ABSTRACT

The synthesis and design of new phosphines is a continuing area of interest. In designing new phosphines there are a number of design features that need be considered. For palladium catalyzed coupling reactions, sterically demanding and electron releasing ligands are generally most effective in promoting the reaction.

In evaluating the hydrophobic phosphines utilized in the Suzuki coupling, the neopentyl derivatives of TTBP (tri-tert-butylphosphine) were investigated. The effect of the addition of a neopentyl group increases the cone angle and impacts the electron donation by decreasing it relative to TTBP. The application in Suzuki coupling shows that a palladium catalyst with a neopentyl phosphine ligand demonstrates good to excellent yields with aryl bromides at room temperature.

In the design of new phosphines, building in polar groups generates the ability to take advantage of using water as a solvent or co-solvent. The synthesis of the water soluble ligands DTBPPS (di-tert-butylphosphoniumpropane sulfonate) and DAPPS (di-adamantylphosphoniumpropane sulfonate) led to their testing in Sonogashira and Suzuki coupling reactions. Both ligands give catalysts that show good to excellent conversion of aryl bromides to products at room temperature. For aryl chlorides elevated temperatures are required.

In expanding the water-soluble ligands into other palladium coupling reactions, DAPPS was developed in the carbonylation of aryl bromides. The palladium/DAPPS-catalyzed carbonylation coupling reactions show good to excellent conversion of aryl bromides to
carbonylated products. This is the first example of a water-soluble alkylphosphine promoting carbonylation of an aryl bromide.
DEDICATION

This thesis is dedicated to everyone who helped me and guided me through the trials and tribulations of creating this manuscript. In particular, my family and close friends who stood by me throughout the time taken to complete this document. I also dedicate this work to people that doubted my work ethic or intellect as their doubt fueled my desire to finish.
### LIST OF ABBREVIATIONS AND SYMBOLS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>$n$-Bu</td>
<td>normal butyl</td>
</tr>
<tr>
<td>$n$-BuLi</td>
<td>normal butyl lithium</td>
</tr>
<tr>
<td>$t$-Bu Amphos</td>
<td>(2-Di-$t$-butylphosphinoethyl)trimethylammonium chloride</td>
</tr>
<tr>
<td>$t$-Bu-pip-phos</td>
<td>-(di-tert-butylphosphino)-N,N-dimethylpiperidinium chloride</td>
</tr>
<tr>
<td>Cy$_3$P</td>
<td>tricyclohexylphosphine</td>
</tr>
<tr>
<td>Cy-pip-phos</td>
<td>4-(Dicyclohexylphospino)-N,N-dimethylpiperidinium chloride</td>
</tr>
<tr>
<td>DABP</td>
<td>diadamantylbutylphosphine</td>
</tr>
<tr>
<td>DAPPS</td>
<td>diadamantylphosphoniumpropane sulfonated</td>
</tr>
<tr>
<td>DCPES</td>
<td>dicyclohexylphosphinoethanesulfonate sodium salt</td>
</tr>
<tr>
<td>DFT</td>
<td>density functional theory</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DTBNpP</td>
<td>di-$t$-butylneopentylphosphine</td>
</tr>
<tr>
<td>DTBPPS</td>
<td>di-$t$-butylphosphoniumpropane sulfonated</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>GAP</td>
<td>HOMO - LUMO</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest Occupied Molecular Orbital</td>
</tr>
<tr>
<td>L</td>
<td>generic ligand</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest Unoccupied Molecular Orbital</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
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<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>NMO</td>
<td>4-Methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>PG</td>
<td>polar group</td>
</tr>
<tr>
<td>PMe₃</td>
<td>trimethylphosphine</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PTA</td>
<td>1,3,5 triazophosphadamantane</td>
</tr>
<tr>
<td>R</td>
<td>generic alkyl group</td>
</tr>
<tr>
<td>RCM</td>
<td>ring closing metathesis</td>
</tr>
<tr>
<td>ROMP</td>
<td>ring opening metathesis polymerization</td>
</tr>
<tr>
<td>TBDNpP</td>
<td>tert-butyl-dineopentyl phosphine</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THMP</td>
<td>tris(hydroxymethyl)phosphine</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N-tetramethylethylenediamine</td>
</tr>
<tr>
<td>TNpP</td>
<td>trineopentylphosphine</td>
</tr>
<tr>
<td>TPP</td>
<td>triphenylphosphine</td>
</tr>
<tr>
<td>TPPMS</td>
<td>triphenylphosphine monosulfonate</td>
</tr>
<tr>
<td>TTBP</td>
<td>tri-tert-butylphosphine</td>
</tr>
<tr>
<td>TPPTS</td>
<td>triphenylphosphine trisulfonate</td>
</tr>
<tr>
<td>X</td>
<td>-Br, -Cl, -I, -OTs, -OTf.</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

I would like this opportunity to say a special thank to the people that have aided in the success of finishing my graduate studies. My attendance to graduate school at the University of Alabama I attribute to Professor Robert Holman. Professor Kevin H. Shaughnessy served as my mentor, advisor, and friend. Professor Shaughnessy showed me his endless patient and was always willing to help every step along the way. Additionally, my family showed me their support, in particular my parents helped me through my graduate career and undergraduate career making sacrifices in their own life.

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DAPPS were: Hannah Box, Quentin Sonnier, Sarabeth McLendon, Ellie Killian, and Fallon Brown. In addition Joel Schoenberg provided work in other projects not presented in this document. There were also many other undergrads that worked in the Shaughnessy research group that deserve mention: Caitlin Prickett, Jason Crowell, Strud Tutwiler, Joanna Smith, Nick Massie, Paul Guevara, Brent Graves, Jake Porter, Allan Algood, Tyler James, Duncan Harmon, Emily Wayman, Emily Pair, Jared Carpenter, Joanna Smith, Paul Guevara, and Jane Moore.

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CHAPTER 1. Review of Water-Soluble Alkyl Phosphine Ligands

1.1 INTRODUCTION

Phosphine ligands have emerged as some of the most widely utilized ligands in catalysis. Phosphines are used because of their activation of a metal center towards desired reactivity. In particular, ligands including trialkylphosphines and dialkyl(2-biphenyl)phosphines have emerged as the most widely used. Carbenes ligands have been used as well. Phosphine and carbene ligands coordinated to a metal center to provide a reactivity enhancement compared to the metals alone. In addition to the hydrophobic phosphine ligands in the literature, numerous water-soluble analogs of these ligands have been reported as well.

To understand the role of the phosphine ligands in palladium catalyzed reactions, it is helpful to evaluate the steps present along a catalytic pathway (Scheme 1.1). Many palladium-catalyzed reactions follow a similar mechanistic pathway and therefore a general mechanistic view can provide insight as to the factors that influence catalytic activity of a palladium/ligand complex. The oxidative addition step (Scheme 1.1) is typically the rate determining step associated in this reaction. Hartwig and coworkers, extensively studied the 14 electron Pd[P(o-C₆H₄Me)₃]₂ complex which undergoes oxidative addition leading to dimeric monophosphine palladium phenyl complexes. The monophosphine complex undergoes oxidative addition. Previous work in our group with bulky alkylphosphines also suggests that a L₂Pd complex undergoes ligand dissociation to generate a LPd complex prior to oxidative
addition. Oxidative addition is promoted by electron rich metal center. Strongly $\sigma$-donating ligands such as alkyl phosphines and carbenes enhance electron density at the metal center.$^{28,29}$

Scheme 1.1 Generic mechanism for palladium catalyzed coupling reactions.$^2$

Once oxidative addition occurs into the C-X bond, transmetalation/ligand substitution follows. In this second step, the metal center acts as an electrophile toward the incoming nucleophile, which is opposite of the oxidative addition necessity. It is therefore desirable for the newly generated Pd(II) center to be electropositive to facilitate nucleophilic attack. Additionally, the metal center should be spatially or sterically accessible to the incoming nucleophile. Ligands around the metal center can sterically hinder incoming nucleophiles if they
are too large. However, in the reductive elimination/migratory insertion step, larger ligand sizes tend to promote these events. It is therefore necessary to manage the size of the ligand such that neither the transmetalation/ligand substitution nor the reductive elimination/migratory insertion steps are inhibited. Additionally, steric bulk promotes ligand dissociation that as previously noted leads to the proposed active monophosphine palladium catalyst. For palladium catalysis, sterically demanding strongly electron releasing ligands are known to generate more active catalysts.

While the generation of a highly active catalyst has been the driving force in design of many ligands, the separation of the catalyst from the desired product, and the recovery of the catalyst has proved difficult. Due to the great cost of transition metals, the limited ability to recover them from reactions causes a great deal of concern industrially. Additionally, the need for separation of the metal from the product at the low levels allowable in pharmaceuticals or foods render homogenous catalysts unattractive.\textsuperscript{30} The employment of aqueous/biphasic systems allows for the potential to segregate the product into an organic layer and the catalyst in the aqueous phase facilitating easier separation. Additionally, the use of water as a solvent is attractive due to its unique properties: availability, low flammability, low relative toxicity, cost, and environmental impact.\textsuperscript{31,32}

The first report of a hydrophilic palladium-catalyzed cross-coupling system was introduced by Casalnuovo,\textsuperscript{33} who used of TPPMS, a triphenylphosphine monosulfonate and Pd(OAc)$_2$ to promote cross-coupling. Since this initial report, there have been numerous efforts in synthesizing hydrophilic catalysts, mostly surrounding the triphenylphosphines or trialkylphosphines.\textsuperscript{34,35}

While the arylphosphate-based ligands have been utilized with polar groups to generate water soluble catalyst systems, catalysts derived from these ligands show limited reactivity (aryl
iodides at moderate to high temperatures). More attention in recent years has been given to ligands that are similar in steric and electronic properties to TTBP (tri-tert-butylphosphine). Most of this attention is due to fact that TTBP has been demonstrated to couple aryl bromides and chlorides with low catalyst loadings and reaction temperatures below 100 °C. The focus of this review will be with water-soluble alkylphosphines as these are most applicable to the ligands utilized and developed in this group.

1.2 Synthesis of Cationic Water-Soluble phosphines

The incorporation of an ammonium group is one mode of making a phosphine water soluble. Steltzer reported on a pair of ammonium salt water soluble alkyl phosphines (Scheme 1.2). The starting PH$_3$ is reacted with an ammonium alkyl ammonium chloride to yield a
water-soluble intermediate that can itself be considered a water-soluble phosphine; however
alkylation of the phosphine leads to the desired products. Both these ligands contain straight
chain alkyl phosphines. While more interesting ligands for palladium catalysis are those ligands
having bulkier groups surrounding the phosphine.

Scheme 1.3 Synthesis of Grubbs ammonium salt phosphines.\textsuperscript{38}
Grubbs reported the synthesis of sterically demanding phosphines Cy-pip-phos and Cy-amphos (Figure 1.3) in 1996 and their application in ROMP and RCM metathesis catalysts. These ligands both contain polar groups (ammonium for Cy-pip-phos, and Cy-amphpos) allowing them to have solubility in water. Grubbs’ approach was to utilize a borane-protected dicyclohexylphosphine to react with an alkyl amine followed by quaternization with MeI. Once the borane-protected phosohine salt is synthesized, it had to be deprotected with morpholine to

**Scheme 1.4** Synthesis of t-Bu amphos and t-Bu pip-phos.\(^{39}\)
give the water soluble ammonium salt. Grubbs also synthesized both these ligands going through the ammonium salt starting material rather than quaternization after alkylation of the phosphine. The method of using ammonium starting material explored by Grubbs was not as effective as the neutral starting material by lowering yield. Shaughnessy and coworkers developed another set of ligands similar to the ammonium salt ligands developed by Grubbs. The implementation of \( t \)-Bu groups in place of cyclohexyl groups increases the steric parameter associated with both ligands, while the ammonium group again maintains the water solubility (\( t \)-Bu amphos and \( t \)-Bu pip-phos) (Scheme 1.4).

1.3 Synthesis of Anionic Water-Soluble Phosphines.

Scheme 1.5 Synthesis of DCPES\(^{38} \)

Grubbs reported on the synthesis of DCPES ligand in 1996 (Scheme 1.5) and its application in a cross-metathesis catalyst.\(^{38} \) The protected phosphine was reacted with the
bromoalkyl sulfonate once it is deprotonated with $n$-BuLi. Once the borane-protected ligand was synthesized it was deprotected with morpholine. While this ligand was useful in olefin metathesis, it shows limited ability in palladium catalysis.

![Scheme 1.6](image)

**Scheme 1.6** Synthesis of water-soluble alkylphosphines containing Buchwald’s ligand backbone$^{40}$

A number of water soluble phosphine ligands have been synthesized containing Buchwald type backbone.$^{40}$ The dialkylbiphenylphosphines can be made soluble through the addition of a sulfonate to the biphenyl portion of the molecule. This can be accomplished through two methods. The first method is the addition of $\text{H}_2\text{SO}_4$ to the 2,6-dimethoxy-ortho-biphenyl backbone followed by deprotonation of the sulfonic acid with NaOH (Scheme 1.6). The second method is to use oleum to replace the para-isopropyl group on the trisubstituted biphenyl backbone. Both ligands have been applied to palladium-catalyzed Suzuki and Sonogashira couplings reactions. Both show reasonable activity with aryl chlorides and bromides at room temperature. However, the syntheses of these ligands are a multistep process making them less attractive towards commercial usage.
Hanson and co-workers reported on the sulfonation of a family of phosphines containing an alkyl chains (1-3 and 6 carbon chain) appended on the terminus of a sulfonated aromatic. These ligands were utilized with Rh in hydroformylation reactions and not applied to palladium most likely due to its lack of steric demand. The synthesis of the ligand starts with the corresponding alkyl Gringard being reacted with PCl$_3$ followed by sulfonation with fuming H$_2$SO$_4$ (Scheme 1.7).

Beller synthesized another water soluble ligand (Scheme 1.8), a trisulfonated amino phosphine. A sultone is reacted with an alkyl amine (-Me or -$n$-Bu) followed by pH adjustment to provide the sodium salt and free amine. The free amine is reacted with P(CH$_2$OH)$_3$ via condensation to provide the trialkyl, trisulfonated phosphine.

Plenio synthesized a class of ligands based upon 9-fluorenyldialkylphosphines (Scheme 1.9). These ligands, contain sulfonated groups, one on the fluorenyl substituent, and the other on a benzyl group attached to the 9-position of the fluorenyl. These ligands have been used in the Suzuki and Sonogashira coupling reactions for aryl bromides and chlorides, but require elevated temperatures for aryl bromides (50 $^\circ$C) and aryl chlorides (100 $^\circ$C) in Sonogashira coupling and Suzuki coupling for activated and deactivated substrates. Additionally, these ligands are a multi step route to a water-soluble phosphine making them less attractive for commercial usage. Plenio also synthesized a water soluble carbene precursor utilized in Suzuki
coupling with the polar sulfonate groups making the ligand soluble.\textsuperscript{46} This ligand is able to promote coupling of aryl chlorides at 100 °C in Suzuki coupling.

![Scheme 1.8 Synthesis of tris(N-methyl-N-2-sodiumsulfonatoethylaminobutyl)-phosphine\textsuperscript{42}](image)

In addition to both ammonium and sulfonate groups, carboxylate groups have been demonstrated to allow phosphine ligands to have water solubility. Sheldrick and co-workers were able to a synthesize tricyclohexyl derivative containing a carboxylate group (Scheme 1.10).\textsuperscript{47} The borane-protected dicyclohexyl phosphine is reacted with a cyclohexyl-α,β unsaturated carbonyl. The result from the 1,4 addition is the tricyclohexyl substituted phosphine containing a methyl ester. This methyl ester is simply hydrolyzed to the carboxylic acid to yield the water-soluble carboxylate salt.
Scheme 1.9 Plenios water soluble ligand synthesis. \(^{43-45,48}\)

Scheme 1.10 Synthesis of Sheldrick’s water soluble ligand based upon Cy\(_3\)P. \(^{47}\)
1.4 Water-soluble phosphine ligand synthesis (neutral ligands)

The installation of a polar group onto a phosphine ligand has led to several advancements in aqueous phase catalysis. However, cationic and anionic polar groups are not a necessity for water solubility. There are a number of ways of making ligands water soluble by attaching a neutral group to the phosphine that itself is water soluble. An example of attaching a water soluble group to a phosphine is from Miyaura utilizing a gluconamide tail. This gluconamide contains the Buchwald backbone (Scheme 1.11). The synthesis of the gluconamide containing ligand proceeds through a Suzuki coupling followed by LiBr exchange. The resulting Li nucleophile is reacted with the ClPR₂ (R = Cy or t-Bu). Then the cyano group is reduced to the amine and the gluconamide functional group is installed. The gluconamide -Buchwald ligands were tested in Suzuki coupling in neat water and give good to excellent yields at 80 °C for both aryl chlorides and bromides. While the yields are good, the synthesis of the ligand is many steps therefore it is not particularly interesting for commercial usage.

