Production of alkyl lactate esters by the alkoxycarbonylation of vinyl acetate

A thesis presented by

Adam J. Rucklidge

to the

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In application for

THE DEGREE OF DOCTOR OF PHILOSOPHY

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Abstract

The methoxycarbonylation of vinyl acetate to methyl 2 and 3-(acetoxy)methylpropanoate has been studied using a variety of bidentate phosphine ligands in the presence of a palladium precursor and acid. In some cases $(Bu^t_2P(CH_2)_nPBu^t_2$ and 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (DTBPMB) the ligands were already known, but new syntheses were established for a variety of other ligands, mostly with xylene backbones. The compounds of general formula 1,2-$(RR'PCH_2)C_6H_4$ were synthesised either from the reaction of *o*-xylene with a mixture of KO^tBu and *n*-BuLi, followed by R_2PCl (R = ^{t}Bu, R = ^{i}Pr, R = Ph, R = Et) or by the reaction of $LiPRR'(BH_3)$ with 1,2-bis(dichloromethyl)benzene (R = ^{t}Bu R' = ^{i}Pr). $LiPRR'(BH_3)$ was in turn prepared from the reaction of PRR'Cl with $NaBH_4$ to form PRR'H, and the subsequent reaction with *n*-BuLi. Similar reactions were used to prepare 1,2-bis(di-*tert*-butylphosphinomethyl)naphthalene (borane protected route) and 2,3-bis(di-*tert*-butylphosphinomethyl)naphthalene (dianion route). The synthesis of unsymmetrical ligands such as $^tBu_nPr_{2-n}PCH_2C_6H_4PCH_2{}^tBu_2$ (n = 0 or 1) proved much more problematic. Eventually, they were successfully prepared from the sequential reaction of the cyclic sulphates with Li $PR^iPr(BH_3)$ (R = ^{i}Pr or ^{t}Bu) and Li $P^tBu_2(BH_3)$.

During the methoxycarbonylation of vinyl acetate, the competing transesterification with methanol to give methyl acetate and dimethoxyethane *via* ethanal, usually drastically reduces the yield. The addition of tertiary phosphines such as PEt_3, but not DTBPMB, catalyses the degradation reaction, as does methanesulphonic acid. However, provided that the ligand is present in excess over the acid, so that all the acid is present as the phosphonium salt, the degradation reaction does not occur even at 80 °C.

The phosphonium salt is sufficiently acidic to allow protonation of the palladium catalyst and DTBPMB promotes good activity for the methoxycarbonylation of vinyl acetate even under very mild conditions (1 bar CO, 25 °C). Optimisation studies have allowed the branched:linear (b:l) to be improved from 1.2 at 30 bar and 80 °C to 3.6:1 at 1 bar and 25 °C. 1,2-bis(di-*tert*-butylphosphinomethyl)naphthalene and 2,3-bis(di-*tert*-butylphosphinomethyl)naphthalene both give very similar results, but the other ligands are all inferior. The relative importance of steric and electronic effects on the reaction selectivity are discussed.

Abbreviations

δ	chemical shift
1,2-DTBPMN	1,2-bis(di-tert-butylphosphinomethyl)napthalene
2,3-DTBPMN	2,3-bis(di-tert-butylphosphinomethyl)napthalene
$^{31}P\{1H\}$	phosphorus, proton decoupled
acac	η^2-acetylacetone
b	branched
BCPE	1,2-bis(9-phosphabicyclo[3,3,1]nonyl)ethane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BQ	benzoquinone
CHIRAPHOS	(2R,3R)-bis(diphenylphosphino)butane
CO	carbon monoxide
d	doublet
dba	trans,trans-dibenzylideneacetone
DBU	1,6-diazobicyclo[5.4.0]undec-7-ene
dcpe	1,2-bis(dicyclohexylphosphino)ethane
DCPMB	1,2-bis(dicyclohexylphosphinomethyl)benzene
DIBPP	1,3-bis(di-iso-propylphosphino)propane
DIOP	(-)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPPMB	1,2-bis(di-iso-propylphosphinomethyl)benzene
DMF	N,N-dimethylformamide
DMP	dimethylpyridine
dmpe	1,2-bis(dimethylphosphino)ethane
DPPB	1,4-bis(diphenylphosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPMB	1,2-bis(diphenylphosphinomethyl)benzene
DPPP	1,3-bis(diphenylphosphino)propane
DTBPB	1,4-bis(di-tert-butylphosphino)butane
DTBPE	1,2-bis(di-tert-butylphosphino)ethane
DTBPMB	1,2-bis(di-tert-butylphosphinomethyl)benzene

DTBPP	1,3-bis(di-tert-butylphosphino)propane
Et	ethyl
EtOH	Ethanol
GC	gas chromatography
GCMS	gas chromatography mass spectrometry
^{i}Pr	iso-propyl
IR	infrared
l	linear
Me	methyl
MeOAc	methyl acetate
MeOH	methanol
MEP	methyl propanoate
MSA	methanesulphonic acid
NBS	N-bromo succinimide
NMR	nuclear magnetic resonance
OAc	acetate
OMs	mesylate
OTf	Triflate
PBu_3	tributylphosphine
PEt_3	Triethylphosphine
Ph	phenyl
PLA	polylactic acid
PPh_3	Triphenylphosphine
ppm	parts per million
p-TSA	para-toluene sulphonic acid
PVP	Polyvinyl pyrollidone
rpm	revolutions per minute
RT	room temperature
s	singlet
TBIPPMB	1,2-bis(tert-butyl-iso-propylphosphinomethyl)benzene
^{t}Bu	tert-butyl

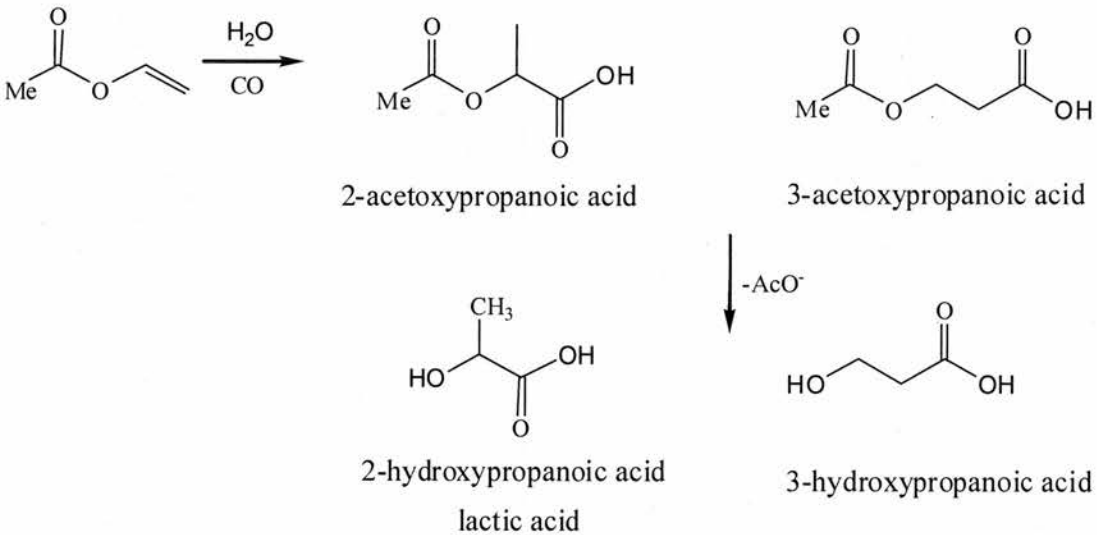
TMF	trimethylformate
TOF	turn over frequency
TON	turn over number
Tppts	tri(m-sulfophenyl)phosphine solution
tr	triplet
VAM	vinyl acetate
Xantphos	9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene

Contents

Chapter 1 - Introduction to the alkoxycarbonylation of vinyl acetate

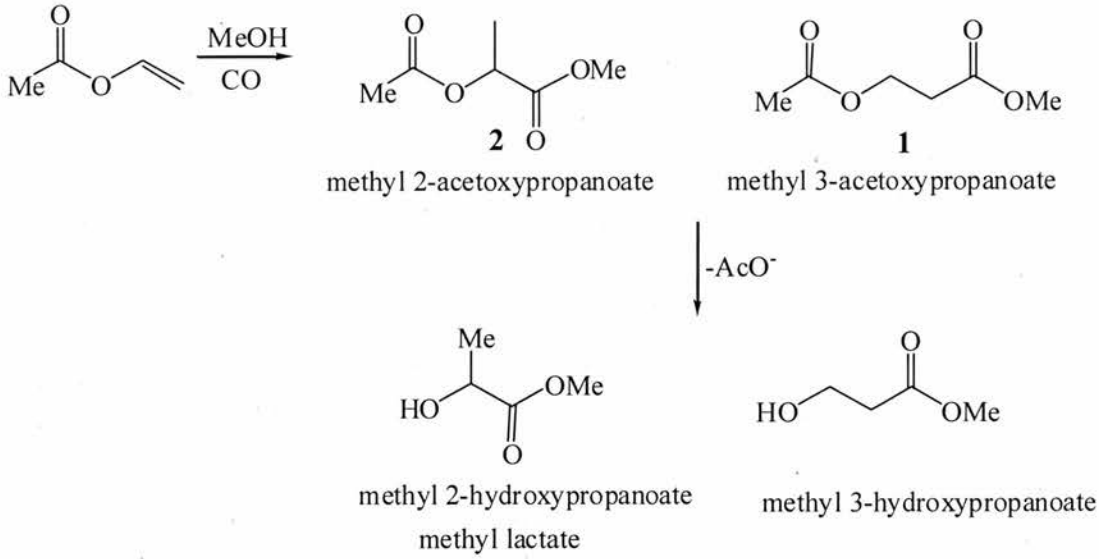
1.1 Background

In the last several years there have been various claims that the esters and polymers of lactic acid will begin to play an important role in the solvent and plastic businesses. From a petrochemical perspective this is an interesting set of target molecules as the carbonylation of vinyl acetate monomer (VAM) with CO, using water as a hydrogen source, produces the acetate-protected lactic acid (Scheme 1.1). Vinyl acetate is a good feedstock as it is cheap and readily available from ethene and acetic acid via the Wacker process. The position of carbonylation can be either a or ß to the acetoxy group affording the branched and linear isomers respectively. The removal of the acetoxy group produces the hydroxypropanoic acids.



Scheme 1.1 - Hydrocarbonylation of vinyl acetate with CO and water to produce hydroxy propanoic acids.

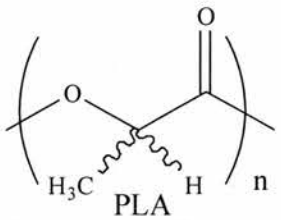
The replacement of an alcohol for the water produces the ester rather than the acid. The production of methyl lactate is shown in Scheme 1.2



Scheme 1.2 - Methoxycarbonylation of vinyl acetate with CO and methanol to produce hydroxypropanoates.

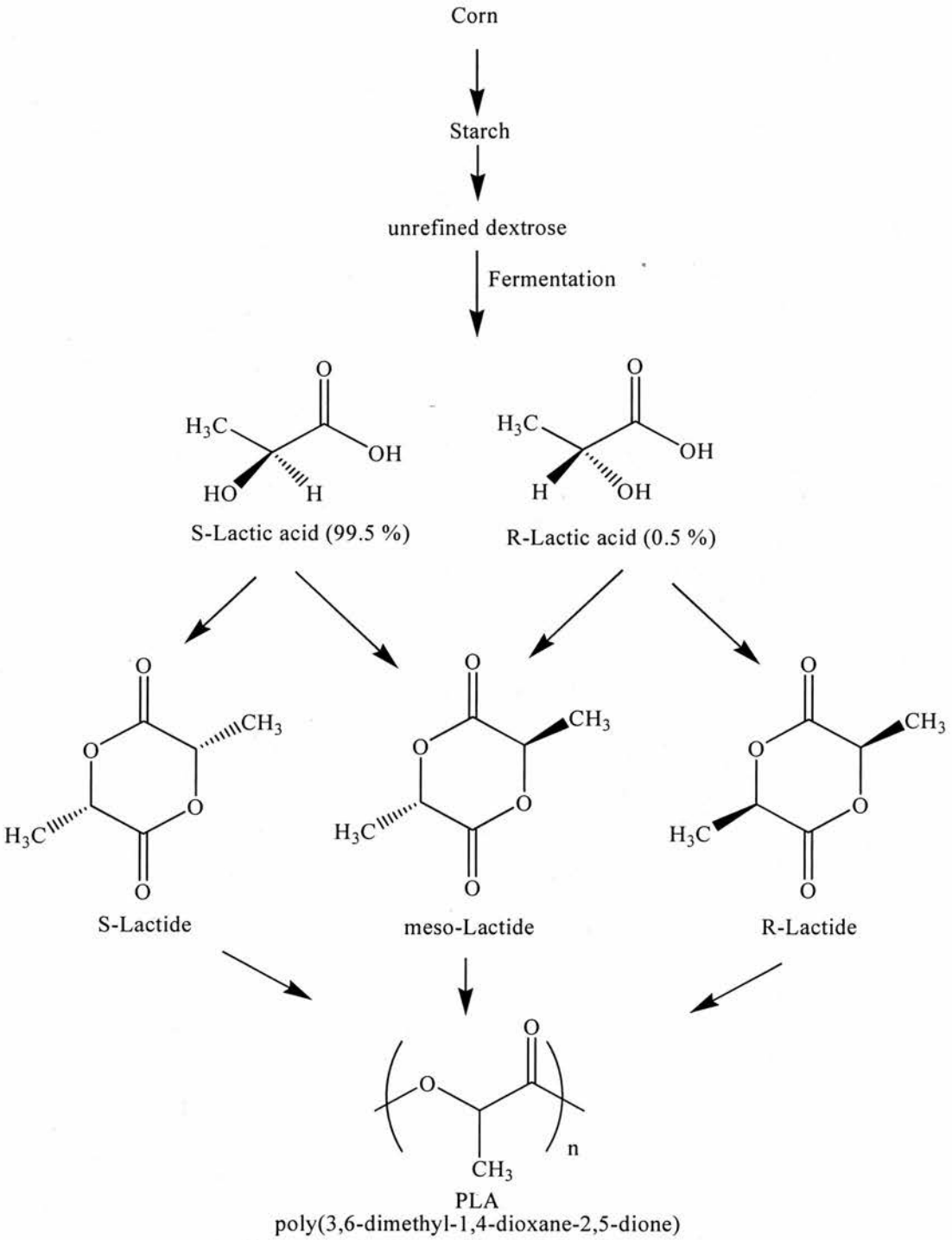
1.1.1 Why polylactic acid and ethyl lactate?

Political and consumer pressures are encouraging manufacturing industries to develop processes and products that are both safe and environmentally friendly. It is also desirable to manufacture goods, which, when their lifetime of usage has expired, can be easily destroyed to non-toxic components. Items such as carrier bags and fast-food boxes are "use once and dispose of" items which either have to be incinerated or end up on a rubbish tip taking years to decay. The search for suitable biodegradable plastics is intensifying. One approach involves the use of lactate esters. Lactate esters can be polymerised to form polylactic acid and if the monomers are predominantly the S enantiomer the resulting polymer is biodegradable and has properties similar to those of polyethylene and polystyrene.



poly(3.6-dimethyl-1,4-dioxane-2,5-dione)

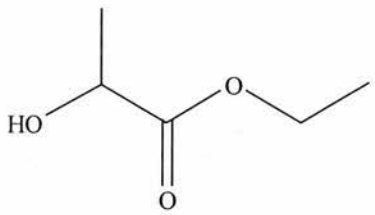
Polylactic acid (PLA) is a polymer that has sparked interest in recent years due to its biodegradable nature. Currently the main producer of polylactic acid is Cargill Dow who have built and commissioned a 140 000 t year^{-1} plant in Nebraska.[1] Their technology uses a renewable feedstock, which in this case is lactic acid, produced by the fermentation of glucose obtained from corn. This fermentation produces predominantly the S enantiomer (99.5 %) and only trace amounts of the R enantiomer (0.5 %). These acids are then reacted without the presence of a solvent to produce a cyclic dimer intermediate called a lactide. These are purified by vacuum distillation and with the application of heat these dimers ring open to form the polymers (Scheme 1.3). Careful control of the ratio of R and S lactic acids in the chain allows a 'family' of polymers to be produced. Polymers with high levels of the S enantiomer produce crystalline materials and when the R concentration increases above 15 % the material becomes amorphous. PLA can be used for all applications where the traditional hydrocarbon based polymers such as polyethylene, polystyrene and polypropylene are employed. PLA fibre is well suited for a wide range of technical textile applications due to it being lightweight and having low moisture adsorption, high wicking and low flammability. It is worth noting that Cargill Dow plan initially to focus on marketing the output from their single new plant but their current business plan calls for three new PLA production facilities this decade in Europe, Asia and one other unspecified location.



Scheme 1.3 - Formation of PLA from corn

Ethyl lactate has been identified as an alternative green solvent.[2] Unlike many solvents ethyl lactate is so benign that the U.S. Food and Drug Administration (FDA) approved

its use in food products years ago. This alternative solvent is non-toxic, has low volatility, is biodegradable and has excellent solvent properties. It is capable of replacing 80 % of the 3.8 million tons of solvent used in the US every year. Unfortunately, until recently ethyl lactate has been too expensive for widespread use at ~\$1.60 - \$2.00 lb^{-1}. Argonne, an Illinois based company, have a patent for the low-cost synthesis of high purity ethyl lactate. They claim that they will be able to sell ethyl lactate at a price less than \$1.00 lb^{-1}, which is cheap enough to be able to replace a range of toxic and environment damaging solvents such as chlorofluorocarbons, methylene chloride and ethylene glycol ethers. Cargill Dow is also producing ethyl lactate from lactide and ethanol, which are two renewable resources.



ethyl lactate

1.2 Overview of current alkoxycarbonylation technologies

Over the last 10 years there has been an increase in the number of publications – both academic and patents – detailing the formation of acid and ester oxygenates from unsaturated molecules. The majority of these publications report the use of a palladium catalysed homogeneous reaction with other transition metals being employed to a lesser extent. Of the unsaturated substrates, alkenes – particularly ethene - and vinyl aromatics - such as styrene – have received the majority of the investigators' attention. This is because the methoxycarbonylation of ethene produces methyl propanoate; a

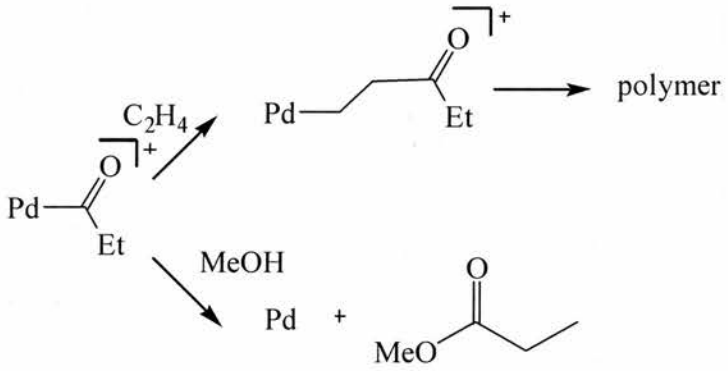
precursor to methyl acrylate, and the methoxycarbonylation of styrene forms an intermediate in the synthesis of the non-steroidal anti-inflammatory drug Ibuprofen.

This review will be split into two sections. Firstly the various catalyst systems and the ensuing catalytic results will be examined. This will be dealt with by detailing the Pd catalysed alkoxycarbonylation of ethene, styrene and some other substrates in turn, paying close attention to the differing regioselectivities. Finally an examination of the various proposed mechanisms for the alkoxycarbonylation of unsaturated compounds will be undertaken. This will take into consideration both direct evidence such as the detection of catalyst intermediates and indirect evidence such as the product distribution and reaction rates of various catalytic systems.

For the purpose of this review the process of the formation of an ester from the reaction of a carbon-carbon double bond, carbon monoxide and an alcohol will be referred to as alkoxycarbonylation. There are various examples from the literature that will be reviewed here where the author refers to the process as hydroesterification. The use of alkoxycarbonylation is clearer as the alcohol type is readily identified i.e. methoxycarbonylation uses methanol to form the methyl ester.

1.3 Alkoxycarbonylation vs copolymerisation

Alkoxycarbonylation and CO/alkene copolymerisation are two closely related processes. Assuming a hydride mechanism is in operation (see section 1.8.1) both processes start in the same fashion. However once the acyl species is formed there are two different outcomes (Scheme 1.4). In alkoxycarbonylation the methanolysis of the acyl generates the ester product and the initial catalytic species is regenerated. For copolymerisation a second alkene molecule reacts with the acyl to form an alkyl, which in turn reacts with CO reforming an acyl. This alkene-CO insertion repeats and the copolymer forms. Termination leads to dissociation from the catalyst and regeneration of the active catalyst.

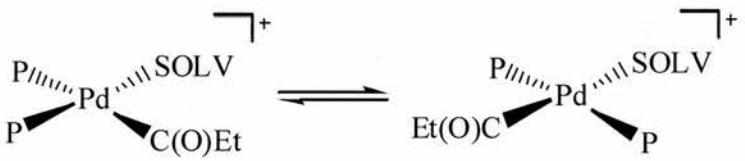


Scheme 1.4 – Chain propagation *vs* chain termination

It has been shown that it is possible to control which of the two regimes is entered by careful use of coordinating phosphine ligands. Generally, if a bidentate phosphine is used then the catalysis favours chain growth, whereas if a monodentate phosphine is used, the selectivity reverts to ester formation. This is because in the diphosphine complex the phosphorus atoms are – except in very special cases – coordinated *cis* to each other. This forces the growing chain and the remaining free coordination site to be

cis to one another, which is required for the migratory insertion reactions. This results in the rate of chain growth being faster than the rate of methanolysis and copolymer is produced.

When monophosphines are used the two coordinated phosphines prefer to be *trans* to one another. This results in the growing chain and the free coordination space being mutually *trans*. In this coordination environment it would be expected that no reaction could occur as the two groups to undergo migratory insertion are *trans* to one another. However there is a fast equilibrium between the *trans* and the *cis* isomers, which allows the correct geometry to be obtained. Once the acyl has been formed the *cis* isomer isomerises back to the *trans* thus stopping further chain growth and methanolysis produces methyl propanoate (Scheme 1.5).

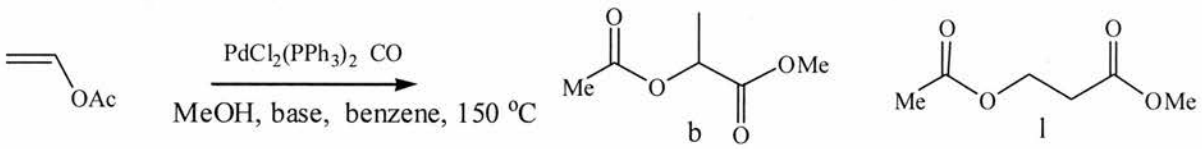


Scheme 1.5 – Equilibrium between *cis* and *trans* isomers

1.4 Pd catalysed alkoxycarbonylation of vinyl acetate

The first example in the literature of the alkoxycarbonylation of vinyl acetate is in a patent by Drent in 1992.[3] It was shown as an example that the methoxycarbonylation of vinyl acetate can be carried out using a catalyst made *in situ* from palladium acetate and 1,3-bis(di-*tert*-butylphosphino)propane in a ratio of 1:2.5 with *tert*-butylsulphonic acid included. Methanol and diglyme (1:2) are used as solvents and the solution is heated to 75 °C under a CO pressure of 40 bar. The reaction rate was measured as 200 moles of ester produced per gram of palladium per hour, with a branched to linear ratio (b:l) of 2:1. There is no indication if there where any side products produced.

Another example of vinyl acetate methoxycarbonylation is in a paper by Kudo *et. al.*.[4] They carried out the methoxycarbonylation of enol esters using $[PdCl_2(PPh_3)_2]$ as a catalyst (Scheme 1.6).



Scheme 1.6 - Methoxycarbonylation of vinyl acetate

Reaction condition optimisation was carried out varying the temperature (Figure 1.1), base type (Figure 1.2) catalyst, base/Pd ratio (Figure 1.3) and carbon monoxide pressure (Figure 1.4).

As can been seen in the Figure 1.1 as the temperature is increased there is an increase in the quantity of methyl acetate produced. This is due to the methanolysis of vinyl acetate. As the temperature increases the conversion of vinyl aceate increases.

However the yield of methyl 2-acetoxypropanoate is maximised at 110 °C with a yield of 50 %.

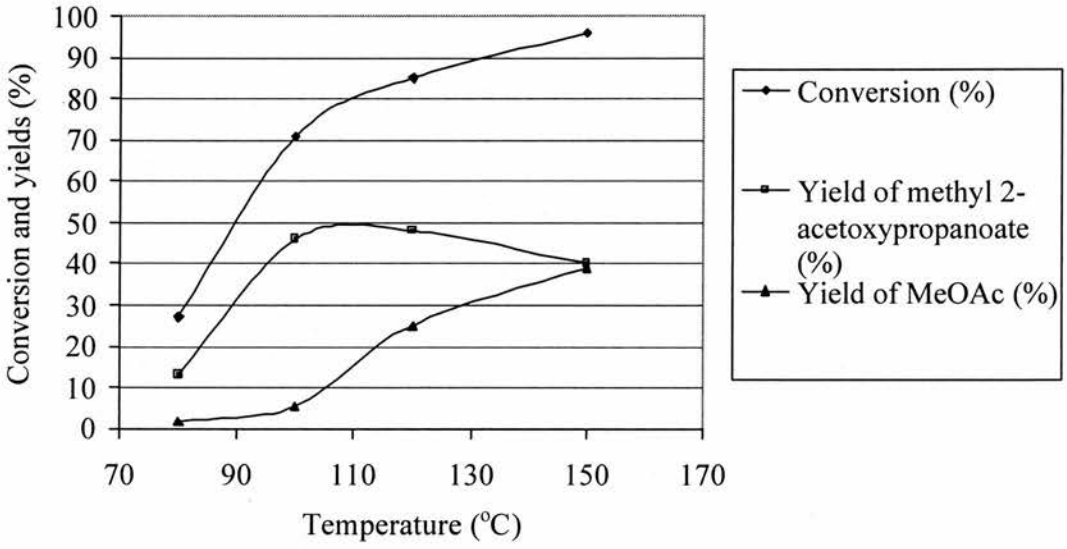


Figure 1.1 - Performance of $[PdCl_2(PPh_3)_2]$ catalyst at different temperatures.[4] Reaction conditions - $[PdCl_2(PPh_3)_3]$ (2.5 mmol), VAM (2.0 mmol), MeOH (0.1 mmol), 2,6-dimethylpyridine (0.1 mmol), CO pressure (150 atm), reaction time = 5 hours.

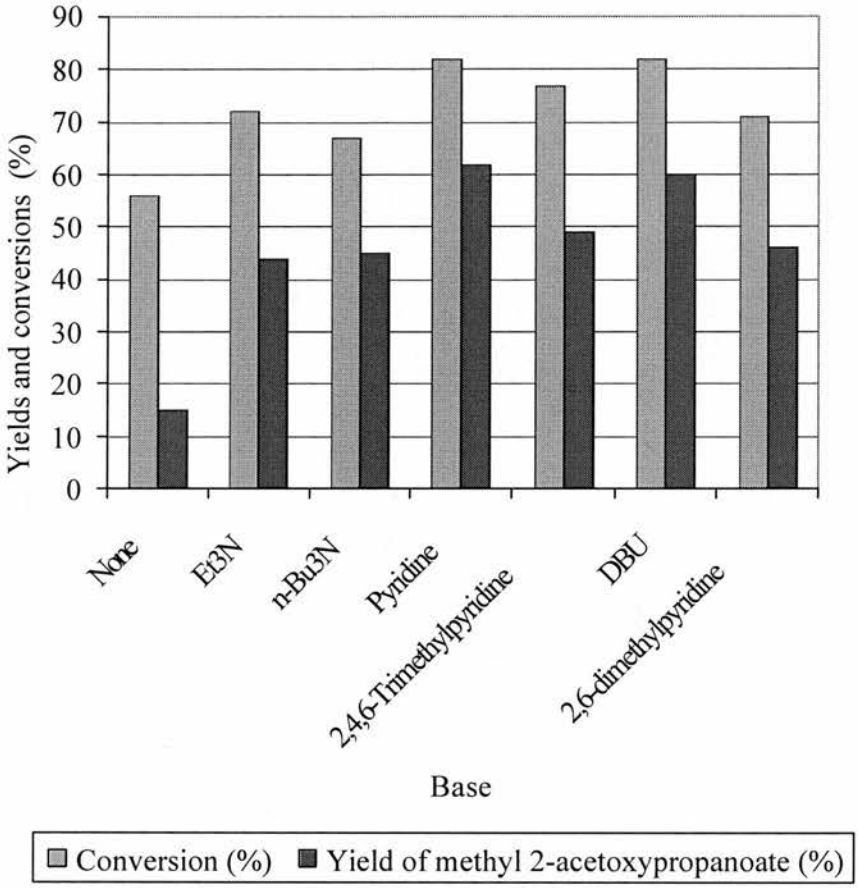


Figure 1.2 - Performance of $[PdCl_2(PPh_3)_2]$ catalyst with different bases.[4] Reaction conditions - $[PdCl_2(PPh_3)_3]$ (2.5 mmol), VAM (2.0 mmol), MeOH (0.1 mmol), base (0.1 mmol), CO pressure (150 atm), temperature = 100 °C, reaction time = 5 hours

If no base is added there is very little methyl 2-acetoxypropanoate produced. The addition of an amine increases the yield of the desired product to between 44 % and 62 %. In all cases there is still a lot of unaccounted for vinyl acetate which is likely to have been converted to methyl acetate.

The following catalyst systems were examined, $[PdCl_2(PPh_3)_2]$, $[PdBr_2(PPh_3)_2]$, $[PdI_2(PPh_3)_2]$, $[PdCl_2(P(OPh)_3)_2]$, $PdCl_2$, $PdCl_2$ + P(*p*-tolyl)$_3$, $[PdCl_2(PBu_3)_2]$, $[PdCl_2(dppe)]$, $[PdCl_2(dppb)]$, $[Pd(PPh_3)_4]$, and $[PtCl_2(PPh_3)_2]$. In addition to

$[PdCl_2(PPh_3)_2]$ only $[PdBr_2(PPh_3)_2]$, $[PdI_2(PPh_3)_2]$ and $PdCl_2$ + P(*p*-tolyl)$_3$ were found to work, with conversions of 66, 51, and 73 % respectively.

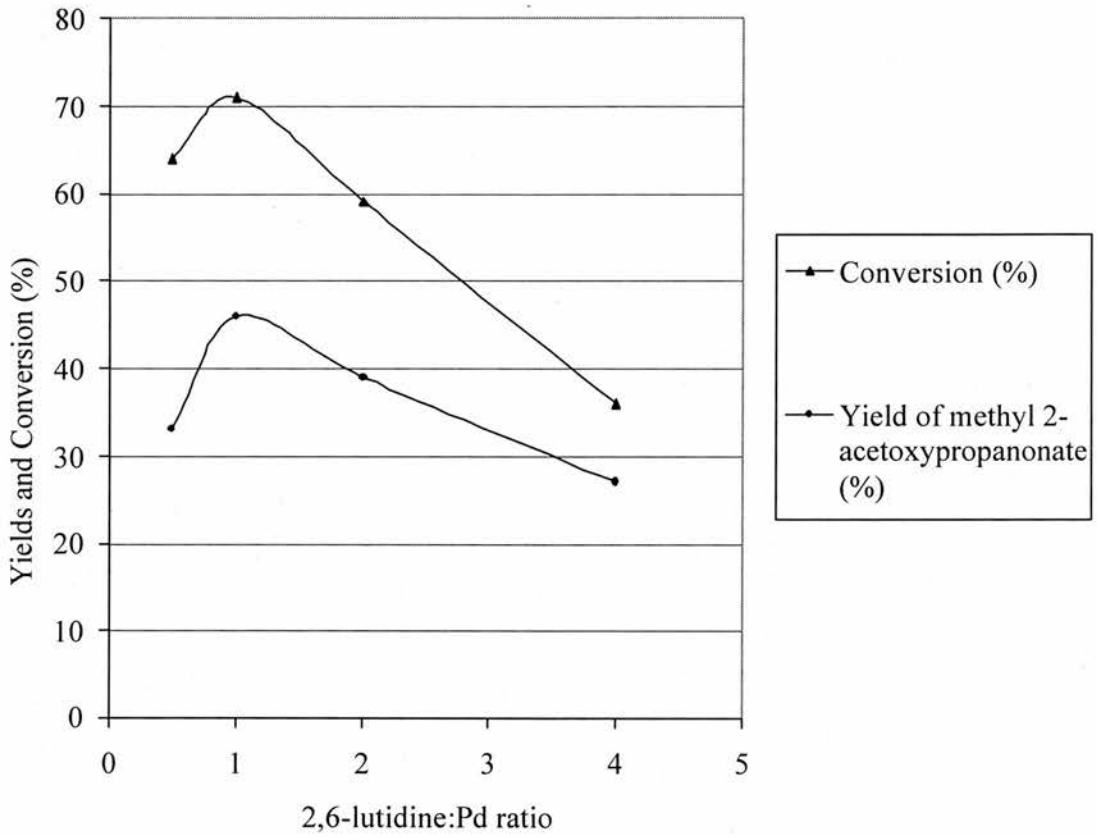


Figure 1.3 - Effect of lutidine/Pd ratio on the methoxycarbonylation of vinyl acetate.[4] Reaction conditions - $[PdCl_2(PPh_3)_3]$ (2.5 mmol), VAM (2.0 mmol), MeOH (0.1 mmol), CO pressure (150 atm), temperature = 100 °C, reaction time = 5 hours.

The conversion of vinyl acetate is largest (71 %) when the ratio of 2,6-lutidine:Pd is 1:1. As the ratio increases the conversion decreases.

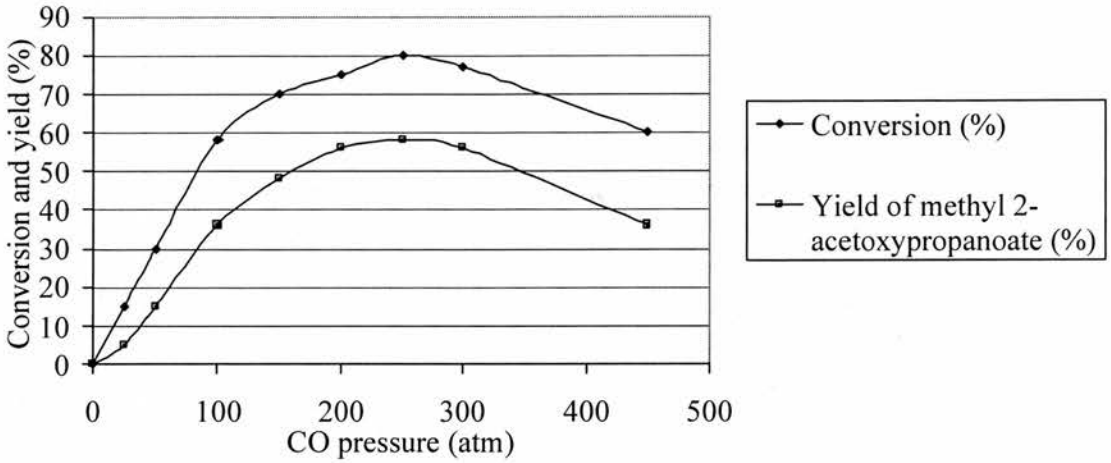
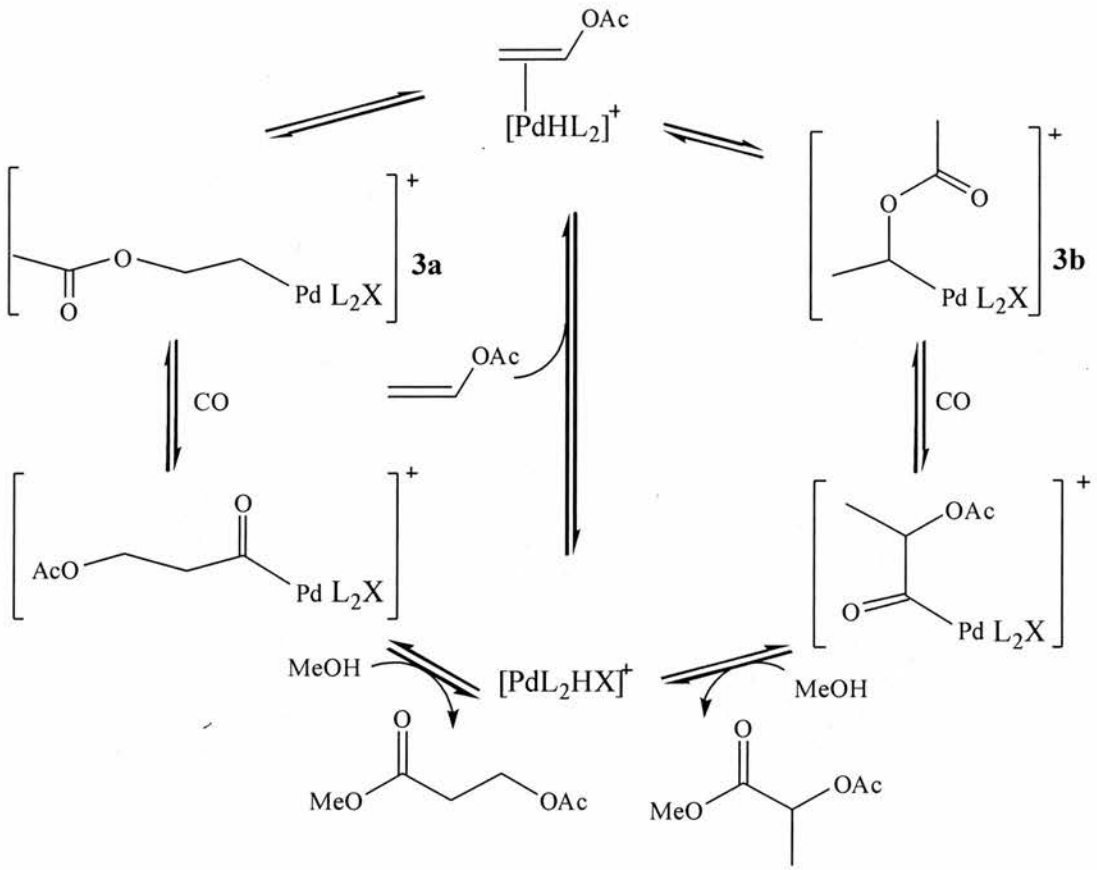


Figure 1.4 - Performance of $[PdCl_2(PPh_3)_2]$ catalyst with varying CO pressure.[4] Reaction conditions - $[PdCl_2(PPh_3)_3]$ (2.5 mmol), VAM (2.0 mmol), MeOH (0.1 mmol), 2,6-dimethylpyridine (0.1 mmol), temperature = 100 °C, reaction time = 5 hours.

As the CO pressure was increased there was an increase in the conversion of vinyl acetate, the maximum occurring at 350 atm with a yield of 80 %. This is also the optimal pressure for the yield, which is 58 % of methyl 2-acetoxypropanaote. The CO pressure has little effect on the selectivity of the reaction to the desired branched product.

Using all the condition and rate data, the hydride mechanism was proposed (Scheme 1.7) which will be discussed in detail in section 1.8. Assuming the hydride mechanism is in operation the regioselectivity of vinyl acetate methoxycarbonylation depends on the relative stabilities of the two palladium-alkyl(II) intermediates (**3a** or **3b**). A negative charge develops on the a-carbon of the palladium-alkyl intermediate, which is stabilised by the electron-withdrawing acetate group. This is not the case in intermediate **3a** due to the remoteness of the acetate group from the negative carbon

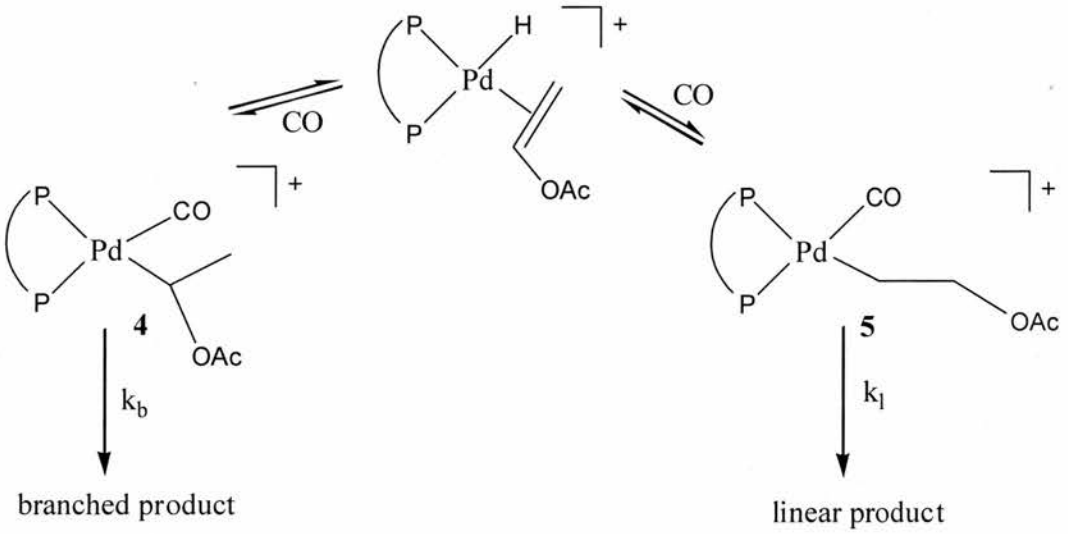
atom and as a result the methoxycarbonylation favours the formation of the branched product on electronic grounds.



Scheme 1.7 - Proposed mechanism for the methoxycarbonylation of vinyl acetate. X = solvent, CO, vinyl aceate or MeOH

It is also possible that the branched product is favoured due to the different rates of the palladium-alkyl with carbon monoxide (Scheme 1.8). If the migratory insertion of the branched alkyl **(4)** into the Pd-CO bond (k_b) is faster than into the linear isomer **(5)** (k_l) there will be more branched product produced. As there is an equilibrium between the palladium-alkyl complexes and the palladium-hydride-vinyl acetate complex, as the

branched alkyl-palladium complex reacts, more of **4** forms to reset the equilibrium thus favouring the formation of the branched acyl isomer.



Scheme 1.8 - Carbonylation of palladium-alkyls

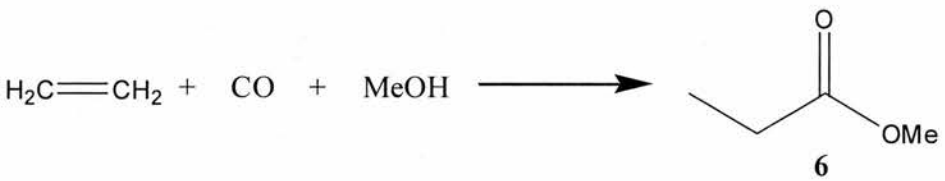
The most recent report of the methoxycarbonylation of vinyl acetate was in a poster presentation at the 14th International Symposium of Homogeneous Catalysis in Munich.[5] Tanaka *et. al.* showed that the use of the electron rich diphosphine bis-1,2(di-*tert*-butylphosphinomethyl)benzene (DTBPMB) with palladium can give high rates for the production of the desired ester products. They tested the effect of using methanesulphonic acid that was both free in solution and bound to a solid polymer. It was found that the polymer bound acid improved the rate but decreased the b:l ratio. It was reported that the polymer bound acid reduced the level of hydrolysis of the acetate group of the ester product.

Table 1.1 - Effect of acid on methoxycarbonylation of vinyl acetate.[5] Pd (0.025 mmol), DTBPMB (0.025 mmol), VAM (10 mmol), CO pressure (6 atm), temperature = 60 °C. a = percentage of carbonylated product that has been hydrolysed to the alcohol

Acid	Acid:Pd	TON	b:l	% OH[a]
MSA	15	2167	3.0:1	50
Argonout-SO_3H	12	3090	2.5:1	5

1.5 Pd catalysed alkoxycarbonylation of ethene

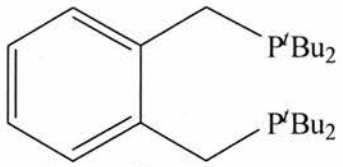
The methoxycarbonylation of ethene produces methyl propanoate (MEP) **(6)** (Scheme 1.9).



6

Scheme 1.9 - Production of methyl propanoate

There has been a considerable amount of research on this process not least by Lucite International who in 1999 announced a new commercial process for the manufacture of MEP. Eastham and Tooze patented this technology for ICI Plc in 1996,[6] - which became Lucite International - publishing the results in 1999.[7] They reported that they could produce MEP from ethene with an activity of 12 000 moles of ethene consumed per mole of palladium per hour. They used a Pd catalyst with an electron rich bidentate diphosphine **(7)**, and methane sulphonic acid (MSA) in MeOH, heated at 80 °C with an equimolar ratio of ethene and carbon monoxide at a total pressure of 10 bar.

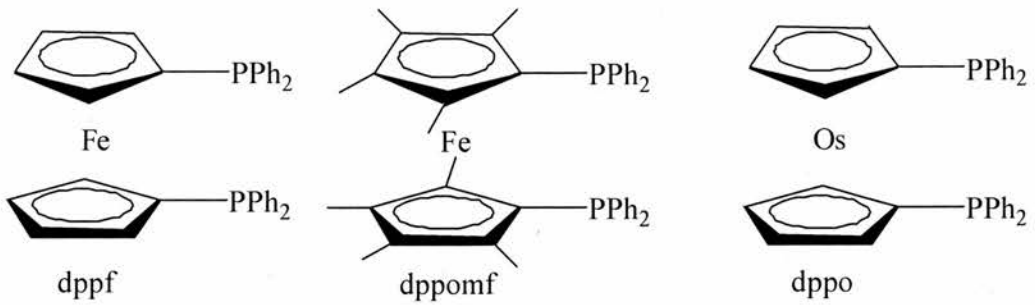


7

The inherent electron richness of this ligand, 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (DTBPMB) **(7)**, is vitally important. When the *o*-xylene backbone of the ligand was kept and the two-alkyl substituents on the phosphorus atoms were changed from *t*-butyl to *i*-propyl, the activity decreased by a factor of 60, to 200 moles of ethene consumed per mole of palladium per hour.

Recently it has been shown that it is possible to form alkyl propanoates using less electron rich diphosphines coordinated to palladium. The carbonylation of ethene with phenols in the presence of [(DIPPP)PdH(PR$_3$)][OPh] (DIPPP = 1,3-bis(di-*iso*-propylphosphino)propane, R = Et, Cy) at temperatures of 150 °C in a toluene solution has been reported.[8] Significantly no activity was seen if the phenol was replaced by either the less acidic methanol or ethanol. There was no effect of changing the R group on the trialkylphosphine.

Another class of diphosphine ligand has been shown to successfully carbonylate ethene to MEP. The ligands 1,1'-bis(diphenylphosphino)ferrocene (dppf) **(10)**, 1,1'-bis(diphenylphosphino)octamethylferrocene) (dppomf) **(9)** and 1,1'-bis(diphenylphosphino)osmocene (dppo) **(8)** were used to form various Pd complexes.[9-11]



10 **9** **8**

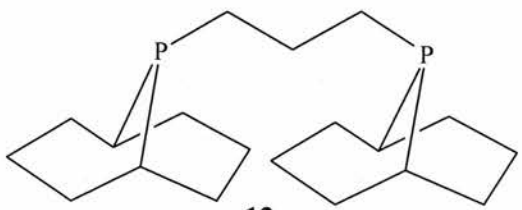
The different complexes were used in the methoxycarbonylation of ethene (Table 1.2). Complexes with dppomf and dppo coordinated gave 100 % selectivity to MEP. This was in direct contrast to the dppf ligand that gives a whole host of oligomers and polyketones. Oligomers and polyketones are formed when propagation rather than termination occurs once the acyl group has been formed.

Table 1.2 - Methoxycarbonylation of ethene.[10] Reaction conditions: Catalyst (0.01 mmol); 1:1 CO/C_2H_4 (40 bar), MeOH (100 ml), Temperature = 85 °C, Reaction time = 1 hour. TON = moles of ethene incorporated (moles cat)$^{-1}$. BQ =1,4-benzoquinone, alt-E-CO = alternating co-polymer, A = methyl 4-oxohexanoate, B = dimethyl succinate and C = dimethyl 4-oxoheptanedionate. x = productivity as grams of product (gram sof Pd)$^{-1}$

Catalyst	TsOH (mmol)	BQ (mmol)	Alt-E -CO	MEP^x	A^x	B^x	C^x
$[Pd(H_2O)_2(dppf)][OTs]_2$	0.2	0.8	1785	1085	1274	40	1280
$[Pd(PPh_3)(dppf)][BF_4]_2$	0.2	0.8	714	799	1008	62	1310
$[Pd(H_2O)_2(dppomf)][OTs]_2$	0.2	0.8	0	513	0	0	0
$[Pd(PPh_3)(dppomf)][BF_4]_2$	0.2	0.8	0	629	0	0	0
[Pd(OTs)(dppo)][OTs]	0.4	0	0	402	0	0	0

The Shell Oil Company filed a patent in 1995 for the process of the carbonylation of ethylenically unsaturated compounds.[12] They show that it is possible to butoxycarbonylate ethene using palladium(II) acetate with either 1,2-P,P'-bis(9-phosphabicyclo[3,3,1]nonyl)ethane (BPBNE) **(11)** or 1,3-P,P'-bis(9-phosphabicyclo[3,3,1]nonyl)propane (BPBNP) **(12)**. Under comparable conditions the

ethane backbone ligand **(11)** gave a faster rate. The addition of the base 3,4-dimethylpyridine (DMP) improves the rate, as does the addition of the drying agent trimethyl orthoformate (TMF). The fastest rate is 1150 moles of ethene (g palladium)$^{-1}$ hour^{-1}. It is obtained using the following system, $Pd(OAc)_2$ (0.25 mmol), BPBNE (0.6 mmol), *n*-butanol (50 ml), DMP (10 mmol), TMF (5 ml), ethene:CO 1.5:1, total pressure = 50 bar, temperature = 135 °C.



12

1,3-P,P'-bis(9-phosphabicyclo[3,3,1]nonyl)propane (BPBNP)

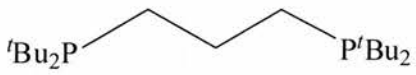
A patent followed this work in 2000,[13] which claimed that the introduction of various additives had a marked effect on the rate of the reaction (Table 1.3). They claimed various examples of the butoxycarbonylation of ethene.

Table 1.3 - $Pd(OAc)_2$ (0.25 mmol), BPBNE (0.6 mmol), butanol (20 cm^3), butyl propanoate (40 cm^3), NEt_3 (5 ml), ethene (10 bar), CO pressure (15 bar), temperature (125 °C), reaction time = 2 hours. DPP = 2,2-di(*p*-phyla)propane. * rate = moles of ester formed per mole of Pd per hour.

Entry	MSA (mmol)	HCl (mmol)	Propanoic acid (mmol)	DPP (g)	Phenol (g)	Rate*	Selectivity (%)
1	0.5	0	0	0	0	300	100
2	0.5	0.25	0	0	0	1200	100
3	0	0	2	10	0	1200	100
4	0.5	0.25	0	0	5	4000	100
5	0.5	0.25	0	0	10	8000	100

The inclusion of an alcohol that is more acidic than butanol i.e. DPP and phenol, increases the rate of the production of the butyl propanoate. The addition of an acid will suppress ionisation of the alcohol.

In 1992 Shell[3] filed an ethene alkoxycarbonylation patent this time using di-*tert*-butyl groups on the phosphorus atoms rather than the bicyclononyl groups.



13

1,3-bis(di-*tert*-butylphosphino)propane (DTBPP)

A selection of the results reported are shown, detailing the importance of various reaction parameters.

Table 1.4 - $Pd(OAc)_2$ (0.1 mmol), MeOH (20 cm^3), methyl propanoate (30 cm^3), ethene pressure (20 bar), CO pressure (40 bar), temperature = 100 °C, * rate = g of ester formed per g of palladium per hour.

Ligand	Ligand (mmol)	MSA (mmol)	H_2 (bar)	Rate*	Selectivity (%)
DTBPP **(13)**	0.3	0.25	0	5000	> 98
DTBPP **(13)**	0.3	0.25	5	13000	>98
PPh_3	0.3	0.25	0	< 10	N/A
PPh_3	3	2	0	400	> 98

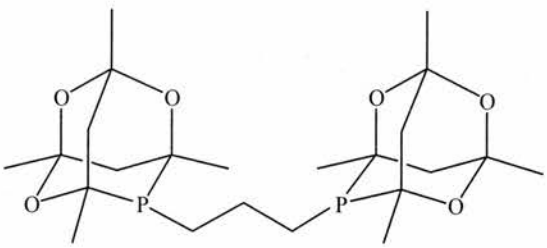
As can be seen the bulky electron rich diphosphine, DTBPP, is required to give suitable activity. If triphenylphosphine is used then an increase in both phosphine and acid concentration is required to bring about any conversion of ethene.

Drent[14] carried out further work using this system but slightly varied the substituents on the phosphorus atoms. As can be seen in Table 1.5 slight changes in the alkyl groups of the phosphorus atoms causes dramatic changes in the selectivity of the catalysis. Changing the alkyl groups of the 2 phosphorus atoms from *tert*-butyl to *sec*-butyl groups switches the selectivity of ethene carbonylation to the formation of diethyl ketone (y =1).

Table 1.5 – Alkoxycarbonylation of ethene and CO. Reaction conditions: $Pd(OAc)_2$ (0.1 mmol), ligand (0.12 mmol), MSA (0.25 mmol), MeOH (50 cm^3), methyl propanoate (30 cm^3), ethene pressure (20 bar), CO pressure (20 bar), temperature = 120 °C. * = [mol (mol Pd^{-1} h^{-1})] DSBPP – 1,3-bis(di-*sec*-butylphosphino)propane

		Ethene selectivity to products (%)						
		$H[CH_2CH_2CO]_xOCH_3$			$H[CH_2CH_2CO]_yCH_2CH_3$			
Ligand	Activity*	x=1	x=2	x=3	y=1	y=2	y=3	Higher
DTBPP	25000	97.4	-	-	2.6	-	-	-
DSBPP	4000	1.5	10.6	0.6	1.3	74.6	0.1	~ 10

A further example from Shell of electron donating diphosphines giving good rates for the methoxycarbonylation of ethene is the use of *meso/rac*-1,3-bis(phospha-adamantyl)propanes **(14-15)**.[15]



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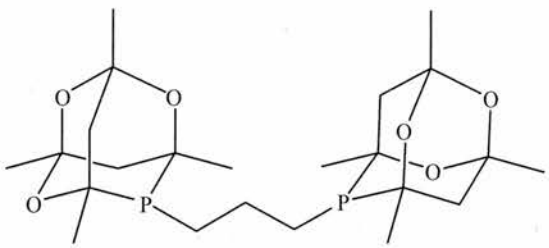

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A mixture of *meso/rac* diphosphine (0.15 mmol) with $Pd(OAc)_2$ (0.1 mmol) and MSA (0.25 mmol) dissolved in MeOH (50 cm^3) and pressurised with ethene (20 bar) and CO (30 bar). This was heated to 90 °C for 5 hours. The average rate per mole of ester produced per mole of palladium per hour was reported as 10 000 with a selectivity to MEP of > 99 %. This is slightly slower than the DTBPMB ligand. If the C_3 backbone was replaced for a C_2 the rate dropped to 4000 and the product was not MEP but polyketone with a molecular weight of 2000.

Doherty[16] has shown that the product selectivity of the Pd catalysed reaction of ethene with CO in MeOH is dependent upon the relative orientation of the coordinating

phosphorus atoms. Using the ligands with cyclohexyl or norbornyl backbone **(16-19)** to form the precursor $[(PnP)Pd(OAc)_2]$ dramatically differing product distributions can be obtained. Copolymerisation of ethylene with CO was carried out and the results are summarised in Table 1.6.

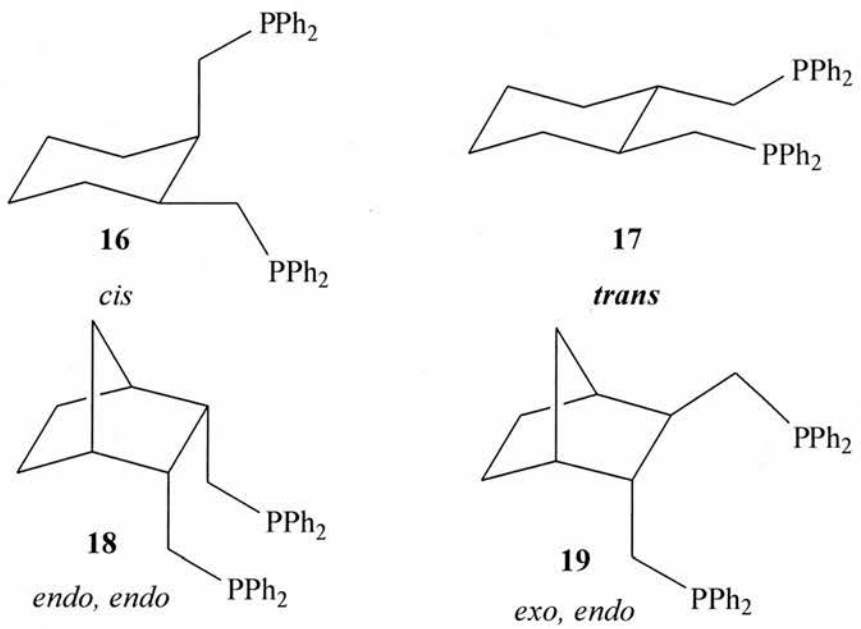


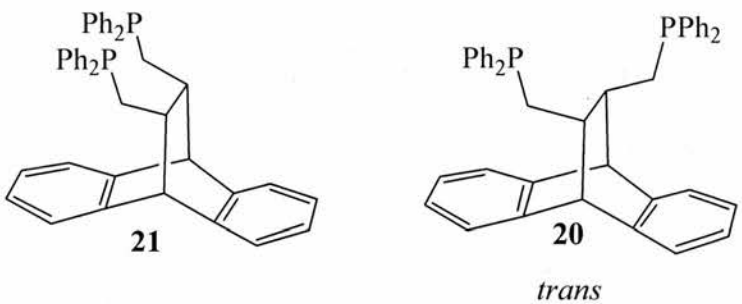
Table 1.6 - Summary of ethylene/CO. Reaction conditions: MeOH (50 cm^3) with 0.10 g of ligand precursor and MSA (1.0 mmol), CO pressure (5 bar), hydrogen pressure (5 bar), temperature = 90 °C, reaction time = 1 hour. *Rf* = Average no of ethene units in the chain

Ligand	Mass of Polymer (g)	Mass of MEP (g)	Productivity/g polyketone (mol cat)$^{-1}$ h^{-1}	*Rf*	Productivity/g MEP (mol cat)$^{-1}$ h^{-1}
16	7.3	0	33 000	16	0
17	2.7	0	7 260	20	0
18	1.5	0	6 060	13	0
19	1.1	13.7	5 000	14	62 270

It can be clearly seen that going from the *endo,endo* **(18)** to the *exo,endo* **(19)** there is a dramatic change in selectivity. On first inspection it seems that for the *exo,endo* the polymer chain growth is primarily only one repeating unit (MEP) with some polyketone

produced. This is because the termination step is viable after a single carbonylation step with ligand **19**.

