The Development And Application Of New Palladium Catalysts In Challenging C-N And C-O Bond Forming Reactions

by

Christopher B. Lavery

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ABSTRACT

In the pursuit of increasingly efficient and/or new chemical transformations, homogeneous transition metal catalysts are proving to be invaluable components of the synthetic chemist's toolbox. Notwithstanding the many important contributions made to the area of synthetic chemistry utilizing other transition metal catalysts, palladium-catalyzed cross-coupling techniques have been demonstrated to allow for a plethora of otherwise very difficult or even impossible bond forming reactions to be realized. In this context, appropriately designed ancillary ligands, which upon binding to a metal center can influence metal-centred reactivity, have played an essential role in the advancement of palladium-catalyzed cross-coupling reactions. This thesis describes a multi-faceted approach to the identification of effective ligands for the palladium-catalyzed construction of (sp^2)carbon-nitrogen and -oxygen bonds.

A new series of P,O-DalPhos ligands were developed and applied in the synthesis of of *N*-substituted indoles via tandem palladium-catalyzed cross-coupling/cyclizations of *ortho*-alkynylhalo(hetero)arenes with primary amines. Notably, one P,O-DalPhos variant, OTips-DalPhos, was demonstrated to offer the broadest known substrate scope in this important class of transformations, affording a variety of structurally diverse indoles and related heterocyclic derivatives in high yields.

Also described herein is the identification of the previously reported ligand BippyPhos as an extremely robust and versatile ligand in both palladium-catalyzed carbon-nitrogen and -oxygen cross-coupling applications. Indeed, the use of a Pd/BippyPhos catalyst enabled the cross-coupling of a range of (hetero)aryl (pseudo)halides with primary and secondary amines, NH heterocycles, amides, ammonia and hydrazine, with representative examples being accommodated in air. The unprecedented scope of the Pd/BippyPhos catalyst in carbon-nitrogen cross-coupling allowed for the development of two novel one-pot, two-step syntheses of *N*-aryl heterocycles from ammonia, *ortho*-alkynylhalo(hetero)arenes and (hetero)aryl halides through tandem *N*-arylation/hydroamination reactions. A marked selectivity profile was also observed for the Pd/BippyPhos catalyst and successfully exploited in the chemoselective monoarylation of substrates featuring two distinct and potentially reactive NH-containing moieties. Finally, Pd/BippyPhos mixtures served as robust and efficient catalysts for the hydroxylation of a range of (hetero)aryl halides and *ortho*-alkynyl(halo)heteroarenes to form phenols and phenol-derived heterocycles. A significant number of these transformations proceed at room temperature, and have been conducted on the benchtop under air using unpurified solvents with negligible loss in reactivity when compared to parallel transformations conducted under inert-atmosphere conditions.

LIST OF ABBREVIATIONS AND SYMBOLS USED

Å	angstrom
δ	chemical shift
η	hapticity (contiguous donor atoms)
κ	hapticity (non-contiguous donor atoms)
1-Ad	1-adamantyl
Anal. Calcd.	analysis calculated
BHA	Buchwald-Hartwig amination
Bn	benzyl
br	broad
nBu	n-butyl
secBu	sec-butyl
tBu	tert-butyl
cat.	catalytic
ccd	charge-coupled device
cod	1,5-cyclooctadiene
d	doublet *or* day(s)
dba	dibenzylideneacetone
dd	doublet of doublets
ddd	doublet of doublets of doublets
D*i*PPF	1,1'-bis(diisopropylphosphino)ferrocene
dp	doublet of pentets
DP	DavePhos
DMSO	dimethyl sulfoxide
dt	doublet of triplets
E	heteroatom
equiv	equivalent(s)
ESI	electrospray ionization
GC	gas chromatography
h	hour(s)
HRMS	high-resolution mass spectrometry

Hz	hertz
J	coupling constant
L	neutral 2-electron donor ligand
L_n	generic ligand set
m	multiplet
m	meta
M	generic transition metal *or* mol/L *or* molecular ion
Me	methyl
min	minute(s)
MDP	Mor-DalPhos
mol	mole(s)
m/*z*	mass-to-charge ratio
NBS	*N*-bromosuccinimide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
o	ortho
OAc	acetate
ORTEP	Oak Ridge thermal ellipsoid plot
OTs	tosylate (*p*-toluenesulfonate)
p	para
PCT	patent cooperation treaty
pent	pentet
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
Ph	phenyl
ppm	parts per million
iPr	iso-propyl
nPr	n-propyl
PTFE	poly(tetrafluoroethylene)
q	quartet
RT	room temperature
s	singlet

t	triplet
THF	tetrahydrofuran
TLC	thin-layer chromatography
X	(pseudo)halide

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CHAPTER 1 INTRODUCTION

1.1 SYNTHETIC CHEMISTRY AND THE CONCEPT OF SUSTAINABILITY

The combined research efforts of chemists from all disciplines have established a chemical enterprise that supplies many of the essential living needs for today's population. Indeed, our evolving knowledge of chemistry has allowed us to live longer and healthier lives through medical advancements, provide food and nourishment for an exponentially growing population, and will play a key role in our overcoming the challenges in transitioning from finite to renewable energy resources.[1] A common thread linking such advancements in the quality and sustainability of life is the area of synthetic chemistry. No longer than two centuries ago it was believed that organic molecules could only be accessed through biological processes.[1] Today, chemists can synthesize molecules of tremendous complexity with high levels of selectivity and stereocontrol. The successful synthesis of some natural products, such as Vitamin B12, have been described as accomplishments comparable to the construction of the great pyramids at a molecular level.[1,2] Notwithstanding the remarkable progress that has been made in chemical synthesis, the associated poor efficiency with many state-of-the-art synthetic methodologies presents chemists with a new and potentially even greater set of challenges to overcome.

The concept of green and sustainable chemistry has been deservedly gaining much attention over the past two decades.[3,4] A procedure for quantifying synthetic efficiency, known as the E factor,[5] has been developed and revealed that for every kilogram of fine chemical or pharmaceutical product made there are 5-100 kilograms of chemical waste generated.[1] Such highly inefficient synthetic methodologies place great stress on our environment, natural resources, and potentially world health.[1,3,4] The concept of green and sustainable chemistry aims to circumvent such detrimental stresses by calling on chemists to develop new and innovative chemical syntheses that are more resource and energy efficient, atom economical, product selective, operationally simple, and environmentally safer.[3,6] In this context, homogeneous transition metal catalysis is proving to be an invaluable component of the synthetic chemist's toolbox.[7]

1.2 Homogeneous Transition Metal Catalysis as a Sustainable Synthetic Methodology

As described in Section 1.1, identifying new and/or increasingly efficient methodologies for the synthesis of organic molecules represents one of the most important challenges synthetic chemists currently face. Notwithstanding the importance of other categories of catalysis (e.g. heterogeneous catalysis, electrocatalysis or biocatalysis), homogeneous transition metal catalysis has come to play a key role in addressing this challenge owing to the inherent propensity for catalyst tuning, both sterically and electronically by strategic ligand design and/or choice of metal. In fact, there are multiple facets of homogeneous transition metal catalysis that are in parallel with the ideology of green and sustainable chemistry. Homogeneous transition metal catalysis has been shown to be broadly useful and able to accommodate a variety of hybridized and highly functionalized reaction partners with high product selectivity.[8] Utilizing a catalytic methodology in itself allows synthetic chemists to avoid the use of stoichiometric amounts of reagents, which places less strain on our natural resources. Furthermore, strategic catalyst design can enable reaction temperatures to be lowered, ideally to room temperature, and organic protecting groups to be avoided which provides obvious environmental and atom economical advantages.[7] Finally, the accommodation of safer solvents and renewable feedstock chemicals are also important targets in homogeneous transition metal catalysis.[1,3] While many important contributions have been made to the field of homogeneous catalysis employing a diversity of transition metals, palladium complexes are among the most robust and diverse in terms of reactivity profile.[8]

1.3 The Origins of Palladium-Catalyzed Cross-Coupling and the Importance of Ligand Design

Palladium-catalyzed cross-coupling has evolved to be an extremely powerful methodology for the construction of carbon-carbon and carbon-heteroatom bonds.[9-14] It has found numerous applications in the synthesis of pharmaceuticals,[15-17] natural products[18] and novel organic materials.[19] The early stages of development in palladium-catalyzed cross-coupling focused on carbon-carbon bond forming methodologies. In

2010, the Nobel Prize in Chemistry was jointly awarded to Ei-ichi Negishi,[20] Akira Suzuki[21] and Richard Heck for their pioneering work in the palladium-catalyzed formation of carbon-carbon single bonds dating back to the early 1970s.[8] The discoveries of Heck, Negishi and Suzuki revolutionized the way synthetic chemists thought about accessing organic molecules and inspired a plethora of research that demonstrated the robust nature of such transformations.[8] The generic reaction schemes and corresponding proposed mechanisms for the Negishi, Suzuki and Heck reactions are shown in Figure 1–1.[8]

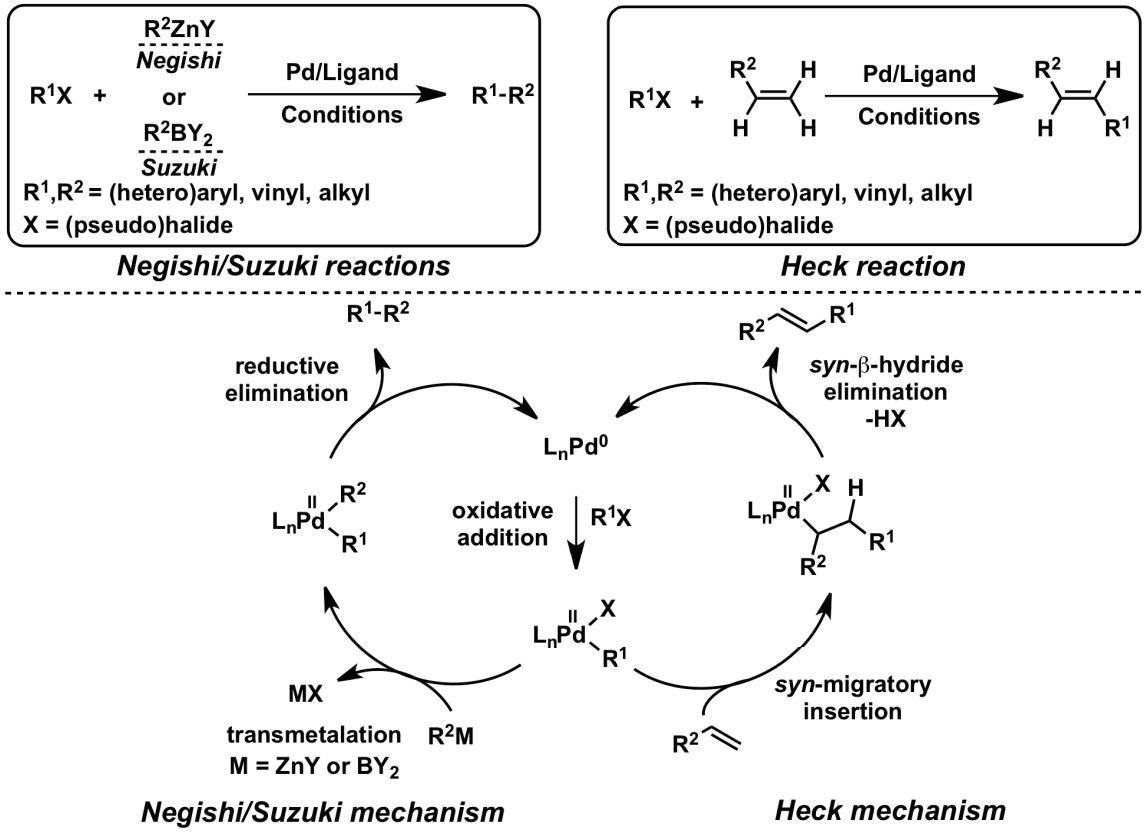

Figure 1–1. Generic reaction schemes and mechanisms for Negishi, Suzuki and Heck cross-coupling.

Negish and Suzuki reactions involve the cross-coupling of an organozinc or organoboron compound, respectively, with an organo(pseudo)halide whereas the Heck reaction involves the cross-coupling of an olefin species with an organo(pseudo)halide. The first step in the mechanism for each of these cross-coupling reactions is common to

all three and involves the oxidative addition of an organo(pseudo)halide to a catalytically active L_nPd^0 species. This is the point at which the Heck mechanism diverges from the Negishi and Suzuki mechanism. In Heck cross-coupling, the reaction proceeds by alkene coordination (not shown in Figure 1–1 for sake of simplicity) to the oxidative addition Pd^{II} complex, followed by *syn*-migratory insertion. The so-formed Pd^{II} species then undergoes *syn*-β-hydride elimination to afford the target alkene product and subsequent base-promoted elimination of HX regenerates the catalytically active L_nPd^0 species. However, in Negishi and Suzuki cross-coupling, the reaction proceeds by the oxidative addition Pd^{II} complex undergoing a transmetalation reaction with an organozinc or organoboron compound, respectively, to form the Pd^{II} species that undergoes reductive elimination to afford the target product.

While relatively simple ancillary ligands, such as PPh_3 for example, were used for the earliest discoveries within the field of palladium-catalyzed cross-coupling, as the field matured and the pursuit of more complex transformations under increasingly milder conditions ensued, the importance of strategic ligand design was realized.[22] For example, it is now well understood that in *most* palladium-catalyzed cross-coupling applications, sterically demanding and electron-rich ligands, such as trialkylphosphines or N-heterocyclic carbenes, offer the best chance for desirable reactivity.[22] This is owing to the fact that such ligands readily promote the formation of a catalytically active monoligated Pd^0 species, facilitate the oxidative addition of electron-rich or deactivated aryl halides and afford increased rates of reductive elimination by imparting steric congestion at the palladium centre.[22,23] However, it is important to note that these described ligand attributes should only be viewed as guiding principles. There are multiple aspects of design that play an important role in determining the overall utility of a ligand in a given cross-coupling reaction, particularly in cases where selectivity issues and/or unwanted side reactions arise. In keeping with the ultimate goal of targeting more efficient and sustainable syntheses, it is also highly desirable that ligand syntheses be expedient, modular and high yielding. Representative examples from the several major classes of ligands that generally adhere to these guidelines and have found widespread application in palladium-catalyzed cross-coupling will be presented in Section 1.4 (Figure 1–5).

Recent advancements made in the Nobel Prize-winning Suzuki and Negishi carbon-carbon bond forming reactions exemplify the importance of ligands in enabling reaction development. For example, while PPh_3 serves as an adequate ligand in Suzuki reactions employing less sterically demanding reaction partners, when employing aryl (pseudo)halides and aryl boronic acids that both feature di-*ortho*-substitution, more sophisticated ligand frameworks are required.[22] This is owing to the difficulty of such sterically demanding aryl boronic acids to transmetallate with an oxidative addition complex featuring a di-*ortho*-substituted aryl group and avoid undesirable competing protodeboronation processes.[22] However, several ligands have been developed that support active catalyst platforms for this challenging transformation; selected examples are shown in Figure 1–2.

In 2004, building off of their previous success in challenging Suzuki reactions,[24] the Buchwald research group developed an effective and general palladium-based catalyst system supported by their biaryl monophosphine ligand, SPhos (Figure 1–2), that is capable of cross-coupling 2,6-substituted aryl bromides with 2,6-dimethylphenylboronic acid to generate tetra-*ortho*-substituted biaryls in synthetically useful yields.[25] The methoxy groups featured on the non-phosphorus containing aryl ring in SPhos are believed to play a key role in enabling such desirable reactivity as their lone pairs can interact with palladium and/or add electron density to the ligand backbone, therefore aiding in the stabilization of catalytic intermediates and circumventing unwanted side reactions such as protodeboration.[25]

More recently, the Organ research group developed a palladium-based catalyst system utilizing the concept of "flexible" sterically demanding carbene ligands[10,26] that are capable of cross-coupling a variety of 2,6-disubstituted aryl bromides and chlorides with 2,6-disubstituted aryl boronic acids to generate tetra-*ortho*-substituted biaryls in synthetically useful yields.[27] Specifically, the authors employed their PEPPSI (pyridine-enhanced precatalyst preparation stabilization and initiation) technology supported by an N-heterocyclic carbene (NHC) ligand featuring pendant isopentyl substitution on the ligand N-aryl groups, commonly referred to as Pd-PEPPSI-IPent, to affect this difficult class of Suzuki reactions (Figure 1–2).

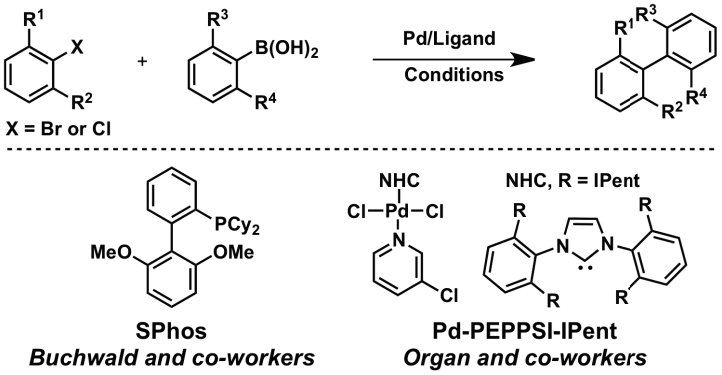

Figure 1–2. Generic reaction scheme for Suzuki cross-coupling of di-*ortho*-substituted substrates and selected examples of ligands capable of accommodating such substrates.

While Figure 1–2 does not represent an exhaustive list of ligands capable of affecting Suzuki reactions employing di-*ortho*-substituted reaction partners, these represent selected state-of-the-art examples that serve to highlight the key role of ligand design in enabling challenging transformations.[22]

As previously mentioned, judicious ligand design has also played a key role in advancing the Negishi reaction. The accommodation of secondary alkylzinc reagents in the Negishi reaction represents a significant challenge due to competing β-hydride elimination and isomerization processes that afford undesired linear products.[22] While several ligands have been reported to affect such challenging substrates in this transformation,[22] the research groups of Buchwald and Organ have recently shown the ability for the ligands CPhos[28] and IPent[29], respectively, to provide unprecedented selectivity for the generation of target branched products (Figure 1–3.). It is believed that the fast reductive elimination rates provided by the steric bulk of CPhos and IPent are responsible for such desirable reactivity.[22]

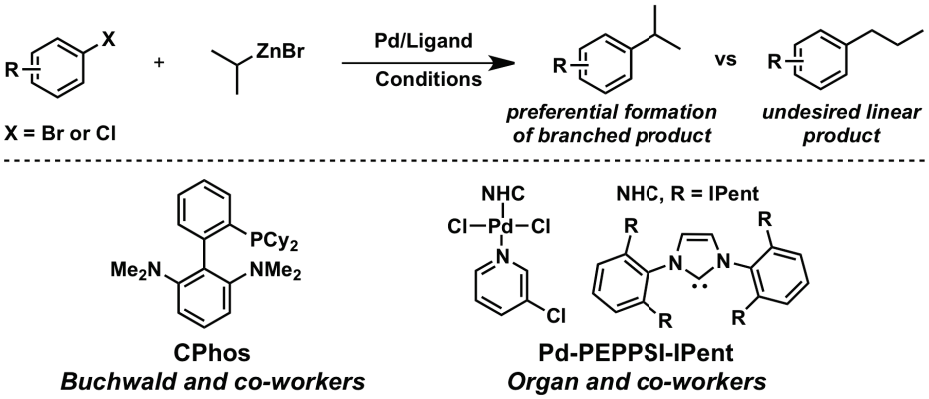

Figure 1–3. Generic reaction scheme for Negishi cross-coupling of secondary alkylzinc substrates with aryl halides and selected examples of ligands capable of accommodating such substrates.

Beyond the specific examples discussed for the Suzuki and Negishi reactions, the field of palladium-catalyzed carbon-carbon bond formation has seen tremendous progress and has matured into a robust synthetic methodology. Furthermore, palladium-catalyzed carbon-carbon bond forming technologies have served to lay the foundations for palladium-catalyzed carbon-heteroatom bond forming processes which, as previously eluded to, have also found important applications in synthetic chemistry.

1.4 Palladium Catalyzed Carbon-Nitrogen Bond Formation

The ubiquitous nature of (sp^2)carbon-nitrogen bonds in compounds of synthetic interest, and the lack of methodologies for their construction that are both mild and generally applicable, served as inspiration for the development of palladium-catalyzed (sp^2)carbon-nitrogen bond forming technologies. Ground-breaking work by Migita and co-workers in 1983 involving the palladium-catalyzed cross-coupling of a tributyltin amine species with aryl bromides to generate arylamines set the stage for the discovery of the reaction that is now known as Buchwald-Hartwig amination (BHA).[30] In 1995 the research groups of Buchwald and Hartwig both independently discovered that the aminotin species in Migita's system could be replaced by a free NH-containing amine in combination with a judiciously chosen base, such as NaO*t*Bu or $LiN(SiMe_3)_2$.[31,32] This discovery brought palladium-catalyzed carbon-nitrogen cross-coupling to the masses and indeed significant progress has been made, with BHA emerging as another indispensible component of the synthetic chemist's toolkit.[33] Over the past two decades, contributions

to BHA by research groups in both academia and industry, has facilitated the accommodation of sterically and electronically divergent substrates including ammonia, hydrazine, amines, amides, and NH heterocycles in combination with a variety of (hetero)aryl (pseudo)halides.[33-35] The generic reaction scheme and proposed mechanism for BHA are shown in Figure 1–4.

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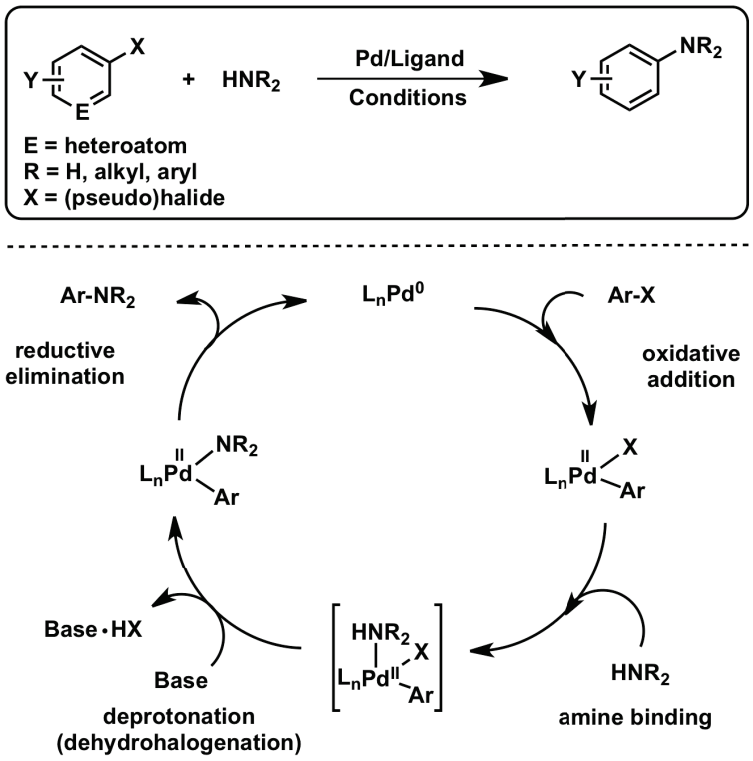


Figure 1–4. Generic reaction scheme and mechanism for BHA.

The proposed mechanism for the BHA reaction is analogous in many ways to the previously described palladium-catalyzed cross-coupling mechanisms discussed in Section 1.3. The first step involves oxidative addition of a (hetero)aryl (pseudo)halide to a catalytically active L_nPd^0 species to form a Pd^{II} oxidative addition intermediate of the type [L_nPd(aryl)(X)]. The next steps involve amine binding to the [L_nPd(aryl)(X)] intermediate, followed by base promoted dehydrohalogenation to form a [L_nPd(aryl)(NR_2)] intermediate, which can then go on to reductively eliminate the target arylamine product and regenerate the catalytically active L_nPd^0 species.

Not unlike most palladium-catalyzed cross-coupling methodologies, the course of BHA is largely ligand controlled; as such, ligand design has also played a crucial role in the expansion of this field.[22,36] Indeed, the guiding principle that strongly donating and sterically demanding ligands offer desirable reactivity benefits in palladium-catalyzed cross-coupling applications (Section 1.3), also holds true in BHA. Representative examples from some of the major ligand classes include bulky, electron-rich trialkylphosphines ($P(tBu)_3$[37-41] and cataCXium A[42,43]), bisphosphines with large bite angles (XantPhos[44-46] and JosiPhos[34,47-50]), sterically demanding carbenes (iPr[51-53]) and mixed P,N donor ligands (MorDalPhos[54-58] and MeDalPhos[59]), as well as (hetero)biaryl monophosphine ligands featuring large dialkylphosphino groups (RuPhos BrettPhos,[35,60,61] BippyPhos,[62,63] and Ad-BippyPhos[64,65]). While many highly active catalyst systems for BHA have been reported beyond the representative examples shown in Figure 1–5, from a practical perspective those ligands (ligand precursors, or their respective palladium pre-catalysts) that offer robust tolerance of air and moisture, easily implemented catalytic protocols, wide substrate scope and commercial availability are most likely to experience significant uptake by end-users.

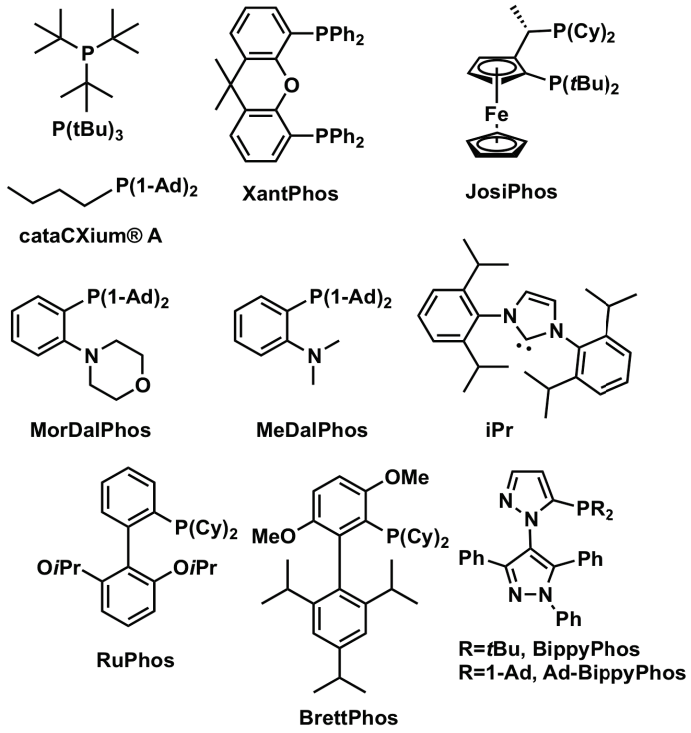


Figure 1–5. Representative examples of some of the major ligand classes that have found important applications in BHA.

Despite significant advances in BHA catalysis, a number of notable challenges persist. Conceivably the most important challenge remaining in BHA is the identification of a single palladium/ligand catalyst system exhibiting broad substrate scope and generality with respect to both the NH-containing and (hetero)aryl (pseudo)halide coupling partners. For example, reports in the literature of a single palladium/ligand catalyst system capable of accommodating such electronically and structurally divergent substrates as ammonia (pKa of protonated ammonia = 9.25) and indole (pKa of protonated indole = -3.6) are still lacking.[66,67] Furthermore, significant issues still remain in expanding the scope of (hetero)aryl (pseudo)halides employed in BHA. For instance, aryl methanesulfonates (aryl mesylates) have proven to be particularly challenging coupling partners in BHA owing to their propensity to revert back to their corresponding phenol and/or undergo unwanted side reactions under catalytic conditions.[13] The development of newly designed ligands in combination with further investigation of previously established ligands represents an effective methodology for addressing outstanding challenges in BHA. Chapters 2 and 3 of this thesis will discuss the use of

such tactics in addressing catalyst generality issues in BHA and the resulting consequence of newly defined reactions.

1.5 Palladium Catalyzed Carbon-Oxygen Bond Formation

Next to nitrogen, oxygen is the most commonly occurring heteroatom found in man-made organic products.[11] This is owing to the fact that chemists have found important applications for hydroxy- and ether-based molecules in accessing a variety of compounds of synthetic interest.[11] Therefore, in light of increasingly stringent sustainability demands, much attention is being payed to the identification of new and/or more efficient methodologies for the construction of carbon-oxygen bonds.[6,11] In this regard, and given the lack of alternative mild and generally applicable methods, transition metal catalysis is proving to be a versatile tool in carbon-oxygen bond formation.[3,11] Specifically, palladium-catalyzed cross-coupling technologies are playing a key role in advancing this important class of bond forming reactions.[6,11] Whereas multiple novel palladium/ligand catalyst systems have been developed for the construction of diaryl and aryl-alkyl ethers through carbon-oxygen bond forming reactions,[11,64,68-71] this thesis will focus on the palladium-catalyzed synthesis of phenols through transformations of (sp^2)carbon-X (X = halide) bonds.

As previously eluded to, phenols are among the most important synthons for the construction of a variety of naturally occurring and biologically active products.[11,72,73] Moreover, the phenol moiety itself is present in a number of top-selling pharmaceuticals; selected examples are depicted in Figure 1–6.

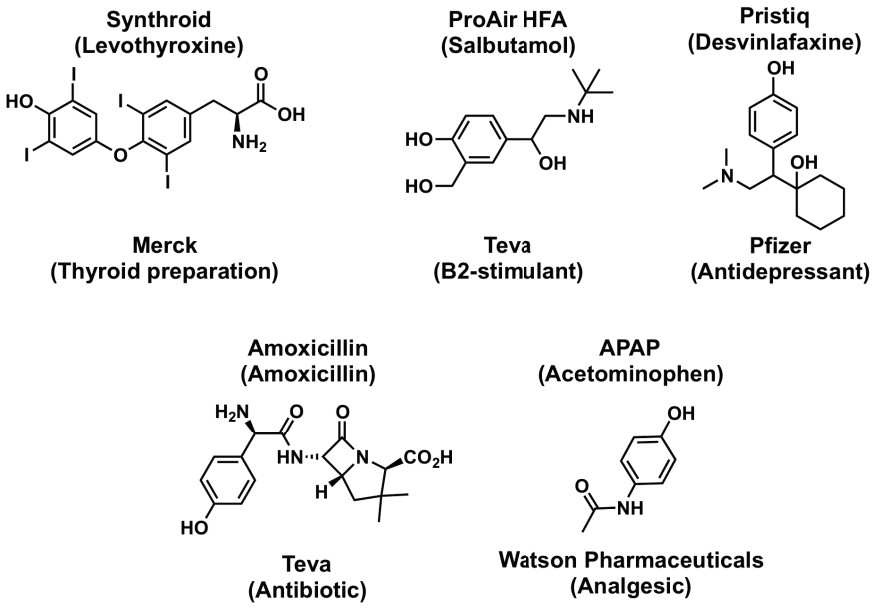


Figure 1–6. Selected examples of top-selling pharmaceuticals that contain the phenol moiety.

Classical methods for preparing phenols include nucleophilic aromatic substitution of activated aryl halides, copper promoted transformations of diazoarenes and synthetic routes utilizing reactive benzyne intermediates.[74,75] However, these protocols are limited in scope and utility owing to the relatively harsh reaction conditions that are required, as well as the electronic demands and limited availability of the requisite starting materials.[11,72-75] Recently, some copper-based catalysts have been identified for the synthesis of phenols, either by the oxidation of aryl boronic acids or the direct hydroxylation of (hetero)aryl halides using hydroxide salts.[76-83] However, the need for high metal/ligand loadings and harsh reaction conditions, as well as their typically poor performance with synthetically useful aryl chlorides,[84] represent important practical drawbacks. In this context, the use of palladium-based catalysts for such transformations, specifically those utilizing hydroxide salts as nucleophiles, has been shown to offer significant reactivity advantages, including increased scope, lower catalyst loadings, and milder reaction conditions.[85-91] Whereas the palladium-catalyzed hydroxylation of (hetero)aryl halides (Figure 1–7) represents a conceptually attractive tool for the preparation of phenols, the catalyst/ligand employed must be judiciously chosen so as to overcome potential challenges, including but not restricted to: catalyst inhibition by free

hydroxide anions (1, Figure 1–7); difficult carbon-oxygen bond reductive elimination owing to the small size of the hydroxide group (2, Figure 1–7); and uncontrolled arylation of the target phenol to the afford the undesired diaryl ether (3, Figure 1–7).

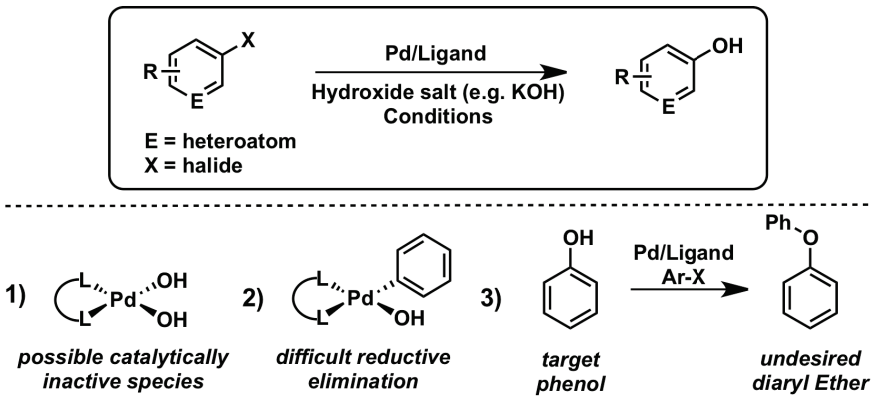


Figure 1–7. Generic reaction scheme for the palladium-catalyzed hydroxylation of (hetero)aryl halides and challenges associated with such transformations.

Notwithstanding the progress made in palladium-catalyzed hydroxylation of (hetero)aryl halides (specific examples will be provided in Section 4.1), the relative scarcity of palladium-based catalysts that have proven effective in promoting the hydroxylation of (hetero)aryl halides provides motivation for further investigation. Of particular interest is the development of alternative catalysts based on a single palladium/ligand pair, which offer broad scope in the (hetero)aryl halide under mild conditions. Moreover, from a practical perspective the identification of catalyst systems of this type that are derived from commercially available components, and that prove capable of operating under air using bench-top synthetic protocols, would represent a useful advance in terms of enabling the broader uptake of such hydroxylation protocols by synthetic chemists. Chapter 4 of this thesis will discuss such a catalyst system that is capable of furnishing a broad spectrum of phenols and phenol-derived benzofurans from (hetero)aryl bromides and chlorides in a manner that is competitive with the best catalyst systems reported to date, while also demonstrating for the first time the viability of employing bench-top reaction protocols in such transformations.

1.6 Overview of Thesis

The research discussed in this thesis represents a multifaceted approach for developing catalysts to address outstanding challenges in carbon-nitrogen (BHA) and carbon-oxygen bond forming reactions, as illustrated by the Venn diagram in Figure 1–8.

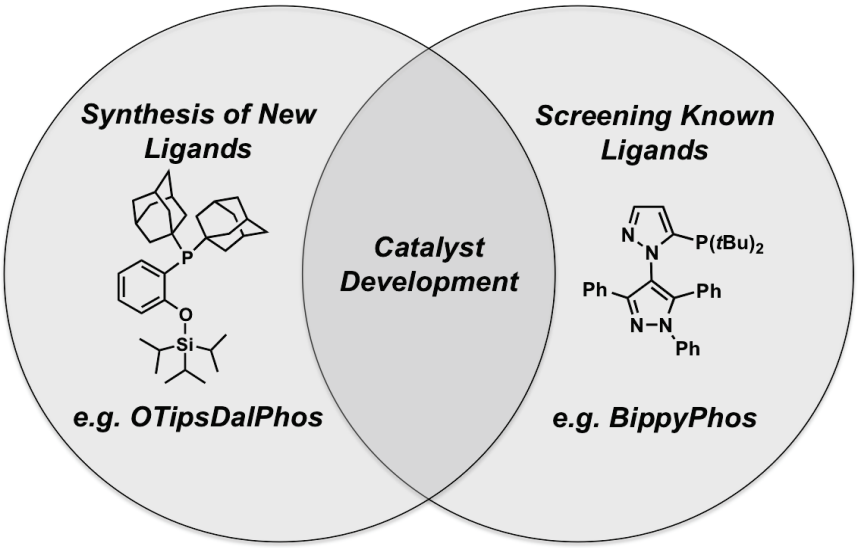


Figure 1–8. Venn diagram representing a multifaceted approach to catalyst development.

Chapter 2 represents the approach to catalyst development illustrated by the left side of the Venn diagram in Figure 1–8 – synthesizing and screening new ligands. Previous research in the Stradiotto group established the broadly useful nature of P,N-DalPhos ligands in various palladium-catalyzed cross-coupling applications.[92] To evaluate conceptually the effect on catalysis caused by replacing the nitrogen-containing moiety with an oxygen-containing moiety in the DalPhos motif, a new series of P,O-DalPhos ligands was developed and assessed in targeted BHA reactions. Specifically, one P,O-DalPhos variant, OTips-DalPhos, was demonstrated to offer the broadest known substrate scope in the palladium-catalyzed carbon-nitrogen cross-coupling/cyclization of *ortho*-alkynylhalo(hetero)arenes with primary amines, affording indoles and related heterocyclic derivatives in high yield (Figure 1–9). Owing to the broadly useful nature of OTips-DalPhos in this useful class of transformations, several new P,O-DalPhos variants were also prepared to further investigate the affect of the oxygen-containing moiety on catalysis.

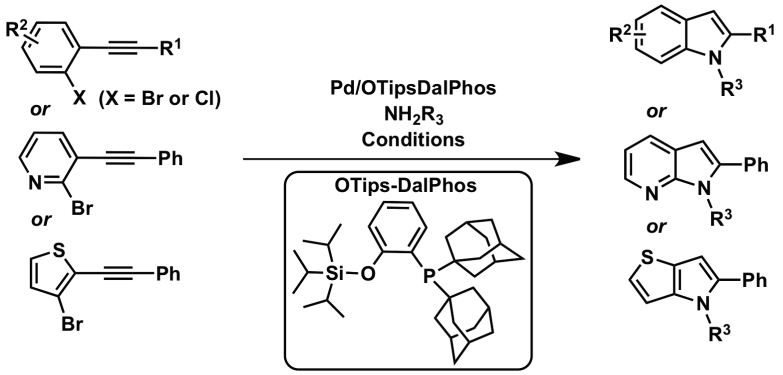


Figure 1–9. Generic reaction scheme of OTips-DalPhos facilitating the palladium-catalyzed carbon-nitrogen cross-coupling/cyclization of *ortho*-alkynylhalo(hetero)arenes with primary amines.

Chapters 3 and 4 of this thesis represent the approach to catalyst development illustrated by the right side of the Venn diagram in Figure 1–8 – further investigation into the reactivity of previously established ligands. While numerous ligands have been developed for very specific applications, a more broad understanding of their reactivity profile often remains to be established. Therefore, in the literature there is a rich, relatively untapped source of ligands that should be screened more broadly to see if they have any reactivity benefits to provide beyond there initially reported applications.

In Chapter 3, the identification of the previously reported ligand, BippyPhos, as being capable of facilitating the palladium-catalyzed amination of a variety of functionalized (hetero)aryl chlorides, as well as bromides and tosylates, with representative examples conducted in air (Figure 1–10), is discussed. The successful transformations described include primary amines, secondary amines, NH heterocycles, amides, ammonia and hydrazine (1 to 11, Figure 1–10), thus demonstrating the largest scope in the NH-containing coupling partner reported for a single palladium/ligand catalyst system. The palladium/BippyPhos catalyst system was also shown to exhibit the broadest demonstrated substrate scope for transition metal-catalyzed cross-coupling of (hetero)aryl chlorides with NH-indoles (8, Figure 1–10). Furthermore, the remarkable ability of the palladium/BippyPhos catalyst system to promote both the selective monoarylation of ammonia and the *N*-arylation of indoles was exploited in the development of a novel one-pot, two-step synthesis of *N*-aryl heterocycles from ammonia, *ortho*-alkynylhalo(hetero)arenes and (hetero)aryl halides via tandem *N*-

arylation/hydroamination reactions (4 to 7, Figure 1–10), similar to the type of transformation discussed in Chapter 2. While the scope in the NH-containing coupling partner is broad, the palladium/BippyPhos catalyst system also displays a marked selectivity profile that was successfully exploited in the chemoselective monoarylation of substrates featuring two distinct and potentially reactive NH-containing moieties (11, Figure 1–10). Additionally, the first crystallographically characterized (BippyPhos)Pd^{II} complex, which confirms the ability of this synthetically useful ligand to adopt a bidentate binding motif, is presented in Chapter 3.

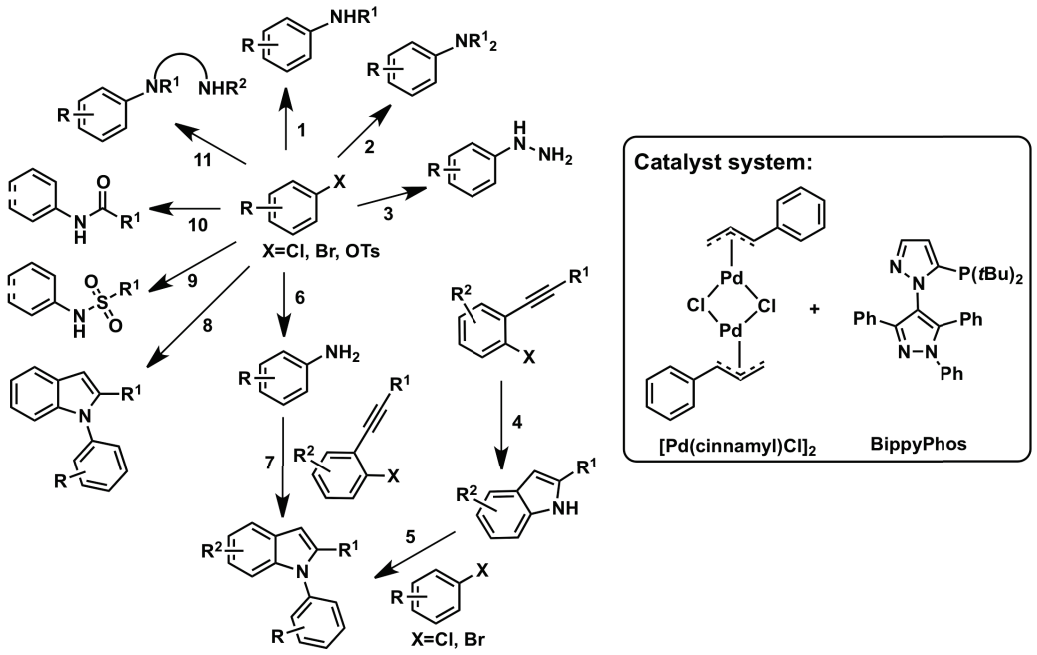


Figure 1–10. Representation of the palladium-catalyzed carbon-nitrogen bond forming reactions achieved when using BippyPhos; NH-containing coupling partners not depicted for simplicity.

In Chapter 4, the synthetic utility of the ligand BippyPhos is shown to be extended to palladium-catalyzed carbon-oyxgen bond formation. Specifically a palladium/BippyPhos catalyst system is demonstrated to be robust and efficient for the hydroxylation of a range of structurally diverse (hetero)aryl halides with broad substrate scope (Figure 1–11). Included in this reactivity survey is the successful synthesis of substituted benzofurans and related heteroatomic derivatives, which are formed via the hydroxylation of *ortho*-alkynylhalo(hetero)arenes (Figure 1–11). Notably, a significant number of the reactions

reported proceed at room temperature, and have been conducted on the benchtop under air using unpurified solvents with negligible loss in reactivity versus related transformations conducted under inert-atmosphere conditions.

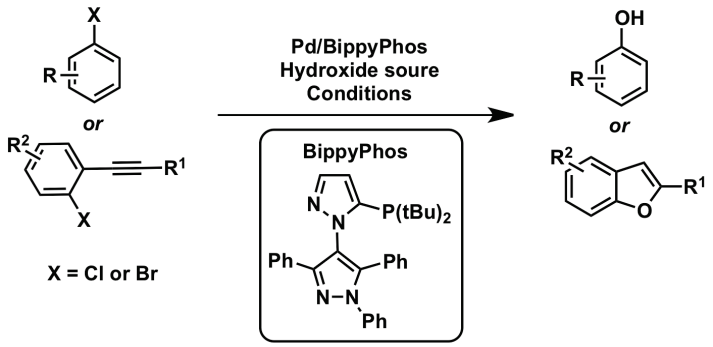


Figure 1–11. Generic reaction scheme of BippyPhos facilitating the palladium-catalyzed synthesis of phenols and phenol-derived heterocycles.

Chapter 5 provides a succinct conclusion and summary of the key findings presented in this thesis, in addition to a discussion of future research directions for building upon the research presented herein.

CHAPTER 2 DEVELOPMENT OF A NEW SERIES OF P,O-DalPhos LIGANDS AND APPLICATION IN THE PALLADIUM-CATALYZED SYNTHESIS OF SUBSTITUTED INDOLES

2.1 INTRODUCTION

In addition to being among the most ubiquitous heterocycles in nature, the indole framework represents a privileged sub-structure in the design of pharmaceutical agents, owing to the ability of such derivatives to bind to a diversity of receptors with high affinity.[93] Despite the numerous "classical" methods for preparing indoles (e.g. Fischer indole synthesis and variants thereof involving the Japp-Klingemann reaction and enamine-diazonium cation coupling,[93,94] reductive cyclization indole synthesis,[93,95] Nenitzescu indole synthesis[93,96] or Plieninger indole synthesis)[93] the need for efficient synthetic protocols that enable the selective assembly of functionalized indoles under relatively mild conditions has inspired the examination of transition metal-catalyzed methodologies, most notably those employing palladium.[97-101] Indeed, the application of palladium catalysis has revolutionized indole synthesis, and several novel disconnection strategies have been established, including (but not restricted to) those starting from *ortho*-alkynylanilines or *ortho*-haloanilines, and their derivatives.[97-102] A complementary yet less well-explored pathway to the indole core structure involving palladium-catalyzed amine arylation using *ortho*-alkynylhaloarene synthons (pre-formed or prepared *in situ*), followed by base-mediated cyclization of the resultant *ortho*-aminophenylacetylene,[103-107] was pioneered by Ackermann and co-workers.[102,108-111] This modular carbon-nitrogen cross-coupling/cyclization cascade is conceptually attractive in terms of diversifying the indole framework, in that substituted alkynyl moieties can be installed easily by use of Sonogashira coupling protocols, and the substitution at nitrogen can be varied by the choice of primary amine coupling partner. Following a brief catalyst optimization campaign, Ackermann and co-workers[108-111] identified $Pd(OAc)_2$/iPr·HCl (5 mol% each; 105-120 °C) as being optimal when using *ortho*-alkynylhaloarenes in combination with a range of primary amine reagents (Figure 2–1). However, some limitations exist with regard to the demonstrated substrate scope in these[108-111] and some closely related reports;[112,113] there is only one report of the successful utilization of the challenging substrate methylamine (R^3 = Me, Figure 2–1),[50] synthons featuring heterocycles attached to the alkynyl terminus (R^1 position, Figure 2–1) have not been documented, and the use

of *ortho*-alkynylhalo(hetero)arene substrates is limited to two examples from the Ackermann group,[111] in which 4-azaindoles (E = N, Figure 2–1) are formed using sterically demanding amine reaction partners.

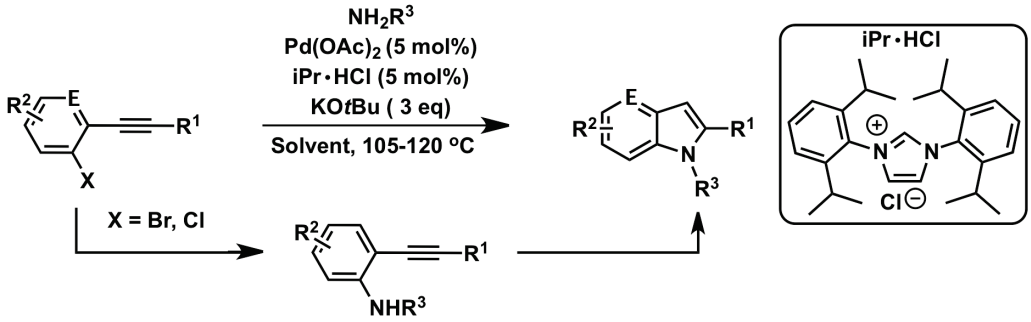


Figure 2–1. $Pd(OAc)_2$/iPr·HCl catalyst system capable of cross-coupling *ortho*-alkynylhaloarenes with a range of primary amine reagents.

As mentioned in Section 1.6, previous research in the Stradiotto group has demonstrated the broadly useful nature of P,N-DalPhos ligands in various palladium-catalyzed cross-coupling applications. Specifically, one P,N-DalPhos variant, Mor-DalPhos, has been shown to facilitate the selective monoarylation of challenging substrates such as ammonia,[56] hydrazine[57] and acetone (Figure 2–2).[92,114,115]

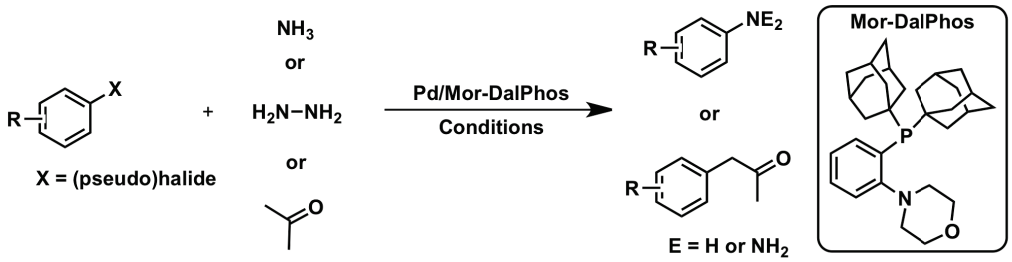


Figure 2–2. Generic reaction scheme representing the ability of Mor-DalPhos to facilitate the palladium-catalyzed monoarylation of ammonia, hydrazine and acetone.

In building on the success of Mor-DalPhos, and as part of ongoing research efforts in the Stradiotto group directed toward the design and application of new modular ancillary ligands for use in transition metal-catalyzed transformations, the synthetically useful cascade carbon-nitrogen cross-coupling/cyclization reaction shown in Figure 2–1 was chosen to be used as a challenging testing ground for new ligand design. In particular, the

development of a catalyst system that could offer broad scope in such a transformation in accommodating both large and small amine coupling partners, as well as a diversity of *ortho*-alkynylhaloarene substrates including those featuring heterocyclic functionality, at relatively low catalyst loading (< 5 mol% Pd/ligand) was identified as an important goal. In Section 2.2, the new and easily prepared DalPhos ligand variant, OTips-DalPhos, which exhibits this desired reactivity profile, is reported.

2.2 Results and Discussion

2.2.1 Synthesis of OTips-DalPhos

Encouraged by the utility in palladium-catalyzed carbon-nitrogen and carbon-carbon cross-coupling chemistry of Mor-DalPhos, which features an ortho-di(1-adamantyl)phosphino ($P(1\text{-}Ad)_2$) group appended to an N-phenylmorpholine core (Figure 2–2), the development of new DalPhos variants featuring alternative heteroatom pairings, including phosphorus and oxygen,[116] became of particular interest. Additionally, replacing the nitrogen heteroatom within the DalPhos motif with a more electronegative oxygen heteroatom (3.44 for oxygen *vs.* 3.04 nitrogen, using the Pauling scale)[117] would result in the ligand featuring a weaker, potentially even hemilabile, secondary interaction with the palladium centre during catalysis which could possibly lead to additional reactivity benefits in certain targeted applications (Figure 2–3). While there are ligands in the literature featuring phosphorus-oxygen heteroatom pairings,[35,61,116] ligands that are designed to bind in a bidentate fashion through both phosphorus and oxygen, as in the DalPhos motif, are relatively unexplored.

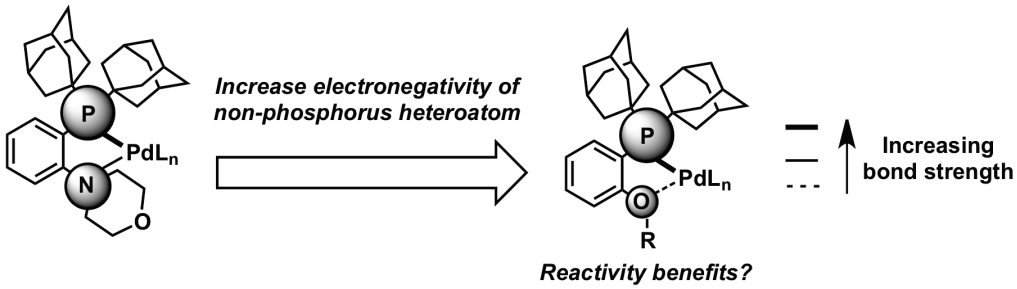
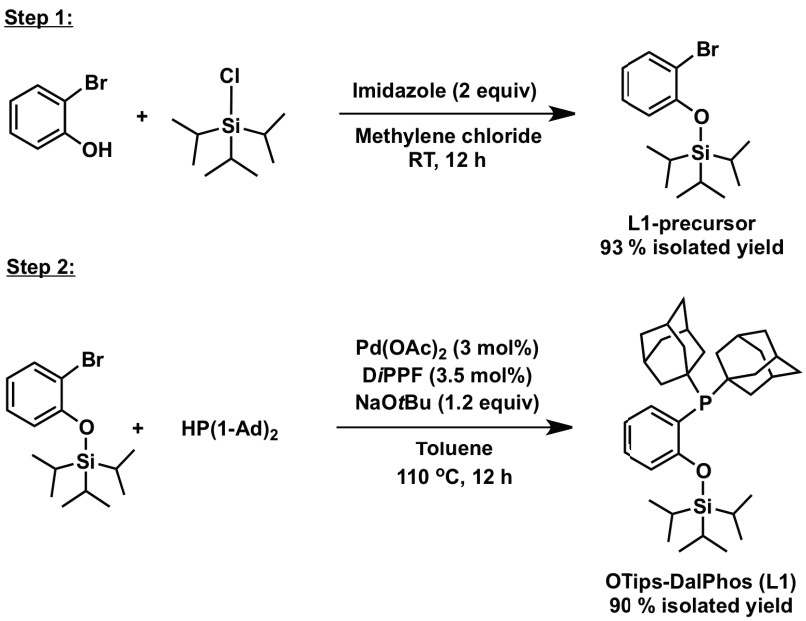


Figure 2–3. Graphical representation of replacing the nitrogen heteroatom within the DalPhos motif with a more electronegative oxygen heteroatom and the resulting effect on ligand-palladium interactions. Relative electronegativities are indicated by the size of the sphere around the heteroatom and a smaller sphere size indicates that the heteroatom is more electronegative.

In seeking modular and expedient synthetic protocols, the silylation of phenols was particularly attractive given the ease of silicon-oxygen bond formation, the commercial availability of structurally diverse R_3SiCl synthons, and the well-documented chemical behaviour of aryl silylethers. In fact, SiR_3-groups are among the most popular phenolic hydroxyl protecting groups used in organic synthesis and their stability over a wide range of conditions is known.[118-121] Indeed, treatment of *ortho*-bromophenol with $i Pr_3SiCl$ in the presence of imidazole afforded the known triisopropylsilyl ether[122] (**L1-precursor**) in 93 % yield (Step 1, Scheme 2–1), which was converted to OTips-DalPhos (**L1)** via palladium-catalyzed phosphorus-carbon bond formation employing $(1\text{-Ad})_2PH$ in 90 % yield (Step 2, Scheme 2–1).



Scheme 2–1. Synthesis of OTips-DalPhos (**L1**).

In contrast to related dialkylarylphosphines featuring small *ortho*-alkyl ether substituents,[123] only a single rotamer of **L1** is observable in solution (^{1}H, ^{13}C, and ^{31}P NMR). Presumably this rotamer corresponds to the solid state structure (Figure 2–4), where the triisopropylsilyl moiety is distal to the adamantyl groups. This orientation would appear to enable the binding of both phosphorus and oxygen to palladium as needed during catalysis.

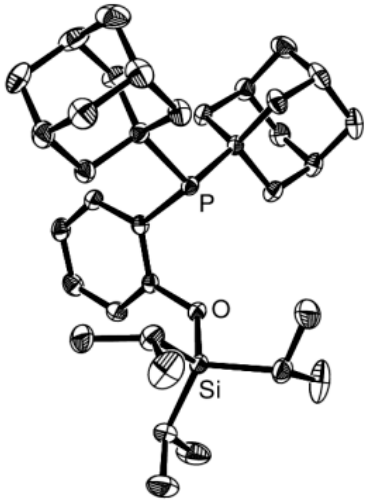


Figure 2–4. ORTEP diagram for **L1** shown with 50% ellipsoids and with hydrogen atoms ommitted for clarity. Selected interatomic distances (Å): P-Caryl, 1.8460(13); O-Caryl, 1.3726(16); Si–O, 1.6716(10).

2.2.2 Ligand Screen for Palladium-Catalyzed Synthesis of 2-Phenylindoles from 1-Bromo-2-(phenylethynyl)benzene

In a preliminary effort to assess the ability of palladium/**L1** (2.5 mol% each) catalyst mixtures to furnish indoles via carbon-nitrogen cross-coupling/cyclization processes, the reaction of 1-bromo-2-(phenylethynyl)benzene with structurally diverse primary amines was surveyed (Figure 2–5). The choice of palladium precursor was based on the success of the $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos catalyst system (for further discussion regarding the utility of $[Pd(cinnamyl)Cl]_2$ in cross-coupling catalysis, see Section 3.2.1),[92] and for comparison parallel reactions were conducted with the *para*-isomer (**L1′**) of OTips-DalPhos, as well as DavePhos, iPr and Mor-DalPhos. These comparator ligands were selected in order to explore both the influence of the ligand connectivity (**L1** *vs*. **L1′**) and choice of *ortho*-heteroatomic fragment (P,O in **L1** *vs.* P,N in Mor-DalPhos), as well as to benchmark the observed catalytic performance of **L1** against prominent ligands that have proven useful in the synthesis and functionalization of indoles (DavePhos[124] and iPr[108-111]). Among the ligands surveyed, only **L1** afforded each of the four target indoles (**2-1**–**2-4**) in high yield under the test conditions employed. The use of $MeNH_2$ served to differentiate **L1** from each of **L1′**, DavePhos and iPr (in addition to the poor performance of DavePhos with 1-$AdNH_2$). In contrast, while Mor-DalPhos performed reasonably well

in combination with $MeNH_2$ (76 %), the yields obtained with the other substrates (18–63 %) were markedly inferior to those obtained when using **L1**.

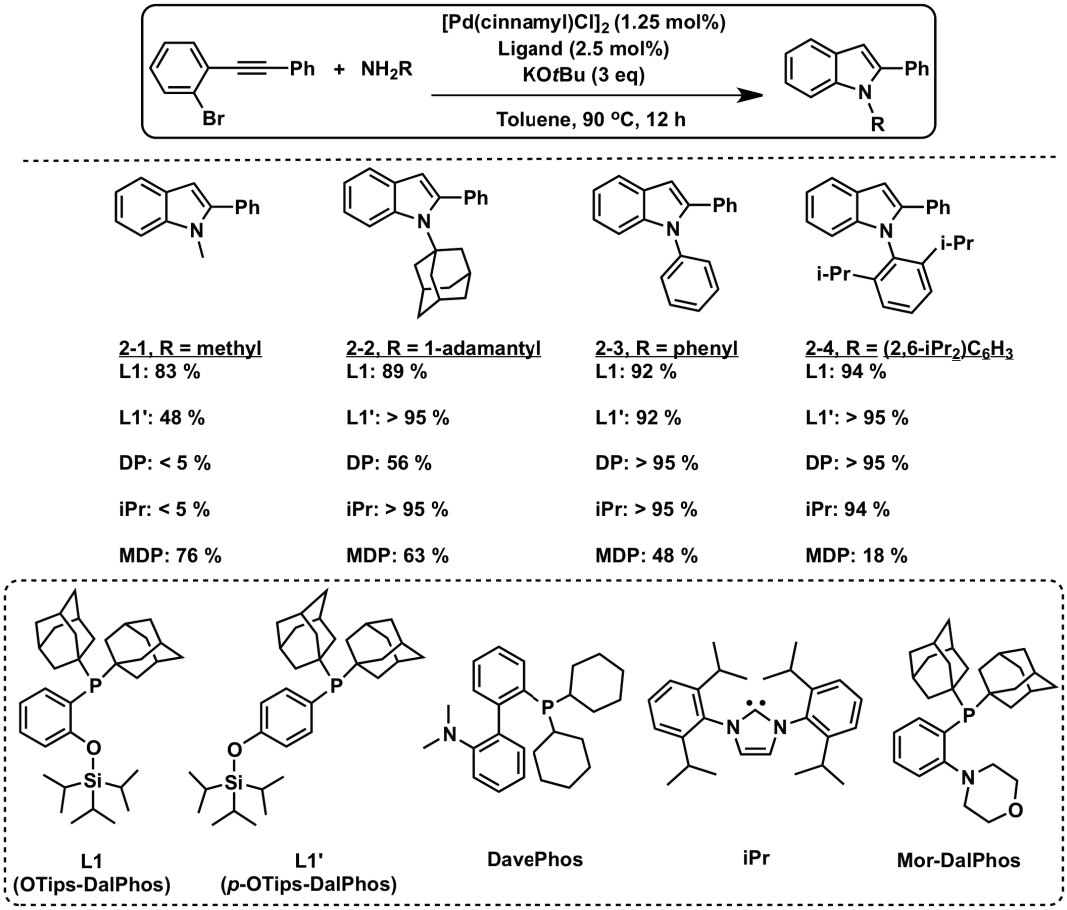


Figure 2–5. Ligand screen for the palladium-catalyzed synthesis of 2-phenylindoles from 1-bromo-2-(phenylethynyl)benzene. Isolated yields for **L1**, otherwise yields are given on the basis of calibrated GC data (see Section 2.4). Abbreviations: DP = DavePhos, MDP = Mor-DalPhos.

