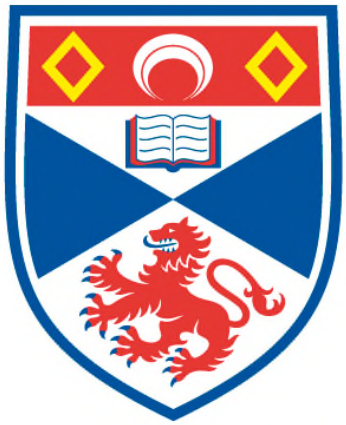
Pd CATALYSED SYNTHESIS OF PHOSPHINES FOR HOMOGENEOUS CATALYSIS

Karen Serena Damian

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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Pd catalysed synthesis of phosphines for homogeneous catalysis

A thesis submitted for the degree of Ph.D. by

Karen Serena Damian

Under the Supervision of Dr. Matthew L. Clarke

School of Chemistry
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Dedicated to

Anna Maria and Franco

If I am walking with two other men, each of them will serve as my teacher. I will pick out the good point of the one and imitate them, and the bad points of the other and correct them in myself.

Confucius

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Abstract

The synthesis of ligands has been identified as the limitation for wider application of catalytic asymmetric synthesis. Indeed, synthesis of phosphorus-based ligands, has been often shown to be challenging and not always efficient. It has also been observed that subtle changes in the ligand structure can lead to big differences in the catalytic activity of the ligand when coordinated to a metal. Therefore, it was considered useful to develop a methodology in order to obtain a library of phosphines.

The first chapter of the thesis is a review of recent development in catalytic phosphine synthesis.

In the second chapter of this thesis, the microwave mediated Suzuki cross coupling reaction has been investigated. In particular, attention has been focussed on the coupling of different arylboronic acids to chloroarylphosphine oxides, which are, in general, considered challenging coupling partners for this type of reaction. The reaction conditions have been optimised starting from the coupling of phenylboronic acid to tris(4-chlorophenyl)phosphine oxide. Different solvents, bases, and catalysts have been then tested and the better conditions have been developed for this substrate. Indeed, it was shown that the coupling occurs in only 30 minutes at 140 °C, leading to reasonably high yields. These conditions were then applied to two other different chloroarylphosphine oxides with a range of boronic acids, with the aim to verify if the optimised reaction conditions could be applied to other substrates and it was noticed that good yields could be attained. This methodology led us to obtain a library of phosphine oxides. It was then decided to investigate the reduction of phosphine oxides under microwave irradiation. This reaction occurs under conventional heating but it can take several hours. It was observed that reaction times could be importantly reduced when reducing some phosphine oxides under microwave heating. It was found that some phosphine oxides are reduced rapidly under conventional conditions but for more difficult substrates to reduce there are significant advantage to microwave method.

We decided to investigate the microwave mediated P-C bond forming reaction, with the aim to rapidly synthesise a library of phosphines cleanly. The conditions were optimised at first using *o*-trifluoromethylbromobenzene as the substrate. Once the appropriate reaction conditions and catalyst were identified, the reaction was run on other substrates to verify that this could be a general methodology for the synthesis of phosphines. It was found that it is indeed a general method for the synthesis of monophosphines. However, the synthesis of diphosphines with the microwave assisted P-C bond forming reaction on dibromo- and diiodo- aryl compounds proved to be very challenging.

The fourth chapter presents different attempts for the synthesis of the new ligand Ph-DuPHOS. The synthesis of this ligand was considered interesting because of the previous results of other

phospholane-based ligands, such as Ph-BPE and Me-DuPHOS. However, the synthesis of this ligand has proven to be elusive. A monodentate P-N phospholane-based ligand was prepared and its catalytic activity was tested in the rhodium catalysed hydrogenation of alkenes. Moreover, a bidentate (1,2-bisphospholano)xylene ligand was also prepared and its catalytic activity was also tested in the rhodium catalysed hydrogenation of alkenes.

This latter ligand was also used in the hydroxycarbonylation of styrene, since for this reaction bulky diphosphines are required to give branched selectivity. In hydroxycarbonylation it is very rare to give good branched selectivity and there were no examples of substantial enantioselectivity prior to this work. The high regioselectivity and moderate e.e.'s observed suggest promise for future studies. Finally, mechanistic studies on the hydroxycarbonylation of styrene have been carried out in order to investigate the intermediates involved in the reaction as well as the role of the promoters. The possibility of (1-chloroethyl)benzene was proposed as the active intermediate of the reaction. Our results have disproved this possibility, suggesting that the reaction is likely to proceed through the hydride mechanism.

Abbreviations

δ	Chemical shift, in parts per millions down-field of internal standard
Ar	Aromatic
BINAP	2,2’-Bis-(diphenylphosphino)-1,1’-binaphtyl
Bu	Butyl
Cat	Catalyst
d	Doublet (NMR)
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	Dichloromethane
dd	doublet of doublets (NMR)
dppb	1,4-Bis-(diphenylphosphino)butane
dppe	1,2-Bis-(diphenylphosphino)ethane
dppf	1,1’-Bis-(diphenylphosphino)ferrocene
dippf	1,1’-Bis-(diisopropylphosphino)ferrocene
e.e.	enantiomeric excess
EI	Electron Impact (MS)
eq	Equivalent
ES-	Negative ion electronspray (MS)
ES+	Positive ion electronspray (MS)
Et	Ethyl
g	gram
h	hour
HexaPHEMP	4,4’-5,5’-6,6’-hexamethylbiphenyl
HPLC	High Pressure Liquid Chromatography
HRMS	High Resolution Mass Spectrum
IR	Infrared
J	Coupling constant (NMR)
L	Ligand
L-DOPA	3-(3,4-dihydroxyphenyl)-L-alanine
m	metha
M	Moles per litre
m	multiplet (NMR)

Me	Methyl
MeCN	Acetonitrile
mg	Milligram
min	Minute
ml	Millilitre
mmol	Millimole
mol	Mole
MS	Mass Spectrum
° C	Celsius degree
p	para
Ph	Phenyl
PhanePhos	4,12-Bis(diphenylphosphino)-[2.2]-paracyclophane
ppm	Part per million
PTSA	*p*-toluenesulfonic acid
q	Quartet (NMR)
r.t.	Room temperature
s	Singlet (NMR)
t	Triplet (NMR)
^{t}Bu	tert-Butyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
TOF	Turn over frequency
TON	Turn over number
TsOH	Tosic acid

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Chapter 1

Palladium catalysed P-C bond forming reactions

1.1 Introduction

In the last couple of decades, metal catalysed asymmetric synthesis has revolutionised the synthesis of enantioenriched compounds. Indeed, it is a very useful methodology for obtaining enantiopure products in high yields without the need of the expensive and time demanding procedures for the isolation of single enantiomers from a racemic mixture. Three of the pioneers of the field shared the Nobel Prize in 2001; Noyori[1] and Knowles[2] for their work on catalytic asymmetric hydrogenation and Sharpless[3] for his work on catalytic asymmetric oxidation, have made many developments in the area.

An example that highlights the importance of asymmetric catalytic reactions is the industrial synthesis of *L*-DOPA established by Knowles team working for Monsanto. With the rhodium complex of a P-chiral-C_2-symmetric chelating diphosphine, DIPAMP **(1)**, an enantiomeric excess of over 99% has been obtained in the hydrogenation of dehydroamino acids (fig. 1.1):

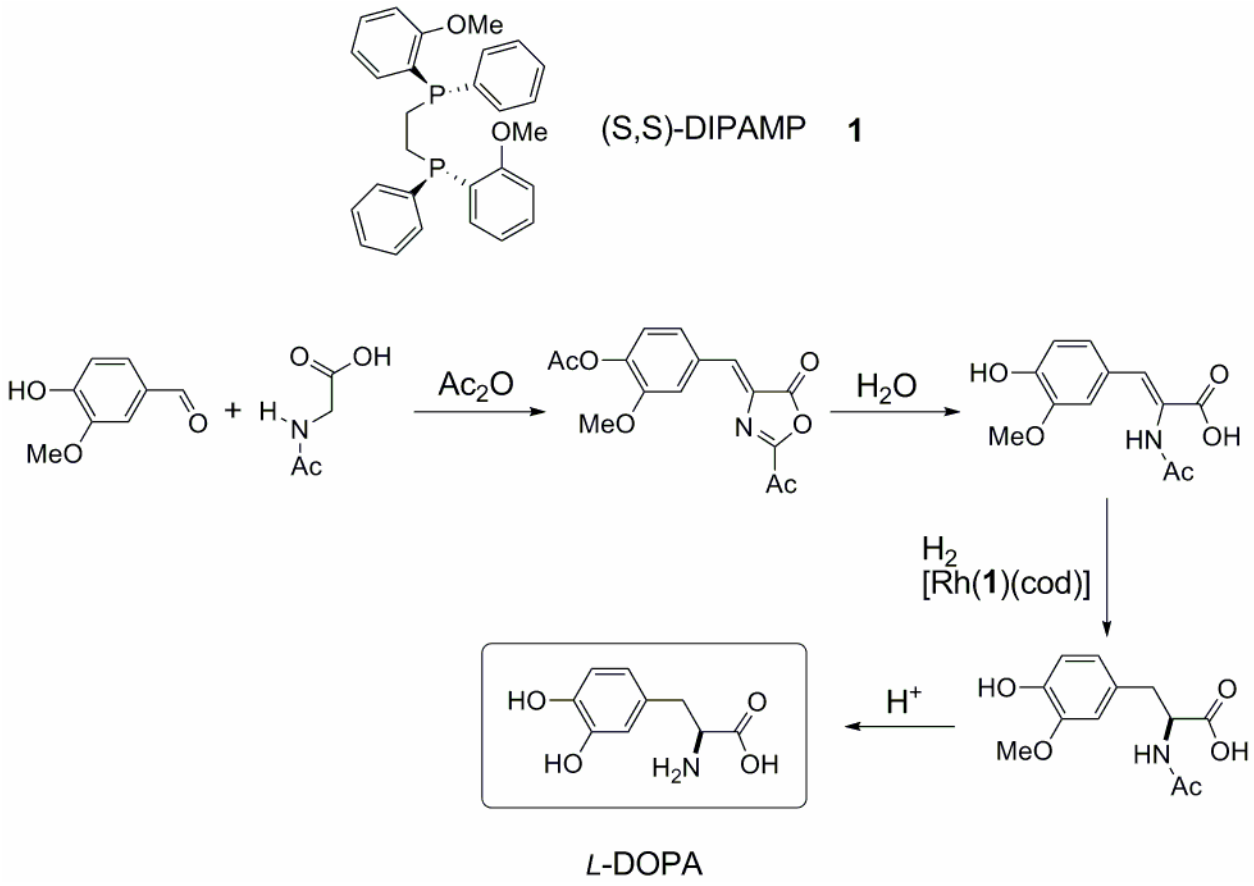


Fig. 1.1 Synthesis of *L*-DOPA

However, this is not the first of a long series of examples of industrial enantioselective catalytic synthesis, indeed there is still not a wide application in industry of catalytic asymmetric synthesis.

Despite there being hundreds and hundreds of enantiopure products, only 20 or 30 are produced using asymmetric transition metal catalysis. This is mainly due to the fact that it is quite demanding in terms of time and money to identify the right catalyst to yield the desired product in high ee. A good example of this key problem has been the development of an industrial asymmetric imine hydrogenation process for the synthesis of the herbicide ingredient (*S*)-metolachlor[4] (fig. 1.2); it took 14 years to set up an industrial scale process to deliver (*S*)-metolachlor in 80% ee. This example is just one among many that highlights that the slow step in catalysis optimisation is ligand synthesis rather than catalyst testing.

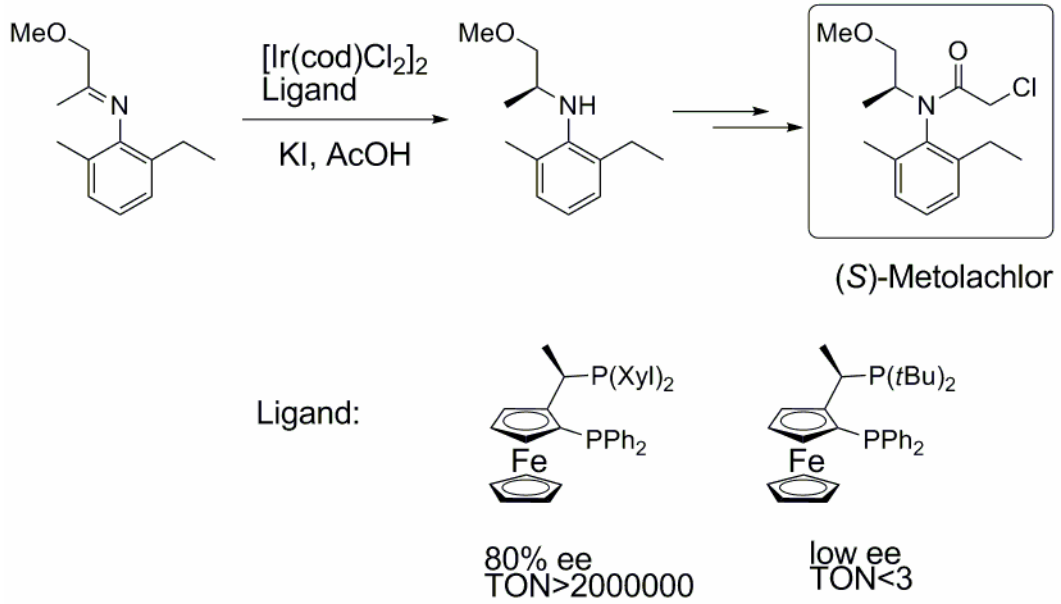


Fig. 1.2 The industrial imine hydrogenation used in the synthesis of (S)-Metolachlor

So far, phosphine-based compounds are the most successful compounds used as ligands in asymmetric transformations. Therefore, it is necessary to focus the attention in the synthesis of phosphines. In this thesis, several strategies that could be used for the synthesis of chiral ligands will be discussed. There is a demand for a clean method to prepare phosphine-based ligands, in part because of the air-sensitivity that such compounds often show, which can make the purification step quite problematic. Moreover, many phosphines have been prepared by using nasty reagents or through very reactive intermediates, and this again has been identified as a drawback, in particular if the scale up of these reactions to industrial level is considered.

The metal catalysed P-C bond forming reaction could be then a suitable methodology to avoid the use of highly reactive reagents for the preparation of phosphines, and also can be the only method for the preparation of certain ligands.

1.2 Where did the idea of metal-catalysed P-C bond forming reaction came from? A bit of history

In the last three decades, palladium-catalysed C-C bond forming reactions have gained more and more interest and variants of this reaction, using different organometallic nucleophiles, (fig. 1.3) have found widespread applications in organic synthesis.[5]

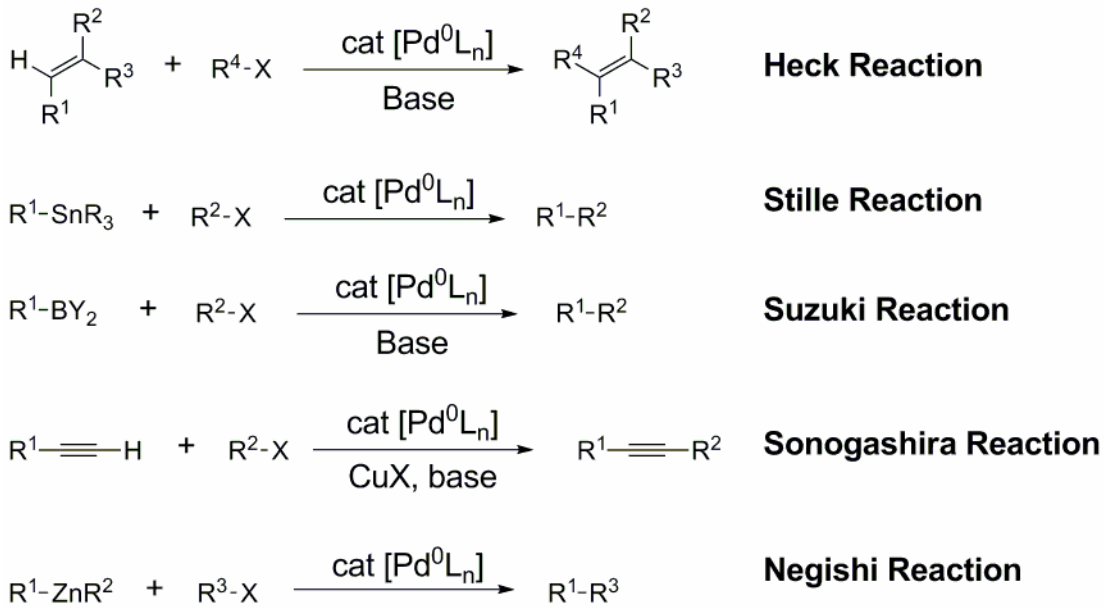


Fig. 1.3 Variants on the palladium-catalysed C-C bond forming reaction

However, the metal-catalysed coupling reaction using non-organometallic nucleophiles has been relatively underexplored until recently.

One of the first C-X bond forming reaction to be successfully investigated was the C-N bond forming reaction. One of the very first examples was reported by Migita and co-workers in the early 1980s, in which *N*,*N*-diethylamino-tributyltin was coupled to different aryl bromides in the presence of a palladium catalyst.[6] The reaction was investigated in depth by Buchwald and Hartwig in the mid 1990s,[7-11] who arrived to the palladium catalysed cross coupling reaction of free amines with different aryl halides using very mild reaction conditions.[12-14] The successful work of Buchwald and Hartwig on C-N bond forming reactions has led the scientific community to apply this methodology to a wide range of non-organometallic nucleophiles, including oxygen-, sulfur-, boron-, silicon-, phosphorus- nucleophiles, the latter being at the top of our list of interests.

1.3 The palladium catalysed P-C bond forming reaction

A key theme in this research project has been attempting to improve methodology for the synthesis of phosphines, and part of this project has investigated microwave-accelerated P-C bond forming reactions. It therefore seems appropriate to review the literature on metal catalysed P-C cross-coupling reactions. For reasons of brevity and the focus of this project, hydrophosphination of alkenes and alkynes[15-17] or addition of dialkylphosphites,[18-20] hypophosphonous esters[21] and hypophosphites[22, 23] to aryl halides are outside the scope of this review.

The first palladium-catalysed reaction of aryl halides with phosphorus-based nucleophiles was reported in the early 1980s by Hirao and co-workers in the preparation of phosphonates (fig. 1.4):[24]

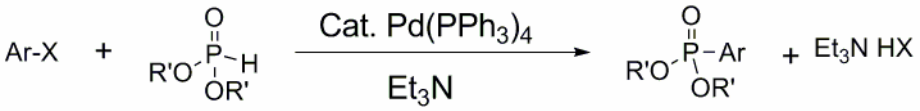


Fig. 1.4 First example of palladium catalysed C-P bond formation

This methodology proved to be very useful for preparing aryl phosphonates, as the Arbuzov and the Michaelis-Becker reactions could only lead to the formation of alkyl phosphonates. These results provided the basis for the metal catalysed formation of other phosphorus-based compounds including phosphines.

1.3.1 The phospha-Stille reaction

The palladium-catalysed P-C bond forming reaction was investigated for the preparation of aryl phosphines by Stille and co-workers in 1987.[25] (Trimethylsilyl)diphenylphosphine and tributylstannyl diphenylphosphine were used as the nucleophiles. The proposed mechanism is shown in fig. 1.5:

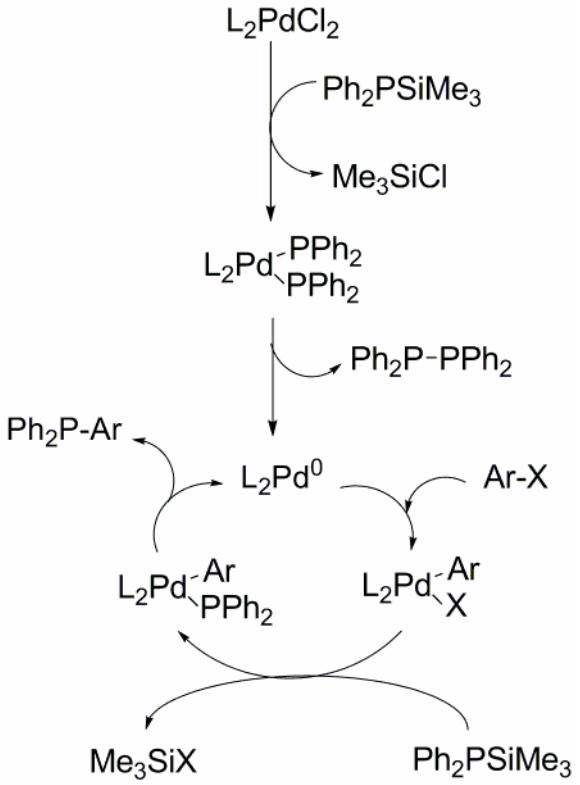


Fig. 1.5 Proposed mechanism for the P-C bond forming reaction

The catalytic cycle shown in figure 1.5 was based on the known reaction of bis(triphenylphosphido)palladium with (trimethylsilyl)diphenylphosphine to give the bis(diphenylphosphino)palladium(II) complex. This phosphine complex can undergo reductive elimination to give tetraphenyldiphosphine and the required palladium(0) catalyst.[26]

Oxidative addition of the aryl halide to the Pd(0) complex occurs, followed by transmetallation between (trimethylsilyl)diphenylphosphine and the arylpalladium halide. The arylated phosphine is then obtained upon reductive elimination.

Stille and co-workers also proved that stannylphosphine react twice as fast as the silyl phosphide. In the eary 2000s, work using the stannyl phosphide as the phosphinating agent has been reported by Rossi and co-workers: they reported high conversions to the product when coupling 1-iodonaphthalene with nBu$_3$SnPPh$_2$ in the presence of a palladium catalyst.[27] The activity of Me$_3$SnPPh$_2$ and KPPh$_2$ as phosphinating agents was also tested but these reactants were not found to be as efficient as nBu$_3$SnPPh$_2$. Chloro- and bromo-naphthalene were also used as substrate but very low yields were detected. 1-Naphthyl *p*-methyl-benzensulfonate also proved to be an unsuccessful substrate, as only yields up to 30% were obtained with the main product of the reaction being the cleavage product 1-naphthol, even in the presence of LiCl, which is believed to promote the reductive elimination when using arenesulfonates as substrates.[28, 29] However, the use of silyl phosphide is preferred over stannyl phosphide not only because the starting material

trimethylsilyl chloride is cheaper, but also because trimethylsilyl compounds are not as toxic as trimethylstannyl derivatives.

The work of Stille and co-workers attracted the attention of phosphorus chemists as it extended the palladium catalysed reaction to phosphine synthesis. However, few drawbacks of this methodology have to be highlighted: first of all, even if many functional groups are tolerated, it has been shown in the work of Rossi that the reaction on nitroiodobenzene leads to the reduction of the nitro group to the amino group, and this reductive effect of the stannyl reagent might limit the substrate scope. Moreover, it would be more useful to use directly the phosphines, without the need of preparing the silyl or stannyl derivative.

1.3.2 Coupling of primary and secondary phosphines to aryl halides

With the use of diphenylphosphine and phenylphosphine as starting material, a great variety of tertiary phosphines can be obtained by palladium-catalysed P-C bond forming reaction with arylhalides, although there are many significant limitations.

This approach has been used by Stelzer and co-workers[30] in 1996: their aim was to prepare water soluble phosphines, therefore they were interested in using as starting material for the P-C coupling reaction arylhalides substituted with polar functionalities (OH, NH_2, COOH and SO_3M; M = Na, K). Thus, a high tolerance to different derivatives was needed. The reactions were carried out in organic solvents pure or mixed with water; organic amines, or KOAc and NaOAc were used as bases and $Pd(OAc)_2$ or $Pd(Ph_3P)_4$ were used as catalysts. Reasonable to good yields were obtained, as shown in table 1:

Entry	Phosphine	Ar-X	Solvent	Base	Time(h)/ T(°C)	Product	Y(%)
1[(a)]	Ph_2PH	4-MeC_6H_4I	DMA	KOAc	1.5/130	4-MeC_6H_4-PPh_2	80
2[(a)]	Ph_2PH	3-HOOC-C_6H_4I	CH_3CN	NEt_3	12/80	3-HOOC-C_6H_4-PPh_2	58
3[(a)]	Ph_2PH	3-HOOC-C_6H_4Br	DMA	NBu_3	170/125	3-HOOC-C_6H_4-PPh_2	76
4[(b)]	Ph_2PH	2-H_2N-C_6H_4I	CH_3CN/H_2O	NEt_3	34/80	2-H_2N-C_6H_4- PPh_2	62
5[(a)]	Ph_2PH	2,6-$Br_2C_5NH_3$	DMA	NaOAc	2/130	2,6-($Ph_2P)_2$- C_5NH_3	67
6[(a)]	$PhPH_2$	3-HOOC-C_6H_4I	CH_3CN	NEt_3	70/85	(3-HOOC-$C_6H_4)_2PPh$	60
7[(b)]	$PhPH_2$	4-NaO_3S-C_6H_4I	CH_3OH	NEt_3	12/70	4-NaO_3S-C_6H_4-PPhH	78
8[(b)]	$PhPH_2$	4-NaO_3S-C_6H_4I	CH_3OH	NEt_3	12/70	4-NaO_3S-C_6H_4-PPhH	3
9[(b)]	$PhPH_2$	H_2N-C_6H_4I	CH_3CN/H_2O	NEt_3	70/75	(H_2N-$C_6H_4)_2PPh$	80

Table 1.1 Palladium-catalysed P-C cross coupling reaction between Ph_2PH, $PhPH_2$ and aryl-iodides (bromides)
Catalysts used: (a) $Pd(OAc)_2$, 0.05-0.6mol%; (b) $Pd(Ph_3P)_4$, 1-2 mol%

It was demonstrated that the starting materials of the reaction summarised in table 1 did not react under the conditions reported in the absence of the palladium catalyst.

The P-C coupling reactions between Ph_2PH and arylbromides proceeds much slower and with harsher conditions (higher temperature and stronger base) than those with the corresponding iodo analogues: this can be observed by comparing entry 2 with entry 3 in table 1. 2,6-dibromopyridine, however (entry 5), reacts easily with Ph_2PH, giving the diphosphine in reasonable yield, due to the activated character of the two C-Br bonds.

The use of phenylphosphine as a coupling partner could be useful for the preparation of phenylphosphines substituted with two different aryl groups (entry 6 and 9). In this reaction, as for the coupling of arylhalides with Ph_2PH, the catalysts employed were either $Pd(OAc)_2$ or $Pd(Ph_3P)_4$. Organic amines were used as bases in organic solvents used pure or in mixtures with water. The reaction proceeds stepwise, as shown in figure 1.6:

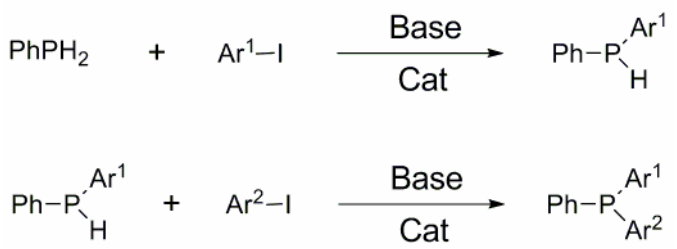


Fig. 1.6 Stepwise arylation of phenylphosphine with aryliodides

The secondary phosphine with a mono-sulphonated phenyl group (entry 7, table 1) can be obtained by selective arylation of $PhPH_2$ in high yields with the formation of only small quantities of the tertiary derivative (entry 8, table 1). It is possible that the arylation of $PhPH_2$ ceases after a short time because of decomposition of the catalyst: the addition of more catalyst could restart the reaction leading to the trisubstituted phosphine.

Stelzer and co-workers have reported the synthesis of chiral tertiary phosphines by consecutive Pd-catalysed P-C coupling reaction,[31] using a 1:1 molar ratio of $Pd_2(dba)_3$ chloroform adduct and 1,3-bis(diphenylphosphino)-propane as the catalyst (fig. 1.7): [32]

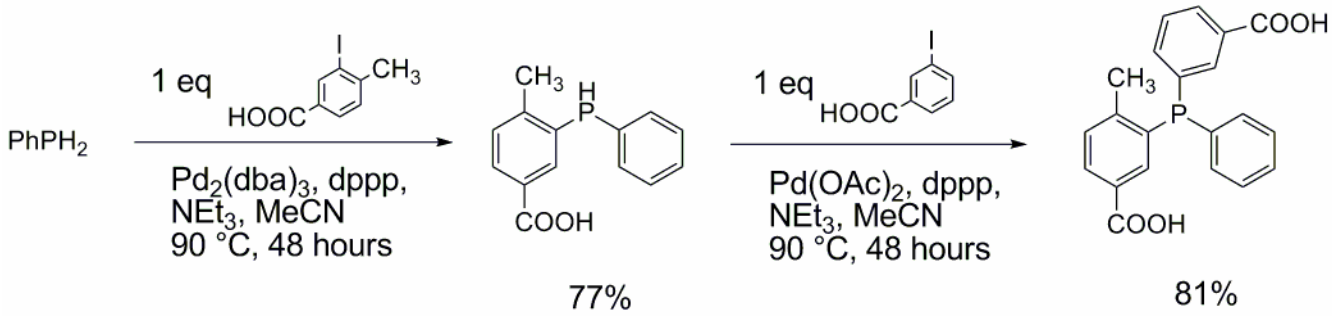


Fig. 1.7 Consecutive Pd catalysed P-C coupling reaction to yield chiral tertiary phosphines

This consecutive palladium catalysed P-C coupling reaction approach was also used in the preparation of mixed-ligands phosphinophosphonates (fig. 1.8):

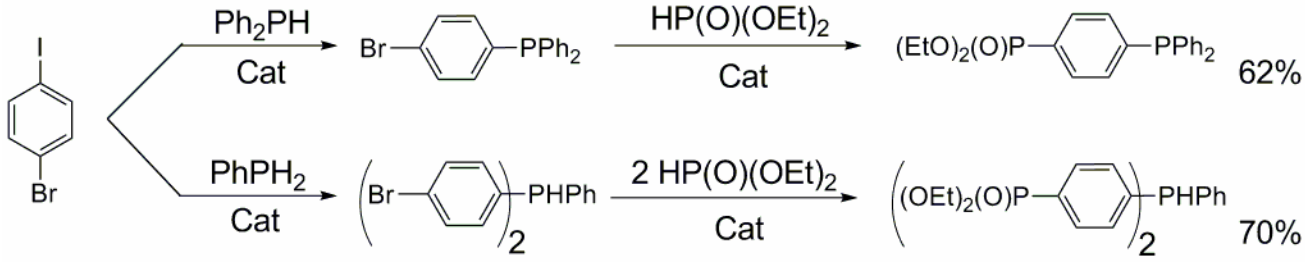


Fig. 1.8 Consecutive Pd-catalysed P-C coupling reaction in the synthesis of mixed-ligands phosphinophosphonates

The examples of consecutive palladium-catalysed P-C bond forming reactions, together with the wide variety of substituted aryliodides that have been successfully coupled to diphenylphosphine[30, 32] highlight the broad applicability of this methodology, with the number and position of the substituents in the aromatic ring of the arylhalide having no significant influence on the yields providing aryl iodides are used.

1.3.3 Mechanism of the palladium-catalysed coupling of phosphines to arylhalides

The mechanism for the direct coupling of phosphines to arylhalides is similar to the one proposed by Stille and co-workers (see paragraph 1.6.1 and fig. 1.6)[25], as well as the one proposed by Buchwald and co-workers for the palladium-catalysed amination of arylbromides.[7]

Indeed, the catalytic cycle (see fig. 1.9) starts with the oxidative addition of the aryliodides to the catalytically active Pd(0) species **A**, to yield the intermediate **B**. The base-assisted nucleophilic displacement of the iodide by the diarylphosphido group gives the intermediate **C**. The product is formed upon reductive elimination, with the catalyst **A** being obtained back again.

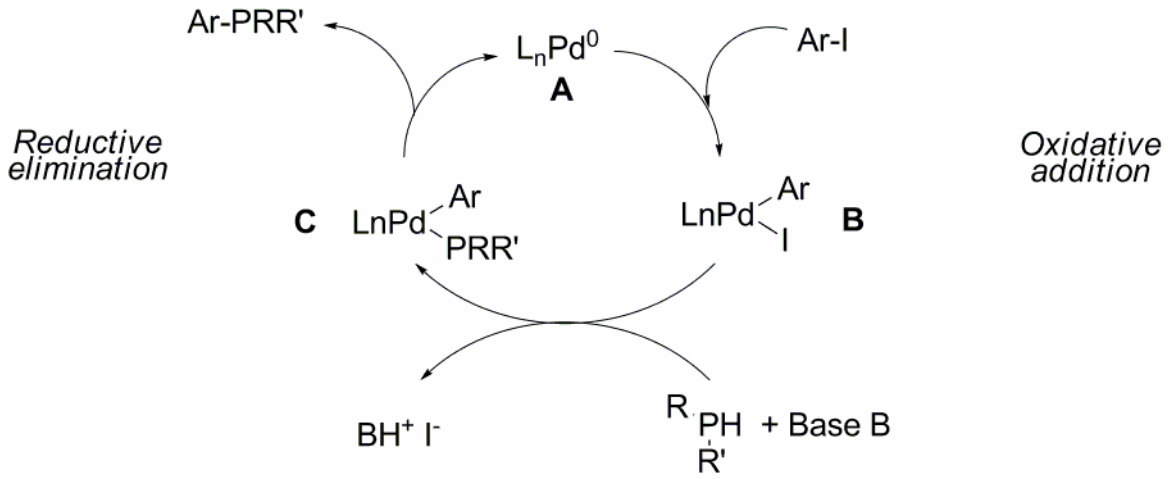


Fig. 1.9 Proposed catalytic cycle in the palladium-catalysed coupling of phosphines to arylhalides

The intermediates involved in this process have been isolated and identified in a mechanistic study carried out by Brown and co-workers.[18]

1.4 Nickel P-C cross-coupling reaction

Nickel mediated phosphine synthesis has also been described. Thus, even if nickel catalysed P-C cross coupling fall outside the scope of this review, it is still noteworthy to mention a few successful examples.

Possibly the most important example for the nickel catalysed P-C bond forming reaction is its use for the synthesis of BINAP. Indeed, the original synthetic route for BINAP reported by Noyori and co-workers (fig. 1.10) holds several drawbacks: the yield of the initial bromination reaction is quite low, with evolution of hot HBr. Moreover, the resolution late in the sequence results in a low overall yield (14%):[33]

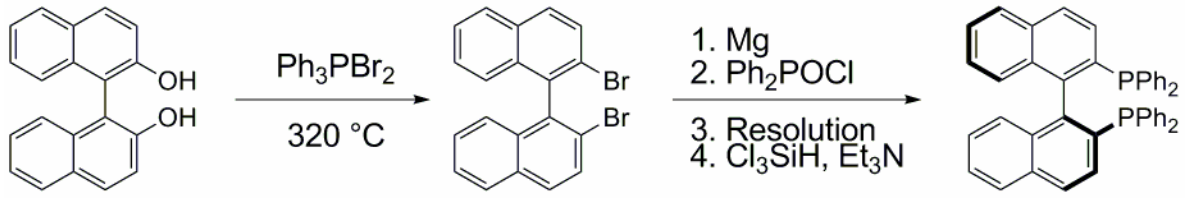


Fig. 1.10 Noyori's synthesis of BINAP

Thus, Cai and co-workers proposed a nickel catalysed direct diphosphination on the chiral ditriflate of binaphthol. The reaction was successful, giving 75% yield of the product:

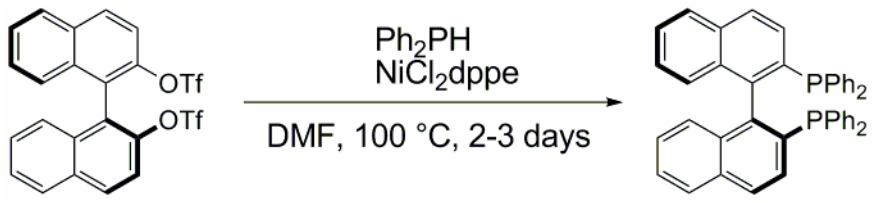


Fig. 1.11 Cai's synthesis of BINAP

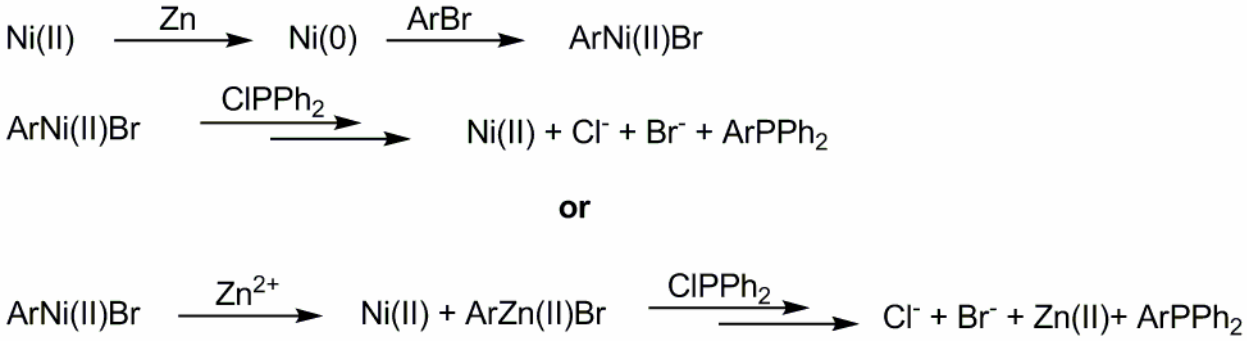
The palladium catalysed reaction was also tried, using $Pd(OAc)_2$ and 1,4-bis-(diphenylphosphino)-butane as the catalytic system, although no conversion to the product was obtained.

The work of Cai and co-workers was a very important achievement, and it is indeed the route used nowadays for the industrial preparation of BINAP.[34]

Other research groups used the nickel catalysed P-C bond forming reaction to prepare several phosphines. Laneman and co-workers described the nickel catalysed coupling of diphenylphosphine chloride to aryl bromides and triflates in the presence of zinc: the zinc is believed to play a dual role in the reaction. It reduces Ni(II) to Ni(0) and it provides Ph_2PZnCl for transmetallation.[35]

Chan and co-workers used Laneman's procedure for the synthesis of several atropisomeric *P,N* ligands, using $Ni(PPh_3)_2Cl_2$ as the catalyst.[36]

Le Gall and co-workers also used the nickel catalysed P-C bond forming reaction proposed by Laneman and considered $NiBr_2$(bipyridine) a better catalyst of choice. Moreover, they also proposed a mechanism, shown in fig. 1.12:



1.12 Proposed mechanism for Nickel catalysed P-C bond forming reaction

The catalytic cycle starts with the zinc reduction of the divalent nickel precursor into a zerovalent complex. This Ni(0) complex undergoes oxidative addition with the aryl bromide, giving the corresponding ArNi(II)Br complex. At this stage, two routes can be considered: either diphenylphosphine chloride reacts with the complex obtained (ArNi(II)Br) to give the desired product as has been discussed for the palladium catalysed reaction, or a transmetallation reaction could first occur between ArNi(II)Br and Zn^{2+} giving ArZnBr, which in turn reacts with

diphenylphosphine chloride, to yield the aimed product. This second route has been previously reported.[37]

1.5 Applications of the palladium-catalysed P-C bond formation

The palladium-catalysed P-C bond forming reaction has seen some significant applications, even if there is still not a wide use of this methodology.

1.5.1 Synthesis of catalysts bound to polymers

Liese and co-workers focussed their attention in the preparation of catalysts bound to homogeneously soluble polymers: this system was considered useful as it combines the advantages of a chemical catalyst, which is soluble in organic solvents, and of an enzyme, which can work in a continuous operation system. Indeed, soluble polymer-bound catalysts (chemzymes) can be retained by ultrafiltration membranes like enzymes and therefore can be applied in the so-called chemzyme membrane reactor. The preparation of their ligand needed the synthesis of two different synthons (fig. 1.13), which were both prepared by direct palladium-catalysed phosphination:[38]

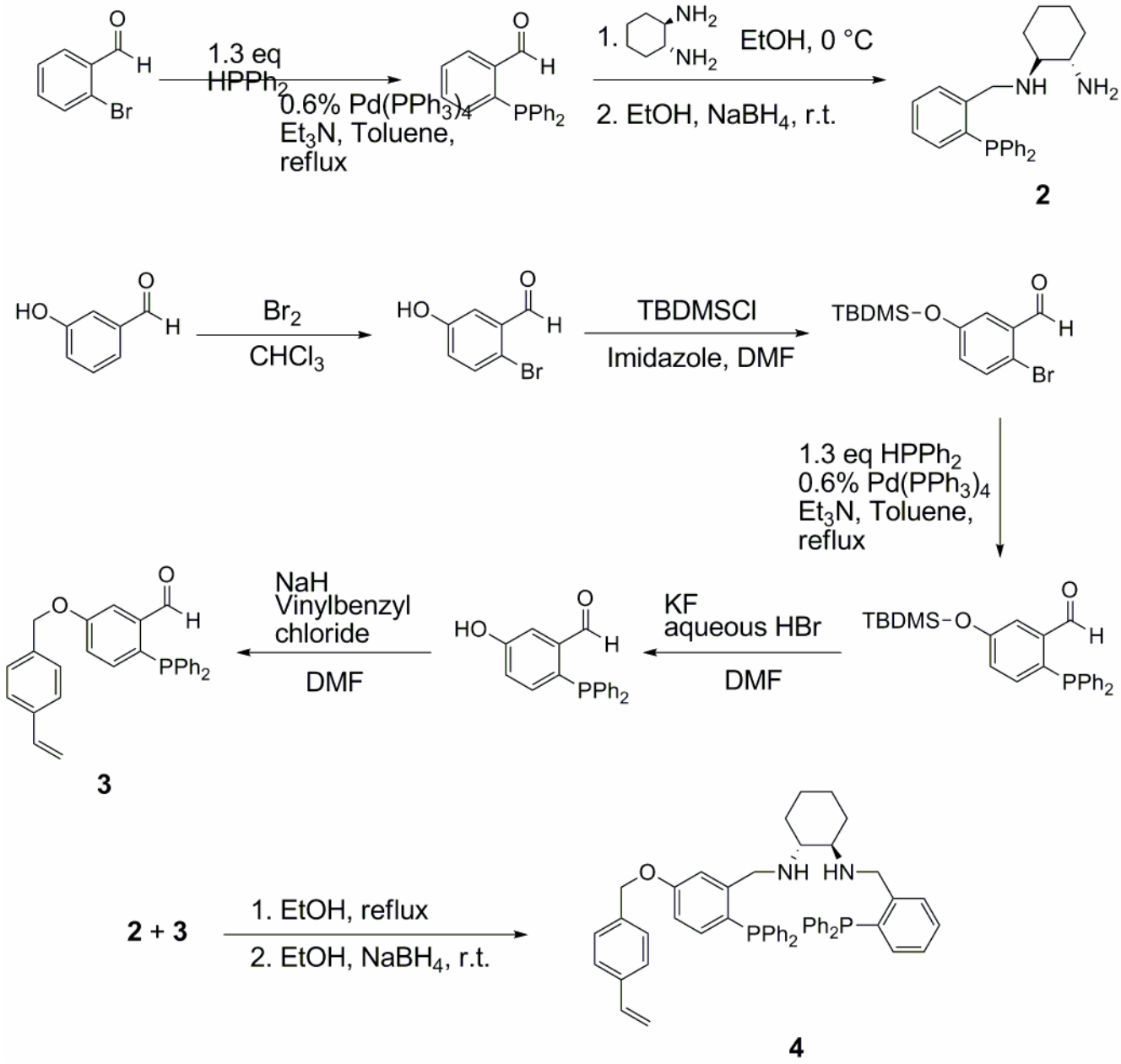


Fig. 1.13 Ligand synthesised by Liese and co-workers, for the preparation of a soluble polymer-bound catalyst

In both the preparations of (**2**) and (**3**), the palladium-catalysed phosphination gave high yields (85% in the preparation of (**2**) and 80% in the preparation of (**3**)). This synthetic procedure was preferred as no protection of the aldehyde was required.

The ruthenium complex of ligand (**4**) was prepared and was eventually attached to the hydrosiloxane moieties of the methylhydrosiloxane-dimethylsiloxane copolymer via hydrosilylation. This chemzyme was then tested in the transfer hydrogenation of acetophenone.

1.5.2 Preparation of P-chiral phosphines

The palladium-catalysed P-C bond forming reaction has been also used for the preparation of P-chiral phosphines. These ligands have been often prepared by resolution or by using stoichiometric amount of a chiral auxiliary.[39, 40]

Glueck and co-workers reported that Pd-catalysed cross-coupling of a racemic secondary phosphine PH(R)(R') with an aryl halide or triflate can be used to prepare P-chirogenic phosphine with control of stereochemistry at phosphorus by dynamic kinetic resolution. Indeed, catalyst (**5**)[41] was used to couple (**6**) to phenyl iodide, giving high yields (from 60% to 90%) and good enantiomeric excess values (from 42% to 78%) (fig.1.14). Phenyl bromide and triflate could also be used, although lower enantiomeric excess was obtained. The reaction was complete after one hour, using toluene as the solvent: it was noticed that in polar solvents the e.e. decreased slightly. It was also highlighted that running the reaction at higher temperature led to a decrease in e.e.:[42, 43]

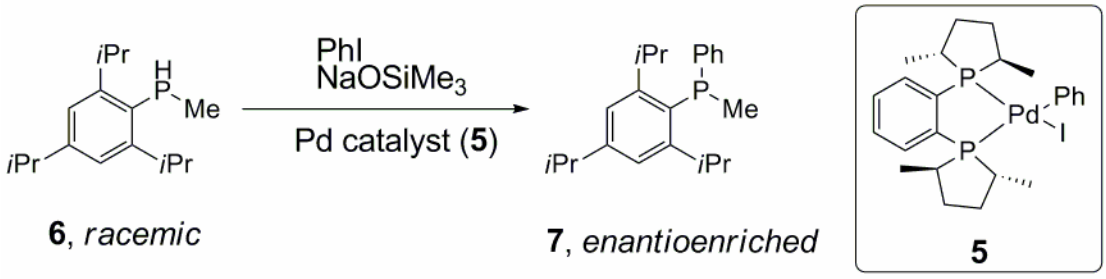


Fig. 1.14 Pd-catalysed phosphination for the synthesis of chiral phosphines

The same research group also investigated both the mechanism of the reaction (fig. 1.15) and the origin of the enantioselectivity (fig.1.16):

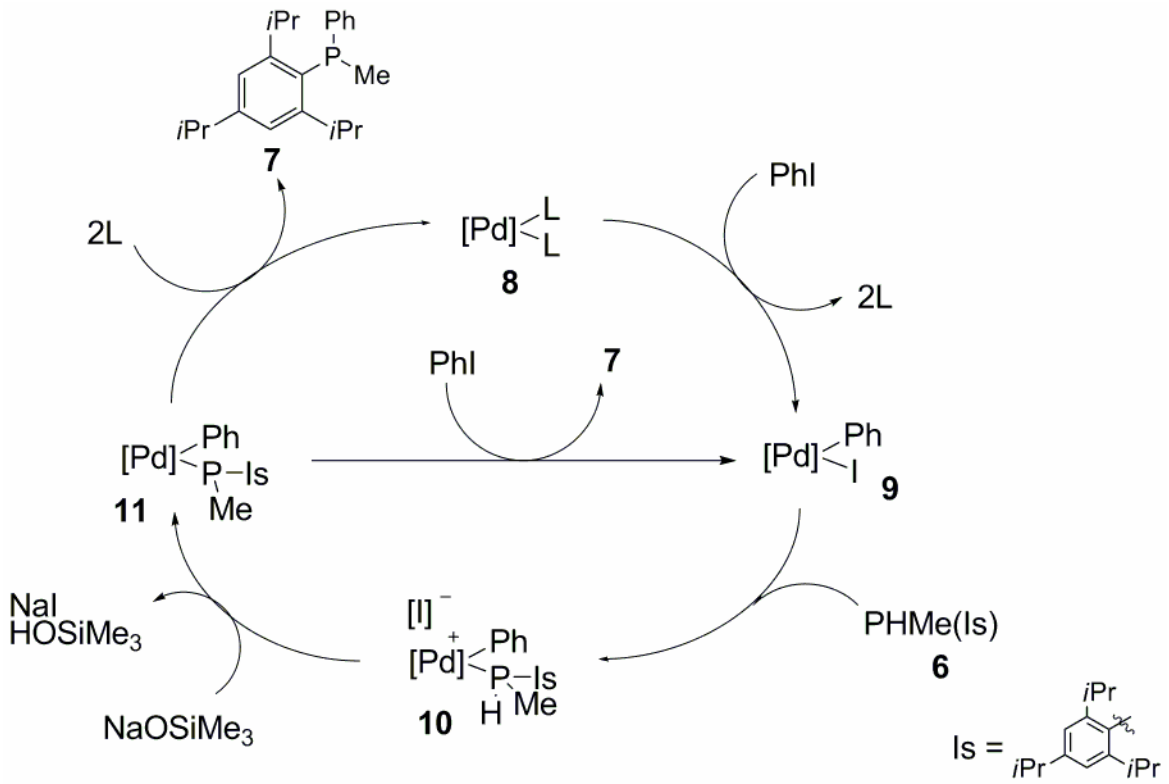


Fig. 1.15 Pd-catalysed mechanism proposed by Glueck and co-workers

The mechanism proposed by Glueck and co-workers is similar to the general mechanism shown above, a part from a different role of the base suggested (fig. 1.9). Oxidative addition of phenyl iodide to the palladium catalyst gives (**9**), followed by displacement of the iodide from the phosphine (**6**), leading to (**10**) as a mixture of diastereomers. It is likely that interaction between the base and (**10**) gives complex (**11**). To investigate the role of the base, the triflate salt of (**10**) was prepared and it was then observed that the base reacts with (**10-OTf**) to give (**11**), whereas neither complex (**9**) nor the phosphine (**6**) reacts with $NaOSiMe_3$. The product can be formed by reductive elimination.