This difference was demonstrated again using ligands with an anthracene backbone[17]. It was found that the selectivity to MEP when using the *trans* **(20)** isomer was greater than 70 %, with the remaining selectivity being to low weight polyketone. The *cis* **(21)** isomer exclusively produced the polyketone with a much higher molecular weight. The overall rate for carbonylation (MEP + polyketone formation) is much higher for the *cis* ligand than for the *trans*.



Scheme 1.10 - Anthracene backbone diphosphines

1.6 Methoxycarbonylation of linear alkenes (C>2)

Once the alkene has more that 2 carbon atoms there is a regioselectivity issue with the carbonylation of the unsaturated bond. With the simplest case of propene there are two possible isomers for the methoxycarbonylation. If the terminal carbon is carbonylated the linear product methyl butyrate is formed. If the internal carbon of a carbon-carbon double bond is carbonylated methyl 2-methylpropanoate is formed. Another issue for alkenes > C_3 is that there is a possibility for the carbon-carbon double bond to isomerise. It is then possible for the carbonylation of the double bond in any of these isomers to occur, leading to a number of possible isomeric esters.

DTBPMB/Pd has also been used for the methoxycarbonylation of higher alkenes.[18] A patent for the methoxycarbonylation of alkenes (C = 6) showing high rates and selectivities to the linear ester has been filed. It was found that the methoxycarbonylation of hexene could be performed at room temperature with a conversion after 3 hours of 100 % with a l:b ratio of 100:1.[19] It was subsequently shown that if the various isomers of octene were used the selectivity to linear ester was still extremely high (l:b >30:1). However, for internal alkenes the conversion was lower and to achieve high conversion the reaction had to be performed at 80 °C with a CO pressure of 30 bar. This shows that the rates of reaction are in the order: carbonylation of C_1 > isomerisation of carbon-carbon double bond >> carbonylation of internal carbon-carbon double bond. This was demonstrated in a kinetics study of the methoxycarbonylation of 1-octene at 40 °C and 10 bar of CO analysed by monitoring the CO uptake. It was found that there were two distinctly different first-order regimes in operation. The first ($k = 3.9 \times 10^{-4}\ s^{-1}$) is the direct methoxycarbonylation of l-octene and the second slower region ($k = 1.7 \times 10^{-4}\ s^{-1}$) corresponds to the tandem isomerisation-methoxycarbonylation of internal octenes.

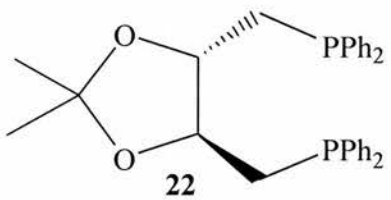
Using the *meso/rac* **(14-15)** ligands the methoxycarbonylation of longer chain alkenes was undertaken. As the size of the substrate alkene increased the rate of carbonylation decreased. In the case of propene a linear to branched (l:b) ratio of 4:1 was obtained. If α-tetradecene (C=14) was used the same regioselectivty was obtained but at a much slower rate. The l:b ratio observed when internal C_{14} alkenes were used was also 4:1. Again this shows that the carbonylation of internal carbon-carbon double bonds is much slower than for terminal carbon-carbon double bonds. The overall rate of ester

formation for the terminal alkene over the internal is faster by a factor of 2.5, which shows that isomerisation is the rate-limiting step.

1.7 Methoxycarbonylation of styrene and vinylnapthalene

Due to the interest in the synthesis of the anti-inflammatory drugs ibuprofen and naproxen, the branched alkoxycarbonylation of both styrene and vinyl naphthalene derivatives has been rigorously studied.

Early work was carried out on methylstyrene with reports in the literature stating varying degrees of success with simple chelating ligands such as DIOP **(22)**.

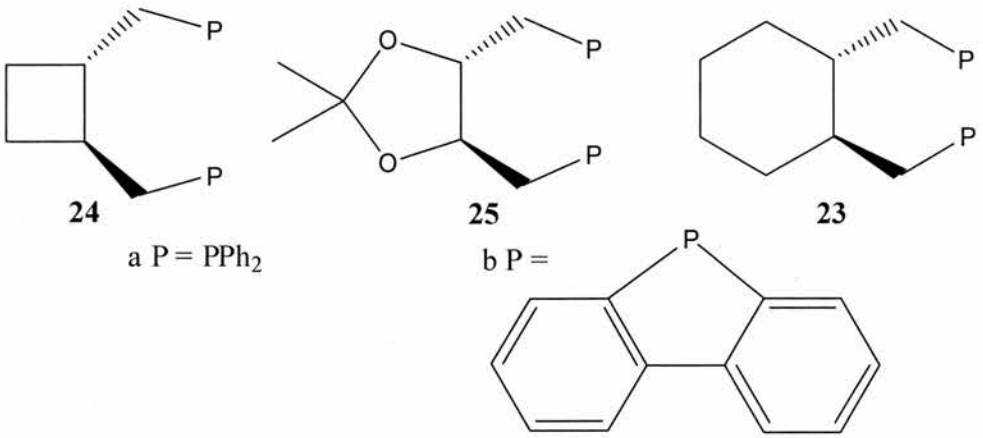


22

DIOP

When used with a Pd(0) source the enantiomeric excess (e.e.) was claimed to be poor.[20] Also Hayashi *et. al.*[21] claimed that after 19 hours $[PdCl_2(PhCN)_2]$ and DIOP had converted methylstyrene and *iso*-propyl alcohol with a conversion of 83% and an e.e. of 8.9%. However Consiglio[22] reported that with $PdCl_2$, DIOP can give a product with a maximum optical purity of 50% when the DIOP/Pd ratio is 0.5 suggesting that the ligand is only coordinated through one phosphorus atom.

Dibenzophospholes **(24-23)** can achieve a maximum e.e. of 93 % when used with a Pd(II) precursor.[21] The systems tested are detailed in Table 1.7.



24 **25** **23**

a P = PPh_2

b P =

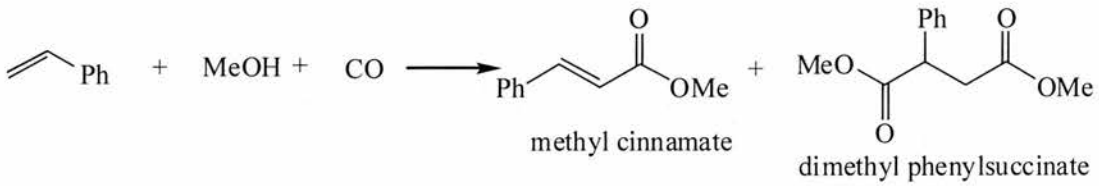
Table 1.7 - Palladium catalysed asymmetric hydroesterification of methylstyrene.[21] Reaction conditions [$PdCl_2(PhCN)_2$] (0.115 mmol), ligand (0.230 mmol), methylstyrene (23 mmol), *i*-PrOH (11.5 cm^3), CO pressure = 220 atm, temperature = 100 °C.

Phosphine	Reaction time (hour)	Conversion (%)	Selectivity to ester (%)	enantiomer	e.e.%
24a	45	68	98	S	40
24b	85	66	97	S	40
25a	21	33	91	S	44
25b	19	83	99	S	8.9
23a	162	53	94	S	7.3
23b	42	23	81	R	22

A palladium/copper chloride mixed system was used with other chiral phosphine ligands. Using (R)- or (S)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (BNNPA) the alkoxycarbonylation of either isobutylstyrene or 2-vinyl-6-methoxynapthalene was carried out with a maximum yield of branched ester of 89% and 71% respectively. The enantiomeric excess was in the region of 70-80% depending on the reaction conditions. Interestingly, if the reaction was carried out at room temperature with a CO pressure of 1 bar there was no formation of linear acids.

A recent article by Bianchini *et. al.*[23] reported the carbonylation of styrene to various carbonylation products (Scheme 1.11). The main targets were the selective conversion

to either the unsaturated ester methyl cinnamate or the double carbonylation product dimethyl phenylsuccinate.



Scheme 1.11 - Methoxycarbonylation of styrene producing methyl cinnamate and dimethyl phenylsuccinate

However, the by-products from these reactions were the linear and branched saturated esters, methyl 3-phenylpropanoate and methyl 2-phenylpropanoate respectively. Using various bidentate phosphine ligands on Pd they envisaged the methoxycarbonylation of styrene. A CO pressure of 70 bar and a reaction temperature of 80 °C was used with the addition of 1,4-benzoquinone (BQ). The authors claim that the addition of BQ is required as the final step in the formation of methyl cinnamate is the β–H elimination from the palladium-alkyl producing a palladium-hydride and the mono-carbonylated product. The palladium(II)-hydride is then reduced to Pd(0) by the action of the BQ on the hydride. The partially reduced BQ then reacts with MeOH thus allowing the oxidation of the palladium and the formation of a palladium(II)-methoxide species, which the authors believe to be the active catalyst. The effect of the phosphine ligand on the selectivity is shown in Table 1.8.

Table 1.8 - Effect of phosphine ligand on carbonylation of styrene catalysed by $[Pd(P\text{-}P)(NCMe)_2]$ complexes. Reaction conditions : Catalyst (0.01 mmol), styrene (2 mmol), BQ (2 mmol), MeOH (20 ml), temperature = 80 °C, CO pressure = 70 bar, reaction time = 3 hours.

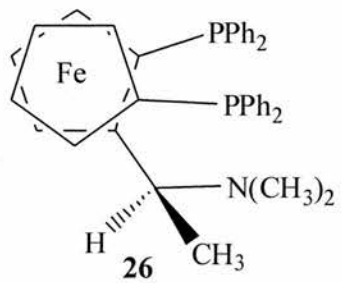
Ligand	Conversion (%)	Selectivity to methyl 2-phenylpropanoate (%)	Selectivity to methyl 3-phenylpropanoate (%)	Selectivity to methyl cinnamate (%)	Selectivity to dimethyl phenylsuccinate (%)
dppe	28.0	0.0	0.3	68.1	1.1
meso-dppb	33.4	0.0	0.5	63.0	1.9
rac-dppb	33.8	0.3	1.2	55.5	0.9
Cyclo-tetraphos	64.3	0.0	0.0	29.2	6.5

The other products are not detailed and in the case of *cyclo*-tetraphos this is ~65 % of the products. The remaining products are likely to be oligomers formed from styrene-CO copolymerisation. Moving down the entries in the table it can be seen that there is an increase in conversion along with a decrease in rigidity of the backbone of the diphosphine. It was also found that as the binding affinity of the co-ligand decreased ($MeCN<bipy<OAc^-$) the selectivity to the cinnamate increased. This behaviour can be rationalised as the proposed mechanism for this chemistry involves a β-H elimination in a Pd(II) square planar intermediate. For this both the facile creation of a free coordination site and a flexible P-P backbone to lower the energy of the interaction within the metal-β-H intermediate are required.

Bianchini also added TsOH to the system and as a result they found that the overall yield of carbonylated products increased along with the selectivity towards the unsaturated ester (but not at the expense of saturated esters).

The authors propose that the catalytic intermediate for the production of the saturated esters is the Pd-hydride species rather than Pd-CO_2Me, as an increase in selectivity to these compounds is accompanied by an increase in the production of ketones which can only be formed from a hydride species.

The work reported by Oi[24] involved an attempt at asymmetric alkoxycarbonylation using a cationic Pd(II) system. Firstly a chiral sulphonic acid was used but this led to no stereochemical selectivity. Using the ferrocene containing aminophosphine ligand, ((S)-1-[(R)-1',2-bis(diphenylphosphino)-ferrocenyl]ethyldiamine) ((S)-(R)-BPPFA) **(26)** the alkoxycarbonylation of styrene gave a yield of 17% with a selectivity of branched to linear of only 1:1. However an enantiomeric excess of 86% to the S form of the branched isomer was obtained.



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By using cationic catalyst precursors the required ionic hydride palladium species are smoothly generated in situ and Oi *et. al.*[24] found that it was possible to carry out the alkoxycarbonylation of styrene under mild conditions. Using $Pd(OAc)_2/PPh_3$/*p*-toluene sulphonic acid as a catalyst, a yield of 95% with selectivity to the branched ester of 93% was obtained when the system was left under a CO pressure of 20 atm at room temperature for 20 hours. Upon replacement of styrene with 4-isobutylstyrene, from

which the branched ester related to ibuprofen, a yield of 76% with 95% selectivity was achieved.

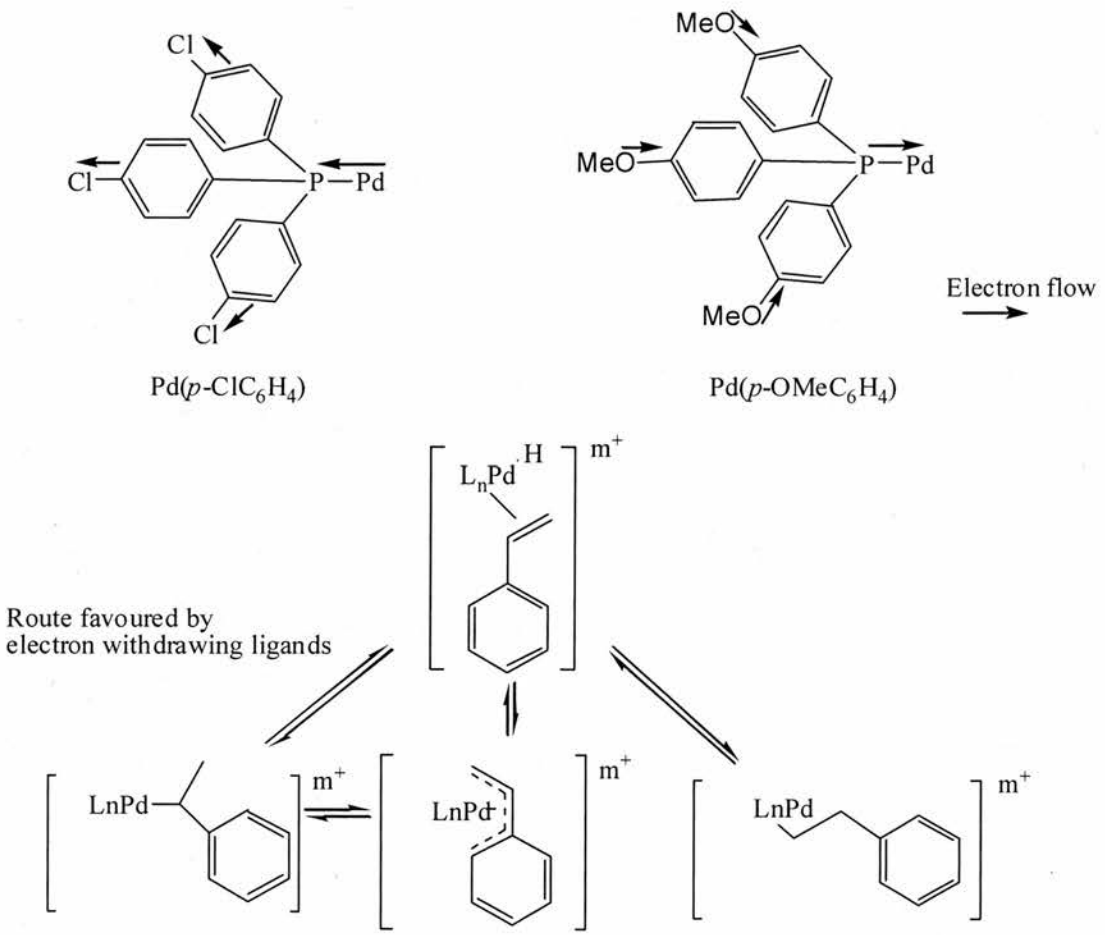
To promote the coordination of reactants to the metal centre an *in situ* formed $[Pd(OTs)_2(PPh_3)_2]$ catalyst has been used for the methoxycarbonylation of styrene.[25] The catalyst precursors $Pd(OAc)_2$, PPh_3 and *p*-toulenesulphonic acid (*p*-TSA) were mixed in the ratio of 1/4/10. $[Pd(OAc)_2(PPh_3)_2]$ is formed which converts to the active catalyst on reaction with the *p*-TSA. The reactivity of this catalyst is greater than that of $[PdCl_2(PPh_3)_2]$ due to the weakly coordinating tosylate ligands, which effectively leave free coordination sites on the metal. The phosphine ligand was changed and it was found that PPh_3 gave the best conversion (84.2%) as shown in Table 1.9. Also no reaction was observed for PCy_3, PBu_3, and $P(OPh)_3$.

Table 1.9 - Effects of ligands in the methoxycarbonylation of styrene.[25] Reaction conditions : $Pd(OAc)_2$ (0.06 mmol), ligand (0.24 mmol), styrene (14.5 mmol), *p*-TSA (0.6 mmol), MeOH (23 ml), water (2000 ppm), CO pressure = 34 bar, temperature = 55 °C, reaction time = 1 hour.

Ligand	Conversion (%)	b:l ratio
PPh_3	84.2	0.66
$P(p\text{-tol})_3$	39.8	0.34
$P(m\text{-tol})_3$	39.0	0.41
$P(p\text{-MeOC}_6H_4)_3$	10.6	0.26
$P(p\text{-ClC}_6H_4)_3$	20.5	2.27

The trend in conversion can be rationalised; if the ligands are not basic the styrene bonds too strongly to the palladium and if the ligand is too basic then the styrene coordination to the palladium is disfavoured. As the ligand type effects the branch:linear ratio, this suggests that the ligand plays an important role in the

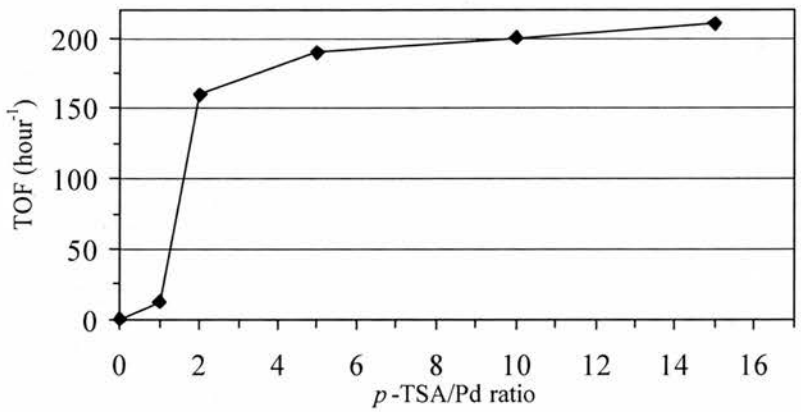
regioselective step. As the steric hindrance of the ligands varies little, the effects must be electronic in origin. Electron withdrawing groups on the phenyl group of the ligand makes the phosphorus atom a poor σ-donor and a good π-acceptor. This decreases the electron density on the Pd metal centre and the formation of the branched isomer is favoured (Scheme 1.12)



L= Phosphorus ligand, TsO-, CO or solvent; n = 2, 3 or 4; m = 0 or 1.

Scheme 1.12 - Stabilisation of catalytic intermediates in the alkoxycarbonylation of styrene using different substituents on the phosphine ligands.

The concentration of the *p*-TSA affects the catalytic activity as shown in Scheme 1.13. Not only does the *p*-TSA form the catalytic species but it also helps reactivate any Pd(0) that is formed during the reaction.



Scheme 1.13 - Effect of concentration of *p*-TSA on the rate of methoxycarbonylation of styrene.[25] Reaction conditions: $Pd(OAc)_2$ (0.06 mmol), PPh_3 (0.24 mmol), styrene (14.5 mmol), MeOH (solvent), water (2000 ppm), CO pressure = 34 bar, temperature = 55 °C, reaction time = 1 hour,

Many other chiral ligands have been studied such as neomenthyldiphenylphosphine (NMDPP)[20] with Pd(0) and trifluoroacetic acid for the methoxycarbonylation of methylstyrene. Using CO at 1 bar the e.e. obtained was 52 %. As the CO pressure was increased above 2 bar the asymmetric induction was lost which may be due to preferential coordination of CO at higher pressures over the coordination of the diphosphine. The enantioselectivity is believed to be due to a faster rate of carbonylation of one of the two diastereoisomers and the difference in the two rates lessens as the pressure increases.

The supporting of Pd based catalysts on the clay montmorillonite has been investigated by Alper giving a heterogeneous type catalyst but with the selectivity of homogeneous chemistry.[26, 27] Firstly $Pd(OAc)_2$ was immobilized on montmorillonite[26] and was tested as a catalyst for the methoxycarbonylation of styrene. The best conditions were found and are detailed in Scheme 1.14. This gave a conversion of 100% and a yield of the branched ester of 94 %.

$$PhCH{=}CH_2 + MeOH + CO \xrightarrow[C_6H_6,\,24\ hour]{Pd\text{-}clay,\ PPh_3\ HCl} PhCH(CH_3)COOMe$$

125 °C 40 atm CO

$Pd/PPh_3/PhCH{=}CH_2$ - 1/5/500

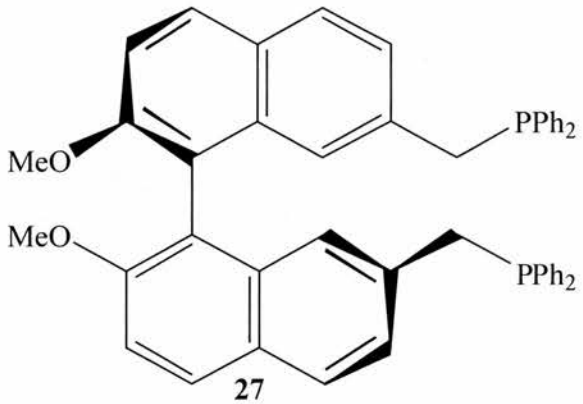
Scheme 1.14 - Methoxycarbonylation of styrene using $Pd(OAc)_2$ supported on montmorillonite clay

The use of $[PdCl_2(PPh_3)_2]$ on montmorillonite in the presence of chiral phosphines was reported by Nozaki *et. al.*.[27] The results are summarised in Table 1.10.

Table 1.10 - Methoxycarbonylation of styrene catalysed by montmorillonite-diphenylphosphinepalladium(II) chloride with different chiral ligands.[27] Reaction conditions – Pd (0.002 mmol), ligand (0.01 mmol), HCl (0.1 cm^3), styrene (0.1 mmol), MeOH (6 mmol) benzene 10 cm^3), temperature = 125 °C, CO pressure = 45 bar, reaction time = 25 hours

Ligand	Conversion (%)	b/l	% e.e.
None	0	-	-
PPh_3	100	100/0	-
NMDPP	77	100/0	1.8(S)
(R)-MeO-MOP	78	100/0	5.0(R)
(S,S)-Phosphalone	49	98/2	2.4(R)
(S)-BNPPA	0	-	-
(R)-BINAP	22	50/50	Not determined
(R,R)-DIOP	12	<10/> 90	Not reported
(R)-New ligand (27)	23	100/0	12.0(S)
(R,S)-BINAPHOS	52	86/14	6.0(S)

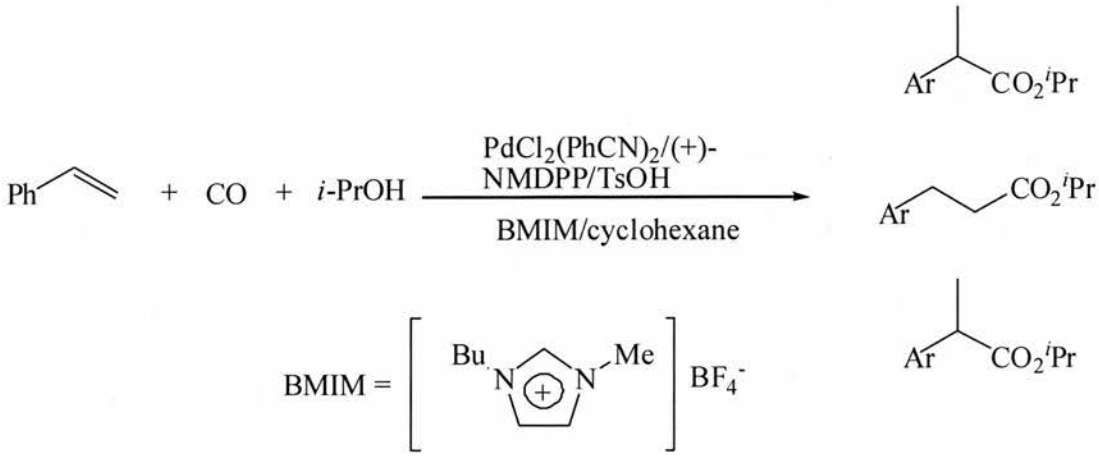
The successful 'new ligand' above is (R)-7,7'-bis(diphenylphosphinomethyl)-2,2'-dimethoxy-1,1'-binaphthyl **(27)** which has a large bite angle an important feature for good enantiomeric selectivity.[27]



27

This work apparently contradicted that carried out by Alper,[26] as Alper was unable to achieve any catalytic activity with the bulkier ligands as they were too large to enter the pores (8Å) of the clay. However, the clay used by Nozaki had a slightly larger spacing of 15Å and presumably allows the larger ligands to intercalate.

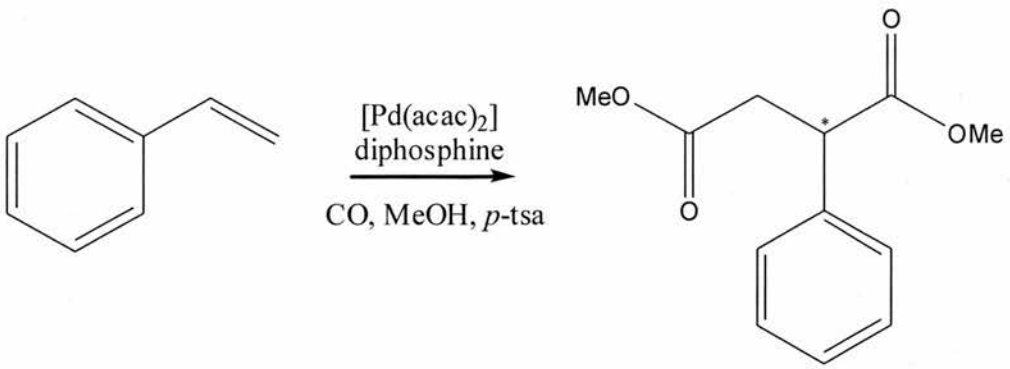
To ease the separation of the product from the catalytic system, it is possible to immobilize the catalysis in an ionic liquid. If an ionic liquid is used so that the organic product is immiscible, the product can be simply decanted after the reaction has finished. Alper *et. al.*[28] carried out the alkoxycarbonylation in the ionic liquid 1-*n*-butyl-3-methylimadazoliumtetrafluroborate salt (BMIM) with *iso*-propanol and cyclohexane as the organic solvent (Scheme 1.15).



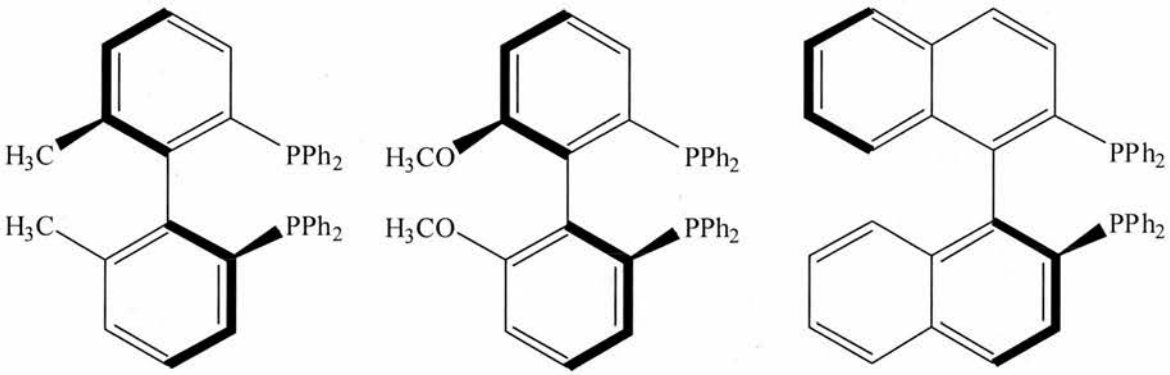
Scheme 1.15 - Alkoxycarbonylation of styrene in ionic liquids.

Using $[PdCl_2(PhCN)_2]$/(+)-NMDPP as the catalyst, the alkoxycarbonylation of styrene and its derivatives was investigated. The selectivity to the branched ester was nearly 100 % when the reaction was carried out under a CO pressure of 10 bar at 70 °C. Even though a chiral phosphine ligand was used, the asymmetric induction was <5 %, which was disappointing. The purely organic solvent system produced similar results. Unfortunately under the optimal reaction conditions the catalyst species decomposed and the ionic liquid system was not able to be used at maximum recycle efficiency.

The bis-alkoxycarbonylation of styrene was first reported in 1993 by Consiglio *et. al.*[29] (Scheme 1.16). Using the ligands **(28-30)** with $[Pd(acac)_2]$ and *p*-TSA it was found that it was possible to achieve an enantioselectivity of up to 93 % (S). However the maximum yield of the dimethyl phenylsuccinate (DMPS) obtained was only 58 %. The other products obtained were small amounts of the mono-carbonylation products and the majority was oligomeric products.

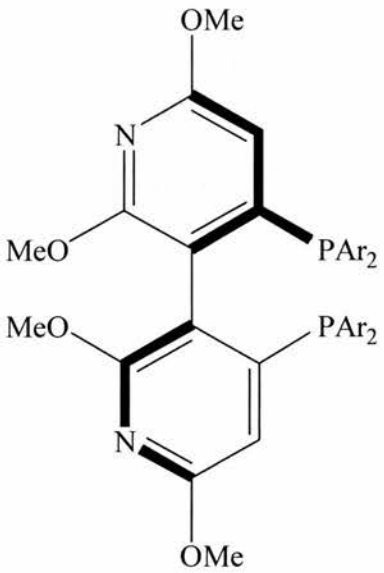


Scheme 1.16 - Bis-methoxycarbonylation of styrene



28 **29** **30**

This was followed in 2003 by a paper by Chan *et. al.*[30] who reported an improved chemoselectivity for the bis-methoxycarbonylation of styrene using the ligand **31** and the results are shown in Table 1.11.



31

a Ar = Ph

b Ar = 4-MePh

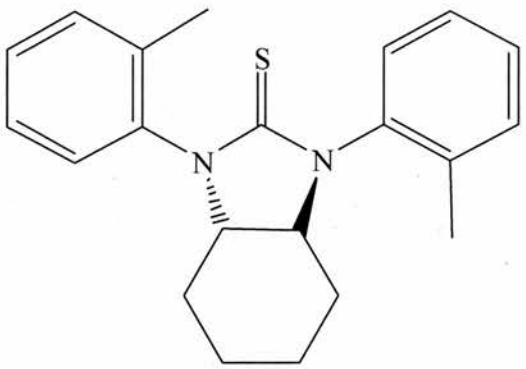
c Ar = 3,5-Me_2P

Table 1.11 – Bis-methoxycarbonylation of styrene. Catalyst (7 μmol), styrene (0.9 mmol), MeOH (1 cm^3), BQ (1.8 mmol), CO pressure = 152 bar at RT, temperature = 50 °C, reaction time = 20 hours. MPP = methyl 2-phenylpropionate, MC = methyl cinnamate. a = yields based on converted styrene. Rest of material is unidentified oligomeric by-products.

Catalyst Precursor	Conversion (%)	MPP[a] (%)	MC[a] (%)	DMPS[a] (%)	e.e. DMPS (%)
31a	67	2.7	20	71	83 *(R)*
31b	58	4.4	24	52	82 (*R*)
31c	56	1.7	28	42	82 (*R*)

Using P-Phos ligands it was found that the chemoselectivity to the desired product DMPS is as high as 71 % for (R)-P-Phos with a enantioselectivity of 83 % (R).

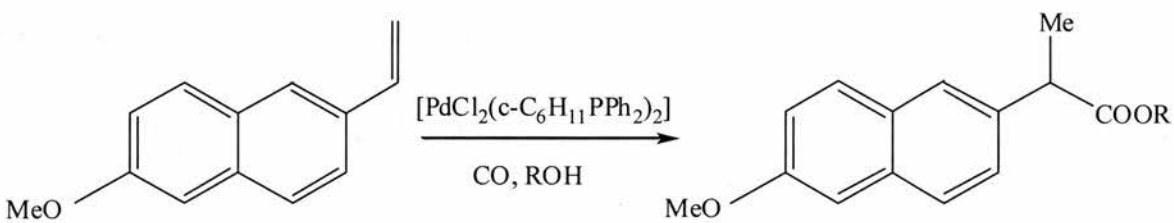
Yang *et. al.*[31] have shown that ligands based upon thiourea are suitable ligands for the bis-methoxycarbonylation of styrene. They tried various thiourea ligands and found that ligands with large steric bulk around the nitrogen atoms give high selectivity to the desired product, DMPS. The best ligand **(32)** gave a styrene conversion of 90 % using the following conditions, [$PdCl_2$] (2.5 mol%), (2.5 mol%), CuCl (20 mol%), CO:O_2 4:1 (balloon pressure), MeOH, temperature = 50 °C and reaction time = 20 hours.



32

It is believed that the sterically hindered ligands give higher activity because of the formation of low-coordinate complexes.

The alkoxycarbonylation of 6-methoxy-2-vinylnapthalene,[32] the naproxen precursor, has been reported using the catalyst $[PdCl_2(c\text{-}C_6H_{11}PPh_2)_2]$. When the reaction was carried out in EtOH/THF for 72 hours at 100 °C with a CO pressure of 40 bar, the conversion was 100 % with a selectivity to the branched product of 95 % (Scheme 1.17)

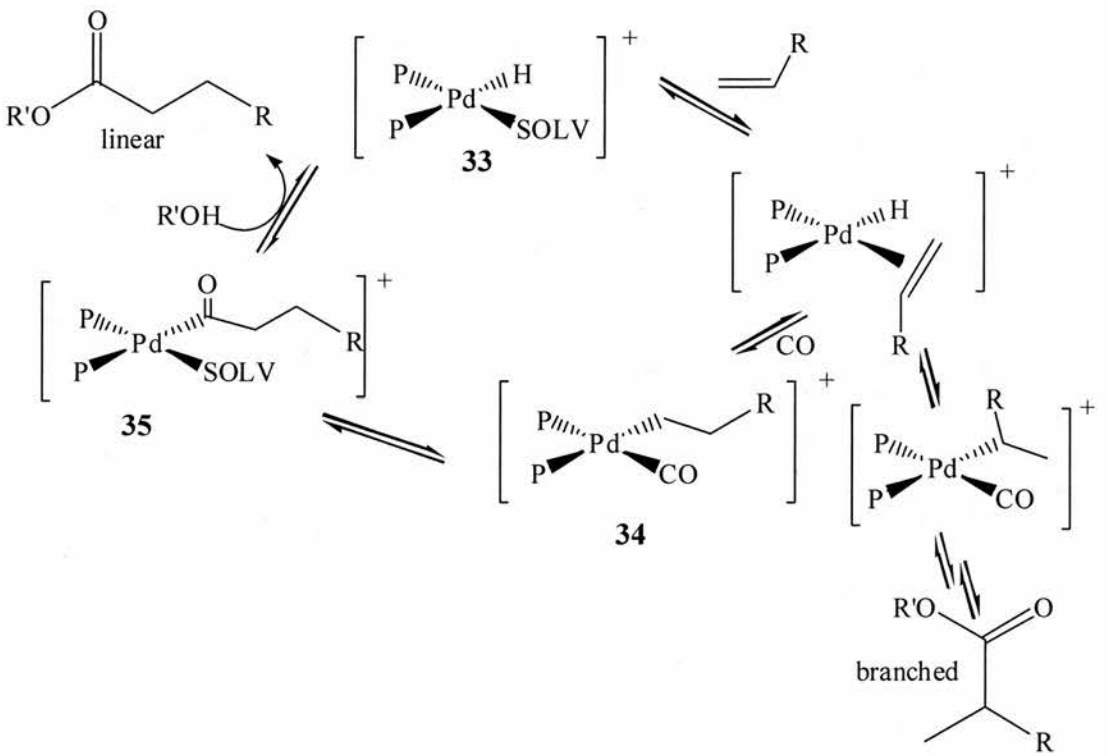


Scheme 1.17 - Alkoxycarbonylation of 6-methoxy-2-vinylnapthalene

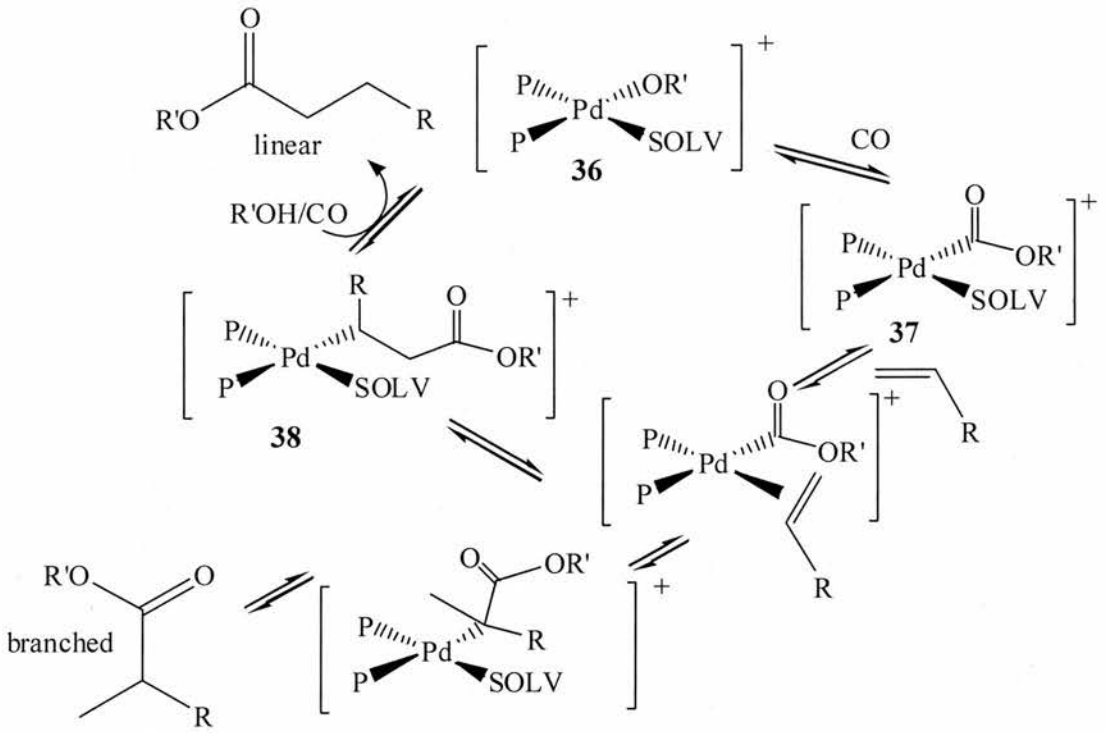
1.8 Mechanism

1.8.1 Hydride vs carbomethoxy cycle

There are two possible mechanisms for the alkoxycarbonylation of alkenes, the hydride (Scheme 1.18) and the carbomethoxy mechanism (Scheme 1.19).



Scheme 1.18 - Hydride mechanism for the palladium-catalysed alkoxycarbonylation of alkenes



Scheme 1.19 – Carbomethoxy mechanism for the palladium-catalysed alkoxycarbonylation of alkenes

The hydride mechanism starts with a 16e⁻ palladium (II) hydride cation **(33)** that coordinates the alkene, and the hydride migrates onto the carbon-carbon double bond to form a 16e⁻ palladium-alkyl cation **(34)**. It is at this point that the regiochemistry of the ester product is determined. This is due to the ability of the hydride to migrate onto the a or ß carbon of the double bond. The coordination of CO leads to alkyl migration onto the CO forming a palladium-acyl **(35)**, which, upon reaction with an alcohol, liberates the desired ester and reforms the initial palladium-hydride.

The carbomethoxy mechanism starts with a 16e⁻ palladium-alkoxide species **(36)**, which in the presence of carbon monoxide forms a palladium-carboalkoxy species **(37)**. Once alkene is coordinated carbomethoxy migration to the carbon-carbon double bond forms

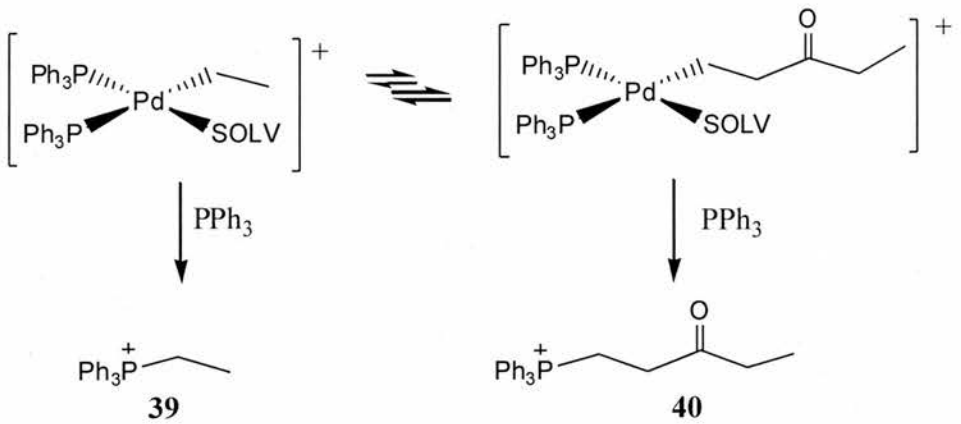
the palladium alkyl species **(38)**. It is at this point that the regiochemistry is determined giving either a linear or branched ester product. Reaction with an alcohol gives the ester and regenerates the palladium-alkoxide species.

In both cases the final step of the catalytic cycle is the reaction of an alcohol with the organo-palladium complex. The nature of this reaction is unclear and will be discussed in detail later.

Clearly the two proposed mechanisms are different but evidence for both has been published. Both sides of the argument will be presented and conclusions will be drawn.

1.8.1.1 Evidence for hydride mechanism

Due to the commercialisation of the production of methyl propanoate from ethene, carbon monoxide and methanol by Lucite International there have been a number of papers in the last 5 years investigating the mechanistic aspects of the reaction. The first evidence reported for the hydride mechanism was the formation of alkyl phosphonium salts in the catalysis solution.[33] Palladium acetate, triphenylphosphine and *p*-toulene sulphonic acid (1:20:20) were dissolved in methanol and heated at 100 °C in an ethene-carbon monoxide atmosphere. Samples where removed from the reactor and analysed by GC-MS. It was found that there was the formation of 3 phosphonium salts with, methyl-, ethyl **(39)**, and 3-oxypentyl-**(40)** triphenylphosphonium cations. The methyl salt is derived from the reaction of triphenylphosphine with methyl *p*-toluene sulphonate and is a non-metal catalysed reaction. However the remaining two salts are only formed in the presence of the palladium and can be attributed to the interruption of the palladium-acyl species present in the system (Scheme 1.20)

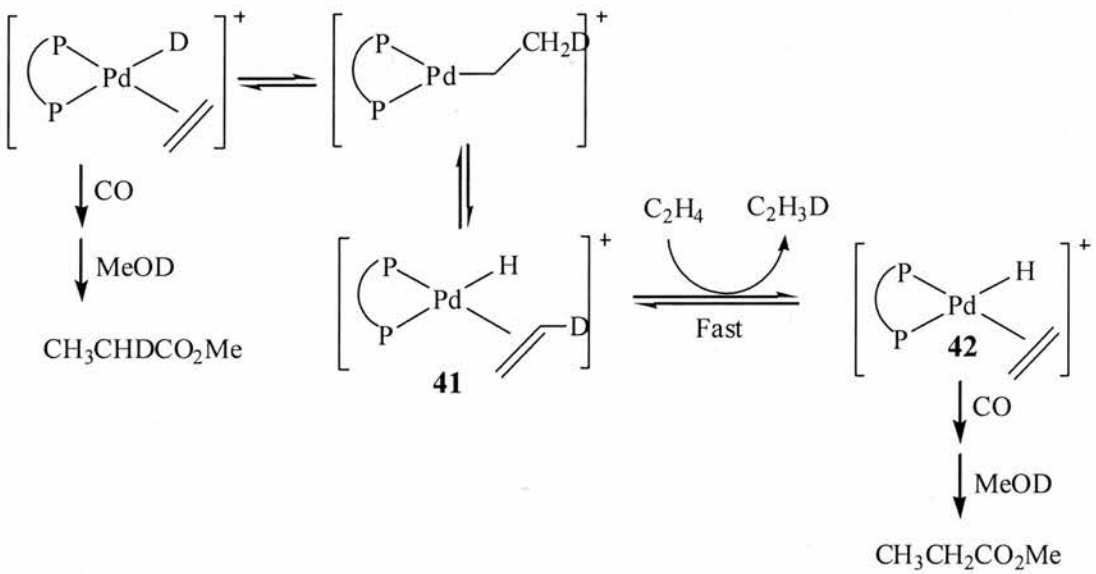


Scheme 1.20 - Formation of alkyl phosphonium salts

The non-observation of phosphonium salts derived from the intermediates in the carbomethoxy cycle does not rule out the possibility of the carbomethoxy cycle as the rate of reaction between the alkyl-palladium formed prior to the liberation of the product **(38)** and the triphenylphosphine may not be fast enough to compete with the next step in the catalytic cycle.

Further evidence from catalytic systems has been sought using deuterium labelling. When Eastham *et. al.*[34] carried out the methoxycarbonylation of ethene using d_1-methanol as the solvent, they observed the formation of both $CH_2DCH_2CO_2Me$ and CH_3CHDCO_2Me in equal amounts. Also the non-deuteriated ester (< 10 %) was observed along with $CH_2DCHDCO_2Me$ (< 4 %). These four products can be explained by both the hydride and carbomethoxy mechanisms. However when the same reaction was carried out in two different reactors with differing gas volumes under slow stirring conditions ensuring that the mass transport was poor, two very different results are obtained. In the case where there was a small headspace of gas the produced methyl propanoate formed had a mix of 1-5 deuterium atoms with the proportion of deuteriated isotopomers remaining constant throughout the reaction. In the large reactor a high

proportion of d^0 and d^1 with small amounts of d^2 in the early stages is observed. As the reaction proceeds a greater amount of deuteriation is seen. Both catalytic cycles can explain all the results except the carbomethoxy mechanism cannot explain the d^0 ester at the beginning of the reaction in the large headspace reactor. This is because in the carbomethoxy cycle the termination step must involve protonation of the C atom bound to the Pd in the Pd-$CH_2CH_2CO_2Me$ intermediate and this must lead to a product that contains at least one deuterium. However, the hydride mechanism can explain this as the exchange between complexes with coordinated deuteriated ethene **(41)** and non-deuteriated ethene **(42)** is faster than CO coordination to the palladium-alkyl intermediate when there is low CO availability.

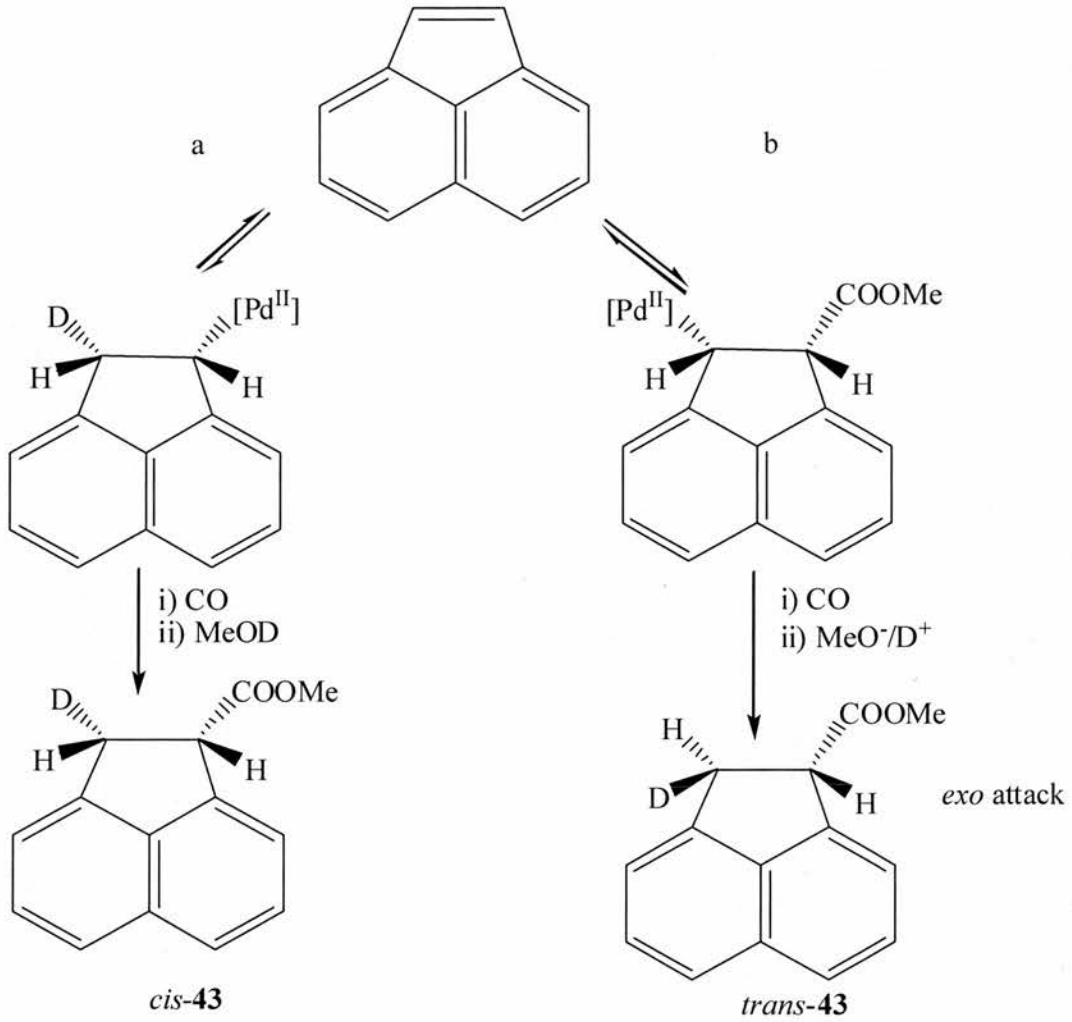


Scheme 1.21 - Explanation of d^0 methyl propanoate production with low CO availability *via* the hydride mechanism

This result has also been observed by Jimenez-Rodriguez *et. al.*[19] in the methoxycarbonylation of 1-octene. With MeOD as the solvent there was a considerable

amount of d^0-methyl nonanoate in the early stages of the reaction. This can only be explained by the hydride mechanism.

Girones *et. al.*[35] have shown that the methoxycarbonylation of acenapthylene proceeds *via* a hydride mechanism (Scheme 1.22a). The solvent for the catalysis was MeOH-d_1 and the majority of the product was the mono-deuteriated *cis* isomer of acenapthene-1-carboxcylic acid methyl ester **(43)**. If the carbomethoxy route were present the *trans* isomer of **43** should dominate as the selectivity occurs at the protonolysis elimination step (Scheme 1.22b). The *trans* isomer would be favoured as this occurs by the less hindered *exo* protonolysis. Also no other by products of the carbomethoxy cycle are detected.



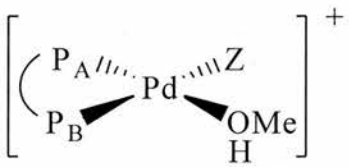
Scheme 1.22 - Methoxycarbonylation of acenaphthylene a) Production of *cis*-**43** *via* hydride mechanism b) Production of *trans*-**43** *via* carbomethoxy mechanism

The intermediates of the hydride mechanism for the methoxycarbonylation of ethene have been synthesised and spectroscopically characterised by Eastham *et. al.*.[36] The reaction of [Pd(L-L)(dba)] (L-L = DTBPMB, dba = *trans,trans*-(PhCH=CH$_2$)CO) with either HBF_4 or CF_3SO_3H in MeOH in the presence of either oxygen or benzoquinone (BQ) gives a palladium-hydride complex [Pd(L-L)H(MeOH)]X (X = BF_4^-, or $CF_3SO_3^-$) **(44)**. The coordination of the solvent is confirmed as the $^{31}P\{^1H\}$ NMR of the phosphorus atom *trans* to the alcohol varies with different alcohols, i.e. MeOH - δ =

77.5 ppm, *n*-PrOH - δ = 68.5 ppm. Upon reaction of **44** with one equivalent of ethene at room temperature the $^{31}P\{H\}$ NMR changes to give two new signals, and upon addition of more ethene there is no further reaction. This new complex is assigned as [Pd(L-L)Et(MeOH)]X (X = BF_4^-, or $CF_3SO_3^-$) **(45)**. It dissolves in THF at –78 °C with displacement of the MeOH by THF. The addition of CO to a THF solution of complex **45** immediately yields the acyl complex $[Pd(L\text{-}L)COEt(THF)]^+$ **(46)**, whilst the addition of MeOH to a solution of **46** immediately leads to the regeneration of the palladium-hydride **(44)** and the production of methyl propanoate. It was believed that palladium-hydrides are oxidised to palladium-methoxy species in MeOH in the presence of an oxidant thus the dominant catalysis should be the carbomethoxy cycle. However it was found that bubbling oxygen through a MeOH solution of **44** at 80 °C produced no change in the $^{31}P\{^1H\}$ NMR spectrum thus proving that palladium-hydrides do not necessarily convert to the palladium-alkoxides when dissolved in an alcohol in the presence of an oxidant.

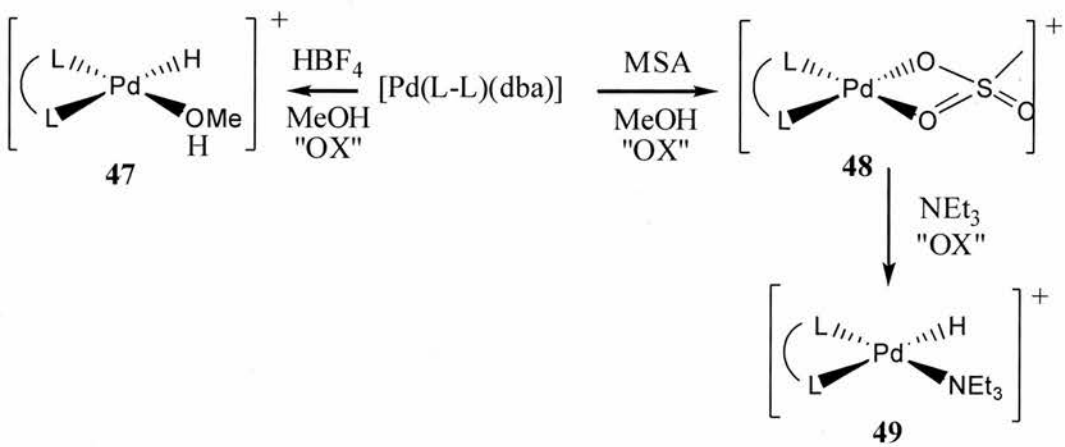
Table 1.12 - $^{31}P\{^1H\}$ NMR of intermediates in the alkoxycarbonylation of ethene. P-P = DTBPMB

Z	δP_A	δP_B	^2J(P-H) (Hz)
H **(44)**	25.8	77.5	17
Et **(45)**	36.1	68.0	31
COEt **(46)**	32.5	79.9	40



It has been reported by Clegg *et. al.*[37] that the ease of formation of the palladium-hydride in MeOH depends upon the nature of the acid used. If an acid with a strongly coordinating anion is used i.e. HCl, the complex [Pd(L-L)Cl$_2$] is formed from [Pd(L-L)(dba)]. If HBF_4 is used the hydride forms instantly as the BF_4^- does not coordinate

allowing coordination of the MeOH which then forms the palladium-hydride (**47,** Scheme 1.23). However, if $MeSO_3H$ – the acid in the commercial process – is used there is not immediate formation of the palladium-hydride at room temperature. The anion coordinates as a bidentate ligand giving the complex $[Pd(L\text{-}L)(\eta^2\text{-}MeSO_3)]^+$ **(48)** which is highly stable in coordinating solvents such as THF and MeOH. This bidentate coordination mode of the sulphonate ion is rare and monodentate coordination is usually observed. As the dissociation of the $MeSO_3^-$ is slow, forcing conditions are required to upset the coordination allowing a MeOH molecule to coordinate, that in turn will form the hydride. The addition of pyridine forces the $MeSO_3^-$ to pass from η^2 to η^1, which with MeOH as the solvent leads to coordination of MeOH and formation of the palladium-hydride-pyridine complex **(49)**. It is also possible to form the palladium-hydride with MSA through thermal activation as after refluxing $[Pd(L\text{-}L)(\eta^2\text{-}MeSO_3)]^+$ in MeOH for 1 hour the hydride is formed. This shows the validity of the method of catalyst preparation used in the industrial process operated by Lucite International.



Scheme 1.23 - Formation of palladium-hydrides using different acids

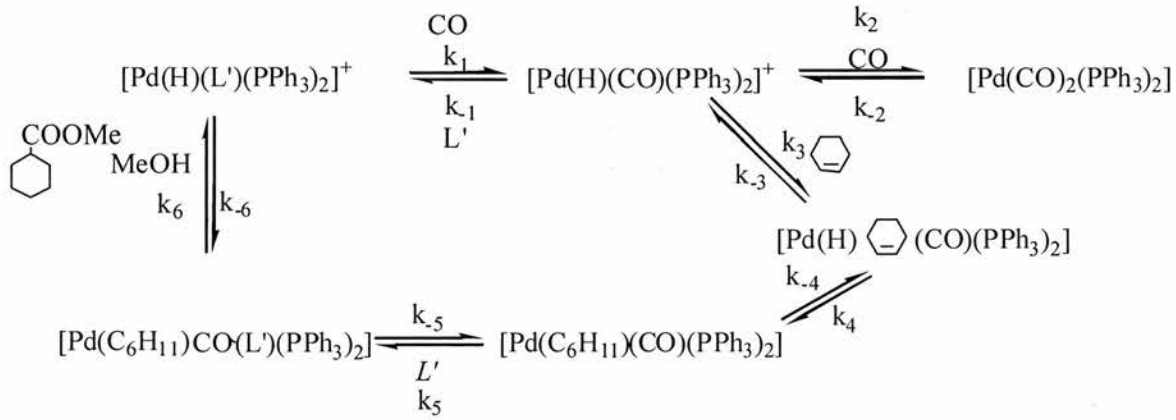
It would be expected that the substitution of platinum for palladium (3rd row transition metal for a 2nd row in the same group) would lead to a similar performance in the catalysis. However it has been demonstrated that for methoxycarbonylation poor rates up to 4 orders of magnitude lower are achieved.[38] Wolowska *et. al.* carried out an NMR study on the Pt system to determine why the rates are considerably worse. The formation of the metal-hydride and metal-alkyl species proceeds in the same manner as for palladium. On addition of carbon monoxide to the system at 193 K the acyl species does not form rapidly as is seen for palladium. CO insertion does not occur until the solution is warmed to 293 K. Upon cooling the solution back to 193 K the acyl reverts to the alkyl complex. It was noted that the resting states of all the intermediates was the carbonyl adduct rather than the solvento adduct as seen in the palladium case due to the greater affinity of platinum for CO. This means that in the presence of CO the thermodynamic sink of the catalysis is the $[Pt(L\text{-}L)H(CO)]^+$ complex which is unreactive towards ethene coordination, so the platinum-ethyl species is slow to form.

