USING KETONES AS CATALYST ACTIVATORS IN PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS

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ABSTRACT

PEPPSI-IPr (**1**) has become a very useful catalyst over the past decade. It has shown to be successful with almost every type of cross-coupling reaction that currently exists. These transformations have been used in catalytic studies and the pharmaceutical industry. This study used PEPPSI-IPr and 3-pentanone to greatly improve the yield of the Buchwald-Hartwig amination of various aryl bromides and aniline. This suggests that the ketone acted as the activator where aniline cannot. The importance of using the ketone as an activator for catalysis will be shown in various ways. This transformation has been successful with both sterically hindered and electronically modified substrates. However, the electron-rich substrates proved to produce higher yields than their electron-deficient counterparts. The transformation showed slight favor of sterically hindered substrates over non-hindered ones. The reaction mechanism for ketone activation remains unknown. The goal of this study was to gain further knowledge of how the ketone affects the reaction to better understand how this mechanism occurs. Other conditions of these reactions include low catalyst loading (PEPPSI-IPr, **1**), the use of NaO-*t*-Bu as the base and dry toluene as the solvent over a range of temperatures, 20-80 °C. This study also demonstrated the importance of reagent addition order, and how it affected the transformation. The culmination of this study showed that without the ketone, the reaction was not very successful, producing 3-12% yields; however, with the ketone, most conditions afford yields between 60-100%. In order to convey the importance of the ketone in this reaction, we studied the affect of increasing ketone concentrations and temperatures on the 4-bromoanisole and 2-bromotoluene substrates in addition to a reaction rate profile for 4-bromoanisole.

DEDICATION

This thesis is dedicated to my dear friends and family who helped see me through every step of my undergraduate and graduate degrees. There were many hard nights, but their love and support helped me push through. Also, to Hercules, my dog. Thank you for the company you kept me during those long hard nights and for getting me out of the house when I needed it the most.

LIST OF ABBREVIATIONS AND SYMBOLS

2°, 3°	Secondary, Tertiary
α	Alpha (position)
β	Beta (position)
γ	Gamma (position)
θ	Cone angle for $\%V_{bur}$
μ	Micro (measurement)
o	Ortho position
π	Pi bond
σ	Sigma bond
GC	Gas chromatography
GCMS	Gas chromatography – Mass spec
IR	Infrared
L	Ligand
L_2Pd	General di-ligand palladium complex
M	Metal
M-C	Metal carbon bond
M-N	Metal nitrogen bond
m/z	Mass-to-charge ratio
NHC	N-heterocyclic carbene
p*	p-orbital antibonding

PEPPSI	Pyridine-enhanced precatalyst preparation stabilization and initiation
ppm	Parts per million
PR_3	General trialkyl phosphine complex
R	General substituent
RT	Room temperature
RX	Alkyl, aryl or alkenyl halide bond
RZnX	Alkyl, aryl or alkenyl zinc halide bond
TON	Turnover number
$\%V_{bur}$	% buried volume

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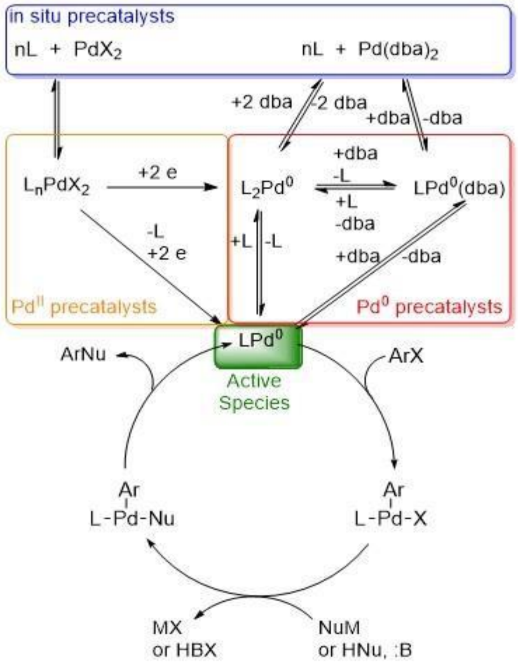
1 Introduction

1.1 Overview of Cross-Coupling

Historically, cross-coupling reactions are known for aiding in the formation of new C-C bonds where synthetic formation without the use of a catalyst proves difficult or impossible. Recently, hetero-coupling reactions, such as C-N bond formation, have become more understood, which then led to their widespread use. Cross-coupling reactions are comprised of three stages: oxidative addition, transmetalation, and reductive elimination.[1] For amination reactions, the transmetallation step is not transmetallation but instead the coordination then deprotonation of the amine. In order to initiate this cycle, a L-Pd^0 species must be generated. This L-Pd^0 active species can be formed by reduction of a pre-catalyst, which will be discussed later in further detail. At the end of the cycle, the metal-ligand active species will be regenerated. The generic mechanism for both generation of the activation species and the catalytic cycle are shown in **Scheme 1.**



Scheme 1. General Pd^0 and Pd^{II} catalytic pathways and incorporation of the active Pd species into the cross-coupling cycle.[7]

Once the active species has been formed, the palladium oxidatively inserts into the aryl halide bond forming an aryl palladium halide[1] complex (or other metal complex). Oxidative addition can occur by four different pathways: 1) concerted, 2) S_N2, 3) radical and 4) ionic.[2] For aryl halides, it is concerted.

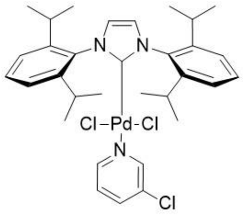
Next, the new aryl Pd halide will undergo transmetalation with an organoreagent such as aniline. In the case of transmetalation, there are now two C-M bonds, and for amination, a new N-M and C-M bond.[1] From here, the newly formed aryl palladium-amido complex[1] will be deprotonated and undergo reductive elimination.

1.2 Types of Cross-Coupling

There are many well-known cross-coupling reactions. Some of the most well-known are Negishi, Suzuki, Kumada, and Buchwald-Hartwig. These four reaction types will be examined for their work with varying PEPPSI-precatalyst compounds.

1.2.1 Negishi Couplings

The Negishi reaction forms new bonds using an organozinc reagent as the coupling partner.[3] Negishi type reactions with PEPPSI-IPr (**1**) afford a wide spectrum of functionality such as esters, nitriles, amides and acetates. [3] These reactions even maintain TMS functionality under room temperature reaction conditions. The results given by these reactions shows the potential for coupling substrates containing biologically active components and potential for synthesis of natural product intermediates.[2] The following Negishi reactions have produced successful yields: sp^3(RX)- sp^3(RZnX), sp^3- sp^2, sp^2- sp^3, and



PEPPSI-IPr
(Pyridine-Enhanced Precatalyst
Preparation Stabilization and Initiation)
1

Figure 1. PEPPSI-IPr structure and name.

sp^2- sp^2 couplings. Some advantages of using PEPPSI-IPr in Negishi couplings are no glove-box handling; prototypical and advance couplings are possible; reactions are successful at RT within a few hours; and they selectively activate bromide over chloride, which allows for a diverse range of halides: Cl, Br, I, OTs, OMs, or OTf. [2]

1.2.2 Suzuki Couplings

Suzuki reactions couple organoborons with alkyl, aryl, and alkenyl halides or triflates.[1] PEPPSI-IPr and Suzuki conditions were successful in affording a wide range of electron-rich (deactivated) and electron-poor (activated) substrates.[5] This catalyst system is used for industrial and academic laboratory research applications on a global scale. The Suzuki reactions between an aryl halide and an organo-M reagent, PEPPSI-IPr and other varying conditions were accomplished using lab bench techniques (no glove box), however, the precatalyst was weighed and activated in situ while under and inert blanket of gas.[2] The Organ group coupled trialkyl boranes with bromoalkanes to afford n-heptyl benzene. This shows that these processes can form sp^3- sp^3 bonds, which has been a difficult task with phosphine-Pd precatalysts. Due to the flexibility of the catalyst, these reactions have the potential to form drug intermediates, heteroaromatics, and bulky organic building blocks of varying electronic character.[2] Advantages of using PEPPSI-IPr include no glove-box handling; boronic acids and trifluoroborates are well tolerated; no preference of one halide, bromide and chloride, over the other; strong and mild bases applied successively; and success with base sensitive substrates.[2]

1.2.3 Kumada Couplings

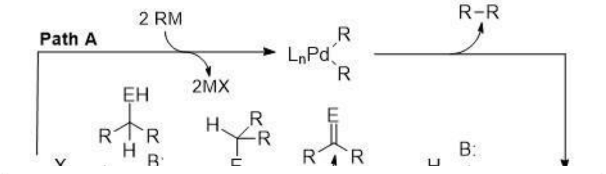
The Kumada reaction couples aryl halides and Grignard reagents with Pd^0.[1] Some setbacks with Kumada couplings are high catalyst loadings and high temperatures.[2] On a positive note, these reactions produced good yields with sterically hindered aryl chlorides; electron-rich and electron-poor tolerance of ether, TMS and alkynyl functionalities; heteroaromatic substrates; and functionalized 5-aryl substituted indoles.[2]

1.2.4 Buchwald-Hartwig Aminations

Buchwald-Hartwig aminations form palladium catalyzed C-N bonds. Most of the catalytic focus has been on bulky, electron-rich phosphines as ancillary ligands of choice in the past. The Organ group found excellent success with coupling aryl chlorides and bromides with amines. Morpholine, aryl amines and adamantylamines are all proven to be facile in these reactions to afford a variety of aryl- and biarylamines.[6] Pd-NHC complexes can also form atom-economical products in an aromatic C-N bond-forming process.

1.3 Precatalysts

There are many ways to produce the active LPd^0 catalyst species. The Pd^0 precatalyst pathway can be helpful because it already contains the desired oxidative state, however, ligand dissociation from the L_2Pd^0 complexes often occurs at a large energy barrier, thereby slowing the initiation down, especially at room temperature.[7] The Pd^{II} precatalysts are the most



Scheme 2. Path A) reduction by organometallic coupling partners; Path B) β-hydride elimination as the reducing ligand because it does not bind as or coordinated alkyl groups, amines, or alkoxides followed by deprotonation of the Pd-hydride; Path C) reduction by phosphine ligands.

widely used because they are air stable, unlike Pd^0 sources. Reactions with these precatalysts can be run in air with no degradation in yield.[7] The only downside to the Pd^{II} species is having to reduce them before they can enter the catalytic cycle.

The three possible reduction pathways for Pd^{II} to active Pd^0 are illustrated in **Scheme 2.** Path A would give the reductive elimination product. This requires an organometallic coupling partner, such as the Suzuki or Negishi reactions. Path B, β-elimination, requires an alcohol or amine with a β-H to undergo reduction. Meanwhile, Path C occurs with triarylphosphines and acetate anions rather than NHC complexes.

Once the metal-ligand complex has been reduced to the active LPd^0 species, it enters the catalytic cycle. At the end of the catalytic cycle, there will be a new C-C or C-heteroatom bond, and if the reduction mechanism follows Path A or B, the LPd^0 will be regenerated.

2 Development of PEPPSI-IPr

In 2010, Rich F. Heck, Ei-ichi Negishi, and Akira Suzuki were jointly awarded the Nobel Prize in Chemistry for "palladium-catalyzed cross-couplings in organic synthesis".[8] These were developed after discovery that NHC-M complexes are successful competitors for phosphine-M complexes. In many cases, NHC-M complexes are more stable due to the reasons such as strong σ-bonding between NHC complexes and metals, p-orbital through space interaction stabilization and back-bonding from the metal center into the p*-orbital of the carbene carbon. Each of these will be discussed in greater length below.

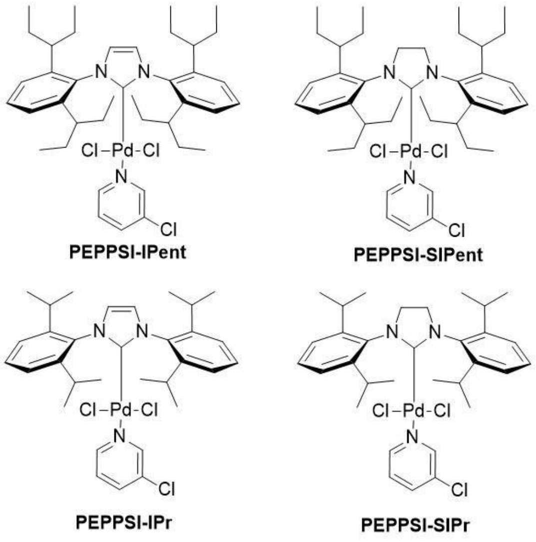
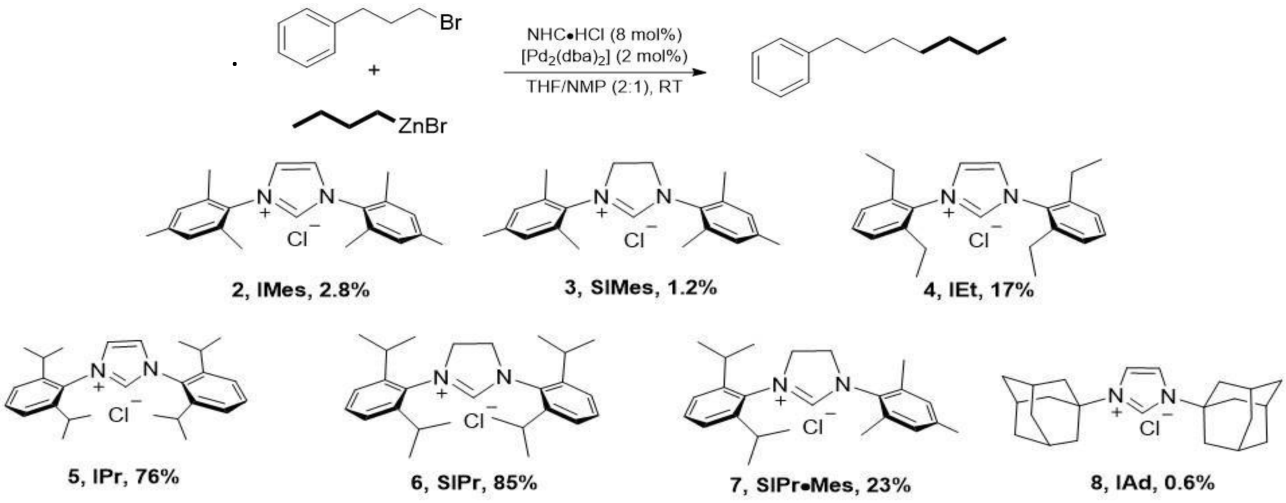


Figure 2. PEPPSI-Complexes.

PEPPSI stands for “Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation”. The PEPPSI-precatalyst family contains many useful and state-of-the-art catalytic functions. Some of the most popular and facile are -SIPr, -IPr, IPent, and -IPent^{Cl} (**Figure 2**). However, here we focused on PEPPSI-IPr as it is the most widely used catalyst from this group. There are two major components that led to the success these catalysts have had: The N-heterocyclic carbene (NHC) ligand and the throw away pyridine ligand.[9] The intricacies of these components will be discussed in more detail later in this section.



Scheme 3. Structure and activity of IMes, SIMes, IEt, IPr, SIPr, SIPr·Mes, IAd.[14]

2.1 History and Use of N-Heterocyclic Carbene Development

In 1968, N-heterocyclic carbenes were independently produced by Wanzlick and Schönherr[10] and Öfele[11] and attracted very little interest from the chemistry community until 1991 when Arduengo et al.[12] discovered the first stable, crystalline NHC (**8, Scheme 3**). Once revealed, Herrmann et al.[13] (in 1995) recognized the potential this class of compounds had as spectator ligands in transition-metal complexes.

Although there were many NHC complexes developed, only those made from imidazolium or 4,5-dihydroimidazolium salts have been used widely for homogeneous catalysis so far.[7,14] It has also been recently noted that preformed metal-ligand complexes can be used to generate the active catalyst species.[7]

2.1.2 PR_3 vs NHC

These NHC complexes are closely related to the electron-rich, trialkyl-phosphine (PR_3) ligands. They are both excellent σ-donors, thereby enabling the Pd to oxidatively insert into bonds that typically prove challenging.[15] The most active PR_3 ligands for palladium cross-coupling are the bulky 2° and 3° alkyl substituents. This results in the PR_3 ligands having a large cone angle (θ), which leads to a large, steric topography surrounding the Pd. While this steric bulk helps facilitate certain parts of catalysis, it leads to an increased dissociation rate of the M-PR_3 bond due to the large cone angle.[16] Dissociation, even temporarily, leaves enough room for alternate pathways to occur, such as β-H elimination, that breaks the catalyst.[15] However, even though both NHC complexes and PR_3 ligands have similar ligating abilities, NHC complexes are more desirable for a number of reasons which will be discussed below.

The NHC-Pd complex has afforded excellent yields with many types of both traditional C-C bond cross-coupling reactions and C-heteroatom coupling reactions. This is due to the strong NHC-Pd bond as shown in **Figure 3**.[9] The strong bond is due to the strong electron donation of the electron rich carbene to the metal center and the electron donating ability of NHC complexes. These factors contribute to a longer lifetime of the catalyst for NHC complexes over phosphines and a consistent reactivity throughout the reaction.[9] The more stable the ligand-metal complex is, the more it improves the catalysts' stability and the overall lifetime during the reaction, especially for high-temperature cross-coupling protocols. It has been found that on average, these NHC-Pd bonds can withstand temperatures of at least 250 °C before they begin to decompose.[13]

In the Pd-NHC bond, the lone pair is bound to the metal creating a neutral two electron donor bond. The Pd is said to back donate to the NHC p* orbital but is thought to be a negligible effect.[12] The atomic orbital diagrams in **Figure 3** demonstrates the different stabilization effects NHC complexes have on Pd (**9-11**) and the difference in geometry of the steric bulk (**12 & 13**). Structure **9** shows how the three neighboring p-orbitals (N-C-N) stabilize the carbene carbon upon donation of the electrons from the carbene to the metal (**11**). The strong sigma bond (**11**) and stabilization from the p-orbitals (**9**) contributes to the strength of the M-NHC bond that makes this complex successful for a wide variety of transformations. The back-bonding donation of the metal into the p-orbital on the carbene carbon (**10**) also contributes to the strength of this interaction. NHC complexes with ruthenium[17] and nickel[18] have considerably stronger bonds to the metal atom than do phosphines. This was confirmed by thermochemical and computational studies.[14] It seems as though most NHC complexes, if not all, can simply replace phosphines in reactions without changing any of

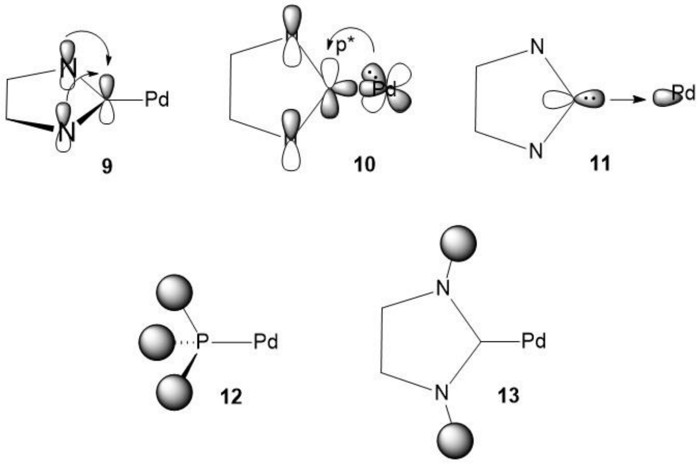
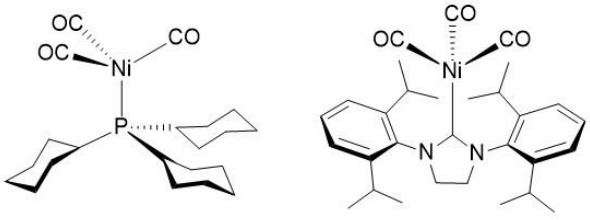


Figure 3. 9: through-space interactions of the nitrogen and carbene p-orbitals; **10**: back-bonding donation of electrons form the metal to the NHC carbene p-orbital. **11**: σ-bonding interaction between the carbene electrons and the metal; **12** & **13**: difference of ligand bulk geometry in PR_3 (**12**) vs. NHC (**13**).

the conditions. Unfortunately, unlike the expansive database on phosphine substituents, NHC complexes have limited data available on their functionality.[16, 19]



14 %V_{bur} 29.6 **15** %V_{bur} 36.1

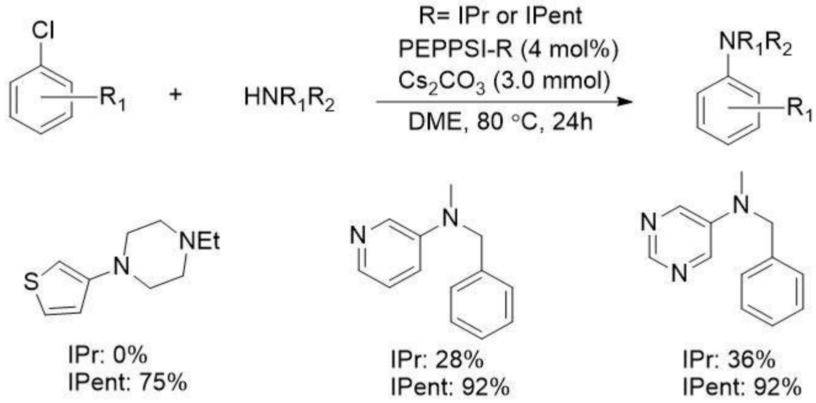
Figure 4. %V_{bur} of PR_3 (**14**) vs NHC (**15**).