It is worth noting that two control experiments were performed using **L1** to investigate the possibility of silicon-oxygen bond cleavage occurring under catalytic conditions. In the first control experiment, a toluene solution of **L1** was heated at 120 °C in the presence of 60 equivalents of KO*t*Bu for 14 h and using trimesitylphosphine as an internal standard; no ligand degradation was observed by use of ^{31}P NMR analysis. In the second control experiment a catalytic reaction was run using similar conditions to those reported herein but at a 50 mol% catalyst loading which would allow for loss of the silane

moiety from **L1** (e.g. as triisopropylsilyl chloride) to be observed by GC analysis; no such ligand degradation was observed.

2.2.3 Scope of [Pd(cinnamyl)Cl]$_2$/OTips-DalPhos Catalyzed Cross-Coupling of Primary Amines with *ortho*-Alkynylhalo(hetero)arenes

Having established **L1** as a stable and effective ligand for the desired carbon-nitrogen cross-coupling/cyclization processes en route to indoles, the scope in the amine and *ortho*-alkynylhalo(hetero)arene reaction partners was explored further (Figure 2–6). In building upon the results featured in Figure 2–5, 1-bromo-2-(phenylethynyl)benzene, as well as the chloro derivative, proved to be suitable substrates in combination with a range of amine coupling partners, providing the target indoles derived from *t*BuNH$_2$ (**2-5**), various hindered and unhindered aryl amines including those featuring electron-donating and electron-withdrawing substituents (**2-6**–**2-10**), and for the first time, *N*-methylpiperazine (**2-11**) in 61–96 % yield. The use of a methylated variant of 1-bromo-2-(phenylethynyl)benzene was also tolerated, affording the corresponding indoles derived from MeNH$_2$ (88%, **2-12**), 1-AdNH$_2$ (91 %, **2-13**), and (2,6-Me$_2$C$_6$H$_3$)NH$_2$ (89 %, **2-14**) in high isolated yield. A fluorine-containing *ortho*-alkynylbromoarene substrate also worked well with the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system, enabling the isolation of indoles derived from MeNH$_2$ (83 %, **2-15**), 1-AdNH$_2$ (90 %, **2-16**), and DippNH$_2$ (Dipp = (2,6-*i*Pr$_2$)C$_6$H$_3$; 93 %, **2-17**) in excellent yield.

The use of *ortho*-alkynylbromoarene substrates featuring substitution on the alkynyl terminus other than phenyl was also successful. In the case of the reaction of 1-bromo-2-(trimethylsilylethynyl)benzene with 1-AdNH$_2$, concurrent protodesilylation was observed, thereby providing access to the corresponding parent indole featuring a hydrogen at the C2 position (82 %, **2-18**). Alternatively, the use of 1-bromo-2-(propylethynyl)benzene afforded cleanly the corresponding indoles derived from MeNH$_2$ (67 %, **2-19**), 1-AdNH$_2$ (86 %, **2-20**), and (2,6-Me$_2$C$_6$H$_3$)NH$_2$ (89 %, **2-21**).

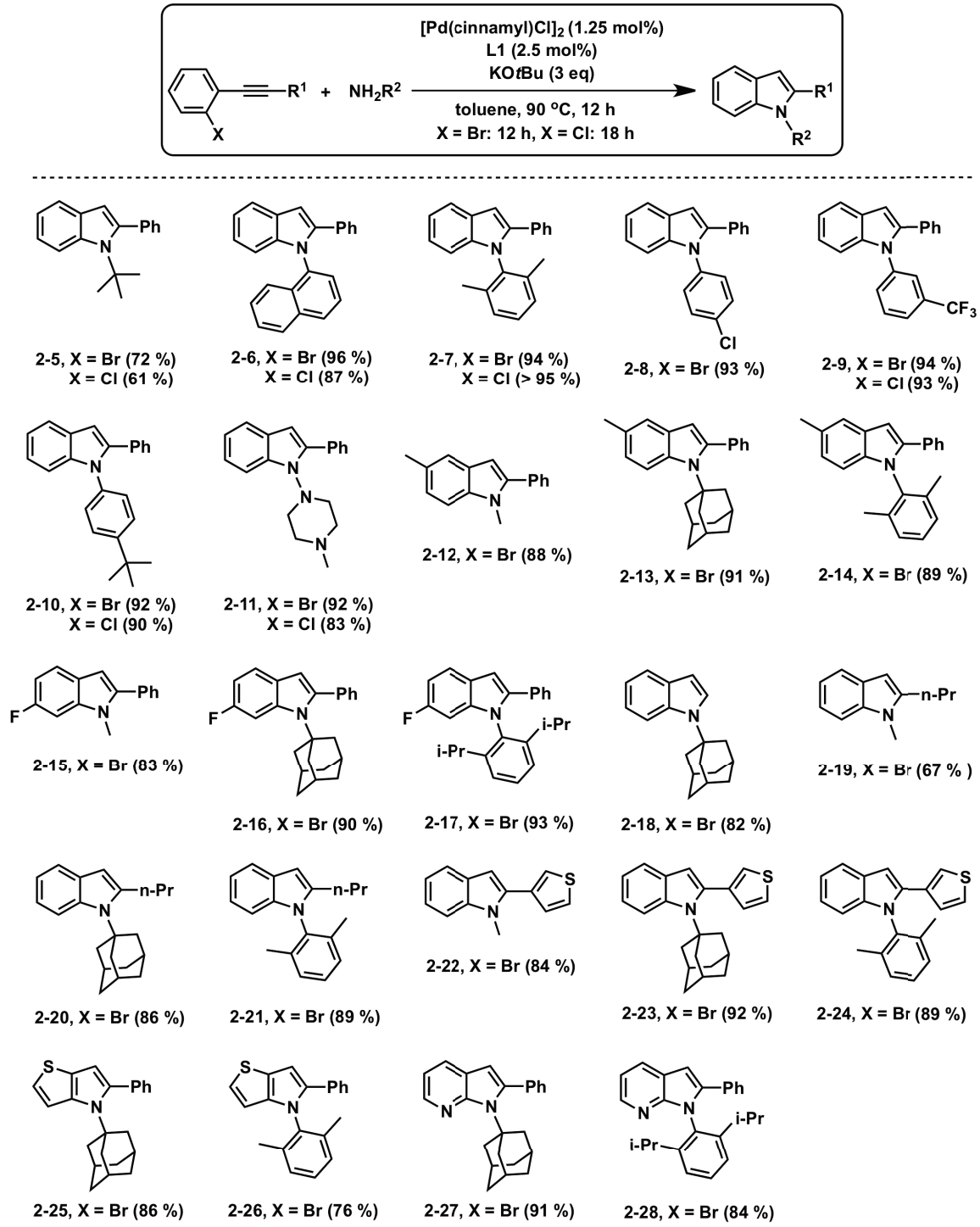


Figure 2–6. Scope of the [Pd(cinnamyl)Cl]$_2$/**L1** catalyzed cross-coupling of primary amines with *ortho*-alkynylhalo(hetero)arenes. Isolated yields for X = Br; for X = Cl, yield determined on the basis of calibrated GC data (see section 2.4).

Having succeeded in applying the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system to the synthesis of indoles featuring primarily hydrocarbon substituents, attention was next

turned to substrates featuring heterocyclic moieties. Despite the relevance of hetero-functionalized indoles in medicinal chemistry, scant attention has been paid thus far to the synthesis of such species via palladium-catalyzed carbon-nitrogen cross-coupling/cyclization protocols. Pleasingly, the incorporation of a thiophen-3-yl fragment onto the alkynyl terminus was well-tolerated, affording *N*-substituted indoles featuring a C2-thiophen-3-yl substituent (84–92 %, **2-22**–**2-24**). Furthermore, the synthesis of the thienopyrroles **2-25** (86 %) and **2-26** (76 %) was achieved for the first time by use of palladium-catalyzed carbon-nitrogen cross-coupling/cyclization methods. There exists only one other report in the literature for accessing products with similar organic frameworks to those featured in **2-25** and **2-26** involving a copper- and acid-assisted cyclization of an *N*-Phenyl pyrrole with a pendant C2-SCH_2CO_2H group.[125] However, this methodology is inherently limited in scope and utility owing to its low functional group tolerance.

Azaindoles are particularly more challenging to prepare than their corresponding indole analogues and many of the "classical" methods for preparing indoles are not applicable to azaindole synthesis.[126] This can be attributed to the change in electronics of the π-system caused by the electron-deficient pyridine ring featured in azaindoles.[126] Therefore, it was particularly gratifying that the synthesis of the 7-azaindoles **2-27** (91 %) and **2-28** (84 %) could also be achieved for the first time by employing the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system in this carbon-nitrogen cross-coupling/cyclization transformation. There is only one non-metal catalyzed report in the literature for accessing structurally similar products to the 7-azaindoles **2-27** and **2-28** that makes use of a photochemical and thermal ring contraction methodology.[127] It is also worth noting that in 2009, Fagnou and co-workers described an elegant palladium-catalyzed site-selective azaindole direct arylation methodology to prepare 7-azaindole products structurally similar to **2-27** and **2-28**, however, only *N*-Methyl azindoles were synthesized.[128]

2.2.4 Expanding Upon the OTips-DalPhos Structural Motif in the Development of a New Series of P,O-DalPhos Ligands

Inspired by the unprecedented reactivity of **L1** in the synthesis of *N*-substituted indoles and related heterocyclic products, a series of new P,O-DalPhos ligand variants

(**L2**–**L5**) featuring structurally varied silicon moieties was prepared (Figure 2–7) in an analogous manner to **L1** (Scheme 2–1). **L2**–**L5** were also subjected to the same thermal and base stability tests described for **L1** in Section 2.2.2 and in no case was ligand degradation observed. It is worth noting that attempts to synthesize P,O-DalPhos variants featuring $Si(NMe_2)_3$, $Si(nBu)_3$, or $Si(secBu)_3$ groups were unsuccessful. In these cases the ligand precursors generated from Step 1 of the synthetic protocol (Scheme 2–1) could be successfully prepared, but attempts to employ the so-formed ligand precursors in Step 2 (Scheme 2–1) resulted in the formation of multiple inseparable phosphorus-containing products as observed by use of ^{31}P NMR analysis.

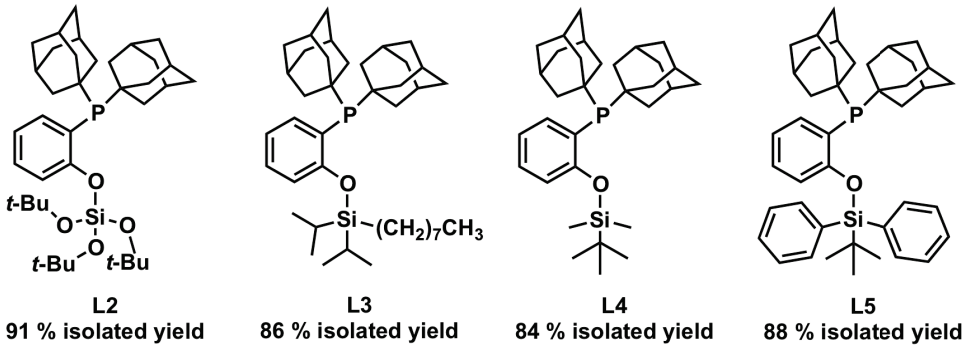


Figure 2–7. P,O-DalPhos variants prepared featuring different silicon-moieties. Yields provided are overall yields from both steps of ligand syntheses.

The newly prepared P,O-DalPhos ligand variants, **L2**–**L5**, were also tested and compared to **L1** in the palladium-catalyzed cross-coupling/cyclization of 1-bromo-2-(phenylethynyl)benzene under similar reaction conditions and with the same structurally diverse primary amines employed in Figure 2–5; however, this time ammonia was also included in the screening process as a challenging NH coupling partner (Figure 2–8). The purpose of these head-to-head reactivity comparison experiments was to determine the effect of varying the SiR_3 groups featured in **L1**–**L5** on catalytic performance in these benchmark reactions.

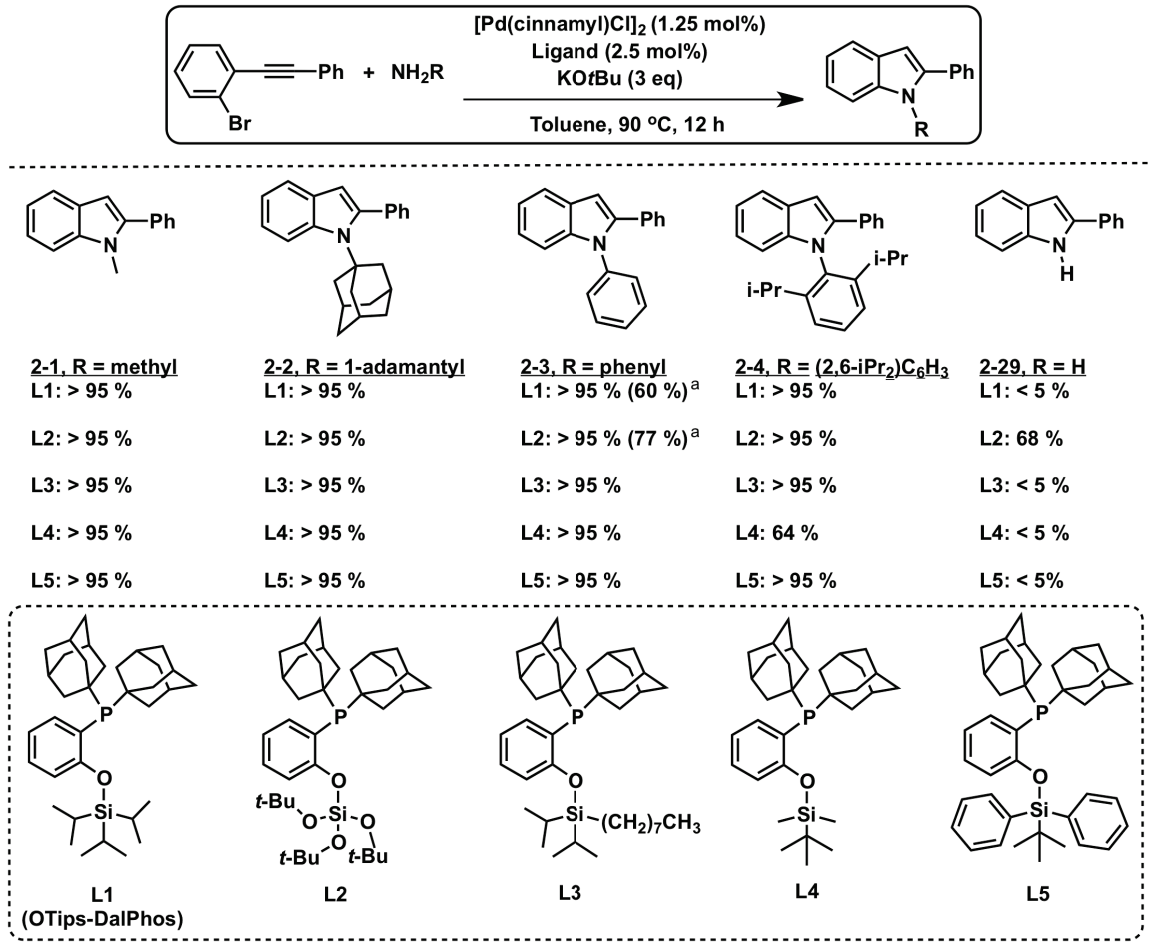


Figure 2–8. P,O-DalPhos ligand screen for the Pd-catalyzed synthesis of 2-phenylindoles from 1-bromo-2-(phenylethynyl)benzene. Yields are given on the basis of calibrated GC data (see section 2.4). [a]Catalyst loading employed was 0.63 mol% $[Pd(cinnamyl)Cl]_2$ and 1.25 mol% ligand.

The screening reactions in Figure 2–8 demonstrated similar efficiency for all of the P,O-DalPhos variants with most of the amine cross-coupling partners tested. Indeed, when employing $MeNH_2$, 1-$AdNH_2$, $PhNH_2$ and $DippNH_2$, ligands **L1**, **L2**, **L3** and **L5** each afforded > 95 % conversion to the target *N*-substituted indoles. However, when employing $DippNH_2$ with **L4**, a considerable amount of hydrodehalogenated product (diphenylacetylene) was observed and only 64 % of the 1-bromo-2-(phenylethynyl)benzene was converted to the target *N*-substituted indole. Ammonia also proved to be another differentiating amine cross-coupling partner, as only one of the P,O-DalPhos variants screened (**L2**) afforded non-negligible conversion to the corresponding target NH-indole (68 %, **2-29**). Additionally, two reactions were conducted employing

L1 and **L5** in combination with $PhNH_2$ as the amine cross-coupling partner at a decreased catalyst loading (0.63 mol% $[Pd(cinnamyl)Cl]_2$ and 1.25 mol% ligand). At these lower loadings, **L2** provided higher conversion to the corresponding *N*-substituted indole (77 %) than did **L1** (60 %). Collectively, these results suggest that the SiR_3 group is indeed having an impact on the catalytic performance of these P,O-DalPhos ligands. Furthermore, these data also suggest that there could be reactivity advantages provided in certain applications by increasing the steric bulk of the silicon moiety featured in these ligand frameworks.

2.3 Summary and Conclusions

In summary, the catalytic utility of the new and easily prepared P,O-DalPhos ligand variant, **L1** (OTips-DalPhos) was established through an investigation of the palladium-catalyzed cascade carbon-nitrogen cross-coupling/cyclization of *ortho*-alkynylhalo(hetero)arene substrates with primary amines. At relatively low loadings, the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system offers remarkably broad scope in the amine reaction partner, enabling the use of small (e.g. $MeNH_2$) and large (e.g. 1-$AdNH_2$) alkylamines, various hindered and unhindered aryl amines including those featuring electron-donating and electron-withdrawing substituents, as well as *N*-methylpiperazine. Significant structural variation within the *ortho*-alkynylhalo(hetero)arene substrates was also well-tolerated, leading to indoles featuring alkyl, aryl, and heteroaryl substitution at the C2 position, as well as to substituted thienopyrroles and 7-azaindoles. This body of work represents the most extensive and varied substrate scope to be demonstrated thus far for this class of transformations (11 amines, 8 *ortho*-alkynylhalo(hetero)arenes, 28 examples in total). Notably, a PCT patent application has been filed on OTips-DalPhos (**L1**) and this material is now commercially available from Sigma Aldrich. Encouraged by the desirable performance of **L1**, several new P,O-DalPhos ligand variants were prepared (**L2–L5**) and also screened in this catalytic application. The results from these screening reactions confirm that the silicon moiety featured in this class of ligands does indeed impact both the ligand stability and the catalytic performance. In this regard, the choice of SiR_3 group can be used as a tuning element in modulating metal reactivity, with

P,O-DalPhos variants featuring more sterically demanding SiR_3 groups representing particularly attractive targets of future inquiry.

2.4 EXPERIMENTAL SECTION

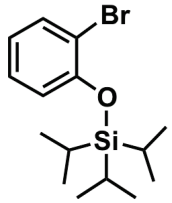
2.4.1 General Considerations

Unless otherwise noted, all reactions were set up inside a dinitrogen-filled inert atmosphere glovebox and worked up in air using benchtop procedures. Toluene used in the synthesis of **L1–L5**, and also in the catalytic transformations was deoxygenated by sparging with dinitrogen followed by passage through an mBraun double column solvent purification system packed with alumina and copper-Q5 reactant. $[Pd(cinnamyl)Cl]_2$,[129] di(1-adamantyl)phosphine,[130] and (4-bromophenoxy)silanes[131] were prepared according to literature protocols. The *ortho*-alkynylhaloarene substrates were prepared by using literature synthetic protocols involving Sonogashira reactions of aryl iodides[132,133] or bromides[134] with appropriate terminal alkyne precursors. Reactions employing methylamine were conducted using commercially available 2.0 M solutions of methylamine in tetrahydrofuran. C_6D_6 was degassed by using at least three repeated freeze-pump-thaw cycles and stored over 4 Å molecular sieves for 24 h prior to use. All other chemicals were obtained from commercial sources in high purity and used as received. Column chromatography was carried out using Silicycle SiliaFlash 60 with particle size 40-63 μm (230-400 mesh). Gas chromatography (GC) data were obtained on a Shimadzu GC-2014 equipped with a SGE BP-5 30 m, 0.25 mm I.D. column. In cases where conversions and yields are given on the basis of gas chromatography experiments, the data were corrected by calibration using dodecane as an internal standard and product identity was confirmed by comparison with authentic samples. All ^1H NMR (500 MHz), ^{13}C NMR (125.8 MHz) and ^{31}P NMR (202 MHz) spectra were recorded at 300 K. Chemical shifts are expressed in parts per million (ppm) using the solvent signal $CDCl_3$ (^1H 7.26 ppm, ^{13}C 77.36 ppm) or C_6D_6 (^1H 7.15 ppm, ^{13}C 128.62 ppm) as an internal reference. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet. All coupling constants (*J*) are reported in Hertz (Hz). In some cases fewer than expected independent carbon 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). Special thanks is given to Nicolas Rotta-Loria who helped with the synthesis of **L2** and **L3** and also performed the P,O-DalPhos ligand screen reactions (Section 2.2.4).

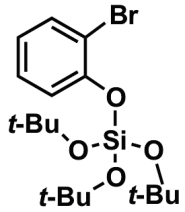
2.4.2 Synthesis and Characterization of P,O-DalPhos Ligand Variants

General Procedure for Step 1: To an oven dried screw-capped vial was added a magnetic stir bar, imidazole (629 mg, 9.2 mmol), 2-bromophenol (536 μL, 4.6 mmol) and 9.0 mL of methylene chloride. The appropriate chlorosilane (5.1 mmol) was then added dropwise with constant magnetic stirring. The vial was sealed under dinitrogen with a cap containing a PTFE septum and was removed from the glovebox and stirred vigorously at ambient temperature. Full consumption of starting material and quantitative formation of one new product was observed after 16 h by removing a 50 μL aliquot of the reaction mixture by syringe and filtering through a Celite plug, followed by dilution of the eluent with methylene chloride for GC and thin layer chromatography (TLC) analysis. At this point, the reaction mixture was diluted with ethyl acetate (100 mL) and water (50 mL). The layers were separated and the organic layer was washed with water (3 x 50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to afford crude product, which was then purified by column chromatography to afford pure target product.



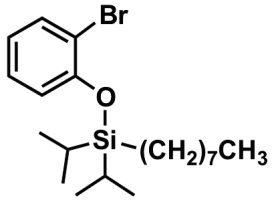
(L1-precursor) (2-bromophenoxy)triisopropylsilane.

The title compound was synthesized according to the **General Procedure for Step 1** and purified by column chromatography on silica gel using hexanes in 93 % yield (1.41 g, 4.28 mmol). ^{1}H NMR ($CDCl_3$): δ 7.52 (dd, J = 7.9 Hz, 1.7 Hz, 1H), 7.15 (m, 1H), 6.90 (d,d, J = 8.1 Hz, 1.4 Hz, 1H), 6.80 (m, 1H), 1.34 (sept, J = 7.4 Hz, 3H), 1.14 (d, J = 7.4 Hz, 18H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 153.3, 133.8, 128.5, 122.3, 120.0, 115.4, 18.3, 13.3. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[122]



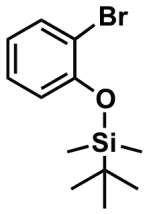
(L2-precursor) 2-bromophenyl tri-tert-butyl orthosilicate.

The title compound was synthesized according to the **General Procedure for Step 1** and purified by column chromatography on silica gel using hexanes in 93 % yield (1.80 g, 4.28 mmol) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.51 (dd, J = 8 Hz, J = 2 Hz, 1H), 7.28 (m, 1H), 7.16 (m, 1H), 6.80 (m, 1H), 1.36 (s, 27H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 151.9, 133.6, 128.0, 122.6, 120.0, 114.2, 73.9, 31.4; *m/z* ESI$^+$ found 441.1060 $[M+Na]^+$ calculated for $C_{18}H_{31}Br_1Na_1O_4Si_1$ 441.1067.



(L3-precursor) (2-bromophenoxy)diisopropyl(octyl)silane.

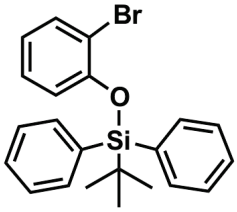
The title compound was synthesized according to the **General Procedure for Step 1** and purified by column chromatography on silica gel using hexanes in 84 % yield (1.54 g, 3.86 mmol) as a light yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.52 (dd, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.15 (m, 1 H), 6.83, (dd, J = 8 Hz, J = 1.5 Hz, 1 H), 6.80 (m, 1 H), 1.44-1.39 (m, 2 H), 1.32-1.21 (m, 12H), 1.10-1.09 (m, 12H), 0.90-0.83 (m, 5H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 153.2, 133.5, 128.3, 122.2, 120.0, 115.3, 34.0, 32.1, 29.4, 29.3, 23.2, 22.8, 17.8, 14.3, 13.3, 11.7. *m/z* ESI$^+$ found 421.1533 $[M+Na]^+$ calculated for $C_{20}H_{35}Br_1Na_1O_1Si_1$ 421.1523.



(L4-precursor) (2-bromophenoxy)(tert-butyl)dimethylsilane.

The title compound was synthesized according to the **General Procedure for Step 1** and purified by column chromatography on silica gel using hexanes in 87 % yield (1.15 g,

4.00 mmol). ^{1}H NMR ($CDCl_3$): δ 7.52 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1H), 7.17 (m, 1H), 6.88 (dd, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H), 6.82 (m, 1H), 1.05 (s, 9H), 0.26 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 152.8, 133.6, 128.4, 122.6, 120.5, 115.6, 25.9, 18.6, -4.0. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[135]

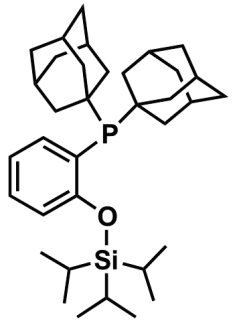


(L5-precursor) (2-bromophenoxy)(tert-butyl)diphenylsilane.

The title compound was synthesized according to the **General Procedure for Step 1** and purified by column chromatography on silica gel using hexanes in 88 % yield (1.67 g, 4.04 mmol). ^{1}H NMR ($CDCl_3$) : δ 7.95-7.93 (m, 4H), 7.60 (dd, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H), 7.46-7.50 (m, 2H), 7.41-7.44 (m, 4H), 6.87 (m, 1H), 6.75 (m, 1H), 6.53 (dd, *J* = 8.5 Hz, *J* = 1.5 Hz, 1H), 1.21 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 152.6, 135.8, 133.6, 132.6, 130.4, 128.4, 128.2, 122.4, 120.2, 115.0, 27.3, 20.4. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[136]

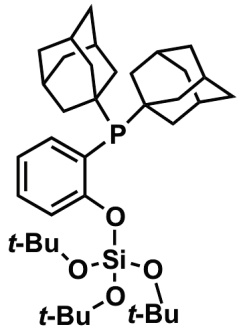
General Procedure for Step 2: To an oven dried screw-capped vial was added a stir bar, the desired ligand precursor (2.1 mmol), $Pd(OAc)_2$ (14.4 mg, 0.0640 mmol, 3 mol%), 1,1'-bis(diisopropylphosphino)ferrocene (31.3 mg, 0.0747 mmol, 3.5 mol%), NaO*t*Bu (246 mg, 2.5 mmol) and 5 mL of toluene. The resulting suspension was stirred until homogeneous and then di(1-adamantyl)phosphine (645 mg, 2.1 mmol) was added. The vial was sealed under dinitrogen with a cap containing a PTFE septum, removed from the glovebox, placed in a temperature-controlled aluminum heating block set at 110 °C and vigorous magnetic stirring was initiated. After 12 h, ^{31}P NMR analysis of the reaction mixture confirmed the consumption of di(1-adamantyl)phosphine and the quantitative formation of one new phosphorus-containing product. The vial containing the reaction mixture was then cooled and opened to air, and on the benchtop the reaction mixture was then filtered through a plug of silica, which in turn was washed with methylene chloride.

Removal of the solvent from the combined eluent afforded the target product, which was further purified by recrystallization from cold hexanes.



(L1) di(adamantan-1-yl)(2-((triisopropylsilyl)oxy)phenyl)phosphine.

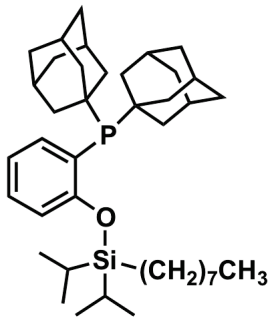
The title compound was synthesized according to the **General Procedure for Step 2** in 90 % yield (1.04 g, 1.89 mmol) as a beige solid. ^{1}H NMR ($CDCl_3$): δ 7.65 (dt, J_{HH} = 7.65 Hz, 1.7 Hz, 1H), 7.18 (m, 1H), 6.88 (m, 1H), 6.80 (m, 1H), 1.96 (m, 6H), 1.90 (m, 12H), 1.67 (s, 12H), 1.34 (sept, J = 7.6 Hz, 3H), 1.15 (d, J_{HH} = 7.5 Hz, 18H); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 161.4 (d, $J_{P,C}$ = 20 Hz), 137.7, 129.7, 125.6 (d, $J_{P,C}$ = 26 Hz) 119.2, 118.7, 42.1 (d, $J_{P,C}$ = 14 Hz), 37.5, 37.0 (d, $J_{P,C}$ = 28 Hz), 29.3 (d, $J_{P,C}$ = 8 Hz), 18.6, 13.6; ^{31}P{^{1}H} NMR ($CDCl_3$): δ 12.2; *m/z* ESI^{+} found 551.3835 $[M+H]^{+}$ calculated for $C_{35}H_{56}O_1P_1Si_1$ 551.3833. Crystals for x-ray analysis were obtained by allowing a saturated hexanes solution L1 to slowly evaporate.



(L2) tri-*tert*-butyl (2-(di(adamantan-1-yl)phosphino)phenyl) orthosilicate.

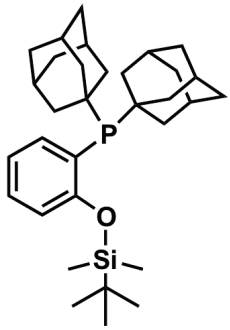
The title compound was synthesized according to the **General Procedure for Step 2** in 90 % yield (1.21 g, 1.89 mmol) as a beige solid. ^{1}H NMR ($CDCl_3$): δ 7.66 (m, 1H), 7.25 (m, 1H), 7.21 (m, 1H), 6.89 (m, 1H), 1.98-1.96 (m, 6H), 1.87-1.85 (s, 12H), 1.65 (s, 12H), 1.38 (s, 27H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 160.4 (d, $J_{P,C}$ = 23 Hz), 137.1, 129.4, 124.6 (d, $J_{P,C}$ = 27 Hz), 119.4, 119.2, 73.6, 42.0 (d, $J_{P,C}$ = 14 Hz), 37.2, 36.9 (d, $J_{P,C}$ = 27

Hz), 31.5, 29.0 (d, $J_{P,C}$ = 9 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ 11.7; *m/z* ESI^+ found 641.4126 $[M+H]^+$ calculated for $C_{38}H_{62}O_4P_1Si_1$ 641.4126.



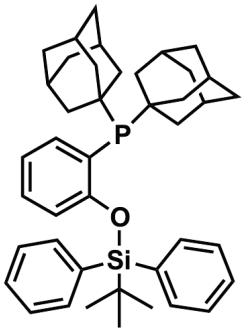
(L3) di(adamantan-1-yl)(2-((diisopropyl(octyl)silyl)oxy)phenyl)phosphine.

The title compound was synthesized according to the **General Procedure for Step 2** in 88 % yield (1.15 g, 1.85 mmol) as a beige solid. ^{1}H NMR ($CDCl_3$): δ 7.65 (d, *J* = 7.5 Hz, *J* = 6 Hz, 1H), 7.21 (m, 1H), 6.90 (m, 1H), 6.83 (m, 1H), 2.00-1.92 (m, 18H), 1.71 (s, 12H), 1.43-1.39 (m, 2H), 1.35-1.24 (m, 12H), 1.16-1.11 (m, 12H), 0.93-0.86 (m, 5h); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 161.5 (d, $J_{P,C}$ = 24 Hz), 137.5, 129.6, 125.7 (d, $J_{P,C}$ = 27 Hz), 119.2, 118.9, 42.3 (d, $J_{P,C}$ = 22 Hz), 37.3, 36.9, (d, $J_{P,C}$ = 25 Hz), 34.3, 32.2, 29.5, 29.1 (d, $J_{P,C}$ = 9 Hz), 23.6, 22.9, 18.1, 14.4, 13.8, 12.3; $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ 12.5; *m/z* ESI^+ found 621.4621 $[M+H]^+$ calculated for $C_{40}H_{66}O_1P_1Si_1$ 621.4615.



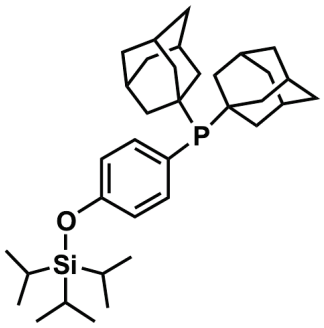
(L4) di(adamantan-1-yl)(2-((tert-butyldimethylsilyl)oxy)phenyl)phosphine.

The title compound was synthesized according to the **General Procedure for Step 2** in 80 % yield (854 mg, 1.68 mmol) as a beige solid. ^{1}H NMR ($CDCl_3$): δ 7.66 (m, 1H), 7.20 (m, 1H), 6.91 (m, 1H), 6.83 (m, 1H), 1.95-1.88 (m, 18 H), 1.67 (s, 12H), 0.232 (s, 6H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 161.1 (d, $J_{P,C}$ = 25 Hz), 137.7, 129.8, 126.4 (d, $J_{P,C}$ = 24 Hz), , 119.7, 119.2, 42.1 (d, $J_{P,C}$ = 13 Hz), 37.4, 37.0 (d, $J_{P,C}$ = 26 Hz), 29.1 (d, $J_{P,C}$ = 7 Hz), 26.4, 18.2. $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ 12.1.



(L5) di(adamantan-1-yl)(2-((tert-butyldiphenylsilyl)oxy)phenyl)phosphine.

The title compound was synthesized according to the procedure **General Procedure for Step 2** in 88 % yield (1.86 g, 1.85 mmol) as a beige solid. ^{1}H NMR ($CDCl_3$): δ 7.77-7.76 (m, 4H), 7.69 (d, J = 7.2 Hz, 1H), 7.42-7.39 (m, 2H), 7.36-7.33 (m, 4H), 6.89 (m, 1H), 6.82 (m, 1H), 6.44 (m, 1 H), 2.05-1.92 (m, 18H), 1.70 (s, 12H), 1.17 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 162.1 (d, $J_{P,C}$ = 21 Hz), 137.4, 135.9, 133.6, 129.8, 129.4, 127.8, 125.6 (d, $J_{P,C}$ = 26 Hz), 119.6, 119.5, 42.2 (d, $J_{P,C}$ = 14 Hz), 37.3, 37.0 (d, $J_{P,C}$ = 26 Hz), 29.1 (d, $J_{P,C}$ = 8 Hz), 26.8, 20.1 ppm; ^{31}P{^{1}H} NMR ($CDCl_3$): δ 11.5.



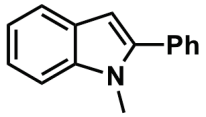
(2-L1') di(adamantan-1-yl)(4-((triisopropylsilyl)oxy)phenyl)phosphine.

Attempts to isolate the title compound according the **General Procedure for Step 2** resulted in ligand degradation owing to air sensitivity issues. Instead the following adapted procedure for **Step 2** was employed: To an oven dried screw-capped vial was added a stir bar, (4-bromophenoxy)triisopropylsilane (844 mg, 2.5 mmol), $Pd(OAc)_2$ (17.4 mg, 0.0768 mmol, 3 mol%), 1,1'-bis(diisopropylphosphino)ferrocene (37.5 mg, 0.0896 mmol, 3.5 mol%), NaO*t*Bu (295 mg, 3.0 mmol) and 6 mL of toluene. The resulting suspension was stirred until apparently homogeneous and then di(1-adamantyl)phosphine (774 mg, 2.5 mmol) was added. The vial was sealed under dinitrogen with a cap containing a PTFE septum, removed from the glovebox, placed in a

temperature-controlled aluminum heating block set at 110 °C and vigorous magnetic stirring was initiated. After 8 h, ^{31}P NMR analysis of the reaction mixture confirmed the consumption of di(1-adamantyl)phosphine and the quantitative formation of one new phosphorus-containing product. The vial containing the reaction mixture was allowed to cool to room temperature and then brought back inside the glovebox for workup under an inert atmosphere. The reaction mixture was filtered through a plug of Celite and alumina, which in turn was washed with methylene chloride. Removal of the solvent from the combined eluent afforded the crude product, which was further purified by washing with cold pentane (3 x 3 mL) to afford pure product in 72 % yield (986 mg, 1.80 mmol) as a beige solid. ^{1}H NMR (C_6D_6): δ 7.73-7.70 (m, 2H), 6.95 (br m, 2H), 2.11-2.03 (m, 12H), 1.87 (br s, 6H), 1.64 (s, 12H), 1.19-1.12 (m, 21H); ^{13}C{^{1}H} NMR (C_6D_6) δ 158.0, 142.6 (br), 137.1 (br), 127.6 (d, $J_{P,C}$ = 30 Hz), 120.2, 120.1, 42.8 (d, $J_{P,C}$ = 13 Hz), 37.9, 37.4 (d, $J_{P,C}$ = 24 Hz), 29.9 (d, $J_{P,C}$ = 8 Hz), 18.7, 13.6; ^{31}P{^{1}H} NMR (C_6D_6): δ 38.5. *m/z* ESI^{+} found 551.3822 $[M+H]^{+}$ calculated for $C_{35}H_{56}O_1P_1Si_1$ 551.3833.

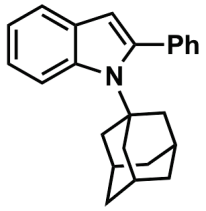
2.4.3 General Catalytic Protocol and Characterization of Isolated Reaction Products

General Catalytic Protocol: To an oven dried screw-capped vial was added a stir bar, $[Pd(cinnamyl)Cl]_2$ (3.2 mg , 0.0063 mmol, 1.25 mol%), **L1** (6.8 mg, 0.013 mmol, 2.5 mol%), and 2.0 mL of toluene. The mixture was then stirred magnetically for 2 minutes at which point KO*t*Bu (168 mg, 1.5 mmol) was added. The mixture was then stirred briefly followed by the addition of *ortho*-alkynylhalo(hetero)arene (128.6 mg, 0.5 mmol) in 3 x 1.0 mL portions of toluene, as well as the appropriate amine (0.55 mmol). The vial was sealed under dinitrogen with a cap containing a PTFE septum, removed from the glovebox, placed in a temperature-controlled aluminum heating block set at 90 °C and vigorous magnetic stirring was initiated. Reaction progress was monitored by use of TLC or GC methods and after complete consumption of the aryl halide (12 h), the reaction mixture was cooled, diluted with ethyl acetate (50 mL) and washed with water (50 mL). The layers were separated and the organic layer was washed with water (3 x 50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to afford crude product that was further purified by column chromatography.



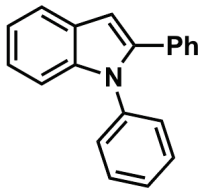
(2-1) 1-methyl-2-phenyl-1*H*-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 20:1 hexanes:ethyl acetate in 83 % yield (86 mg, 0.42 mmol), however, addition via syringe of methylamine as a 2.0 M solution in tetrahydrofuran (0.300 mL, 0.55 mmol) was performed outside of the glovebox. ^{1}H NMR ($CDCl_3$): δ 7.68 (d, J = 7.8 Hz, 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), 3.79 (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. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[137]



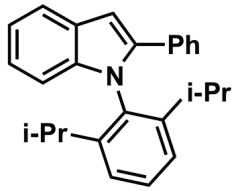
(2-2) 1-Adamantan-1-yl-2-phenyl-1*H*-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1 hexanes:ethyl acetate in 89 % yield (152 mg, 0.45 mmol). ^{1}H NMR ($CDCl_3$): δ 7.85 (d, J = 8.4 Hz, 1H), 7.59 (dd, J = 7.7 Hz, 0.6 Hz, 1H), 7.44-7.40 (m, 2H), 7.37-7.33 (m, 3H), 7.19-7.15 (m, 1H), 7.12-7.09 (m, 1H), 6.30 (s, 1H), 2.30 (d, J = 5.0 Hz, 6H), 2.11 (s, 3H), 1.72-1.65 (m, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 141.8, 139.9, 136.8, 130.5, 129.5, 127.7, 127.6, 120.9, 120.6, 119.6, 116.1, 107.0, 61.2, 43.7, 36.5, 30.6. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[111]



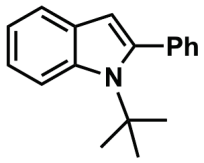
(2-3) 1,2-Diphenyl-1*H*-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1→20:1 hexanes:ethyl acetate in 92 % yield (124 mg, 0.46 mmol). ^{1}H NMR ($CDCl_3$): δ 7.79 (m, 1H), 7.52-7.44 (m, 3H), 7.43-7.31 (m, 8H), 7.30-7.25 (m, 2H), 6.91 (d, *J* = 1.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 140.8, 139.1, 138.6, 132.7, 129.3, 129.0, 128.4, 128.2, 128.1, 127.4, 127.3, 122.4, 120.8, 120.6, 110.7, 103.8. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[138]



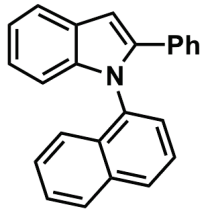
(2-4) 1-(2,6-diisopropylphenyl)-2-phenyl-1H-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1 hexanes:ethyl acetate in 94 % yield (166 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.41–7.39 (m, 3H), 7.37 (s, 1H), 7.31-7.21 (m, 5H), 7.08 (s, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 2.47 (sept., *J* = 6.9 Hz, 2H), 1.08 (d, *J* = 6.8 Hz, 6H), 0.96 (d, *J* = 6.8 Hz, 6H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 148.2, 141.3, 140.1, 134.0, 132.8, 129.8, 128.5, 128.1, 128.0, 127.6, 124.6, 122.3, 120.7, 120.7, 111.5, 102.2, 28.5, 25.4, 23.4. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[111]



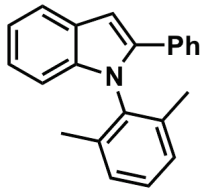
(2-5) 1-(tert-butyl)-2-phenyl-1H-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1 hexanes:ethyl acetate in 72 % yield (89 mg, 0.36 mmol). ^{1}H NMR ($CDCl_3$): δ 7.74 (dd, *J* = 8.5 Hz, 0.7 Hz, 1H), 7.59 (d,d, *J* = 7.6 Hz, 0.4 Hz, 1H), 7.43-7.42 (m, 2H), 7.38-7.35 (m, 3H), 7.19 (m, 1H), 7.12 (m, 1H), 6.32 (d, *J* = 0.7 Hz, 1H), 1.61 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 142.2, 138.5, 137.6, 130.5, 129.3, 127.9, 127.7, 121.0, 120.8, 119.7, 115.4, 106.5, 59.2, 32.4. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[139]



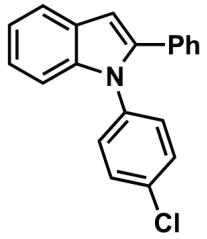
(2-6) 1-(naphthalen-1-yl)-2-phenyl-1H-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1→20:1 hexanes:ethyl acetate in 96 % yield (153 mg, 0.48 mmol). ^{1}H NMR ($CDCl_3$): δ 8.02-7.98 (m, 2H), 7.84 (dt, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H), 7.59-7.53 (m, 3H), 7.47-7.41 (m, 2H), 7.33-7.31 (m, 2H), 7.27 (m, 1H), 7.21-7.15 (m, 4H), 7.03 (d, *J* = 0.8 Hz, 1H), 6.91 (dt, *J* = 8.3 Hz, *J* = 0.9 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 142.5, 140.6, 135.7, 134.7, 132.9, 131.8, 128.9, 128.6, 128.5, 128.4, 127.6, 127.5, 127.4, 126.9, 125.8, 124.0, 122.6, 121.0, 120.8, 111.6, 103.6. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[138]



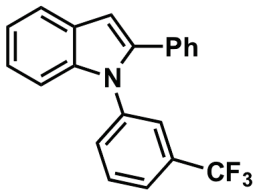
(2-7) 1-(2,6-dimethylphenyl)-2-phenyl-1H-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1→20:1 hexanes:ethyl acetate in 94 % yield (140 mg, 0.47 mmol) as a white crystalline solid. ^{1}H NMR ($CDCl_3$): δ 7.75 (m, 1H), 7.32-7.25 (m, 6H), 7.23-7.17 (m, 4H), 6.93 (d, J = 0.6 Hz, 1H), 6.87 (m, 1H), 1.92 (s, 6H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 140.7, 138.0, 137.6, 136.7, 132.9, 128.70, 128.65, 128.51, 128.4,5 127.7, 127.6, 122.4, 120.7, 120.5, 110.7, 102.4, 18.0; *m/z* ESI^+ found 298.1279 $[M+H]^+$ calculated for $C_{22}H_{20}N_1$ 298.1590.



(2-8) 1-(4-chlorophenyl)-2-phenyl-1H-indole.

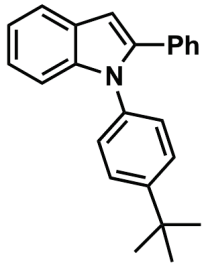
The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 20:1 hexanes:ethyl acetate in 92 % yield (140 mg, 0.46 mmol). ^{1}H NMR ($CDCl_3$): δ 7.72 (m, 1H), 7.42-7.40 (m, 2H), 7.31-7.27 (m, 6H), 7.24-7.20 (m, 4H), 6.83 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 140.9, 139.1, 137.4, 133.2, 132.5, 129.8, 129.5, 129.3, 128.7, 127.8, 122.9, 121.3, 121.0, 110.7, 104.5. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[140]



(2-9) 1-(3-trifluoromethyl)-2-phenyl-1H-indole.

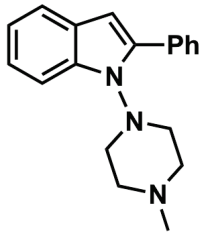
The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 20:1 hexanes:ethyl acetate in 94

% yield (159 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 7.71 (m, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.58 (s, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.31-7.22 (m, 7H), 6.84 (d, J = 0.4 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 140.9, 139.5, 138.9, 132.3, 132.1 ($J_{C,F}$ = 66 Hz), 131.5, 130.2, 129.3, 128.8, 128.7, 128.0, 125.0 ($J_{C,F}$ = 4 Hz), 124.1 ($J_{C,F}$ = 4 Hz), 123.1, 121.8 ($J_{C,F}$ = 272 Hz), 121.5, 121.2, 110.5, 104.9. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[138]



(2-10) 1-(4-(tert-butyl)phenyl)-2-phenyl-1H-indole.

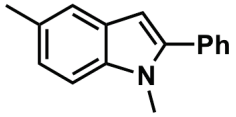
The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 20:1 hexanes:ethyl acetate in 92 % yield (150 mg, 0.46 mmol). ^{1}H NMR ($CDCl_3$): δ 7.73 (m, 1H), 7.47-7.44 (m, 2H), 7.36-7.26 (m, 6H), 7.23-7.20 (m, 4H), 6.84 (s, 1H), 1.40 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 150.5, 141.1, 139.4, 136.1, 133.0, 129.1, 128.5, 128.4, 127.8, 127.5, 126.4, 122.5, 120.8, 120.8, 111.1, 103.8, 35.0, 31.8. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[124]



(2-11) 1-(4-methylpiperazin-1-yl)-2-phenyl-1H-indole.

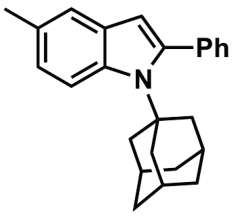
The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 6:4 methylene chloride:ethyl acetate in 92 % yield (134 mg, 0.46 mmol). ^{1}H NMR ($CDCl_3$): δ 7.75 (d, J = 8.2 Hz, 1H), 7.68-7.67 (m, 2H), 7.63 (d, J = 7.7 Hz, 1H), 7.46-7.43 (m, 2H), 7.37 (m, 1H), 7.19 (m, 1H), 7.14 (m, 1H), 6.54 (s, 1H), 4.01 (dt, J = 2.2 Hz, 10.9 Hz, 2H), 3.12 (d, J = 11.1 Hz,

2H), 2.83 (d, J = 11.8 Hz, 2H), 2.37 (s, 3H), 2.31 (dt, J = 2.6 Hz, 11.2 Hz, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 140.7, 135.7, 132.7, 129.5, 128.1, 127.8, 127.3, 121.7, 121.4, 120.3, 112.1, 100.2, 55.6, 52.1, 46.3. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[141]



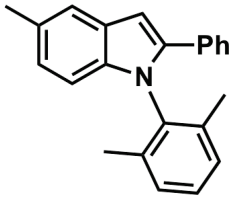
(2-12) 1,5-dimethyl-2-phenyl-1H-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 20:1 hexanes:ethyl acetate in 88 % yield (97 mg, 0.44 mmol), however, addition via syringe of methylamine as a 2.0 M solution in tetrahydrofuran (0.300 mL, 0.55 mmol) was performed outside of the glovebox. ^{1}H NMR ($CDCl_3$): δ 7.56-7.53 (m, 2H), 7.51-7.48 (m, 2H), 7.46 (m, 1H), 7.42 (m, 1H), 7.29 (d, J = 8.3 Hz, 1H), 7.11 (dd, J = 8.4 Hz, 1.3 Hz, 1H), 6.52 (d, J = 0.7 Hz, 1H), 3.76 (s, 3H), 2.51 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 141.9, 137.2, 133,3 129.6, 129.4, 128.8, 128.5, 128.1, 123.6, 120.5, 109.6, 101.5, 31.5, 21.8. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[142]



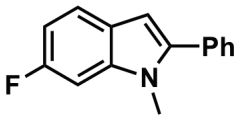
(2-13) 1-Adamantan-1-yl-5-methyl-2-phenyl-1*H*-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 20:1 hexanes:ethyl acetate in 91 % yield (163 mg, 0.46 mmol) as a white crystalline solid. ^{1}H NMR ($CDCl_3$): δ 7.72 (d, J = 8.6 Hz, 1H), 7.42-7.40 (m, 2H), 7.37 (s, 1H), 7.34-7.33 (m, 3H), 6.99 (d, J = 8.6 Hz, 1H), 6.21 (s, 1H), 2.44 (s, 3H), 2.28 (d, J = 2.3 Hz, 6H), 2.09 (s, 3H), 1.71-1.64 (m, 6H); ^{13}C[143] NMR ($CDCl_3$): δ 142.0, 139.1, 135.2, 130.5, 129.8, 128.8, 127.6, 127.5, 122.2, 120.6, 115.7, 106.5, 61.0, 43.7, 36.6, 30.5, 21.4; *m/z* ESI^{+} found 342.2219 $[M+H]^{+}$ calculated for $C_{25}H_{28}N_1$ 344.2216.



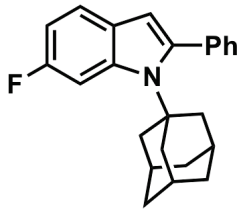
(2-14) 1-(2,6-Dimethyl-phenyl)-5-methyl-2-phenyl-1*H*-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1→20:1 hexanes:ethyl acetate in 89 % yield (139 mg, 0.45 mmol) as a white crystalline solid. ^{1}H NMR ($CDCl_3$): δ 7.55 (s, 1H), 7.32-7.25 (m, 6H), 7.20-7.18 (m, 2H), 6.86 (s, 1H), 6.78 (d, J = 8.3 Hz, 1H), 2.53 (s, 3H), 1.93 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 140.7, 137.6, 136.9, 136.4, 133.0, 129.8, 128.7, 128.6, 128.5, 127.6, 127.5, 124.0, 120.4, 110.4, 101.9, 21.7, 18.0; *m/z* ESI$^+$ found 312.1753 $[M+H]^+$ calculated for $C_{23}H_{22}N_1$ 312.1747.



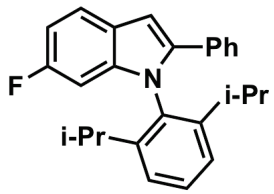
(2-15) 6-Fluoro-1-methyl-2-phenyl-1*H*-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1 hexanes:ethyl acetate in 83 % yield (93 mg, 0.42 mmol) as an off-white solid, however, addition via syringe of methylamine as a 2.0 M solution in tetrahydrofuran (0.300 mL, 0.55 mmol) was performed outside of the glovebox. ^{1}H NMR ($CDCl_3$): δ 7.54-7.49 (m, 4H), 7.44 (m, 1H), 7.32-7.27 (m, 2H), 7.02 (dt, J = 2.5 Hz, 9.2 Hz, 1H), 6.54 (s, 1H), 3.76 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 158.3 (d, $J_{C,F}$ = 234 Hz), 143.5, 135.3, 132.8, 129.7, 128.9, 128.5, 128.4, 110.5 (d, $J_{C,F}$ = 13 Hz), 110.2 (d, $J_{C,F}$ = 26 Hz), 105.5 (d, $J_{C,F}$ = 23 Hz), 101.9 (d, $J_{C,F}$ = 23 Hz), 31.7; *m/z* ESI$^+$ found 226.1026 $[M+H]^+$ calculated for $C_{15}H_{13}F_1N_1$ 226.1027.



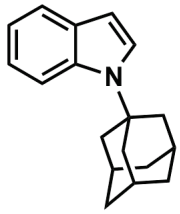
(2-16) 1-Adamantan-1-yl-6-fluoro-2-phenyl-1*H*-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1 hexanes:ethyl acetate in 90 % yield (163 mg, 0.45 mmol) as a white crystalline solid. ^{1}H NMR ($CDCl_3$): δ 7.75 (dd, *J* = 9.2 Hz, 4.3 Hz, 1H), 7.42-7.40 (m, 2H), 7.37-7.35 (m, 3H), 7.21 (dd, *J* = 9.2 Hz, 2.7 Hz, 1H), 6.91 (dt, *J* = 2.8 Hz, 9.1 Hz, 1H), 6.25 (d, *J* = 0.6 Hz, 1H), 2.27 (d, *J* = 2.9 Hz, 6H), 2.11 (s, 3H). 1.69-1.66 (m, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 157.6 (d, $J_{C,F}$ = 235 Hz), 143.5 , 138.6, 133.4, 130.4, 129.9 (d, $J_{C,F}$ = 10 Hz), 127.9, 127.6, 116.6 (d, $J_{C,F}$ = 9 Hz), 108.8 (d, $J_{C,F}$ = 25 Hz), 106.8 (d, $J_{C,F}$ = 4 Hz), 105.3 (d, $J_{C,F}$ = 22 Hz), 61.4, 43.8, 36.5, 30.5; *m/z* ESI^{+} found 346.1954 [M+H]$^{+}$ calculated for $C_{24}H_{25}F_1N_1$ 346.1966.



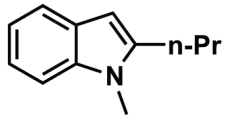
(2-17) 1-(2,6-Diisopropyl-phenyl)-6-fluoro-2-phenyl-1*H*-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1 hexanes:ethyl acetate in 93 % yield (173 mg, 0.47 mmol) as an off-white solid. ^{1}H NMR ($CDCl_3$): δ 7.54 (t, *J* = 7.7 Hz, 1H), 7.41 (dd, *J* = 9.4 Hz, 2.4 Hz, 1H), 7.36-7.33 (m, 4H), 7.29-7.24 (m, 3H), 6.99 (d, *J* = 0.7 Hz, 1H), 6.93 (dt, *J* = 2.5 Hz, 9.1 Hz, 1H), 6.83 (dd, *J* = 8.9 Hz, 4.5 Hz, 1H), 2.40 (sept, *J* = 6.9 Hz, 2H), 1.04 (d, *J* = 6.9 Hz, 6H), 0.93 (d, *J* = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 158.6 (d, $J_{C,F}$ = 235 Hz), 148.1, 142.9, 136.7, 133.8, 132.5, 130.0, 128.5, 128.3, 128.1, 127.9, 124.7, 112.1 (d, $J_{C,F}$ = 26 Hz), 110.6 (d, $J_{C,F}$ = 25 Hz), 105.4 (d, $J_{C,F}$ = 24 Hz), 102.1 (d, $J_{C,F}$ = 4 Hz), 28.5, 25.4, 23.4; *m/z* ESI^{+} found 394.1946 [M+Na]$^{+}$ calculated for $C_{26}H_{26}F_1N_1Na_1$ 394.1941.



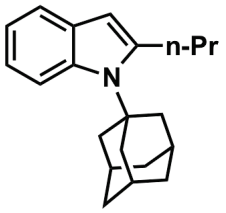
(2-18) 1-Adamantan-1-yl-1*H*-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1 hexanes:ethyl acetate in 82 % yield (109 mg, 0.41 mmol). ^{1}H NMR ($CDCl_3$): δ 7.74 (m, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 3.4 Hz, 1H), 7.14 (m, 1H), 7.07 (m, 1H), 6.46 (dd, J = 8.3 Hz, 0.6 Hz, 1H), 2.38 (d, J = 2.9 Hz, 6H), 2.29 (s, 3H), 1.86-1.81 (m, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 134.8, 130.6, 124.6, 121.6, 120.6, 119.1, 114.1, 100.4, 57.0, 42.5, 36.8, 30.2. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[144]



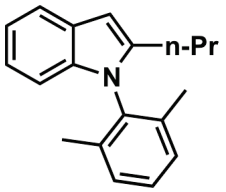
(2-19) 1-Methyl-2-propyl-1*H*-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 40:1 hexanes:ethyl acetate in 67 % yield (58 mg, 0.34 mmol) as a light yellow oil, however, addition via syringe of methylamine as a 2.0 M solution in tetrahydrofuran (0.300 mL, 0.55 mmol) was performed outside of the glovebox. ^{1}H NMR ($CDCl_3$): δ 7.54 (d, J = 9.2 Hz, 1H), 7.28 (s, 1H), 7.15 (m, 1H), 7.07 (m, 1H), 6.26 (d, J = 0.7 Hz, 1H), 3.67 (s, 3H), 2.72 (t, J = 7.6 Hz, 2H), 1.76 (m, 2H), 1.06 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 141.6, 137.8, 128.4, 120.9, 120.2, 119.6, 109.1, 99.2, 29.7, 29.3, 22.4, 14.3. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[145]



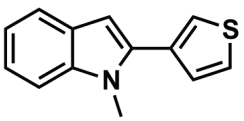
(2-20) 1-Adamantan-1-yl-2-propyl-1*H*-indole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1 hexanes:ethyl acetate in 86 % yield (133 mg, 0.43 mmol) as white solid. ^{1}H NMR ($CDCl_3$): δ 7.77 (d, *J* = 8.4 Hz, 1H), 7.49 (m, 1H), 7.04 (m, 2H), 6.68 (s, 1H), 2.98 (t, *J* = 7.7 Hz, 2H), 2.56 (d, *J* = 2.5 Hz, 6H), 2.27 (s, 3H), 1.87-1.73 (m, 8H), 1.04 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 143.1, 136.8, 129.6, 120.3, 119.8, 118.8, 115.6, 103.4, 61.3, 42.6, 36.7, 34.7, 30.6, 24.4, 14.7; *m/z* ESI$^+$ found 294.2218 $[M+H]^+$ calculated for $C_{21}H_{28}N_1$ 294.2216.