Toniolo[39] has carried out a study on the kinetics of the alkoxycarbonylation of cyclohexene using $[Pd(PPh_3)_2(TsO)_2]$ as a catalyst. To ensure that the reaction was under chemical control and not in a mass transport limited regime the catalytic reaction was carried out at various temperatures (80 °C – 100 °C) with a range of stirrer speeds (5 Hz – 24 Hz (300 rpm – 1440 rpm)). It was found that at all temperatures the TOF was independent of the stirrer speed indicating that gas-liquid mass transfer is not rate determining. (Reaction conditions were - $Pd(PPh_3)_2(TsO)_2$ (0.1 mmol), PPh_3 (0.6 mmol), TsOH (0.8 mmol), MeOH (40 cm^3), cyclohexene (10 cm^3), H_2O (800 ppm), CO pressure (20 bar), in a 250 cm^3 autoclave).

By varying the concentration of catalyst and carrying out the reaction at different temperatures it can be seen from the plot of initial reaction rate against catalyst concentration that the reaction is first order in catalyst concentration, with an activation energy of 19.5 kcal mol^{-1}. The dependence on the concentration of cyclohexene is also first order but the dependence on CO pressure is non-linear. The following rate equation fits the experimental data for the effect of CO pressure on the initial rate (error between proposed and actual rate is less than 4 %).

$$r_o = k_1 p_{CO}(1 + k_2 p_{CO} + k_3 p^2 CO)^{-1}$$

The proposed mechanism for the alkoxycarbonylation of cyclohexene is shown below.



Scheme 1.24 - Mechanism for the methoxycarbonylation of cyclohexene

The authors believe that the rate-determining step in the cycle is the attack of MeOH on the Pd-acyl species as the intermediate $[Pd(PPh_3)_2(COR)Cl]$ **(50)** has been isolated from the hydroesterification of propene and 1-hexene with $[Pd(PPh_3)_2Cl_2]$ as the precursor.[12,13] This may not be the case as the following equilibrium may be present with the fast coordination of the chloride ion keeping the palladium out of the catalytic cycle.

$$[Pd(PPh_3)_2(COR)(SOLV)]^+ \rightleftharpoons [Pd(PPh_3)_2(COR)Cl]$$

However the authors believe that the isolation of this species type suggests that all steps prior to the methanolysis are fast. Considering this, the rate equation for the formation of the ester is

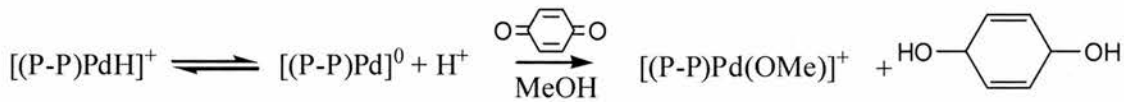
$$r = k_6[Pd((CO)C_6H_{11})(L')(PPh_3)_2][CH_3OH] - k_{-6}[Pd(H)(L')(PPh_3)_2][C_6H_{11}CO_2Me]$$

The three activation energies for three of the processes have been calculated as:

$$E_1 = 19.0 \text{ kcal mol}^{-1}$$
$$E_2 = 23.6 \text{ kcal mol}^{-1}$$
$$E_3 = 5.5 \text{ kcal mol}^{-1}$$

1.8.1.2 Evidence for the carbomethoxy cycle

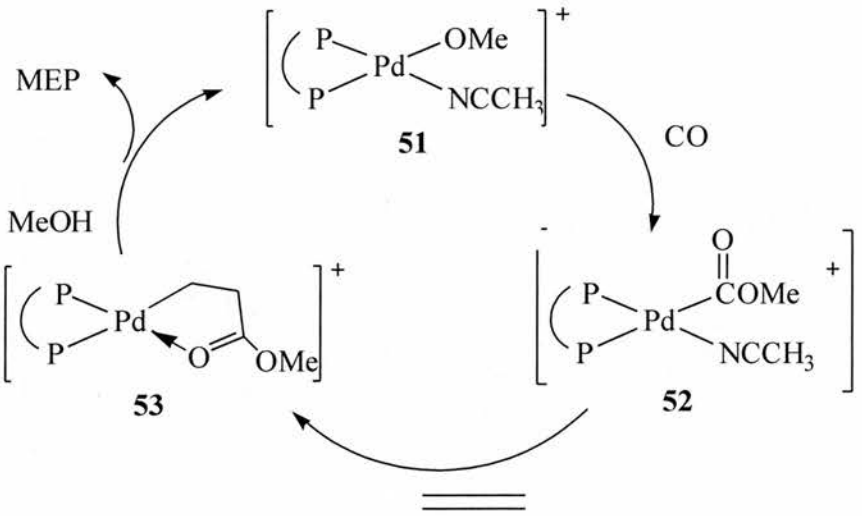
The best evidence for the carbomethoxy cycle has been in the instability of the Pd-hydride complexes in alcohols in the presence of an oxidant. Benzoquinone (BQ) is commonly added to catalytic systems where the solvent is MeOH and as palladium-hydride species are unstable this results in the belief that the catalysis occurs *via* a carbomethoxy mechanism (Scheme 1.25)



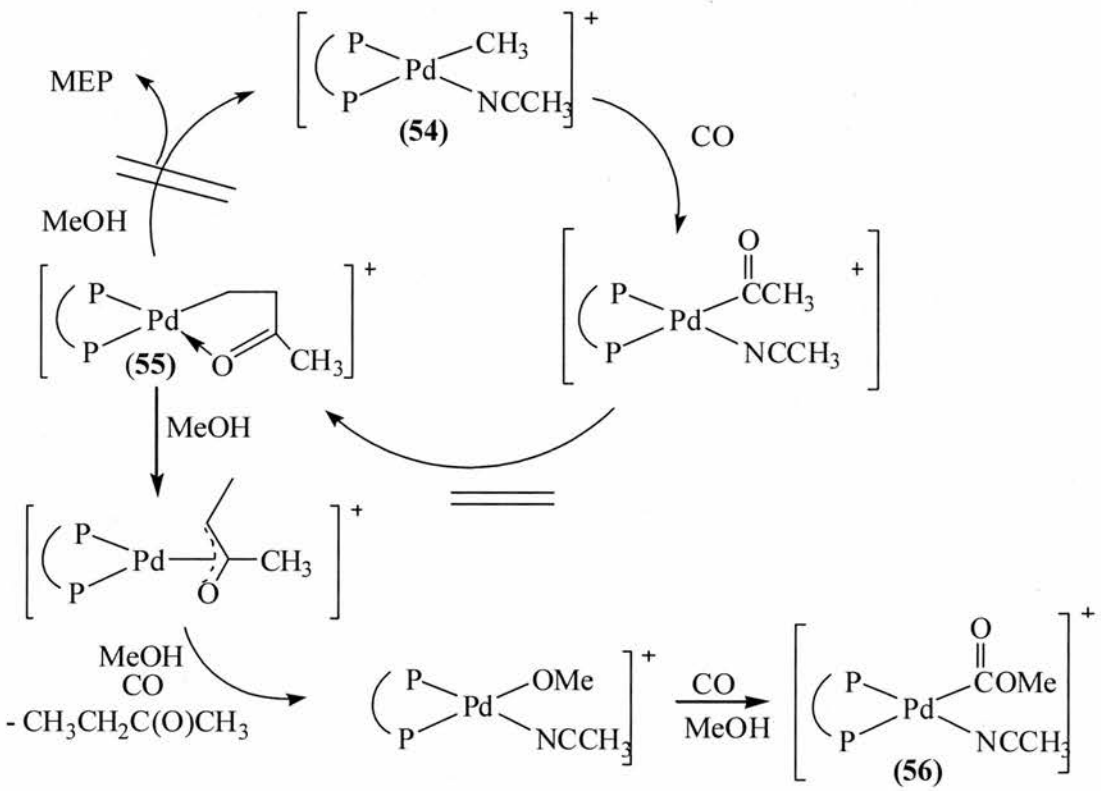
Scheme 1.25 - Conversion of palladium-hydrides to palladium-methoxides through the action of benzoquinone

Iggo and co-workers[40] have recently synthesised and characterised the intermediates for the carbomethoxy cycle. $[Pd(DIBPP)(OMe)(CH_3CN)]^+$ (DIBPP = 1,3-bis(*iso*-butylphosphino)propane) **(51)** is formed by the reaction of

$[Pd(DIBPP)(CH_3CN)_2][CF_3SO_3]_2$ with triethylamine. This readily reacts with CO to form the stable palladium-ester species **(52)** (Scheme 1.26). CO insertion into the Pd-methoxide bond is irreversible as the complex can be taken to dryness *in vacuo* and when redissolved there is no evidence by $^{31}P\{^1H\}$ NMR of decarbonylation. Upon reaction with ethene at room temperature the ester converts to a palladium-alkyl **(53)**. When ^{13}CO was used the $^{13}C\{^1H\}$ NMR spectrum shows a doublet ($^2J_{PC}$ = 10 Hz) for the ester carbonyl, indicating the formation of a 5-membered chelate in complex **53**. Addition of MeOH immediately releases methyl propanoate from the catalytic cycle and in the presence of CO the palladium-ester is reformed. The discrepancy between this study and the catalytic systems that give high rates for either alkoxycarbonylation or co-polymerisation is that the palladium-methoxide **(51)** was synthesised using a base where an acid is added to the catalysis solution. However, the ability to access the methoxide cycle is possible from the palladium-hydride cycle. The palladium-methyl complex, $[Pd(DIBPP)(CH_3)(CH_3CN)]^+$ **(54)** was synthesised – and was used as the starting point of the study (Scheme 1.27). This corresponds to the palladium-ethyl complex formed after insertion of the ethene into the palladium-hydride bond. This palladium-methyl complex reacts readily with CO and then ethene to form a ß-keto chelate complex **(55)**. It was found that this complex isomerises in the presence of MeOH to form an enolate which then reacts with MeOH and CO to form the palladium ester complex **(56)** – presumably *via* the palladium-methoxide. The authors believe that this proves that the mechanism must be carbomethoxy as this cycle is entered – and locked into – regardless of the starting complex.



Scheme 1.26 - Isolated intermediates in the carbomethoxy cycle for ethene alkoxycarbonylation



Scheme 1.27 - Model studies showing the hydride mechanism crossing to the carbomethoxy cycle in the absence of oxidant.

It previously had been reported that the rate of ethene insertion into a palladium-carbomethoxy bond was much slower than into a palladium-hydride bond. However in this study it was shown that the rates of the two processes were comparable and gave complete conversion after tens of minutes at low temperature.

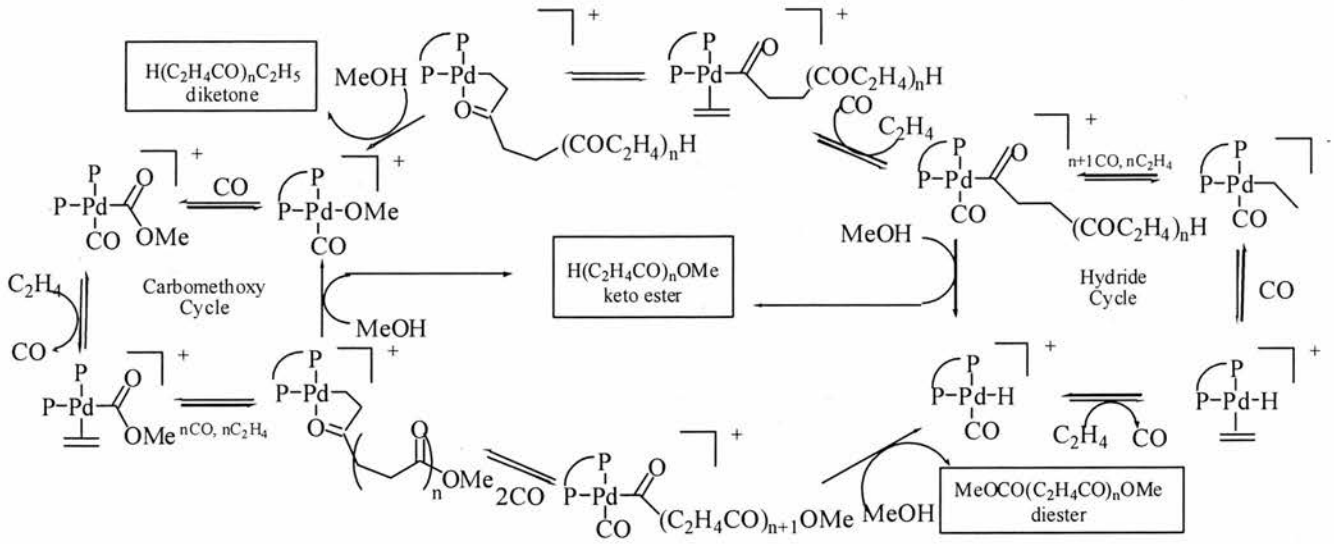
1.8.1.3 Evidence for hydride and carbomethoxy mechanisms working in tandem

It is possible to determine if both the carbomethoxy and hydride cycles are operating in tandem in these alkene-CO coupling reactions by analysing the end groups of the products (Table 1.13).

Table 1.13 - End group analysis of alkene-CO coupling reactions elucidating which of either the hydride or the carbomethoxy cycle is in operation

End group 1	End group 2	Starting complex	Complex regenerated	Mechanism
Alkyl	Ester	Hydride	Hydride	Hydride
Ester	Alkyl	Methoxide	Methoxide	Carbomethoxy
Alkyl	Alkyl	Hydride	Methoxide	Hydride crossing over to carbomethoxy
Ester	Ester	Methoxide	Hydride	Carbomethoxy crossing over to hydride

If there is only one of the catalytic cycles in operation then all the products will have an alkyl and an ester end. As both of the mechanisms produce this product type it is not possible to determine which one is in action. However if there is either an alkyl-alkyl or an ester-ester product present then it can be concluded that the two cycles must be operating in tandem (Scheme 1.28).



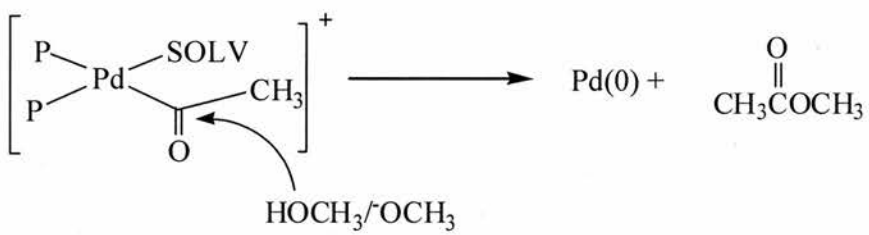
Scheme 1.28 - Mechanism for end group analysis

1.8.2 Mechanism of methanolysis of the acyl species

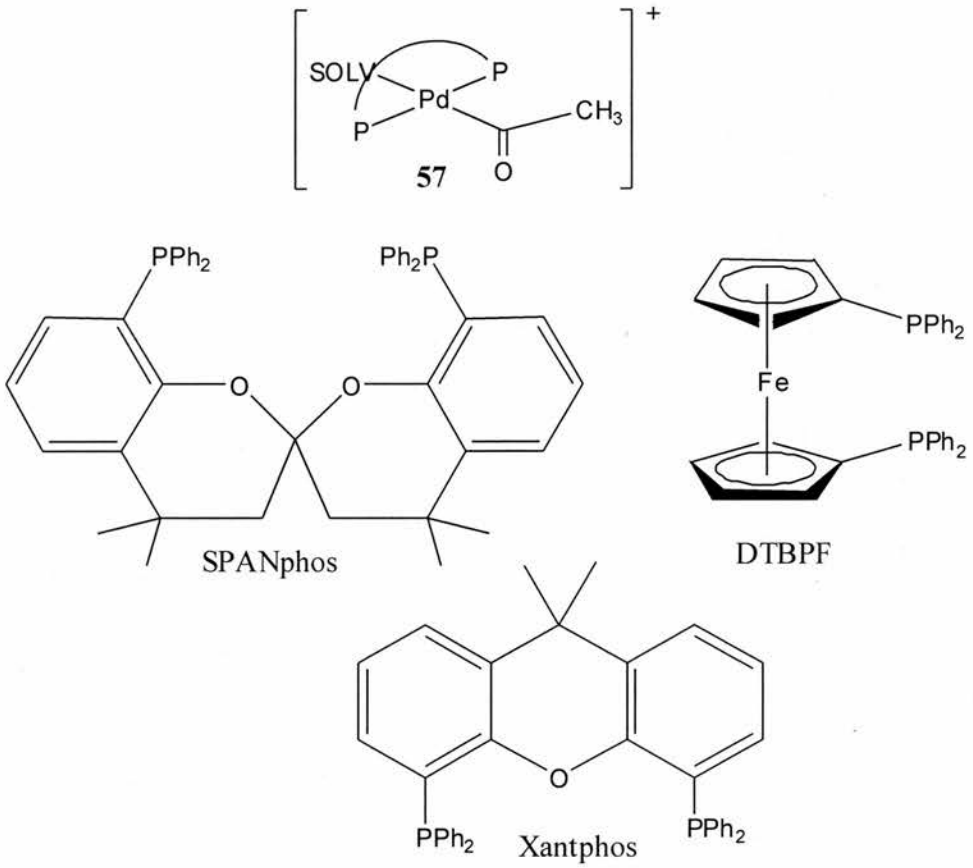
In the system used by Lucite International for the methoxycarbonylation of ethene,[7] high rates are achieved with the use of the diphosphine DTBPMB. This ligand is a very good s-donor, which results in all of the intermediates being very electron rich. In the proposed hydride cycle the final step is the methanolysis of the acyl species, which releases the methyl propanoate and regenerates the palladium-hydride. The methanolysis is equivalent to the nucleophilic attack of MeOH on the acyl species. As this acyl is electron rich it is surprising that this is a viable reaction. However there are various mechanisms in the literature, which attempt to explain this.

Van Leeuwen *et. al.*[41] have recently outlined 4 possible mechanisms for the methanolysis model of acetyl-palladium complexes. The first mechanism is the attack of MeOH from the outer sphere directly onto the acetyl-carbon (Scheme 1.29). The authors discounted this mechanism, as they were unable to react palladium-acyl

complexes coordinated with diphosphines in a *trans* configuration **(57)** with MeOH (Scheme 1.30). This suggests that the methanolysis of the acyl groups require *cis* complexes. Interestingly is that the palladium acetyl complexes are synthesised by the reaction of the palladium-methyl complex with CO. For this to happen the CO and the methyl groups must be coordinated in a *cis* fashion to allow the CO insertion. This could be accomplished by either the replacement of one of the phosphines by the stronger ligating power of CO or *via* a short lived 5-coordinate $18e^-$ intermediate.



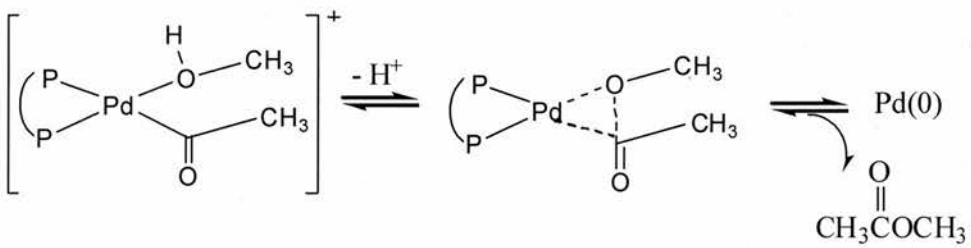
Scheme 1.29 - Attack of MeOH from the outer sphere on the acetyl carbon



Scheme 1.30 – Coordination of diphosphine in *trans* configuration

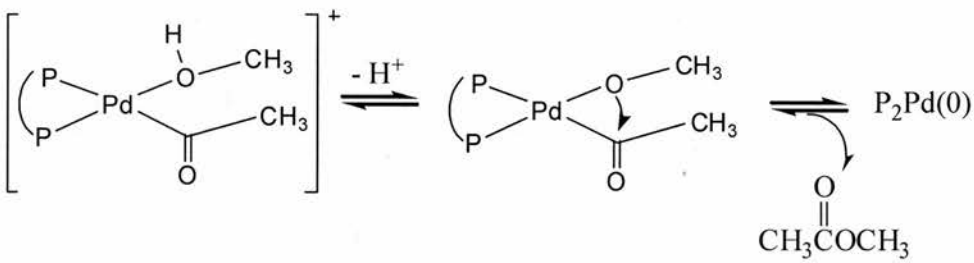
Another possible mechanism is the oxidative addition of MeOH to form a 6 coordinate Pd(IV) cationic species, which can then reductively eliminate the product to leave the palladium(II)-hydride. The authors discount this mechanism as oxidative addition of alcohols requires an acidic alcohol, such as phenol, reacting with a Pd(0) complex. However, if an electron rich diphosphine is coordinated the resultant electron rich palladium(II) may be easily oxidised to Pd(IV) to reduce some of the electron density on the metal centre. This may be the mechanism as fast methanolysis occurs when the electron rich DTBPMB is used in alkene alkoxycarbonylation.[7, 19]

As van Leeuwen *et. al.* claim that *cis* diphosphines are required and the reaction proceeds not *via* coordinated methoxide they propose two possible routes to accommodate this. The first of which is the concerted reductive elimination of the product where the carbon-oxygen bond is formed as the palladium-carbon and palladium-oxygen bond are broken.



Scheme 1.31 - Mechanism for the concerted reductive coupling of methanol and acyl groups

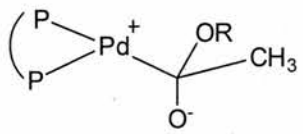
Another option is the reductive elimination that is nearer to a migratory insertion as the methoxide can nucleophilically attack the electrophilic carbonyl group (Scheme 1.32).



Scheme 1.32 - Mechanism for the reductive coupling of methanol and acyl groups *via* a neutral Pd(II) complex

The authors favour the mechanism in Scheme 1.32 as the acyl carbon is sp^2 hybridised which is stabilised as shown in Scheme 1.33 and can be protonated with loss of ester in the acidic medium. However, with an electron rich diphosphine bound to palladium the

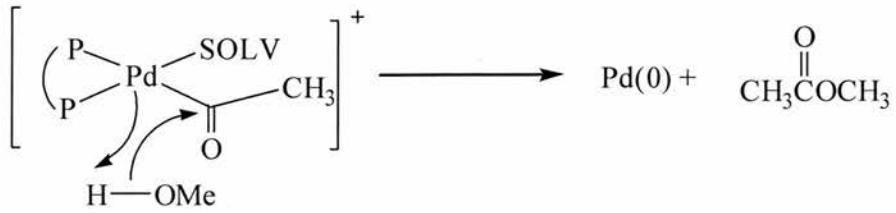
loss of the hydroxy proton would be unexpected due to the high electron density on the palladium.



Scheme 1.33 - Stabilisation of intermediate after migration of methoxide onto acyl, prior to the loss of ester

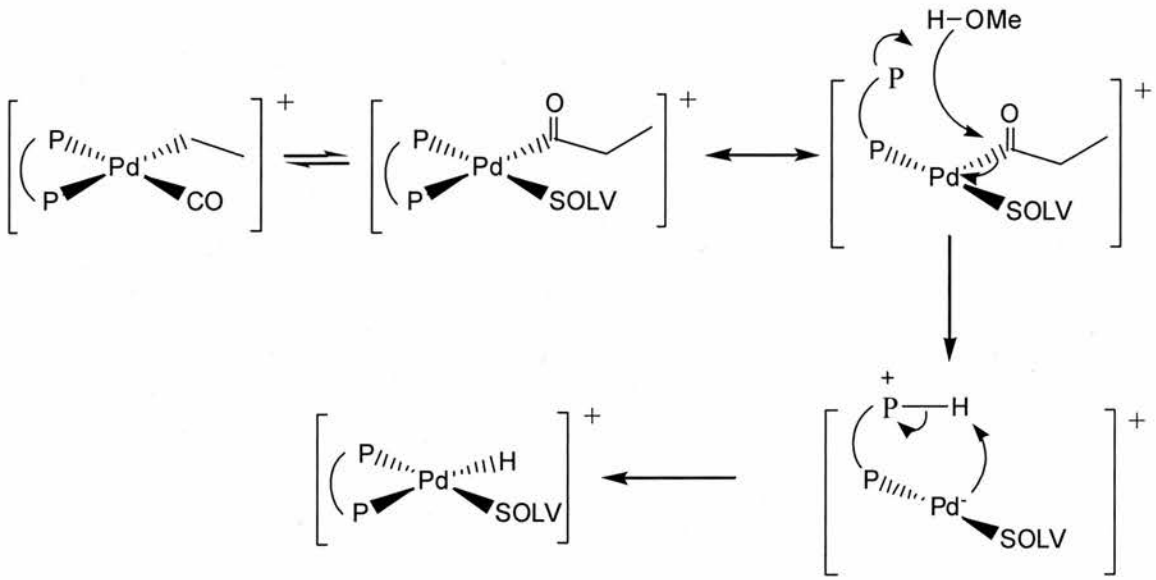
It was found that [(*cis*-L-L)Pd(C(O)CH_3)(CH_3OH)] reacts very quickly to form methyl acetate. However, in the absence of CO the palladium-acyl-methanol complex decarbonylated to form the palladium-methyl-methanol species. There is also competition between CO and methanol coordination and as a result methyl acetate formation is dependant upon the CO pressure. As shown in Scheme 1.32 the proton is removed from the methanol prior to the migratory reaction. This can be performed by either water, the alcohol, the anion or palladium(0) complexes.

Pugh and Drent[42] propose that the mechanism for the methanolysis of the palladium-acyl species is the polarization of the methanol O-H bond by the basic diphosphine-palladium species. This promotes attack of methoxide on the acyl and regeneration of the palladium-hydride species. This may all happen in a concerted fashion as shown in Scheme 1.34.



Scheme 1.34 - Methanolysis of palladium-acyl proposed by Pugh and Drent

A completely different mode of methanolysis has been proposed by Cole-Hamilton *et. al.*.[43] To overcome the problem of the nucleophilic attack of MeOH on the electron rich acyl carbon it is proposed that once the acyl is formed the diphosphine becomes unidentate. It is likely that the phosphorus atom *trans* to the acyl group would dissociate due to the high *trans* influence exerted by the acyl group. The elongation of this bond can be seen in the x-ray crystal structure of [Pd{C(O)Me}Cl(7)] reported by Clegg *et. al.*.[44] The Pd-P bond *trans* to the chloride which is 231.77(8) pm compared to the Pd-P bond *trans* to the acyl group is 248.12(9) pm and one of the longest palladium-phosphorus bonds known. This strong *trans* influence dramatically reduces the electron density on the acyl group and as a result the attack of methanol can easily occur. Once the methanolysis has occurred and the palladium-hydride is reformed the steric crowding is reduced which allows for the rechelating of the phosphine. A variation of this mechanism has been proposed by Eastham where the free phosphine is quaternised by MeOH – possible for basic phosphines in acidic media - which further reduces the electron density on the metal. As the phosphonium ion is close to the metal centre, the proton can be easily delivered back to the palladium thus reforming the active hydride species (Scheme 1.35).

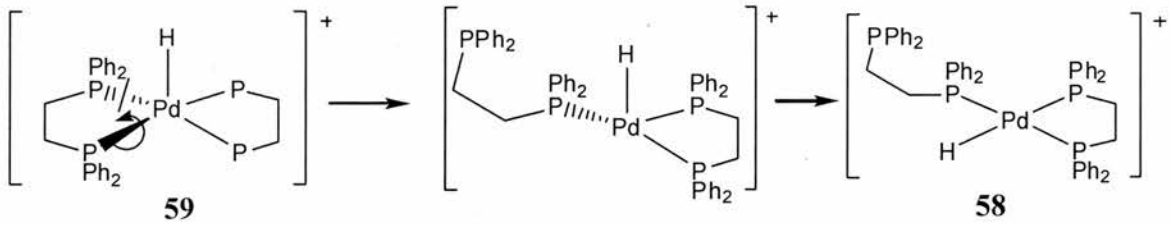


Scheme 1.35 - Methanolysis of the Pd-acyl *via* a phosphine loss mechanism

There has been a recent report of this type of mechanism for a palladium-diphosphine complex. Aresta *et. al.*[45] have reported that the following reaction occurs.

$$2\ [Pd(DPPE)_2H]CF_3SO_3 \longrightarrow [Pd(DPPE)_2] + [Pd(DPPE)_2][CF_3SO_3]_2 + H_2$$

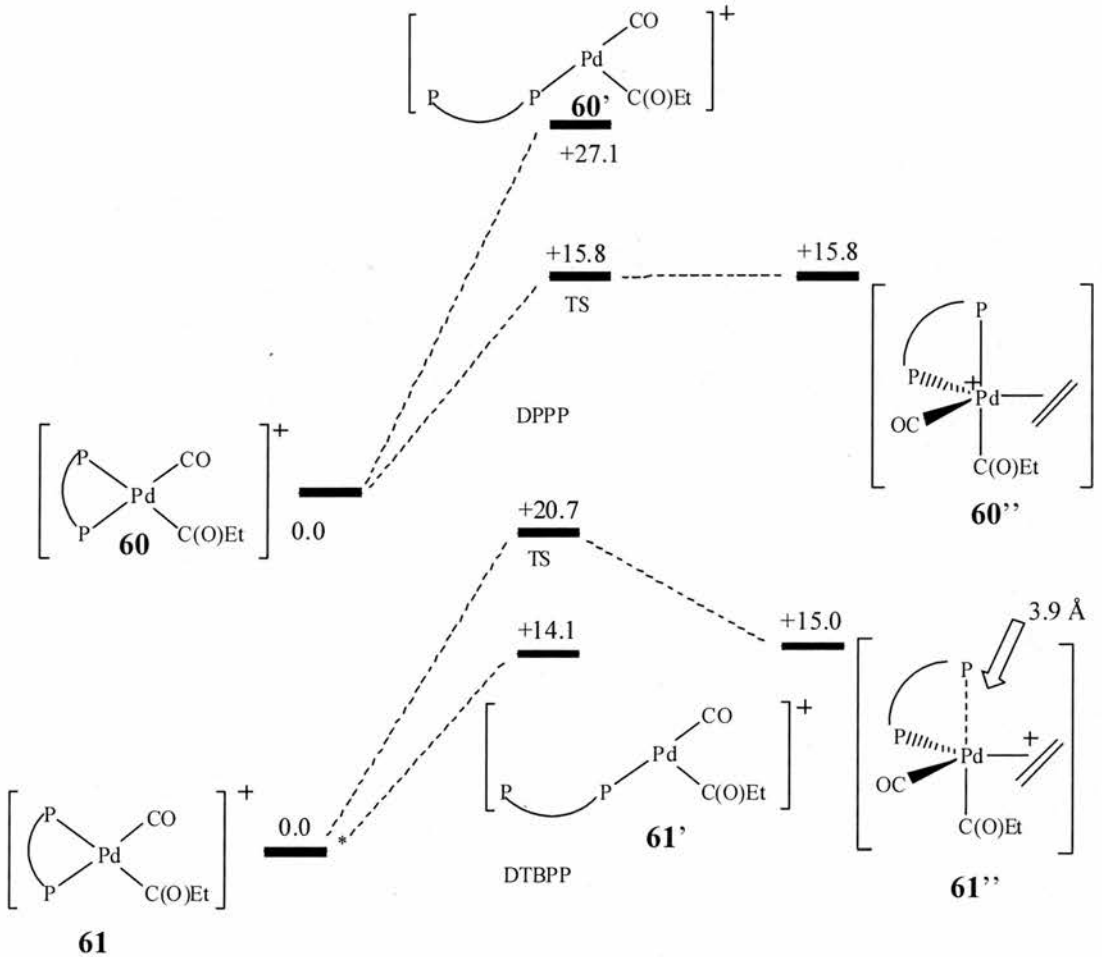
During the reaction a new hydride signal was observed in the ^1H NMR spectrum at - 4.70 ppm with a $^2J_{PH}$ coupling of 220 Hz which was assigned as arising from a hydride *trans* to a phosphorus atom in a square planar configuration **(58)**.



59 **58**

DFT/COSMO calculations were performed on the dpe (diphosphonylethane) analogue to determine the geometry of the proposed square planar complex. It was found that the new four coordinate system **58** was only 3.4 kcal mol^{-1} more unstable than complex **59** when solvent stabilisation was taken into consideration. Also the activation energy in the solvent was only 5.4 kcal mol^{-1} above complex **59** making this process thermodynamically and kinetically feasible.

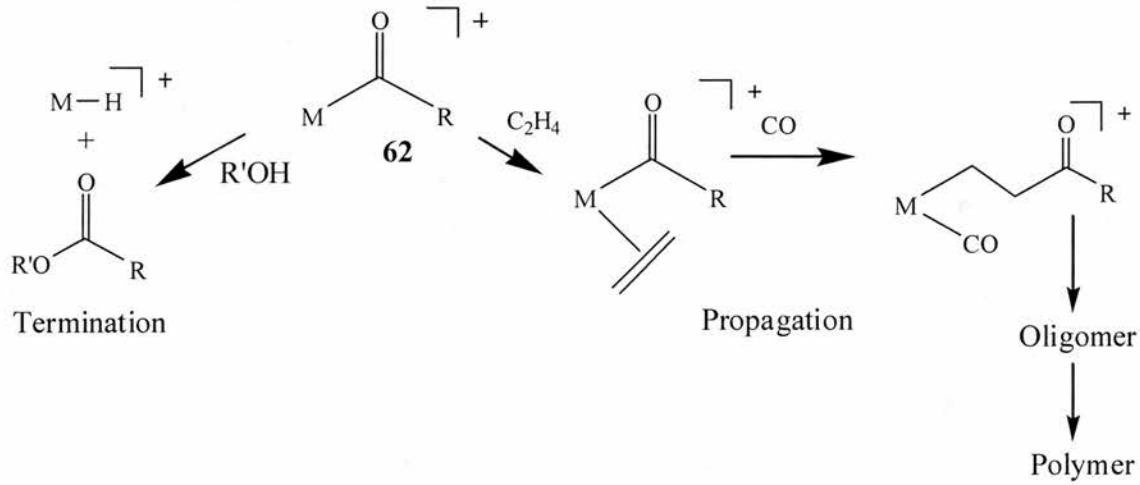
A molecular mechanics study has been carried out by Macgregor[46] on the outcome of the reaction of ethene with the palladium-acyl species. It is found that in the $[Pd(DPPP)\{C(O)Et\}(CO)]^+$ **(60)** complex the coordination of ethene is the favoured process with the formation of a 5-coordinate species with a ?G of 15.8 kcal mol^{-1} **(60'')**. This compares to a ?G value of 27.1 kcal mol^{-1} for the process of phosphine loss **(60')**. However if the ligand is changed from DPPP to the bulkier DTBPP ligand there is a distinct change in the relative energies. Now the phosphine loss is the favoured process with a ?G = 14.1 kcal mol^{-1} **(61')** compared to 15.0 kcal mol^{-1} *via* a transition state of +20.7 kcal mol^{-1} for the coordination of ethene **(61'')**. It is also of interest that in the DTBPP 5-coordinate intermediate the phosphorus arm *trans* to the acyl group is fully dissociated with a Pd-P distance of 3.9 Å.



Scheme 1.36 - MM calculations for the outcome of $[Pd(P\text{-}P)\{C(O)Et\}(CO)]^+$ where P-P = a) DPPP and b) DBPP

1.8.3 Termination vs. Propagation

The alkoxycarbonylation of an alkene and the copolymerisation of an alkene and carbon monoxide are two very closely related processes. If a hydride mechanism is considered it is the fate of the palladium-acyl **(62)** intermediate that determines the outcome of the reaction. For the alkoxycarbonylation of an alkene to occur there must be immediate termination of the first acyl group to form the ester. If propagation occurs through ethene coordination instead, then an oligomer or after many catalytic repeats, a copolymer is formed (Scheme 1.37).



Scheme 1.37 - Termination vs propagation

It can be seen from the examples published by Eastham *et. al.*[7] that the effect of the catalyst system is very subtle on the resulting reaction selectivity. They found that using the *ortho*-xylene backbone for their diphosphine ligand in the methoxycarbonylation of xylene gave dramatically different results depending upon the remaining two substituents on the phosphorus atoms. If only *tertiary*-butyl groups were used (7), the catalyst system gave high selectivity to methyl propanoate (99.9 %). However, if the alkyl groups are *iso*-propyl groups the selectivity to methyl propanoate reduces to 20 % with the remainder being oligomers and polyketones.

The rate of methanolysis of palladium-acetyl was shown by van Leeuwen[41] to be dependent upon the *cis* coordinating diphosphine used. As the steric bulk of the diphosphine increases a high rate of methanolysis occurs and if less bulky ligands i.e. dppp are used then further coordination and insertion of an alkene is preferred. Smaller ligands still reduce the overall rate of the entire process. For termination the critical bite angle is ~ 103° which is seen in the complex [(DTBPMB]Pd(CH_3)Cl], containing the highly active DTBPMB ligand for the production of methyl propanoate. If the *tert*-

butyl groups are replaced by the less bulky phenyl or phosphole groups then the selectivity moves towards polymerisation. This is rationalised due to the increase in overall steric bulk around the metal as the organic group increases in size. When the bulky ligands such as DTBPMB are used, the available coordination space remaining in the palladium-acyl complex is limited. This is only large enough for the coordination of either MeOH or CO. This is because the alkene binds through interaction of its π orbitals with the metal d-orbitals and as a result the alkene coordinates side onto the metal and requires a larger free volume for coordination. Insertion of CO into a palladium acyl bond is non-favoured, which only leaves termination by methanolysis possible.[41]

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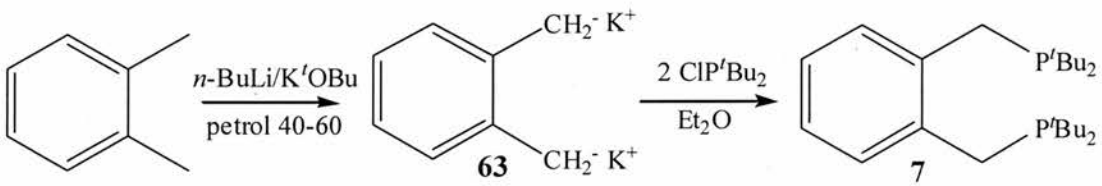
Chapter 2 - Synthesis of diphosphines

2.1 Synthesis of DTBPMB and symmetrical derivatives

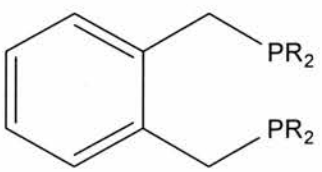
The preparation of DTBPMB is patented by Lucite International.[1] It is synthesised by the double deprotonation of *o*-xylene by a combination of *n*-butyl lithium and potassium *tert*-butoxide. This mixture of alkali metal reagents has a greater basicity than just *n*-butyl lithium and this so-called 'super base,' developed by Schlosser,[2] is required for the deprotonation of benzylic methyl groups. The dipotassium salt formed **(63)** is a brick red solid, which when reacted with two equivalents of di-*tert*-butylchlorophosphine forms the diphosphine.



Scheme 2.1 – Synthesis of DTBPMB

This strategy was used to synthesise various symmetrical derivatives that were required for the catalysis. They were all solids – except DIPPMB - that were recrystallised from MeOH and a summary of the $^{31}P\{^{1}H\}$ NMR spectra is shown in Table 2.1.

Table 2.1 – Chemical shifts in the $^{31}P\{^{1}H\}$ NMR spectrum of 1,2-bis(dialkylphosphinomethyl)benzene



R groups			δ_P (ppm)
R = ^{t}Bu	DTBPMB	**(7)**	28.7
R = ^{i}Pr	DIPPMB	**(64)**	5.2
R= Ph	DPPMB	**(65)**	- 12.3
R = Et	DEPMB	**(66)**	-18.1

As the reason for synthesising the various derivatives was to vary the electron donating power of the diphosphine it was decided to make 1,2-bis(*tert*-butyl-*iso*-

propylphosphinomethyl)benzene (TBIPPMB) which would lead to a level of electron donation between the di-*iso*-propyl **(64)** and di-*tert*-butyl derivatives **(7)**. The borane adduct - 1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene-borane **(67)** - was synthesised by the reaction of lithium *tert*-butyl-*iso*-propylphosphide-borane with α,α-*o*-dichloroxylene. The use of dialkylphosphino-borane adducts in synthesis will be discussed in detail in section 2.2.3.3. This yielded a white solid which had a broad peak in the $^{31}P\{^{1}H\}$ NMR spectrum at 40 ppm. As each of the two phosphorus atoms is chiral, the synthesised product has two diastereomers. This leads to two different sets of signals in the NMR spectrum. Each of the two diastereomers should give one signal in the $^{31}P\{^{1}H\}$ NMR spectrum. In an attempt to resolve the two signals, the spectrum was recorded on a 500 MHz instrument and the partial spectrum is shown in Figure 2.1. The methylene region of the ^{1}H NMR spectrum recorded on a 500 MHz spectrometer is shown in Figure 2.2. There are 4 signals for the peaks of the methylene protons as each of the two diastereomers has two chemically inequivalent diastereotopic protons. Each of the protons couple to the phosphorus atom ($^{2}J_{PH}$) and the other proton on the same carbon ($^{2}J_{HH}$) and as a result each signal is a doublet of doublets. However, as can be seen in Figure 2.2, two of the signals look like a triplet which is due to the frequency of the two coupling constants being so similar that the spectrometer is unable to separate both sets of doublets. The characterisation of the methylene region is shown in Figure 2.3. For the *meso* compound, the chemical shifts of the two hydrogen atoms are similar so that an ABX an pattern is observed. This manifests itself by increased relative intensity of the doublets closer to the other resonances (at $\delta = 3.29$ and $\delta = 3.38$).

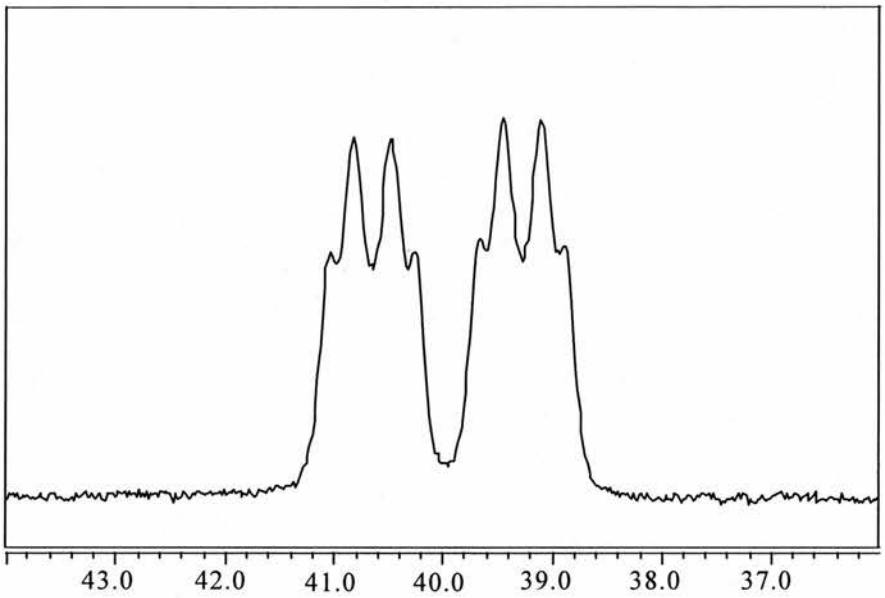


Figure 2.1 - $^{31}P\{^{1}H\}$ NMR spectrum of 1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene-borane (**67**) recorded on a 500 MHz instrument.

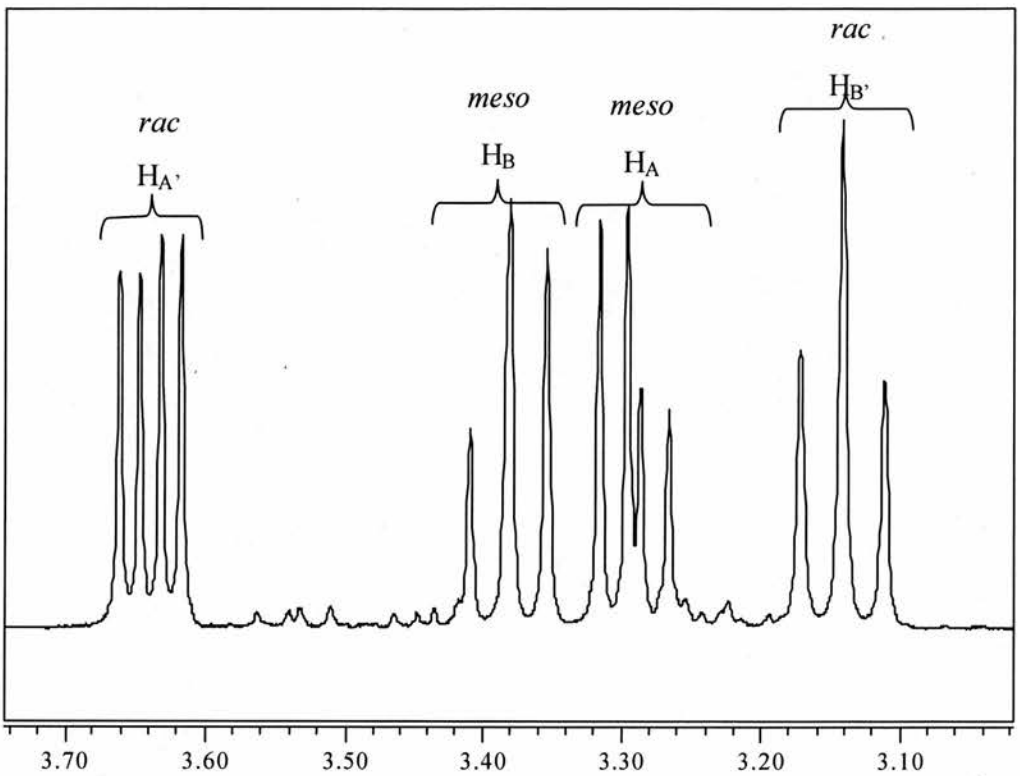


Figure 2.2 - ^{1}H NMR spectrum of the methylene region of 1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene-borane (**67**) recorded on a 500 MHz instrument

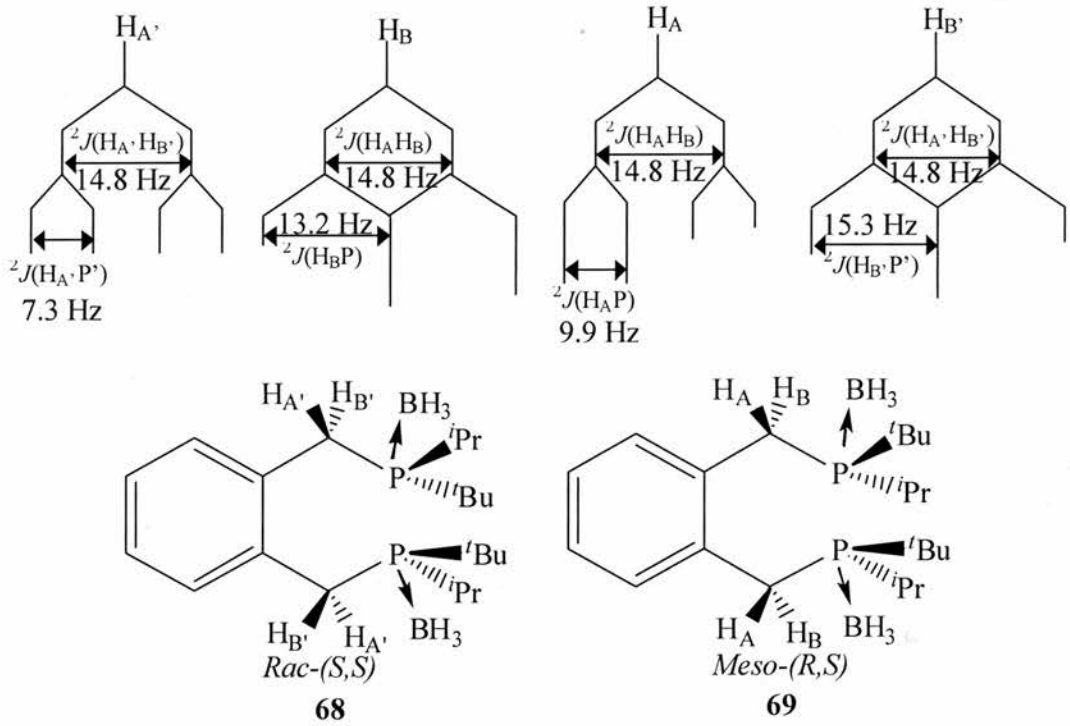


Figure 2.3 - Interpretation of methylene region of the ^{1}H NMR spectrum of the methylene region of both diastereoisomers of 1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene-borane (**67**) recorded on a 500 MHz instrument

The two diastereomers were separated by fractional crystallisation from MeOH. A racemic mixture containing all four diastereomers yielded colourless crystals enriched in the *rac* diastereomer. It was possible to obtain a diastereomerically pure sample after three recrystallisations of the collected crystals. To determine which enantiomer had crystallised, the crystal structure was recorded and the molecular structure can be seen in Figure 2.4. The crystal structure shown is the diastereomer where both of the phosphorus atoms have *R* chirality and is the *rac* diastereomer. The $^{31}P\{^{1}H\}$ NMR spectrum was recorded on the 500 MHz spectrometer and shows a quartet at 39.2 ppm

with a coupling constant of $^{1}J_{PB}$ = 50 Hz. The ^{1}H NMR spectrum shows that it is the two sets of peaks at 3.15 and 3.65 ppm that are from the *rac* isomer.

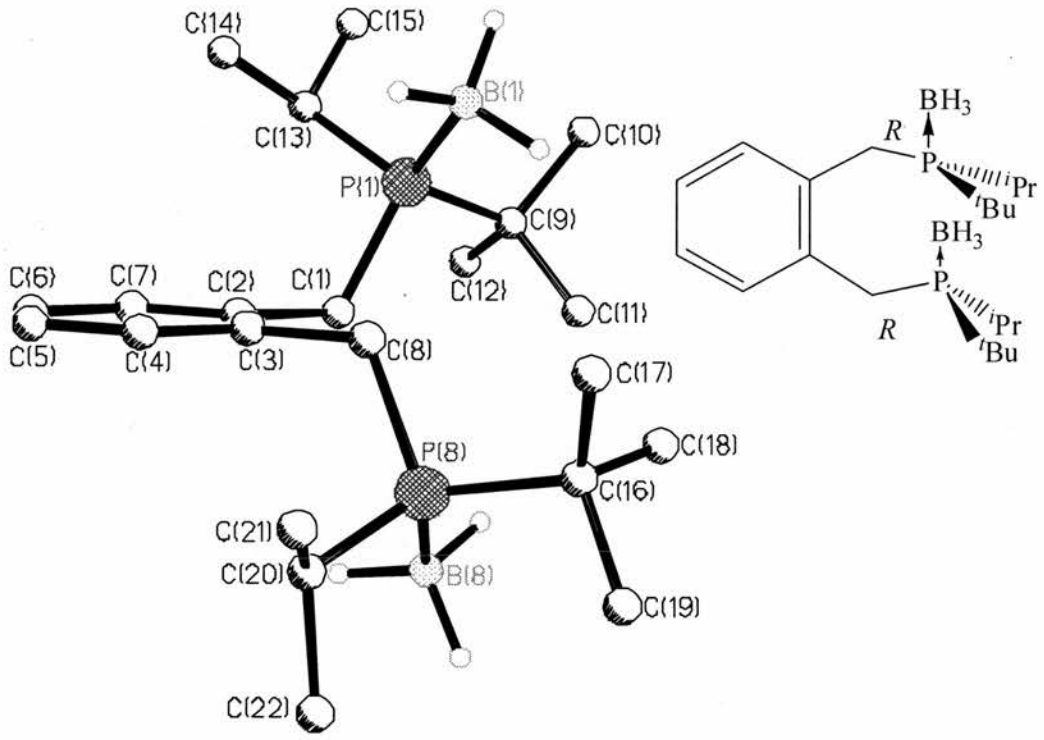


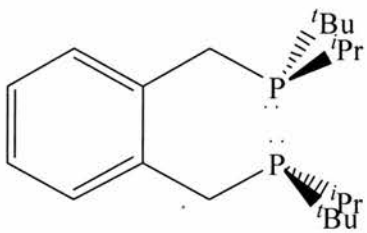
Figure 2.4 – Molecular structure of the *R,R* enantiomer in *rac*-1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene **(68)**.

The *meso* diastereomer was obtained by taking the solution from the crystallisation of the *rac* diastereomer and removing the solvent *in vacuo* which left a white solid enriched in the *meso* isomer. This was recrystallised from MeOH as colourless plates. The $^{31}P\{^{1}H\}$ NMR spectrum was recorded on the 500 MHz spectrometer and shows a quartet at 40.7 ppm with a coupling constant of $^{1}J_{PB}$ = 50 Hz. The ^{1}H NMR spectrum shows that it is the two sets of peaks at 3.29 and 3.38 ppm that are from the *meso* isomer. Unfortunately the determination of the molecular structure of the *meso*

diastereomer was not possible as the crystals grown did not diffract sufficiently to allow the data to be fully solved. However it was possible to obtain the unit cell, which was of a sensible size for the molecule and distinctly different from that of the *rac* diastereoisomer. This leads us to believe that this is indeed the *meso* diastereoisomer.

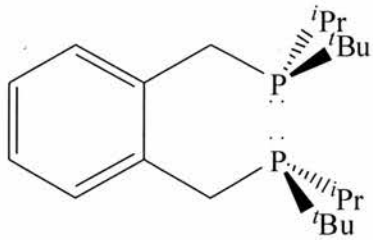
The racemic sample of 1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene-borane was dissolved in diethylamine and heated under reflux for 16 hours which successfully removed the borane protecting group. After suitable workup 1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene **(70)** was left as a colourless oil which had two peaks in the $^{31}P\{^{1}H\}$ NMR spectrum at 11.4 and 12.5 ppm.

Both diastereomers of the free phosphine were obtained by dissolving the appropriate phosphine-borane adduct in diethylamine and heating under reflux for 16 hours. After an appropriate workup the two diastereomers were isolated as colourless oils. The $^{31}P\{^{1}H\}$ NMR spectrum was recorded and the chemical shifts are shown in Figure 2.5.



Rac **(71)**

δ_P = 11.4 ppm



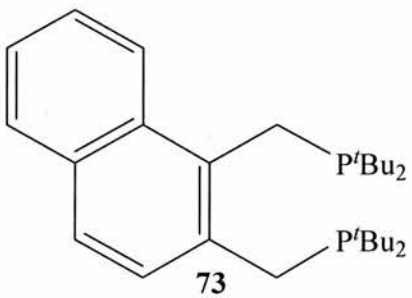
Meso **(72)**

δ_P = 12.5 ppm

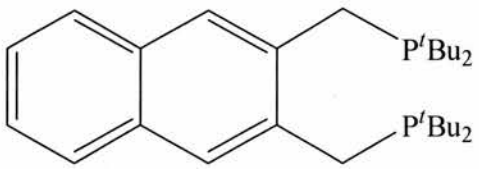
Figure 2.5 – chemical shift of $^{31}P\{^{1}H\}$ NMR spectrum of diastereomers of 1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene

2.1.1 Synthesis of *ortho*-bis(di-*tert*-butylphosphinomethyl)naphthalene

To determine whether adding a second aromatic ring onto the rear of the backbone would affect the catalysis, two isomers of the naphthalene backbone derivatives were synthesised. The two isomers of interest were 1,2-bis(di-*tert*-butylphosphinomethyl)naphthalene (1,2-DTBPMN **(73)**) and 2,3-bis(di-*tert*-butylphosphinomethyl)naphthalene (2,3-DTBPMN **(74)**).



73

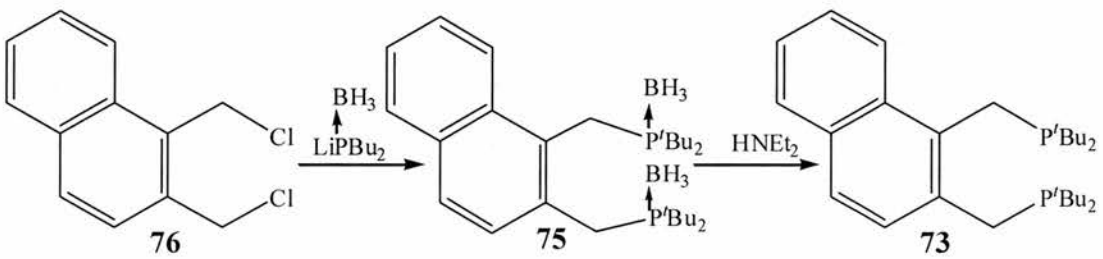


74

The method of Eastham *et. al.*[1] was used in an attempt to synthesise both isomers. Only in the case of the 2,3- isomer did the double deprotonation of the methyl groups of dimethylnaphthalene with *n*-butyl lithium and potassium *tert*-butoxide followed by the reaction with di-*tert*-butylchlorophosphine yield the desired product. This was obtained as a white crystalline solid with a peak in the $^{31}P\{^1H\}$ NMR spectrum at 26.3 ppm.

As the method of Eastham *et. al.*[1] did not yield the 1,2- isomer a different strategy was required. The reaction of lithium di-*tert*-butylphosphide-borane with 1,2-bis(chloromethyl)naphthalene was used and the rationale behind it will be discussed in more detail in section 2.2.3.3 (Scheme 2.2). This methodology yielded a white solid which was recrystallised from hexane to give 1,2-bis(di-*tert*-butylphosphinomethyl)naphthalene-borane **(75)** which showed a broad peak in the $^{31}P\{^1H\}$ NMR spectrum at 53.1 ppm. To remove the borane protecting groups, **75** was

dissolved in diethylamine and heated under reflux for 4 hours. After a suitable workup the resulting white solid was recrystallised from hot MeOH to give 1,2-bis(di-*tert*-butylphosphinomethyl)naphthalene as colourless crystals. This gave two peaks in the $^{31}P\{^{1}H\}$ NMR spectrum at 34.4 and 35.5 ppm due to the slightly different phosphorus environments.



