INVESTIGATIONS OF A NEW AND IMPROVED PRECATAYLST FOR PALLADIUM CATALYZED CROSS COUPLING REACTIONS

by

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Abstract

Little attention has been given to the formation of the putative PdL_2 species required for Pd-catalyzed cross-coupling reactions. Active species are generally difficult to store due to air-sensitivity and are therefore formed *in situ* at unknown rates and in unknown yields via a variety of palladium precatalysts. Commonly employed Pd(0) and Pd(II) precatalysts are often relatively ineffective because they generate only low concentrations of the bis(phosphine) species PdL_2 under most reaction conditions. This thesis describes the use of the easily synthesized and easily handled $Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)(\eta^5\text{-}C_5H_5)$ (**I**) as a superior precursor than any other documented system for the *in situ* formation of PdL_2. Rapid and quantitative formation of active catalyst solutions allow us to demonstrate that **I** is also the best precatalyst known for PdL_2-catalyzed cross-coupling reactions. We discuss the Suzuki-Miyaura reaction of 4-bromoanisole with phenylboronic acid and demonstrate that, under mild reaction conditions, higher initial rates and higher conversions with **I** can be obtained compared with other common precatalysts ($Pd(OAc)_2$, $Pd(PPh_3)_4$, Pd_2dba_3, etc.) containing a variety of phosphine ligands. This methodology has also been extended to other cross-coupling reactions, as we demonstrate that higher initial rates and higher conversions with **I** can be obtained for a variety of Mizoroki-Heck arylations and Buchwald-Hartwig aminations.

Acknowledgements

When I start to reflect on my time at Queen's, I am reminded of all of the people that helped me in countless ways reach this milestone. Although I can't thank every single one of them, I'd like to give a stick-tap to the most important ones.

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To my family, it goes without saying that I would not be where I am without your constant love and support. I hope I've made you proud because it ain't easy being the middle child.

To the whole Baird Lab, past and present, thanks for making this a great ride. You know who you are. I still expect timely return of all the stolen NMR tubes.

To everyone else who I have crossed paths with during my time in Kingston, for better or for worse: Kevin, Jay, Bivian, Phil, Brando, Kyle, Derek, Dave, Jason, Leroy, and everyone else who bruntingly forgot to use the stairs.

And finally, I suppose I have to thank the Montreal Canadiens for rarely making it far in the playoffs so I could concentrate on my research.

Statement of originality

I hereby certify that all of the work described within this thesis is the original work of the author. Any published (or unpublished) ideas and/or techniques from the work of others are fully acknowledged in accordance with the standard referencing practices.

Andrew William Fraser

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List of Symbols and Abbreviations

acac	acetylacetonato
Allyl	propenyl
Ar	aryl group
Å	Ångström
br.	broad
^{n}Bu	n-butyl
^{t}Bu	tert-butyl
° C	degrees Celsius
Cp	cyclopentadienyl (η^5-C_5H_5)
Cy	cyclohexyl
^{13}C NMR	carbon NMR
δ	chemical shift in ppm
d	doublet
dba	dibenzylideneacetone
DFT	density functional theory
DMF	dimethylformamide
dppb	1,1’-bis(diphenylphosphino)butane
dppe	1,1’-bis(diphenylphosphino)ethane
dppf	1,1’-bis(diphenylphosphino)ferrocene

dppm	1,1’-bis(diphenylphosphino)methane
Et	ethyl
GC	gas chromatography
g	grams
η	hapticity
h	hour
ΔH	enthalpy change
$\Delta H^{\ddagger}$	enthalpy of activation
^{1}H NMR	proton NMR
Hz	hertz
J	coupling constant
L	litres
m	multiplet
m	meta
M	moles/litre
Me	methyl
MeOH	methanol
mg	milligrams
MHz	megahertz
min	minute
mL	mililitres

mol	moles
mmol	milimoles
µL	microlitres
NMR	nuclear magnetic resonance
o	ortho
OAc	acetate
OTf	triflate
p	para
Ph	phenyl
^{31}P NMR	phosphorus NMR
ppm	parts per million
^{i}Pr	isopropyl
R	alkyl group
s	singlet
ΔS	entropy change
$\Delta S^{\ddagger}$	entropy of activation
t	triplet
THF	Tetrahydrofuran
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

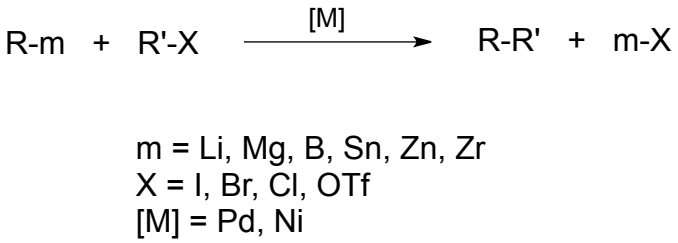
Chapter 1

Introduction

1.1 The Cross-Coupling Reaction

It is generally accepted that the landscape of organic synthesis has been transformed by the development of transition metal-catalyzed cross-coupling reactions. This broad category of transformations has opened the doors for the synthesis of many complex organic molecules that were once either very difficult or inaccessible by previous synthetic means. Consequently, the field of catalytic cross-coupling has expanded at an astounding rate, which has been detailed in many reviews and books.[1-10] The importance of these transformations with respect to chemical synthesis was recognized with the awarding of the 2010 Nobel Prize in Chemistry to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki "for palladium-catalyzed cross couplings in organic synthesis".

The breadth of cross-coupling reactions has evolved significantly over the past several decades, and can in general be described as the coupling between an organometallic nucleophile (R-m) and an organic electrophile (R-X) in the presence of a transition metal catalyst (M). This process can be visualized as an assisted exchange (Scheme 1).[1-10]



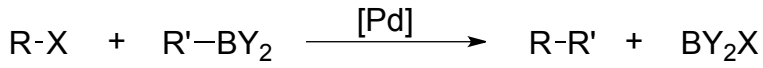
Scheme 1 - General scheme for catalytic cross-coupling reactions.

By varying the organometallic reagent (R-m), a wide variety of reactions are available to choose from, each having their own set of conditions and limitations. Perhaps the most widely employed reaction is the Suzuki-Miyaura reaction, in which an organoboron nucleophile (m = B) is coupled to an accompanying organic electrophile.[1,3,4,11]

1.2 Suzuki-Miyaura Reaction

The Suzuki-Miyaura reaction has established itself as possibly the most important palladium-catalyzed cross-coupling reaction in organic synthesis.[1,3,4,11] While it had been reported as early as 1975 by Negishi that organoboronic acids can undergo cross-coupling when stoichiometric amounts of palladium are employed,[12] Akira Suzuki and Norio Miyaura demonstrated in 1979 that palladium only need be present in catalytic amounts for the reaction to proceed.[13] The methodology involves the coupling of an organic electrophile and organoboron nucleophile in the presence of a palladium catalyst (Scheme 2). A

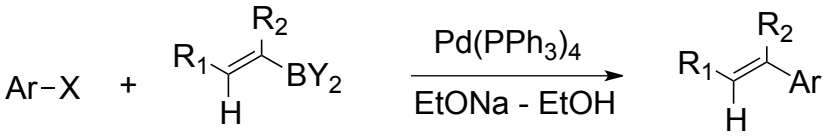
wide variety of organoboron compounds are commercially available and/or easily synthesized,[14] and for the most part are environmentally benign and non-toxic, in contrast to to earlier coupling partners containing tin, lithium, etc.



R = aryl, vinyl, benzyl
R' = alkyl, aryl, vinyl
X = I, Br, Cl, OTf
Y = OH, OR

Scheme 2. General Suzuki-Miyaura cross-coupling reaction.

In most cases, an aryl halide, ArX, is coupled catalytically to an organoborate $[ArBY_2Y']^-$, generated in situ from a neutral organoboronic acid or ester. Miyaura and Suzuki first described the coupling of aryl halides with alk-1-enylboranes with $Pd(PPh_3)_4$ in the presence of sodium ethoxide (Scheme 3).[13]



Scheme 3. Suzuki-Miyaura coupling of aryl halides and alk-1-enylboranes.[13]

The reaction has been extended considerably to a point where a wide variety of organic electrophiles and boronates can now be coupled, and a considerable number of reviews and books have been devoted to this subject.[1,4,14,15] Because

this body of this work is devoted more to the mechanistic features of the reaction, the synthetic utility will not be discussed in much detail here.

1.2.1 Mechanism of the Suzuki-Miyaura Reaction

The mechanism of the Suzuki-Miyaura reaction has been explored both experimentally[16-18] and theoretically,[19-24] and its features are similar to other palladium-catalyzed cross-couplings. The most widely accepted catalytic cycle (Figure 1) involves oxidative addition of an aryl halide to a bisphosphinepalladium(0) complex, PdL_2, to form a square-planar Pd(II) complex, transmetallation with an organoborate species, and finally reductive elimination of the organic substrates with regeneration of the active PdL_2 catalyst.[16-18]

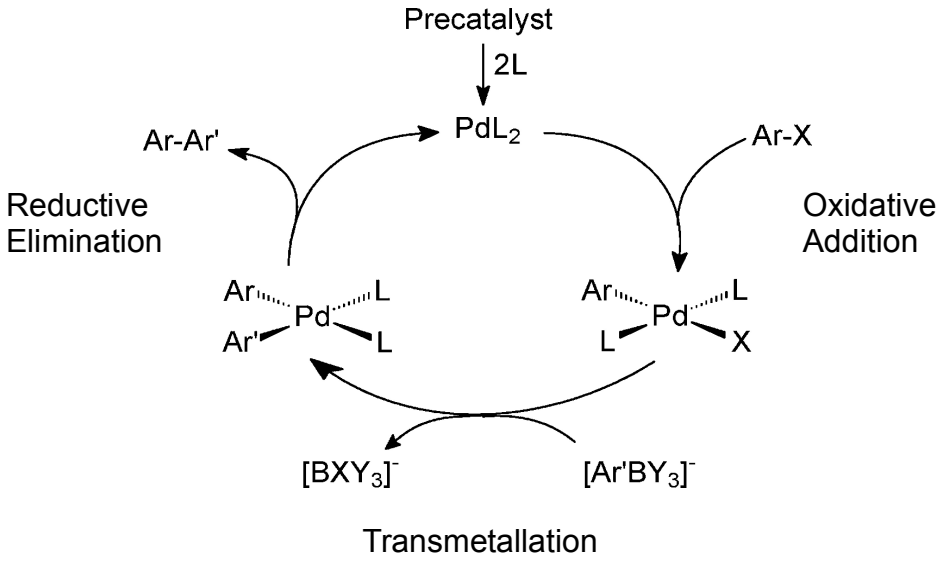
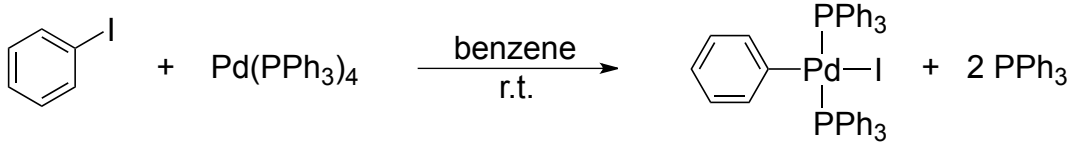


Figure 1. Generally accepted catalytic cycle of the Suzuki-Miyaura reaction.

The organoborate species required for transmetallation $[Ar'BY_3]^-$ is generally generated *in situ* from an analogous organoboronic acid or ester ($ArBY_2$, Y = OH or OR) to allow the organic constituent to be sufficiently anionic to transfer to Pd.[4]

1.2.2 Oxidative Addition

Some of the earliest work that describes the oxidative addition of aryl halides to Pd(0) compounds dates back to 1971, where Fitton and Rick describe the addition of aryl halides to $Pd(PPh_3)_4$.[25] They found that oxidative addition of PhI to $Pd(PPh_3)_4$ takes places readily at room temperature to form $PdIPh(PPh_3)_2$ (Scheme 4).

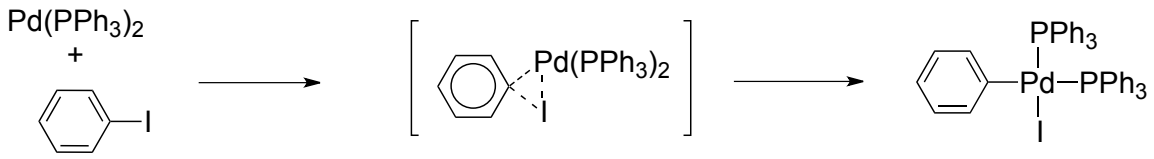


Scheme 4. Oxidative addition of PhI to $Pd(PPh_3)_4$.[25]

PhBr can also undergo oxidative addition at 80 °C, but both PhCl and PhF were found to be unreactive at temperatures up to 135 °C. This established the trend of reactivity such that PhI > PhBr > PhCl and PhF. Chlorobenzenes substituted with electron-donating groups were also found to be ineffective, but oxidative addition was shown to proceed with chlorobenzenes with electron-withdrawing groups. These findings suggested that oxidative addition is similar to that of

nucleophilic aromatic substitution.[25] This work was complemented by Fauvarque in 1981, who through a kinetic study of oxidative addition of PhI to $Pd(PPh_3)_4$ (via the reactive intermediate $Pd(PPh_3)_2$), demonstrated the similarities to nucleophilic aromatic substitution.[26] They attribute the observation that PhI undergoes faster oxidative addition than the analogous PhBr due to the a weaker C-I bond than that of C-Br.

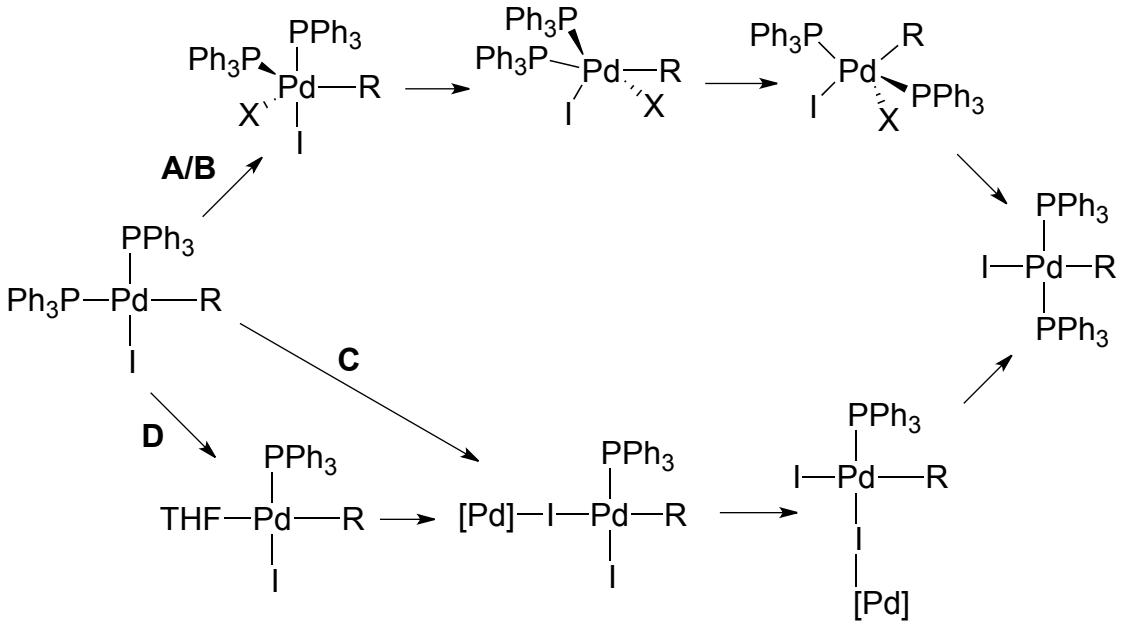
Plüger and Amatore[27] argue that oxidative addition proceeds through a concerted neutral three-centered intermediate, rather than an ionic intermediate that had previously been proposed by Fauvarque[26] and Fitton[25] (Scheme 5).



Scheme 5. Proposed oxidative addition of PhI to $Pd(PPh_3)_2$.[27]

Plüger and Amatore showed that solvent variation from THF to toluene had no effect on the observed activation parameters ($\Delta H^{\ddagger}$ = +75 kJ/mol and $\Delta S^{\ddagger}$ = +7 J/mol•K in toluene) and thus suggests a neutral transition state. Solvent variation would have an impact on the activation parameters for an ionic transition state, therefore oxidation proceeds via concerted neutral three-centered intermediate rather than via a mechanism similar to nucleophilic aromatic substitution.

Although the product of oxidative addition, $PdRXL_2$, is initially *cis*- in geometry, it readily undergoes isomerization to the *trans*- configuration.[16,27] Casado and Espinet investigated possible mechanisms for this isomerization and determined that there are in fact at least four concurrent bimolecular pathways, two autocatalytic, and two solvent assisted (Scheme 6).[16]



A: X = I-[Pd]
B: X = THF

Scheme 6. Proposed mechanisms of *cis-trans* isomerization of $PdRI(PPh_3)_2$.[16]

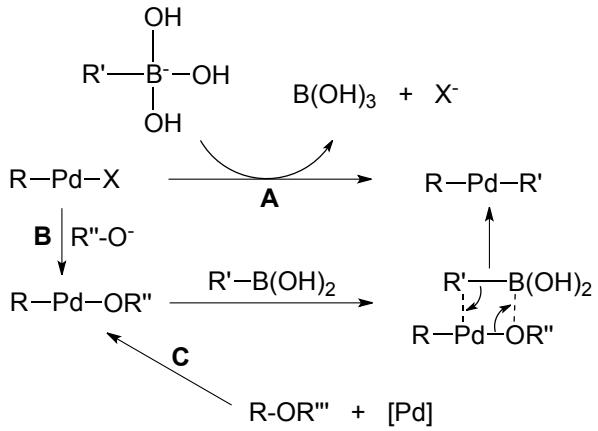
1.2.3 Transmetallation

The mechanism of the transmetallation step in the Suzuki-Miyaura reaction is dependent on both the organoboron reagent and conditions

employed,[14] and this variability is likely one of the reasons that this step in the catalytic cycle has been less explored and understood than oxidative addition.[11] The driving force for transmetallation is the difference in electronegativities of boron and palladium. In the case of Suzuki-Miyaura conditions, boron is less electronegative than palladium, which results in R-group transfer from boron to the more electronegative palladium center.

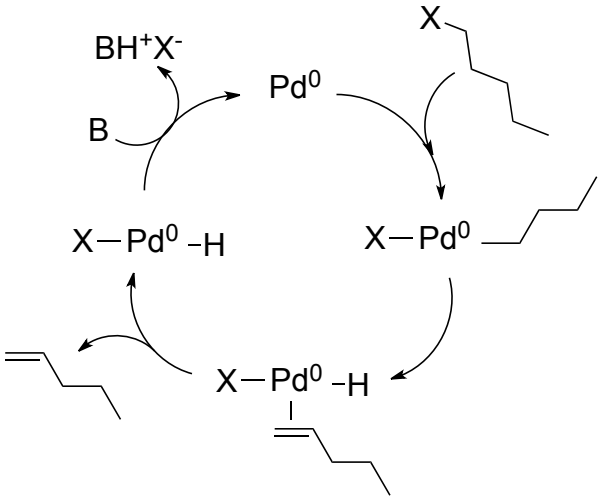
Three-coordinate organoboron reagents themselves have C-B bonds that are generally too weakly nucleophilic to undergo transmetallation, and require quaternization for R-group transfer to Pd.[4,11,28] This is accomplished by addition of an anion in the form of an inorganic salt such as Na_2CO_3, K_2CO_3, NaOH, K_3PO_4, Cs_2CO_3, or CsF to the reaction, as either a suspension or aqueous solution, which undergoes coordination to the Lewis-acidic boron.[1]

Miyaura has proposed three different pathways by which transmetallation may occur, each a function of the organoboron reagent employed (Scheme 7).[1,11] Pathway **A** involves transmetallation with $[R'\text{-}B(OH)_3]^-$ which in solution exists in equilibrium with $R\text{-}B(OH)_2$ and base. Pathway **B** involves substituting X^- with an incoming anionic base $R''\text{-}O^-$ (R = H, alkyl, acetyl) on the palladium center, which then undergoes transmetallation with the organoboronic acid. The third pathway, **C**, involves direct oxidative addition of the substrate (e.g. phenyl trifluoroacetate) to palladium, which then can transmetallate with an organoboronic acid via pathway **B** without the addition of a base.



Scheme 7. Three proposed pathways for transmetallation in the Suzuki-Miyaura reaction (ligands omitted for clarity).[11]

It should also be noted that, in the case that one of the organic coupling partners possesses a β-hydrogen, β-hydride elimination of olefinic by-products (Scheme 8) is typically favored over the desired transmetallation product.[29,30]

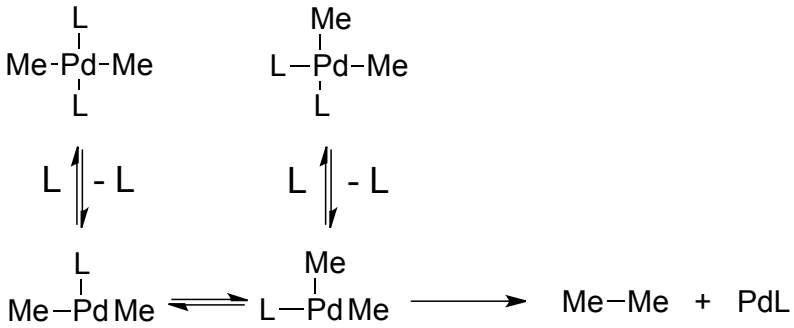


Scheme 8. Catalytic cycle for β-hydride elimination

1.2.4 Reductive Elimination

As with oxidative addition, reductive elimination is a common step in many palladium-catalyzed reactions, and is not limited to Suzuki-Miyaura reactions. It is however, less studied that its oxidative addition counterpart.

The last step in the Suzuki-Miyaura reaction, it is the process in which the coupled product is released from the Pd(II) complex, $PdRR'L_2$, simultaneously regenerating the catalytically active $Pd(0)L_2$ species. During a mechanistic investigation, Stille and Gille have shown that reductive elimination of ethane from *cis*-$PdMe_2L_2$ is inhibited in the presence of excess L, and the *trans*-analogue required isomerization to the *cis*- geometry before reductive elimination would take place (Scheme 9).[18]

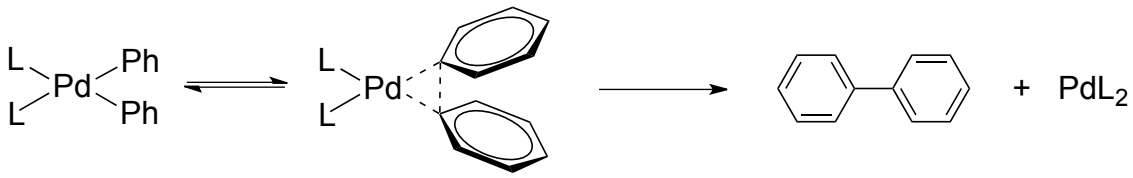


Scheme 9. Isomerization and reductive elimination of $PdMe_2L_2$.[18]

Complexes that possess chelating ligands, such as $Pd(dppe)Me_2$ eliminate much slower, which implied that elimination of dialkylpalldium(II)

complexes is a dissociative process that requires a *cis*- geometry in order to occur.

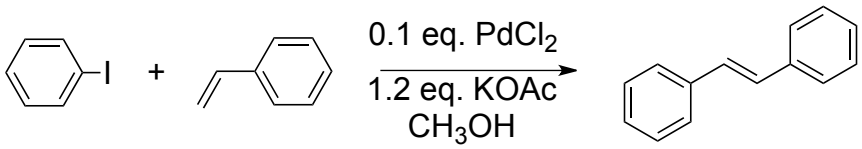
Diarylpalladium(II) complexes have greater relevance to the Suzuki-Miyaura reaction, and proceed through a slightly different mechanism than dialkyl- species.[14] Adoption of a *cis*- geometry is still required, but elimination is believed to occur via a concerted mechanism where dissociation of L does not take place (Scheme 10).



Scheme 10. Concerted reductive elimination of $PdAr_2L_2$.[14]

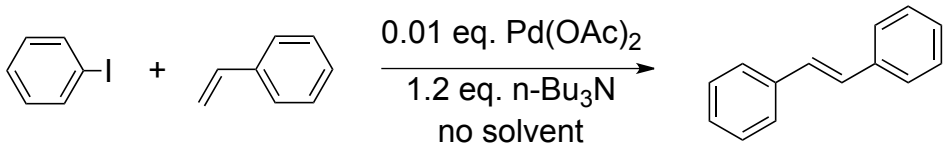
1.3 Heck-Mizoroki Reaction

The Heck-Mizoroki reaction can easily be defined as the palladium-catalyzed functionalization of an alkene. The original reaction was described by Mizoroki in 1971, which involves the coupling of iodobenzene and styrene to form stilbene in methanol at 120 °C using palladium chloride and potassium acetate (Scheme 11).[31]



Scheme 11. Formation of stilbene described by Mizoroki.[31]

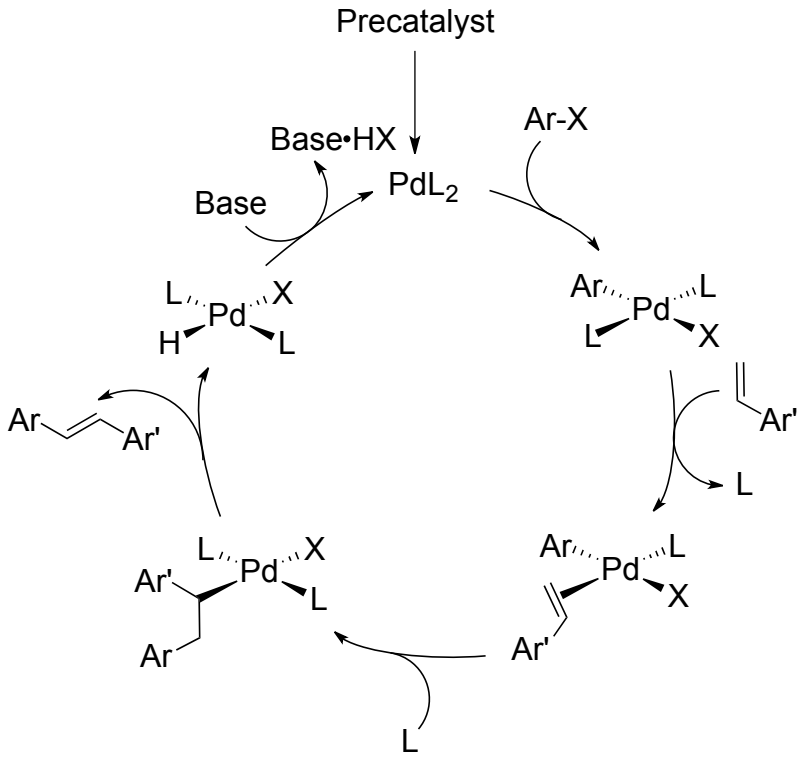
In 1972, Heck independently discovered the formation of stilbene from iodobenzene and styrene, albeit with a slightly different source of palladium, $Pd(OAc)_2$ and a hindered amine as a base, n-Bu_3N (Scheme 12).[32]



Scheme 12. Formation of stilbene described by Heck.[32]

1.3.1 Mechanism of the Heck-Mizoroki Reaction

The first step in the catalytic cycle is oxidative addition of an aryl halide to the active Pd(0) catalyst, as is the case with most reactions catalyzed by palladium. In the second step, an incoming alkene displaces a phosphine ligand to form a π palladium(II) complex. Insertion of the alkene into the σ-aryl Pd-C bond and re-coordination of a phosphine ligand leads to the four-coordinate σ-alkylpalladium complex, which undergoes β-hydride elimination to release the newly formed substituted alkene. The Pd(0) catalyst is regenerated by base-assisted reductive elimination.[4]

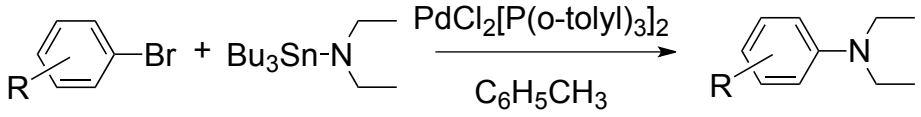


Scheme 13. General catalytic cycle of a Heck-Mizoroki reaction.