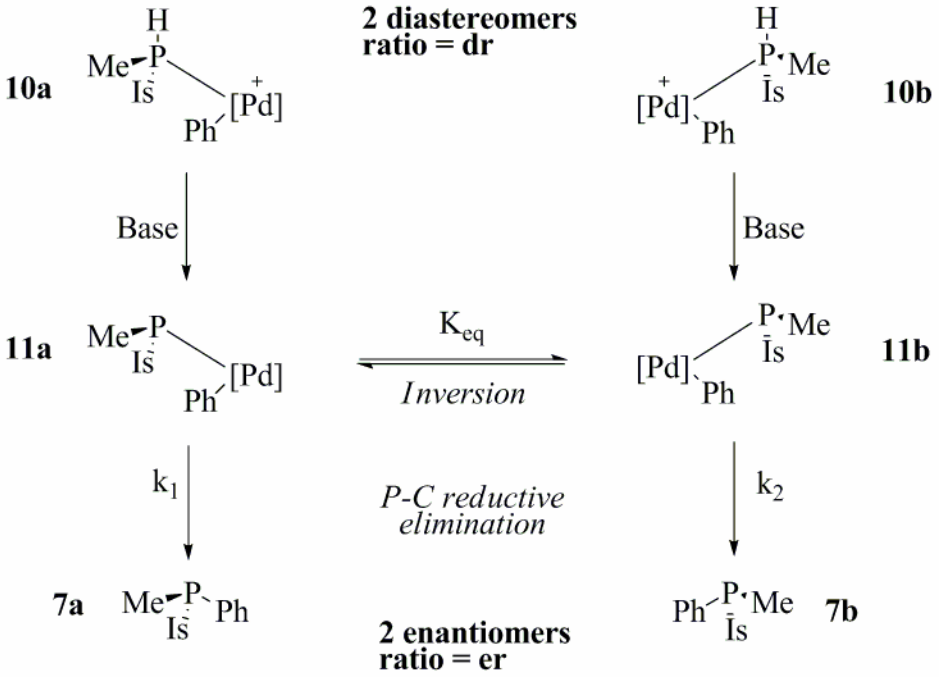


Fig. 1.16 Origin of the enantioselectivity

An interesting study in trying to identify the origin of the enantioselectivity was also carried out. Two possible extreme routes to enantioselection were considered by Glueck and co-workers. If (**11a**) and (**11b**) undergo reductive elimination at similar rates, faster than the inversion at the phosphorus, then the enantioselectivity of the product would reflect their thermodynamic ratio (K_{eq}). On the other hand, if interconversion of (**11a**) and (**11b**) is faster than reductive elimination, their relative rates of reductive elimination could control the ee ($k_1 \neq k_2$). The diastereomeric mixture of complexes (**10**) was deprotonated to give the product (**7**): the initial diastereomeric ratio (*dr*) of the metal phosphide was to be different from the obtained enantiomeric ratio (*er*) of the product, suggesting that the interconversion occurs more quickly than the reductive elimination, thus their relative abundance and reductive elimination rates is more likely to lead to a different *er* from the starting value of *dr*.

1.5.2.1 Palladium catalysed synthesis of phosphines: effect of the product in the catalysis and enantioselectivity of the reaction itself

Glueck and Rheingold also investigated the possibility to prepare a phosphine containing stereocentres both at the phosphorus and at a carbon. With this in mind, (**13**) was prepared through a palladium-catalysed coupling reaction (see fig. 1.17):

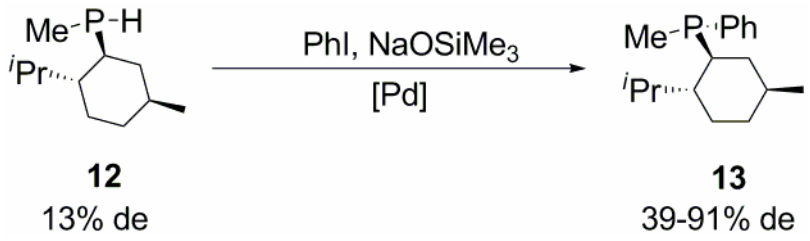
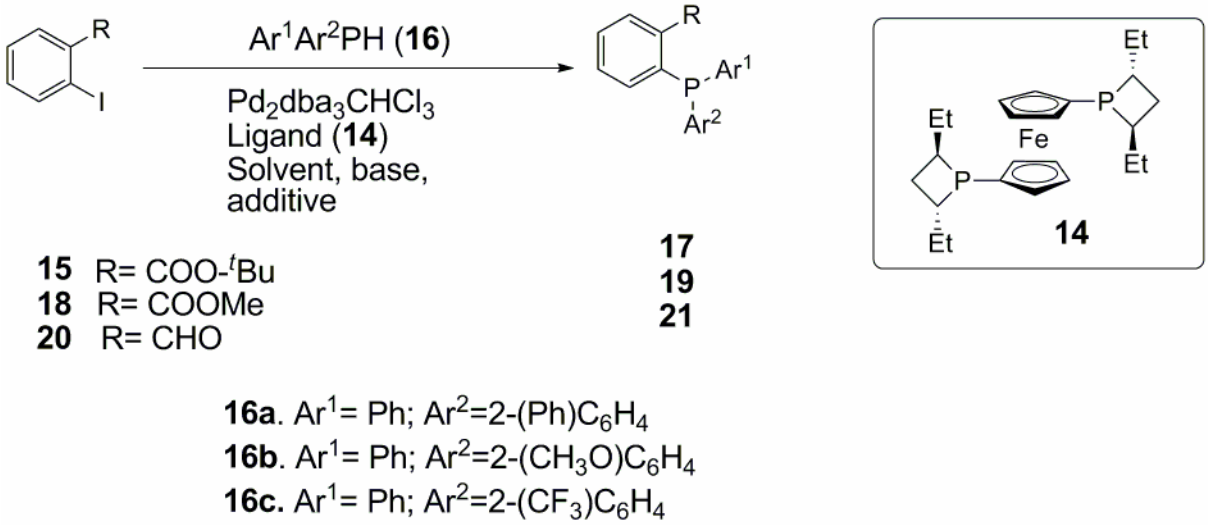


Fig. 1.17 Pd-catalysed phosphination for the synthesis of a phosphine with both P and C stereocentres

Different chiral catalysts were tested, like Pd((*R*,*R*)-Me-Duphos)(*trans*-stilbene)[44] or Pd((*R*,*R*)-^{i}Pr-Duphos)(*trans*-stilbene),[44] which gave good yields and diastereomeric excess values. Furthermore, it was noticed that achiral catalysts also gave high diastereomeric excess; it was suggested that the product (**13**) might act as a ligand in a palladium complex to catalyse the selective synthesis of more (**13**) (chirality breeding). However, the observation that the palladium complex of (**13**) is partially transformed into its diastereomers during catalysis, together with several other intermediates, led them to conclude that although this was an example of chirality breeding, more successful results in this direction could be obtained using chiral bidentate ligands.[45]

Helmchen and co-workers also used the palladium-catalysed P-C bond forming reaction for preparing P-chiral triarylphosphines. The aforementioned palladium complex (**5**) [41] was considered not an easy catalyst to work with, because of its stability problems (it has to be stored in the dark at -25 °C), therefore different commercially available ligands were screened, among which the ferrocene derivative Et-FerroTANE (**14**) yielded high enantioselectivity (see table 1.2). Moreover, it was noticed that addition of LiBr as an additive could have a positive effect on the reaction in some cases (see for example entry 4 in comparison to entries 1, 2 and 3 in table 1.2):[46]

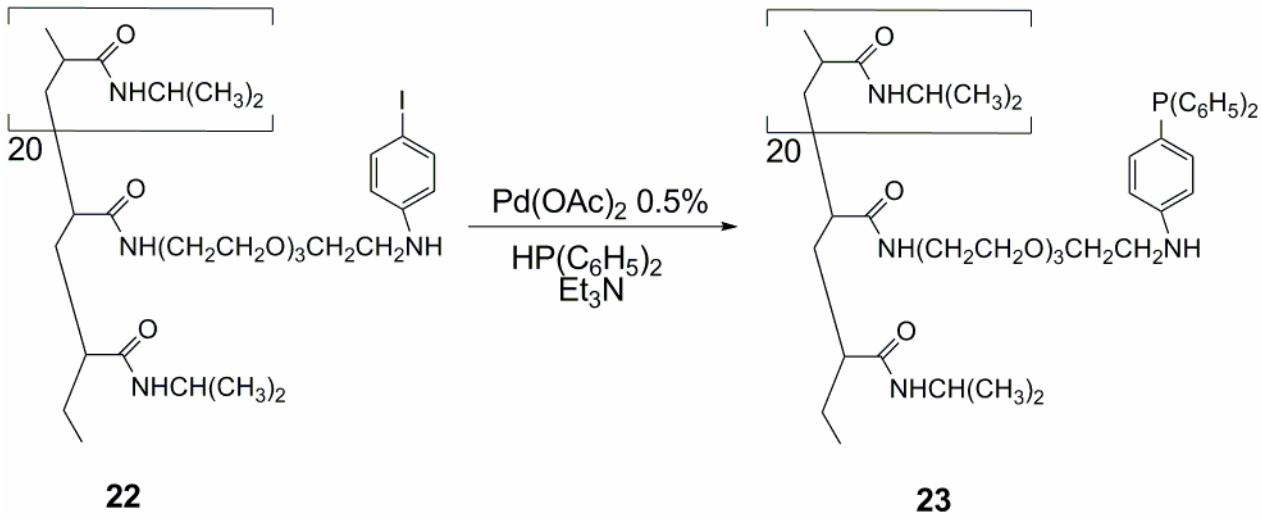


Scheme 1.1

Entry	Aryl iodide	Phosphine (16)	Base	Additive	Time (d)	Yield	ee (%)
1	15	16a	NEt_3	-	3	63	71
2	15	16a	NEt_3	LiF	2	76	66
3	15	16a	NEt_3	LiCl	3	66	86
4	15	16a	NEt_3	LiBr	1	76	90
5	15	16b	NEt_3	LiBr	2	79	40
6	15	16c	NEt_3	LiBr	2	39	93
7	18	16a	NEt_3	LiBr	2	69	85
8	20	16a	NEt_3	LiBr	2	71	63

Table 1.2 Pd-catalysed P-C cross-coupling according to Scheme 1.1 (solvent: THF; base: NEt_3; r.t.)

Helmchen and co-workers also suggested that the P-C cross-coupling is potentially prone to autocatalysis, particularly in the case of bidentate ligands. Even if further experiments were not reported to support this, it is a quite likely possibility. Indeed, a few years before, Bergbreiter and co-workers reported an example in which the palladium catalysed P-C bond forming reaction was used to prepare a ligand that could catalyse its own synthesis, in the presence of a palladium source.[47] Specifically, the synthesis of a self-replicating polymeric phosphine ligand system was described (fig. 1.18), as it was considered useful to take advantage of the solubility properties of the polymer for the purification of the product:



22 **23**

1.18 Synthesis of the polymeric phosphines using P-C cross coupling

In order to show that the product (**23**) can positively interfere in the catalysis of its own formation from (**22**), a small amount of (**23**) was added to the starting material (**22**): by ^{1}H-NMR it was possible to observe a faster disappearance of (**22**) after 10 minutes, compared to the reaction run

without addition of the small amount of the product, thus suggesting that the product (**23**) acts as a ligand for a catalyst that forms itself.[47]

1.5.3 Further development of the palladium catalysed P-C bond forming reaction

Several palladium catalysed P-C cross-coupling reactions have been presented. As previously discussed, these results have been very useful for elucidating different mechanistic aspects of the reaction, with the aim of using this reaction as a practical tool for the synthesis of different phosphine-based ligands.

However, together with the need to use aryl iodide as substrates, another drawback of this challenging reaction is the long reaction time that often is required: this reaction would be indeed a much more attractive synthetic tool if the reaction times were shorter. This disadvantage prompted Kappe and co-workers to investigate the microwave assisted palladium catalysed P-C bond forming reaction.

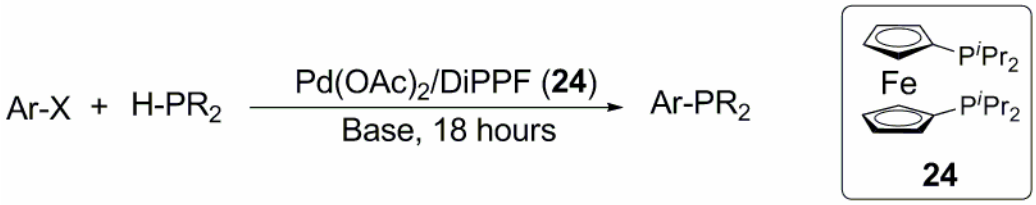
Microwave mediated C-C as well as C-heteroatom coupling reactions have been proven to successfully reduce reaction times from hours or days to minutes[48] (new research on microwave assisted C-C and C-P cross-coupling reactions will be discussed in chapter 2 and 3 respectively of the present thesis).

Thus Kappe and co-workers looked into the coupling of phenyl iodide to diphenylphosphine, using *N*-methyl-pyrrolidone as the solvent, KOAc as the base and $Pd(OAc)_2$ as the catalyst and found out that in only 20 minutes in the microwave at 200 °C, 92% of the coupled product could be obtained. While optimising the reaction conditions, it was noticed that a 50% excess of the phenyl iodide was necessary to reach such a high yield, moreover it was also observed that at higher temperatures the yield dropped due to decomposition of the catalyst.[49] In the same paper, it was also reported that surprisingly the use of Pd/C as a catalyst for the same reaction could lead to even higher yields in only 3 minutes.

As expected, the coupling of diphenylphosphine to aryl bromides or triflates proved more difficult, and required longer reaction times and more complex catalytic systems, though giving lower yields (optimised reaction conditions lead to 59% isolated yield using bromobenzene as starting material and the Hermann's palladacycle as catalyst, and to 61% isolated yield using phenyl triflate as starting material and $Ni(dppe)Cl_2$ as catalyst).[49] No other aryl bromides were investigated.

These results obtained by the research group of Kappe were an important step forward in the investigation of the palladium catalysed P-C cross-coupling reaction. However, the use of aryl

iodides as starting materials was still considered a limitation of the methodology: indeed, a much wider range of aryl bromides or even better aryl chlorides are more readily available at lower cost. Buchwald and co-workers investigated the use of diisopropyl ferrocene (**24**) as the ligand, together with $Pd(OAc)_2$ in the coupling of aryl halides to different disubstituted phosphines (see table 1.2). Indeed, their successful results in the coupling of aryl bromides and chlorides to different thiols using this catalytic system reported in the same paper, led them to investigate if ligands having di(*sec*-alkyl)phosphino groups could be efficient ligands also for the P-C cross-coupling reaction:[50]



Scheme 1.2

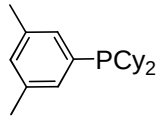
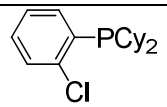
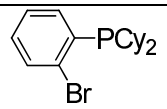
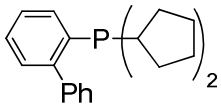
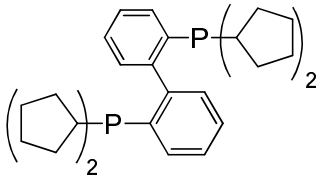
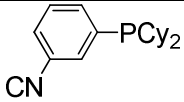
Entry	Product	Ar-X	Base	Solvent	Temp. °C	Yield (%)
1		$3,5(Me)_2C_6H_3Br$	NaO*t*-Bu	Toluene	80	87
2		$3,5(Me)_2C_6H_3Br$	Cs_2CO_3	Dioxane	80	82
3		$3,5(Me)_2C_6H_3I$	Cs_2CO_3	Dioxane	80	85
4		$3,5(Me)_2C_6H_3Br$	NaO*t*-Bu	Toluene	100	76
5		$3,5(Me)_2C_6H_3Br$	Cs_2CO_3	DMF	120	63
6		$3,5(Me)_2C_6H_3Cl$	Cs_2CO_3	Diglyme	120	75

Table 1.3 Pd-catalysed P-C bond formation using ligand (24) (a) The reaction was carried out for 6 hours; (b) 0.5 mmol of ArBr was used.

In table 1.3 the interesting results of Buchwald and co-workers are reported. This has been the first example of the palladium catalysed P-C cross-coupling on aryl chlorides in reasonably high yields: as expected, a higher temperature was required. However, these conditions did not lead to such high

yields if using the unactivated 4-chlorotoluene as the coupling partner of dicyclohexylphosphine, and relatively few examples were investigated. No diarylphosphines coupling to aryl bromides or chlorides were reported.

1.6 Synthesis of phosphine oxides *via* palladium catalysed coupling reaction

The palladium catalysed P-C bond forming reaction is a very useful methodology. However, phosphines are not easy compounds to handle because of their tendency to easily undergo oxidation. This characteristic has often been a limitation for their synthesis, in particular when a purification procedure such as column chromatography is required. This problem can be avoided with the direct preparation of phosphine oxides, which can usually be purified easily. Subsequently, reduction of the phosphine oxide can lead to the desired product in pure form (the reduction of phosphine oxides is discussed in detail in chapter 3 of the present thesis). Phosphine oxides can also be obtained using catalytic methods.

One of the first examples reported in the literature for the palladium catalysed synthesis of phosphine oxides was published by Morgans and co-workers in the early 1990s.[20] Their interest in investigating this reaction raised from the increasing importance that BINAP was gaining in those years; indeed, the synthesis of ligands structurally related to BINAP was of particular interest. Enantiomerically pure 1,1'-bi-2-naphthol triflate was used as the substrate. At first, synthesis of binaphthyl phosphonates was considered, from which it was then possible to prepare a variety of binaphthyl phosphines with different substitutions at phosphorus. Thus a method published earlier was tested for such transformation.[51] However, low yields of the monosubstituted product were obtained. The procedure described by Dolle and co-workers[52] was then adapted: both a phosphine oxide and a phosphonate were tested as phosphorylating agent. High yields were obtained in both cases, though only of the monosubstituted products (fig. 1.19):

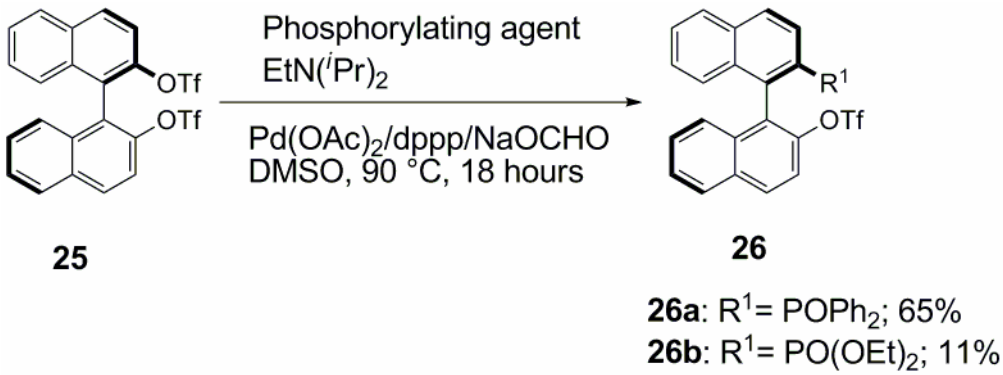


Fig. 1.19 Palladium catalysed synthesis of phosphine oxides and phosphonates

Morgans and co-workers were not successful in preparing BINAP derivatives, however it is worthy to mention their work as it was one of the first examples of palladium catalysed P-C coupling on aryl triflates and it set the basis for the further development on this type of transformations.

1.6.1 Applications of the Morgans' procedure in the synthesis of novel ligands

The procedure proposed by Morgans and co-workers described in the previous paragraph has seen a wide application, as such or with some modifications, in the preparation of monophosphine oxides: subsequent reduction of the phosphine oxides has given monodentate ligands and binaphthyl P,N ligands, which have been found useful in many catalytic reactions, such as allylic cyanation, allylic alkoxycarbonylation or hydrovinylation, just to mention some of them.

Palladium catalysed synthesis of monophosphine oxides was used by Hayashi and co-workers for the preparation of several 2-(diarylphosphino)-1,1'-binaphthyls (**27**) was described;[53-56] RajanBabu and co-workers recently described the synthesis of 2-(diarylphosphino)-1,1'-binaphthyls substituted in the 3' position (**28**).

The research group of Brown[57] slightly modified Morgans' system to introduce variation to the aryl substituents of a series of phosphine-amines (**29**) by coupling the appropriate secondary phosphine oxide. Guiry and co-workers also described the preparation of two different phosphine-amines (**30a**) and (**30b**).[58, 59] It has to be noted that in the synthesis of these phosphine-amines, both research groups found that the nickel catalysed coupling of secondary phosphine in the presence of a base gave higher yields compared to those obtained by coupling the phosphine oxides.

Vyskočil, Kočovský and co-workers also prepared their binaphthyl P,N ligands (**31**) and (**32**) by palladium catalysed coupling of the phosphine oxides (all the aforementioned ligands obtained using Pd/phosphines oxide method are shown in fig. 1.20):

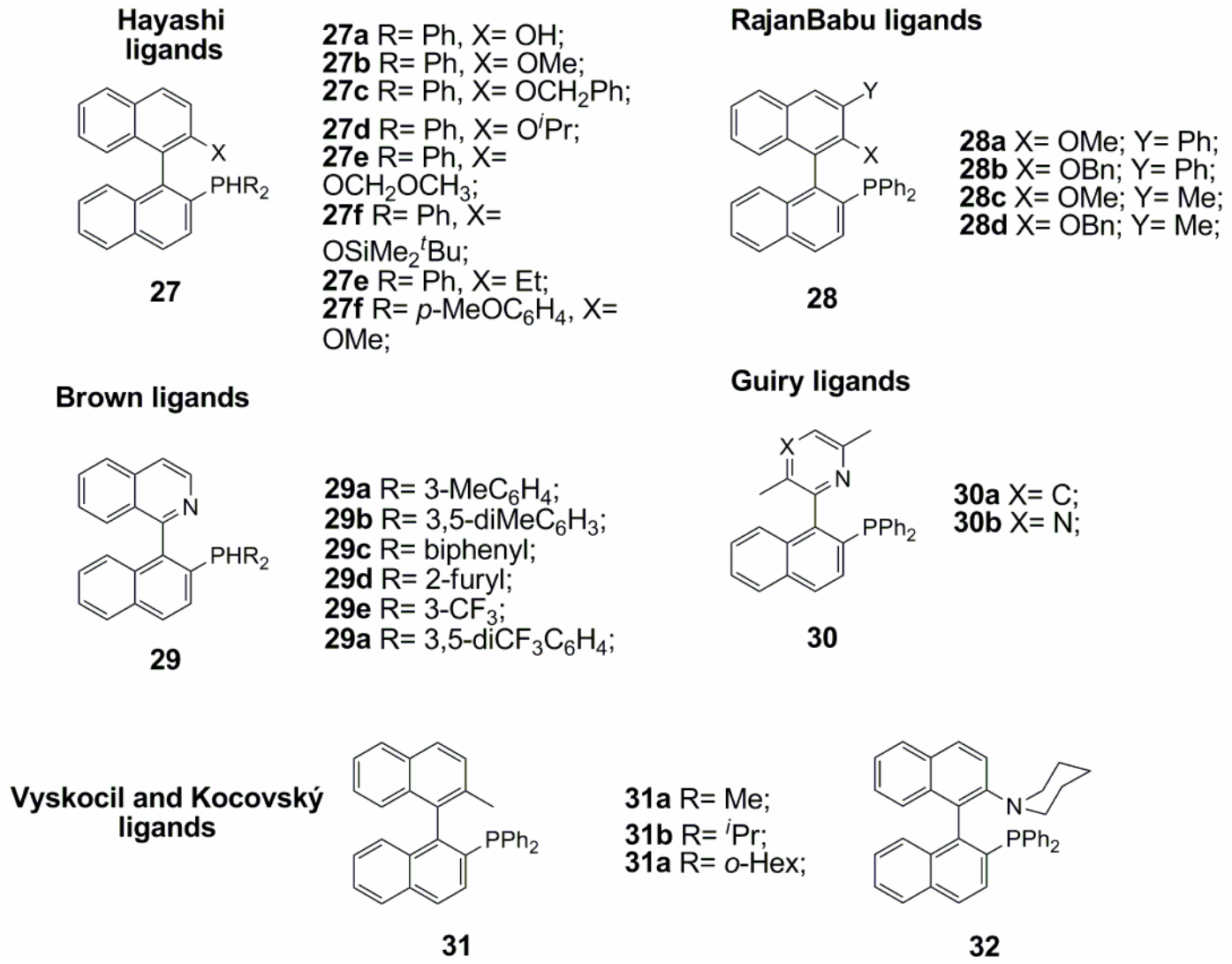


Fig. 1.20 Monophosphines synthetised through palladium catalysed cross- coupling of phosphine oxides

All these ligands synthesised using Morgans' procedure highlights the possibility to prepare various ligands without interference of the reagents with other functional groups present in the molecule.

Of course, when performing the reaction it is necessary to take into consideration the steric hindrance of the substrates. An example in which steric effects did not allow the palladium catalysed coupling of diphenylphosphine oxide to occur was observed by Bringmann and co-workers (fig. 1.21).

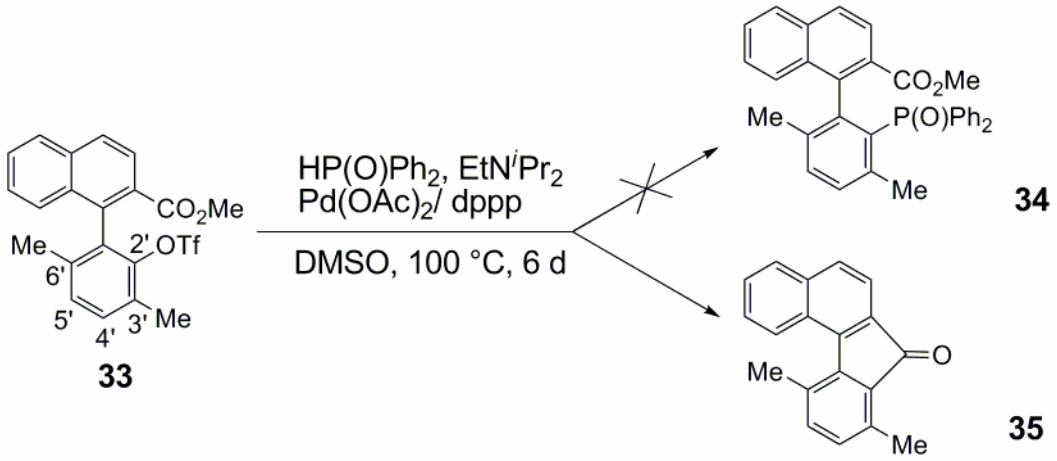


Fig. 1.22 Interference of high steric hindrance in the palladium catalysed coupling of $P(O)Ph_2$

The steric hindrance at the substitution site C-2' of (**33**) is due to the bulky substituted naphthyl residue at C-1' and also to the presence of the methyl group in position C-3'. This bulkiness around the substitution site C-2' did not allow the P-C coupling to occur, instead a novel palladium mediated ring closure was observed, giving (**35**) rather than (**34**) as the final product. It was demonstrated that the extra steric hindrance caused by the presence of the methyl group in position C-3' was responsible for the failure in introducing the phosphine oxide, which is already sterically demanding by itself. Indeed, the P-C coupling was successful when performed on a regioisomeric compound of (**33**), in which the methyl group is in position C-4'.[60]

Even if the direct coupling of a phosphine would be ideal, the research on palladium catalysed cross-coupling of phosphine oxides has been an important contribution. Indeed, it can help with purification problems, due to air stability of phosphine oxides.

1.7 Secondary phosphine-boranes

In the previous paragraph, the palladium catalysed synthesis of phosphine oxides has been described. In particular, it has been highlighted that this method can overcome potential problems in the preparation of phosphines that are sensitive to air and moisture. However, reduction of phosphine oxides can sometimes be problematic, in particular when working with sterically hindered or electron-rich phosphine oxides.[61]

1.7.1 Use of phosphine-borane for the synthesis of its derivatives

Another method that has been thus employed to avoid oxidation of phosphines during their synthesis, and the potentially difficult reductions of phosphine oxides is the use of phosphine boranes. Moreover, in some cases, boranes have also been proposed to have a role as an activating agent for the phosphorus atom.[62]

Compounds containing a P-B moiety have been known since the early 1900 and their physicochemical properties have been investigated. They present straightforward standard structures, which resemble those of phosphine, phosphine oxides and phosphonium cations. Phosphine-boranes are often inert towards oxygen and moisture and sometimes towards strong acids and bases: these properties are possibly due to the low polarities and polarisibilities of the P-B and B-H bonds.[63-65]

Imamoto and co-workers were amongst the first to consider borane as a useful protecting group in the synthesis of phosphines. In fact, they reported in the early 1990s the synthesis of phosphine boranes starting from phosphine oxides and disubstituted phosphine chlorides: phosphine boranes can be prepared from free phosphine as well, but it was also considered useful to avoid handling air sensitive and reactive starting materials (fig. 1.22):[62, 66]

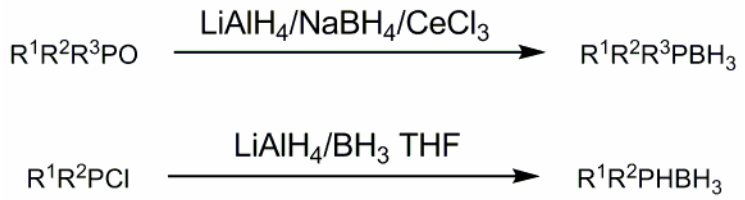


Fig. 1.22 General procedure for the preparation of phosphine-boranes starting from phosphine oxides or chlorides

In the preparation of the phosphine boranes starting from phosphine oxides, it was noticed that $CeCl_3$ was necessary for the reaction to occur. It was proposed that the trivalent cerium plays dual roles: it activates the phosphine oxide by coordination so that the deoxygenation with $LiAlH_4$ proceeds readily, and it activates $NaBH_4$ to facilitate reaction with the intermediate phosphine to form the product.

Imamoto's research group focussed its attention on using phosphine boranes to prepare various derivatives. Figure 1.23 summarises the reaction of diphenylphosphine-borane, used as a model study, with different electrophiles in the presence of a base. The reactions proceeded under mild conditions and a wide selection of functionalised phosphine-boranes can be obtained:[67]

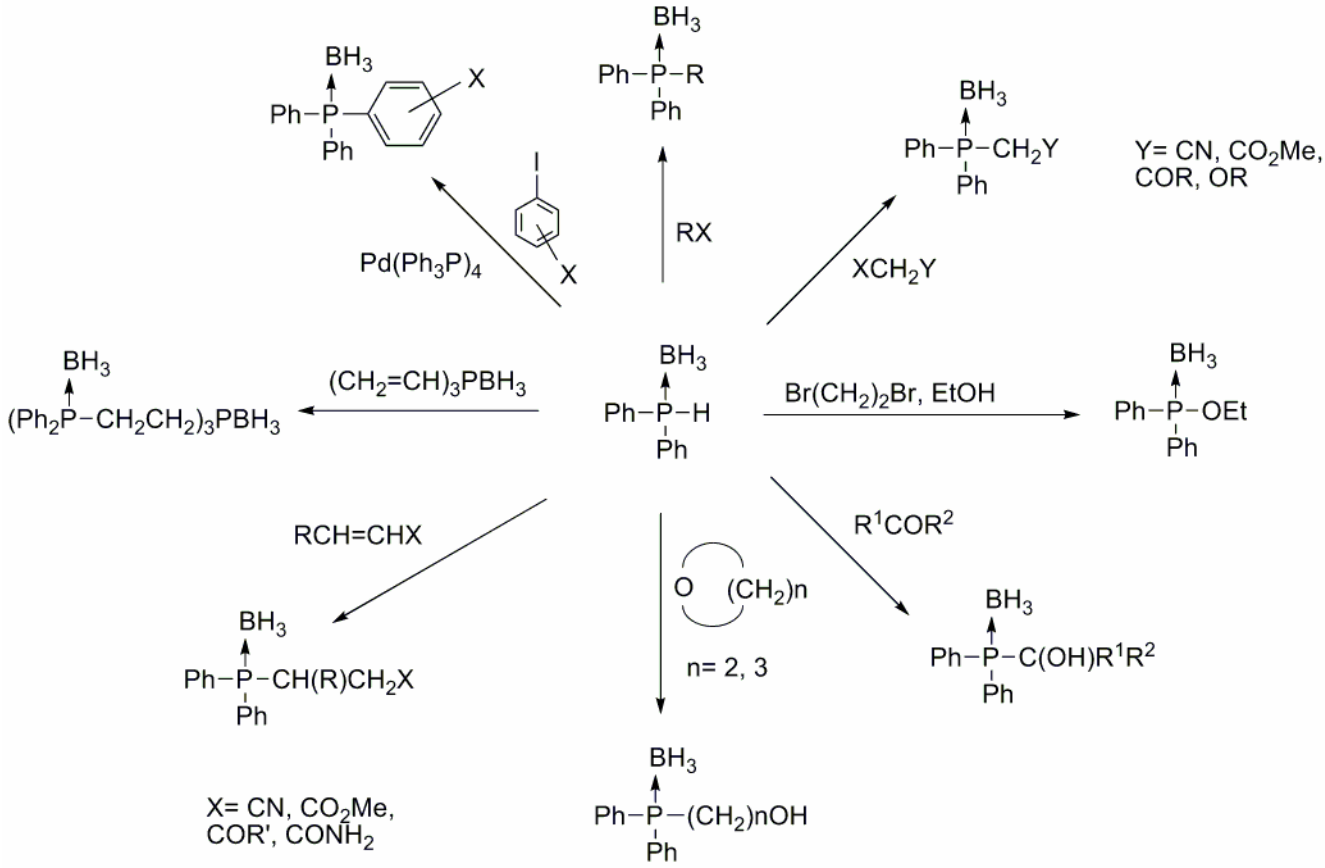


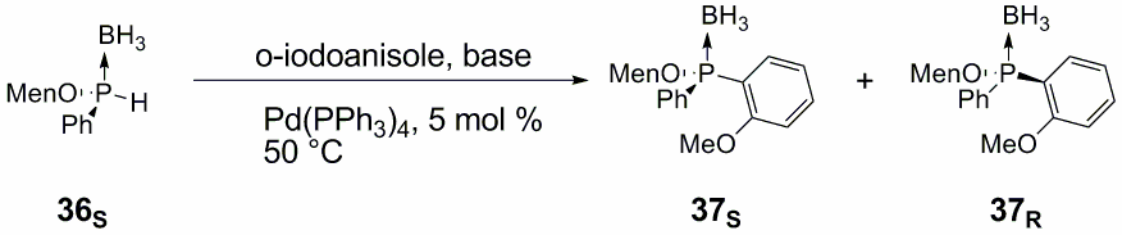
Fig. 1.23 Reaction of diphenylphosphine-borane with various electrophiles

As it is shown in figure 1.23, among the different reactions which diphenylphosphine-borane can undergo, the palladium catalysed cross-coupling has been also proved to be successful.

1.7.2 Palladium catalysed phosphination using secondary phosphine-boranes

Imamoto and co-workers used the palladium catalysed P-C bond forming reaction with phosphine-boranes in the synthesis of P-chiral phosphines. Interestingly, this work led them to observe that the reaction could occur with inversion of configuration at phosphorus,[68, 69] contrary to what normally happens in the electrophilic arylation of chiral tetracoordinate organophosphorus compounds having a P-H bond.[70, 71] Specifically, the role of the solvent was highlighted as it can deeply affect the stereochemistry of the palladium catalysed cross-coupling reaction. Indeed, the reaction of menthyloxyphenylphosphine-borane (**36**) with *o*-iodoanisole in the presence of a base and using $Pd(PPh_3)_4$ as the catalyst was reported (scheme 1.3); reaction conducted in acetonitrile resulted in complete retention of configuration, whereas inversion of configuration occurred in THF. It was also noticed that temperature played a role in optical purity, since at 50 °C the reaction in acetonitrile proceeded with complete retention of configuration, whereas at higher temperatures the

optical purity of the product slightly decreased. Moreover, also the base was demonstrated to play a role in the stereoselectivity of the reaction, and in particular when using THF as the solvent it was noticed that retention of configuration occurred if Ag_2CO_3 was employed as a base, whereas almost complete inversion of configuration was observed when using K_2CO_3 or CH_3COOK as the base:[68, 69]



36_S **37_S** **37_R**

Scheme 1.3

Entry	Base	Solvent	Time (hours)	Yield %	37_S:37_R
1	K_2CO_3	CH_3CN	16	96	100:0
2	K_2CO_3	CH_3CN	16	39	80:20
3	K_2CO_3	DMF	16	60	5:95
4	CH_3COOK	THF	48	55	3:97
5	Ag_2CO_3	THF	12	67	99:1

Table 1.4 Palladium catalysed cross-coupling Reaction of 36_S with o-iodoanisole

The mechanism explaining this solvent effect on the stereochemical outcome is not completely understood, but Imamoto and co-workers supposed that the stereochemistry of the product is determined at the transmetallation step in the catalytic cycle. Thus, it is possible that in a polar solvent like acetonitrile, the proton abstraction from the secondary phosphine-borane by the base occurs readily and the generated naked phosphorus anion attacks the palladium atom with retention of configuration; on the contrary, in a less polar solvent, like THF, the proton abstraction and the attack on the palladium occur simultaneously, resulting in the inversion of configuration in the product (fig. 1.24): [68, 69]

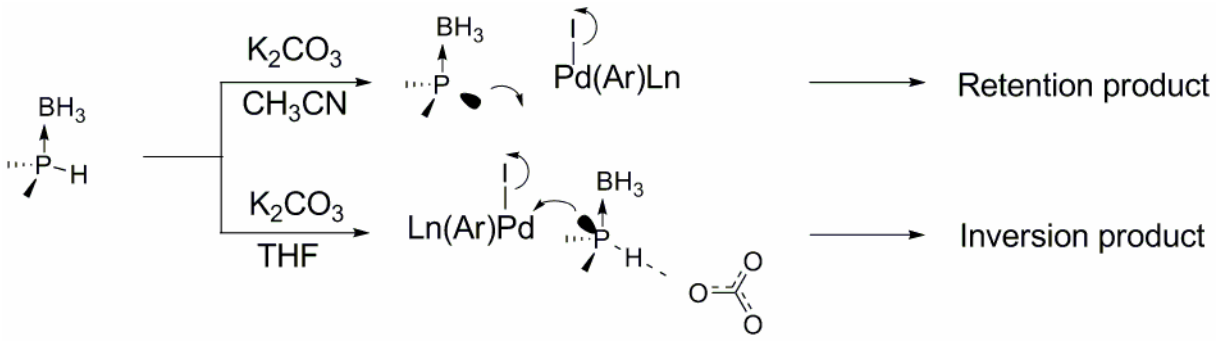


Fig. 1.24 Proposed mechanism for the solvent effect in the stereoselectivity of the palladium catalysed P-C bond formation using phosphine-boranes

The possibility that the phosphine-borane anion could racemize before Pd-P bond formation was proposed not only by Imamoto and co-workers[68, 69, 72] but also by Wolfe and Livinghouse.[73]

1.7.2.1 Cu(I) as co-catalyst in the palladium catalysed phosphination with phosphine-boranes

An important observation of Livinghouse and co-workers regarding the palladium catalysed P-C cross-coupling reaction was that the addition of Cu(I) as a co-catalyst together with palladium increased the yields at milder conditions. Indeed, the reaction of methylphenylphosphine-borane with phenyl iodide, in the presence of a base and $Pd(PPh_3)_4$ as the catalyst in THF at room temperature led to a low conversion to the product in 5 days; on the contrary, by keeping the same reaction conditions and adding catalytic amounts of CuI, much higher conversion to the product in shorter time was obtained. The beneficial effect of Cu(I) as co-catalyst in several Pd(0) mediated coupling reactions has been previously observed,[74-76] however Livinghouse and co-workers were the first ones to attempt this reaction in the preparation of phosphorus-based compounds. The reaction conditions were optimised and a range of phosphine-boranes were then obtained using this procedure. The proposed reaction path for this P-C coupling catalysed by Pd(0)/Cu(I) is shown in figure 1.25:[77, 78]

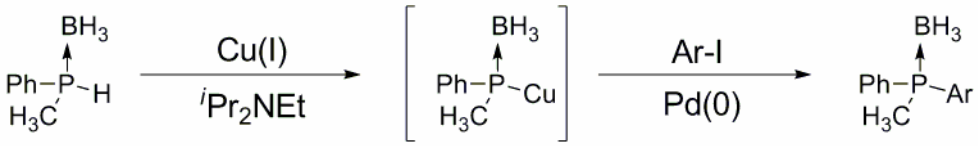


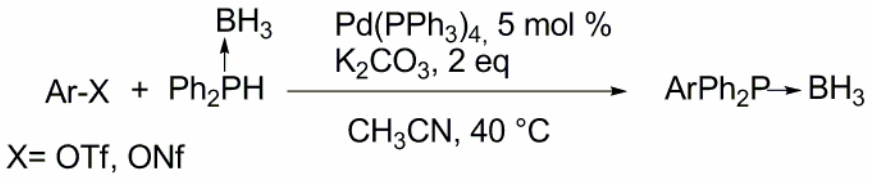
Fig. 1.25 Proposed path for the P-C cross coupling reaction catalysed by Pd(0), with Cu(I) as co-catalyst

1.7.2.2 Aryl triflates and nonaflates as coupling partners in the palladium catalysed cross-coupling with phosphine-boranes

Aryl iodides are the most common substrates used in palladium catalysed P-C bond forming reactions because of their high reactivity. However, their limited availability and high cost reduce the number of aryl groups that can be used as coupling partners.

Lipshutz and co-workers interestingly described the possible use of aryl triflates and nonaflates in the palladium catalysed reaction with diphenylphosphine boranes: the use of nonaflates has been described before in the Negishi cross- coupling reaction.[79]

In their study, Lipshutz and co-workers preferred aryl nonaflates over aryl triflates as they are easily prepared and involve a less costly precursor. Moreover, in some cases a higher reactivity was observed with the arylnonaflates compared to its triflate derivative. An example shown of this higher reactivity has been the nonaflate of 2-naphthol (table 1.4, entry 1): the corresponding triflate was completely inert to the standard coupling conditions used, while the nonaflate gave quantitative conversion to the triarylphosphine-borane. Some of Lipshutz's results are reported in table 1.4:[80]



Scheme 1.4

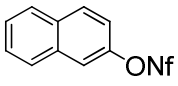
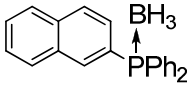
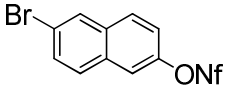
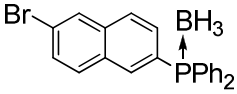
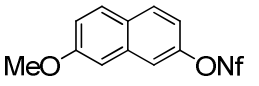
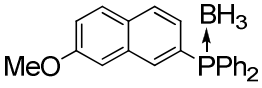
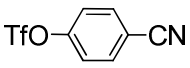
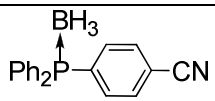
Entry	Nonaflate/Triflate	Product	Time (hours)	Yield (%)
1			3	100
2			4	93
3			5	95
4			4	67[(a)]

Table 1.4 Coupling reactios of aryl triflates/nonaflates with dihpenylphosphie-borane (a) $Pd(dba)_2$ and dppf were used instead of $Pd(PPh_3)_4$.

Lipshutz and co-workers also tried to use a different catalytic system (entry 4, table 1.4), but in the conditions they used, $Pd(PPh_3)_4$ proved to be more efficient, leading to higher yields. Moreover, it was also pointed out that the use of phosphine-boranes with aryl triflates and nonaflates is a valuable method unless heteroaryl substrates are used, since the presence of the heterocyclic nitrogen decomplexes the borane.

The use of phosphine-boranes in the palladium mediated phosphination reaction has also been developed by Gaumont and co-workers,[81, 82] and importantly it has been useful in isolating the intermediates of the mechanism for the palladium-catalysed P-C bond forming reaction.[18]

1.7.3 Deprotection of phosphine-boranes

Of course, when working with phosphine-boranes, the removal of the borane group is necessary, in order to get eventually the desired free phosphines. One of the most common methods described for the deprotection of phosphine-borane is the use of amines. Indeed, Imamoto and co-workers in their early work on phosphine-borane described the decomplexation of the borane group by using diethylamine.[62] Le Corre and co-workers tested different amines in the deprotection of benzyldiphenylphosphine-borane, and found out that DABCO was leading to the complete removal of the borane group under the conditions they used. Moreover, in the same paper it was also considered that toluene is the solvent of choice for this type of transformation, as it renders the phosphine-borane complex and the amine soluble, without being too polar. In fact it was noticed that the decomplexation rate decreased rapidly if performed in polar solvents, like dichloromethane, acetonitrile or methanol.[83] Because of the reversibility of the reaction, an excess of the amine is generally used.

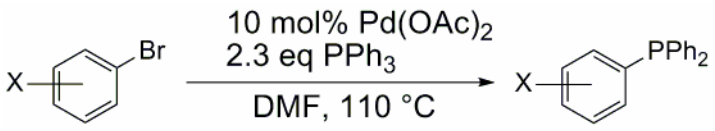
However, the use of amines for the deprotection of phosphine-boranes has proved to be inefficient when working with hindered, electron-rich phosphine-boranes. Livinghouse and co-workers have thus developed an alternative method for the removal of the borane group under acidic conditions: this other option has been considered on the basis of Imamoto's work[67] who described the reaction of different phosphine-boranes with methanesulfonic acid and trifluoromethanesulfonic acid. Livinghouse and co-workers thus tested different acids for the decomplexation step and found out that the commercially available $HBF_4 \cdot OMe_2$ proved to be the most efficacious in terms of rate as well as isolated yields of the free phosphine. By treating the phosphine-borane with $HBF_4 \cdot OMe_2$, the phosphinium-borane salt is given: the free phosphine is obtained after hydrolysis with aqueous $NaHCO_3$.[84, 85]

The methods described above are nowadays the most commonly used for the deprotection of phosphine-boranes and allowed the synthesis of many otherwise elusive phosphorus-based ligands.

1.8 Palladium catalysed phosphination using triarylphosphines

So far, different palladium catalysed P-C bond forming reactions have been described. All these methods have been used in the synthesis of phosphine-based ligands, and on top of that provided a basis for mechanistic work. However, all these methods held some drawbacks: when direct coupling of arylphosphines is carried out, the use of air sensitive phosphines is in general required, and this is a limitation, in particular when purification of the product is needed; the use of phosphine oxides or phosphine boranes allows in general easy purification, but their use implies the addition of one more step to the synthetic route (reduction and deboronation respectively). Furthermore, the use of trimethylsilyl diphenylphosphine is limited to aryl iodides and cannot tolerate aldehyde functional groups.

A method that circumvents these drawbacks has been proposed by Chan and co-workers: this new palladium catalysed reaction involves the use of triarylphosphines as the phosphinating agents. Moreover, it allows the synthesis of phosphines starting from functionalised aryl bromides (see table 1.6):[86]



Scheme 1.5

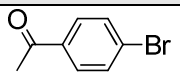
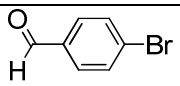
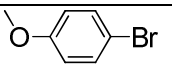
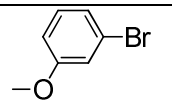
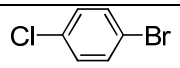
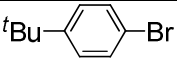
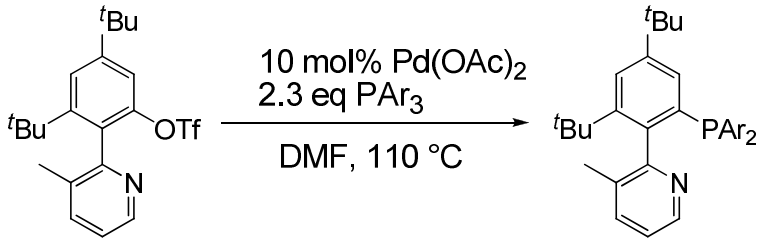
Entry	Substrate	Time (hours)	Yield (%)
1		20	40
2		64	32
3		24	27
4		18	38
5		20	51
6		19	59

Table 1.6 Pd catalysed phosphination of aryl bromides usig triphenylphosphine

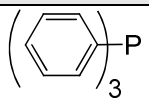
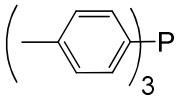
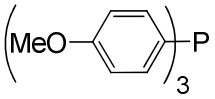
Table 1.6 reports the first results obtained by Chan and co-workers in the palladium catalysed phosphination using triphenyl phosphine as the phosphinating agent. Different triarylphosphines

have also been employed on *p*-bromoacetophenone, giving moderate yields.[86] The results obtained were not brilliant, as conversions remained moderate, but further investigation has been carried out, as the reaction is potentially quite powerful. Indeed, the reaction conditions were optimised: different palladium catalysts were tested, and $Pd(OAc)_2$ was identified as the best choice because it is air stable and it allows the use of other triarylphosphines as phosphinating agents other than triphenylphosphine. Moreover, it was noticed that the rate and the yield increased by increasing the catalyst loading from 5 to 10 mol %. However, further increase of the amount of catalyst did not lead to much different results. A solvent study brought to the conclusion that polar and aprotic solvents had to be used to obtain high conversions: in particular, DMF was recognised as the solvent of choice. The amount of the phosphinating agent had to be between 2.3 and 2.5 equivalents: indeed, stoichiometric amounts or large excess led to low yields. In the latter case, it was considered that large amounts of the tertiary phosphine could decrease the catalytic activity by forming coordinatively saturated and catalytically less active palladium species. Finally, the effect of the temperature was investigated, and it was found that no reaction occurred below 100 °C. It was necessary to keep the temperature between 110-125 °C to achieve reasonable yields. At higher temperature no reaction occurred, probably because of decomposition of the catalyst.

