PALLADIUM N-HETEROCYCLIC CARBENE COMPLEXES IN CROSS-COUPLING REACTIONS: LIGAND AND CATALYST DEVELOPMENT

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ABSTRACT

Palladium N-Heterocyclic Carbene
Complexes in Cross-Coupling Reactions: Ligand and Catalyst Development

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The synthesis of biaryls through transition metal catalyzed cross-coupling reactions has been instrumental for synthetic organic chemists. The Hiyama reaction, which features organosilicon derived cross-coupling partners with aryl chlorides, remains relatively underdeveloped compared to other cross-coupling reactions. In this thesis, it is demonstrated that bench stable Palladium N-Heterocyclic Carbene (NHC) precatalysts of the general type [(NHC)Pd(allyl)Cl] are highly active in the Hiyama cross-coupling of activated aryl chlorides with low catalyst loading. Notably, this research demonstrates that catalysts featuring sterically less demanding NHCs display higher activity in this reaction, which contrasts with other cross-coupling reactions. Preliminary mechanistic investigations including *in situ* reaction monitoring by ^{19}F NMR spectroscopy have uncovered side reactions. These side reactions may explain the low catalytic performance observed with unactivated substrates. These studies could help to further develop this reaction and improve catalytic performance. Additional investigations have also been made into ligand development by altering the electronics of sterically hindered NHC ligands for use in other cross-coupling reactions.

Acknowledgements

I would like to begin by thanking my supervising professor, Dr. Eric Keske. I learnt something new everyday under your mentorship. Your guidance through my studies was indispensable. I am very appreciative for the knowledge that you have bestowed upon me. I will always remember cleaning up after you and moving labs multiple times, being your first honours and master's student. And I know that deep down you love country music and mayonnaise. Keep the Futurama and Simpsons references alive. I never understood them, you tried your best and you failed miserably. The lesson is, never try.

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completing in the lab. You felt like the little brother of the lab group, and you were so motivated to dive into everything new that you took on.

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List of Abbreviations and Symbols

Ac	Acetyl
acac	Acetylacetonate
Ad	adamantyl
Bu	butyl
^{o}C	Celsius
C-C	carbon-carbon
cat.	catalytic amount
dba	dibenzylideneacetone
DME	dimethoxyethane
DMF	N,N'-dimethylformamide
DMPE	1,2-bis(dimethylphosphanyl)ethane
DMSO	dimethyl sulfoxide
DPPP	1,3-bis(diphenylphosphanyl)propane
equiv.	equivalent(s)
Et	ethyl
EtOH	ethanol
GC-MS	gas chromatography-mass spectrometry
HRMS	high resolution mass spectrometry
hr(s).	hour(s)
Hz	hertz
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
*i*Pr	isopropyl

IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IPr*	1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazo- 2-ylidene
IR	Infrared spectroscopy
J	coupling constant
K	kelvin
L	ligand
Me	methyl
MeOH	methanol
Mes	2,4,6-trimethylphenyl
min	minute
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
NR	no reaction
PEPPSI	Pyridine Enhanced Precatalyst Preparation Stabilization and Initiation™
Ph	phenyl
ppm	parts per million
RT	room temperature
SIMes	1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene
SIPr	1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene
O*t*Am	t-amylate
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBA	tetrabutyl ammonium
TBAF	tetrabutyl ammonium fluoride

*t*Bu	*tert*-butyl
TFT	trifluorotoluene
THF	tetrahydrofuran
TLS	turnover limiting step
XRD	x-ray diffraction

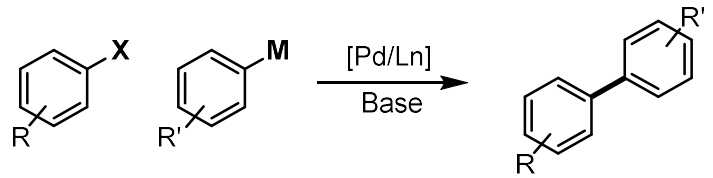
Chapter 1. Introduction to Cross-coupling, Palladium, and N-Heterocyclic Carbenes

1.1 Transition Metal Cross-coupling Reactions: An Overview

The development of cross-coupling reactions which generate biaryl products has been a major landmark in synthetic organic chemistry.[1] Without the use of cross-coupling reactions, biaryl compounds can be very challenging to synthesize by conventional means. As these moieties are prominently featured in the structure of many pharmaceuticals, drug development and discovery has been heavily dependent on cross-coupling reactions.[2]

Because of this, the development of reactions involving the formation of carbon-carbon (C-C) bonds are a significant area of study in synthetic chemistry. As organic molecules are composed largely of carbon, C-C bond forming methods can lead to new synthetic avenues ultimately pushing the limits of what can be accomplished within the scientific community.

Some of the most effective examples of C-C bond formation are transition metal catalyzed cross-coupling reactions. These reactions are completed with the use of an aryl halide or pseudohalide and an aryl organometallic nucleophile, in the presence of a base and a transition metal catalyst, often palladium (Scheme 1-1).[3]



X = I, Br, Cl
M = MgBr, $B(OH)_2$, $Si(OMe)_3$

Scheme 1-1. *General transition metal catalyzed cross-coupling reaction.*[3]

Using a transition metal catalyst, the biaryl products can be generated from precursors that would otherwise represent a significant synthetic feat in the absence of the catalyst.[3] Numerous ligands which coordinate to the metal catalyst have been demonstrated to modify the properties of the metal, ultimately affecting catalytic activity of the metal species throughout the reaction (Figure 1-1). For example, electron-rich and sterically bulky ligands such as phosphines and N-Heterocyclic Carbenes (NHCs) have been demonstrated to be very active in most cross-coupling reactions (Figure 1-1).[3]

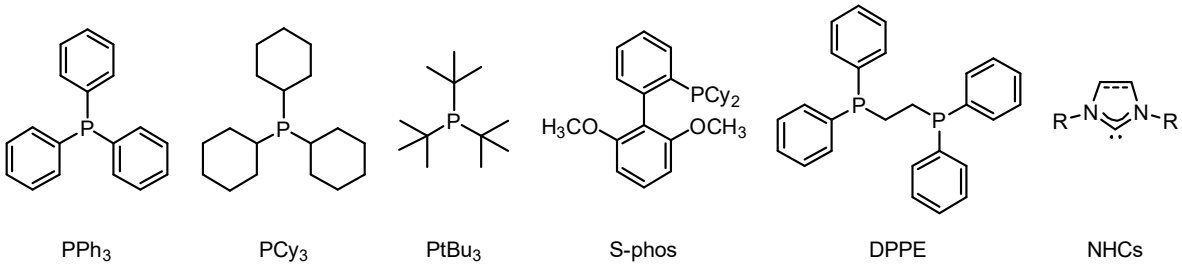
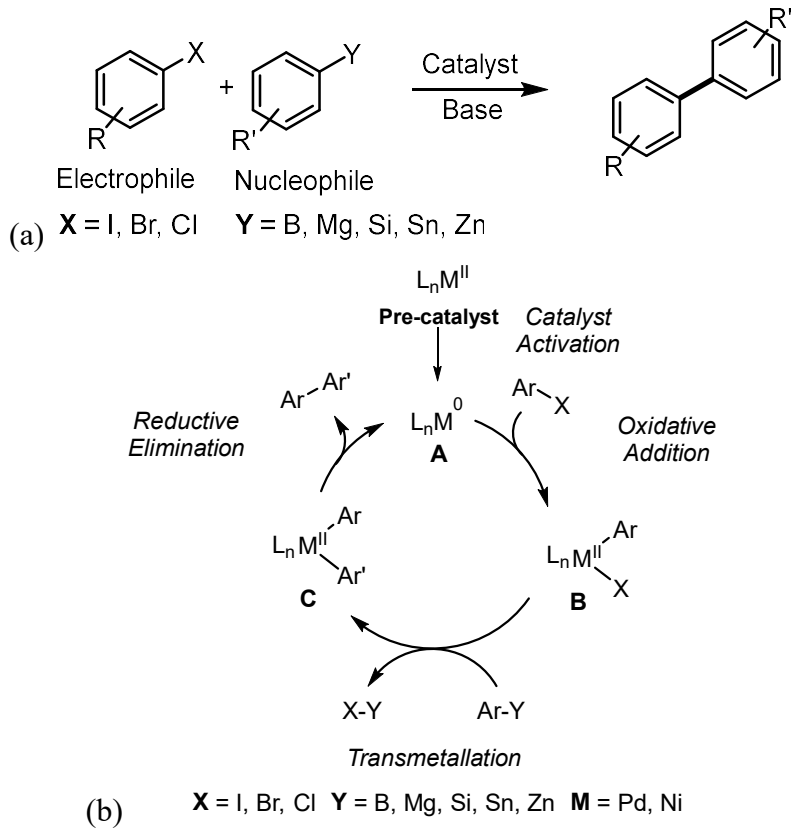


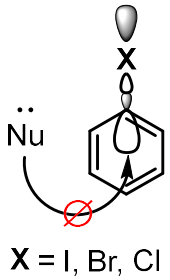
Figure 1-1. *Common ligands used in cross-coupling reactions (R = alkyl, aryl).*[3]

The catalytic cycle of a general cross-coupling reaction is displayed in Scheme 1-2. Upon activation of a pre-catalyst, the active palladium(0) (or nickel) catalyst **A** is generated *in-situ*.[3,4] Oxidative addition of an aryl halide results in a palladium(II) intermediate, **B**.[3,4] Through transmetallation with an organometallic reagent, a second aryl group is transferred to the palladium center resulting in intermediate **C**.[3,4] Depending on the specific reaction, the base is typically involved in the transmetallation step. Lastly, through reductive elimination, the final product is released regenerating the active catalyst **A**.[3,4]



Scheme 1-2. *(a) Standard cross-coupling reaction and (b) the catalytic cycle of a standard cross-coupling reaction.*[3,4]

Aryl halides are incompatible as electrophiles in many organic reactions making the synthesis of biaryl compounds very challenging. For example, sp^2 hybridized electrophiles, such as aryl halides, cannot be used in S_N2 reactions due to the alignment of the σ*-antibonding orbital in sp^2 hybridized carbon systems.[4] An incoming nucleophile is hindered by the ring structure and cannot attack the σ* orbital of the electrophile carbon-leaving-group bond (C-X) as displayed in Scheme 1-3.[4]

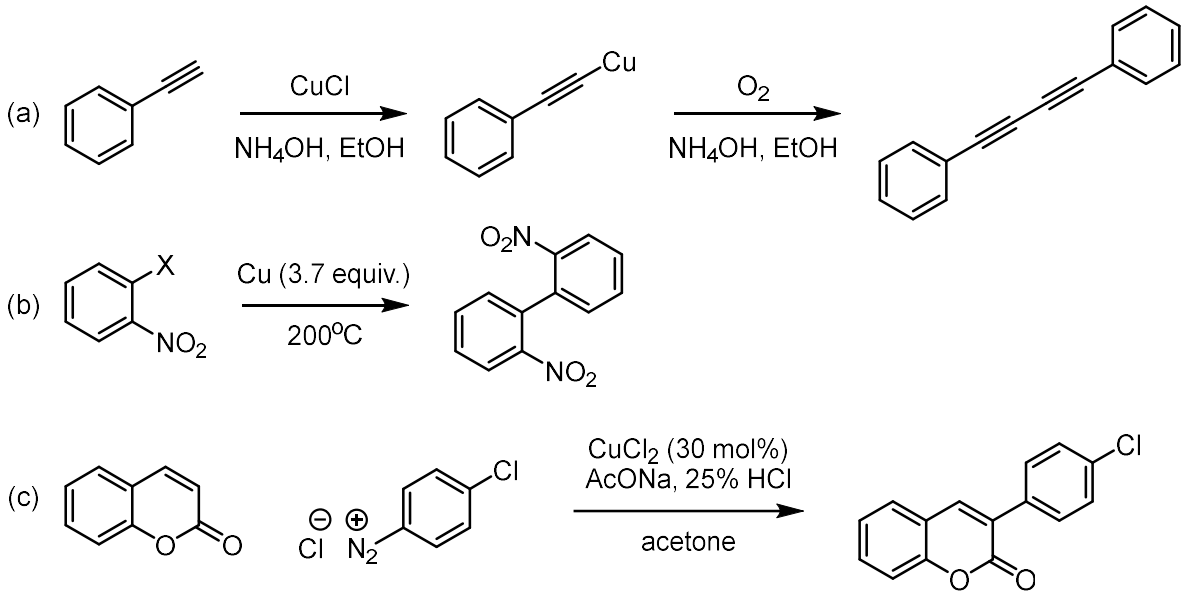


Scheme 1-3. *Inaccessible nucleophilic attack on the anti-bonding σ* orbital of an aryl halide electrophile.*

In contrast, in cross-coupling reactions the palladium(0) catalyst is capable of activating an aryl halide through an oxidative addition mechanism giving facile access to their use as electrophiles.[3] By using a palladium catalyst we can effectively overcome the limitations of sp^2 hybridized species for use as electrophiles in substitution reactions. As a result, cross-coupling reactions have been a groundbreaking achievement in the field of synthetic chemistry.[3,5]

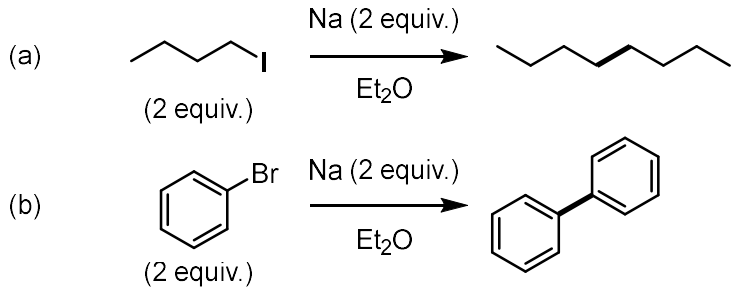
1.1.1 Transition Metals in Cross-coupling.

Early investigations into transition metal coupling reactions involved the use of copper catalysts when, in 1869, Glaser performed a homo-coupling reaction between different copper acetylides to form new *sp*-*sp* C-C bonds (Scheme 1-4a).[6,7] The Glaser coupling paved the way for a multitude of coupling reactions. It was followed by the copper-mediated Ullmann homo-coupling reaction in 1901, that capitalized on the foundation of the Glaser coupling, instead utilizing aryl halides to form new sp^2-sp^2 C-C bonds (Scheme 1-4b).[8] In 1939, Meerwein was then able to demonstrate the use of copper catalysts in sp^2-sp^2 C-C bond forming cross-coupling reactions between aryl diazonium salts and coumarin (Scheme 1-4c).[9]



Scheme 1-4. *(a) Glaser,[6,7] (b) Ullmann[8] and (c) Meerwein's[9] coupling utilizing copper.*

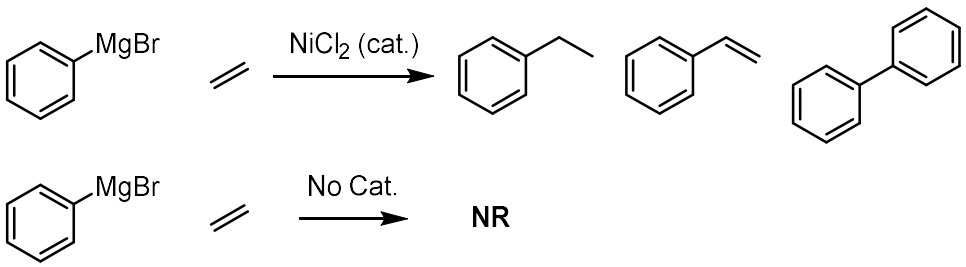
Independently, in 1855 and 1862, Wurtz[10] and Fittig,[11] respectively, developed chemistry that utilized metallic sodium in coupling. Wurtz displayed homo-coupling that resulted from the use of metallic sodium towards alkyl halides resulting in the formation of sp^3-sp^3 C-C bonds (Scheme 1-5a). Fittig displayed homo-coupling of aryl halides with the same metallic sodium chemistry resulting in the formation of sp^2-sp^2 C-C bonds (Scheme 1-5b).



Scheme 1-5. *(a) Wurtz[10] and (b) Fittig[11] utilizing metallic sodium.*

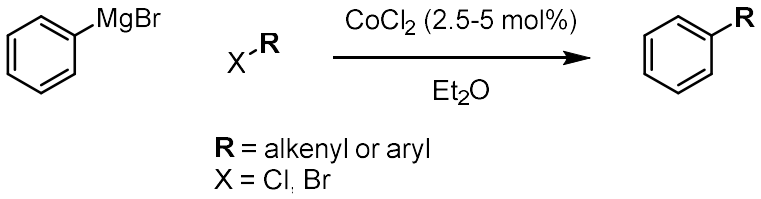
This later inspired the development of reactions without the use of metallic sodium or potassium to avoid the harsh conditions that accompanied these reagents. The

employment of Grignard reagents came underway in 1914 by Bennett and Turner for the formation of sp^2-sp^2 C-C bonds.[12] Furthermore, in 1923 Job[13] utilized nickel dichloride paired with Grignard reagents to study the use of nickel as a catalyst in cross-coupling reactions. This was the first demonstration of nickel reported in the synthetic formation of C-C bonds (Scheme 1-6).



Scheme 1-6. *Job's proof of concept utilizing nickel.*[13]

This later evolved into the work of Kharasch, who in 1941,[14] reported the successful cross-coupling of a Grignard reagent with aryl and alkenyl halides with the use of a cobalt catalyst, demonstrating the first use of cobalt in a cross-coupling reaction (Scheme 1-7).

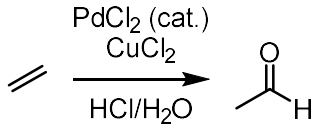


Scheme 1-7. *Kharasch's cross-coupling utilizing cobalt.*[14]

With the foundation built by Job, Meerwein, and Kharasch, investigations into the development of transition metal catalyzed cross-coupling reactions have exponentially grown. While there have been reports of catalytic systems featuring copper, nickel, and cobalt, this thesis will focus on palladium catalyzed cross-coupling reactions which has been the most extensively studied metal in these reactions.

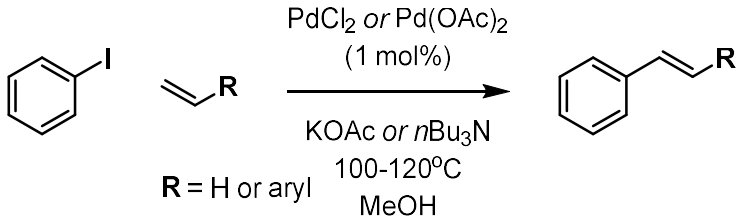
1.1.2 Palladium in Cross-coupling reactions

From 1968 to 1972, reports by Heck and Mizoroki would influence research in organopalladium chemistry throughout history. Heck capitalized on the Wacker process that was developed in 1959 (Scheme 1-8).[15]



Scheme 1-8. *The Wacker Process.*[15]

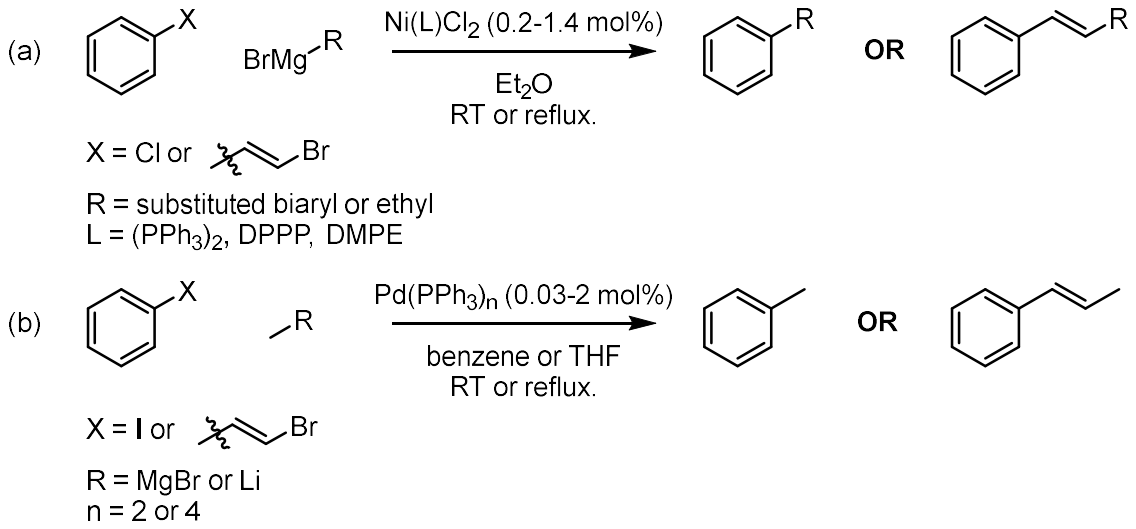
The Wacker process was the first display of palladium in catalysis on an industrial scale. The Wacker process involves the formal addition of H_2O across an alkene utilizing a palladium catalyst system. As such, the Pd is directly involved in the addition to the π-system of the alkene. The Mizoroki-Heck reaction expands upon this foundation instead resulting in the formation of a new C-C bond across the alkene. (Scheme 1-9).[16–26] The Mizoroki-Heck reaction utilizes a palladium catalyst to cross-couple an sp^2-hybridized organohalide with an alkene in the presence of a base. The Mizoroki-Heck reaction is commonly credited as the first palladium-catalyzed cross-coupling reaction reported.



Scheme 1-9. *Mizoroki-Heck cross-coupling.*

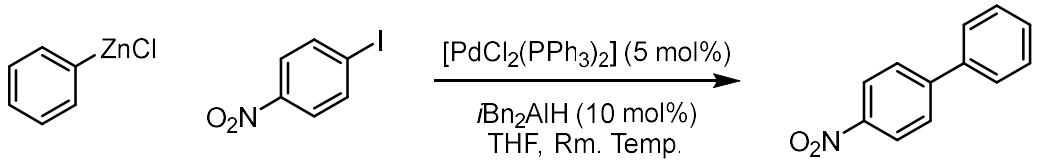
Another reaction that played a key role in the development of palladium catalysts for use in C-C bond forming reactions was the Corriu-Kumada cross-coupling reaction. In 1972, this report explored the use of nickel as a catalyst,[27] but the reactivity of the nickel

catalyst was fine-tuned for higher activity with the use of phosphine ligands.[28–30] This established new methods of control over the reactivity of transition metal catalysis in cross-coupling reactions. Further research into the Corriu-Kumada cross-coupling reaction revealed that the use of a palladium catalyst provided a broader substrate scope with aryl bromide and iodide substrates. Similarly, these palladium catalysts could be fine-tuned with the use of ligands, such as phosphines, to improve the activity of the catalyst without sacrificing substrate selectivity (Scheme 1-10).[31–34]



Scheme 1-10. *Corriu-Kumada cross-coupling utilizing (a) nickel and (b) palladium.*[28–34]

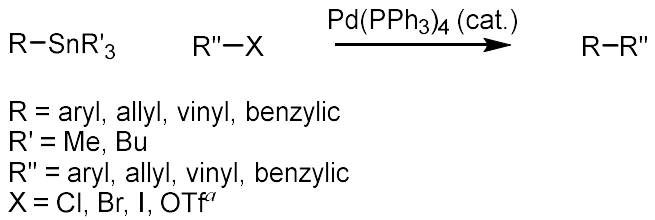
Further investigations into the Corriu-Kumada reaction were conducted by Negishi and coworkers in 1976. This report broadened the scope of organometallic partners by utilizing organozinc reagents (Scheme 1-11).[35]



Scheme 1-11. *Negishi cross-coupling utilizing palladium.*[35,36]

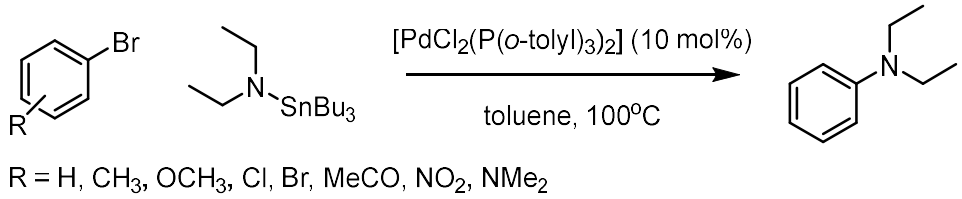
Palladium precatalysts were also reported in place of nickel in the cross-coupling with organoalanes.[34] After Negishi's report, came a flood of experimentation around alterations

to the organometallic coupling partner. In 1978, the conclusions drawn from the work of Migita[37–39] influenced Stille and coworkers to develop a reaction that was compatible with a broad range of functional groups. This was accomplished by instead using organostannanes as the organometallic nucleophilic component. In terms of functional group compatibility, the air and moisture stability of the organostannanes represents a large advancement. This is especially true when compared to the use of air and moisture unstable organometallic cross-coupling partners, as in Grignard reagents in the Kumada and organozinc reagents in the Negishi. Reactions which utilize organostannanes are commonly referred to as Migita-Stille cross-coupling reactions (Scheme 1-12).[40,41]



Scheme 1-12. *Migita-Stille cross-coupling.* [41]
[a]With LiCl

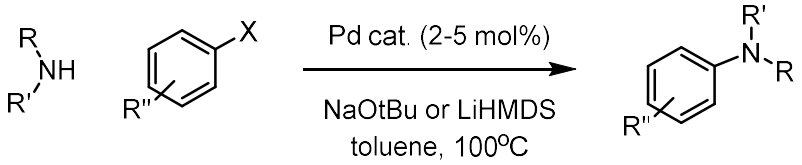
Similarly, Migita[42] reported the successful use of tin amides in C-N bond forming reactions utilizing a palladium catalyst. This was the first reported palladium catalyzed C-N bonding forming reaction (Scheme 1-13). While monumental in discovery, the utility of toxic tin-based reagents clearly represents a problem from the perspective of practicality.



Scheme 1-13. *Migita's amidostannane cross-coupling.*[42]

Buchwald[43] and Hartwig[44] independently reported in 1995 that the amidostannane reagent from Migita's work could be replaced with a secondary amine in the presence of a

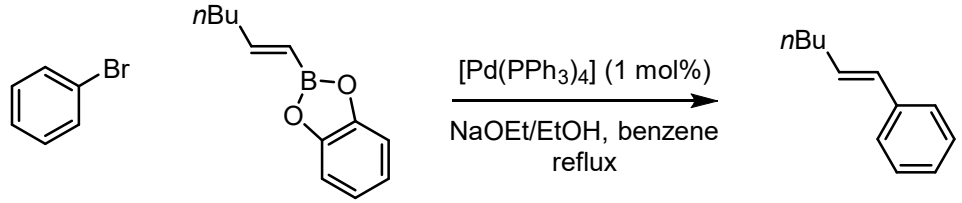
strong base such as either NaOtBu or LiHMDS. This led to the ability to generate C-N bonds in a highly selective manner without the use of highly toxic and environmentally dangerous tin reagents (Scheme 1-14).



Scheme 1-14. *Buchwald-Hartwig amination*.[43,44]

Similarly, the high level of toxicity associated with the tin-based reagents utilized in the Migita-Stille cross-coupling reaction, and the air-sensitivity of Grignard and organozinc reagents led to interest in developing reactions utilizing less toxic and more robust organometallic coupling partners under milder reaction conditions.

In 1979[45] Suzuki and Miyaura reported the successful C-C bond forming cross-coupling reaction featuring an organohalide and an alkenylborane. The alkenylboranes were readily available from hydroboration of alkynes, and represented a much more user friendly, and less toxic alternative to previous methods (Scheme 1-15). Key to the success of this reaction was the use of a base to help activate the organoboron reagent, as it was originally hypothesized that a four-coordinate boronate reagent would have increased nucleophilicity. This reaction has been further adapted and extended towards the use of convenient and bench stable phenylboronic acids under notably milder conditions than previously reported cross-coupling reactions.[46,47]

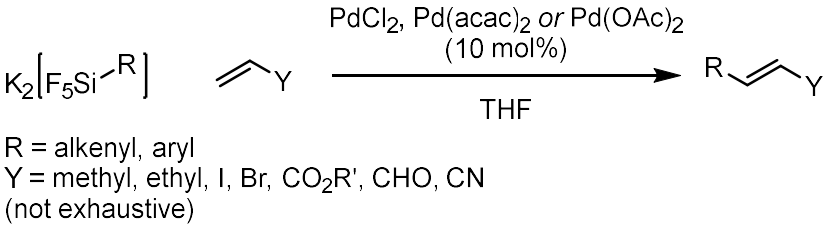


Scheme 1-15. *Suzuki-Miyaura cross-coupling.*[46,47]

From this, the Suzuki-Miyaura reaction has become one of the most well-known and commonly utilized cross-coupling reactions in the scientific community. The Suzuki-Miyaura reaction is particularly attractive by virtue of the increased air-stability of the reagents when compared to those utilized by Negishi, as well as the decrease in toxicity of the reaction compared to the Stille reaction.[46,47] Of particular note as well, the Suzuki-Miyaura reaction has remarkable functional group tolerance due to the mild nature of the organoboron nucleophiles.

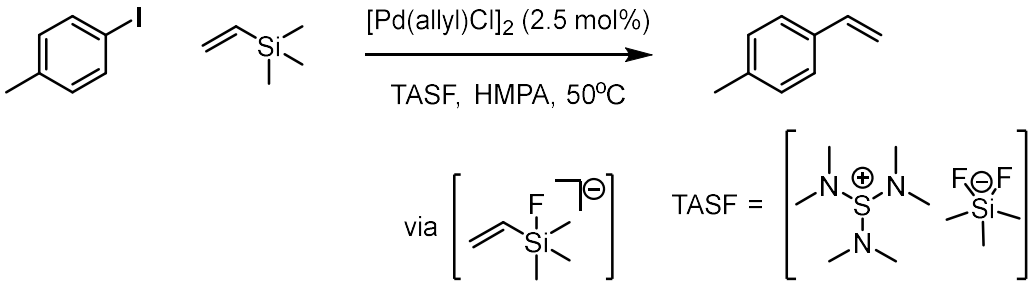
The era of less toxic reagents was afoot especially towards the development of organometallic coupling partners. In 1975, Matusomoto reported the cross-coupling of disilane compounds for the preparation of aryl silane derivatives. This was an important transformation as it not only gave access to aryl trialkylsilanes, it also demonstrated the possibility of using organosilicon derived nucleophiles in cross-coupling reactions.[48] Organosilicon reagents are particularly sought after due to their high degree of stability, along with their low toxicity. This report was further important as coupling of the aryl trialkylsilane product was not observed under the reaction conditions, indicating that aryl trialkylsilanes are not sufficiently nucleophilic to transmetallate to the catalyst. The lack of reactivity of aryl trialkylsilane under these conditions is likely an indication of their low nucleophilicity derived from the less polarized C-Si bond. Further developments into the use of silicon analogs as a possible organometallic cross-coupling partner would not be demonstrated for almost another decade. It was not until 1982 when Kumada[49] displayed

the cross-coupling of organopentafluorosilicates in palladium cross-coupling reactions (Scheme 1-16).



Scheme 1-16. *Kumada utilizing silicon analogs.*[49]

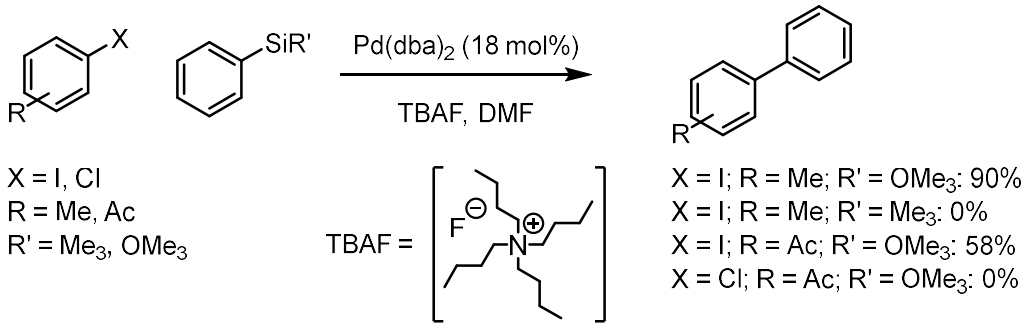
In 1988, from the work of Kumada, Hiyama demonstrated that the activation of the organosilane cross-coupling partner could be accomplished via the addition of a fluoride base such as TASF tris(diethylamino)sulfonium difluorotrimethylsilicate (Scheme 1-17).[50]



Scheme 1-17. *Hiyama cross-coupling.*[50]

In the absence of a fluoride, no product formation was observed, and it was postulated that the fluoride was necessary to activate the silicon-organometallic cross-coupling partner towards transmetallation by the formation of an intermediate silicate.[50,51]

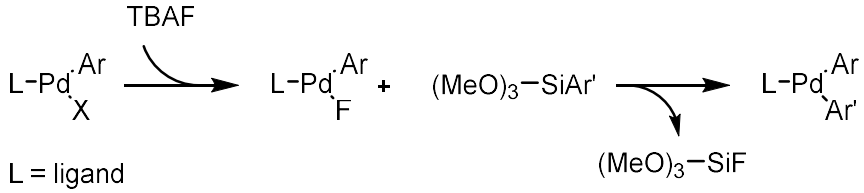
Further research into the use of organosilicon derivatives resulted in the use of trialkoxyphenylsilanes in the Hiyama reaction from the work of DeShong in 1999.[52] This research demonstrated the increased nucleophilicity of the trialkoxyphenylsilanes when compared to their trialkylphenylsilane counterparts (Scheme 1-18).[52]



Scheme 1-18. *DeShong's employment of phenylalkoxysilanes.*[52]

DeShong also demonstrated the limitations of the Hiyama reaction with the absence of product formation when utilizing aryl chlorides as opposed to their aryl iodide counterparts (Scheme 1-18).[52]

In 2014, Jutand[53] and coworkers demonstrated that a fluoride-mediated metathesis occurred pre-transmetallation (Scheme 1-19). They also displayed that transmetallation appeared to occur via the 4-coordinate trialkoxyphenylsilane, as opposed to a hypervalent silicon species. It was therefore hypothesized to operate through a 4-membered transition state with a Pd-F bond. The driving force for the transmetallation was therefore the formation of the thermodynamically stable Si-F bond (Scheme 1-19).[53]



Scheme 1-19. *Salt metathesis forming a Pd-F bond, followed by transmetallation.*

Due to the low toxicity and low environmental impact of organosilicon reagents, the Hiyama cross-coupling reaction provided an alternative to the previously utilized organometallic cross-coupling partners from the Negishi, Migita-Stille, and Suzuki-Miyaura cross-coupling reactions. As such, the Hiyama reaction is an attractive cross-coupling reaction with the potential to have a large impact on the scientific community.

But, in comparison to the Suzuki-Miyaura, Mizoroki-Heck, Corriu-Kumada, Negishi, and Migita-Stille cross-coupling reactions, the Hiyama reaction is relatively underdeveloped.

Improvements to cross-coupling reactions then shifted from the organometallic coupling partner to the ligands bound to the metal of the catalyst to help improve catalyst efficiencies and activity. As previously stated, Kumada displayed the use of phosphines as ligands in nickel and palladium catalyzed cross-coupling reactions which demonstrated the influence that the ligand could have on the formation of product in the reaction.[27–30]

1.2 N-Heterocyclic Carbenes: An Overview

Historically, phosphines have been heavily utilized as ligands in many forms of late transition metal catalysis.[1,54–56] This is largely due to the ability of phosphines to stabilize homogeneous transition metal species, while imparting tunable properties to the catalyst. As a result of their heavy usage, a wide variety of different phosphines are commercially available as well. A major downfall of these ligands is that they tend to be air-sensitive as well as an increased degradation of the P-C bond at higher temperatures.[57] Extensive developments dedicated to improving activity and efficiency of the catalytic systems in cross-coupling reactions have also centered around the usage of N-Heterocyclic Carbenes (NHCs) in these reactions.

Carbenes are neutral divalent carbons that have six valence electrons[58] which can exist in either a singlet state or a triplet state.[59] The multiplicity of carbene differs by the spins and the orbital occupancy of their valence electrons. A singlet carbene has two paired valence electrons occupying the same orbital (consisting of opposing spins), whereas a triplet carbene has two unpaired valence electrons occupying distinct orbitals (consisting

of the same spin).[59] As such, the chemical reactivity of singlet and triplet carbenes are diametrically opposed due to their electron configurations. Specifically, triplet carbenes tend to be electrophilic in nature, and singlet carbenes tend to be nucleophilic in nature (Figure 1-2).

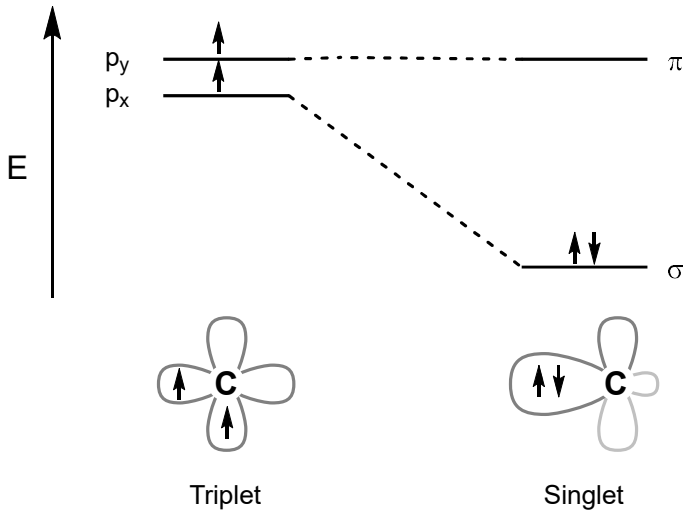
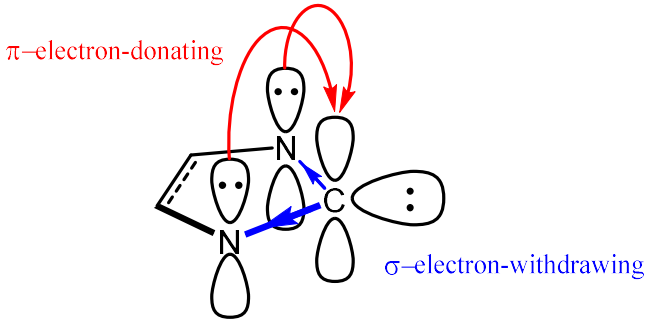


Figure 1-2. *Triplet and singlet carbene carbons.*

NHCs exist as singlet carbenes, and different properties of the NHC can be observed through inductive and mesomeric interactions influenced by the backbone substituents as well as the nitrogen atoms flanking the carbene carbon (Scheme 1-20).[58]



Scheme 1-20. *Nitrogen-carbene interactions through π-donation (red) and σ-withdrawal (blue).*[60]

This is done through the ability of each nitrogen to electronically stabilize the carbene-carbon through mesomeric interactions from their pi-electrons donating into the empty sp^2-

hybridized orbital (often called the p-pi orbital) of the carbene-carbon. As well as the inductive effects of the nitrogens: from the s-orbital of the carbene-carbon back to the flanking nitrogen atoms. This provides a very promising scaffold for NHCs as ligands for transition metals (*vide infra*).[58]

The most common form of an NHC is an imidazole-derived heterocycle, where the nitrogen atoms are flanking either side of a carbene-carbon within the ring. Many variations on this theme have been reported. The NHC backbone can be saturated, unsaturated, or be based on a different heterocycle. The N-substituents or "wing-tip" groups may also come in many different forms (Figure 1-3).[58]

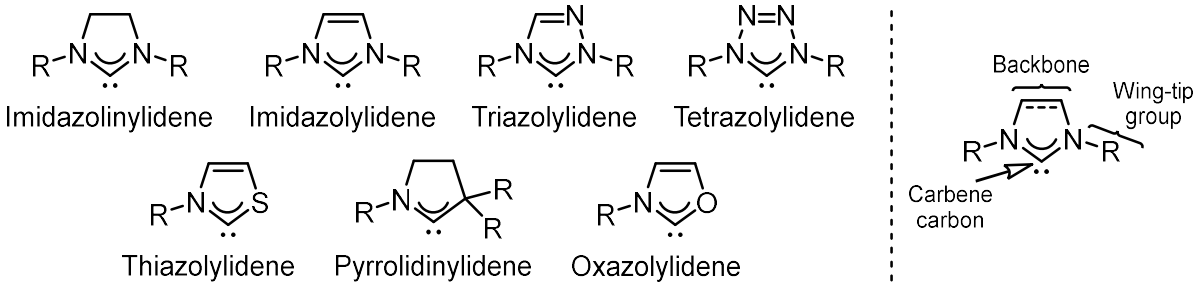
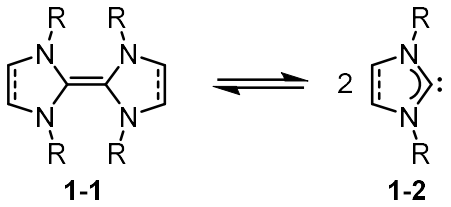


Figure 1-3. *Common carbene structure with structural labelling.*

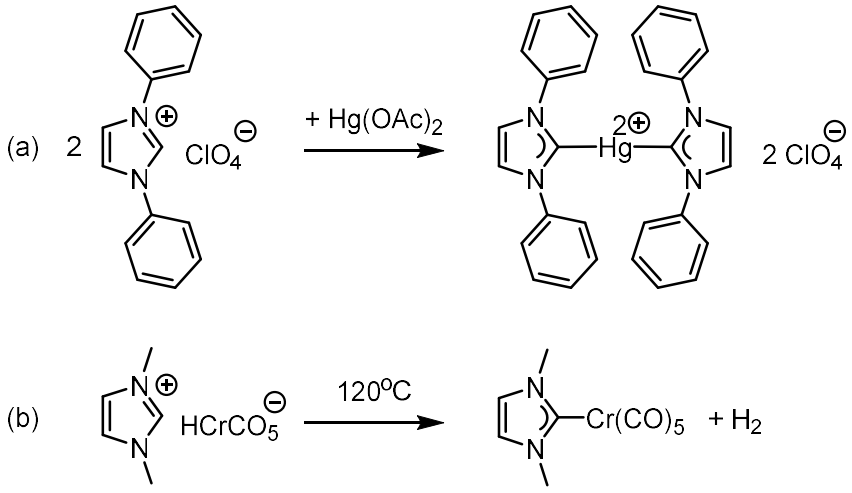
The electronic and steric effects of an NHC can be altered by various structural modifications.[61] Utilizing smaller wing-tip groups impart less steric shielding to the carbene and may result in a decrease in kinetic stability of the free carbene when compared to bulkier NHCs. The opposite effect would be displayed with larger wing-tip groups.[61] The kinetic stability of an NHC is due to the Wanzlick equilibrium.[62] When an NHC has smaller wing-tip groups, the Wanzlick equilibrium kinetically favours the dimerized enetetramine by coupling of two equivalents of carbene, **1-1**. By introducing larger wing-tip groups, the carbene is stabilized and therefore, the Wanzlick equilibrium favours the free NHC (**1-2**, Scheme 1-21).