A method based on %V_{bur} is capable of determining the direct comparison of steric effects for 3° phosphines (**14**) and NHC complexes (**15**) (**Figure 4**).[9,15] Cone angles are normally used to determine the amount of steric bulk; however, this method is only useful for symmetric ligand structures. Cone angles are not the most efficient method for NHC complexes and chelating ligands due to their unsymmetrical geometry. The %V_{bur} method utilizes x-ray structures to determine how much of a hypothetical sphere is covered, or "buried", by the ligand.[20]

2.1.3 Steric and Electronic Affects

The Organ group demonstrated that the bulkiness close to the metal center can play a role in many steps of the catalytic cycle.[9] The step that is most affected by the steric bulk is transmetallation because it is seen to be the rate-limiting step, at least for the alkyl-alkyl Negishi reaction.[9, 15, 21] However, the bulk of the NHC also increases the rate of both oxidative addition and reductive elimination.

Many studies show that using bulky carbenes as ligands – notably, IPr (**5**) and SIPr (**6**) – has significantly outperformed the traditional phosphine ligands, PR_3, in terms of catalytic transformations. Adding bulky substituents on the nitrogen atoms is very important because these substituents stabilize the thermodynamically less stable carbenes.[14] This occurs because it creates a tighter pocket around the metal center. The tightness around the metal center increases as the bulk increases, and steric bulk prevents dimerization. Whereas, the steric bulk of phosphines is comprised of three substituents and is contained in a flexible, cone shape that points away from the metal center. This makes it difficult for the phosphines to effectively crowd the metal center, thereby limiting their catalytic potential. In catalysis, steric bulk promotes low-coordination number and reductive elimination. In the late 1990s, it was found that palladium catalysts were much more effective for cross-coupling reactions when the ligands were sterically demanding and strongly electron-donating.[7] Such ligands were capable of coupling deactivated substrates, such as, electron-rich heteroaryl halides, aryl chlorides and aryl sulfonates. When NHC ligand-metal complexes are substituted with bulky branching at the 2,6-positions, they tend to be the most active catalysts.[7] This is because the 2,6-positions are closest to the Pd center. The bigger the substituents on the NHC ligand, the more they will push away the other ligands from the palladium. This occurs to relieve strain, created by the NHC, of the less strongly bound ligands. IPr is the most popular NHC ligand, but it is not necessarily the most active one. Larger



Scheme 4. Activity of IPr vs. IPent. [9]

branched NHC complexes such as IPent (**Figure 2**) generally, afford higher catalytic activity than do IPr (**Figures 1 and 2**) ligands (**Scheme 4**.).[14] This goes to show that the various IPr ligands afford the highest yield due to their bulkiness.[14] The bulk around the metal needs to be "fluid" or "conformationally flexible" in order to increase efficiency of the catalyst. The following factors are thought to be useful for increasing catalytic activity: branching at the benzylic carbon of the *ortho*-alkyl substituent, increasing steric bulk, and flexible steric bulk in the alkyl substituent.[9]

An advantage to working with NHC complexes over phosphines is that the steric and electronic properties can be controlled and separated in NHC complexes where they cannot in phosphines.[14] The nitrogen substituents of NHC complexes and their electronic properties are not directly connected to the carbene itself, and therefore have a limited effect on the electron density of this atom.[22, 23] This is why the electronically variant substituents on the nitrogen do not have a strong effect on the yield. A study was done testing the effects of electronic substituents of NHC complexes on catalytic activity. They found that for the aromatic rings, unlike the sterically bulky substituents, electronic variations of substituents do not alter the activity very much.[14] To demonstrate the preference of NHC complexes over phosphines, IR was taken on four different CO containing compounds, $Ni(CO)_3(IMes)$, $Ni(CO)_3(IPr)$, $Ni(CO)_3(P^tBu_3)$, and $Ni(CO)_3(PPh_3)$, with CO (A_1) stretching values of 2050.7, 2051.5, 2056.1 and 2068.9 cm^{-1}, respectively. These were all taken in the solvent, CH_2Cl_2.[22] Results show that NHC complexes are stronger σ-electron donors than the most electron-rich phosphines. A carbene complex with electron-withdrawing groups did not

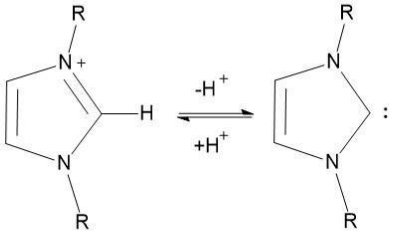


Figure 5. H-affinity of NHC in equilibrium to show potential for basic activity of the carbene carbon.

hinder the insertion activity of the carbene into deactivated chloroarenes.[14] Due to the high proton affinities at the carbene carbon, NHC complexes are some of the strongest neutral bases known (pK_a >23) (**Figure 5**).[24] NHC complexes in their raw form are highly air and moisture sensitive. They require handling in a glovebox under strictly inert conditions. To overcome these obstacles, a palladium source can be added to the imidazolium salt precursor before or during addition of coupling partners to avoid handling the NHC precursor by itself.[14]

2.2 Pd^{II} vs Pd^0 – Highly Active, Singly Ligated Pd-NHC Precatalyst

In order for the catalytic cycle to begin, it requires the formation or addition of the LPd^0 active species. Any of the three oxidation states, LPd^0, LPd^I, or LPd^{II}, can be added as the catalyst. The Pd^0 species is already in the reduced form, but these kinds of compounds usually tend to be very air-, moisture-, and light-sensitive. Pd^I or Pd^{II}, are considered to be precatalysts because they must first undergo a reduction before they can enter the catalytic cycle. The one and two coordinated species tend to be more air- and moisture-stable than their fellow Pd^0 species.

The difficulty of using the in situ activation method is that the generation of the active species requires the use of excess ligand. This is undesirable. The in situ methods usually require up to 4 mol% of the catalyst species whereas the precatalyst species only requires 1 mol%.[15] For example, assume the catalytically active species is the same for both cases of activation, in situ active catalyst [$Pd_2(dba)_3$ (4 mol%)] vs. precatalyst (PEPPSI-IPr (1 mol%)).[15] The turnover number (TON) study done on these two forms, in situ vs precatalyst, produced 7.5 and 300 TON's respectively. This means that only a small amount of active catalyst is actually being generated by the in situ protocol.[15] The in situ protocols have many setbacks, such as being air and moisture sensitive, having highly sensitive reaction conditions, and being poorly reproduceable from one experiment to the next depending on lab techniques. To avoid these issues, a series of discrete NHC-Pd^0 and NHC-Pd^{II} complexes were prepared (**-IPr and -IPent, Figure 2**; **Figure 6**).[15] The Pd^0 and Pd^{II} species will be the focus of this section and their general reduction pathways can be seen in **Scheme 1**. The Pd^0 species is already in the desired oxidation state to enter catalysis, but usually requires complex handling. The Pd^{II} species is the more stable in terms of handling but must be reduced to the Pd^0 species before entering the catalytic cycle. Even though both Pd^0 and Pd^{II} can both be used as precatalysts in cross-coupling reactions, Pd^{II} is preferred because of its low cost and higher stability than Pd^0. Pd^0-NHC compounds also tend to be unstable in air and have limited, un-attractive synthetic routes that discourage their use as precatalysts.[14] It has also been shown through calculations that NHC ligands have a higher affinity to Pd^{II} than to Pd^0.[25] Not only that, but doubly ligated Pd^{II}-NHC complexes have a lower activity than Pd^0. This is most likely due to the strong bond between

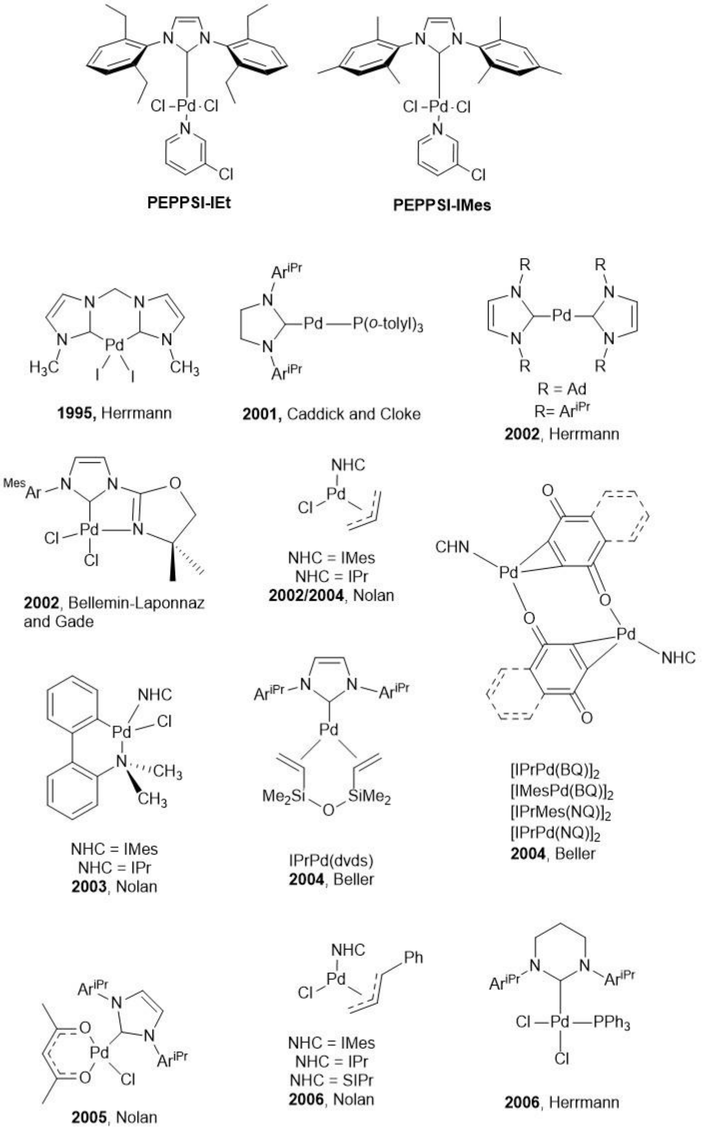


Figure 6. Series of discrete NHC-Pd^0 and NHC-Pd^{II} species.[15]

NHC complexes and the Pd^{II} to afford $(NHC)_2Pd^0$. In order to generate the active species, one of these NHC complexes will have to dissociate. This has shown to be difficult to achieve due to the strength of the M-L bond between Pd and the NHC complexes.[14] On the other hand, Pd^{II} precatalysts are more efficient when they contain a second ligand more labile than a second NHC would be.

Chelating and pincer carbene ligands are more stable than their monodentate counterparts. However, since chelating NHC complexes require a high synthetic investment, monodentate ligands have been the focus of the development for general, synthetically useful carbenes. [7, 25] Having a monodentate ligand is also important in cross-coupling chemistry because there needs to be an open coordination spot for the activation of the Pd-L complex to occur. NHC-Pd^{II} complexes tend to be the most attractive precatalyst due to their stability to air, moisture and heating. They also can be stored long-term while maintaining their chemical integrity.

The generation of the Pd^{II} complex can be accomplished by one of two ways: the complexation of the NHC to the metal-center or by addition of imidazolium salts in the presence of a base to form the NHC in situ.[14] Stronger bases such as KO-t-Bu can be used, however weaker bases, like Cs_2CO_3 or NaOAc, tend to be preferred. The mechanism for such generation and transfer of the carbene in the presence of a weak base is still unknown. The bulky IPr (**5**) and SIPr (**6**) are the most active and versatile ligands for Pd-NHC-catalyzed reactions.[14] Bulky phosphines analogous to Pd-NHC complexes have shown to have excellent activity, so the same behavior could be expected from these NHC ligands.[27]

The initial coordination of Pd to the NHC forms the metal-ligand complex that will later be synthesized into the full precatalyst, PEPPSI-IPr (**1**) or others. The formation of the M-L bond leaves three coordination spots vacant to be filled with replaceable ligands.[14] These ligands can determine the ease or difficulty of the activation and reaction. Therefore, it is important to choose ligands that are facile. The oxidation state at the metal and the nature of the replaceable ligands determines the stability of the complex.[14] The most common formation of IPr adducts is with simple Pd salts such as $Pd(OAc)_2$ and $PdCl_2$. This is an important precursor complex because the two chlorines in $PdCl_2$ function as extremely facile ligands on the Pd-PEPPSI metal center in addition to the throw away ligand.

2.3 Importance of the Pyridine Ligand

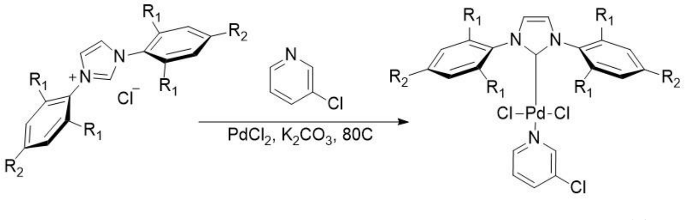
NHC-Pd^{II} complexes are more air- and moisture-stable than their fellow NHC-Pd^0 species and synthetically easier to prepare.[15] LPd^{II} complexes do, however, require an activation step. This means the other ligands need to be easily removable/replaceable to promote sufficient catalytic activity. A “dummy” ligand can be used in catalytic preparation and/or stabilization, but it must be sufficiently labile to initiate reduction to LPd^0. They also should not have a significant re-binding rate, as this will poison the catalyst species. Grubbs and co-workers found that replacing phosphine ligands with pyridine ligands improves the rate of initiation in NHC-Ru-cat olefin metathesis.[26] When 3-bromopyridine is the ligated species for the NHC-Ru complexes, it initiates the reaction three times as fast as pyridine itself. However, 3-bromopyridine is toxic, so the Organ group used a less toxic alternative, 3-chloropyridine.[15] This is how the PEPPSI complexes in **Figures 2 and 6** were created. The use of 3-cholorpyridine as the “throw away” ligand provides stability in preparation of precatalysts and are neither air-, moisture-, nor light-sensitive and can be stored indefinitely on the shelf.[15]

This leads into the complexation of the pyridine ligand, 3-chloropyridine, seen in PEPPSI complexes. It is the bottom ligand in **Figure 1**. The 3-chloropyridine ligand forms the fourth coordination site as a pyridine "throw away" ligand.[7] This ligand provides stability for the PdNHC complex. During the initiation of the catalytic cycle, it serves a "throw away" ligand.[27] It has also been shown that the pyridine ligand has a lower binding energy to Pd^0 than to Pd^{II}.[14] This suggests that the dissociation of the pyridine ligand takes place after the initial formation of the Pd^0 species. The excess of this throw away ligand, 3-chloropyridine, could be recycled through distillation for the next reaction but is such a negligible amount that this is not necessary.[14]

The pyridine, like the NHC ligand, is tunable and affects the performance of the PEPPSI precatalyst. Sterically unhindered pyridines afford a more active catalyst than do sterically hindered pyridines.[7] This is the opposite effect as seen in NHC ligands. Bulky pyridines have no problem dissociating, but they prove difficult to stabilize the active catalyst, which then results in short catalyst lifetimes.[7]

2.4 PEPPSI

As previously mentioned, the steric and electronic properties of both the NHC ligand and the pyridine ligand can either increase or decrease catalytic efficiency. The optimal catalytic conditions found in PEPPSI-IPr are the large bulky substituents on the 2,6-poisitons of the benzenes and the sterically limited pyridine ligand.[9] Other PEPPSI catalysts such as second generation PEPPSI-IPent, have shown to be better catalysts



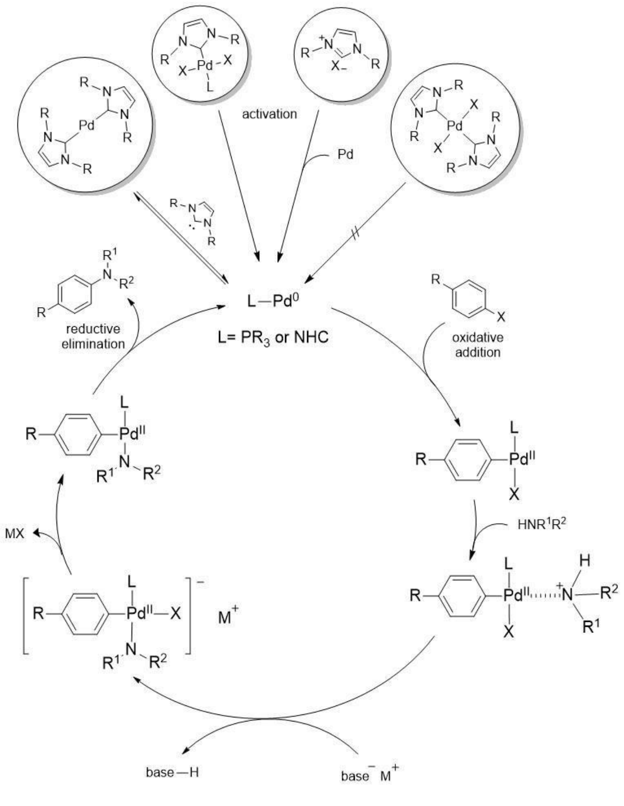
Scheme 5. PEPPSI precatalysts preparation.[14]

than PEPPSI-IPr, as shown in **Scheme 4**. However, IPr is a first generation PEPPSI catalyst, which leads it to be the most widely used member of this family.[9] It is formed from the imidazolium salt with palladium chloride in the presence of K_2CO_3 and the preferred pyridine ligand. The scheme for activation can be seen in **Scheme 5.**[7]

There are many advantages to PEPPSI catalysts. They are extremely stable in air and exposure to moisture. They are also cost-competitive and are considered a "one component catalyst", meaning they do not require additional ligands. They can survive excess heat, such as 120 °C in DMSO, for hours without decomposing or decomposition by ^{1}H-NMR.[28]

3 Buchwald-Hartwig Amination using PEPPSI-IPr

Historically, reactions of aryl and vinyl halides coupling with heteroatom nucleophiles were neither studied much nor successful.[1] But over the past twenty-five years or so, the coupling of aryl halides with amines became a standard procedure. The Buchwald-Hartwig cross-coupling reaction, as previously mentioned, forms C-N bonds. **Scheme 6** illustrates the catalytic cycle of this process. This reaction-type now has a large substrate scope with fast rates and high turnover numbers, for the most part.[1]



Scheme 6. General catalytic amination of the Buchwald- Hartwig cross-coupling reaction.[9]

Products from this reaction type have been applied to synthesis of biologically active molecules. They have also been applied to the field of electronics. Aryl bromides are more reactive than aryl chlorides for this catalytic process. Both primary and secondary amines have generated a large reaction scope as well.[1] It has also been found that NHC complexes catalyze the coupling of amines and chlorines at RT.