Scheme 1.11 Synthesis of Miyaura’s neutral gluconamide water-soluble ligand.
Sinou takes a similar approach for synthesizing a water soluble phosphine taken by Miyaura in that he makes the 2’-bromo-4-benzonitrile (Scheme 1.12).\textsuperscript{50} This is followed by the hydrolysis of the cyano group to the carboxylic acid. The sugar unit is installed from the D-glucosamine to give the water soluble ligand. The glucosamine-Buchwald type ligand was tested in Suzuki coupling and gave good yields at 60 °C for aryl bromides and 80 °C for aryl chlorides in toluene/EtOH/H\textsubscript{2}O (3/2/2). Once again, the synthesis of the ligand is many steps making it less attractive for commercial usage.

\begin{center}
\includegraphics[width=\textwidth]{scheme110.png}
\end{center}

\textbf{Scheme 1.10} Sinou’s synthesis of water-soluble ligand with a neutral sugar unit.\textsuperscript{50}

While many ligands have groups that allow them to have solubility in water, there are a number of ligands that themselves are water soluble without the addition of some extra group. A good example of a ligand that is inherently water-soluble is the THMP phosphine.\textsuperscript{51} The THMP ligand is used in the conversion of allyl alcohols to ketones, alkene hydration, hydroformylation,\textsuperscript{52} and hydrogenation. The ligand has three –OH groups making it water-soluble. Another ligand that is inherently water soluble is PTA. The PTA ligand has many
applications in synthesis: hydroamination,\textsuperscript{53} hydrogenation,\textsuperscript{54-56} and various other synthetic applications\textsuperscript{57}. Additionally there are many derivatives of PTA that have been synthesized (Figure 1.1).

\begin{center}
\begin{tabular}{c c c}
\text{THMP} & \text{PTA} \\
\text{DAPTA} & \text{DmoPTA} & \text{THPTA} \\
\text{P} & \text{Me} & \text{Me} & \text{Me} & \text{Me} & \text{Me} & \text{Me} & \text{Me} & \text{Me} \\
\text{N} & \text{N} & \text{N} & \text{N} & \text{N} & \text{N} & \text{N} & \text{N} & \text{N} \\
\text{P} & \text{Me} & \text{I} & \text{Ph} & \text{Ph} \\
\text{OH} & \text{CO}_2\text{Li} & \text{I}^- & \text{I}^- & \text{OH} & \text{Ph} \\
\end{tabular}
\end{center}

\textbf{Figure 1.1} THMP and PTA derivatives.\textsuperscript{47,58-64}

\subsection*{1.5. Conclusions}

Numerous water-soluble phosphines have been synthesized, however relatively few alkyl or nonaryl ligands have been synthesized. These ligands have varying sources of water solubility groups including cationic and anionic groups. The ammonium group is an excellent example of the water soluble cationic group while sulfonate and carboxylate groups are good examples of anionic groups, glycosides and sugar units are examples of neutral groups that make
a ligand soluble in water. Additionally there are ligands that inherently are water soluble from their nature (THMP and PTA). These ligands have yet to be applied to palladium catalysis.

2.1 Previous efforts to assess electronic donation of phosphines.

The exploration of electron donation was first presented by Müller and Strohmeier in 1967 by ranking phosphines in order of electronic donation based on metal CO IR stretching frequencies. Tolman followed in the 70’s by evaluating the CO IR stretching frequency of nickel/phosphine carbonyl compounds of 70 different phosphine ligands. The effect that the phosphine has on the metal center is transferred to the CO through back bonding of the metal center and can be measured in the shift in carbonyl stretching frequency. The result from this extensive evaluation of phosphine ligands is a ~55 cm$^{-1}$ (~0.7 kJ/mol) range for evaluating electron donating ability. Vastag utilized a $trans$-(L)$_2$Rh(CO)Cl complex (Equation 2.1) to describe the same event, with the range of TTBP to Ph$_3$P being 57 cm$^{-1}$. With phosphine/palladium catalysts being able to promote reactions at room temperature and others requiring temperatures in excess of 150 °C the small (~55 cm$^{-1}$) range in IR stretching frequencies may not be sufficient to describe activity. Many (L)$_2$Rh(CO)Cl complexes are normally square planar, however Baker reports that the geometry of the (TTBP)$_2$Rh(CO)Cl deviates from square planar geometry the $trans$-TTBP ligands are not 180° from each other, therefore as the angle of the ligand about the metal center deviates from linearity, the resulting distortion will be transferred to the CO stretching frequency. The sensitive nature of the geometry of these complexes therefore would suggest that another method be employed to verify
the precedence set forth by Müller, Strohmeier Tolman, and Vastag. The measurement of the electron donation is important since oxidative addition is promoted by strongly σ-donating ligands such as trialkyl phosphines.\textsuperscript{28,29} In palladium catalysis, knowing the donating ability of the ligand is important as oxidative addition is the first step in many of these reactions.

\[
\begin{align*}
[Rh(norboradiene)\text{Cl}_2]_2 & \xrightarrow{1) R_3P(2\text{ equiv})} \text{PR}_3 \quad \text{Cl-Rh-CO} \\
& \xrightarrow{2) \text{CO, CH}_2\text{Cl}_2} \quad \text{PR}_3
\end{align*}
\tag{2.1}
\]

In addition to measuring CO bond stretching frequencies, computational experiments have been undertaken.\textsuperscript{3} This approach measures, computationally, the relative energy of the molecules in their ground state. Additionally, the bond dissociation energy of the phosphine was determined. A measure of the HOMO energies and the difference between the HOMO and LUMO provides the GAP energy. The stronger the phosphine is bound to the palladium, and the greater the GAP, theoretically correlates to greater donation of electron density into the metal center. One problem that should be noted is that the computational data disagrees with the data from Rh-CO stretching frequencies for TTBP and DTB\textsubscript{Np}P. The calculated HOMO for DTB\textsubscript{Np}P is 4.50 eV and the HOMO for TTBP is 4.51 eV. The calculated HOMO energies suggest that DTB\textsubscript{Np}P is more electron releasing, albeit a small difference. The HOMO levels disagree with what is noted in the Rh-CO stretching frequencies (TTBP being 1921 and DTB\textsubscript{Np}P being 1939) suggesting that TTBP is more electron releasing. Therefore, it is necessary to develop an additional means of comparing phosphines to establish a trend that can be utilized in addition to the current methods of computational and Rh-CO stretching frequencies.
The two methods presented thus far, measuring a CO bond stretching frequency and computational approach, both have their significant weakness. For the CO stretching frequency, there is a geometric constraint and the effect of the other ligands sterically interacting with the phosphine and its coordination to the metal center. For computational studies to be meaningful, there always has to be experimental data to support its findings. It is therefore useful to derive another method that can be utilized to explain the electronic donation of a phosphine into a metal center. Taylor in 1982 reported on the use of phosphorous-selenium coupling as a measure of the electronic donation by a phosphine. In this system the $^{1}J_{P-Se}$ coupling is measured by $^{31}P$ NMR spectroscopy. The nature of the groups, size and geometric shape, around the P atom directly affect the magnitude of this $^{1}J_{P-Se}$ coupling. This $^{1}J_{P-Se}$ coupling has been demonstrated for PPh$_3$ and a number of triaryl derivatives. The trend seems to be that a diphenylalkylphosphine has a lower coupling constant than triarylphosphines, which in turn should equate the diphenylalkylphosphine having greater electron donating ability over the triphenylphosphines.

The size of a ligand is represented by its cone angle, for monodentate ligands. The measure of this parameter was crudely performed by Tolman in the 70’s. This crude adaptation of ball and stick models (Figure 2.1) laid the foundation for measuring the angle by which the groups around the phosphine surrounded the metal center. Under Tolman’s method for measuring the cone angle, the alkyl groups around the metal center were placed in the most compact conformation possible, then the angle from the center of the metal to the apex of the alkyl groups around the phosphine was measured. Recent efforts have used computer modeling programs to determine the cone angle of many phosphine ligands. The computational method uses the lowest energy conformation of the alkyl groups on the phosphine. Using Tolman’s method, the cone angle for TTBP is reported to be 182°, while when cone its cone angle was
determined from LDFT-optimization using the STERIC program appended to a Pd atom the cone angle was determined to be $194^\circ$.

![Tolman's angle](image)

**Figure 2.1** Representation of Tolman’s model for calculating cone angle

### 2.2 Results and Discussion

#### 2.2.1 Synthesis of DTBPPS and DAPPS.

In designing the new ligands for palladium coupling reactions the following considerations are taken into account: steric demand and electronic donating ability. As previously mentioned alkylphosphines are generally electron donating and the incorporation of bulky groups should lead to sterically demanding ligands. Additionally, the selection of an anionic polar group over neutral or cationic group should provide a more strongly electron donating phosphine. The approach taken was to react a dialkyl phosphine with 1,3-propanesultone (Scheme 2.1). This $S_N2$ reaction provides means to the water-soluble $-\text{SO}_3^-$ group and a phosphonium salt. The isolation of this salt is simple as it is zwitterionic and insoluble in ethereal solvents. Additionally, the starting materials are soluble in ethereal solvents and can be washed away upon filtration yielding pure ligand.
2.2.2 Evaluation of electron donation by phosphines

When considering the design and implementation of new phosphine ligands into metal catalysis, the establishment of the electron donation is useful. The ability to use $^{31}$P NMR spectroscopy as a method to assess electronic donation using the $^{1}$J$_{P-Se}$ coupling could be useful. The expectation would be that the smaller the coupling constant, the longer the bond, the more electron releasing the phosphine would be (Equation 2.1). Initial investigation into the alkylphosphines ligands shows that there is only a marginal difference between TTBP and DTBNpP (Table 2.1). Additionally, when evaluating the diadamantyl alkyl phosphines, they demonstrate lower coupling constants than TTBP; which is suggestive that they are the more electron releasing. When comparing TTBP to the neopentyl phosphines, the trend is that TTBP is the most electron releasing, followed by DTBNpP then followed by TNpP, and the lowest in that series is the TBDNpP. This trend is different form the a trends obtained in Rh-CO bond
stretching frequencies and computational data, when TNpP would be the least electron releasing by these measures, as it has the highest Rh-CO stretching frequency and the highest HOMO energy with a larger GAP spread in the series of neopentyl phosphines.

![Figure 2.2 Structures of the phosphine ligands utilized.](image)

Figure 2.2 Structures of the phosphine ligands utilized.

\[
\begin{align*}
R_3P &+ Se \\
\text{Solvent, Room temp} \\
16 h &\rightarrow R_3P-Se \\
\end{align*}
\]
Table 2.1 Comprehensive table of cone angle and electronic donation experiments.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>$\Theta_{DFT}$ (°)</th>
<th>$\Theta_{Tolman}$ (°)</th>
<th>HOMO</th>
<th>GAP (eV)</th>
<th>Ni(CO)$_3$L (cm$^{-1}$)</th>
<th>$\nu$Rh-CO (cm$^{-1}$)</th>
<th>$J_{P-Se}$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cy$_3$P</td>
<td>170</td>
<td>2056.4</td>
<td></td>
<td>674</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAPPS</td>
<td>170</td>
<td>2056.4</td>
<td></td>
<td>680</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DABP</td>
<td>170</td>
<td>2056.4</td>
<td></td>
<td>683</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTBP</td>
<td>194</td>
<td>2056.1</td>
<td></td>
<td>686</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTBPPS</td>
<td>195</td>
<td>2056.1</td>
<td>1921</td>
<td>686</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTBBP</td>
<td>198</td>
<td>2056.1</td>
<td>1939</td>
<td>692</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTBPnN</td>
<td>227</td>
<td>2068.9</td>
<td></td>
<td>701</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBNpN</td>
<td>210</td>
<td>2068.9</td>
<td></td>
<td>707</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPP</td>
<td>173</td>
<td>2068.9</td>
<td></td>
<td>730</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Cone angle values determined using STERIC program from LDFT optimized LPd(0).  
$^b$Tolman’s cone angles.$^{66}$  
$^c$HOMO energy at the B3LYP level.  
$^d$GAP = $E_{[\text{HOMO}]} - E_{[\text{LUMO}]}$  
$^e$Ni(CO)$_3$L (cm$^{-1}$) taken from Tolman.$^{66}$  
$^f$Reaction utilized Equation 2.1.  
$^g$Carbonyl stretching frequency taken from Shaughnessy.$^3$  
$^h$Carbonyl stretching frequency taken from Vastag.$^{67}$

The TPP ligand showed the highest coupling constant of this group which is expected as it is the least electron releasing. Additionally, TPP has a small cone angle relative to the other ligands in the series therefore should have the shortest P-Se bond length and the largest coupling constant. However, both DAPB and DAPPS have small cone angles as well, but demonstrate smaller coupling constants. The smaller coupling constants should be attributed to the greater electron donation. Seemingly the sulfonated group has a marginal positive effect on the electron donating ability of the ligand. In comparing similar ligands, DTBPP shows the same coupling constant as the DTBBP ligand. This is most likely because they are similar in structure with DTBBP being effectively half the DTBPP ligand. The DTBPP ligand is a chelating phosphine with a propyl chain in between each phosphorous atom, while the DTBBP ligand has a butyl chain and no other phosphine. Each phosphorous atom in the chelating ligand would coordinate
to a single selenium atom. The resulting complex demonstrates that each end of the chelating phosphine behaves similarly to non-chelating DTBBP.

In evaluating the neopentylphosphines against TTBP, computationally, there is little difference between each ligand. The Rh(CO)L complex show a 29 cm$^{-1}$ difference between TTBP and TNpP. In evaluating the $^1J_{\text{P-Se}}$ coupling constant, TTBP demonstrates the lowest coupling constant followed by DTBNpP, TNpP, and TBDNpP. In the $^1J_{\text{P-Se}}$ coupling constants for TTBP and the neopentylphosphines there is marginal difference in the range of coupling (686-707 Hz) (Table 2.1). In understanding the increase in coupling constant an argument can be made about a neopentyl arm having the ability to distort its geometry to accommodate the selenium atom attached to the phosphine can thereby facilitate a shortening of the P-Se bond.

When considering the water-soluble ligands, DAPPS when complexed to selenium, has the lowest $^1J_{\text{P-Se}}$ coupling constant in the series evaluated. While the DABP ligand has only a 3 Hz difference in coupling constant compared to DAPPS. DAPPS and DABP ligands differ only in the terminus of their respective alkyl chain. The DTBPPS ligand shows the same $^1J_{\text{P-Se}}$ coupling constant as TTBP, therefore our expectation would be they should perform similarly.

When evaluating the reaction between the di-tert-butyl(3-chloropropane)phosphine, a much lower coupling constant was obtained (426 Hz) (Scheme 2.2). The coupling constant being 426 Hz was too low for solely an electronic effect. The lower coupling constant suggest a different bonding situation. There are a number of reports of [R$_3$P-Se-R’] (R and R’ are aryl) compound in the literature, however there are few examples with alkyl groups, and there are no cyclic structures found. However, Godfrey$^{72}$ reports on a number of R$_3$P-Se(Ph)Br (R = Ph, Me, Ph, Cy, etc) having $^1J_{\text{P-Se}}$ coupling constant ranging from 427-438 Hz. Indorato also synthesized a tributyl(methylseleno) phosphium salt and reported its $^1J_{\text{P-Se}}$ coupling constant to be 417 Hz.$^{73}$ The coupling constant we noted from the di-tert-butyl(3-chloropropane)phosphine reacting with
selenium falls in the range of an alkyl phosphine alkyl selenium compound. Reasonably the cyclized product could be formed. To our knowledge the cyclization is the first molecule of its type to have been synthesized, however further characterization is ongoing.

![Scheme 2.2](image-url) The reaction di-tert-butyl(3-chloropropane)phosphine with Se.

### 2.3 Conclusion

The use of the $^{1}J_{P,Se}$ in addition to $^{31}P$ NMR can be used in the evaluation of the electron donating ability of a phosphine. The usefulness of the combination of a phosphine with a selenium atom is the absence of the effect of other ligands on the metal center influencing the donation of the phosphine. From the comparison of DAPPS to DAPB there appears to be positive effect on the electronic donation. In comparing the chelating DTBPP and DTBBP ligands have the same coupling constant most likely because they are similar in structurally. The comparison between DTBPPS and TTBP demonstrate same coupling constant, nearly the same cone angle and therefore should show similar activity. Additionally the reaction of di-tert-butyl(3-chloropropane)phosphine and selenium in the presence of DABCO leads to the cyclized
product. The cyclized product coupling constant (426 Hz) falls in the range of an alkyl(alkylseleno)phosphonium compound.

2.4 Experimental

2.4.1 General reaction conditions for ligand synthesis.

All reagents were used from their supplier as received without further purification. Dioxane was oxygenated via sparging with nitrogen prior to use. The reactions were set up in a nitrogen filled glove box in a 2-neck round bottom flask with a reflux condenser and a nitrogen adaptor. The reactions were allowed to react for 16 h under reflux. After the reflux time had expired, the reactions were cooled to room temperature, filtered and washed with 3 x 10 ml portions of ethyl ether.