Scheme 1-21. *The Wanzlick equilibrium.*[63]

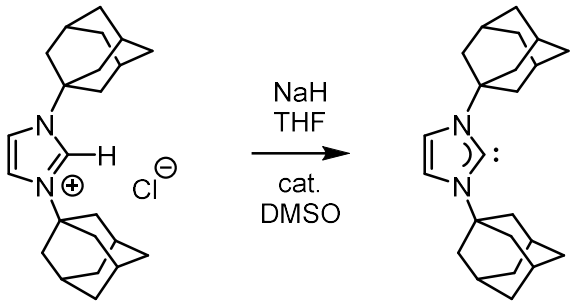
1.2.1 Discovery of N-Heterocyclic Carbenes

Over the past century, there have been many reported attempts to synthesize and isolate free carbenes, only to be met with failure.[64] Free carbenes have short lifespans, thereby making their initial utility in organic chemical synthesis as reactive intermediates.[65,66] Because of their reactivity and short lifespan, methods to isolate stable free carbenes were extremely slow to develop. The first investigations into more stable carbenes, was conducted by Wanzlick and coworkers in 1962 where they suggested an *in situ* synthesis and trapping of the free carbene.[67] Following Wanzlick's practical proposal, in 1968, Wanzlick and Öfele independently investigated NHCs as ligands in metal complexes (Scheme 1-22).[68,69]



Scheme 1-22. *(a) Wanzlick*[68] *and (b) Öfele's reported complexes involving NHCs.*[68,69]

While Wanzlick and Öfele demonstrated the existence and viability of NHCs as reactive species *in-situ*, NHCs were not isolated in their free form until Arduengo reported the first crystal structure of a free NHC in 1991.[66] This report was monumental in confirming the improved electronic stability of the carbene imparted from the heterocyclic ring as Wanzlick[67] hypothesized. Additionally, the isolation of this species also helped to confirm the Wanzlick equilibrium as an increased kinetic stability was demonstrated due to the steric bulk of the adamantyl substituents that he employed as the wingtip groups (Scheme 1-23).[66]



Scheme 1-23. *Arduengo's free NHC synthesis.*[66]

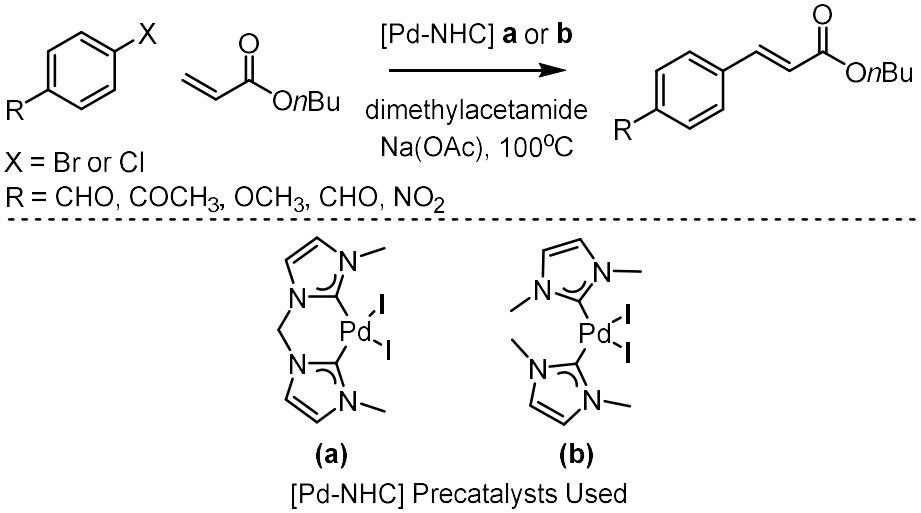
Arduengo proposed that the adamantyl groups were necessary for the isolation of the free carbene, as previous works had demonstrated that the isolation of the NHC was not achievable with sterically less hindered wingtip groups.[62] This was a display of the shielding effects that the steric wing-tip groups have on the carbene-carbon.[66] Nonetheless, despite their increased stability, free NHCs still display a high sensitivity to air and moisture making their handling challenging.[66,70,71]

Upon the demonstration of NHCs as ligands for transition metals, and their isolation as free species, NHCs were initially viewed as mere phosphine mimics.[55] Because of the decreased toxicity compared to phosphines, NHCs were viewed as appropriate substitutes.[55] However, the unique steric and electronic parameters of NHCs compared to

phosphines have rendered these species as complementary to phosphines in catalysis (*vide infra*).

1.2.2 N-Heterocyclic Carbenes Utilized in Cross-coupling Reactions

After Arduengo's isolation of a free NHC, Herrmann was the first to demonstrate that NHC metal complexes were active in catalysis in 1995 (Scheme 1-24).[72] Specifically, Pd-NHC precatalysts were found to be active in the Heck reaction of aryl halides at high temperatures. Since Herrmann's demonstration, there has been extensive research that has contributed to the development of NHCs as ligands in cross-coupling reactions.

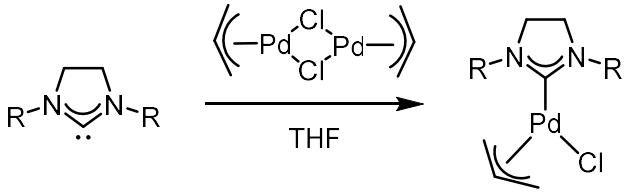


Scheme 1-24. *Herrmann's first display of NHCs in catalysis.*[72]

The high bond dissociation energy between an NHC and a metal is attributed to the strong σ-donor capabilities of the NHC.[55] This allows for the carbon-metal bond to be more chemically and thermally inert to cleavage.[73] Following the work by Arduengo and Herrmann, *in situ* generation of a Pd-NHC catalyst was accomplished by Nolan[74] in 1999. This was a convenient display of the ability for an *in situ* generated free-carbene to form and attack the palladium metal to form the complex that would further react in the Suzuki-

Miyaura cross-coupling reaction. His optimized system utilized IMes-HCl, $Pd_2(dba)_3$, and a weak base to cross-couple aryl chlorides with aryl boronic acids.

Nolan further displayed the utility of NHCs in cross-coupling reactions by synthesizing preformed species of general formula [(NHC)Pd(allyl)Cl] with several known NHC ligands in 2002.[75] Nolan described the synthesis of these species by treatment of $[Pd(allyl)Cl]_2$ with the free NHC, which required the use of a glove box to keep the free NHC under an inert atmosphere, protecting it from decomposition (Scheme 1-25).[75,76] He also found that at lower temperatures, the larger sterically hindered Pd-NHC complexes achieved greater yields in catalysis than the smaller less sterically hindered complexes.

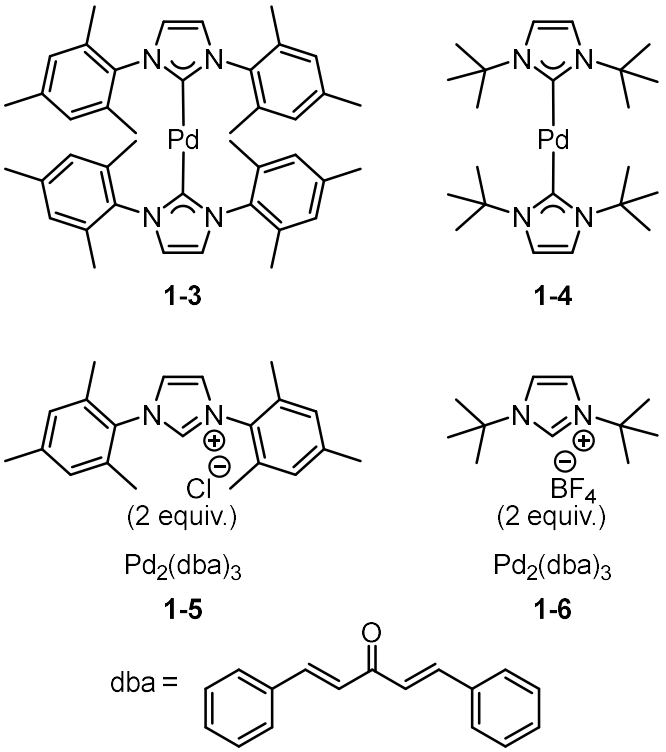


Scheme 1-25. *Nolan's free-NHC synthesis of [(NHC)Pd(allyl)Cl] complexes; IMes, ItBu, IPr, SIPr, IAd.*[75]

Isolating the free-NHC is not trivial, and as such many researchers have utilized *in situ* methods to generate desired precatalysts for catalytic reactions instead using the NHC-HCl salt. But, if the catalyst is synthesized *in situ*, the exact nature of the catalyst structure is ambiguous.[77] By instead using the preformed complex vs. the *in situ* generated system in a cross-coupling reaction, one may assume to obtain similar results, but this is not always the case.

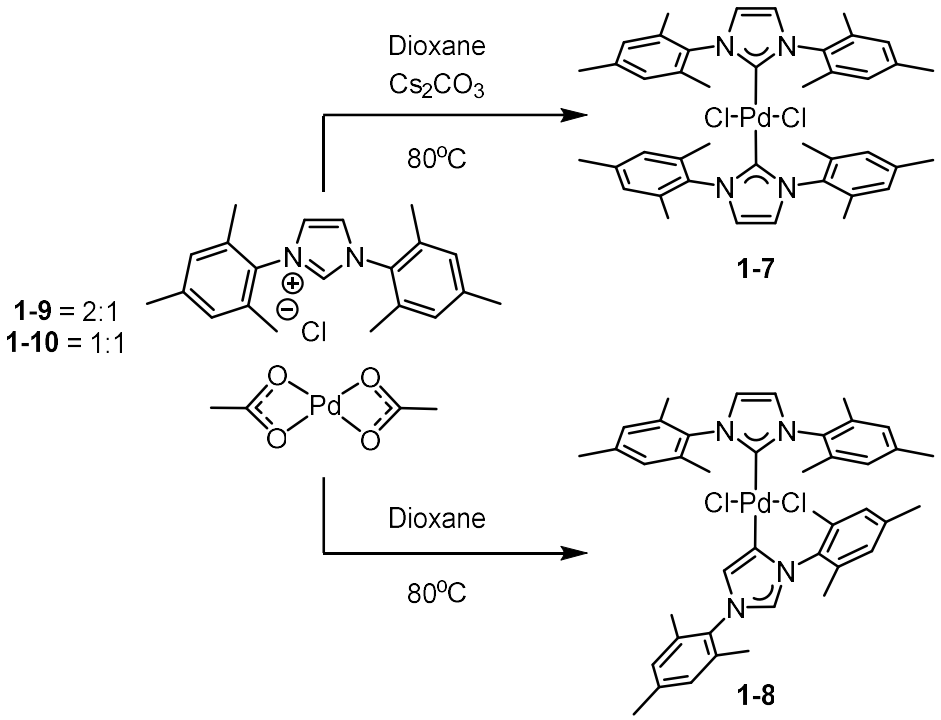
In 2000, assuming the bis(NHC) complex to be the active catalyst, Herrmann[78] synthesized and isolated the bis(NHC) complexes, **1-3** and **1-4**, and compared them to the *in situ* generated catalyst counterparts, **1-5** and **1-6**, in a Suzuki-Miyaura cross-coupling (Scheme 1-26). It was displayed that the preformed IMes-substituted NHC (**1-3**) had no

activity in the reaction, but the *in situ* generated counterpart (**1-5**) performed very well, and surprisingly, the opposite was observed with the *t*Bu-substituted NHC (**1-4** vs. **1-6**).[78]



Scheme 1-26. *Preformed catalysts **1**-**3** and **1**-**4** and in situ generated catalysts **1**-**5** and **1**-**6**.*[78]

In Nolan's work in 2004,[77] the preformed complexes, **1-7** and **1-8**, were synthesized and compared to their *in situ* counterparts at varying ratios of IMes-HCl and $Pd(OAc)_2$, **1-9** (2:1, respectively) and **1-10** (1:1). The expected compound **1-7** was formed in the presence of a base, but with the omission of base, an unexpected **1-8** was formed instead. Compound **1-8** displayed the Pd was coordinated to the expected C(2) position of one IMes ligand and the C(5) position of the other IMes ligand (Scheme 1-27).[77]



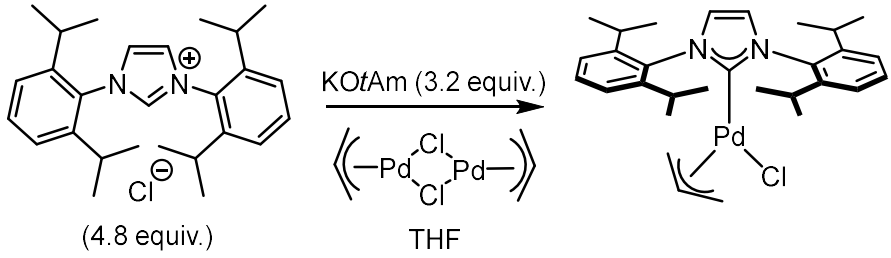
Scheme 1-27. *Synthesis of (a) **1-7** and **1-8** and (b) in situ generated catalysts **1-9** and **1-10**.*[77]

This was the first report of such a complex, which was supported by the ^{1}H NMR spectral data and single crystal XRD.[77] This brought up questions as to what the active catalyst was more likely to be, so experiments were conducted to compare the catalytic activity of **1-7** and **1-8** vs. *in situ* generated catalysts **1-9** and **1-10**. Surprisingly, the "unusual" complex **1-8** was deemed to be superior for the Suzuki-Miyaura and Mizoroki-Heck cross-couplings of aryl chlorides and aryl bromides, respectively. This result supported that the active palladium species was most likely a monoligated palladium complex, as the C(5) bound NHC could more easily dissociate from the palladium center.[77]

From the work of Herrmann and Nolan (*vide supra*), the importance of the conditions employed was demonstrated.[77] The unpredictability of the Pd-NHC synthesized *in situ* is notable. When comparing the two reports by Nolan[77] and Herrmann,[78] the seemingly contrasting results are foreshadowing. Where Nolan described that the preformed "unusual" catalyst was superior in the Suzuki-Miyaura cross-coupling,

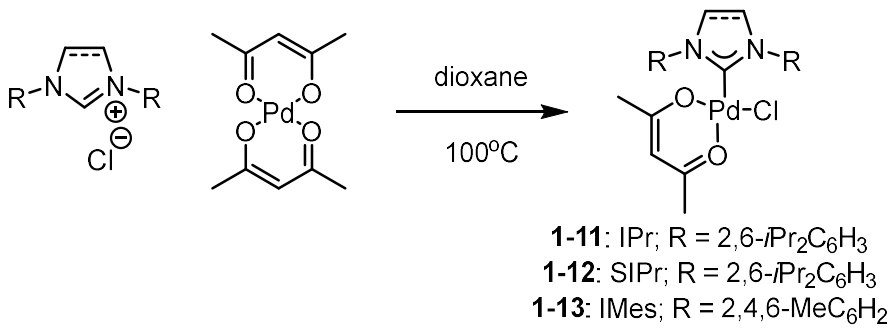
Herrmann described that the *in-situ* system was dominant. But, upon a closer view, the active catalyst in each research could be inferred as a monoligated Pd-NHC, and therefore their results were more similar than they anticipated.

Given the unpredictability of the NHC catalysts generated *in situ*, pre-formed and well-defined Pd-NHC complexes became attractive for use in catalysis. In 2004, Nolan[79] reported the synthesis for many [(NHC)Pd(allyl)Cl] type complexes. This procedure utilized the isolation of the free carbene as in Scheme 1-24, apart from one complex. For the synthesis of [(IPr)Pd(allyl)Cl] the NHC-HCl salt was utilized to determine the possibility of a one-pot procedure, which was successful (Scheme 1-28).



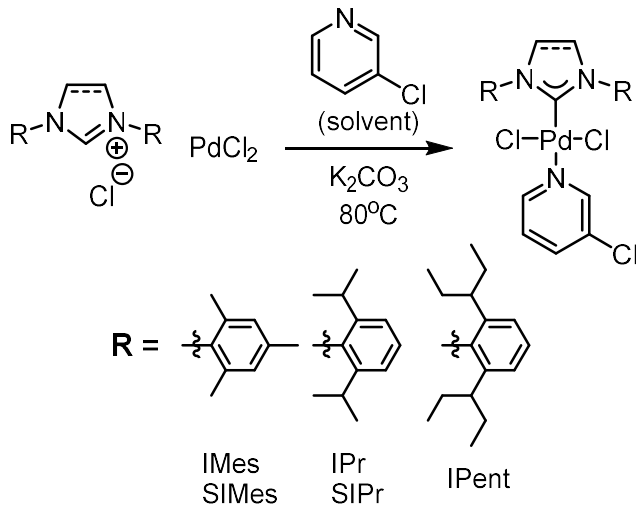
Scheme 1-28. *Nolan's development of a one-pot procedure for [(IPr)Pd(allyl)Cl].*[79]

In 2006, Nolan reported the synthesis for [(IPr)Pd(acac)Cl],[80] **1-11**, and later applied the same procedure for the synthesis of [(SIPr)Pd(acac)Cl],[81] **1-12**, and [(IMes)Pd(acac)Cl],[82] **1-13** (Scheme 1-29). This procedure not only avoided the use of the free NHC but could also be generated in a one-pot procedure.



Scheme 1-29. *Nolan's one-pot synthesis of [(IPr)Pd(acac)Cl],*[80] *[SIPr)Pd(acac)Cl],*[81] *and [(IMes)Pd(acac)Cl].*[82]

Independent and complimentary to Nolan, in 2006 Organ and coworkers reported the preparation of novel PEPPSI (Pyridine-Enhanced Precatalyst, Preparation, Stabilization, and Initiation) complexes. As pre-formed Pd-NHC precatalysts often require harsh conditions or inert atmospheres with anhydrous solvents, Organ and coworkers sought to develop a more robust and widely applicable method. Organ's goal was to develop a facile synthesis for a highly active, stable and easy-to-prepare-and-handle Pd-NHC complex.[83] These efforts resulted in the novel pre-formed PEPPSI complexes which displayed catalytic activity in a variety of different reactions, and the synthesis of the complexes appeared to be trivial when utilizing different NHCs (Scheme 1-30).[83] With a synthetic procedure for Pd-NHC precatalysts that displayed as facile, this was a very exciting development.

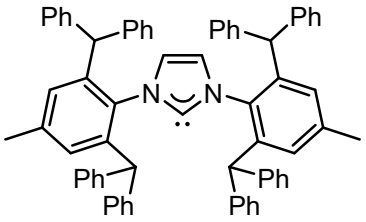


Scheme 1-30. *Synthesis of PEPPSI precatalysts.*[83]

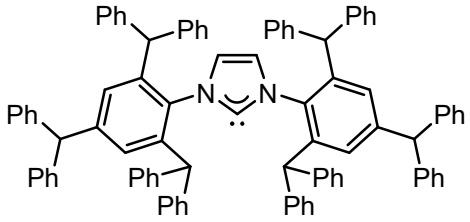
The development of the Pd-PEPPSI-IPent was introduced by Organ and coworkers in 2009.[84] The novel IPent ligand features larger, more sterically bulky wing-tip groups which provides the metal center with increased flexible steric bulk[85,86] relative to other NHC ligands that Organ[84] deemed beneficial for increasing the activity in cross-coupling.

In addition, in 2010 Marko[87] further increased the library of sterically bulky NHC ligands by reporting the synthesis of IPr* which utilized 2,6-(diphenylmethane)-4-methyl-phenyl wingtip groups. The increased electron-donor properties were also displayed when compared to other NHC ligands through the IR stretching frequency of a C=O-bound ligand in [Rh(IPr*)$(CO)_2$Cl].[87] Following this, in 2021, Szostak and coworkers[88] developed another sterically bulky ligand that implemented an additional diphenylmethane substituent in the *para*-position of the wing-tip group of IPr*-HCl, known as IPr#-HCl (Scheme 1-31). This ligand also displayed high promise as a ligand in catalysis through its electron donating properties as demonstrated by the IR spectrum monitoring of the C=O stretches of [Rh(IPr#)$(CO)_2$Cl].[88]

(a)



(b)



Scheme 1-31. *Sterically Bulkier Ligands: (a) IPr*[87] and (b) IPr#.*[88]

The utilization of flexible and sterically bulky ligand-containing complexes displayed as highly active in Buchwald-Hartwig aminations.[84–88] Further research into the use of Pd-NHC complexes is still being developed today to utilize their properties in cross-coupling reactions.

1.3 Research Objectives

From the abundant research around Pd-NHCs in cross-coupling reactions, their high activity was attractive for use as ligands in our cross-coupling reactions. It was also clear from the literature that the Hiyama cross-coupling reaction was highly underutilized in chemical synthesis. Therefore, investigations into the development of a new catalytic system for the Hiyama cross-coupling of aryl chlorides with trimethoxyphenylsilanes utilizing convenient, bench-stable, and easy to prepare Pd-NHC precatalysts which would have widespread use was a main objective of this thesis.

Chapter 2 describes our investigations into the Hiyama cross-coupling reaction, revealing unproductive side reactions that consume the organometallic cross-coupling partner. We endeavored to investigate the mechanism of this transformation through

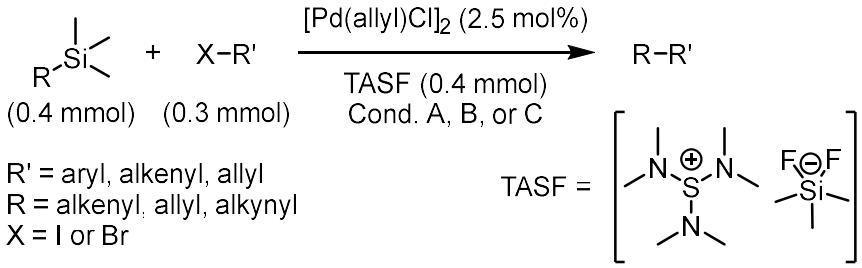
reaction monitoring by GC-MS and ^{19}F NMR spectroscopy. In future research, alterations to the organometallic cross-coupling partner to circumvent these side reactions would be attempted. From these studies, we also found that precatalysts bearing smaller NHCs preformed better in the Hiyama cross-coupling reaction under our reaction conditions. This was noteworthy as ample amount of literature speaks to the use of sterically larger ligands to obtain higher yields. Because of the inclination that larger ligands perform better in cross-coupling reactions, the synthesis of some novel electronically modified, sterically bulky Pd-NHC complexes were also investigated in Chapter 3. Completed in tandem with Chapter 2, Chapter 3 outlines multiple attempts to mimic literature procedures. After several attempts, we were finally able to synthesize a highly sought-after sterically bulky NHC ligand that we further electronically modified. In future research, these ligands would be investigated in the Buchwald Hartwig amination of aryl chlorides under mild conditions, as sterically larger ligand-bearing catalysts have been known to flourish. Furthermore, the electronically diverse functional groups installed into the NHC ligands would allow us to determine what effects these groups have on catalytic activity in this reaction.

Chapter 2: Investigations into the Pd-NHC Catalyzed Hiyama Cross-Coupling Reaction of Aryl Chlorides

2.1. Hiyama Cross-coupling Reaction

As mentioned previously, the development of transition metal catalyzed cross-coupling reactions has been invaluable within synthetic organic chemistry. While a variety of different cross-coupling reactions have been reported to date, several of these reactions require the use of air and moisture sensitive organometallic reagents such as Grignard reagents in the Corriu-Kumada coupling, or organozinc reagents in the Negishi coupling.[89] Alternatively, these reactions sometimes utilize highly toxic organometallic reagents such as organotin reagents as in the Migita-Stille reaction.[90] In contrast, the Hiyama reaction presents an exciting alternative as it utilizes organosilanes (typically trialkoxysilanes) as cross-coupling partners.[91–93]

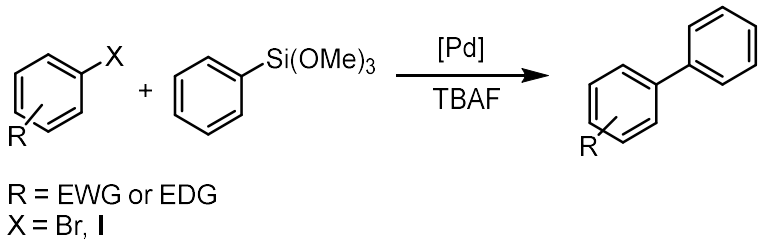
The first reported cross-coupling reaction involving fluoride-activated organosilane reagents was reported in 1988.[50] The paper described the cross-coupling of different vinyl, ethynyl, and allyl trimethylsilanes with aryl, vinyl, and allyl halides (iodides and bromides). The reaction was completed with tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) and 2.5 mol% catalyst loading of $[Pd(allyl)Cl]_2$ (Scheme 2-1).



Scheme 2-1. *Hiyama Reaction. Cond: (A) HMPA (0.3 mL), 50°C, (B) $P(OEt)_3$ (0.015 mmol), THF (0.3 mL), 50°C, (C) THF (0.3 mL), RT.*[50]

More common usage of the Hiyama cross-coupling reaction tends to rely on an aryl halide electrophile and an aryl organosiloxane nucleophile, as DeShong[52] utilized, in the

presence of fluoride. This is due to the ease of preparation and the bench stability of the organosiloxanes. This reaction generally utilizes a palladium or nickel catalyst to form a sp^2-sp^2 C-C bond giving the biaryl product in the presence of a fluorinated base (Scheme 2-2).[94–96]



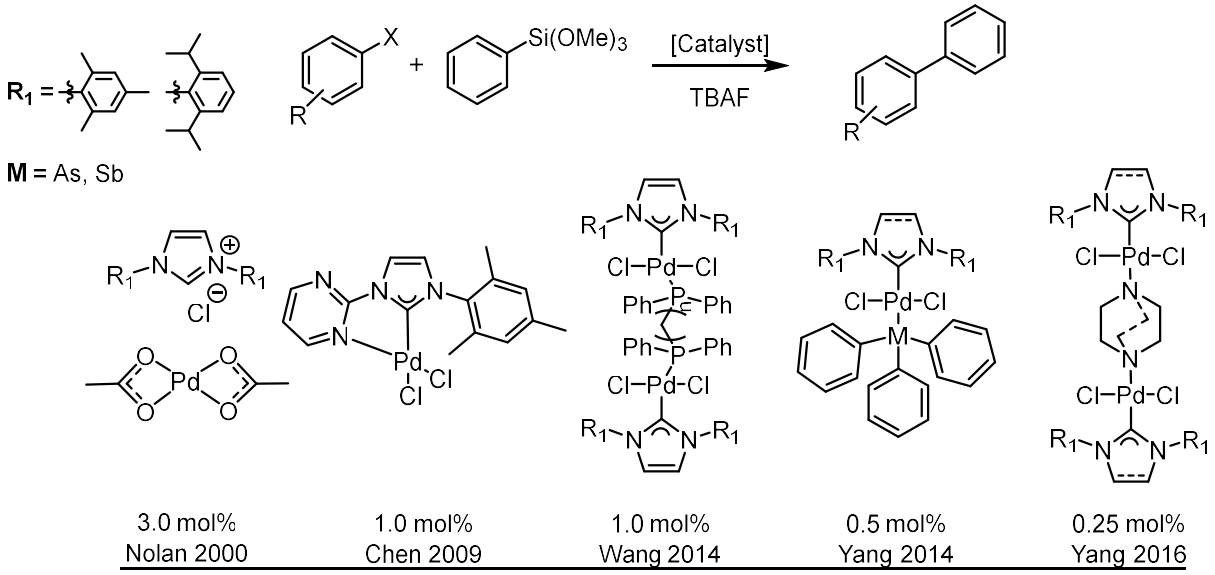
Scheme 2-2. *Simplified Hiyama cross-coupling reaction.*

Historically, the Hiyama cross-coupling reaction has been comparatively underutilized in the chemical synthesis of drugs.[2] In general, organosilicon reagents display low toxicity, commercial availability and remarkable air and moisture stability.[97,98] As such, the use of aryl trialkoxysilane nucleophiles requires the use of a fluoride base for their activation ultimately facilitating transmetallation to the catalyst.[91] Due to the decreased environmental impact of the silicon derived byproducts, the overall reaction is considered to be a green alternative to other cross-coupling reactions, and is of great interest particularly on industrial scale.[91–93] However, the decreased reactivity of aryl siloxanes has largely limited the Hiyama reaction to more reactive substrates such as aryl iodides and bromides, often requiring higher catalyst loadings. As a result of these drawbacks, the synthetic application of the Hiyama reaction has been quite limited. If active catalysts could be uncovered to facilitate the reaction of less reactive substrates, such as aryl chlorides, new synthetic applications of the Hiyama reaction would likely result.

2.2. N-Heterocyclic Carbenes Utilized in the Hiyama Cross-coupling Reaction

Palladium NHC complexes have been heavily investigated in cross-coupling reactions.[55] Despite this however, the Hiyama reaction has scantly been reported with Pd-NHC catalysts. In 2000, Nolan[99] reported the use of an *in situ* formed precatalyst from $Pd(OAc)_2$ and IPr-HCl for the coupling of aryl halides with phenyl- or vinyltrimethoxysilanes in the presence of TBAF. This system was only active towards aryl bromides and electron deficient aryl chlorides.[99] In 2009, Chen[100] and coworkers reported the use of palladium complexes coordinated to chelating NHC ligands featuring pyrimidine wingtip groups for coupling of aryl halides with trimethoxyphenylsilane in the presence of TBAF. This system was also only active towards aryl bromides and electron deficient aryl chlorides.[100] In 2014, Wang and coworkers reported the use of a dinuclear Pd-NHC-phosphine species, which utilized microwave heating for coupling of aryl chlorides with trimethoxyphenylsilane in the presence of TBAF.[101] While a larger substrate scope was reported, the requirement for microwave heating and the elaborate catalyst structure limited this system from widespread application.

Similarly, Yang and coworkers reported that Pd-NHC catalysts coordinated to ligands such as, DABCO or piperazine, and arsines and were operable at low catalyst loadings for coupling of aryl chlorides with trimethoxyphenylsilane in the presence of TBAF.[102,103] However, once again, the catalyst structures in these systems were comparatively elaborate, using potentially toxic arsenic-based ligands and were not appropriate for wide-spread usage (Scheme 2-3).



Scheme 2-3. *Hiyama cross-coupling reaction, showing readily available Pd-NHC pre-catalysts use in literature.*[99–103]

For the palladium catalyst, an NHC ligand seemed promising for use in this reaction as they have been demonstrated to be among the most active catalysts in cross-coupling reactions such as the Suzuki-Miyaura cross-coupling reaction.[3] Due to their strong electron donating abilities, NHCs produce particularly electron rich transition metal complexes that have been used to routinely activate the less reactive aryl chlorides. By using Pd-NHC catalysts, the Hiyama cross-coupling could have the potential to be a highly efficient alternative to other methods. This particularly true as NHCs have been found to increase the stability of the catalyst, operate at higher temperatures, and have ability to cross-couple difficult substrates.[90] As such, our research group was interested in exploring the reactivity of well-known and easily preparable Pd-NHC precatalysts in the Hiyama reaction or aryl chlorides and trimethoxyphenylsilanes. Our goal was to uncover a catalyst structure which was highly active, user friendly and economical.

2.3. Results and Discussion

2.3.1. PEPPSI, Palladium Acetylacetonate, and Palladium Allyl Chloride Precatalysts: Trials of Procedural Reproducibility

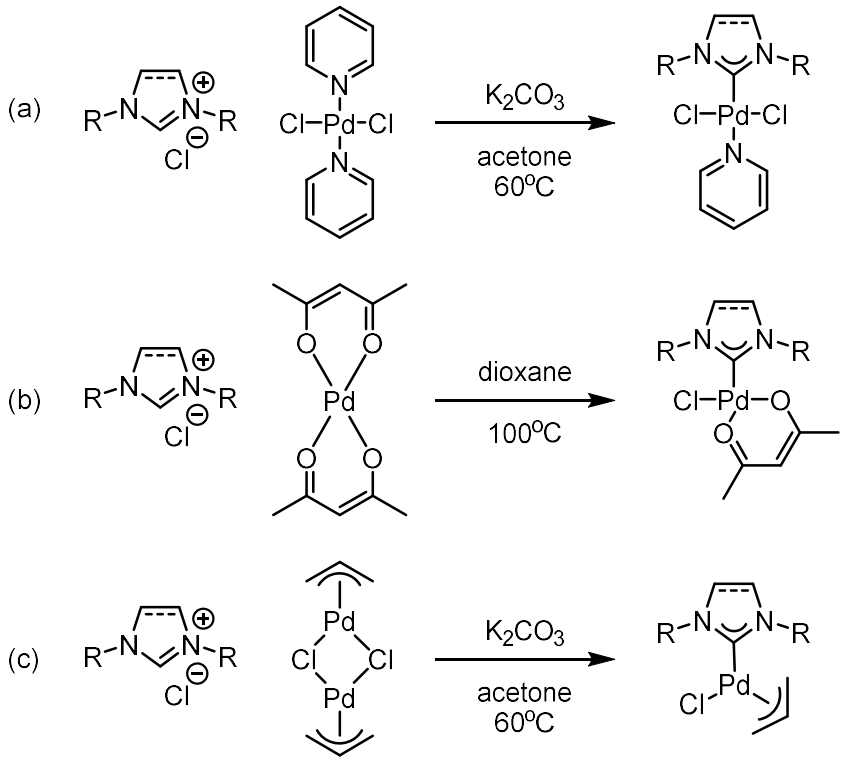
One of the objectives that this thesis sought to accomplish was the utilization of convenient, bench-stable, and easy to prepare Pd-NHC precatalysts in the Hiyama reaction. To initiate our study, we selected precatalysts of the general types Pd-PEPPSI-NHC,[83] [(NHC)Pd(acac)Cl][80] and [(NHC)Pd(allyl)Cl][104] as these catalysts have all been reported in the literature to be highly active across cross-coupling reactions. Upon their preparation, precatalysts Pd-PEPPSI-NHC, [(NHC)Pd(acac)Cl], and [(NHC)Pd(allyl)Cl], featuring common ligands IMes, SIMes, IPr, and SIPr, would be subjected to the same reaction conditions and compared for their catalytic activity.

We began by attempting the synthetic procedures reported by Organ and Nolan for the preparation of our precatalysts. From the original preparation of PEPPSI complexes by Organ,[83] an altered procedure reported by Nolan[105] instead used $[PdCl_2(pyr)_2]$ that resulted in a simple pyridine ring in place of the original 3-chloropyridine ring from Organ's PEPPSI complexes. For the synthesis of [(NHC)Pd(pyr)Cl] (PEPPSI with a simple pyridine), the NHC-HCl salt was reacted with $[PdCl_2(pyr)_2]$ and K_2CO_3 in acetone for 3 hours at 60 ^oC.[105]

Further, we also attempted the synthesis of [(NHC)Pd(acac)Cl] reported by Nolan: the NHC-HCl salt was reacted with $Pd(acac)_2$ in dioxane under argon overnight at 100 ^oC.[80]

For the general synthesis of [(NHC)Pd(allyl)Cl] type complexes first the generation of the free NHC upon treatment of the NHC-HX salt with a strong base was conducted, followed by the incorporation of $[Pd(allyl)Cl]_2$.[75,79,80] However, these protocols require the

use of a glovebox, which we viewed as a limitation. So, from a report by Nolan,[104] we attempted the synthesis of [(NHC)Pd(allyl)Cl] type complexes utilizing a weak base, K_2CO_3, in place of a strong base in acetone (Scheme 2-4).



Scheme 2-4. *Attempted procedures to synthesize (a) [(NHC)Pd(pyr)Cl],*[105] *(b) [(NHC)Pd(acac)Cl],*[80] *and (c) [(NHC)Pd(allyl)Cl].*[104] *R = IMes, SIMes, IPr, SIPr.*

In our hands, none of these procedures (Scheme 2-4) were reproducible, as the ^{1}H NMR spectra obtained only appeared to contain the unreacted NHC-HCl salt. The only complexes that were reproducible from the literature were specifically [(IMes)Pd(acac)Cl] and [(SIMes)Pd(acac)Cl] from review of the ^{1}H NMR spectra. Due to this, new syntheses were required to develop the reactions to a more user-friendly adaptation.

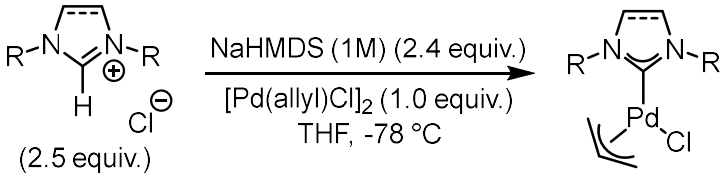
As such, we instead prepared [(NHC)Pd(allyl)Cl] complexes through a one-pot procedure developed in our laboratories. This reaction featured the strong base NaHMDS. (*vide infra*). The use of a strong base could be viewed as adverse, but the synthesis was reproducible and more user-friendly. More importantly, these procedures had short

reaction times, and conveniently required only a balloon of inert atmosphere to be successful.

2.3.2. A Novel Synthesis of [(NHC)Pd(allyl)Cl type complexes: Super Easy, Barely an Inconvenience

We were drawn to the [(NHC)Pd(allyl)Cl] precatalysts due to their reported high activity in cross-coupling reactions.[103] To access these structures, we explored their synthesis by treating an excess of the desired NHC-HCl salt with the strong base NaHMDS at -78°C in THF under argon in the presence of $[Pd(allyl)Cl]_2$ giving the desired products in high yield after column chromatography. The procedure was first tested for the preparation of [(IMes)Pd(allyl)Cl], **2-1**, which resulted a good yield of 82%. We then applied the procedure to the other common NHCs, as well as the more sterically encumbered IPr*-HCl (**2-7**). Complexes **2-1 – 2-5** were all air and moisture stable and synthesized in the yields listed (Table 2-1).

Table 2-1. *Synthesis of [(NHC)Pd(allyl)Cl] precatalysts.*



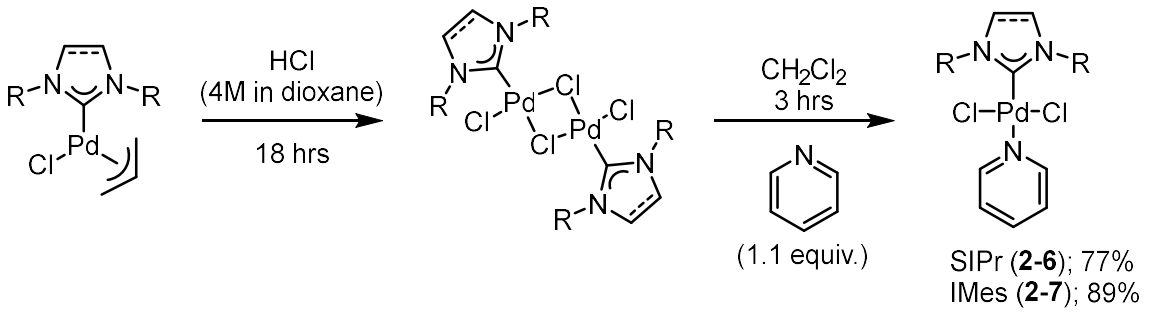
Product	Product	[a]Yield (%)
2-1	[(IMes)Pd(allyl)Cl]	82
2-2	[(SIMes)Pd(allyl)Cl]	74
2-3	[(IPr)Pd(allyl)Cl]	92
2-4	[(SIPr)Pd(allyl)Cl]	96
2-5	[(IPr*)Pd(allyl)Cl	80

[a]*Isolated Yield*

Because our procedure followed an *in situ* generated free-NHC pathway, the worry of instability of the free-NHC was not of high concern.[73] Indeed, the free-NHC was

generated *in situ*, under an inert atmosphere without requiring the isolation and storage of the air sensitive free-NHC. Importantly, this procedure does not require the use of a glove box.

For the synthesis of [(NHC)Pd(pyr)Cl_2] type complexes, from a modified procedure by Organ,[106] the [(SIPr)Pd(allyl)Cl] and [(IMes)Pd(allyl)Cl] complexes were reacted with HCl (4 M in dioxane) to afford a Pd-dimer species to then react further with pyridine in dichloromethane (CH_2Cl_2). This procedure required multiple steps to acquire the desired [(NHC)Pd(pyr)Cl_2] precatalysts **2-6** and **2-7**, displayed in Scheme 2-5.



Scheme 2-5. *Synthesis of [(NHC)Pd(pyr)Cl].*[106]

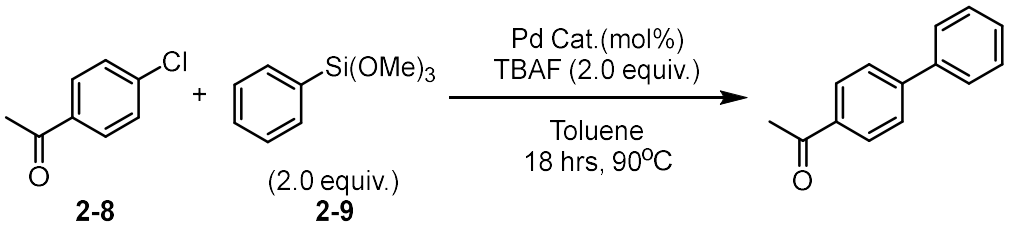
A notable observation from Scheme 2-5 is that to achieve the [(NHC)Pd(pyr)Cl_2] type precatalysts, the [(SIPr)Pd(allyl)Cl] and [(IMes)Pd(allyl)Cl] complexes were first required to be synthesized to react forward to form a dimer to then begin synthesis of the anticipated [(SIPr)Pd(pyr)Cl_2] and [(IMes)Pd(pyr)Cl_2] precatalysts (**2-6** and **2-7**).[106] This drew us to the conclusion that the ease of preparation of the [(NHC)Pd(ally)Cl] family was much more user-friendly and reproducible.

2.3.3. Optimizing the Hiyama Reaction by GC-MS: Catalyst Determination and Mechanistic Studies

With precatalysts **2-1** – **2-5** in-hand, we sought to optimize the Hiyama reaction of aryl chlorides and trimethoxyphenylsilane. To begin our optimizations, we tested different aryl chloride substrates, and compared their results by GC-MS.

Our investigations began with the reaction of 4-chloroacetophenone (**2-8**) with 2 equiv. of trimethoxyphenylsilane (**2-9**) and TBAF at 90 °C in anhydrous toluene. Our preliminary results indicated that higher yields were obtained in this reaction for ligands IMes and SIMes relative to the sterically larger ligands IPr and SIPr (Table 2-2). This was noteworthy as typically sterically larger ligands result in higher activities in cross-coupling reactions (*vide infra*).[84] This may speak to unique features of the Hiyama reaction which has been previously unreported.