3.1 Oxidative Addition

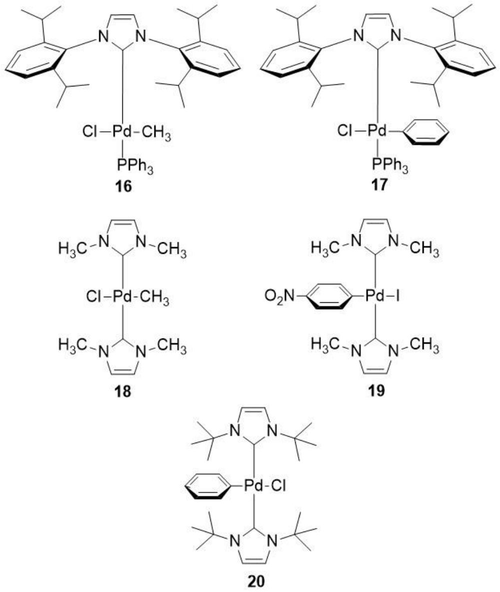
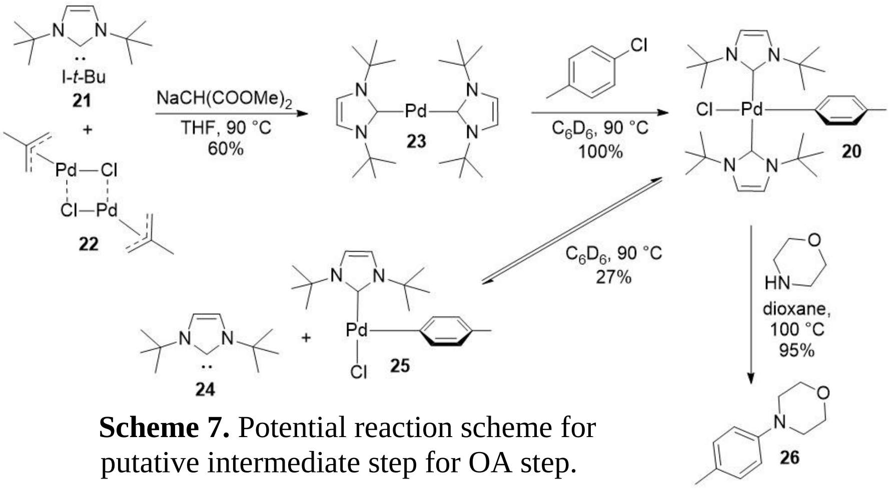


Figure 7. Coordination complex intermediates.[1]

The oxidative addition step needs a low-coordinate palladium(0) species to form the aryl palladium complex. This step also tends to be the turnover limiting step of the catalytic cycle for aryl bromides.[1] The oxidative addition step increases in rate as the ligand increase in bulkiness, which is why the hindered monodentate ligand complexes undergo rapid oxidative addition (OA). This occurs because the steric hindrance of the ligand causes it to dissociate more readily and creates a higher concentration of the unsaturated intermediates.[14]

Ligands that are electron rich also increase catalytic activity. In cases where OA is the rate limiting

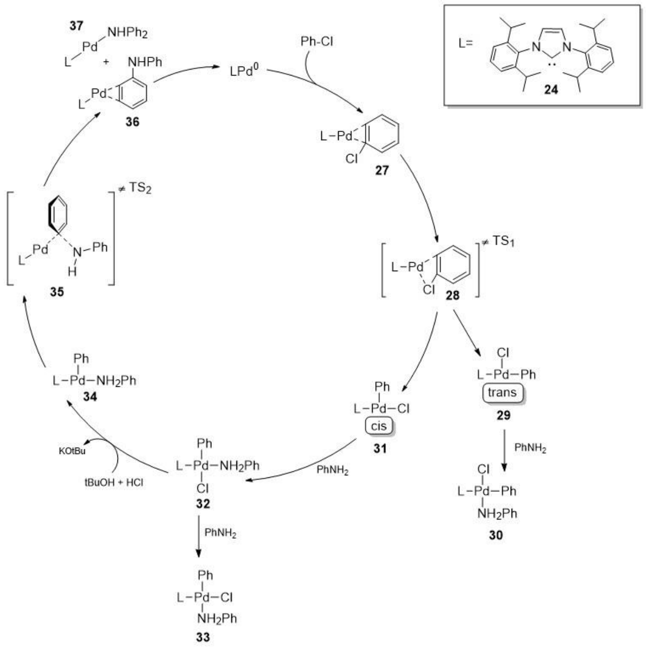


Scheme 7. Potential reaction scheme for putative intermediate step for OA step.

step, electron-rich metal centers tend to react faster. This is due to the increased electron presence at the metal, which is the electron donor. The more electron rich, the higher affinity the NHC complexes have towards the metal. Oxidative addition of aryl halides has the following rate trend: ArI > ArBr > ArCl. The ArBr shows preferred selectivity over ArCl due to this trend.[1] This is primarily due to the bond strength of the CX bond. The potential intermediates (**16-19**) in **Figure 7** are extremely stable and therefore not facile enough to be likely candidates for direct participation in the catalytic cycle. However, there is one possible intermediate that could lead to the cis-T-shaped intermediate, see **20, Scheme 7,** seen after the OA step.[14] Heating **20** in [D_6]benzene resulted in the dissociation of the free carbene I-*t*-Bu, thereby forming a tricoordinate species (**25, Scheme 7**). **25** is the suspected be the T-shaped, intermediate (**31**) that proceeds with the catalytic cycle. This T-shaped intermediate requires the aryl halide components to be cis to each other in order for reductive elimination to occur (**25**).[14] In some instances, the halogen could coordinate to Pd^0 to accelerate the OA step. The oxidative addition of aryl bromides and chlorides is generally the turnover-limiting step.[1] This then leads to the transmetallation step.

3.2 Ligand Substitution

The traditional transmetallation step occurs when the aryl palladium-halide reacts with another organometallic reagent and base to form an arylpalladium-oragano[1] complex on which the organoreagent coordinates to the open coordination site on the T-shaped complex forming a 4-coordinate complex[14] by one of several possible mechanisms. This is the least understood step of the catalytic cycle.



Scheme 8. The catalytic cycle of many cross-coupling results, including the geometry of the intermediates.

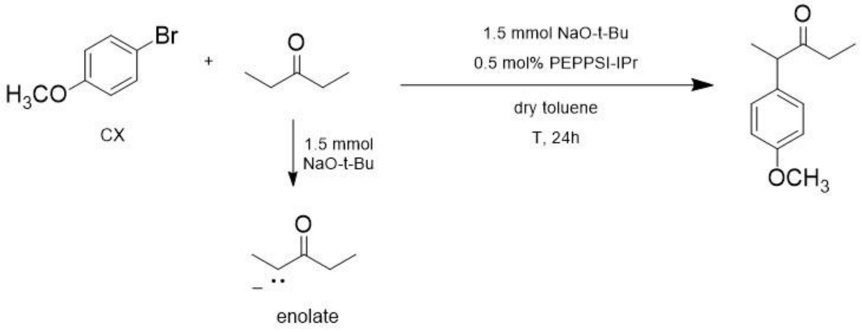
However, for aminations, the amine coordinates and is then deprotonated as opposed to undergoing a transmetalation step. From here, this coordinated and deprotonated species proceeds with reductive elimination. Studies show that the amine coordinate and/or the deprotonation of the metal amine complex during transmetallation step are the rate limiting steps of this cycle.[9] To aid in these transformations, a strong base, like KO-t-Bu or NaO-t-Bu, are added. The base deprotonate the amine.[1] The reaction is thermodynamically driven by formation of the inorganic salt.[14] The 4 coordinate complex (**32, Scheme 8**) reacts with base to produce t-BuOH and M-X leaving the Pd complex as a tri-coordinate, T-shaped complex (**34, Scheme 8**) with the two components of the new C-N bond cis to one another.[14] It is also true that reductive elimination can sometimes occur from the 4-coordinate complex (**32**).[1] Ligands that are sterically bulky or electron rich can increase the rate and function of this reaction step as well, however little is known on the true electronic effects on the reaction. However, for the amination cross-coupling, this does not happen. Instead it occurs by coordination of the amine to the palladium and deprotonation of the coordinated amine by a base. This arylpalladium-amido complex then undergoes reductive elimination. [1]

3.3 Reductive Elimination

Once the 3-coordinate, T-shaped complex has arranged itself with the new C-N bond forming ligands cis in orientation (**31**), reductive elimination can occur. The arylpalladium-amido complex reductively eliminates the aryl amine product which also regenerates the starting palladium(0) species.[1] Reductive elimination (RE) tends to control the scope and yield of the reaction where OA controls the rate. RE is also significantly affected by the steric and electronic properties of the ancillary and reacting ligands. Steric hinderance accelerates RE because the complex wants to reduce the steric congestion of the palladium(II) species present in sterically hindered ligands. Pd^{II}-aryl complexes tend to reductively eliminate faster than Pd^{II}-alkyl complexes which is why cross-coupling reactions do well with formation of a bond with either two sp^2-hybridized centers or one sp^3-hybridized center and one sp-hybridized center, but not so well with two sp^3 hybridized centers.[1] RE also goes faster with two symmetric ligands that are strongly participatory in the RE or two unsymmetrical ligands of which there is a great difference in electron donating and withdrawing propensities between them. RE is affected by electronic properties in addition to steric properties. RE prefers electron poor complexes over electron-rich, however, if the ligand is bulky enough, the steric hindrance makes the electronic affects negligible.[1] β-hydrogen elimination of the amido group is a major side reaction of the aryl palladium-amido complex, post transmetalation. The formation of this species can be suppressed by adding steric bulk to the reagents because steric hinderance favors RE over β-hydrogen elimination.[1] RE decreases coordination number of the complex while β-hydrogen elimination increases it.

4 α-arylation of Enolates

Enolates are the deprotonated form of a carbonyl compound. These compounds can be derived from ketones, amides or esters, all of which demonstrate similar chemical properties in terms of α-arylation.[2] α-arylation of enolates are reactions known for coupling aryl and vinyl halides and sulfonates with compounds that have slightly acidic C-H bonds (**Scheme 9**).[1] The carbonyl of the enolate complex pulls electron density away from its α-carbons, which as a result, makes the hydrogens at those positions extremely labile. This characterization makes the enolate complexes very reactive with compounds such as aryl and vinyl halides, as previously mentioned. Once the enolate complex has bound its first aryl halide at the α-position, the α-position becomes even more acidic than before. This typically leads to binding of a second aryl halide compound. This does not occur for alkyl halides.



Scheme 9. Alpha-arylation reaction with demonstrated enolate compound.

Monoarylation of these complexes is the more desirable coupling transformation over the double arylation. In fact, the ease in formation of such doubly arylated products is the downfall of such an excellent reaction. To combat this excess arylation, studies have been done on quenching the reaction once it has reached the monoarylated form (**38**). This was demonstrated by Zheng et al. when they found that increasing the equivalence of the amide created a ratio favorable towards the monoarylated product (**38, Figure 8**).[4] Their studies were performed using amides, however, the reaction profiles of amides and enolates of other carbonyls are comparable

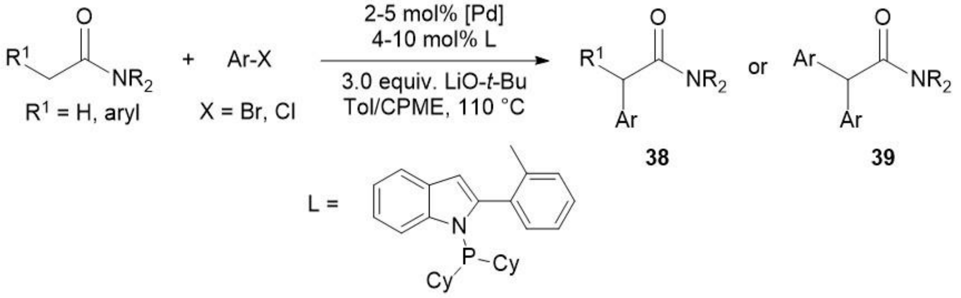


Figure 8. Amide mono- and di-arylated reaction scheme.[4]

due to their similarity in structure. They both show coupling at the α-position and are both suspect to diarylation. Understanding how these reactions work can help facilitate better understanding how the ketone might function as the activator for the LPd^{II} species.

5 Prior Use of Additives as Activator

There are certain desirable organoreagents that have proven unsuccessful at activating the Pd^{II} species. For example, our studies were done on coupling aryl halides with aniline. The coupling of these two compounds opens the doors to many new reaction potentials, such as couplings of biologically active molecules and the pharmaceutical industry. Aniline by itself is incapable of reducing the Pd^{II} to Pd^{0}. In order to successfully couple these partners, an activator is needed to reduce the Pd. The Organ group scraped the surface of using activators to increase functionality of using palladium catalyst complexes for amination.[6] They tried coupling 2-halide-1,3-dimethylbenzene with thiophenol at varying temperatures and with varying activator species, see (**Scheme 10, Table 1**). Their findings indicate that without the additive, no reactions occurs, but with an activator, these couplings can achieve >98% conversion.

Scheme 10. Coupling of aryl halides with thiophenol using a separate activator species to reduce Pd^{II}.

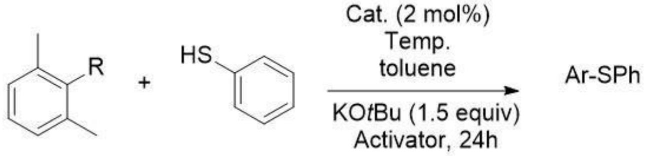


Table 1. Coupling of aryl halides with thiophenol using a separate activator species to reduce Pd^{II}.

Entry	R	T [°C]	Activator Species	Yield of Product[a] [%]
1	Cl	40	-	0
2	Br	40	Morpholine (2.5 mol%)	99
3	Br	23	Bu_2Mg (8 mol%)	98
4	Br	70	LiO*i*Pr (20 mol%)	98
5	Cl	23	LiO*i*Pr (20 mol%)	98
6	Br	23	LiO*i*Pr (20 mol%)	99

[a] Isolated product yields performed by Organ group.[6]

6 Summary

As a culmination of efforts by Wanzlick and Schönherr[10], Öfele[11], Arduengo[12] and Herrmann[13], use of NHC-complexes as catalysts have become popular and widely used over the past 30 years. Organ's[9] development of the PEPPSI precatalyst family, proved to help cross-coupling reactions occur more smoothly. The more notable improvement seen with these catalysts is the stability in handling them. They can be prepped on the bench top whereas other NHC-Pd ligand complexes and phosphines require more complicated prep, such as glove box handling or use of inert gas. His precatalyst known as PEPPSI-IPr[9, 28] has become the most popular precatalyst to use. It is by far the most successful of the 1st generation PEPPSI family. Organ then developed an even more successful precatalyst known as PEPPSI-IPent. This is the most efficient catalyst known to date out of all NCH and phosphine ligands. Organ also experimented with the use of enolate complexes as activators, in catalytic amounts, for reduction of palladium from Pd^{II} to Pd^0 in place of organoreagents that cannot do so.[6] His endeavors were successful, producing >98% conversion. We decided to expand upon this study in order to further investigate the mechanism of transformation that occurs during this activation state, as it is not very well known. This will be the topic of discussion in the next chapter.

CHAPTER 2: KETONE ACTIVATION OF PEPPSI-IPR IN AMINE AND KETONE ARYLATION REACTIONS

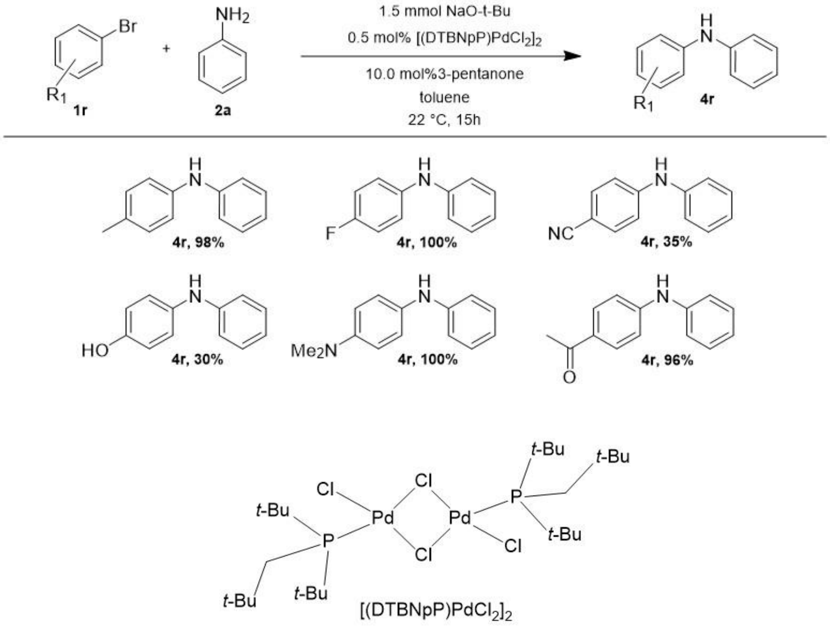
1 Introduction

PEPPSI precatalysts have become a crucial element to many cross-coupling reactions. However, it has made the most significant impact on the Buchwald-Hartwig aminations. Since the inception of PEPPSI-IPr (**1**), the most widely used and facile NHC precatalyst at the time, Buchwald-Hartwig aminations have seen excellent success. The trouble with these reactions, however, is that many organoreagents such as aniline, were unable to reduce the Pd^{II} species to Pd^0. To mitigate this, Organ et. al[9] tried adding catalytic amounts of an activator, such as morpholine, Bu_2Mg, and Li*Oi*Pr, to serve as the activating species when the coupling reagents could not and found that these transformations afforded excellent yields.[6] The mechanism upon which this occurs is still under investigation.

2 Using Ketone as the Activator

2.1 Previous Use of Ketone as the Activator (Dr. Ethan Hu)

Our group has also produced excellent yields following a similar approach. Hu et al.[29] initially tried using isopropanol (*i*-Pr-OH) as an additive, similar to the work Organ did seen in **Scheme 10, Table 1.** They found that it produced yields of 20-100% at 40 °C under the conditions in **Scheme 11.** An interesting find came about during their study. At first, the team did not understand why the isopropanol was producing such a wide range of yields. After further study, they tracked down the source. The syringes used to add the *i*-Pr-OH were being rinsed with acetone. This small amount of acetone had a great enough effect on the reaction to drastically increase the yields up to 100%. This led to an investigation on what other ketones might be a better activator than isopropanol (**Figure 9, Scheme 12.**)



Scheme 11. Reaction scheme for Hu’s work with 3-pentanone and $[(DTBNpP)PdCl_2]_2$.[29]

They found that ketones were in fact the cause of the increased yields. The three boxed in ketones in **Figure 9,** acetone (**40**), 3-pentanone (**42**) and mesityl oxide (**47**) respectively, are the three ketones Hu et al. chose to focus on as the

Scheme 12. Reaction scheme and results of ketone as additive.[29]

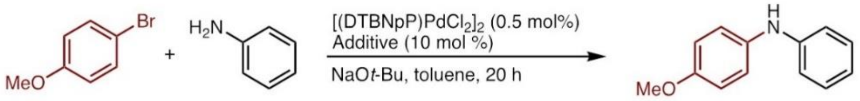
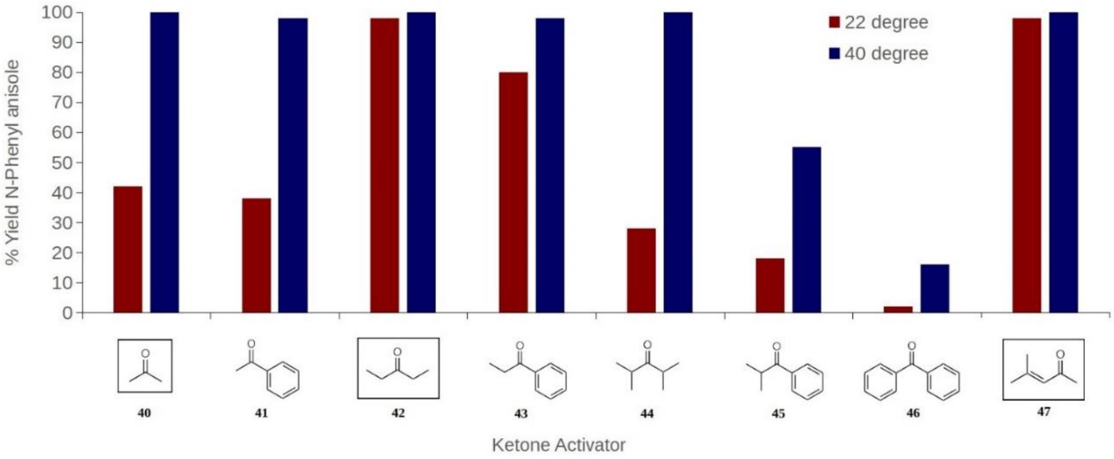


Figure 9. Reaction scheme and results of ketone as additive.[29]



3-pentanone and mesityl oxide afforded the best results and acetone was the original ketone of interest. What's interesting about the three most successful ketones at 22 °C, 3-pentanone (**42**), propiophenone (**43**), and mesityl oxide (**47**) is their availability for reduction. 3-pentanone (**42**) and propiophenone (**43**) both have an β-H available for β-elimination reduction of the ketone during activation, however, the mesityl oxide (**47**) does not. Acetone (**40**) similarly does not have a β-H and is still moderately successful in comparison to the best yields from this study (**42, 43, 47**). This means that another reduction pathway is possible, which will be discussed in the mechanistic section later.

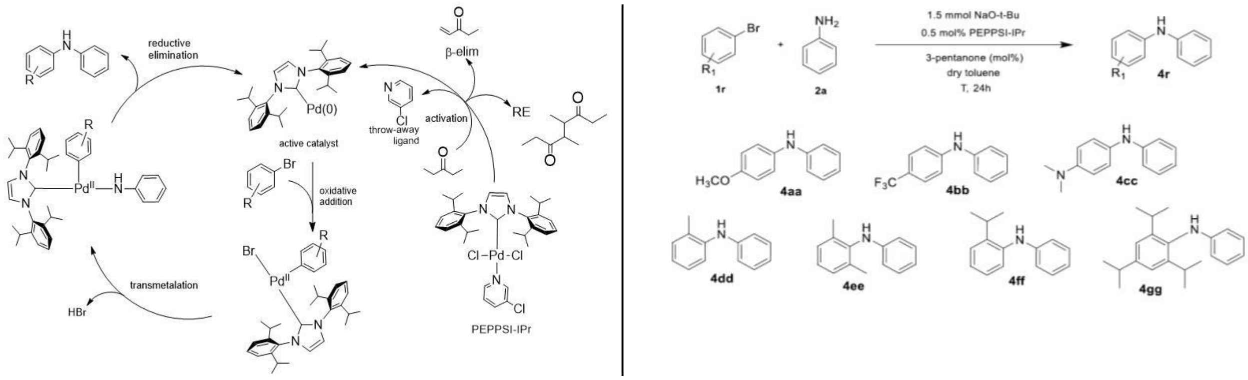
3-pentanone is an effective activator for the $[(DTBNpP)PdCl_2]_2$ precatalyst in the coupling of aryl bromides and aniline (**Scheme 11**). Having shown that 3-pentanone is successful in acting as the activator for the $[(DTBNpP)PdCl_2]_2$ precatalyst, we aimed to expand its use to the widely used PEPPSI-IPr precatalyst. When coupling aryl halides with aniline without the use of the ketone, there is no obvious reductant. Although, PEPPSI precatalysts have afforded successful yields at higher temperatures without these activator species. We hypothesized that 3-pentanone would act as an effective reductant for PEPPSI catalysts allowing for successful activity under milder conditions.

