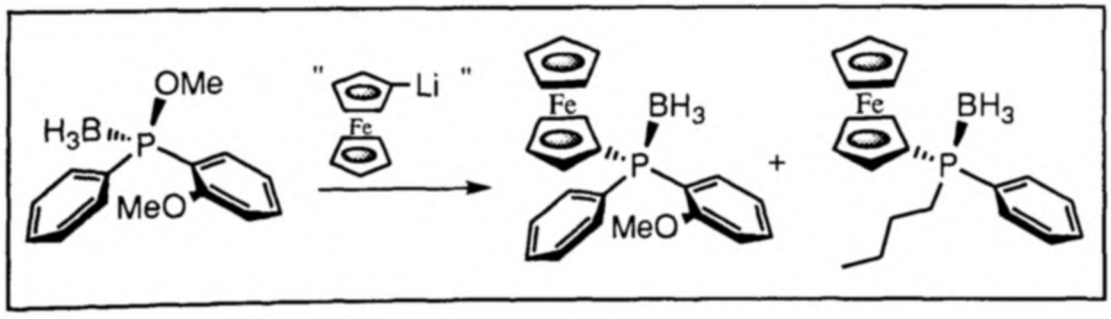
## (S)-*t*-Butyl-(2-methoxyphenyl)-phenyl phosphine borane




*t*-Butyllithium (8.8 ml, 1.7 M in hexane, 15 mmol) was slowly added to a stirred ethereal solution of (+)-(R)-methyl-(2-methoxyphenyl)phenylphosphinite-P-borane (2.60 g, 10 mmol, 50 ml of ether) at -60°C. The reaction was slowly warmed to rt over 6 h and stirred overnight. The reaction was quenched by slow addition of water (20 ml) at 0°C and the organics extracted into ether (3 x 30 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield an off white powder. This material was purified by column chromatography (flash silica, ethyl acetate / pentane : 1 / 10) to yield a white powder (1.46 g, 51%); m.p. 85-87°C. Found: C 71.48; H, 8.16, $C_{17}H_{24}BOP$ requires C 71.35; H 8.45 %. $[\alpha]_D^{23}$ +9.3 (c 0.505, MeOH); $\delta_H$ (500 MHz, $CDCl_3$) 7.987 (1H, ddd, $J_{H6}$ 1.5, $J_{H5}$ 7.7, $J_P$ 12.6, °An-H6), 7.696 (2H, ddd, $J_{meta}$ 6.8, $J_{para}$ 1.6, $J_P$ 8.8, Ph-ortho H), 7.500

(1H, dd, $J_{H3}$ 8.3, $J_{H5}$ 7.5, °An-H4), 7.411 (1H, dt, $J_{meta}$ 7.3, $J_{ortho}$ 1.7, Ph-para H), 7.374 (2H, ddd, $J_{para}$ 2.1, $J_{ortho}$ 6.8, $J_P$ 7.3, Ph-meta H) 7.069 (1H, ddd, $J_{H4}$ 7.5, $J_{H6}$ 7.7, $J_P$ 1.0, °An-H5), 6.912 (1H, dd, $J_{H4}$ 8.3, $J_P$ 3.4, °An-H3), 3.579 (3H, s, $OCH_3$) and 1.346 (9H, d, $J_P$ 14.4, $C(CH_3)_3$); $\delta_C$ (62.8 MHz, $CDCl_3$) 161.0 (°An-$C_2$), 137.4 (d, $J_P$ 12.1, °An-$C_6$), 133.2 (°An-$C_4$), 132.4 (d, $J_P$ 9.1, Ph-ortho C), 130.4 (d, $J_P$ 53.5, Ph-ispo C), 129.8 (Ph-para C), 127.8 (d, $J_P$ 9.1, Ph-meta C), 120.8 (d, $J_P$ 10.6, °An-$C_5$), 116.4 (d, $J_P$ 48.8, °An-$C_1$), 111.4 (d, $J_P$ 4.5, °An-$C_3$), 54.7 ($OCH_3$), 31.5 (d, $J_P$ 32.2, $(CH_3)_3\underline{C}$) and 28.0 (d, $J_P$ 2.4, $(\underline{C}H_3)_3C$); $\delta_P$ (101.3 MHz, $CDCl_3$) 36.74 (br, $J_B$ 57.3); $\delta_B$ (80.21 MHz, $CDCl_3$) -37.8 (dq, $J_P$ 57.3); $\upsilon_{max}$ (KBr) 3089, 3064, 2960 ($C(CH_3)_3$ C-H st.), 2867 ($C(CH_3)_3$ C-H st.), 2839 ($OCH_3$), 2354 ($BH_3$), 1588 (Ar-H vib), 1573, 1471, 1434, 1399 ($C(CH_3)_3$), 1371 ($C(CH_3)_3$), 1274, 1251, 1181, 1163, 1129, 1101, 1020, 802, 759 (Ar-H bend), 741 (Ar-H bend), 697 (Ph-H bend) and 636; *m/z* ($EI^+$) 285 (M-1, 15%), 272 (M-$BH_3$, 100), 273 (M-$BH_3$, 15), 216 (M-$^t$Bu-$BH_3$, 90%), 183 (30), 138 (M-Ph-$^t$Bu-$BH_3$, 60), 108 (An, 30), 91 (50), 77 (Ph, 10) and 57 ($^t$Bu, 30).

## (S)-Ferrocenyl-(2-methoxyphenyl)-phenyl-phosphine borane and *n*-butyl-ferrocenyl-phenyl-phosphine borane

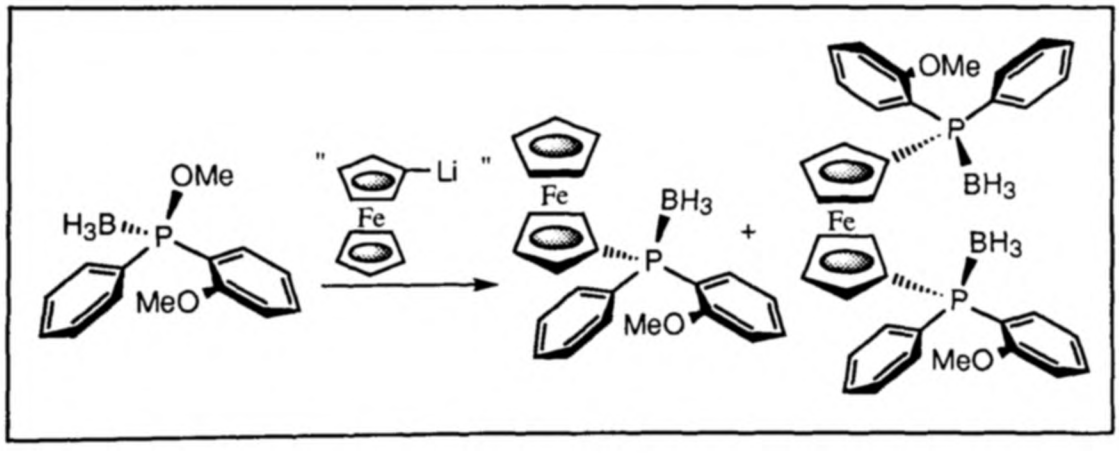



(R)-Methyl-(2-methoxyphenyl)-phenylphosphine borane (260 mg, 1 mmol, 10 ml of ether) was slowly added to a stirred ethereal solution of ferrocenyl lithium, prepared from the reaction of *n*-butyl lithium with mercurichloroferrocene, at -30°C. The reaction was slowly warmed to rt and stirred for 40 h. The reaction was quenched by slow addition

of water (10 ml) and the organics extracted into ether (3 x 20 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield an orange solid. This material was purified by column chromatography (flash silica, ethyl acetate / pentane : 1 / 20) to remove ferrocene ($R_f$ 1) and the less polar fractions were seperated by TLC ($H_f$ 254, ethyl acetate / pentane : 1 / 20). Unreacted starting material and (S)-ferrocenyl-(2-methoxyphenyl)-phenyl-phosphine borane elute together ($R_f$ 0.5) and were seperate by fractional crystallisation (dichloromethane / pentane, -20°C) to yield pure (S)-2-methoxyphenyl-ferrocenyl-phenyl-boranophosphine as orange crystals; m.p. 150-152°C; $[\alpha]_D^{25}$ -93.6 (c 0.125, $CH_2Cl_2$); $\delta_H$ (500 MHz, $CDCl_3$) 7.790 (1H, ddd, $J_{H4}$ 1.7, $J_{H5}$ 7.6, $J_P$ 13.4, °An-H6), 7.531 (2H, ddd, $J_{meta}$ 8.0, $J_{para}$ 1.1, $J_P$ 11.5, Ph-ortho H), 7.494 (1H, ddd, $J_{H3}$ 8.2, $J_{H5}$ 8.2, $J_{H6}$ 0.9, °An-H4), 7.415-7.327 (3H, m, Ph-meta/para H), 7.071 (1H, ddd, $J_{H4}$ 8.2, $J_{H6}$ 7.5, $J_P$ 0.8, °An-H5), 6.885 (1H, dd, $J_{H4}$ 8.2, $J_P$ 3.7, °An-H3), 4.689 (1H, s, Fc-ortho H), 4.531 (1H, s, Fc-ortho-H'), 4.494 (2H, s, Fc-meta H), 4.040 (5H, s, Fc'-H), 3.468 (3H, s, $OCH_3$) and 1.543-0.896 (3H, br m, $BH_3$); $\delta_C$ (125.8 MHz, $CDCl_3$) 160.8 (°An-$C_2$), 135.4 (d, $J_P$ 12.1, °An-$C_6$), 133.3 (°An-$C_4$), 132.6 (d, $J_P$ 62.1, Ph-ipso C), 131.3 (d, $J_P$ 10.3, Ph-ortho C), 129.9 (Ph-para C), 127.8 (d, $J_P$ 10.7, Ph-meta C), 120.8 (d, $J_P$ 11.1, °An-$C_5$), 119.6 (d, $J_P$ 58.7, °An-$C_1$), 111.8 (d, $J_P$ 3.8, °An-$C_3$), 73.8 (d, $J_P$ 11.3, Fc-ortho C), 73.4 (d, $J_P$ 7.9, Fc-ortho C'), 71.6 (d, $J_P$ 8.1, Fc-meta C), 71.3 (d, $J_P$ 8.5, Fc-meta C'), 69.6 ('Fc-C), 68.4 (d, $J_P$ 70.6, Fc-ipso C) and 55.2 ($OCH_3$); $\delta_P$ (202.5 MHz, $CDCl_3$) 15.02 (br d, $J_B$ 75.2); $\upsilon_{max}$ (KBr) 3102, 3065, 2994, 2939, 2836 ($OCH_3$), 2373 ($BH_3$), 2342 ($BH_3$), 2258 ($BH_3$), 1589 (Ar-H vib), 1573, 1480, 1465, 1430 (P-Ph), 1411, 1278, 1253, 1167, 1108, 1063, 1025, 1013, 829, 763 (Ar-H out of plane bend), 743 (Ar-H bend), 700 (Ph-H bend), 689 (Ph-H bend), 619, 490, 475 and 453; *m/z* ($EI^+$) 414 (M, 10%), 401 (M-$BH_3$, 30), 400 (M-$BH_3$, 100), 323 (M-$BH_3$-Ph, 5), 293 (M-$BH_3$-An, 10), 186 (Fc, 30), 170 (15) and 121 (30). *n*-Butyl-ferrocenyl-phenyl-boranophosphine was isolated from the TLC plates ($R_f$ 0.1) after removal of solvent as a yellow oil (4 mgs, 1%); $\delta_H$ (500 MHz, $CDCl_3$) 7.771 (2H, ddd, $J_{meta}$ 8.3, $J_{para}$ 2.0, $J_P$ 9.9, Ph-ortho H), 7.502-7.430 (3H, m, Ph-meta/para H), 4.533 (1H, m, Fc-ortho-H),