3-(di-tert-butylphosphonium)propylsulfonate (DTBPPS): Di-tert-butyl phosphine (6.75 ml) was added to 1,3-propane sultone (.024 mol, 2.98 g) along with 40 ml of dioxane. The reaction yielded a white powder (100%, 15.67 g). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.96 (d, $J = 484.9$ Hz, 1H), 3.00 (t, $J = 6.6$ Hz, 2H), 2.60, (m, 2H), 2.36 (m, 2H) 1.54 (d, $J = 16.1$ Hz, 18H), $^{13}$C NMR (CDCl$_3$ 126 MHz): $\delta$ 50.9 (d, $J = 11.9$ Hz), 32.7 (d, $J = 35.7$ Hz), 27.4, 22.8 (d, $J = 4.5$ Hz) 13.7 (d, 40.3 Hz) . $^{31}$P NMR (202 MHz, -DMSO-d$_6$) $\delta$: 44.7 (d, $J = 450.4$ Hz)

3-(di-adamantyl-propylphosphine) propylsulfonate (DAPPS): Diadamantyl phosphine that was prepared using literature preparation,$^7$ (2.15 mmol, 650 mg) was added to 1,3-propane sultone (2.45 mmol, 0.3 g) along with 10 mL of dioxane. The reaction yielded a white powder (34%, 0.315 g). $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 5.7 (d, $J = 463.4$ Hz, 1H), 2.60 (t, $J = 6.9$ Hz, 2H), 2.07 (d, $J = 27.4$ Hz, 18H), 1.97 (m,6H), 1.81 (d, $J = 11.7$ Hz, 6H), 1.72 (d, $J = 11.9$Hz , 6H) $\delta$ $^{13}$C NMR (126 MHz, CDCl$_3$): 42.8, 37.9, 37.3 (d, $J = 33.9$ Hz), 36.3 (d, $J = 54.2$ Hz), 25
2.4.2 General procedure for making R₃P-Se.

All reagents were used from their supplier as received without further purification. The THF was freshly distilled from sodium and benzophenone, and the MeOH (methanol) was purchased anhydrous and sparged with nitrogen to remove oxygen. Neopentyl phosphines and TTBP were used as solutions in toluene.

All reactions were set up in a nitrogen filled dry box into a 1 dram vial with a PTFE coated stir bar and septa top. The selenium powder was added to the vial followed by the ligand. The vial was removed from the dry box where it was charged with solvent. The reactions were allowed to stir at room temperature for 16 h, and then filtered through a Pasteur pipette packed with a Kim wipe. The solvent was removed under reduced pressure.

2.4.3 General procedure for protonated ligands.

In a nitrogen filled dry box, the ligand was placed into a 1 dram vial along with Se powder and Na₂CO₃. The vial was removed from the dry box where it was charged with THF for hydrophobic ligands or MeOH for water-soluble ligands. The reaction was allowed to stir for 16 h followed by filtration through a Pasteur pipette packed with a Kim wipe. The solvent was removed with under reduced pressure.

Table 2.2 Entry 1: Cy₃P-Se: Using the general procedure, Cy₃P (60 mg, 0.21 mmol), Se powder (45 mg, 0.5 mmol), and 1.0 ml of THF were allowed to react. ³¹P NMR (CDCl₃, 202 MHz) δ 58.3 (d, J = 674 Hz).
Table 2.2 Entry 2: DAPPS-Se: Using the general procedure, DAPPS (53 mg, 0.25 mmol), Se powder (22 mg, 0.26 mmol), Na$_2$CO$_3$ (30 mg, .26 mmol) and 2.0 ml of MeOH were allowed to react. $^{31}$P NMR (CDCl$_3$, 202 MHz) δ 71.1 (d, $J = 680$ Hz)

Table 2.2 Entry 3: DABP-Se: Using the general procedure, DABP(HBr) (55 mg, 0.25 mmol), Se powder (22 mg, 0.26 mmol), Na$_2$CO$_3$ (30 mg, .26 mmol) and 1.0 ml of THF were allowed to react. $^{31}$P NMR (CDCl$_3$, 202 MHz) δ 70.1 (d, $J = 683$ Hz).

Table 2.1 Entry 4: TTBP-Se: Using the general procedure, TTBP (600 µL, 0.2 mmol), Se powder (45 mg, 0.5 mmol), and 1.0 ml of THF were allowed to react. $^{31}$P NMR (CDCl$_3$, 202 MHz) δ 92.5 (d, $J = 686$ Hz).

Table 2.2 Entry 5: DTBPPS-Se: Using the general procedure, DTBPPS (134 mg, 0.5 mmol), Se powder (45 mg, 0.5 mmol), Na$_2$CO$_3$ (58 mg, 0.51 mmol) and 2.0 ml of THF were allowed to react. $^{31}$P NMR (CDCl$_3$, 202 MHz) δ 81.5 (d, $J = 686$ Hz).

Table 2.2 Entry 6: DTBPP-Se: Using the general procedure, DTBPP(2 HBr) (247 mg, 0.5 mmol), Se powder (45 mg, 0.5 mmol), Na$_2$CO$_3$ (116 mg, 1.1 mmol) and 2.0 ml of THF were allowed to react. $^{31}$P NMR (CDCl$_3$, 202 MHz) δ 76.8 (d, $J = 692$ Hz).

Table 2.2 Entry 7: DTBNpP-Se: Using the general procedure, DTBNpP (1.1 ml, 0.2 mmol), Se powder (45 mg, 0.5 mmol), and 1.0 ml of THF were allowed to react. $^{31}$P NMR (CDCl$_3$, 202 MHz) δ 67.3 (d, $J = 699$ Hz).

Table 2.2 Entry 8: DTBBP-Se: Using the general procedure, DTBBP(HBr) (70.68 mg, 0.25 mmol), Se powder (22 mg, 0.26 mmol), Na$_2$CO$_3$ (30 mg, .26 mmol) and 2.0 ml of THF were allowed to react. $^{31}$P NMR (CDCl$_3$, 202 MHz) δ 76.7 (d, $J = 692$ Hz).

Table 2.2 Entry 9: TNpP-Se: Using the general procedure, DTBNpP (1.15 ml 0.2 mmol), Se powder (45 mg, 0.5 mmol), and 1.0 ml of THF were allowed to react. $^{31}$P NMR (CDCl$_3$, 202 MHz) δ 18.1 (d, $J = 701$ Hz).
Table 2.2 Entry 10: TBDNpP-Se: Using the general procedure, TBDNpP (1.1 ml, 0.2 mmol), Se powder (45 mg, 0.5 mmol), and 1.0 ml of THF were allowed to react. $^{31}$P NMR (CDCl$_3$, 202 MHz) $\delta$ 40.5 (d, $J = 707$ Hz).

Table 2.2 Entry 11: Ph$_3$P-Se: Using the general procedure, Ph$_3$P (20 mg, 0.08 mmol), Se powder (13 mg, 0.17 mmol), and 1.0 ml of THF were allowed to react. $^{31}$P NMR (CDCl$_3$, 202 MHz) $\delta$ 30.31 (d, $J = 730$ Hz).
CHAPTER 3. Palladium-Catalyzed Coupling Reactions of Neopentyl Phosphines

3.1 Introduction

3.1.1 Palladium Catalysis

The ability to generate new carbon-carbon (C-C), carbon-nitrogen (C-N), carbon-oxygen (C-O) and other carbon-heteroatom bonds is of particular use to a variety of industries. The resulting products generated through making new carbon-carbon or carbon-heteroatom bonds have various applications (optical devices, drugs, agrochemicals etc). Transition metal catalysts can help in the synthesis of these molecules. In particular palladium catalysts can be a useful tool for the synthetic chemist as they are powerful methods for producing C-C and carbon-heteroatom bonds. Suzuki reported on the ability to couple aryl halides with aryl boronic acid derivatives using palladium/phosphine catalyst. Interestingly, this was one of the first examples of palladium catalysis in aqueous/organic media.

3.1.2 Mechanism of Palladium-Catalyzed Suzuki Coupling Reactions

To understand the role of the palladium phosphine catalyst, it is helpful to evaluate what steps are present along the catalytic pathway (Scheme 3.1). Many palladium catalyzed reactions follow a similar mechanistic pathway; however, the central focus to this point is the
Suzuki coupling reaction. The oxidative addition step is typically the rate determining step associated in this reaction (Scheme 3.1).\textsuperscript{23,24}

![Suzuki coupling mechanism diagram]

**Scheme 3.1** Generic Suzuki coupling mechanism

Transmetalation occurs after the oxidative addition step (Scheme 3.1). It has been postulated that transmetalation occurs because the newly generated Pd\textsuperscript{II} is more electropositive than the Pd\textsuperscript{0} and is readily available to accept an incoming nucleophile.\textsuperscript{77} Once transmetalation occurs, reductive elimination is facilitated. Once transmetalation occurs, reductive elimination is quick to follow making its observation difficult to track, apart from measuring the appearance of product. However, there is evidence of a palladium phosphine/borate complex (Equation 3.1) being generated \textit{in situ} from the complexation of an activated boronate to a Pd\textsuperscript{II} aryl halide complex.\textsuperscript{78} This intermediate is observable via $^{31}$P NMR in the $^{3}$J\textsubscript{P,B} coupling. The observation
of the intermediate is important in understanding how the mechanism proceeds. Should this coordination occur, then boronic esters may not coordinate easily to sterically hindered Pd catalysts without a prior hydrolysis to the boronic acid.

\[
\begin{align*}
\text{Ph}_2\text{Pd} & \quad \text{Ph} \quad \text{CF}_3 \quad \text{Br} \\
\nonumber 
\xrightarrow{\text{(HO)}_2\text{B} \quad \text{Ph}} \\
\text{Ph}_2\text{Pd} & \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{H} \quad \text{BOH} \quad \text{OH} \\
\nonumber 
\text{+ KBr} \\
\text{(3.1)}
\end{align*}
\]

DFT calculations by Maseras and co-workers\textsuperscript{79} suggest that the base will displace the halide from the oxidatively added palladium aryl halide complex (Scheme 3.2). This observation fits with our previous argument (Equation 3.1), that a borate complex is generated. The palladium/base catalyst will coordinate the boronic acid allowing the aryl group to be transferred to the palladium. Additionally, the borate complex explains the necessity of the base for the reaction to occur. Maseras comments that the halide ligand could undergo the same coordination with boron, however the energy barrier pathway is unfavorable.

\[
\begin{align*}
\text{Ph}_3\text{Pd} & \quad \text{Br} \\
\nonumber 
\xrightarrow{- \text{OH}} \\
\text{Ph}_3\text{Pd} & \quad \text{OH} \\
\nonumber 
\xrightarrow{- \text{B(OH)}_2} \\
\text{Ph}_3\text{Pd} & \quad \text{Br} \\
\nonumber 
\xrightarrow{- \text{B(OH)}_2} \\
\text{Ph}_3\text{Pd} & \quad \text{Br}
\end{align*}
\]

**Scheme 3.2** Most probable intermediate for transmetalation in Suzuki coupling according to DFT experiments.\textsuperscript{79}
The final step along the catalytic pathway is the reductive elimination step (Scheme 3.1). Stille, in the early 80’s, demonstrated that reductive elimination occurs through a cis-palladium complex (Scheme 3.3). In the cases where the complex is locked in a cis conformation, no isomerization is needed, however cis geometry is required. Where isomerization cannot occur, to attain reductive elimination another mechanism occurs. Recent DFT studies suggest that reductive elimination can proceed through differing intermediates depending on the phosphine utilized. This study suggests, that P(Me)₃ proceeds through the 4-coordinate intermediate, while the PCy₃ proceeds trough a T-shaped intermediate the TPP complex has the ability to proceed through either pathway.

![Scheme 3.3 Isomerization of Pd(CH₃)₂(PPh₃) to allow reductive elimination.](image)

**3.1.3 Palladium catalysis with phosphine ligands**

Previous and continuing efforts centering on the pursuit of “ligand free” catalytic palladium systems have generated a great deal of attention. The major idea being that a palladium surface or the surface to which it is attached (palladium impregnated in a polymer or
mesoporous silica\textsuperscript{84} can activate itself without the assistance of a phosphine or carbene type ligand. The limitation associated with this type of catalysis is that more reactive substrates (activated aryl iodide or bromide) must be used employing high reaction temperatures and long times. The drawbacks associated with “ligand free” palladium catalysts facilitate the need for the palladium surface to be activated. This activation can be brought about by coordination of a ligand (phosphine carbene, or some other activating agent). While numerous efforts for synthesizing ligands have been undertaken, trialkylphosphines are the most pertinent for this discussion as they are generally provide a more reactive catalyst.\textsuperscript{1-3,5,7,85-87} In particular, TTBP (Figure 3.1) has generated a great deal of this interest as it has been utilized in the various palladium coupling reactions. After the Tosh company reported on TTBP providing excellent reactivity and selectivity towards N-arylation of pipperazines,\textsuperscript{88} many other research groups followed with using them in other palladium catalyzed coupling reactions including: amination,\textsuperscript{1} Heck,\textsuperscript{85} Suzuki,\textsuperscript{89} carbonylation,\textsuperscript{8} Sonogashira,\textsuperscript{7} and many couplings.

![Various alkyl phosphines used in palladium catalyzed-coupling reactions](image)

**Figure 3.1** Various alkyl phosphines used in palladium catalyzed-coupling reactions
It has become widely accepted that sterically demanding, electron rich phosphine ligands facilitate catalytic activity in the aforementioned palladium catalyzed coupling reactions. These sterically demanding ligands promote ligand dissociation from the proposed L₂Pd⁰ complex. This steric demand creates the ability for one of the ligands to dissociate which prior to the rate-limiting step associated with oxidative addition or aryl bromides.⁹⁰ The use of TTBP in catalytic systems, has become widely accepted. It is therefore a useful option to develop a catalyst system that can be a useful alternative to TTBP. In evaluating other catalytic systems, more consideration needs to be given to ligands that are different in cone angle and electronic donation as there might be a more optimum combination for various palladium catalyzed coupling reactions not yet discovered. The substitution of a neopentyl group for a tert-butyl group offers an interesting venue to explore varying cone angles and electronic donation while staying similar TTBP.

The initial studies using the neopentyl phosphines were in Pd amination cross-coupling of aryl halides.³ This investigation suggested that palladium catalyst utilizing DTBNpP had the ability to out perform one having TTBP. This result suggests that an optimal cone angle and electronic donation may be mandated for amination chemistry. If amination has an optimal range of cone angle and electronic donation, then perhaps other palladium catalyzed reactions (Suzuki, Sonogashira, Heck, etc) would have an optimal range as well.
3.2 Results and Discussion

3.2.1 Neopentyl derivatives of TTBP in Suzuki Coupling

Initial investigation was to utilize conditions developed by Fu (Equation 3.3), which were unsuccessful. This lack of success could come from a number of sources, wet KF or the inability of the neopentyl phosphines to catalyze the reactions under Fu’s conditions.

![Chemical Reaction Image]

The lack of success associated with Fu’s conditions led to pursuit of a different set of conditions. Initial investigation was to pursue a medium through which a cheap base and solvent could be employed. Investigation led to use biphasic conditions, as water is relatively cheap and would allow using an inorganic base (Equation 3.3). However, the use of water solely, creates a problem as many of the substrates are insoluble in water. Our approach was to add an organic solvent, (THF) to solubilize the substrates under classical Suzuki conditions. Vigorous stirring mixes each phase well enough to allow reaction to proceed.

Since, DTBNpP, TBDNpP, and TNPpP perform similarly in Suzuki coupling; it is helpful to evaluate their catalytic ability relative to each other and TTBP with respect to time.

![Chemical Reaction Image]
competitive rate study was performed (Equation 3.5), we see that TTBP is the fastest to promote coupling with the reaction nearly complete after 45 min (Figure 3.2). The DTBNpP ligand was the next to reach completion, in 60 min, followed by the TBDNpP at 120 min, and the TNpP was still not finished after 4 h. All of the neopentyl ligands, with the exception of TNpP, perform well and finish the reaction rapidly. The rapid nature of these catalysts suggests that Suzuki coupling has a broad range of cone angles and electronic donation that are effective.

**Rate comparison of Neopentyl Phosphines**

![Graph showing rate comparison of neopentyl phosphines against TTBP using Equation 3.5](image)

**Figure 3.2** Rate evaluation of neopentyl phosphine ligands against TTBP using Equation 3.5

Once an optimal protocol was established (Equation 3.5) for Suzuki coupling, investigation into numerous substrates was performed. In the investigation, evaluation of activated, non-activated and deactivated substrates was carried out. Activated aryl halides, have
electron withdrawing groups at ortho- and/or para-positions respective to the halide, while deactivated have electron donating groups ortho- and/or para to the halide. In addition, the steric accessibility of a substrate onto the catalyst was evaluated. Both DTB\textit{N}p\textit{P} and TBD\textit{N}p\textit{P} (Figure 3.2) performed well in coupling of activated, de-activated, and neutral aryl bromides. However, for the sterically demanding 2-bromo-\textit{meta}-xylene, DTB\textit{N}p\textit{P} was ineffective at promoting activity. In contrast T\textit{N}p\textit{P} was able to promote coupling of 2-bromo-\textit{meta}-xylene (Table 3.1). The T\textit{N}p\textit{P} is interesting because according to computational data, T\textit{N}p\textit{P} has the largest cone angle. The T\textit{N}p\textit{P} promoting coupling of sterically hindered substrates is counter to the expectation. The ligand with the largest cone angle in the series would not be expected to couple a sterically hindered substrate while the smaller ligands don’t promote reaction. However, if we consider a neopentyl group as having more conformational freedom than a \textit{tert}-butyl group then a neopentyl arm can adapt itself to accommodate a substrate around a metal center. Additionally, the ability of T\textit{N}p\textit{P} to couple bromo-\textit{meta}-xylene having the largest cone angle suggests that the single cone angle value for phosphine containing a group with conformational freedom may not be reflective of its actual size. Moreover, a range of angles might be a better representation rather than a single number.

