The Development of Catalysts for the Monoarylation of Ammonia and Related Challenging Cross-Coupling Reactions

by

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ABSTRACT

The use of homogeneous organometallic catalysis for otherwise challenging chemical transformations is a concept that has gained significant interest in recent decades, providing access to a variety of useful chemical products. The catalytic reactivity of transition metals and ancillary ligands that bind to the metal center has played an important role in such methods, with notable breakthroughs being Nobel Prize-winning reactions such as olefin metathesis (2005) and palladium-catalyzed C-C cross-coupling (2010). The content of this thesis discloses the development of palladium-based catalysts for the monoarylation of ammonia and related challenging cross-coupling reactions, including an unprecedented indole synthesis from ammonia, carbonylative couplings of aryl halides, and acetone α-arylation as well as amination employing phenol-derived aryl methanesulfonates.

A thorough examination of the $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos catalyst system revealed details of the catalyst formation process and provided a guide for the development of precatalysts for otherwise challenging room-temperature ammonia monoarylations. The oxidative addition complex [(κ^2-*P,N*-Mor-DalPhos)Pd(Ph)Cl] proved to be the optimal catalyst for accommodating the coupling of a variety of aryl halides and tosylates with ammonia at room temperature. Applying ammonia to the synthesis of indoles, for the first time, gave access to NH-indoles directly using *o*-alkynyl bromoarenes as substrates. Pd/JosiPhos mixtures displayed superior catalytic activity to Pd/Mor-DalPhos in this process. Further studies involving the synthesis of catalytically relevant Pd complexes revealed that the bulky arylalkyne ligand may induce loss of ammonia from Mor-DalPhos catalytic intermediates, and that inhibition by the alkyne substrate through metal binding is also a contributing factor prior to oxidative addition.

Palladium-catalyzed aminocarbonylation reactions were successfully executed using a DalPhos ligand variant containing a pyridine as the nitrogen group (Pyr-DalPhos). Several different aryl and some heteroaryl bromides were tolerated in the coupling reaction with ammonia and carbon monoxide gaseous reagents, resulting in synthetically useful isolated yields of aryl amide products. Carbonylative versions of Heck couplings and acetone mono-α-arylation were performed using a pyrrole DalPhos and Me-DalPhos, respectively; however, these were found to give inferior yields of the desired chalcone or 1,3-diketone in comparison to common phosphine ligands used in such carbonylative processes.

Mixtures of Mor-DalPhos and $[Pd(cinnamyl)Cl]_2$ were determined to be ideal for effecting the first examples of ketone α-arylation utilizing aryl methanesulfonates (mesylates) as well as expanding the scope of amination reactions involving these non-halide aryl electrophiles to primary aliphatic amines for the first time. These transformations featured acetone and methylamine as coupling partners, both of which can be problematic substrates with respect to monoarylation but were found to be coupled with ease in this chemistry. The scope of aryl mesylates in the ketone α-arylation was limited to electron-rich and electron-neutral substrates, where *ortho*-substitution and electron-withdrawing groups were not accommodated within the aryl reagent. Several different functional groups and substitution patterns were tolerated in the amination process, with chemoselectivity being demonstrated at the primary amine position for substrates containing multiple NH sites.

LIST OF ABBREVIATIONS AND SYMBOLS USED

α	alpha position – first carbon adjacent to a carbonyl group in this thesis
β	beta position – second carbon adjacent to a carbonyl group in this thesis
Å	angstrom
δ	chemical shift
η	hapticity - eta (contiguous donor atoms)
κ	hapticity - kappa (non-contiguous donor atoms)
μm	micrometer(s)
1-Ad	1-adamantyl
Anal.	analysis
Ar	aryl
BHA	Buchwald-Hartwig amination
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
Bn	benzyl
Boc	tert-butyloxy carbonyl
br	broad
calcd.	calculated
cat.	catalytic or catalyst
CCD	charge-coupled device
COSY	homonuclear shift correlation spectroscopy
conv.	conversion
Cp	cyclopentadienyl, η^5-C_5H_5
Cy	cyclohexyl
d	doublet
dd	doublet of doublets
dba	dibenzylideneacetone
DEPTQ	distortionless enhancement by polarization transfer including quaternary carbon detection
DiPPF	1,1′-bis(diisopropylphosphino)ferrocene

DMSO	dimethyl sulfoxide
DPPF	1,1'-bis(diphenylphosphino)ferrocene
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
GC	gas chromatography
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazide
HSQC	heteronuclear single quantum correlation
HRMS	high-resolution mass spectrometry
Hz	hertz
iPr	iso-propyl
$J_{XX'}$	coupling constant between atom X and atom X'
L	neutral 2-electron donor ligand
LIKAT	Leibniz Institute for Catalysis
M	mega *or* mol/L *or* molecular ion
m	multiplet
Me	methyl
M-DP	Mor-DalPhos
Mes	mesitylene
mg	milligram(s)
mL	milliliter(s)
MTBE	methyl *tert*-butyl ether
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
nPent	n-pentyl
nPr	n-propyl
o	ortho
OAc	acetate
OMs	methanesulfonate or mesylate

ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf	trifluoromethanesulfonate or triflate
OTs	*p*-toluenesulfonate or tosylate
ppm	parts per million
PTFE	poly(tetrafluoroethylene)
q	quartet
R	generic substituent
rt	room temperature
s	singlet
t	triplet
*t*Bu	tert-butyl
TBS	tert-butyl-dimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N,N*-tetramethylethylenediamine
TMS	trimethylsilyl
tol	tolyl
X	halide substituent *or* anionic ligand

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CHAPTER 1 INTRODUCTION

1.1 General Introduction: Catalysis in Chemical Synthesis

One of the major challenges in synthetic chemistry is the development of sustainable methods for the conversion of simple feedstock molecules or abundant chemicals to value-added products. Key requirements associated with such processes are the use of inexpensive reagents, mild reaction conditions, elimination of stoichiometric additives, high product yield and selectivity, benign solvents and simple isolation procedures.[1] Catalysis offers the opportunity to work towards these goals of sustainability. Pharmaceutical drugs, polymer materials and other commodity chemicals are just a few examples of the valuable products that have been synthesized through catalytic applications.[2] Catalysis embodies environmentally and energetically beneficial practices in that catalysts lower the activation energy for a given process, they can be used in sub-stoichiometric amounts, and in certain cases they can be recycled for further use. Of particular interest in this context are green chemistry methods, since the amount of waste production using more conventional synthetic approaches can be reduced through the use of a catalyst. For example, fine chemicals and pharmaceuticals manufactured in industry typically generate a high waste to product ratio (5:1-100:1 by mass), resulting from multi-step processes, stoichiometric amounts of reaction mediators, and solvent. Employing a catalyst can decrease the number of synthetic steps involved and also avoid the byproducts of unnecessary stoichiometric additives, thereby demonstrating greater atom economy.[1, 3] Additionally, catalysis can induce reactivity of otherwise unreactive molecules, providing direct access to new products that could not be synthesized by alternative protocols.

Notably, several different forms of catalysts that persist throughout synthetic chemistry include acids, bases, enzymes, and main group elements. One of the most important classes of catalysts are transition metal-based systems, which will be the focus for the remainder of the thesis. Significant breakthroughs in the area of catalysis have been achieved over the years including such processes as olefin polymerization (1963) and asymmetric hydrogenation (2001), which were recognized through Nobel Prizes, as fundamental catalytic transformations.[4] Both reactions show the utility of catalysis in

taking feedstock chemicals, in these cases simple alkenes or H_2, and converting them to more valuable products. Notably, these processes exploit organometallic materials as catalysts, the former involving heterogeneous species and the latter homogeneous compounds. Heterogeneous refers to the catalyst being in a different phase than the reagents and products, whereby the catalyst is often a solid or on a solid support with the reagents in solution or in the gas phase. Conversely, homogeneous catalysis occurs when the catalyst and the reagents are in the same phase, usually a liquid phase in which both are soluble.[5]

Whereas heterogeneous catalysis has been more widely used in industrial chemical manufacturing, the interest in homogeneous catalysis employing organometallic compounds has grown significantly in recent years. The 2005 Nobel Prize in Chemistry was awarded for the development of alkene metathesis, a process catalyzed by molybdenum and ruthenium complexes in which two alkenes are reacted to form a desired alkene. Only five years later, the Prize was awarded for palladium-catalyzed cross-coupling reactions in organic synthesis, a process that has allowed for direct access to carbon-carbon linkages (i.e. aryl- or alkenyl-carbon) that are difficult to form by more traditional means.[6] Both of these methodologies have been applied to the synthesis of bulk chemicals, pharmaceuticals and fine chemicals in industry.[7]

1.2 Palladium-Catalyzed C-C Cross-Coupling Reactions

1.2.1 Overview of C-C Cross-Coupling

Extensive work done in the area of palladium-catalyzed C-C cross-coupling has given rise to a broad spectrum of new reaction classes. As mentioned in the previous section, some of these key reactions include Suzuki, Negishi and Heck cross-coupling (for which the 2010 Nobel Prize in chemistry was awarded) which employ boron, zinc and alkenes as coupling reagents, respectively. In Suzuki coupling, an sp^3, sp^2, or sp-hybridized carbon-boron reagent (i.e. aryl, allyl, alkenyl, alkynyl or alkyl) is coupled with an aryl, alkenyl or alkyl halide to form a new C-C bond in the product. Similarly, Negishi uses aryl, alkenyl, alkynyl or acyl halides with organozinc coupling partners to form a newly coupled product in the presence of a palladium or nickel catalyst. Both of these processes have a general catalytic cycle (Figure 1.1 left) consisting of: i) oxidative

addition of the organohalide to the metal catalyst; ii) transmetalation to expel the stoichiometric metal reagent and form an intermediate diorgano-metal species; and iii) reductive elimination of the final coupled product to regenerate the metal catalyst. Through a slightly different catalytic cycle (Figure 1.1 right), Heck coupling results in the formation of a new C-C bond between an aryl or alkenyl halide and an alkene. In place of the organometallic reagent, an alkene enters the catalytic cycle and reacts with the oxidative addition intermediate resulting in a palladium-alkyl species. In turn, this undergoes a C-C bond-rotation followed by syn β-hydride elimination to form an arylated or alkenylated olefin. The remaining palladium-hydride then reductively eliminates HX in the presence of base to regenerate the palladium(0) species.[5, 8]

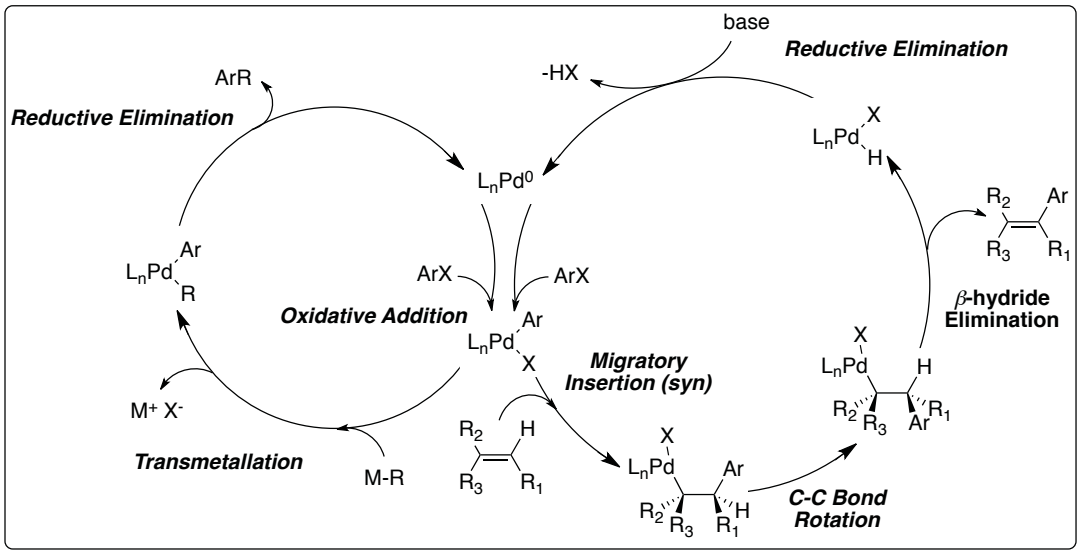


Figure 1.1 Catalytic cycles for C-C cross-coupling involving metal reagents (left) or alkenes (right).

Another related cross-coupling reaction that employs metal reagents is known as Stille coupling. The same catalytic cycle applies to this reaction, as shown in Figure 1.1 (left), but rather than using zinc or boron, organotin reagents are used. Trialkyltin compounds carrying allyl, aryl or alkenyl groups take part in the reaction with acyl, alkenyl or aryl halides.[8] Although tin reagents are more stable than those reagents of Suzuki and Negishi coupling, they are more toxic, making this methodology applicable to small-scale reactions but not very attractive on larger scale.[5]

1.2.2 Ligand Effects

A significant contributor to the observed catalytic reactivity in these C-C bond formations is the identity of the ligand (L_n) on the palladium metal centre, where there could be one or multiple ligands present (e.g. n = 2) or several donor sites within a single ligand (chelating effects). The steric and electronic properties of the ligand have been shown to directly influence catalyst performance, through the individual steps of the catalytic cycle.[5] Ligands featuring multiple donor atoms or chelating ligands avoid undesired side products but can cause lower rates of oxidative addition and intermediary catalytic steps in comparison to monodentate ligands (e.g. mono- vs. bisphosphines); that is, bidentate ligands stabilize reactive intermediates but do not easily allow for open coordination sites needed within such catalytic species. Typically, sterically hindered electron-rich ligands such as trialkylphosphines and *N*-heterocyclic carbenes increase the rates of both oxidative addition and reductive elimination, allowing for challenging aryl bromides, chlorides and pseudohalides to undergo cross-coupling under milder conditions.[9] For oxidative addition, the bulky ligand promotes both coordinative unsaturation and electron richness at palladium, leading to a fast reaction with the aryl halide. Unwanted steric congestion caused by the bulky ligands can be alleviated through reductive elimination, thus causing this step to proceed at an increased rate when using larger ligands.[5, 10]

In regard to more difficult coupling reactions where selectivity, catalyst turnover and undesired side reactions become problematic, additional ligand factors that influence catalytic reactivity beyond sterically demanding/electron-donating groups for active Pd species need to be taken into consideration.[11] These factors include structural features that induce flexibility or rigidity within the LPd complexes to promote Suzuki reactions of bulky aryl coupling partners. Furthermore, isomerized products are avoided in Negishi and Suzuki couplings of secondary C(sp^3)-nucleophiles through modifications in ligand electronic properties. These and other ligand characteristics have led to significant advancements in cross-coupling reactions forming carbon-heteroatom bonds.

1.2.3 Related C-C and C-X Coupling Processes

With the advent of these C-C bond-forming processes, many different cross-

coupling reactions have developed. Stille coupling led the way to Buchwald-Hartwig amination, a palladium-catalyzed reaction to generate new C-N bonds including industrially relevant aryl amine products.[12] Several mechanistically similar carbon-heteroatom coupling reactions have stemmed from this method including the formation of C-O, C-S,[13] and C-F linkages[14] to form phenols or ethers, thioethers and aryl fluorides, respectively. Also associated with C-C cross-coupling is the Pd-catalyzed α-arylation of α-CH-acidic compounds such as ketones, which generates synthetically useful aryl ketone products.[15] Furthermore, cross-coupling reactions incorporating carbon monoxide, as an important pathway to construct carboxylic acid derivatives, have also recently emerged.[16] Palladium-catalyzed C-N cross-coupling (Buchwald-Hartwig amination), α-arylation and carbonylative versions of both will be discussed further in the coming sections.

1.3 Palladium-Catalyzed C-N Cross-Coupling Reactions

1.3.1 Traditional C-N Bond-Forming Methods

Prior to the development of the aforementioned metal-catalyzed processes for C-C and C-X bond formations, of which many now represent the state-of-the-art for such syntheses, alternative methods were employed. A selection of stoichiometric reactions generating new C-N bonds are listed below:[8, 17]

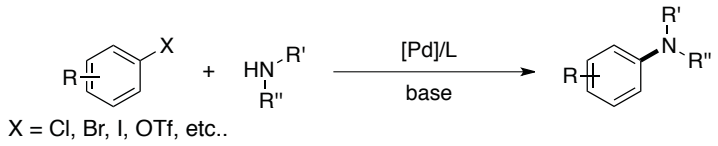
1. Nitration of benzene via electrophilic aromatic substitution followed by metal reduction forming aniline.
2. Nucleophilic aromatic substitution through an activated aryl halide or a benzyne intermediate to produce an aryl amine.
3. Nucleophilic bimolecular or unimolecular substitution of alkyl halides yielding alkyl amines.
4. Mitsonobu reaction in which a primary or secondary alcohol is converted to a secondary or tertiary amine.
5. Reductive amination to form secondary alkyl amines from ketones; reductive amination in the Mannich reaction leads to aminoalkylated derivatives of carbonyl substrates.

6. Ullmann biaryl amine synthesis - a copper-mediated process producing diaryl-substituted amines at high temperatures.

All of these methods involve the use of stoichiometric reagents (acids, bases, metals etc…) and/or form amines with undesired selectivity (i.e. mixtures of amine products). For these reasons, and given the ubiquitous nature of C-N bonds in biologically active target compounds as well as in sought-after conjugated materials, there is an increasing interest in the development of alternative protocols that minimize waste production and promote desired selectivity, specifically for the formation of less accessible C(sp^2)-N linkages. Palladium-catalyzed C-N cross-coupling (Buchwald-Hartwig amination) represents an attractive synthetic protocol that satisfies these requirements.

1.3.2 Progress in C-N Cross-Coupling (Buchwald-Hartwig Amination, BHA)

The first report of a C-N bond-forming process using a palladium catalyst stemmed from Stille coupling, in which a tin amide reagent was coupled with bromobenzene;[18] however, further studies revealed that amines could be directly coupled with aryl bromides without the use of tin.[19] The research groups of John Hartwig and Stephen Buchwald concomitantly demonstrated these advances and have continued to provide significant contributions to the development of C-N and related cross-coupling chemistry. Buchwald-Hartwig Amination (BHA) has become an indispensable C-N bond-forming technique for both academic and industrial settings, gaining access to otherwise difficult-to-prepare (hetero)aryl amine products (Scheme 1.1).



Scheme 1.1 General scheme for Pd-catalyzed cross-coupling of aryl halides and N-H containing substrates.

The catalytic cycle of BHA consists of similar intermediate steps to those found in coupling reactions between aryl halides and carbon nucleophiles, including oxidative

addition, amine coordination/deprotonation (analogous to transmetalation) and reductive elimination (Figure 1.2).[5]

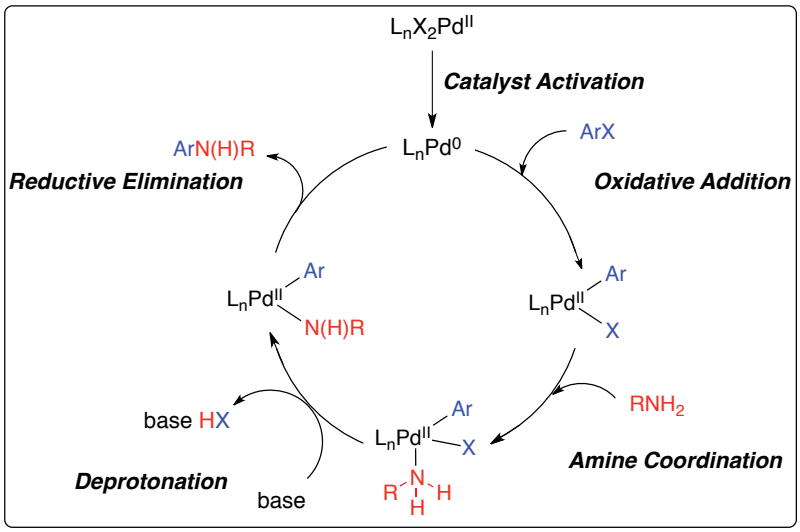


Figure 1.2 Representative catalytic cycle of C-N cross-coupling processes.

Initially, a Pd(0) or Pd(II) source (e.g. Pd_2dba_3 or $Pd(OAc)_2$) undergoes catalyst activation involving ligand dissociation and/or reduction to generate the active Pd(0) species. In the presence of aryl halide, this active intermediate proceeds through oxidative addition forming either a monomeric or dimeric aryl palladium(II) halide, depending on ligand interactions. Coordination of the amine and deprotonation by added base leads to the aryl palladium(II) amido species, which may be a three-coordinate 14-electron complex or a four-coordinate 16-electron complex, resulting from the nature of the ligand.[19a] Alternatively, the use of alkoxide base first forms an aryl palladium(II) alkoxide that undergoes protonation by the amine to produce the palladium amide and alcohol. Reductive elimination involving the aryl palladium (II) amido yields the desired aryl amine product and reduces the Pd(II) species to regenerate the active Pd(0) complex.

The rate-limiting step of this process is often oxidative addition; however, reductive elimination of the aryl palladium(II) amido has been shown to influence the substrate scope and yield.[5] The different electronic properties of the aryl and amido ligands on palladium dictate the rate of reductive elimination; palladium intermediates with less electron-rich aryl groups and more electron-rich amido groups will generally lead to an increased rate in comparison to alternative scenarios such as palladium species

with electron-neutral ligands.[20] In regard to undesired catalytic pathways, the amido intermediate complex can undergo β-hydride elimination leading to a hydrodehalogenated arene product (ArH) instead of the desired aryl amine ($ArNH_2$). Furthermore, the amine can induce ligand displacement leading to catalyst deactivation, and uncontrolled polyarylation of aryl amine products can also occur. The effects of the ancillary ligand must also be considered with respect to the catalytic cycle.[9a, 13b, 21] Some ligand factors to take into consideration are: i) favourable formation of initial "Pd-L" complexes; ii) promotion of fast oxidative addition via unstable monoligated LPd(0) species; iii) selectivity in coordination of the amine; iv) steric/electronic influences to accelerate reductive elimination; and v) prevention of catalyst deactivation or decomposition.

The choice of base, solvent, palladium source, and especially the ligand have significantly improved the scope and selectivity of BHA. However, the catalyst system and conditions in each case tend to vary depending on the combination of amine and aryl halide coupling partners.[22] The scope of aryl halides and pseudohalides currently applicable to this transformation include bromides, chlorides,[9d] triflates,[23] tosylates,[24] benzenesulfonates,[25] nonaflates[26] as well as a few examples of more atom-economical mesylates.[27] Aryl iodides have proven to be more difficult substrates than expected related to aryl chlorides and bromides on the basis of C-X bond strengths, possibly due to catalyst deactivation via the formation of stable iodide bridging structures,[28] although some catalyst systems have circumvented these issues.[29] The scope of amine coupling partners that can be accommodated with most BHA catalyst systems is limited to primary and/or secondary aliphatic and aromatic amines. Although these amines may pose difficulties through catalyst deactivation and polyarylation pathways, recent developments in ligand design have addressed these and related challenges in C-N cross-coupling.[11]

There are myriad options available in choosing a suitable ligand for achieving desired performance in a BHA reaction. As discussed in Section 1.2.2, some of the more important and widely used ligand classes are sterically hindered and strongly σ-donating monophosphines,[9a, 21-22, 30] bidentate bisphosphines,[13b, 31] as well as *N*-heterocyclic carbenes (NHCs) (Figure 1.3).[9c, 32] Buchwald's biaryldialkylphosphines[22] have inspired

heterocyclic analogs to be developed by Beller, Singer and others including arylpyrrol-, arylpyrazol- and arylindol-based phosphine ligands.[17a, 33] Alternative ligand classes feature P-N and P-O linkages. Early work in C-N cross-coupling employed bisphosphines such as BINAP, which proved to be a superior class of ligands in comparison to monodentate variants such as tri-*ortho*-tolylphosphine, since the substrate scope could be extended to couplings of alkyl amines with aryl bromides.[5] The development of bulky more electron-rich trialkylphosphines (i.e. P(*t*Bu)$_3$) and NHCs led to the efficient coupling of aryl chlorides at temperatures as low as room temperature.

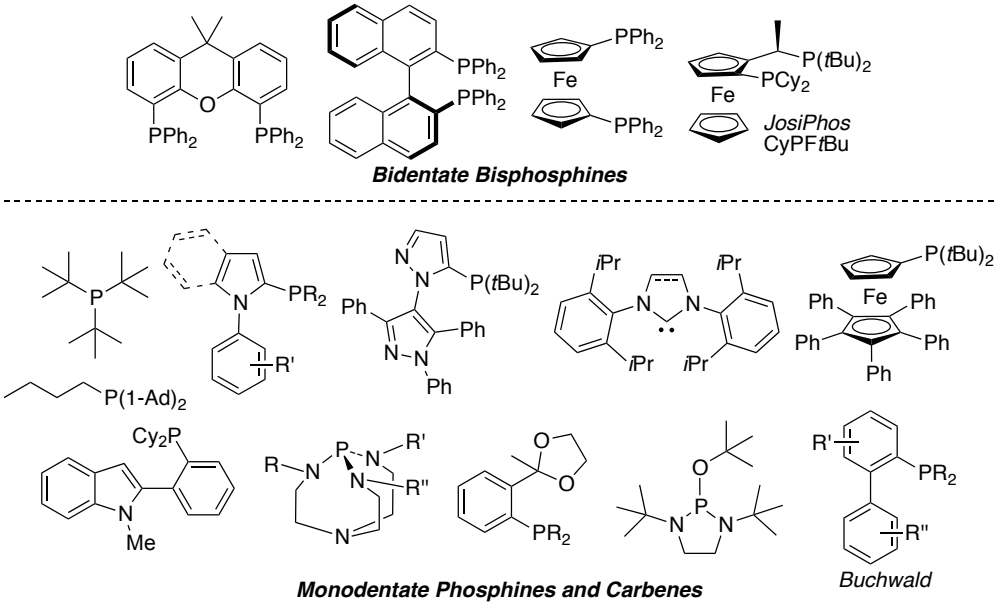


Figure 1.3 Some common ligands employed in Pd-catalyzed C-N cross-coupling developed prior to work by the Stradiotto group.

With more than 20 variants, Buchwald's biaryl dialkylphosphines have gained the widest application in C-N cross-coupling. Buchwald ligands are generally "task-specific" in that certain variants are well suited for particular substrates such as heteroaryl halides or primary alkyl amines.[22, 34] Although Hartwig has not directed his research efforts toward novel ligand design in amination chemistry, he has focused on the application of catalysts incorporating bidentate bisphosphines.[13b, 35] Most notably, he identified the previously known JosiPhos ligand CyPF*t*Bu as affording a catalyst system that was able to couple difficult substrates such as halopyridines, chloroarenes and primary amines with less than 1 mol% catalyst loadings. This ligand was particularly useful for the selective monoarylation of primary amines and ammonia[31b, 36] in comparison to less

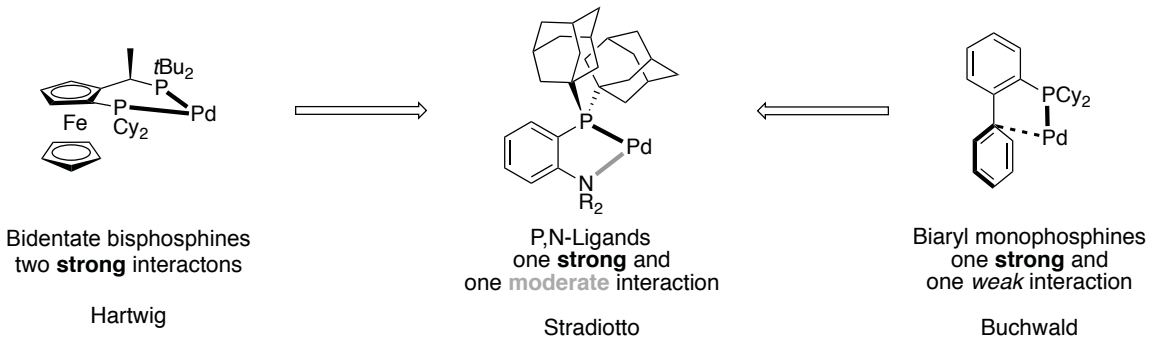
effective catalyst systems containing Buchwald ligands[37] or NHCs.

Although there has been significant progress in C-N coupling chemistry with respect to ligand design, substrate scope and conditions, there still remain several unmet challenges in this reaction class. As mentioned earlier, current catalyst systems have been developed for specific groups of aryl halide or amine substrates; these tend to lose activity when applied to a wider substrate scope. A general or universal catalyst that can be employed with a variety of coupling partners would avoid the necessity of catalyst optimization and allow for amination processes to be more broadly applicable to non-expert end-users. With respect to amine tolerability, small nucleophiles including methylamine, ammonia and hydrazine can be troublesome, arising from catalyst deactivation pathways and lack of product selectivity for monoarylation. Only recently have these issues been addressed though further developments are needed. Furthermore, the scope of aryl pseudohalides derived from phenols has been limited to those with high leaving group activity such as toluenesulfonates and trifluoromethanesulfonates, whereas the more electron-rich derivative methanesulfonate, has not received the same attention, despite the significant synthetic potential of such reagents. These challenges related to substrate scope will be addressed in the following chapters.

1.4 Previous Work in the Stradiotto Research Group

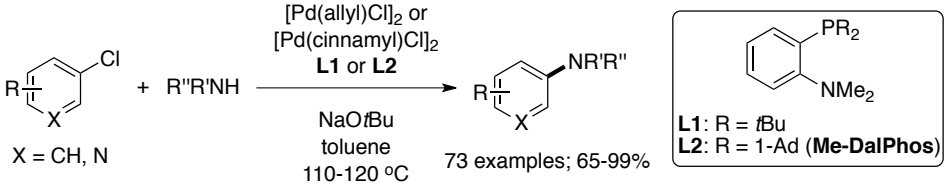
Efforts in the Stradiotto group have been directed towards the design, synthesis and application of novel ligands in challenging palladium-catalyzed cross-coupling reactions. Work in this area was inspired by the ligand design approaches of Buchwald and Hartwig (Scheme 1.2). Buchwald biaryl dialkylphosphine ligands generate a palladium catalyst that has both a strong phosphine interaction and a week *ipso*-carbon interaction to the metal centre.[21] The JosiPhos ligand, implemented in C-N cross-coupling by Hartwig, is a chelating ligand that forms two strong phosphine interactions to the palladium metal centre upon formation of a catalytic complex. Stradiotto ligands were designed to be an intermediate class between these two extremes, with one strong interaction and one moderate interaction to palladium. This was achieved initially with the synthesis of a P,N-phenylene structural motif and resulted in a few first-generation "DalPhos" ligands, the most notable being Me-DalPhos.[38] It was hypothesized that these

P,N-type ligands could provide beneficial catalytic activity in challenging BHA reactions through potential hemilability of the nitrogen moiety and promotion of oxidative addition and reductive elimination steps due to an intermediate electronic profile in comparison to the P,C (Buchwald) and P,P-type (Hartwig) ligands.



Scheme 1.2 Key palladium-ligand interactions of mono- and bidentate phosphines leading to P,N-ligands.

In order to address some limitations in BHA that existed at the time, specifically catalyst generality for a wide substrate scope and use of low catalyst loadings, a ligand screen containing structurally related P- and N-donor fragments was executed by the Stradiotto group. Me-DalPhos and a di-*tert*-butylphosphino (-P(tBu)$_2$) variant were found to form highly active palladium catalysts for the BHA of a broad range of aryl and heteroaryl chlorides with primary and secondary aliphatic and aromatic amines (Scheme 1.3). Not only did this new ligand class demonstrate high versatility for general C-N cross-coupling but it also performed at catalyst loadings as low as 0.02 mol% Pd.



Scheme 1.3 Novel P,N-phenylene ligands for the amination of (hetero)aryl chlorides.

When both ligands were screened for the monoarylation of ammonia, Me-DalPhos gave considerably higher conversion of chlorobenzene and an improved mono:diarylation ratio in comparison to the -P(tBu)$_2$ ligand. In screening other aryl chlorides, however, only sterically biased substrates allowed for the desired monoarylated product to be formed selectively; a lack of *ortho*-substitution resulted in poor ratios of

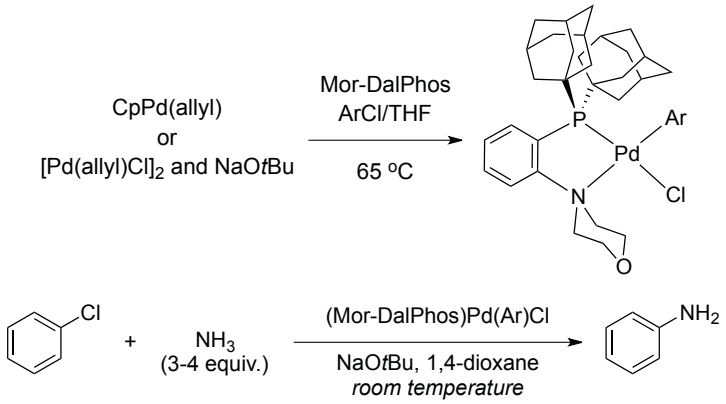
mono- to diarylation in most cases. Furthermore, a large excess of ammonia (10 equivalents) was required under these conditions. Thus, an alternative ligand suitable for selective ammonia monoarylation was needed that would tolerate a wide variety of aryl chlorides using minimal amounts of ammonia. The development of a second generation P,N-phenylene ligand synthesized for this purpose (Mor-DalPhos) will be discussed in Chapter 2.

1.5 Overview of Thesis Research

The research compiled in this thesis document will further develop the themes of ligand design and catalytic applications currently studied in the Stradiotto group. Two principal strategies for catalyst development that will be highlighted in the coming chapters are that of a catalytic and a stoichiometric approach; the former involving the development of a catalyst system for an unknown target reaction and the latter incorporating fundamental experiments to understand the reactivity of a given metal-ligand complex leading to new catalysis. Progress throughout the thesis research has typically followed the catalytic technique, where stoichiometric studies of transition metal complexes have been performed as a secondary measure to gain mechanistic insight into newly developed or improved transformations. In this context, the main goals of this dissertation are: 1) to establish an understanding of the palladium/Mor-DalPhos catalyst system in ammonia arylation with respect to mechanism and substrate scope (Chapters 2 and 3); and 2) to expand the reactivity profile of the DalPhos ligand set to more challenging C-N and related cross-coupling processes (Chapters 4 and 5).

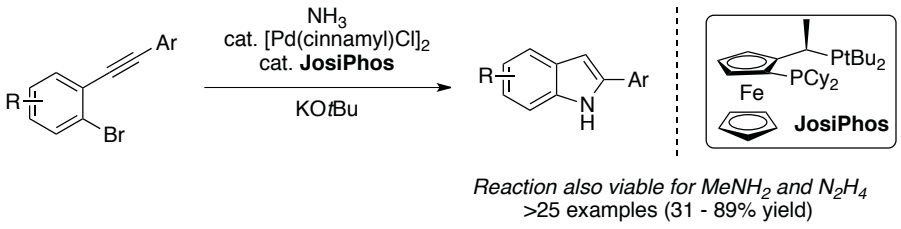
In Chapter 2, a thorough investigation of the Pd/Mor-DalPhos catalyst system in the context of ammonia arylation under mild conditions is discussed. The results of these investigations include stoichiometric reactivity studies directed towards understanding the catalyst formation process and the binding modes of the Mor-DalPhos ligand. Furthermore, an analysis will be presented pertaining to the influence of the palladium source on the efficiency with which putative catalytic intermediates are generated, and the influence of varying the Pd-aryl group in precatalysts of the type [(κ^2-*P,N*-Mor-DalPhos)Pd(aryl)Cl] on catalytic performance. Synthetic studies establishing the expanded *room-temperature* substrate scope of ammonia monoarylation, encompassing a

range of (hetero)aryl (pseudo)halides (X = Cl, Br, I, OTs) with a diverse set of substituents (alkyl, aryl, ether, thioether, ketone, amine, fluoro, trifluoromethyl, and nitrile), are also disclosed.



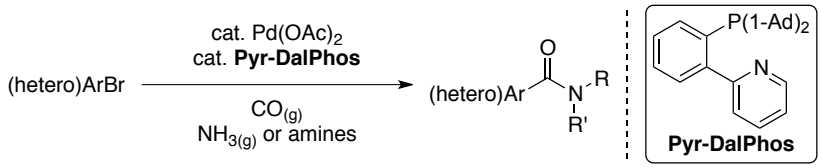
Scheme 1.4 Synthesis of Pd/Mor-DalPhos oxidative addition complexes and application in ammonia cross-coupling at room temperature.

Chapter 3 features a new synthesis of indoles employing ammonia for the first time, through an initial palladium-catalyzed cross-coupling followed by an alkyne cyclization. The developed protocol allows for the unprecedented use of methylamine or hydrazine as coupling partners, forming *N*-methyl and *N*-amino indoles, respectively. Notably, the reaction is catalyzed by $[Pd(cinnamyl)Cl]_2$/JosiPhos mixtures, which were found to achieve superior catalytic activity in comparison to the Mor-DalPhos-based catalyst system in the presence of alkyne-containing substrates. In this vein, Chapter 3 also describes efforts to gain a mechanistic understanding of problems associated with this indole synthesis when catalyzed by the Pd/Mor-DalPhos system. The investigations provide insight into the catalyst inhibition that occurs by alkyne substrates for Pd/Mor-DalPhos catalytic species and also help to explain the increased activity of the JosiPhos system.



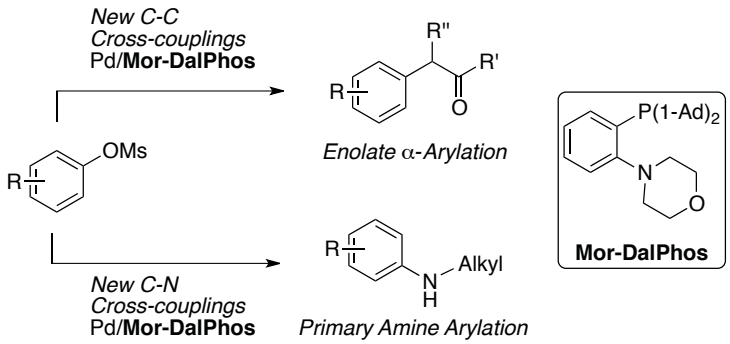
Scheme 1.5 Palladium/JosiPhos-catalyzed synthesis of indoles via ammonia cross-coupling-alkyne cyclization chemistry.

Chapter 4 concerns carbonylative cross-coupling methods, which are becoming increasingly popular protocols among synthetic chemists to access carboxylic acid functionalities. The first part of the chapter examines variants of the DalPhos ligand family in a palladium-catalyzed carbonylative amination reaction using carbon monoxide and ammonia as reagents to access aryl amides. As a result of this survey, the Pyr-DalPhos ligand was identified as being effective for the selective aminocarbonylation of (hetero)aryl bromides with ammonia as well as primary and secondary alkyl amines. As part of this study, a (Mor-DalPhos)Pd(Cl)-benzoyl complex was prepared and crystallographically characterized, thereby showing the viability of the carbonyl insertion step. The second part of the chapter features a description of efforts to employ DalPhos-based catalysts in additional carbonylative versions of cross-coupling reactions, such as Heck coupling and the challenging α-arylation of acetone.



Scheme 1.6 Aminocarbonylation of (hetero)aryl bromides with ammonia and amines using a Pd/Pyr-DalPhos catalyst system.

The content of Chapter 5 recounts the development of challenging palladium-catalyzed cross-coupling reactions of aryl methanesulfonates (mesylates), specifically the first examples of monoarylation of ketones and primary alkyl amines. Use of the $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos catalyst system enabled a range of functionalized aryl mesylates to be utilized in combination with cyclic and acyclic dialkyl ketones, as well as with primary and secondary amine coupling partners, including chemoselective examples. Both acetone and methylamine, which can represent challenging reactions partners in their own right, proved compatible under the optimized conditions.



Scheme 1.7 Addressing challenges in palladium-catalyzed cross-couplings of aryl mesylates.

The conclusion of the thesis is provided in Chapter 6, including a general summary of the research content as well as proposed future endeavors that seek to address some outstanding challenges in the thesis research and to further extend or apply the methodologies presented herein.

CHAPTER 2 APPLICATION AND EXAMINATION OF THE PALLADIUM/MOR-DALPHOS CATALYST SYSTEM IN THE SELECTIVE MONOARYLATION OF AMMONIA AT ROOM TEMPERATURE

2.1 INTRODUCTION

Given the broad application of anilines in industrial chemistry,[12] the production of aniline from ammonia using a metal-catalyzed C-N bond-forming reaction is highly sought-after. Ammonia, being the simplest N-H containing species, also poses significant challenges in regard to the formation of C-N bonds, as a result of its size, basicity and bond strength. In attempting to cross-couple ammonia, displacement of the catalyst ancillary ligand leading to catalytically inactive ammine complexes is often observed; intermediate aryl-palladium-amido complexes also tend to form unwanted stable bridging structures rather than undergoing reductive elimination. A further challenge arises from the fact that the product arylamine is often a more suitable substrate in comparison to ammonia, thereby resulting in di- and triarylation.[39] In this context, the ancillary ligand must be chosen carefully in order to circumvent all of the aforementioned undesirable reactivity pathways. Significant progress has been made in the development of copper catalysts for ammonia monoarylation,[39a-c] with the more successful systems featuring carbonyl-based ancillary ligands such as L-proline,[40] 2,4-pentadione,[41] or a 2-pyridinyl-β-ketone.[42] Nonetheless, copper-based catalysts often exhibit a number of limitations, including the need for high catalyst loadings and temperatures, and poor activity with (hetero)aryl chloride and pseudohalide coupling partners.[43] In this regard, palladium-based catalyst systems currently offer optimal performance for the monoarylation of ammonia.

As mentioned earlier in Section 1.3.2, the research groups of Hartwig,[31b, 36, 44] Buchwald[37, 45] and also Beller[46] have each contributed to the development of useful BHA protocols for selective ammonia monoarylation (Figure 2.1). Hartwig and co-workers demonstrated that the bulky bisphosphine ligand JosiPhos (CyPF-*t*Bu)[47] in conjunction with $Pd[P(o\text{-tol})_3]_2$ could monoarylate ammonia with a variety of aryl halides and sulfonates (≥50 °C). These JosiPhos-based catalysts do suffer from substrate scope challenges with respect to the monoarylation of electronically deactivated and sterically

unhindered aryl chloride substrates, the use of relatively high reaction temperatures, and in certain examples, the need for high pressures of ammonia.

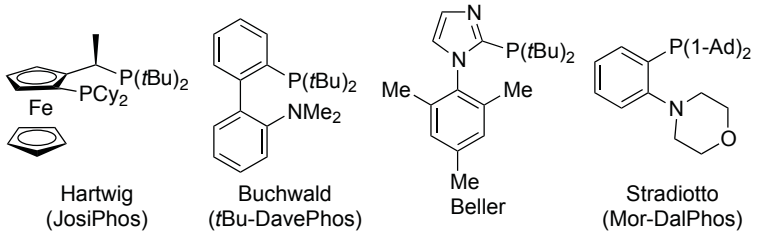


Figure 2.1 Important ligands for selective ammonia monoarylation with (hetero)aryl (pseudo)halides.

The biaryl monophosphine ligand *t*Bu-DavePhos (Figure 2.1) has been employed in the arylation of ammonia (80-120 ^{o}C).[37, 45b] Although this initial report featured only four examples of monoarylated products,[37] it was later demonstrated that the same ligand could be employed in Pd-catalyzed ammonia cross-couplings for the synthesis of benzodiazepines and related biologically active heterocycles.[45b] Beller and coworkers have also shown that 2-phosphino-*N*-arylimidazole-based monophosphines support active palladium catalysts for the monoarylation of ammonia, albeit at high temperatures (120-140 ^{o}C) and elevated inert gas pressures (10 bar N_2).

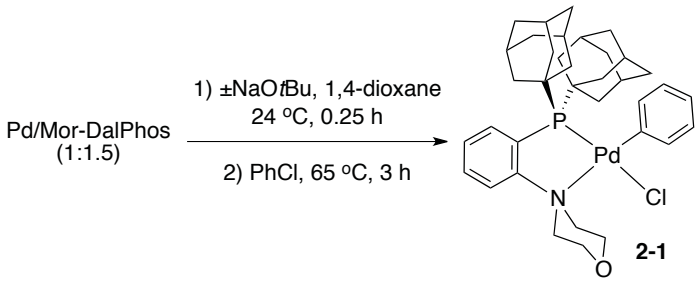
The Stradiotto group set out to develop a new P,N-phenylene ligand that would address the substrate scope limitations observed previously for ammonia monoarylation employing their "first-generation" Pd/Me-DalPhos catalyst system (Section 1.4).[48] A series of ligand variants containing the bulky di(1-admantyl)phosphino ($P(1\text{-}Ad)_2$) fragment were synthesized and subsequently tested in the BHA of ammonia using a challenging deactivated coupling partner, 4-chlorotoluene.[49] This ligand screen identified Mor-DalPhos (Figure 2.1) to be highly effective, achieving good conversion (84%) and excellent mono- to diarylation selectivity (14:1) for the test substrate. In using $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos mixtures, electron-rich, electron-poor, and heterocyclic products of ammonia monoarylation were prepared (50-110 °C) in high isolated yields from mainly aryl chlorides and some aryl tosylates. Whereas Pd/Mor-DalPhos precatalyst mixtures did not allow for the room temperature BHA of aryl chlorides and ammonia, unprecedented room-temperature transformations of a small number of aryl chlorides were achieved by use of the oxidative addition complex [(κ^2-*P,N*-Mor-

DalPhos)Pd(Ph)Cl] (**2-1**) as the precatalyst (see Figure 2.2). Encouraged by these initial results, a more thorough investigation of the Pd/Mor-DalPhos catalyst system was carried out in the context of ammonia monoarylation under mild conditions in an effort to better understand the underlying factors of this unique catalytic reactivity. The results of this experimentation are described below.

2.2 Results and Discussion

2.2.1 Screening of Palladium Sources and Synthesis of an Oxidative Addition Complex

In the initial development of ammonia monoarylation employing Mor-DalPhos at elevated temperatures (50-110 °C), $[Pd(cinnamyl)Cl]_2$ was found to be a suitable palladium source. In order to better understand the factors that might enable the BHA of ammonia at room temperature with a broad substrate scope, a reactivity survey was conducted in which several Pd^0 and Pd^{II} reagents were treated with Mor-DalPhos (and NaO*t*Bu in the case of chloride or acetate precursors[50] to achieve reduction of Pd^{II} species to Pd^0) at room temperature for 0.25 h, followed by the addition of chlorobenzene and heating at 65 °C for 3 h (Figure 2.2). The aim here was to indirectly measure the amount of the putative Mor-DalPhos/Pd^0 species that formed after 0.25 h by detecting the appearance of the presumed oxidative addition catalytic intermediate [(κ^2-*P,N*-Mor-DalPhos)Pd(Ph)Cl] (**2-1**). Control experiments confirm that **2-2** (*vide infra)* is rapidly (<5 min) and quantitatively transformed into an ill-defined mixture containing free Mor-DalPhos ligand as well as new phosphorus-containing species (80.9 and 54.0 ppm). As such, the assumption that heating serves only to promote the formation of the targeted oxidative addition complex (**2-1**) when using $[Pd(cinnamyl)Cl]_2$ is justified.

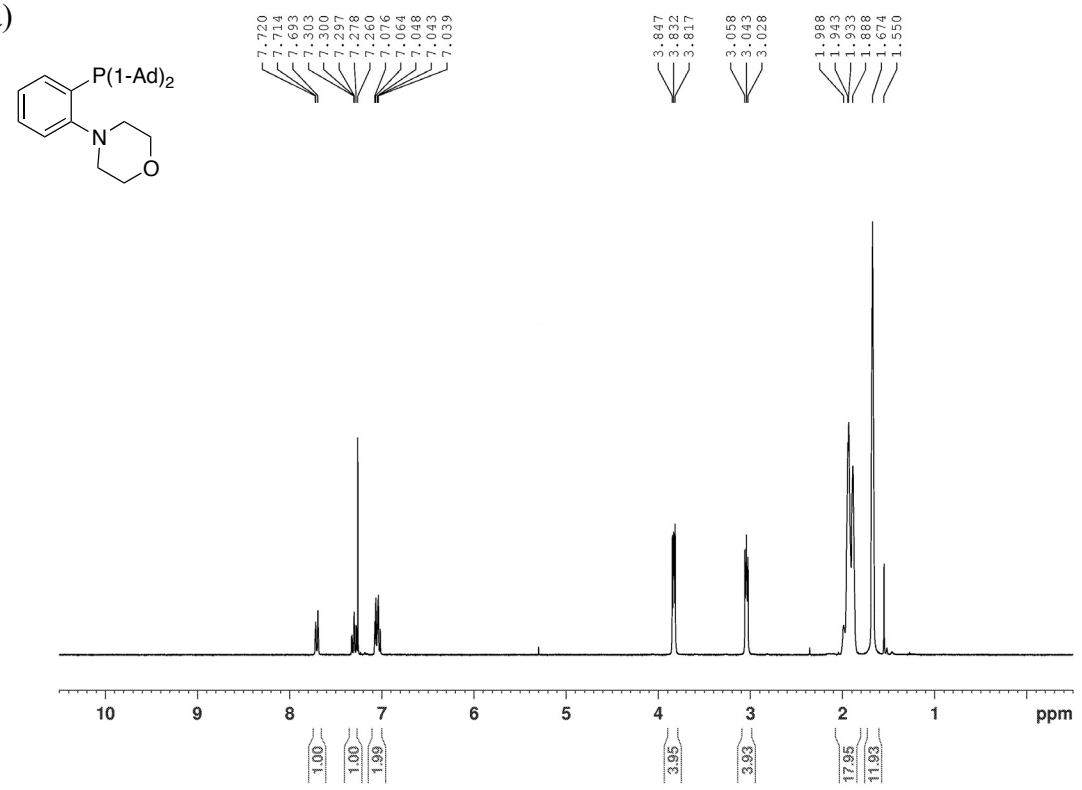


$[Pd(cinnamyl)Cl]_2$	CpPd(cinnamyl)	$Pd(OAc)_2$	$Pd[P(o\text{-tol})_3]_2$	Pd_2dba_3
>95%	22%	14%	>95%	>95%

Figure 2.2 Survey of palladium sources for the *in situ* generation of a putative (Mor-DalPhos)/Pd^0 species.
General conditions: Pd source (5 mol% Pd), Mor-DalPhos (7.5 mol%), NaO*t*Bu (2 equiv. for chloride or acetate precursors), 1,4-dioxane (0.5 M), PhCl (1.0 equiv.), followed by the addition of CH_2Cl_2. Yields determined on the basis of ^{31}P NMR analysis with $PMes_3$ as an internal standard.

An authentic sample of **2-1** was prepared in 93% isolated yield by heating [CpPd(allyl)] and Mor-DalPhos in a 1:1 mixture of chlorobenzene and THF at 65 °C for 18 h. Solution NMR data support the identity of **2-1** as the expected square-planar complex in which Mor-DalPhos is bound to Pd in a κ^2-P,N bidentate fashion. This is suggested by the reduction in apparent symmetry of the ligand, whereby four diastereotopic morpholino resonances are observed in the ^1H NMR spectrum of **2-1** between 5.29 and 3.30 ppm (Figure 2.3b), while only two resonances (3.83 and 3.04 ppm) are observed for the free ligand (Figure 2.3a).

a)



b)

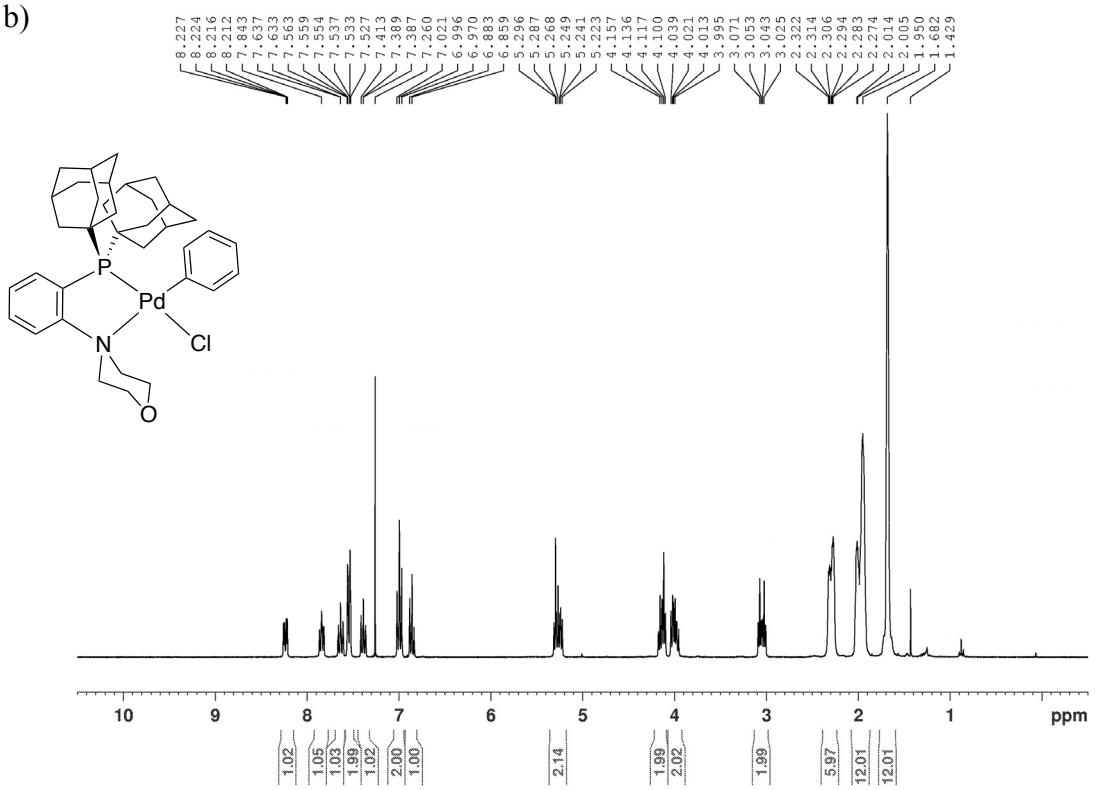
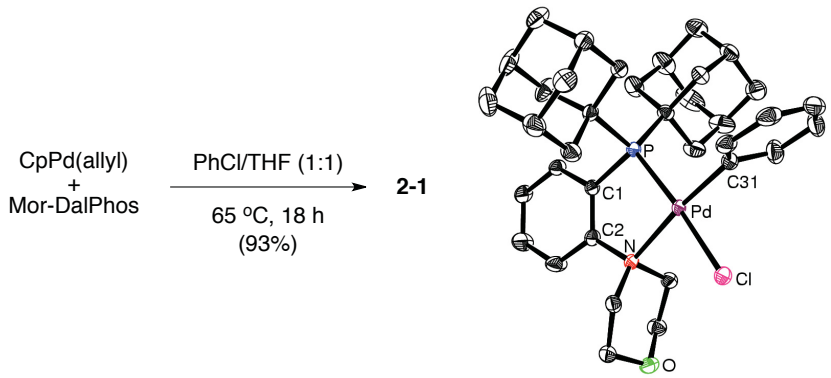


Figure 2.3 ^{1}H NMR spectra (300 MHz, $CDCl_3$) of Mor-DalPhos (a) and the oxidative addition complex **2-1** (b).

The structure of **2-1** was also confirmed by the use of single-crystal X-ray diffraction techniques (Scheme 2.1), which reveals the expected *trans*-disposition of chloride and phosphine ligands within the complex as a result of the greater *trans*-directing ability of phosphorus relative to nitrogen. Selected metrical parameters for the structure of **2-1** and each of the other crystallographically characterized compounds reported herein are collected in Table 2.1 (see Section 2.2.2).