Once the reaction conditions were optimised, the reaction was employed for the synthesis of P,N ligands, starting from aryltriflates and using different triarylphosphines as phosphinating agents (see table 1.7):[87, 88]



Scheme 1.6

Entry	Triarylphosphine	Time (days)	Yield (%)
1		4.5	68
2		4.5	60
3		3.5	60

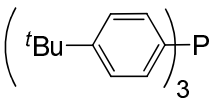
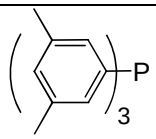
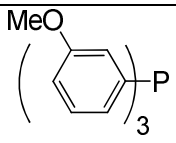
4		4	55
5		4	58
6		5	55

Table 1.7 Palladium catalysed phosphination with different triarylphosphines for the preparation of P,N ligands, as shown in scheme 1.6

It was noticed that sterically hindered *ortho*-substituted triarylphosphines did not react and this is possibly due to a retardant effect of the triarylphosphine on the aryl/aryl exchange.

1.8.1 Mechanism of palladium catalysed phosphination

The palladium mediated phosphination using triarylphosphines occurs because of the facile aryl/aryl exchange between the aryl groups bound to the palladium with the one bound to the phosphorus:

Fig. 1.26 Aryl/aryl exchange in palladium catalysed reactions

This aryl/aryl exchange has been observed in the past as an undesired side reaction that occurred in many cross coupling reactions.[89]

In figure 1.27 it is illustrated the possible mechanism for the palladium catalysed phosphination, using triarylphophines as phosphinating agents:[88]

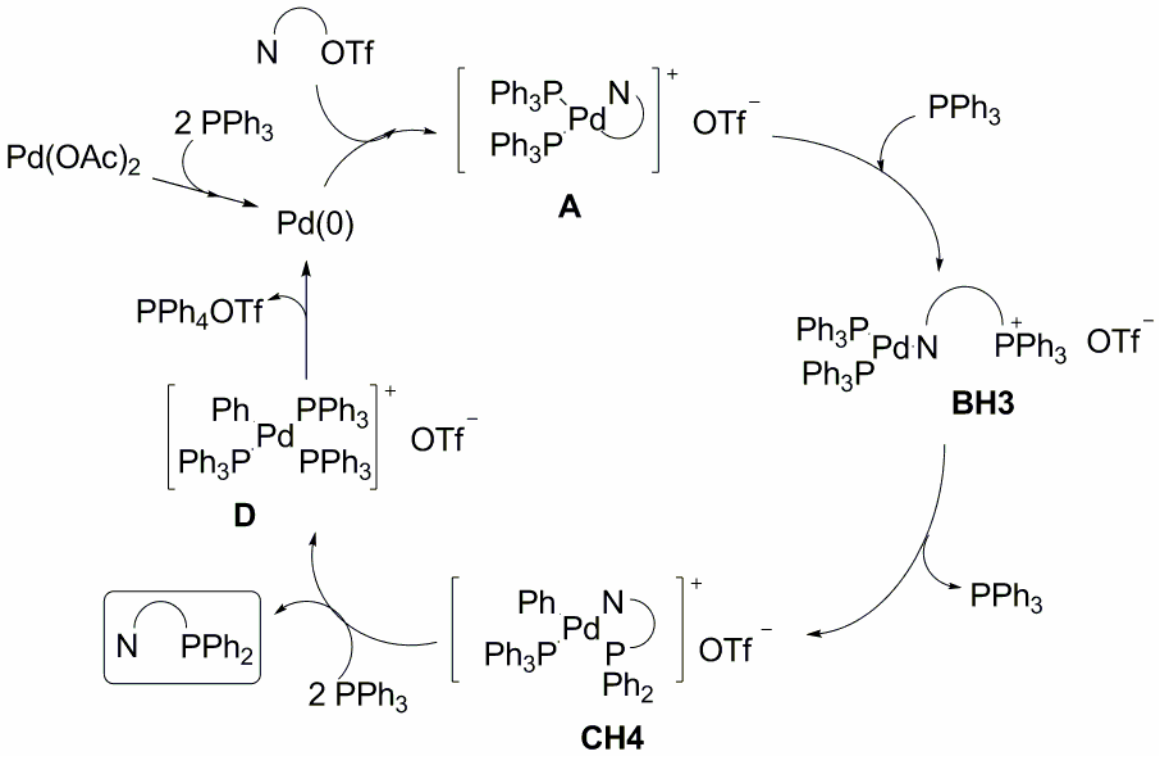


Fig. 1.27 Proposed mechanism for the palladium catalysed phosphination with triarylphosphines as phosphinating agents

Palladium acetate is reduced *in situ* by triphenylphosphine and the active catalyst is obtained. This Pd(0) species undergoes oxidative addition with pyridylphenyl triflate to give complex **A**. In the presence of triphenylphosphine, the newly formed complex **A** undergoes reductive elimination to produce the phosphonium salt **B**. As previously said, sterically hindered *ortho*-substituted triarylphosphines do not work in this type of reaction, and that is probably due to their incapability of forming this phosphonium salt.

Once formed, complex **B** undergoes oxidative addition, leading to the formation of complex **C**. Finally, ligand substitution of complex **C** by triphenylphosphine to the palladium complex generates the product and complex **D**. Reductive elimination of complex **D** leads to regeneration of the active catalyst and tetraphenylphosphonium triflate is also formed as co-product. Tetraphenylphosphonium triflate was detected by NMR and isolated. Moreover, the importance of the coordination of the pyridine-nitrogen was confirmed: in fact, it was noticed that no reaction occurred on substrate (**38**), which has a *tert*-butyl group adjacent to the pyridine-nitrogen, and this is probably due to the lack of coordination between the palladium and the nitrogen, which is prevented by the sterically hindered *tert*-butyl group (fig. 1.28):

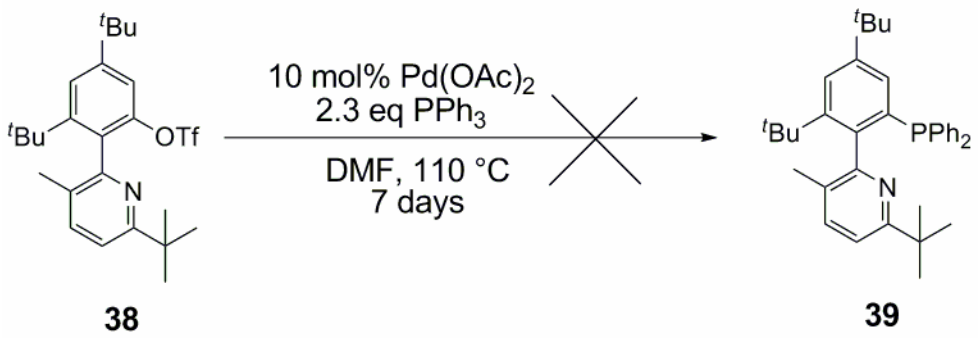


Fig. 1.28 Palladium catalysed phosphination on substrate (38)

The palladium catalysed phosphination using triarylphosphines as phosphinating agents has seen some application and further investigation of the reaction conditions.[89, 90]

Indeed, Chan and co-workers proposed[90] a potentially very useful method for preparing a wide variety of phosphines. However, further work might be necessary, in trying to increase the yields and to get over the problems given with sterically hindered reagents.

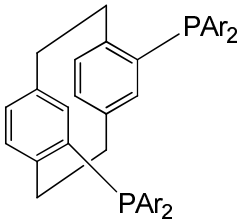
1.9 Aim of the project

In this PhD project, several related topics have been studied with a general theme of improving methodology for the synthesis of phosphines.

In chapter 3, a study on P-C bond forming reactions is presented. The preceding review should highlight the potential importance of Pd catalysed P-C bond forming reactions, but also note that the reaction is rarely practiced on aryl bromide substrates.

Indeed, there are several papers that explicitly state difficulties encounted with aryl bromides, whereas other merely report lower yields, longer reaction times and fewer examples. Secondly, bulky aryl halides (and triflates) can also be problematic substrates to couple.

These issues had some particular relevance to my industrial sponsor Chirotech, who desired efficient synthetic procedures to three families of ligands that had proven problematic. Phanephos and its derivatives can be made using lithium-halogen exchange reaction using *tert*-butyl lithium, but the pyrophoric nature and lack of functional group tolerance of organolithiums was causing problems in the larger scale synthesis.



HexaPHEMP cannot be prepared in a single step from (**40**) (see fig. 1.29), and instead requires a long low yielding synthesis:

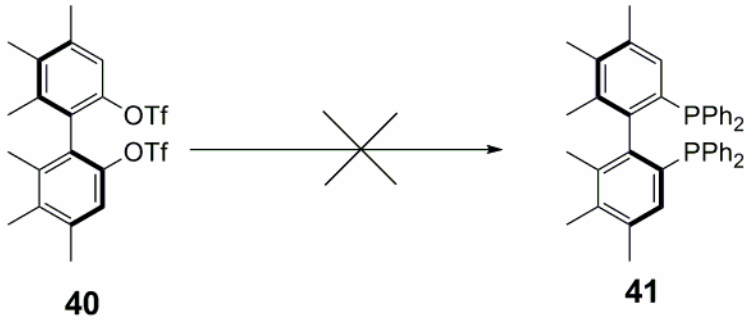


Fig. 1.29 Desired synthetic route to HexaPHEMP

Phenyl-Duphos has never been made, but was envisaged to be a very interesting chiral ligand that might be synthesised from diiodobenzene using palladium catalysed P-C bond forming reaction (see fig. 1.30):

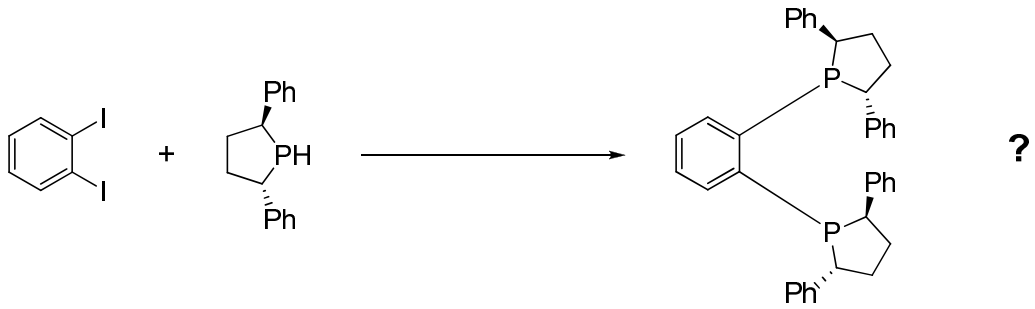


Fig. 1.30 Proposed synthetic route for Ph-Duphos

We therefore initiated a study into optimising palladium catalysed P-C bond forming reactions using microwave heating that will be discussed in chapter 3. This led to using more traditional organophosphorus methodology for the synthesis of a new phospholane that was evaluated in one of the most promising but challenging asymmetric reactions, hydroxycarbonylation (discussed in chapter 4).

It was also identified that given how difficult P-C bond forming reactions can be and that subtle changes to the structure of the aryl groups in chiral diarylphosphino substituted ligands can have massive effects on the ligands performance. It would therefore be desirable to rapidly modify a single chiral diarylphosphino precursor into a library of phosphine ligands. In chapter 2, studies towards using microwave accelerated cross-coupling to modify chloroarylphosphine oxides are presented.

1.10 References

1 R. Noyori, *Angew. Chem. Int. Ed.*, 2002, **41**, 2008.
2 W. Knowles, *Acc. Chem. Res.*, 1983, **16**, 106.
3 K. B. Sharpless, *Angew. Chem. Int. Ed.*, 2002, **41**, 2024.
4 H.-U. Blaser, *Adv. Synth. Catal.*, 2002, **344**, 17.
5 K. C. Nicolaou, P. G. Bulger, and D. Sarlah, *Angew. Chem. Int. Ed.*, 2005, **44**, 4442.
6 M. Kosugi, M. Kameyama, and T. Migita, *Chem. Lett.*, 1983, 927.
7 A. S. Guram, R. A. Rennels, and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 1995, **34**, 1348.
8 J. P. Wolfe, S. Wagaw, and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 7215.
9 M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, 1996, **118**, 7217.
10 M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*,1995, **117**, 4708.
11 J. Louie and J. F. Hartwig, *Tet. Lett.*, 1995, **36**, 3609.
12 J. P. Wolfe and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 1999, **38**, 2413.
13 B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, 1999, **576**, 125.
14 J. F. Hartwig, *Angew. Chem. Int. Ed.*, 1998, **37**, 2046.
15 K. N. Harrison, P. A. T. Hoye, A. G. Orpen, P. G. Pringle, and M. B. Smith, *J. Chem. Soc., Chem. Comm.*, 1989, 1096.
16 P. A. T. Hoye, P. G. Pringle, M. B. Smith, and K. Worboys, *J. Chem. Soc., Dalton Trans.*, 1993, 269.
17 E. Costa, P. G. Pringle, and K. Worboys, *Chem. Comm.*, 1998, 49.
18 A.-C. Gaumont, J. M. Brown, M. B. Hursthouse, and S. J. Coles, *Chem. Comm.*,1999, 63.
19 A. L. Casalnuovo and J. C. Calabrese, *J. Am. Chem. Soc.*,1990, **112**, 4324.
20 L. Kurz, G. Lee, D. Morgans Jr., M. J. Waldyke and T. Ward, *Tet. Lett.*, 1990, **31**, 6321.
21 S. N. L. Bennet and R. G. Hall, *J. Chem. Soc. Perkin Trans. 1*, 1995, 1145.
22 A. W. Schwabacher and A. D. Stefanescu, *Tet. Lett.*, 1996, **37**, 425.
23 Y. R. Dumond and J.-L. Montchamp, *J. Organomet. Chem.*, 2002, **653**, 252.
24 T. M. T. Hirao, N. Yamada, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 909.
25 S. E. Tunney and J. K. Stille, *J. Org. Chem.*, 1987, **52**, 748.
26 C. Eaborn, K. J. Odell, A. Pidcock, *J. Organomet. Chem.*, 1979, **170**, 105.
27 S. E. Martin, M. Bonaterra, R. A. Rossi, *J. Organomet. Chem.*, 2002, **664**, 223.
28 W. J. Scott, G. T. Crisp and J. K. Stille, *J. Am. Chem. Soc.*,1984, **106**, 4630.
29 E. M. Echavarren and J. K. Stille, *J. Am. Chem. Soc.*, 1987, **109**, 5478.
30 O. Herd, M. Hingst, M. Tepper, O. Stelzer, *J. Organomet. Chem.*, 1996, **522**, 69.
31 F. Bitterer, O. Herd, A. Hessler, M. Kuhnel, K. Rettig, and W. S. Shelrick, O. Stelzer, S. Nagel, and N. Rosch, *Inorg. Chem.*, 1996, **35**, 4103.
32 M. Hingst, D. J. Brauer, K. W. Kottsieper, C. Liek, M. Tepper, T. Nickel, O. Stelzer, W. S. Sheldrick, *J. Organomet. Chem.*, 2002, **645**, 14.
33 K. M. Hidemasa Takaya, K. Mashima, K. Koyano, M. Yagi, H. Kumobayashi, T. Taketomi, S. Akutagawa, and R. Noyori, *J. Org. Chem.*, 1986, **51**, 629.
34 D. Cai, J. F. Payack, D. R. Bender, D. L. Hughes, T. R. Verhoeven, and P. J. Reider, *J. Org. Chem.*, 1994, **59**, 7180.
35 D. J. Ager, A. Eisenstadt and S. A. Laneman, *Chem. Comm.*, 1997, 2359.
36 F. Y. Kwong, A. S. C. Chan, K. S. Chan, *Tetrahedron*, 2000, **56**, 8893.
37 K. P. Langer, R. Sttirmer, and P. Knochel, *Tet. Asymm.*, 1997, **8**, 715.
38 S. Laue, L. Greiner, J. Woltinger, and A. Liese, *Adv. Synth. Catal.*, 2001, **343**, 711.
39 K. M. Pietrusiewicz and M. Zablocka, *Chem. Rev.*,1994, **94**, 1375.
40 A. Grabulosa, G. Muller, *Coord. Chem. Rev.*, 2007, **251**, 25.
41 D. Drago and P. S. Pregosin, *Organometallics*, 2002, **21**, 1208.
42 J. R. Moncarz, N. F. Laritcheva and D. S. Glueck, *J. Am. Chem. Soc.*, 2002, **124**, 13356.

43 N. F. Blank, J. R. Moncarz, T. J. Brunker, C. Scriban, B. J. Anderson, O. Amir, D. S. Glueck, L. N. Zakharov, J. A. Golen, C. D. Incarvito, and A. L. Rheingold, *J. Am. Chem. Soc.*, 2007, **129**, 6847.

44 T. J. Brunker, N. F. Blank, J. R. Moncarz, C. Scriban, B. J. Anderson, D. S. Glueck, L. N. Zakharov, J. A. Golen, R. D. Sommer, C. D. Incarvito, and A. L. Rheingold, *Organometallics*, 2005, **24**, 2730.

45 N. F. Blank, K. C. McBroom, D. S. Glueck, W. S. Kassel, and A. L. Rheingold, *Organometallics*, 2006, **25**, 1742.

46 C. Korff and G. Helmchen, *Chem. Comm.*, 2004, 530.

47 D. E. Bergbreiter, Y. S. Liu, S. Furyk and B. L. Case, *Tet. Lett.*, 1998, **39**, 8799.

48 M. Larhed, C. Moberg, and A. Hallberg, *Acc. Chem. Res.*, 2002, **35**, 717.

49 A. Stadler and C. O. Kappe, *Org. Lett.*, 2002, **4**, 3541.

50 M. Murata and S. L. Buchwald, *Tetrahedron*, 2004, **60**, 7397.

51 K. S. Petrakis and T. L. Nagabhushan, *J. Am. Chem. Soc.*,1987, **109**, 2831.

52 R. E. Dolle, S. J. Schmidt, and L. I. Kruse, *J. Chem. Soc., Chem. Comm.*, 1987, 904.

53 T. Hayashi, *Acc. Chem. Res.*, 2000, **33**, 354.

54 T. Hayashi, *J. Organomet. Chem.*, 1999, **576**, 195.

55 A. Torii, Y. Uozumi, S. Y. Lee, and T. Hayashi, *J. Org. Chem.*, 1993, **58**, 1945.

56 T. Hayashi, S. Hirate, K. Kitayama, H. Tsuji, A. Torii, and Y. Uozumi, *J. Org. Chem.* 2001, **66**, 1441.

57 H. Doucet, J. M. Brown, *Tet. Asymm.*, 1997, **8**, 3775.

58 M. McCarthy and P. J. Guiry, *Tetrahedron*, 1999, **55**, 3061.

59 M. McCarthy, R. Goddard, and P. J. Guiry, *Tet. Asymm.*, 1999, **10**, 2797.

60 G. Bringmann, C. Vedder, M. Pfeiffer, and D. Stalke, *Chem. Comm.*, 1998, 1211.

61 H.C. Wu, J. Q. Yu, and J. B. Spencer, *Org. Lett.*, 2004, **6**, 4675.

62 T. Imamoto, T. Kusumoto, N. Suzuki and K. Sato, *J. Am. Chem. Soc.*, 1985, **107**, 5301.

63 H. Schmidbaur, *J. Organomet. Chem.*, 1980, **200**, 287.

64 A. B. Burg, and R. I. Wagner, *J. Am. Chem. Soc.*, 1953, **75**, 3872.

65 E. L. Gamble and P. Gilmont, *J. Am. Chem. Soc.*, 1940, **62**, 717.

66 T. Oshiki, T. Imamoto, T. Onozawa, T. Kusumoto, and K. Sato, *J. Am. Chem. Soc.*, 1990, **112**, 5244.

67 T. Imamoto, *Pure and Appl. Chem.*, 1993, **65**, 655.

68 T. Oshiki and T. Imamoto, *J. Am. Chem. Soc.*, 1992, **114**, 3975.

69 T. Imamoto, T. Oshiki, T. Onozawa, M. Matsuo, T. Hikosaka, and M. Yanagawa, *Heteroat. Chem.*, 1992, **3**, 563.

70 J. Zhang, Y. Xu, G. Huang, *Tet. Lett.*, 1989, **30**, 949.

71 Y. Xu, J. Zhang, G. Huang and H. Guo, *Tet. Lett.*, 1988, **29**, 1955.

72 T. Miura, H. Yamada, S. Kikuchi, and T. Imamoto, *J. Org. Chem.*, 2000, **65**, 1877.

73 B. Wolfe and T. Livinghouse, *J. Am. Chem. Soc.*, 1998, **120**, 5116.

74 L. S. Liebeskind and S. W. Riesinger, *J. Org. Chem.*, 1993, **58**, 408.

75 S. Arcadia, S. Cacchi, and F. Marinellia, *Tet. Lett.*, 1989, **30**, 2581.

76 E. Piers and M. A. Romero, *J. Am. Chem. Soc.*, 1996, **118**, 1215.

77 M. Al-Masum, G. Kumaraswamy, and T. Livinghouse, *J. Org. Chem.*, 2000, **65**, 4776.

78 T. Livinghouse, M. Al-Masum, *Tet. Lett.*, 1999, **40**, 7731.

79 M. Rottlander and P. Knochel, *J. Org. Chem.*, 1998, **63**, 203.

80 B. H. Lipshutz, D. J. Buzar and C. S. Yun, *Tet. Lett.*, 1999, **40**, 201.

81 H. Vallette, S. Pican, C. Boudou, J. Levillain, and J. C. Plaquevent, and A. C. Gaumont, *Tet. Lett*, 2006, **47**, 5191.

82 S. Pican and A. C. Gaumont, *Chem.Comm.*, 2005, 2393.

83 H. Brisset, Y. Gourdon, P. Pellon and M. Le Corre, *Tet. Lett.*, 1993, **34**, 4523.

84 L. McKinstry and T. Livinghouse, *Tet. Lett*, 1994, **35**, 9319.

85 L. McKinstry and T. Livinghouse, *Tetrahedron*, 1995, **51**, 7655.
86 F. Y. Kwong and K. S. Chan, *Chem. Comm.*, 2000, 1069.
87 F. Y. Kwong and K. S. Chan, *Organometallics*, 2000, **19**, 2058.
88 F. Y. Kwong and K. S. Chan, *Organometallics*, 2001, **20**, 2570.
89 F. Y. Kwong, C. W. Lai, M. Yu and K. S. Chan, *Tetrahedron*, 2004, **60**, 5635.
90 C. W. Lai, F. Y. Kwong and K. S. Chan, *Tet. Lett.*, 2002, **43**, 3537.

Chapter 2

Suzuki cross coupling of chloroarylphosphine oxides

2.1 Introduction

The Suzuki cross coupling is one of the most useful palladium-catalysed cross-coupling reaction. The first example was published by Suzuki and co-workers in 1979[1] (fig. 2.1) and since then it has attracted the interest of the scientific community.

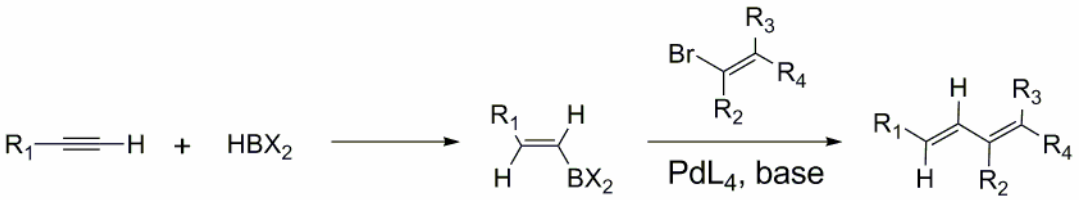


Fig. 2.1 First example of the Suzuki cross-coupling reaction

In this carbon-carbon bond forming reaction, organoboron reagents are used: tertiary boranes could be used, but arylboronic acids are most often employed because of the large variety that are commercially available. Organoboronic acids are non-toxic, stable to air, moisture and heat; furthermore they have shown a wide tolerance to many functional groups. In addition, boron-containing by-products of the Suzuki cross-coupling can easily be separated from the desired compound. All these characteristics make the Suzuki reaction an attractive tool for the synthesis of complex organic compounds, e.g. natural products[2] or more specifically biaryls compounds,[3] which are interesting compounds not only for academic research but also for industrial production of fine chemicals.

An example of the use of the Suzuki cross coupling reaction in the pharmaceutical industry can be found in the synthesis of Losartan (fig. 2.2), a drug developed for the treatment of high blood pressure and heart failure:[4, 5]

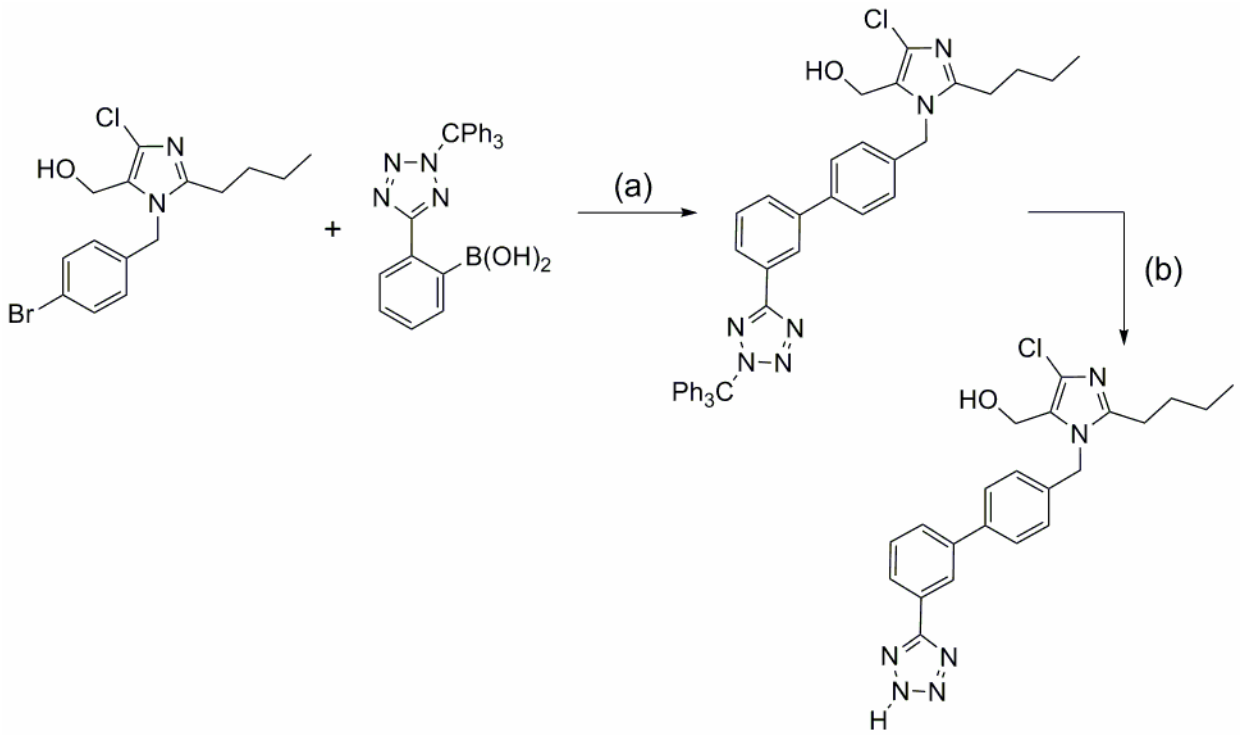


Fig.2.2 Key steps of the synthesis of Losartan
(a) Catalyst prepared in situ: PPh_3 and $Pd(OAc)_2$ (4/1) stirred at r.t. for 30 minutes in diethylmethene/THF 4/1; K_2CO_3, reflux for 6 hours; (b) H_2SO_4, CH_3CN/H_2O 1/1.

2.2 Mechanism of the Suzuki cross coupling reaction

The catalytic cycle of the Suzuki cross coupling reaction using monodentate phosphines, shown in fig. 2.3, starts with the insertion of the palladium complex into the C-X bond of the electrophile (oxidative addition), affording a stable *trans*-organopalladium(II) complex, with the leaving group X^- coordinated to the metal centre. The transmetalation reaction with the organoboronic acid then takes place, leading to the diorganopalladium(II) complex and $X\text{-}B(OH)_2$. After isomerisation from *trans* to *cis*, the following reductive elimination step gives the coupling product and regenerates the catalytically active palladium(0) species.[6, 7] Intermediates **(I)** and **(II)** have been characterised, lending support to this catalytic cycle.[8]

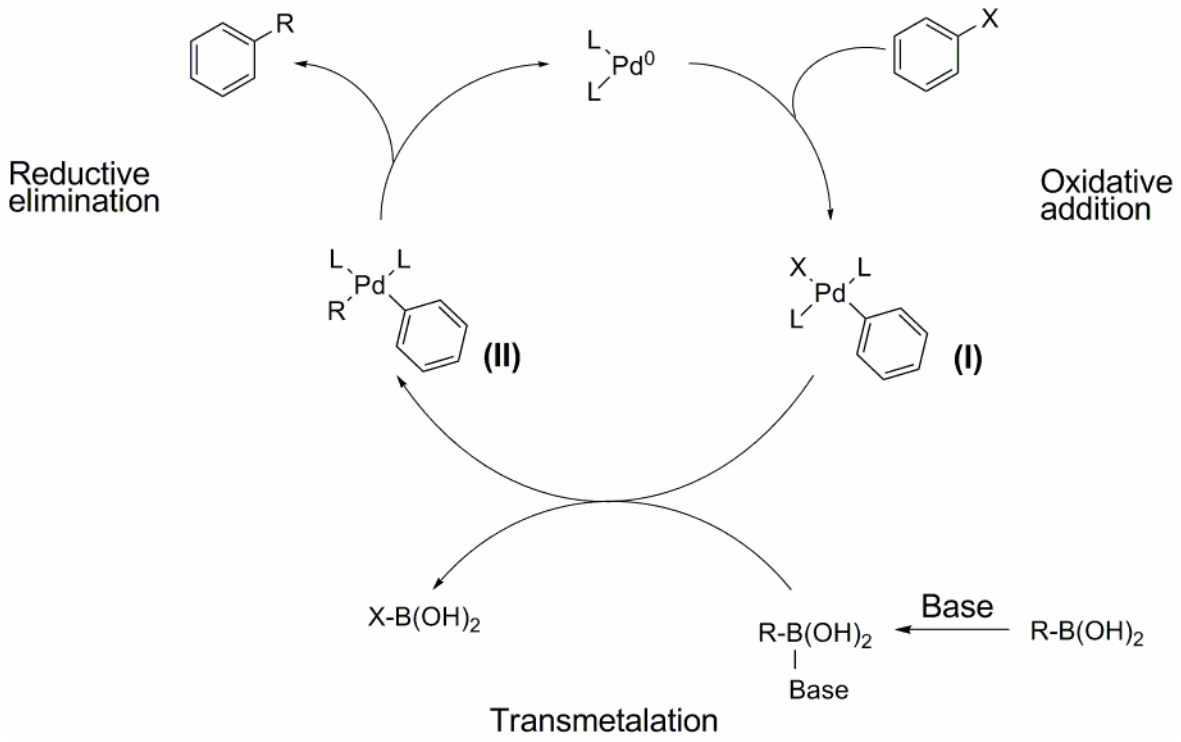


Fig. 2.3 Simplified mechanism of the Suzuki reaction

2.2.1 Effect of the base in the Suzuki cross coupling reaction

Already from the very first examples of the Suzuki cross coupling reaction shown, the use of a base has been found out to be necessary for the reaction to proceed[1, 9, 10].

One explanation for the need of the base can be due to the fact that the transmetallation step between the organopalladium(II) halides and the organoboron compound does not occur readily, because of the low nucleophilicity of the organic group on the boron atom. The nucleophilic character of the organic group on the boron atom can be enhanced by quaternizing the boron using a negatively charged base (see fig. 2.4).

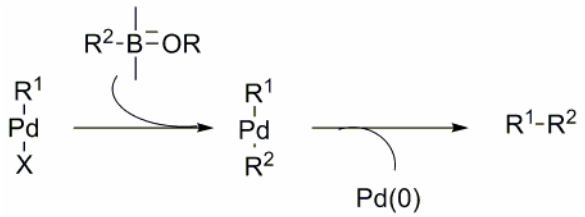


Fig 2.4 Base-assisted activation of the organoboron species

An alternative role of the base shown is its effect in the activation of the palladium. It is possible that the formation of Ar-Pd-OR, where –OR is the base, from Ar-Pd-X, assists the transmetalation step (fig. 2.5):[11]

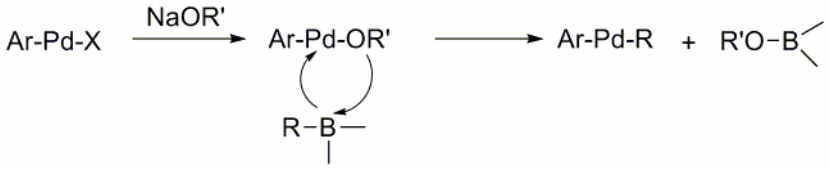


Fig. 2.5 Base-assisted activation of the palladium(II) species

However, a strong base could be in some cases incompatible with the functional groups present in the desired reagents: fluorides salts, and in particular CsF, have been found to be useful bases for the Suzuki cross coupling reaction.[12]

2.3 Suzuki cross-coupling reactions of aryl chlorides

The order of reactivity of the aryl halides is PhI>PhBr>PhCl, which is consistent with the strength of Ar-X bond (bond dissociation energies for Ph-X: I: 65 kcal mol^{-1}; Br: 81 kcal mol^{-1}; Cl: 96 kcal mol^{-1}). However, chloroaryl compounds would be much more useful substrates, because of their low cost and for the wider diversity of readily available compounds, making them attractive substrates both in small scale and industrial applications.[13]

The low reactivity of aryl chlorides is usually attributed to their high stability, which disfavour oxidative addition, the first step in the Suzuki cross-coupling reaction.[14] Suzuki cross coupling can readily occur on chloro-substituted nitrogen heterocycles, as these sorts of substrates are activated toward oxidative addition. Representative examples are reported in fig. 2.6:

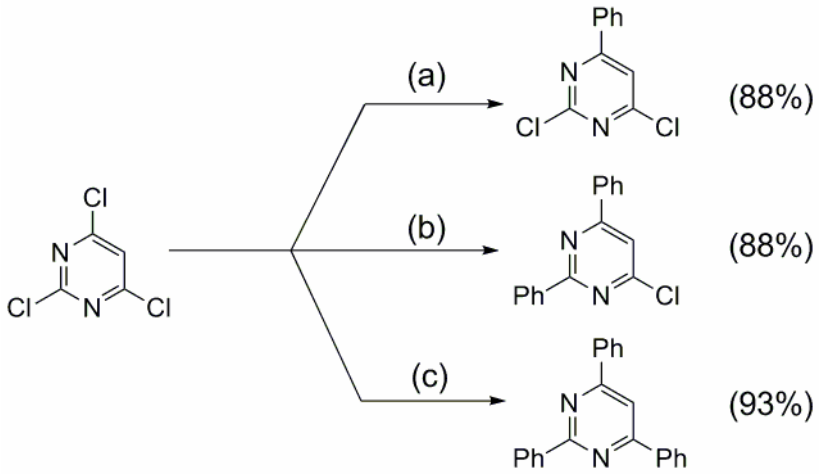


Fig. 2.6 Suzuki cross-coupling reaction on chloro-substituted nitrogen heterocycles[15] (a) 1eq $PhB(OH)_2$, Na_2CO_3, 5%mol $Pd(OAc)_2$, 10%mol PPh_3, glyme, reflux, 18h; (b) 2eq $PhB(OH)_2$, Na_2CO_3, 2.5%mol $Pd(OAc)_2$, 5%mol PPh_3, glyme, reflux, 24h; (c) 3eq $PhB(OH)_2$, Na_2CO_3, 2.5%mol $Pd(OAc)_2$, 5%mol PPh_3, glyme, reflux, 24h.

Non heteroaryl electron-deficient aryl chlorides undergo oxidative addition as well. A couple of examples are shown in fig. 2.7:

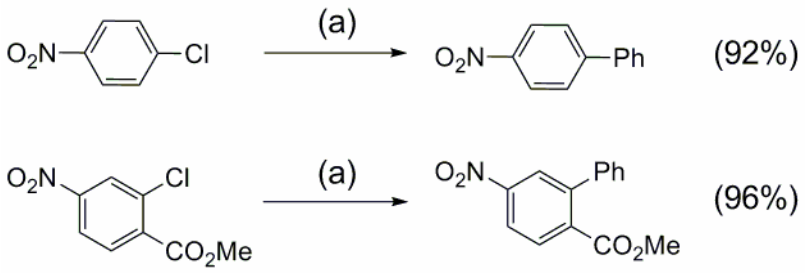


Fig 2.7 Suzuki cross coupling on non heteroaryl electron-deficient aryl chlorides[16] (a) 2.4eq $PhB(OH)_2$,CsF, 5%mol $Pd(OAc)_2$, 5%mol dppp, 1-methyl-2-pyrrolidinone, 100 °C, 10h.

Initially, tetrakis(triphenylphosphine)palladium(0) was used as the catalyst for the Suzuki cross coupling reaction.[7, 17] *In situ* mixtures of palladium(0) or palladium (II) sources were also used, though not always leading to better results. These catalysts were useful for the coupling of aryl bromides, iodides, triflates and also for π-deficient heteroaryl chlorides.

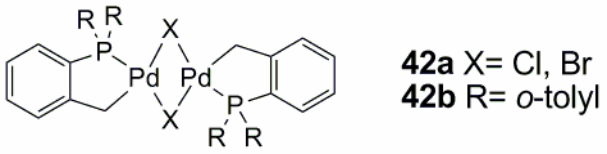
However, because of the high demand of a wider selection of arylchlorides as substrates for the Suzuki cross-coupling reaction, lots of work has been carried out. In particular, a large variety of ligands has been synthesised to overcome the problem of the coupling of arylboronic acids with inactivated arylchlorides.

2.4 Ligand development for the palladium-catalysed Suzuki cross-coupling reaction of inactivated arylchlorides

2.4.1 Palladacycle complexes as catalyst precursors

Palladacycle complexes have been developed since the 1990's for the use in the Suzuki cross coupling reaction. These catalysts have shown high activity and longevity, that would positively affect recycling protocols: these aspects, together with their stability to air and moisture, have contributed to their further investigation.[18-21]

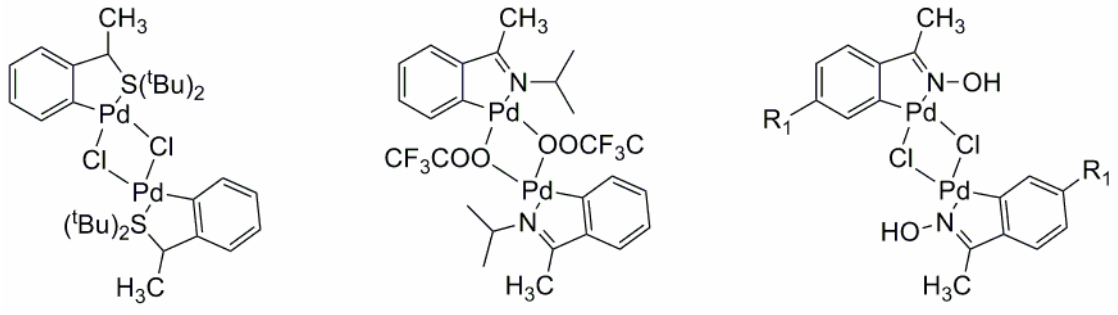
Herrmann and co-workers tested the activity of catalyst **(42)** both in the Heck[22] and in the Suzuki[23] reaction.



42

In both cases, high yields were reported using either aryl chlorides or bromides as substrates. A few observations were also highlighted. First of all, no palladium deposits were observed, or only traces were present with longer reaction time (over 25 hours), suggesting a long-term stability. The turnover number (TON) reached values of 200,000 with bromoarenes, although high concentration of the catalyst was necessary for the coupling of aryl chlorides. Importantly, P-C bond cleavage, that commonly occurs at around 130 °C, was not observed, leading to the formation of no side products, one of the causes for the low yields obtained in the Suzuki cross coupling reaction previously reported.[24, 25]

Moreover, phosphine free complexes have also been investigated (see fig. 2.8): Monteiro and co-workers have developed sulfur-containing palladacycles, like (**43**), as successful catalysts for activated aryl chlorides at room temperature;[26] Weissman and co-workers introduced the imine complex (**44**) as another successful catalyst for the Suzuki cross-coupling reaction: in particular, this catalyst has shown really high TON (TON over 100000) with nonactivated aryl bromides;[27] Nàjera's research group demonstrated that air- and water- stable oxime-derived palladacycles (**55**) are suitable catalysts for the coupling of boronic acids with aryl and heteroaryl chlorides in water.[28]

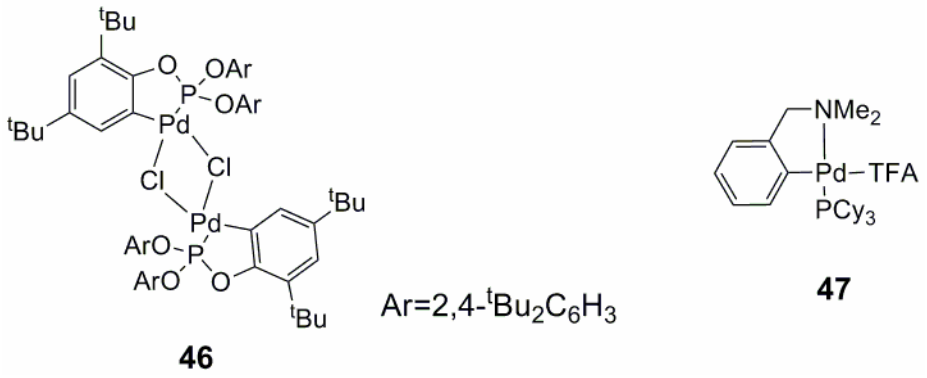


43 **44** **45a: R_1=OH** **45a: R_1=H**

Fig. 2.8 Phosphine free palladacycles

Interesting work has been carried out from Bedford and co-workers. In the late 90s they found complex (**46**) to be really active for the Suzuki cross coupling of aryl bromides, but not of even activated aryl chlorides.[29] Subsequently, on the basis of the work previously reported by Littke and

Fu, that showed that palladium catalysts formed *in situ* with PCy_3 gave reasonable activity, and research that demonstrated that pre-formed Pd(0) complexes of the type [Pd(diene)(PCy_3)] are very active, Bedford and co-workers prepared complex (**47**) (figure 2.9). Keeping in mind their own previous findings, they considered necessary the presence, in the catalyst structure, of PCy_3: this resulted to be a successful move, as high conversions to the coupled product were obtained, starting from both electron rich and poor aryl chlorides:[30]



46 **47**

Fig 2.9 Catalysts developed by Bedford

The following step of their research consisted in using the catalyst formed from PCy_3 and (**46**) in the Suzuki cross-coupling reaction of aryl chlorides, and again they obtained reasonable conversions with high TON.[31-33]

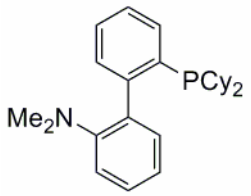
Thus, palladacyclic catalysts in the Suzuki cross coupling reaction have proven to be successful. Their stability to air and moisture, together with the high activity, make this class of catalysts quite attractive for the use in industrial processes.

2.4.2 Monodentate, bulky phosphines as ligands for the Suzuki cross coupling reaction

In the late 1990's attention focused on bulky and electron-donating phosphines, since these ligands make the palladium centre electron-rich and thus possibly more effective in the activation of the strong C-Cl bond. As aforementioned (section 2.3), Shen has investigated the use of the simple PCy_3 complex [$PdCl_2(PCy_3)_2$] in the Suzuki cross coupling reaction, gaining good results for the coupling of boronic acids to electron-poor aryl chlorides (see fig. 2.7).[16] This ended up being a good starting point in the further investigations on the matter from other research groups. Indeed, Littke and Fu investigated the activity of different trialkyl-phosphines in the coupling of boronic acids to aryl chlorides and found that good activity is shown by using PCy_3 complexes formed *in situ* with [$Pd_2(dba)_3$], but that bulkier P^tBu_3 used in place of PCy_3 gave even higher conversions to the

coupled product[34]. Moreover, Littke and Fu demonstrated that the ratio L:Pd of 1:1 gives the optimal activity, whereas increasing the ratio to 2:1 decreases the rate of the catalysis. These data lead to an outline for the general features of a catalyst for the Suzuki cross coupling reaction or arylchlorides: first of all, palladium complexes with bulky phosphines have shown to be more active; in addition, from the P:Pd ratio studies, the active catalyst is likely to be the mono-phosphine species. These two aspects are possibly related to each other, as the larger the phosphine, the higher the stability of the active catalyst with respect to decomposition. Steric properties of the ligand were proved to dominate over the electronic properties in some examples of the Suzuki cross coupling reaction on aryl chlorides.[35, 36]

In 1998 Buchwald and co-workers reported the first example of Suzuki cross coupling reaction on unactivated aryl chlorides at room temperature. Together with these impressive results, they also introduced a new class of phosphine ligands bearing a biaryl moiety, destined to lead the scene for palladium catalysed carbon-carbon and carbon-heteroatom bond forming reactions:[37]



48

This was just the first one of a very long list of successful ligands, a few of which are shown in fig. 2.10.

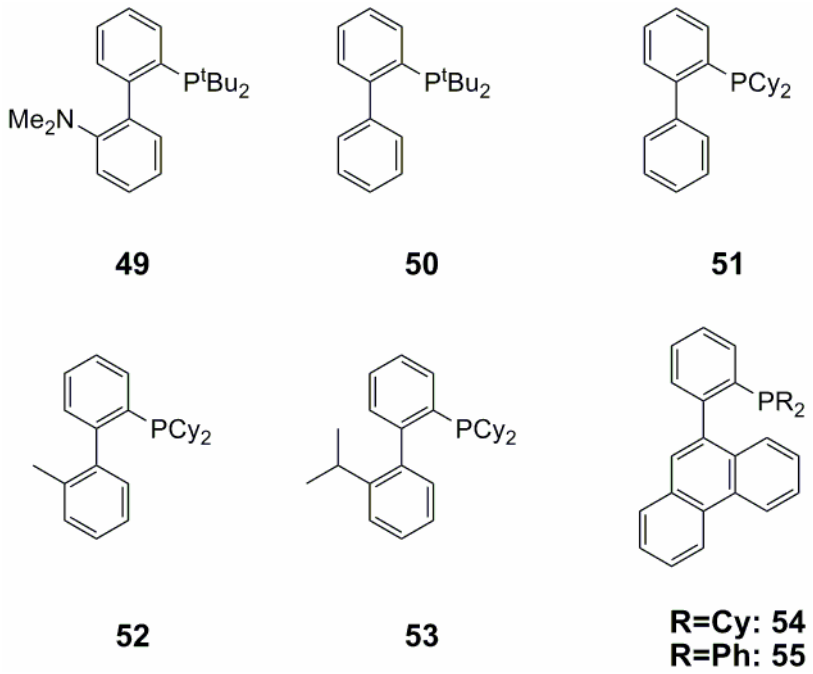


Fig. 2.10 Buchwald's ligands

Ligands (**49**), (**50**) and (**51**) were also tested in the Suzuki cross coupling of unactivated aryl chlorides, giving high conversions at room temperature, with better activities shown by using the catalyst obtained with (**51**) (TON of 10^8 at 100 °C).[38] More ligands were then developed with the aim to couple hindered 2,6-disubstituted halides with hindered 2,6-disubstituted boronic acids; apart from (**50**), they all gave good conversions to the sterically hindered product,[39] but the catalyst based on the phenanthrene phosphine (**54**) proved to be particularly active.[40] Buchwald and co-workers explained this outstanding performance of their catalysts with the presence in the structure of an electron-rich phosphine, which promotes the oxidative addition of even unactivated aryl chlorides and the tight binding to the palladium, thus preventing precipitation of the catalyst; moreover, the steric hindrance eases the reductive elimination. A model was also proposed suggesting that the *o*-phenyl moiety might be oriented in such way that an interaction between the aromatic π system and the metal is favoured. This interaction may also orient the aromatic ring of the substrate perpendicular to the coordination plane which should be the most stereoelectronically favourable conformation for the reductive elimination.[38, 39] This model was proved by crystallographic evidence[40]. The development of all these exceptional ligands prompted Buchwald and co-workers to prepare a ligand that could be of a more general use, together with the ability to make really hindered biaryls at low catalyst loadings for a wider range of substrates. In addition, it would be ideal to work at room temperature. A good combination of all these characteristics were found in ligand (**56**):[41]

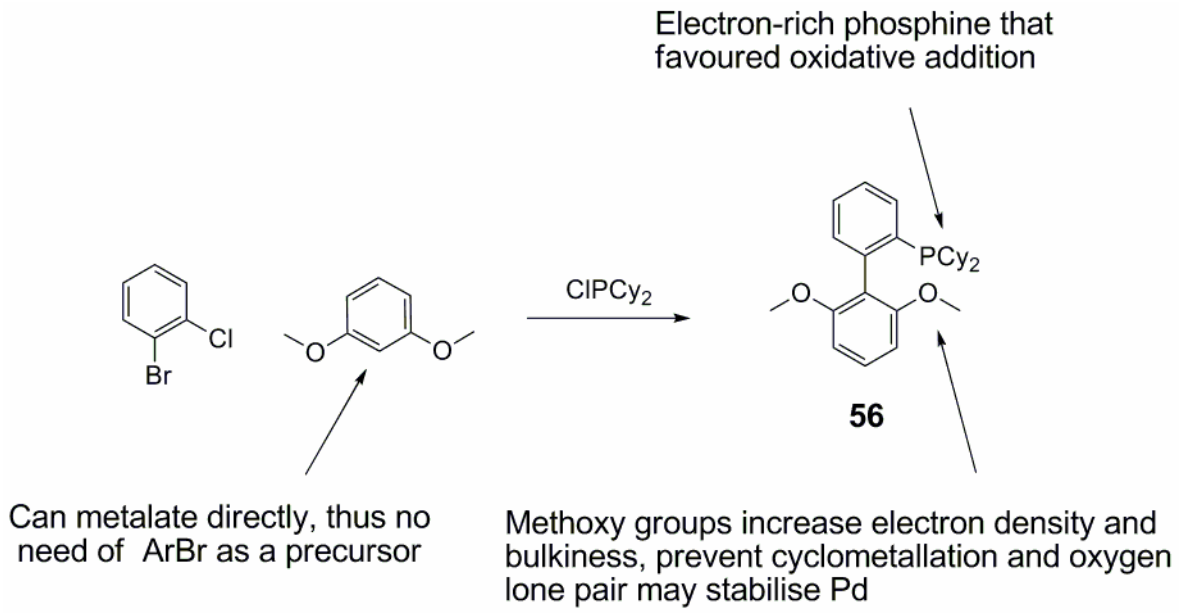
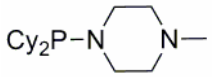


Fig 2.11 Ideal catalyst reasoned by Buchwald and co-workers

The introduction of methoxy groups in the non-phosphinated ring leads to an increase of electron density on the ring, which could possibly enhance the π-interaction with the metal described above and contributes to the steric hindrance of the ligand, that was previously found to positively affect the catalyst activity for the palladium catalysed C-N coupling.[42] Moreover, the lone pair of the two oxygens interacts with the palladium, rendering the complex more stable. The presence of the two methoxy groups also prevents cyclometallation, which would diminish the catalyst life. This ligand is also attractive from a synthetic point of view: the methoxy groups make it possible a direct metallation, avoiding the need of the aryl bromide. The catalyst formed *in situ* from ligand (**56**) and using $Pd(OAc)_2$ as a palladium source gave good yields for inactivated aryl chlorides and bromides coupled to sterically hindered boronic acids. Reasonable catalyst loadings were used, in some cases really short reaction times were detected. Mostly the temperature was kept between 90 and 110 °C, but good results have also been reported for reactions run at room temperature.[41]

2.4.3 Other catalysts proposed to form mono-ligated Pd species

The P-N ligand (**57**) of catalyst (**58**) was first reported by Clarke, Woollins and Cole Hamilton in 2001,[43] with the aim to prepare a new exceptionally electron-rich, bulky and hemilabile ligand for the palladium catalysed Suzuki cross coupling reaction.[44]



57

N-dicyclohexylphosphino-N-methylpiperazine (**57**) gave good results in the cross coupling of different aryl chlorides with phenylboronic acid, using $Pd_2(dba)_3$ as the palladium source.[43] A significant observation from these studies was the critical importance of the second N-methyl group; a ligand derived from piperidine was far less active. The N-methyl group is likely to increase the concentration of mono-ligated Pd(0) species during reaction. Moreover, the catalyst formed *in situ* from $[Pd(allyl)Cl]_2$ and (**57**) was used to catalyse the microwave accelerated Hiyama cross coupling:[45] here, it was also proposed that the desired reactive palladium-monophosphine catalyst is formed by initial co-ordination of the phosphine to form (**58**), followed by allylic amination (fig. 2.12):

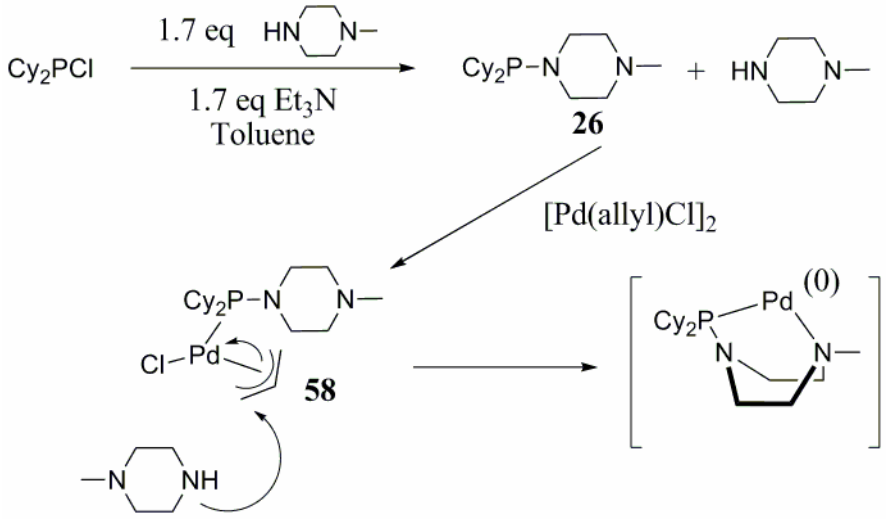


Fig. 2.12 Possible reactive palladium monophosphine catalyst

Good conversions to the products were also subsequently reported by Clarke and co-workers in the microwave assisted Suzuki cross coupling reaction of various aryl chlorides with different arylboronic acid using **(58)** as the catalyst,[46] building on the promising preliminary results described in this chapter.