While both DTB\textit{N}p\textit{P} and TBD\textit{N}p\textit{P} generate more robust catalyst with palladium with aryl bromides when compared to T\textit{N}p\textit{P} (Table 3.2), moving to deactivated aryl chlorides at elevated temperatures, we see a reversal in reactivity. We postulate that the DTB\textit{N}p\textit{P} and TBD\textit{N}p\textit{P} palladium catalysts decompose more rapidly at the elevated temperatures thereby, terminating their reactivity. When we challenge the catalyst to choose between bromide and chloride, the catalyst chooses the bromide exclusively (Entry 10, Table 3.2).
Table 3.2  Isolated yields from Suzuki coupling using Pd/neopentyl phosphine catalyst

<table>
<thead>
<tr>
<th>Aryl Halide</th>
<th>Boronic Acid</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC-Br</td>
<td>B(OH)$_2$</td>
<td>NC-Ph</td>
<td>DTBNpP 94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBDNpP 94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TNpP 84</td>
</tr>
<tr>
<td>O-Me</td>
<td>B(OH)$_2$</td>
<td>O-Ph</td>
<td>DTBNpP 98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBDNpP 91</td>
</tr>
<tr>
<td>MeO-Me</td>
<td>B(OH)$_2$</td>
<td>MeO-Ph</td>
<td>DTBNpP 99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBDNpP 99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TNpP 85$^a$</td>
</tr>
<tr>
<td>Me-Me</td>
<td>B(OH)$_2$</td>
<td>Me-Ph</td>
<td>DTBNpP 95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBDNpP 93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TNpP 99</td>
</tr>
<tr>
<td>Me-Me</td>
<td>B(OH)$_2$</td>
<td>Me-Ph</td>
<td>DTBNpP 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBDNpP 0$^b$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TNpP 87$^a$</td>
</tr>
<tr>
<td>MeO-Me</td>
<td>F-B(OH)$_2$</td>
<td>MeO-FPh</td>
<td>DTBNpP 80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeO-Me</td>
<td>F-F-B(OH)$_2$</td>
<td></td>
<td>DTBNpP 95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeO-Me</td>
<td>Cl-B(OH)$_2$</td>
<td>MeO-ClPh</td>
<td>DTBNpP 40$^b$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBDNpP 78$^b$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TNpP 80$^b$</td>
</tr>
<tr>
<td>Cl-Me</td>
<td>B(OH)$_2$</td>
<td>Cl-Ph</td>
<td>DTBNpP 85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TNpP 80</td>
</tr>
<tr>
<td>NC-Cl</td>
<td>Cl-B(OH)$_2$</td>
<td>NC-ClPh</td>
<td>DTBNpP 73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBDNpP 99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TNpP 99</td>
</tr>
</tbody>
</table>

Reaction conditions were those shown in Equation 3.4 at 23 °C.  

a) reaction temperature 80 °C.  
b) reaction temperature 100 °C.
3.2.2 Neopentyl Ligands in Enolate coupling

Hartwig, in the late 90’s, reported on the ability to α-arylate ketones using a palladium/phosphine ligand catalyst. After this initial report, there have been a number of investigations into the use of ketones, amides, and other enolate sources. In addition to presenting the reactions, Hartwig performed a number of mechanistic studies associated with the reaction. The mechanism that is accepted follows that presented by Hartwig, and follows many of the other palladium catalyzed coupling reaction mechanisms (Scheme 3.4).

Scheme 3.4 An adaptation of Hartwig’s proposed mechanism for enolate coupling.
Table 3.2  Isolated yields from enolate coupling experiments.

<table>
<thead>
<tr>
<th>Aryl Halide</th>
<th>Enolate Source</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br-NC</td>
<td>DTBNpP 76</td>
<td></td>
<td>no rxn a</td>
</tr>
<tr>
<td>MeO-Br</td>
<td>DTBNpP 99</td>
<td></td>
<td>no rxn a</td>
</tr>
<tr>
<td>Me-Br</td>
<td>DTBNpP 99</td>
<td></td>
<td>no rxn a</td>
</tr>
<tr>
<td>Me-Br</td>
<td>DTBNpP 90</td>
<td></td>
<td>no rxn a</td>
</tr>
<tr>
<td>MeO-Br</td>
<td>DTBNpP 98</td>
<td></td>
<td>no rxn a</td>
</tr>
<tr>
<td>MeO-Cl</td>
<td>DTBNpP 95</td>
<td></td>
<td>no rxn a</td>
</tr>
<tr>
<td>Me-Cl</td>
<td>DTBNpP 86 °</td>
<td></td>
<td>no rxn a</td>
</tr>
<tr>
<td>MeO-Cl</td>
<td>DTBNpP 92</td>
<td></td>
<td>no rxn a</td>
</tr>
<tr>
<td>MeO-B</td>
<td>DTBNpP no rxn</td>
<td></td>
<td>no rxn a</td>
</tr>
<tr>
<td>MeO-B</td>
<td>DTBNpP no rxn</td>
<td></td>
<td>no rxn a</td>
</tr>
</tbody>
</table>

Conditions used were the one from Equation 3.6 run at 80 °C.  a)  Reaction temperature 120 °C.  
b)  Reactiton temperature 100 °C
Efforts in promoting α-arylation of ketones with palladium/phosphine catalysts have led to the neopentylphosphines being applied to this reaction. Attempts to couple non-sterically demanding substrates, propiophenone, acetophenone, and 1,3-cyclohexanone all proved unsuccessful, even at elevated temperatures. However; activity from isobutyrophene was noticed. A range of activated and deactivated substrates were evaluated. Good to excellent productivity was seen with activated and deactivated substrates. Additionally, we saw no reactivity from catalysts derived from palladium and TBDNpP or TNpP. Good to excellent isolated yields from 80-100 °C with both deactivated aryl chlorides and bromides. For sterically hindered aryl bromides and chlorides require 100 °C to afford excellent yield. The inability to couple smaller substrates and the ability to couple larger substrates suggests that a more sterically demanding catalyst would perform better. Additionally, the inactivity of 1,3-pentanedione suggests once deprotonated provides acetyacetonate which is an excellent ligand for metals, thereby inhibiting the reaction.

\[
\begin{align*}
&\text{Br} \quad \text{Pd}_2(\text{dba})_3 \quad 0.5 \text{ mol}\% \\
&\text{1 equiv.} \quad \text{Ligand} \quad 1.1 \text{ mol}\% \\
&\text{1.1 equiv.} \quad \text{NaO}t-\text{Bu} \quad (1.1\text{equiv}) \\
&\text{Toluene} \\
\end{align*}
\]

(3.6)

3.3 Conclusions

The investigation into the neopentylphosphine derivatives of TTBP has led us to catalytic systems that have the ability to promote Suzuki and enolate coupling of aryl bromides and
chlorides. Many of the examples provide good to excellent yields for activated and deactivated substrates.

For Suzuki coupling, the use of DTBNpP was effective in coupling aryl bromides at room temperature. However, upon changing the substrate to a deactivated aryl chloride, the palladium/phosphine catalyst was not able to effectively afford good conversion to product at room temperature. The catalyst derived from TNP was more effective at converting aryl chlorides at elevated temperatures whereas DTBNpP is not. Additionally, sterically hindered substrates are able to be coupled with the palladium/TNP catalyst whereas the palladium/DTBNpP catalyst does not. When evaluating rate of the palladium catalysts derived from each ligand, the TTBP catalyst gives a more active catalyst than the DTBNpP catalyst, which is faster than the TBDNpP catalyst, which is much faster than the TNP catalyst. The neopentyl group may accommodate groups on the palladium center thereby lowering a catalysts ability to undergo ligand dissociation or reductive elimination.

The palladium/DTBNpP catalyzed α-arylation of ketones was demonstrated with good to excellent yields at elevated temperatures for iso-butyrophene, but no other enolate source tested was successful. Additionally, TBDNpP and TNP generated unsuccessful catalysts with palladium in α-arylation of ketones at elevated temperatures.

3.4 Experimental

3.4.1 General procedural comments

The ligands utilized in these studies were provided by FMC lithium and are solutions in toluene. The THF utilized was obtained from a solvent still from sodium metal and benzophenone. The toluene utilized was obtained freshly from a solvent still over sodium metal.
Water was taken from a deionized source and sparged for 15 min with nitrogen. All other reagents were used from their source, in general from Acros and Sigma-Aldrich. Silica gel was obtained from Sorbent Technologies and was standard grade, 230 x 400 mesh, 60 Å.

3.4.2 General procedure for the Suzuki coupling of aryl bromides.
In a nitrogen filled dry box, a 1 dram vial was charged with Pd$_2$(dba)$_3$ (0.005 mmol, 4.5 mg), ligand (0.01 mmol), arylboronic acid (1.1 mmol), Na$_2$CO$_3$ (1.10 mmol, 116.0 mg), aryl halide (1 mmol), and THF (1 mL). The vial was then removed from the drybox and charged with deoxygenated water (1 mL). The reaction was stirred at room temperature for 16 h. Gas chromatography was performed using a carbowax column to assess completeness. Reactions carried out at elevated temperatures were stirred in a preheated oil bath. Ethyl acetate (25 mL) was added to the reaction mixture, which was then washed with 2 × 25 mL portions of brine. The organic layer was dried over MgSO$_4$ and the solvent removed under reduced pressure. The crude products were purified using flash chromatography through a short plug of silica gel using a gradient mixture of hexanes and ethyl acetate (100:0-85:15 hexane/EtOAc) as the eluent. All products were spectroscopically pure and consistent with previously reported spectra.

4-Cyanobiphenyl. 4-Bromobenzonitrile (1.00 mmol, 181 mg) and phenylboronic acid (1.30 mmol, 161 mg) were coupled under the general procedure. The product was isolated as a cream-colored solid (DTBnP: 94%, 174 mg; TBDnP: 94%, 174 mg; TNp: 84%, 155 mg). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.72 (d, $J = 8.5$ Hz, 2H), 7.68 (d, $J = 8.2$ Hz, 2H), 7.58 (t, $J = 6.9$ Hz, 2H), 7.47 (t, $J = 7.5$ Hz, 2H), 7.41 (t, $J = 7.5$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 145.7, 139.2, 132.6, 129.1, 128.7, 127.7, 127.2, 118.9, 110.9. mp: 83-84 °C (lit. mp: 86-87 °C).
Alternatively, 4-chlorobenzonitrile (1.00 mmol, 138 mg) was coupled with phenylboronic acid (1.30 mmol, 161 mg) to give the product 73% yield (190 mg) using DTBNP, 99% yield (192 mg) using TBDNP, and 99% yield (203 mg) using TNP.

**4'-Phenylacetophenone.** 4-Bromoacetophenone (1.00 mmol 199 mg) and phenyl boronic acid (1.30 mmol, 161 mg) were coupled under the general procedure. The product was isolated in a as a white solid (DTBNP: 91%, 186 mg; TBDNP: 98%, 192 mg). $^1$H NMR (500 MHz, CDCl$_3$): δ 8.02 (d, $J = 8.4$ Hz, 2H), 7.67 (d, $J = 8.5$ Hz, 2H), 7.61 (d, $J = 7.2$ Hz, 2H), 7.46 (t, $J = 6.9$ Hz, 2H), 7.39 (t, $J = 7.2$ Hz, 1H), 2.62 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 197.6, 145.7, 139.8, 135.8, 128.8, 128.7, 128.1, 127.2, 127.1, 26.7. mp: 116-118 °C (lit mp: 120-121 °C).

**4-Methoxybiphenyl.** 4-Bromoanisole (1 mmol, 125 µL) and phenylboronic acid (1.30 mmol, 161 mg) were coupled under the general procedure. The product was isolated as a white solid (DTBNP: 99%, 183 mg; TBDNP: 94%, 174 mg; TNP: 85%, 156 mg at 80 °C). $^1$H NMR (500 MHz CDCl$_3$): δ 7.56 (d, $J = 7.2$ Hz, 2H), 7.52 (d, $J = 8.8$ Hz, 2H), 7.40 (t, $J = 10.9$ Hz, 1H), 7.29 (t, $J = 7.5$ Hz, 2H), 6.97 (d, $J = 8.8$ Hz, 2H), 3.83 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 159.1, 140.9, 133.8, 128.8, 128.2, 126.8, 126.7, 114.2, 55.4.

Alternative, 4-chloroanisole (1.0mmol 122µL) and phenylboronic acid (1.30 mmol, 161 mg) were coupled under the general procedure, but at 100 °C using dioxane in place of toluene (DTBNP: 40% (GC); TBDNP: 78%, 154 mg; TNP: 80%, 156 mg).

**2-Methylbiphenyl.** 2-Bromotoluene (1.0 mmol, 120µL) and phenylboronic acid (1.30 mmol, 161 mg) were coupled under the general procedure. The product was isolated as a translucent liquid (DTBNP: 95%, 161 mg; TBDNP: 93%, 158 mg; TNP: 99%, 166 mg at 80 °C). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.52 (m, 2H), 7.44 (m, 3H), 7.37 (m, 4H), 2.39 (s, 3H).
$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 142.1, 135.4, 130.5, 130.0, 128.8, 128.2, 127.4, 127.3, 126.8, 125.9, 20.6.

4'-Fluoro-4-methoxybiphenyl. 4-Fluorophenylboronic acid (1.10 mmol, 154 mg) and 4-bromoanisole (1.0 mmol, 125 µL) were coupled under the general procedure using DTBnpP. The product was isolated in an 80% yield as a tan solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.49 (m, 2H), 7.43 (d, $J = 8.8$ Hz, 2H), 7.09 (t, $J = 8.5$ Hz, 2H), 6.96 (d, $J = 8.8$ Hz, 2H), 3.84 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 162.1 (d, 246 Hz), 159.1, 137.0, 132.7, 128.2 (d, $J = 7.3$ Hz), 128.0, 115.5 (d, $J = 21.0$ Hz), 114.3, 55.4. mp: 86-87°C (Lit. mp. 84-86°C).

2,4-Difluoro-4'-methoxybiphenyl. 2,4-Difluorophenylboronic acid (1.10 mmol, 174 mg) and 4-bromoanisole (1.0 mmol, 125 µL) were coupled under the general procedure using DTBnpP. The product was isolated in a 95% yield as a white solid (220.0 mg). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.44 (dd, $J = 1.87$, 7.04 Hz, 2H), 7.38 (m, 1H), 6.98 (d, $J = 8.9$ Hz, 2H), 6.92 (m, 1H), 6.89 (m, 1H), 3.85 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 161.8 (dd, $J = 11.9$, 247.4 Hz), 160.8 (dd, $J = 11.9$, 237.4 Hz), 159.2, 131.1 (dd, $J = 5.49$ Hz), 129.9 (d, $J = 2.7$), 127.3 (d, $J = 1.8$), 125.0 (dd, $J = 3.7$, 13.7 Hz), 114.0, 111.4 (dd, $J = 3.67$, 21.1 Hz), 104.3 (dd, $J = 25.7$ Hz), 55.2.

2-Chlorobiphenyl. Phenylboronic acid (1.30 mmol, 160 mg) and 2-bromochlorobenzene (1.0 mmol, 122 µL) were coupled under the general procedure using TNpP. The product was isolated in a 97% yield as a low-melting, tan solid. GC/MS: 188 (100%), 190 (33%). $^1$H NMR (360 MHz, CDCl$_3$): $\delta$ 7.46 (m, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 140.6, 139.5, 132.6, 131.5, 130.0, 129.5, 128.6, 128.1, 1277, 126.9.
3.4.3 General procedure for the α-arylation of ketones using aryl bromides and chlorides.

In a dry box, a 1 dram vial was charged with Pd$_2$(dba)$_3$ (0.005 mmol, 4.5 mg), ligand (0.01 mmol), NaOt-Bu (1.10 mmol), aryl halide (1 mmol), and toluene (1 mL). The vial was then removed from the drybox and charged with isobutyropheneone (150 µL, 1.0 mmol). The reaction was stirred at room temperature until judged complete by GC. Reactions carried out at elevated temperatures were stirred in a preheated oil bath for 16 h. Ethyl acetate (25 mL) was added to the reaction mixture, which was then extracted with 2 × 25 mL portions of brine. The organic layer was dried over MgSO$_4$ and the solvent removed under reduced pressure. The crude products were purified using flash chromatography through a short plug of silica gel using a gradient mixture of hexanes and ethyl acetate (100:0-85:15 hexane/EtOAc) as the eluent.

2-(4-Cyanophenyl)-2-methyl-1-phenyl-propan-1-one: The general procedure was utilized with 4-bromobenzonitrile (1.0 mmol, 182 mg). After chromatography 197 mg (76%) of a brown solid was isolated. $^1$HNMR (CDCl$_3$, 500 MHz) $\delta$ 7.67 (d, $J$ = 8.5 Hz, 2H), 7.45 (m, 5H), 7.27 (t, $J$ = 7.8 Hz, 2H), 1.65 (s, 6H). $^{13}$CNMR (CDCl$_3$, 126 MHz) $\delta$ 202.1, 151.0, 135.4, 132.8, 132.18, 129.6, 128.2, 126.6, 118.6, 110.9, 51.8, 27.7.