Scheme 2.2 – Synthesis of 1,2-bis(di-*tert*-butylphosphinomethyl)naphthalene

2.2 Synthesis of unsymmetrical derivatives of DTBPMB

One possible mechanism proposed by Cole-Hamilton et. al.[3] for the catalytic methoxycarbonylation of alkenes using diphosphines, involves the decomplexation of one of the phosphorus groups. This converts the diphosphine from a bidentate to a unidentate ligand, which in turn dramatically reduces the electron density on the metal. This allows the nucleophilic attack of a methoxide ion on the metal-bound acyl group, thus forming the required ester product followed by rechelation of the diphosphine.[3]

It has been shown that the use of the electron rich ligand 1,2-bis(di-*tert*-butylphosphinomethyl)benzene, along with Pd as a catalysis metal, leads to high conversion and a fast reaction rate. As the highly electron rich diphosphine will complex strongly with the metal, it would seem that a diphosphine with less electron donating strength would be preferred. However this is not so, as we have shown that

with the 1,2-bis(dialkylphosphinomethyl)benzene family of ligands, the catalytic activity increases with increase of electron donating power of the alkyl groups i.e. ^{t}Bu>^{i}Pr>Et>Ph. It seems that there are two opposing factors influencing the outcome of the catalysis and a ligand that will be superior to 1,2-bis(di-*tert*-butylphosphinomethyl)benzene needs to adhere to the following criteria -

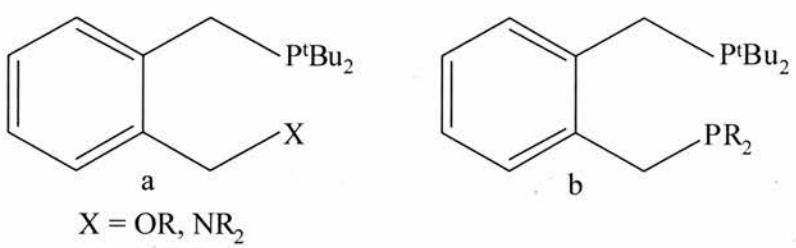
High electron density transferred to the metal => high L? M s donation

Ease of decomplexation of one of the sides of the ligand => low L? M s donation or increased steric bulk

Clearly these are two criteria which have opposing demands on the level of s donation to the palladium metal. As a result a compromise is required.

2.2.1 Possible forms of ligand for meeting electronic criteria

For there to be a decrease in the binding of one of the complexing atoms a less s donating group must be employed on one of the arms of the ligand. This might be achieved in one of two ways. Either 1) a hard donor atom such as oxygen or nitrogen (Scheme 2.3a) could be used or 2) less electron donating groups than ^{t}Bu on one of the phosphorus atoms (Scheme 2.3b) could be used.



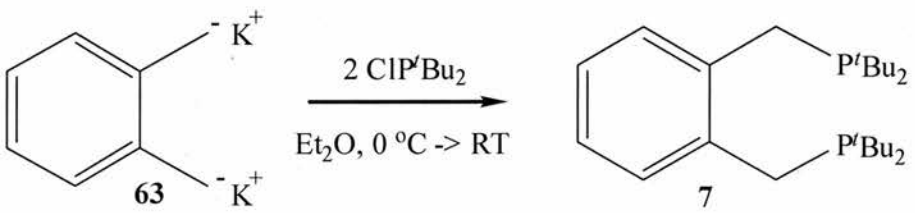
Scheme 2.3

An oxygen donor is of little use as Pd(II) has little affinity for hard donors such as oxygen and fluoride.[4] This may seem advantageous as during the nucleophilic attack of methoxide on the acyl group there would definitely be only one group from the ligand chelated thus keeping the electron density on the metal low. However having only one group coordinated may not impart sufficient electron density to the metal for the earlier steps of the catalytic cycle. Nitrogen is not as hard an atom as oxygen so can coordinate as exemplified in the complex $[Pd(NH_3)_4]Cl_2$[4] but again insufficient electron density may be present on the ligand.

The final possibility is the formation of an unsymmetrical diphosphine. One of the arms of the ligand could be kept as a di-*tert*-butylphosphino group thus providing high electron density to the metal centre. The other arm could contain a less electron donating dialkylphosphino group being, for example with phenyl or *iso*-propyl on the phosphorus atom.

2.2.2 Problems associated with synthesis of 1,2-bis(dialkylphosphinomethyl)benzene

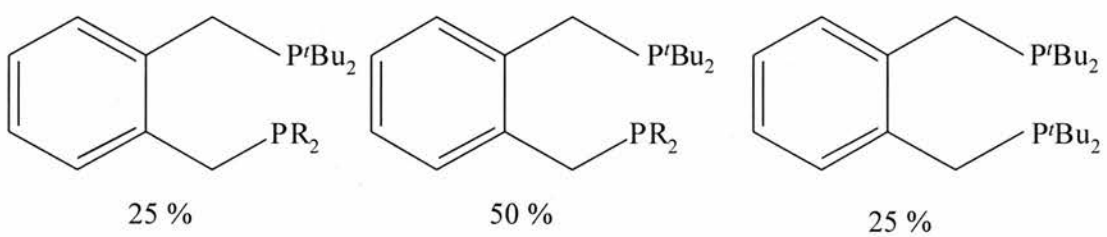
The normal strategy for the production of DTBPMB is the reaction of the dipotassium salt of xylene with two equivalents of di-*tert*-butylchlorophosphine as shown in Scheme 2.4.[1]



63 **7**

Scheme 2.4 – Synthesis of DTBPMB

If this strategy is employed in the synthesis of the unsymmetrical phosphines by the addition of one equivalent of each of the dialkylchlorophosphines it is likely that the product distribution will be a statistical mix of the three possible compounds (Scheme 2.5).

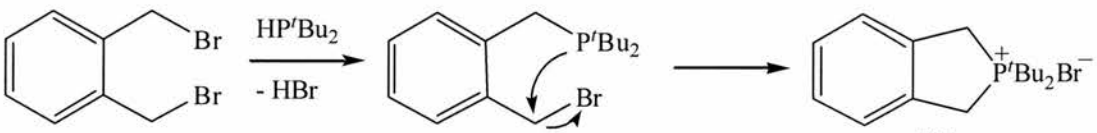


25 % 50 % 25 %

Scheme 2.5

Even if the reaction goes to 100 % completion and all of the 3 products can be separated with 100 % recovery, this is still highly atom inefficient as only one third of the phosphorus starting materials has ended up in the target compound Error! Reference source not found.. The cost of the electron rich phosphines makes this highly undesirable.

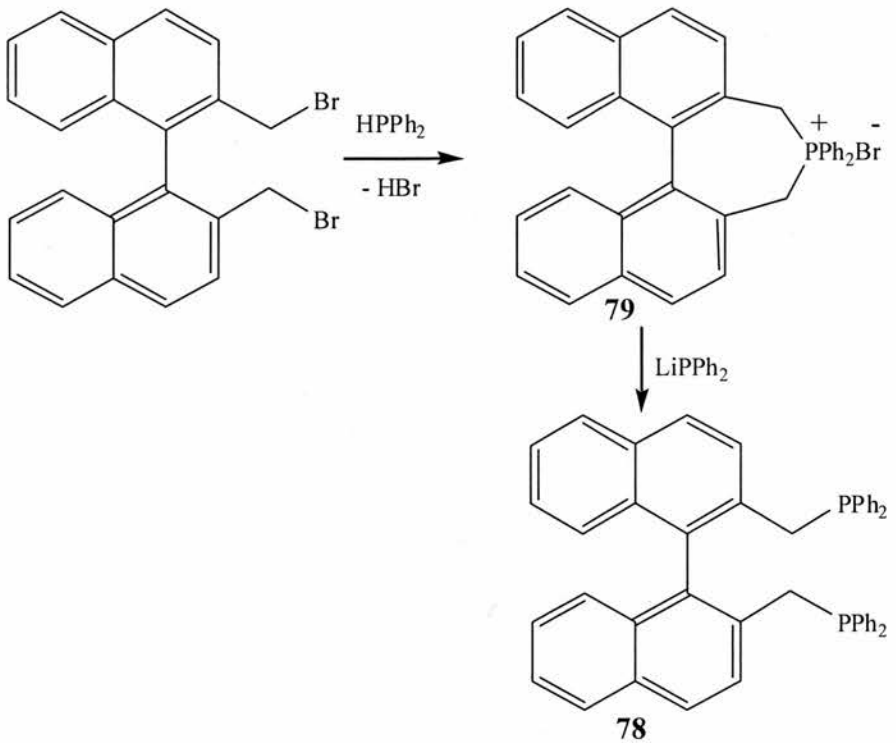
A different strategy for the formation of the carbon-phosphorus bond is the reaction of a secondary phosphine with an alkyl halide to form the phosphonium halide salt. This can then be reacted with a base e.g. NaOAc to reduce the salt to the phosphine. Unfortunately it has been reported that when α,α-dibromoxylene is reacted with di-*tert*-butylphosphine a heterocyclic salt **(77)** is formed (Scheme 2.6).[5]



77

Scheme 2.6 – Formation of heterocycle due to intramolecular attack of the phosphine on the second leaving group

The formation of this type of heterocyclic salt has been used as a tool in the synthesis of bis-diphosphines. Regnat *et. al.*[6] have synthesised the 2,2'-bis(diphenylphosphinomethyl)-1,1'-binaphthyl (NAPHOS) **(78)** *via* a phosphonium bromide salt **(79)**. Once the salt is isolated, the 7 membered ring is opened using lithium diphenylphosphide. This is achieved in an overall yield of 68 %.

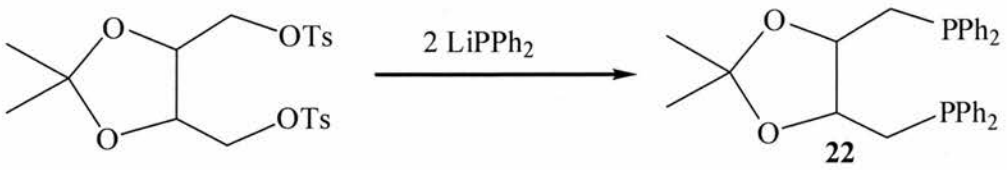


Scheme 2.7 – Synthesis of NAPHOS

However, when the heterocyclic salt **77** is reacted with lithium di-*tert*-butylphosphide there is no reaction. This can be attributed to the stability of the five membered ring of the heterocycle.

Another strategy for the formation of phosphorus-carbon bonds is the reaction of a nucleophilic phosphorus atom with an electrophilic carbon bearing a good leaving group. The most commonly used example of a nucleophilic phosphorus atom is a lithiated secondary phosphine which is readily formed from the secondary phosphine and *n*-butyl lithium. This has been employed successfully in the synthesis of DIOP **(22)** as shown in Scheme 2.8.[7] This can not be used for the same reason as in the phosphonium salt method detailed above. Once the first substitution has occurred there

will be an intramolecular ring closure as the electron lone pair of the first substituted phosphorus atom attacks carbon alpha to the second tosylate group.



22

Scheme 2.8 – Synthesis of DIOP

2.2.3 Stopping the heterocycle forming

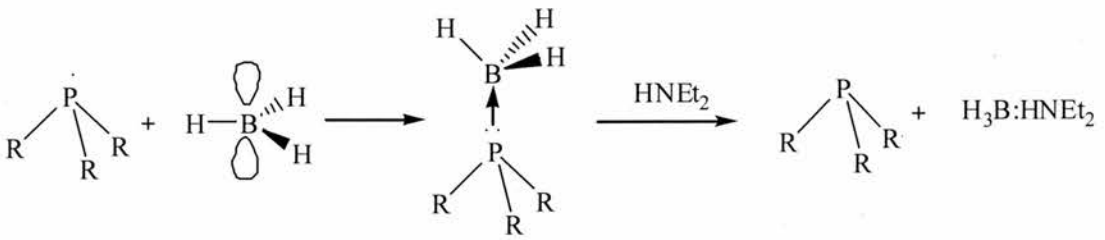
To introduce phosphorus groups to *o*-dibromoxylene without the formation of the stable 5-membered heterocycle the lone-pair of the phosphorus atom must be protected so as to stop it acting as a nucleophile.

Two possible ways to achieve this are 1) Form a phosphine oxide or 2) Form a phosphine-borane adduct.

In the first strategy– the formation of a phosphine oxide – the lone pair of electrons on the phosphorus is used to form a phosphorus-oxygen covalent double bond. This is highly stable under most conditions and the lone pair will not be present to form the heterocycle. Once the phosphorus atoms are attached to the backbone, they can, in principle, be reduced from the P(V) to the P(III) using a number of common methods which will be discussed later.

The phosphine-borane adduct is formed due to the electrophilic nature of borane (BH_3). The boron in BH_3 is planar sp^2 hybridised with an empty s orbital perpendicular to the plane of the B-H bonds (Scheme 2.9).[8] This can accept a pair of electrons, such as a lone pair from an oxygen or phosphorus atom. The dative bond that is formed between

a phosphorus atom and the borane is relatively stable, with increased strength as the electron density on the phosphorus atom increases. The borane group can be removed by heating the adduct in an excess of an amine as the nitrogen atom will remove the borane and form an adduct with the borane itself.



Scheme 2.9 – Reactivity of phosphines with borane

2.2.3.1 Use of phosphine oxides

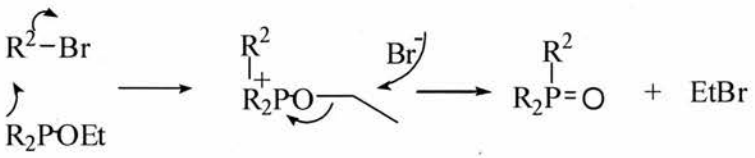
There are various ways to form a phosphorus-oxygen double bond. The simplest – and usually most annoying way for a phosphorus chemist – is the reaction of molecular oxygen with a P(III) compound. The rate of reaction increases as the electron density on the phosphorus atom increases. It is for this reason that solid triphenylphosphine can be handled in air while the much more electron rich tri-*tert*-butylphosphine must be handled in an inert atmosphere. This simple oxidation can be speeded up by the use of hydrogen peroxide as the oxygen source. This unfortunately is of no use in the formation of these asymmetric diphosphines as the formation of the P(III) form of the ligand is also unattainable.

Another method for the formation of a phosphine oxide is the Michealis-Arbuzov rearrangment[†]. This is the reaction between an alkyl halide and a phosphorus(III) compound with an alkoxy group present.

Scheme 2.10 – Arbuzov rearrangement

The size and electronic properties of R' determines the rate of the reaction, with the fastest rate being when R'= Me and slowest with R'= Ph. Also the nature of the R'-X generated is important as this is able to undergo the Arbuzov rearrangement with the phosphinite. However if R'= Me or Et, the generated halogenated species - methyl halide and ethyl halide - are volatile enough to boil immediately out of the reaction mixture as the toluene solution is heated under reflux.

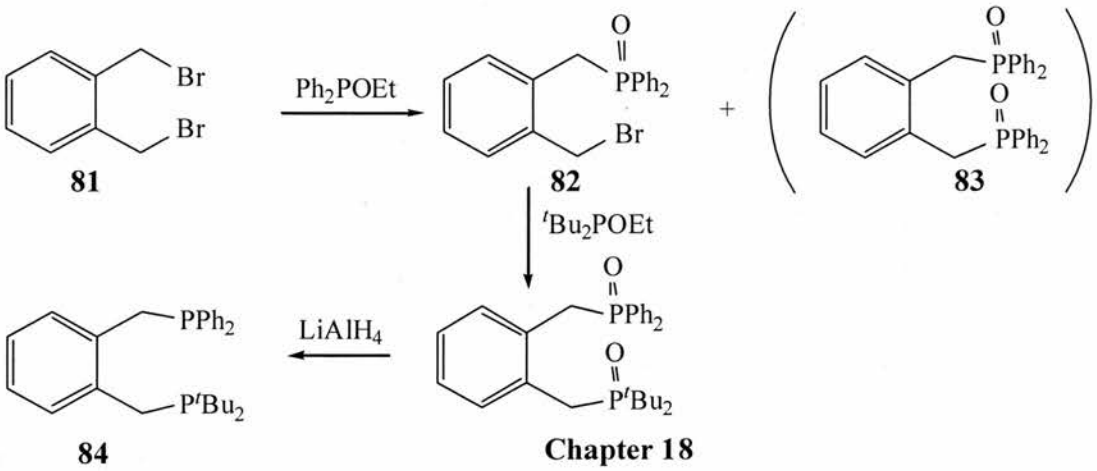
The rearrangement proceeds *via* the following mechanism.



Scheme 2.11 – Mechanism for the Arbuzov rearrangement

For the production of the target unsymmetric diphosphines the following reaction can be employed.

[†] Also commonly referred to as the Arbuzov rearrangement or the Arbuzov reaction.



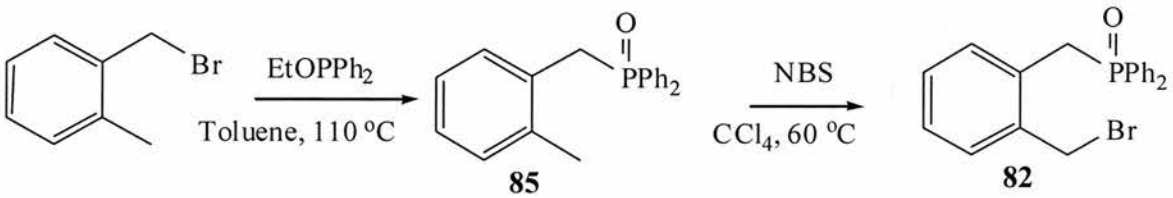
Scheme 2.12 – Synthesis of 1-(di-*tert*-butylphosphinomethyl)-2-(diphenylphosphinomethyl)benzene **(84)** *via* phosphine oxides

The synthesis of compound **82** was attempted using a phosphinite: dibromoxylene ratio of 1:1. After heating under reflux for 30 minutes and subsequently working up by addition of water and extraction of the products into dichloromethane it was found that the reaction was not selective and the product distribution was a 1:2:1 mix of the dibromo:monobromo-monophosphine oxide:diphosphine oxide **(81:82:83)**. However the separation of the three compounds was possible as their solubility in toluene varied sufficiently. The mixture was stirred in toluene at room temperature which dissolved only the dibromoxylene. After filtering, the residue was heated to near boiling in toluene, which dissolved only the monobromo-monophosphine oxide. After filtering, the solvent was removed *in vacuo* leaving a crude white solid, which was recrystallised, from chloroform.

The product distribution was moved slightly in favour of the monobromo-monophosphine oxide **(82)** by increasing the relative amounts of dibromoxylene to

phosphinite. Also lowering the temperature of the reaction mixture to 70 °C improved the selectivity, as the monophosphine oxide is partially soluble in toluene at this temperature, and once formed will precipitate thus inhibiting any further reaction. With these two considerations it was possible to isolate **82** in 36 % yield. This reaction is still not fully atom efficient with respect to the phosphorus atoms but ethyl diphenylphosphinite is commercially available and relatively cheap.

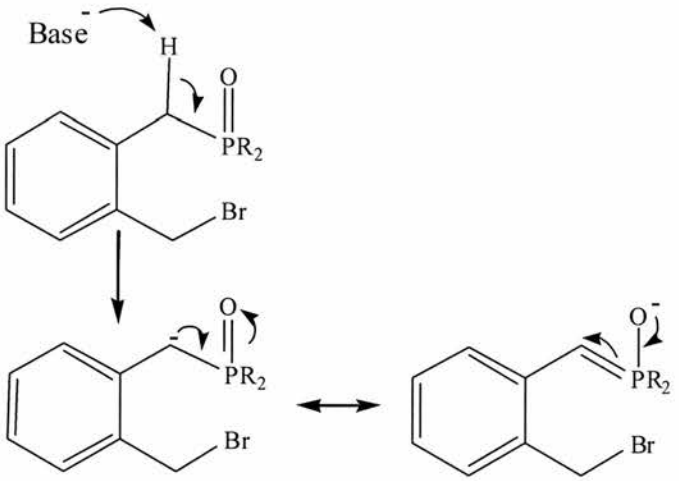
It is possible to synthesise 1-diphenylphosphorylmethyl-2-bromomethyl-benzene by a more atom efficient method. The problem with the attempted single Arbuzov rearrangement with α,α–dibromoxylene is the presence of the second bromine atom. If only one bromine atom were present during the first Arbuzov reaction and the second bromine atom introduced later, this would lead to both a more atom efficient and cleaner reaction (Scheme 2.13).



Scheme 2.13 – Synthesis of 2-diphenylphosphorylmethylbenzyl bromide

This sequence of reactions could be achieved by reacting 2-methylbenzyl bromide with ethyl diphenylphosphinite. After refluxing for one hour the solvent was removed to leave a pure white product and the $^{31}P\{^{1}H\}$ NMR spectrum showed a peak at 29.5 ppm. This compound was then reacted with *N*-bromosuccimide with a catalytic amount of dibenzoylperoxide as an initiator to form the desired mono-phosphine oxide **(82)** in an atom efficient manner.

The next step was the incorporation of the di-*tert*-butylphosphino group onto the other arm of the xylene backbone. This was tried by three methods 1) *via* the formation of the phosphonium bromide salt with di-*tert*-butylphosphine, 2) S_N2 substitution of the bromine with lithium di-*tert*-butylphosphide and 3) the Arbuzov rearrangement with alkyl di-*tert*-butylphosphinite. Routes one and two were tried first as the phosphorus compounds were either commercially available or easily synthesised. Route one was unsuccessful as no reaction occurred and the starting material was recovered. Unfortunately the use of the lithium phosphide (route 2) was also unsuccessful as the methylene protons next to the phosphine oxide are acidic (c.f. protons next to a carbonyl group) and were abstracted by the basic lithium salt (Scheme 2.14).

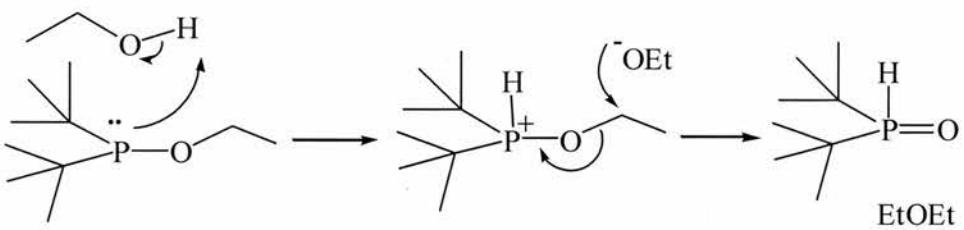


Scheme 2.14 – Increased acidity of methylene protons due to the resonance stabilisation from the phosphine oxide.

As none of the derivatives of the family of alkyl di-*tert*-butylphosphinites were commercially unavailable the required derivatives were prepared from di-*tert*-butylchlorophosphine. Sodium was dissolved in ethanol to form a solution of sodium ethoxide in ethanol to which di-*tert*-butylchlorophosphine was added slowly. The mixture was allowed to stir for an hour. Stirring was stopped to allow the white

precipitate – sodium chloride – to settle and the solution was then filtered. Toluene was added and the EtOH was removed *in vacuo*. A $^{31}P\{^{1}H\}$ NMR spectrum of the toluene solution showed a peak at 165 ppm which was consistent with the literature[9] for ethyl di-*tert*-butylphosphinite. This solution was slowly added to a refluxing toluene solution of the monobromide-monophosphine oxide **(82)** and after complete addition the solution was allowed to reflux for a further hour. A $^{31}P\{^{1}H\}$ NMR spectrum of the solution showed incomplete consumption of the starting phosphinite and a peak at 68 ppm attributed to $HP(O)^{t}Bu_2$.[9] It was also a surprise that there was no peak for the di-*tert*-butylphosphine oxide group in the $^{31}P\{^{1}H\}$ NMR spectrum.

It is possible that due to their highly basic nature, alkyl di-*tert*-butylphosphinites are capable of reacting with alcohol at elevated temperatures to form the secondary phosphine oxide. The alkyl di-*tert*-butylphosphinite is able to deprotonate the ethanol and the formed ethoxide ion attacks the phosphinite in an analogous fashion to the Arbuzov reaction (Scheme 2.15). To ensure that no ethanol was left, the solution of phosphinite in toluene was stirred with CaH_2 overnight.

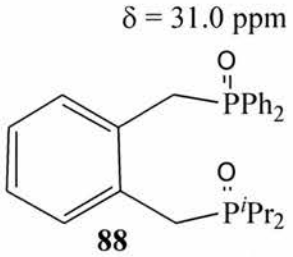


Scheme 2.15 – Reaction of ethyl di-*tert*-butylphosphinite with EtOH

To increase the reactivity of the phosphinites, methyl di-*tert*-butylphosphinite **(86)** was used and the Arbuzov rearrangement was carried out in xylene to allow a greater reaction temperature. After 3 hours the $^{31}P\{^{1}H\}$ NMR spectrum of the solution showed

no starting phosphinite left and a peak at 63 ppm in the same region as that for benzyldi-*tert*-butylphosphine oxide.[9] The xylene was removed *in vacuo* to leave a white sludge which upon recrystallisation from ethyl acetate gave a pure white product in 16 % yield. This was characterised as 1-diphenylphosphorylmethyl-2-di-*tert*-butylphosphorylmethylbenzene **(80)**. The proton NMR spectrum showed two distinct doublets for the methylene groups with a splitting of 13 Hz for the coupling to the phosphorus(V) atoms. In the $^{31}P\{^{1}H\}$ NMR spectrum there were two doublets present at 31.4 ppm and 62.6 ppm for the phenyl and *tert*-butyl substituted phosphine oxides. Both these peaks had a coupling constant of 4 Hz, which is due to long range P-P coupling.

1-diphenylphosphorylmethyl-2-di-*iso*-propylphosphorylmethyl-benzene **(88)** was made in an analogous way by reacting 2-diphenylphosphorylmethylbenzyl bromide **(82)** with ethyl di-*iso*-propylphosphinite **(87)** in toluene. After heating under reflux for 6 hours, the solution was cooled to leave a white solid, which upon recrystallisation gave the product as a colourless solid. The $^{31}P\{^{1}H\}$ NMR spectrum of **88** showed two peaks at 31.0 and 56.3 ppm which could be assigned as shown in Scheme 2.16. Both peaks were doublets with a coupling constant of 4 Hz, which is due to the long range P-P coupling. No $^{i}Pr_2P(O)H$ was observed due to the lower basicity of ethyl di-iso-propylphosphinite which was not able to deprotonate the EtOH.

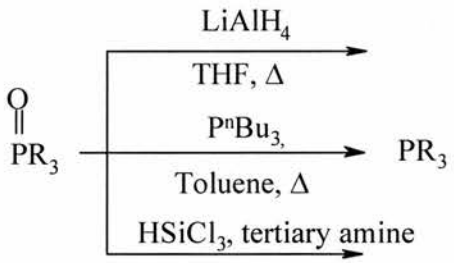


88

Scheme 2.16 - $^{31}P\{^{1}H\}$ NMR spectrum assignments for 1-diphenylphosphorylmethyl-2-di-*iso*-propylphosphorylmethyl-benzene **(88)**

2.2.3.2 Reduction of phosphine oxides

For the complexation of the diphosphine to occur it is necessary for the phosphorus atoms of the ligand to be P(III) and not P(V). There are several methods of reducing a phosphine oxide to the corresponding free phosphine. The most common examples are shown in Scheme 2.17.

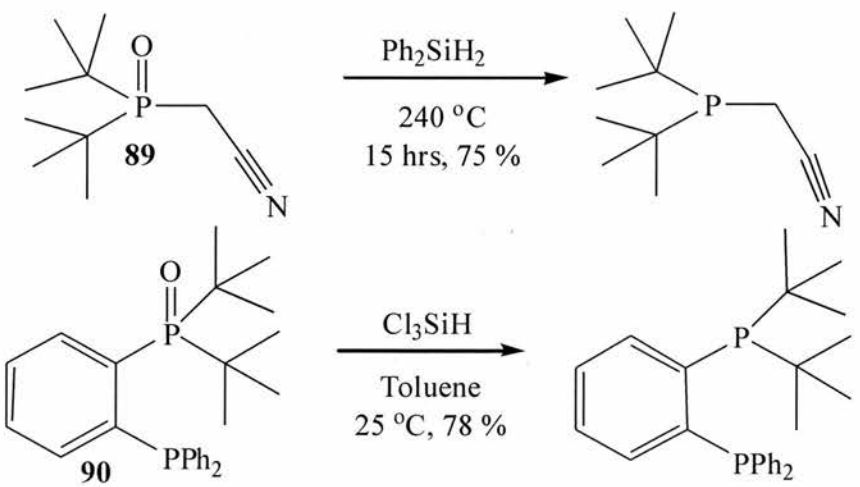


Scheme 2.17

The method that uses tri-*n*-butylphosphine to reduce the phosphine oxides relies on the electron richness of the tri-*n*-butylphosphine, which is able to remove the oxygen from the other phosphorus atom and become oxidised itself. For this reaction to work the phosphine to be produced must be much less electron rich than tri-*n*-butylphosphine. As the diphosphine oxide that we are trying to reduce contains a di-*tert*-butylphosphine oxide group this method was expected to be unsuccessful, so was not attempted.

The use of $LiAlH_4$ was tried and this was found to be unsuccessful in the reduction of the diphosphine oxide **80** as there was no effect of either of the phosphorus atoms.

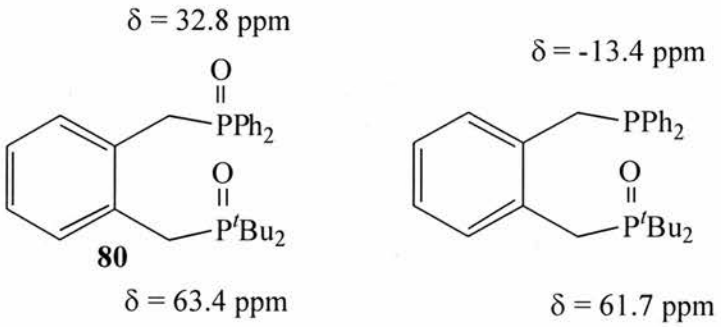
The reduction using silicon hydrides was discovered in 1964 by Fitzche and co-workers[10] and the use of these reagents is now common place in organophosphorus chemistry. The use of trichlorosilane and a tertiary amine – such as triethylamine or pyridine – is the most common method used today as high yields are achieved under mild conditions without affecting the other functional groups within the molecule. There are two examples of a silane mediated reduction of a *tert*-butylphosphine oxide moiety in the literature. They report considerably different reaction conditions with Dahl *et. al.*[11] reporting that cyanomethyl-di-*tert*-butylphosphine oxide **(89)** could be reduced in 75 % yield by heating it at 240 °C hours in diphenylsilane for 15 hours. Gray *et. al.*[12] reduced the unsymmetrical phosphine oxide **(90)** in 78 % by stirring at room temperature with trichlorosilane in toluene.



Scheme 2.18

The phosphorus atoms in both of these examples are less electron rich than the diphosphine that we required to reduce. However, the reduction of the unsymmetric

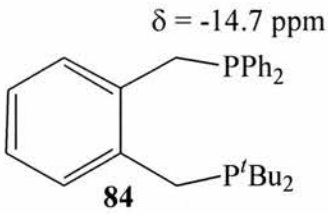
tert-butyl-phenyl phosphine oxide **(80)** was attempted by refluxing it in xylene with a 1:1 ratio of triethylamine and trichlorosilane. As the triethylamine is a strong enough base to deprotonate the trichlorosilane – an integral part of the mechanism – a triethylammonium salt forms. As the reaction heats up, both the silane (bp = 31 °C) and triethylamine (bp = 89 °C) boil out of the reaction solution and upon condensing in the condenser react with each other to form a white solid. This solid does not fall back into the reaction mixture so the concentration of silane and amine in the reaction mixture is constantly dropping. The reaction was monitored by removing a sample from the reaction mixture and obtaining a $^{31}P\{^{1}H\}$ NMR spectrum of the solution. After 16 hours refluxing, 50 % of the diphenylphosphine oxide was reduced. This product mixture gave four peaks in the NMR spectrum, which can be assigned as shown in Scheme 2.19



Scheme 2.19

After the addition of more amine and trichlorosilane and heating under reflux for 36 hours in total another sample was removed from the reaction. The $^{31}P\{^{1}H\}$ NMR spectrum showed no peak at 32.8 ppm suggesting that all of the diphenylphosphine oxide had been reduced. This complements the disappearance of the peak at 63.4 ppm. There was also the formation of two new peaks, one of which is at 25.4 ppm

corresponding to -P^{t}Bu$_2$.[5] These two peaks can be assigned to the desired product of 1-diphenylphosphinomethyl-2-di-*tert*-butylphosphinomethylbenzene **(84)**.



84

Scheme 2.20

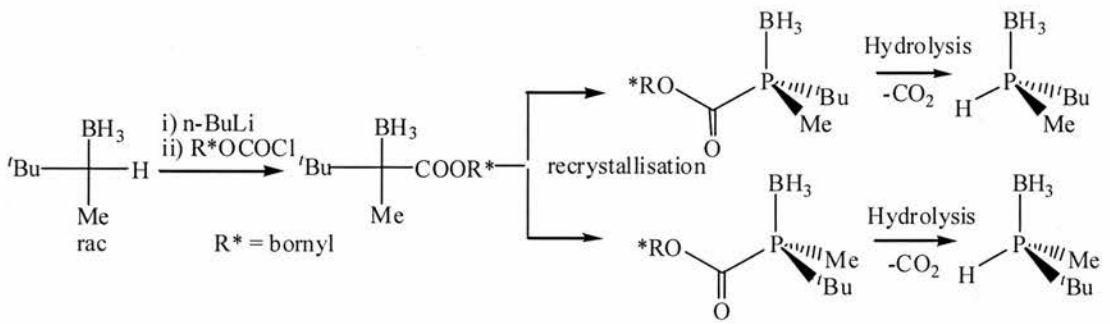
This seems encouraging except that another peak was present in the $^{31}P\{^1H\}$ NMR spectrum at –39.6 ppm which can be tentatively assigned to diphenylphosphine (Ph_2PH).

As the reaction still gave incomplete conversion of the *tert*-butylphosphine oxide to the reduced form it was decided to perform the reduction in a sealed autoclave to ensure that all of the silane and amine remained in the reaction mixture. Also a large molar excess of amine/silane to phosphine was used (50:1). Again xylene was used as the solvent and the autoclave was heated in an oven at 150 °C for 54 hours. After this time the autoclave was opened in a glovebag under an atmosphere of nitrogen. The $^{31}P\{^1H\}$ NMR spectrum of the solution showed that the dominant peak was at –39.6 ppm (Ph_2PH) and there was three other peaks present, at 28.5 ppm, 22.5 ppm and –12.9 ppm. As the spectrum was collected with considerable quantities of solid floating in the solution and the spectrometer was unlocked only a tentative assignment can be made of the signals as being benzyldi-*tert*-butylphosphine (36 ppm[13]), di-*tert*-butylphosphine[14] and benzyldiphenylphosphine (-9.3 ppm[15]) respectively.

The reduction of 1-diphenylphosphorylmethyl-2-di-*iso*-propylphosphorylmethyl-benzene **(88)** was attempted by heating under reflux the phosphine oxide in diphenylsilane. After heating for 9 hours the $^{31}P\{^{1}H\}$ NMR spectrum of the solution showed that there was incomplete reduction of the di-*iso*-propylphosphine oxide group but there was a new peak at 5.9 ppm which corresponds to benzyldi-*iso*-propylphosphine.[16]

2.2.3.3 Use of Borane protected phosphines

Another method of tying up a lone pair of electrons is the formation of phosphorus-borane adducts, which are air stable and usually highly crystalline materials. These adducts have been used in the field of asymmetric phosphine synthesis as the different enantiomers of [(1S)-*endo*-2-bornyloxycarbonyl](*tert*-butyl)methylphosphine-borane can be separated by recrystallisation from hexane which after hydrolysis affords the optically pure secondary phosphine-borane (Scheme 2.21).[17]

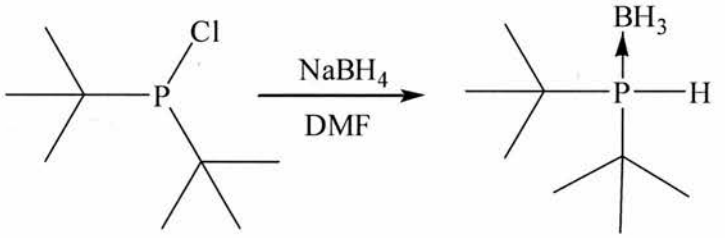


Scheme 2.21 – Formation of optically pure secondary phosphine-boranes.

If non-enantiomerically pure phosphines are required they can be synthesised in one of two ways. Either the secondary phosphine can be reacted with BH_3-THF adduct and the product recrystallised from hexane, or the secondary chlorophosphine can be reacted

with sodium borohydride in DMF. The sodium borohydride route is preferential as the secondary chlorophosphine is cheaper than the secondary phosphine itself.

Di-*tert*-butylphosphine-borane **(91)** was synthesised by the addition of di-*tert*-butylchlorophosphine to a cooled (0 °C) DMF solution of excess sodium borohydride (Scheme 2.22). This mixture was allowed to stir overnight and the solution was quenched with water. The product was extracted with diethyl ether (3 x 20 cm^3) and the solvent was removed *in vacuo* leaving a crude white solid which was recrystallised from hexane affording colourless needles. The $^{31}P\{^1H\}$ NMR spectrum shows a quartet peak 49.0 ppm with a coupling constant of $^1J_{PB}$ = 49 Hz. The ^1H NMR spectrum showed a doublet of quartets, $^1J_{PH}$ = 351 Hz and $^2J_{BH}$ = 7 Hz for the hydrogen directly bonded to the phosphorus atoms.



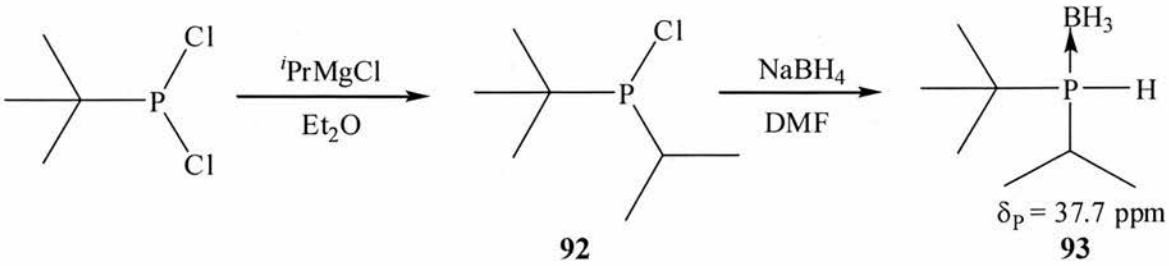
δ_P = 49.0 ppm

91

Scheme 2.22 – Synthesis of di-*tert*-butylphosphine-borane

To synthesise the mixed *tert*-butyl-*iso*-propylphosphine-borane **(93)**, *tert*-butyldichlorophosphine was dissolved in diethyl ether and a hexane solution of *iso*-propylmagnesium chloride was added slowly (Scheme 2.23). After stirring, the solution was filtered and the solvent was removed *in vacuo* leaving a yellow oil. The method used to synthesise **91** was employed to convert the *tert*-butyl-*iso*-propylchlorophoshine

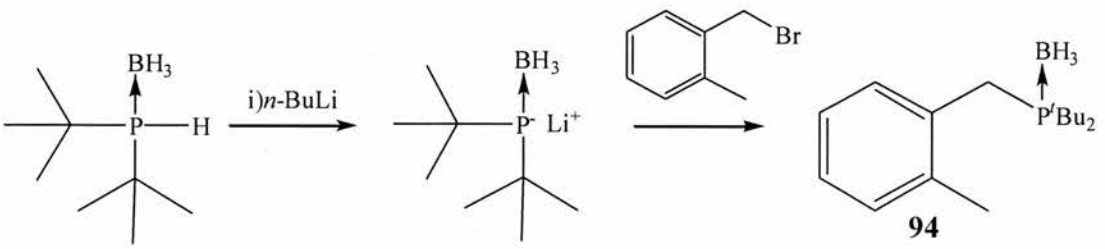
(92) into the secondary borane adduct. The final product was a clear oil for which the $^{31}P\{^{1}H\}$ NMR spectrum showed a quartet at 37.7 ppm with a $^{1}J_{PB} = 50$ Hz.



92 **93**

Scheme 2.23 – Synthesis of *tert*-butyl-*iso*-propylphosphine-borane

The reaction of one equivalent of lithiated **91** with 1,2-bis(chloromethyl)benzene is expected to lead to the formation of the statistical mix of the non-, mono- and di-substituted phosphines so was not attempted. 2-methylbenzyldi-*tert*-butylphosphine-borane **(94)** was synthesised by the addition of a THF solution of $LiPBu_2(BH_3)$ to a 0 °C cooled THF solution of 2-methylbenzylbromide (Scheme 2.24). The resulting mixture was allowed to warm to room temperature and, after stirring for 3 hours, the reaction was quenched with water and the product extracted with diethyl ether. The $^{31}P\{^{1}H\}$ NMR spectrum showed a quartet at 48.2 ppm with a $^{1}J_{PB}$ coupling of 50 Hz.

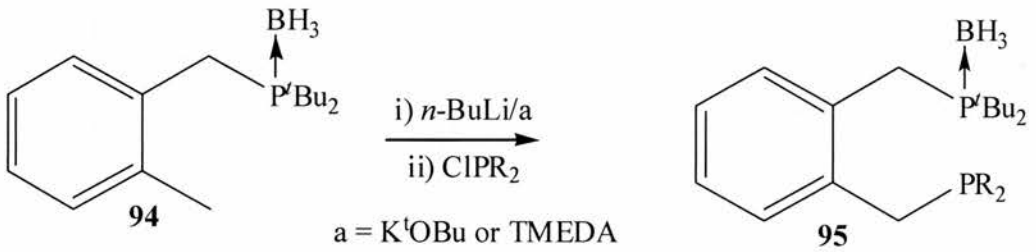


94

Scheme 2.24 – Synthesis of 2-methylbenzyldi-*tert*-butylphosphine-borane

The next step in the synthesis of the unsymmetrical diphosphines was the functionalisation of the unsubtituted methyl group attached to the aromatic ring. It was

believed that it would be possible to deprotonate the methyl group using a base such as *n*-butyl lithium-K^{t}OBu or *n*-butyl lithium-TMEDA. After the attempted deprotonation various secondary chlorophosphines were to be added to synthesise various forms of **95**.



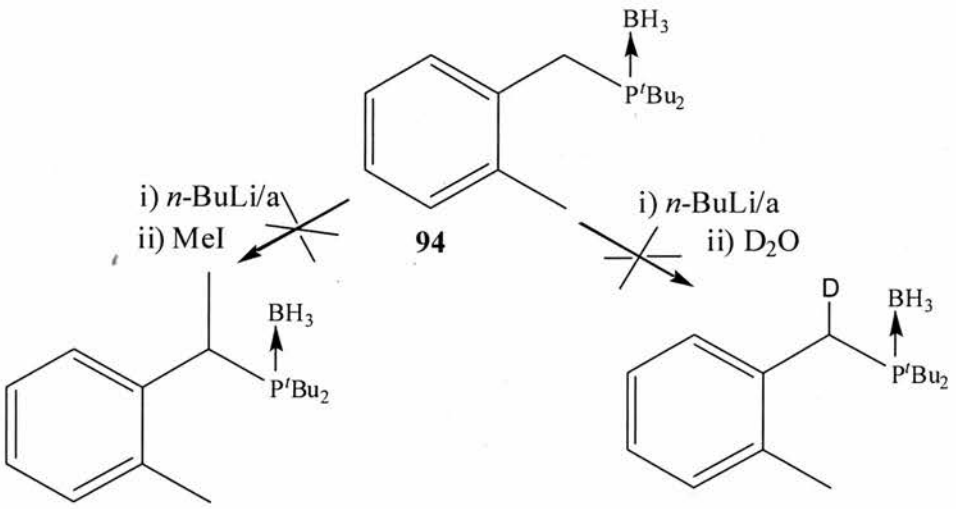
94 **95**

Scheme 2.25 – Synthesis of 1-(di-*tert*-butylphosphinoboratomethyl)-2-(dialkylphosphinomethyl)benzene **(95)**

Using both combinations of base it was found that the solution changed colour from colourless to red when the *n*-butyl lithium was added. The formation of a red colour is indicative of a benzyl alkali species. Upon addition of the chlorodi-*iso*-propylphosphine the colour was lost suggesting the reaction had taken place. However after subsequent workup only the starting material **94** was recovered. This was attributed to one of three reasons. Firstly the methyl group could have only been partially lithiated and as a result **95** was unable to form. Secondly it was possible that the methylene group alpha to the phosphine-borane was activated and it was this position that was being lithiated. The steric bulk due to the *tert*-butyl could then result in the nucleophilic attack of the deprotonated methylene upon the phosphine being unfavourable. If any lithiation had occurred but had not reacted with the electrophile, adding water during workup would reprotonate the organolithium and regenerate starting compound **94**. Lastly it could be possible that the borane group could be deprotonated but this seems unlikely as the dative bond from the lone pair of the

phosphorus to the borane results in the electron density on the borane group strengthening the borane-hydrogen bond making them difficult to remove with base.

To determine if **94** was being deprotonated at the methylene group the reactive electrophile, methyl iodide, was added after the base in an attempt to methylate the methylene group. However, it was found that only the starting material could be recovered. In this case as there was so much steric bulk around the methylene group even methyl iodide was unable to react with the organolithium reagent, it was decided to attempt to deprotonate **94** and then quench the reaction with deuterium oxide (D_2O). If this did deprotonate the methylene group the resulting deuterated product should show a triplet in the $^{31}P\{^{1}H\}$ NMR spectrum. This did not happen and it was concluded that there was no protonation of **94**. (Scheme 2.26)



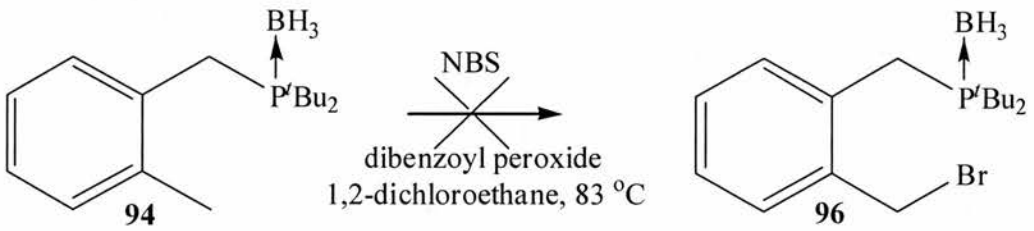
a = K^{t}OBu or TMEDA

Scheme 2.26

Instead of deprotonating the methyl group it was attempted to introduce a leaving group such as a bromine atom and form 2-di-*tert*-butylphosphinoboratomethylbenzyl bromide

(96). This would allow the reaction with lithiated secondary phosphine to produce the required product, **95**.

The replacement of one of the protons with a bromine atom on a benzylic methyl group is carried out using a radical reaction. It is possible to react toluene with N-bromosuccinimide (NBS) with a radical initiator such as dibenzoyl peroxide. **94** was heated with NBS and dibenzoyl peroxide in 1,2-dichloroethane for one hour. Once cooled the reaction was quenched with water and upon subsequent workup only starting material was recovered. This was a surprising result as the bromination of benzylic methyl groups is very fast and gives a high yield of brominated product. However the lack of reactivity can possibly be explained by the loss of a hydrogen radical from the borane group which stops any bromination taking place.



Scheme 2.27 – Attempted synthesis of Synthesis of 2-methylbenzyldi-*tert*-butylphosphine-borane bromide

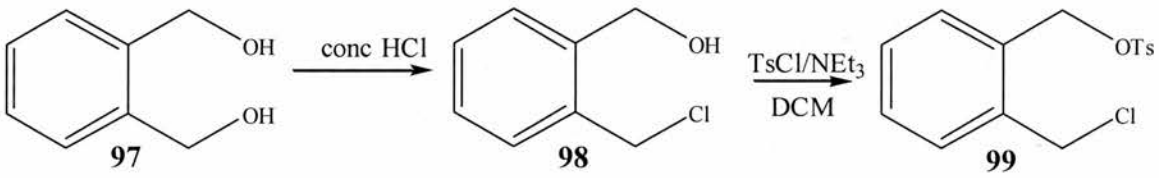
As it was found not to be possible to introduce the second leaving group after the first phosphorus-borane was bonded to the xylene backbone a new strategy was required. The reaction of a lithium dialkyphosphide with dibromoxylene is a nucleophilic substitution reaction. The rate of reaction for an S_N2 mechanism is dependent on two factors – 1) how good a nucleophile is being used and 2) how good a leaving group is being used.

How good a leaving group is depends upon its basicity and the less basic the anion the better the leaving group. The order of ability of anions to leave for traditional leaving groups is:

$$Cl^- << Br^- < I^- < {}^-OAc < {}^-OMs < {}^-OTf$$

It was decided that it may be possible to synthesise a xylene molecule with two leaving groups of very different reactivity with respect to nucleophilic substitution. The target molecule was 2-chloromethylbenzyl tosylate **(99)**. The tosylate was chosen rather than the more reactive mesylate or triflate because the tosylate will be crystalline thus easing purification.

The synthesis of **99** was from the tosylation of 2-hydroxymethylbenzyl chloride **(98)**, which is prepared from 1,2-bis(hydroxymethyl)benzene **(97)**.



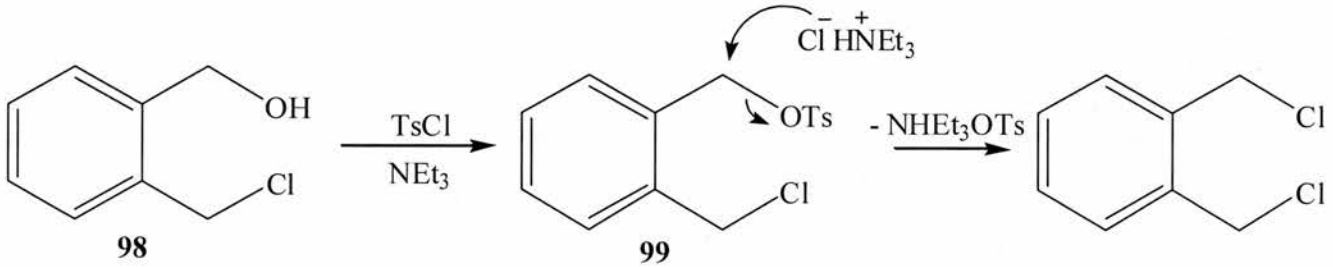
97 **98** **99**

Scheme 2.28 - Synthesis of 2-chloromethylbenzyl tosylate

The preparation of **98** was by the addition of 1,2-bis(hydroxymethyl)benzene to concentrated hydrochloric acid cooled to 0 °C[18]. The solution was allowed to stir for one hour after which time the acid solution was slowly added to water. The product was extracted with diethyl ether and the ^1H NMR spectrum showed signals at 4.71, 4.67 and 4.62 ppm. These are for the methylene protons of the desired product **98** (4.71 and 4.62 ppm) and the third at 4.67 ppm due to the methylene protons of α,α-

dichloroxylene which is the result of disubstitution of hydroxy for chloride. To increase the selectivity to the hydroxy/chloride product the reaction of 1,2-bis(hydroxymethyl)benzene with hydrochloric acid was repeated but as soon as the solution went slightly cloudy (30 minutes) the reaction was stopped by immediate addition to water and subsequent work-up. This improved the selectivity as only trace amounts of the dichloride was present. **98** was purified by recrystallisation from hot hexane.

To convert the alcohol group to a tosylate, **98** was dissolved in dichloromethane along with triethylamine. The solution was cooled to 0 °C and tosyl chloride was added portion wise. The solution was allowed to warm to room temperature and stir for 2 hours. After addition of water the product was extracted with diethyl ether and the solvent removed *in vacuo*. The ^{1}H NMR spectrum showed only one peak for the methylene protons which corresponds to α,α–dichloroxylene. This is formed due to the replacement of the tosylate leaving group by a chloride ion.



98 **99**

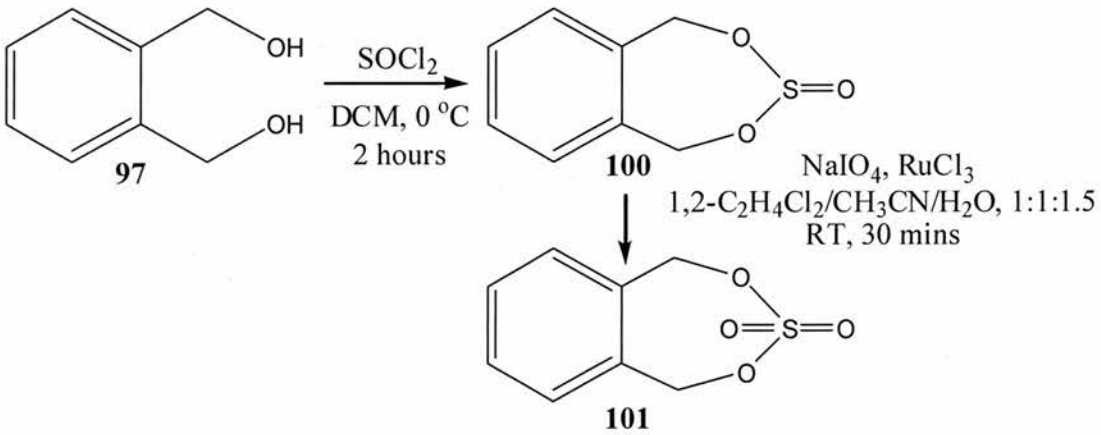
Scheme 2.29 – Synthesis of α,α–dichloroxylene from **98**

The reaction was repeated but was stopped after 30 minutes and again it was found that all of **98** was converted to α,α–dichloroxylene and this strategy was not investigated any further.

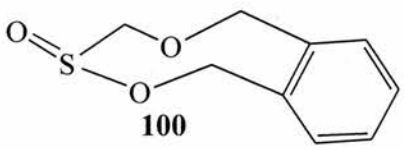
2.2.3.4 Utilisation of cyclic sulphates

It was reported at the 14th ISHC by Consiglio and co-workers[19] that it is possible to make unsymmetrical derivatives of 1,2-bis(di-*tert*-butylphosphino)benzene using a cyclic sulphate. Using a method developed by Sharpless[20] it is possible to form a cyclic sulphate, *via* a cyclic sulphite, from a dialcohol which, when reacted with one equivalent of a nucleophile, will give only the mono-substituted product.[21] A further addition of a second nucleophile and the subsequent substitution occurs giving the desired product.

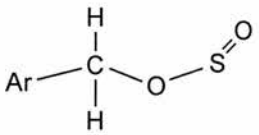
The cyclic sulphite **(100)** of 1,2-bis(dihydroxymethyl)benzene was prepared by the reaction with thionyl chloride in dichloromethane at 0 °C for 2 hours (Scheme 2.30). This yielded a solid product, which gave 2 equal intensity doublets in the ^{1}H NMR spectrum at 4.52 and 5.79 ppm both with a coupling constant of 14 Hz. These can be assigned to the methylene protons due to the unsymmetrical nature of the cyclic sulphite. As the sulphur is in a ring the methylene protons are inequivalent due to the sulphur not being fully oxidised. This leads to the oxygen and lone pair of electrons being on opposite sides of the ring, which leads to the inequivalent protons (Scheme 2.31).



Scheme 2.30 – Synthesis of cyclic sulphate **(101)**



Cyclic sulphite



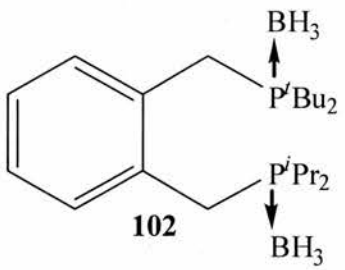
Side view of 7 membered ring

Scheme 2.31

To fully oxidise the sulphur, **100** was reacted with sodium periodate. This reaction was catalysed with $RuCl_3$. After 30 minutes of stirring at room temperature the cyclic sulphate **(101)** was obtained as a white solid. The ^1H NMR spectrum of the sulphate showed only one signal for the methylene protons at 5.36 ppm.

101 was dissolved in THF, cooled to –78 °C and a THF solution of $LiP^tBu_2(BH_3)$ was added dropwise. After complete addition the solution was warmed to room temperature and stirred for 30 minutes. A $^{31}P\{^1H\}$ NMR spectrum of the solution was recorded and showed a broad peak at 50.3 ppm indicative of benzyldi-*tert*-butylphosphine-borane. The solution was recooled to –78 °C and a THF solution of $LiP^iPr_2(BH_3)$ was added drop wise after which the solution was allowed to warm to room temperature and stir

for 3 hours. The reaction was quenched with water and the product extracted with diethyl ether to yield a white solid which was recrystallised from hexane as colourless crystals. The $^{31}P\{^{1}H\}$ NMR spectrum showed two broad signals, at 50.0 ppm and 36.2 ppm corresponding to the two different phosphorus - borane adducts. The ^{1}H NMR spectrum showed two doublets for the methylene protons at 3.13 and 3.25 ppm with coupling constants of 12 Hz, assigned as $^{2}J_{PH}$. The analysis allowed the assignment of the compound as 1-di-*tert*-butylphosphinomethyl-2-di-*iso*-propylphosphinomethylbenzene-borane **(102)**.



102

The methyl region of the ^{1}H NMR spectrum of **102** is shown in Figure 2.6. The doublet marked † has a coupling constant of $^{3}J_{PH}$ = 12 Hz and is assigned for the methyl group protons of the *tert*-butyl groups. The *iso*-propyl signals are two sets of doublets of doublets (* + ?). Each set of signals is due to the methyl protons coupling to the proton on the tertiary carbon ($^{3}J_{HH}$ = 7 Hz) and to the phosphorus atom ($^{3}J_{PH}$ = 14 Hz). There are two sets of signals because the methyl groups are diastereotopic as shown in Scheme 2.32.