All the findings described above made the Suzuki cross coupling reaction a useful tool for the synthesis of biaryl-based compounds, which is really important as the biaryl unit is present in several types of compounds, including natural products, polymers, molecules of medicinal interest and, of specific interest for us, ligands.

2.5 The potentials of the Suzuki cross coupling reaction in ligand synthesis

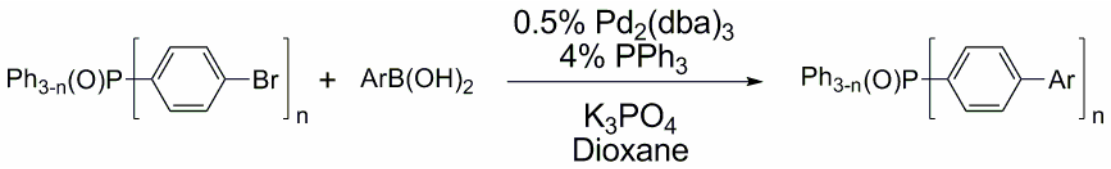
2.5.1 Why ligand libraries?

The Chemical industries are still producing chiral molecules using classical resolution methods and this is mainly due to the fact that catalytic systems are often substrate dependent: a catalyst can perform brilliantly with a specific substrate, but can lead to low conversion and/or enantiomeric excess for another structurally similar substrate. Thus, it is time consuming to screen known ligands or to synthesise new ones for preparing a specific chiral intermediate.
Hence a good approach to try to make asymmetric catalysis more widely used could be the synthesis of ligand libraries that can be eventually screened in parallel, using the modern technology for catalyst screening. This idea arose from the observation that a subtle modification in the catalyst can highly affect catalytic activity. Indeed, there is currently great interest in methodology designed to make ligand libraries.[47-52] Very significant change in catalyst performance has been observed by subtle alteration of the aryl groups in diarylphosphino ligands.

We envisaged that the use of the Suzuki cross coupling reaction on chloroaryl phosphine oxides could meet the prerequisites necessary for the development of families of phosphine oxides (and subsequently phosphines). We felt this would certainly be the case if aryl chloride coupling was possible since the use of a chloro-aryl functionality does not limit the types of phosphine structures that can be accessed. The use of phosphine oxides offers a stable system to work with, which is needed to prepare a much larger range of mono and di-phosphines. However, long reaction times are often needed for the Suzuki cross coupling reaction, thus, it was considered that the use of microwave heating[53-58] could shorten the reaction times and increase the yields of challenging reactions.
The first examples of microwave-assisted cross coupling reaction have been reported in 1996 by Hallberg and co-workers: the Suzuki and the Stille coupling reactions were carried out on solid-phase and good yields were gained after only 3.8 minutes of microwave heating, with minimal decomposition of the solid support;[55] moreover, the same research group also described examples of palladium catalysed Heck, Suzuki and Stille coupling reactions carried out on aryl bromides and iodides in a microwave and again reported high conversions to the coupled products after only few minutes.[59] Since then, lots of work has been carried out to develop microwave-assisted coupling reactions, with the aim to keep the time of the reaction short, reduce the catalyst loading, use

environmentally friendly solvents (i.e. water) and of course, with the intent to obtain the coupled product in high yields, starting from aryl chlorides.[60-64]

With our aim in mind, the work of Xiao and co-workers was of special interest, as they used the Suzuki[65-67] reaction under conventional heating to functionalise bromoaryl phosphine oxides, yielding good conversions to the products:



Scheme 2.1

Entry	Ar	n	Temperature (°C)	Time (h)	Yield (%)
1	Ph	3	100	20	91
2	Ph	2	100	20	96
3	Ph	1	100	20	96
4	4-CH_3-C_6H_4	3	110	24	91
5	4-CH_3-C_6H_4	1	110	24	90
6	4-CH_3O-C_6H_4	1	110	24	89
7	4-F-C_6H_4	1	110	24	91

Table 2.1 Suzuki coupling on aryl phosphine oxides with different aryl boronic acids[66]

At first, they actually attempted the Heck reaction on tris(4-chlorophenyl)phosphine oxide (**59**), considering the strong electron withdrawing effect of the P=O moiety, which can facilitate the oxidative addition of the aryl halide to the active Pd(0) species, though even under forcing conditions and longer reaction times, good conversion to the product was not yielded.

Thus, this work of Xiao and co-workers was analysed and few observations came up: first of all, the reaction times were considered too long, if the methodology was considered for the preparation of a library; moreover, the use of chloroaryl phosphine oxides could widen the types of phosphine structure that could be readily accessed, because of the larger availability of chloroaryl compounds that could be employed to prepare different chloroarylphosphine oxides as starting materials, together with the advantage of working with air stable phosphine oxides.

We envisaged that the combined use of one of the special ligands for aryl chloride cross coupling and microwave heating could enable this method to be extended, modifying chloroaryl phosphine oxides, and thus provide the basis for an efficient synthesis of a ligand library:

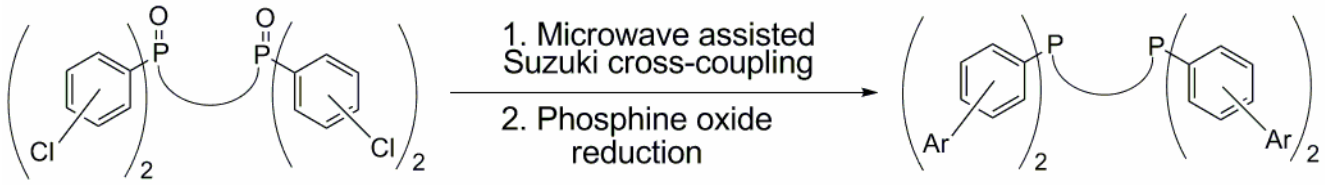


Fig. 2.13 Proposed synthetic pathway for the synthesis of phosphine-based ligand libraries

2.6 Results

2.6.1 Suzuki cross coupling of tris(4-chlorophenyl)phosphine oxide under conventional conditions

As a model study for the conversion of chloroaryl phosphine oxides into biaryl substituted aryl phosphine oxides, the Suzuki cross coupling of tris(4-chlorophenyl)phosphine oxide (**59**) with phenylboronic acid was investigated with the aim of preparing (**62**).

Xiao and co-workers, in their attempt of cross-coupling reactions on this substrate, used as a catalyst the Herrmann-Beller palladacycle.[22] We considered the use of one of the Buchwald catalysts described on paragraph 2.4.2, as more likely to activate these aryl chlorides. Thus ligand (**48**)[39] was chosen, using $Pd(OAc)_2$ as the palladium source:

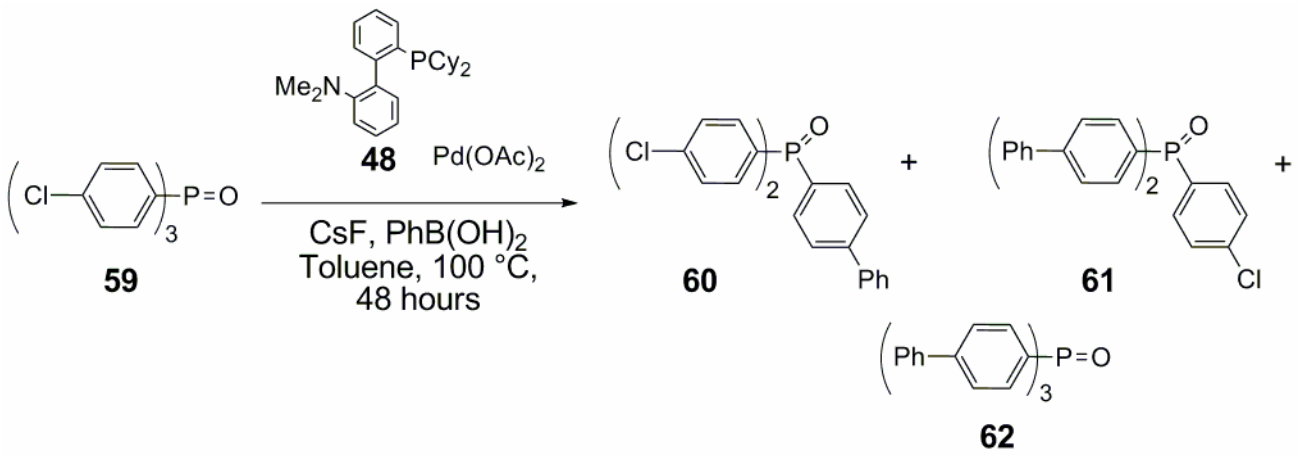


Fig. 2.14 Suzuki cross-coupling under conventional conditions of 59 with phenylboronic acid

Only the monoarylated product (**60**) was obtained in 43% isolated yield. Some unreacted starting material (**59**) was observed in the $^{31}P\{^{1}H\}$NMR of the reaction mixture, and no presence of the diarylated (**60**) or triarylated (**61**) products was detected.

As expected, and as previously noted by Xiao and co-workers, this chloroaryl phosphine oxide was a quite reluctant cross-coupling partner, even if a catalyst that is normally excellent for aryl chloride cross –coupling was used.

It was then decided to use this substrate (**59**) as a model study in the investigation of its coupling with phenylboronic acid under microwave heating.

2.6.2 Suzuki cross coupling of tris(4-chlorophenyl)phosphine oxide under microwave conditions

The Suzuki cross coupling reaction of (**59**) was then carried out in the microwave. We kept the time of the reaction and the temperature constant, 30 minutes at 140 °C, a part from one single example in which the temperature was raised to 170 °C (see table 2.2, entry 2), without giving a better conversion to the product (**62**). Moreover, 10 equivalents of phenylboronic acid were used in each attempt (3.3 equivalents per Ar-Cl). Different catalysts, solvent systems and bases were used, with the aim to find out the best condition for this reaction (see table 2.2):

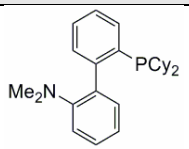
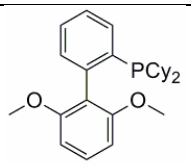
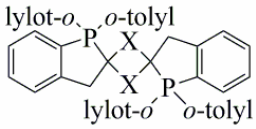
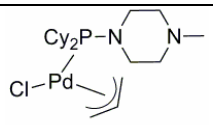
Entry	Catalyst	Solvent	Base	Conversion into[b]			Unreacted (59)[b]
				(60)	(61)	(62)	
1	 **48** $Pd(OAc)_2$	MeCN	CsF	-	<5	95	-
2[c]		MeCN	CsF	-	23	77	-
3		MeCN	K_3PO_4	-	>95	-	-
4[d]		Dioxane	CsF	-	90	10	-
5	 **56** $Pd(OAc)_2$	Dioxane	K_3PO_4	80	-	20	-
6		MeCN	CsF	8	92	-	-
7	 **42b**	Dioxane	K_3PO_4	21	15	49	15
8[e]	$Pd(OAc)_2$	Dioxane	CsF	-	-	-	100
9	 **58**	MeCN	CsF	-	-	>90	-

Table 2.2 Screening of different catalysts, bases and solvents for the Suzuki cross coupling of 59 with phenyl boronic acid under microwave conditions a)Reaction conditions: 10 eq $PhB(OH)_2$, 2.5% pre-catalyst, 10 eq base, 5 ml solvent; 140 °C, 30 minutes, microwave heating; b) % of conversions determined by ^{31}P NMR spectroscopy directly from reaction mixture; the relative positions of the peaks were assigned by spiking experiments; c) 170 °C; d) 5 eq of base and $PhB(OH)_2$; 5% $Pd(OAc)_2$;

This screening of different pre-catalysts, solvents and bases gave us good indications on which conditions were likely to work best. First of all, we were delighted to see that starting off from (**59**), the formation of the triarylated compound (**62**) was possible for the first time.[66] We were aware of some examples of microwave assisted Suzuki cross coupling reaction of aryl bromides and chlorides with different aryl boronic acids, that gave reasonable to good results in the presence of solely $Pd(OAc)_2$[64]. Thus, it was necessary to make sure that the catalytic activity was not coming exclusively from $Pd(OAc)_2$. As expected, by running the cross coupling reaction in the presence of only $Pd(OAc)_2$, full recovery of the starting material (**59**) was obtained (see entry 8).

At this point, a few pre-catalysts were tested. It was noted that the Buchwald catalyst (**48**) gave almost complete conversion to the product (**62**), with only a small presence of the diarylated compound (**61**), when the reaction was carried out at 140 °C, in acetonitrile and using as a base CsF (entry 1): in fact, the attempt to push the reaction to higher temperatures (170 °C, entry 2) reduced the conversion into (**62**), in favour of (**61**); the use of dioxane or acetonitrile with K_3PO_4 as a base instead of CsF also led to the formation of mainly (**61**). These results were promising, in particular if it was considered that the same pre-catalyst gave only the monoarylated product (**60**) not even in high yield, when the reaction was heated for 48 hours in an oil bath, as described in 2.6.1.

It was interesting to try the "latest generation" Buchwald catalyst (**56**)[41], (see fig. 2.14) and which was shown to be very active also in the cross coupling of inactivated aryl chlorides to boronic acids (see paragraph 2.4.2). However, for our system, the pre-catalyst formed from $Pd(OAc)_2$ and (**56**) did not lead to the desired product (**62**), but favoured the formation of the mono- and diarylated compound (**60**) and (**61**), according to the solvent and the base used (see entry 5 and 6).

Only one attempt was spent in testing the activity of Herrmann and Beller catalyst (**42b**)[22] (entry 7). However, a mixture of the three possible products was obtained, together with some unreacted starting material.

It was pleasing to find that catalyst (**58**) was giving almost full conversion into the triarylated product (**62**). Catalyst (**58**) had previously been prepared by Clarke *in situ* (and characterised by NMR) but in this work, we found it conveniently isolated and stored for many months in air.

Due to the good results in table 2.3, and its ready availability, it was decided to use catalyst (**58**) for the coupling of different phosphine oxides to a range of boronic acids.

2.6.3 Suzuki cross coupling of 3-chloro-phenyldiphenylphosphone oxide and 3,5-dichlorophenyl(diphenyl)phosphine oxide under microwave conditions

It was considered interesting and a completion of this work to verify if the successful conditions developed for the aforementioned microwave accelerated Suzuki cross coupling reaction of the phosphine oxide used as a model study could be extended in the coupling of different chloroaryl phosphine oxides with different arylboronic acids.

With this in mind, at first 3-chlorophenyl(diphenyl)phosphine oxide (**63**) was prepared using the classical procedure of reacting the Grignard reagent with diphenylphosphine chloride, followed by oxidation. It was then subjected to the microwave assisted procedure with pleasing results.

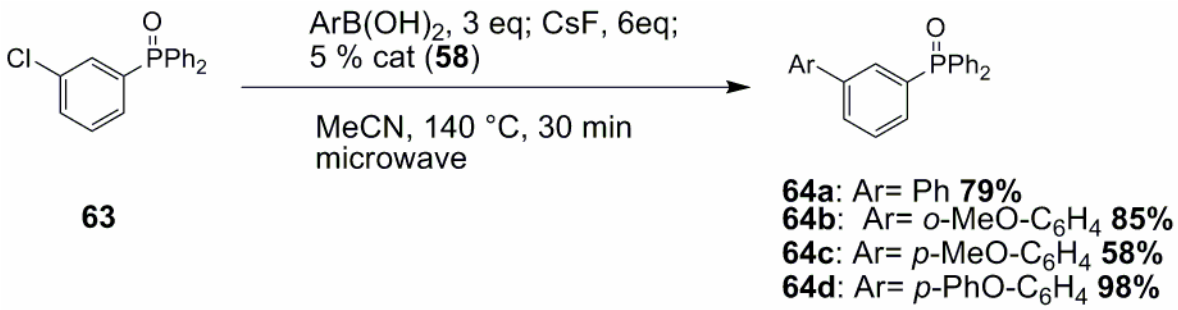


Fig. 2.15 Microwave accelerated cross-coupling of 3-chloroaryl phosphine oxide (63) Yields are for isolated pure compounds after chromatography.

Moreover, 3,5-dichlorophenyl(diphenyl)phosphine oxide (**65**) was prepared in a similar manner and used as a substrate for the Suzuki reaction of different arylboronic acids to verify if the conditions found could work also with a potentially more challenging double coupling:

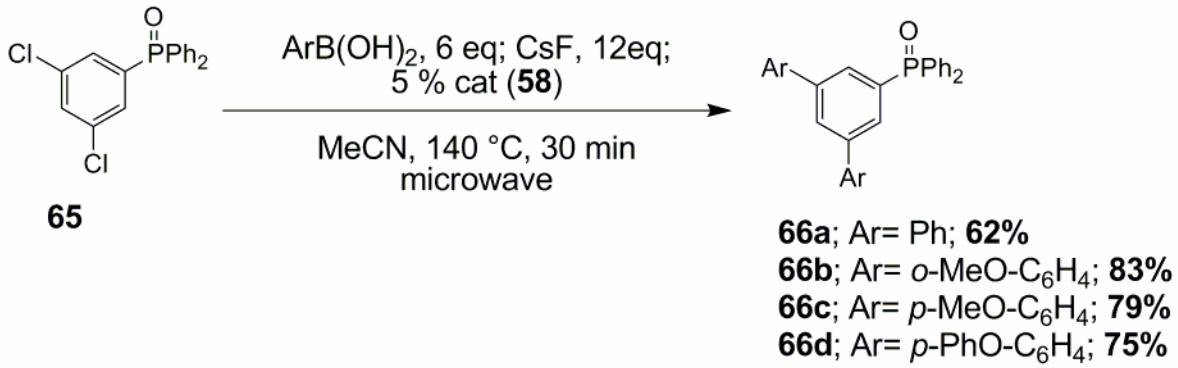


Fig. 2.16 Microwave accelerated cross-coupling of 3,5-dichloroaryl phosphine oxide (65) Yields are for isolated pure compounds after chromatography.

The crude ^{31}P NMR showed in all cases almost full conversion into the products. However upon purifications of the compounds (**64**) and (**66**) by chromatography, lower but still good yields were obtained, and this is due to the fact that phosphine oxides do not elute well on silica.
Moreover, it was also noted that running the reaction at ~0.15 mmol phosphine oxide/ 5 ml solvent led to higher conversions than at higher concentrations, and this was probably due to the slow stirring when running the reaction in a 5 ml microwave vial. The importance of efficient stirring was also recently reported by Kappe and co-workers[68], who observed that efficient agitation of microwave-heated reaction is essential, otherwise temperature gradients may develop, which could negatively affect in particular heterogeneous solutions.
The good to high yields obtained in the coupling of (**63**) and (**65**) with different arylboronic acids, proved that this protocol has the potential to be used with different chloroaryl phosphine oxides. Subsequently, other members of the group demonstrated that catalyst (**58**) was quite useful in coupling simpler (more reactive) aryl chlorides with a range of boronic acids within 20 minutes of microwave heating.[46]

At this point, one of our aims has been partially achieved; indeed, in the last few paragraphs a successful protocol has been described for the preparation of families of structurally related phosphine oxides using microwave accelerated Suzuki cross coupling reactions. The reaction times were only half an hour for reactions that did not proceed using conventional heating. The use of chloroaryl phosphine oxides was necessary because of the electron-withdrawing properties of the P=O moiety that renders the chloroaryl compounds less reluctant to undergo Suzuki cross coupling reaction under microwave heating; in addition, the use of phosphine oxides makes manipulations easier, thanks to their stability to air and moisture.
Nevertheless, a library of ligands requires free phosphines. It was then necessary to reduce our phosphine oxides: with the idea of building up a library always in our mind, it was desirable to gain reduction in short time and with full conversion. Thus, the idea of investigating microwave accelerated reduction of phosphine oxides was considered.

2.6.4 Microwave accelerated reduction of phosphine oxides

Xiao and co-workers reduced their arylphosphine oxides with trichlorosilane in the presence of triethylamine.[65, 69] This is a common reaction that generally occurs by refluxing the reagents for 4-48 hours hours in toluene or xylene, leading to full conversion into the product, in particular if reducing arylated phosphine oxides.

The mechanism of this reaction was investigated in the sixties by Horner and Balzer first[70] and their proposed mechanism is shown in fig. 2.17:

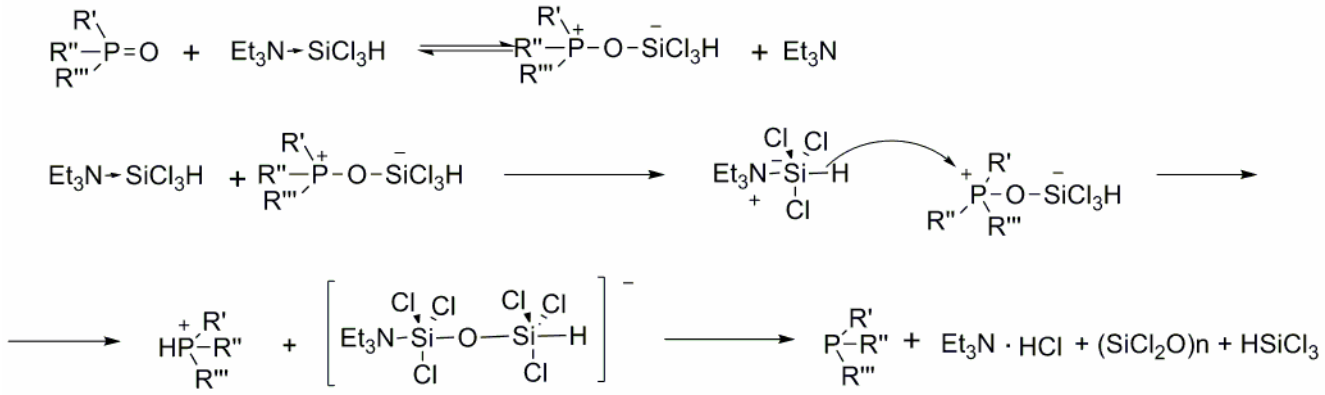


Fig. 2.17 Mechanism for the reduction of phosphine oxides proposed by Horner and Balzer

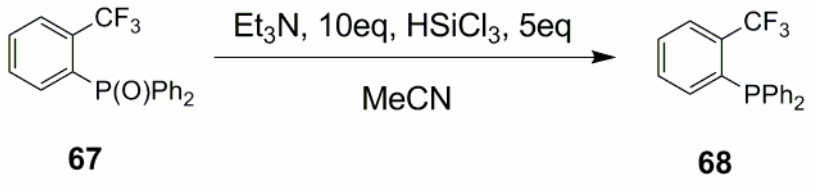
It was then considered to use this reaction to reduce the phosphine oxides of our library, and it was believed that running the reaction in the microwave would have given full conversion into the tertiary phosphine in a much shorter time.

Thus, to investigate the microwave assisted reduction of phosphine oxides, tris(*n*-butyl)-phosphine oxide was chosen at first as a model study, since this is likely to be one of the most difficult phosphine oxides to reduce. The temperature, the solvent and the quantities of the reagents were kept constant (145 °C in acetonitrile, with 5 equivalents of $HSiCl_3$ and 10 equivalents of triethylamine), whereas different reaction times were tried: the best result obtained was in 45 minutes, with approximately 65% conversion into the reduced phosphine (in this case the conversions were estimated by integration of $^{31}P\{^{1}H\}$ NMR without calibration). This was not a bad result, though it was necessary to gain full conversion, to avoid any time consuming purification.

Triphenylphosphine oxide was then chosen for the investigation of the microwave assisted reduction of phosphine oxides, considering that the phosphine oxides of the library prepared were triaryl phosphines.

The temperature, solvent and quantities of trichlorosilane and triethylamine were kept the same as for the reduction of tris(*n*-butyl)-phosphine oxide, and again different reaction times were tested in the microwave: it was pleasing to note that in only 5 minutes the reaction went to completion. However, stirring for 5 minutes the reagents without the microwave (large exotherm), the reaction was complete as well. This phosphine oxide is clearly very easy to reduce in constrast to many of the reactions in the literature that are only complete after many hours at high temperatures.

A comparison between the microwave mediated reduction versus the reduction run in conventional conditions was carried out on phosphine oxide (**65**). With this substrate it was necessary to run the reaction in the microwave, to achieve high conversions in half a hour. Indeed, in such a short time, no reasonable conversion to the reduced product (**66**) was attained using conventional conditions (fig. 2.18):



Scheme 2.2

Reaction time (min)	Conversion[(a)] (%)	
	Microwave assisted [(b)]	Conventional conditions [(c)]
5	62	-
10	80	6
20	90	8
30	92	10

Table 2.3 Reduction of (67) microwave mediated and under conventional conditions (a) The conversion values were calculated using ^{19}F-NMR spectroscopy; (b) Microwave at 145 °C; (c) Reflux

Thus, some phosphine oxides are clearly very easily reduced in short reaction times, but more oxygen sensitive phosphines require significant heating.

At this point, it was necessary to try the reduction of the phosphine oxides prepared. The starting material (**65**), and the products of the Suzuki coupling (**66a**) and (**66d**) were successfully reduced to the correspondent tertiary phosphine in just 10 minutes in the microwave, giving full conversion into the product (by ^{31}P{^{1}H}NMR):

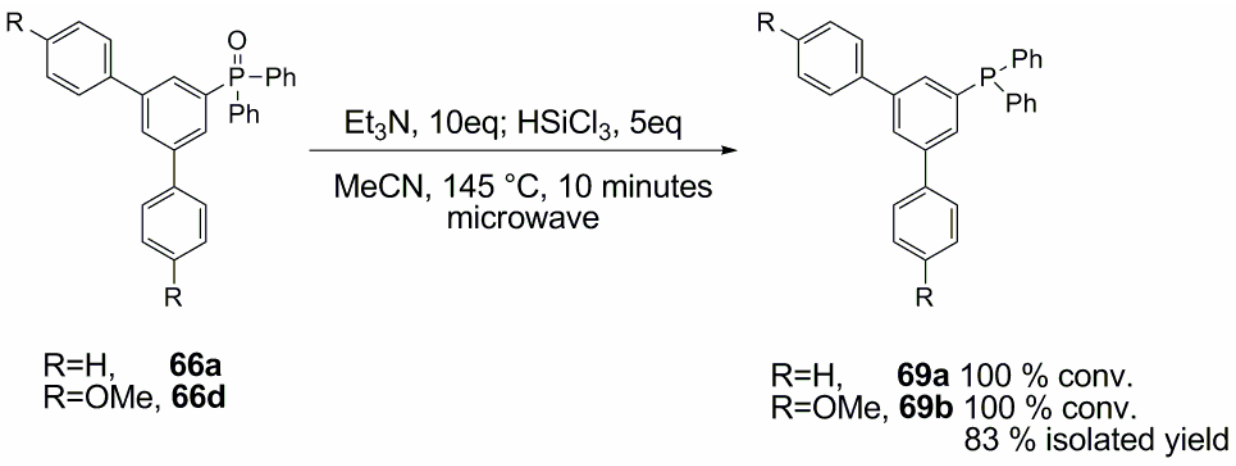


Fig. 2.18 Microwave accelerated reduction of 66a and 66d

Isolation of the tertiary phosphine, which was carried out by complete removal of acetonitrile under vacuum, dissolution in dry and degassed dichloromethane, followed by a filtration through a short pad of silica and subsequent removal of dichloromethane, gave 83% of isolated yield.

So far it has been shown that under microwave heating, it is possible to couple different arylphosphine oxides to various arylboronic acids in high yield in only half a hour. The reduction of the phosphine oxides obtained is possible in short times in the microwave.
The reduction of the phosphine oxides was performed directly on the crude reaction mixture from the cross coupling: however this resulted in a multi-component reaction mixture, and due to the presence of many side products the purification proved to be too problematic, with the potential risk of oxidising the phosphine. On the other hand, when the starting material is pure phosphine oxide, a filtration through silica is sufficient, which is easily performed under nitrogen.

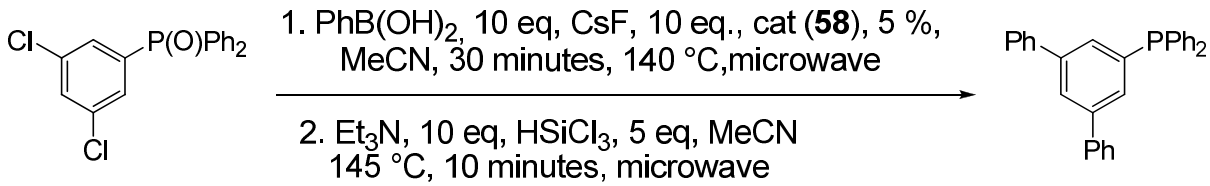


Fig. 2.19 Tandem process for the direct synthesis of the phosphine

This necessity of chromatographic purification of the oxides is the drawback for this protocol, as it lengthens the time required for obtaining a library.

2.6.5 Attempted preparation of phanephos-based ligands using our methodology

Paracyclophane derived phosphines have been used in asymmetric catalysis as chelating bisphosphines. They present planar chirality (the two enantiomers are shown in Fig. 2.20)[71] and the first X-ray structure was determined in 1998[72]:

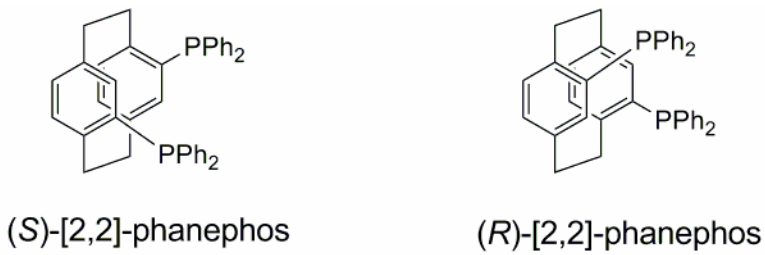


Fig. 2.20 (*S*) and (*R*) enantiomers of phanephos

Phanephos has been used to prepare Rh[73, 74], Ru[75-77] and Ir[78] catalysts that have been successfully used in asymmetric hydrogenation of olefins, ketones and amides, and are used commercially by Chirotech.

On the basis of the excellent results reported, it was interesting to prepare ligands structurally related to phanephos, with the aim to test them in the hydrogenation of even more tricky substrates.

2.6.5.1 Our approach in the attempt to prepare a phanephos-based library

One strategy to achieve a library of phanephos-based ligands is to prepare the chloroaryl substituted variant of phanephos (**71**), and to introduce diversity in the structure by substitution at the chloride using the microwave assisted Suzuki cross coupling reaction (fig. 2.21):

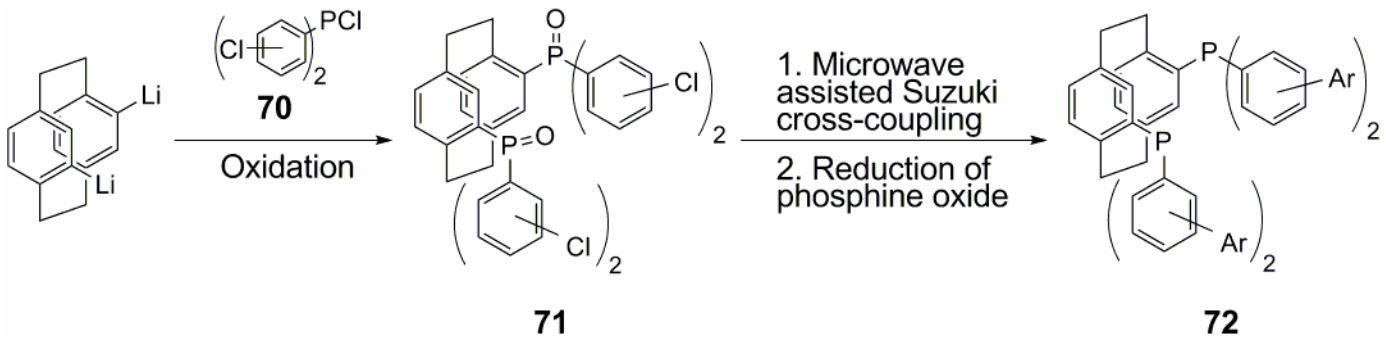


Fig. 2.21 Proposed approach for the preparation of phanephos-based library

To prepare the starting material for the phanephos library (**71**), it was necessary to prepare first the reagent (**70**).

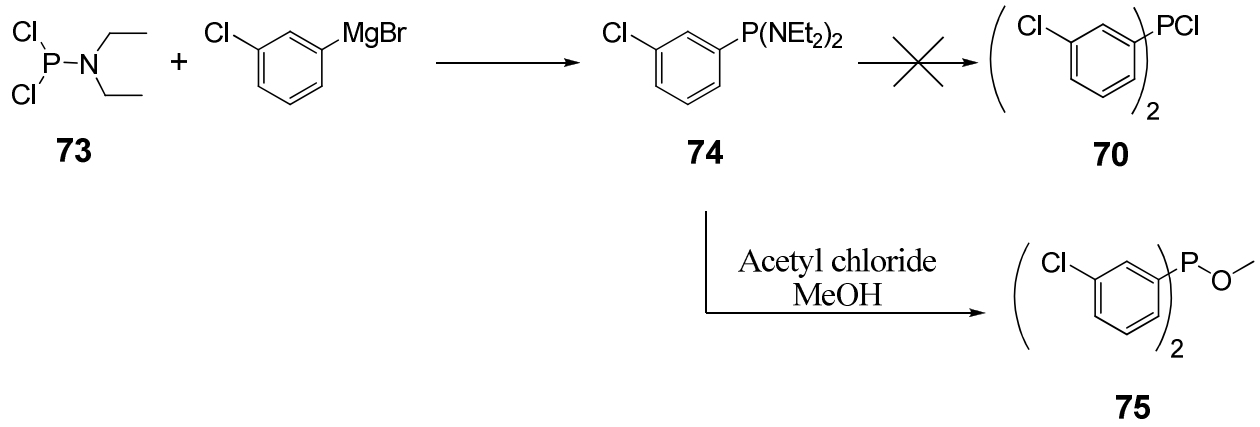


Fig. 2.22 Attempted preparation of (70) and preparation of (75)

Formation of phosphoramide (**74**) was straightforward, in quantitative yield. However, the subsequent formation of (**70**) was more tricky than expected. To the solution of (**74**), different quantities of a solution of HCl in dry diethyl ether were added, without achieving any success. It was also tried to prepare HCl with acetyl chloride and methanol (1.2/1), but again it was not possible to drive the reaction to completion.

It was reported in literature the use of alkoxide leaving groups in phosphorus chemistry:[79] it was then decided to change the leaving group, from the chloride to a methoxide (**75**), by adding an equivalent of methanol and a slight excess of acetyl chloride. The desired phosphinite (**75**) was obtained, but in the following step failed to react with the dilithated paracyclophane, probably because of the weaker properties of the methoxide as a leaving group:

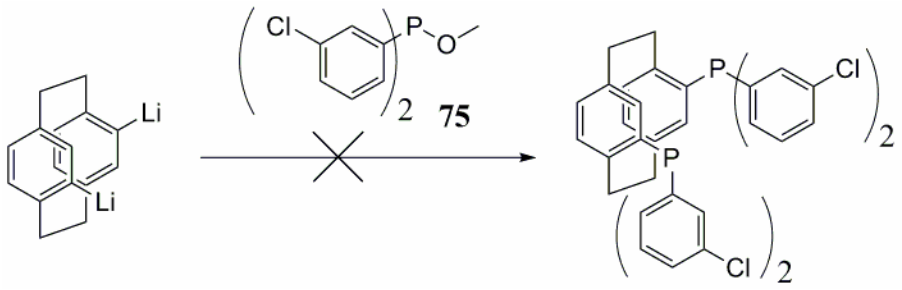


Fig. 2.23 Attempt to prepare di[2,2]-bis(parachlorophenyl)phosphino-paracyclophane

Another attempt in preparing (**70**) was made by treating the secondary phosphine oxide (**76**)[79] with trichlorophosphine:[80]

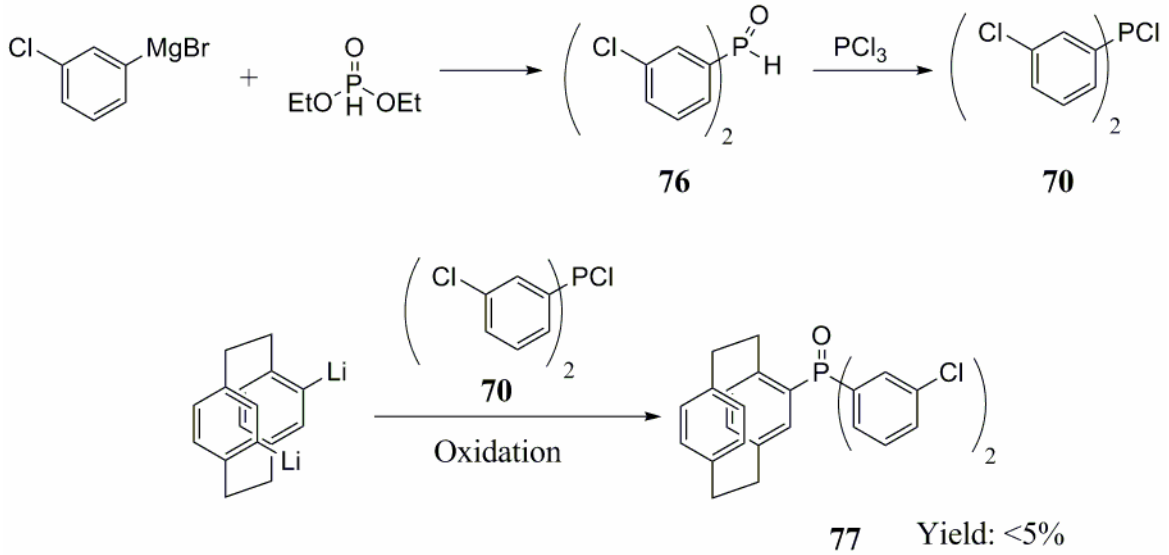


Fig. 2.24 Further attempt for the preparation of (32)

The reaction of chlorophenylmagnesium bromide with diethylphosphite gave compound (**76**) as the main product, but small amounts of side products were also present in the $^{31}P\{^{1}H\}$NMR. Isolation of (**76**) with chromatography proved to be problematic, with possible further oxidation of (**76**) to the correspondent phosphinic acid. Thus, the crude secondary phosphine was used in the next reaction.
Treatment of (**76**) with PCl_3 for 24 hours at room temperature gave only 50% conversion to (**70**), an unexpected result, if it is considered that for a phospholano-compound reported in the literature and successfully repeated by us, full conversion was achieved in just a few minutes at low temperature[80]. Even if full conversion to (**70**) was not achieved, the reaction with the dilithiated paracyclophane was tried anyway, but only a very small conversion to the monosubstituted compound (**77**) was obtained.

2.7 Conclusions and future works

The Suzuki cross coupling reaction could be a useful tool to modify structurally related phosphines, thus obtaining a family of structurally related compounds. We have investigated the microwave accelerated Suzuki reaction using chloroarylphosphine oxides as model studies, with the aim to get the reaction to work on the reluctant chloroaryl coupling partners in a short time.
This chapter reports our findings on the matter:

- The coupling of different arylboronic acids with different chloroarylphosphine oxides occurs in just half a hour in the microwave, achieving generally reasonable to high yields.
- The resulting, modified phosphine oxides have been successfully reduced in the microwave; however it has been observed that conventional heating allows the reduction of some of these phosphine oxides in short time as well.
- It has been demonstrated that it is possible to build up a library of phosphine oxides using this protocol. However chromatographic purification of the oxides is required prior to reduction.
- It was desirable to use this methodology for the preparation of a family of ligands structurally related to phanephos, however the preparation of the starting material for preparing this library proved to be problematic.

Thus, it would be interesting to optimise the preparation for the starting material of the ligand library and subsequently apply variation using the microwave assisted Suzuki cross coupling reaction. However, after consultation with Chirotech, it was decided that the disadvantages associated with chromatographic purification of the phosphine oxides and the non-facile

synthesis of the di(chloroaryl) phosphine chlorides meant such a process may not be a practical for industrial catalyst screening, and we therefore closed this chapter of my research. Despite these drawbacks, the methodology presented could still find use in phosphine synthesis in the case of reactions where the chloroaryl precursors are easily available and a specific functionalised di-aryl motif is required.

2.8 References

1 N. Miyaura, K. Yamadam and A. Suzuki, *Tet. Lett*, 1979, **36**, 3437.
2 K. C. Nicolaou, P. G. Bulger, and D. Sarlah, *Angew. Chem. Int. Ed.*, 2005, **44**, 4442.
3 S. P. Stanforth, *Tetrahedron*, 1998, **54**, 263.
4 G. B. Smith, G. C. Dezeny, D. L. Hughes, A. 0. King, and T. R. Verhoeven, *J. Org. Chem.*, 1994, **59**, 8151.
5 R. D. Larsen, A. O. King, C. Y. Chen, E. G. Corley, B. S. Foster, F. E. Roberts, C. Yang, D. R. Lieberman, R. A. Reamer, and P. J. Reider, Y. S. Lo, L. T. Romano, A. S. Brookes, D. Meloni, J. R. Moore, and J. F. Arnett, *J. Org. Chem.*, 1994, **59**, 6391.
6 'Transition metals for Organic Synthesis', ed. M. Beller and C. Bolm, WILEY-VCH Verlag GmbH & Co. KGaA, 2004.
7 A. Suzuki and N. Miyaura, *Chem. Rev.*, 1995, **95**, 2457.
8 A. O. Aliprantis, J. W. Canary, *J. Am. Chem. Soc.*, 1994, **116**, 6985.
9 N. Miyaura and A. Suzuki, *Chem. Comm.*, 1979, 866.
10 A. Suzuki, *Acc. Chem. Res.*, 1982, **15**, 178.
11 J. Tsuji, 'Palladium Reagents and Catalysts', JOHN WILEY & SONS, 1995.
12 S. W. Wright, D. L. Hageman, and L. D. McClure, *J. Org. Chem.*, 1994, **59**, 6095.
13 A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.*, 2002, **41**, 4177.
14 P. Fitton and E. A. Rick, *J. Organomet. Chem.*, 1971, **28**, 287.
15 J. M. Schomaker and T. J. Delia, *J. Org. Chem.*, 2001, **66**, 7125.
16 W. Shen, *Tet. Lett*, 1997, **38**, 5575.
17 D. F. O'Keefe, M. C. Dannock, S. M. Marcuccio, *Tet. Lett.*, 1992, **33**, 6679.
18 A. C. Bellina, R. Rossi, *Synthesis*, 2004, **15**, 2419.
19 R. B. Bedford, *Chem. Comm.*, 2003, 1787.
20 J. Dupont, M. Pfeiffer, J. Spencer, *Eur. J. Inorg. Chem.*, 2001, 1917.
21 W.A. Herrmann, V. P. W. Bohm, C. P. Reisinger, *J. Organomet. Chem.*, 1999, **576**, 23.
22 W. A. Herrmann, C. Brossmer, K. Ofele. C. P. Reisinger, T. Priermeier, M. Beller and H. Fischer, *Angew. Chem. Int. Ed.*, 1995, **34**, 1844.
23 M. Beller, H. Fischer, Wolfgang W. A. Herrmann, C. Brossmer, K. Ofele, *Angew. Chem. Int. Ed.*, 1995, **34**, 1848.
24 W. A. Herrmann, K. Brossmer, Oefele, C. BM. Beller, and H. Fischer, *J. Organomet. Chem.*, 1995, **491**, C1.
25 S. Gibson, D. F. Foster, D. J. Cole-Hamilton, G. R. Eastham, R. P. Tooze, *Chem. Comm.*, 2001, 779.
26 D. Zim, A. S. Gruber, G. Ebeling, J. Dupont, and A. L. Monteiro, *Org. Lett.*,2000, **2**, 2881.
27 H. Weissman and D. Milstein, *Chem. Comm.*, 1999, 1901.
28 L. Botella and C. Najera, *Angew. Chem. Int. Ed.*, 2002, **41**, 179.
29 D. A. Albisson, R. B. Bedford, S. E. Lawrence and P. N. Scully, *Chem. Comm.*, 1998, 2095.
30 R. B. Bedford and C. S. J. Cazin, *Chem. Comm.*, 2001, 1540.
31 R. B. Bedford, C. S. J. Cazin, and S. L. Hazelwood, *Angew. Chem. Int. Ed.*, 2002, **41**, 4120.
32 R. B. Bedford and S. L. Welch, *Chem. Comm.*, 2001, 1418.
33 R. B. Bedford, S. L. Hazelwood, M. E. Limmert, D. A. Albisson, S. M. Draper, P. N. Scully, S. J. Coles, and M. B. Hursthouse, *Chemistry--A European Journal*, 2003, **9**, 3216.
34 G. C. Fu and A. F. Littke, *Angew. Chem. Int. Ed.*, 1998, **37**.
35 D. Price and N. S. Simpkins, *Tet. Lett.*, 1995, **36**, 6135.
36 S. Y. Liu, M. J. Choi, G. C. Fu *Chem. Comm.*, 2001, 2408.
37 D. W. Old, J. P. Wolfe, and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 9722.
38 J. P. Wolfe and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 1999, **38**, 2413.