Table 2-2. *Altering reaction conditions through GC-MS.*

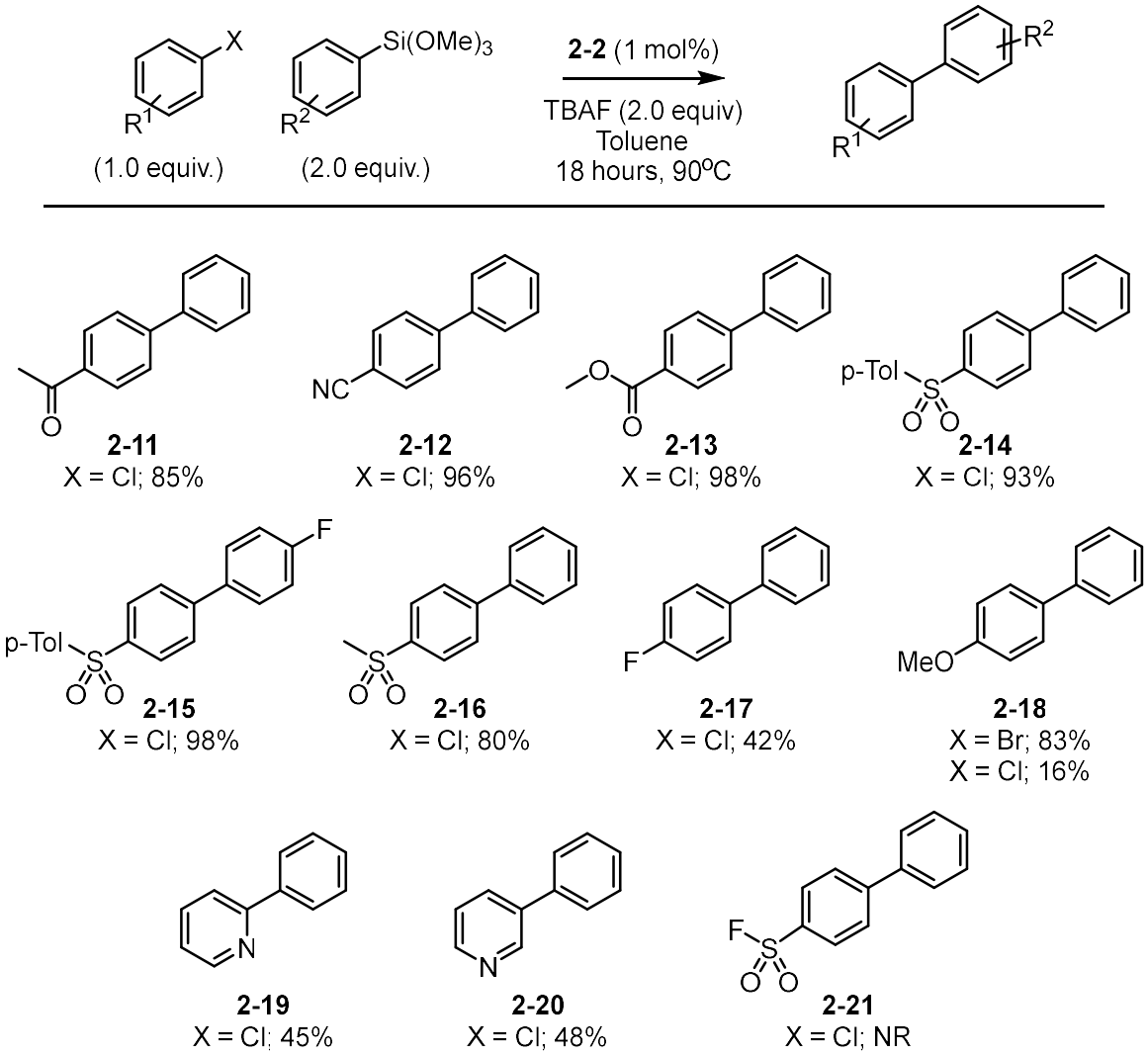


2-8 **2-9**

Entry	Catalyst (mol%)	Solvent	[a]Yield (%)
1	**2-1** (0.5)	Toluene	68
2	**2-2** (0.5)	Toluene	73
3	**2-3** (0.5)	Toluene	57
4	**2-4** (0.5)	Toluene	50
5	**2-5** (0.5)	Toluene	23
6	[b]**2-10** (0.5)	Toluene	71
7	**2-2** (0.5)	Dioxane	62
8	**2-2** (0.5)	[c]DMF	24
9	**2-2** (0.5)	[d]TFT	>99
10	**2-2** (1.0)	Toluene	>99 (85)

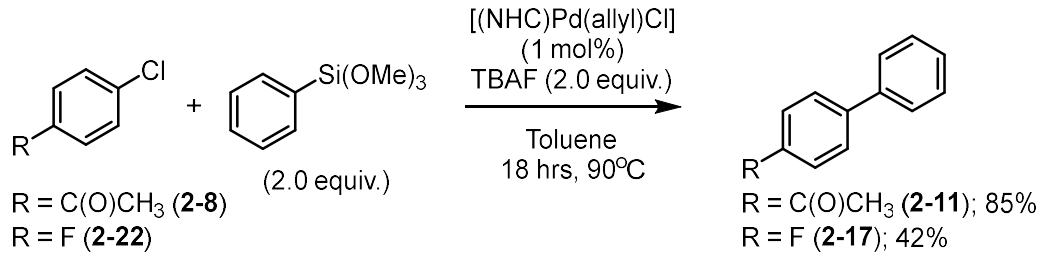
General Conditions: 2-8 (0.6 mmol), **2-9** (1.2 mmol), catalyst (mol%), TBAF (1M in THF – 1.2 mmol) in solvent (4 mL) at 90°C for 18 hours. [a]Yields determined by GCMS using undecane as an internal standard (1.0 equiv.), run in duplicate. Isolated yields in parentheses. [b][(IMes)Pd(acac)Cl]. [c]*N'N*-dimethylformamide. [d]Trifluorotoluene.

To test another catalyst architecture, [(IMes)Pd(acac)Cl] (**2-10**) was also utilized in this transformation (Table 2-2, Entry 6), and the results were very similar to that of [(IMes)Pd(allyl)Cl] (**2-1**) (Entry 1). This result could be an indication that both precatalysts form the same active catalyst in solution. Due to its high reactivity in this transformation, [(SIMes)Pd(allyl)Cl] (**2-2**) was the chosen one as the precatalyst for on-going studies. Toluene was crowned the solvent champion, marginally outcompeting dioxane and vastly outcompeting DMF. While TFT was found to be the best solvent, its higher cost was seen as detrimental. By increasing the catalyst loading to 1.0 mol%, full conversion was observed when utilizing toluene, which was selected as optimal conditions. This catalytic system was then applied to a variety of aryl halides with the substrate scope displayed in Scheme 2-6. Aryl halides featuring a wide variety of electron withdrawing groups were well tolerated in the 4-position of the aryl chloride.



Scheme 2-6. *General Conditions: aryl halide (0.6 mmol),* ***2-9*** *(1.2 mmol), TBAF (1M in THF) (1.2 mmol) in toluene (4 mL) at 90 °C for 18 hours. Isolated yields. NR is no reaction.*

We observed a large difference in the reactivity of 4-fluorochlorobenzene (**2-22**) to produce compound **2-17** compared to other substrates featuring electron withdrawing groups. This observation is likely due to the substrate, **2-22**, not being electronically activated. Consistent with the literature, substantially lower isolated yields were observed when compared with the reactivity of 4-chloroacetophenone (**2-8**) (Scheme 2-7). Furthermore, with 4-fluorochlorobenzene as a substrate, noticeable amounts of Pd black were observed after 4 hours suggesting appreciable catalyst decomposition. This was observed much less with electron withdrawing substrates such as in the synthesis of **2-11** – **2-16**.



Scheme 2-7. *Comparisons between isolated yields from substrate **2-8** and **2-22**.*

Electron rich aryl chlorides are commonly reported as substrates in other cross-coupling reactions with similar Pd-NHC catalysts. As such we hypothesized that the lower yields obtained with **2-17** and **2-18** were not related to difficulties with the oxidative addition process. Instead, we hypothesized the low reactivity with these substrates was related to specific features of this reaction which required further investigation.

To further develop our insight into this reaction, we monitored the formation of **2-11** by GC-MS with precatalysts [(SIMes)Pd(allyl)Cl] (**2-2**) and [(IPr)Pd(allyl)Cl] (**2-3**). In both cases, no induction period was observed indicating rapid *in-situ* catalyst activation. Precatalyst **2-2** was able to achieve an 82% conversion within 2 hours and a 92% conversion after 4 hours. On the other hand, precatalyst **2-3** appeared to display a faster initial rate, followed by a premature exhaustion of catalytic activity after approximately 1 hour (Figure 2-1). As the primary differences between **2-2** and **2-3** are steric in nature, we hypothesized that a deactivation pathway may be at play which is sensitive to the sterics of the ligand.

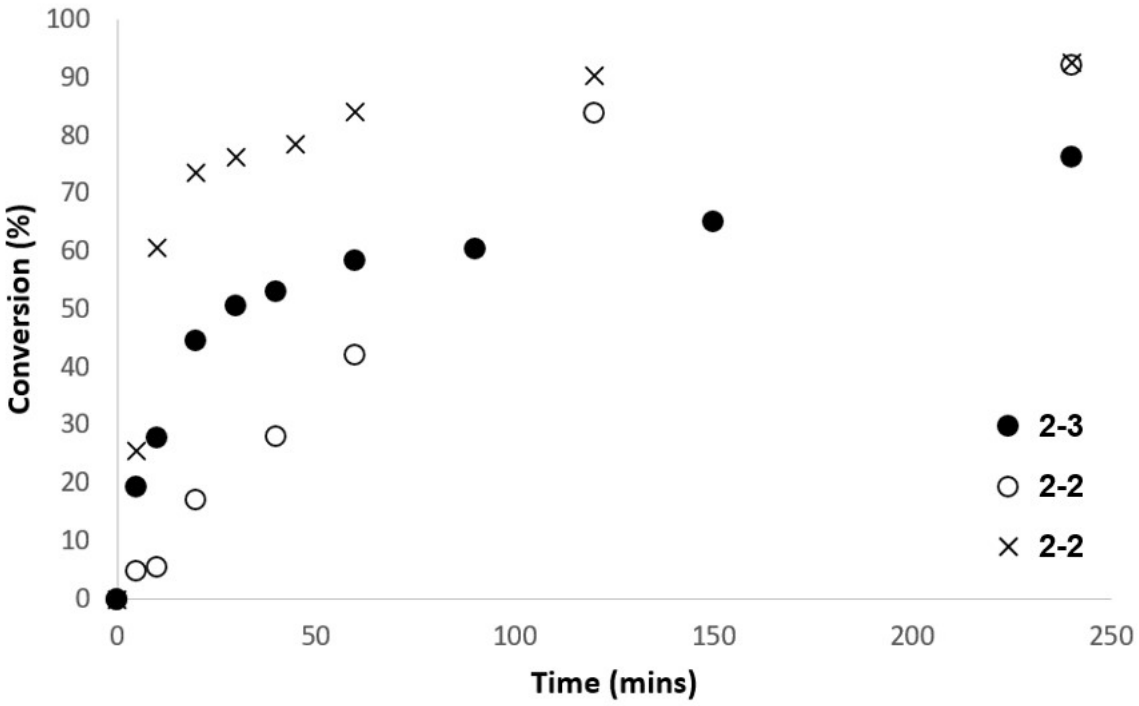
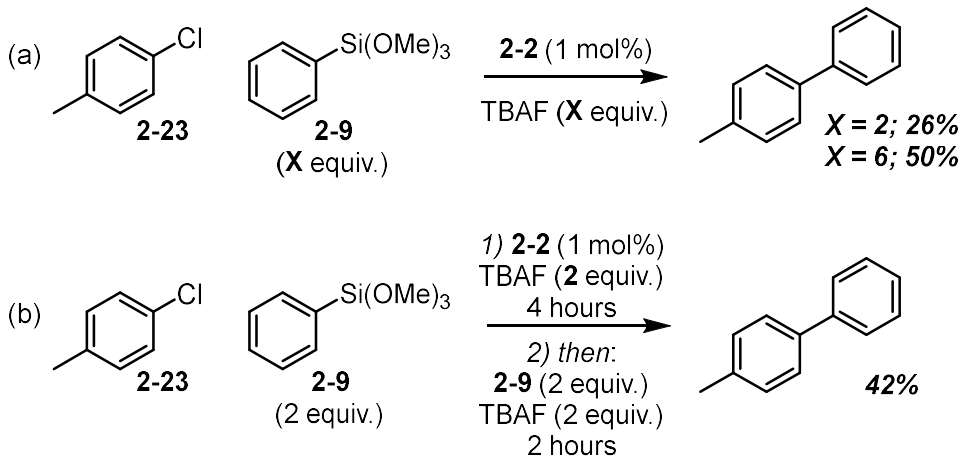


Figure 2-1. *Temporal concentration plot for the formation of **2-11** with precatalysts **2-2** and **2-3**; ● = 4-COCH₃PhCl; **O** = 4-COCH₃PhCl, and for the formation of **2-18** from aryl bromide substrate; **X** = 4-OMePhBr.*

We also compared the formation of **2-18** from the aryl chloride and aryl bromide substrates with **2-2** as a precatalyst under the otherwise same conditions. For this transformation, the electron donating methoxy group was expected to hinder this transformation with the aryl chloride. Indeed, only trace product was observed after 4 hours using 4-chloroanisole as a substrate. However, reaction of the more reactive 4-bromoanisole displayed increased reactivity giving nearly full conversion after 2 hours (Figure 2-1). Due to the low reactivity of 4-chloroanisole compared to the rapid reaction of 4-bromoanisole we began to hypothesize that a deactivation pathway may be present hindering product formation with less reactive substrates.

To gain further insight into this transformation, we probed the effect of varying the concentration of **2-9** and TBAF in this reaction (Scheme 2-8).



Scheme 2-8. *Varying amount of **2-9** and TBAF in toluene at 90 °C (a) 18 hours (b) 6 hours.*

Scheme 2-8 highlights the affect of increasing the concentration of both TBAF and **2-9** while using **2-2** as a precatalyst. To begin, a control reaction was performed using 2 equiv. of **2-9** and TBAF with 1 equiv. of aryl halide (**2-23**) at 90 °C achieving 26% conversion. From this, an increase in yield from 26% to 50% was observed as opposed to the expected 75% from tripling the amount of TBAF and **2-9** in the reaction which was noteworthy (Scheme 2-8a). A study was also conducted initially utilizing 2 equiv. each of TBAF and **2-9** for 4 hours and then added an additional 2 equiv. of TBAF and **2-9** to react for an additional 2 hours (Scheme 2-8b). This also displayed an increase in yield from 26% to 42%. The increase in conversion observed upon addition of **2-9** and TBAF may suggest that the poor catalytic performance is not associated with catalyst decomposition. Instead, we began to hypothesize that a major side reaction was the unproductive consumption of **2-9** under the reaction conditions. From our reaction monitoring, we had observed the formation of acetophenone as a byproduct in low concentration. Similarly, on further inspection of the reaction mixtures of Table 2-2 (*vide supra*), protiodehalogenation was observed in all cases, and a trend began to appear. For precatalysts **2-1** – **2-2** and **2-3** – **2-4**, a small amount of acetophenone was present (≤2% and ≤7%, respectively), but for the

much larger precatalyst bearing the IPr* ligand (**2-5**), we observed a much larger amount of acetophenone produced (49%).

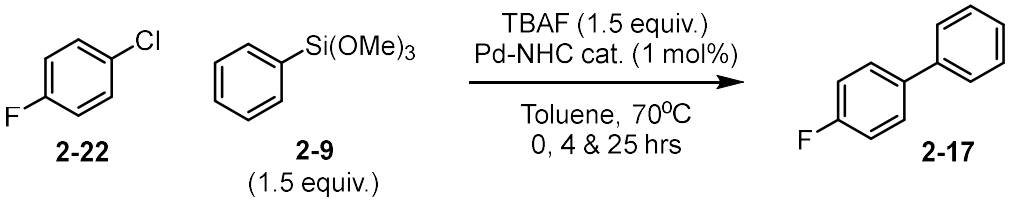
This observation was noteworthy, but from the products observed in the GC-MS we were not able to infer how the protiodehalogenated product was forming. Protiodehalogenation has been previously reported as a common side product with challenging sterically hindered substrates[107] likely originating from a palladium hydride species formed *in-situ*. From this, we turned to utilizing ^{19}F NMR spectroscopy to study the reaction of 4-fluorochlorobenzene (**2-22**) under these conditions. This substrate was previously observed to give a moderate 42% yield under the same conditions (**2-17**) and was therefore ideal as a substrate to study deactivation pathways.

2.3.3.1. Reaction Optimization and Monitoring by ^{19}F NMR Spectroscopy

2-22 was chosen as a model substrate for catalytic reaction optimizations, as reaction progress could be followed by ^{19}F NMR spectroscopy to observe byproducts that could be forming and to better understand any side reactions that may be present.

Accordingly, we explored the reaction of **2-22** with 1.5 equiv. of $PhSi(OMe)_3$, varying the identity of the precatalyst (1 mol%) in the presence of 1.5 equiv. of tetrabutylammonium fluoride (TBAF) in toluene at 70^{o}C. 1-Fluoronaphthalene was used as an internal standard, and reaction aliquots at 0, 4, and 25 hours were analyzed via ^{19}F NMR spectroscopy. (Table 2-3).

Table 2-3. *Reaction monitoring by ^{19}F NMR spectroscopy.*



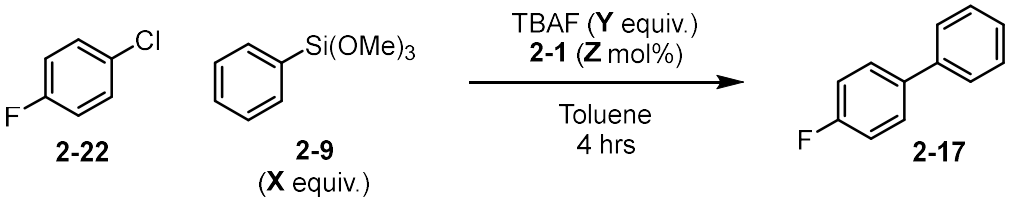
Entry	Catalyst	[a]Yield (%)
1	**2-1**	47
2	**2-2**	46
3	**2-3**	35
4	**2-4**	42
5	**2-6**	40
6	**2-7**	51
7	[b]**2-24**	48

General conditions: Added **2-22** (32 µL, 0.3 mmol, 1.0 equiv.), **2-9** (83 µL, 0.45 mmol, 1.5 equiv.), the indicated catalyst (1 mol %), 1.0 M TBAF in THF (0.45 mL, 0.45 mmol, 1.5 equiv.), 1-fluoronaphthalene standard (40 µL, 0.3 mmol, 1.0 equiv.), and anhydrous toluene (3 mL) to a thrice nitrogen purged culture tube. The reaction was stirred for 5 minutes, and an aliquot of 0.25 mL was removed from the reaction solution for peak analysis on the ^{19}F NMR (T_0). The reaction was then heated and stirred at 70 °C for 4 hours. Reaction was quenched with EtOAc and an aliquot of 0.25 mL was removed from the reaction solution for peak analysis on the ^{19}F NMR (4 Hrs) using $CDCl_3$. Product confirmed on GC-MS (172.1 m/z). [a]Average of replicates. [b][(SIMes)Pd(acac)Cl]. No change in yield after 4 hours; 25 hours is excluded.

Further optimizations were completed, and we continually observed the pattern that complexes containing a smaller NHC ligand were more efficient in this transformation, confirming our previous results.

The direct comparisons between [(NHC)Pd(allyl)Cl], [(NHC)Pd(acac)Cl], and [(NHC)Pd(pyr)Cl] type complexes displayed that there were no differences when comparing them between like ligands. This further supported that the most probable active catalyst was the same for each of the pre-catalysts (presumably a mono-ligated Pd-NHC complex). We further investigated the effect of temperature on the reaction followed by varying concentration of **2-9** and the TBAF base, as well as the catalyst loading (Table 2-4).

Table 2-4. *Further optimizations by ^{19}F NMR spectroscopy*



2-22 **2-9** (**X** equiv.) **2-17**

Entry	Catalyst Loading (Z mol%)	Temperature (°C)	TBAF (Y equiv.)	2-9 (X equiv.)	[a]Yield (%)
[a]1	1	70	1.5	1.5	47
2	1	50	1.5	1.5	25
3	1	90	1.5	1.5	45
4	1	70	1.5	3.0	16
5	1	70	3.0	3.0	75
6	2	70	1.5	1.5	61
7	2	70	3.0	3.0	76

General conditions: Added **2-22** (32 µL, 0.3 mmol, 1.0 equiv.), **2-9** (indicated equiv.), **2-1** (indicated mol %), 1.0 M TBAF in THF (indicated equiv.), 1-fluoronaphthalene standard (40 µL, 0.3 mmol, 1.0 equiv.), and anhydrous toluene (3 mL) to a thrice nitrogen purged culture tube. The reaction was stirred for 5 minutes, and an aliquot of 0.25 mL was removed from the reaction solution for peak analysis on the ^{19}F NMR (T_0). The reaction was then heated and stirred at the indicated temperature for 4 hours. An aliquot of 0.25 mL was removed from the reaction solution for peak analysis on the ^{19}F NMR (4 Hrs) using $CDCl_3$. Product confirmed on GC-MS (172.1 m/z). [a]Table 2-3, Entry 1. [a]Average of replicates.

There was a significant impact observed from the temperature on the reaction as a change to 50 °C resulted in a decreased yield from 47% (Table 2-4, Entry 1) to 25% (Entry 2). The increase in temperature from 70 °C to 90 °C had no noticeable change in yield (Entry 3). Doubling the concentration of **2-9** while maintaining fluoride concentration to see if a larger yield would be observed surprisingly resulted in a decrease in yield from 47% (Entry 1) to 16% (Entry 4). When the concentration of **2-9** and TBAF were both doubled this resulted in a noticeable increase in yield from 47% (Entry 1) to 75% (Entry 5). From this, the catalyst loading was also doubled resulting in an increase in yield from 47% (Entry 1) to 61% (Entry 6). The next reaction combined the variations of Entry 5 and Entry 6 (double cat. loading, **2-9**, and TBAF) and this displayed a change in yield from 61% (Entry 6) to 76% (Entry 7), but negligible change in yield from 75% (Entry 5) to 76%

(Entry 7). This displayed that a proportional increase of TBAF and **2-9** increased the yield more so than an increase in catalyst loading. From an economical perspective this was also preferred.

During our studies, we observed two additional unknow signals in the ^{19}F NMR spectrum at δ-119.6 ppm and δ-129.3 ppm (Figure 2-2).

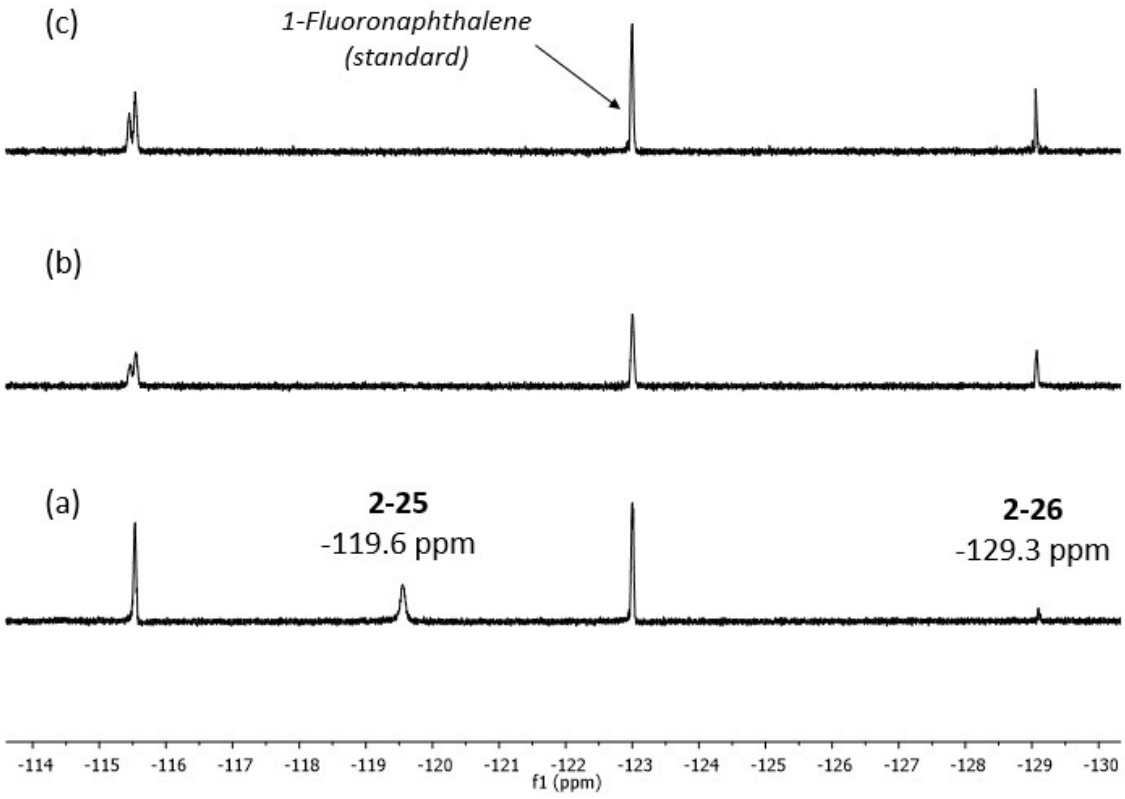


Figure 2-2. *Overlayed representative ^{19}F NMR spectra detailing reaction monitoring depicted in Table 2-3 and 2-4. (a) T = 0, (b) T = 4 hours, (c) T = 25 hours.*

To help identify these signals, we analyzed the ^{19}F NMR spectra of all reagents and expected byproducts. In *separate* tubes we had: fluorobenzene (potential byproduct), TBAF (base) and trimethoxyphenylsilane (nucleophile; **2-9**) together, TBAF alone, and 4-fluorochlorobenzene (substrate; **2-22**); 1-fluoronaphthalene as the standard (Figure 2-3).

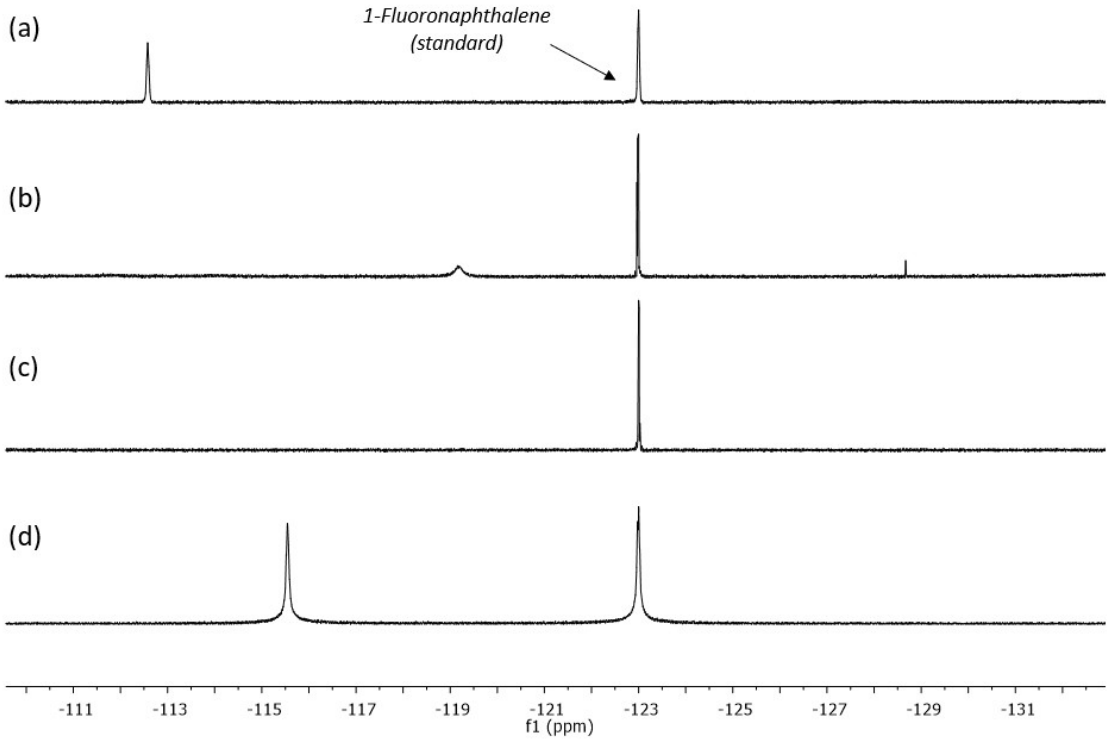
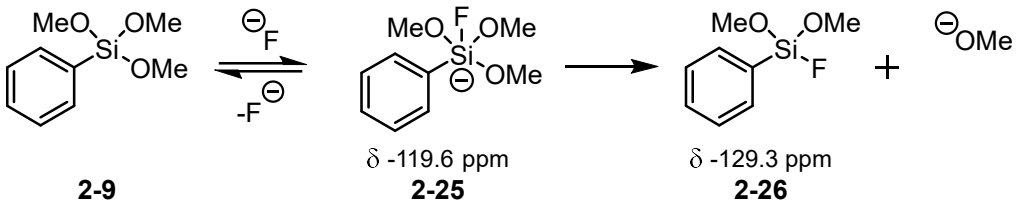


Figure 2-3. *Reference ^{19}F NMR spectra for (a) fluorobenzene, (b) TBAF and siloxane (**2-9**), (c) TBAF, and (d) 4-fluorochlorobenzene (**2-22**), all with 1-fluoronaphthalene standard.*

In addition to the starting material and standard at T=0 (Figure 2-2), we attributed the species present at δ-119.6 ppm to the hypervalent silane species **2-25**,[108] and we hypothesized the species at δ-129.3 ppm as **2-26** which could form upon fluoride displacement of the methoxy group, shown in Scheme 2-9.[109]



Scheme 2-9. *Side reaction of the siloxane nucleophile (**2-9**).*

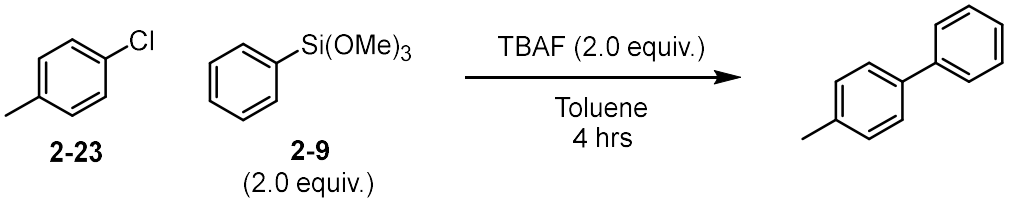
After 4 hours of heating, ^{19}F NMR spectroscopy displayed the complete consumption of the signal at δ-119.6 ppm and the growth of the species at δ-129.3 ppm. Further reaction led to no further conversion. The hypervalent species at δ-119.6 ppm, **2-25**, has been

demonstrated to be in equilibrium with $PhSi(OMe)_3$, **2-9**. While the equilibrium between the $PhSi(OMe)_3$ (**2-9**) and the hypervalent species (**2-25**) is known, transmetallation is believed to occur through the $PhSi(OMe)_3$ and a Pd-F species.[53] We therefore concluded that the formation of **2-26** was likely irreversible, and **2-26** is likely unreactive under the reaction conditions. In addition, the observation of **2-26** by ^{19}F NMR spectroscopy has not been previously reported to our knowledge (Figure 2-2). The degradation of **2-9** in the presence of fluoride has been previously hypothesized for the Hiyama reaction as a potential side reaction.[107,109] Because we believe that **2-25** is in equilibrium with the active species **2-9**, the disappearance of the signal at δ-119.6 ppm (**2-25**) can be attributed to the full consumption of **2-9**. Following this, by the additional observation of the reaction after 24 hours, no additional product was observed to form upon the disappearance of the signal at δ-119.6 ppm further supporting our hypothesis.

2.3.3.2. Combining ^{19}F NMR spectroscopy and GC-MS data

In order to probe the origin of **2-26**, we also studied the reaction of **2-23** with **2-9** with and without precatalyst (Table 2-5). If the formation of **2-26** follows the reaction in Scheme 2-9, we reasoned that it should form even in absence of precatalyst. Indeed, in both cases, **2-25** and **2-26** were clearly observed by ^{19}F NMR spectroscopy, confirming the pathway in Scheme 2-9 as a viable route of formation.

Table 2-5. *Conversion of **2-25** to **2-26** by ^{19}F NMR Spectroscopy.*



2-23 **2-9** (2.0 equiv.)

Time (min)	With 2-2	Without 2-2
0	0	0
30	21	12
60	50	30
240	100	83

General Conditions: **2-23** (0.3 mmol), **2-9** (0.6 mmol), [with **2-2** (1 mol%)], TBAF (1M in THF – 0.6 mmol), 1-fluoronaphthalene as internal standard (0.3 mmol) in toluene (3 mL) at 90°C for 4 hours. Aliquots of 0.2 mL aliquot removed at each timepoint and run in 0.3 mL $CDCl_3$. [a]Yields determined by ^{19}F NMR spectroscopy.

Figure 2-4 displays the ^{19}F NMR spectra utilizing **2-2** as a precatalyst, which demonstrates the full consumption of **2-25** after 2 hours. Upon the addition of extra TBAF and **2-9**, **2-25** was again observed by ^{19}F NMR spectroscopy.

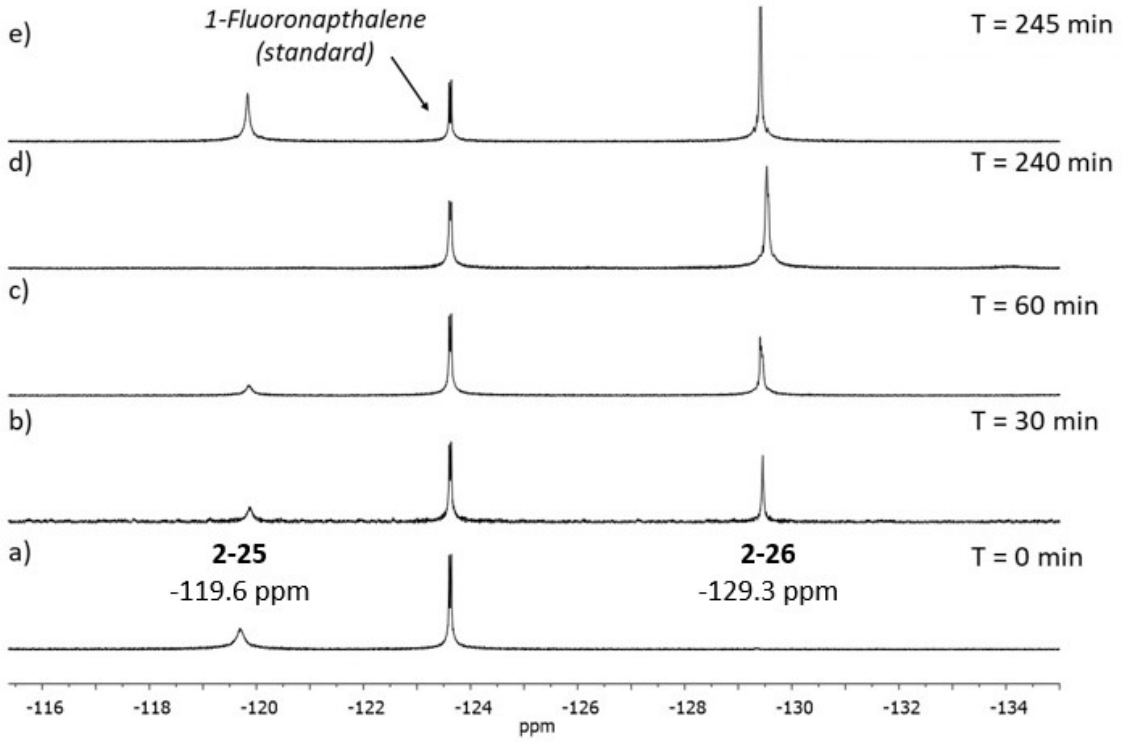


Figure 2-4. *^{19}F NMR spectra overlayed displaying conversion of **2-25** to **2-26** in the presence of Pd-cat (**2-2**). Note: e) was taken 5 minutes after injection of additional 2 equiv. TBAF and **2-9**.*

Similar results were observed in absence of **2-2** (Figure 2-5). However, the consumption of **2-25** appeared to be occurring at a decreased rate (Table 2-5). Indeed, even after 2 hours of reaction time, **2-25** could still be observed by ^{19}F NMR spectroscopy. This likely suggests that the formation of **2-26** via the route proposed in Scheme 2-9 may not be the only route for its formation.

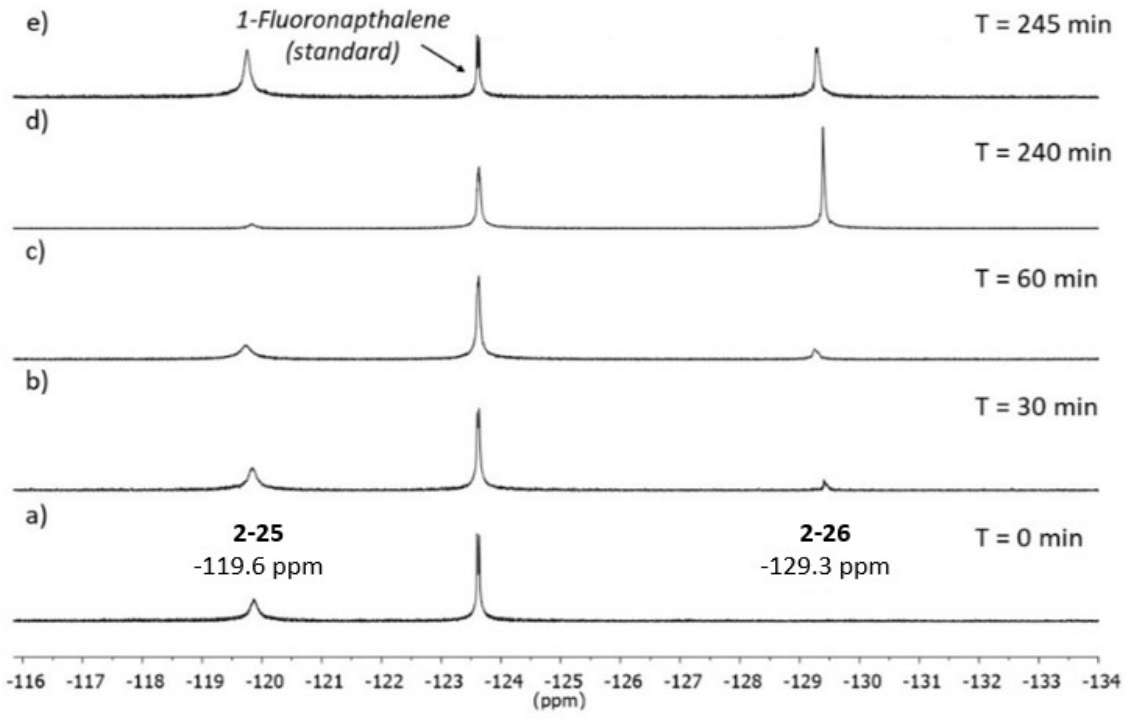
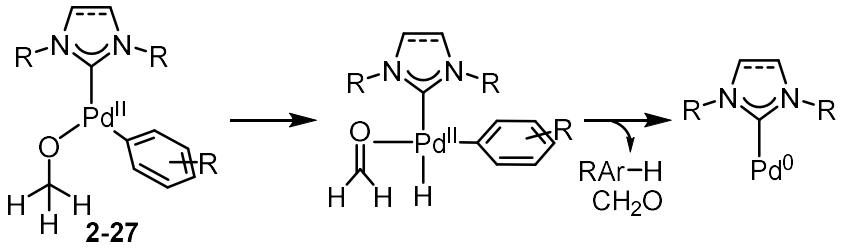


Figure 2-5. *^{19}F NMR spectra overlayed displaying conversion of **2-25** to **2-26** in the absence of Pd-cat. Note: e) was taken 5 minutes after injection of additional 2 equiv. TBAF and **2-9**.*

From the reaction monitoring experiments performed previously that were analyzed by GC, acetophenone was observed as a byproduct (*vide supra*). The formation of **2-26** would occur concurrently with the formation of methoxide which could go on to form a palladium-methoxide intermediate that could undergo β-hydride elimination to form the dehalogenated substrate (Scheme 2-10). This could be affected by the ligand bound,

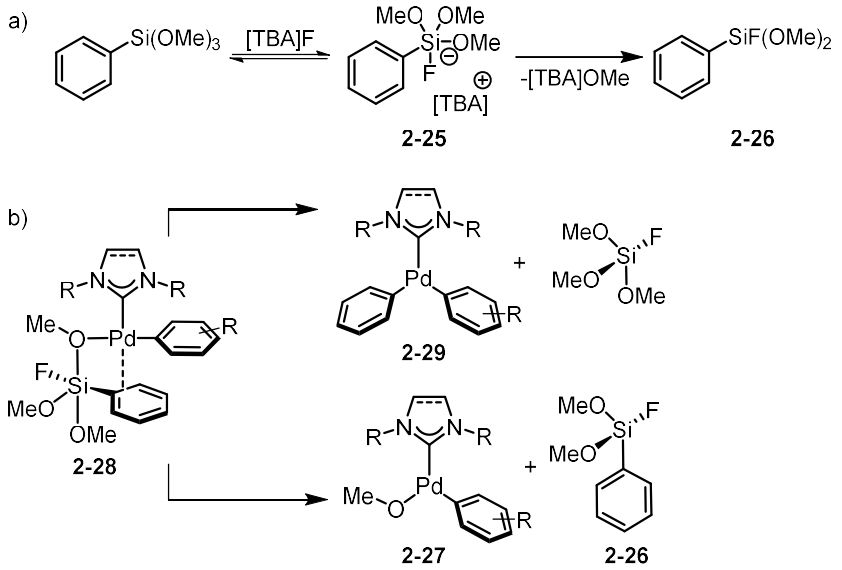
suggesting why precatalyst **2-3** has premature deactivation in the reaction monitoring studies.



Scheme 2-10. *Proposed β-hydride elimination; formation of the protiodehalogenated substrate.*

Intrinsically, **2-27** could be an intermediate of this reaction based upon a previously reported β-hydride elimination mechanism to explain activation mechanisms of similar precatalysts.[110] This also implies that the formation of the protiodehalogenated substrate could be indirect evidence of **2-26**.

As such, we propose the two possible pathways for the formation of **2-26** displayed in Scheme 2-11. To our knowledge, there are no reports of side reactions being observed in the literature.