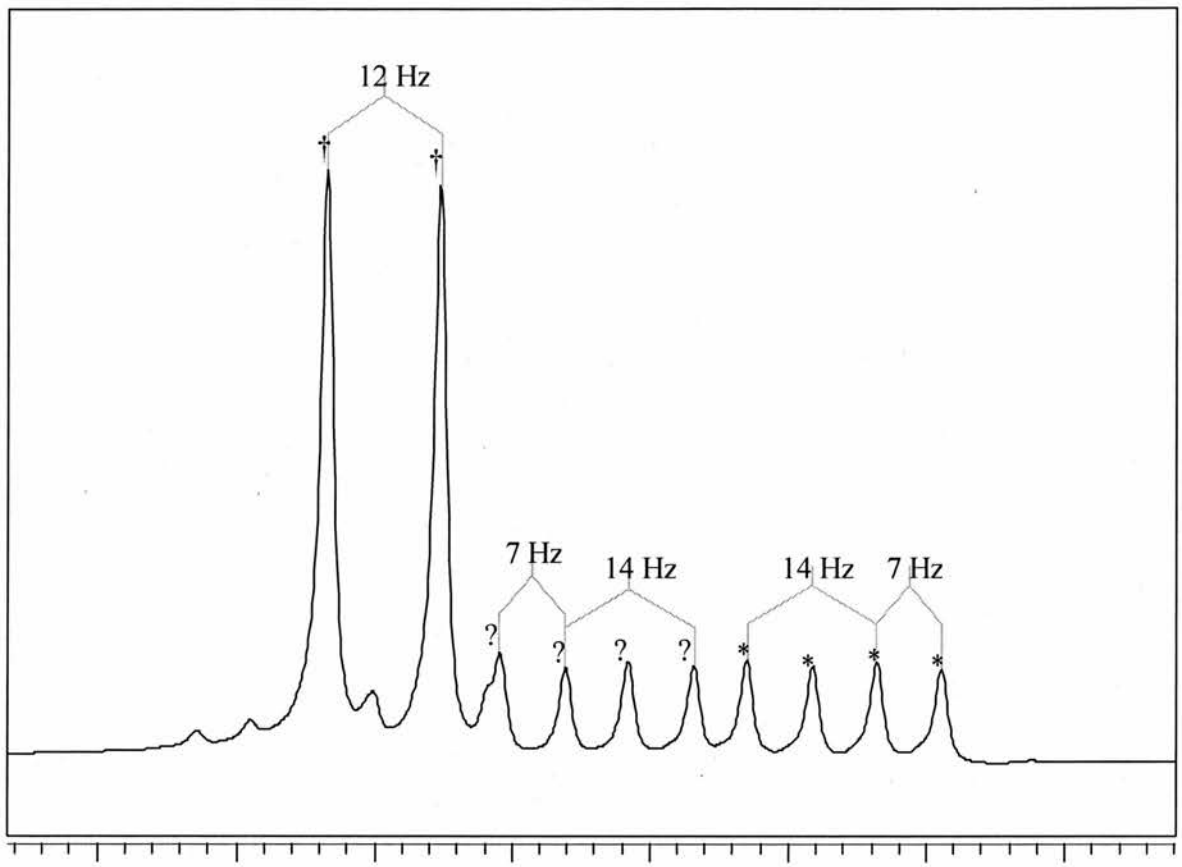
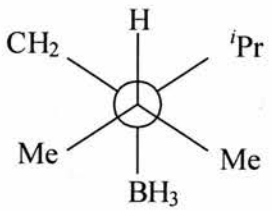


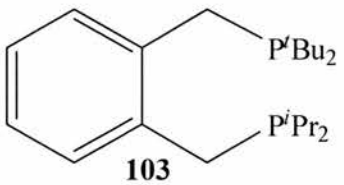
Figure 2.6 – ^{1}H NMR spectrum of the methyl region of **102** * = CH_3 of ^{i}Pr, ? = CH_3 of ^{i}Pr and † = CH_3 of ^{t}Bu



Scheme 2.32 – Newman projection along C-P bond of the unsymmetrical phosphorus in **102**

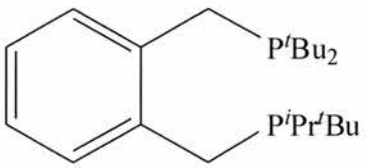
To remove the borane group, **102** was dissolved in triethylamine and heated under reflux in an inert atmosphere overnight. Upon cooling, the triethylamine was removed *in vacuo*. The residue was dissolved in toluene and passed through a silica column.

Upon evaporation of the toluene, a crude white solid was left which when recrystallised from MeOH yielded a white powder. The $^{31}P\{^{1}H\}$ NMR showed two peaks at 4.9 and 28.1 ppm which corresponds to the di-*iso*-propyl- and di-*tert*-butylphopshinobenzyl environments respectively. This allows the assignment of the compound as 1-di-*tert*-butylphosphinomethyl-2-di-*iso*-propylphosphinomethylbenzene **(103)**.



103

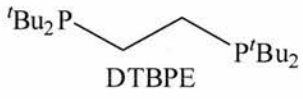
This strategy was also used to synthesise the derivative 1-di-*tert*-butylphosphinomethyl-2-*tert*-butyl-*iso*-propylphosphinomethylbenzene. After the reaction of the LiP^{t}Bu$_2$(BH$_3$) with **101**, a THF solution of LiP^{t}Bu^{i}Pr(BH$_3$) was added slowly. After stirring at room temperature for 3 hours the reaction was quenched with water and the product extracted with diethyl ether. After removal of the solvent *in vacuo* a crude white solid was left which recrystallised from hexane as colourless crystals of 1-di-*tert*-butylphosphinomethyl-2-*tert*-butyl-*iso*-propylphosphinomethylbenzene-borane **(104)**. The $^{31}P\{^{1}H\}$ NMR spectrum showed two broad peaks at 41.8 and 50.1 ppm corresponding to the BzP^{t}Bu^{i}Pr(BH$_3$) and BzP^{t}Bu$_2$(BH$_3$) groups respectively. **104** was dissolved in diethylamine and heated under reflux for 16 hours. Upon suitable workup the product was recrystallised from MeOH as a white powder. The $^{31}P\{^{1}H\}$ NMR spectrum showed two singlets at 16.7 and 28.6 ppm. This allows the assignment of the compound as 1-di-*tert*-butylphosphinomethyl-2-*tert*-butyl-*iso*-propylphosphinomethylbenzene **(105)**.



105

2.3 Synthesis of bis(di-*tert*-butylphosphino)alkanes

One of the only examples of vinyl aceate methoxycarbonylation in the literature is a Pd system with 1,3-bis(di-*tert*-butylphosphino)propane (DTBPP).[22] It was decided to synthesise this ligand and other members of the ligand family that have shorter (1,2-bis(di-*tert*-butylphosphino)ethane (DTBPE)) and longer carbon backbones (1,4-bis(di-*tert*-butylphosphino)butane) (DTBPB)).



DTBPE

106

DTBPP

13

DTBPB

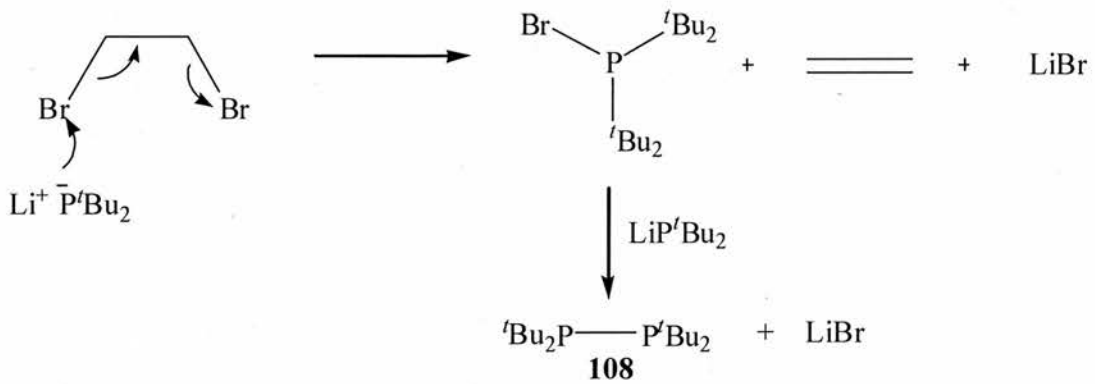
107

1,3-bis(di-*tert*-butylphosphino)propane was prepared by the published method of Carr *et. al.*.[23] H^{t}PBu$_2$ was reacted with *n*-butyl lithium in diethyl ether cooled to 0 °C to form di-*tert*-butylphosphide. To this 1,3-dibromopropane was added over a period of 20 minutes The resulting solution was warmed to room temperature and stirred for three hours during which time the yellow colour from the lithium phosphide disappeared and a white salt was formed. The reaction was quenched with water and the product extracted with petroleum ether (boiling range 40-60 °C). The solvent was removed *in vacuo* which left an oil which had a signal in the $^{31}P\{^1H\}$ NMR spectrum at 26.9 ppm.

1,4-bis(di-*tert*-butylphosphino)butane was synthesised in the same way as the propane analogue except 1,4-dibromobutane was used as the electrophile. This yielded the

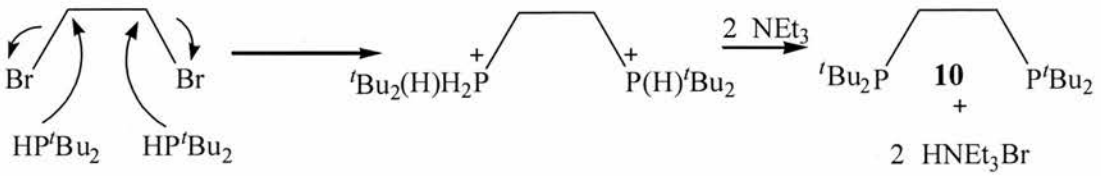
diphosphine as a white solid which was recrystallised from hexane. The $^{31}P\{^{1}H\}$ NMR spectrum showed a peak at 30.2 ppm.

When 1,2-dibromoethane was reacted with the lithium diphosphide in an attempt to synthesise the C2 backbone derivative it was found that in the $^{31}P\{^{1}H\}$ NMR spectrum of the reaction solution there was a peak at 38.1 ppm. This is a assigned as $^{t}Bu_2PP^{t}Bu_2$ **(108)**.[24] This is possible as the $LiP^{t}Bu_2$ is able to act as a base as well as a nucleophile. The phosphide extracts one of the bromine atoms with the electrons from the carbon-bromine bond forming a carbon-carbon double bond with loss of bromide to form lithium bromide and ethene as shown in Scheme 2.33. This bromodi-*tert*-butylphosphine is able to react with the lithium di-*tert*-butylphosphide to form the P-P coupled species.



Scheme 2.33– Formation of $^{t}Bu_2PP^{t}Bu_2$ from $LiP^{t}Bu_2$ and dibromoethane

In an attempt to stop the base like action of phosphide, the synthesis of 1,2-(di-*tert*-butylphosphino)ethane was attempted *via* the diphosphonium bromide salt. Upon formation of a trialkylphosphonium salt it is possible to obtain the free diphosphine by addition of a base such as triethylamine followed by a suitable workup (Scheme 2.34).



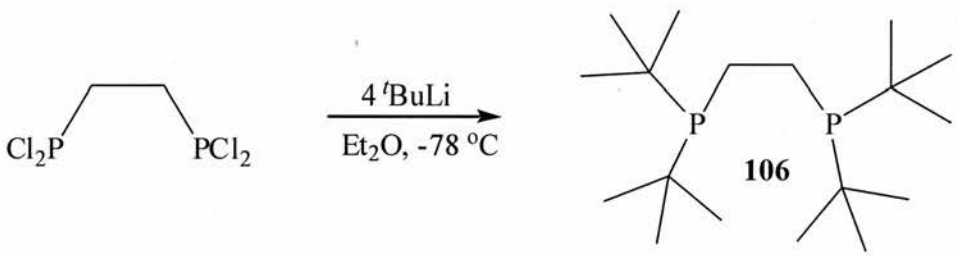
Scheme 2.34 – Synthesis of 1,2-bis(di-*tert*-butylphosphino)ethane *via* a phosphonium bromide salt

Di-*tert*-butylphosphine was heated overnight under an inert atmosphere in an acetonitrile solution of 1,2-dibromoethane. After the reaction was cooled a $^{31}P\{^1H\}$ NMR spectrum of the reaction solution was recorded and the major peak was at 21 ppm which corresponds to unreacted secondary phosphine. There was also a small peak at 68 .3 ppm which is the secondary phosphine oxide.

It is possible to synthesise the alkane backbone ligands using a different strategy.[25] A bis(dichlorophosphino)alkane can be reacted with a suitable alkyl nucleophile to form the required substituted diphosphine. It is possible to commercially obtain 1,2-bis(dichlorophosphino)ethane which can be reacted with either a Grignard reagent or an alkyl lithium. To a diethyl ether solution of 1,2-bis(dichlorophosphino)ethane, di-*tert*-butylmagnesium chloride was slowly added. After stirring for two hours at room temperature the $^{31}P\{^1H\}$ NMR spectrum showed a peak at 128.0 ppm which corresponds to a alkyl-*tert*-butylchlorophosphine. This is possible if only one substitution at each phosphorus atom occurs. This may be possible if the Grignard reagent is not a good enough nucleophile to carryout the final substitution. This maybe because the steric bulk around the phosphorus atom is too great resulting in the final substitution being too sterically hindered. The lack of the full substitution by bulky alkyl Grignard reagents is used in the synthesis of di-*tert*-butylchlorophosphine as the

addition of 3 equivalents of *tert*-butylmagnesium chloride with phosphorus trichloride will only produce the secondary chlorophosphine.

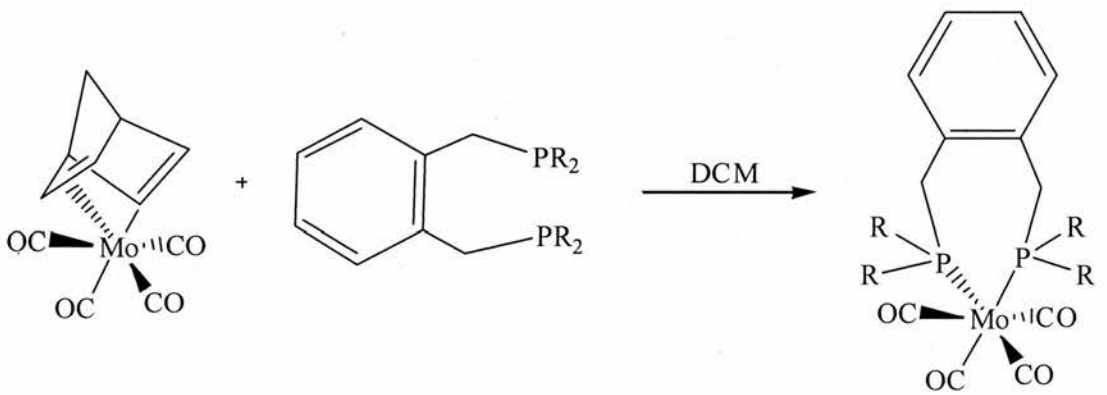
Poerschke *et. al.*[25] overcame this problem in the synthesis of 1,2-bis(di-*tert*-butylphosphino)ethane from 1,2-bis(dichlorophosphino)ethane by using *tert*-butyl lithium rather than the corresponding Grignard reagent (Scheme.2.35). 4 equivalents of *tert*-butyl lithium were added to a diethyl ether solution of 1,2-bis(dichlorophosphino)ethane cooled to –78 °C. After warming to room temperature and stirring for one hour the reaction was quenched with water and after a suitable workup a white solid was left which was recrystallised from MeOH. The $^{31}P\{^{1}H\}$ NMR spectrum shows a signal at 38.6 ppm which agrees with the published literature value.[25]



Scheme.2.35 – Synthesis of 1,2-bis(di-*tert*-butylphosphino)ethane[25]

2.4 Synthesis of $[Mo(CO)_4(L)]$ complexes (L = diphosphine)

To determine the electron donating power of the diphosphines the $[Mo(CO)_4L]$ (L = diphosphine) complexes were synthesised and the FTIR spectrum of $[Mo(CO)_4L]$ was recorded. The synthetic method of Zubiri *et. al.*[26] was used with slight modification. $[(norb)Mo(CO)_4]$, (norb = norbornadiene) and a diphosphine were dissolved in dichloromethane and heated under reflux for 2 hours after which time the solution was cooled and concentrated *in vacuo.* The product was precipitated by the addition of MeOH (Scheme 2.36).



Scheme 2.36 – Synthesis of $[Mo(CO)_4L]$

2.5 Summary

Various diphosphines were prepared using a number of synthetic routes. Firstly, the two *tert*-butyl groups on each phosphorous atom of 1,2-bis(di-*tert*-butylphosphinomethyl)benzene were changed to give the di-*iso*-propyl, diphenyl, diethyl and *tert*-butyl-*iso*-propyl derivatives. These were prepared by one of two routes. The dialkyl derivatives were prepared by the route of Eastham *et. al.*.[1] Xylene-α,α'-diyl dipotassium, which is a brick red solid, was prepared from *o*-xylene and Sclosser's base (mix of *n*-BuLi and K^{t}OBu). This dianion was reacted with two equivalents of dialkylchlorophosphine to give the desired product.

1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene was prepared *via* the phosphine-borane adduct. *tert*-butyl-*iso*-propylphosphine-borane was prepared by the reaction of *iso*-propylmagnesium chloride with *tert*-butyldichlorophosphine followed by the reaction with $NaBH_4$. This secondary phosphine-borane was deprotonated with *n*-BuLi and then reacted with α,α–dichloroxylene, thus forming the diphosphine-borane. The borane adduct was essential as this stopped the formation of a stable 5-membered heterocycle. This ring is formed from the intramolecular cyclisation of the first added phosphine as it reacts with the other $-CH_2Br$ in the *ortho* position. This reaction occurs as the lone pair of electrons on the first phosphorus atom is nucleophilic enough to promote an S_N2 type reaction at the second methylene group and form a phosphonium chloride salt. The borane protecting group was removed to give the free diphosphine by heating under reflux the borane adduct in diethylamine.

The 1,2- and 2,3- isomers of *ortho*-bis(di-*tert*-butylphosphinomethyl)naphthalene were synthesised. The 2,3- isomer was prepared *via* the dianion route with 2,3-dimethylnaphthalene and the 1,2-isomer was synthesised using the borane adduct procedure with 1,2-bis(chloromethyl)naphthalene and di-*tert*-butylphosphine-borane.

To obtain a diphosphine with the xylene backbone that had differing electron density on the two phosphorus atoms, 1-di-*tert*-butylphosphinomethyl-2-di-*iso*-propylphosphinomethylbenzene and 1-di-*tert*-butylphosphinomethyl-2-*tert*-butyl-*iso*-propylphosphinomethylbenzene were prepared. These unsymmertic diphosphine targets were problematic, as the addition of only one equivalent of phosphine in the two methods outlined above gave a mixture of the non-, mono- and di-substituted derivatives. Various synthetic strategies based around the use of the Arbuzov rearrangement to make phosphine oxides were attempted. However this method was found to be unsuitable as the reduction of the di-*tert*-butylphosphine oxides was found to be difficult. The usual methods for reduction of phosphine oxides were found not to be powerful enough to abstract the oxygen from these extremely electron rich phosphorus atoms. When the temperature of the reaction was increased it was found that the molecule was decomposed into various fragments. However it was found that these unsymmetrical diphosphines could be prepared *via* a borane-adduct intermediate. The cyclic sulphate of 1,2-bis(hydroxymethyl)benzene was prepared and after the subsequent addition of one equivalent of $LiP^tBu_2(BH_3)$ only the monosubstituted product could be detected in the reaction mixture. The addition of either $LiP^tBu^iPr(BH_3)$ or $LiP^iPr_2(BH_3)$ gave the relevant unsymmetrical diphosphine-borane. The borane groups were easily removed by heating the diphosphines in diethylamine.

The [$Mo(CO)_4$(diphosphine)] complexes were prepared by mixing [$Mo(CO)_4$(norbornadiene)] and the diphosphine in dichloromethane and heating under reflux for two hours. The solution was concentrated and the precipitate was washed with MeOH to give the complexes as yellow powders.

2.6 Bibliography

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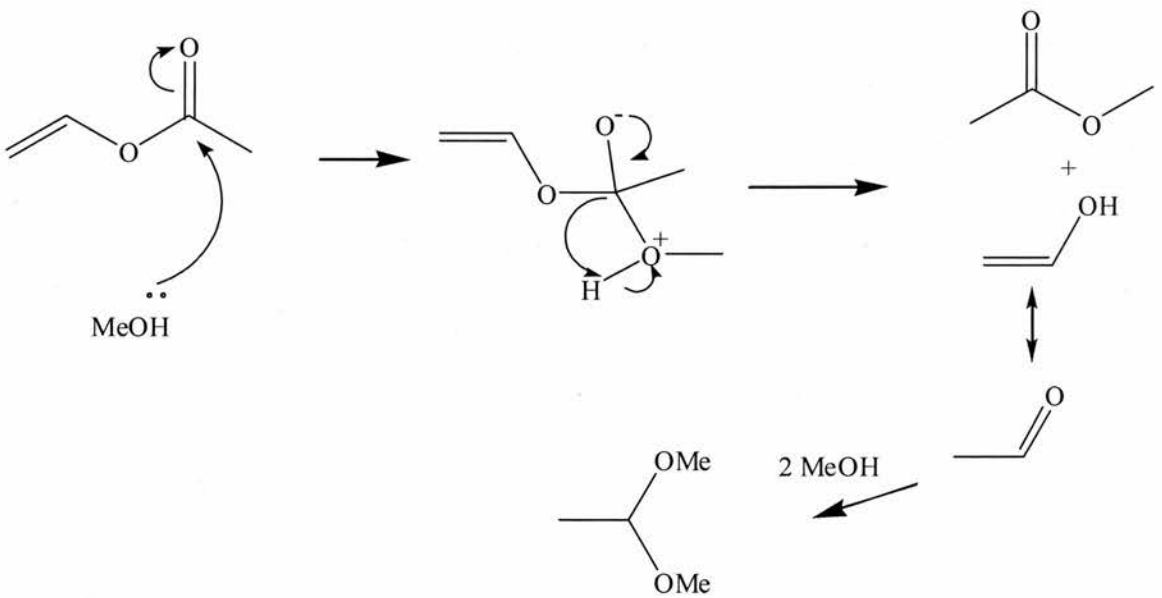
Chapter 3 - Alkoxycarbonylation of vinyl acetate

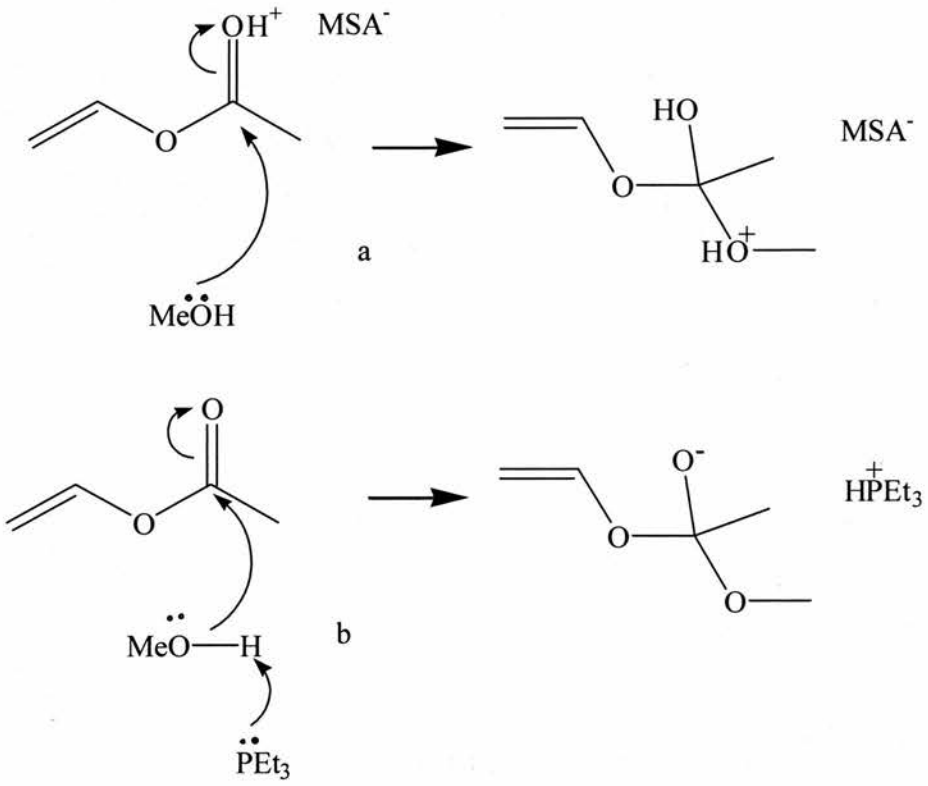
3.1 Stability of vinyl acetate in the presence of either acid or base

For effective catalysis the various substrates i.e. vinyl acetate, MeOH and solvent, must all be stable towards the catalyst system and its additives – except of course to the desired reaction. As vinyl acetate is an ester it is susceptible to nucleophilic attack from either a base or an anion. With MeOH, transesterification to give methyl acetate and vinyl alcohol is possible. The vinyl alcohol intermediates tautomerises to ethanal which is attacked by methanol making the reaction irreversible (Scheme 3.1).



Scheme 3.1 - MeOH attack of vinyl acetate to form MeOAc and 1,1-dimethoxyethane

Any acid (Scheme 3.2a) or base e.g. a phosphine (Scheme 3.2b) could catalyse the attack by MeOH



Scheme 3.2 – a) acid promoted vinyl acetate degradation b) base promoted vinyl acetate degradation.

Four experiments were performed to see if vinyl acetate was stable in the presence of triethylphosphine and/or MSA and the results are shown in Table 3.1

Table 3.1 - Stability test of vinyl acetate. Reaction conditions: vinyl acetate (2 cm^3), MeOH (2 cm^3) in the presence of either PEt_3, DTBPMB or MSA stirred in toluene (9 cm^3) for 3 hours at 80 °C.

Entry	PEt_3	DTBPMB	MSA	VAM (%)	MeOAc (%)
A	0	0	0	100	0
B	0	0	1 mmol	0	100
C	2 mmol	0	0	0	100
D	2 mmol	0	1 mmol	100	0
E	0	1 mmol	0	100	0
F	0	1 mmol	1 mmol	100	0

As will be seen later the catalysis can be carried out at room temperature so the experiment above was repeated at room temperature and the results are summarised in Table 3.2.

Table 3.2– Stability test of vinyl acetate. Reaction conditions: (2 cm^3) and MeOH (2 cm^3) in the presence of either PEt_3, DTBPMB or MSA stirred in toluene (9 cm^3) for 6 hours and then left sitting for a further 54 hours all at room temperature.

Entry	PEt_3	DTBPMB	MSA	VAM (%)	MeOAc (%)
A	0	0	0	100	0
B	0	0	1 mmol	50	50
C	2 mmol	0	0	5	95
D	2 mmol	0	1 mmol	100	0
E	0	1 mmol	0	100	0
F	0	1 mmol	1 mmol	100	0

From the tables it can be seen that in the presence of acid only (entry B), vinyl acetate is not stable. Not surprisingly at room temperature the rate of degradation of the vinyl acetate and MeOH is much slower. If triethylphosphine is the only additive present then there is partial degradation of the vinyl aceate. However, if the only additive is DTBPMB, the phosphine in the highly active catalytic system for the

methoxycarbonylation of ethene,[1] there is no conversion of vinyl acetate to methyl acetate. If both the acid and either of the phosphines are present the vinyl acetate is stable. This may be due to the formation of the phosphonium salt that means there is no free acid in the solution. The proton of the phosphonium salt is acidic enough to protonate the palladium in the highly active catalytic system.

To verify if this could occur and to what extent the equilibrium lies to the side of the phosphonium salt, an NMR tube experiment was carried out. PEt_3 was dissolved in benzene-d_6 and the $^{31}P\{^1H\}$ NMR spectrum was recorded (0.5 mmol in 1 cm^3). MSA was added in 0.1 mmol aliquots and the NMR spectrum rerecorded. It was found that the PEt_3 peak at δ = -18.4 ppm slowly decreased and a peak at δ = 23.3 ppm formed. When 0.7 mmol of MSA had been added there was no PEt_3 present as it had all been converted to the salt (Figure 3.1).

To determine if DTBPMB was able to be protonated by MSA in a stoichiometric ratio, a similar NMR experiment was performed. DTBPMB (0.1 mmol) was dissolved in CH_3OH (0.7 cm^3) and the $^{31}P\{^1H\}$NMR spectrum was recorded and the chemical shift of the only peak was found to be at 34.2 ppm which corresponds to DTBPMB. MSA (0.2 mmol) was added to the NMR tube and the $^{31}P\{^1H\}$NMR spectrum was immediately recorded and the signal corresponding to DTBPMB had disappeared and a new broad peak was present at 47.2 ppm due to the formation of the phosphonium salt, $[1,2\text{-}(^tBu_2P^+(H)CH_2)_2C_6H_4][MSA^-]_2$.

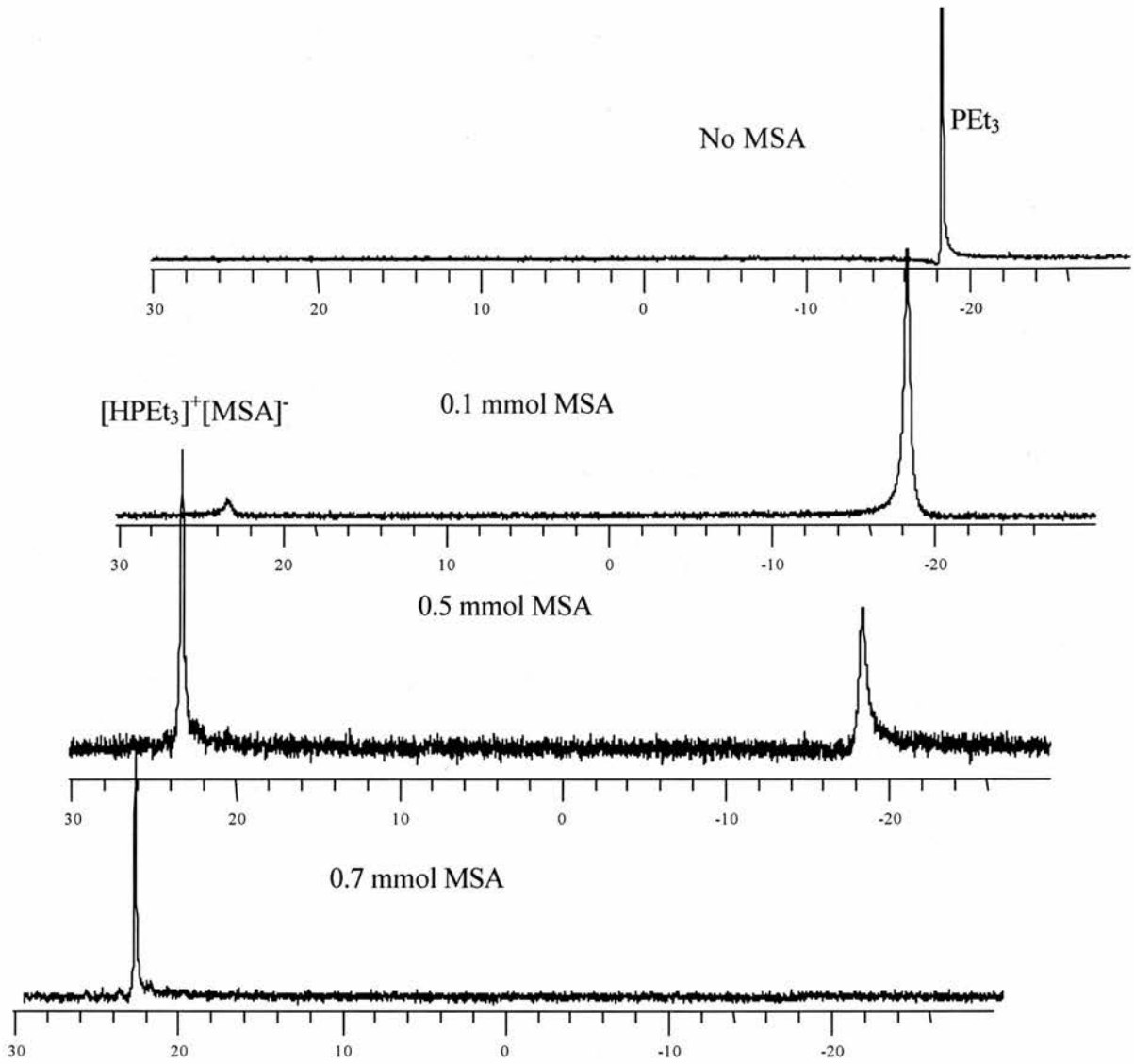


Figure 3.1 – $^{31}P\{^{1}H\}$ NMR of the formation of $[HPEt_3]^+[MSA]^-$ as more MSA is added to a solution of PEt_3 (0.5 mmol) in C_6D_6.

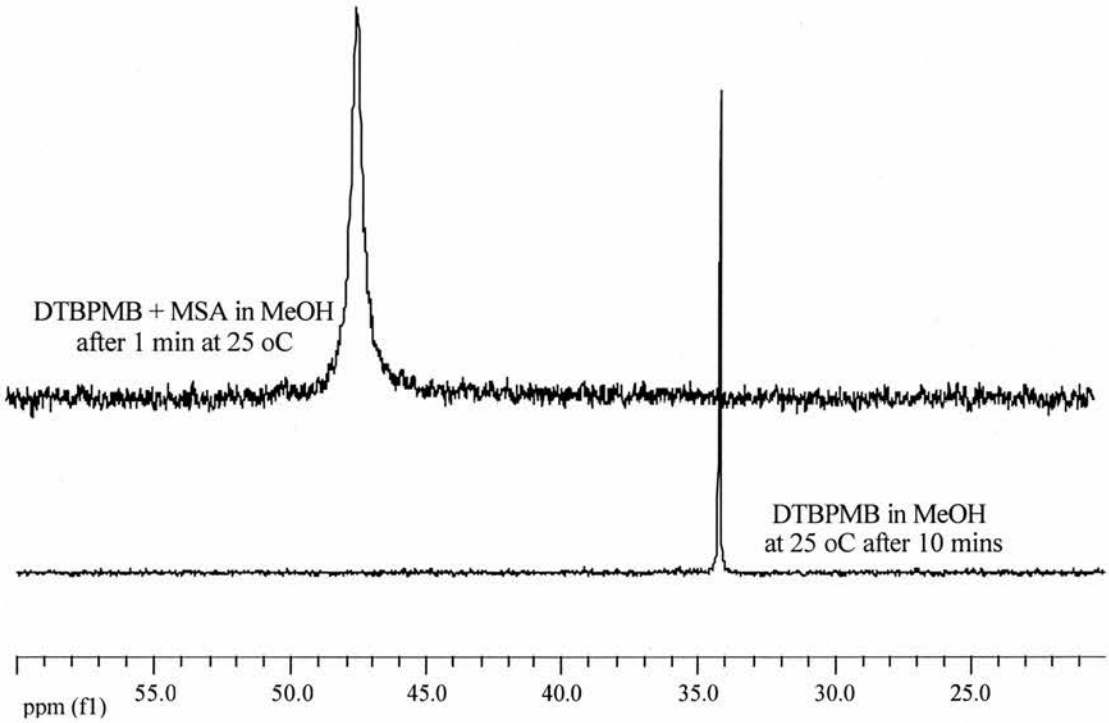


Figure 3.2 - $^{31}P\{^{1}H\}$ NMR of a) DTBPMB in MeOH after 10 minutes at 25 °C and b) DTBPMB + MSA in MeOH after 1 minute at 25 °C due to the formation of [1,2-($^{t}Bu_2P^{+}(H)CH_2)_2C_6H_4$][$MSA^{-}$]$_2$

3.2 Stability of (S)-methyl 2-acetoxy propanoate

A stability trial of (S)-methyl 2-acetoxypropanoate - the desired product from the methoxycarbonylation reactions - in an acidic medium was carried out where (S)-methyl 2-acetoxypropanoate was left in a methanol solution containing MSA. The solutions were left under different conditions for three days and the solutions were analysed by GC-FID (Table 3.3).

Table 3.3 – Stability of (S)-methyl 2-acetoxy propanoate in acidic MeOH. MeOH (2.5 cm^3), (S)-methyl 2-acetoxypropanoate (0.1 cm^{-3}). Time = 3 days.

Sample	MSA (μl)	Temp (°C)	(S)-methyl 2-acetoxy propanoate	MeOAc
A	0	- 20	100 %	0
B	0	25	100 %	0
C	4	- 20	> 99 %	Trace
D	4	25	26 %	74 %

As can be seen at room temperature in acidic medium (sample D) there is significant production of methyl acetate by a transesterification reaction.

3.3 Catalysis with bis(di-*tert*-butylphosphinomethyl)benzene

For ethene, the best methoxycarbonylation catalysis system to date is the palladium-DTBPMB-methane sulphonic acid technology employed by Lucite.[1] This catalyst system was tried for vinyl acetate methoxycarbonylation under the following conditions. $Pd_2(dba)_3$ (10 mg, 0.01 mmol), DTBMPB (8.7 mg, 0.02 mmol), MSA (27 μL, 0.4 mmol), MeOH (18 cm^3) and vinyl acetate (2 cm^3), heated to 80 °C with a CO pressure of 10 bar. This gives a catalysis solution of 1 x 10^{-3} mol L^{-1}, which is 30 times more concentrated than the Lucite International system. After 3 hours the catalysis was stopped and the conversion of vinyl acetate was found to be 100 % with a selectivity to the esters of 9 % and a b:l ratio of 15.6:1. The remaining products were MeOAc and 1,1-dimethoxyethane. These products are expected due to the acidic nature of the catalysis solution. The catalysis was repeated with the omission of the DTBPMB. This led to 100 % conversion of the vinyl acetate but with full selectivity to the degradation products.

The activity of the ligand containing system towards the methoxycarbonylation was encouraging and the system was investigated further varying assorted experimental parameters.

3.3.1 Effect of 1,2-bis(di-*tert*-butylphosphinomethyl)benzene concentration

Following the standard catalytic procedure for elevated temperatures and pressures (Section 4.2.1) the effect of ligand concentration on the catalysis was investigated (Figure 3.3). To ensure that there was no free acid present the acid:ligand ratio was kept constant at 1:1. It is worth noting that upon opening the autoclave no Pd metal was observed in any of the catalytic experiments carried out with the DTBPMB.

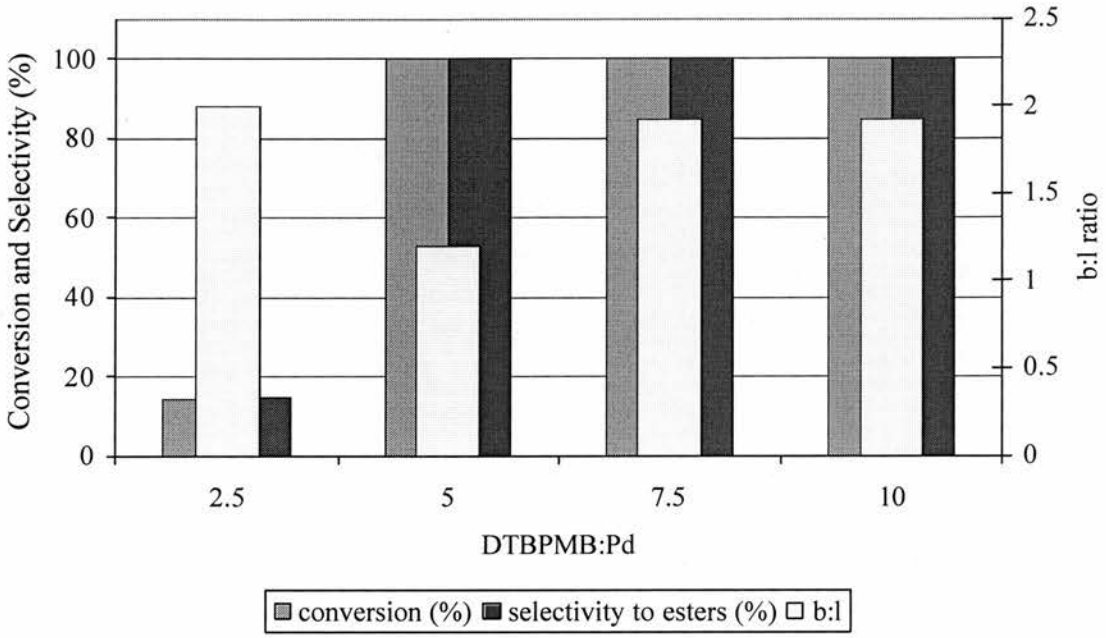


Figure 3.3 - Graph of effect of concentration of DTBPMB on the products from the methoxycarbonylation of vinyl acetate. Reaction conditions: $[Pd_2(dba)_3]$ (0.05 mmol), vinyl acetate (2 cm^3), MeOH (11 cm^3), MSA (= moles of ligand), CO pressure = 30 bar, temperature = 80 °C, reaction time = 3 hours.

As the DTBPMB:Pd ratio is increased the conversion of vinyl acetate increases as does the selectivity to the esters. The increase in conversion may be due to one of two things. Either the increase in phosphine helps the stabilisation of the palladium and stops it precipitating out of solution. This seems unlikely, as there was no visible sign of solid palladium metal at the end of the reaction. The other reason could be due to the increased acidity of the reaction solution due to the addition of more acid. This will be discussed in section 3.4.3. The result for the reaction where the DTBPMB:Pd ratio is 5:1 shows a drop in the b:l ratio. We believe that this is a true result and that the b:l ratio for the DTBPMB:Pd ratio of 2.5:1 is erroneously high due to both the poor

conversion and selectivity. The increase in the b:l ratio is also likely due to the increased acidity of the catalysis solution. (Section 3.4.3)

3.3.2 Effect of temperature with 1,2-bis(di-*tert*-butylphosphinomethyl)benzene

To determine the effect of temperature on the methoxycarbonylation of vinyl acetate the catalysis was carried out at 25 °C, 40 °C, 60 °C, 80 °C and 100 °C and the results are shown in Figure 3.4.

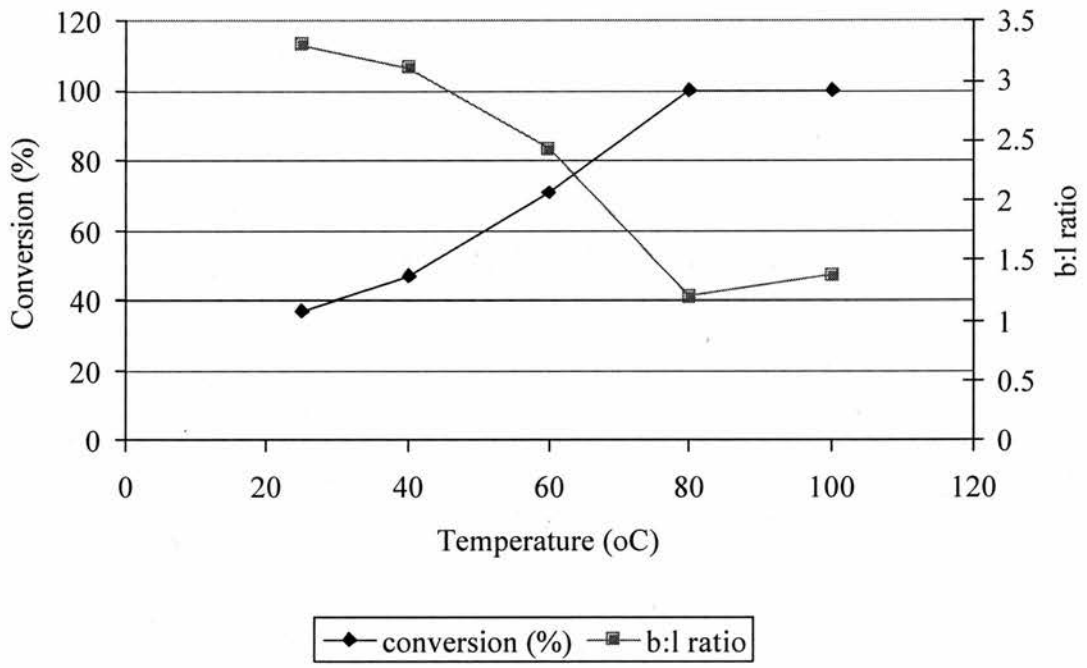
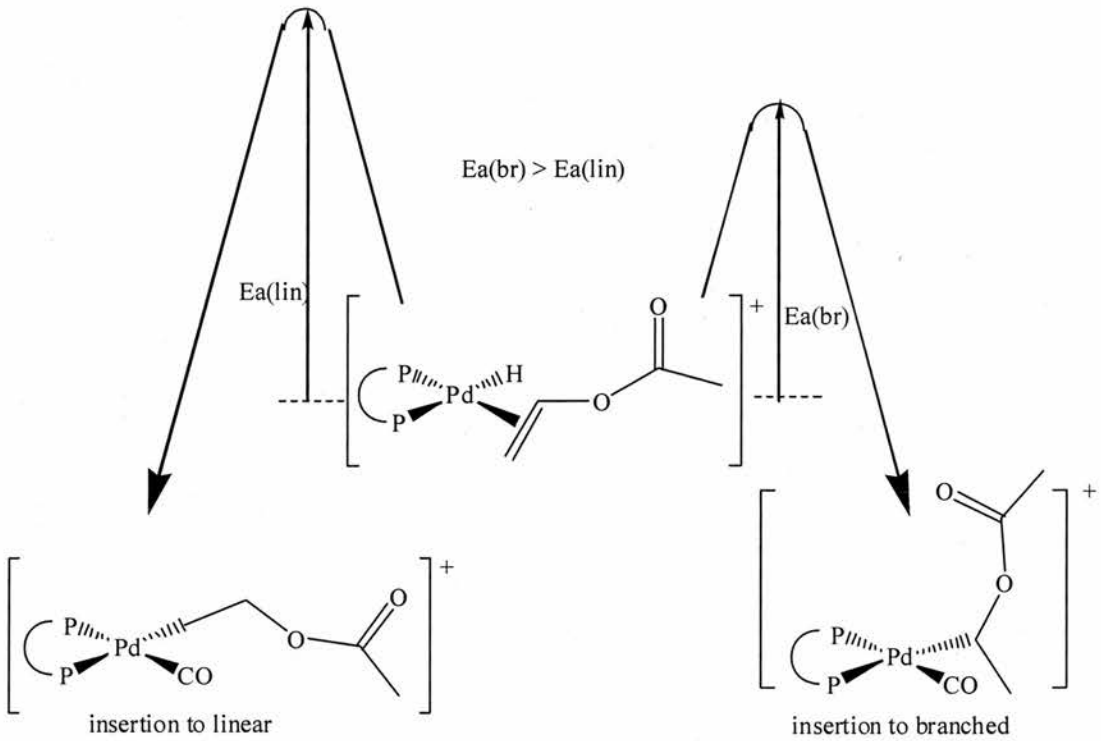


Figure 3.4 - Graph of effect of reactor temperature. Reaction conditions: $[Pd_2(dba)_3]$ (0.05 mmol), DTBPMB (0.5 mmol), vinyl acetate (2 cm^3), MeOH (11 cm^3), and MSA (0.5 mmol), CO pressure (30 bar), reaction time = 3 hours.

All of the reactions carried out gave selectivity to the esters of 100 %. As the temperature was increased the conversion of vinyl acetate increased as expected. 100 % conversion was obtained after 3 hours at temperatures of 80 °C and above. The

improvement in b:l upon lowering the temperature suggests that the pathway to the branched product has a lower activation energy than for the linear. At elevated temperatures the activation barrier is less of a problem and there is a greater amount of the linear product formed.



The relative potential energies of the three intermediates are not accurate.

Scheme 3.3 – Different activation energies to the linear and branched product intermediates.

In the hydrocarboxylation – using water rather than an alcohol - of styrene to 3- (linear) and 2-phenylpropionic acids (branched), the published[2] activation energies are 105 and 30 kJ mol^{-1} respectively, which supports the argument above if the situation is similar for vinyl acetate.

This ability to run vinyl acetate methoxycarbonylation at a lower temperature is advantageous as there is an improvement in the b:l ratio.

3.3.3 Effect of CO pressure with 1,2-bis(di-*tert*-butylphosphinomethyl)benzene

To determine whether there was a dependence upon the CO pressure in the methoxycarbonylation of vinyl acetate the catalysis was carried out at various CO pressures (Figure 3.5)

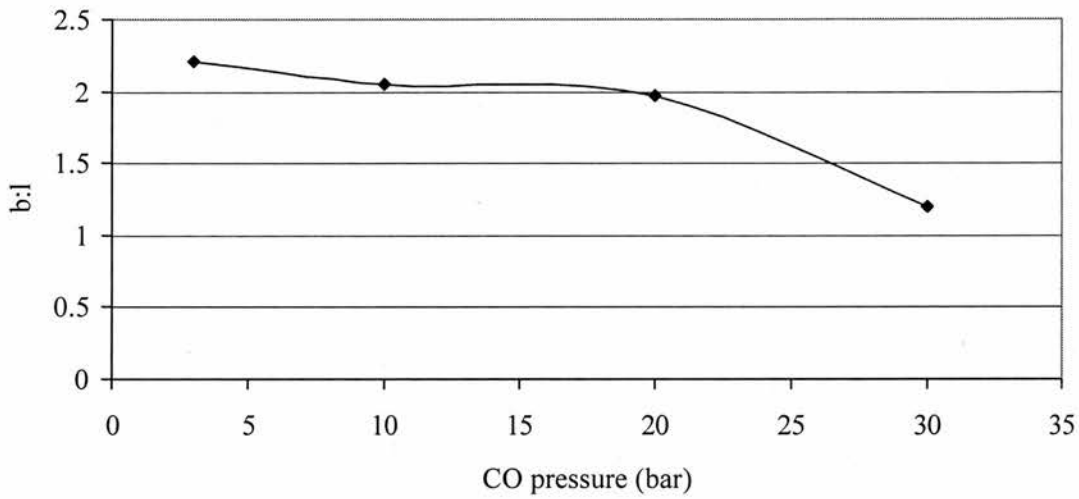
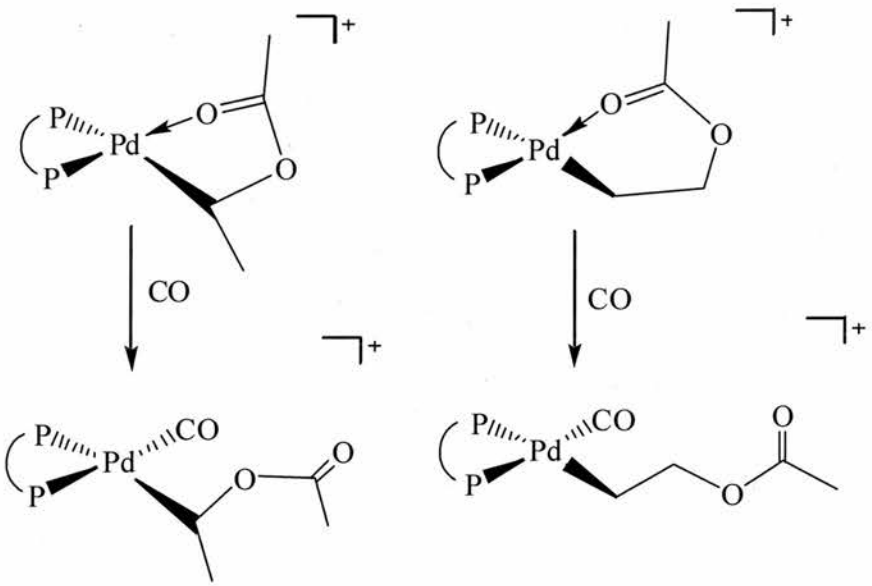


Figure 3.5 - Effect of CO pressure on the b:l ratio of the methoxycarbonylation of vinyl acetate Reaction conditions: $[Pd_2(dba)_3]$ (0.05 mmol), DTBPMB (0.5 mmol), vinyl acetate (2 cm^3), MeOH (11 cm^3), and MSA (0.5 mmol), temperature = 80 °C, reaction time = 3 hours.

The increase in CO pressure leads to a decrease in the b:l ratio of the system.

In the methoxycarbonylation of vinyl acetate it is possible that the branched product is favoured due to the carbonyl oxygen in the palladium-alkyl being able to chelate to form a ring (Scheme 3.4). If the branched isomer is formed, a 5-membered ring is formed but it is the 6-membered ring for the linear isomer. As the 5-membered ring is more stable this leads to a preference in the regioselectivity towards the branched

product. If this mechanism were crucial to the regioselectivity it would be expected that if the chelate ring were unable to form then the regioselectivity towards the branched isomer would decrease. For this chelate ring to form there must be a free coordination site on the palladium for the carbonyl oxygen. As the CO pressure increases there is greater competition between CO coordination and the chelate ring formation. As the CO coordination becomes more preferential at higher pressures the b:l ratio decreases.



Scheme 3.4 – Disruption of stabilising chelate due to increased CO pressure

3.3.4 Effect of time with 1,2-bis(di-*tert*-butylphosphinomethyl)benzene

One interpretation of the data in Figure 3.4 is that the b:l ratio decreases as the conversion increases. In order to test this, the catalysis reaction with DTBPMB was carried out for nine hours to see if the branched: linear selectivity changed compared with a reaction carried out under identical conditions but for three hours. The results can be seen in Table 3.4. There is little difference in the regioselectivity as the difference in percentage selectivity is only 0.3 %. This suggests that the fall off in

regioselectivity with increasing temperature is genuinely related to the temperature rather than the conversion.

Table 3.4 – Effect of time on the methoxycarbonylation of vinyl acetate. Reaction conditions: $Pd_2(dba)_3$ (0.05 mmol), DTBPMB (0.5 mmol), MSA (0.5 mmol), MeOH (11 cm^3), VAM (2 cm^3), acid (0.5 mmol), temperature = 25 °C, reaction time = 3 hours.

Time (hours)	Conversion of vinyl acetate (%)	Selectivity to esters (%)	Selectivity to branched ester (%)	b:l
3	35	100	78.3	3.6
9	58	100	78.0	3.5

3.3.5 Effect of acid type

To determine if the acid type affects the catalysis the methanesulphonic acid was replaced with hydrochloric acid. A diethyl ether solution of the acid was used and the results can be seen in Table 3.5. As can be seen there is no effect on the selectivity to the branched isomer. However there is a reduction in the conversion of the vinyl acetate which could be due to the coordination of chloride ions to the palladium which blocks free coordination sites and as a result either vinyl acetate or carbon monoxide are unable to coordinate and thus the rate of reaction is reduced.

Table 3.5 – Effect of acid type on the methoxycarbonylation of vinyl acetate. Reaction conditions: $Pd_2(dba)_3$ (0.05 mmol), DTBPMB (0.5 mmol), MeOH (11 cm^3), VAM (2 cm^3), acid (0.5 mmol), temperature = 25 °C, reaction time = 3 hours.

Acid	Conversion of vinyl acetate (%)	Selectivity to esters (%)	b:l
MSA	35	100	3.6
HCl	6	100	3.6

3.3.6 Addition of PEt_3 as a co-catalyst

As the reaction solution cannot be acidic or too basic, PEt_3 was added in an attempt to complex the acid and leave DTBPMB unprotonated so that it would be capable of chelating to any free palladium. Also this allowed the increase of the acid concentration without increasing the amount of expensive DTBPMB. There was no reaction in either of the two experiments attempted. This suggests that PEt_3 binds to the vacant sites on the palladium and inhibits the catalysis. The reaction conditions are summarised in Table 3.6.

Table 3.6 - Summary of reaction conditions with PEt_3 as a co-catalyst. $[Pd_2(dba)_3]$ (0.05 mmol), DTBPMB (0.4 mmol), MeOH (23 cm^3), VAM (2 cm^3), MSA (27µl. 0.4 mmol). CO atmospheric pressure with constant supply temperature = 25 °C.

Pd (mmol)	DTBPMB (mmol)	MSA (mmol)	PEt_3 (mmol)
0.1	0.4	0.4	0.4
0.1	0.4	1.0	1.0

3.3.7 Optimisation of reaction conditions for DTBPMB

As shown in sections 3.3.1 - 3.3.3 the b:l ratio can be improved by the use of lower temperatures and lower CO pressures. In our hands the maximum branched to linear ration obtained of 3.6:1 with a conversion of 35 % using the following conditions: $Pd_2(dba)_3$ (0.05 mmol), 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (0.5 mmol), MSA (0.5 mmol), temperature = 25 °C and CO pressure = 3 bar.

Some additional experiments were carried out by Graham Eastham at Lucite International. Working at lower palladium concentrations he studied the effect of acid

concentration and of the addition of polyvinyl pyrollidone (PVP), which stabilises colloidal palladium stopping further aggregation and the resulting precipitation of palladium. The results can be seen in Table 3.7. Although direct conclusions are difficult because the set of experiments is incomplete, a comparison of entries 2 and 3, where there is an increased palladium and PVP concentrations causes a slight rate decrease with no change in selectivity. This may suggest that PVP inhibits the reaction as the reaction rate is first order in palladium concentration but doubling the palladium concentration certainly does not double the rate. A comparison of entries 1 and 3 shows that the rate decreases when PVP concentration is increased, thus probably masking the effect of DTBPMB concentration at least under these conditions. As the acid concentration was increased (entries 3-5) there was little effect on the reaction rate but the b:l ratio increased to a maximum level of 5:1 when the Pd:DTBPMB:MSA ratio was 1:5:10. The effect of the acid concentration will be discussed in section 3.4.3.

Table 3.7 – Large scale reaction condition optimisation work carried out by Lucite International. Reaction conditions: Vinyl acetate (50 cm^3), MeOH (300 cm^3), CO pressure = 10 bar, temperature = 100 °C, reaction time = 3 hours. Rate = (moles of product produced (mol of Pd)$^{-1}$ hr^{-1}).

$Pd_2(dba)_3$ (mmol)	DTBPMB (mmol)	MSA (mmol)	PVP (g)	VAM conversion (%)	Rate	b:l
0.050	0.25	0.25	0	83	5630	2.5:1
0.025	0.5	0.25	0.34	66	4488	2:1
0.050	0.5	0.25	1.35	60	4070	2:1
0.050	0.5	0.50	1.35	55	3730	3:1
0.050	0.5	1.00	1.35	60	4070	5:1

3.4 Derivatives of DTBPMB

Phosphines that are coordinated to metals exert both a steric and electronic effect on the metal. The effect of a particular ligand on the metal centre can be predicted by an examination of its structure. This approach also allows the rational design of ligands to bring about a certain change in the catalysis.

To determine what makes the DTBPMB ligand such an active catalyst various derivatives of the DTBPMB ligand were designed and synthesised. Two different aspects were investigated; 1) the backbone of the ligand was altered and 2) the substituents on the phosphorus atoms were varied.

The effect of changing the backbone changes the natural bite angle of the ligand. This parameter was defined by Casey and Whiteker[3] in 1990 as the chelation angle that is preferred between P-M-P. This angle is calculated using molecular mechanics and only takes into consideration the influence of the ligand backbone with no effect from electronic preferences from the metal. The effect of backbone chain length upon natural bite angle for a series of bis(diphenylphosphino)alkanes is shown in Table 3.8.

Table 3.8 – Natural bite angle of the bis(diphenylphosphino)alkane series of ligands[4]

Ligand	No of C atoms in backbone	Bite angle
DPPE	2	79°
DPPP	3	87°
DPPB	4	99°

As the number of carbon atoms of a diphosphine is increased the natural bite angle increases.