39 J. P. Wolfe, R. A. Singer, B. H. Yang, and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 9550.
40 J. Yin, M. P. Rainka, X. Zhang, S.L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 1162.
41 S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2004, **43**, 1871.
42 E. R. Strieter, D. G. Blackmond, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 13978.
43 M. L. Clarke, D. J. Cole Hamilton and J. D. Woollins, *J. Chem. Soc. Daltron Trans*, 2001, 2721.
44 D. J. C.-H. Matthew L. Clarke, Alexandra M. Z. Slawin and J. Derek Woollins, *Chem. Comm.*, 2000, 2065.
45 M. L. Clarke, *Adv. Synth. Catal.*, 2005, **347**, 303.
46 M. L Clarke, M. B. France, , J. A Fuentes, E. J. Milton and G. J. Roff, *Beilstein J. Org. Chem.*, 2007, 3:18.
47 M. Weis, C. Waloch, W. Seiche, and B. Breit, *J. Am. Chem. Soc.*, 2006, **128**, 4188.
48 X.-B. Jiang, L. Lefort, P. E. Goudriaan, A. H. M. de Vries, P. W. N. M. van Leeuwen, J. G. de Vries, and J. N. H. Reek, *Angew. Chem. Int. Ed.*, 2006, **45**, 1223.
49 J. G. de Vries and L. Lefort, *Chem. Eur. J.*, 2006, **12**, 4722.
50 J. N. H. Reek, M. Roeder, P. E. Goudriaan, P. C. J. Kamer, P. W. N. M. Van Leeuwen, and V. F. Slagt, *J. Organomet. Chem.*,2005, **690**, 4505.
51 a. U. P. Cesare Gennari, *Chem. Rev.*, 2003, 3071.
52 S. R. Gilbertson, S. E. Collibee, and A. Agarkov, *J. Am. Chem. Soc.*, 2000, **122**, 6522.
53 C. O. Kappe, *Angew. Chem. Int. Ed.*, 2004, **43**, 6250.
54 C. M. Mats Larhed, and Anders Hallberg, *Acc. Chem. Res.*, 2002, **35**, 717.
55 G. L. Mats Larhed, Anders Hallberg, *Tet. Lett.*, 1996, **37**, 8219.
56 D. M. P. M. a. D. R. Baghurst, *Chem. Soc. Rev.*, 1991, **20**, 1.
57 F. S. Richard Gedye, Kenneth Westaway, Humera Ali, Lorraine Baldisera, and L. L. a. J. Rousell, *Tet. Lett.*, 1986, **27**, 279.
58 T. L. B. Raymond J. Giguere, and Scott M. Duncan, *Tet. Lett.*, 1986, **27**, 4945.
59 M. L. a. A. Hallberg, *J. Org. Chem.*, 1996, **61**, 9582.
60 R. K. Arvela and N. E. Leadbeater, *Org. Lett.*, 2005, **7**, 2101.
61 R. B. Bedford, C. P. Butts, T. E. Hurst, and P. Lidstroem, *Adv. Synth. & Catal.*, 2004, **346**, 1627.
62 N. E. Leadbeater and M. Marco, *Angew. Chem. Int. Ed.*, 2003, **42**, 1407.
63 L. M. Klingensmith and N. E. Leadbeater, *Tet. Lett.*, 2003, **44**, 765.
64 N. E. Leadbeater and M. Marco, *Organic Letters*, 2002, **4**, 2973.
65 C. Baillie and J. Xiao, *Tetrahedron*, 2004, **60**, 4159.
66 L. Xu, J. Mo, C. Baillie, and J. Xiao, *J. Organomet. Chem.*,2003, **687**, 301.
67 C. Baillie, W. Chen, and J. Xiao, *Tet. Lett.*, 2001, **42**, 9085.
68 M. A. Herrero, J. M. Kremsner, and C. O. Kappe, *J. Org. Chem.*, 2008, **73**, 36.
69 W. C. C. Baille, J. Xiao, *Tet. Lett*, 2001, **42**, 9085.
70 L. H. a. W. D. Balzer, *Tet. Lett.*, 1965, **17**, 1157.
71 P. J. Pye and K. Rossen, *Tet. Asymm.*, 1998, **9**, 539.
72 P. W. Dyer, P. J. Dyson, S. L. James, C. M. Martin, and P. Suman, *Organometallics*, 1998, **17**, 4344.
73 P. J. Pye, K. Rossen, R. A. Reamer, N. N. Tsou, R. P. Volante, and P. J. Reider, *J. Am. Chem. Soc.*, 1997, **119**, 6207.
74 A. Zanotti-Gerosa, C. Malan, and D. Herzberg, *Org. Lett.*, 2001, **3**, 3687.
75 P. J. Pye, K. Rossen, R. A. Reamer, R. P. Volante, and P. J. Reider, *Tet. Lett.*,1998, **39**, 4441.
76 M. J. Burk, W. Hems, D. Herzberg, C. Malan, and A. Zanotti-Gerosa, *Org. Lett.*, 2000, **2**, 4173.

77 D. Chaplin, P. Harrison, J. P. Henschke, I. C. Lennon, G. Meek, P. Moran, C. J. Pilkington, J. A. Ramsden, S. Watkins, and A. Zanotti-Gerosa, *Org. Process Res. Dev.*, 2003, **7**, 89.
78 T. Focken, G. Raabe, and C. Bolm, *Tet. Lett.*, 2004, **15**, 1693.
79 R. L. Wife, A. B. Van Oort, J. A. Van Doorn, and P. W. N. M. Van Leeuwen, *Synthesis*, 1983, 71.
80 M. E. Fox, M. Jackson, I. C. Lennon, J. Klosin, and K. A. Abboud, *J. Org. Chem.*, 2008, **73**, 775.

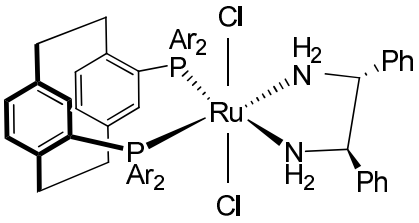
Chapter 3

Palladium catalysed P-C bond forming reactions

3.1 Phanephos, HexaPHEMP and Ph-BPE and their activity in catalytic asymmetric hydrogenation

3.1.1 Phanephos

In the previous chapter a few words have been said about paracyclophane (see paragraph 2.6.5). Indeed, good results have been reported in hydrogenation using phanephos-based catalysts.
Pye and co-workers reported the first phanephos-based Rh catalyst, that was shown to be a highly enantioselective catalyst for the hydrogenation of dehydroamino acid methyl esters, under very mild conditions.[1,2] Ruthenium catalysed hydrogenation of β-keto-esters[3] and [Ru(phanephos)(diamine)Cl_2] catalysed reduction of ketones[4, 5] have also been reported.



Ar= Ph, Xyl

As previously said, [$RuCl_2$(phanephos)(DPEN)] is already commercially available. However, the synthesis of this ligand (fig. 3.1) requires the use of *t*BuLi, which limits the large scale synthesis, due to the dangerous pyrophoric character of this reagent. Moreover, chromatography is needed to purify the product, lowering the yields due to oxidation during this procedure:

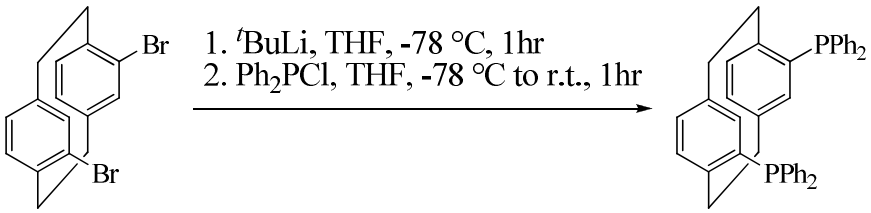
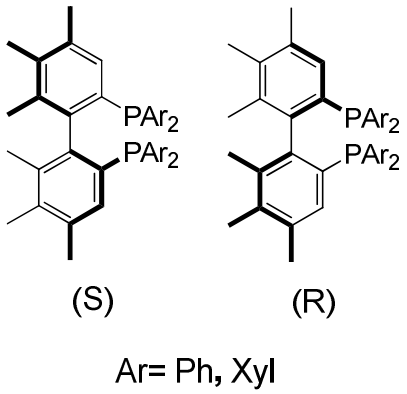


Fig. 3.1 Synthetic route for phanephos

Chirotech were extremely interested in developing a Pd catalysed route to phanephos, and this provided an incentive into our investigation into Pd catalysed P-C bond forming reaction.

3.2.2 HexaPHEMP

HexaPHEMP was also developed by Chirotech as a surrogate for the patent protected BINAP ligands and it actually shows improved catalytic performance in many cases. [6, 7]



Some derivatives of hexaPHEMP, as for example xylyl-hexaPHEMP, have also been developed and the activities of their Ru-complexes have then been investigated in the asymmetric hydrogenation of different substrates.

However, the synthetic pathway to prepare HexaPHEMP is quite demanding in term of time and thus money (three chromatography purification steps are required), and is not efficient since the overall yield is very low (13%) (fig. 3.2):

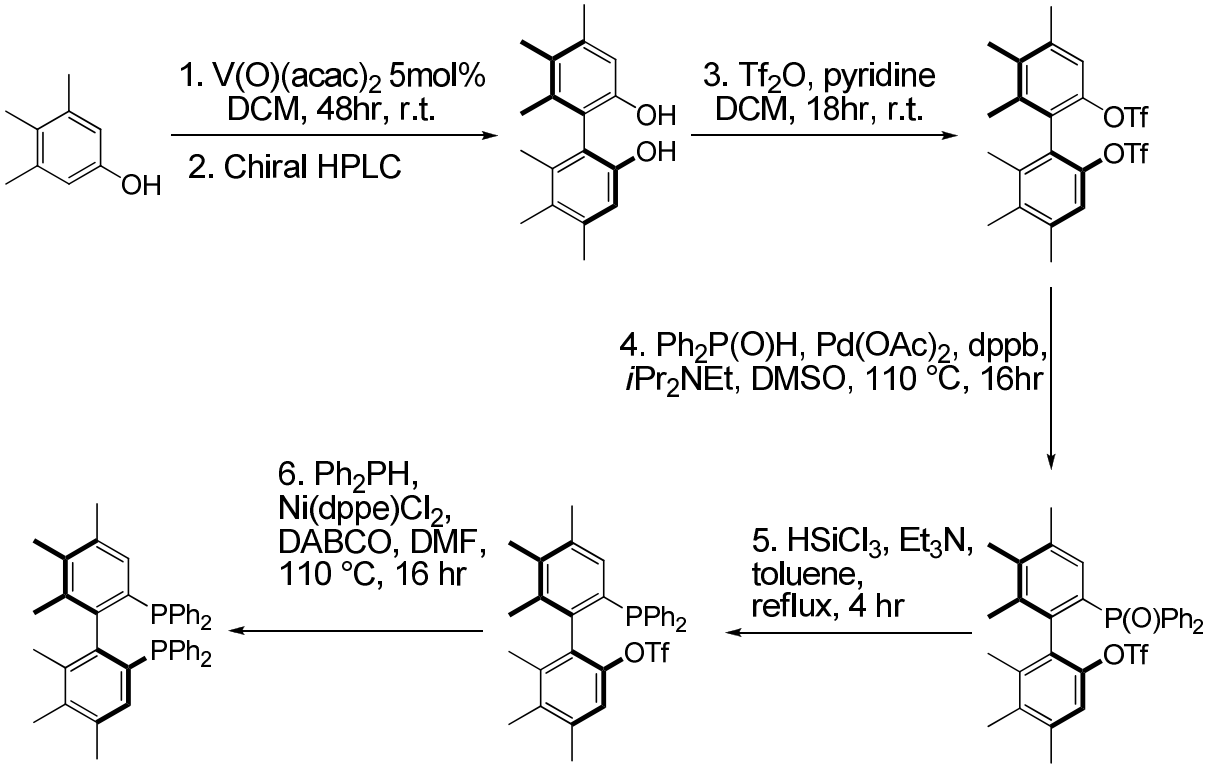
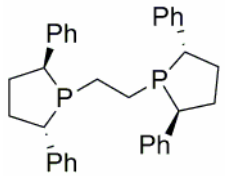


Fig. 3.2 Synthetic pathway for HexaPHEMP

This is definitely not an ideal synthesis, in particular if the large scale preparation of this diphosphine is considered. Again, it was considered ideal to develop a palladium catalysed P-C bond forming reaction, to reduce the number of steps and higher the overall yield.

3.2.3 Ph-BPE

Another very successful ligand that has been prepared by Chirotech is 1,2-bis(2,5-diphenylphospholano)ethane (Ph-BPE).[8]



Ph-BPE

Ligands with 2,5-disubstituted phospholane structural motif (fig. 3.3) have been introduced by Burk and co-workers in the early 1990s:[9-11]

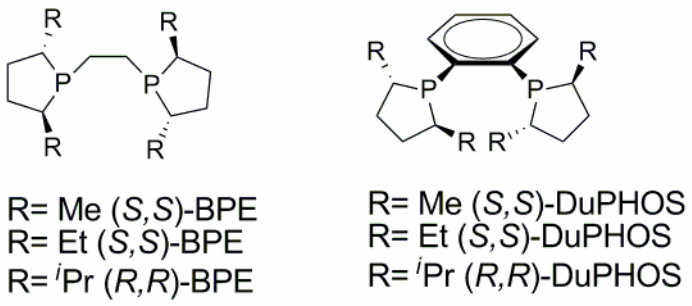


Fig. 3.3 Phospholane-based ligands developed by Burk and co-workers

Me-DuPHOS and Et-DuPHOS provided very good rhodium catalysts for the asymmetric hydrogenation of dehydroaminoacids[12] and β-monosubstituted italconates.[13]

Having seen the success of BPE and DuPHOS ligands, a modular extension to the 2,5-disubstituted bisphospholane family of ligands were the aryl analogues. However, these analogues could not be prepared using the synthetic route shown in figure 3.6, due to the sensitivity of the corresponding cyclic sulphate towards basic conditions and racemisation.[14, 15]

Thus, Pilkington and co-workers prepared Ph-BPE (**85**)[8] from 2,5-diphenylphospholanic acid as previously prepared by Fiaud and co-workers (fig. 3.4):[15]

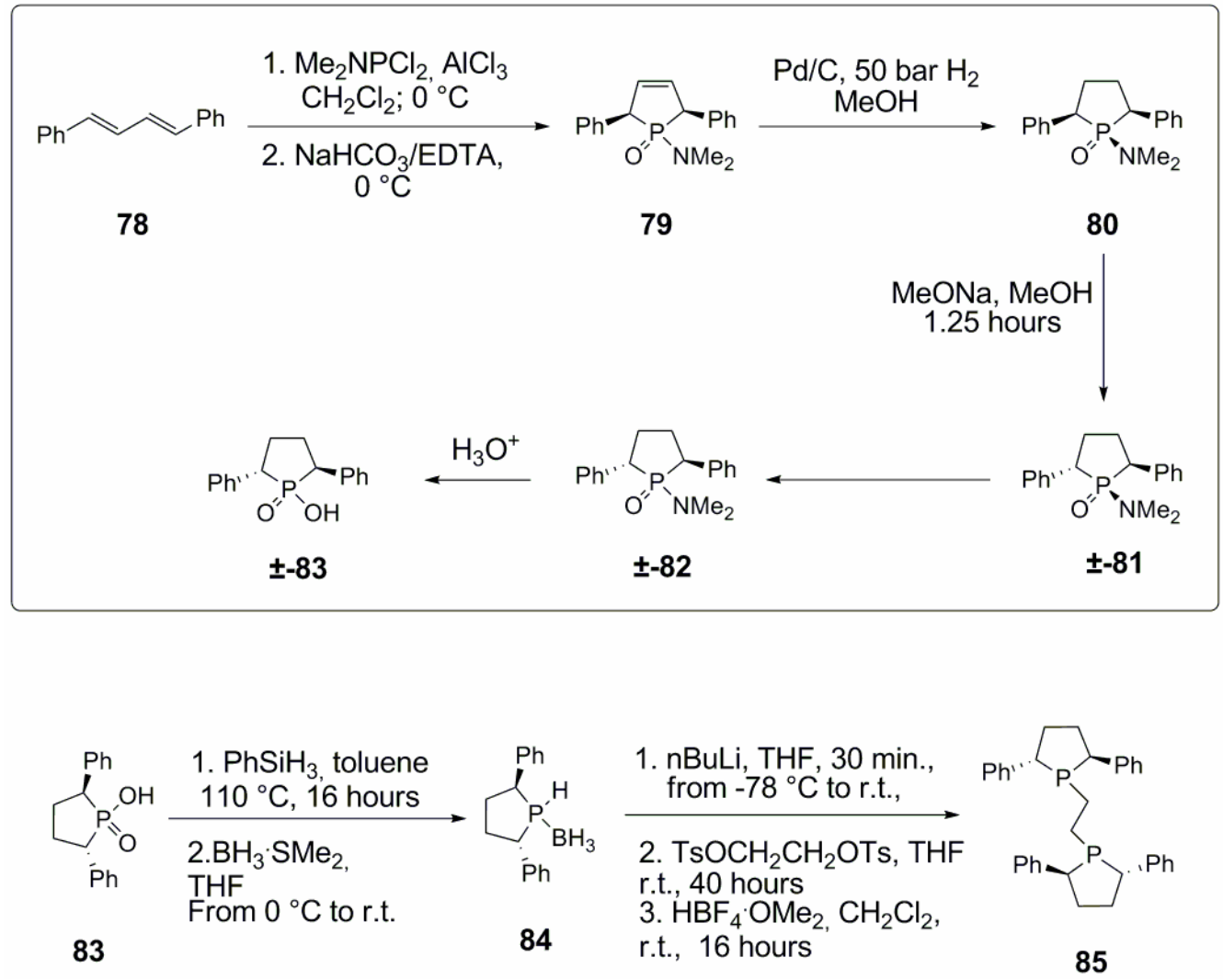


Fig. 3.4 Synthetic route for Ph-BPE (98)

Ph-BPE gives catalysis results at least comparable to DuPHOS and better than Me-BPE and Et-BPE in the rhodium catalysed asymmetric hydrogenation of few challenging substrates.[8]

Furthermore, Ph-BPE was also reported as an excellent ligand for the rhodium-catalysed asymmetric hydroformylation of olefins. It is likely that this better activity of Ph-BPE in hydroformylation compare to other phospholane-based ligands is due to the presence of the electron-withdrawing phenyl rings: indeed, it is well established that electron-poor phosphines lead to more active catalysts in rhodium-catalysed hydroformylation.[16]

3.2.3.1 Why Ph-DuPHOS?

It has been noticed that the rigid backbone of DuPHOS ligands compared to BPE ones could lead to a more efficient chirality transfer to the substrate. Moreover, 1,2-bis(tertiaryphosphino)-benzene ligands systems are known to be tightly binding chelates able to stabilise a wide variety of transition

metals. In transition metal catalysis, it is important to maintain the chirality, *ergo* the ligand at the metal centre:[17] it is believed that the high enantioselectivity given by DuPHOS ligands is also given by this capability of tightly binding the ligand to the metal.

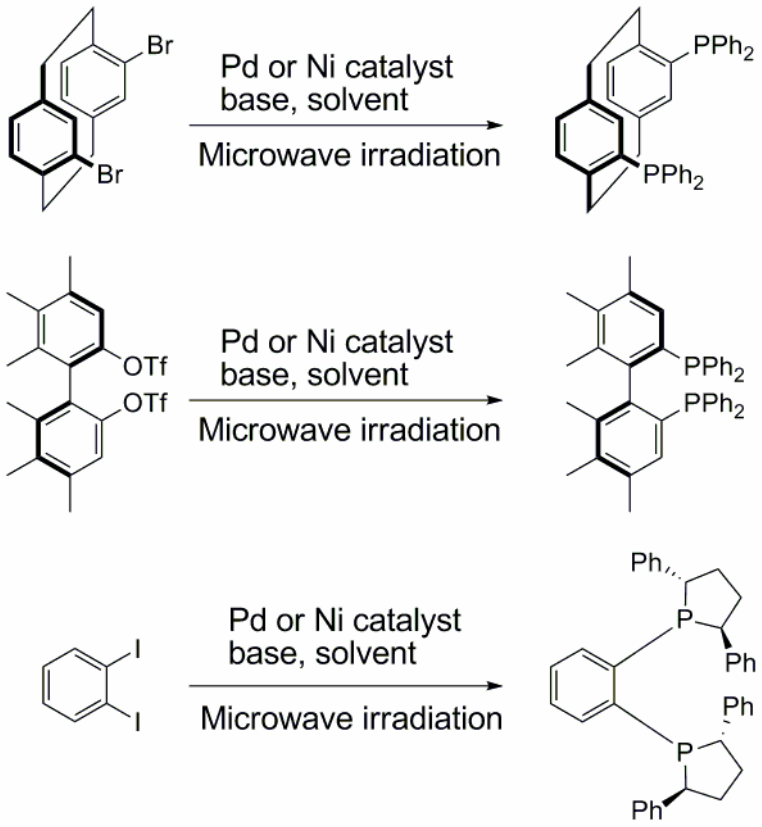
It was therefore considered that a ligand with both these structural motifs (rigid backbone and 2,5-diphenylphospholane) could lead to an interesting catalytic activity.

We envisaged that by developing a palladium catalysed P-C bond forming reaction, we could propose a different synthetic pathway not only for Phanephos and HexaPHEMP, but also for Ph-BPE, with a reduced number of steps and reaction times. Moreover, it could become the method of choice for preparing the elusive Ph-DuPHOS.

3.3 Microwave assisted palladium catalysed P-C bond forming reaction

In the introduction of this thesis, the direct carbon-phosphorus bond formation via metal-catalysed cross coupling reaction of secondary phosphines with aryl halides of triflates has been reviewed.[18,19] Kappe and co-workers reported a few moderately successful examples of palladium catalysed P-C cross coupling reaction of aryl iodides with diphenylphosphine carried out in the microwave: reasonable to good conversions were obtained in the coupling of diphenylphosphine with iodobenzene in 2 to 20 minutes, according to the catalyst used ($Pd(OAc)_2$, Pd/C or $Pd(PPh_3)_4$). The coupling of diphenylphosphine to bromobenzene required longer reaction time (30 minutes) and the Herrmann's palladacycle[20] catalyst to yield 59% of the product, with no other examples reported.[21]

These findings prompted us to consider the microwave assisted P-C bond forming reaction for the synthesis of Phanephos, HexaPHEMP, and DuPHOS, as shown in fig. 3.5:



3.5 Ideal synthetic pathway for Phanephos and HexaPHEMP and the hypothetical Ph-DuPHOS

We envisaged that finding out the appropriate reaction conditions, *i.e.* adequate catalyst, nucleophile reagent, solvent, temperature and reaction time, we could find a good solution for the problematic synthetic pathways aforementioned.

3.3.1 Different nucleophiles for the P-C cross coupling with the 2-trifluoromethyl bromobenzene

Our initial investigation focussed on the microwave accelerated P-C cross coupling reaction using, the bulky ortho-substituted trifluoromethyl bromobenzene (**86**) as a model substrate (fig.3.6). The chosen substrate also gave us the advantage to monitor the reaction by ^{19}F NMR (and $^{31}P\{^{1}H\}$NMR). This shows a distinctive quartet in its $^{31}P\{^{1}H\}$ NMR spectrum [δ= -9.3 ppm] and a doublet in its ^{19}F NMR [δ= -56.5 ppm]. Different nucleophiles were investigated in the P-C bond forming reaction, together with different solvent systems. At first, dippf/$Pd(OAc)_2$ was used as catalytic system, because of the interesting results obtained by Buchwald and co-workers in the coupling of aryl bromides and some aryl chlorides with disubstituted phosphines, reported while this work was getting underway:[22]

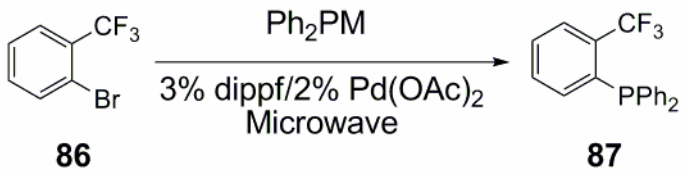


Fig. 3.6 General reaction scheme for the investigation of the microwave-assisted P-C coupling reaction

3.3.1.1 P-C bond formation using Ph_2PZnCl

The first nucleophile tested was Ph_2PZnCl. Ph_2PZnCl can be prepared cheaply from Ph_2PCl and Zn metal[23]. However, since it has been reported that this synthesis is dependent on the quality of the Zn metal, it was preferred to prepare the reagent by a new route, that we felt it would be more reproducible for the purposes of comparing to other phosphides (fig. 3.7):

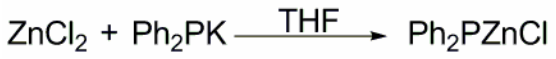
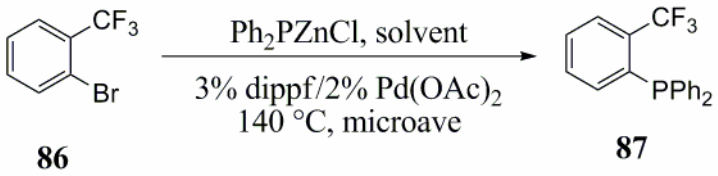


Fig. 3.7 Preparation of Ph_2PZnCl

Different amounts of the organozinc reagent Ph_2PZnCl, together with different solvent systems and reaction times were at first examined (table 3.1):



Scheme 3.1

Entry	Ph_2PZnCl, eq	Solvent	Time (min)	Conv (%)[(a)]
1	2	THF	10	7
2	1.3	THF	10	16
3	1.3	THF/DMF 50/50	10	42
4	1.3	THF/DMF 50/50	20	53
5	1.3	NMP	10	23
6	1.2	DMF	20	<5

Table 3.1 Different conditions for the microwave assisted P-C bond forming reaction using Ph_2PZnCl as a nucleophile (a) The conversion values were worked out using the integral of ^{19}F NMR

It was noticed that it was beneficial to use a slight excess of the reagent, as using double the amount of the zinc reagent needed was leading to lower conversions to the product (**87**). Moreover, the mixture of THF/DMF was identified as the best solvent system among the ones tested.

However, we reasoned that these results were not satisfactory, in light of our final aim to try these reaction conditions for the double P-C coupling of the more complex [2,2]-dibromoparacyclophane.

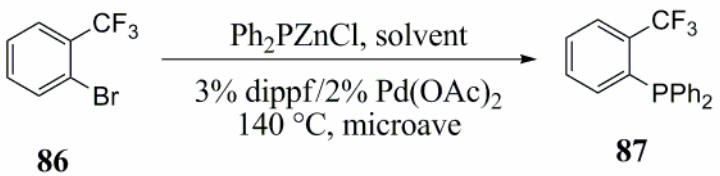
3.3.1.2 P-C bond formation using Ph_2PSiMe_3

It was decided to try a different nucleophile for the P-C bond forming reaction, and with this in mind Ph_2PSiMe_3 was then prepared (fig. 3.8):

Fig. 3.8 Preparation of Ph_2PSiMe_3

Keeping the same catalytic system (dippf/$Pd(OAc)_2$) and the same temperature (140 °C) as in the previous attempts with Ph_2PZnCl, different reaction times and solvent systems were tried using (**86**) as a substrate. It was decided to keep the amount of the silane reagent constant at 1.2 equivalent, because of the previous finding that a large excess negatively affect the conversion to the product (**87**).

However, as it is shown in table 3.2, the use of Ph_2PSiMe_3 as a nucleophile gave lower conversions to the product compared to the use of the zinc reagent. In most silicon cross-couplings, fluoride salts are added to enhance the nucleophilicity of the reagent. Surprisingly this had not been investigated in the coupling of silyl phosphines.[24, 25] The use of CsF as an additive led to better results compare to the ones obtained without it, but it was once more considered that this nucleophile would not have given much success for the P-C coupling of the bulkier substrates we had in mind.



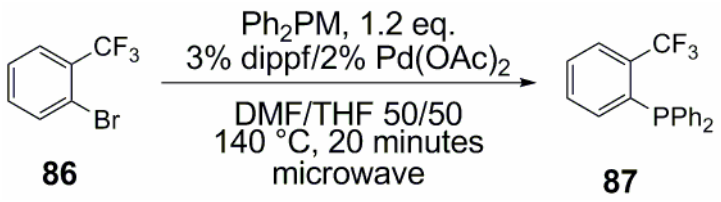
Scheme 3.2

Entry	Solvent	Time	Conv (%)[a]
1	THF/NMP 50/50	10	<10
2	THF/NMP 50/50	20	<10
3	THF/NMP 50/50	30	<10
4	DMF	10	<10
5	DMF	20	<10
6	DMF	30	<10
7	THF/DMF 50/50	10	<10
8	THF/DMF 50/50	20	<10
9	THF/DMF 50/50	30	<10
10	THF/NMP 50/50	10	<10
11	THF/NMP 50/50	20	<10
12	THF/NMP 50/50	30	<10
13[b]	THF/DMF 50/50	10	24
14[b]	THF/DMF 50/50	20	25

Table 3.2 Different conditions for the microwave assisted P-C bond forming reaction using Ph_2PSiMe_3 as a nucleophile (a) The conversion values were worked out using the integral of ^{19}F NMR; (b) 2 eq. of CsF were added.

3.3.1.3 P-C bond formation using other nucleophilic reagents

It was considered that other nucleophilic phosphide reagents should be tested using the same catalyst. The temperature, the solvent and the concentration of the nucleophilic reagent were also kept constant and these constant conditions were decided as they gave better results in the previous attempt with the model substrate in use (table 3.3):



86 **87**

Scheme 3.3

Entry	Ph_2PM	Conv (%)[a]
1	Ph_2PZnCl	53
2	Ph_2PSiMe_3	<10
3	Ph_2PSiMe_3/CsF[b]	25
4	Ph_2PH/DABCO[b]	91
5	Ph_2PK	7
6	$Ph_2P(O)H$/DABCO[b]	0
7	Ph_2PMgBr	36

Table 3.3 Different nucleophilic reagents for the microwave assisted P-C bond forming reaction (a) The conversion values were worked out using ^{19}F and $^{31}P\{^1H\}$ NMR; (b) 2 equivalents of additive.

From the data reported in table 3.3, it is clear that the best system for getting the microwave-assisted P-C bond formation in only 20 minutes is to use the system Ph_2PH/DABCO (entry 4), using $Pd(OAc)_2$/dippf as the catalyst. Although acceptable conversions were obtained in the presence of Ph_2PZnCl (entry 1), the other nucleophilic reagents did not lead to reasonable conversion to the product (**87**). The result obtained with Ph_2PK as the nucleophile is possibly surprising (entry 5): since the strongly basic character of Ph_2PK led us to consider it as a strong nucleophile, therefore a better conversion was expected, if formation of the Pd-P bond was rate-determining.

From table 3.3, as well as by reading the literature (see chapter 1), it is evident that the palladium catalysed P-C bond forming reaction is often problematic and the reasons for this are still not well understood. One possibility is that the phosphine that acts as the nucleophile interferes in the formation of the active catalyst, leading to the formation of an inactive palladium species: this was observed when a phosphonate was used as the nucleophile.[26] To test if this was a possibility in our case, an experiment was performed: the reaction shown in Scheme 3.3 was carried out and stopped after 6 minutes and it was observed that when 2 equivalents of diphenylphosphine were used, a conversion of 50 % to the product was obtained, whereas when 8 equivalents of diphenylphosphine were used, only a 3 % conversion to the product was observed (chart 3.1):

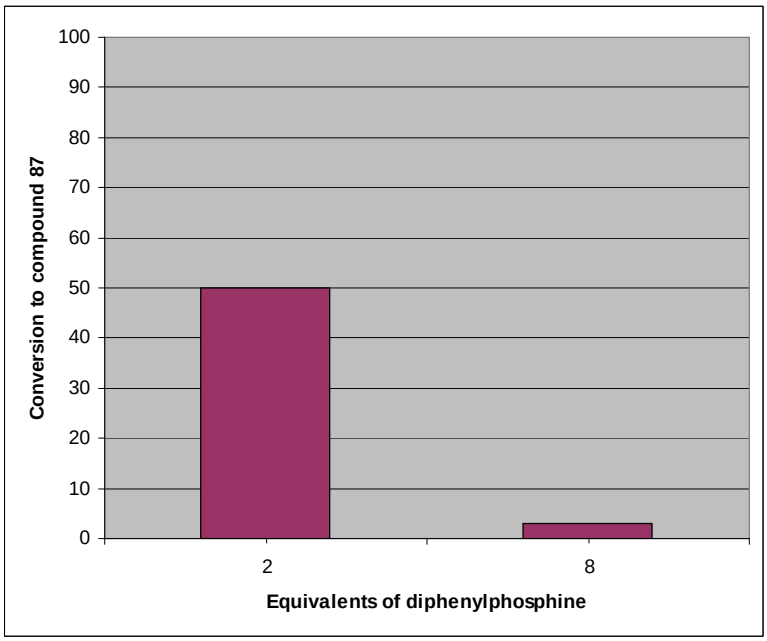


Chart 3.1 Percentage conversion to product (87) at different amounts of Ph_2PH and DABCO after 6 minutes (Ph_2PH/DABCO 1/2)

These experiments suggest that the nucleophile might interfere with the active catalyst.

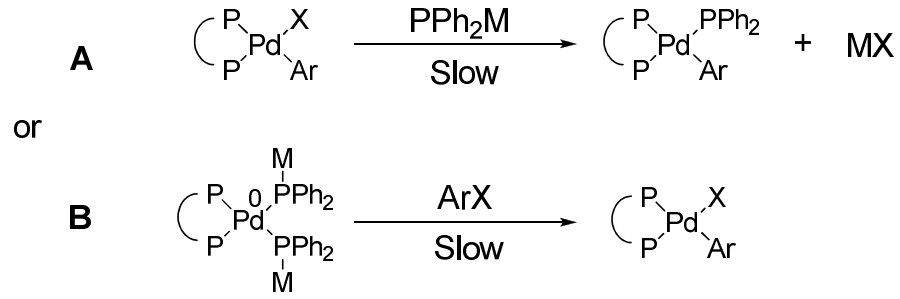
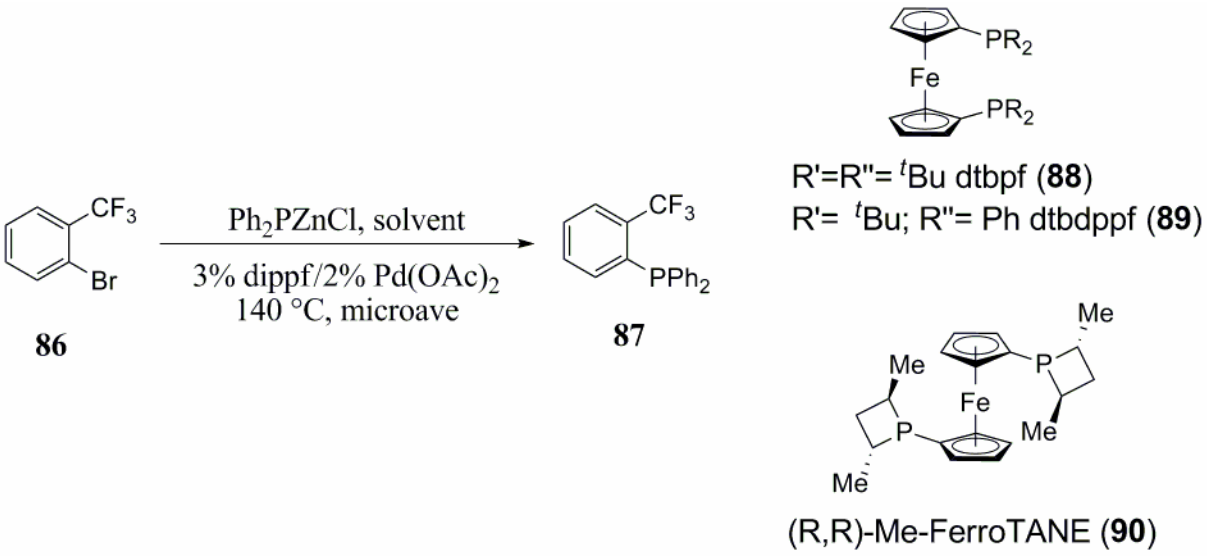


Fig. 3.9 Possible first steps in the P-C coupling reaction

Two possible problematic steps in the palladium catalysed P-C bond forming reaction are shown in figure 3.9. In scheme A the substitution by the phosphide could be problematic since the phosphorus compounds are bulky nucleophiles. In scheme B the initial formation of a diphosphine complex by coordination of the metallated diphenylphosphine derivative to the palladium could slow the oxidative addition of ArX. In our experiment, shown in chart 3.1, it was noted that by adding a higher amount of the diphenylphosphine, lower conversion to the product was obtained. One possibility could be the formation of an inactive palladium complex, such as Pd(dippf)(Ph_2PH)$_2$ (shown in B). Therefore, according to these preliminary observations, pathway A is possibly more likely to occurwithout problems or at a faster rate compare to pathway B. Further investigations are necessary to acquire more information on the operating mechanism.

3.3.2 Investigation of different catalysts for the microwave-assisted P-C cross coupling reaction

In all the reactions described above, the catalytic system used has been Pd(OAc)$_2$/dippf. Moreover, the nucleophilic reagent that gave the best result with substrate (**86**) was Ph_2PH/DABCO, with reasonable results obtained also with Ph_2PZnCl. This latter reagent is easy to prepare and potentially cheaper compare to Ph_2PH, so it was considered useful to screen different catalysts in the P-C cross-coupling of (**86**) with these two nucleophiles that gave the best results, to verify if better conversions to the product (**87**) could be obtained (see table 3.4):



Scheme 3.4

Entry	Catalyst, 2%	Ph_2PM, 1.2eq	Conv(%)[a]
1	dippf/$Pd(OAc)_2$ 1.5/1	Ph_2PH/DABCO[b]	91
2		Ph_2PZnCl	53
3	[$Pd(dippf)Cl_2$]	Ph_2PH/DABCO[b]	25
4		Ph_2PZnCl	0
5	[$Ni(dippf)Cl_2$]	Ph_2PH/DABCO[b]	0
6		Ph_2PZnCl	0
7	PPh_3/ $Pd(OAc)_2$ 4/1	Ph_2PH/DABCO[b]	65
8		Ph_2PZnCl	38
9	dppe/$Pd(OAc)_2$ 1.5/1	Ph_2PH/DABCO[b]	14
10		Ph_2PZnCl	21
11	[$Pd(dppf)Cl_2$]	Ph_2PH/DABCO[b]	10
12		Ph_2PZnCl	0
13	[$Ni(dppf)Cl_2$]	Ph_2PH/DABCO[b]	<10
14	dppf/$Pd(OAc)_2$ 1.5/1	Ph_2PH/DABCO[b]	9
15	[$Pd(dtbpf)Cl_2$]	Ph_2PH/DABCO[b]	4
16	dtbpf/ $Pd(OAc)_2$ 1.5/1	Ph_2PH/DABCO[b]	4
17	[$Pd(dtbdppf)Cl_2$]	Ph_2PH/DABCO[b]	5
18	Dtbdppf/ $Pd(OAc)_2$ 1.5/1	Ph_2PH/DABCO[b]	5
19	FerroTANE/$Pd(OAc)_2$ 1.5/1	Ph_2PH/DABCO[b]	62
20	$Pd(OAc)_2$	Ph_2PH/DABCO[b]	0

Table 3.4 Screening of different catalyst for the microwave assisted P-C cross coupling reaction of (86) (a) The conversion values were calculated using ^{19}F and $^{31}P\{^1H\}$ NMR; (b) 2 equivalents of DABCO.

This screening proved that the microwave-assisted P-C bond forming reaction on (**86**) was giving the best result by using dippf/$Pd(OAc)_2$ as the catalytic system and Ph_2PH as the nucleophile in the presence of DABCO as a base. It is also interesting to notice that the formation of the catalyst *in*

situ is necessary for getting high conversion to the product (**87**): indeed, by using the preformed catalyst [Pd(dippf)Cl_2] (entries 3 and 4) only a small amount of the product (**87**) is formed.

Surprisingly, the catalytic system PPh_3/Pd$(OAc)_2$ gave an appreciable result with both the nucleophilic reagents (entries 7 and 8), but the conversions are still way below that obtained with dippf/Pd$(OAc)_2$.

Nickel-based catalysts were also tested, because of the many examples reported in the literature of nickel catalysed P-C bond forming reactions.[19,27-29] However, poor activity was observed when using [Ni(dppf)Cl_2] (entry 13) and no conversion to the product was detected when using [Ni(dippf)Cl_2] (entries 5 and 6).

The results for the activity of bulkier ligands in the palladium catalysed P-C bond forming reaction are also reported in table 3.4. Indeed, it has been previously described that hindered ligands promote oxidative addition and reductive elimination, but not transmetallation:[30] it was considered that these characteristics could lead to high conversions to (**87**) in the P-C cross-coupling. FerroTANE (**90**) (entry 19) gave a reasonable conversion to the product, whereas ligands (**88**) and (**89**) did not lead to good conversions, neither when the catalyst was prepared beforehand (entries 15 and 17) nor when it was prepared *in situ* (entries 16 and 18). Given the magnitude of the ligand effects it is possible that for these bulky ligands, the transmetallation of the phosphide (scheme A in fig. 3.9) becomes problematic as well as the oxidative addition. It was also confirmed that a ligand is necessary for the reaction to occur, as Pd$(OAc)_2$ by itself did not give any conversion to the product (entry 20).

3.3.3 P-C bond forming reaction under conventional heating

During our investigation of the microwave-mediated P-C cross-coupling reaction, it was decided to fulfil our curiosity and verify if the reaction could occur under conventional heating. A few examples were already reported by Buchwald and co-workers,[22] who described the P-C cross coupling to occur using dippf/Pd$(OAc)_2$ as the catalytic system. However long reaction times were described (from 6 to 18 hours).

Thus, a reaction with the substrate (**86**) used previously as a model study was carried out using the organozinc reagent as nucleophile and dippf/Pd$(OAc)_2$ as catalyst. The reaction was run in DMF and not in the solvent mixture THF/DMF used in the reactions run under microwave heating, to make sure to reach the desired temperature of 140 °C would be reacted. After 20 minutes of heating the reaction mixture, ^{19}F and $^{31}P\{^1H\}$ NMR showed no presence of product (**87**). The reaction was heated for 7 hours and the presence of the product was confirmed by ^{19}F and $^{31}P\{^1H\}$ NMR (90 %

conversion). For this example, the phosphine was isolated in 56 % yield by column chromatography after air oxidation (fig. 3.10):

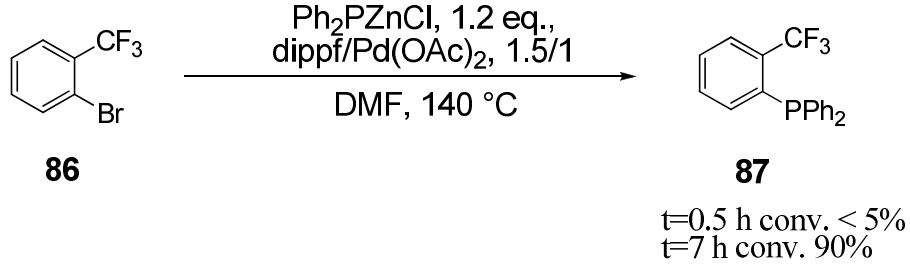


Fig. 3.10 Palladium catalysed P-C cross-coupling in conventional conditions, using Ph_2PZnCl as the phosphinating agent

This experiment shows that the P-C coupling of (**86**) is possible under conventional conditions, however by carrying out the reaction in the microwave, the reaction time can be remarkably reduced.

3.3.4 Microwave assisted P-C cross coupling reaction on different substrates

In the last paragraphs, the optimisation of the reaction conditions for the coupling of (**86**) with Ph_2PH has been described. It has been found that in the presence of the catalytic system dippf/$Pd(OAc)_2$, in the solvent mixture THF/DMF, the reaction under microwave heating gave good conversion to the product **(87)** in only 20 minutes.

The microwave-assisted protocol described above was tested for the coupling of diphenylphosphine to *o*-iodo- and *o*-chloro-trifluoromethylbenzene (fig. 3.11):

Fig. 3.11 Microwave assisted coupling of Ph_2PH to (86a) and (86b), using the conditions optimised for (86) The conversion values were calculated using ^{19}F and $^{31}P\{^1H\}$ NMR.

As expected, the microwave assisted P-C bond forming reaction performed on (**86a**) gave almost full conversion to the product (>95%). On the other hand, by coupling Ph_2PH to (**86b**), no product was observed and mainly starting material was recovered.

At this point, it was considered useful to verify if the protocol optimised would give good results if used with different substrates (see fig. 3.12):

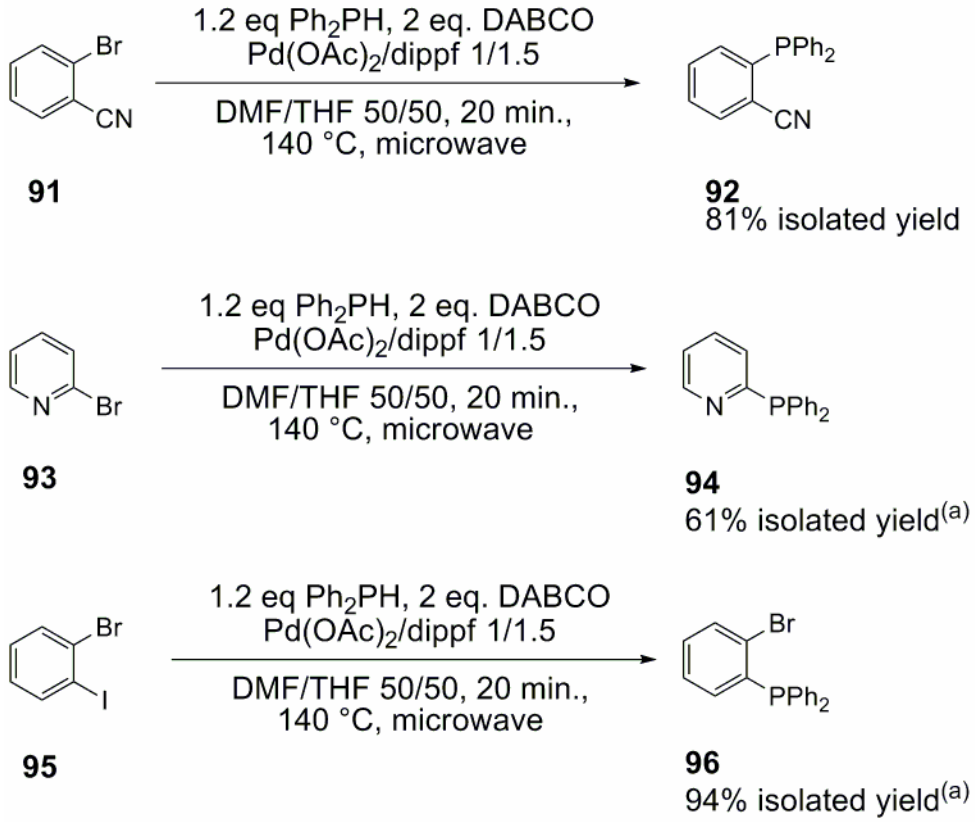


Fig. 3.12 Microwave assisted P-C cross coupling on different substrates using the protocol we optimised (a) The yield was based on the isolated yield of the phosphine oxide obtained after oxidation using H_2O_2.

It was pleasing to notice that the reaction conditions we used led to high conversions to the products, also by using different substrates. These substrates ((**91**), (**93**) and (**95**)) present electron withdrawing groups which are likely to be responsible of a faster rate in the oxidative addition to palladium. The products (**92**), (**94**) and (**96**) have been previously prepared. Compound (**92**) have been prepared in low yield even after very long reaction time (37% yield in 2.5 days) through palladium-catalysed phosphination of the aryl triflate with triphenylphosphine.[30] Another route was described, leading to compound (**92**) in higher yield (70% yield), as well as compound (**94**) in 67% yield and involved the reaction of diphenylphosphine magnesium chloride to the adequate aryl fluorides.[31] This route is not ideal because of the need of the electrochemical preparation of diphenylphosphine magnesium chloride and also because it uses aryl fluorides, which are in general quite expensive and not a wide variety is commercially available. One synthetic pathway described for the preparation of (**96**) used a microwave-assisted palladium catalysed reaction, however a lower yield was obtained.[32] These observations highlights that the conditions developed by us and

described in this chapter are quite efficient in terms of reaction time and yield. Moreover, the preparation of compound (**96**) could be quite handy as it is possible to introduce different functional groups by displacement of the bromine.

For (**94**) and (**96**) it was necessary to oxidise the product before column chromatography, due to the air sensitive nature of the free phosphine, whereas with (**92**) it was possible to run the chromatography column, without getting oxidation of the compound.

3.3.4.1 Microwave-assisted double P-C coupling

So far, the optimisation of a protocol for P-C bond formation has been described using microwave heating. Moreover, it has also been reported that these conditions are useful for several different substrates (see previous paragraph). However, our ultimate goal was to obtain phanephos, HexaPHEMP and Ph-DuPHOS using a palladium catalysed double P-C cross coupling. It was then considered useful to try the optimised conditions for the double P-C coupling of Ph_2PH with model substrates (fig. 3.13):

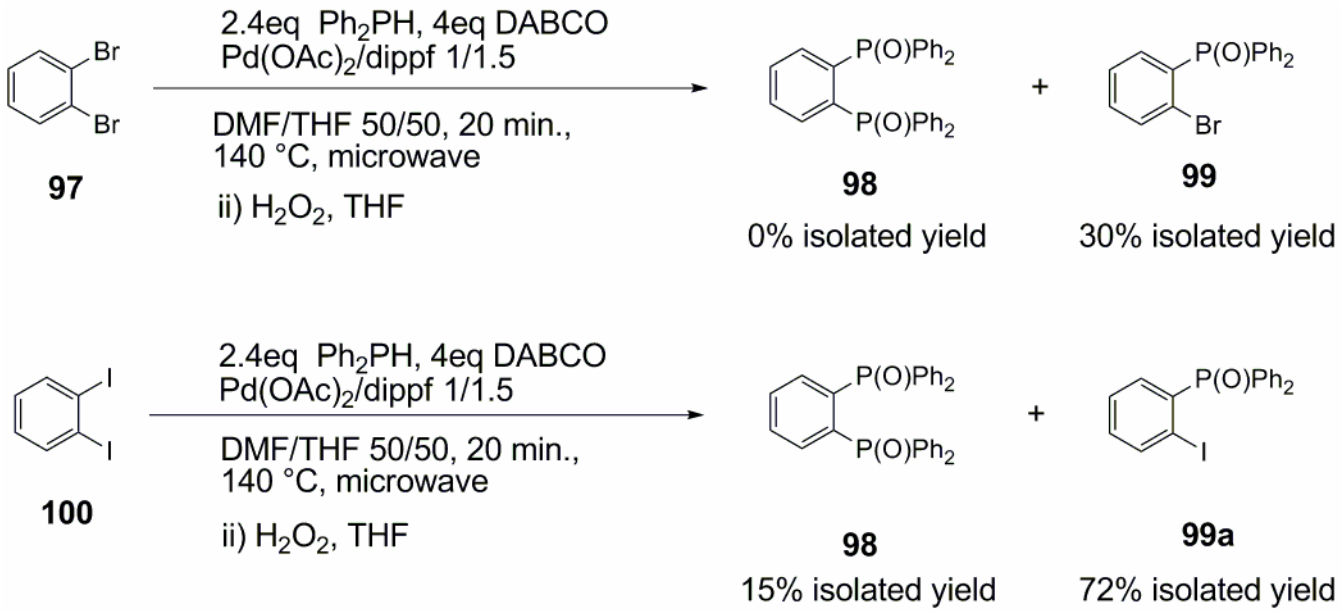


Fig. 3.13 Double P-C coupling on *o*-dibromo- and *o*-diiodobenzene

In the double P-C cross coupling, there is the disadvantage of the formation of the mono-coupled compound as a side product. This was also observed by performing the reaction on (**97**) and (**100**), the two model substrates of our choice. Indeed, the P-C coupling of (**97**) gave only a low conversion to the isolated mono-coupled product (**99**), and no desired product (**98**) was observed. On the other hand, by performing the reaction on *o*-diiodobenzene (**100**), both mono- and di-

coupled products were observed, with a reasonable yield for the formation of the monophosphine product (**99a**), accompanied by 15% of the di-coupled product (**98**).