1.4 Buchwald-Hartwig Amination

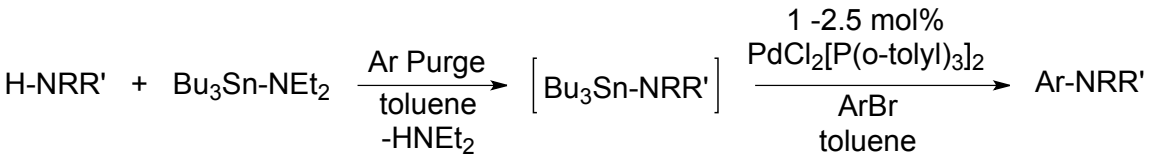
The Buchwald-Hartwig amination differs from the Suzuki-Miyaura and Heck-Mizoroki reactions in that it involves catalytic carbon-nitrogen bond formation via the coupling of an amine and aryl halide. The first example of a palladium catalyzed C-N bond formation dates back to 1983, when Migita and coworkers reported the cross-coupling of several aryl bromides and N,N-diethylamino-tributyl tin in the presence of 1 mol% of $PdCl_2[P(o\text{-}tolyl)_3]_2$ (Scheme 14).[33] A substrate scope revealed that good yields were obtained when only a

neutral, sterically unhindered aryl bromide was employed. The reaction was however limited by the necessity to use thermally and moisture sensitive tributyltin amides.



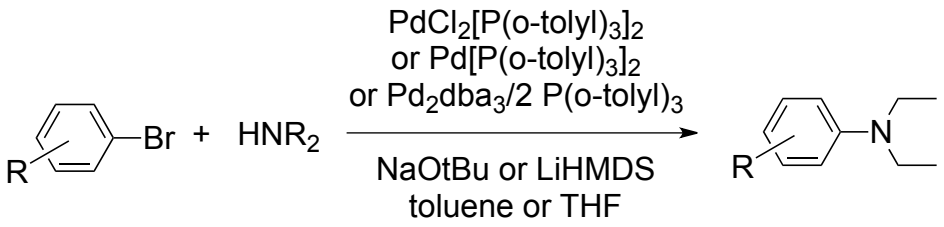
Scheme 14. Coupling of Ar-Br and n-Bu_3SnEt_2 by $PdCl_2[P(o\text{-}tolyl)_3]_2$.[33]

In 1994, Hartwig et al. published a systematic study of Migita's work and demonstrated that $Pd[P(o\text{-}tolyl)_3]_2$ was the active catalyst, which reacts with an aryl bromide via oxidative addition.[34] The same year Buchwald and Gurman described a method where the tin amide could be generated *in situ* by an amine exchange reaction (Scheme 15).[35]



Scheme 15. Buchwald's amine exchange reaction.[35]

The following year, both Hartwig[36] and Buchwald[37] extended the reaction to include free amines, which can be coupled in the presence of a bulky base such as KO^tBu and LiHMDS (Scheme 16).

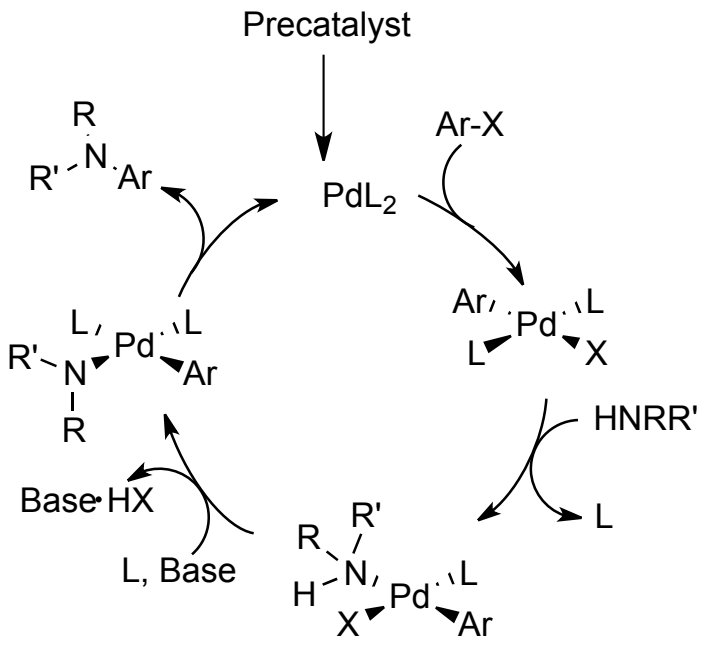


Scheme 16. Palladium catalyzed cross-coupling of Ar-Br and HNR_2.[36,37]

These findings laid the framework for so-called "first-generation" Buchwald-Hartwig catalyst systems, with future work focusing on more sophisticated phosphine ligands to accommodate a wider variety of substrates. In the following years, aryl iodies, chlorides and triflates became suitable coupling partners, and reactions were run at lower temperatures with weaker bases.

1.4.1 Mechanism of the Buchwald-Hartwig Amination

Shown in Scheme 17 is the generally accepted catalytic cycle for the amination reaction.[2] The first mechanistic feature is the same as the previously described Suzuki-Miyaura and Heck-Mizoroki reactions, with an aryl halide reacting with the Pd(0) catalyst via oxidative addition. The palladium (II) aryl amide is typically formed by direct displacement of the halide by the amide. Reductive elimination of the C-N bond results in formation of the desired arylamine and regeneration of the Pd(0) catalyst.



Scheme 17. General catalytic cycle for a Buchwald-Hartwig Amination.[2]

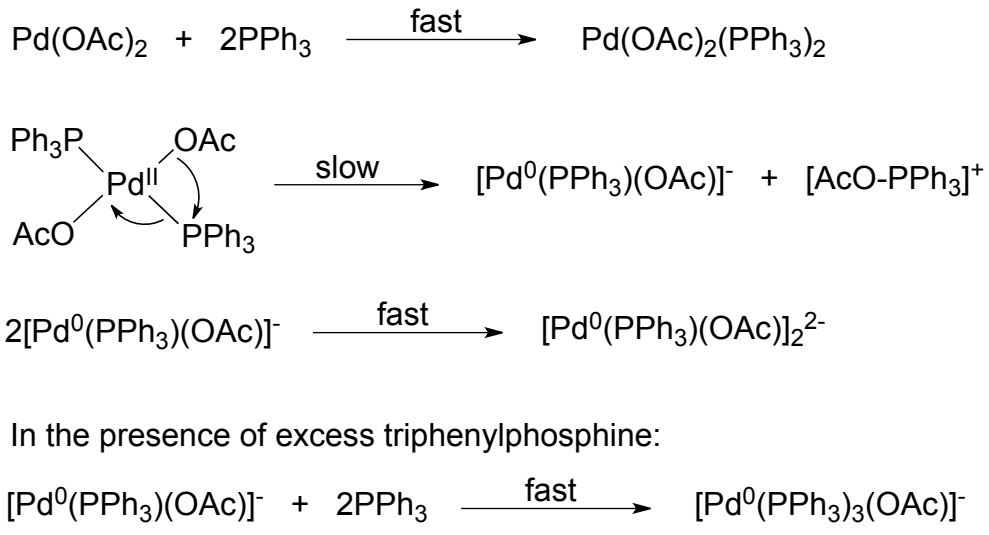
1.5 Common Palladium Precursors

Although specific catalytically active compounds such as $Pd(PCy_3)_2$ and $Pd(PBu^t_3)_2$ have long been available[38] and a general route to compounds of this type has recently been reported,[39] Pd(0) compounds are in fact air-sensitive and pre-formed catalysts of the type PdL_2 are rarely used. Instead the vast majority of palladium-catalyzed cross-coupling studies utilize much more easily manipulated, commercially available precatalysts.

1.5.1 $Pd(OAc)_2$

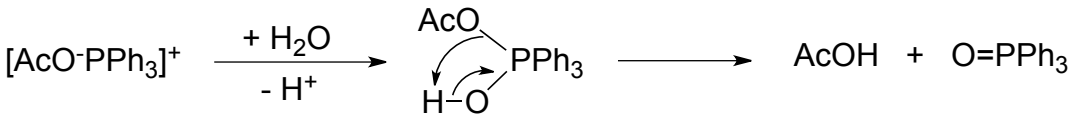
A commonly employed precursor for a variety of palladium catalyzed cross-coupling reactions is $Pd(OAc)_2$. The active catalyst is thought to be generated via reduction to Pd(0) by addition of phosphine to a suspension or solution of the Pd(II) salt. There is, however, little evidence that this reduction takes place either rapidly or completely.

Seminal work by Amatore and Jutand has shown that $Pd(OAc)_2$ reacts with an excess of PPh_3 to form a Pd(0) complex that can react via oxidative addition with an aryl halide.[40-42] $Pd(OAc)_2$ in the presence of only 2 equivalents of PPh_3 generates a Pd(0) complex that is not stable in solution, but a stable complex can be generated in the presence of an excess (5 equivalents) of PPh_3.[40] The reduction of Pd(II) takes places via an intramolecular reaction of $Pd(OAc)_2(PPh_3)_2$ with the role of excess PPh_3 ligands being to stabilize the resultant Pd(0) complex (Scheme 18).[40,41]



Scheme 18. Intramolecular reduction of $Pd(OAc)_2$ by PPh_3 to form Pd(0).[40,41]

The formation of triphenylphosphine oxide from reaction of the corresponding phosphonium acetate with water is shown in Scheme 19.



Scheme 19. Formation of triphenylphosphine oxide from phosphonium acetate.[41]

As mentioned above, the resultant Pd(0) complex from the reduction of $Pd(OAc)_2$ by excess PPh_3 is $[Pd(PPh_3)OAc]^-$. Amatore *et al.* have shown that, upon addition of acetate ions (via nBu_4NOAc) to a solution of $Pd(PPh_3)_4$, $[Pd(PPh_3)_3OAc]^-$ is formed almost quantitatively.[42] At no point are $Pd(PPh_3)_3$ or $Pd(PPh_3)_2$ detectable in solution in the presence of acetate ions. ^{31}P NMR

experiments showed that dissociation of PPh_3 takes place, albeit only in low concentrations to form $[Pd(PPh_3)_2OAc]^-$ (Scheme 20).

$$Pd(PPh_3)_4 + OAc^- \longrightarrow [Pd(PPh_3)_3(OAc)]^- + PPh_3$$
$$[Pd(PPh_3)_3(OAc)]^- \longrightarrow [Pd(PPh_3)_2(OAc)]^- + PPh_3$$

Scheme 20. Acetate ion addition to $Pd(PPh_3)_4$ in solution.[42]

$[Pd(PPh_3)_2OAc]^-$ will however, undergo oxidative addition with PhI via a 5-coordinate phenylpalladium complex to form $PdPh(PPh_3)_2OAc$.[41]

It was also shown that $Pd(OAc)_2$ can be reduced by other phosphines. Mandai *et al.* have shown that an unidentified catalytically competent Pd(0) complex can be formed by the 1:1 reaction of $Pd(OAc)_2$ with PBu^n_3 in THF or benzene (Scheme 21).[43]

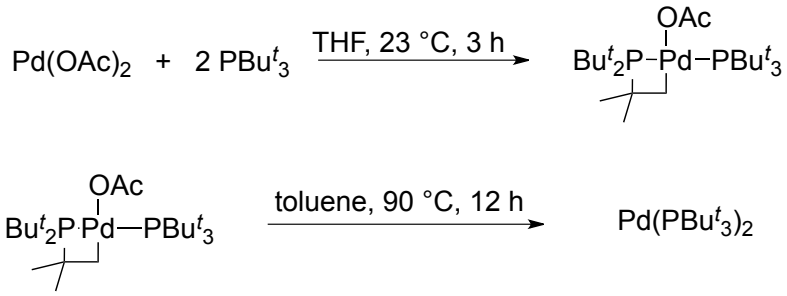
$$Pd(OAc)_2 + PBu^n_3 \longrightarrow [Pd^0] + O{=}PBu^n_3 + 2\,CH_3CO(O)COCH_3$$

Scheme 21. Reduction of $Pd(OAc)_2$ in the presence of PBu^n_3.[43]

PMe_2Ph and $PMePh_2$ also reduce $Pd(OAc)_2$ to some extent at 60 °C in DMF.[41] This added to the notion that some phosphines are able to reduce some Pd(II) salts, although the resulting Pd(0) species are not always identified. Interestingly, in the case of phosphines containing aliphatic groups, reduction appears to become disfavored as the steric bulk of the aliphatic groups increase.

Bulkier phosphines, which are traditionally used in cross-coupling reactions, may cause reduction to become problematic.

It has been recently shown by Henderson *et al.* that under mild conditions, the bulky phosphine PBu^t_3 does not form active Pd(0) when reacted with $Pd(OAc)_2$, but instead a cyclometallated species $[(PBu^t_3)Pd(CH_2C(CH_3)2PBu^t_2)(OAc)]$.[44] Quite forcing conditions were required for the reduction to catalytically active Pd(0) (Scheme 22), obviously demonstrating that $Pd(OAc)_2$ + PBu^t_3 is a poor system for generating a potential cross-coupling catalyst.

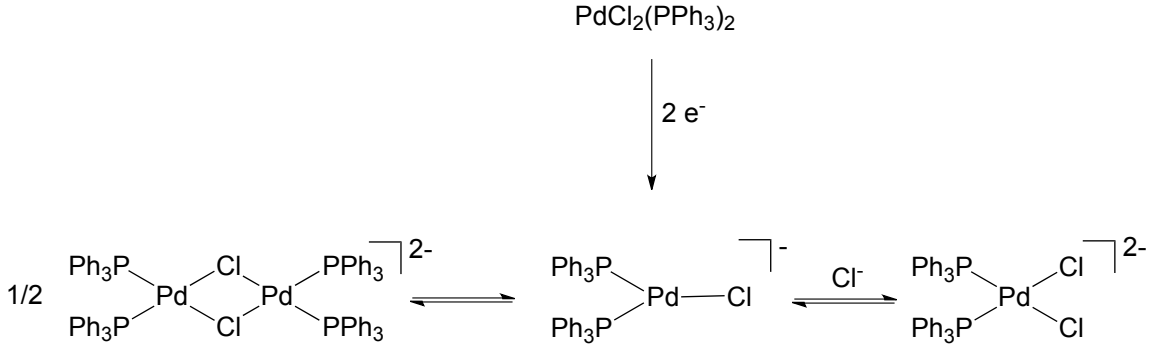


Scheme 22. Cyclometallation of PBu^t_3 by $Pd(OAc)_2$.[44]

1.5.2 $PdX_2(PPh_3)_2$

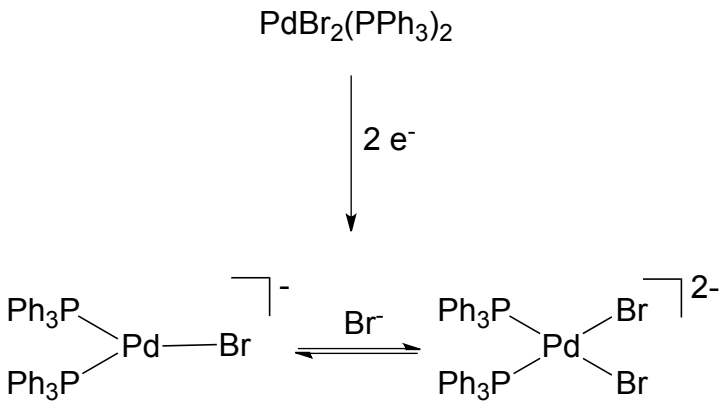
Palladium(II) compounds of the type $PdX_2(PPh_3)_2$, formed from the reaction of PdX_2 and $2PPh_3$ either *in situ* or prior to the reaction, have long been used as a source of palladium in cross-coupling reactions. Although $PdX_2(PPh_3)_2$ itself is stable in solution, it was thought that catalytically active $Pd(PPh_3)_2$ can be

quantitatively generated from the pre-catalyst via chemical or electrochemical reduction,[45,46] an improvement from the oft used $Pd(PPh_3)_4$, *vida infra*. Amatore *et al.* have demonstrated that, under experimental conditions, the formation of $Pd(PPh_3)_2$ does in fact not take place, but three anionic Pd complexes form in equilibrium upon reduction of $PdCl_2(PPh_3)_2$ (Scheme 23).[46,47]



Scheme 23. Electrochemical reduction of $PdCl_2(PPh_3)_2$.[46,47]

When the bromide analogue is employed, two species are found to be present at equilibrium (Scheme 24).[46,47] Both systems were shown to undergo oxidative addition with PhI to form $PdPhI(PPh_3)_2$.



Scheme 24. Electrochemical reduction of $PdBr_2(PPh_3)_2$.[46]

Halide ions have been shown to stabilize $Pd(PPh_3)_2$, thus decreasing its reactivity with PhI, but kinetic studies have shown that there is a rate increase when compared to the employment of $Pd(PPh_3)_4$.[46] This is attributed to the fact that $Pd(PPh_3)_4$ must dissociate 2 PPh_3 ligands to undergo oxidative addition.[46]

1.5.3 $Pd(PPh_3)_4$

$Pd(PPh_3)_4$ is one of the most commonly used palladium pre-catalysts in cross-coupling chemistry. An 18-electron complex, it dissociates in solution to tris-ligated 16-electron $Pd(PPh_3)_3$.[48,49] It was discovered later that the catalytically active $Pd(PPh_3)_2$ is required for oxidative addition,[26] and therefore an additional PPh_3 ligand must dissociate for cross-coupling to take place. In solution, the equilibrium heavily favors the tris-ligated complex, with dissociation of a second

PPh_3 disadvantageous, and the catalytically active species is, in fact, very low in concentration (Scheme 25).[42]

$$Pd(PPh_3)_4 \rightleftharpoons Pd(PPh_3)_3 + PPh_3 \quad K_1 >> 1$$

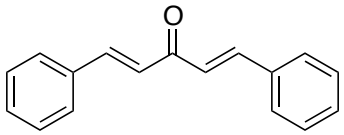
$$Pd(PPh_3)_3 \rightleftharpoons Pd(PPh_3)_2 + PPh_3 \quad K_2 << 1$$

Scheme 25. Dissociation equilibria associated with $Pd(PPh_3)_4$ in solution.[26]

The propensity of Pd(0) to participate in such equilibria is found not only with PPh_3, but with a variety of other mono-dentate phosphines. Low-ligated species where n = 2 or 3 are possible, and it appears that steric hindrance plays the dominant role on the coordination number and equilibrium. The preference for phosphines to adopt low-coordination numbers follows the trend: PMe_3 ~ PMe_2Ph ~ $PMePh_2$ < PPh_3 < P^iPr_3 < PCy_3.[48] Phosphines with particularly large cone angles (PCy_3, PBu^t_3) can form isolable complexes of the form PdL_2, further suggesting that steric bulk is the determining factor for the degree of coordination. The consequence of this is such that less bulky phosphines produce very little low-ligated catalytically active species for oxidative addition, and the dominant species in solution is in fact a catalytically inactive complex of higher coordination.

1.5.4 $Pd(dba)_2$/$Pd_2(dba)_3$

Other palladium(0) precursors of the type $Pd(dba)_2$ and $Pd_2(dba)_3$ (dba = trans,trans-dibenzylideneacetone, Scheme 26) are commonly used for the formation of Pd(0) catalysts. They have advantages over $Pd(PPh_3)_4$ in that they are air-stable and are therefore more easily handled and stored. As with $Pd(PPh_3)_4$, the starting complex is already in the 0 oxidation state, thus no chemical or electrochemical reduction is required.



Scheme 26. Structure of trans,trans-dibenzylideneacetone (dba).

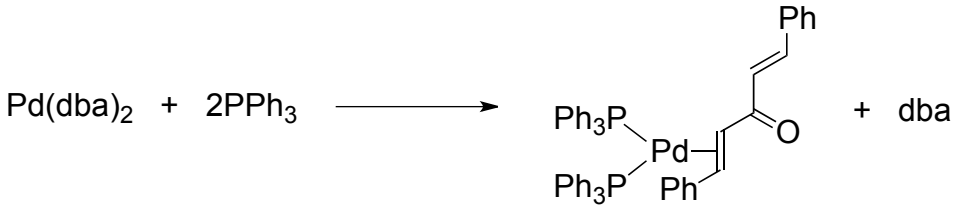
It has been thought that upon addition of a solution of desired phosphine to $Pd(dba)_2$ (either mono- or bidentate phosphines), catalytically active PdL_2 can easily be generated by displacing both dba ligands (Scheme 27).

$$Pd(dba)_2 + 2PPh_3 \longrightarrow Pd(PPh_3)_2 + 2dba$$

Scheme 27. Formation of $Pd(PPh_3)_2$ from $Pd(dba)_2$ + $2PPh_3$

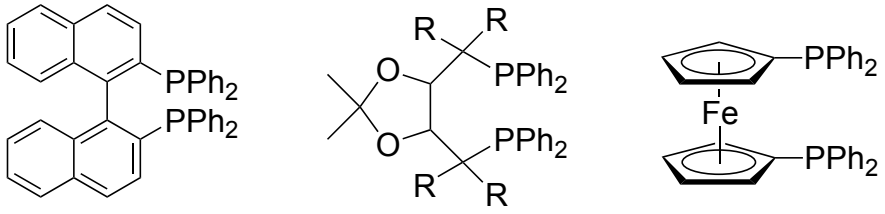
Amatore and Jutand have demonstrated[50] however, that dba is in fact a non-innocent ligand and remains coordinated to the palladium center to form complexes of the type $Pd(dba)L_2$. In the case of triphenylphosphine, two PPh_3 ligands displace one dba ligand to form the tris-ligated complex $Pd(dba)(PPh_3)_2$

in which one dba remains coordinated to the palladium via one of the double bonds (Scheme 28).[51] This behavior is also seen for other monodentate phosphines such as 3-trifurylphosphine.[50]



Scheme 28. Monoligation of Pd(0) by dba in the presence of PPh_3.[51]

Bidentate phosphines (L-L) show similar consequences when added to $Pd(dba)_2$.[52] Phosphines such as BINAP, DOP, and dppf (Scheme 29) form complexes of the type Pd(dba)(L-L) *in situ*, which are essentially unreactive towards oxidative addition.



BINAP DIOP dppf

Scheme 29. Structure of DINAP, DIOP and dppf.

Dissociation of dba in equilibrium with tris-ligated complexes of palladium influences the amount of catalytically available palladium to undergo oxidative addition (Scheme 30).[51,52]

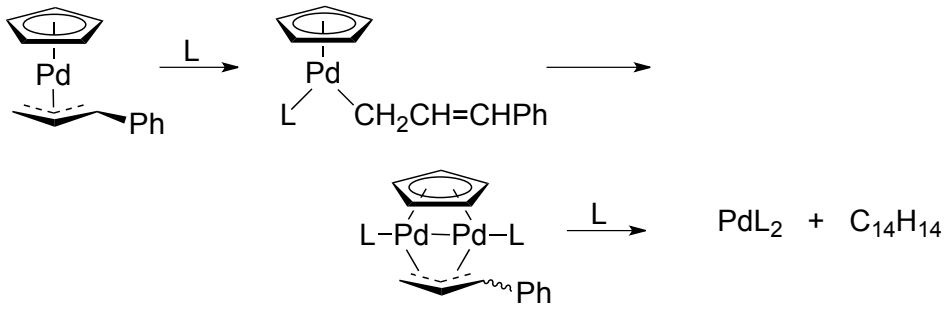
$$Pd(dba)(PPh_3)_2 \rightleftharpoons Pd(PPh_3)_2 + dba \quad K = 0.14$$

Scheme 30. Equilibrium between dba ligated Pd(0) and $Pd(PPh_3)_2$.[51,52]

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

In 2009, Norton *et al.* from the Baird lab reported the potential of Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5) (**I**) as a new precursor for Pd(0)L_2 compounds.[53] This easily synthesized and manipulated compound was shown to react under mild conditions with various mono- and bidentate phosphines to form Pd(0) rapidly and quantitatively.

Shown via a series of ^1H and ^{31}P NMR experiments in toluene-d_8, **I** reacts with various phosphines via reduction elimination of the Cp and 1-phenylallyl substituents to form stoichiometric amounts of the bis-ligated PdL_2 compound, shown in Scheme 31. Reactions of **I** with commonly employed monodentate phosphines (PPh_3, $PMePh_2$ and PCy_3) were relatively slow at room temperature, but complete conversion to Pd(0) was achieved within 1 h at 75 °C. Bulkier phosphines such as $PMeBu^t_2$ and PBu^t_3 also reacted swiftly at 75 °C, requiring < 1 h for full conversion.



Scheme 31. Reaction of I with two equivalents of phosphine to produce PdL_2.[53]

Reactions with bidentate phosphines (dppe, dppp and dppf) also yielded stoichiometric Pd(0), but only 2:1 species (ligand:Pd) were observed regardless if one or two equivalents of phosphine were added to the reaction mixture. Reactions with two equivalents were fast at 75 °C, with complete conversion taking place in < 10 m for dppe and dppp, and 1 h for dppf.

In the presence of 4 equivalents of PhI, PdL_2 reacted via oxidative addition to form $PdPhIL_2$ (L = monodentate phosphine) within a matter of minutes at 25 °C in toluene-d_8. In the case of the bidentate phosphines investigated, oxidative addition was relatively slower. $Pd(dppe)_2$ and $Pd(dppp)_2$ required several minutes at 75 °C**,** and $Pd(dppf)_2$ took overnight at 25 °C to cleanly convert to PdPhIL.

I was shown to be a superior precursor to PdL_2 to other commonly used pre-catalysts mentioned here because of its ability to form Pd(0) quantitatively. From a practical standpoint, it is easily synthesized and purified, and is air and thermally stable. Is also avoids the disadvantages of other precusors such as $Pd(PPh_3)_4$ (low activity as PdL_3 is dominant species in solution), Pd_2dba_3 (dba is

not completely displaced by phosphines) and Pd(II) salts (extent of reduction to Pd(0) is not known). It is, therefore, reasonable to expect that **I** would be a much more competent precatalyst for reactions catalyzed by species of the type $Pd(0)L_2$, which is the main hypothesis of this work.

1.6 Research Aims

What becomes apparent when perusing the extensive literature is that cross-coupling reactions catalyzed by bis-phosphine palladium(0) compounds seem to be affected by not only the chosen catalyst ligand, but also the chosen palladium pre-catalyst. This begs the question is the phosphine in question inherently better for the catalytic cycle, which is oft thought, or is possible that the phosphine of choice is better at activating the precatalyst. In the case of palladium(II) precursors, the phosphine serves as the reducing agent, and it is conceivable that certain phosphines are merely better reducing agents for certain palladium(II) precursors than others. Incomplete reduction to palladium(0) would give the illusion that the phosphine is a poor performer in the catalytic cycle than if complete conversion to Pd(0) was achieved. Another factor to consider is whether a palladium-phosphine complex prefers a coordinatively unsaturated configuration such as PdL_2, or higher coordination numbers, PdL_3 and PdL_4, as is the case of PPh_3. The difficulty in assessing actual catalytic species has been

recognized,[54] with the authors claiming that the "literature has grown into a morass, with an endless list of hypothesized or claimed true catalytic species."[54]

As mentioned previously, based on the work of Norton *et al.*, **I** has been shown to be a very competent precursor to $Pd(0)L_2$ compounds, where L = phosphine.[53] We strive to extend this work by hypothesizing that **I** is an excellent precatalyst for reactions catalyzed by bis-phosphine palladium(0) compounds.