The mixed results of the electronically varied substrates for both our and Hu's work demonstrates that cross-coupling reactions are only slightly affected by electronic properties. Instead, the larger the bulk of the electronically variant substrates, the higher the yields. We can better understand this concept by using the A-values (kcal/mol) from chair conformations to demonstrate the energy barrier each substituent has. The A-values for the R groups used in this study are the following[30]: OMe – 0.6 (kcal/mol), 0.75; CF_3 – 2.1; NMe_2 – 2.1; Me – 1.7; di-Me –

1.7 x 2; i-Pr – 2.15; tri-i-Pr – 2.15 x 3. The CF_3 and NMe_2 have the largest values but are in the *para*-position and do not affect the metal center as strongly as *ortho*-substituted aryl bromides. The NMe_2 likely produces slightly larger yields than CF_3 because of its electron donating ability. OMe has a low steric value, but has the greatest electron donating ability out of all the substituents we studied. On the other hand, the sterically hindered substrates are located in the *ortho*-positions, which is closer to the metal center and will have a stronger affect than the *para*-positioned substrates. We saw that the larger the substituent, the greater the yield produced. The same goes for the substrates with two *o*-positioned attachments. The substrates with two *o*-positioned substituents (1,3-dimethylbromobenzene and 1,3,5-triisopropyl-2-bromobenzene) gave even greater yield than that of the monosubstituted ones (2-bromoluene and 2isopropylbenzene).

Other important findings of this study were the affect the order of addition has on the % conversion and the identification of a by-product produced by the afforded amine arylation reactions.

2.2 Amination of Aryl Bromides with Aniline, PEPPSI-IPr, NaO-*t*-Bu, and the Activating Ketone Species, 3-pentanone



Scheme 13. Buchwald-Hartwig reaction cycle (left) used for scheme (right).

For these reactions, a ketone (3-pentanone) was used as the activator (**Scheme 13**). We are not exactly sure of the mechanism for this reaction. We have data supporting the successful employment of this species, but no tangible evidence of the exact pathway. As will be discussed in the results and discussion section, we have afforded all the compounds on the right side of the figure in 60 - 100% conversion for all except **4bb** and **4cc.**

3 Results and Discussion

3.1 Optimization

We found that 20 ºC and 40 ºC were not suitable for effective conversion – entries 1-4. There are not any significant yields until the 60 ºC portion of this study. Entry 6 has the widest range of yields of them all. We found that the change in reagent addition order was the cause of such a wide variety of yields. The conditions for this entry, 60 ºC with 7.2 mol% 3-pentanone, were the first to afford decent yields. We also found that roughly the same yield (~80%) is found at 60 ºC with 21.6 and 28.8 mol% and 80 ºC with 7.2 mol% – entries 8, 9, 11. The most optimal conditions for the reaction shown directly below, is with 96.1% yield at 80ºC with 14.4 mol% – entry 11. Each of these data points are the average of many sub data points for simplification purposes. For example, entry 11 in **Table 2** is the average of 3 data points, all of which could be of different orders of addition.

The optimal conditions for Hu's catalyst were 4-bromoaniosle (1 mmol), aniline (1.2 mmol), $[(DTBNpP)PdCl_2]_2$ (0.5 mol%), NaO-t-Bu (1.5 mmol), 3-pentanone (7.2 mol%) in dry toluene at 20 ºC. When these conditions were used with the PEPPSI-IPr (**1**) catalyst, it provided 1.4-6.1% yield as seen in entry 2, **Scheme 14, Table 2.** These poor results led to a full optimization study, shown below, of both the percentage used of the activator ketone – 3pentanone – and the temperature.

Scheme 14. Optimization of reaction conditions.

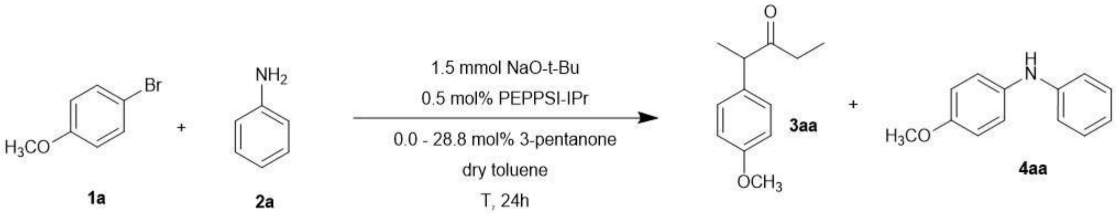


Table 2. Optimization of reaction conditions.

Entry	T [°C]	3-pentanone **3a** [mol %]	Yield of **3aa**[c] [%]	Yield of **4aa**[c] [%]
1[b]	20	3.6	< 1.0	1.4
2[b]	20	7.2	< 1.0	1.4 - 6.1
3[b]	20	10.9	< 1.0	2.6
4[b]	40	7.2	< 1.0	7.7 – 7.9
5[b]	60	0.0	< 1.0	14.0
6[b]	60	7.2	< 1.0	19.6 – 51.1
7[b]	60	14.4	< 1.0	58.2 – 82.0
8[b]	60	21.6	< 1.0	80.6
9[b]	60	28.8	< 1.0	80.4
10[b]	80	0.0	< 1.0	11.9
11[b]	80	7.2	< 1.0	76.2 – 88.0
12[b]	80	14.4	< 1.0	96.1

[a] Reactions were performed using 1.0 equiv. of **1a** and a 1.2 equiv. of **2a** on a 1.0 mmol scale.
[b] Order of Addition is unknown and varied.
[c] GC yield.

3.2 Order of Addition

Entries 1-12 in **Table 3** were all run in the same conditions. The only thing that differs is the order of addition of reactants. The orders of addition of entries 1-12 are unknown as they were not thought to be significant at the time. The realization that the order was important came about by trying and failing to replicate the original 51.0% yield of this reaction. Below are all the data points associated with this specific set of conditions prior to finding the best order of addition. Entries 1-11 have a conversion spread of 31.5% yield. This can be compared to the spread of entries 12-18, which is 16.7%. In order to determine the effect of addition order, entries 12-18 were performed with varied orders of addition, which can be found in **Table 4** labeled by their entry number. It is to be noted that it was not until after the initial study of entries 12-17 that entry 18 was added. Due to this, the remaining reactions were run with the conditions of entry 17 denoted by a * – following in the order of: toluene, aryl bromide, activator ketone, aniline. However, the difference between entries 17 and 18 is approximately 10.0%. Due to lack of time and conservation of resources, the reactions were not re-run with the conditions of entry 18. It is very possible that during the optimization period of this study, the order in entry 18 was used and not realized. This could explain why it was difficult to replicate this data with not paying careful attention to the order of addition.

Scheme 15. Importance of Order of Addition.

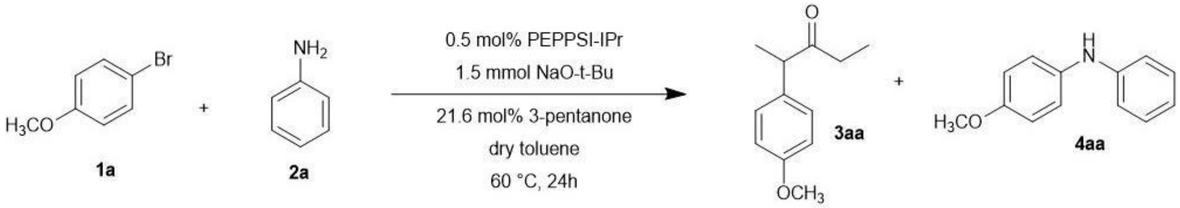


Table 3. Importance of Order of Addition.

Entry	T [°C]	3-pentanone **3a** [mol %]	Yield of **3aa**[b] [%]	Yield of **4aa**[b] [%]
1	60	7.2	< 1.0	19.6
2	60	7.2	< 1.0	21.1
3	60	7.2	< 1.0	24.0
4	60	7.2	< 1.0	25.1
5	60	7.2	< 1.0	25.8
6	60	7.2	< 1.0	26.4
7	60	7.2	< 1.0	31.5
8	60	7.2	< 1.0	37.8
9	60	7.2	< 1.0	43.5
10	60	7.2	< 1.0	51.0
11	60	7.2	< 1.0	51.1
12	60	21.6	4.2	70.4
13	60	21.6	4.5	72.8
14	60	21.6	4.2	75.3
15	60	21.6	5.1	76.3
16	60	21.6	4.6	78.2
17*	60	21.6	4.5	78.3
18	60	21.6	3.9	87.1

[a] Reactions were performed using 1.0 equiv. of **1a** and a 1.2 equiv. of **2a** on a 1.0 mmol scale.
[b] GC Yield.
[c] Range of entries **1-11** is 31.5% yield. Range of entries **12-18** is 16.7%.

Table 4. Order of addition descriptions listed by entry number.
(A) 4-bromoanisole; (B) 3-pentanone; (C) aniline; (D) Toluene

12) D > C > B > A	16) D > B > C > A
13) D > C > A > B	17*) D > A > B > C
14) D > A > C > B	18) A > B > C > D
15) D > B > A > C	

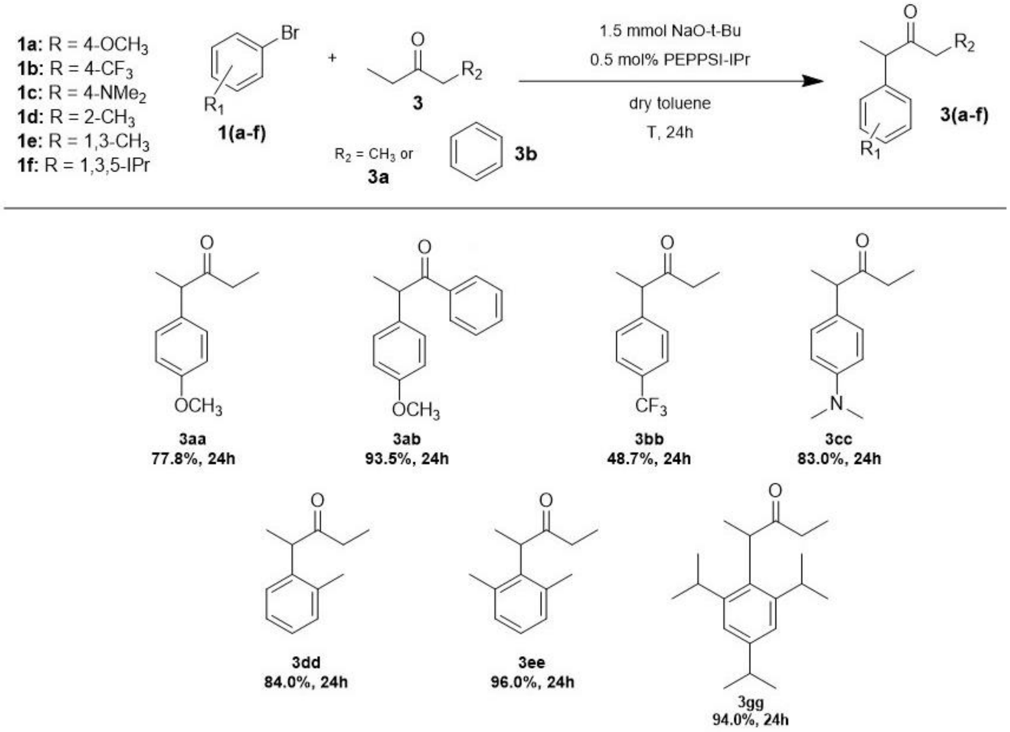
3.3 α-Arylated By-Product

A very small amount of byproduct with a retention time in the 4-5-minute region on the gas chromatography spectra was observed during these reactions. It was suspected that this peak was the alpha-arylation of the ketone. To test this hypothesis, propiophenone was used to observe any change in the retention time of this peak. This was tested with two aryl bromides: 4bromoanisole and 4-bromobenzonitrile. The 4-bromobenzonitrile was removed from the study due to reasons that will be discussed later.

The peaks in question for both aryl bromides with propiophenone came off the column before the original peaks with 3-pentanone. This confirmed that there was in fact a correlation between the peak in question and the ketone. This outcome is puzzling because propiophenone is heavier than 3-pentanone. Its by-product should come off the GC column at a later time than the 3-pentanone by-product. It is possible for the 3-pentanone by-product to actually be the di-αarylated ketone, which would explain the 3-pentanone peak being higher. However, the weight of the diarylated product is similar in comparison to that of the amine arylated product, which shows up around 9.80 minutes. This was not seen in the GC spectra. Instead, the suspect 3pentanone by-product comes off at ~5.86 minutes whereas the propiophenone by-product comes off at ~4.82 minutes. GCMS was done to confirm the suspected products. The results showed evidence that the alpha by product that is being made. We found that the suspected 3-pentanone by-product peak afforded a mass-to-charge ratio of 135.1 m/z, 136.3 m/z and 192.2 m/z. The propiophenone by-product afforded a mass-to-charge ratio of 105.1 m/z, 106.1 m/z, 242.8 m/z. The molecular weight of the α-arylated 3-pentanone and 4-bromoanisole product is 192 g/mol and the α-arylated propiophenone and 4-bromoanisole product is 240 g/mol. This corresponds to the mass-to-charge ratio found in the GCMS. To further test this, the aryl bromide

(1 mmol eq.) was reacted with 3-pentanone in one set of reactions and propiophenone in another (1.2 mmol eq.). The same PEPPSI-IPr (0.5 mol%), NaO-t-Bu (1.5 mmol), and dry toluene at 60 ºC conditions were used for all four reactions. The major alpha-arylation peaks measured via GC were the same for the peaks in question for the corresponding amine-arylation product spectra. A separate alpha-arylation reaction was completed for every amine-arylation set up (**Scheme 16**). Below are the afforded yields taken by GC.

Scheme 16. Alpha reactions.



3.4 Amine Arylation

The table below contains all the amine products, the isolated yields of the amine products and alpha-arylation products. The sterically hindered products (entries 21 – 23) gave better yields than the less hindered substrates (entries 17 – 20). Meanwhile, both the electron donating and withdrawing species resulted in lower yields (entries 7 – 16). The sterically hindered substrates can be coupled under milder conditions with excellent yields whereas the electron-rich and deficient substrates require higher temperatures and higher ketone mol% and give lower conversions. The electron withdrawing aryl bromide (product **4bb**) gave approximately 25-41% yield while the electron donating species (product **4aa**) affords 53-86% yield. The electron donating aryl bromide for product **4cc** (4-bromo-*N*,*N*-dimethylaniline) is suspected to yield 6.1 – 33.9%; although, this reaction did once produce a peak at ~13 minutes (GC) showing a suspect 85% yield that has not been reproduced, thus far. It is noteworthy to mention the same yield trends for the aminations are seen in the alpha-arylation (entries 1-6) products above. **Table 5** shows a comparison of the steric aminations versus the electronically variant ones. The yield for all the sterically hindered products resulted in >95%. This is 45% greater than the highest yield seen for CF_3 (**4bb**) and NMe_2 (**4cc**). The OMe (**4aa**), producing up to 85% yield, is the only electronically variant substrate that can compare to the sterically hindered ones.

Scheme 17. Amine products.

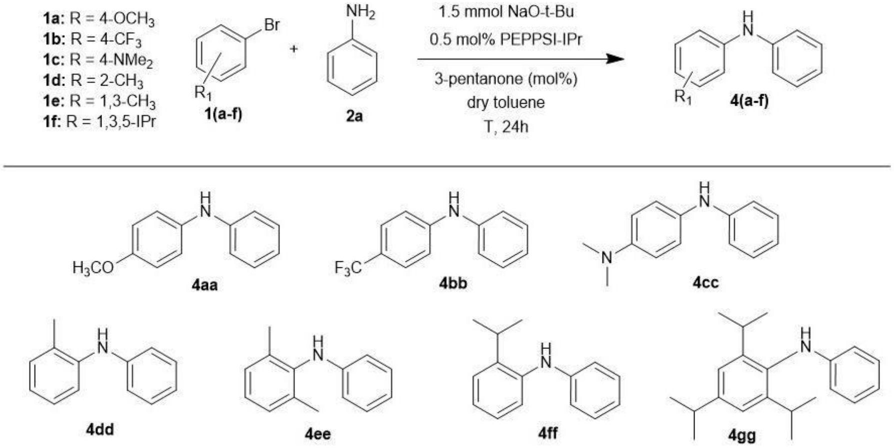


Table 5. Amine products.

Entry	Product	T [°C]	3-pentanone **3a** [mol %]	Yield of **4r**[b] [%]	Yield of **4r**[c] [%]
1	3aa	60	1.2 mmol	80.3	-
2	3bb	60	1.2 mmol	48.7	-
3	3cc	60	1.2 mmol	83.0[d] (2x aryl: 17.0%)	-
4	3dd	60	1.2 mmol	84.0	82.4%
5	3ee	60	1.2 mmol	96.0	-
6	3gg	60	1.2 mmol	94.0	-
7	4aa	60	0.0	2.50	-
8	4aa	80	0.0	11.9	-
9	4aa	60	14.4	53.1-61.3	-
10	4aa	60	21.6	65.3	-
11	4aa	80	14.4	86.4	-
12	4aa	80	21.6	85.7	-
13	4bb	60	14.4	25.3	-
14	4bb	80	14.4	32.9 - 41.2	-
15	4cc	60	14.4	6.1[d]	-
15	4cc	60	21.6	11.5[d]	-
15	4cc[e]	60	21.6	15.5[d]	-
16	4cc[e]	80	14.4	33.9	-
17	4dd	60	21.6	99.7	86.9
18	4dd	80	14.4	100.0	83.5
19	4ee	60	21.6	95.1	90.5
20	4ee	80	14.4	99.9	92.6
21	4ff	60	21.6	99.6	92.7
22	4gg	60	21.6	99.4	94.6
23	4gg	80	14.4	100.0	94.4

[a] Reactions were performed using 1.0 equiv. of **1(a-f)** and a 1.2 equiv. of **2a** on a 1.0 mmol scale.

[b] GC yield.

[c] Isolated yield.

[d] This reaction afforded two vastly different results. The first trial gave 6.1% yield at ~11.7 minutes (GC) and 85.0% yield at ~13.1 minutes (GC). The second trial was run with the exact same conditions and gave 6.7% yield at ~11.6 minutes (GC). The peak at ~13 minutes was not replicated in trial two and thrown out due to time constraints.

[e] 1.0 mol% of PEPPSI-IPr was used instead of 0.5 mol%.

In **Table 6**, the effect of the addition of propiophenone can be observed. The [f] indicates when propiophenone was used in place of 3-pentanone. Entries 4 and 8 show that higher yields of amine product are obtained using 3-pentanone as the activator compared to using propiophenone. Yields with 3-pentanone were 28-45% higher than with propiophenone. This information could prove helpful when trying to understand how the activator plays a role in successful catalysis of these Buchwald-Hartwig aminations. It could be that the 3-pentanone provides a quicker and more affective reduction pathway than propiophenone. **Table 6** also shows the effect that the ketone has in general on catalysis of electron rich substrates. When no ketone is used, the yield is 2.5% and 11.9% respectively for 60 ºC and 80 ºC. As the loading of the ketone increases, the product yield also greatly increases. Each of these reactions follow the optimal order of addition in entry 17, **Tables 3 and 4**.

Scheme 18, Table 6 along with **Figures 10 and 11** demonstrate the effect of a ketone gradient on a temperature gradient. Entries 1-9 represent the ketone gradient of **4aa** whereas entries 12-27 represent that of **4dd**. Note that entries 10 and 11 are only included to compare the affects of 3-pentanone with propiophenone. They are not included in the ketone gradient. The gradient for **4aa** can be compared to **4dd** to show how the different bromides respond to the ketone. **Figure 10** shows the continual increase in yield for 4-bromoanisole parallel to the increase in ketone mol% for the 60 ºC conditions. In slight contrast, the 80 ºC conditions show that there is a high point in its ketone gradient at 14.4 mol% affording 91.9% yield. It then drops as you continue to increase the ketone mol%. **Figure 11** demonstrates the extremely successful and mild conditions for 2-bromotoluene. It takes very little heat and very little ketone to produce >98% conversion. **Figures 10 and 11** are a very important visual as it demonstrates how important the addition of the ketone is.

Scheme 18. Ketone Gradient (4-bromoanisole and 2-bromotoluene).

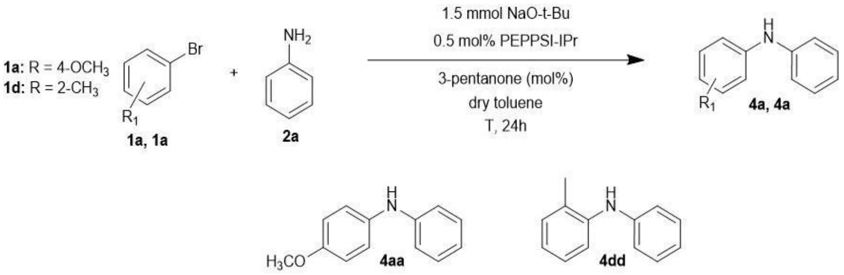
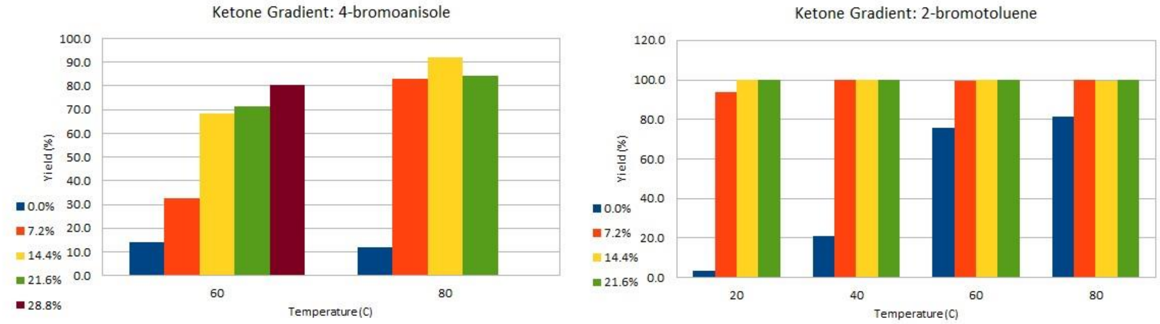


Table 6. Ketone Gradient (4-bromoanisole and 2-bromotoluene).