2-(4-Methoxyphenyl)-2-methyl-1-phenyl-propan-1-one: The general procedure was utilized with 4-bromoanisole (1.0 mmol, 138 µL). After chromatography 252 mg (99%) of a yellow liquid was isolated. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.48 (d, $J$ = 8.5 Hz, 2H), 7.34 (t, $J$ = 7.3 Hz, 1H), 7.22 (m, 4H), 6.88 (d, $J$ = 8.8, 2H), 3.79 (s, 3H), 1.57 (s, 6H). $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 203.9, 158.3, 137.1, 136.4, 131.5, 129.6, 127.9, 126.7, 114.3, 55.1, 50.6, 27.8.$^{104}$

Alternatively, 4-chloroanisole (1.0 mmol, 122 µL) was used to give 234 mg (92%) of a yellow liquid.
**2-(4-Methylphenyl)-2-methyl-1-phenyl-propan-1-one:** The general procedure was utilized with 2-bromoanisole (1.0 mmol, 125 µL). After chromatography 242 mg (95%) of a yellow liquid was isolated. $^1$HNMR (CDCl$_3$, 500 MHz) $\delta$ 7.53 (d, $J = 7.3$ Hz, 2H), 7.38 (t, $J = 7.3$ Hz, 1H), 7.25 (m, 6H), 7.25, 2.37 (s, 3H), 1.61 (s, 6H). $^{13}$CNMR (CDCl$_3$, 126 MHz) $\delta$ 203.9, 142.2, 136.4, 136.3, 131.5, 129.6, 128.3, 125.5, 51.0, 27.8, 21.0.

Alternatively, 4-chlorotoluene (1.0 mmol, 118 µL) was used to give 219 mg (86%) of a yellow.

**2-(2-Methylphenyl)-2-methyl-1-phenyl-propan-1-one:** The general procedure was utilized with 2-bromoanisole (1.0 mmol, 125 µL). After chromatography 242 mg (95%) of a yellow liquid was isolated. $^1$HNMR (CDCl$_3$, 500 MHz) $\delta$ 7.95 (d, $J = 6.9$ Hz, 1H), 7.57 (d, $J = 8.2$ Hz, 1H), 7.44 (t, $J = 7.6$ Hz, 1H), 7.35 (t, $J = 7.6$ Hz, 1H), 7.30 (t, $J = 7.6$ Hz, 1H), 7.17 (m, 2H), 7.01 (d, $J = 7.6$ Hz), 2.04 (s, 3H), 1.64 (s, 6H), 105

Alternatively, 2-chlorotoluene (1.0 mmol, 118 µL) was used to give 219 mg (86%) of a yellow.

**2-(2-Methoxyphenyl)-2-methyl-1-phenyl-propan-1-one:** The general procedure was utilized with 2-bromoanisole (1.1 mmol, 138 µL). After chromatography 2249 mg (98%) of a yellow liquid was isolated. $^1$H NMR (CDCl$_3$, 360 MHz) $\delta$ 7.60 (d, $J = 7.3$ Hz, 2H), 7.49 (d, $J = 7.7$ Hz, 1H), 7.31 (t, $J = 7.5$ Hz, 1H), 7.23 (m, 1H), 7.16 (m, 2H), 7.04 (t, $J = 7.5$Hz, 1H), 6.65 (d, $J = 8.2$H), 3.35(s, 3H), 1.62 (s, 6H). $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 203.6, 156.5, 136.1, 135.7, 131.4, 128.5, 128.1, 127.6, 125.0, 121.2, 111.4, 54.7, 26.7.

liquid.
CHAPTER 4. Palladium-Catalyzed Coupling Reactions Using DTBPPS and DAPPS

4.1 Palladium catalyzed coupling reactions in aqueous media

Traditionally organic chemistry has been carried out in media that is organic in nature itself.\textsuperscript{34} This premise follows the convention that chemists use of “like dissolves like”. The commercial use of organic solvents, however; creates a number of environmental and economic issues. Traditional organic solvents are usually volatile, flammable, and have toxicity issues associated with their use. To overcome these problems, there have been a number of efforts to avoid the use of traditional organic solvents. These efforts have been in designing new molecules with low volatility/flammability (ionic liquids), the use of supercritical fluids (CO\textsubscript{2}), and implementation of water or a co-solvent/water solution. Water offers a unique situation as it is one of the earth’s most abundant solvents, and has been referred to as the solvent of life. With water, there are a number of drawbacks. Water typically is not a good solvent for organic compounds as it potentially reacts with many organic functional groups to produce undesired products. It also polar thereby allowing it to only dissolve things of similar polarity, which for organics is typically not the case. When water is employed as a co-solvent (typically with a traditional organic solvent) some of these drawbacks can be overcame, however, the same problems of traditional organic solvents aforementioned still apply.\textsuperscript{106}

Transition metal catalyzed coupling reactions have emerged as an area of great interest over the past several decades. The interest in transition metal catalysts mostly comes from the
power and utility of the transition metal catalysts that have been developed. When considering transition metal catalysis, there are a number of interesting areas, some of these are olefin metathesis, C-C, C-N, C-H, C-O bond forming reactions, insertion of CO, polymerizations, and many others. In most of these processes, the transition metal leaches into the product offering up concerns as to the toxicity level that the catalyst presents in the product. To overcome the metal catalyst presence in the product, there have been a number of efforts to prevent leaching have been undertaken. Attaching the catalytic material to a solid support, the implementation of a polar group onto the catalyst there by causing an ability to use biphasic conditions, or a simple mechanical separation (filtration or some type of distillation) is employed to aid in the purification of products. Each of these offers both positives and negatives, however our focus in these efforts have been in attaching a polar group to the catalyst allow for decantation of an organic layer from an aqueous.

It has become widely accepted that sterically demanding, electron rich phosphine ligands facilitate catalytic activity in the aforementioned palladium catalyzed coupling reactions. For palladium catalysis, generally speaking, an electron rich sterically demanding phosphine is preferable. Grubbs reported synthesis of sterically demanding phosphines Cy-pip-phos and DCPES ligands (Figure 4.1) in 1996. These ligands both contain polar groups (ammonium for Cy-pip-phos, and sulfonate for DCPES) allowing them to have solubility in water. These ligands however have not been able to afford efficient coupling of aryl bromides nor aryl chlorides at room temperature in palladium catalyzed coupling reactions. Shaughnessy and co-workers undertook the synthesis of $t$-Bu-amphos, following a similar synthetic scheme proposed by Grubbs, to attempt to over come the inability to couple aryl bromides and chlorides efficiently at room temperature. The $t$-Bu-amphos ligand has been demonstrated to perform better than the Cy-pip-phos and DCPES. In these classes of ligands the steric parameters and electronic
donation play a role in the ability of the ligand to generate catalysts with palladium that perform well. It is thought that the ammonium/cationic group withdraws electron density from the phosphorus atom thereby disabling its ability to donate its electron density into the metal center it is coordinated with (Figure 4.1). Whereas an anionic group, such as a sulfonate, is less likely to withdraw electron density from the phosphorus atom, thereby allowing it to donate its electron density into the metal center it is coordinated with. While a number of ligands with polar groups have been synthesized, the alkyl type seemingly shows greater activity over those with aryl substituents. Aryl groups can be attributed to have a slight withdrawing effect associated with the aromatic ring being attached to the phosphine.

![Figure 4.1](image)

**Figure 4.1** Dipole moments showing electron withdraw and donation from polar groups attached to phosphine

### 4.2 Synthesis of water soluble alkyl phosphines

Water-soluble phosphines are of interest for many aforementioned reasons. The design associated with many of these ligands follows a simple pattern. Most of them have some alkyl portion and a polar group facilitating its water solubility. Typical polar groups are: -NR₃, -CO₂Na, -OH, -PO₃Na, and -SO₃Na. Each of these groups offers different effects on the
phosphines size, shape, and electronic donating ability. While much work has been done with aryl phosphines,\textsuperscript{34} it is beyond the scope of this discussion to consider aryl, or benzyl phosphines.

There have been many efforts working with the various sulfonated forms of triphenylphosphine, however, for the purpose of this discussion we will focus on water-soluble alkyl phosphines. One of the first examples of these alkyl water-soluble ligands was presented by Steltzer, in the stepwise aminoalkylation of PH$_3$ with the corresponding chloroammino alkane, followed by selective quaternization of the amine group, to the trialkylammoniumphosphine.\textsuperscript{37,108} The overriding drawback from this synthetic approach is that in each step the phosphine is air sensitive toward oxidation. Additionally, there can be concern with free amine and phosphine having reactivity with electrophiles. Not long after this, Grubbs reported on the use of phosphine-borane complexes as starting materials for synthesis of water-soluble phosphines (Scheme 4.1).\textsuperscript{38} The protection of the phosphine with borane offers air stability, until deprotonation, allows for metallation with lithium reagents, and activates the phosphine toward reacting with an electrophile. Additionally, once the phosphine is alkylated, the protecting group can be removed with either a large excess of a nucleophilic amine, or tetrafluoroboric acid.\textsuperscript{109,110}

Beller\textsuperscript{42} presented a different approach in synthesis of a water-soluble phosphine by taking trishydroxymethylphospine and introducing a dialkylamine (generated from the coresponding alkylamine ring opening a propane sultone) to give the trisubstituted phosphine. Bakos utilized cyclic sulfonates to generated mono and dialkyl phosphines that are water soluble. Roundhill demonstrated that the bromoethyl phosphonate and sulfonate could be utilized as akyl chains with a polar group to generate a water-soluble phosphine\textsuperscript{111}, which was later employed by Grubbs in his synthesis of DCPES.\textsuperscript{38}
4.3 Results and discussion

The motivation for pursuit in synthesizing new water-soluble phosphine ligands is there are a number of drawbacks associated with many current ligands. Taking a general approach, many water-soluble phosphines don’t perform as well as hydrophobic ligands. Additionally the water-soluble ligands require multistep synthetic approaches. These drawbacks are motivation for making new phosphines that can combine positive steric demand and electron donation and into a simple synthetic approach. The most pertinent example would be \( t \)-BuAmphos. This ligand is a several step synthesis to generate a ligand that can promote Suzuki couplings of arylbromides at room temperature but has difficulty with Sonogashira couplings (requiring elevated temperature).\(^{39,107}\)

The successful synthesis of the water-soluble ligands DTBPPS and DAPPS led to examining them in a number of palladium catalyzed coupling reactions. The initial efforts were to demonstrate that both DTBPPS and DAPPS had the ability to catalyze Suzuki-Miyarua coupling reactions. Previous conditions developed for \( t \)-Bu-amphos (Equation 4.1), which were to use 1:1 water/acetonitrile as the solvent and carbonate as a base, 1.1/1 L/Pd ratio, and 1 mol% Pd, were evaluated. The reaction was not optimized, however the conditions evaluated initially proved to be successful in affording good product conversion at room temperature.

In evaluating the catalyst, a number of substrates were chosen. Deactivated substrates are ones with both sterically hindering side groups off the aromatic, and those that are electron rich at the C-X bond. The more active of the catalysts between DTBPPS and DAPPS should be able to accomplish this in an efficient manner. Given that both DTBPPS and DAPPS have been established to have electron donation similar to TTBP (Table 4.1), the expectation is that they will perform accordingly. \((\text{Equation 4.1})\).
In evaluating the catalytic abilities for both DTBPPS and DAPPS in Suzuki coupling, the selection of water/CH$_3$CN as a solvent system was made based on previous success with t-Bu amphos.\textsuperscript{39} Additionally, the initial experiments examined showed great success; therefore no other solvent system or bases were screened for isolated yields. The catalyst derived from palladium and DTBPPS demonstrates good productivity for converting activated and deactivated aryl bromides in Suzuki coupling (Table 4.1). Additionally, the DTBPPS ligand shows good productivity for sterically hindered deactivated substrates (Table 4.1). The sterically hindered substrate is interesting as it is doubly ortho-substituted and shows excellent productivity (94% isolated yield). Additionally, the most interesting substrate is 4-bromophenol. This substrate has an acidic proton that makes the substrate more soluble in water once exposed to a base. This substrate is also problematic as it becomes more electron rich, or deactivated, once deprotonated. Lastly, the substrate doesn’t require installation of a protecting to allow its solubility in the solvent system. The good productivity is also seen in DAPPS as well; however, it was not evaluated with as many substrates as it showed no distinct advantage over DTBPPS. Both ligands are very comparable to t-BuAmphos ligand in Suzuki coupling reactions for activated, deactivated and sterically hindered substrates\textsuperscript{39}. 

\begin{equation}
\begin{array}{c}
\text{Br} \quad \text{B(OH)$_2$} \\
R \quad \text{equiv.} \\
1 \quad \text{equiv.} \\
\text{R=OMe, CH$_3$CN,} \\
\text{OH, N(Me)$_2$} \\
"R=H, OMe, CN. \\
\end{array}
\end{equation}
Table 4.1. Isolated yields from room temperature aryl bromide Suzuki coupling with DTBPPS and DAPPS

<table>
<thead>
<tr>
<th>Aryl Halide</th>
<th>Boronic Acid</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
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<tr>
<td>NC-Br</td>
<td>(Me)₂N-Br</td>
<td>NC-Br</td>
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</tr>
<tr>
<td>MeO-Br</td>
<td>(Me)₂N-Br</td>
<td>MeO-Br</td>
<td>DAPPS 77</td>
</tr>
<tr>
<td>Me</td>
<td>(Me)₂N-Br</td>
<td>Me</td>
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</tr>
<tr>
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<td>MeO-Br</td>
<td>DAPPS 97</td>
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<tr>
<td>Me</td>
<td>(Me)₂N-Br</td>
<td>Me</td>
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<td>(Me)₂N-Br</td>
<td>MeO-Br</td>
<td>DAPPS 85</td>
</tr>
<tr>
<td>HO-Br</td>
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<td>HO-Br</td>
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<td>(Me)₂N-Br</td>
<td>(Me)₂N-Br</td>
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Reaction conditions utilized were from Equation 4.1. Reaction temperature 23 °C.
Once the demonstration of good productivity, conversion of starting material to product, was established in the Suzuki coupling, the focus was changed to the Sonogashira coupling. Just as in Suzuki coupling, activated and deactivated substrates were evaluated. Excellent productivity was demonstrated for activated and deactivated substrates with phenyl acetylene. Additionally, excellent productivity was demonstrated with sterically hindered substrate bromo-meta-xylene. The greatest interest is in the activity of activated aryl chloride at room temperature and the deactivated aryl chloride at 80 °C. The combination of DTBPPS and DAPPS with palladium generate an active catalyst that phosphine promoting a deactivated aryl chloride, whereas t-Bu-Amphos was not able to promote deactivated aryl chlorides. The electron donating ability of the DTBPPS and DAPPS suggest that when coordinated to palladium that they should generate a catalyst that is electron rich enough to efficiently promote oxidative addition of aryl chloride. Additionally, the size of the ligand is sufficient to promote reductive elimination. It should also be noted that classical Sonogashira reactions require a copper co-catalyst; however, copper inhibits the progress of these phosphine/palladium catalysts.
Table 4.2 Isolated yields from Sonogashira coupling using DTBPPS and DAPPS

<table>
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<tr>
<th>Aryl Halide</th>
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<th>Product</th>
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</tr>
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<td></td>
</tr>
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</table>

Reaction conditions were those in Equation 4.2. a) indicates reactions run at 80 °C.
4.4 Conclusions

Both DTBPPS and DAPPS in combination with Pd(OAc)$_2$ show excellent activity in coupling aryl bromides in Suzuki and Sonogashira coupling. They both show reasonable activity at coupling deactivated, activated, sterically hindered aryl bromides at room temperature. Additionally, DTBPPS has been demonstrated to couple activated aryl chlorides at room temperature and deactivated aryl chlorides at 80 °C in Sonogashira coupling. Both ligands promote Sonogashira coupling in the absence of a copper co-catalyst.

The electron donating ability of both DTBPPS and DAPPS are greater than that of $t$-Bu amphos. Both ligands are similar in electronic nature to TTBP. The size of DTBPPS is similar to TTBP, while DAPPS is smaller in size. The electron donating ability of both DTBPPS and DAPPS allow them promote oxidative additionally effectively. As previously stated the more strongly electron releasing an alkylphosphine, the more likely it will promote oxidative addition. Since both DTBPPS and DAPPS can activate deactivated aryl chlorides with a small amount of heat, they are strongly electron releasing. While they both promote Suzuki and Sonogashira coupling well with aryl bromides, more work needs to be done in expanding them into other coupling reactions.

4.5 Experimental

4.5.1 General Comments:

All chemicals were used from the supplier as received. Water was obtained from a deionized source and was sparged for 15 min prior to use. Acetonitrile was sparged for 15 min prior to use. Silica gel was obtained from Sorbent Technologies and was standard grade, 230 x 400 mesh, 60 Å. Gas chromatography analysis was performed on a carbowax column.
4.5.2 General Suzuki coupling protocol:

In a 10 ml round bottom flask containing a magnetic stir bar and a septum in a nitrogen filled drybox chemicals were added in the following order: Pd(OAc)$_2$ (0.02 mmol, 5.3 mg), Na$_2$CO$_3$ (1.10 mmol, 116 mg), phenyl boronic acid (1.30 mmol, 160 mg) and ligand (DTBPPS: 0.021 mmol, 6.0 mg or DAPPS: 0.021 mmol, 9.0 mg). The round bottom flask was removed from the drybox where it was charged with aryl halide (1 mmol), water (2 mL) and acetonitrile (2 mL). Reactions were allowed to stir at room temperature for 16 h. The reactions were evaluated by GC to ensure reaction completeness. Complete reactions were extracted from 30 mL of brine with 3 x 20 mL ethyl acetate. The organic layer was dried over MgSO$_4$ and the solvent removed under reduced pressure. Flash chromatography using silica gel was utilized to purify products eluting with a gradient of hexane and ethyl acetate (ranging from 100% hexane to 70/30 hexane/ethyl acetate) over silica gel. Solvent was removed under reduced pressure to give the product.