4.463 (1H, m, Fc-meta H), 4.429 (1H, m, Fc-meta H'), 4.366 (1H, m, Fc-ortho-H'), 4.175 (5H, s, Fc' H), 2.063 (2H, M, $PC\underline{H}_2$), 1.599 (2H, m, $PCH_2C\underline{H}_2$), 1.430-0.650 (3H, br m, $BH_3$), 1.361 (2H, m, $PCH_2CH_2C\underline{H}_2$) and 0.883 (3H, dd, $J_H$ 7.2, $J_H$ 7.2, $CH_3$); $\delta_C$ (62.9 MHz, $CD_3COCD_3$) 132.9 (d, $J_P$ 8.0, Ph-ortho C), 131.8 (Ph-para C), 129.3 (d, $J_P$ 8.0, Ph-meta C), 72.4 (d, $J_P$ 8.0, Fc-$C_{2,3,4,5}$), 71.9 (d, $J_P$ 8.0, Fc-$C_{2,3,4,5}$), 70.4 ('Fc-C), 27.5 (d, $J_P$ 39.8, $PCH_2$), 26.2 ($PCH_2\underline{C}H_2$), 24.6 (d, $J_P$ 13.8, $PCH_2CH_2\underline{C}H_2$) and 13.8 ($CH_3$); $\delta_P$ (101 MHz, $CD_3COCD_3$) 13.33 (br); *m/z* ($EI^+$) 364 (M, 5%), 350 (M-$BH_3$, 70), 293 (FcPhP, 100), 273 (FcBuP, 5), 186 (Fc, 15), 121 ($PhPBH_3$, 50) and 109 (20); *m/z* (CI, $NH_4^+$) 380 (M+$NH_2$, 100%), 363 (M-1, 20), 350 (M-$BH_3$, 60), 351 (55), 293 (FcPhP, 30), 273 (FcBuP, 55), 187 (Fc+H, 20) and 186 (Fc, 10).

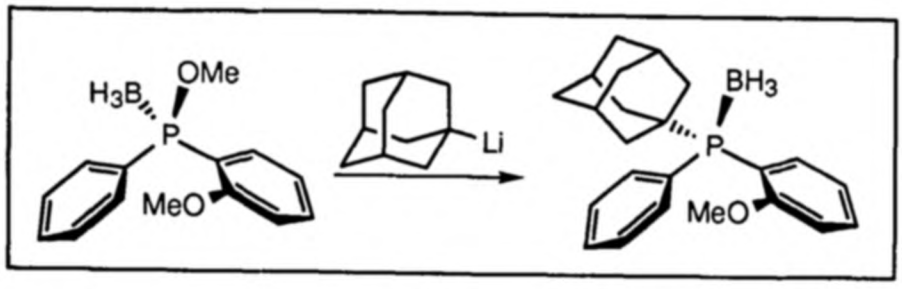
## (S)-Ferrocenyl-(2-methoxyphenyl)-phenylphosphine borane and (S,S)-bis(phenyl-(2-methoxyphenyl)phosphine borano) ferrocene




*t*-Butyllithium (2.95 ml, 1.7M) was slowly added to a THF (5 ml) solution of ferrocene (1.10 g) at 0°C. This solution was stood for 25 min at 0°C and then added to a THF (5 ml) solution of (S)-methyl-(2-methoxyphenyl)-phenylphosphine borane (1.56 g, 6 mmol). After stirring overnight, the reaction was quenched by the addition of water (15 ml) and the organics extracted with ether (3 x 35 ml) and dried ($MgSO_4$). The solvent was

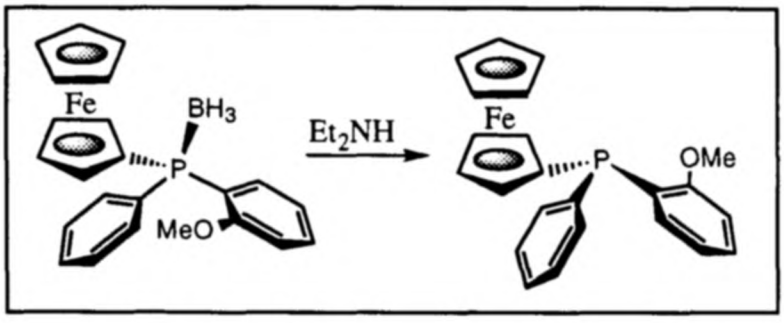
removed *in vacuo* to yield an orange solid which was purified by column chromotography (flash silica, ethyl acetate / pentane : 1 / 3) to yield (S)-ferrocenyl-(2-methoxyphenyl)-phenyl-phosphine borane ($R_f$ 1) as the major product (1.66 g, 67 %). This material had identical spectroscopic properties to an authentic sample prepared from chloromercuriferrocene. A second ferrocenyl phosphine borane compound eluted from the column ($R_f$ 0.6) and was identified as (S,S)-bis(phenyl-(2-methyloxyphenyl)phosphine borano) ferrocene (58 mg, 3%); m.p. 78-80°C; $[\alpha]_D^{25}$ -62.6 (c 0.05, $CH_2Cl_2$); $\delta_H$ (500 MHz, $CDCl_3$) 7.671 (2H, ddd, $J_{H4}$ 1.6, $J_{H5}$ 7.6, $J_P$ 13.4, °An-H6), 7.459 (6H, m, Ph-ortho/para H), 7.387 (2H, ddd, $J_{H3}$ 8.2, $J_{H5}$ 7.6, $J_{H6}$ 1.8, °An-H4), 7.324 (4H, ddd, $J_{para}$ 7.7, $J_{ortho}$ 7.7, $J_P$ 2.3, Ph-meta H), 7.031 (2H, ddd, $J_{H4}$ 7.6, $J_{H6}$ 7.6, $J_P$ 1.1, °An-H5), 6.840 (2H, dd, $J_{H4}$ 8.2 .$J_P$ 3.8, °An-H3), 4.449 (2H, s, Fc-ortho H), 4.415 (2H, dd, $J_{meta'}$ 1.1, $J_P$ 1.1, Fc-meta H), 4.440 (2H, dd, $J_P$ 1.1, $J_{meta}$ 1.1, Fc-meta H'), 4.349 (2H, s, Fc-ortho H) and 3.425 (6H, s, $OCH_3$); $\delta_C$ (125.8 MHz, $CDCl_3$) 160.8 (°An-$C_2$), 135.2 (d, $J_P$ 12.4, °An-$C_6$), 133.4 (°An-$C_4$), 132.0 (d, $J_P$ 53.1, Ph-ipso C), 131.3 (d, $J_P$ 9.5, Ph-ortho C), 130.1 (Ph-para C), 127.9 (d, $J_P$ 10.6, Ph-meta C), 120.8 (d, $J_P$ 11.6, °An-$C_5$), 119.1 (d, $J_P$ 59.0, °An-$C_1$), 111.8 (°An-$C_3$), 74.6 (Fc-C), 74.6 (Fc-C), 74.5 (Fc-C), 73.9 (Fc-C), 69.8 (d, $J_P$ 68.1, Fc-ipso C) and 55.2 ($OCH_3$); $\delta_P$ (202.5 MHz, $CDCl_3$) 14.58 (br d, $J_B$ 35.5); $\upsilon_{max}$ (KBr) 3421, 2963, 2849 ($OCH_3$), 2369 ($BH_3$), 2343 ($BH_3$), 1718, 1654, 1589 (Ar-H vib), 1574, 1478, 1431, 1262, 1172, 1104, 1060, 1029, 802, 758 (Ar-H out of plane bend), 741 (Ar-H bend), 698 (Ph-H bend), 637 and 612; *m/z* ($EI^+$) 614 (M-$(BH_3)_2$, 30%), 537 (M-Ph-$(BH_3)_2$, 5), 507 (M-An-$(BH_3)_2$, 5), 470 (10), 400 (M-P-An-Ph-$(BH_3)_2$, 30), 354 (10), 307 (10), 278 (10), 246 (FcP2, 15), 233 (15), 226 (15), 215 (AnPhP, 30), 186 (Fc, 35), 170 (70), 152 (30), 137 (50), 121 (90), 91 (100) amd 77 (Ph, 40).

(S)-(1-Adamantyl)-(2-methoxyphenyl)-phenylphosphine borane



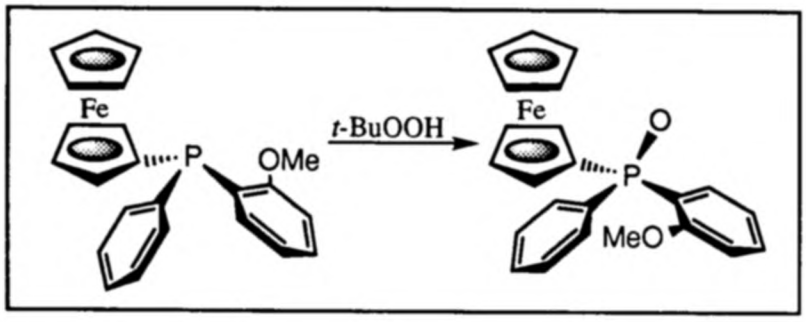

1-Adamantyllithium (20 ml, 0.12 M in ether) was added to (S)-methyl-(2-methoxyphenyl)-phenylphosphine borane (52 mg, 0.2 mmol) and the solution heated to 40°C. After 56 h heating, the reaction was quenched with water (20 ml) and the organics extracted into ether (3 x 20 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford a white solid which was purified by thin layer chromatography (ethyl acetate / pentane : 1 / 1, $R_f$ 0.4) to yield (S)-(1-adamantyl)-(2-methoxyphenyl)-phenylphosphine borane as a sticky white solid (27 mg, 37 %); $\delta_H$ (500 MHz, $CDCl_3$) 8.006 (1H, ddd, $J_{H4}$ 1.7, $J_{H5}$ 7.7, $J_P$ 12.8, °An-H6), 7.696 (2H, ddd, $J_{meta}$ 8.0, $J_{para}$ 1.2, $J_P$ 9.8, ortho H), 7.507 (1H, dddd, $J_{H3}$ 7.3, $J_{H6}$ 1.7, $J_{H5}$ 7.3, °An-H4), 7.418-7.339 (3H, m, meta/para H), 7.071 (1H, dddd, $J_{H3}$ 1.1, $J_P$ 1.6, $J_{H4}$ 7.3, $J_{H6}$ 7.7, °An-H5), 6.930 (1H, dd, $J_{H4}$ 8.3, $J_P$ 3.3, °An-H3), 3.612 (3H, s, OMe), 2.054 (6H, br d, $J_P$ 20.0, $PCCH_2$), 2.003 (2H, s, $PCCH_2C\underline{H}$) and 1.723 (6H, s, $PCCH_2CHC\underline{H_2}$); $\delta_C$ (125.7 MHz, $CDCl_3$) 161.00 (°An-$C_2$), 137.99 (d, $J_P$ 12.7, °An-$C_6$), 133.2 (°An-$C_4$), 132.70 (d, $J_P$ 7.3, Ph-ortho C), 129.76 (Ph-para C), 127.79 (d, $J_P$ 10.0, Ph-meta C) 120.96 (d, $J_P$ 11.2, °An-$C_5$), 115.52 (d, JP 48.4, An-C1), 111.27 (°An-$C_3$), 54.69 ($OCH_3$), 38.17 (Ad-C), 36.51 (Ad-C), 34.93 (d, $J_P$ 30.8, $P\underline{C}CH_2$) and 28.50 (d, J 9.5, $PC\underline{C}H_2$); $\delta_P$ (202.5 MHz, $CDCl_3$) 34.60 (br d, $J_B$ 73.5); *m/z* ($EI^+$) 363 (M-1, 5%), 350 (M-$BH_3$, 20), 215 (M-Ad, 10), 183 (10), 152 (10), 135 (Ad, 100)), 107 (An, 45), 93 (45) and 77 (Ph, 20).