(2-21) 1-(2,6-Dimethyl-phenyl)-2-propyl-1*H*-indole.

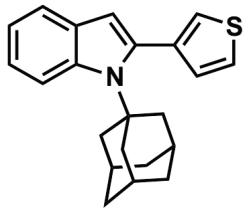
The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1 hexanes:ethyl acetate in 89 % yield (117 mg, 0.45 mmol) as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.66 (d, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.26-7.25 (m, 2H), 7.14 (t, *J* = 7.1 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.5 (s, 1H), 2.40 (t, *J* = 7.6 Hz, 2H), 1.91 (s, 6H), 1.72 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 141.3, 138.0, 136.8, 135.9, 128.7, 128.6, 121.1, 119.9, 119.8, 109.8, 99.5, 29.1, 21.5, 17.7, 14.3; *m/z* ESI$^+$ found 264.1747 $[M+H]^+$ calculated for $C_{19}H_{22}N_1$ 264.1747.



(2-22) 1-Methyl-2-thiophen-3-yl-1*H*-indole.

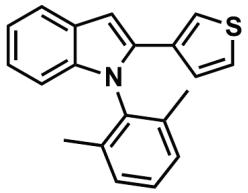
The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 40:1 hexanes:ethyl acetate in 84

% yield (89 mg, 0.42 mmol), however, addition via syringe of methylamine as a 2.0 M solution in tetrahydrofuran (0.300 mL, 0.55 mmol) was performed outside of the glovebox. ^{1}H NMR ($CDCl_3$): δ 7.62 (dt, *J* = 7.8 Hz, 0.9 Hz, 1H), 7.44 (m, 1H), 7.40 (m, 1H), 7.36 (m, 1H), 7.30 (m, 1H), 7.24 (m, 1H), 7.14 (m, 1H), 6.60 (d, *J* = 0.7 Hz, 1H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 138.4, 136.7, 133.7, 128.7, 128.0, 126.1, 123.5, 122.0, 120.7, 120.2, 109.8, 101.7, 31.4. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[50]



(2-23) 1-Adamantan-1-yl-2-thiophen-3-yl-1*H*-indole.

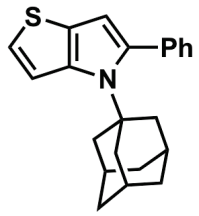
The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1 hexanes:ethyl acetate in 92 % yield (161 mg, 0.46 mmol) as a pale yellow solid. ^{1}H NMR ($CDCl_3$): δ 7.87 (d, *J* = 8.5 Hz, 1H), 7.60 (dd, *J* = 7.7 Hz, 0.6 Hz, 1H), 7.31 (m, 1H), 7.30 (m, 1H), 7.20 (m, 1H), 7.15 (dd, *J* = 4.6 Hz, 1.5 Hz, 1H), 7.12 (m, 1H), 6.39 (s, 1H), 2.38 (d, *J* = 2.7 Hz, 6H), 2.17 (s, 3H), 1.78-1.72 (m, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 138.5, 136.9, 136.0, 113.0, 129.3, 124.2, 124.1, 120.9, 120.8, 119.5, 116.0, 107.2, 61.1, 43.1, 36.6, 30.6; *m/z* ESI^{+} found 334.1609 $[M+H]^{+}$ calculated for $C_{22}H_{24}N_1S_1$ 334.1624.



(2-24) 1-(2,6-Dimethyl-phenyl)-2-thiophen-3-yl-1*H*-indole.

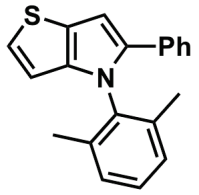
The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1 hexanes:ethyl acetate in 89 % yield (135 mg, 0.45 mmol) as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.68 (m, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.22-7.21 (m, 4H), 7.13 (dp, *J* = 7.0 Hz, *J* = 1.3 Hz, 2H), 6.92 (d, *J* = 0.7 Hz, 1H), 6.80 (m, 1H), 6.58 (t, *J* = 2.1 Hz, 1H), 1.86 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 138.2, 137.8, 136.9, 135.6, 133.4, 129.2, 129.0, 128.4, 127.5, 125.5, 122.5, 120.7, 120.2,

110.4, 101.7, 17.9; *m/z* ESI$^+$ found 304.1140 $[M+H]^+$ calculated for $C_{20}H_{18}N_1S_1$ 304.1154.



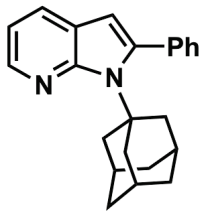
(2-25) 4-Adamantan-1-yl-5-phenyl-4*H*-thieno[3,2-*b*]pyrrole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1 hexanes:ethyl acetate in 86 % yield (150 mg, 0.43 mmol) as a pale yellow solid. ^{1}H NMR ($CDCl_3$): δ 7.47-7.45 (m, 2H), 7.37-7.36 (m, 3H), 7.29 (m, 1H), 7.08 (d, *J* = 5.4 Hz, 1H), 6.23 (d, *J* = 0.4 Hz, 1H), 2.22 (d, *J* = 2.9 Hz, 6H), 2.11 (s, 3H), 1.70-1.64 (m, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 139.8, 139.0, 138.3, 131.5, 127.8, 127.5, 124.0, 121.2, 115.9, 104.4, 61.7, 44.2, 36.4, 30.4; *m/z* ESI$^+$ found 334.1632 $[M+H]^+$ calculated for $C_{22}H_{24}N_1S_1$ 334.1624.



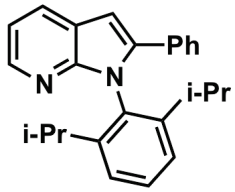
(2-26) 4-(2,6-Dimethyl-phenyl)-5-phenyl-4*H*-thieno[3,2-*b*]pyrrole.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 50:1 hexanes:ethyl acetate in 76 % yield (115 mg, 0.38 mmol) as a pale yellow solid. ^{1}H NMR ($CDCl_3$): δ 7.22-7.12 (m, 6H), 7.09-7.08 (m, 2H), 7.02 (d, *J* = 5.2 Hz, 1H), 6.76 (s, 1H), 6.52 (dd, *J* = 5.2 Hz, *J* = 0.3 Hz, 1H), 1.91 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 141.9, 139.4, 138.0, 137.0, 133.4, 128.7, 128.6, 127.0, 126.9, 124.0, 123.8, 111.3, 101.2, 18.2. *m/z* ESI$^+$ found 304.1152 $[M+H]^+$ calculated for $C_{20}H_{18}N_1S_1$ 304.1154.



(2-27) 1-Adamantan-1-yl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 20:1 hexanes:ethyl acetate in 91 % yield (157 mg, 0.46 mmol) as an off-white solid. ^{1}H NMR ($CDCl_3$): δ 8.32 (dd, J = 4.6 Hz, 1.7 Hz, 1H), 7.80 (dd, J = 7.8 Hz, 1.7 Hz, 1H), 7.44-7.42 (m, 2H), 7.37-7.35 (m, 3H), 7.03 (dd, J = 7.8 Hz, 4.6 Hz, 1H), 6.21 (s, 1H), 2.48 (d, J = 2.6 Hz, 6H), 2.07 (s, 3H), 1.75-1.62 (m, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 150.5, 142.3, 141.3, 138.4, 130.6, 128.1 127.7, 121.3, 115.9, 104.2, 62.5, 43.1, 36.6, 30.6; *m/z* ESI^{+} found 329.2010 $[M+H]^{+}$ calculated for $C_{23}H_{25}N_2$ 329.2012.



(2-28) 1-(2,6-Diisopropyl-phenyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine.

The title compound was synthesized according to the **General Catalytic Protocol** and purified by column chromatography on silica gel using 20:1 hexanes:ethyl acetate in 84 % yield (149 mg, 0.42 mmol) as an off-white solid. ^{1}H NMR ($CDCl_3$): δ 8.40 (dd, J = 4.7 Hz, 1.5 Hz, 1H), 7.99 (dd, J = 7.8 Hz, 1.6 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.33-7.32 (m, 2H), 7.30-7.28 (m, 2H), 7.24-7.23 (m, 3H), 7.11 (dd, J = 7.8 Hz, 4.7 Hz, 1H), 6.91 (s, 1H), 2.36 (sept, J = 6.8 Hz, 2H), 1.03 (d, J = 6.9 Hz, 6H), 0.90 (d, J = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 150.8, 147.7, 143.9, 141.7, 133.0, 132.3, 130.1, 128.4, 128.1, 124.5, 120.5, 116.9, 100.1, 28.9, 25.0, 23.2; *m/z* ESI^{+} found 355.2174 $[M+H]^{+}$ calculated for $C_{25}H_{27}N_2$ 355.2169.

2.4.4 Crystallaographic Solution and Refinement Details for **L1**

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 a sample that was mounted in inert oil and transferred to a cold gas stream on

the diffractometer. Gaussian integration (face-indexed) was employed as the absorption correction method and the structure was solved by use of direct methods. The structure was refined by use of full-matrix leastsquares 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. 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. Additional crystallographic information is provided in the Appendix.

CHAPTER 3 BippyPhos: A SINGLE LIGAND WITH UNPRECEDENTED SCOPE IN THE BUCHWALD-HARTWIG AMINATION OF (HETERO)ARYL CHLORIDES

3.1 INTRODUCTION

As described in Section 1.4, the palladium-catalyzed cross-coupling of (hetero)aryl (pseudo)halides with NH-containing substrates Figure 1–4, commonly referred to as Buchwald-Hartwig Amination (BHA), has matured into a robust methodology that has many important synthetic applications. The primary driving force behind the rapid evolution of BHA into a broadly useful methodology has, and will continue to be, strategic ligand design. Within the field of BHA, reactivity challenges have typically been addressed via the development of tailor-made, task-specific ligands. While useful, this has created challenges for practitioners of BHA, when face with varied target applications. Indeed, absent from the literature are reports of a single Pd/ligand catalyst system with demonstrated widespread ability to promote the cross-coupling of (hetero)aryl (pseudo)halides with electronically and structurally diverse NH-containing substrates ranging from relatively acidic indoles (pKa of protonated indole = -3.6) , to amines, to more nucleophilic NH-containing substrates including hydrazine and ammonia (pKa of protonated ammonia = 9.25) (Figure 3–1).

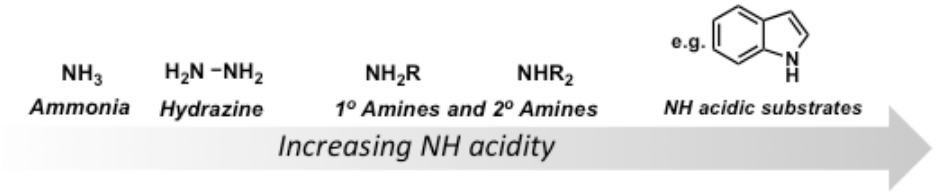


Figure 3–1. Graphical representation of the electronic and structural differences between the different types of NH-containing substrates the can be employed in BHA.

While some limited progress towards addressing deficiencies in the scope of the NH-containing coupling partner have been achieved through the use of multiple ligand catalytic systems,[61] in general the practicing synthetic chemist is required to assemble and/or screen an inventory of ligands for which only task-specific synthetic utility has been established; this is especially true when embarking upon a new BHA application for which optimal conditions are not clearly specified in the literature.[36,60] While the

acquisition and use of a toolkit of commercially available ligands can accomplish some synthetic objectives, selecting a ligand and optimizing conditions for each NH-containing substrate is both cost and time ineffective, especially for the non-specialist. In this regard, the identification of a single Pd/ligand catalyst system, derived from commercially available air-stable components, which could serve as a reliable "first-choice" for use in a diversity of BHA applications, would represent an important achievement in the quest to expand the scope, utility and usage of BHA chemistry in both academic and industrial settings.

In Section 3.2, the development and application of a $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system, which offers such a desirable reactivity profile, is described. The application of this catalyst system toward the arylation of ammonia, hydrazine, primary and secondary amines, diamines, amides, and indoles with a variety of functionalized aryl and heteroaryl halides at moderate to low catalyst loadings is disclosed. The unprecedented scope of this catalyst system toward NH-containing substrates also facilitated the development of a new one-pot, two-step tandem synthesis of *N*-aryl heterocycles from ammonia, *ortho*-alkynylhaloarenes and (hetero)aryl halides. A marked NH-substrate selectivity preference of the catalyst system was identified and exploited in the chemoselective monoarylation of substrates featuring two distinct and potentially reactive NH-containing moieties.

3.2 Results and Discussion

3.2.1 Catalyst Screening

In the search to find a practical catalyst system with improved generality in the BHA of aryl chlorides with a wide range of NH-containing substrates, screening of representative commercially available ligands (Figure 1–5) in judiciously selected BHA reactions using conditions adapted from literature protocols was conducted.[55-57,59,70,124,146] In this context, the *N*-arylation of primary amines, secondary amines, indole, and ammonia with chlorobenzene using 1 mol% $[Pd(cinnamyl)Cl]_2$ and 4 mol% ligand was investigated. $[Pd(cinnamyl)Cl]_2$ was selected as a palladium source as it is commercially available, easily synthesized and handled on the benchtop,[129] has proven useful in combination with most of the ligands featured in Figure 1–5,[52,56,57,59,68,147] and readily

forms the desired ligated catalytically active Pd^0 species by nucleophilic attack on the η^3-bound cinammyl group of the generated precatalyst complex.[36,148] More challenging aryl chloride substrates were primarily focused on because they are typically less expensive and more readily available from commercial sources in comparison to the corresponding aryl bromides and iodides. It should be noted that there is literature precedent for the use of several of the commercial ligands featured in the preliminary BHA screen (Figure 3–2) in some of the BHA transformations explored. However, direct reactivity comparisons between ligand classes based on literature data are difficult to make because additives, bases, solvents, palladium sources and concentration are not consistent. Details of the screening reaction conditions can be found in the Section 3.4. GC analysis allowed determination of yields on the basis of calibration curves generated from authentic product samples using the internal standard calibration method (Figure 3–2).

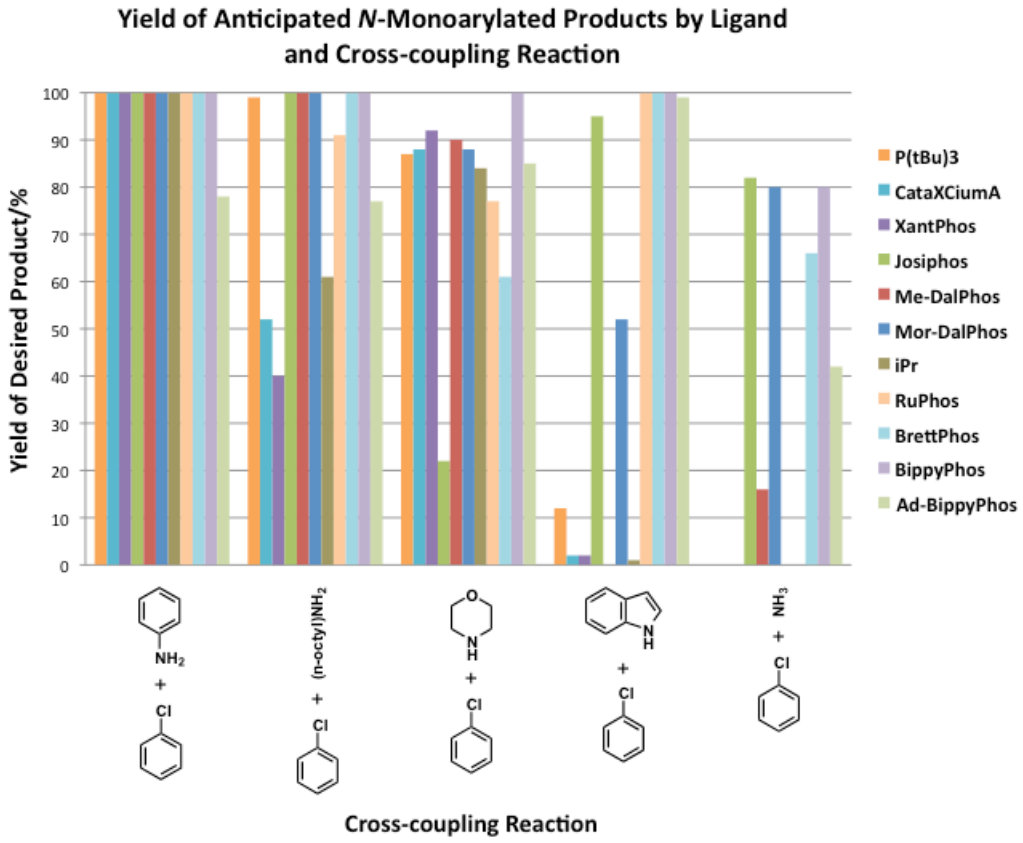


Figure 3–2. Yields of anticipated carbon-nitrogen cross-coupling products after 18 h at 1 mol% $[Pd(cinnamyl)Cl]_2$ (Pd:L = 1:2). Yields were determined on the basis of GC analysis of reaction mixtures. GC calibration curves were generated with authentic

products using the internal standard calibration method with dodecane as an internal standard. For detailed reaction conditions see the Section 3.4. See Figure 1–5 for ligand structures.

The ligand classes behaved as expected in the cross-coupling reactions screened, on the basis of literature reports of their *N*-arylation abilities.[34,35,37-42,44-48,51,53,54,56,59-64,149] The majority of the catalyst systems were effective in the arylation of primary and secondary amines, with some exceptions: both cataCXium A and XantPhos gave low yields of *N*-phenyloctylamine while JosiPhos and BrettPhos gave low yields of *N*-phenylmorpholine. JosiPhos, BrettPhos, RuPhos, BippyPhos and Ad-BippyPhos were effective in the *N*-arylation of indole affording high yields of *N*-phenylindole, but only JosiPhos, MorDalPhos and BippyPhos were effective in the selective monoarylation of ammonia to generate aniline (see Figure 1–5 for ligand structures). Notably, of all the ligands screened, only BippyPhos gave appreciable yields of each desired carbon-nitrogen cross-coupling product (Figure 3–2). Repeating the reaction screen with the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system at 0.5 mol% $[Pd(cinnamyl)Cl]_2$ loading resulted in a decrease in GC yield for the products of the *N*-arylation reactions of morpholine and indole of > 10 %, but no decrease in GC yield for the products generated with the other NH-containing cross-coupling partners. These encouraging results led us to focus on the further application of the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system in the cross-coupling of functionalized (hetero)aryl halides with a wide range of NH-containing substrates, in an effort to establish a broadly useful catalyst system for BHA.

3.2.2 Previous BippyPhos Applications in Buchwald-Hartwig Amination

The non-proprietary, air-stable ligand BippyPhos was first disclosed in 2006 by Singer and co-workers,[62] along with a demonstration of its utility in the BHA of primary and secondary alkyl and aryl amines. An additional report in 2008 outlined a kilogram-scale synthesis of BippyPhos along with its further application in a limited selection of palladium-catalyzed carbon-nitrogen, carbon-oxygen and carbon-carbon cross-coupling reactions with (hetero)aryl chlorides.[63] Following these initial reports, BippyPhos has been applied in a small number of other palladium-catalyzed carbon-nitrogen (Figure 3–3) and carbon-oxygen cross-coupling reactions, and is now commercially available from multiple sources.

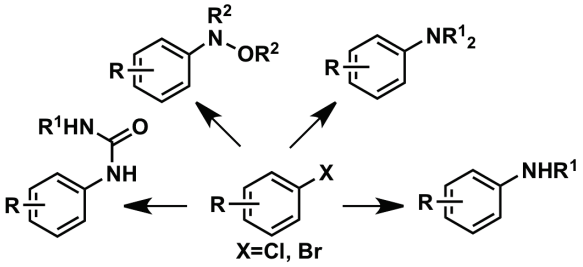


Figure 3–3. Previous Applications of Pd/BippyPhos catalyst systems in carbon-nitrogen cross-coupling reactions. NH-containing coupling partners not depicted for simplicity.

Pd/BippyPhos catalyst systems have been used to facilitate the C-N cross-coupling of primary and secondary amines,[63,149] substituted hydroxylamines,[150,151] ureas[152,153] and, in two isolated examples, imidazoles[154] (Figure 3–3). In addition to carbon-nitrogen bond formation, there are also several examples where a Pd/BippyPhos catalyst system is used to facilitate carbon-oxygen bond formation, with primary alcohols,[63,64] and carbon-carbon bond formation.[63,155]

Having established for the first time the unusual ability of this [Pd(cinnamyl)Cl]$_2$/BippyPhos catalyst system to promote the monoarylation of the rather divergent coupling partners such as ammonia and indole (Figure 3–2), BHA reactions involving challenging NH-containing cross-coupling partners, for which the utility of Pd/BippyPhos catalysts had yet to be demonstrated, were investigated.

3.2.3 Expanding the BippyPhos Reactivity Profile to Ammonia and Hydrazine

The selective monoarylation of ammonia with aryl chlorides by use of BHA protocols has proven to be a considerable challenge. Difficulties in achieving appropriate levels of catalytic activity and selectivity in such transformations can be attributed in part to preferential uptake of the product aniline leading to di- and triarylation, and the decreased propensity of requisite [L_nPd(Ar)(NH_2)] intermediates to undergo reductive elimination.[156] These challenges were largely overcome through the development of the [Pd(P(*o*-tol)$_3$)$_2$]/JosiPhos catalyst system, which proved capable of selectively monoarylating ammonia with aryl halides and sulfonates,[47] as well as the [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos catalyst system, which is able to selectively monoarylate ammonia with a variety of functionalized (hetero)aryl halides under mild

conditions with low catalyst loadings.[56] The recent development of the BHA of ammonia with aryl halides has been reviewed in detail.[157-159] Although the reaction now has precedent, there are still relatively few reported catalyst systems capable of achieving this selective transformation.

In addition to sharing the aforementioned challenges associated with employing ammonia as a reaction partner in BHA, hydrazine presents additional difficulties owing to its strong reducing abilities and potential for side-reactions involving N-N bond cleavage. In 2010, the Stradiotto group disclosed the first examples of the selective monoarylation of hydrazine, by use of the $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos catalyst system at loadings of 5-10 mol% Pd.[57] Following this publication, only one other report of palladium-catalyzed hydrazine cross-coupling has appeared, which employed as catalysts palladacycles derived from Buchwald's biaryl monophosphine ligands.[160] Encouraged by the observation in the screening exercise (Figure 3–2) that $[Pd(cinnamyl)Cl]_2$/BippyPhos mixtures catalyze the selective monoarylation of ammonia using chlorobenzene, this chemistry was explored further. As a starting point, published conditions developed for the BHA of ammonia (Figure 3–4)[56] and hydrazine (Figure 3–5)[57] in combination with selected representative (hetero)aryl chlorides were employed.

Gratifyingly the $[Pd(cinnamyl)Cl]_2$/BippPhos catalyst system afforded the desired monoarylated aniline products (Figure 3–4) in high isolated yields (62–83%, **3-1**–**3-3**). Representative electron-rich (**3-1**), electron-poor (**3-2**), and heterocyclic (**3-3**) aryl chlorides were each successfully cross-coupled with ammonia; a more detailed examination of ammonia monoarylation in the context of indole synthesis employing $[Pd(cinnamyl)Cl]_2$/BippyPhos will be provided in Section 3.2.4.

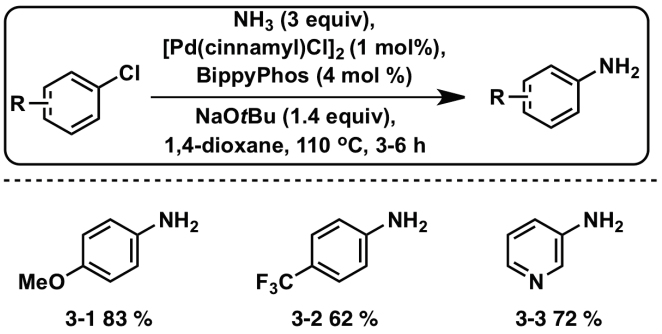


Figure 3–4. The $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyzed cross-coupling of ammonia with (hetero)aryl chlorides.

Extension of the catalyst system to the challenging monoarylation of hydrazine required a derivatization step, as the arylhydrazine products resulting from the initial cross-coupling reaction were found to be of varying stability. Reaction of the arylhydrazine intermediates generated following the successful carbon-nitrogen cross-coupling of hydrazine and the aryl chloride in neat acetylacetone at 110 ˚C gave the corresponding *N*-arylpyrazole derivatives, which in turn were isolated and characterized. Application of the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system to hydrazine monoarylation (Figure 3–5) afforded the corresponding *N*-arylpyrazoles in good isolated yields (46-93 %, **3-4**–**3-12**)

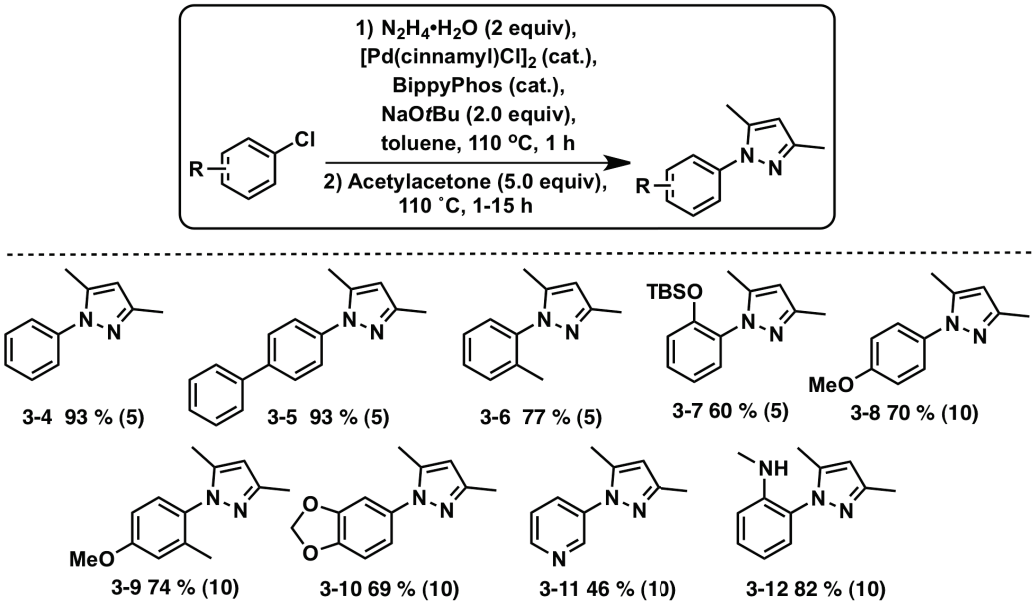


Figure 3–5. The $Pd(cinnamyl)Cl]_2$/BippyPhos catalyzed cross-coupling of hydrazine with (hetero)aryl chlorides (mol% $[Pd(cinnamyl)Cl]_2$ (x) given in parentheses; isolated yields).

A variety of electron-neutral (**3-4**, **3-5**), electron-rich (**3-8**, **3-9**) and *ortho*-substituted (**3-6**, **3-7**, **3-9**, **3-12**) aryl chlorides were successfully accommodated at a 5-10 mol% Pd loading. A heteroaryl chloride was tolerated as well (**3-11**), albeit in lower isolated yield. The reaction also displays functional group tolerance and chemoselectivity with a silyl-protected alcohol (**3-7**) and a secondary amine (**3-12**) each being accommodated under the reaction conditions. Attempts to employ 1-chloro-4-fluorobenzene in the reaction resulted in defluorination of the starting material to give **3-4** as the final product in 62 % yield. Although the catalyst loadings used herein are higher than those reported recently by Buchwald in a continuous flow system,[160] they are within the same range used for the [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos catalyst system.[57] The [Pd(cinnamyl)Cl]$_2$/BippyPhos catalyst system also has an advantage over the [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos catalyst system in that it can accommodate electron-rich aryl chloride substrates (**3-8**, **3-9**, **3-10**) in synthetically useful isolated yields (69–74 %).

3.2.4 Utilizing BippyPhos in Complementary Routes for Accessing Substituted Indoles

As described Section 2.1, the indole core structure is arguably one of the most scrutinized organic frameworks in synthetic medicinal chemistry, and is featured in a diverse array of pharmaceutical compounds.[93] Also as previously mentioned, limitations associated with traditional preparative routes to indoles have inspired the development of more efficient, selective and modular metal-catalyzed protocols that in turn have transformed modern indole synthesis.[97,99-102] An attractive alternative, and perhaps more direct, method for accessing functionalized indoles to the method employed in Chapter 2 (i.e. palladium-catalyzed cross-coupling/cyclization of *ortho*-alkynylhalo(hetero)arenes with primary amines), involves transition metal-catalyzed *N*-arylation of NH-indoles with (hetero)aryl halides. However, such transformations have proven challenging owing to the relatively poor nucleophilicity and high NH acidity of NH-indoles, as well as due to the potential for competing *N*- and *C*-arylation.[36] In 2000 and 2002, Buchwald and co-workers disclosed breakthrough catalyst systems based on Pd_2dba_3/biarylphosphine[124] or CuI/diamine[161] mixtures, respectively, which are capable of promoting such transformations. However, practical drawbacks still exist with these and other reported catalysts systems, including in the case of copper systems the need for high metal/ligand

loadings as well as the poor reactivity observed with (hetero)aryl chloride reagents. Furthermore, no single Pd/ligand catalyst system that exhibits broad reactivity scope in the *N*-arylation of NH-indoles with aryl halides has been reported to date, and among those reports that have appeared in the literature, successful transformations involving the use of (hetero)aryl chlorides are very few.

Inspired by the success of the [Pd(cinnamyl)Cl]$_2$/BippyPhos catalyst system for the *N*-arylation of indole as observed in the preliminary ligand screening (Figure 3–2), reaction conditions that address some of the important shortcomings associated with the cross-coupling of NH-indoles with (hetero)aryl (pseudo)halides were identified. Under the conditions outlined in Figure 3–6, a selection of (hetero)aryl chlorides and bromides featuring electron-donating and -withdrawing substituents were found to be well-accommodated, forming the corresponding *N*-arylated indoles in synthetically useful isolated yields (71–93 %, **2-3**, **3-13**–**3-25**). Specifically, when employing the parent indole as the coupling partner, both chlorobenzene and phenyl tosylate (as proof-of-principle), were shown to be well-tolerated with no appreciable difference in reactivity observed (**3-13**).

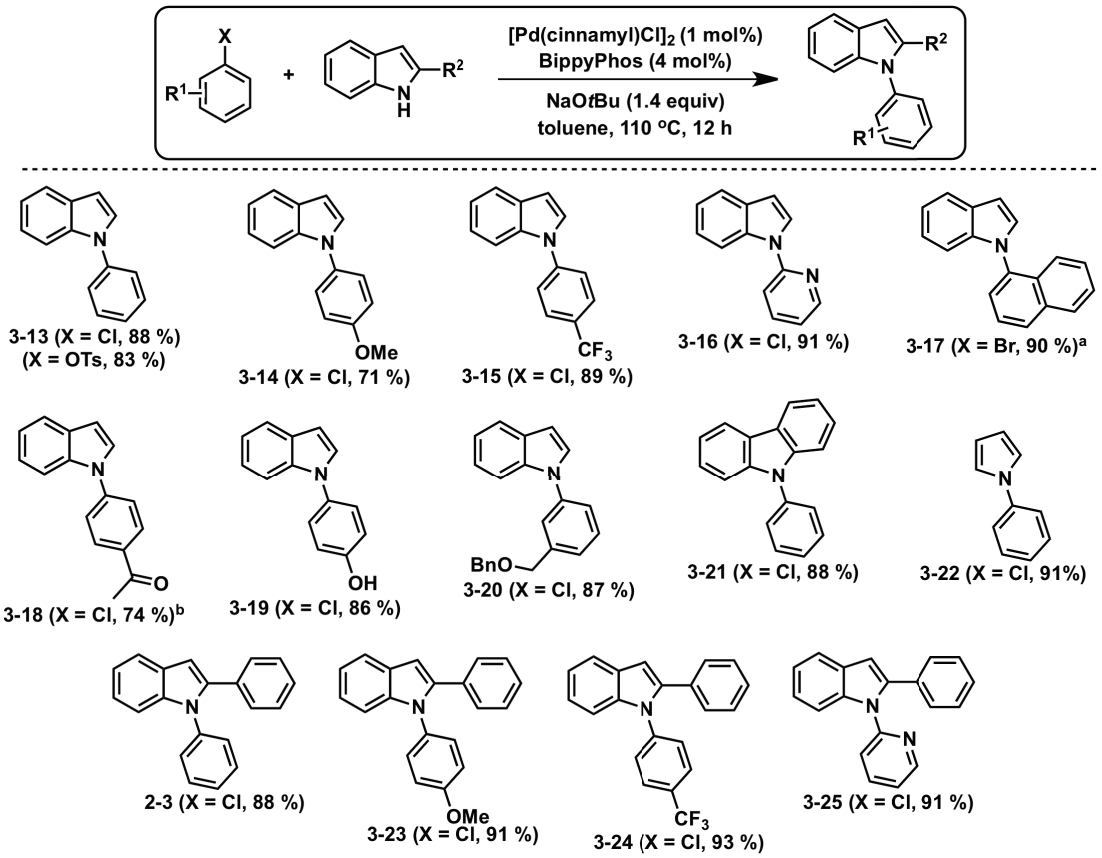


Figure 3–6. The $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyzed *N*-arylation of indoles and related heterocycles (isolated yields). [a]4 mol% Pd, 8 mol% ligand. [b]K_3PO_4 used as the base.

Aryl chlorides featuring 4-methoxy (**3-14)** or 4-trifluoromethyl groups (**3-15**) proved to be successful coupling partners, as did 2-chloropyridine (**3-16**). Whereas *ortho*-substitution on the (hetero)aryl halide was in general not well tolerated by the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system in this reaction setting, bromonaphthalene was shown to be an effective coupling partner, leading to **3-17**. Gratifyingly, substrates featuring synthetically relevant keto, phenol and benzyl ether moieties were each well accommodated (**3-18**–**3-20**). Carbazole and pyrrole were also shown to be effective coupling partners with chlorobenzene (**3-21**, **3-22**). Finally, the more sterically demanding 2-phenylindole was selectively cross-coupled with a representative collection of (hetero)aryl chlorides (**2-3**, **3-23**–**3-24**), thereby demonstrating that C2-substituted indoles can be accommodated. While diverse functionality and varied substitution has previously been demonstrated in this transformation by employing (hetero)aryl iodides

and bromides, the [Pd(cinnamyl)Cl]$_2$/BippyPhos catalyst system featured herein exhibits the broadest known substrate scope for the metal-catalyzed cross-coupling of (hetero)aryl chlorides with NH-indoles.

While the [Pd(cinnamyl)Cl]$_2$/OTips-DalPhos catalyst system described in Chapter 2 signifficantly advanced the synthesis of *N*-substituted indoles via palladium-catalyzed cross-coupling/cyclization methodologies, some important challenges do still exist. For example, in the only report of such cross-coupling/cyclization transformations thus far in the literature involving ammonia,[50] which makes use of the [Pd(cinnamyl)Cl]$_2$/JosiPhos catalyst system, scope in the *ortho*-alkynylhalo(hetero)arene reagent was limited to bromide variants; furthermore, heteroaryl halides as well as *ortho*-alkynylbromoarenes featuring sp^3-substituents at the alkyne terminus proved incompatible with this catalyst system.

In the quest to overcome these notable limitations, and in an effort to harness the unusual capabilities of the [Pd(cinnamyl)Cl]$_2$/BippyPhos catalyst system in the monoarylation of both ammonia and NH-indoles, attention was next turned to developing unprecedented one-pot, two-step syntheses of functionalized *N*-arylated indoles directly from ammonia in which three distinct carbon-nitrogen bonds are formed in a highly selective manner. Two possible routes for accessing *N*-arylated indoles from ammonia in this manner were envisioned: i) monoarylation of ammonia with an *ortho*-alkynylhaloarene in the presence of excess base to form an NH-indole that can then be cross-coupled with an aryl halide to form the corresponding *N*-arylated indole (Method A, Figure 3–7); or ii) monoarylation of ammonia with an aryl halide to form an aniline that can then be cross-coupled with an *ortho*-alkynylhaloarene in the presence of excess base to form the corresponding substituted *N*-arylated indole (Method B, Figure 3–7).

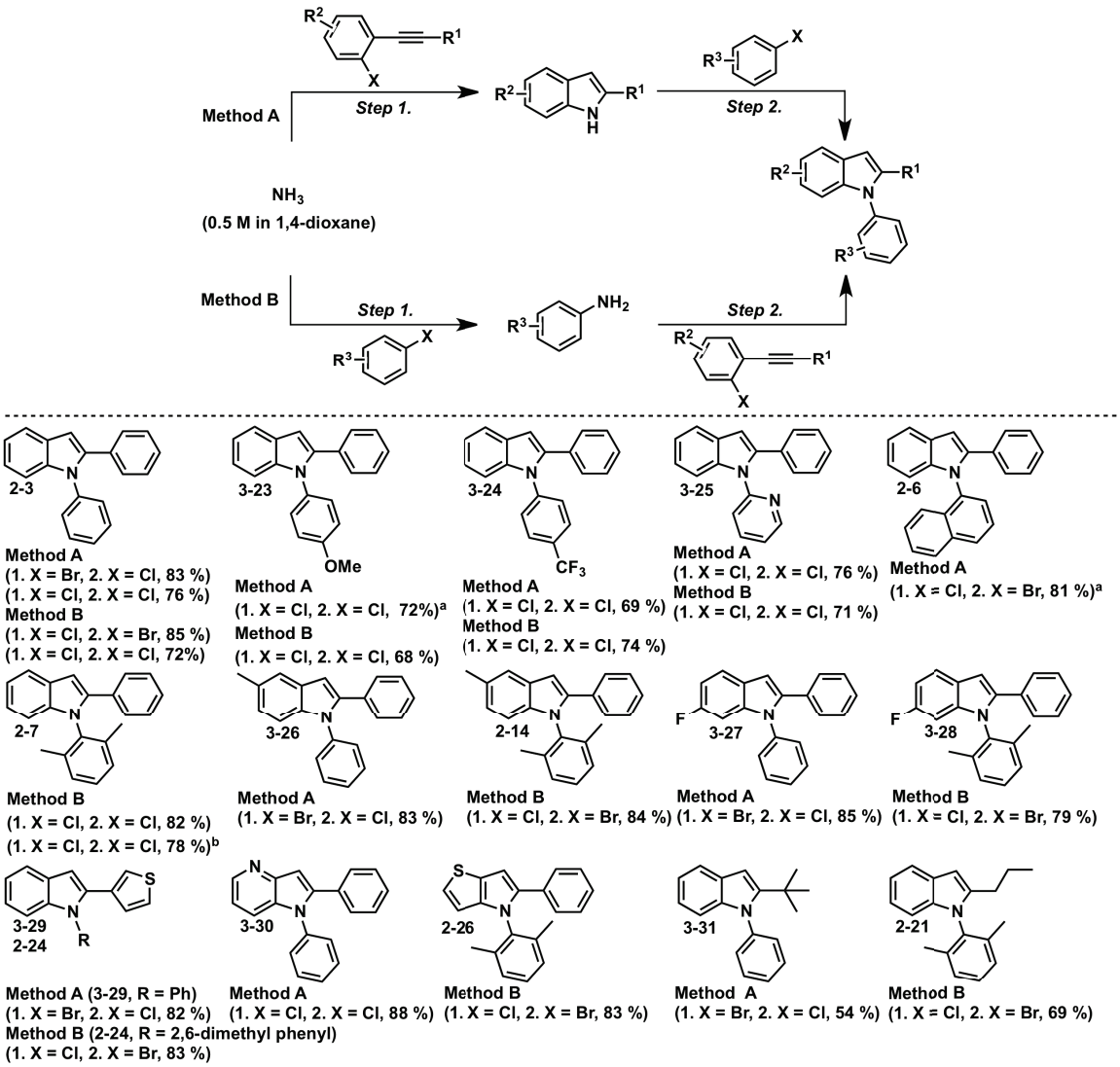


Figure 3–7. Scope of $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyzed synthesis of substituted indoles from ammonia by way of a one-pot, two-step procedure (isolated yields). Method A conditions: Step 1. ArX (1 equiv), ammonia (3 equiv), if X = Br, $[Pd(cinnamyl)Cl]_2$/BippyPhos (1 mol%/4 mol%), if X = Cl, $[Pd(cinnamyl)Cl]_2$/BippyPhos (2 mol%/8 mol%), KO*t*Bu (3 equiv), 1,4-dioxane, 110 °C, 8 h; Step 2. ArX (1 equiv), $[Pd(cinnamyl)Cl]_2$/BippyPhos (1 mol%/4 mol%), NaO*t*Bu (1.4 equiv), toluene, 110 °C, 12 h. Method B conditions: ArX (1 equiv), ammonia (3 equiv), $[Pd(cinnamyl)Cl]_2$/BippyPhos (1 mol%/4 mol%), NaO*t*Bu (1.4 equiv), 1,4-dioxane, 110 °C, 3-6 h; Step 2. Ar-X (1 equiv), $[Pd(cinnamyl)Cl]_2$/BippyPhos (1 mol%/4 mol%), KO*t*Bu (1.4 equiv), toluene, 110 °C, 8 h. [a]Method A, Step 2. $[Pd(cinnamyl)Cl]_2$/BippyPhos (2 mol%/8 mol%). [b]Reaction conducted under air.

Gratifyingly the [Pd(cinnamyl)Cl]$_2$/BippyPhos catalyst system proved capable of promoting the formation of substituted *N*-arylated indoles via each of these reaction pathways, providing access to a variety of functionalized indoles and related heterocyclic derivatives in synthetically useful isolated yields (54–85 % total over both steps, **2-3**, **2-6**, **2-7**, **2-14**, **2-21**, **2-24**, **2-26** and **3-23**–**3-31**). Under the conditions outlined in Figure 3–7, 2-phenylindole **2-3** could be readily accessed via Method A or Method B by employing either 1-bromo- or 1-chloro-2-(phenylethynyl)benzene and chlorobenzene in the appropriate steps. The successful combination of ammonia with an *ortho*-alkynylchloroarene in Step 1 of Method A represents an important practical advancement in this transformation, in that previously only *ortho*-alkynylbromoarenes could be employed.[50]

In exploring this chemistry further, *N*-aryl indoles featuring methoxy, trifluoromethyl, 2-pyridyl, and naphthyl *N*-aryl groups were also efficiently prepared via Method A employing 1-chloro-2-(phenylethynyl)benzene in Step 1 along with the appropriate (hetero)aryl chlorides in Step 2 (**2-6** and **3-23**–**3-25**). Notably, indoles **3-23**–**3-25** could also be straightforwardly prepared via Method B by use of appropriate (hetero)aryl chloride reagents. In exploring the scope of Method B further, 2,6-chloro-*meta*-xylene was employed successfully, affording the corresponding doubly *ortho*-substituted *N*-aryl indole (**2-7**) in 82 % isolated yield. When repeating the synthesis of **2-7** by employing Method B under air, no significant difference in reactivity was observed (78 % isolated yield). Attention was next turned to investigating substitution on the *ortho*-alkynylhaloarene, using chlorobenzene as the standard reaction partner in Step 2 of Method A and 2,6-chloro-*meta*-xylene in Step 1 of Method B. Pleasingly, both methylated and fluorinated derivatives of 1-bromo-2-(phenylethynyl)benzene were well tolerated in both Methods A and B, affording the corresponding indoles (**2-14** and **3-26**–**3-28**) in high isolated yield (79–85 %). The use of *ortho*-alkynylhaloarenes featuring heteroaromatic substitution at the alkynyl terminus as well as within the alkynylarene backbone was also successful. Specifically, a thiophen-3-yl moiety on the alkynyl terminus was well-tolerated in both Methods A and B, yielding the corresponding *N*-substituted indoles featuring a thiophen-3-yl fragment in the C2 position (**2-24** and **3-29**). It is worthy of mention that the use of 3-chloro-2-(phenylethynyl)pyridine in Method A

to form the corresponding 4-azaindole (**3-30**, 88 %) represents the first successful reaction of an *ortho*-alkynylhaloheteroarene with ammonia in such palladium-catalyzed indole syntheses. Similarly, 3-bromo-2-(phenylethynyl)thiophene could easily be accommodated in Method B to form the respective thienopyrrole (**2-26**, 83 %). Finally, *ortho*-alkynylhaloarenes featuring alkyl substitution at the alkynyl terminus, in the form of a *tert*-butyl group in Method A and an *n*-propyl group in Method B, were successfully converted to the corresponding *N*-aryl indoles featuring alkyl substitution in the C2 position (**2-21** and **3-31**). The success of 1-bromo-2-(3,3-dimethylbut-1-yn-1-yl)benzene in Method A leading to **3-11** represents the first example of an *ortho*-alkynylhaloarene featuring alkyl substitution at the alkynyl terminus to be successfully cross-coupled with ammonia, thereby further demonstrating the robust scope of the [Pd(cinnamyl)Cl]$_2$/BippyPhos catalyst system.

3.2.5 Expanding the BippyPhos Reactivity Profile to Amides and Sulfonamides

Organic amides are challenging substrates for intermolecular carbon-nitrogen cross-coupling reactions due to their low nucleophilicity and ability to bind in a bidentate fashion to a metal-center once deprotonated, providing an additional barrier to the reductive elimination of *N*-arylamide products.[162] In 2000, Yin and Buchwald reported the use of the Pd(OAc)$_2$/XantPhos system, which was capable of promoting the intermolecular cross-coupling of aryl halides, including activated aryl chlorides with primary amides and sulfonamides at catalyst loadings between 1-4 mol% Pd.[163] Subsequent use of a Pd(OAc)$_2$/biaryl monophosphine catalyst system allowed for the cross-coupling of a broader scope of aryl chlorides and aryl mesylates at 1 mol% Pd,[164-166] and moving to the [Pd(allyl)Cl]$_2$/JackiePhos catalyst system allowed for the cross-coupling of aryl chlorides with acyclic secondary amides and carbamates.[167] Notwithstanding these selected advances, reports of the palladium-catalyzed amidation of aryl chlorides remain limited. In an initial publication, Singer and co-workers reported on the poor performance of the Pd(OAc)$_2$/BippyPhos catalyst system for the cross-coupling of aryl chlorides and amides.[63] Subsequently, the Pd$_2$(dba)$_3$/BippyPhos catalyst system has been reported to couple aryl bromides and chlorides to a variety of aryl, benzyl and aliphatic ureas,[153] and the [Pd(allyl)Cl]$_2$/BippyPhos catalyst system has been employed

successfully in the coupling of an aryl bromide with methanesulfonamide, although this catalyst system was not applied to a broader aryl chloride or amide substrate scope.[168] Despite these few recent reports, a Pd/BippyPhos catalyst system for cross-coupling aryl halides with amides with broad scope has not been reported to date.

Initial efforts in amide cross-coupling focused on the identification of suitable conditions for the cross-coupling of chlorobenzene and acetamide with the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system. Preliminary investigations indicated that 1,4-dioxane and *tert*-butanol were the optimal solvents and both potassium carbonate and potassium phosphate were effective bases for this transformation. The standard optimized conditions involved heating the amide or sulfonamide (1.0 equiv) with the aryl chloride (1.0 equiv), potassium carbonate (2 equiv), BippyPhos (2-5 mol%) and $[Pd(cinnamyl)Cl]_2$ (0.5-1.25 mol%) at 90 ˚C for 18 h in 1,4-dioxane (Figure 3–8).

Using these standard conditions, functionalized (hetero)aryl chlorides were successfully cross-coupled with a variety of amides and sulfonamides in synthetically useful yields (44–99 %, **3-32**–**3-54**; Figure 3–8). Chlorobenzene was successfully cross-coupled under the standard conditions with amides (**3-32**, **3-40**, **3-46**) and sulfonamides (**3-49**, **3-50**). Substitution in the *ortho*-position was also tolerated and 2-chlorotoluene was successfully cross-coupled with amides (**3-35**, **3-45**, **3-48**). Electron-poor 4-chlorobenzotrifluoride was also cross-coupled with amides (**3-34**, **3-42**, **3-47**), sulfonamides (**3-52**, **3-53**) and formamide (**3-54**). Electron-rich 4-chloroanisole proved to be a more challenging coupling partner. Under the standard cross-coupling conditions at a catalyst loading of 2.5 mol% Pd, **3-33** was only isolated in 59% and **3-41** in 54%. However, changing the base to K_3PO_4 and the solvent to *tert*-butanol allowed 4-chloroanisole to be accommodated in the reaction at a 2.5 mol% Pd loading to give **3-33** in a 92 % yield and **3-41** in a 99 % yield. 2-Chloropyridine and 3-chloropyridine were each successfully coupled with representative amides (**3-38**, **3-39**, **3-43**, **3-44**) when using the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system in *tert*-butanol solvent. 2-Chloropyridine could also be coupled with *p*-tolylbenzenesulfonamide (**3-51**), albeit in a low yield. The functional group tolerance of the catalyst system was further demonstrated via the successful cross-coupling of two other heterocyclic aryl chlorides (**3-36, 3-37**) with acetamide.

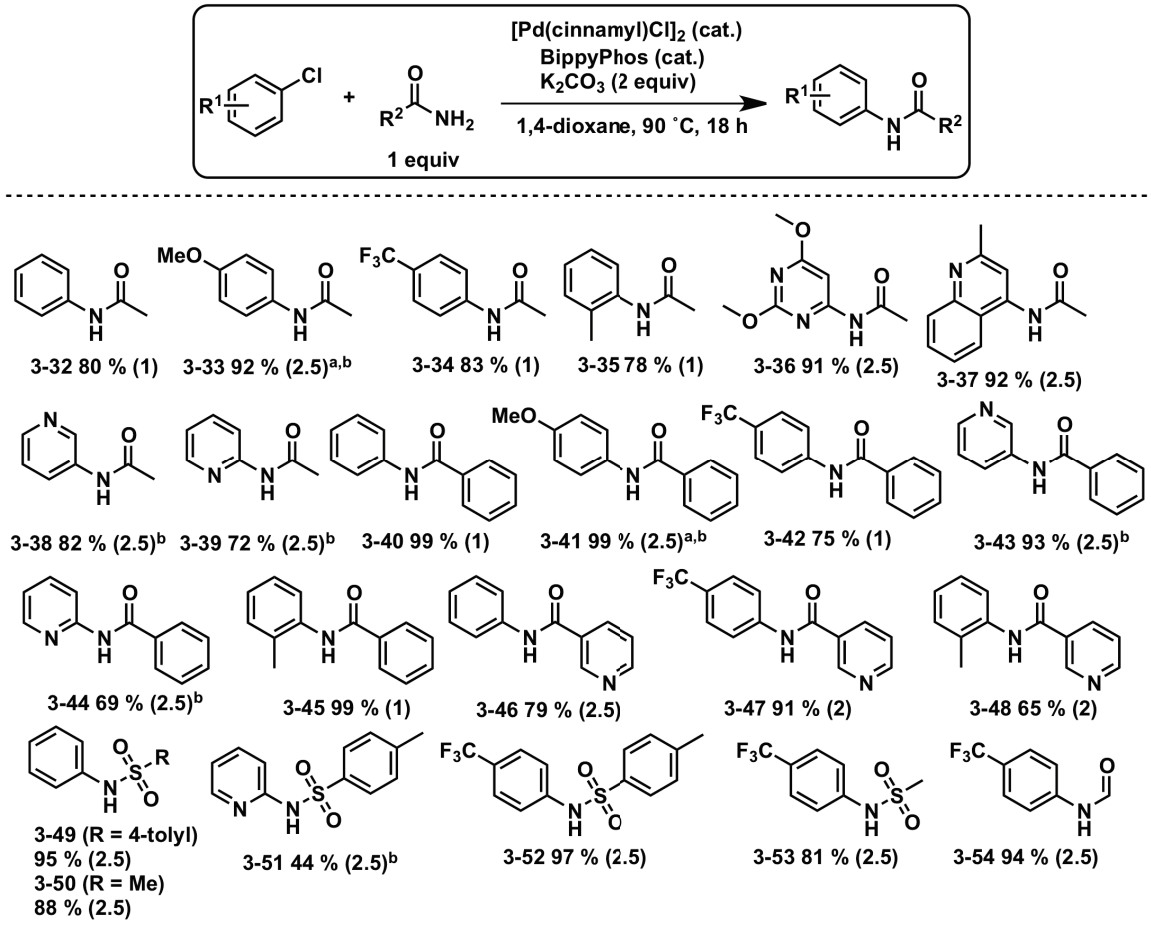


Figure 3–8. Scope for the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyzed cross-coupling of amides and sulfonamides with (hetero)aryl chlorides and bromides (mol% $[Pd(cinnamyl)Cl]_2$ (x) given in parentheses; isolated yields). [a]K_3PO_4 used as base. [b]*t*BuOH used as solvent.

Under the standard conditions, *N*-butylacetamide, an acyclic secondary amide, could not be cross-coupled with chlorobenzene. Attempts were made to optimize the base, solvent and reaction temperature; nonetheless, the product could not be isolated in a synthetically useful yield. Despite this particular scope limitation, the results presented herein establish that the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system can accommodate a broad scope of functionalized (hetero)aryl chlorides in combination with primary amides or sulfonamides as cross-coupling partners.

3.2.6 Utilizing BippyPhos in Challenging Secondary Amine, Low Catalyst Loading, and Amine Competition Experiments

Although the $Pd(OAc)_2$/BippyPhos catalyst system has proven capable of cross-coupling both primary and secondary amines with aryl halides at 0.5-1.0 mol% Pd,[63,149] attention was next focused on investigating the application of $[Pd(cinnamyl)Cl]_2$/BippyPhos to challenging secondary amine substrates. Using this catalyst system, dihexylamine (**3-56**) and heptaethyleneimine (**3-57**) each were successfully arylated in synthetically useful yields using 2 mol% Pd (Figure 3–9). This was a gratifying result as there are very few reports of cross-coupling these substrates with aryl chlorides.[169-174]

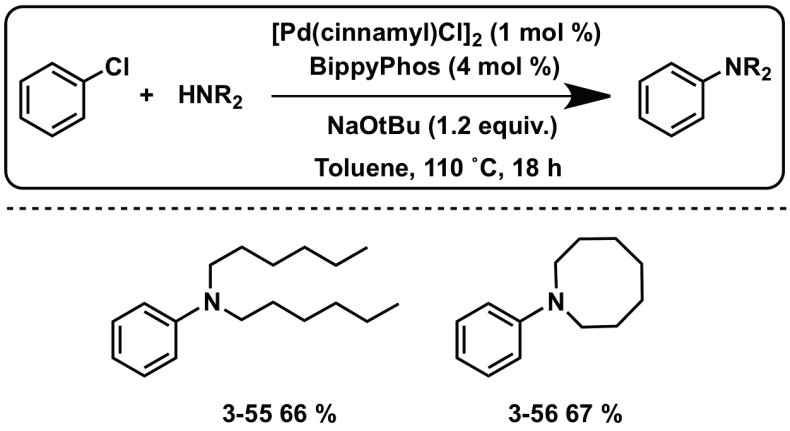


Figure 3–9. Selected application of the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system for the cross-coupling of challenging secondary amines with chlorobenzene (isolated yields).

Beyond applying the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system to BHA reactions involving the particularly challenging NH-containing substrates discussed thus far, its efficiency in cross-coupling 4-chloroanisole (a representative electronically deactivated aryl chloride) with a series of more commonly employed, yet synthetically relevant, primary and secondary amines, over the course of 24 h (unoptimized) at 110 °C, was also investigated (Figure 3–10).

It was pleasing to observe quantitative conversion of 4-chloroanisole to form the target cross-coupling products (**3-57**–**3-63**) with a range of primary and secondary alkyl- and arylamines employing catalyst loadings as low as 0.05-0.3 mol% Pd (Pd:BippyPhos, 1:2). At the outset, the lowest catalyst loadings at which full conversion of 4-

chloroanisole could be achieved were determined for the sterically differing primary alkylamines methylamine (0.1 mol% Pd, **3-57**), *n*-octylamine (0.05 mol% Pd, **3-58**) and 1-adamantylamine (0.3 mol% Pd, **3-59**). While aniline (0.3 mol% Pd, **3-60**) was also easily accommodated at such low catalyst loadings, the more hindered 2,6-dimethylaniline proved somewhat more challenging under similar conditions, requiring a slightly higher catalyst loading (0.5 mol% Pd, **3-61**) to achieve full conversion. Finally, it was confirmed that these protocols could be extended to the hydrazine derivative, 4-methylpiperazin-1-amine (0.3 mol% Pd, **3-62**), and the secondary alkylamine, morpholine (0.3 mol% Pd, **3-63**) as coupling partners. Collectively, these results further exemplify the broadly useful nature of the [Pd(cinnamyl)Cl]$_2$/BippyPhos catalyst system in BHA chemistry involving commonly encountered primary and secondary amine reaction partners, and bring to light the preference of this catalyst system for smaller, more nucleophilic primary amines over less nucleophilic primary arylamines, as well as secondary alkylamines.

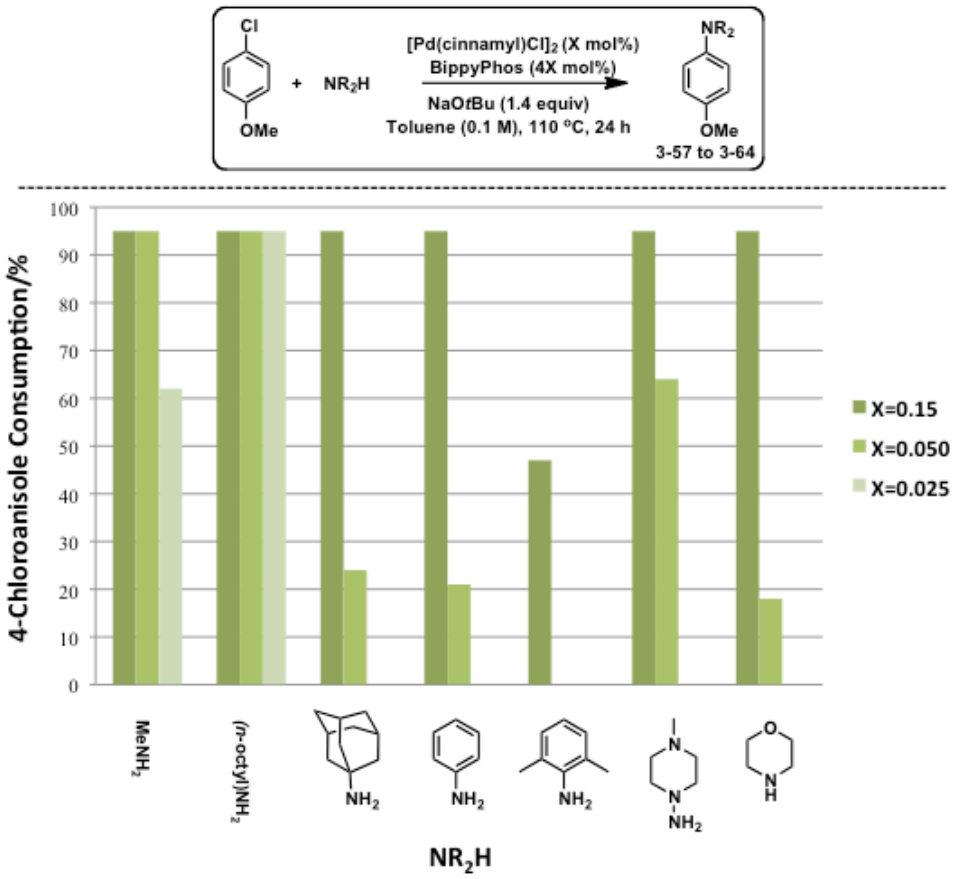


Figure 3–10. [Pd(cinnamyl)Cl]$_2$/BippyPhos catalyzed cross-coupling of primary and secondary amines with 4-chloroanisole at low catalyst loadings. Conversions were determined on the basis of GC analysis of reaction mixtures. A GC calibration curve was generated with 4-chloroanisole using the internal standard calibration method with dodecane as an internal standard. Product identity was determined on the basis of retention time comparison with authentic product samples.

To further demonstrate the substrate preferences of the Pd(cinnamyl)Cl]$_2$/BippyPhos catalyst system, a set of amine arylation competition experiments were carried out using chlorobenzene as the aryl halide (Figure 3–11).