These results showed that the one pot double P-C bond forming reaction does not occur easily, giving mainly the mono-coupled compound, and only a low yield of the desired di-coupled compound is obtained, even when starting from a diiodo substituted substrate, which more readily undergoes P-C cross-coupling reaction.

3.3.5 Microwave-assisted P-C cross coupling reaction on [2,2]-dibromo-paracyclophane

The results shown in the previous paragraphs demonstrate that it is possible to obtain the P-C bond forming reaction under microwave heating on different substrates by using dippf/$Pd(OAc)_2$ as catalytic system, and Ph_2PH as the nucleophile, in the presence of DABCO. However, the results obtained for the one-pot double P-C bond forming reaction described in the previous paragraph were not encouraging, as it was shown that the di-coupled product could be obtained only in low yield and only if starting from a diiodo-substituted substrate.

Nonetheless, it was decided to try the microwave-assisted P-C bond forming reaction on the bulkier [2,2]-dibromo-paracyclophane, to verify if it was possible to prepare Phanephos by using this protocol. Of course, also in this case, we were aware of the fact that by coupling Ph_2PH to (**101**), it is possible to have the formation not only of the product (**102**), but also of side products (**103**) and (**104**), as shown in fig.3.14. Doping experiments using pure phanephos and a mixture containing (**103**) and (**104**) synthesised by treatment of (**101**) with 2 equivalents of *tert*-buthyl lithium, followed by Ph_2PCl, which gave (**102**), (**103**) and (**104**) (NMR and MS evidence) confirmed that (**102**), (**103**) and (**104**) have different chemical shifts.

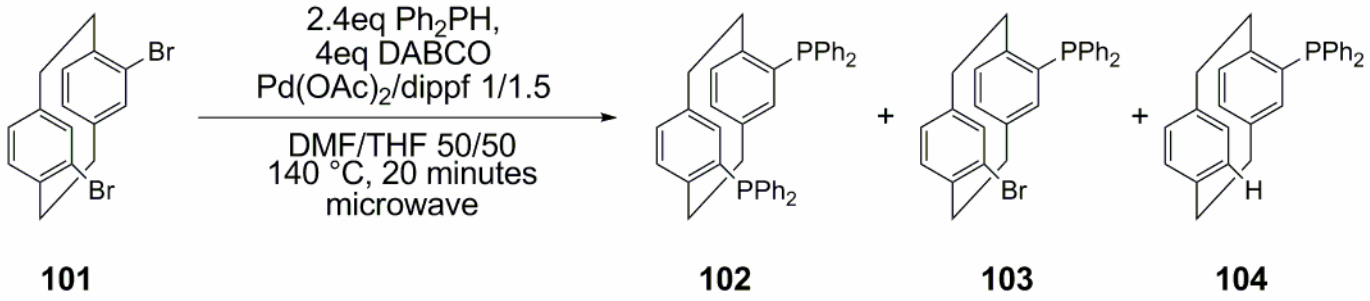


Fig. 3.14 Possible products of the metal catalysed P-C bond forming on [2,2]-dibromo-paracyclophane

The conditions for the synthesis of (**102**) were optimised, keeping temperature (140 °C) and the catalytic system (dippf and $Pd(OAc)_2$) constant. The solvent system and reaction time were modified, and Ph_2PZnCl, Ph_2PSiMe_3 and Ph_2PH were used as the nucleophiles. The ratios between

the possible products of the reaction, (**102**), (**103**) and (**104**) were calculated on the crude $^{31}P\{^{1}H\}$ NMR, in order to have an idea on which could be the better reaction conditions. In all these attempts, it was noted that other side products were also present in the final reaction mixture. When using Ph_2PZnCl, it was observed that by adding double the amount of the nucleophile, a mixture of the three possible products (**102**), (**103**) and (**104**) was mainly obtained, even when the reaction was left in the microwave for a longer time (the longest reaction time tried was 2.5 hours). Isolation of the desired product (**102**) from the two side products (**103**) and (**104**) would not be easy therefore it was preferred to further investigate the reaction, in order to find reaction conditions that could lead only to the formation of (**102**). It was then decided to use a slight excess of the nucleophile (2.2 equivalents) and in 0.5 hour, using an equal mixture of DMF and THF, compound (**103**) was the only phanephos-type compound obtained. Ph_2PSiMe_3 (2.4 equivalents) was also tried, in the presence of CsF (4 equivalents), and using DMF and THF (1:1) as the solvent system. However, by changing the reaction time, a mixture of the three possible products was always obtained, making Ph_2PSiMe_3 not the ideal nucleophile for this reaction. Finally, Ph_2PH in the presence of DABCO was tested as the nucleophile, but again a mixture of the three possible products (**102**), (**103**) and (**104**) was obtained.

It was then decided to quantify the conversion to the product (**102**) using an expternal standard. The conversion was worked out by using as external standard of triethylphosphine oxide. A $^{31}P\{^{1}H\}$ NMR of a known concentration of Phanephos was taken in the presence of a capillary tube containing triethylphosphine oxide dissolved in deuterated benzene and the integrals of the two peaks were recorded. The same capillary tube containing the solution of triethylphosphine oxide was then used as a calibrant to determine the phanephos concentration in the real reaction. It was noted that by using the conditions optimised with the model substrate (**86**), only a 13% conversion to the product (**102**) is obtained. It was also noticed that the reaction led mainly to the formation of the mono-coupled compound (**103**) and traces of (**104**) were also present in the reaction mixture.

After a significant number of further attempts at coupling phosphide nucleophiles to (**101**) failed to give promising results, this approach was abandoned.

It was ultimately disappointing that the microwave protocol does work for different substrates, but not for the double coupling of a bulky substrate such as dibromo paracyclophane.

3.3.6 Microwave-assisted P-C cross-coupling reaction for the preparation of Ph-DuPHOS

As aforementioned (see paragraph 3.3), one of the reasons that made us interested in developing a microwave protocol for the metal catalysed P-C bond forming reaction was trying to prepare the

new ligand Ph-DuPHOS. Indeed, Chirotech tried to prepare this ligand, however it proved to be elusive.

The microwave protocol developed was then tested in the attempt of the synthesis of the Ph-DuPHOS precursor (fig. 3.15):

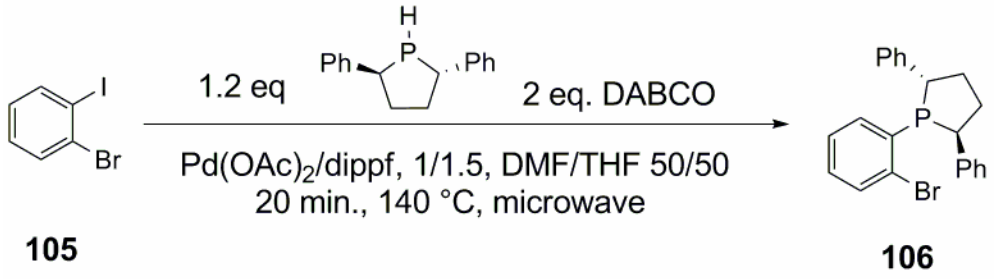


Fig. 3.15 Attempt of the synthesis of the Ph-DuPHOS precursor (106), using the microwave mediated P-C cross-coupling reaction

However, the microwave-mediated synthesis of (**106**) was soon abandoned, because mainly starting material was recovered.

Other (unsuccessful) attempts were carried out in trying to prepare Ph-DuPHOS, and this will be discussed in the next chapter, along with the successful synthesis and application of a new phenylphospholane ligand.

3.4 Conclusions

The microwave-assisted P-C bond forming reaction was investigated: different nucleophiles and catalytic systems, together with different solvents and reaction times were tested and it was found that the P-C coupling of the bulky *o*-trifluoromethyl bromobenzene was possible in only 20 minutes if using $Pd(OAc)_2$/dippf as the catalytic system, Ph_2PH as the nucleophile in the presence of DABCO and the solvent mixture THF/DMF. It was also noted that this protocol led to high yields for a range of substrates.

However, the one-pot double P-C bond forming reaction proved to be difficult even if using the more reactive *o*-diiodobenzene, leading to only a low conversion to the desired di-coupled product and mainly to the mono-coupled one.

The protocol was used in trying to prepare phanephos, but as expected only a small conversion to the product was obtained, the mono-substituted one being again the main product of the reaction.

Finally, microwave-mediated synthesis of the monophospholane intermediate for the preparation of Ph-DuPHOS was tested, however it proved to be inefficient.

3.5 References

1 P. J. Pye, K. Rossen, R. A. Reamer, N. N. Tsou, R. P. Volante, and P. J. Reider, *J. Am. Chem. Soc.*, 1997, **119**, 6207.
2 A. Zanotti-Gerosa, C. Malan, and D. Herzberg, *Org. Lett.*, 2001, **3**, 3687.
3 P. J. Pye, K. Rossen, R. A. Reamer, R. P. Volante, and P. J. Reider, *Tet. Lett.*, 1998, **39**, 4441.
4 M. J. Burk, W. Hems, D. Herzberg, C. Malan, and A. Zanotti-Gerosa, *Org. Lett.*, 2000, **2**, 4173.
5 D. Chaplin, P. Harrison, J. P. Henschke, I. C. Lennon, G. Meek, P. Moran, C. J. Pilkington, J. A. Ramsden, S. Watkins, and A. Zanotti-Gerosa, *Org. Proc. Res. Dev.*, 2003, **7**, 89.
6 J. P. Henschke, M. J. Burk, C. G. Malan, D. Herzberg, J. A. Peterson, A. J. Wildsmith, C. J. Cobley, and G. Casy, *Adv. Synth. Catal.s*, 2003, **345**, 300.
7 C. J. Cobley and J. P. Henschke, *Adv. Synth. Catal.*, 2003, **345**, 195.
8 C. J. Pilkington and A. Zanotti-Gerosa, *Org. Lett.*, 2003, **5**, 1273.
9 J. E. F. Mark J. Burk, and Richard L. Harlow, *Organometallics*, 1990, **9**, 2653.
10 M. J. Burk, *J. Am. Chem. Soc.*, 1991, **113**.
11 M. J. Burk, J. E. Feaser, and R. L. Harlow, *Tet. Asymm.*, 1991, **2**, 569.
12 J. E. Feaser, M. J. Burk, W. A. Nugent, and R. L. Harlow, *J. Am. Chem. Soc.*, 1993, **115**, 10125.
13 M. J. Burk, F. Bienewald, M. Harris, and A. Zanotti-Gerosa, *Angew. Chem. Int. Ed.*, 1998, **37**, 1931.
14 C. J. Pilkington and A. Zanotti-Gerosa, *Org. Lett.* 2003, **5**, 1273.
15 F. Guillen, M. Rivard, M. Toffano, J. Y. Legros, J. C. Daran, and J. C. Fiaud, *Tetrahedron*, 2002, **58**, 5895.
16 M. Dieguez, O. Pamies and C. Claver, *Tet. Asymm.*, 2004, **15**, 2113.
17 J. T. C. Shiuh-Tzung Liu, S. M. Peng, Y. L. Hsiao, and M. C. Cheng, *Inorg. Chem.* 1990, **29**, 1169.
18 D. J. Brauer, M. Hingst, K. W. Kottsieper, C. Liek, T. Nickel, M. Tepper, O. Stelzer, and W. S. Sheldrick, *J. Organomet. Chem.*, 2002, **645**, 14.
19 D. Cai, J. F. Payack, D. R. Bender, D. L. Hughes, T. R. Verhoeven, and P. J. Reider, *J. Org. Chem.*, 1994, **59**, 7180.
20 W.A. Herrmann, V. P. W. Boehm, C. P. Reisinger, *J. Organomet. Chem.*, 1999, **576**, 23.
21 A. Stadler and C. O. Kappe, *Org. Lett*, 2002, **4**, 3541.
22 M. Murata and S. L. Buchwald, *Tetrahedron*, 2004, **60**, 7397.
23 T. Hayashi, M. Konishi, K. Yokota, and M. Kumada, *J. Organomet. Chem.*, 1985, **285**, 359.
24 K. T. Jun-ichi Yoshida, M. Takahashi, and M. Kumad, *Tet. Lett.*, 1978, **25**, 2161.
25 K. A. Horn, *Chem. Rev.*, 1995, **95**, 1317.
26 M. Kalek and J. Stawinski, *Organometallics*, 2007, **26**, 5840.
27 M. McCarthy, R. Goddard, and P. J. Guiry, *Tet. Asymm.*, 1999, **10**, 2797.
28 M. McCarthy and P. J. Guiry, *Tetrahedron*, 1999, **55**, 3061.
29 M. L. Clarke, A. G. Orpen, P. G. Pringle, and E. Turley, *Dalton Trans.* 2003, 4393.
M. L. Clarke and M. Heydt, *Organometallics*, 2005, **24**, 6475.
30 F.Y.Kwong, C.W.Lai and K.S. Chan, *Tet. Lett.*, 2002, **43**, 3537.
31 X M. Nechab, E. Le Gall, M. Troupel, J. Nedelec, *J. Organomet. Chem.*, 2006, **691**, 1809.
32 X A. Stadler and C. O. Kappe, *Org. Lett*, 2002, **4**, 3541.

Chapter 4

Phospholane-based ligands in hydrogenation and hydroxycarbonylation

4.1 Introduction

In the previous chapter, I briefly described phospholane-base ligands, which are amongst the most important ligands in rhodium catalysed hydrogenation of challenging olefins, and ruthenium catalysed ketone reduction.

These achievements have prompted many research groups to prepare derivatives of phospholane-based ligands, to eventually test in different asymmetric catalytic reactions. Alkyl substituted phospholane are generally prepared from cyclic sulfates, as shown below,[1] whereas, as already discussed, phenyl substituted phospholanes use different precursors that are ultimately derived from the 2,5-diphenyl phospholanic acid (**83**) (see fig. 3.4 of the previous chapter).[2, 3]

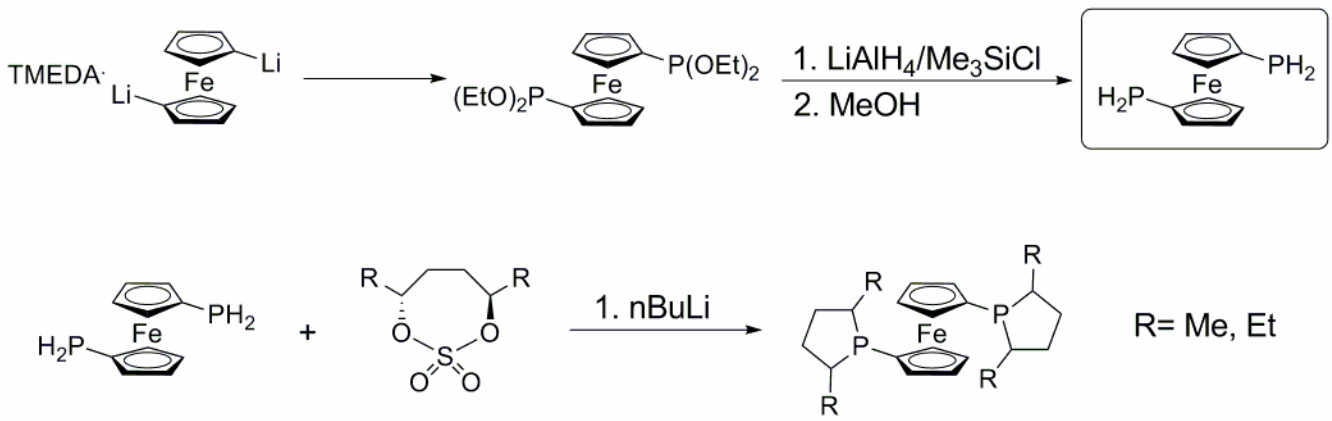


Fig. 4.1 Synthesis of phospholane-based ligands with ferrocene backbone

Some of the alkyl phospholane prepared and used successfully in catalysis are shown in fig. 4.2:[2, 4-18]

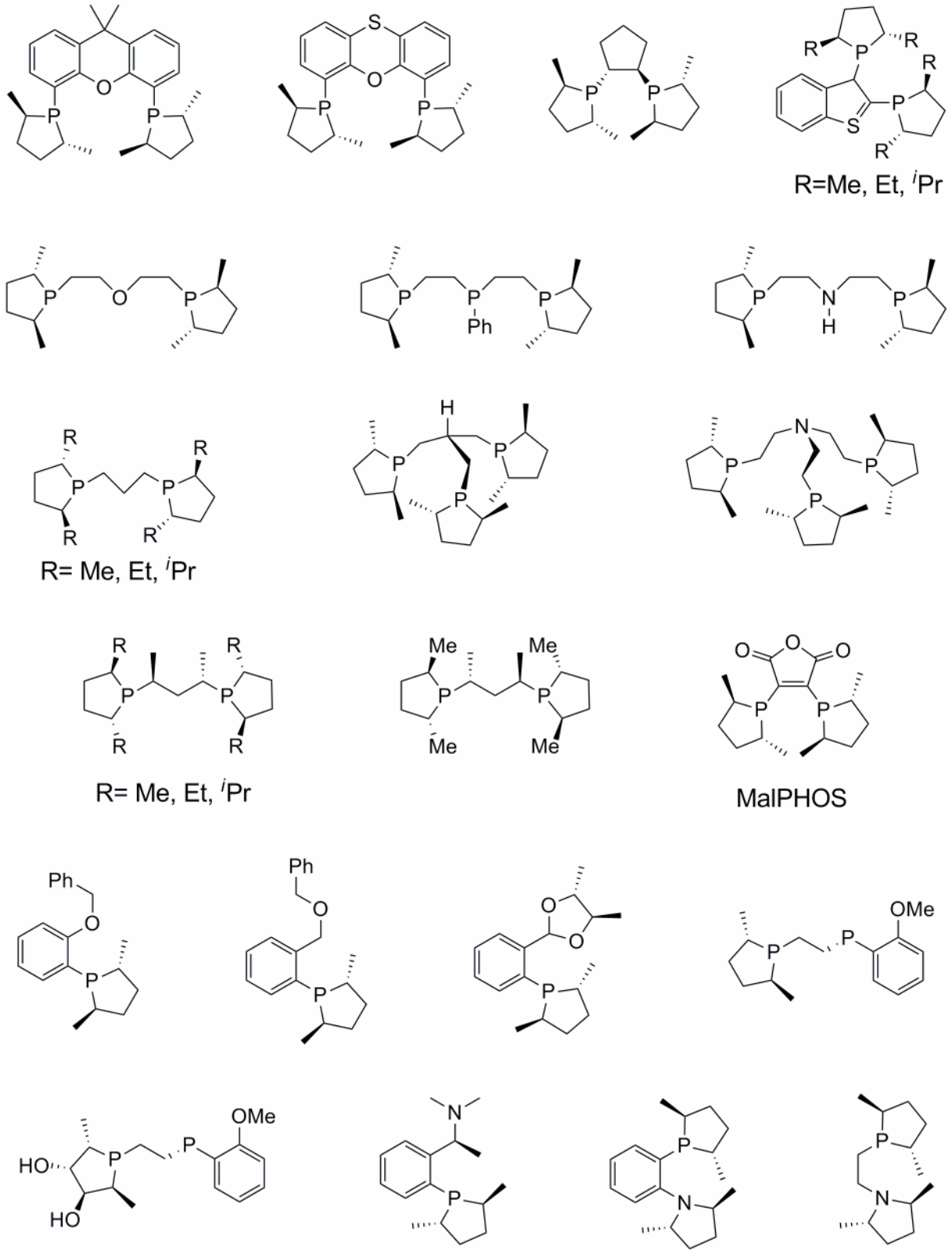


Fig. 4.2 Phospholane-based ligands

An interesting synthetic approach has been proposed by Stelzer and co-workers for the preparation of mixed ligands containing the phospholane motif. Indeed, a palladium-catalysed P-C bond forming reaction was used to introduce diphenylphosphine on *ortho*-bromoiodobenzene, as it was previously described by the same group.[19, 20] Subsequently, the *ortho*-bromide is lithiated and reacted with bis(dimethylamino)chlorophosphine. The intermediate obtained can be reduced to the primary phosphine, and the phospholane ring can be therefore introduced as previously shown[21] (fig. 4.3):

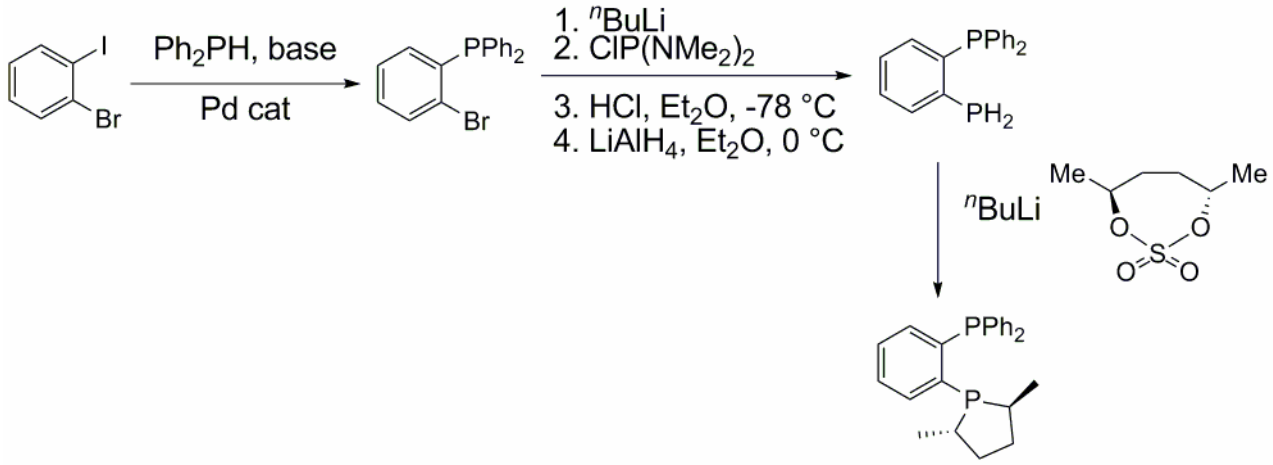


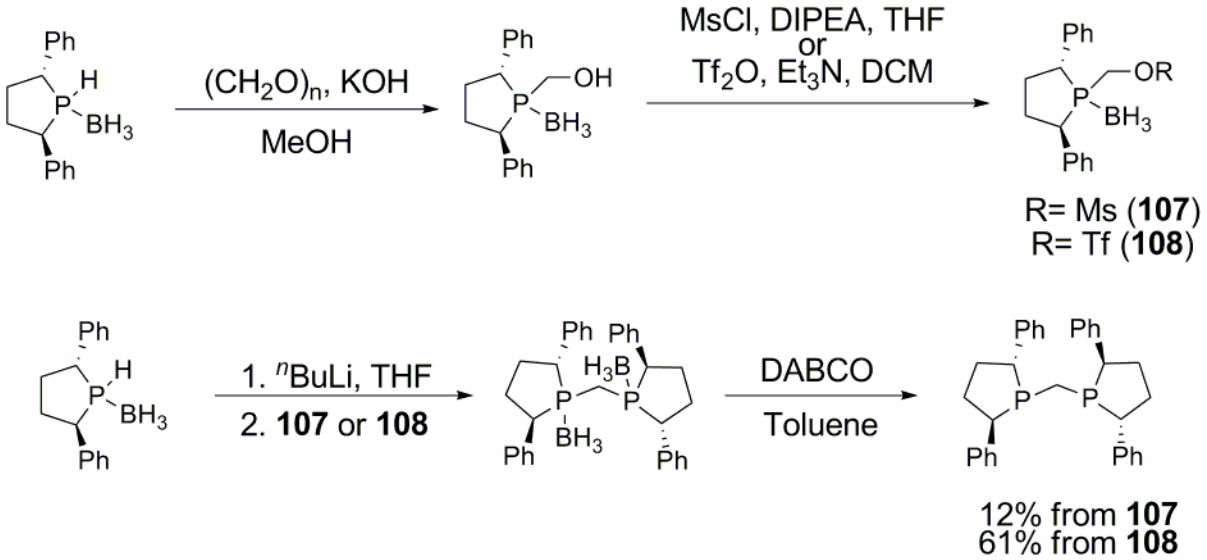
Fig. 4.3 Synthesis of C1 symmetric diphosphines containing the phospholane ring

It is possible to prepare derivatives of this ligand by simply modifying the diarylphosphine. Indeed, a similar synthetic pathway has also been employed by Saito and co-workers.[22]

4.2 Synthesis of phospholane-based ligands starting from different synthons

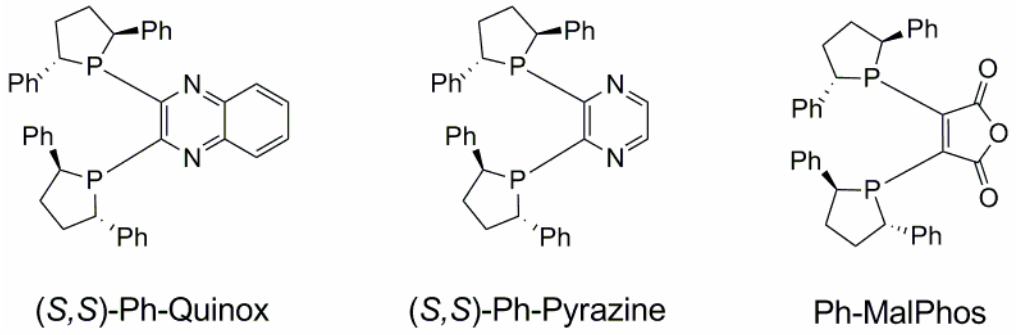
In the previous chapter (paragraph 3.2.3) the synthesis of Ph-BPE was described. It has been pointed out that the original synthetic pathway described by Burk and co-workers could not be used with 2,5-diphenylphospholane-based ligands because of the sensitivity of the corresponding cyclic sulfate towards basic conditions as well as racemisation. Therefore, the 2,5-phospholanic acid prepared by Fiaud and co-workers[23] has been used as starting material in the synthetic pathway for Ph-BPE (fig. 3.7 in paragraph 3.2.3).

A similar synthetic approach has been used for the synthesis of Ph-BPM (shown in fig. 4.4), a ligand that has given high enantioselectivities in the rhodium catalysed hydrogenation of alkenes and moderate ones in the ruthenium catalysed hydrogenation of imines:[24]



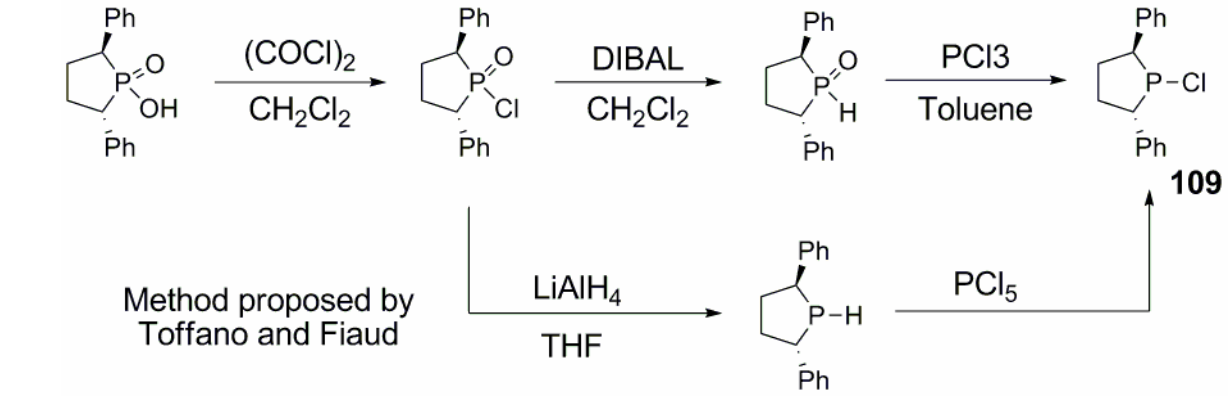
4.4 Synthesis of Ph-BPM

Other ligands have also been prepared at Chirotech, using this synthetic pathway, like Ph-Quinox, Ph-Pyrazine and Ph-MalPhos (fig. 4.5):



4.5 Some 2,5-diphospholane ligands synthetised at Chirotech

The bis-2,5-diphenylphospholane derivative of ferrocene was also prepared at Chirotech. The most straightforward way to prepare these sorts of ligands is by dilithiation of ferrocene followed by reaction of the dilithioferrocene with an electrophile.[1] This meant that the appropriate electrophile was needed and therefore, a synthetic procedure was developed at Chirotech to prepare 1-chlorophospholane (**109**) (fig. 4.6).[25] Fiaud, Toffano and co-workers proposed an alternative process to (**109**):[26]



4.6 Synthesis of (109) by Chirotech and alternative procedure proposed by Toffano and Fiaud

With this synthon (**109**) in their hand, the preparation of the ferrocene diphospholane ligand was achieved in reasonable yield.[25]

All the ligands prepared by Chirotech and described above (Ph-Quinox, Ph-Pyrazine and Ph_MalPhos) showed very high enantioselectivities in the rhodium catalysed hydrogenation of prochiral alkenes.

In the previous chapter, the rationale for Ph-DuPHOS synthesis was described (paragraph 3.2.3.1). Given the attractive combination of steric and electronic effects that Ph-BPE provides, we considered synthesising a range of phenyl-phospholane ligands, including the much sought after Ph-DuPHOS.

4.3 Results

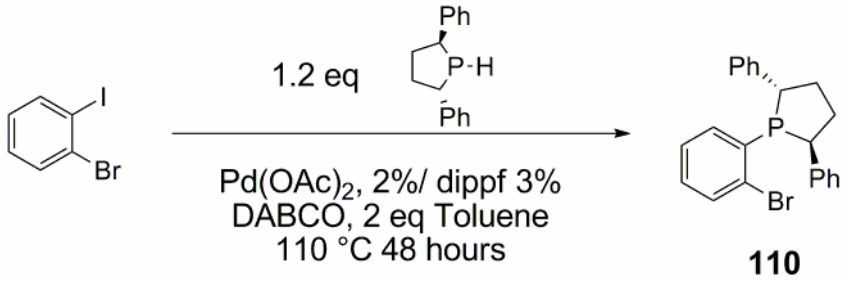
4.3.1 Attempts in the synthesis of Ph-DuPHOS

In the previous chapter (paragraph 3.3.6) an unsuccessful attempt in preparing Ph-DuPHOS by microwave accelerated Pd-catalysed P-C bond formation was described. Thus, different conventional procedures had to be considered.

In the previous pages, the synthesis of a variety of ligands from phospholanic acid was described. Indeed, the secondary phospholane could be used, either protected with borane or not, or the chlorophospholane (**109**) could also be prepared easily and in reasonably high yields, as shown in fig. 4.6. All these synthons were therefore prepared by us from the enantiomerically pure phospholanic acid provided by Chirotech.

At first, the synthesis of the monophospholane was attempted, with the idea of eventually using it as starting material for the synthesis of the desired Ph-DuPHOS.

The palladium catalysed coupling between 1-bromo-2-iodobenzene and the secondary phospholane was also attempted under conventional conditions (fig. 4.7), in light of the work that was previously carried out on model studies and that has been described in the previous chapter:



4.7 Attempt to prepare (110) using palladium catalysed cross-coupling

The reaction was run at first for 24 hours, but mainly starting material was observed by $^{31}P\{^{1}H\}$ NMR. The mixture was then heated for a further 24 hours. However mainly starting material was again observed, making this approach not ideal for the synthesis of (**110**). Therefore, different synthetic routes were tried, which are shown in fig. 4.8. Synthetic route A was adapted from the work reported by Reetz and co-workers,[27] whereas route B was considered on the basis of Knochel's work:[28] both of these routes led to the product, and the latter pathway was found to be more practical as very low temperature was not required.

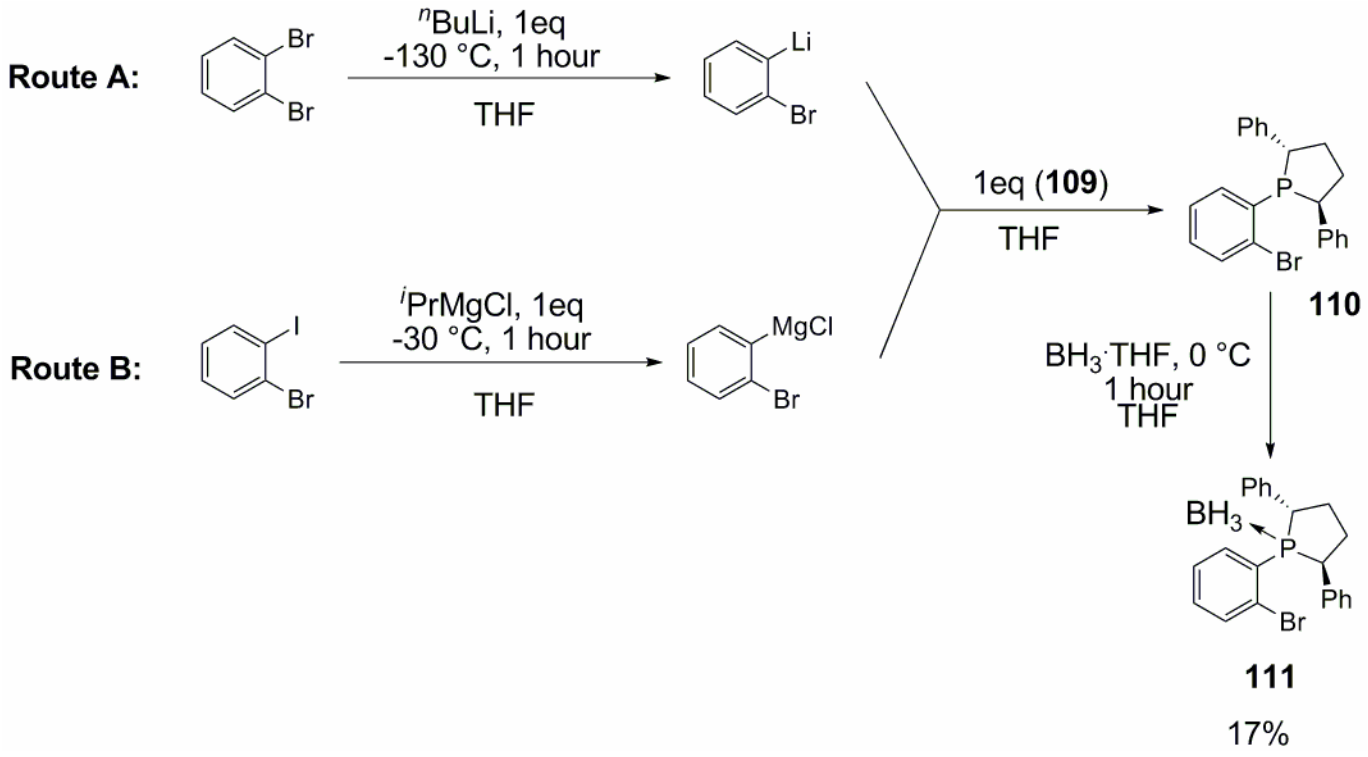


Fig. 4.8 Preparation of the monophospholane intermediate (111)

In both cases, monophospholane (**110**) was obtained in high conversions (as determined by $^{31}P\{^{1}H\}$ NMR). However, the phospholane borane (**111**) was prepared to ease purification by chromatography. The presence of oxidised species, recovered from the column, suggested that compound (**111**) is not stable to this purification procedure. Alumina was also used instead of silica for the chromatography, and the column was attempted at low temperature but with no improvements in yield.

Once intermediate (**111**) was prepared, the introduction of the second phospholane ring was attempted, as shown in fig. 4.9:

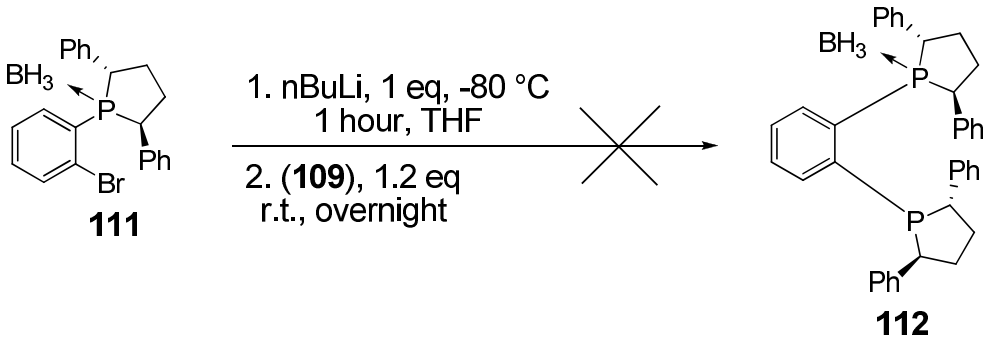


Fig. 4.9 Attempt to prepare Ph-DuPHOS from (28)

The conditions used were chosen considering the work of Urnezius and co-workers.[29] However mainly starting material was observed. The reaction was attempted by using isolated (**111**) as well as directly after borane protection of (**110**), without chromatography. The reaction was also tried on (**110**) but this was recovered unreacted at the end of the reaction.

The preparation of the Grignard reagent starting from both (**110**) and (**111**) was also attempted. Magnesium was previously activated either by stirring with a crystal of iodine for few hours or by treating in with catalytic amount of dibromoethane. However, upon addition of (**110**) and stirring of the reaction mixture at room temperature overnight, again only starting material was recovered (fig. 4.10):

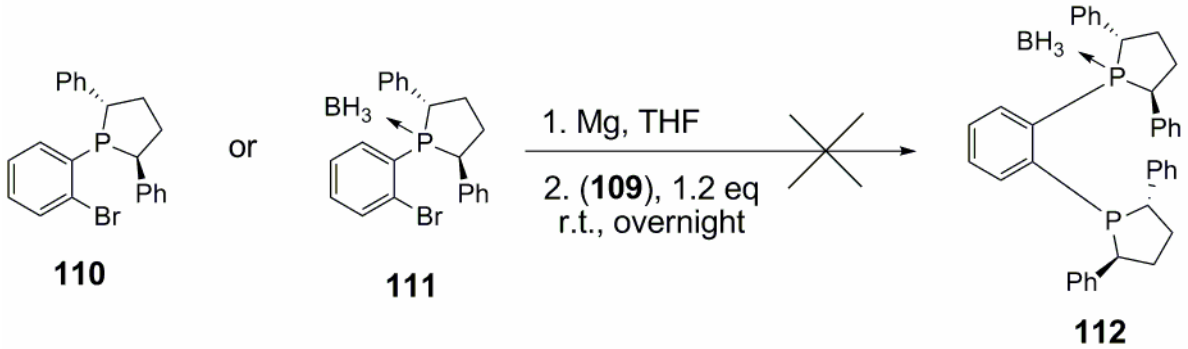


Fig. 4.10 Attempt to prepare Ph-DuPHOS preparing the Grignard from (110) or (111)

A couple of speculative attempts were also made in trying to obtain Ph-DuPHOS in a one pot reaction, as shown in fig. 4.11:

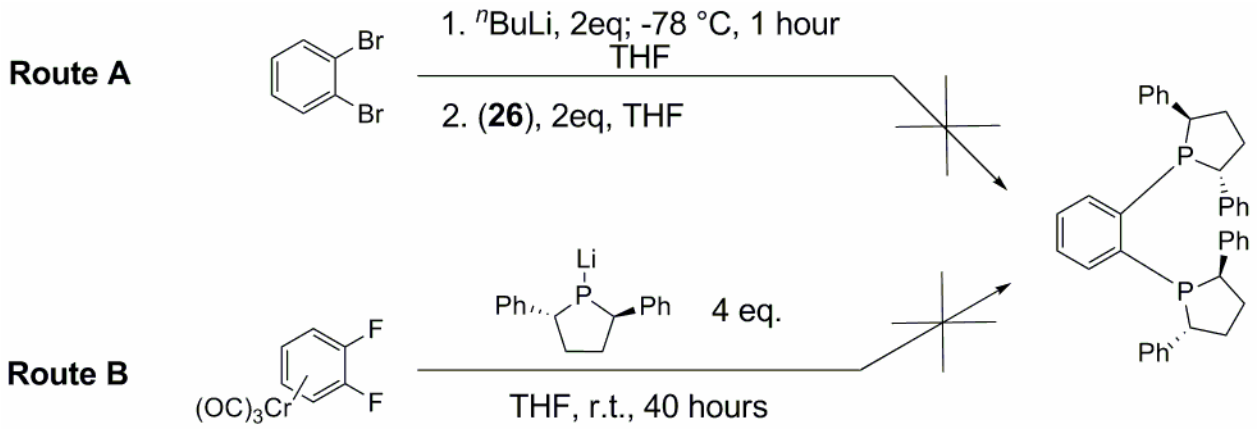


Fig. 4.11 Attempts in preparing Ph-DuPHOS in a one pot reaction

None of the routes shown in fig. 4.11 gave the desired product. Route B was considered in light of the work of Imamoto and co-workers, who prepared different phosphines using this nucleophilic aromatic substitution.[30]

All these unsuccessful attempts led us to conclude that Ph-DuPHOS can not be made using known procedures. It is possible to prepare the monophospholane intermediate, however it is not possible to introduce the second phospholane ring. The steric hindrance of the phospholane ring with the two phenyl groups in positions 2 and 5 might be the main reason why it is not possible to have the two substituents in *ortho* positions of the aromatic backbone.

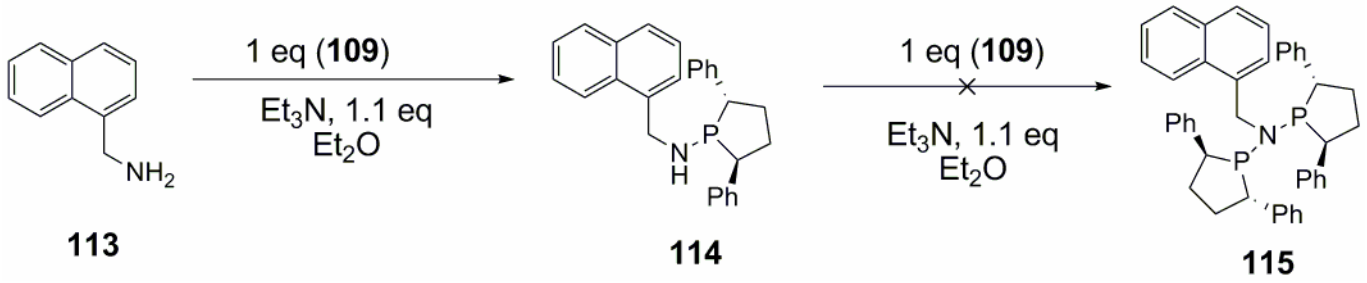
4.3.2 Synthesis of phospholane-based ligands

*4.3.2.1 Attempted synthesis of P-N-P ligand (**115**), and successful synthesis of a monodentate phosphine-amine*

The difficulties encountered in the synthesis of Ph-DuPHOS made us abandon that target. However, it was considered worthwhile to try to prepare different phospholane-based ligands, to eventually test in catalytic asymmetric synthesis.

Our first target was to prepare a P-N-P ligand with the two 2,5-diphenylphospholane moieties. Indeed, it was considered that a P-N-P ligand could positively affect the catalytic activity of the metal complex of the ligand, as this class of ligands has been found to improve performance in several reactions.[31-35]

Therefore, it was decided to prepare ligand (**115**), and the synthetic route shown in fig. 4.12 was used:



4.12 Attempt of synthesis of (115)

The monosubstituted compound (**114**) was obtained quantitatively. However the following step for the introduction of the second phospholane ring was not successful and starting material was recovered. The deprotonation of the secondary amine of (114) was also attempted using butyl lithium. However even this approach did not lead to the desired P-N-P ligand (**115**).

Purification of (**114**) was straightforward, by filtration through a short pad of silica to remove the excess of triethylamine. The monophospholane ligand is air sensitive, and extreme care is necessary during the purification procedure, to avoid formation of the oxide. Indeed, in one of the attempts, oxidation occurred of the intermediate (**114**). Crystals easily grew and were submitted for X-ray analysis (fig. 4.13):

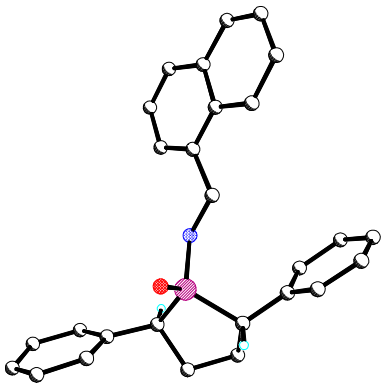
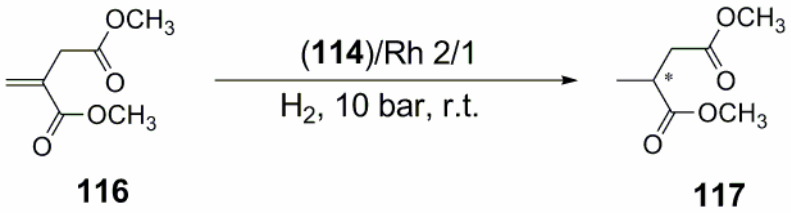


Fig. 4.13 X-ray of (114) oxide

Thus, only the monosubstituted compound (**114**) was obtained, whereas the P-N-P ligand (**115**) proved to be elusive. Even if this was not our target, it was decided to test the catalytic activity in rhodium catalysed asymmetric hydrogenation using this monodentate ligand, in light of the interesting results reported by Fiaud, Toffano and co-workers.[36]



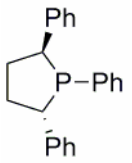
Scheme 4.1

Entry	% mol	Rh source	Solvent	Time (hours)	Conv. (%)	ee (%)[(a)]
1	0.05	$[Rh(COD)Cl]_2$	CH_2Cl_2	16	0	n.d.
2	0.05	$[Rh(COD)Cl]_2$	Toluene	16	<5	n.d.
3	0.5	$[Rh(COD)Cl]_2$	Toluene	16	<5	n.d.
4	0.5	$[Rh(COD)Cl]_2$	AcOEt	16	0	n.d.
5	0.5	$[Rh(COD)Cl]_2$	MeOH	16	100	<10
6	0.5	$Rh(COD)_2BF_4$	MeOH	16	100	65
7	0.5	$Rh(COD)_2BF_4$	MeOH	3	83	29

Table 4.1 Rhodium-catalysed hydrogenation using the monodentate ligand (114) L/Rh=2/1 (a) enantioselectivities were determined by HPLC using Chiral OD-H column

As it is reported in table 4.1, two different sources of rhodium were tested, with $Rh(COD)_2BF_4$ proving to be a better choice. Different solvents were also tried in the reaction, and it was in methanol that the best results were obtained. Furthermore, it was observed that with ligand (**114**), higher enantioselectivity was obtained under these conditions (entry 6), compared to the

enantioselectivity obtained by Fiaud, Toffano and co-workers, when ligand (**118**) was used (see entry 2, table 4.2):[36]



118

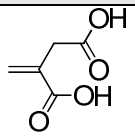
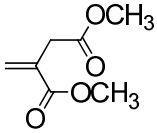
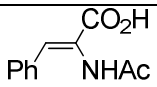
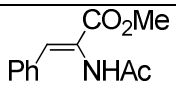
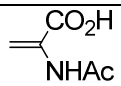
Entry[(a)]	Substrate	$T_{1/2}$	Conv. %	e.e. %
1		30	100	52
2		8	100	39
3		8	100	68
4		23	100	82
5		4	100	58

Table 4.2 Catalytic asymmetric hydrogenation using 118-Rh complex, reported by Fiaud and co-workers (a) All reactions were carried out in methanol, at room temperature in the presence of 1 mol % of the catalyst, under 1 bar of H_2

Once the reaction conditions were optimised, other substrates were tested, some of which are common substrates used when testing rhodium catalysed hydrogenation of olefins (table 4.3, entries 1 and 2), whereas other ones are intermediates for pharmaceutical compounds (table 4.3, entries 3-5). These results are reported below in table 4.3:

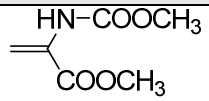
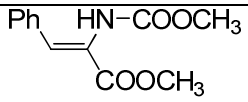
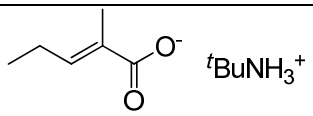
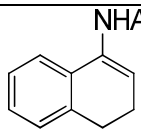
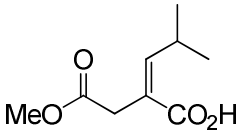
Entry[a]	Substrate	Conv. (%)	ee (%)[c]
1[b]		90	16
2		20	69
3		8	26
4		70	5
5		0	n.d.

Table 4.3 Rhodium catalysed hydrogenation on different substrates using (37) as ligand (a) (**37**)/$Rh(cod)_2BF_4$ 2/1, 0.005 mmol % catalyst, 2 mmol substrate, 3 hours, 10 bar H_2, MeOH, r.t; (b) After 16 hours 100 % conversion and 2 % ee were obtained; (c) enantioselectivities were determined by GC.

