STUDIES ON THE OPTIMIZATION OF BUCHWALD-HARTWIG AMINATION OF ARYL HALIDES

by

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Abstract

Developing new catalyst systems for cross-coupling reactions such as Buchwald-Hartwig aminations has been one of the remarkable topics in the palladium-catalyzed, cross-coupling reaction research area.

In this thesis, the use of the easily synthesized and handled Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5) (**I**) as a catalyst precursor for Buchwald-Hartwig amination of aryl halides was investigated utilizing various phosphines (P^tBu_3, Xphos and Mor-Dalphos), different phosphine (L) to Pd ratios (L:Pd = 2:1 and 1:1) and different procedures; in situ generation of PdL_n prior to addition of other reactants (Method A) and in situ generation of PdL_n in the presence of aryl halide but prior to the addition of other reactants (Method B). The reaction profiles are monitored by gas chromatography (GC) and the effect of each of the mentioned parameters on the reaction rate is determined. The reaction profiles of **I** with various phosphines are also compared with those of other precursors, $Pd_2(dba)_3$, $Pd(OAc)_2$ and [Pd(η^3-1-Ph-C_3H_4)Cl]$_2$ (**IV**).

In spite of a large number of studies involving modification of Buchwald-Hartwig amination reactions by developing new precursors and phosphines, fewer studies have been carried out on catalytic mechanisms and there is still ambiguity about the catalytically active species in these palladium-catalyzed reactions. This study on a representative Buchwald-Hartwig amination finds that, in Buchwald-Hartwig aminations, various species might be participating as the catalytically active species via various mechanisms, utilizing different catalyst

systems. This finding is contrary to the observations for other cross-coupling reactions such as Suzuki-Miyaura and Mizoroki-Heck in which the efficient formation of putative PdL_2 from $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)(\eta^5\text{-}C_5H_5)$ (**I**) resulted in higher initial rates and higher conversions under mild reaction conditions, than other common precatalysts ($Pd(OAc)_2$, $Pd(PPh_3)_4$, Pd_2dba_3, etc.) containing a variety of phosphine ligands. Therefore, to further our studies, the solution chemistry of **I** and **IV** with P^tBu_3, XPhos and Mor-DalPhos has been studied by ^1H NMR and ^{31}P NMR spectroscopy. All intermediates observed were characterized by NMR spectroscopy.

Acknowledgements

In these acknowledgements, I would like to express my gratitude to many people for their help and encouragements throughout my doctoral studies. Firstly, to my supervisor, Dr. Michael Baird for giving me the opportunity to be part of his research group. I sincerely appreciate your guidance, friendship and patience. Working with your group has been a great inspiration to me.

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I would like to thank all the past and present members in the Baird group, especially Andrew, Alex, Kevin, Dave, Nicole, Xin, Adeela and of course Shirley Baird, for all the good times and memories.

Thanks to Emilia and Rolf for all the support from the first day of my stay in Canada. Great thank-you to Dr. Nahid Aghighi, I have truly appreciated your encouragements. I would also like to thank all of my friends at Queen's University, Hanna, Mona, Klaus, Marina, Calista, Gillian, John, Lili, Raya and Marjan, thank-you for making my PhD experience as much as enjoyable as it could be.

Lastly and most importantly, I would like to express my deepest gratitude to my parents and dear sister, Sarah, for the endless love and support. I wouldn't be where I am without you.

Co-Authorship

All published papers resulting from this thesis have been co-authored with my supervisor, Dr. M. C. Baird, along with undergraduate students, D.M.E Tom and X. Zhang.

In particular, the following publications are based on chapters of this thesis:

1. Borjian, S.; Tom, D. M. E.; Baird, M. C. "Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5) (**I**) as a Catalyast Precursor for Buchwald Hartwig Amination Reactions", *Organometallics* **2014**, 33, 3928, is based on Chapter 2.
2. Borjian, S.; Tom, D. M. E.; Baird, M. C. "NMR Studies of the Species Present in Cross-coupling Catalysis Systems Involving Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5) (**I**) and [Pd(η^3-1-Ph-C_3H_4)Cl]$_2$ (**IV**) Activated by P^{t}Bu$_3$, XPhos and Mor-Dalphos: Nonexistance of Pd(XPhos)$_n$ and Pd(Mor-Dalphos)$_n$ (n= 1, 2) at Moderate Temperatures", *Organometallics* **2014**, 33, 3936, is based on Chapter 3.
3. Zhang, X.; Borjian, S.; Baird, M. C. "An Investigation of the Formation and Entrapment of Palladium(0)-PPh_3 Species to Give Products with Low (<3:1) Ligand:Pd Ratios", submitted, is based on Chapter 4. It was carried out under my supervision in parallel with and complementing a much more extensive, analogous study by me which involved other phosphines but was not included in my thesis because of time considerations.

Statement of Originality

The research discussed in this work was carried out or directed by the author in the Department of Chemistry at Queen's University under the supervision of Dr. M. C. Baird. D.M.E Tom carried out duplicate runs of the amination reactions to complement work done by the author in order to check for reproducibility (some of the plots shown in chapter 2). X. Zhang carried out NMR experiments in Chapter 4 under my supervision and in parallel with analogous, as yet unreported, experiments carried out by me.

Sogol Borjian Borojeni

September, 2014

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List of Abbreviations

Ad	Adamantyl
Ar	aryl group
Å	Ångström
^{t}Am	*tert*-amylate (*tert*-pentoxide)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
br	broad
BrettPhos	2-(dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
^{t}Bu	*tert*-butyl
° C	degrees Celsius
Cp	cyclopentadienyl (η^5-C_5H_5)
Cy	cyclohexyl
^{13}C NMR	carbon NMR
COSY	correlation spectroscopy
δ	chemical shift in ppm
d	doublet
DavePhos	2-dicyclohexylphosphino-2′-(N,N-dimethylamino)biphenyl
dba	dibenzylideneacetone
DMF	dimethylformamide
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
Et	ethyl
equiv	equivalent

GC	gas chromatography
g	grams
h	hour
^{1}H NMR	proton NMR
Hz	hertz
HMBC	hetereonuclear multiple bond coherence
HSQC	heteronuclear single quantum coherence
J	coupling constant
m	multiplet
m	meta
M	moles/litre
Me	methyl
MeOH	methanol
mg	milligrams
MHz	megahertz
min	minute
mL	millilitres
mol	moles
mmol	millimoles
Mor-Dalphos	di(1-adamantyl)-2-morpholinophenylphosphine
µL	microlitres
NMR	nuclear magnetic resonance
o	ortho

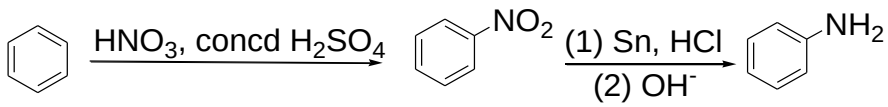
OAc	acetate
OMs	mesylate (salt of methanesulfonic acid)
p	para
Ph	phenyl
^{31}P NMR	phosphorus NMR
ppm	parts per million
iPr	isopropyl
R	alkyl group
RuPhos	2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
s	singlet
t	triplet
THF	tetrahydrofuran
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Chapter 1

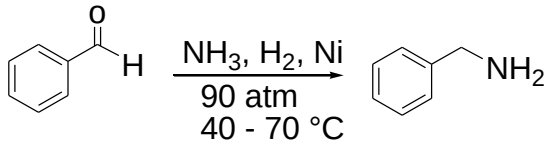
Introduction

1.1 Buchwald-Hartwig Amination of Aryl Halides

Early studies of reactions to form C-N bonds involved nucleophilic aromatic substitution (Scheme 1), reductive amination (Scheme 2) and Ullmann reactions (Scheme 3). The examples of nucleophilic aromatic substitution and reductive amination reactions as well as the general scheme of Ullmann reaction are shown in Schemes 1, 2 and 3. As is observed, each of these has serious limitations,[1-3] such as need for high temperature or pressure, use of strong acids or reducing agents, and there has always been a need for more versatile reactions under milder conditions.

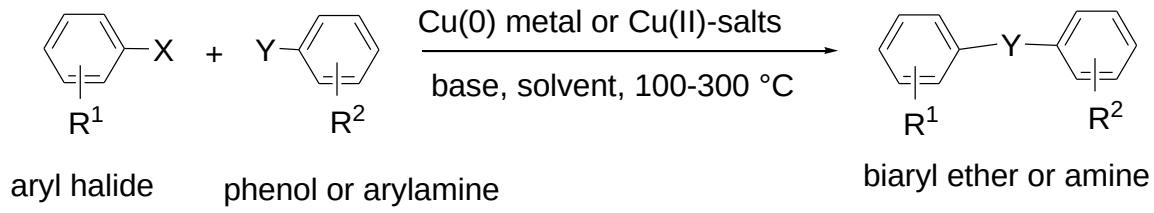


Scheme 1. Aromatic substitution of benzene.



Benzaldehyde Benzylamine (89%)

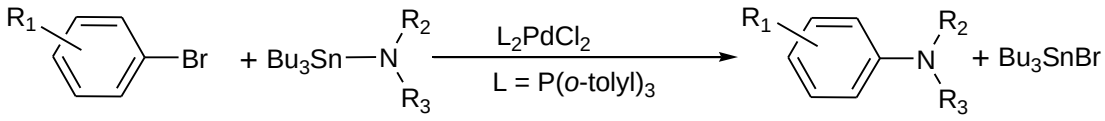
Scheme 2. Reductive amination of Benzaldehyde.



Scheme 3. Ullmann reaction.

Because of the drawbacks of the previous methods to form C-N bonds, such as cost, synthetic efficiency, toxicity and safety, new metal-catalyzed methods have been developed, especially involving palladium.

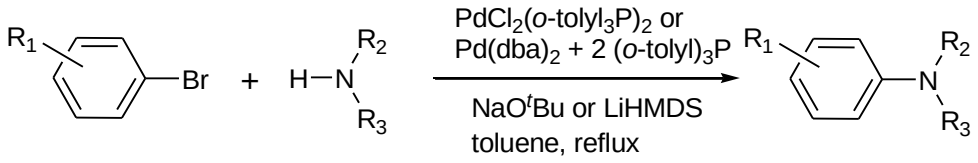
Migita, Kosugi and coworkers developed palladium(0)-catalyzed aminations of bromoarenes by using tin amides as nucleophiles in 1983 (Scheme 4).[1]



Scheme 4. Palladium(0)-catalyzed aminations developed by Migita & Kosugi.

Although this method could not be generally useful because of the toxicity of tin amide compounds and limited efficiency in synthesis of various arylamines, it prompted further research in this area.

In the late 1990s, Buchwald and Hartwig separately established new palladium(0)-catalyzed reactions in which amines were used directly as nucleophiles in the presence of bases to synthesize substituted amines without the need to use tin amides (Scheme 5). These palladium-catalyzed amination reactions came to be known as Buchwald-Hartwig amination reactions.



Scheme 5. Primary developed Buchwald-Hartwig aminations.

In their initial work, Buchwald and Hartwig successfully aminated aryl bromides with secondary amines[2,3] but found that applications to primary amines were problematic because of side reactions involving β-hydride elimination and bis-arylation (see below). Studies were therefore continued to develop new ligands to solve this problem, both groups developing new classes of ligands which will be discussed in detail in the ligand section below. The mechanism of the overall process was also established.

Several hundred publications on this subject have appeared since the early work, as have a number of useful reviews.[4-8] Catalytic systems involving ligands other than phosphines have been investigated. However, only phosphine systems will be discussed in this thesis.

1.2 Mechanism of Buchwald-Hartwig Amination

Research into the Buchwald-Hartwig reaction has involved investigations of four key variables, palladium catalyst precursors, ligands, bases and solvents. Other factors such as temperature, order of addition, precursor loading, ligand to precursor ratio and even the rate of stirring, affect reaction rates and/or product distributions.

Different catalytic cycles for Buchwald-Hartwig reactions have been proposed depending on the ligands used and the substrates. However, a catalytic cycle

which has been suggested by Buchwald for dialkylbiaryl phosphines in a recent paper[9] is depicted in Figure 1. After the formation of the catalytic species $Pd(0)L_n$ (n commonly = 2; sometimes n = 1; L = tertiary phosphines), there follows oxidative addition of the aryl halide to $Pd(0)L_n$ and coordination of the amine to the resulting palladium(II) intermediate. Base deprotonates the amine and the arylamine product is formed by reductive elimination as the catalyst is regenerated.

The rate of oxidative addition depends on the electronic and steric properties of the catalyst and substrate. The more electron-rich and sterically unhindered the catalyst, the higher the rate of the oxidative addition. The nature of the halide also affects the rate (I > Br > Cl > F) because the carbon-halogen bonds are broken during the oxidative addition step.

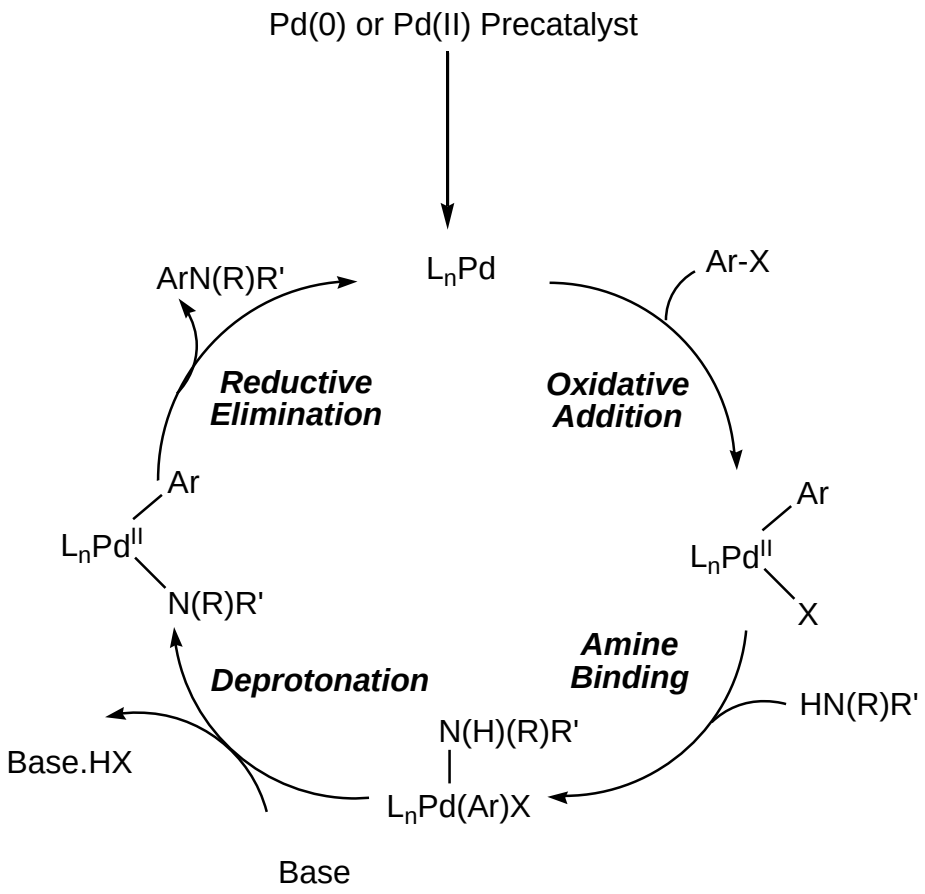


Figure 1. Catalytic cycle for palladium-catalyzed amination.

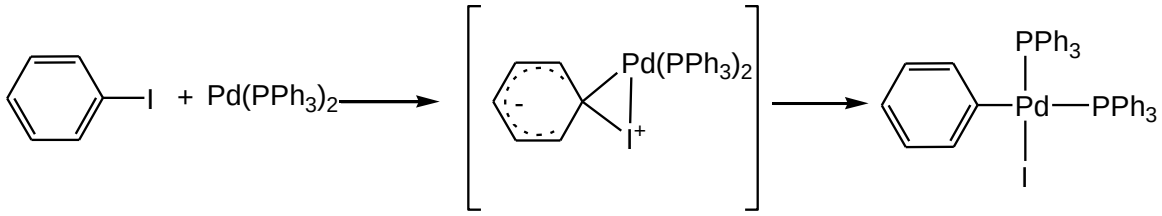
The rate of amine coordination depends on the catalyst and the substrate properties. When the amine substrate is more basic and/or is sterically unhindered, the rate of amine binding is higher. The rate of deprotonation of the bound amine is determined by the acidity of the amine, which increases on coordination to the metal. Reductive elimination is a function of the metal/ligand properties. Since reductive elimination causes the metal to be more electron-rich and reduces the steric strain, bulkier and electron poor ligands will increase the rate of reductive elimination.

1.2.1 Oxidative Addition

Oxidative addition to Pd(0) is the first step in most of the catalytic cycles of palladium-catalyzed cross-coupling reactions such as Buchwald-Hartwig amination (Figure 1). It is the rate determining step in many of the proposed mechanisms, and compounds of the type PdArXL, which are oxidative addition products, have exhibited anticipated catalytic activity.[10-14] Therefore, oxidative addition has received substantial attention in the literature. It has been attempted to maximize the rate of the oxidative addition by using different palladium precursor/ligands systems, understand the oxidative addition mechanisms for different catalyst systems and characterize the obtained products.[15-27]

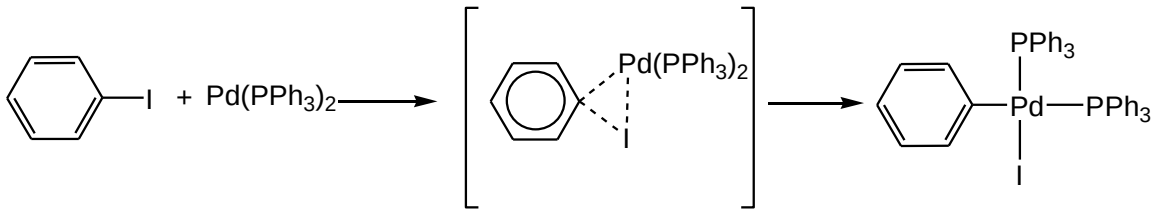
Fitton et al.[28] did the earliest research on oxidative addition of aryl halides to Pd(0), reporting that the oxidative addition of iodobenzene to $Pd(PPh_3)_4$ results in the formation of $PdIPh(PPh_3)_2$ at room temperature. It was shown subsequently that oxidative addition of bromobenzene takes place at 80 °C but chlorobenzene was found to be unreactive, even at 135 °C. According to these observations, PhI > PhBr > PhCl, was found to be the relative reactivity of aryl halides. Moreover, activated aryl chlorides containing electron withdrawing groups exhibited greater reactivity in oxidative addition, which suggested that the mechanism of oxidative addition may be similar to that of nucleophilic aromatic substitution. Further studies by Fauvarque et al. confirmed the previously obtained results by Fitton et al.. Their kinetic study on oxidative addition confirmed the mechanism similarity

to that of the nucleophilic aromatic substitution and it was proposed that the product is formed via a reactive $Pd(PPh_3)_2$ intermediate (Scheme 6).[29]



Scheme 6. Proposed oxidative addition mechanism of $Pd(PPh_3)_2$ by Fauvarque et al..

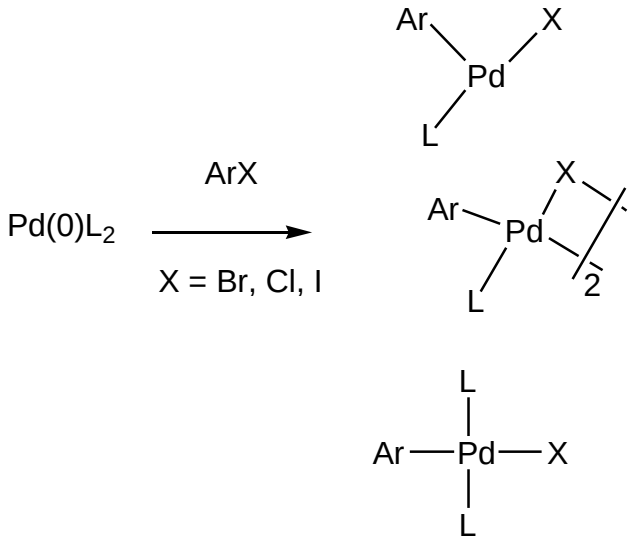
Later, Pflüger and Amatore argued against the oxidative addition mechanism proposed by Fauvarque and Fitton, in which the intermediate was an ionic specie as shown in Scheme 6. Pflüger and Amatore's experiments in solvents with different polarities (THF and toluene) demonstrated that the activation parameters are similar in the two solvents. Therefore, they suggested that the intermediate for the oxidative addition is not an ionic species and oxidative addition proceeds via a neutral concerted, three-centered intermediate (Scheme 7).[30]



Scheme 7. Proposed oxidative addition mechanism of $Pd(PPh_3)_2$ by Pflüger and Amatore.

The oxidative addition product, $PdArXL_n$, has been reported to exist as *cis* and *trans*-geometry (n=2); *cis*-$PdArXL_2$ forms initially and *trans*-$PdArXL_2$ is almost always observed and/or isolated.[31]

Many further studies were carried out on the mechanism of oxidative addition and the formed products, using various catalyst systems and aryl halides. It has been suggested that, depending on the identity of the halide and the steric bulk of the ligand, mono-(PdArXL) or bis ligated ($PdArXL_2$), or dimeric species may form (Scheme 8).[20,21,24]



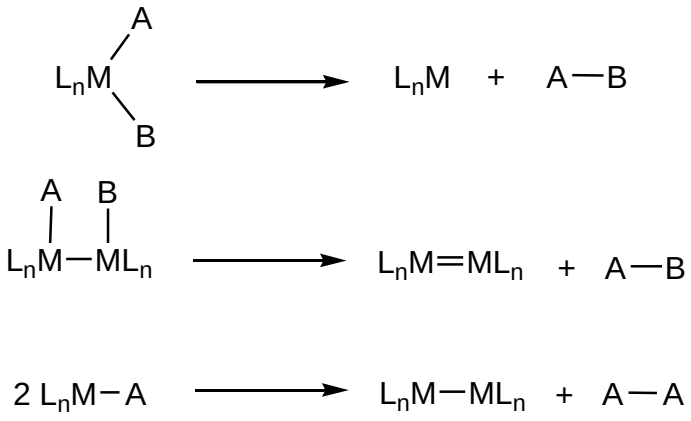
Scheme 8. Proposed oxidative addition products based on halide identity and ligand.

In all of these studies, the aryl halide was added to the $Pd(0)L_2$ and it was assumed that the oxidative addition product in any of the previously mentioned structures, would be the only product. However, further investigation revealed other results, for example, the oxidative addition of bromobenzene to $Pd[P^tBu_3]_2$ can generate a variety of catalytic and non-catalytic species such as

$[(P^tBu_3)Pd(\mu\text{-}Br)]_2$, $(P^tBu_3)_2Pd(H)Br$, $[Pd(P^tBu_3)_2(C(CH_3)_2CH_2)(\mu\text{-}Br)]_2$ and $^tBu_3P{\cdot}HBr$ in addition to the mono-phosphine species $PdPhBr(P^tBu_3)$.[23]

1.2.2 Reductive Elimination

As the product forming step in most of the cross-coupling catalytic cycles such as Buchwald-Hartwig amination reactions, reductive elimination has been studied in detail. Reductive elimination is the reverse reaction of oxidative addition and mechanisms pathways of reductive elimination might be concerted, ionic or radical-based. Depending on the number of the metal centers in the complex, product are formed through different chemical reactions (Scheme 9).[32]

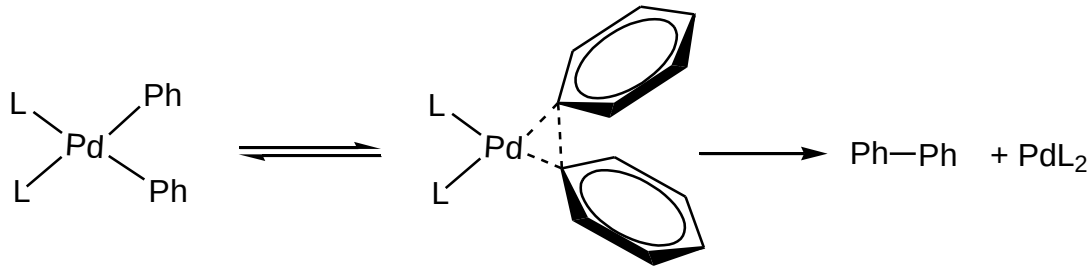


Scheme 9. Different reactions for reductive elimination product formation.

Various factors affect the rate of the reductive elimination reactions such as metal center, ligand and their properties, coordination number and geometry of the complex. For example, complexes containing more sterically hindered ligands undergo faster reductive elimination than those with less sterically hindered ligands.[33] Moreover, Gillie demonstrated that complexes

with the ligands in *cis* position reacted faster than the *trans* isomer and prior isomerization of the *trans* complex to *cis* was required before the reductive elimination occured.[34]

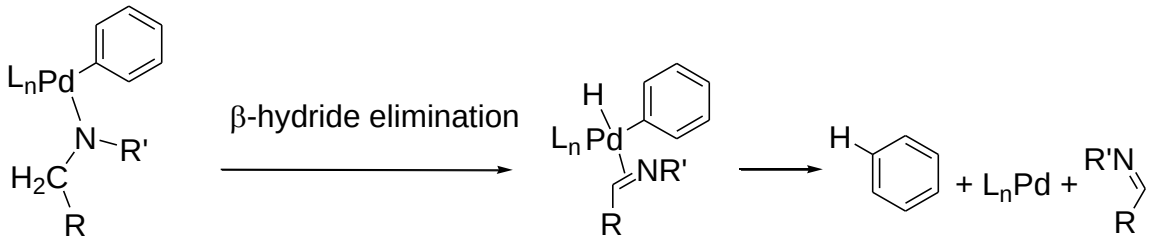
Investigations of reductive elimination reactions resulting in formation of carbon-heteroatom bonds have started more recently than those generating non-polar C-H or C-C bonds. It has been shown that, the reductive elimination from the arylpalladium(II) complexes occur via non-ionic, non-radical concerted mechanism (Scheme 10).[35,36]



Scheme 10. Reductive elimination of $PdAr_2L_2$ via non-ionic, non-radical, concerted mechanism.

1.2.3 β-Hydride Elimination

β-Hydride elimination involves the transfer of the β-hydrogen of the alkyl group to the metal and formation of a double bond (Scheme 11). In the Buchwald-Hartwig reaction (Figure 1), if the alkyl group attached to palladium center possesses a β-hydrogen, β-hydride elimination of the oxidative addition product may compete with the reductive elimination reaction and preempt desired reductive elimination (Scheme 11).



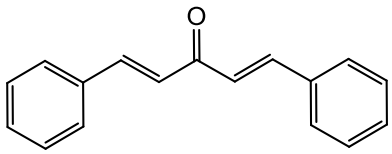
Scheme 11. Representative reaction of β-hydride elimination in Buchwald-Hartwig amination.

1.3 Common Palladium Precursors

$Pd(OAc)_2$ and $Pd_2(dba)_3$ (dba = PhCH=CHCOCH=CHPh) are the common and the primary precursors which have been used for Buchwald-Hartwig reactions and they are still being used. The palladium catalyst must be in the 0 oxidation state before the catalytic cycle initiates, and therefore the palladium(II) in $Pd(OAc)_2$ must be reduced prior to catalysis initiation (see sections 1.3.1 and 1.3.2). $PdCl_2$ is another palladium(II) precursor which has been used and has been reported to be efficient in the amination of aryl bromides using diphosphines but not very promising with mono-phosphines.[37] Palladium loadings for these reactions vary from 0.01 mol% to 2-5 mol%. The cinnamyl compound $[Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_5)Cl]_2$ (**IV)** has recently been claimed to be superior to **I** for some amination reactions (see section 1.3.3).[11]

1.3.1 $Pd_2(dba)_3$

In the case of $Pd_2(dba)_3$ (dba = dibenzylideneacetone), the oxidation state of palladium is already 0 and there is no need for reduction.[38] In this case reaction with phosphines L gives species of the type $Pd(dba)L_2$ rather than $Pd(0)L_n$;[39,40] the three coordinate species are more sterically hindered and therefore less active, but nonetheless function as useful catalysts. The structure of dba (dibenzylideneacetone) is shown in Scheme 12.

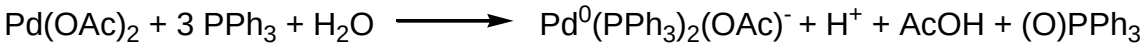


Scheme 12. Structure of *trans,trans*-dibenzylideneacetone (dba).