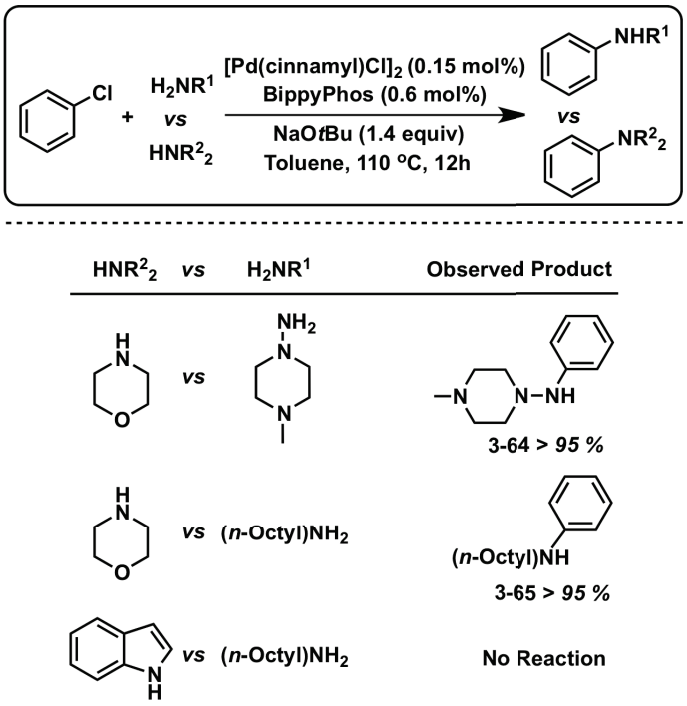


Figure 3–11. Application of the [Pd(cinnamyl)Cl]$_2$/BippyPhos catalyst system in amine competition experiments. Conversions were determined on the basis of GC analysis of reaction mixtures. A GC calibration curve was generated with chlorobenzene using the internal standard calibration method with dodecane as an internal standard. Product identity was determined on the basis of retention time comparison with authentic product samples.

Indeed, under the conditions outlined in Figure 3–11, the catalyst system preferentially cross-coupled the primary amines 4-methylpiperazin-1-amine (**3-64)** or *n*-octylamine (**3-64**) over morpholine, despite the fact that morpholine had proven to be a competent substrate in this chemistry (Figure 3–10). Interestingly, when employing *n*-octylamine and indole as the competing NH-containing substrates, no conversion of chlorobenzene was observed. Evidently indole acts a catalyst inhibitor at the low loadings employed, effectively shutting down the otherwise feasible *n*-octylamine arylation reaction. This latter phenomenon is consistent with the observation that higher loadings of [Pd(cinnamyl)Cl]$_2$/BippyPhos (1 mol%/4 mol%) are needed in order to promote the efficient cross-coupling of chlorobenzene and indole (**3-13**, Figure 3–6).

3.2.7 Utilizing Bippyphos in the Chemoselective Arylation of Diamines

The many difficulties associated with chemoselective palladium-catalyzed transformations have been described in the literature.[175] Among these, the identification

of highly effective catalysts for BHA that are capable of chemoselectively arylating diamine substrates featuring two different and potentially competitive NH moieties remains a persistent challenge – one that has received relatively little attention in the chemical literature.[49,55,176-185] Given the distinct preference exhibited by the [Pd(cinnamyl)Cl]$_2$/BippyPhos catalyst system in the low catalyst loading (Figure 3–10) and amine competition experiments (Figure 3–11) for relatively small, nucleophilic primary amines, it was envisioned that this catalyst system should be capable of chemoselectively arylating appropriate diamine substrates.

It was pleasing to observe that the [Pd(cinnamyl)Cl]$_2$/BippyPhos catalyst system could indeed be applied successfully in such chemoselective transformations (Figure 3–12), affording a number of structurally varied monoarylated diamine products in high isolated yields (73-93 %, **3-66**–**3-77**). In keeping with the previously observed trends, the selective monoarylation of the primary alkylamine moiety in N^1-phenylethane-1,2-diamine was achieved with a range of hindered or unhindered (hetero)aryl chlorides featuring electron-donating or withdrawing groups (**3-66**–**3-70**).

For proof-of-principle, the synthesis of **3-67** was reexamined under air, and separately using phenyl tosylate as an aryl pseudohalide coupling partner; in both cases only modest decreases in yield were observed. While the ability of the [Pd(cinnamyl)Cl]$_2$/BippyPhos catalyst system to arylate *n*-octylamine is inhibited in the presence of indole at the 1 mol% Pd loading level (Figure 3–11), at higher catalyst loadings (5 mol% Pd, 10 mol% BippyPhos) the presence of an indole moiety within a diamine is accommodated, as evidenced by the selective monoarylation of the primary amine fragment in tryptamine (**3-71**).

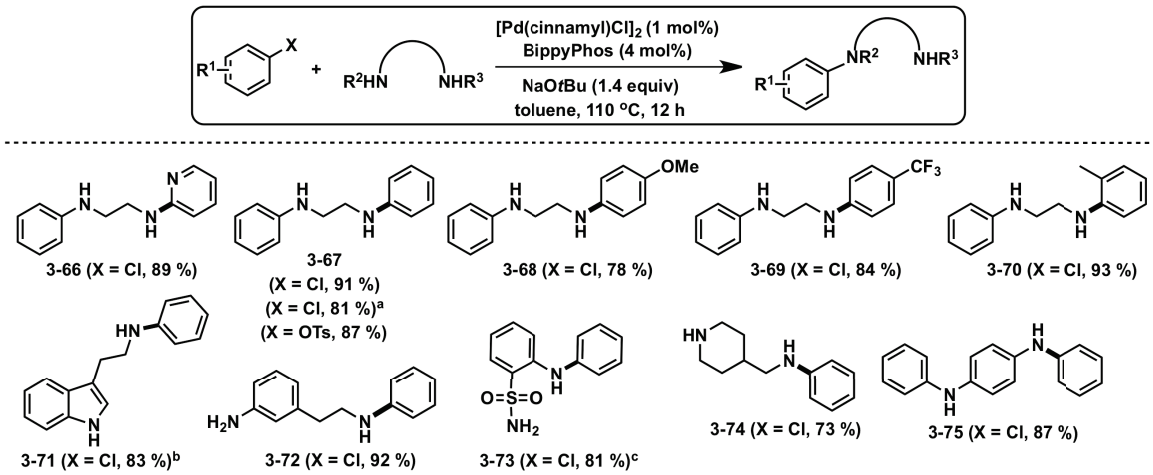


Figure 3–12. Scope of $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyzed chemoselective monoarylation of diamine substrates (isolated yields). [a]Experiment was conducted under air. [b]$[Pd(cinnamyl)Cl]_2$/BippyPhos (5 mol%/10 mol%) [c]K_2CO_3 (1.5 equiv), 1,4-Dioxane, 90 ˚C.

Furthermore, the preferential arylation of the primary alkylamine moiety could also be achieved in diamine substrates featuring competing primary arylamine (**3-72**) and secondary cyclic dialkylamine (**3-74**) fragments. Despite the preferential arylation of primary alkylamines over arylamines that was established for this catalyst system (Figure 3–10), primary arylamine fragments were selectively monoarylated in diamine substrates featuring contending sulfonamide (**3-73**) and secondary arylamine (**3-75**) functionalities. In the case of **3-73**, further support for the spectroscopic identification of the product was obtained by use of single-crystal X-ray diffraction techniques. It is worth noting that similar NH-substrate selectivity profiles to that which was demonstrated herein for the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system have also been described for palladium catalysts supported by Mor-DalPhos[55] and BrettPhos[181,182,186] (see Figure 1–5 for ligand structures).

3.2.8 Investigation Into the Binding Mode of BippyPhos

Inspired by the broadly useful nature of the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system in the BHA of (hetero)aryl (pseduo)halides as demonstrated herein, investigations into understanding how BippyPhos binds to palladium were performed. Perhaps surprisingly, while BippyPhos has proven useful in a number of palladium-catalyzed transformations (Section 3.2.2), the palladium coordination chemistry of this ligand

remained unexplored. It was observed that treatment of BippyPhos with [Pd(cod)Cl_2] in methylene chloride at 24 °C over the course of 1 h affords the crystallographically characterized [(κ^2-*P*,*C*-BippyPhos)PdCl_2] complex (**C1**) as an orange solid in 84 % isolated yield (Figure 3–13).

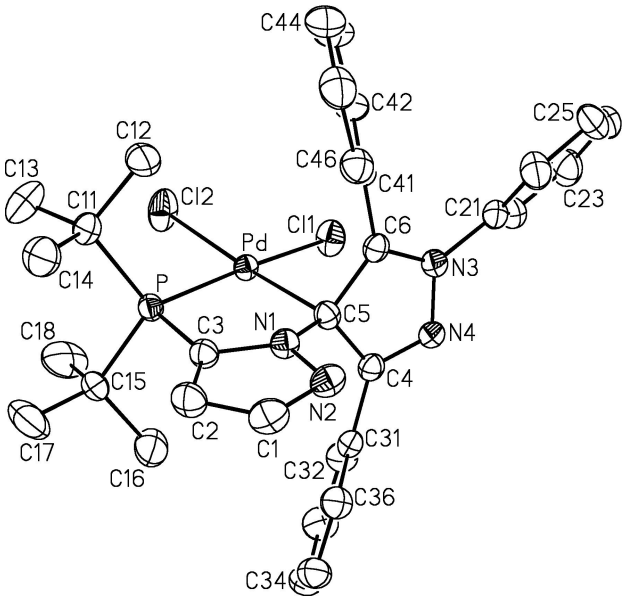


Figure 3–13. ORTEP diagram of [(κ^2-*P*,*C*-BippyPhos)PdCl_2] (**C1**) shown with 50% displacement ellipsoids; all hydrogen atoms have been omitted for clarity. Selected interatomic distances (Å): Pd-Cl1 2.3443(5); Pd-Cl2 2.3020(6); Pd-P 2.2629(5); Pd-C5 2.220(2).

Palladium is coordinated in a κ^2-*P*,*C*-bidentate fashion to BippyPhos in **C1** via phosphorus and the *ipso* carbon of the lower pyrazole ring. The observation that the Pd-Cl1 is longer than the corresponding Pd-Cl2 distance is in keeping with the anticipated stronger *trans*-directing ability of phosphorus relative to what would be expected to be a comparatively weak Pd-C5 (*ipso*) interaction. The κ^2-*P*,*C* bonding motif in **C1** is reminiscent of that observed within analogous Pd^{II} complexes of Buchwald's family of biarylphosphine ligands.[35] The denticity displayed by BippyPhos in Figure 3–13 demonstrates that it is at least capable of binding to palladium in a bidentate fashion during catalysis.

3.3 Summary and Conclusions

In summary, the results presented herein establish the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system as accommodating the largest scope of NH-containing substrates in Buchwald-Hartwig amination (BHA) reported to date for a single Pd/ligand catalyst system. Utilizing this catalyst system in the cross-coupling of functionalized (hetero)aryl halides, the previously known reactivity profile for Pd/BippyPhos catalysts[63,64,149-154] has been expanded signifficantly to now include the sterically/electronically varied and challenging NH-containing substrates ammonia, hydrazine, indole, amides, and sulfonamides (see Figure 1–10 for a graphical summary).

During the course of this research, it was established that the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system exhibits the broadest demonstrated substrate scope for metal-catalyzed cross-coupling of (hetero)aryl chlorides with NH-indoles reported thus far in the literature. Furthermore, the broadly useful nature of the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system was exploited in the development of a novel and versatile one-pot, two-step synthesis of *N*-aryl indoles and related heterocyclic derivatives involving three sequential and selective carbon-nitrogen bond-forming steps starting from ammonia. Through a series of low catalyst loading and amine competition experiments, a clear catalyst preference for smaller, more nucleophilic primary amines coupling partners was delineated and subsequently exploited in the chemoselective monoarylation of a range of substrates featuring two distinct and potentially competitive NH moieties. Throughout, proof-of-principle experiments confirmed the ability of the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system to operate under air. Also reported herein is the first crystallographically characterized (BippyPhos)Pd^{II} complex, which confirms the ability of this useful ligand to adopt a bidentate binding motif in a manner similar to Buchwald's biarylphosphine ligand class.

While not a "universal" catalyst for BHA, the unprecedented breadth and depth of scope established herein for the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system in terms of the NH-containing coupling partner offers an important practical advance to the many users of this ubiquitous carbon-nitrogen bond-forming reaction. In particular, the establishment of a single and reliable "first-choice" for use in addressing the diversity of challenging BHA applications that are faced by synthetic chemists is certain to increase

the accessibility and adoptability of the methodology for non-specialists in both academia and industry.

3.4 EXPERIMENTAL SECTION

3.4.1 General Considerations

All reactions were set up inside a dinitrogen-filled, inert atmosphere glovebox (unless otherwise indicated) and isolated under standard benchtop conditions. Toluene and methylene chloride used in the glovebox were deoxygenated by purging with dinitrogen followed by passage through a double column solvent purification system equipped either with one alumina-packed column and one column packed with copper-Q5 reactant (toluene), or two alumina-packed columns (methylene chloride). 1,4-Dioxane and diethyl ether were dried over Na/benzophenone followed by distillation under an atmosphere of dinitrogen. *tert*-Butanol was dried over CaH_2 followed by distillation under an atmosphere of dinitrogen. All solvents used within the glovebox were stored over activated 4 Å molecular sieves. Me-DalPhos,[59] Mor-DalPhos,[56] and $[Pd(cinnamyl)Cl]_2$[129] were prepared according to literature procedures. The *ortho*-alkynylhaloarene substrates were prepared using literature synthetic protocols involving Sonogashira reactions of aryl iodides[132,133] or bromides[134] with the appropriate terminal alkyne precursors. All other reagents, solvents and materials were used as received from commercial sources. Flash column chromatography was performed on silica gel (SiliaFlash P60, Silicycle) or 150 mesh Brockmann III activated, neutral alumina oxide, as indicated. Gas chromatography (GC) data were obtained on a Shimadzu GC-2014 equipped with a SGE BP-5 30 m, 0.25 mm I.D. column. All ^{1}H NMR (500 MHz or 300 MHz) and ^{13}C NMR (125.8 MHz or 75.4 MHz) spectra were recorded at 300 K. Chemical shifts are expressed in parts per million (ppm) using the solvent signals $CDCl_3$ (^{1}H 7.26 ppm, ^{13}C 77.36 ppm) or DMSO-*d6* (^{1}H 2.50 ppm, ^{13}C 39.52 ppm) as internal references. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet. All coupling constants (*J*) are reported in Hertz (Hz). In some cases fewer than expected independent carbon 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). Elemental analyses were performed by Midwest Microlab, LLC, Indianapolis, IN (USA). Special thanks is given to Dr. Sarah Crawford who performed the initial ligand screen in Section 3.2.1 and the cross-coupling reactions employing hydrazine (Section 3.2.3), amides and sulfonamides (Section 3.2.5).

3.4.2 Procedure for Commercial Ligand Screening

GC analysis of reaction aliquots was used to determine all product yields and conversions. Yields and conversions were measured relative to the dodecane internal standard, based on calibrations generated from analytically pure samples of the products and starting materials.

Toluene Catalyst Stock Solution: $[Pd(cinnamyl)Cl]_2$ (7.2 mg, 0.015 mmol), ligand (0.06 mmol) and 3 mL of toluene were added to a oven dried vial equipped with a stir bar and stirred until dissolution was complete. The resulting catalyst stock solution was used immediately.

1,4-Dioxane Catalyst Stock Solution: $[Pd(cinnamyl)Cl]_2$ (4.8 mg, 0.010 mmol), ligand (0.04 mmol) and 2 mL of 1,4-dioxane were added to a oven dried vial equipped with a stir bar and stirred until dissolution was complete. The resulting catalyst stock solution was used immediately.

Cross-Coupling of Chlorobenzene and Amines: A 0.5 mL aliquot of the toluene stock solution was added to a vial containing NaO*t*Bu (33.6 mg, 1.4 equiv) and stirred 5 min. Dodecane (40.9 mL, 0.18 mmol) was added followed by chlorobenzene (25.3 μL, 25 mmol, 1.0 equiv) and then 1˚ or 2˚ amine (0.30 mmol, 1.2 equiv, [aniline, 27.3 μL, *n*-octylamine, 49.5 μL; morpholine, 26.2 μL]) was added and the vial was sealed with a cap containing a PTFE septum and removed from the glovebox. The reaction mixture was heated to 110 ˚C with stirring for 18 h. An aliquot was sampled (0.1 to 0.25 mL), filtered through SiO_2 into a GC vial, diluted with methylene chloride to approximately 1 mL and analyzed by GC.

Cross-Coupling of Chlorobenzene and Indole: A 0.5 mL aliquot of the toluene stock solution was added to a vial containing NaO*t*Bu (33.6 mg, 1.4 equiv) and indole (30.6 mg, 0.26 mmol, 1.05 equiv). Dodecane (40.9 μL, 0.18 mmol) was added followed by chlorobenzene (25.3 μL, 0.25 mmol, 1.0 equiv) and the vial was sealed with a cap

containing a PTFE septum and removed from the glovebox. The reaction mixture was heated at 110 ˚C with stirring for 18 h. An aliquot was sampled (0.1 to 0.25 mL), filtered through SiO_2 into a GC vial, diluted with methylene chloride to approximately 1 mL and analyzed by GC.

Cross-Coupling of Chlorobenzene and Ammonia: A 0.5 mL aliquot of the 1,4-dioxane stock solution was added to a vial containing NaO*t*Bu (48.1 mg, 2.0 equiv) and stirred 5 min. Dodecane (40.9 μL, 0.18 mmol) was added followed by chlorobenzene (25.3 μL, 0.25 mmol, 1.0 equiv) and then 1,4-dioxane (0.5 mL) and the vial was sealed with a cap containing a PTFE septum and removed from the glovebox. A 0.5 M solution of NH_3 in 1,4-dioxane (1.5 mL, 3 equiv) was added and the reaction mixture was heated to 90 ˚C with stirring for 18 h. An aliquot was sampled (0.1 to 0.25 mL), filtered through SiO_2 into a GC vial, diluted with methylene chloride to approximately 1 mL and analyzed by GC.

3.4.3 General Catalytic Protocols

General Catalytic Protocol for the Arylation of Ammonia with Aryl Chlorides (GP1A):

To an oven dried screw-capped vial was added a stir bar, [Pd(cinnamyl)Cl]2 (2.6 mg , 0.005 mmol, 1 mol%), BippyPhos (10.1 mg, 0.02 mmol, 4 mol%), and 2 mL of 1,4-dioxane. The resulting mixture was then stirred for approximately 2 minutes at which point NaOtBu (67.3 mg, 0.7 mmol, 1.4 equiv) was added. The mixture was then stirred briefly followed by the addition of the aryl halide (0.5 mmol). The vial was sealed with a cap containing a PTFE septum, removed from the glovebox and 3 mL of a 0.5 M solution of ammonia in 1,4-dioxane was added via syringe, resulting in a 0.1 M reaction mixture in aryl halide. The vial was then placed in a temperature-controlled aluminum heating block set at 110 °C and stirred vigorously. Reaction progress was monitored by use of TLC or GC methods and after complete consumption of the aryl halide (3-6 h), the reaction mixture was cooled and filtered through a short plug of silica on Celite and washed with 15 mL of methylene chloride. After concentrating the so-formed mixture under reduced pressure, the crude product was purified by column chromatography.

General Catalytic Protocol for the Arylation of Hydrazine with Aryl Chlorides (GP1B):

$[Pd(cinnamyl)Cl]_2$ (2.5-5 mol%), BippyPhos (7.5-15 mol% ligand) and NaO*t*Bu (2.0 equiv) were added to an oven dried screw-capped vial and stirred in toluene for 5 min, after which the aryl chloride substrate (1 equiv) was added. The vial was sealed with a cap containing a PTFE septum and removed from the glovebox and hydrazine hydrate (2.0 equiv) was added. The reaction was placed in a temperature-controlled aluminum heating block set at 110 ˚C for 1 h, during which time a black precipitate formed. The vial was removed from the heating block, left to cool to ambient temperature and then filtered through a short plug of neutral alumina (Brockmann III activated), which was washed with 50:1 methylene chloride:methanol. The resulting filtrate was concentrated, transferred to a vial and 2,4-pentanedione (0.25 mL) was added. The vial was sealed with a cap containing a PTFE septum and placed in a temperature-controlled aluminum-heating block set at 110 ˚C for 3-18 h. The vial was removed from the heating block, left to cool to ambient temperature and purified by column chromatography.

General Catalytic Procedure for the Arylation of N-H Heterocycles and Secondary Amines with Aryl Chlorides and Tosylates (GP2):

To an oven dried screw-capped vial was added a stir bar, $[Pd(cinnamyl)Cl]_2$ (2.6 mg , 0.005 mmol, 1 mol%), BippyPhos (10.1 mg, 0.02 mmol, 4 mol%), and 1 mL (0.5 M [ArX]) of toluene. The resulting mixture was then stirred for approximately 2 minutes at which point NaO*t*Bu (67.3 mg, 0.7 mmol, 1.4 equiv) was added. The mixture was then stirred briefly followed by the addition of the aryl (pseudo)halide (0.5 mmol) and then the amine (0.53 mmol, 1.05 equiv). The vial was sealed with a cap containing a PTFE septum, removed from the glovebox and placed in a temperature-controlled aluminum heating block set at 110 °C and stirred vigorously. Reaction progress was monitored by use of TLC or GC methods and after complete consumption of the aryl halide (8-18 h), the reaction mixture was cooled and filtered through a short plug of silica on Celite and washed with 15 mL of methylene chloride. After concentrating the so-formed mixture under reduced pressure, the crude product was purified by column chromatography.

General Catalytic Procedure for Two-Step, One-Pot Synthesis of Substituted Indoles from Ammonia (GP3):

Method A: *Step 1:* To an oven dried screw-capped vial was added a stir bar, $[Pd(cinnamyl)Cl]_2$ (2.6 mg, 0.005 mmol, 1 mol%), BippyPhos (10.1 mg, 0.02 mmol, 4 mol%), and 1 mL of 1,4-dioxane. The resulting mixture was then stirred for approximately 2 minutes at which point KO*t*Bu (168.3 mg, 1.5 mmol, 3 equiv) was added. The mixture was then stirred briefly followed by the addition of the 2-haloalkynylarene (0.5 mmol) in 2 x 0.5 mL portions of 1,4-dioxane. The vial was sealed with a cap containing a PTFE septum, removed from the glovebox and 3 mL of a 0.5 M solution of ammonia in 1,4-dioxane was added via syringe, resulting in a 0.1 M reaction mixture in 2-haloalkynlarene. The vial was then placed in a temperature-controlled aluminum heating block set at 110 °C and stirred vigorously. Reaction progress was monitored by use of TLC or GC methods and after complete consumption of the 2-haloalkynylarene (8 h), the reaction mixture was cooled, concentrated under vacuum and brought back into the glovebox.

Step 2: To the resulting vial from *Step 1* was added $[Pd(cinnamyl)Cl]_2$ (2.6 mg , 0.005 mmol, 1 mol%), BippyPhos (10.1 mg, 0.02 mmol, 4 mol%), and 1 mL (0.5 M [ArX]) of toluene. The resulting mixture was then stirred for approximately 2 minutes at which point NaO*t*Bu (67.3 mg, 0.7 mmol, 1.4 equiv) was added. The mixture was then stirred briefly followed by the addition of the aryl halide (0.5 mmol, 1 equiv). The vial was sealed with a cap containing a PTFE septum, removed from the glovebox and placed in a temperature-controlled aluminum heating block set at 110 °C and stirred vigorously. Reaction progress was monitored by use of TLC or GC methods and after complete consumption of the aryl halide (12 h), the reaction mixture was cooled and filtered through a short plug of silica on Celite and washed with 15 mL of methylene chloride. After concentrating the so-formed mixture under reduced pressure, the crude product was purified by column chromatography.

Method B:

Step 1: To an oven dried screw-capped vial was added a stir bar, $[Pd(cinnamyl)Cl]_2$ (2.6 mg, 0.005 mmol, 1 mol%), BippyPhos (10.1 mg, 0.02 mmol, 4 mol%), and 2 mL of 1,4-dioxane. The resulting mixture was then stirred for approximately 2 minutes at which

point NaO*t*Bu (67.3 mg, 0.7 mmol, 1.4 equiv) was added. The mixture was then stirred briefly followed by the addition of the aryl halide (0.5 mmol). The vial was sealed with a cap containing a PTFE septum, removed from the glovebox and 3 mL of a 0.5 M solution of ammonia in 1,4-dioxane was added via syringe, resulting in a 0.1 M reaction mixture in aryl halide. The vial was then placed in a temperature-controlled aluminum heating block set at 110 °C and stirred vigorously. Reaction progress was monitored by use of TLC or GC methods and after complete consumption of the aryl halide (3-6 h), the reaction mixture was cooled, concentrated under vacuum and brought back into the glovebox.

Step 2: To the resulting vial from *Step 1* was added $[Pd(cinnamyl)Cl]_2$ (2.6 mg , 0.005 mmol, 1 mol%), BippyPhos (10.1 mg, 0.02 mmol, 4 mol%), and 1 mL of toluene. The resulting mixture was then stirred for approximately 2 minutes at which point KO*t*Bu (168.3 mg, 1.5 mmol, 3 equiv) was added. The mixture was then stirred briefly followed by the addition of the 2-haloalkynylarene (0.5 mmol, 1 equiv) in 2 x 0.5 mL portions of toluene, resulting in a 0.25 M reaction mixture in 2-haloalkynylarene. The vial was sealed with a cap containing a PTFE septum, removed from the glovebox and placed in a temperature-controlled aluminum heating block set at 110 °C and stirred vigorously. Reaction progress was monitored by use of TLC or GC methods and after complete consumption of the aryl halide (8 h), the reaction mixture was cooled and filtered through a short plug of silica on Celite and washed with 15 mL of methylene chloride. After concentrating the so-formed mixture under reduced pressure, the crude product was purified by column chromatography.

****Note: For the experiment conducted under air,* ***GP3****,* ***Method B*** *was followed. However, when the vial was brought outside of the glovebox it was opened to air for 1 minute and then recapped.*

General Catalytic Protocol for the Arylation of Amides and Sulfonamides with Aryl Chlorides (GP4):

$[Pd(cinnamyl)Cl]_2$ (0.50-1.25 mol%), BippyPhos, (2-5 mol%), base (K_2CO_3 *or* K_3PO_4, 0.75 mmol), solvent (1,4-dioxane *or t*BuOH, 1 mL), amide (0.50 mmol) and a stir-bar were added to an oven dried screw-capped vial. Aryl halide (0.50 mmol) was then added and the vial was sealed with a cap containing a PTFE septum, removed from the

glovebox and placed in a temperature-controlled aluminum heating block set at 90 ˚C for 18 h. The vial was removed from the heating block and left to cool to ambient temperature. The crude reaction mixture was dissolved in ethyl acetate (10 mL) and poured onto brine (10 mL). The layers were separated and the organic layer was extracted with ethyl acetate (2 x 10 mL). The organic fractions were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography.

General Catalytic Protocol for Low Catalyst Loading Experiments (GP5):

A 2 mL toluene stock solution was prepared containing $[Pd(cinnamyl)Cl]_2$ (5 mg , 0.010 mmol) and BippyPhos (19.2 mg, 0.04 mmol). From this solution, either 26 μL (0.025 mol% $[Pd(cinnamyl)Cl]_2$, 0.1 mol% BippyPhos), 52 μL (0.05 mol% $[Pd(cinnamyl)Cl]_2$, 0.2 mol% BippyPhos), 156 μL (0.15 mol% $[Pd(cinnamyl)Cl]_2$, 0.6 mol% BippyPhos), or 260 μL (0.25 mol% $[Pd(cinnamyl)Cl]_2$, 1 mol% BippyPhos) was added to a vial containing 4-chloroanisole (71.2 mg, 0.5 mmol), amine (0.55 mmol, 1.1 equiv), and NaO*t*Bu (67.3 mg, 0.7 mmol, 1.4 equiv). The vial was then diluted to 1 mL (0.5 M [ArX]), sealed with a cap containing a PTFE septum, removed from the glovebox and placed in a temperature-controlled aluminum heating block set at 110 °C and stirred vigorously for 12 h. GC conversions and yields are given on the basis of gas chromatography experiments, whereby the data was corrected by calibration using dodecane as an internal standard and product identity was confirmed by comparison with authentic samples.[59,187-192]

****Note: When employing methylamine **GP5** was followed; however, it was added outside of the glovebox via syringe as a 2.0 M solution in tetrahydrofuran (1.5 mmol, 3 equiv).*

General Catalytic Protocol for Competition Experiments (GP6):

A 2 mL toluene stock solution was prepared containing $[Pd(cinnamyl)Cl]_2$ (5 mg , 0.010 mmol) and BippyPhos (19.2 mg, 0.04 mmol). From this solution, 156 μL (0.15 mol% $[Pd(cinnamyl)Cl]_2$, 0.6 mol% BippyPhos) was added to a vial containing chlorobenzene (62.2 μL, 0.5 mmol), the two competing amines (0.55 mmol of each, 1.1 equiv of each), and NaO*t*Bu (67.3 mg, 0.7 mmol, 1.4 equiv). The vial was then diluted to 1 mL (0.5 M [ArX]), sealed with a cap containing a PTFE septum, removed from the glovebox and

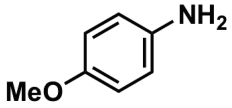
placed in a temperature-controlled aluminum heating block set at 110 °C and stirred vigorously for 12 h. GC conversions and yields are given on the basis of gas chromatography experiments, whereby the data was corrected by calibration using dodecane as an internal standard and product identity was confirmed by comparison with authentic samples.[188,190,193,194]

General Catalytic Protocol for Chemoselective Arylation of Diamines (GP7):

To an oven dried screw-capped vial was added a stir bar, $[Pd(cinnamyl)Cl]_2$ (2.6 mg, 0.005 mmol, 1 mol%), BippyPhos (10.1 mg, 0.02 mmol, 4 mol%), and 1 mL (0.5 M [ArX]) of toluene. The resulting mixture was then stirred for approximately 2 minutes at which point NaO*t*Bu (67.3 mg, 0.7 mmol, 1.4 equiv) was added. The mixture was then stirred briefly followed by the addition of the aryl (pseudo)halide (0.5 mmol) and then the amine (0.5 mmol, 1 equiv). The vial was sealed with a cap containing a PTFE septum, removed from the glovebox and placed in a temperature-controlled aluminum heating block set at 110 °C and stirred vigorously. Reaction progress was monitored by use of TLC or GC methods and after complete consumption of the aryl halide (8-12 h), the reaction mixture was cooled and filtered through a short plug of silica on Celite and washed with 15 mL of methylene chloride. After concentrating the so-formed mixture under reduced pressure, the crude product was purified by column chromatography or by washing with cold hexanes (3 x 5 mL).

****Note: For the experiment conducted under air, **GP7** was followed. However, when the vial was brought outside of the glovebox it was opened to air for 1 minute and then recapped.*

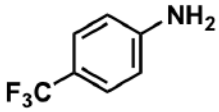
3.4.4 Synthesis and Characterization of Isolated Reaction Products



(3-1) 4-Methoxy-phenylamine.

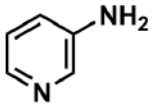
The title compound was synthesized according to **GP1A** and purified by flash column chromatography on silica gel using 20:1→10:1 hexanes:ethyl acetate in 83 % yield (51 mg, 0.42 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.79 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H), 3.47 (br s, 2H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 152.9,

140.1, 116.5, 114.9, 55.8. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[195]



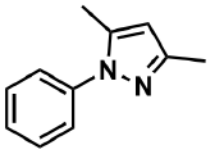
(3-2) 4-Trifluoromethyl-phenylamine.

The title compound was synthesized according to **GP1A** and purified by flash column chromatography on silica gel using 20:1→10:1 hexanes:ethyl acetate in 62 % yield (50 mg, 0.31 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.4 Hz, 2H), 3.98 (br s, 2H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 149.6, 126.8 (d, J_{CF} = 4 Hz), 125.1 (q, J_{CF} = 270 Hz), 120.2 (q, J_{CF} = 31 Hz), 114.4. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[196]



(3-3) Pyridin-3-ylamine.

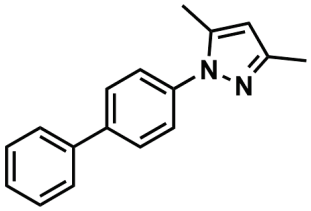
The title compound was synthesized according to **GP1A** and purified by flash column chromatography on silica gel using ethyl acetate in 72 % yield (34 mg, 0.36 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 1H), 8.01 (s, 1H), 7.07-6.95 (m, 2H), 3.70 (br s, 2H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 142.6, 139.9, 137.5, 123.7, 121.4. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[197]



(3-4) 3,5-Dimethyl-1-phenyl-1*H*-pyrazole.

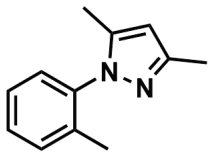
The title compound was synthesized from chlorobenzene, according to **GP1B**, and purified by flash column chromatography on silica gel using 1:4 ethyl acetate:hexanes in a 93 % isolated yield (80 mg, 0.46 mmol) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46-7.41 (m, 4H), 7.35-7.32 (m, 1H), 5.99 (s, 1H), 2.30 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 149.1, 140.0, 139.5, 129.1, 127.3, 124.9, 107.0, 13.6, 12.5;

m/z ESI$^+$ found 173.1077 $[M+H]^+$ calculated for $C_{11}H_{13}N_2$ 173.1073. Spectral data are in close agreement with previously reported ^{13}C NMR characterization data for the title compound.[198]



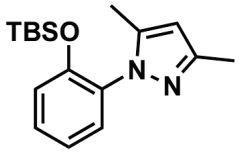
(3-5) 1-(Biphenyl-4-yl)-3,5-dimethyl-1*H*-pyrazole.

The title compound was synthesized according to **GP1B**, and purified by flash column chromatography on silica gel using 1:4 ethyl acetate:hexanes in a 93 % isolated yield (116 mg, 0.46 mmol) as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 7.5 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 6.03 (s, 1H), 2.36 (s, 3H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 149.2, 140.3, 140.1, 139.5, 139.2, 129.0, 127.7, 127.6, 127.2, 125.0, 107.2, 13.7, 12.6; *m/z* ESI$^+$ found 249.1396 $[M+H]^+$ calculated for $C_{17}H_{17}N_2$ 249.1386.



(3-6) 3,5-Dimethyl-1-*o*-tolyl-1*H*-pyrazole.

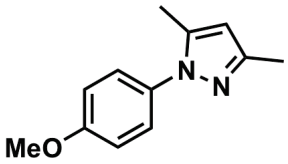
The title compound was synthesized according to **GP1B**, and purified by flash column chromatography on silica gel using 2:3 ethyl acetate:hexanes in a 77 % isolated yield (72 mg, 0.39 mmol) as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.62-7.49 (m, 4H), 6.24 (s, 1H), 2.57 (s, 3H), 2.33 (s, 6H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 148.6, 140.3, 138.9, 136.4, 130.9, 129.0, 128.1, 126.6, 105.1, 17.4, 13.8, 11.4; *m/z* ESI$^+$ found 209.1045 $[M+Na]^+$ calculated for $C_{12}H_{14}N_2Na$ 209.1049.



(3-7) 1-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-3,5-dimethyl-1*H*-pyrazole.

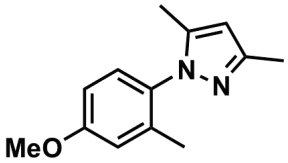
The title compound was synthesized according to **GP1B**, and purified by flash column chromatography on silica gel using 1:4 ethyl acetate:hexanes in a 60 % isolated yield (90

mg, 0.30 mmol) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (t, *J* = 8.5 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.89 (s, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 5.97 (s, 1H), 2.29 (s, 6H), 0.98 (s, 9H), 0.21 (s, 6H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 156.2, 149.0, 141.1, 139.5, 129.8, 119.1, 118.0, 116.9, 107.0, 25.8, 18.3, 13.7, 12.6, 4.3; *m/z* ESI$^+$ found 303.1885 $[M+H]^+$ calculated for $C_{17}H_{27}N_2OSi$ 303.1887.



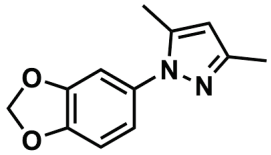
(3-8) 1-(4-Methoxyphenyl)-3,5-dimethyl-1*H*-pyrazole.

The title compound was synthesized according to **GP1B** and purified by flash column chromatography on silica gel using 1:4 ethyl acetate:hexanes in a 70 % isolated yield (70 mg, 0.35 mmol) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.29 (m, 2H), 6.95-6.92 (m, 2H), 5.95 (s, 1H), 3.82 (s, 3H), 2.27 (s, 3H), 2.22 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 158.8, 148.6, 139.5, 133.1, 126.4, 114.1, 106.3, 55.6, 13.6, 12.2; *m/z* ESI$^+$ found 225.1004 $[M+Na]^+$ calculated for $C_{12}H_{14}N_2NaO$ 225.0998. Spectral data are in close agreement with previously reported ^{13}C NMR characterization data for the title compound.[199]



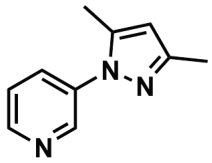
(3-9) 1-(4-Methoxy-2-methylphenyl)-3,5-dimethyl-1*H*-pyrazole.

The title compound was synthesized according to **GP1B**, and purified by flash column chromatography on silica gel using 1:4 ethyl acetate:hexanes in a 74 % isolated yield (80 mg, 0.46 mmol) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (s, 1H), 7.16 (dd, *J* = 4.0 Hz, *J* = 8.5 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 5.95 (s, 1H), 3.86 (s, 3H), 2.28 (s, 3H), 2.24 (s, 6H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 157.1, 148.5, 139.5, 132.7, 127.8, 127.6, 123.5, 109.8, 106.2, 55.7, 16.4, 13.7, 12.3; *m/z* ESI$^+$ found 217.1335 $[M+H]^+$ calculated for $C_{13}H_{17}N_2O$ 217.1335.



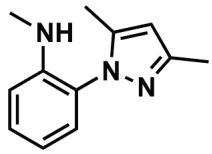
(3-10) 1-(Benzo[*d*][1,3]dioxol-5-yl)-3,5-dimethyl-1*H*-pyrazole.

The title compound was synthesized according to **GP1B**, and purified by flash column chromatography on silica gel using 2:3 ethyl acetate:hexanes in a 69 % isolated yield (75 mg, 0.35 mmol) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (s, 1H), 6.84 (s, 2H), 6.02 (s, 2H), 5.95 (s, 1H), 2.27 (s, 3H), 2.24 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 148.8, 148.0, 147.0, 139.6, 134.2, 118.8, 108.1, 106.9, 106.5, 101.8, 13.6, 12.3; *m/z* ESI$^+$ found 202.1345 $[M+H]^+$ calculated for $C_{12}H_{16}N_3$ 202.1339.



(3-11) 3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)pyridine.

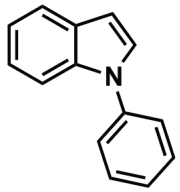
The title compound was synthesized according to **GP1B**, and purified by flash column chromatography on silica gel using 1:19 methanol:methylene chloride in a 46 % isolated yield (40 mg, 0.23 mmol) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.74 (d, *J* = 2.5 Hz, 1H), 8.58 (dd, *J* = 1.5 Hz, *J* = 4.8 Hz, 1H), 7.81 (ddd, *J* = 1.5 Hz, *J* = 2.5 Hz, *J* = 8.1 Hz, 1H), 7.40 (dd, *J* = 4.8 Hz, *J* = 8.1 Hz, 1H), 6.04 (s, 1H), 2.34 (s, 3H), 2.30 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 150.3, 148.3, 145.6, 139.9, 136.7, 131.9, 123.8, 108.0, 13.7, 12.5; *m/z* ESI$^+$ found 217.0982 $[M+H]^+$ calculated for $C_{12}H_{13}N_3O_2$ 217.0972.



(3-12) 2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-*N*-methylaniline.

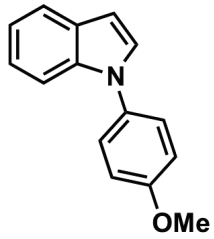
The title compound was synthesized according to **GP1B**, and purified by flash column chromatography on silica gel using 1:19 methanol:methylene chloride in a 82 % isolated yield (83 mg, 0.41 mmol) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (t, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.66 (s, 1H), 6.58 (dd, *J* = 2.0 Hz, *J* = 8.5 Hz,

1H), 3.85 (s, 1H), 2.85 (s, 3H), 2.29 (s, 6H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 150.2, 148.7, 141.1, 139.5, 129.5, 113.6, 111.7, 108.9, 106.7, 30.8, 13.7, 12.6; *m/z* ESI^+ found 196.0852 $[M+Na]^+$ calculated for $C_{10}H_{11}N_3Na$ 196.0845.

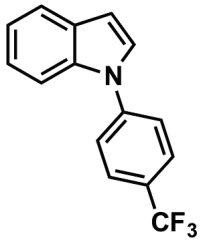


(3-13) 1-Phenyl-1*H*-indole.

The title compound was synthesized according to **GP2** and purified by flash column chromatography on silica gel using 20:1 hexanes:ethyl acetate in, when X = Cl, 88 % yield (85 mg, 0.44 mmol); when X = OTs, 83 % yield (80 mg, 0.42 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (m, 1H), 7.68 (m, 1H), 7.60-7.59 (m, 4H), 7.47-7.43 (m, 2H), 7.36-7.25 (m, 2H), 6.79 (dd, *J* = 5.4 Hz, *J* = 1.1 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 139.9, 136.0, 129.7, 129.4, 128.0, 126.5, 124.5, 122.5, 121.2, 120.5, 110.6, 103.7. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[194]

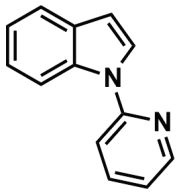


(3-14) 1-(4-Methoxy-phenyl)-1*H*-indole.The title compound was synthesized according to **GP2** and purified by flash column chromatography on silica gel using 20:1→10:1 hexanes:ethyl acetate in 71 % yield (79 mg, 0.36 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.48-7.45 (m, 2H), 7.35 (d, *J* = 3.2 Hz, 1H), 7.28 (m, 1H), 7.23 (m, 1H), 7.11-7.08 (m, 2H), 6.73 (d, *J* = 3.1 Hz, 1H), 3.94 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 158.4, 136.5, 133.0, 129.1, 128.5, 126.2, 122.3, 121.2, 120.3, 114.9, 110.6, 103.1, 55.8. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[124]



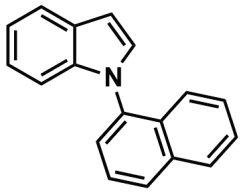
(3-15) 1-(4-Trifluoromethyl-phenyl)-1*H*-indole.

The title compound was synthesized according to **GP2** and purified by flash column chromatography on silica gel using 20:1→10:1 hexanes:ethyl acetate in 89 % yield (116 mg, 0.45 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85-7.83 (m, 2H), 7.77 (d, J = 7.8 Hz, 1H), 7.70-7.65 (m, 3H), 7.41 (d, J = 3.3 Hz, 1H), 7.34-7.26 (m, 2H), 6.80 (d, J = 3.3 Hz, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 143.3, 135.9, 130.2, 128.6 (q, J_{CF} = 32 Hz), 127.9, 127.4 (q, J_{CF} = 3 Hz), 124.5 (q, J_{CF}=256 Hz), 124.4, 123.4, 121.9, 121.5, 110.8, 105.4. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[143]



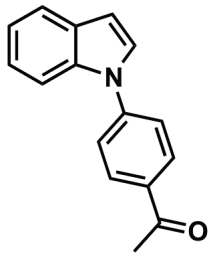
(3-16) 1-Pyridin-2-yl-1*H*-indole.

The title compound was synthesized according to **GP2** and purified by flash column chromatography on silica gel using 10:1 hexanes:ethyl acetate in 91 % yield (88 mg, 0.46 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (m, 1H), 8.30 (dd, J = 8.8 Hz, J = 0.9 Hz, 1H), 7.83-7.73 (m, 3H), 7.51 (m, 1H), 7.49 (m, 1H), 7.32 (m. 1H), 7.17 (m, 1H), 6.78 (dd, J = 3.8 Hz, J = 0.9 Hz, 1H); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 152.6, 149.0, 138.4, 135.2, 130.5, 126.0, 123.2, 121.3, 120.1, 114.5, 113.1, 110.6. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[200]



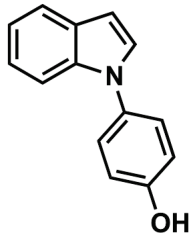
(3-17) 1-Naphthalen-1-yl-1*H*-indole.

The title compound was synthesized according to **GP2**, using $[Pd(cinnamyl)Cl]_2$ (5.2 mg, 0.01 mmol, 2 mol%), BippyPhos (20.2 mg, 0.04 mmol, 8 mol%), and purified by flash column chromatography on silica gel using 20:1→10:1 hexanes:ethyl acetate in 90 % yield (110 mg, 0.45 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06-8.02 (m, 2H), 7.86 (m, 1H), 7.66-7.56 (m, 4H), 7.51-7.44 (m, 2H), 7.32-7.20 (m, 2H), 7.14 (m, 1H), 6.88 (dd, *J* = 5.4 Hz, *J* = 1.3 Hz, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 138.1, 136.2, 134.5, 130.7, 129.9, 128.6, 128.4, 127.1, 126.8, 126.6, 125.6, 125.2, 123.5, 122.3, 121.0, 120.3, 111.0, 103.0. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[201]



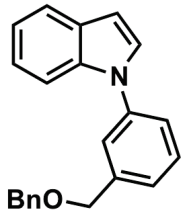
(3-19) 1-(4-Indol-1-yl-phenyl)-ethanone.

The title compound was synthesized according to **GP2**, using K_3PO_4 as the base, and purified by flash column chromatography on silica gel using 20:1→10:1 hexanes:ethyl acetate in 74 % yield (87 mg, 0.37 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (dt, *J* = 9.1 Hz, *J* = 2.5 Hz, 2H), 7.75-7.61 (m, 4H), 7.40 (d, *J* = 3.5 Hz, 1H), 7.33-7.22 (m, 2H), 6.77 (dd, *J* = 3.5 Hz, *J* = 0.8 Hz, 1H), 2.68 (s, 3H); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 196.9, 143.9, 135.5, 134.7, 130.1, 130.0, 127.4, 123.4, 123.0, 121.5, 121.1, 110.7, 105.2, 26.7. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[194]



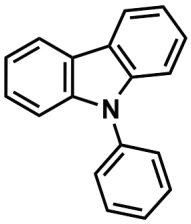
(3-19) 4-Indol-1-yl-phenol.

The title compound was synthesized according to **GP2** and purified by flash column chromatography on silica gel using 10:1→5:1 hexanes:ethyl acetate in 86 % yield (90 mg, 0.43 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 7.2 Hz, *J* = 2.0 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.42-7.37 (m, 2H), 7.32 (m, 1H), 7.26 (dt, *J* = 10.3 Hz, *J* = 1.5 Hz, 2H), 7.00-6.95 (m, 2H), 6.73 (d, *J* = 3.4 Hz, 1H), 5.51 (br s, 1H); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 154.3, 136.4, 133.0, 129.0, 128.4, 126.3, 126.0, 122.3, 121.1, 120.2, 116.6, 116.3, 110.5, 103.0. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.



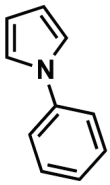
(3-20) 1-(3-Benzyloxymethyl-phenyl)-1*H*-indole.

The title compound was synthesized according to **GP2** and purified by flash column chromatography on silica gel using 50:1→20:1 hexanes:ethyl acetate in 87 % yield as light yellow oil (136 mg, 0.44 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.67 (s, 1H), 7.67 (t, *J* = 7.7 Hz, 1H) 7.57-7.43 (m, 8H), 7.39-7.32 (m, 2H), 6.83 (d, *J* = 3.1 Hz, 1H), 4.76 (s, 4H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 140.4, 140.1, 138.2, 135.9, 129.8, 129.5, 128.6, 128.1, 127.9, 125.7, 123.6, 123.5, 122.5, 121.3, 120.5, 110.7, 103.8, 72.6, 71.7; *m/z* ESI^{+} found 336.1357 $[M+Na]^{+}$ calculated for $C_{22}H_{19}NNaO$ 336.1359.



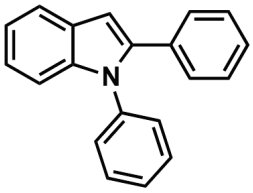
(3-21) 9-Phenyl-9*H*-carbazole.

The title compound was synthesized according to **GP2** and purified by flash column chromatography on silica gel using 50:1→20:1 hexanes:ethyl acetate in 88 % yield (107 mg, 0.44 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (dt, J = 8.1 Hz, J = 0.9 Hz, 2H), 7.70-7.65 (m, 4H), 7.58-7.49 (m, 5H), 7.44-7.39 (m, 2H); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 141.0, 137.9, 130.0, 127.5, 127.3, 126.1, 123.5, 120.4, 120.0, 109.9. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[202]



(3-22) 1-Phenyl-1H-pyrrole.

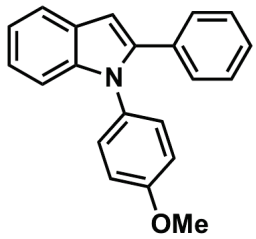
The title compound was synthesized according to **GP2** and purified by flash column chromatography on silica gel using 10:1 hexanes:ethyl acetate in 91 % yield (65 mg, 0.46 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.47 (m, 4H), 7.32 (m, 1H), 7.18 (s, 2H), 6.45 (s, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 140.9, 129.7, 125.8, 120.7, 119.5, 110.6. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[203]



(2-3) 1,2-Diphenyl-1*H*-indole.

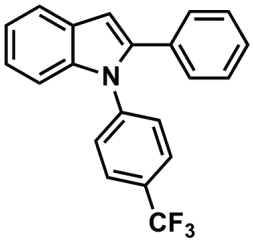
The title compound was synthesized according to **GP2** and purified by flash column chromatography on silica gel using 50:1→20:1 hexanes:ethyl acetate in 88 % yield (119 mg, 0.44 mmol). The title compound was also synthesized according to **GP3** and purified

by flash column chromatography on silica gel using 50:1→20:1 hexanes:ethyl acetate in, when employing **Method A** and in *Step 1.* X = Br, *Step 2.* X = Cl, 83 % yield (112 mg, 0.42 mmol); when employing **Method A** and in *Step 1.* X = Cl, *Step 2.* X = Cl, 76 % yield (102 mg, 0.38 mmol); when employing **Method B** and in *Step 1.* X = Cl, *Step 2.* X = Br, 85 % yield (114 mg, 0.43 mmol); when employing **Method B** and in *Step 1.* X = Cl, *Step 2.* X = Cl, 72 % yield (97 mg, 0.36 mmol). Please refer to Section 2.4.3 for characterization data of the title compound.



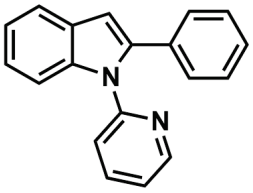
(3-23) 1-(4-Methoxy-phenyl)-2-phenyl-1*H*-indole.

The title compound was synthesized according to **GP2**, using $[Pd(cinnamyl)Cl]_2$ (5.2 mg, 0.01 mmol, 2 mol%), BippyPhos (20.2 mg, 0.04 mmol, 8 mol%), and purified by flash column chromatography on silica gel using 30:1→10:1 hexanes:ethyl acetate in 91 % yield (136 mg, 0.46 mmol). The title compound was also synthesized according to **GP3** and purified by flash column chromatography on silica gel using 30:1→10:1 hexanes:ethyl acetate in, when employing **Method A** and in *Step 1.* X = Cl, *Step 2.* X = Cl, 72 % yield (108 mg, 0.36 mmol); when employing **Method B** and in *Step 1.* X = Cl, *Step 2.* X = Cl, 68 % yield (102 mg, 0.34 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (m, 1H), 7.40-7.30 (m, 9H), 7.03-6.97 (m, 2H), 6.88 (s, 1H), 3.90 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 158.6, 141.0, 139.5, 132.7, 131.4, 129.2, 129.0, 128.2, 127.3, 122.3, 120.6, 120.5, 114.5, 110.7, 103.2, 55.5. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[204]



(3-24) 2-Phenyl-1-(4-trifluoromethyl-phenyl)-1*H*-indole.

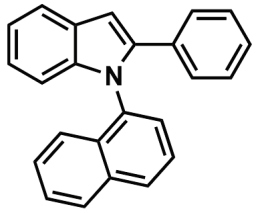
The title compound was synthesized according to **GP2** and purified by flash column chromatography on silica gel using 30:1→10:1 hexanes:ethyl acetate in 93 % yield (157 mg, 0.47 mmol) as an off-white powder. The title compound was also synthesized according to **GP3** and purified by flash column chromatography on silica gel using 30:1→10:1 hexanes:ethyl acetate in, when employing **Method A** and in *Step 1.* X = Cl, *Step 2.* X = Cl, 69 % yield (116 mg, 0.35 mmol); when employing **Method B** and in *Step 1.* X = Cl, *Step 2.* X = Cl, 74 % yield (125 mg, 0.37 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79-7.73 (m, 3H), 7.44-7.38 (m, 3H), 7.35-7.27 (m, 7H), 6.91 (d, J = 1.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75.4 MHz, $CDCl_3$): δ 141.8, 140.6, 138.7, 132.2, 129.0, 128.6, 128.5, 128.2, 127.7, 126.5 (q, J_{CF} = 6 Hz), 124.0 (q, J_{CF} = 270 Hz), 122.9, 121.3, 120.9, 110.3, 105.0; *m/z* ESI^{+} found 338.1148 $[M+H]^{+}$ calculated for $C_{21}H_{15}F_3N_1$ 338.1151.



(3-25) 2-Phenyl-1-pyridin-2-yl-1*H*-indole.

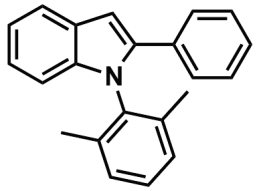
The title compound was synthesized according to **GP2** and purified by flash column chromatography on silica gel using 30:1→10:1 hexanes:ethyl acetate in 91 % yield (123 mg, 0.46 mmol). The title compound was also synthesized according to **GP3** and purified by flash column chromatography on silica gel using 30:1→10:1 hexanes:ethyl acetate in, when employing **Method A** and in *Step 1.* X = Cl, *Step 2.* X = Cl, 76 % yield (103 mg, 0.38 mmol); when employing **Method B** and in *Step 1.* X = Cl, *Step 2.* X = Cl, 71 % yield (96 mg, 0.36 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (dd, J = 4.9 Hz, J = 1.2 Hz, 1H), 7.81-7.76 (m, 2H), 7.65 (dt, J = 7.8 Hz, J = 1.9 Hz, 1H), 7.39-7.29 (m, 7H), 7.26 (m, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.91 (s, 1H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 152.1, 149.3, 140.1, 138.6, 137.9, 132.8, 128.8, 128.5, 127.6, 123.2, 122.1, 121.7, 121.5,

120.7, 111.7, 105.7. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[205]



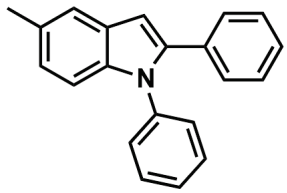
(2-6) 1-Naphthalen-1-yl-2-phenyl-1*H*-indole.

The title compound was synthesized according to **GP3**, using $[Pd(cinnamyl)Cl]_2$ (5.2 mg, 0.01 mmol, 2 mol%), BippyPhos (20.2 mg, 0.04 mmol, 8 mol%) in **Method A**, *Step 2.*, and purified by flash column chromatography on silica gel using 50:1→20:1 hexanes:ethyl acetate in, when employing **Method A** and in *Step 1.* X = Cl, *Step 2.* X = Br, 81 % yield (130 mg, 0.41 mmol). Please refer to Section 2.4.3 for characterization data of the title compound.



(2-7) 1-(2,6-Dimethyl-phenyl)-2-phenyl-1*H*-indole.

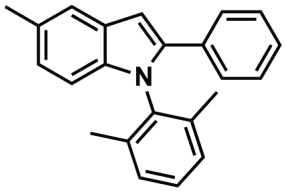
The title compound was synthesized according to **GP3** and purified by flash column chromatography on silica gel using 50:1→20:1 hexanes:ethyl acetate in, when employing **Method B** and in *Step 1.* X = Cl, *Step 2.* X = Cl, 82 % yield (122 mg, 0.41 mmol); when employing **Method B** under air and in *Step 1.* X = Cl, *Step 2.* X = Cl, 78 % yield (117 mg, 0.39 mmol). Please refer to Section 2.4.3 for characterization data of the title compound.



(3-26) 5-Methyl-1,2-diphenyl-1*H*-indole.

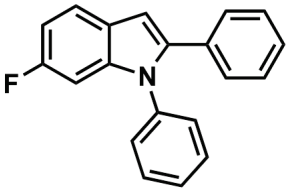
The title compound was synthesized according to **GP3** and purified by flash column chromatography on silica gel using 50:1→20:1 hexanes:ethyl acetate in, when employing

Method A and in *Step 1.* X = Br, *Step 2.* X = Cl, 83 % yield (118 mg, 0.42 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (m, 1H), 7.50-7.38 (m, 3H), 7.37-7.26 (m, 8H), 7.08 (dd, *J* = 14.1 Hz, *J* = 2.2 Hz, 1H), 6.81 (s, 1H), 2.55 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 140.8, 138.8, 137.6, 132.8, 130.0, 129.3, 128.9, 128.6, 128.2, 128.0, 127.2, 127.1, 124.0, 120.3, 110.4, 103.4, 21.5. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[204]



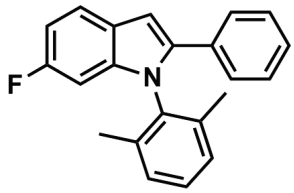
(2-14) 1-(2,6-Dimethyl-phenyl)-5-methyl-2-phenyl-1*H*-indole.

The title compound was synthesized according to **GP3** and purified by flash column chromatography on silica gel using 50:1→20:1 hexanes:ethyl acetate in, when employing **Method B** and in *Step 1.* X = Cl, *Step 2.* X = Br, 84 % yield (132 mg, 0.42 mmol). Please refer to Section 2.4.3 for characterization data of the title compound.



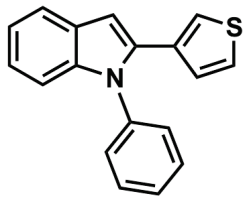
(3-27) 6-Fluoro-1,2-diphenyl-1*H*-indole.

The title compound was synthesized according to **GP3** and purified by flash column chromatography on silica gel using 30:1→10:1 hexanes:ethyl acetate in, when employing **Method A** and in *Step 1.* X = Br, *Step 2.* X = Cl, 85 % yield (123 mg, 0.43 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (dd, *J* = 8.9 Hz, *J* = 5.4 Hz, 1H), 7.50-7.37 (m, 3H), 7.31-7.27 (m, 7H), 7.05-6.96 (m, 2H), 6.82 (d, *J* = 0.8 Hz, 1H); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 160.2 (d, J_{CF} = 248 Hz), 141.3 (d, J_{CF} = 5 Hz), 139.2 (d, J_{CF} = 13 Hz), 138.3, 132.3, 129.5, 128.8, 128.2, 127.9, 127.5, 127.4 (d, J_{CF} = 13 Hz), 124.7, 121.3 (d, J_{CF} = 10 Hz), 109.4 (d, J_{CF} = 25 Hz), 103.6, 97.2 (d, J_{CF} = 25 Hz). Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[204]



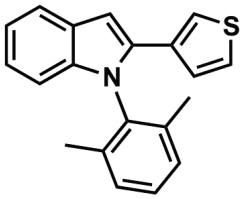
(3-28) 1-(2,6-Dimethyl-phenyl)-6-fluoro-2-phenyl-1*H*-indole.