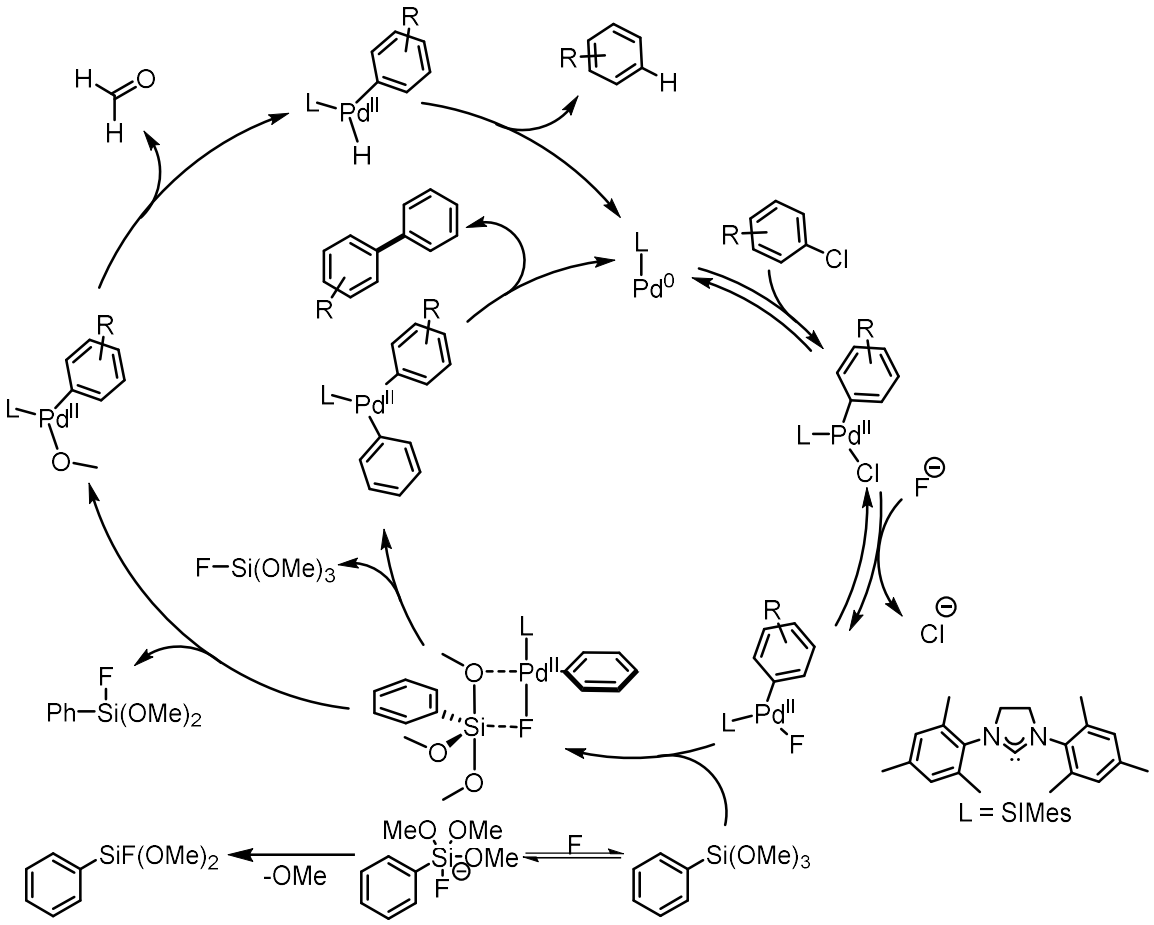


Scheme 2-11. *Proposed scheme for the formation of **2-26.***

Thus, we have demonstrated that the use of trialkoxyphenylsilanes in cross coupling reactions can suffer from deactivation pathways. We have further demonstrated that the rate of **2-9** decomposition is dependent on the nature of the ligand bound to the catalyst. As we obtained high yields of cross coupled products when using electron-deficient aryl chlorides, or electron-rich aryl bromides, it appears that the amount of **2-9** decomposition observed is also dependent on the nature of the aryl halide substrate regardless of the nature of the catalyst.

We have demonstrated that the Hiyama reaction is very rapid, and with active substrates, high yields are obtained in short reaction times. If the catalyst is carefully chosen, full conversion to biaryl product is observed before decomposition of **2-9** is complete. However, this is not the case with less reactive substrates.

As the productive Hiyama reaction proceeds, our studies show that the concentration of **2-9** is continually depleted overtime as a side reaction. We hypothesize therefore that less reactive substrates, such as electron-rich aryl chlorides, which are expected to undergo slower reaction in general, inherently suffer from lower concentrations of **2-9** than with more reactive substrates. We believe this to be the origin of the observed poor catalyst activity in the Hiyama reaction of Pd-NHC precatalysts tested herein. As such, we believe our results show that unproductive consumption of **2-9** is directly related to poor catalytic activity observed with challenging substrates. From our results, a proposed catalytic cycle of the Hiyama cross-coupling reaction is displayed in Scheme 2-12.



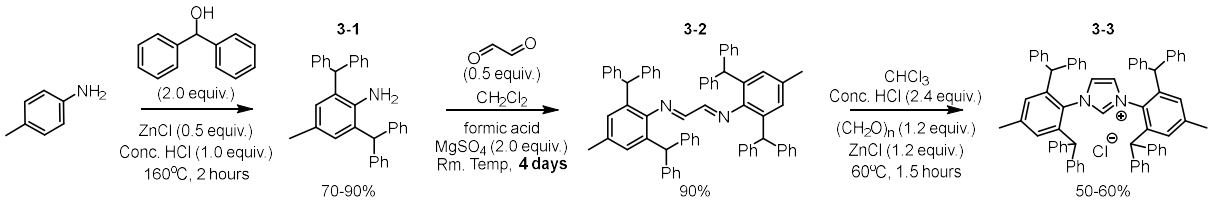
Scheme 2-12. *Proposed catalytic cycle of the Hiyama reaction when utilizing trialkoxyphenylsilanes*

Our studies have demonstrated that despite the high reactivity of aryl trialkoxysilanes towards palladium catalysts, the side reaction which these reagents may undergo greatly limit their potential in synthetic applications. As such, future work in our research group is dedicated to the analysis of alternative organosilane reagents which are less likely to undergo this side reaction.

Chapter 3. Tuning of Sterically Bulky N-Heterocyclic Carbenes

3.1. Sterically Bulky N-Heterocyclic Carbenes (NHCs)

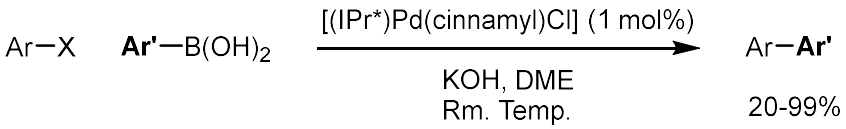
The dominance of sterically hindered ligands in cross-coupling reactions was a broadly accepted concept among research groups.[84–88] The report detailing the synthesis of IPr* by Marko and coworkers[87] was very significant as it gave access to sterically hindered NHC ligands from readily available starting materials. The synthesis of IPr*-HCl was accomplished in three steps (Scheme 3-1 and 3-3a). For the first step, *p*-toluidine was reacted with benzhydrol in the presence of $ZnCl_2$ and HCl at 160 °C giving **3-1**. **3-1** was then reacted in dichloromethane with aqueous glyoxal, magnesium sulfate ($MgSO_4$), and a catalytic amount of formic acid to generate **3-2** after multiple days of stirring**.** The final step involved the reaction of **3-2** with paraformaldehyde in the presence of $ZnCl_2$ and HCl to form the imidazole ring. From the synthesis of **3-3**, Marko and coworkers did not report on catalysis utilizing IPr* as a ligand in this paper, but the authors provided a proof of concept that the ligand could be synthesized as well as metallated onto rhodium and silver.[87]



Scheme 3-1. *Marko's procedure for synthesis of IPr*-HCl.*[87]

Early use of IPr* in catalytic reactions was reported by Nolan in 2012.[111] Nolan described the use of IPr* in [(IPr*)Pd(cinnamyl)Cl] for use in a Suzuki-Miyaura cross-coupling reaction for the formation of very challenging tetra-*ortho*-substituted biaryls (Scheme 3-2).[111] The reaction featured *ortho*-substituted aryl halide substrates, *ortho*-substituted aryl bromide nucleophiles, KOH as the base, dimethoxyethane (DME) as the

solvent, and a 1 mol% catalyst loading of the [(IPr*)Pd(cinnamyl)Cl] precatalyst at room temperature; for more difficult substrates, 65°C.[111]

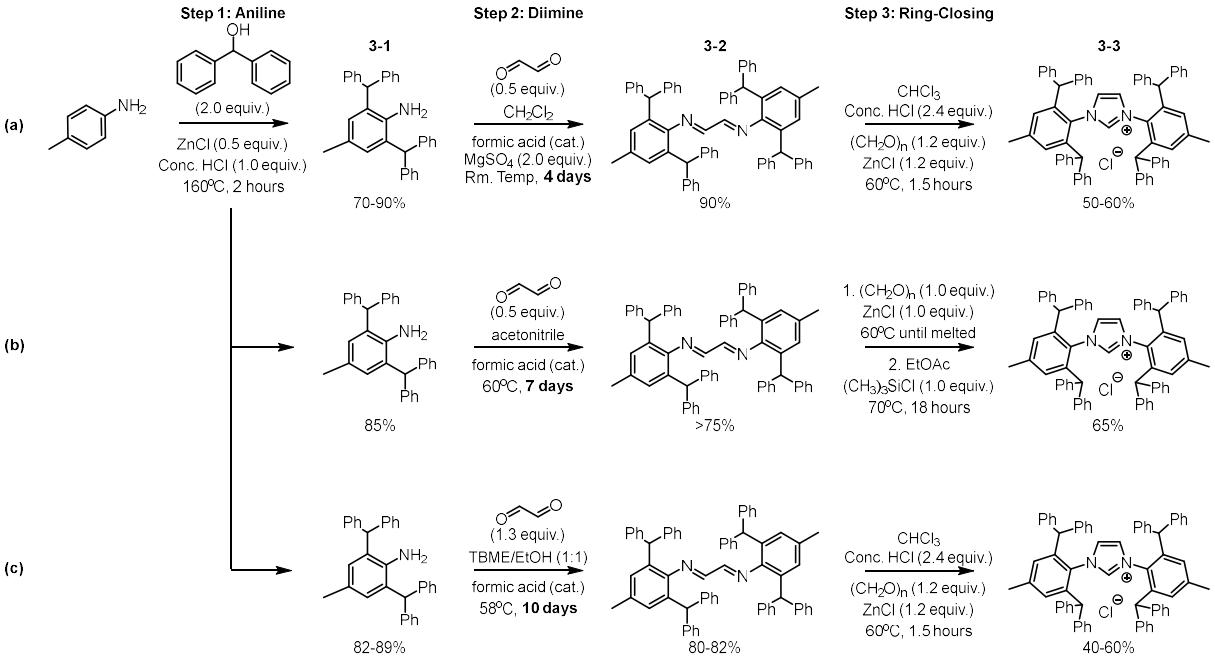


Scheme 3-2. *Nolan's milder procedure for synthesis of tetra-ortho-substituted biaryls.*[111]

Nolan further demonstrated that milder conditions were achievable by employing IPr* as a ligand when compared to other reactions that attempted to achieve the same products with stronger, more expensive bases and higher catalyst loading with sterically smaller NHC ligands.[112] Nolan also displayed the superior steric bulk and flexibility of the IPr* ligand over other previously-reported bulky NHCs by mapping their sterics.[111] Specifically, a detailed study of the topography of IPr* containing complexes displayed a large increase in steric bulk in some areas surrounding the metal center, but was less bulky in other areas. In other words, the ligand was able to have flexible-steric bulk around the metal center to adjust to incoming substrates.[111] In 2012, Nolan and coworkers further reported the preparations of [(IPr*)Pd(acac)Cl][113] and Pd-PEPPSI-IPr*,[114] both of which were reported to have high yields for Buchwald-Hartwig aminations of aryl chlorides. From these results, a balance between the ligand's ability to stabilize the active palladium species and still favour the substrate interaction was necessary.[115]

From the investigations of IPr* in catalysis, many other researchers also implemented IPr* into their portfolio. In 2015, Delaude[116] attempted to reproduce Marko's procedure, but had difficulties with the first step being under pressure. Delaude then altered Marko's first step of the procedure to be reacted in an open flask and observed no consequences for the formation of the aniline (**3-1**, Scheme 3-3b).[116]

The second step for Delaude's procedure involved a switch to the solvent acetonitrile, an increase in temperature to 60°C, and an increase in reaction time to seven days to give **3-2**. The third step was also altered from Marko's procedure to make the IPr*-HCl (**3-3**). Delaude had reported made these changes to the synthetic procedures in order to aide in the reproducibility issues that he observed with Marko's procedures.[116]



Scheme 3-3. *(a) Marko's[87] procedure for synthesis of IPr*-HCl. (b) Delaude's[116] alterations and (c) Wang's[117] alterations.*

An additional alteration to Marko's synthesis of IPr*-HCl was reported by Wang[117] in 2018 (Scheme 3-3c). Wang implemented this procedure to produce IPr*-HCl derivatives that had alterations on the 2,6-(diphenylmethane)phenyl groups. Wang kept Marko's first and third step the same but altered the second step for the formation of the diimine (**3-2**). The second step for Wang's procedure involved a switch to the solvent 1:1 TBME:EtOH (*tert*-butyl methyl ether:ethanol), an increase in temperature to 58°C, and an increase in reaction time to ten days. This proceeded resulted in the diimine (**3-2**) which was further reacted under Marko's conditions.

In 2021, Szostak[88] reported the development of another IPr*-derived ligand synthesized from the same first two steps (**3-1** and **3-2**) as IPr* reported by Marko.[87] With the implementation of a larger ligand in the *para*-position, they found that alterations to the synthesis of **3-3** was necessary due to the increase in retro-Friedel-Crafts products. With a milder cyclization to afford **3-3**, they instead reacted **3-2** with paraformaldehyde and TMSCl in ethyl acetate at 70 ºC to afford the IPr#-HCl salt.

Despite the high catalytic activity which was reported for IPr* species in catalysis, the lack of reports of this ligand by other researchers was curious. Furthermore, the repeated reports of improved syntheses for IPr*-HCl suggests that there may be reproducibility problems with the preparation of this exciting ligand precursor.

There have been several reports of sterically larger ligands displaying higher activity in cross-coupling reactions.[84,111,113,114] However, the resulting ligands are typically not particularly modular. Specifically, the fine-tuning of the steric and electronic parameters of sterically encumbering NHCs is a challenging process. As such, this thesis also sought to investigate the development of electronically modified, sterically bulky NHC ligands, and investigate their metallation. Investigations into their metallation was completed through our 'super easy, barely an inconvenience' metallation procedure in the hopes of implementing them in the Buchwald-Hartwig amination reactions.

3.2. Results and Discussion

3.2.1. A Synthetic Dive into Literature Displeasures

From the reports of Marko,[87] we attempted the first step of his IPr*-HCl synthesis by running the reaction in an open vessel as Delaude[116] had suggested. This resulted in a

moderate isolated yield on our first attempt of the aniline, **3-1**, which was confirmed by GC-MS and by ^{1}H NMR spectroscopy (61%, **3-4**, Scheme 3-4). After we had **3-1** in-hand, we proceeded to attempt the synthesis of the diimine **3-2**. Following Marko's procedure, which reportedly required four-days of stirring, all our attempts resulted in the re-isolation of **3-1** as determined by ^{1}H NMR spectroscopy. We hypothesize the origin of this is associated with the significant steric bulk of **3-1**, preventing its use as a nucleophile towards glyoxal.

Following this, we then attempted to reproduce Delaude's altered procedure which was increased to seven days in acetonitrile at 60^{o}C.[116] In our hands, this procedure was also irreproducible, as **3-1** was reisolated as observable by ^{1}H NMR spectroscopy. Following this, we then sought to reproduce Wang's[118] altered second procedure which was increased to ten days in a one-to-one solvent of TBME and EtOH at 58^{o}C. Remarkably, in our hands this procedure was also met with failure and returned **3-1** as observable by ^{1}H NMR spectroscopy.

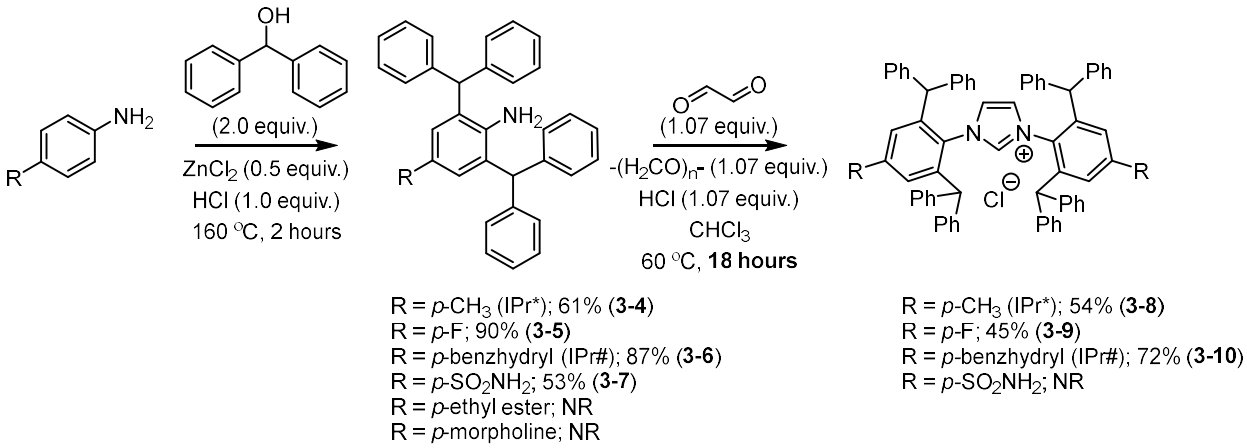
As such, all reported procedures for the preparation of **3-2** attempted were met with failure in our hands (Scheme 3-3). We attempted to find a new procedure that would afford us our desired product in a timely manner without having to wait four business days or more.

3.2.2. The Triumph of Marko (2010) and Tran (2022)

From our trials and errors, we found that the first step to synthesize **3-1** by Marko was reproducible based on our GC-MS and ^{1}H NMR spectrum obtained.[87] We thus continued to synthesize **3-1** by this procedure, as it was a facile route to do so. However,

we found that **3-1** could be purified by an improved procedure by simply washing with MeOH and the resulting solid was recrystallized from hot EtOAc.

During our studies, in 2022, Tran and coworkers[119] reported a procedure to synthesize IPr*-HCl in just two steps. The second step of this procedure ultimately resulted in **3-3** directly from **3-1** via a one-pot reaction without the isolation of the diimine, **3-2**. This combined with the first procedure by Marko was a very short synthesis of IPr*-HCl. Tran's second step required the addition of concentrated HCl to a solution of aniline, aqueous glyoxal and paraformaldehyde in chloroform (Scheme 3-4).



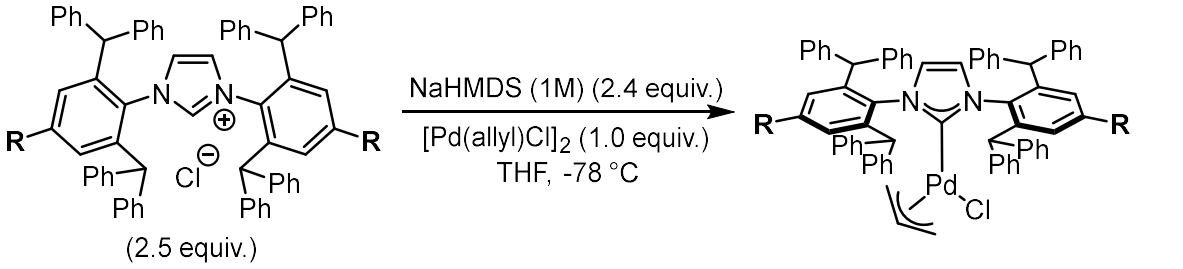
Scheme 3-4. *Isolated yield of the anilines (Marko's procedure) and NHC-HCl salts (Tran's procedure).*[87,119]

We then attempted to use this simple method for the the synthesis of electronically modified structures by installing different groups in the *para*-position of the starting aniline (Scheme 3-4). To follow the IPr*-aniline (**3-4**) that resulted in an isolated yield of 61%, we also synthesized *p*-F-IPr*-aniline (90% - **3-5**), IPr#-aniline (87% - **3-6**), *p*-SO_2NH_2-IPr*-aniline (53% - **3-7**); all confirmed by their ^1H and ^{13}C NMR spectra. Unfortunately, the *p*-ethylester-IPr*-aniline and *p*-morpholine-IPr*-aniline both resulted in no product displayed by the ^1H NMR spectra.

With anilines **3-4** to **3-7** in-hand, we subjected them to Tran's procedure. This afforded us with IPr*-HCl (80% - **3-8**), *p*-F-IPr*-HCl (45% - **3-9**), and IPr#-HCl (72% - **3-10**). Unfortunately, the p-SO_2NH_2-IPr*-HCl resulted in intractable mixtures as displayed by the ^{1}H NMR spectrum.

3.2.3. Metallating the Ligand: Super Easy, Barely an Inconvenience

From the synthesis of the NHC-HCl salts, we were also able to utilize our 'super easy, barely an inconvenience' procedure detailed in Chapter 2.3.2, to metallate the ligands (Scheme 3-5).



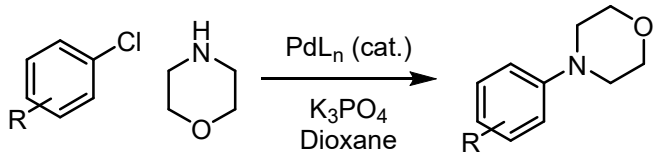
R = *p*-CH_3 (IPr*); 54% (**3-8**)
R = *p*-F; 45% (**3-9**)
R = *p*-benzhydryl (IPr#); 72% (**3-10**)

R = *p*-CH_3 (IPr*); 80% (**3-11**)
R = *p*-F; 78% (**3-12**)
R = *p*-benzhydryl (IPr#); 64% (**3-13**)

Scheme 3-5. *Isolated yield of novel [(NHC)Pd(allyl)Cl] precatalysts.*

The metallation was successful for three of the synthesized IPr*-HCl derivatives to give [(IPr*)Pd(allyl)Cl] (80% - **3-11**), [(*p*-F-IPr*)Pd(allyl)Cl] (78% - **3-12**), and [(IPr#)Pd(allyl)Cl] (64% - **3-13**) confirmed by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy. All three complexes, to our knowledge, have not been reported in the literature. In addition, a high-resolution mass spectrum was obtained for each complex (**3-11**, **3-12** and **3-13**).

Future work will be to expand the scope of these compounds with other substitutents, and then investigate precatalysts **3-11**, **3-12**, and **3-13** in the Buchwald-Hartwig aminations of aryl chlorides (Scheme 3-6).



Scheme 3-6. *Buchwald-Hartwig amination to be studied using complexes **3-11** – **3-13**.*

Sterically hindered NHCs have been previously reported to be excellent ligands in the Buchwald-Hartwig amination. Additionally, Organ has previously demonstrated that the installation of electron withdrawing groups to the backbone of NHCs results in catalysts with higher activity.[120] As such, we hypothesize that IPr* derivatives reported herein which feature electron withdrawing groups may lead to more active pre-catalysts in this transformation.

Chapter 4: Conclusions and Future Work

In chapter 2, investigations into the Hiyama reaction were conducted with a novel reaction monitoring method invoked. By viewing the Hiyama reaction through the lens of ^{19}F NMR spectroscopy in tandem with GC-MS, we were able to demonstrate that the bench-stable and easy to prepare [(NHC)Pd(allyl)Cl] precatalysts were highly effective in the Hiyama cross-coupling of aryl bromides and aryl chlorides featuring electron-withdrawing substituents. The precatalysts synthesized from our 'super easy, barely an inconvenience' procedure via a one-pot method resulted in consistently high yields. The less sterically hindered IMes (**2-1**) and SIMes (**2-2**) bearing precatalysts performed superior under our reaction conditions in the Hiyama cross-coupling relative to the sterically bulkier precatalysts containing IPr (**2-3**), SIPr (**2-4**), and IPr* (**2-5**). The reaction of aryl chlorides bearing a more electron-donating substituent resulted in poor yields that we believe have been reasoned through our observations through ^{19}F NMR spectroscopy and GC-MS reaction monitoring. The origin of the poor catalytic performance is believed to be due to the alternative reaction pathway that consumes **2-9**. From our investigations, this byproduct could likely be $FSiPh(OMe)_2$ (**2-26**). From these investigations, our results display that future work necessary would involve the use of other organosilicon cross-coupling partners in the Hiyama cross-coupling reaction, such as silanoates, as opposed to trialkoxysilanes that undergo decomposition pathways.

In chapter 3, the improved methodology to develop sought-after sterically flexible ligands was divulged. The combined procedures of Marko and Tran with our own alterations to the reaction work-up have resulted in a promising synthesis to achieve IPr*-derivatives. Alterations to the para-position of the wing-tip groups of IPr* display promise

for metallations, but ortho-substituted NHC-HCl salts have displayed that their purification is not trivial. Future work would involve focussing on the alterations to the *para*-substituted position of the IPr*-ligand, and the integration of novel IPr*-derived metallated precatalysts into the Buchwald-Hartwig amination. The development of altered *para*-substituted IPr*-NHCs would be continued to fully unravel the potential that IPr*-ligand precatalysts have to offer. These electronically modified ligands were successfully synthesized, and testing their electron-donor capabilities will soon be underway. The development of the Keske family of catalysts will soon be upon us with electronically altered IPr*-derived ligands.

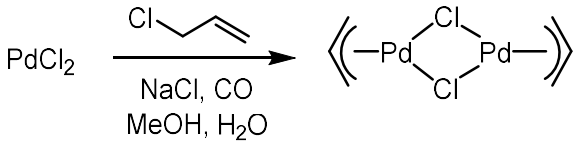
Appendix A: Experimental

General Considerations:

All reactions were carried out under an argon or nitrogen atmosphere unless otherwise noted. All reactions utilized standard Schlenk techniques. Anhydrous solvents (1,4-dioxane, toluene, and *N,N'*-dimethylformamide) were purchased from Acros Organics or Sigma Aldrich and were stored under argon. Anhydrous tetrahydrofuran was purchased from Sigma Aldrich and stored on 4Å molecular sieves under an argon atmosphere. Sodium hexamethyldisilazide (NaHMDS) and Tetrabutylammonium fluoride (TBAF) were purchased as 1M solutions in THF from Sigma Aldrich and stored under an argon atmosphere at 5°C. All chemical reagents were purchased from commercial suppliers and utilized without further purification. Column chromatography was executed using silica gel 60 (230-400 mesh) purchased from Sigma Aldrich. Thin layer chromatography (TLC) spots were viewed using a UV light at 254 nm while utilizing pre-coated Polygram® SIL G/UV_{254} TLC sheets. NHC precursors IPr-HCl, SIPr-HCl, IMes-HCl, and SIMes-HCl were synthesized by published procedures.[121–123] 4-Fluorophenyl(trimethoxy)silane,[124] 1-chloro-4-tosylbenzene,[125] and 1-chloro-4-(methylsulfonyl)benzene[125] were synthesized via literature procedures. Catalytic reactions were executed in 16x125 culture tubes purchased from VWR. ^{1}H NMR spectra were measured on a Varian INOVA 500 MHz or a Bruker Ascend 400 MHz spectrometer where noted at 298K. Chemical shifts are reported in delta (δ) units, expressed in parts per million (ppm) downfield from tetramethylsilane (TMS) using solvent as an internal standard ($CDCl_3$; δ7.27 ppm or $(CD_3)_2SO$; δ2.50 ppm). $^{13}C\{^{1}H\}$ NMR spectra were recorded at 125 MHz or 100 MHz where noted. Chemical shifts are reported as above using the solvent as an internal standard ($CDCl_3$; δ77.23 ppm or $(CD_3)_2)SO$; δ39.52). ^{19}F NMR spectra were recorded at 470 MHz or 376 MHz where noted. High resolution mass spectrometry was performed in the Water Quality Centre at Trent University using a Thermo Qexactive Orbitrap ESI in positive ion mode. LRMS and conversions of catalytic reactions were determined by GCMS using an Agilent 7890B GC equipped with a HP-5MS UI column and a 5977A MSD.

Preparation of palladium precursors

Synthesis of [Pd(allyl)Cl]$_2$

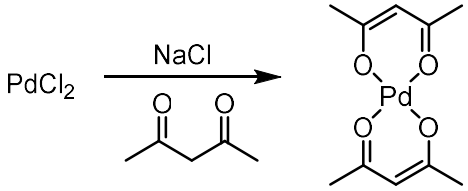


From a procedure adapted from the literature,[126] a 100 mL round bottom flask sealed with a rubber septum under an argon atmosphere was charged with $PdCl_2$ (888 mg, 5.0 mmol) and NaCl (660 mg, 11.2 mmol) and was dispersed in a mixture of degassed H_2O (4 mL) and degassed MeOH (24 mL). The reaction solution was then charged with allyl chloride (2.4 mL, 29.5 mmol). The argon balloon was exchanged with a carbon monoxide balloon and the solution stirred over 18 hours at room temperature. The brown/red coloured heterogeneous solution slowly became homogeneous and yellow. The solution was then poured into 120 mL of H_2O and extracted in CH_2Cl_2 (20 mL) three times. The organic layers were collected and dried with $MgSO_4$, filtered, and concentrated *in vacuo* giving a yellow powder, which was recrystallized by layering hexanes onto a concentrated CH_2Cl_2 solution at 5 °C giving canary yellow-coloured crystals in 804.2 mg (88%) yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.51-5.42 (m, 1H), 4.12 (d, J = 6.7 Hz, 2H), 3.05 (d, J = 12.1 Hz, 2H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 111.31, 63.10 ppm.

Synthesis of [Pd(acac)$_2$]

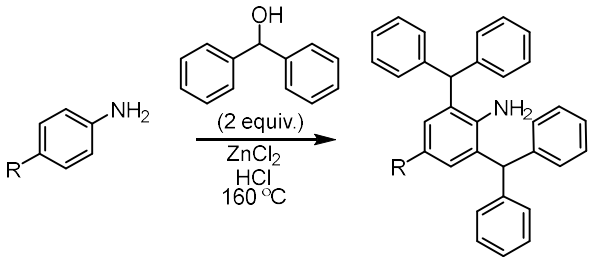


Following the procedure reported by Lee and coworkers,[127] $PdCl_2$ (500 mg, 2.82 mmol) and NaCl (165.0 mg, 2.82 mmol) were combined as solids in a 50 mL round bottom flask and dispersed in 13 mL of degassed MeOH. The solution was stirred at room temperature for 24 hours. At this time, an addition 13 mL of MeOH was added, followed by acetylacetone (633 µL, 6.20 mmol) and sodium carbonate (299mg, 2.82 mmol), and the solution was stirred at room temperature for 24 hours. This solution was then filtered, and washed with H_2O to give a yellow-orange powder which was recrystallized from acetone to give orange crystals in 721 mg (2.37 mmol, 84%) yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.43 (s, 2H), 6.16 (s, 12H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 187.4, 101.7, 25.6 ppm.

Preparation of 2,6-disubstituted Anilines

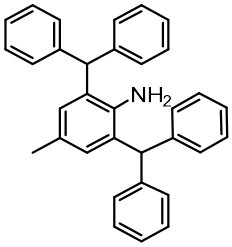


General Procedure for preparation of anilines

Benzhydrol (15.00 g, 81.4 mmol, 2 equiv.) and *p*-substituted aniline (40.7 mmol) were added to an open 70 mL trap (24/40 joint) as solids and melted together at 160 °C in a heating block with stirring. In a 4 dram vile, $ZnCl_2$ (2.71 g, 20.4 mmol, 0.5 equiv.) was dissolved into conc. HCl (3.4 mL, 40.7 mmol, 1 equiv.). This solution was then added dropwise to the aniline solution at 160 °C. **Caution:** gas released. The resulting mixture was stirred at 160 ˚C for 2 hours resulting in a thick glassy solid. The tube was cooled to room temperature, and CH_2Cl_2 (15 mL) was added to the tube along with H_2O (5mL). The tube was then sonicated to dissolve the mixture. The contents were then transferred to a separatory funnel, diluted with 20 mL of CH_2Cl_2, and washed with brine. The organic layers were combined, dried with $MgSO_4$, filtered, then concentrated *in vacuo*.

The solid was then dispersed into MeOH (30 mL) and refluxed for 30 minutes. The solution was cooled to room temperature, and filtered on a frit, giving a white powder. The product can be further purified by recrystallization from hot EtOAc.

Synthesis of IPr*-aniline (3-4)



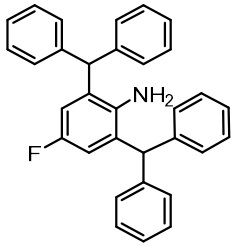
Following the general procedure using *p*-toluidine (4.36 g) giving 10.86 g (24.7 mmol, 61%) as a white solid, after recrystallization from EtOAc. Spectral data matches literature.[87]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (t, *J* = 7.3 Hz, 8H), 7.24 (t, *J* = 7.3 Hz, 4H), 7.12 (d, *J* = 7.4 Hz, 8H), 6.41 (s, 2H), 5.49 (s, 2H), 2.05 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ142.94, 139.64, 129.73, 129.56, 129.25, 128.66, 126.78, 52.59, 21.22 ppm.

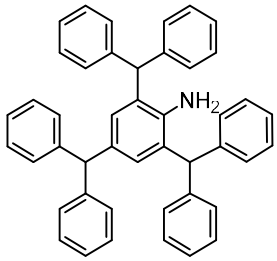
MS (EI): calc'd for $C_{33}H_{29}N$ m/z: 439.2 (M^+); found m/z: 439.2.

Synthesis of *p*-F IPr*-aniline (3-5)



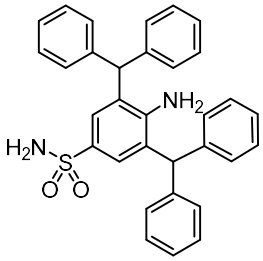
Following the general procedure using *p*-fluoroaniline (4.52 g, 3.85 mL) giving 16.36 g (36.9 mmol, 90%) as a white solid after reflux in MeOH.
^{1}H NMR (500 MHz, $CDCl_3$): δ7.31 (t, *J* = 7.3 Hz, 8H), 7.25 (t, *J* = 7.3 Hz, 4H), 7.10 (d, *J* = 7.1 Hz, 8H), 6.34 (d, *J* = 9.8 Hz, 2H), 5.46 (s, 2H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$): δ157.09, 155.22, 142.18, 138.20, 131.17, 129.60, 128.86, 128.58, 127.11, 115.47, 115.28, 52.57, 52.56 ppm.
^{19}F NMR (470 MHz, $CDCl_3$): δ-125.39 ppm.
MS (EI): calc'd for $C_{32}H_{29}NF$ m/z: 443.2 (M^+); found m/z: 443.2.

Synthesis of IPr#-aniline (3-6)



Following the general procedure using aniline (3.79 g, 3.70 mL) and benzhydrol (22.5 g, 122.1 mmol) giving 21.05 g (35.6 mmol, 87%) as a white solid after reflux in MeOH. Spectral data matches literature.[88]
^{1}H NMR (500 MHz, $CDCl_3$): δ7.29 (d, *J* = 9.7 Hz, 3H), 7.26 – 7.12 (m, 15H), 7.07 (d, *J* = 7.1 Hz, 9H), 6.93 (d, *J* = 7.0 Hz, 4H), 6.41 (s, 2H), 5.47 (s, 2H), 5.21 (s, 1H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$): δ144.96, 142.73, 140.41, 132.70, 129.94, 129.57, 129.27, 129.15, 128.60, 128.10, 126.71, 125.88, 56.32, 52.63 ppm.

Synthesis of p-SO_2NH_2-IPr*-aniline (3-7)

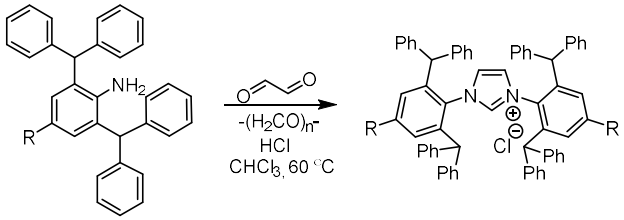


Following the general procedure using sulfanilamide (7.0 g). The general procedure was modified as follows: after stirring for 2 hours resulting in a thick glassy solid, the tube was cooled to room temperature, and CH_2Cl_2 (15 mL) was added to the tube along with H_2O (5mL). The tube was then sonicated, and an orange solid remained. The solid was filtered through a frit and washed with acetone until white giving 10.89 g (21.6 mmol, 53%) as a white solid.

^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ7.32 (t, *J* = 7.5 Hz, 8H), 7.24 (t, *J* = 7.3 Hz, 4H), 7.09 (d, *J* = 7.9 Hz, 8H), 6.90 (s, 2H), 5.72 (s, 2H) ppm.

^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ146.49, 142.86, 130.62, 129.64, 128.82, 127.34, 126.93, 126.28, 50.60 ppm.

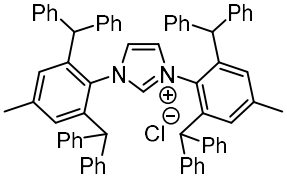
Preparation of NHC-HCl salts



General Procedure for preparation of NHC-HCl salts

To a 150 mL round-bottom flask was added substituted aniline (9.80 mmol), 40% glyoxal (1.2 mL, 10.5 mmol), solid paraformaldehyde (600 mg, 10.5 mmol), $CHCl_3$ (30 mL) and a large egg-shaped stir bar. The reaction mixture was heated to 60 °C and conc. HCl (900 µL,10.5 mmol) was slowly added dropwise. The resulting mixture was stirred for 18 hours. Upon cooling to room temperature, the compound was extracted into CH_2Cl_2, and washed with water and brine. The organic layers were combined, dried with $MgSO_4$, filtered, then concentrated *in vacuo*. The resulting solid was then dispersed in 1:1 hexane:EtOAc and refluxed for 30 min. The resulting solution was filtered, and the product was dried *in vacuo* to give the desired products.

Synthesis of IPr*-HCl (3-8)

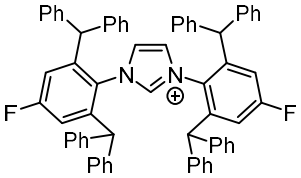


Following the general procedure using 4.30 g (9.80 mmol) of **3-4** giving 2.49 g (2.62 mmol, 54%) as a white powder. Spectral data matchs literature.[87]

^{1}H NMR (500 MHz, $CDCl_3$): δ13.02 (s, 1H, carbene-H), 7.29 (s, 2H), 7.24 (t, *J* = 7.1 Hz, 14H), 7.19 (t, *J* = 6.3 Hz, 6H), 7.17 – 7.10 (m, 14H), 6.81 – 6.76 (m, 13H), 5.49 (s, 2H), 5.29 (s, 4H), 2.20 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ142.72, 142.07, 141.66, 140.79, 131.00, 130.27, 130.21, 129.41, 128.84, 128.75, 127.12, 127.05, 123.54, 51.55, 22.05 ppm. *Despite our best efforts, the carbene carbon could not be located.*

Synthesis of p-F IPr*-HCl (3-9)



Following the general procedure using 4.34 g (9.80 mmol) of **3-5** giving 2.10 g (2.2 mmol, 45%) as a green-ish powder.

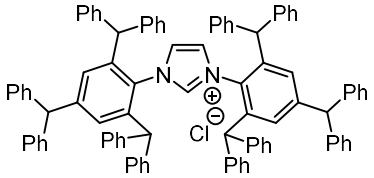
^{1}H NMR (500 MHz, $CDCl_3$): δ13.34 (s, 1H, carbene-H), 7.31 – 7.28 (m, 8H), 7.25 – 7.22 (m, 12H), 7.19 (d, *J* = 7.2 Hz, 4H), 7.14 (t, *J* = 7.3 Hz, 8H), 6.78 (d, *J* = 7.3 Hz, 8H), 6.71 (d, *J* = 8.9 Hz, 4H), 5.47 (d, *J* = 1.2 Hz, 2H), 5.34 (s, 4H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ164.69 (C, carbene), 162.68, 144.43, 144.36, 141.94, 141.28, 130.14, 129.20, 129.09, 128.97, 128.34, 127.47, 123.47, 117.77, 117.66 – 117.56, 60.60, 51.71.

^{19}F NMR (470 MHz, $CDCl_3$): δ-105.57 ppm.

HRMS: calc'd for $C_{67}H_{51}ClF_2N_2$ 921.4 $[M\text{-}Cl]^+$; 921.3973 found.

Synthesis of IPr#-HCl (3-10)



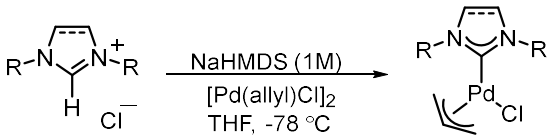
Following the general procedure using 5.80 g (9.80 mmol) of **3-6** giving 4.40 g (3.50 mmol mmol, 72%) as a white powder after recrystallization from 1:1 hexane:EtOAc. Spectral data matches literature.[88]

^{1}H NMR (400 MHz, $CDCl_3$): δ13.02 (s, 1H, carbene-H), 7.19 – 7.05 (m, 44H), 6.91 (d, *J* = 6.9 Hz, 8H), 6.72 (s, 4H), 6.68 (d, *J* = 7.3 Hz, 8H), 5.60 (s, 2H), 5.34 (s, 2H), 5.29 (s, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ147.21 (C, carbene), 142.85, 142.46, 141.93, 140.70, 131.69, 130.69, 129.95, 129.38, 129.29, 128.77, 128.70, 128.54, 127.05, 126.90, 126.58, 123.57, 56.34, 51.51 ppm.

Preparation of Pd-NHC precursors

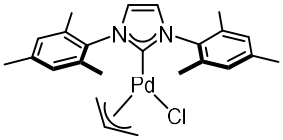
Preparation of [(NHC)Pd(allyl)Cl] complexes



General procedure for the preparation of [(NHC)Pd(allyl)Cl] complexes

$[Pd(allyl)Cl]_2$ (80 mg, 0.22 mmol) and NHC-HCl (0.52 mmol) were dissolved into 12 mL of anhydrous THF in a 50 mL round bottom flask under argon. The flask was cooled to -78 °C over 10 minutes. A solution of NaHMDS (1M in THF – 0.52 mL, 0.52 mmol) was added dropwise and the solution was stirred for an additional 10 minutes before removing the cold bath. The solution was allowed to warm to room temperature over 2 hours. During this time, lightening in colour of the solution, and the precipitation of white solid was generally observed. The flask was then exposed to air where 0.5 mL of MeOH was added and all volatiles were removed *in vacuo*. The residue was then dispersed in CH_2Cl_2 and run through a short pad of silica gel eluting with CH_2Cl_2. The resulting residue was triturated with hexanes and dried *in vacuo*. The resulting product could be recrystallized by layering hexanes onto a concentrated solution of CH_2Cl_2.

Synthesis of [(IMes)Pd(allyl)Cl] (2-1)

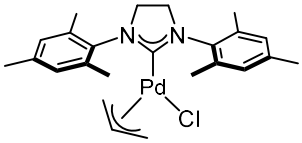


Following the general procedure using $[Pd(allyl)Cl]_2$ (80.0 mg, 0.22 mmol) and IMes-HCl (178.9 mg, 0.53 mmol), in 12 mL of anhydrous THF with 0.52 mL of NaHMDS (1M in THF) giving 177.6 mg (0.36 mmol, 82%) as an off-white solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.09 (s, 2H), 6.97 (s, 4H), 4.86 (ddd, *J* = 19.5, 12.8, 7.2 Hz, 1H), 3.88 (dd, *J* = 7.4, 2.4 Hz, 1H), 3.20 (d, *J* = 6.8 Hz, 1H), 2.82 (d, *J* = 13.4 Hz, 1H), 2.33 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H), 1.80 (d, *J* = 11.9 Hz, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 183.9 (C, carbene), 139.0, 136.0, 135.6, 129.2, 129.2, 123.1, 114.4, 72.5, 49.3, 21.3, 18.5, 18.4 ppm.

Synthesis of [(SIMes)Pd(allyl)Cl] (2-2)

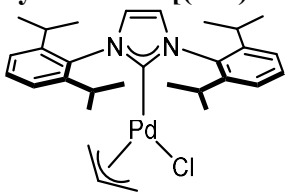


Following the general procedure using $[Pd(allyl)Cl]_2$ (80.0 mg, 0.22 mmol) and SIMes-HCl (181.0 mg, 0.53 mmol), in 12 mL of anhydrous THF with 0.52 mL of NaHMDS (1M in THF) giving 160.4 mg, (0.33 mmol, 74%) as a white solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.92 (s, 4H), 4.86 – 4.72 (m, 1H), 4.04 – 3.95 (m, 4H), 3.82 (dd, *J* = 7.5, 2.3 Hz, 1H), 3.26 (d, *J* = 7.0 Hz, 1H), 2.75 (d, *J* = 13.3 Hz, 1H), 2.43 (s, 6H), 2.42 (s, 6H), 2.29 (s, 6H), 1.77 (d, *J* = 11.7 Hz, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 211.5 (C, carbene), 138.3, 136.1, 129.6, 114.9, 73.2, 51.4, 49.5, 21.3, 18.7, 18.6 ppm.