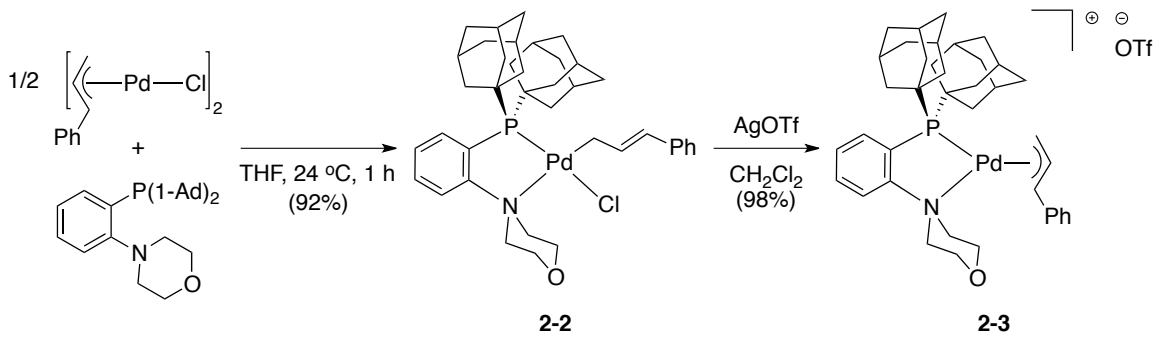


Scheme 2.1 Synthesis and ORTEP diagram of **2-1** shown with thermal ellipsoids at 50% displacement. All hydrogen atoms have been omitted for clarity.

Less than 25% conversion to **2-1** was observed when using either [CpPd(cinnamyl)][51] or $Pd(OAc)_2$ under room temperature activation conditions employed, whereas the use of Pd_2dba_3, $Pd[P(o\text{-tol})_3]_2$, or $[Pd(cinnamyl)Cl]_2$, afforded high yields of the target complex **2-1**. Altering the duration of the first room-temperature activation step of the reaction (5-30 min) resulted in negligible variation of the amount of **2-1** that formed for all palladium sources examined. Given that dba and $P(o\text{-tol})_3$ have the significant potential to exhibit an inhibiting effect under catalytic conditions as result of their strong ligand donor abilities, it was concluded that $[Pd(cinnamyl)Cl]_2$ was the palladium source of choice for this application.[52]

2.2.2 Synthesis of Pd/Mor-DalPhos Precatalyst Complexes

Encouraged by the diversity of reports highlighting the reactivity benefits that can be derived from the use of preformed palladium-ligand complexes in BHA chemistry,[13b, 31b, 32a, 53] precatalysts featuring Mor-DalPhos were prepared. Efforts were directed towards the synthesis of adducts derived from $[Pd(cinnamyl)Cl]_2$, as well as Pd/Mor-DalPhos-containing species that are of relevance to room temperature BHA chemistry involving ammonia. The first part of this study involved determining the identity of the species formed in the precatalyst mixture. Combining Mor-DalPhos (2 equiv.) with $[Pd(cinnamyl)Cl]_2$ in THF afforded the [(κ^2-*P,N*-Mor-DalPhos)Pd(η^1-cinnamyl)Cl] complex (**2-2**) as an analytically pure yellow solid isolated in 92% yield (Scheme 2.2).



2-2 **2-3**

Scheme 2.2 Synthesis of Pd/Mor-DalPhos complexes featuring η^1- or η^3-cinnamyl coordination.

The features of the cinnamyl ^{1}H NMR resonances of **2-2** are consistent with the proposed η^1 formulation, with the two alkenyl protons appearing at 6.76 and 6.37 ppm, and the resonance for the Pd-CH_2 group appearing at 3.61 ppm (Figure 2.4); literature data for other Pd(η^1-cinnamyl) complexes also demonstrate three allyl signals (two alkenyl and one CH_2) in the ^{1}H NMR.[54] Similar to the ^{1}H NMR spectrum of **2-1**, it is also evident in this case that the ligand is bound in an unsymmetrical κ^2-*P,N* fashion, as demonstrated by the diastereotopic morpholino resonances. The solution η^1-cinnamyl structure proposed for **2-2** on the basis of NMR data was further verified through a single-crystal analysis of the yellow crystalline material that was grown from the bulk isolated solid (Figure 2.5). Indeed, the presence of an η^1-cinnamyl ligand in the solid-state structure of **2-2** is immediately evident, with the C(1)-C(2) (1.466(5) Å), C(2)-C(3) (1.336(5) Å), and C(3)-C(4) (1.465(5) Å) distances in keeping with single, double and single bonds, respectively.

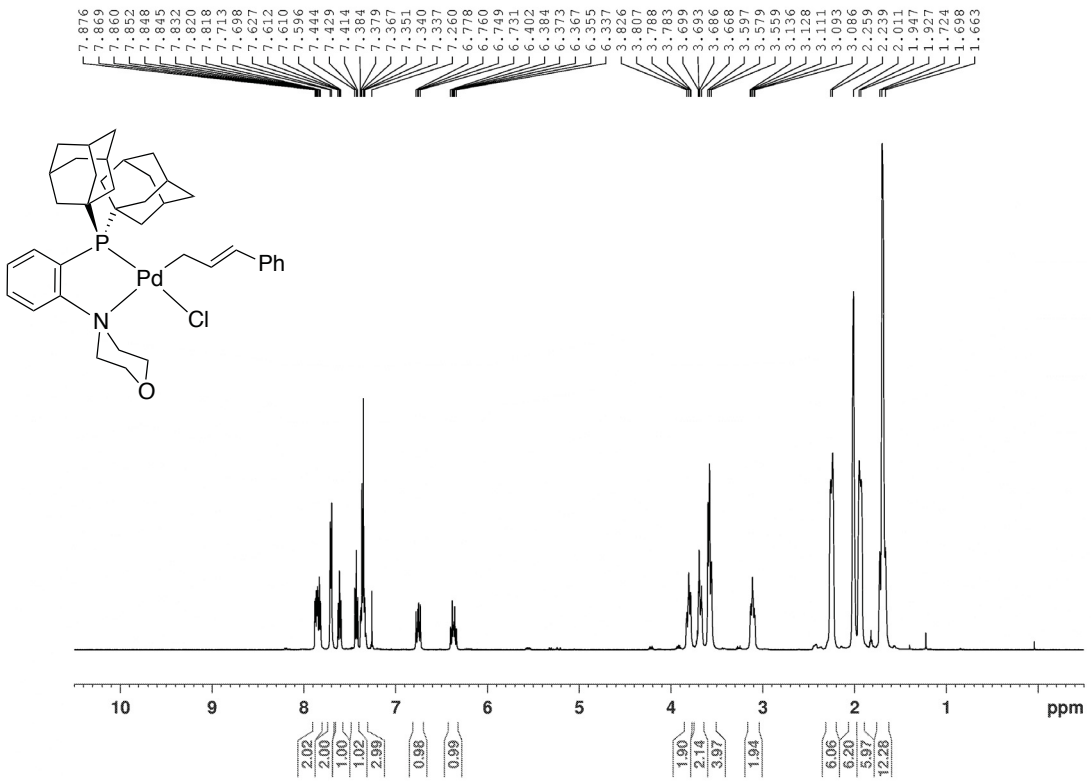


Figure 2.4 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of [(κ^2-*P,N*-Mor-DalPhos)Pd(η^1-cinnamyl)Cl] (**2-2**).

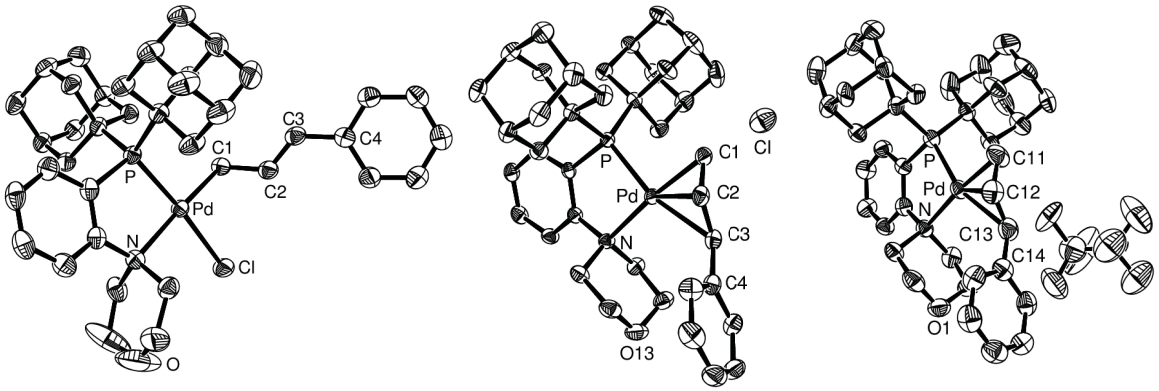


Figure 2.5 ORTEP diagrams of **2-2** (left), **2-2'**·CH_2Cl_2·H_2O (middle) and **2-3**·$CHCl_3$ (right) shown with 50% displacement ellipsoids. All hydrogen atoms and solvate molecules have been omitted for clarity.

Interestingly, a small quantity of red crystalline material formed from the same mother liquor from which the yellow single crystals of **2-2** had grown. Single-crystal X-

ray analysis enabled the identification of this red material as **2-2'**, the cationic η^3-cinnamyl isomer of **2-2** featuring an outer-sphere chloride counteranion (Figure 2.5). The analogous triflate complex [(κ^2-*P,N*-Mor-DalPhos)Pd(η^3-cinnamyl)]OTf (**2-3**, Scheme 2.2) was prepared by treatment of **2-2** with AgOTf, which upon isolation afforded **2-3** as an analytically pure solid in 98% isolated yield. The observation of four distinct allylic-type resonances in the ^{1}H NMR spectrum of **2-3** (6.32, 6.18, 3.98 and 3.11 ppm, Figure 2.6) is in keeping with an η^3-cinnamyl coordination mode in solution, which in turn was confirmed in the solid state on the basis of single-crystal X-ray diffraction data. Each of **2-2'** and **2-3** exhibit an unsymmetrically bound η^3-cinnamyl ligand in the solid state, with the Pd-CH_2 distance being significantly shorter than the other two Pd-C distances in each complex (Table 2.1). The facile and clean formation of **2-2**, and the observation that both **2-2** and **2-2'** can be produced from the same crystallization solution, suggest that these isomeric complexes represent the catalytic species that are formed initially when combining Mor-DalPhos and [Pd(cinnamyl)Cl]$_2$ during catalyst pre-activation. Although complexes **2-2** and **2-3** proved incapable of catalyzing room temperature BHA involving ammonia and chlorobenzene (see Table 2.2), these precatalysts did effectively mediate the transformation at elevated temperatures (3 mol% Pd, 110 °C 1 h), achieving full conversion with high monoarylation selectivity.

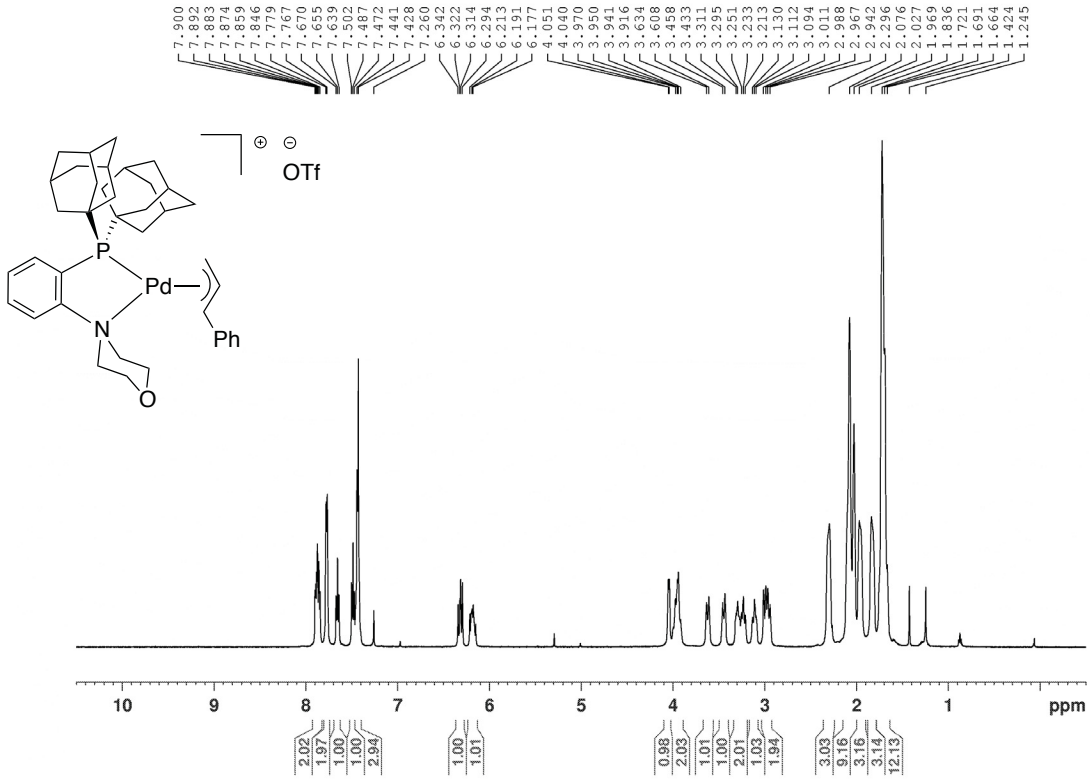


Figure 2.6 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of [(κ^2-*P,N*-Mor-DalPhos)Pd(η^3-cinnamyl)]OTf (**2-3**).

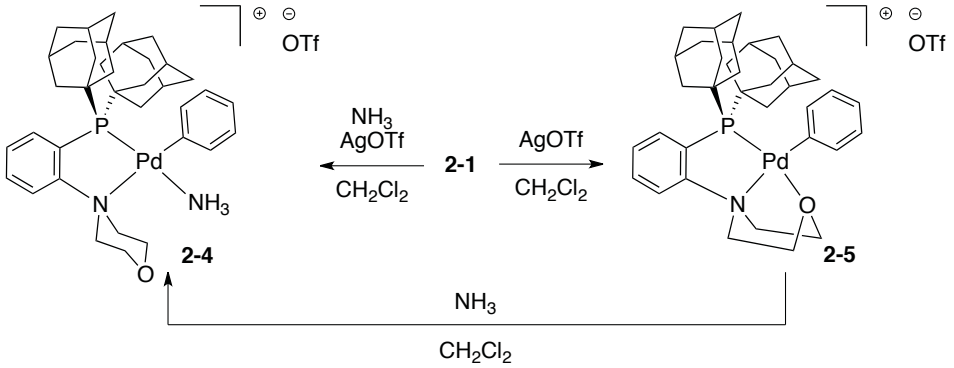
Table 2.1 Selected interatomic distances [Å] for crystallographically characterized complexes in this chapter.

	Pd-P	**Pd-N**	**Pd-Cl**	**Pd-C$_{aryl}$**	**P-C$_{aryl}$**	**N-C$_{aryl}$**
2-1	2.2563(7)	2.253(2)	2.3873(7)	2.001(3)	1.831(3)	1.468(3)
2-2[a]	2.2357(9)	2.261(3)	2.3952(9)	-	1.840(4)	1.464(4)
2-2'[b]	2.2666(4)	2.2625(14)	-	-	1.8375(17)	1.479(2)
2-3[c]	2.2774(16)	2.212(5)	-	-	1.829(6)	1.476(7)
2-4[d]	2.2733(4)	2.2138(16)	-	2.0009(17)	1.8335(16)	1.474(2)
2-5[e]	2.2207(8)	2.116(2)	-	2.001(3)	1.859(3)	1.463(4)
2-5[f]	2.2188(8)	2.110(2)	-	2.008(3)	1.848(3)	1.460(4)
2-6	2.2572(5)	2.2260(16)	2.3818(5)	2.000(2)	1.840(2)	1.468(3)
2-8	2.2625(7)	2.230(2)	2.3832(7)	2.005(3)	1.836(3)	1.478(3)
2-9	2.2591(7)	2.214(2)	2.3735(7)	1.990(3)	1.838(3)	1.467(4)

[a] Pd-C(1) 2.074(3); C(1)-C(2) 1.466(5); C(2)-C(3) 1.336(5); C(3)-C(4) 1.465(5). [b] Pd-C(1) 2.0951(17); Pd-C(2) 2.2432(17); Pd-C(3) 2.5100(18); C(1)-C(2) 1.418(3); C(2)-C(3) 1.374(3); C(3)-C(4) 1.470(3). [c] Pd-C(11) 2.053(6); Pd-C(12) 2.249(6); Pd-C(13) 2.580(7); C(11)-C(12) 1.420(9); C(12)-C(13) 1.377(10); C(13)-C(14) 1.458(9). [d] Pd-N(1) (minor disorder component) 2.215(6); N-Caryl (minor disorder component) 1.470(7); Pd-N(2) 2.1308(15). [e] Pd-O 2.227(2). [f] Within the second crystallographically independent molecule of **2-5**; Pd-O 2.228(2).

2.2.3 Reactivity of the Oxidative Addition Complex

Ancillary ligand displacement by ammonia represents a challenge that must be addressed when using ammonia as a substrate. In this regard, an examination was undertaken to study the behavior of Mor-DalPhos within a proposed catalytic intermediate (**2-1**) upon exposure to excess ammonia. It was expected that ammonia might displace the N-donor of the ligand since ammonia is smaller and more Lewis basic than the morpholino fragment in this case. Treatment of **2-1** with 3-10 equivalents of ammonia in 1,4-dioxane afforded no detectable reactivity, as observed by ^{31}P NMR techniques, suggesting that the Mor-DalPhos ligand is neither hemilabile nor completely displaced under these conditions. In probing the coordination chemistry of **2-1** further, the cationic ammine adduct **2-4** was successfully prepared upon addition of AgOTf to **2-1** in the presence of excess ammonia (Scheme 2.3); complex **2-4**·CH_2Cl_2 was isolated as an analytically pure solid in 90% yield. The ammine resonance in **2-4** is clearly visible among the adamantyl signals in the ^{1}H NMR spectrum of **2-4** and the ammine signal does not disappear upon prolonged exposure of the sample to vacuum. Solid-state structural data obtained for **2-4** are consistent with the corresponding solution-NMR characterization.



Scheme 2.3 Reactivity of the oxidative addition product **2-1** under halide abstraction conditions.

Preliminary efforts to generate a [(Mor-DalPhos)Pd(Ph)(NH_2)] intermediate were carried out in which **2-4** was treated with $NaN(TMS)_2$ at room temperature. ^{31}P NMR data obtained from the resulting mixtures indicated the formation of multiple phosphorus-containing species, including free Mor-DalPhos. Performing the same reaction in the presence of chlorobenzene resulted in the regeneration of **2-1** (as observed by use of ^{31}P

NMR spectroscopy) in the absence of detectable impurities. Interestingly, carrying out halide abstraction from **2-1** using AgOTf in the absence of ammonia allowed for the clean formation of a single new product **2-5**, as indicated in the ^{31}P NMR spectrum. Solution ^{1}H NMR data revealed the presence of both Mor-DalPhos and phenyl groups in this new complex, and X-ray diffraction analysis demonstrated tridentate connectivity within **2-5**, identified as [(κ^3-*P,N,O*-Mor-DalPhos)Pd(Ph)]OTf (Scheme 2.3). Complex **2-5** exhibits a distorted square-planar geometry in which the oxygen donor has taken the former coordination site of the abstracted chloride (Figure 2.7). The structure of **2-5** confirms the ability of the Mor-DalPhos ligand to respond to a decrease in the coordination number at Pd through the provision of a third ligating group. Perhaps when employing reagents with more labile leaving groups (e.g. aryl triflates) in catalysis, the tridenate κ^3-*P,N,O* ligation of the Mor-DalPhos ligand might represent an important stabilizing interaction for catalytic Pd species. The lability of the oxygen donor in **2-5** was confirmed by the clean formation of **2-4** when **2-5** was treated with ammonia (3 equiv.) followed by stirring at room temperature for 3 h.

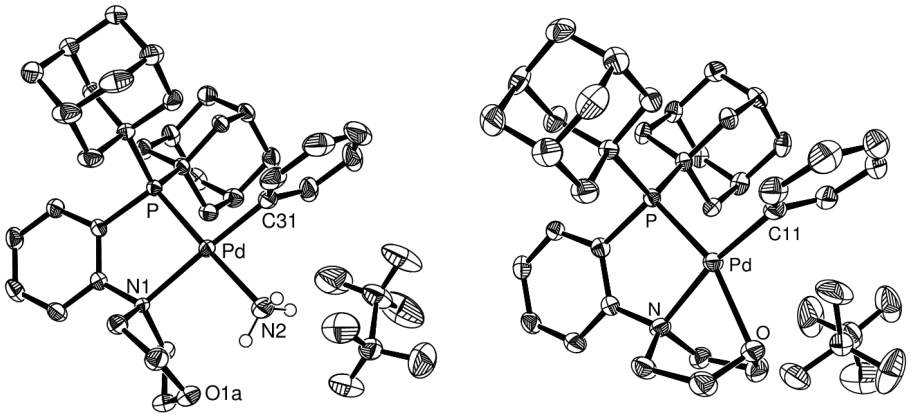


Figure 2.7 ORTEP diagrams of **2-4**·CH_2Cl_2 (left) and **2-5** (right) shown with 50% displacement ellipsoids. All hydrogen atoms and solvate molecules have been omitted for clarity.

2.2.4 Catalytic Studies and Synthesis of Oxidative Addition Variants

In considering the possibility of oxidative addition complexes of the type [(κ^2-*P,N*-Mor-DalPhos)Pd(Ar)Cl] as being intermediates in the BHA of (hetero)aryl chlorides (Ar = aryl or heteroaryl) with ammonia in the presence of Pd/Mor-DalPhos catalysts, the utility of these and related complexes as precatalysts for otherwise challenging room temperature ammonia arylation reactions was evaluated in more detail. Remarkably, the

use of 5 mol% of **2-1** at room temperature allowed a >90% conversion of chlorobenzene and 76% GC yield of aniline after 12 h (Table 2.2, entry 1); similar results were achieved when using the ammine adduct **2-4** (Table 2.2, entry 2). In employing either [Pd(cinnamylCl]$_2$/Mor-DalPhos mixtures (Table 2.2, entry 3) or the related preformed complexes **2-2** or **2-3** (Table 2.2, entries 4 and 5), both a low conversion of the chlorobenzene and poor yields (<25%) of the target aniline were obtained at room temperature. [Pd{P(*o*-tol)$_3$}$_2$]/JosiPhos, which has been utilized successfully in the arylation of ammonia at elevated temperatures,[36] and the oxidative addition complex [(JosiPhos)Pd(Ph)Cl] (by analogy with **2-1**)[44] both performed poorly under the room temperature conditions applied, affording less than 20% GC yield of aniline (Table 2.2, entries 6 and 7).

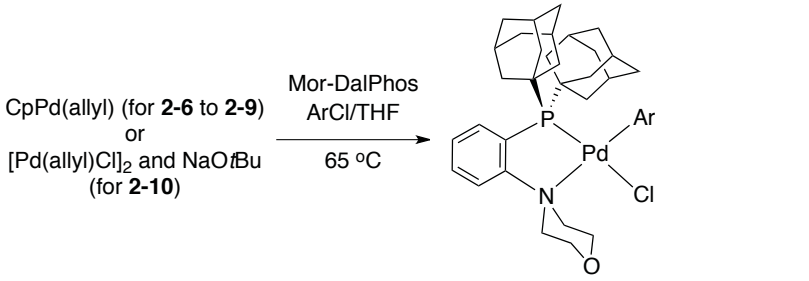
Table 2.2 Catalyst screening for room temperature ammonia arylation with chlorobenzene.[a]

Entry	Pd cat (5 mol%)	GC conv. [%][b]	GC yield [%][b]
1	[(M-DP)Pd(Ph)Cl] (**2-1**)	91	76
2	[(M-DP)Pd(Ph)NH_3]OTf (**2-4**)	84	75
3	[Pd(cinnamylCl]$_2$/M-DP	30	23
4	[(M-DP)Pd(cinnamyl)Cl] (**2-2**)	22	14
5	[(M-DP)Pd(cinnamyl)]OTf (**2-3**)	30	22
6	[Pd{P(*o*-tol)$_3$}$_2$]/JosiPhos	23	15
7	[(JosiPhos)Pd(Ph)Cl]	14	13
	[(M-DP)Pd(Ar)Cl]		
8	Ar = 4-PhOMe (**2-6**)	64	53
9	Ar = 4-PhMe (**2-7**)	84	68
10	Ar = 2-PhMe (**2-8**)	90	76
11	Ar = 4-PhCF_3 (**2-9**)	68	58
12	Ar = 3-pyridyl (**2-10**)	82	73

[a] General conditions: Pd source (5 mol%); plus 7.5 mol% ligand for entries 3 and 6), NaO*t*Bu (2 equiv.), PhCl (1.0 equiv), 1,4-dioxane (0.1 M); M-DP = Mor-DalPhos. [b] Conversions and yields were determined on the basis of calibrated GC data with dodecane as the internal standard.

Having identified **2-1** as being a suitable precatalyst for the BHA of chlorobenzene with ammonia at room temperature, evaluation of the possible impact of varying the aryl group within precatalyst **2-1** on the catalytic performance was carried out. A set of [(κ^2-*P,N*-Mor-DalPhos)Pd(Ar)Cl] derivatives with 4-OMe (**2-6**), 4-Me (**2-7**), 2-Me (**2-8**), and 4-CF_3 (**2-9**) substitution was successfully prepared and isolated, starting from [CpPd(allyl)] in a manner similar to that employed for the synthesis of the parent phenyl complex **2-1** (Scheme 2.4). Although attempts to synthesize the 3-pyridyl variant

2-10 by this protocol failed, the combination of $[Pd(allyl)Cl]_2$, Mor-DalPhos, and NaO*t*Bu in a solution of THF/3-chloropyridine (2:1 by volume) generated the desired complex over the course of 3 h at 65 °C, thereby enabling the isolation of **2-10** in 90% yield. The solution NMR characterization of **2-6** to **2-10** was corroborated in the case of **2-6**, **2-8** and **2-9** by single-crystal X-ray diffraction data. The solid-state structures of these complexes (Figure 2.8) feature the expected square-planar geometry and relative disposition of the ligands around palladium, as was observed for **2-1** (Scheme 2.1).



Ar = 4-anisolyl (**2-6**, 79%)
Ar = 4-tolyl (**2-7**, 66%)
Ar = 2-tolyl (**2-8**, 75%)
Ar = 4-trifluoromethylphenyl (**2-9,** 80%)
Ar = 3-pyridyl (**2-10**, 90%)

Scheme 2.4 Synthesis of oxidative addition complexes with variation of the aryl group.

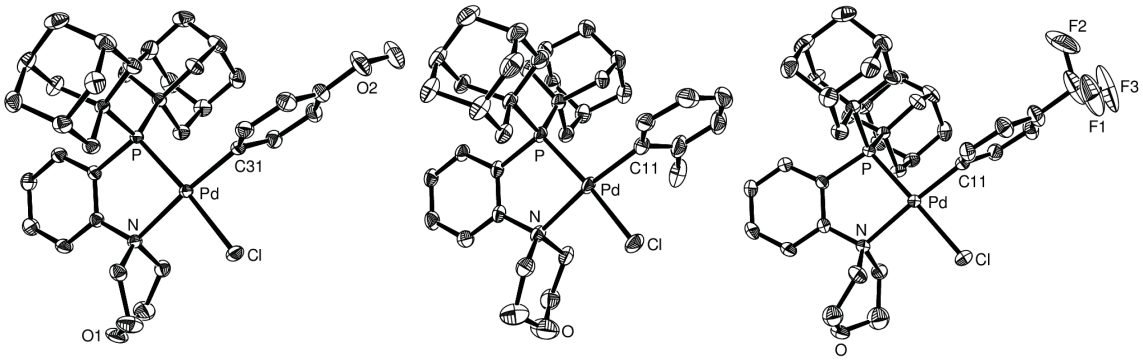


Figure 2.8 ORTEP diagrams of oxidative addition complexes **2-6**·CH_2Cl_2 (left), **2-8**·CH_2Cl_2 (middle), **2-9**·CH_2Cl_2 (right) shown with 50% displacement ellipsoids. All hydrogen atoms and solvate molecules have been omitted for clarity.

In testing each of the complexes (5 mol% Pd) for the room temperature BHA of chlorobenzene with ammonia to give aniline, all proved to be effective as precatalysts (Table 2.2, entries 8-12). In comparing the performance of **2-1** to that of **2-6** to **2-10** in terms of the yield of aniline, there is an inherent bias towards **2-1** given that this

precatalyst contains the parent phenyl ligand, which in turn can continue on to form the target unsubstituted aniline product. In contrast, precatalysts **2-6** to **2-10** feature (hetero)aryl ligands that generate the corresponding substituted anilines (for **2-6** to **2-9**) and 3-aminopyridine (for **2-10**) upon initial catalytic turnover, thereby leading to an artificially lower product yield (up to 5%) for these later precatalysts. This notwithstanding, it is apparent that the performance of precatalysts **2-6** and **2-9**, which feature electron-donating (4-anisolyl) and -withdrawing (4-trifluoromethylphenyl) Pd-aryl ligands respectively, is inferior to that of the parent complex **2-1**, the tolyl variants **2-7** and **2-8**, and the 3-pyridyl precatalyst **2-10**. Whereas the performance of precatalyst **2-8** could be considered marginally better than that of **2-1** in terms of the conversion to aniline in the room temperature test reaction (Table 2.2, entries 1 and 10), **2-1** was deemed to be the preferred precatalyst for this reaction on the basis of the higher-yielding synthesis of **2-1** (93%) versus **2-8** (75%).

The variation of some additional experimental parameters was examined in an effort to optimize reactivity. The use of 2 mol% **2-1** as a precatalyst afforded only 27% conversion of chlorobenzene (cf. 91% conversion, 76% yield with 5 mol% **2-1**; Table 2.2, entry 1), and when substituting NaO*t*Bu for alternative bases (K_3PO_4, Cs_2CO_3, or LiHMDS), the yield did not improve. Also, the use of 7.5 mol% **2-2** did not exceed the capabilities of **2-1** as the 5 mol% loading level. Thus, the use of 5 mol% of **2-1** and NaO*t*Bu as the base was employed for examining the scope of reactivity.

2.2.5 Substrate Scope of Room Temperature Ammonia Arylation

A variety of aryl and heteroaryl halides and tosylates were accommodated under the room temperature ammonia-arylation conditions (Figure 2.9). To compare the substrate scope in its entirety, the substrates presented herein include the small number of aryl chlorides established prior to the structural and reactivity study featured in this chapter (**2-1a** to **2-1-j**), and also new examples demonstrating an expanded scope **(2-11** to **2-28**). Although good yields were obtained for the parent aniline (**2-11**), the *ortho*-tolyl variant (**2-13**), and the 4-CF_3-variant (**2-14**), comparatively poor yields were obtained under analogous conditions with 4-chloroanisole, 4-chlorotoluene and 3-chloropyridine (leading to **2-12**, **2-1c**, and **2-15**, respectively); either poor conversion or selectivity for

the target aniline derivatives was the source of difficulty. The ability of this catalyst system to accommodate aryl bromides and iodides was demonstrated in reactions leading to **2-14**. In general, *ortho* substitution proved to be particularly favourable among the chloride substrates that were examined (**2-13**, **2-1a**, **2-1b**, **2-19**, **2-21**, **2-22**, and **2-27**), affording good to high isolated yields. Attempts to prepare **2-22** from 1-bromonaphthalene achieved only 50% conversion, and thus resulted in a poor isolated yield. Chemoselective room temperature ammonia-arylation reactions were successful for the formation of **2-1j** and **2-16**, resulting in the desired ammonia-coupled products in high yields despite the presence of potentially competitive primary and secondary aniline functionalities. Additional functional-group tolerance was established in the formation of anilines featuring fluoro (**2-17** to **2-21**), benzyl ether (**2-1d**), thioether (**2-1i**), nitrile (**2-1e**), and ketone (**2-1f**) substituents. Nitrogen-containing heterocycles that were also tolerated in this chemistry include chloroquinolines (**2-1g**, **2-27**) and a pyrrolylphenyl substrate (**2-26**). The demonstrated substrate scope was broadened further by use of a selection of aryl tosylates, which provided the corresponding anilines in yields ranging from 45-86% (**2-11**, **2-23** to **2-28**). Although these reactions were routinely carried out under inter-atmosphere conditions for convenience, the prototypical reaction of chlorobenzene and ammonia could be executed without the use of a glovebox. The solid components NaO*t*Bu and **2-1** were weighed out in air and placed under nitrogen, followed by addition of the reactants and 1,4-dioxane. Upon stirring the mixture at room temperature for 16 h, **2-11** was generated in 81% yield on the basis of calibrated GC analysis.

Despite the broad efficacy of **2-1** for catalyzing room temperature, ammonia-arylation reactions, some limitations in the substrate scope were identified. Notably, our efforts to extend the scope to include alternative aryl chloride or tosylate substrates, including those featuring base-sensitive addenda (hydroxyl or ester substituents) or other heteroaryl chlorides (thiophene or benzodioxole), were unsuccessful. In all cases, low yields of the product aniline derivative were observed due to either lack of consumption of, or degradation of the starting material.

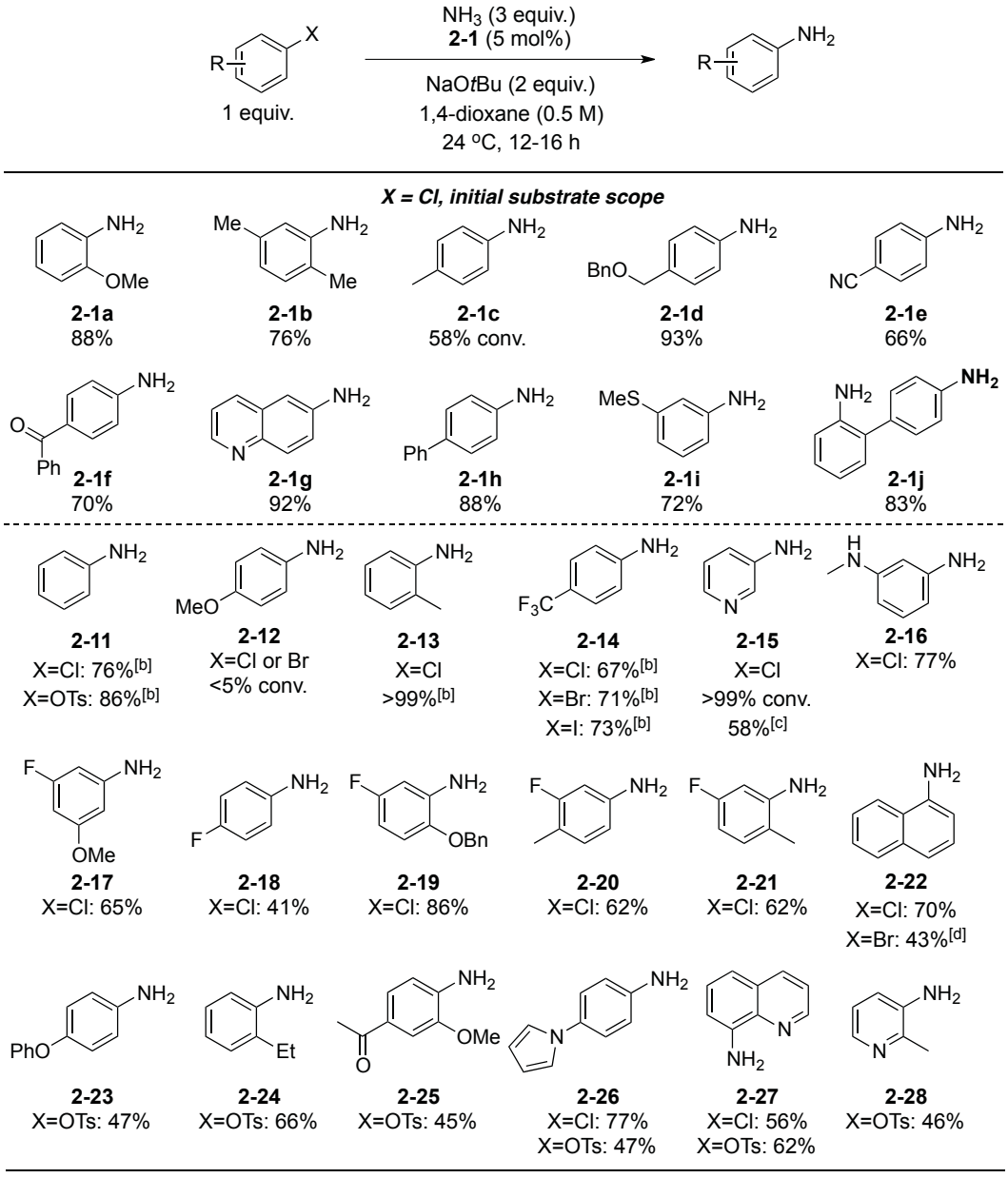


Figure 2.9 Room temperature cross-coupling of aryl halides and tosylates with ammonia.[a]
[a] Conversions were determined by GC analysis and yields are of isolated material unless otherwise indicated. [b] Yields were determined on the basis of calibrated GC data with dodecane as an internal standard. [c] Yield was determined on the basis of ^{1}H NMR data with 1,3,5-trimethoxybenzene as an internal standard. [d] Yield of isolated product with approximately 50% conversion of ArBr was determined on the basis of GC analysis.

2.3 SUMMARY AND CONCLUSIONS

The results in this chapter describe an examination of the Pd/Mor-DalPhos catalyst system in the context of ammonia monoarylation under mild conditions.

Stoichiometric reactivity studies established that the combination of $[Pd(cinnamyl)Cl]_2$ and Mor-DalPhos (1:2) generates the adduct [(κ^2-*P,N*-Mor-DalPhos)Pd(η^1-cinnamyl)Cl] (**2-2**), which, upon treatment with base followed by the addition of chlorobenzene, affords the presumptive catalytic intermediate [(κ^2-*P,N*-Mor-DalPhos)Pd(Ph)Cl] (**2-1**). The lack of reactivity observed upon exposure of **2-1** to an excess of ammonia suggests that the Mor-DalPhos ligand is neither hemilabile nor completely displaced under these conditions. Although treatment of **2-1** with AgOTf in the presence of excess ammonia afforded the ammine adduct [(κ^2-*P,N*-Mor-DalPhos)Pd(Ph)NH_3]OTf (**2-4**), in the absence of ammonia the tridentate complex [(κ^3-*P,N,O*-Mor-DalPhos)Pd(Ph)]OTf (**2-5**) was obtained, thereby revealing the capacity of Mor-DalPhos to stabilize low-coordinate Pd catalytic intermediates. In surveying the catalytic abilities of these various Mor-DalPhos/Pd^{II} complexes for challenging room-temperature ammonia monoarylation reactions, including a set of [(κ^2-*P,N*-Mor-DalPhos)Pd(Ar)Cl] derivatives (**2-6** to **2-10**) featuring various aryl (Ar) ligands, **2-1** was identified as the optimal precatalyst. The scope of the room-temperature ammonia monoarylation that was enabled through the use of 5 mol% of **2-1** was found to encompass a range of (hetero)aryl chlorides, bromides, iodides and tosylates with a diversity of functional groups. The ability to conduct reactions of this type under benchtop conditions was also demonstrated with one example.

2.4 Experimental Section

2.4.1 General Considerations

Unless otherwise noted, all manipulations were conducted under dinitrogen within an inert-atmosphere glovebox, utilizing glassware that was oven-dried (130 °C) and evacuated while hot prior to use. Pentane and dichloromethane were deoxygenated by sparging with dinitrogen followed by passage through a double-column solvent purification system purchased from MBraun Inc. equipped with either one alumina-packed column and one column packed with copper-Q5 reactant (pentane) or two alumina-packed columns (dichloromethane). 1,4-Dioxane, THF and diethyl ether were each dried over Na/benzophenone followed by distillation under an atmosphere of dinitrogen. Deuterated solvents (Cambridge Isotopes) were degassed by using three

repeated freeze-pump-thaw cycles and stored over 4 Å molecular sieves for 24 h prior to use. All solvents were stored under dinitrogen over activated 4 Å molecular sieves. Mor-DalPhos,[49] [CpPd(allyl)],[55] [CpPd(cinnamyl)],[51] and [Pd(cinnamyl)Cl]$_2$[56] were prepared according to literature procedures. Silver trifluoromethanesulfonate (Strem), CyPF*t*Bu-JosiPhos (Solvias), and 0.5 M solutions of ammonia in 1,4-dioxane (Aldrich) were used as received. Ammonia cross-coupling reactions were best conducted with fresh bottles (<2 weeks after opening) of 0.5 M ammonia in 1,4-dioxane. ^{1}H, ^{13}C, and ^{31}P NMR characterization data were collected at 300 K on a Bruker AV-500 spectrometer operating at 500.1, 125.8, and 202.5 MHz (respectively), with chemical shifts reported in parts per million downfield of $SiMe_4$ (for ^{1}H and ^{13}C) and 85% H_3PO_4 in D_2O (for ^{31}P). Column chromatography was carried out using Silicycle SiliaFlash 60 with particle size 40-63 μm (230-400 mesh). Conversions and yields based on gas chromatography data were corrected by calibration with internal standards of dodecane and product identity was confirmed on the basis of ^{1}H NMR and/or by comparison with authentic samples. Structural elucidation was enabled through analysis of ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC, and DEPTQ-135 data. In some cases, fewer than expected unique ^{13}C NMR resonances were observed, despite prolonged acquisition times, and the OTf signals are not assigned. NMR data were acquired with the technical assistance of Dr. Michael Lumsden (NMR-3, Dalhousie University), while mass spectrometric data were acquired by Mr. Xiao Feng (Mass Spectrometry Laboratory, Dalhousie University). Chemical shifts of common trace ^{1}H NMR impurities ($CDCl_3$, ppm): H_2O, 1.56; EtOAc, 1.26, 2.05, 4.12; Et_2O, 1.21, 3.48; CH_2Cl_2, 5.30; $CHCl_3$, 7.26. Elemental analyses were performed by Canadian Microanalytical Service Ltd., Delta, BC (Canada) and Midwest Microlab, LLC, Indianapolis, IN (USA).

2.4.2 Synthesis and Characterization Data

Representative procedure for the synthesis of oxidative addition complexes, (κ^2-*P,N*-Mor-DalPhos)Pd(Ph)Cl (2-1): To a vial containing CpPd(allyl) (330 mg, 1.55 mmol) was added Mor-DalPhos (690 mg, 1.49 mmol) followed by 6 mL THF and 6 mL chlorobenzene. The vial was sealed, removed from the glovebox and heated at 65 ^{o}C for 12 h. The reaction was concentrated to approximately 6 mL and the resulting slurry was

washed with pentane (3 X 5 mL) and dried to yield **2-1** as a pale grey powder in 93% yield (943 mg, 1.38 mmol). Crystals of **2-1**·CH_2Cl_2 suitable for X-ray diffraction analysis were obtained from vapor diffusion of diethyl ether into a dichloromethane solution of **2-1**. ^{1}H NMR ($CDCl_3$): δ 8.23 (dd, *J* = 3.4, 8.3 Hz, 1H, ArH), 7.84 (t, *J* = 7.0 Hz, 1H, ArH), 7.64 (t, *J* = 7.7 Hz, 1H, ArH), 7.54 (d, *J* = 7.7 Hz, 2H, Pd-Ph), 7.39 (t, *J* = 7.7 Hz, 1H, ArH), 7.00 (t, *J* = 7.6 Hz, 2H, Pd-Ph), 6.86 (t, *J* = 7.2 Hz, 1H, Pd-Ph), 5.27 (m, 2H, morph CH_2), 4.13 (m, 2H, morph CH_2), 4.00 (m, 2H, morph CH_2), 3.05 (m, 2H, morph CH_2), 2.29 (m, 6H, 1-Ad CH), 2.00 (m, 12H, 1-Ad CH), 1.68 (br s, 12H, 1-Ad CH). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 160.6 (d, J_{PC} = 12.6 Hz, aryl C_{quat}), 141.7 (Pd-Ph C_{quat}), 138.9 (Pd-Ph CH), 136.2 (aryl CH), 132.6 (aryl CH), 128.9 (d, J_{PC} = 29.9 Hz, aryl CH), 127.7 (d, J_{PC} = 28.5 Hz, aryl C_{quat}), 126.6 (Pd-Ph CH), 126.0 (d, J_{PC} = 4.3 Hz, aryl CH), 122.9 (Pd-Ph CH), 62.0 (morph CH_2), 55.2 (morph CH_2) , 40.8 (1-Ad CH_2), 36.4 (1- Ad CH_2), 28.7 (1-Ad CH). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 59.3. Anal. Calcd for $C_{36}H_{47}PdClPNO$: C 63.32; H 6.94; N 2.05. Found: C 63.03; H 6.92; N 2.05.

(*κ*^{2}-*P,N*-Mor-DalPhos)Pd(4-PhOMe)Cl (2-6): Isolated as a grey powder in 79% yield (331 mg, 0.46 mmol). ^{1}H NMR (CDCl3): δ 8.23 (dd, *J* = 2.9, 7.8 Hz, 1H, ArH), 7.84 (m, 1H, ArH), 7.63 (m, 1H, ArH), 7.40-7.36 (m, 3H, ArH), 6.68 (m, 2H, ArH), 5.25 (m, 2H, morph CH_2), 4.13 (m, 2H, morph CH_2), 3.99 (m, 2H, morph CH_2), 3.75 (s, 3H, OCH_3), 3.05 (m, 2H, morph CH_2), 2.29 (m, 6H, 1-Ad), 2.00-1.94 (12H, 1-Ad), 1.68 (br s, 12 H, 1-Ad). ^{13}C{1H} NMR ($CDCl_3$): δ 160.6 (d, J_{PC} = 12.5 Hz, aryl C_{quat}), 156.2 (Pd-aryl C_{quat}), 138.5 (Pd-aryl CH), 136.2 (aryl CH), 132.6 (aryl CH), 128.9 (d, J_{PC} = 7.5 Hz, aryl CH), 127.6 (d, J_{PC} = 28.2 Hz, (Pd-aryl C_{quat}), 125.9 (d, J_{PC} = 4.4 Hz, aryl CH), 112.8 (Pd-aryl CH), 62.0 (morph CH_2), 55.2 (morph CH_2), 55.0 (OCH_3), 43.2 (d, J_{PC} = 14.1 Hz, 1-Ad C_{quat}), 40.8 (1-Ad CH_2), 36.4 (1-Ad CH_2), 28.6 (d, J_{PC} = 9.3 Hz, 1-Ad CH). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 59.6. Anal. Calcd for $C_{37}H_{49}PdCl_1PNO_2$: C 62.34; H 6.93; N 1.97. Found: C 62.44; H 6.86; N 1.72.

(*κ*^{2}-*P,N*-Mor-DalPhos)Pd(4-PhMe)Cl (2-7): Isolated as an off-white solid in 66% yield (46.3 mg, 0.066 mmol). ^{1}H NMR ($CDCl_3$): δ 8.23 (m, 1H, ArH), 7.84 (m, 1H, ArH), 7.63 (m, 1H, ArH), 7.40-7.37 (m, 3H, 2 Pd-ArH, ArH), 6.83 (d, *J* = 7.9 Hz, 2H, Pd-ArH),

5.29-5.23 (m, 2H, morph CH_2), 4.15-4.11 (m, 2H, morph CH_2), 4.02 -3.97 (m, 2H, morph CH_2), 3.06-3.01 (m, 2H, morph CH_2), 2.31-2.28 (m, 6H, 1-Ad CH_2), 2.23 (s, 3H, $ArCH_3$), 2.01-1.99 (m, 6H, 1-Ad CH_2), 1.95-1.94 (m, 6H, 1-Ad CH), 1.71-1.65 (m, 12H, 1-Ad CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 160.5 (d, J_{PC} = 12.6 Hz, aryl C_{quat}), 138.3 (Pd-aryl CH), 136.5 (Pd-aryl C_{quat}), 136.1 (aryl CH), 132.5 (aryl CH), 131.6 (Pd-aryl C_{quat}), 128.8 (d, J_{PC} = 7.5 Hz, aryl CH), 127.7 (Pd-aryl CH), 127.5 (aryl C_{quat}), 126.9 (d, J_{PC} = 4.4 Hz, aryl CH), 62.0 (Morph CH_2), 55.1 (Morph CH_2), 43.2 (d, J_{PC} = 14.2 Hz, 1-Ad C_{quat}), 40.7 (1-Ad CH_2), 36.4 (1-Ad CH_2), 28.7 (d, J_{PC} = 9.4 Hz, 1-Ad CH), 21.0 (Ar CH_3). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 59.4. Anal. Calcd for $C_{37}H_{49}ClNOPPd$: C, 63.79; H, 7.09; N, 2.01. Found: C, 63.58; H, 6.89; N, 1.92.

(κ^2-*P,N*-Mor-DalPhos)Pd(2-PhMe)Cl (2-8): Isolated as a beige powder in 75% yield (52.4 mg, 0.075 mmol). ^1H NMR ($CDCl_3$): δ 8.23 (ddd, J = 8.4, 3.6, 1.0 Hz, 1H, ArH), 7.88 (m, 1H, ArH), 7.63 (m, 1H, ArH), 7.53 (m, 1H, Pd-ArH), 7.38 (m, 1H, ArH), 6.89 (m, 1H, Pd-ArH), 6.85-6.80 (m, 2H, Pd-ArH), 5.30 (m, 1H, morph CH_2), 5.21 (m, 1H, morph CH_2), 4.18-4.12 (m, 2H, morph CH_2), 4.03-3.96 (m, 2H, morph CH_2), 3.09-2.99 (m, 2H, morph CH_2), 2.87 (s, 3H, $ArCH_3$), 2.45 -2.43 (m, 3H, 1-Ad CH_2), 2.13-2.03 (m, 9H, 1-Ad CH/CH_2), 1.86 (br s, 6H, 1-Ad CH/CH_2), 1.79-1.71 (m, 6H, 1-Ad CH_2), 1.66-1.59 (m, 6H, 1-Ad CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 160.3 (d, J_{PC} = 12.8 Hz, aryl C_{quat}), 142.4 (Pd-aryl C_{quat}), 142.0 (d, J_{PC} = 3.6 Hz, Pd-aryl C_{quat}), 137.4 (d, J_{PC} = 2.7 Hz, Pd-aryl CH), 135.8 (aryl CH), 132.5 (aryl CH), 128.9 (d, J_{PC} = 7.3 Hz, aryl CH), 128.6 (Pd-aryl CH), 127.9 (d, J_{PC} = 28.2 Hz, aryl C_{quat}), 126.0 (d, J_{PC} = 4.2 Hz, aryl CH), 123.4 (Pd-aryl CH), 123.1 (Pd-aryl CH), 62.0 (Morph CH_2), 61.9 (Morph CH_2), 55.2 (Morph CH_2), 54.6 (Morph CH_2), 42.7 (d, J_{PC} = 15.1 Hz, 1-Ad C_{quat}), 42.5 (d, J_{PC} = 12.9 Hz, 1-Ad C_{quat}), 41.0 (1-Ad CH_2), 39.7 (1-Ad CH_2), 36.4 (1-Ad CH_2), 36.3 (1-Ad CH_2), 28.8 (Ar CH_3), 28.8 (d, J_{PC} = 9.4 Hz, 1-Ad CH), 28.5 (d, J_{PC} = 9.2 Hz, 1-Ad CH). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 58.3. Anal. Calcd for $C_{37}H_{49}ClNOPPd$: C, 63.79; H, 7.09; N, 2.01. Found: C, 63.88; H, 6.97; N, 1.89.

(κ^2-*P,N*-Mor-DalPhos)Pd(4-PhCF$_3$)Cl (2-9): Isolated as an off-white powder in 80% yield (59.7 mg. 0.080 mmol). ^1H NMR ($CDCl_3$): δ 8.24 (dd, J = 8.4, 3.1 Hz, ArH), 7.84

(m, 1H, ArH), 7.70 (d, J = 7.8 H, 2H, Pd-ArH), 7.65 (m, 1H, ArH), 7.41 (t, J = 7.6 Hz, ArH), 7.21 (d, J = 8.1 Hz, 2H, Pd-ArH), 5.28-5.23 (m, 2H, morph CH_2), 4.16-4.11 (m, 2H, morph CH_2), 4.03-3.98 (m, 2H, morph CH_2), 3.09-3.04 (m, 2H, morph CH_2), 2.29-2.26 (m, 6H, 1-Ad CH_2), 1.96 (br s, 12H, 1-Ad CH/CH_2), 1.68 (br s, 12H, 1-Ad CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 160.4 (d, J_{PC} = 12.5 Hz, aryl C_{quat}), 149.3 (Pd-aryl C_{quat}), 138.7 (Pd-aryl CH), 136.1 (aryl CH), 132.8 (aryl CH), 128.8 (d, J = 7.6 Hz, aryl CH), 127.1 (d, J_{PC} = 29.1 Hz, aryl C_{quat}), 126.2 (d, J_{PC} = 4.6 Hz, aryl CH), 125.2 (J_{CF} = 270.7 Hz, CF_3), 125.0 (J_{CF} = 31.8 Hz, Pd-aryl C_{quat}), 122.4 (Pd-aryl CH), 61.9 (morph CH_2), 55.4 (morph CH_2), 43.4 (d, J_{PC} = 14.4 Hz, 1-Ad C_{quat}), 40.8 (1-Ad CH_2), 36.3 (1-Ad CH_2), 28.6 (d, J_{PC} = 9.3 Hz, 1-Ad CH). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 60.5. Anal. Calcd for $C_{37}H_{46}ClF_3NOPPd$: C, 59.20; H, 6.18; N, 1.87. Found: C, 59.15; H, 6.22; N, 1.90.

(κ^2-*P,N*-Mor-DalPhos)Pd(3-pyridyl)Cl (2-10): To a vial containing $[Pd(allyl)Cl]_2$ (57.6 mg, 0.158 mmol, 0.525 equiv.) was added Mor-DalPhos (46.4 mg, 0.100 mmol, 1.0 equiv.), NaO*t*Bu (34.6 mg, 0.360 mmol, 1.2 equiv.), 3-chloropyridine (1 mL) and THF (2 mL). The resulting brown mixture was sealed, removed from the glovebox and heated at 65 ºC for 3 h, at which time complete consumption of the ligand was confirmed by use of ^{31}P NMR. The resulting slurry was concentrated to dryness, dissolved in DCM (2 mL) and filtered (removing insoluble impurities). The filtrate was triturated with DCM-Et_2O (1:1, 2 x 2 mL) and DCM-pentane (1:1, 3 x 2 mL) mixtures forming a pale orange powder which was dried in vacuo for several days to afford the desired compound (containing 5.5% Et_2O as observed by ^1H NMR) in 90% yield (184.7 mg, 0.270 mmol). Anal. Calcd for $C_{35}H_{46}ClN_2OPPd$: C, 61.49; H, 6.78; N, 4.10. Found: C, 61.11; H, 6.73; N, 3.87. ^1H NMR ($CDCl_3$): δ 8.77 (d, J = 1.6 Hz, 1H, pyridyl-H), 8.24 (ddd, J = 8.4, 3.5, 0.9 Hz, 1H, ArH), 8.04 (dd, J = 4.7, 1.5 Hz, 1H, pyridyl-H), 7.85-7.80 (m, 2H, pyridyl + ArH), 7.65 (m, 1H, ArH), 7.41 (m, 1H, ArH), 6.93 (dd, J = 7.8, 4.7 Hz, 1H, pyridyl-H), 5.29-5.24 (m, 2H, morph CH_2), 4.16-4.11 (m, 2H, morph CH_2), 4.03-3.98 (m, 2H, morph CH_2), 3.10-3.05 (m, 2H, morph CH_2), 2.26 (br s, 6H, 1-Ad CH_2), 1.95 (br s, 12H, 1-Ad CH/CH_2), 1.67 (br s, 12H, 1-Ad CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 160.4 (d, J_{PC} = 12.5 Hz, aryl C_{quat}), 157.0 (pyridyl CH), 146.4 (pyridyl CH), 143.9 (pyridyl CH), 138.5 (pyridyl C_{quat}), 136.0 (aryl CH), 132.9 (aryl CH), 128.7 (d, J_{PC} = 7.8 Hz, aryl CH), 127.0 (d, J_{PC} =

29.5 Hz, aryl C_{quat}), 126.2 (d, J_{PC} = 4.6 Hz, aryl CH), 122.7 (pyridyl CH), 61.9 (morph CH_2), 55.5 (morph CH_2), 55.4 (morph CH_2), 43.4-43.3 (m, 1-Ad C_{quat}), 40.8 (1-Ad CH_2), 36.3 (1-Ad CH_2), 28.6 (d, J_{PC} = 9.3 Hz, 1-Ad CH). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 61.9.