(S)-Ferrocenyl-(2-methoxyphenyl)-phenylphosphine




Diethylamine (5 ml) was added to (S)-ferrocenyl-(2-methoxyphenyl)-phenylphosphine borane (62 mg, 0.15 mmol) and the solution heated to 46°C for 8 h. The diethylamine was then removed under reduced pressure to yield the crude product which was passed through a short silica column (flash silica, toluene as eluent). Solvent was removed under reduced pressure to yield an orange solid (59 mg, 98%); m.p. 127-129°C; $\delta_H$ (500 MHz, $CDCl_3$) 7.464 (2H, ddd, $J_{ortho/para}$ 5.8, $J_{ortho/para}$ 8.1, $J_P$ 2.2, Ph-meta H), 7.334 (3H, m, Ph-ortho/para H), 7.295 (1H, ddd, $J_{H4}$ 1.8, $J_{H5}$ 6.4, $J_P$ 8.2, °An-H6), 6.912 (1H, ddd, $J_{H3}$ 8.2, $J_{H6}$ 1.8, $J_{H5}$ 7.3, °An-H4), 6.869 (1H, dd, $J_{H4}$ 7.3, $J_{H6}$ 7.3, °An-H5), 6.832 (1H, dd, $J_{H4}$ 8.2, $J_P$ 4.5, °An-H3), 4.399 (1H, s, Fc-H), 4.337 (1H, s, Fc-H), 4.280 (1H, s, Fc-H), 4.109 (5H, s, Fc'-H), 3.843 (1H, s, Fc-H) and 3.721 (3H, s, $OCH_3$); $\delta_C$ (125.7 MHz, $CDCl_3$) 160.8 (d, $J_P$ 15.6, °An-$C_2$), 138.1 (d, $J_P$ 8.0, °An-$C_6$), 133.6 (d, $J_P$ 19.8, °An-$C_4$), 130.0 (Ph-para C), 128.4 (Ph-ortho C), 128.1 (d, $J_P$ 11.8, Ph-ispo C), 127.9 (d, $J_P$ 6.9, Ph-meta C), 120.7 (°An-$C_5$), 110.2 (°An-$C_3$), 75.7 (d, $J_P$ 4.8, Fc-ispo C), 74.0 (d, $J_P$ 25.1, Fc-C), 72.2 (d, $J_P$ 4.4, Fc-C), 70.9 (d, $J_P$ 6.2, Fc-C), 70.4 (Fc-C), 69.1 (Fc'-C) and 55.6 ($OCH_3$); $\delta_P$ (101.3 MHz, $Et_2NH$) -26.4; *m/z* ($EI^+$) 400 (M, 100%), 401 (M, 20), 323 (M-Ph, 10), 293 (M-An, 10), 226 (10), 215 (15), 186 (Fc, 40), 170 (25) and 121 (65).

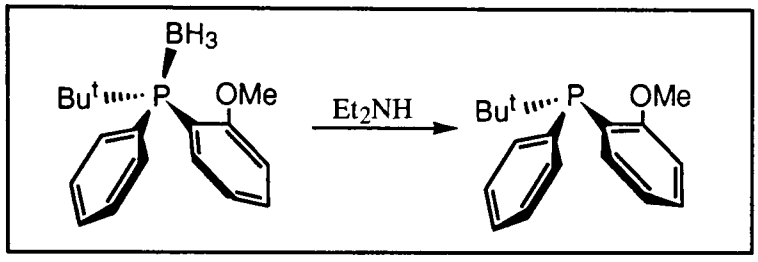
(R)-Ferrocenyl-(2-methoxyphenyl)-phenylphosphine-oxide




*t*-Butyl hydroperoxide (0.07 ml, 3.0M in iso-octane, 0.2 mmol) was slowly added to a diethylamine solution of (S)-ferrocenyl-(2-methoxyphenyl)-phenylphosphine (41 mg, 0.1 mmol) and stirred for 4 h. Water was then added (10 ml) and the organics extracted into ether (3 x 20 ml) and dried ($MgSO_4$). Solvent was removed under reduced pressure to yield an oil which slowly crystallised (42 mg, 98 %); m.p. 163-165°C. $[\alpha]_D^{25}$ -51.6 (c 0.11, $CH_2Cl_2$); $\delta_H$ (500 MHz, $CDCl_3$) 7.983 (1H, ddd, $J_{H4}$ 1.7, $J_{H5}$ 7.6, $J_P$ 13.4, °An-H6), 7.686 (2H, ddd, $J_{meta}$ 7.0, $J_{para}$ 1.4, $J_P$ 12.7, Ph-ortho H), 7.512 (1H, dd, $J_{H3}$ 8.1, $J_{H5}$ 8.1, °An-H4), 7.451 (1H, dt, $J_{meta}$ 7.2, $J_{ortho}$ 1.4, Ph-para H), 7.388 (2H, dt, $J_{para}$ 7.2, $J_{ortho}$ 7.0, Ph-meta H), 7.118 (1H, ddd, $J_{H4}$ 8.1, $J_{H6}$ 7.4, $J_P$ 1.6, °An-H5), 6.890 (1H, dd, $J_{H4}$ 8.1, $J_P$ 5.3, °An-H3), 4.604 (1H, s, Fc-H), 4.484 (1H, s, Fc-H), 4.452 (2H, d, $J_P$ 4.2, Fc-H), 4.141 (5H, s, Fc'-H) and 3.530 (3H, s, $OCH_3$); $\delta_C$ (125.8 MHz, $CDCl_3$) 160.3 (°An-$C_2$), 135.8 (d, $J_P$ 112.0, Ph-ispo C), 134.3 (°An-$C_6$), 133.6 (°An-$C_4$), 130.9 (Ph-para C), 130.8 ( Ph-meta C), 127.7 (d, $J_P$ 12.5, Ph-ortho C), 122.9 (d, $J_P$ 106.9, °An-$C_1$), 120.7 (d, $J_P$ 11.0, °An-$C_5$), 111.5 (°An-$C_3$), 72.8 (d, $J_P$ 12.9, Fc-H), 72.1 (d, $J_P$ 13.1, Fc-H), 71.2 (d, $J_P$ 10.7, Fc-H), 70.9 (d, $J_P$ 10.4, Fc-H), 69.5 (Fc'-C) and 55.2 ($OCH_3$); $\delta_P$ (202.6 MHz, $CDCl_3$) 28.2; $\upsilon_{max}$ (KBr) 3088, 3066, 2841 ($OCH_3$), 1654, 1590 (Ar-H vib.), 1578, 1482, 1465, 1439, 1387, 1367, 1313, 1285 (P=O), 1247, 1193, 1161, 1139, 1106, 1020, 823, 767 (Ar-H out of plane bend), 752 (Ar-H out of

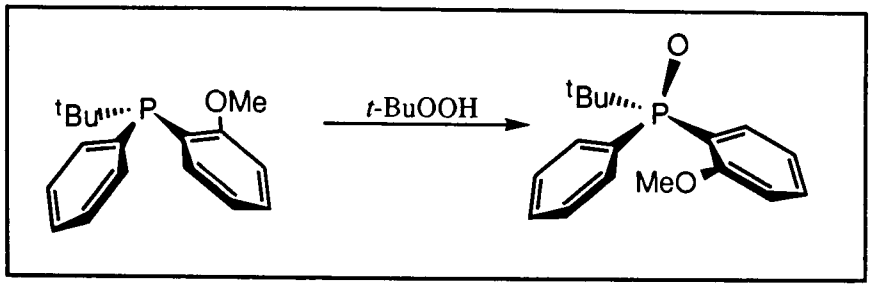
plane bend), 738 (Ar-H out of plane bend), 715 and 572; *m/z* ($EI^+$) 416 (M, 100%), 417 (M, 25), 351 (M-Cp, 20), 335 (10), 273 (10), 215 (15) and 186 (Fc, 10).

## (S)-*t*-Butyl-(2-methoxyphenyl)-phenylphosphine



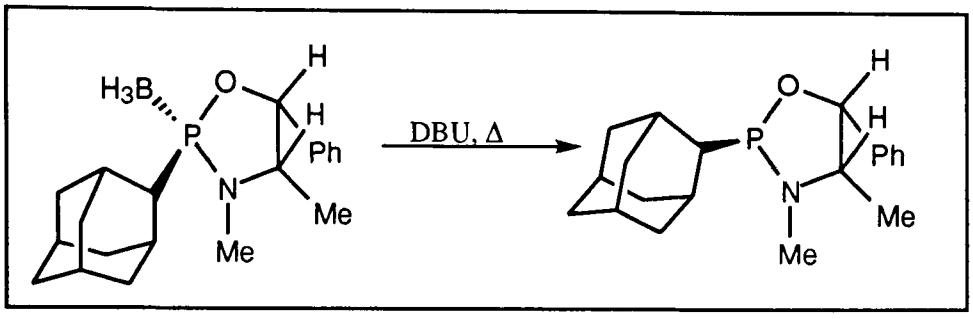

Diethylamine (3ml) was added to (S)-*t*-butyl-(2-methoxyphenyl)-phenylphosphine borane (572 mg, 2 mmol) and the solution heated to 50°C for 12 h. The diethylamine was then removed under reduced pressure to yield the crude product which was passed through a short silica column (flash silica, toluene as eluent). Solvent was removed under reduced pressure to yield a thick oil (534 mg, 98%); $\delta_H$ (500 MHz, $CDCl_3$) 7.531 (2H, ddd, $J_{meta}$ 5.2, $J_{para}$ 3.5, $J_P$ 9.6, Ph-ortho H), 7.450 (1H, ddd, $J_{H4}$ 1.7, $J_{H5}$ 7.5, $J_P$ 3.8, °An-H6), 7.325 (1H, ddd, $J_{H3}$ 8.2, $J_{H6}$ 1.7, $J_{H5}$ 7.4, °An-H4), 7.310-7.288 (3H, m, Ph-meta/para H), 7.110 (1H, ddd, $J_{H4}$ 7.4, $J_{H6}$ 7.4, $J_P$ 0.8, °An-H5), 6.980 (1H, dd, $J_{H4}$ 8.2, $J_P$ 4.4, °An-H3), 3.737 (3H, s, $OCH_3$) and 1.228 (9H, d, $J_P$ 12.5, $C(CH_3)_3$); $\delta_C$ (125.7 MHz, $CDCl_3$) 162.1 (°An-$C_2$), 134.7 (°An-$C_6$), 134.4 (d, $J_P$ 20.0, °An-$C_4$), 129.9 (Ph-ortho ), 128.1 (Ph-para C), 127.7 (d, $J_P$ 6.3, Ph-meta C), 120.4 (°An-$C_5$), 110.7 (°An-$C_3$), 55.4 ($OCH_3$), 30.6 (d, $J_P$ 15.0, $(CH_3)_3\underline{C}$) and 28.8 (d, $J_P$ 14.4, $(\underline{C}H_3)_3C$); $\delta_P$ (101.3 MHz, $Et_2NH$) 7.60; *m/z* ($EI^+$) 273 (M+1, 15%), 272 (M, 65), 217 (M-$^t$Bu+H, 10), 216 (M-$^t$Bu, 100), 183 (40), 138 (M-$^t$Bu-Ph, 100), 137 (50), 108 (An, 60), 91 (80) and 57 ($^t$Bu, 40).