The monodentate ligand (**114**) did not prove to be exceptional in rhodium catalysed hydrogenation of different olefins: reasonable enantioselectivity was obtained with substrate in entry 2, even if better results were obtained by Fiaud, Toffano and co-workers on this substrate (see entry 4, table 2). The pharmaceutical intermediates were not hydrogenated successfully (entries 3-5). Thus, even if some activity was observed in the hydrogenation of olefins using the monodentate ligand (**114**), it was not considered good enough to justify further investigation.

*4.3.2.1 Synthesis of ligand (**119**)*

In the previous paragraph all the attempts in trying to prepare Ph-DuPHOS are described. However, none of those methods allowed us to get to our target ligand. It was then decided to prepare a ligand structurally similar to Ph-DuPHOS, *i.e.* a diphospholane-based ligand with a rigid backbone.

We considered that a xylene backbone could confer some rigidity to the ligand. Moreover, it was reasoned that from a synthetic point of view, this ligand should be readily accessed, as the two diphenylphospholane rings are further apart, reducing problems with steric hindrance limiting the introduction of the second phospholane ring, as possibly happened in the attempts of synthesising Ph-DuPHOS.

The xylyl-bis(diphenylphospholane) ligand (**119**) was prepared as shown in fig. 1.14:

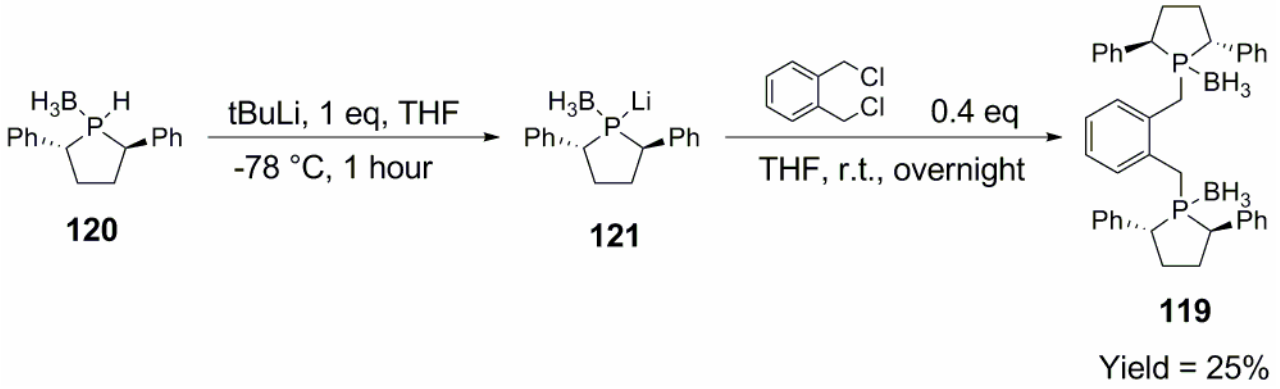


Fig. 1.14 Synthesis of ligand (119)

The pure product (**119**) was obtained, even if only in 25% isolated yield. A $^{31}P\{^{1}H\}$ NMR spectrum of the reaction mixture revealed that product (**119**) was the main product, along with some unidentified minor impurities. Therefore, purification was required. Column chromatography was performed to isolate the product and it is likely that the loss of the borane during the isolation procedure significantly lowered the yield.

The reaction was also attempted with the secondary phospholane without borane protection, but higher yields were obtained when using pure (**120**). Moreover, the starting material (**120**) could be generated *in situ* making the overall synthesis more convenient although chromatography was still required. The borane-protected diphospholane (**119**) was deprotected by using $HBF_4{\cdot}OMe_2$, which gave full conversion to the deprotected ligand. Tertiary amines were also tried for the deprotection, but proved to be less effective as some borane remained.

The bidentate ligand prepared (**119**) was briefly tested in rhodium catalysed asymmetric hydrogenation. However poor enantioselectivity was observed (as is shown below in table 4.4):

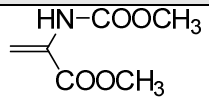
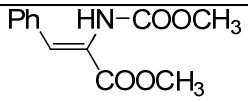
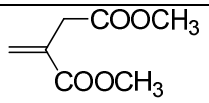
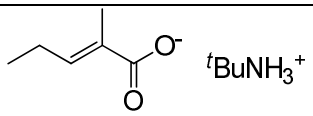
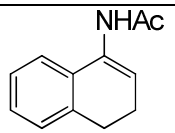
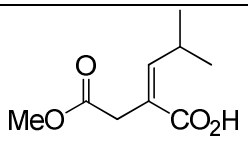
Entry[a]	Substrate	Conv. (%)	ee (%)[b]
1		100	37.5
2		100	0
3		100	0
3		88	28
4		100	37.5
5		0	n.d.

Table 4.4 Rhodium catalysed hydrogenation on different substrates using (37) as ligand (a) (**37**)/$Rh(cod)_2BF_4$ 2/1, 0.005 mmol % catalyst, 2 mmol substrate, 3 hours, 10 bar H_2, MeOH, r.t.; (b) enantioselectivities were determined by GC.

It was then decided to test the catalytic activity of the ligand in palladium catalysed enantioselective hydroxycarbonylation, since xylene backboned ligands are uniquely effective in the related methoxycarbonylation of ethylene, and recent results from our group suggested that a bulky diphosphine such as (**119**) might perform well.

4.3.3 Hydroxycarbonylation of styrene

Fig. 4.15 Hydroxycarbonylation of alkenes

Hydroxycarbonylation of alkenes allows the direct synthesis of carboxylic acids: indeed, according mainly to the catalyst used, it is possible to prepare either branched or linear acids, as is shown in fig. 4.15. One of the most important applications of hydroxycarbonylation of alkenes is to convert vinylarenes into branched carboxylic acids, which can be useful synthetic building blocks, but in particular they represent an important class of anti-inflammatory agents. Many routes have been described for the preparation of these compounds,[37] but a regioselective hydroxycarbonylation

followed by a classical resolution to separate the two enantiomers has been found to be commercially viable, and is used in the production of for example (*S*)-Naproxen. Therefore, this catalytic reaction has attracted the attention of the scientific community, with the aim to develop this process in both regio- and stereoselective.[38]

Two mechanism were initially reported in the literature and have been well described in a review by Claver, van Leeuwen and co-workers (fig. 4.16):[39]

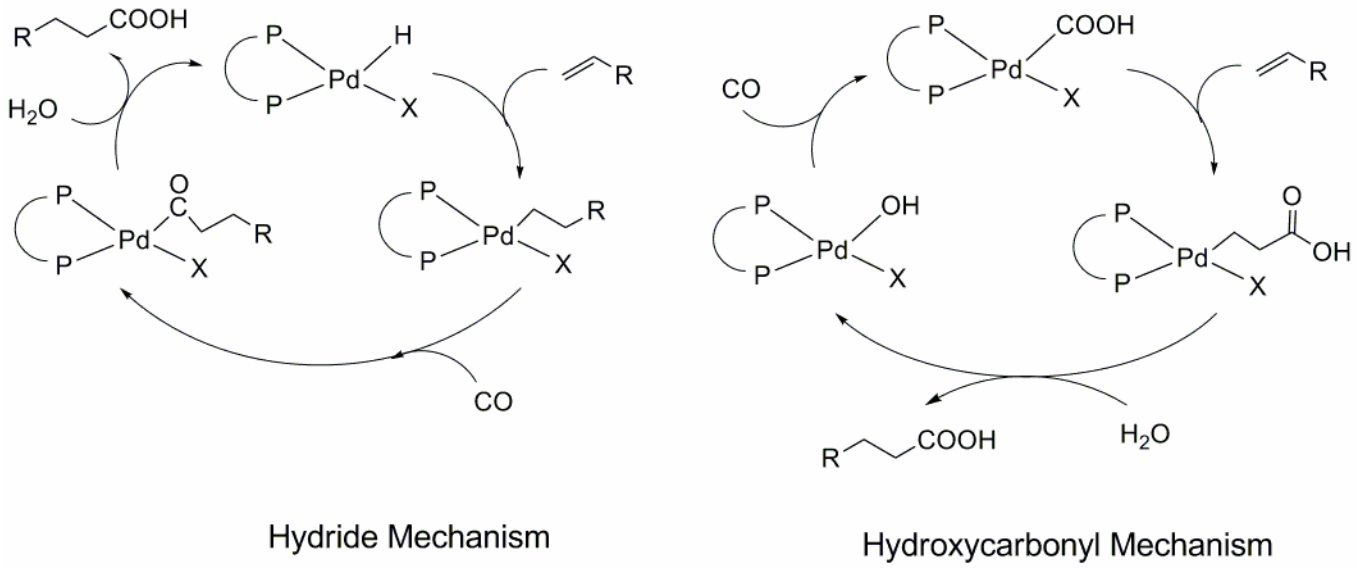


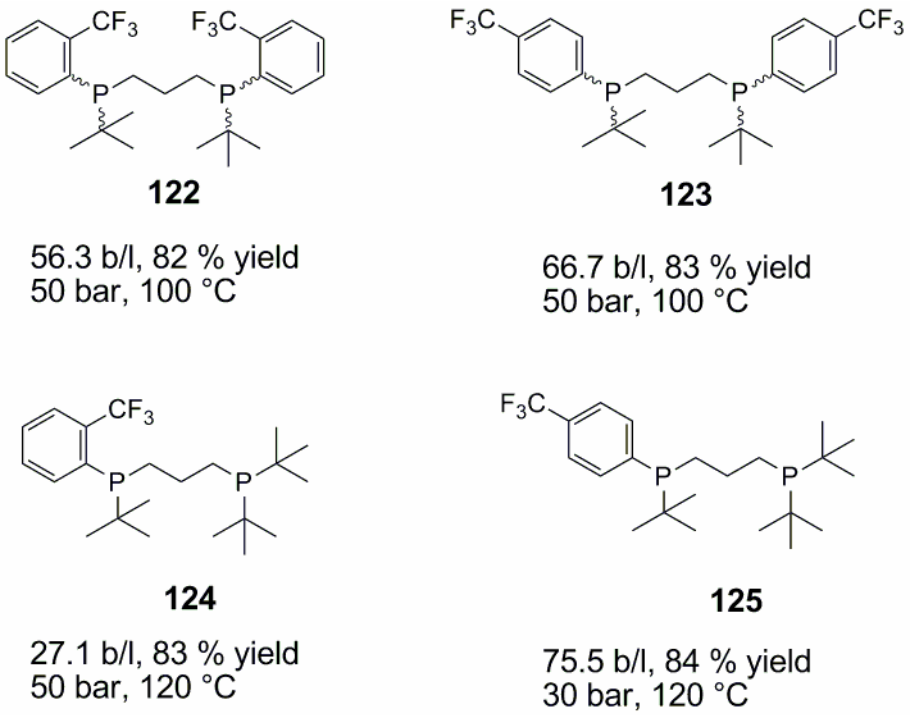
Fig. 4.16 Simplified mechanisms for the the two proposed hydroxycarbonylation mechanism

The hydride mechanism starts with the alkene insertion into a palladium hydride bond and ends with hydrolysis to yield the acid. The hydroxycarbonyl mechanism starts with alkene insertion into the palladium hydroxycarbonyl bond before hydrolysis followed by CO insertion into the palladium hydroxyl bond to regenerate the active species. The hydride mechanism is considered to be more likely, as described by Claver, van Leeuwen and co-workers.[39]

Several studies have been also carried out to investigate suitable ligands to yield both regio- and stereoselectivity, and this has led to the findings that, in general, monodentate phosphines favour the production of the branched product[40-42] whereas bidentate ligands favoured the synthesis of linear acids.[39, 41, 43] However, the use of monodentate ligands allows much less control of stereochemistry of the reaction. An attempt has been reported by Claver and co-workers, to prepare highly hindered monodentate phosphetanes, with the aim to use their limited freedom for achieving high enantioselectivity. High selectivity towards the branched product was observed (up to 99:1) though low enantioselectivities (up to 29 % e.e., at 94 % conversion, b:l=97:3) have been obtained.[44] Bidentate ligands were also tested in the hydroxycarbonylation of styrene, achieving, as expected, lower regioselectivity compared to monodentate ligands, though low enantioselectivities

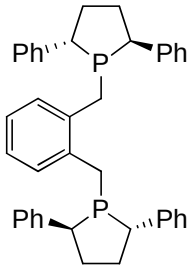
were reported as well. To the best of our knowledge, for hydroxycarbonylation of styrene using bidentate ligands the highest selectivity is 11 % e.e. using BINAP.[43]

Even if the aforementioned work of Claver and co-workers did not prove to be successful,[44] it prompted Clarke and Frew to prepare bulky bidentate ligands, to eventually test in this catalytic reaction. These bulky bidentate ligands shown in fig. 4.17 gave indeed good selectivity towards the branched product:[45]



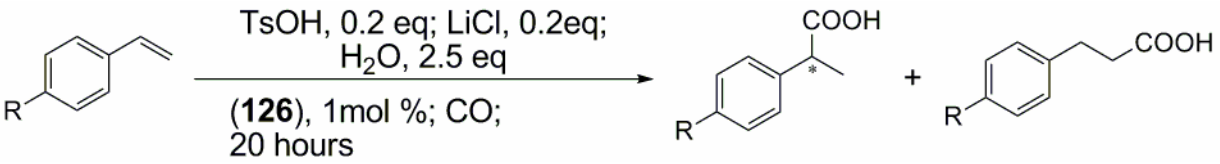
4.17 Bidentate ligands used by Frew and Clarke in hydroxycarbonylation

The palladium dichloride complexes of both ligands (**122**) and (**123**) proved to be very active in hydroxycarbonylation, giving good isolated yields and in particularly the palladium complex of ligand (**124**) gave high conversion to the product (98.7%) and unexpectedly high branched to linear ratio (75.5:1), using 50 bar of CO and running the reaction at 100 °C for 16 hours. The ligands shown in figure 4.17 are racemic. Another ligand that gave promising although slightly less impressive results was 1,2-bis-ditertiarybutyl-phosphinoxylene. Therefore it was considered that the deprotected enantiopure diphospholane ligand (**126**) could give good regioselectivity, because of its bulkiness and moreover enantioselectivity might also be obtained.



126

In the reactions performed by Frew, LiCl and para-toluensulphonic acid (TsOH) were employed, in light of the conditions previously used by Chaudhari and co-workers using PPh_3 derived catalysts.[41] It was also pointed out that the presence of these promoters is fundamental for the achievement of good yields and good branched to linear ratios. Different promoters were also investigated, but TsOH and LiCl proved to be the combination of choice. Moreover, methylethylketone was used as the solvent to allow the reactants, catalyst and promoters to give a homogeneous solution. These conditions were also used in this present study, to get comparable results, with the only difference being the catalyst (table 4.5). The palladium dichloride catalyst was preprared directly before the catalytic reactions by mixing ligand (**126**) with $[PdCl_2(MeCN)_2]$ in DCM followed by removal of solvent. $^{31}P\{^1H\}$ NMR monitoring confirmed that the ligand is transformed into a complex that is tentatively assigned as [Pd(**126**)Cl_2], although it was not isolated.



Scheme 4.2

Entry	R	Temp. °C	P. (bar)	Yield	b/l	ee %[(b)]
1	H	100	50	53	29/1	20
2	H	150	50	15	25/1	n.d.[(a)]
3	^{t}Bu	100	50	44	Branched	41
4	H	120	50	<5	21/1	n.d.[(a)]
5	^{t}Bu	120	50	12	Branched	49.6
6	^{t}Bu	120	30	19	15/1	n.d.[(a)]
7	^{t}Bu	100	30	10	Branched	n.d.[(a)]

Table 4.5 Hydroxycarbonylation using (126) as the catalyst (a) enantioselectivities not determined due to insufficient amount of product; (b) Enantioselectivities were determined by adding 0.5 eq of optically active DPEN with respect to the acid.

By using $[PdCl_2(MeCN)_2]$/(**126**) in the hydroxycarbonylation of styrene, it can be highlighted that at 50 bar, the branched to linear ratio is still unusually high for a diphosphine system (entries 1 and

2). For the hydroxycarbonylation of styrene, it is considered that a bidentate catalyst is expected to give very poor branched selectivity.

At higher pressure, 100 °C gave higher yields (entry 1), whereas at higher temperatures the yields drop (entries 2 and 4). Enantioselectivities were not easily determined, as the reaction had to be run on a very small scale, since only bare minimum of catalyst was prepared. It was noticed that higher enantioselectivities were obtained when performing the hydroxycarbonylation on *para*-tertbutylstyrene (entries 5 and 3). Moreover, by using this latter substrate, the same temperature dependence with the better yield and regioselectivity being obtained at 100 °C at 50 bar pressure (entry 3 compared to entry 5). At 30 bar pressure a better yield was obtained at higher temperature (entries 6 and 7).

With the aim to improve the regio- and stereoselectivity in the hydroxycarbonylation, it was considered that a bidentate ligand with two different phosphorus-based moieties could lead to more successful results. This idea stems from considering that in Frew's work, the best yield and regioselectivity were obtained when using the non-symmetric diphosphine (**125**). Therefore, it was proposed to prepare a similar ligand, with the phospholane ring in place of the aryl-*tert*butylphosphine moiety.

Thus, phosphine borane (**127**) was prepared, using the synthetic route shown in fig. 4.18:

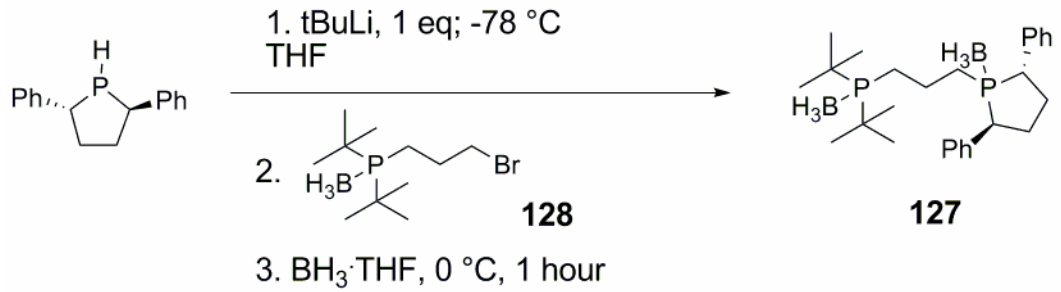


Fig. 4.18 Synthesis of (127) Reagent (**128**) was added to the lithiated phospholane keeping the reaction at -78 °C; the reaction was run for 60 hours.

(**127**) was obtained in very poor yield (18%), the loss of the borane group during purification of the product being a major issue, and due to shortage of reagents and the overall inefficiency of this synthesis it was not possible to prepare sufficient amount to test it in hydroxycarbonylation. Crystals easily formed and in fig. 4.19 the X-ray structure is shown:

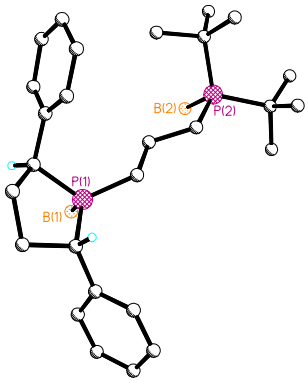


Fig. 4.19 X-ray of the borane protected ligand (127)

4.3.4 Mechanistic studies on the hydroxycarbonylation of styrene

In the last paragraph it has been pointed out the need of LiCl and TsOH as promoters in the hydroxycarbonylation, in order to achieve high yields and good branched to linear ratios.[41] Few research groups have investigated the role of the promoters in the hydroxycarbonylation. Sheldon and co-workers showed that the reactivity of the catalyst increases when weakly coordinating anions are used: they proposed that this is due to the occupation of free coordination sites on the palladium which inhibits the coordination of the reactants.[40,46] Moreover, the regioselectivity of the reaction is also affected by the nature of the counter anion of the acid used as co-catalyst. Indeed, it has been observed that coordinating anions like chloride favours the formation of the branched acids, but with low activity, whereas weakly coordinating anions favours the formation of linear acids.[47,48] Claver and co-workers also observed that the regioselectivities generally obtained for mono- and diphosphines (branched and linear respectively) can be different depending on the nature of the counter anion (table 4.6):[48]

Entry	Acid	Ligand	% Conversion	b/l
1	TsOH	PPh_3	89	25/75
2		dppb	18	26/74
3	HCl	PPh_3	90	100/0
4		dppb	31	22/78
5	HBr	PPh_3	49	97/3
6		dppb	23	50/50
7	HI	PPh_3	14	85/15
8		dppb	61	60/40

Table 4.6 Pd catalysed hydroxycarbonylation of styrene in the presence of PPh3 or dppb: influence of the acidic medium

Indeed, from Claver's results shown in table 4.6, it is possible to observe that in the presence of TsOH or HCl as acidic medium, the regioselectivity is as expected, towards the linear product when a bidentate ligand is used (entries 2 and 4) and towards the branched product when a monodentate ligand is used (entries 1 and 3). However, in the presence of HBr and HI it is noticed that by using a bidentate ligand, the linear acid is not the main product of the reaction as it would be expected.
Therefore it is likely that the reaction mechanism of hydroxycarbonylation depends on the nature of both the counter anion and the phosphine. This observation is of particular interest as it would be ideal to use a diphosphine ligand (which allows more control of stereochemistry of the reaction) with the optimum promoter, in order to increase both the regio- and enantioselectivity. Thus, an investigation on the mechanism of the hydroxycarbonylation was considered necessary. Besides, we were really intrigued by the work of Chaudhari and co-workers, in which it was suggested a different role of LiCl. Indeed, it was shown that the carbonylation of 1-(4-isobutylphenyl)ethanol to give the branched acid (Ibuprofen) might proceed by the formation of 4-isobutylstyrene at first, and then of 1-(4-isobutylphenyl)-chloride (fig. 4.20):

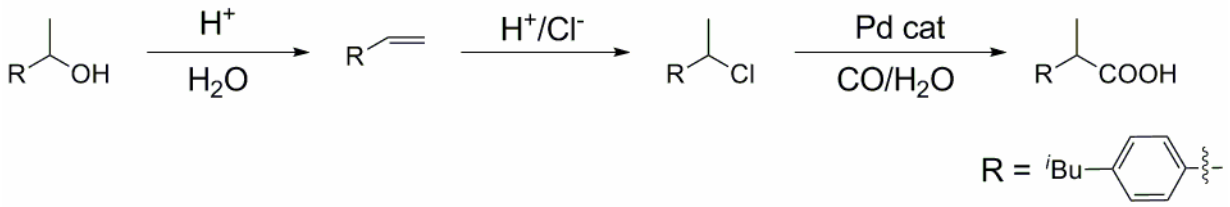


Fig. 4.20 Formation of 1-(4-isobutylphenyl)-chloride as intermediate for carbonylation, proposed by Chaudhari and co-workers

To support this mechanism, they run the carbonylation of 4-isobutylstyrene in the presence of TsOH only and they observed that after 6 hours only traces of the product formed. On the other hand, when the reaction was run in the presence of both TsOH and LiCl, enhanced rate was observed, together with high regioselectivity towards the branched product. Moreover, 1-(4-isobutylphenyl)-chloride was also placed under hydroxycarbonylation conditions and it was noticed that the addition of catalytic amounts of TsOH led to the branched product (excess of TsOH gave 4-isobutylstyrene), as well as it happened by adding both TsOH and LiCl. When no promoters were added, the hydroxycarbonylation of 1-(4-isobutylphenyl)-chloride resulted significantly slow.[42,49,50] This work appeared very interesting, as it would mean that the high selectivity for the branched product would in part depend on the Markovnikov addition of HCl to the double bond, before any catalysis takes place. In figure 4.21, the mechanism proposed by Chaudhari and co-workers is shown:

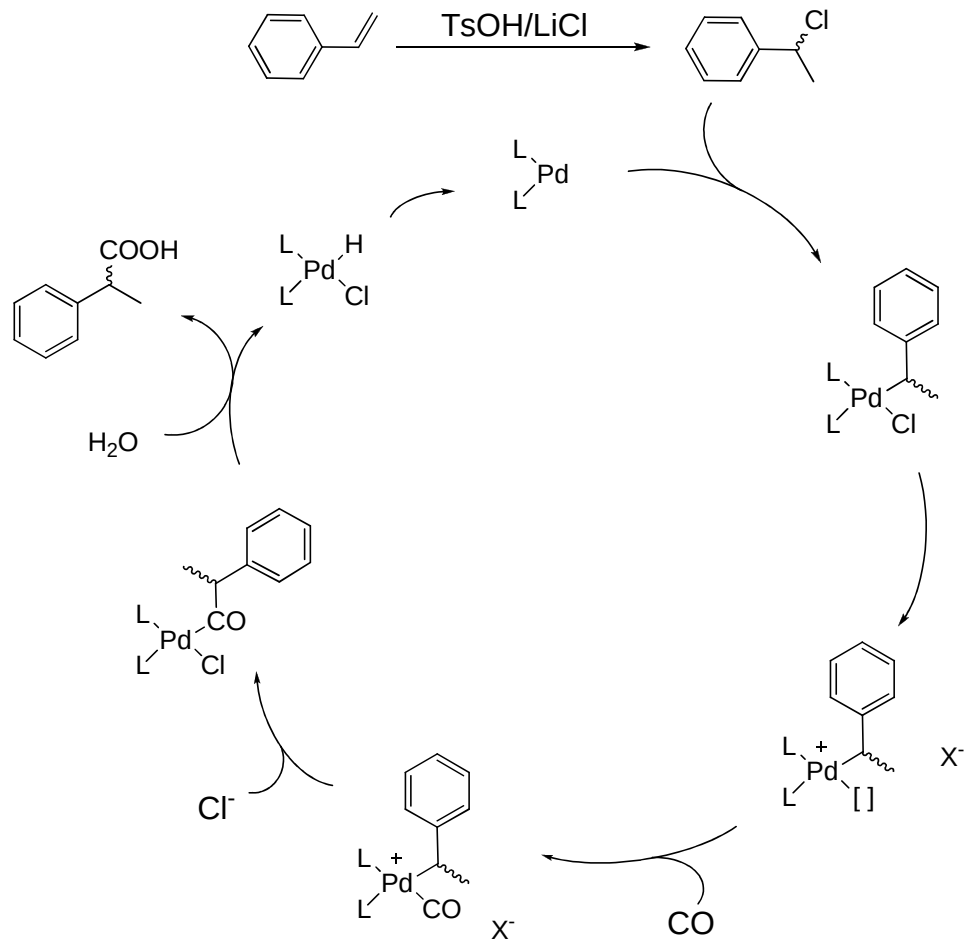
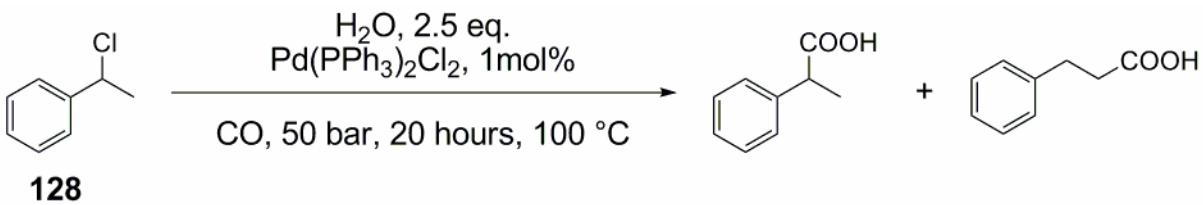


Fig. 4.21 Hydroxycarbonylation mechanism proposed by Chaudhari and co-workers

However, we considered that not enough evidence was shown to support their conclusions. In fact, we considered possible the formation of the chloride intermediate as they proposed, but we envisaged that it was necessary to investigate if that was actually the active intermediate as Chaudhari and co-workers stated.

Thus, it was decided to prepare (1-chloroethyl)benzene (**128**) and to hydroxycarbonylate it, in order to see if the product would form (see scheme 4.3). Four different reactions were run: in the presence of both TsOH and LiCl (entry 1, table 4.7), with no promoters at all (entry 4, table 4.7), by adding only TsOH (entry 3, table 4.7) and by adding only LiCl (entry 2, table 4.7):



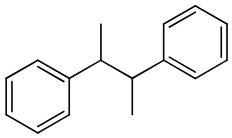
128

Scheme 4.3

Entry	TsOH, mol %	LiCl, mol %	Yield	b/l
1	20	20	n.d.	n.d.
2	0	20	n.d.	n.d.
3	20	0	Traces of acid[(b)]	-[(a)]
4	0	0	n.d.	n.d.

Table 4.7 Hydroxycarbonylation of (1-chloroethyl)benzene with different promoters' systems (a) yield and b/l were not determined due to insufficient amount; (b) The presence of the acid was detected by GC-MS in very low yield.

After running the reaction for 20 hours, neither the branched nor the linear acid formed, no matter if both TsOH and LiCl or either of the two were present or not. The starting material (**128**) was consumed, giving products, that possibly are due to its polymerisation.

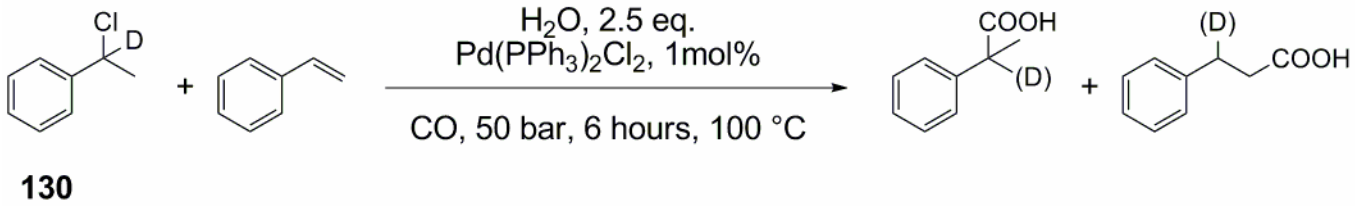


129

GC-MS and ^{1}H NMR are consistent with compound (**129**) being formed as the major product of the reaction. However this compound was not isolated and fully characterised.

To further confirm that (**128**) is not the active substrate of the reaction, but also to verify if styrene is the species that undergoes hydroxycarbonylation to give the acid, a new experiment was considered. It was decided to prepare the deuterated form of (1-chloroethyl)benzene and to run the hydroxycarbonylation reaction on the equal mixture of this deuterated substrate (**130**), together with styrene (see scheme 4.4). The hydroxycarbonylation was stopped after 6 hours, with the aim to identify any possible intermediate that might form in the early stages of the reaction and to compare the degree of the deuterium in the product acid, if any. We envisaged that this experiment would give us information on which catalytic cycle occurs. In fact, if the Chaudhari mechanism took place, the deuterated acid would be expected to be the main product, as it would formed from the deuterated form of (1-chloroethyl)benzene. Only a small amount, if any, of non- deuterated acid (formed from styrene) would be expected after 6 hours, as it would be necessary first the conversion of styrene to its active intermediate, (1-chloroethyl)benzene, making this pathway longer. On the other hand, if the hydride mechanism occurred, the non-deuterated form of the acid would be expected as the main product after 6 hours, with possibly a small amount of deuterated acid, coming from the deuterated styrene formed from the reduction of the deuterated (1-chloroethyl)benzene.

As in the previous experiments, all the four different combinations with the two promoters TsOH and LiCl were tried (table 4.8):



Scheme 4.4

Entry	PTSA, mol %	LiCl, mol %	Isolated yield (%)	b/l
1	20	20	26 (non-deuterated acid)	46/1
2	20	0	18 (non-deuterated acid)	1.2/1
3	0	20	Trace of product[(b)]	-[(a)]
4	0	0	18 (non-deuterated acid)	20/1

Table 4.8 Hydroxycarbonylation of the equal mixture of (130) and styrene (a) b/l ratio not determined due to insufficient amount; (b) The presence of the acid was confirmed by GC-MS.

This procedure led us to identify the presence of deuterated styrene, when the reaction was run either in the presence of solely TsOH (entry 2), or when none of the promoters was present (entry 4). By GC-MS the formation of (**128**) was not detected, suggesting that the reaction is not likely going through (**128**) to form the acid. To further support this latter observation, it was noticed that the product formed did not present deuterium, leading us to the conclusion that it formed from styrene and not from the deuterated starting material (**130**).

These results disprove the idea proposed by Chaudhari and co-workers, that the role of TsOH and LiCl is to form the chloroethyl benzene, which in turn can act as the active substrate. Maybe some chloroethyl benzene forms from styrene, but from these results it is possible to consider this equilibrium towards styrene. Moreover, from these results it is also possible to confirm the role of the promoters aforementioned. Indeed, when only TsOH is added (entry 2), only a small amount of branched acid is formed, supporting the proposed idea that non strongly coordinating acids favour the formation of the linear product. When only LiCl is added (entry 3), only traces of product are observed, confirming that strongly coordinating promoters negatively affect the catalytic activity in the hydroxycarbonylation. The higher conversion to the acid and the best branched to linear ratio is obtained when both the promoters are present (entry 1). This might be due to the fact that chloride is no longer free to act as coordinating anion which decreases the reaction rate, but in the presence of TsOH is likely to form HCl.

Finally, when both the promoters are not present, only a small amount of the product is formed, suggesting that the rate of the reaction is significantly decreased.

With these experiments it was possible to confirm that the hydroxycarbonylation of styrene does not proceed through chloroethyl benzene. The promoters are important as they affect the rate and the

regioselectivity of the reaction. A fine balance between strong enough coordinating anion to give branched selectivity, but not so strong as to deactivate the catalyst is needed.

4.4 Conclusions

In this chapter the synthesis of different bis-2,5-diphenylphospholane-based ligands was described. Their catalytic activity was tested in both hydrogenation and hydroxycarbonylation. It was reasoned that none of the ligands prepared and tested in the rhodium catalysed hydrogenation of alkenes could be considered the catalyst of choice.

The importance of hydroxycarbonylation was also pointed out, and the interest in a bidentate ligand for obtaining the branched acid in high stereoselectivity was also highlighted, although the existing literature suggests that only monodentate ligands favour the formation of the branched product.

Previous results in the group provided the basis for using optically active bidentate phospholane-based ligands for the palladium catalysed hydroxycarbonylation of alkenes. Reasonably good results were obtained, if it is considered the challenging nature of this reaction. Indeed, these results could constitute the basis for further investigations in this catalytic reaction, by using different conditions and different bulky catalysts. The e.e. and regioselectivity obtained appear to be the best reported to date for hydroxycarbonylation of styrene using bidentate ligands.

Finally, in order to gain some more information about the mechanism of hydroxycarbonylation, and in particular about the role of the promoters, some mechanistic experiments have been carried out and the results obtained confirm that the reaction is likely to occur through the hydride mechanism.

4.5 References

1 M. J. Burk, M. F. Gross, *Tet. Lett.*, 1994, **35**, 9363.
2 M. J. Burk, *J. Am. Chem. Soc.,* 1991, **113**, 8518.
3 M. J. Burk, J. E. Feaster, W. A. Nugent, and R. L. Harlow, *J. Am. Chem. Soc.,* 1993, **115**, 10125.
4 U. Berens, U. Englert, S. Geyser, J. Runsink, and A. Salzer, *Eur. J. Org. Chem.,* 2006, 2100.
5 A. Zhang, and T. V. RajanBabu, *Org. Lett.*, 2004, **6**, 1515.
6 J. Holz, A. Monsees, H. Jiao, J. You, I. V. Komarov, C. Fischer, K. Drauz, and A. Borner, *J. Org. Chem.,* 2003, **68**, 1701.
7 P. C. J. Kamer, P. W. N. M. van Leeuwen, and J. N. H. Reek, *Acc. Chem. Res.*, 2001, **34**, 895.
8 E. Fernandez, A. Gillon, K. Heslop, E. Horwood, D. J. Hyett, A. G. Orpen, and P. G. Pringle, *Chem. Comm.,* 2000, 1663.
9 M. J. Burk, A. Pizzano, J. A. Martin, L. M. Liable-Sands, and A. L. Rheingold, *Organometallics*, 2000, **19**, 250.
10 M. Nandi, J. Jin, and T. V. RajanBabu, *J. Am. Chem. Soc.,* 1999, **121**, 9899.
11 D. Carmichael, H. Doucet, and J. M. Brown, *Chem. Comm.*, 1999, 261.
12 P. Dierkers, S. Ramdeehul, L. Barloy, A. De Cian, J. Fischer, P. C. J. Kamer, P. W. N. M. van Leeuwen and J. A. Osborn, *Angew. Chem. Int. Ed.*, 1998, **37**, 3116.
13 P. von Matt and A. PfaItz, *Angew. Chem. Int. Ed.*, 1993, **32**, 566.
14 N. Sakai, S. Mano, N. Kyoko, and H. Takaya, J. Am. Chem. Soc., 1993, **115**, 7033.
15 M. J. Burk, J. E. Feaser, and R. L. Harlow, *Tet. Asymm*, 1991, **2**, 569.
16 M. J. Burk, J. E. Feaser, and R. L. Harlow, *Organometallics*, 1990, **9**, 2653.
17 I. Toth, B. E. Hanson, and M. E. Davis, *Organometallics*, 1990, **9**, 675.
18 M. J. Burk, and R. L. Harlow, *Angew. Chem. Int. Ed.,* 1990, **29**, 1462.
19 D. J. Brauer, M. Hingst, K. W. Kottsieper, C. Liek, M. Tepper, T. Nickel, O. Stelzer, W. S. Sheldrick, *J. Organomet. Chem.*, 2002, **645**, 14.
20 D. J. Brauer, M. Hingst, K. W. Kottsieper, C. Liek, T. Nickel, M. Tepper, O. Stelzer, and W. S. Sheldrick, *J. Organomet.Chem.*, 2002, **645**, 14.
21 K. W. Kottsieper, U. Kuhner, O. Stelzer, *Tet. Asymm.*, 2001, **12**, 1159.
22 K. Matsumura, H. Shimizu, T. Saito, and H. Kumobayashi, *Adv. Synth. Catal.*, 2003, **345**, 180.
23 F. Guillen, M. Rivard, M. Toffano, J.-Y. Legros, J.-C. Daran, and J.-C. Fiaud, *Tetrahedron*, 2002, **58**, 5895.
24 M. Jackson and I. C. Lennon, *Tet. Lett.*, 2007, **48**, 1831.
25 M. E. Fox, M. Jackson, I. C. Lennon, J. Klosin, and K. A. Abboud, *J. Org. Chem.,*, 2008, **73**, 775.
26 A. Galland, J. M. Paris, T. Schlama, R. Guillot, J. C. Fiaud, and M. Toffano, *Eur. J. Org. Chem.*, 2007, 863.
27 M. T. Reetz, and A. Gosberg, *Tet. Asymm.*, 1999, **10**, 2129.
28 S. Demay, M. Lotz, K. Polborn and P. Knochel, *Tet. Asymm.*, 2001, **12**, 909.
29 N. Kongprakaiwoot, R. L. Luck, E. Urnezius, *J. Organomet. Chem.*, 2004, **689**, 3350.
30 K. Katagiri, H. Danjo, K. Yamaguchi, and T. Imamoto, *Tetrahedron*, 2005, **61**, 4701.
31 S. L. Parisel, N. D. Moorcroft, A. Jutand, D. J. Aldous b and and K. K. Hii, *Org. Biomol. Chem.*, 2004, **2**, 301.
32 W. Weng, C. Guo, R. Celenligil-Cetin, B. M. Foxman and O. V. Ozerov, *Chem. Comm.*, 2006, 197.
33 S. J. Dossett, D. F. Wass, M. D. Jones, A. Gillon, A. G. Orpen, J. S. Fleming, and P. G. Pringle, *Chem. Comm.,* 2001, 699.

34 E. Killian, K. Blann, A. Bollmann, J. T. Dixon, S. Kuhlmann, M. C. Maumela, H. Maumela, D. H. Morgan, P. Nongodlwana, M. J. Overett, M. Pretorius, K. Hoefener, and P. Wasserscheid, *J. Mol. Catal. A: Chemical*, 2007, **270**, 214.

35 J. T. Dixon, M. J. Green, F. M. Hess, and D. H. Morgan, *J. Organomet. Chem.*, 2004, **689**, 3641.

36 A. Galland, C. Dobrota, M. Toffano, and J. C. Fiaud, *Tet. Asymm.*, 2006, **17**, 2354.

37 J. P. Rieu, A. Boucherle, H. Cousse and G. Mouzin, *Tetrahedron*, 1986, **42**, 4095.

38 H. Alper, and N. Hamel, *J. Am. Chem. Soc.*, 1990, **112**, 2803.

39 I. del Rio, C. Claver, and P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.*, 2001, 2719.

40 G. Verspui, G. Papadogianakis, R. A. Sheldon, *Catal. Today*, 1998, **42**, 449.

41 A. Seayad, S. Jayasree, and R. V. Chaudhari, *Org. Lett.* 1999, **1**, 459.

42 S. Jayasree, A. Seayad, and R. V. Chaudhari, *Chem. Comm.*, 1999, 1067.

43 I. del Rio, N. Ruiz, C. Claver, L. A. van der Veen, and P. W. N. M. van Leeuwen, *J. Mol. Catal. A: Chemical*, 2000, **161**, 39.

44 B. Munoz, A. Marinetti, A. Ruiz, S. Castillon, C. Claver, *Inorg. Chem. Comm.*, 2005, **8**, 1113.

45 J. J. R. Frew, M. L. Clarke, U. Mayer, H. Van Rensburg, and P. T. Robert, *Dalton Trans.*, 2008, 1976.

46 G. Verspui, J. Feiken, G. Papadogianakis, R. A. Sheldon, *J. Mol. Catal. A: Chemical*, 1999, **146**, 299.

47 C. Bonnet, A. L. Monteiro, I. Tkatchenko, *J. Mol. Catal. A: Chemical*, 1999, **143**, 131.

48 I. del Rio, N. Ruiz, C. Claver, *Inorg. Chem. Comm.*, 2000, **2**, 166

49 S. Jayasree, A. Seayad and R. V. Chaudhari, *Catal. Lett.*, 1999, **61**, 99

50 S. Jayasree, A. Seayad, B. R. Sarkar, R. V. Chaudhari, *J. Mol. Catal. A: Chemical*., 2002, **181**, 221.

Conclusions

This thesis has focused on the synthesis of new ligands for use in catalytic asymmetric reactions. In particular, a new methodology that could lead to libraries of phosphine-based ligands in shorter time was desired, in light of the observation that the slow step in the development of new catalysts is not the screening of the catalysts but the synthesis of ligands. Thus, palladium catalysed C-C and P-C bond forming reactions were investigated, with the specific idea in mind of using the palladium catalysed P-C bond forming reaction for the synthesis of diphosphines, and the palladium catalysed C-C bond forming reaction for preparing derivatives of the diphosphines.

In addition, the increasing amount of scientific literature on the successful use of a microwave for speeding up cross-coupling reactions has prompted us to investigate these palladium catalysed reactions in the microwave.

This work began with the investigation of the microwave assisted Suzuki-cross coupling reaction of chloroarylphosphine oxides with phenylboronic acid. It had already been reported in literature that this reaction could work under conventional conditions using bromoarylphosphine oxides, but not using chloroarylphosphine oxides. The use of chloroarylphosphine oxides would be preferable due to the wider availability and lower cost of arylchlorides. At first we confirmed that the reaction does not work under conventional heating with a chloroarylphosphine oxide chosen as model study, even when the reaction was run for several hours at high temperature. Then, the reaction was attempted in the microwave and in just half an hour reasonable yields of the product were obtained. To the best of our knowledge, this was the first example of a reaction which does not occur under conventional heating even with forcing conditions, being successful under microwave heating.

Few common catalysts that have proven to be successful for the Suzuki cross coupling reaction were tested, but the catalyst that gave the best results was found to be a catalyst previously prepared by Clarke. Once the conditions were optimised, a different chloroarylphosphine oxide was chosen to couple to different and bulkier aryl boronic acids. It was pleasing to observe that the methodology developed could be successfully applied to different systems. Moreover, a dichloroarylphosphine oxide was also used as the starting material, and this led us to discover that our system could easily lead to the synthesis of disubstituted arylphosphine oxides. The only drawback of this methodology was the necessity for column chromatography to isolate the products, but it can still be considered a useful way to prepare bulky arylphophine oxides.

It was also observed that the reduction of phosphine oxides could in some cases be sped up under microwave heating, shortening the reactions times from even several hours to minutes. However, a

general method for the reduction of phosphine oxides has not been found, as it was observed that challenging phosphine oxides were not easily reduced even in the microwave.

The microwave-mediated palladium catalysed P-C bond forming reaction was then investigated. The bulky *o*-trifluoromethyl-bromobenzene was chosen for use in a model study, as we were interested in finding out if the reaction could proceed on bulky substrates. Different nucleophiles were tested and secondary diphenylphosphine in the presence of DABCO was found to be the best nucleophile, allowing the reaction to proceed with high yield in just 20 minutes, giving high conversions. Moreover, different catalysts were also tested in the reaction and dippf base palladium complex was found to be the catalyst of choice. This reaction was proven to be applicable to different bromoaryl substrates, always producing high yields. It was interesting to discover that not the strongest nucleophiles did not produce the best results. Also of interest was the fact that increasing the amount of nucleophile meant the reaction would not proceed. This difference might be due to interference of the nucleophile with the active palladium catalyst. However, some mechanistic and kinetic studies are necessary to clarify the reasons behind this behaviour.
Because our interest was in using this methodology for the synthesis of bidentate ligands, the microwave-mediated P-C bond forming reaction was attempted with view to obtaining double coupling. However, when using *o*-diiodobenzene as starting material, only a low yield of the diphosphine was obtained. We also attempted to prepare phanephos and the new ligand Ph-DuPHOS by this method, but again no success was achieved. It is possible that steric hindrance in the desired products was the reason behind this lack of success. It is possible that further investigation into the mechanism of the reaction will allow the double coupling to work in the future.

As was previously mentioned, Ph-DuPHOS was a new ligand that we were interested in preparing, particularly because of the successful results in asymmetric catalysis of Ph-BPE, which gave better results compare to Me-BPE and Et-BPE and also by observing the interesting results obtained with Me-DuPHOS. Indeed, it was considered that a rigid backbone could lead to very good results in asymmetric catalysis. Different attempts were therefore made in trying to prepare Ph-DuPHOS, however the synthesis of this ligand remained elusive.
In an effort to prepare a new P-N-P phospholane-based ligand, a monodentate phospholane-based P-N ligand was prepared: this ligand was tested in rhodium catalysed asymmetric hydrogenation of alkenes, based on good results obtained by Fiaud and co-workers with a monodentate phospholane-base ligand. Reasonable results, comparable to the ones reported in literature, were obtained.

In keeping with the design of ligands with rigid backbones, a different ligand with a xylyl backbone was successfully prepared. This ligand was tested in hydroxycarbonylation of styrene, in light of the previous results obtained in our lab by Frew. Indeed, it was observed that bulky bidentate ligands can lead to the formation of the branched product in high regioselectivity. This observation is contrary to pre-existing dogma in hydroxycarbonylation, which states that monodentate are the ligand of choice for obtaining the branched product. Using this new bidentate phospholane-based ligand, reasonable regioselectivities and moderately high enantiomeric excesses were achieved, a good result considering the challenging nature of this reaction. It might be possible that fine-tuning the electronic properties of these bidentate phospholane-based ligands, will lead to better region- and enantioselectivities.

Chapter 5

Experimental

5.1 General experimental procedures and instrumentation

All chemicals and solvents are standard laboratory grade, obtained from commercial sources and were used as received, unless stated otherwise. Dry, degassed solvents were used for reactions unless otherwise indicated. Normal grade solvents were used for chromatography. Solvents were removed by rotary evaporation on a Heidolph labrota 4000. Flash column chromatography (eluents given in brackets) was performed using Davisil silica gel Fluorochem 60Å, particle size 35-70 micron.

Microwave reactions were carried out in a Biotage® initiator using 5ml heavy-walled reactor vials equipped with an air tight seal. The temperature is measured by an Infra Red Temperature Probe that measures the temperature on the surface of the vial. The pressure is measured by direct reading of the deflection of the septa on the vial using a load cell behind the inner part of the cavity lid.

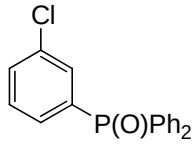
Routine NMR data were recorded either on a Bruker Avance 300 (^{1}H at 300 MHz, 13C at 75 MHz, ^{19}F at 282 MHz, ^{31}P at 121MHz) or a Bruker Avance II 400 (^{1}H at 400 MHz, ^{13}C at 100 MHz, ^{19}F at 376 MHz, ^{31}P at 121 MHz). ^{1}H and ^{13}C spectra were referenced to external tetramethylsilane, 19F spectra were referenced to external trichlorofluoromethane, and ^{31}P spectra were referenced to external phosphoric acid. Chemical shifts are expressed in parts per million. Chemical ionisation mass spectroscopy and electron ionisation mass spectroscopy were performed on a Micromass GCT spectrometer. Electrospray mass spectroscopy was performed on a Micromass LCT spectrometer. All were operated by Mrs Caroline Horsburgh. Microanalysis was carried out for C and H using an EA 1110 CHNS CE Instruments elemental analyser by Mrs S. Williamson. Infra-red absorbtion spectra were recorded on a Perkin Elmer GX-FTIR System spectrometer.

Dry diethyl ether, petroleum ether, THF, toluene and DCM were obtained from an Innovative Technologies Puresolve 400 solvent still.

5.2 Example procedure for Suzuki coupling reactions

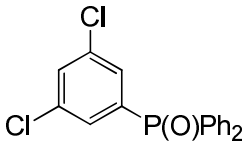
The triarylphosphine oxide **(1)** (0.15g; 0.4mmol), together with the catalyst (2.5%), $ArB(OH)_2$ (0.38g; 3.1mmol) and base (10eq) indicated in table 2.3 were dissolved in the solvent (5ml) and placed in a microwave vial, and sealed under nitrogen before running the reaction in the microwave. The conversion values shown in table 2.3 were calculated through ^{31}P NMR (121.4 MHz; C_6D_6): **(62)** δ_P 29.7; **(61)** δ_P 29.8; **(60)** δ_P 29.9; starting material **(59)** δ_P 29.2.