To test the hypothesis that **I** might be significantly superior to other commonly employed precatalysts mentioned here in its ability to form PdL_2 and hence generate catalytically active species, this thesis describes an investigation in which we compare **I** with compounds $Pd(OAc)_2$, $Pd(PPh_3)_4$, Pd_2dba_3, $PdCl_2$, etc, as catalyst precursors. We select representative reactions for Suzuki-Miyaura, Heck-Mizoroki and Buchwald-Hartwig couplings, in the hope to demonstrate that **I** results in higher yields, while employing shorter reaction times and lower temperatures. We note here that our intention has not been to develop new catalysts per se but rather to investigate the potentially greater competence of **I** relative to other catalyst precursors most commonly utilized. In addition, we also aim to apply this methodology to Ni catalysis, and explore potentially useful precursors to Ni(0).

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Chapter 2

Experimental

2.1 Physical Methods

Where indicated, syntheses were carried out under a dry, deoxygenated argon atmosphere using 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. Handling and storage of air-sensitive organometallic compounds were done in an MBraun Labmaster glove box. Solvents (anhydrous THF, hexanes and toluene) were stored in 18 L containers packaged under nitrogen; they were dried by passage through columns of activated alumina (Innovative Technology Solvent Purification System) and stored over activated 4 Å molecular sieves. Dioxane was dried by storage over activated 4 Å molecular sieves for at least 48 hours under an argon atmosphere. 4 Å molecular sieves were activated by heating at 225 °C overnight in a vacuum oven.

NMR spectra were recorded using Bruker AV 300 (^{31}P: 121.5 MHz, ^{13}C: 75.4 MHz), AV 400 (^{31}P: 163.0 MHz, ^{13}C: 100.6 MHz), AV 500 (^{31}P: 202.3 MHz, ^{13}C: 125.7 MHz) and AV 600 (^{31}P: 242.9 MHz, ^{13}C: 150.9 MHz) spectrometers. ^{31}P NMR spectra were referenced with respect to external 85% H_3PO_4, while ^{1}H and ^{13}C NMR spectra were referenced to TMS via the residual protons signals of

the deuterated solvents. All chemical shifts are reported on the δ (ppm) scale with positive values referring to chemical shifts downfield from 0 ppm.

GC analysis was conducted on a Varian 3900 GC equipped with a CP-8400 autosampler, a CP-1177 injector, an FID detector and a Varian WCOT Fused Silica column (CP-Sil 8CB, 25 m x 0.32 mm ID, DF = 0.52).

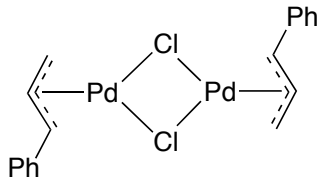
IR spectra were acquired on a Perkin-Elmer Spectrum One FT-IR spectrometer.

2.2 Chemical Supplies

All supplies were purchased from either Aldrich or Strem and used without further purification with the exception of PPh_3, which was recrystallized from dry and deoxygenated MeOH. C_7D_8, C_6D_6, $CDCl_3$ and CD_2Cl_2 were dried by storage over activated 4 Å molecular sieves for at least 48 hours under an argon atmosphere. $PdCl_2$ was obtained on loan courtesy of Johnson Matthey.

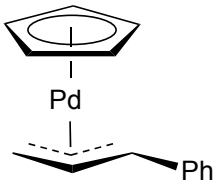
2.3 Preparation of Palladium Compounds

2.3.1 Synthesis of $[Pd(\eta^3\text{-}1\text{-}Ph\text{-}C_3H_4)Cl]_2$



This compound was prepared according to the procedure described by Auburn *et al*.[1] $PdCl_2$ (0.5 g, 2.8 mmol) and LiCl (0.5 g, 11.8 mmol) were stirred in air in warm distilled water (3 mL) for 1 h. A solution of cinnamyl chloride (1.6 mL, 10.9 mmol) in 95 % ethanol (10 mL) was added to the stirring solution. $CO_{(g)}$ was bubbled through the solution for 1.5 h, during which time an oily orange-yellow product began to form. The flow of $CO_{(g)}$ was discontinued and the solution was left stirring for 3 h at 25 °C under a CO atmosphere. Immediately prior to filtration, the solution was stirred for 30 min at 0 ºC. The product was collected by suction filtration and washed with cold methanol (10 mL). The product was recrystallized from chloroform by addition of diethyl ether, yielding a yellow crystalline solid. Yield: 0.679 g, 92 %. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.05 (d, J 11.7 Hz, 1H), 3.98 (d, J 6.6 Hz, 1H), 4.64 (d, J 11.5 Hz, 1H), 5.81 (td, J 11.5 Hz, 6.7 Hz, 1H), 7.27 (t, J 7.1 Hz, 2H), 7.34 (t, J 7.1 Hz, 1H), 7.50 (d, J 7.1 Hz, 2H). Lit.[1]: ^{1}H NMR (dmso-d_6): δ 3.83 (d, *J* 10 Hz, 2H), 5.13 (d, *J* 12 Hz, 1H), 6.40 (dt, 12 Hz, 10 Hz, 1H), 7.0-7.8 (m, 5H).

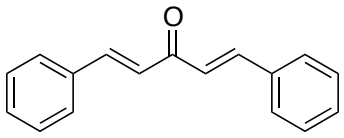
2.3.2 Synthesis of Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5) (I)



This compound was prepared according to the procedure described by Norton *et al*.[2] A solution of NaCp in THF (2.0 M, Aldrich) (1.45 mL, 2.90 mmol NaCp) was diluted by THF (20 mL) in a dropping funnel and added dropwise to a suspension of [Pd(η^3-1-Ph-C_3H_4)Cl]$_2$ (0.601 g, 1.16 mmol) in THF (20 mL) at -78 °C. The resulting deep purple solution was stirred for 30 min then warmed to room temperature. The solvent was removed at room temperature under vacuum and the product was extracted using three 20 mL portions of hexanes. The filtrate was reduced under vacuum, yielding an oily purple solid. The solid was dissolved in a minimum of hexanes and purple crystals were collected at -40 ºC. Beautiful purple-red crystals can be obtained by sublimation at 40 ºC at 1 x 10^{-3} Torr. Yield: 0.565 g, 84 %. ^{1}H NMR (C_7D_8, 600 MHz): δ 2.16 (d, J 10.5 Hz, 1H), 3.36 (d, J 6.1 Hz, 1H), 3.84 (d, J 9.8 Hz, 1H), 5.14 (ddd, J 10.5 Hz, 9.8 Hz, 6.1 Hz, 1H), 5.63 (s, 5H), 6.98 - 7.03 (m, 3H), 7.24-7.27 (m, 2H). Lit.[2]: ^{1}H NMR (toluene-d_8) δ 2.16 (d, J = 10.5 Hz, 1H, H(3a)), 3.36 (d, J = 6.1 Hz, 1H, H(3s)), 3.84 (d, J=9.8 Hz, 1H, H(1)), 5.14 (ddd, J = 6.1, 9.8, 10.5 Hz, 1H, H(2)), 5.63 (s, 5H, C5H5), 6.98-7.03 (m, 3H, Ph), 7.24-7.27 (m, 2H, Ph).

2.3.3 Synthesis of Pd_2dba_3

2.3.3.1 Synthesis of dibenzylacetone (dba)



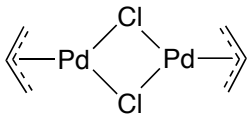
The following compound was prepared as described by Conard and Dolliver.[3] A solution of benzaldehyde (2.0 mL, 19.6 mmol) and acetone (0.73 mL, 10.0 mmol) was added dropwise over 30 minutes to a stirring solution of NaOH (2.0 g, 50 mmol) in H_2O (20 mL) and ethanol (16 mL). The resulting yellow crystalline precipitate was filtered and recrystallized from ethyl acetate at -30 ºC. Yield: 2.1 g, 89 %. ^{1}H NMR ($CDCl_3$, 400 Mhz): δ 7.10 (d, 2H), 7.41 (m, 6H), 7.62 (m, 4H), 7.75 (d, 2H). Lit[4]: ^{1}H NMR ($CDCl_3$): δ 7.76 10 (d, 2H), 7.46 (m, 6H), 7.11 (d, 2H).

2.3.3.2 Synthesis of Pd_2dba_3

The following compound was prepared as described by Ukai *et al*.[5] To a stirring solution of dibenzylacetone (2.1 g, 9.0 mmol) and NaOAc (1.78 g, 21.7 mmol) in hot MeOH (70 mL, 50 ºC) was added $PdCl_2$ (0.479 g, 21.3 mmol). After 5 minutes, the solution had turned dark red, where it was left stirring for a further 3 hours. Upon cooling in an ice bath, the reaction had precipitated a purple product, which was filtered and washed with H_2O and acetone. Recrystallized from $CHCl_3$: ether (60 mL : 80 mL). Yield: 0.492 g, 41 %. ^{1}H NMR ($CDCl_3$): δ

7.05 (2H, d), 7.30-7.60 (m, 6H) 7.70 (2H, d). Lit[4]: ^{1}H NMR ($CDCl_3$): δ 7.76 (2H, d, ^3J = 13.4 Hz) , 7.11 (2H, d, ^3J = 13.4 Hz);

2.3.4 Synthesis of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$



This compound was prepared according the procedure described by Tatsuno *et al*.[6] $PdCl_2$ (0.219g, 1.25 mmol) was suspended in a solution of LiCl (0.11 g, 2.6 mmol) in MeOH (3.5 mL) and H_2O (0.5 mL) and stirred for 1 hour to give a red solution. Allyl chloride (0.34 mL, 4.2 mmol) was then added, and $CO_{(g)}$ bubbled through the solution for 3 hours, after which had turned from red to yellow. H_2O (20 mL) was added and the resulting solution was extracted with $CHCl_3$ (3 x 10 mL). After drying over Na_2SO_4, $CHCl_3$ was removed in vacuo to give a yellow, crystalline product. Yield: 0.192 g, 84 %. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.03 (d, J = 12.1 Hz, 2H), 4.10 (d, J = 6.7 Hz, 2H), 5.45 (tt, J = 6.6 Hz, 12.1 Hz, 1H). Lit.[6]: ^{1}H NMR ($CDCl_3$) δ 3.03 (d, J = 12.0 Hz, anti CH2), 4.10 (d, J = 7.1 Hz, syn CH2), 5.48 (CH, t).

2.4 General Considerations for Cross-Coupling Experiments

In order to compare the efficacies of commonly used palladium precursors with **I**, it was determined that reaction profiles would give more detailed

information about how a reaction proceeds over time than typical isolated yield reactions. Reaction profiles were obtained by periodically monitoring reactions by GC (see Appendix for example GC spectra and calibration curves of products). A typical experiment involving withdrawing a sample from the reaction vessel at specified times, diluting with toluene, obtaining conversion of starting material to products via GC and plotting data to give a conversion vs. time graph. Reactions were carried out until either complete conversion had been obtained, or conversion to products had reached a plateau and consumption of starting materials no longer proceeded. Reactions were done in duplicate and triplicate and were always within 5 % conversion for each trial.

2.4.1 Suzuki-Miyaura Coupling

2.4.1.1 NMR Scale Reaction of I + PPh_3 alone

In an NMR tube in the glovebox, I (0.0072 g, 0.025 mmol) and PPh_3 (0.0131 g, 0.050 mmol) were dissolved in 90% 1,4-dioxane/10% C_6D_6 (0.5 mL). The NMR tube was placed into a pre-heated NMR probe at 75 ºC, and monitored periodically by ^{31}P NMR for 2 hours.

2.4.1.2 Synthesis of 4-methoxy-1,1'-biphenyl using I + PPh_3 as Catalyst

In a test tube under argon, I (0.0072 g, 0.025 mmol) and PPh_3 (0.0131 g, 0.050 mmol) were dissolved in 1,4-dioxane (1 mL) and stirred at RT ºC for 30 min

after which the solution had changed colour from purple to brown. 4-Bromoanisole (0.067 mL, 0.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.0732 g, 0.6 mmol) and Cs_2CO_3 (0.1955 g, 0.6 mmol) and the reaction was stirred at 50 ºC for 24 hours. The reaction was diluted with Et_2O (10 mL), filtered through a pad of Celite, and evaporated in vacuo. The residue was dissolved in toluene (20.0 mL) and conversion to 4-methoxy-1,1'-biphenyl was determined by GC. Yield: 62 %.

2.4.1.3 Profile of 4-methoxy-1,1'-biphenyl formation using I + PPh_3 as Catalyst

Performed in triplicate. In a test tube under argon, I (0.036 g, 0.125 mmol) and PPh_3 (0.066 g, 0.250 mmol) were dissolved in 1,4-dioxane (5 mL) and stirred at 50 ºC for 1 hour, after which the solution had changed colour from purple to brown. 4-Bromoanisole (0.314 mL, 2.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.366 g, 3.0 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was allowed to continue stirring at 50 ºC. At specified times, stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (20.0 mL) and analyzed by GC.

2.4.1.4 Profile of 4-methoxy-1,1'-biphenyl formation using $Pd(OAc)_2$ + PPh_3 as Catalyst

Performed in triplicate. In a test tube under argon, $Pd(OAc)_2$ (0.028 g, 0.125 mmol) and PPh_3 (0.098 g, 0.375 mmol) were dissolved in 1,4-dioxane (5 mL). 4-Bromoanisole (0.314 mL, 2.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.366 g, 3.0 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was stirred at 50 ºC, and at specified times stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (20.0 mL) and analyzed by GC.

2.4.1.5 Profile of 4-methoxy-1,1'-biphenyl formation using $Pd(PPh_3)_4$ as Catalyst

Performed in triplicate. In a test tube under argon, $Pd(PPh_3)_4$ (0.144 g, 0.125 mmol) was dissolved in 1,4-dioxane (5 mL). 4-Bromoanisole (0.314 mL, 2.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.366 g, 3.0 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was stirred at 50 ºC, and at specified times stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (20.0 mL) and analyzed by GC.

2.4.1.6 NMR Scale Reaction of I + PCy_3 alone

In an NMR tube in the glovebox, I (0.0072 g, 0.025 mmol) and PCy_3 (0.0140 g, 0.050 mmol) were dissolved in 90% 1,4-dioxane/10% C_6D_6 (5 mL). The NMR tube was placed into a pre-heated NMR probe at 75 ºC, and monitored periodically by ^{31}P NMR for 2 hours.

2.4.1.7 Profile of 4-methoxy-1,1'-biphenyl formation using I + PCy_3 as Catalyst

Performed in triplicate. In a test tube under argon, I (0.036 g, 0.125 mmol) and PCy_3 (0.070 g, 0.250 mmol) were dissolved in 1,4-dioxane (5 mL) and stirred at 75 ºC for 2 hours, after which the solution had changed colour from purple to brown. 4-Bromoanisole (0.314 mL, 2.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.366 g, 3.0 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was stirred at 50 ºC, and at specified times stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (20.0 mL) and analyzed by GC.

2.4.1.8 Profile of 4-methoxy-1,1'-biphenyl formation using $Pd(OAc)_2$ + PCy_3 as Catalyst

Performed in triplicate. In a test tube under argon, $Pd(OAc)_2$ (0.028 g, 0.125 mmol) and PCy_3 (0.105 g, 0.375 mmol) were dissolved in 1,4-dioxane (5 mL). 4-Bromoanisole (0.314 mL, 2.5 mmol) was added via syringe, followed by

the addition of phenylboronic acid (0.366 g, 3.0 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was stirred at 50 ºC, and at specified times stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (20.0 mL) and analyzed by GC.

2.4.1.9 Profile of 4-methoxy-1,1'-biphenyl formation using Pd_2dba_3 + PCy_3 as Catalyst

Performed in triplicate. In a test tube under argon, Pd_2dba_3 (0.0572 g, 0.0625 mmol) and PCy_3 (0.070 g, 0.250 mmol) were dissolved in 1,4-dioxane (5 mL). 4-Bromoanisole (0.314 mL, 2.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.366 g, 3.0 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was stirred at 50 ºC, and at specified times stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (20.0 mL) and analyzed by GC.

2.4.1.10 NMR Scale Reaction of I + P^tBu_3 alone

In an NMR tube in the glovebox, I (0.0072 g, 0.025 mmol) and P^tBu_3 (0.0101 g, 0.050 mmol) were dissolved in 90% 1,4-dioxane/10% C_6D_6 (5 mL).

The NMR tube was placed into a pre-heated NMR probe at 75 ºC, and monitored periodically by ^{31}P NMR for 2 hours.

2.4.1.11 Profile of 4-methoxy-1,1'-biphenyl formation using I + P^tBu_3 as Catalyst

Performed in triplicate. In a test tube under argon, I (0.036 g, 0.125 mmol) and P^tBu_3 (0.051 g, 0.250 mmol) were dissolved in 1,4-dioxane (5 mL) and stirred at 75 ºC for 1.5 hours, after which the solution had changed colour from purple to brown. 4-Bromoanisole (0.314 mL, 2.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.366 g, 3.0 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was stirred at 50 ºC, and at specified times stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (20.0 mL) and analyzed by GC.

2.4.1.12 Profile of 4-methoxy-1,1'-biphenyl formation using $Pd(OAc)_2$ + P^tBu_3 as Catalyst

Performed in triplicate. In a test tube under argon, $Pd(OAc)_2$ (0.028 g, 0.125 mmol) and P^tBu_3 (0.076 g, 0.375 mmol) were dissolved in 1,4-dioxane (5 mL). 4-Bromoanisole (0.314 mL, 2.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.366 g, 3.0 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was stirred at 50 ºC, and at specified times stirring was

briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (20.0 mL) and analyzed by GC.

2.4.1.13 Profile of 4-methoxy-1,1'-biphenyl formation using Pd_2dba + P^tBu_3 as Catalyst

Performed in triplicate. In a test tube under argon, Pd_2dba_3 (0.0572 g, 0.0625 mmol) and P^tBu_3 (0.050 g, 0.250 mmol) were dissolved in 1,4-dioxane (5 mL). 4-Bromoanisole (0.314 mL, 2.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.366 g, 3.0 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was stirred at 50 ºC, and at specified times stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (20.0 mL) and analyzed by GC.

2.4.1.14 Profile of 4-methoxy-1,1'-biphenyl formation using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ + P^tBu_3 as Catalyst

Performed in duplicate. In a test tube under argon, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.0229 g, 0.0625 mmol) and P^tBu_3 (0.050 g, 0.250 mmol) were dissolved in 1,4-dioxane (5 mL). 4-Bromoanisole (0.314 mL, 2.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.366 g, 3.0 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was stirred at 50 ºC, and at specified times stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL

syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (20.0 mL) and analyzed by GC.

2.4.1.15 Profile of 4-methoxy-1,1'-biphenyl formation using $PdCl_2$ + P^tBu_3 as Catalyst

Performed in duplicate. In a test tube under argon, $PdCl_2$ (0.0222 g, 0.125 mmol) and P^tBu_3 (0.050 g, 0.250 mmol) were dissolved in 1,4-dioxane (5 mL). 4-Bromoanisole (0.314 mL, 2.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.366 g, 3.0 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was stirred at 50 ºC, and at specified times stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (20.0 mL) and analyzed by GC.

2.4.2 Phosphine Scope

2.4.2.1 Profile of 4-methoxy-1,1'-biphenyl formation using I + PMe_3 as Catalyst

Performed in duplicate. In a test tube under argon, I (0.036 g, 0.125 mmol) and PMe_3 (0.25 mL of 1M in THF, 0.250 mmol) were dissolved in 1,4-dioxane (5 mL) and stirred at 50 ºC for 1 hour, after which the solution had changed colour from purple to brown. 4-Bromoanisole (0.314 mL, 2.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.366 g, 3.0 mmol) and

Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was stirred at 50 ºC, and at specified times stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (20.0 mL) and analyzed by GC.

2.4.2.2 Profile of 4-methoxy-1,1'-biphenyl formation using I + PMe_2Ph as Catalyst

Performed in duplicate. In a test tube under argon, I (0.036 g, 0.125 mmol) and PMe_2Ph (0.036 mL, 0.250 mmol) were dissolved in 1,4-dioxane (5 mL) and stirred at 50 ºC for 1 hour, after which the solution had changed colour from purple to brown. 4-Bromoanisole (0.314 mL, 2.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.366 g, 3.0 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was stirred at 50 ºC, and at specified times stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (20.0 mL) and analyzed by GC.

2.4.2.3 Profile of 4-methoxy-1,1'-biphenyl formation using I + P^tBu_2Me as Catalyst

Performed in duplicate. In a test tube under argon, I (0.036 g, 0.125 mmol) and P^tBu_2Me (0.049 mL, 0.250 mmol) were dissolved in 1,4-dioxane (5 mL) and stirred at 50 ºC for 1 hour, after which the solution had changed colour from

purple to brown. 4-Bromoanisole (0.314 mL, 2.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.366 g, 3.0 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was stirred at 50 ºC, and at specified times stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (20.0 mL) and analyzed by GC.

2.4.2.4 Profile of 4-methoxy-1,1'-biphenyl formation using I + $P(OPh)_3$ as Catalyst

Performed in duplicate. In a test tube under argon, I (0.036 g, 0.125 mmol) and $P(OPh)_3$ (0.065 mL, 0.250 mmol) were dissolved in 1,4-dioxane (5 mL) and stirred at 50 ºC for 1 hour, after which the solution had changed colour from purple to brown. 4-Bromoanisole (0.314 mL, 2.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.366 g, 3.0 mmol) and Cs_2CO_3 (1.63 g, 5.0 mmol). The reaction was stirred at 50 ºC, and at specified times stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (20.0 mL) and analyzed by GC.

2.4.3 Ligand-Free Synthesis of 4-methoxy-1,1'-biphenyl using I as Catalyst

In a test tube under argon, I (0.0072 g, 0.025 mmol) was dissolved in 1,4-dioxane (1 mL). 4-Bromoanisole (0.063 mL, 0.5 mmol) was added via syringe, followed by the addition of phenylboronic acid (0.0732 g, 0.6 mmol) and Cs_2CO_3 (0.1955 g, 0.6 mmol) and stirred at 50 ºC for 18 hours. The reaction was diluted with Et_2O (10 mL), filtered through a pad of Celite, and evaporated in vacuo. The residue was dissolved in toluene (20.0 mL) and conversion to 4-methoxy-1,1'-biphenyl determined by GC. Yield: 17 %.

2.4.4 Evaulation of Phenylboronic acid Degradation

2.4.4.1 Synthesis of Phenylboroxine

The following was synthesized by the procedure reported by Washburn *et al*.[7] Phenylboronic acid (5.0 g, 41 mmol) was placed on a watch-glass and heated at 120 °C for 3 hours in an oven. ^{1}H NMR ($CDCl_3$), δ 8.25 (d, o-H), 7.51 (t, m-H), 7.60 (t, p-H); (dioxane-C_6D_6, 90:10), δ 8.16 (d, o-H), 7.40 (t, m-H), 7.48 (t, p-H). Lit.[8]: ^{1}H NMR: δ 8.13 (d, o-H), 7.27 (t, m-H), 7.33 (t, p-H).

2.4.4.2 Conversion of Phenylboronic acid to Phenylboroxine

The following experiment was based on a modified procedure reported by Washburn *et al*.[7] In an NMR tube, phenylboronic acid (0.010 g, 0.082 mmol) was

dissolved in dioxane-C_6D_6 (90:10) (0.6 mL) and the ^1H NMR spectra were acquired at 25, 35, 45, 55, 65 and 75 °C.

2.4.4.3 Reaction of Phenylboronic Acid with Cs_2CO_3

In an NMR tube, a sample of phenylboronic acid (0.010 g, 0.082 mmol) and Cs_2CO_3 (0.053 g, 0.164 mmol) were suspended in dioxane-C_6D_6 (90:10) (0.6 mL) and the ^1H NMR spectra were acquired at 25, 35, 45, 55, 65 and 75 °C, followed by acquisition at 25 °C after cooling.

2.5 Mizoroki-Heck Coupling

2.5.1 Synthesis of *trans*-methyl cinnamate from chlorobenzene and methyl acrylate

2.5.1.1 Profile of *trans*-methyl cinnamate formation using I + P^tBu_3 as Catalyst

Performed in duplicate. In a test tube under argon, I (0.0216 g, 0.075 mmol) and P^tBu_3 (0.0303 g, 0.150 mmol) were dissolved in 1,4-dioxane (5 mL) and stirred at 75 ºC for 1.5 hours, after which the solution had changed colour from purple to brown. Chlorobezene (0.253 mL, 2.5 mmol) and methyl acrylate (0.450 mL, 5.0 mmol) was added via syringe, followed by the addition of Cs_2CO_3 (0.896 g, 2.75 mmol). The reaction was stirred at 95 ºC, and at specified times stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL

syringe and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (10.0 mL) and analyzed by GC.

2.5.1.2 Profile of *trans*-methyl cinnamate formation using $Pd(OAc)_2$ + P^tBu_3 as Catalyst

Performed in duplicate. Under an atmosphere of argon, $Pd(OAc)_2$ (0.0168 g, 0.075 mmol) and P^tBu_3 (0.0455g, 0.225 mmol) were combined in 5 mL of dioxane. Chlorobenzene (0.253 mL, 2.5 mmol), methyl acrylate (0.450 mL, 5.0 mmol) and Cs_2CO_3 (0.896 g, 2.75 mmol) were added in succession and the mixture was stirred at 95 °C for 22 h. 0.2 mL aliquots were removed at specified intervals, diluted with 10 mL of ethyl ether, filtered through a pad of Celite with 2x10 mL ethyl ether, concentrated in vacuo to a solid, dissolved in 10.0 mL of toluene/hexadecane (0.0034 M) and analysed by GC.

2.5.1.3 Profile of *trans*-methyl cinnamate formation using Pd_2dba_3 + P^tBu_3 as Catalyst

Performed in duplicate. Under an atmosphere of argon, $Pd_2(dba)_3$ (0.0343 g, 0.0375 mmol) and P^tBu_3 (0.0303g, 0.15 mmol) were combined in 5 mL of dioxane. Chlorobenzene (0.253 mL, 2.5 mmol), methyl acrylate (0.450 mL, 5.0 mmol) and Cs_2CO_3 (0.896 g, 2.75 mmol) were added in succession and the mixture was stirred at 95 °C for 22 h. 0.2 mL aliquots were removed at specified intervals, diluted with 10 mL of ethyl ether, filtered through a pad of Celite with

2x10 mL ethyl ether, concentrated in vacuo to a solid, dissolved in 10.0 mL of toluene/hexadecane (0.0034 M) and analysed by GC.

2.5.2 Synthesis of *trans*-stilbene from bromobenzene and styrene

2.5.2.1 Synthesis of *trans*-stilbene using I + P^tBu_3 as Catalyst

Under an atmosphere of argon, I (0.0130 g, 0.045 mmol) and P^tBu_3 (0.0182 g, 0.09 mmol) were combined in 3 mL of DMF and stirred at 75 °C for 1.5 h. To the resulting brown solution was added bromobenzene (0.16 mL, 1.5 mmol), styrene (0.21 mL, 1.8 mmol) and triethylamine (0.25 mL, 1.8 mmol) and the mixture was stirred at 80 °C for 1 h. The reaction was cooled and analyzed by GC. Yield: 96 %.

2.5.2.2 Profile of *trans*-stilbene formation using I + P^tBu_3 as Catalyst

Performed in duplicate. Under an atmosphere of argon, I (0.0130 g, 0.045 mmol) and P^tBu_3 (0.0182 g, 0.09 mmol) were combined in 3 mL of DMF and stirred at 75 °C for 1.5 h. To the resulting brown solution was added bromobenzene (0.16 mL, 1.5 mmol), styrene (0.21 mL, 1.8 mmol) and triethylamine (0.25 mL, 1.8 mmol) and the mixture was stirred at 80 °C for 1 h. 0.1 mL aliquots were removed at specified intervals, diluted with 9.9 mL of toluene/hexadecane (0.0034 M) and analysed by GC.

2.5.2.3 Synthesis of *trans*-stilbene formation using $Pd(OAc)_2$ + P^tBu_3 as Catalyst

Under an atmosphere of argon, $Pd(OAc)_2$ (0.0101 g, 0.045 mmol) and P^tBu_3 (0.0273 g, 0.0135 mmol) were combined in 3 mL of DMF. Bromobenzene (0.16 mL, 1.5 mmol), styrene (0.21 mL, 1.8 mmol) and triethylamine (0.25 mL, 1.8 mmol) were added to the mixture and the reaction stirred at 80 °C for 1 h. The reaction was cooled and analyzed by GC. Yield: < 1 %.