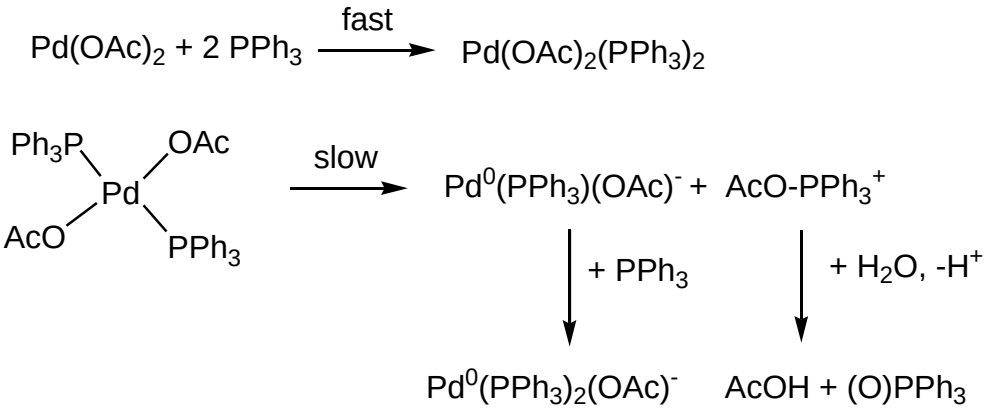
1.3.2 $Pd(OAc)_2$

Historically, reduction has often been effected by phosphines such as PPh_3 which generates the palladium(0) complex $[Pd(OAc)L_2]^-$ in addition to oxidized phosphorus byproducts (Scheme 13).[41-48] Amatore and Jutand have shown that using 2 equivalents of PPh_3 does not result in the formation of Pd(0) compound and at least 3 equivalents of PPh_3 is needed. However, as noted previously,[49] there is very little evidence that reductions are effected to a useful extent by other phosphines in general.

overall reaction:

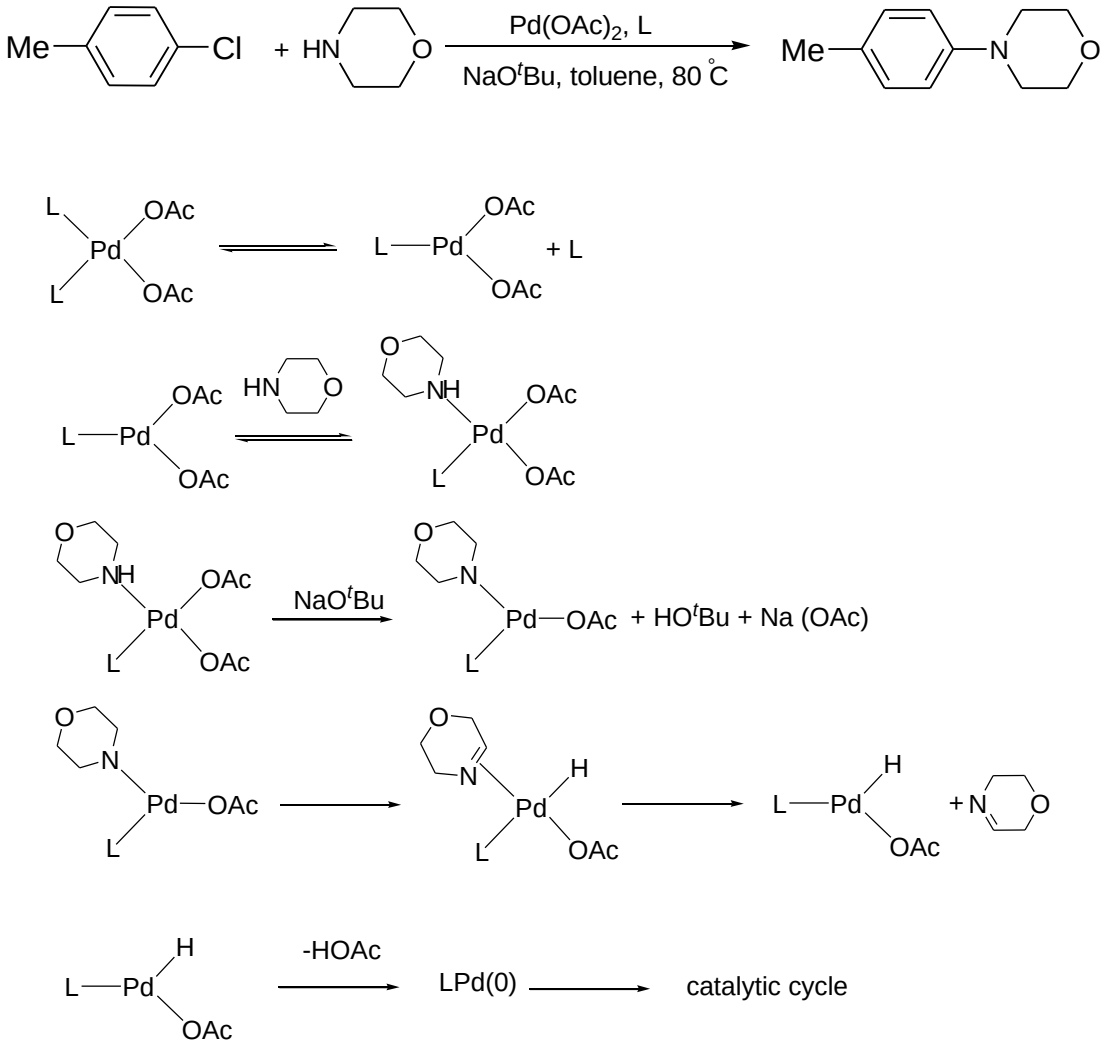


reaction steps:



Scheme 13. Reduction of $Pd(OAc)_2$ by PPh_3 to form Pd(0) in the presence of 2 or 3 equiv of PPh_3 and water.

In many cases amine substrates containing β-hydrogen atoms, are the reducing agent, via a reduction process shown in Scheme 14.[50]



Scheme 14. Mechanism for catalyst activation by amines.

For amines lacking β-hydrogens, such as anilines, reduction is slow and more reducing amines which contain β-hydrogen atoms (Et_3N or *i*-Pr_2NH) are added.[51]

1.3.3 $[Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)Cl]_2$ (IV)

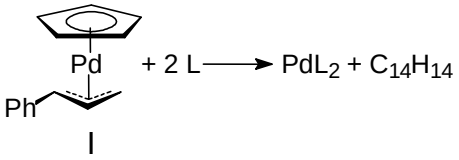
$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ has been used as a precursor for various cross-coupling reactions by different groups and inconsistent results have been reported for this precursor. For example Fors et al. used $[(allyl)PdCl]_2$ with dialkylbiarylphosphine ligands as the catalyst system for the amination of 4-chloroanisole with aniline using NaO^tBu in dioxane at 80 °C and they found it not to be productive for the representative reaction.[52] Furthermore, Biscoe et al. also confirmed the inefficiency of $[(allyl)PdCl]_2$/XPhos catalyst system for the same reaction.[53] Fraser et al. demonstrated that the allyl compound $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ is a relatively poor precursor for Suzuki-Miyaura reactions.[49] However, Lundgren et al. developed catalysts based on P,N-ligands (2-(di-*tert*-butylphosphino)-N,N-dimethylaniline or 2-(di-1-adamantylphosphino)-N,N-dimethylaniline with $[(allyl)PdCl]_2$, finding that they catalyzed cross-coupling of various aryl and heteroaryl chlorides with a diverse range of amines under low catalyst loadings and with excellent functional group tolerance and chemoselectivity.[54]

The cinnamyl analogue, $[Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)Cl]_2$, has been used more recently and it has been showed that it is a very efficient precursor under certain conditions for some cross-coupling reactions. For example, Banerjee et al. reported successful hydroamidation of electron-deficient N-heterocyclic amides and sulfonamides with 1,3-dienes and vinyl pyridines in the presence of $[Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)Cl]_2$ and 1,3-bis(diphenylphosphino)propane or 1,4-bis(dicyclohexylphosphino)butane as ligands.[55]

The Stradiotto group has extensively used this precursor recently as well. In their recent research, they utilized mostly a $[Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)Cl]_2$/Mor-DalPhos combination as a catalyst for various cross-coupling reactions. For example, they used it for chemoselective mono-N-arylation of primary and secondary aliphatic amines such as methylamine. Aryl mesylates featuring electron-donating or electron-withdrawing functionality, ortho-substitution, as well as base-sensitive groups have been used as electrophiles in these reactions.[56]

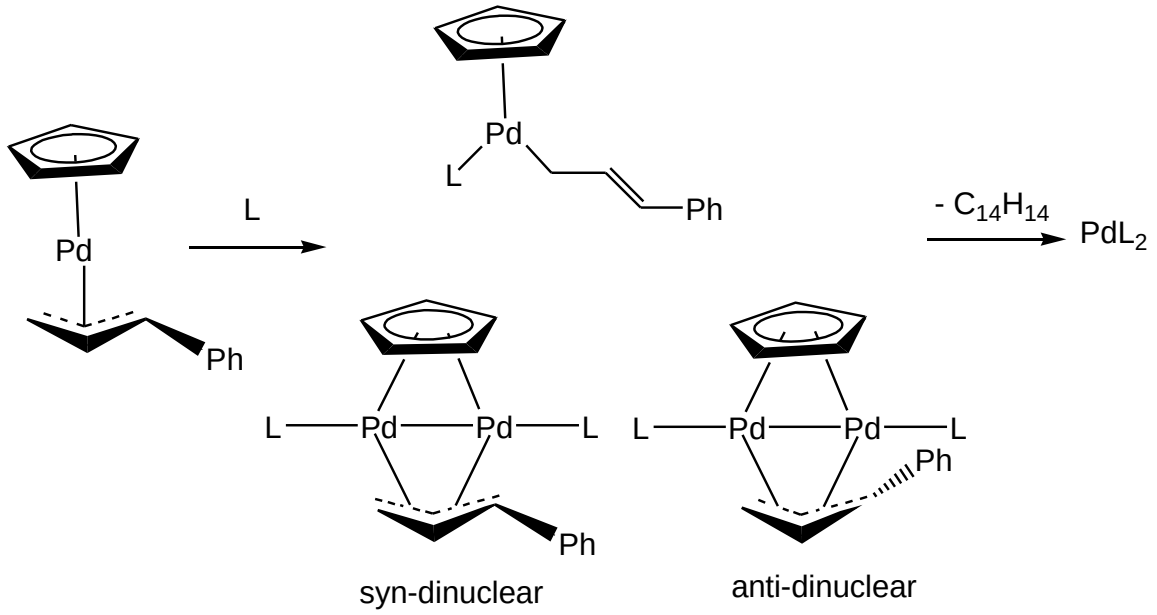
1.3.4 $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)(\eta^5\text{-}C_5H_5)$ (I)

Norton et al. have previously reported that easily synthesized, user-friendly, thermally and air-stable compound $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)(\eta^5\text{-}C_5H_5)$ (**I**) reacts rapidly with a number of phosphines L to form the compounds PdL_2 as in eq. 1.[57]



I (1)

The formation of three types of intermediates, σ-allyl and dinuclear complexes, was observed en route to PdL_2. The proposed route to PdL_2 formation is shown in Scheme 15.



Scheme 15. Reaction mechanism when a tertiary phosphine ligand L is reacted with $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_5)(\eta^5\text{-}C_5H_5)$. The σ-allyl and dinuclear complexes were observed in different amounts for different ligands.

The Baird group continued studies on this precursor and Fraser et al. have compared **I** utilizing various ligands for example Suzuki-Miyaura,[49] Heck-Mizoroki[58] and Sonogashira[58,59] cross-coupling reactions, with catalyst systems based on $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $PdCl_2$ and $Pd(OAc)_2$. They have shown that, catalyst systems based on **I** have been more efficient than the frequently utilized, alternative precursors mentioned above. Additionally the latter precursors do not generate two-coordinate palladium(0) catalytic species (see sections 1.3.1 and 1.3.2).

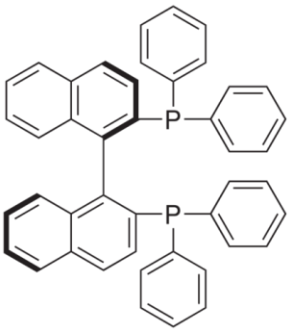
$Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)(\eta^5\text{-}C_5H_5)$ has been utilized by others for various cross-coupling reactions. Braunschweig et al. used it as a precursor for the synthesis of a heteroleptic (phosphine)(NHC)Pd(0) compound, $Pd(PCy_3)$(N,N'-bis(*tert*-butyl)-

imidazol-2-ylidene);[60] and they obtained high yields using **I** while other precursors resulted in the formation of product mixtures. Cramer et al. reported the successful use of Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5) for the synthesis of palladium(0) complexes containing a series of new electron rich phosphines. These complexes are used as catalysts for enantioselective C(sp^3)–H functionalization.[61] The **I**/XPhos catalyst system was also shown to be much more effective than was $Pd_2(dba)_3$/XPhos catalyst system for a series of Buchwald-Hartwig amination reactions.[62,63] Other research groups also demonstrated that desired products were obtained with higher selectivity using **I** as precursor.[64-66]

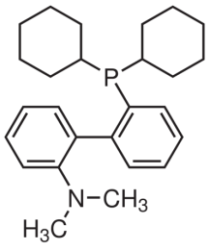
1.4 Commonly Used Phosphines

As indicated above, the nature of the phosphine ligand L is expected to have a major influence on Buchwald-Hartwig reactions and structure-reactivity relationships have been sought utilizing several palladium precursors, notably $Pd(OAc)_2$ and $Pd_2(dba)_3$.[7,9,38,67,68] Shown in Scheme 16 are many of the ligands used.

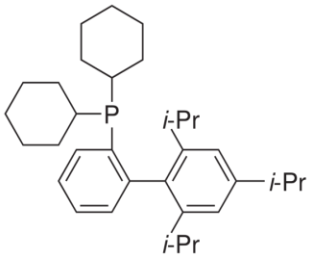
Implicit in these studies has been the assumption that they have generally involved catalysts of the type $Pd(0)L_2$ and hence that ligand comparisons are valid; as pointed out above,[39-47] this assumption may generally not be valid. We return to this theme below.



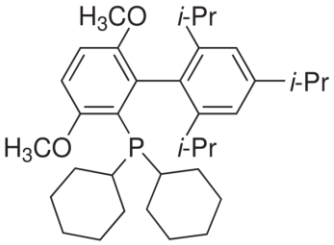
BINAP



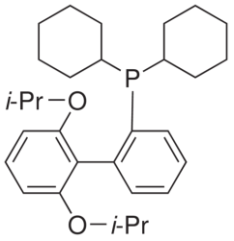
DavePhos



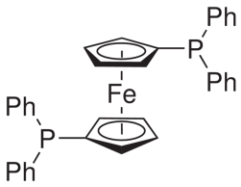
XPhos



BrettPhos

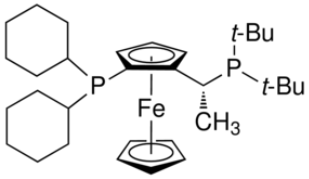


RuPhos

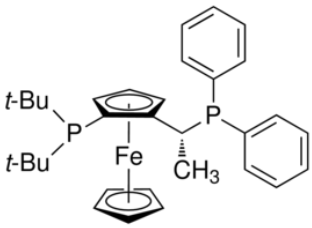


DPPF

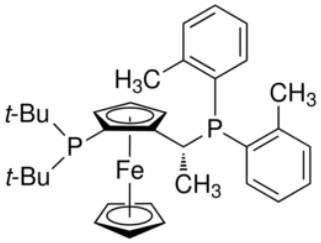
JosiPhos ligands



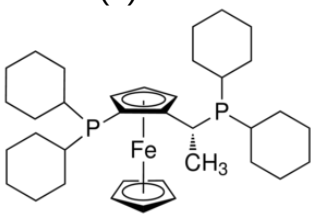
(a)



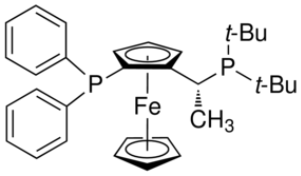
(b)



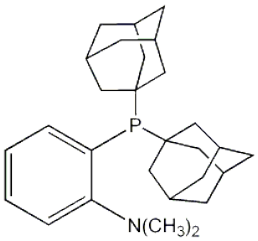
(c)



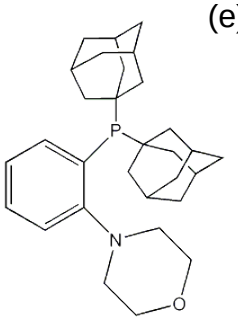
(d)



(e)



Me-DalPhos (Stradiotto)



Mor-DalPhos (Stradiotto)

Scheme 16. Important ligands utilized in amination studies.

Ligand properties are expected to affect the rates of oxidative addition and reductive elimination in the catalytic cycle, and it is expected that electron-rich ligands should facilitate the oxidative addition step by increasing the electron density around the metal. Bulky ligands should inhibit oxidative addition, but should also assist dissociation of $Pd(0)L_2$ to Pd(0)L,[21,26,69-71] which is generally believed to be more active in the catalytic cycle. That said, too much steric bulk also seems to decrease the efficient binding of ligand to palladium and bulk palladium metal precipitates.[72]

P(*o*-Tol)$_3$ was the first monodentate ligand used (Kosugi et al.) to effect amination by palladium-based catalysts (Scheme 4).[6] This ligand was also used by Buchwald and Hartwig in their early studies. Research on ligand design has received considerable attention in recent years, and the development and assessment of ligand structures has passed through various stages. For instance, Buchwald anticipated that bidentate ligands would prevent β-hydride elimination and investigated the use of BINAP (Scheme 16). It was found that the $Pd_2(dba)_3$/BINAP catalyst system promoted the monoarylation of primary amines and increased the yield of products obtained using substrates that had previously performed poorly.[73] At the same time, Hartwig explored the use of DPPF (Scheme 16), which improved on the amination of primary amines by promoting reductive elimination over β-hydride elimination because of its coordination geometry and bite angle.[74]

Buchwald followed with the development of a series of new monodentate phosphines exemplified by DavePhos, XPhos, BrettPhos and RuPhos, shown in

Scheme 16. These ligands are all air-stable and easily handled, and they can be prepared by one-step procedures.[75,76] DavePhos was the first of this type to be studied and, when combined with $Pd_2(dba)_3$ and $Pd(OAc)_2$, it demonstrated good results for arylation of both primary and secondary amines with various aryl halides with low catalyst loading; when combined with $Pd_2(dba)_3$, it sometimes showed high yields at room temperature.[77] Subsequently it was shown that DavePhos does not bind the metal via the nitrogen atom, and thus there seemed to be no need for the amino group to have an effective catalyst for some substrates.[78,79] There resulted the development of new biaryl ligands such as XPhos which will be discussed in detail below.

It was also demonstrated that BrettPhos and RuPhos are very effective ligands for a wide variety of C-N cross-coupling reactions of amines. BrettPhos first became famous because of its ability to effect amination of aryl mesylates.[80] Even XPhos was not successful for those substrates although it was efficient for aryl sulfonates. BrettPhos further showed high efficiency for arylation of primary amines with aryl chlorides and it can promote the selective arylation of primary amines over secondary ones in diamine substrates.[80-82] RuPhos is more efficient for secondary amines.[9, 80-82]

Bidentate ligands of the Josiphos family were developed because of two potential benefits that they might have over monodentate ligands. First, because of their bulky groups, it was anticipated that they could prevent a second arylation of the secondary amine products in the case of primary amine substrates. Secondly, because of the chelate effect, they are less likely to be

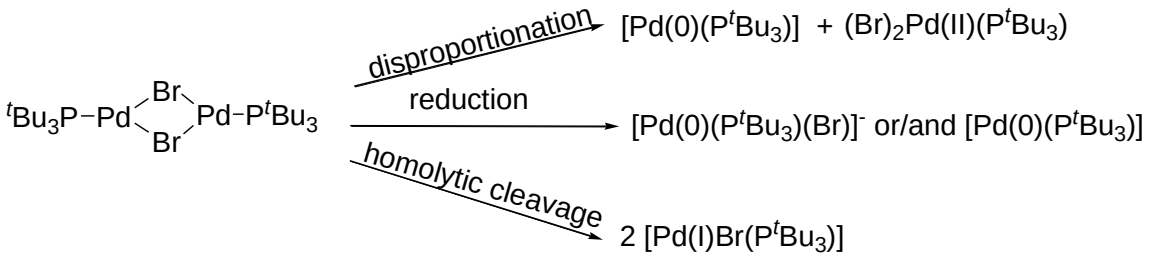
displaced by either nucleophilic amine substrates or heteroaromatic halides, either of which can result in catalyst deactivation. For these reasons, catalysts utilizing these ligands are efficient for coupling of halopyridines, ammonia, primary amines and other challenging substrates.[83-85]

Although extensive research has been done in this area, there remain some challenges such as stopping the reaction at the often desirable monoarylation stage for e.g. ammonia and hydrazine. Chemoselective transformations, in which one amine might undergo preferential arylation in the presence of another, and generally, the development of a catalyst system which can be useful for various substrates under mild conditions, remain interesting challenges. Among the studies on these challenges, new phenyl-based P,N-ligands, Me-Dalphos and Mor-Dalphos (Scheme 16), have been developed by the Stradiotto group. Because of the ability of these ligands to form strong phosphine- and weak nitrogen-palladium interactions, these ligands apparently stabilize palladium metal centres efficiently. Catalysts based on these ligands, formed from the otherwise little used precursor $[(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)PdCl]_2$, exhibit good performance for the monoarylation of ammonia and hydrazine.[10,86] Mor-DalPhos is discussed in detail below.

1.4.1 P^tBu_3

$Pd(OAc)_2$ or $Pd_2(dba)_3/P^tBu_3$ has been used as a catalyst system by Koie et al. for amination reactions, and was found to be efficient for a general substrate scope of unactivated chlorides.[87] Littke and Fu investigated the efficiency of Pd/P^tBu_3 catalyst systems for various cross-coupling reactions such as Suzuki,

Heck, Stille and Negishi.[88-91] They obtained high yields for the Suzuki coupling of arylboronic acids with aryl and vinyl halides utilizing the $Pd_2(dba)_3/P^tBu_3$ catalyst system.[88] They also developed the Heck reaction of various aryl chlorides and bromides under mild conditions utilizing $Pd_2(dba)_3/P^tBu_3$ catalyst and Cy_2NMe as the base rather than Cs_2CO_3.[89] Hartwig et al. modified the method of using P^tBu_3, and obtained high yields in the coupling of cyclic secondary amine such as morpholine with aryl bromides such as 2-bromotoluene at room temperature while using 0.8:1 as the ratio of P^tBu_3 to palladium (using $Pd(OAc)_2$ or $Pd(dba)_2$ as precursor). They also showed that using same ligand/catalyst ratio, room temperature coupling of acyclic secondary amines such as dibutylamine with aryl bromides such as *p*-bromotoluene is possible as is amination of aryl chloride at room temperature.[92] $Pd(OAc)_2$ and $Pd_2(dba)_3$ were mostly used as palladium sources in these reactions, but Hartwig and co-workers also showed that the palladium dimer,[93] $[(P^tBu_3)Pd(\mu\text{-}Br)]_2$, can be used as a precursor for cross-coupling reactions.[94] Rapid amination of various aryl chlorides and bromides with secondary cyclic and acyclic amines was observed using this palladium dimer. The activity of this precursor was attributed to the cleavage into two monomeric units, i.e. reactive mono-ligated 12-electron Pd(0) complex $[Pd(0)(P^tBu_3)]$ and a Pd(II) dibromide $[Pd(II)(Br)_2(P^tBu_3)]$, or reduction to either $2[Pd(0)(P^tBu_3)]$ or $[Pd(0)(Br)(P^tBu_3)]^-$ or homolytic cleavage to $2[Pd(I)(Br)(P^tBu_3)]$ by the combination of substrate and base (Scheme 17).[94,95]

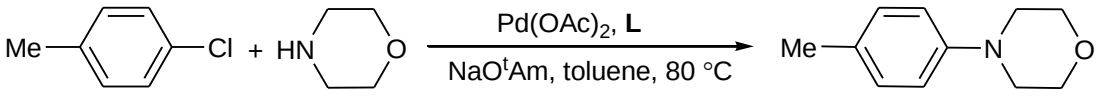


Scheme 17. Proposed activity route of $[(P^tBu_3)Pd(\mu\text{-}Br)]_2$.

1.4.2 Xphos

XPhos was one of the more important structural derivative discoveries in the mono-phosphine biaryl ligands class. Following this discovery in 2003 by Huang et al.,[96] extensive research has been done utilizing this ligand for palladium-catalyzed aminations by the Buchwald group between years 2003-2008.[50,52,97-103] This ligand facilitates the amination of aryl chlorides under mild conditions and is efficient for chemoselective amination of, for example, aniline in the presence of other N-H containing groups such as amides, aliphatic amines or indoles.[51,97,98]

Moreover, catalyst activation was investigated by monitoring the sequential reactions for representative amination of *p*-chlorotoluene with morpholine in toluene utilizing various mono-phosphine biaryl ligands (Scheme 18).[50]



Scheme 18. Amination of *p*-chlorotoluene with morpholine in toluene utilizing various mono-phosphine biaryl ligands.

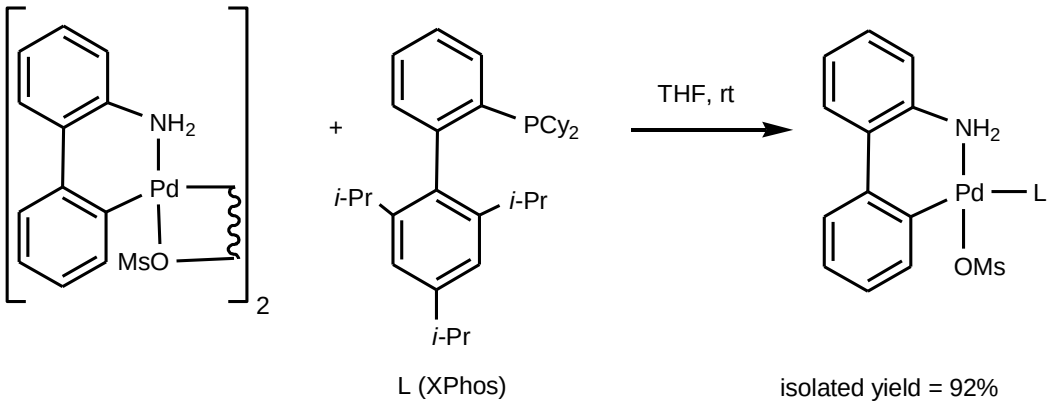
It was demonstrated that the bulkiest ligand, XPhos, resulted in accelerated rate as well as increased stability required for the studied reaction. In a separate

study using isotope-labeling (using deuterated morpholine), Strieter et al. showed that the presence of the substituants on aryl ortho positions in XPhos, prevents the formation of the palladacycle and leads to optimal catalyst activity.[99]

Despite different results obtained from studies on the effect of water on palladium-catalyzed cross-couplings, a water-mediated formation of active catalyst protocol using $Pd(OAc)_2$/XPhos has been developed by Fors et al.. Lower catalyst loading, shorter reaction times, exclusion of additives in reaction of aryl chloride with amides has been obtained applying this protocol.[52]

$Pd_2(dba)_3$/XPhos has been also used for the arylation of ammonia and it was found that, the catalyst system generates primary, secondary or tertiary amines with different ratios under various reaction conditions.[101]

Bruno et al. also showed that this biaryl mono-phosphine can be used as the starting material for the synthesis of a new series of palladium precatalysts based on the 2-aminobiphenyl mesylate palladacycle in a facile way (scheme 19).[104]



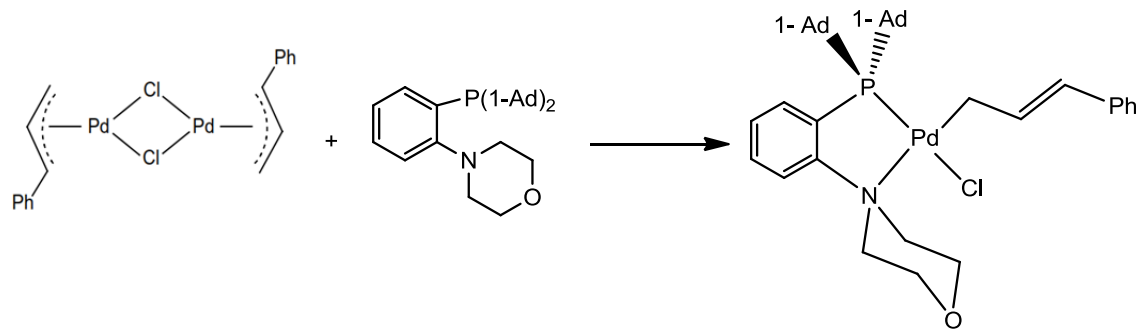
Scheme 19. Preparation of mesylate precatalyst utilizing XPhos.

1.4.3 Mor-Dalphos

Among the studies of challenges in choosing the best precatalyst/ligand combination, new phenyl-based P,N-ligands, Me-Dalphos and Mor-Dalphos (Scheme 16), have been developed by the Stradiotto group. It has been reported that these ligands stabilize palladium metal centres efficiently because of their ability to form strong phosphine- and weak nitrogen-palladium interactions. Catalysts based on these ligands and precursor $[(\eta^3\text{-1-Ph-}C_3H_4)PdCl]_2$, exhibit good performance for the monoarylation of ammonia and hydrazine.[10,86]

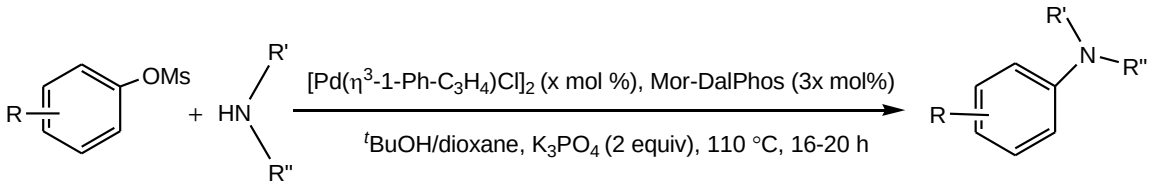
The $[(\eta^3\text{-1-Ph-}C_3H_4)PdCl]_2$/Mor-DalPhos catalyst system was used for cross-coupling of a broad range of functionalized and base sensitive (hetero)aryl chlorides and primary or secondary amines. It has been found that this catalyst system is effective for the amination reactions under aqueous conditions without the use of additives such as co-solvents or surfactants; as well as under neat (solvent-free) conditions and without the rigorous exclusion of air.[13,14]

In further studies, it has been shown that Mor-DalPhos reacts with $[(\eta^3\text{-1-Ph-}C_3H_4)PdCl]_2$ at room temperature and the chloride bridges cleave to give a square planar chloro-η^1-cinnamyl complex in which the Mor-DalPhos chelates via the phosphorus and nitrogen atoms (Scheme 20).[11]



Scheme 20. Reaction of $[(\eta^3\text{-1-Ph-}C_3H_4)PdCl]_2$ with Mor-DalPhos at room temperature.