(κ^2-*P,N*-Mor-DalPhos)Pd(η^1-cinnamyl)Cl (2-2): A vial was charged with Mor-DalPhos (139.1 mg, 0.300 mmol, 1.0 equiv.), $[Pd(cinnamyl)Cl]_2$ (77.7 mg, 0.300 mmol, 1.0 equiv) and THF (4 mL). The resulting clear orange solution was stirred at room temperature for 1 h during which time the reaction became cloudy and grew lighter in colour, forming a milky yellow solution. The presence of a new product (**2-2**) was confirmed by use of ^{31}P NMR techniques. The resulting slurry was concentrated to dryness, washed with Et_2O (5 x 2 mL) until the washings remained colourless and dried to afford the title compound as a yellow powder in 92% yield (200 mg, 0.277 mmol). Anal. Calcd for $C_{39}H_{51}ClNOPPd$: C, 64.82; H, 7.11; N, 1.94. Found: C, 64.55; H, 7.02; N, 1.89. Crystals suitable for single-crystal X-ray diffraction analysis were obtained from vapour diffusion of hexanes into a dichloromethane/ethyl acetate solution of the title compound. ^1H NMR ($CDCl_3$): δ 7.88-7.82 (m, 2H, ArH), 7.71-7.70 (m, 2H, cin Ph), 7.61 (m, 1H, ArH), 7.43 (m, 1H, ArH), 7.38-7.33 (m, 3H, cin Ph), 6.76 (dd, *J* = 14.5, 8.8 Hz, 1H, alkenyl H), 6.37 (m, 1H, alkenyl H), 3.83-3.78 (m, 2H, morph CH_2), 3.71-3.67 (m, 2H, morph CH_2), 3.60-3.56 (m, 4H, Pd-CH_2/morph CH_2), 3.14-3.09 (m, 2H, morph CH_2), 2.26-2.24 (m, 6H, 1-Ad CH_2), 2.01 (br s, 6H, 1-Ad CH), 1.95-1.93 (m, 6H, 1-Ad CH_2), 1.72-1.66 (m, 12H, 1-Ad CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 160.3 (d, J_{PC} = 14.1 Hz, aryl C_{quat}), 136.9 (d, J_{PC} = 6.3 Hz, Ph C_{quat}), 135.7 (aryl CH), 133.0 (aryl CH), 129.4 (Ph CH), 128.6 (aryl CH), 127.8 (Ph CH), 127.4 (d, J_{PC} = 28.9 Hz, aryl C_{quat}), 127.4 (aryl CH), 126.6 (d, J_{PC} = 7.6 Hz, aryl CH), 122.5 (d, J_{PC} = 17.4 Hz, alkenyl CH), 114.5 (alkenyl CH), 65.0 (Morph CH_2), 58.5 (Morph CH_2), 43.0 (d, J_{PC} = 12.1 Hz, 1-Ad C_{quat}), 41.1 (1-Ad CH_2), 36.2 (1-Ad CH_2), 35.7 (Pd-CH_2), 28.7 (d, J_{PC} = 9.3 Hz, 1-Ad CH). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 75.4.

[(κ^2-*P,N*-Mor-DalPhos)Pd(η^3-cinnamyl)]OTf (2-3): To a vial containing **2-2** (72.3 mg, 0.100 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added silver trifluoromethanesulfonate (28.3 mg, 0.110 mmol, 1.1 equiv). The resulting yellow solution was stirred for ~ 1 h during which time a gray precipitate formed. Reaction completion was determined by the

presence of a single new phosphorus-containing species as observed by ^{31}P NMR methods. The mixture was filtered over Celite and the filtrate was treated with pentane (3 mL) to afford a yellow solid in solution, which in turn was separated from the solvent and washed with pentane (2 x 3 mL). The solid was dried to afford the title compound as a yellow powder in 98% yield (81.6 mg, 0.098 mmol). Anal. Calcd for $C_{40}H_{51}F_3NO_4PPdS$: C, 57.45; H, 6.15; N, 1.67. Found: C, 57.22; H, 6.12; N, 1.74. Crystals suitable for single-crystal X-ray diffraction analysis were obtained via slow evaporation of a $CHCl_3$ solution of the title compound. ^1H NMR ($CDCl_3$): δ 7.90-7.84 (m, 2H, ArH), 7.79-7.77 (m, 2H, cin Ph), 7.65 (m, 1H, ArH), 7.48 (t, J_{PC} = 7.6 Hz, 1H, ArH), 7.46-7.42 (m, 3H, cin Ph), 6.32 (dd, J = 9.8 Hz, 1H, allyl CH), 6.18 (m, 1H, allyl CH), 4.05 (d, J = 5.5 Hz, 1H, allyl CH), 4.00-3.92 (m, 2H, morph CH_2), 3.64 (m, 1H, morph CH_2), 3.45 (m, 1H, morph CH_2), 3.32-3.22 (m, 2H, morph CH_2), 3.11 (m, 1H, allyl CH), 3.01-2.94 (m, 2H, morph CH_2), 2.30-2.27 (m, 3H, 1-Ad CH_2), 2.08-1.97 (m, 12H, 1-Ad CH/CH_2), 1.84 (br s, 3H, 1-Ad CH_2), 1.73-1.67 (m, 12H, 1-Ad CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 160.1 (d, J_{PC} = 14.6 Hz, aryl C_{quat}), 135.7 (aryl CH), 135.5 (d, J_{PC} = 6.9 Hz, Ph C_{quat}), 133.5 (aryl CH), 129.8 (Ph CH), 129.6 (Ph CH), 128.6 (m, Ph CH), 128.0 (d, J_{PC} = 4.1 Hz, aryl CH), 126.6 (aryl CH), 126.5 (d, J_{PC} = 28.9 Hz, aryl C_{quat}), 119.3 (d, J_{PC} = 20.7 Hz, allyl CH), 109.9 (d, J_{PC} = 7.0 Hz, allyl CH), 65.3 (Morph CH_2), 64.0 (Morph CH_2), 58.9 (Morph CH_2), 58.6 (Morph CH_2), 43.1 (d, J_{PC} = 11.7 Hz, 1-Ad C_{quat}), 42.6 (d, J_{PC} = 13.0 Hz, 1-Ad C_{quat}), 41.8 (1-Ad CH_2), 41.3 (1-Ad CH_2), 41.1 (allyl CH_2), 36.2 (1-Ad CH_2), 28.6 (d, J_{PC} = 4.2 Hz, 1-Ad CH). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 79.1.

[(κ^2-*P,N*-Mor-DalPhos)Pd(Ph)NH_3]OTf·CH_2Cl_2 (2-4·CH_2Cl_2): A vial was charged with **2-1** (341 mg, 0.50 mmol) followed by CH_2Cl_2 (5 mL). The vial was sealed, transferred out of the glovebox and NH_3 (0.5 M in 1,4-dioxane, 3.00 mL, 1.50 mmol) was added. The solution was stirred briefly, and then was transferred back into the glovebox, at which point silver trifluoromethanesulfonate (141 mg, 0.55 mmol) was added. The resulting mixture was stirred for 30 minutes at room temperature during which time a gray precipitate formed. ^{31}P NMR analysis of the reaction mixture indicated complete conversion to a single new phosphorus-containing species. The precipitate was removed by filtration over Celite and the solution was concentrated under vacuum. The resulting

solid was washed with pentane/CH_2Cl_2 (5 x 2 mL) and concentrated to afford **2-4**·CH_2Cl_2 as a light brown solid in 90% yield (406 mg, 0.45 mmol). Crystals of **2-4**·CH_2Cl_2 suitable for X-ray diffraction analysis were obtained from vapor diffusion of diethyl ether into a dichloromethane solution of **2-4**. ^{1}H NMR ($CDCl_3$): δ 8.13 (m, 1H, ArH), 7.83 (t, *J* = 6.6 Hz, 1H, ArH), 7.69 (t, *J* = 7.6 Hz, 1H, ArH), 7.52 (d, *J* = 7.9 Hz, 2H, Pd-Ph), 7.45 (t, *J* = 7.5 Hz, 1H, ArH), 7.06 (t, *J* = 7.5 Hz, 2H, Pd-Ph), 6.93 (t, *J* = 7.1 Hz, 1H, Pd-Ph), 4.33 (m, 2H, morph CH_2), 4.07 (br s, 4H, morph CH_2), 3.24 (m, 2H, morph CH_2), 2.64 (br s, 3H, NH_3), 2.25-2.23 (m, 6H, 1-Ad), 1.97 (br s, 12H, 1-Ad), 1.68 (br s, 12H, 1- Ad). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 160.6 (m, aryl C_{quat}), 143.2 (Ph C_{quat}), 137.7 (Pd-Ph CH), 135.9 (aryl CH), 133.3 (aryl CH), 127.8 (Pd-Ph CH), 127.1 (d, J_{PC} = 7.5 Hz, aryl CH), 126.6 (aryl CH), 124.0 (Pd- Ph CH), 61.6 (morph CH_2), 55.6 (morph CH_2), 43.1 (d, J_{PC} = 5.4 Hz, 1-Ad C_{quat}), 40.6 (1-Ad CH_2), 36.1 (1-Ad CH_2), 28.4 (d, J_{PC} = 0.5 Hz, 1-Ad CH). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 61.7. Anal. Calcd for $C_{38}H_{52}Pd_1Cl_2P_1N_2O_4S_1F_3$: C 50.80; H 5.84; N 3.12. C 50.84; H 5.90; N 3.30.

[(κ^3-*P,N,O*-Mor-DalPhos)Pd(Ph)]OTf (2-5): To a vial containing **2-1** (102.4 mg, 0.150 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added silver trifluoromethanesulfonate (42.4 mg, 0.165 mmol, 1.1 equiv). The resulting yellow solution was stirred for ~ 1 h during which time a gray precipitate formed. Reaction completion was determined by the presence of a single new phosphorus-containing species as observed by ^{31}P NMR methods. The mixture was filtered over Celite, the collected eluent was concentrated to a minimum volume (<1 mL), and the remaining solution was treated with pentane (3 mL) to afford a yellow solid (fresh precipitate) in solution, which was separated from the solvent and washed with pentane (3 x 3 mL). The solid was dried in vacuo at 75 ^{o}C for 60 hrs (approx. 3 days) to afford the title compound as an analytically pure light yellow powder in 95% yield (113.1 mg, 0.142 mmol). Anal. Calcd for $C_{37}H_{47}F_3NO_4PPdS$: C, 55.81; H, 5.95; N, 1.76. Found: C, 55.74; H, 5.92; N, 1.92. Crystals suitable for single-crystal X-ray diffraction analysis were obtained from vapor diffusion of diethyl ether into a dichloromethane solution of the title compound.^{1}H NMR ($CDCl_3$): δ 8.16 (dd, *J* = 7.5, 3.0 Hz, 1H, ArH), 7.80-7.72 (m, 2H, ArH), 7.57-7.52 (m, 3H, 2 Pd-Ph + ArH), 7.14-7.11 (m, 2H, Pd-Ph), 7.07 (m, 1H, Pd-Ph), 4.61-4.56 (m, 2H, morph CH_2), 4.27-4.22 (m, 2H,

morph CH_2), 3.87-3.85 (m, 2H, morph CH_2), 3.72 (br s, 2H, morph CH_2), 2.29-2.26 (m, 6H, 1-Ad CH_2), 2.03 (br s, 12H, 1-Ad CH/CH_2), 1.72 (br s, 12H, 1-Ad CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 154.6 (aryl C_{quat}), 145.3 (Pd-Ph C_{quat}), 136.5 (Pd-Ph CH), 135.7 (aryl CH), 134.2 (aryl CH), 128.7 (d, J_{PC} = 5.0 Hz, aryl CH), 128.4 (d, J_{PC} = 32.9 Hz, aryl C_{quat}), 127.8 (Pd-Ph CH), 127.1 (d, J_{PC} = 7.5 Hz, ArH), 125.2 (Pd-Ph CH), 68.1 (morph CH_2), 54.7 (morph CH_2), 43.9 (d, J_{PC} = 15.9 Hz, 1-Ad C_{quat}), 41.0 (1-Ad CH_2), 36.1 (1-Ad CH_2), 28.5 (d, J_{PC} = 9.6 Hz, 1-Ad CH). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 78.8 (br s).

Representative protocol for room temperature ammonia monoarylation: A vial containing a magnetic stir bar, **2-1** (17.1 mg, 0.0025 mmol, 5.0 mol%), NaO*t*Bu (96.1 mg, 1.00 mmol, 2.0 equiv.) and 1,4-dioxane (2.000 mL) was charged with 3-chloro-5-fluoroanisole (0.0635 mL, 0.50 mmol, 1.0 equiv.). The resulting cloudy solution was stirred briefly, sealed with a cap containing a PTFE septum and was removed from the glovebox, followed by the addition of NH_3 as a 0.5 M solution in 1,4-dioxane (3.000 mL, 1.5 mmol). The solution was stirred magnetically at room temperature overnight (14-20 h) and the reaction progress was monitored by use of TLC or GC methods. After complete consumption of the aryl halide, the reaction was filtered over Celite, concentrated and silica powder (0.5-1.0 g) was added to the crude material. The solvent was removed from the silica-product mixture and the compound was purified by column chromatography with 15-20% EtOAc/hexanes and allowed to dry on the benchtop overnight to afford 3-fluoro-5-methoxyaniline (**2-17**) as an orange oil in 65% yield (46 mg, 0.33 mmol). ^1H NMR ($CDCl_3$): δ 6.04 (dt, J = 11.0, 2.3 Hz, 1H), 6.02-5.99 (m, 2H), 3.77-3.74 (m, 5H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 164.7 (d, J_{CF} = 241.5 Hz, C_{quat}), 161.8 (d, J_{CF} = 13.8 Hz, C_{quat}), 148.7 (d, J_{CF} = 13.8 Hz), 96.7, 95.0 (d, J_{CF} = 23.9 Hz), 92.0 (d, J_{CF} = 25.1 Hz), 55.5. Agrees with data previously reported in the literature.[49]

N-methylbenzene-1,3-diamine (2-16). Purified by column chromatography (35% EtOAc/hexanes) and isolated as a thick purple oil from the corresponding chloride in 77% yield (47 mg, 0.39 mmol). ^1H NMR ($CDCl_3$): δ 6.98 (t, J = 7.8 Hz, 1H), 6.10-5.97 (m, 2H), 5.96 (d, J = 2.5 Hz, 1H), 3.60 (br s, 3H), 2.80 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ

150.7, 147.6, 130.1, 104.9, 103.8, 99.1, 30.8. Agrees with data previously reported in the literature.[49]

4-fluoroaniline (2-18). Purified by column chromatography (10% EtOAc/hexanes) and isolated as a dark orange oil in 41% yield (23 mg, 0.21 mmol) from the corresponding chloride. ^{1}H NMR ($CDCl_3$): δ 6.88-6.83 (m, 2H), 6.64-6.60 (m, 2H), 3.54 (br s, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 156.6 (d, J_{CF} = 235.2 Hz), 142.5, 116.2 (d, J_{CF} = 7.5 Hz), 115.8 (d, J_{CF} = 22.6 Hz). Agrees with the commercially available material (CAS: 371-40-4).

2-(benzyloxy)-5-fluoroaniline (2-19). Purified by column chromatography (10% EtOAc/hexanes) and isolated as a yellow oil in 86% yield (93 mg, 0.43 mmol) from the corresponding chloride. ^{1}H NMR ($CDCl_3$): δ 7.44-7.38 (m, 4H), 7.35 (m, 1H), 6.75 (dd, J = 8.8, 5.5 Hz, 1H), 6.46 (dd, J = 9.8, 3.0 Hz, 1H), 6.36 (td, J = 8.5, 3.0 Hz, 1H), 5.04 (s, 2H), 3.93 (br s, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 158.1 (d, J_{CF} = 236.4 Hz), 142.6, 138.0 (d, J_{CF} = 11.3 Hz), 137.1, 128.7, 128.2, 127.8, 112.9 (d, J_{CF} = 10.1 Hz), 103.5 (d, J_{CF} = 22.6 Hz), 102.3 (d, J_{CF} = 26.4 Hz), 71.3. HRMS (ESI/$[M+Na]^+$) calcd. for $C_{13}H_{12}FNNaO$: 240.0795. Found: 240.0793.

3-fluoro-4-methylaniline (2-20). Purified by column chromatography (20% EtOAc/hexanes) and isolated as a dark yellow oil in 62% yield (39 mg, 0.31 mmol) from the corresponding chloride. ^{1}H NMR ($CDCl_3$): δ 6.93 (m, 1H), 6.38-6.35 (m, 2H), 3.61 (br s, 2H), 2.14 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 162.0 (d, J_{CF} = 242.7 Hz), 146.0 (d, J_{CF} = 10.1 Hz), 131.9 (d, J_{CF} = 6.3 Hz), 114.3 (d, J_{CF} = 17.6 Hz), 110.8, 102.3 (d, J_{CF} = 25.1 Hz), 13.8. Agrees with data previously reported in the literature.[49]

3-fluoro-6-methylaniline (2-21). Purified by column chromatography (10-12% EtOAc/hexanes) and isolated as a yellow oil in 62% yield (39 mg, 0.31 mmol) from the corresponding chloride. ^{1}H NMR ($CDCl_3$): δ 6.93 (m, 1H), 6.38-6.35 (m, 2H), 3.62 (br s, 2H), 2.15 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 162.0 (d, J_{CF} = 242.7 Hz), 146.0 (d, J_{CF} = 11.3 Hz), 131.9 (d, J_{CF} = 7.5 Hz), 114.3 (d, J_{CF} = 12.6 Hz), 110.7 (d, J_{CF} = 2.5 Hz), 102.3

(d, J_{CF} = 25.2 Hz), 13.8 (d, J_{CF} = 2.5 Hz). Agrees with data previously reported in the literature.[49]

1-naphthylamine (2-22). Purified by column chromatography (10% EtOAc/hexanes) and isolated as a brown solid in 70% yield (50 mg, 0.35 mmol) from the corresponding chloride and in 43% yield (31 mg, 0.217 mmol) from the corresponding bromide. ^{1}H NMR ($CDCl_3$): δ 7.85-7.82 (m, 2H), 7.51-7.46 (m, 2H), 7.37-7.31 (m, 2H), 6.80 (dd, *J* = 7.1, 1.4 Hz, 1H), 4.13 (br s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 142.2, 134.5, 128.7, 126.4, 126.0, 125.0, 123.7, 120.9, 119.1, 109.8. Agrees with data previously reported in the literature.[49]

4-phenoxyaniline (2-23). Purified by column chromatography (20% EtOAc/hexanes) and isolated in 47% yield (43 mg, 0.23 mmol) from the corresponding tosylate as a light brown solid. ^{1}H NMR ($CDCl_3$): δ 7.31-7.27 (m, 2H), 7.02 (m, 1H), 6.95-6.93 (m, 2H), 6.90-6.87 (m, 2H), 6.70-6.67 (m, 2H), 3.60 (br s, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 159.0, 148.7, 142.8, 129.6, 122.2, 121.3, 117.3, 116.4. Agrees with data previously reported in the literature.[57]

2-ethylaniline (2-24). Purified by column chromatography (15% EtOAc/hexanes) and isolated as an orange oil in 66% yield (40 mg, 0.33 mmol) from the corresponding tosylate. ^{1}H NMR ($CDCl_3$): δ 7.08 (d, *J* = 7.5 Hz, 1H), 7.05 (td, *J* = 7.5, 1.5 Hz, 1H), 6.77 (td, *J* = 7.5, 1.0 Hz, 1H), 6.69 (dd, *J* = 7.8, 1.3 Hz, 1H), 3.62 (br s, 2H), 2.53 (q, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 144.1, 128.5, 128.0, 126.9, 118.9, 115.5, 24.1, 13.1. Agrees with the commercially available material (CAS: 578-54-1).

1-(4-amino-3-methoxyphenyl)ethanone (2-25). Purified by column chromatography (30% EtOAc/hexanes) and isolated as a beige solid in 45% yield (37 mg, 0.22 mmol) from the corresponding tosylate. ^{1}H NMR ($CDCl_3$): δ 7.46-7.44 (m, 2H), 6.65 (m, 1H), 4.31 (br s, 2H), 3.90 (s, 3H), 2.52 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 196.7, 146.6, 141.8,

128.0, 124.3, 112.6, 109.3, 55.7, 26.2. HRMS (ESI/[M+Na]+) calcd. for C9H11NNaO2: 188.0682. Found: 188.0680.

4-(1*H*-pyrrol-1yl)aniline (2-26). Purified by column chromatography (20-25% EtOAc/hexanes) and isolated as an orange solid in 47% (X = OTs, 37 mg, 0.23 mmol) and 77% yield (X = Cl, 61 mg, 0.39 mmol). ^{1}H NMR ($CDCl_3$): δ 7.21-7.18 (m, 2H), 6.99 (t, *J* = 2.2 Hz, 2H), 6.74-6.71 (m, 2H), 6.33 (t, *J* = 2.2 Hz, 2H), 3.69 (br s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 144.7, 133.1, 122.5, 119.8, 115.8, 109.6. Agrees with data previously reported in the literature.[49]

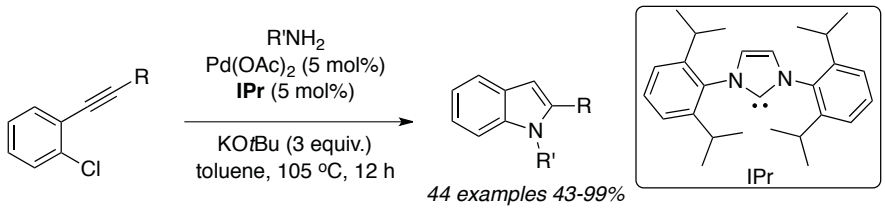
8-aminoquinoline (2-27). Purified by column chromatography (20-30% EtOAc/hexanes) and isolated as a brown solid in 56% yield (X=Cl, 41 mg, 0.28 mmol) and in 62% yield (X=OTs, 45 mg, 0.31 mmol). ^{1}H NMR ($CDCl_3$): δ 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.07 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.38-7.32 (m, 2H), 7.16 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.93 (dd, *J* = 7.5, 1.1 Hz, 1H), 5.00 (br s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 147.6, 144.1, 138.5, 136.1, 129.0, 127.5, 121.5, 116.2, 110.1. Agrees with the commercially available material (CAS: 578-66-5).

3-amino-2-picoline (2-28). Purified by column chromatography on deactivated alumina (30% EtOAc/CH_2Cl_2) and isolated as a yellow solid in 46% yield (25 mg, 0.23 mmol) from the corresponding tosylate. ^{1}H NMR ($CDCl_3$): δ 7.94 (dd, *J* = 4.7, 1.4 Hz, 1H), 6.96 (m, 1H), 6.91 (m, 1H), 3.60 (br s, 2H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 143.9, 140.5, 139.5, 122.2, 121.3, 20.5. Melting Point: 112-115 ^{o}C. Agrees with data previously reported in the literature.[58]

CHAPTER 3 SYNTHESIS OF INDOLES EMPLOYING AMMONIA, METHYLAMINE AND HYDRAZINE, AND STOICHIOMETRIC REACTIVITY STUDIES

3.1 INTRODUCTION

Although the inexpensive and readily available nature of ammonia makes it an attractive nitrogen source, the use of ammonia presents considerable difficulties in most metal-catalyzed reactions, especially in comparison to other classes of substituted amines. Despite considerable research efforts directed towards the metal-catalyzed synthesis of indoles and related heterocycles,[59] the direct use of ammonia in such transformations has not been previously reported. As discussed in Chapter 2, the palladium-catalyzed cross-coupling of ammonia and aryl (pseudo)halides has only recently been developed,[31b, 36-37, 39a-c, 44, 46b, 49] and such catalyst systems generally lack the activity and versatility that can be achieved in the arylation of primary or secondary amines.[5, 13b, 22] Considering the importance of the indole framework in molecules of biological relevance,[59-60] and inspired by the work of Ackermann in the field of tandem arylation-hydroamination chemistry involving primary amines or amides (Scheme 3.1),[61] one could envision a tandem synthesis of N-H indoles employing an initial ammonia cross-coupling followed by a hydroamination/cyclization step.

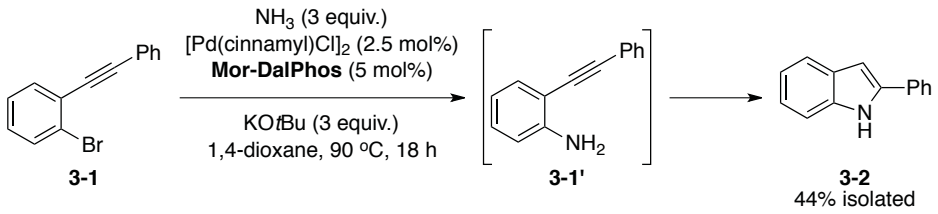


Scheme 3.1 Previous work by Ackermann of a tandem indole synthesis via amine arylation-hydroamination.

In this portion of my thesis research, efforts were directed towards the use of ammonia as well as related small nucleophilic N-H substrates (methylamine and hydrazine) that also prove challenging in monoarylation reactions, to deliver the corresponding N-H, N-Me, and N-amino indoles, respectively. As introduced in Section 1.5, stoichiometric experiments carried out in this study as a secondary approach to gain insight into the observed catalytic behavior are also discussed.

3.2 Palladium-Catalyzed Synthesis of Indoles via Ammonia Cross-Coupling-Alkyne Cyclization

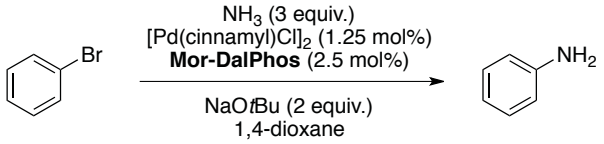
It was hypothesized that the synthesis of 2-substituted NH-indoles could be achieved by the union of the palladium-catalyzed cross-coupling of ammonia with 2-bromophenylacetylene (**3-1**), followed by the base-mediated hydroamination of the resultant 2-amino arylalkyne (**3-1'**). After a range of conditions were screened, mixtures of $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos[48-49, 62] yielded the desired 2-arylindole (**3-2**) in a maximum isolated yield of 44% (Scheme 3.2), as well as considerable amounts of hydrodehalogenated product diphenylacetylene.



Scheme 3.2 Pd/Mor-DalPhos-catalyzed cross-coupling of ammonia to form indole.

Considering the high yields reported for the formation of anilines[49] employing the Pd/Mor-DalPhos catalyst system, and the base-mediated hydroamination of intermediates such as **3-1'** to form indoles reported by Knochel,[63] it was concluded that the *ortho*-alkyne was a detrimental factor in the reaction; indeed, this proved to be the case upon carrying out related test reactions. The standard cross-coupling of ammonia with bromobenzene was executed with and without 20 mol% diphenylacetylene at 65 and 110 ^{o}C (Table 3.1). The reaction proceeded as expected with high yields obtained at both temperatures (entries 1 and 3). However, in the presence of a sub-stoichiometric amount of alkyne, catalysis was inhibited at high temperature as well as completely deactivated at lower temperature (entries 2 and 4, respectively). Additional test reactions were performed using 20 mol% 2-phenylindole (entry 5), which further demonstrated the incompatibility of these substrate classes (i.e. alkyne and indole) with ammonia arylation employing the Pd/Mor-DalPhos catalyst; full conversion of the aryl bromide was achieved, with a poor ratio of mono to diarylated products (6.4:1) observed.

Table 3.1 Ammonia arylation test reactions with sub-stoichiometric quantities of additives.[a]



Entry	Additive	Time (h)	Temp (^{o}C)	GC yield [%][b]
1[c]	none	1.25	110	91
2[d]	0.20 equiv. PhCCPh	1.25	110	70
3	none	2	65	82
4	0.20 equiv. PhCCPh	2	65	-- (<5 % conv.)
5[e]	0.20 equiv. 2-phenylindole	1.25	110	67

[a] PhBr (0.200 mmol), 0.5 M NH_3/1,4-dioxane (0.600 mmol), [Pd(cinnamyl)Cl]$_2$ (1.25 mol%), Mor-DalPhos (2.5 mol%), NaO*t*Bu (0.4 mmol) in 1,4-dioxane (0.8 mL). [b] Yields determined on the basis of calibrated GC data using dodecane as an internal standard. [c] 26:1 ratio of mono:diarylation. [d] 3:1 mono:diarylation. [e] 6.4:1 mono:diarylation.

In an effort to develop a more effective catalytic process, active and commonly employed ligands for Pd-catalyzed amination reactions were screened (Figure 3.1). While ligands such as *t*Bu-DavePhos, S-Phos, X-Phos, P(*t*Bu)$_3$, DiPPF, Q-Phos, TrippyPhos, IPr, and selected cata*CX*ium ligands gave poor results, JosiPhos (CyPF*t*Bu) provided the desired indole product in 89% GC yield. As discussed in Section 2.1, JosiPhos has been shown by Hartwig and co-workers to be a highly effective ligand for amine cross-coupling,[31c, 64] including ammonia.[31b, 36, 44]

Using JosiPhos as the optimal ligand, variation of the standard reaction conditions (Table 3.2) demonstrated the important role of KO*t*Bu as the base. The use of KOH, Cs_2CO_3 or NaO*t*Bu failed to deliver **3-2** in high yields, but in some cases delivered the uncyclized aniline; for example, 2-(phenylethynyl)aniline (**3-1'**) could be isolated in 89% yield when using NaO*t*Bu (2 equiv.) with Pd/JosiPhos catalyst mixtures.[46b] Performing the reaction with lower catalyst loading (0.5 mol% [Pd(cinnamyl)Cl]$_2$) resulted in a decreased yield of the desired product (56% GC yield), although full conversion of the starting material was still observed. Aryl chlorides or tosylates were found to be incompatible substrates with the current reaction conditions, resulting in either lack of conversion or decomposition of starting material to the phenol precursor, respectively. While [Pd(cinnamyl)Cl]$_2$ provided the highest yield of **3-2**, other Pd sources could be employed such as $Pd_2(dba)_3$ or Pd[P(o-tol)$_3$]$_2$ (73 and 83% GC yield, respectively).

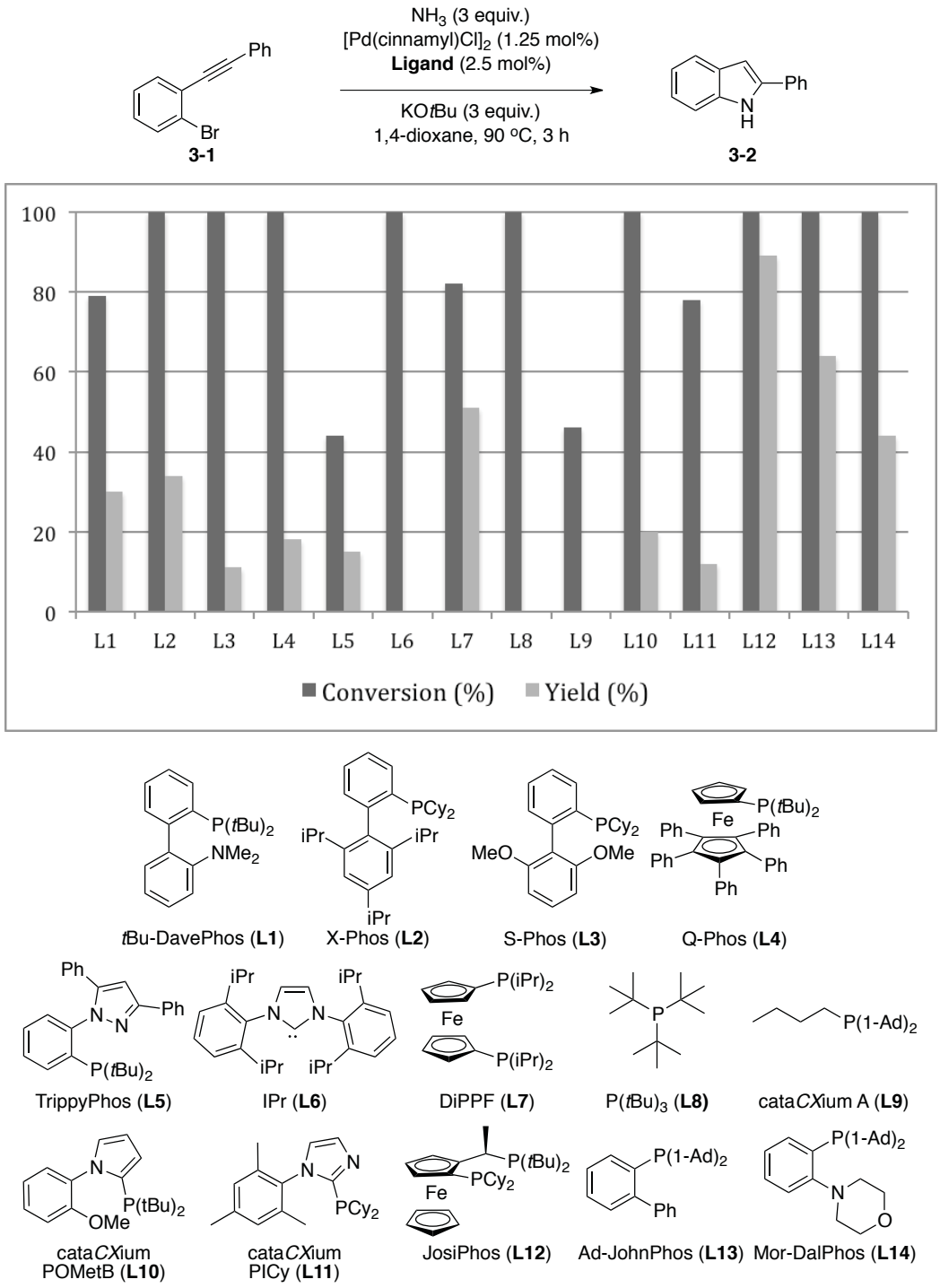
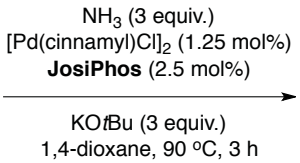


Figure 3.1 Ligand screen for the Pd-catalyzed synthesis of 2-phenylindole from ammonia and 2-bromophenylacetylene.
Reaction conditions: 0.1 mmol scale, Pd/L = 1:1, NH_3 = 0.3 mmol, KO*t*Bu = 0.3 mmol, 90 °C in 1,4-dioxane. Conversions of **3-1** and yields of **3-2** are based on calibrated GC data using dodecane as an internal standard. Isolated yield shown for **L14** using 5 mol% Pd after 18 h reaction time.

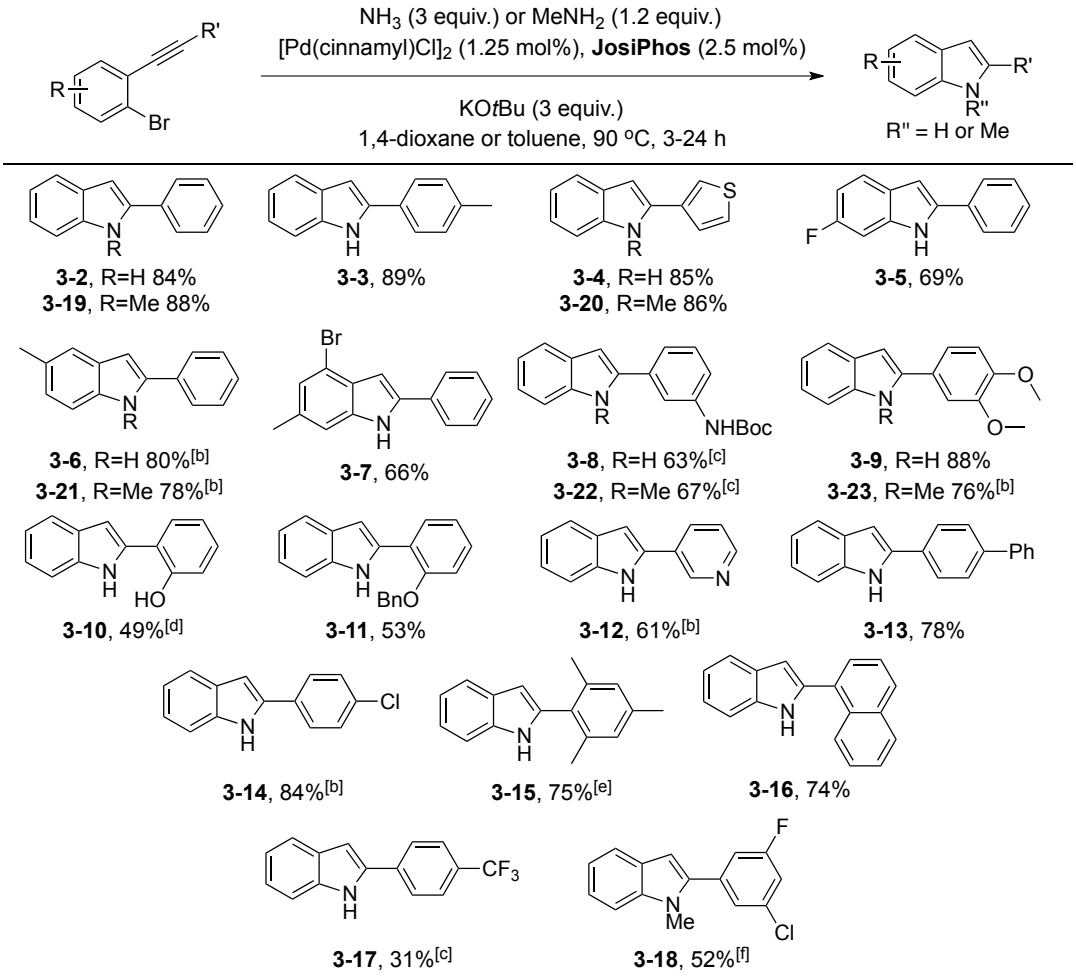
Table 3.2 Variation of conditions for the ammonia cross-coupling-alkyne cyclization process.



Entry	Variation from standard conditions	GC Conv.[b]	GC yield [%][b]
1	none	>99	89
2	NaO*t*Bu instead of KO*t*Bu	>99	<5 (89)[c]
3	KOH instead of KO*t*Bu	61	<5
4	Cs_2CO_3 instead of KO*t*Bu	54	--
5	toluene instead of 1,4-dioxane	>99	62
6	Pd:L ratio 1:2 instead of 1:1	>99	89
7	0.5 mol% $[Pd(cinnamyl)Cl]_2$	>99	56
8	ArCl instead of ArBr	<5	--
9	ArOTs instead of ArBr	>99	-[d]
10	Pd_2dba_3 instead of $[Pd(cinnamyl)Cl]_2$	>99	73
11	$Pd[P(o\text{-tol})_3]_2$ instead of $[Pd(cinnamyl)Cl]_2$	>99	83
12	0.08 M [ArBr] instead of 0.0625 M	>99	89

[a] Standard reaction conditions: 0.1 mmol scale, [Pd]/L=1:1, NH_3=0.3 mmol and KO*t*Bu=0.3 mmmol, 90 °C, in 1,4-dioxane (0.0625 M in substrate). [b] Conversions of ArBr and yields of indole are based on calibrated GC data using dodecane as an internal standard. [c] Isolated yield of 2-(phenylethynyl)aniline at 18 h reaction time. [d] Full consumption of ArOTs; only corresponding phenol observed.

Having identified a suitable catalyst for the direct synthesis of 2-phenylindole (**3-2**) from ammonia using commercially available stock solutions (0.5 M NH_3 in 1,4-dioxane), the scope of the reaction was explored with various 2-bromophenylalkynyl substrates (Figure 3.2), which were generated via Sonogashira coupling reactions (see Section 3.5 for details). A variety of substituents on the remote arene ring of the alkyne were tolerated; for instance, heterocycle-containing examples such as 3-thiophene (**3-4**) and 2-pyridine (**3-12**) proceeded in good yields (85% and 61%), as did phenylacetylenes with alkyl, ether or halogen groups. The reaction appears relatively insensitive to *ortho*-substitution on the arene ring at the 2-position, as 2-arylindoles **3-10**, **3-11**, **3-15**, and **3-16** were formed in moderate to good yields. An indole featuring an NHBoc-group (**3-8**) could be prepared without complication from the additional amine functionality in 63% yield. The *tert*-butyldimethylsilyl-protected bromoalkyne precursor was found to undergo concurrent deprotection to yield the phenol-containing product **3-10**, albeit in slightly reduced yield (49%), while use of a benzyl protecting group gave the corresponding indole **3-11** in 53% yield with the benzyl moiety intact.



[a] Reaction conditions: 0.5 mmol scale, Pd/L = 1:1, NH_3 = 1.5 mmol or $MeNH_2$ = 0.6 mmol , KO*t*Bu = 1.5 mmol, 90 °C in 1,4-dioxane (NH indoles, 3 h reaction time) or in toluene (NMe indoles, 16-24 h). Yields are of isolated material. [b] 5 mol% Pd used. [c] 3.5-4.0 equiv. of base used. [d] From TBS-protected alcohol substrate. [e] 6.0 equiv. base, 110 °C, 48 h. [f] 3.0 equiv. Cs_2CO_3, 3.0 equiv. KO*t*Bu, 48 h.

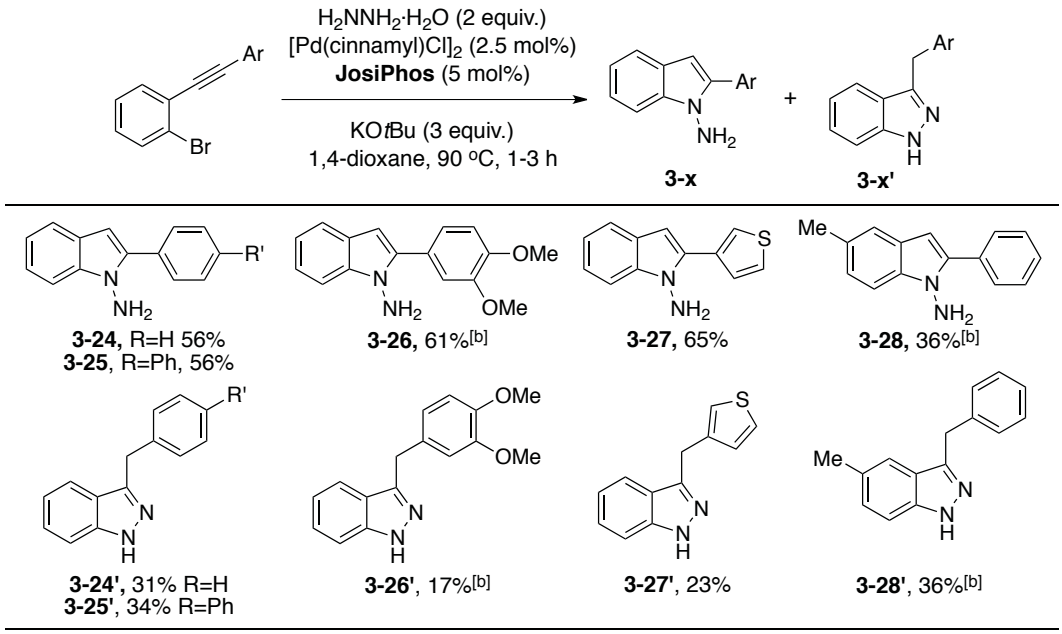
Figure 3.2 Scope of the Pd-catalyzed cross-coupling of ammonia or methylamine with 2-alkynylbromoarenes.[a]

Brief examination of the reactivity of substrates with substitution on the bromoarene resulted in 4, 5, or 6-substituted indoles in generally good yields, including product **3-7** - a viable precursor for further metal-catalyzed cross-coupling. While for convenience an inert atmosphere glovebox was employed for the setup of most catalytic experiments, use of a glovebox is not necessary. For example, in the reaction of **3-1**, the catalyst components and base could be weighed out in air and placed under dinitrogen prior to introduction of the reactants and solvent to give **3-2** in 84% yield, as observed by use of GC analysis methods.

Some limitations of this indole synthesis were established during substrate scope studies. Heterocyclic coupling partners with the heteroatom *ortho* to the bromo or alkyne group gave low yields. The reactions appears limited to aryl-substituted alkyne groups, as replacement at this position (R', Figure 3.2) with silyl (TMS), alkyl (propyl or hexyl) or alkenyl groups resulted in degradation of the starting material without significant product formation.

Given the success of the Pd/JosiPhos system to deliver NH-indoles from ammonia, other challenging amine partners were tested in order to expand the scope of the reaction. Methylamine[27a, 38, 65] could be employed to directly prepare N-methylated indoles, with yields similar to those of ammonia for select substrates (Figure 3.2, **3-18** to **3-23**). Notably, dihalogenated indole **3-18** was obtained using a two-step one-pot procedure, in which amine cross-coupling was first achieved by using Cs_2CO_3 as base followed by treatment with KO*t*Bu to mediate cyclization to indole. These results, combined with the comprehensive studies of Hartwig,[5, 31b, 31c, 36, 44, 64b-d] suggest that Pd/JosiPhos mixtures may have broad-ranging scope for tandem cross-coupling/cyclization reactions to yield N-functionalized indoles.

The first example of Pd-catalyzed hydrazine cross-coupling to generate aryl hydrazines was recently reported by the Stradiotto group,[62b] and in applying hydrazine hydrate in this chemistry, N-substituted amino indoles were successfully formed from 2-bromophenylalkynes (Figure 3.3).[66-67] Under the standard conditions using 5 mol% Pd, the N-aminoindole **3-24** was formed in 56% yield, along with indazole product **3-24'** (31%) after 1 h. Attempts to bias the product ratio by altering the base, solvent or including additives ($CuCl_2$ or Ag_2CO_3) were not successful. A brief survey of additional substrates proved other N-aminoindoles could be formed in moderate yields (36-65%). Given the difficulties associated with the use of hydrazine as a nitrogen-source in cross-coupling reactions, this transformation represents a significant contribution towards the establishment of direct routes to hydrazine-derived heterocycles.



[a] Standard conditions: 0.5 mmol scale, [Pd]/L = 1:1, N_2H_4•H_2O = 1.0 mmol, KO*t*Bu = 1.5 mmol, 90 °C in 1,4-dioxane. [b] ^{1}H NMR yield relative to 1,3,5-trimethoxybenzene.

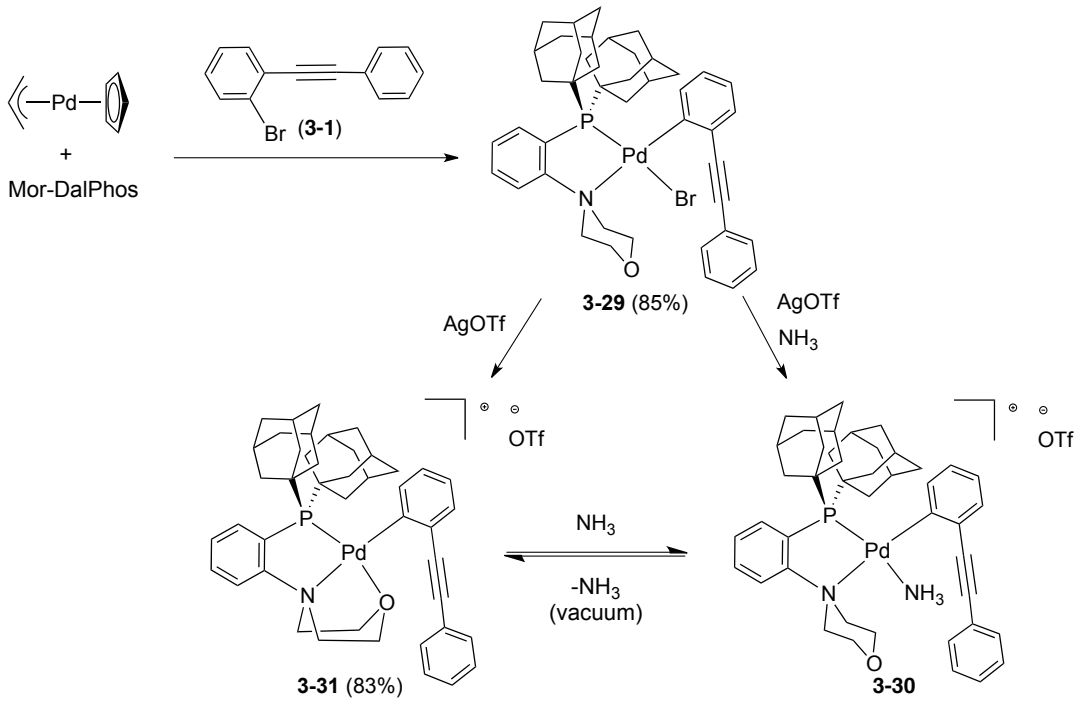
Figure 3.3 Pd-catalyzed cross-coupling of hydrazine with 2-alkynylbromoarenes.[a]

3.3 Stoichiometric Reactivity Relevant to the Palladium/Mor-DalPhos-Catalyzed Cross-Coupling of Ammonia and 1-Bromo-2-(phenylethynyl)benzene

In an effort to shed some light on the divergent behaviour of Mor-DalPhos and JosiPhos in this catalytic chemistry, a brief stoichiometric reactivity survey relevant to the Mor-DalPhos/Pd-catalyzed cross-coupling of ammonia and bromoalkynylarene **3-1** was performed, including selected comparisons to the analogous JosiPhos-based catalyst system. The results of these studies include the unique observation of a κ^3-P,N,O binding mode for the Mor-DalPhos ligand.

As previously discussed, the oxidative addition of aryl halides to *in situ* generated (Mor-DalPhos)Pd^0 species has been shown to occur under mild conditions, and the arylation of ammonia using this catalyst system proceeds smoothly with *ortho*-substituted aryl halides other than bromoalkynylarenes (see Chapter 2). Given these observations, attention was initially focused on examining the spectroscopic and structural features of the product obtained from C-Br oxidative addition of **3-1** to (Mor-DalPhos)Pd^0, in an effort to assess whether alkyne coordination to Pd(II) in this putative catalytic

intermediate might underpin the relatively poor performance of the Mor-DalPhos/Pd system with this substrate. Treatment of [CpPd(allyl)] with Mor-DalPhos in the presence of **3-1** in THF solution afforded the desired complex **3-29** as an analytically pure beige solid in 85% isolated yield (Scheme 3.3).



Scheme 3.3 Synthesis and reactivity of an oxidative addition complex featuring an alkynyl aryl group.

Solution NMR spectroscopic characterization data support the identity of **3-29** as being the expected square-planar complex, devoid of any significant Pd···alkyne interactions. Indeed, the alkyne carbon ^{13}C NMR chemical shifts observed for **3-29** (90.0 and 97.0 ppm) are only very modestly downfield of those of **3-1** (88.0 and 93.9 ppm). The crystallographic characterization of **3-29** corroborates these solution NMR data; an ORTEP diagram is presented in Figure 3.4, which confirms the κ^2-P,N nature of the Mor-DalPhos ligand, the trans disposition of Br and P as well as that of C and N (in keeping with the greater trans-directing abilities of P relative to N), and the notably long Pd···alkyne contacts (3.200(3) and 3.891(3) Å).

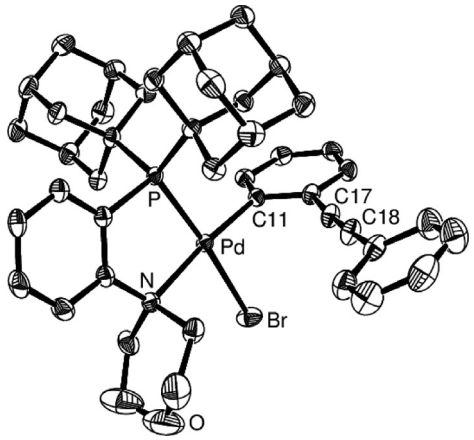


Figure 3.4 ORTEP diagram of **3-29**·CH_2Cl_2 shown with 50% displacement ellipsoids. All hydrogen atoms and the dichloromethane solvate have been omitted for clarity. Selected interatomic distances (Å): Pd-P, 2.2681(7); Pd-N, 2.232(2); Pd-Br 2.5154(4); Pd-C11, 2.011(3); Pd···C17, 3.200(3); Pd···C18, 3.891(3).

The Stradiotto group has demonstrated previously that treatment of [(κ^2-*P,N*-Mor-DalPhos)Pd(Ar)Cl] (Ar = Ph (**2-1**), 4-$MeOC_6H_4$) with AgOTf in the presence of 3 equiv. of ammonia in a mixture of dichloromethane and 1,4-dioxane affords isolable cationic ammine complexes that resist loss of ammonia upon exposure to vacuum (see Section 2.2).[49] Under similar conditions **3-29** is transformed cleanly into the analogous cationic ammine complex **3-30** (Scheme 3.3). In monitoring the progress of the reaction by using ^{31}P NMR spectroscopic methods, the disappearance of **3-29** (56.3 ppm) is accompanied by the clean formation of **3-30** (62.6 ppm); the ammine ligand in **3-30** gives rise to a broad ^{1}H NMR resonance at 2.82 ppm. However, efforts to isolate **3-30** via removal of the reaction solvent in vacuo resulted in a decrease in the intensity of the ^{31}P NMR resonance associated with **3-30** and the appearance of a single new phosphorus-containing species (**3-31**; δ (^{31}P) 80.0). Efforts to generate **3-31** rationally were successful via the addition of AgOTf to **3-29** in the absence of ammonia, and in turn **3-31** was isolated as an analytically pure dark yellow solid in 83% isolated yield. Treatment of solutions of **3-31** with 3 equiv. of ammonia resulted in the clean regeneration of the ammine adduct **3-30**, as observed in the ^{31}P NMR spectrum of the reaction mixture. The observed propensity of **3-30** to release ammonia differs from the earlier discussed complex [(κ^2-*P,N*-Mor-DalPhos)Pd(Ph)(NH_3)]OTf (**2-4**) – a phenomenon that was initially attributed to the possible competitive binding of the alkyne fragment to Pd, leading to **3-31**. However, as in **3-29**, the frequencies of the ^{13}C NMR resonances

associated with the alkyne carbons in **3-31** (93.7 and 90.1 ppm) are inconsistent with the existence of significant Pd···alkyne interactions. The crystallographic characterization of **3-31** is in keeping with this assertion; an ORTEP diagram of this complex is presented in Figure 3.5.