4-Methoxybiphenyl. 4-Bromoanisole (1.00 mmol, 125 µL) and phenylboronic acid (1.30 mmol, 161 mg) were coupled under the general procedure. The product was isolated as a white solid (DTBPPS: 94%, 174 mg; DAPPS: 97%, 178 mg) $^1$H NMR (500 MHz, CDCl$_3$): $^1$H NMR (500 MHz CDCl$_3$): δ 7.55 (d, $J = 7.3$Hz, 2H), 7.41 (t, $J = 7.6$ Hz, 2H), 7.30(t, $J = 7.3$Hz, 1H) 6.98 (d, $J = 8.8$Hz, 2H) 3.89 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 159.1, 140.9, 133.8, 128.8, 128.2, 126.8, 126.7, 114.2, 55.4.$^9$9

2-Methylbiphenyl. 2-Bromotoluene (1.00 mmol, 120 µL) and phenylboronic acid (1.30 mmol, 161 mg) were coupled under the general procedure. The product was isolated as a colorless liquid (DTBPPS: 72%, 120 mg, DAPPS: 85%, 144mg). $^1$H NMR (500 MHz, CDCl$_3$):
δ 7.59 (d, 1H), 7.41 (m, 3H), 7.32 (m, 1H), 7.24 (m, 4H). 2.39 (s, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ 142.1, 135.3, 130.2, 130.0, 129.8, 129.2, 128.7, 128.3, 127.2, 127.1 126.7, 20.6.\(^{100}\)

4-Methylbiphenyl 4-Bromotoluene (1.00 mmol, 120 µL) and phenylboronic acid (1.30 mmol, 161 mg) were coupled under the general procedure. The product was isolated as a colorless liquid (DTBPPS: 98%, 166 mg, DAPPS: 93%, 158 mg). \(^1\)H NMR (360 MHz, CDCl\(_3\)): δ 7.56 (d, \(J = 7.88\) Hz, 2H), 7.48 (d, \(J = 8.20\) Hz, 2H), 7.40 (t, \(J = 8.20\) Hz, 2H), 7.30 (t, \(J = 7.57\) Hz, 1H), 7.23 (d, \(J = 8.20\) Hz), 2.38 (s, 3H).\(^39\)

4-Cyanobiphenyl. 4-Bromobenzonitrile (1.00 mmol, 181 mg) and phenylboronic acid (1.30 mmol, 161 mg) were coupled under the general procedure. The product was isolated as a cream-colored solid (DTPSP: 99%, 181 mg DAPPS 77%, 144mg). \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.72 (d, \(J = 8.2\) Hz, 2H), 7.68 (d, \(J = 8.2\) Hz, 2H), 7.58 (t, \(J = 6.5\) Hz, 2H), 7.47 (t, \(J = 6.5\) Hz, 2H), 7.41(t, \(J = 7.2\) Hz, 1H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ 145.7, 139.2, 132.6, 129.1, 128.7, 127.7, 127.2, 118.9, 110.9. mp: 83-84 °C.\(^{112}\)

2-Methoxybiphenyl. 2-Bromoanisole (1.00 mmol, 124 µL) and phenylboronic acid (1.30 mmol, 160 mg) were coupled under the general procedure. The product was isolated as a translucent liquid (DTBPPS: 66%, 121 mg). \(^1\)H NMR (360 MHz, CDCl\(_3\)): δ 7.65 (d, \(J = 7.0\) Hz 2H), 7.53 (t, \(J = 7.3\) Hz, 2H), 7.44 (m, 3H), 7.15 (d, \(J = 7.3\) Hz, 1H), 7.1 (d, \(J = 9.8\) Hz, 1H), 3.9 (s, 3H). \(^{13}\)C NMR (90.6 MHz, CDCl\(_3\)): δ 156.4, 138.5, 130.8, 129.5, 128.6, 127.9, 126.9, 120.8, 111.1, 55.5.\(^{113}\)

2,6-Dimethylbiphenyl. 2-Bromo-\(m\)-xylene (1.00 mmol, 133µL) and phenylboronic acid (1.30 mmol, 160 mg) were coupled under the general procedure. The product was isolated as a translucent liquid (DTBPPS: 57%, 105 mg). \(^1\)H NMR (360 MHz, CDCl\(_3\)): δ 7.51 (t, \(J = 7.3\) Hz, 2H), 7.48 (t, \(J = 7.3\) Hz, 1H) 7.3 (m, 5H) 2.1 (s, 6H). \(^{13}\)C NMR (90.6 MHz, CDCl\(_3\)): δ 141.8, 141.0, 136.0, 129.0, 128.4, 127.2, 127.0, 126.6, 20.8.\(^{113}\)
**4,4'-Dimethoxybiphenyl.** 4-Bromoanisole (1.00 mmol, 125 μL) and 4-methoxyphenlboronic acid (1.10 mmol, 168 mg) were coupled under the general procedure. The product was isolated as an orange colored solid (DTBPPS: 88%, 184 mg). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.52, (d, $J$ = 8.5 Hz, 4H), 7.00 (d, $J$ = 8.8 Hz, 4H), 3.88 (s, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 158.8, 133.5, 127.7, 114.2, 55.3.$^{114}$

**4-Cyano,4'-methoxybiphenyl.** 4-Bromoanisole (1.00 mmol, 125μL) and 4-cyanophenlboronic acid (1.10 mmol, 162 mg) were coupled under the general procedure. The product was isolated as a tan colored solid (DTBPPS: 99%, 214mg). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.71, (d, $J$ = 8.5 Hz, 2H), 7.66 (d, $J$ = 8.3 Hz, 2H), 7.56 (d, $J$ = 8.3 Hz, 2H), 7.03 (d, $J$ = 8.3 Hz, 2H) 3.89 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 160.3, 145.2, 132.6, 131.5, 128.4, 127.1, 119.0, 114.6, 110.2, 55.4.$^{114}$

**2-Hydroxybiphenyl.** 4-Bromophenol (1.00 mmol, 173µL) and Na$_2$CO$_3$ (2.20 mmol, 232 mg) were coupled under the general procedure. The product was isolated using an acidic aqueous workup and column chromatography to give a white colored solid (DTBPPS: 96%, 195mg). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.53, (d, $J$ = 8.2 Hz, 2H), 7.48 (d, $J$ = 8.5 Hz, 2H), 7.41 (t, $J$ = 7.2 Hz, 2H), 7.31 (d, $J$ = 7.2 Hz, 1H), 6.90 (d, $J$ = 8.5 Hz), 5.85 (s, 1H)$^{115}$

**N,N-4(dimethylamino)biphenyl.** 4-Bromoaniline (1.00 mmol, 125μL) and 4-cyanophenlboronic acid (1.10 mmol,162 mg) were coupled under the general procedure. The product was isolated as a tan colored solid (DTBPPS: 99%, 214mg). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ . 7.55 (d, $J$ = 6.9 Hz, 2H), 7.50 (d, $J$ = 8.2 Hz, 2H), 7.39 (t, $J$ = 8.2 Hz), 7.29 (d, $J$ = 9.1 Hz), 7.25 (t, $J$ = 7.5 Hz 1H), 6.80 (d, $J$ = 8.8 Hz, 2H), 2.98 (s, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 129.3, 128.6, 127.7, 127.2, 126.3, 126.0, 114.1, 112.8, 40.6.$^{116}$

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4.5.3 General Sonogashira coupling protocol:

To a 10 mL round bottom flask containing a magnetic stir bar and a septum in a nitrogen filled glove box the chemicals were added in the following order: Pd(OAc)$_2$ (0.02 mmol, 5.3 mg), CsOH (1.10 mmol, 165 mg) and ligand (DTBPPS: 0.021 mmol, 6.0 mg or DAPPS: 0.021 mmol, 9.0 mg). The round bottom flask was removed from the drybox where it was charged with alkyne (1.10 mmol) and aryl halide (1.00 mmol). Reactions were further charged with water (2 ml) and acetonitrile (2 ml). Reactions were allowed to stir at room temperature overnight unless otherwise noted. The reactions were evaluated by GC to ensure reaction completeness. Complete reactions were extracted from 30 ml of brine with 3 x 20 mL ethyl acetate. The organic layer was dried over MgSO$_4$ and solvent was removed under reduced pressure. Silica gel flash chromatography was utilized to purify products eluting with a gradient of hexane and ethyl acetate (ranging from 100% hexane to 70/30 hexane/ethyl acetate). Solvent was removed under reduced pressure to give the product.

4-(Phenylethynyl)anisole. The above procedure was carried out using 4-bromoanisole (1.00 mmol, 125 µL) and phenylacetylene (1.10 mmol, 125 µL). The product was isolated to give a tan colored solid (DTBPPS: 87%, 181 mg; DAPPS: 69%, 144 mg) 4-Chloroanisole (1.00 mmol 122 µL) at 80°C was evaluated also (DTBPPS 73%, 153.6 mg DAPPS 64%, 132.4 mg). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.52 (d, $J$ = 7.9 Hz, 2H), 7.47 (d, $J$ = 9.1 Hz, 2H), 7.3 (m, 3H), 6.88 (d, $J$ = 8.8 Hz, 2H), 3.83 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 159.7, 133.1, 131.5, 128.3, 127.9, 123.6, 115.4, 114.0, 89.4, 88.1, 55.3. mp: 56-58 °C (lit mp: 56-58 °C)

4-(Phenylethynyl)benzonitrile. The above procedure was carried out using 4-bromobenzonitrile (1.00 mmol, 182.5 mg) and phenylacetylene (1.10 mmol, 125 µL). The product was isolated to give a tan colored solid (DTBPPS: 98%, 231mg; DAPPS: 93%, 188mg) $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.63 (d, $J$ = 8.5 Hz, 2H), 7.60 (d, $J$ = 8.2 Hz, 2H), 7.54 (m, 2H),
The above procedure was carried out using 2-bromotoluene (1.00 mmol, 120 µL) and phenylacetylene (1.10 mmol, 125 µL). The product was isolated as a red oil (DTBPPS: 76%, 146 mg DAPPS: 68%, 131 mg). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.53 (d, J = 7.6 \text{ Hz}, 2H), 7.49 (d, J = 7.6 \text{ Hz}, 1H), 7.32 (m, 3H), 7.21 (d, J = 3.7 \text{ Hz}, 2H), 7.16 (m, 1H), 2.51 (s, 3H). 13C NMR (126 MHz, CDCl\(_3\)): \(\delta 140.3, 131.9, 131.5, 129.5, 128.4, 128.3, 128.2, 125.6, 123.6, 123.1, 93.4, 88.4, 20.8.\(^2\)

**2-(Phenylethynyl)toluene.** The above procedure was carried out using 2-bromotoluene (1.00 mmol, 120 µL) and phenylacetylene (1.10 mmol, 125 µL). The product was isolated as a red oil (DTBPPS: 76%, 146 mg DAPPS: 68%, 131 mg). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.53 (d, J = 7.6 \text{ Hz}, 2H), 7.49 (d, J = 7.6 \text{ Hz}, 1H), 7.32 (m, 3H), 7.21 (d, J = 3.7 \text{ Hz}, 2H), 7.16 (m, 1H), 2.51 (s, 3H). 13C NMR (126 MHz, CDCl\(_3\)): \(\delta 140.3, 131.9, 131.5, 129.5, 128.4, 128.3, 128.2, 125.6, 123.6, 123.1, 93.4, 88.4, 20.8.\(^2\)

**4-(4-Methoxyphenyl)-3-butyn-1-ol.** The above procedure was carried out using 4-bromoanisole (1.00 mmol, 125.2 µL) and 3-butyn-1-ol (1.10 mmol, 86 µL). The crude product mixture was purified by column chromatography to afford the product as a yellow solid (DTBPPS: 130 mg, 74%; DAPAP: 175 mg, 99%). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.34 (d, J = 8.8 \text{ Hz}, 2H), 6.82 (d, J = 8.8 \text{ Hz}, 2H), 3.8, (m, 5H), 2.67 (t, J = 6.3 \text{ Hz}, 2H), 1.85 (s, 1H). 13C NMR (126 MHz, CDCl\(_3\)): \(\delta 159.3, 133.0, 115.5, 113.9, 84.7, 82.3, 61.2, 55.3, 23.8.\(^2\)

**2-(Phenylethynyl)-m-xylene.** 2-Bromo-1,3-dimethylbenzene (1.00 mmol, 133 µL) and phenyl acetylene (1.1mmols, 125µL). The crude product was purified by flash column chromatography to give a brown colored liquid (DTBPPS: 178 mg, 86%; DAPAP: 175 mg, 90%). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.57 (d, J = 7.9, 1H), 7.38 (m, 2H), 7.2 (m, 1H), 7.1 (d, J = 7.5, 2H), 13C NMR (126 MHz, CDCl\(_3\)): \(\delta 132.5, 131.4, 128.44, 128.36, 127.8, 127.4, 126.7, 123.9, 123.0, 21.1.\(^2\)

**4'-(Phenylethynyl)acetophenone.** The above procedure was carried out using 4-bromoacetophenone (1.0 mmol, 199 mg) and phenylacetylene (1.1 mmol, 125 µL). The crude product mixture was purified by column chromatography to give the product as a brown solid (DTBPPS: 210 mg, 99%, DAPPS: 170 mg, 83%). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.94 (d, J = 8.5 \text{ Hz}, 2H), 7.61 (d, J = 8.5 \text{ Hz}, 2H), 7.55 (m, 2H), 7.37 (m, 3H), 2.63 (s, 3H). 13C NMR (126
MHz, CDCl₃): δ 197.3, 136.2, 121.8, 121.7, 128.8, 128.5, 128.3, 128.2, 122.7, 92.7, 88.6, 26.6.
mp: 94-96 °C.²
CHAPTER 5. Palladium Catalyzed Carbonylation of Aryl Bromides Using Sterically
Demanding Zwitterionic Trialkylphosphonium Sulfonates as Air Stable Precursors.

5.1 Introduction

5.1.1 Background

Palladium-catalyzed coupling reactions have become powerful tools for formation of
numerous carbon-carbon and carbon-heteroatom bonds. Many of these reactions are
useful due to their ability to generate aryl ketones, esters, and amides through palladium catalysis
offers a great deal of utility. Additionally, these carbonyl containing functional groups can
lead to other useful functional groups.

While the generation of a highly active catalysts has been the driving force in design of
many ligands, the separation of the catalyst from the desired product, and the recovery of the
catalyst have proven to often be difficult. Due to the great cost of transition metals and limited
ability to recover them from reactions causes a great deal of concern industrially. Additionally
the need for separation of the metal from the product in ppm levels allowable for pharmaceutical
or food causes homogenous catalysts unattractive. The employment of aqueous/biphasic
systems allows the potential to segregate the product into an organic layer and the catalyst in the
aqueous media facilitating easier separation. Additionally, the use of water as a solvent is
attractive due to its unique properties: availability, low flammability, low relative toxicity, cost,
and environmental impact.
Palladium catalyzed coupling reactions in aqueous media is not a new practice. Suzuki reported on the ability to couple aryl halides with aryl boronic acid derivatives using palladium/phosphine catalysts.\textsuperscript{119} The first report of a hydrophilic catalyst system was by Casalnuovo,\textsuperscript{33} in the use of TPPMS, a triphenylphosphine derivative with a sulfonated group, and Pd(OAc)\textsubscript{2} to promote cross coupling. Since this initial report, there have been numerous efforts in synthesizing hydrophilic catalysts, mostly surrounding the triphenylphosphine or alkylbiphenylphosphine backbone.\textsuperscript{34,35}

While the aryl phosphine based ligands have been utilized with polar groups to generate water soluble catalyst systems, many of these reactions show limited reactivity (aryl iodides at moderate to high temperatures). More attention in recent years has been given to ligand that are similar in steric and electronic properties to TTBP. Most of this attention is due to fact that TTBP has been demonstrated to couple aryl bromides and chlorides with low catalyst loadings and reaction temperatures below 100 \textdegree C. Shaughnessy and co-workers recently reported on the use of a pair of water-soluble phosphine ligands DTBPPS and DAPPS having the ability to promote Suzuki and Sonogashira couplings under mild to modest reaction conditions in coupling both aryl bromides and aryl chlorides (23-80 \textdegree C).\textsuperscript{120} These ligands, have offered a great deal of advantages in that they are easily synthesized, purified, and are zwitterionic salts that are air stable until deprotonated (Scheme 5.1).

In the early 70’s Heck and co-workers demonstrated that a palladium/phosphine catalyst could promote the conversion of an aryl or vinyl halides to esters and amides.\textsuperscript{121,122} In these reactions a palladium (II) source, triphenylphosphine, CO, and a base was utilized to promote the carbonylation of the starting halide (vinyl, aryl, benzyl, bromide or, iodide) to the desired product. The interest in this reaction comes from its wide industrial application.\textsuperscript{123}
Milstein and co-workers noted that the initial oxidative addition step was rate limiting when considering the reactions with aryl chlorides.\textsuperscript{124-126} Additionally, he noted that the use of an alkyl bidentate ligand generated a more effective catalyst than the bi-aryl chelating ligand. He proposed that the more electronically donating a ligand is the better it will promote oxidative addition. Nomura reported on the use of P(Cy)$_3$ and the bidentate derived dicyclohexyl phosphines promoting the carbonylation of aryl chlorides.\textsuperscript{127} Beller investigated the use of ferrocenylphosphines and demonstrated their ability to promote carbonylation.\textsuperscript{128} The biggest downfall of many of these catalytic systems is that they require high temperatures (temperatures in excess of 140 °C). Most likely because CO bound to a metal center withdraws electron density from the palladium preventing oxidative addition. Additionally, these reactions require higher catalyst loadings or a bidentate phosphine ligand.