Synthesis of [(IPr)Pd(allyl)Cl] (2-3)

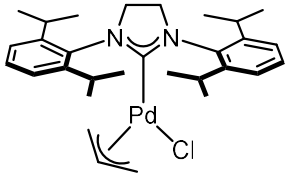


Following the general procedure using $[Pd(allyl)Cl]_2$ (80.0 mg, 0.22 mmol) and IPr-HCl (225.5 mg, 0.53 mmol), in 12 mL of anhydrous THF with 0.52 mL of NaHMDS (1M in THF) giving 232.3 mg (0.40 mmol, 92%) as a white solid after purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43 (t, *J* = 7.8 Hz, 1H), 7.28 (dd, *J* = 6.7, 5.8 Hz, 3H), 7.16 (s, 1H), 4.87 – 4.76 (m, 1H), 3.91 (dd, *J* = 7.5, 2.0 Hz, 1H), 3.13 (dt, *J* = 13.5, 6.7 Hz, 1H), 3.05 (d, *J* = 7.0 Hz, 1H), 2.87 (dt, *J* = 13.6, 6.8 Hz, 1H), 2.78 (d, *J* = 13.4 Hz, 1H), 1.59 (d, *J* = 12.0 Hz, 1H), 1.40 (d, *J* = 6.7 Hz, 3H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 186.27 (C, carbene), 146.35, 146.12, 135.98, 130.04, 124.27, 124.03, 123.91, 114.30, 72.66, 49.65, 28.73, 28.66, 26.67, 25.91, 23.09, 22.94 ppm.

Synthesis of [(SIPr)Pd(allyl)Cl] (2-4)

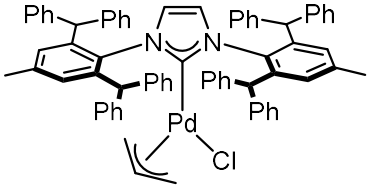


Following the general procedure using $[Pd(allyl)Cl]_2$ (80.0 mg, 0.22 mmol) and SIPr-HCl (226.5 mg, 0.52 mmol), in 12 mL of anhydrous THF with 0.52 mL of NaHMDS (1M in THF) giving 242.3 mg (0.42 mmol, 96%) as a white solid after purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (t, *J* = 7.7 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 4H), 4.82 – 4.70 (m, 1H), 4.14 – 3.96 (m, 4H), 3.89 (d, *J* = 7.5 Hz, 1H), 3.47 (dp, *J* = 37.5, 7.0 Hz, 4H), 3.55 – 3.38 (m, 4H), 3.02 (d, *J* = 6.4 Hz, 1H), 2.74 (d, *J* = 13.4 Hz, 1H), 1.47 (d, *J* = 6.6 Hz, 6H), 1.37 (d, *J* = 6.6 Hz, 6H), 1.29 (d, *J* = 6.9 Hz, 6H), 1.25 (d, *J* = 6.9 Hz, 6H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 213.4 (C, carbene), 147.5, 147.2, 136.5, 129.2, 124.5, 114.8, 73.3, 54.2, 50.0, 28.7, 28.7, 26.8, 26.8, 24.0, 23.8 ppm.

Synthesis of [(IPr*)Pd(allyl)Cl] (2-5/3-11)



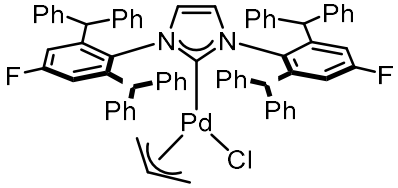
The general procedure was modified as follows. $[Pd(allyl)Cl]_2$ (50.0 mg, 0.14 mmol) and IPr*-HCl (325.0 mg, 0.34 mmol), were dispersed in 7.5 mL of anhydrous THF at -78 °C and 0.33 mL of NaHMDS (1M in THF) was added dropwise. After workup following the general procedure, the residue was dispersed in $CHCl_3$ and loaded onto a short pad of silica gel eluting with CH_2Cl_2 giving 246.3 mg (0.22 mmol, 80%) as an off-white solid. The resulting product could be recrystallized by layering hexanes onto a concentrated solution of $CHCl_3$.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.29 (m, 8H), 7.26 – 7.18 (m, 12H), 7.11 (dd, *J* = 6.8, 2.4 Hz, 12H), 6.84 – 6.80 (m, 12H), 5.86 (d, *J* = 3.5 Hz, 4H), 5.20 (s, 2H), 4.61 – 4.52 (m, 1H), 4.11 (dd, *J* = 7.2, 1.7 Hz, 1H), 3.00 (d, *J* = 13.6 Hz, 1H), 2.63 (d, *J* = 6.7 Hz, 1H), 2.20 (s, 6H), 1.11 (d, *J* = 12.0 Hz, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 184.46 (C, carbene), 144.68, 144.56, 143.74, 143.65, 141.53, 141.41, 138.50, 135.96, 130.67, 130.59, 130.21, 130.08, 129.41, 129.39, 128.37, 128.18, 126.47, 126.40, 126.38, 123.35, 114.94, 77.42, 77.16, 76.91, 72.00, 51.53, 51.47, 31.75, 21.92 ppm.

HRMS: calc'd for $C_{73}H_{68}N_2Pd$ 1059.3870 $[M\text{-}Cl]^+$; found 1059.3870.

Synthesis of [(*p*-F-IPr*)Pd(allyl)Cl] (3-12)



The general procedure was modified as follows. $[Pd(allyl)Cl]_2$ (50.0 mg, 0.14 mmol) and *p*-F-IPr*-HCl (326.0 mg, 0.34 mmol), were dispersed in 7.5 mL of anhydrous THF at -78 °C and 0.33 mL of NaHMDS (1M in THF) was added dropwise. After workup following the general procedure, the residue was dispersed in $CHCl_3$ and loaded onto a short pad of silica gel eluting with CH_2Cl_2 giving 242 mg (0.22 mmol, 78%) as an off-white solid. The resulting product could be recrystallized by layering hexanes onto a concentrated solution of $CHCl_3$.

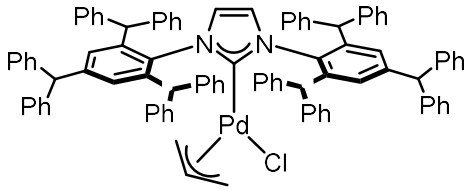
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.27 (m, 14H), 7.26 – 7.19 (m, 9H), 7.17 – 7.09 (m, 14H), 6.78 – 6.71 (m, 5H), 5.88 (d, *J* = 2.5 Hz, 4H), 5.18 (s, 2H), 4.73 – 4.64 (m, 1H), 4.20 (d, *J* = 7.5 Hz, 1H), 3.08 (d, *J* = 13.4 Hz, 1H), 2.69 (d, *J* = 7.4 Hz, 1H), 1.22 (d, *J* = 12.2 Hz, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ185.20 (C, carbene), 163.02, 161.03, 144.66, 143.63, 142.61, 134.02, 130.25, 129.04, 128.39, 126.82, 126.61, 123.20, 116.44, 115.03, 72.49, 51.78 – 51.29, 29.70 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ-109.63 ppm.

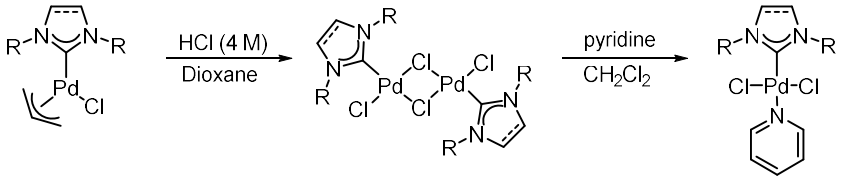
HRMS: calc'd for $C_{70}H_{55}ClF_2N_2Pd$ 1067.34 $[M\text{-}Cl]^+$; 1067.3358 found.

Synthesis of [(IPr#)Pd(allyl)Cl] (3-13)



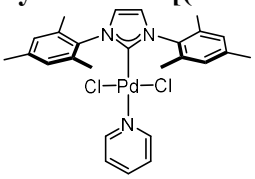
The general procedure was modified as follows. $[Pd(allyl)Cl]_2$ (50.0 mg, 0.14 mmol) and IPr#-HCl (426.0 mg, 0.34 mmol), were dispersed in 7.5 mL of anhydrous THF at -78 °C and 0.33 mL of NaHMDS (1M in THF) was added dropwise. After workup following the general procedure, the residue was dispersed in $CHCl_3$ and loaded onto a short pad of silica gel eluting with CH_2Cl_2 giving 252 mg (0.18 mmol, 64%) as a white solid. The resulting product could be recrystallized by layering hexanes onto a concentrated solution of $CHCl_3$.
^{1}H NMR (500 MHz, $CDCl_3$): δ7.23 – 7.02 (m, 55H), 6.92 (d, *J* = 6.8 Hz, 9H), 6.77 (dd, *J* = 13.2, 5.4 Hz, 14H), 5.92 (s, 2H), 5.77 (s, 2H), 5.35 (s, 2H), 5.34 (s, 2H), 4.49 – 4.37 (m, 1H), 4.10 (d, *J* = 6.8 Hz, 1H), 2.93 (d, *J* = 13.3 Hz, 1H), 2.53 (d, *J* = 6.8 Hz, 1H), 1.08 (d, *J* = 12.2 Hz, 1H) ppm.
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ184.32 (C, carbene), 144.61, 144.50, 144.32, 143.46, 143.34, 141.47, 141.40, 136.43, 130.95, 130.77, 130.38, 130.33, 129.37, 129.33, 129.30, 128.48, 128.40, 128.14, 128.12, 126.44, 126.40, 123.43, 115.08, 71.83, 67.32, 56.44, 51.73, 51.66 ppm.
HRMS: calc'd for $C_{96}H_{77}ClN_2Pd$ 1363.51 $[M\text{-}Cl]^+$; 1363.5115 found.
calc'd for $C_{67}H_{51}ClF_2N_2$ 921.4 $[M\text{-}Cl]^+$; 921.3973 found

Preparation of [(NHC)Pd(pyr)Cl] complexes



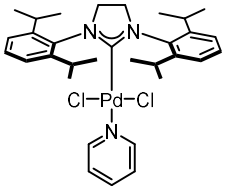
General procedure for the preparation of [(NHC)Pd(pyr)Cl] complexes:
Pd-PEPPSI-NHC type complexes were prepared via a two-step procedure modified from a procedure reported by Organ.[128] The [(NHC)Pd(allyl)Cl] complex (**1-4**) was added to a flame dried 4 dram vial containing a stir bar sealed with a rubber septum under inert atmosphere. HCl (4 M in dioxane) was then injected via syringe, and the resulting solution was stirred at room temperature for 18 hours. The resulting solution was then evaporated to dryness in vacuo to dryness resulting in $[(NHC)PdCl_2]_2$ which were carried through directly without any purification.
The resulting $[(NHC)PdCl_2]_2$ was dissolved into 2 mL of CH_2Cl_2 and pyridine (21 µL, 0.26 mmol) was added via micropipette, and the solution was stirred for 3 hours at room temperature. The resulting mixture was loaded directly onto a small plug of silica gel, eluting with CH_2Cl_2. $[(NHC)Pd(pyr)Cl_2]$ complexes were obtained upon evaporation of all volatiles in vacuo and could be recrystallized by layering hexanes onto a concentrated CH_2Cl_2 solution.

Synthesis of [(IMes)Pd(pyr)Cl] (2-6)



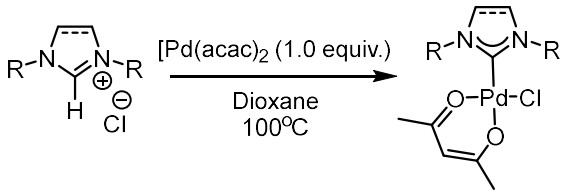
Following the general procedure using [(IMes)Pd(allyl)Cl] (195 mg, 0.4 mmol) and 2 mL of 4M HCl in dioxane to give $[Pd(SIMes)Cl_2]_2$ which was then treated with 12 µL of pyridine and 2 mL of CH_2Cl_2 to afford 200 mg (0.36 mmol, 89%) of product as an off-white solid. Spectral data matches literature.[83]
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (d, *J* = 4.9 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.11 (dd, *J* = 7.6, 6.5 Hz, 2H), 7.08 (s, 2H), 7.06 (s, 4H), 2.39 (s, 6H), 2.37 (s, 12H) ppm.

Synthesis of [(SIPr)Pd(pyr)Cl_2] (2-7)



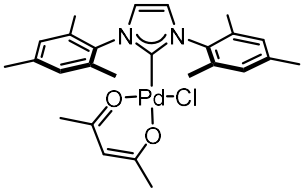
Following the general procedure using [(SIPr)Pd(allyl)Cl] (230 mg, 0.4 mmol) and 2 mL of 4M HCl in dioxane to give $[Pd(SIPr)Cl_2]_2$ which was then treated with 12 µL of pyridine and 2 mL of CH_2Cl_2 to afford 200 mg (0.31 mmol, 77%) of product as an off-white solid. Spectral data matches literature.[83]
^{1}H NMR (500 MHz, $CDCl_3$): δ8.52 (d, *J* = 5.0 Hz, 2H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.31 (d, *J* = 7.7 Hz, 4H), 7.11 – 7.07 (m, 2H), 4.07 (s, 4H), 3.61 (dt, *J* = 13.5, 6.6 Hz, 4H), 1.58 (d, *J* = 6.6 Hz, 12H), 1.27 (d, *J* = 6.9 Hz, 12H) ppm.

Preparation of [(NHC)Pd(acac)Cl] complexes



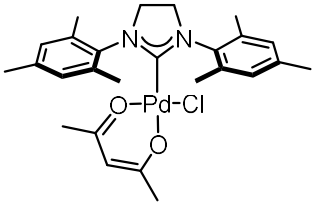
General Procedure for the Preparation of [(NHC)Pd(acac)Cl] complexes:
A flame dried culture tube under argon was charged with [$Pd(acac)_2$] (1 equiv.) and NHC-HCl (1.05 equiv.) and dissolved into anhydrous dioxane. The flask was sealed and heated to 105 °C for 18 hours. The reaction was returned to room temperature, and solvent was removed in vacuo, The residue was dissolved into CH_2Cl_2 and filtered through a small pad of silica gel, eluting with 100% CH_2Cl_2. The products could be recrystallized by layering hexane onto a concentrated solution of CH_2Cl_2. Obtained spectral data matched previously reported literature.[127]

Synthesis of [(IMes)Pd(acac)Cl] (2-10)



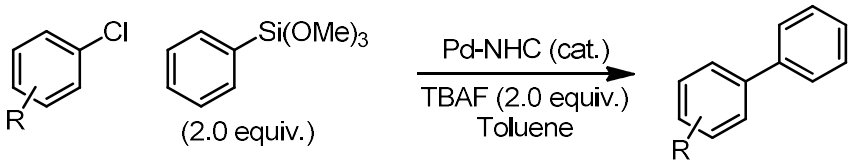
Following the general procedure using $Pd(acac)_2$ (80.0 mg, 0.26 mmol) and IMes-HCl (92.0 mg, 0.27 mmol) in 0.75 mL of dioxane, giving 104.2 mg (0.19 mmol, 73%) as a lightly yellow solid.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (s, 2H), 7.06 – 6.97 (m, 4H), 5.13 (s, 1H), 2.38 (s, 3H), 2.36 – 2.10 (m, 6H), 1.83 (s, 3H), 1.78 (s, 3H) ppm.
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 187.28 (C, carbene), 183.27, 153.99, 139.38, 136.66, 135.77, 135.11, 129.89, 129.01, 123.94, 99.79, 27.27, 25.72, 21.36, 18.98, 17.96 ppm.

Synthesis of [(SIMes)Pd(acac)Cl] (2-24)



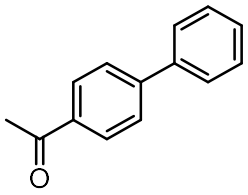
Following the general procedure using $Pd(acac)_2$ (80.0 mg, 0.26 mmol) and SIMes-HCl (92.5 mg, 0.27 mmol) in 0.75 mL of dioxane, giving 86.5 mg (0.16 mmol, 60%) as a lightly yellow solid.
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (d, J = 32.0 Hz, 4H), 5.10 (s, 1H), 4.09 – 3.93 (m, 4H), 2.53 (s, 6H), 2.36 (s, 6H), 2.33 (s, 6H), 1.83 (s, 3H), 1.79 (s, 3H) ppm.
^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ187.32 (C, carbene), 185.52, 183.10, 138.62, 137.68, 136.45, 135.00, 130.24, 129.24, 99.78, 51.21, 51.06, 27.32, 25.89, 21.30, 19.21, 18.20 ppm.

Hiyama cross-coupling of aryl chlorides



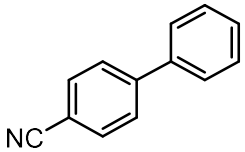
General procedure for the Hiyama cross-coupling of aryl chlorides:
An oven dried culture tube sealed with a rubber septum and under a N_2 atmosphere was charged with precatalyst. Anhydrous solvent was added via syringe, followed by the addition of aryl chloride (0.6 mmol), aryl siloxane (220 µL, 1.2 mmol), and undecane (130 µL, 0.6 mmol) as an internal standard. TBAF (1M in THF – 1.2 mL, 1.2 mmol) was then injected via syringe. Solutions were typically homogeneous and colourless. The culture tube was sealed, wrapped in parafilm and heated in an aluminum heating block at the indicated temperature. After the indicated time, the reaction was cooled to room temperature, quenched with the addition of EtOAc, and ran through a plug of silica gel eluting with EtOAc, and all volatiles were removed *in vacuo*. The residue was then applied directly to column chromatography eluting with hexanes/EtOAc.

Synthesis of 4-Acetylbiphenyl (2-11):



Following the general procedure using 4-chloroacetophenone (78 µL, 0.6 mmol), $PhSi(OMe)_3$ (220 µL, 1.2 mmol), [Pd(SIMes)(allyl)Cl] (3.0 mg, 0.006 mmol) and TBAF (1M in THF – 1.2 mL, 1.2 mmol) in 4 mL of anhydrous toluene at 90 °C for 18 hours. Giving 100.5 mg (0.51 mmol, 85%) of product as a white solid after column chromatography using first hexane, followed by hexane:EtOAc (10:1).
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 – 8.03 (m, 2H), 7.73 – 7.69 (m, 2H), 7.67 – 7.63 (m, 2H), 7.52 – 7.47 (m, 2H), 7.45 – 7.40 (m, 1H), 2.66 (s, 3H) ppm.
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.95, 146.02, 140.11, 136.10, 129.17, 129.13, 128.45, 127.50, 127.45, 26.89 ppm.
LRMS: calc'd for $C_{14}H_{12}O$ 196.1 [M^+]; found 196.1

Synthesis of 4-Cyanobiphenyl (2-12):



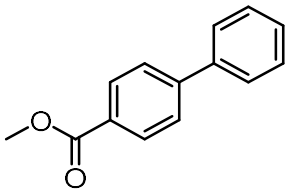
Following the general procedure using 4-chlorobenzonitrile (83.0 mg, 0.6 mmol), $PhSi(OMe)_3$ (220 μL, 1.2 mmol), [Pd(SIMes)(allyl)Cl] (3.0 mg, 0.006 mmol) and TBAF (1M in THF – 1.2 mL, 1.2 mmol) in 4 mL of anhydrous toluene at 90 °C for 18 hours. Giving 103.0 mg (0.57 mmol, 96%) of product as a white solid after column chromatography using hexane, followed by hexane:EtOAc (10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 – 7.66 (m, 1H), 7.63 – 7.57 (m, 1H), 7.53 – 7.47 (m, 1H), 7.47 – 7.41 (m, 1H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 145.94, 139.44, 132.85, 129.36, 128.91, 127.99, 127.49, 119.19, 111.18 ppm.

LRMS: Calc'd for C_1H_9N 179.1 [M^+]; found 179.1

Synthesis of 4-phenyl methylbenzoate (2-13):



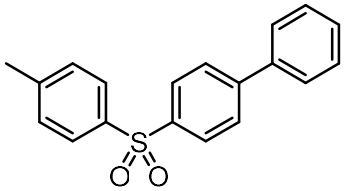
Following the general procedure using 1-chloro-4-methylbenzoate (102.0 mg, 0.6 mmol), $PhSi(OMe)_3$ (220 μL, 1.2 mmol), [Pd(SIMes)(allyl)Cl] (3.0 mg, 0.006 mmol) and TBAF (1M in THF – 1.2 mL, 1.2 mmol) in 4 mL of anhydrous toluene at 90 °C for 18 hours. Giving 125.0 mg (0.59 mmol, 98%) of product as a white solid after column chromatography using hexane:EtOAc (4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 – 8.09 (m, 2H), 7.71 – 7.60 (m, 4H), 7.52 – 7.44 (m, 4H), 7.44 – 7.38 (m, 1H), 3.95 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.3, 145.9, 140.3, 130.3, 129.2, 128.4, 127.5, 127.3, 52.4 ppm.

LRMS: Calc'd for $C_{14}H_{12}O_2$ 212.1 [M^+]; found 212.1

Synthesis of 4-Tosyl-1,1'biphenyl (2-14):



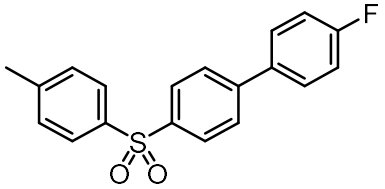
Following the general procedure using 1-chloro-4-tosylbenzene (160.0 mg, 0.6 mmol), $PhSi(OMe)_3$ (220 µL, 1.2 mmol), [Pd(SIMes)(allyl)Cl] (3.0 mg, 0.006 mmol) and TBAF (1M in THF – 1.2 mL, 1.2 mmol) in 4 mL of anhydrous toluene at 90 °C for 18 hours. Giving 171.0 mg (0.55 mmol, 93%) of product as a white solid after column chromatography using hexane:EtOAc (4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.62 – 7.55 (m, 1H), 7.52 – 7.39 (m, 2H), 7.34 (d, *J* = 8.3 Hz, 1H), 2.43 (s, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 146.2, 144.4, 140.8, 139.5, 139.0, 130.2, 129.3, 128.8, 128.3, 128.1, 127.9, 127.6, 21.8 ppm.

LRMS: Calc'd for $C_{19}H_{16}O_2S$ 308.1 [M^+]; found 308.1

Synthesis of 4-Fluoro,4'-Tosyl-1,1'biphenyl (2-15):



Following the general procedure using 1-chloro-4-tosylbenzene (160.0 mg, 0.6 mmol), 4-F-$PhSi(OMe)_3$ (230.0 µL, 1.2 mmol), [Pd(SIMes)(allyl)Cl] (3.0 mg, 0.006 mmol) and TBAF (1M in THF – 1.2 mL, 1.2 mmol) in 4 mL of anhydrous toluene at 90 °C for 18 hours. Giving 191.9 mg (0.59 mmol, 98%) of product as a white solid after column chromatography using hexane, followed by hexane:EtOAc (10:1).

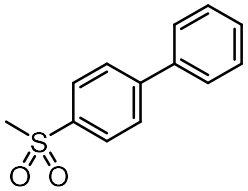
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.53 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.15 (t, *J* = 8.6 Hz, 2H), 2.41 (s, 3H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 163.3 (d, *J* = 248.5 Hz), 145.1, 144.4, 140.8, 138.9, 135.5 (d, *J* = 3.3 Hz), 130.1, 129.2 (d, *J* = 8.2 Hz), 128.3, 127.9, 127.9, 116.2 (d, *J* = 21.7 Hz), 21.8 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -113.4 ppm

LRMS: Calc'd for $C_{19}H_{15}FO_2S$ 326.1 [M^+]; found 326.1

Synthesis of 4-(methylsulfonyl)-1,1'-biphenyl (2-16):



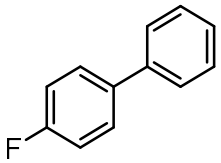
Following the general procedure using 1-chloro-4-(methylsulfonyl)benzene (114.0 mg, 0.6 mmol), $PhSi(OMe)_3$ (220 µL, 1.2 mmol), [Pd(SIMes)(allyl)Cl] (3.0 mg, 0.006 mmol) and TBAF (1M in THF – 1.2 mL, 1.2 mmol) in 4 mL of anhydrous toluene at 90 °C for 18 hours. Giving 112.4 mg (0.48 mmol, 80%) of product as a white solid after column chromatography using hexane, followed by hexane:EtOAc (10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.65 – 7.58 (m, 2H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.47 – 7.42 (m, 1H), 3.11 (s, 3H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 146.9, 139.3, 139.3, 129.3, 128.9, 128.2, 128.1, 127.6, 44.8 ppm.

LRMS: Calc'd for $C_{13}H_{12}O_2S$ 232.0 [M^+]; found 232.0

Synthesis of 4-Fluorobiphenyl (2-17):



According to the general procedure, 4-fluorochlorobenzene (64 µL 0.6 mmol), $PhSi(OMe)_3$ (220 µL, 1.2 mmol), [Pd(IMes)(allyl)Cl] (3.0 mg, 0.006 mmol) and TBAF (1M in THF – 1.2 mL, 1.2 mmol) in 4 mL of anhydrous toluene at 90 °C for 18 hours. Giving 43.3 mg (0.25 mmol, 42%) of product as a white solid after column chromatography using hexane:EtOAc (20:1).

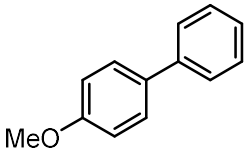
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 – 7.54 (m, 4H), 7.48 – 7.42 (m, 2H), 7.38 – 7.33 (m, 1H), 7.17 – 7.11 (m, 2H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.6 (d, *J* = 246.2 Hz), 140.4, 137.5 (d, *J* = 3.5 Hz), 128.9, 128.8 (d, *J* = 8.1 Hz), 127.4, 127.2, 115.7 (d, *J* = 21.4 Hz) ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ -115.51 ppm

LRMS: calc'd for $C_{12}H_9F$ 172.1 [M^+]; found 172.1

Synthesis of 4-methoxy biphenyl (2-18):



From 4-Bromo Anisole

Following the general procedure using 1-bromo-4-methoxybenzene (75 µL, 0.6 mmol), $PhSi(OMe)_3$ (220 µL, 1.2 mmol), [Pd(SIMes)(allyl)Cl] (3.0 mg, 0.006 mmol) and TBAF (1M in THF – 1.2 mL, 1.2 mmol) in 4 mL of anhydrous toluene at 90 °C for 18 hours. Giving 92.1 mg (0.5 mmol, 83%) of product as a white solid after column chromatography using hexane, followed by hexane:EtOAc (10:1).

From 4-Chloro Anisole

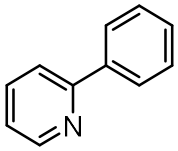
Following the general procedure using 1-chloro-4-methoxybenzene (73 µL, 0.6 mmol), $PhSi(OMe)_3$ (220 µL, 1.2 mmol), [Pd(SIMes)(allyl)Cl] (3.0 mg, 6 µmol) and TBAF (1M in THF – 1.2 mL, 1.2 mmol) in 4 mL of anhydrous toluene at 90 °C for 18 hours. Giving 17.7 mg (0.1 mmol, 16%) of product as a white solid after column chromatography using hexane, followed by hexane:EtOAc (10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 – 7.51 (m, 4H), 7.42 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.02 – 6.96 (m, 2H), 3.86 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.4, 141.1, 134.0, 128.9, 128.4, 126.9, 126.9, 114.5, 55.6 ppm.

LRMS: calc'd for $C_{13}H_{12}O$ 184.1 [M^+]; found 184.1

Synthesis of 2-phenylpyridine (2-19):



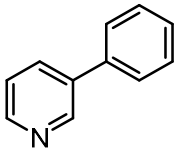
Following the general procedure using 2-chloropyridine (56 µL, 0.6 mmol), $PhSi(OMe)_3$ (220 µL, 1.2 mmol), [Pd(SIMes)(allyl)Cl] (3.0 mg, 6 µmol) and TBAF (1M in THF – 1.2 mL, 1.2 mmol) in 4 mL of anhydrous toluene at 90 °C for 18 hours. Giving 41.6 mg (0.27 mmol, 45%) of product as a transparent yellow oil after column chromatography using hexane, followed by hexane:EtOAc (10:1, then 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ8.90 (s, 1H), 8.64 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.60 – 7.57 (m, 2H), 7.49 (dd, J = 11.3, 4.0 Hz, 2H), 7.43 – 7.36 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ157.65, 149.80, 139.52, 137.00, 129.18, 128.95, 127.13, 122.30, 120.80 ppm.

LRMS: calc'd for $C_{11}H_9N$ 155.1 [M^+]; found 155.1

Synthesis of 3-phenylpyridine (2-20):



Following the general procedure using 3-chloropyridine (56 µL, 0.6 mmol), $PhSi(OMe)_3$ (220 µL, 1.2 mmol), [Pd(SIMes)(allyl)Cl] (3.0 mg, 6 µmol) and TBAF (1M in THF – 1.2 mL, 1.2 mmol) in 4 mL of anhydrous toluene at 90 °C for 18 hours. Giving 45.0 mg (0.29 mmol, 48%) of product as a transparent yellow oil after column chromatography using hexane, followed by hexane:EtOAc (10:1, then 1:1).

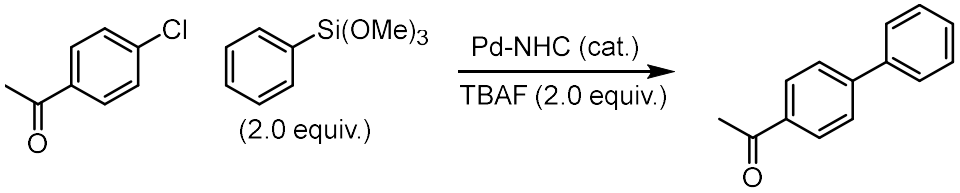
^{1}H NMR (500 MHz, $CDCl_3$): δ8.71 (s, 1H), 8.01 (d, *J* = 7.3 Hz, 2H), 7.79 – 7.73 (m, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.25 (t, *J* = 6.7 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ148.49, 148.36, 138.00, 134.59, 129.27, 128.31, 127.34 ppm.

LRMS: calc'd for $C_{11}H_9N$ 155.1 [M^+]; found 155.1

Reaction Monitoring

GC-MS



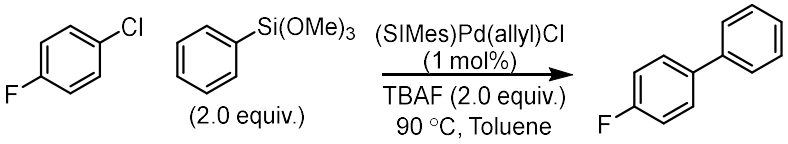
General Procedure: An oven dried 50 mL Schlenk Flask under N_2 atmosphere and sealed with a rubber septum was charged with catalyst (1 mol%). Anhydrous toluene was added via syringe, followed by the addition of aryl chloride (0.6 mmol), aryl siloxane (220 µL, 1.2 mmol), and undecane (130 µL, 0.6 mmol) as an internal standard. TBAF (1M in THF – 1.2 mL, 1.2 mmol) was then injected via syringe (T = 0) and the Schlenk flask was heated in a 90 ºC silicone oil bath. At each indicated timepoint, 0.1 mL aliquots were taken via syringe (while at 90 ºC) and diluted with 1 mL EtOAc, then run through a short plug of silica gel with an additional 2 mL of EtOAc. Each time-point was then analyzed by GC-MS (**Table A1**).

Table A-1. *Conversions of product over time with precatalyst **2-2** and **2-3**.*

Precatalyst 2-2		**Precatalyst 2-3**	
Time (min)	**Conversion (%)**	**Time (min)**	**Conversion (%)**
0	0	0	0
5	4.9	5	19.3
10	5.4	10	27.8
20	17.1	20	44.5
40	28.1	30	50.5
60	42.2	40	53.1
120	83.8	60	58.5
240	92.1	90	60.4
		150	65.1
		240	76.3

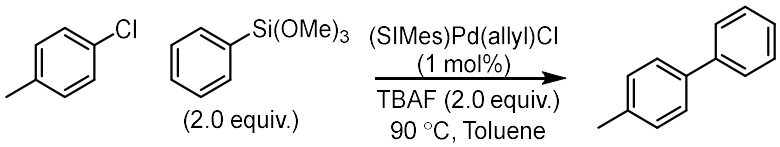
^{19}F NMR Spectroscopy

4-Fluorochlorobenzene



General Procedure: An oven dried 25 mL Schlenk Flask under N_2 atmosphere and sealed with a rubber septum was charged with catalyst (1 mol%). Anhydrous toluene (3 mL) was added via syringe, followed by the addition of aryl chloride (0.6 mmol), aryl siloxane (220 µL, 1.2 mmol), and 1-Fluoronapthalene (39 µL, 0.6 mmol) as an internal standard. TBAF (1M in THF – 1.2 mL, 1.2 mmol) was then injected via syringe (T = 0) and the Schlenk flask was heated in a 90 ºC silicone oil bath. A 0.1 mL aliquot was taken via syringe (while at 90 ºC) at each indicated timepoint and diluted with 0.4 mL of $CDCl_3$, then analyzed by ^{19}F NMR spectroscopy.

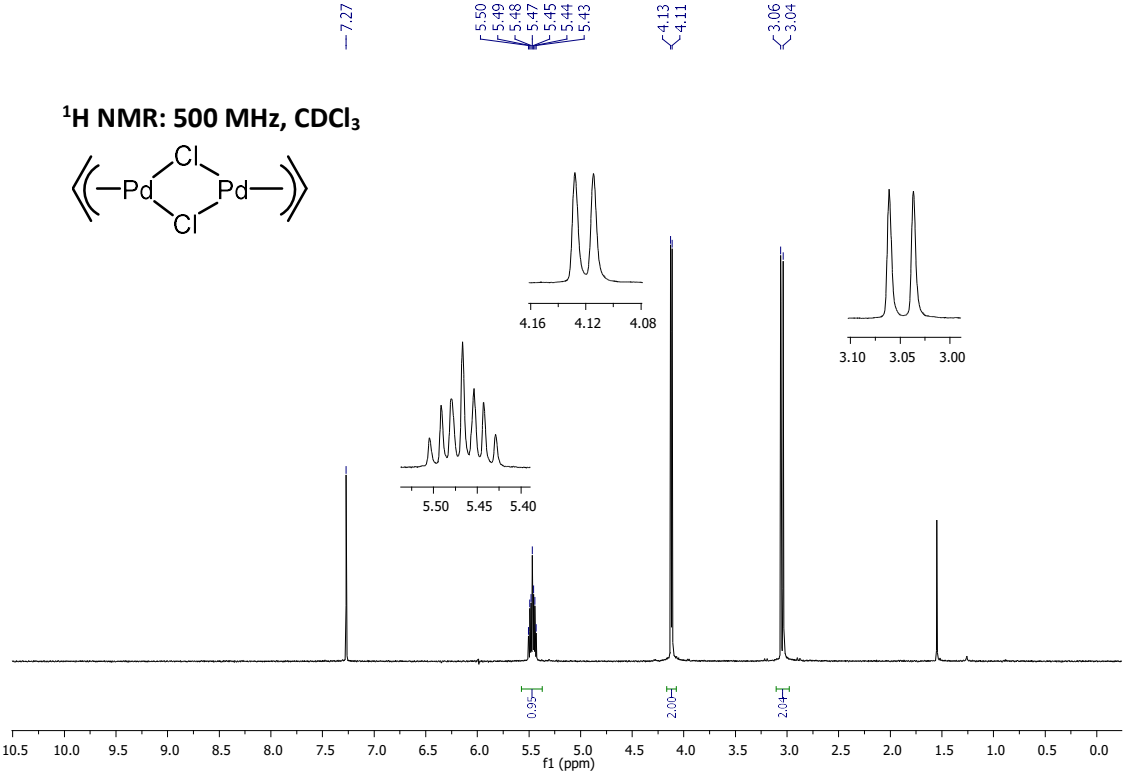
4-Chlorotoluene



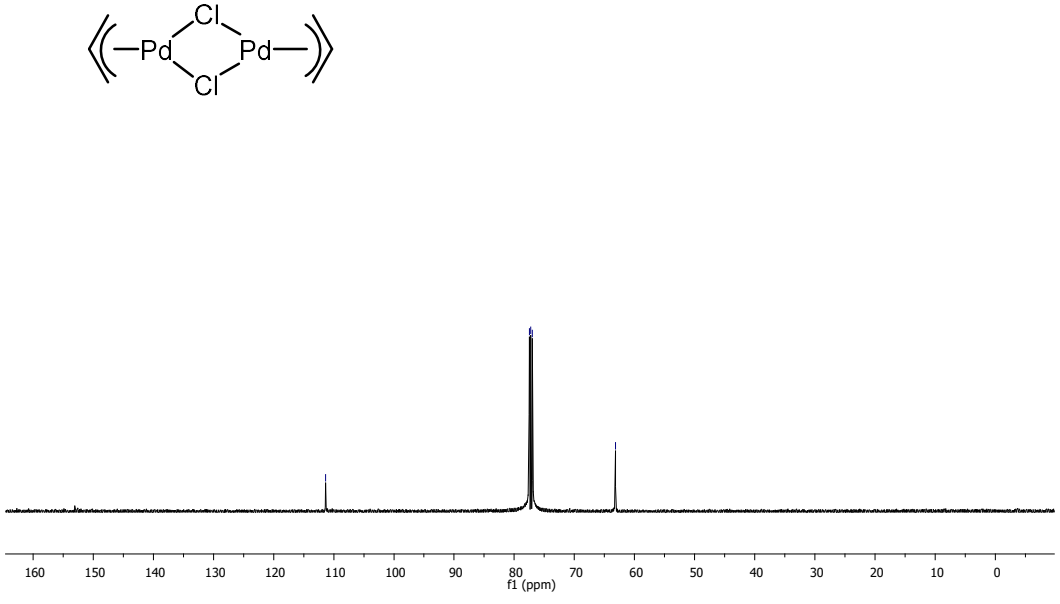
General Procedure: Two 25 mL Schlenk flasks under an atmosphere of N_2 and sealed with a rubber septum: One flask was charged with precatalyst **2** (1.5 mg, 0.003 mmol). To both flasks, anhydrous toluene (3 mL) was added via syringe, followed by the addition of 4-chlorotoluene (35 µL, 0.3 mmol), trimethoxyphenylsilane (112 µL, 0.6 mmol), and 1-fluoronapthalene (39 µL, 0.3 mmol) as an internal standard. TBAF (1M in THF – 0.6 mL, 0.6 mmol) was then injected via syringe to both flasks (T = 0). An aliquot was removed from both flasks, diluted with 0.3 mL of $CDCl_3$ and analyzed by ^{19}F NMR spectroscopy. Both flasks were then heated in a 90 ºC silicone oil bath. At each indicated timepoint, a 0.2 mL aliquot was taken via syringe from each flask (while at 90 °C) and diluted with 0.3 mL of $CDCl_3$, and then analyzed by ^{19}F NMR spectroscopy. After the 4-hour aliquot was removed, trimethoxyphenylsilane (112 µL, 0.6 mmol) and TBAF (1M in THF, 0.6 mL, 0.6 mmol) were injected via syringe to both flasks, continuing to stir for an additional five minutes in the 90 ºC silicone oil bath before the final aliquot was taken in the same manner.