Entry	T [°C]	3-pentanone **3a** [mol %]	PEPPSI [mol %]	Yield of **4r**[b] [%]
1[c]	60	0.0	0.5	14.0
2[c]	60	7.2	0.5	32.5
3[c]	60	14.4	0.5	68.3
4[c]	60	21.6	0.5	71.4
5[c]	60	28.8	0.5	80.4
6[c]	80	0.0	0.5	11.9
7[c, e]	80	7.2	0.5	83.0[e]
8[c]	80	14.4	0.5	91.9
9[c]	80	21.6	0.5	84.2
10	60	21.6[f]	0.5	45.8
11	80	14.4[f]	0.5	46.7
12[d]	20	0.0	0.5	3.44
13[d]	20	7.2	0.5	20.8
14[d]	20	14.4	0.5	75.6
15[d]	20	21.6	0.5	81.6
16[d]	40	0.0	0.5	94.0
17[d]	40	7.2	0.5	99.9
18[d]	40	14.4	0.5	99.4
19[d]	40	21.6	0.5	100.0
20[d]	60	0.0	0.5	99.9
21[d]	60	7.2	0.5	100.0
22[d]	60	14.4	0.5	100.0
23[d]	60	21.6	0.5	99.7
24[d]	80	0.0	0.5	100.0
25[d]	80	7.2	0.5	100.0
26[d]	80	14.4	0.5	100.0
27[d]	80	21.6	0.5	99.8

[a] Reactions were performed using 1.0 equiv. of **1r** and a 1.2 equiv. of **2a** on a 1.0 mmol scale.
[b] GC Yield.
[c] Entries 1-9 yield **4bb.**
[d] Entries 12-27 yield **4ee**.
[e] Entry 7's yield is based off entry 10, **Table 1**. This is the average of three data points from the optimization portion of this study. Note that these three entries could be of the same or all different orders of addition. This data is included here in **Table 6** to show the gradient affect for 80 ºC with 7.2 mol% 3-pentanone as there is not such a data point for the optimal order of addition.
[f] Propiophenone as ketone.

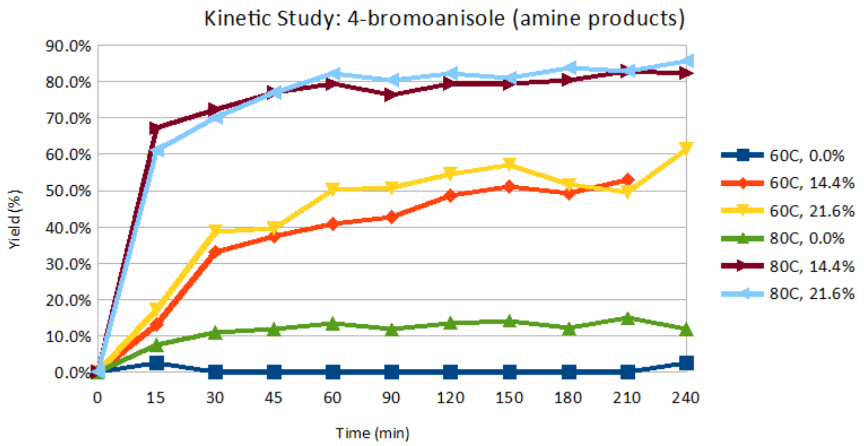
Figure 10. Ketone Gradient: 4-bromoanisole (left) and 4-bromotoluene (right).



A kinetic study was done on six different reaction conditions for 4-bromoanisole. It gave the best yield for each reaction condition from all the electronically variant aryl bromide studies. The temperature seems to be the main indicator in how well the reaction works, at least within the first four hours. The reaction for both 60 ºC and 80 ºC appear to be done around 150 minutes (2.5 hours) shown in **Figure 11**. After this point, the yield rises very slowly. The yield will continue to increase with a 24h study as reflected in the tabulated values above.

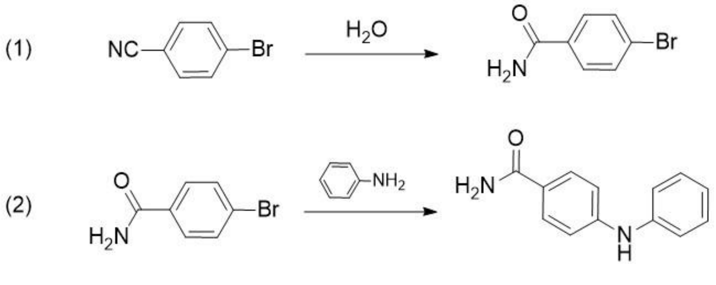
The six reactions in **Figure 11** contain the following: According to the general procedure 4-bromoanisole (125.0 µL, 1.0 mmol), aniline (110.0 µL, 1.2 mmol), NaO-*t*-Bu (144.0mg, 1.5 mmol) reacted with varying amounts of 3pentanone at either 60 ºC or 80 ºC. The format of the legend is – temperature; mol% of ketone.

Figure 11. Kinetic Study: 4-bromoanisole (4 hours).



3.5 Other: 4-bromobenzonitrile

There is one aryl bromide (4-bromobenzonitrile) that is not in any of these data tables. We thought we saw what the product peak in decent yield via GC was. However, GCMS of the amine-arylated reaction shows that two unexpected products are being made. We saw the aniline peak at 4.2 minutes but not the alpha-arylated or the amine-arylated product. Instead, we saw a peak at 7.3 minutes with mass-to-charge ratios of 183.0 m/z, 185.0 m/z, 198.2 m/z, 199.1 m/z, and 201.1 m/z. At 11.4 mins, we saw mass-to-charge ratios of 184.3 m/z, 197.1 m/z, 207.1 m/z, 212.3 m/z, 213.4 m/z. For both the unknown 7.3 and 11.4 minute peaks, there were additional GCMS mass-to-charge ratios at lower ratios than above but will be excluded here for simplicity. See the experimental section for these values.



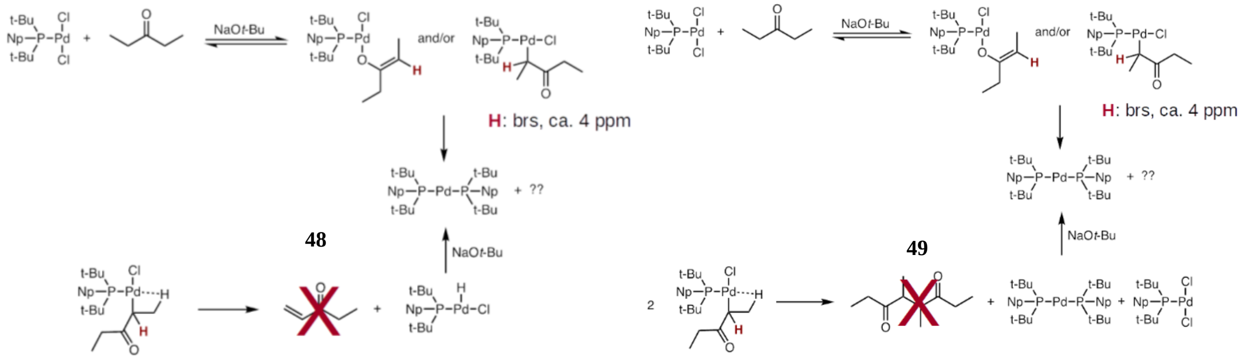
Scheme 19. Suspected products of the 4-bromobenzonitrile amine-arylated reaction.

After analyzing the GCMS, it is clear that there are other undesired products being formed as opposed and in addition to the desired secondary amine. The expected alpha-arylated and amine-arylated products have respective molar weights of 187 g/mol and 194 g/mol. Neither of these weights were found in either unknown peak. We suspect that the 4-bromobenzonitrile could be reacting with water (reaction 1, **Scheme 19**) to produce an amide with a weight of 200 g/mol, which aligns with the unknown peak at 7.3 minutes. The 11.4 minute peak is suspected to be the amine-arylated product (reaction 2, **Scheme 19**) of the hydrolyzed 4-bromobenzonitrile seen in the 7.3 minute peak. It has a weight of 213 g/mol, which aligns with the mass-to-charge ratios of 11.4 minutes. This data shows evidence that the suspected alpha- and amine-arylation of 4-bromobenzonitrile is not happening. For this reason, it was excluded from the remainder of the study.

4 Potential Reaction Schemes

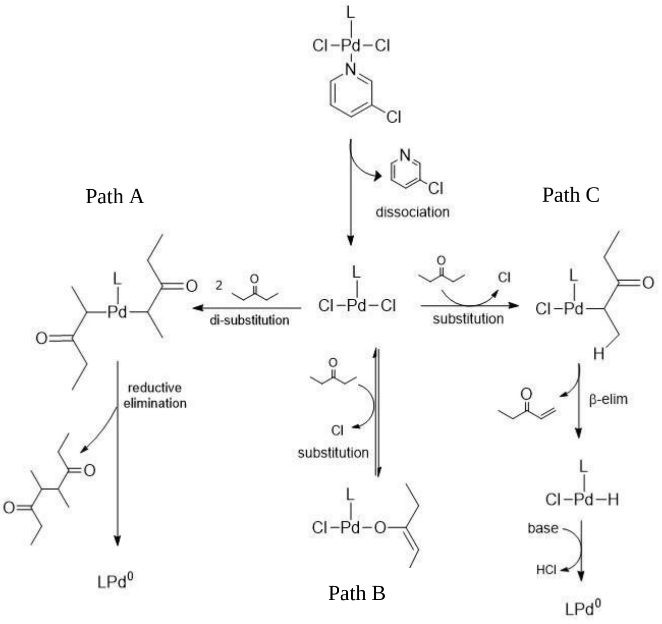
4.1 Hu's Reaction Study

Hu et al. discussed two possible mechanistic pathways for the $[(DTBNpP)PdCl_2]_2$ precatalyst reduction pathway. He suspected that the reduction occurs either by β-H elimination (**48**) or reductive elimination (**49**) (**Scheme 20**). A ^{1}H-NMR was done on the reaction between 3-pentanone and the $[(DTBNpP)PdCl_2]_2$ to afford an unexpected find. There was no evidence that the reductive elimination product was being made. There was, however, evidence that potentially supports the β-H elimination product (**48**). There was a peak observed that corresponds with the α-C on the alkene side of the β-H elimination product (**48**). This could also correspond to the O-bound enolate of this same reaction. It was also observed that the active LPd^0 species is being made. If it is the O-bound species, it is unclear how it reduces the precatalyst to form the LPd^0 species.



Scheme 20. The two hypothesized precatalyst reduction schemes for Hu's reactions.

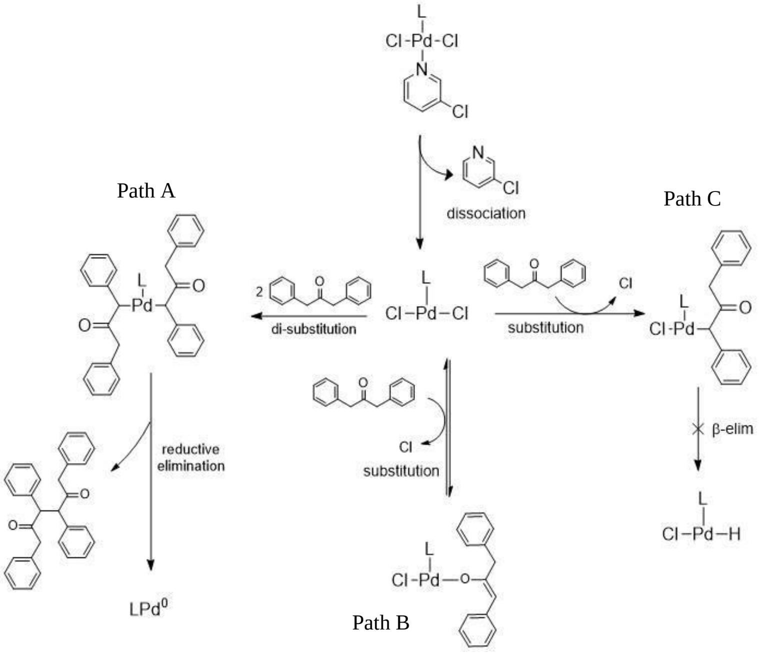
4.2 Buchwald-Hartwig Cross-Coupling with Aniline Scheme



Scheme 21. Three potential pathways for 3-pentanone to reduce/react with the LPdCl-complex. Path A: reductive elimination; Path B: enolate oxygen binding; Path C: β-elimination.

The pathway of activation by such compounds is still not clear nor is it studied much. There are two pathways of reduction: 1) reductive elimination (RE); and 2) βelimination. These reaction mechanisms are very well known, but how the ketone ligates to metal and then reduces it is unclear. **Scheme 21** demonstrates the three potential pathways of which the ketone possibly takes. Pathway descriptions are in the caption. Paths A and C are also demonstrated in **Scheme 2.** Path B shows the possibility of the oxygen in the enol tautomer of 3-pentanone binding to the metal as opposed to the α-position. This is an unlikely hypothesis because there is no obvious way to reduce the LPd^0 from this structure. Paths A and C are the most likely candidates for this transformation. Both lead to generation of the LPd^0, which initiates the catalytic cycle. Without this, the coupling reaction cannot proceed. **Schemes 1, 2 and 6** also demonstrate the various ways LPd^0 can be generated, however, the LPd^{II} pathway, from **Scheme 1**, is the only one relevant to the Buchwald-Hartwig activation issue using 3-pentanone. The Organ study, **Scheme 10, Table 1**, demonstrates the use of three major organoreagents: morpholine, Bu_2Mg, and Li isopropanol (LiO*i*Pr). All of which can undergo both Path A and C. Morpholine and LiO*i*Pr could also have the potential to get hung up in Path B. **Scheme 13** shows the potential pathways of the activation step in relevance to the catalytic cycle, one being RE and the other β-elimination.

4.3 Hypothesized Investigation of Reductive Elimination Scheme

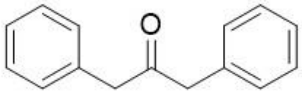


Scheme 22. Hypothesized activation pathways for 1,3-diphenyl-2-propanone.

In order to distinguish one reductive pathway from another, a study could be done to isolate these. A good example for isolating the reductive elimination pathway is shown in **Scheme 22**. This method uses 1,3-diphenyl-2-propanone (**50**) to reduce the Pd^{II} species. If the reaction is successful using this ketone, then RE is more than likely the activation mechanism taking place. B-elimination cannot occur with this ketone because there is no β-H present in neither

Path B nor Path C. If it produces little to no yield, then it is either β-elimination or a more obscure pathway. This ketone is fairly easy to synthesize and is commercially available.

Another possible reduction pathway could be through γ-elimination of Path B in **Scheme 21**. The ethyl chains on the carbonyl are flexible enough to twist into position.


1,3-diphenyl-2-propanone

50

Figure 12. Structure of 1,3-diphenyl-2-propanone used in **Scheme 22**.

CHAPTER 3: EXPERIMENTAL SECTION

General Procedures: **Procedure for Alpha and Amine Arylation via Cross-Coupling**

To a glass vial, preferably 3 mL to minimize gelling of the reaction, was added a 4 cm stir bar and 0.5 mol% PEPPSI-IPr (3.4 mg, 5 µmol), which was measured in open air. If the aryl bromide (1.0 mmol) was solid, it was added at this point. The vial was covered with a Kimwipe secured by a rubber band and was transferred alongside a septum cap into the glove box. There NaO-*t*-Bu (144.0 mg,1.5 mmol) was added. The vial was sealed with rubber a septa cap and removed from the glove box. The remaining reagents were added to a vial in the following order via syringe: dry toluene (3.5 mL), aryl bromide (1.0 mmol), 3-pentanone (0.0 mmol – 0.288 mmol), aniline or ketone (1.2 mmol). The vials were then secured with copper wire and placed in an oil bath at the desired temperature with oil fully covering the components. The reaction was allowed to stir for ~24 hrs. Afterwards, GC was used to determine conversion. During the kinetic study, the GC samples were quenched with saturated NH_4Cl solution (0.5 mL) and EtOAc (0.5 mL) to ensure the reaction had fully stopped in the GC sample. The products were then isolated via column chromatography using EtOAc/hexane (0% - 10%) as eluant. The combined fractions were concentrated by rotary evaporator and dried under high vacuum (ca. 0.1 mTorr). TLC with 10% EtAcO/Hexane as the solvent was used to identify the fractions containing the desired product. H-NMR and GCMS were used to confirm and identify the isolated products.

During the kinetic study, a sample was taken in the following time pattern (unit – minutes): 15, 30, 45, 60, 90, 120, 150, 180, 210, 240. These aliquots were then analyzed using GC. The preferred order of addition of reagents is as follows: 0.5 mol% PEPPSI-IPr (3.4 mg, 5 µmol), NaO-*t*-Bu (144.0 mg,1.5 mmol), dry toluene (3.5 mL), aryl bromide (1.0 mmol), 3pentanone (0.0 mmol – 0.288 mmol), aniline or ketone (1.2 mmol). Other orders of addition yield varying and lesser yields.

Amine arylated reactions:

4-methoxy-N-phenylaniline. According to the general procedure 4-bromoanisole (125.0 µL, 1.0 mmol), aniline (110.0 µL, 1.2 mmol):

(option 1) 3-pentanone (15.3 µL, 0.144 mmol) were coupled at 80 °C for 24 h. GC analysis indicated 86.4% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0%, 5% then 10% EtAcO/hexane) to afford the product as a dark salmon solid (the isolated mass and % conversion were not reliable enough to report).

(option 2) 3-pentanone (23.0 µL, 0.216 mmol) were coupled at 60 °C for 24 h. GC analysis indicated 69.8% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0%, 5% then 10% EtAcO/hexane) to afford the product as a dark salmon solid (the isolated mass and % conversion were not reliable enough to report).

(option 3) 3-pentanone (23.0 µL, 0.216 mmol) were coupled at 80 °C for 24 h. GC analysis indicated 85.7% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0%, 5% then 10% EtAcO/hexane) to afford the product as a dark salmon solid (the isolated mass and % conversion were not reliable enough to report).

(option 4) 3-pentanone (15.3 μL, 0.144 mmol) were coupled at 60 °C for 24 h. GC analysis indicated 53.1% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0%, 5% then 10% EtAcO/hexane) to afford the product as a dark salmon solid (the isolated mass and % conversion were not reliable enough to report).

^{1}H NMR ($CDCl_3$-d, 500 MHz): δ 7.31 (t, 1H, J=7.95 Hz, p-pos benzene ring), 7.15 (d, 2H, J=8.94 Hz, aromatic CH), 7.00 – 6.92 (m, 6H, aromatic CH), 5.59 (s, 1H, NH), 3.87 (s, 3H, OCH_3) ppm. ^{13}C NMR ($CDCl_3$-d, 500 MHz): δ 155.3, 145.3, 135.9, 129.4, 122.2, 119.6, 115.8, 114.8 ppm.

MS (GC-MS): 15.49 min (73.0 m/z, 76.8, 207.3, 290.0, 291.4, 305.2, 206.4); 10.35 – amine product – (77.0, 128.2, 184.2, 185.3, 199.2, 200.3); 7.90 – alpha by-product – (135.1, 192.4); 5.57 – 4-bromoanisole – (62.0, 63.0, 64.0, 64.8, 77.1, 92.1, 143.0, 145.0, 170.0, 171.0, 173.0, 186.0, 188.0, 189.1); 5.13 (68.0, 162.2); 4.20 – aniline – (65.0, 66.0, 93.1).

4-(phenylamino)benzonitrile. According to the general procedure 4-bromobenzonitrile (182.0 mg, 1.0 mmol), aniline (110.0 μL, 1.2 mmol) 3-pentanone (15.3 μL, 0.144 mmol) were coupled at 60 °C for 24 h. GC analysis was inconclusive in determining what the product is. The reaction mixture was worked up as described in the general procedure. This reaction did not produce an identifiable product, nor did it produce enough of any product/by-product to be isolated. MS (GC-MS): 11.34 min (73.1 m/z, 77.0, 78.0, 167.0, 197.1, 207.4, 212.3, 213.4); 7.28 (51.1, 63.1, 76.1, 77.1, 78.2, 91.1, 92.1, 104.1, 118.2, 119.2, 198.2, 199.1, 201.1); 4.209 – aniline – (65.0, 66.1, 93.1).