The title compound was synthesized according to **GP3** and purified by flash column chromatography on silica gel using 30:1→10:1 hexanes:ethyl acetate in, when employing **Method B** and in *Step 1.* X = Cl, *Step 2.* X = Br, 79 % yield (125 mg, 0.40 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (dd, J = 8.6 Hz, J = 5.3 Hz, 1H), 7.33-7.27 (m, 6H), 7.21-7.20 (m, 2H), 6.99 (dt, J = 8.6 Hz, J = 2.3 Hz, 1H), 6.91 (s, 1H), 6.57 (dd, , J = 9.8 Hz, J = 2.0 Hz, 1H), 1.94 (s, 6H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 160.3 (d, J_{CF} = 238 Hz), 141.3 (d, J_{CF} = 4 Hz), 138.1 (d, J_{CF} = 11 Hz), 137.5, 136.4, 132.7, 128.8, 128.6, 127.6, 127.5, 124.5, 121.4 (d, J_{CF} = 10 Hz), 109.2 (d, J_{CF} = 25 Hz), 102.2, 96.9 (d, J_{CF} = 26 Hz), 18.0; *m/z* ESI^{+} found 316.1486 [M+H]$^{+}$ calculated for $C_{22}H_{19}F_1N_1$ 316.1496.



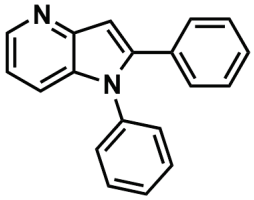
(3-29) 1-Phenyl-2-thiophen-3-yl-1*H*-indole.

The title compound was synthesized according to **GP3** and purified by flash column chromatography on silica gel using 50:1→20:1 hexanes:ethyl acetate in, when employing **Method A** and in *Step 1.* X = Br, *Step 2.* X = Cl, 82 % yield (114 mg, 0.41 mmol) as an off-white powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (m, 1H), 7.55-7.44 (m, 3H), 7.37-7.34 (m, 2H), 7.25-7.17 (m, 4H), 7.07 (dd, J = 8.4 Hz, J = 2.2 Hz, 1H), 6.88 (dd, J = 4.9 Hz, J = 2.2 Hz, 1H), 6.86 (s, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 139.0, 138.6, 136.0, 133.1, 129.5, 128.5, 128.1, 127.9, 125.1, 122.3, 122.2, 120.6, 120.4, 110.5, 102.7; *m/z* ESI^{+} found 276.0838 [M+H]$^{+}$ calculated for $C_{18}H_{14}N_1S_1$ 276.0841.



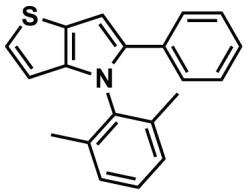
(2-24) 1-(2,6-Dimethyl-phenyl)-2-thiophen-3-yl-1*H*-indole.

The title compound was synthesized according to **GP3** and purified by flash column chromatography on silica gel using 50:1→20:1 hexanes:ethyl acetate in, when employing **Method B** and in *Step 1.* X = Cl, *Step 2.* X = Br, 83 % yield (127 mg, 0.42 mmol). Please refer to Section 2.4.3 for characterization data of the title compound.



(3-30) 1,2-Diphenyl-1*H*-pyrrolo[3,2-*b*]pyridine.

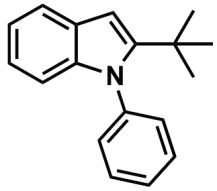
The title compound was synthesized according to **GP3** and purified by flash column chromatography on silica gel using ethyl acetate in, when employing **Method A** and in *Step 1.* X = Cl, *Step 2.* X = Cl, 88 % yield (120 mg, 0.44 mmol) as brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (dd, *J* = 4.9 Hz, *J* = 1.4 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.47-7.39 (m, 3H), 7.33-7.23 (m, 7H), 7.10 (dd, *J* = 8.6 Hz, *J* = 4.9 Hz, 1H), 7.02 (s, 1H). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 146.7, 144.4, 143.9, 137.6, 132.2, 131.7, 129.5, 129.1, 128.3, 128.0, 127.8, 127.7, 117.6, 117.1, 104.5; *m/z* ESI$^+$ found 271.1229 $[M+H]^+$ calculated for $C_{19}H_{15}N_2$ 271.1230.



(2-26) 4-(2,6-Dimethyl-phenyl)-5-phenyl-4*H*-thieno[3,2-*b*]pyrrole.

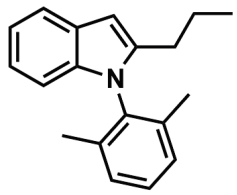
The title compound was synthesized according to **GP3** and purified by flash column chromatography on silica gel using 30:1→10:1 hexanes:ethyl acetate in, when employing

Method B and in *Step 1.* X = Cl, *Step 2.* X = Br, 83 % yield (126 mg, 0.42 mmol). Please refer to Section 2.4.3 for characterization data of the title compound.



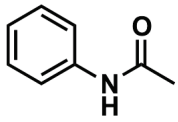
(3-31) 2-(*tert*-butyl)-1-phenyl-1*H*-indole.

The title compound was synthesized according to **GP3** and purified by flash column chromatography on silica gel using ethyl acetate in, when employing **Method A** and in *Step 1.* X = Br, *Step 2.* X = Cl, 54 % yield (54 mg, 0.22 mmol) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (m, 1H), 7.58-7.54 (m, 3H), 7.46-7.43 (m, 2H), 7.18-7.07 (m, 2H), 6.72 (d, *J* = 13.7 Hz, 1H), 6.55 (d, *J* = 1.0 Hz, 1H), 1.34 (s, 9H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 150.7, 140.9, 140.3, 130.8, 129.1, 128.6, 126.9, 121.2, 119.8, 119.6, 110.3, 99.3, 33.3, 31.1; *m/z* ESI^+ found 272.1406 $[M+Na]^+$ calculated for $C_{18}H_{19}N_1Na_1$ 272.1410.



(2-21) 1-(2,6-Dimethyl-phenyl)-2-propyl-1*H*-indole.

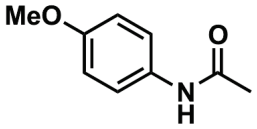
The title compound was synthesized according to **GP3** and purified by flash column chromatography on silica gel using 50:1→20:1 hexanes:ethyl acetate in, when employing **Method B** and in *Step 1.* X = Cl, *Step 2.* X = Br, 69 % yield (91 mg, 0.35 mmol). Please refer to Section 2.4.3 for characterization data of the title compound.



(3-32) *N*-Phenylacetamide.

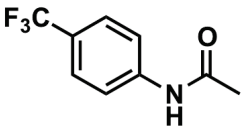
The title compound was synthesized according to **GP4**, using K_2CO_3 and 1,4-dioxane, and purified by flash column chromatography on silica gel using 1:1 ethyl acetate:hexanes in a 80 % isolated yield (54 mg, 0.40 mmol) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.10

(t, J = 7.5 Hz, 1H), 2.16 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 168.7, 138.0, 129.1, 124.4, 120.1, 24.7; *m/z* ESI^+ found 158.0570 $[M+Na]^+$ calculated for C_8H_9NNaO 158.0576. Spectral data are in agreement with previously reported ^{13}C NMR characterization data for the title compound.[206]



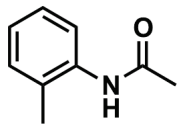
(3-33) *N*-(4-Methoxyphenyl)acetamide.

The title compound was synthesized according to **GP4**, using K_3PO_4 and *tert*-butanol, and purified by flash column chromatography on silica gel using ethyl acetate in a 92 % isolated yield (76 mg, 0.46 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.77 (s, 1H), 7.47 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.0 Hz, 2H), 3.70 (s, 3H), 2.00 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, DMSO-*d6*): δ 167.7, 155.0, 132.5, 120.5, 113.8, 55.1, 23.8; *m/z* ESI^+ found 188.0684 $[M+Na]^+$ calculated for $C_9H_{11}NNaO_2$ 188.0682. Spectral data are in agreement with previously reported ^{13}C NMR characterization data for the title compound.[207]



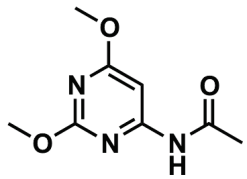
(3-34) *N*-(4-(Trifluoromethyl)phenyl)acetamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and 1,4-dioxane, and purified by flash column chromatography on silica gel using 1:1 ethyl acetate:hexanes in a 83 % isolated yield (84 mg, 0.42 mmol) as a white solid^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.30 (s, 1H), 7.78 (d, J = 7.5 Hz, 2H), 7.65 (d, J = 7.5 Hz, 2H), 2.08 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, DMSO-*d6*): δ 169.0, 142.9, 126.0 (q, J_{CF} = 4 Hz), 124.4 (q, J_{CF} = 269 Hz), 123.0 (q, J_{CF} = 32 Hz) 118.8, 24.1; *m/z* ESI^+ found 226.0450 $[M+Na]^+$ calculated for $C_9H_8F_3NNaO$ 226.0450. Spectral data are in agreement with previously reported ^{13}C NMR characterization data for the title compound.[208]



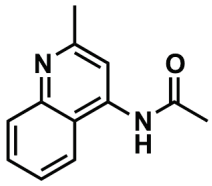
(3-35) *N*-*o*-Tolylacetamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and 1,4-dioxane, and purified by flash column chromatography on silica gel using 1:1 ethyl acetate:hexanes in a 78 % isolated yield (58 mg, 0.39 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.27 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.0 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 2.19 (s, 3H), 2.05 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 168.1, 136.5, 131.5, 130.2, 125.9, 125.00, 124.97, 23.3, 17.9; *m/z* ESI$^+$ found 172.0736 [M+Na]$^+$ calculated for $C_9H_{11}NNaO$ 172.0733. Spectral data are in agreement with previously reported ^{13}C NMR characterization data for the title compound.[209]

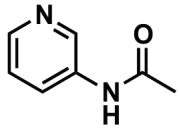


(3-36) *N*-(2,6-Dimethoxypyrimidin-4-yl)acetamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and 1,4-dioxane, and purified by flash column chromatography on silica gel using 3:7 ethyl acetate:hexanes in a 91 % isolated yield (90 mg, 0.46 mmol) as a light yellow oil. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.65 (s, 1H), 7.07 (s, 1H), 3.862 (s, 3H), 3.858 (s, 3H), 2.08 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 172.4, 170.4, 164.3, 159.8, 87.3, 54.3, 53.8, 24.1; *m/z* ESI$^+$ found 220.0691 [M+Na]$^+$ calculated for $C_8H_{11}N_3NaO_3$ 220.0693.

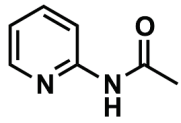


(3-37) ***N*-(2-Methylquinolin-4-yl)acetamide.** The title compound was synthesized according to **GP4**, using K_2CO_3 and 1,4-dioxane, and purified by flash column chromatography on silica gel using 1:9 methanol:methylene chloride in a 92 % isolated yield (92 mg, 0.46 mmol) as a light yellow solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.13 (s, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 8.01 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 2.60 (s, 3H), 2.26 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 169.8, 159.0, 148.2, 141.5, 129.3, 128.7, 124.9, 122.1, 119.1, 112.0, 25.3, 24.2; *m/z* ESI$^+$ found 201.1021 $[M+H]^+$ calculated for $C_{12}H_{13}N_2O$ 201.1022. Spectral data are in agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[210]



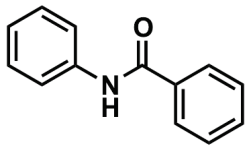
(3-38) ***N*-(Pyridin-3-yl)acetamide.**

The title compound was synthesized according to **GP4**, using K_2CO_3 and *tert*-butanol, and purified by flash column chromatography on silica gel using 1:19 methanol:methylene chloride in a 82 % isolated yield (56 mg, 0.42 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.16 (s, 1H), 8.71 (d, *J* = 2.0 Hz, 1H), 8.24 (d, *J* = 4.5 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.32 (dd, *J* = 4.5 Hz, *J* = 8.0 Hz, 1H), 2.07 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 168.9, 144.0, 140.6, 135.9, 125.9, 123.6, 23.9; *m/z* ESI$^+$ found 159.0531 $[M+Na]^+$ calculated for $C_7H_8N_2NaO$ 159.0529. Spectral data are in agreement with previously reported ^{13}C NMR characterization data for the title compound.[211]



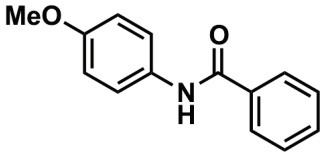
(3-39) *N*-(Pyridin-2-yl)acetamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and *tert*-butanol, and purified by flash column chromatography on silica gel using ethyl acetate in a 72 % isolated yield (49 mg, 0.36 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.46 (s, 1H), 8.29-8.28 (m, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.75 (td, *J* = 2.0 Hz, *J* = 8.0 Hz, 1H), 7.07 (dd, *J* = 4.5 Hz, *J* = 8.0 Hz, 1H), 2.08 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 169.3, 152.1, 147.9, 138.1, 119.2, 113.3, 23.9; *m/z* ESI$^+$ found 159.0526 $[M+Na]^+$ calculated for $C_7H_8N_2NaO$ 159.0529. Spectral data are in close agreement with previously reported ^{13}C NMR characterization data for the title compound.[212]



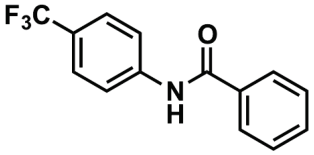
(3-40) *N*-Phenylbenzamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and 1,4-dioxane, and purified by flash column chromatography on silica gel using 3:7 ethyl acetate:hexanes in a 99 % isolated yield (98 mg, 0.49 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.26 (s, 1H), 7.96 (d, *J* = 7.0 Hz, 2H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 165.6, 139.2, 135.0, 131.6, 128.6, 128.4, 127.7, 123.7, 120.4; *m/z* ESI$^+$ found 220.0731 $[M+Na]^+$ calculated for $C_{13}H_{11}NNaO$ 220.0733. Spectral data are in close agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[213]



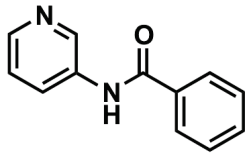
(3-41) *N*-(4-Methoxyphenyl)benzamide.

The title compound was synthesized according to **GP4**, using K_3PO_4 and *tert*-butanol, and purified by flash column chromatography on silica gel using 3:7 ethyl acetate:hexanes in a 99 % isolated yield (112 mg, 0.49 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.14 (s, 1H), 7.95 (d, *J* = 7.5 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 3.74 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 165.1, 155.5, 135.1, 132.2, 131.4, 128.4, 127.6, 122.0, 113.7, 55.2; *m/z* ESI$^+$ found 250.0830 [M+Na]$^+$ calculated for $C_{14}H_{13}NNaO_2$ 250.0838. Spectral data are in close agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[214]



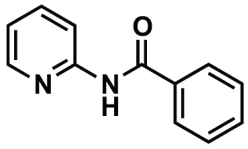
(3-42) *N*-(4-(Trifluoromethyl)phenyl)benzamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and 1,4-dioxane, and purified by flash column chromatography on silica gel using 1:4 ethyl acetate:hexanes in a 75 % isolated yield (79 mg, 0.38 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.59 (s, 1H), 8.02 (d, *J* = 8.5 Hz, 2H), 7.98 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.64-7.61 (m, 1H), 7.56 (t, *J* = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 166.1, 142.9, 134.5, 132.0, 128.5, 127.8, 125.9 (q, J_{CF} = 4 Hz), 124.4 (q, J_{CF} = 269 Hz), 123.6 (q, J_{CF} = 31 Hz), 120.1; *m/z* ESI$^+$ found 288.0613 [M+Na]$^+$ calculated for $C_{14}H_{10}F_3NNaO$ 288.0607. Spectral data are in agreement with previously reported ^{13}C NMR characterization data (recorded in acetone-*d6*) for the title compound.[215]



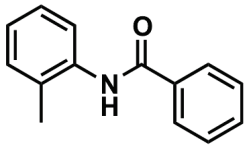
(3-43) *N*-(Pyridin-3-yl)benzamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and *tert*-butanol, and purified by flash column chromatography on silica gel using 1:9 methanol:methylene chloride in a 93 % isolated yield (92 mg, 0.46 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.47 (s, 1H), 8.95 (d, *J* = 2.5 Hz, 1H), 8.32 (d, *J* = 4.5 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.0 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.40 (dd, *J* = 4.5 Hz, *J* = 8.0 Hz, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 166.0, 144.6, 142.0, 135.9, 134.4, 131.9, 128.5, 127.8, 127.3, 123.5; *m/z* ESI$^+$ found 199.0862 $[M+H]^+$ calculated for $C_{12}H_{11}N_2O$ 199.0866. Spectral data are in agreement with previously reported ^{13}C NMR characterization data for the title compound.[216]



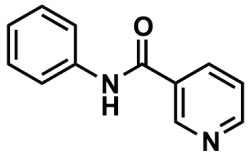
(3-44) *N*-(Pyridin-2-yl)benzamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and *tert*-butanol, and purified by flash column chromatography on silica gel using ethyl acetate in a 69 % isolated yield (68 mg, 0.34 mmol) as a light yellow solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.79 (s, 1H), 8.39 (d, *J* = 1.5 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.03 (d, *J* = 7.5 Hz, 2H), 7.84 (td, *J* = 1.5 Hz, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.17 (dd, *J* = 4.5 Hz, *J* = 7.0 Hz, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 166.0, 152.2, 147.9, 138.1, 134.1, 131.9, 128.4, 128.0, 119.8, 114.7; *m/z* ESI$^+$ found 221.0690 $[M+Na]^+$ calculated for $C_{12}H_{10}N_2NaO$ 221.0685. Spectral data are in close agreement with previously reported ^{13}C NMR characterization data for the title compound.[216]



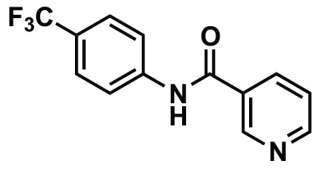
(3-45) *N*-*o*-Tolylbenzamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and 1,4-dioxane, and purified by flash column chromatography on silica gel using 3:7 ethyl acetate:hexanes in a 99 % isolated yield (107 mg, 0.49 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.89 (s, 1H), 8.00 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H*)*, 7.17 (t, *J* = 7.5 Hz, 1H), 2.24 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 165.3, 136.4, 134.5, 133.8, 131.5, 130.3, 128.4, 127.6, 126.6, 126.0, 17.9; *m/z* ESI$^+$ found 234.0895 $[M+Na]^+$ calculated for $C_{14}H_{13}NNaO$ 234.0889. Spectral data is similar to previously reported ^{13}C NMR characterization data (recorded in $CDCl_3$) for the title compound.[217]



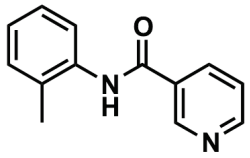
(3-46) *N*-Phenylnicotinamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and 1,4-dioxane, and purified by flash column chromatography on silica gel using ethyl acetate in a 79 % isolated yield (78 mg, 0.40 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.45 (s, 1H), 9.11 (d, *J* = 2.0 Hz, 1H), 8.77 (dd, *J* = 1.5 Hz, *J* = 5.0 Hz, 1H), 8.30 (dt, *J* = 1.5 Hz, *J* = 6.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.57 (dd, *J* = 5.0 Hz, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.13 (t, *J* = 7.5 Hz*,* 1H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 164.1, 152.1, 148.7, 138.9, 135.5, 130.6, 128.7, 124.0, 123.5, 120.4; *m/z* ESI$^+$ found 221.0693 $[M+Na]^+$ calculated for $C_{12}H_{10}N_2NaO$ 221.0685. Spectral data are in agreement with previously reported ^{13}C NMR characterization data (recorded in $CDCl_3$) for the title compound.[218]



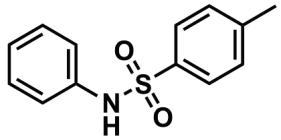
(3-47) *N*-(4-(Trifluoromethyl)phenyl)nicotinamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and 1,4-dioxane, and purified by flash column chromatography on silica gel using ethyl acetate in a 91 % isolated yield (121 mg, 0.46 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.77 (s, 1H), 9.13 (d, J = 2.0 Hz, *1H*), 8.79 (dd, *J* = 2.0 Hz, *J* = 5.0 Hz, 1H), 8.32 (dt, *J* = 2.0 Hz, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.59 (dd, *J* = 5.0 Hz, *J* = 8.0 Hz, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 164.6, 152.4, 148.8, 142.5, 135.6, 130.2, 126.0 (q, J_{CF} = *4 Hz*), 124.4 (q, J_{CF} = *269 Hz*), 123.9 (q, J_{CF} = *31 Hz*), 123.6, 120.2; *m/z* ESI$^+$ found 289.0551 [M+Na]$^+$ calculated for $C_{13}H_9F_3N_2NaO$ 289.0559.



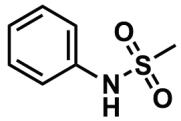
(3-48) *N*-*o*-Tolylnicotinamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and 1,4-dioxane, and purified by flash column chromatography on silica gel using ethyl acetate in a 65 % isolated yield (69 mg, 0.33 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.10 (s, 1H), 9.15 (s, 1H), 8.78 (d, *J* = 3.5 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 7.58 (dd, *J* = 5.0 Hz, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 8.0 Hz*,* 1H), 2.25 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 163.9, 152.1, 148.7, 136.0, 135.4, 133.7, 130.4, 130.1, 126.6, 126.3, 126.1, 123.6, 17.9; *m/z* ESI$^+$ found 235.0844 [M+Na]$^+$ calculated for $C_{13}H_{12}N_2NaO$ 235.0842.



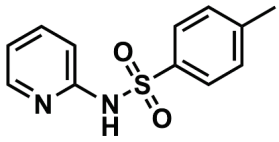
(3-49) 4-Methyl-*N*-phenylbenzenesulfonamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and 1,4-dioxane, and purified by flash column chromatography on silica gel using 3:7 ethyl acetate:hexanes in a 95 % isolated yield (118 mg, 0.48 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.22 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.00 (t, *J* = 7.5 Hz, 1H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 143.2, 137.8, 136.7, 129.7, 129.1, 126.7, 123.9, 119.9, 21.0; *m/z* ESI$^+$ found 270.0573 [M+Na]$^+$ calculated for $C_{13}H_{13}NNaO_2S$ 270.0559. Spectral data are in agreement with previously reported ^{13}C NMR characterization data for the title compound.[219]



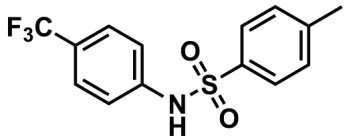
(3-50) *N*-Phenylmethanesulfonamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and 1,4-dioxane, and purified by flash column chromatography on silica gel using 3:7 ethyl acetate:hexanes in a 88 % isolated yield (75 mg, 0.44 mmol) as a light orange oil. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.73 (s, 1H), 7.33 (t, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 8.0 Hz, 1H), 2.97 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 138.4, 129.3, 123.8, 119.7, 39.2; *m/z* ESI$^+$ found 194.0246 [M+Na]$^+$ calculated for $C_7H_9NNaO_2S$ 194.0246. Spectral data are in agreement with previously reported ^{13}C NMR characterization data for the title compound.[220]



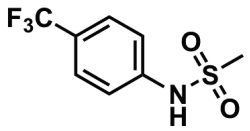
(3-51) 4-Methyl-*N*-(pyridin-2-yl)benzenesulfonamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and *tert*-butanol, and purified by flash column chromatography on silica gel using ethyl acetate in a 44 % isolated yield (55 mg, 0.22 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 11.87 (s, 1H), 8.01 (d, *J* = 5.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.71-7.68 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 1H), 6.86 (t, *J* = 6.5 Hz, 1H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 153.0, 142.5, 140.2, 138.9, 129.4, 126.6, 125.6, 115.8, 113.5, 21.0; *m/z* ESI$^+$ found 271.0519 $[M+Na]^+$ calculated for $C_{12}H_{12}N_2NaO_2S$ 271.0512. Spectral data are in close agreement with previously reported ^{1}H NMR characterization data for the title compound.[221]



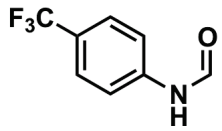
(3-52) 4-Methyl-*N*-(4-(trifluoromethyl)phenyl)benzenesulfonamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and 1.4-dioxane, and purified by flash column chromatography on silica gel using 3:7 ethyl acetate:hexanes in a 97 % isolated yield (153 mg, 0.49 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.84 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 143.8, 141.7, 136.4, 129.9, 126.7, 126.5 (q, J_{CF} = 4 Hz), 124.2 (q, J_{CF} = 270 Hz), 123.6 (q, J_{CF} = 32 Hz), 118.6, 21.0; *m/z* ESI$^+$ found 338.0431 $[M+Na]^+$ calculated for $C_{14}H_{12}F_3NNaO_2S$ 338.0433. Spectral data are in agreement with previously reported ^{13}C NMR characterization data for the title compound.[219]



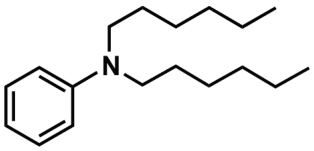
(3-53) *N*-(4-(Trifluoromethyl)phenyl)methanesulfonamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and 1.4-dioxane, and purified by flash column chromatography on silica gel using 3:7 ethyl acetate:hexanes in a 81 % isolated yield (97 mg, 0.41mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.34 (s, 1H), 7.69 (d, *J* = 9.0 Hz, 2H), 7.37 (d, *J* = 9.0 Hz, 2H), 3.10 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 142.3, 127.1 (q, J_{CF} = 4 Hz), 124.8 (q, J_{CF} = 270 Hz), 123.8 (q, J_{CF} = 32 Hz), 118.3, 39.8; *m/z* ESI$^+$ found 262.0122 [M+Na]$^+$ calculated for $C_8H_8F_3NNaO_2S$ 262.0120. Spectral data are in agreement with previously reported ^{13}C NMR characterization data (recorded in $CDCl_3$) for the title compound.[222]



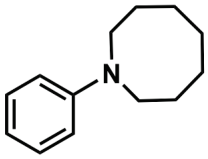
(3-54) *N*-(4-(Trifluoromethyl)phenyl)formamide.

The title compound was synthesized according to **GP4**, using K_2CO_3 and 1,4-dioxane, and purified by flash column chromatography on silica gel using 1:1 ethyl acetate:hexanes in a 94 % isolated yield (84 mg, 0.44 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.57 (s, 1H, *cis*), 10.47 (d, *J* = 10.0 Hz, 1H, *trans*), 8.96 (d, *J* = 10.0 Hz, 1H, *trans*), 8.36 (s, 1H, *cis*), 7.79 (d, *J* = 8.5 Hz, 2H, *cis*), 7.69-7.65 (m, 4H, *cis* + *trans*), 7.39 (d, *J* = 8.4 Hz, 2H, *trans*); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 162.6 (*trans*), 160.2 (*cis*), 142.2 (*trans*), 141.7 (*cis*), 126.6 (q, J_{CF} = 4 Hz, *trans*), 126.1 (q, J_{CF} = 4 Hz, *cis*), 124.3 (q, J_{CF} = 270 Hz, *cis*), 123.64 (q, J_{CF} = 32 Hz, *cis*), 123.59 (q, J_{CF} = 32 Hz, *cis*), 119.1 (*cis*), 117.0 (*trans*); *m/z* ESI$^+$ found 212.0293 [M+Na]$^+$ calculated for $C_8H_6F_3NNaO$ 212.0294.

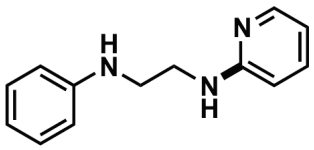


(3-55) *N*,*N*-Dihexylaniline.

The title compound was synthesized according to **GP2**, and purified by flash column chromatography on silica gel using 1:9 ethyl acetate:hexanes in a 66 % isolated yield (186 mg, 0.71 mmol) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (t, J = 7.5 Hz, 2H), 6.64-6.60 (m, 3H), 3.24 (t, J = 7.5 Hz, 4H), 1.57 (t, J = 7.5 Hz, 4H), 1.35-1.31 (m, 12H), 0.90 (t, J = 7.5 Hz, 6H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 148.3, 129.3, 115.1, 111.8, 51.2, 31.9, 27.3, 27.0, 22.9, 14.2; *m/z* ESI^{+} found 262.2521 $[M+H]^{+}$ calculated for $C_{18}H_{32}N$ 262.2529. Spectral data are in agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[223]

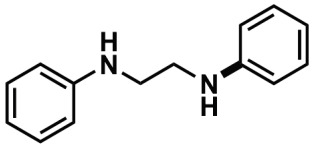


(3-56) 1-Phenylazocane. The title compound was synthesized according to **GP2**, and purified by flash column chromatography on silica gel using 1:9 ethyl acetate:hexanes in a 67 % isolated yield (132 mg, 0.70 mmol) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24-7.21 (m, 2H), 6.69 (d, J = 8.0 Hz, 2H), 6.64 (t, J = 7.5 Hz, 1H), 3.45 (t, J = 5.5 Hz, 4H), 1.76-1.74 (m, 4H), 1.58-1.53 (m, 6H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 148.4, 129.3, 115.1, 111.2, 50.7, 27.4, 27.2, 27.0; *m/z* ESI^{+} found 190.1584 $[M+H]^{+}$ calculated for $C_{13}H_{20}N$ 190.1590. Spectral data are in agreement with previously reported ^{1}H NMR characterization data for the title compound.[224]



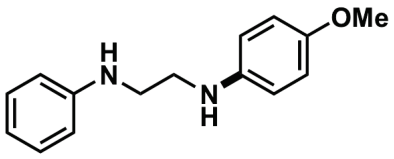
(3-66) *N*-Phenyl-*N*'-pyridin-2-yl-ethane-1,2-diamine.

The title compound was synthesized according to **GP7** and purified by washing the crude product with cold hexanes (3 x 5 mL) in 89 % yield (95 mg, 0.45 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.4 Hz, 1H), 7.43 (m, 1H), 7.24-7.19 (m, 2H), 6.76 (t, *J* = 12.2 Hz, 1H), 6.67-6.60 (m, 3H), 6.42 (d, *J* = 13.9 Hz, 1H), 4.91 (br s, 1H), 4.22 (br s, 1H), 3.63-3.58 (m, 2H), 3.41-3.39 (m, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 158.8, 148.2, 148.1, 137.4, 129.3, 117.5, 113.2, 112.9, 107.6, 44.0, 41.4. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[55]



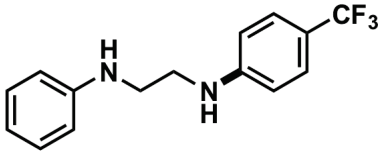
(3-67) *N,N'*-Diphenyl-ethane-1,2-diamine.

The title compound was synthesized according to **GP7** and purified by washing the crude product with cold hexanes (3 x 5 mL) in, when X = Cl, 91 % yield (97 mg, 0.46 mmol); when under air and X = Cl, 81 % yield (85.9 mg, 0.41 mmol); when X = OTs, 87 % yield (92.3 mg, 0.44 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.28 (m, 4H), 6.85 (dt, *J* = 12.3 Hz, *J* = 1.7 Hz, 2H), 6.75-6.73 (m, 4H), 3.90 (br s, 2H), 3.45 (s, 4H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 148.2, 129.5, 117.9, 113.1, 43.4. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[225]



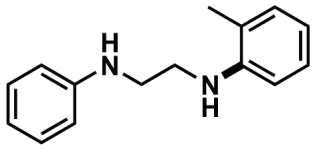
(3-68) *N*-(4-Methoxy-phenyl)-*N*'-phenyl-ethane-1,2-diamine.

The title compound was synthesized according to **GP7** and purified by washing the crude product with cold hexanes (3 x 5 mL) in 78 % yield (95 mg, 0.39 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.19 (m, 2H), 6.84-6.80 (m, 2H), 6.76 (m, 1H), 6.70-6.65 (m, 4H), 3.78 (s, 3H), 3.39 (m, 4H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 152.5, 148.1, 142.2, 129.3, 117.8, 115.0, 114.6, 113.1, 55.8, 44.4, 43.4. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[55]



(3-69) *N*-Phenyl-*N*'-(4-trifluoromethyl-phenyl)-ethane-1,2-diamine.

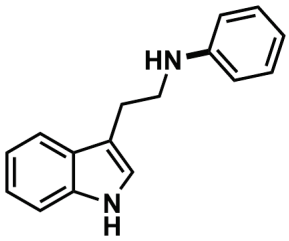
The title compound was synthesized according to **GP7** and purified by washing the crude product with cold hexanes (3 x 5 mL) in 84 % yield (118 mg, 0.42 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.45 (m, 2H), 7.28-7.23 (m, 2H), 6.81 (t, J = 7.7 Hz, 1H), 6.72-6.65 (m, 4H), 4.26 (br s, 1H), 3.82 (br s, 1H), 3.45 (s, 1H); $^{13}C\{^{1}H\}$ NMR (75.4 MHz, $CDCl_3$): δ 150.6, 147.9, 129.8 (q, J_{CF} = 4 Hz), 126.8, 125.0 (q, J_{CF} = 269 Hz), 119.2 (q, J_{CF} = 34 Hz), 118.1, 113.1, 112.1, 43.1, 42.9. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[55]



(3-70) *N*-Phenyl-*N*'-*o*-tolyl-ethane-1,2-diamine.

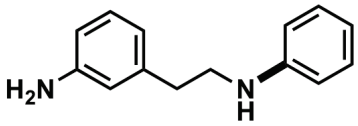
The title compound was synthesized according to **GP7** and purified by washing the crude product with cold hexanes (3 x 5 mL) in 93 % yield (105 mg, 0.47 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.18 (m, 4H), 6.89-6.75 (m, 5H), 3.91 (br s, 1H), 3.83 (br s, 1H), 3.53 (s, 4H), 2.24 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 148.3, 146.1, 130.4, 129.5, 127.3, 122.5, 117.9, 117.5, 113.2, 110.0, 43.5, 43.4, 17.6. Spectral data are in good

agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[55]



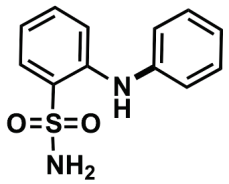
(3-71) [2-(1H-Indol-3-yl)-ethyl]-phenyl-amine.

The title compound was synthesized according to **GP7**, using $[Pd(cinnamyl)Cl]_2$ (6.5 mg, 0.01 mmol, 2.5 mol%), BippyPhos (25.3 mg, 0.05 mmol, 10 mol%), and purified by flash column chromatography on silica gel using 10:1→5:1 hexanes:ethyl acetate in 83 % yield (98 mg, 0.42 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (br s, 1H), 7.71 (m, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.32-7.19 (m, 4H), 7.04 (s, 1H), 6.80 (m, 1H), 6.72-6.68 (m, 2H). 3.82 (br s, 1H), 3.55 (t, *J* = 7.1 Hz, 2H), 3.15 (t, *J* = 6.8 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (75.4 MHz, $CDCl_3$): δ 148.3, 136.6, 129.4, 127.5, 122.2, 122.1, 119.5, 118.9, 117.5, 113.4, 113.2, 111.3, 44.1, 25.2. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[226]



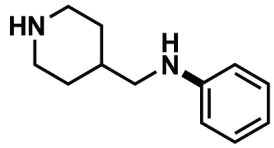
(3-72) 3-(2-Phenylamino-ethyl)-phenylamine.

The title compound was synthesized according to **GP7** and purified by flash column chromatography on silica gel using 10:1→5:1 hexanes:ethyl acetate in 92 % yield (98 mg, 0.46 mmol) as brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.21 (m, 2H), 7.10-7.04 (m, 2H), 6.76 (dt, *J* = 7.8 Hz, *J* = 1.1 Hz, 1H), 6.71-6.65 (m, 4H), 3.66 (br s, 3H), 3.39 (t, *J* = 7.3 Hz, 2H), 2.86 (t, *J* = 7.2 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (75.4 MHz, $CDCl_3$): δ 148.3, 144.9, 129.6, 129.3, 129.1, 117.4, 115.4, 113,1, 45.3, 34.7; *m/z* ESI^{+} found 213.1390 $[M+H]^{+}$ calculated for $C_{14}H_{17}N_2$ 213.1386.



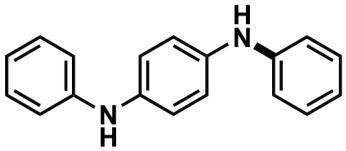
(3-73) 2-(Phenylamino)benzenesulfonamide.

The title compound was synthesized according to **GP4**, and purified by flash column chromatography on silica gel using 3:7 ethyl acetate:hexanes in a 81 % isolated yield (101 mg, 0.41 mmol) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 7.77 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.56 (s, 2H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 2H), 6.92 (t, *J* = 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-*d6*): δ 141.2, 141.0, 133.1, 129.4, 128.6, 128.5, 122.7, 120.7, 118.6, 115.7; *m/z* ESI^{+} found 271.0521 $[M+Na]^{+}$ calculated for $C_{12}H_{12}N_2NaO_2S$ 271.0512. Crystals for x-ray diffraction were produced by cooling a 1:4 methylene chloride:pentane solution of **3-73** to -33 ˚C.



(3-74) Phenyl-piperidin-4-ylmethyl-amine.

The title compound was synthesized according to **GP7** and purified by washing the crude product with cold hexanes (3 x 5 mL) in 73 % yield (69 mg, 0.37 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (t, *J* = 8.6 Hz, 2H), 6.70 (t, *J* = 7.6 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 2H), 3.75 (br s, 1H), 3.12 (d, *J* = 12.6 Hz, 2H), 3.02 (d, *J* = 5.7 Hz, 2H), 2.62 (dt, *J* = 12.4 Hz, *J* = 1.9 Hz, 2H), 1.81-1.68 (m, 4H), 1.21 (dq, *J* = 13.2 Hz, *J* = 4.3 Hz, 2H); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 148.4, 129.3, 117.1, 112.6, 50.3, 46.5, 36.2, 31.6. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[181]



(3-75) ***N,N'*-Diphenyl-benzene-1,4-diamine.**

The title compound was synthesized according to **GP7** and purified by flash column chromatography on silica gel using 5:1 hexanes:ethyl acetate in 87 % yield (113 mg, 0.44 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (t, *J* = 7.4 Hz, 4H), 7.11-7.03 (m, 8H), 6.92 (t, *J* = 6.5 Hz, 2H), 5.61 (br s, 2H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 144.8, 137.7, 129.5, 121.1, 120.2, 116.5. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title compound.[181]

3.4.5 Synthesis and Characterization of **C1**

To a magnetically stirred solution of $Pd(cod)Cl_2$ (0.10 g, 0.35 mmol) in methylene chloride (2 mL) was added a methylene chloride (2 mL) solution of BippyPhos (0.18 g, 0.35 mmol) resulting in a transparent orange solution. After 1 h of magnetic stirring at ambient temperature, ^{31}P NMR analysis of the reaction mixture confirmed the consumption of BippyPhos and quantitative formation of a new phosphorus-containing product (**3-C1**). The solvent and other volatiles were removed in vacuo and the residual solid was washed with pentane (3 x 2 mL) and then Et_2O (3 x 2 mL). Subsequent removal of the solvents in vacuo afforded **C1** as an analytically pure orange solid (0.20 g, 0.29 mmol, 84 %). Anal. Calcd for $C_{32}H_{35}Cl_2N_4PPd$: C 56.19; H 5.19; N 8.19. Found: C 55.87; H 4.82; N 8.21. ^{1}H NMR ($CDCl_3$): δ 8.17 (d, *J* = 2.1 Hz, 1H), 7.76-7.74 (m, 2H), 7.41-7.49 (m, 2H), 7.45-7.44 (m, 2H), 7.40-7.37 (m, 2H), 7.35-7.31 (m, 4H), 7.30-7.27 (m, 2H), 6.57 (d, *J* = 2.1 Hz, 1H), 1.10 (d, *J* = 16.2 Hz, 9H), 0.99 (d, *J* = 16.0 Hz, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 163.7, 159.9, 147.0 (d, *J* = 13 Hz), 143.0 (d, *J* = 39.9 Hz), 138.0, 131.3, 130.5, 130.1, 130.0, 129.9, 129.2, 129.0, 128.8, 128.7, 128.1, 127.0, 114.8, 95.9, 39.2 (d, *J* = 9 Hz), 39.1 (d, *J* = 11 Hz), 29.5 (d, *J* = 54 Hz), 29.4 (d, *J* = 54 Hz). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ 45.5. Crystals for x-ray diffraction were produced by diffusing diethyl ether into a saturated methylene chloride solution of **C1**.

3.4.6 Crystallographic Solution and Refinement Details for **3-73** and **C1**

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 a sample that was mounted in inert oil and transferred to a cold gas stream on the diffractometer. Gaussian integration (face-indexed) was employed as the absorption correction method and the structure was solved by use of direct methods. The structure was refined by use of full-matrix leastsquares 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. 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. Additional crystallographic information is provided in the Appendix.

CHAPTER 4 Pd_2dba_3/BippyPhos: A ROBUST CATALYST SYSTEM FOR THE HYDROXYLATION OF ARYL HALIDES WITH BROAD SCOPE

4.1 INTRODUCTION

As outlined in Section 1.5, hydroxy- and ether-functionalized molecules have found important applications in pharmaceutical product synthesis (Figure 1–6). As such, much attention is being paid to the identification of increasingly efficient methodologies for the construction of carbon-oxygen bonds. In this context, palladium-catalyzed technologies are playing a key role in advancing this important class of bond forming reactions. This is clearly demonstrated by the application of palladium catalysts in the synthesis of phenols and phenol-derived heterocycles via the direct hydroxylation of aryl halides.

The first report of the direct hydroxylation of aryl halides (bromides and chlorides) was published by Buchwald and co-workers in 2006 utilizing a palladium catalyst supported by either *t*BuXPhos or Me_4*t*BuXPhos (Figure 4–1) at elevated temperatures (80-100 °C), whereby the optimal ligand was identified on a substrate-dependent basis.[91] Following an initial report in 2009 regarding the successful application of one of their sterically demanding imidazole-based monophosphine ligands (Figure 4–1) in analogous catalytic hydroxylation chemistry (100-120 °C),[88] Beller and co-workers subsequently disclosed that upon moving from Pd_2dba_3 to [Pd(cod)(CH_2SiMe_3)$_2$] mixtures with their imidazole-based monophosphine ligand, the hydroxylation of aryl halides can be achieved at room temperature.[87] Such mild conditions enabled the use of substrates featuring nitrile and trifluoromethyl substituents, which are otherwise prone to hydrolysis at elevated temperatures under typical catalytic conditions. More recently, Chern and co-workers reported on the use of a catalyst system comprised of Herrmann's palladacycle (Figure 4–1) and *t*BuXPhos under microwave irradiation; however, elevated temperatures were required in order to achieve suitable reactivity (115-150 °C).[86]

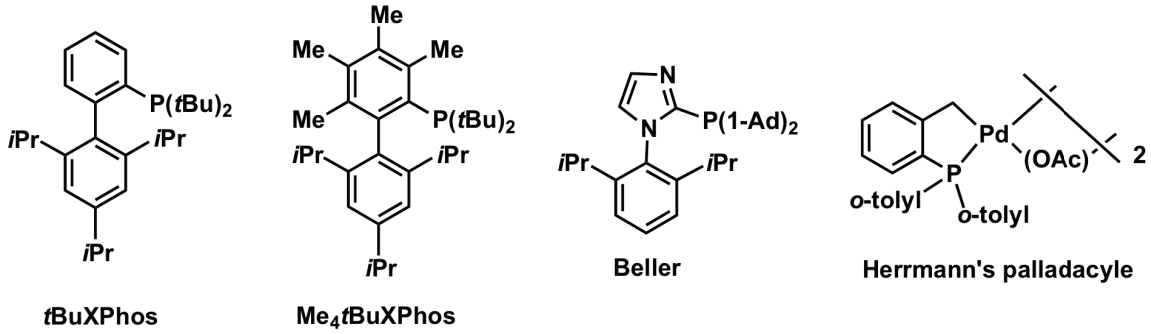


Figure 4–1. Previously reported ligands and pre-catalysts used in the palladium-catalyzed hydroxylation of aryl halides.

Notwithstanding these advances, and as mention in Section 1.5, the relative scarcity of palladium-based catalysts that have been shown to be capable of facilitating the hydroxylation of (hetero)aryl halides serves as motivation for additional investigation. Furthermore, catalysts based on a single palladium/ligand pair, which offer a broad scope of reactivity in the (hetero)aryl halide reaction partner under mild conditions, and without the need for microwave irradiation, would be highly advantageous. In this context, efforts were focused on identifying a catalyst system of this type that was derived from commercially available components and capable of operating under air using bench-top synthetic protocols. As previous eluded to, the identification of such a catalyst system would represent a practical and useful advance in terms of enabling the broader uptake of such hydroxylation protocols by synthetic chemists in both academic and industrial settings. In Section 4.2, a Pd_2dba_3/BippyPhos catalyst system is described (see Figure 1–5 for structure of BippyPhos) that is capable of furnishing a wide array of phenols and phenol-derived benzofurans from (hetero)aryl bromides and chlorides in a manner that is competitive with the best catalyst systems reported to date, while also demonstrating for the first time the viability of employing bench-top reaction protocols in such transformations.

4.2 Results and Discussion

4.2.1 Ligand, Palladium Source and Base Optimization for Palladium-Catalyzed Direct Hydroxylation of 2- Bromomesitylene

In keeping with the Stradiotto group interests in addressing current limitations associated with the use of small and/or challenging substrate classes in palladium-

catalyzed cross-coupling chemistry,[56,57,114] initial efforts focused on the development of a hydroxylation catalyst system based on one of the DalPhos ligands.[92,115] In seeking a catalyst system that would have the ability to operate at room temperature, and using conditions inspired by the work of Buchwald[91] and Beller,[87] the hydroxylation of bromomesitylene was selected as the test reaction using commercially available Pd_2dba_3 as the palladium source (Pd_2dba_3, 2 mol%; ligand, 8 mol%; $CsOH{\cdot}H_2O$, 3 equiv.; THF, 0.5 M; 24 °C; 12 h). Remarkably, after screening a selection of our DalPhos ligands including Mor-DalPhos,[56[9d]] Pyr-DalPhos,[227] and OTips-DalPhos (Chapter 2), that had been shown to perform well in various palladium-catalyzed C-N cross-coupling applications, along with a selection of other commercially available ligands of note in palladium-catalyzed C-O cross-coupling chemistry (*t*BuXPhos, iPr, JosiPhos, BippyPhos, Cy-BippyPhos, and TrippyPhos; Figure 4–2), only the Pd_2dba_3/BippyPhos catalyst system proved capable of achieving non-negligible conversions of the starting bromomesitylene under the stringent test conditions employed, affording the target phenol (2,4,6-trimethylphenol, **4-1**) in 89 % isolated yield.

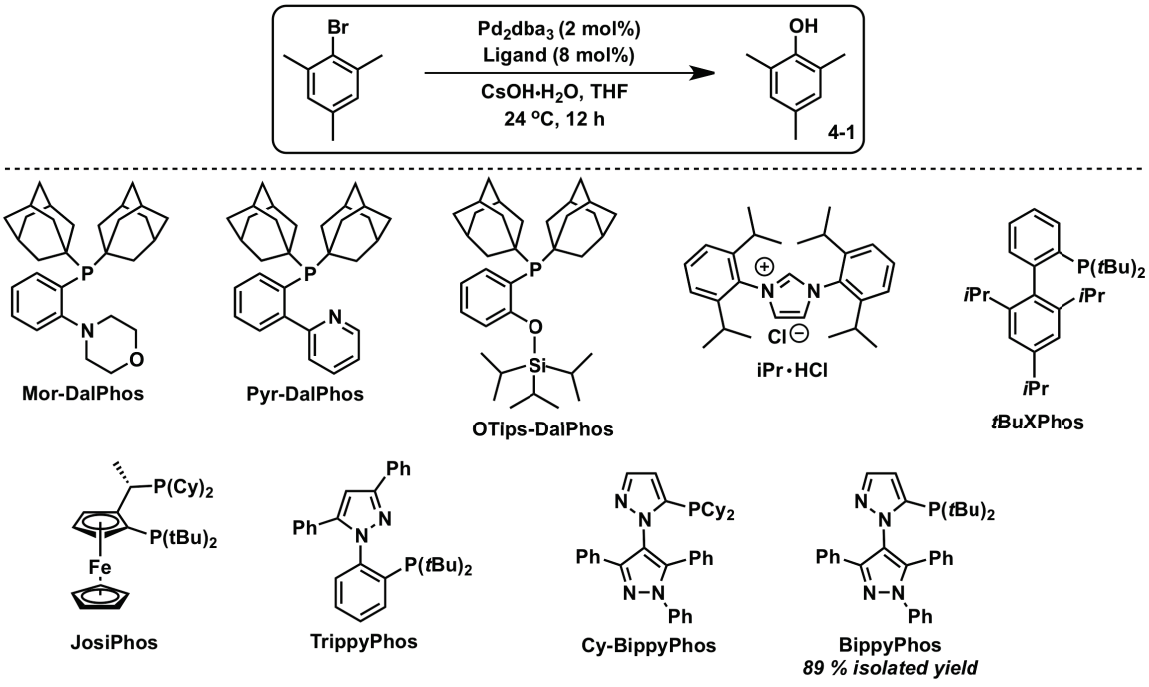


Figure 4–2. Structures of ligands screened in the palladium-catalyzed room temperature hydroxylation of bromomesitylene. With the exception of BippyPhos, negligible

consumption of the starting material was observed on the basis of calibrated GC data (see Section 4.4) when employing any of the other ligands shown.

Notably, less than 30 % yield of the target phenol was obtained under similar conditions when using BippyPhos in combination with either $Pd(OAc)_2$ or $[Pd(cinnamyl)Cl]_2$, despite the utility of the latter palladium source when used with BippyPhos in carbon-nitrogen cross-coupling (Chapter 3). Furthermore, negligible conversion was achieved when using the Pd_2dba_3/BippyPhos catalyst system under analogous conditions employing LiOH, NaOH, KOH or $NMe_4OH{\cdot}H_2O_5$, thereby confirming the important role of $CsOH{\cdot}H_2O$ in this reaction system.

4.2.2 Scope of Pd_2dba_3/BippyPhos Catalyzed Cross-Coupling of (Hetero)aryl Halides and *Ortho*-Alkynylhalo(hetero)arenes with $CsOH{\cdot}H_2O$

Having identified the Pd_2dba_3/BippyPhos catalyst system as being effective for the hydroxylation of bromomesitylene under mild conditions, attention was next turned to exploring the scope of reactivity (Figure 4–3). Gratifyingly, a wide array of (hetero)aryl bromides and chlorides were converted to the respective phenols in synthetically useful isolated yields (24-100 °C; 63–93 %, **4-2**–**4-17**). Bromobenzene and chlorobenzene, along with their methylated derivatives, were each successfully employed as substrates, affording the target phenols in good to excellent isolated yields (**4-2**–**4-5**). Naphthyl and biphenyl halides were also successfully accommodated as reaction partners (**4-6**–**4-8**), as were aryl halides featuring *tert*-butyl or methoxy groups (**4-9** and **4-10**).

While no appreciable difference in reactivity was observed between structurally analogous aryl bromides and chlorides (**4-4**–**4-6**), the ability to selectively hydroxylate the bromide position in 1-bromo-4-chlorobenzene was demonstrated (**4-11**). Furthermore, substrates possessing electron-withdrawing fluoro (**4-12**), trifluoromethyl (**4-13**), cyano (**4-14**), or keto (**4-15**) functionality, which have proven to be particularly challenging in such transformations, were each accommodated under mild reaction conditions (24 or 65 °C). Nitrogen-containing heterocycles (8-bromoquinoline and 2-chloropyridine) were also transformed into the corresponding phenols (**4-16** and **4-17**) in high isolated yields. In keeping with the expected slow carbon-oxygen reductive elimination from putative intermediates of the type [(BippyPhos)Pd(aryl)OH], aryl halides bearing methyl

substituents in the *ortho* position reacted most efficiently to furnish the corresponding phenols in excellent yield at room temperature, as did 1-bromo- and 1-chloronapthalene. While higher temperatures were required in order to achieve efficient conversion for alternative substrates, such reactions proceeded smoothly affording the target phenol.

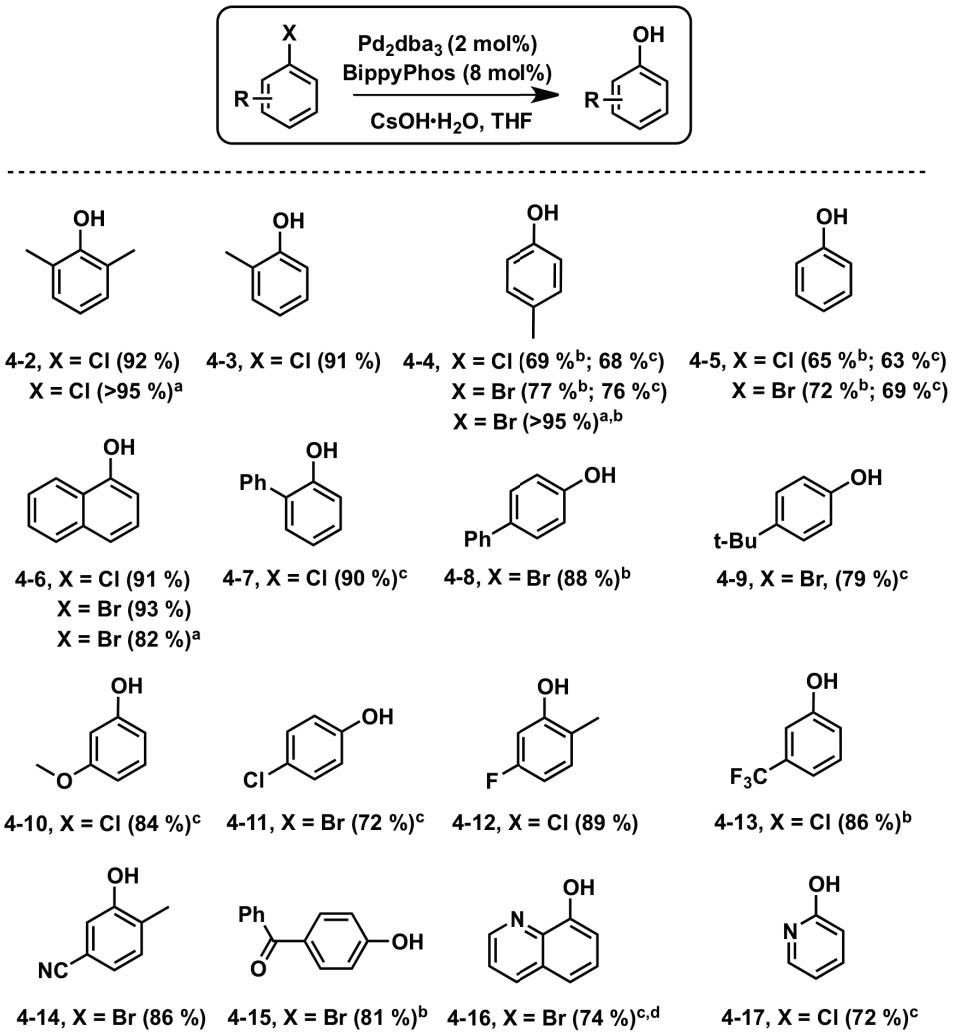


Figure 4–3. Scope of Pd_2dba_3/BippyPhos catalyzed cross-coupling of (hetero)aryl halides with $CsOH{\cdot}H_2O$ to form phenols. Reactions at 24 °C unless stated; 20 h reaction time (unoptimized); yields are of isolated product unless stated. [a]Reaction performed under air; yields are reported on the basis of calibrated GC data (see Section 4.4). [b]65 °C. [c]100 °C, 1,4-dioxane. [d]Pd/BippyPhos loading = 8/12 mol%.

Phenols can serve as synthons in the formation of sought-after oxygen containing heterocycles such as benzofurans.[11,72,73,100] In this context, attention was next turned towards investigating the utility of the Pd_2dba_3/BippyPhos catalyst system in enabling

tandem carbon-oxygen cross-coupling/hydrophenoxylation processes starting from *ortho*-haloalkynylarenes (Figure 4–4). Reports of such transformations are limited to a single publication from Buchwald and co-workers, wherein three examples in total (one using *t*BuXPhos, two using Me_4*t*BuXPhos) are featured.[91] Gratifyingly, the use of the Pd_2dba_3/BippyPhos catalyst system allowed for the preparation of benzofurans and related heteroaromatic derivatives featuring diverse substitution in high isolated yields (78–93 %, **4-18**–**4-24**). Under the conditions outlined in Figure 4–4, 1-bromo- and 1-chloro-2-(phenylethynyl)benzene were each readily converted to the corresponding C2-phenyl substituted benzofuran (**4-18**); methyl or fluoro substitution on the aryl bromide were also well-tolerated, affording **4-19** and **4-20**. 2-Bromoalkynylarene substrates featuring *n*-propyl or thiophen-3-yl substitution at the alkyne terminus also proved to be suitable substrates in combination with the Pd_2dba_3/BippyPhos catalyst system, producing the corresponding substituted benzofurans (**4-21** and **4-22**) in high isolated yields. In turning attention to reactions involving heteroaryl halides, we were pleased to observe that the use of 2-bromo-3-(phenylethynyl)thiophene enabled the formation of the thienofuran **4-23**, while the use 2-bromo-3-(phenylethynyl)pyridine proceeded smoothly to give the furopyridine **4-24**, each in high isolated yield.

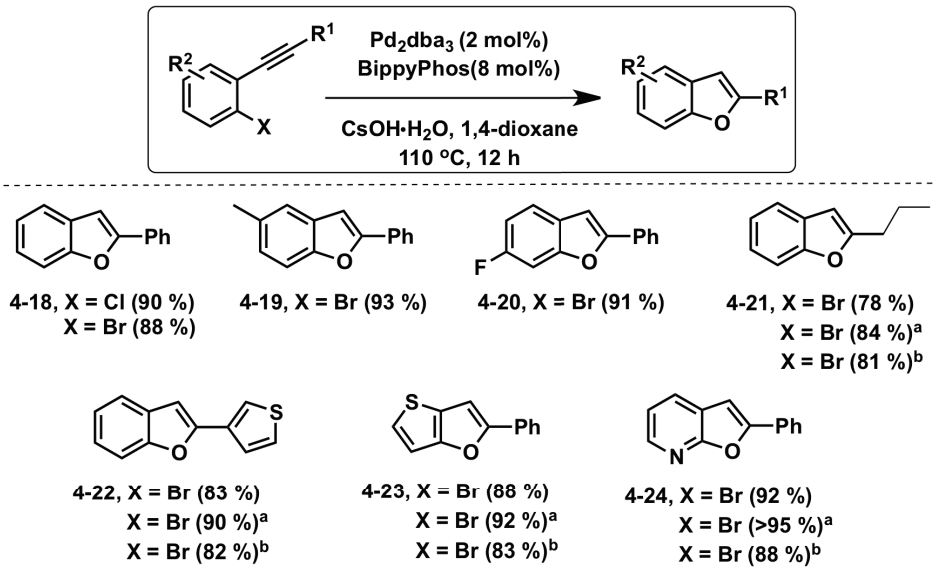


Figure 4–4. Scope of Pd_2dba_3/BippyPhos catalyzed cross-coupling of *ortho*-alkynylhaloarenes with $CsOH{\cdot}H_2O$ to form benzofuran derivatives; yields are of isolated product unless stated. [a]Reaction performed under air; yields are reported on the basis of

calibrated GC data (see Section 4.4). [b]Reaction performed under air using benchtop quality 1,4-dioxane that was used as received from supplier; yields are reported on the basis of calibrated GC data (see Section 4.4).

For convenience, the reactions presented herein were typically setup within a dinitrogen-filled glovebox using purified solvents. However, control experiments employing representative substrates confirmed that hydroxylation reactions employing the Pd_2dba_3/BippyPhos catalyst system can be conducted under significantly less-rigorous conditions, including under air and using benchtop quality solvent that had not been pre-treated or purified in any way. This represents the first report of palladium-catalyzed aryl halide hydroxylation to be conducted under such non-inert conditions. Initial investigations confirmed that the hydroxylation of bromomesitylene to give **4-1** (24 ºC, THF) proceeds quantitatively when the reaction is conducted under air, including when using unpurified, benchtop quality solvent. Having confirmed subsequently that reactions conducted in air leading to **4-2**, **4-4** and **4-6** were also successful (Figure 4–3), the synthesis of **4-21**–**4-24** under benchtop conditions was rexamined. Gratifyingly, in all cases the Pd_2dba_3/BippyPhos catalyst system proved to be robust, maintaining high activity and conversions to the target furan, even while operating under air and/or when using benchtop quality solvents (Figure 4–4). These results further establish the practical utility of the Pd_2dba_3/BippyPhos catalyst system for the hydroxylation of aryl halides under a range of experimental conditions.