(R)-*t*-Butyl-(2-methoxyphenyl)-phenylphosphine oxide



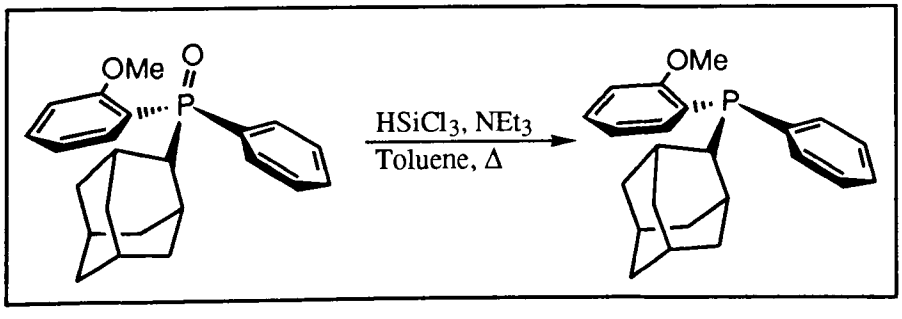

*t*-Butyl hydroperoxide (0.2 ml, 3.0 M in iso-octane, 0.6 mmol) was slowly added to an ethereal solution of (S)-*t*-butyl-(2-methoxyphenyl)-phenyl-phosphine (109 mg, 0.4 mmol in 10 ml of ether) and stirred for 4 h. Water was then added (50 ml) and the organics extracted into ether (3 x 20 ml) and dried ($MgSO_4$). Solvent was removed under reduced pressure to yield an oil which slowly crystallised (113 mg, 98%); m.p. 148-150°C. $[\alpha]_D^{25}$ +42.6 (c 0.94, $CH_2Cl_2$); $\delta_H$ (500 MHz, $CDCl_3$) 8.166 (1H, ddd, $J_{H4}$ 1.8, $J_{H5}$ 7.6, $J_P$ 12.0, °An-H6), 7.941 (2H, ddd, $J_{meta}$ 8.0, $J_{para}$ 1.1, $J_P$ 10.9, Ph-ortho H), 7.494 (1H, ddd, $J_{H3}$ 8.3, $J_{H6}$ 1.8, $J_{H5}$ 7.5, °An-H4), 7.411-7.382 (3H, m, Ph-meta/para H), 7.110 (1H, dd, $J_{H4}$ 7.5, $J_{H6}$ 7.6, °An-H5), 6.915 (1H, dd, $J_{H4}$ 8.3, $J_P$ 5.1, °An-H3), 3.748 (3H, s, $OCH_3$) and 1.266 (9H, d, $J_P$ 15.4, $C(CH_3)_3$); $\delta_C$ (62.8 MHz, $CDCl_3$) 159.6 (°An-$C_2$), 136.1 (d, $J_P$ 4.8, °An-$C_6$), 133.5 (°An-$C_4$), 132.0 (d, $J_P$ 8.4, Ph-ortho), 130.9 (d, $J_P$ 3.0, Ph-para C), 127.7 (d, $J_P$ 12.3, Ph-meta C), 121.1 (d, $J_P$ 10.6, °An-$C_5$, ), 110.8 (d, $J_P$ 6.0, °An-$C_3$), 54.6 ($OCH_3$), 34.7 (d, $J_P$ 71.6, $(CH_3)_3\underline{C}$) and 26.0 ($(\underline{C}H_3)_3C$); $\delta_P$ (101.3 MHz, $CDCl_3$) 43.30; $\upsilon_{max}$ (KBr) 3452, 2946, 2862 ($OCH_3$), 2310, 2043, 1589, 1576, 1461 (P-Ph st.), 1392 ($C(CH_3)_3$), 1363 ($C(CH_3)_3$), 1317, 1273 (P=O), 1156, 1137, 1099 and 1072; *m/z* ($EI^+$) 288 (M, 20%), 289 (M+1, 20), 232 (M-$^t$Bu+1, 100%), 231 (M-$^t$Bu, 50%), 199 (40), 141, 107 (An, 10), 77 (Ph, 20) and 57 ($^t$Bu, 10).

## (2S,4S,5R)-3,4-Dimethyl-2-adamantyl-5-phenyl-1,3,2-oxazaphospholidinone




1,8-Diazabicyclo[5,4,0]undec-7-ene (150µl, 10 mmol) was added to a toluene (3 ml) solution of (2S, 4S, 5R)-3,4-dimethyl-2-adamantyl-5-phenyl-1,3,2-oxazaphospholidin-2-borane at rt. The solution was then heated for 11 h at 100°C before being cooled to rt. $^{31}P$ NMR analysis revealed the reaction had gone to completion but all attempts to isolate the phosphine failed due to the air sensitivity of the compound.

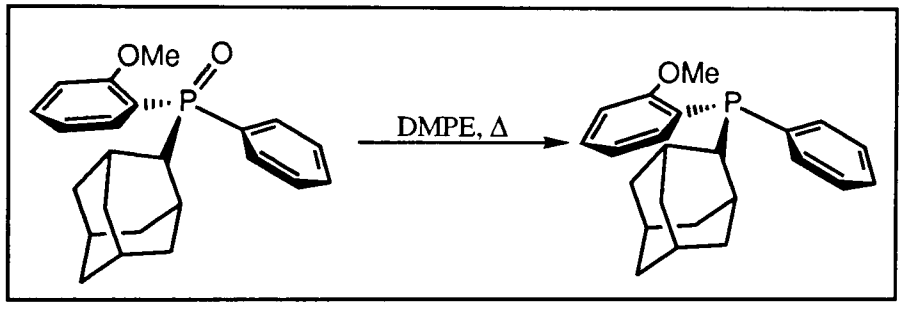
## Attempted reduction of (R)-2-adamantyl-(2-methoxyphenyl)-phenylphosphine oxide with trichlorosilane




Trichlorosilane (270 µl, 2.70 mmol) was added to a toluene solution (15 ml) of (R)-2-adamantyl-(2-methoxyphenyl)-phenylphosphine oxide (123 mg, 0.34 mmol) at rt. Triethylamine (470 µl, 3.40 mmol) was then added and dense white fumes were liberated.

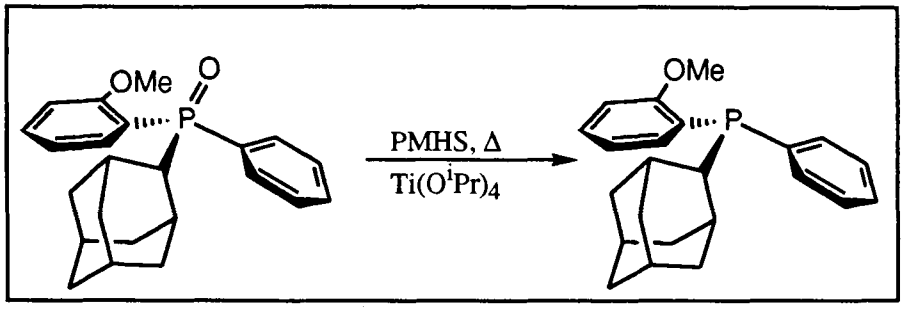
The solution was refluxed for 17 h before being cooled to 0°C. Sodium hydroxide (20 ml, 2N) was slowly added with vigerous stirring and the organic layer extracted with dichloromethane (3 x 20 ml). After drying ($MgSO_4$) and solvent removal *in vacuo*, $^1H$ NMR analysis revealed no reaction had occured and this was confirmed by $^{31}P$ NMR analysis.

## Attempted reduction of (R)-2-adamantyl-(2-methoxyphenyl)-phenylphosphine oxide with N,N,N',N'-tetraethylenediphosphine




(R)-2-Adamantyl-(2-methoxyphenyl)-phenylphosphine oxide (37 mg, 0.1 mmol) was dissolved in solvent (2 ml, toluene or THF) in an 8 mm NMR tube and N,N,N',N'-tetraethylenediphosphine (100 mg) added to the solution. The tube was sealed and the solution heated to just below reflux (101°C for toluene, 60°C for THF). The solution was monitored by $^{31}P$ NMR but showed no reaction after 2 weeks and was thus abandoned.

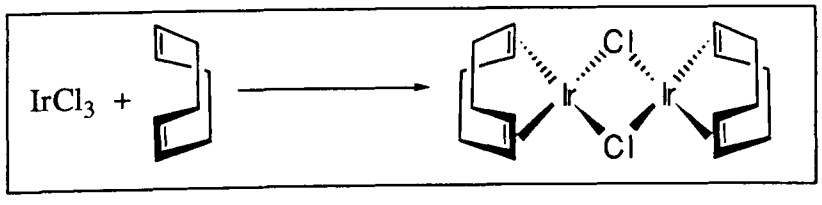
(S)-2-Adamantyl-(2-methoxyphenyl)-phenylphosphine




Titanium isoproxide (67μl) was added to a THF solution of (R)-2-adamantyl-(2-methoxyphenyl)-phenylphosphine oxide (57 mg, 2 ml of THF) and polymethylhydrosiloxane (PMHS, 5 ml) in an 8mm NMR tube. Bubbles are seen and the solution was then heated to 75°C going dark blue over 4 h. The reaction was monitored by $^{31}$P NMR and was complete after 72 h. Various methods of isolation were attempted without success and it proved impossibe to seperate the phosphine from the PMHS. $\delta_P$ (101.3 MHz, PMHS) -21.20.

## 5.3 Metal Complexes

Di-μ-chloro-bis(1,5-cyclooctadiene)diiridium

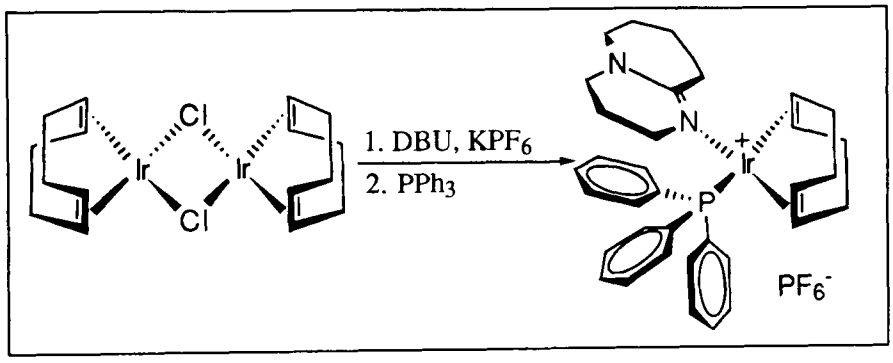



[81]

Following the procedure of Cotton, isopropanol (4 ml) and water (5 ml) were added to iridium chloride (800 mg, 2.7 mmol) and 1,5 cyclooctadiene (1.06 g) and the resulting black solution was heated to 66°C for 36 h. Orange crystaline material precipates during heating and was collected by cooling the solution to rt and removing the solvent by

syringe. The resulting material was washed with methanol and dried in air yielding bright red crystals (647 mg, 72%); m.p. 205-207. $\delta_H$ (200 MHz, $CDCl_3$) 4.24 (8H, d, J 2.6, olefinic H), 2.27 (8H, m, $CH_2$) and 1.59-1.47 (8H, m, $CH_2$); $\upsilon_{max}$ (KBr) 3457, 2978, 2964, 2933, 2905, 2877, 2828, 2361, 1643 (C=C st.), 1472, 1446, 1424, 1322, 999, 978, 969, 904 and 869; *m/z* (Electrospray) 358 (COD-Ir-MeCN+O, 100%), 342 (COD-Ir-MeCN, 25), 317 (COD-Ir+O, 10) and 301 (COD-Ir, 15).