The Stradiotto group also developed the use of $[Pd(\eta^3\text{-1-Ph-}C_3H_4)Cl]_2$/Mor-DalPhos catalyst system for the Buchwald-Hartwig amination of inexpensive aryl mesylates with primary aliphatic amines (Scheme 21). They developed an amination protocol with good chemoselectivity which favored the cross-coupling of primary amines.[56]



Scheme 21. Amination protocol using Mor-Dalphos.

1.5 Reagents

1.5.1 Bases

Choosing a suitable, sufficiently strong base is another key factor in palladium-catalyzed amination reactions. NaO^{t}Bu was the first base used[3,11] and it has been extensively used with dialkylbiaryl phosphine ligand systems by Buchwald and co-workers. KO^{t}Bu exhibits the same efficiency in some of these reactions,[105] but both of these bases have some limitations because the functional group tolerance for substrates is limited.[9] Because of these limitations, some studies have been done using the less basic NaOMe which exhibits better functional group tolerance.[106,107] NaOPh is another less basic reactant which has been shown to be efficient for the arylation of heteroaryl amines, in part because of good solubility in dioxane.

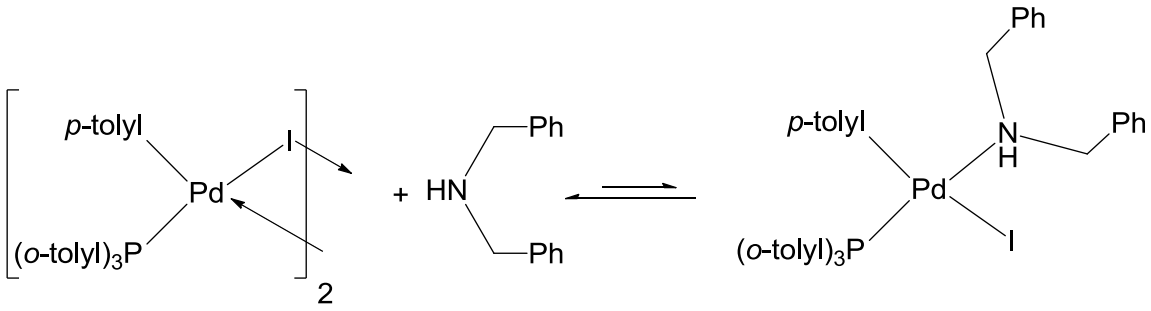
LHMDS (lithium hexamethyldisilazide) allows the amination of aryl halides even when they contain protic functional groups such as phenol, aliphatic alcohols and amides, and it is also valuable in amination of haloheterocycles possessing a free NH group.[97,100,82] This base has been considered recently because of the ease of storage and handling in THF and toluene solutions.[9] Hydroxide bases KOH, NaOH have also been used recently because they are inexpensive, but they generally give lower reaction rates than do alkoxides.[51,82] Weak bases such as Cs_2CO_3, K_3PO_4 and K_2CO_3 have been investigated in efforts to increase the functional group tolerance.[108] In cases where these bases are used in non-polar solvents, it is assumed that deprotonation of palladium-

bound amine occurs at the solid-liquid boundary so particle size and shape of the inorganic bases will be important in the rate of the reaction.[108-110]

1.5.2 Electrophiles

Aryl bromides were the first electrophiles widely used for Buchwald-Hartwig reactions; however, aryl chlorides have attracted increased attention recently because of their lower cost and higher availability. Although the C-Cl bond strength is higher than C-Br, affecting the rate of oxidative addition, the new ligands discussed above often overcome this problem and amination of aryl chlorides has been reported at room temperature.[7-9,50,51,53,77,111-121]

Aryl iodides are among the easiest substrates for C-N bond forming cross-coupling reactions; however, being more expensive and less available, aryl bromides are preferred. In addition it has been suggested that the iodide dimers formed after addition of aryl iodide to the PdL complex such as $\{Pd[P(o\text{-}tol)_3](p\text{-}C_6H_4OMe)(\mu\text{-}I)\}_2$ when 4-iodoanisole used as aryl iodide, is more stable than the mono amine iodide complex formed after addition of amine such as dibenzylamine (Scheme 22). This tendency of the equilibrium between the mono and dimer complexes to amine dissociation renders the aryl iodides more challenging substrates.[122] By choosing the appropriate base and solvent, Buchwald[81,114,123] and Verkade[124,125] reported amination of aryl iodides in high yields.



Scheme 22. Equilibrium between the mono and dimer iodide complexes to amine dissociation.

Phenol-based arenesulfonic acid esters such as aryl trifluoromethanesulfonic acid esters (triflates),[36] nonafluorobutanesulfonic acid esters (nonaflates)[126], p-toluenesulfonic acid esters (tosylates)[127] and methanesulfonic acid esters (mesylates)[80,128,129] can also be used as the electrophiles for amination reactions. Among them aryl triflates are the most reactive to oxidative addition but they are prone to hydrolysis by water; aryl nonaflates undergo hydrolysis more slowly.[130-132] Aryl tosylates are slower in oxidative addition but their cost is lower than aryl triflates so they have attracted considerable attention.[127] Aryl mesylates are even slower in oxidative addition but amination of aryl mesylates has been reported using Brettphos and ^{t}BuBrettphos by Buchwald group and an amino phosphine ligand by So et al., both with $Pd(OAc)_2$.[80,128,129]

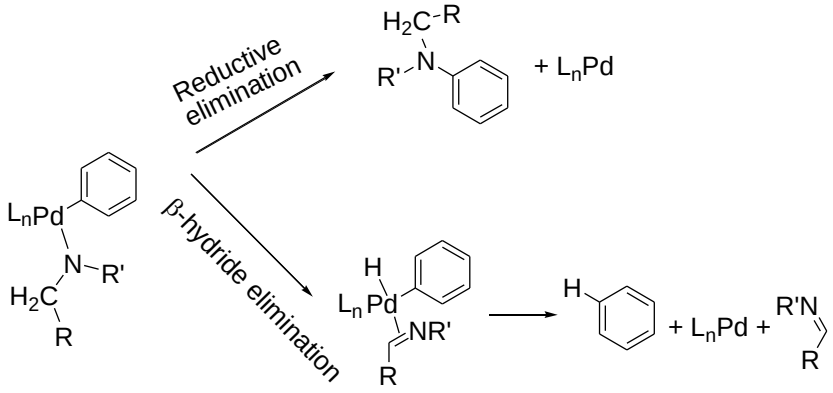
Heteroaryl halides such as halo-pyridines, -quinolines and -pyrimidines are another group of electrophiles which has been studied[84,85,112] but there are some difficulties in using this group of aryl halides. For example, deactivation of the catalyst may occur if the heteroatoms coordinate to the metal[20] and these substrates have less solubility in common solvents for amination reaction such as dioxane and toluene.[81,82]

1.5.3 Amine Nucleophiles

Various amine nucleophiles have been studied in recent years for Buchwald-Hartwig reactions and, based on reviews,[7,9,38,133] different reaction conditions were used. However, most of the systems are based on $Pd_2(dba)_3$ and $Pd(OAc)_2$ with different ligands but these catalyst precursors are not as efficient as once believed (see sections 1.3.1 and 1.3.2).

1.5.3.1 Secondary Amines

Arylation of cyclic secondary amines such as piperidine, pyrrolidine, piperazine, N-methylpiperazine and morpholine are among the first reported palladium-catalyzed amination reactions and most ligands are efficient.[3,74] This can be due to the fact that cyclic palladium(II) amide intermediates are less prone to β-hydride elimination compared to acyclic amide intermediates. A general mechanism for two competing pathways, reductive elimination and β-hydride elimination is depicted in Scheme 23.



Scheme 23. Competitive pathways, reductive elimination and β-hydride elimination.

Arylation of acyclic secondary amines such as dibutylamine and 2,4-diethylazetidine is more difficult because of the tendency of these substrates to undergo β-hydride elimination. RuPhos was reported to be an efficient ligand for arylation of both cyclic and acyclic secondary amines, but the arylation of hindered secondary amines with ortho-substituted aryl halides is still challenging. This may be due to the higher rate of β-hydride elimination.[80-82]

1.5.3.2 Primary Amines

Numerous studies have been done on primary aliphatic amines. The early studies were on alkylamines such as *n*-hexylamine, *n*-butylamine and diethylene triamine but the research was not limited to these, and arylations of more complicated primary amines were successfully carried out using various palladium catalyst systems. However, arylation of these substrates remains one of the challenging amination reactions because of the possibility of formation of side products resulting from β-hydride elimination and bis-arylation; primary amine substrates have two available hydrogens which can undergo arylation and the products will be a mixture of mono and bis arylation products in addition to β-hydride elimination.[134,135] BrettPhos was reported to be efficient for monoarylation of these substrates and the selectivity for monoarylation of primary amines in the presence of secondary amines.[80,82]

Aromatic primary amines, such as aniline derivatives, are one of the easiest substrates because of the lack of β-hydrogen atoms although double arylation can be a competing pathway. It should be noted that, by using the right ligand, it is possible to achieve the desired selectivity. Buchwald reported that in the

presence of primary amines, using XPhos allows the selective arylation of anilines.[51]

1.5.3.3 Ammonia

Although ammonia is the simplest amine, the use of homogeneous catalysts for this substrate was not common until recently.[10,16,136,137] In the arylation of ammonia, selectivity, i.e. obtaining primary amines over diaryl- and triarylamines, is one of the big issues. The first metal catalyzed arylation of ammonia used copper metal as a catalyst at high temperatures and pressures; there was considerable formation of side products.[138]

In 2006 the first palladium-catalyzed amination of aryl halides with ammonia, using 5.5 bar of ammonia pressure with NaO^tBu base and 1 mol % of a preformed Josiphos-ligated palladium(II) complex [(CyPF-^{t}Bu)$PdCl_2$], was reported. Hartwig showed that the ligand in this catalyst system is not replaced by ammonia, and that selective monoarylation is achieved with aryl halides.[137]

In 2007 Buchwald reported using $Pd_2(dba)_3$ with biarylphosphine ligands. In this protocol, a commercially available solution of ammonia (0.5 M in 1,4-dioxane) was used as the source of ammonia. By changing the substitutions on the biaryl ligand, various selectivities for anilines and diarylamines were obtained.[101]

Recently Stradiotto reported using of Mor-DalPhos with $[Pd(cinnamyl)Cl]_2$ for the arylation of ammonia. This catalyst system gave high yields of primary arylamines at room temperature. NaO^tBu was used as a base and solutions of ammonia 0.5 M in 1,4-dioxane was used as the source of ammonia.[10]

1.6 Research Objectives

Considering the challenges remaining in the Buchwald-Hartwig reactions, there are still many aspects which attract the attention of organometallic researchers. One of the targets is running the amination reactions under milder conditions. Although numerous studies have been reported in recent years, there is still need for further modifications, especially for more challenging substrates. The development of new ligands and precursors is among the most important topics in this research area, with much of the key research being done by the Buchwald and Hartwig groups. Thus introduction of a new air and thermally stable precursor that can be efficient for amination of various substrates under milder conditions is point of interest of organometallic chemists and the chemical industry.

The easily handled, air stable pre-catalyst, Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5) (**I**) has been reported recently by Norton et al. to react with many phosphines L to efficiently form catalyst precursors PdL_2[57] and, in a series of experiments involving a conventional Suzuki-Miyaura cross-coupling reaction runs under a set of standard conditions, Fraser et al. have found that **I** is a considerably more efficient catalyst precursor than are more commonly used precursors.[49]

Since the 2009 Norton paper,[57] other groups have also utilized **I** to more effectively generate palladium(0) complexes for various purposes.[60-62] Moreover, in the Baird group, Fraser et al. and Jaksic et al. showed that **I** is efficient in Heck arylation, Sonogashira coupling as well as amination reactions.[58,59]

In my research, we are investigating an extension of previous work done on cross-coupling reactions in the Baird group, for the generation of catalysts for amination reactions of aryl halides using **I** with different ligands. We also investigate the solution chemistry of different catalyst systems by NMR spectroscopy.

1.6.1 Developing of Efficient New Catalyst Systems for Buchwald-Hartwig Amination

In order to develop a catalyst system based on easily-synthesized and air-stable precursor **I**, which results in higher yields under milder conditions, the efficiency of **I** activated with various phosphines is compared with conventional catalyst precursors for Buchwald-Hartwig amination reactions.

Moreover, the effect of different parameters such as L:Pd ratio and activation process is investigated.

1.6.2 Investigation of the Solution Chemistry of Various Catalyst Systems Based on I or IV with Various Phosphines

Considering the scarcity of studies on the catalytic mechanisms, solution chemistry was studied by NMR spectroscopy to obtain a better understanding of the species formed in the catalytic cycle using **I** as a precursor. Characterizing these species and knowing if they are the catalytically active species would simplify the modification of further palladium-catalyzed cross-coupling reactions.

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Chapter 2

$Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)(\eta^5\text{-}C_5H_5)$ (I) as a Catalyast Precursor for Buchwald Hartwig Amination Reactions

2.1 Preface

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2.2 Introduction

A wide variety of palladium-catalyzed carbon-carbon and carbon-heteroatom bond forming methodologies are available through reactions catalyzed by palladium(0) compounds commonly believed to be of the type PdL_2 (L = tertiary phosphines).[1] In the general case, an aryl halide ArX (X = Cl, Br, I) reacts catalytically with a carbon- or heteroatom-based nucleophile Nuc^- to form the coupled product Ar-Nuc. The most widely accepted catalytic cycle (Figure 2) typically involves oxidative addition of ArX to PdL_2 to give aryl-palladium(II) species $PdArXL_2$, followed by displacement of X^- by Nuc^- and reductive elimination of Ar-Nuc, an overall process which has been much studied.[2]

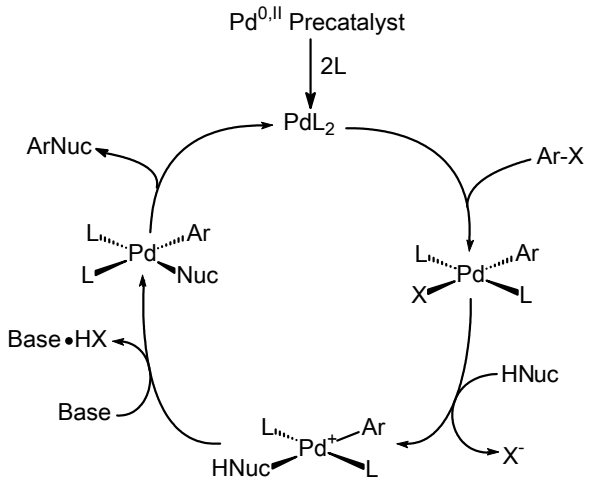
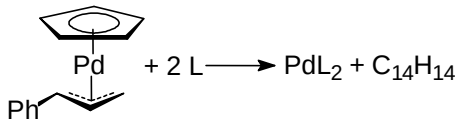


Figure 2. General catalytic cycle for Buchwald-Hartwig amination.

However, preformed PdL_2 species can be difficult to synthesize, store and handle, and are rarely utilized directly. As a result, the vast majority of palladium-catalyzed cross-coupling investigations have employed less sensitive and hence more easily managed catalyst precursors such as $Pd(PPh_3)_4$, $Pd_2(dba)_3$ (dba = dibenzylideneacetone), $PdCl_2$ and/or $Pd(OAc)_2$; these can be converted to catalytically active species which have frequently been assumed to be PdL_2 in accord with the accepted mechanism of Scheme 1[1,3a] As we have noted,[3a] however, very little is known about the rates or extents of reduction of Pd(II) precursors, and while these and the Pd(0) precursors $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ often do generate functional catalyst systems, the catalytically active species have rarely been identified or even characterized in any way. Indeed, in those few cases where Pd(0) species have been identified in solution, they are almost never the oft presumed, generally desired species PdL_2, but rather sterically hindered, three-coordinate complexes containing a variety of neutral and anionic ligands depending on the mode of formation.[4-6]

It follows therefore that catalyst systems based on e.g. $Pd_2(dba)_3$, $PdCl_2$ and $Pd(OAc)_2$ should not be assumed to be chemically synonymous, i.e. that they react generally with ligands L to form identical catalytic species. Thus the very large number of reported cross-coupling studies which have assumed equivalency in the chemistries of these precursors in order to make comparisons of relative ligand efficacies may have reached inaccurate conclusions. These potentially serious issues have also been recognized by others,[7a,b,8c,j,l,m,y] as has the complementary, oft monumental problem of actually ascertaining the optimal conditions for any cross-coupling reaction in particular let alone for such reactions in general (see also below).[7c,d,8n,p,s]

That said, a simple, unequivocal quantitative route for the general synthesis of Pd(0)-based catalysts useful for a very large number of cross-coupling reactions involving multiple substrates has long been thought desirable and, assuming the general utility of bis-phosphine palladium(0) catalysts, we have previously suggested utilization of easily synthesized, user-friendly, thermally and air-stable compound $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)(\eta^5\text{-}C_5H_5)$ (**I**). As we have shown, **I** reacts rapidly with a number of phosphines L to efficiently form the compounds PdL_2 as in eq. 1.[3]



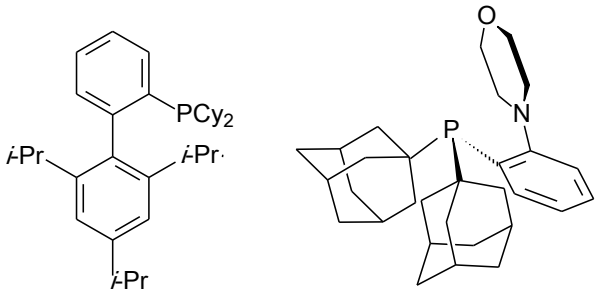
(1)

I

We have previously compared and contrasted **I** as a precursor for representative Suzuki-Miyaura,[3a] Heck-Mizoroki[3c] and Sonogashira[3c,e] cross-coupling reactions with catalyst systems based on $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $PdCl_2$ and $Pd(OAc)_2$, which as mentioned above have been frequently utilized in spite of the fact that they do not generate two-coordinate palladium(0) catalytic species. Subsequent to, and citing our reports that catalyst systems formed from **I** are generally much more active than the more conventional catalyst systems, the general "scarcity of detailed studies concerning the mechanism and efficiency" of catalyst generating processes has been noted.[7b]

Since our initial disclosure of the merits of utilizing $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)(\eta^5\text{-}C_5H_5)$ for synthesis of palladium(0) compounds,[3b] others have also demonstrated its utility. Thus Braunschweig et al. found $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)(\eta^5\text{-}C_5H_5)$ to be useful for the high yield synthesis of a heteroleptic (phosphine)(NHC)Pd(0) compound, $Pd(PCy_3)$(N,N'-bis(*tert*-butyl)-imidazol-2-ylidene);[9a] other precursors resulted in the formation of mixtures. Similarly Cramer et al. found $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)(\eta^5\text{-}C_5H_5)$ to be "the best" precursor for the synthesis of palladium(0) complexes containing a series of new electron rich phosphines, used as catalysts for enantioselective $C(sp^3)$–H functionalization.[9b] In addition, and in a direct comparison, the **I**/XPhos catalyst system is much more effective for a series of Buchwald-Hartwig amination reactions than is the more conventional $Pd_2(dba)_3$/XPhos catalyst system.[9c,d] In related work, Cramer et al.,[9e] Lin, Fairlamb et al.[9f] and Skrydstrup et al.[9g] found in various contexts that utilization of

I rather than conventional alternatives resulted in higher selectivity to desired products and/or greater ease of purification of products.



Scheme 24. XPhos and Mor-DalPhos structures.

As an extension of our previous work[3] and to assess further the general effectiveness of **I**, we have initiated an investigation in which we compare the competence of **I** as a catalyst precursor with catalyst systems based on $Pd_2(dba)_3$ (**II**), $Pd(OAc)_2$ (**III**) and $[Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)Cl]_2$ (**IV**) for Buchwald-Hartwig amination reactions (eq. 2).[8]

$$\text{Ar-X + NHRR'} \xrightarrow[\text{base}]{\text{Pd catalyst}} \text{Ar-NRR'} \quad (\text{R, R' = H, alkyl, aryl}) \qquad (2)$$

Comparisons of **I**, **II** and **III** have been standard fare in our studies because of the extent to which the latter two have been utilized.[3] Although we earlier demonstrated that the allyl compound $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ is a relatively poor precursor for Suzuki-Miyaura reactions,[3a] the cinnamyl analogue **IV** has recently been claimed to be superior to **I** for some amination reactions[10a] and its inclusion in this study seemed warranted. As ligands L we have utilized P^tBu_3, XPhos and Mor-DalPhos, the first because we have consistently

obtained relatively high conversions using this phosphine for Suzuki-Miyaura,[3a] Heck-Mizoroki[3c] and Sonogashira[3c,e] cross-coupling reactions and also because P^tBu_3 is generally recognized as being one of the generally superior ligands for amination reactions.[8j] XPhos is included as a representative of a very effective series of 3rd generation ligands developed by Buchwald et al. for amination reactions involving aryl chlorides and unactivated aryl halides,[8j,n] while Mor-DalPhos is representative of a series of ligands developed while this work was in progress and utilized effectively with **IV**.[10]

A generic catalytic cycle for amination reactions is shown in Figure 3,[8] and the resemblance to the general catalytic cycle shown in Figure 2 is apparent.

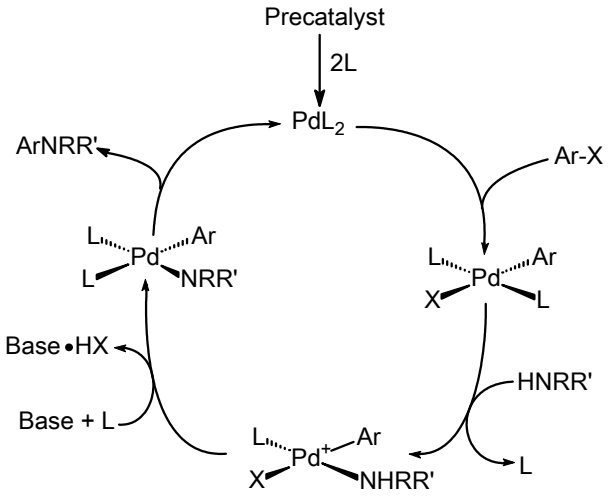


Figure 3. Generic catalytic cycle for Buchwald-Hartwig amination reaction.

That said, there is a sense in the literature that there are several variations on this general mechanism for palladium-catalyzed C-N coupling, and that multiple mechanistic pathways may be possible depending on the substrate and the

ligands coordinated to the palladium. Indeed, the nature of the rate-determining step may depend on a number of factors including substrate structure, nature of the halide, catalyst structure, the L:Pd ratio and the base.[8j,w-y] Unfortunately, very broad ranges of catalyst precursors, reaction conditions and modes of optimization appear in the literature and it has long been recognized that full comprehension of the reaction conditions which are of importance for any individual substrate is extremely challenging and that attempts to make broad comparisons of catalyst systems remain somewhat problematic.[8j]

Compounding the mechanistic perplexities of palladium(0) catalyzed amination reactions, a major development in recent years has involved the synthesis of a plethora of new ligand systems of astonishing variety and, on occasion, uncertainty with respect to their (possibly unique) roles.[8] As mechanistic knowledge increased,[8f,j-m] there has also developed an increasing awareness that particular types of ligand structures seemed to lend themselves to greater success in coupling certain specific classes of reactants, and a wide variety of electron-rich and/or sterically hindered, mono- and bidentate ligands has been reported.[8] However, although at one time there seemed to be hope that a “universal tool box” might be developed, encompassing a narrow set of ligated compounds which would cross-couple most types of substrates with high turnover frequencies under mild conditions and with low catalyst concentrations,[8h] it is now recognized that there are no combinations of ligands and catalyst precursors which are successful for a majority of combinations of substrates, i.e. no “magic bullets”.[8p,t]

2.3 Experimental

2.3.1 General Procedures

All syntheses were carried out under a dry, deoxygenated argon or nitrogen atmosphere with standard Schlenk line techniques. Argon was deoxygenated by passage through a heated column of BASF copper catalyst and then dried by passing through a column of 4 Å molecular sieves. Solvents were dried by passage through activated alumina and were then stored under an argon atmosphere for a minimum of 24 h over 3 Å molecular sieves which had been activated by heating at 225 °C, 10^{-2} torr for several days. Phosphines were purchased from Strem Chemicals, all other compounds from Sigma-Aldrich. Johnson-Matthey generously provided us the $PdCl_2$. Handling and storage of air sensitive compounds was carried out in an MBraun Labmaster glove box. NMR spectra were recorded on a 500 MHz spectrometer with ^1H NMR data being referenced to TMS via the residual proton signals of the deuterated solvents, and GC experiments were carried out using a GC equipped with a 0.32 mm fused silica column and an FID. The injector temperature was set at 250 ºC, initial column temperature at 140 ºC, and detector temperature at 250 ºC. Hexadecane was added as an internal standard, and GraphPad Software Prism Version 5.03 was used for curve fitting. Each plot is the average of 3-8 runs, experiments performed by different people in order to check the reproducibility. Compound **I**, $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)(\eta^5\text{-}C_5H_5)$,was prepared as in the literature.[3b,17] The temperature was controlled by the probe thermometer connected to the hotplate stirrer.

2.3.2 General Experimental Methodologies for Determining Reaction Profiles

2.3.2.1 Utilizing Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5) (I) (in Situ Generation of PdL_n Prior to Addition of Other Reactants: Method A)

For L:Pd reactant ratios of 2:1, 0.0028 g **I** (0.01 mmol) was combined with 0.004 g P^{t}Bu$_3$ (0.02 mmol), 0.009 g XPhos (0.02 mmol) or 0.009 g Mor-Dalphos (0.02 mmol); for L:Pd ratios of 1:1, 0.002 g P^{t}Bu$_3$ (0.01 mmol), 0.0047 g XPhos (0.01 mmol) or 0.0046 g Mor-Dalphos (0.01 mmol) were used. In all cases, these reactants were combined in 3 mL of dioxane and stirred at 75°C for 1 h. The temperature was then raised to 80 °C, and 4-bromoanisole (0.187 g, 1 mmol) or 4-chloroanisole (0.143 g, 1 mmol), morpholine (0.105 g, 1.2 mmol) and sodium *tert*-butoxide (0.135 g, 1.4 mmol) were added to the resulting brown solutions and the mixtures were stirred at 80 °C for 2 h; 0.1 mL aliquots were removed at specified intervals, diluted with ~10 mL of dioxane and analysed by GC.

2.3.2.2 Utilizing Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5) (I) (in Situ Generation of PdL_n in Presence of Chloro- or Bromoanisole but Prior to Addition of Other Reactants; Method B)

In this series of experiments, the palladium and phosphine reactants were combined as above but in the presence of 4-bromoanisole (0.187 g, 1 mmol) or 4-chloroanisole (0.143 g, 1 mmol) in 3 mL of dioxane. The reaction mixtures were stirred at 75 °C for 1 h, and then the temperature of the solution was raised to 80 °C; at this point 0.105 g morpholine (1.2 mmol) and 0.135 g sodium *tert*-butoxide

(1.4 mmol) were added and the mixtures were stirred at 80 °C for 2 h.; 0.1 mL aliquots were removed at specified intervals, diluted with ~10 mL of dioxane and analysed by GC.

2.3.2.3 Utilizing $Pd_2(dba)_3$ (II)

In this series of experiments, 0.0045 g $Pd_2(dba)_3$ (0.005 mmol) was combined with 0.004 g P^tBu_3 (0.02 mmol) or 0.009 g XPhos (0.02 mmol) in 3 mL of dioxane; 0.187 g 4-bromoanisole (1 mmol) (or 0.143 g 4-chloroanisole (1 mmol)), 0.105 g morpholine (1.2 mmol) and 0.135 g sodium *tert*-butoxide (1.4 mmol) were added to each mixture, which was then stirred at 80 °C for 2 h; 0.1 mL aliquots were removed at specified intervals, diluted with ~10 mL of dioxane and analysed by GC.

2.3.2.4 Utilizing $Pd(OAc)_2$ (III)

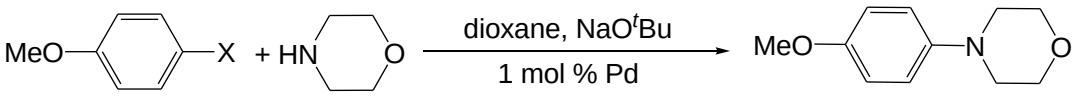
In this series of experiments, 0.022 g $Pd(OAc)_2$ (0.01 mmol) was combined with 0.006 g P^tBu_3 (0.03 mmol) or 0.014 g XPhos (0.03 mmol) in 3 mL of dioxane; 0.187 g 4-bromoanisole (1 mmol) (or 0.143 g 4-chloroanisole (1 mmol)), 0.105 g morpholine (1.2 mmol) and 0.135 g sodium *tert*-butoxide (1.4 mmol) were added to each mixture, which was stirred at 80 °C for 2 h; 0.1 mL aliquots were removed at specified intervals, diluted with ~10 mL of dioxane and analysed by GC.