4.3 Summary and Conclusions

In summary, a robust and efficient catalyst system for the hydroxylation of aryl halides comprised of Pd_2dba_3 and Bippyphos was identified. In utilizing the Pd_2dba_3/BippyPhos catalyst system, a diversity of (hetero)aryl halides were transformed to the corresponding phenols, with a significant number of these transformations proceeding at room temperature. This catalytic chemistry was also successfully applied in the synthesis of structurally diverse benzofurans and related heteroatomic derivatives, which are formed via the hydroxylation of *ortho*-alkynylhalo(hetero)arenes. Notably, the performance of Pd_2dba_3/BippyPhos is competitive with the best catalyst systems reported thus far in the literature for such transformations. Moreover, by using the

Pd_2dba_3/BippyPhos catalyst system the first examples of palladium-catalyzed aryl halide hydroxylation to be conducted under air and using unpurified, as-received reaction solvents, which proceed with negligible loss in reactivity relative to transformations conducted under inert-atmosphere conditions was achieved, thereby offering a useful practical advance. It is envisioned that the desirable performance of the commercially available Pd_2dba_3/BippyPhos catalyst system will facilitate the broader uptake of palladium-catalyzed hydroxylation protocols by end-users in both academic and industrial settings.

4.4 Experimental Section

4.4.1 General Considerations

Unless otherwise noted, all reactions were set up inside a dinitrogen-filled inert atmosphere glovebox and worked up in air using benchtop procedures. Unless otherwise noted, 1,4-dioxane and THF used in the catalytic transformations were dried over Na/benzophenone followed by distillation under an atmosphere of dinitrogen. $[Pd(cinnamyl)Cl]_2$ used in the palladium source evaluation experiments was prepared according to a literature protocol.[129] *Ortho*-haloalkynylarene substrates were prepared by using literature synthetic protocols involving Sonogashira reactions of aryl iodides[132,133] or bromides[134] with appropriate terminal alkyne precursors. BippyPhos, Cy-BippyPhos and TrippyPhos were provided as gifts from Digital Specialty Chemicals. All other chemicals were obtained from commercial sources in high purity and used as received. Flash column chromatography was performed on silica gel (SiliaFlash P60, Silicycle) or 150 mesh Brockmann III activated, neutral alumina oxide, as indicated. Gas chromatography (GC) data were obtained on a Shimadzu GC-2014 equipped with a SGE BP-5 30 m, 0.25 mm I.D. column. In the case where conversions and yields are given on the basis of gas chromatography experiments, the data were corrected by calibration using dodecane as an internal standard and product identity was confirmed by comparison with authentic samples. All ^{1}H NMR (500 MHz) and ^{13}C NMR (125.8 MHz) spectra were recorded at 300 K. Chemical shifts are expressed in parts per million (ppm) using the solvent signals $CDCl_3$ (^{1}H 7.26 ppm, ^{13}C 77.36 ppm) or DMSO-*d6* (^{1}H 2.50 ppm, ^{13}C 39.52 ppm) as internal references. Splitting patterns are indicated as follows: br,

broad; s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet. All coupling constants (*J*) are reported in Hertz (Hz). In some cases fewer than expected independent carbon 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). Special thanks is given to Nicolas Rotta-Loria who helped with the synthesis and characterization of some of the catalytic reaction products (Section 4.2.2).

4.4.2 General Catalytic Protocols

General Catalytic Protocol A (GPA, Phenol synthesis):

To an oven dried screw-capped vial was added a stir bar, Pd_2dba_3 (4 mol%), BippyPhos (8 mol%), $CsOH{\cdot}H_2O$ (3 mmol), (hetero)aryl halide (1 mmol) and 2 mL of THF (24 °C or 65 °C) or 1,4-dioxane (110 °C). The vial was then sealed under dinitrogen with a cap containing a PTFE septum, removed from the glovebox and placed in a temperature-controlled aluminum heating block set at the required temperature and stirred vigorously. Reaction progress was monitored by use of TLC or GC methods and after complete consumption of the aryl halide was observed (8-20 h), the reaction mixture was allowed to cool, if necessary, and then acidified with 2 N aqueous HCl and diluted with water. The resulting solution was extracted with either ethyl acetate or ether (3x2 mL). The collected organic extractions were dried over sodium sulfate, filtered and concentrated to afford crude product which was further purified by use of column chromatography. **GPA** conditions: [a]THF, 24 °C; [b]THF, 65 °C; [c]1,4-dioxane, 110 °C.

General Catalytic Protocol B (GPB, Benzofuran synthesis):

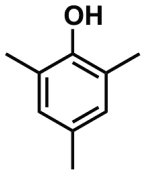
To an oven dried screw-capped vial was added a stir bar, Pd_2dba_3 (4 mol%), BippyPhos (8 mol%), $CsOH{\cdot}H_2O$ (3 mmol), *ortho*-alkynylhaloarene (1 mmol) and 2 mL of 1,4-dioxane. The vial was then sealed under dinitrogen with a cap containing a PTFE septum, removed from the glovebox, placed in a temperature-controlled aluminum heating block set at 110 °C and stirred vigorously. Reaction progress was monitored by use of TLC or GC methods and after complete consumption of the *ortho*-alkynylhaloarene was observed (12 h), the reaction mixture was cooled, diluted with ethyl acetate (50 mL) and washed with water (3x50 mL). The layers were separated and dried over sodium sulfate, filtered

and concentrated to afford crude product which was further purified by use of column chromatography.

Experiments Conducted Under Air:

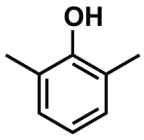
GPA and **GPB** were followed in the case of experiments conducted under air with the exception that reactions were set up on the benchtop (using where noted unpurified, as-received solvents). The yields reported for these experiments are given on the basis of gas chromatography experiments, the data were corrected by calibration using dodecane as an internal standard and product identity was confirmed by comparison with authentic samples.

4.4.3 Synthesis and Charterization of Isolated Reaction Products



(4-1) 2,4,6-Trimethyl-phenol.

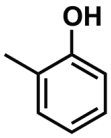
Following **GPA**, the title compound was isolated as a white solid (X = Br, 89 %[a], 109 mg, 0.89 mmol). The extraction was performed with ethyl acetate, and an ether:pentane (1:4) eluent system was used for column chromatography. ^{1}H NMR ($CDCl_3$): δ 6.80 (s, 2H), 4.45 (s, 1H), 2.23 (s, 3H), 2.22 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 150.2, 129.6, 129.4, 123.1, 20.7, 16.1. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[87] The title product was also formed under air (> 95 %[a]).



(4-2) 2,6-Dimethyl-phenol.

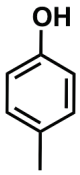
Following **GPA**, the title compound was isolated as a colorless oil (X = Cl, 92 %[a], 112 mg, 0.92 mmol). The extraction was performed with ether, and an ether:pentane (1:10) eluent system was used for column chromatography. ^{1}H NMR ($CDCl_3$): δ 7.00 (d, J = 7.5 Hz, 2H), 6.79 (apparent t, J = 7.5 Hz, 1H), 4.64 (s, 1H), 2.28 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 152.3, 128.7, 123.1, 120.3, 16.0. Spectral data are in good agreement with

previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[87] The title product was also formed under air (> 95 %[a]).



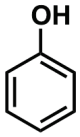
(4-3) 2-Methyl-phenol.

Following **GPA**, the title compound was isolated as a colorless oil (X = Cl, 91 %[a], 98 mg, 0.91 mmol). The extraction was performed with ether, and an ether:pentane (1:10) eluent system was used for column chromatography.^{1}H NMR ($CDCl_3$): δ 7.16 (d, J = 7.4 Hz, 1H), 7.12 (dt, J = 8.0 Hz, J = 1.2 Hz, 1H), 6.89 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 4.99 (s, 1H), 2.29 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 153.9, 131.3, 127.3, 124.0, 121.0, 115.1, 16.3. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[87]



(4-4) 4-Methyl-phenol.

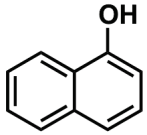
Following **GPA**, the title compound was isolated as a light yellow oil (X = Cl, 69 %[b], 75 mg, 0.69 mmol; 68 %[c], 74 mg, 0.68 mmol), (X = Br, 77 %[b], 83 mg, 0.77 mmol; 76 %[c], 82 mg, 0.76 mmol). The extraction was performed with ether, and an ether:pentane (1:10) eluent system was used for column chromatography. ^{1}H NMR ($CDCl_3$): δ 7.04 (d, J = 8.1 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 5.73 (s, 1H), 2.32 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 153.2, 130.4, 115.5, 20.7. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[87] Title product was also formed under air (X = Br, > 95 %[b]).



(4-5) Phenol.

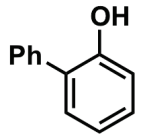
Following **GPA**, the title compound was isolated as a white solid (X = Cl, 65 %[b], 61 mg, 0.65 mmol; 63 %[c], 59 mg, 0.63 mmol), (X = Br, 72 %[b], 68 mg, 0.72 mmol; 69 %[c], 65 mg,

0.76 mmol). The extraction was performed with ether, and an ether:pentane (1:5) eluent system was used for column chromatography. ^{1}H NMR ($CDCl_3$): δ 7.315-7.28 (m, 2H), 6.99 (m, 1H), 6.90 (m, 2H), 5.78 (br s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 155.5, 129.8, 120.9, 115.5. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[87]



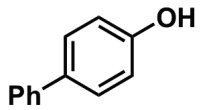
(4-6) Naphthalen-1-ol.

Following **GPA**, the title compound was isolated as a white solid (X = Cl, 91 %[a], 131 mg, 0.91 mmol), (X = Br, %[a], 134 mg, 0.93 mmol). The extraction was performed with ethyl acetate, and an ethyl acetate:hexanes (1:10) eluent system was used for column chromatography. ^{1}H NMR ($CDCl_3$): δ 8.20 (m, 1H), 7.83 (m, 1H), 7.53-7.49 (m, 2H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.32 (m, 1H), 6.82 (dd, *J* = 7.4 Hz, *J* = 0.8 Hz, 1H), 5.32 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 151.7, 135.1, 128.0, 126.8, 126.2, 125.6, 124.7, 121.9, 121.0, 108.9. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[87] The title product was also formed under air (X = Br, 82 %[a]).



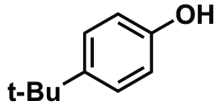
(4-7) Biphenyl-2-ol.

Following **GPA**, the title compound was isolated as a white solid (X = Cl, 90 %[c], 153 mg, 0.90 mmol). The extraction was performed with ethyl acetate, and an ethyl acetate:hexanes (1:20→1:10) eluent system was used for column chromatography. ^{1}H NMR (DMSO-d6): δ 9.42 (s, 1H), 7.45-7.43 (m, 2H), 7.30-7.26 (m, 2H), 7.19-7.13 (m, 2H), 7.06 (m, 1H), 6.86 (dd, *J* = 8.1 Hz, *J* = 1.1 Hz, 1H), 6.77 (dt, *J* = 7.4 Hz, *J* = 1.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (DMSO-d6): δ 155.3, 139.6, 131.3, 130.1, 129.5, 128.9, 128.7, 127.4, 120.4, 117.0. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[85]



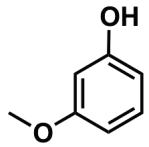
(4-8) Biphenyl-4-ol.

Following **GPA**, the title compound was isolated as a white solid (X = Br, 88 %[b], 150 mg, 0.88 mmol). The extraction was performed with ethyl acetate, and an ethyl acetate:hexanes (1:20→1:10) eluent system was used for column chromatography. ^{1}H NMR (DMSO-d6): δ 9.48 (s, 1H), 7.49-7.46 (m, 2H), 7.41-7.38 (m, 2H), 7.32-7.29 (m, 2H), 7.17 (m, 1H), 6.79-6.76 (m, 2H); ^{13}C{^{1}H} NMR (DMSO-d6): δ 158.1, 141.2, 131.9, 129.7, 128.7, 127.3, 126.9, 116.7. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[228]



(4-9) 4-*tert*-Butyl-phenol.

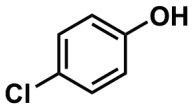
Following **GPA**, the title compound was isolated as a white solid (X = Br, 79 %[c], 119 mg, 0.79 mmol). The extraction was performed with ethyl acetate, and an ethyl acetate:hexanes (1:20) eluent system was used for column chromatography. ^{1}H NMR (DMSO-d6): δ 9.08 (s, 1H), 7.12 (dd, *J* = 6.5 Hz, *J* = 2.0 Hz, 2H), 6.63 (dd, *J* = 6.5 Hz, *J* = 2.0 Hz, 2H), 1.18 (s, 9H). ^{13}C NMR (DMSO-d6): δ 154.9, 140.8, 125.8, 114.6, 33.5, 31.4. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[229]



(4-10) 3-Methoxy-phenol.

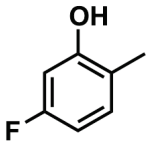
Following **GPA**, the title compound was isolated as a white solid (X = Cl, 84 %[c], 104 mg, 0.84 mmol). The extraction was performed with ethyl acetate, and an ethyl acetate:hexanes (1:10) eluent system was used for column chromatography. ^{1}H NMR ($CDCl_3$): δ 7.14 (t, *J* = 8.3 Hz, 1H), 6.52 (m, 1H), 6.48-6.44 (m, 2H), 6.03 (br s, 1H), 3.77 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 161.0, 157.0, 130.5, 108.3, 106.8, 101.9, 55.6.

Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[79]



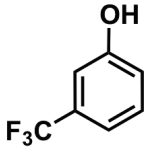
(4-11) 4-Chloro-phenol.

Following **GPA**, the title compound was isolated as a white solid (X =Br, 72 %[c], 93 mg, 0.72 mmol). The extraction was performed with ether, and an ethyl acetate:hexanes (1:5) eluent system was used for column chromatography. ^{1}H NMR (DMSO-d6): δ 9.68 (s, 1H), 7.20 (dd, J = 6.5 Hz, J = 2.0 Hz, 2H), 6.79 (dd, J = 7.0 Hz, J = 2.5 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (DMSO-d6): δ 156.3, 129.1, 122.3, 116.9. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[229]



(4-12) 5-Fluoro-2-methyl-phenol.

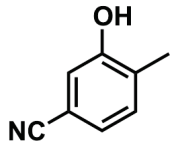
Following **GPA**, the title compound was isolated as an orange oil (X = Cl, 89 %[a], 112 mg, 0.89 mmol). The extraction was performed with ether, and an ethyl acetate:hexanes (1:5) eluent system was used for column chromatography. ^{1}H NMR ($CDCl_3$): δ 7.04 (t, J = 7.5 Hz, 1H), 6.55 (m, 2H), 4.99 (s, 1H), 2.20 (s, 3H); $^{13}C\{^{1}H\}$ NMR (CDCl3): δ 162.0 (d, J = 250 Hz), 154.8 (d, J = 6 Hz), 131.5 (d, J = 10 Hz), 119.4 (d, J = 3 Hz), 107.5 (d, J = 20 Hz), 102.8 (d, J = 24 Hz), 15.3. Spectral data are in good agreement with an authentic commercially available sample.



(4-13) 3-Trifluoromethyl-phenol.

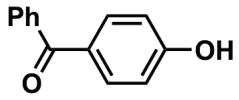
Following **GPA**, the title compound was isolated as a light yellow oil (X = Cl, 86 %[b], 139 mg, 0.86 mmol). The extraction was performed with ethyl acetate, and an ethyl acetate:hexanes (1:10) eluent system was used for column chromatography. ^{1}H NMR ($CDCl_3$): δ 7.36 (t, J = 7.9 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.10 (s, 1H), 7.02 (dd, J = 8.2 Hz, J = 2.5 Hz, 2H), 5.76 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 155.7, 132.4 (q, J = 32

Hz), 130.7, 124.4 (q, J = 270 Hz), 119.2, 118.2 (d, J = 3.7 Hz), 112.7 (d, J = 3.6 Hz). Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[230]



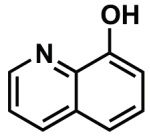
(4-14) 3-Hydroxy-4-methyl-benzonitrile.

Following **GPA**, the title compound was isolated as a white solid (X = Br, 86 %[a], 115 mg, 0.86 mmol). The extraction was performed with ethyl acetate, and an ethyl acetate:hexanes (1:10→1:5) eluent system was used for column chromatography. ^{1}H NMR ($CDCl_3$): δ 7.20 (d, J = 7.7 Hz, 1H), 7.15-7.11 (m, 2H), 6.47 (br s, 1H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 154.9, 132.1, 131.7, 124.7, 119.3, 118.1, 109.7, 16.6. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[87]



(4-15) 4-Hydroxy-benzophenone.

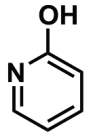
Following **GPA**, the title compound was isolated as an off-white solid (X = Br, 81 %[b], 161 mg, 0.81 mmol). The extraction was performed with ethyl acetate, and an ethyl acetate:hexanes (1:5) eluent system was used for column chromatography. ^{1}H NMR (DMSO-d6): δ 10.46 (s, 1H), 7.68-7.65 (m, 4H), 7.61 (m, 1H), 7.54-7.51 (m, 2H), 6.90 (m, 2H); ^{13}C{^{1}H} NMR (DMSO-d6): δ 194.3, 162.0, 138.1, 132.5, 131.8, 129.1, 128.4, 127.9, 115.3. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[87]



(4-16) Quinolin-8-ol.

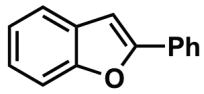
Following **GPA** but with a Pd/BippyPhos loading of 8/12 mol%, the title compound was isolated as an off-white solid (X = Br, 74 %[c], 107 mg, 0.74 mmol). The extraction was performed with ethyl acetate, and a methanol:methylene chloride (1:20) eluent system

was used for column chromatography. ^{1}H NMR (DMSO-d6): δ 9.87 (br s, 1H), 8.85 (dd, *J* = 4.2 Hz, *J* = 1.7 Hz, 1H), 8.32 (dd, *J* = 8.3 Hz, *J* = 1.6 Hz, 1H), 7.54 (dd, *J* = 4.2 Hz, *J* = 4.2 Hz, 1H), 7.44 (t, *J* = 8.1 Hz, 1H), 7.39 (dd, *J* = 8.2 Hz, *J* = 1.4 Hz, 1H), 7.10 (dd, *J* = 7.5 Hz, *J* = 1.4 Hz, 1H); ^{13}C{^{1}H} NMR (DMSO-d6): δ 153.3, 148.1, 138.5, 136.0, 128.8, 127.5, 121.8, 117.7, 111.3. Spectral data are in good agreement with an authentic commercially available sample.



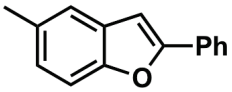
(4-17) Quinolin-8-ol.

Following **GPA**, the title compound was isolated as a brown solid (X = Cl, 72 %[c], 68 mg, 0.72 mmol). The extraction was performed with ethyl acetate, and a methanol:methylene chloride (1:10) eluent system was used for column chromatography. ^{1}H NMR (DMSO-d6): δ 11.61 (br s, 1H), 7.42-7.35 (m, 2H), 6.31 (d, *J* = 9.2 Hz, 1H), 6.15 (d, *J* = 6.5 Hz, 1H); ^{13}C{^{1}H} NMR (DMSO-d6): δ 162.8, 141.0, 135.5, 120.0, 104.9. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[231]



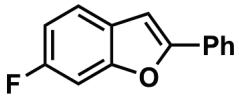
(4-18) 2-Phenyl-benzofuran.

Following **GPB**, the title compound was isolated as a white solid (X = Cl, 90 %, 175 mg, 0.88 mmol), (X = Br, 88 %, 171 mg, 0.90 mmol). An ethyl acetate:hexanes (1:100) eluent system was used for column chromatography. ^{1}H NMR ($CDCl_3$): δ 7.91-7.89 (m, 2H), 7.62 (m, 1H), 7.56 (m, 1H), 7.50-7.47 (m, 2H), 7.38 (m, 1H), 7.32 (m, 1H), 7.26 (m, 1H), 7.06 (d, *J* = 0.9 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 156.2, 155.2, 130.8, 129.6, 129.1, 128.9, 125.3, 124.6, 123.2, 121.2, 11.5, 101.6. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[232]



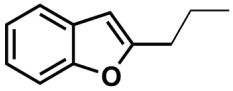
(4-19) 5-Methyl-2-phenyl-benzofuran.

Following **GPB**, the title compound was isolated as a white solid (X = Br, 93 %, 194 mg, 0.93 mmol). An ethyl acetate:hexanes (1:100) eluent system was used for column chromatography. ^{1}H NMR ($CDCl_3$): δ 7.88-7.86 (m, 2H), 7.47-7.41 (m, 3H), 7.38-7.34 (m, 2H), 7.10 (dd, *J* = 8.4 Hz, *J* = 1.3 Hz, 1H), 6.97 (d, *J* = 0.9 Hz, 1H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 156.5, 153.8,132.8, 131.1, 129.8, 129.2, 128.9, 126.0, 125.3, 121.2, 111.1, 101.6, 21.8. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[233]



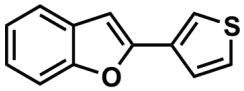
(4-20) 5-Fluoro-2-phenyl-benzofuran.

Following **GPB**, the title compound was isolated as a white solid (X = Br, 91 %, 193 mg, 0.91 mmol). An ethyl acetate:hexanes (1:50) eluent system was used for column chromatography. ^{1}H NMR ($CDCl_3$): δ 7.88-7.86 (m, 2H), 7.55-7.48 (m, 3H), 7.40 (m, 1H), 7.29 (m, 1H), 7.07-7.03 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 161.1 (d, *J* = 245 Hz), 157.0 (d, *J* = 4 Hz), 155.0 (d, *J* = 13 Hz), 130.5, 129.0, 128.8, 125.7, 124.9, 121.3 (d, *J* = 10 Hz), 111.5 (d, *J* = 24 Hz), 101.2, 99.2 (d, *J* = 27 Hz); *m/z* ESI^{+} found 2130.0715 $[M+H]^{+}$ calculated for $C_{14}H_{10}F_1O_1$ 213.0710.



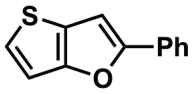
(4-21) 2-Propyl-benzofuran.

Following **GPB**, the title compound was isolated as a yellow oil (X = Br, 78 %, 125 mg, 0.78 mmol). An ethyl acetate:hexanes (1:100) eluent system was used for column chromatography. ^{1}H NMR ($CDCl_3$): δ 7.48 (d, *J* = 7.4 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.19 (m, 2H), 6.38 (s, 1H), 2.75 (t, *J* = 7.5 Hz, 2H), 1.78 (sextet, *J* = 7.5 Hz, 2H), 1.02 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 159.7, 154.9, 129.2, 123.3, 122.6, 120.4, 111.0, 102.1, 30.6, 21.3, 13.9. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[234] The title product was also formed under air (84 %) and under air using benchtop quality solvent (81 %).



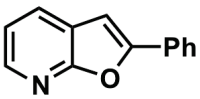
(4-22) 2-Thiophen-3-yl-benzofuran.

Following **GPB**, the title compound was isolated as a white solid (X = Br, 83 %, 166 mg, 0.83 mmol). An ethyl acetate:hexanes (1:100→1:50) eluent system was used for column chromatography. ^{1}H NMR ($CDCl_3$): δ 7.75 (dd, *J* = 2.9 Hz, *J* = 1.2 Hz, 1H), 7.58 (dd, *J* = 7.5 Hz, *J* = 6.5 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.48 (dd, *J* = 5.1 Hz, *J* = 1.2 Hz, 1H), 7.42 (dd, *J* = 5.1 Hz, *J* = 2.9 Hz, 1H), 7.29 (dt, *J* = 7.3 Hz, *J* = 1.3 Hz, 1H), 7.22 (dt, *J* = 7.6 Hz, *J* = 1.0 Hz, 1H), 6.86 (d, *J* = 0.5 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 155.1, 153.4, 133.2, 129.7, 126.9, 125.5, 124.5, 123.3, 121.8, 121.2, 111.4, 101.4. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[235] The title product was also formed under air (90 %) and under air using benchtop quality solvent (82 %).



(4-23) 2-Phenyl-thieno[3,2-b]furan.

Following **GPB**, the title compound was isolated as a light pink oil (X = Br, 88 %, 176 mg, 0.88 mmol). An ethyl acetate:hexanes (1:50) eluent system was used for column chromatography. ^{1}H NMR ($CDCl_3$): δ 7.78 (d, *J* = 8.2 Hz, 1H), 7.61 (m, 1H), 7.44 (m, 1H), 7.39 (m, 1H), 7.38-7.29 (m, 2H), 7.18 (m, 1H), 7.05 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 132.2, 131.8, 129.1, 128.8, 128.7, 127.6, 127.4, 125.6, 124.2, 111.3, 101.4; *m/z* ESI^{+} found 201.0364 $[M+H]^{+}$ calculated for $_{12}H_9S_1O_1$ 201.0369. The title product was also formed under air (92 %) and under air using benchtop quality solvent (83 %).



(4-24) 2-Phenyl-furo[2,3-b]pyridine.

Following **GPB**, the title compound was isolated as a pale yellow solid (X = Br, 91 %, 178 mg, 0.91 mmol). An ethyl acetate:hexanes (1:50) eluent system was used for column chromatography.^{1}H NMR ($CDCl_3$): δ 8.29 (dd, *J* = 4.8 Hz, *J* = 1.7 Hz, 1H), 7.92-7.88 (m, 3H), 7.46 (dt, *J* = 7.3 Hz, *J* = 1.6 Hz, 2H), 7.38 (tt, *J* = 6.7 Hz, *J* = 1.2 Hz, 1H), 7.21 (dd, *J* = 7.6 Hz, *J* = 4.9 Hz, 1H), 7.00 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 162.2, 155.9, 144.2,

129.9, 129.8, 129.6, 129.2, 125.5, 121.8, 119.8, 100.3. Spectral data are in good agreement with previously reported ^{1}H and ^{13}C NMR characterization data for the title product.[236] The title product was also formed under air (> 95 %) and under air using benchtop quality solvent (83 %).

CHAPTER 5 CONCLUSIONS

5.1 CHAPTER 2 SUMMARY AND FUTURE DIRECTIONS

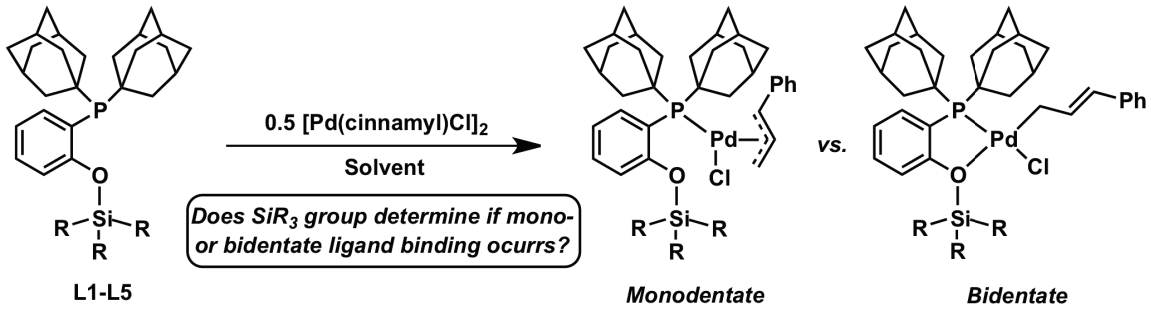
5.1.1 Chapter 2 Summary

In Chapter 2 the new and easily prepared OTips-DalPhos ligand (**L1**) was shown to offer remarkably broad substrate scope at relatively low loadings in the palladium-catalyzed carbon-nitrogen cross-coupling/cyclization of *ortho*-alkynylhalo(hetero)arenes with a wide range of stucturally and electronically diverse primary amines to afford indoles and related heterocyclic derivatives in synthetically useful yields. A PCT patent application has been filed on OTips-DalPhos and this material is now commercially available from Sigma Aldrich. Inspired by the success of OTips-DalPhos in this catalytic application, several new P,O-DalPhos ligand variants were prepared (**L2–L5**) to investigate the effect of varying their silicon moieties on catalytic performance. The findings presented in Chapter 2 confirm that the silicon moiety featured in this class of ligands does indeed impact both the ligand stability and catalytic performance. There was only one P,O-DalPhos variant, **L2**, which features a bulky tri-*t*butoxy silyl group, that proved capable of accommodating ammonia in palladium-catalyzed carbon-nitrogen cross-coupling/cyclization applications. Moreover, **L2** also outperformed OTips-DalPhos in this chemistry in head-to-head comparison reactions employing aniline as the amine coupling for bromo-2-(phenylethynyl)benzene at decreased catalyst loadings. These results suggest that the choice of SiR_3 groups can be used as a tool to modulate catalyst activity and that P,O-DalPhos variants featuring more sterically demanding SiR_3 groups represent attractive targets of future investigation.

5.1.2 Chapter 2 Future Directions

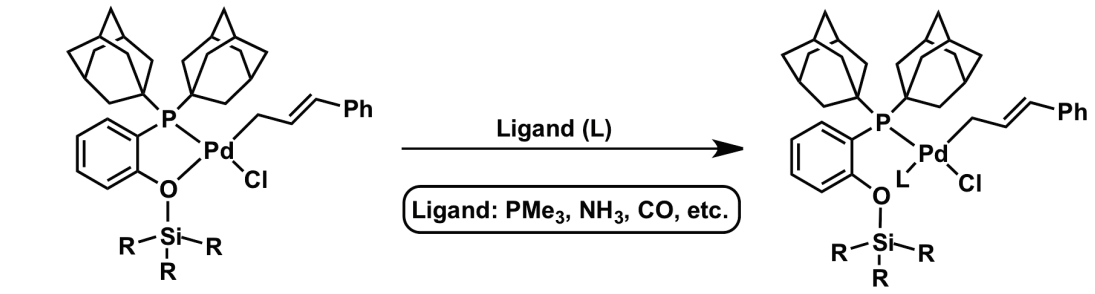
There is still research needed to fully appreciate the catalytic influence of the silicon moities featured in the newly developed series of P,O-DalPhos ligands (**L1–L5**) that were disclosed in Chapter 2. Understanding the binding modes of **L1–L5** would provide greater insight into such matters. Therefore, it will be necessary to prepare palladium coordination complexes of the P,O-DalPhos ligands for NMR (^{1}H, ^{13}C and ^{31}P) and X-ray crystallographic analysis to elucidate the denticity of **L1–L5**, and also to see if there is a change in denticity depending upon the nature of SiR_3 group. Such complexes could straightforwardly be prepared by reaction of equimolar amounts of **L1–L5** and a

palladium source (e.g. $[Pd(cinnamyl)Cl]_2$) in an appropriate solvent (Scheme 5-1); reaction progress could easily monitored by use of ^{31}P NMR analysis. The proposed products in Scheme 5-1 are based on previous studies performed investigating the binding mode of Mor-DalPhos with palladium.[56,58]



Scheme 5-1. Synthesis of palladium coordination complexes supported by **L1**–**L5**.

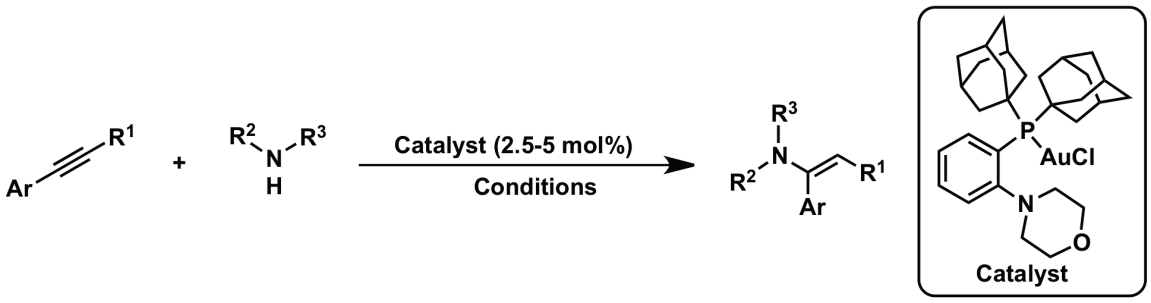
As described in Section 2.2.1, it is conceivable that the oxygen heteroatom featured in these P,O-DalPhos ligands is capable of interacting with palladium in a hemilable fashion. This would involve **L1**–**L5** adopting a bidentate binding mode (see bidentate product in Scheme 5-1) unless in the presence of a competitive nucleophile/ligand capable of displacing the oxygen donor atom at palladium. Furthermore, this phenomenon could be a contributing reason to the demonstrated ability of this class of ligands to accommodate such a diversity of reaction partners in palladium-catalyzed carbon-nitrogen cross-coupling/cyclization chemistry. The propensity for **L1**–**L5** to exhibit hemilabile interactions with palladium could easily be probed by reacting [(P,O-DalPhos)Pd(cinnamyl)Cl] complexes with competitive ligands to look for ligand displacement involving the P,O-DalPhos ligand framework (Scheme 5–2). These experiments could also easily be monitored by ^{31}P NMR analysis but full NMR characterization (^{1}H, ^{13}C and ^{31}P) and X-ray crystallographic analysis would be required to unequivocally confirm ligand displacement in the reaction products.



Scheme 5–2. Reaction scheme for probing the hemilability nature of P,O-DalPhos ligands.

Future work for this series of P,O-DalPhos ligands will also include testing their utility in other palladium-catalyzed applications such as sterically hindered Suzuki reactions of the type described in Section 1.3 (see Figure 1–2). If these ligands are indeed hemilabile, this could be a beneficial attribute in accommodating the sterically demanding tetra-*ortho*-substituted coupling partners employed in these challenging carbon-carbon cross-coupling reactions. There is also literature precedent to suggest that ligands featuring P,O-heteroatom pairings will perform well in this type of chemistry.[25]

Finally, the useful nature of a (Mor-DalPhos)AuCl catalyst system in the regio- and stereoselective hydroamination of internal alkynes has been described (Scheme 5–3).[237] Therefore, additional future work in this area will involve synthesizing analgous (P,O-DalPhos)AuCl catalysts, and evaluating there efficacy in similar transformations.



Scheme 5–3. (Mor-DalPhos)AuCl catalyzed hydroamination of internal alkynes.

Research goals in this area would include allowing for decreased catalyst loadings, accommodation of mild and/or benchtop condtions, and synthesizing catalytic intermediates to help shed light on the unknown mechanism of this gold-catalyzed carbon-nitrogen bond forming transformation.

5.2 Chapter 3 Summary and Future Directions

5.2.1 Chapter 3 Summary

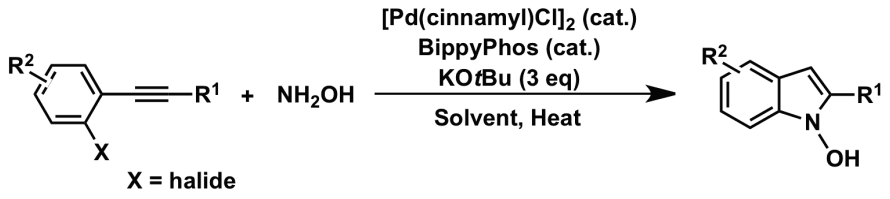
In Chapter 3, [Pd(cinnamyl)Cl]$_2$/BippyPhos mixtures were shown to be capable of catalyzing the amination of a variety of functionalized (hetero)aryl chlorides, as well as bromides and tosylates, at moderate to low catalyst loadings including representative examples conducted in air. The successful transformations described in Chapter 3 include primary and secondary amines, NH heterocycles, amides, sulfonamides, ammonia and hydrazine, thus demonstrating the largest scope in NH-containing coupling partner reported for a single Pd/ligand catalyst system. Use of the [Pd(cinnamyl)Cl]$_2$/BippyPhos catalyst system also allowed for the broadest demonstrated substrate scope for the metal-catalyzed cross-coupling of (hetero)aryl chlorides with NH-indoles to be established. Furthermore, the remarkable and unusual ability of [Pd(cinnamyl)Cl]$_2$/BippyPhos mixtures to catalyze both the selective monoarylation of ammonia and the *N*-arylation of indoles was exploited in the development of a new one-pot, two-step synthesis of *N*-aryl heterocycles from ammonia, *ortho*-alkynylhalo(hetero)arenes and (hetero)aryl halides via tandem *N*-arylation/hydroamination reactions. While the scope in the NH-containing coupling partner was shown to be broad, a marked selectivity profile for [Pd(cinnamyl)Cl]$_2$/BippyPhos catalyst system was identified and successfully exploited in the chemoselective monoarylation of substrates featuring two chemically distinct and potentially reactive NH-moieties. Also disclosed in Chapter 3 was the first crystallographically characterized (Bippyphos)Pd^{II} complex, in which palladium is coordinated in a κ^2-*P*,*C*-bidentate fashion to BippyPhos via phosphorus and the *ipso* carbon of the lower pyrazole ring. The observed binding motif in BippyPhos is similar to that which is observed for Buchwald's popular biarylphosphine ligand class.

5.2.2 Chapter 3 Future Directions

The accommodation of unprotected hydroxylamine as an NH-substrate in BHA applications remains an outstanding challenge. This is owing to the highly unstable nature and potential for unwanted side reactions (i.e. Bamberger rearrangements or disproportionation processes) of the *N*-arylhydroxylamine products that would be formed in such catalytic transformations. Furthermore, in addition to sharing the same potential for unwanted di- or even tri-arylated products being formed when employing ammonia as

a reaction partner in BHA, unprotected hydroxylamine poses chemoselective (*N*-arylation *vs. O*-arylation) issues as well. There exist two reports in the literature describing the use of Pd/BippyPhos catalysts for the formation of *N*-arylhydroxylamines in which protected hydroxylamines are employed and the so-formed products are subjected to deprotection conditions.[150,151] While these reports represent important progress towards the goal of accommodating free hydroxylamine in palladium-catalyzed cross-coupling, from an atom economical point-of-view the requirement of protecting groups is not ideal (Section 1.2).

It is envisioned that employing unprotected hydroxylamine in palladium-catalyzed carbon-nitrogen cross-coupling/cyclizations of the type described in Chapter 2 and Section 3.2.6 (specifically Method A, Step 1 in Figure 3–7) to form *N*-hydroxyindoles could be a viable methodolgy to control the selectivity and stability issues associated with employing unprotected hydroxylamine in palladium-catalyzed carbon-nitrogen cross-coupling applications. *N*-hydroxyindoles are considerably more stable than *N*-arylhydroxylamines and have been recently gaining significant attention owing to their useful nature as synthetic building blocks and potential biological relevance.[238-240] Therefore, future research directions for Chapter 3 will include applying the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system to carbon-nitrogen cross-coupling/cyclization reactions of *ortho*-alkynylhaloarenes with unprotected hydroxylamine to form *N*-hydroxy indoles as illustrated in Scheme 5–4.



Scheme 5–4. Proposed $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyzed carbon-nitrogen cross-coupling/cyclization of *ortho*-alkynylhaloarenes with unprotected hydroxylamine to form *N*-hydroxyindoles.

If appropriate conditions could be identified for the synthesis of *N*-hydroxyindoles by employing the $[Pd(cinnamyl)Cl]_2$/BippyPhos catalyst system in this useful carbon-nitrogen cross-coupling/cyclization transformation (Scheme 5–4) it would represent the first successful accommodation of unprotected hydroxylamine in palladium-catalyzed

cross-coupling chemistry, thereby adding a very useful component to the already diverse reactivity profile of the ligand BippyPhos.

5.3 Chapter 4 Summary and Future Directions

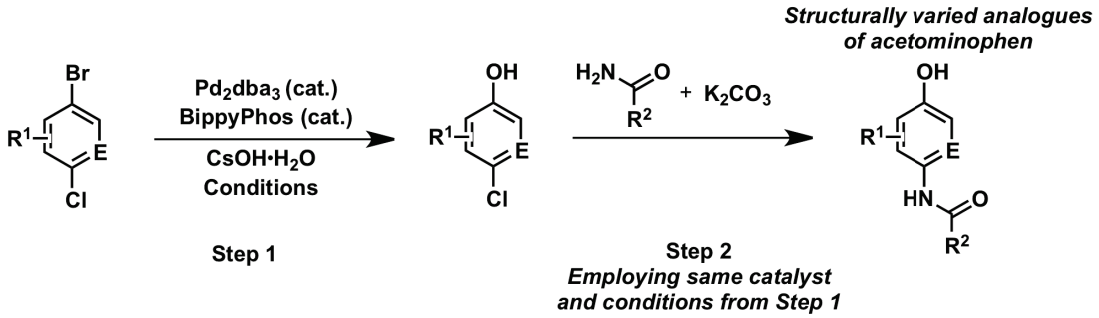
5.3.1 Chapter 4 Summary

In Chapter 4, a ligand reactivity survey identified Pd_2dba_3/BippyPhos mixtures as a promising catalyst for the hydroxylation of (hetero)aryl halides. Gratifyingly, in utilizing the Pd_2dba_3/BippyPhos catalyst system, a diversity of (hetero)aryl halides were transformed to the corresponding phenols, with a significant number of *ortho*-substituted substrates being accommodated at room temperature. Moreover, the successful synthesis of substituted benzofurans and related heteroatomic derivatives was achieved by employing the Pd_2dba_3/BippyPhos catalyst system in tandem *ortho*-alkynylhalo(hetero)arene hydroxylation/hydrophenoxylation transformations. Indeed, Pd_2dba_3/BippyPhos was shown to be competitive with the best catalyst systems reported thus far in the literature for such hydroxylation techniques. Furthermore, the first examples of palladium-catalyzed aryl halide hydroxylation to be conducted under air and using unpurified, as-received reaction solvents, which proceed with negligible loss in reactivity relative to transformations conducted under inert-atmosphere conditions, was achieved by using Pd_2dba_3/BippyPhos. As previously mentioned, it is envisioned that the desirable, robust, and efficient performance of the commercially available Pd_2dba_3/BippyPhos catalyst system will facilitate the broader uptake of palladium-catalyzed hydroxylation protocols in both academic and industrial settings.

5.3.2 Chapter 4 Future Directions

In an effort to demonstrate the useful nature and applicability of the Pd_2dba_3/BippyPhos catalyst system described in Chapter 4 for synthesizing phenols, in combination with the demonstrated ability of Pd/BippyPhos mixtures to accommodate a variety primary amides in BHA applications (Section 3.2.5), future research will involve applying these two methodologies in the synthesis of a series of structurally varied acetominophen analogues (see Figure 1–6 for structure of acetominophen). The biological relevance of acetominophen is illustrated by the fact that it is one of the most commonly used analgesics in the world, primarily being consumed for mild pain relief

and to reduce fevers. Notwithstanding the well-established acidification and/or reduction techniques for preparing acetominophen,[241,242] a methodology that would easily allow for structurally varied analogues of this biologically relevant compound under relatively mild conditions and with good functional group tolerance could have important applications in the identification of increasingly effective non-opiate analgesics or compounds possessing other desirable biological properties. A proposed one-pot, two-step methodology that could offer such adavantages is shown Scheme 5–5.

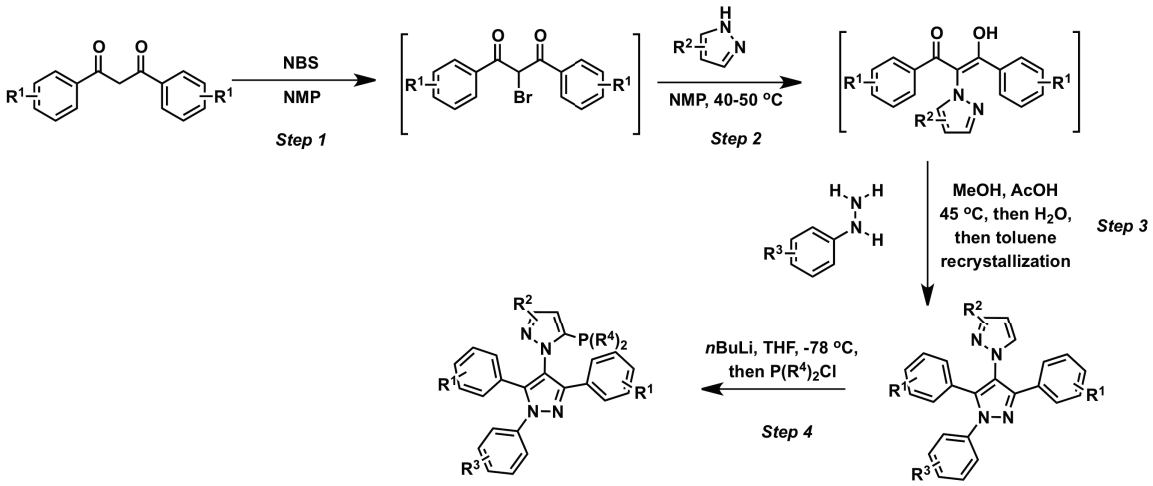


Scheme 5–5. A proposed one-pot, two-step Pd/BippyPhos catalyzed synthesis of structurally varied acetominophen analogues. E = N; R^1 = aryl, alkyl or H; R^2 = aryl, alkyl or H.

In step 1 of the proposed methodology presented in Scheme 5–5, the ability of Pd_2dba_3/BippyPhos mixtures to catalyze the hydroxylation of 1-bromo-4-chlorobenzene, and potentially variants thereof, is exploited to generate an intermediate product that in step 2 can be subjected to the amidation conditions described in Section 3.2.5 to form the target acetominophen analogues. Presumably, the demonstrated broad substrate scope for Pd/BippyPhos mixtures in both of these hydroxylation (Chapter 4) and amidation (Section 3.2.5) transformations would indeed allow for a variety of structurally diverse acetominophen analogues to be prepared for further investigation.

Furthermore, in building off the results presented in Chapter 4, additional future work will involve synthesizing more sterically demanding variants of BippyPhos. It is believed that employing BippyPhos variants capable of imparting greater steric influence at palladium could help facilitate carbon-oxygen reductive elimination from [L_nPd(aryl)OH] intermediates featuring aryl groups that lack *ortho*-substitution and in turn, allow for decreased reaction temperatures when employing such aryl halides in palladium-

catalyzed hydroxylation applications. In this context, each step in the reported synthesis of BippyPhos[63] can be exploited to prepare variants thereof with increased steric profiles (Scheme 5–6). For example in Step 1, functionalized 1,3-diphenylpropane-1,3-dione variants could be employed (R^1 = alkyl or aryl) to increase the steric bulk of the non-phosphorus containing ring in BippyPhos. Furthermore, substituted pyrazoles (R^2 = alkyl or aryl) and/or substituted aryl hydrazines (R^3 = alkyl or aryl) could be used in Steps 2 and 3, respectively, to add to the steric profile of both pyrazole rings featured in the BippyPhos motif. Finally in Step 4, employing a chlorophosphine featuring bulkier alkyl groups (e.g. R^4 = 1-adamantyl) would afford a ligand with the abililty to impart a greater steric influence on the metal centre. It is worth noting that a BippyPhos variant featuring 1-adamantyl groups at phosphorus has already been prepared,[64] however no other changes to the ligand framework were or have been described.



Scheme 5–6. Literature adapted synthesis of BippyPhos leading to more sterically demanding variants. NBS = *N*-bromosuccinimide; NMP = *N*-methyl-2-pyrrolidinone.

As previously eluded to, presumably the use of more sterically demanding BippyPhos variants in palladium-catalyzed applications in which reductive elimination is rate limiting, including the hydroxylation of aryl halides, would allow for increased reaction rates and the accommodation of milder conditions to be achieved.

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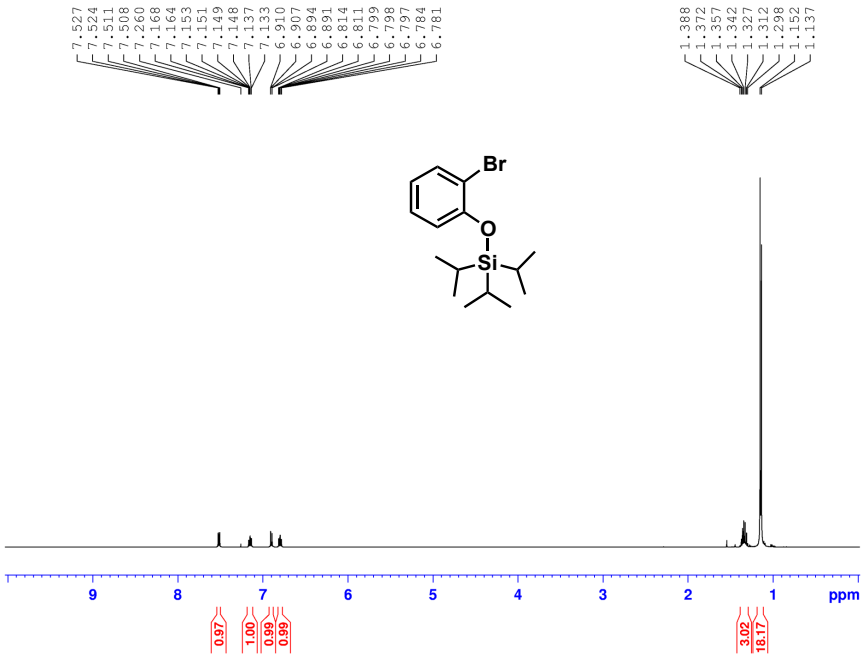
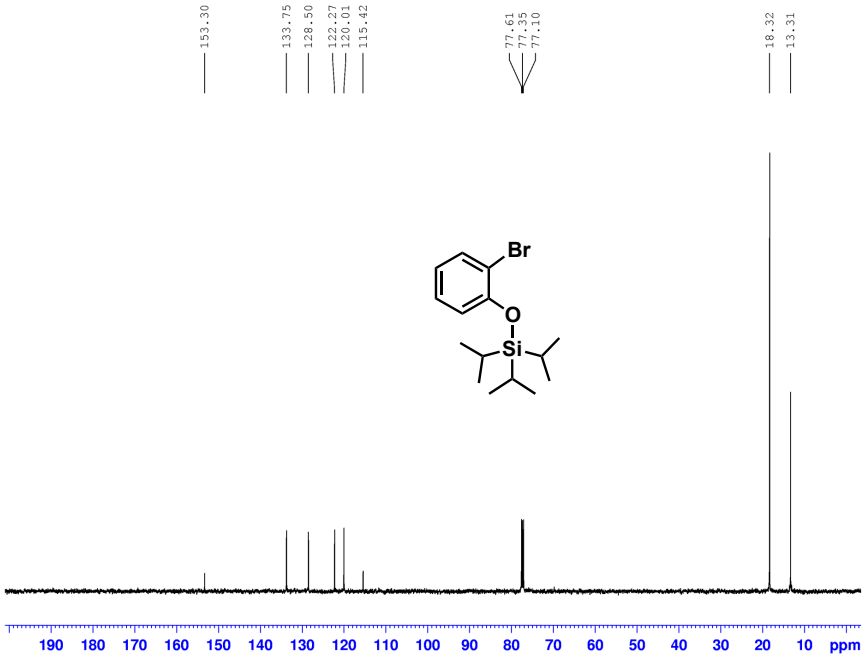
APPENDIX

In the proceeding pages, representative NMR spectral data for the reaction products reported in Chapters 2, 3 and 4 of this thesis will be presented. Additionally, crystallographic experimental details for **L1** (Table A–1), **3-37** (Table A–2) and **C1** (Table A–2) will be provided.

^{1}H NMR of **L1-precursor** ($CDCl_3$, 500 MHz, 300 K)

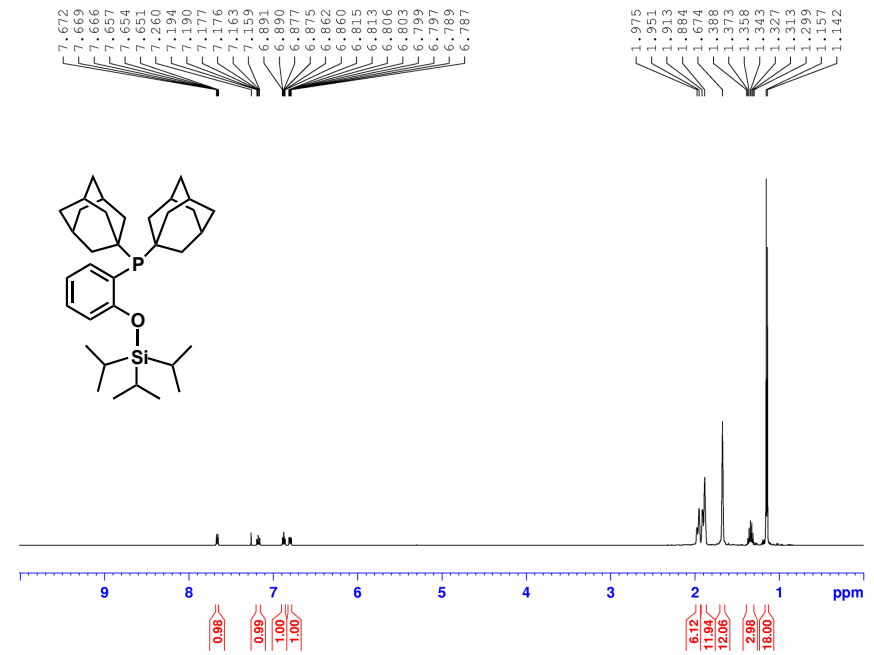


^{13}C{^{1}H} NMR of **L1-precursor**, ($CDCl_3$, 125.8 MHz, 300 K)

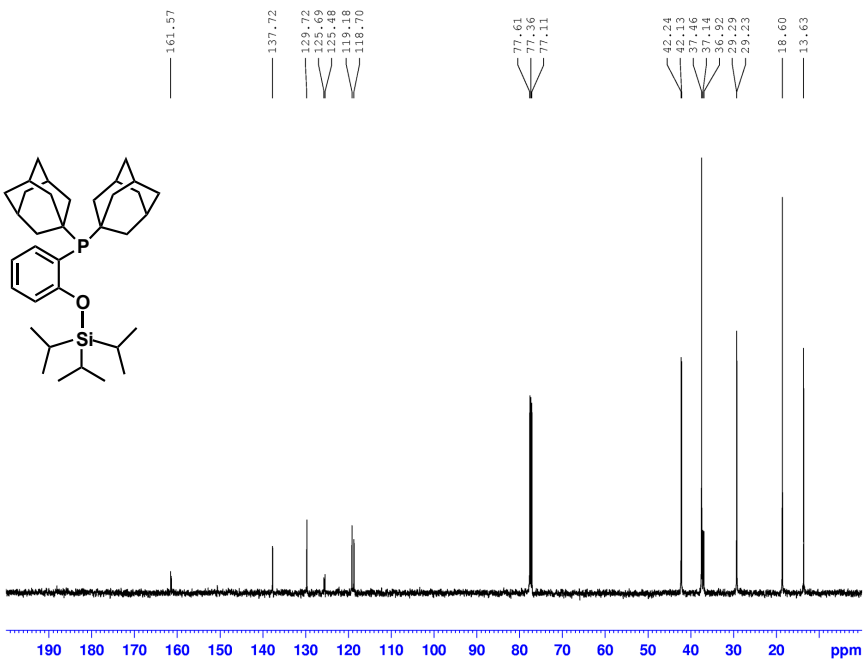


^{31}P NMR of **L1** ($CDCl_3$, 202 MHz, 300 K)

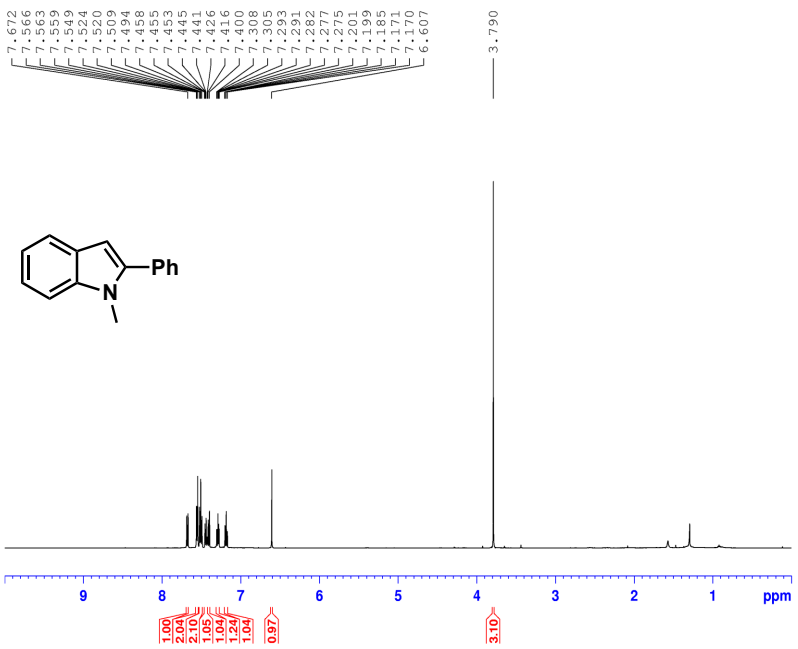
^{1}H NMR of **L1** ($CDCl_3$, 500 MHz, 300 K)



$^{13}C\{^{1}H\}$ NMR of **L1** ($CDCl_3$, 125.8 MHz, 300 K)



^{1}H NMR of **2-1**, (CDCl$_3$, 500 MHz, 300 K)



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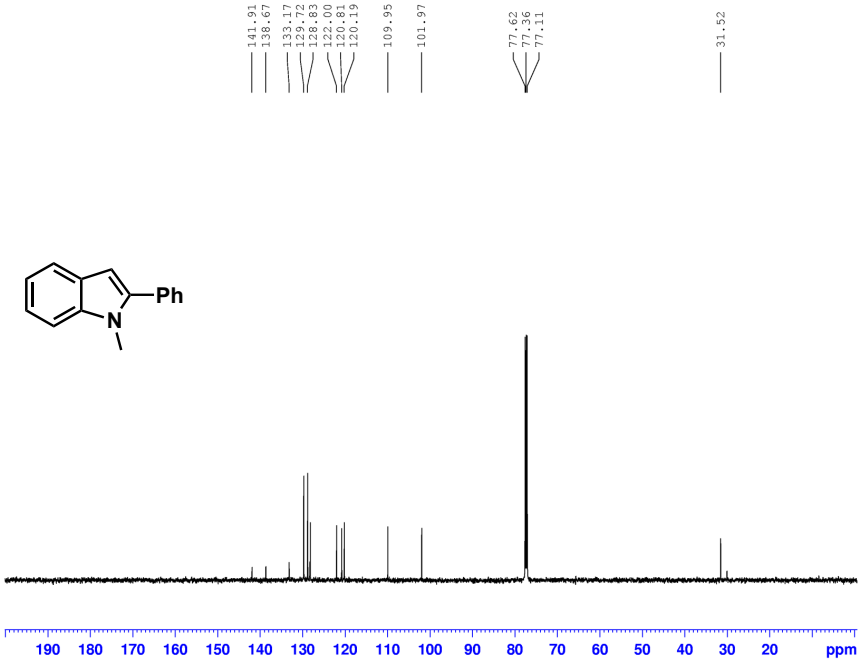
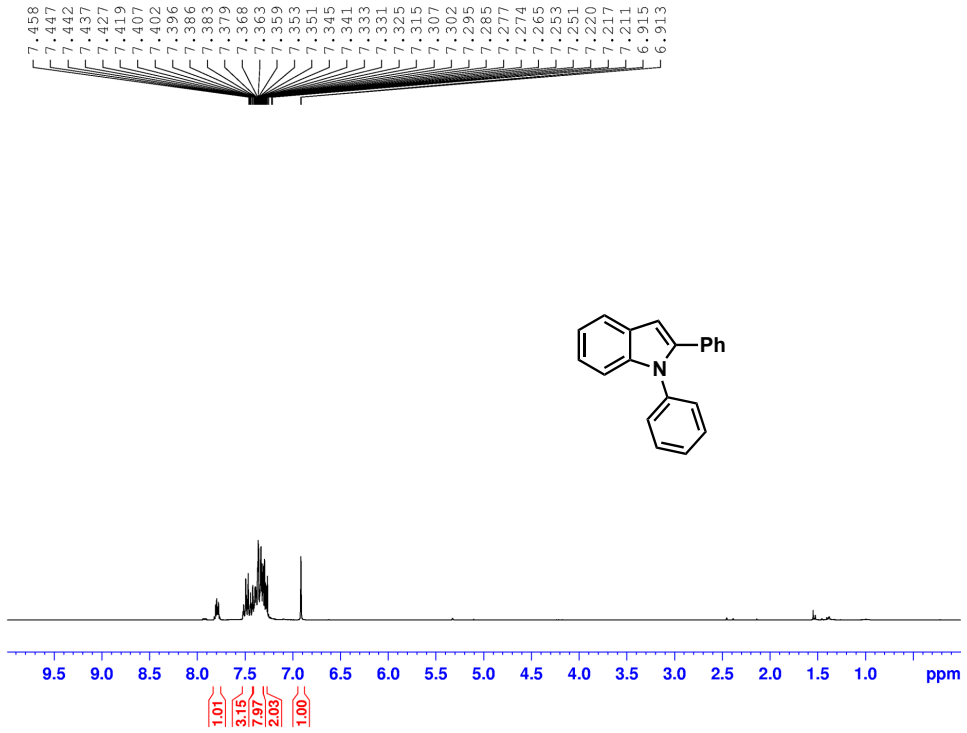