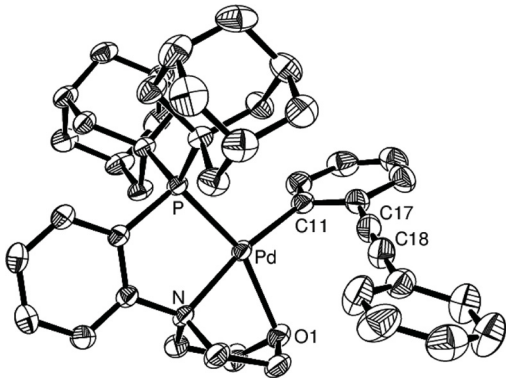
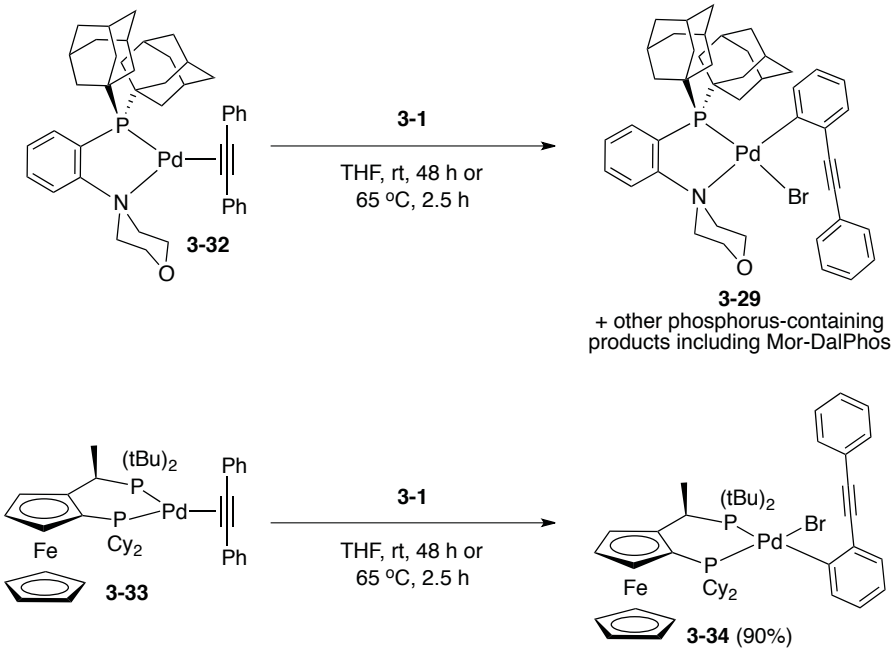


Figure 3.5 ORTEP diagram of **3-31**·OEt_2 shown with 50% displacement ellipsoids. All hydrogen atoms, the diethyl ether solvate, and the triflate counteranion have been omitted for clarity. Selected interatomic distances (Å): Pd-P, 2.2264(7); Pd-N, 2.106(3); Pd-O, 2.246(2); Pd-C11, 1.997(3); Pd···C17, 3.148(4); Pd···C18, 3.790(4).

The Pd···alkyne distances in **3-31** (3.148(4) and 3.790(4) Å), while statistically shorter than the related contacts in **3-29**, can still be viewed as being sufficiently long so as to preclude significant Pd···alkyne bonding interactions. Rather, the coordinative and electronic unsaturation that results from the loss of ammonia in **3-30** is instead apparently compensated by the Mor-DalPhos ligand adopting a tridentate κ^3-P,N,O binding motif, as was also the case with **2-5**. On the basis of these observations, it appears that the congestion imposed by the *o*-(phenylethynyl)phenyl ligand, rather than the propensity of this fragment to engage in π-bonding to Pd, may represent the primary factor leading to the loss of ammonia and the formation of **3-31**. It is unclear whether cationic ammonia adducts analogous to **3-30**, arising from the displacement of (pseudo)halide (X) on Pd by ammonia in Ar-X oxidative addition products such as **3-29**, represent important reactive intermediates in the Mor-DalPhos/Pd-catalyzed cross-coupling of ammonia with **3-1** or other aryl (pseudo)halides. However, should such intermediates be accessible, the ability of the Mor-DalPhos ligand to adopt a κ^3-P,N,O binding motif in response to the loss of ammonia promoted by the presence of a sterically demanding Pd-Ar ligand (such as *o*-(phenylethynyl)phenyl) may contribute in part to the inferior catalytic performance of

the Mor-DalPhos/Pd catalyst system, relative to catalysts featuring ligands that are not obviously capable of tridentate coordination (e.g. JosiPhos).

The diminished performance of the Pd/Mor-DalPhos catalyst in the monoarylation of ammonia when using **3-1** in comparison to (for example) PhBr is not likely attributable to the C-N reductive elimination step, given that the more sterically demanding aryl group in **3-1** should promote reductive elimination in a putative intermediate of the type [(κ^2-*P,N*-Mor-DalPhos)Pd(NH_2)(Ar)]. Alkyne coordination to (Mor-DalPhos)Pd^0 species generated following C-N reductive elimination involving substrate **3-1**, the derived aniline prior to cyclization, and/or the diphenylacetylene that is formed as a byproduct in the catalysis (*vide supra*) might also inhibit the Pd/Mor-DalPhos catalyst system. As such, attention was focused on examining the efficiency of C-Br oxidative addition of **3-1** to the [L_2Pd(PhCCPh)] complexes **3-32** (L_2 = Mor-DalPhos) and **3-33** (L_2 = JosiPhos) to give the Pd^{II} products **3-29** and **3-34**, respectively (Scheme 3.4).



Scheme 3.4 C-Br oxidative addition for comparison of Mor-DalPhos and JosiPhos Pd complexes.

In monitoring the reaction of the JosiPhos complex **3-33** with 1 equiv. of **3-1** in THF at room temperature (over 48 h) or 65 °C (over 2.5 h), clean conversion to the anticipated oxidative addition product **3-34** was observed by use of ^{31}P NMR methods.

The identity of **3-34** was confirmed via independent synthesis; the addition of **3-1** to a mixture of JosiPhos and [CpPd(allyl)] afforded compound **3-34** as an analytically pure solid in 90% isolated yield as a single isomer on the basis of NMR spectroscopic data. The assigned stereochemistry of **3-34** is given by analogy with the crystallographically characterized analogue [(κ^2-*P,P*-JosiPhos)Pd(Br)(Ph)], which features Br trans to the PCy_2 group.[68]

Treatment of the Mor-DalPhos precursor **3-32** with **3-1** under analogous experimental conditions resulted in the consumption of **3-32**, along with the formation of multiple phosphorus-containing species, including the target oxidative addition product **3-29** and free Mor-DalPhos ligand. These observations qualitatively suggest that the comparatively poor catalytic performance of Mor-DalPhos/Pd mixtures, relative to the JosiPhos-based catalyst, in the monoarylation of **3-1** and relative derivatives may be attributable in part to the inefficiency with which putative [(Mor-DalPhos)Pd(alkyne)] species re-enter the catalytic cycle via Ar-X oxidative addition.

3.4 Summary and Conclusions

This chapter first discussed the development of a straightforward method for the synthesis of 2-arylindoles directly from ammonia through a tandem cross-coupling/alkyne hydroamination sequence. The challenging amine partners, methylamine and hydrazine, were also shown to form indole-type structures using the optimal Pd/JosiPhos catalyst system. Considering the unusually poor activity of Mor-DalPhos in this amination chemistry (<50% isolated yield of **3-2**), further studies were executed to seek out a mechanistic explanation for the difference in catalytic activity of JosiPhos versus Mor-DalPhos in the indole synthesis. Thus, efforts to identify possible modes of Mor-DalPhos/Pd catalyst inhibition were also explained when using alkynyl substrate **3-1** for the monoarylation of ammonia. In the course of these studies, neither the oxidative addition product **3-29** nor the corresponding product derived from bromide abstraction using AgOTf (**3-31**) featured significant Pd···alkyne interactions in solution or the solid state. These observations would appear to rule out substrate inhibition arising from intramolecular alkyne coordination to Pd following C-Br oxidative addition. The ability of Mor-DalPhos to adopt a tridentate structure in **3-31** similar to **2-5** was identified and

may play a role in Pd-catalyzed amination processes, especially where the (pseudo)halide ligand is labile. Although cationic ammine complex **2-4** is an isolable complex that resists loss of ammonia upon prolonged exposure to vacuum, the more facile loss of ammonia from **3-30** to give **3-31** precluded the isolation of **3-30**. It is feasible that the capacity of the Mor-DalPhos ligand to adopt a κ^3-P,N,O binding motif in response to the loss of ammonia promoted by the sterically demanding Pd-(arylalkyne) (**3-1**) ligand could contribute to the challenges encountered with this or similar substrates when using the Mor-DalPhos/Pd catalyst system. Finally, in contrast to the clean C-Br oxidative addition of **3-1** to [(JosiPhos)Pd(alkyne)] complex **3-33** that was observed (giving **3-34**), the analogous chemistry involving [(Mor-DalPhos)Pd(alkyne)] (**3-32**) afforded the target oxidative addition product **3-29**, accompanied by the generation of free Mor-DalPhos and other unknown phosphorus-containing species. These observations suggest that the inefficiency with which putative [(Mor-DalPhos)Pd(alkyne)] species re-enter the catalytic cycle via C-Br oxidative addition may also contribute to the observed inferior performance of Mor-DalPhos/Pd versus JosiPhos/Pd catalyst systems in the BHA of **3-1** using ammonia.

3.5 Experimental Section

3.5.1 General Considerations

All manipulations were conducted under dinitrogen within an inert atmosphere glovebox, utilizing glassware that was oven-dried (130 ºC) and evacuated while hot prior to use. Toluene, pentane, and dichloromethane were deoxygenated by sparging with dinitrogen followed by passage through a double column solvent purification system purchased from MBraun Inc. equipped either with one alumina-packed column and one column packed with copper-Q5 reactant (pentane), or two alumina-packed columns (dichloromethane). THF, 1,4-dioxane, and diethyl ether were each dried over Na/benzophenone followed by distillation under an atmosphere of dinitrogen. Deuterated solvents (Cambridge Isotopes), used for characterization of Pd complexes, were degassed by using three repeated freeze-pump-thaw cycles and stored over 4 Å molecular sieves for 24 h prior to use. All solvents were stored under dinitrogen over activated 4 Å molecular sieves. $[Pd(cinnamyl)Cl]_2$,[56] Mor-DalPhos,[49] and [CpPd(allyl)][55] were

prepared according to literature procedures. Silver trifluoromethanesulfonate (Strem), CyPF*t*Bu-JosiPhos (Solvias), diphenylacetylene (Aldrich) and 0.5 M solutions of ammonia in 1,4-dioxane (Aldrich) were used as received. Each of the 2-alkynylbromoarene substrates (including **3-1**) were prepared by using literature synthetic protocols involving Sonogashira reactions of aryl iodides[69] or bromides[70] with appropriate terminal alkyne precursors. Ammonia cross-coupling reactions were best conducted with fresh bottles (<2 weeks after opening) of 0.5 M NH_3 in 1,4 dioxane. All methylamine cross-coupling reactions were conducted with 2.0 M $MeNH_2$ in THF, and all hydrazine reactions were conducted with 98% $N_2H_4 \cdot H_2O$. Column chromatography was carried out using Silicycle SiliaFlash 60 with particle size 40-63 μm (230-400 mesh). Conversions and yields based on gas chromatography data were corrected by calibration with internal standards of dodecane and product identity was confirmed on the basis of ^1H NMR and/or by comparison with authentic samples. ^1H, ^{13}C, and ^{31}P NMR characterization data were collected at 300K on a Bruker AV-500 spectrometer operating at 500.1, 125.8, and 202.5 MHz (respectively) with chemical shifts reported in parts per million downfield of $SiMe_4$ (for ^1H and ^{13}C) and 85% H_3PO_4 in D_2O (for ^{31}P). Structural elucidation was enabled through analysis of ^1H-^1H COSY, ^1H-^{13}C HSQC, ^1H-^{13}C HMBC, and DEPTQ-135 data. In some cases, fewer than expected unique ^{13}C NMR resonances were observed, despite prolonged acquisition times, and the OTf signals are not assigned. Elemental analyses were performed by Canadian Microanalytical Service Ltd., Delta, BC (Canada) and Midwest Microlab, LLC, Indianapolis, IN (USA).

3.5.2 Synthesis and Characterization Data

1-Bromo-2-(phenylethynyl)benzene (3-1): A screw-cap vial was charged with $Pd(PPh_3)_2Cl_2$ (0.01 equiv.) and CuI (0.05 equiv.). The vial was sealed with a cap containing a PTFE septum and removed from the glovebox, followed by addition of 1-bromo-2-iodobenzene (1.00 mL, 8.00 mmol), phenylacetylene (1.03 mL, 9.60 mmol) and Et_3N ([ArI]=0.3 M) via syringe. The solution was allowed to stir at room temperature and the reaction progress was monitored by use of TLC. After complete consumption of the aryl iodide (12-24 h), the reaction was filtered over a plug of Celite onto which a thin layer of silica had been deposited. The collected filtrate was diluted with EtOAc (50 mL)

and washed with 1M HCl (1 x 70 mL) and 1:1 water:brine (1 x 70 mL). The organic fractions were dried with Na_2SO_4, concentrated to dryness and the residue was purified by use of column chromatography eluting with hexanes to yield a colourless oil (**3-1**) in quantitative yield. ^{1}H NMR ($CDCl_3$): δ 7.64-7.55 (m, 4H), 7.39-7.36 (m, 3H), 7.30 (td, *J* = 1.2, 7.5 Hz, 1H), 7.19 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 133.2, 132.4, 131.7, 129.4, 128.6, 128.4, 127.0, 125.6, 125.4, 122.9, 93.9, 88.0.

Tandem reaction of ammonia with *o*-alkynylaryl bromides to form NH-indoles:
From a stock solution in 1,4-dioxane, 3.2 mg (0.00625 mmol, 1.25 mol%) of [Pd(cinnamyl)Cl]$_2$ was added to a vial containing the Josiphos ligand CyPF*t*Bu (6.9 mg, 0.0125 mmol, 2.50 mol%). The mixture was diluted to 2.000 mL with additional 1,4-dioxane and then stirred for 2 minutes. To this solution was added KO*t*Bu (168 mg, 1.5 mmol), the mixture was stirred briefly and 1-bromo-2-(phenylethynyl)benzene (128.6 mg, 0.5 mmol) was added in 3 x 1 mL portions of 1,4-dioxane. The vial was sealed with a cap containing a PTFE septum and removed from the glovebox, followed by the addition of NH_3 as a 0.5 M solution in 1,4-dioxane (3.000 mL, 1.5 mmol). The solution was heated at 90 ^oC and the reaction progress was monitored by use of TLC or GC methods. After complete consumption of the aryl bromide (3 h), the reaction was cooled, diluted with EtOAc (40 mL) and washed with water (60 mL) followed by 1:1 water/brine (60 mL). The organic fractions were dried with Na_2SO_4, filtered and silica powder (0.5-1.0 g) was added to the crude material. The solvent was removed from the silica-product mixture and the compound was purified by column chromatography with 5% EtOAc/hexanes to afford 2-phenyl-1*H*-indole (**3-2**) as a yellow solid in 84% yield (81 mg, 0.42 mmol).

2-phenyl-1*H*-indole (3-2). ^{1}H NMR ($CDCl_3$): δ 8.33 (br s, 1H, NH), 7.68-7.64 (m, 3H), 7.47-7.44 (m, 2H), 7.41 (m, 1H), 7.34 (m, 1H), 7.21 (m, 1H), 7.14 (m, 1H), 6.85 (dd, *J* = 1.0, 2.2 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 137.8, 136.8, 132.3, 129.2, 129.0, 127.7, 125.1, 122.3, 120.7, 120.3, 110.9, 100.0. Agrees with data previously reported in the literature.[61c]

2-(4-methylphenyl)-1*H*-indole (3-3). The representative protocol was followed to afford the product as a yellow solid in 89% yield (92 mg, 0.44 mmol). ^{1}H NMR ($CDCl_3$): δ 8.29 (br s, 1H), 7.63 (m, 1H), 7.58-56 (m, 2H), 7.40 (m, 1H), 7.27-7.25 (m, 2H), 7.19 (m, 1H), 7.13 (m, 1H), 6.80 (dd, J = 0.9, 2.1 Hz, 1H), 2.41 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 138.0, 137.6, 136.6, 129.7, 129.5, 129.3, 125.0, 122.1, 120.5, 120.2, 110.8, 99.4, 21.2. Agrees with data previously reported in the literature.[72]

2-(3-thienyl)-1*H*-indole (3-4). The representative protocol was followed to afford the product as a beige solid in 85% yield (85 mg, 0.43 mmol). ^{1}H NMR ($CDCl_3$): δ 8.22 (br s, 1H), 7.62 (m, 1H), 7.43-7.41 (m, 3H), 7.39 (m, 1H), 7.20 (m, 1H), 7.13 (m, 1H), 6.71 (dd, J = 0.9, 2.1 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 136.4, 134.1, 134.0, 129.0, 126.7, 125.7, 122.3, 120.6, 120.3, 119.1, 110.7, 99.9. Agrees with data previously reported in the literature.[73]

6-fluoro-2-phenyl-1*H*-indole (3-5): The representative protocol was followed to afford the product as a yellow solid in 69% yield (73 mg, 0.35 mmol). ^{1}H NMR (CD_3OD): δ 7.66-7.64 (m, 2H), 7.37 (dd, J = 5.4, 8.7 Hz, 1H), 7.33-7.29 (m, 2H), 7.18 (m, 1H), 6.97 (dd, J = 2.3, 9.8 Hz, 1H), 6.70-6.66 (m, 2H). The N-H proton is not visible due to exchange with the deuterated solvent; $^{13}C\{^{1}H\}$ NMR (CD_3OD): 161.4 (d, J_{CF} = 236.3 Hz), 140.2, 138.9 (d, J_{CF} = 13.4 Hz), 134.1, 130.1, 128.5, 127.4, 126.1, 122.1 (d, J_{CF} = 10.1 Hz), 109.0 (d, J_{CF} = 24.9 Hz), 99.8, 98.1 (d, J_{CF} = 26.1 Hz). HRMS (ESI/$[M+H]^+$) calcd. for $C_{14}H_{11}FN$: 211.0870. Found: 212.0877.

5-methyl-2-phenyl-1*H*-indole (3-6). The representative protocol was followed using 2.5 mol% $[Pd(cinnamyl)Cl]_2$ (6.5 mg, 0.0125 mmol) and 5 mol% Josiphos (13.9 mg, 0.025 mmol) to afford the product as a yellow solid in 80% yield (84 mg, 0.40 mmol). ^{1}H NMR ($CDCl_3$): δ 8.24 (br s, 1H), 7.67-7.65 (m, 2H), 7.46-7.41 (m, 3H), 7.33-7.29 (m, 2H), 7.02 (dd, J = 1.3, 8.3 Hz, 1H), 6.76 (dd, J = 0.9, 2.2 Hz, 1H), 2.45 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 137.9, 135.1, 132.5, 129.5, 129.5, 129.0, 127.6, 125.0, 124.0, 120.3, 110.5, 99.5, 21.5. Agrees with data previously reported in the literature.[74]

4-bromo-6-methyl-2-phenyl-1*H*-indole (3-7). The representative protocol was followed using 10% EtOAc/hexanes for column chromatography to afford the product as a beige solid in 66% yield (94 mg, 0.33 mmol). ^{1}H NMR ($CDCl_3$): δ 8.32 (br s, 1H), 7.67-7.64 (m, 2H), 7.47-7.43 (m, 2H), 7.34 (m, 1H), 7.13 (dd, *J* = 0.5, 1.1 Hz, 1H), 7.12 (m, 1H), 6.82 (dd, *J* = 0.9, 3.2 Hz, 1H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 137.8, 137.2, 133.5, 131.9, 129.1, 127.9, 127.9, 125.1, 124.7, 114.1, 110.1, 99.9, 21.5. HRMS (ESI/[M+H]+) calcd. for $C_{15}H_{13}BrN$: 286.0226. Found: 286.0223.

***tert*-butyl-3-(1*H*-indol-2-yl)phenylcarbamate (3-8).** The representative protocol was followed using 3.5 equiv. of KO*t*Bu (196.4 mg, 1.75 mmol) and 10% EtOAc/hexanes for column chromatography to afford the product as a beige solid in 63% yield (97 mg, 0.31 mmol). ^{1}H NMR ($CDCl_3$): δ 8.44 (br s, 1H), 7.90 (br s, 1H), 7.62 (dd, *J* = 0.8, 7.9 Hz, 1H), 7.39 (dd, *J* = 0.9, 8.1 Hz, 1H), 7.88-7.32 (m, 2H), 7.19 (m, 1H), 7.14-7.10 (m, 2H), 6.83 (dd, *J* = 0.9, 2.1 Hz, 1H), 6.57 (br s, 1H), 1.56 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 152.8, 139.0, 137.6, 136.8, 133.2, 129.5, 129.1, 122.3, 120.6, 120.1, 120.0, 117.5, 114.8, 111.0, 100.1, 80.8, 28.3. HRMS (ESI/[M+H]+) calcd. for $C_{19}H_{21}N_2O_2$: 308.1598. Found: 309.1602.

2-(3,4-dimethoxyphenyl)-1*H*-indole (3-9). The representative protocol was followed using 20% EtOAc/hexanes for column chromatography to afford the product as a beige solid in 88% yield (111 mg, 0.44 mmol).^{1}H NMR (CD_3OD): δ 7.50 (m, 1H), 7.39 (d, *J* = 2.1 Hz, 1H), 7.37-7.35 (m, 2H), 7.06 (m, 1H), 7.01-6.96 (m, 2H), 6.70 (d, *J* = 0.8 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H). The N-H proton is not visible due to exchange with the deuterated solvent; ^{13}C{^{1}H} NMR (CD_3OD): δ 150.9, 150.2, 139.6, 138.9, 130.9, 127.8, 122.5, 121.0, 120.5, 119.2, 113.4, 112.0, 110.4, 99.0, 56.7, 56.7. Agrees with data previously reported in the literature.[75]

2-(2-hydroxyphenyl)-1*H*-indole (3-10). The representative protocol was followed using the TBS-protected substrate as starting material and 10% EtOAc/hexanes for column chromatography to afford the product as a yellow solid in 49% yield (51 mg, 0.24 mmol).

^{1}H NMR ($CDCl_3$): δ 9.24 (br s, 1H), 7.70 (dd, *J* =1.6, 7.8 Hz, 1H), 7.66 (m, 1H), 7.42 (m, 1H), 7.23-7.20 (m, 2H), 7.15 (m, 1H), 7.04 (m, 1H), 6.92 (dd, *J* = 1.0, 8.1 Hz, 1H), 6.87 (dd, *J* = 0.9, 2.2 Hz, 1H), 5.62 (br s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 151.9, 136.4, 134.8, 128.9, 128.3, 128.3, 122.2, 121.5, 120.4, 120.1, 119.1, 116.5, 111.0, 100.1. Agrees with data previously reported in the literature.[76]

2-(2-(benzyloxy)phenyl)-1H-indole (3-11). The representative protocol was followed using 5-20% EtOAc/hexanes for column chromatography to enable the isolation of the product as a yellow solid in 53% combined yield (80 mg, 0.27 mmol). **3-10** was also isolated from the reaction as a light brown solid in 34% yield (36 mg, 0.17 mmol).
^{1}H NMR ($CDCl_3$): δ 9.76 (br s, 1H), 7.90 (dd, *J* = 1.5, 7.7 Hz, 1H), 7.64 (m, 1H), 7.53-7.51 (m, 2H), 7.49-7.42 (m, 3H), 7.29 (m, 1H), 7.19 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.16-7.08 (m, 4H), 6.94 (dd, *J* = 0.8, 2.2 Hz, 1H), 5.24 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 154.9, 136.3, 136.0, 135.8, 128.9, 128.6, 128.5, 128.3, 127.9, 127.7, 121.9, 121.7, 121.0, 120.2, 119.7, 113.5, 110.8, 99.7, 71.3. HRMS (ESI/[M+H]+) calcd. for $C_{21}H_{18}NO$: 300.1383. Found 300.1377.

2-(3-pyridyl)-1*H*-indole (3-12). The representative protocol was followed using 2.5 mol% [Pd(cinnamyl)Cl]$_2$ (6.5 mg, 0.0125 mmol) and 5 mol% Josiphos (13.9 mg, 0.025 mmol) with heating for 4 h. The crude material was purified using column chromatography employing 50% EtOAc/hexanes to afford the product as a beige solid in 61% yield (59 mg, 0.30 mmol). ^{1}H NMR (CD_3OD): δ 8.97 (d, *J* = 1.8 Hz, 1H), 8.42 (dd, *J* = 1.3, 4.8 Hz, 1H), 8.19 (m, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.47 (ddd, *J* = 0.6, 4.8, 8.0 Hz, 1H), 7.41 (dd, *J* = 0.8, 8.2 Hz, 1H), 7.16-7.12 (m, 1H), 7.02 (m, 1H), 6.93 (d, *J* = 0.7 Hz, 1H). The N-H proton is not visible due to exchange with the deuterated solvent; ^{13}C{^{1}H} NMR (CD_3OD): δ 148.4, 146.8, 139.4, 135.4, 134.3, 131.1, 130.5, 125.6, 123.7, 121.7, 121.0, 112.4, 101.6. Agrees with data previously reported in the literature.[77]

2-(4-biphenyl)-1*H*-indole (3-13). The representative protocol was followed to obtain the crude material, which was washed with dichloromethane (50 mL) to afford the pure product as a light brown solid in 78% yield (105 mg, 0.39 mmol). ^{1}H NMR ((CD_3)$_2$SO):

δ 11.59 (br s, 1H), 7.96 (d, *J* = 8.0 Hz, 2H), 7.74 (dd, *J* = 7.9, 18.2 Hz, 4H), 7.55-7.36 (m, 5H), 7.12 (m, 1H), 7.01 (m, 1H), 6.96 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($(CD_3)_2SO$): δ 139.5, 138.8, 137.2, 131.3, 129.0, 128.7, 127.5, 127.1, 126.4, 125.5, 121.6, 120.0, 119.4, 111.3, 98.9. HRMS (ESI/[M+H]+) calcd. for $C_{20}H_{16}N$: 270.1277. Found 270.1272.

2-(4-chlorophenyl)-1*H*-indole (3-14). The representative protocol was followed using 2.5 mol% $[Pd(cinnamyl)Cl]_2$ (6.5 mg, 0.0125 mmol) and 5 mol% Josiphos (13.9 mg, 0.025 mmol) to afford the product as a yellow solid in 84% yield (96 mg, 0.42 mmol). ^{1}H NMR ($CDCl_3$): δ 8.28 (br s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.60-7.57 (m, 2H), 7.43-7.40 (m, 3H), 7.22 (m, 1H), 7.14 (m, 1H), 6.82 (m, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 136.9, 136.7, 133.4, 130.9, 129.2, 129.1, 126.3, 122.7, 120.7, 120.5, 110.9, 100.4. Agrees with data previously reported in the literature.[61c]

2-mesityl-1*H*-indole (3-15): The representative protocol was followed using 6.0 equiv. of KO*t*Bu (336.6 mg, 3.00 mmol) at 110 ^{o}C for 60 h. The crude product was purified using 2% EtOAc/hexanes for column chromatography to afford the product as a yellow solid. This solid was initially washed followed by recrystallization using hexanes to give the pure product as a white solid in 75% combined yield (88 mg, 0.37 mmol). ^{1}H NMR ($CDCl_3$): δ 7.86 (br s, 1H), 7.68 (m, 1H), 7.41 (ddd, *J* = 0.9, 1.8, 8.0 Hz, 1H), 7.22 (m, 1H), 7.17 (m, 1H), 7.00 (d, *J* = 0.6 Hz, 2H), 6.41 (dd, *J* = 0.9, 2.2 Hz, 1H), 2.38 (s, 3H), 2.18 (s, 6H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 138.2, 138.2, 136.2, 135.9, 130.0, 128.8, 128.1, 121.4, 120.3, 119.7, 110.6, 102.6, 21.1, 20.4. HRMS (ESI/[M+H]+) calcd. for $C_{17}H_{18}N$: 236.1434. Found 236.1433.

2-(1-naphthenyl)-1*H*-indole (3-16). The representative protocol was followed using 2% EtOAc/hexanes for column chromatography to afford the product as an orange solid in 74% yield (90 mg, 0.37 mmol). ^{1}H NMR ($CDCl_3$): δ 8.34 (m, 1H), 8.30 (br s, 1H), 7.94 (m, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.73 (m, 1H), 7.65 (dd, *J* = 1.2, 7.1 Hz, 1H), 7.57-7.51 (m, 3H), 7.46 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.27 (m, 1H), 7.21 (m, 1H), 6.82 (dd, *J* = 0.9, 2.1 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 136.7, 136.3, 133.9, 131.5, 131.1, 128.8, 128.6,

128.5, 127.2, 126.7, 126.2, 125.7, 125.3, 122.2, 120.6, 120.2, 110.8, 103.7. Agrees with data previously reported in the literature.[78]

2-(4-(trifluoromethyl)phenyl)-1H-indole (3-17). The representative protocol was followed using 2.5 mol% $[Pd(cinnamyl)Cl]_2$ (6.5 mg, 0.0125 mmol) and 5 mol% Josiphos (13.9 mg, 0.025 mmol) with heating overnight. The crude material was purified using column chromatography employing 5% EtOAc/hexanes to afford the product as an off-white solid in 31% yield (41 mg, 0.16 mmol). ^{1}H NMR (CD_3OD): δ 7.95 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.41 (dd, J = 0.8, 8.2 Hz, 1H), 7.14 (m, 1H), 7.03 (m, 1H), 6.94 (s, 1H). The N-H proton is not visible due to exchange with the deuterated solvent; $^{13}C\{^1H\}$ NMR (CD_3OD): δ 139.4, 138.1, 137.6, 130.5, 129.8 (q, J_{CF} = 32.4 Hz), 126.9 (d, J_{CF} = 3.6 Hz), 126.5, 126.0 (q, J_{CF} = 270.8 Hz), 123.7, 121.8, 121.0, 112.5, 101.8. HRMS (ESI/[M+H]+) calcd. for $C_{15}H_{11}F_3N$: 262.0838. Found 262.0839.

2-(phenylethynyl)aniline (3-1'). The representative protocol was followed using 2.0 equiv. NaO*t*Bu (96.1 mg, 1.0 mmol) in place of KO*t*Bu to afford the product as a yellow solid in 89% yield (86 mg, 0.45 mmol). ^{1}H NMR ($CDCl_3$): δ 7.56-7.54 (m, 2H), 7.40-7.33 (m, 4H), 7.16 (m, 1H), 6.76-6.73 (m, 2H), 4.29 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 147.7, 132.1, 131.4, 129.7, 128.3, 128.2, 123.3, 117.9, 114.3, 107.9, 94.7, 85.9. Agrees with data previously reported in the literature.[63b]

Tandem reaction of methylamine with *o*-alkynylaryl bromides to form NMe-indoles: From a stock solution in toluene, 3.2 mg (0.00625 mmol, 1.25 mol%) of $[Pd(cinnamyl)Cl]_2$ was added to a vial containing Josiphos ligand CyPF*t*Bu (6.9 mg, 0.0125 mmol, 2.50 mol%) in 5.200 ml toluene followed by stirring for 2 minutes. To this solution was added KO*t*Bu (168.3 mg, 1.5 mmol). The mixture was stirred briefly and 1-bromo-2-(phenylethynyl)benzene (128.6 mg, 0.500 mmol) was added in portions using a total amount of 1.250 mL of toluene. The vial was sealed with a cap containing a PTFE septum and removed from the glovebox, followed by the addition of NH_2CH_3 as a 2.0 M solution in tetrahydrofuran (0.300 mL, 0.6 mmol). The solution was heated to 90 °C and

the reaction progress was monitored using by TLC or GC methods. After complete consumption of the aryl bromide (16-24 h), the reaction was cooled, diluted with EtOAc (40 mL) and washed with water (70 mL) followed by 1:1 water/brine (70 mL). The organic fractions were dried with Na_2SO_4, filtered and silica powder (0.5-1.0 g) was added to the crude material. The solvent was removed from the product-silica mixture and the compound was purified by column chromatography with hexanes to afford 1-methyl-2-phenyl-1*H*-indole (**3-19**) as a yellow solid in 88% yield (91 mg, 0.44 mmol).

1-methyl-2-phenyl-1*H*-indole (3-19). ^{1}H NMR ($CDCl_3$): δ 7.70-7.68 (m, 1H), 7.57-7.55 (m, 2H), 7.53-7.49 (m, 2H), 7.44 (m, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.30 (m, 1H), 7.20 (m, 1H), 6.62 (s, 1H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 141.9, 138.7, 133.2, 129.7, 128.8, 128.3, 128.2, 122.0, 120.8, 120.2, 109.9, 102.0, 31.5. Agrees with data previously reported in the literature.[79]

2-(3-chloro-5-fluorophenyl)-1-methyl-1*H*-indole (3-18). The representative protocol was followed using 4.0 equiv. Cs_2CO_3 (651.6 mg, 2.00 mmol) with heating overnight. A solution of 3.0 equiv. KO*t*Bu (168.3 mg, 1.5 mmol) in toluene was then added to the reaction mixture followed by heating overnight. The crude material was purified using column chromatography employing hexanes to afford the product as a yellow oil in 52% yield (68 mg, 0.26 mmol). ^{1}H NMR ($CDCl_3$): δ 7.65 (m, 1H), 7.38 (m, 1H), 7.32-7.28 (m, 2H), 7.18 (m, 1H), 7.15-7.12 (m, 2H), 6.61 (d, J = 0.5 Hz, 1H), 3.77 (s, 3H); ^{13}C DEPTQ-135 NMR ($CDCl_3$): δ 162.8 (d, J_{CF} = 250.0 Hz), 139.0, 136.2 (d, J_{CF} = 8.8 Hz), 135.5 (d, J_{CF} = 11.3 Hz), 128.0, 125.5, 125.4, 122.8, 121.2, 120.6, 115.8 (d, J_{CF} = 23.9 Hz), 114.9 (d, J_{CF} = 22.7 Hz), 110.1, 103.3, 31.7. HRMS (ESI/[M+H]+) calcd. for $C_{15}H_{12}ClFN$: 260.0637. Found: 260.0636.

1-methyl-2-(thiophen-3-yl)-1*H*-indole (3-20). The representative protocol was followed using column chromatography employing 0-2% EtOAc/hexanes to afford the product as a yellow solid in 86% yield (92 mg, 0.43 mmol). ^{1}H NMR ($CDCl_3$): δ 7.66 (m, 1H), 7.46 (m, 1H), 7.42 (dd, J = 1.5, 3 Hz, 1H), 7.38 (m, 1H), 7.32 (dd, J = 1.5, 5 Hz, 1H), 7.27 (m, 1H), 7.18 (m, 1H), 6.63 (d, J = 0.5 Hz, 1H), 3.82 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ

138.4, 136.7, 133.7, 128.8, 128.1, 126.2, 123.5, 122.0, 120.7, 120.2, 109.8, 101.8, 31.4. HRMS (ESI/[M+H]+) calcd. for $C_{13}H_{12}NS$: 214.0685. Found: 214.0686.

1,5-Dimethyl-2-phenyl-1*H*-indole (3-21). The representative protocol was followed using 2.5 mol% $[Pd(cinnamyl)Cl]_2$ (6.5 mg, 0.0125 mmol), 5 mol% Josiphos (13.9 mg, 0.025 mmol) and 0-5% EtOAc/hexanes for column chromatography to afford the product as a yellow solid in 78% yield (86 mg, 0.39 mmol). ^{1}H NMR ($CDCl_3$): δ 7.54-7.51 (m, 2H), 7.49-7.46 (m, 2H), 7.44 (m, 1H), 7.40 (m, 1H), 7.27 (m, 1H), 7.09 (dd, *J* = 1.5, 8.5 Hz, 1H), 6.51 (d *J* = 0.7 Hz, 1H), 3.74 (s, 3H), 2.49 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 142.0, 137.2, 133.3, 129.6, 129.4, 128.8, 128.5, 128.1, 123.6, 120.4, 109.6, 101.5, 31.6, 21.8. Agrees with data previously reported in the literature.[80]

***tert*-butyl-3-(1-methyl-1*H*-indol-2-yl)phenylcarbamate (3-22).** The representative protocol was followed using 4.0 equiv. of KOtBu (224.4 mg, 2.00 mmol) and 10% EtOAc/hexanes for column chromatography to afford the product as a yellow solid in 67% yield (108 mg, 0.34 mmol). ^{1}H NMR ($CDCl_3$): δ 7.64 (m, 1H), 7.54 (br s, 1H), 7.40-7.36 (m, 3H), 7.26 (m, 1H),7.20-7.15 (m, 2H), 6.59 (br s, 1H), 6.57 (s, 1H), 3.76 (s, 3H), 1.55 (s, 9H); ^{13}C{1H} NMR ($CDCl_3$): δ 153.0, 141.5, 138.9, 138.7, 133.9, 129.4, 128.2, 124.3, 122.0, 120.8, 120.2, 119.8, 188.3, 109.9, 102.1, 81.1, 31.6, 28.7. HRMS (ESI/[M+H]+) calcd. for $C_{20}H_{23}N_2O_2$: 323.1754. Found: 323.1767.

2-(3,4-dimethoxyphenyl)-1-methyl-1*H*-indole (3-23). The representative protocol was followed using 6.0 equiv. of KOtBu (224.4 mg, 2.00 mmol), heating overnight at 110 ^{o}C and 20% EtOAc/hexanes for column chromatography to afford the product as a light brown solid in 76% yield (101 mg, 0.38 mmol). ^{1}H NMR ($CDCl_3$): δ 7.64 (d, *J* = 8 Hz, 1H), 7.37 (d, *J* = 8 Hz, 1H), 7.25 (m, 1H), 7.16 (m, 1H), 7.08-7.04 (m, 2H), 6.98 (d, *J* = 8 Hz, 1H), 6.54 (s, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.75 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 149.3, 149.1, 141.8, 138.5, 128.2, 125.8, 122.2, 121.8, 120.6, 120.2, 113.0, 111.4, 109.9, 101.4, 56.3, 56.3, 31.4. HRMS (ESI/[M+H]+) calcd. for $C_{17}H_{18}NO_2$: 268.1332. Found: 268.1353.

Tandem reaction of hydrazine monohydrate with *o*-alkynylaryl bromides: From a stock solution in 1,4-dioxane, 6.5 mg (0.0125 mmol, 2.50 mol%) of $[Pd(cinnamyl)Cl]_2$ was added to a vial containing Josiphos ligand CyPF*t*Bu (13.8 mg, 0.0250 mmol, 5.0 mol%). The mixture was diluted to 2.000 mL with additional 1,4-dioxane and then was stirred for 2 minutes. To this solution was added KO*t*Bu (168 mg, 1.5 mmol), the mixture was stirred briefly and 1-bromo-2-(phenylethynyl)benzene was added in 3 x 1 mL portions of 1,4-dioxane. The vial was sealed with a cap containing a PTFE septum and removed from the glovebox, followed by the addition of $N_2H_4 \cdot H_2O$ (0.050 mL, 1.0 mmol). The solution was heated at 90 ^oC and the reaction progress was monitored by use of TLC methods. After complete consumption of the aryl bromide (1 h), the reaction was cooled, diluted with EtOAc (40 mL) and washed with water (70 mL) followed by 1:1 water/brine (70 mL). The organic fractions were dried with Na_2SO_4, filtered and silica powder (0.5-1.0 g) was added to the crude material. The solvent was removed and the compound was purified by column chromatography with 10-30% EtOAc/hexanes to afford 2-phenyl-1*H*-indol-1-amine (**3-24**) as a beige solid in 56% yield (58 mg, 0.28 mmol) and 2-phenyl-1*H*-indazole (**3-24'**) in 31% yield (32 mg, 0.15 mmol) also as a beige solid.

2-phenyl-1*H*-indol-1-amine (3-24). ^1H NMR ($CDCl_3$): δ 7.71-7.69 (m, 2H), 7.62 (d, J = 7.8 Hz, 1H), 7.50-7.47 (m, 3H), 7.40 (m, 1H), 7.28 (m, 1H), 7.17 (m, 1H), 6.57 (s, 1H), 4.50 (br s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 141.0, 138.6, 131.9, 129.2, 128.4, 127.8, 125.6, 122.1, 120.5, 120.3, 108.9, 99.7. HRMS (ESI/$[M+H]^+$) calcd. for $C_{14}H_{13}N_2$: 209.1073. Found: 209.1062.

3-benzyl-1*H*-indazole: (3-24'): ^1H NMR ($CDCl_3$): δ 10.43 (br s, 1H), 7.55 (dt, J = 1.0, 8.2 Hz, 1H), 7.41 (dt, J = 0.9, 8.4 Hz, 1H), 7.36-7.33 (m, 3H), 7.31-7.28 (m, 2H), 7.22 (m, 1H), 7.09 (m, 1H), 4.39 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 145.9, 141.3, 138.9, 128.8, 128.5, 126.8, 126.3, 122.1, 120.5, 120.4, 109.8, 33.7. HRMS (ESI/$[M+H]^+$) calcd. for $C_{14}H_{13}N_2$: 209.1073. Found: 209.1070.

2-(biphenyl-4-yl)-1*H*-indol-1-amine: (3-25). The representative protocol was followed

using 5-40% EtOAc/hexanes for column chromatography to afford the indole as a beige solid in 56% yield (79 mg, 0.28 mmol) and the indazole as a beige solid in 34% yield (48 mg, 0.17 mmol). ^{1}H NMR ($(CD_3)_2SO$): δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.78-7.74 (m, 4H), 7.55 (t, *J* = 8.0 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.40 (m, 1H), 7.20 (m, 1H), 7.06 (m, 1H), 6.63 (s, 1H), 5.92 (s, 2H); ^{13}C{^{1}H} NMR ($(CD_3)_2SO$): δ 139.7, 139.7, 138.9, 138.7, 131.2, 129.4, 129.0, 127.5, 126.6, 126.4, 125.0, 121.3, 119.9, 119.6, 110.0, 98.2. HRMS (ESI/$[M+H]^+$) calcd. for $C_{20}H_{17}N_2$: 285.1386. Found: 285.1376.

3-(biphenyl-4-ylmethyl)-1*H*-indazole (3-25'): ^{1}H NMR ($CDCl_3$): δ 9.89 (br s, 1H), 7.60 (m, 1H), 7.57-7.55 (m, 2H), 7.54-7.52 (m, 2H), 7.45-7.39 (m, 5H), 7.36 (m, 1H), 7.32 (m, 1H), 7.11 (m, 1H), 4.40 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 146.0, 141.3, 140.9, 139.3, 138.0, 129.2, 128.7, 127.3, 127.1, 127.0, 126.8, 122.1, 120.5, 120.5, 109.7, 33.3. HRMS (ESI/$[M+H]^+$) calcd. for $C_{20}H_{17}N_2$: 285.1386. Found: 285.1380.

2-(3,4-dimethoxyphenyl)-1*H*-indol-1-amine (3-26). The representative protocol was followed using 35-40% EtOAc/hexanes for column chromatography to afford the indole as a beige solid in 61% yield (82 mg, 0.31 mmol) and the indazole as a beige solid in 10% yield (14 mg, 0.052 mmol). An accurate ^{1}H NMR yield was obtained of the crude product mixture relative to 1,3,5-trimethoxybenzene (61% and 17%, respectively). ^{1}H NMR ($CDCl_3$): δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.44 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.26 (m, 3H), 7.16 (m, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.52 (d, *J* = 0.7 Hz, 1H), 4.58 (s, 2H) (NH_2), 3.94 (s, 6H) (3H8'/3H9'); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 148.9, 148.7, 140.8, 138.3, 125.6, 124.5, 121.8, 121.7, 120.3, 112.5, 111.0, 108.7, 98.9, 55.9, 55.9. Some carbon peaks are missing due to overlapping signals. HRMS (ESI/$[M+H]^+$) calcd. for $C_{16}H_{17}N_2O_2$: 269.1285. Found: 269.1299.

2-33': 3-(3,4-dimethoxybenzyl)-1*H*-indazole (3-26'). ^{1}H NMR ($CDCl_3$): δ 10.22 (br s, 1H), 7.55 (m, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.34 (m, 1H), 7.08 (m, 1H), 6.89-6.85 (m, 2H), 6.79 (d, *J* = 8.2 Hz, 1H), 4.31 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 148.9, 147.5, 146.2, 141.3, 131.5, 126.7, 122.0, 120.7, 120.5, 120.4, 112.0, 111.1, 109.7, 55.8, 55.8, 33.4. HRMS (ESI/$[M+H]^+$) calcd. for $C_{16}H_{17}N_2O_2$: 269.1285.

Found: 269.1308.

2-(thiophen-3-yl)-1H-indol-1-amine (3-27). The representative protocol was followed using 20-25% EtOAc/hexanes for column chromatography to afford the indole as a beige solid in 65% yield (70 mg, 0.33 mmol) and the indazole as a beige solid in 23% yield (25 mg, 0.12 mmol). ^{1}H NMR ($CDCl_3$): δ 7.93, (dd, *J* = 3.0, 1.2 Hz, 1H), 7.60 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.52 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.41-7.38 (m, 2H), 7.26 (m, 1H), 7.16 (m, 1H), 6.60 (d, *J* = 0.8 Hz, 1H), 4.62 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 138.3, 136.0, 132.3, 128.0, 125.7, 125.2, 122.8, 122.0, 120.5, 120.3, 108.3, 98.5. HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{12}H_{11}N_2S$: 215.0637. Found: 215.0644.

3-(thiophen-3-ylmethyl)-1*H*-indazole (3-27'): ^{1}H NMR ($CDCl_3$): δ 10.34 (br s, 1H), 7.57 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.42 (m, 1H), 7.36 (m, 1H), 7.25 (dd, *J* = 5.1, 3.1 Hz, 1H), 7.10 (m, 1H), 7.07 (m, 1H), 7.03 (dd, *J* = 5.0, 3.1 Hz, 1H), 4.39 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 145.5, 141.3, 139.1, 128.5, 126.8, 125.7, 122.0, 121.5, 120.5, 120.4, 109.8, 28.4. HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{12}H_{11}N_2S$: 215.0637. Found: 215.0636.

5-methyl-2-phenyl-1*H*-indol-1-amine (3-28). The representative protocol was followed using 20-25% EtOAc/hexanes for column chromatography to afford the indole as a beige solid in 34% yield (38 mg, 0.17 mmol) and the indazole as a beige solid in 33% yield (37 mg, 0.17 mmol). An accurate ^{1}H NMR yield was obtained of the crude product mixture relative to 1,3,5-trimethoxybenzene, both resulting in 36% yield. ^{1}H NMR ($CDCl_3$): δ 7.71-7.69 (m, 2H), 7.48 (t, *J* = 7.3 Hz, 2H), 7.41-7.38 (m, 3H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.11 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.49 (s, 2H), 2.49 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 141.0, 137.1, 132.0, 129.6, 129.1, 128.3, 127.7, 125.9, 123.7, 120.2, 108.6, 99.2, 21.4. HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{15}H_{15}N_2$: 215.1230. Found: 215.1235.

3-benzyl-5-methyl-1*H*-indazole (3-28'). ^{1}H NMR ($CDCl_3$): δ 10.28 (br s, 1H), 7.34-7.28 (m, 6H), 7.21 (m, 1H), 7.18 (dd, *J* = 8.5, 1.2 Hz, 1H), 4.36 (s, 2H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): 145.1, 140.0, 139.1, 129.7, 128.8, 128.7, 128.5, 126.2, 122.4, 119.4, 109.5, 33.6, 21.3. HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{15}H_{15}N_2$: 215.1230. Found: 215.123.

Synthesis of 3-29. A vial was charged with a magnetic stir bar, Mor-DalPhos (112.1 mg, 0.242 mmol), [CpPd(allyl)] (55.3 mg, 0.260 mmol), 1-bromo-2-(phenylethynyl)benzene (186.5 mg, 0.725 mmol) and THF (2 mL). The vial containing the resulting red-brown reaction mixture was sealed with a PTFE lined cap, removed from the glovebox and heated at 65 ^{o}C for 16 h under the influence of magnetic stirring, at which time the consumption of Mor-DalPhos and the clean formation of **3-29** was confirmed by use of ^{31}P NMR methods. The resulting slurry was concentrated to dryness in vacuo, washed with diethyl ether (5 x 2 mL) until the washings remained colorless, and dried in vacuo to afford **3-29** as an analytically pure beige powder in 85% isolated yield (169.1 mg, 0.204 mmol). Anal. Calcd. for $C_{44}H_{51}Br_1N_1O_1P_1Pd_1$: C 63.89; H 6.21; N 1.69. Found: C 63.62; H 6.19; N 1.41. Crystals suitable for single-crystal X-ray diffraction analysis were obtained from vapor diffusion of diethyl ether into a concentrated dichloromethane solution of **3-29**. ^{1}H NMR ($CDCl_3$): δ 8.18 (dd, J = 8.0, 2.5 Hz, 1H, ArH), 7.87 (m, 1H, ArH), 7.61 (m, 1H, ArH), 7.56 (d, J = 8.0 Hz, 1H, Pd-ArH), 7.46-7.44 (m, 2H, alkyne Ph), 7.36 (m, 1H, ArH), 7.28 (m, 1H, Pd-ArH), 7.24-7.18 (m, 3H, alkyne Ph), 6.97 (m, 1H, Pd-ArH), 6.84 (m, 1H, Pd-ArH), 5.50 (m, 1H, morph CH_2), 5.40 (m, 1H, morph CH_2), 4.22 (m, 1H, morph CH_2), 3.99-3.92 (m, 2H, morph CH_2), 3.85 (m, 1H, morph CH_2), 3.10 (m, 1H, morph CH_2), 2.91 (m, 1H, morph CH_2), 2.48-2.45 (m, 3H, 1-Ad CH_2), 2.27-2.26 (m, 3H, 1-Ad CH_2), 2.13-2.05 (m, 6H, 1-Ad CH/CH_2), 1.89-1.75 (15H, 1-Ad CH/CH_2), 1.59-1.56 (m, 3H, 1-Ad CH). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 160.3 (d, J_{PC} = 12.6 Hz, aryl C_{quat}), 145.4 (d, J_{PC} = 5.0 Hz, Pd-aryl C_{quat}), 138.7 (Pd-aryl CH), 136.0 (aryl CH), 132.5 (aryl CH), 131.6 (Pd-aryl CH), 131.3 (alkyne Ph C_{quat}), 131.1 (alkyne Ph 2CH), 128.8 (d, J_{PC} = 7.5 Hz, aryl CH), 128.2 (alkyne Ph 2CH), 127.5 (alkyne Ph CH), 127.4 (d, J_{PC} = 27.7 Hz, aryl C_{quat}), 126.1 (Pd-aryl CH), 126.0 (d, J_{PC} = 5.0 Hz, aryl CH), 125.0 (Pd-aryl C_{quat}), 122.7 (Pd-aryl CH), 97.0 (alkyne), 90.0 (alkyne), 62.2 (morph CH_2), 61.7 (morph CH_2), 56.4 (morph CH_2), 55.2 (morph CH_2), 43.4 (1-Ad C_{quat}), 43.3 (d, J_{PC} = 25.2 Hz, 1-Ad C_{quat}), 41.3 (1-Ad CH_2), 39.3 (1-Ad CH_2), 36.3 (1-Ad CH_2), 36.0 (1-Ad CH_2), 28.8-28.6 (m, 1-Ad CH_2). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 56.3.

Generation of 3-30. A vial was charged with a magnetic stir bar, **3-29** (44.2 mg, 0.0534

mmol), and CH_2Cl_2 (2 mL). The vial was sealed with a PTFE lined cap equipped with a septum, was transferred out of the glovebox, and NH_3 (0.5 M in 1,4-dioxane, 0.321 mL, 0.160 mmol) was added via syringe. The solution was stirred briefly, and then was transferred back into the glovebox, at which point the cap was removed, silver trifluoromethanesulfonate (15.1 mg, 0.0588 mmol) was added, and the vial was resealed with the cap. The resulting mixture was stirred magnetically for 1 h at room temperature during which time a gray precipitate formed. ^{31}P NMR analysis of the reaction mixture indicated the consumption of **3-29** and complete conversion to a single new phosphorus-containing species (**3-30**). The precipitate was removed by filtration over Celite, the filtrate was triturated with pentane (2 x 2 mL) and the mixture was concentrated to apparent dryness affording the desired product **3-30** as a yellow powder (50.5 mg isolated) that was found to contain varying amounts of 1,4-dioxane (ca. 0.75 equiv.), as well as trace amounts of other solvents used in the synthesis. Our efforts to obtain solvent-free samples of **3-30** for elemental analysis were thwarted by the loss of the ammine ligand from **3-30** (to give **3-31**) upon prolonged exposure to vacuum. ^1H NMR ($CDCl_3$): δ 8.07 (dd, J = 8.4, 3.1 Hz, 1H, ArH), 7.87 (m, 1H, ArH), 7.70 (m, 1H, ArH), 7.65 (d, J = 7.7 Hz, 1H, Pd-ArH), 7.46 (m, 1H, ArH), 7.38-7.36 (m, 3H, Pd-ArH, Ph), 7.29-7.28 (m, 3H, Ph), 7.07 (td, J = 7.5, 1.3 Hz, 1H, Pd-ArH), 7.00 (m, 1H, Pd-ArH), 4.37 (m, 1H, morph CH_2), 4.13-4.07 (m, 3H, morph CH_2), 3.96-3.89 (m, 2H, morph CH_2), 3.33 (m, 1H, morph CH_2), 3.20 (m, 1H, morph CH_2), 2.82 (br s, 3H, NH_3), 2.42-2.39 (m, 3H, 1-Ad CH_2), 2.25-2.23 (m, 3H, 1-Ad CH_2), 2.10 (br s, 6H, 1-Ad CH/CH_2), 1.88-1.69 (m, 15H, 1-Ad CH/CH_2), 1.60-1.58 (m, 3H, 1-Ad CH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 160.9 (d, J_{PC} = 12.8 Hz, aryl C_{quat}), 148.3 (Pd-aryl C_{quat}), 138.2 (Pd-aryl CH), 135.9 (aryl CH), 133.8 (aryl CH), 133.0 (Pd-aryl CH), 131.0 (alkyne Ph CH), 129.4 (alkyne Ph C_{quat}), 128.8 (alkyne Ph CH), 128.6 (aryl CH), 127.5 (alkyne Ph CH), 127.1 (m, aryl CH), 126.1 (d, J_{PC} = 29.2 Hz, aryl C_{quat}), 124.6 (alkyne Ph CH), 123.3 (Pd-Ar C_{quat}), 122.1 (aryl CH), 119.6 (aryl CH), 94.5 (alkyne), 90.3 (alkyne), 61.7 (morph CH_2), 61.6 (morph CH_2), 56.4 (morph CH_2), 56.0 (morph CH_2), 43.4 (d, J_{PC} = 16.2 Hz, 1-Ad C_{quat}), 42.8 (d, J_{PC} = 14.7 Hz, 1-Ad C_{quat}), 41.3 (1-Ad CH_2), 39.6 (1-Ad CH_2), 36.3 (1-Ad CH_2), 35.9 (1-Ad CH_2), 28.7-28.5 (m, 1-Ad CH). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 62.6.

Synthesis of 3-31. To a vial containing a magnetic stir bar, **3-29** (100.0 mg, 0.121 mmol), and CH_2Cl_2 (3 mL) was added silver trifluoromethanesulfonate (34.2 mg, 0.133 mmol) and the resulting mixture was stirred magnetically for 1 h at room temperature, at which time complete consumption of **3-29** and conversion to a new product (**3-31**) was confirmed by use of ^{31}P NMR. The reaction mixture was filtered and resulting filtrate was concentrated and dried in vacuo to afford a green-yellow solid. The solid was washed with diethyl ether (4 x 2 mL) to afford the **3-31** as a dark yellow powder in 83% yield (89.5 mg, 0.100 mmol). Anal. Calcd. for $C_{45}H_{51}F_3N_1O_4P_1Pd_1S_1$: C 60.30; H 5.74; N 1.56. Found: C 60.55; H 5.66; N 1.49. Crystals suitable for X-ray diffraction analysis were obtained from vapor diffusion of diethyl ether into a dichloromethane solution of **3-31**. ^1H NMR ($CDCl_3$): δ 8.12 (dd, J = 8.5, 3.5 Hz, 1H, ArH), 7.81 (t, J = 7.5 Hz, 1H, ArH), 7.75 (m, 1H, ArH), 7.61 (m, 1H, Pd-ArH), 7.56 (m, 1H, ArH), 7.44 (m, 1H, Pd-ArH), 7.37-7.34 (m, 2H, alkyne Ph), 7.31-7.29 (m, 3H, alkyne Ph), 7.14-7.09 (m, 2H, Pd-ArH), 4.82 (br s, 1H, morph CH_2), 4.69 (br s, 1H, morph CH_2), 4.23-4.19 (m, 2H, morph CH_2), 3.98 (br s, 1H, morph CH_2), 3.86 (br s, 1H, morph CH_2), 3.60 (br s, 2H, morph CH_2), 2.42-2.27 (m, 6H, 1-Ad CH_2), 2.13 (br s, 6H, 1-Ad CH_2/CH), 1.97-1.71 (m, 15H, 1-Ad CH_2/CH), 1.61-1.58 (m, 3H, 1-Ad CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 153.8 (m, aryl C_{quat}), 148.8 (Pd-aryl C_{quat}), 136.6 (Pd-aryl CH), 135.6 (aryl CH), 134.2 (aryl CH), 133.2 (Pd-aryl CH), 130.6 (alkyne Ph CH), 129.7 (Pd-aryl C_{quat}), 128.8-128.4 (aryl CH and C_{quat}), 126.8 (d, J_{PC} = 7.5 Hz, aryl CH), 126.5 (Pd-aryl CH), 124.7 (Pd-aryl CH), 122.9 (alkyne Ph C_{quat}), 121.7 (aryl CH), 119.2 (aryl CH), 93.7 (alkyne C_{quat}), 90.1 (alkyne C_{quat}), 70.3 (m, morph CH_2), 55.3 (morph CH_2), 54.8 (morph CH_2), 43.9 (d, J_{PC} = 16.4 Hz, 1-Ad C_{quat}), 43.5 (d, J_{PC} = 15.1 Hz, 1-Ad C_{quat}), 41.2 (1-Ad CH_2), 40.0 (1-Ad CH_2), 36.0 (1-Ad CH_2), 35.6 (1-Ad CH_2), 28.6-28.4 (m, 1-Ad CH). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 80.0.