Appendix B: NMR Spectral Data

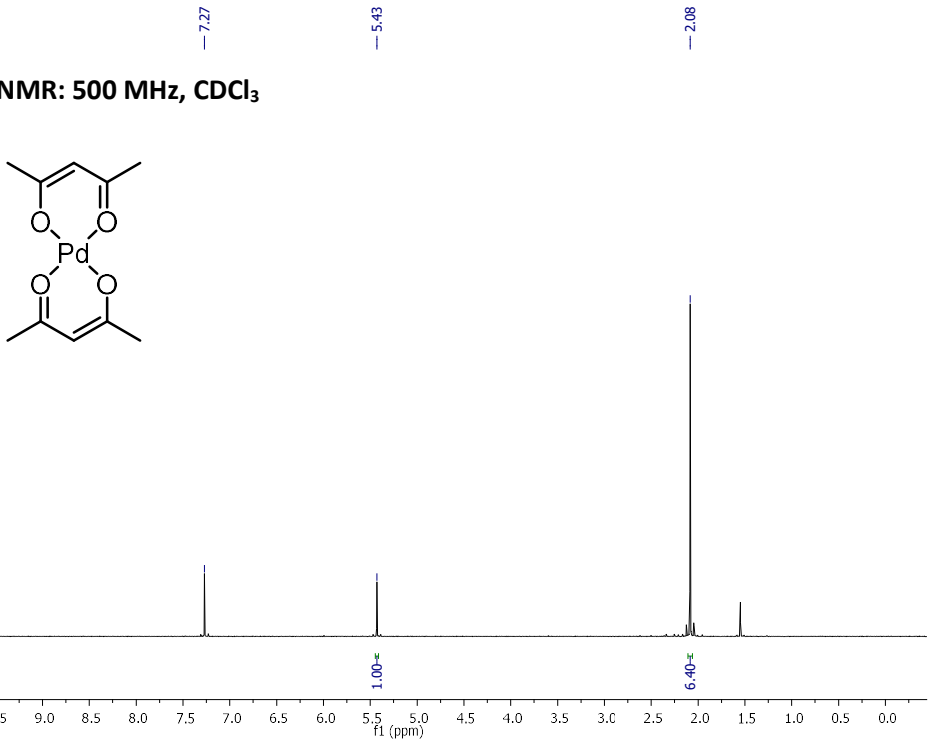
^{1}H NMR: 500 MHz, $CDCl_3$



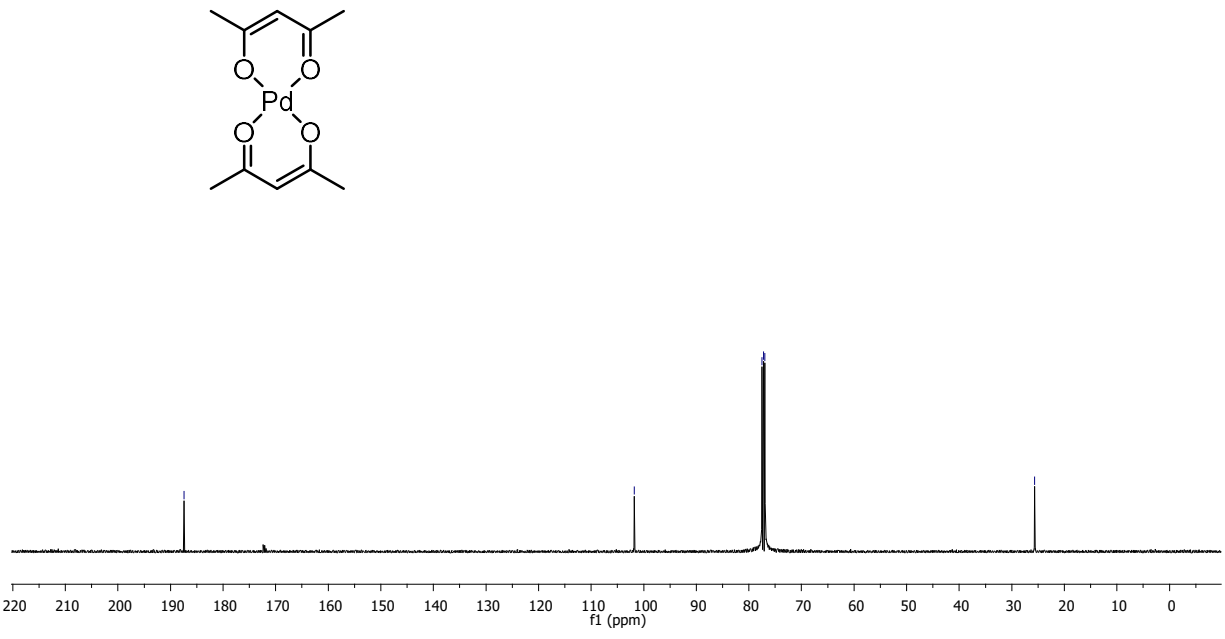
$^{13}C\{^{1}H\}$ NMR: 125 MHz, $CDCl_3$



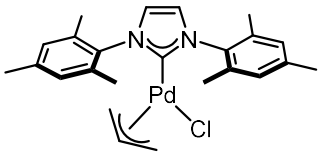
^{1}H NMR: 500 MHz, $CDCl_3$



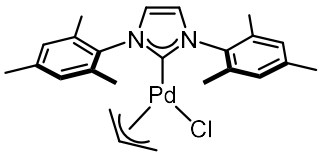
$^{13}C\{^{1}H\}$ NMR: 125 MHz, $CDCl_3$



^{1}H NMR: 500 MHz, $CDCl_3$
Precatalyst 2-1

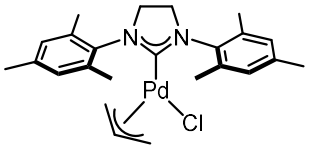


$^{13}C\{^{1}H\}$ NMR: 125 MHz, $CDCl_3$
Precatalyst 2-1



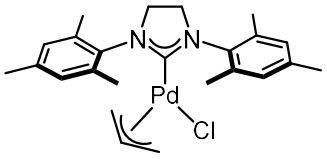
^{1}H NMR: 500 MHz, $CDCl_3$

Precatalyst 2-2



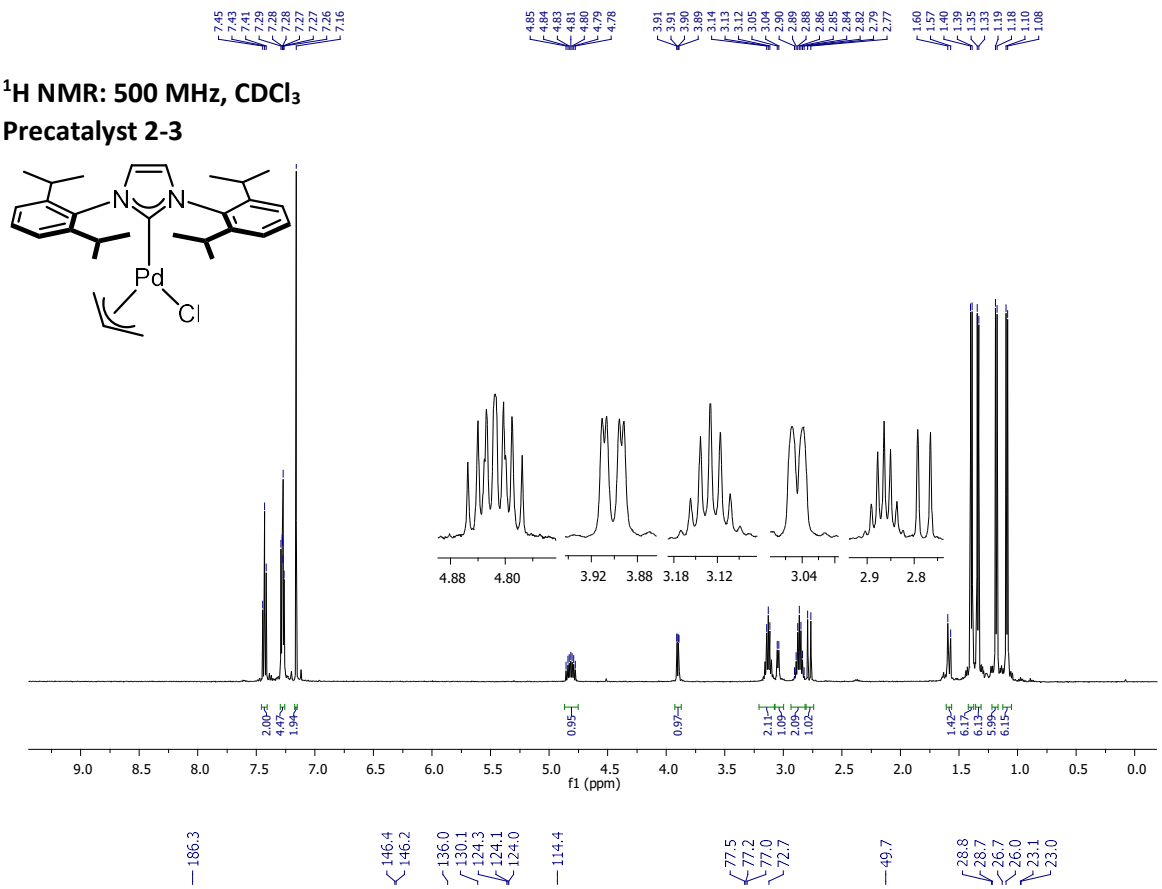
^{13}C{^{1}H} NMR: 125 MHz, $CDCl_3$

Precatalyst 2-2



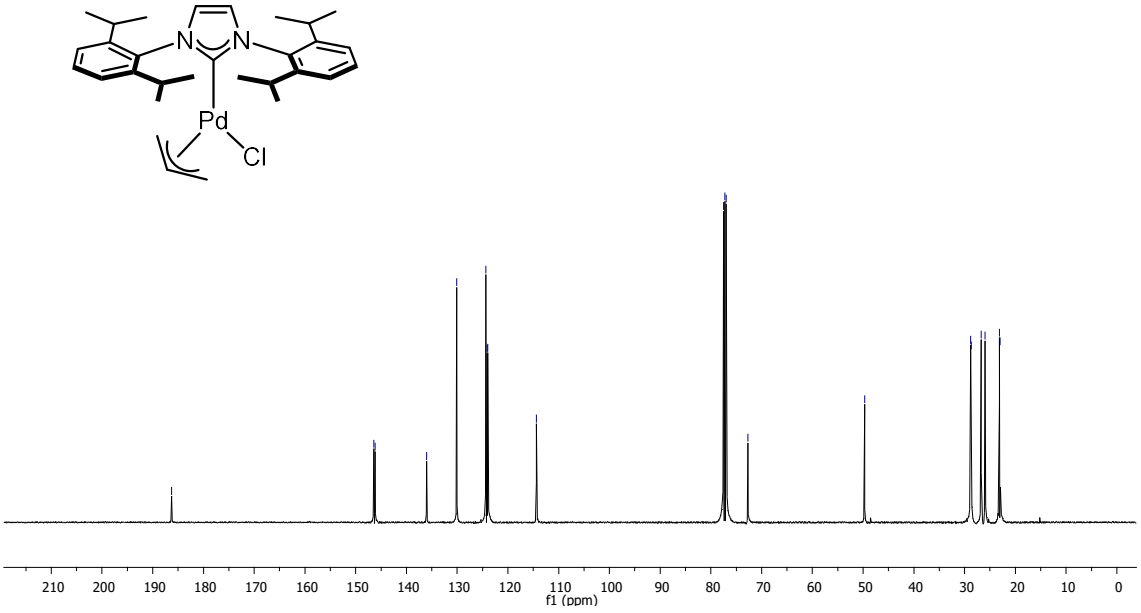
^{1}H NMR: 500 MHz, $CDCl_3$

Precatalyst 2-3



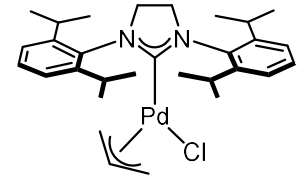
$^{13}C\{^{1}H\}$ NMR: 125 MHz, $CDCl_3$

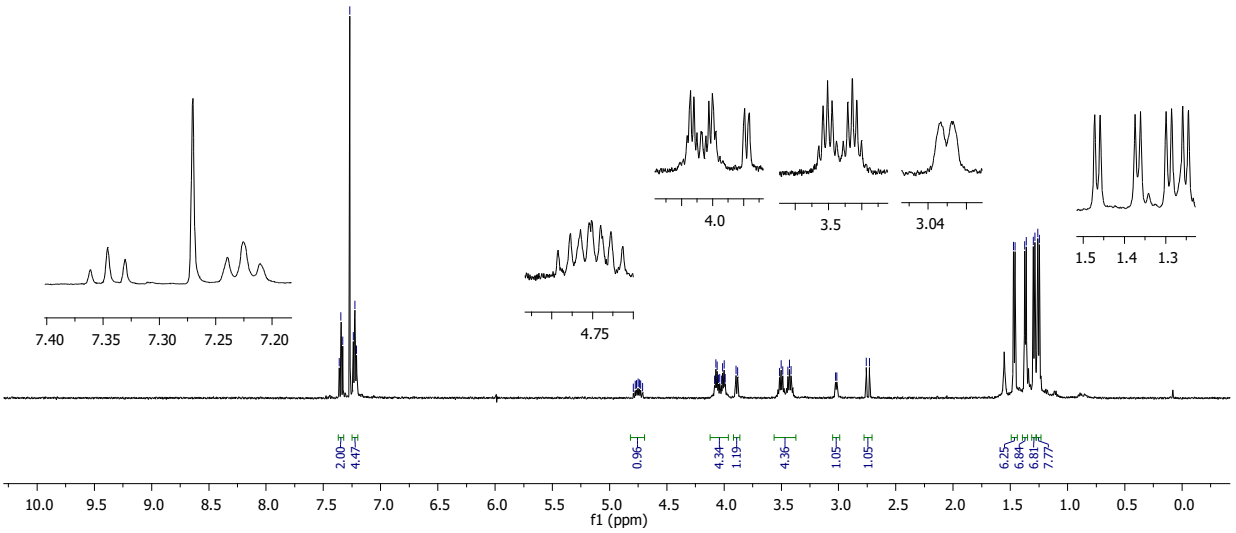
Precatalyst 2-3



^{1}H NMR: 500 MHz, $CDCl_3$

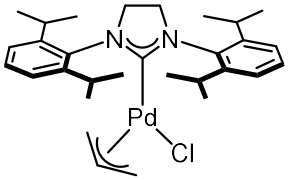
Precatalyst 2-4

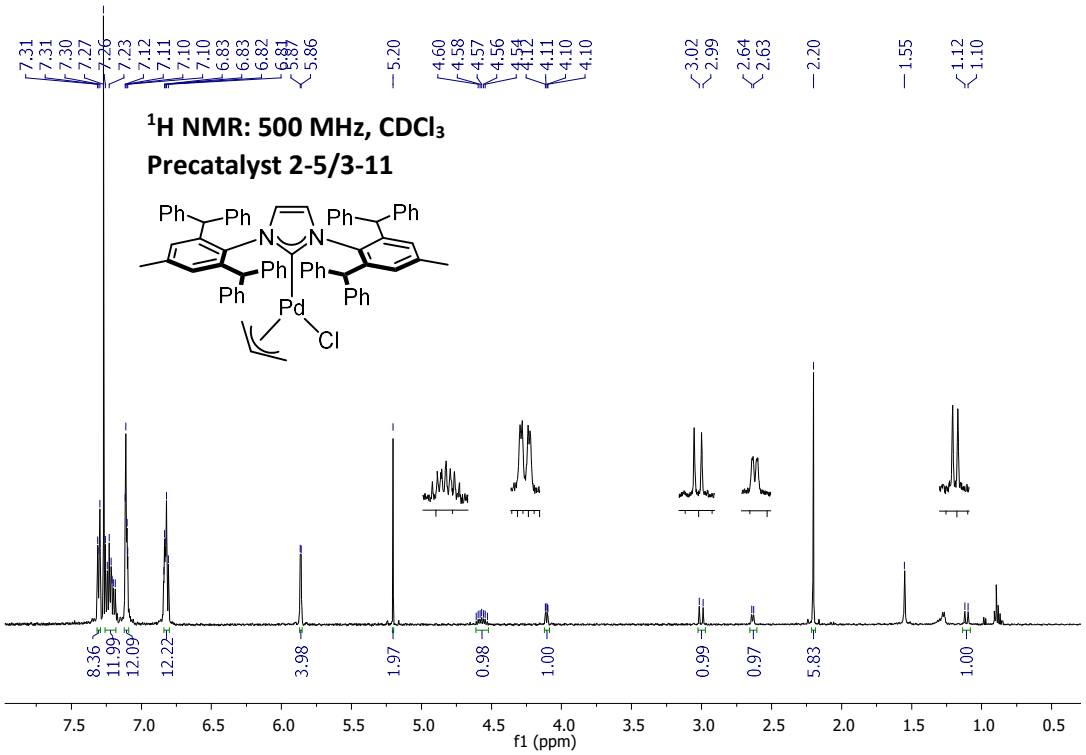




^{13}C{^{1}H} NMR: 125 MHz, $CDCl_3$

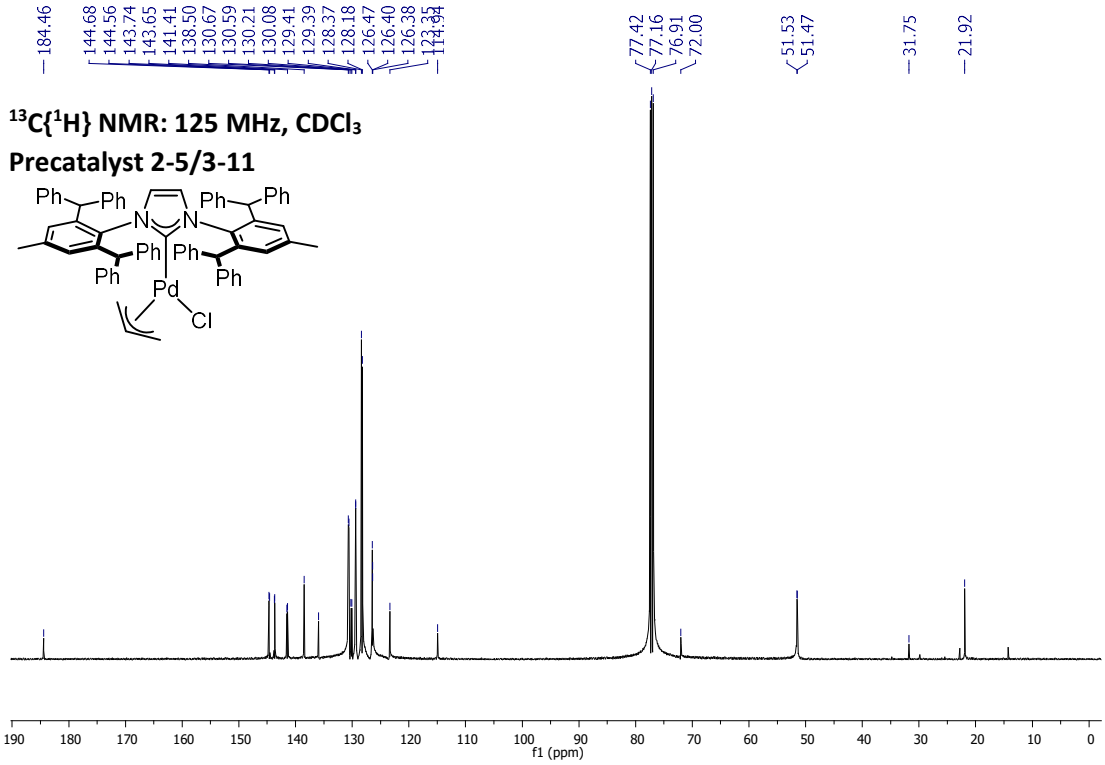
Precatalyst 2-4





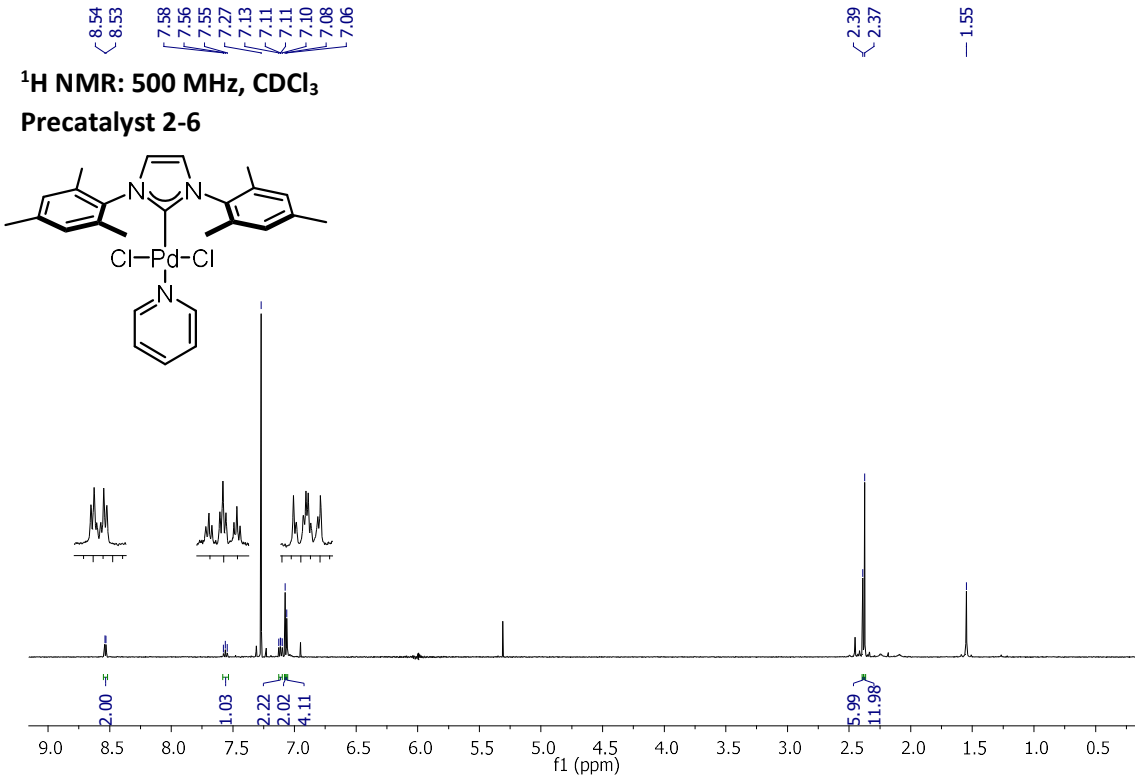
^{1}H NMR: 500 MHz, $CDCl_3$

Precatalyst 2-5/3-11



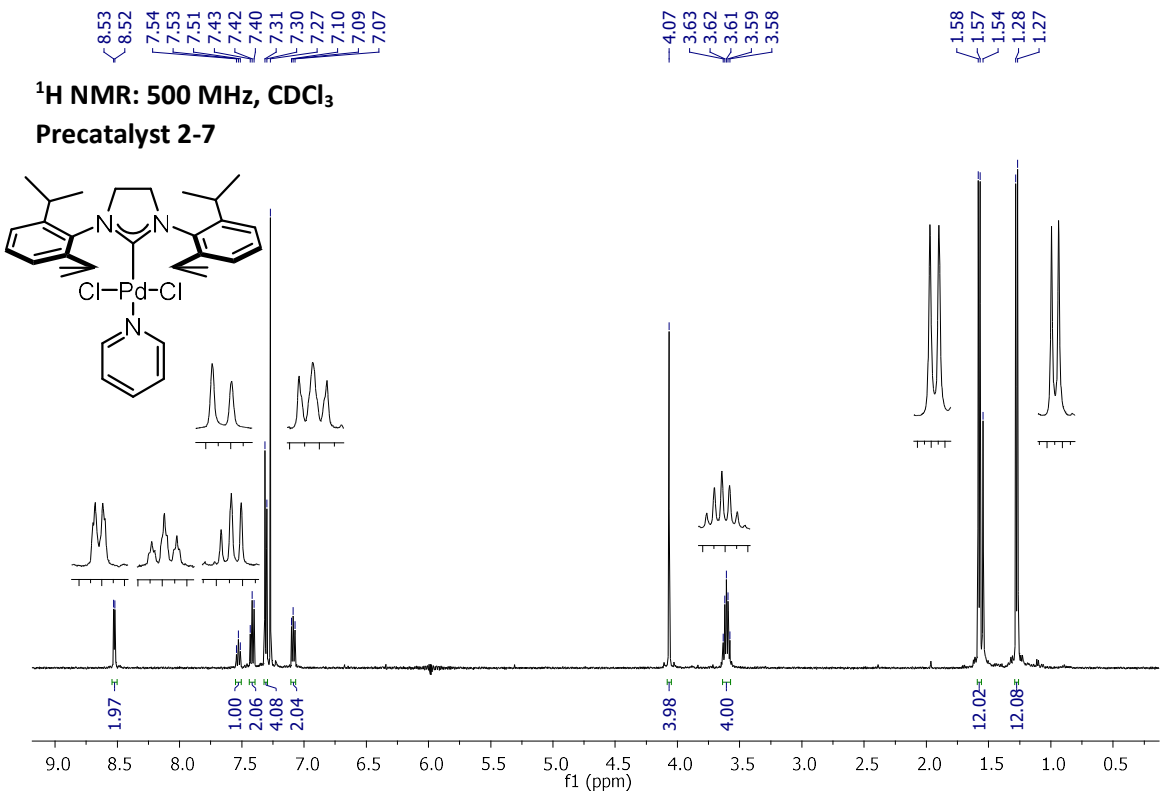
^{13}C{^{1}H} NMR: 125 MHz, $CDCl_3$

Precatalyst 2-5/3-11



^{1}H NMR: 500 MHz, $CDCl_3$

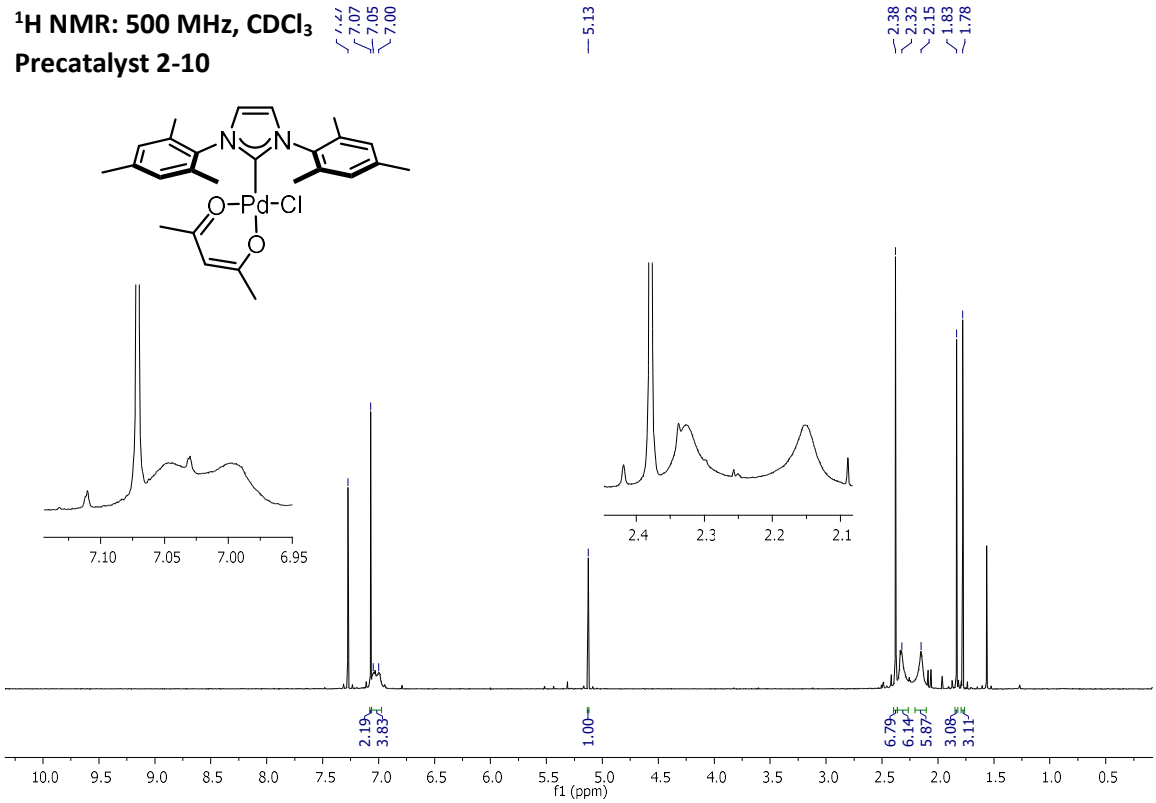
Precatalyst 2-6



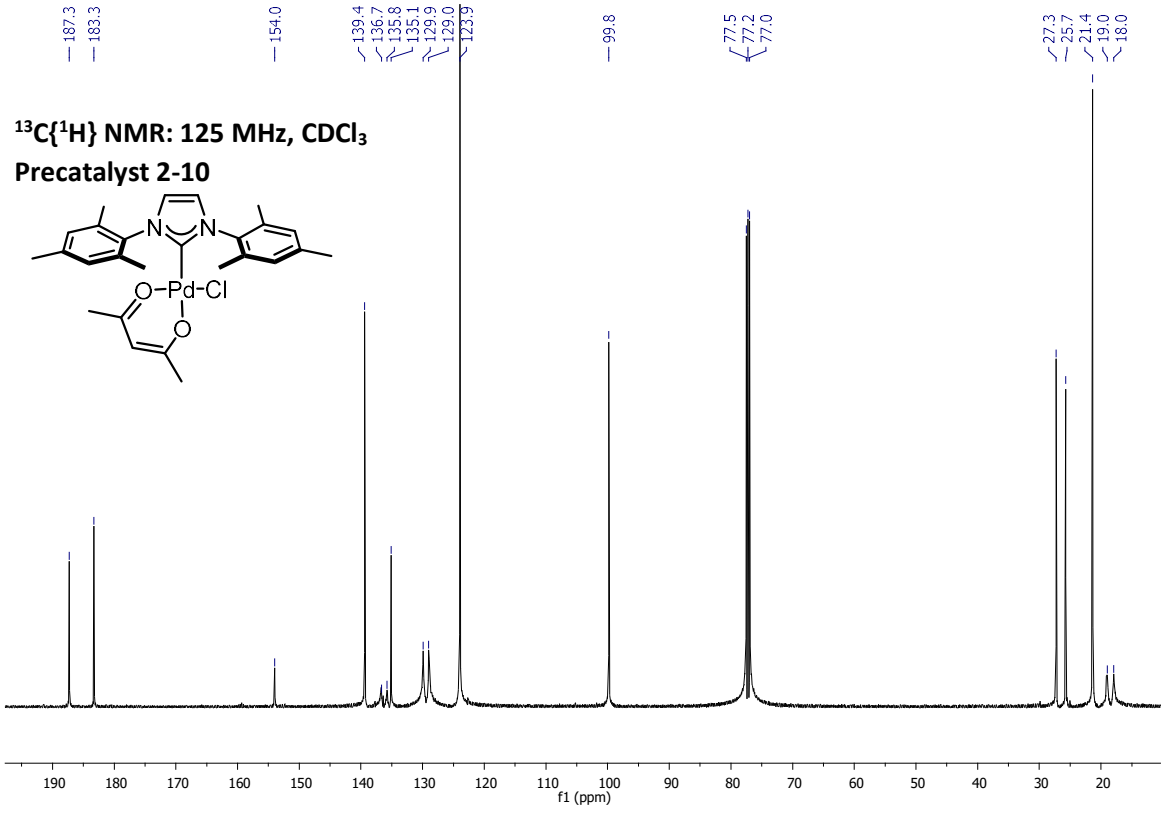
^{1}H NMR: 500 MHz, $CDCl_3$

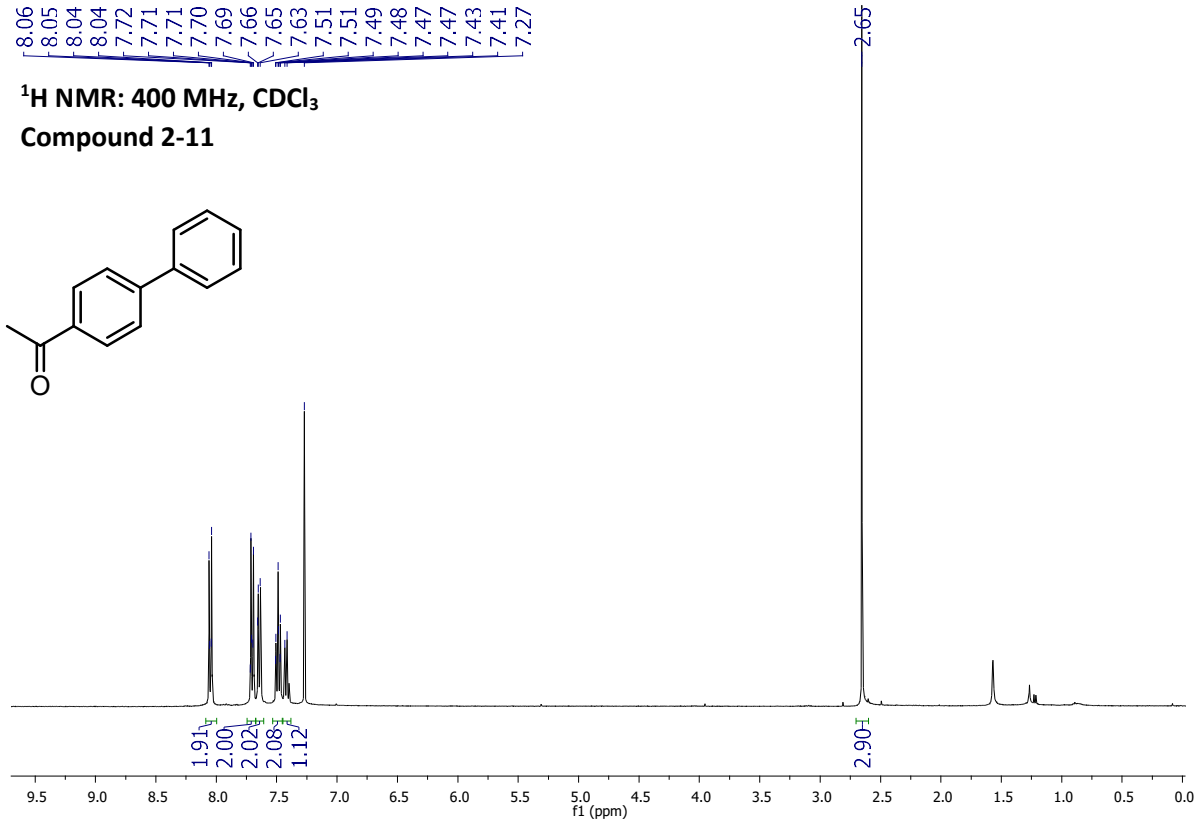
Precatalyst 2-7

^{1}H NMR: 500 MHz, $CDCl_3$
Precatalyst 2-10



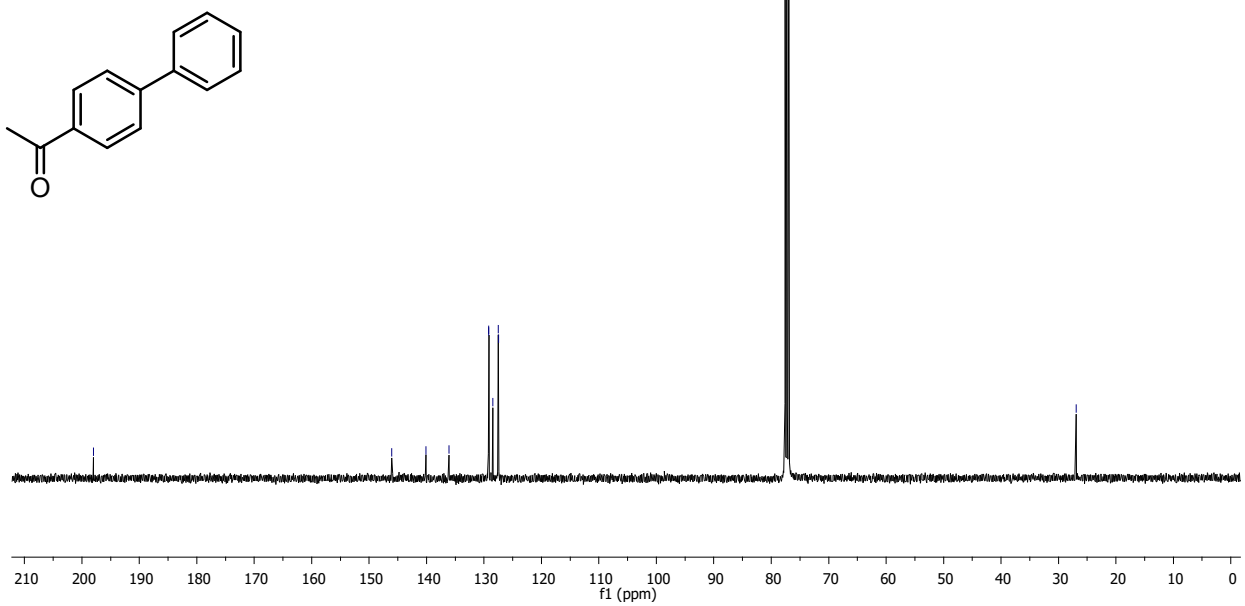
^{13}C{^{1}H} NMR: 125 MHz, $CDCl_3$
Precatalyst 2-10