N-phenyl-4-(trifluoromethyl)aniline. According to the general procedure 4-bromobenzotrifluoride (140.0 µL, 1.0 mmol), aniline (110.0 µL, 1.2 mmol) 3-pentanone (15.3 µL, 0.144 mmol) were coupled at 80 °C for 24 h. GC analysis indicated 11.4% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0% then 5% EtAcO/hexane) to afford the product as a wet, brown solid (the mass and % conversion were not reliable enough to report). MS (GC-MS): 9.29 min – amine product – (65.0 m/z, 68.9, 167.1, 237.1, 238.2); 4.229 – aniline – (65.0, 66.0, 93.1); 3.22 – 4-bromobenzotrifluoride – (69.0, 74.1, 75.1, 76.1, 80.9, 95.1, 125.1, 145.1, 146.3, 224.0, 226.0).

N^1,N^1-dimethyl-N^4-phenylbenzene-1,4-diamine. According to the general procedure 4-bromo-N,Ndimethylaniline (200.1 mg, 1.0 mmol), aniline (110.0 µL, 1.2 mmol) 3-pentanone (15.3 µL, 0.144 mmol) were coupled at 80°C for 24 h. Note that 1.0 mol% of the PEPPSI-IPr catalyst was used instead of the general 0.5 mol%. GC analysis indicated 33.9% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0%, then 5% EtAcO/hexane) to afford the product as a wet, brown solid (the reaction that afforded 88.6% yield was not salvaged and as a result, no isolated mass or analysis can be done, see **Table 5**). The second trial only produced ~6% yield, which is too small to isolate. MS (GC-MS): 13.29 min (77.0 m/z, 78.2, 93.1, 274.1, 276.0); 12.71 – amine product – (193.0, 194.1); 9.82 (74.0, 75.1, 76.0, 156.8, 182.9, 184.9, 200.9, 207.1); 6.40 (68.0, 75.0, 76.0, 102.1, 180.9, 182.9); 4.20 – aniline – (65.1, 66.0, 93.1).

2-methyl-N-phenylaniline. According to the general procedure 2-bromotoluene (120.4 μL, 1.0 mmol), aniline (110.0 μL, 1.2 mmol):

(option 1) 3-pentanone (15.3 μL, 0.144 mmol) were coupled at 80 °C for 24 h. GC analysis indicated 100.0% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0% EtAcO/hexane) to afford the product as a dark green/brown oil (142.8 mg, 83.5%).

(option 2) 3-pentanone (23.0 μL, 0.216 mmol) were coupled at 60 °C for 24 h. GC analysis indicated 99.7% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0% EtAcO/hexane) to afford the product as a dark green/brown oil (148.6 mg, 86.9%).

^{1}H NMR ($CDCl_3$-d, 500 MHz): δ 7.34-6.95 (m, 9H, aromatic CH), 5.34 (s, 1H, NH), 2.22 (s, 1H, CH_3) ppm. ^{13}C NMR ($CDCl_3$-d, 500 MHz): δ 144.0, 141.2, 130.9, 129.3, 128.3, 126.4, 122.0, 120.4, 118.8, 117.4, 17.83 ppm.

2,6-dimethyl-N-phenylaniline. According to the general procedure 2-bromo-1,3dimethylbenzene (133.1 μL, 1.0 mmol), aniline (110.0 μL, 1.2 mmol):

(option 1) 3-pentanone (15.3 μL, 0.144 mmol) were coupled at 80 °C for 24 h. GC analysis indicated 99.9% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0% EtAcO/hexane) to afford the product as a dark brown oil (171.4 mg, 92.6%).

(option 2) 3-pentanone (23.0 μL, 0.216 mmol) were coupled at 60 °C for 24 h. GC analysis indicated 95.1% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0% EtAcO/hexane) to afford the product as a dark brown oil (167.5 mg, 90.5%).

^{1}H NMR (CDCl$_3$-d, 500 MHz): δ 7.15-7.04 (m, 5H, benzene CH), 6.72 (t, J=7.32 Hz, 1H, p-pos sub. ring), 6.48 (d, J=7.66 Hz, 1H, m-pos benzene ring), 5.21 (s, 1H, NH), 2.18 (s, 6H, CH$_3$) ppm. ^{13}C NMR (CDCl$_3$-d, 500 MHz): δ 146.2, 138.2, 135.9, 129.2, 128.5, 125.7, 118.1, 113.5, 18.29 ppm.

2-isopropyl-N-phenylaniline. According to the general procedure 2isopropylbromobenzene (153.1 µL, 1.0 mmol), aniline (110.0 µL, 1.2 mmol): 3pentanone (23.0 µL, 0.216 mmol) were coupled at 60 °C for 24 h. GC analysis indicated 99.6% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0% EtAcO/hexane) to afford the product as a dark brown oil (184.6 mg, 92.7%). ^{1}H NMR (CDCl$_3$-d, 500 MHz): δ 7.31 (d, J=7.96 Hz, 2H, o-pos benzene ring), 7.24 – 7.19 (m, 2H, aromatic CH), 7.14 (t, J=7.54 Hz, 1H, p-pos benzene ring), 7.07 (t, J=15.1 Hz, 1H, aromatic CH), 6.87 – 6.82 (m, 4H, aromatic CH), 5.40 (s, 1H, NH), 7 (s, 1H), 1.24 (d 6H, IPr H) ppm. ^{13}C NMR (CDCl$_3$-d, 500 MHz): δ 145.3, 140.7, 139.5, 129.2, 126.4, 126.1, 123.5, 121.9, 119.7, 116.4, 27.6, 23.0 ppm.

2,4,6-triisopropyl-N-phenylaniline. According to the general procedure 2-bromo-1,3,5triisopropylbenzene (205.0 µL, 1.0 mmol), aniline (110.0 µL, 1.2 mmol):

(option 1) 3-pentanone (15.3 µL, 0.144 mmol) were coupled at 80 °C for 24 h. GC analysis indicated 100.0% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0% EtAcO/hexane) to afford the product as a salmon pink solid (227.7 mg, 94.4%).

(option 2) 3-pentanone (23.0 µL, 0.216 mmol) were coupled at 60 °C for 24 h. GC analysis indicated 99.4% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0% EtAcO/hexane) to afford the product as a salmon pink solid (228.1 mg, 94.6%).

^{1}H NMR ($CDCl_3$-d, 500 MHz): δ 7.12 (t, J=7.64 Hz, 2H, m-pos benzene ring), 7.05 (s, 2H, o-pos benzene ring), 6.67 (t, J=7.30 Hz, 1H, p-pos benzene ring), 6.47 (d, J=8.29 Hz, 2H, m-pos substituted benzene), 5.02 (s, 1H, NH), 3.18 (septet, J= 6.94 Hz, 2H, CH on o-pos IPr), 2.92 (septet, J=7.10, 6.80, 7.10 Hz, 1H, CH on p-pos IPr), 1.29 (d, J=6.90 Hz, 6H, CH_3 on p-pos IPr), 1.14 (d, J=6.90 Hz, 12H, CH_3 on o-pos IPr) ppm. ^{13}C NMR ($CDCl_3$-d, 500 MHz): δ 148.4, 147.4, 147.2, 132.7, 129.1, 121.7, 117.3, 112.8, 34.2, 28.2, 24.1, 23.9 ppm.

α-arylated reactions:

2-(4-methoxyphenyl)pentan-3-one. According to the general procedure 4-bromoanisole (125.0 µL, 1.0 mmol) and:

(option 1) 3-pentanone (127.6 µL, 1.2 mmol) were coupled at 60 °C for 24 h. GC analysis indicated 77.8% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0%, 5% then 10% EtAcO/hexane) to afford the product as a colorless liquid (the isolated mass and % conversion are not reliable enough to report).

(option 2) propiophenone (159.5 μL, 1.2 mmol) were coupled at 60 °C for 24 h. GC analysis indicated 93.5% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0%, 5% then 10% EtAcO/hexane) to afford the product as a brown oil (the isolated mass and % conversion are not reliable enough to report).

MS (GC-MS): 12.70 min – suspected double alpha product – (135.1 m/z, 136.3, 298.3); 7.89 – alpha product – (135.1, 136.3, 192.2).

2-(4-(trifluoromethyl)phenyl)pentan-3-one. According to the general procedure 4-bromobenzotrifluoride (140.0 μL, 1.0 mmol) and 3-pentanone (127.6 μL, 1.2 mmol) were coupled at 60 °C for 24 h. GC analysis indicated 48.7% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0%, 5% EtAcO/hexane) to afford the product as a brown oil (the mass and % conversion were not reliable enough to report).

2-(4-aminophenyl)pentan-3-one. According to the general procedure 4-bromo-N,Ndimethylaniline (200.0 mg, 1.0 mmol) and 3-pentanone (127.6 μL, 1.2 mmol) were coupled at 60 °C for 24 h. GC analysis indicated 83.0% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0%, 5% EtAcO/hexane) to afford the product as a red/brown liquid (the mass and % conversion was not reliable enough to report,). ^{1}H NMR ($CDCl_3$-d, 500 MHz): δ 7.07 (d, J=9.43 Hz, 2H, o-position), 6.69 (d, J=8.71 Hz, 2H, m-position), 3.66 (q, J=6.86 Hz, 3H, terminal CH_3 substituted side), 2.93 (s, 6H, N-methyl H), 2.46-2.29 (m, 2H, non-sub alpha position), 1.36 (d, J=7.10 Hz, 1H, alpha position), 0.96 (t, J=7.10 Hz, 3H, terminal CH_3 nonsubstituted side) ppm. ^{13}C NMR ($CDCl_3$-d, 500 MHz): δ 148.4, 147.4, 147.2, 132.7, 129.1, 121.7, 117.3, 112.8, 34.2, 28.2, 24.1, 23.89 ppm.

2-(o-tolyl)pentan-3-one. According to the general procedure 2-bromotoluene (120.0 µL, 1.0 mmol) and 3-pentanone (127.6 µL, 1.2 mmol) were coupled at 60 °C for 24 h. GC analysis indicated 84.0% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0% then 5% EtAcO/hexane) to afford the product as a light-yellow liquid (141.0 mg, 82.4%). The H- and C-NMR show that a pure product, or a product in isomerization was made. The NMRs were not clean enough to determine if the product was pure.

2-(2,6-dimethylphenyl)pentan-3-one. According to the general procedure 2-bromo-1,3dimethylbenzene (133.0 µL, 1.0 mmol) and 3-pentanone (127.6 µL, 1.2 mmol) were coupled at 60 °C for 24 h. GC analysis indicated 96.0% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0% then 5% EtAcO/hexane) to afford the product as a golden, yellow oil (the mass and % conversion was not reliable enough to report). There was not enough salvageable product to obtain a successful H- or C-NMR.

2-(2,4,6-triisopropylphenyl)pentan-3-one. According to the general procedure 2-bromo-1,3,5triisopropylbenzene (205.0 µL, 1.0 mmol) and 3-pentanone (127.6 µL, 1.2 mmol) were coupled at 60 °C for 24 h. GC analysis indicated 94.0% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography using solvent system (0% then 5% EtAcO/hexane) to afford the product as a golden, yellow oil (the mass and % conversion were not reliable enough to report). There was not enough salvageable product to obtain a successful H- or C-NMR.

CHAPTER 4: CONCLUSION

This study demonstrates the importance of the affect using a ketone has on the catalysis of these Buchwald-Hartwig and enolate coupling reactions. Without the activator, the reaction yields little to no product, or has harsh conditions if the yield is greater than 50.0%. In contrast, the couplings utilizing 3-pentanone produce yields within the 60-100% conversion range. The sterically demanding aryl bromides afford 100% conversion with very little ketone and at temperatures as low as 20 °C. The electron-rich and -deficient substrates had a harder time producing high yields. 4-bromoanisole was the most successful of the electronically modified substrates. Another key component to this study is the order of addition of reagents. During the optimization phase, creating reproducible yields became an obstacle to the project. An investigative study was done to find the optimal order of addition. The first six reactions performed afforded the optimal order to be: toluene > aryl bromide > ketone > aniline. An additional reaction was done later to unexpectedly show that adding toluene last greatly improved the yield (aryl bromide > ketone > aniline > toluene). The difference between what we thought was the optimal order and the latter is a 16.7% difference in conversion. Due to time and simplicity, the order of addition in entry 17 was already being used for most of this study.

To save time and resources, we did not repeat the reactions with the new optimal yield. During the investigation of the Buchwald-Hartwig amination, we found a by-product peak in the GC that was consistent throughout all varieties of aryl bromide. After looking into it, we found that these reactions produce a small amount of by-product between the ketone and aryl bromide. Initially, the same reaction conditions for 60 an 80 °C with 21.6 and 14.4 mol%, respectively, of 3-

pentanone were run with propiophenone to observe a shift in the suspected GC peak. To further confirm the identity of the suspected peak, reactions of the aryl bromide with a stoichiometric amount of the ketone allowed the identity of these peaks to be confirmed by NMR.

Ideas for future projects include:

- Testing the theory of electronic effects versus steric ones by comparing an aryl bromide substituted with a sterically hindered and electronically demanding attachment at the same position on the ring.
- Using different ketones to challenge the hypothesized pathways of the ketone activation, such as RE specific and β- or γ- elimination specific pathways, by isolating the pathway to only one option.

Things we did not have time to accomplish were:

- Successful isolation an identification of 3aa – 3cc, 3ee – 3gg, 4aa – 4cc products.

REFERENCES

[1] PEPPSI™ Catalyst. https://www.sigmaaldrich.com/technicaldocuments/articles/chemfiles/peppsi-catalyst0.html (accessed Nov 18, 2019).

[2] Hartwig, J. F. *Organotransition Metal Chemistry: from bonding to catalysis*; University Science Books: Sausalito, CA., **2010**.

[3] Negishi, *E.* Palladium- or Nickel-Catalyzed Cross Coupling. A New Selective Method for Carbon-Carbon Bond Formation. *Acc. Chem. Res*. **1982**, *15*, 340.

[4] Zheng, B.; Jia, T.; Walsh, P. J. A General and Practical Palladium-Catalyzed Direct α-Arylation with Aryl Halides. *Adv. Synth. Catal.* **2014**, *356*, 165-178.

[5] Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. A User-Friendly, All-Purpose Pd-NHC (NHC=N-Heterocyclic Carbene) Precatalyst for the Negishi Reaction: A Step Towards a Universal Cross-Coupling Catalyst. *Chem. Eur. J.* **2006**, *12 (18)*, 4749-4755.

[6] Sayah, M.; Organ, M. G. Carbon-Sulfur Bond Formation of Challenging Substrates at Low Temperature by Using Pd-PEPPSI-IPent. *Chem. Eur. J.* **2011**, *17*, 11719-11722.

[7] Shaughnessy, K. H. Development of Palladium Precatalysts That Efficiently Generate Pd(0) Active Species. *Isr. J. Chem.* **2019**, *Vol (NA)*, Page No. (NA).

[8] Hou, *S.* Highly Efficient, General Procedure for the Preparation of Alkylzinc Reagents from Unactivated Alkyl Bromides and Chlorides. *Org. Lett*. **2003**, *5*, 423.

[9] Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. The Development of Bulky Palladium NHC Complexes for the Most-Challenging Cross-Coupling Reactions. *Angew. Chem. Int. Ed.* **2012**, *51(14)*, 3314–3332.

[10] Wanzlick, H. W.; Schönherr, H. J. Direct Synthesis of a Mercury Salt-Carbene Complex. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 141 – 142.

[11] Öfele, K. *J.* 1,3-Dimethyl-4-imidazolinyliden-(2)-pentacarbonylchrom ein neuer übergangsmetall-carben-komplex. *J. Organomet. Chem.* **1968**, *12*, 42 – 43.

[12] Arduengo III, A. J.; Harlow, R. L.; Kline, M. A Stable Crystalline Carbene. *J. Am. Chem. Soc.* **1991**, *113*, 361 – 363.

[13] Herrmann, W. A.; Elison, M.; Fischer, J.; Kchter, C.; Arthus, G. R. J. Metal Complexes of N-Heterocyclic Carbenes – A New Structural Principle for Catalysts in Homogeneous Catalysis. *Angew. Chem. Int. Ed.* **1995**, *34 (21)*, 2371 – 2373.

[14] Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. Palladium Complexes of N-Heterocyclic Carbenes as Catalysts for Cross-Coupling Reactions—A Synthetic Chemists Perspective. *Angew. Chem. Int. Ed.* **2007**, *46* (16), 2768–2813.

[15] Organ, M. G; Chass, G. A.; Fang, D.-C.; Hopkinson, A. C.; Valente, C. Pd-NHC (PEPPSI) Complexes : Synthetic Utility and Computational Studies into Their Reactivity. *Synthesis*. **2008**, *17*, 2776 – 2797.

[16] Tolman, C. A. Steric Effects of Phosphorus Ligands in Organometallic Chemistry and Homogeneous Catalysis. *Chem. Rev*. **1977**, *77*, 313.

[17] Hillier, A. C.; Sommer, W. J.; Yong, B. S.; Petersen, J. L.; Cavallo, L.; Nolan, S. P. A Combined Experimental and Theoretical Study Examining the Binding of N-Heterocyclic Carbenes (NHC) to the Cp*RuCl (Cp* = η^5-C_5Me_5) Moiety: Insight into Stereoelectronic Differences between Unsaturated and Saturated NHC Ligands. *Organometallics*. **2003**, *22*, 4322 – 4326.

[18] Dorta, R.; Stevens, E. D.; Hoff, C. D.; Nolan, S. P. Stable, Three-Coordinate $Ni(CO)_2$(NHC) (NHC = N-Heterocyclic Carbene) Complexes Enabling the Determination of Ni-NHC Bond Energies. *J. Am. Chem. Soc.* **2003**, *125*, 10490 – 10491.

[19] Cavallo, L.; Correa, A.; Costabile, C.; Jacobsen, H. Steric and Electronic Effects in the Bonding of N-Heterocyclic Ligands to Transition Metals. *J. Organomet. Chem.* **2005**, *690*, 5407 – 5413.

[20] Falivene, L.; Credendino, R.; Poater, A.; Petta, A.; Serra, L.; Oliva, R.; Scarano, V.; Cavallo, L. SambVca 2. A Web Tool for Analzing Catalytic Pockets with Topographic Steric Maps. *Organometallics*. **2016**, *35*, 2286.

[21] O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Chass, G. A.; Hadei, N.; Hopkinson, A. C.; Organ, M. G.; Setiadi, D. H.; Tang, T.-H.; Fang, D.-C. Easily Prepared Air- and Moisture-Stable Pd-NHC (NHC = N-Heterocyclic Carbene) Complexes: A Relable, User-Friendly, Highly Active Palladium Precatalyst for the Suzuki-Miyaura Reaction. *Tetrahedron*. **2005**, *61*, 9723 – 9735.

[22] Dorta, R.; Stevens, E. D.; Scott, N. M.; Costabile, C.; Cavallo, L.; Hoff, C. D.; Nolan, S. P. Steric and Electronic Properties of N-Heterocyclic Carbenes (NHC): A Detailed Study of Their Interaction with $Ni(CO)_4$. *J. Am. Chem. Soc.* **2005**, *127*, 2485 – 2495.

[23] Chianese, A. R.; Li, X.; Janzen, M. C.; Faller, J.W.; Crabtree, R. H. Rhodium and Iridium Complexes of N-Heterocyclic Carbenes via Transmetallation: Structure and Dynamics. *J. Organomet. Chem.* **2003**, *22*, 1663-1667.

[24] Chen, H.; Justes, D. R.; Cooks, R. G. Proton Affinities of N-Heterocyclic Carbene Super Bases. *Org. Lett.* **2005**, *7*, 3949 – 3952.

[25] Peris, E.; Crabtree, R. H.; Recent Homogeneous Catalytic Applications of Chelate and Pincer N-Heterocyclic Carbenes. *Coord. Chem. Rev.* **2004**, *248*, 2239 – 2246.

[26] Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. G. A Practical and Highly Active Ruthenium-Based Catalyst that Effects the Cross Metathesis of Acrylonitrile. *Angew. Chem. Int. Ed.* **2002**, *41*, 4035.

[27] Marshall, W. J.; Grushin, V. V. Synthesis, Structure, and Relative Elimination Reactions of the First (σ-Aryl)palladium Complex Stabilized by IPr N-Heterocyclic Carbene. *J. Organomet. Chem.* **2003,** *22*, 1591 – 1593.

[28] Palladium-Catalyzed Cross Couplings in Organic Synthesis http://nobelprize.org/nobel_prizes/chemistry/laureates/2010/index.html.