2.5.2.4 Profile of *trans*-stilbene formation using $Pd(OAc)_2$ + P^tBu_3 as Catalyst

Performed in duplicate. Under an atmosphere of argon, $Pd(OAc)_2$ (0.0101 g, 0.045 mmol) and P^tBu_3 (0.0273 g, 0.135 mmol) were combined in 3 mL of DMF. Bromobenzene (0.16 mL, 1.5 mmol), styrene (0.21 mL, 1.8 mmol) and triethylamine (0.25 mL, 1.8 mmol) were added in succession and the mixture was stirred at 80 °C for 1 h. 0.1 mL aliquots were removed at specified intervals, diluted with 9.9 mL of toluene/hexadecane (0.0034 M) and analysed by GC.

2.5.2.5 Synthesis of *trans*-stilbene using Pd_2dba_3 + P^tBu_3 as Catalyst

Under an atmosphere of argon, Pd_2dba_3 (0.0206 g, 0.0225 mmol) and P^tBu_3 (0.0182 g, 0.090 mmol) were combined in 3 mL of DMF. Bromobenzene (0.16 mL, 1.5 mmol), styrene (0.21 mL, 1.8 mmol) and triethylamine (0.25 mL,

1.8 mmol) were added to the mixture and the reaction stirred at 80 °C for 1 h. The reaction was cooled and analyzed by GC. Yield: 89 %.

2.5.2.6 Profile of *trans*-stilbene formation using Pd_2dba_3 + P^tBu_3 as Catalyst

Performed in duplicate. Under an atmosphere of argon, $Pd_2(dba)_3$ (0.0206 g, 0.0275 mmol) and P^tBu_3 (0.0182 g, 0.09 mmol) were combined in 3 mL of DMF. Bromobenzene (0.16 mL, 1.5 mmol), styrene (0.21 mL, 1.8 mmol) and triethylamine (0.25 mL, 1.8 mmol) were added in succession and the mixture was stirred at 80 °C for 1 h. 0.1 mL aliquots were removed at specified intervals, diluted with 9.9 mL of toluene/hexadecane (0.0034 M) and analysed by GC.

2.5.3 Synthesis of stilbene from chlorobenzene and styrene

2.5.3.1 Profile of *trans*-stilbene formation using I + P^tBu_3 as Catalyst

Performed in duplicate. In a test tube under argon, I (0.0216 g, 0.075 mmol) and P^tBu_3 (0.0303 g, 0.150 mmol) were dissolved in 1,4-dioxane (5 mL) and stirred at 75 ºC for 1.5 hours, after which the solution had changed colour from purple to brown. Chlorobezene (0.253 mL, 2.5 mmol) and styrene (0.573 mL, 5.0 mmol) was added via syringe, followed by the addition of Cs_2CO_3 (0.896 g, 2.75 mmol). The reaction was stirred at 95 ºC, and at specified times stirring was briefly stopped, 0.2 mL of the reaction with withdrawn with a 1 mL syringe

and diluted by ~10 mL Et_2O. The sample was then filtered through a pad of Celite, dissolved in toluene (10.0 mL) and analyzed by GC.

2.6 Buchwald-Hartwig Amination

2.6.1 Synthesis of bis(4-methoxyphenyl)amine from 4-bromoanisole and anisidine

2.6.1.1 Profile of bis(4-methoxyphenyl)amine formation using I + XPhos as Catalyst

Performed in triplicate. In a test tube under argon, I (0.0087 g, 0.030 mmol) and XPhos (0.0286 g, 0.060 mmol) were dissolved in toluene (3 mL) and stirred at 80 ºC for 1 hour, where the solution turned from purple to brown. 4-Bromoanisole (0.188 mL, 1.5 mmol), anisidine (0.222 g, 1.8 mmol) and NaO^tBu (0.202 g, 2.1 mmol) were added in succession and the reaction was stirred at 80 °C for 2 hours. Samples (0.2 mL) were taken with a 1 mL syringe periodically, diluted to 10.0 mL with toluene and analyzed by GC.

2.6.1.2 Profile of bis(4-methoxyphenyl)amine formation using Pd_2dba_3 + XPhos as Catalyst

Performed in triplicate. In a test tube under argon, Pd_2dba_3 (0.0155 g, 0.015 mmol) and XPhos (0.0286 g, 0.060 mmol) were dissolved in toluene (3 mL). 4-Bromoanisole (0.188 mL, 1.5 mmol), anisidine (0.222 g, 1.8 mmol) and

NaO^tBu (0.202 g, 2.1 mmol) were added in succession and the reaction was stirred at 80 °C for 2 hours. Samples (0.2 mL) were taken with a 1 mL syringe periodically, diluted to 10.0 mL with toluene and analyzed by GC.

2.6.2 Synthesis of bis(4-methoxyphenyl)amine from 4-chloroanisole and anisidine

2.6.2.1 Synthesis of bis(4-methoxyphenyl)amine using I + XPhos as Catalyst

In a test tube under argon, I (0.0029 g, 0.010 mmol) and XPhos (0.0095 g, 0.020 mmol) were dissolved in toluene (1 mL) and stirred at 80 ºC for 1 hour, where the solution turned from purple to brown. 4-Chloroanisole (0.061 mL, 0.5 mmol), anisidine (0.0862 g, 0.7 mmol) and NaO^tBu (0.0576 g, 0.6 mmol) were added in succession and the reaction was stirred at 80 °C for 18 hours. The reaction was diluted with Et_2O (10 mL), filtered through a plug of Celite and evaporated to give a brown oil, which crystalized upon standing for several hours. The crystalline material was taken up in Et_2O, filtered through a silica plug and recrystallized from heptane. Yield: 52 %. ^1H NMR ($CDCl_3$ 300 MHz) δ 7.02 (dd, *J* = 6.9, 2.1 Hz, 4H), 6.84 (dd, *J* = 6.9, 2.1 Hz, 4H), 3.81 (s, 6H). Lit.[9]: ^1H NMR (500 MHz, $CDCl_3$): δ = 6.97 (d, J = 8.9 Hz, 4 H), 6.85 (d, J = 9.0 Hz, 4 H), 5.32 (s, 1 H), 3.79 (s, 6 H) ppm.

2.6.2.2 Synthesis of bis(4-methoxyphenyl)amine using Pd_2dba_3 + XPhos as Catalyst

In a test tube under argon, Pd_2dba_3 (0.052 g, 0.005 mmol) and XPhos (0.0095 g, 0.020 mmol) were dissolved in toluene (1 mL). 4-Chloroanisole (0.061 mL, 0.5 mmol), anisidine (0.0862 g, 0.7 mmol) and NaO^tBu (0.0576 g, 0.6 mmol) were added in succession and the reaction was stirred at 80 °C for 18 hours. The reaction was diluted with Et_2O (10 mL), filtered through a plug of Celite and evaporated to give a brown oil, which crystalized upon standing for several hours. The crystalline material was taken up in Et_2O, filtered through a silica plug and recrystallized from heptane. Yield: 12 %. ^1H NMR ($CDCl_3$ 300 MHz) δ 7.02 (dd, *J* = 6.9, 2.1 Hz, 4H), 6.84 (dd, *J* = 6.9, 2.1 Hz, 4H), 3.81 (s, 6H). Lit.[9]: ^1H NMR (500 MHz, $CDCl_3$): δ = 6.97 (d, J = 8.9 Hz, 4 H), 6.85 (d, J = 9.0 Hz, 4 H), 5.32 (s, 1 H), 3.79 (s, 6 H) ppm.

2.6.2.3 Synthesis of bis(4-methoxyphenyl)amine using $Pd(OAc)_2$ + XPhos as Catalyst

In a test tube under argon, $Pd(OAc)_2$ (0.0045 g, 0.02 mmol) and XPhos (0.0289 g, 0.06 mmol) were dissolved in toluene (2 mL). 4-Chloroanisole (0.124 mL, 1.0 mmol), anisidine (0.148 g, 1.2 mmol) and NaO^tBu (0.134 g, 1.4 mmol) were added in succession and the reaction was stirred at 90 °C for 18 hours. The reaction was diluted with Et_2O (10 mL), filtered through a plug of Celite and evaporated to give a brown oil, which showed only trace product (< 1 %) via GC.

2.6.3 Synthesis of 2-chloro-*N*-(pyridine-3-yl)pyridin-3-amine

2.6.3.1 Synthesis of 2-chloro-*N*-(pyridine-3-yl)pyridin-3-amine using I + XPhos as Catalyst

In a test tube under argon, I (0.0087 g, 0.030 mmol) and XPhos (0.0286 g, 0.060 mmol) were dissolved in toluene (2 mL) and stirred at 70 ºC for 2 hours, where the solution turned from purple to brown. 3-bromo-2-chloropyridine (0.192 g, 1.0 mmol), 3-aminopyridine (0.113 g, 1.2 mmol) and NaO^tBu (0.115 g, 1.2 mmol) were added in succession and the reaction was stirred at 95 °C for 48 hours. The reaction was diluted with Et_2O (10 mL), filtered through a plug of Celite and evaporated to give a brown oil, which was purified on silica gel eluting with 10 % EtOAc/hexanes. Yield 72 %. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 8.70 (d, *J* = 2.8 Hz, 1H), 8.26 (dd, *J* = 4.8, 1.2 Hz, 1H), 8.19 (dq, *J* = 8.4, 1.2 Hz, 1H), 8.12 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.23 (dd, *J* = 8.4, 4.8 Hz, 1H), 7.07 (s, 1H), 6.64 (dd, *J* = 7.6, 4.8 Hz, 1H). Lit.[10]: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 8.70 (d, *J* = 2.8 Hz, 1H), 8.26 (dd, *J* = 4.8, 1.2 Hz, 1H), 8.19 (dq, *J* = 8.4, 1.2 Hz, 1H), 8.12 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.23 (dd, *J* = 8.4, 4.8 Hz, 1H), 7.07 (s, 1H), 6.64 (dd, *J* = 7.6, 4.8 Hz, 1H).

2.6.3.2 Synthesis of 2-chloro-*N*-(pyridine-3-yl)pyridin-3-amine using Pd_2dba_3 + XPhos as Catalyst

In a test tube under argon, Pd_2dba_3 (0.0137 g, 0.015 mmol) and XPhos (0.0286 g, 0.060 mmol) were dissolved in toluene (2 mL). 3-bromo-2-

chloropyridine (0.192 g, 1.0 mmol), 3-aminopyridine (0.113 g, 1.2 mmol) and NaO^tBu (0.115 g, 1.2 mmol) were added in succession and the reaction was stirred at 95 °C for 48 hours. The reaction was diluted with Et_2O (10 mL), filtered through a plug of Celite and evaporated to give a brown oil, which was purified on silica gel eluting with 10 % EtOAc/hexanes. Yield 12 %. ^1H NMR ($CDCl_3$ 400 MHz) δ 8.70 (d, *J* = 2.8 Hz, 1H), 8.26 (dd, *J* = 4.8, 1.2 Hz, 1H), 8.19 (dq, *J* = 8.4, 1.2 Hz, 1H), 8.12 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.23 (dd, *J* = 8.4, 4.8 Hz, 1H), 7.07 (s, 1H), 6.64 (dd, *J* = 7.6, 4.8 Hz, 1H). Lit. [10]: ^1H NMR ($CDCl_3$ 400 MHz) δ 8.70 (d, *J* = 2.8 Hz, 1H), 8.26 (dd, *J* = 4.8, 1.2 Hz, 1H), 8.19 (dq, *J* = 8.4, 1.2 Hz, 1H), 8.12 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.23 (dd, *J* = 8.4, 4.8 Hz, 1H), 7.07 (s, 1H), 6.64 (dd, *J* = 7.6, 4.8 Hz, 1H).

2.6.3.3 Synthesis of 2-chloro-*N*-(pyridine-3-yl)pyridin-3-amine using $Pd(OAc)_2$ + XPhos as Catalyst

In a test tube under argon, $Pd(OAc)_2$ (0.0067 g, 0.03 mmol) and XPhos (0.0286 g, 0.060 mmol) were dissolved in toluene (2 mL). 3-bromo-2-chloropyridine (0.192 g, 1.0 mmol), 3-aminopyridine (0.113 g, 1.2 mmol) and NaO^tBu (0.115 g, 1.2 mmol) were added in succession and the reaction was stirred at 95 °C for 48 hours. The reaction was diluted with Et_2O (10 mL), filtered through a plug of Celite and evaporated to give a brown oil, which showed no product by TLC and only trace (< 1 %) via GC.

2.6.4 Synthesis of *N*-(4-methoxyphenyl)morpholine

2.6.4.1 Synthesis of *N*-(4-methoxyphenyl)morpholine using I + XPhos as Catalyst

In a test tube under argon, I (0.0029 g, 0.01 mmol) and P^tBu_3 (0.0040 g, 0.02 mmol) were dissolved in dioxane (3 mL) and stirred at 75 ºC for 1.5 hours, where the solution turned from purple to brown. 4-Bromoanisole (0.126 mL, 1.0 mmol), morpholine (0.103 g, 1.2 mmol) and NaO^tBu (0.135 g, 1.4 mmol) were added in succession and stirred at 80 °C for 2 hours until 4-Bromoanisole appeared consumed by TLC. The reaction was cooled, filtered and solvent evaporated under reduced pressure. The residue was purified on silica gel eluting with 20% EtOAc/hexanes. Yield: 99 %. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.06 (t, 4H), 3.77 (s, 3H), 3.86 (t, 3H), 6.87 (m, 4H). Lit.[11]: ^{1}H NMR (300MHz, $CDCl_3$): δ 3.03-3.07 (m, 4H, OCH2), 3.77 (s, 3H, OCH3), 3.84-3.87 (m, 4H, NCH2), 6.83-6.94 (m, 4H, Ar).

2.6.4.2 Synthesis of *N*-(4-methoxyphenyl)morpholine using Pd_2dba_3 + XPhos as Catalyst

In a test tube under argon, Pd_2dba_3 (0.0045 g, 0.005 mmol) and P^tBu_3 (0.0040 g, 0.02 mmol) were dissolved in dioxane (3 mL). 4-Bromoanisole (0.126 mL, 1.0 mmol), morpholine (0.103 g, 1.2 mmol) and NaO^tBu (0.135 g, 1.4 mmol) were added in succession and stirred at 80 °C for 2 hours. The reaction was cooled, filtered and solvent evaporated under reduced pressure. The residue was

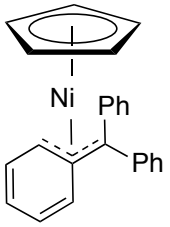
purified on silica gel eluting with 20% EtOAc/hexanes. Yield: 48 %. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.06 (t, 4H), 3.77 (s, 3H), 3.86 (t, 3H), 6.87 (m, 4H). Lit.[11]: ^{1}H NMR (300MHz, $CDCl_3$): δ 3.03-3.07 (m, 4H, OCH2), 3.77 (s, 3H, OCH3), 3.84-3.87 (m, 4H, NCH2), 6.83-6.94 (m, 4H, Ar).

2.6.4.3 Synthesis of *N*-(4-methoxyphenyl)morpholine using $Pd(OAc)_2$ + XPhos as Catalyst

In a test tube under argon, $Pd(OAc)_2$ (0.0022 g, 0.01 mmol) and P^tBu_3 (0.0060 g, 0.03 mmol) were dissolved in dioxane (3 mL). 4-Bromoanisole (0.126 mL, 1.0 mmol), morpholine (0.103 g, 1.2 mmol) and NaO^tBu (0.135 g, 1.4 mmol) were added in succession and stirred at 80 °C for 2 hours. The reaction was cooled, filtered and solvent evaporated under reduced pressure. The residue was purified on silica gel eluting with 20% EtOAc/hexanes. Yield: 73 %. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.06 (t, 4H), 3.77 (s, 3H), 3.86 (t, 3H), 6.87 (m, 4H). Lit.[11]: ^{1}H NMR (300MHz, $CDCl_3$): δ 3.03-3.07 (m, 4H, OCH2), 3.77 (s, 3H, OCH3), 3.84-3.87 (m, 4H, NCH2), 6.83-6.94 (m, 4H, Ar).

2.7 Synthesis of Ni compounds

2.7.1 Synthesis of (η^5-Cp)(η^3-benzyl-7,7-diphenyl)nickel (II)



This compound was prepared according the procedure described by Pasynkiewicz *et al*.[12] Under an atmosphere of argon, to a solution of triphenylmethane (3.0 g, 12.5 mmol) in THF (25 mL) was added dropwise n-BuLi (4.92 mL of 2.5 M in hexanes, 12.3 mmol) at – 78 °C. The reaction was allowed to slowly warm to room temperature overnight to produce a deep red mixture. The solution was then added dropwise to a solution of $NiCp_2$ (1.65 g, 8.73 mmol) in THF (45 mL) at – 78 °C and stirred overnight. The reaction was filtered through activated basic alumina, solvent removed under reduced pressure and recrystallized from hexanes at 0 °C. Yield: 2.16 g, 67 %. ^{1}H NMR (C_6D_6, 500 MHz): δ 4.94 (s, 5H), 6.18 (d, 2H), 6.96-7.10 (m, 9H), 7.37 (d, 4H). Lit.[12]: ^{1}H NMR (THF-d_8) 7.30–7.15 (m, 13H, H aromatic), 6.15 (m, 2H), 4.93 (s, 5H, Cp).

2.7.2 Reactions of (η^5-Cp)(η^3-benzyl-7,7-diphenyl)nickel with Various Phosphines

In a glovebox, (η^5-Cp)(η^3-benzyl-7,7-diphenyl)nickel (0.0035 g, 0.0095 mmol) and a phosphine (P^tBu_3, P^tBu_2Me, PCy_3, PBu_3, PPh_3, $PMePh_2$, PMe_2Ph,

PEt_3) (0.019 mmol) were dissolved in toluene-d_8 (0.6 mL) in an NMR tube. The sample was placed into an NMR probe preheated to 75 °C and analyzed by ^{1}H and ^{31}P NMR over the course of several hours.

2.8 References

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Chapter 3

Results and Discussion

Previous work by Norton *et al.* has shown Pd(η^3-1-Ph-C_3H_4)(η^5-C_5H_5) (**I**) to be a superior precursor to PdL_2 to other commonly used pre-catalysts mentioned in Chapter 1 because of its ability to form Pd(0) quantitatively.[1] Shown via a series of ^1H and ^{31}P NMR experiments in toluene-d_8, **I** reacts with various phosphines via reductive elimination of the Cp and 1-phenylallyl substituents to form stoichiometric amounts of the bis-ligated PdL_2 compound (Figure 2).

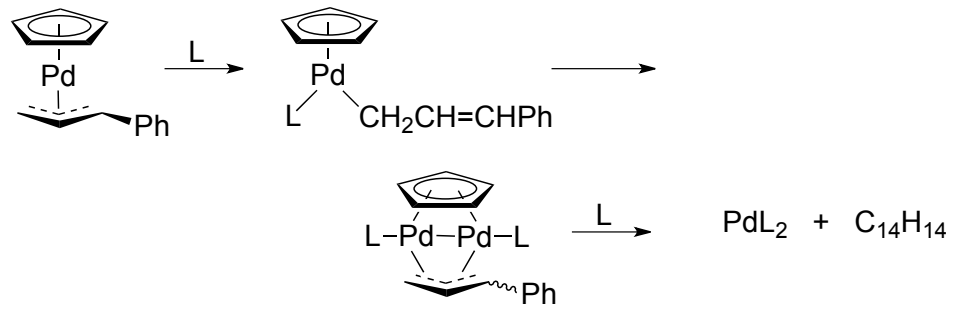

Figure 2. Reaction of I with two equivalents of phosphine to produce PdL_2.[1]

From a practical standpoint, it is easily synthesized and purified, and is air and thermally stable. It also avoids the disadvantages of other precusors such as $Pd(PPh_3)_4$ (low activity as PdL_3 is dominant species in solution), Pd_2dba_3 (dba is not completely displaced by phosphines) and Pd(II) salts (extent of reduction to Pd(0) is not known). It is, therefore, reasonable to expect that **I** would be a much

more competent precatalyst for reactions catalyzed by species of the type $Pd(0)L_2$.

3.1 Suzuki-Miyaura Coupling

To compare the ability of **I** to effect Suzuki-Miyaura coupling with commonly used precursors, a model reaction was selected whereby 4-methoxy-1,1'-biphenyl was formed via cross-coupling of 4-bromoanisole and phenylboronic acid. (Figure 3).

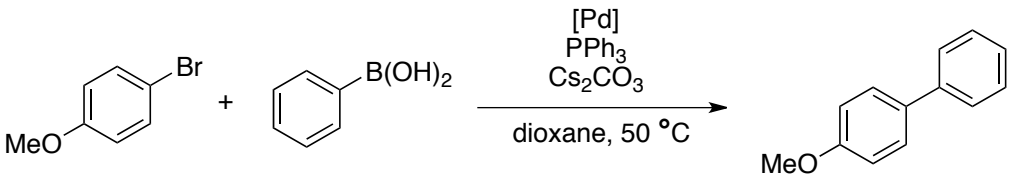

Figure 3. Suzuki-Miyaura coupling of 4-bromoanisole and phenylboronic acid.

The reaction conditions chosen were as follows: 4-bromoanisole (0.5 M) and phenylboronic acid (0.5 M) were reacted in dioxane at 50 °C in the presence of 5 mol% catalyst, 10 mol% PPh_3, and 2 equivalents of Cs_2CO_3. The reason for the selection of coupling partners was twofold; 4-bromoanisole is a more difficult coupling partner than bromobenzene due to the *para*-methoxy group and therefore should better distinguish subtle differences in efficacies of the various precursors. In addition, by employing a substituted aryl halide, we were able to distinguish between the desired product and the homocoupling byproduct,

biphenyl. Under these conditions, **I** was found to generate a 62% isolated yield of 4-methoxy-1,1'-biphenyl after 24 hours. The length at which the reaction was allowed to proceed was, however, arbitrary, and does not give any information about how quickly the reaction requires to reach the maximum. We believed this method is thus a poor technique to compare the relative reaction rates of various precatalysts, and periodic reaction monitoring to give a reaction profile would allow access to a great deal of information and would give a better idea of how a reaction proceeds. The following comparisons are displayed as such, allowing easy visualization of the rates of which substrates are converted to product(s).

3.1.1 Cross-coupling of 4-Bromoanisole with Phenylboronic acid Utilizing PPh_3 as a Ligand

The initial reaction profiles were obtained by repeating the reaction in Figure 3 with three different palladium sources, **I**, $Pd(PPh_3)_4$ and $Pd(OAc)_2$. By analyzing periodic samples by GC, plots of conversion versus time were generated. (Figure 4)

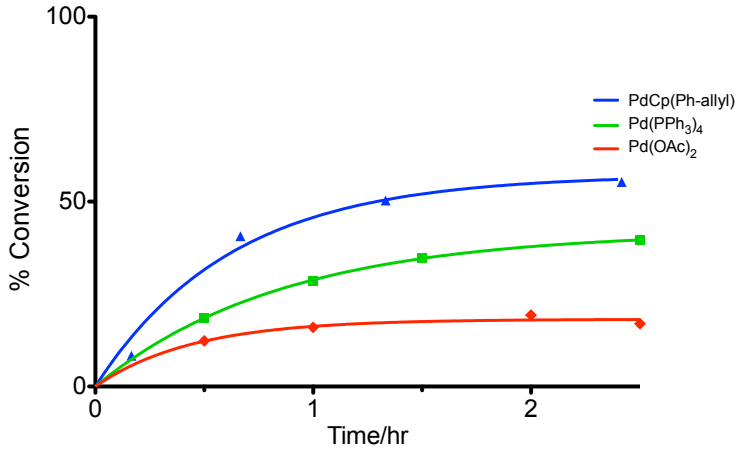

Figure 4. Yield of 4-methoxy-1,1′-biphenyl from the cross-coupling of phenylboronic acid and 4-bromoanisole catalyzed by 5 mol% Pd catalyst systems utilizing I + 2PPh_3, $Pd(PPh_3)_4$, and $Pd(OAc)_2$ + 3PPh_3.

All three reactions were run in triplicate, and in general, the sum of reactants and products were equal to 100%, indicating a good mass balance.

It is quite obvious that $Pd(OAc)_2$ is ineffective for this transformation. This may be due to in part to sluggish reduction of Pd(II) to Pd(0) under these conditions. Successful reactions that employ this precursor generally involve higher reaction temperatures and longer reaction times.[2-5] There is also a common belief that the addition of water is responsible for the reduction to occur, although it has been shown that the rate-determining step toward the formation of Pd(0) from $Pd(OAc)_2(PPh_3)_2$ is an inner-sphere reduction and that the role of water is to convert the oxidized phosphorus species to $O=PPh_3$.[6-10] Amatore and Jutand have shown that $Pd(OAc)_2$ reacts with an excess of PPh_3 to form a Pd(0)

complex that can react via oxidative addition with an aryl halide.[6,7,11] $Pd(OAc)_2$ in the presence of only 2 equivalents of PPh_3 generates a Pd(0) complex that is not stable in solution, but a stable complex can be generated in the presence of an excess (5 equivalents) of PPh_3.[6] The reduction of Pd(II) takes places via an intramolecular reaction of $Pd(OAc)_2(PPh_3)_2$ with the role of excess PPh_3 ligands being to stabilize the resultant Pd(0) complex (Figure 5).[6,7]

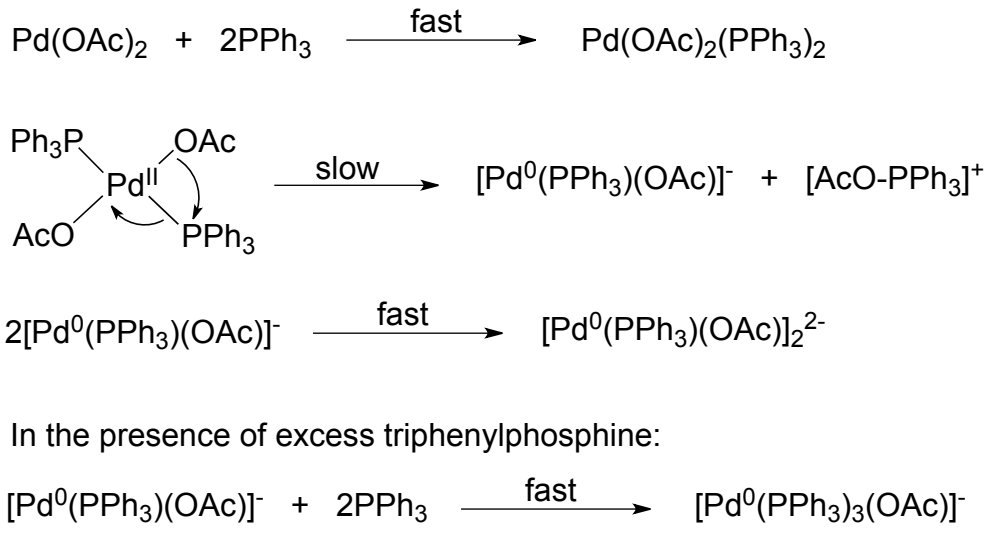

Figure 5. Intramolecular reduction of $Pd(OAc)_2$ by PPh_3 to form Pd(0).[6,7]

The formation of triphenylphosphine oxide from reaction of the corresponding phosphonium acetate with water is shown in Figure 6.

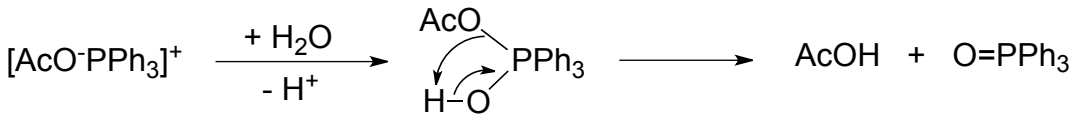

Figure 6. Formation of triphenylphosphine oxide from phosphonium acetate.[7]

In order to assess this claim, we repeated the reaction utilizing $Pd(OAc)_2$ in 20% aqueous dioxane and obtained a reaction profile essentially identical to that using anhydrous dioxane. These findings confirmed that the intrinsic nature of the $Pd(OAc)_2/PPh_3$ system was not affected by the use of anhydrous conditions.