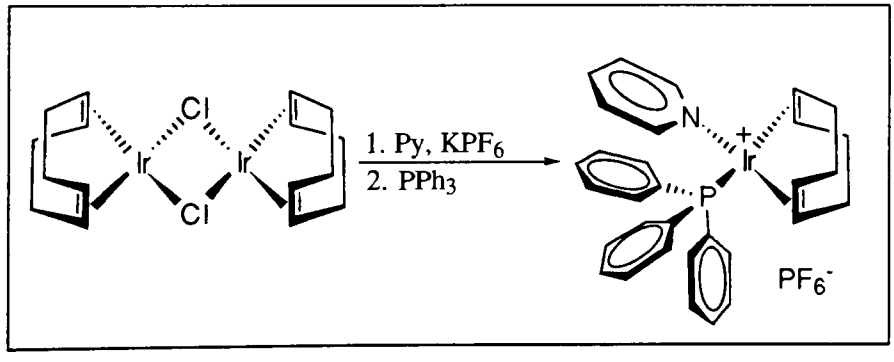
## (1,5-Cyclooctadiene)(1,8-diazabicyclo[5.4.0]undec-7-ene)(pyridine) iridium (I) hexafluorophosphate




Following the general method of Crabtree,[12] di-μ-chloro-bis(1,5-cyclooctadiene)diiridium (67 mg, 0.1 mmol) and potassium hexafluorophosphate (39mg) were dissolved in a mixture of 1,8-diazabicyclo[5.4.0]undec-7-ene (0.15 ml), acetone (1.5 ml), ethanol (1 ml) and water (0.2 ml). The resulting solution was stirred for 30 min and the solvent removed under high vacuum. The resulting bright yellow crystals were washed with water and dried. Dichloromethane (5 ml) was added to the crystals and then triphenylphosphine (43 mg), turning the solution red. The solvent was removed *in vacuo* and the orange crystaline material produced was recrystallised (dichloromethane/ether) to yield bright red crystals (54 mg, 63%) m.p. 181-184°C. $\delta_H$ (500 MHz, $CDCl_3$) 7.642-7.410 (15 H, m, Ar-H), 4.691 (1H, ddd, $J_H$ 4.8, olefinic-H), 4.553 (1H, m, dd, $J_H$ 3.7, olefinic-H), 3.499-3.387 (2H, m, DBU-H), 3.211-3.074 (2H, m, COD), 3.018-2.918

(2H, m, DBU-H), 2.617 (2H, br t, $J_H$ 10.3, DBU-H), 2.430 (2H, ddd, $J_H$ 8.3, $J_H$ 10.8, COD-H), 2.363 ( 2H, ddd, $J_H$ 7.0, $J_H$ 9.7, COD-H), 2.282 (2H, ddd, $J_H$ 3.9, $J_H$ 3.6, $J_H$ 3.8, DBU-H), 2.202 (2H, br d, $J_H$ 7.0, COD-H), 2.128-2.063 (2H, m, DBU-H), 1.904-1.749 (2H, m, COD), 1.721-1.598 (2H, m, COD), 1.552-1.473 (1H, m, DBU-H), 1.450-1.342 (3H, m, DBU-H); $\delta_P$ (101 MHz, $CDCl_3$) 15.7, -143.3 (sept, $J_F$ 713); $\upsilon_{max}$ (KBr) 3436, 3114, 3055, 2981 (C-H st.), 2922, 2836, 1606 (Ph-H vib.), 1485, 1449, 1435, 1361, 1333, 1212, 1095, 847, 757 and 696; *m/z* (FAB) 559 (M-Py, 65%), 534 (M-COD, 75), 453 (M-COD-Py, 100), 391 (70), 377 (M-$PPh_3$, 45), 307 (75), 301 (M-Py-$PPh_3$, 35) and 289 (60); *m/z* (Electrospray, MeCN) 604 (M($^{193}$Ir)-Py+MeCN, 50%), 602 (M($^{191}$Ir)-Py+MeCN, 30%), 595 (55), 593 (30), 563 (M($^{193}$Ir)-py, 100), 561 (M($^{191}$Ir)-Py, 60) and 533 (M($^{191}$Ir)-COD, 10).

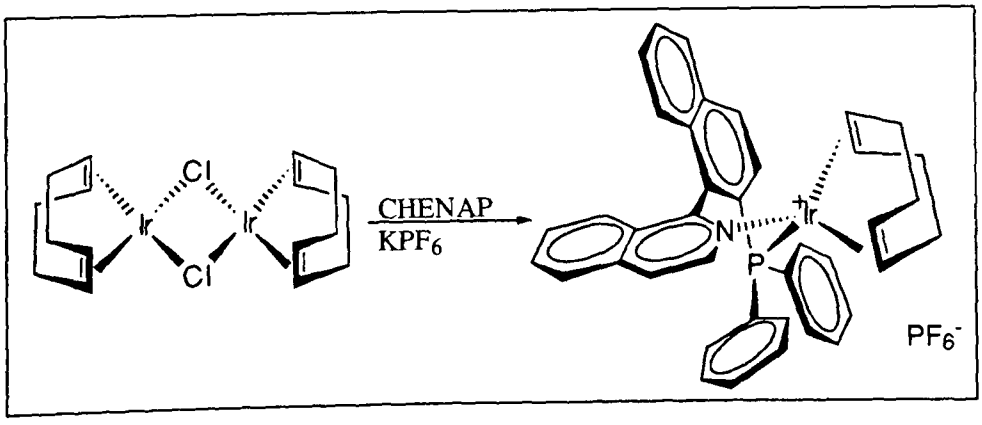
## (1,5-Cyclooctadiene)(triphenylphosphino)(pyridine)iridium (I) hexafluorophosphate




Following the general method of Crabtree,[12] di-μ-chloro-bis(1,5-cyclooctadiene)diiridium (101 mg, 0.15 mmol) and potassium hexafluorophosphate (58 mg) were dissolved in a mixture of pyridine (0.21 ml), acetone (1.5 ml), ethanol (0.75 ml) and water (0.15 ml). The resulting solution was stirred for 30 min and the solvent removed under high vacuum. The resulting bright yellow crystals were washed with water and dried. Dichloromethane (5 ml) was added to the crystals and then triphenylphosphine (43

mg), turning the solution bright red. The solvent was removed *in vacuo* and the orange crystaline material produced was recrystallised (dichloromethane/ether) to yield bright red crystals (212 mg, 90%) m.p. 174-176°C. $\delta_H$ (500 MHz, $CDCl_3$) 8.730 (2H, dd, $J_{meta}$ 6.6, $J_{para}$ 1.6, Py-ortho H), 8.352 (1H, dd, $J_{para}$ 7.7, $J_{ortho}$ 6.6, Py-meta H), 7.747 (1H, ddt, $J_{meta} = J_{meta'}$ 7.7, $J_{ortho}$ 1.6, Py-para H), 7.563-7.430 (15H, m, $(Ph)_3P$), 7.142 (1H, dd, $J_{para}$ 7.7, $J_{ortho}$ 6.6, Py-meta' H), 4.491 (1H, m, olefinic H), 3.851 (2H, m, olefinic H), 3.618 (1H, m, olefinic H), 2.535-2.388 (4H, m, $CH_2$), 2.038-1.984 (1H, m, CHH), 1.954-1.899( 1H, m, CHH), 1.842 (2H, m, $CH_2$); $\delta_P$ (101 MHz, $CDCl_3$) 17.8, -143.3 (sept, $J_F$ 713); $\upsilon_{max}$ (KBr) 3436, 3114, 3055, 2981 (C-H st.), 2922, 2836, 1606 (Ph-H vib.), 1485, 1449, 1435, 1361, 1333, 1212, 1095, 847, 757 and 696; *m/z* (FAB) 559 (M-Py, 65%), 534 (M-COD, 75), 453 (M-COD-Py, 100), 391 (70), 377 (M-$PPh_3$, 45), 307 (75), 301 (M-Py-$PPh_3$, 35) and 289 (60); *m/z* (Electrospray, MeCN) 604 (M($^{193}$Ir)-Py+MeCN, 50%), 602 (M($^{191}$Ir)-Py+MeCN, 30%), 595 (55), 593 (30), 563 (M($^{193}$Ir)-py, 100), 561 (M($^{191}$Ir)-Py, 60) and 533 (M($^{191}$Ir)-COD, 10).

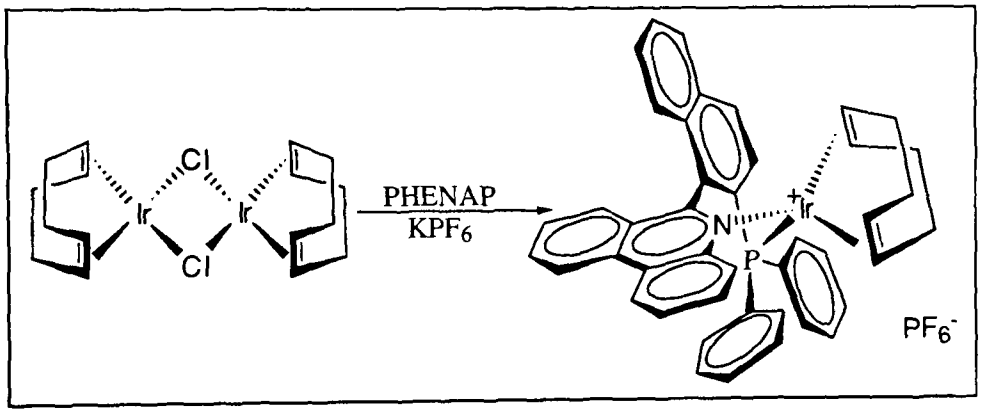
## (1,5-Cyclooctadiene)[1-(S)-(2-diphenylphosphino-1-naphthyl)isoquinoline] iridium (I) hexafluorophosphate




1-(S)-(2-Diphenylphosphino-1-naphthyl)isoquinoline (50 mg, 0.114 mmol) and di-μ-chloro-bis(1,5-cyclooctadiene)diiridium (36 mg, 0.057 mmol) were dissolved in

methanol (5 ml) and stirred for 30 min. Potassium hexafluorophosphate (21 mg, 0.114 mol) in water (2 ml) was added followed by more water (20 ml) to precipatate a red solid which was collected by filteration and washed with more water. The solid was dried *in vacuo* to give the title compound as a orange / red solid (81 mg, 81%); m.p. >300°C; Spectroscopic analysis agreed with that of an authentic racemic sample.

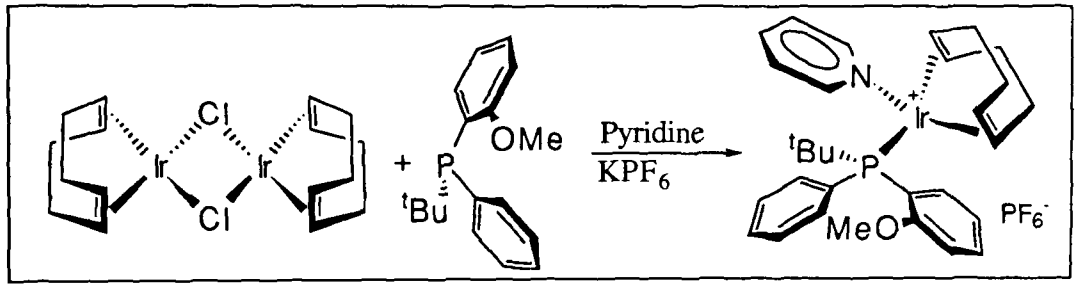
## (1,5-Cyclooctadiene)[6-(+)-[1-(2-diphenylphosphino-1-naphthyl)phenanthridine] iridium (I) hexafluorophosphate




6-(+)-[1-(2-Diphenylphosphino-1-naphthyl)phenanthridine (31 mg, 0.163 mmol) and di-μ-chloro-bis(1,5-cyclooctadiene)diiridium (21 mg) were dissolved in methanol (4 ml) and stirred for 40 min. Potassium hexafluorophosphate (21 mg) in water (2 ml) was added followed by more water (15 ml) to precipatate an orange solid which was collected by filteration and washed with more water. The solid was dried *in vacuo* to give the title compound as a light orange solid (44 mg, 76%); m.p. >300°C, Found C 55.55; H 3.97; N 1.43. $C_{43}H_{36}NP_2F_6Ir$ requires C 55.24; H 3.88; N 1.50. $[\alpha]_D^{21}$ +43.6 (c 0.11, $CH_2Cl_2$);. $\delta_H$ (500 MHz, $CDCl_3$) 8.48 (1H, d, J 7.6, PHENAP-H), 8.39 (1H, d, J 8.4, PHENAP-H), 8.00-7.92 (4H, m, Ar-H), 7.73-7.67 (4H, m, Ar-H), 7.49-7.09 (8H, m, Ar-H), 6.89-6.85 (4H, br m, Ar-H), 6.67 (2H, br, Ar-H), 5.10-4.65 (2H, br, olefinic H), 3.81-3.64 (1H, br, olefin-H), 3.07 (1H, br, olefin-H), 2.14 (4H, br, $CH_2$) and 1.55

(4H, br, $CH_2$); $\delta_P$ (101 MHz, $CDCl_3$) 24.9, -143.3 (sept, $J_F$ 713); $\upsilon_{max}$ (KBr) 1967, 1613, 1581 (Ar-H vib.), 1567, 1524, 1480, 1435 (P-Ph), 1382, 1296, 1225, 1184, 1090, 842, 765, 747, 726, 697, 688 and 513; *m/z* (Electrospray, MeCN) 790 (M($^{193}$Ir), 100%) with expected isotope pattern.