The use of water-soluble phosphines in carbonylation reactions has been demonstrated in addition to hydrophobic phosphines. The use of TPPTS (triphenylphosphine trisulfonate) (Figure 5.2) and palladium was demonstrated by Sheldon and coworkers in their carbonylation of 1-(4-isobutylphenyl) ethanol to ibupropen.\textsuperscript{129,130} This starting material is a benzyl alcohol and doesn’t involve a halide starting material, however the use of HI suggests that the oxidative addition necessity proceeds through a benzyl iodide. Another water soluble, PNS ligand (Figure 5.2), was utilized along with palladium to carbonylate benzyl bromide to a methyl ester.\textsuperscript{131} However, this reaction gives modest yields (70%) with benzyl bromides after 5 h and with 4 equivalents of PNS to palladium at 50 °C. The last water soluble phosphine reported in the literature used in carbonylation is $N,N$-bis(diphenylphosphinomethyl)-N-ethylphosphonic acid-1,5-diamino-3-oxapentane (Figure 5.2).\textsuperscript{132} Again this ligand in association with palladium is able to promote carbonylation of benzyl chloride in water to the corresponding benzoic acid. These reported ligands are all utilized in benzyl substituted carbonylations, with no demonstrated
work done with aryl substituted halides. Additionally, the high catalyst loadings, elevated ligand to palladium ratio, the elevated temperatures, limited scope, and reaction times pose a problem with water-soluble ligands utilized in carbonylation reactions over traditional hydrophilic phosphines without these limitations.

Figure 5.2 Examples of ligands utilized in palladium catalyzed carbonylation.

In 2006 Beller and coworkers reported on the use of diadamantylbutylphosphine(cataCXium® A) and TTBP (tri-tert-butyolphosphate) (Figure 5.2) having the ability to promote palladium catalyzed carbonylation of aryl bromides. The use of these ligands in combination with palladium as hydrophilic catalysts presents an interesting insight as to using DTBPPS and DAPPS in combination with palladium as catalysts for
carbonylation. These water-soluble ligands offer the potential to recover and recycle the catalyst after reaction completion potentially making them more attractive than their hydrophilic counterparts. Additionally, for the generation of carboxylic acids, the solvent selection of water may allow the palladium catalysts to perform to a higher level than other hydrophilic ligand derived palladium catalysts.

5.1.2 Mechanism

When considering designing ligands for reactions, it is useful to consider the mechanism associated with the catalytic cycle for the reaction of interest. For carbonylation, there have been many mechanistic studies performed. However, Barnard, in his 2008 review, states that there is still some uncertainty and disagreements in later steps of the mechanism. While there is uncertainty and arguments associated with the mechanism, there are several events that give rise to the accepted mechanism: active catalyst generation, oxidative addition, CO binding, insertion of the carbonyl, attack of the nucleophile (usually solvent but can be other nucleophiles present), and generation of the product.

The initial step in the reaction, catalyst formation, can be accomplished from both Pd(II) and Pd(0) starting materials. While both sources can be utilized, the Pd(0) is known to undergo oxidative addition, therefore the Pd(II) must be reduced. Reduction of Pd(II) can be accomplished in a number of ways. The palladium can coordinate a solvent molecule containing β-hydrogens, undergo containing β-hydride elimination followed by subsequent deprotonation of the metal center; the metal center can coordinate CO followed by attack by water and elimination H₂ and CO₂ gas (also known as water gas shift); it can coordinate the base and undergo similar outcome from coordinating the solvent; or the phosphine itself can reduce the Pd(II) (Figure 5.3). In any event the reduction occurs and the phosphine ligands associate to the Pd center. It is
interesting to note that coordination of CO withdraws electron density from the metal center making oxidative addition more difficult.\textsuperscript{126} For optimal activity, steric and electronic factors come into view when designing a phosphine for carboxylation. Osborn found that there is a small range of cone angles that are optimal for carboxylation (160-180\textdegree).\textsuperscript{124} Additionally, it is important to maintain the electronic donation of the phosphine ligand into the metal center at its highest level.

\begin{center}
\includegraphics[width=0.7\textwidth]{figure5.3.png}
\end{center}

\textbf{Figure 5.3} The various paths for Pd(0) generation.

The second step of the reaction would be oxidative addition, assuming that the CO has yet to coordinate to the metal center. Much work has been done in this area, as it is the initial step of many Pd catalyzed coupling reactions. The oxidative addition step is typically the rate determining step associated with many palladium catalyzed coupling reactions.\textsuperscript{23,24} However, Osborn determined that the oxidative addition was not the rate limiting step for carboxylation.\textsuperscript{124}
Oxidative addition is promoted by strongly $\sigma$-donating ligands (such as phosphines).\textsuperscript{28,29} Additionally, for C-C bond forming reactions, Hartwig has demonstrated that electron rich sterically demanding phosphines accelerate oxidative addition.\textsuperscript{133} It is also known that strong $\pi$-acceptors (alkenes, CO) inhibit oxidative addition by allowing back bonding from the metal center thereby reducing the electron density of the catalyst. Therefore coordination of CO would inhibit a palladium/phosphine catalysts ability to undergo oxidative addition. Thus, more strongly electron donating ligands would be preferred for carbonylation to promote oxidative addition and overcome CO reducing the electron density of the Pd center.

\[ \text{L}_2\text{Pd}(0) \xrightarrow{\text{X}} \text{L}_2\text{Pd} \xrightarrow{\text{CO}} \left[ \begin{array}{c} \text{OC} \\ \text{L}_2\text{Pd} \end{array} \right] \]

\[ \left[ \begin{array}{c} \text{L}_2\text{Pd} \\ \text{CO} \end{array} \right]^+ \]

\[ \xrightarrow{\text{HNu, Base}} \]

\[ \text{Nu} \]

\textbf{Figure 5.4} Simplified Yamamoto suggested mechanistic pathway.\textsuperscript{134}
Once oxidative addition occurs, the coordination of CO would be the next step along the mechanistic pathway assuming that this does not occur in another step. Yamamoto suggests that the CO coordinates to the palladium center with 2 phosphine ligands attached to it (either monodentate or bidentate) to generate a 5 coordinate species (Figure 5.4). Once this CO coordinates, it becomes electrophilic enough to be attacked by a nucleophile (R₂NH/R₂N⁻, ROH/RO⁻, etc). The incoming carbamate ligand thereby displaces the halide creating an anionic ligand that can reductively eliminate to generate the product. Heck studied the 4 coordinate and 5 coordinate intermediate that could be generated, and he proposed that dissociation of a ligand in the 5 coordinate intermediate would be mandated for the CO to migrate into a position (cis to the phenyl) were it is able to be inserted into by the phenyl ligand. (Figure 5.5).

![Figure 5.5](image-url) The binding of CO according to Heck’s studies.

The resulting coordination of CO leads to the next step along the mechanistic pathway. There are two proposed pathways that can result from this point; the Yamamoto proposed pathway aforementioned, and the Heck pathway. According to Heck, the 4-coordinate Pd(Ph)(CO)LX complex would undergo a migratory insertion into the CO by the
phenyl group thereby creating a vacant site for a neutral ligand to coordinate. The generation of this 4-coordinate Pd(Ph)(CO)LX can come from several possible sources, a phosphine, solvent molecule, nucleophile, which in many instances can be the solvent.

![Plausible mechanism of palladium catalyzed carbonylation](image)

**Figure 5.6** Plausible mechanism of palladium catalyzed carbonylation

The last step along the mechanistic pathway is the generation of the product from newly generated Pd-acyl. Product generation can come from the reductive elimination of the palladium nucleophile complex or simply attack of the nucleophile to the carbonyl palladium complex.
causing generation of Pd(0) to restart the catalytic cycle. According to Barnard, there remains to be a full understanding of this step in carbonylation reactions. However, we can compile the aforementioned steps into a general mechanistic outlook (Figure 5.6).

5.2 Results and Discussion

The initial investigation into carbonylation of bromoanisole (a deactivated substrate) in n-butanol and TMEDA using water-soluble phosphine/palladium catalyst utilized conditions set forth by Beller. The ligands, various temperatures, catalyst loading, and L/Pd ratios and base were screened (Table 5.1). The absence of success with DTBPPS and success with DAPPS facilitated its use as our ligand for activation. With catalyst loading, the most successful catalyst system was a 1.1/1 L/Pd ratio and 0.33mol%Pd. In the comparison of bases, we saw limited reaction completion with Na₂CO₃, however, TMEDA facilitated the reaction to go to completeness.

Table 5.1 Reaction optimization results

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Base</th>
<th>Temperature</th>
<th>L/Pd ratio</th>
<th>Catalyst loading</th>
<th>Scale</th>
<th>% Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTBPPS</td>
<td>TMEDA</td>
<td>115 °C</td>
<td>1.1:1</td>
<td>1 mol%</td>
<td>2 mmol</td>
<td>10%</td>
</tr>
<tr>
<td>DAPPS</td>
<td>TMEDA</td>
<td>115 °C</td>
<td>1.1:1</td>
<td>1 mol%</td>
<td>2 mmol</td>
<td>80%</td>
</tr>
<tr>
<td>DAPPS</td>
<td>Na₂CO₃</td>
<td>115 °C</td>
<td>1.1:1</td>
<td>1 mol%</td>
<td>2 mmol</td>
<td>5%</td>
</tr>
<tr>
<td>DAPPS</td>
<td>TMEDA</td>
<td>115 °C</td>
<td>3:1</td>
<td>1 mol%</td>
<td>2 mmol</td>
<td>90%</td>
</tr>
<tr>
<td>DAPPS</td>
<td>TMEDA</td>
<td>23 °C</td>
<td>1.1:1</td>
<td>1 mol%</td>
<td>2 mmol</td>
<td>0%</td>
</tr>
<tr>
<td>DAPPS</td>
<td>TMEDA</td>
<td>115 °C</td>
<td>1.1:1</td>
<td>0.5 mol%</td>
<td>2 mmol</td>
<td>65%</td>
</tr>
<tr>
<td>DAPPS</td>
<td>TMEDA</td>
<td>115 °C</td>
<td>1.1:1</td>
<td>0.33mol%</td>
<td>6 mmol</td>
<td>88%</td>
</tr>
</tbody>
</table>

Reactions carried out in an autoclave Parr reactor, 20 bar CO pressure, with n-butanol solvent, non-gas induction stir component and 16 h reaction time. a). The % conversion is consumption of starting material evaluated via gas chromatography.
Table 5.1. Isolated yields for butyl esters from aryl bromides carbonylation using palladium/DAPPS catalyst.

<table>
<thead>
<tr>
<th>Aryl Halide</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="NC" />Br</td>
<td><img src="image" alt="NC" />O</td>
<td>92</td>
</tr>
<tr>
<td><img src="image" alt="O" />H</td>
<td><img src="image" alt="O" />OBu</td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="R" />O</td>
<td>85*</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="R" />OBu</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="MeO" />Br</td>
<td><img src="image" alt="MeO" />O</td>
<td>99</td>
</tr>
<tr>
<td><img src="image" alt="Me" />Br</td>
<td><img src="image" alt="Me" />O</td>
<td>57</td>
</tr>
<tr>
<td><img src="image" alt="MeO" />Me</td>
<td><img src="image" alt="MeO" />O</td>
<td>47</td>
</tr>
<tr>
<td><img src="image" alt="F3C" />Br</td>
<td><img src="image" alt="F3C" />O</td>
<td>96</td>
</tr>
<tr>
<td><img src="image" alt="Cl" />Br</td>
<td><img src="image" alt="Cl" />O</td>
<td>57</td>
</tr>
<tr>
<td><img src="image" alt="Cl" />Br</td>
<td><img src="image" alt="Cl" />O</td>
<td>54</td>
</tr>
</tbody>
</table>

Reactions were run under the conditions in Equation 5.1 *conversion to the 1,4 diester and 1,4 diacid-ester.
Once a good protocol was established, various aryl bromides were evaluated under these conditions (Equation 5.1). Selection of aryl bromides that had electron releasing (deactivating) groups (Table 5.2), electron withdrawing (activating) groups (Table 5.2), and electron neutral (Table 5.2) substituents was established to test the scope of the catalysts ability. In evaluating the deactivated substrates, lowered productivity was noticed, in particular when the sterically hindered substrates were tested. According to Barnard\textsuperscript{137} sterically hindered substrates give lower yields. This is expected as the 4-coordinate complex oxidative addition with an ortho-substituted aromatic substituent sterically hinders CO binding to the complex and inhibits migratory insertion, thereby making it difficult to afford product. However, the ortho-substituted aromatic shows good productivity suggesting that the electronic effect of the deactivating group is not an issue for causing lowered productivity. Interestingly, the aldehyde ester product was not generated from bromobenzaldehyde, but \(^1\)H NMR spectrum of the product showed a mixture of the 1,4-diester and the 1,4-acid ester mixture. When given the choice, the catalyst selectively functionalizes the bromo over the chloro position with the lower yield but incomplete conversion occurred. The absence of completion in the reaction could be due to catalyst decomposition.

\[
\begin{align*}
\begin{array}{c}
R \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \Quad
The use of DAPPS phosphine ligand along with palladium is the first example of a water-soluble alkylphosphine promoting conversion of an aryl bromide to an ester. Additionally, it is the first example of a water-soluble phosphine/palladium catalyst promoting carbonylation of a non-benzylic substrate. The practicality of the reaction coupled with its extremely low catalyst loading and potential for catalyst recovery makes this system very useful. Additionally, when compared to the cataCXium® A systems, a lower catalyst loading was used. Moreover, the ability to generate the sterically hindered esters facilitates their use in larger more complex molecules containing ortho-substituted aromatics not demonstrated by cataCXium® A systems. The leaching of the palladium into the product has yet to be assessed.

### Table 5.2 Reaction optimization for carboxylic acid synthesis.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Palladium source</th>
<th>base</th>
<th>water/THF</th>
<th>% conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPPS</td>
<td>Pd(OAc)$_2$</td>
<td>Na$_2$CO$_3$</td>
<td>100/0</td>
<td>75%</td>
</tr>
<tr>
<td>DAPPS</td>
<td>Pd(OAc)$_2$</td>
<td>TMEDA</td>
<td>100/0</td>
<td>57%</td>
</tr>
<tr>
<td>DAPPS</td>
<td>Pd(OAc)$_2$</td>
<td>NaOH</td>
<td>100/0</td>
<td>0%</td>
</tr>
<tr>
<td>DAPPS</td>
<td>Na$_2$(PdCl)$_4$</td>
<td>Na$_2$CO$_3$</td>
<td>100/0</td>
<td>23%</td>
</tr>
<tr>
<td>DAPPS</td>
<td>Pd(OAc)$_2$</td>
<td>Na$_2$CO$_3$</td>
<td>6/3</td>
<td>82%</td>
</tr>
<tr>
<td>DAPPS</td>
<td>Pd(OAc)$_2$</td>
<td>Na$_2$CO$_3$</td>
<td>6/1</td>
<td>99%</td>
</tr>
<tr>
<td>DAPPS</td>
<td>Pd(OAc)$_2$</td>
<td>Na$_2$CO$_3$</td>
<td>1/1</td>
<td>73%</td>
</tr>
</tbody>
</table>

Reactions carried out in an autoclave Parr reactor, 20 bar CO pressure, 1:1.1 Pd/L ratio, non-gas induction stir component and 16 h reaction time. a). The % conversion is consumption of starting material evaluated via gas chromatography.

In changing the solvent system we are able to change the resulting carbonylated product. Changing to water allows the conversion to carboxylic acids (Equation 5.2). For the generation of carboxylic acids, maintenance of the same catalyst loadings led good to excellent yields. In optimization of the carboxylic acid reaction, a small amount of THF was added to the reaction mixture to afford good conversion of the starting materials to the product. Notably a ratio of 6:1 was optimal, and any deviance from that ratio led to less than complete conversion (Table 5.2).
Most likely, the increasing THF ratio inhibits the starting material from being solubilized by the water thereby decreasing the rate of catalysis. Interestingly, greater isolated yield is noticed from sterically hindered substrates where as in the esterification, limited productivity was noted. This suggests that water may be able to facilitate the substitution of CO onto palladium better than butanol. The better substitution may be a function of greater solubility of CO in water over butanol or that the cleavage of the palladium acyl is really the rate determining step. Additionally, we see the same selectivity of the acid being generated in the position were the bromine resided over the chlorine. Testing the catalysts scope, again the range of activated deactivated, and neutral substrates were evaluated.

\[
\begin{align*}
R &= -\text{OMe}, -\text{COMe}, \text{ or } -\text{Me} \\
R' &= \text{H}, \text{ or } -\text{Me}
\end{align*}
\]
Table 5.2. Isolated yields for butyl esters from aryl bromides carbonylation using palladium/DAPPS catalyst.