The other frequently used catalyst precursor, $Pd(PPh_3)_4$, exhibited somewhat greater activity, reaching ~40% conversion after 2.5 h. **I** was clearly the most effective of the three, exhibiting a higher initial rate and producing a higher yield of product over the course of the experiment. The observation that the reaction rate leveled off well before 100% conversion will be discussed below. Note that use of **I** alone, without added phosphine, was ineffective.

3.1.2 Cross-coupling of 4-Bromoanisole with Phenylboronic acid Utilizing PCy_3 as a Ligand

The second comparison study involved cross-coupling of the same substrates, substituting PPh_3 with PCy_3 as the phosphine. PCy_3 has been shown to be an effective phosphine for a variety of cross-coupling reactions when employed with a variety of palladium precursors.[12-16] As can been seen in Figure 7, the $PCy_3/Pd(OAc)_2$ system gave only trace amounts of product, suggesting that PCy_3 is a poor reducing agent under these conditions.

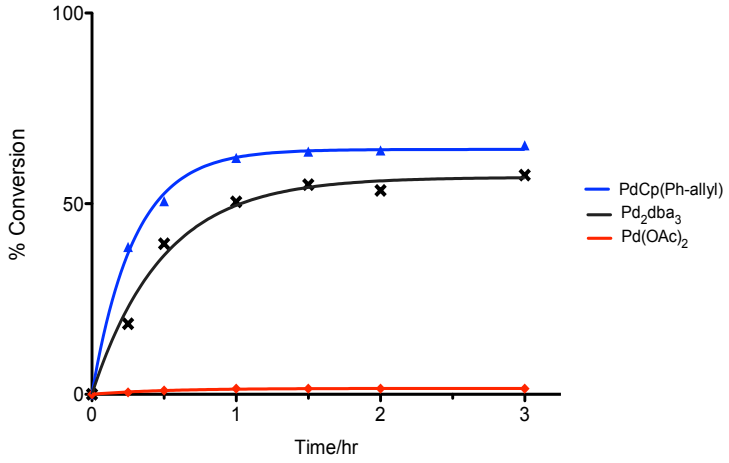

Figure 7. Yield of 4-methoxy-1,1′-biphenyl from the cross-coupling of phenylboronic acid and 4-bromoanisole catalyzed by 5 mol% Pd catalyst systems utilizing I + 2PCy_3, 0.5Pd_2dba_3 + 2PCy_3, and $Pd(OAc)_2$ + 3PCy_3.

It must be noted that effective transformations that utilize $PCy_3/Pd(OAc)_2$ are typically performed at much higher temperatures.[12-16] In addition, as with catalysts based on PPh_3, water is frequently (but not always) added to PCy_3,[12-16] although the possible role(s) of water with ligands L other than triarylphosphines have not been thoroughly determined. Water has been reported to be necessary for the reduction of $Pd(OAc)_2$ by the bidentate phosphine binap,[17] but a subsequent investigation involving reduction by another bidentate phosphine, dppp, revealed that intramolecular reduction by coordinated dppp occurs, as with PPh_3, but that the redox reaction is reversible. The water serves merely to shift the equilibrated reaction to completion.[18] Water is apparently not required in reactions involving $Pd(OAc)_2$ activation by P^nBu_3,[19,20] PMe_2Ph,[7] and $PMePh_2$,[7]

but as with the $PPh_3/Pd(OAc)_2$ system, a cross-coupling reaction was carried out in 20% aqueous dioxane. Only a 4% yield of coupled product was obtained after 3 h, and thus again the added water had no effect on the yield of the cross-coupling reaction. Catalyst precursors Pd_2dba_3 and **I** resulted ultimately in higher, comparable conversions, but use of the latter resulted in a higher initial rate of coupling and **I** is certainly more effective at short reaction times. As with the PPh_3 system, the reactions did not go to completion.

3.1.3 Cross-coupling of 4-Bromoanisole with Phenylboronic acid Utilizing P^tBu_3 as a Ligand

The bulky, strongly electron-donating P^tBu_3, which is normally very effective,[12-15,21] was next employed to further comparisons of **I** with conventional palladium catalyst precursors (Figure 8). As was found with the $Pd(OAc)_2/PPh_3$ and $Pd(OAc)_2/PCy_3$ systems, the palladium(II)-based catalyst systems $Pd(OAc)_2/P^tBu_3$ and $PdCl_2/P^tBu_3$ exhibited low efficacies, although in this case the use of aqueous dioxane with $Pd(OAc)_2$ resulted in a higher conversion (48%) after 2.5 h.

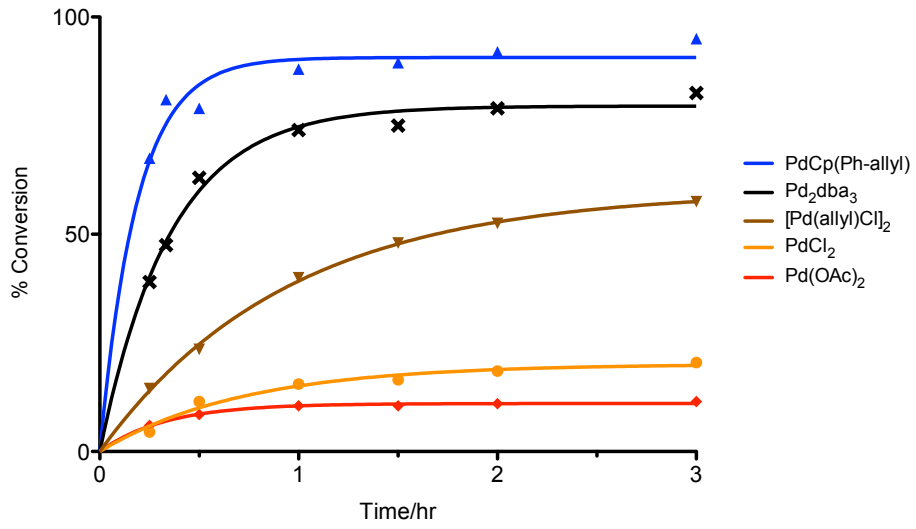

Figure 8. Yield of 4-methoxy-1,1′-biphenyl from the cross-coupling of phenylboronic acid and 4-bromoanisole catalyzed by 5 mol% Pd catalyst systems utilizing I + 2P^{t}Bu$_3$, 0.5Pd$_2$dba$_3$ + 2P^{t}Bu$_3$, 0.5[Pd(η^3-C$_3$H$_5$)Cl]$_2$ + 2P^{t}Bu$_3$, PdCl$_2$ + 3P^{t}Bu$_3$, and Pd(OAc)$_2$ + 3P^{t}Bu$_3$.

Interestingly, a ^{31}P NMR investigation of the Pd(OAc)$_2$/P^{t}Bu$_3$ reaction mixture indicated that one of the major palladium species in solution was a cyclometallated complex of the type reported previously (δ -9.04 ppm) (Figure 9).[22,23]

Figure 9. Cyclometallation of Pd(OAc)$_2$ and P^{t}Bu$_3$.[23]

Stambuli *et al.* have investigated in depth the reaction of Pd(OAc)$_2$ with

P^tBu_3, and found that cyclometallation takes place rapidly at 23 °C. Reduction to the catalytically active $Pd(P^tBu_3)_2$ requires much higher temperatures however, forming via thermal decomposition after heating in toluene at 90 °C for 12 hr.[23] The ^{31}P NMR spectrum (Figure 10) also exhibited resonances at δ 65.5 (s), 62.2 (s), and 51.7 (w), possibly indicating the presence of free P^tBu_3[24] and $[Pd(C_6H_4OMe)(\mu\text{-}Br)(P^tBu_3)]_2$ (Figure 11), the product of oxidative addition of 4-bromoanisole to $Pd(P^tBu_3)_2$;[21] there was no evidence for $Pd(P^tBu_3)_2$ (δ 84.7).[24]

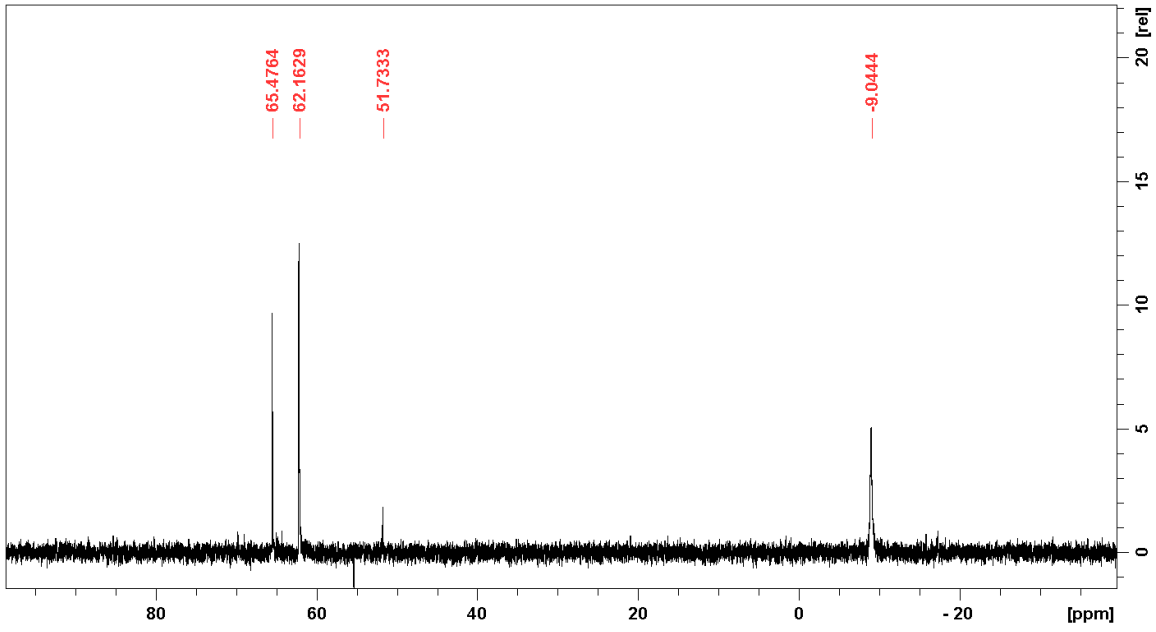

Figure 10. ^{31}P NMR spectrum of the crude reaction utilizing $Pd(OAc)_2$ shown in Figure 8.

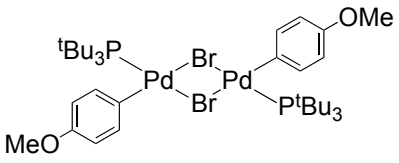

Figure 11. The product of oxidative addition of 4-bromoanisole to $Pd(P^tBu_3)_2$.[21]

The catalyst systems based on $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and Pd_2dba_3 exhibited somewhat better activities, but the use of **I** resulted clearly in a higher initial rate of coupling and higher conversions over all time periods. Near-quantitative conversion to 4-methoxy-1,1'-biphenyl was achieved within 1 h using **I**.

3.1.4 Phenylboronic Acid Degradation

As indicated in Figures 2-4, the profiles of those reactions, which were not essentially completed within 1 h, tended to level off after about 1 h. In an effort to determine whether this behavior was a result of catalyst deactivation or of side reactions involving the phenylboronic acid, an experiment was carried out involving the **I**/PPh_3 catalyst system, analogous to that shown in Figure 1. After about 2 h, at which point cross-coupling had definitely ceased, an additional 1 equiv of phenylboronic acid was added to the reaction mixture. As is shown in Figure 12, cross-coupling continued and thus the problem clearly did not involve catalyst deactivation.

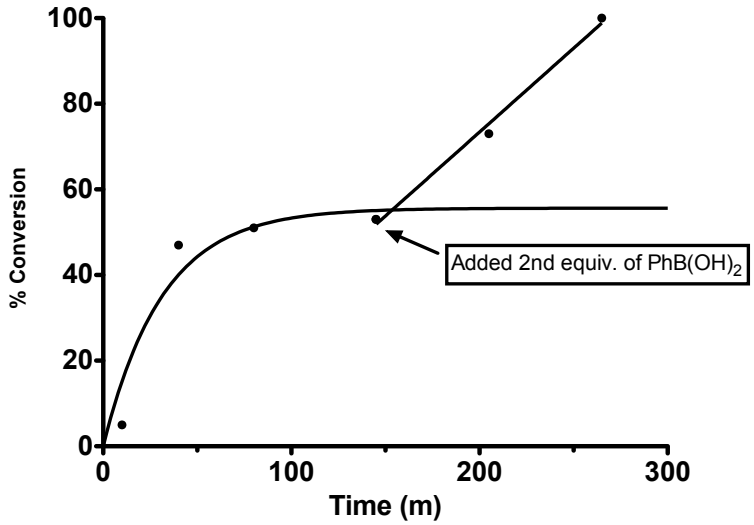

Figure 12. Yield of 4-methoxy-1,1′-biphenyl from the cross-coupling of phenylboronic acid and 4-bromoanisole catalyzed by 5 mol % I; another 1 equiv of phenylboronic acid was added after 3 h.

Interestingly, if phenylboronic acid is present in a 2- or 3-fold molar excess of phenylboronic acid at the beginning of a reaction, essentially quantitative yield of cross-coupling product is formed within 1 h (Figure 13).

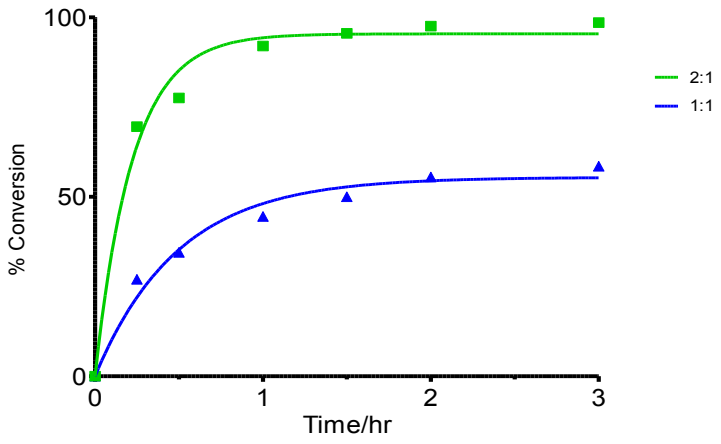

Figure 13. Yield of 4-methoxy-1,1′-biphenyl from the cross-coupling of 4-bromoanisole and phenylboronic acid (1 and 2 equiv) catalyzed by 5 mol % I.

This finding is rather surprising, as it means that the **I**/PPh_3 catalyst system may be comparable in activity to the I/P^tBu_3 catalyst system if phenylboronic acid is present in excess.

In any case, these results indicate that the originally added phenylboronic acid was for some reason no longer available for cross-coupling after about 1 h and a brief investigation of possible mode(s) of deterioration to less active species was carried out. Moreno-Mañas et al. have identified several side reactions of phenylboronic acid which can occur during Suzuki−Miyaura cross-coupling reactions,[25] including protodeboronation to give benzene, homocoupling to give biphenyl, hydroxylation to give phenol, and dehydration to give phenylboroxine (Figure 14).

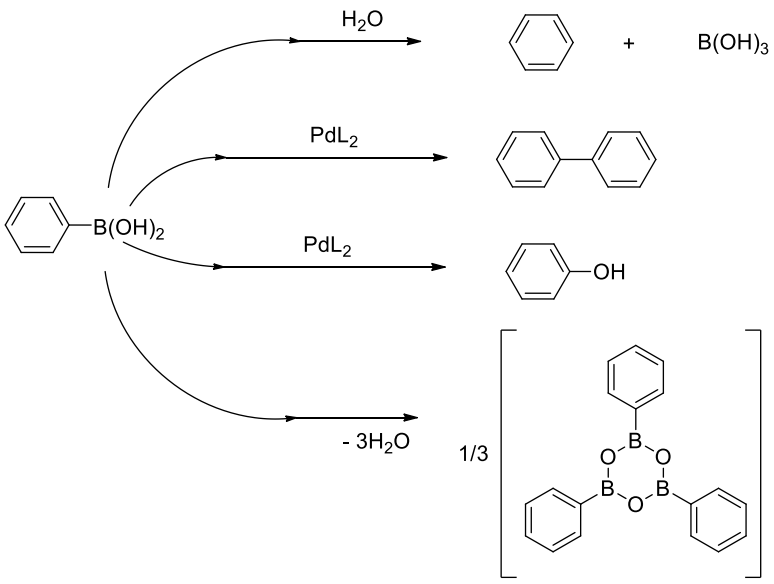

Figure 14. Degradation pathways of phenylboronic acid.[25]

In general, our GC studies did not reveal the presence of benzene as a byproduct and yields of biphenyl and phenol were too low (< 5%) to account for the discrepancies. Phenylboroxine has been reported to exhibit relatively low cross-coupling activity in other systems,[26,27] and we found that it is indeed much less effective than is phenylboronic acid in its ability to cross-couple with 4-bromoanisole. When employed in lieu of phenylboronic acid (Figure 15), freshly synthesized phenylboroxine leads to ~ 50% conversion after 3 h with the **I**/P^tBu_3 system, (Figure 16) and only ~ 20% conversion with the **I**/PPh_3 system (Figure 17).

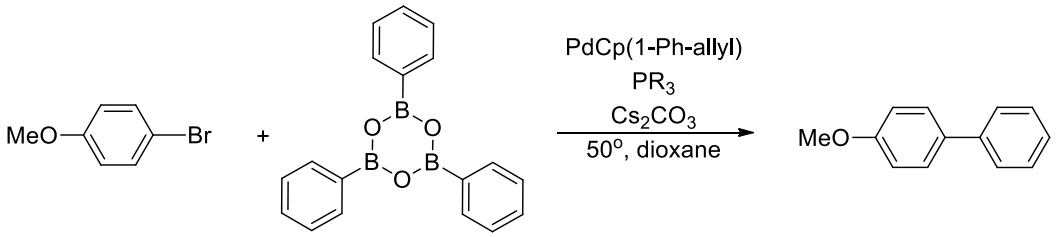

Figure 15. Cross-coupling of 4-bromoanisole and phenylboroxine utilizing I as a source of Pd.

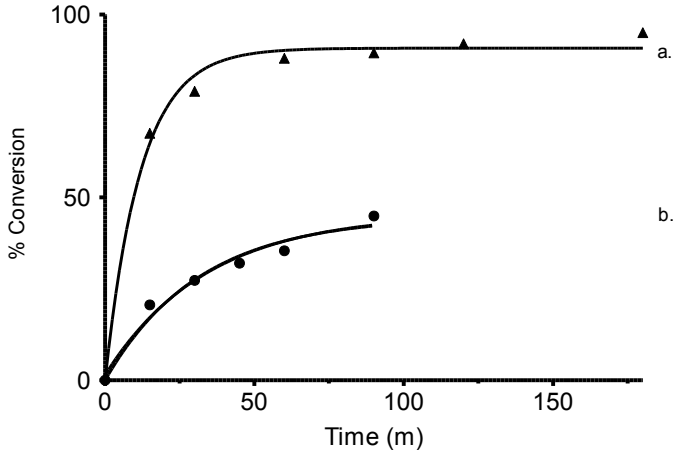

Figure 16. Cross-coupling of 4-bromoanisole and a) phenylboronic acid, or b) phenylboroxine utilizing I/2P^{t}Bu$_3$ catalyst system.

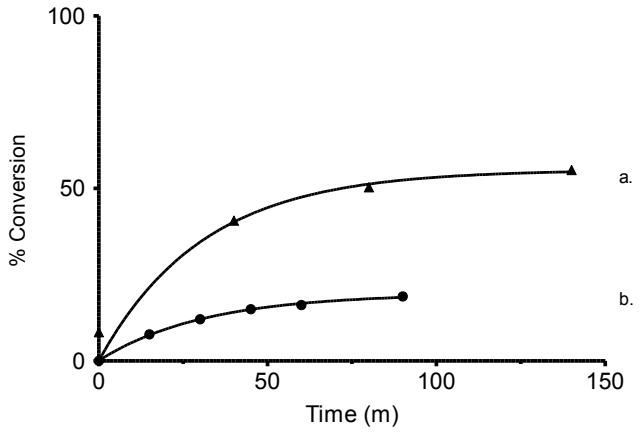

Figure 17. Cross-coupling of 4-bromoanisole and a) phenylboronic acid, or b) phenylboroxine utilizing I/2PPh_3 catalyst system.

As phenylboroxine is likely to be formed at the temperature used in the cross-coupling experiments,[28] we initially considered the possibility that dehydration of the phenylboronic acid was the reason for the lowering of activity. This hypothesis was dispelled, of course, when it was shown that water has no effect on the efficacy of the $Pd(OAc)_2/PPh_3$ or $Pd(OAc)_2/PCy_3$ systems. Thus, added water enhances neither the reduction of $Pd(OAc)_2$ nor the concentration of active phenyl-boron species.

However, there is a strong sense in the literature that unexpectedly facile dehydration of phenylboronic acid can result in the presence of phenylboroxine impurities,[29-32] presumed to decrease reactivity; water is therefore frequently added to commercial phenylboronic acid reaction mixtures in an attempt to convert any phenylboroxine present to phenylboronic acid.[27,33] To the contrary,

however, Tokunaga et al. have provided an alternative scenario. They find that the exchange process between phenylboronic acid and phenylboroxine (Figure 18) occurs sufficiently slowly on the NMR time scale that the ^1H chemical shifts are readily distinguishable.[34]

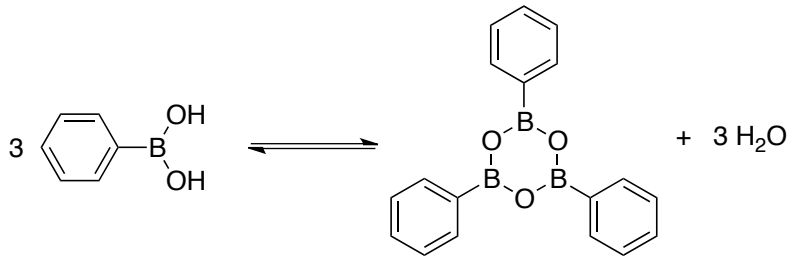

Figure 18. Equilbrium between phenylboronic acid and phenylboroxine.

Using the NMR data, K for the equilibrium shown was determined in $CDCl_3$ and found to be such that a solution of phenyboronic acid over a range of temperatures actually contains about 75% or more of the phenyl-boron moieties present as phenylboroxine.

A new bottle of phenylboronic acid was purchased (Strem Chemicals, min 97%), and an IR spectrum was acquired as a Nujol mull. As can be seen in Figure 19, an –OH stretching frequency at 3247 cm^{-1} and what is thought to be a B-OH stretching at 691 cm^{-1} demonstrates that the bottle indeed contains pure phenylboronic acid.[35] An IR spectrum of freshly prepared phenylboroxine (Figure 20) showns an absence of an –OH stretching frequency, and a new band at 702 cm^{-1}, which is thought to arise from B-O-B stretching in phenylboroxine.[35] An examination of a sample of phenylboronic acid by ^1H NMR spectroscopy in an

anhydrous NMR solvent reveals the presence of a very large proportion of phenylboroxine (Figure 21), suggesting incorrectly that the sample is initially badly contaminated (and probably leading to the aforementioned attempts to suppress dehydration of phenylboronic acid by adding water).

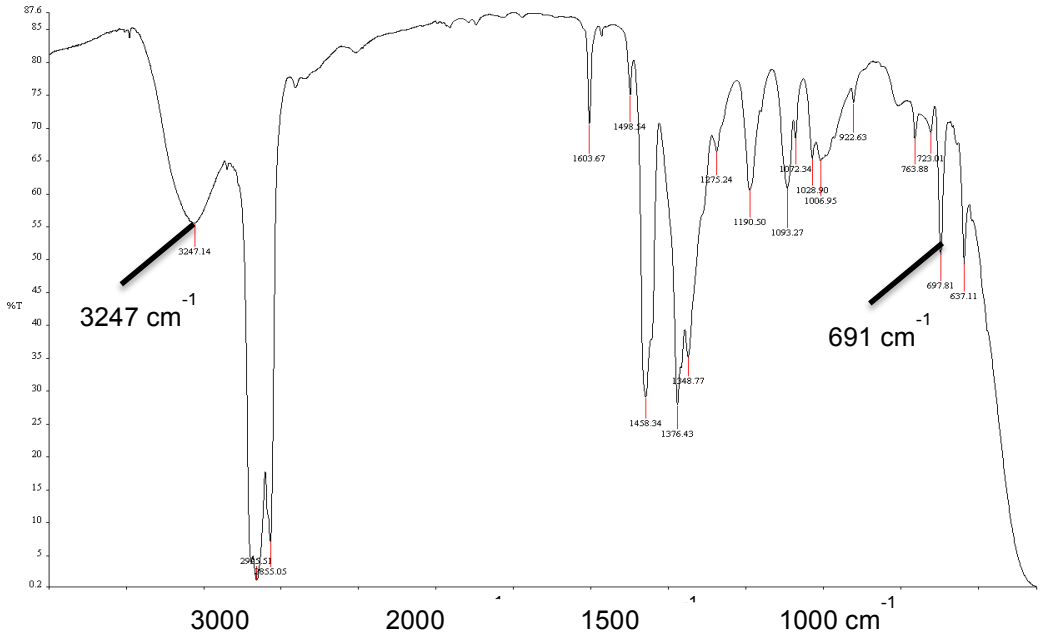

Figure 19. IR spectrum of phenylboronic acid prepared as a Nujol mull.

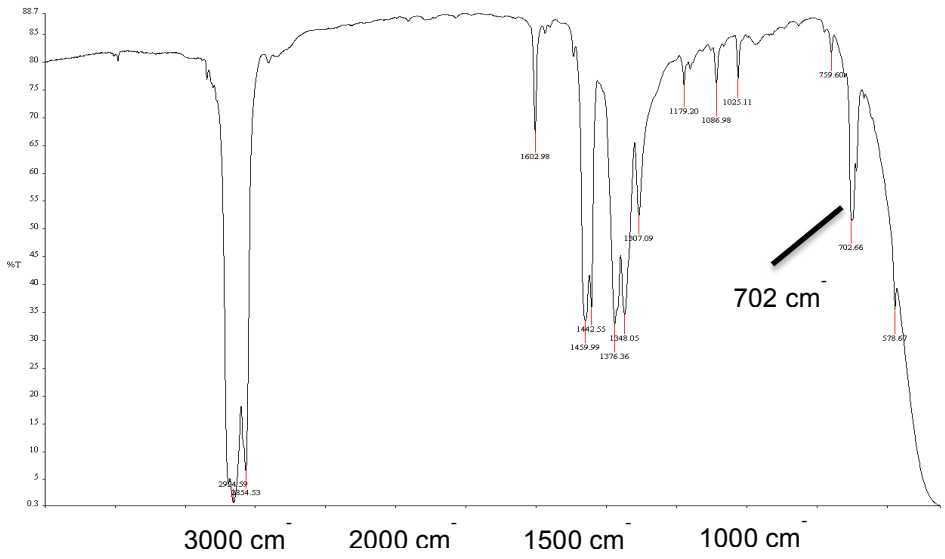

Figure 20. IR spectrum of phenylboroxine prepared as a Nujol mull.