2.3.2.5 Utilizing $[Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)Cl]_2$ (IV)

For L:Pd reactant ratios of 2:1, 0.0026 g **IV** (0.005 mmol) was combined with 0.004 g P^tBu_3 (0.02 mmol), 0.009 g XPhos (0.02 mmol) or 0.009 g Mor-Dalphos (0.02 mmol); for L:Pd reactant ratios of 1:1; 0.002 g P^tBu_3 (0.01 mmol), 0.0047 g XPhos (0.01 mmol) or 0.0046 g Mor-Dalphos (0.01 mmol) were combined in 3 mL of dioxane; 0.187 g 4-bromoanisole (1 mmol) (or 0.143 g 4-chloroanisole (1 mmol)), 0.105 g morpholine (1.2 mmol) and 0.135 g sodium *tert*-butoxide (1.4 mmol) were added to the mixtures which were stirred at 80 °C for 2 h; 0.1 mL aliquots were removed at specified intervals, diluted with ~10 mL of dioxane and analysed by GC.

2.4 Results and Discussion

Palladium(0) catalyzed amination reactions have been carried out under a wide variety of conditions, the important variables being palladium precursors, ligands, solvents, bases, and temperature.[8] There are thus many ways in which we could have initiated our investigation, and we chose to begin with an study of the conventional amination reactions of 4-bromo- and 4-chloroanisole with morpholine, depicted in eq. 3.



(3)

All reactions were carried out in dioxane at 80 °C using sodium *tert*-butoxide as base and 1 mol % of each of the catalyst precursors. Sodium *tert*-butoxide

and dioxane are commonly used as base and solvent for amination reactions[8] and, in contrast to reactions in DMF, no side products were observed in reactions carried out in dioxane.

Reactions involving **I** and P^tBu_3 were initially carried much as previously;[3a-c,e] the 2:1 compound $Pd[P^tBu_3]_2$ was preformed by heating a stirred solution containing **I** and two molar equivalents of P^tBu_3 in dioxane at 75°C for 1h. The temperature of the reaction mixture was then raised to 80 °C, the reactants were added, and the disappearance of 4-bromo- or 4-chloroanisole and the appearance of 4-(4-methoxyphenyl)morpholine at 80 °C were monitored by GC. Each reaction was carried out 3-8 times and, in general, good mass balances were achieved. This procedure will henceforth be referred to as Method A.

As our investigation proceeded, we also developed a complementary procedure, henceforth called Method B, in which we generated $Pd[P^tBu_3]_2$ from **I** in the presence of an excess of 4-bromo- or 4-chloroanisole in dioxane at 75°C for 1h. The reaction mixture was then heated to 80 °C and the other reactants were added, and the procedure then continued as in Method A. By utilizing this alternative approach, we thought we might be able to induce the formation of important types of intermediates which participate in catalytic cycles (Figures 2 and 3) but which are derived from preformed 2:1 complexes only with difficulty (see below).

Procedures involving $Pd_2(dba)_3$ (**II**) and $Pd(OAc)_2$ (**III**) were as previously described[3a-c,e] and involved combinations of **II** or **III** with P^tBu_3 in appropriate ratios followed by addition of all of the reactants and heating as above. To our

knowledge, there are no suggestions in the literature that these catalyst systems require induction periods. Compound **IV** has been utilized far less and no optimized protocol seems to have been proposed. We therefore proceeded much as with **II** and **III**, albeit with the phosphine always being added to the $[Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)Cl]_2$ solution prior to addition of the other reactants. The L:**IV** ratio of 4:1 is arbitrary, as more than one mode of activation of this catalyst precursor may be relevant (see below). However, the L:Pd ratio of 2:1 is at least comparable to the ratios utilized for precatalysts **I**-**III**.

Reaction profiles for the formation of (4-methoxyphenyl)morpholine from amination of 4-bromoanisole with morpholine using the **I**/2P^{t}Bu$_3$, **II**/4P^{t}Bu$_3$, **III**/3P^{t}Bu$_3$ and **IV**/4P^{t}Bu$_3$ catalyst systems are shown in Figure 4. Also shown is the disappearance of 4-bromoanisole for the reaction involving **I**.

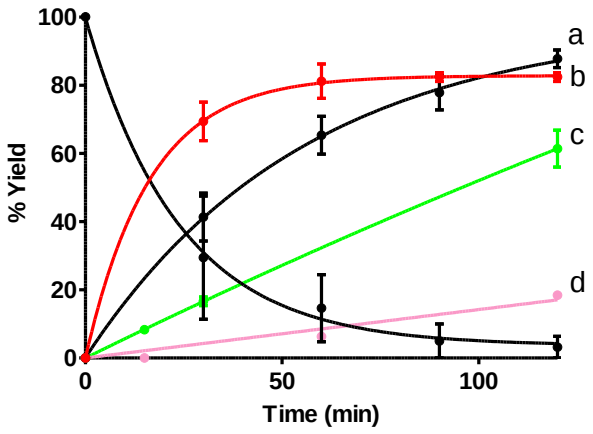


Figure 4. Reaction profiles for the formation of 4-(4-methoxyphenyl)morpholine from the amination of 4-bromoanisole with morpholine catalyzed by 1 mol% Pd catalyst systems (a) **I**/2P^{t}Bu$_3$ (Method A), (b) **IV**/4P^{t}Bu$_3$, (c) **III**/3P^{t}Bu$_3$, (d) **II**/4P^{t}Bu$_3$. Also shown is the loss of 4-bromoanisole accompanying (a).

As can be observed, the **I**/2P^{t}Bu$_3$ catalyst system clearly exhibited a higher initial rate than did the **II**/4P^{t}Bu$_3$ and **III**/3P^{t}Bu$_3$ catalyst systems, and resulted in almost 100% conversion within 2 h. There was also excellent mass balance for the **I**/2P^{t}Bu$_3$ catalyst system. In contrast, the Pd(OAc)$_2$ and Pd$_2$(dba)$_3$ catalyst systems were significantly less effective, as was found previously for Suzuki-Miyaura,[3a] Heck-Mizoroki[3c] and Sonogashira[3c,e] cross-coupling reactions. Interestingly the **IV**/4P^{t}Bu$_3$ catalyst system exhibited a higher initial rate than but a comparable overall conversion to the **I**/2P^{t}Bu$_3$ catalyst system. This result stands in contrast to an earlier study[3a] of Suzuki-Miyaura coupling utilizing the very similar [Pd(η^3-C$_3$H$_5$)Cl]$_2$ but is consistent with another study involving **IV**.[10] We shall discuss this result further below.

The biaryl, monodentate phosphine XPhos is one of the commonly used, often highly effective phosphines for Buchwald-Hartwig reactions.[7,8] To further our study, we have compared catalyst systems based on XPhos for the same reaction and Figure 5 shows reaction profiles for the amination of 4-bromoanisole with morpholine utilizing the **I**/2XPhos and **IV**/4XPhos catalyst systems.

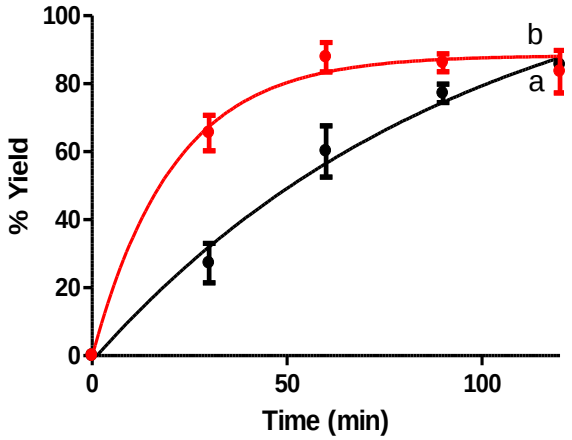


Figure 5. Reaction profiles for the formation of 4-(4-methoxyphenyl)morpholine from the amination of 4-bromoanisole with morpholine catalyzed by 1 mol% Pd catalyst systems utilizing (a) **I**/2XPhos (Method A), (b) **IV**/4XPhos.

As can be seen, the **IV**-based catalyst system again exhibits a higher initial rate than does the **I**-based system although again both are ultimately quite effective. Furthermore the P^{t}Bu$_3$ (Figure 4a,b) and XPhos (Figure 5a,b) systems are seen to be comparable in activity. Indeed, the reaction profile for the **IV**/4XPhos catalyst system is essentially identical to that of the **IV**/4P^{t}Bu$_3$, system shown in Figure 4 while the analogous **I**/2P^{t}Bu$_3$ and **I**/2XPhos reaction profiles are very similar.

Aryl chlorides tend to be less effective cross-coupling partners than the corresponding aryl bromides because of the relative carbon-halogen bond strengths.[8h] For purposes of comparison, we have carried out studies under the same set of conditions as the above using 4-chloroanisole and we show in Figure 6 reaction profiles for the amination of 4-chloroanisole with morpholine by the **I**/2P^{t}Bu$_3$, **IV**/4P^{t}Bu$_3$, **I**/2XPhos and **IV**/4XPhos catalyst systems.

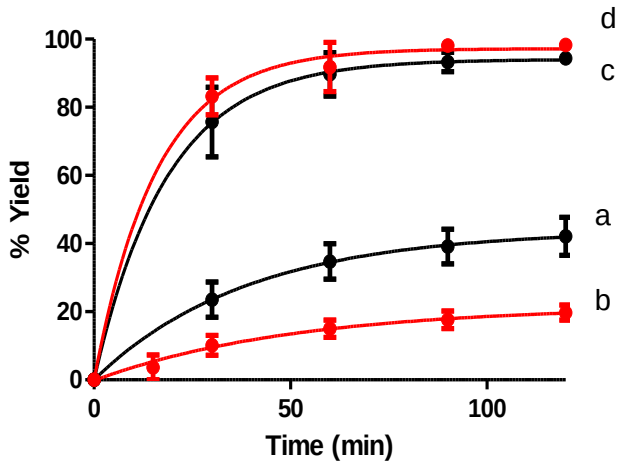


Figure 6. Reaction profiles for the formation of 4-(4-methoxyphenyl)morpholine from the amination of 4-chloroanisole with morpholine catalyzed by 1 mol% Pd catalyst systems utilizing (a) **I**/2P^{t}Bu$_3$ (Method A), (b) **IV**/4P^{t}Bu$_3$, (c) **I**/2XPhos (Method A), (d) **IV**/4XPhos.

As can be seen, the XPhos-based systems are clearly superior to the P^{t}Bu$_3$ systems for both **I** and **IV**. Using XPhos, both **I** and **IV** resulted in almost 100% conversion within 1 h while, in contrast, the **I**/2P^{t}Bu$_3$ and **IV**/4P^{t}Bu$_3$ catalyst systems resulted in conversions only in the 20-40% range. In experiments complementary to those of Figure 6(c) and 6(d) but not shown for reasons of clarity, it was found that catalyst systems based on Pd(OAc)$_2$ and Pd$_2$(dba)$_3$ with XPhos, i.e. **II**/4XPhos and **III**/3XPhos, also resulted in 30-40% conversion, significantly less than the **I**/2XPhos and **IV**/4XPhos systems but comparable in fact to the P^{t}Bu$_3$-based catalysts.

We thus have a set of results which seem in part somewhat inconsistent. With 4-bromoanisole, P^{t}Bu$_3$ and XPhos exhibit comparable qualities as ligands and precatalysts **I** and **IV** give comparable conversions although the latter gets up to speed more quickly. With 4-chloroanisole, the two precatalysts exhibit comparable utility but, in contrast, XPhos is superior to

P^tBu_3. In addition, and quite startling, the **I**/2XPhos and **IV**/4XPhos catalyst systems provide for higher conversions with 4-chloro- than with 4-bromoanisole.[11] As discussed above, this trend is not anticipated on the basis of relative carbon-halogen bond strengths or many other studies, although the finding is not without precedent; similarly anomalous relative cross-coupling activities have been attributed to a mechanism in which the slow step involves transmetallation rather than oxidative addition.[12] We have pointed out above that multiple mechanistic pathways can operate during palladium-catalyzed C-N cross-coupling reactions, and such would seem to be the case here.

Indeed, while the gist of the mechanism shown in Figure 3 remains widely accepted in spite of apparent incongruities,[8] there is experimental[13] and computational[14] evidence that highly reactive 1:1 complexes "PdL" are often the catalytically active species rather than the 2:1 complexes PdL_2 shown. Here the quotes are included because there are indications that the putative 12-electron, mono-ligated species studied actually contain coordinated anions X^- and are better defined as two-coordinate, 14-electron species $[PdLX]^-$;[15] thus the existence of genuine mono-coordinated species seems unlikely. Indeed, the only example of a 1:1 complex which to our knowledge has actually been studied experimentally, $\{Pd[PPh_2(m\text{-}C_6H_4SO_3)\}^-$, undergoes oxidative addition with bromobenzene in the gas phase about 10^4 faster than does the corresponding 2:1 complex $\{Pd[PPh_2(m\text{-}C_6H_4SO_3][PPh_3]^-$.[13i] Thus expectations that "PdL" would be unusually reactive are probably warranted even if the point seems moot from a practical perspective in solution. However, use of **I** to generate palladium(0)

species in the absence of potentially complicating ligands such as halide ions or electron-deficient alkenes does offer a unique opportunity to generate genuine 1:1 species “PdL” if such can exist as reactive intermediates in very low concentrations.

As a result of these considerations, we have therefore also investigated the catalytic properties of palladium(0) species generated in the presence of only one molar equivalent of ligand per gram-atom of palladium. An analogous NMR study of the Pd_2dba_3/P^tBu_3 catalysis system revealed that addition of P^tBu_3 to Pd_2dba_3 at P^tBu_3:Pd ratios in the range 0.5:1 to >2:1 resulted only in the observation of **I**, Pd_2dba_3, free dba and free P^tBu_3 with the relative amounts dependent on the P^tBu_3:Pd ratio.[13b] No mixed ligand species were observed in spite of the fact that mixtures of Pd_2dba_3 and P^tBu_3 in a P^tBu_3:Pd ratio = 1 exhibited higher catalytic activity than did solutions containing predominantly $Pd[P^tBu_3]_2$.

We have accordingly investigated a series of catalytic systems containing a single equivalent of phosphine ligand per palladium atom. The catalyst systems are denoted **I**/1P^tBu_3, **IV**/2P^tBu_3, **I**/1XPhos and **IV**/2XPhos, consistent with the unity L:Pd molar ratios although we cannot make assumptions about the actual catalytic species in solution or even that they are different from those discussed above. Shown in Figure 7 are reaction profiles for the amination of 4-bromoanisole utilizing the **I**/1P^tBu_3 and the **IV**/2P^tBu_3 catalyst systems, i.e. experiments related to those of Figure 4. As can be seen, both catalysts systems are effective, but neither is comparable to the systems shown in Figure 4 in which the L:Pd ratios are 2:1.

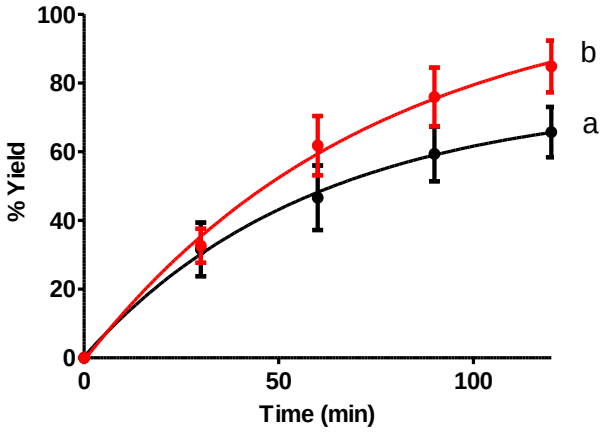


Figure 7. Reaction profiles for the formation of 4-(4-methoxyphenyl)morpholine from the amination of 4-bromoanisole with morpholine catalyzed by 1 mol% Pd catalyst systems utilizing (a) **I**/1P^{t}Bu$_3$ (Method A), (b) **IV**/2P^{t}Bu$_3$.

Of great interest, but not shown, the **I**/1XPhos system was much less active and gave relatively little product (25% after 2h) while the **IV**/2XPhos system gave a reaction profile very similar to the **IV**/2P^{t}Bu$_3$ system shown in Figure 4, i.e. levelling off at about 80% conversion. Thus it seems that very different catalytic activities are obtained on treating **I** with one or two equivalents of XPhos and that, at 1:1 ratios, P^{t}Bu$_3$-based catalyst systems are marginally superior to XPhos-based systems.

Similar experiments were carried out with 4-chloroanisole; the resulting reaction profiles are shown in Figure 8 and are to be compared with the reaction profiles of the corresponding 2:1 systems shown in Figure 6.

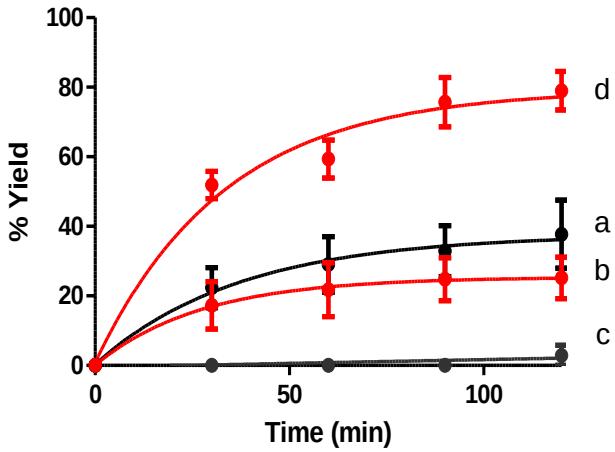


Figure 8. Reaction profiles for the formation of 4-(4-methoxyphenyl)morpholine from the amination of 4-chloroanisole with morpholine catalyzed by 1 mol% Pd catalyst systems utilizing (a) **I**/1P^{t}Bu$_3$ (Method A), (b) **IV**/2P^{t}Bu$_3$, (c) **I**/1XPhos (Method A), (d) **IV**/2XPhos.

As can be seen, changing the P^{t}Bu$_3$:Pd ratio has essentially no effect on conversions using either **I** or **IV**. In contrast, the XPhos-based systems were either somewhat less effective (**IV**/2XPhos) or considerably less effective (**I**/1XPhos). Lower conversions are obtained when the P^{t}Bu$_3$:Pd and the XPhos:Pd ratios are 1:1 rather than 2:1 for both 4-chloroanisole and 4-bromoanisole. Thus, for reasons which at this point are not obvious and are in contrast to the results obtained with the Pd$_2$dba$_3$/P^{t}Bu$_3$ catalysis system,[13b] catalyst systems based on **I** and **IV** are not generally more effective when the initial L:Pd ratio is 1:1 rather than 2:1, and major questions concerning the nature of the species in solution and within the catalytic cycles remain unanswered.

As described in the Experimental Section, we have also developed a procedure which complements the heretofore conventional procedure (Method

A) for generating $Pd[P^tBu_3]_2$. The new procedure, henceforth Method B, involves heating **I** with one or two molar equivalents of P^tBu_3 (or XPhos, Mor-Dalphos) in dioxane at 75°C for 1h as previously but now in the presence of an excess of 4-bromo- or 4-chloroanisole. The reaction mixtures are then taken to 80 °C, the other reactants are added and the reactions are monitored by GC as in Method A. The idea here, of course, is to attempt to intercept catalytically active 1:1 palladium(0) species via their oxidative addition to palladium(II) species which lie on or feed readily into a catalytic cycle.

Precedents for this approach have resulted in varied conclusions. On the one hand, presumed intermediates in the catalytic cycle, compounds of the type PdArXL, have with some ligands L been isolated and found to exhibit the anticipated catalytic activity.[10,13d-f] However, in a case of relevance here, the oxidative addition of bromobenzene to $Pd[P^tBu_3]_2$ can generate a variety of catalytic and non-catalytic species in addition to the mono-phosphine species $PdPhBr(P^tBu_3)$.[16]

In Figure 9 we illustrate the effectiveness of Method B for reactions involving **I** by showing reaction profiles for the amination of 4-bromo- and 4-chloroanisole using the **I**/2P^tBu_3 and **I**/2XPhos catalyst systems.

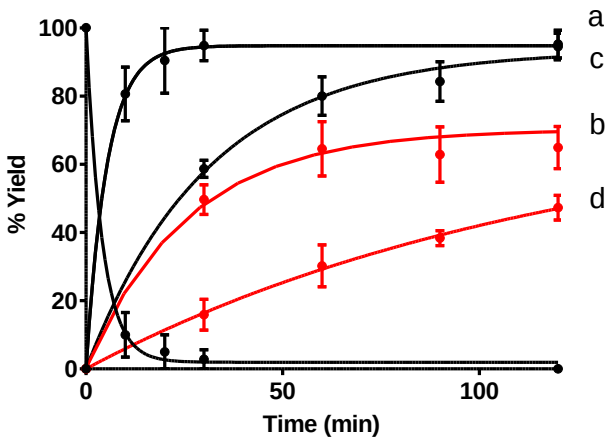


Figure 9. Reaction profiles for the formation of 4-(4-methoxyphenyl)morpholine from (a) 4-bromoanisole using **I**/2P^{t}Bu$_3$, (b) 4-chloroanisole using **I**/2P^{t}Bu$_3$, (c) from 4-bromoanisole using **I**/2XPhos and (d) from 4-chloroanisole using **I**/2XPhos. All experiments utilize Method B; also shown is the loss of 4-bromoanisole accompanying (a).

As can be seen, the reaction profile for the **I**/2P^{t}Bu$_3$ catalyst system generated via this procedure is definitely superior to that formed using Method A (Figure 4a). Indeed, near quantitative conversion was observed within 30 min, with excellent mass balance, and thus the activity of this catalyst system is superior to all others discussed to this point. The conversion of 4-chloroanisole (Figure 9b), although lower than that of 4-bromoanisole, is also significantly higher than that observed using Method A (Figure 6a). In contrast the conversion of 4-bromoanisole using the **I**/2XPhos catalyst system (Figure 9c) is very similar to that obtained using method A (Figure 6c), albeit with a slower initial rate, while the analogous conversion of 4-chloroanisole (Figure 9d) is decidedly inferior to the procedure involving Method A (Figure 6c).

We have also assessed utilization of Method B with the 1:1 catalyst systems, **I**/1P^{t}Bu$_3$ and **I**/1XPhos, with results for 4-bromo- and 4-chloroanisole shown in Figure 10.

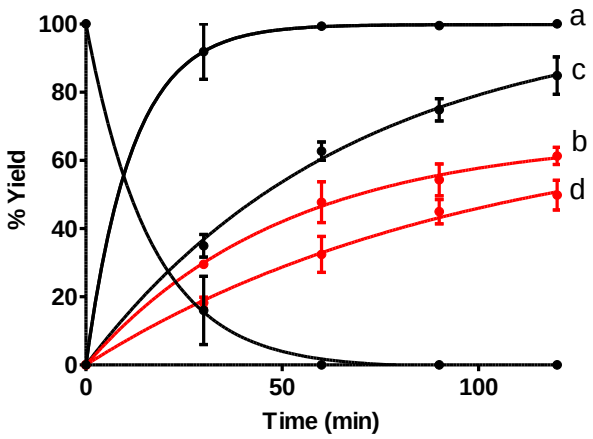


Figure 10. Reaction profiles for the formation of 4-(4-methoxyphenyl)morpholine from (a) 4-bromoanisole using **I**/1P^{t}Bu$_3$, (b) from 4-chloroanisole using **I**/1P^{t}Bu$_3$, (c) from 4-bromoanisole using **I**/1XPhos and (d) from 4-chloroanisole using **I**/1XPhos. All experiments utilize Method B; also shown is the loss of 4-bromoanisole accompanying (a).

Comparing the data for Method B in Figures 9 and 10, it is clear that in all cases, the 1:1 catalyst systems are slightly less effective than the corresponding 2:1 systems. In contrast, comparing the results of Figure 10 with those for 1:1 reactions using Method A (Figures 7 and 8), clearly Method B remains superior.

Finally, and analogous to the above experiments involving P^{t}Bu$_3$ and XPhos, we have also assessed the activities of the **I**/Mor-Dalphos, **I**/2Mor-Dalphos, **IV**/2Mor-Dalphos and **IV**/4Mor-Dalphos catalyst systems for

amination of 4-bromoanisole; for reactions involving **I**, Methods A and B were both utilized. In all cases, conversions to 4-(4-methoxyphenyl)morpholine were in the range 1-20% and thus, for the conventional amination reactions shown in eq. 3 and under the conditions utilized here, Mor-Dalphos is a relatively ineffective ligand for the chemistry studied here although it clearly has a special place in the amination ligand armamentarium.[10]

2.5 Summary and Conclusions

This study compares $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)(\eta^5\text{-}C_5H_5)$ (**I**) with $Pd_2(dba)_3$ (**II**), $Pd(OAc)_2$ (**III**) and $[Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)Cl]_2$ (**IV**), all activated as appropriate by the addition of P^tBu_3 (ratio of ligand:Pd = 2:1) prior to addition of reactants, as catalyst precursors for the conventional Buchwald-Hartwig amination reactions of 4-bromo- and 4-chloroanisole with morpholine. As anticipated on the basis of previous, analogous investigations of Suzuki-Miyaura, Heck-Mizoroki and Sonogashira cross-coupling reactions, **I** is superior to **II** and **III**; however **IV**, assessed for the first time utilizing our methodology, exhibits faster initial rates and comparable conversions for 4-bromoanisole but not 4-chloroanisole. This study also compares P^tBu_3 with Xphos and Mor-Dalphos (ratios of ligand:Pd = 2:1) as activators for **I** and **IV**, and here the picture becomes much more complicated. The Xphos-based catalysts are found to be comparable with the P^tBu_3-based systems for cross-coupling of 4-bromoanisole but are superior for 4-chloroanisole cross-coupling. Surprisingly, the Xphos-based catalysts also produce higher conversions with 4-chloro- than 4-bromoanisole. The Mor-Dalphos catalyst systems involving both **I** and **IV** are decidedly inferior for the

amination of 4-bromoanisole.

Complementing the above and in order to assess the possibilities that, as suggested in the literature, 1:1 complexes may be more active, we have also investigated catalyst systems involving **I** and **IV** activated by P^tBu_3, Xphos and Mor-Dalphos with ligand:Pd ratios of 1:1. In some cases the 1:1 systems exhibited activities comparable to those of the 2:1 systems, but in general the 1:1 catalyst systems were less active. In a further attempt to intercept catalytically active species, we have carried out a series of experiments in which **I** was activated by P^tBu_3, Xphos and Mor-Dalphos (ratios of ligand:Pd = 2:1 and 1:1) as above but in the presence of 4-bromo- or 4-chloroanisole. The idea was to intercept catalytically active (possibly 1:1) palladium(0) species, which lie on or feed readily into the catalytic cycles, via their oxidative addition to palladium(II) species which lie on or feed readily into the catalytic cycles. The results for Xphos and Mor-Dalphos were not particularly exciting, but the conversions for both 4-bromo- or 4-chloroanisole were significantly higher when **I** was activated in this way by P^tBu_3; near quantitative conversion was observed for 4-bromoanisole within 30 min, with excellent mass balance. Thus the activity of this catalyst system is superior to all others discussed to this chapter.

Finally, although our initial assumption concerning the general utility of bis-phosphine palladium(0) catalysts seems warranted for Suzuki-Miyaura, Heck-Mizoroki and Sonogashira cross-coupling reactions utilizing a variety of phosphines, our current results suggest that amination reactions involving the

use of P^tBu_3, XPhos and Mor-Dalphos are much more complicated. In the following chapter, we utilize NMR spectroscopy to investigate the solution chemistry of **I** and **IV** with P^tBu_3, XPhos and Mor-Dalphos in an effort to identify the species formed. We demonstrate not only that steric requirements prevent Xphos and Mor-Dalphos from forming 2:1 palladium(0) complexes of the type PdL_2, but that 1:1 species PdL are unstable with respect to dissociation to free ligand and palladium metal.

While the implications of these findings for the results in this chapter are not at all obvious, it is now clear that utilization of **I** for the synthesis of palladium(0) complexes can be more complicated than previously thought.

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11. The results, as indicated by the errors bars in each figure, are highly reproducible. Each plot is the average of 3-8 runs, experiments performed by different people and with different batches of **I**.
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Chapter 3

NMR Studies of the Species Present in Cross-coupling Catalysis Systems Involving Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5) (I) and [Pd(η^3-1-Ph-C_3H_4)Cl]$_2$ (IV) Activated by P^{t}Bu$_3$, XPhos and Mor-Dalphos

3.1 Preface

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3.2 Introduction

In the preceding chapter,[1] we compared the efficacies of catalyst systems based on Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5) (**I**), $Pd_2(dba)_3$ (**II**), $Pd(OAc)_2$ (**III**) and [Pd(η^3-1-Ph-C_3H_4)Cl]$_2$ (**IV**) activated by P^{t}Bu$_3$, XPhos and/or Mor-Dalphos for the prototypical Buchwald-Hartwig amination reactions of 4-bromo- and 4-chloroanisole with morpholine.[2] We found, not surprisingly in view of previous studies of Suzuki-Miyaura, Heck-Mizoroki and Sonogashira cross-coupling reactions,[3] that **I** is superior to **II** and **III**; however **IV**, assessed for the first time utilizing our methodology, presented apparent anomalies. Interestingly, comparisons of P^{t}Bu$_3$ with Xphos and Mor-Dalphos (ratios of ligand:Pd = 2:1) as activators for **I** and **IV** also revealed complications. The Xphos-based catalysts were comparable with the P^{t}Bu$_3$-based systems for cross-coupling of 4-bromoanisole but were superior for 4-chloroanisole cross-coupling and also produce higher conversions with 4-chloro- than 4-bromoanisole. The Mor-

Dalphos catalyst systems involving both **I** and **IV** are decidedly inferior for the amination of 4-bromoanisole.

Complementing the above and in order to assess the possibilities that, as suggested in the literature, 1:1 complexes may be more active, we also investigated catalyst systems involving **I** and **IV** activated by P^tBu_3, Xphos and Mor-Dalphos with ligand:Pd ratios of 1:1. In some cases the 1:1 systems exhibited activities comparable to those of the 2:1 systems, but in general the 1:1 catalyst systems were less active.