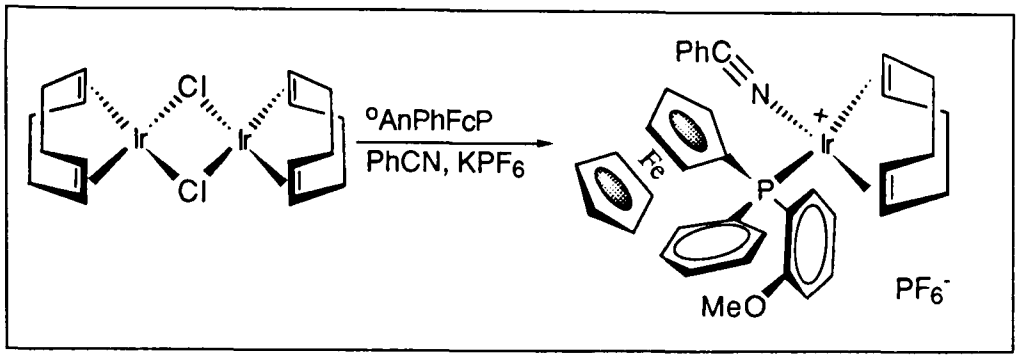
## (1,5-Cyclooctadiene)((R)-*t*-butyl-2-methoxyphenyl-phenylphosphino) (pyridine)iridium (I) hexafluorophosphate




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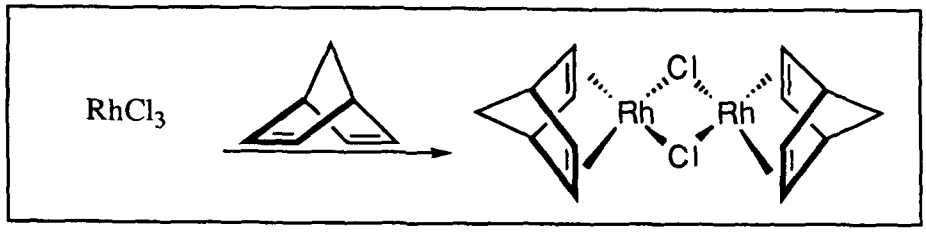
Following the general method of Crabtree, di-μ-chloro-bis(1,5-cyclooctadiene)diiridium (151 mg) and potassium hexafluorophosphate (87 mg) were dissolved in a mixture of pyridine (0.3 ml), acetone (2.5 ml), ethanol (1.1 ml) and water (0.2 ml). The resulting solution was stirred for 30 min and the solvent removed under high vacuum. The resulting bright yellow crystals were washed with water and dried *in vacuo*. Dichloromethane (5 ml) was added to the crystals and then (S)-*t*-butyl-2-methoxyphenyl-phenyl-phosphine (67 mg) turning the solution dark red. The solvent was removed *in vacuo* and the orange crystaline material produced was recrystallised (dichloromethane / ether) to yield bright red crystals (176 mg, 89%) m.p. 105-107°C; $\delta_P$ (101.3 MHz, $CH_2Cl_2$) 31.18, -143.7 (sept, $J_F$ 711); *m/z* (Electrospray, MeCN) 652 (M($^{193}$Ir), 100%) with expected isotope pattern.

## (1,5-Cyclooctadiene)((R)-ferrocenyl-2-methoxyphenyl-phenyl phosphino)(pyridine)iridium (I) hexafluorophosphate



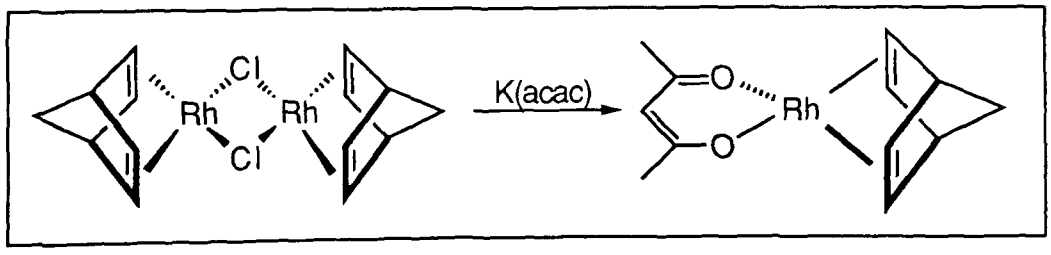

Following the general method of Crabtree,[121] di-μ-chloro-bis(1,5-cyclooctadiene)diiridium (42 mg) and potassium hexafluorophosphate (24 mg) were dissolved in a mixture of benzonitrile (0.15 ml), acetone (1 ml), ethanol (0.5 ml) and water (0.1 ml). The resulting solution was stirred for 30 min and the solvent removed under high vacuum. The resulting bright yellow crystals were washed with water and dried *in vacuo*. Dichloromethane (5 ml) was added to the crystals and then (S)-ferrocenyl-2-methoxyphenyl-phenyl-phosphine (38 mg) turning the solution red. The solvent was removed *in vacuo* and the light pink material produced was recrystallised (dichloromethane / ether) to yield (1,5-cyclooctadiene)((R)-ferrocenyl-2-methoxyphenyl-phenyl phosphino)(pyridine)iridium (I) hexafluorophosphate crystals (34 mg, 38%); m.p. 180-182°C. $[\alpha]_D^{25}$ +67.3 (c 0.05, $CH_2Cl_2$); $\delta_H$ (500 MHz, $CDCl_3$); $\delta_P$ (101.3 MHz, $CD_3COCD_3$) 11.83, -142.5 (sept, $J_F$ 707); *m/z* (Electrospray, MeCN) 701 ($M(^{193}Ir)$-BzCN, 100%) with expected isotope pattern.

Bis-bicyclo[2,2,1]hepta-2,5-diene chloro-μ-chlorodirhodium




To a stirred solution of rhodium (III) chloride (2.72 g, 10.32 mmol) in dry 90% ethanol (40 ml) was added freshly distilled norborna-2,5-diene (7.80 ml). The solution was stirred under argon for 48 h at rt. The dark red solution slowly produced a yellow precipitate, which was filtered and then dried to afford bis-bicyclo[2,2,1]hepta-2,5-diene chloro-μ-chlorodirhodium (2.89 g, 69%); m.p. 41-43°C; $\delta_H$ (200 MHz, $CDCl_3$) 3.936 (8H, *m*, =CH), 3.846 (4H, *s*, CH) and 1.198 (4H, *s*, $CH_2$); $\upsilon_{max}$ (KBr) 1379, 1303 and 1181 $cm^{-1}$.

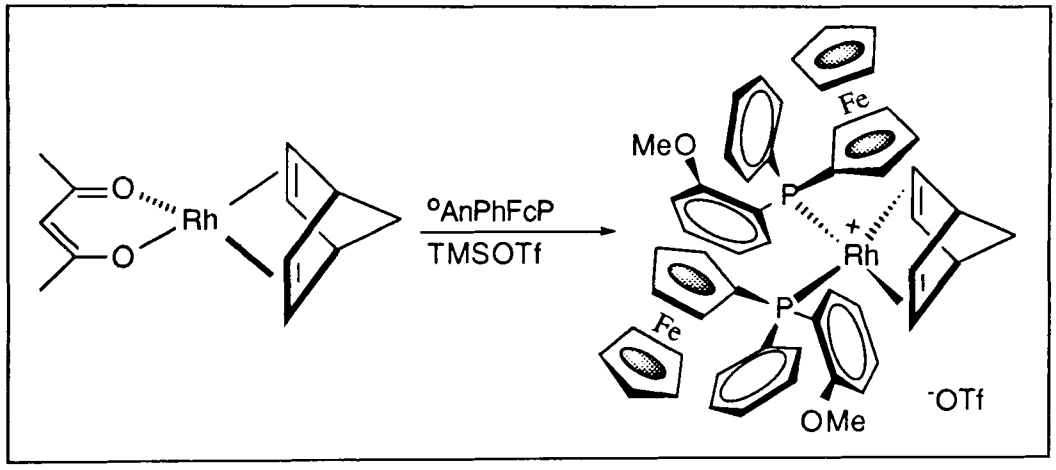
(Bicyclo[2,2,1]hepta-2,5-diene-2,4-pentanedionato)rhodium




To a solution of bisbicyclo[2,2,1]hepta-2,5-diene chloro-4-chloro dirhodium (1.579 g) in dry THF (40 ml) was added potassium acetylacetonate hemihydrate (1.519 g). The suspension was stirred vigorously for 4 h, filtered and the solvent removed from the filtrate under reduced pressure. The resulting complex was then sublimed under reduced pressure to yield bicyclo[2,2,1]hepta-2,5-diene-2,4-pentanedionatorhodium as bright yellow crystals (3.58 g, 73%), m.p. 172-175°C, $\delta_H$ (200 MHz, $CDCl_3$) 5.33 (1H, *s*,

=CH), 3.97 (4H, *dd*, CH=CH), 3.015 ( 2H, *br*, =CH-CH), 1.94 (6H, *s*, $CH_3$), and 1.254 (2H, *t*, $CH_2$); $\delta_C$ (50.3 MHz, $CDCl_3$) 187.10 (C=O), 100.15 (COCHCO), 60.78 ($CH_2$), 52.81 (CH=CH), 59.50 ($CHCH_2$) and 27.17($CH_3$). $\upsilon_{max}$ (KBr) 3436, 3014, 2907, 1578, 1519, 1380, 1265 and 789 $cm^{-1}$.