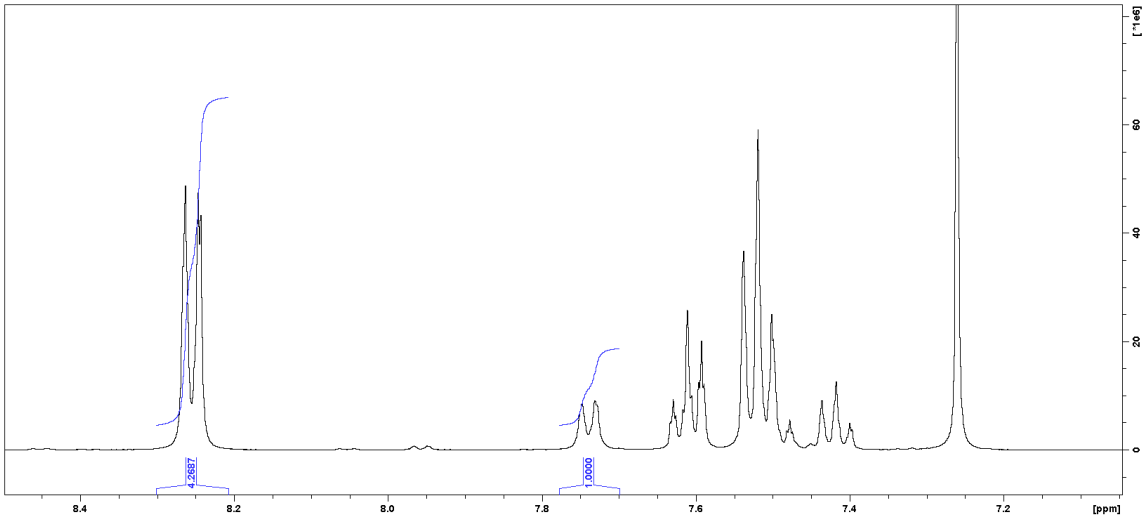

Figure 21. ^{1}H NMR spectrum of phenylboronic acid in $CDCl_3$.

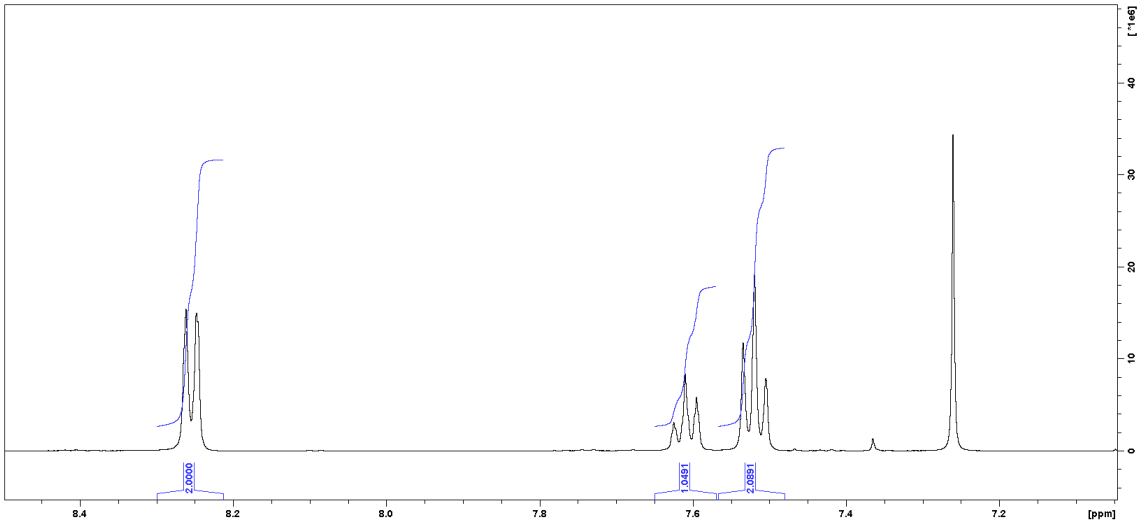

Figure 22. ^{1}H NMR spectrum of phenylboroxine in $CDCl_3$.

One can distinguish between the aromatic protons of phenylboronic acid and phenyboroxine by examining a ^{1}H NMR spectrum of pure phenylboroxine in anhydrous $CDCl_3$ (Figure 22), as the *ortho*- protons are found at δ 7.75 and 8.25 ppm respectively.

In the case of cross-coupling experiments, added water is therefore not required to **"**restore**"** the dehydrated phenylboronic acid, as the equilibrium of phenylboronic acid to phenylboroxine (Figure 18) shifts to the left as phenylboronic acid is consumed via e.g. transmetalation. That said, it seemed clear that the phenylboronic acid present in the above reaction mixtures must be deteriorating in some way, and an ^{1}H NMR spectrum was obtained of a typical reaction mixture containing phenylboronic acid and cesium carbonate in dioxane. Although phenyboronic acid and phenylboroxine were present in the expected

proportions in a freshly prepared solution, addition of cesium carbonate resulted in the ^{1}H resonances of both being quickly replaced by resonances of at least six new phenyl-containing compounds (o-H doublets at **δ** 7.47, 7.67, 7.73, 7.83, 7.89, 7.98) (Figure 23).

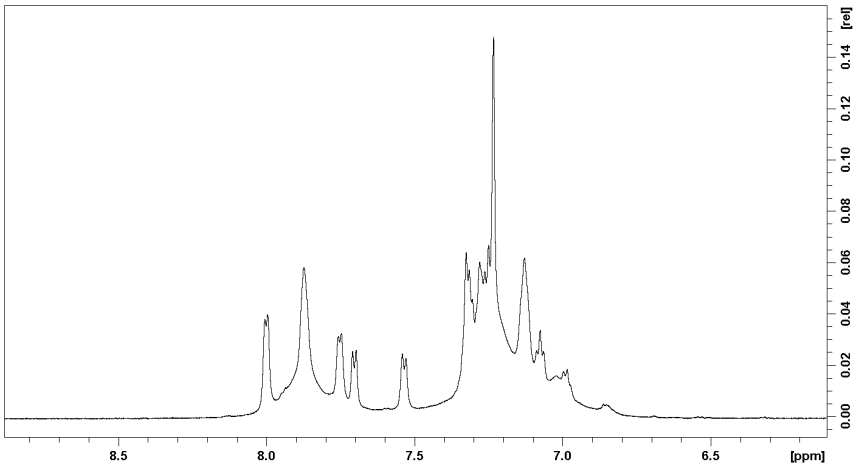

Figure 23. ^{1}H NMR spectrum of phenylboronic acid and Cs_2CO_3 in dioxane after heating to 50 °C followed by cooling to 25 °C.

Brief heating to 50 °C followed by cooling to 25 °C revealed the presence of additional unidentifiable resonances, and the experiment was abandoned, since it seemed very unlikely that identification of the new compounds was possible.

3.2 Mizoroki-Heck Coupling

3.2.1 Cross-coupling of Chloro- and Bromobenzene with Methyl Acrylate

An initial study on the ability of **I** to effect Mizoroki-Heck reactions compared to other commonly used precursors involved the formation of *trans*-methyl cinnamate from methyl acrylate and chlorobenzene (Figure 24).

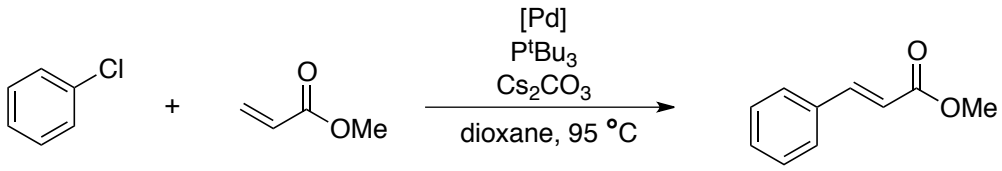

Figure 24. Heck coupling of chlorobenzene and methyl acrylate to form *trans*-methyl cinnamate.

The conditions for this reaction were chosen from a study performed by Littke and Fu,[36] where P^{t}Bu$_3$ was shown as an effective ligand towards aryl chloride activation. In addition, the selection of P^{t}Bu$_3$ was also based on findings in the preceding chapter that this ligand is particularly effective for Suzuki-Miyaura cross-coupling reactions.[36-39] The reaction profiles involving **I**, Pd_2dba_3 and $Pd(OAc)_2$ as palladium sources are shown in Figure 25, each activated with the appropriate amount of phosphine, at 95 °C.

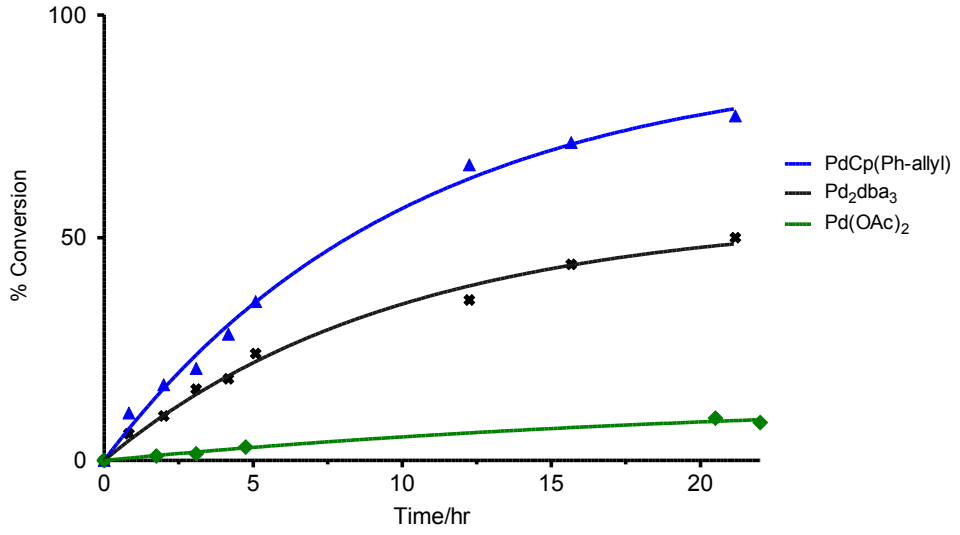

Figure 25. Yield of trans-methyl cinnamate from the cross-coupling of chlorobenzene and methyl acrylate catalyzed by 3 mol% Pd catalyst systems utilizing I + 2P^{t}Bu$_3$, 0.5Pd$_2$dba$_3$ + 2P^{t}Bu$_3$, and Pd(OAc)$_2$ + 3P^{t}Bu$_3$.

As can be seen, catalyst efficacies vary in the order **I**/P^{t}Bu$_3$ > Pd$_2$dba$_3$/P^{t}Bu$_3$ >> Pd(OAc)$_2$/P^{t}Bu$_3$, as was found previously for Suzuki−Miyaura coupling by the same catalyst systems. The Pd(OAc)$_2$/P^{t}Bu$_3$ system is particularly poor at effecting this transformation, which may be due to the preferential formation of the cyclometallated species discussed previously prior to decomposition to the catalytically active Pd(P^{t}Bu$_3$)$_2$. After 22 h, some palladium black was also observed in the reaction tube, also suggesting catalyst decomposition. The Pd$_2$dba$_3$/P^{t}Bu$_3$ catalyst system is moderately effective, leading to 56 % conversion after 22 h. Also of note is that the conversion data obtained utilizing catalyst system are in reasonable agreement, given that

reaction conditions are not precisely identical, with Littke and Fu's work.[36] The **I**/P^{t}Bu$_3$ catalyst system is obviously superior in this case, giving 76 % conversion over the same period, although some palladium metal was also observed at the end of the reaction.

When the less difficult bromobenzene is employed in lieu of chlorobenzene in DMF at 80°C, **I** is by far the most superior catalyst precursor, giving ~90% conversion within 45 min, while catalysts based on Pd_2dba_3 and $Pd(OAc)_2$ resulted in <5% conversion (Figure 26).

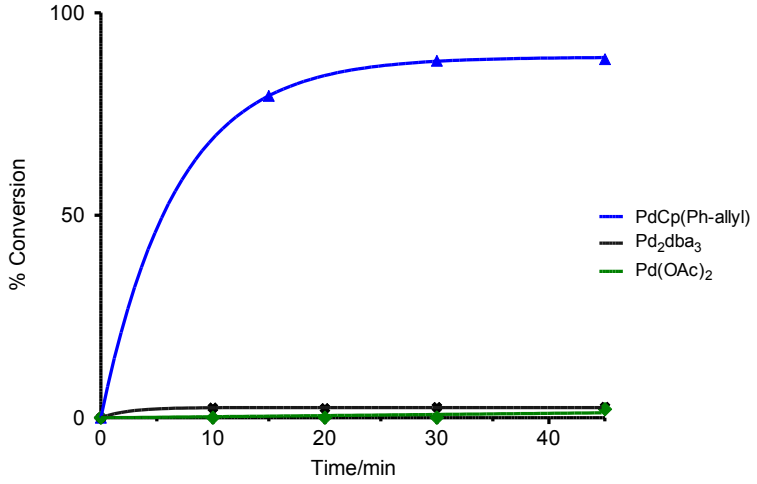

Figure 26. Yield of trans-methyl cinnamate from the cross-coupling of bromobenzene and methyl acrylate catalyzed by 3 mol% Pd catalyst systems utilizing I + 2P^{t}Bu$_3$, 0.5Pd$_2$dba$_3$ + 2P^{t}Bu$_3$, and Pd(OAc)$_2$ + 3P^{t}Bu$_3$.

The increased activity of the **I**/P^tBu_3 system can be attributed to the fact that the actual catalyst, $Pd(P^tBu_3)_2$, is formed in much higher yields by employing **I**, as has been demonstrated in previous Suzuki-Miyaura trials.

3.2.2 Cross-coupling of Bromobenzene with Styrene

Similar results were observed when an analogous cross-coupling study of the synthesis of *trans*-stilbene from bromobenzene and styrene was performed (Figure 27).

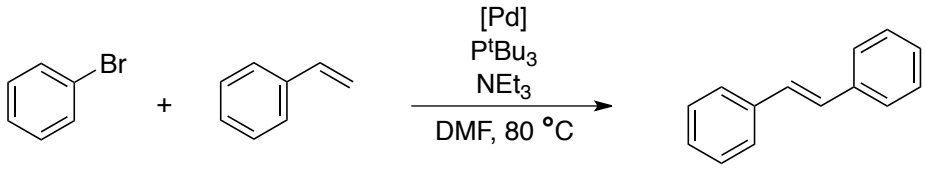

Figure 27. Heck coupling of bromobenzene and styrene to form *trans*-stilbene.

When **I** was employed as a precursor, 96% conversion was achieved within 30 min. Pd_2dba_3 achieved only 30% conversion over the same time frame, taking 1.5 h to to reach completion. In contrast, $Pd(OAc)_2$ produced only trace amounts (<1%) over 30 min, and only 10% after 24 h (Figure 28).

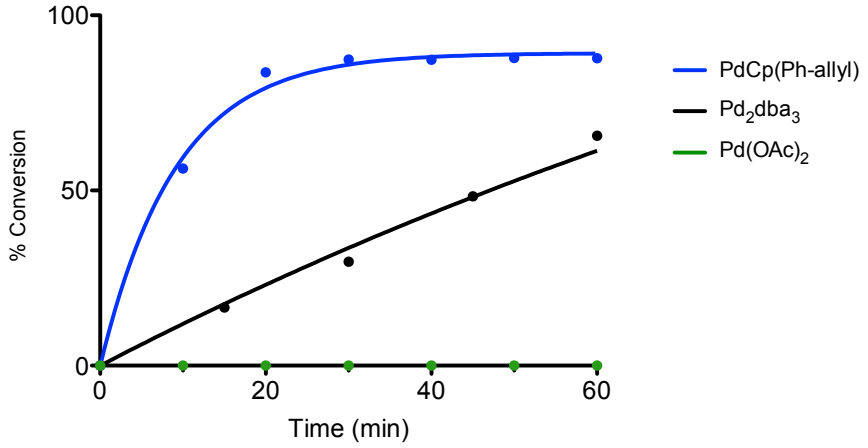

Figure 28. Yield of trans-stilbene from the cross-coupling of bromobenzene and styrene catalyzed by 3 mol% Pd catalyst systems utilizing I + 2P^{t}Bu$_3$, 0.5Pd$_2$dba$_3$ + 2P^{t}Bu$_3$, and Pd(OAc)$_2$ + 3P^{t}Bu$_3$.

3.3 Buchwald-Hartwig Coupling

3.3.1 Cross-coupling of Bromo- and Chlorobenzene with 4-Anisidine

As an extension of our previous work on palladium catalyzed carbon-carbon bond formation reactions, investigations of the capability of **I** to effect carbon-nitrogen bond formation was carried out. The initial trial reaction chosen to differentiate between analogous palladium precursors was the formation of bis(4-methoxyphenyl)amine from 4-bromoanisole and 4-anisidine (Figure 29).

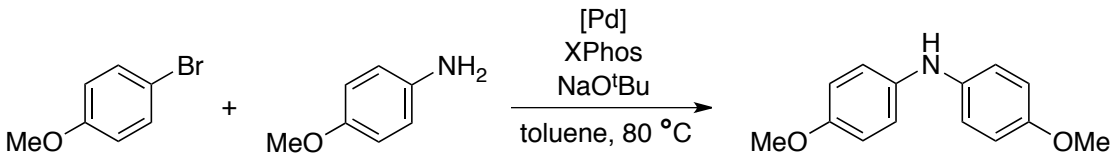

Figure 29. Synthesis of bis(4-methoxyphenyl)amine via Buchwald-Hartwig coupling of 4-bromoanisole and 4-anisidine.

Compounds of this type are of industrial relevance, as they have been shown to be effective antioxidants additive in engine lubricants.[40] XPhos was chosen as a suitable phosphine for the reaction, as it has been shown to be an effective ligand for Buchwald-Hartwig amination reactions.[41-43] Unsurprisingly, **I** was superior to Pd_2dba_3 in it's ability to effect the transformation, achieving near completion after an hour at 80 °C. Pd_2dba_3 achieved ~75% over the same time frame, and took an additional hour to reach completion, as shown in Figure 30.

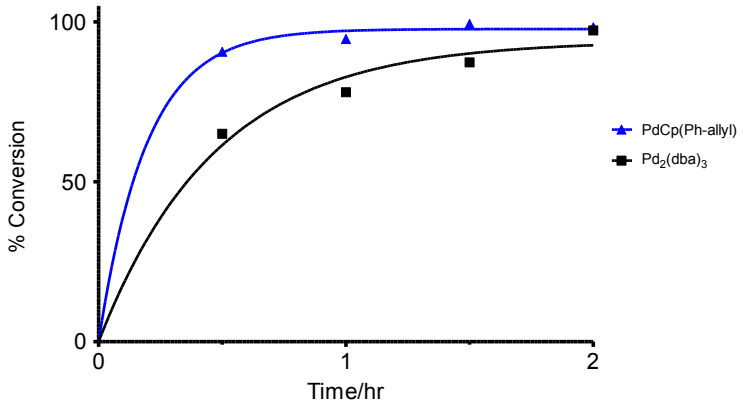

Figure 30. Yield of bis(4-methoxyphenyl)amine from the cross-coupling of 4-bromoanisole and 4-anisidine catalyzed by 3 mol% Pd catalyst systems utilizing I + 2XPhos, 0.5Pd_2dba_3 + 2XPhos.

Synthesis of bis-(4-methoxyphenyl)amine was also carried from the analogous 4-chloroanisole utilizing Pd_2dba_3, $Pd(OAc)_2$ and **I** as precursors (Figure 31).

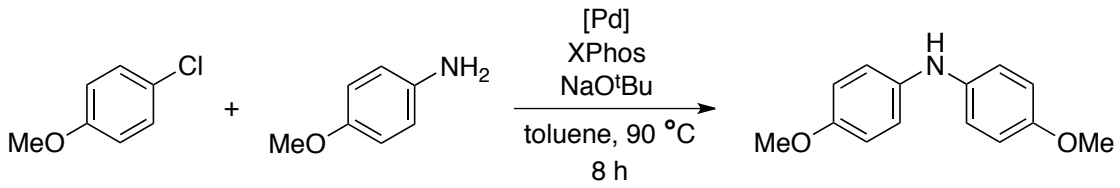

Figure 31. Synthesis of bis(4-methoxyphenyl)amine via Buchwald-Hartwig coupling of 4-chloroanisole and 4-anisidine.

I proved to be superior, affording a 77% isolated yield after 8 h, with Pd_2dba_3 affording only a 56% isolated yield over the same time frame. Interestingly, $Pd(OAc)_2$ afforded only a trace yield that was detected by GC, even when the reaction was left for 18 h.

3.3.2 Cross-coupling of 3-Bromo-2-chloropyridine with 3-Aminopyridine

Buchwald-Hartwig coupling of pyridines is often difficult because of what is believed to be catalyst inactivation by coordination of the pyridine substrate to the metal center.[44-46] The reaction that was chosen to demonstrate the superiority of **I** was the synthesis of 2-chloro-*N*-(pyridine-3-yl)pyridin-3-amine, which was previously reported to be possible in 56% yield from 2-chloro-3-iodopyridine and 3-aminopyridine, but required a prohibitive 15 mol% $Pd(OAc)_2$ and 30 mol%

XanthPhos and refluxing dioxane for 48 hours.[47] Coupling of the more difficult 3-bromo-2-chloropyridine substrate with 3-aminopyridine utilizing XPhos (Figure 32) showed only trace amounts of disubstituted amine product and starting materials after 48 hours when $Pd(OAc)_2$ was employed as a palladium source, and 12 % isolated yield when $Pd_2(dba)_3$ was employed as a palladium source.

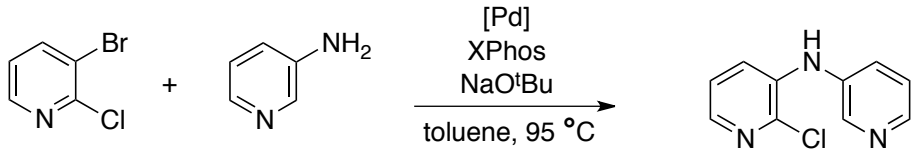

Figure 32. Synthesis of 2-chloro-*N*-(pyridine-3-yl)pyridin-3-amine via Buchwald-Hartwig coupling of 2-chloro-3-bromopyridine and 3-aminopyridine.

Reaction with **I**, however, resulted in a 72 % isolated yield after 48 hours. ESI-MS confirmed that the reaction is selective for coupling at the 3-bromo position over the 2-chloro position, and some palladium black is observed which suggests slight catalyst degradation over the course of the reaction.

3.3.3 Cross-coupling of 4-Bromoanisole with Morpholine

In addition to C-N coupling reactions of primary amines, comparisons of **I** with Pd_2dba_3 and $Pd(OAc)_2$ were also made by coupling to secondary amines. Formation of *N*-(4-methoxyphenyl)morpholine via Buchwald-Hartwig coupling of 4-bromoanisole and morpholine was studied, employing again P^tBu_3 as the phosphine (Figure 33).

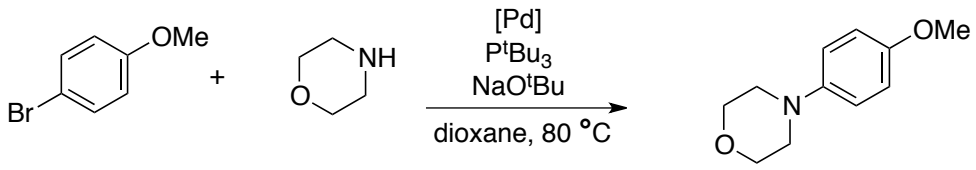

Figure 33. Synthesis of N-(4-methoxyphenyl)morpholine via Buchwald-Hartwig coupling of 4-bromoanisole and morpholine.

When **I** is employed as the palladium source, complete conversion to product is achieved after 2 h, and a 99% isolated yield can be obtained. Interestingly, in this reaction, $Pd(OAc)_2$ is a more competent palladium precursor than Pd_2dba_3, with a 73% isolated yield obtained after the same time period, whereas Pd_2dba_3 manages to only lead to a 48% yield.

3.4 Potential new Ni-based catalysts

Over the past several years, there has been considerable research into employing Ni-based catalysts for cross-coupling reactions especially those involving alkyl substrates, with many reviews recently appearing over the past decade.[48-51] While aryl, vinyl and benzyl halides often oxidatively add readily to PdL_2 species, alkyl halides generally react relatively slowly or not at all. In addition alkylpalladium compounds, once formed, often undergo facile β-hydrogen elimination to alkene and hydrido-palladium byproducts, thereby preempting the desired cross-coupling reaction. Research since about the mid-

1990s has shown that many nickel-based catalysts, circumvent these problems; oxidative additions of alkyl electrophiles proceed relatively quickly, while β-hydrogen elimination reactions proceed more slowly than and thus are often not competitive with reductive elimination steps which yield cross-coupled products.[48-51] $Ni(acac)_2$, $NiCl_2$, $NiBr_2$, and $Ni(cod)_2$ (cod = cyclooctadiene) are most commonly employed as precatalysts,[48-51] although much less research has been carried out to date on the actual catalytic species that are generated *in situ*. It would be reasonable to assume that these Ni precatalysts also have the same inherent drawbacks as their Pd counterparts as discussed previously in this chapter and in Chapter 1. Thus we decided to apply the same methodology towards synthesizing a Ni(II) precursor which might undergo *in situ* formation of quantitative Ni(0) catalysts in the presence of phosphine ligands.

3.4.1 Synthesis of (η^5-Cp)(η^3-benzyl-7,7-diphenyl)nickel

After surveying the literature, (η^5-Cp)(η^3-benzyl-7,7-diphenyl)nickel (**II**) (Figure 34), an 18-electron Ni(II) complex containing both η^5-Cp and η^3-allyl ligands analogous to **I**, was selected as a potential precatalyst towards the formation of Ni(0) catalysts.[52]

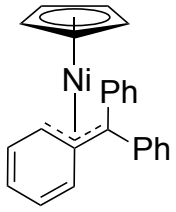

Figure 34. Structure of (η^5-Cp)(η^3-benzyl-7,7-diphenyl)nickel (II).

Although the chemistry of the compound has heretofore been relatively unexplored, it wasn't unreasonable to assume that **II** may very well undergo reductive elimination in the same fashion as **I** in the presence of PR_3 to form $Ni(PR_3)_x$.

II was readily synthesized[52] from the reaction of nickelocene and triphenylmethyl lithium in a 67% yield after recrystallization, with the ^{1}H NMR spectrum shown in Figure 35.

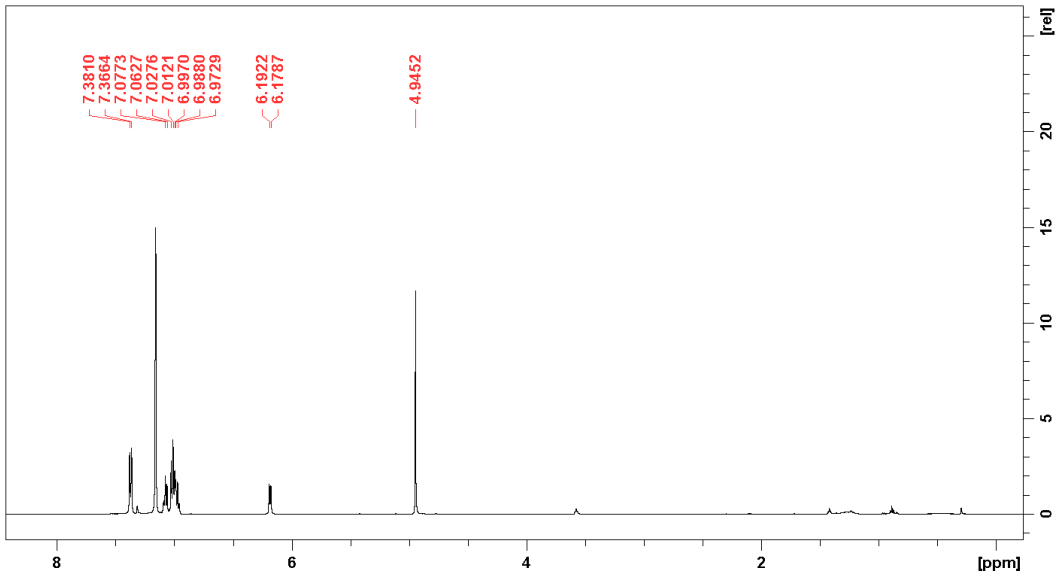

Figure 35. Full ^{1}H NMR spectrum of II in C_6D_6.