Another parameter of possible importance in catalytic reactions is the cone angle which was introduced by Tolman[5] in 1977. It is defined as the angle that is subtended from the coordinating metal when a cone is drawn that takes in all of the steric bulk of the ligand under coordination (Figure 3.6). As the steric bulk of the R increases the cone angle also increases (Table 3.9).

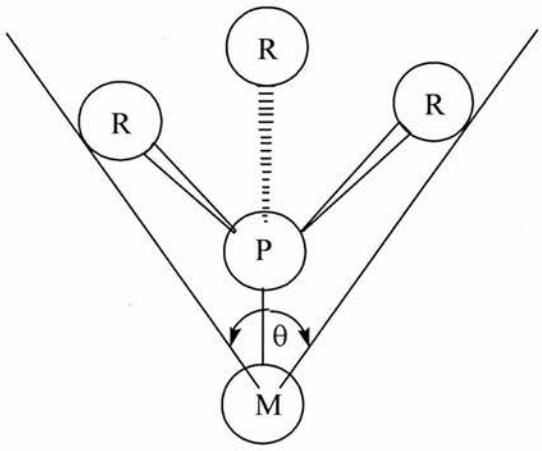


Figure 3.6 – Definition of the Tolman angle

Table 3.9 – Effect of R group on cone angle for tertiary posphines[5]

R group	Cone angle
Me	118°
Et	132°
Ph	145°
^{i}Pr	160°
^{t}Bu	182°

For a diphosphine a useful parameter is the pocket angles which were defined by Baron *et. al.*[6] in 1996. The pocket angle is the interior cone angle of a chelating diphosphine.

However for each diphosphine there are two pocket angles; the parallel angle (?¡) and the perpendicular angle (?-) (Figure 3.7). ?¡ is defined as the angle that is subtended between 2 planes perpendicular to the PdP_2 plane meeting at the metal and just touching the extremities of the ligand. ? is the angle subtended between 2 planes parallel to the P2 vector. The pocket angle can be used to visualise the volume of the coordination sphere that remains for occupation by other coordinating groups. The effect of changing the alkyl groups on 1,2-bis(dialkylphosphino)ethane can be seen in Table 3.10.

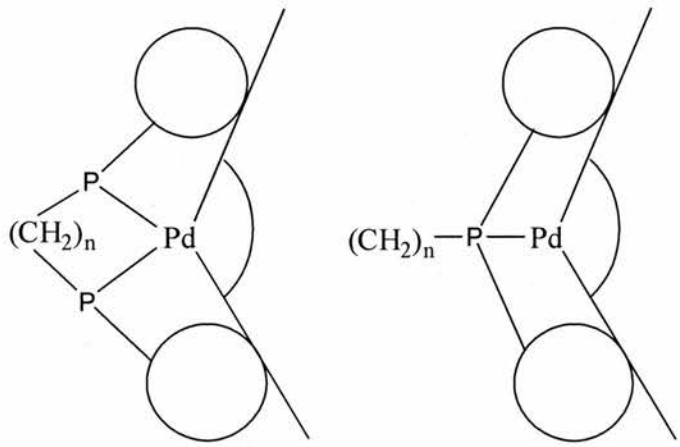


Figure 3.7 – Definition of pocket angles

Table 3.10 – Effect of R groups on the phosphorus atoms of diphosphines on the pocket angles

Ligand	?¡	?-
dmpe	141°	174°
dppe	132°	129°
dcpe	106°	115°

This parameter is useful as the smaller the pocket the greater the steric interactions between the phosphine and the other coordinated moieties. This may influence the reactivity of a particular complex i.e. if there are two different molecules that could coordinate, the smaller one would preferentially coordinate if the pocket angle is small. In the methoxycarbonylation of vinyl acetate the regioselectivity of reaction is

determined at the point of hydride migration onto the palladium bound alkene. The two different alkyl groups produced have widely different steric bulk. For the linear product, the α–carbon is bonded to the palladium, two hydrogen atoms and the remainder of the molecule. For the branched isomer the α–carbon is bonded to the palladium, one methyl group, one hydrogen atom and the remainder of the molecule (Figure 3.8). If the pocket angle is small there will be less of an interaction between the linear-alkyl and the diphosphine making this the preferred route.

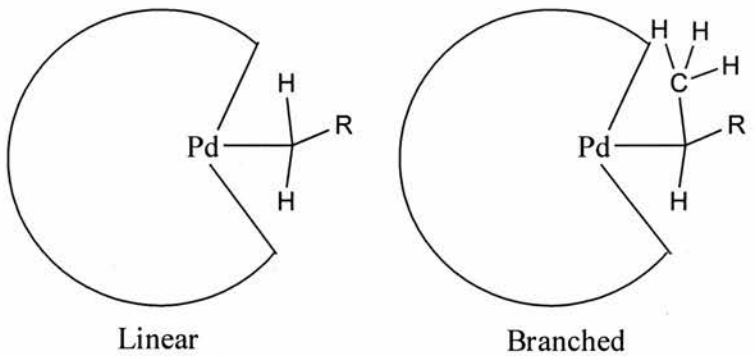


Figure 3.8 – Steric interactions between the alkyl species and the diphosphine

As a high branched selectivity is required for the methoxycarbonylation of vinyl acetate it would be expected that if the pocket angle of the diphosphine is increased the selectivity of the catalysis would improve.

The other influence of a bound phosphine or another coordinated ligand is electronic. A phosphorus atom is a good s-donor and π–acceptor of electrons. The greater the electron donating power of the substituents that are attached to the phosphorus atom the more the phosphorus can donate s-electron density to the coordinated metal. This can have a great effect on the catalysis by making the metal more or less basic. The stability of catalytic intermediates can be manipulated by correct control of the electron density

on the metal. There are several general rules that can be used to gauge the electron donating power of a phosphine. The atom that is attached to the phosphorus atom needs to be examined:

1) The electron donating power increases in the following order N>C>O

2) For carbon substituents the electron donating power increases; aromatic C < 1° alkyl < 2° alkyl < 3° alkyl eg. $PPh_3 < PMe_3 < P^iPr_3 < P^tBu_3$

3) For the same carbon type the greater the number of carbon atoms the greater the electron donating power eg. $P(CH_3)_3 < P(CH_2CH_3)_3 < P(CH_2CH_2CH_3)_3$

Using these rules an indication of the relative electron donating power of a range of phosphines can be estimated. It is possible to obtain a semi-quantitative measure of the electron donating power of a phosphine by measuring the υ_{CO} of the nickeltricarbonylphosphine complex. The higher the wavenumber the higher the energy of the CO stretch which signifies a higher electron donating power. For diphosphines the υ_{CO} of $[Mo(CO)_4(P\text{-}P)]$ is measured. Examples of this are shown in Table 3.11.

Table 3.11 – Tables of ?$_{CO}$ stretch of $Ni(CO)_3L$ and $Mo(CO)_4(L_2)$ complexes indicating the relative electron donating power of the diphosphines.

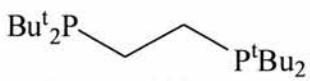
Ligand (L)	?$_{CO}$ of $Ni(CO)_3L$ (cm^{-1})[5]
P^tBu_3	2056.1
PMe_3	2064.1
PPh_3	2068.9
$P(OMe)_3$	2079.5

Ligand (L_2)	?$_{CO}$ of $Mo(CO)_4(L_2)$ (cm^{-1})[7]
$(C_2F_5)_2PCH_2CH_2P(C_2F_5)_2$	2064
$Et_2PCH_2CH_2PEt_2$	2012
dppe	2021

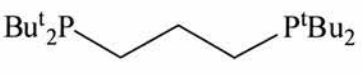
Keeping these different influences in mind different ligands were synthesised and their catalytic activity examined. The synthesis of the diphosphines are detailed in Chapter 3.

3.4.1 Changing the backbone

DTBPMB has a semi-rigid backbone as the central two carbons are aromatic. The effect of replacing the xylene by straight alkyl chains was studied. The following diphosphines were tested, 1,2-bis(di-*tert*-butylphosphino)ethane (DTBPE) **(109)**, 1,3-bis(di-*tert*-butylphosphino)propane (DTBPP) **(7)** and 1,4-bis(di-*tert*-butylphosphino)butane (DTBPB) **(110)**.



109



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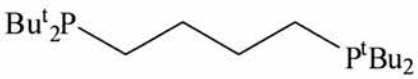

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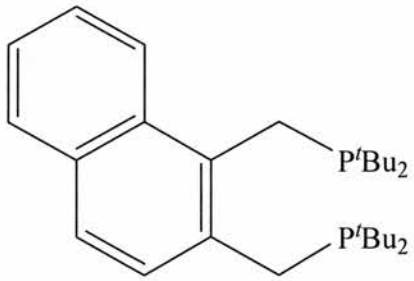
The results obtained are shown in Table 3.12. Ligand **109** produced no ester product but there was no degradation of the vinyl acetate showing that all of the acid was present as the phosphonium salt. The ligand (**110**) with the four carbon backbone produced only trace amounts of the ester product. However a considerable amount of vinyl acetate was degraded to MeOAc. This is surprising as there were enough phosphorus atoms present to bind all of the acid in the solution, and this should have

prevented vinyl acetate degradation. When DTBPP **(13)** was used there was nearly full conversion of the vinyl acetate with 100 % selectivity to the esters. Unfortunately the b:l ratio was only 0.79:1. Under the same reaction conditions with DTBPMB the b:l ratio is 1.2:1. Drent[8] has reported that the when ligand 13 with $[Pd(OAc)_2]$ was used in the methoxycarbonylation of vinyl acetate a b:l ratio of 2:1 was obtained. Drent used a reaction temperature of 75 °C and a CO pressure of 40 bar as opposed to 80 °C and 30 bar used in this study.

Table 3.12 – Methoxycarbonylation of vinyl acetate using bis(di-*tert*-butylphosphino)alkanes. Reaction conditions: $Pd_2(dba)_3$ (0.05 mmol), vinyl acetate (2 cm^3), MeOH (11 cm^3), and MSA (0.5 mmol)), CO pressure (30 bar), temperature = 80 °C, reaction time = 3 hours.

Ligand	Vinyl acetate conversion (%)	Selectivity to esters (%)	b:l
DTBPE **(109)**	100	0	N/A
DTBPP **(13)**	97	100	0.79:1
DTBPB **(110)**	70	2	0.87:1

Another modification to the backbone of DTBPMB is to keep the backbone primarily the same and to add extra aromatic rings to the xylene backbone. The ligands 1,2-bis(di-*tert*-butylphosphinomethyl)naphthalene (1,2-DTBPMN) **(111)** and the 2,3-bis(di-*tert*-butylphosphinomethyl)napthalene (2,3-DTBPMN) **(112)** were synthesised and employed in the catalysis.



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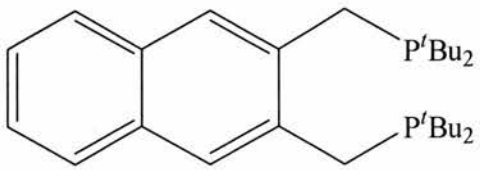


74

In the case of ligand **73** there are two slightly different phosphorus environments due to the unsymmetric aromatic system. The two ligands were tested in the methoxycarbonylation of vinyl acetate and the results, compared with those from DTBPMB can be seen in Table 3.13.

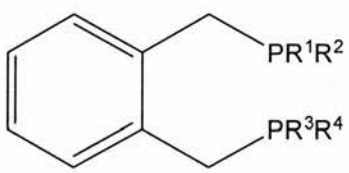
Table 3.13 – Methoxycarbonylation of vinyl acetate. Reaction conditions: $Pd_2(dba)_3$ (0.05 mmol), ligand (0.5 mmol), MSA (0.5 mmol), vinyl acetate (22 mmol), MeOH (11 cm^3), CO pressure = 3 bar, temperature = 25°C, reaction time = 3 hours

Ligand	Vinyl acetate conversion (%)	Selectivity to esters (%)	b:l
DTBPMB	35	100	3.6:1
1,2-DTBPMN	18	100	3.6:1
2,3-DTBPMN	15	100	3.6:1

The only difference between the benzene backbone ligand and the 2 napthalene ligands is that the conversion is slightly higher in the benzene case.

3.4.2 Changing the substituents on the phosphorus atoms

As previously discussed the other alteration that can be made to the architecture of a phosphine to change its influence on the metal is to vary substituents on the phosphorus atoms. In the modifications shown so far only the backbone has been modified. To determine if the other two groups attached to each of the phosphorus atoms must be *tert*-butyl groups the DTBPMB ligand was modified. The following ligands were either synthesised or obtained and were tested in the methoxycarbonylation of vinyl acetate.



R groups		
$R^1=R^2=R^3=R^4 = {}^t\text{Bu}$	DTBPMB	**(7)**
$R^1=R^2=R^3=R^4 = \text{Cy}$[1]	DCPMB	**(113)**
$R^1=R^2=R^3=R^4 = {}^i\text{Pr}$	DIPPMB	**(64)**
$R^1=R^2=R^3=R^4 = \text{Ph}$	DPPMB	**(65)**
$R^1=R^2=R^3=R^4 = \text{Et}$	DEPMB	**(66)**
$R^1=R^3= {}^t\text{Bu}$, $R^2=R^4 = {}^i\text{Pr}$	TBIPPMB	**(70)**
$R^1=R^3= {}^t\text{Bu}$, $R^2=R^4 = {}^i\text{Pr}$	*rac*- TBIPPMB	**(71)**
$R^1=R^3= {}^t\text{Bu}$, $R^2=R^4 = {}^i\text{Pr}$	*meso*-TBIPPMB	**(72)**
$R^1=R^2= {}^t\text{Bu}$, $R^3=R^4 = {}^i\text{Pr}$	Bu_2-Pr_2-XYL	**(114)**
$R^1=R^2= R^3= {}^t\text{Bu}$, $R^4 = {}^i\text{Pr}$	BuPr-Bu_2-XYL	**(115)**

1 – BP Chemicals are thanked for a sample of DCPMB

Table 3.14 - Methoxycarbonylation of vinyl acetate. Pd (0.1 mmol), ligand (0.5 mmol), MSA (0.5 mmol), vinyl acetate (22 mmol), MeOH (11 cm^3), CO = 3 bar, temperature = RT, reaction time = 3 hours

Ligand	Substituents on P	Conversion of vinyl acetate (%)	Selectivity to esters (%)	b:l
DTBPMB **(7)**	$^tBu_4$	35	100	3.6:1
DCPMB[†] **(113)**	Cy_4	100	0	N/A
DIPPMB **(64)**	$^iPr_4$	100	0	N/A
DPPMB **(65)**	Ph_4	100	0	N/A
DEPMB **(66)**	Et_4	100	0	N/A
TBIPPMB **(70)**	$^tBu_2{}^iPr_2$	7	100	0.8:1
rac- TBIPPMB **(71)**	$^tBu_2{}^iPr_2$	8	100	0.8:1
meso-TBIPPMB **(72)**	$^tBu_2{}^iPr_2$	7	100	0.8:1
103	$^tBu_2{}^iPr_2$	47	28	1.4:1
115	$^tBu_3{}^iPr$	13	85	2.0:1

To determine the level of s-donation of the different diphosphines the $[Mo(CO)_4(L)]$ complex was synthesised for a range of the diphosphines. The complexes of **7**,**73**,**74**,**113**,**64** and **70** were obtained and the IR spectrum of the complexes were recorded in dichloromethane and the spectrum of $[Mo(CO)_4$**113**$]$ in dichloromethane is shown in Figure 3.9.

[†] BP Chemicals are thanked for a sample of DCPMB.

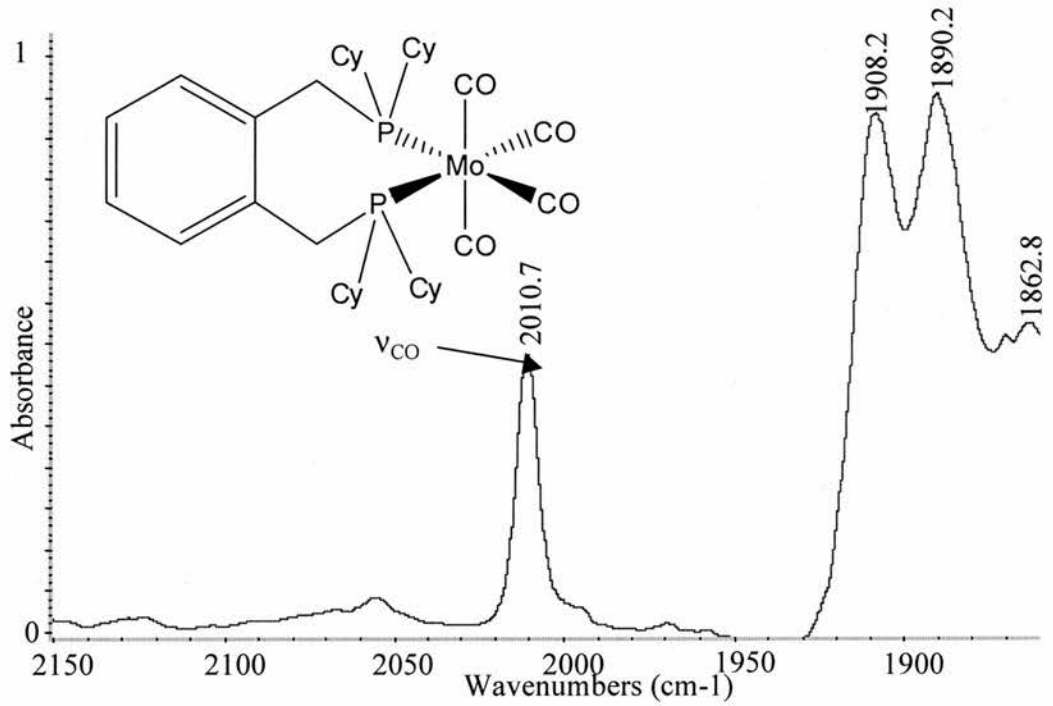


Figure 3.9 – FTIR spectrum of [Mo(CO)$_4$**113**] in CH_2Cl_2

The position of the ν_{CO} for the complexes prepared can be seen in Table 3.15.

Table 3.15 - $\bar{\nu}_{CO}$ stretch of [Mo(CO)$_4$L] recorded in dichloromethane

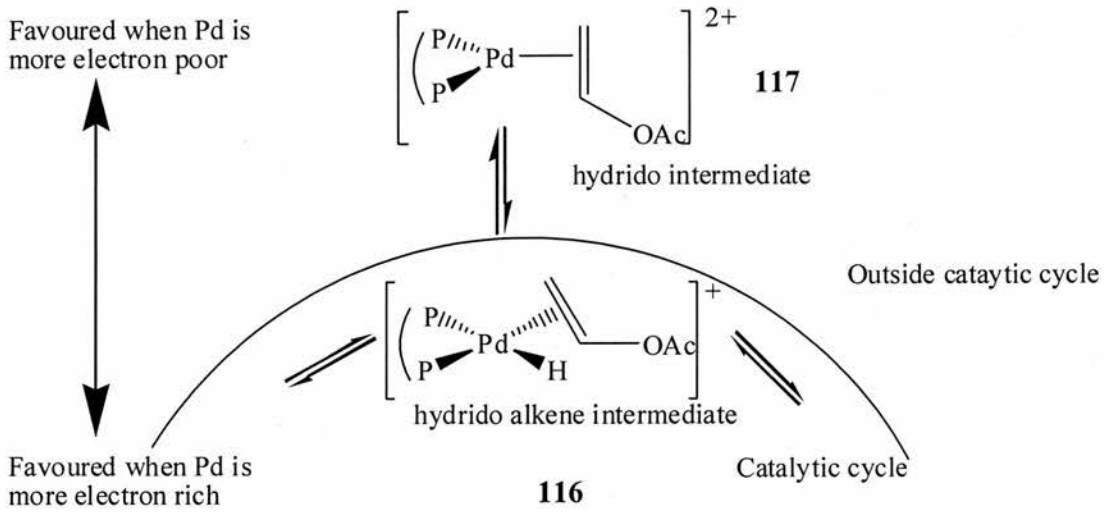
L	$^{-}\nu_{CO}$ (cm^{-1})
64	2019[6]
70	2013
113	2010
73	2008
74	2008
7	2006

It can be assumed that ligands **103** and **115** have an overall electron donating ability between DTBPMB and DIPPMB. This is due to the substituents attached to the phosphorus atoms. The lower the value of ν_{CO} for [Mo(CO)$_4$L] the more electron

donating the diphosphine is to the metal. If the three tetra-*tert*-butyl ligands (**7**, 73, 74) are compared it can be seen that the two napthalene derivatives are slightly less electron donating than the diphosphine with the benzene backbone ligand. This is due to the larger aromatic system on the backbone which removes electron density from the phosphorus atoms and hence from the complex. The differences are very small, however, because of the insulating effects of the methylene groups.

If the catalytic results in Table 3.13 and Table 3.14 are examined it can be seen that as the electron donating power of the diphosphine increases the reaction rate, the selectivity to the esters and the b:l ratio all increase.

The increased rate of the reaction could be due to the equilibrium between the hydrido **(116)** and non-hydrido alkene **(117)** catalytic species (Scheme 3.5). As the electron density on the metal increases the hydrido side of the equilibrium is favoured ensuring that more of the Pd is in the catalytic cycle rather than in the unprotonated resting state. Another way of looking at this is that when less electron donating groups such as phenyl are employed protonation is harder and less Pd is in the catalytic cycle and hence the effective catalyst concentration is reduced.



Scheme 3.5 – Equilibrium between hydrido and hydrido-alkene intermediates removing Pd from the catalytic cycle.

The improved selectivity to the esters is due to the increased basicity of the phosphine. As the phosphine basicity increases the acid more readily reacts with the phosphine and ensures that the acid is not present to promote the degradation of the vinyl acetate.

On first inspection it would be expected that the regioselectivity might be controlled by the steric influences exerted by the ligand. The formation of the palladium-alkyl species is by the process of the migration of a hydride onto the palladium bound alkene. This process can form one of two isomers, the linear and the branched. As the branched isomer has more steric bulk it would be expected that in a crowded coordination sphere this would be the sterically unfavoured product. The cone-angle of each of the phosphorus atoms increases with increased electron density (except DPPMB **65**), due to the steric bulk of the alkyl groups bonded to phosphorus atoms, and as a result the pocket angle decreases. However the DTBPMB (**7**) ligand gave the best b:l ratio for the

series of ligands tested. The suggests that the b:l ratio is not primarily influenced by steric effects.

As the degree of branched product increases with increased electron donating power it can then be reasoned that the regiochemical control of the catalytic cycle is electronic. As the electron density on the palladium is increased due to the greater s-donation from the phosphine the more stable alkyl complex will be the one that is better able to reduce the electron density on the metal. For vinyl acetate, the preferred alkyl will be the branched isomer as the acetate group can reduce the electron density due to a stabilising resonance. This is the opposite effect from that expected from alkyls derived from propene where the linear isomer is preferred over the branched. This is because a primary carbanion is more stable than a secondary carbanion.

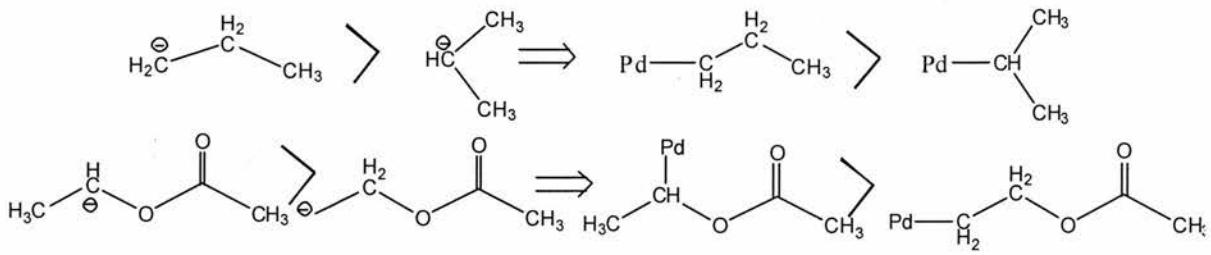
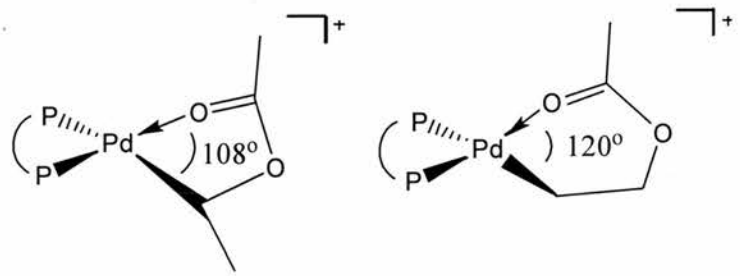


Figure 3.10 – Relative stabilities of various carboanions

The decrease in branched selectivity occurs when both the pocket angle and σ–donation decreases. As it would be expected that the small pocket angle is trying to force the catalysis to produce a linear product it seems that for the vinyl acetate the electronic factors are more important and as a result the branched alkyl is usually produced preferentially, but this effect will be amplified for the more electron donating.

Another possible explanation for the increase in the branched isomer formation as the pocket angle decreases may be that the carbonyl oxygen in the palladium-alkyl is able to bind to the palladium to form a chelate ring. For the branched isomer a 5-membered ring would be formed and a 6-membered for the linear isomer. Using the angles of geometric shapes the branched isomer ring will have an internal angle of 108° and the linear isomer will have an angle of 120°. In the linear case there may be an increase in steric interactions close to the coordination sphere between the ring and the ligand, and as a result this leads to a more sterically unstable isomer.



If the chelate does form then a further consideration is the relative stability of the two different rings. The branched isomer will be favoured due to the formation of the more stable 5 membered ring and hence there will be a preference for the formation of the branched isomer.

3.4.3 Effect of acid concentration on the methoxycarbonylation of acid

As shown in section Chapter 3 vinyl acetate is unstable towards methanolysis particularly in the presence of either acid or base. This reaction requires acid (we use MSA) to work successfully, but the degradation can be inhibited if the diphosphine is in excess over the MSA. In this case, the acid required for the catalytic cycle is presumably $[(^{t}Bu_2P(H)CH_2)]_2C_6H_4]^{2+}$ or possibly a protonated unidentate diphosphine.

As the successful catalysis system uses the strong acid methane sulphonic the effect of acid concentration on the catalytic system was examined. The results can be seen in Figure 3.11 and Figure 3.12.

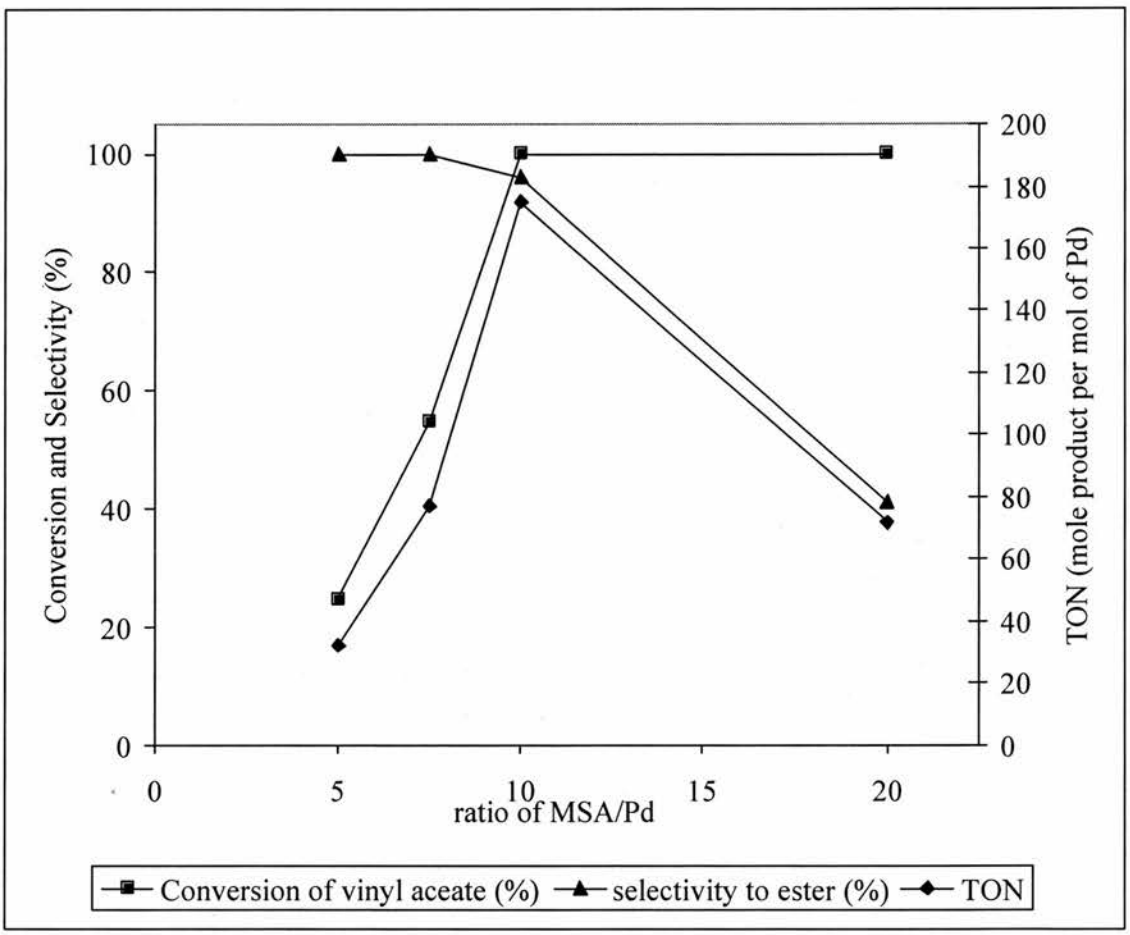


Figure 3.11 – Graph of effect of acid concentration on the rate and selectivity of the methoxycarbonylation of vinyl acetate. Reaction conditions: $Pd_2(dba)_3$ (0.1 mmol), 1,2-DTBPMN (0.5 mmol), vinyl acetate (22 mmol), MeOH (11 cm^3), CO pressure = 3 bar, temperature = 25 °C, reaction time = 3 hours

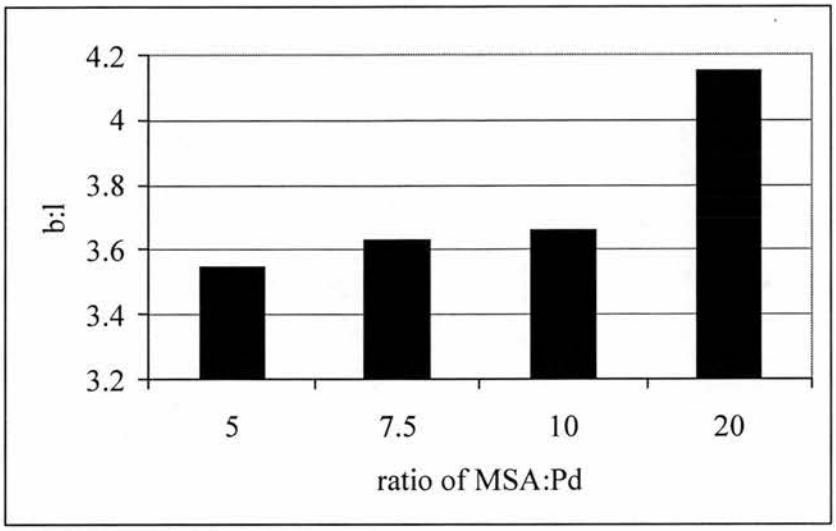


Figure 3.12 - Graph of effect of acid concentration on the selectivity of the methoxycarbonylation of vinyl acetate. $Pd_2(dba)_3$ (0.1 mmol), 1,2-DTBPMN (0.5 mmol), vinyl acetate (22 mmol), MeOH (11 cm^3), CO pressure = 3 bar, temperature = 25 °C, reaction time = 3 hours.

As can be seen in Figure 3.11 there is an optimum acid concentration with regards to the number of turnovers of vinyl acetate that produce ester product. As the acid concentration is increased there is an increase in rate until the maximum rate at a Pd:MSA ratio of 1:10 is reached. After this the TON decreases dramatically. The decrease in TON is not due to the decrease in the rate of methoxycarbonylation but is due to the removal of vinyl acetate from the system due to the degradation process. It can be assumed that as the solvent system becomes more acidic the rate would increase.

At the point of maximum TON there are also the first signs of vinyl acetate degradation. Assuming all the palladium is coordinated by diphosphine any uncoordinated phosphine reacts in a stoichiometric ratio with the acid and the number of moles of each of the different species present is shown in Table 3.16. It must be noted that every mole of

phosphine can react with two moles of acid due to its diphosphine nature. The first point where vinyl acetate degradation is observed is where there is not enough phosphine to tie up the acid as the phosphonium salt. This is a clear indication of how sensitive the vinyl acetate is to acidic medium.

Table 3.16 – Quantities of different species present in reactor solution with different quantities of acid added. Pd = 0.1 mmol, 1,2-DTBPNM = 0.5 mmol

acid added (mmol)	phosphine-palladium complex (mmol)	phosphonium salt (mmol)	free phosphine (mmol)	free acid (mmol)
0.5	0.1	0.5	0.3	0
0.7	0.1	0.7	0.1	0
1.0	0.1	0.8	0	0.2
2.0	0.1	0.8	0	1.2

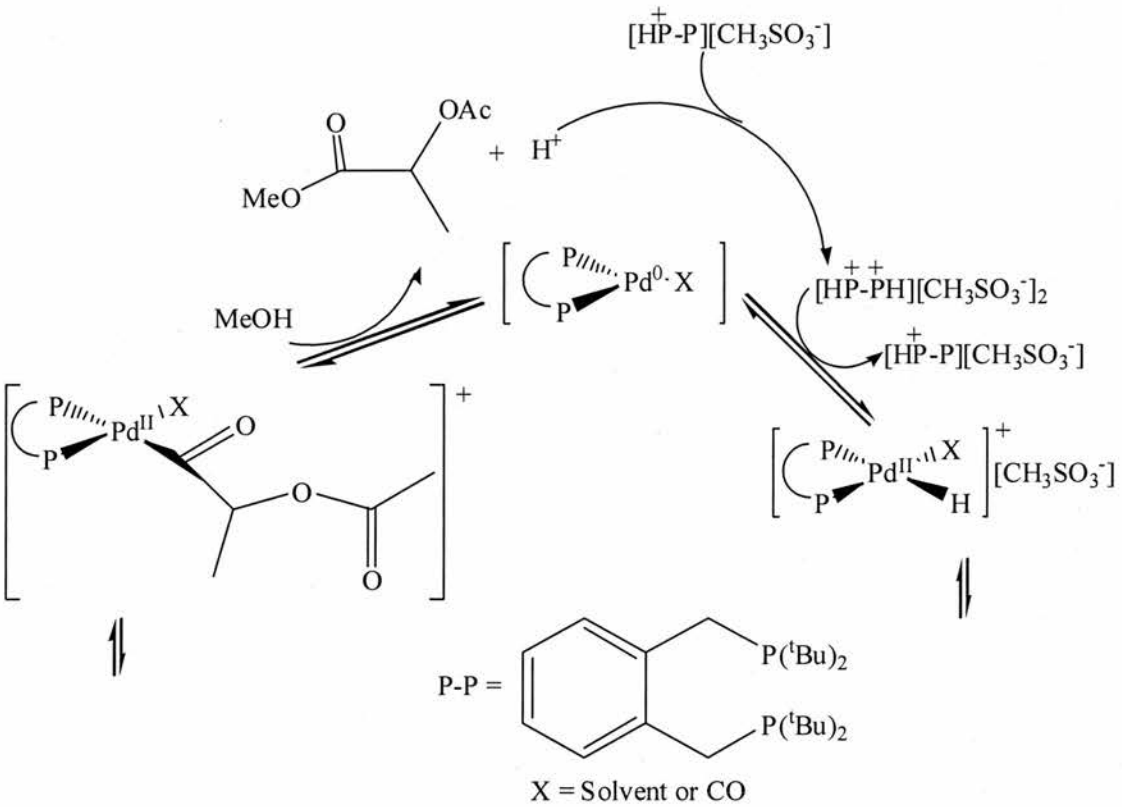
As seen in Figure 3.12 as the concentration of acid increases the branched to linear ratio also increases. This can be due to one of two things. The increased acidity of the reaction solution either 1) promotes the hydride migration on to only one carbon of the carbon-carbon double bond or 2) has a greater stabilising affect on the branched-palladium-alkyl intermediate than the linear isomer.

If the first scenario is considered, for increased selectivity to the branched product, there must be promotion of the hydride migration onto the terminal carbon atom and thus increased formation of the branched palladium-alkyl complex. As acid is included in the system it is possible that the carbonyl oxygen of the vinyl acetate is protonated and as a result increases the electron withdrawing nature of the acetate group. This increases the positive charge on the β–carbon atom and the migration of the hydride onto this carbon atom will be increased. As a result the selectivity to the linear ester will

increase. As the selectivity to the branched product increases with increased acid concentration it suggests that the carbonyl of the vinyl acetate is not protonated.

As seen in section 3.3.3 an increase in CO pressure increases the formation of the linear product. This effect is attributed to the breaking of the 5 membered chelate, which stabilises the branched palladium-alkyl intermediate. If the protonation of the carbonyl oxygen of the produced alkyl group does occur, this would inhibit the formation of the chelate ring as the protonated oxygen atom would be unable to bond to the palladium. However, this would increase the electron withdrawing nature of the protonated acetate group, which would further stabilise the negative charge on the carbon atom bonded to the palladium atom. This evidence suggests that the influence of greatest importance for determining the regioselectivity of the hydride migration is the stabilisation by the acetate group of the negative charge on the carbon atom of the alkyl bonded to the palladium.

The role of the MSA is primarily to act as a proton donor, promoting the formation of the hydride species in the catalytic cycle. However, the acid is not present as the free species but as the phosphonium salt (Section 3.1). For the hydride to be generated it must be possible for the salt to release a proton at the required time. This may be after the acyl species has undergone methoxide attack to release the product from the complex leaving the Pd in oxidation state = 0 [Pd(0)] and the salt is then capable of supplying a proton to reform the Pd(II) hydride species (Scheme 3.6).



Scheme 3.6 - Role of acid as a salt with phosphine - capable of protonating Pd(0) species.

The protons are also able to activate the MeOH before the nucleophilic attack of the acyl intermediate to liberate the product and reform the hydride species.

3.5 Kinetic studies

A limitation of the standard autoclaves used for routine catalyst testing is that the stirring employed is *via* a magnetic bead, which leads to the possibility of poor mass transport. If the reaction is fast and there is insufficient CO being dissolved into the reaction solution the results obtained can be misleading as side reactions may become more competitive. As the 1,2-bis(di-*tert*-butylphosphinomethyl)benzene system was working well the catalysis was performed on a microreactor that has mechanical stirring

capable of 1000 rpm and is able to operate under a constant gas pressure. The gas uptake during the reaction can be monitored and meaningful kinetics data obtained.

The reaction was carried out twice – at both 60 °C and 80 °C and a summary of the two runs are shown in Table 3.17.

Table 3.17 – Summary of reactions carried out at constant pressure. Reaction conditions - Pd (0.1 mmol), DTBPMB (0.5 mmol), vinyl acetate (1 cm^3), MeOH (1 cm^3), toluene (3 cm^3), CO pressure = 30 bar, temperature = 80 °C, reaction time = 3 hours

Temperature (°C)	Time (hr)	Conversion (%)	Selectivity to ester (%)	b:l
60	4	67.3%	49.2%	2.5
80	5	93.8%	54.3%	2.3

In summary it was found that at 60 °C the reaction was very slow and no kinetic analysis could be performed. However at 80 °C the reaction was clearly first order in vinyl acetate with a rate of $k = 1.7 \times 10^{-4}\ s^{-1}$.

As the best b:l ratios are obtained with low temperatures and low CO pressures a kinetic study of the methoxycarbonylation of vinyl acetate with Pd and 1,2-DTBPMN **(73)** was performed. As the microreactor used needs a minimum of 10 bar of gas in the reactor the CO was mixed with nitrogen in a ratio of 1:9 and the reactor pressurised to 10 bar thus making the pressure of CO in the reactor 1 bar. The reaction was run for 24 hours and the CO uptake measured after which the solution was analysed by GC and the results are shown in Table 3.18

Table 3.18 - Methoxycarbonylation of vinyl aceate under constant CO pressure. Reaction conditions – $Pd_2(dba)_3$ (0.05 mmol), 1,2-DTBPMN (0.5 mmol), MSA (0.5 mmol), vinyl acetate (2 cm^3), MeOH (11 cm^3), $CO:N_2$, 1:9 (10 bar)

Temperature (°C)	Time (hr)	Conversion (%)	Selectivity to ester (%)	b:l
25	24	63.5	67.2	3.4

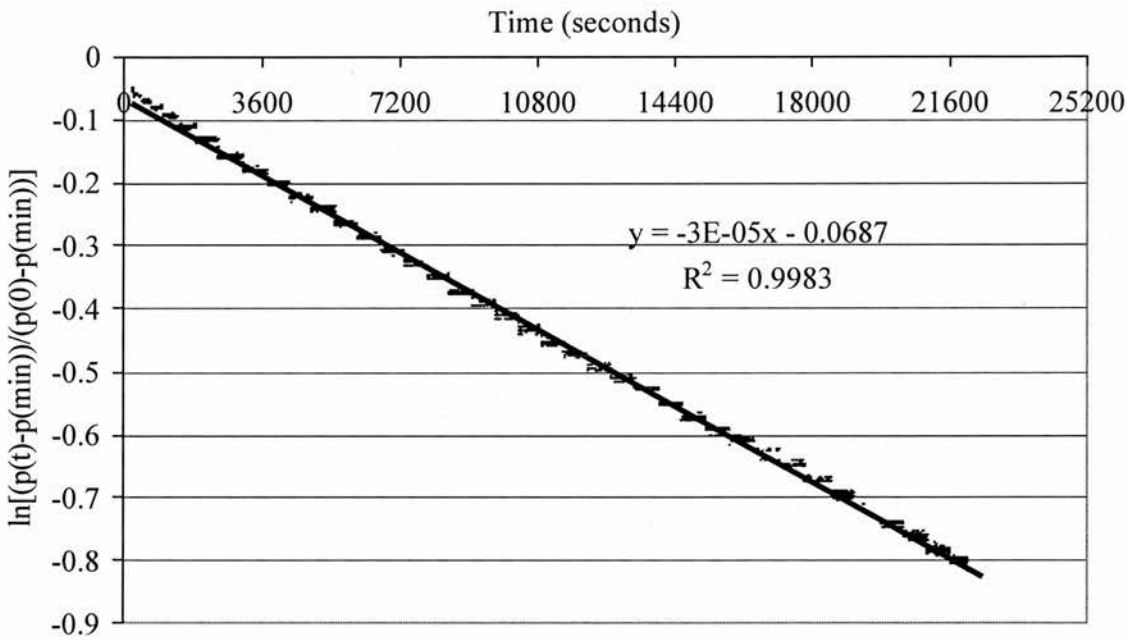


Figure 3.13 – Plot of $\ln[(p_t - p_{min})/(p_0 - p_{min})]$ vs time for the methoxycarbonylation of vinyl acetate under constant CO pressure conditions over the first 6 hours of the reaction. Reaction conditions: $Pd_2(dba)_3$ (0.05 mmol), 1,2-DTBPMN (0.5 mmol), MSA (0.5 mmol), vinyl acetate (2 cm^3), MeOH (11 cm^3), $CO:N_2$, 1:9 (10 bar), temperature = 25 °C.

After 24 hours 64 % of the vinyl aceate had been converted of which only 67 % had been converted to the ester product. The unexpected methanolysis reaction can be attributed to the long period that the reaction was carried out for. It may be possible

that any small quantities of oxygen in the system had oxidised the phosphine and as a result the acid was unable to form the phosphonium salt and then catalysed the vinyl aceate degradation. However kinetic rates can be extracted from the CO uptake data as the plot of $\ln[(p_t - p_{min})/(p_0 - p_{min})]$ vs time is a straight line over the first 6 hours (21600 s). This indicates that the reaction is first order in vinyl acetate over this time period. The gradient of this line gives the order of reaction which is $k = 0.00005\ s^{-1}$.

3.6 Mechanistic considerations

From the mechanistic studies that have been carried out on the DTBPMB system for the methoxycarbonylation of alkenes it has been shown that the catalytic cycle follows the hydride mechanism.[9-11] As palladium-hydrides are renowned for their instability it can be reasoned that the success of the DTBPMB system is due to the high degree of electron donation, which stabilises $[PdH(DTBPMB)X]^+$ (X = CO or VAM). If this is the only criteria that is necessary for a successful ligand it should be possible to carry out the catalysis with other electron rich ligands. However as shown in section 3.4.1 not all electron rich diphosphines are successful. DTBPE **(109)** showed no activity towards the methoxycarbonylation of vinyl acetate. This can be rationalised if the methanolysis of the palladium-acyl is considered which has been shown to be the rate determining step in the hydride catalytic cycle.[12] When the electron rich phosphines are used this will indeed be a slow step as the nucleophilic attack of either MeOH or methoxide on the electron rich acyl will be an energetically demanding reaction. For this step in the catalytic cycle to be speeded up the Pd metal centre must lose a considerable amount of its' electron density. As previously discussed in section 1.8.2 this can happen in one of two ways, either 1) the reductive elimination of methoxide

onto the acyl carbon to produce the product[13] or 2) the diphosphine can become unidentate, which will dramatically reduce the electron density on the metal making the acyl species susceptible to nucleophilic attack.[14]

In route 1 the first process is the breaking of the oxygen-hydrogen bond in the coordinated MeOH. This process is made easier if the oxygen-hydrogen bond is weakened. If the coordinated diphosphine is supplying electron density to the metal centre it would be expected that the oxygen-hydrogen bond would be stronger than if a less electron rich diphosphine is used. However the use of an excess of basic phosphine would promote the removal of the proton from the alcohol due to the phosphines action as a base. However it has been shown that the rate of reaction increases as the acidity of the reaction solution increases (section 3.4.3). If this proton loss process was happening there should be a negative effect on the rate as more acid is added.

If the second route is considered the fundamental difference between it and the first is the dissociation of one of the phosphorus atoms from the coordination sphere of the palladium prior to the methanolysis step. For this process to occur there must be some driving force to overcome loss of stabilisation due to the chelate effect. If DTBPMB and DTBPE are compared it would be expected that the 7 membered ring formed with the Pd and the DTBPMB ligand would break easier due to the higher stability of the 5 membered ring in the case of DTBPE. The driving force can originate from one of two places – either electronic effects of the other groups on the palladium or from some steric interactions between the various coordinated groups. The acyl group has a strong *trans* influence and as a result the Pd-P bond *trans* to the acyl will be longer and weaker than the other Pd-P bond *trans* to the coordinated solvent group. This does lead to an

inbuilt asymmetry in the molecule and there will be a natural point for the diphosphine to become unidentate. The x-ray crystal structure of [Pd{C(O)Me}Cl] has been reported and the Pd-P bond *trans* to the acyl group is 248.12 pm long compared to the Pd-P bond *trans* to the chloride which is 231.8 pm. This long bond is one of the longest palladium-phosphorus bonds known.[15]

Steric interactions seem to play an important role in the selectivity between either termination (production of an ester) or chain propagation (formation of an oligomer). The molecular mechanics calculations performed by Macgregor show that when there is a clear difference in reactivity between a $[Pd\{C(O)C_2H_5\}\{dppe\}CO]^+$ and $[Pd\{C(O)C_2H_5\}\{DTBPE\}CO]^+$.[16] In the dppe case ethene will coordinate to form a 5 coordinate species and which will presumably go on to form oligomers. However in the $[Pd\{C(O)C_2H_5\}\{DTBPE\}CO]^+$ case ethene does not want to coordinate as the activation energy is higher than the loss of one phosphine arm and the 3 coordinate species is more stable than the 5 coordinate species. This means that as soon as the electron density on the Pd drops due to phosphine arm loss, the methanolysis of the acyl group becomes fast and the acyl is quickly converted to ester, which immediately dissociates form the Pd, removing the steric strain allowing the diphosphine to rechelate and the Pd-hydride to form.

3.7 Summary

In the presence of either acid or base, vinyl acetate can react with methanol to form methyl acetate and 1,2-dimethoxyethane (the later is formed *via* acetaldehyde). It was found that in the presence of methanesulphonic acid (MSA), vinyl acetate was rapidly converted to the degradation products at both room and elevated temperatures. If triethylphosphine – which can act as a base – was added instead of the acid and found to be catalyse the vinyl acetate degradation. However, it was found that if 1,2-bis(di-*tert*-butylphosphinomethyl)benzene – the diphosphine ligand leading to high activity in the palladium catalysed methoxycarbonylation of ethene[17] – was present as the base there was no degradation of the vinyl acetate even at 80 °C. When either phosphine was present together with the acid (phosphine in excess), the vinyl acetate degradation did not occur.

A catalytic system prepared *in situ* from $[Pd_2(dba)_3]$, MSA and 1,2-bis(di-*tert*-butylphosphinomethyl)benzene, promotes the formation of the methyl esters of 2- and 3- acetoxypropanoic acid from vinyl aceate. The effects of ligand concentration, temperature and CO pressure were investigated. It was found that as the ligand and acid concentration were increased, the conversion of vinyl acetate increased and at Pd:Ligand:MSA ratio of 1:7.5:7.5, the conversion and selectivity to ester were both 100 %, when the reaction solution was heated to 80 °C under a CO pressure of 30 bar. Under these conditions the branched to linear (b:l) ratio was 1.2:1. As the temperature of the system was reduced the selectivity to the ester remained at 100 % with an expected drop in conversion. However, there was an improvement in the b:l ratio which at 25 °C was 3.3:1. Assuming a hydride mechanism is in operation this increase in

branched selectivity is rationalised by a higher activation energy for the migration of the hydride onto the vinyl acetate to form the alkyl complex which leads to the linear rather than the branched ester. As the temperature increases this activation energy becomes more accessible and there is an increase in the formation of the linear product. It was found that as the CO pressure was reduced, there was an improvement in the b:l ratio. This may be due to the formation of a chelate in the palladium-alkyl complex. The oxygen of the carbonyl group in the acetate is able to coordinate to the palladium. In the branched isomer a 5 membered ring is formed and a 6 membered ring in the linear complex. If this mechanism is in operation there may be a stabilisation of the palladium-alkyl due to the more stable 5 membered ring. As the CO pressure is increased there is competition for the fourth coordination site between the CO and the oxygen of the carbonyl group and as a result the chelate is broken and the stabilisation effect is lost. In our hands the optimal b:l ratio was obtained using the following conditions: $Pd_2(dba)_3$ (0.05 mmol), 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (0.5 mmol), MSA (0.5 mmol), temperature = 25 °C and CO pressure = 3 bar. Using these conditions the branched to linear ratio was 3.6:1 with a conversion of vinyl acetate of 35 % in 3 hours.

In the hydride mechanism – which is the accepted catalytic cycle – the mode of methanolysis is unclear. The most active catalyst system known uses the electron rich diphosphine 1,2-bis(di-*tert*-butylphosphinomethyl)benzene In this case the attack of methanol on the acyl group which liberates the ester product and regenerates the palladium-hydride seems difficult. One of the proposed mechanisms involves the uncoordination of one of the phosphine arms which will dramatically reduce the

electron density on the palladium and hence make the acyl group more susceptible to nucleophilic attack by the methanol.[18] As the phosphorus atoms in 1,2-bis(di-*tert*-butylphosphinomethyl)benzene are extremely electron rich they form a strong bond to the palladium which may inhibit the phosphine arm loss mechanism. If the electron density on the phosphorus atoms is reduced this may increase the rate of the methanolysis step and of the overall reaction rate. The high linear selectivity of 1,2-bis(di-*tert*-butylphosphinomethyl)benzene with substrates such as octene is due to the small pocket angle of the diphosphine. If the steric bulk on the phosphorus atoms were reduced this would increase the pocket angle and reduce the steric interactions between other coordinated groups. This might improve the b:l ratio for vinyl acetate methoxycarbonylation. With these two criteria in mind 1,2-$(R^1R^2PCH_2)C_6H_4$ ($R^1 = R^2 = {}^i$Pr; $R^1 = R^2$ = Cy; $R^1 = R^2$ = Et; $R^1 = R^2$ = Ph and $R^1 = {}^t$Bu, $R^2 = {}^i$Pr) were tested in the methoxycarbonylation and it was found that these diphosphines, except the mixed derivative, converted all of the vinyl acetate to MeOAc. The mixed diphosphine was basic enough to react with all of the acid so there was 100 % selectivity to the ester but only a conversion of 7 % with a b:l ratio of 0.8:1.

Assuming that the phosphine arm loss mechanism is in operation if one of that making one of the phosphorus atoms less electron rich would be slightly weaker and ease the loss of coordination. Keeping the degree of sigma electron donation of the phosphorus atoms as high as possible, unsymmetrical diphosphines may give improved rates. Using the conditions that gave the best b:l ratio using 1-di-*tert*-butylphosphinomethyl-2-di-*iso*-propylphosphinomethylbenzene and 1-di-*tert*-butylphosphinomethyl-2-*tert*-buty-*iso*-propylphosphinomethylbenzene were tested as ligands in the palladium catalysed

methoxycarbonylation of vinyl acetate. It was found that the b:l ratio was 1.4 and 2.0:1 respectively. However the selectivity to ester was only 28 and 85 % respectively. This was because the diphosphine was not acidic enough to react with all of the acid.

The backbone of the ligand was varied to see how a change in the bite angle of the diphosphine would affect the methoxycarbonylation of vinyl acetate. The aromatic backbone was replaced by an alkyl carbon chain to make $^{t}Bu_2P(CH_2)_nP^{t}Bu_2$ (n = 2, 3, 4). Drent has shown that, with the propane backbone derivative, the methoxycarbonylation of vinyl acetate is possible. We found that of these three ligands only the propane backbone gave conversion of the vinyl acetate to the esters. At 80 °C and with a CO pressure of 30 bar the conversion was 97 % with 100 % selectivity to the esters and a b:l ratio of 0.79:1.

An extra benzene ring was added on to 1,2-bis(di-*tert*-butylphosphinomethyl)benzene to give two isomeric diphosphines, 1,2-bis(di-*tert*-butylphosphinomethyl)naphthalene and 2,3-bis(di-*tert*-butylphosphinomethyl)naphthalene. At 25 °C and a CO pressure of 3 bar they gave 100 % selectivity to the esters in the methoxycarbonylation of vinyl acetate. However the conversions were only 18 and 15 % respectively, compared to 35 % for 1,2-bis(di-*tert*-butylphosphinomethyl)benzene under the same conditions. However under these low temperature and low pressure conditions the three ligands show the same regioselectivity with a b:l ratio of 3.6:1. This decrease in conversion could be due to the slight decrease in electron density on the phosphorus atoms due to the second electron withdrawing aromatic ring on the backbone.

3.8 Bibliography

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Chapter 4 - Experimental

All manipulations of air-sensitive materials were carried out in oven-dried glassware using standard Schlenk line and catheter tubing techniques under a dry, deoxygenated argon atmosphere. Argon was dried through a chromium(II)/silica glass column.

Solid and liquid chemicals were purchased from Aldrich, Acros, Avacodo and Strem and used as received. All gases were purchased from BOC.

Petroleum ether 40-60°, diethyl ether and THF were distilled over sodium dipheylketyl. Dichloromethane was distilled over calcium hydride and toluene was distilled over sodium. Vinyl acetate was distilled over calcium chloride and was stored at 0 °C in a flask wrapped in tinfoil to exclude light.

Proton, phosphorus and carbon NMR were recorded on a Varian 300, a Bruker 300 or a Varian 500 NMR spectrometer. NMR spectra were recorded on a Varian 300 spectrometer. ^{1}H and ^{13}C spectra were referenced internally to deuteriated solvents: $CDCl_3$ (^{1}H δ = 7.26 ppm, ^{13}C δ = 77.23 ppm), CD_2Cl_2 (^{1}H δ = 5.35 ppm, ^{13}C δ = 53.8 ppm). ^{31}P NMR were referenced to external 85 % H_3PO_4.

Infrared spectra were obtained using a Nicolet Avatar 360 FTIR spectrometer controlled *via* the OMNIC operating system.

Gas Chromatographic analyses were carried out on a Hewlett-Packard 5890 series gas chromatograph equipped with both a flame ionisation detector (GC-FID) (Quantitative analyses) and a Hewlett-Packard 5890 series mass selective detector for qualitative analyses. The gas chromatograph was interfaced with a Hewlett-Packard chemstation for the determination of peak areas by electronic integration. Both the GC-MS and GC-FID determination of products employed a Supeclo™ MDN-35 [bonded and

crosslinked, 35% phenyl / 65% methylpolysiloxane] fused silica capillary column 30 m x 0.25 mm x 0.25 μm film thickness. The carrier gas used was helium and the flow rate was 2.0 cm^3 min^{-1} and for the FID it was 2.3 cm^3 min^{-1}.

4.1 Stability of vinyl acetate in acid/base conditions

Four round bottom flasks containing a small magnetic stirrer bead were stoppered with a subaseal and had all oxygen removed by placing them under vacuum and filling with argon *via* a needle. Toluene (9 cm^3), MeOH (2 cm^3) and vinyl acetate (2 cm^3) were injected into the flask followed by the varying combination of methanesulphonic acid and phosphine. They were then heated to the required temperature and left stirring for 3 hours. Afterwards they were cooled and the sample taken for analysis.

4.2 Catalysis reactions

4.2.1 Example of a reaction in a high pressure autoclave

Tris(dibenzylideneacetone)dipalladium (45.7 mg, 0.05 mmol) was weighed into a Schlenk tube in a glove box along with 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (197 mg, 0.5 mmol). MeOH (6 cm^3) was added followed by methanesulphonic acid (32 μl, 0.5 mmol) and the mixture stirred until all the solid had dissolved. The resulting solution was transferred by cannula to a prepared autoclave with no glass liner. The Schlenk tube was rinsed with MeOH (5 cm^3) thus ensuring all of the catalyst was transferred. Vinyl acetate (2 cm^3) was added to the injector port and the entire autoclave was isolated and then pressurised to 20 bar with CO. The catalyst solution was heated to 80 °C. The injector port was pressurised to 25 bar with CO and the vinyl acetate was injected using the positive CO pressure. The pressure was then raised to 30

bar and the system sealed and left to stir for 3 hours. After this time the autoclave was placed in a bucket of ice to speed up cooling and once the solution temperature reached 0 °C the CO was slowly vented. The autoclave was then opened and the solution was stored in the freezer until being analysed.

4.2.2 Reaction in a Fischer-Porter Bottle

Tris(dibenzylideneacetone)dipalladium (45.7 mg, 0.05 mmol) was weighed into a Schlenk tube in a glove box along with 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (197 mg, 0.5 mmol). MeOH (6 cm^3) was added followed by methane sulphonic acid (32 µl, 0.5 mmol) and the mixture was stirred until all the solid had dissolved. The resulting solution was transferred by cannula to a Fischer-Porter bottle. Vinyl acetate (2 cm^3) was added to the Schlenk tube with MeOH (5 cm^3), which was then transferred by cannula to the Fisher-Porter. The Fischer-Porter bottle was filled with CO to a pressure of 3 bar, heated to the required temperature and stirred for three hours. As the pressure of the CO dropped more CO was introduced to ensure that the pressure never dropped below 2 bar. After 3 hours the Fisher-Porter bottle was cooled, slowly vented and opened and the solution was stored in the freezer until analysed.