[29] Hu, E. Ketones' Activation on Pd(II) Precatlyst for the Buchwald-Hartwig Amination Reaction. *Manuscript in Preparation.*

APPENDIX

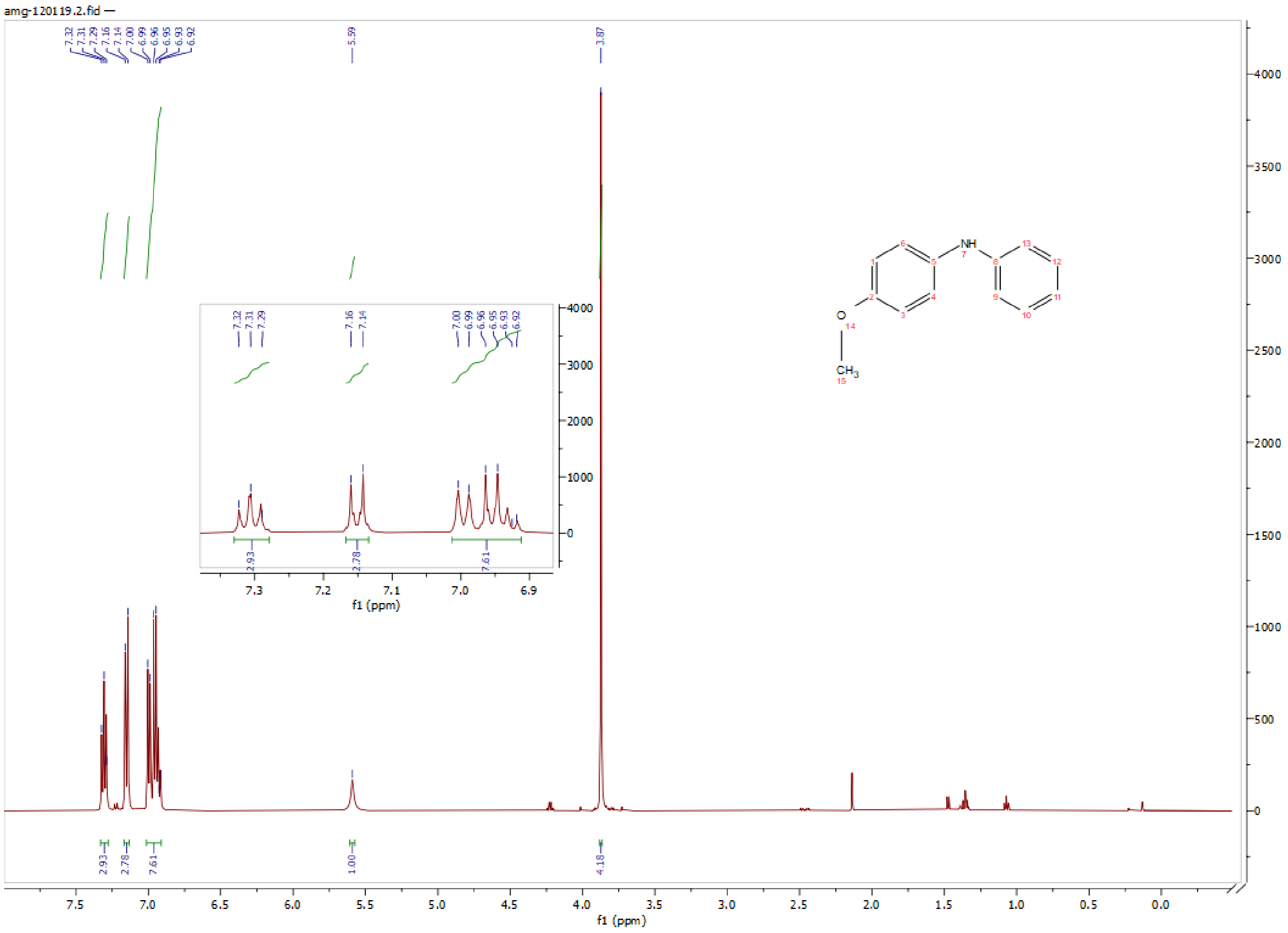


Figure A.1. ^{1}H NMR ($CDCl_3$-d, 500 MHz) of compound 4-methoxy-N-phenylaniline.

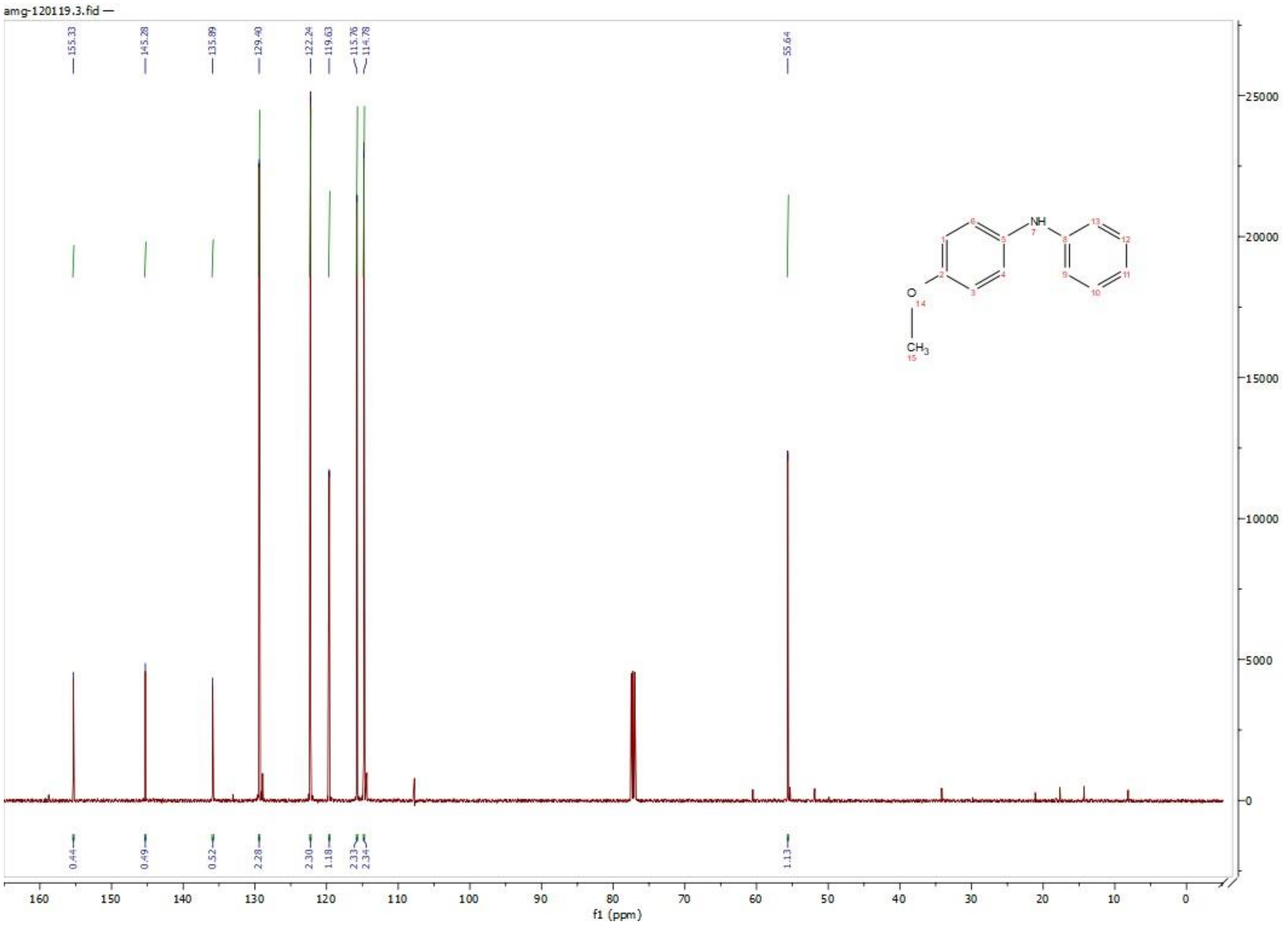


Figure A.2. ^{13}C NMR (CDCl$_3$-d, 500 MHz) of compound 4-methoxy-N-phenylaniline.

Figure A.3. ^{1}H NMR ($CDCl_3$-d, 500 MHz) of compound 2-methyl-N-phenylaniline.

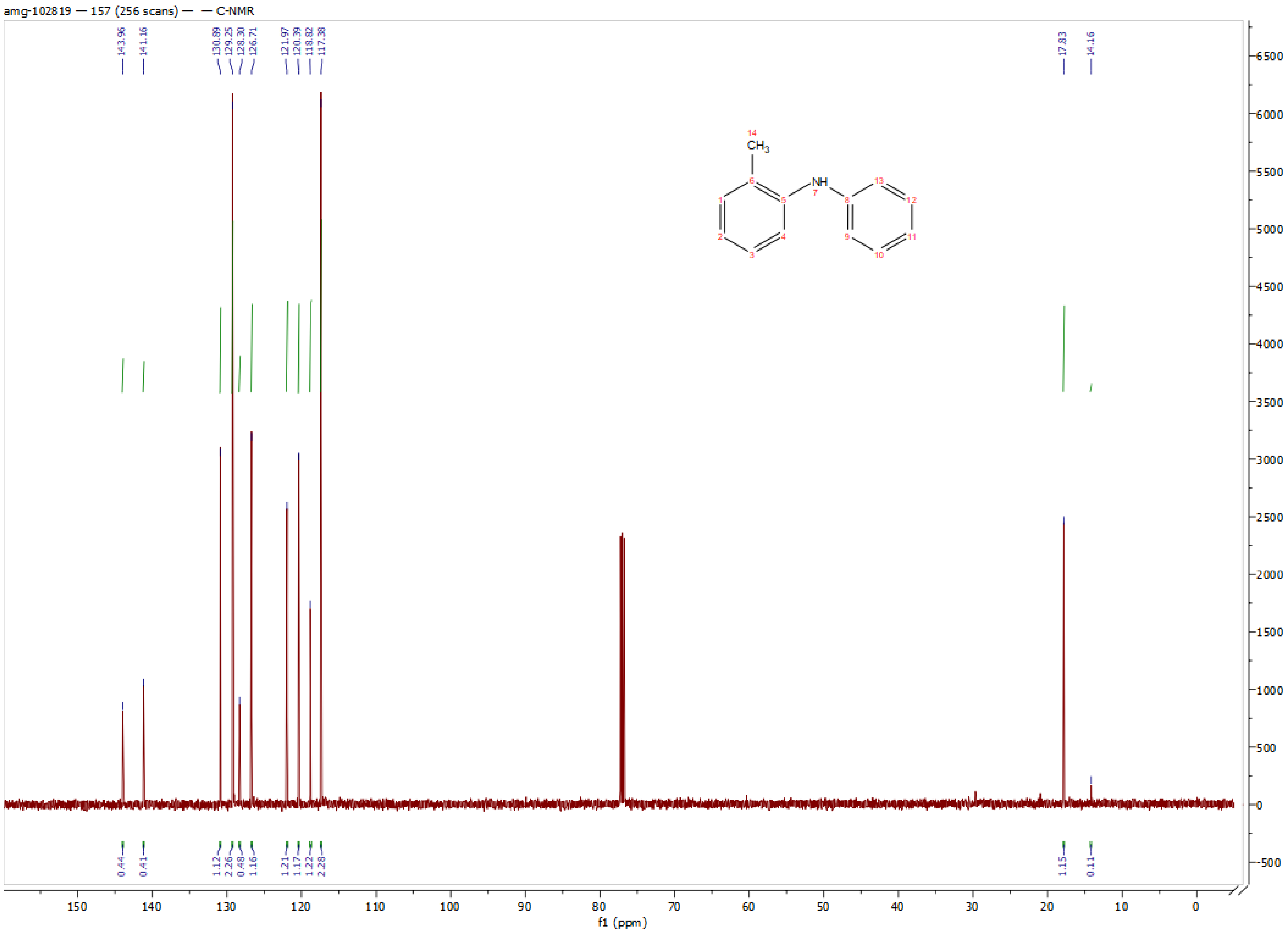


Figure A.4. ^{13}C NMR (CDCl$_3$-d, 500 MHz) of compound 2-methyl-N-phenylaniline.

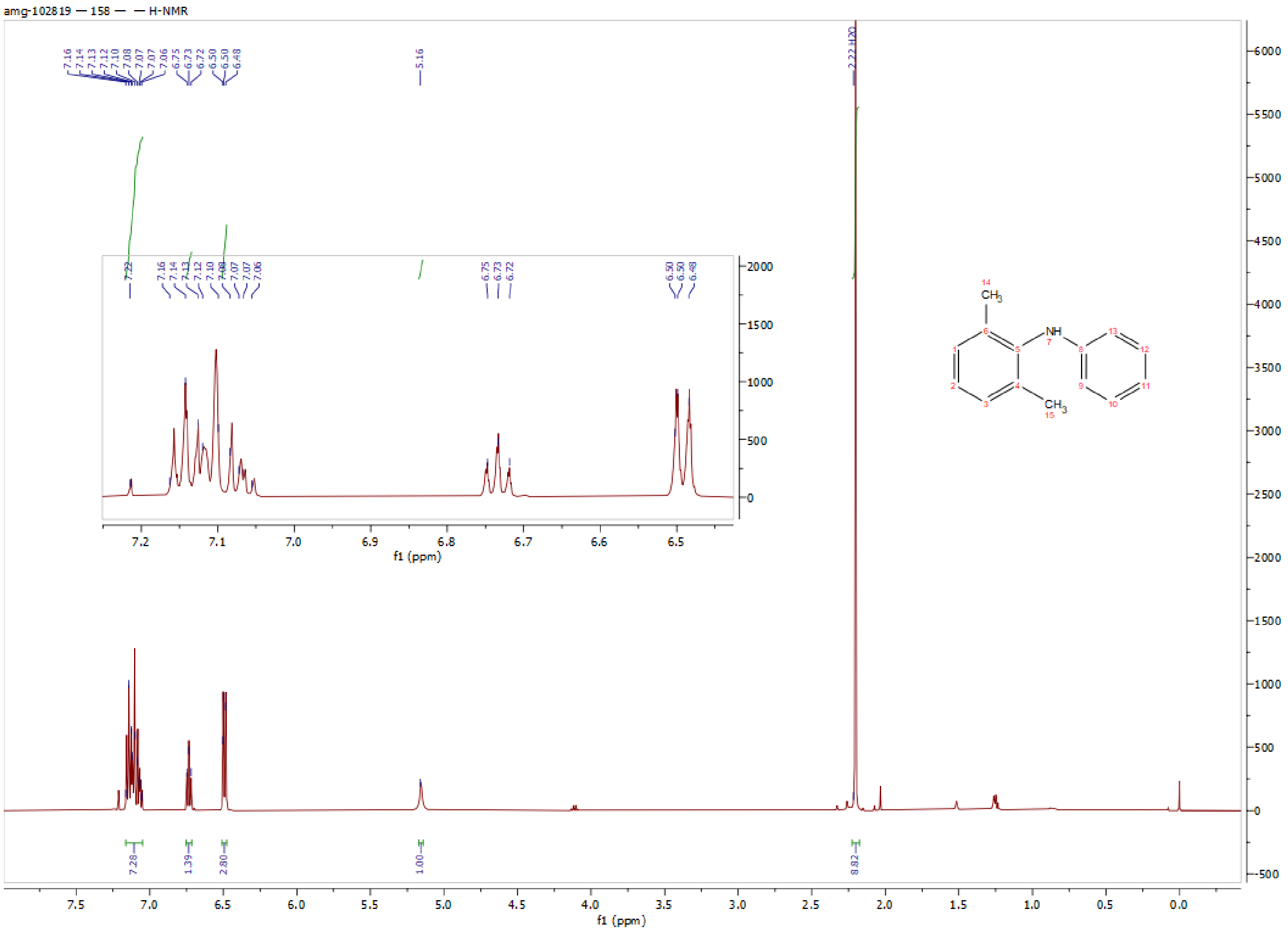


Figure A.5. ^{1}H NMR ($CDCl_3$-d, 500 MHz) of compound 2,6-dimethyl-N-phenylaniline.

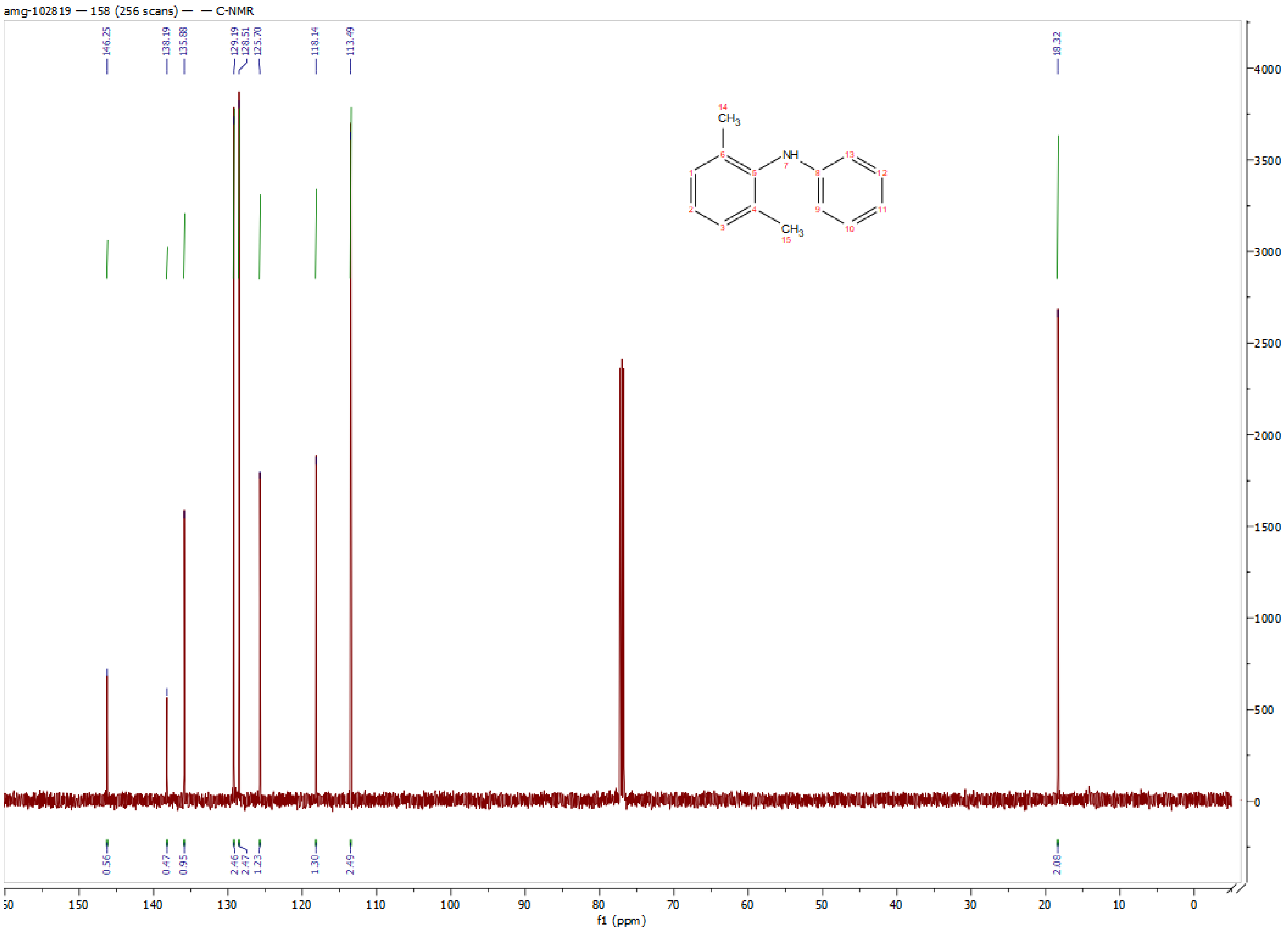


Figure A.6. ^{13}C NMR ($CDCl_3$-d, 500 MHz) of compound 2,6-dimethyl-N-phenylaniline.

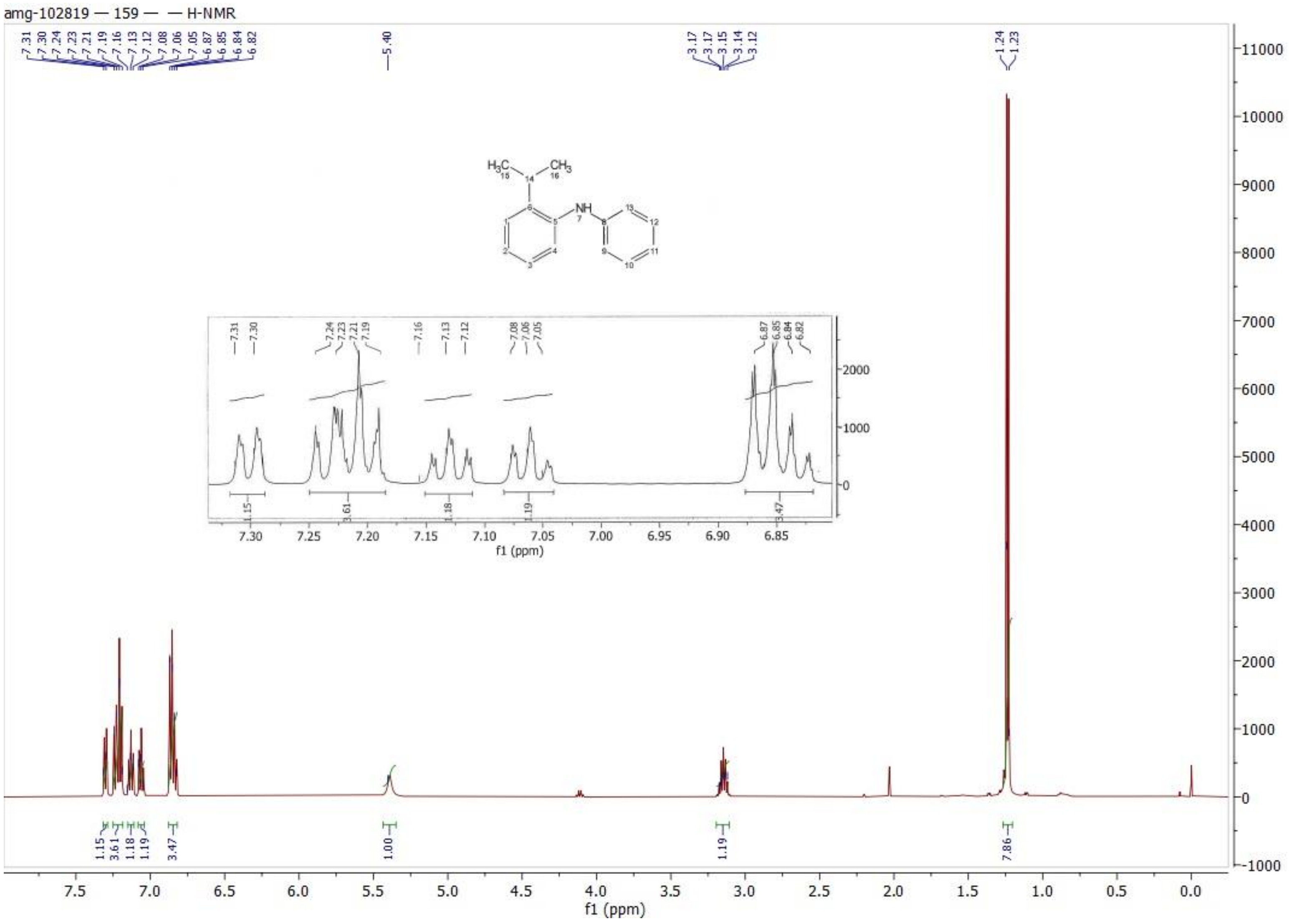


Figure A.7. ^{1}H NMR ($CDCl_3$-d, 500 MHz) of compound 2-isopropyl-N-phenylaniline.