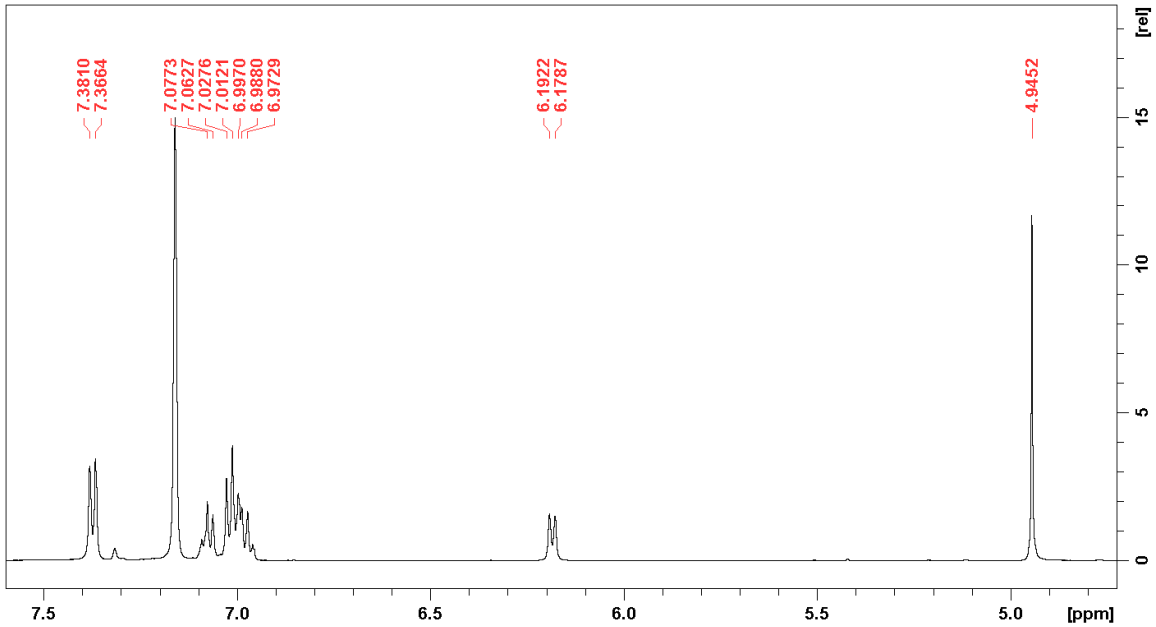

Figure 36. ^{1}H NMR spectrum of II in C_6D_6 (5-7.5 ppm).

The singlet at δ 4.94 can be assigned to the five cyclopentadienyl protons. A doublet at δ 6.18 integrates to two protons, which can be assigned to two fluxional allylic protons, and aromatic signals resonate at δ 6.97 – 7.38. This agrees well with literature, which lists these resonances at δ 4.95, 6.15 and 7.15 - 7.30 respectively.[52] Bonding of the compound can be described as a benzyl ligand η^3-coordinated at the C(2), C(1) and C(7) position to a NiCp fragment with its crystal structure being reported by Pasynkiewicz *et al*.[52]

3.4.2 Preliminary Investigations of the Reaction of II with Phosphines.

The following series of investigations are very preliminary; a series of ^{31}P and ^{1}H NMR experiments were carried out to assess if **II** does indeed undergo reactions with several monodentate phosphines. We anticipated that if **II** were to undergo phosphine coordination, the Cp and benzyl fragment might very well undergo reductive elimination, resulting in the disappearance of the Cp resonance at δ 4.91 in the ^{1}H NMR spectrum. The ^{31}P NMR spectrum would also show new resonance(s) for a Ni-phosphine complex, and a decrease in intensity or disappearance of the resonance for free phosphine.

3.4.2.1 Reaction of II with 2 PPh_3.

In an NMR tube**, II** was reacted with two equivalents of PPh_3 in toluene-d_8 for 24 h at RT, in the hopes of forming $Ni(PPh_3)_2$ and the organic reductive elimination product(s). The resulting ^{31}P NMR spectrum (Figure 37) shows no free PPh_3 resonance which appears at δ -4.9[1], initially indicating a reaction had occurred. What is found is one sharp resonance at δ 21.6. $Ni(PPh_3)_4$ has been previously characterized by ^{31}P NMR spectroscopy, with a single broad resonance appearing at δ 22.26 at RT in DMF-d_7[53] and δ 24.1 at -80 °C,[54] which suggests that Ni-phosphine complex of this type may have formed.

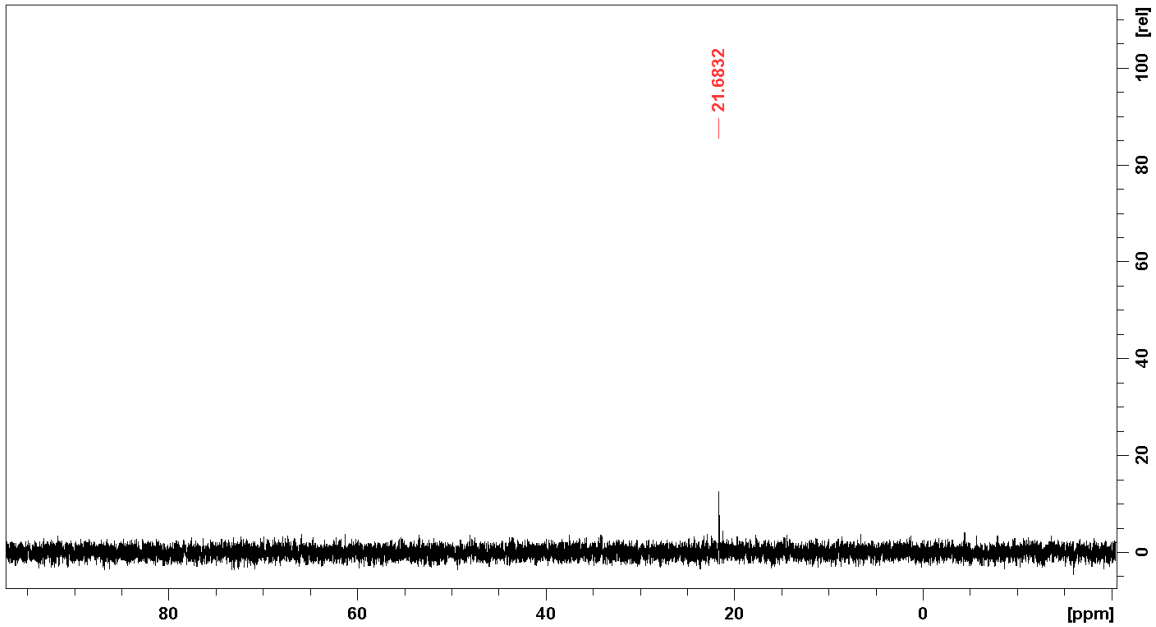

Figure 37. ^{31}P NMR spectrum of II + 2 PPh_3 in toluene-d_8.

The ^{1}H NMR spectrum (Figure 38) shows that a considerable Cp peak at δ 4.91 still remains, indicating that not all of **II** has reacted. In addition to the aromatic resonance attributed to **II**, several new aromatic resonances also appear at δ 6.8 and δ 7.7, which appear to be exchange-broadened. There are new sharp aromatic resonances at δ 7.1, which could possibly due to reductive elimination products. There is also a new broad resonance appearing slightly up-field from the allylic resonance of **II**. It could be postulated that **II** preferentially forms $Ni(PPh_3)_4$ instead of the bis-ligated $Ni(PPh_3)_2$, and $Ni(PPh_3)_4$ and **II** are both in solution. It appears that a reaction between PPh_3 and **II** has occurred, and further investigation is required to elucidate the product(s).

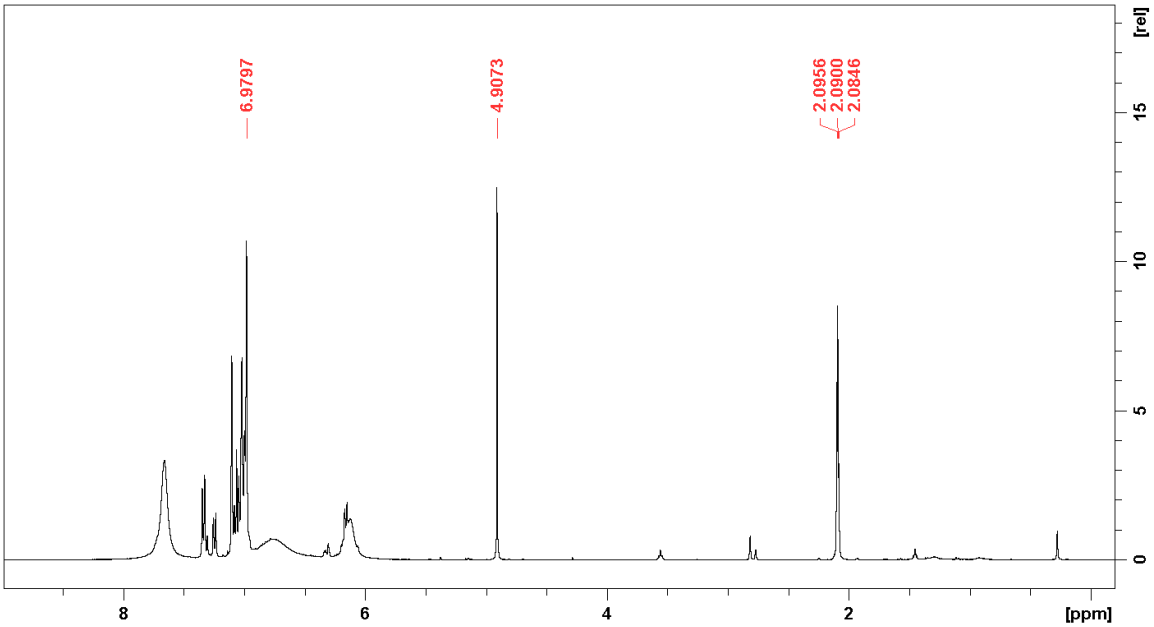

Figure 38. ^{1}H NMR spectrum of II + 2 PPh_3 in toluene-d_8.

3.4.2.2 Reaction of II with 2 PCy_3.

In an NMR tube**, II** was reacted with two equivalents of PCy_3 in toluene-d_8 for 3 h at 75 °C, in the hopes of forming $Ni(PCy_3)_2$ and the organic reductive elimination product(s). The resulting ^{31}P NMR spectrum (Figure 39) shows three sharp resonances at δ 9.9, 37.7 and 45.2, initially indicating a reaction had occurred. The resonance at δ 9.9 can be attributed to free phosphine (lit. δ 9.9[1]), and is larger in intensity than the other two resonances. As seen with PPh_3 and $Ni(PPh_3)_4$,[53] the phosphine resonance shifts downfield upon coordination compared with the free phosphine, which is another indication that PCy_3 has formed a coordination complex with Ni.

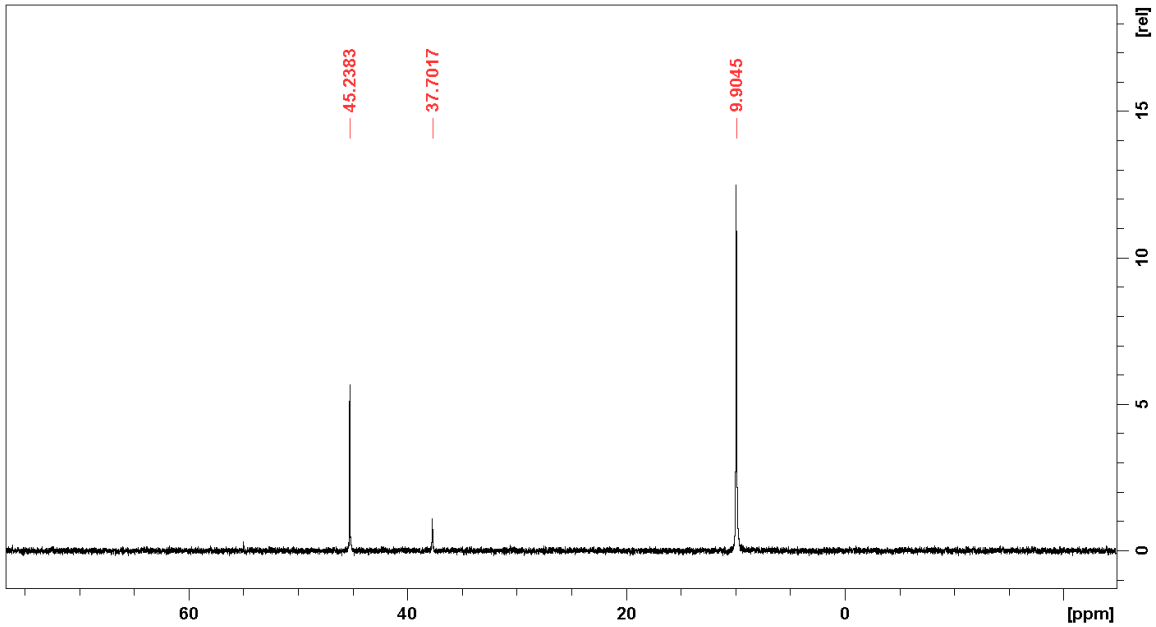

Figure 39. ^{31}P NMR spectrum of II + 2 PCy_3 in toluene-d_8.

The ^{1}H NMR spectrum of the reaction (Figure 40) shows the Cp singlet at δ 4.91 has decreased in intensity yet has not completely disappeared and two new singlets at δ 5.1 and δ 5.4 have appeared. Aliphatic cyclohexyl protons resonances appear from δ 1 – 2, yet it is difficult to assign these to either free or coordinated PCy_3. In any case, it appears that a reaction between PCy_3 and **II** has occurred, and further investigation is required to elucidate the product(s).

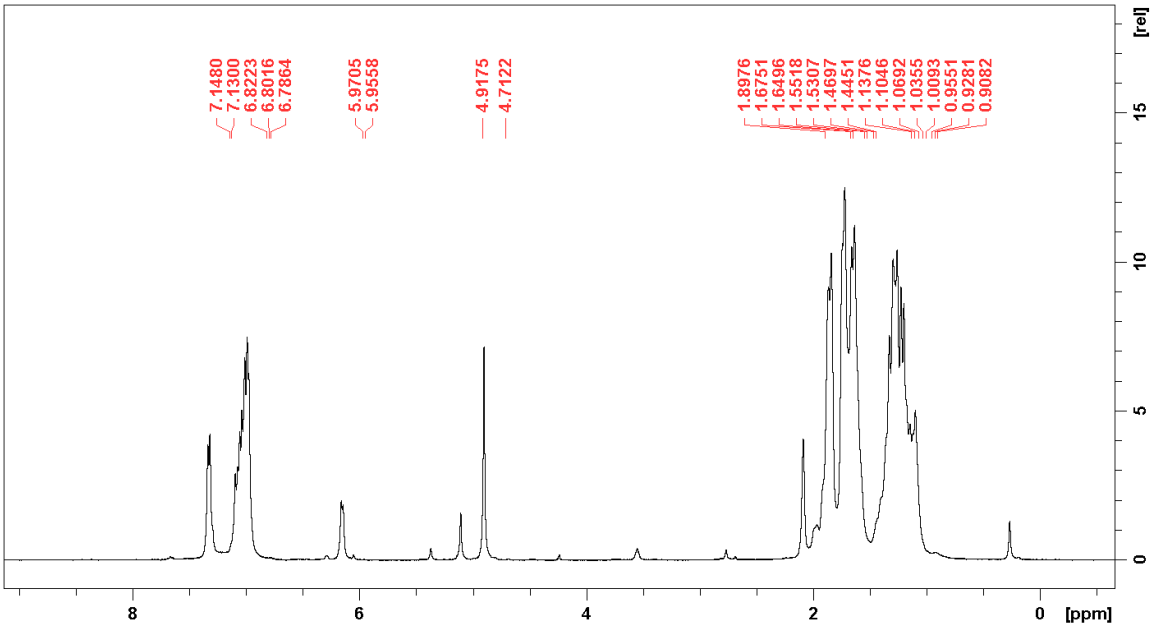

Figure 40. ^{1}H NMR spectrum of II + 2 PCy_3 in toluene-d_8.

3.4.2.3 Reaction of II with 2 P^nBu_3.

In an NMR tube**, II** was reacted with two equivalents of P^nBu_3 in toluene-d_8 for 3 h at 75 °C, in the hopes of forming $Ni(P^nBu_3)_2$ and the organic reductive elimination product(s). The resulting ^{31}P NMR spectrum (Figure 41) shows no free P^nBu_3 resonance (δ -31.1[55]), and one large resonance at δ 41.2 , and two resonances at δ 17.4 and δ 15.0 which are much smaller in intensity. As seen with PPh_3 and $Ni(PPh_3)_4$,[53] the phosphine resonance shifts downfield upon coordination compared with the free phosphine, which is an indication that P^nBu_3 has formed a coordination complex with Ni.

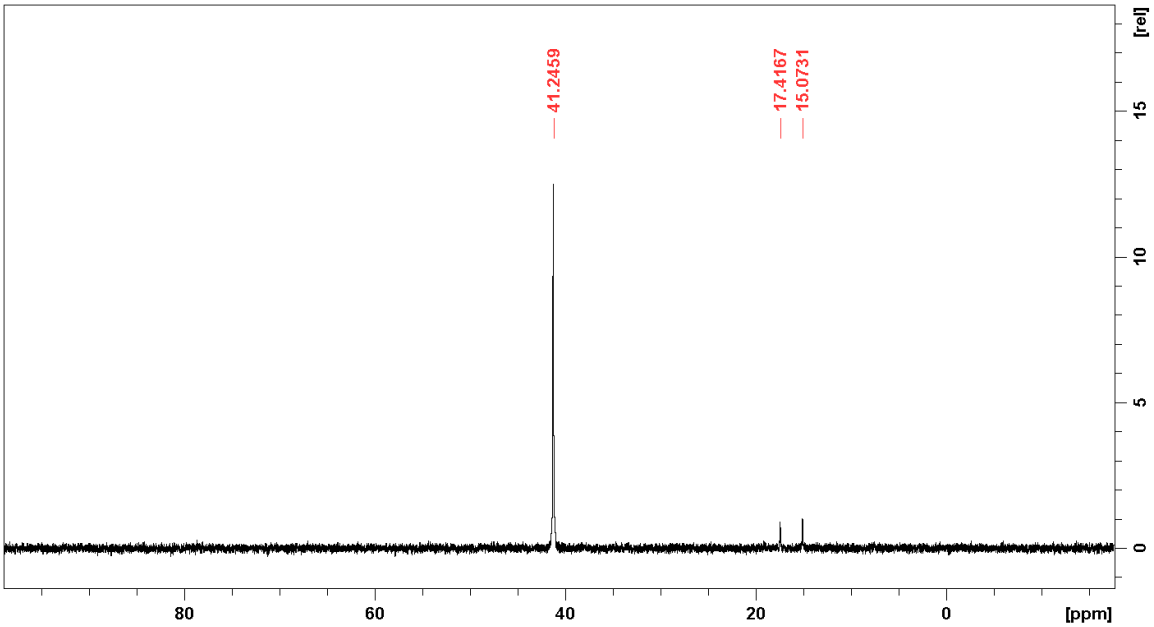

Figure 41. ^{31}P NMR spectrum of II + 2 P^{n}Bu$_3$ in toluene-d$_8$.

The ^{1}H NMR spectrum shows the Cp singlet at δ 4.91 has completely disappeared, indicating again the formation of a Ni-phosphine complex, and also that further investigation is required to elucidate the product(s).

3.4.2.4 Reaction of II with 2 PEt$_3$.

In an NMR tube**, II** was reacted with two equivalents of PEt_3 in toluene-d_8 for 3 h at 75 °C, in the hopes of forming $Ni(PEt_3)_2$ and the organic reductive elimination product(s). The resulting ^{31}P NMR spectrum (Figure 42) shows no free PEt_3 resonance (δ -18.9[55]), and only one large resonance at δ 44.8. As seen with PPh_3 and $Ni(PPh_3)_4$,[53] the phosphine resonance shifts downfield upon

coordination compared with the free phosphine, which is an indication that PEt_3 has formed a coordination complex with Ni.

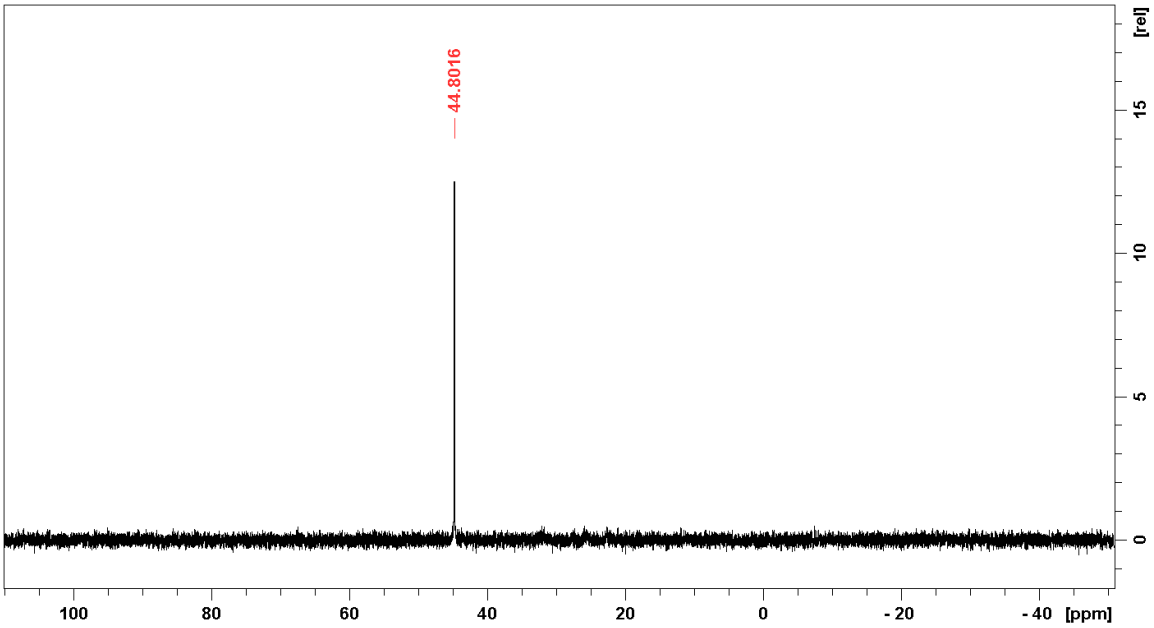

Figure 42. ^{31}P NMR spectrum of II + 2 PEt_3 in toluene-d_8.

The ^{1}H NMR spectrum shows the Cp singlet at δ 4.91 has completely disappeared, indicating again the formation of a Ni-phosphine complex, and also that further investigation is required to elucidate the product(s).

3.4.2.5 Reaction of II with 2 $PMePh_2$

In an NMR tube, **II** was reacted with two equivalents of $PMePh_2$ in toluene-d_8 for 24 h at RT, in the hopes of forming $Ni(PMePh_2)_2$ and the organic reductive elimination product(s). The resulting ^{31}P NMR spectrum (Figure 43)

shows no free $PMePh_2$ resonance (-25.9[1]), and only one large resonance at δ 3.9. As seen with PPh_3 and $Ni(PPh_3)_4$,[53] the phosphine resonance shifts downfield upon coordination compared with the free phosphine, which is an indication that $PMePh_2$ has formed a coordination complex with Ni.

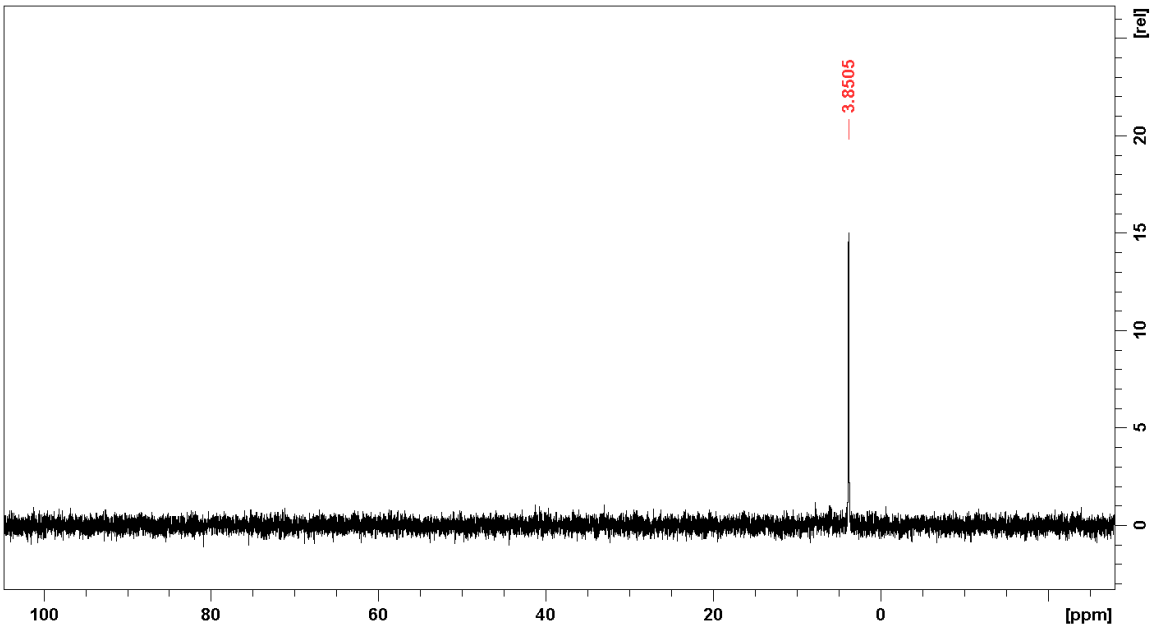

Figure 43. ^{31}P NMR spectrum of II + 2 $PMePh_2$ in toluene-d_8.

The ^1H NMR spectrum shows the Cp singlet at δ 4.91 has completely disappeared, indicating again the formation of a Ni-phosphine complex, and also that further investigation is required to elucidate the product(s).

3.4.2.6 Reaction of II with 2 P^tBu_3 and 2 PMe_2Ph

In an NMR tube**, II** was reacted with two equivalents of P^tBu_3 in toluene-d_8 for 24 h at RT, in the hopes of forming $Ni(P^tBu_3)_2$ and the organic reductive elimination product(s). The resulting ^{31}P NMR spectrum showed only one sharp peak at δ 62.2, attributed to free P^tBu_3 (lit. 62.2[1]), indicating no reaction had taken place. P^tBu_3 has a relatively large cone angle of 182°[56] which many be too large to react with the metal center, so two equivalents of the much smaller phosphine PMe_2Ph was added to the solution. PMe_2Ph has a much smaller cone angle of 122°[56] and reacted quantitatively with **II** to give a ^{31}P NMR resonance at δ - 9.5, showing no free phosphine (lit. δ – 41.1[57]) or oxide (lit. δ 44.4) (Figure 44).

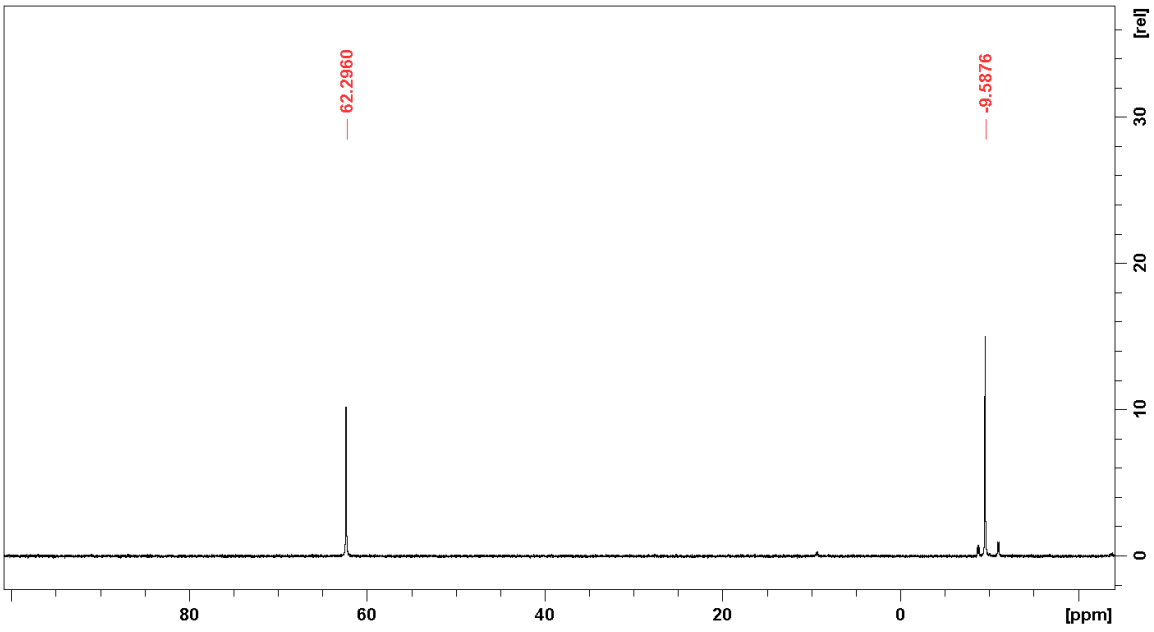

Figure 44. ^{31}P NMR spectrum of II + 2 P^tBu_3 + 2 PMe_2Ph in toluene-d_8.