Generation of 3-32. A vial charged with a magnetic stir bar, Mor-DalPhos (75.0 mg, 0.162 mmol), [CpPd(allyl)] (36.1 mg, 0.170 mmol), diphenylacetylene (31.7 mg, 0178 mmol) and THF (1.8 mL) was removed from the glovebox and heated at 65 ^oC for 2-4 h, under the influence of magnetic stirring and with monitoring by use of ^{31}P NMR techniques. When the consumption of Mor-DalPhos and the formation of **3-32** was

observed, the reaction was then concentrated to dryness in vacuo and the resulting residue was washed with cold pentane (5 x 2 mL, pre-cooled to -30 ºC) and dried in vacuo to afford the desired product **3-32** as a light brown powder (41.2 mg isolated). Our efforts to obtain **3-32** in analytically pure form were thwarted by the propensity of this material to retain fractional amounts of solvent, despite prolonged exposure to vacuum. ^{1}H NMR (THF-d_8): δ 7.93-7.90 (m, 2H, ArH), 7.54 (t, J = 7.0 Hz, 1H, ArH), 7.34-7.33 (m, 5H, ArH), 7.18-7.15 (m, 4H, ArH), 7.03-7.00 (m, 2H, ArH), 5.28-5.24 (m, 2H, morph CH_2), 3.78-3.76 (m, 2H, morph CH_2), 3.15-3.10 (m, 2H, morph CH_2), 2.70-2.68 (m, 2H, morph CH_2), 2.12-2.10 (m, 6H, 1-Ad CH_2), 1.92-1.89 (m, 6H, 1-Ad CH_2), 1.81 (br s, 6H, 1-Ad CH), 1.63 (br s, 12H, 1-Ad CH_2). ^{13}C{^{1}H} NMR (THF-d_8): δ 161.8 (d, J_{PC} = 18.9 Hz, aryl C_{quat}), 136.6 (aryl CH), 133.0 (d, J_{PC} = 15.1 Hz, aryl C_{quat}), 131.7 (aryl CH), 128.3 (alkyne Ph CH), 128.1 (alkyne Ph CH), 126.7 (aryl CH), 126.2 (d, J_{PC} = 5.1 Hz, aryl CH), 124.6 (alkyne Ph CH), 68.3 (morph CH_2), 58.9 (morph CH_2), 42.1 (d, J_{PC} = 6.3 Hz, 1-Ad CH_2), 39.3 (d, J_{PC} = 5.0 Hz, 1-Ad C_{quat}), 37.4 (1-Ad CH_2), 29.7 (d, J_{PC} = 9.2 Hz, 1-Ad CH). ^{31}P{^{1}H} NMR (THF-d_8): δ 60.3.

Generation of 3-33. A vial was charged with a magnetic stir bar, JosiPhos (56.0 mg, 0.101 mmol), [CpPd(allyl)] (22.5 mg, 0.106 mmol), diphenylacetylene (19.7 mg, 0.111 mmol) and THF (1.2 mL). The vial containing the resulting red-brown reaction mixture was sealed with a PTFE lined cap, and was removed from the glovebox and heated at 65 ^{o}C for 2 h, at which time complete conversion to the desired product (**3-33**) was confirmed by use of ^{31}P NMR methods. The resulting red solution was concentrated to dryness in vacuo, washed with cold pentane (3 x 2 mL, precooled to -30 ^{o}C) and dried in vacuo to afford an orange powder (64.5 mg isolated). Although we have thus far not been able to isolate **3-33** in analytically pure form due to the presence of minor unidentified impurities, the NMR characterization data obtained from this material are consistent with the target complex (**3-33**, >90% pure on the basis of ^{31}P NMR data); as such the crude material obtained was used without further purification. ^{1}H NMR (THF-d_8): δ 7.22-7.20 (m, 2H, Ph), 7.16-7.13 (m, 2H, Ph), 7.09-7.04 (m, 4H, Ph), 6.99 (m, 1H, Ph), 6.89 (m, 1H, Ph), 4.66 (br s, 1H, Cp CH), 4.52 (br s, 1H, Cp CH), 4.32 (br s, 1H, Cp CH), 4.22 (s, 5H, C_5H_5), 3.16 (m, 1H, C*H*Me), 2.50 (m, 1H, Cy), 2.22 (m, 1H, Cy), 1.98-0.85 (m, 41H,

Cy, *CH_3, CMe_3). ^{13}C NMR (THF-d_8): δ 141.5 (m, Ph C_{quat}), 140.4 (m, Ph C_{quat}), 128.4 (Ph CH), 128.1 (Ph CH), 127.9 (Ph CH), 127.8 (Ph CH), 124.7 (d, J_{PC} = 70.4 Hz, alkyne), 124.6 (Ph CH), 124.0 (Ph CH), 122.3 (d, J_{PC} = 64.1 Hz, alkyne), 98.0 (dd, J_{PC} = 18.9, 7.5 Hz, Cp C_{quat}), 75.9 (m, Cp C_{quat}), 73.3 (Cp CH), 70.0 (m, Cp CH), 69.8 (C_5H_5), 68.0 (d, J_{PC} = 3.8 Hz, Cp CH), 39.1 (d, J_{PC} = 13.8 Hz, Cy), 37.8 (*C*Me_3), 36.2 (*C*Me_3), 35.5 (dd, J_{PC} = 16.4, 4.3 Hz, Cy), 35.2 (m, *C*HMe), 32.1 (d, J_{PC} = 7.8 Hz, Cy), 31.8 (d, J_{PC} = 8.3 Hz, C*Me*$_3$), 31.6 (d, J_{PC} = 8.2 Hz, C*Me*$_3$), 30.6 (Cy), 30.0 (d, J_{PC} = 8.2 Hz, Cy), 28.6-27.2 (m, Cy), 17.7 (d, J_{PC} = 5.3 Hz, CH*Me*). $^{31}P\{^1H\}$ NMR (THF-d_8): δ 85.7 (d, J_{PP} = 8.1 Hz), 22.4 (d, J_{PP} = 6.1 Hz).

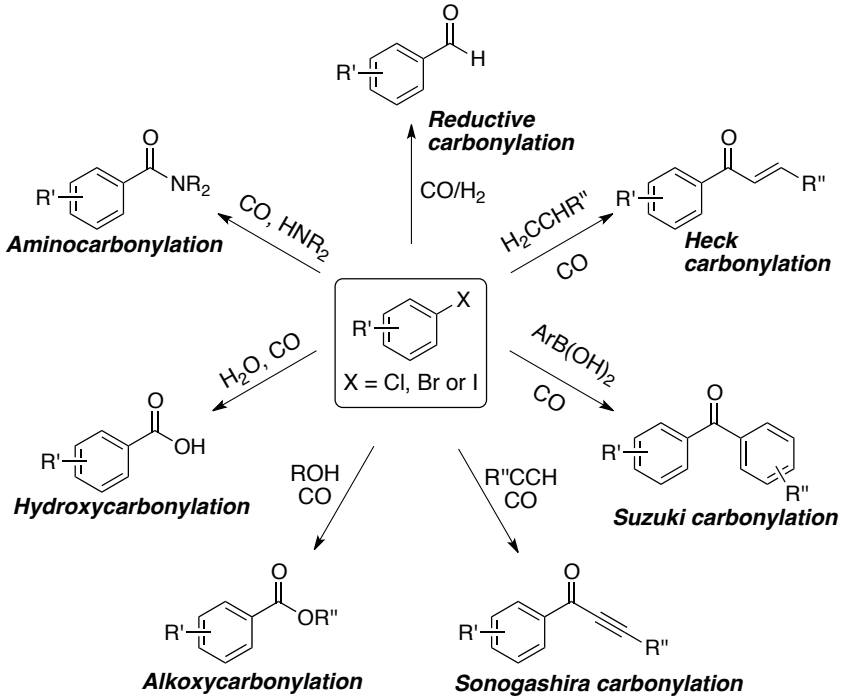
Synthesis of 3-34. A vial was charged with a magnetic stirbar, JosiPhos (55.5 mg, 0.100 mmol), [CpPd(allyl)] (22.3 mg, 0.105 mmol), 1-bromo-2-(phenylethynyl)benzene (51.4 mg, 0.200 mmol) and THF (1 mL). The vial containing the resulting red-brown mixture was sealed with a PTFE lined cap, removed from the glovebox and heated at 65 ^oC for 16 h, at which time complete conversion to the desired product (**3-34**) was confirmed by use of ^{31}P NMR methods. The resulting orange slurry was concentrated to dryness in vacuo, washed with Et_2O (10 x 2 mL) until the washings remained colorless and dried in vacuo to afford **3-34** as an orange powder in 90% yield (82.7 mg, 0.090 mmol). Anal. Calcd. for $C_{46}H_{61}P_2Fe_1Br_1Pd_1$: C 60.16; H 6.70. Found: C 59.87; H 6.66. ^1H NMR ($CDCl_3$): δ 7.53-7.51 (m, 2H, Ph), 7.39-7.31 (m, 4H, Ph, Pd-ArH), 7.17 (d, *J* = 7.6 Hz, 1H, Pd-ArH), 7.09 (m, 1H, Pd-ArH), 6.85 (t, *J* = 7.3 Hz, 1H, Pd-ArH), 4.95 (s, 1H, Cp CH), 4.50 (br s, 1H, Cp CH), 4.45 (m, 1H, Cp CH), 4.25 (s, 5H, C_5H_5), 3.15 (m, 1H, C*H*Me), 2.67 (m, 1H, Cy), 2.54 (m, 1H, Cy), 2.46-2.31 (m, 3H, Cy), 2.08 (m, 1H, Cy), 1.91-1.77 (m, 10H, Cy, CH*Me*), 1.72-1.09 (m, 27H, Cy, CMe_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 160.3 (d, J_{PC} = 118.0 Hz, Pd-aryl C_{quat}), 138.0 (Pd-aryl CH), 131.9 (d, J_{PC} = 5.7 Hz, Pd-aryl CH), 131.8 (alkyne Ph CH), 129.7 (Pd-aryl C_{quat}), 128.2 (alkyne Ph CH), 128.1 (Pd-aryl CH), 127.6 (alkyne Ph CH), 125.5 (alkyne Ph C_{quat}), 122.8 (Pd-aryl CH), 97.4 (dd, J_{PC} = 14.2, 6.9 Hz, Cp C_{quat}), 95.2 (alkyne), 89.6 (alkyne), 73.2 (dd, J_{PC} = 27.5, 10.8 Hz, Cp C_{quat}), 72.8 (Cp CH), 69.6 (C_5H_5), 69.3 (d, J_{PC} = 7.4 Hz, Cp CH), 68.3 (d, J_{PC} = 5.3 Hz, Cp CH), 42.6 (d, J_{PC} = 22.4 Hz, Cy), 38.8 (*C*Me_3), 37.3 (*C*Me_3), 33.5 (d, J_{PC} = 31.5 Hz, Cy), 32.4 (d, J_{PC} = 4.3 Hz, *C*HMe), 32.0 (C*Me*$_3$), 31.1 (d, J_{PC} = 3.9 Hz, C*Me*$_3$), 29.7 (Cy), 28.3 (Cy), 27.7 (d,

J_{PC} = 8.3 Hz, Cy), 27.2 (d, J_{PC} = 11.1 Hz, Cy), 27.0 (d, J_{PC} = 14.3 Hz, Cy), 26.6 (Cy), 17.9 (d, J_{PC} = 6.2 Hz, CH*Me*). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ 73.2 (d, J_{PP} = 34.4 Hz), 17.3 (d, J_{PP} = 34.5 Hz).

CHAPTER 4 CARBONYLATIVE CROSS-COUPLING REACTIONS EMPLOYING PALLADIUM/DALPHOS CATALYST SYSTEMS

4.1 INTRODUCTION

Palladium-catalyzed carbonylative couplings of aryl and vinyl halides are gaining increasing interest among synthetic chemists as an important pathway for the construction of carboxylic acid derivatives.[16, 81] The Beller research group has been a key player in this area of palladium catalysis with recent contributions including carbonylative Heck,[82] Sonogashira[83] and Suzuki[84] couplings as well as aminocarbonylation (Scheme 4.1).[85]



Scheme 4.1 Summary of common carbonylative cross-coupling processes.

Carbonylative amination reactions had been restricted to primary and secondary amines until Beller and co-workers reported for the first time the use of ammonia gas, giving direct access to synthetically useful primary aromatic and heteroaromatic amides.[86] The direct synthesis of primary aromatic amides via amincarbonylation of (hetero)aryl bromides and chlorides using palladium catalyst systems was developed based on either cata*CX*iumA (22 examples, GC yields 30-98%, 3 isolated yields 80-91%)

or DPPF (22 examples, GC yields 30-98%, 3 isolated yields 85-90%) ligands (Figure 4.1).[86]

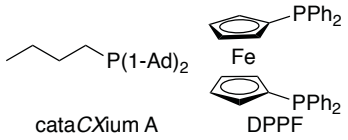


Figure 4.1 Successful ligands for the Pd-catalyzed aminocarbonylation of (hetero)aryl halides.

An important feature of this reaction is the dual role of ammonia as both nucleophile and base. This protocol was later extended to phenols through the in situ generation of aryl nonaflates.[87] While effective approaches using benzoic acids or acid chlorides,[88] as well as ammonia surrogates ($N(TMS)_2$, tBuNH$_2$) have been reported as a means of preparing primary aryl amides,[89] these lack the atom economy associated with using ammonia and carbon monoxide directly in combination with widely available aryl halides.[90]

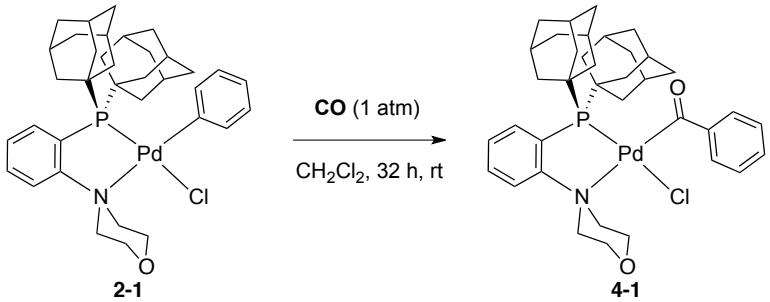
Considering the utility of DalPhos ligands in challenging ammonia arylations (see Chapter 2),[38, 49, 91] and the recent establishment of aminocarbonylation protocols employing gaseous ammonia and carbon monoxide,[86] evaluation of the capabilities of DalPhos ligands in palladium-catalyzed aminocarbonylation was of interest. This chapter describes carbonylative amination reactions of (hetero)aryl bromides featuring ammonia and other amine coupling partners, utilizing a Pd/DalPhos catalyst system. Pd/Mor-DalPhos mixtures have also been successful in ketone α-arylations, including acetone as a coupling partner.[62a, 92] Thus, the DalPhos ligand family was also applied to related C-C carbonylative cross-couplings, including the previously unprecedented carbonylative α-arylation of acetone.

4.2 Results and Discussion

4.2.1 Aminocarbonylation Reactions Employing Pyr-DalPhos

Interest in Pd/DalPhos-catalyzed carbonylative amination reactions began when it was observed that [(κ^2-*P,N*-Mor-DalPhos)Pd(Ph)Cl] (**2-1**) was cleanly transformed into [(κ^2-*P,N*-Mor-DalPhos)Pd(COPh)Cl] (**4-1**) upon exposure to an atmosphere of CO (Scheme 4.2). This transformation establishes the validity of a carbonyl insertion step

involving the putative oxidative addition catalytic intermediate **2-1**, and related DalPhos derivatives.



Scheme 4.2 Conversion of the oxidative addition product **2-1** to the Pd-benzoyl complex **4-1**.

Complex **4-1**·0.5(CH_2Cl_2) was successfully isolated as an analytically pure solid in quantitative yield. Solution NMR characterization data agree with the proposed structure of **4-1** as being a square planar complex containing a benzoyl group. Notably, the ^{13}C NMR resonance of the carbonyl group appears significantly more downfield (220.8 ppm) of the aromatic region in agreement with a Pd-C(O)Ph connectivity[86c] and in contrast with typical benzoyl groups found in organic frameworks (e.g. benzamide 170 ppm, benzaldehyde 192 ppm, benzoic acid 172 ppm). Single crystal X-ray diffraction data obtained for crystals of **4-1**·CH_2Cl_2 supports the solution NMR analyses; an ORTEP diagram of **4-1**·CH_2Cl_2 is shown in Figure 4.2.

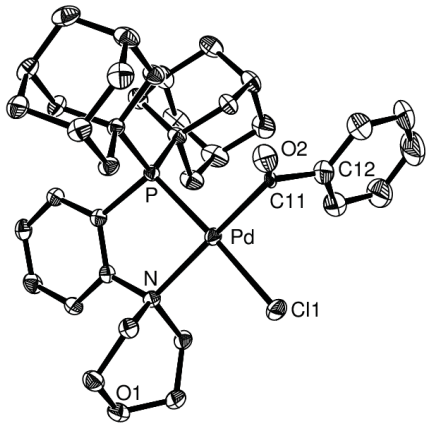


Figure 4.2 ORTEP diagram of **4-1**·CH_2Cl_2 shown with 50% displacement ellipsoids. All hydrogen atoms and the dichloromethane solvate have been omitted for clarity. Selected interatomic distances (Å): Pd-P, 2.2630(7); Pd-N, 2.233(2); Pd-Cl, 2.3796(7); P-Caryl, 1.846(3); N-Caryl, 1.464(3); Pd-C(O)CPh, 2.055(3); PdC(O)-CPh, 1.553(4).

Encouraged by the facile formation of **4-1**, a range of previously reported DalPhos ligands[49] were screened in the benchmark aminocarbonylation of bromobenzene forming benzamide (**4-2**, Figure 4.3). The choice of conditions was based on those that had previously proven effective for such transformations (i.e. $Pd(OAc)_2$, ligand, 1,4-dioxane, 100 ^oC, 16 h).[86] Under the test conditions (2 mol% Pd, 6 mol% ligand, 2 bar CO, 2 bar NH_3), it was surprising to see most catalysts featuring phenylene P,N-ligands achieved either little to no conversion of the starting material and/or poor yield of **4-2**. Among the ligands surveyed, the pyridine-derived ligand **L17** (Pyr-DalPhos) proved most effective, affording nearly 50% conversion and a promising yield. Although they both perform well in ammonia arylation,[49] Mor-DalPhos (**L14**) and the related piperidine derivative **L15** afforded poor conversions with no product, while Me-DalPhos (**L16**), benzyl (**L18**) and pyrrole (**L19**) variants gave both little conversion and product. Interestingly, the diphenylphosphine ligand **L20** was more effective than Mor-DalPhos under these test conditions, affording modest conversion and yield. On the basis of the results obtained with **L17**, optimization was continued with this ligand in an effort to achieve full conversion (Table 4.1).

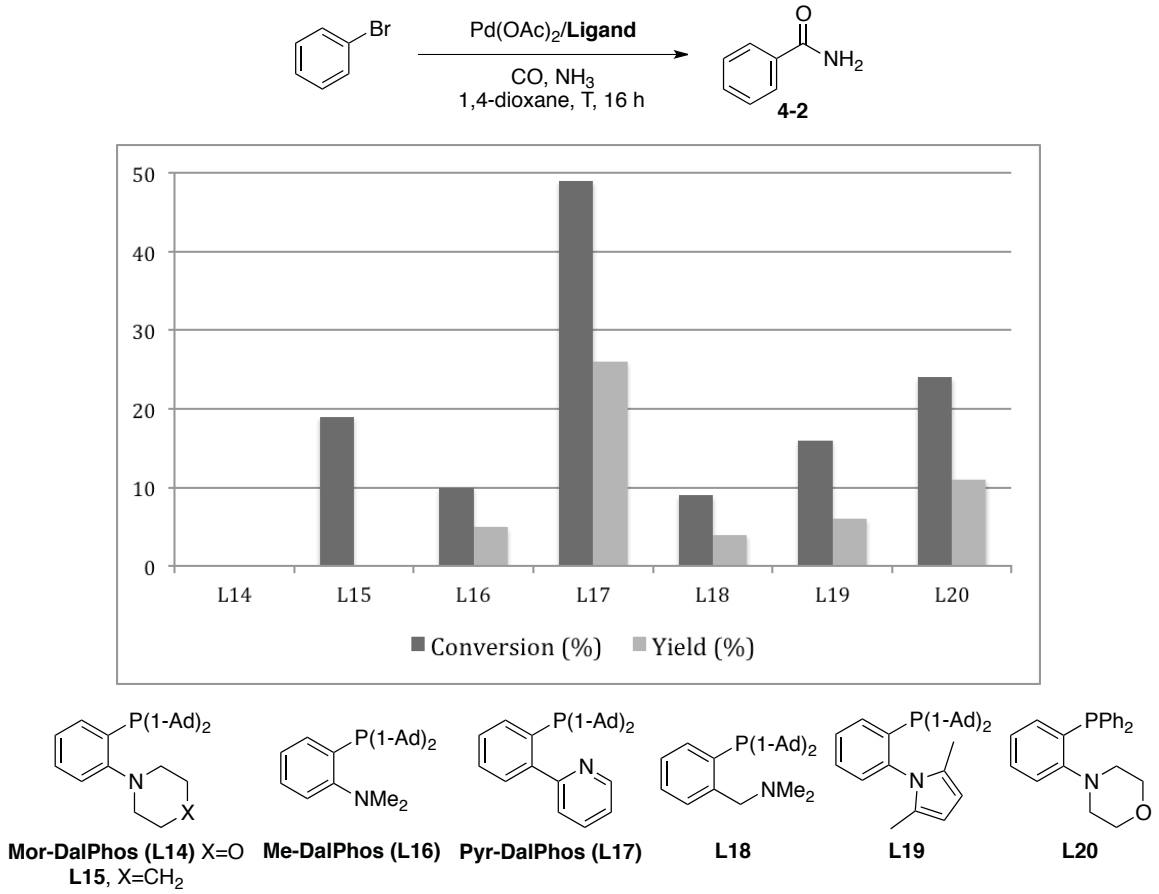
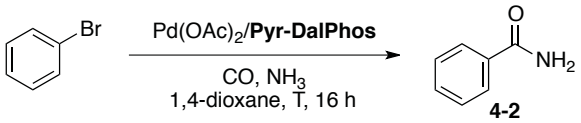


Figure 4.3 Ligand screening for the palladium-catalyzed aminocarbonylation of bromobenzene. General reaction conditions: bromobenzene (1 mmol), $Pd(OAc)_2$ (0.02 mmol), ligand (0.06 mmol), CO (2 bar), NH_3 (2 bar), 1,4-dioxane (2 mL), 100 ^oC, 16 h. Conversions and yields were determined by use of GC data based on bromobenzene using hexadecane as an internal standard.

The use of increased pressures of CO and NH_3 was first examined in an attempt to push the reaction towards full consumption of bromobenzene. However, this change in pressure was not beneficial for the Pyr-DalPhos catalyst system (Table 4.1, entry 1). At a higher temperature (120 ^oC), conversion was greatly improved, affording a significant increase in yield (Table 4.1, entry 2). A modest decrease in the conversion was observed when less ligand was used (Table 4.1, entry 3), although the yield did not suffer (68 vs 62%). When the Pd loading was doubled (4 mol%), near complete conversion was obtained; however, similar results were obtained when using standard loading (2 mol%) and 1 M concentration of bromobenzene in 1,4-dioxane (Table 4.1, entries 4 and 5). Continuing at the higher concentration, good conversion but only moderate yield resulted when using a decreased Pd:L ratio (Table 4.1, entry 6), while an increase to 3 mol% Pd

gave access to the best yields (Table 4.1, entries 7 and 8). Thus, isolated yields (72 vs 79%) determined the optimal Pd:L ratio (1:3).

Table 4.1 Optimization of reaction conditions: variation of pressure, temperature, palladium loading and concentration.[a]



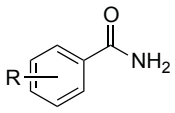
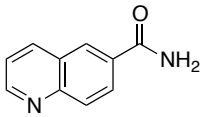
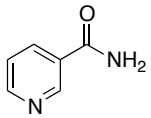
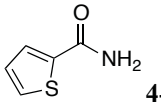
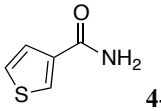
4-2

Entry	Variation from the initial conditions	GC Conv. [%][b]	GC yield [%][b]
1	Increase pressure to 10 bar CO, 4 bar NH_3	7	5
2	120 ^oC instead of 100 ^oC	85	62
3[c]	Pd:L = 1:2	78	68
4[c]	4 mol% Pd, 12 mol% L	98	87
5[c]	[PhBr] = 1 M	99	83
6[c]	Pd:L = 1:2, 1 M	93	61
7[c,d]	3 mol% Pd, 6 mol% L	97	>95 (72)
8[c,d]	3 mol% Pd, 9 mol% L	97	>95 (79)

[a] Initial reaction conditions: bromobenzene (1 mmol), $Pd(OAc)_2$ (0.02 mmol), Pyr-DalPhos (0.06 mmol), CO (2 bar), NH_3 (2 bar), 1,4-dioxane (2 mL), 100 ^oC, 16 h. [b] Conversion and yield were determined by GC based on bromobenzene using hexadecane as an internal standard. [c] 120 ^oC. [d] [PhBr] = 1 M (isolated yield in parentheses).

Once Pd/Pyr-DalPhos catalyst mixtures had been identified as being effective for the standard aminocarbonylation of bromobenzene, the scope of reactivity with CO and NH_3 (Table 4.2) was surveyed. It is worth mentioning that in order to fully establish the practical synthetic utility of this process, isolated yields were obtained for all examples. It was found that the reaction was tolerant of activated and deactivated bromoarenes, *ortho*-substitution as well as some heterocycles. Electron-donating substituents -Me and -OMe (Table 4.2, entries 2 and 4) gave the best yields (89 and 96%, respectively), while electron-deficient ring systems were also coupled successfully (Table 4.2, entries 5 and 6). Nitrogen-containing heterocycles 6-quinoline (Table 4.2, entry 8) and 3-pyridine (Table 4.2, entry 9) worked well in the reaction, as did 2- and 3-substituted thiophene derivatives (Table 4.2, entries 10 and 11). Notably, an NH-containing substrate (Table 4.2, entry 7) was accommodated under the reaction conditions, displaying the chemoselective capabilities of the reaction.

Table 4.2 Palladium-catalyzed aminocarbonylation of aryl bromides.[a]

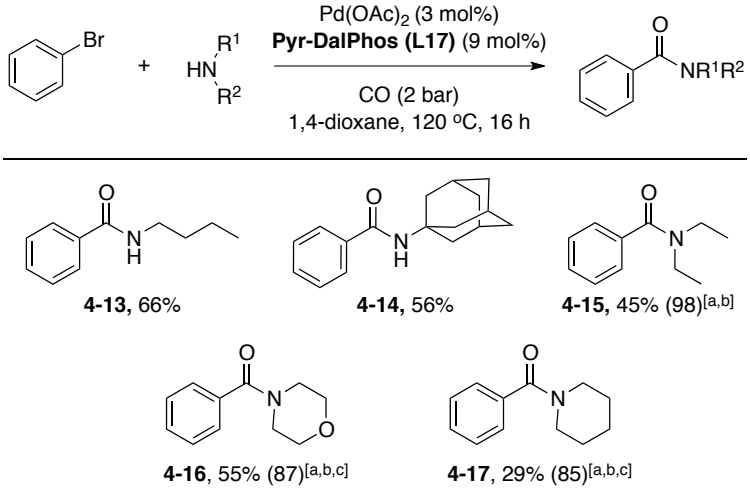
Entry	Product	Yield [%][b]	Entry	Product	Yield [%][b]
			8	 **4-9**	84
1	R= H, **4-2**	79	9	 **4-10**	76
2	R = 4-Me, **4-3**	89			
3	R = 2-Me, **4-4**	70	10	 **4-11**	59
4	R = 4-OMe, **4-5**	96			
5	R = 4-CF_3, **4-6**	76			
6	R = 4-CN, **4-7**	40	11	 **4-12**	76
7[c]	R = 4-NHMe, **4-8**	56			

[a] General reaction conditions: aryl bromide (1 mmol), $Pd(OAc)_2$ (0.03 mmol), Pyr-DalPhos (0.09 mmol), CO (2 bar), NH_3 (2 bar), 1,4-dioxane (1 mL). [b] Isolated yield. [c] 140 ^oC, 16 h.

Other sterically congested bromide substrates were not as well-accommodated in aminocarbonylation as was 2-bromotoluene (Table 4.2, entry 3; 70% yield). 1-Bromonaphthalene resulted in poor yield, 2-bromo-*N*-methylaniline afforded only low conversion and 2-bromomesitylene did not form any desired product. Furthermore, aryl chlorides proved to be unreactive substrates using either the optimized conditions or with increased temperature and time (i.e. 140 ^oC, 20 h). When compared to the previously published reports of such aminocarbonylations using either Pd/cata*CX*ium A or Pd/DPPF catalysts,[86] this current system has similar yields for those aryl bromide substrates previously reported (Table 4.2, entries 1-6 and 9-10). In contrast, however, both previously established catalyst systems were capable of transforming 1-bromonaphthalene as well as several aryl chloride substrates. New examples applied herein to this aminocarbonylation method include heterocyclic aryl amides obtained in high isolated yields (Table 4.2, entries 8 and 11), a potentially competitive aniline derivative (Table 4.2, entry 7) and also *N*-alkyl (di)substituted amides (Figure 4.4).

Having screened a variety of aryl bromides, attention was then given to the use of different amines, in place of ammonia, to form *N*-substituted amides using the Pd/Pyr-DalPhos catalyst system. Electron-rich amines were successfully coupled to afford both secondary and tertiary amides. The secondary amines required *N,N,N,N*-

tetramethylethylenediamine (TMEDA) as the base in order to achieve good conversions for these reactions. For the primary amines, *n*-butyl and 1-adamantyl groups gave moderate yields of corresponding amides, where the amines acted as both nucleophile and base. Although significant optimization was attempted using aniline, increased temperature and different bases (TMEDA, Et_3N) were not sufficient to attain full conversion of bromobenzene; purification of isolated material also proved difficult. It should be noted that this lower reactivity of the primary and secondary amines compared to ammonia provides the basis to perform selective monoarylation reactions.



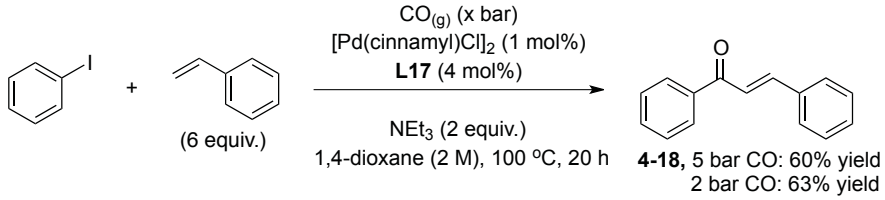
[a] Conversion (in parentheses) was determined by GC based on bromobenzene using hexadecane as an internal standard. [b] TMEDA (0.75 eq.) was used as base. [c] Heated at 140 °C, 20 h.

Figure 4.4 Palladium-catalyzed aminocarbonylation of bromobenzene with alkylamines.
General reaction conditions: bromobenzene (1 mmol), amine (2 mmol if solid or 0.4-0.9 mL if liquid), $Pd(OAc)_2$ (0.03 mmol), Pyr-DalPhos (0.09 mmol), CO (2 bar), 1,4-dioxane (0.6-1 mL), 120 °C, 16 h; isolated yields provided.

4.2.2 Preliminary Investigations with Carbonylative C-C Cross-Coupling Reactions

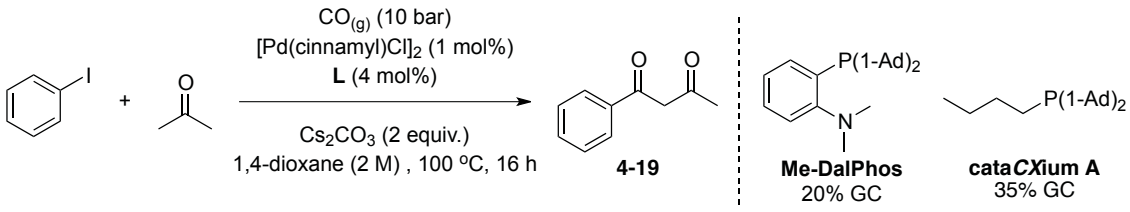
The catalytic reactivity of DalPhos ligand variants was also tested in carbonylative Heck coupling and ketone α-arylation chemistry. In carrying out a ligand survey similar to that presented in Figure 4.3, it was found that only **L19** formed an active Pd catalyst for the coupling of iodobenzene, styrene (used in excess) and CO gas resulting in the formation of the carbonylative Heck product **4-18** (Scheme 4.3). Bromobenzene was not a competent coupling partner in this reaction and resulted in poor conversion to **4-18**. A few functionalized aryl iodides containing 4-OMe, 4-CF_3 or 2-Me

groups were selected to test the substrate scope but these did not perform as well as iodobenzene under the reaction conditions (2 bar CO); purification proved difficult and poor yield of product was obtained. Considering that the carbonylative synthesis of chalcone products has been well documented in the literature with high yields and wide scope of substrates,[82] no further efforts were made to develop this Pd/**L19**-catalyzed process.



Scheme 4.3 Palladium-catalyzed carbonylative Heck coupling of iodobenzene and styrene.

The Stradiotto group has recently found that the Pd/Mor-DalPhos catalyst is highly active for the mono-α-arylation of acetone, previously a challenging and unreported reaction, as well as other ketones.[62a, 92] Building on this success, it was envisioned that a DalPhos variant could facilitate a carbonylative version of the reaction. Carbonylative α-arylation of ketones has been previously reported, although the scope did not extend to acetone and required the use of a non-commercially available stoichiometric reagent that would generate CO in situ.[93] Thus, employing gaseous CO to synthesize 1,3-diketones would be a new development in the area of palladium-catalyzed α-arylation of ketones. The project was initiated with a standard ligand screen, including the DalPhos ligand variants (**L14-L20**) and cata*CX*ium A (see Figure 3.2, **L9**), which is known for its efficacy in carbonylative coupling reactions.[16a] For the coupling of iodobenzene and acetone (10 equiv.) under 10 bar CO (Scheme 4.4), preliminary results for both Me-DalPhos and cata*CX*ium A gave high conversions but low GC yields of the 1,3-diketone product **4-19**.



Scheme 4.4 Synthesis of a 1,3-diketone via the palladium-catalyzed carbonylative α-arylation of acetone.

Although Me-DalPhos displayed some catalytic activity, cata*CX*ium A in comparison, was able to achieve a superior yield of **4-19**. Thus, further reaction development and optimization was performed using $[Pd(cinnamyl)Cl]_2$/cata*CX*ium A mixtures. This work is not described herein, as these studies were conducted by a research collaborator (J. Schranck and M. Beller, LIKAT-Rostock).

4.3 Summary and Conclusions

This chapter detailed efforts to identify DalPhos ligands that can be utilized for carbonylative cross-coupling reactions, primarily aminocarbonylation. The synthesis of [(κ^2-*P,N*-Mor-DalPhos)Pd(COPh)Cl] (**4-1**) provided evidence for the viability of a carbonyl insertion step in carbonylative coupling reactions employing a Pd/DalPhos catalyst. A palladium catalyst system featuring the ligand Pyr-DalPhos (**L17**) demonstrated significant catalytic activity from a screen of DalPhos variants for the aminocarbonylation of bromobenzene with ammonia. The substrate scope incorporated a variety of electronically activated and deactivated aryl bromides, as well as some heteroaryl examples such as pyridyl and thiophenyl bromides. It is important to note the dual role of ammonia in these reactions as both a nucleophile and base. The scope was extended to primary and secondary alkyl amines as reactive partners, where diethylamine, morpholine and piperidine required an external base (TMEDA) to achieve high conversion of bromobenzene and modest yields of product. In comparison to the previous reports on aminocarbonylation, these results demonstrate synthetically useful isolated yields and an expanded substrate scope to substituted amines. To examine further the capabilities of the DalPhos ligand set in carbonylative cross-coupling reactions, a screening of ligands was executed for carbonylative Heck coupling and carbonylative α-arylation of ketones. Although the pyrrole DalPhos variant **L19** showed good catalytic activity for the reaction of iodobenzene, styrene and CO to form **4-18**, poor results were obtained with other aryl iodides. Use of the Pd/Me-DalPhos catalyst system allowed for the first example of a palladium-catalyzed carbonylative α-arylation of acetone to be executed; reaction of iodobenzene, acetone and CO resulted in a low yield of 1,3-diketone **4-19** (20% GC yield). Cata*CX*ium A was later identified as a superior ligand in this chemistry.

4.4 Experimental Section

4.4.1 General Considerations

For the preparation of complex **4-1**: Unless otherwise noted, all manipulations were conducted under dinitrogen within an inert-atmosphere glovebox, utilizing glassware that was oven-dried (130 °C) and evacuated while hot prior to use. Pentane and dichloromethane were deoxygenated by sparging with dinitrogen followed by passage through a double-column solvent purification system purchased from MBraun Inc. equipped with either one alumina-packed column and one column packed with copper-Q5 reactant (pentane) or two alumina-packed columns (dichloromethane). Deuterated chlorofrom (Cambridge Isotopes) was degassed by using three repeated freeze−pump−thaw cycles and stored over 4 Å molecular sieves for 24 h prior to use. All solvents were stored under dinitrogen over activated 4 Å molecular sieves. The DalPhos ligands were prepared according to literature procedures,[38, 49, 62a] as was complex **2-1**.[49] ^{1}H, ^{13}C, and ^{31}P NMR characterization data were collected at 300 K on a Bruker AV-500 spectrometer operating at 500.1, 125.8, and 202.5 MHz (respectively), with chemical shifts reported in parts per million downfield of $SiMe_4$ (for ^{1}H and ^{13}C) and 85% H_3PO_4 in D_2O (for ^{31}P). Structural elucidation was enabled through analysis of $^{1}H–^{1}H$ COSY, $^{1}H–^{13}C$ HSQC, $^{1}H–^{13}C$ HMBC, and DEPTQ-135 data. NMR data were acquired with the technical assistance of Dr. Michael Lumsden (NMR-3, Dalhousie University), X-ray diffraction experiments were executed by Dr. Robert McDonald (X-ray Crystallography Laboratory, Department of Chemistry, University of Alberta) and elemental analyses were performed by Midwest Microlab, LLC, Indianapolis, IN (USA).

For the preparation of (hetero)aryl amides: Unless otherwise stated, all reactions were set-up using standard Schlenk techniques under argon. Chemicals were purchased from Fluka, Aldrich, Alfa Aesar and Strem and used as received. 1,4-Dioxane was distilled over CaH_2 and stored under argon, *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was distilled/stored under air, and *n*-butylamine and morpholine were distilled/stored under argon. ^{1}H and ^{13}C NMR characterization data were collected at 300 K on a Bruker AV-300 or AV-400 spectrometers operating at 300.1 and 75.5 MHz or 400.1 and 100.6 MHz (respectively) and with chemical shifts reported in parts per million downfield of

$SiMe_4$. Mass spectra were in general recorded on an AMD 402/3 or an HP 5989A mass selective detector operated by the LIKAT analytics department.

4.4.2 Synthesis and Characterization Data

Synthesis of [(κ^2-Mor-DalPhos)Pd(COPh)Cl]·0.5(CH_2Cl_2) (4-1): A 50 mL Schlenk flask equipped with a magnetic stir bar was charged with a solution of **2-1** (102.4 mg, 0.150 mmol, 1.0 equiv) in dichloromethane (6 mL). The flask was sealed with a Teflon screw cap, removed from the glovebox and transferred to the Schlenk line. The solution was degassed via 3 consecutive freeze-pump-thaw cycles and refilled with an atmosphere of carbon monoxide. After 2-3 minutes of exposure, the solution was sealed and allowed to stir at room temperature for 32 hrs under a static atmosphere of CO, during which time the reaction turned from a clear brown to green. The reaction flask was then transferred back into the glovebox and examined by use of ^{31}P NMR methods, which confirmed full conversion to a new phosphorus-containing species. The reaction mixture was concentrated in vacuo to a minimum volume (<1 mL) and the remaining solution was treated with pentane (3 mL) to afford a green precipitate, which was separated from the solvent supernatant and washed with pentane (3 x 3 mL). The solid, which was found to retain various amounts of dichloromethane even upon prolonged drying under vacuum, was dried in vacuo at 75 ^oC for 60 hrs to afford the title compound as a green powder (containing 0.5 equiv. CH_2Cl_2 as observed by ^1H NMR) in >99% yield (112.7 mg, 0.150 mmol). Anal. Calcd for $C_{37}H_{47}ClNO_2PPd·0.5(CH_2Cl_2)$: C, 59.81; H, 6.42; N, 1.86. Found: C, 59.46; H, 6.11; N, 1.75. Crystals suitable for X-ray diffraction analysis were obtained from vapor diffusion of diethyl ether into a dichloromethane solution of **4-1**·0.5(CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 8.22-8.16 (m, 3H, 2 Ph + ArH), 7.80 (m, 1H, ArH), 7.61 (m, 1H, ArH), 7.38-7.35 (m, 4H, 3 Ph + ArH), 5.11 (m, 1H, morph CH_2), 4.96 (m, 1H, morph CH_2), 4.20-4.13 (m, 2H, morph CH_2), 4.04-4.01 (m, 2H, morph CH_2), 3.07 (m, 1H, morph CH_2), 2.98 (m, 1H, morph CH_2), 2.44 (br s, 3H, 1-Ad CH_2), 2.03 (br s, 9H, 1-Ad CH/CH_2), 1.83-1.81 (m, 3H, 1-Ad CH_2), 1.71-1.65 (m, 9H, 1-Ad CH/CH_2), 1.46-1.44 (m, 3H, 1-Ad CH_2), 1.32-1.27 (m, 3H, 1-Ad CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 220.8 (d, J_{PC} = 11.3 Hz, CO C_{quat}), 160.0 (d, J_{PC} = 12.6 Hz, aryl C_{quat}), 142.8 (d, J_{PC} = 12.6 Hz, Ph C_{quat}), 136.0 (aryl CH), 132.4 (aryl CH), 131.2 (Ph CH), 130.6 (Ph CH),

128.8 (d, J_{PC} = 6.3 Hz, aryl CH), 128.0 (Ph CH), 127.6 (d, J_{PC} = 28.9 Hz, aryl C_{quat}), 126.0 (d, J_{PC} = 3.8 Hz, aryl CH), 62.0 (morph CH_2), 54.5 (morph CH_2), 53.6 (CH_2Cl_2), 43.1 (d, J_{PC} = 15.1 Hz, 1-Ad C_{quat}), 41.8 (d, J_{PC} = 12.6 Hz, 1-Ad C_{quat}), 40.7 (1-Ad CH_2), 40.3 (1-Ad CH_2), 36.3 (1-Ad CH_2), 36.0 (1-Ad CH_2), 28.9 (d, J_{PC} = 8.8 Hz, 1-Ad CH), 28.5 ((d, J_{PC} = 7.5 Hz, 1-Ad CH). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 57.2.

General Procedure for the Synthesis of Aryl Amides: To six 4-mL glass vials was added $Pd(OAc)_2$ (3 mol%, 6.7 mg), Pyr-DalPhos (**L17**; 9 mol%, 41.0 mg), aryl bromide (1.00 mmol, if solid) and a magnetic stir bar. All vials were placed in a metal alloy plate, sealed with a cap containing a Teflon-rubber faced septum and an inlet needle, and then the vials were evacuated/backfilled with argon three times. 1,4-Dioxane (1.00 mL) and aryl bromide (1.00 mmol, if liquid) were injected into each vial, stirred briefly and the alloy plate with vials was transferred into a 300-mL autoclave (Parr Instruments 4560 series) under an atmosphere of argon. The autoclave was then flushed with NH_3 three times, followed by addition of NH_3 (2 bar) and CO (2 bar) at room temperature. The autoclave was heated at 120 ^oC for 16 h, at which point the autoclave was cooled and the pressure slowly released at room temperature. All reaction vials were removed from the autoclave, the contents of each were filtered over Celite, the filter was washed with a sufficient amount of EtOAc and CH_2Cl_2 (10-20 mL of each) and the resulting filtrate concentrated to dryness on silica powder. The crude material was then purified by column chromatography (heptane/ethyl acetate) to afford the desired aryl amide as a solid.

For the preparation of benzamide (4-2): Bromobenzene was used as the aryl bromide and the crude material was purified with 0-50% ethyl acetate/heptane to afford the desired product as an off-white solid in 79% yield (95.5 mg, 0.788 mmol). ^1H NMR (DMSO-d_6): δ 7.98 (br s, 1H), 7.89-7.85 (m, 2H), 7.55-7.41 (m, 3H), 7.37 (br s, 1H). $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 168.0 (C=O), 134.3 (C_{quat}), 131.3, 128.3, 127.5. Agrees with data previously reported in the literature.[86a]

***p*-Toluamide (4-3).** The representative protocol was followed using 4-bromotoluene and purified with 0-60% ethyl acetate/heptane to afford the desired product as an off-white solid in 89% yield (119.9 mg, 0.887 mmol). ^{1}H NMR (DMSO-d_6): δ 7.89 (br s, 1H), 7.78-7.76 (m, 2H), 7.26-7.23 (m, 3H), 2.34 (s, 3H). $^{13}C\{^{1}H\}$ NMR (DMSO-d_6): δ 167.9 (C=O), 141.1 (C_{quat}), 131.5 (C_{quat}), 128.8, 127.6, 21.0 (CH_3). Agrees with commercially available material from Aldrich (CAS: 619-55-6).

***o*-Toluamide (4-4).** The representative protocol was followed using 2-bromotoluene and purified with 0-60% ethyl acetate/heptane to afford the desired product as an off-white solid in 70% yield (94.1 mg, 0.696 mmol).^{1}H NMR (DMSO-d_6): δ 7.70 (br s, 1H), 7.36-7.28 (m, 3H), 7.23-7.17 (m, 2H), 2.36 (s, 3H). $^{13}C\{^{1}H\}$ NMR (DMSO-d_6): δ 171.1 (C=O), 137.1 (C_{quat}), 135.2 (C_{quat}), 130.5, 129.2, 127.1, 125.5, 19.6 (CH_3). Agrees with commercially available material from Aldrich (CAS: 527-85-5).

***p*-Anisamide (4-5).** The representative protocol was followed using 4-bromoanisole and purified with 0-70% ethyl acetate/heptane to afford the desired product as a yellow solid in 96% yield (144.7 mg, 0.957 mmol). ^{1}H NMR (DMSO-d_6): δ 7.87-7.82 (m, 3H), 7.19 (br s, 1H), 6.99-6.95 (m, 2H), 3.80 (s, 3H). $^{13}C\{^{1}H\}$ NMR (DMSO-d_6): δ 167.5 (C=O), 161.6 (C_{quat}), 129.4, 126.5 (C_{quat}), 113.4, 55.4 (CH_3). Agrees with commercially available material from Aldrich (CAS: 3424-93-9).

4-(Trifluoromethyl)benzamide (4-6). The representative protocol was followed using 4-bromobenzotrifluoride and purified with 0-60% ethyl acetate/heptane to afford the desired product as a light brown solid in 76% yield (143.5 mg, 0.759 mmol). ^{1}H NMR (DMSO-d_6): δ 8.21 (br s, 1H), 8.06 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.2 Hz, 2H), 7.64 (br s, 1H). $^{13}C\{^{1}H\}$ NMR (DMSO-d_6): δ 166.9 (C=O), 138.2 (d, J_{CF} = 0.9 Hz, C_{quat}), 131.3 (q, J_{CF} = 31.9 Hz, C_{quat}), 128.4 (CH), 125.3 (q, J_{CF} = 3.6 Hz, CH), 124.0 (q, J_{CF} = 272 Hz, CF_3). Agrees with data previously reported in the literature.[94]

4-Cyanobenzamide (4-7). The representative protocol was followed using 4-bromobenzonitrile and purified with 0-60% ethyl acetate/heptane to afford the desired

product as a beige solid in 40% yield (57.8 mg, 0.395 mmol). ^{1}H NMR (DMSO-d_6): δ 8.22 (br s, 1H), 8.04-8.01 (m, 2H), 7.95-7.93 (m, 2H), 7.69 (br s, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6): δ 166.5 (C=O), 138.3 (C_{quat}), 132.4, 128.3, 118.4 (C_{quat}), 113.7 (C_{quat}). Agrees with data previously reported in the literature.[95]

4-(Methylamino)benzamide (4-8). The representative protocol was followed using 4-bromo-*N*-methylaniline and heating at 140 °C for 16 h. The crude material was purified via preparative TLC with 75% ethyl acetate/heptane to afford the desired product as a yellow solid in 56% yield (84.3 mg, 0.561 mmol). ^{1}H NMR (DMSO-d_6): δ 7.68-7.63 (m, 2H), 7.55 (br s, 1H), 6.87 (br s, 1H), 6.52-6.48 (m, 2H), 6.17 (q, J = 1.2 Hz, 1H), 2.70 (d, J = 5.1 Hz, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6): δ 168.1 (C=O), 152.3 (C_{quat}), 129.1, 120.7 (C_{quat}), 110.3, 29.4 (CH_3). HRMS (ESI/$[M]^+$) calcd. for $C_8H_{10}N_2O$: 150.07876. Found: 150.07919.

6-Quinolinecarboxamide (4-9). The representative protocol was followed using 4-bromoquinoline and purified with 0-100% ethyl acetate/heptane to afford the desired product as a beige solid in 84% yield (144.6 mg, 0.840 mmol). ^{1}H NMR (DMSO-d_6): δ 8.98 (dd, J = 4.2, 1.7 Hz, 1H), 8.55 (d, J = 1.9 Hz, 1H), 8.45 (dd, J = 8.4, 1.0 Hz, 1H), 8.24 (br s, 1H), 8.21 (dd, J = 5.2, 2.0 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.61-7.57 (m, 2H). ^{13}C{^{1}H} NMR (DMSO-d_6): δ 167.5 (C=O), 152.1, 148.7 (C_{quat}), 137.1, 132.2 (C_{quat}), 128.9, 128.3, 128.0, 127.1 (C_{quat}), 122.1. HRMS (ESI/$[M+H]^+$) calcd. for $C_{10}H_9N_2O$: 173.0709. Found: 173.0706.

Nicotinamide (4-10). The representative protocol was followed using 3-bromopyridine and purified with 20-100% ethyl acetate/heptane to afford the desired product as a yellow solid in 76% yield (92.6 mg, 0.758 mmol). ^{1}H NMR (DMSO-d_6): δ 9.03 (dd, J = 2.2, 0.6 Hz, 1H), 8.69 (dd, J = 4.8, 1.7 Hz, 1H), 8.22-8.19 (m, 2H), 7.62 (br s, 1H), 7.49 (ddd, J = 7.9, 4.8, 0.7 Hz, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6): δ 166.5 (C=O), 151.9, 148.7, 135.2, 129.7 (C_{quat}), 123.5. Agrees with commercially available material from Aldrich (CAS: 98-92-0).

2-Thiophenecarboxamide (4-11). The representative protocol was followed using 2-bromothiophene and purified with 60% ether/heptane on a preparative TLC plate to afford the desired product as a beige solid in 59% yield (74.7 mg, 0.587 mmol). ^{1}H NMR (DMSO-d_6): δ 7.97 (br s, 1H), 7.75-7.72 (m, 2H), 7.39 (br s, 1H), 7.12 (dd, *J* = 5.0, 3.7 Hz, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6): δ 162.9 (C=O), 140.3 (C_{quat}), 131.0, 128.7, 127.9. Agrees with data previously reported in the literature.[95]

3-Thiophenecarboxamide (4-12). The representative protocol was followed using 3-bromothiophene and purified with 0-60% ethyl acetate/heptane to afford the desired product as a yellow solid in 76% yield (97.0 mg, 0.763 mmol). ^{1}H NMR (DMSO-d_6): δ 8.13 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.79 (br s, 1H), 7.55 (dd, *J* = 5.0, 2.9 Hz, 1H), 7.48 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.24 (br s, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6): δ 163.7 (C=O), 138.0 (C_{quat}), 129.0, 127.2, 126.6. Agrees with data previously reported in the literature.[96]

Aminocarbonylation of Bromobenzene with Substituted Amines: Up to six 4-mL glass vials were charged with $Pd(OAc)_2$ (3 mol%, 6.7 mg), Pyr-DalPhos (**L4**; 9 mol%, 41.0 mg), amine (2.00 mmol, if solid) and a magnetic stir bar. All vials were placed in a metal alloy plate, sealed with a cap containing a Teflon-rubber faced septum and an inlet needle, and then the vials were evacuated/backfilled with argon three times. 1,4-Dioxane (0.60 or 1.00 mL), amine (0.40 or 0.90 mL, if liquid) and bromobenzene (1.00 mmol) were injected into each vial, stirred briefly and the alloy plate with vials was transferred into a 300-mL autoclave (Parr Instruments 4560 series) under an atmosphere of argon. The autoclave was then flushed with CO three times, followed by addition of CO (2 bar) at room temperature. The autoclave was heated at 120 ^{o}C for 16 h, at which point the autoclave was cooled and the pressure slowly released at room temperature. All reaction vials were removed from the autoclave, the contents of each were filtered over Celite, the filter was washed with a sufficient amount of EtOAc and CH_2Cl_2 (10-20 mL of each) and the resulting filtrate concentrated to dryness on silica powder. The crude material was then purified by column chromatography (heptane/ethyl acetate) to afford the desired aryl amide.

***N*-Butylbenzamide (4-13).** The representative protocol was followed using *n*-butylamine (0.900 mL) and purified with 0-25% ethyl acetate/heptane to afford the desired product as a pink residue in 66% yield (116.6 mg, 0.658 mmol). ^{1}H NMR ($CDCl_3$): δ 7.78-7.74 (m, 2H), 7.51-7.39 (m, 3H), 6.20 (br s, 1H), 3.49-3.42 (m, 2H), 1.65-1.55 (m, 2H), 1.47-1.35 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 167.5 (C=O), 134.8 (C_{quat}), 131.3, 128.5, 126.8, 39.8 (CH_2), 31.7 (CH_2), 20.1 (CH_2), 13.8 (CH_3). HRMS (ESI/$[M+H]^+$) calcd. for $C_{11}H_{16}NO$: 178.1226. Found: 178.1230. Agrees with data previously reported in the literature.[97]

***N*-Adamantylbenzamide (4-14).** The representative protocol was followed using 1-adamantylamine (2.0 mmol) and purified with 0-10% ethyl acetate/heptane to afford the desired product as a yellow solid in 56% yield (142.8 mg, 0.559 mmol). ^{1}H NMR (Acetone-d_6): δ 7.83-7.79 (m, 2H), 7.49-7.36 (m, 3H), 6.93 (br s, 1H), 2.19-2.18 (m, 6H), 2.08 (br s, 3H), 1.74-1.72 (m, 6H). $^{13}C\{^{1}H\}$ NMR (Acetone-d_6): δ 166.8 (C=O), 137.4 (C_{quat}), 131.4, 128.9, 127.9, 52.6 (Ad C_{quat}), 42.1 (CH_2), 37.2 (CH_2), 30.4 (CH). HRMS (ESI/$[M+H]^+$) calcd. for $C_{17}H_{22}NO$: 256.1696. Found: 256.1691.