4.2.3 Reactions in microreactor

Tris(dibenzylideneacetone)dipalladium (45.7 mg, 0.05 mmol) was weighed into a Schlenk tube in a glove box along with 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (197 mg, 0.5 mmol). MeOH (6 cm^3) was added followed by methane sulphonic acid (32 µl, 0.5 mmol) and the mixture was stirred until all the solid had dissolved. The resulting solution was syringed into the microreactor. The Schlenk tube was rinsed with

MeOH (5 cm^3) thus ensuring all of the catalyst was transferred. The reactor was then filled with N_2 to a pressure of 9 bar. The reactor was left at room temperature and vinyl acetate (2 cm^3) was added to the injection port located directly above the reactor. The ballast vessel was pressurised with CO to a pressure of 25 bar and the mass flow controller was set to 10 bar. The vinyl acetate was injected into the reactor using the positive gas pressure of 1 bar (difference between reactor and mass flow controller setting). As the CO was consumed within the reactor the mass flow controller added CO to the vessel thus keeping the reactor pressure at 10 bar. As the CO was added from the ballast vessel the resultant drop in pressure was monitored. After the required time the reactor was slowly vented and opened and the solution was stored in the freezer until analysed.

4.2.4 Analysis of catalytic solutions

The catalytic solution was analysed as follows. The reactor solution was transferred with washing with MeOH to a volumetric flask (25 cm^3). An aliquot of the solution (100 µl) was added to a volumetric flask (1 cm^3) and a standard solution of 1-undecane (1.0 mmol L^{-1} solution in toluene) was added to dilute the solution to 1 cm^3. The sample was injected into a gas chromatograph with a FID detector where the temperature was held a 40 °C for 5 minutes, then raised at a rate of 20 °C min^{-1} for 24 minutes after which it was held at 260 °C for 24 minutes. The chromatograph was quantified using the peak from the added 1-undecane and the calibration graphs of the compounds of interest relative to 1-undecane.

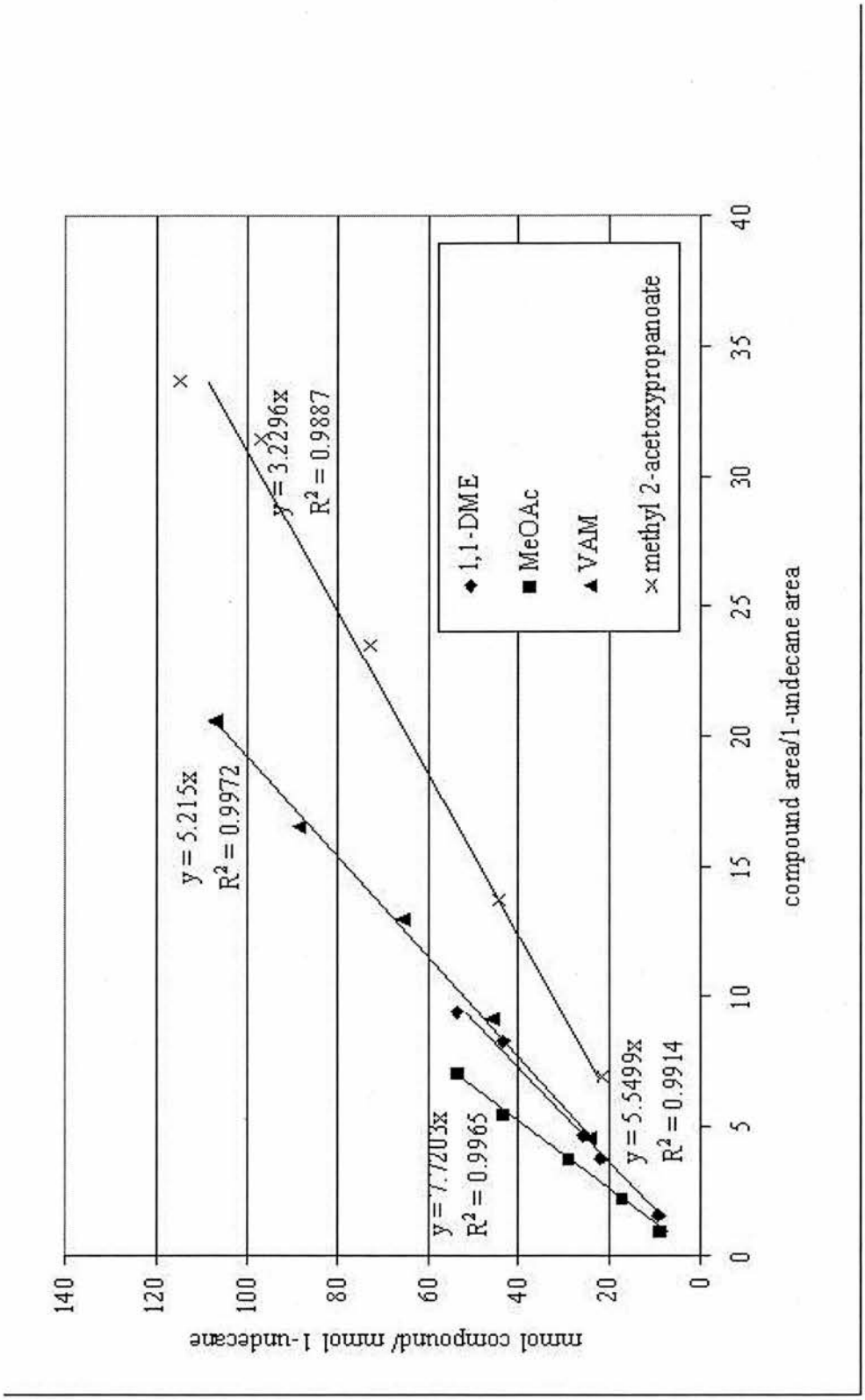
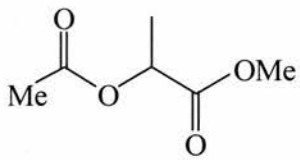


Figure 4.1 – Calibration graph of (mmol of compound/mmol of 1-undecane) against (peak area of compound/area of 1-undeane). Peak area from GC-FID chromatograph.

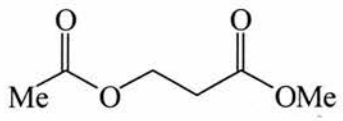
4.3 Unclassified organic compounds

4.3.1 Synthesis of (S)-methyl 2-acetoxy propanoate (1)



(S)-methyl 2-hydroxypropanoate (5.2 g, 50 mmol) was added to a solution of acetic anhydride (10 cm^3), triethylamine (10 cm^3) and 4-dimethylaminopyridine (DMAP) (0.5 g, 4 mmol) and the solution was stirred overnight. The product was extracted with diethyl ether (3 x 20 cm^3) and the combined organic phases washed with saturated sodium bicarbonate (2 x 20 cm^3). The organic phase was dried over magnesium sulphate and the diethyl ether and acetic anhydride removed *in vacuo* to leave (S) methyl 2-acetoxy propanoate which was purified by distillation. (1.31 g, 18 %). bp = 172 °C (Lit.[1] = 172 °C). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.56 (d, $^3J_{HH}$ = 6 Hz, 3 H, CHCH_3,), 2.21 (s, 3 H, C(O)CH_3), 3.82 (s, 3 H, OCH_3), 5.37 (quartet, $^3J_{HH}$ = 6 Hz, 1 H, C*H*CH_3,); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): 17.3 (s, C(*C*H_3)), 21.0 (s, *C*H_3C(O)), 52.6 (s, *C*H_3O), 68.8 (s, C(O)*C*(CH_3)O), 170.6 (s, *C*O), 171.5 (s, *C*O).

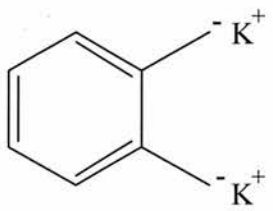
4.3.2 Preparation of methyl-3-acetoxypropanoate (2)[2]



β–propiolactone (1.5 g, 20 mmol) was added dropwise to a stirred solution of concentrated sulphuric acid (0.1 g) in acetyl chloride (4.87 ml, 68 mmol). The resulting solution was then heated under reflux for 20 minutes. After standing for 2 hours the remaining acetyl chloride was removed by distillation at atmospheric pressure. The residue was purified by short path distillation to yield the title product. (0.93 g, 32 %). bp = 89 °C (12 mmHg) (Lit.[3] = 81 °C (10 mmHg)). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 2.05 (s, 3 H, CH_3CO), 2.58 (tr, $^{3}J_{HH}$ = 7 Hz, 2 H, CH_2CH_2CO), 3.24 (s, 3 H, OCH_3), 3.85 (tr, $^{3}J_{HH}$ = 7 Hz, 2 H, OCH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): 21.1 (s, $CH_3C(O)$), 52.6 (s, CH_3O), 68.8 (s, $C(O)C(CH_3)O$), 170.3 (s, CO), 171.6 (s, CO).

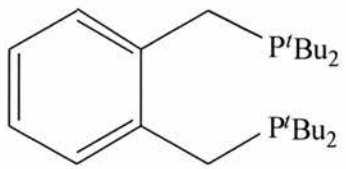
4.4 Synthesis of phosphine ligands

4.4.1 Synthesis of xylene-α,α'-diyl dipotassium $[K_2(C_8H_8^{2-}]^4$ (63)



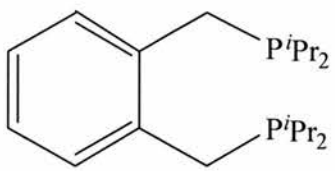
Dry and degassed *o*-xylene (5.00 g, 47.2 mmol) was mixed with petroleum ether 40-60° (150 cm^3) before adding potassium *tert*-butoxide (10.56 g, 94.3 mmol. The solution was cooled to –78 °C and *n*-butyl lithium (1.6 M in hexane, 60 ml, 94.3 mmol) was added. The flask was then allowed to warm to room temperature and the solution was heated under reflux for 1 hour. Once cooled the solution was filtered and the brick red residue was washed with petroleum ether 40-60°. The solid was then dried *in vacuo* and transferred to the glove box (8.61 g, 47.2 mmol, 100 %).

4.4.2 Synthesis of 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (DTBPMB) (7)[5]



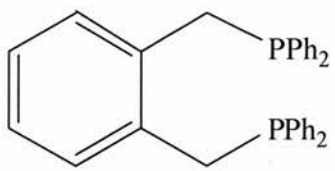
The dipotassium xylene salt **(63)** (2.52 g, 13.8 mmol) was dissolved in dry degassed diethyl ether (60 cm^3) and cooled to –78 °C. Di-*tert*-butylchlorophosphine (5.00 g, 27.6 mmol) was added slowly over a period of 10 minutes and the solution was allowed to warm to room temperature before stirring for 16 hours. The solution was removed by filtration and the potassium chloride salt was washed with diethyl ether (2 x 30 cm^3). The combined diethyl ether fractions were reduced in volume *in vacuo* to leave a light yellow oil which was recrystallised from hot methanol yielding the title compound as a colourless solid. (560 mg, 10 %). mp = 73 – 74 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.13 (d, $^3J_{PH}$ = 11 Hz, 36 H, PCC*H*$_3$), 2.99 (d, $^2J_{PH}$ = 3 Hz, 4 H, ArC*H*$_2$P), 7.05 (m, 2 H, Ar*H*), 7.53 (m, 2 H, Ar*H*); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$, 298 K) δ = 28.7 (s, BzP^{t}Bu$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K) δ = 26.4 (d, $^1J_{PC}$ = 24 Hz, P*C*CH$_3$), 29.9 (d, $^2J_{PC}$ = 13 Hz, PC*C*H$_3$), 32.3 (d, $^1J_{PC}$ = 23 Hz, ArCH$_2$P), 125.2 (s, *ArH*), 130.8, (d, $^3J_{PC}$ = 14 Hz, *Ar*CH$_2$P), 138.7 (d, $^2J_{PC}$ = 10 Hz, *Ar*CH$_2$P).

4.4.3 Synthesis of 1,2-bis(di-*iso*-propylphosphinomethyl)benzene (DIPPMB) (64)



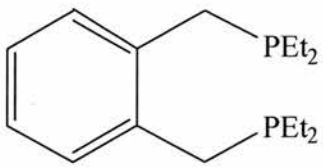
The dipotassium xylene salt **(63)** (2.86 g, 15.7 mmol) was dissolved in diethyl ether (100 cm^3) and cooled to –20 °C. Chlorodi-*iso*-propylphosphine (5 g, 32.7 mmol) was added slowly and the solution allowed to warm to room temperature after which was stirred overnight. The solution was removed by filtration and the potassium chloride salt was washed with diethyl ether. The diethyl ether was removed from the combined fractions *in vacuo* and the resulting oil was purified by distillation. (355 mg, 6 %) (Found: C, 69.11 %; H, 11.01 % Calc. for $C_{20}H_{36}P_2$: C, 70.96 %; H, 10.72 %). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.06 (dd, $^3J_{PH}$ = 12 Hz, $^1J_{HH}$ = 7 Hz, 12 H, PCHC*H*$_3$), 1.08 (dd, $^3J_{PH}$ = 12 Hz, $^1J_{HH}$ = 7 Hz, 12 H, PCHC*H*$_3$), 1.73 (m, 3 H, PC*H*CH$_3$), 3.05 (s, 4 H, ArC*H*$_2$P), 7.00 – 7.08 (m, 2 H, Ar*H*), 7.12 – 7.20 (m, 2 H, Ar*H*); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$, 298 K) δ = 5.2 (s, BzP^{i}Pr$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K) δ = 19.4 (d, $^2J_{PC}$ = 12 Hz, PCH*C*H$_3$), $^2J_{PC}$ = 19.7 (d, 13 Hz, PCH*C*H$_3$), 23.3 (d, $^1J_{PC}$ = 15 Hz, P*C*HCH$_3$), 27.9 (d, $^1J_{PC}$ = 8 Hz, ArC*H*$_2$P), 28.6 (d, ^{1}J$_{PC}$ = 8 Hz, ArC*H*$_2$P), 126.0 (s, *Ar*), 131.1 (s, *Ar*), 131.2 (s, *Ar*), 137.8 (s, *Ar*CH$_2$P); Accurate ES(+)-MS = 339.2365 (Calculated for $C_{20}H_{37}P_2$ = 339.2371 $[M - H]^+$)

4.4.4 Synthesis of 1,2-bis(diphenylphosphinomethyl)benzene (DPPMB) (65)[6]



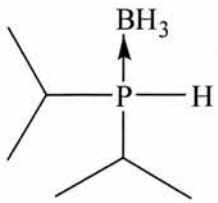
The dipotassium xylene salt **(63)** (2.86 g, 15.7 mmol) was dissolved in dry degassed diethyl ether (100 cm^3) and cooled to –20 °C. Chlorodiphenylphosphine (5.6 cm^3, 31.4 mmol) was added slowly and the solution allowed to warm to room temperature after which it was stirred overnight. The solution was removed by filtration and the potassium chloride salt was washed with diethyl ether. The diethyl ether was removed from the combined fractions *in vacuo* and the residue was recrystallised from THF/hexane (450 mg, 6 %). mp = 126 °C (Lit[6]. = 127 – 129 °C); ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 3.30 (s, PC*H*$_2$Ar), 6.72 (m, 2 H, Ar*H*), 6.89 (m, 2 H, Ar*H*), 7.30 (m, 20 H, Ar*H*); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$, 298 K) δ = -12.3; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K) δ = 33.45 (d, $^1J_{PC}$ = 8 Hz, ArC*H*$_2$P), 126.3 (*s*, Ar), 128.4 (s, *Ar*), 128.5 (*s*, Ar), 133.6 (s, *Ar*), 131.2 (s, *Ar*), 137.2 (s, *Ar*P), 137.8 (s, *Ar*CH$_2$P);

4.4.5 Synthesis of 1,2-bis(diethylphosphinomethyl)benzene (DEPMB) (66)[5]



The dipotassium xylene salt **(63)** (2.24 g, 12.3 mmol) was dissolved in dry degassed diethyl ether (75 cm^3) and cooled to –78 °C. Chlorodiethylphosphine (3.07 g, 24.6 mmol) was added slowly over a period of 10 minutes and the solution was allowed to warm to room temperature before stirring for 16 hours. The solution was removed by filtration and the potassium chloride salt was washed with diethyl ether (2 x 30 cm^3). The combined diethyl ether fractions were reduced in volume *in vacuo* to leave colourless solid was recrystallised from hot methanol yielding the title compound as a colourless solid. (610 mg, 18 %). (Found: C, 68.16 %; H, 10.27 % Calc. for $C_{16}H_{28}P_2$: C, 68.06 %; H, 10.00 %). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.08 (d tr, $^3J_{PH}$ = 14 Hz $^3J_{PH}$ = 7 Hz, 12 H, PCH_2CH_3), 1.72 (quart, $^3J_{HH}$ = 7 Hz, 8 H, PCH_2CH_3), 2.78 (d, $^2J_{PH}$ = 3 Hz, 4 H, $ArCH_2P$), 7.38 (m, 2 H, Ar*H*), 7.50 (m, 2 H, Ar*H*); $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$, 298 K) δ = -18.2 (s, $BzPEt_2$); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) δ = 9.5 (d, $^1J_{PC}$ = 12 Hz, PCH_2CH_3), 18.5 (d, $^2J_{PC}$ = 11 Hz, PCH_2CH_3), 32.1 (d, $^1J_{PC}$ = 18 Hz, $ArCH_2P$), 125.3 (s, *ArH*), 130.8, (d, $^3J_{PC}$ = 14 Hz, *Ar*CH_2P), 138.6 (d, $^2J_{PC}$ = 9 Hz, *Ar*CH_2P).

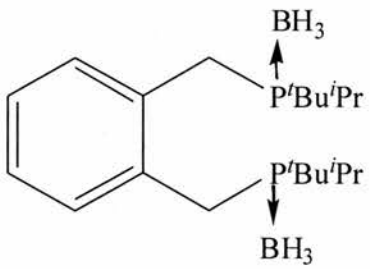
4.4.6 Synthesis of *tert*-butyl-*iso*-propylphosphine-borane (93)



Tert-butyldichlorophosphine (9.72 g, 61.1 mmol) was dissolved in diethyl ether (50 cm^3) and cooled to 0 °C. To this *iso*-propylmagnesium chloride (2 mol L^{-1} in hexane, 30. 5 cm^3, 61 mmol) was slowly added and the solution was allowed to warm to room temperature. A $^{31}P\{^1H\}$ NMR spectrum of the solution was recorded and the only signal present was at 139.9 ppm which is consistent with literature values for $^tBuC^iPrP$[7]. The solution was filtered and the residue washed with diethyl ether (2 x 20 cm^3). The combined organic layers had the solvent removed *in vacuo* leaving a yellow oil. This oil was slowly added to a DMF (20 cm^3) solution of $NaBH_4$ (3.02 g, 80 mmol) cooled to 0 °C. Upon complete addition the solution was allowed to warm to room temperature and stir for 16 hours. Water (20 cm^3) was added carefully and the resultant solution was extracted with diethyl ether (3 x 30 cm^3). The combined organic layers were washed successively with water (2 x 20 cm^3) and brine (2 x 20 cm^3) and then dried over $MgSO_4$. The solvent was removed *in vacuo* leaving the title product as a clear oil. (7.22 g, 81 %). (Found: C, 57.35 %; H, 13.93 % Calc. for $C_7H_{20}BP$: C, 57.58 %; H, 13.81 %). ^1H NMR (300 MHz, $CDCl_3$, 298 K): δ = 0.18 (br quart, $^1J_{BH}$ = 50 Hz, PH(BH_3), 1.09 (dd, $^3J_{PH}$ = 13 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHCH_3), 1.15 (dd, $^3J_{PH}$ = 13 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHCH_3), (1.22 (d, $^3J_{PH}$ = 14 Hz, 18 H, PCCH_3), 2.29 (dd, $^3J_{HH}$ = 7 Hz, $^2J_{PH}$ = 2 Hz, 1 H, PC*H*CH_3), 3.92 (d quart, $^1J_{PH}$ = 352 Hz, $^2J_{BH}$ = 7 Hz, P*H*(BH_3);

$^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$, 298 K) δ = 37.7 (quart, $^{1}J_{PB}$ = 50 Hz); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$, 298 K) δ = 17.2 (s, $PCHCH_3$), 20.9 (s,$PCHCH_3$ 25.5 (d, 26 Hz, $PCCH_3$), 26.3 (s, $PCCH_3$).

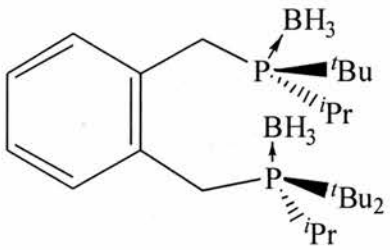
4.4.7 Synthesis of *racemic* 1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene-borane (67)



tert-butyl-*iso*-propylphosphine-borane (93) (3.78 g, 25.9 mmol) was dissolved in THF (30 cm^3) and cooled to 0 °C. To this solution,. *n*-butyl lithium (2.5M in hexane, 10.3 cm^3, 25.9 mmol) was added slowly after which the solution was allowed to warm to room temperature and stirred for 30 minutes. The solution was cooled to 0 °C and a THF (20 cm^3) solution of α,α-*o*-dichloroxylene (2.23 g, 12.8 mmol) was added dropwise with the solution temperature not being allowed to rise above 5 °C. Upon complete addition the solution was allowed to warm to room temperature and stir for 16 hours. Water (30 cm^3) was added to the solution and the layers separated. The aqueous layer was extracted with diethyl ether (2 x 30 cm^3) and the combined organic layers washed with water (30 cm^3) and 10 % brine (2 x 30 cm^3). The organic layer was dried with $MgSO_4$ and the solvent was removed *in vacuo* to leave a white solid, which was recrystallised, from hexane as colourless crystals (4.36 g, 93 %). (mp = 153 – 154 °C). (Found: C, 66.85 %; H, 11.92 % Calc. for $C_{22}H_{46}B_2P_2$: C, 67.04 %; H, 11.76 %). ^{1}H

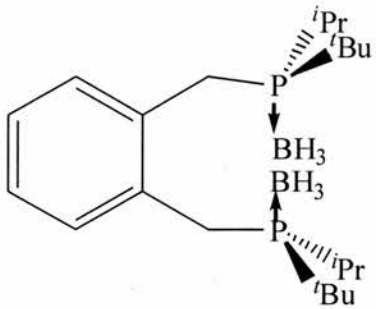
NMR (500 MHz, CD_2Cl_2 , 298 K): δ = 0.29 (q, $^1J_{PB}$ = 85 Hz, 6 H, PB*H*$_3$), 1.07 (dd, $^3J_{PH}$ = 14 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHC*H*$_3$), 1.07 (dd, $^3J_{PH}$ = 13 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHC*H*$_3$), 1.25 (d, $^3J_{PH}$ = 13 Hz, 9 H, PCC*H*$_3$), 1.26 (dd, $^3J_{PH}$ = 14 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHC*H*$_3$), 1.28 (d, $^3J_{PH}$ = 13 Hz, 9 H, PCC*H*$_3$), 1.28 (dd, $^3J_{PH}$ = 13 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHC*H*$_3$), 1.99 (dd, $^2J_{PH}$ = 7 Hz, $^3J_{HH}$ = 7 Hz, , 2 H, PC*H*CH$_3$), 2.02 (dd, $^2J_{PH}$ = 7 Hz, $^3J_{HH}$ = 7 Hz, , 2 H, PC*H*CH$_3$),3.14 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 15 Hz, 1 H, Ar(C*H*H)P), 3.29 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 10 Hz, 1 H, Ar(C*H*H)P), 3.38 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 13 Hz, 1 H, Ar(C*H*H)P), 3.64 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 7 Hz, 1 H, Ar(C*H*H)P), 7.16 (m, 3 H, Ar*H*), 7.29 (m, 1 H, Ar*H*); ^{31}P NMR (202 MHz, CD_2Cl_2 , 298 K): δ = 39.2 (quartet, ^1J = 50 Hz, *rac*-BzP^{t}Bu$_2$), 40.7 (quartet, ^1J = 50 Hz, *meso*-BzP^{t}Bu$_2$) ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K) δ = 19.3 (d, 40 Hz, PCH*C*H$_3$), 19.5 (d, 54 Hz, PCH*C*H$_3$), 23.9 (d, 28 Hz, P*C*HCH$_3$), 24.2 (d, 28 Hz, P*C*HCH$_3$), 25.2 (d, 26 Hz, P*C*CH$_3$), 25.4 (d, 25 Hz, P*C*CH$_3$), 27.7 (d, 6 Hz, PC*C*H$_3$), 27.8 (s, PC*C*H$_3$), 31.5 (d, 28 Hz, Ar*C*H$_2$P^{t}Bu^{i}Pr), 31.6 (d, 28 Hz, Ar*C*H$_2$P^{t}Bu^{i}Pr), 127.4 (s, *Ar*H), 127.4 (s, *Ar*H), 132.1 (s, *Ar*H), 132.5 (s, *Ar*H), 134.5 (m, *Ar*CH$_2$P^{t}Bu$_2$^{i}Pr$_2$), 134.9 (m, *Ar*CH$_2$P^{t}Bu$_2$^{i}Pr$_2$); Accurate ES(+)-MS = 417.3159 (Calculated for $C_{22}H_{46}P_2B_2Na$ = 417.3159, [M + Na^+])

4.4.8 Preparation of *rac*-1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene-borane (68)



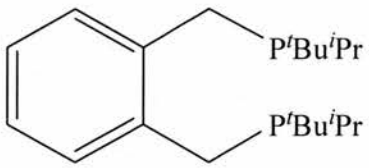
A racemic mixture containing all 4 diastereomers of 1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene-borane was dissolved in hot MeOH and was left to cool. The colourless crystals produced were collected by filteration and recrystallised 3 more times from MeOH until the product was diastereomerically pure. The configuration of the structure was determined by single crystal X-ray diffraction. mp = 167 °C. (Found: C, 67.13 %; H, 11.57 % Calc. for $C_{22}H_{46}B_2P_2$: C, 67.04 %; H, 11.76 %). ^{1}H NMR (500 MHz, CD_2Cl_2 , 298 K): δ = 0.29 (q, $^1J_{PB}$ = 85 Hz, 3 H, PB*H*$_3$), 1.07 (dd, $^3J_{PH}$ = 13 Hz, $^3J_{HH}$ = 7 Hz, 6 H, PCHC*H*$_3$), 1.28 (d, $^3J_{PH}$ = 13 Hz, 18 H, PCC*H*$_3$), 1.28 (dd, $^3J_{PH}$ = 13 Hz, $^3J_{HH}$ = 7 Hz, 6 H, PCHC*H*$_3$), 1.99 (dd, $^2J_{PH}$ = 7 Hz, $^3J_{HH}$ = 7 Hz, , 2 H, PC*H*CH$_3$), 3.14 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 15 Hz, 2 H, Ar(C*H*H)P), 1.99 (3.64 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 7 Hz, 2 H, Ar(C*H*H)P), 7.29 (m, 4 H, Ar*H*); ^{31}P NMR (202 MHz, CD_2Cl_2 , 298 K): δ = 39.2 (quartet, ^1J = 50 Hz, *rac*-BzP^{t}Bu$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K) δ = 19.3 (d, 40 Hz, PCH*C*H$_3$), 23.9 (d, 28 Hz, P*C*HCH$_3$), 25.2 (d, 26 Hz, P*C*CH$_3$), 27.8 (s, PC*C*H$_3$), 31.6 (d, 28 Hz, Ar*C*H$_2$P^{t}Bu^{i}Pr), 127.4 (s, *Ar*H), 132.1 (s, *Ar*H), 134.9 (m, *Ar*CH$_2$P^{t}Bu$_2$^{i}Pr$_2$); Accurate ES(+)-MS = 417.3165 (Calculated for $C_{22}H_{46}P_2B_2Na$ = 417.3159, [M + Na$^+$])

4.4.9 Preparation of *meso*-1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene-borane (69)



The solvent of the solution left from the first recrystallisation of **68** was removed *in vacuo* and the solid was recrystallised from hot MeOH. The colourless crystals produced were collected by filtration and recrystallised 3 more times from MeOH until the product became diastereomerically pure. The configuration of the structure was determined by single crystal X-ray diffraction. mp = 140 °C. (Found: C, 67.32 %; H, 11.62 % Calc. for $C_{22}H_{46}B_2P_2$: C, 67.04 %; H, 11.76 %). ^{1}H NMR (500 MHz, CD_2Cl_2 , 298 K): δ = 0.29 (q, $^1J_{PB}$ = 85 Hz, 6 H, PB*H*$_3$), 1.07 (dd, $^3J_{PH}$ = 13 Hz, $^3J_{HH}$ = 7 Hz, 6 H, PCHC*H*$_3$), 1.25 (d, $^3J_{PH}$ = 13 Hz, 18 H, PCC*H*$_3$), 1.26 (dd, $^3J_{PH}$ = 14 Hz, $^3J_{HH}$ = 7 Hz, 6 H, PCHC*H*$_3$), 2.02 (dd, $^2J_{PH}$ = 7 Hz, $^3J_{HH}$ = 7 Hz, , 2 H, PC*H*CH$_3$), 3.29 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 10 Hz, 2 H, Ar(C*H*H)P), 3.38 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 13 Hz, 2 H, Ar(C*H*H)P), 7.29 (m, 4 H, Ar*H*); ^{31}P NMR (202 MHz, CD_2Cl_2 , 298 K): δ = 40.7 (quartet, ^1J = 50 Hz, *meso*-BzP^{t}Bu$_2$) ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K) δ = 19.5 (d, 54 Hz, PCH*C*H$_3$), 24.2 (d, 28 Hz, P*C*HCH$_3$), 25.4 (d, 25 Hz, P*C*CH$_3$), 27.7 (d, 6 Hz, PC*C*H$_3$), 31.5 (d, 28 Hz, Ar*C*H$_2$P^{t}Bu^{i}Pr), 127.4 (s, *Ar*H), 132.5 (s, *Ar*H), 134.5 (m, *Ar*CH$_2$P^{t}Bu$_2$^{i}Pr$_2$); Accurate ES(+)-MS = 365.2521 (Calculated for $C_{22}H_{39}P_2$ = 365.2527, $[M - H]^+$)

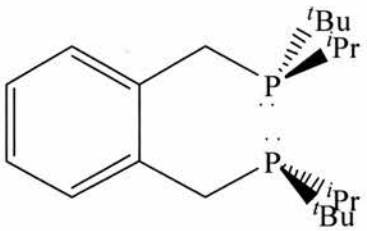
4.4.10 Synthesis of *racemic* 1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene (70)



Racemic-1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene-borane (67) (450 mg, 1.1 mmol) was dissolved in degassed diethylamine (20 cm^3) and heated under reflux for 16 hours. The solution was cooled and the solvent was removed *in vacuo*. The white paste was dissolved in toluene (10 cm^3) and the solution was passed through a short column of silica under an inert atmosphere. The column was washed with toluene (20 cm^3) and the solvent was subsequently removed *in vacuo* to leave a clear oil. (346 mg, 86 %). (Found: C, 72.29 %; H, 11.28 % Calc. for $C_{22}H_{40}P_2$: C, 72.09 %; H, 11.00 %). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.06 (dd, $^3J_{PH}$ = 14 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHC*H*$_3$), 1.07 (dd, $^3J_{PH}$ = 13 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHC*H*$_3$), 1.10 (dd, $^3J_{PH}$ = 14 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHC*H*$_3$), 1.10 (d, $^3J_{PH}$ = 14 Hz, 9 H, PCC*H*$_3$), 1.11 (dd, $^3J_{PH}$ = 14 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHC*H*$_3$), 1.12. (dd, $^3J_{PH}$ = 13 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHC*H*$_3$), 1.72 (dd, $^2J_{PH}$ = 7 Hz, $^3J_{HH}$ = 7 Hz, , 2 H, PC*H*CH$_3$), 1.73 (dd, $^2J_{PH}$ = 7 Hz, $^3J_{HH}$ = 7 Hz, , 2 H, PC*H*CH$_3$), 2.90 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 15 Hz, 1 H, Ar(C*H*H)P), 2.95 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 10 Hz, 1 H, Ar(C*H*H)P), 2.99 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 13 Hz, 1 H, Ar(C*H*H)P), 2.35 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 7 Hz, 1 H, Ar(C*H*H)P), 7.56 (m, 4 H, Ar*H*); ^{31}P NMR (121 MHz, CD_2Cl_2 , 298 K): δ = 11.4 (s, *rac*-BzP^{t}Bu$_2$), 12.5 (s, *meso*-BzP^{t}Bu$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K) δ = 19.3 (d, 16 Hz, PCH*C*H$_3$), 19.7 (d, 18 Hz, PCH*C*H$_3$), 23.4 (d, 12 Hz, P*C*HCH$_3$), 23.5 (d, 12 Hz, P*C*HCH$_3$), 26.3 (d, 25

Hz, P*C*CH$_3$), 26.4 (d, 25 Hz, PC*C*H$_3$), 29.9 (d, 14 Hz, PCC*H*$_3$), 30.0 (d, 14 Hz, PCC*H*$_3$), 30.3 (d, 15 Hz, Ar*C*H$_2$P^{t}Bu^{i}Pr), 30.5 (d, 15 Hz, Ar*C*H$_2$P^{t}Bu^{i}Pr), 126.1 (s, *Ar*H), 126.4 (s, *Ar*H), 128.3 (s, *Ar*H), 128.7 (s, *Ar*H), 137.5 (m, *Ar*CH$_2$P^{t}Bu$_2$^{i}Pr$_2$), 137.7 (m, *Ar*CH$_2$P^{t}Bu$_2$^{i}Pr$_2$); Accurate ES(+)-MS = 417.3159 (Calculated for $C_{22}H_{46}P_2B_2Na$ = 417.3178, [M + Na$^+$])

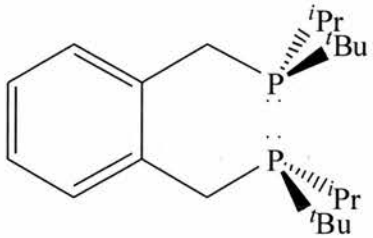
4.4.11 Synthesis of *rac*-1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene (15)



rac-1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene-borane (68) (322 mg, 0.8 mmol) was dissolved in degassed diethylamine (20 cm^3) and heated under reflux for 16 hours. The solution was cooled and the solvent was removed *in vacuo*. The white paste was dissolved in toluene (10 cm^3) and the solution was passed through a short column of silica under an inert atmosphere. The column was washed with toluene (20 cm^3) and the solvent was subsequently removed *in vacuo* to leave a clear oil. (215 mg, 72 %). (Found: C, 72.36 %; H, 11.15 % Calc. for $C_{22}H_{40}P_2$: C, 72.09 %; H, 11.00 %). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.06 (dd, $^3J_{PH}$ = 14 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHC*H*$_3$), 1.11 (dd, $^3J_{PH}$ = 14 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHC*H*$_3$), 1.12 (dd, $^3J_{PH}$ = 13 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHC*H*$_3$), 1.73 (dd, $^2J_{PH}$ = 7 Hz, $^3J_{HH}$ = 7 Hz, , 2 H, PC*H*CH$_3$), 2.90 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 15 Hz, 1 H, Ar(C*H*H)P), 2.35 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 7 Hz, 1 H, Ar(C*H*H)P), 7.56 (m, 4 H, Ar*H*); ^{31}P NMR (121 MHz, CD_2Cl_2 , 298 K): δ = 11.4 (s,

rac-BzP^{t}Bu$_2$); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) δ = 19.3 (d, 16 Hz, PCH*C*H$_3$), 19.7 (d, 18 Hz, PCH*C*H$_3$), 23.4 (d, 12 Hz, P*C*HCH$_3$), 23.5 (d, 12 Hz, P*C*HCH$_3$), 26.3 (d, 25 Hz, P*C*CH$_3$), 26.4 (d, 25 Hz, P*C*CH$_3$), 29.9 (d, 14 Hz, PC*C*H$_3$), 30.0 (d, 14 Hz, PC*C*H$_3$), 30.3 (d, 15 Hz, Ar*C*H$_2$P^{t}Bu^{i}Pr), 30.5 (d, 15 Hz, Ar*C*H$_2$P^{t}Bu^{i}Pr), 126.1 (s, *Ar*H), 128.7 (s, *Ar*H), 137.7 (m, *Ar*CH$_2$P^{t}Bu$_2$^{i}Pr$_2$); Accurate ES(+)-MS = 365.2515 (Calculated for $C_{22}H_{39}P_2$ = 365.2527, $[M - H]^+$)

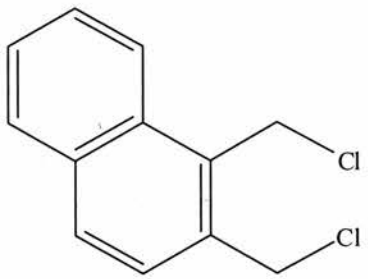
4.4.12 Synthesis of *meso*-1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene (14)



meso-1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene-borane **(69)** (450 mg, 1.2 mmol) was dissolved in degassed diethylamine (20 cm^3) and heated under reflux for 16 hours. The solution was cooled and the solvent was removed *in vacuo*. The white paste was dissolved in toluene (10 cm^3) and the solution was passed through a short column of silica under an inert atmosphere. The column was washed with toluene (20 cm^3) and the solvent was subsequently removed *in vacuo* to leave a clear oil. (334 mg, 83 %). (Found: C, 72.18 %; H, 11.14 % Calc. for $C_{22}H_{40}P_2$: C, 72.09 %; H, 11.00 %). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.07 (dd, $^3J_{PH}$ = 13 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHC*H*$_3$), 1.10 (dd, $^3J_{PH}$ = 14 Hz, $^3J_{HH}$ = 7 Hz, 3 H, PCHC*H*$_3$), 1.10 (d, $^3J_{PH}$ = 14 Hz, 9 H, PCC*H*$_3$), 1.72 (dd, $^2J_{PH}$ = 7 Hz, $^3J_{HH}$ = 7 Hz, , 2 H, PC*H*CH$_3$), 2.95 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 10 Hz, 1 H, Ar(C*H*H)P), 2.99 (dd, $^2J_{HH}$ = 15 Hz, $^2J_{PH}$ = 13 Hz, 1 H, Ar(C*H*H)P),

7.58 (m, 4 H, Ar*H*); ^{31}P NMR (121 MHz, CD_2Cl_2, 298 K): δ = 12.5 (s, BzP^tBu_2); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) δ = 19.3 (d, 16 Hz, $PCHCH_3$), 19.7 (d, 18 Hz, $PCHCH_3$), 23.4 (d, 12 Hz, $PCHCH_3$), 23.5 (d, 12 Hz, $PCHCH_3$), 26.3 (d, 25 Hz, $PCCH_3$), 26.4 (d, 25 Hz, $PCCH_3$), 29.9 (d, 14 Hz, $PCCH_3$), 30.0 (d, 14 Hz, $PCCH_3$), 30.3 (d, 15 Hz, $ArCH_2P^tBu^iPr$), 30.5 (d, 15 Hz, $ArCH_2P^tBu^iPr$), 126.4 (s, *Ar*H), 128.7 (s, *Ar*H), 137.5 (m, $ArCH_2P^tBu_2{}^iPr_2$); Accurate ES(+)-MS = 365.2541 (Calculated for $C_{22}H_{39}P_2$ = 365.2527, $[M - H]^+$)

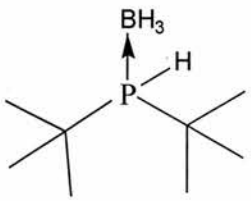
4.4.13 Synthesis of 1,2-bis(chloromethyl)napthalene (76)



1-chloromethyl-2-methylnapthalene (5.16 g, 27.1 mmol) was dissolved in 1,2-dichloroethane (30 cm^3) along with dibenzoyl peroxide (150 mg). The solution was stirred until all solids were dissolved and N-chlorosuccinimide (3.73 g, 28 mmol) was added. The solution was heated under reflux and stirred for 40 hours. The solution was cooled and the solid removed by filtration and washed with cold 1,2-dichloroethane (10 cm^3). The solution was washed with water (3 x 30 cm^3) and the organic layer dried over $MgSO_4$. The solvent was removed *in vacuo,* the crude yellow solid dissolved in hot benzene:hexane (1:1) and filtered hot to remove any remaining succinimide compounds. The solution was cooled and the title compound recrystallised as a white solid. (4.61 g, 76 %). mp = 131 °C. (Found: C, 64.49 %; H, 3.66 % Calc. for $C_{12}H_{10}Cl_2$: C, 64.60 %;

H, 3.61 %). ^{1}H NMR (300 MHz, acetone-d_6, 298 K): δ = 4.95 (s, 2 H, PhC*H*$_2$Cl), 5.26 (s, 2 H, PhC*H*$_2$Cl), 7.51 (d, $^{3}J_{HH}$ = 8.3 Hz, 2 H, Ar*H*), 7.57 (tr, $^{3}J_{HH}$ = 8.3 Hz, 2 H, Ar*H*), 7.86 (d, $^{3}J_{HH}$ = 8.4 Hz, 2 H, Ar*H*), 8.18 (d, $^{3}J_{HH}$ = 8.5 Hz, 1H, *Ar*CH$_2$Cl); ^{13}C NMR (75 MHz, acetone-d_6, 298 K): δ = 40.2 (s, PhCH$_2$Cl), 45.2 (s, PhCH$_2$Cl), 125.9 (s, *Ar*H), 128.5 (s, *Ar*H), 129.1 (s, *Ar*H), 129.6 (s, *Ar*H), 130.5 (s, *Ar*H), 131.8 (s, *Ar*H), 133.4 (s, ArH), 134.0 (s, *Ar*H), 135.7 (s, *Ar*H), 136.5 (s, *Ar*H). MS EI: 226.0 (M(^{37}Cl).

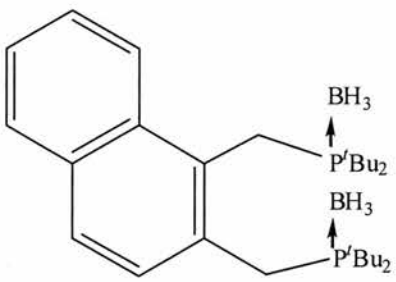
4.4.14 Synthesis of di-*tert*-butylphosphine-borane (91)



Sodium borohydride (1.30 g, 34 mmol) was dissolved in dry and degassed DMF (30cm^3). The solution was cooled to 0 °C and di-*tert*-butylchlorophosphine (6.00 g, 33.2 mmol) was added dropwise. Upon complete addition the solution was allowed to warm to room temperature and stir for 16 hours. To the solution, water was slowly added (30 cm^3) followed by diethyl ether (30 cm^3). The layers were separated, the aqueous layer extracted with diethyl ether (2 x 20 cm^3) and the combined organic layers washed with water (30 cm^3) and brine (2 x 30 cm^3). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo* to leave a white solid which was recrystallised from hexane to afford the title compound as colourless crystals. (4.88 g, 92 %). mp = 41 °C. (Found: C, 63.82 %; H, 13.92 % Calc. for $C_8H_{22}BP$: C, 60.04 %; H, 13.86 %). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.34 (d, $^{3}J_{PH}$ 13 Hz, 18 H, PC*C*H$_3$), 4.12 (dq, $^{1}J_{PH}$ = 351 Hz, $^{2}J_{HB}$ 7 Hz); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$, 298 K)

δ = 49.0 (quartet, $^{1}J_{PB}$ 49 Hz, BzP(BH_3)(^{t}Bu)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 29.3 (d, $^{2}J_{PC}$ 2 Hz, PC(CH_3)$_3$), 30.2 (d, $^{1}J_{PC}$ 28 Hz, PC(CH_3)$_3$). Accurate ES(+)-MS = 183.1456 (Calculated for $C_{22}H_{39}P_2$ = 183.1450, $[M + Na]^+$)

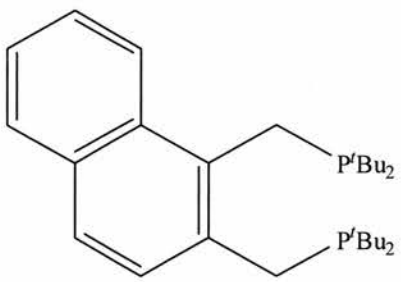
4.4.15 Synthesis of 1,2-bis(di-*tert*-butylphosphinomethyl)napthalene-borane (75)



Di-*tert*-butylphosphine-borane (91) (2.04 g, 12.8 mmol) was dissolved in diethyl ether (30 cm^3) and cooled to –30 °C. To this solution, *n*-butyl lithium (2.5M in hexane, 5.2 cm^3, 6.4 mmol) was added slowly. The resulting solution was allowed to warm to room temperature and stirred for 3 hours. The solution was cooled to 0 °C and a diethyl ether (20 cm^3) solution of 1,2-dichloromethylnapthalene (76) (1.20 g, 5.3 mmol) was added dropwise, not allowing the temperature to rise above 5 °C. Upon complete addition the solution was allowed to warm to room temperature and stir for 16 hours. Water (30 cm^3) was added and the layers separated. The aqueous layer was extracted with diethyl ether (2 x 30 cm^3) and the combined organic layers washed with water (30 cm^3) and brine (2 x 30 cm^3). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* to leave an off white oil. To this hexane was added and the title compound crystallised as a pure white solid (1.08 g, 43 %). mp = (173 – 174 °C). (Found: C, 71.62 %; H, 10.73 % Calc. for $C_{28}H_{50}P_2B_2$: C, 71.51 %; H, 10.72 %) ^{1}H NMR (300

MHz, $CDCl_3$, 298 K): δ = -0.02 – 2.11 (br, 42 H; B*H*$_3$ & CC*H*$_3$), 3.18 – 4.40 (br, 4 H), 7.45 (tr, 7.0 Hz, 1 H, Ar*H*), 7.53 (tr, 7.0 Hz, 1 H, Ar*H*), 7.68 (d, 8.5 Hz, 1 H, Ar*H*), 7.80 (d, 8.5 Hz, 1 H, Ar*H*), 7.92 (d, 8.5 Hz, 1 H, Ar*H*), 8.15 (d, 8.5 Hz, 1 H, Ar*H*); ^{31}P NMR (121 MHz, $CDCl_3$, 298 K) δ = 53.1 (br tr, $^1J_{PB}$ = 94 Hz, BzP^{t}Bu$_2$(BH$_3$)); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 22.4 (d, $^1J_{PC}$ 22 Hz, P*C*(CH$_3$)$_3$), 26.7 (d, $^1J_{PC}$ 23 Hz, P*C*(CH$_3$)$_3$), 29.0 (d, $^2J_{PC}$ 14 Hz, PC(*C*H$_3$)$_3$), 33.6 (d, $^1J_{PC}$ 25 Hz, Ph*C*H$_2$P), 34.6 (d, $^1J_{PC}$ 25 Hz, Ph*C*H$_2$P), 125.0 (s, *Ar*H), 125.7 (s, *Ar*H), 126.2 (s, *Ar*H), 127.0 (s, *Ar*H), 128.7 (s, *Ar*H, 129.3 (s, *Ar*H), 130.8 (s, *Ar*H), 133.2 (s, *Ar*H), 133.4 (s, *Ar*H), 134.3 (s); MS ES(+): m/z = 495 (M + Na).

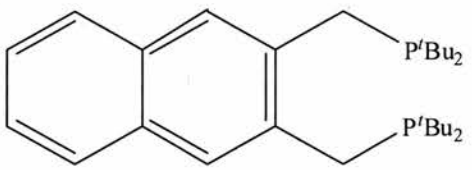
4.4.16 Synthesis of 1,2-bis(di-tert-butylphosphinomethyl)naphthalene (73)



1,2-bis(di-*tert*-butylphosphinomethyl)naphthalene-borane (1.08 g, 2.3 mmol) was dissolved in degassed diethylamine (20 cm^3) and heated under reflux. The solution was cooled and the solvent was removed *in vacuo*. The white solid was dissolved in toluene (10 cm^3) and the solution was passed through a short column of silica under an inert atmosphere. The column was washed with toluene (30 cm^3) and the solvent was subsequently removed *in vacuo* to leave an off white solid which was recrystallised from MeOH to yield the title compound. (854 mg, 84 %). mp = 144 – 145 °C. (Found: C, 75.43 %; H, 10.62 % Calc. for $C_{28}H_{46}P_2$: C, 75.64 %; H, 10.43 %). ^{1}H NMR (300

MHz, $CDCl_3$, 298 K): δ = 1.14 (d, $^3J_{PH}$ = 11 Hz, 18 H, PCCH_3), 1.15 (d, $^3J_{PH}$ = 10 Hz, 18 H, PCCH_3), 3.25 (d, $^2J_{PH}$ = 3 Hz, 2 H, ArCH_2P), 3.52 (br s, 2 H, ArCH_2P), 7.38 (m, 1 H, *Ar*H), 7.47 (m, 1 H, *Ar*H), 7.58 (d, $^3J_{HH}$ = 8 Hz, 1 H, *Ar*H), 7.73 (m, 2 H, *Ar*H), 8.40 (d, $^3J_{HH}$ = 8 Hz, 1 H, *Ar*H); $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$, 298 K) δ = 34.4 (s, Bz*P*^{t}Bu$_2$), 35.4 (s, Bz*P*^{t}Bu$_2$); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) δ = 27.7 (d, 23 Hz. PCCH_3), 29.8 (d, 13 Hz, PCCH_3), 29.9 (d, PCCH_3), 32.1 (d, 22 Hz, ArCH_2P^{t}Bu$_2$), 32.4 (d, 25 Hz, ArCH_2P^{t}Bu$_2$), 124.5 (s, *Ar*H), 125.0 (s, *Ar*H), 125.7 (s, *Ar*H), 125.8 (s, *Ar*H), 128.4 (s, *Ar*H), 129.3 (s, *Ar*H), 129.6 (s, *Ar*H), 132.5 (d, 11 Hz, *Ar*CH_2P), 133.1 (d, 5 Hz, *Ar*CH_2P); Accurate ES(+)-MS = 444.3149 (Calculated for $C_{28}H_{47}P_2$ = 445.3153)

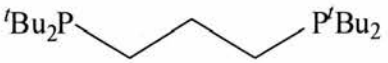
4.4.17 Synthesis of 2,3-bis(di-*tert*-butylphosphinomethyl)napthalene (74)



To a diethyl ether (10 cm^3) solution of 2,3-dimethylnapthalene (2.56 g, 16.4 mmol) and K^{t}OBu (4.03 g, 36 mmol) cooled to –78 °C, n-butyl lithium (2.5 M in hexane, 14.4 cm^3, 36 mmol) was added slowly. The solution was allowed to warm to room temperature and then heated under reflux for 2 hours. The solution was cooled to 0 °C and di-*tert*-butylchlorophosphine (6.84 cm^3, 6.50 g, 36 mmol) was added over 20 minutes. The solution was warmed to room temperature and allowed to stir for 16 hours during which time a salt formed. The solution was filtered and water (10 cm^3) was slowly added. The layers were separated and the product extracted from the aqueous layer with diethyl ether (2 x 20 cm^3). The combined organic layers were washed successively with water

(20 cm^3) and brine (2 x 20 cm^3) and dried over magnesium sulphate. The solvent was removed *in vacuo* leaving a white solid which was recrystallised from hot MeOH (4.92 g, 68 %). mp = 148 °C. (Found: C, 75.39 %; H, 10.66 % Calc. for $C_{28}H_{46}P_2$: C, 75.64 %; H, 10.43 %). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.16 (d, $^3J_{PH}$ = 11 Hz, 36 H, PCHC*H*$_3$), 3.22 (d, $^2J_{PH}$ = 4 Hz, 4 H, ArC*H*$_2$P), 7.36 (m, 2 H, Ar*H*), 7.75 (m, 2 H, Ar*H*), 8.06 (m, Ar*H*); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$, 298 K) δ = 26.3 (s, BzP^{t}Bu$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K) δ = 27.3 (d, $^1J_{PC}$ = 24 Hz, PCCH_3), 32.5 (d, $^2J_{PC}$ = 13 Hz, PCCH_3), 33.3 (d, $^1J_{PC}$ = 23 Hz, ArCH_2P), 125.4 (s, *ArH*), 127.3 (s, *ArH*), 129.4 (s, *ArH*), (s, Ar*H*), 132.2 (s, *Ar*), 138.4 (dd, $^3J_{PC}$ = 10 Hz, $^4J_{PC}$ = 2 Hz, *Ar*CH_2P); Accurate ES(+)-MS = 445.3138 (Calculated for $C_{28}H_{47}P_2$ = 445.3153 $[M - H]^+$)

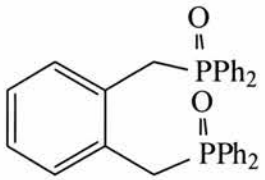
4.4.18 Synthesis of 1,3-bis(di-*tert*-butylphosphino)propane (13)[8]



Di-*tert*-butylphosphine (2.0 g, 13.8 mmol) was added to diethyl ether (30 cm^3) and cooled to 0 °C. To this solution, *n*-butyl lithium (1.6 M in hexane, 8.6 cm^3, 13.8 mmol) was slowly added with stirring. After 20 minutes the solution had turned yellow and 1,3-dichloropropane (0.68 cm^3, 0.82 g, 7.3 mmol) was added slowly over a period of 20 minutes. During this time a salt formed. The reaction was allowed to warm to room temperature and stir for a further 3 hours. After this the solvent was removed *in vacuo* and petroleum ether 40-60° (10 cm^3) was added followed by water (30 cm^3). The organic layer was removed and the aqueous layer re-extracted with petroleum ether (3 x 30 cm^3). The organic fractions were combined and the solvent was removed *in vacuo* to leave an oil which was purified by short path distillation. (235 mg, 10 %) bp = 120 -

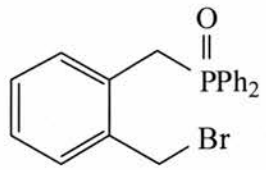
121 °C (0.01 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.10 (d, $^{3}J_{PH}$ = 11 Hz, 36 H, PCCH_3), 1.62 (m, 2 H, $PCH_2CH_2CH_2P$), 1.83 (m, 4 H, $PCH_2CH_2CH_2P$); $^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$, 298 K) δ = 31.5 (s, $CH_2P^tBu_2$); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$, 298 K) δ = 23.4 (dd, 13 Hz, 15 Hz, $PCH_2CH_2CH_2P$), 29.9 (d, 14 Hz, $PCCH_3$), 31.4 (tr, 27 Hz, $PCH_2CH_2CH_2P$), 31.5 (d, 23 Hz $PCCH_3$).

4.4.19 Synthesis of 1,2-bis(diphenylphosphorylmethyl)benzene (83)[9]



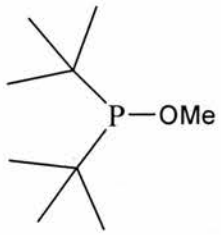
a,a-dibromoxylene (2.30 g, 8.7 mmol) was dissolved in toluene (20 cm^3) and heated under reflux. To this a toluene (10 cm^3) solution of ethyl diphenylphosphinite (4.14 g, 18.0 mmol, 2.1 eq) was added slowly. The solution was stirred with heating for 1 hour, after which it was allowed to cool. The solvent was removed *in vacuo* to leave a crude white solid which was recrystallised from ethanol to give colourless crystals (3.35 g, 76 %). mp = 283 – 284 °C (Lit.[10] = 284 °C) ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K): δ = 3.96 (d, 12 Hz, 4 H, PhCH_2P(O)), 6.65-6.85 (m, 4 H, *Ar*H), 7.30-7.50 (m, 12 H, *Ar*H), 7.50-7.70 (m, 8 H, *Ar*H); $^{31}P\{^{1}H\}$ NMR (121 MHz, CD_2Cl_2. 298 K) δ = 30.8 (s, $BzP(O)^{Ph}{}_2$); $^{13}C\{^{1}H\}$ NMR (75 MHz, CD_2Cl_2. 298 K) δ = 35.7 (d, 67 Hz, $PhCH_2P(O)Ph_2$), 127.3 (s, *Ar*H), 129.3 (d, 11 Hz, *Ar*H), 131.8 (d, 11 Hz, *Ar*H), 131.9 (s, *Ar*H), 132.3 (d, 16 Hz, *Ar*H). 133.1 (d, 26 Hz, *Ar*$CH_2P(O)$), 134.5 (s, *Ar*$CH_2P(O)$) MS-CI m/z = 507.56 ([M+1).

4.4.20 Synthesis of 2-diphenylphosphorylmethylbenzyl bromide (82)[11]



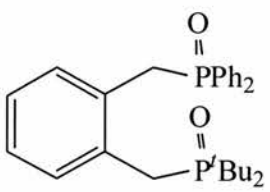
a,a-dibromoxylene (12.78 g, 48.4 mmol) was dissolved in toluene (20 cm^3) and heated to 70 °C. To this a toluene (10 cm^3) solution of ethyl diphenylphosphinite (11.14 g, 48.4 mmol) was added slowly. The solution was stirred with heating for 1 hour after which the solution was allowed to cool. The solution was filtered and the residue washed with cold toluene. The off white solid was heated in toluene (50 cm^3) to 100 °C and immediately filtered. This was repeated with the remaining solid. The solvent was removed *in vacuo* from the two combined toluene solutions to leave a crude white solid, which was recrystallised from chloroform to give the title compound as colourless crystals (6.82 g, 36 %). mp = 206 °C (Lit.[11] = 206 – 207 °C). ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K): δ = 3.84 (d, 13 Hz, 2 H, PhC*H*$_2$P(O)), 4.70 (s, 2 H, PhC*H*$_2$Br), 6.78 (d, 8 Hz, 1 H, Ar*H*), 7.04 (tr, 8 Hz, 1 H, Ar*H*), 7.17 (tr, 8 Hz, 1 H, Ar*H*), 7.32 (d, 8 Hz, 1 H, Ar*H*), 7.32 – 7.52 (m, 6 H, Ar*H*), 7.55 – 7.68 (m, 4 H, Ar*H*); ^{31}P{^{1}H} NMR (121 MHz, CD_2Cl_2, 298 K) δ = 29.5 (BzP(O)Ph$_2$); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2,. 298 K) δ = 34.2 (s, PhCH_2Br), 35.9 (d, 65 Hz, PhCH_2P(O)Ph$_2$), 126.2 (d, 3 Hz, *Ar*H), 129.4 (d, 12 Hz, *Ar*H), 131.5 (2 Hz, *Ar*H), 131.7 (d, 9 Hz, *Ar*H), 132.4 (d, 5 Hz, *Ar*H), 132.7 (d, 3 Hz, *Ar*H), 121.2 (d, 27 Hz, *Ar*H), 133.3 (*Ar*CH$_2$), 134.5 (*Ar*CH$_2$); MS-CI m/z = 385 (50 %, [M+1] based on ^{79}Br), 387 (50 %, [M+1] based on ^{81}Br).