In this chapter, we investigate by NMR spectroscopy the solution chemistry of **I** and **IV** with P^tBu_3, XPhos and Mor-Dalphos in an effort to better understand the apparent mechanistic incongruities noted above.

3.3 Experimental

3.3.1 General Procedures

All syntheses were carried out under a dry, deoxygenated argon or nitrogen atmosphere with standard Schlenk line techniques. Argon was deoxygenated by passage through a heated column of BASF copper catalyst and then dried by passing through a column of 4 Å molecular sieves. Solvents were dried by passage through activated alumina and were then stored under an argon atmosphere for a minimum of 24 h over 3 Å molecular sieves which had been activated by heating at 225 °C, 10^{-2} torr for several days. Phosphines were purchased from Strem Chemicals, all other compounds from Sigma-Aldrich. Johnson-Matthey generously provided us the $PdCl_2$. Handling and storage of air sensitive compounds was carried out in an MBraun Labmaster glove box. NMR

spectra were recorded on a 500 MHz spectrometer with ^{1}H NMR data being referenced to TMS via the residual proton signals of the deuterated solvents. Compound **I**, Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5), and **IV** were prepared as in the literature.[3b,16] The probe thermometer connected to the hotplate stirrer was used to control the temperature.

3.3.2 General Experimental Methodologies

3.3.2.1 Utilizing Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5) (I)

For L:Pd reactant ratios of 2:1, 0.0057 g **I** (0.02 mmol) was combined with 0.008 g P^{t}Bu$_3$ (0.04 mmol), 0.019 g XPhos (0.04 mmol) or 0.018 g Mor-Dalphos (0.04 mmol); for L:Pd ratios of 1:1, 0.0057 g **I** (0.02 mmol) was combined with 0.004 g P^{t}Bu$_3$ (0.02 mmol), 0.009 g XPhos (0.02 mmol) or 0.009 g Mor-Dalphos (0.02 mmol) in 0.6 mL of benzene-d_6 or toluene-d_8 in an NMR tube. The reaction mixtures were shaken briefly, placed in an oil bath at 75 °C, and monitored at 30 min intervals by ^{1}H and ^{31}P NMR spectroscopy (1D, COSY, ^{1}H-^{31}P HMBC) at 25 °C.

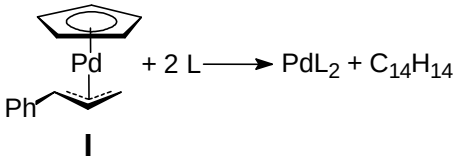
3.3.2.2 Utilizing [Pd(η^3-1-Ph-C_3H_4)Cl]$_2$ (IV)

For L:Pd reactant ratios of 2:1, 0.0052 g **IV** (0.01 mmol) was combined with 0.008 g P^{t}Bu$_3$ (0.04 mmol) or 0.019 g XPhos (0.04 mmol); for L:Pd ratios of 1:1, 0.0052 g **IV** (0.01 mmol) was combined with 0.004 g P^{t}Bu$_3$ (0.02 mmol) or 0.009 g XPhos (0.02 mmol) in 0.6 mL of benzene-d_6 or toluene-d_8 in NMR tube. The reaction mixtures were shaken briefly, placed in an oil bath at 75 °C, and

monitored at 30 min intervals by ^{1}H and ^{31}P NMR spectroscopy (1D, COSY, ^{1}H-^{31}P HMBC) at 25 °C.

3.4 Results and Discussion

We previously demonstrated that **I**[1,3a-c,e] and its parent compound, Pd(η^3-C_3H_5)(η^5-C_5H_5),[3g] react with a variety of phosphines L to form palladium(0) species of the type PdL_n (eq. 1).



I (1)

Of distinct interest and utility, the products could be formed very efficiently and in the absence of competing ligands such as anions and dba, and could also in many cases be identified unambiguously using ^{1}H and ^{31}P NMR spectroscopy. We were thus able to show that $Pd[PCy_3]_2$, $Pd[PMe^tBu_2]_2$, $Pd[PCy_3][PMe^tBu_2]$ and $Pd[P^tBu_3]_2$ can all be readily formed as in eq. 1 and that $Pd[P^tBu_3]_2$ exhibits no inclination to increase its coordination number. In contrast, we were also able to show that $Pd[PCy_3]_2$ and $Pd[PMe^tBu_2]_2$ react readily with added PCy_3 or PMe^tBu_2 to form homo- and heteroleptic 3:1 coordination compounds and thus, as anticipated,[4] that ligand steric requirements play a significant role in deciding the maximum coordination numbers possible.

We also demonstrated that while treatment of **I** with three molar equivalents of $PMePh_2$ or PPh_3 in toluene generates the corresponding tris

complexes PdL_3, treatment with only two molar equivalents in the same solvent and in the temperature range 50-75 ºC results in the formation of palladium metal in addition to the tris complexes.[3b] The reaction sequence shown in eq. 4 seems implied.

$$3\ Pd(\eta^3\text{-}1\text{-}R\text{-}C_3H_4)(\eta^5\text{-}C_5H_5) + 6\ L \xrightarrow{-3\ C_8H_9R} 3\ PdL_2 \longrightarrow Pd + 2\ PdL_3 \qquad (4)$$

R = H, Ph

Thus while the smaller phosphines can stabilize Pd(0) as three (and four) coordinate complexes, as has long been known,[4] the corresponding 2:1 complexes are, at moderate temperatures, unstable with respect to the disproportionation shown in the second step of eq. 4.

To our knowledge, the instability of 2:1 complexes of smaller phosphines has not previously been recognized, although their roles as cross-coupling catalysts have been considered seriously.[5] However, energies for the first dissociation reaction shown in eq. 5 for compounds of the types PdL_2 are calculated to be 19-33 kcal/mol,[5] depending on the phosphines considered and the computational methodologies employed.

$$PdL_2 \longrightarrow PdL + L \qquad (5)$$

Less is known about the corresponding Pd-P bond dissociation energies for the resulting 1:1 species PdL, but the Pd-P bond lengths of PdL are calculated to be shorter than those of PdL_2 by ~0.1 Å[5] and thus the bonds are presumably somewhat stronger than 19-33 kcal/mol.

Since the enthalpy of atomization of palladium metal is ~91 kcal/mol[6]

while the decomposition reaction of eq. 6 involves a positive entropy change, it follows that all Pd(0) precatalysts of the type PdL_n must be thermodynamically unstable with respect to dissociation to palladium metal and free phosphine as in eq. 6. This is because breaking the Pd-P bonds to form Pd metal results in an energy change (~91 kcal/mol) which is greater than the approximate energy required to break the Pd-P bonds of PdL_2 or PdL (~19-50 kcal/mol). The entropy change is positive as well. Therefore, in general, it is likely that the reaction of eq. 6 proceeds as shown.

$$PdL_2 \longrightarrow Pd + 2\ L \qquad (6)$$

As to why steric bulk might stabilize bis-phosphine complexes, we suggest tentatively that the more sterically demanding ligands prevent the close approach of Pd atoms which might be necessary to permit aggregation to metal particles. We note that the behaviour noted here resembles that observed with $Pd(\eta^3\text{-}C_3H_5)(\eta^5\text{-}C_5H_5)$[3g] which, on heating in the absence of potential ligands, reductively eliminates $C_5H_5\text{-}C_3H_5$ and deposits palladium metal.[7]

In complementary attempts to gain further information about the nature of the palladium(0) species present in solution prior to and during catalytic cross-coupling reactions, we have now extended our earlier NMR investigations (^1H, ^{31}P) of the reaction of **I** with P^tBu_3. We find that, when reacted in a 1:1 molar ratio in toluene-d_8, half of the **I** reacts to give $Pd[P^tBu_3]_2$, there being evidence of neither a 1:1 species nor of the precipitation of palladium metal.

We have also investigated reactions of **I** with Xphos and Mor-Dalphos and

of **IV** with P^tBu_3 and Xphos. Reactions of **I** with XPhos would not be anticipated to form 2:1 species because of the enormous steric requirements of this ligand; its cone angle is estimated to be ~256º, much greater than that of e.g. P^tBu_3 (182º).[8] However, complexes of biaryl ligands such as XPhos are believed to be stabilized by π-bonding of the non-phosphorus-containing ring of the biaryl group,[9] and thus a chelated 1:1 species Pd(XPhos) may be capable of existence.

NMR experiments involving the reaction of **I** with XPhos were carried out in toluene-d_8, solutions of XPhos and **I** (1:1 and 2:1 molar ratios) being monitored by ^1H and ^{31}P NMR spectroscopy. At both molar ratios, ^1H NMR spectra indicated that no reaction had occurred within 30 min at room temperature, the singlet Cp resonance of **I** remaining prominent. However, the resonances of **I** had almost completely disappeared within 1 h at 75 ºC and resonances of the reductive elimination product, $C_{14}H_{14}$, had grown in, much as in eq. 1; in addition, palladium metal powder had precipitated. Surprisingly the only strong resonance in the ^{31}P spectra was that of free XPhos, although a number of very weak resonances of unidentifiable palladium(0) species in the range δ 20-85 were also observed (Figure 11) .

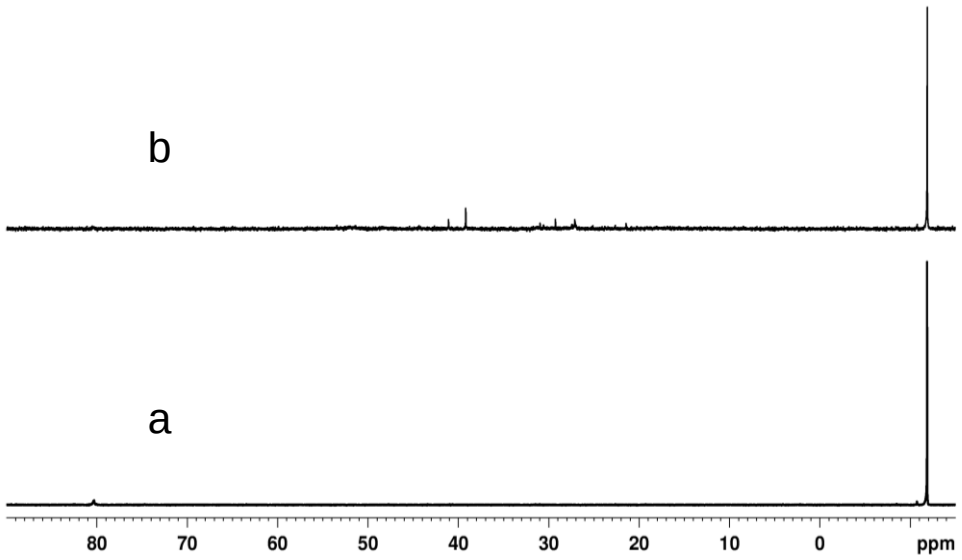


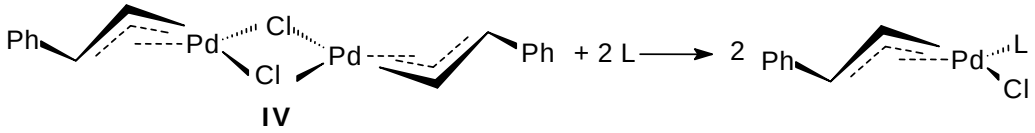
Figure 11. ^{31}P NMR spectra showing the progress of the reaction of **I** with XPhos (1:1 molar ratio) (a) at room temperature immediately after mixing, and (b) after 1 h at 75 ºC. A large number of the very weak resonances in the range δ 20-85 were unidentifiable, therefore no further investigation was done for assignments of the resonances in that range.

Incidentally, the palladium metal powder which precipitated was found not to function as a catalyst for amination cross-coupling reactions; thus traces of palladium metal do not contribute inadvertently to any of the catalytic processes described in this and previous work, as might otherwise be anticipated.[10]

Similar experiments were carried out in toluene-d_8 utilizing Mor-Dalphos and, although the reactions of **I** with this ligand were slightly slower than those with XPhos, the result was much the same; precipitation of palladium metal left the free ligand as the only major phosphorus-containing product.

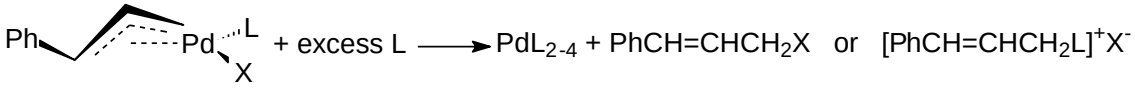
Compound **I** is stable for at least 10 h under these conditions, and thus it is clear that both XPhos and Mor-Dalphos react with **I** in solution to induce reductive elimination of $C_{14}H_{14}$ but that the resulting palladium-containing products are not stable with respect to palladium metal formation. As with bis-phosphine complexes of small ligands, it seems that the palladium atoms of the presumed PdXphos and PdMor-Dalphos are sufficently exposed that palladium atoms can react and aggregate.

Reactions of dimeric η^3-allylic such as **IV** with tertiary phosphine ligands have been much studied, and frequently result in cleavage of the chloro bridges and formation of monomeric Pd(II) products as in eq 7.[11] (Mor-DalPhos has previously been shown to react readily with **IV** at room temperature to cleave the chloride bridges and form both a chloro-η^1-cinnamyl complex and a cationic η^3-cinnamyl complex; in both the Mor-DalPhos chelates via the phosphorus and nitrogen atoms.[12]) In addition, palladium(0) compounds can also be formed via reactions thought to involve combination of the allylic moiety with a nucleophile which may be anionic or neutral as in eq. 8.



IV

(7)



(8)

Formation of the palladium(0) and allylic products can in principle involve intermolecular nucleophilic attack on an η^3-allylic ligand or intramolecular reductive elimination from an η^1-allylic species.[11b,c,e,g-i]

In this investigation we have studied the reactions of **IV** with P^tBu_3 (P^tBu_3:Pd ratio 2:1) in toluene-d_8 at 75 °C by ^1H and ^{31}P NMR spectroscopy. Several products, in varying proprortions depending on the the time elapsed, were observed and identified (see Figure 12 for ^{31}P NMR spectroscopic results) although attempts to isolate them were unsuccessful.

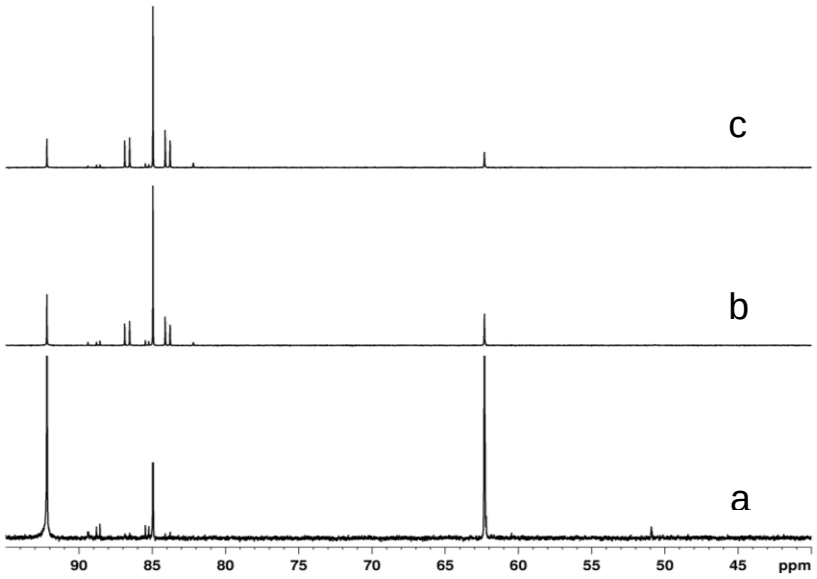


Figure 12. ^{31}P NMR spectra showing the progress of the reaction of **IV** with P^tBu_3 (P:Pd ratio 2:1) in toluene-d_8 (a) at room temperature immediately after mixing, (b) after 30 min at 75 ºC, and (c) after 1 h at 75 ºC.

As is clear in Figure 12a, the ^{31}P NMR spectrum of an initially formed mixture at room temperature exhibited the resonances of P^tBu_3 and $Pd[P^tBu_3]_2$ at δ 62.2 and 85.0,[3b,g] respectively, in addition to a strong new singlet at δ

92.3 and weaker resonances in the region δ 83-90 and at δ 50.9. Within an hour, the resonance of free P^tBu_3 became very weak as the resonance of $Pd[P^tBu_3]_2$ increased in intensity (Figures 12b, 12c).

Athough resonances in the ^1H NMR spectrum overlapped somewhat with resonances of other species, rendering assignments tenuous, the species with the ^{31}P resonance at δ 92.3 appeared to be $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)Cl(P^tBu_3)$. This compound seems not to have been prepared previously but is a reasonable product on the basis of eq. 7. We also note that the relatively low field ^{31}P chemical shifts of the closely related $Pd(\eta^3\text{-}C_3H_5)Cl(P^tBu_3)$ (δ 82.5 in CH_2Cl_2,[11f] δ 86.0 in $CDCl_3$[11j]) and $Pd(\eta^3\text{-crotyl})Cl(P^tBu_3)$ (δ 89.7 in $CDCl_3$)[11i] are consistent with our proposed identification of $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)Cl(P^tBu_3)$, and it is interesting to note that the resonance of $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)Cl(P^tBu_3)$ weakens over an hour as that of $Pd[P^tBu_3]_2$ increases in intensity. Thus $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)Cl(P^tBu_3)$ may be an intermediate in the formation of $Pd[P^tBu_3]_2$.

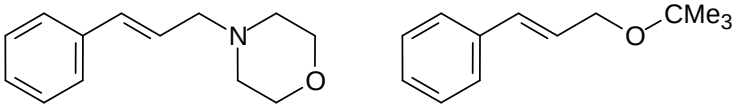
The resonance at δ 50.9 was very weak, largely because the compound responsible for it precipitated from solution as colorless crystals; it seemed, however, to be more soluble in benzene-d_6 in which its ^{31}P resonance became much stronger at room temperature prior to precipitation. The compound giving rise to the resonance appears not to have been described in the literature but was, fortuitously, encountered during a parallel line of inquiry in which the bromide salt of the phosphonium cation, $[PhC_3H_4P^tBu_3]^+$ was identified by ^1H and ^{31}P NMR spectroscopy and X-ray crystallography.[13] The product formed here was separated from the NMR solution, washed with

toluene and dried. It exhibits essentially identical ^{1}H and ^{31}P NMR spectra (CD_2Cl_2) as $[PhC_3H_4P^tBu_3]Br$, and is identified as $[PhC_3H_4P^tBu_3]Cl$, a reasonable byproduct during the formation of $Pd[P^tBu_3]_2$ as in eq. 8.

Interestingly, two weak new doublets were also observed in the initial room temperature spectrum, the constituents of an AB quartet at δ 85.3, 88.6 (J_{PP} 48.2 Hz). These resonances weakened further over an hour, being replaced by the constituents of another AB quartet at δ 84.1, 86.7 (J_{PP} 66.8 Hz). The two sets of AB quartets are reminiscent of ^{31}P NMR spectra of syn and anti dinuclear palladium(I) species of the types $Pd_2L_2(\mu\text{-}1\text{-}Ph\text{-}C_3H_4)(\mu\text{-}Cp)$[3b,g] and $Pd_2L_2(\mu\text{-}1\text{-}Ph\text{-}C_3H_4)(\mu\text{-}Cl)$,[14] in which the ^{31}P nuclei are non-equivalent because of the asymmetry of the bridging cinnamyl ligand. The P-P coupling constants observed for the latter compounds are similar to that observed here although no P^tBu_3 analogue was reported. We therefore attribute the two sets of resonances to syn and anti isomers of $Pd_2(P^tBu_3)_2(\mu\text{-}1\text{-}Ph\text{-}C_3H_4)(\mu\text{-}Cl)$ although it is not clear how this compound would form. Analogous di-μ-halo compounds of the type $Pd_2L_2(\mu\text{-}X)_2$ are known to be formed and involved during cross-coupling reactions.[15]

We also briefly investigated the species formed on treating a toluene-d_8 solution of **IV** and P^tBu_3 (P^tBu_3:Pd 2:1) with NaO^tBu and morpholine, the reactants utilized during our amination reactions. Interestingly, addition of 4 eqivalents of NaO^tBu to the mixture of **IV** and P^tBu_3 at room temperature resulted in the appearance of the ^{31}P resonances of $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)Cl(P^tBu_3)$ (weak) and $Pd[P^tBu_3]_2$ (moderate), in addition a relatively

strong resonance of unreacted P^tBu_3. On the subsequent addition of morpholine to the solution and warming to 75 ºC, the resonance of Pd(η^3-1-Ph-C_3H_4)Cl(P^tBu_3) disappeared immediately and the major ^{31}P resonance observed was that of Pd[P^tBu_3]$_2$ although a small amount of freeP^tBu_3 remained. Inspection of the ^1H NMR spectrum at this stage revealed the presence of *N*-cinnamylmorpholine and cinnamyl-*tert*-butyl ether in a ~5:1 ratio.



N-cinnamylmorpholine Cinnamyl-*t*-butyl ether

Scheme 25. *N*-cinnamylmorpholine and cinnamyl-*tert*-butyl ether structures.

Thus, in the absence of bases, Pd[P^tBu_3]$_2$ can be partially formed by the coupling of cinnamyl and P^tBu_3 ligands to form the phosphonium cation [$PhC_3H_4P^tBu_3$]$^+$. However, addition of a combination of NaO^tBu and morpholine results rapidly in the formation of Pd[P^tBu_3]$_2$ via the coupling of allylic with either alkoxy or amido groups.

We also investigated the reaction of **IV** with XPhos by monitoring the solutions of XPhos and **IV** (2:1 molar ratio) in toluene-d_8 at room temperature and 75 ºC by ^1H and ^{31}P NMR spectroscopy. It was found that, at room temperature, about 65 % of the XPhos reacted immediately and a broad ^{31}P resonance appeared at δ ~56. At this point, the ^1H NMR spectrum showed that all of the **IV** had reacted and that a new set of cinnamyl resonances had

appeared at δ 5.52 (dt, J = 12.6, 9.4 Hz), 4.96 (dd, J = 10, 12.6 Hz), 2.90 (br) and 2.23 (br).

To investigate the system further, ^{1}H and ^{31}P NMR spectra were run at −70 °C and it was found that the broad resonance at δ ~56 had decoalesced to two resonances of unequal (~4:3) intensities at δ 54.7 (br) and 56.9 (vbr). The ^{1}H resonances of the cinnamyl ligand also decoalesced, that at δ 5.52 to resonances at δ 5.43 and 5.60 and that at δ 4.96 to resonances at δ 5.07 and 4.93; the apparent decoalescence of the two broad resoances at δ 2.90 and 2.23 were more difficult to define because of extensive overlap with other resonances. While firm assignments are impossible at this stage, the spectral evidence is consistent with either [(η^3- cinnamyl)Pd(Xphos)]Cl or (η^3-cinnamyl)Pd(Xphos)Cl, both consistent with eq. 7.

We favour slightly the former, ionic structure both for steric reasons and because the decoalescence patterns observed in the ^{1}H and the ^{31}P NMR spectra are reminiscent of similar observations reported previously for three-coordinate compounds of the type PdArXL where L = an Xphos and similar ligands.[9] Here exchange between two or more conformations of the coordinated ligand, possibly stabilized by arene-Pd interactions, resulted in broad, averaged NMR spectra at higher temperatures and decoalesced spectra at lower temperatures. In the three-coordinate complex [(cinnamyl)Pd(Xphos)]Cl, the vacant site provides for arene-Pd interactions analogous to those invoked for the compounds PdArXL. (We note that **IV** reacts with Mor-Dalphos similarly, producing both η^1- and η^3- species.[12])

Complementing the results reported here, we are also investigating by ^{1}H and ^{31}P NMR spectroscopy the interesting intermediate species formed when **I** and **IV** react with various phosphines in the presence of excess bromobenzene.[1,13]

3.5 Summary and Conclusions

In an effort to extend our previous studies into the palladium(0) species formed when **I** reacts with tertiary phosphines, we have investigated by ^{1}H and ^{31}P NMR spectroscopy the reactions of **I** with $P^{t}Bu_3$, Xphos and Mor-Dalphos (1:1, 2:1 molar ratios) in toluene at 75 ºC. As anticipated on the basis of previous work,[1,3] all induced reductive elimination of $C_{14}H_{14}$, showing that all had reacted with the otherwise thermally stable **I**. However, while a deficiency of $P^{t}Bu_3$ resulted only in the formation of $Pd[P^{t}Bu_3]_2$, the major products formed ultimately with Xphos and Mor-Dalphos were, surprisingly, palladium metal and the free ligand. Other phosphorus-containing products were present at very low concentrations and presumably account for the catalysis previously observed,[1] but clearly neither Xphos nor Mor-Dalphos can support Pd(0) as either 1:1 or 2:1 complexes at moderate tempertatures.

We have also investigated the products formed when **IV** is treated with $P^{t}Bu_3$ ($P^{t}Bu_3$:Pd 2:1), $NaO^{t}Bu$ and morpholine, i.e. the mixture producing catalysis.[1] On adding $NaO^{t}Bu$ at room temperature and prior to disappearance of unreacted $P^{t}Bu_3$, a small amount of $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)Cl(P^{t}Bu_3)$ and rather more $Pd[P^{t}Bu_3]_2$ formed quickly. On the subsequent addition of morpholine to the solution and warming to 75 ºC, the resonance of $Pd(\eta^3\text{-}1\text{-}Ph\text{-}$

C_3H_4)Cl(P^tBu_3) disappeared and the major ^{31}P resonance observed was that of Pd[P^tBu_3]$_2$. Inspection of the ^1H NMR spectrum at this stage revealed the presence of *N*-cinnamylmorpholine and cinnamyl-*tert*-butyl ether in a ratio of ~4:3. These results are consistent with palladium(0) formation via either direct attack at the η^3-1-Ph-C_3H_4 ligand by alkoxide or amide anions or reductive elimination of η^1-1-Ph-C_3H_4 alkoxide or amide ligands.

Our results in this investigation demonstrate the utility of **I** for not only generating useful catalytic species, but also for making possible useful investigations of phosphine palladium(0) complexes in the absence of other potential ligands, anionic or neutral. Therefore, in the following chapter, we investigate the formation and entrapment of the Pd(0)-PPh_3 with low (<3:1) ligand:Pd ratios in the presence of the exess aryl halide.

3.6 References

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Chapter 4

An Investigation of the Formation and Entrapment of Palladium(0)-PPh_3 Species to Give Products with Low (<3:1) Ligand:Pd Ratios

4.1 Preface

The material described in this chapter has been submitted as: Zhang, X.; Borjian, S.; Baird, M. C., submitted.

4.2 Introduction

A number of very useful carbon-carbon and carbon-heteroatom bond forming methodologies are available through reactions catalyzed by palladium(0) compounds of the type PdL_2 (L = tertiary phosphines)[1]. In the general case, an aryl halide ArX (X = Cl, Br, I) reacts catalytically with a carbon- or heteroatom-based nucleophile Nuc^- to form the coupled product Ar-Nuc. The most widely accepted catalytic cycle (Figure 2) typically involves oxidative addition of ArX to PdL_2 to give aryl-palladium(II) species $PdArXL_2$, followed by displacement of X^- by Nuc^- and reductive elimination of Ar-Nuc.[2]

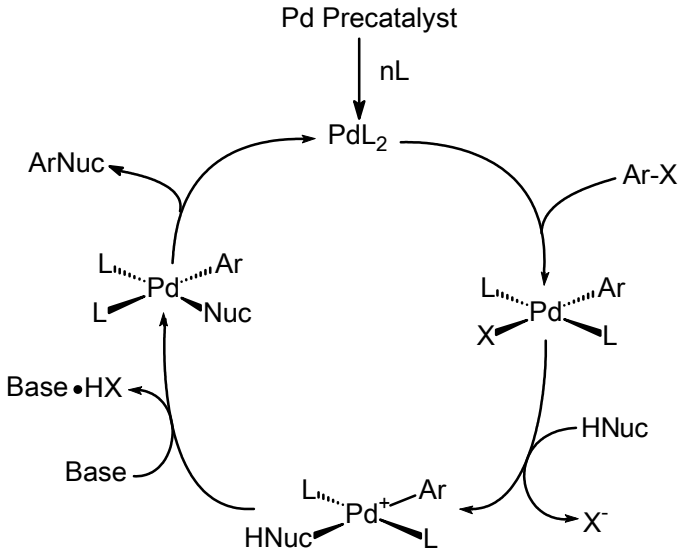


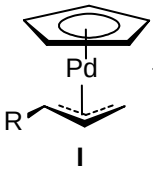
Figure 2. General catalytic cycle for Buchwald-Hartwig amination.

Although the importance of 2:1 species shown in Figure 2 is frequently posited, there is also experimental[3] and computational[4] evidence that more reactive 1:1 complexes “PdL” may sometimes be the catalytically active species. Here the quotes are included because there are indications that putative 12-electron, mono-ligated solution species actually contain coordinated anions X^- and are better defined as two-coordinate, 14-electron species $[PdLX]^-$.[5] Be that as it may, at least one example of a genuine 1:1 complex has been studied experimentally, $\{Pd[PPh_2(m\text{-}C_6H_4SO_3)\}^-$. This triaryl phosphine complex undergoes oxidative addition with bromobenzene in the gas phase about 10^4 faster than does an analogous 2:1 complex $\{Pd[PPh_2(m\text{-}C_6H_4SO_3][PPh_3]^-$,[3i] and thus expectations that “PdL” would be unusually reactive are certainly warranted and have resulted in a number of efforts to detect their presence.