The ^{1}H NMR spectrum also shows the complete disappearance of the Cp singlet at δ 4.91. Interestingly, there did not appear to be any mixed phosphine complexes which one might anticipate via phosphine dissociation if $Ni(PMe_2Ph)_x$ was in fact being formed.

3.5 Future Work

While it does appear that **II** is reacting with various monodentate phosphines, further ^{1}H and ^{31}P NMR characterization is required to elucidate the product(s). Due to time constraints, it was not possible to fully characterize these species.

Ultimately, the goal here was to develop a general route towards Ni(0) catalysts for use in cross coupling reactions. As mentioned above, it does appear that **II** is reacting with various phosphines, and it would be useful to attempt several cross coupling reactions (Suzuki-Miyaura, Mizoroki-Heck, etc) to assess the competency of **II**/phosphines towards these transformations.

3.6 References

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Chapter 4

Summary and Conclusions

Our results clearly confirm our hypothesis that combinations of **I** with various representative phosphines would generate catalyst solutions which are much more active than catalyst systems obtained using combinations of commonly used catalyst precursors $Pd(OAc)_2$, $Pd(PPh_3)_4$, Pd_2dba_3, etc. with the same phosphines. The reason almost certainly lies in the fact that **I** generates catalytically active species PdL_2 quickly and quantitatively while the others do not, in part for the reasons discussed herein. A second advantage of the use of **I** is that the Pd(0) products PdL_2 are formed under rigorously anhydrous conditions. The potential benefits of carrying out cross-coupling chemistry in the absence of water have also been noted herein. The potential problems associated with use of commonly used catalyst precursors are discussed above and have been recognized by others but there seems previously to have been little recognition of this fact and they all continue to be used frequently. However, while our studies show that Pd_2dba_3 can be effective for Suzuki−Miyaura, Mizoroki-Heck and Buchwald-Hartwig cross-coupling reactions, catalyst systems based on reduction of palladium(II) are unreliable and, in the absence of experiments explicitly demonstrating the actual formation in high yields of the anticipated palladium(0) compounds, should not be utilized when comparing the effectiveness of various phosphine ligands in cross-coupling reactions. However,

we are not claiming to have discovered the optimal catalyst for these cross coupling reactions, only an excellent procedure for generating specifically catalysts of the type PdL_2, if these are what one wishes to employ.

The work herein has led to the following publications:

1. Fraser, A. W.; Besaw, J. E.; Hull, L. E.; Baird, M. C. *Organometallics* **2012,** *31,* 2470.
2. Fraser, A. W.; Jaksic, B. E.; Batcup, R.; Sarsons, C. D.; Woolman, M.; Baird, M. C. *Organometallics* **2013,** *32,* 9.
3. Jaksic, B. E.; Jiang, J.; Fraser, A. W.; Baird, M. C. *Accepted.*

Our results have also provided the first evidence available, to our knowledge, for the negative consequences of phenylboronic acid degradation during the course of Suzuki−Miyaura cross coupling reactions. Our reaction profiles also provide information on the time scale over which this side reaction is a factor affecting yields of cross-coupled products. Most publications in the area of catalytic cross-coupling reactions report isolated yields, obtained on termination of reactions after arbitrary periods of time. In such studies, little distinction can be made between catalytic reactions which are still proceeding at the point of termination and those whose rates have decreased to zero before the point of termination. The advantages of reactions, which are completed within a relatively short time span, well before the point of termination, likewise remain unappreciated. Thus use of isolated yields in comparisons of various ligand systems can also be misleading.

We continue our investigations of **I** as a uniquely efficient precursor for the generation of catalysts of the type PdL_2 for cross-coupling reactions of various substrates with emphasis on more challenging substrates for Suzuki−Miyaura, Mizoroki-Heck, and Buchwald-Hartwig reactions.

Appendix

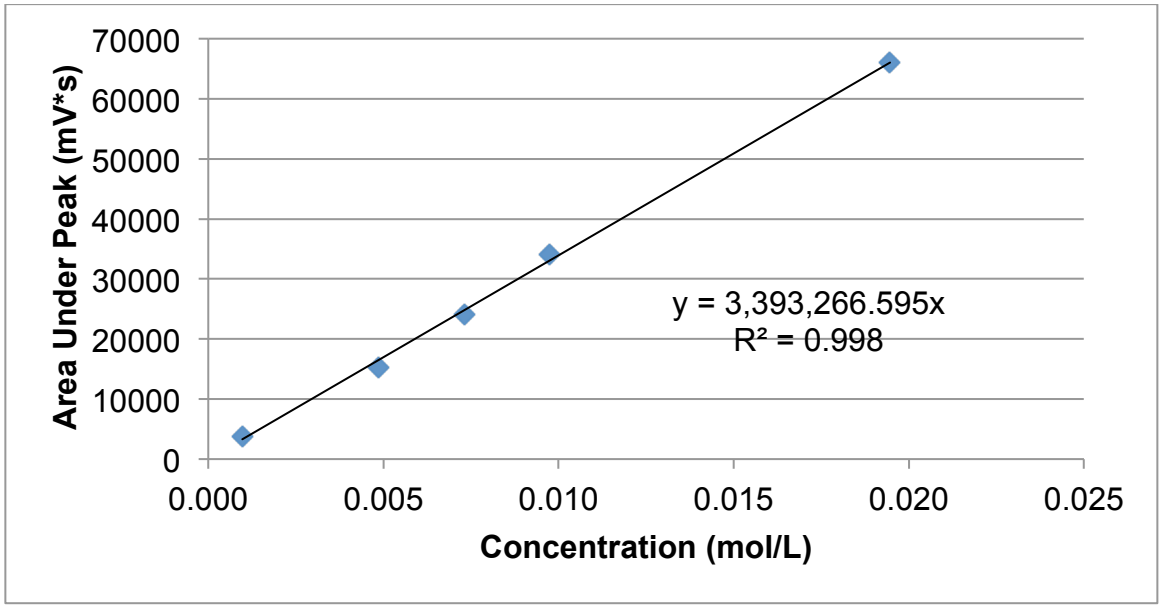

Figure 1. Calibration curve for 4-bromoanisole

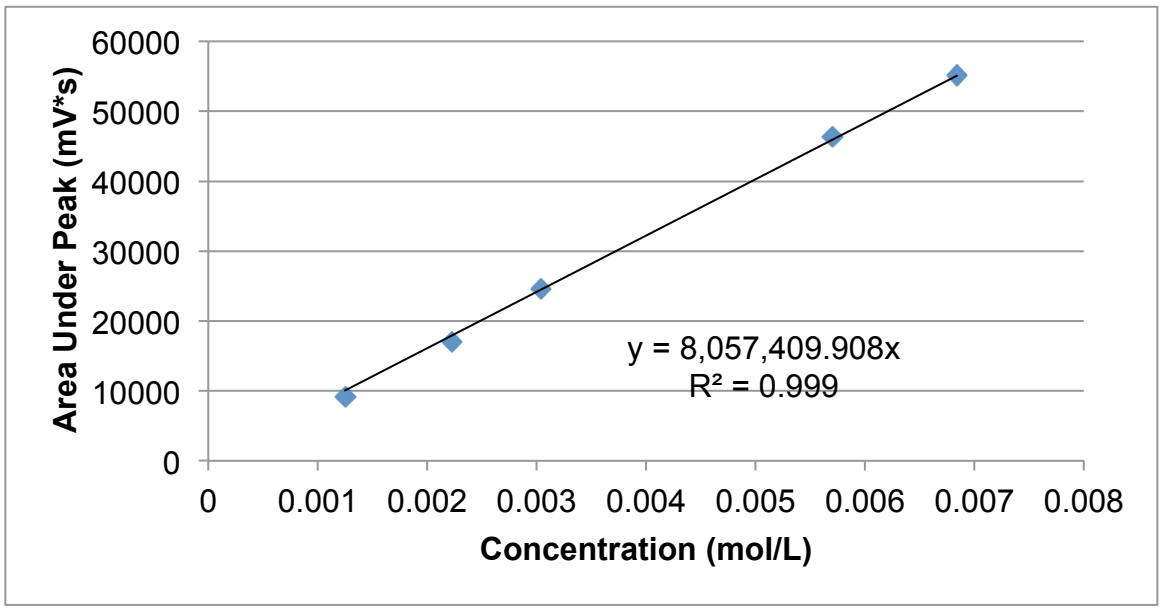

Figure 2. Calibration curve for 4-methoxybiphenyl

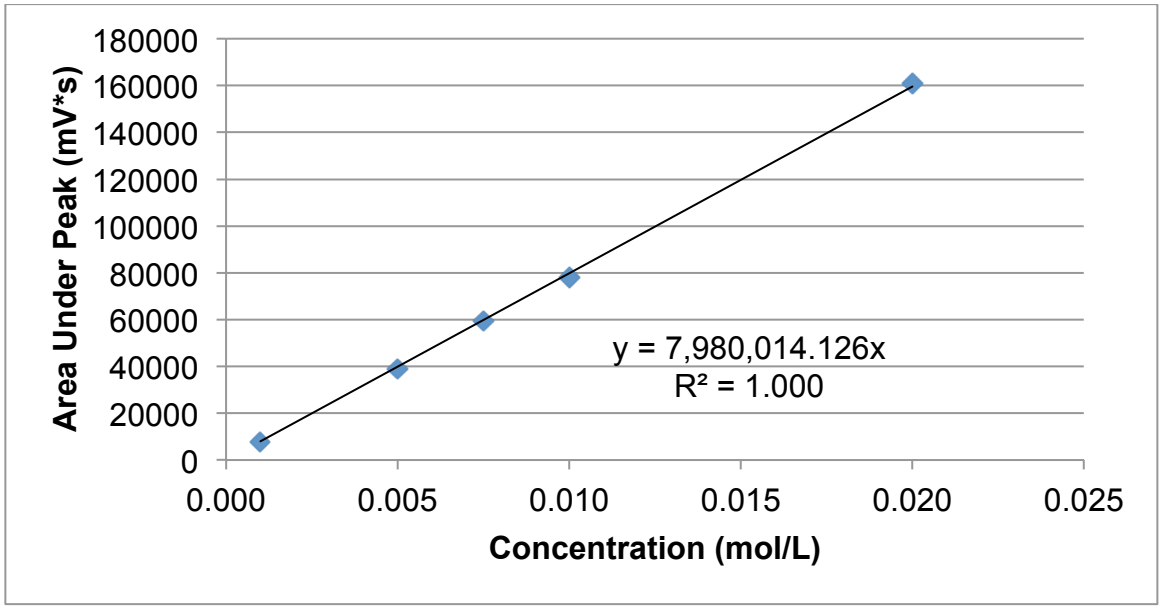

Figure 3. Calibration curve for biphenyl

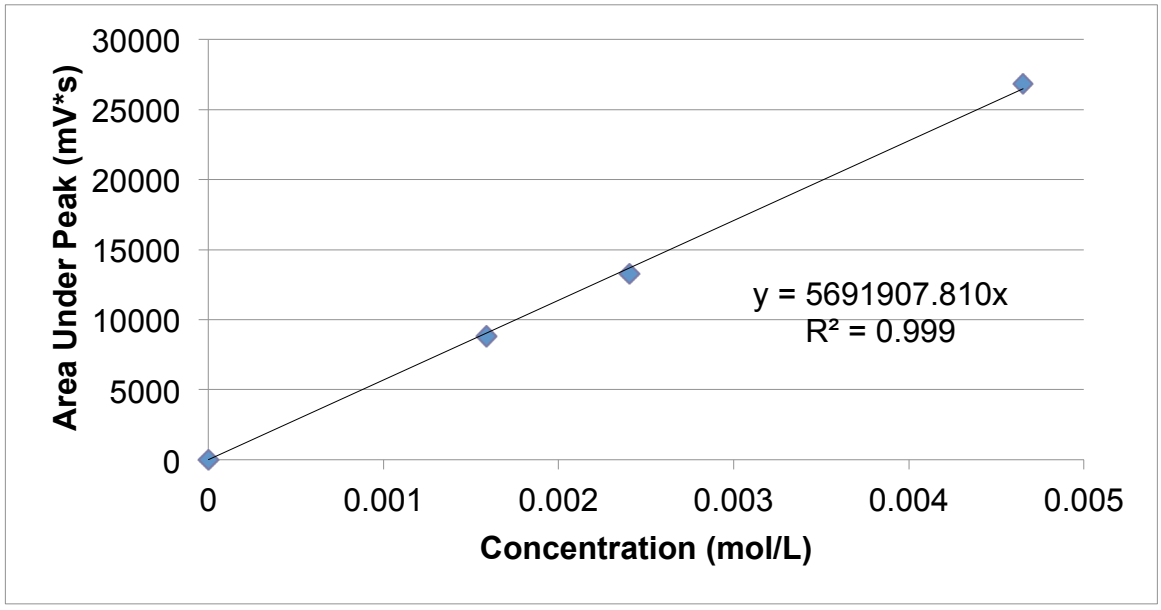

Figure 4. Calibration curve for bis(4-methoxyphenyl)amine

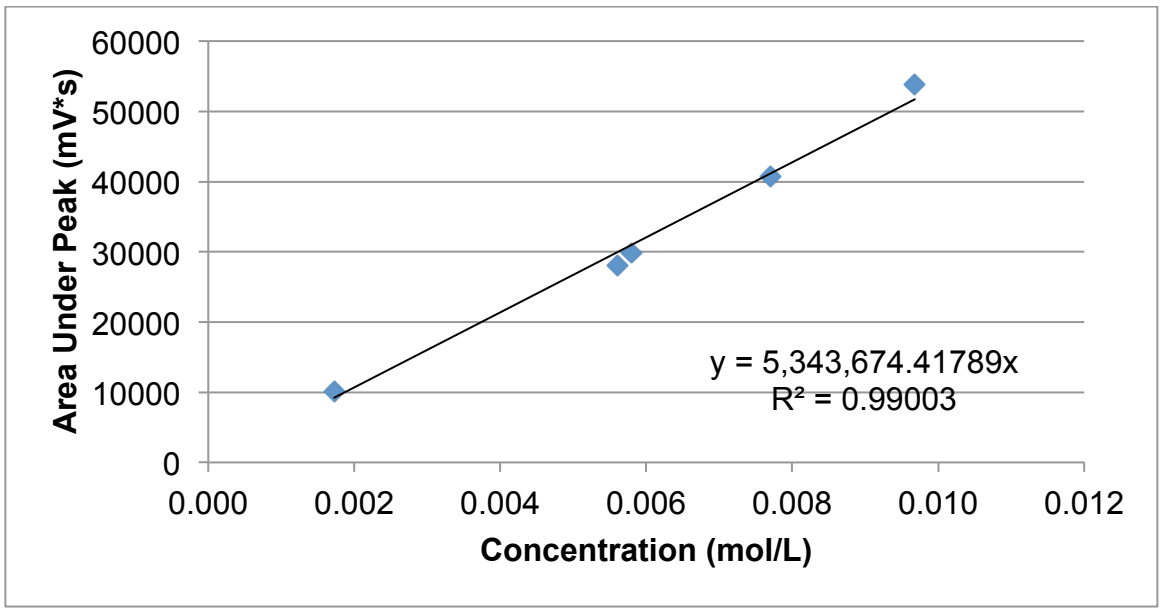

Figure 5. Calibration curve for E-methylcinnamate

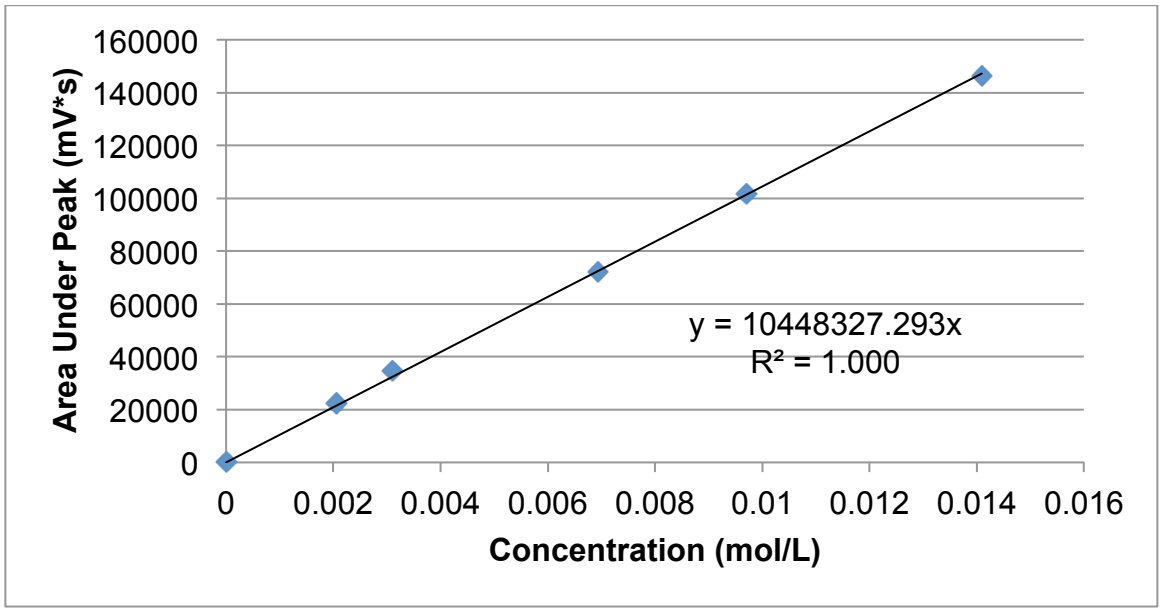

Figure 6. Calibration curve for E-stilbene

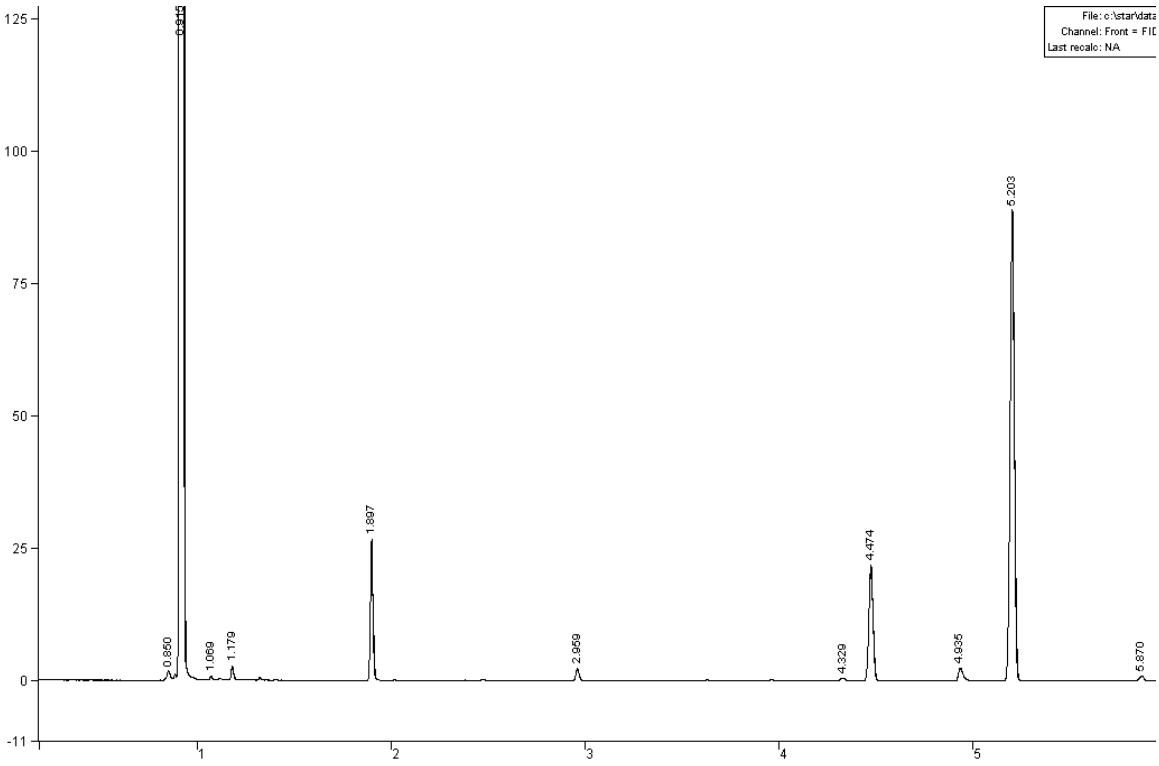

Figure 7. GC spectrum of 3.1.1 with 4-methoxybiphenyl at 5.203 min.

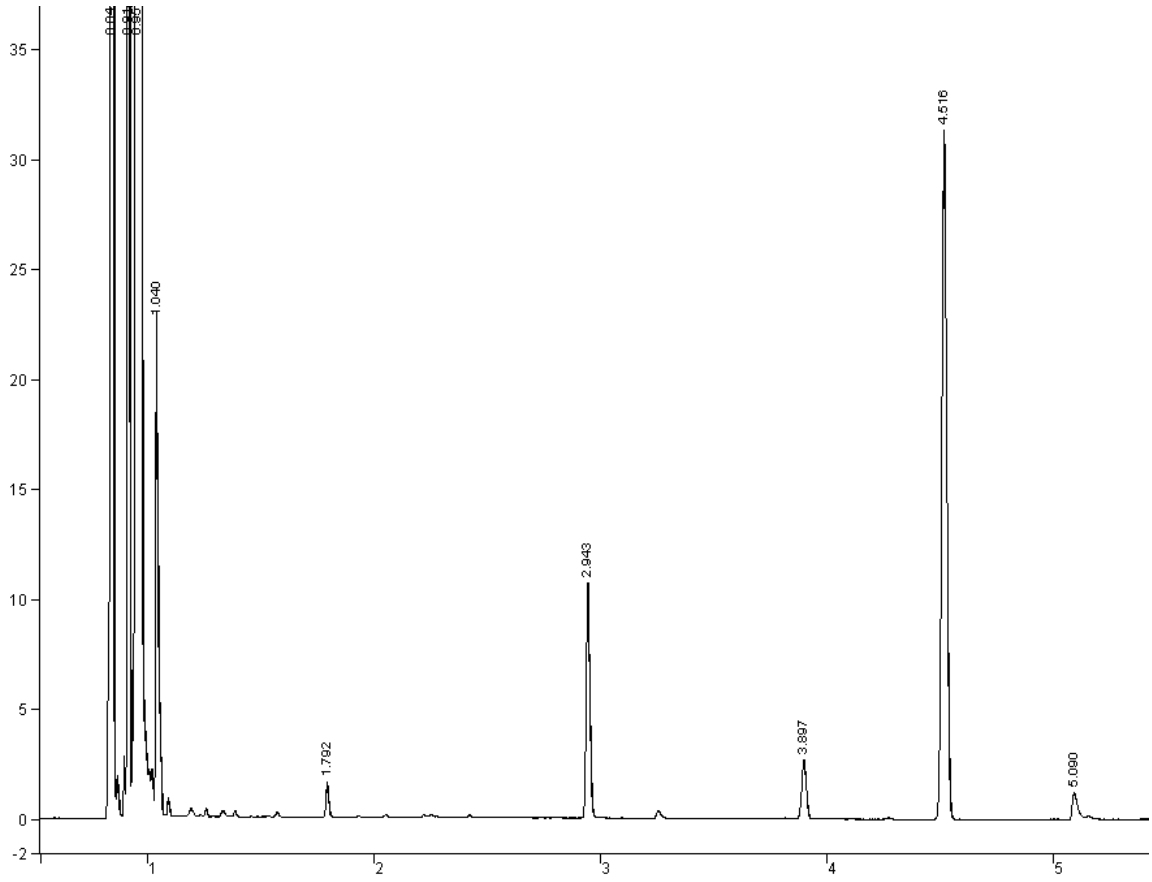

Figure 8. GC spectrum of 3.2.1 with *trans*-methylacrylate at 4.516 min.

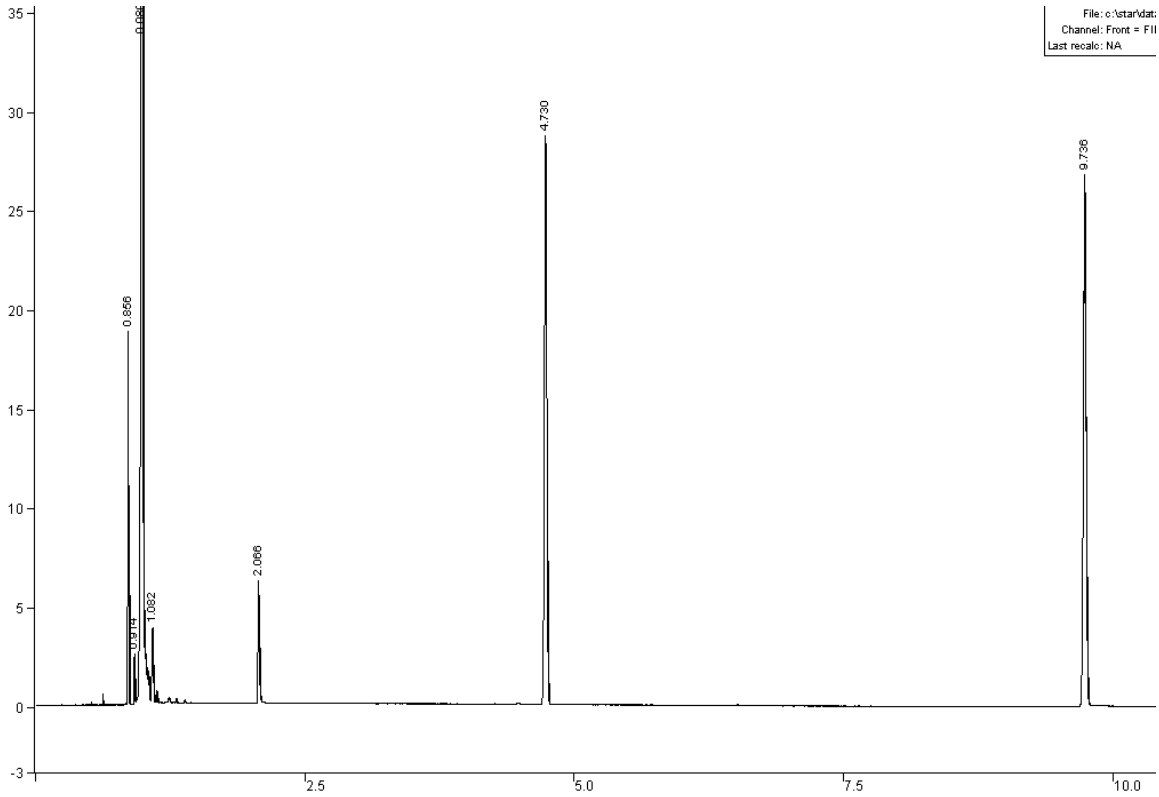

Figure 9. GC spectrum of 3.3.1 with bis(4-methoxyphenyl)amine at 9.736 min.