4.4.21 Synthesis of Methyl di-*tert*-butylphosphinite (xylene solution) (86)



Sodium (0.5 g, 21.7 mmol) was dissolved in dry and degassed methanol (20 cm^3) and cooled to 0 °C. To this solution, di-*tert*-butylchlorophosphine (3.24 g, 17.9 mmol) was added slowly. After complete addition the solution was allowed to warm to room temperature and stir for 1 hour. *o*-xylene (20 cm^3) was added and the majority of the MeOH was removed *in vacuo*. The solution was filtered into a flask containing calcium hydride (3 g). The solution was left overnight to remove any traces of methanol. The solution was then filtered and was ready for further use. $^{31}P\{^1H\}$ NMR (121 MHz, *o*-$C_6H_4(CH_3)$, 298 K) $\delta = 165.0$.

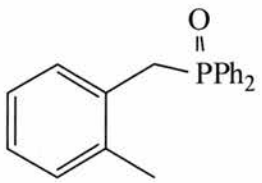
4.4.22 Synthesis of 1-diphenylphosphorylmethyl-2-di-*tert*-butylphosphorylmethylbenzene (80)



1-diphenylphosphorylmethyl-2-bromomethyl-benzene (0.87 g, 6.5 mmol) was dissolved in xylene (20 cm^3) and heated to 140 °C under an inert atmosphere. To this a xylene (10 cm^3) solution of methyl di-*tert*-butylphosphinite (3.15 g, 17.9 mmol) was added slowly. The solution was stirred with heating for 6 hours after which it was allowed to cool. The

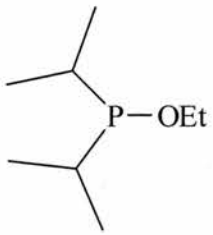
solution was filtered and the residue was washed with cold toluene. The off white solid was heated in toluene to 100 °C and immediately filtered. This was repeated with the remaining solid. The solvent was removed *in vacuo* from the two combined hot toluene solutions to leave a crude white solid, which was recrystallised from chloroform to give white crystals (0.48 g, 16 %). (Found: C, 71.83 %; H, 7.93 % Calc. for $C_{28}H_{36}O_2P_2$: C, 72.09 %; H, 7.78 %). (^{1}H NMR (300 MHz, CD_2Cl_2, 298 K): δ =1.21 (d, $^3J_{PH}$ = 12 Hz, 18 H, P(O)CC*H*$_3$), 3.51 (d, $^2J_{PH}$ = 13 Hz, 2 H, PhC*H*$_2$P(O)^{t}Bu$_2$), 4.46 (d, $^2J_{PH}$ = 13 Hz, 2 H, PhC*H*$_2$P(O)Ph$_2$), 6.86 (d, 8 Hz, 1 H, Ar*H*), 6.97 (tr, 8 Hz, 1 H, Ar*H*), 7.02 (tr, 8 Hz, 1 H, Ar*H*), 7.29 (d, 8 Hz,1 H, Ar*H*), 7.42 – 7.59 (m, 6 H, Ar*H*), 7.70 – 7.81 (m, 4 H, Ar); ^{31}P{^{1}H} NMR (121 MHz, CD_2Cl_2, 298 K) δ = 31.4 (d, $^5J_{PP}$ = 4 Hz, P(O)Ph$_2$), 62.6 (d, $^5J_{PP}$ = 4 Hz, P(O)^{t}Bu$_2$); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2, 298 K) δ = 20.7 (s, P(O)C*C*H$_3$), 25.7 (d, 42 Hz, P(O)*C*CH$_3$), 31.2 (d, 57 Hz, Ar*C*H$_2$P(O)Bu$_2$), 35.8 (d, 67 Hz, PhCH$_2$P(O)Ph$_2$), 126.3 (d, 3 Hz, *Ar*H), 127.6 (d, 3 Hz, *Ar*H), 129.3 (d, 12 Hz, *Ar*H), 130.0 (d, 3 Hz, *Ar*H), 131.3 (d, 5 Hz, *Ar*H), 131.8 (d, 9 Hz, *Ar*H), 132.5 (9 Hz, *Ar*H), 133.3 (s, *Ar*CH$_2$), 134.6 (s, *Ar*CH$_2$); MS-EI(+) = 466.22 ([M$^+$]), 353.08 (100 %, [M$^+$ – 2 Ph + 1]).

4.4.23 Synthesis of 1-diphenylphosphorylmethyl-2-methylbenzene (85)



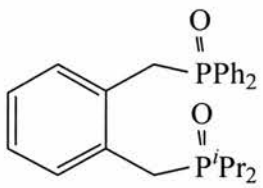
2-methylbenzyl bromide (2.77 g, 15 mmol) was dissolved in toluene (20 cm^3) and heated under reflux. To this a toluene (10 cm^3) solution of ethyl diphenylphosphinite (4 g, 17 mmol, 1.1 eq) was slowly added. The solution was stirred with heating for 3 hours after which the solution was allowed to cool. After 2 hours a white solid had precipitated which was filtered, washed with hexane and dried under vacuum (3.37 g, 73 %). mp = 136 – 138 °C (Lit.[12] = 139 – 140 °C) ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K): δ = 2.12 (s, 3 H, PhCH_3), 3.58 (d, $^2J_{PH}$ = 13 Hz, 2 H, PhCH_2P(O)), 6.78 – 6.89 (m, 2 H, *Ar*H), 6.95 – 7.08 (m, 2 H, *Ar*H), 7.32 – 7.50 (m, 6 H, *Ar*H), 7.55 – 7.65 (m, 4 H, *Ar*H); ^{31}P{^{1}H} NMR (121 MHz, CD_2Cl_2, 298 K) δ = 29.5; ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2,. 298 K) δ = 21.6 (s, ArCH_3), 36.0 (d, 65 Hz, PhCH_2P(O)Ph_2), 126.1 (s, *Ar*H), 129.4 (s, *Ar*H), 131.8 (*Ar*H), 131.9 (s *Ar*H), 132.4 (s, *Ar*H), 132.7 (s, *Ar*H), 121.2 (s, *Ar*H), 133.3 (*Ar*CH_2), 137.6 (*Ar*CH_3); MS-EI(+) = 306.12 ([M^+])

4.4.24 Synthesis of ethyl di-*iso*-propylphosphinite (toluene solution) (87)



Sodium (83 mg, 3,6 mmol) was dissolved in dry and degassed ethanol (20 cm^3) and cooled to 0 °C. To this solution chlorodi-*iso*-propylphosphine (0.41 g, 2.7 mmol) was added slowly. After complete addition the solution was allowed to warm to room temperature and stir for 1 hour. Toluene (20 cm^3) was added and the majority of the ethanol was removed *in vacuo*. The solution was then filtered and was ready for further use. $^{31}P\{^1H\}$ (121 MHz, EtOH, 298 K) δ = 110.2 ppm.

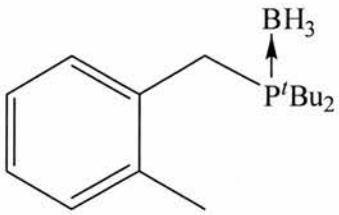
4.4.25 Synthesis of 1-diphenylphosphorylmethyl-2-di-*iso*-propylphosphorylmethylbenzene (88)



1-diphenylphosphorylmethyl-2-bromomethylbenzene (1.05 g, 2.7 mmol) was dissolved in toluene (50 cm^3) and heated under reflux. To this a toluene (10 cm^3) solution of ethyl di-iso-propylphosphinite (0.49 g, 3.0 mmol) was added slowly. The solution was stirred with heating for 6 hours after which the solution was allowed to cool. The solution was filtered and the residue washed with cold toluene. The off white solid was heated in toluene to 100 °C and immediately filtered. This was repeated with the remaining solid.

The solvent was removed *in vacuo* from the two combined hot toluene to leave a crude white solid, which was recrystallised from chloroform to give white crystals (0.48 g, 41 %). (Found: C, 70.90 %; H, 7.36 % Calc. for $C_{26}H_{32}P_2O_2$: C, 71.22 %; H, 7.36 %) ^{1}H NMR (300 MHz, CD_2Cl_2, 298 K): δ =1.07 (m, 12 H, C*H*$_3$CH), 1.92 (m, 2 H, MeC*H*P(O)), 3.32 (d, 11 Hz, 2 H, PhC*H*$_2$P(O)^{i}Pr2), 4.24 (d, 11 Hz, 2 H, PhC*H*$_2$P(O)Ph$_2$), 6.82 (d, 8 Hz, 1 H, *Ar*H), 6.91 (tr, 8 Hz, 1 H, *Ar*H), 7.09 (m, 2 H, *Ar*H), 7.33 – 7.52 (m, 6 H, *Ar*H), 7.60 – 7.72 (m, 4 H, *Ar*H); ^{31}P{^{1}H} NMR (121 MHz, CD_2Cl_2, 298 K) δ = 31.0 (d, $^5J_{PP}$ = 4 Hz, P(O)Ph$_2$), 56.3 (d, $^5J_{PP}$ = 4 Hz, P(O)^{i}Pr$_2$); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2, 298 K) δ = 16.5 (d, 8 Hz, P(O)CH*C*H$_3$), 26.4 (d, 64 Hz, P(O)*C*HCH$_3$), 30.6 (d, 54 Hz, Ph*C*H$_2$P(O)^{i}Pr$_2$), 36.0 (d, 66 Hz, Ph*C*H$_2$P(O)Ph$_2$), 127.2 (d, 3 Hz, *Ar*H), 127.6 (d, 2 Hz, *Ar*H), 129.3 (d, 12 Hz, *Ar*H), 131.8 (d, 9 Hz, *Ar*H), 132.1 (d, 2 Hz, *Ar*H), 132.5 (d, 2 Hz, *Ar*H), 132.6 (d, 1 Hz, *Ar*H), 132.7 (*Ar*), 133.0 (*Ar*), 133.4 (*Ar*); MS-EI(+) = 438.19 ([M$^+$]).

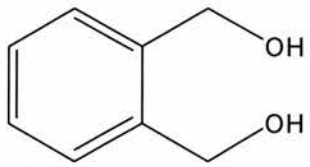
4.4.26 Synthesis of 2-methylbenzyldi-*tert*-butylphosphine-borane (94)



Di-*tert*-butylphosphine-borane (3.25 g, 20.2 mmol) was dissolved in THF (30 cm^3) and cooled to 0 °C. To this solution, *n*-butyl lithium (2.5M in hexane, 8.1 cm^3, 20.2 mmol) was added slowly and was then allowed to warm to room temperature and stirred for 1 hour. The solution was cooled to 0 °C and a THF (20 cm^3) solution of 2-methylbenzyl bromide (3.72 g, 20.2 mmol) was added dropwise, not allowing the temperature to rise above 5 °C. Upon complete addition the solution was warmed to room temperature and stir for 16 hours. Water (30 cm^3) was added to the solution and the layers separated. The aqueous layer was extracted with diethyl ether (2 x 30 cm^3) and the combined organic layers washed with water (30 cm^3) and brine (2 x 30 cm^3). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* to leave a white solid which was recrystallised from hexane as a pure white solid (5.33 g, 78 %). mp = 80 °C. (Found: C, 72.64 %; H, 12.31 % Calc. for $C_{16}H_{30}PB$: C, 72.74 %; H, 11.45 %). (Found: C, 72.56 %; H, 11.28 % Calc. for $C_{16}H_{30}BP$: C, 72.74 %; H, 11.45 %). ^1H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.25 (d, $^3J_{PH}$ = 12 Hz, 18 H, PCCH_3), 2.42 (s, 3 H, ArCH_3), 3.18 (d, $^2J_{PH}$ = 12 Hz, 2 H, ArCH_2P), 6.07 – 7.16 (m, 3 H, Ar*H*), 7.72 –7.78 (m, 1 H, Ar*H*); $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$, 298 K) δ = 48.2 (quartet, $^1J_{PB}$ = 50 Hz, BzP^{t}Bu$_2$(BH_3)); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) δ = 21.2 (s, $ArCH_3$), 22.0 (d, 24 Hz, PCCH_3), 33.4 (d, 26 Hz, ArCH_2P), 126.14 (s, *Ar*H), 127.1 (s, *Ar*H), 131.0 (s,

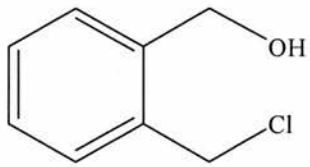
*Ar*H), 131.5(s, *Ar*H), 133.7 (d, 3 Hz, *Ar*CH_2P), 133.7 (d, *Ar*Me); EI(+)-MS = 264.20 (28 %, [M^+]), 194.11 (100 %, [M-Bu-BH_3+1]).

4.4.27 Synthesis of 1,2-bis(hydroxymethyl)benzene (97)[13]



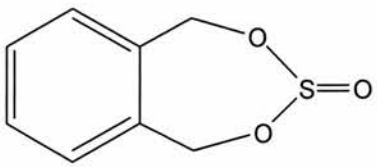
$LiAlH_4$ (10 g, 0.26 moles) was suspended in THF (200 cm^3) and cooled to 0 °C. With vigorous stirring, a THF (50 cm^3) solution of phthalic acid (30.5 g, 0.26 moles) was slowly added over a period of 1 hour. After complete addition the solution was allowed to warm to room temperature and stir for 2 hours. Water (50 cm^3) was added with caution and the solution was stirred for 1 hour after which time water (100 cm^3) and NaOH (10 % aqueous solution, 40 cm^3) were added. The solid was filtered and washed with ethyl acetate (3 x 100 cm^3). The combined organic layers were washed with brine (3 x 50 cm^3) and dried with magnesium sulphate. The solvent was removed *in vacuo* to leave a solid which was recrystallised from hot diethyl ether. (31.9 g, 89 %). mp = 63 °C (Lit.[14] = 63 °C). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 3.9 (br s, 2 H, ArCH_2O*H*), 4.65 (s, 4 H, ArCH_2OH), 7.23 – 7.45 (m, 4 H, Ar*H*); $^{13}C\{^1H\}$ NMR (121 MHz, $CDCl_3$, 298 K) δ = 63.7 (s, ArCH_2OH), 61.9 (s, ArCH_2Cl), 128.4 (s, *Ar*H), 130.0 (s, *Ar*H), 135.1 (s, *Ar*H), 138.9 (s, *Ar*CH_2OH).

4.4.28 Synthesis of 2-(chloromethyl)benzyl) alcohol (98)[15]



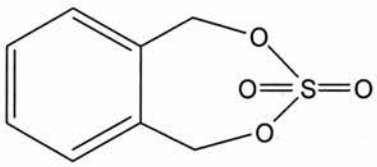
1,2-bis(hydroxymethyl)benzene (97) (7.43 g, 54 mmol) was dissolved in concentrated hydrochloric acid (30 cm^3) and stirred for 30 minutes by which time the solution had started to become cloudy. The solution was carefully added to water (100 cm^3) and the product was extracted with diethyl ether (3 x 50 cm^3). The combined organic layers were washed successively with water (3 x 30 cm^3), 10 % sodium bicarbonate solution (20 cm^3), water (30 cm^3) and brine (2 x 30 cm^3). The organic layer was dried over magnesium sulphate and the solvent removed *in vacuo* leaving a white solid which was recrystallised from hot hexane. (6.30 g, 75 %). mp= 52 °C (Lit.[16] = 51.0 – 51.5 °C) ^1H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.92 (br s, 1 H, $ArCH_2OH$), 4.62 (s, 2 H, $ArCH_2OH$), 4.71 (s, 2 H, $ArCH_2Cl$), 7.12 – 7.40 (m, 4 H, Ar*H*); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) δ = 43.5 (s, $ArCH_2Cl$), 61.9 (s, $ArCH_2OH$), 127.9 (s, *Ar*H), 128.4 (s, *Ar*H), 128.9 (s, *Ar*H), 130.0 (s, *Ar*H), 135.1 (s, $ArCH_2Cl$), 138.9 (s, $ArCH_2OH$).

4.4.29 Synthesis of 1,5-dihydro-benzo[1,3,2]dioxathie-3-oxide (100)[17]



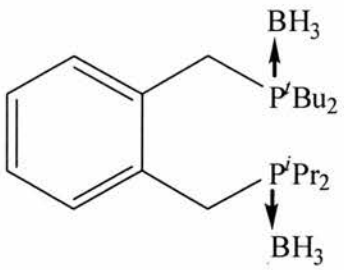
1,2-bis(hydroxymethyl)benzene (97) (3.73 g, 27 mmol) was dissolved in dichloromethane (40 cm^3) and cooled to 0 °C. A dichloromethane (5 cm^3) solution of thionyl chloride (4.17 g, 35 mmol, 1.3 eq) was added slowly. The solution was stirred for 2 hours after which time water (10 cm^3) was added carefully. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 cm^3). The combined organic layers were washed with water (10 cm^3) and brine (2 x 10 cm^3) and dried over $MgSO_4$. The solvent was removed *in vacuo* to leave a colourless solid (4.53 g, 91 %). mp = 37 °C (Lit.[18] = 36 – 37 °C). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 4.52 (d, $^2J_{HH}$ = 14 Hz, 2 H, PhCH*H*OS(O)), 5.02 (d, $^2J_{HH}$ = 14 Hz, 2 H, PhC*H*HOS(O)), 7.24 – 7.38 (m, 4 H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 63.2 (s, CH_2OS(O)), 128.79 (s, *Ar*H), 128.81 (s, *Ar*H) 136.3 (s, *Ar*CH_2).

4.4.30 Synthesis of 1,5-dihydro-benzo[1,3,2]dioxathie-3,3-dioxide (101)[17]



100 (4.42 g, 24 mmol) was dissolved in 1,2-dichloroethane (10 cm^3), acetonitrile (10 cm^3) and water (15 cm^3). To this $NaIO_4$ (11.55 g, 54 mmol, 2.25 eq) and $RuCl_3.H_2O$ (23 mg, 0.1 mmol) were added and the resultant solution was stirred for 30 minutes. After this time the solution was extracted with dichloromethane (3 x 20 cm^3) and the combined organic layers were washed with water (20 cm^3) and brine (2 x 20 cm^3). The organic layer was dried with $MgSO_4$ and the solvent removed *in vacuo* to leave a white solid (4.60 g, 96 %). ^1H NMR (300 MHz, $CDCl_3$, 298 K): δ = 5.43 (s, 4 H, $PhCH_2OS(O)_2$), 7.35 – 7.40 (m, 2 H, aromatic) 7.42 – 7.47 (m, 2 H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 62.9 ($PhCH_2OS(O)$), 128.5 (*Ar*), 136.3 (*Ar*).

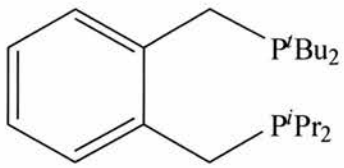
4.4.31 Synthesis of 1-di-*tert*-butylphosphinomethyl-2-di-*iso*-propylphosphinomethylbenzene-borane (102)



Di-*tert*-butylphosphine-borane (574 mg, 3.6 mmol) was dissolved in THF (20 cm^3) and cooled to 0 °C. To this *n*-butyl lithium (2.5 M hexane solution, 1.45 cm^3, 3.6 mmol) was slowly added and the solution was allowed to warm to room temperature. This solution was slowly added to a THF (30 cm^3) solution of **101** (581 mg, 3.6 mmol) cooled to –78 °C. After complete addition the solution was warmed to room temperature and allowed to stir for 30 minutes. A $^{31}P\{^1H\}$ NMR spectrum of the solution showed one peak at 50.3 ppm indicating full deprotonation of the phosphine. The solution was recooled to –78 °C, and a THF (20 cm^3) solution of $LiP^tBu^iPr(BH_3)$ – prepared from di-*iso*-propylphosphine-borane (476 mg, 3.6 mmol) and *n*-butyl lithium (2.5 M hexane solution, 1.45 cm^3, 3.6 mmol) - was added slowly. Once all of the solution was added the solution was allowed to warm to room temperature and stir for three hours. After this time, water (20 cm^3) was carefully added and the solution was extracted with diethyl ether (3 x 20 cm^3). The combined organic layers were washed successively with water (20 cm^3) and brine (2 x 20 cm^3). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo* leaving a crude solid which was recrystallised from hexane affording the title product as colourless crystals (1.12 g, 79 %). mp = 114 - 115 °C. (Found: C, 66.82 %; H, 11.56 % Calc. for $C_{22}H_{46}B_2P_2$: C, 67.04

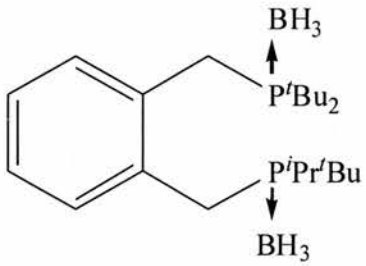
%; H, 11.76 %) ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = -0.45 – 0.92 (br m, 6 H, P-BH_3), 0.93 (dd, $^{3}J_{PH}$ = 14 Hz, $^{3}J_{HH}$ = 7 Hz, 6 H, PCHCH_3), 1.02 (dd, $^{3}J_{PH}$ = 14 Hz, $^{3}J_{HH}$ = 7 Hz, 6 H, PCHCH_3), 1.09 (d, $^{3}J_{PH}$ = 12 Hz, 18 H, PCCH_3), 1.82 (d sept, $^{2}J_{PH}$ = 10 Hz, $^{3}J_{HH}$ = 7 Hz, 2 H, PCHCH$_3$), 3.13 (d, $^{2}J_{PH}$ = 12 Hz, 2 H, ArCH_2P), 3.25 (d, $^{2}J_{PH}$ = 12 Hz, 2 H, ArCH_2P), 7.10 – 7.22 (m, 3 H, Ar), 7.55 – 7.62 (m, 1 H, Ar); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$. 298 K) δ = 35.2 (m, BzP(BH$_3$)^{i}Pr$_2$), 50.0 (m, BzP(BH$_3$)^{t}Bu$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$. 298 K) δ = 17.8 (d, 8 Hz, PCHCH$_3$), 22.0 (d, 32 Hz, PCHCH$_3$), 24.4 (d, 24 Hz, PCCH$_3$), 26.7 (d, 26 Hz, ArCH$_2$P^{i}Pr$_2$), 29.0 (d, 14 Hz, PCCH$_3$), 33.3 (d, 24 Hz, ArCH$_2$P^{t}Bu$_2$), 127.0 (s, ArH), 127.1 (s, *Ar*H), 131.6 (s, *Ar*H), 132.9 (s, *Ar*H), 131.1 (s, *Ar*CH$_2$), 135.0 (s, *Ar*CH$_2$); ES(+)-MS = 417.27 (100 %, [M+Na^{+}], based on ^{11}B)

4.4.32 Synthesis of 1-di-*tert*-butylphosphinomethyl-2-di-*iso*-propylphosphinomethylbenzene (103)



102 (0.96 g, 2.4 mmol) was dissolved in diethylamine (10 cm^3) and refluxed under a nitrogen atmosphere for 16 hours. The solution was cooled and the diethylamine was removed *in vacuo* leaving a white paste which was dissolved in toluene (10 cm^3) and passed through a plug of silica. Toluene (10 cm^3) was used to wash the column and the solvent was removed *in vacuo* from the combined organic fractions leaving a crude white solid. Upon recrystallising from MeOH the title product was obtained as a white powder (0.82 g, 93 %). mp = 43 – 44 °C. (Found: C, 72.29 %; H, 11.28 % Calc. for $C_{22}H_{40}P_2$: C, 72.10 %; H, 11.00 %) ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 0.93 (dd, $^3J_{PH}$ = 14 Hz, $^3J_{HH}$ = 7 Hz, 6 H, PCHCH_3), 1.02 (dd, $^3J_{PH}$ = 14 Hz, $^3J_{HH}$ = 7 Hz, 6 H, PCHCH_3), 1.09 (d, $^3J_{PH}$ = 12 Hz, 18 H, PCCH_3), 1.82 (d sept, $^2J_{PH}$ = 10 Hz, $^3J_{HH}$ = 7 Hz, 2 H, PC*H*CH_3), 3.13 (d, $^2J_{PH}$ = 12 Hz, 2 H, ArCH_2P), 3.25 (d, $^2J_{PH}$ = 12 Hz, 2 H, ArCH_2P), 7.10 – 7.22 (m, 3 H, Ar), 7.55 – 7.62 (m, 1 H, Ar); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$. 298 K) δ = 5.3 (s, BzP^{i}Pr$_2$), 28.5 (s, BzP^{t}Bu$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$. 298 K) δ = 17.6 (d, 8 Hz, PCH*C*H_3), 22.2 (d, 32 Hz, P*C*HCH_3), 24.4 (d, 24 Hz, Ar*C*H_2P^{i}Pr$_2$), 26.8 (d, 26 Hz, P*C*CH_3), 30.1 (d, 24 Hz, PC*C*H_3), 33.5 (d, 24 Hz, Ar*C*H_2P^{t}Bu$_2$), 127.0 (s, *Ar*H), 127.1 (s, *Ar*H), 131.6 (s, *Ar*H), 132.9 (s, *Ar*H), 131.1 (s, *Ar*CH_2), 135.0 (s, *Ar*CH_2); Accurate ES(+)-MS = 367.2691 (Calculated for $C_{22}H_{41}P_2$ = 367.2684 $[M - H]^+$)

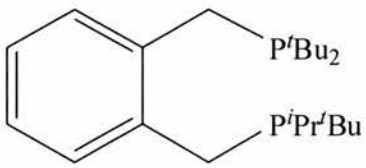
4.4.33 Synthesis of 1-di-*tert*-butylphosphinomethyl-2-*tert*-butyl-*iso*-propylphosphinomethylbenzene-borane (104)



Di-*tert*-butylphosphine-borane (91) (511 mg, 3.2 mmol) was dissolved in THF (20 cm^3) and cooled to 0 °C. To this *n*-butyl lithium (2.5 M hexane solution, 1.3 cm^3, 3.2 mmol) was slowly added and the solution allowed to warm to room temperature. This solution was slowly added to a THF (30 cm^3) solution of **101** (516 mg, 3.2 mmol) cooled to –78 °C. After complete addition the solution was warmed to room temperature and allowed to stir for 30 minutes. A $^{31}P\{^1H\}$ NMR spectrum of the solution gave one peak at 50.3 ppm indicating full deprotonation of the phosphine. The solution was recooled to –78 °C and a THF (20 cm^3) solution of $LiP^tBu^iPr(BH_3)$ – prepared from *tert*-butyl-*iso*-propylphosphine-borane (467 mg, 3.2 mmol) in THF cooled to 0 °C and *n*-butyl lithium (2.5 M hexane solution, 1.3 cm^3, 3.2 mmol) - was added slowly. Once all the solution was completely added the solution was allowed to warm to room temperature and stir for three hours. After this time water (20 cm^3) was carefully added and the solution was extracted with diethyl ether (3 x 20 cm^3). The combined organic layers were washer successively with water (20 cm^3) and brine (2 x 20 cm^3). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo* leaving a crude solid. This was recrystallised from hexane affording the title product as colourless crystals (1.20 g, 87 %). mp = 151 °C. (Found: C, 67.71 %; H, 12.05 % Calc. for $C_{23}H_{48}B_2P_2$: C, 67.67 %;

H, 11.85 %) ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = - 0.11 – 1.02 (m, 6 H, PBH_3), 1.12 (dd, $^{3}J_{PH}$ = 14 Hz, $^{3}J_{HH}$ = 7 Hz, 3 H, PC*H*CH_3), 1.28 (dd, $^{3}J_{PH}$ = 14 Hz, $^{3}J_{HH}$ = 7 Hz, 3 H, PCHC*H*$_3$), 1.25 (d, $^{3}J_{PH}$ = 12 Hz, 9 H, PCC*H*$_3$), 1.29 (d, $^{3}J_{PH}$ = 12 Hz, 9 H, PCC*H*$_3$) , 1.30 (d, $^{3}J_{PH}$ = 12 Hz, 9 H, PCC*H*$_3$), 2.03 (d sept, $^{2}J_{PH}$ = 11 Hz, $^{3}J_{HH}$ = 7 Hz, 1 H, PC*H*CH_3), 3.18 – 3.68 (m, 4 H, ArC*H*$_2$P), 7.10 – 7.21 (m, 3 H, Ar*H*), 7.53 – 7.63 (m, 1 H, Ar*H*); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$, 298 K) δ = 41.8 (quartet, $^{1}J_{PB}$ = 72 Hz, P^{t}Bu^{i}Pr(BH_3)), 50.1 (quartet, $^{1}J_{PB}$ = 74 Hz, P^{t}Bu$_2$(BH_3)); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K) δ = 19.2 (d, 11 Hz, PCH*C*H_3), 23.7 (d, 28 Hz, P*C*HCH_3), 24.8 (d, 24 Hz, $ArCH_2$P^{i}Pr^{t}Bu), 25.5 (d, 26 Hz, P*C*CH_3), 29.0 (d, 7 Hz, PC*C*H_3), 33.3 (d, 7 Hz, Ar*C*H_2P^{t}Bu$_2$), 127.0 (s, *Ar*H), 131.7 (s, *Ar*H), 132.9 (s, *Ar*H), 133.6 (*Ar*CH_2P), 135.0 (*A*rCH_2P) MS(+)-MS = 431.30 (100 %, based on ^{11}B)

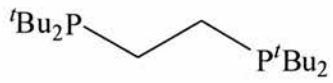
4.4.34 Synthesis of 1-di-*tert*-butylphosphinomethyl-2-*tert*-butyl-*iso*-propylphosphinomethylbenzene (105)



104 (0.85 g, 2.1 mmol) was dissolved in diethylamine (10 cm^3) and was refluxed under a nitrogen atmosphere for 16 hours. The solution was cooled and the diethylamine was removed *in vacuo* leaving a white paste which was dissolved in toluene (10 cm^3) and passed through a plug of silica. Toluene (10 cm^3) was used to wash the column and the solvent was removed from the combined organic fractions *in vacuo* leaving a crude white solid. Upon recrystallising from MeOH the title product was obtained as a white powder (0.67 g, 85 %). mp = 68 – 69 °C. (Found: C, 72.29 %; H, 11.28 % Calc. for

$C_{23}H_{42}P_2$: C, 72.59 %; H, 11.12 %). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.02 (dd, $^3J_{PH}$ = 10 Hz, $^3J_{HH}$ = 7 Hz, 6 H, PCHCH_3), 1.05 (d, $^3J_{PH}$ = 11 Hz, 9 H, PCCH_3), 1.06 (d, $^3J_{PH}$ = 11 Hz, 9 H, PCCH_3), 1.07 (d, $^3J_{PH}$ = 11 Hz, 9 H, PCCH_3), 2.96 (m, 4 H, ArCH_2P), 6.98 (m, 2 H, Ar*H*), 7.23 (m, 1 H, Ar*H*), 7.52 (m, 1 H, Ar*H*); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$, 298 K) δ = 16.7 (s, BzP^{t}Bu^{i}Pr), 28.6 (s, BzP^{t}Bu$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K) δ = 20.9 (d, 9 Hz, PCH*C*H$_3$), 22.7 (d, 18 Hz, P*C*HCH$_3$), 24.1 (d, 20 Hz, P*C*CH$_3$), 26.4 (d, 24 Hz, P*C*CH$_3$), 27.1 (d, 24 Hz, PhCH_2P^{t}Bu^{i}Pr), 29.1 (d, 13 Hz, PC*C*H$_3$), 30.3 (d, 13 Hz, PC*C*H$_3$), 32.3 (d, 23 Hz, PhCH_2P^{t}Bu$_2$), 125.7 (d, 20 Hz, Ar*H*), 131.0 (d, 10 Hz, Ar*H*), 131.3 (d, 14 Hz, Ar*H*), 131.4 (d, 17 Hz, Ar*H*), 138.2 (d, 7 Hz, *Ar*CH$_2$P), 139.1 (d, 11 Hz, *Ar*CH$_2$P); Accurate ES(+)-MS = 381.2845 (Calculated for $C_{23}H_{43}P_2$ = 381.2840 $[M - H]^+$)

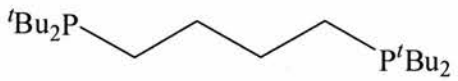
4.4.35 Synthesis of 1,2-bis(di-*tert*-butylphosphino)ethane (106)[19]



Bis(dichlorophosphino)ethane (1.88 g, 10.3 mmol) was dissolved in diethyl ether (20 cm^3) and cooled to –78 °C. With stirring *tert*-butyl lithium (1.7 M in pentane, 19.4 cm^3, 33 mmol) was added over half an hour and the solution was allowed to warm to room temperature. The solution was stirred for a further hour. A ^{31}P{^{1}H} NMR spectrum of the solution was recorded to verify that all of the chlorophosphine had reacted and the major peak, corresponding to the desired product, was observed at d 38.6 ppm. The diethyl ether was removed *in vacuo*, petroleum ether 40-60° (20 cm^3) was added and the solution filtered. The remaining solid (LiCl) was washed with more petroleum ether 40-60° (2 x10 cm^3) and the combined organic aliquots washed with water (20 cm^3).

The organic layer was decanted and dried over magnesium sulphate. The solution was filtered and the petroleum ether 40-60° removed in *vacuo* to leave a white residue that was recrystallised from MeOH (20 cm^3). After the flask was left at –78 °C overnight the MeOH was removed by filtration to leave pure white crystals (482 mg, 1.5 mmol, 19 %). mp = 75 –76 °C (Lit[19]. = 76 °C); ^1H NMR (300 MHz, $CDCl_3$, 298 K): δ =1.59 (s, 4 H, PCH_2CH_2P), 1.72 (d, $^3J_{PH}$ = 10.7 Hz, 16 H, $PCCH_3$); $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$, 298 K) δ = 38.6; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) δ = 24.2 (dd, 15 Hz, 14 Hz, $^tBu_2PCH_2CH_2P^tBu_2$), 29.9 (d, 14 Hz, $PCCH_3$), 31.5 (d, 23 Hz, $PCCH_3$).

4.4.36 Synthesis of 1,4-bis(di-*tert*-butylphosphino)butane (107)



n-butyl lithium (1.6 M in hexane, 8.17 cm^3, 13.1 mmol) was slowly added to THF (20 cm^3) solution of di-*tert*-butylphosphine (1.86 g, 12.7 mmol). The solution was cooled to -78 °C and 1,4-dichlorobutane (744 mg, 6.36 mmol) was added slowly over a period of 20 minutes. The mixture was allowed to warm to room temperature and stir for a further 3 hours. After this degassed water (10 cm^3) was carefully added and the layers separated. The organic layer was washed with water (10 cm^3) and brine (2 x 20 cm^3). The organic layer was separated, dried over $MgSO_4$, and the solvent was removed *in vacuo*. The resultant solid was recrystallised as colourless plates from hot MeOH. (2.03 g, 92 %). mp = 44 – 45 °C. (Found: C, 79.15 %; H, 12.96 % Calc. for $C_{20}H_{44}P_2$: C, 69.32 %; H, 12.80 %). ^1H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.12 (d, $^3J_{PH}$ = 14 Hz, 36 H, $PCCH_3$), 1.35 (m, 4 H, $PCH_2CH_2CH_2CH_2P$), 1.58 – 1.68 (m, 4 H, $PCH_2CH_2CH_2CH_2P$); $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$, 298 K) δ = 30.2 (s, $CH_2P^tBu_2$);

$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) δ = 21.3 (d, 15 Hz, $PCCH_3$), 30.0 (d, 14 Hz, $PCCH_3$), 31.5 (d, 20 Hz,), 33.1 (dd, 25 Hz, 12 Hz, $PCH_2CH_2CH_2CH_2P$); Accurate ES(+)-MS = 347.2996 (Calculated for $C_{20}H_{45}P_2$ = 347.2997 $[M - H]^+$)

4.5 Synthesis of organometallic complexes

4.5.1 Synthesis of tetracarbonyl(norbornadiene) molybdenum(0)[20]

$[Mo(CO)_6]$ (3.81 g, 14.4 mmol) was dissolved in THF (50 cm^3) and heated under reflux for 24 hours. Norbornadiene (1.75 g, 18.5 mmol) was added, and the solution was stirred for 5 hours after which a further portion of norbornadiene (1.75 g, 18.5 mmol) was added. The solution was heated under reflux for 24 hours after which the solution was allowed to cool and the solvent was removed *in vacuo* leaving a green solid to which petroleum ether 40-60° was added. The solution was filtered hot, and upon cooling, the title compound recrystallised as olive green plates. (1.73 g, 40 %). mp = 79 °C. ^1H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.27 (tr, $^3J_{HH}$ = 1.25 Hz, 2 H, CH_2), 3.71 (trtr, $^3J_{HH}$ = 2.4 Hz, $^3J_{HH}$ = 1.25 Hz, 2 H, *CH*), 4.85 (tr, $^3J_{HH}$ = 1.25 Hz, 2 H, *CH*=C*H*); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) δ = 49.5 (s, *CH*), 65.4 (s, CH_2), 78.9 (s, *CH*=*CH*), 214.6 (s, Mo-*CO*), 218.6 (s, M-*CO*). Selected IR data (CH_2Cl_2 solution) ν(cm^{-1}) = 2041 (Mo-CO), 1951 (Mo-CO), 1950 (Mo-CO), 1888 (Mo-CO).

4.5.2 Synthesis of (1,2-bis(di-*tert*-butylphosphinomethyl)benzene)tetracarbonyl molybdenum(0)

[$Mo(CO)_4$(norbornadiene)] (150 mg, 0.5 mmol) was dissolved in dichloromethane (10 cm^3) and DTBPMB (200 mg, 0.5 mmol) was added. The solution was heated under reflux for 2 hours and then cooled. MeOH (10 cm^3) was added and the dichloromethane was removed *in vacuo* precipitating a yellow solid. The solution was filtered and the solid was washed with MeOH. (173 mg, 57 %). 190 °C (decomp.) (Found: C, 55.98 %; H, 7.42 % Calc. for $C_{28}H_{44}MoO_4P_2$: C, 55.81 %; H, 7.36 %). ^1H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.40 (d, $^3J_{PH}$ = 11 Hz, 36 H, PCC*H*$_3$), 3.42 (d, $^2J_{PH}$ = 5 Hz, 4 H, ArC*H*$_2$P^{t}Bu$_2$), 7.11 (m, 2 H, Ar*H*), 7.34 (m, 2 H, Ar*H*); $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$, 298 K) δ = 57.9; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) δ = 30.1 (s, PC*C*H$_3$), 31.6 (d, 14 Hz, PC*C*H$_3$), 37.2 (d, 4 Hz, Ar*C*H$_2$P^{t}Bu$_2$), 126.3 (s, *Ar*H), 132.4 (s, *Ar*H), 135.5 (s, *Ar*), 207.4 (d, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O), 213.3 (tr, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O), 215.8 (tr, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O), 215.3 (d, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O). Selected IR data (CH_2Cl_2 solution) ν(cm^{-1}) = 2006 (Mo-CO), 1894 (Mo-CO), 1878 (Mo-CO), 1859 (Mo-CO).

4.5.3 Synthesis of (1,2-bis(dicyclohexylphosphinomethyl)benzene)tetracarbonyl molybdenum(0)

$[Mo(CO)_4(norbornadiene)]$ (18 mg, 0.06 mmol) was dissolved in dichloromethane (10 cm^3) and DCPMB (30 mg, 0.06 mmol) was added. The solution was heated under reflux for 2 hours and then cooled. MeOH (10 cm^3) was added and the dichloromethane was removed *in vacuo* precipitating a yellow solid. The solution was filtered and the solid was washed with MeOH. (25 mg, 58 %). 195 °C (decomp.). (Found: C, 60.92 %; H, 7.50 % Calc. for $C_{36}H_{52}MoO_4P_2$: C, 61.19 %; H, 7.42 %). ^1H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.22 (m, 14 H, Cy*H*), 1.48 (m, 8 H, Cy*H*), 1.82 (m, 22 H, Cy*H*), 3.02 (d, $^2J_{PH}$ = 12 Hz, 4 H, ArCH_2PCy_2), 6.98 (m, 2 H, Ar*H*), 7.12 (m, 2 H, Ar*H*), $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$, 298 K) δ = 28.9. Selected IR data (CH_2Cl_2 solution) ν(cm^{-1}) = 2011 (Mo-CO), 1908 (Mo-CO), 1890 (Mo-CO), 1862 (Mo-CO).

4.5.4 Synthesis (1,2-bis(di-*tert*-butylphosphinomethyl)napthalene)tetracarbonyl molybdenum(0)

$[Mo(CO)_4(norbornadiene)]$ (100 mg, 0.3 mmol) was dissolved in dichloromethane (10 cm^3) and 1,2-DTBPMN (182 mg, 0.3 mmol) was added. The solution was heated under reflux for 2 hours and then cooled. MeOH (10 cm^3) was added and the dichloromethane was removed *in vacuo* precipitating a yellow solid. The solution was filtered and the solid was washed with MeOH. (141 mg, 62 %). 187 °C (decomp.) (Found: C, 58.62 %; H, 7.32 % Calc. for $C_{32}H_{46}MoO_4P_2$: C, 58.89 %; H, 7.10 %). ^1H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.52 (m, 36 H, PCCH_3), 3.56 (d, $^2J_{PH}$ = 12 Hz, 2

H, ArCH_2P^{t}Bu$_2$), 3.91 (d, $^2J_{PH}$ = 8 Hz, 2 H, ArCH_2P^{t}Bu$_2$), 7.38 – 7.62 (m, 4 H, Ar*H*), 7.78 (d, $^3J_{HH}$ = 6 Hz, 1 H, Ar*H*), 8.21 (d, $^3J_{HH}$ = 6 Hz, 1 H, Ar*H*); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$, 298 K) δ = 58.0 (d, $^5J_{PP}$ = 24 Hz, BzP(^{t}Bu$_2$)Mo), 61.1 (d, $^5J_{PP}$ = 24 Hz, BzP(^{t}Bu$_2$)Mo), ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K) δ = 25.2 (s, PCCH_3), 31.6 (d, 14 Hz, PCCH_3), 38.1 (d, 6 Hz, ArCH_2P^{t}Bu$_2$), 38.7 (d, 4 Hz, ArCH_2P^{t}Bu$_2$), 124.9 (s, *Ar*H), 125.7 (s, *Ar*H), 126.3 (s, *Ar*H), 127.0 (s, *Ar*H), 129.3 (s, *Ar*H), 131.6 (s, *Ar*), 133.3 (s, *Ar*), 135.4 (s, *Ar*), 207.3 (d, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O), 213.4 (tr, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O), 215.4 (tr, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O), 215.8 (d, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O). Accurate ES(+)-MS = 649.1880 (Calculated for $C_{31}H_{46}P_2O_3Na^{98}Mo$ = 649.1874, [M – CO + Na^+]); Selected IR data (CH_2Cl_2 solution) ν(cm^{-1}) = 2007 (Mo-CO), 1896 (Mo-CO), 1880 (Mo-CO), 1860 (Mo-CO).

4.5.5 Synthesis of (2,3-bis(di-*tert*-butylphosphinomethyl)napthalene)tetracarbonyl molybdenum(0)

$[Mo(CO)_4(norbornadiene)]$ (100 mg, 0.3 mmol) was dissolved in dichloromethane (10 cm^3) and 2.3-DTBPMN (182 mg, 0.3 mmol) was added. The solution was heated under reflux for 2 hours and then cooled. MeOH (10 cm^3) was added and the dichloromethane was removed *in vacuo* precipitating a yellow solid. The solution was filtered and the solid was washed with MeOH. (118 mg, 52 %). 189 °C (decomp.) (Found: C, 58.64 %; H, 7.34 % Calc. for $C_{32}H_{46}MoO_4P_2$: C, 58.89 %; H, 7.10 %). ^1H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.38 (d, $^3J_{PH}$ = 11 Hz, 36 H, PCC*H*$_3$), 3.40 (d, $^2J_{PH}$ = 4 Hz, 4 H, ArC*H*$_2$P^{t}Bu$_2$), 7.35 (m, 2 H, Ar*H*), 7.62 (m, 2 H, Ar*H*), 7.71 (s, 2 H, Ar*H*); $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$, 298 K) δ = 60.9 (s, BzP(^{t}Bu$_2$)Mo); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 298 K) δ = 30.4 (s), 31.7 (d, 14 Hz) 38.2 (s), 126.6 (s, *Ar*H), 127.2 (s, *Ar*H), 132.1 (s, *Ar*), 132.2 (s, *Ar*H), 135.5 (s, *Ar*), 207.4 (d, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O), 213.4 (tr, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O), 215.2 (tr, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O), 215.3 (d, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O). Accurate ES(+)-MS = 649.1880 (Calculated for $C_{31}H_{46}P_2O_3Na^{98}Mo$ = 649.1879, [M – CO + Na^+]); Selected IR data (CH_2Cl_2 solution) $\nu(cm^{-1})$ = 2007 (Mo-CO), 1900 (Mo-CO), 1881 (Mo-CO), 1861 (Mo-CO).

4.5.6 Synthesis of (1,2-bis(di-*iso*-propylphosphinomethyl)benzene)tetracarbonyl molybdenum(0)

[$Mo(CO)_4$(norbornadiene)] (100 mg, 0.3 mmol) was dissolved in dichloromethane (10 cm^3) and DIPPMB (101 mg, 0.3 mmol) was added. The solution was heated under reflux for 2 hours and then cooled. MeOH (10 cm^3) was added and the dichloromethane was removed *in vacuo* precipitating a yellow solid. The solution was filtered and the solid was washed with MeOH. (97 mg, 59 %). 186 °C (decomp.). (Found: C, 52.49 %; H, 6.74 % Calc. for $C_{24}H_{36}MoO_4P_2$: C, 52.75 %; H, 6.64 %). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.24 (dd, $^3J_{PH}$ = 14 Hz, $^3J_{HH}$ = 7 Hz, 12 H, PCHCH_3), 1.28 (dd, $^3J_{PH}$ = 14 Hz, $^3J_{HH}$ = 7 Hz, 12 H, PCHCH_3), 2.12 (sept, $^3J_{HH}$ = 7 Hz, 4 H, PC*H*CH_3), 3.03 (d, $^2J_{PH}$ = 7 Hz, 4 H, ArCH_2P^{i}Pr$_2$), 7.02 (m, 2 H, Ar*H*), 7.14 (m, 2 H, Ar*H*); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$, 298 K) δ = 35.5 (s, BzP(^{i}Pr$_2$)Mo); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K) δ = 19.0 (s, PCH*C*H_3), 19.9 (s, PCH*C*H_3), 27.6 (d, $^1J_{PC}$ = 9 Hz, P*C*HCH_3), 31.4 (s, ArCH_2P), 126.9 (s, *Ar*), 131.7 (s, *Ar*H), 135.9 (s, *Ar*CH_2P), 207.4 (d, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O), 213.1 (tr, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O), 215.2 (tr, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O), 215.0 (d, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O); Selected IR data (CH_2Cl_2 solution) ν(cm^{-1}) = 2019 (Mo-CO), 1924 (Mo-CO), 1908 (Mo-CO), 1869 (Mo-CO).

4.5.7 Synthesis of (1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene)tetracarbonyl molybdenum(0)

[Mo(CO)$_4$(norbornadiene)] (100 mg, 0.3 mmol) was dissolved in dichloromethane (10 cm^3) and BIPPMB (110 mg, 0.3 mmol) was added. The solution was heated under reflux for 2 hours and then cooled. MeOH (10 cm^3) was added and the dichloromethane was removed *in vacuo* precipitating a yellow solid. The solution was filtered and the solid was washed with MeOH. (109 mg, 63 %). 189 °C (decomp.) (Found: C, 53.65 %; H, 8.13 % Calc. for $C_{26}H_{46}MoO_4P_2$: C, 53.79 %; H, 7.99 %). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 1.25 (dd, $^3J_{PH}$ = 14 Hz, $^3J_{HH}$ = 7 Hz, 6 H, PCHCH_3), 1.27 (dd, $^3J_{PH}$ = 14 Hz, $^3J_{HH}$ = 7 Hz, 6 H, PCHCH_3), 1.40 (d, $^3J_{PH}$ = 11 Hz, 18 H, PCCH_3), 2.10 (sept, $^3J_{HH}$ = 7 Hz, 2 H, PCHCH$_3$), 3.38 (d, $^2J_{PH}$ = 7 Hz, 4 H, ArCH_2P^{t}Bu^{i}Pr), 7.06 (m, 2 H, ArH), 7.13 (m, 2 H, ArH); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$, 298 K) δ = 42.1 (s, BzP(^{t}Bu^{i}Pr)Mo); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K) δ = 19.1 (s, PCHCH_3), 19.9 (s, PCHCH_3), 25.3 (s, PCCH_3), 27.4 (d, $^1J_{PC}$ = 9 Hz, P$CHCH_3$), 30.2 (s, PCCH_3), 31.4 (s, ArCH_2P), 126.5 (s, *Ar*), 131.7 (s, *Ar*H), 136.1 (s, *Ar*CH$_2$P), 207.3 (d, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O), 213.1 (tr, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O), 215.3 (tr, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O), 214.9 (d, $^2J_{PC}$ = 8 Hz, P-Mo-*C*O); Selected IR data (CH_2Cl_2 solution) ν(cm^{-1}) = 2013 (Mo-CO), 1909 (Mo-CO), 1893 (Mo-CO), 1864 (Mo-CO).

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Chapter 5 – Conclusions and further work

The alkoxycarbonylation of vinyl acetate is an industrially important reaction because the branched ester product is the acetyl protected monomer of a potentially biodegradable polymer (polylactic acid). Also specifically the ethyl ester of lactic acid can be used as an eco-friendly solvent.

In the presence of methanol, vinyl acetate can be degraded to methyl aceate and 1,1-dimethoxyethane. This reaction is both acid and base catalysed. To determine the extent of this side reaction, methanesulphonic acid (MSA), triethylphosphine and 1,2-bis(di-*tert*-butylphosphinomethyl)benzene were independently added to a toluene solution of vinyl acetate and methanol. It was found that MSA or triethylphosphine, but not 1,2-bis(di-*tert*-butylphosphinomethyl)benzene promoted the formation of the methyl acetate and 1,1-dimethoxyethane. However, this side reaction could be eliminated if both the acid and one of the phosphines were added together. This is because the phosphonium salt was formed which effectively removes the acid and base from the solution.

A palladium catalytic cycle promoted by the addition of the electron rich diphosphine and 1,2-bis(di-*tert*-butylphosphinomethyl)benzene and methanesulphonic acid, was found to give full conversion of vinyl acetate to methyl 2- and 3- acetoxy propanoates with 100 % selectivity to the esters and a b:l ratio of 1.2:1. With optimisation of the reaction conditions it was possible to improve the branched selectivity to 3.6:1 when the reaction was carried out at 25 °C and under a CO pressure of 3 bar. No side reaction was observed as and 1,2-bis(di-*tert*-butylphosphinomethyl)benzene was in excess over the acid.

In an attempt to improve the reaction rate and selectivity to the branched ester various diphosphines were synthesised. Derivatives of 1,2-bis(di-*tert*-butylphosphinomethyl)benzene were prepared with different groups on the phosphorus atoms. It was found that the di-*iso*-propyl, dicyclohexyl, diethyl or diphenyl derivatives were not active in the methoxycarbonylation of vinyl acetate. With these ligands it was found that all of the vinyl aceate was converted to methyl acetate due to the inability of the diphosphines to bind all of the acidic protons in the solution and acid catalysed vinyl acetate degradation occurred. With $(^tBu^iPrPCH2)_2C_6H_4$ it was found that there was 7 % conversion of the vinyl acetate with a b:l ratio of 0.8 %.

An extra aromatic ring was added to the backbone of 1,2-bis(di-*tert*-butylphosphinomethyl)benzene to produce two isomeric ligands - 1,2-bis(di-*tert*-butylphosphinomethyl)naphthalene and 2,3-bis(di-*tert*-butylphosphinomethyl)naphthalene. In the methoxycarbonylation of vinyl acetate it was found that these ligands were not as active as 1,2-bis(di-*tert*-butylphosphinomethyl)benzene but they did give the same regioselectivity.

The backbone of the ligand was changed for an aliphatic chain. 1,2-bis(di-*tert*-butylphosphino)ethane, 1,3-bis(di-*tert*-butylphosphino)propane and 1,4-bis(di-*tert*-butylphosphino)butane were synthesised and tested in the methoxycarbonylation of vinyl acetate. Only the propane backbone derivative gave any activity in the methoxycarbonylation of vinyl acetate and a b:l ratio of 0.79:1 was obtained.

This work has shown that the production of methyl 2-acetoxypropanoate from vinyl acetate is possible using a palladium catalysed system promoted by 1,2-bis(di-*tert*-

butylphosphinomethyl)benzene. However the regioselectivity is not high enough to the branched isomer for commercial applications. This needs to the main aim of work that follows on from this thesis. There are two aspects of the system that can be looked at to improve the b:l ratio.

Firstly the ligand system could be changed. From work presented here it seems that a ligand that is highly σ-donating is required. Electron donating groups such as methoxide could be added to the aromatic ring in the backbone or different groups could be added to the phosphorus atom. A high electron donating group that has small steric bulk should increase the b:l ratio. Aminophosphines are known to the extremely electron rich but unfortunately the phosphorus-nitrogen bond is very labile in the presence of methanol.

This work has shown that as the acid concentration increases there is an increase in the branched to linear ratio. Due to the problem of acid promoted vinyl acetate degradation the addition of large amounts of free acid to the system cannot be tolerated. An area that could be investigated is the addition of various proton sources which will allow the formation of the palladium-hydride species but will not promote conversion of vinyl aceate to methyl acetate. As phosphonium salts have been shown to be effective other organic salts could be investigated eg triethylammonium methanesulphonate.

Also for this to be a technology that could lead to the formation of polylactic acid, the S enantiomer must be formed and chiral phosphines will be required. Once a system has been found that gives suitable b:l selectivity, the conversion of the diphosphine to a chiral analogue will need to be undertaken. As the phosphine design for high b:l ratios

is carried out it is worth while thinking about the introduction of groups that have chiral centres. In the 1,2-bis(di-*tert*-butylphosphinomethyl)benzene case there are two potential places of chirality, the phosphorus atom itself or the substitution of the methylene bridge between the benzene ring and the phosphorus atom

Appendix 1

X-Ray Crystallography Data

Crystallography data was performed using a Rigaku Mercury diffractometer; in all cases a minimum of a full hemisphere of data with small 'slices' were collected. Mo-Ka radiation was used from a rotating anode 007 system and multiscan adsorption corrections were applied. All of the non-H atoms were refined anisotropically with the C-H hydrogen atoms being refined in idealised geometries. B-H geometries were idealised with a isotropic thermal parameter. All calculations employed the SHELXTL program system.1

1. SHELXTL, Bruker AXS, Madison, WI, 1999.

Appendix 1.1 – X-ray Crystallography data for 1,2-bis(*tert*-butyl-*iso*-propylphosphinomethyl)benzene

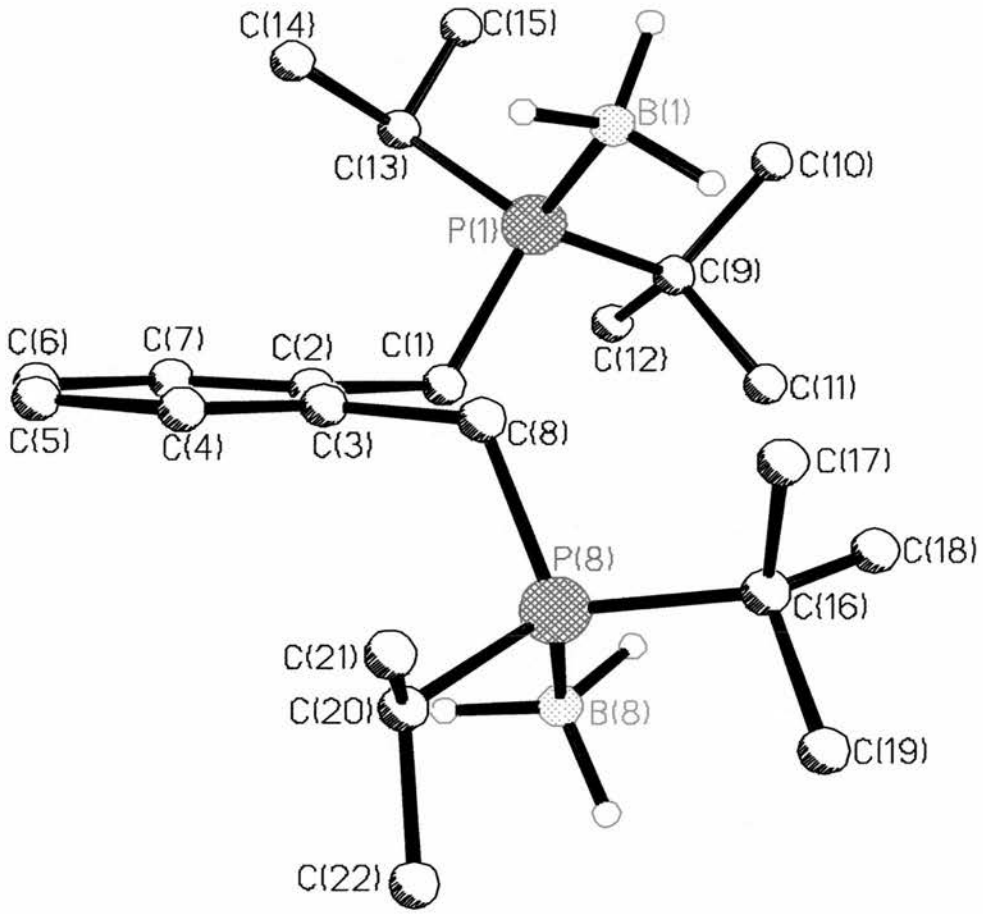

Table 1. Crystal data and structure refinement for ARDCH1.

Identification code	ardch1	
Empirical formula	C22 H46 B2 P2	
Formula weight	394.15	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 12.630(2) Å	α = 90°.
	b = 18.239(2) Å	β = 110.869(4)°.
	c = 11.595(2) Å	γ = 90°.
Volume	2495.6(7) $Å^3$	
Z	4	
Density (calculated)	1.049 Mg/m^3	
Absorption coefficient	0.179 mm^{-1}	
F(000)	872	
Crystal size	0.20 x 0.15 x 0.15 mm^3	
Theta range for data collection	2.06 to 25.34°.	
Index ranges	-11<=h<=14, -16<=k<=21, -13<=l<=9	
Reflections collected	15220	
Independent reflections	4467 [R(int) = 0.0224]	
Completeness to theta = 25.34°	97.8 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.8865	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4467 / 0 / 242	
Goodness-of-fit on F^2	0.993	
Final R indices [I>2sigma(I)]	R1 = 0.0352, wR2 = 0.0905	
R indices (all data)	R1 = 0.0376, wR2 = 0.0931	
Largest diff. peak and hole	0.357 and -0.253 e.Å$^-$	