To this end there have been several attempts to trap low coordinate number species such as “PdL” by generating them in the presence of aryl halides ArX

which may oxidatively add to give three-coordinate species PdArXL. The latter can in principle be isolated, characterized and assessed for catalytic ability, but precedents for this approach have resulted in varied conclusions. In some instances, compounds of the type PdArXL, have indeed been isolated and found to exhibit the anticipated catalytic activity.[7,8] However it has also been found that oxidative addition of bromobenzene to $Pd[P^tBu_3]_2$ generates, in addition to the mono-phosphine oxidative addition product $PdPhBr(P^tBu_3)$, a variety of products such as $PdHBr(P^tBu_3)_2$, $[Pd(\mu\text{-}Br)_2P^tBu_3]_2$ and a compound containing metallated P^tBu_3 ligands.[8] Thus the jury is still out on the potential value of trapping experiments in general, and further studies are certainly warranted.

We have previously shown that the compound $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)(\eta^5\text{-}C_5H_5)$ (**I**) reacts cleanly with a variety of tertiary phosphines (L) which coordinate and induce reductive elimination of non-coordinating $PhC_3H_4\text{-}C_5H_5$ to form palladium(0) phosphine complexes PdL_n (n = 2, 3) depending on the ligand steric requirements and electronic properties.[6]



$$\mathbf{I} + n\,L \longrightarrow PdL_n\,(n = 2, 3) + C_{14}H_{14} \qquad (9)$$

In the case of L = PPh_3, treatment of **I** with three molar equivalents in toluene in the temperature range 50-75 ºC generates the corresponding tris complex $Pd(PPh_3)_3$ but treatment with only two molar equivalents under the same conditions results not in the formation of $Pd(PPh_3)_2$ but in the precipitation of

palladium metal and generation of the tris complex.[6b] The reaction sequence of eq. 10 seems implied.

$$3\ Pd(\eta^3\text{-}1\text{-}R\text{-}C_3H_4)(\eta^5\text{-}C_5H_5) + 6\ PPh_3 \xrightarrow{-3\ C_{14}H_{14}} 3\ "Pd(PPh_3)_2" \longrightarrow Pd + 2\ Pd(PPh_3)_3 \quad (10)$$

Thus while PPh_3 can stabilize Pd(0) as three (and four) coordinate complexes, as has long been known,[9a-d] the corresponding 2:1 complex $Pd(PPh_3)_2$ is at moderate temperatures unstable with respect to the disproportionation shown in the second step of eq. 10. Although its role in the oxidative addition of aryl halides to $Pd(PPh_3)_{3,4}$ has been implicated in a much cited kinetic investigation which found that oxidative addition is hindered by the addition of free PPh_3,[9e] in fact the involvement of $Pd(PPh_3)_2$ was “assumed” and a possible role for the 1:1 analogue seems not to have been considered. We wondered, therefore, if participation of either might be demonstratable via entrapment experiments of the type discussed above.

Since **I** stands alone for its ability to generate the species $PdL_{2,3}$ in the absence of potentially complicating ligands such as halide ions,[6a-c,e] its use to generate palladium(0) species offers a unique opportunity to generate genuine 1:1 or 2:1 species $Pd(PPh_3)_{1,2}$ if such exist as reactive intermediates. In an effort to trap these 1:1 and/or 2:1 intermediates, we have carried out reactions of **I** with deficiencies of PPh_3 in the presence of a five-fold excess of bromobenzene. The study has resulted in the observation by NMR spectroscopy of several mono-PPh_3 products, all of which are characterized and identified spectroscopically.

4.3 Experimental

4.3.1 General Procedures

All reactions were carried out under an atmosphere of dry, deoxygenated argon using Schlenk line techniques. All supplies were purchased from Sigma-Aldrich or Strem and were used without further purification with the exception of PPh_3, which was recrystallized from dry and deoxygenated MeOH. Deuterated NMR solvents were dried by storage under nitrogen for a minimum of 24 h over 4 Å molecular sieves which had been activated by heating at 225 °C, 10^{-2} torr for several days. NMR spectra are recorded on Bruker AV-500 and -600 NMR spectrometers.

4.3.2 General Experimental Methodology to Prepare Reaction Mixtures

Under nitrogen, **I** (0.0072 g, 0.025 mmol), PPh_3 (0.0066 g, 0.025 mmol) and bromobenzene (0.0196 g, 0.125 mmol) were dissolved in 0.6 mL of toluene-d_8. Room temperature ^1H and ^{31}P NMR spectra were obtained immediately, and the sample was then placed in an oil bath at 50 °C, heated for 30 min and then cooled to room temperature to obtain subsequent ^1H and ^{31}P NMR spectra. The sample was then reheated at 50 °C for a further 30 min, and cooled again for ^1H and ^{31}P NMR spectra to be run.

4.3.3 General Experimental Methodology to Study Catalysis

A solution of **I** (0.007 g, 0.025 mmol), PPh_3 (0.0066 g, 0.025 mmol) and bromobenzene (0.0196 g, 0.125 mmol) in 0.6 ml of toluene) was heated at 50 °C for 30 min. The solvent was then removed under reduced pressure and the

mixture was combined with 4-bromoanisole (0.187 g, 1 mmol), morpholine (0.105 g, 1.2 mmol), sodium *tert*-butoxide (0.135, 1.4 mmol) in 1.5 ml of dioxane. The reaction temperature was raised to 80 °C and held at this temperature for 24 h; 0.1 mL aliquots were removed at specified intervals, diluted with ~10 mL of dioxane and analysed by GC.

4.4 Results and Discussion

Reactions were carried out using mixtures of **I** and PPh_3 (PPh_3:Pd = 1:1) in toluene-d_8 in the presence of five equivalents of PhBr, and were monitored by ^1H and ^{31}P NMR spectroscopy. The reaction mixtures generally changed from dark purple (the colour of **I**) to brown after adding PPh_3 and PhBr, eventually becoming dark orange after being heated at 50 °C.

The resonances of neither free PPh_3 (δ –4.9) nor $Pd(PPh_3)_3$ (δ 22.9)[6b] were observed in the first spectrum taken (Figure 13a), not because they had been consumed (see below) but almost certainly because of severe exchange broadening between the two compounds.[9c] Observed instead were the resonances of the σ-allylic species $Pd(\eta^5\text{-}C_5H_5)(\eta^1\text{-}Ph\text{-}C_3H_4)(PPh_3)$ (**II'**, δ 44.8 (s))[6b] and of the dinuclear species $Pd_2L_2(\mu\text{-}C_5H_5)(\mu\text{-}Ph\text{-}C_3H_4)$ **III'** (two AB quartets: syn-**III'a**, δ 24.5, 26.2, J_{PP} 95 Hz; anti-**III'b**, δ 23.0, 26.8, J_{PP} 139 Hz)),[6b] in addition to a very weak singlet at δ 40.3 (**IV'**) (Figure 13a).

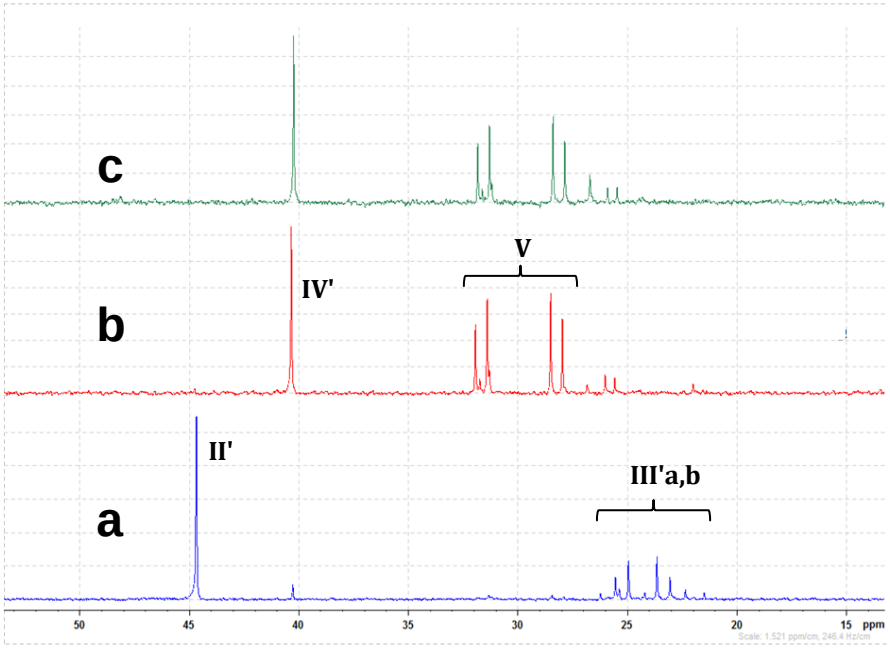


Figure 13. Room temperature ^{31}P NMR spectra of a 1:1 reaction mixture of **I** and PPh_3 in the presence of 5 equivalents of PhBr (a) immediately after mixing, (b) after 30 min at 50 °C, (c) after 60 min at 50 ºC.

On heating the reaction mixture for 30 min at 50 °C (Figure 13b), the ^{31}P resonance of **II'** disappeared while those of **III'a** and **III'b** weakened, the latter relatively slowly. The singlet at δ 40.3 (**IV'**) strengthened and the components of a new AB quartet appeared at δ 28.2 and 31.6 (J_{PP} = 86 Hz) (**V**). Compounds **IV'** and **V** were the major species in solution after 60 min at 50 °C (Figure 13c) although small amounts of **III'** persisted and a weak singlet at δ 26.9 grew in; some palladium metal was also apparent within 90 min. While the weak resonance at δ 26.9 cannot be assigned, at no point did there appear even weak resonances attributable to the potential products of oxidative addition, *trans*-$PdBrPh(PPh_3)_2$ (δ 22.9[10a]) or $[PdBrPh(PPh_3)]_2$ (δ 30.4[10a]). The salt $(Ph_4P)Br$ is also a conceivable product,[10] but its resonance at δ ~23[10b] was also absent.

The course of the reaction at 50 °C was also monitored by ^{1}H NMR spectroscopy with results as in Figure 14. The presence of the resonances of **I** throughout (Figures 14a-c) indicates that considerable proportions of starting materials (**I**, and PPh_3 since their initial ratio was 1:1) remained even after heating at 50 °C for 60 min, although a number of new resonances attributable to new species **IV'** and **V** were also observed (Figure 14b). Notably absent were the Pd-C_6H_5 resonances of *trans*-$PdBrPh(PPh_3)_2$ at δ 6.3, 6.45 and 6.9,[10a] confirming conclusions about this compound reached above on the basis of the ^{31}P NMR spectral data.

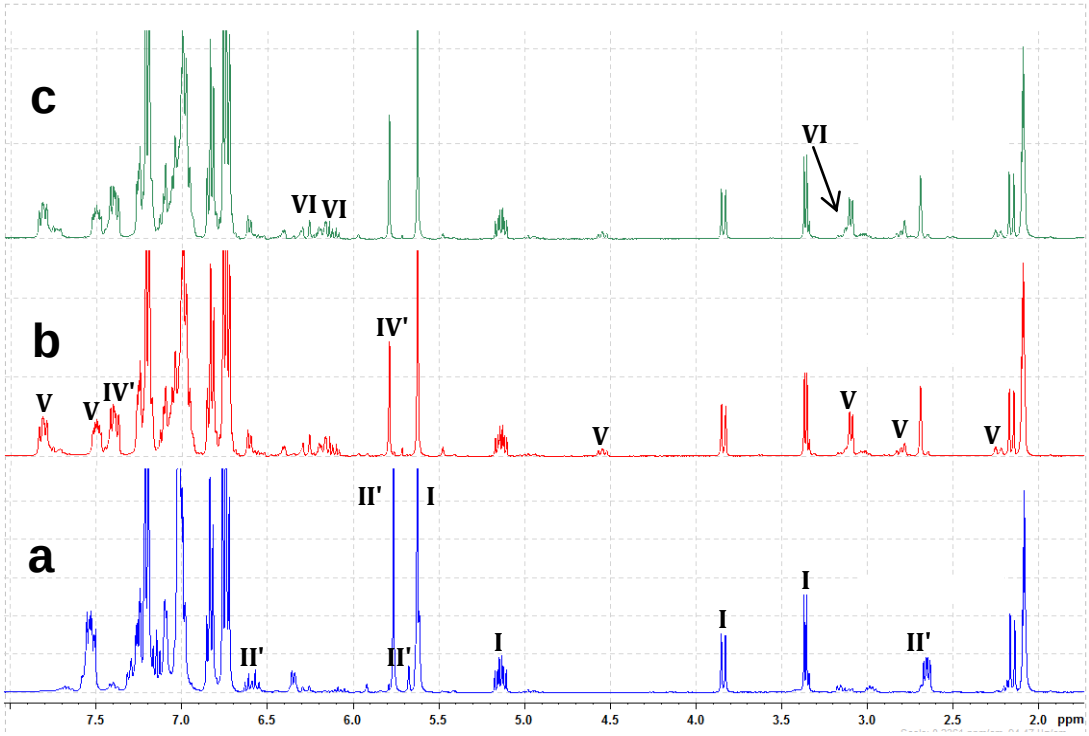


Figure 14. Room temperature ^{1}H NMR spectra of a 1:1 reaction mixture of **I** and PPh_3 in the presence of 5 equivalents of PhBr (a) immediately after mixing, (b) after 30 min at 50 °C, (c) after 60 min at 50 °C. The resonances of **I** and Pd(η^5-C_5H_5)(η^1-Ph-C_3H_4)(PPh_3) (**II'**) are indicated in Figure 14a, those of PdPh(η^5-C_5H_5)(PPh_3) (**IV'**) and Pd_2(μ-*anti*-1-Ph-C_3H_4)(μ-Br)(PPh_3)$_2$ (**V**) Figure 14b, those of *trans*-1,3-diphenylpropene (**VI**) in Figure 14c.

In order to verify that the new species required PhBr for their formation, the reaction was repeated in the absence of PhBr. Reaction mixtures containing only PPh_3 and **I** in toluene-d_8 at 50 °C were monitored by ^{31}P NMR spectroscopy for 60 min, and it was found that while the resonances of **II'** and **III'a**,**b** appeared, as expected,[6b] neither **IV'** nor **V** were formed; after 60 min at 50 °C, some palladium metal had precipitated.

In order to facilitate assignments of the new ^{1}H resonances shown in Figures 14b,c, a series of ^{1}H-^{31}P HMBC, COSY, NOESY and ^{1}H-^{13}C HSQC experiments were carried out with results as in e.g. Figure 15.

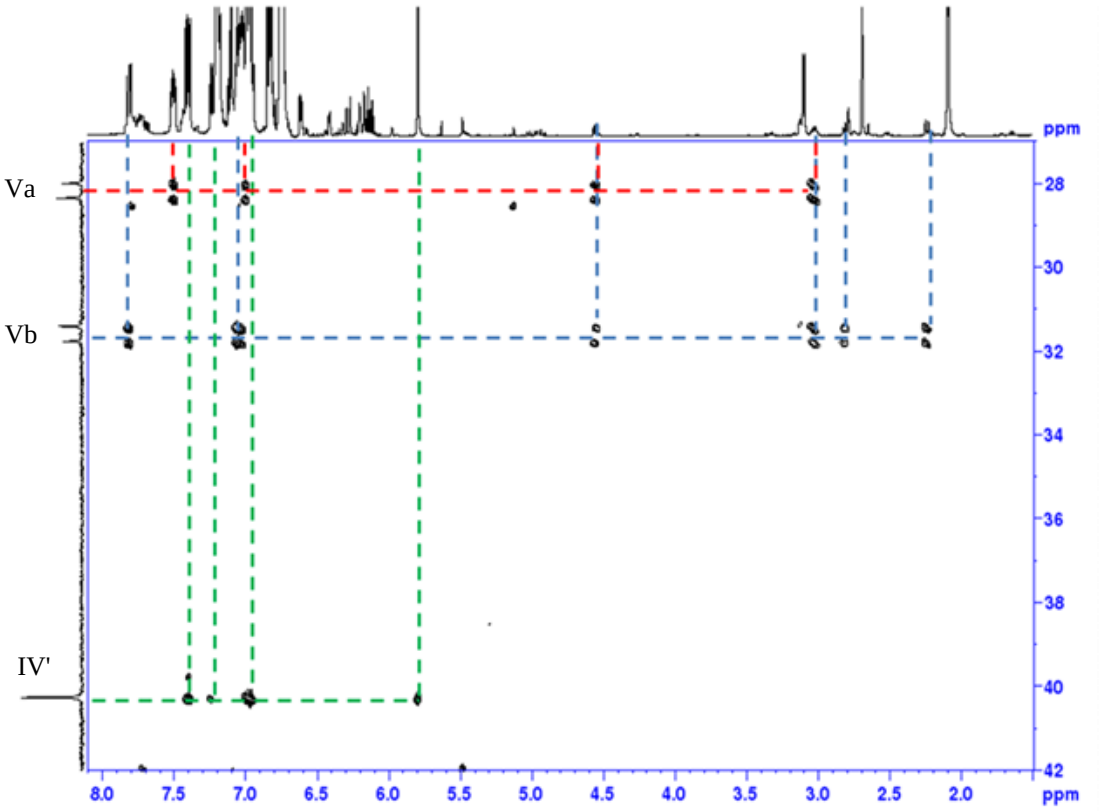


Figure 15. ^{1}H-^{31}P HMBC spectrum of a 1:1 reaction mixture of **I** and PPh_3 with 5 equivalents of PhBr after heating for 30 min at 50 °C in toluene-d_8.

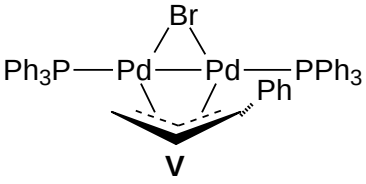
As can be seen in the ^{1}H-^{31}P HMBC spectrum of Figure 15, the ^{31}P resonance of **IV'** at δ 40.3 correlates with a well-defined η^5-C_5H_5 resonance at δ 5.79 (d, J_{PH} 1.5 Hz) and strong phenyl resonances at δ ~6.97, ~7.25 and ~7.40. The fact that the η^5-C_5H_5 resonance is a doublet suggests that **IV'** contains a single PPh_3 and thus reasonable candidates are $PdBr(\eta^5\text{-}C_5H_5)(PPh_3)$ and $PdPh(\eta^5\text{-}C_5H_5)(PPh_3)$. Both are known compounds, the former reported to be dark green and to exhibit a η^5-C_5H_5 resonance at δ 5.39 (d, J_{PH} 2.55) and a ^{31}P resonance at δ 31.8 in C_6D_6.[11] The latter is reported to be orange-yellow and to exhibit a η^5-C_5H_5 resonance at δ 5.7 (d, J_{PH} 1.5) and a ^{31}P resonance at δ 40.4 (solvents not specified).[12] On this basis, **IV'** is identified as $PdPh(\eta^5\text{-}C_5H_5)(PPh_3)$, the Pd-Ph resonances being obscured by the more intense PPh_3 and/or PhBr resonances and therefore not identified. On the basis of an HSQC experiment, the ^{13}C chemical shift of the η^5-C_5H_5 ligand of **IV'** is δ 97.0 (J_{CH} = 170.6 Hz).

The most obvious feature of the ^{31}P NMR spectrum of **V** is, of course, the fact that it comprises an AB spin system; thus **V** probably contains a μ-Ph-C_3H_4 group, as shown in Table 1 and similar to **III'**.[6b] As can also be seen in the ^{1}H-^{31}P HMBC spectrum (Figure 15), the ^{31}P resonance of **V** at δ 28.2 correlates with apparent allylic resonances at δ 3.03 (m, $^{3}J_{HH}$ 8.6 Hz, 12.8 Hz; J_{PH} 4 Hz) and 4.55 (m, $^{3}J_{HH}$ 8.6 Hz; J_{PH} 8.6 Hz) in addition to aromatic resonances at δ ~7.00 and ~7.51, while that at δ 31.6 correlates with apparent allylic resonances at δ 2.25 (m, $^{2}J_{HH}$ 1.2 Hz; $^{3}J_{HH}$ 12.8 Hz; J_{PH} 2 Hz) and 2.80 (m, $^{2}J_{HH}$ 1.2 Hz; $^{3}J_{HH}$ 8.6 Hz; J_{PH} 9.5 Hz) in addition to those at δ 3.03 and 4.55 and to aromatic

resonances at δ ~7.05 and ~7.82. (Note that elucidations of J values were greatly facilitated by comparisons of 1D ^{1}H NMR spectra with ^{31}P-decoupled ^{1}H NMR spectra).

On the basis of the above data, it seems certain that **V** contains 1-Ph-allylic and PPh_3 ligands but not a η^5-C_5H_5 ligand and we note that the ^{1}H and ^{31}P NMR data are very similar to those of $Pd_2(\mu\text{-}1\text{-}Ph\text{-}C_3H_4)(\mu\text{-}Cl)(PPh_3)_2$,[13] analogous to anti-**III** structurally but containing a bridging chloride rather than a bridging C_5H_5 group. Therefore we formulate **V** as $Pd_2(\mu\text{-anti-}1\text{-}Ph\text{-}C_3H_4)(\mu\text{-}Br)(PPh_3)_2$, with ^{1}H NMR assignments as in Table 1. It is probable that the *syn*-isomer also forms initially, consistent with weak ^{31}P resonances in the vicinity of those of **V**, but the observed *trans*-species is the more stable isomer, as with **III'a**,**b**.

Table 1. ^{1}H NMR data for allylic H atoms of $Pd_2(\mu\text{-}anti\text{-}1\text{-}Ph\text{-}C_3H_4)(\mu\text{-}Br)(PPh_3)_2$ (**V**).

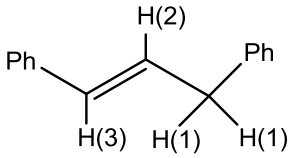
Structure	Site	δ_H	J_{HH} (Hz)
	H geminal to Ph	4.55	$^{3}J_{HH}$ 8.6 Hz; J_{PH} 8.6 Hz
	Center H	3.03	$^{3}J_{HH}$ 8.6 (2×), 12.8 Hz; J_{PH} 4 Hz
	Syn H	2.80	$^{2}J_{HH}$ 1.2 Hz; $^{3}J_{HH}$ 8.6 Hz; J_{PH} 9.5 Hz
	Anti H	2.25	$^{2}J_{HH}$ 1.2 Hz; $^{3}J_{HH}$ 12.8 Hz; J_{PH} 2 Hz

V

These assignments were confirmed by a COSY experiment which demonstrated correlations between the resonance at δ 2.25 and those at δ 2.80 and 3.03, between that at δ 2.80 and those at δ 2.25 and 3.03, between that at δ 3.03 and those at δ 2.25, 2.80 and 4.55 and between those at δ 4.55 and 3.03. In addition, and again consistent with these assignments, a NOESY experiment exhibited correlations between the resonance at δ 2.25 and that at δ 2.80, in addition to a phenyl resonance at δ 6.62, between the resonance at δ 3.03 and that at 4.55 and between the latter and a phenyl resonance at δ 6.62. Allylic ^{13}C NMR data, gleaned from an HSQC experiment, are as follows: C(1): δ 58.6 (J_{CH} 156.6 Hz), C(2): δ 65.5 (J_{CH} 153.9 Hz), C(3): δ 36.7 (J_{CH} 156.6 Hz). These data are all consistent with data for allylic complexes in the literature.[14]

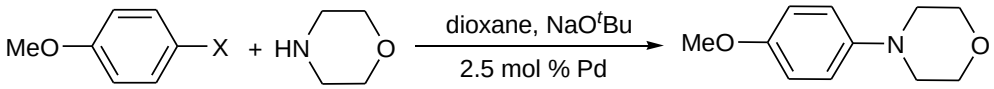
Finally, we attempted to identify any organic product(s) formed during the formation of **IV'** and **V**. As indicated above, all ^{1}H NMR spectra exhibit resonances of the products of reductive elimination, $C_{14}H_{14}$, reported previously by Norton et al.. [6b] However, careful inspection of ^{1}H NMR spectra revealed also the presence of another by-product, expected to be and ultimately identified as *trans*-1,3-diphenylpropene (**VI**). Assignments for this structure are presented in Table 2, and are supported by NOESY spectra. The compound, of the type obtained in Mizoroki-Heck reactions, is presumably a product of reductive elimination from some unidentified intermediates.

Table 2. ^{1}H assignments and proposed structure for the by-product, *trans*-1,3-diphenylpropene (**VI**).

Structure	^{1}H assignments (toluene-d_8)	Lit. ($CDCl_3$, 100 MHz)[15]
	δ H(1): 3.10 ($^{3}J_{HH}$ 7 Hz)	δ H(1): 3.48 ($^{3}J_{HH}$ 5 Hz)
	δ H(2): 6.08 ($^{3}J_{HH}$ 7 Hz, 15.7 Hz)	δ H(2): 6.25 ($^{3}J_{HH}$ 5 Hz,16 Hz)
	δ H(3): 6.30 ($^{3}J_{HH}$ 15.7 Hz)	δ H(3): 6.40 ($^{3}J_{HH}$ 16 Hz)

4.4.1 Catalysis by the I/PPh_3/PhBr System

Experiments to assess the efficacy of the **I**/PPh_3/PhBr combination as a cross-coupling catalyst utilized the conventional C-N coupling reaction of bromoanisole with morpholine in the presence of sodium *tert*-butoxide to give 4-(4-methoxyphenyl)morpholine (eq. 11).[16]



(11)

The reactions were monitored by GC, with conversions amounting only to ~17% after 24 h. While Pd(η^5-C_5H_5)(Ph)(PPh_3) has not previously, to our knowledge, been investigated for any cross-coupling reactions, the compound Pd_2(μ-Br)$_2$(P^tBu_3)$_2$, related to Pd_2(μ-anti-1-Ph-C_3H_4)(μ-Br)(PPh_3)$_2$ (**V**) has been shown to exhibit useful catalytic activity for a variety of cross-coupling reactions including aminations[17] and one might anticipate that **V** would exhibit better activity than it did.

4.5 Summary and Conclusions

Reaction of **I** with deficiencies of PPh_3 initially produced the σ-allylic species $Pd(\eta^5\text{-}C_5H_5)(\eta^1\text{-}Ph\text{-}C_3H_4)(PPh_3)$ (**II'**) and the *syn*- and *anti*-isomers of the dinuclear species $Pd_2L_2(\mu\text{-}C_5H_5)(\mu\text{-}Ph\text{-}C_3H_4)$ (**III'**), which we have shown previously to be intermediates on the path to palladium(0) species.[6b] However, when the reaction is carried out in the presence of excess PhBr, any palladium(0) products formed are trapped and two unanticipated mono-phosphine palladium complexes are obtained, $Pd(Ph)(\eta^5\text{-}C_5H_5)(PPh_3)$ (**IV'**) and $Pd_2(\mu\text{-}anti\text{-}1\text{-}Ph\text{-}C_3H_4)(\mu\text{-}Br)(PPh_3)_2$ (**V**) in addition to an organic compound, *trans*-1,3-diphenylpropene. The anticipated products of oxidative addition, *trans*-$PdBrPh(PPh_3)_2$ and $[PdBrPh(PPh_3)]_2$, were not observed, and thus bromobenzene trapping of palladium(0) compounds of PPh_3 are very different from those observed elsewhere with a variety of phosphine ligands.[7,8]

Palladium compounds **IV'** and **V** were found to be very stable at higher temperatures, and their solutions are poor catalysts for the amination of bromoanisole by morpholine.

4.6 References.

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Chapter 5

Conclusions and Future Work

5.1 Summary and Conclusions

The catalyst systems based on Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5) (**I**) and various phosphines (P^tBu_3, XPhos and Mor-DalPhos and ratio of ligand:Pd = 2:1) were compared with the ones based on other previously common precursors, $Pd_2(dba)_3$ (**II**), $Pd(OAc)_2$ (**III**) and [Pd(η^3-1-Ph-C_3H_4)Cl]$_2$ (**IV**). They were all activated by the addition of the ligands prior to the addition of other reactants and used as catalyst for the representative Buchwald-Hartwig amination reactions of 4-bromo- and 4-chloroanisole with morpholine. Analogous investigations of Suzuki-Miyaura, Heck-Mizoroki and Sonogashira cross-coupling reactions showed that **I** is superior to other precursors; similar results were obtained regarding **II** and **III**. **IV** which was assessed for the first time in our studies, exhibited faster initial rates and comparable conversions for 4-bromoanisole but not 4-chloroanisole. The Xphos-based catalysts were comparable with the P^tBu_3-based systems for cross-coupling of 4-bromoanisole; however they resulted in higher conversions with 4-chloro- than 4-bromoanisole. The Mor-Dalphos catalyst systems involving both **I** and **IV** were inferior for the amination of 4-bromoanisole using this methodology.

We have also investigated catalyst systems involving **I** and **IV** activated by P^tBu_3, Xphos and Mor-Dalphos (ligand:Pd ratio of 1:1) in order to investigate the assumption of 1:1 complexes being the catalytically active species. In general the 1:1 catalyst systems were found to be less active. In order to

intercept catalytically active (possibly 1:1) palladium(0) species, we have also carried out a series of experiments in which the activation of **I** with the ligands was done in the presence of 4-bromo- or 4-chloroanisole. The conversions for both 4-bromo- or 4-chloroanisole were significantly higher utilizing **I**/P^{t}Bu$_3$; near quantitative conversion was observed for 4-bromoanisole within 30 min, with excellent mass balance. Thus the activity of this catalyst system is superior to all others discussed in this thesis.

Our current results suggest that amination reactions involving the use of P^{t}Bu$_3$, XPhos and Mor-Dalphos are much more complicated than the previously cross-coupling reactions reported in previous papers by the Baird group and that utilization of **I** for the synthesis of palladium(0) complexes can be more complicated than previously thought.