[Di-(R,R)-(ferrocenyl-2-methoxyphenyl-phenylphosphino)] [bicyclo[2,2,1]hepta-2,5-diene]rhodium trifluoromethanesulphonate

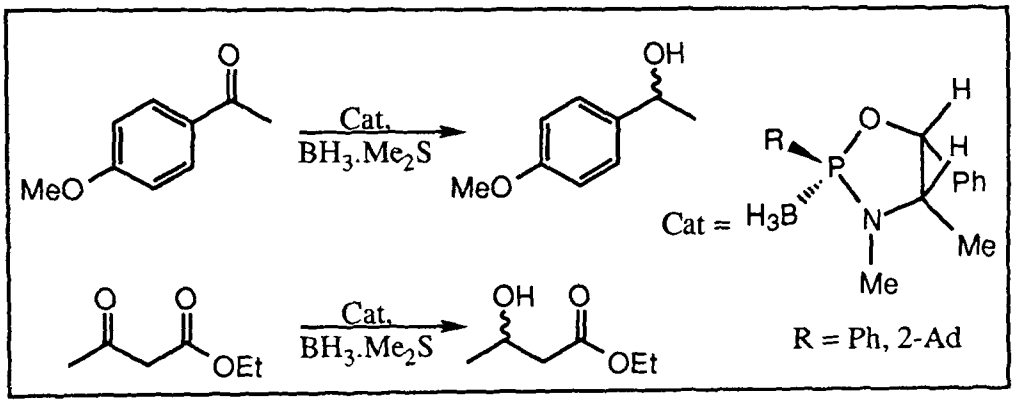



Following the general method of Brown, bicyclo[2,2,1]hepta-2,5-diene-2,4-pentanedionato rhodium (14 mg, 0.063 mmol) was placed in a Schlenk tube and evacuated for 10 min, purged with argon and cooled to -78°C. THF (1 ml) was added and the solution was help *in vacuo* for a further 10 min, flushed with argon and warmed to rt. Trimethylsilyltrifluoromethanesulphonate (13 µl) was added to the yellow solution and the mixture was stirred for 10 min. (S)-Ferrocenyl-2-methoxyphenyl-phenyl phosphine (40 mg, 0.1 mmol) was added to the solution turning it bright orange. After 10 min stirring, pentane was layered on top of the THF layer which resulted in instant crystallisation. [Di-(R,R)-(ferrocenyl-2-methoxyphenyl-phenylphosphino)] [bicyclo[2,2,1]hepta-2,5-diene] rhodium trifluoromethanesulphonate was obtained as dark red crystals (29 mg, 53%); m.p.

97-99°C; $[\alpha]_D^{25}$ +120 (c 0.14, $CH_2Cl_2$); $\delta_P$ (101.3 MHz, $CD_3CD_3$) 19.85 (br d, $J_{Rh}$ 162); *m/z* (Electrospray, MeCN) 995 (M, 100%) with expected isotope pattern.

## 5.4 Catalytic reactions

Borane reduction of ketones - General Procedure




Catalytic

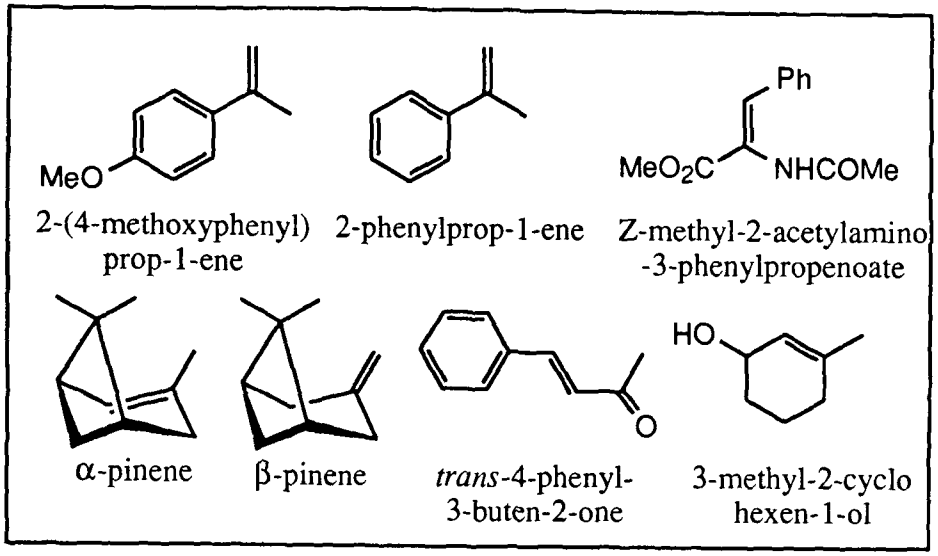
A toluene solution (5 ml) of (2S, 4S, 5R)-3,4-dimethyl-2-adamantyl-5-phenyl-1,3,2-oxazaphospholidine-2-borane (7.55 mg, 11 mol %) and borane dimethylsulphide complex (110 ml, 2M in THF) were added to 4-methoxyacetophenone (30 mg, 0.23 mmol) at rt. The reaction solution was heated to 100°C and stirred overnight. The solution was removed *in vacuo* to yield an oil which was purified by tlc ($H_f$ 254, ethyl acetate / hexane : 1 / 3, $R_f$ 0.4) to yield 1-(4-methoxyphenyl)ethan-1-ol as an oil (26 mg, 85%); $\delta_H$ (200 MHz, $CDCl_3$) 7.32 (2H, d, $J_{H2,6}$ 8.6, Ar-H3,5), 6.91 (2H, d, $J_{H3,5}$ 8.6, Ar-H2,6), 4.88 (1H, dq, $J_{OH}$ 2.8, $J_{CH3}$ 6.4, CHOH), 3.82 (3H, s, $OCH_3$), 1.81 (1H, br, OH), 1.50 (3H, d, $J_{CH}$ 6.4, $CHC\underline{H}_3$).

## Stoichiometric

A toluene solution (5 ml) of (2S, 4S, 5R)-3,4-dimethyl-2-adamantyl-5-phenyl-1,3,2-oxazaphospholidine-2-borane (75.5 mg, 0.22 mmol) was added to 4-methoxyacetophenone (30 mg, 0.23 mmol) at rt. The reaction solution was heated to 100°C and stirred overnight. The solvent was removed *in vacuo* to yield an oil which was purified by tlc (Hf 254, ethyl acetate / hexane : 1 / 3, $R_f$ 0.4) to yield 1-(4-methoxyphenyl)ethan-1-ol as an oil (2 mg, 7%). $^1$H NMR analysis was identical to an authentic sample.

## Homogeneous Hydrogenation-General Procedure

A stock solution of substrate (0.5 mmol) in degassed solvent (2.5 ml, methanol or 1,2 dichloromethane) and a stock solution of catalyst (various amounts) were prepared . A portion of substrate solution (500 µl, 0.1 mmol) and a known volume of catalyst solution were placed in the constant volume apparatus along with enough solvent to make the total volume up to 1 ml under a flow of argon. The reaction vessel was sealed and then cooled to -78°C and evacuated to below 0.1 mbar. The apparatus was then filled with argon and the freeze-pummp-thaw technique was repeated a further 2 times. The reaction vessel was then filled with hydrogen and subjected to another 3 cycles of the freeze-pump-thaw method. On the final cycle, the hydrogen pressure was set to 1500 mbar and the reaction chamber isolated. The reaction vessel was warmed to the required temperature (usually 25°C) and kept at that temperature with the aid of a water circulator fitted with a thermostat. After a short period, the pressure in the apparatus stabilized and the monitoring of the reaction began along with stirring of the reaction solution. After the reaction was complete, the reaction solution was removed from the vessel and passed through a short florisil column to afford hydrogenated substrate after solvent removal. The substrates reduced are shown in Figure 1.




2-(4-methoxyphenyl) prop-1-ene | 2-phenylprop-1-ene | Z-methyl-2-acetylamino -3-phenylpropenoate

α-pinene | β-pinene | *trans*-4-phenyl-3-buten-2-one | 3-methyl-2-cyclo hexen-1-ol

Figure 1

## 2-(4-Methoxyphenyl)prop-1-ene

2-(4-Methoxyphenyl)prop-1-ene was hydrogenated with (1,5-cyclooctadiene)[1-(+/-)-(2-diphenylphosphino-1-naphthyl)isoquinoline] iridium (I) hexafluorophosphate to afford 2-(4-methoxyphenyl)propane after workup as an oil; $\delta_H$ (200 MHz, $CDCl_3$) 7.13 (2H, d, $J_{H3}$ 8.5, Ar-2H), 6.86 (2H, d, $J_{H2}$ 8.5, Ar-3H), 3.80 (3H, s, $OCH_3$), 2.60 (2H, q, $J_{CH3}$ 7.6, $CH_2$) and 1.22 (3H, t, $J_{CH2}$ 7.6, $CH_3$).

## 2-Phenylprop-1-ene

2-Phenylprop-1-ene was hydrogenated with a variety of iridium catalysts to afford 2-phenylpropane after workup as an oil; $\delta_H$ (200 MHz, $CDCl_3$) 7.35-7.15 (5H, m, Ph), 2.92 (1H, sept, $J_{CH3}$ 6.9, PhCH) and 1.26 (6H, d, $J_{CH}$ 6.9, $CH(CH_3)_2$).

## Z-Methyl-2-acetylamino-3-propenoate

Z-Methyl-2-acetylamino-3-propenoate was hydrogenated with a variety of rhodium and iridium catalysts to afford methyl-2-acetylamino-3-phenylpropenoate after workup as a white powder, m.p. 83-85°C; $\delta_H$ (200 MHz, $CDCl_3$) 7.31-7.10 (5H, m, Ph), 5.93 (1H, d, $J_{CH}$ 6.3, NH), 4.89 (1H, ddd, $J_{NH}$ 6.3, $J_{C\underline{H}H}$ 5.7, $J_{CH\underline{H}}$ 5.7, CH), 3.73 (3H, s, $OCH_3$), 3.15 (1H, dd, $J_{C\underline{H}H}$ 13.8, $J_{CH}$ 5.7, CH<u>H</u>), 3.10 (1H, dd, $J_{CH\underline{H}}$ 13.8, $J_{CH}$ 5.7, C<u>H</u>H) and 1.98 (3H, s, $COCH_3$).

## α-Pinene

α-Pinene was hydrogenated with a variety of iridium catalysts to afford pinane after workup as an oil; $\delta_H$ (200 MHz, $CDCl_3$) 2.36-2.26 (1H, m, CH), 2.20-1.30 (8H, m, alkane H), 1.19 (3H, s, $CH_3$) and 0.86 (1H, d, $J_H$ 8.9, CH).

## β-Pinene

β-Pinene was hydrogenated with a variety of iridium catalysts to afford pinane after workup as an oil; $\delta_H$ (200 MHz, $CDCl_3$) 2.36-2.26 (1H, m, CH), 2.20-1.30 (8H, m, alkane H), 1.19 (3H, s, $CH_3$) and 0.86 (1H, d, $J_H$ 8.9, CH).

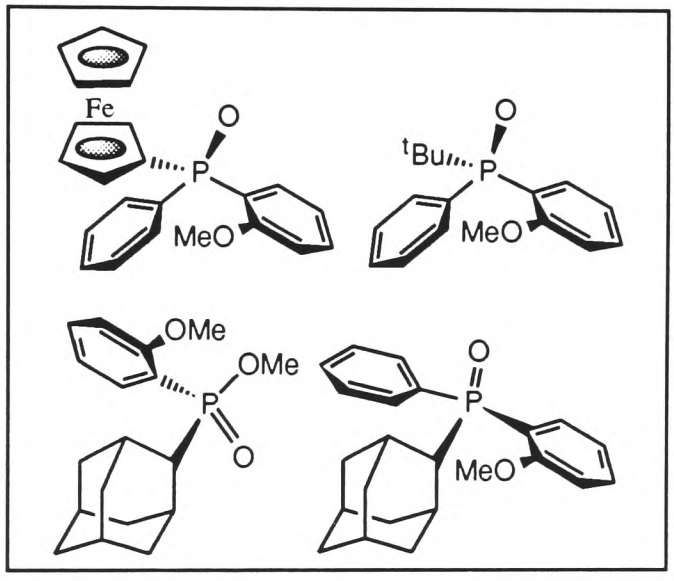
## 3-Methyl-2-cyclohexen-1-ol

3-Methyl-2-cyclohexen-1-ol was hydrogenated with a variety of iridium catalysts to afford 3-methylcyclohexan-1-ol after workup as an oil; $\delta_H$ (200 MHz, $CDCl_3$) 4.06 (1H, br, OH), 2.01-1.46 (10H, m, $CH_2$ / CH) and 0.89 (3H, d, $J_{CH}$ 7.0, $CH_3$).