***N,N*-Diethylbenzamide (4-15).** The representative protocol was followed using diethylamine (0.900 mL) and also TMEDA as base (0.75 equiv.). The crude material was purified with 0-30% ethyl acetate/heptane to afford the desired product as a yellow oil in 45% yield (80.3 mg, 0.453 mmol). ^{1}H NMR ($CDCl_3$): δ 7.40-7.34 (m, 5H), 3.63-3.26 (br m, 4H), 1.24-1.14 (br m, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 171.5 (C=O), 137.3 (C_{quat}), 129.2, 128.5, 126.4, 43.4, 39.4, 14.1, 13.2. HRMS (ESI/$[M+H]^+$) calcd. for $C_{11}H_{16}NO$: 178.12264. Found: 178.12298. Agrees with data previously reported in the literature.[98]

Morpholin-4-yl-phenyl-methanone (4-16). The representative protocol was followed using morpholine (0.400 mL), TMEDA as base (0.75 equiv.) and heating at 140 ^{o}C for 20 h. The crude material was purified with 0-30% ethyl acetate/heptane to afford the desired product as an orange solid in 55% yield (105.5 mg, 0.552 mmol). (400 MHz) ^{1}H NMR ($CDCl_3$): δ 7.41-7.37 (m, 5H), 3.77-3.35 (br m, 8H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 170.5

(C=O), 135.4 (C_{quat}), 129.9, 128.6, 127.2, 67.0, 48.3, 42.7. HRMS (ESI/$[M+H]^+$) calcd. for $C_{11}H_{14}NO_2$: 192.1019. Found: 192.103.

Piperdin-1-yl-phenyl-methanone (4-17). The representative protocol was followed using piperidine (0.400 mL), TMEDA as base (0.75 equiv.) and heating at 140 ^oC for 20 h. The crude material was purified with 0-18% ethyl acetate/heptane to afford the desired product as an orange solid in 29% yield (55.7 mg, 0.294 mmol). ^1H NMR ($CDCl_3$): δ 7.38 (br s, 5H), 3.72-3.43 (br m, 4H), 1.72-1.59 (m, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ170.4 (C=O), 136.6 (C_{quat}), 129.5, 128.5, 126.9, 26.2, 24.7. HRMS (ESI/$[M+H]^+$) calcd. for $C_{12}H_{16}NO$: 190.12264. Found: 190.12271.

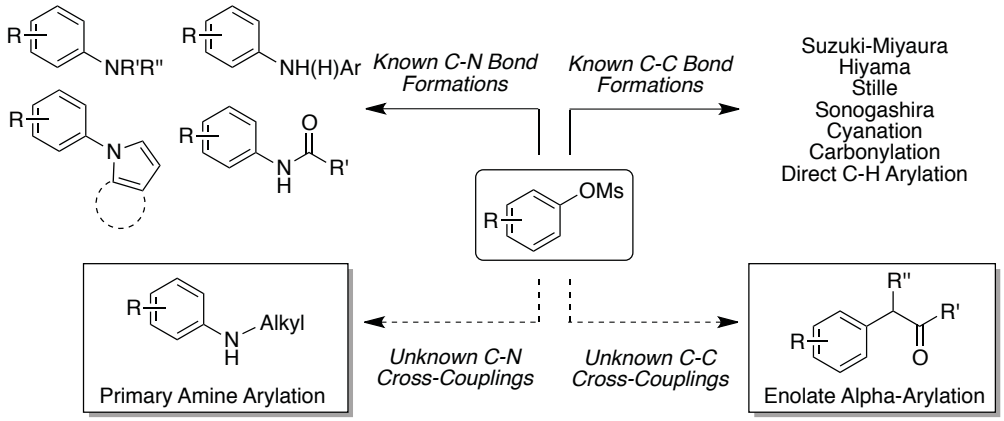
CHAPTER 5 ADDRESSING CHALLENGES IN PALLADIUM-CATALYZED CROSS-COUPLINGS OF ARYL MESYLATES: MONOARYLATION OF KETONES AND PRIMARY ALKYL AMINES

5.1 INTRODUCTION

As discussed in Chapter 1, the development of palladium-catalyzed bond-forming processes has revolutionized modern organic synthesis on both bench-top and industrial scales.[5, 88a, 99] Following what became the Nobel Prize winning contributions of Heck, Negishi and Suzuki in establishing the field of palladium-catalyzed C-C cross-coupling chemistry,[6a, 100] a diversity of alternative and highly effective C-C and C-X (X = N, O, S, *etc.*) bond-forming protocols have emerged. In this process, the optimization of reaction conditions including palladium source, solvent, base, and perhaps most notably ligand has enabled a range of otherwise challenging electrophilic reaction partners to be accommodated,[11, 32a, 33] including aryl chlorides as well as pseudo-halides such as aryl tosylates. Despite this significant progress, comparatively few catalyst systems capable of accommodating aryl methanesulfonates (mesylates) as reaction partners have been reported; the identification of appropriate catalytic conditions that facilitate turnover of the aryl mesylate, including C-O bond activation while circumventing phenol formation (ArO-S bond cleavage), has proven to be a daunting challenge. Nonetheless, significant interest in the use of aryl mesylates as reaction partners persists owing to their low cost, high stability and greater atom economy in comparison to related aryl tosylates or triflates.[101] Furthermore, the derived byproduct following cross-coupling, methanesulfonic acid ($MeSO_3H$), is naturally occurring and undergoes biodegradation in wastewater processing.[102]

The use of aryl mesylates in palladium-catalyzed C-C cross-coupling chemistry, including but not restricted to Suzuki–Miyaura, Hiyama, Stille and Sonogashira reactions, has been described.[101] Conversely, the successful application of aryl mesylates in analogous enolate α-arylation chemistry, a powerful and complementary reaction class developed by Buchwald,[103] Hartwig[104] and others,[105] has yet to be reported (Scheme 5.1). Moreover, while a small number of publications by the groups of Kwong[27b] and Buchwald[27a, 106] detailing the use of aryl mesylates in now-ubiquitous

Buchwald-Hartwig amination chemistry have appeared, these are limited to the arylation of anilines, amides, pyrrolic amines, and secondary aliphatic amines. No examples of the cross-coupling of primary aliphatic amines and aryl mesylates have been reported to date (Scheme 5.1).



Scheme 5.1 Scope of C-C and C-N cross-couplings of aryl mesylates, and reactions to be discussed in this chapter.

Given that palladium-catalyzed enolate α-arylation and Buchwald-Hartwig amination are among the most widely utilized metal-catalyzed C-C and C-N bond-forming methods in modern synthetic chemistry, the identification of catalytic systems capable of accommodating aryl mesylates into such reaction manifolds represents an important target in the effort to further expand the scope of these important protocols. This chapter reports the first examples of enolate α-arylation chemistry, wherein aryl mesylate coupling partners are employed in combination with cyclic and acyclic dialkyl ketones. Also included are the first Buchwald-Hartwig amination reactions involving the combination of primary aliphatic amine and aryl mesylate electrophiles.

The mono-α-arylation of carbonyl compounds with (hetero)aryl (pseudo)halides represents a broadly useful C-C bond-forming reaction that has been extended to a range of α-C-H acidic substrates.[15a] Regarding the parent ketone acetone, mono-α-arylation poses a particular challenge due to the presence of several reactive C-H bonds that increase in acidity upon initial arylation, thus leading to undesired polyarylated products. These challenges have been addressed only recently, with the first examples of acetone mono-α-arylation being reported by the Stradiotto group[62a] employing the [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos catalyst system in combination with both (hetero)aryl

halides and tosylates. Subsequently, Ackermann[107] reported the use of a Pd/XantPhos catalyst for the coupling of aryl imidazolylsulfonates with acetone and other ketones.

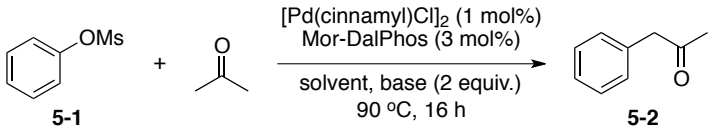
Although a vast combination of (hetero)aryl (pseudo)halides and amines can be cross-coupled by using established BHA methods, the scope of phenol-derived (hetero)aryl electrophiles that have been successfully employed thus far is limited almost exclusively to benzenesulfonates, tosylates, triflates and nonaflates;[23-26, 101a, 101b] only two research groups have achieved C-N cross-coupling reactions of aryl mesylates.[27, 101a, 106] Kwong first reported the coupling of anilines and secondary amines with aryl mesylates employing his Pd/CM-Phos catalyst system;[27b] the scope of the amine reaction partner was limited primarily to anilines and pyrrolic amines, with only three examples of secondary aliphatic amines, and no examples involving primary alkyl amines. Soon after, Buchwald reported the use of the Pd/BrettPhos catalyst system for the coupling of aryl mesylates with anilines, in which only six transformations in total were described.[27a] More recently, the Pd/X-Phos catalyst system has been shown to effectively couple amides with a variety of aryl mesylate partners.[106]

Given the absence of literature reports describing either enolate α-arylation employing aryl mesylates, or the cross-coupling of primary aliphatic amines with aryl mesylates, and the limited number of transformations involving secondary dialkyl amines, focus was turned towards addressing these reactivity limitations. The results of these experiments are described herein.

5.2 Results and Discussion

Encouraged by the desirable performance of $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos in the mono-α-arylation of ketones,[62a, 92] initial efforts were directed towards the identification of suitable reaction conditions employing this catalyst system for the hitherto unknown mono-α-arylation of acetone with phenyl mesylate (**5-1**) to form phenylacetone (**5-2**; Table 5.1). Central to this effort was the quest to identify a suitable base/catalyst pairing that would promote the desired acetone mono-α-arylation reaction while avoiding phenol formation.

Table 5.1 Optimization of the palladium-catalyzed mono-α-arylation of acetone with phenyl mesylate.[a]



5-1 **5-2**

Entry	Solvent (*x* M)	Base	GC Conv. [%][b]	GC yield [%][b]
1	acetone (0.5 M)	Cs_2CO_3	>99	54
2	acetone (0.5 M)	K_3PO_4	95	43
3	1,4-dioxane (0.5 M)	Cs_2CO_3	81	33
4	*t*BuOH (0.5 M)	Cs_2CO_3	>99	14
5[b]	*t*BuOH (0.5 M)	K_3PO_4	>99	78, 56
6[b]	*t*BuOH (0.125 M)	K_3PO_4	>99	87, 84
7[b]	1,4-dioxane (0.125 M)	K_3PO_4	>99	79, 79
8[b]	*t*BuOH/1,4-dioxane (1:1, 0.125 M)	K_3PO_4	>99	85, 85
9	*t*BuOH/1,4-dioxane (1:1, 0.125 M)	Cs_2CO_3	91	31
10[c]	*t*BuOH/1,4-dioxane (1:1, 0.125 M)	NaO*t*Bu	>99	4
11	*t*BuOH/1,4-dioxane (1:1, 0.125 M)	CsF	38	24
12	*t*BuOH/1,4-dioxane (1:1, 0.125 M)	K_2CO_3	48	52

[a] Reaction conditions: 0.2-0.4 mmol **5-1** ([**5-1**]= x M), 10 equiv. acetone except for entries 1 and 2, [Pd]/L ratio=2:3. Conversions and yields determined on the basis of calibrated GC data of **5-1** and **5-2** using dodecane as an internal standard. [b] Yields of duplicate reactions provided. [c] Phenol observed as the major side product.

In adapting the previously optimized conditions established for the mono-α-arylation of acetone with aryl halides and tosylates,[12] the use of 1 mol% $[Pd(cinnamyl)Cl]_2$, 3 mol% Mor-DalPhos, and Cs_2CO_3 as base in acetone (Table 5.1, entry 1) resulted in full conversion of **5-1**, affording the target product **5-2** in 54% GC yield. Substituting K_3PO_4 as the base resulted in high conversion but slightly lower yield of **5-2** (Table 5.1, entry 2). At relatively high concentration of **5-1** (0.5 M), high conversions but low yields resulted from either the use of 1,4-dioxane or *t*-butanol with 10 equiv. of acetone. (Table 5.1, entries 3 and 4). Replacing Cs_2CO_3 with K_3PO_4 in *t*-butanol allowed for both full conversion and a significant increase in the GC yield of **5-2** (Table 5.1, entry 5). However, performing this reaction in duplicate gave inconsistent yields (78 vs 56%), which is believed to be a result of the reactions forming very viscous, non-uniform mixtures upon heating. To circumvent these issues, the reaction concentration was decreased to 0.125 M using *t*-butanol (Table 5.1, entry 6), resulting in high and reproducible yields of **5-2**; however, the reaction mixtures continued to become viscous, thereby preventing uniform stirring. Employing 1,4-dioxane under these dilute conditions allowed for more uniform stirring but gave a slightly lower reproducible yield of **5-2** (Table 5.1, entry 7). Thus, it was decided to employ these two solvents together in

a 1:1 ratio; under these conditions **5-2** was obtained in reproducible GC yields of 85% (Table 5.1, entry 8). Performing the reaction in the absence of ligand and/or palladium resulted in approximately 50% conversion of **5-1**, with no formation of **5-2** observed. Alternative bases were also tested under these optimal solvent conditions (NaO*t*Bu, CsF, K_2CO_3; Table 5.1, entries 10-12) but were shown to give poor conversion of **5-1** and/or low yield of **5-2**, thereby establishing K_3PO_4 as the optimal base for this transformation.

In an effort to assess the influence of the ancillary ligand on the course of the reaction, a judiciously selected range of mono- and bisphosphines that have proven effective in the palladium-catalyzed α-arylation of carbonyl compounds, in Buchwald-Hartwig amination, or in alternative cross-coupling applications employing aryl mesylates, were tested under the optimized conditions (Figure 5.1). Both Me-DalPhos and P(*o*-tol)$_2$-DalPhos afforded minimal conversion and none of the desired product **5-2**; similarly poor results were obtained with XantPhos (under the optimized conditions described herein or under previously reported conditions[13]), BippyPhos and a palladacycle/X-Phos catalyst. Furthermore, the use of the JosiPhos variant CyPF*t*Bu, or ligands used to facilitate C-N cross-coupling reactions of aryl mesylates (CM-Phos and BrettPhos), in each case afforded GC yields of **5-2 (**29-42%) that were inferior to yields obtained when using the Mor-DalPhos-based catalyst.

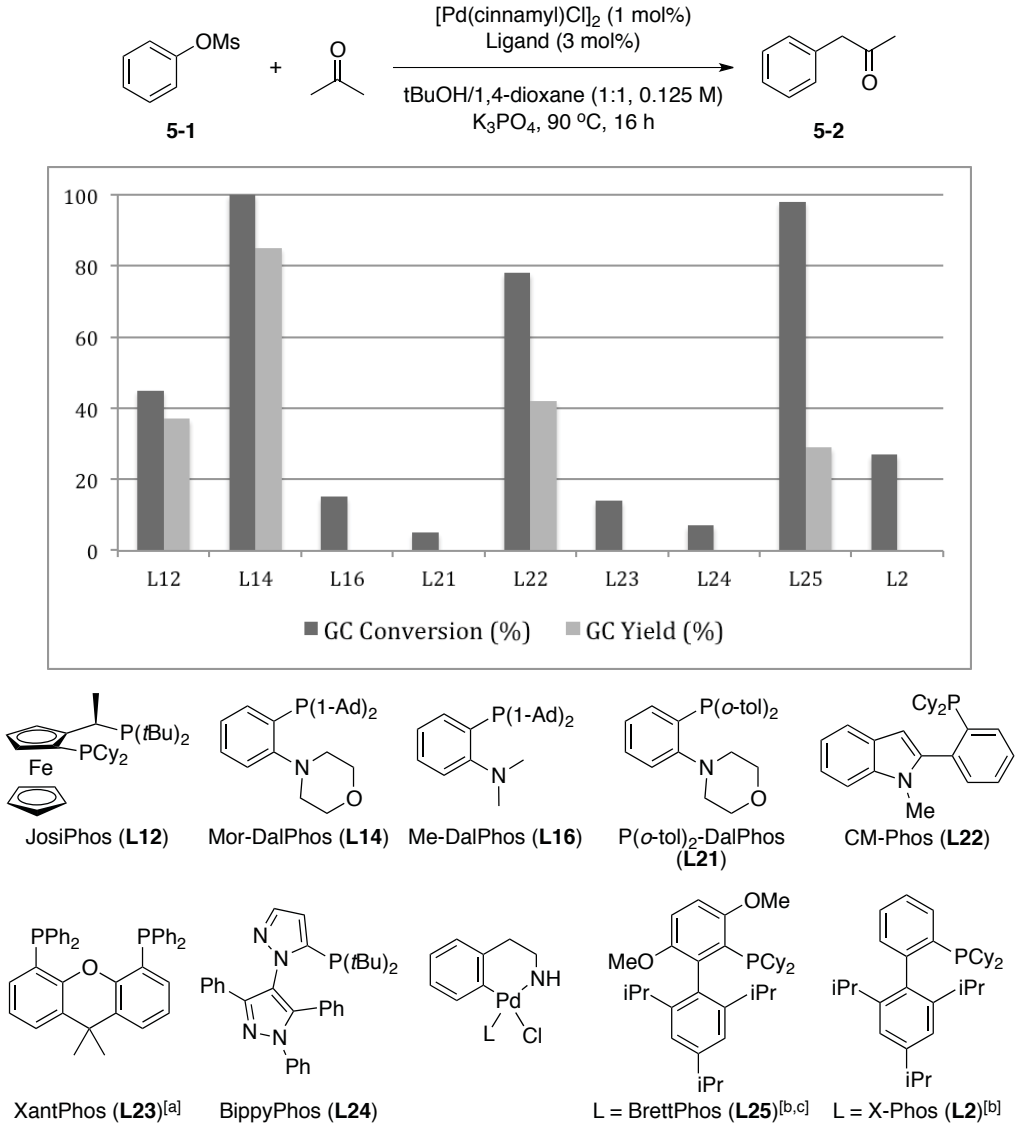


Figure 5.1 Ligand comparisons in the mono-α-arylation of acetone with phenyl mesylate. Reaction conditions: 0.4 mmol **5-1**, 10 equiv. acetone, [Pd]:L ratio = 2:3. Conversions and yields determined on the basis of calibrated GC data using dodecane as an internal standard. Phenol is the major side product in most cases. [a] 23% conv., 0% yield with secondary conditions: 5 mol% $Pd(OAc)_2$, 10 mol% XantPhos, 14 equiv. acetone, 2 equiv. Cs_2CO_3, 1,4-dioxane (0.25 M), 80 °C. [b] 2 mol% palladacycle, 2 mol% ligand. [c] Significant polyarylation observed.

Having established the suitability of the $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos catalyst system as well as optimal conditions for the coupling of acetone and phenyl mesylate, the scope of aryl mesylates was then explored in the mono-α-arylation of acetone (Figure 5.2). Electron-neutral and electron-rich aryl mesylates were well tolerated in the reaction affording >80% yields of the benzyl methyl ketone products (**5-2** to **5-7**). Fused aryl mesylate substrates also proved to be good reaction partners (**5-8** and **5-9**), including a

quinoline derivative. Substituted (hetero)biaryl benzyl ketone derivatives were also prepared in this manner (47-77%, **5-10**-**5-13**), demonstrating the tolerance of pyrrole (**5-10**), 4-trifluoromethylphenyl (**5-12**) and 4-benzonitrile (**5-13**) substituents within the mesylate reagent. A 4-phenoxyphenyl-derived product (**5-14**) was also obtained in a high isolated yield (83%) that was comparable to that obtained for the more electron-rich 4-methoxy analogue (**5-4**, 84%).

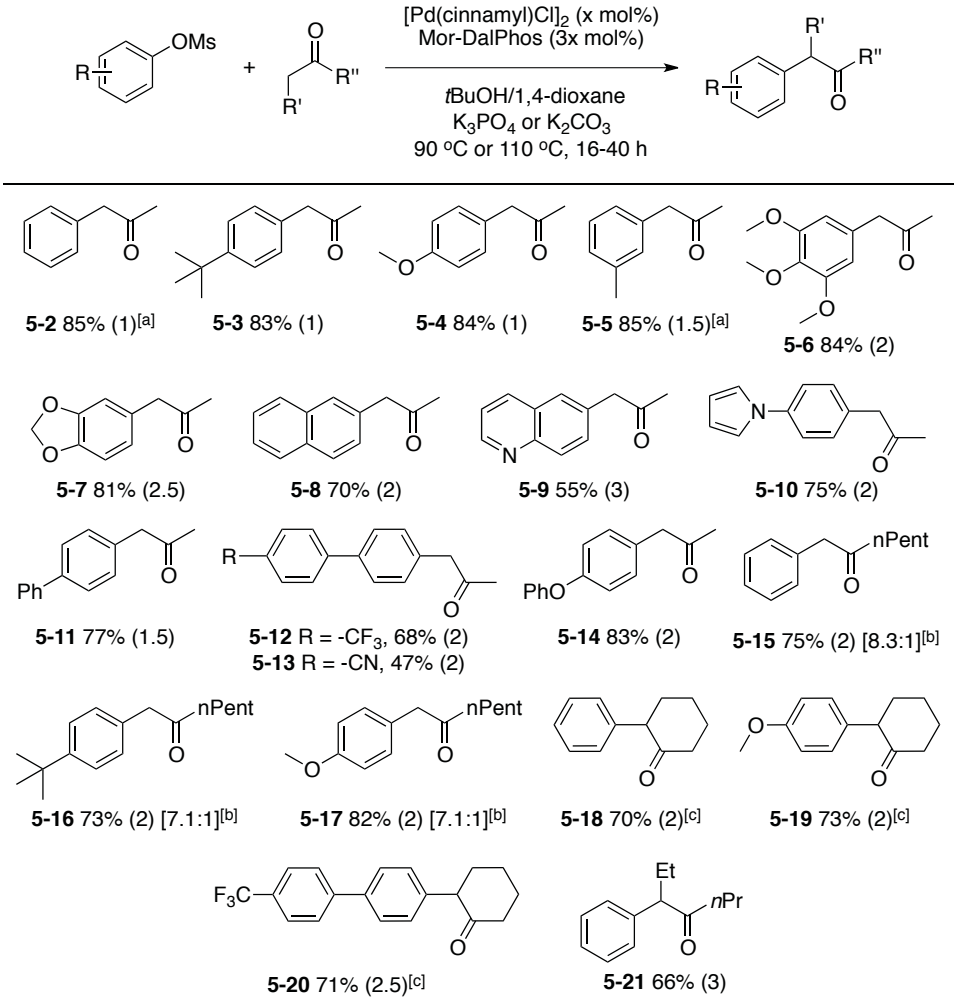


Figure 5.2 Scope of the palladium-catalyzed *α*-arylation of ketones with aryl mesylates. Reaction conditions: 0.6-0.8 mmol ArOMs, 5-10 equiv. ketone, [Pd]:L = 2:3, [ArOMs]=0.5-0.125 M, see Section 5.4. Yields are of isolated material, mol% $[Pd(cinnamyl)Cl]_2$ indicated in parentheses. [a] Yield determined on the basis of calibrated GC data using dodecane as an internal standard. [b] Mixture of regioisomers; ratio indicated in brackets with major product shown. [c] Used *t*-butanol solvent, K_2CO_3, 110 °C.

Efforts to optimize the established conditions to allow for the accommodation of electron-poor and *ortho*-substituted aryl mesylates were unsuccessful, mainly resulting in

decomposition of the starting materials to the corresponding aryl alcohol. Nevertheless, the scope was extended to the use of other linear and cyclic aliphatic ketones. 2-Heptanone and cyclohexanone were found to be suitable coupling partners, affording the desired benzyl ketones in high isolated yields (**5-15** to **5-20**). For the products formed from 2-heptanone (**5-15** to **5-17**), a mixture of regioisomers was obtained in each case, where the major product corresponded to monoarylation at the α-methyl position and the minor at the α-CH_2-C_4H_9 of the ketone (determined on the basis of ^{1}H NMR data); these could not be easily separated by use of column chromatography. Changing the base to K_2CO_3 at 110 ^oC (0.5 M [ArOMs] in *t*-butanol) allowed for cyclohexanone mono-α-arylation (**5-18** to **5-20**). Additionally, 4-heptanone was accommodated in this chemistry under more forcing reaction conditions, providing **5-21** in 66% isolated yield. Attempts to α-arylate acetophenone were successful to a certain extent; employing CsF as the base afforded 68% yield of a mixture of mono- and diarylation products in a 7.6:1 ratio favouring mono-α-arylation. Thus, further optimization is required in order to promote the selective mono-α-arylation of aryl ketone coupling partners.

Encouraged by the success in developing the first examples of enolate α-arylation employing aryl mesylate coupling partners, attention was then focused on expanding the scope of BHA chemistry to primary alkyl amines involving such challenging electrophiles using [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos mixtures (Figure 5.3).[49, 62b, 108] It was pleasing to find that cyclic dialkyl amines such as morpholine (**5-22** and **5-23**) and pyrrolidine (**5-24**) afforded the corresponding aryl amines in excellent yields. Dimethylamine performed similarly well both with phenyl mesylate producing **5-25** (98%), as well as with a xylyl mesylate where the derived volatile aryl amine was obtained in high isolated yield (80%, **5-26**). Notably, octylamine was well tolerated in reactions employing either the parent phenyl mesylate **5-1** (98%, **5-27**) or the more sterically hindered *o*-tolyl mesylate (62%, **5-28**). Aniline, serving as a representative example of primary aromatic amines, proved to be a favourable reaction partner in this system, requiring low catalyst loading (1 mol% Pd) and achieving nearly quantitative yield of diphenylamine (**5-29**). Both cyclohexylamine and the hydrazine derivative 1-amino-4-methylpiperazine, were also mono-*N*-arylated successfully, each in >80% isolated yield (**5-30** and **5-31**).

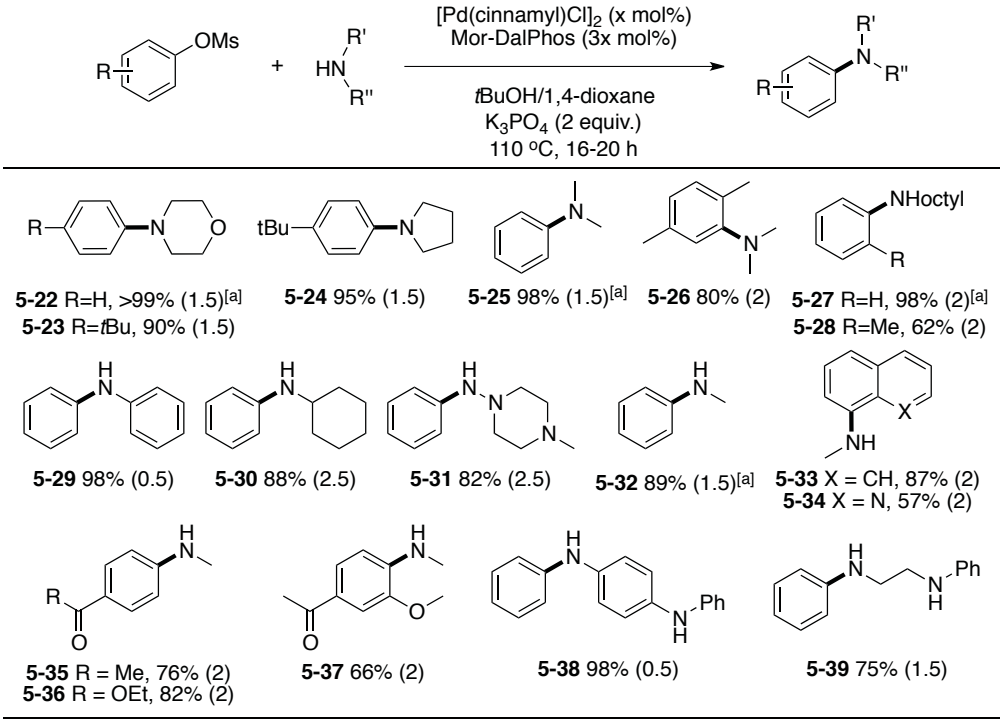


Figure 5.3 Scope of the palladium-catalyzed amination of aryl mesylates.
Reaction conditions: 0.6-1.0 mmol ArOMs, 1.1-5 equiv. amine, [Pd]:L = 2:3, [ArOMs]=0.25-0.1 M, see Section 5.4. Yields are of isolated material, mol% $[Pd(cinnamyl)Cl]_2$ indicated in parentheses. [a] Yield determined on the basis of calibrated GC data using dodecane as an internal standard.

In select cases, reactions employing morpholine, dimethylamine or octylamine in combination with sterically hindered or electronically activated aryl mesylates resulted in minimal formation of the desired aniline derivative due to competing background reactions involving sulfonyl transfer.[109] For example, in the reaction of 3-pyridylmethanesulfonate with morpholine, the major product isolated was *N*-methanesulfonylmorpholine, as confirmed by ^{1}H NMR and HRMS techniques. However, methylamine, which can be a challenging substrate in its own right in BHA chemistry,[27a, 38, 65, 108, 110] was employed without difficulty in cross-coupling reactions involving aryl mesylates featuring *ortho*-substitutents and/or electron-withdrawing groups. The standard reaction of methylamine with phenyl mesylate (**5-1**) proceeded cleanly affording the target aniline (**5-32**) in high yield, as did the analogous reaction leading to the naphthyl derivative (**5-33**); 8-quinolinyl mesylate was also accommodated in this chemistry (**5-34**). The acetophenone derivatives **5-35** and **5-37** were synthesized in good yields, thereby establishing the ability to conduct N-H arylation reactions

chemoselectively in the presence of functionality featuring enolizable protons as well as electron-withdrawing, base-sensitive functional groups. Further functional group tolerance was established in the synthesis of the ethyl ester **5-36** (82%). Finally, substrates containing two potentially reactive N-H sites were selectively monoarylated at the primary amine sites (**5-38** and **5-39**), thereby further demonstrating the chemoselective capabilities of this transformation.

5.3 Summary and Conclusions

The findings in this chapter establish the first examples of ketone mono-α-arylation using aryl mesylates, as well as for the first time the amination of these inexpensive phenol derivatives with primary aliphatic amines. The $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos catalyst system allowed for a range of substituted aryl mesylates to be coupled with both cyclic and acyclic dialkyl ketones, including acetone – normally a challenging reagent in mono-α-arylation chemistry. Applying these optimized ketone α-arylation conditions to Buchwald-Hartwig amination enabled the mono-*N*-arylation of primary and secondary aliphatic amines, including methylamine, employing aryl mesylates featuring electron-donating or electron-withdrawing functionality, *ortho*-substitution, as well as base-sensitive groups. Furthermore, the amination protocol displayed chemoselectivity, favoring cross-coupling of the primary amine in each case. This work expands the range of coupling partners that can be accommodated with aryl mesylates, and also expands further the scope of reactions catalyzed by the Pd/Mor-DalPhos system utilizing inexpensive non-halide arene starting materials.

5.4 Experimental Section

5.4.1 General Considerations

Unless otherwise noted, all reactions were setup inside a dinitrogen-filled inert atmosphere glovebox and worked up in air using benchtop procedures. 1,4-Dioxane and *tert*-butanol (Aldrich) were dried over Na/benzophenone or CaH_2 (respectively) followed by distillation under an atmosphere of dinitrogen. Dichloromethane was deoxygenated by sparging with dinitrogen followed by passage through an mBraun double column solvent

purification system packed with alumina and copper-Q5 reactant. $[Pd(cinnamyl)Cl]_2$[56] was prepared according to a literature procedure or purchased from Aldrich; all other ligands and chemicals were obtained from either Strem or Aldrich in high purity. All methylamine and dimethylamine cross-coupling reactions were conducted with bottles of 2.0 M $MeNH_2$ and 2.0 M Me_2NH in THF. Column chromatography was carried out using Silicycle SiliaFlash 60 with particle size 40-63 μm (230-400 mesh) or using neutral alumina oxide (150 mesh) Brockmann-3 (activated); silica was employed unless otherwise stated. Conversions and yields based on gas chromatography data were corrected by calibration with internal standards of dodecane and product identity was confirmed on the basis of ^1H NMR and/or by comparison with authentic samples. In cases where characterization data for known compounds matches that previously reported in the literature, the corresponding reference is provided. Unless otherwise indicated, ^1H and ^{13}C NMR characterization data were collected at 300 K on a Bruker AV-500 spectrometer operating at 500.1 and 125.8 MHz (respectively) with chemical shifts reported in parts per million downfield of $SiMe_4$. In some cases, fewer than expected unique ^{13}C NMR resonances were observed, despite prolonged acquisition times. NMR data were acquired with the technical assistance of Dr. Michael Lumsden (NMR-3, Dalhousie University), while mass spectrometric data were acquired by Mr. Xiao Feng (Mass Spectrometry Laboratory, Dalhousie University). Chemical shifts of common trace ^1H NMR impurities ($CDCl_3$, ppm): t-butanol, 1.44; H_2O, 1.56; EtOAc, 1.26, 2.05, 4.12; CH_2Cl_2, 5.30; $CHCl_3$, 7.26; (DMSO-d_6, ppm): DMSO, 2.50; H_2O, 3.33.

5.4.2 Synthesis and Characterization

Synthesis of Aryl Mesylates: All previously reported aryl mesylates were prepared according to literature procedures[111] from their corresponding phenols with MsCl (1.2 equiv.) in the presence of anhydrous pyridine (5 equiv.) and anhydrous CH_2Cl_2 ([ArOH] = 1.23 M). Data for previously unreported aryl mesylates and corresponding precursors are provided below.

4'-(trifluoromethyl)-[1,1'-biphenyl]-4-ol. Prepared from 4-chloro-4'-(trifluoromethyl)-1,1'-biphenyl (3.5 mmol) using a literature procedure[113] and purified with 25%

EtOAc/hexanes by using column chromatography to afford the product as a beige powder in 83% yield (697 mg, 2.9 mmol). ^{1}H NMR ($CDCl_3$): δ 7.67-7.63 (m, 4H), 7.51-7.48 (m, 2H), 6.95-6.92 (m, 2H), 4.84 (s, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 155.9, 144.3, 132.7, 128.8, 127.0, 125.8 (J_{CF} = 3.5 Hz), 116.0. Some ^{13}C peaks are not visible due to strong C-F coupling and overlapping peaks. Agrees with data previously reported in the literature.[112]

4'-hydroxy-[1,1'-biphenyl]-4-carbonitrile. Prepared from 4'-chloro-[1,1'-biphenyl]-4-carbonitrile (5.3 mmol) using a literature procedure[113] and purified with 25% EtOAc/hexanes by using column chromatography to afford the product as a yellow solid in 72% yield (773 mg, 2.9 mmol). ^{1}H NMR (DMSO-d_6): δ 9.81 (s, 1H), 7.85-7.83 (m, 2H), 7.80-7.78 (m, 2H), 7.60 (d, J = 7.0 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (DMSO-d_6): δ 158.4, 144.7, 132.8, 128.8, 128.4, 126.6, 119.1, 116.0, 108.7. Agrees with data previously reported in the literature.[114]

4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl methanesulfonate. Prepared using literature methods[111] on a 2.85 mmol scale and purified with 20-30% EtOAc/hexanes by using column chromatography to afford the product as an off-white solid in 99% yield (896 mg, 2.82 mmol). ^{1}H NMR (DMSO-d_6): δ 7.93-7.91 (m, 2H), 7.87-7.83 (m, 4H), 7.50-7.49 (m, 2H), 3.44 (s, 3H). $^{13}C\{^{1}H\}$ NMR (DMSO-d_6): δ 149.3, 142.9, 137.7, 128.9, 128.2 (J_{CF} = 31.9 Hz), 127.7, 125.9 (J_{CF} = 3.4 Hz), 124.3 (J_{CF} = 272 Hz), 123.0, 37.5. Some ^{13}C peaks are not visible due to strong C-F coupling and overlapping peaks. HRMS (ESI): calcd for $C_{14}H_{11}F_3NaO_3S$ (M+Na): 339.0273; found: 339.0274.

4'-cyano-[1,1'-biphenyl]-4-yl methanesulfonate. Prepared using literature methods[111] on a 3.84 mmol scale and purified with 30-50% EtOAc/hexanes by using column chromatography to afford the product as a beige crystalline solid in 87% yield (915 mg, 3.34 mmol). ^{1}H NMR (DMSO-d_6): δ 7.96-7.94 (m, 2H), 7.91-7.90 (m, 2H), 7.88-7.86 (m, 2H), 7.51-7.48 (m, 2H), 3.44 (s, 3H). $^{13}C\{^{1}H\}$ NMR (DMSO-d_6): δ 149.5, 143.4, 137.4, 133.0, 129.0, 127.8, 123.0, 118.8, 110.4, 37.5. HRMS (ESI): calcd for $C_{14}H_{11}NNaO_3S$ (M+Na): 296.0352; found: 296.0345.

4-phenoxyphenyl methanesulfonate. Prepared using literature methods[111] on a 3.5 mmol scale to afford the product as a white solid in quantitative yield (944 mg). ^{1}H NMR (DMSO-d_6): δ 7.44-7.40 (m, 2H), 7.38-7.35 (m, 2H), 7.18 (m, 1H), 7.10-7.04 (m, 4H), 3.38 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6): δ 156.2, 155.6, 144.4, 130.2, 124.0, 119.6, 119.0, 37.1. HRMS (ESI): calcd for $C_{13}H_{12}NaO_4S$ (*M*+Na): 287.0349; found: 287.0351.

2,5-dimethylphenyl methanesulfonate. Prepared using literature methods[111] on a 2.5 mmol scale and purified with 10% EtOAc/hexanes by using column chromatography to afford the product as a white crystalline solid in 87% yield (434 mg, 2.2 mmol). ^{1}H NMR ($CDCl_3$): δ 7.14 (d, *J* = 7.7 Hz, 1H), 7.10 (s, 1H), 7.02 (m, 1H), 3.18 (s, 3H), 2.33 (s, 3H), 2.31 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 147.8, 137.6, 131.7, 128.2, 128.0, 122.6, 38.2, 21.0, 16.3. HRMS (ESI): calcd for $C_9H_{12}NaO_3S$ (*M*+Na): 223.0399; found: 223.0401.

Representative procedure for the coupling of aryl mesylates with acetone: In a dinitrogen-filled glovebox, a screw-cap vial was charged with a stir bar, Mor-DalPhos (8.3 mg, 0.018 mmol, 3 mol%), K_3PO_4 (254.7 mg, 1.2 mmol, 2.0 equiv.) and *tert*-butylphenyl methanesulfonate (137.0 mg, 0.6 mmol) followed by 0.3 mL of a stock solution (10.3616 mg/mL concentration) of $[Pd(cinnamyl)Cl]_2$ (0.012 mmol, 2 mol% Pd, Pd:L = 2:3) in 1,4-dioxane. To the mixture was then added 2.1 mL of 1,4-dioxane, 2.4 mL of *t*-butanol ([PhOMs]=0.125 M, 1:1 1,4-dioxane/*t*-butanol) and acetone (0.440 mL, 6 mmol, 10 equiv.). The vial was capped, stirred briefly, removed from the glovebox and placed in a temperature-controlled aluminum-heating block preset to 90 ^{o}C. The reaction stirred for 16-20 h, at which time TLC confirmed full consumption of starting material. The reaction was then cooled, diluted with EtOAc (30 mL) and washed with 1:1 water/brine (50 mL). The aqueous extract was washed with an additional 10 mL EtOAc and the organic extracts were then combined, dried with Na_2SO_4 and filtered. Silica powder (0.5-1.0 g) was then added to the solution of crude material. The solvent was removed from the silica-product mixture and the compound was purified by use of column chromatography with 5% EtOAc/hexanes to yield 1-(4-*tert*-butylphenyl)propan-2-one (**5-3**) as a colourless oil in 83% yield (95 mg, 0.50 mmol). ^{1}H NMR ($CDCl_3$): δ

7.37-7.34 (m, 2H), 7.15-7.13 (m, 2H), 3.67 (s, 2H), 2.16 (s, 3H), 1.32 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 206.9, 150.1, 131.3, 129.2, 125.8, 50.7, 34.6, 31.5, 29.5. Agrees with that previously reported in the literature.[62a]

1-(4-methoxyphenyl)propan-2-one (5-4). The representative procedure was followed to afford the product as a colourless oil in 84% yield (83 mg, 0.51 mmol) containing 5% of a possible diarylated product. ^{1}H NMR ($CDCl_3$): δ 7.13-7.10 (m, 2H), 6.89-6.86 (m, 2H), 3.80 (s, 3H), 3.63 (s, 2H), 2.14 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 207.0, 158.8, 130.5, 126.4, 114.3, 55.4, 50.3, 29.3. Agrees with data previously reported in the literature.[62a]

1-(3,4,5-trimethoxyphenyl)propan-2-one (5-6). The representative procedure was followed using 4 mol% Pd and purified using 25-35% EtOAc/hexanes to afford the product as a white solid in 84% yield (113 mg, 0.50 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.40 (s, 2H), 3.83 (s, 6H), 3.82 (s, 3H), 3.61 (s, 2H), 2.16 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 206.4, 153.5, 137.2, 129.9, 106.5, 60.9, 56.2, 51.3, 29.3. Agrees with data previously reported in the literature.[107]

1-(benzo[*d*][1,3]dioxol-5-yl)propan-2-one (5-7). The representative procedure was followed using 5 mol% Pd and 0.5 M [ArOMs] on a 0.800 mmol scale and purified with 10% EtOAc/hexanes to afford the product as a brown oil in 81% yield (116 mg, 0.65 mmol) containing 5% of a possible diarylated product. ^{1}H NMR ($CDCl_3$): δ 6.77 (d, J = 7.9 Hz, 1H), 6.68 (d, J = 1.3 Hz, 1H), 6.64 (dd, J = 7.9, 1.2 Hz, 1H), 5.95 (s, 2H), 3.60 (s, 2H), 2.15 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 206.7, 148.0, 146.8, 127.9, 122.7, 109.9, 108.6, 101.2, 50.7, 29.3. Agrees with data previously reported in the literature.[62a]

1-(naphthalen-2-yl)propan-2-one (5-8). The representative procedure was followed using 4 mol% Pd, 0.5 M [ArOMs] on a 0.800 mmol scale using and purified with 6-8% EtOAc/hexanes to afford the product as an orange oil in 70% yield (103 mg, 0.56 mmol). ^{1}H NMR ($CDCl_3$): δ 7.84-7.80 (m, 3H), 7.68 (s, 1H), 7.51-7.45 (m, 2H), 7.33 (dd, J = 8.4, 1.6 Hz, 1H), 3.86 (s, 2H), 2.19 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 206.6, 133.7,

132.6, 131.9, 128.6, 128.3, 127.8, 127.7, 127.5, 126.4, 126.0, 51.3, 29.5. Agrees with data previously reported in the literature.[107]

1-(quinolin-6-yl)propan-2-one (5-9). The representative procedure was followed using 6 mol% Pd, 0.5 M [ArOMs] on a 0.800 mmol scale and purified using 40% EtOAc/CH_2Cl_2 on alumina followed by 30% EtOAc/CH_2Cl_2 on silica to afford the product as a yellow oil in 55% yield (82 mg, 0.44 mmol). ^{1}H NMR ($CDCl_3$): δ 8.90 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.11 (m, 1H), 8.08 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 1.3 Hz, 1H), 7.55 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.90 (s, 2H), 2.22 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 205.9, 150.5, 147.6, 135.9, 132.7, 131.3, 130.0, 128.4, 128.1, 121.5, 50.8, 29.7. Agrees with data previously reported in the literature.[107]

1-(4-(1H-pyrrol-1-yl)phenyl)propan-2-one (5-10). The representative procedure was followed using 4 mol% Pd, 0.25 M [ArOMs] on a 0.800 mmol scale and purified using 20% MTBE/hexanes on alumina to afford the product as a beige solid in 75% yield (120 mg, 0.60 mmol). ^{1}H NMR ($CDCl_3$): δ 7.38-7.36 (m, 2H), 7.26-7.25 (m, 2H), 7.08-7.07 (m, 2H), 6.35-6.34 (m, 2H), 3.73 (s, 2H), 2.20 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 206.2, 139.9, 131.6, 130.7, 120.9, 119.4, 110.6, 50.3, 29.6. Agrees with data previously reported in the literature.[62a]

1-([1,1'-biphenyl]-4-yl)propan-2-one (5-11). The representative procedure was followed using 3 mol% Pd, 0.25 M [ArOMs] on a 0.800 mmol scale and purified using 8-9% EtOAc/hexanes to afford the product as a orange solid in 77% yield (130 mg, 0.62 mmol). ^{1}H NMR ($CDCl_3$): δ 7.60-7.57 (m, 4H), 7.46-7.43 (m, 2H), 7.36 (m, 1H), 7.30-7.28 (m, 2H), 3.76 (s, 2H), 2.21 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 206.5, 140.8, 140.1, 133.3, 130.0, 128.9, 127.6, 127.4, 127.2, 50.7, 29.5. Agrees with data previously reported in the literature.[107]

1-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)propan-2-one (5-12). The representative procedure was followed using 4 mol% Pd, 0.25 M [ArOMs] and purified using 20% MTBE/hexanes on alumina followed by 8% EtOAc/hexanes on alumina to afford the

product as a white solid in 68% yield (113 mg, 0.41 mmol). ^{1}H NMR ($CDCl_3$): δ 7.71-7.67 (m, 4H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 3.77 (s, 2H), 2.22 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 206.1, 144.4, 138.7, 134.4, 130.2, 129.5 (q, J_{CF} = 32.7 Hz), 127.7, 127.5, 125.9 (J_{CF} = 3.8 Hz), 124.4 (J_{CF} = 271.7 Hz), 50.6, 29.7. Some ^{13}C peaks are not visible due to strong C-F coupling and overlapping peaks. HRMS (ESI): calcd for $C_{16}H_{13}F_3NaO$ (*M*+Na): 301.811; found: 301.0798.

1-(4'-cyano-[1,1'-biphenyl]-4-yl)propan-2-one (5-13). The representative procedure was followed using 4 mol% Pd with a reaction time of 24 h and purified using 40% MTBE/hexanes on alumina to afford the product as an off-white solid in 47% yield (66 mg, 0.28 mmol). ^{1}H NMR ($CDCl_3$): δ 7.73-7.71 (m, 2H), 7.68-7.66 (m, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 3.78 (s, 2H), 2.22 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 205.9, 145.3, 138.1, 134.9, 132.8, 130.4, 127.8, 127.7, 119.1, 111.1, 50.6, 29.7. HRMS (ESI): calcd for $C_{16}H_{13}NNaO$ (*M*+Na): 258.0889; found: 258.0897.

1-(4-phenoxyphenyl)propan-2-one (5-14). The representative procedure was followed using 4 mol% Pd and purified using 10% MTBE/hexanes on alumina to afford the product as a beige oil in 83% yield (113 mg, 0.50 mmol). ^{1}H NMR ($CDCl_3$): δ 7.35-7.32 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.98-6.97 (m, 2H), 3.68 (s, 2H), 2.18 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 206.6, 157.2, 156.5, 130.9, 129.9, 129.1, 123.5, 119.1, 119.1, 50.3, 29.5. Agrees with data previously reported in the literature.[62a]

Representative procedure for the coupling of aryl mesylates with 2- or 4-heptanone: In a dinitrogen-filled glovebox, a screw-cap vial was charged with a stir bar, $[Pd(cinnamyl)Cl]_2$ (15.5 mg, 0.06 mmol, 4 mol% Pd), Mor-DalPhos (41.7 mg, 0.09 mmol, 6 mol%), K_3PO_4 (636.8 mg, 3 mmol, 2.0 equiv.) and phenyl methanesulfonate (258 mg, 1.5 mmol) 0.6 mL of 1,4-dioxane, 0.6 mL of *t*-butanol ([PhOMs]=0.5 M, 1:1 1,4-dioxane/*t*-butanol) and 2-heptanone (2.089 mL, 15 mmol, 10 equiv.). The vial was capped, stirred briefly, removed from the glovebox and placed in a temperature-controlled aluminum-heating block preset to 90 ^{o}C. The reaction stirred for 16-20 h, at

which time TLC confirmed full consumption of starting material. The reaction was then cooled, diluted with EtOAc (30 mL) and washed with 1:1 water/brine (50 mL). The aqueous extract was washed with an additional 10 mL EtOAc. The organic extracts were then combined, dried with Na_2SO_4, filtered and silica powder (0.5-1.0 g) was added to the solution of crude material. The solvent was removed from the silica-product mixture and the compound was purified by use of column chromatography with 2% EtOAc/hexanes to yield 1-phenylheptan-2-one (**5-15**) as a colourless oil in 75% yield (214 mg, 1.13 mmol) as a 8.3:1 mixture of regioisomers, as determined on the basis of ^{1}H NMR data (characterization data listed for that of the major product only). ^{1}H NMR ($CDCl_3$): δ 7.34-7.31 (m, 2H), 7.26 (m, 1H), 7.21-7.20 (m, 2H), 3.68 (s, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 1.55 (apparent pentent, *J* = 7.5 Hz, 2H), 1.31-1.18 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 208.8, 134.5, 129.5, 128.8, 127.1, 50.3, 42.1, 31.4, 23.6, 22.5, 14.0. HRMS (ESI): calcd for $C_{13}H_{18}NaO$ (*M*+Na): 213.1250; found: 213.1241.

1-(4-(tert-butyl)phenyl)heptan-2-one (5-16). The representative procedure was followed using 0.6 mmol ArOMs and 2% EtOAc/hexanes for purification to afford the product as a colourless oil in 73% yield (108 mg, 0.44 mmol) as a 7.1:1 mixture of regioisomers. ^{1}H NMR ($CDCl_3$): δ 7.35-7.34 (m, 2H), 7.14-7.13 (m, 2H), 3.65 (s, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 1.58-1.52 (m, 2H), 1.31 (s, 9H), 1.29-1.19 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 209.1, 149.9, 131.4, 129.2, 127.9, 125.8, 49.8, 42.1, 34.6, 31.5, 23.6, 22.6, 14.1. HRMS (ESI): calcd for $C_{17}H_{26}NaO$ (*M*+Na): 269.1876; found: 269.1885.

1-(4-methoxyphenyl)heptan-2-one (5-17). The representative procedure was followed using 0.6 mmol ArOMs and 5 equiv. 2-heptanone, and purified with 5% EtOAc/hexanes to afford the product as a colourless oil in 82% yield (108 mg, 0.49 mmol) as a 7.1:1 mixture of regioisomers. ^{1}H NMR ($CDCl_3$): δ 7.13-7.10 (m, 2H), 6.88-6.85 (m, 2H), 3.80 (s, 3H), 3.61 (s, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.57-1.51 (m, 2H), 1.29-1.19 (m, 4H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 209.3, 158.7, 130.5, 126.6, 114.2, 55.4, 49.4, 41.9, 31.4, 23.6, 22.6, 14.0. Agrees with data previously reported in the literature.[107]

3-phenylheptan-4-one (5-21). The representative procedure was followed using 0.8 mmol of PhOMs with 5 equiv. 4-heptanone, 6 mol% Pd and 40 h reaction time followed by purification with 5% EtOAc/hexanes to afford the product as a yellow oil in 66% yield (101 mg, 0.53 mmol). ^{1}H NMR ($CDCl_3$): δ 7.33-7.30 (m, 2H), 7.24 (m, 1H), 7.21-7.20 (m, 2H), 3.52 (t, *J* = 7.0 Hz, 1H), 2.35-2.31 (m, 2H), 2.06 (m, 1H), 1.70 (m, 1H), 1.50 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H), 0.79 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 210.8, 139.2, 128.9, 128.5, 127.2, 60.9, 44.0, 25.4, 17.3, 13.7, 12.3. HRMS (ESI): calcd for $C_{13}H_{18}NaO$ (*M*+Na): 213.1250; found: 213.1240.

Representative procedure for the coupling of aryl mesylates with cyclohexanone: In a dinitrogen-filled glovebox, a screw-cap vial was charged with a stir bar, [Pd(cinnamyl)Cl]$_2$ (6.2 mg, 0.024 mmol, 4 mol% Pd, Pd:L = 2:3), Mor-DalPhos (16.7 mg, 0.036 mmol, 6 mol%), K_2CO_3 (165.9 mg, 1.2 mmol, 2.0 equiv.), phenyl methanesulfonate (103 mg, 0.6 mmol), 1.2 mL of *t*-butanol ([PhOMs]=0.5 M) and cyclohexanone (0.621 mL, 6 mmol, 10 equiv.). The vial was capped, stirred briefly, removed from the glovebox and placed in a temperature-controlled aluminum-heating block preset to 110 ^{o}C. The reaction stirred for 16-20 h, at which time TLC confirmed full consumption of starting material. The reaction was cooled, diluted with EtOAc (30 mL) and washed with 1:1 water/brine (50 mL). The aqueous extract was washed with an additional 10 mL EtOAc. The organic extracts were then combined, dried with Na_2SO_4, and filtered. Silica powder (0.5-1.0 g) was added to the crude material, and the solvent was removed from the silica-product mixture. The compound was purified by use of column chromatography with 5% EtOAc/hexanes to yield 2-phenylcyclohexanone (**5-18**) as a yellow solid in 70% yield (73 mg, 0.42 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.31 (m, 2H), 7.26 (m, 1H), 7.16-7.12 (m, 2H), 3.62 (dd, *J* = 11.8, 5.4 Hz, 1H), 2.58-2.40 (m, 2H), 2.28 (m, 1H), 2.20-1.95 (m, 3H), 1.92-1.79 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 210.4, 138.9, 128.7, 128.5, 127.0, 57.5, 42.3, 35.2, 28.0, 25.5. Agrees with material commercially available from Aldrich.

2-(4-methoxyphenyl)cyclohexanone (5-19). The representative procedure was followed with a reaction time of 36 h and purified using 10% EtOAc/hexanes to afford the product as a yellow solid in 73% yield (90 mg, 0.44 mmol). ^{1}H NMR ($CDCl_3$): δ 7.07-7.05 (m, 2H), 6.89-6.87 (m, 2H), 3.80 (s, 3H), 3.57 (dd, *J* = 12.3, 5.5 Hz, 1H), 2.53 (m, 1H), 2.46 (m, 1H), 2.26 (m, 1H), 2.15 (m, 1H), 2.03-1.96 (m, 2H), 1.84-1.79 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 210.9, 158.6, 131.0, 129.6, 113.9, 56.7, 55.4, 42.3, 35.4, 28.0, 25.5. Agrees with data previously reported in the literature.[115]

2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)cyclohexanone (5-20). The representative procedure was followed using 5 mol% Pd and purified on alumina with 20% MTBE/hexanes to afford the product as a white solid in 71% yield (135 mg, 0.42 mmol). ^{1}H NMR ($CDCl_3$): δ 7.68 (s, 4H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 3.68 (dd, *J* = 12.3, 5.3 Hz, 1H), 2.58 (m, 1H), 2.50 (m, 1H), 2.33 (m, 1H), 2.19 (m, 1H), 2.11-2.03 (m, 2H), 1.90-1.84 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 210.3, 144.6, 139.1, 138.5, 129.3, 129.3 (q, J_{CF} = 32.5 Hz), 127.5, 127.4, 125.8 (q, J_{CF} = 3.5 Hz), 124.5 (q, J_{CF} = 272 Hz), 57.3, 42.4, 35.4, 28.0, 25.5. HRMS (ESI): calcd for $C_{19}H_{17}F_3NaO$ (*M*+Na): 341.1124; found: 341.1111.