^{1}H NMR: 400 MHz, $CDCl_3$

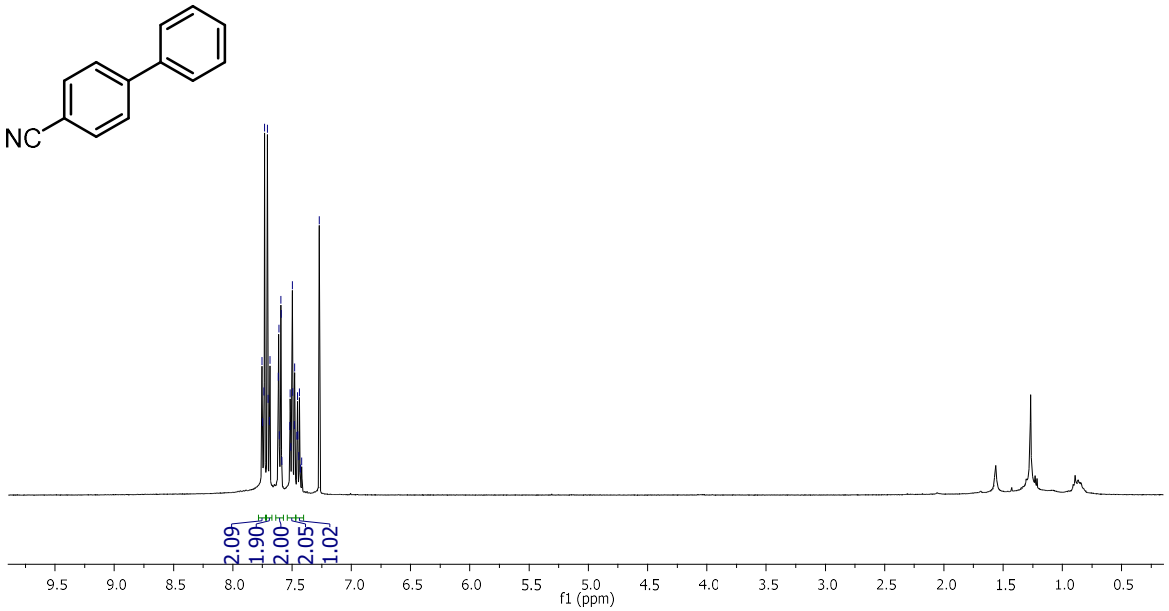
Compound 2-11



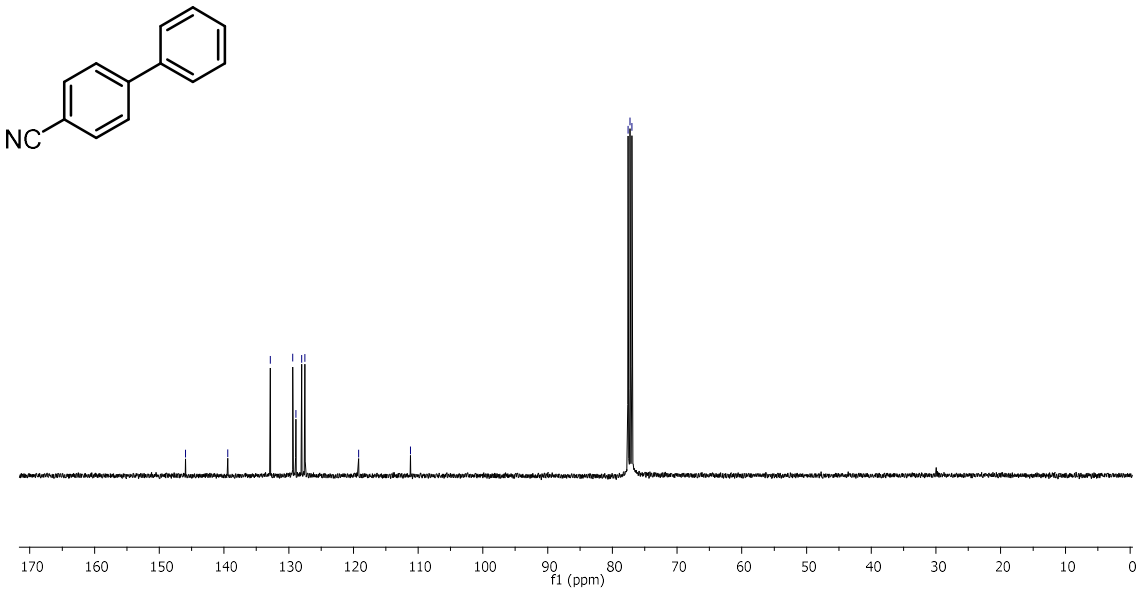
^{13}C{^{1}H} NMR: 100 MHz, $CDCl_3$

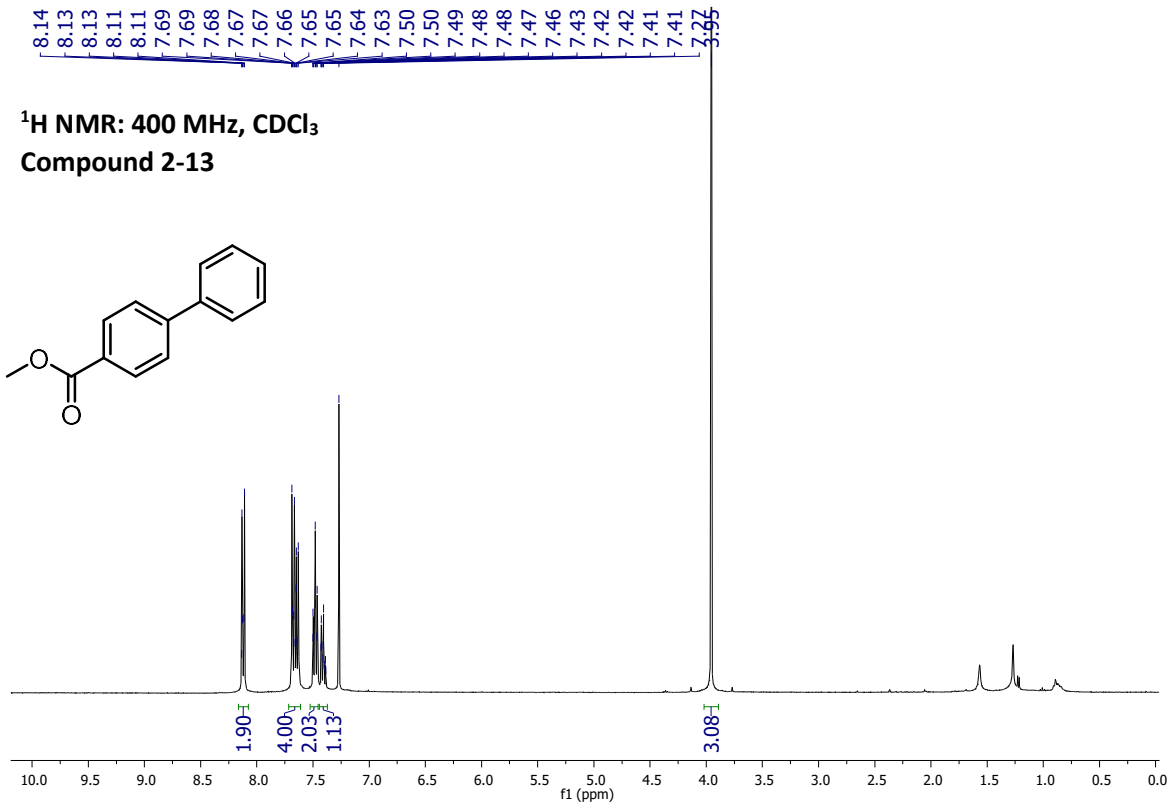
Compound 2-11

^{1}H NMR: 400 MHz, $CDCl_3$
Compound 2-12

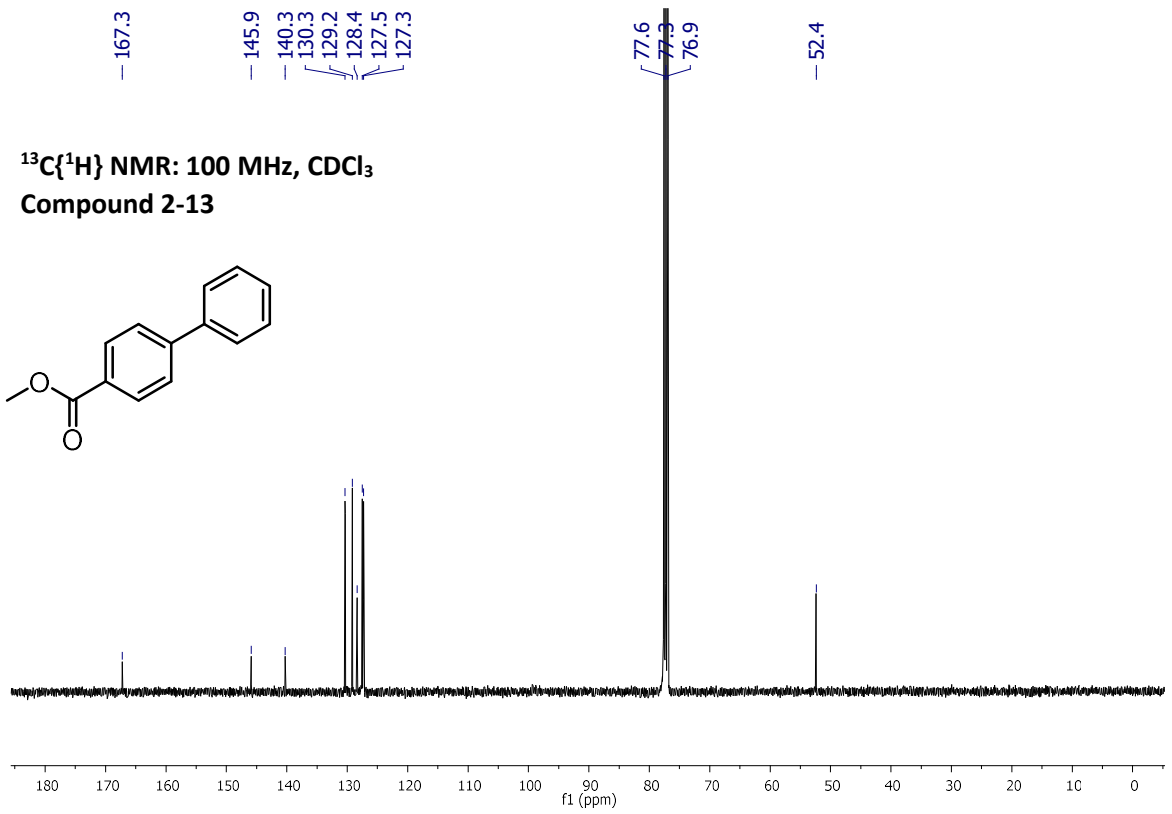


^{13}C{^{1}H} NMR: 100 MHz, $CDCl_3$
Compound 2-12

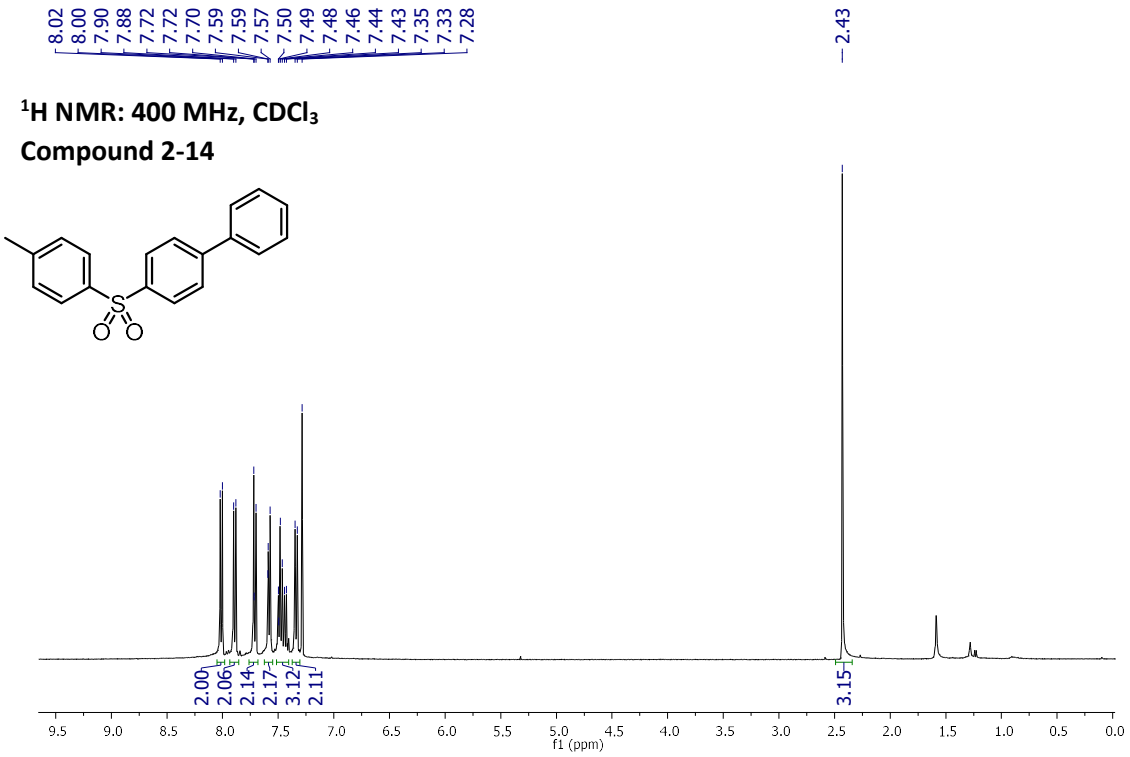




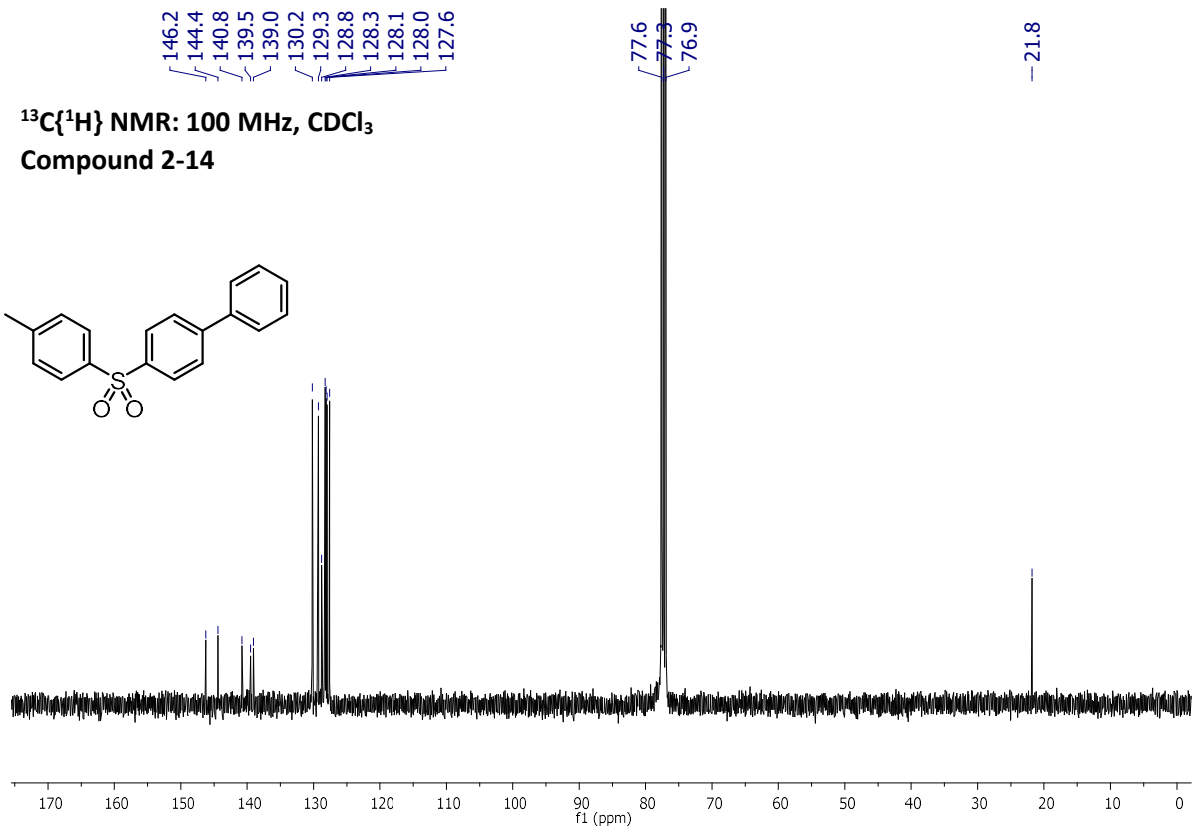
^{1}H NMR: 400 MHz, $CDCl_3$
Compound 2-13



$^{13}C\{^{1}H\}$ NMR: 100 MHz, $CDCl_3$
Compound 2-13

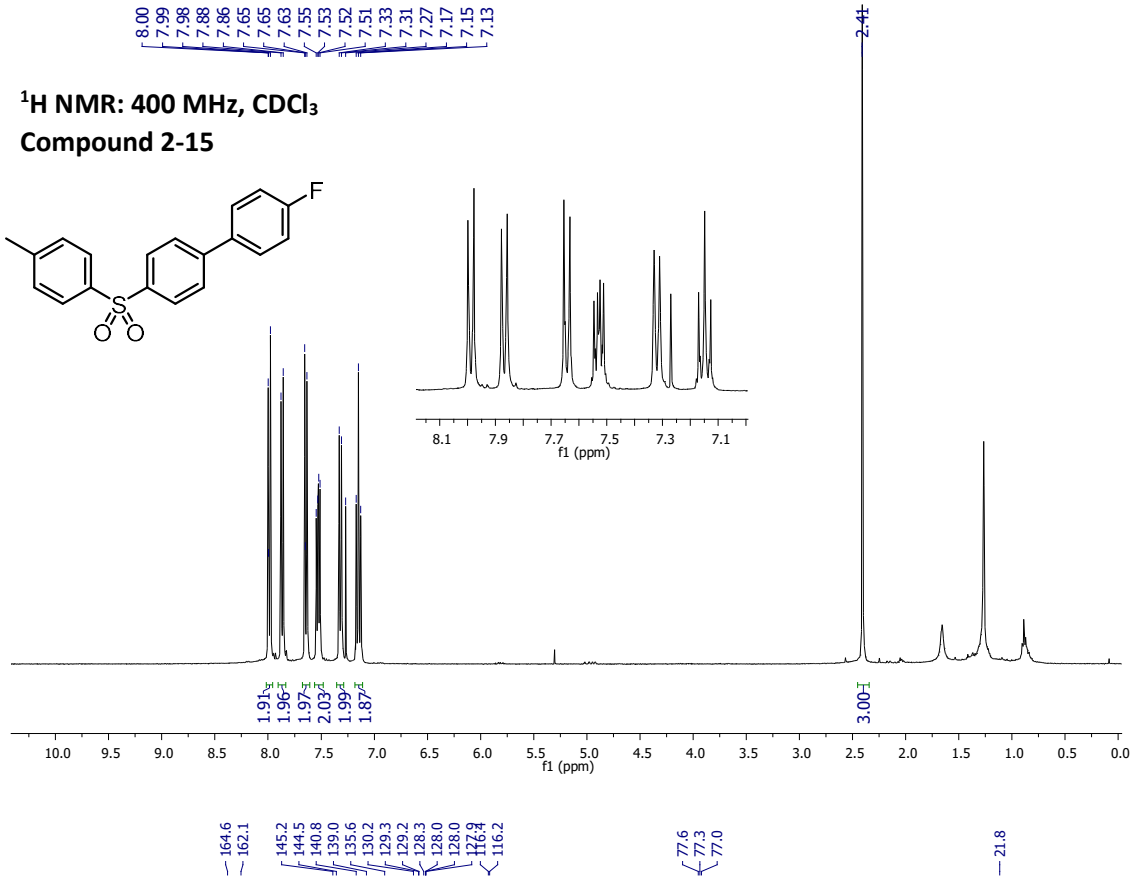


^{1}H NMR: 400 MHz, $CDCl_3$
Compound 2-14

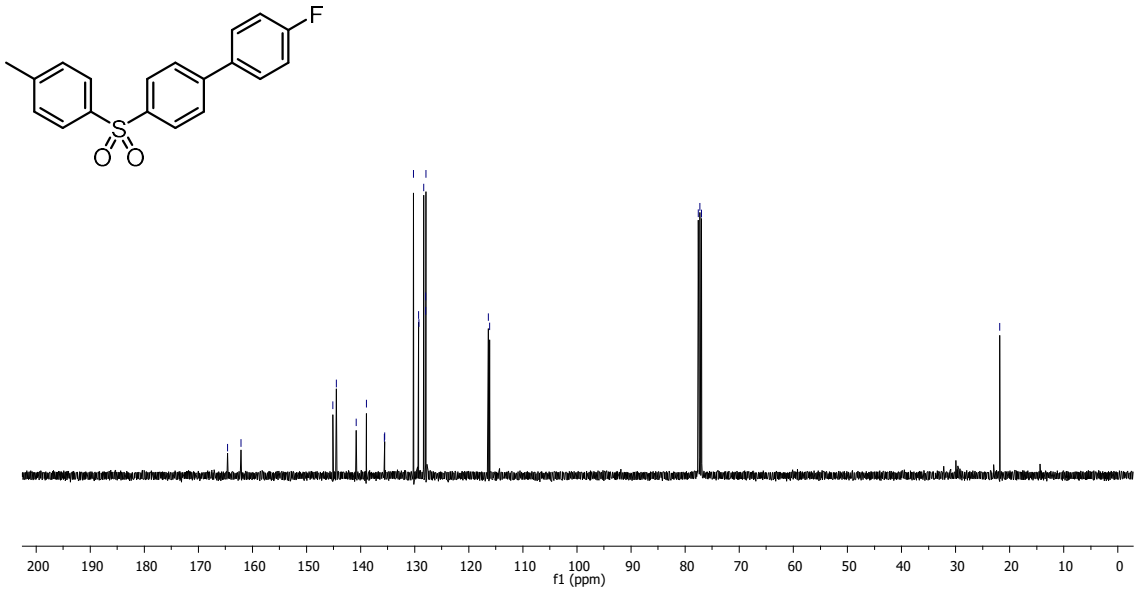


^{13}C{^{1}H} NMR: 100 MHz, $CDCl_3$
Compound 2-14

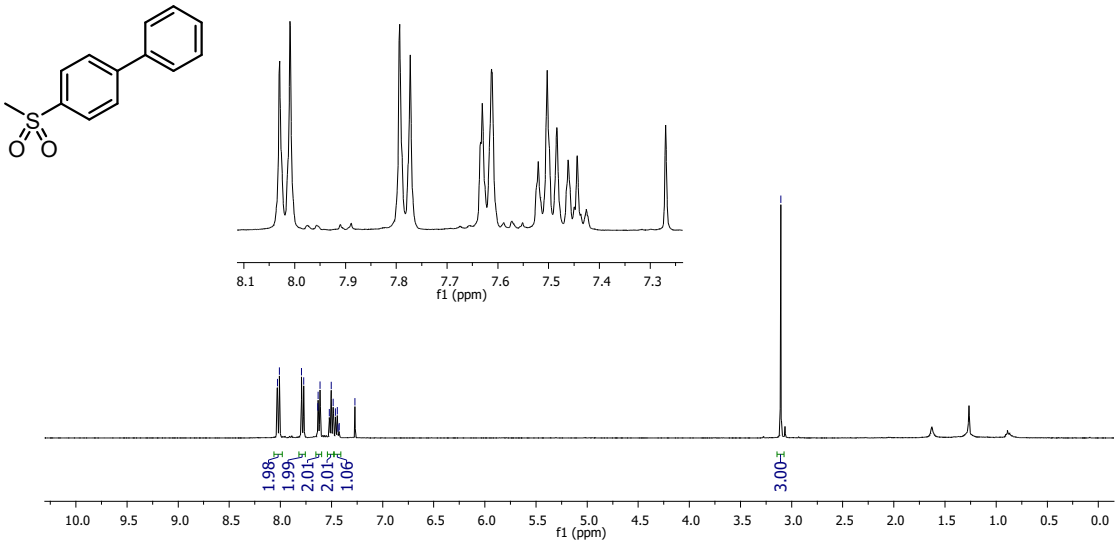
^{1}H NMR: 400 MHz, $CDCl_3$
Compound 2-15



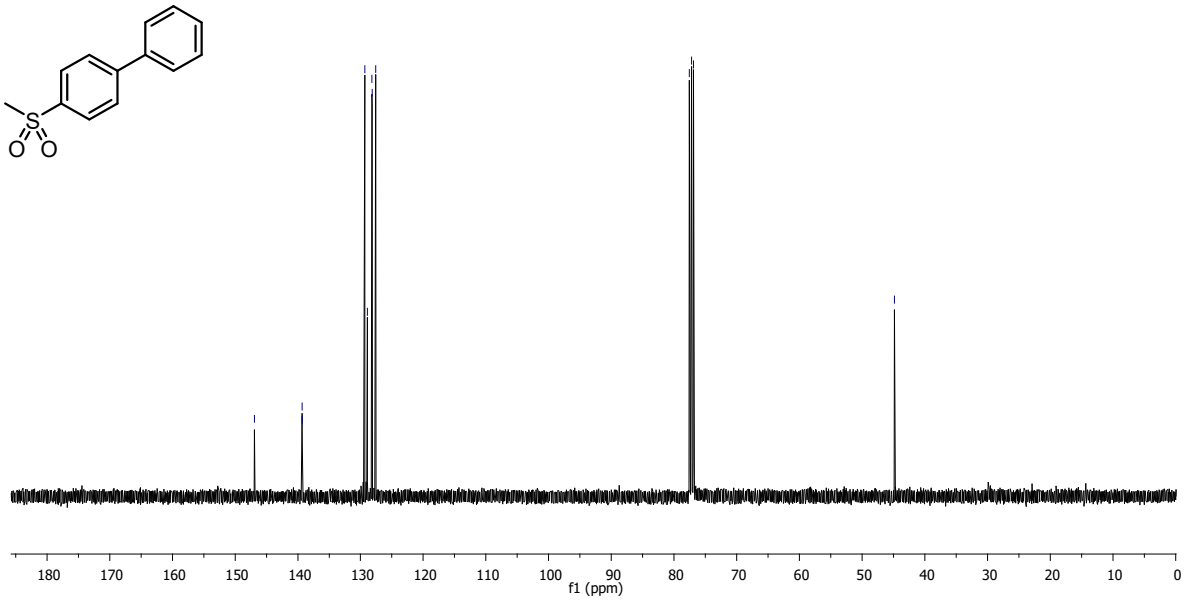
^{13}C{^{1}H} NMR: 100 MHz, $CDCl_3$
Compound 2-15



^{1}H NMR: 400 MHz, $CDCl_3$
Compound 2-16

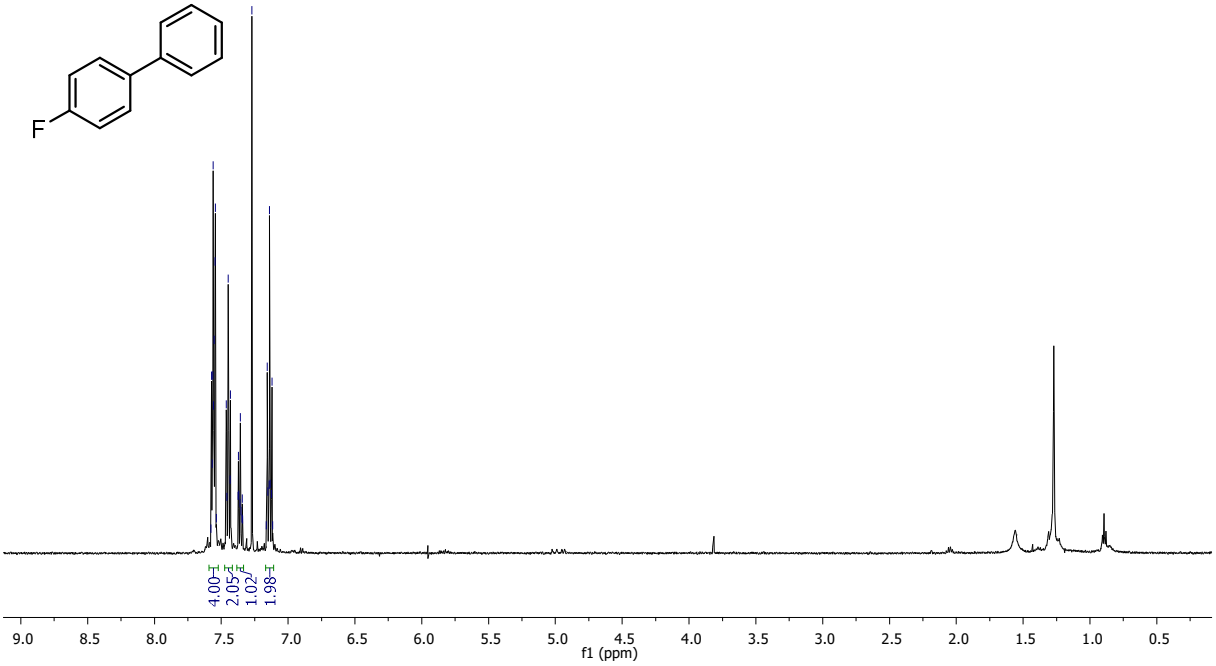


^{13}C{^{1}H} NMR: 100 MHz, $CDCl_3$
Compound 2-16



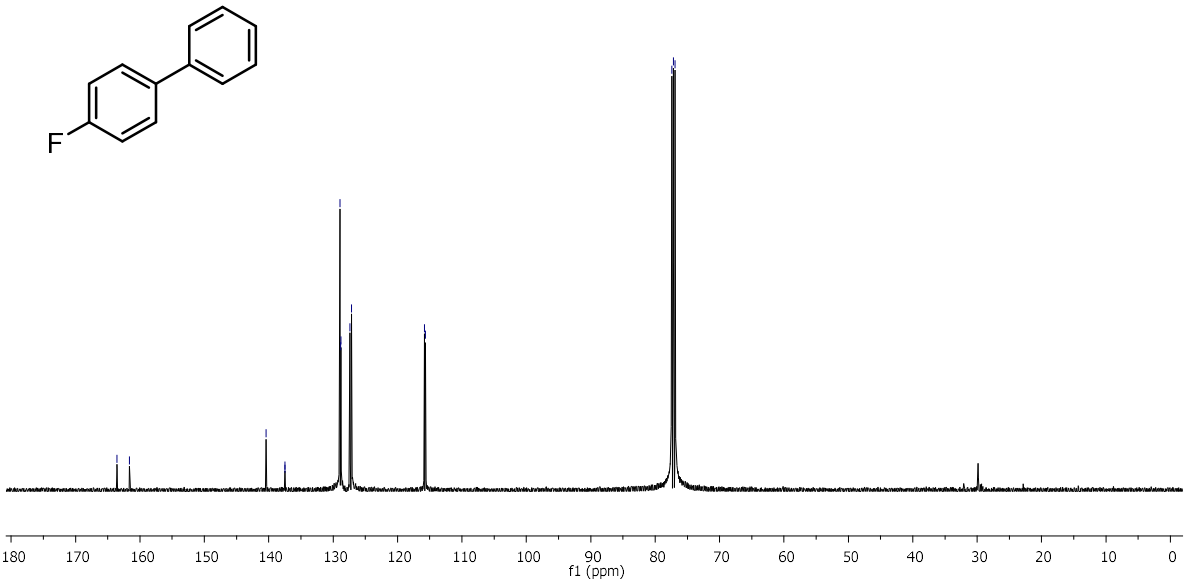
^{1}H NMR: 500 MHz, $CDCl_3$

Compound 2-17



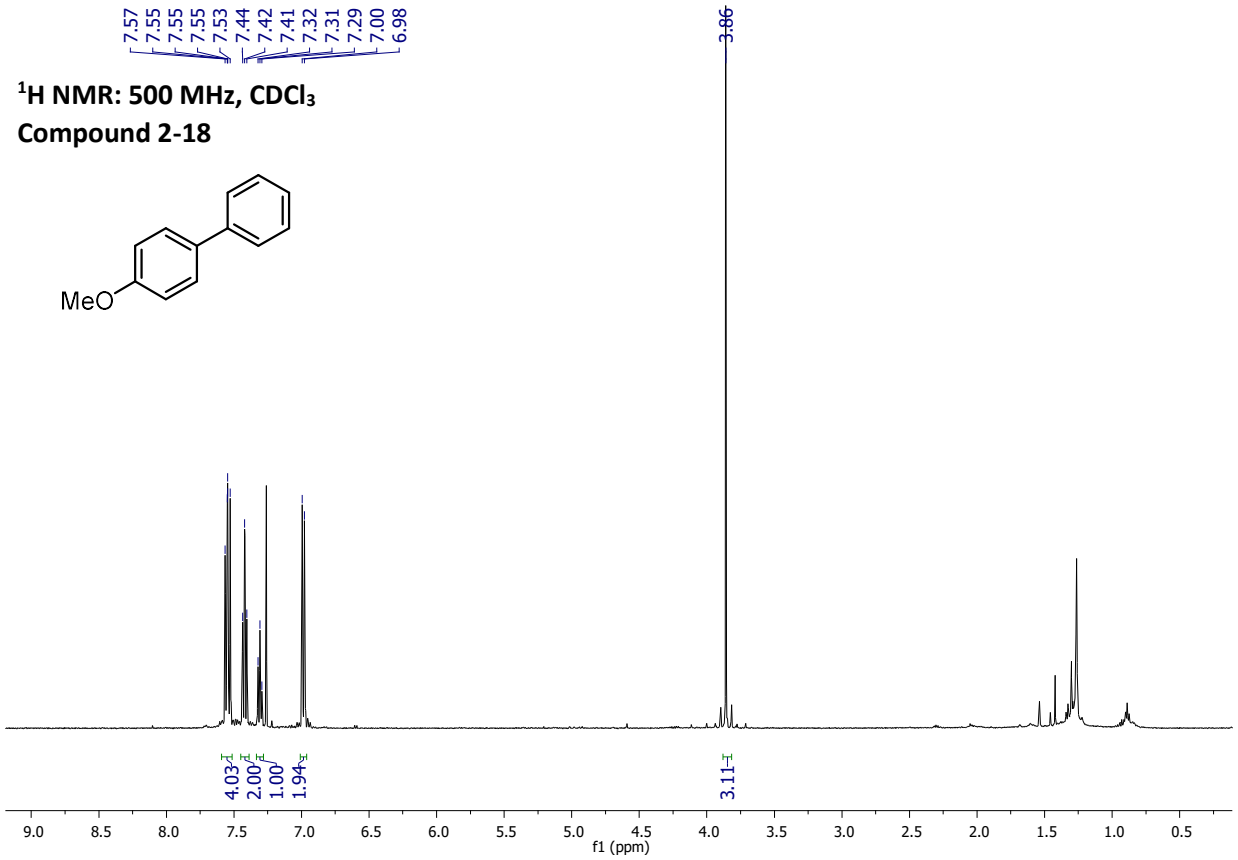
^{13}C{^{1}H} NMR: 125 MHz, $CDCl_3$

Compound 2-17



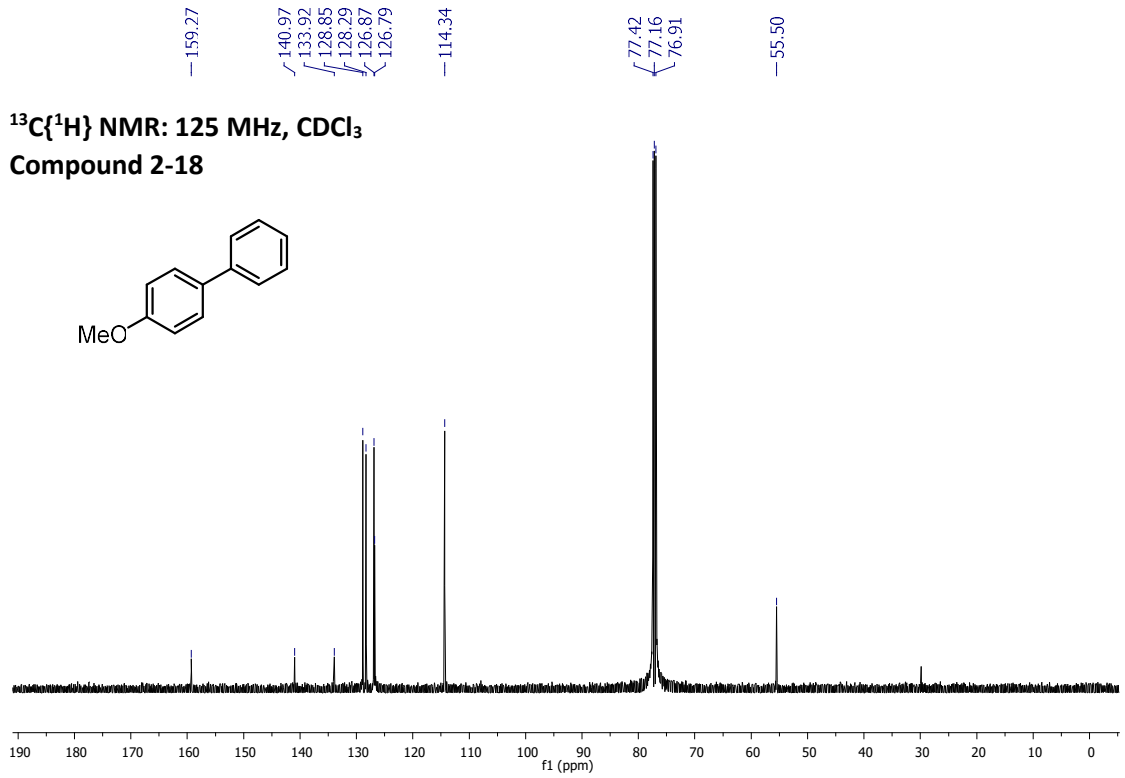
^{1}H NMR: 500 MHz, $CDCl_3$

Compound 2-18

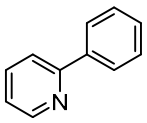


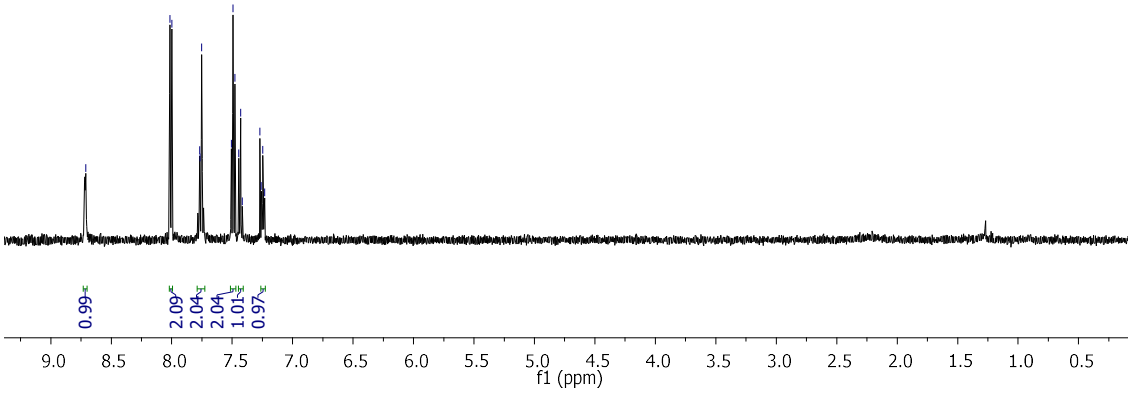
^{13}C{^{1}H} NMR: 125 MHz, $CDCl_3$

Compound 2-18

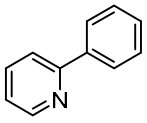


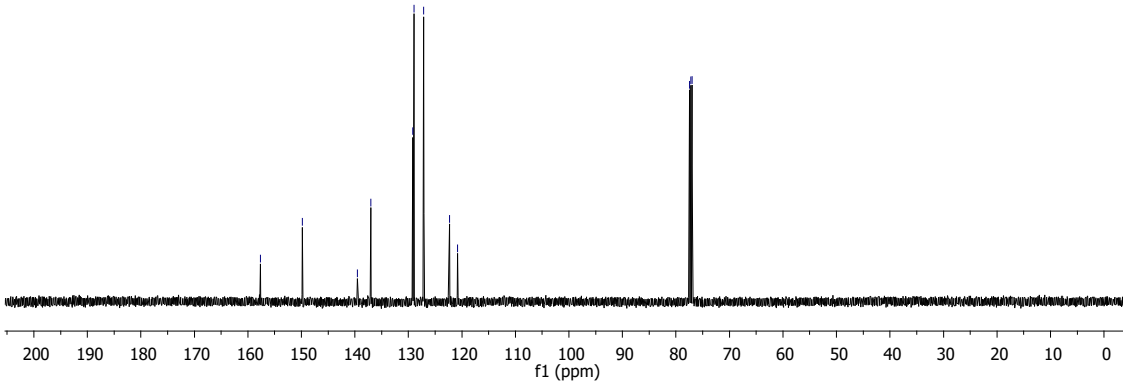
^{1}H NMR: 500 MHz, $CDCl_3$
Compound 2-19



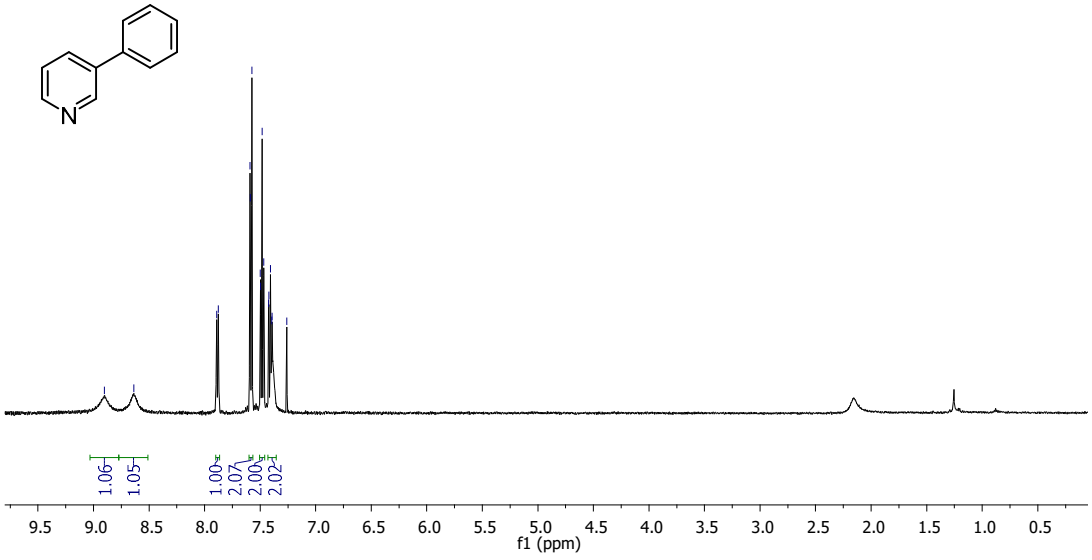


$^{13}C\{^{1}H\}$ NMR: 125 MHz, $CDCl_3$
Compound 2-19

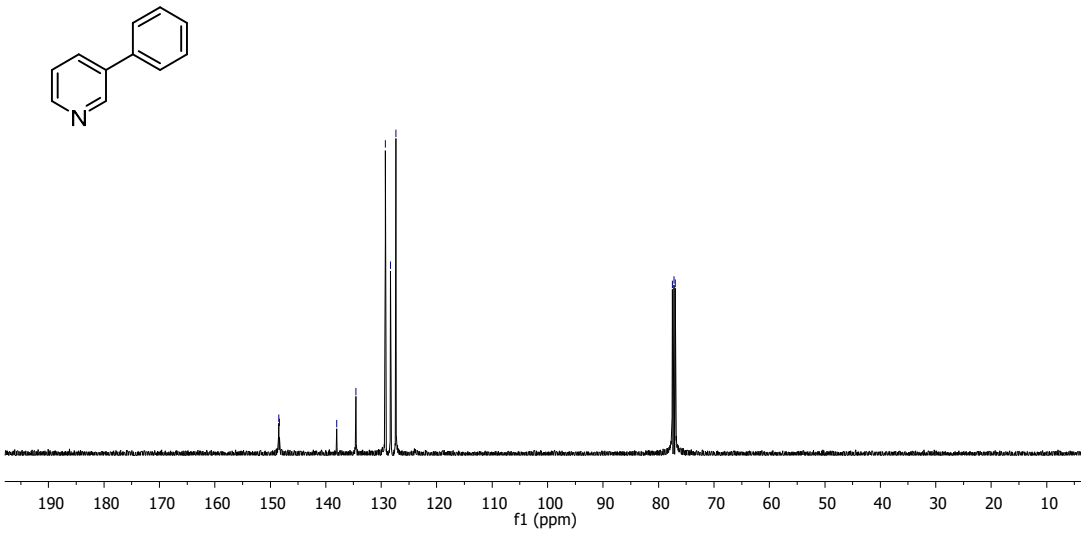


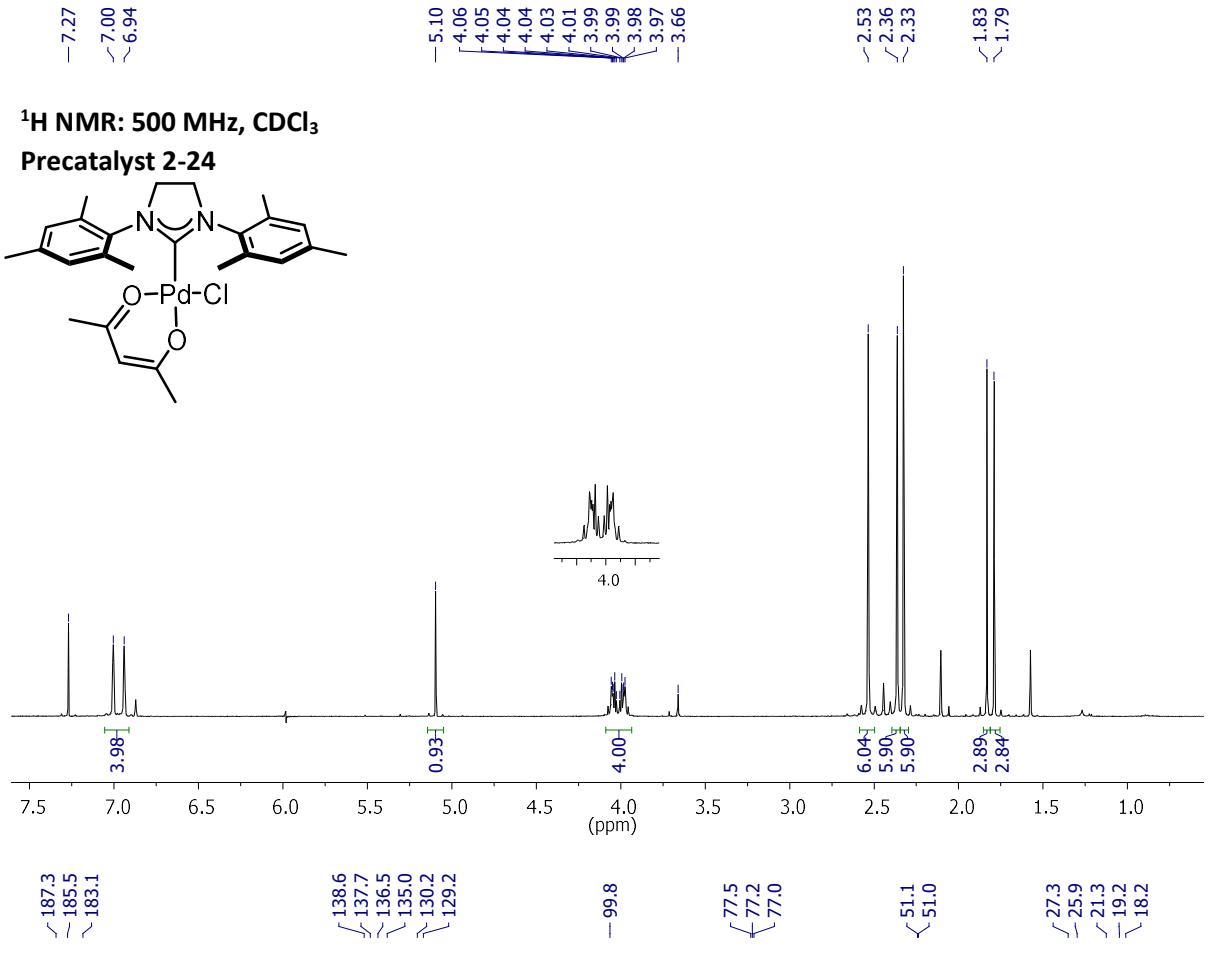


^{1}H NMR: 500 MHz, $CDCl_3$
Compound 2-20



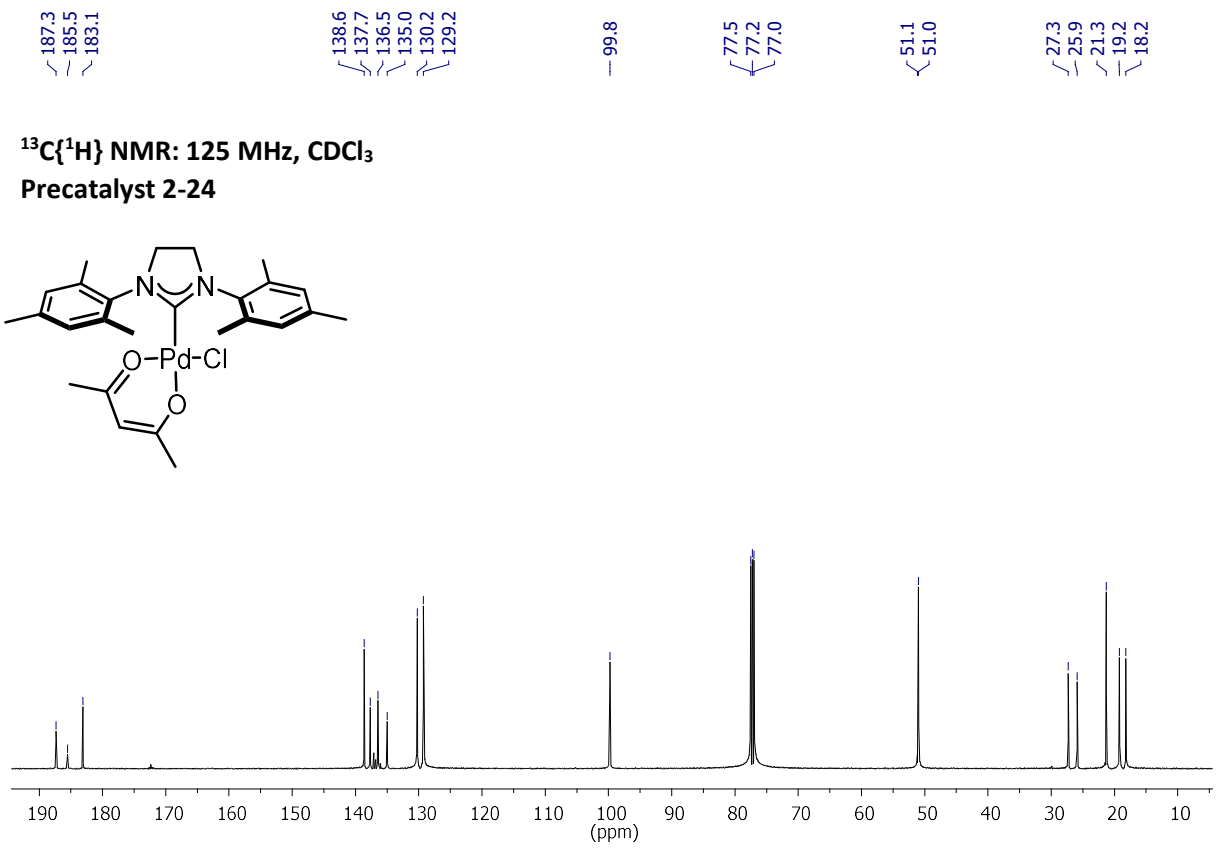
^{13}C{^{1}H} NMR: 125 MHz, $CDCl_3$
Compound 2-20