^{1}H NMR of **2-3**, (CDCl$_3$, 500 MHz, 300 K)



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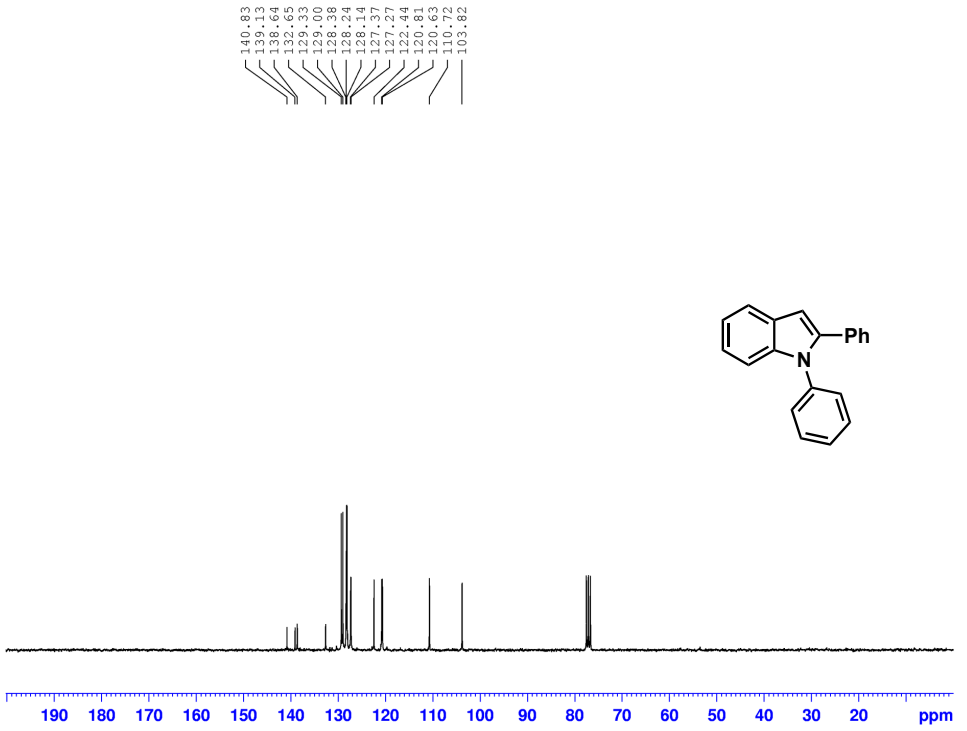
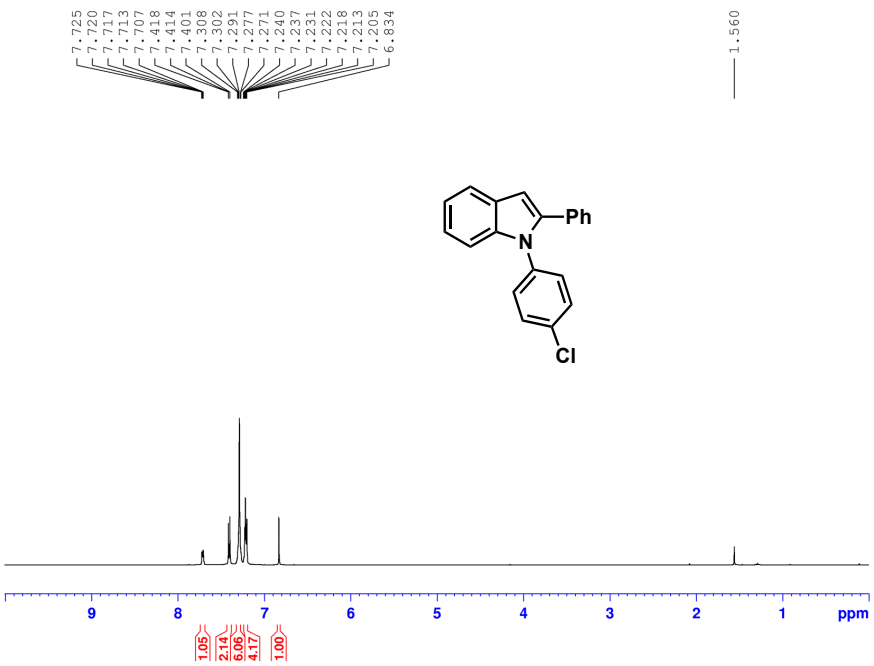
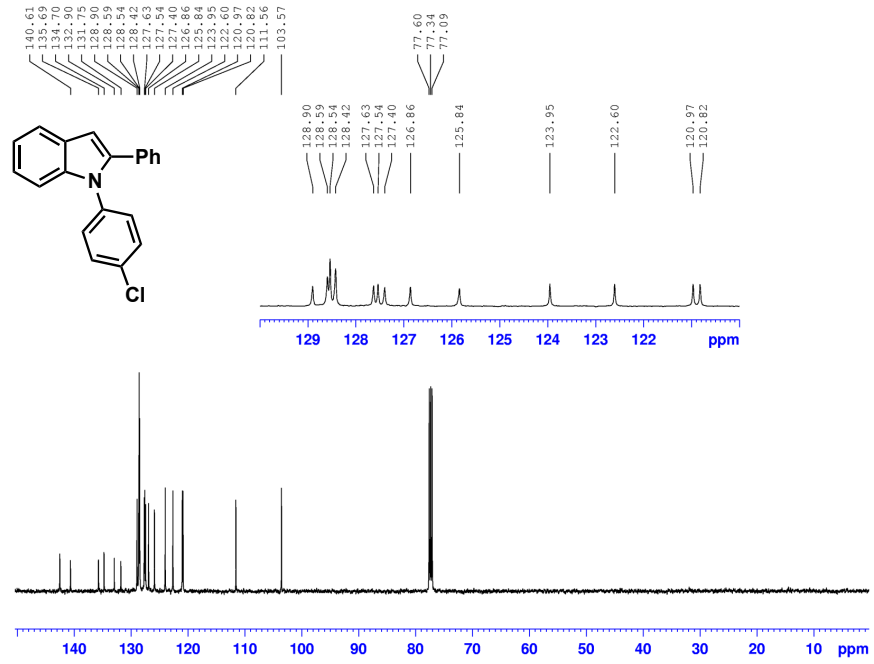


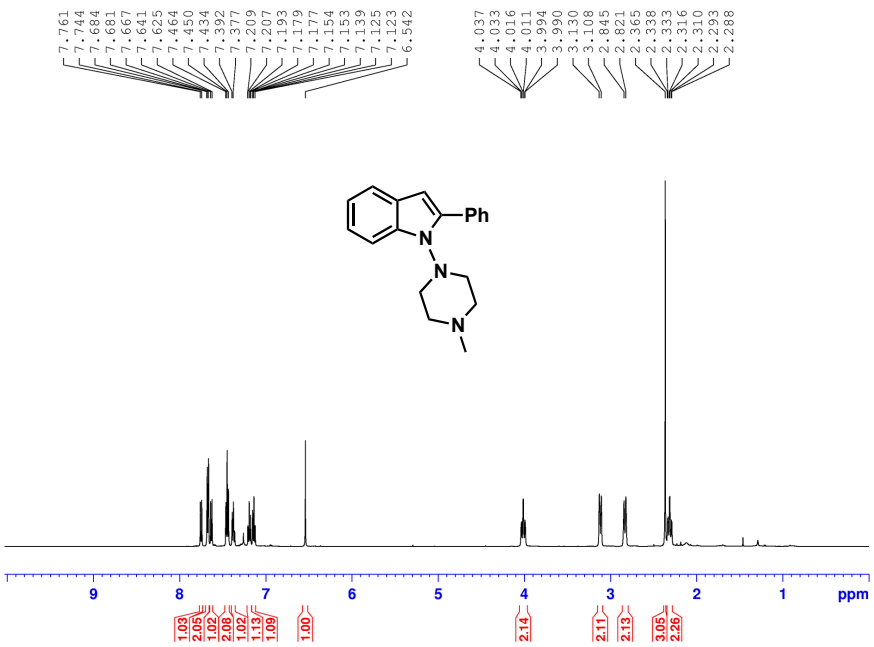
^{1}H NMR of **2-8**, ($CDCl_3$, 500 MHz, 300 K)



^{13}C{^{1}H} NMR of **2-8**, ($CDCl_3$, 125.8 MHz, 300 K)



^{1}H NMR of **2-11**, ($CDCl_3$, 500 MHz, 300 K)



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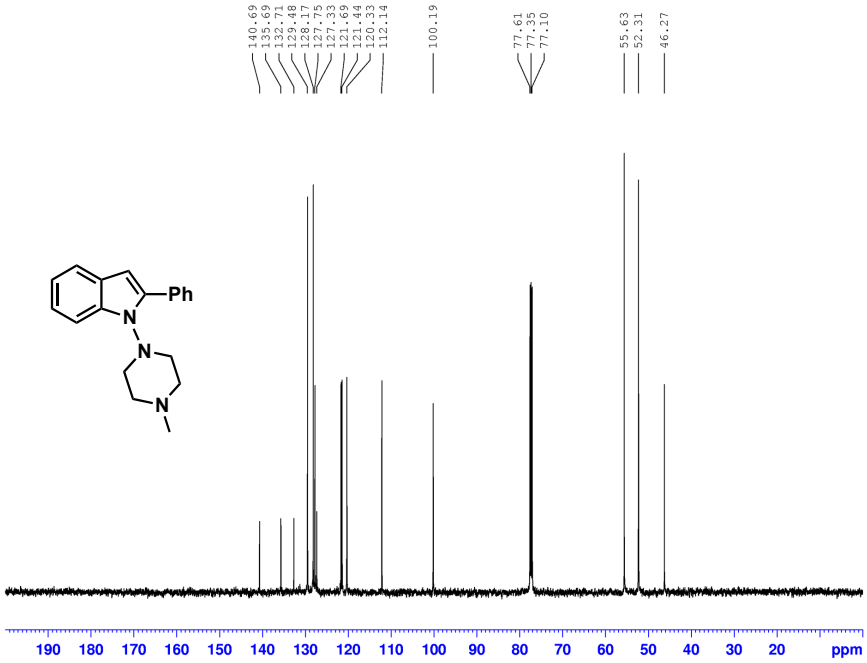
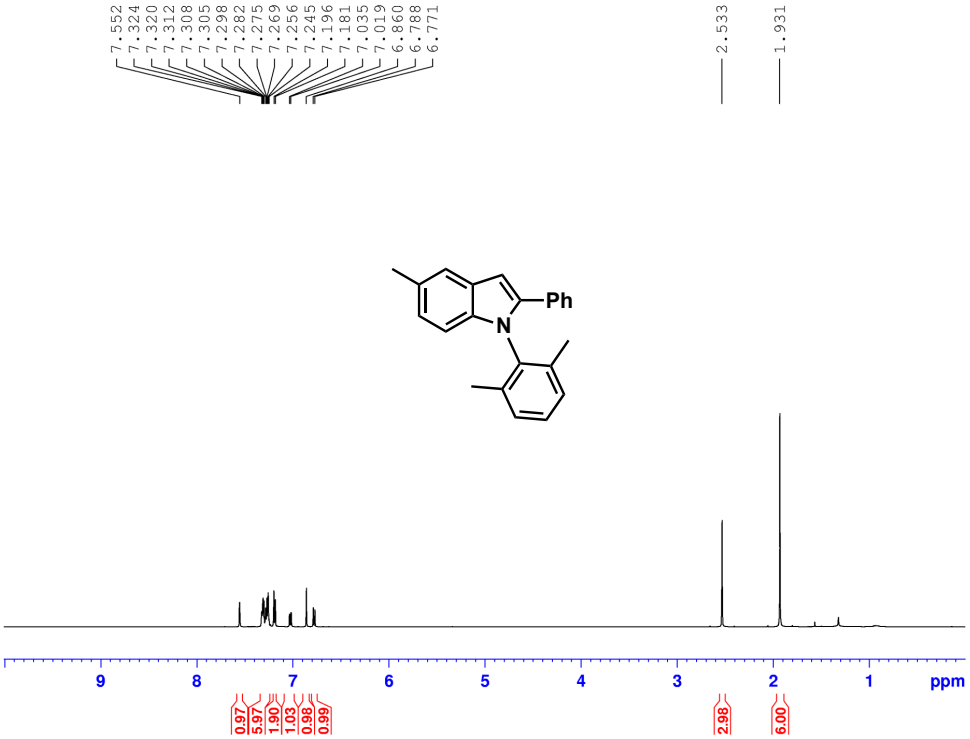


^{1}H NMR of **2-14**, ($CDCl_3$, 500 MHz, 300 K)



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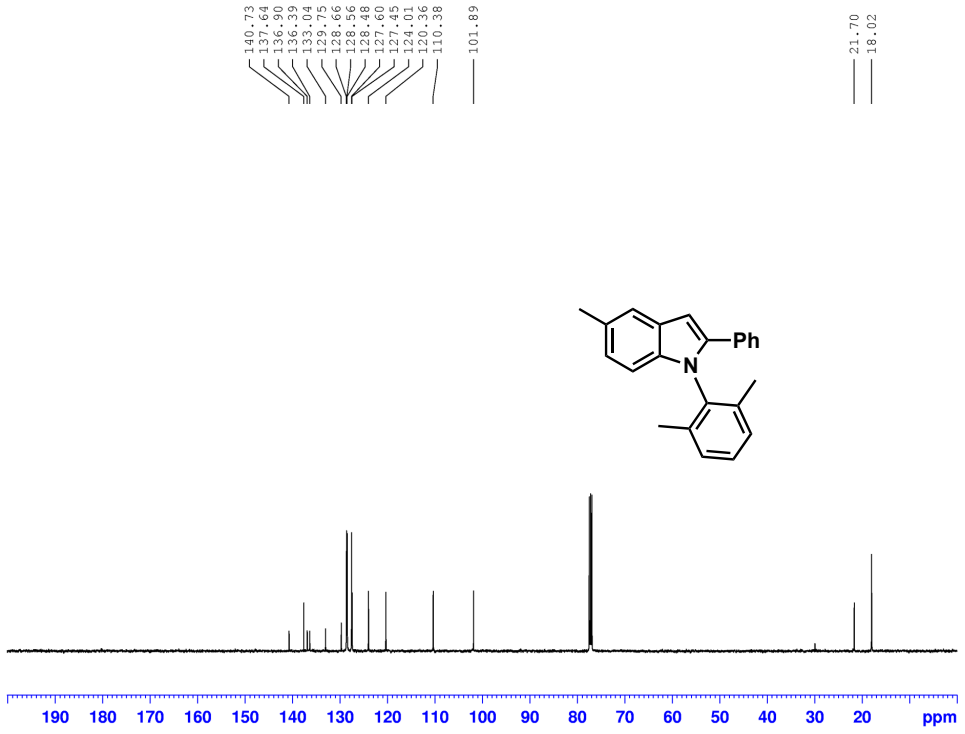
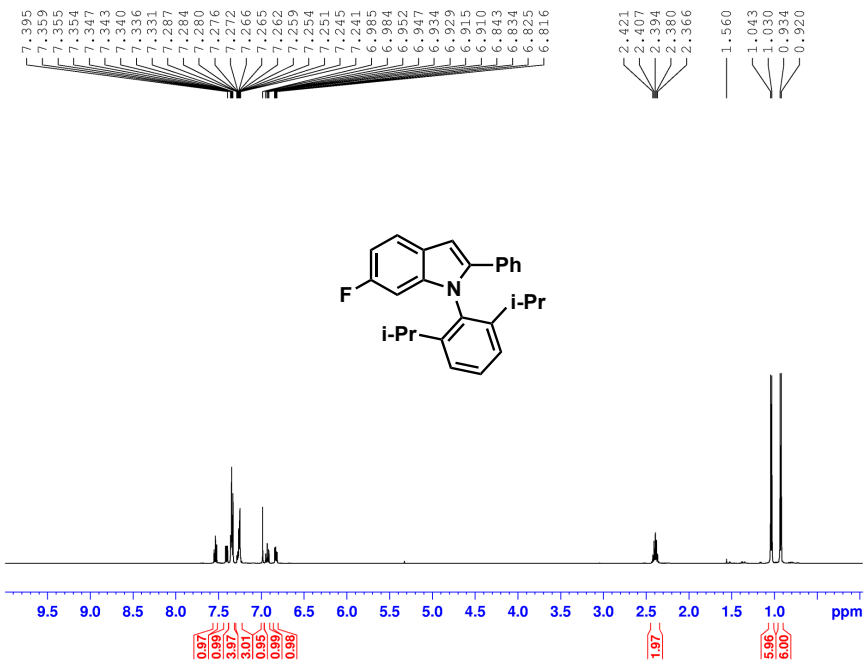
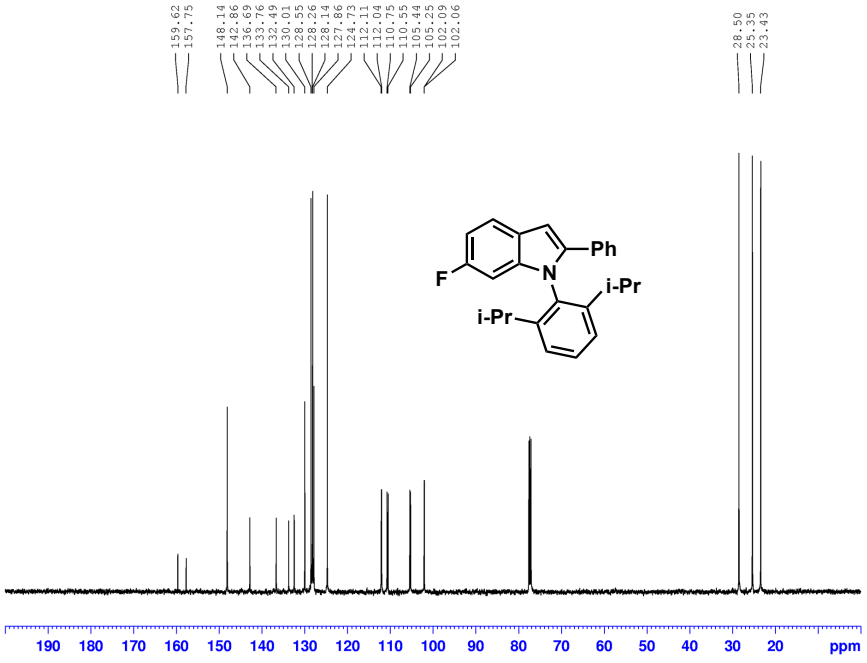


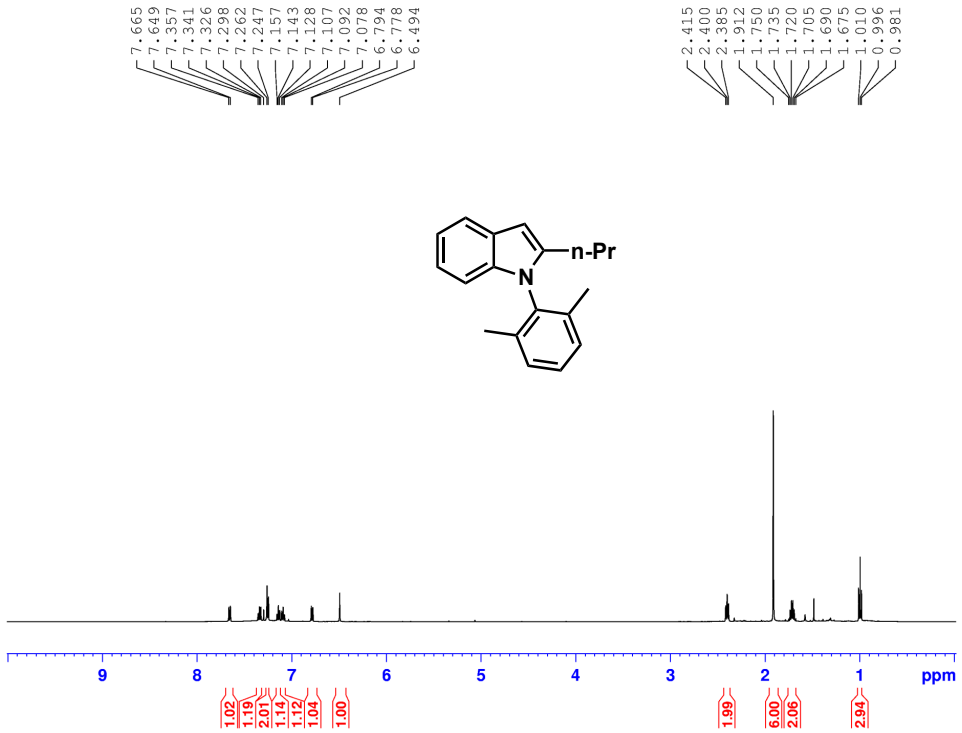
^{1}H NMR of **2-17**, ($CDCl_3$, 500 MHz, 300 K)



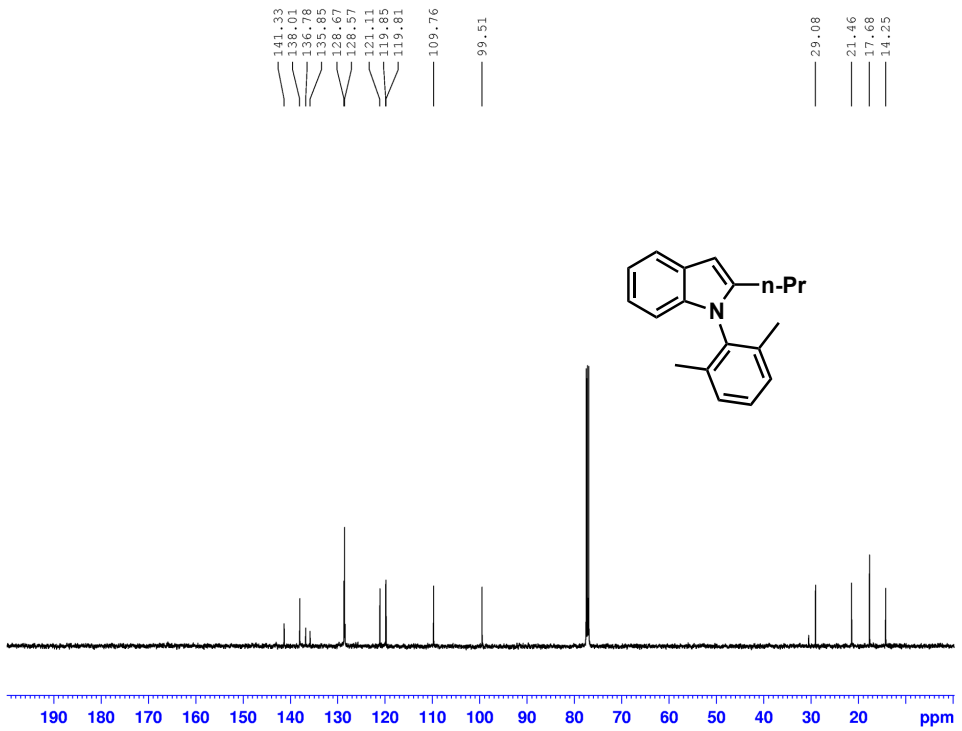
^{13}C{^{1}H} NMR of **2-17**, ($CDCl_3$, 125.8 MHz, 300 K)



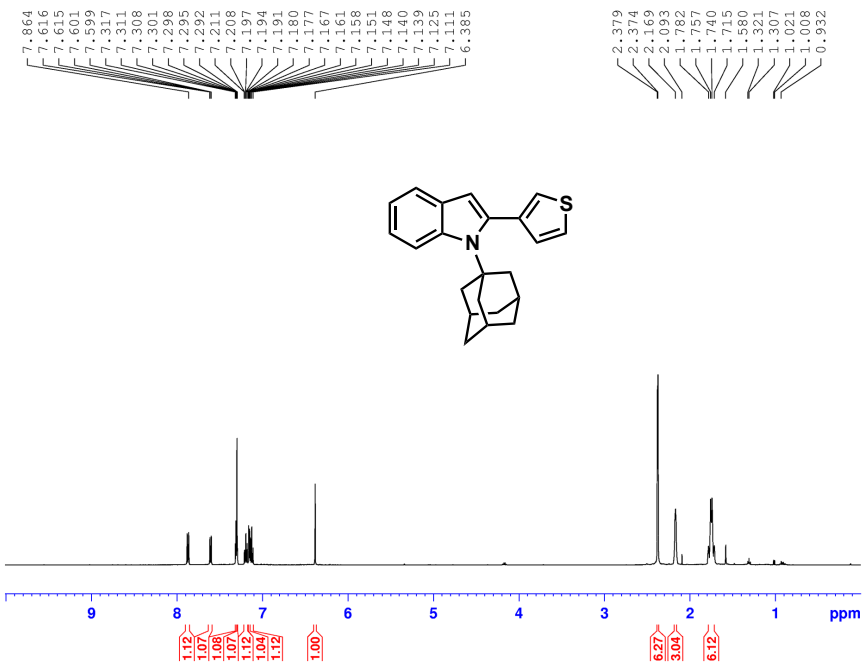
^{1}H NMR of **2-21**, ($CDCl_3$, 500 MHz, 300 K)



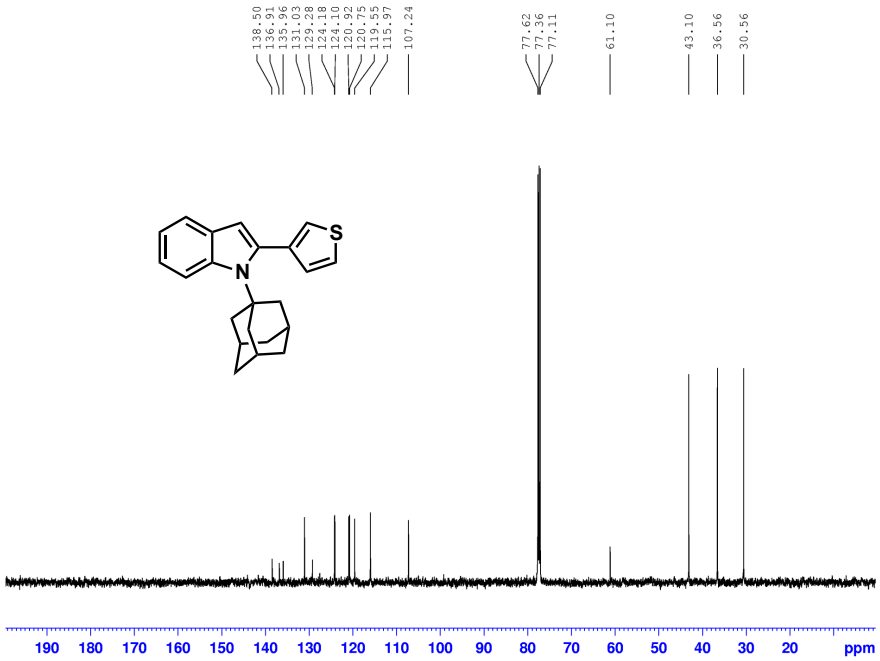
^{13}C{^{1}H} NMR of **2-21**, ($CDCl_3$, 125.8 MHz, 300 K)



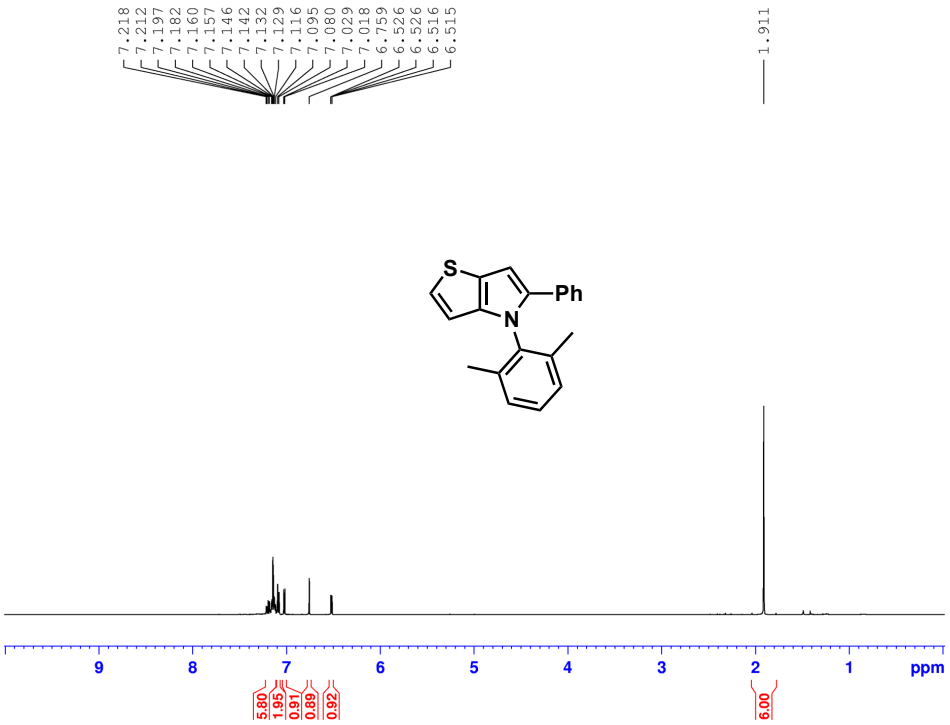
^{1}H NMR of **2-23**, ($CDCl_3$, 500 MHz, 300 K)



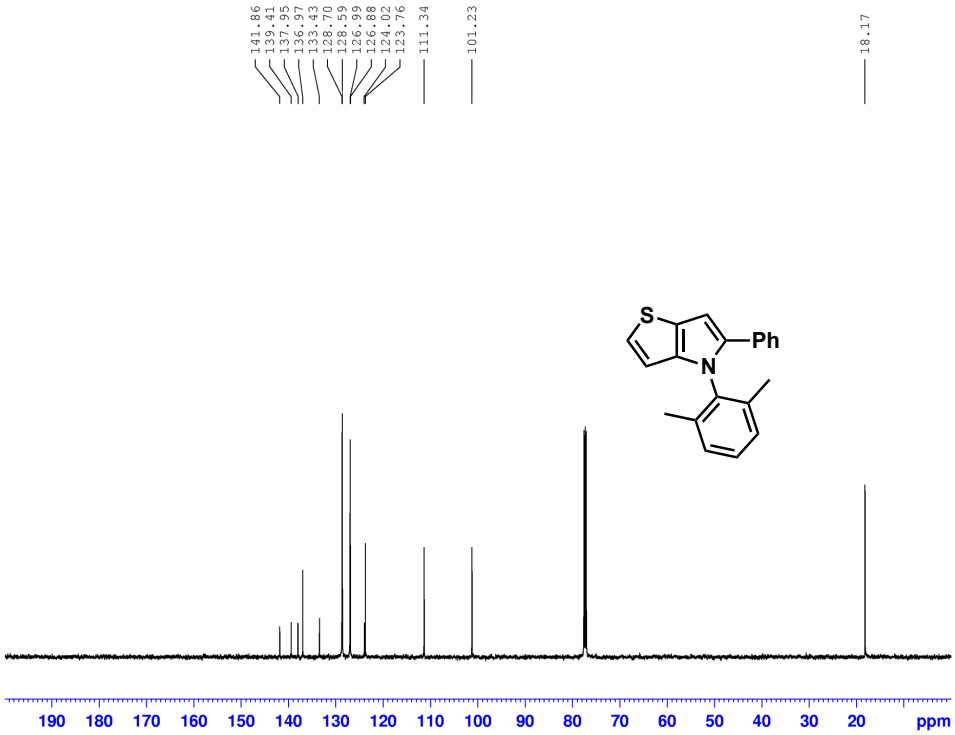
^{13}C{^{1}H} NMR of **2-23**, ($CDCl_3$, 125.8 MHz, 300 K)



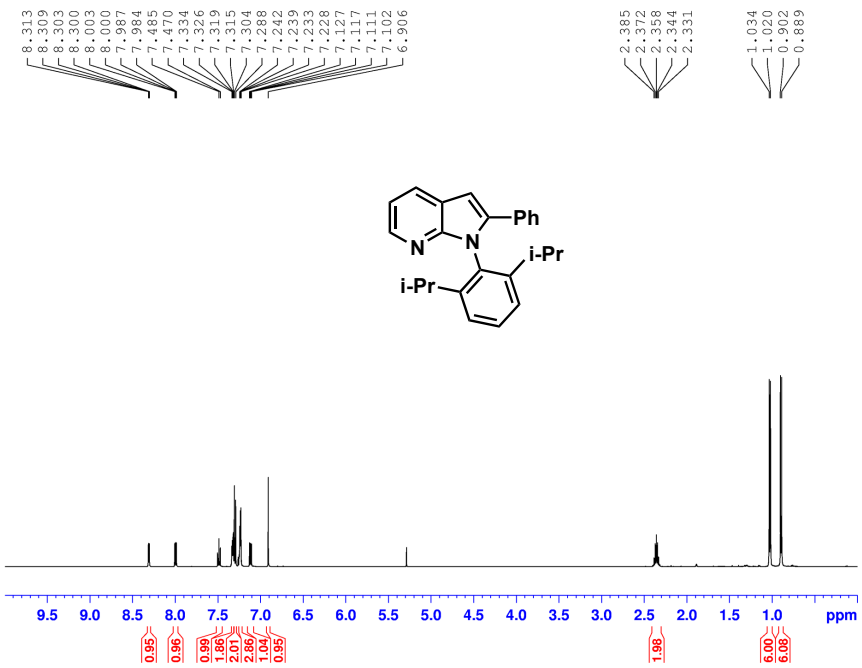
^{1}H NMR of **2-26**, ($CDCl_3$, 500 MHz, 300 K)



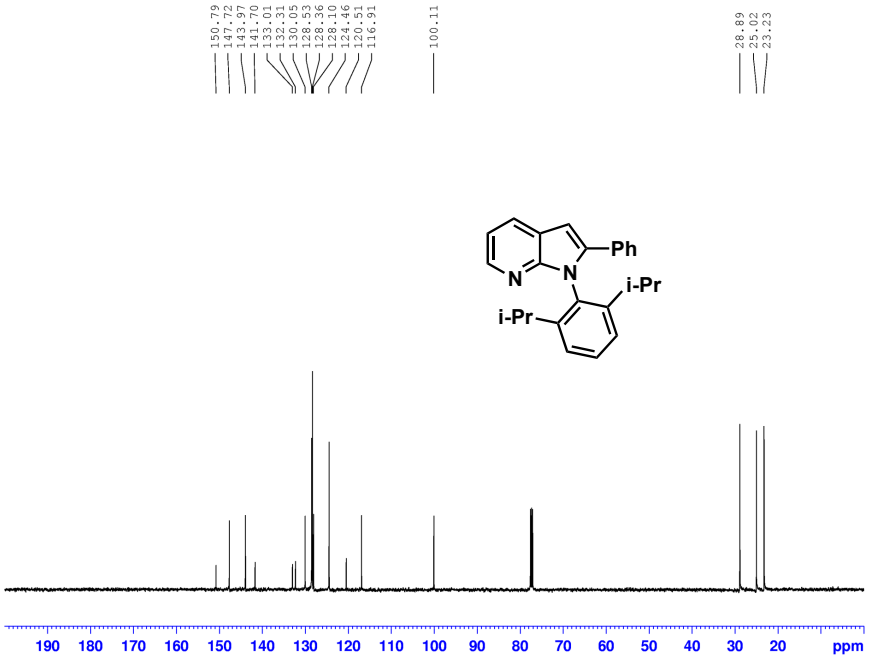
^{13}C{^{1}H} NMR of **2-26**, ($CDCl_3$, 125.8 MHz, 300 K)



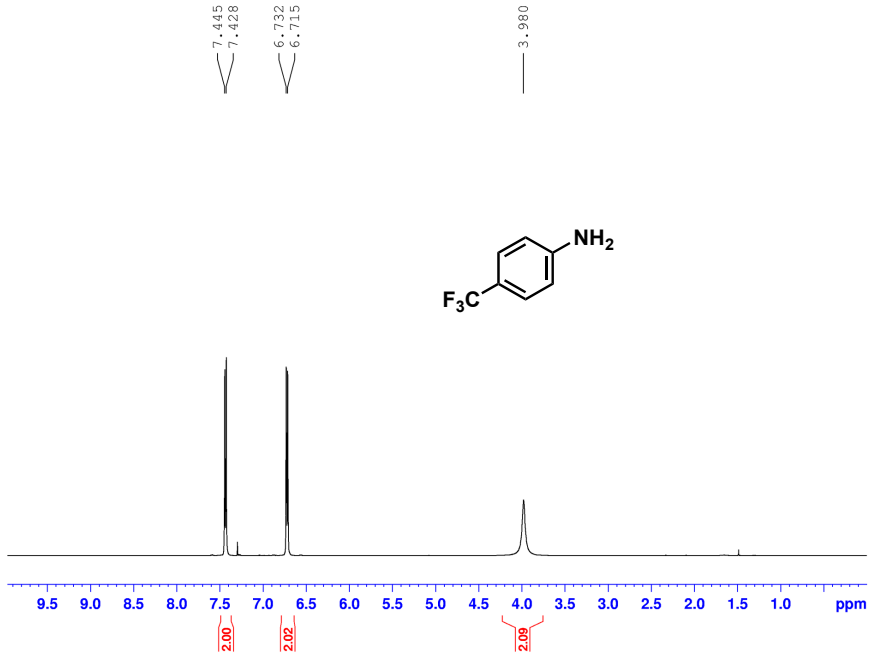
^{1}H NMR of **2-28**, ($CDCl_3$, 500 MHz, 300 K)



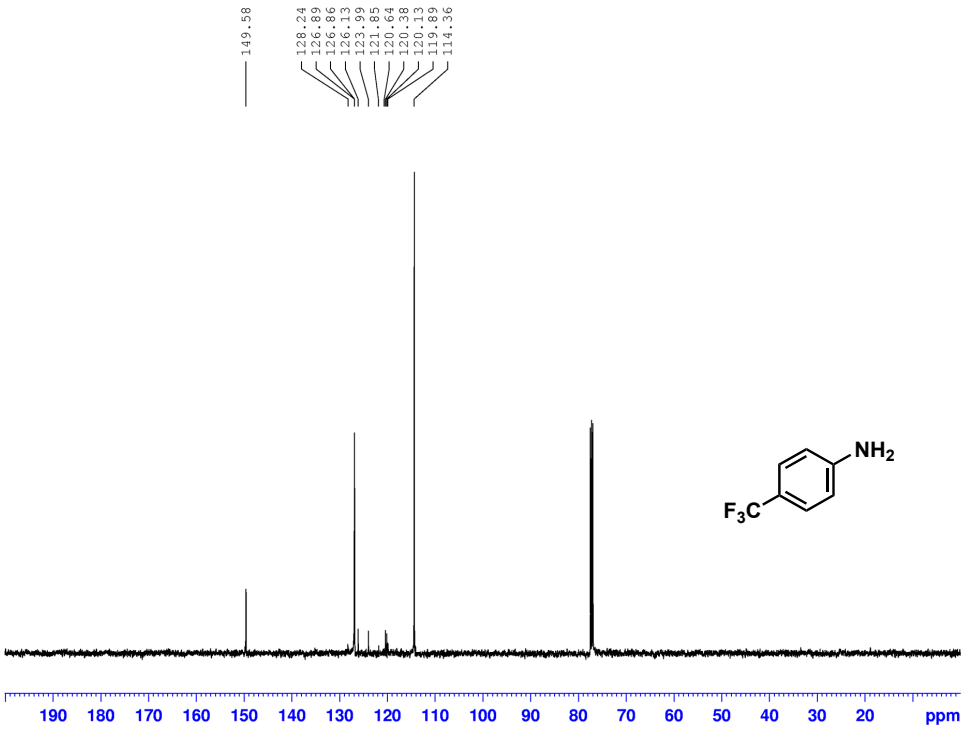
^{13}C{^{1}H} NMR of **2-28**, ($CDCl_3$, 125.8 MHz, 300 K)



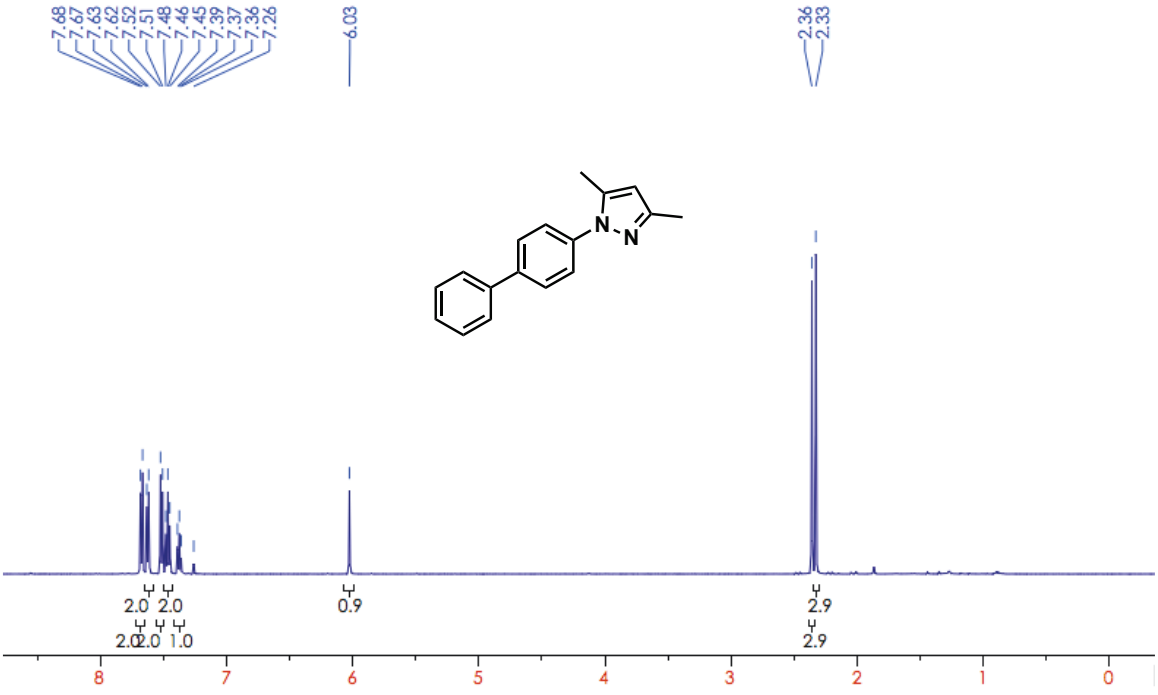
^{1}H NMR of **3-2**, (CDCl$_3$, 500 MHz, 300 K)



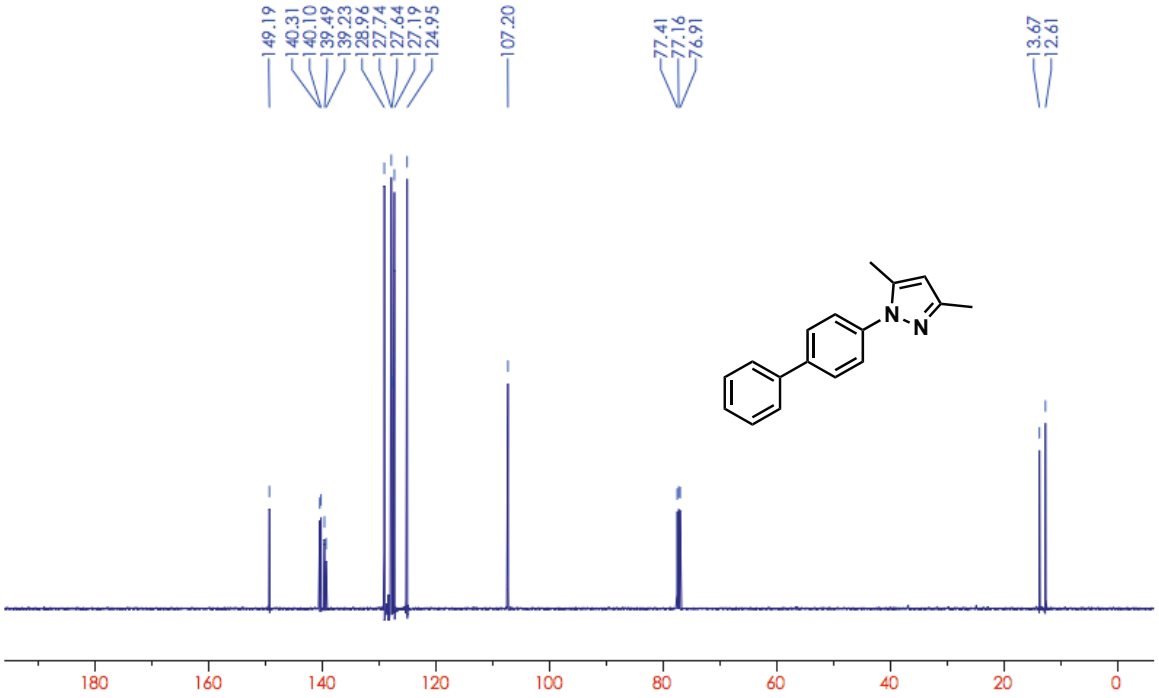
^{13}C{^{1}H} NMR of **3-2**, (CDCl$_3$, 125.8 MHz, 300 K)



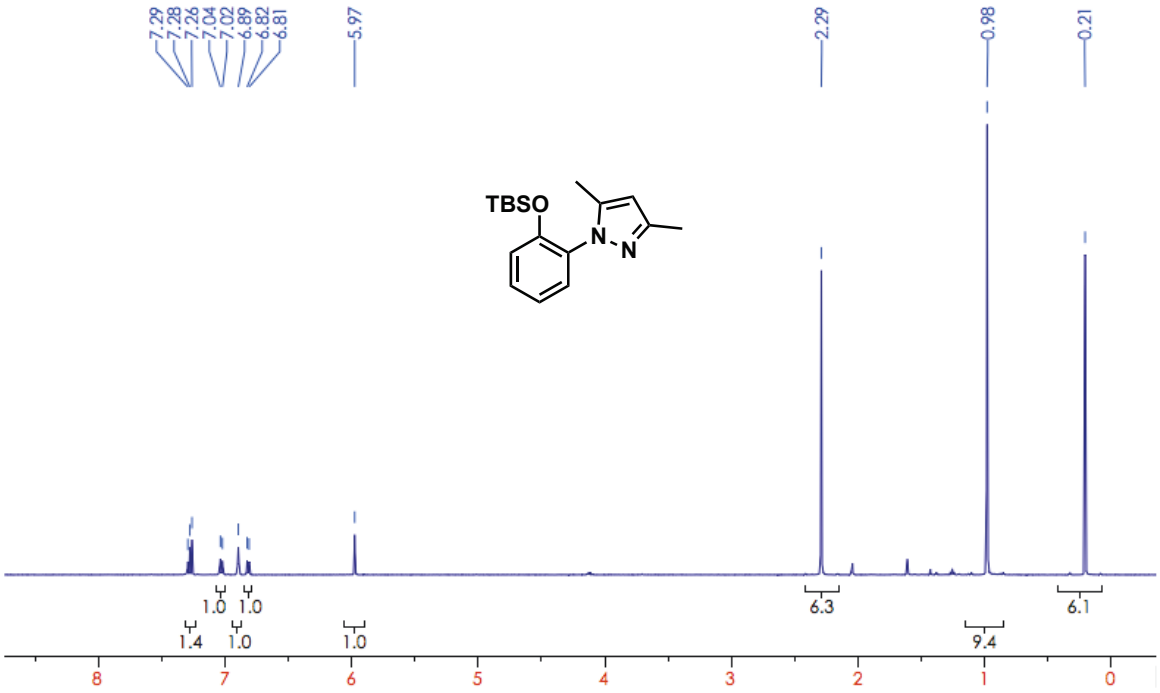
^{1}H NMR of **3-5**, ($CDCl_3$, 500 MHz, 300 K)



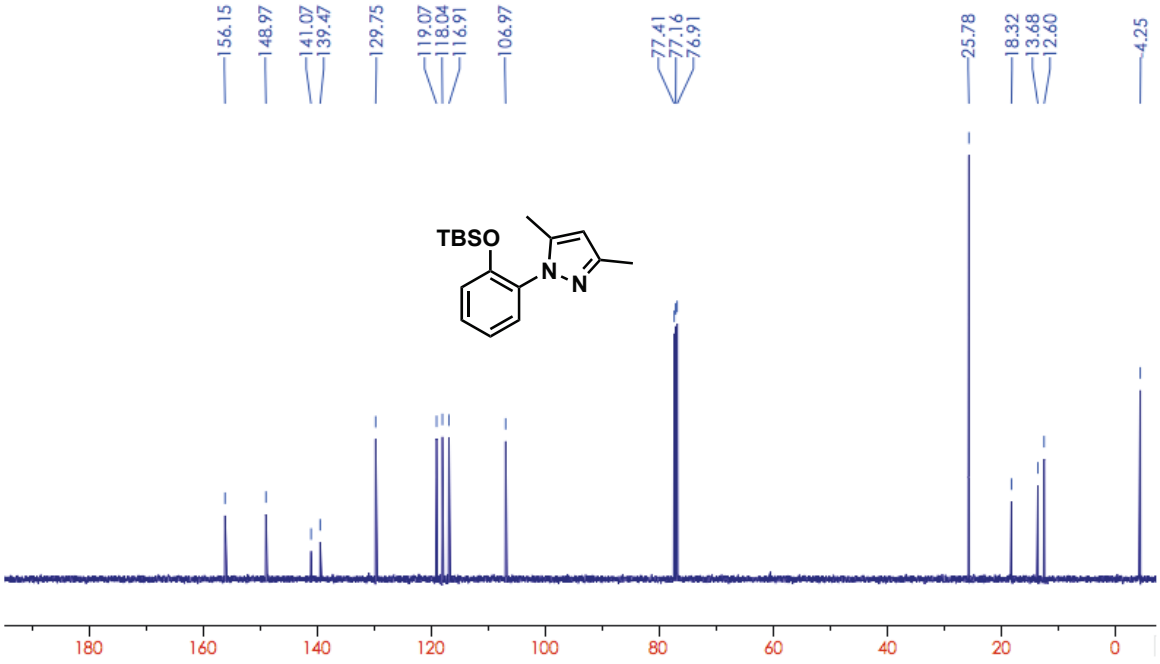
^{13}C{^{1}H} NMR of **3-5**, ($CDCl_3$, 125.8 MHz, 300 K)



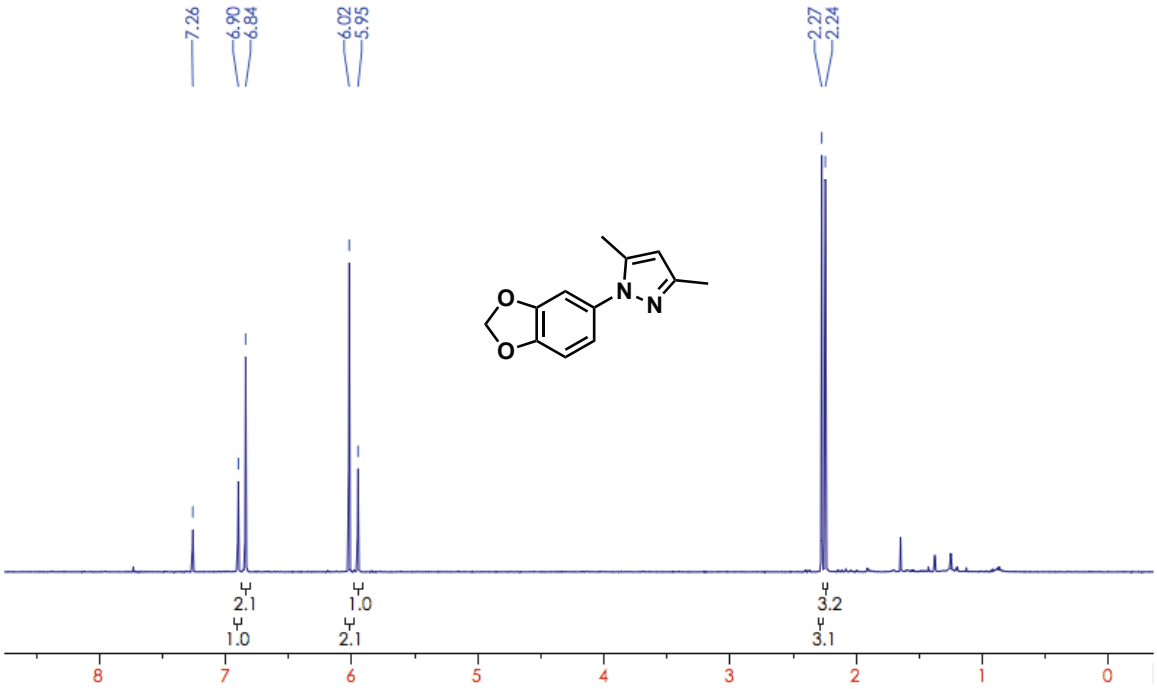
^{1}H NMR of **3-7**, ($CDCl_3$, 500 MHz, 300 K)



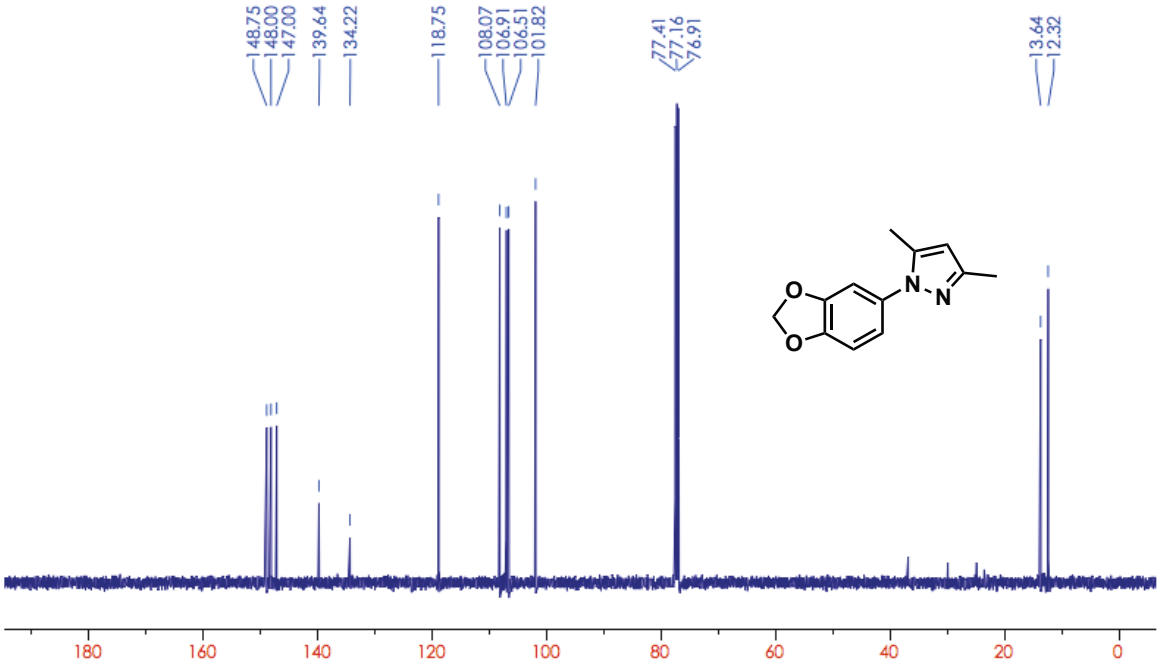
^{13}C{^{1}H} NMR of **3-7**, ($CDCl_3$, 125.8 MHz, 300 K)



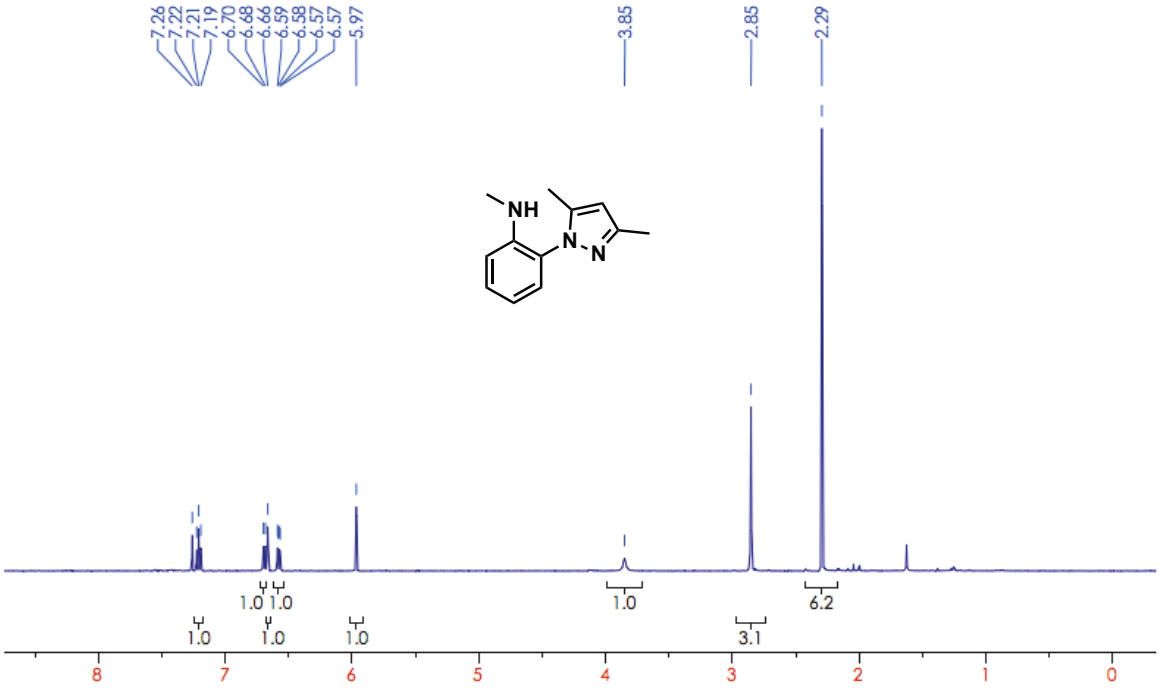
^{1}H NMR of **3-10**, ($CDCl_3$, 500 MHz, 300 K)



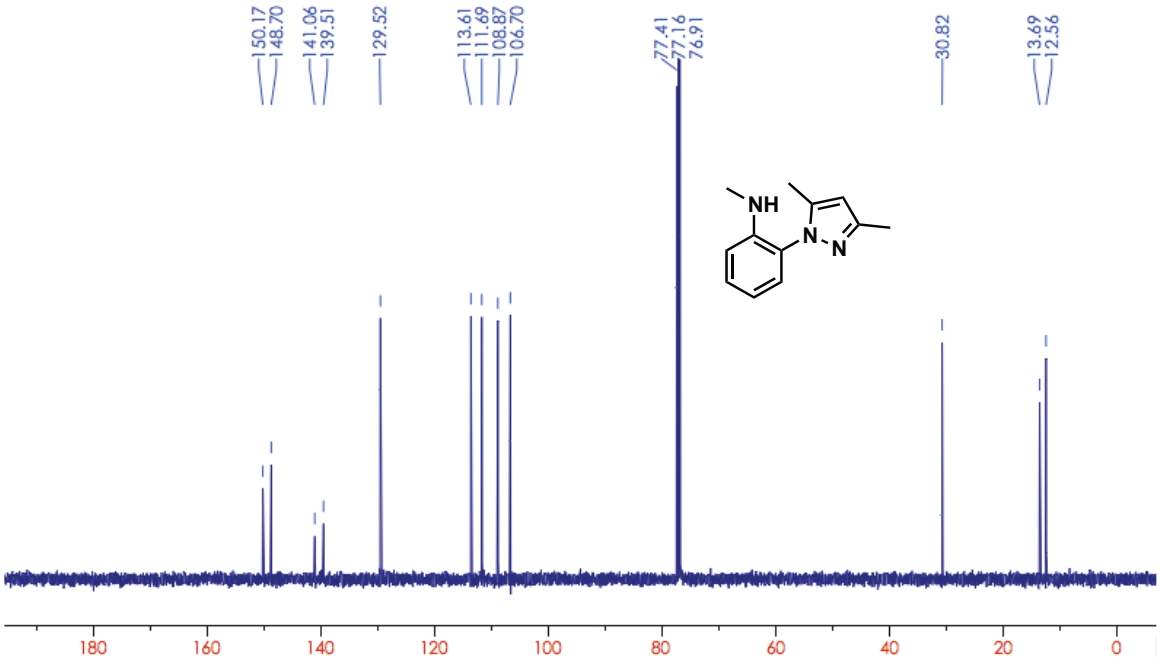
^{13}C{^{1}H} NMR of **3-10**, ($CDCl_3$, 125.8 MHz, 300 K)