<table>
<thead>
<tr>
<th>Aryl Halide</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO(-)Br</td>
<td>MeO(-)CO(\sim)OH</td>
<td>82</td>
</tr>
<tr>
<td>Me(-)CO(-)Br</td>
<td>Me(-)CO(\sim)OH</td>
<td>40</td>
</tr>
<tr>
<td>Me(-)Br</td>
<td>Me(-)CO(\sim)OH</td>
<td>93</td>
</tr>
<tr>
<td>Me(-)Br</td>
<td>Me(-)CO(\sim)OH</td>
<td>84</td>
</tr>
<tr>
<td>MeO(-)Cl</td>
<td>MeO(-)CO(\sim)OH</td>
<td>67</td>
</tr>
</tbody>
</table>

Reaction conditions were from Equation 5.2

5.3 Conclusions

To our knowledge we have demonstrated the first alkyl only water-soluble phosphine palladium catalyst system for the carbonylation of aryl bromides. The DAPPS/Pd catalyst is able
to afford good to excellent conversion to the desired products with relatively low ligand to palladium ratio and low catalyst loading. The advantage of this system over many others is the low catalyst loadings, low ligand to palladium ratio, and its water-solubility. Additionally, we are able to convert aryl bromides to acids and esters respectively by simply changing the solvent system from butanol to water/THF. The ability to change the solvent coupled with potential catalyst recovery allows a great deal of versatility in the catalyst.

5.4 Experimental

5.4.1 General information

All reactions were assembled in a nitrogen-filled dry box with the addition of Pd source, ligand, base, and aryl halide performed followed by sealing of the bomb. Additionally, all reactions were carried out in a Parr brand stainless steel 100 ml high pressure autoclave with an overhead non-gas induction stir mechanism. The autoclave was fit with a port to accept a rubber septum for the introduction of solvents. All solvents were sparged for a minimum of 15 min before introducing into the reactor with nitrogen gas. The Parr bomb was placed in the reactor after being charged with solvent where it was filled to 20 bar of CO and released to 2 bar 3 times. The final fill was to 20 bar at room temperature. The reactions were allowed to react at specified temperature while stirring at 415 rpm. Gas chromatography was performed on the reactions to assess reaction progress.

5.4.2 Synthesis of butyl esters

The following was added to the Parr bomb in order: Pd(OAc)$_2$ (4.5 mg, 0.02 mmol), DAPPS (9.0 mg, 0.021 mmol), aryl halide (6.0 mmol), and TMEDA (540 μL, 4.5 mmol). The bomb was sealed and removed from the dry box and charged with butanol (6 ml). The vessel
was pressurized to 20 bar of CO at room temperature. The reactions were run for 16 h at 115 °C then allowed to cool to room temperature. Gas chromatography was performed to assess reaction completeness. All reactions were extracted with 3 x 30 ml ethyl ether and 30 ml of water. This extraction was followed by removal of solvent under reduced pressure followed by purification through a short plug of silica gel with gradient solvent (hexane/ethyl acetate) ranging from 100:0 to 85:15.

**n-Butyl 4-cyanobenzoate:** Using general procedure, 4-bromobenzonitrile (1.09 g, 6 mmol) was used. After chromatography 1.23 g (92%) was recovered of a tan solid. $^1$H NMR (360 MHz, CDCl$_3$): $\delta$ 8.14 (d, $J = 8.6$ Hz, 2H), 7.74 (d, $J = 8.6$ Hz, 2H), 4.36 (t, $J = 6.6$ Hz, 2H), 1.77 (m, 2H), 1.47 (m, 2H), 0.99 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (90.4 MHz, CDCl$_3$): $\delta$ 165.0, 134.3, 132.2, 130.0, 118.0, 116.3, 65.6, 30.6, 19.2, 13.7.

**n-Butyl 2-methylbenzoate:** Using general procedure, 2-bromotoluene (720 µL, 6 mmol) was used. After chromatography 0.6602 g (57%) was recovered of a tan liquid. $^1$H NMR (360 MHz, CDCl$_3$): $\delta$ 7.90 (d, $J = 8.2$ Hz, 1H), 7.37 (t, $J = 7.5$ Hz, 1H), 7.25 (m, 2H), 4.30 (t, $J = 6.6$ Hz, 2H), 1.77 (p, $J = 7.7$ Hz, 2H), 2.60 (s, 3H), 1.73 (m, 2H), 1.47 (m, 2H), 0.98 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (126.4 MHz, CDCl$_3$): $\delta$ 167.8, 140.0, 131.8, 131.6, 130.5, 125.6, 64.6, 30.8, 21.7, 19.3, 13.7.

**n-Butyl 2-(methyl)anisolate:** Using general procedure, 2-methyl4-bromoanisole (850 µL, 6 mmol) was used. After chromatography 1.423 g (96%) was recovered of a tan liquid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.93 (d, $J = 9.1$ Hz, 1H), 6.75 (d, $J = 2.5$ Hz, 2H), 6.74 (s, 1H) 4.23 (t, $J = 6.6$ Hz, 2H), 3.83 (s, 3H), 1.77 (p, $J = 7.7$ Hz, 2H), 2.60 (s, 3H), 1.73 (m, 2H), 1.47 (m, 2H), 0.98 (t, $J = 7.6$ Hz, 3H). $^{13}$CNMR (126.4 MHz, CDCl$_3$): $\delta$ 167.2, 162.2, 142.9, 132.9, 122.2, 116.9, 110.9, 64.3, 55.2, 30.9, 22.3, 19.4, 13.7.
**n-Butyl 4-(trifluoromethyl)benzoate:** Using general procedure, 4-trifluoromethylbromobenzene (1.25 ml, 6 mmol) was used. After chromatography 1.423 g (96%) was recovered of a tan liquid. $^1$HNMR (360 MHz, CDCl$_3$): $\delta$ 8.16 (d, $J = 8.2$ Hz, 2H), 7.70 (d, $J = 8.7$ Hz, 2H), 4.37 (t, $J = 6.6$ Hz, 2H) 1.77 (p, $J = 7.7$ Hz, 2H), 1.49 (m, 2H), 0.99 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (90.4 MHz, CDCl$_3$): $\delta$ 165.5, 134.2, 133.8, 133.1 (q, $J = 140.1$ Hz), 132.1, 130.0, 125.4, 65.4, 30.7, 19.3, 13.7.$^{139}$

**n-Butyl 2-(chloro)benzoate:** Using general procedure, 2-bromochlorobenzene (700 µL, 6 mmol) was used. After chromatography 689 mg (54%) was recovered of a tan liquid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.80 (d, $J = 7.5$ Hz, 1H), 7.43 (d, $J = 8.2$ Hz, 1H), 7.37 (t, $J = 8.2$ Hz, 1H) 7.28 (t, $J = 7.6$ Hz, 2H) 4.37 (t, $J = 6.6$, 2H), 1.75 (m, 2H), 1.47 (m, 2H), 0.97 (t, $J = 7.3$ Hz, 3H).$^{140}$

**n-Butyl 4-(chloro)benzoate:** Using general procedure, 2-bromochlorobenzene (700 µL, 6 mmol) was used. After chromatography 689 mg (54%) was recovered of a tan liquid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.00 (d, $J = 8.9$ Hz, 1H), 7.41 (d, $J = 8.4$ Hz, 1H), 4.33 (t, $J = 6.6$, 2H), 1.76 (m, 2H), 1.49 (m, 2H), 1.00 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (90.4 MHz, CDCl$_3$): $\delta$ 165.7, 139.2, 132.7, 130.9, 129.0, 65.1, 30.7, 19.3, 13.7.$^{136}$

### 5.4.3 Synthesis of carboxylic acids

The following was added to the Parr bomb in order: Pd(OAc)$_2$ (4.5 mg, 0.02 mmol), DAPPS (9.0 mg, 0.021 mmol), aryl halide (6.00 mmol), Na$_2$CO$_3$ (2.40 g, 12.6 mmol), and THF. sealed and removed from the dry box and charged with water (6 ml). The reactions were run for 16 h then allowed to cool to room temperature. Ethyl ether was added to the bomb (10ml), the bomb was shaken and allowed to settle followed by gas chromatography of the organic layer to assess reaction completeness. The reaction mixture was filtered followed by an extraction with
3x 30 ml ethyl ether and 20 ml of water. The aqueous layer was acidified to pH 1 with 10% HCl followed by filtration and 2x 10 ml washings with deionized water.

4-Methoxybenzoic acid: Using general procedure, 4-bromoanisole (850 µL, 6 mmol) was used. After filtration 913 mg (99%) was recovered of a white solid. $^1$H NMR (500 MHz, DMSO-d$_6$): δ 12.61 (s, 1H), 7.90 (d, $J = 8.8$ Hz, 2H), 7.00 (t, $J = 8.8$ Hz, 2H) 3.81 (s, 3H). $^{13}$C NMR (126.4 MHz, DMSO-d$_6$): δ 166.9, 131.3, 122.9, 113.7, 55.3.\(^{139}\)

4-Acetylbenzoic acid: Using general procedure, 4-bromoanisole (850 µL, 6 mmol) was used. After filtration (99%) was recovered of a white solid. $^1$H NMR (500 MHz, DMSO-d$_6$): δ 8.06 (m, 5H), 2.63 (s, 3H). $^{13}$C NMR (126.4 MHz, DMSO-d$_6$): δ 197.8, 166.7, 139.9, 134.6, 129.6, 128.4, 27.1.\(^{141}\)

2-Methylbenzoic acid: Using general procedure, 2-bromotoluene (720 µL, 6 mmol) was used. After filtration 756 mg (93%) was recovered of a white solid. $^1$H NMR (500 MHz, DMSO-d$_6$): δ 12.80 (s, 1H), 7.84 (d, $J = 7.3$ Hz, 1H), 7.45 (t, $J = 7.5$ Hz, 1H) 7.30(d, $J = 7.5$ Hz, 3H), 2.54 (s, 3H). $^{13}$C NMR (126.4 MHz, DMSO-d$_6$): δ 168.6, 138.9, 131.6, 131.39, 130.37, 130.1, 125.7, 21.1.\(^{142}\)

4-Methylbenzoic acid: Using general procedure, 4-bromotoluene (720 µL, 6 mmol) was used. After filtration 688mg (84%) was recovered of a white solid. $^1$HNMR (500 MHz, DMSO-d$_6$): δ 12.77 (s, 1H), 7.83 (d, $J = 8.2$ Hz, 2H), 7.30 (d, $J = 8.2$ Hz, 2H), 2.37 (s, 3H). $^{13}$C NMR (126.4 MHz, CDCl$_3$): δ 167.7, 143.5, 129.8, 129.6, 128.5, 21.6.\(^{143}\)

2-Chlorobenzoic acid: Using general procedure, 2-bromochlorobenzene (700 µL, 6 mmol) was used. After filtration 636 mg (67%) was recovered of a white solid. $^1$H NMR (360 MHz, CDCl$_3$): δ 13.41 (s, 1H), 7.80 (m, 1H), 7.55 (m, 2H), 7.44 (m, 1H). $^{13}$C NMR (126.4 MHz, DMSO-d$_6$): δ 167.2, 133.0, 132.0, 131.9, 131.2, 131.1, 127.7.\(^{144}\)
REFERENCES


(65) Strohmeier, W.; Mulle, F. J. Chemische Berichte 1967, 100, 2812.


(77) Amatore, C.; Carre, Emmanuelle; Jutand, A.; Medjou, Y. *Organometallics* 2002, 21, 4540-4545.


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Figure A34. 2-(4-Methoxyphenyl)-2-methyl-1-phenyl-propan-1-one $^{13}$C NMR (CDCl$_3$, 126MHz)
Figure A35. 2-(4-Methylphenyl)-2-methyl-1-phenyl-propan-1-one $^1$H NMR (CDCl$_3$, 500 MHz)
Figure A36. 2-(4-Methylphenyl)-2-methyl-1-phenyl-propan-1-one $^{13}$C NMR (CDCl$_3$, 126MHz)
Figure A37. 2-(2-Methylphenyl)-2-methyl-1-phenyl-propan-1-one $^1$H NMR (CDCl$_3$, 500 MHz)
Figure A38. 2-(2-Methylphenyl)-2-methyl-1-phenyl-propan-1-one $^{13}$C NMR (CDCl$_3$, 126MHz)
Figure A39. 4-Methylbiphenyl $^1$H NMR (CDCl$_3$, 360 MHz)
Figure A40. 2,6-dimethylbiphenyl $^1$H NMR (CDCl$_3$, 500 MHz)
Figure A41. 2,6-dimethylbiphenyl $^{13}$C NMR (CDCl$_3$, 126 MHz)
Figure A42. 4,4’-Dimethoxybiphenyl $^1$H NMR (CDCl$_3$, 500 MHz)
Figure A43. 4,4'-Dimethoxybiphenyl $^{13}$C NMR (CDCl$_3$, 126 MHz)
Figure A44. 4-Cyano,4’-methoxybiphenyl $^1$H NMR (CDCl$_3$, 500 MHz)
Figure A45. 4-Cyano,4'-methoxybiphenyl $^{13}$C NMR (CDCl$_3$, 126 MHz)
Figure A46. 2-Hydroxybiphenyl $^1$H NMR (CDCl$_3$, 500 MHz)
Figure A47. N,N-4-(dimethylamino)biphenyl $^1$H NMR (CDCl$_3$, 500 MHz)
Figure A48. N,N-4-(dimethylamino)biphenyl $^{13}$C NMR (CDCl$_3$, 126 MHz)
Figure A49. 4-(Phenylethynyl)anisole $^1$H NMR (CDCl$_3$, 500 MHz)
Figure A50. 4-(Phenylethynyl)anisole $^{13}$C NMR (CDCl$_3$, 126 MHz)
Figure A51. 4-(Phenylethynyl)benzonitrile $^1$H NMR (CDCl$_3$, 500 MHz)
Figure A52. 4-(Phenylethynyl)benzonitrile $^{13}$C NMR (CDCl$_3$, 126 MHz)
Figure A53. 2-(Phenylethynyl)toluene $^1$H NMR (CDCl$_3$, 126 MHz)
Figure A54. 2-(Phenylethynyl)toluene $^{13}$C NMR (CDCl$_3$, 126 MHz)
Figure A55. 4-(4-Methoxyphenyl)-3-butyne-1-ol $^1$H NMR (CDCl$_3$, 500 MHz)
Figure A56. 4-(4-Methoxyphenyl)-3-butyne-1-ol $^{13}$C NMR (CDCl$_3$, 126 MHz)
Figure A57. 2-(Phenylethynyl)-m-xylene $^1$H NMR (CDCl$_3$, 500 MHz)
Figure A58. 2-(Phenylethynyl)-m-xylene $^{13}$C NMR (CDCl$_3$, 126 MHz)
Figure A59. 4'-[(Phenylethynyl)acetophenone] $^1$H NMR (CDCl$_3$, 500 MHz)
Figure A60. 4'-((Phenylethynyl)acetophenone$^{13}$C NMR (CDCl$_3$, 126 MHz)
Figure A61. *n*-Butyl 4-(cyano)benzoate $^1$H NMR (CDCl$_3$ 360MHz)
Figure A62. n-Butyl 4-(cyano)benzoate $^{13}$C NMR (CDCl$_3$, 360MHz)
Figure A63. *n*-Butyl 4-methoxybenzoate $^1$H NMR (CDCl$_3$, 360MHz)
Figure A65. *n*-Butyl 2-methyl-4-anisolate $^1$H NMR (CDCl$_3$, 500MHz)
Figure A66. $n$-Butyl 2-methyl-4-anisolate $^{13}$C NMR CDCl$_3$, 500MHz
Figure A67. $n$-Butyl 2-methylbenzoate $^{13}$C NMR (CDCl$_3$, 500MHz)
Figure A68. n-Butyl 4-(trifluoromethyl)benzoate $^1$H NMR (CDCl$_3$, 360MHz)
Figure A69. *n*-Butyl 4-(trifluoromethyl)benzoate $^{13}$C NMR (CDCl$_3$, 360MHz)
Figure A70. $n$-Butyl 2-(chloro)benzoate H NMR (CDCl$_3$, 500MHz)
Figure A71. *n*-Butyl 4-(chloro)benzoate $^1$H NMR (CDCl$_3$, 360MHz)
Figure A72. \textit{n-Butyl 4-(chloro)benzoate}\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 90.4MHz)
Figure A73 4-Methoxybenzoic acid $^1$H NMR (DMSO-$d_6$, 500MHz)
Figure A74. 4-Methoxybenzoic acid $^{13}$C NMR (DMSO-d$_6$, 500MHz)
Figure A75. 4-Acetylbenzoic acid $^1$HNMR acid (DMSO-$d_6$, 500MHz)
Figure 76. 4-Acetylbenzoic acid $^{13}$C NMR acid (DMSO-$d_6$, 26MHz)
Figure 77. 2-Methylbenzoic acid $^1$H NMR (DMSO-d$_6$, 500MHz)
Figure 78. 2-Methylbenzoic acid $^{13}$C NMR (DMSO-$d_6$, 126.4MHz)
Figure 79. 4-Methylbenzoic acid $^1$H NMR (DMSO-d$_6$, 500MHz)
Figure 80. 4-Methylbenzoic acid $^{13}$C NMR (DMSO-$d_6$, 126.4MHz)
Figure 81. 2-Chlorobenzoic acid $^1$H NMR (DMSO-d$_6$, 500MHz)
Figure 82. 2-Chlorobenzoic acid $^{13}$C NMR (DMSO-$d_6$, 126.4MHz)