## 5.5 Determination of Enantiomeric Excesses

### 1. NMR Methods

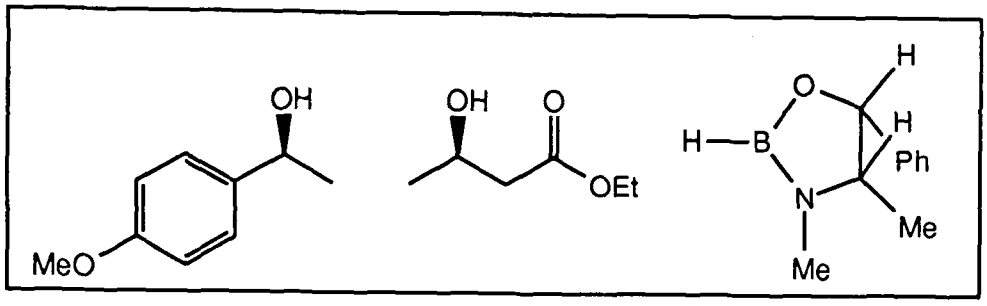
### Phosphine Oxides




A NMR tube containing 5 mg of phosphine oxide in 500 μl of deuterochloroform had 250 μl of 0.05M (R)-(-)-(3,5-dinitrobenzoyl)-α-methylbenzylamine solution added to it. The $^1$H NMR spectrum was recorded and if baseline seperation had not been achieved another alequot of 250 μl of chiral shift reagent solution was added. This procedure was repeated until baseline seperation was achieved. In the cases of (R)-ferrocenyl-(2-methoxyphenyl)phenylphosphine oxide and (R)-*t*-butyl-(2-methoxyphenyl)phenyl phosphine oxide, the anisyl methoxy reasonance split and the enantiomeric excess could be calculated. In the case of (+)-(S)-methyl-(2-adamantyl)-(2-methoxyphenyl)phosphinate, both methoxy peaks were fully resolved. No splitting of the methoxy reasonance was seen with (R)-(2-adamantyl)-(2-methoxyphenyl)-phenylphosphinate but the hydrogen ortho to

phosphorus (°An-H6) on the anisyl moiety did split and the enantiomeric excess was determined from this splitting.

## Secondary Alcohols




(4S,5R)-4-Methyl-5-phenyl-1,3,2-oxazaborolidine was used to determine the enantiomeric excess of 1-(4-methoxyphenyl)ethan-1-ol and ethyl-3-hydroxypropanoate. The procedure used involved charging a 5 mm NMR tube with 0.01 mmol of alcohol and degassing thoroughly *via* the freeze thaw method. (4S,5R)-4-Methyl-5-phenyl-1,3,2-oxazaborolidine (0.011 mmol) was then added to the tube followed by 500 µl of deutero toluene. The reaction mixture was gently agitated and a gas was given off. After 20 min, bubbling stopped and a $^1$H 500 MHz spectrum was taken. The secondary methyl peak was clearly resolved in both cases and integration of these diastereotopic peaks gave the enantiomeric excess.

## 2. Chiral Capillary Gas Chromatography

Chiral capillary gas chromatography was used to determine the enantiomeric excess of α-pinene, 3-methyl-2-cyclohexene-1-ol, 3-methylhexen-1-ol, 2-cyclohexen-1-ol and methyl-2-acetylamino-3-phenylpropanoate produced in various reactions. The general method involved removal of any metal from the catalyst by passing the reaction mixture through a short florisil column using dichloromethane as the eluent. 10 mg of the metal free

products were then dissolved in 2 ml of HPLC grade dichloromethane and 1 μl of this solution was injected into either a CYDEX B column or a XE-60-S-Val-S-A-PEA column. Table 23 gives the retension times ($t_X$) and the temperatures used to determine the enantiomeric excesses of the substrates.

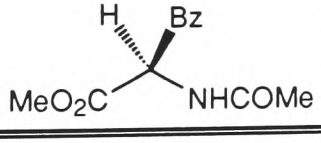
| Substrate | Coulmn | Temp. (°C) | Pres. (psi) | Ret. Time ($t_X$) |
|---|---|---|---|---|
|  | CYDEX B | 60 | 10 | 18.91 (-)-(S)<br>20.18 (+)-(R) |
|  | CYDEX B | 80 | 10 | 31.45<br>36.66 |
|  | CYDEX B | 80 | 10 | 26.17<br>27.04 |
|  | CYDEX B | 60 | 12 | 40.94<br>43.58 |
|  | XE-60-S-Val<br>-S-A-PEA | 170 | 10 | 62.68 (R)<br>66.00 (S) |

Table 23

# Chapter 6

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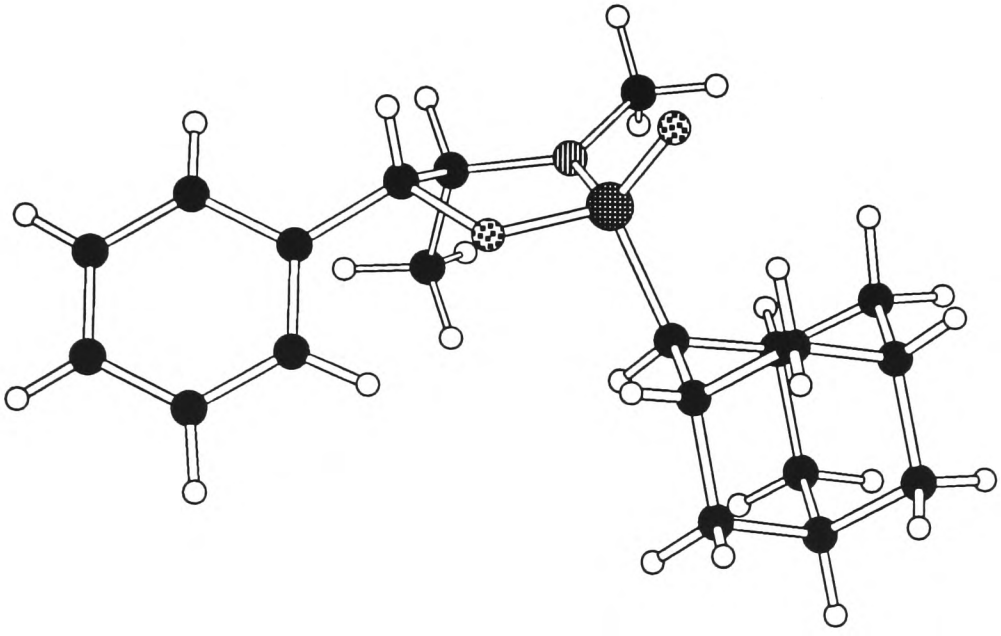
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# Chapter 7

Appendices

## Appendix I



X-ray crystal structure of $C_{20}H_{28}NO_2P$ - ($R_P$) **41**

Crystal data and details of data collection and structure refinement for ($R_P$) **41**

| | |
|---|---|
| Empirical formula | $C_{20}H_{28}NO_2P$ |
| Formula weight | 345.40 |
| Space group | $P2_12_12_1$ |
| Unit cell dimensions | a = 11.145(3) |
| | b = 12.089(4) |
| | c = 13.961(4) |
| Volume | 1881.0(10)Å$^3$ |
| Z | 4 |
| Density | 1.220 g cm$^{-3}$ |
| F(000)/e | 744 |
| Number of unique reflections | 3303 |
| Number of observed reflections | 2622 |
| Final residuals | R 0.368 |
| | $R_W$ 0.847 |
| Weighting scheme | $1/[\sigma^2(F)+nF^2]$ (n=0.0531) |

Atomic coordinates (x $10^4$) for compound $R_P$ **41** with esds in parentheses

| Atom | x | y | z |
|---|---|---|---|
| O1 | 5509.4(13) | 9344.3(13) | 5295.0(12) |
| P2 | 6248.4(5) | 8417(5) | 5857.3(5) |
| N3 | 5069(2) | 7873(2) | 5857.3(2) |
| C4 | 3952(2) | 8474(2) | 6204.5(2) |
| C5 | 4223(2) | 9117(2) | 5273(2) |
| O6 | 6969(2) | 7644(2) | 5286(2) |
| C7 | 5064(4) | 6804(3) | 6850(4) |
| C8 | 3588(3) | 9188(3) | 7044(2) |
| C9 | 3553(2) | 10169(2) | 5128(2) |
| C10 | 2357(2) | 10124(3) | 3829(2) |
| C11 | 1707(3) | 11077(3) | 4710(3) |
| C12 | 2215(3) | 12089(3) | 4864(3) |
| C13 | 3392(3) | 12149(2) | 5162(3) |
| C14 | 4058(2) | 11199(2) | 5295(2) |
| C15 | 7115(2) | 9251(2) | 6682(2) |
| C16 | 7657(3) | 8639(2) | 7542(2) |
| C17 | 8713(4) | 7919(3) | 7236(3) |
| C18 | 9675(3) | 8638(4) | 6786(3) |
| C19 | 9163(3) | 9200(4) | 5911(3) |
| C20 | 8117(3) | 9940(2) | 6203(2) |
| C21 | 8534(4) | 10804(3) | 6928(3) |
| C22 | 9066(3) | 10231(3) | 7803(2) |
| C23 | 10118(3) | 9514(5) | 7503(4) |
| C24 | 8097(3) | 9509(3) | 8259(2) |

Temperature factors (x $10^4$) of non-hydrogen atoms for compound $R_P$ **41** with esds in parentheses

| Atom | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| O1 | 362(8) | 556(10) | 558(10) | 105(9) | 48(8) | -32(7) |
| P2 | 419(3) | 418(3) | 516(3) | -36(3) | 120(3) | 21(3) |
| N3 | 498(11) | 449(11) | 691(15) | 134(11) | -18(11) | -60(10) |
| C4 | 413(12) | 488(13) | 550(13) | 45(12) | -2(10) | -108(12) |
| C5 | 388(11) | 467(13) | 467(13) | -560(12) | -7(11) | -55(10) |
| O6 | 638(11) | 599(11) | 816(14) | -209(10) | 58(11) | 108(9) |
| C7 | 860(3) | 580(2) | 950(3) | 250(2) | 80(2) | -90(2) |
| C8 | 680(2) | 890(2) | 540(2) | 70(2) | 140(2) | 80(2) |
| C9 | 430(13) | 466(12) | 418(12) | -11(10) | 9(10) | -29(10) |
| C10 | 530(2) | 570(2) | 690(2) | 9(15) | -80(13) | -46(13) |
| C11 | 510(2) | 820(2) | 800(2) | 130(2) | -50(2) | 120(2) |
| C12 | 730(2) | 600(2) | 880(2) | 130(2) | 100(2) | 180(2) |
| C13 | 820(2) | 460(2) | 890(2) | -19(15) | 90(2) | -7(15) |
| C14 | 540(2) | 510(13) | 660(2) | -9(13) | -10(14) | -64(12) |
| C15 | 397(11) | 414(12) | 574(15) | -29(11) | 41(12) | 35(11) |
| C16 | 620(2) | 610(2) | 489(15) | 78(13) | -23(13) | -37(13) |
| C17 | 840(2) | 750(2) | 890(2) | 30(2) | -270(2) | 270(2) |
| C18 | 480(2) | 1350(4) | 970(3) | -150(3) | -60(2) | 300(2) |
| C19 | 520(2) | 1270(3) | 720(2) | -110(2) | 200(2) | -210(2) |
| C20 | 590(2) | 650(2) | 537(15) | 170(14) | -133(14) | -151(14) |
| C21 | 830(2) | 690(2) | 860(2) | 90(2) | -180(2) | -290(2) |
| C22 | 670(2) | 900(2) | 660(2) | -300(2) | -170(2) | -190(2) |
| C23 | 550(2) | 1530(4) | 990(3) | 60(3) | -230(2) | -90(2) |
| C24 | 820(2) | 880(2) | 510(2) | 20(2) | -90(2) | -90(2) |