5.2.1 Synthesis of 3-chlorophenyl-diphenylphosphine (63)



Mg (0.6 g; 25.9 mmol) was placed in a Schlenk under nitrogen and activated by stirring with a crystal of iodine. Dry and degassed THF was then added. 1-bromo-3-chlorobenzene (5 g; 26.1 mmol) was added dropwise at 0 °C and the mixture was stirred at room temperature until complete reaction of the magnesium. The solution was filtered through cannula and cooled to -78 °C. Chlorodiphenylphosphine (1.9 g; 8.7 mmol) was added dropwise and the mixture was stirred overnight at room temperature. An excess of H_2O_2 (solution in H_2O) was added to the crude mixture, which was stirred for 1 hour. The mixture was washed with water and extracted with dichloromethane (3x50 ml). The organic layer was dried with $MgSO_4$ and the solvent remove. The product was purified with chromatography column (80/20 AcOEt/Hexane) (1.8 g; 5.6 mmol; 65 %). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.26-7.51 (m, 9H, Ar*H*), 7.53-7.63 (m, 5H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 128.7 (d, $^{2}J_{C\text{-}P}$ 12.271 Hz; Ar*C*), 130.1 (t, Ar*C*), 131.8 (Ar*C*), 131.9 (Ar*C*), 132.0 (Ar*C*),131.2 (Ar*C*), 132.1 (Ar*C*), 132.3 (d, $^{3}J_{C\text{-}P}$ 2.7 Hz; Ar*C*), 132.6 (Ar*C*), 134.8 (d, $^{1}J_{C\text{-}P}$ 51.7 Hz; Ar*C*), 135.3 (d, $^{1}J_{C\text{-}P}$ 65.3 Hz, Ar*C*); ^{31}P{^{1}H}-NMR (121.5MHz) δ 28.2; LRMS (CI+) m/z 312.05 ($(M+H)^+$, 100%); HMRS (CI+): m/z calc'd for $C_{18}H_{15}OPCl$: 313.0547, found: 313.0549.

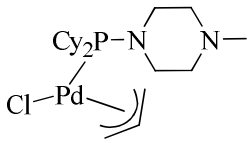
5.2.2 Synthesis of 3,5-chlorophenyl-diphenylphosphine (65)



Mg (0.3 g; 14.7 mmol) was placed in a Schlenk under nitrogen and activated by stirring with a crystal of iodine. Dry and degassed THF was then added. 1-bromo-3,5-dichlorobenzene (3.2 g; 14.1 mmol) was added dropwise at 0 °C and the mixture was stirred at room temperature until complete reaction of the magnesium. The solution was filtered through cannula and cooled to -78 °C. Chlorodiphenylphosphine (1.1 g; 4.8 mmol) was added dropwise and the mixture was stirred overnight at room temperature. An excess of H_2O_2 was added to the crude mixture, which was stirred for 1 hour. The mixture was washed with water and extracted with dichloromethane (3x50 ml). The organic layer was dried with $MgSO_4$ and the solvent remove. The product was purified with chromatography column (80/20 AcOEt/Hexane) (1.0 g; 2.9 mmol; 60 %).

^{1}H-NMR (300MHz, $CDCl_3$) δ 7.38-7.64 (m, 13H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 129.2 (d, $^{2}J_{C-P}$ 12.4 Hz; Ar*C*), 130.5 (d, $^{2}J_{C-P}$ 10.2 Hz; Ar*C*), 130.8 (Ar*C*), 132.2 (Ar*C*), 132.4 (Ar*C*),132.5 (Ar*C*), 133.0 (d, $^{3}J_{C-P}$ 2.7 Hz; Ar*C*), 136.1 (d, $^{1}J_{C-P}$ 16.8 Hz; Ar*C*), 136.7 (Ar*C*), 138.0; ^{1}P{^{1}H}-NMR (121.5MHz) δ 27.3; LRMS (CI+) m/z 347.01($(M+H)^+$, 100%); HMRS (CI+): m/z calc'd for $C_{18}H_{14}OCl_2P$: 347.0150, found: 347.0159.

5.2.3 Synthesis of N-methylpiperazine-dicycloexylphosphine-allyl palladium chloride (58)



N-methylpiperazine (0.48g; 477mmol) and triethylamine (0.48g; 660mmol) were placed in a schlenk tube under nitrogen and dry diethyl ether (20ml) added. The solution was cool down to 0 °C and dicyclohexylchlorophosphine (1g; 0.0043mmol) was added dropwise. The solution was then stirred at room temperature overnight. The reaction was monitored by phosphorus NMR (^{31}P{^{1}H}-NMR (121.5MHz, C_6D_6) δ 76.12).

10ml of the ligand solution were transferred to a Schlenk flask containing allylpalladium chloride dimer (0.2g; 0.0014mmol) and the resulting solution stirred for 3 hours. The yellow precipitate that formed was filtered and washed with ether.

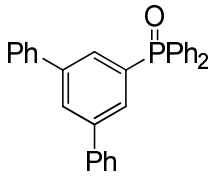
^{1}H-NMR (300MHz, $CDCl_3$) δ 1.18-1.41 (m, 11H, cy), 1.61-1.99 (m, 11H, cy), 2.17-2.41 (m, 4H, Pyp-*H*), 2.22 (s, 3H, NCH_3), 2.61 (d, 1H, J=11.9 Hz; allyl-*H*), 3.21 (br-s, 4H, Pyp-*H*), 3.49 (d, 1H, J=6.4 Hz; allyl-*H*), 3.59 (dd, 1H, J=13.8 Hz; J=10.0 Hz; allyl-*H*), 4.60 (t,1H, J=13.6 Hz; allyl-*H*), 5.42 (m, 1H, allyl-*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 26.42, (CH_2, cy), 26.79 (CH_2, cy), 26.93 (CH_2, cy), 26.99 (CH_2, cy), 27.01 (CH_2, cy), 28.34 (CH_2, cy), 28.61 (CH_2, cy), 28.93 (CH_2, cy), 28.97 (CH_2, cy), 29.01 (CH_2, cy), 36.62 (d, $^{1}J_{C-P}$ 31.0 Hz; CH, cy), 46.26 (NCH_3), 50.32 (4xCH_2, Pyp), 53.12 (d, 1CH_2, J=2.9 Hz; Pyp), 56.13 (d, 1CH_2, J=6.7 Hz; Pyp), 80.23 (CH_2, allyl), 80.54 (CH_2, allyl), 116.80 (CH_2, allyl); ^{31}P{^{1}H}-NMR (121.5MHz; $CDCl_3$) δ 96.87.

5.2.3 Microwave assisted synthesis of the library

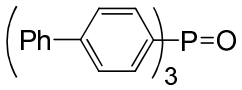
*5.2.3.1 Example procedure for Suzuki cross-coupling on substrates (**63**)*

To a microwave vial it was added (**63**) (0.1g; 0.29mmol), $PhB(OH)_2$ (0.2g; 1.7mmol), CsF (0.5g; 3.4mmol) and catalyst (**58**) (7mg; 0.0014mmol). The air was displaced with nitrogen and dry

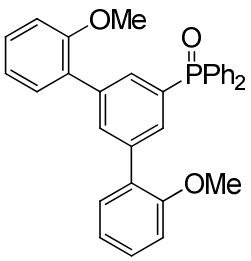
MeCN added (3ml). The reaction was heated in a microwave for 30 minutes at 140° C. This was repeated in a further 5 vials, in order to obtain larger samples for characterisation. The reaction mixtures were then combined, water was added and the organic layer extracted with dichloromethane (3x50ml), dried ($MgSO_4$) and concentrated.



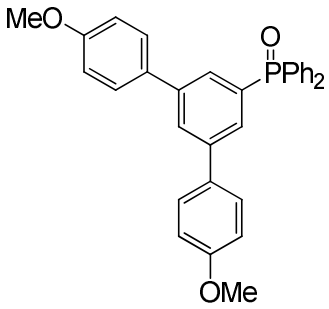
The product (**66a**) was isolated by column chromatography (elution mixture: ethyl acetate/hexane, from 30/70 to 90/10) (454mg; 1.05mmol; 62%) ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.22-7.49 (m, 16H, Ar*H*), 7.63-7.69 (m, 4H, Ar*H*), 7.79 (d, $^{1}J_{H-H}$ 12.1Hz, 2H, Ar*H*), 7.87 (s, 1H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 127.7 (Ar*C*), 128.4 (Ar*C*), 129.1 (d, $^{2}J_{C-P}$ 12.0 Hz, Ar*C*), 129.4 (Ar*C*), 129.9 (Ar*C*), 130.0 (Ar*C*), 132.2 (Ar*C*), 132.5 (Ar*C*), 132.6 (Ar*C*), 133.6 (Ar*C*), 140.4 (Ar*C*), 142.5 (d, $^{1}J_{C-P}$ 12.4 Hz, Ar*C*); ^{31}P{^{1}H}-NMR (121.5MHz) δ 30.57; IR (*KBr*) ν_{max}: 1591 (w), 1572 (w), 1498 (w), 1452 (w), 1412 (m), 1438(m), 1190(s), 1115 (s), 1135 (s), 1023 (w); LRMS (ES+) m/z 453.2 ($(M+Na)^+$, 100%); HMRS (ES+): m/z calc'd for $C_{30}H_{23}ONaP$: 453.1384, found: 453.1384.



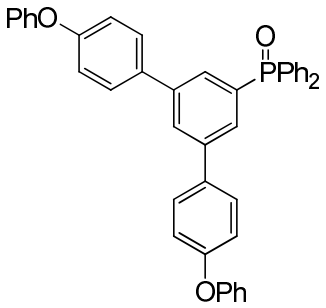
The reaction was carried out using 250mg of starting material (**59**) (5x50mg) and the product **(62)**[1] was isolated by column chromatography (elution mixture: ethyl acetate/hexane, from 30/70 to 90/10); (220mg; 0.43mmol; 67%). ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.29-7.42 (m, 9H, Ar*H*), 7.53-7.56 (m, 6H, Ar*H*), 7.62-7.56 (m, 12H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 127.6 (Ar*C*), 127.7 (Ar*C*), 127.8 (Ar*C*), 128.6 (Ar*C*), 129.4 (Ar*C*), 130.9 (Ar*C*), 132.3 (Ar*C*), 133.1 (d, $^{2}J_{C-P}$ 10.2 Hz, Ar*C*), 140.3 (Ar*C*), 145.2 (d, $^{4}J_{C-P}$ 2.6 Hz, Ar*C*); ^{31}P{^{1}H}-NMR (121.5MHz) δ 30.07; IR (*KBr*) ν_{max}: 1596 (m), 1544(w), 1480 (m), 1443 (w), 1390 (m), 1264 (w), 1183 (s), 1117 (s), 1007 (m); LRMS (ES+) m/z 507.2 ($(M+H)^+$, 100%); HMRS (ES+): m/z calc'd for $C_{36}H_{28}OP$: 507.1878, found: 507.1889.



Reaction carried out using 200mg of starting material (4x50), and the product (**66b**) was isolated by column chromatography (elution mixture: ethyl acetate/hexane, from 30/70 to 90/10) (234mg; 0.48mmol; 83%). ^{1}H-NMR (300MHz, $CDCl_3$) δ 3.64 (s, 6H, 2xOC*H*$_3$), 6.84-6.94 (m, 4H), 7.16-7.28 (m, 10H, Ar*H*), 7.35-7.79 (m, 7H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 55.5 (O*C*H$_3$), 111.2 (Ar*C*), 120.9 (Ar*C*), 128.4 (d, $^{2}J_{C-P}$ 12.0 Hz, Ar*C*), 129.1 (Ar*C*), 129.5 (Ar*C*), 130.7 (Ar*C*), 130.9 (Ar*C*), 131.7 (Ar*C*), 131.8 (Ar*C*), 132.3 (d, $^{2}J_{C-P}$ 9.8 Hz, Ar*C*), 133.6 (Ar*C*), 134.2 (Ar*C*), 138.4 (d, $^{1}J_{C-P}$ 13.1 Hz, Ar*C*), 156.4 (Ar*C*); ^{31}P{^{1}H}-NMR (121.5MHz) δ 30.56; IR (*KBr*) ν_{max}: 1598 (w), 1493 (m), 1410 (m), 1278 (w), 1247 (w), 1247 (m), 1192 (s), 1117 (s), 1022 (m); LRMS (ES+) m/z 513.2 ((M+Na)$^{+}$, 100%); HMRS (ES+): m/z calc'd for $C_{32}H_{27}O_3NaP$: 513.1596, found: 513.1394.

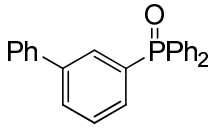


Reaction carried out 400mg of starting material (4x100), and the product (**66c**) was isolated by column chromatography (elution mixture: ethyl acetate/hexane, from 30/70 to 90/10) (444mg; 0.90mmol; 79%). ^{1}H-NMR (300MHz, $CDCl_3$) δ 3.73 (s, 6H, 2xOC*H*$_3$), 6.87 (d, $^{1}J_{H-H}$ 8.6Hz, 4H, Ar*H*), 7.36-7.48 (m, 10H, Ar*H*), 7.63-7.72 (m, 6H, Ar*H*), 7.79 (s, 1H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 55.4 (O*C*H3), 114.4 (Ar*C*), 128.4 (Ar*C*), 128.5 (Ar*C*), 128.7 (Ar*C*), 132.1 (Ar*C*), 132.2 (Ar*C*), 132.6 (Ar*C*), 133.1 (d, $^{1}J_{C-P}$ 26.6 Hz, Ar*C*), 134.3 (Ar*C*), 141.6 (d, $^{1}J_{C-P}$ 12.6 Hz, Ar*C*), 159.6 (Ar*C*); ^{31}P{^{1}H}-NMR (121.5MHz) δ 30.85; IR (*KBr*) ν_{max}: 1608 (m), 1513 (s), 1437 (m), 1288 (w), 1254 (s), 1181 (s), 1117 (m), 1118 (m), 1029 (w); LRMS (ES+) m/z 513.2 ((M+Na)$^{+}$, 100%); HMRS (ES+): m/z calc'd for $C_{32}H_{27}O_3NaP$: 513.1596, found: 513.1600.

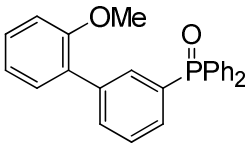


Reaction carried out 300mg of starting material (6x50mg), and the product (**66d**) was isolated by column chromatography (elution mixture: ethyl acetate/hexane, from 30/70 to 90/10), (400mg; 0.65mmol; 75%). ^{1}H-NMR (300MHz, $CDCl_3$) δ 6.95-7.07 (m, 10H, Ar*H*), 7.25-7.30 (m, 4H, Ar*H*),

7.38-7.51 (m, 10H, Ar*H*), 6.64-7.83 (m, 7H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 118.0 (d, $^2J_{C-P}$ 13.5 Hz, Ar*C*), 122.6 (Ar*C*), 127.5 (Ar*C*), 127.6 (Ar*C*), 127.7 (Ar*C*), 127.8 (Ar*C*), 127.9 (Ar*C*), 128.8 (Ar*C*), 130.5 (Ar*C*), 131.0 (Ar*C*), 131.1 (Ar*C*), 132.0 (d, $^2J_{C-P}$ 8.7 Hz, Ar*C*), 133.4 (Ar*C*), 133.8 (Ar*C*), 140.4 (d, $^1J_{C-P}$ 12.6 Hz, Ar*C*), 155.7 (Ar*C*), 156.5 (Ar*C*); $^{31}P\{^1H\}$-NMR (121.5MHz) δ 30.74; IR (*KBr*) ν_{max} (cm^{-1}): 1588 (m), 1508 (m), 1488 (s), 1437 (w), 1238 (s), 1195(w), 1119(w); LRMS (ES+) m/z 637.3 ($(M+Na)^+$, 100%); HMRS (ES+): m/z calc'd for $C_{42}H_{32}O_3P$: 615.2089, found: 615.2092 (0.4 ppm).

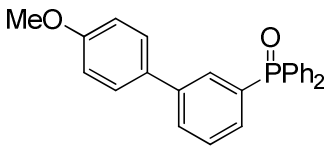


Reaction carried out using 200mg of starting material (4x50mg), and the product (**64a**) was isolated by column chromatography (elution mixture: ethyl acetate/hexane, from 30/70 to 90/10), (179mg; 0.51mmol; 79%). ^{1}H-NMR (300MHz, $CDCl_3$) δ 6.96-7.91 (m, 19H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 127.23 (Ar*C*), 127.9 (Ar*C*), 128.6 (d, $^2J_{C-P}$ 12.1 Hz, Ar*C*), 128.8 (Ar*C*), 128.9 (Ar*C*), 130.6 (Ar*C*), 130.7 (d, $^3J_{C-P}$ 2.9 Hz, Ar*C*), 130.8 (d, $^2J_{C-P}$ 10.13 Hz, Ar*C*), 131.8 (Ar*C*), 132.1 (Ar*C*), 132.2 (Ar*C*), 133.2 (Ar*C*), 133.9 (Ar*C*), 140.0 (Ar*C*), 141.6 (d, $^1J_{C-P}$ 11.9 Hz, Ar*C*); $^{31}P\{^1H\}$-NMR (121.5MHz) δ 30.46; IR (*KBr*) ν_{max}: 1471 (w), 1438 (m), 1398 (w), 1185 (s), 1120 (s); LRMS (ES+) m/z 377.1 ($(M+Na)^+$, 100%); HMRS (ES+): m/z calc'd for $C_{24}H_{19}ONaP$: 377.1071, found: 377.1067.

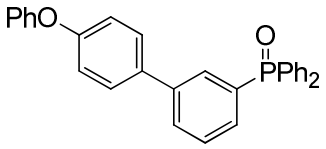


Reaction carried out using 100mg of starting material (2x50mg), and the product (**64b**) was isolated by column chromatography (elution mixture: ethyl acetate/hexane, from 30/70 to 90/10), (104mg; 0.27mmol; 85%). ^{1}H-NMR (300MHz, $CDCl_3$) δ 3.63 (s, 3H, OC*H*$_3$), 6.84-6.94 (m, 2H, Ar*H*), 7.18-7.26 (m, 2H, Ar*H*), 7.34-7.48 (m, 7H, Ar*H*), 7.56-7.67 (m, 6H, Ar*H*), 7.73-7.77 (m, 1H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 55.8 (O*C*H$_3$), 111.6 (Ar*C*), 121.4 (Ar*C*), 128.6 (Ar*C*), 128.9 (d, $^2J_{C-P}$ 12.2 Hz, Ar*C*), 129.6 (Ar*C*), 130.9 (d, $^2J_{C-P}$ 9.6 Hz, Ar*C*), 131.2 (Ar*C*), 131.6 (d, $^2J_{C-P}$ 13.5 Hz, Ar*C*), 132.3 (d, $^3J_{C-P}$ 2.5 Hz, Ar*C*), 132.6 (d, $^2J_{C-P}$ 9.9 Hz, Ar*C*), 133.0 (Ar*C*), 133.4 (d, $^3J_{C-P}$ 2.6 Hz, Ar*C*), 133.6 (Ar*C*), 133.8 (Ar*C*), 139.0 (d, $^1J_{C-P}$ 12.7 Hz, Ar*C*), 156.7 (Ar*C*); ^{31}P-NMR $\{^1H\}$(121.5MHz) δ 30.54; IR (*CDCl*$_3$) ν_{max} (cm^{-1}): 1898 (w), 1820 (w), 1601 (w), 1497 (m), 1465 (m), 1437 (s), 1398 (m), 1261 (m), 1239 (m), 1182 (s), 1119 (s), 1058 (w), 1027 (m); LRMS (ES+)

m/z 407.1 ($(M+Na)^+$, 100%); HMRS (ES+): m/z calc'd for $C_{25}H_{21}O_2NaP$: 407.1177, found: 407.1170.



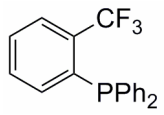
Reaction carried out using 300mg (3x100mg)**,** and the product (**64c**) was isolated by column chromatography (elution mixture: ethyl acetate/hexane, from 30/70 to 90/10), (214mg; 0.56mmol; 58%). ^{1}H-NMR (300MHz, $CDCl_3$) δ 3.70 (s, 3H, OC*H*$_3$), 6.83 (d, $^1J_{H-H}$ 8.7Hz, 2H, Ar*H*), 7.33-7.45 (m, 10H, Ar*H*), 7.58-7.64 (m, 5H, Ar*H*), 7.84 (d, $^1J_{H-H}$ 12.5Hz, 1H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 55.7 (O*C*H$_3$), 114.7 (Ar*C*), 128.7 (Ar*C*), 129.0 (d, $^2J_{C-P}$ 12.1 Hz, Ar*C*), 129.3 (d, $^2J_{C-P}$ 12.8 Hz, Ar*C*), 130.5 (Ar*C*), 130.6 (Ar*C*), 130.7 (Ar*C*), 132.2 (Ar*C*), 132.4 (Ar*C*), 132.6 (Ar*C*), 132.8 (Ar*C*), 133.9 (d, $^1J_{C-P}$ 37.9 Hz, Ar*C*), 141.5 (d, $^1J_{C-P}$ 11.98 Hz, Ar*C*), 160.0 (Ar*C*); ^{31}P{^{1}H}-NMR (121.5MHz) δ 30.53; IR (*KBr*) ν_{max}: 1602 (s), 1570 (w), 1513 (w), 1412 (m), 1339 (s), 1310 (s), 1245 (s), 1171 (s), 1108 (w), 1025 (m); LRMS (ES+) m/z 407.1 ($(M+Na)^+$, 100%); HMRS (ES+): m/z calc'd for $C_{25}H_{21}O_2NaP$: 407.1177, found: 407.1172.



Reaction carried out using 100mg of starting material (2x50mg), and the product (**64d**) was isolated by column chromatography (elution mixture: ethyl acetate/hexane, from 30/70 to 90/10), (139mg; 0.31mmol; 98%). ^{1}H-NMR (300MHz, $CDCl_3$) δ 6.95-7.07 (m, 5H, Ar*H*), 7.24-7.30 (m, 2H, Ar*H*), 7.36-7.50 (10H, Ar*H*), 7.59-7.66 (m, 5H, Ar*H*), 7.86 (d, $^1J_{H-H}$ 12.6Hz, 1H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 117.9 (Ar*C*), 118.1 (Ar*C*), 122.5 (Ar*C*), 127.5 (d, $^3J_{C-P}$ 2.3 Hz, Ar*C*), 127.6 (Ar*C*), 127.9 (d, $^2J_{C-P}$ 12.7 Hz, Ar*C*), 128.8 (Ar*C*), 129.2 (Ar*C*), 129.3 (Ar*C*), 129.5 (Ar*C*), 129.6 (Ar*C*), 131.0 (Ar*C*), 131.1 (Ar*C*), 130.7 (Ar*C*), 131.4 (Ar*C)*, 132.1 (Ar*C*), 132.8 (Ar*C*), 133.8 (Ar*C*), 139.8 (d, $^1J_{C-P}$ 11.9 Hz, Ar*C*), 155.7 (Ar*C*), 156.4 (Ar*C*); ^{31}P{^{1}H} -NMR (121.5MHz) δ 30.50; IR (*KBr*) ν_{max}: 1589 (w), 1509 (w), 1489 (m), 1436 (w), 1239 (m), 1193 (w), 1118 (m); LRMS (ES+) m/z 447.2 ($(M+H)^+$, 100%); HMRS (ES+): m/z calc'd for $C_{30}H_{23}O_2NaP$: 469.1333, found: 469.1320.

5.3 Reduction of phosphine oxides

5.3.1 Procedure for the microwave assisted and conventional condition reduction of 2-trifluorobenzen-1-diphenylphosphine

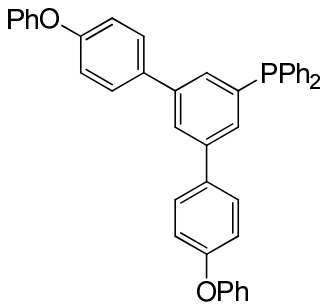


For the microwave assisted reduction, the phosphine oxide (**67**) (50mg, 0.14mmol) was placed in a microwave vial and sealed under an inert atmosphere and dry MeCN added, followed by dry Et_3N (145.2mg, 1.4mmol) and $HSiCl_3$ (93.8mg, 0.72mmol). The reaction was heated in a microwave at 145 °C for the time indicated.[2, 3]

For the reaction carried out at conventional conditions, the phosphine oxide (**67**) was placed in a Schlenk flask under an inert atmosphere and dry MeCN added, followed by dry Et_3N and $HSiCl_3$. The phosphine has been previously reported in literature.[3]

$^{19}F\{^1H\}$ (282.3MHz, C_6D_6) δ -56.7 (d, $^1J_{F-P}$ 54 Hz); ^{31}P-NMR (121.5MHz) δ 4.1 (q, $^1J_{P-F}$ 54Hz).

5.3.2 Procedure of microwave assisted reduction of (66d)



Phosphine oxide (**66d**) (65mg; 0.13mmol) was placed in a microwave vial and sealed under an inert atmosphere and dry MeCN added, followed by dry Et_3N (131.5mg; 1.3mmol) and $HSiCl_3$ (88mg; 0.65mmol). The reaction was heated in a microwave at 145 °C for 10 minutes. MeCN was removed under reduced pressure and the crude was dissolved in dry DCM and pass through a short pad of silica under nitrogen. The solvent was removed under reduced pressure and the NMR sample was prepared using dried and degassed $CDCl_3$ (51mg; 0.11mmol; 83%).

^1H-NMR (300MHz, $CDCl_3$) δ 3.75 (s, 6H, 2xOC*H*$_3$), 6.85-6.88 (m, 4H, Ar*H*), 7.25-7.41(m, 15H, Ar*H*), 7.61 (t, 1H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 55.4 (O*C*H$_3$), 114.25 (Ar*C*), 125.7 (Ar*C*), 128.6 (d, $^2J_{C-P}$ 6.9 Hz, Ar*C*), 130.3 (Ar*C*), 130.5 (Ar*C*), 133.3 (Ar*C*), 133.7 (Ar*C*), 133.9 (Ar*C*), 137.0 (d, $^1J_{C-P}$ 10.1 Hz, Ar*C*), 138.2 (d, $^1J_{C-P}$ 10.7 Hz, Ar*C*), 141.3 (d, $^1J_{C-P}$ 7.6 Hz; Ar*C*), 159.3

(Ar*C*); $^{31}P\{^{1}H\}$-NMR (121.5MHz) δ 3.23; LRMS (CI+) m/z 475.17 $(M+H)^+$; HMRS (CI+): m/z calc'd for $C_{32}H_{28}O_2P$: 475.1815, found: 475.1827.

5.4 Microwave assisted P-C bond forming reaction

5.4.1 Preparation procedures for the nucleophiles used in the palladium catalysed P-C bond forming reaction

5.4.1.1 Preparation of Ph_2PZnCl

$ZnCl_2$ was dissolved in THF in a Schlenk flask under nitrogen. Ph_2PK (solution 0.5M in THF; Aldrich) was added carefully in equimolr quantity at 0 °C, giving a bright red solution: the mixture was stirred at room temperature for at most 1 hour, till a colourless solution was obtained. The solvent was removed under reduced pressure and the white solid was then dissolved in dry toluene and filtered through cannula filtration under nitrogen, to take off the inorganic salt formed. The toluene solution of the product was used directly, without further purification. $^{31}P\{^{1}H\}$ NMR (121.5MHz) δ -38.221;

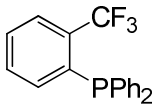
5.4.1.2 Preparation of Ph_2PSiMe_3[4]

Me_3SiCl was placed in a Schlenk flask under nitrogen and THF added. The solution was cooled down at -78 °C and an equimolar quantity of Ph_2PK (solution 0.5M in THF; Aldrich) was slowly added. The mixture was then stirred overnight. THF was removed under reduced pressure and the residue was dissolved in dry toluene and filtered through cannula filtration under nitrogen, to take off the inorganic salt formed. The toluene solution of the product was used directly, without further purification. $^{31}P\{^{1}H\}$-NMR (121.5MHz) δ -55.5;

5.4.1.3 Preparation of Ph_2PMgBr

To a solution of dry MgBr diethyl etherate (Aldrich) in THF, an equimolar quantity of Ph_2PK (solution 0.5M in THF; Aldrich) was slowly added at 0 °C. The mixture was stirred 1 hour. THF was removed under reduced pressure and the residue was dissolved in dry toluene and filtered through cannula filtration under nitrogen, to take off the inorganic salt formed. The toluene solution of the product was used directly, without further purification. $^{31}P\{^{1}H\}$ NMR (121.5MHz) δ -13.64.

5.4.2 Microwave assisted synthesis of 2-trifluorobezen-1-diphenylphosphine (87)

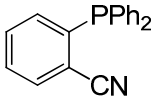


2-Bromobenzotrifluoride (0.1g; 0.44 mmol) was dissolved in 5 ml of the indicated solvent in a Schlenk tube under nitrogen, together with the catalyst and the nucleophilic reagent. The mixture was then transferred to a microwave vial, previously closed and kept under nitrogen. The conversion values were calculated using ^{19}F NMR (and confirmed by ^{31}P{^{1}H}-NMR). The NMR sample was prepared under nitrogen by diluting a portion of the reaction mixture with degassed C_6D_6. ^{31}P{^{1}H} NMR (121.4 MHz; C_6D_6) δ_P= -9.3 ppm (q; $^{4}J_{P-F}$= 54 Hz); ^{19}F NMR (282.3 MHz; C_6D_6) δ_P= -56.8 ppm (d; $^{4}J_{P-F}$= 54 Hz).

Isolation of the phosphine was only carried out after oxidation by exposure to air.

^{1}H-NMR (300MHz, $CDCl_3$) δ 7.28-7.80 (m, 14H, Ar*H*); ^{31}P{^{1}H}-NMR (121.5MHz) δ 34.7; ^{19}F NMR (282.3 MHz; C_6D_6) δ_P= -56.9 ppm LRMS (ES+) m/z 368.99 ($(M+Na)^+$, 100%); HMRS (ES+): m/z calc'd for $C19H14F_3NaOP$: 369.0632, found: 369.0635.

5.4.2 Microwave assisted synthesis of 2-cyanobenzyl-1-diphenylphosphine (92)

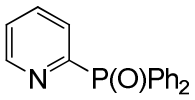


2-bromobenzonitrile (0.5g; 2.75 mmol), $Pd(OAc)_2$ (12.3 mg; 0.0055 mmol), dippf (34.5 mg; 0.0082 mmol) and DABCO (0.6 g; 5.5 mmol) were placed in a microwave vial. The microwave vial was closed and placed under nitrogen. Diphenylphosphine (0.6 g; 3.3 mmol) was then added. The mixture was dissolved in dry DMF/THF (1:1). The reaction was run in the microwave at 140 °C for 20 minutes. The reaction mixture was washed with water and extracted with dichloromethane (3x50ml). The solvent was removed and the product was purified by column chromatography (ethyl acetate/hexane 10/90) (0.64 g; 0.22 mmol; 81 %). This compound has been previously reported in the literature.[2, 5]

^{1}H-NMR (300MHz, $CDCl_3$) δ 6.94-6.98 (m, 1H, Ar*H*), 7.18-7.43 (m, 12H, Ar*H*), 7.61-7.66 (m, 1H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 118.1 (d, $^{2}J_{C-P}$ 6.7 Hz; Ar*C*-CN), 118.5 (*C*N), 129.26 (d, $^{2}J_{C-P}$ 7.2 Hz, Ar*C*), 129.8 (Ar*C*), 132.8 (Ar*C*), 133.8 (Ar*C*), 134.5 (d, $^{2}J_{C-P}$ 4.7 Hz; Ar*C*), 134.3 (Ar*C*), 134.6 (Ar*C*), 135.10 (d, $^{2}J_{C-P}$ 10.9 Hz, Ar*C*), 143.4 (d, $^{2}J_{C-P}$ 19.9 Hz, Ar*C*); ^{31}P{^{1}H}-NMR

(121.5MHz) δ -7.32; LRMS (ES+) m/z 310.03 ($(M+Na)^+$, 100%); HMRS (ES+): m/z calc'd for $C_{19}H_{14}NaP$: 310.0762, found: 310.0754.

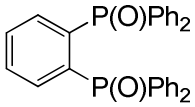
5.4.3 Microwave assisted synthesis of 2-(diphenylphosphine oxide)-pyridine (94)



2-bromopyridine (0.5g; 3.16 mmol), $Pd(OAc)_2$ (14.2 mg; 0.0063 mmol), dippf (39.6 mg; 0.0095 mmol) and DABCO (0.7 g; 6.3 mmol) were placed in a microwave vial. The microwave vial was closed and placed under nitrogen. Diphenylphosphine (0.7 g; 3.8 mmol) was then added. The mixture was dissolved in dry DMF/THF (1:1). The reaction was run in the microwave at 140 °C for 20 minutes. The reaction mixture was washed with water and extracted with dichloromethane (3x50ml). The solvent was removed and the product was purified by column chromatography, prior oxidation with an excess of H_2O_2 (ethyl acetate/hexane 30/70) (0.54 g; 1.93 mmol; 61 %). This compound has been previously reported in the literature.[6]

^{1}H-NMR (300MHz, $CDCl_3$) δ 7.25-7.48 (m, 7H, Ar*H*), 7.70-7.88 (m, 5H, Ar*H*), 8.18-8.28 (t, 1H, Ar*H*), 8.67-8.72 (m, 1H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 124.24 ($^4J_{C-P}$ 2.9 Hz; Ar*C*), 127.24 (Ar*C*), 127.40 (Hz, Ar*C*), 130.48 (Ar*C*), 130.87 ($^4J_{C-P}$ 2.6 Hz; Ar*C*), 131.07 ($^3J_{C-P}$ 9.4 Hz; Ar*C*), 131.86 (Ar*C*), 135.15 ($^3J_{C-P}$ 9.2 Hz; Ar*C*), 149.17 ($^2J_{C-P}$ 19.2 Hz; Ar*C*), 154.56 (Ar*C*), 156.43 (Ar*C*); ^{31}P{^{1}H}-NMR (121.5MHz) δ 20.81; LRMS (CI+) m/z 280.09 ($(M+H)^+$, 100%); HRMS (CI+): m/z calc'd for $C_{17}H_{15}NOP$: 280.0891, found: 280.0885.

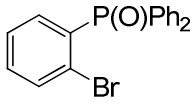
5.4.4 Microwave assisted synthesis of 1,2-bis(diphenylphosphine oxide)-benzene (98)



1,2-diiodobenzene (0.4g; 1.2 mmol), $Pd(OAc)_2$ (11.0 mg; 0.0048 mmol), dippf (30.0 mg; 0.0072 mmol) and DABCO (0.5 g; 4.5 mmol) were placed in a microwave vial. The microwave vial was closed and placed under nitrogen. Diphenylphosphine (0.5 g; 2.9 mmol) was then added. The mixture was dissolved in dry DMF/THF (1:1). The reaction was run in the microwave at 140 °C for 20 minutes. The reaction mixture was washed with water and extracted with dichloromethane (3x50ml). The solvent was removed and the product was purified by column chromatography, prior oxidation with an excess of H_2O_2 (ethyl acetate/hexane 95/5) (84 mg; 0.18 mmol; 15 %). This compound has been previously reported in the literature.[7]

^{1}H-NMR (300MHz, $CDCl_3$) δ 7.19 (m, 8H, Ar*H*), 7.35 (m, 12H, Ar*H*), 7.57 (t, 2H, Ar*H*), 7.75 (m, 2H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 127.01 (m; Ar*C*), 130.20 (m; Ar*C*), 130.54 (Ar*C*), 130.96 (m, Ar*C*), 131.87 ($^{1}J_{C\text{-}P}$ 107.8 Hz; Ar*C*), 135.18 (dd; $^{1}J_{C\text{-}P}$ 90.14 Hz; $^{2}J_{C\text{-}P}$ 8.3 Hz; Ar*C*), 135.09 (t, Ar*C*); ^{31}P{^{1}H}-NMR (121.5MHz) δ 32.079; LRMS (CI+) m/z 501.14 ($(M+Na)^+$, 100%); HRMS (CI+): m/z calc'd for $C_{17}H_{15}NOP$: 501.1150, found: 501.1149.

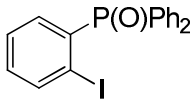
5.4.5 Microwave assisted synthesis of 1-bromo-2-(diphenylphosphine oxide)-benzene (99)



1,2-dibromobenzene (0.2 g; 0.85 mmol), $Pd(OAc)_2$ (8.0 mg; 0.0034 mmol), dippf (21.0 mg; 0.0051 mmol) and DABCO (0.38 g; 3.4 mmol) were placed in a microwave vial. The microwave vial was closed and placed under nitrogen. Diphenylphosphine (0.38 g; 2.0 mmol) was then added. The mixture was dissolved in dry DMF/THF (1:1). The reaction was run in the microwave at 140 °C for 20 minutes. The reaction mixture was washed with water and extracted with dichloromethane (3x50ml). The solvent was removed and the product was purified by column chromatography, prior oxidation with an excess of H_2O_2 (ethyl acetate/hexane 95/5) (82 mg; 0.23 mmol; 30 %). This compound has been previously reported in the literature.[8, 9]

^{1}H-NMR (300MHz, $CDCl_3$) δ 7.05 (m, 2H, Ar*H*), 7.2 (m, 1H, Ar*H*), 7.32-7.38 (m, 6H, Ar*H*), 7.57-7.68 (m, 4H, Ar*H*), 7.95 (m, 1H, Ar*H*) ; ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 125.9 ($^{2}J_{C\text{-}P}$ 11.1 Hz; Ar*C*), 127.5 ($^{2}J_{C\text{-}P}$ 12.5 Hz; Ar*C*), 129.8 (Ar*C*), 131.0 (Ar*C*), 131.1 (Ar*C*), 131.2 (Ar*C*), 132.6 (Ar*C*), 132.5 (Ar*C*), 133.8 ($^{2}J_{C\text{-}P}$ 7.5 Hz; Ar*C*), 134.9 ($^{2}J_{C\text{-}P}$ 10.5 Hz; Ar*C*) ; ^{31}P{^{1}H}-NMR (121.5MHz) δ 33.8; LRMS (CI+) m/z 378.91 ($(M+Na)^+$, 100%).

5.4.5 Microwave assisted synthesis of 1-iodo-2-(diphenylphosphine oxide)-benzene (99a)



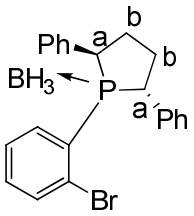
1,2-diiodobenzene (0.4g; 1.2 mmol), $Pd(OAc)_2$ (11.0 mg; 0.0048 mmol), dippf (30.0 mg; 0.0072 mmol) and DABCO (0.5 g; 4.5 mmol) were placed in a microwave vial. The microwave vial was closed and placed under nitrogen. Diphenylphosphine (0.5 g; 2.9 mmol) was then added. The mixture was dissolved in dry DMF/THF (1:1). The reaction was run in the microwave at 140 °C for 20 minutes. The reaction mixture was washed with water and extracted with dichloromethane (3x50ml). The solvent was removed and the product was purified by column chromatography, prior

oxidation with an excess of H_2O_2 (ethyl acetate/hexane 95/5) (348 mg; 0.64 mmol; 72 %). This compound has been previously reported in the literature.[9, 10]

^{1}H-NMR (300MHz, $CDCl_3$) δ 6.9-7.9 (m, 14H, Ar*H*); ^{31}P{^{1}H}-NMR (121.5MHz) δ 33.3; LRMS (ES+) m/z 426.87 ($(M+Na)^+$, 100%).

5.5 Synthesis of diphenylphospholane-based ligands

5.5.1 Synthesis of 1-bromo-2-(diphenylphospholane-borane)-benzene (111)

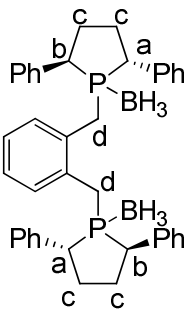


1-bromo-2-iodobenzene (0.5 g, 1.7 mmol) was dissolved in fry and degassed THF. The mixture was placed at -30 °C and exactly 1 equivalent of ^{i}PrMgCl (2M solution in THF, Aldrich) was added dropwise. The mixture was stirred at – 30 °C for 2 hours. One equivalent of chloro-diphenylphospholane freshly prepared was added dropwise keeping the temperature at – 30 °C. The mixture was stirred overnight at room temperature.

The borane-complex was then prepared by adding to the mixture 1 equivalent of borane·THF (1M solution, Aldrich) at 0 °C and stirred 1 hour at room temperature. The product was isolated through column chromatography (20/80 ether/hexane) (0.24, 0.59 mmol, 17%).

^{1}H-NMR (300MHz, $CDCl_3$) δ 1.78-2.24 (m, 4H, b), 2.38-2.52 (m, 2H, a), 6.40-6.56 (m, 3H, Ar*H*), 6.64-6.82 (m, 6H, Ar*H*), 6.96-7.20 (m, 5H, Ar*H*); ^{31}P{^{1}H}-NMR (121.5MHz) δ 59.7 (bm); LRMS (ES+) m/z 409.27 ($(M+H)^+$, 100%); 395.24 ($(M+H-BH_3)^+$, 25%).

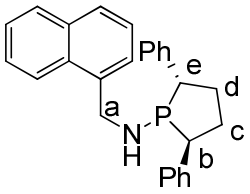
5.5.2 Synthesis of α,α'-bis-(diphenylphospholane-borane)-*o*-xylene (119)



Diphenylphospholane borane (250mg, 0.98 mmol) was dissolved in dry and degassed THF and the mixture was cooled down at -78 °C. 1 equivalent of ^{t}BuLi was added dropwise and the mixture was stirred for one hour at – 78 °C. α,α'-dichloro-*o*-xylene (69 mg, 0.39 mmol) was dissolved in dry and degassed THF and slowly added to the crude mixture of the newly formed lithiated diphenylphospholane borane at -78 °C. The mixture was stirred overnight at room temperature. The product was isolated by column chromatography (20/80 ether/hexane) (60 mg, 0.1 mmol, 25 %).

^{1}H-NMR (300MHz, $CDCl_3$) δ 1.98-2.95 (m, 12H, c and d), 3.33 (m, 2H, a), 3.52 (m, 2H, b), 6.52 (m, 3H, Ar*H*), 6.58-7.49 (m, 21H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 27.25 (d, $^{1}J_{C\text{-}P}$ 22.8 Hz; *C*H_2, d), 28.85 (*C*H_2, c), 32.41 (*C*H_2, b), 43.35 (d, $^{1}J_{C\text{-}P}$ 26.9 Hz; *C*H, a), 45.76 (d, $^{1}J_{C\text{-}P}$ 30.0 Hz; *C*H, b), 125.75 (d, $^{3}J_{C\text{-}P}$ 2.0 Hz; Ar*C*), 126.2 (dd, $^{3}J_{C\text{-}P}$ 5.4 Hz; Ar*C*), 126.67 (d, $^{3}J_{C\text{-}P}$ 3.4 Hz; Ar*C*), 126.9 (Ar*C*), 127.61 (d, $^{3}J_{C\text{-}P}$ 4.6 Hz; Ar*C*), 127.8 (Ar*C*), 130.54 (d, $^{3}J_{C\text{-}P}$ 3.4 Hz; Ar*C*), 134.4 (d, $^{2}J_{C\text{-}P}$ 3.4 Hz; Ar*C*), 135.8 (Ar*C*); ^{1}P{^{1}H}-NMR (121.5MHz) δ 41.2 (bm); LRMS (ES+) m/z 633.23((M+Na)$^{+}$, 100%); HMRS (ES+): m/z calc'd for $C_{42}H_{54}P_2B_2$: 633.3180; found: 633.3183.

5.5.4 Synthesis of N-diphenylphospholane-1-naphtylmethylamine (114)

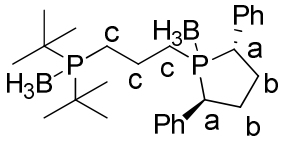


To a solution of dry Et_3N (0.49 g, 4.9 mmol) and dry and degassed ether, it was added 1-naphtylmethylamine (0.7 g, 4.4 mmol). The mixture was cool down at -78 °C. A solution in THF of chlorodiphenylphosphine, freshly prepared (1 equivalent) was slowly added. The mixture was stirred at room temperature overnight. The mixture was filtered through a short pad of silica to remove the excess of Et_3N, yielding the product in quantitative yield.

^{1}H-NMR (300MHz, C_6D_6)δ 1.35 (t, 1H, N*H*), 1.85 (m, 2H, c), 2.13 (m, 2H, d), 2.86 (m, 1H, b), 3.16 (m, 1H, e), 3.60 (dt, 1H, a), 4.12 (m, 1H, a), 7.11 (d, 1H, Ar*H*), 7.29 (m, 13H, Ar*H*), 7.61 (d,

1H, Ar*H*), 7.72 (d, 1H, Ar*H*), 7.92 (d, 1H, Ar*H*); ^{13}C-NMR (75.5MHz, C_6D_6) δ 30.03 (*C*H_2), 32.53 (*C*H_2), 48.7 (d, $^2J_{C\text{-}P}$ 25.1 Hz; *C*H_2, a), 48.9 (d, $^2J_{C\text{-}P}$ 23.6 Hz; *C*H, b), 53.88 (d, $^2J_{C\text{-}P}$ 13.5 Hz; *C*H, e), 123.5 (Ar*C*), 124.1 (Ar*C*), 124.5 (d, $^3J_{C\text{-}P}$ 5.1 Hz; Ar*C*), 124.6 (Ar*C*), 126.6 (Ar*C*), 126.7 (Ar*C*), 126.85 (d, $^4J_{C\text{-}P}$ 3.4 Hz; Ar*C*), 126.9 (Ar*C*), 127.3 (d, $^3J_{C\text{-}P}$ 38.3 Hz; Ar*C*), 130.6, 132.9 (Ar*C*), 136.4 (d, $^2J_{C\text{-}P}$ 11.2 Hz; Ar*C*), 138.5 (Ar*C*), 142.7 (d, $^2J_{C\text{-}P}$ 18.3 Hz; Ar*C*); ^{31}P{^{1}H}-NMR (121.5MHz) δ 74.6; HMRS (CI+): m/z calc'd for $C_{27}H_{27}NP$: 396.1872, found: 396.1881.

5.5.5 Synthesis of (127)



Diphenylphospholane borane (50 mg, 0.2 mmol) was dissolved in dry and degassed THF and the solution was placed at -78 °C. 1 equivalent of ^{t}BuLi (1.5M solution in pentane) was added dropwise and the mixture was stirred for one hour. 3-(diterbutylphosphine borane)-1-bromopropane was dissolved in dry and degassed THF and the solution was added to the THF solution of the lithiated diphenylphospholane borane, at -78 °C. The mixture was stirred overnight at room temperature. The product was isolated through chromatography column (20/80 ether/hexane) (19 mg; 0.35 mmol, 17%).

^{1}H-NMR (300MHz, C_6D_6)δ 1.1 (m, 24H, C(C*H*$_3$)$_3$ and 3xC*H*$_2$ c), 2.25 (bm, 4H, 2xC*H*$_2$ b), 3.45 (bm, 2H, 2xC*H* a), 7.11 (m, 10H, Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 17.67 (C-(*C*H$_3$)$_3$), 18.24 (dd, *C*H$_2$), 27.75 (dd, *C*H$_2$), 29.5 (C-(*C*H$_3$)$_3$), 31.07 (dd, *C*H$_2$), 33.3 (d, $^2J_{C\text{-}P}$ 4.7 Hz; *C*H$_2$, b), 44.9 (q, *C*H, a), 126.13 (d, $^2J_{C\text{-}P}$ 9.8 Hz; Ar*C*), 126.7 (d, $^3J_{C\text{-}P}$ 3.5 Hz; Ar*C*), 127.4 (Ar*C*), 127.8 (Ar*C*); ^{31}P{^{1}H}-NMR (121.5MHz) δ 41.5 (bm), 49. 39 (bm); HMRS (ES+): m/z calc'd for $C_{27}H_{46}B_2NaP_2$: 477.3160, found: 477.3159.

5.5.6 General procedure for hydroxycarbonylation

A glass-lined stainless steel autoclave equipped with a magnetic stirring bead was charged with the catalytic solution, prepared before in a dried and degassed Schlenk tube, containing the catalyst (1 mol%), p-toluenesolfonic acid (0.2 eq.), lithium chloride (0.2 eq.), degassed water (2.5 eq) dissolved in 3ml of dry butan-2-one. The substrate was then added (0.45 mmol) prior to sealing the autoclave. The autoclave was flushed three times with carbon monoxide and finally charged with carbon monoxide to the specific reaction pressure. The reactions were stirred at the same speed for

the desired times at the required temperature using a stainless steel heating jacket connected to a thermocouple and heater. After the desired time passed, the autoclave was opened and the solvent removed. The mixture was dissolved in toluene and worked up with a saturated solution of sodium bicarbonate in water (3x50ml). The inorganic layer was then acidify (HCl, 1M) and the reformed acid was then extracted with dichloromethane (3x50ml). The branched to linear ratio was calculated by NMR. The enantiomeric excess was calculated by NMR prior addition of 0.5 eq of (*S*,*S*)-DPEN.

5.6 References

1 L. Xu, J. Mo, C. Baillie, and J. Xiao, *J. Organomet. Chem.,* 2003, **687**, 301.
2 M. Nechab, E. Le Gall, M. Troupel, J. Y. Nedelec, *J. Organomet. Chem.,* 2006, **691**, 1809.
3 B. Croxtall, J. Fawcett, E. G. Hope and A. M. Stuart, *J. Chem. Soc., Dalton Trans.,* 2002, 491.
4 A. M. Echeavarren, and J. K. Stille, *J. Am. Chem. Soc.*, 1987, **109**, 5478.
5 Y. Wang, C. W. Lai, F. Y. Kwong, W. Jia, and K. S. Chan, *Tetrahedron*, 2004, **60**, 9433.
6 E. C. Carson and S. J. Lippard, *J. Am. Chem. Soc.,* 2004, **126**, 3412.
7 W. Levason, R. Patel, and G. Reid, *J. Organomet. Chem.,* 2003, **688**, 280.
8 C. Baillie and J. Xiao, *Tetrahedron*, 2004, **60**, 4159.
9 D. G. Gillespie, B. J. Walker, D. Stevens, and C. A. McAuliffe, *J. Chem. Soc., Perkin Trans. 1,* 1983, 1697.
10 B. V. Meprathu, M. W. Justik, and J. D. Protasiewicz, *Tet. Lett.*, 2005, **46**, 5187.