We have investigated the reactions of **I** with Xphos and Mor-Dalphos (1:1, 2:1 molar ratios) in toluene at 75 ºC. The appearance of reductive elimination product, $C_{14}H_{14}$, was observed by ^{1}H NMR spectroscopy which showed that all thermally stable **I** had reacted. However, only palladium metal and the free ligand and low concentrations of other phosphorus-containing products were observed which presumably account for the catalysis previously observed. It was clearly demonstrated that none of these two ligands can generate stable Pd(0)L$_n$ (n = 1 or 2) complexes at moderate tempertatures. While similar experiments with P^{t}Bu$_3$ resulted in only the formation of Pd[P^{t}Bu$_3$]$_2$ even utilizing 1:1 molar ratio.

The formation of the catalytically active species from the reaction of **IV** with

P^tBu_3 (P^tBu_3:Pd 2:1) and NaO^tBu and morpholine has been also investigated. Addition of NaO^tBu at room temperature to the mixture of **IV** and P^tBu_3 resulted in a small amount of Pd(η^3-1-Ph-C_3H_4)Cl(P^tBu_3) and more Pd[P^tBu_3]$_2$ formed quickly. Addition of morpholine to the solution and warming to 75 ºC, resulted in the disappearance of the resonance of Pd(η^3-1-Ph-C_3H_4)Cl(P^tBu_3) and Pd[P^tBu_3]$_2$ was the major product. *N*-cinnamylmorpholine and cinnamyl-*tert*-butyl ether peaks were also observed in ^{1}H NMR in a ratio of ~4:3. It confirmed that the palladium(0) was formed via either direct attack at the η^3-1-Ph-C_3H_4 ligand by alkoxide or amide anions or reductive elimination of η^1-1-Ph-C_3H_4 alkoxide or amide ligands.

To extend our studies, the reaction of **I** with PPh_3 in the presence of excess PhBr was also studied. The formation of two palladium complexes, Pd(Ph)(η^5-C_5H_5)(PPh_3) and Pd_2(μ-*anti*-1-Ph-C_3H_4)(μ-Br)(PPh_3)$_2$ as well as the organic compound, *trans*-1,3-diphenylpropene, were confirmed by 1D and 2D NMR spectroscopy. The catalytic properties of the solutions of these thermally stable palladium compounds were assessed for the amination of 4-bromoanisolce by morpholine and it was found that they are poor catalysts for the representative reaction.

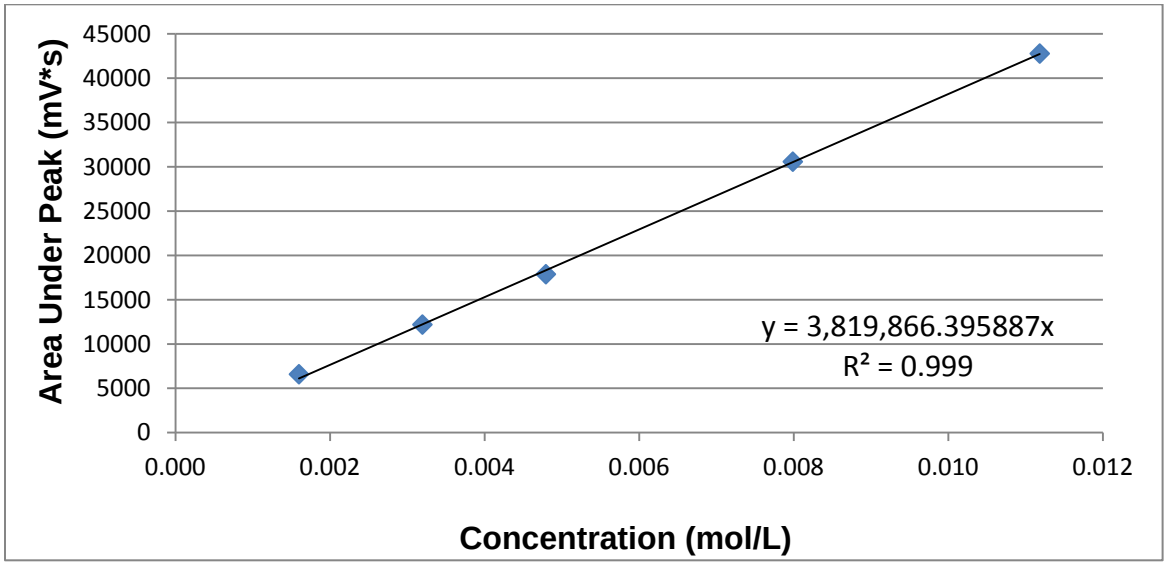
5.2 Future Work

Considering that the number of the phosphine structures used as ligands for cross-coupling reactions increases everyday, investigation of the formation of catalytically active species using other phosphines and Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5) by ^{31}P NMR and ^{1}H NMR would be useful. Moreover, as it is discussed in this thesis, the intermediates formed from oxidative addition might be the active species; Hence, it would be also practical to investigate the formation of these species in the presence of excess aryl halides as well, at different temperatures (rt, 50˚C and 75 ˚C). Additionally, although studying the solution chemistry is helpful concerning the homogeneous catalysis, obtaining the crystals of the newly formed intermediates would be more interesting and useful for the future references.

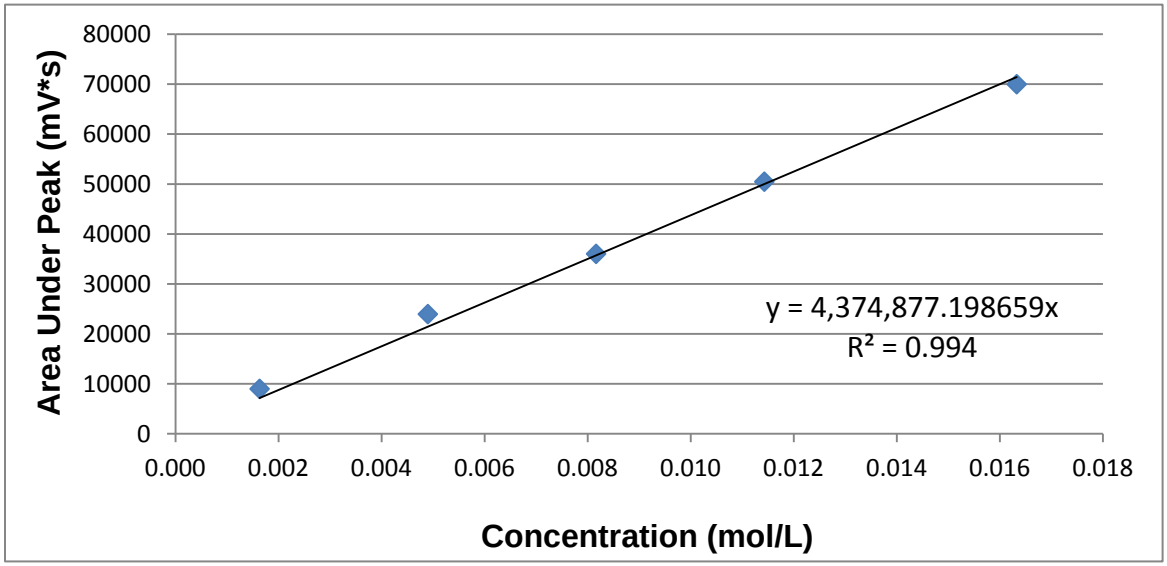
Ultimately, the goal is to generate the catalytically active species; therefore, assessing the efficiency of the above-mentioned formed species for various cross-coupling reactions such as Buchwald-Hartwig, Suzuki-Miyaura and etc would be essential.

Appendix A

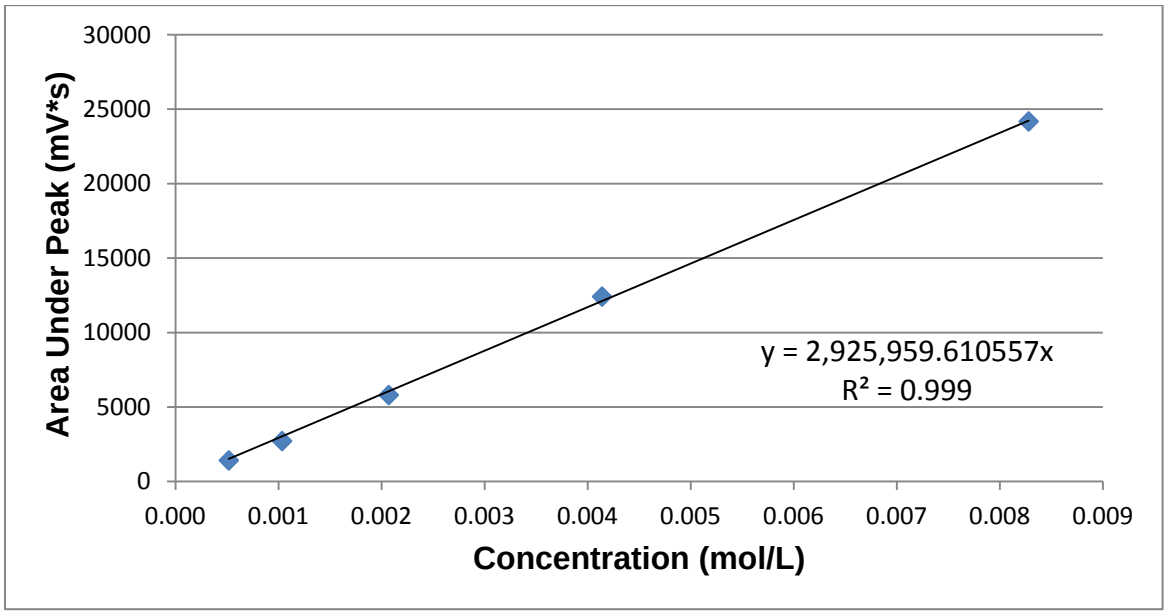
GC Calibration Curves



A. 1. Calibration curve for 4-bromoanisole.



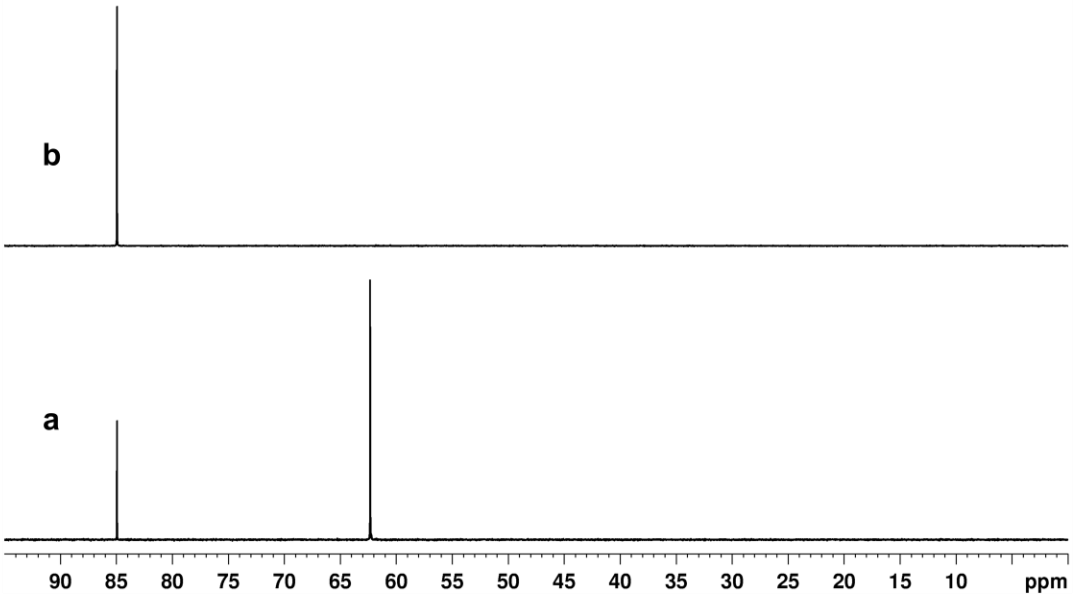
A. 2. Calibration curve for 4-chloroanisole.



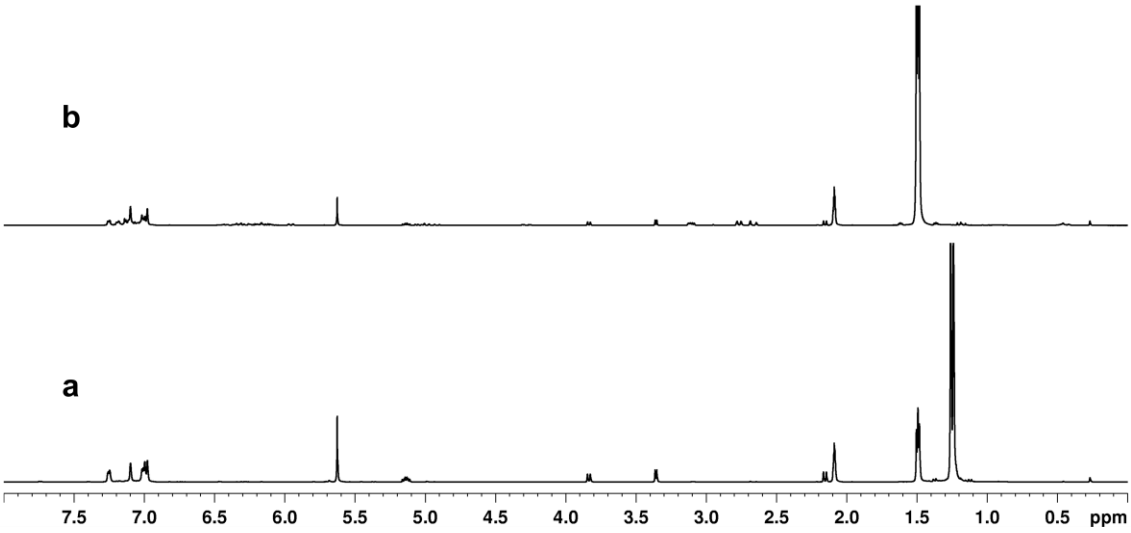
A. 3. Calibration curve for *N*-(4-methoxyphenyl)morpholine.

Appendix B

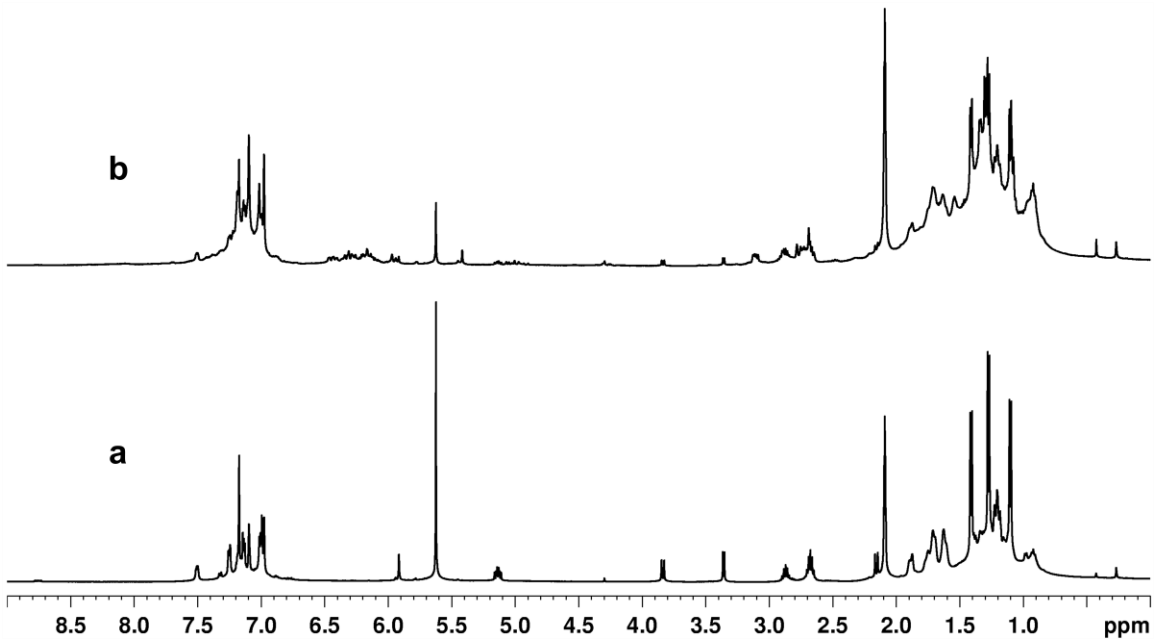
NMR Spectra



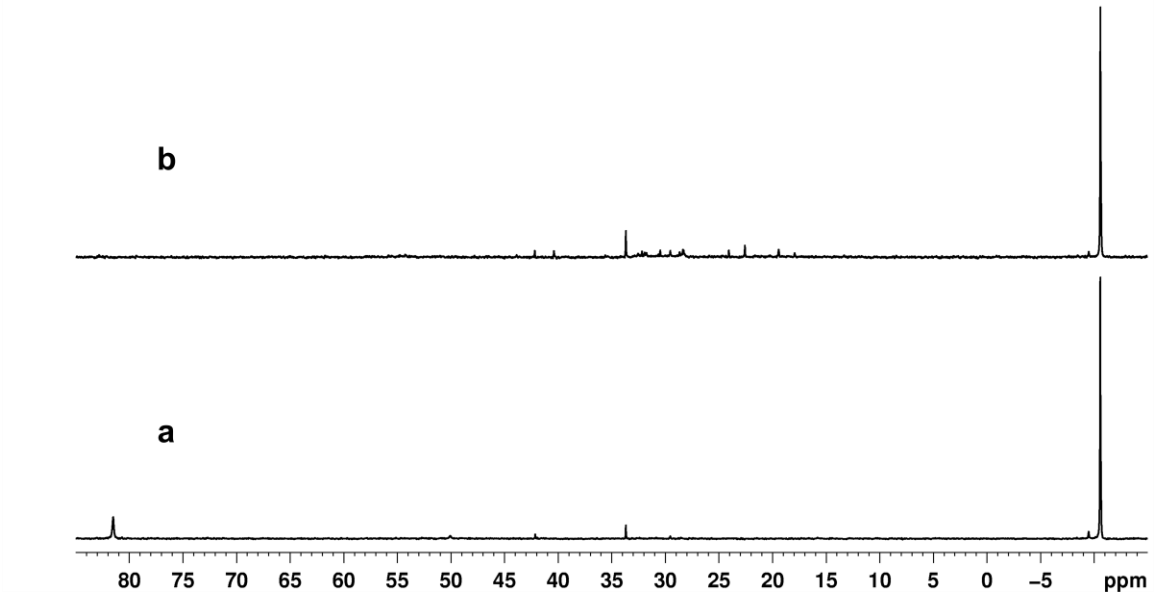
B. 1. ^{31}P NMR spectra showing the progress of the reaction of **I** with P^tBu_3 (P:Pd ratio 1:1) in toluene-d_8 (a) at room temperature immediately after mixing, (b) after 1 h at 75 ºC.



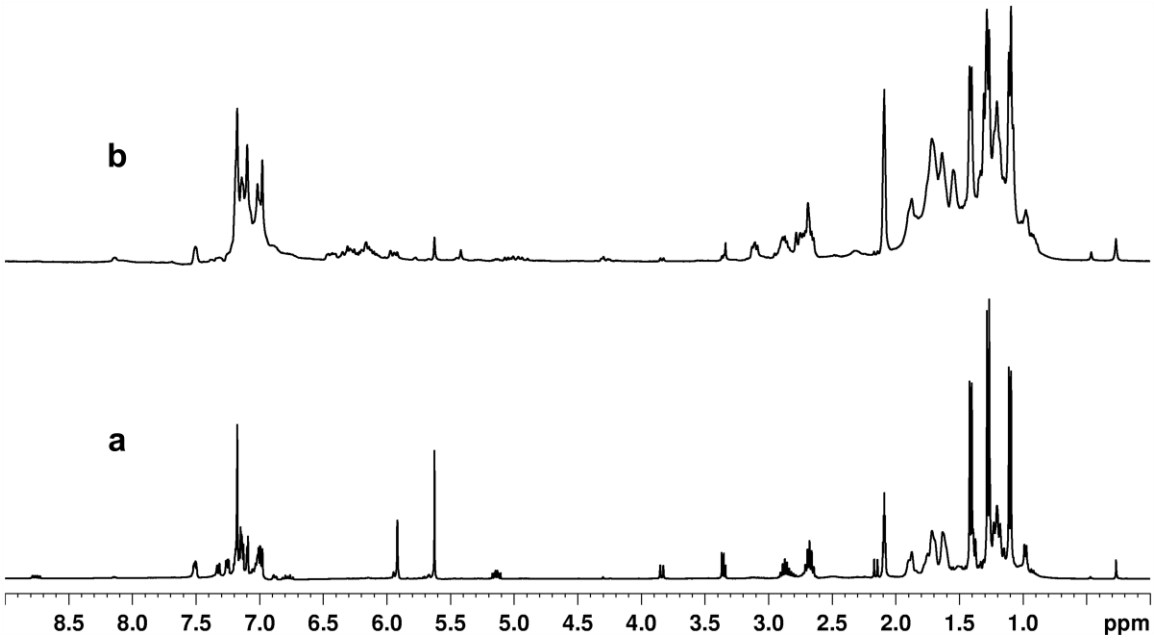
B. 2. ^{1}H NMR spectra showing the progress of the reaction of **I** with P^tBu_3 (P:Pd ratio 1:1) in toluene-d_8 (a) at room temperature immediately after mixing, (b) after 1 h at 75 ºC.



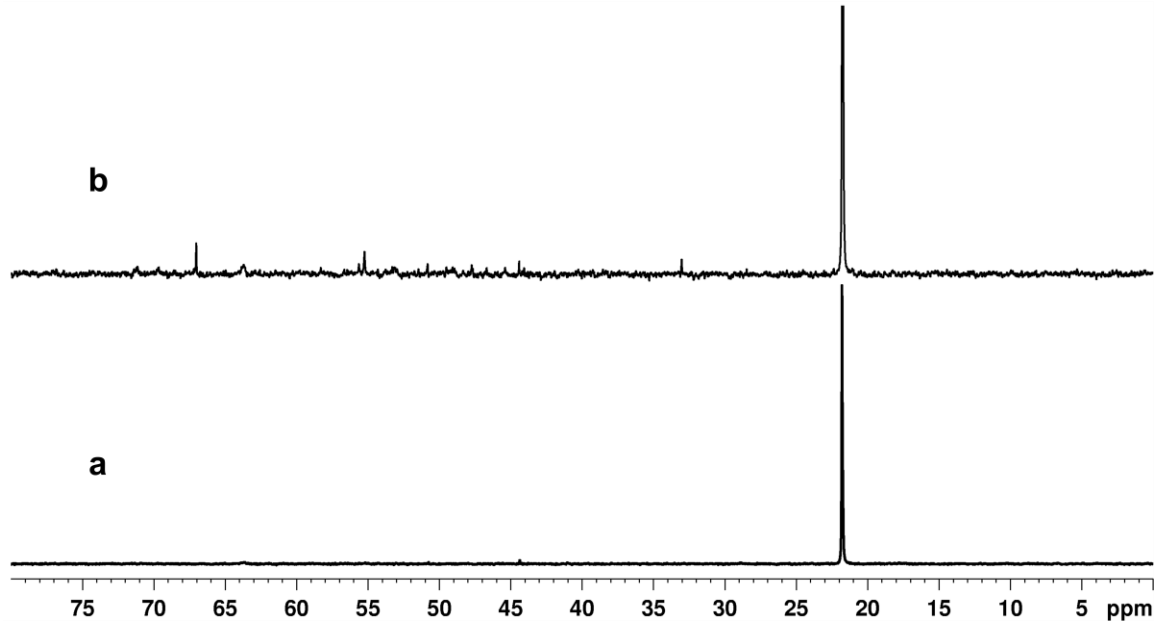
B. 3. ^{1}H NMR spectra showing the progress of the reaction of **I** with XPhos (P:Pd ratio 1:1) in toluene-d_8 (a) at room temperature immediately after mixing, (b) after 1 h at 75 ºC.



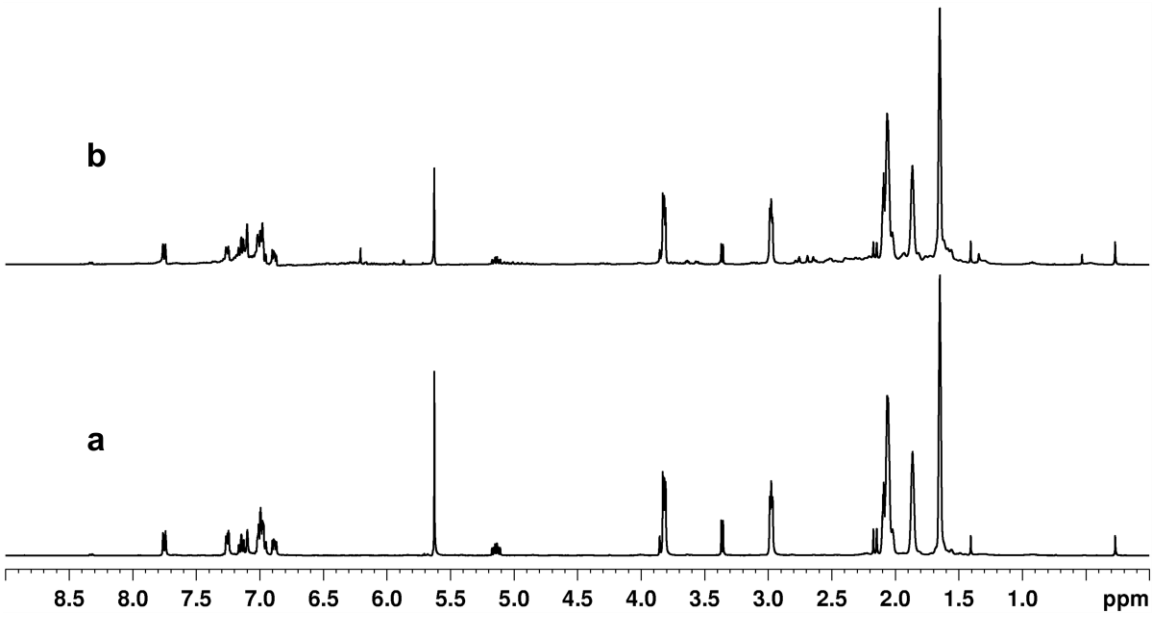
B. 4. ^{31}P NMR spectra showing the progress of the reaction of **I** with XPhos (P:Pd ratio 2:1) in toluene-d_8 (a) at room temperature immediately after mixing, (b) after 1 h at 75 ºC.



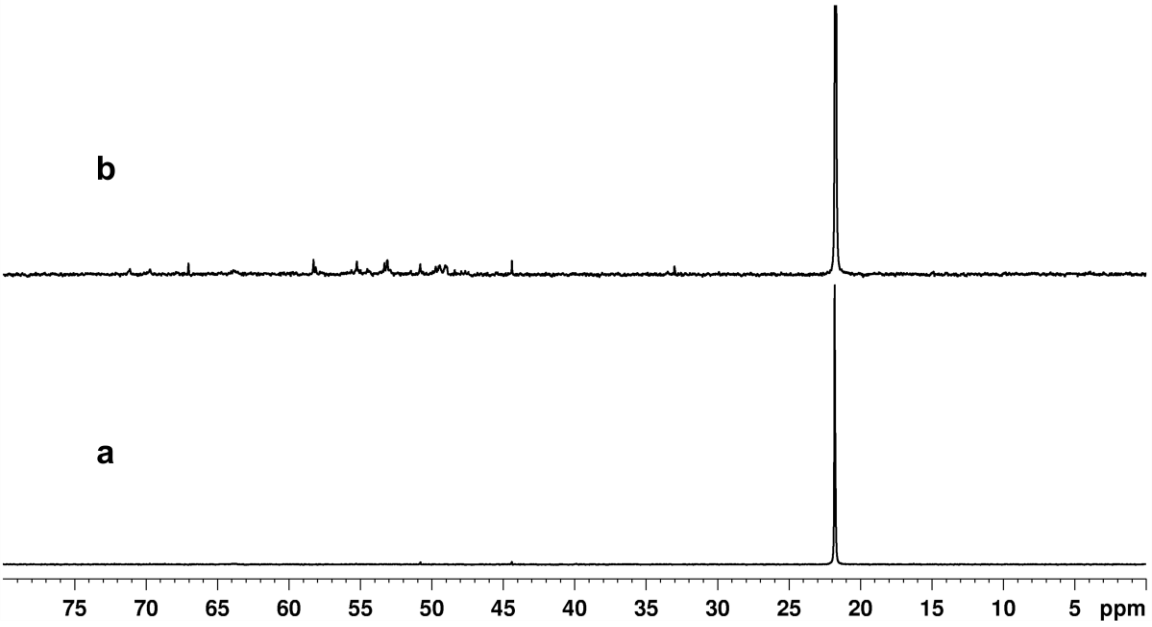
B. 5. ^{1}H NMR spectra showing the progress of the reaction of **I** with XPhos (P:Pd ratio 2:1) in toluene-d_8 (a) at room temperature immediately after mixing, (b) after 1 h at 75 ºC.