Representative procedure for the synthesis of aryl amines from aryl mesylates: In a dinitrogen-filled glovebox, a screw-cap vial was charged with a stir bar, Mor-DalPhos (12.5 mg, 0.027 mmol, 4.5 mol%), K_3PO_4 (254.7 mg, 1.2 mmol, 2.0 equiv.) and *tert*-butylphenyl methanesulfonate (137.0 mg, 0.6 mmol) followed by 0.3 mL of a stock solution (10.3616 mg/mL concentration) of $[Pd(cinnamyl)Cl]_2$ (0.018 mmol, 3 mol% Pd, Pd:L = 2:3) in 1,4-dioxane. To the mixture was then added 4.5 mL of *t*-butanol ([PhOMs]=0.125 M) and morpholine (0.079 mL, 0.9 mmol, 1.5 equiv.). The vial was capped, stirred briefly, removed from the glovebox and placed in a temperature-controlled aluminum-heating block preset to 110 ^{o}C. The reaction stirred for 16-20 h, at which time TLC confirmed full consumption of starting material. The reaction was cooled, diluted with EtOAc (30 mL) and washed with 1:1 water/brine (50 mL). The aqueous extract was washed with an additional 10 mL EtOAc. The organic extracts were then combined, dried with Na_2SO_4, filtered and silica powder (0.5-1.0 g) was added to the

solution of crude material. The solvent was removed from the silica-product mixture and the compound was purified by use of column chromatography with 10% EtOAc/hexanes to yield 4-(4-(*tert*-butyl)phenyl)morpholine (**5-23**) as a beige solid in 90% yield (119 mg, 0.54 mmol). ^{1}H NMR ($CDCl_3$): δ 7.32-7.30 (m, 2H), 6.88-6.86 (m, 2H), 3.87-3.85 (m, 4H), 3.15-3.13 (m, 4H), 1.30 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 149.0, 142.9, 126.1, 115.5, 67.2, 49.7, 34.1, 31.6. Agrees with that previously reported in the literature.[27b]

1-(4-(tert-butyl)phenyl)pyrrolidine (5-24). The representative procedure was followed with purification on alumina using 4% EtOAc/hexanes to afford the product as a beige solid in 95% yield (115 mg, 0.57 mmol). ^{1}H NMR ($CDCl_3$): δ 7.27 (d, J = 8.5 Hz, 2H), 6.54 (d, J = 9.0 Hz, 2H), 3.29-3.26 (m, 4H), 2.00-1.97 (m, 4H), 1.30 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 146.0, 138.1, 126.0, 111.4, 47.8, 33.9, 31.7, 25.6. Agrees with that previously reported in the literature.[27b]

***N,N*,2,5-tetramethylaniline (5-26).** The representative procedure was followed using 1.0 mmol of ArOMs and 4 mol% Pd. The material was loaded as an oil directly on the silica column and eluted with 2% EtOAc/hexanes to afford a yellow oil in 80% yield (120 mg, 0.80 mmol) (Note: this product is volatile). ^{1}H NMR ($CDCl_3$): δ 7.06 (d, J = 7.6 Hz, 1H), 6.85 (s, 1H), 6.78 (d, J = 7.6 Hz, 1H), 2.70 (s, 6H), 2.32 (s, 3H), 2.30 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 152.7, 136.1, 131.1, 129.0, 123.3, 119.2, 44.4, 21.4, 18.1. Agrees with data previously reported in the literature.[116]

2-methyl-*N*-octylaniline (5-28). The representative procedure was followed using 4 mol% Pd and purified using 5% EtOAc/hexanes to afford the product as a colourless oil in 62% yield (81 mg, 0.37 mmol). ^{1}H NMR ($CDCl_3$): δ 7.13 (m, 1H), 7.05 (d, J = 7.3 Hz, 1H), 6.66-6.61 (m, 2H), 3.44 (br s, 1H), 3.15 (t, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.67 (apparent pentet, J = 7.0 Hz, 2H), 1.45-1.40 (m, 2H), 1.37-1.27 (m, 8H), 0.90 (t, J = 6.9 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 146.6, 130.1, 127.3, 121.8, 116.7, 109.7, 44.1, 32.0, 29.8, 29.6, 29.4, 27.4, 22.8, 17.6, 14.3. Agrees with data previously reported in the literature.[38]

diphenylamine (5-29). The representative procedure was followed using 1 mol% Pd and purified using 10% EtOAc/hexanes to afford the product as a beige solid in 98% yield (99 mg, 0.59 mmol). ^{1}H NMR ($CDCl_3$): δ 7.29-7.26 (m, 4H), 7.09-7.08 (m, 4H), 6.94 (t, *J* = 7.4 Hz, 2H), 5.70 (br s, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 143.2, 129.5, 121.1, 117.9. Agrees with material commercially available from Aldrich.

***N*-cyclohexylaniline (5-30).** The representative procedure was followed at 0.25 M [PhOMs] using 5 mol% Pd and purified using 4% EtOAc/hexanes on alumina to afford the product as an orange oil in 88% yield (92 mg, 0.53 mmol). ^{1}H NMR ($CDCl_3$): δ 7.17-7.14 (m, 2H), 6.66 (t, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 7.8 Hz, 2H), 3.52 (br s, 1H), 3.26 (m, 1H), 2.08-2.05 (m, 2H), 1.79-1.75 (m, 2H), 1.66 (m, 1H), 1.42-1.33 (m, 2H), 1.27-1.11 (m, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 147.5, 129.4, 116.9, 113.3, 51.8, 33.6, 26.1, 25.2. Agrees with data previously reported in the literature.[38]

4-methyl-*N*-phenylpiperazin-1-amine (5-31). The representative procedure was followed using 5 mol% Pd and purified using 1% Et_3N/2% MeOH/EtOAc to afford the product as yellow solid in 82% yield (94 mg, 0.49 mmol). ^{1}H NMR ($CDCl_3$): δ 7.21-7.18 (m, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 7.3 Hz, 1H), 4.37 (br s, 1H), 2.78-2.56 (br m, 8H), 2.33 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 147.6, 129.3, 119.6, 113.8, 55.8, 55.3, 46.0. Agrees with data previously reported in the literature.[117]

***N*-methylnaphthalen-1-amine (5-33).** The representative procedure was followed using 4 mol% Pd and purified using 1% MTBE/hexanes to afford the product as a beige oil in 87% yield (82 mg, 0.52 mmol). ^{1}H NMR ($CDCl_3$): δ 7.82-7.79 (m, 2H), 7.48-7.38 (m, 3H), 7.26 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 7.5 Hz, 1H), 4.45 (br s, 1H), 3.03 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 144.6, 134.3, 128.8, 126.8, 125.8, 124.8, 123.6, 119.9, 117.4, 103.9, 31.2. HRMS (ESI): calcd for $C_{11}H_{12}N$ (*M*+H^+): 158.0964; found: 158.0969.

***N*-methylquinolin-8-amine (5-34).** The representative procedure was followed using 4 mol% Pd and purified using 1% MTBE/hexanes to afford the product as a yellow oil in 57% yield (54 mg, 0.34 mmol). ^{1}H NMR ($CDCl_3$): δ 8.71 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.06

(dd, J = 8.3, 1.4 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.37 (dd, J = 8.3, 4.2 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 6.13 (br s, 1H), 3.05 (d, J = 3.9 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 147.0, 146.0, 138.4, 136.1, 128.7, 128.0, 121.5, 113.8, 104.3, 30.2. Agrees with data previously reported in the literature.[118]

4-acetyl-*N*-methylaniline (5-35). The representative procedure was followed using 4 mol% Pd and purified using 30% EtOAc/hexanes to afford the product as a yellow solid in 76% yield (68 mg, 0.46 mmol). ^{1}H NMR ($CDCl_3$): δ 7.84 (d, J = 8.8 Hz, 2H), 6.56 (d, J = 8.8 Hz, 2H), 4.30 (br s, 1H), 2.90 (d, J = 5.0 Hz, 3H), 2.50 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 196.6, 153.2, 130.9, 126.7, 111.2, 30.2, 26.2. Agrees with data previously reported in the literature.[119]

ethyl 4-(methylamino)benzoate (5-36). The representative procedure was followed using 4 mol% Pd and purified using 20% EtOAc/hexanes to afford the product as a yellow solid in 82% yield (88 mg, 0.49 mmol). ^{1}H NMR ($CDCl_3$): δ 7.90-7.87 (m, 2H), 6.56-6.53 (m, 2H), 4.31 (q, J = 7.1 Hz, 2H), 4.18 (br s, 1H), 2.88 (d, J = 4.6 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 167.1, 152.9, 131.6, 118.7, 111.2, 60.3, 30.3, 14.6. Agrees with data previously reported in the literature.[120]

1-(3-methoxy-4-(methylamino)phenyl)ethanone (5-37). The representative procedure was followed using 4 mol% Pd and purified using 20% EtOAc/hexanes to afford the product as a yellow solid in 66% yield (71 mg, 0.40 mmol). ^{1}H NMR ($CDCl_3$): δ 7.56 (d, J = 8.2 Hz, 1H), 7.41 (s, 1H), 6.50 (d, J = 8.3 Hz, 1H), 4.84 (br s, 1H), 3.89 (s, 3H), 2.93 (d, J = 5.0 Hz, 3H), 2.52 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 196.6, 146.2, 144.0, 125.9, 125.2, 107.8, 106.8, 55.7, 29.9, 26.0. HRMS (ESI): calcd for $C_{10}H_{13}NNaO_2$ (M+Na): 202.0838; found: 202.0840.

***N,N'*-diphenyl-*p*-phenylenediamine (5-38).** The representative procedure was followed using 1 mol% Pd and 10% EtOAc/hexanes on alumina for purification to afford the product as an orange solid in 98% yield (153 mg, 0.59 mmol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.86 (s, 2H), 7.20-7.15 (m, 4H), 7.04 (s, 4H), 6.97 (d, J = 8.1 Hz, 4H), 6.72

(t, J = 7.5 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (300 MHz, DMSO-d_6): δ 144.9, 136.5, 129.0, 119.7, 118.3, 115.1. Agrees with commercially available material from Aldrich.

***N,N*-diphenylethylenediamine (5-39).** The representative procedure was followed using 10% EtOAc/hexanes on alumina for purification to afford the product as an orange oil in 75% yield (95 mg, 0.45 mmol). ^{1}H NMR ($CDCl_3$): δ 7.21 (t, J = 7.8 Hz, 4H), 6.75 (t, J = 7.4 Hz, 2H), 6.67 (d, J = 8.1 Hz, 4H), 3.87 (br s, 2H), 3.41 (s, 4H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 148.2, 129.5, 118.0, 113.2, 43.4. Agrees with commercially available material from Aldrich.

CHAPTER 6 CONCLUSIONS

6.1 CHAPTER 2: SUMMARY AND CONCLUSIONS

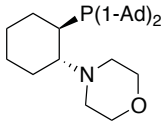
The results described in Chapter 2 of the thesis involve a detailed investigation of the Pd/Mor-DalPhos catalyst system in the context of ammonia monoarylation under room temperature conditions. Several catalytically relevant (Mor-DalPhos)Pd^{II} complexes were synthesized and structurally characterized; these demonstrate the bidentate non-hemilabile nature of the Mor-DalPhos framework. Synthesis of the oxidative addition complex [(κ^2-*P,N*-Mor-DalPhos)Pd(Ph)Cl] (**2-1**) was determined to be best achieved by using [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos mixtures with >95% conversion to **2-1** after addition of base, chlorobenzene and heat. The reaction of [Pd(cinnamyl)Cl]$_2$ and Mor-DalPhos (1:2 ratio) formed [(κ^2-*P,N*-Mor-DalPhos)Pd(η^1-cinnamyl)Cl] (**2-2**), which upon recrystallization generated both η^1 and η^3-cinnamyl (**2-2'**) isomers, as determined by analysis of the solid-state structures. The simultaneous formation of these complexes from the same crystallization solution suggest that they represent initial products formed when mixing [Pd(cinnamyl)Cl]$_2$ and Mor-DalPhos during catalyst pre-activation. Although exposure of **2-1** to up to 10 equiv. of ammonia did not undergo a reaction, ammine adduct [(κ^2-*P,N*-Mor-DalPhos)Pd(NH_3)]OTf (**2-4**) was synthesized via halogen abstraction from **2-1** in the presence of ammonia and displayed good stability in solution as well as under vacuum for extended periods of time. Halogen abstraction from **2-1** in the absence of ammonia produced a new κ^3-P,N,O denticity for the Mor-DalPhos ligand as observed in complex **2-5**, suggesting that the ligand can respond to coordinative unsaturation at Pd. Additional variants of **2-1** were synthesized to evaluate their utility as precatalysts in the room temperature ammonia monoarylation reaction. Varying the electronic or steric properties of the Pd-aryl group (**2-6** to **2-10**) did not significantly influence the catalytic activity in comparison to **2-1**. Thus, utilizing **2-1** as the optimal catalyst (5 mol% Pd loading), an expanded room temperature substrate scope of ammonia arylation employing different aryl and heteroaryl (pseudo)halides was executed with 41 to >99% yields overall. These results collectively provide a better understanding of the Pd/Mor-DalPhos catalyst system in BHA employing ammonia, in terms of catalyst

formation and the development of precatalysts for otherwise challenging room-temperature ammonia monoarylations.

6.2 Chapter 2: Future Work

Regarding further studies of the Pd/Mor-DalPhos catalyst system, a full mechanistic understanding of the ammonia arylation catalytic cycle has yet to be deduced. An arylpalladium amido complex may be observable as a transient species but not isolable under room temperature conditions, which strongly suggests it is not the catalyst resting state, in contrast to Hartwig's JosiPhos-based catalyst system.[44] It is therefore of interest to determine the catalyst resting state, rate-limiting step and overall rate of reaction for ammonia arylation employing Mor-DalPhos. This system could then be compared with that of Hartwig to identify the differences in overall mechanism based on ligand effects (JosiPhos vs. Mor-DalPhos). Key studies would include synthesis and characterization of remaining Mor-DalPhos-containing isolable intermediates (i.e. Pd(0) species), which may or may not be observed in the catalytic reaction by using ^{31}P NMR techniques, and also various kinetic analyses as necessary to determine reaction rate data. Computational studies should also be conducted to provide evidence for a mechanistic proposal employing Pd/Mor-DalPhos catalytic mixtures.

Current efforts in the Stradiotto group are directed towards the synthesis of new DalPhos ligand variants that will aim to improve ammonia monoarylation and other related challenging cross-couplings in terms of affording milder conditions, wider substrate scope, and increased functional group tolerance with lower catalyst loadings. Room temperature reactions using the [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos pre-catalyst mixture have not been achieved for the amination of aryl chlorides. A more Lewis basic version of Mor-DalPhos may promote a more facile oxidative addition step, allowing for room temperature activation and reactions to occur. Possible modifications to the Mor-DalPhos framework include increased electron density and steric bulk at phosphine and/or a cyclohexyl ring as the ligand backbone (as in **6-1**, Figure 6.1). It would be useful to determine the catalytic activity of both the precatalyst mixtures and the corresponding LPd(cinnamyl)Cl preformed complex for these new ligand variants.



6-1

Figure 6.1 A Mor-DalPhos variant containing increased Lewis basicity to test in room temperature reactions.

Given the success of the Pd/Mor-DalPhos catalyst system in the cross-coupling of ammonia and other challenging small nucleophiles such as hydrazine and acetone, structurally analogous substrates like Na_2S or H_2O[121] could also possibly lead to the corresponding thiophenol and phenol products from a (Mor-DalPhos)Pd-catalyzed coupling with aryl halides or pseudohalides (Scheme 6.1) .

Scheme 6.1 Proposed monoarylation reactions of challenging nucleophiles similar to ammonia.

This would expand the collection of nucleophiles that can be accommodated by this catalyst system and also address outstanding limitations in the literature with respect to monoarylation of these coupling partners.

6.3 Chapter 3: Summary and Conclusions

The chemistry discussed in Section 2 highlights the first examples of an indole synthesis directly using ammonia. Initial results employing the Pd/Mor-DalPhos catalyst to facilitate the ammonia cross-coupling/cyclization of 2-bromoalkynylarene **3-1** resulted in less than 50% isolated yield of the desired 2-aryl-NH-indole **3-2**, as well as significant hydrodehalogenation. Related test reactions between bromobenzene and ammonia revealed that such ammonia arylations catalyzed by Pd/Mor-DalPhos mixtures are inhibited in the presence of catalytic amounts of diphenylacetylene or **3-2**. Thus, a screen of relevant cross-coupling ligands was carried out, leading to the identification of the JosiPhos variant CyPF*t*Bu as an optimal ligand for the indole transformation providing a high isolated yield of **3-2** (84%). The substrate scope included various substitution patterns with varied electronic and steric properties featured within either aryl moiety of

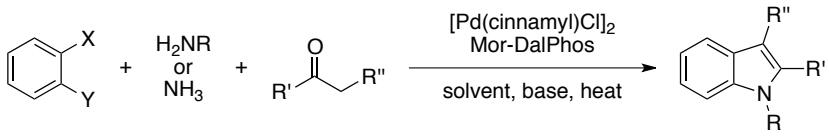
the alkyne. In cases where the terminal group was not aryl (i.e alkyl, H, TMS or alkenyl) full conversion of starting material (decomposition) was observed with no desired indole formed. Despite this limitation, the indole reaction was extended to two other challenging nucleophilic amines, methylamine and hydrazine, forming N-Me and N-amino indoles, respectively.

In Section 3, stoichiometric investigations were described that aim to provide insight into the detrimental effects of **3-1** in ammonia arylation reactions catalyzed by Pd/Mor-DalPhos mixtures. With the synthesis of oxidative addition complex **3-29** and the halogen abstracted product **3-31**, no significant Pd···alkyne interactions were observed (by use of ^{13}C NMR or X-ray diffraction techniques) that might explain catalyst inhibition after C-Br oxidative addition. Similar to **2-5**, κ^3-P,N,O chelation was observed for cationic complex **3-31**, which may play a role during catalysis in cases of coordinative unsaturation at Pd (e.g. with labile X groups). Interestingly, in contrast to **2-4**, [(κ^2-*P,N*-Mor-DalPhos)Pd(NH_3)(Arylalkyne)]OTf (**3-30**) was not stable under prolonged exposure to vacuum, resulting in the loss of ammonia to form **3-31**, which precluded the isolation of **3-30**. This may indicate that ammonia is displaced from the metal coordination sphere during catalysis, due to the increased steric bulk of the alkyne. Corresponding LPd^0(diphenylacetylene) complexes of JosiPhos (**3-33**) and Mor-DalPhos (**3-32**) were then synthesized and converted to their oxidative addition complexes (**3-34** and **3-29**, respectively) via treatment with **3-1**. Clean conversion to **3-34** was observed but in the case of Mor-DalPhos, **3-29** was formed along with free ligand and several other phosphorus-containing species, suggesting that the inefficiency with which putative (Mor-DalPhos)Pd^0(alkyne) species re-enter the catalytic cycle via C-Br oxidative addition may also contribute to the observed inferior activity of Mor-DalPhos/Pd versus JosiPhos/Pd catalyst systems in the BHA of **3-1** using ammonia.

6.4 Chapter 3: Future Work

The indole synthesis presented has been optimized for the generation of 2-arylindoles but is not applicable to other functional groups at the 2-position including, as previously mentioned, H, alkyl, alkenyl or trimethylsilyl. For all these substrates, full consumption of aryl bromide was observed but no indole product was formed. To

develop a more widely applicable methodology in terms of substrate scope, improvement of the current protocols is necessary. This can be done either through identification of a superior catalyst system and/or conditions that would tolerate such substrates or through development of an alternative route to these indole frameworks. The Pd/Mor-DalPhos catalyst system has been effective for both BHA and the mono-α-arylation of methyl ketones, both of which could be combined into a single transformation ultimately resulting in 2-substituted indoles (Scheme 6.2).



Scheme 6.2 Proposed synthesis of indoles employing BHA and ketone α-arylation of an *ortho*-dihaloarene.

Only a single report of this reaction has appeared recently in the literature employing a Pd/DPPF catalyst system.[122] Starting from 1-bromo-2-iodobenzene, a primary alkyl amine and a ketone or aldehyde, 10 examples of N-alkyl indoles were provided in 52-69% isolated yields. However, the substrate scope did not demonstrate the use of ammonia or acetone, which may be accomplished under appropriate conditions utilizing catalytic mixtures of $[Pd(cinnamyl)Cl]_2$ and Mor-DalPhos. New DalPhos variants such as that proposed in Section 6.2 may also prove useful in this reaction. To avoid complex product mixtures, initial screening should focus on a two-step one-pot process, in which either the BHA or mono-α-arylation reaction is performed first, followed by the second C-C or C-N bond-forming step. If the desired indole is formed as the major product, further optimization can be directed towards a true one-pot process.

6.5 Chapter 4: Summary and Conclusions

This chapter features an explanation into the use of Pd/DalPhos catalyst mixtures in carbonylative BHA reactions. The effective synthesis of benzoyl complex [(κ^2-*P,N*-Mor-DalPhos)Pd(COPh)Cl] (**4-1**) suggested that the carbonyl insertion step would be viable for a Pd/DalPhos catalyst system. For the reaction of bromobenzene, ammonia and carbon monoxide, a 79% isolated yield was obtained using $Pd(OAc)_2$/Pyr-DalPhos mixtures. A variety of electronically activated and deactivated aryl bromides were

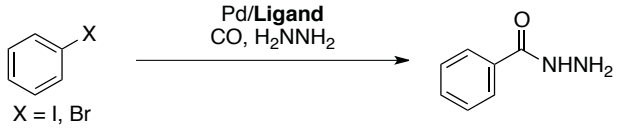
accommodated in this transformation including a heteroaromatic substrate and a chemoselective example (40-96% isolated yields, 11 examples). It is important to note that no extra base was required for these reactions since ammonia acts as both nucleophile and base. In addition to ammonia, *n*-butylamine and adamantylamine were tolerated as well as some dialkyl amines in the presence of an external base.

In an effort to further expand the scope of reactivity of the DalPhos ligand set in the context of carbonylative cross-coupling reactions, a ligand screen was carried out for carbonylative C-C cross-coupling reactions. The pyrrole DalPhos variant **L19** demonstrated considerable activity in the carbonylative Heck coupling of iodobenzene and styrene forming **4-18** in 63% isolated yield. The Pd/**L19** catalyst system displayed inferior results for electronically and sterically influenced aryl iodides with either poor conversion or yield of product, thus preventing further development of the reaction employing **L19**. The first examples of the carbonylative mono-*α*-arylation of acetone were executed utilizing $[Pd(cinnamyl)Cl]_2$/Me-DalPhos mixtures; 20% GC yield of 1,3-diketone product **4-19** was formed from the carbonylative coupling of iodobenzene and acetone. Though this was a significant result, use of cata*CX*ium A as the ligand allowed for an increase in GC yield to 35%. Optimization and further improvement of the reaction conditions were then carried out using cata*CX*ium A, involving a collaboration with the Beller group (Germany)

6.6 Chapter 4: Future Work

In terms of extending the capabilities of the DalPhos ligand set in carbonylative coupling reactions, there are several other possible transformations to be screened including carbonylative Suzuki, Sonogashira and C-O coupling processes. Considering that these have been well documented in the literature, it would be more appealing to pursue a new carbonylative coupling reaction involving challenging nucleophiles with which DalPhos ligands have been successful, such as hydrazine. Aminocarbonylation employing hydrazine has not yet been reported and would be a useful contribution to the carbonylation toolbox (Scheme 6.3). Reaction optimization would require ligand screening of relevant DalPhos ligands (Pyr-DalPhos and **L19**) as well as successful cata*CX*ium ligands in carbonylation chemistry. The source of hydrazine would also have

to be determined from either the monohydrate or hydrochloride considering anhydrous hydrazine is dangerous and would not be suitable for the high-pressure reactor conditions involved.



Scheme 6.3 Proposed synthetic route to benzhydrazide products from aryl halides under carbonylative BHA conditions.

With respect to carbonylative mono-α-arylation, recent reports have only included ketones as substrates. The scope of reactivity for these reactions does not currently encompass related carbonyl-containing compounds such as esters or aldehydes. Thus, additional carbonylation reactions catalyzed by the Pd/cata*CX*ium A system could be performed to test for the tolerability of such α-CH acidic compounds to produce β-keto esters or aldehydes.

6.7 Chapter 5: Summary and Conclusions

Efforts to further develop the scope of reactions catalyzed by the Pd/Mor-DalPhos system were discussed in this chapter utilizing the inexpensive non-halide arene starting materials, aryl methanesulfonates (mesylates). Unprecedented ketone mono-α-arylation using aryl mesylates and the first examples of coupling primary aliphatic amines with such challenging electrophiles were highlighted. Mixtures of $[Pd(cinnamyl)Cl]_2$ and Mor-DalPhos demonstrated high efficiency, after considerable optimization, for the coupling of acetone and **5-1** producing **5-2** in high yield (85%), as observed by analysis of calibrated GC data. Comparable ligands employed in couplings of aryl mesylates, α-arylation or amination reactions proved to be inferior to Mor-DalPhos in this transformation. In pursuing a survey of aryl mesylates, a range of substitution patterns were tolerated in the coupling with both cyclic and acyclic dialkyl ketones, including acetone, which is normally a challenging ketone to mono-α-arylate. In order to address the limitations in the amination of aryl mesylates, the optimized acetone mono-α-arylation conditions were successfully applied to the coupling of primary and secondary alkyl amines with aryl mesylates. Various electron-poor and electron-rich aryl mesylates

formed the corresponding *N*-alkyl anilines as well as those containing *ortho*-substitution and base-sensitive functionality. It was pleasing to see that substrates containing enolizable protons or additional reactive NH sites could also be coupled with ease at the primary amine position, thereby demonstrating the chemoselectivity of the reaction. Considering the success of the Pd/DalPhos catalyst system in this chemistry, it maybe suitable to enable cross-couplings of other related non-halide phenol-derived arenes.

6.8 Chapter 5: Future Work

As mentioned in Section 5.2, the substrate scope of aryl mesylates in the ketone mono-α-arylation reaction did not accommodate *ortho*-substitution or electron-withdrawing groups within the aryl ring. To circumvent these issues, reaction optimization could be performed with one of these problematic substrates (e.g. 4-trifluoromethylphenyl mesylate). Screening of alternative DalPhos ligands, bases, solvent and other variables may enable this reaction to proceed, without significant decomposition, to the desired aryl acetone product (4-trifluoromethyl derivative of **5-2**). It was observed in previous studies from the Stradiotto group on acetone mono-α-arylation that use of electron-poor aryl halides resulted in slower conversion to the α-aryl methyl ketone possibly due to inefficient reductive elimination stemming from a rather electron-rich metal centre.[62a, 123] It was determined that less basic phosphine groups on the ligand allowed for high conversion of electron-deficient aryl bromides in good yields. The same situation may apply for aryl mesylates containing electron-withdrawing groups, suggesting that the application of less electron-rich DalPhos variants would be beneficial (Figure 6.2).

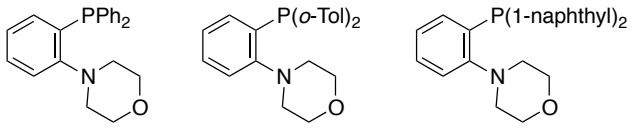
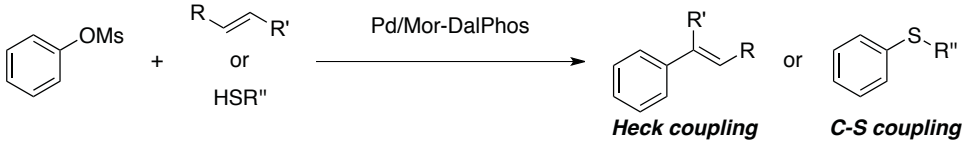


Figure 6.2 Possible DalPhos variants containing less-basic phosphine groups for acetone arylations employing electron-deficient aryl mesylates.

The scope of possible transformations utilizing mesylate reagents could also be extended to Heck couplings, which has been poorly documented in the literature with only a single example.[101a, 124] Thus, the reaction of aryl mesylates with alkenes is an unaddressed limitation in the palladium-catalyzed cross-coupling reactions of these aryl

electrophiles (Scheme 6.4), especially in comparison to well known Heck reactions of aryl halides. Given the environmentally beneficial factors of the mesylate byproduct, development of such Heck couplings would be a significant contribution to this area of catalysis. Furthermore, a completely unprecedented reaction in the literature is the coupling of sulfur nucleophiles with mesylate substrates. Considering the similarities in reactivity between BHA and the palladium-catalyzed cross-coupling to generate thiols,[13b] such a process could be achieved in a straightforward manner employing the Pd/Mor-DalPhos catalyst system. There is the potential issue of the thiol substrate causing catalyst deactivation but previous studies with Josiphos[13b] have shown a bidentate ligand can avoid such problems, suggesting that Mor-DalPhos could also be an effective ligand (Scheme 6.4).



Scheme 6.4 Possible future projects exploring underdeveloped reactions involving coupling of aryl mesylates.

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APPENDIX A CRYSTALLOGRAPHIC DATA

The following pages provide crystallographic details for the Pd complexes reported in Chapters 2 (Section A-1), 3 (Section A-2) and 4 (Section A-3) of the thesis document.

A-1 Crystallographic Solution and Refinement Details for Chapter 2

Crystallographic data were obtained at 180(±2) K on a Nonius Kappa CCD diffractometer (for **2-2** and **2-2'**·CH_2Cl_2·H_2O) or at 193(±2) K (all others) on either a Bruker PLATFORM/SMART 1000 CCD diffractometer or a Bruker D8/APEX II CCD diffractometer, using graphite-monochromated Mo Kα (λ = 0.71073 Å) radiation, and employing samples that were mounted in inert oil and transferred to a cold gas stream on the diffractometer. Programs for diffractometer operation, data collection, and data reduction were supplied by the respective vendors. Absorption correction for **2-2** and **2-2'**·CH_2Cl_2·H_2O was carried out by using a semi-empirical methods from equivalents, while Gaussian integration (face-indexing) was employed for all other samples. In the case of **2-5**, the values of the cell parameters (*a* approximately equal to *c*; β close to 90º) and the relatively high values of R_1 and wR_2 during early refinement cycles suggested that the data might be rotationally twinned. The twin law [0 0 1 0 –1 0 1 0 0] (90º rotation about the *b* axis) was derived by inspection and was applied during refinement using the *SHELXL-97* TWIN instruction. The refined value of the twin fraction (*SHELXL-97* BASF parameter) was 0.4541(5). The structures were solved by use of direct methods, with the exception of **2-8**·CH_2Cl_2, **2-9**·CH_2Cl_2, **2-3**·$CHCl_3$, and **2-5**, for which a Patterson search/structure expansion was employed. Refinements were carried out by use of full-matrix least-squares procedures (on F^2) with R_1 based on $F_o^2 \geq 2\sigma(F_o^2)$ and wR_2 based on $F_o^2 \geq -3\sigma(F_o^2)$. For **2-5**, two crystallographically independent molecules were located in the asymmetric unit and were refined appropriately; an ORTEP of only one of the two crystallographically independent molecules is presented in the text for clarity. In several cases, structural disorder was identified during the solution and refinement process and was modeled in a satisfactory manner (occupancy ratio given in parentheses). For **2-3**·$CHCl_3$, disorder in an adamantyl fragment (55:45) and in the triflate ion (70:30) was noted and the following distance restraints were applied to impose

an idealized geometry upon the minor (30% occupancy) conformer of the disordered triflate ion: d(S1B–C50B) = 1.75(1) Å; d(S1B–O2B) = d(S1B–O3B) = d(S1B–O4B) = 1.45(1) Å; d(F1B–C50B) = d(F2B–C50B) = d(F3B–C50B) = 1.35(1) Å; d(S1B···F1B) = d(S1B···F2B) = d(S1B···F3B) = 2.60(1) Å; d(F1B···F2B) = d(F1B···F3B) = d(F2B···F3B) = 2.10(1) Å; d(O2B···O3B) = d(O2B···O4B) = d(O3B···O4B) = 2.45(1) Å. In the case of **2-6**·CH_2Cl_2 and **2-9**·CH_2Cl_2, the disordered morpholino fragments were treated successfully using a two-position (55:45 and 50:50, respectively) disorder model; the latter structure also featured a disordered trifluoromethyl group (80:20). In the case of **2-9**·CH_2Cl_2, the F–C distances within the rotationally disordered trifluoromethyl group were fixed during refinement: d(F5-1–C17) = d(F2A–C17) = d(F3A–C17) = d(F1B–C17) = d(F2B–C17) = d(F3B–C17) = 1.35(2) Å. Additionally, F–F distances involving the minor (20%) conformer of this CF_3 group were fixed: d(F1B···F2B) = d(F1B···F3B) = d(F2B···F3B) = 2.20(2) Å. Furthermore, within **2-8**·CH_2Cl_2 the following pairs of distances within the disordered morpholino group were constrained to be equal (within 0.03 Å) during definement: d(O5-1–C8A) = d(O1B–C8B); d(O5-1–C9A) = d(O1B–C9B); d(C8A···C9A) = d(C8B···C9B). For **2-6**·CH_2Cl_2 the dichloromethane solvate was modeled in a satisfactory manner by using a two-position (75:25) disorder model. Similarly, the following pairs of distances within the disordered morpholino group (80:20) in **2-4**·CH_2Cl_2 were constrained to be equal (within 0.03 Å) during definement: d(Pd–N5-1) = d(Pd–N1B); d(N5-1–C2) = d(N1B–C2). Refinement of **2-4**·CH_2Cl_2 was further facilitated by using the SADI constraint on the Pd-N1(A,B) and N1(A,B)-C2 fragments. Additional crystallographic information is provided in the accompanying tables, as well as in the deposited CIFs. Anisotropic displacement parameters were employed throughout for the non-hydrogen atoms, and hydrogen atoms were added at calculated positions and refined by use of a riding model employing isotropic displacement parameters based on the isotropic displacement parameter of the attached atom.

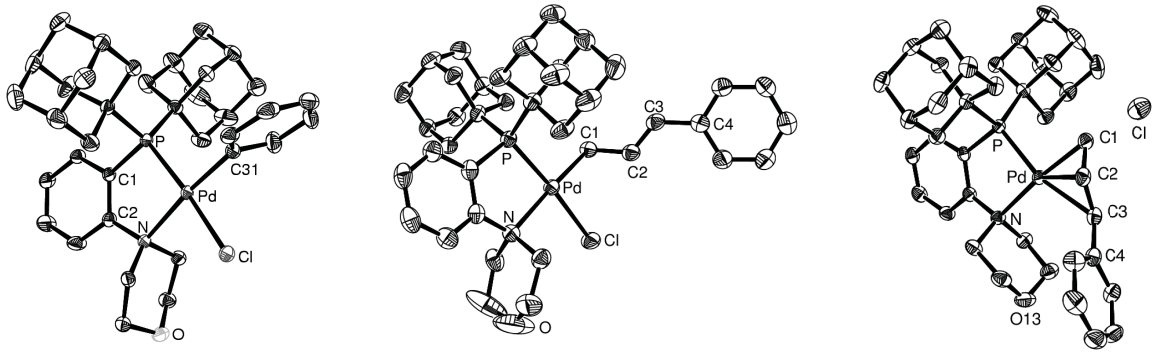
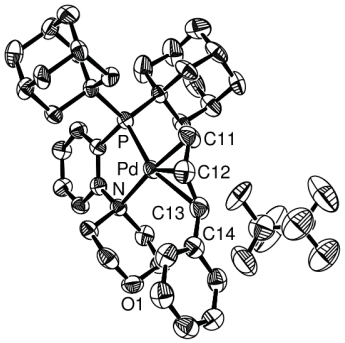
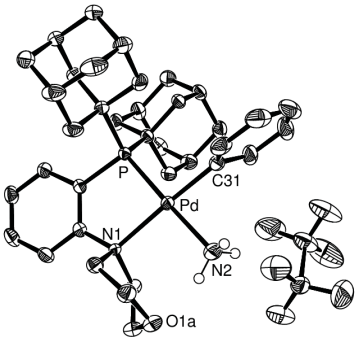


Table A1 Selected crystallographic data for complexes **2-1**·CH_2Cl_2 (left), **2-2** (middle) and **2-2'**·CH_2Cl_2·H_2O (right).

	2-1·CH_2Cl_2	**2-2**	**2-2'**·CH_2Cl_2·H_2O
Empirical formula	$C_{37}H_{49}Cl_3NOPPd$	$C_{39}H_{51}ClNOPPd$	$C_{40}H_{55}Cl_3NO_2PPd$
Formula weight	767.49	722.63	825.57
Crystal dimensions	0.56 × 0.44 × 0.06	0.14 × 0.07 × 0.02	0.21 × 0.16 × 0.14
Crystal system	monoclinic	orthorhombic	triclinic
Space group	$P2_1/c$	$Pbca$	$P(-1)$
a (Å)	10.6689(3)	18.7167(3)	10.3159(2)
b (Å)	14.9085(4)	17.3369(3)	13.0242(2)
c (Å)	21.7424(6)	20.6972(5)	14.3107(3)
α (deg)	90	90	93.773(1)
β (deg)	92.4226 (3)	90	97.134(1)
γ (deg)	90	90	100.615(1)
V (Å^3)	3455.20(16)	6716.0(2)	1867.43(6)
Z	4	8	2
ρ_{calcd} (g cm^{-3})	1.475	1.429	1.468
μ (mm^{-1})	0.847	0.712	0.791
Range of transmission	0.9510–0.6467	0.989–0.916	0.924–0.816
2θ limit (deg)	55.08	50.68	62.00
	$-13 \le h \le 13$	$-22 \le h \le 22$	$-14 \le h \le 14$
	$-19 \le k \le 19$	$-20 \le k \le 20$	$-18 \le k \le 18$
	$-28 \le l \le 28$	$-24 \le l \le 23$	$-20 \le l \le 20$
Total data collected	30066	35001	26840
Independent reflections	7957	6122	11688
R_{int}	0.0152	0.0666	0.0386
Data/restraints/parameters	7957 / 0 / 397	6122 / 0 / 397	11688 / 0 / 439
Goodness-of-fit	1.042	1.015	1.019
$R1$ [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0396	0.0433	0.0339
$wR2$ [$F_o^2 \ge -3\sigma(F_o^2)$]	0.1125	0.0861	0.0910
Largest peak, hole (eÅ^{-3})	2.802, -1.502	0.784, -0.570	0.614, -0.737





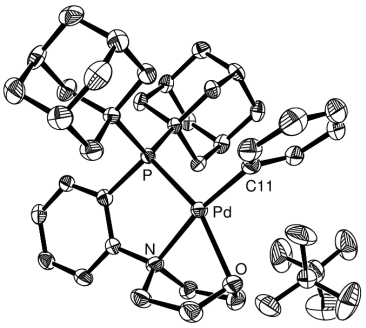


Table A2 Selected crystallographic data for complexes **2-3**·$CHCl_3$ (left), **2-4**·CH_2Cl_2 (middle) and **2-5** (right).

	2-3·$CHCl_3$	**2-4**·CH_2Cl_2	**2-5**
Empirical formula	$C_{41}H_{52}Cl_3F_3NO_4PPdS$	$C_{38}H_{52}Cl_2F_3N_2O_4PPdS$	$C_{37}H_{47}F_3NO_4PPdS$
Formula weight	955.62	898.15	796.19
Crystal dimensions	0.20 × 0.18 × 0.05	0.60 × 0.40 × 0.31	0.23 × 0.21 × 0.15
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/n$	$P2_1/n$
a (Å)	11.7014(5)	9.9383(3)	23.7404(16)
b (Å)	18.2801(7)	14.0246(4)	12.3450(8)
c (Å)	20.0146(8)	27.9969(7)	23.7534(15)
α (deg)	90	90	90
β (deg)	104.3464(6)	91.5962(3)	90.5605(10)
γ (deg)	90	90	90
V (Å^3)	4147.7(3)	3900.71(19)	6961.2(8)
Z	4	4	8
ρ_{calcd} (g cm^{-3})	1.530	1.529	1.519
μ (mm^{-1})	0.785	0.764	0.697
Range of transmission	0.9603–0.8587	0.7998–0.6583	0.9009–0.8557
2θ limit (deg)	51.46	54.96	52.84
	$-14 \le h \le 14$	$-12 \le h \le 12$	$-29 \le h \le 29$
	$-22 \le k \le 22$	$-18 \le k \le 18$	$-15 \le k \le 15$
	$-24 \le l \le 24$	$-26 \le l \le 36$	$-29 \le l \le 29$
Total data collected	30622	33896	56174
Independent reflections	7920	8935	14300
R_{int}	0.0681	0.0113	0.0424
Data/restraints/parameters	7920 / 16 / 604	8935 / 2 / 495	14300 / 0 / 866
Goodness-of-fit	1.032	1.044	1.038
R_1 [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0656	0.0265	0.0267
wR_2 [$F_o^2 \ge -3\sigma(F_o^2)$]	0.1865	0.0688	0.0647
Largest peak, hole (eÅ^{-3})	2.962, -1.262	1.052, -0.561	0.412, -0.452

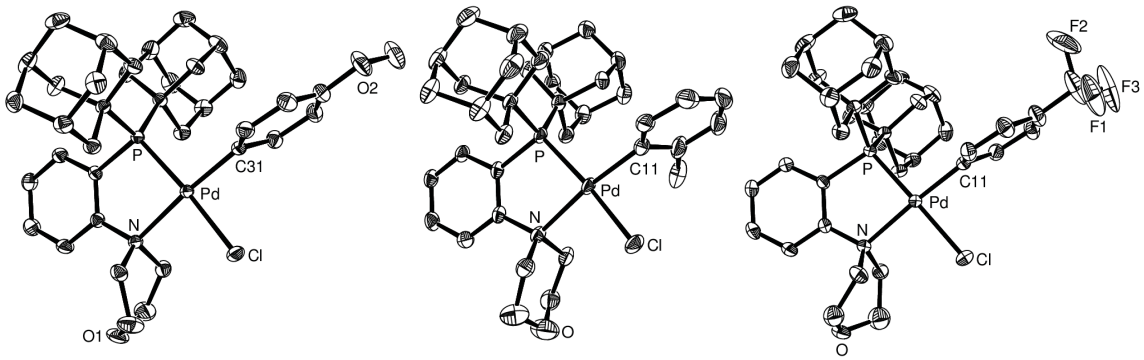
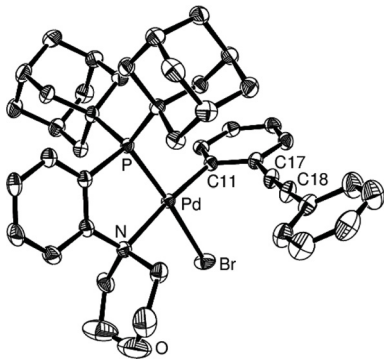


Table A3 Selected crystallographic data for complexes **2-6**·CH_2Cl_2 (left), **2-8**·CH_2Cl_2 (middle) and **2-9**·CH_2Cl_2 (right).

	2-6·CH_2Cl_2	**2-8**·CH_2Cl_2	**2-9**·CH_2Cl_2
Empirical formula	$C_{38}H_{51}Cl_3NO_2PPd$	$C_{38}H_{51}Cl_3NOPPd$	$C_{38}H_{48}Cl_3F_3NOPPd$
Formula weight	797.52	781.52	835.49
Crystal dimensions	0.72 × 0.15 × 0.13	0.36 × 0.20 × 0.19	0.35 × 0.20 × 0.12
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/n$	$P2_1/c$	$P2_1/n$
a (Å)	13.0232(4)	10.7939(7)	12.9743(5)
b (Å)	17.0238(6)	15.0464(10)	17.0077(7)
c (Å)	16.1665(5)	21.4465(14)	16.4029(6)
α (deg)	90	90	90
β (deg)	95.3275(4)	94.6366(8)	96.3224(5)
γ (deg)	90	90	90
V (Å^3)	3568.7(2)	3471.7(4)	3597.5(2)
Z	4	4	4
ρ_{calcd} (g cm^{-3})	1.484	1.495	1.543
μ (mm^{-1})	0.825	0.844	0.831
Range of transmission	0.9025–0.5897	0.8547–0.7521	0.9068–0.7607
2θ limit (deg)	54.96	55.00	55.02
	$-16 \le h \le 16$	$-14 \le h \le 13$	$-16 \le h \le 16$
	$-22 \le k \le 22$	$-19 \le k \le 19$	$-22 \le k \le 22$
	$-20 \le l \le 20$	$-27 \le l \le 27$	$-21 \le l \le 21$
Total data collected	30875	29756	31363
Independent reflections	8147	7925	8247
R_{int}	0.0187	0.0434	0.0252
Data/restraints/parameters	8147 / 0 / 446	7925 / 0 / 407	8247 / 12 / 445
Goodness-of-fit	1.038	1.031	1.049
R_1 [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0293	0.0381	0.0401
wR_2 [$F_o^2 \ge -3\sigma(F_o^2)$]	0.0809	0.0925	0.1082
Largest peak, hole (eÅ^{-3})	1.009, -1.014	1.299, -0.798	1.842, -1.126

A-2 Crystallographic Solution and Refinement Details for Chapter 3

Crystallographic data were obtained at 173(±2) K on a Bruker D8/APEX II CCD diffractometer using a graphite-monochromated Mo Kα (λ = 0.71073 Å) radiation, employing samples that were mounted in inert oil and transferred to a cold gas stream on the diffractometer. Programs for diffractometer operation, data collection, and data reduction (including SAINT) were supplied by Bruker. Gaussian integration (face-indexed) was employed as the absorption correction method for **3-29**•CH_2Cl_2. The crystal of **3-31**•OEt_2 used for data collection was found to display non-merohedral twinning; as such multi-scan (*TWINABS*) was employed as the absorption correction method. Both components of the twin were indexed with the program CELL_NOW (Bruker AXS Inc., Madison, WI, 2004). The second twin component can be related to the first component by a 3.2º rotation about the [1 -0.35 -0.14] axis in real space and about the [-0.71 1/2 1] axis in reciprocal space. Integrated intensities for the reflections from the two components were written into a SHELXL-97 HKLF 5 reflection file with the data integration program SAINT (version 7.68A), using all reflection data (exactly overlapped, partially overlapped and non-overlapped). The refined value of the twin fraction (SHELXL-97 BASF parameter) was 0.3651(11). The structures were solved by use of a Patterson search/structure expansion, and refined by use of full-matrix least-squares procedures (on F^2) with R_1 based on $F_o^2 \geq 2\sigma(F_o^2)$ and wR_2 based on $F_o^2 \geq -3\sigma(F_o^2)$. Anisotropic displacement parameters were employed for all the non-hydrogen atoms. Disorder involving the triflate counteranion in **3-31**•OEt_2 was identified during the solution process. As a result, the distances within the disordered triflate ion were restrained as follows: (a) the S5-1–C95-1 and S1B–C91B distances were constrained to be equal (within 0.03 Å); (b) the F91B–C91B, F92B–C91B, and F93B–C91B distances were constrained to be equal (within 0.03 Å). All hydrogen atoms were added at calculated positions and refined by use of a riding model employing isotropic displacement parameters based on the isotropic displacement parameter of the attached atom. In the case of **3-29**•CH_2Cl_2, which crystallizes in the chiral space group $P2_12_12_1$, the near-zero final refined value of the Flack[71] absolute structure parameter (0.021(6)) confirmed that the correct absolute configuration had been implemented.



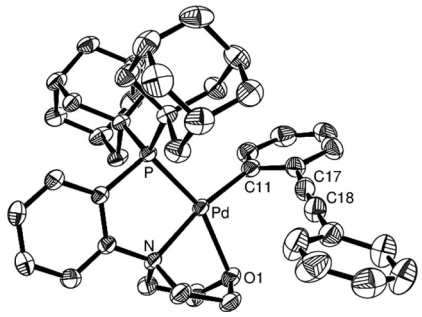


Table A4 Selected crystallographic data for **3-29**·CH_2Cl_2 (left) and **3-31**·OEt_2 (right).

	3-29·CH_2Cl_2	**3-31**·OEt_2
Empirical formula	$C_{45}H_{53}BrCl_2NOPPd$	$C_{49}H_{61}F_3NO_5PSPd$
Formula weight	912.06	970.42
Crystal dimensions	0.48 × 0.17 × 0.09	0.47 × 0.38 × 0.14
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1/n$
a (Å)	10.9036(3)	10.7231(8)
b (Å)	14.6554(4)	16.1892(12)
c (Å)	25.5143(6)	26.826(2)
α (deg)	90	90
β (deg)	90	105.5094(9)
γ (deg)	90	90
V (Å^3)	4077.10(18)	4487.4(6)
Z	4	4
ρcalcd (g cm^{-3})	1.486	1.436
μ (mm^{-1})	1.641	0.556
Range of transmission	0.8610-0.5088	0.9252-0.7812
2θ limit (deg)	55.02	55.40
	$-14 \le h \le 14$	$-13 \le h \le 13$
	$-19 \le k \le 19$	$-0 \le k \le 21$
	$-33 \le l \le 33$	$0 \le l \le 34$
Total data collected	37022	11664
Independent reflections	9345	11664
R_{int}	0.0198	not determined
Data/restraints/parameters	9345 / 0 / 478	11664 / 4 / 583
Goodness-of-fit	1.076	1.145
$R1$ [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0282	0.0481
wR_2 [$F_o^2 \ge -3\sigma(F_o^2)$]	0.0849	0.1239
Largest peak, hole (eÅ^{-3})	1.108, -0.753	1.992, -0.790

A-3 Crystallographic Solution and Refinement Details for Chapter 4

Crystallographic data were obtained at at 193(±2) K on a Bruker D8/APEX II CCD diffractometer, using graphite-monochromated Mo Kα (λ = 0.71073 Å) radiation, and employing samples that were mounted in inert oil and transferred to a cold gas stream on the diffractometer. Programs used for diffractometer operation, data collection, and data reduction, were supplied by Bruker. Gaussian integration (face-indexing) was employed as the absorption correction method. The structure of **4-1**·CH_2Cl_2 was solved by use of a Patterson search/structure expansion and refined by use of full-matrix least-squares procedures (on F^2) with R_1 based on $F_o^2 \geq 2\sigma(F_o^2)$ and wR_2 based on $F_o^2 \geq -3\sigma(F_o^2)$. Anisotropic displacement parameters were employed throughout for the non-hydrogen atoms, and hydrogen atoms were added at calculated positions and refined by use of a riding model employing isotropic displacement parameters based on the isotropic displacement parameter of the attached atom.

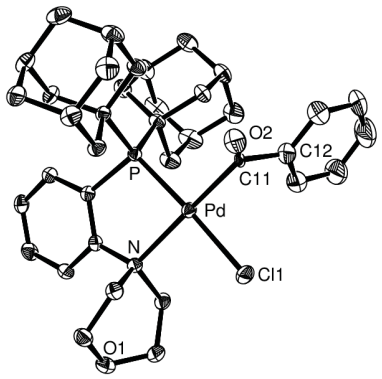


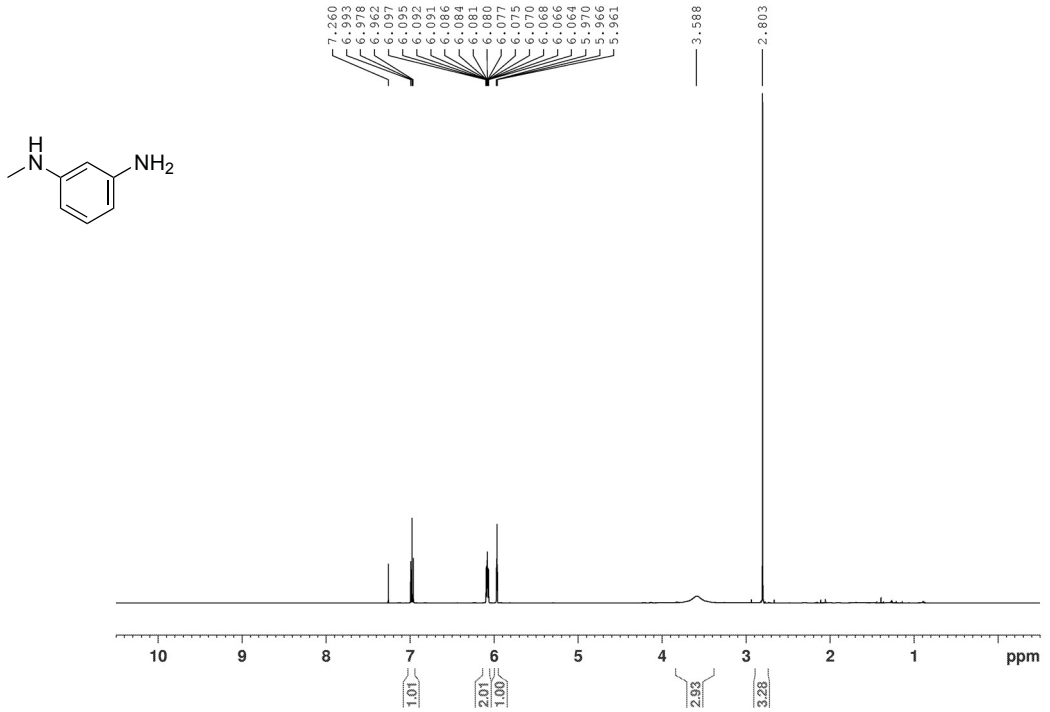
Table A5 Selected crystallographic data for **4-1**·CH_2Cl_2

	4-1·CH_2Cl_2
Empirical formula	$C_{38}H_{49}Cl_3NO_2PPd$
Formula weight	795.50
Crystal dimensions	0.22 × 0.20 × 0.08
Crystal system	triclinic
Space group	*P*(-1)
a (Å)	10.8058(4)
b (Å)	11.2021(4)
c (Å)	16.3196(6)
α (deg)	74.6387(4)
β (deg)	79.1376(4)
γ (deg)	67.9762(4)
V (Å^3)	1757.08(11)
Z	2
ρ_{calcd} (g cm^{-3})	1.504
μ (mm^{-1})	0.837
Range of transmission	0.9330–0.8359
2θ limit (deg)	55.12
	$-14 \le h \le 14$
	$-14 \le k \le 14$
	$-21 \le l \le 21$
Total data collected	15997
Independent reflections	8061
R_{int}	0.0218
Data/restraints/parameters	8061 / 0 / 415
Goodness-of-fit	1.093
R_1 [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0363
wR_2 [$F_o^2 \ge -3\sigma(F_o^2)$]	0.1048
Largest peak, hole (eÅ^{-3})	1.439, -0.753

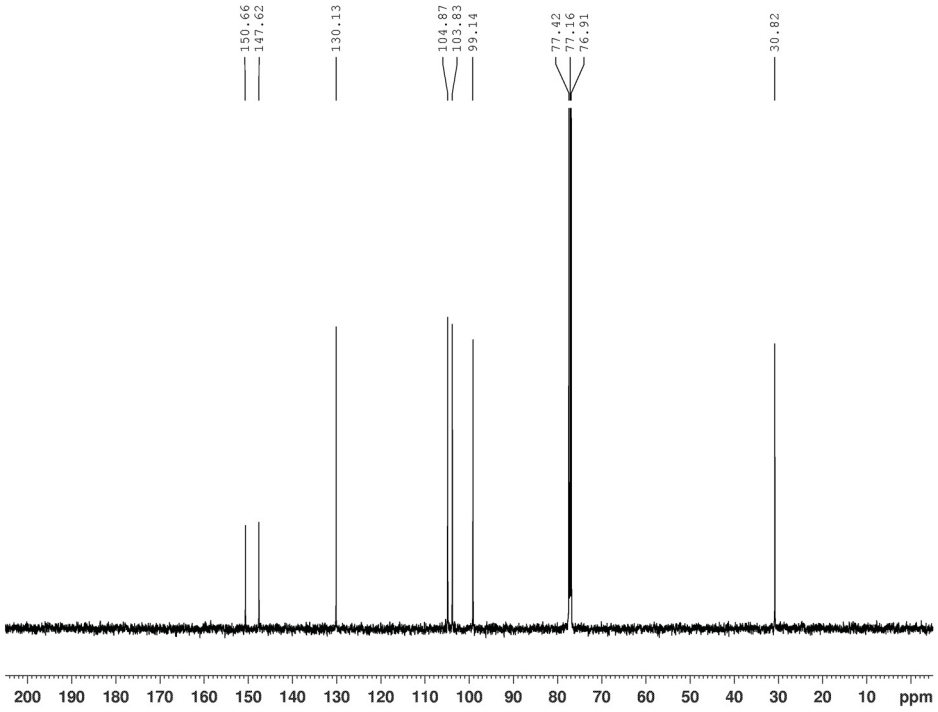
APPENDIX B REPRESENTATIVE NMR SPECTRA

The following pages provide ^{1}H and ^{13}C NMR spectra of representative products reported in Chapters 2 to 5 of the thesis document.