^{1}H NMR: 500 MHz, $CDCl_3$

Precatalyst 2-24

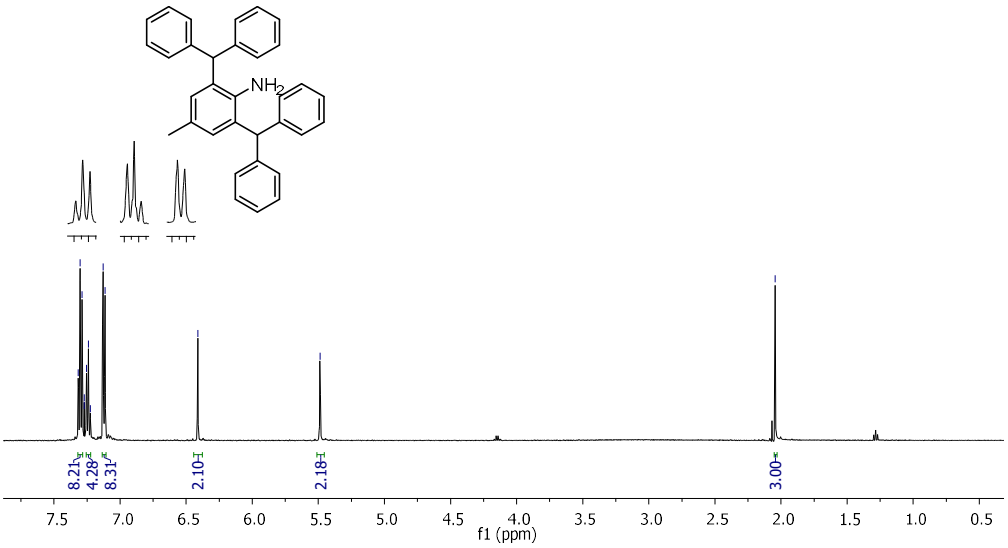


^{13}C{^{1}H} NMR: 125 MHz, $CDCl_3$

Precatalyst 2-24

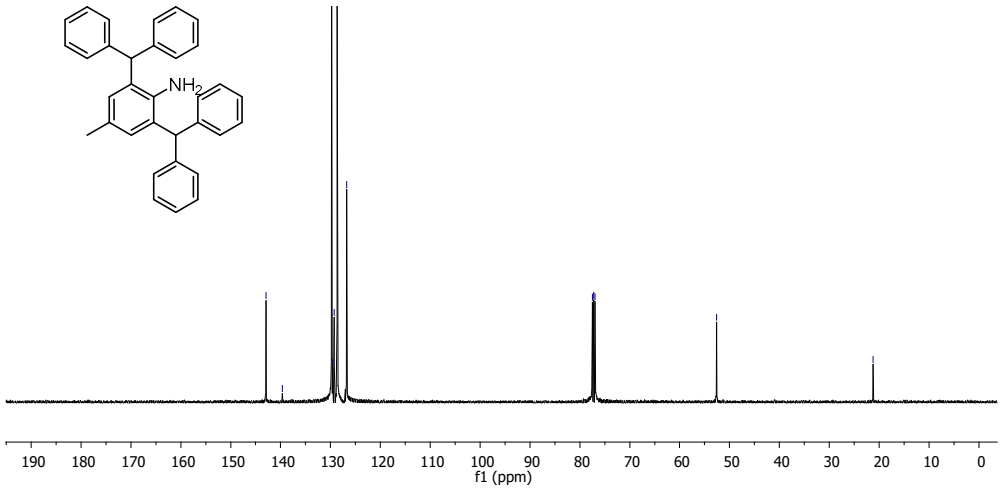
^{1}H NMR: 500 MHz, $CDCl_3$

Aniline 3-4



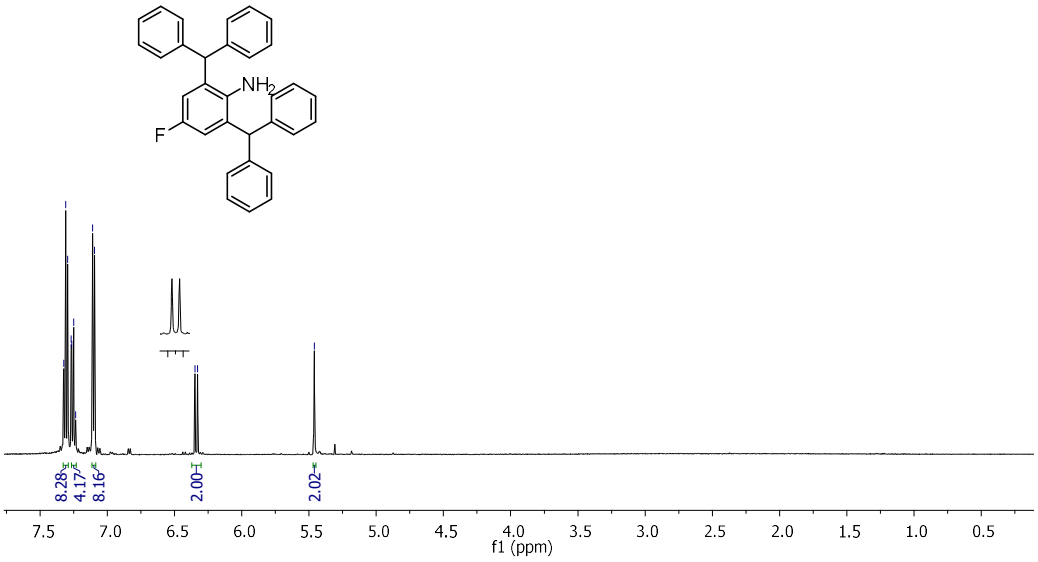
^{13}C {^{1}H} NMR: 125 MHz, $CDCl_3$

Aniline 3-4



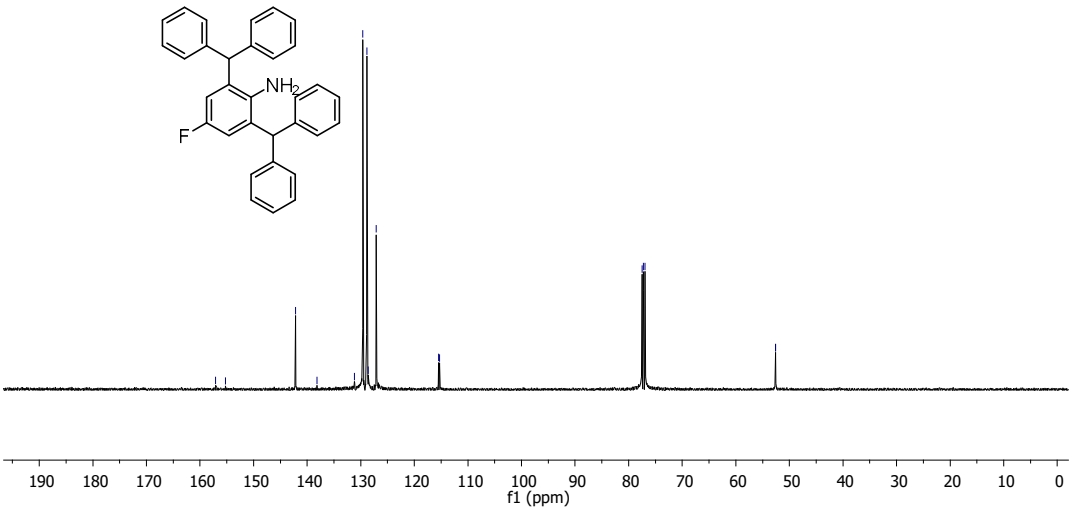
^{1}H NMR: 500 MHz, $CDCl_3$

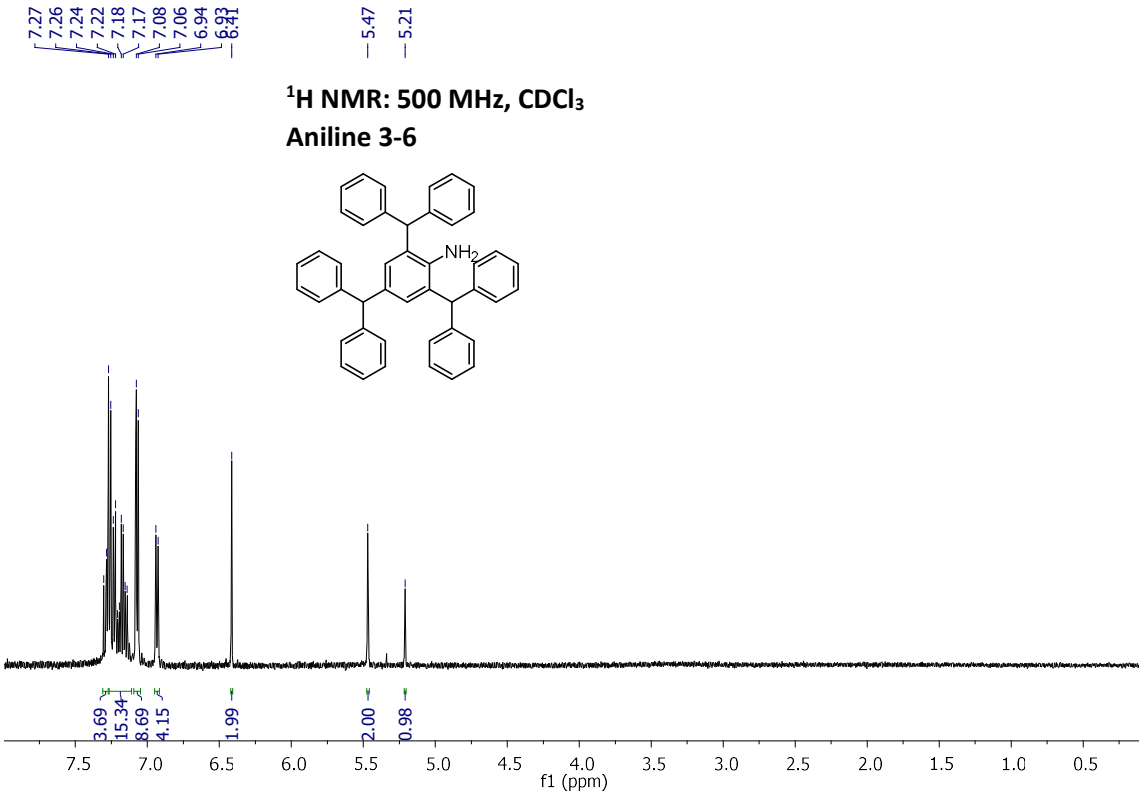
Aniline 3-5



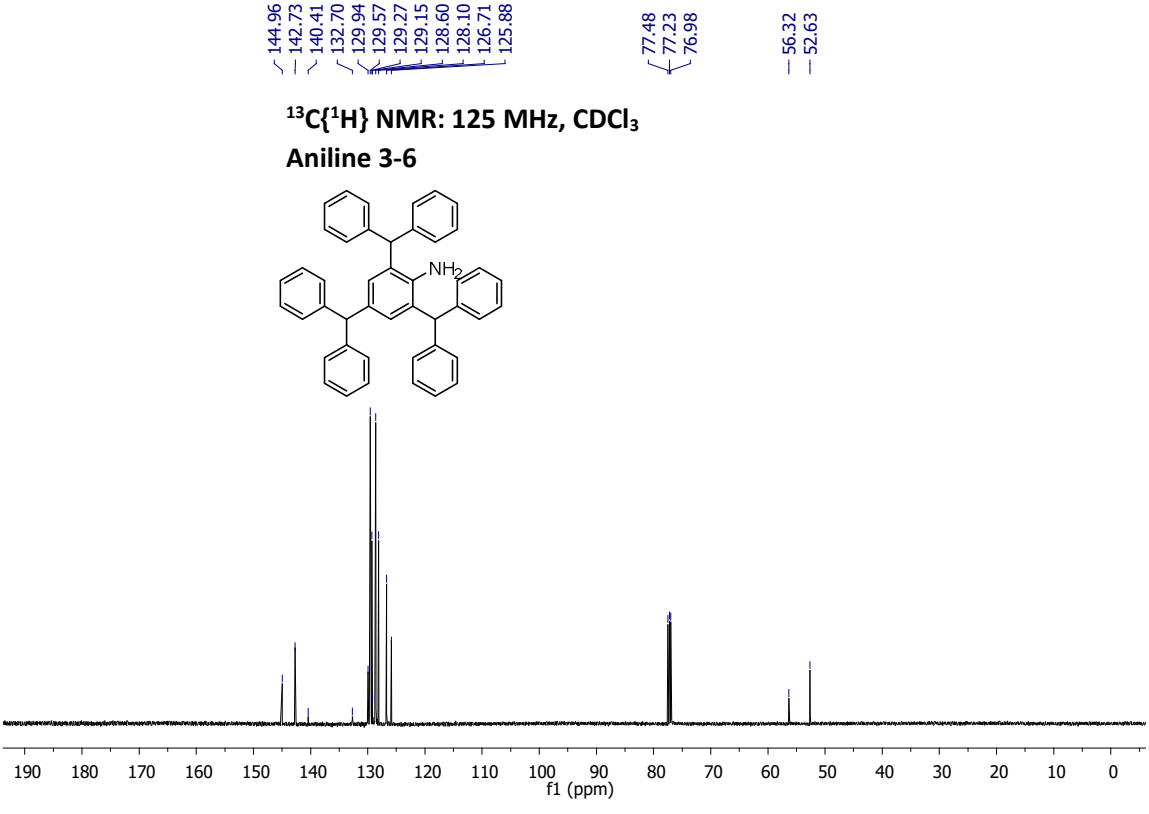
^{13}C{^{1}H} NMR: 125 MHz, $CDCl_3$

Aniline 3-5

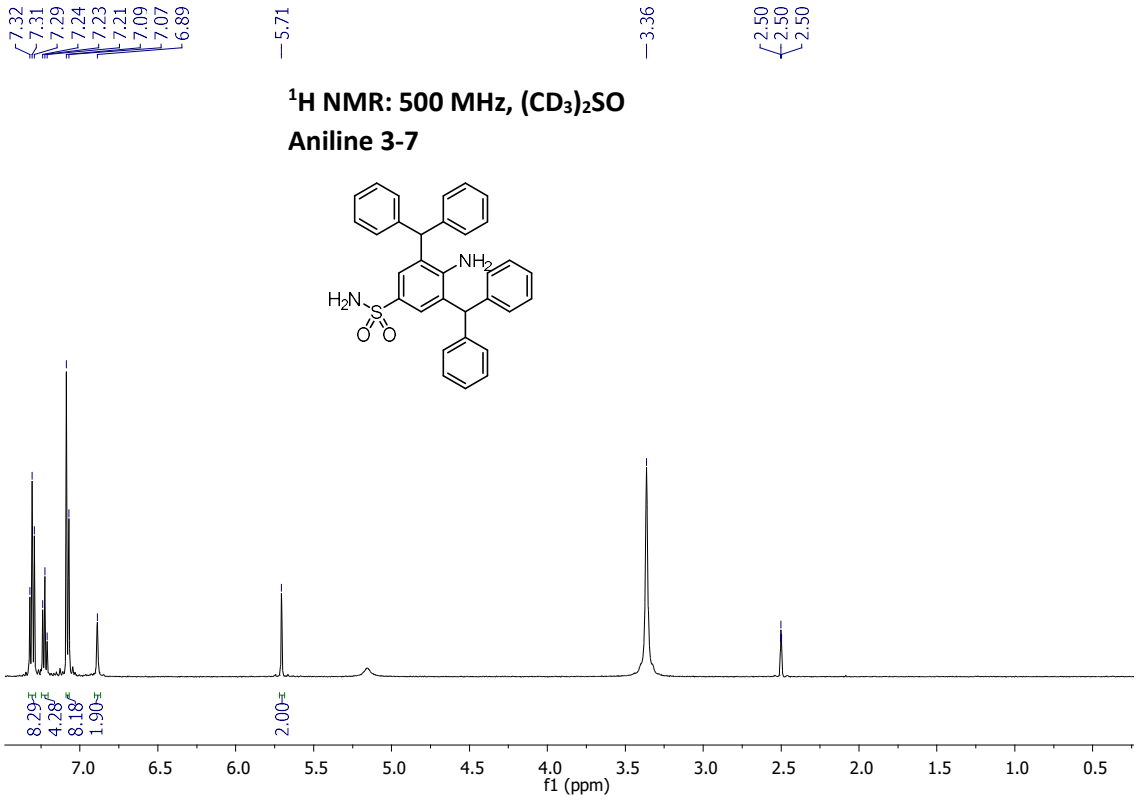




^{1}H NMR: 500 MHz, $CDCl_3$
Aniline 3-6

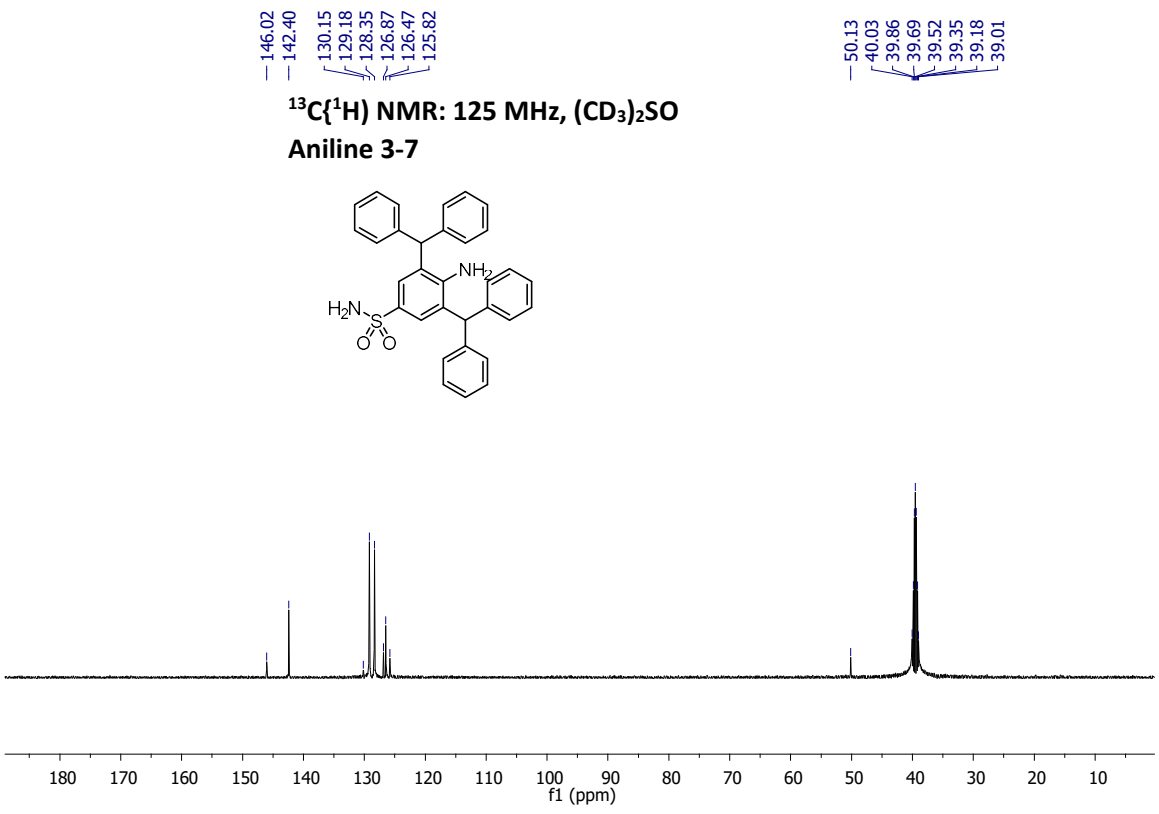


^{13}C{^{1}H} NMR: 125 MHz, $CDCl_3$
Aniline 3-6



^{1}H NMR: 500 MHz, $(CD_3)_2SO$

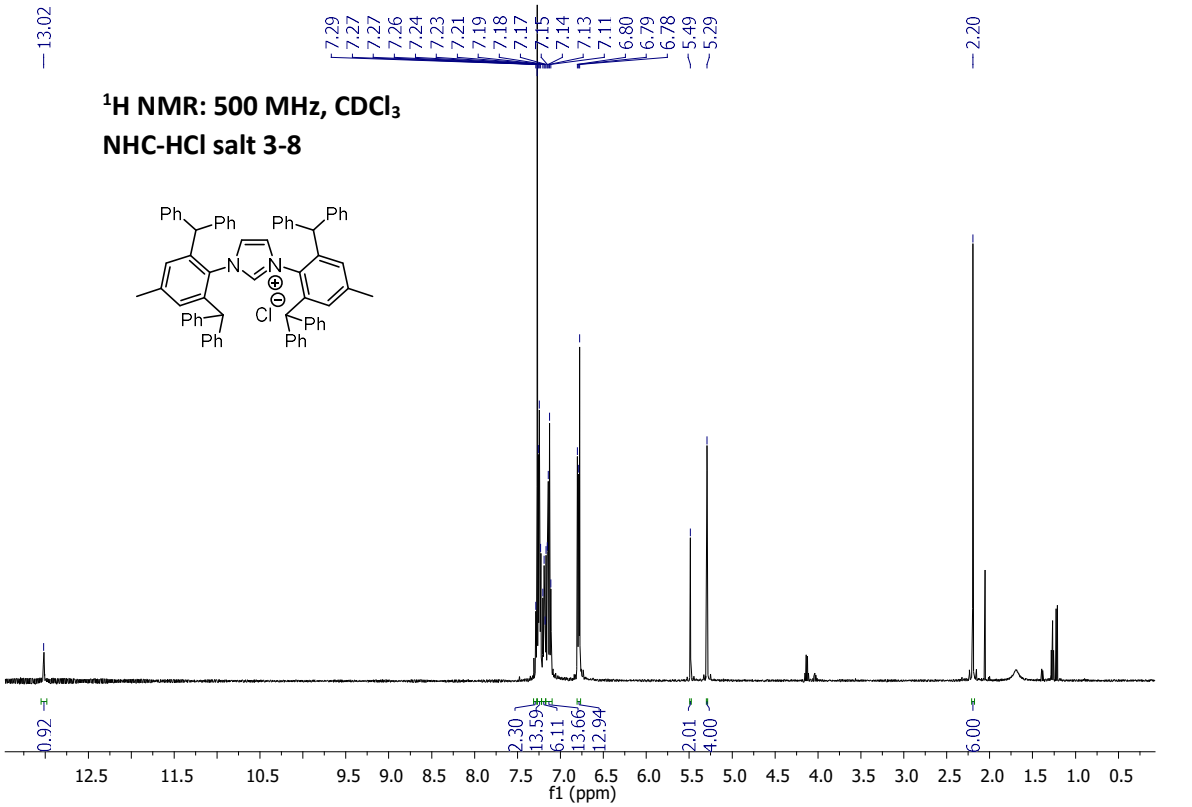
Aniline 3-7



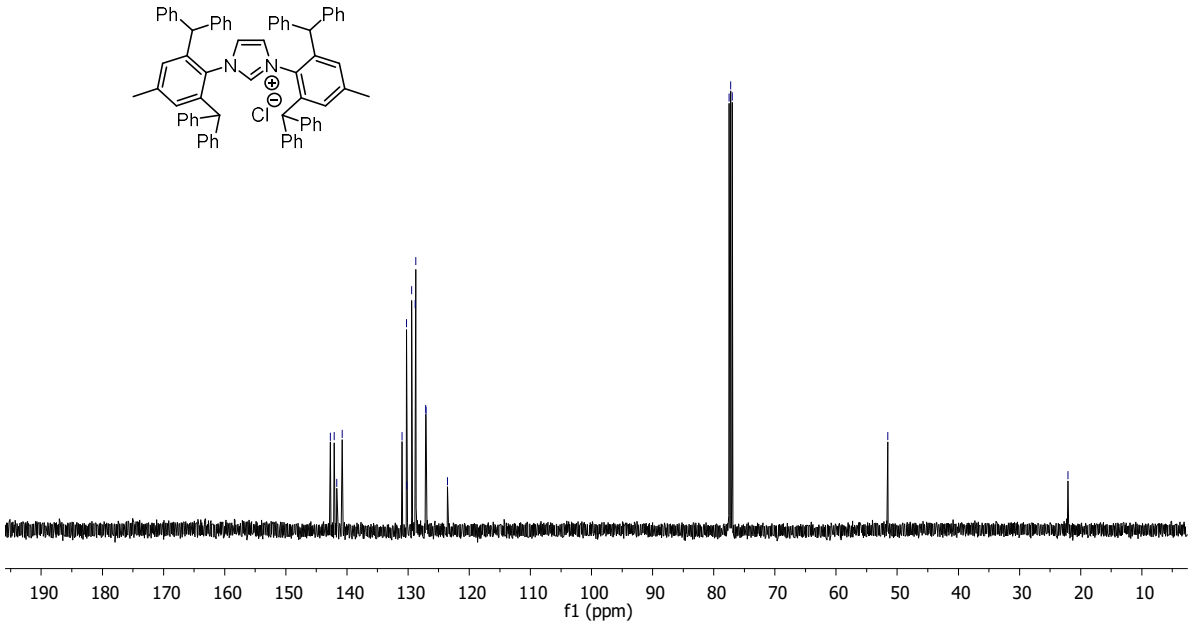
^{13}C{^{1}H) NMR: 125 MHz, $(CD_3)_2SO$

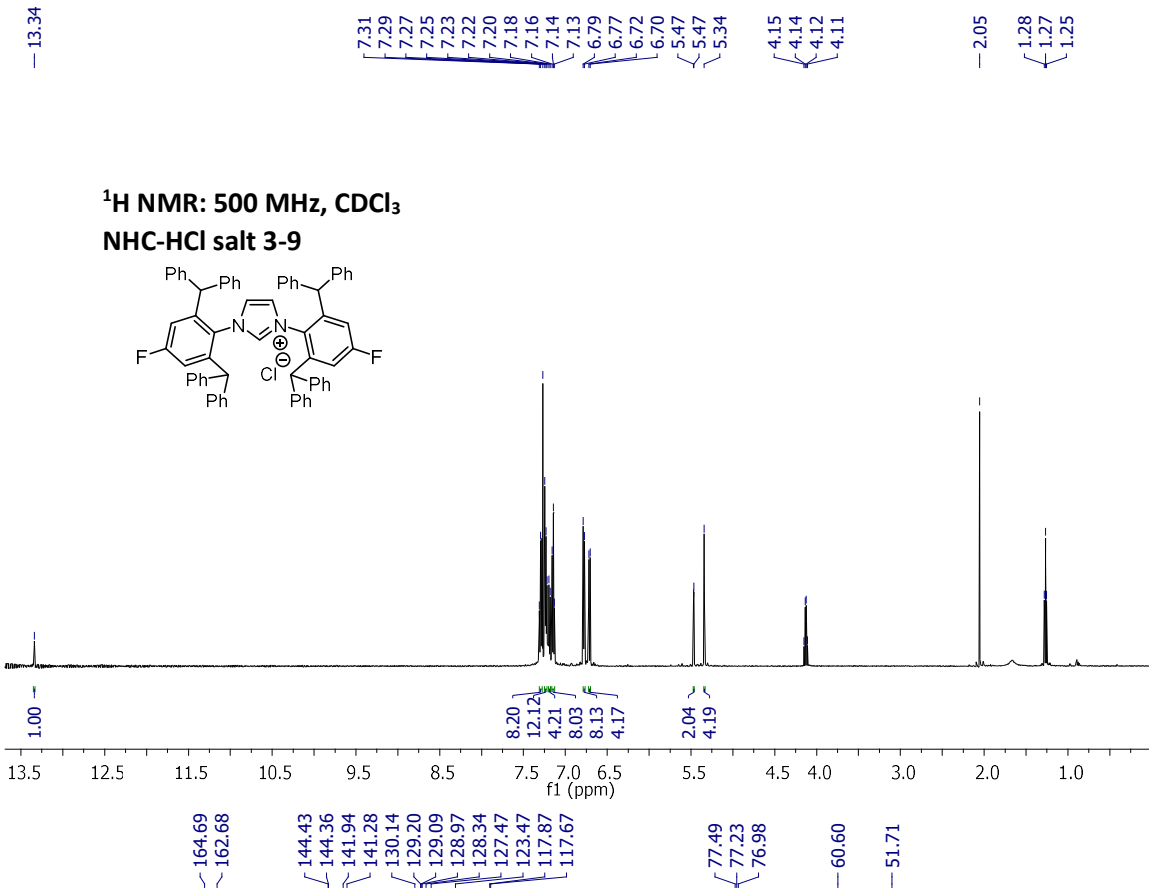
Aniline 3-7

^{1}H NMR: 500 MHz, $CDCl_3$
NHC-HCl salt 3-8



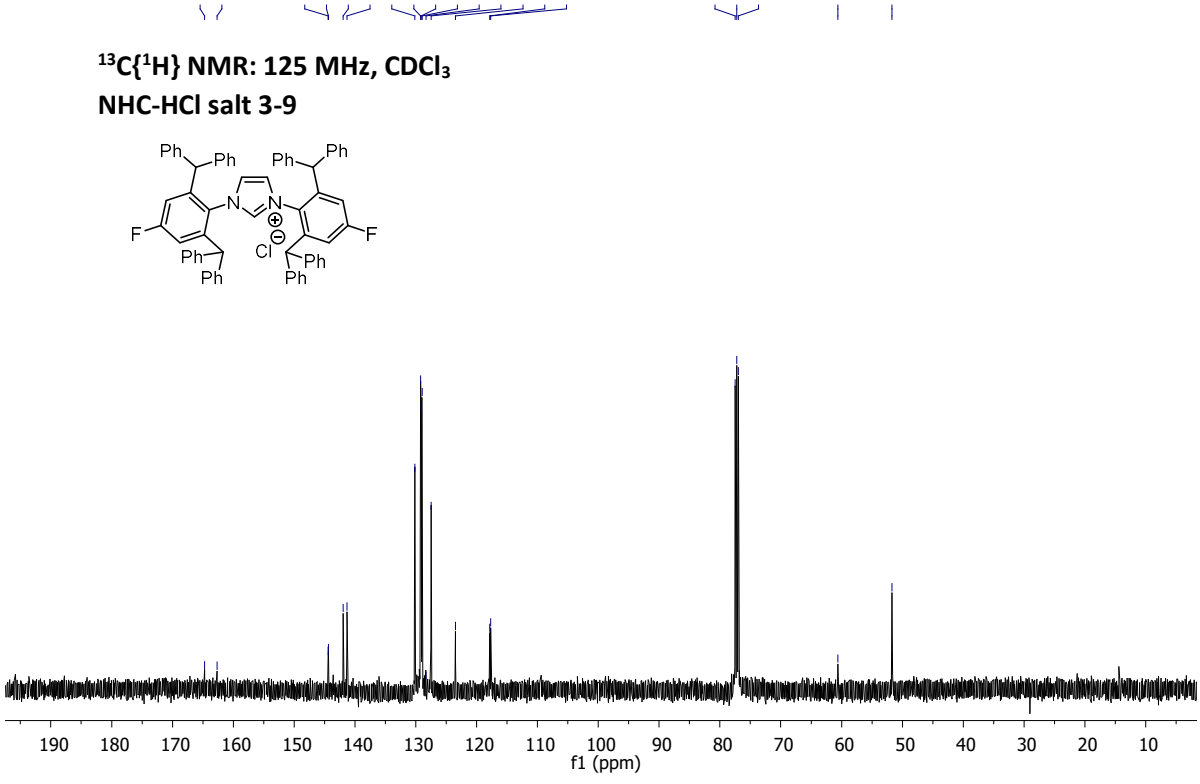
^{1}H NMR: 500 MHz, $CDCl_3$
NHC-HCl salt 3-8





^{1}H NMR: 500 MHz, $CDCl_3$

NHC-HCl salt 3-9

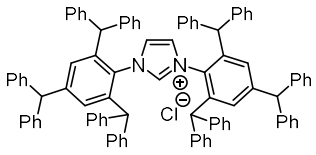


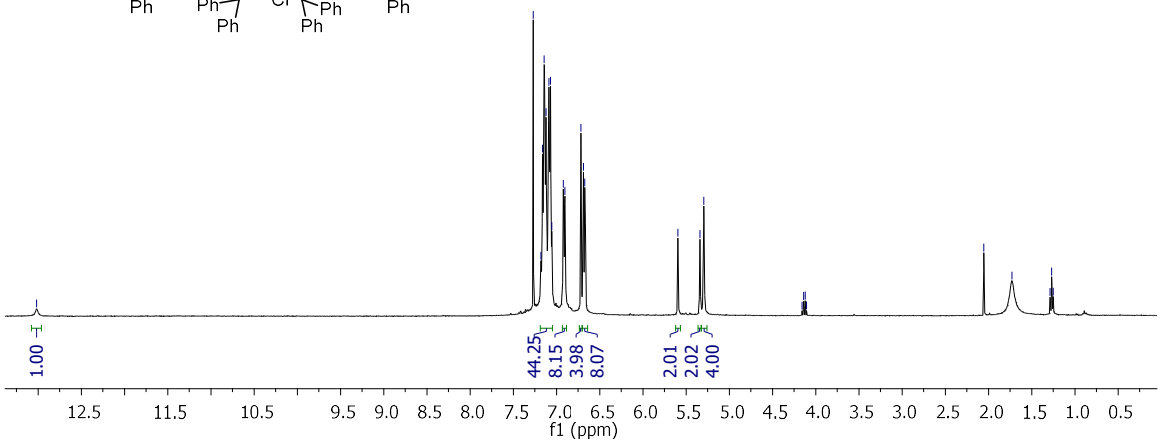
^{13}C{^{1}H} NMR: 125 MHz, $CDCl_3$

NHC-HCl salt 3-9

^{1}H NMR: 400 MHz, $CDCl_3$

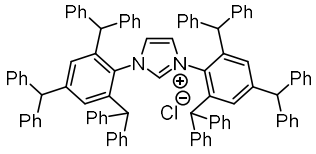
NHC-HCl salt 3-10

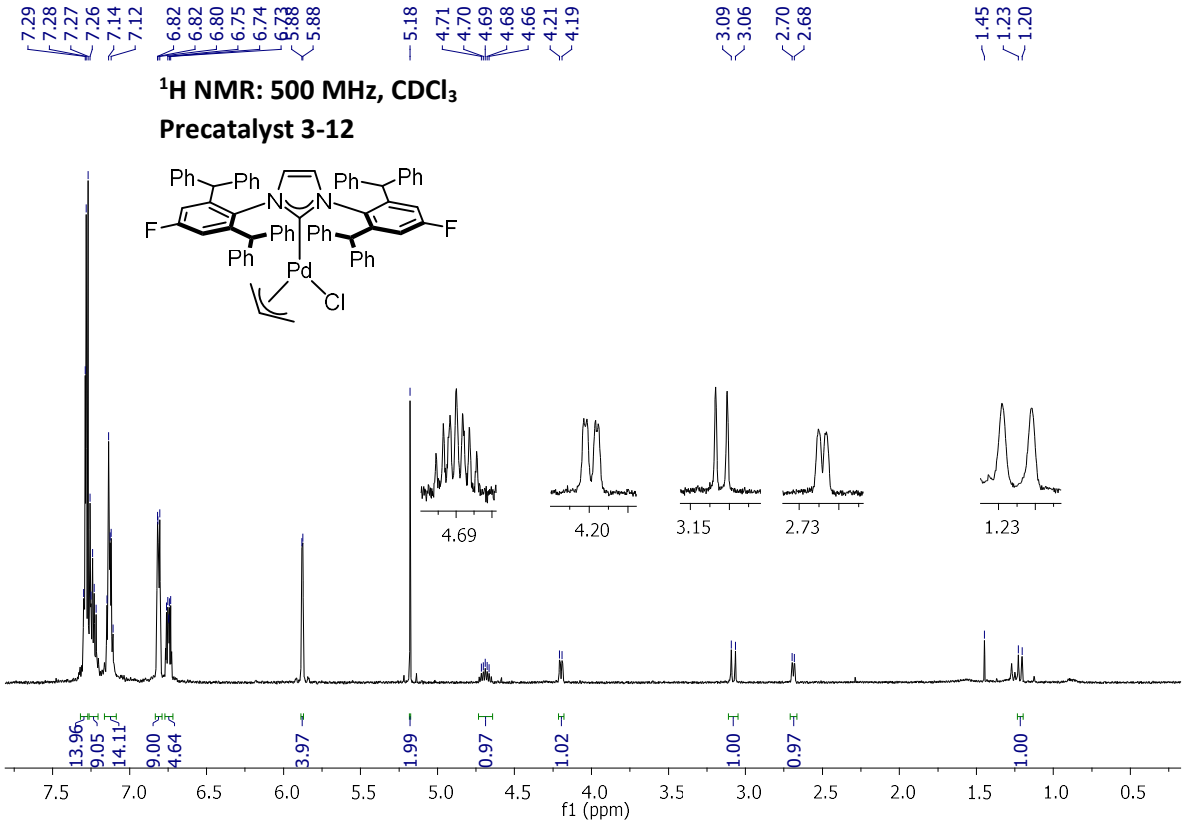




^{13}C{^{1}H} NMR: 100 MHz, $CDCl_3$

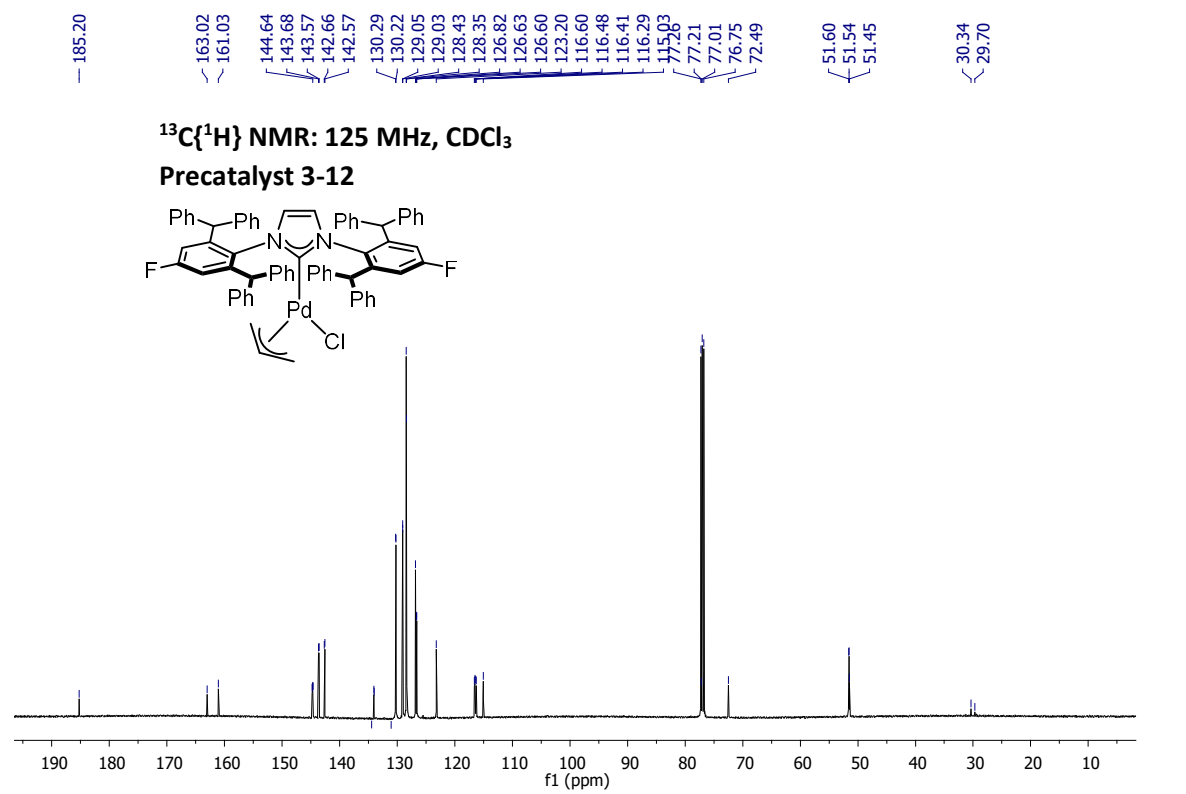
NHC-HCl salt 3-10





^{1}H NMR: 500 MHz, $CDCl_3$

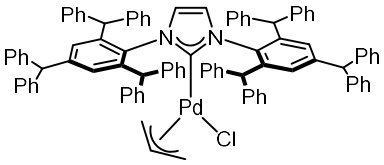
Precatalyst 3-12

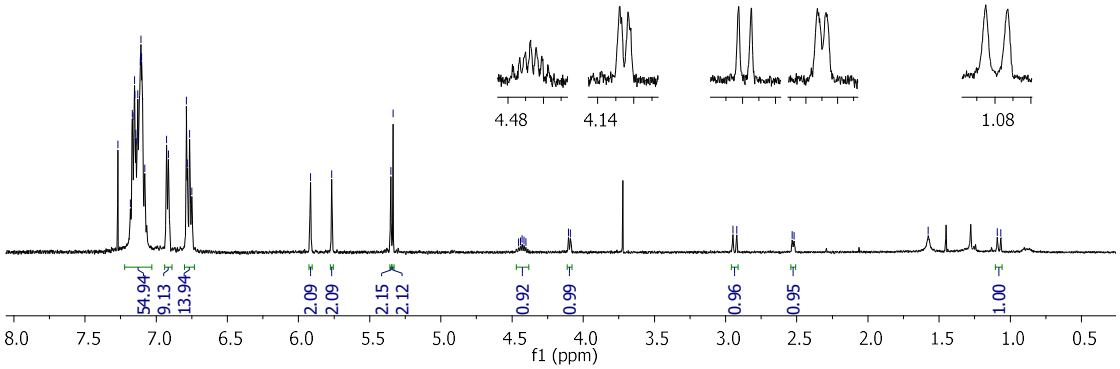


^{13}C{^{1}H} NMR: 125 MHz, $CDCl_3$

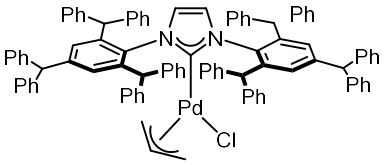
Precatalyst 3-12

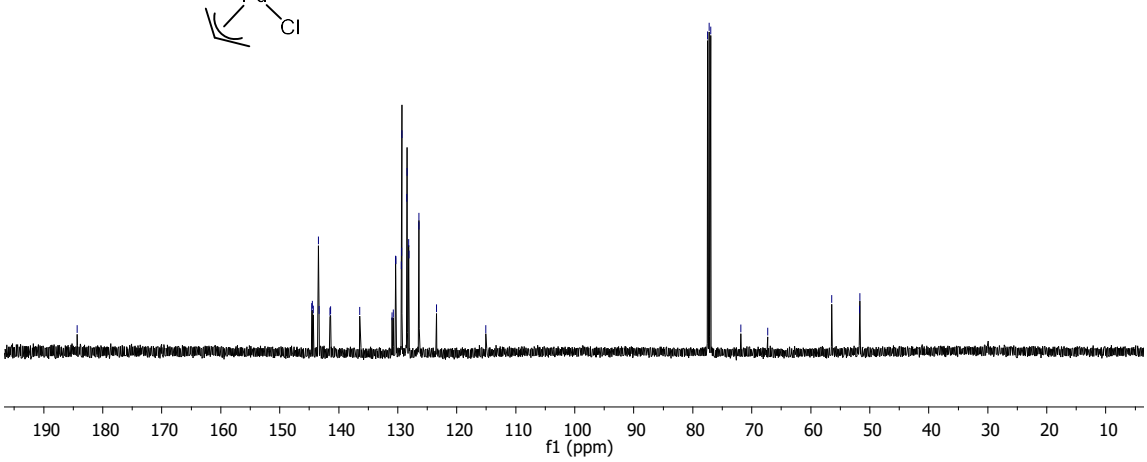
^{1}H NMR: 500 MHz, $CDCl_3$
Precatalyst 3-13





^{13}C{^{1}H} NMR: 125 MHz, $CDCl_3$
Precatalyst 3-13





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