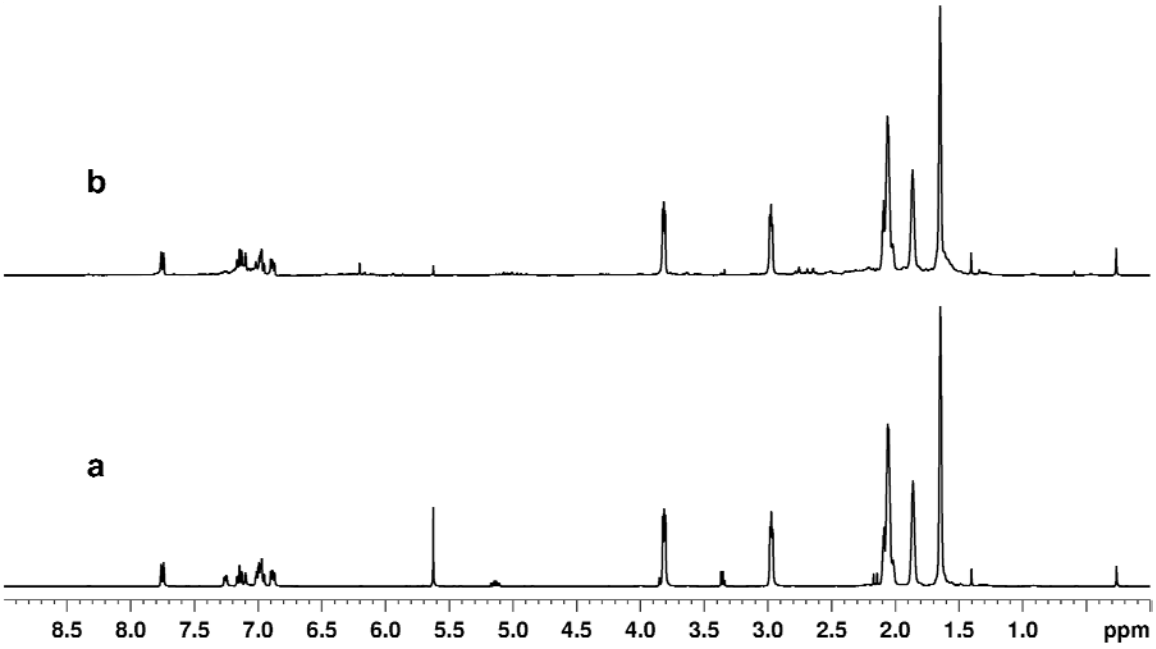
B. 6. ^{31}P NMR spectra showing the progress of the reaction of **I** with Mor-DalPhos (P:Pd ratio 1:1) in toluene-d_8 (a) at room temperature immediately after mixing, (b) after 3 h at 75 ºC.



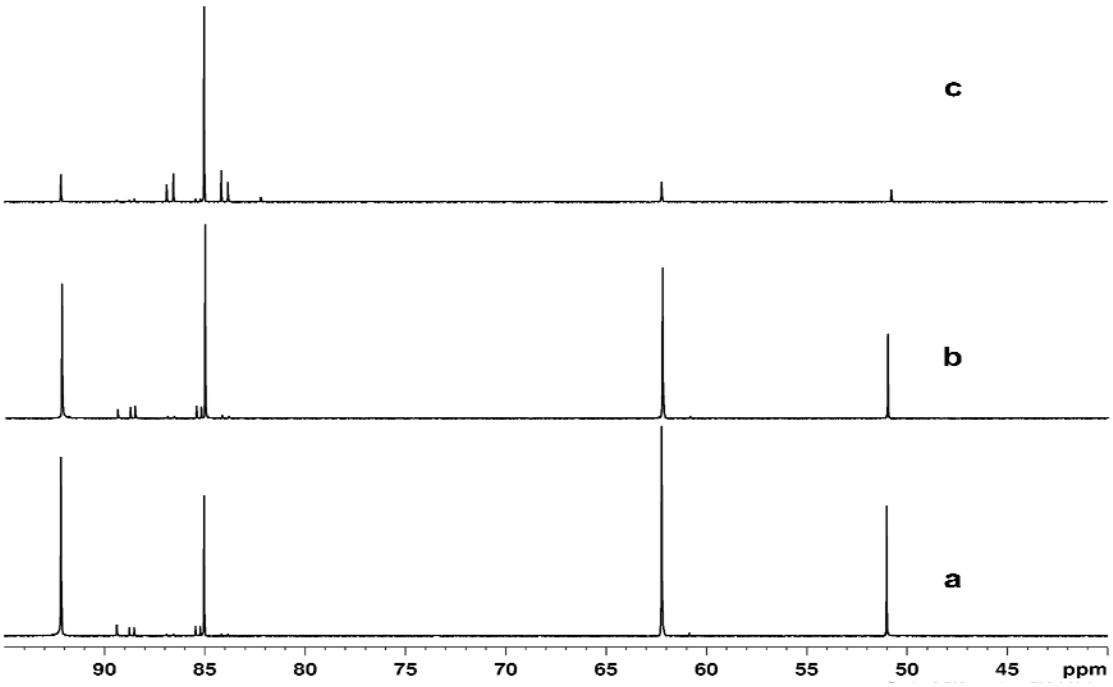
B. 7. ^{1}H NMR spectra showing the progress of the reaction of **I** with Mor-DalPhos (P:Pd ratio 1:1) in toluene-d_8 (a) at room temperature immediately after mixing, (b) after 3 h at 75 ºC.



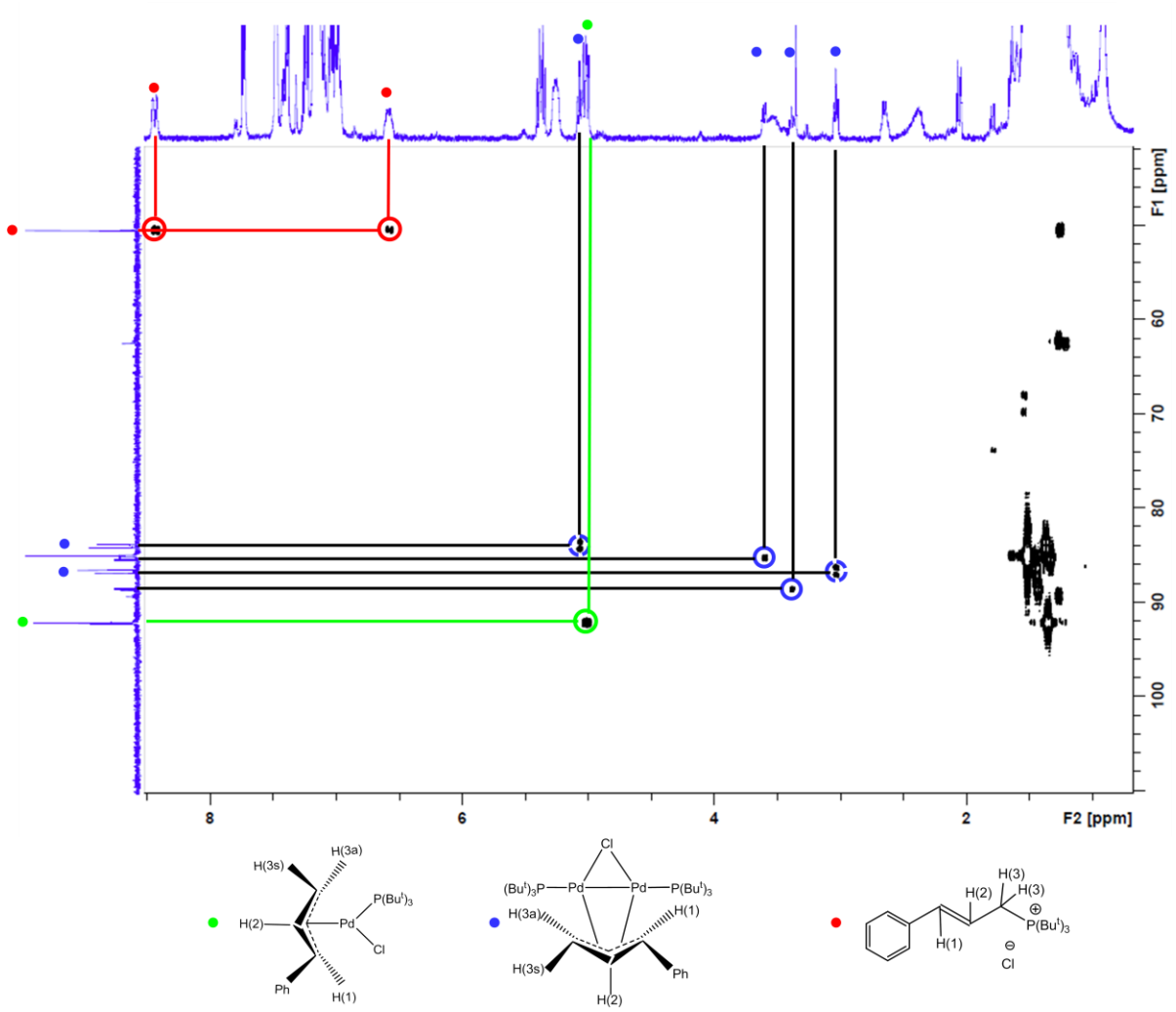
B. 8. ^{31}P NMR spectra showing the progress of the reaction of **I** with Mor-DalPhos (P:Pd ratio 2:1) in toluene-d_8 (a) at room temperature immediately after mixing, (b) after 3 h at 75 ºC.



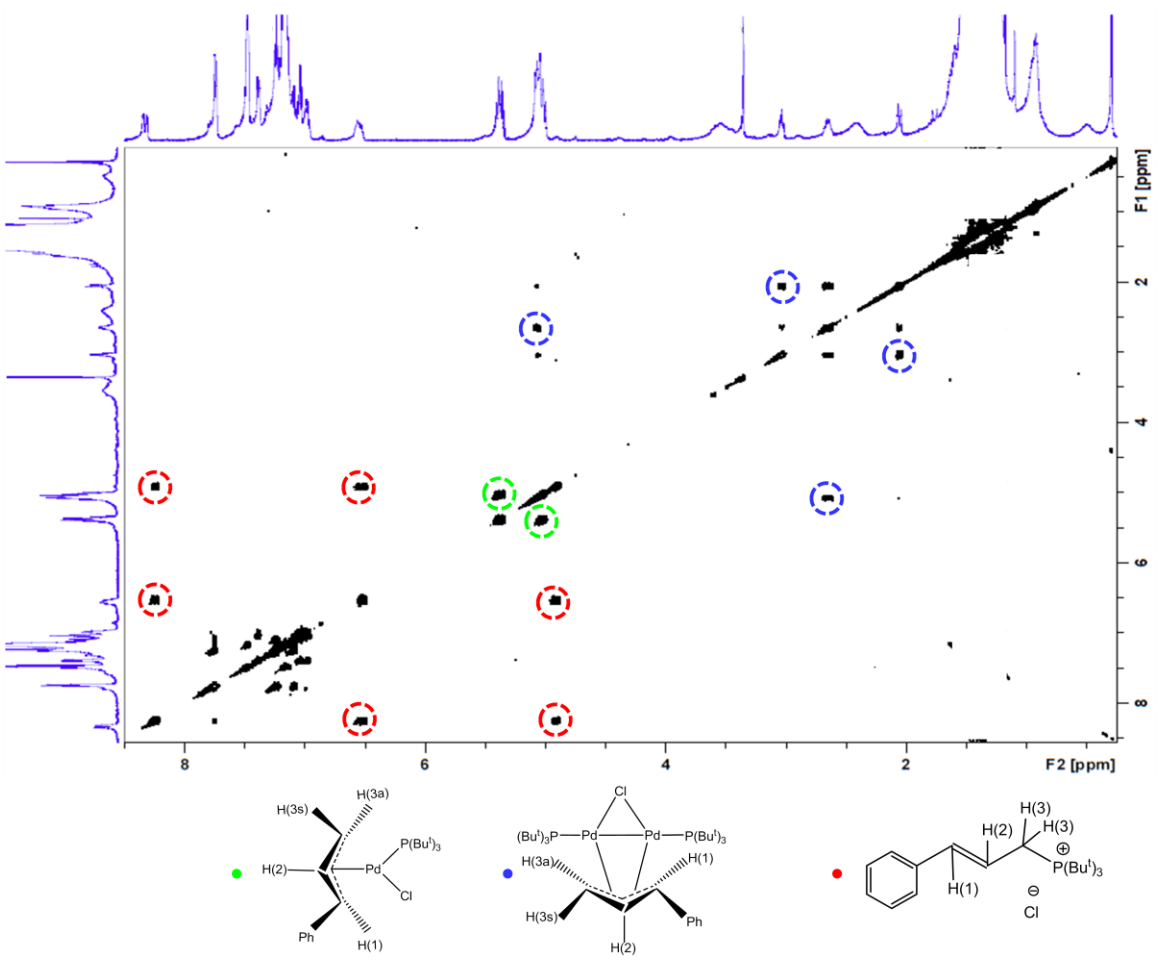
B. 9. ^{1}H NMR spectra showing the progress of the reaction of **I** with Mor-DalPhos (P:Pd ratio 2:1) in toluene-d_8 (a) at room temperature immediately after mixing, (b) after 3 h at 75 ºC.



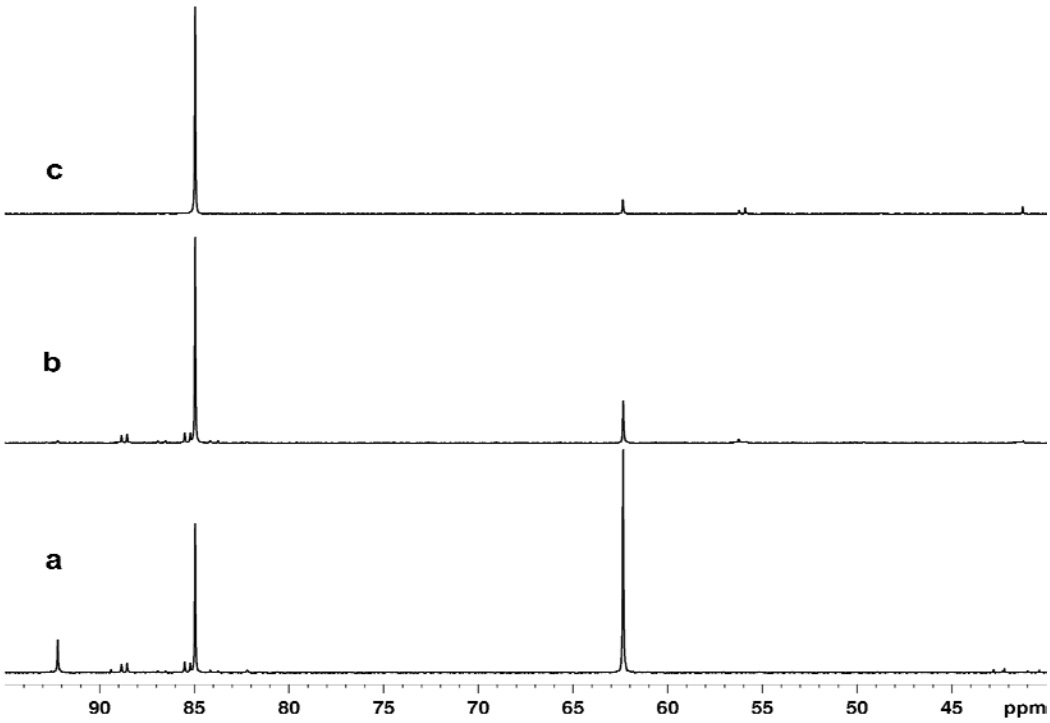
B. 10. ^{31}P NMR spectra showing the progress of the reaction of **IV** with P^tBu_3 (P:Pd ratio 2:1) in C_6D_6 (a) at room temperature immediately after mixing, (b) after 20 min at 75 ºC, and (c) after 1 h at 75 ºC.



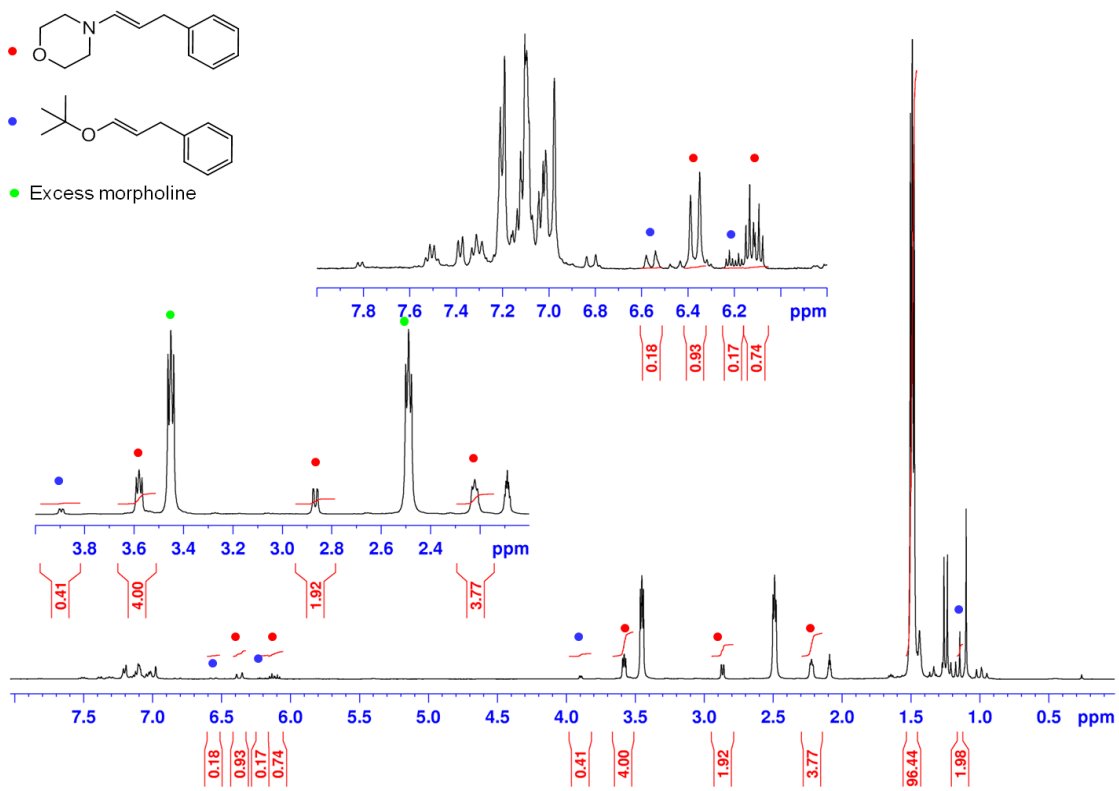
B. 11. ^{1}H-^{31}P HMBC spectrum of the reaction of **IV** with P^{t}Bu$_3$ (P:Pd ratio 2:1) in C_6D_6 after 10 min at 75 ºC.



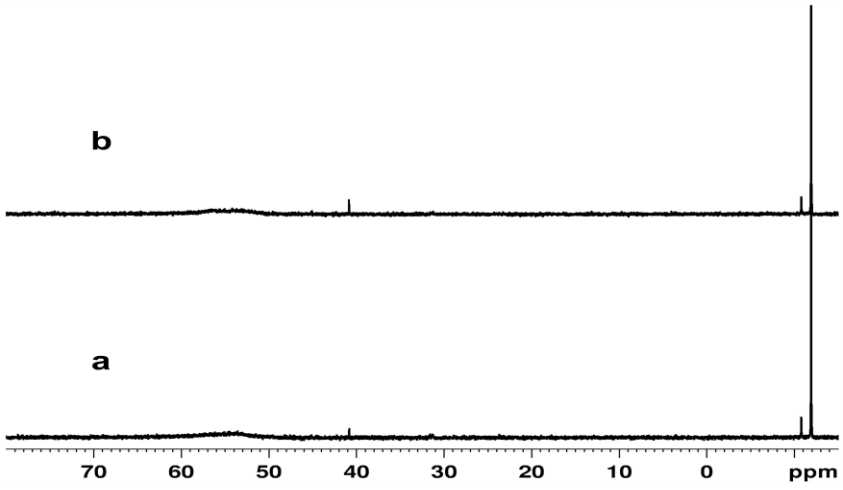
B. 12. COSY spectrum of the reaction of **IV** with P^{t}Bu$_3$ (P:Pd ratio 2:1) in C_6D_6 after 20 min at 75 ºC.



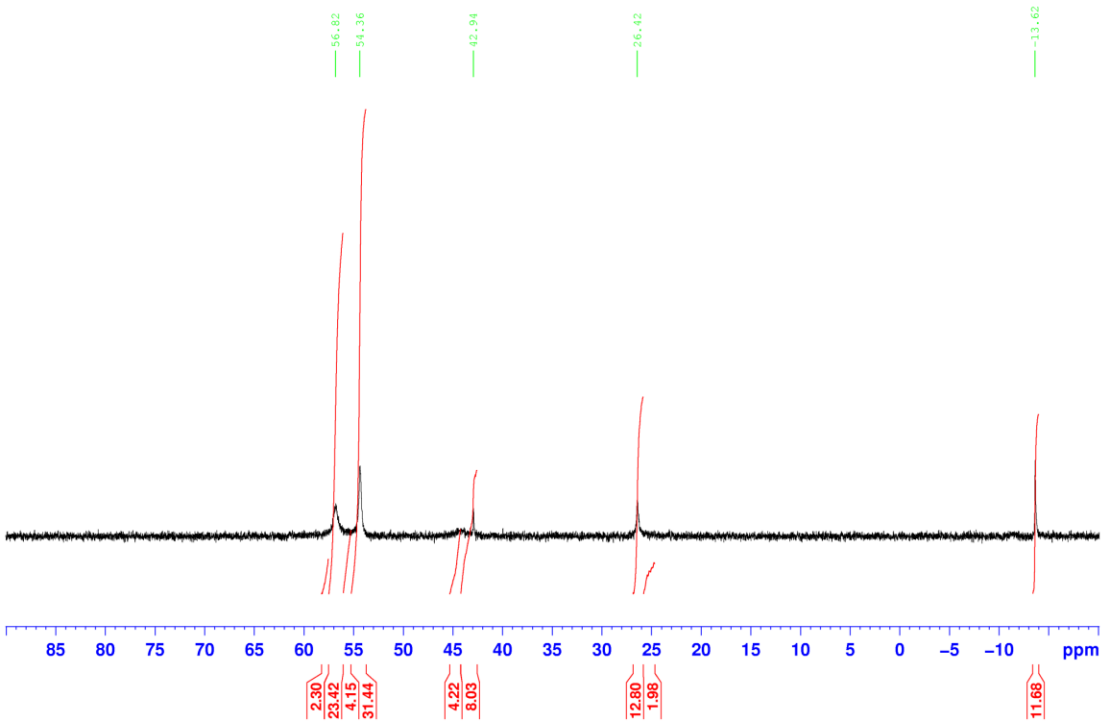
B. 13. ^{31}P NMR spectra showing the progress of the reaction of **IV** with P^tBu_3 (P:Pd ratio 2:1) and 4 equivalents of morpholine and 4 equivalents of NaO^tBu in toluene-d_8 (a) at room temperature immediately after addition of NaO^tBu, (b) at room temperature immediately after addition of NaO^tBu and morpholine, and (c) after 30 min at 75 ºC after addition of NaO^tBu and morpholine.



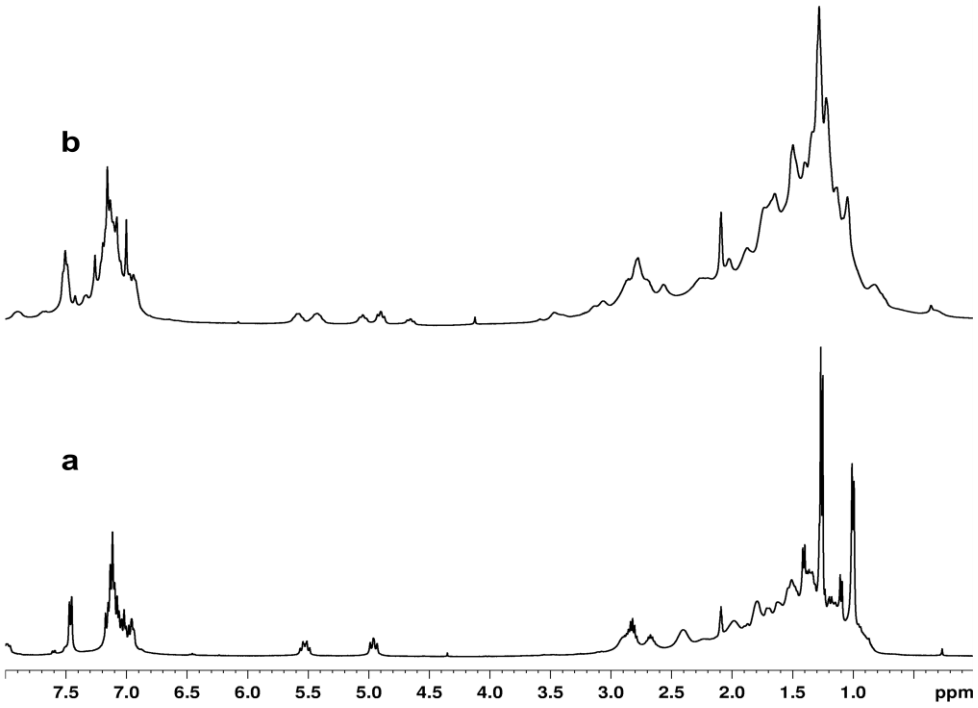
B. 14. ^{1}H NMR spectra showing the progress of the reaction of **IV** with P^{t}Bu$_3$ (P:Pd ratio 2:1) in toluene-d$_8$ in the presence of 4 equivalents of morpholine and 4 equivalents of NaO^{t}Bu, after 30 min at 75 ºC.



B. 15. ^{31}P NMR spectra showing the progress of the reaction of **IV** with XPhos (P:Pd ratio 2:1) in toluene-d$_8$ (a) at room temperature immediately after mixing, (b) after 30 min at 75 ºC.



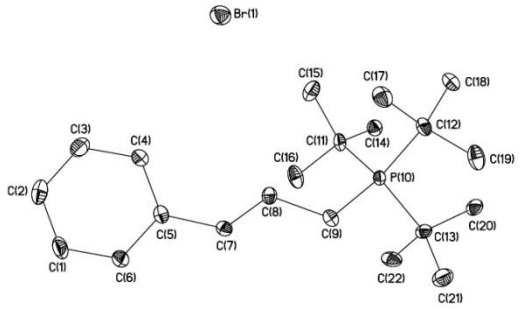
B. 16. ^{31}P NMR spectrum at -70 °C of the reaction of **IV** with XPhos (P:Pd ratio 2:1) in toluene-d_8 after 30 min at 75 ºC.



B. 17. ^{1}H NMR spectra of the reaction of **IV** with XPhos (P:Pd ratio 2:1) in toluene-d_8 after 30 min at 75 ºC (a) at room temperature (b) at -70 °C.

Appendix C

X-ray Crystallographic Data for (1-Ph-C_3H_4)(P^tBu_3)Br



A. Crystal Data

Empirical formula	$C_{21}H_{36}Br_1P_1$
Formula weight	399.38
Crystal Color, Habit	colourless, needle-like
Crystal dimensions (mm)	0.207 × 0.160 × 0.095
Crystal system	monoclinic
Space group	$P2_1/c$
Unit cell parameters	
a (Å)	17.3428(4)
b (Å)	13.9527(3)
c (Å)	17.6509(4)
α (°)	90
β (°)	97.9455(16)
γ (°)	90
V (Å^3)	4230.14(17)
Z	8
F(000)	1696
Density (ρ_{calcd})	1.254 Mg/m^3
Absorption coefficient (μ)	2.019 mm^{-1}

B. Data Collection and Refinement Conditions

Diffractometer	Bruker-AXS Smart Apex II diffractometer
Radiation	monochromated Mo K_α
Wavelength (Mo K_α)	0.71073 Å
Temperature	-93(2) °C [180(2) K]
Scan type	ω-and φ-scans (0.5º/frame, 15 s exposure/frame, 5 sets)
Theta range for data collection	1.880 to 26.337°
Completeness to theta = 25.242°	99.9%
Reflections collected	34283
Index ranges	$-12 \leq h \leq 12$, $-16 \leq k \leq 16$, $-16 \leq l \leq 16$
Independent reflections [$F_o^2 \geq -3\sigma(F_o^2)$]	8583 [R_{int} = 0.0616]
Observed reflections [$F_o^2 > 2\sigma(F_o^2)$]	5499
Absorption correction method	multi-scan [SADABS]
Anomalous Dispersion	For all non-hydrogen atoms
Structure solution method	Direct methods (SIR-2004)
Refinement method	Full-matrix least-squares on F^2 (SHELXL-2013)
Function Minimized	$\Sigma w(\|F_o\|^2 - \|kF_c\|^2)^2$ (k: overall scale factor)
Weighing scheme, w	$w = [\sigma(F_o^2) + (0.0365\ P)^2 + (1.5560\ P)]^{-1}$

$w = [\sigma(F_o^2) + (a\ P)^2 + (b\ P)]^{-1}$

P-factor	$[\mathrm{Max}(F_o^2,0) + 2\ F_c^2]/3$
Data / restraints / parameters	8583 [$F_o^2 \geq -3\sigma(F_o^2)$] / 0 / 433
Reflection (observed)/parameter ratio	13:1
Reflection (data)/parameter ratio	20:1
Goodness-of-fit on F^2	1.013

$GooF = \{\Sigma[w(F_o^2-F_c^2)^2]/(n - p)\}^{1/2}$

n: number of reflections, *p*: number of parameters

Final *R* indices

$R_1 = [\Sigma\|\|F_o\|-\|F_c\|\|]/[\Sigma\|F_o\|]$ for [$F_o^2 > 2\sigma(F_o^2)$]	0.0464
$wR_2 = \{[\Sigma w(F_o^2-F_c^2)^2]/[\Sigma w(F_o^2)^2]\}^{1/2}$ [all data]	0.1026
Max. Shift/Error in Final Cycle	0.001
Largest difference peak and hole	0.407 and -0.481 $e^-/Å^3$
Transmission factor (min)	0.5163 [SADABS]
Transmission factor (max)	0.6737 [SADABS]