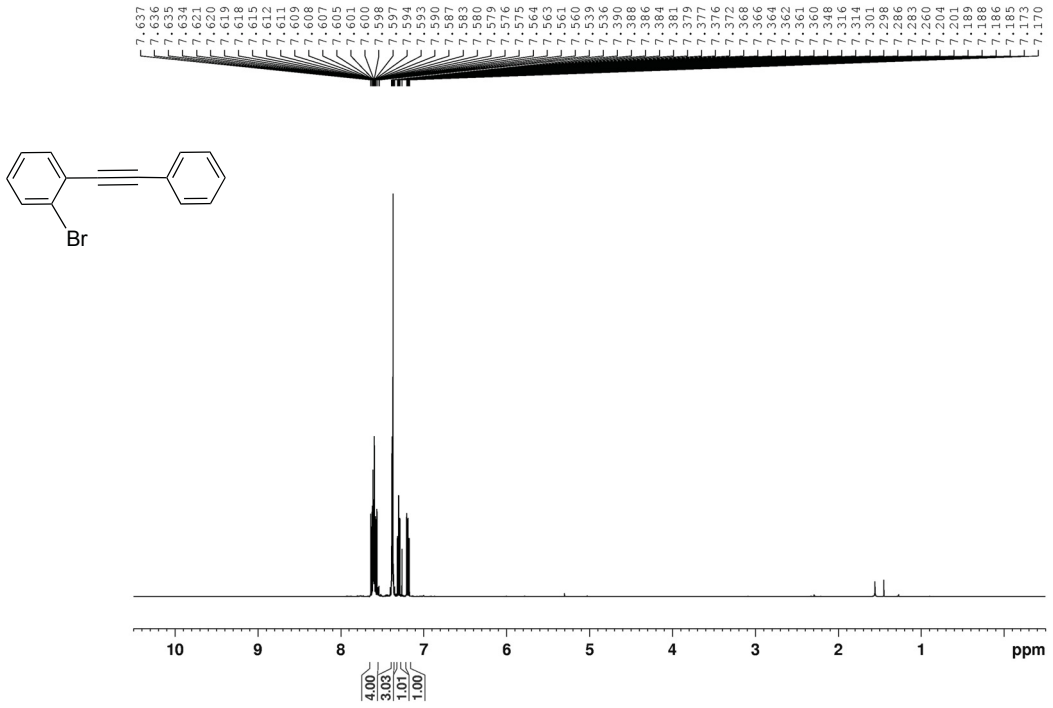
^{1}H NMR of **2-16** ($CDCl_3$, 500 MHz, 300 K)



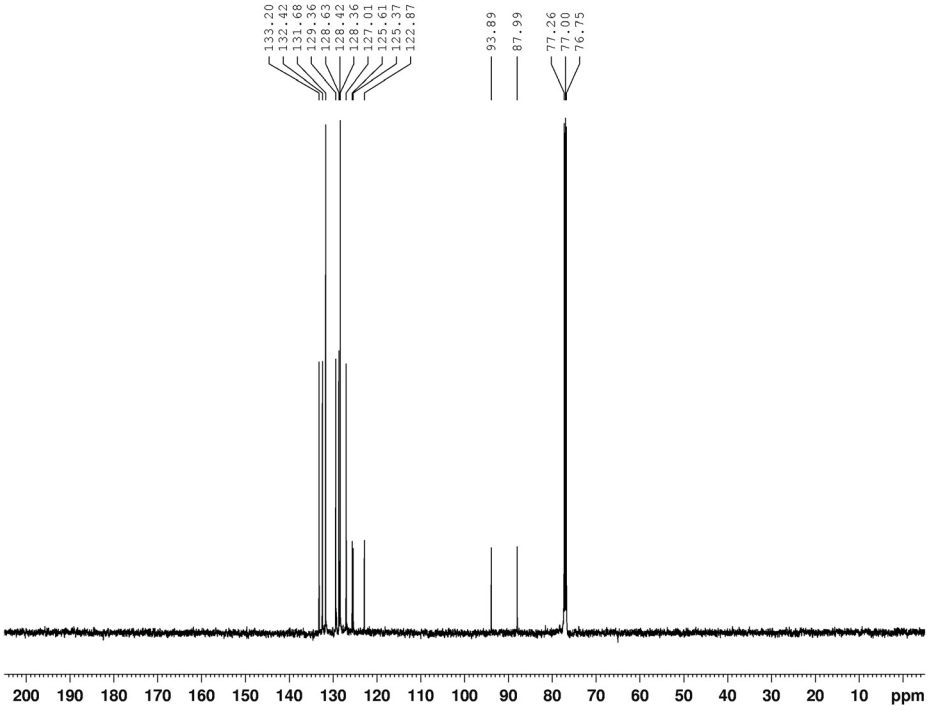
^{13}C NMR of **2-16** ($CDCl_3$, 125 MHz, 300 K)



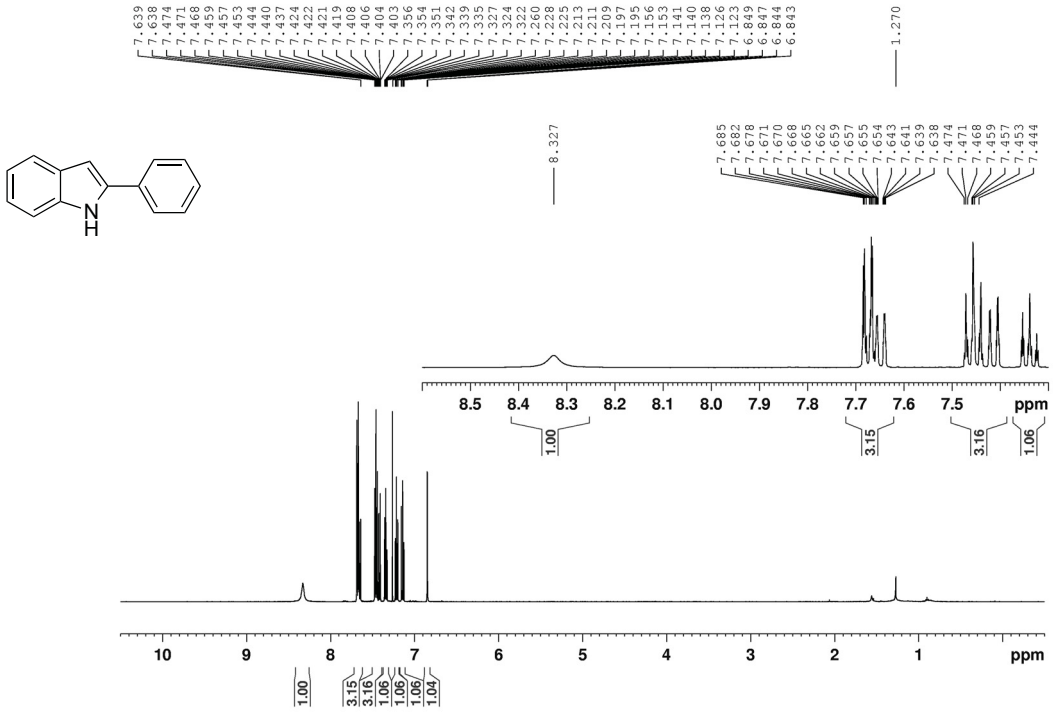
^{1}H NMR of **3-1** ($CDCl_3$, 500 MHz, 300 K)



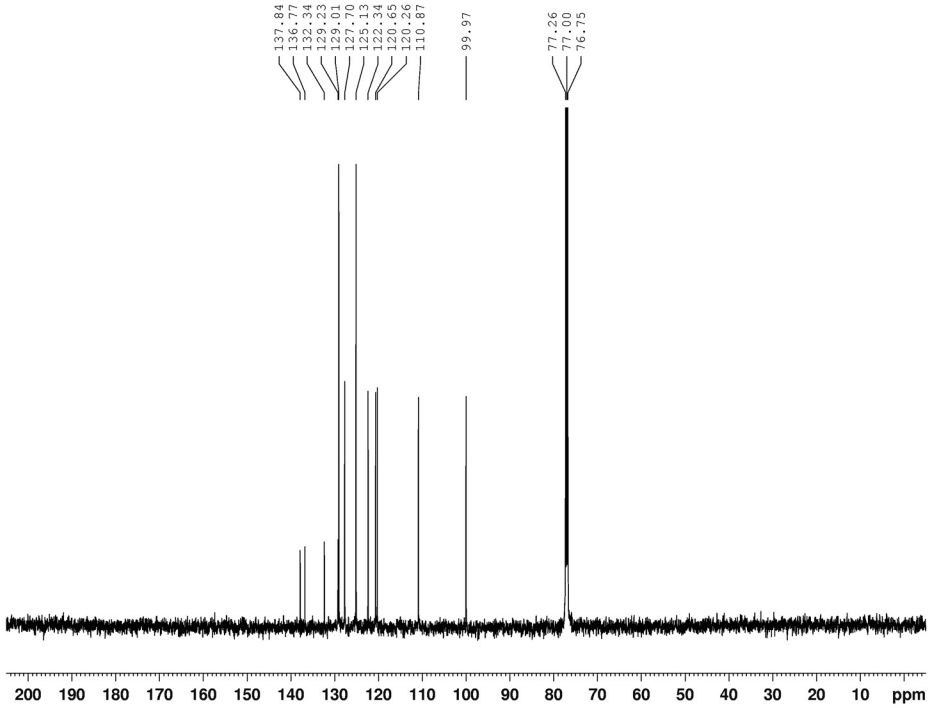
^{13}C NMR of **3-1** ($CDCl_3$, 125 MHz, 300 K)



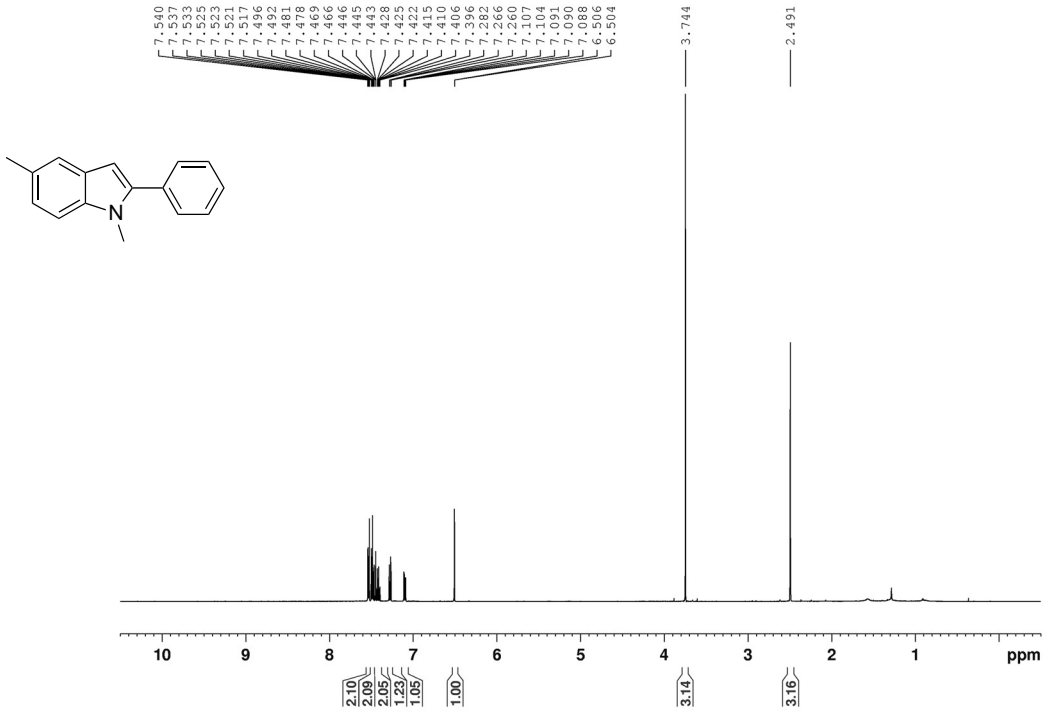
^{1}H NMR of **3-2** ($CDCl_3$, 500 MHz, 300 K)



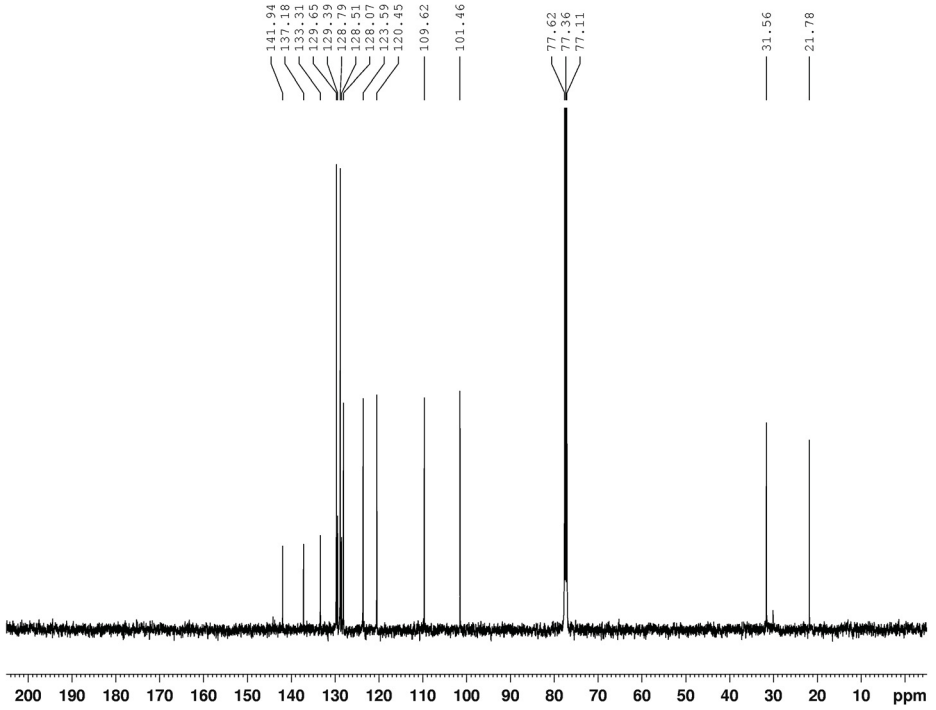
^{13}C NMR of **3-2** ($CDCl_3$, 125 MHz, 300 K)



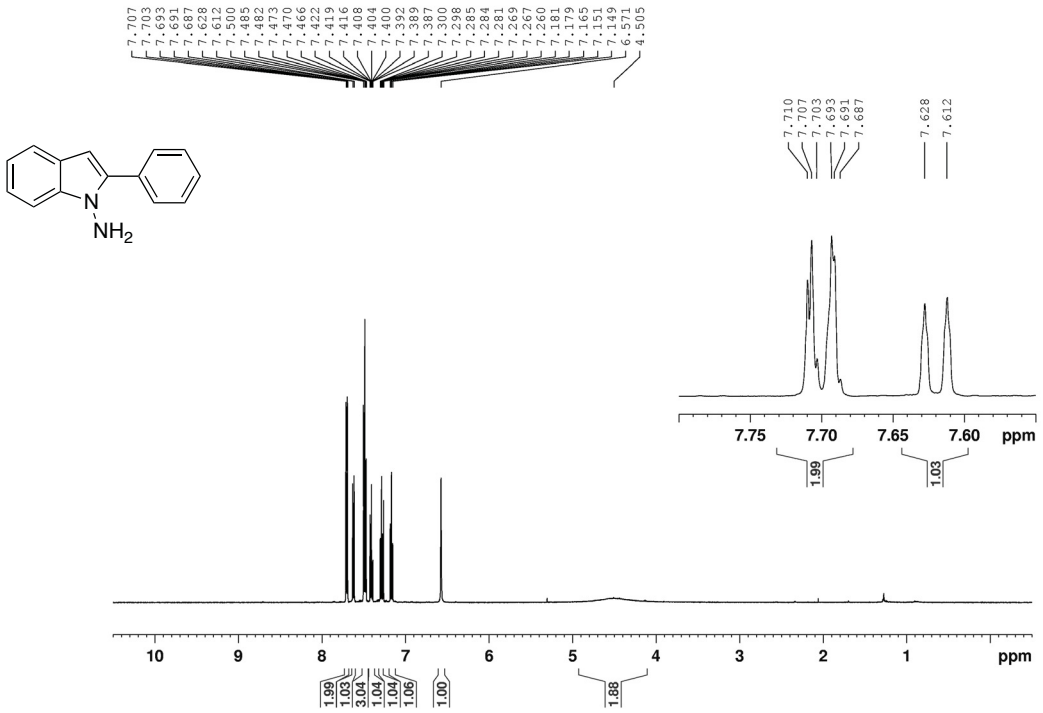
^{1}H NMR of **3-21** ($CDCl_3$, 500 MHz, 300 K)



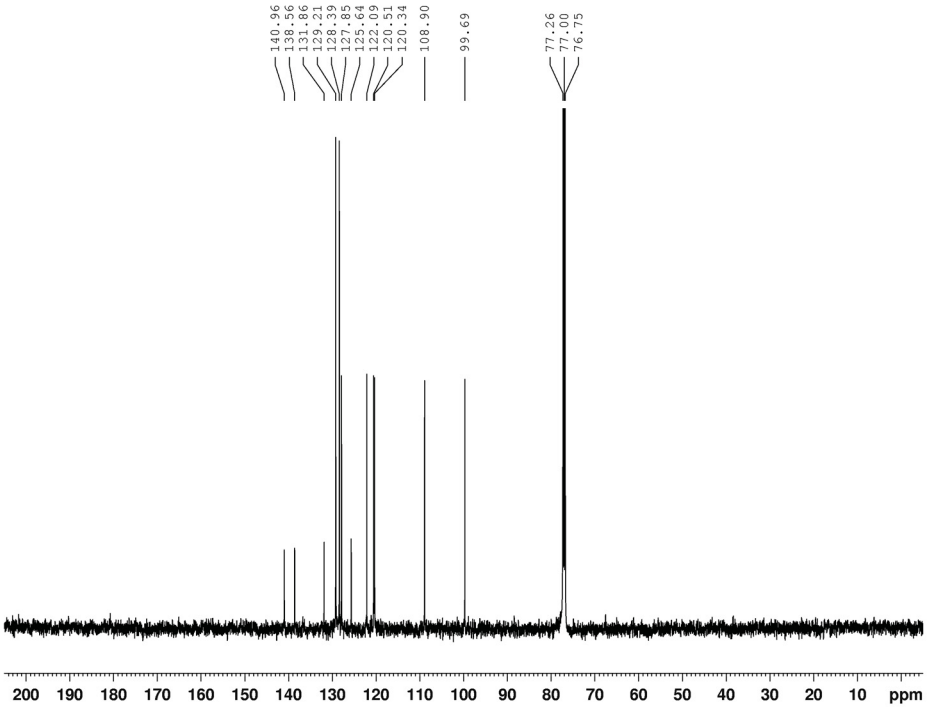
^{13}C NMR of **3-21** ($CDCl_3$, 125 MHz, 300 K)



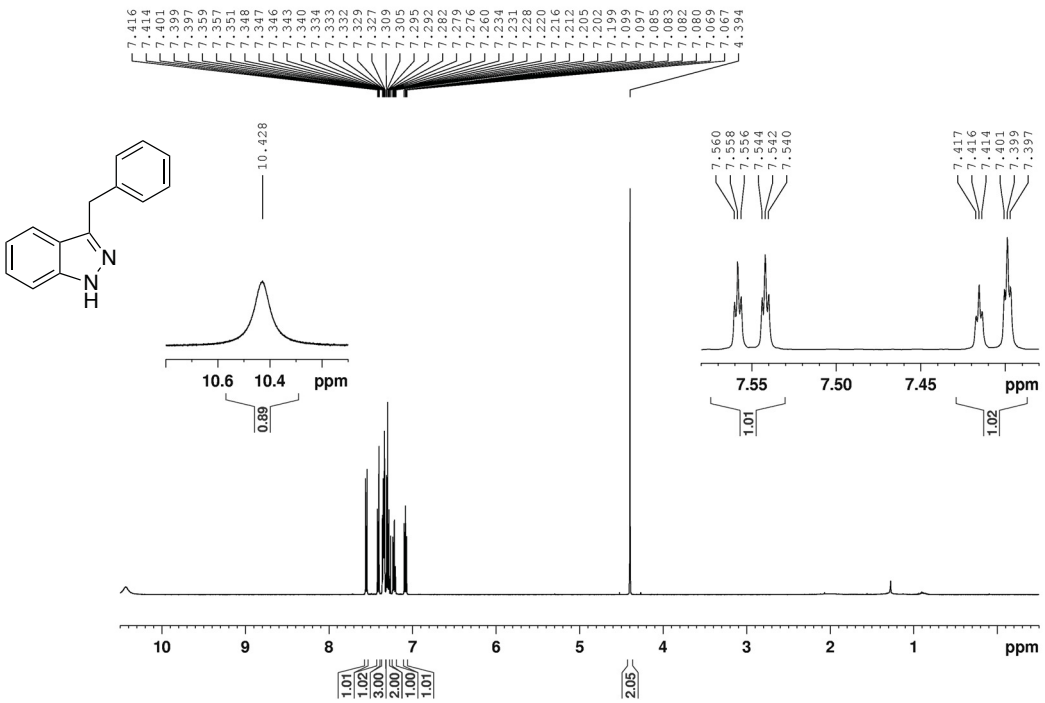
^{1}H NMR of **3-24** ($CDCl_3$, 500 MHz, 300 K)



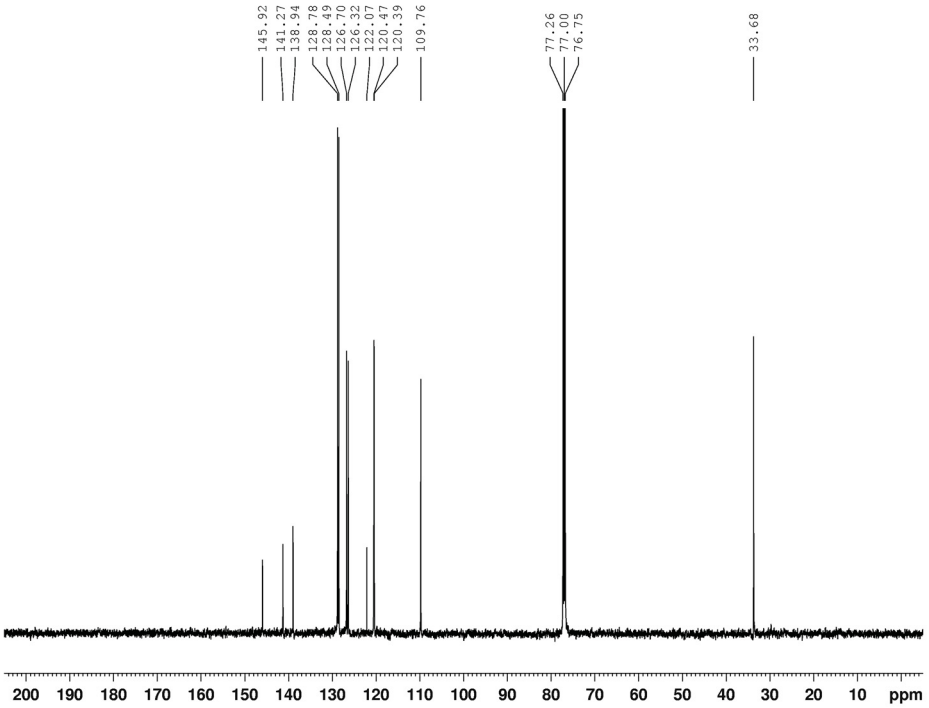
^{13}C NMR of **3-24** ($CDCl_3$, 125 MHz, 300 K)



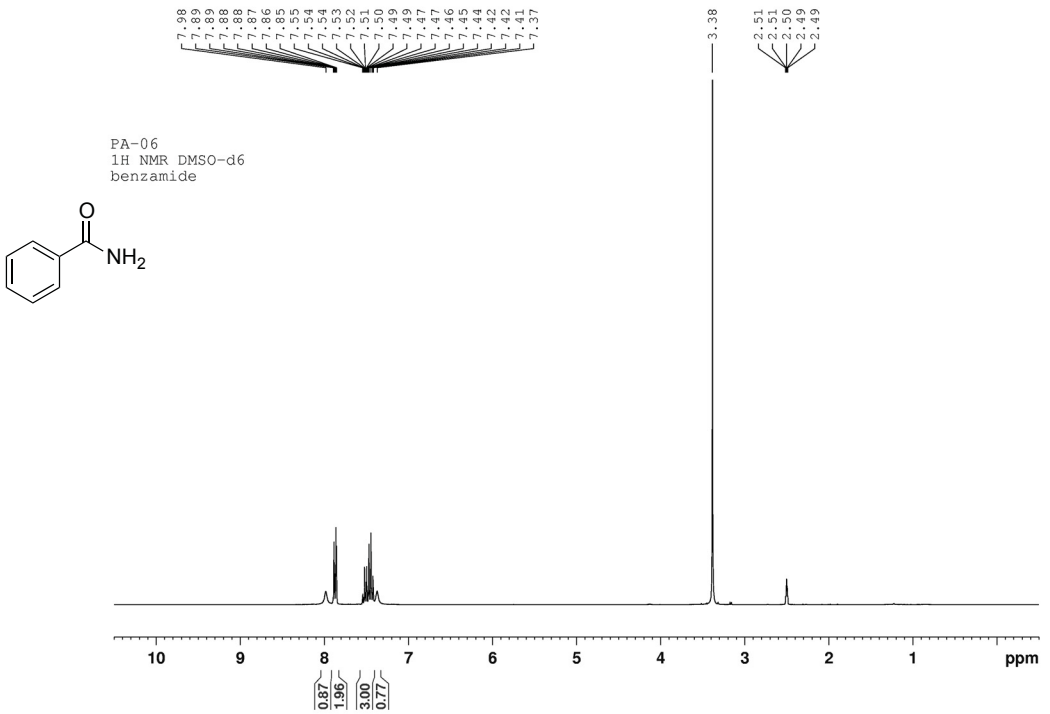
^{1}H NMR of **3-24'** ($CDCl_3$, 500 MHz, 300 K)



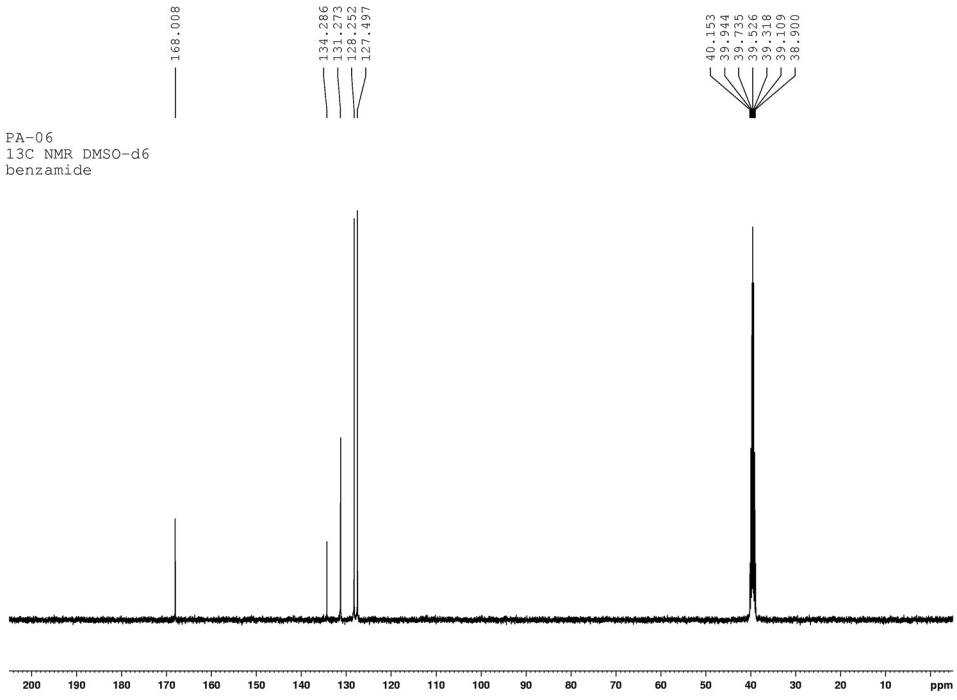
^{13}C NMR of **3-24'** ($CDCl_3$, 125 MHz, 300 K)



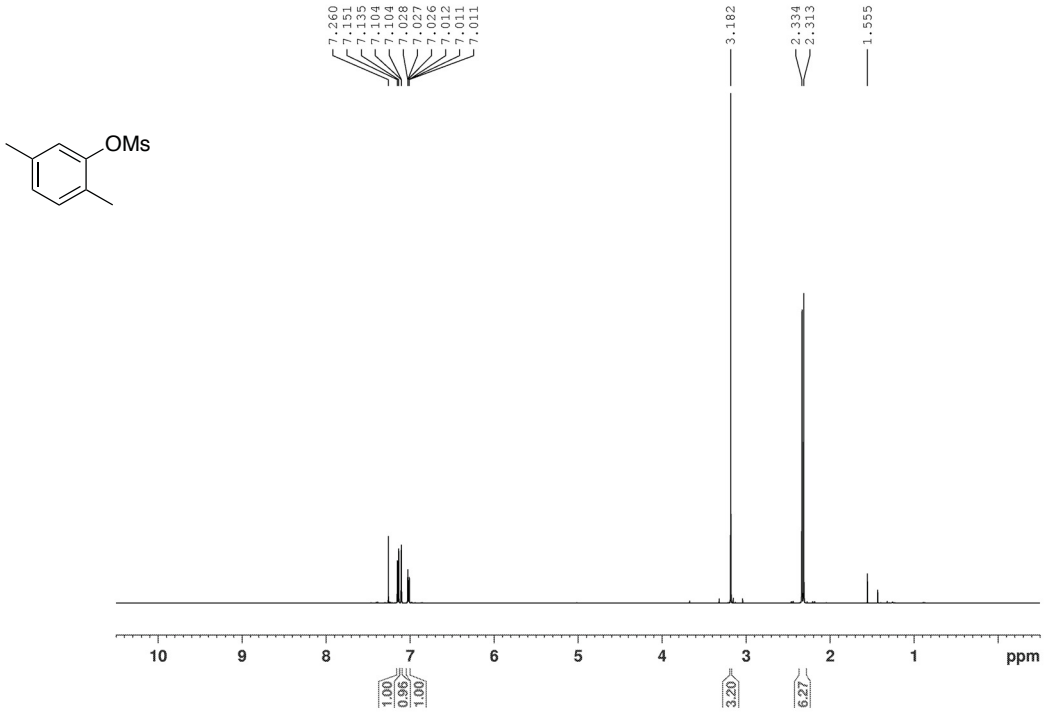
^{1}H NMR of **4-2** (DMSO-d_6, 300 MHz, 300 K)



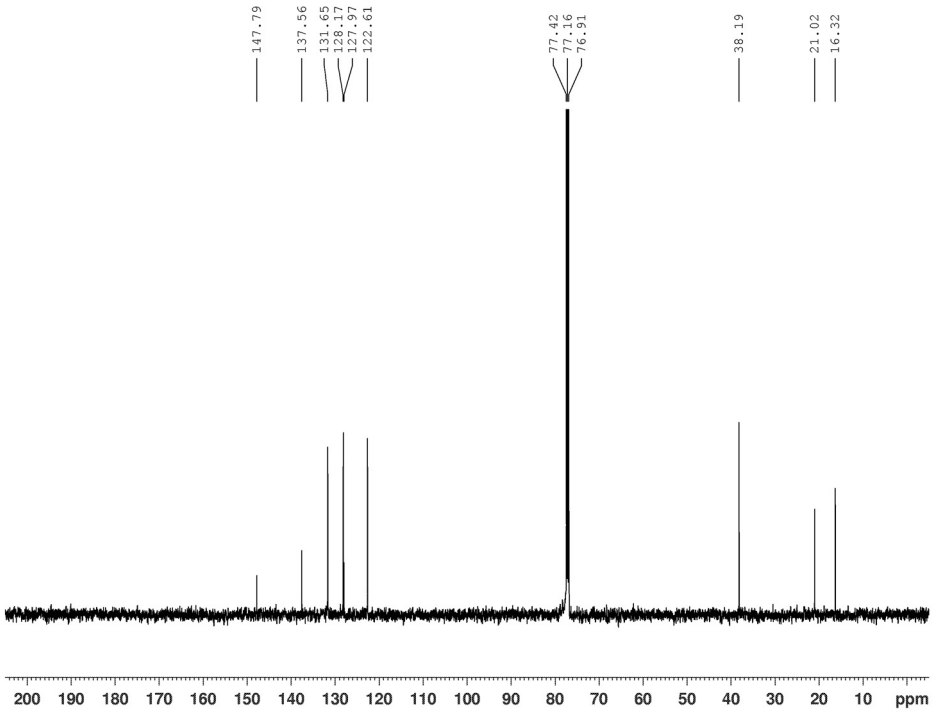
^{1}H NMR of **4-2** (DMSO-d_6, 75 MHz, 300 K)



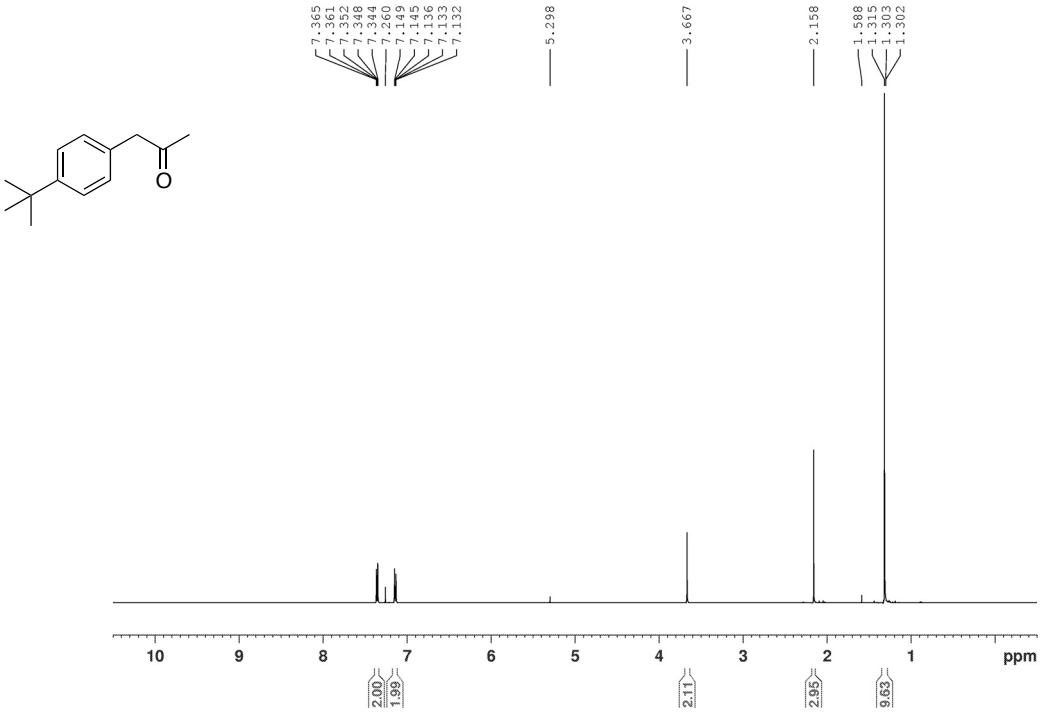
^{1}H NMR of **2,5-dimethylphenyl methanesulfonate** ($CDCl_3$, 500 MHz, 300 K)



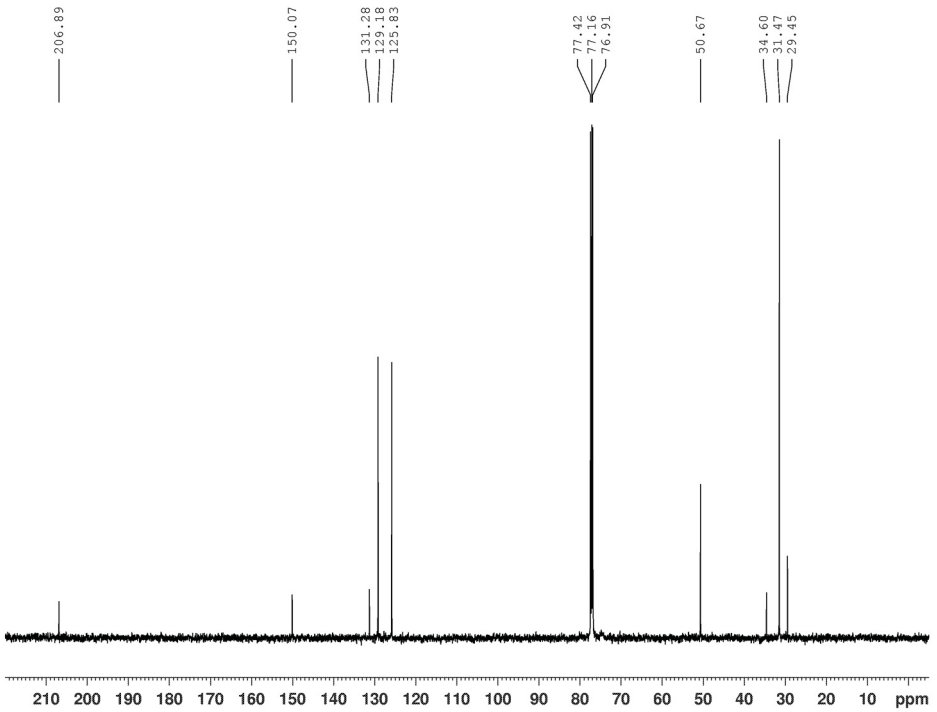
^{13}C NMR of **2,5-dimethylphenyl methanesulfonate** ($CDCl_3$, 125 MHz, 300 K)



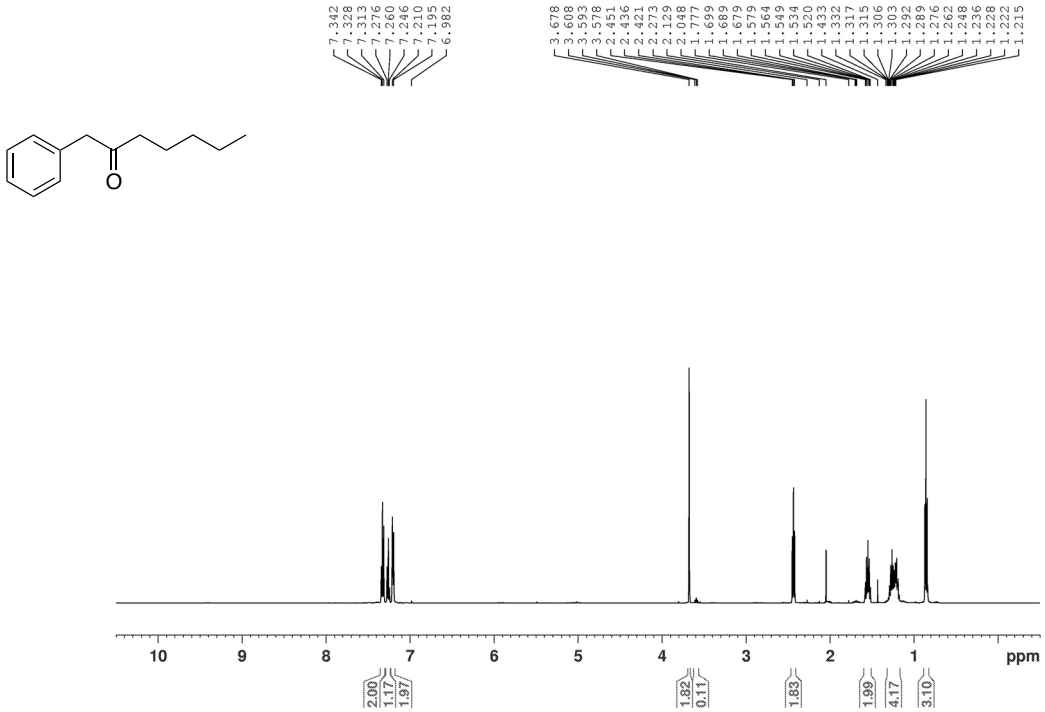
^{1}H NMR of **5-3** ($CDCl_3$, 500 MHz, 300 K)



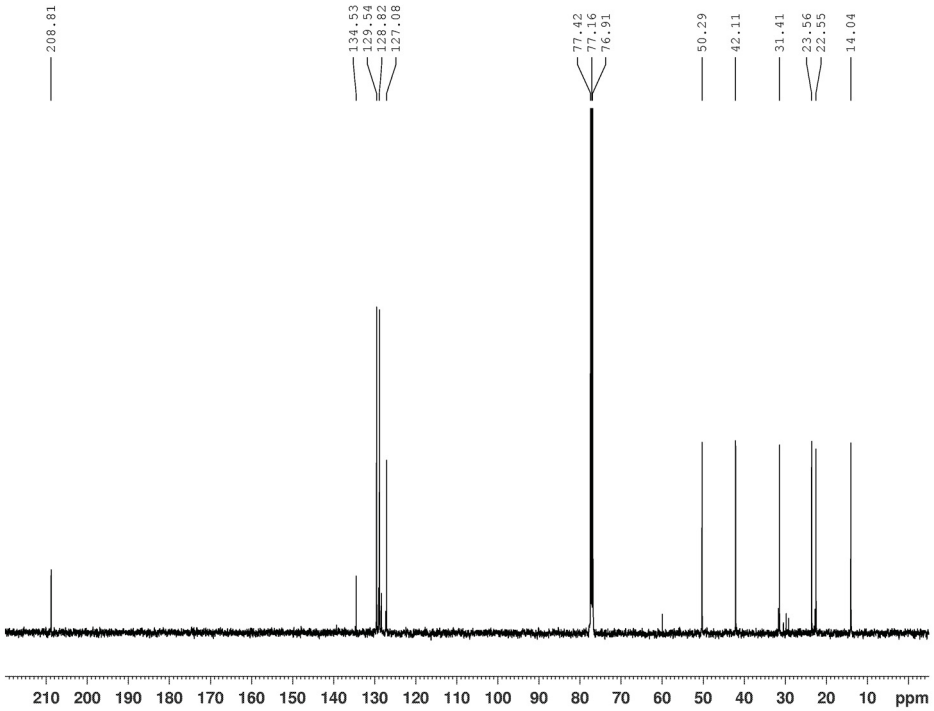
^{13}C NMR of **5-3** ($CDCl_3$, 125 MHz, 300 K)



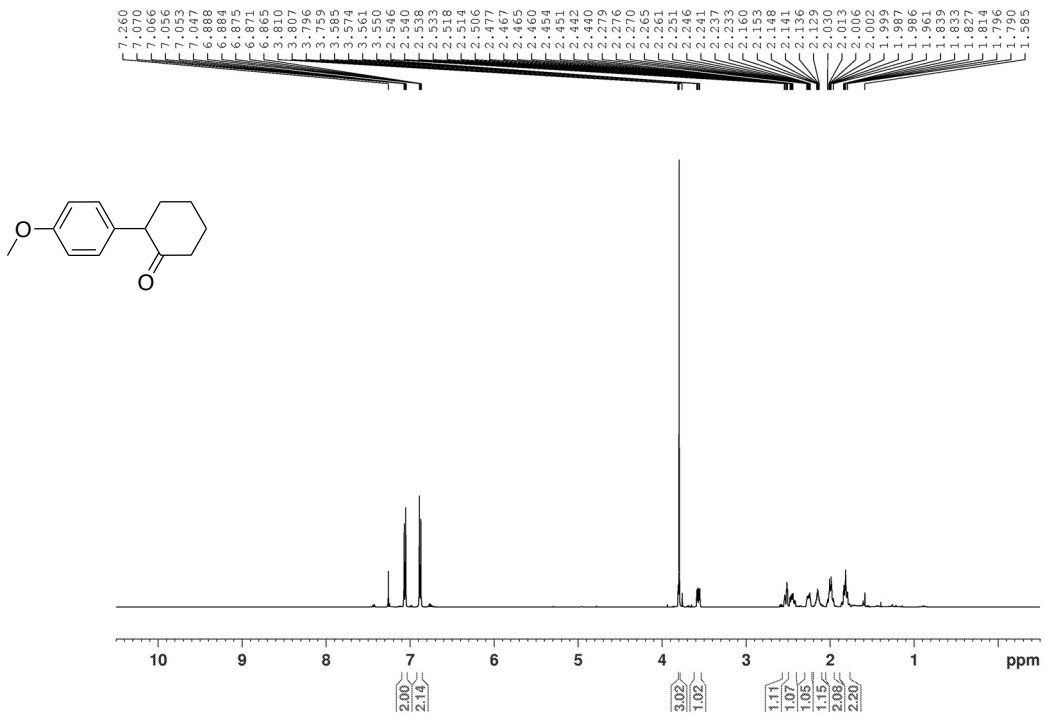
^{1}H NMR of **5-15** ($CDCl_3$, 500 MHz, 300 K)



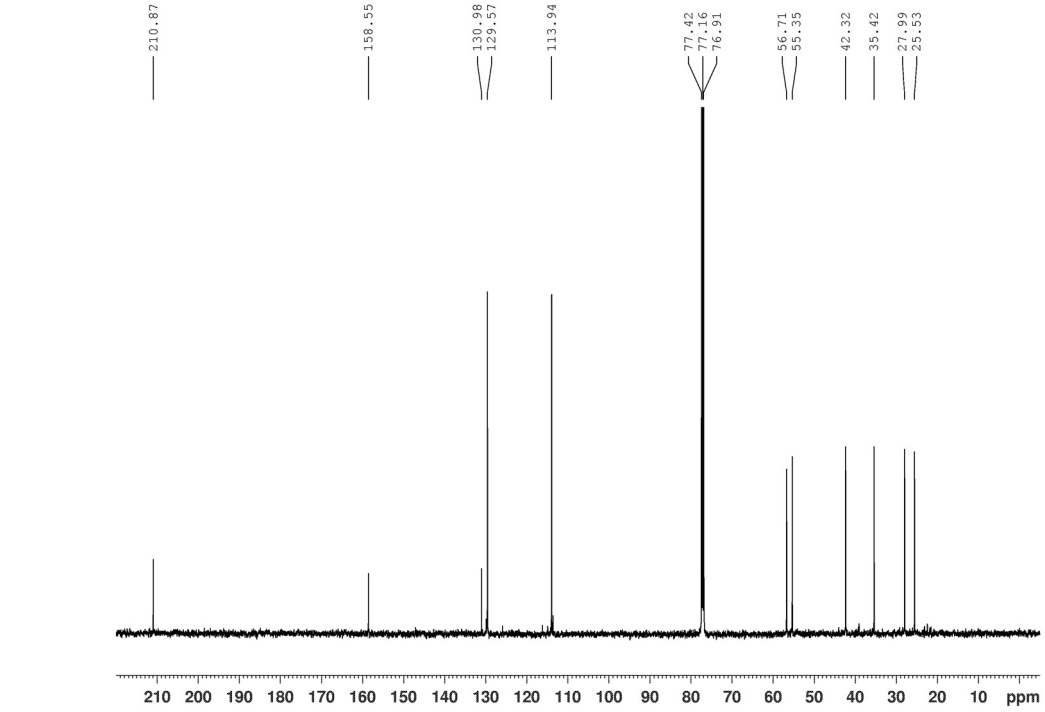
^{13}C NMR of **5-15** ($CDCl_3$, 125 MHz, 300 K)



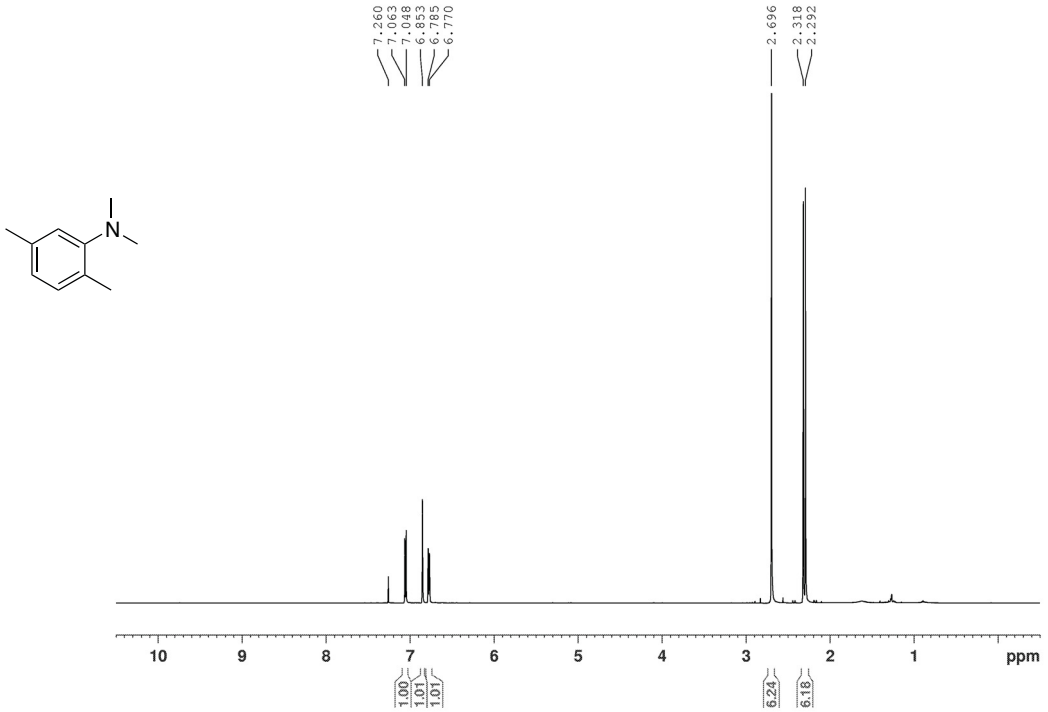
^{1}H NMR of **5-19** ($CDCl_3$, 500 MHz, 300 K)



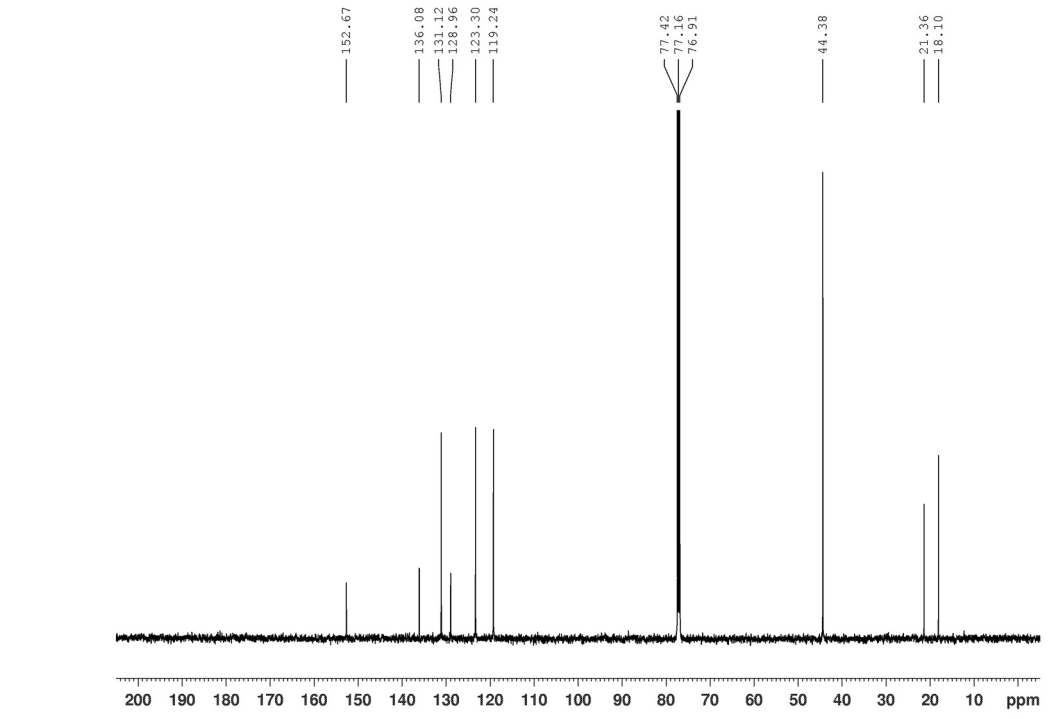
^{13}C NMR of **5-19** ($CDCl_3$, 125 MHz, 300 K)



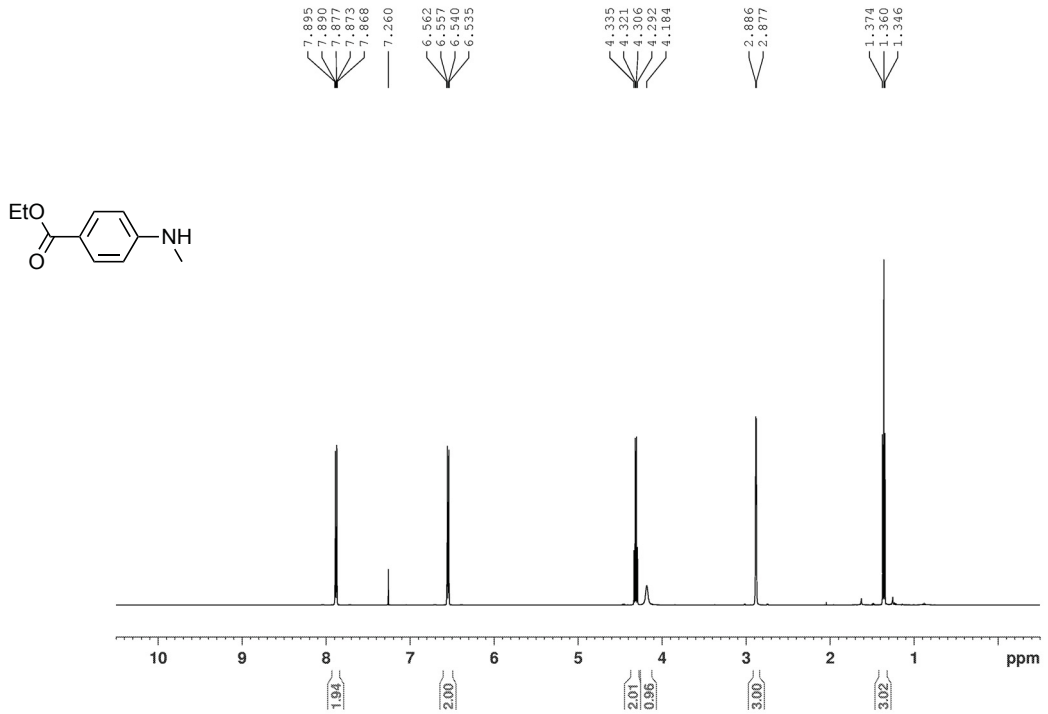
^{1}H NMR of **5-26** ($CDCl_3$, 500 MHz, 300 K)



^{13}C NMR of **5-26** ($CDCl_3$, 125 MHz, 300 K)



^{1}H NMR of **5-36** ($CDCl_3$, 500 MHz, 300 K)



^{13}C NMR of **5-36** ($CDCl_3$, 125 MHz, 300 K)