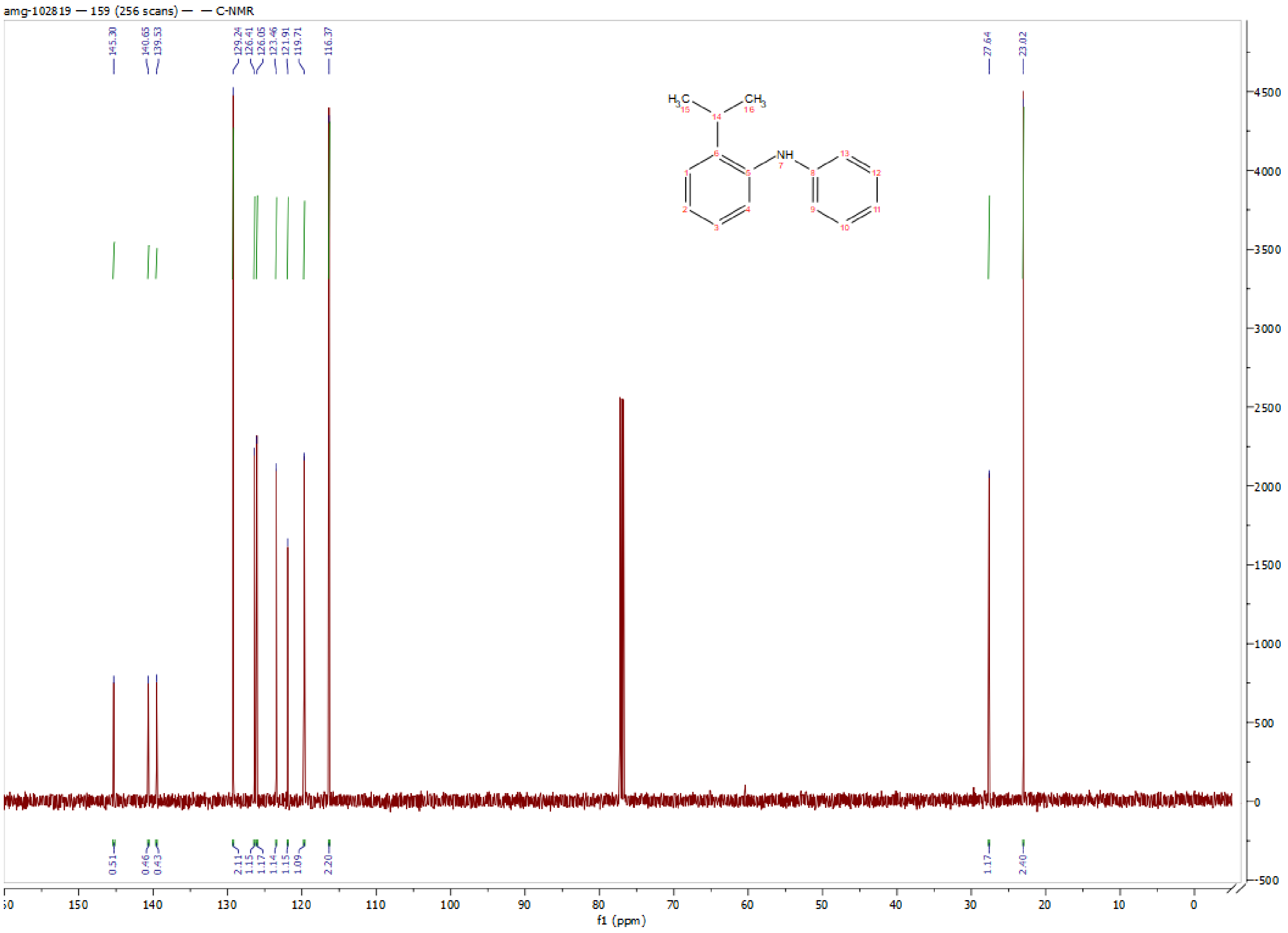


Figure A.8. ^{13}C NMR ($CDCl_3$-d, 500 MHz) of compound 2-isopropyl-N-phenylaniline.

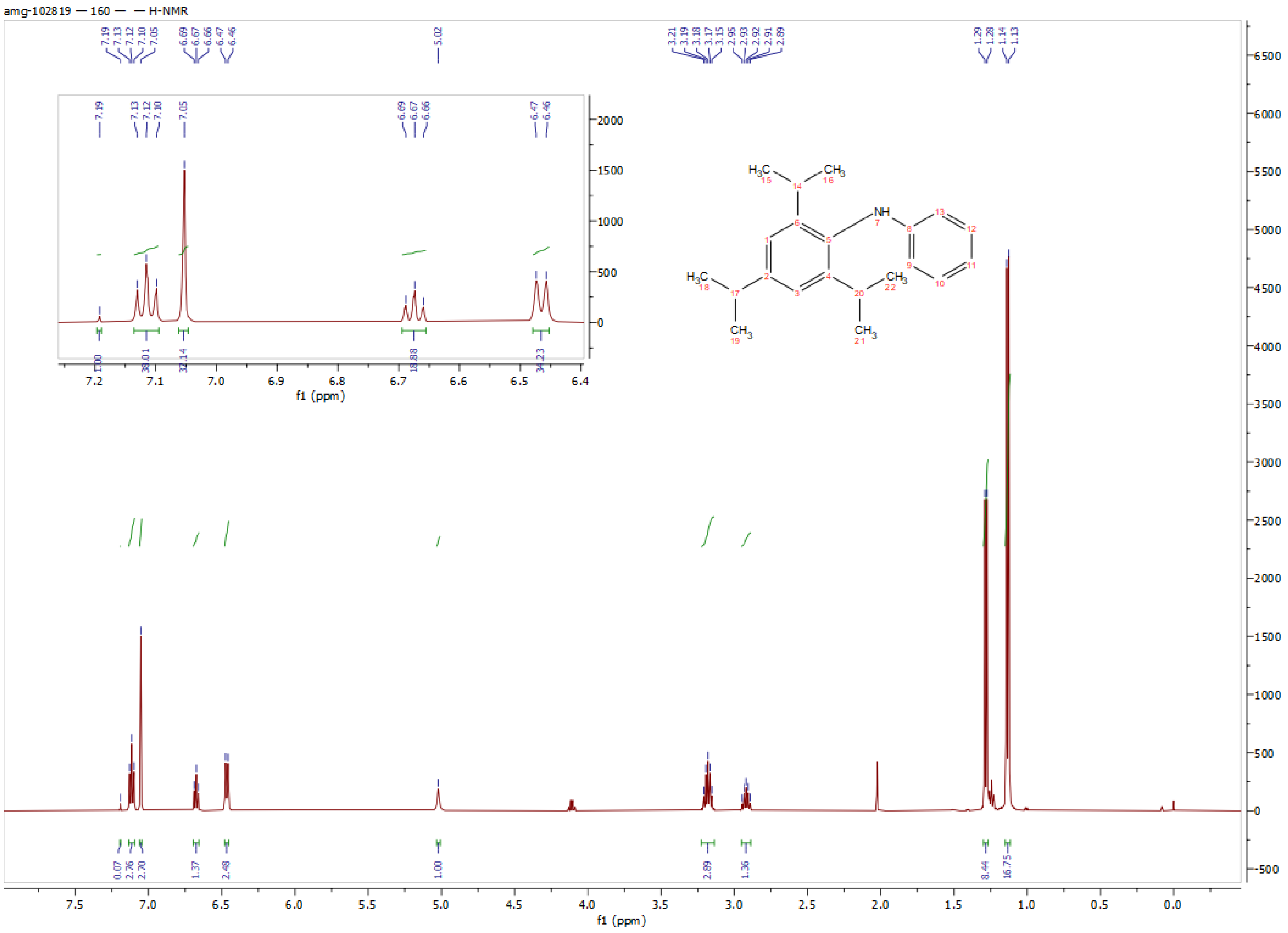


Figure A.9. ^{1}H NMR (CDCl$_3$-d, 500 MHz) of compound 2,4,6-triisopropyl-N-phenylaniline.

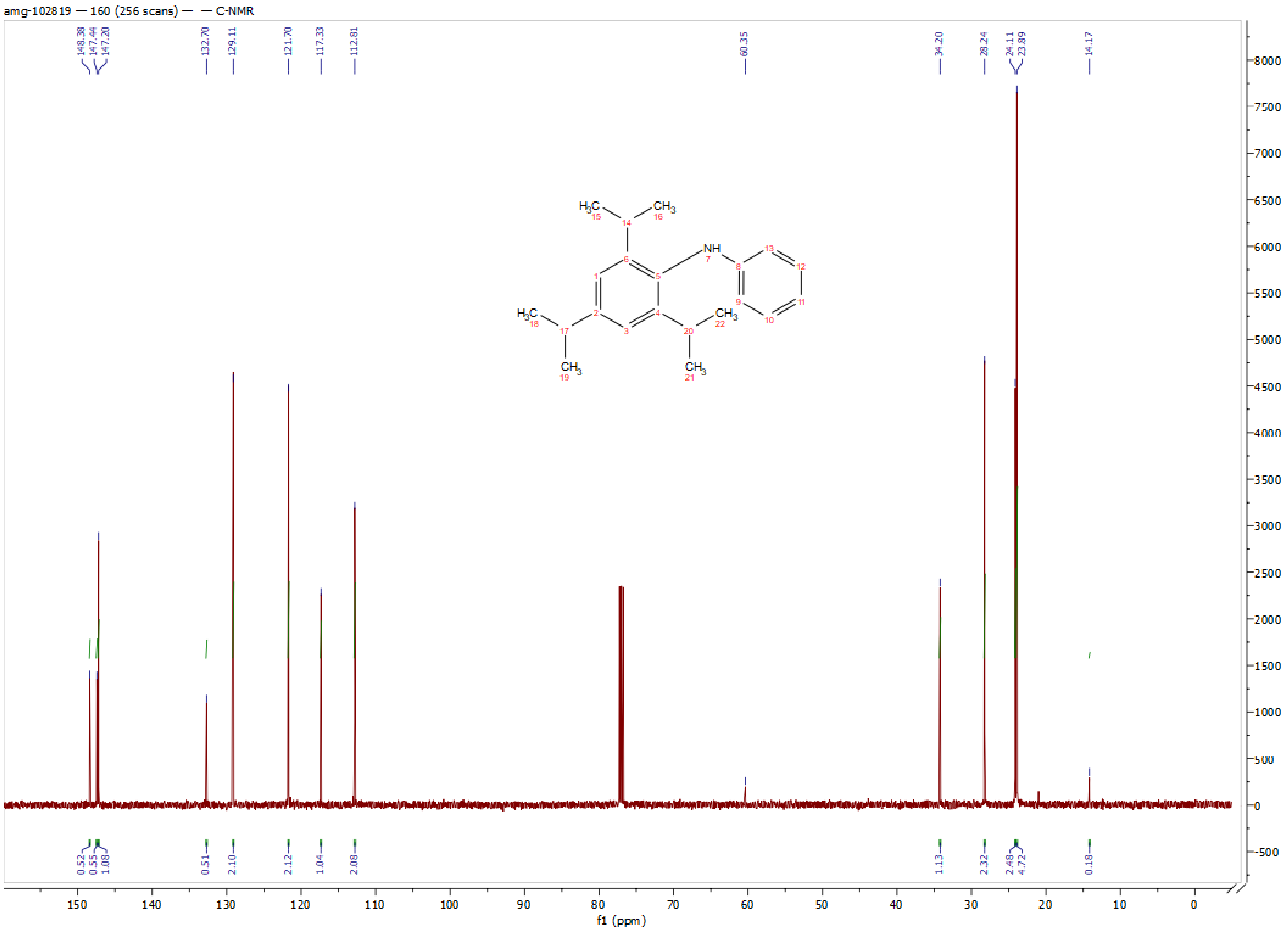


Figure A.10. ^{13}C NMR ($CDCl_3$-d, 500 MHz) of compound 2,4,6-triisopropyl-N-phenylaniline.

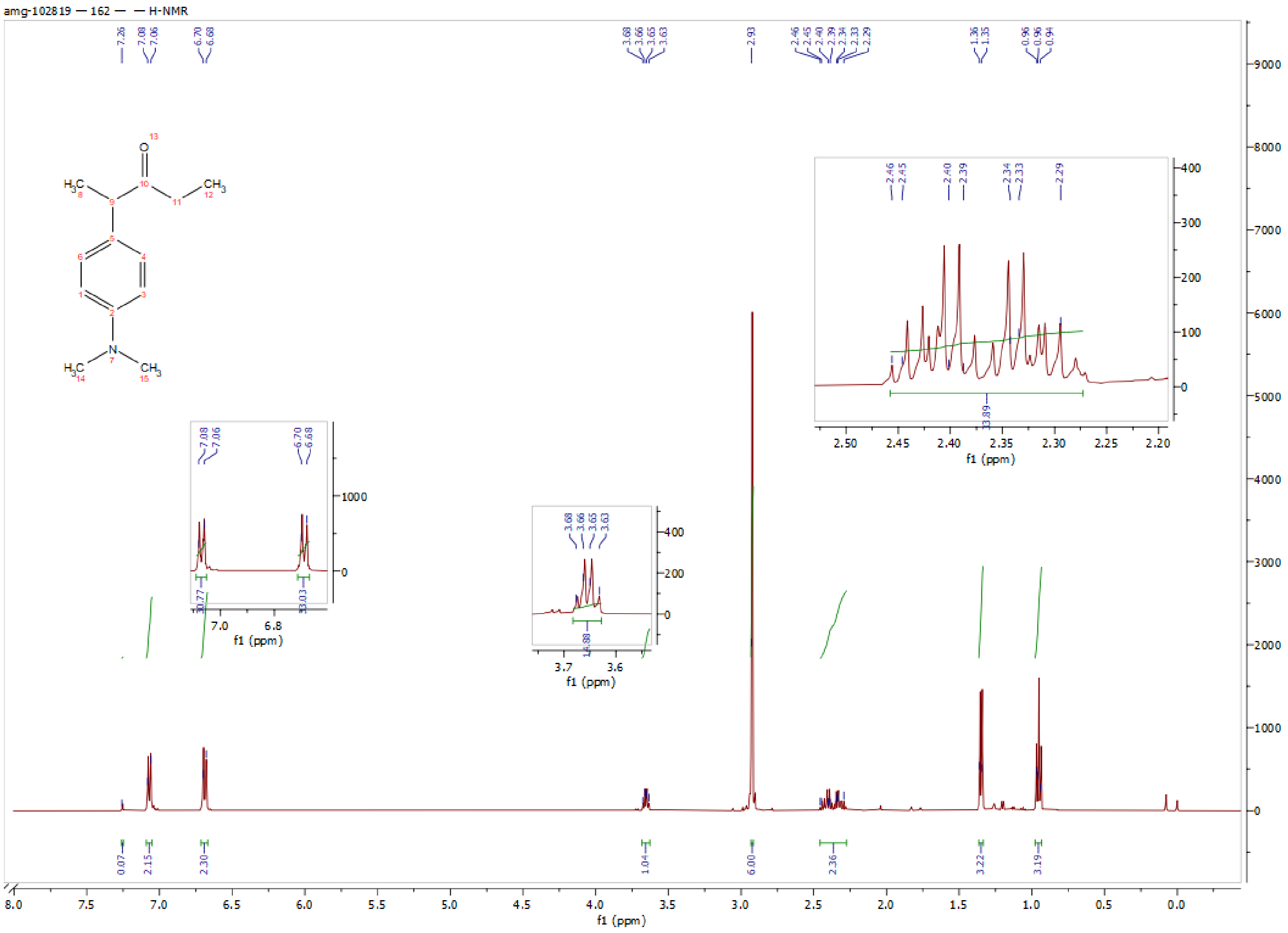


Figure A.11. ^{1}H NMR ($CDCl_3$-d, 500 MHz) of compound 2-(4-(dimethylamino)phenyl)pentan-3-one.

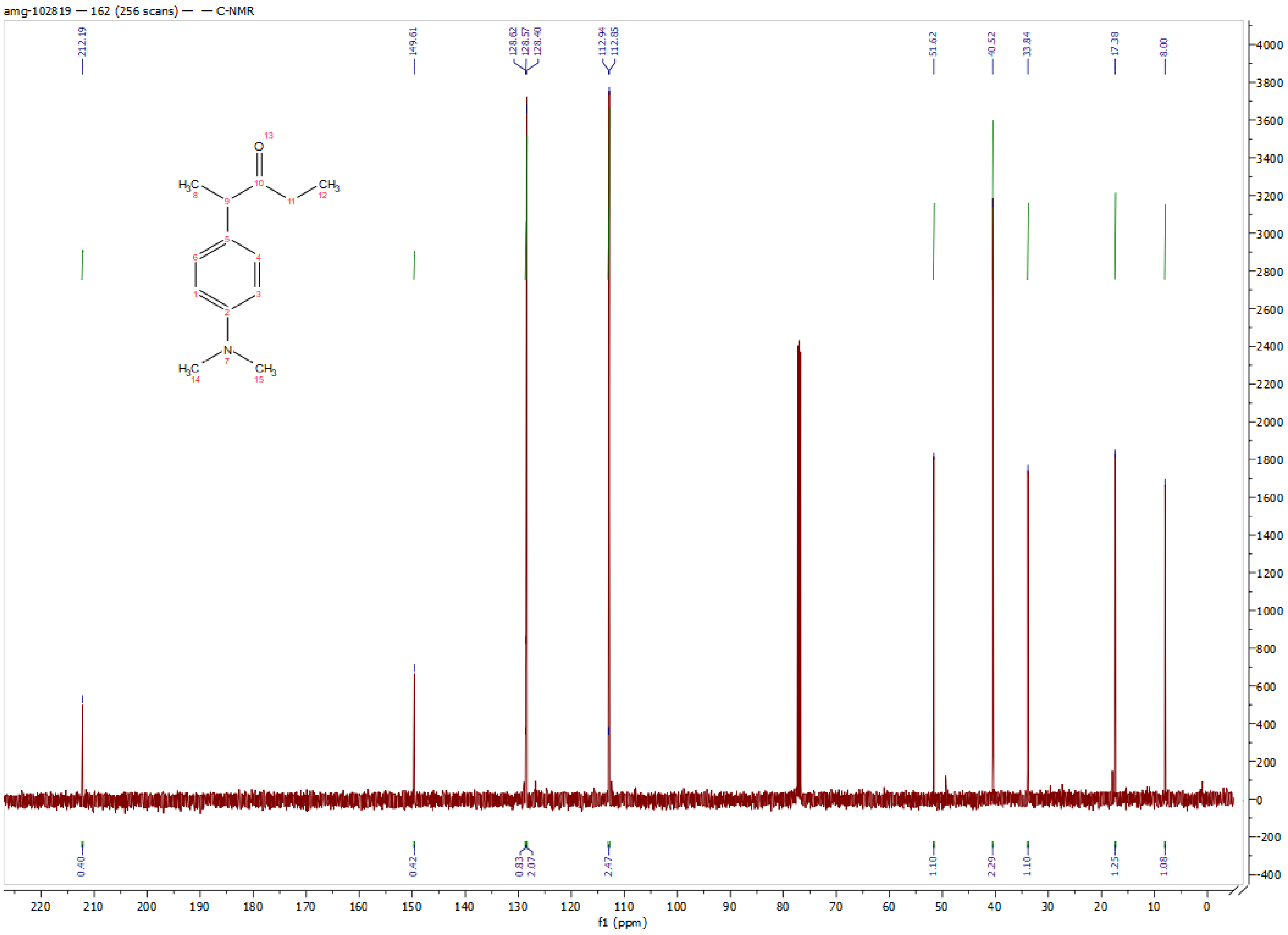


Figure A.12. ^{13}C NMR (CDCl$_3$-d, 500 MHz) of compound 2-(4-(dimethylamino)phenyl)pentan-3-one.