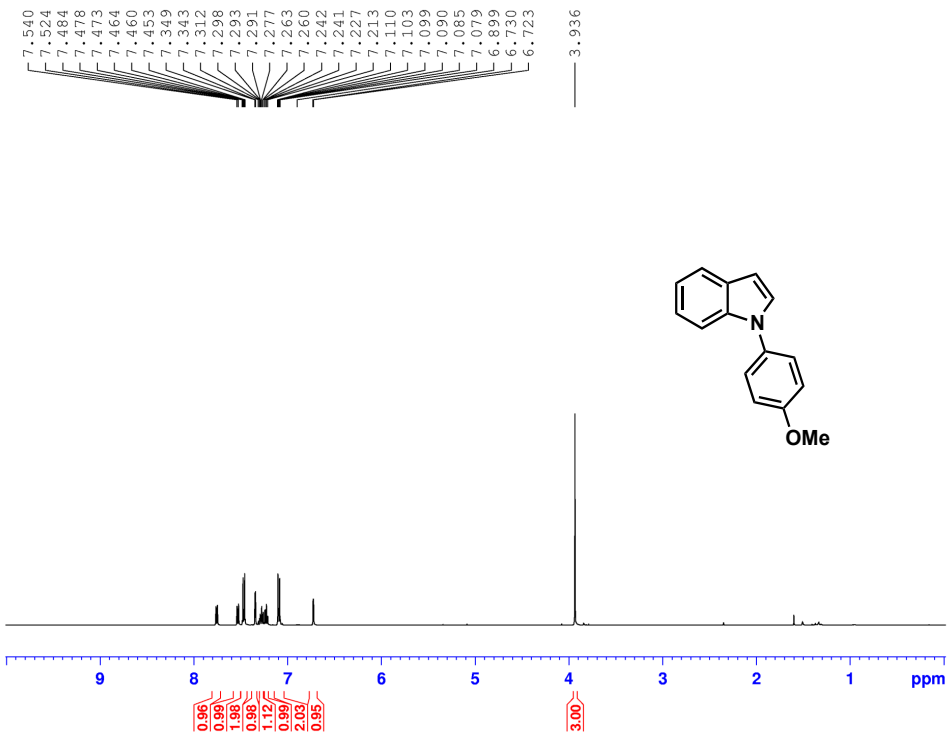
^{1}H NMR of **3-12**, ($CDCl_3$, 500 MHz, 300 K)



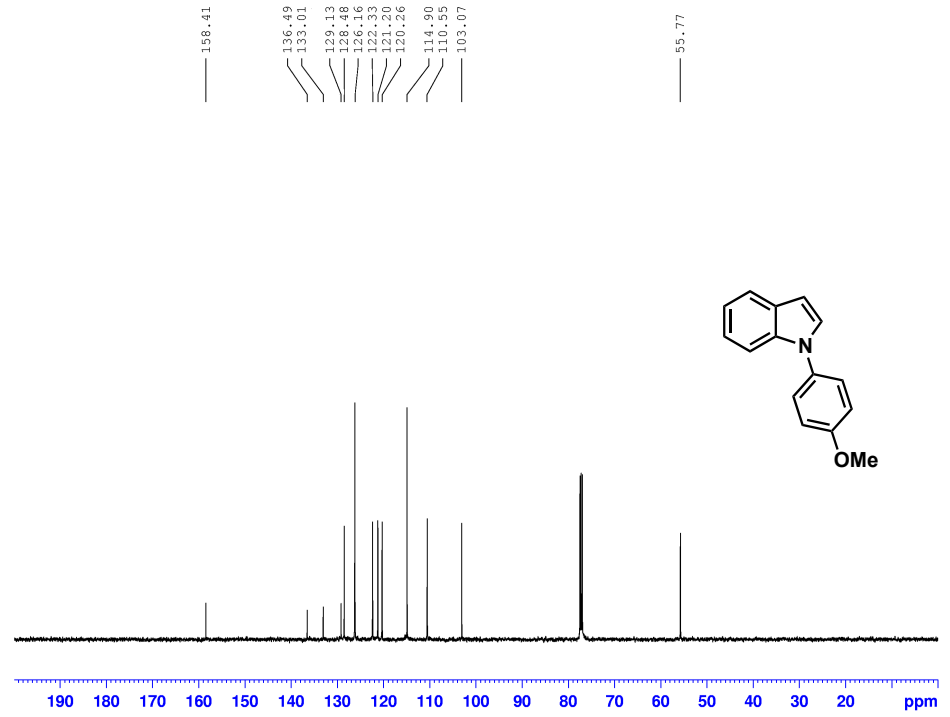
^{13}C{^{1}H} NMR of **3-12**, ($CDCl_3$, 125.8 MHz, 300 K)



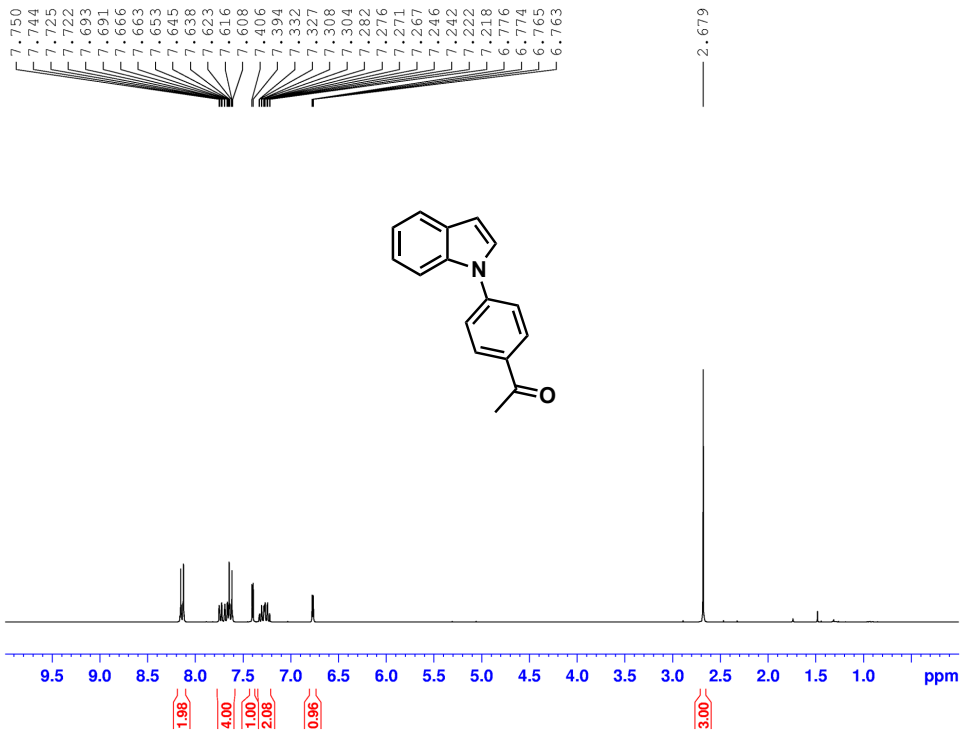
^{1}H NMR of **3-14**, ($CDCl_3$, 500 MHz, 300 K)



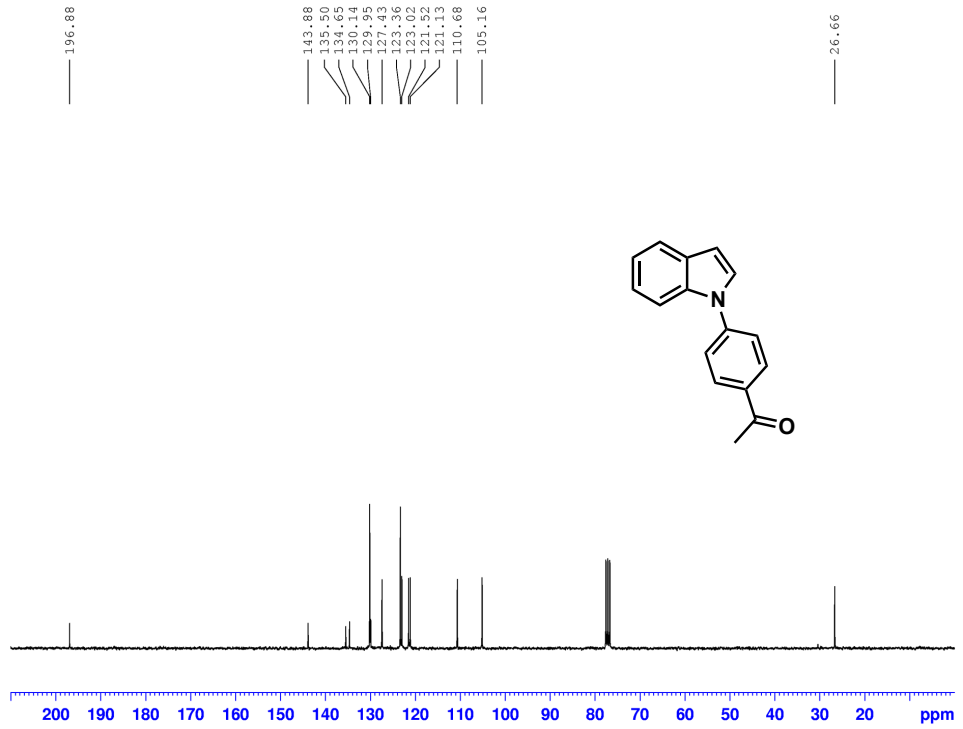
^{13}C{^{1}H} NMR of **3-14**, ($CDCl_3$, 125.8 MHz, 300 K)



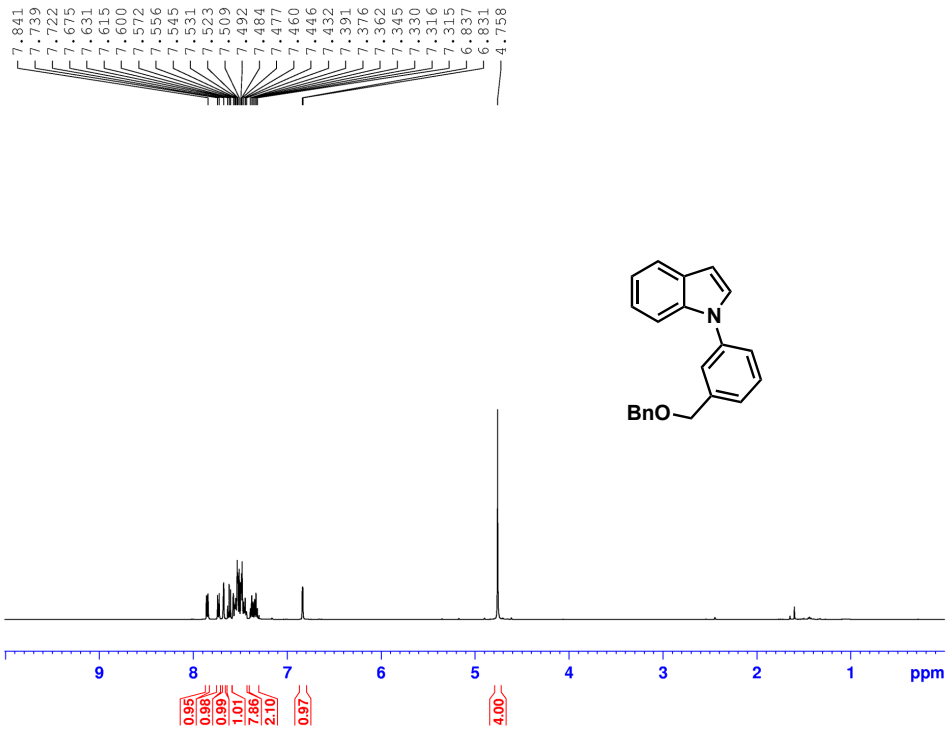
^{1}H NMR of **3-18**, ($CDCl_3$, 500 MHz, 300 K)



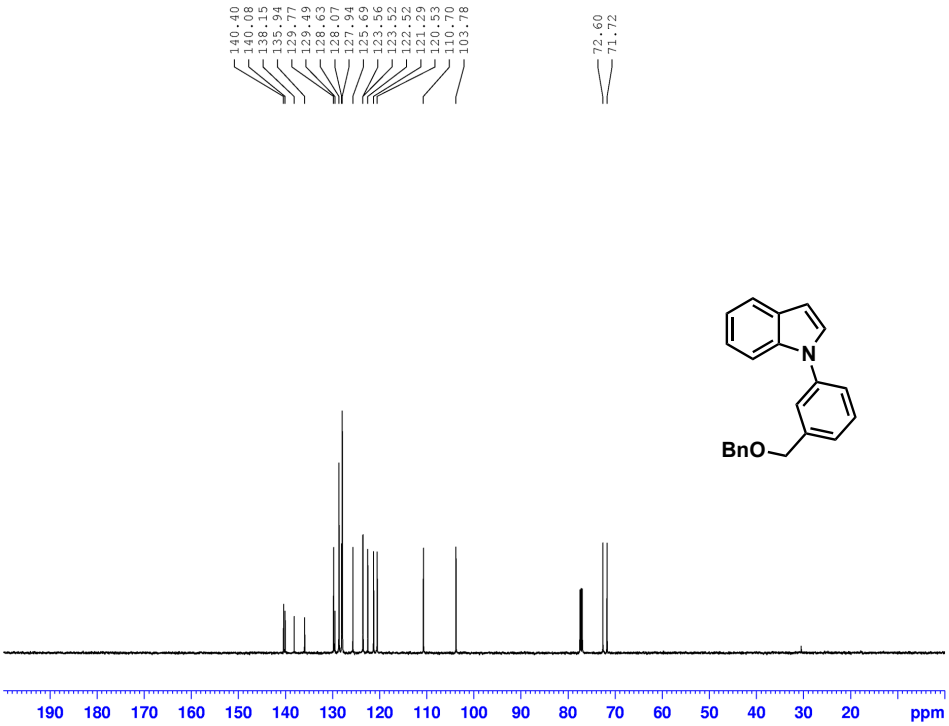
^{13}C{^{1}H} NMR of **3-18**, ($CDCl_3$, 125.8 MHz, 300 K)



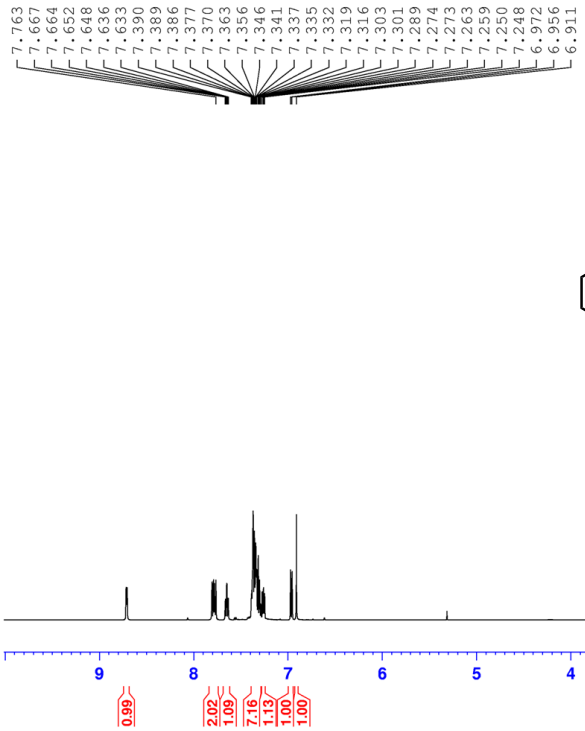
^{1}H NMR of **3-20**, ($CDCl_3$, 500 MHz, 300 K)



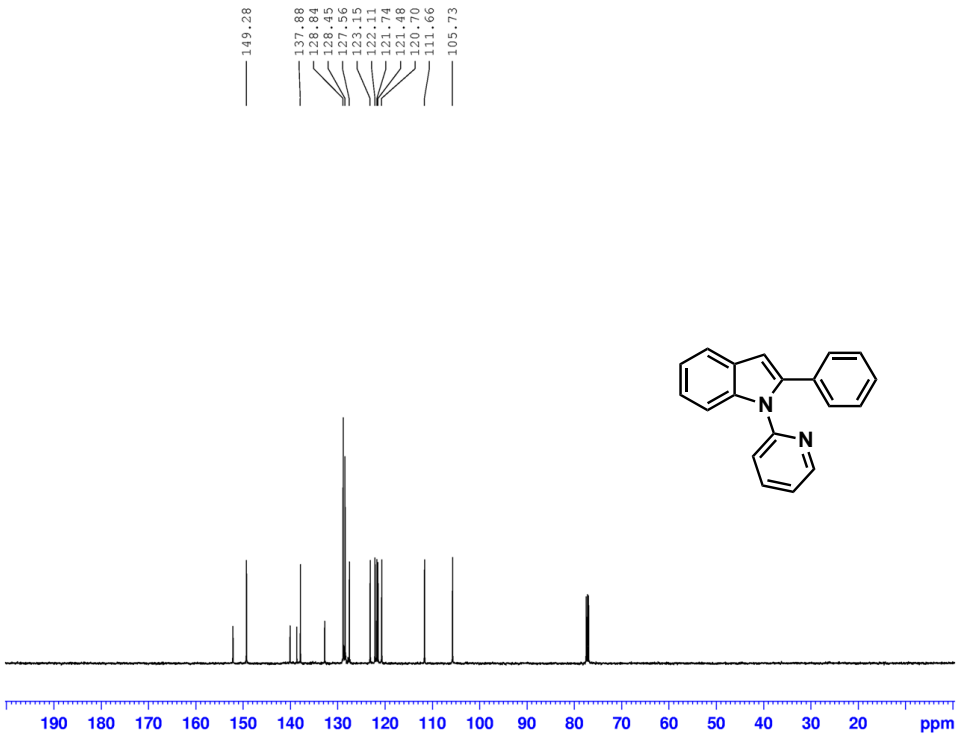
^{13}C{^{1}H} NMR of **3-20**, ($CDCl_3$, 125.8 MHz, 300 K)



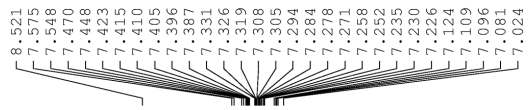
^{1}H NMR of **3-25**, ($CDCl_3$, 500 MHz, 300 K)

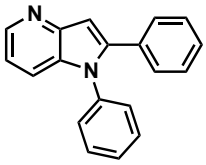


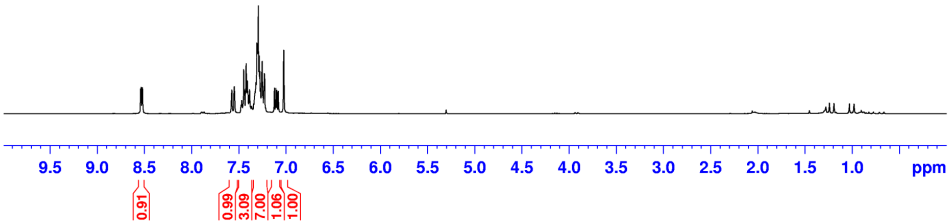
^{13}C{^{1}H} NMR of **3-25**, ($CDCl_3$, 125.8 MHz, 300 K)



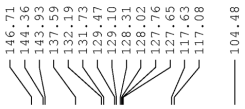
^{1}H NMR of **3-30**, ($CDCl_3$, 300 MHz, 300 K)

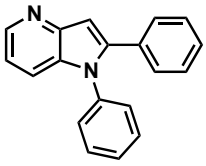


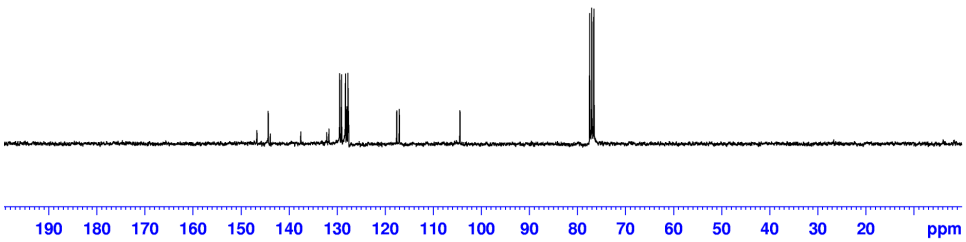




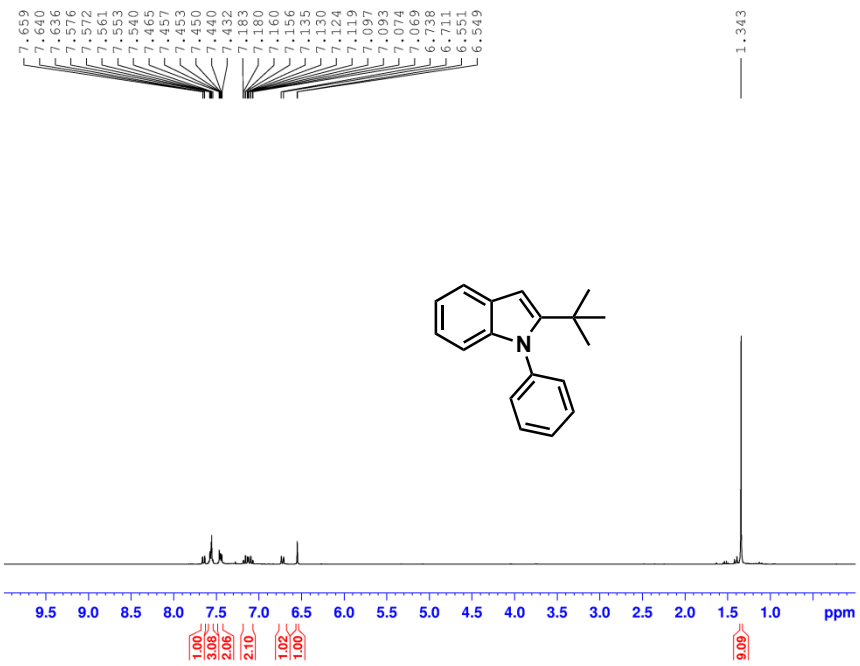
^{13}C{^{1}H} NMR of **3-30**, ($CDCl_3$, 75.4 MHz, 300 K)



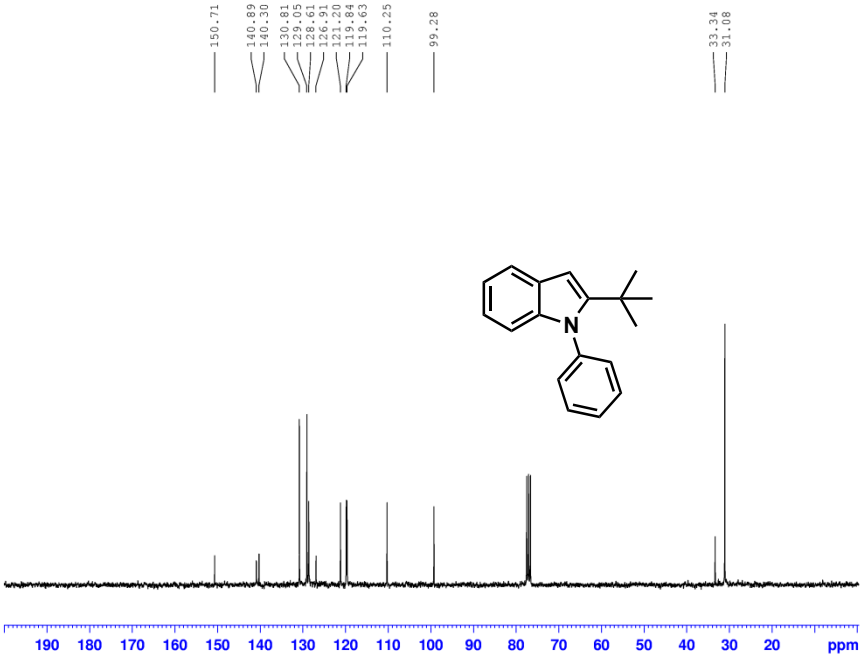




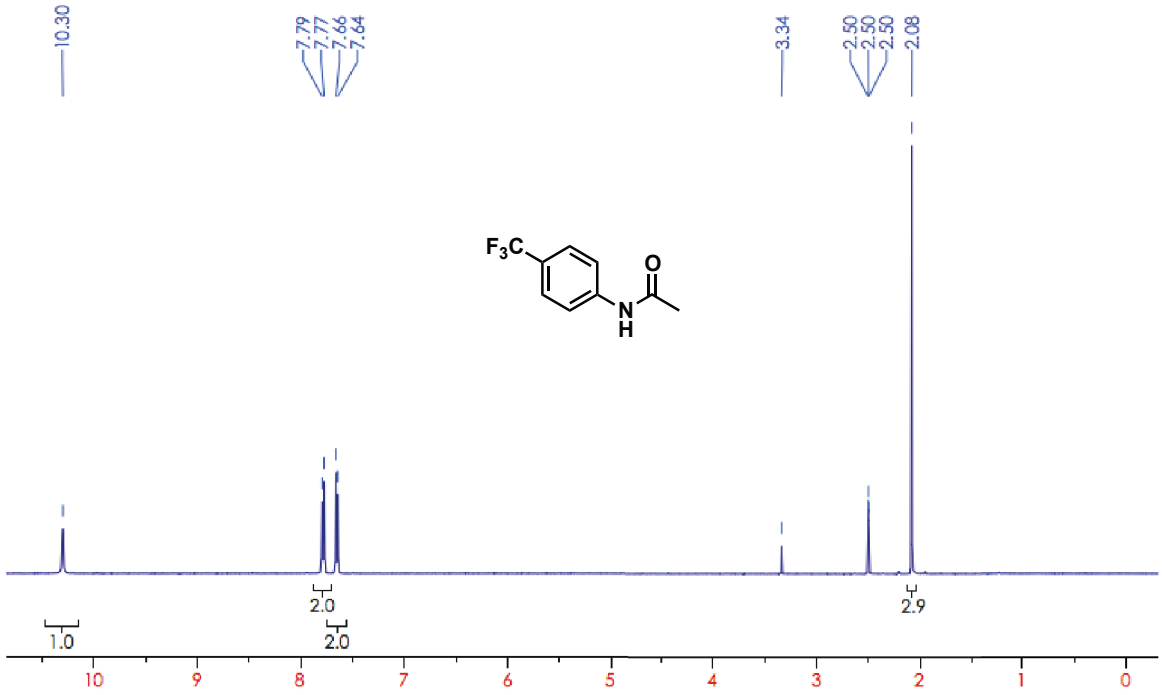
^{1}H NMR of **3-31**, ($CDCl_3$, 500 MHz, 300 K)



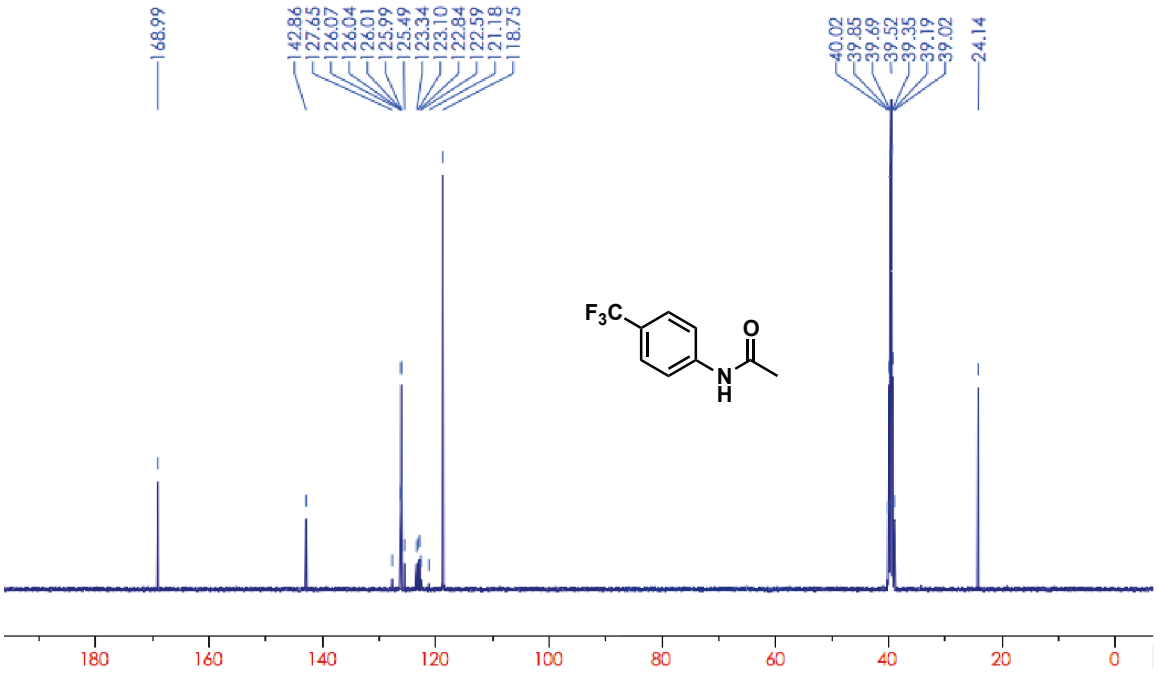
^{13}C{^{1}H} NMR of **3-31**, ($CDCl_3$, 125.8 MHz, 300 K)



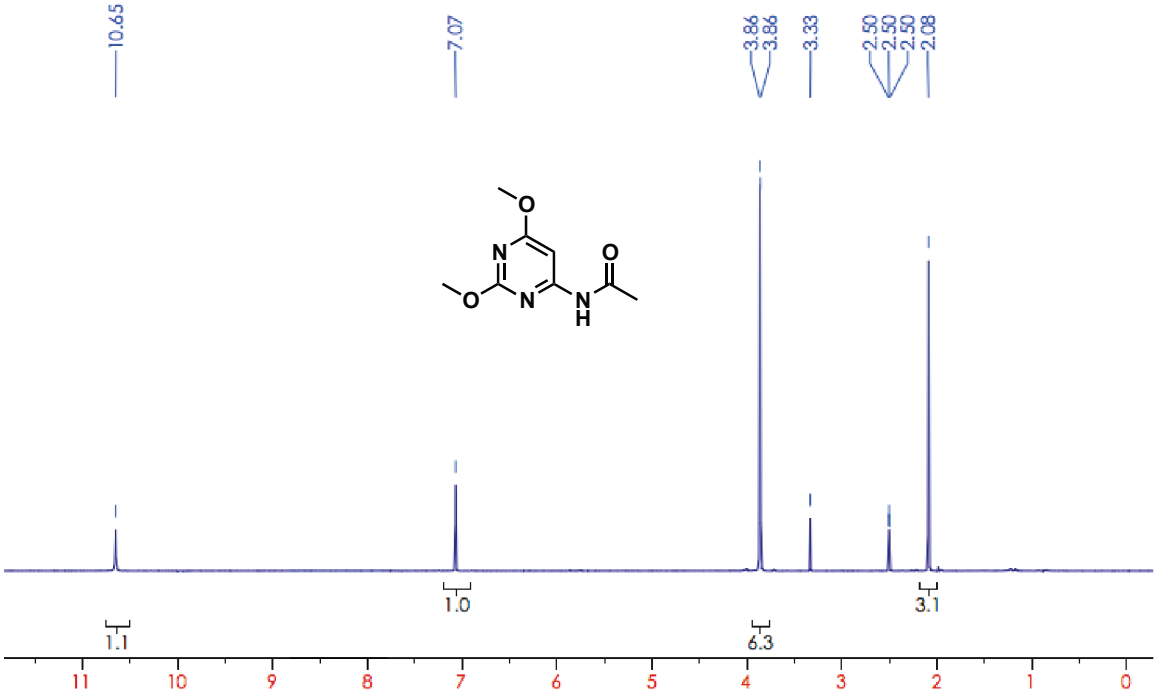
^{1}H NMR of **3-34**, (DMSO-*d6*, 500 MHz, 300 K)



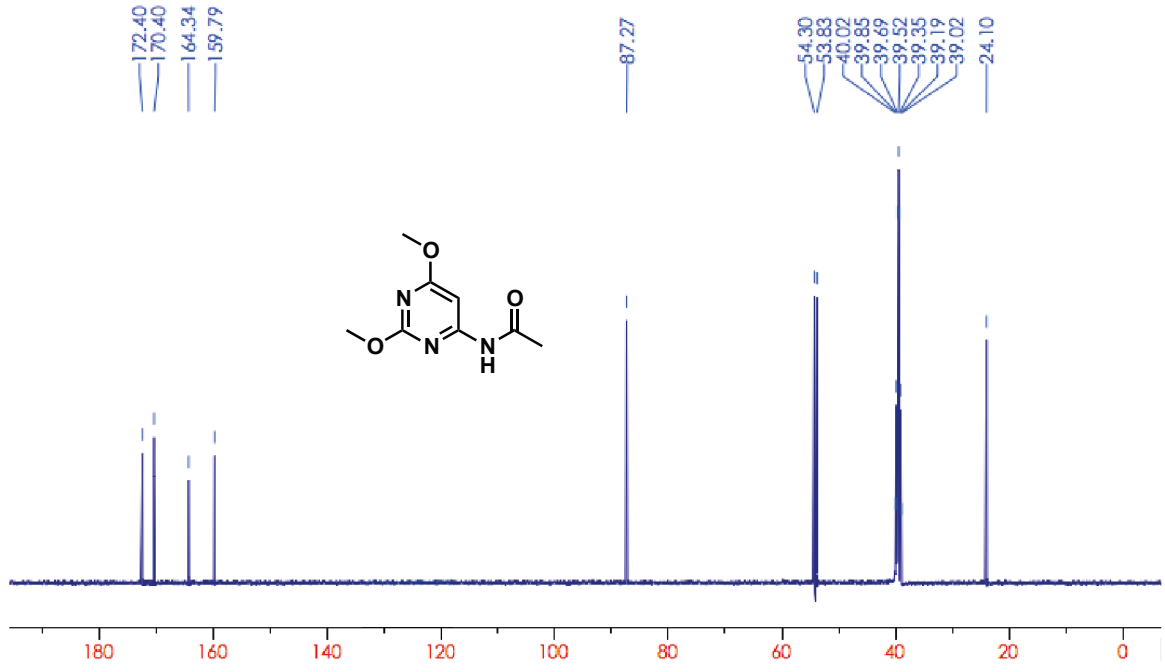
^{13}C{^{1}H} NMR of **3-34**, (DMSO-*d6*, 125.8 MHz, 300 K)



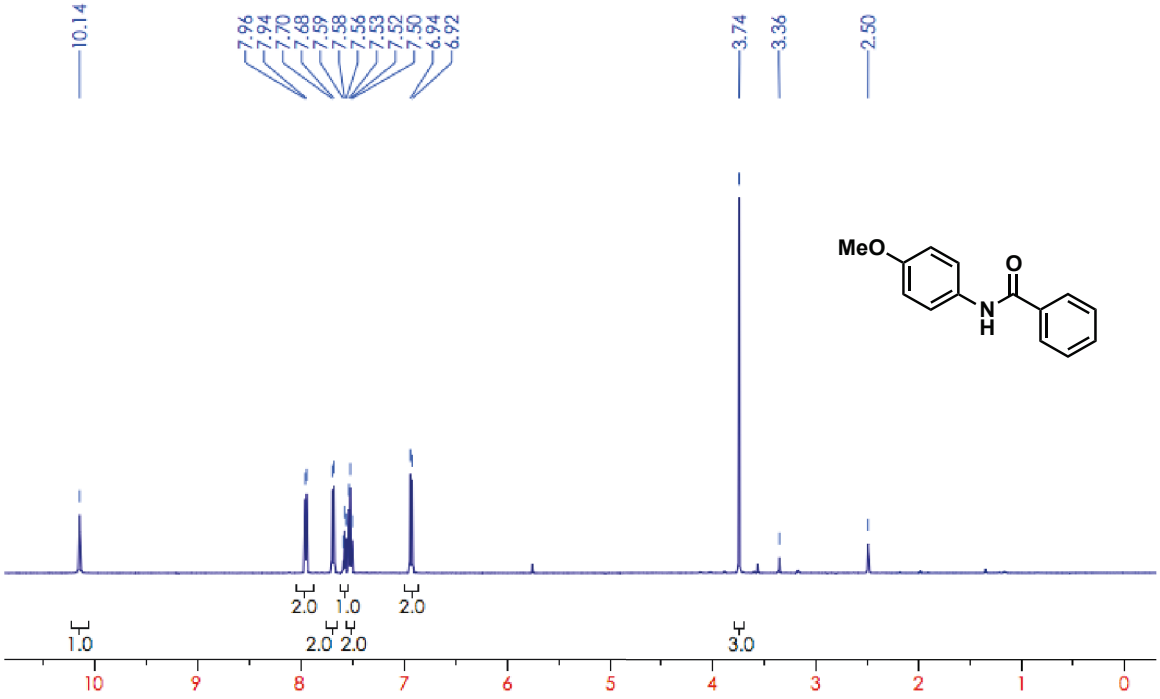
^{1}H NMR of **3-36**, (DMSO-*d6*, 500 MHz, 300 K)



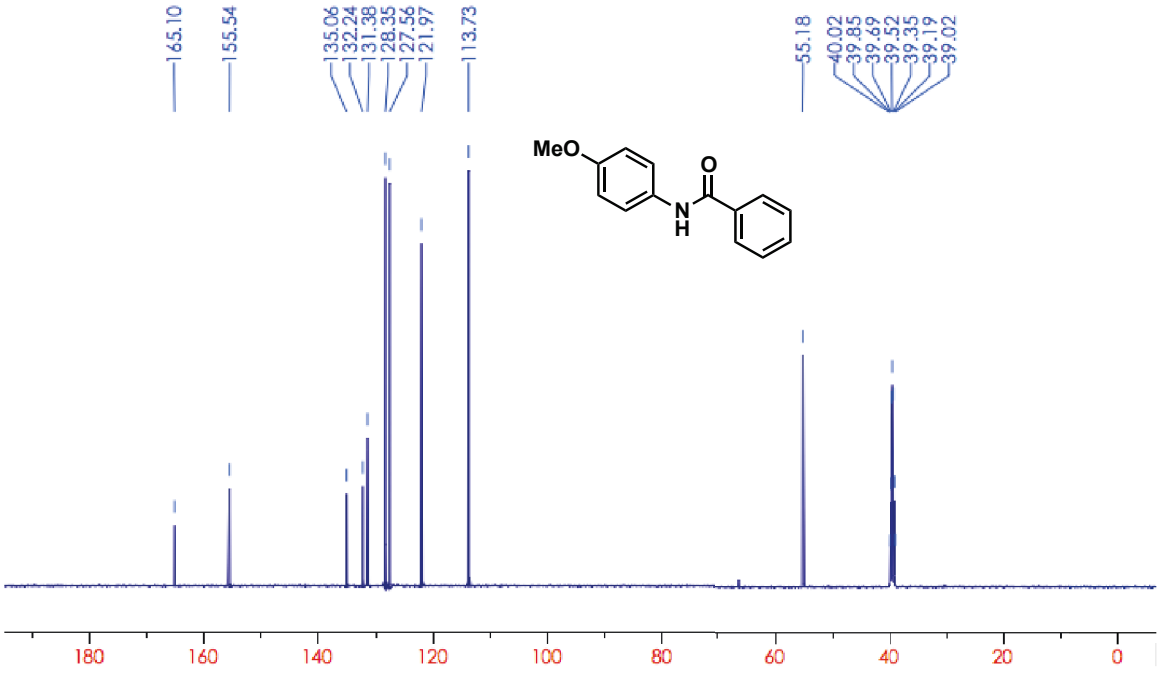
^{13}C{^{1}H} NMR of **3-36**, (DMSO-*d6*, 125.8 MHz, 300 K)



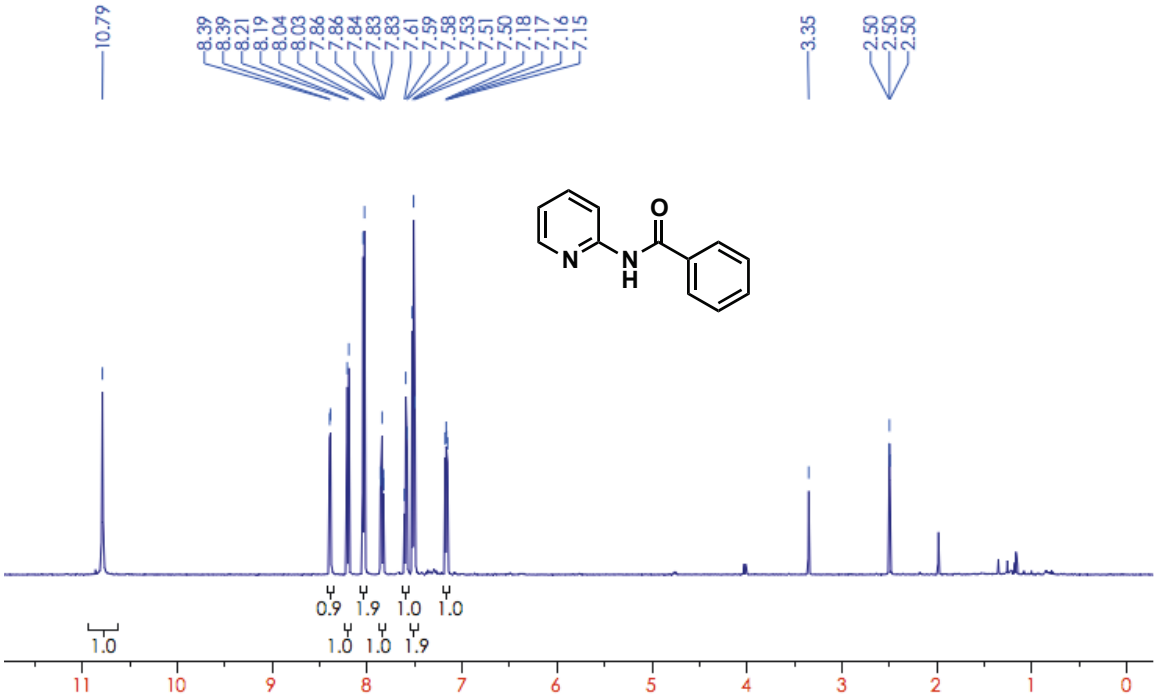
^{1}H NMR of **3-41**, (DMSO-*d6*, 500 MHz, 300 K)



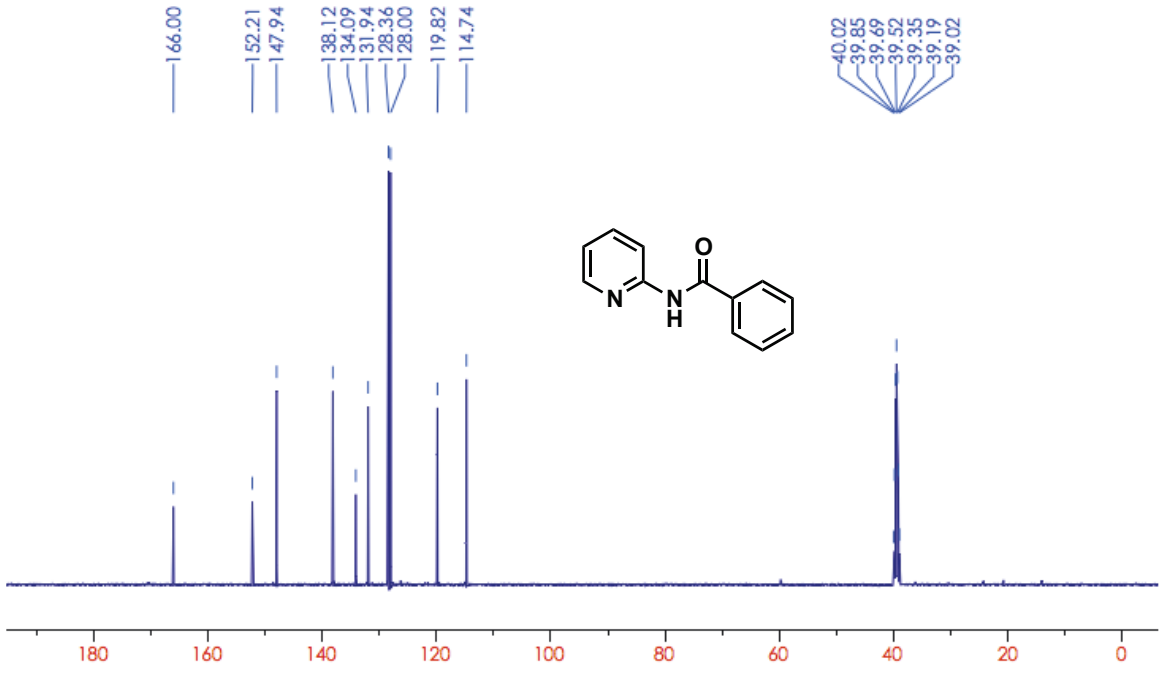
^{13}C{^{1}H} NMR of **3-41**, (DMSO-*d6*, 125.8 MHz, 300 K)



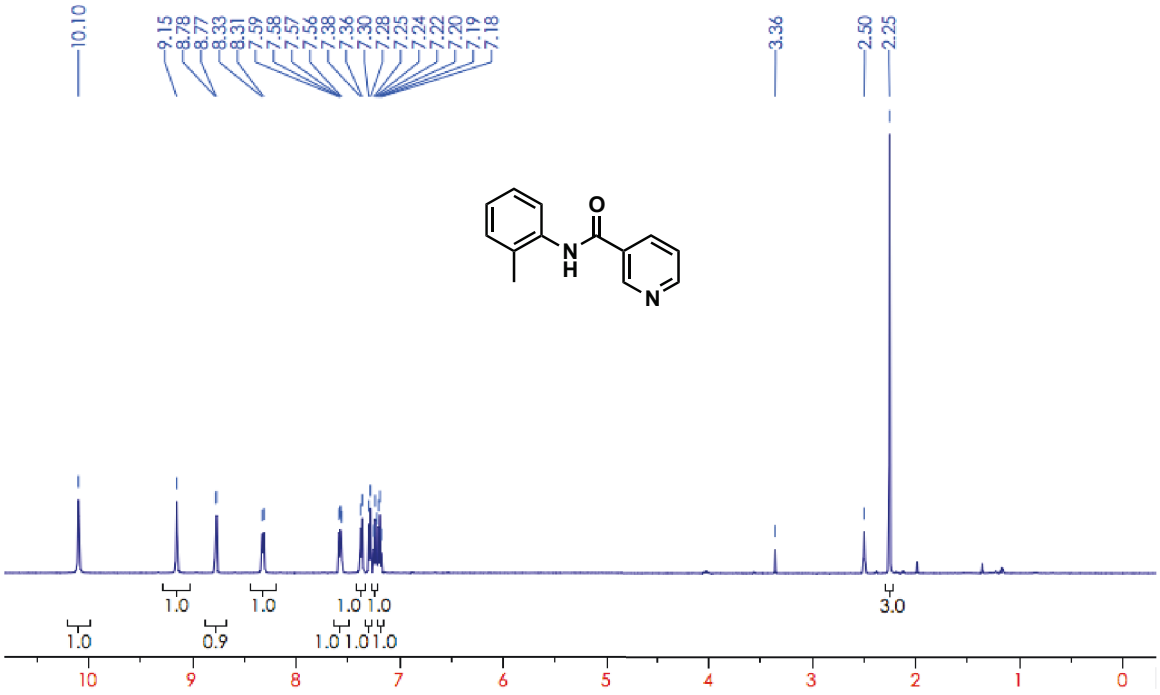
^{1}H NMR of **3-44**, (DMSO-*d6*, 500 MHz, 300 K)



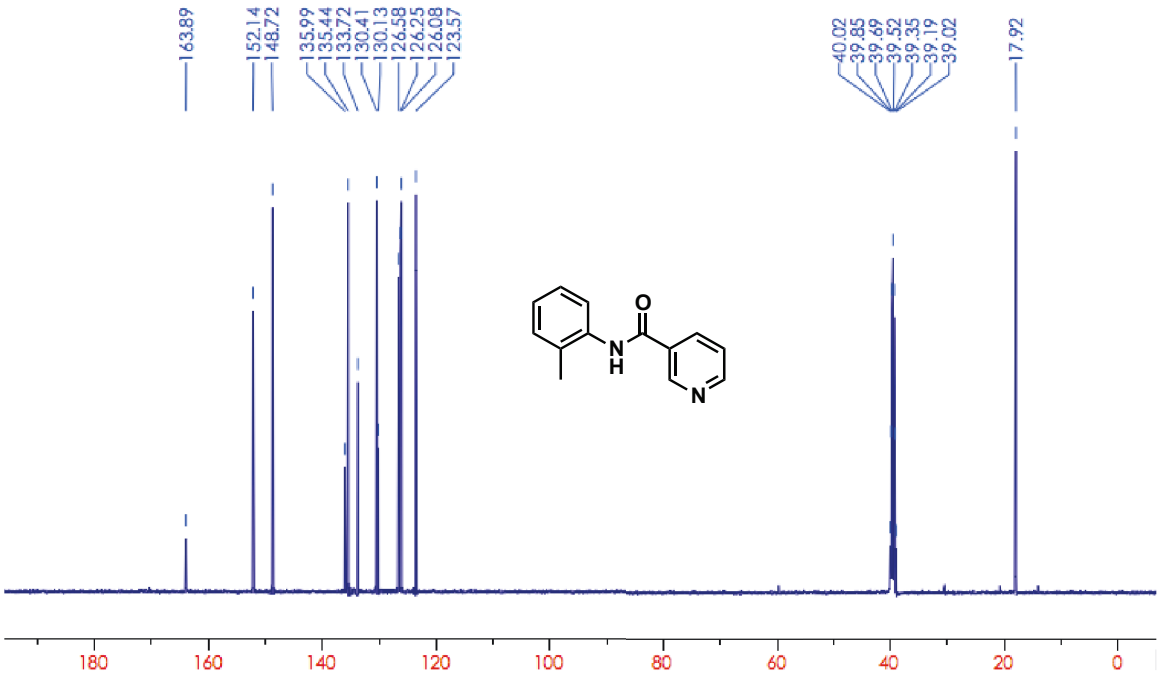
^{13}C{^{1}H} NMR of **3-44**, (DMSO-*d6*, 125.8 MHz, 300 K)



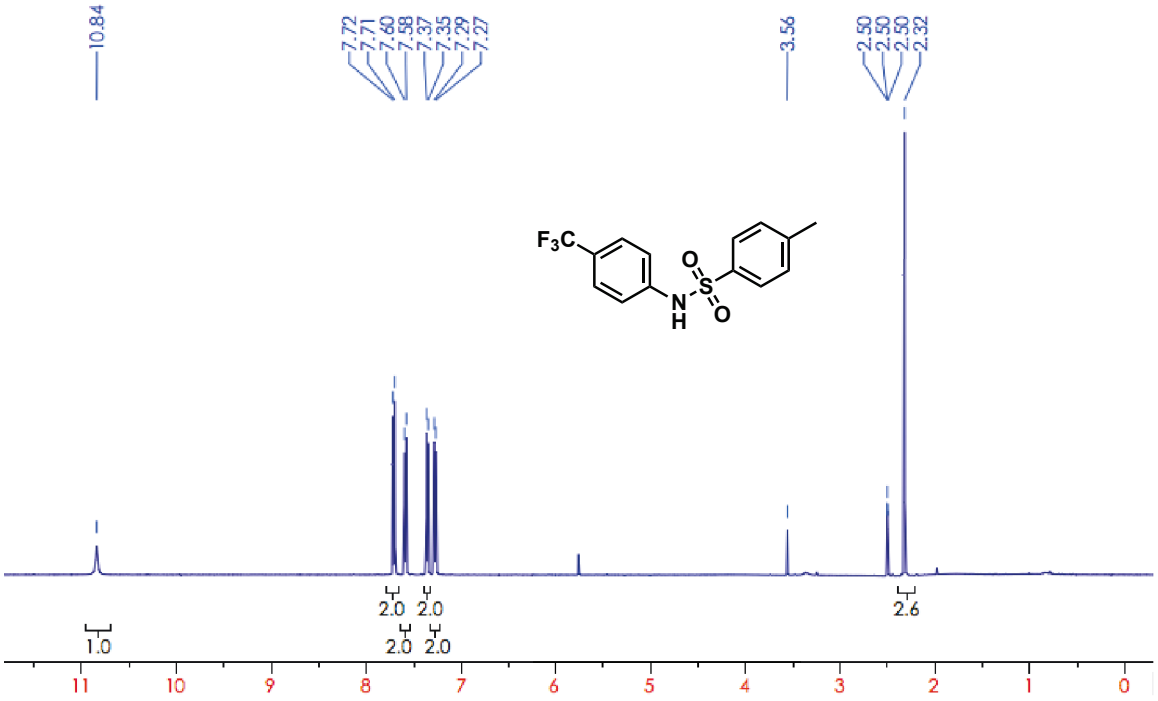
^{1}H NMR of **3-48**, (DMSO-*d6*, 500 MHz, 300 K)



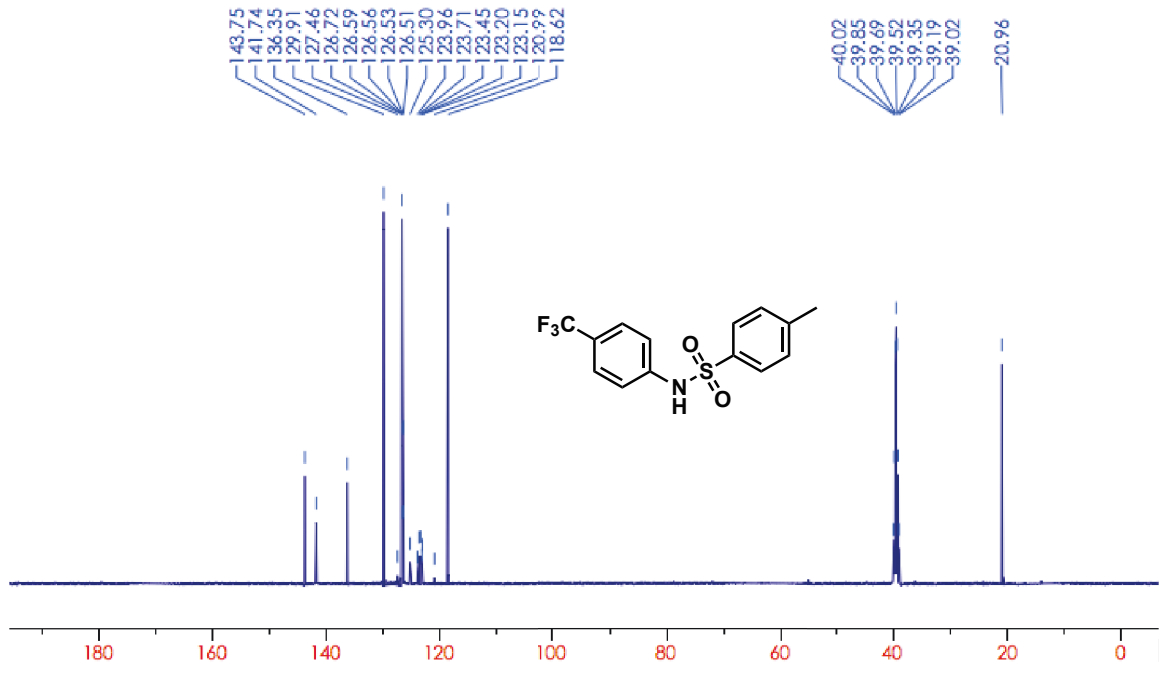
^{13}C{^{1}H} NMR of **3-48**, (DMSO-*d6*, 125.8 MHz, 300 K)



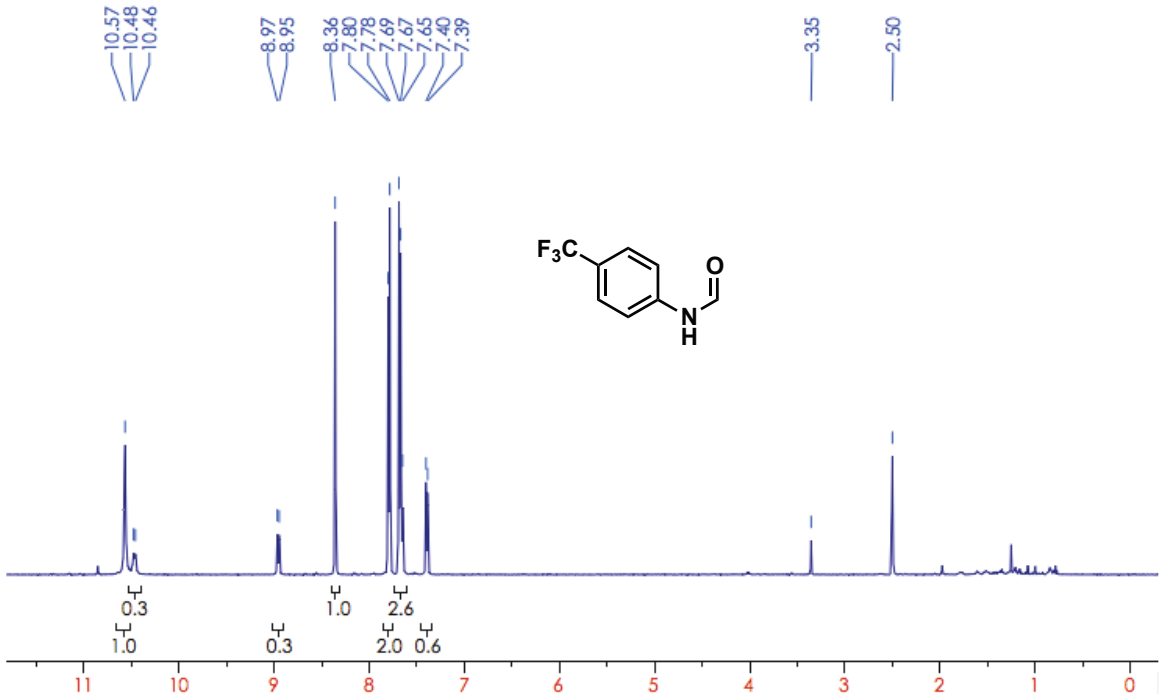
^{1}H NMR of **3-52**, (DMSO-*d6*, 500 MHz, 300 K)



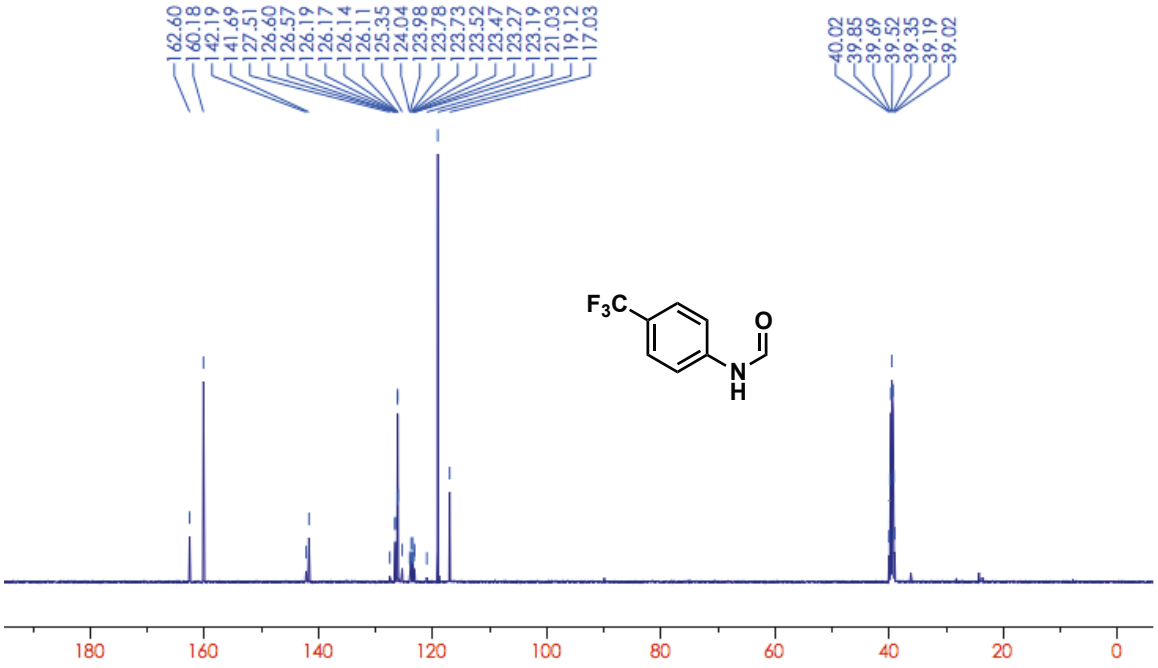
^{13}C{^{1}H} NMR of **3-52**, (DMSO-*d6*, 125.8 MHz, 300 K)



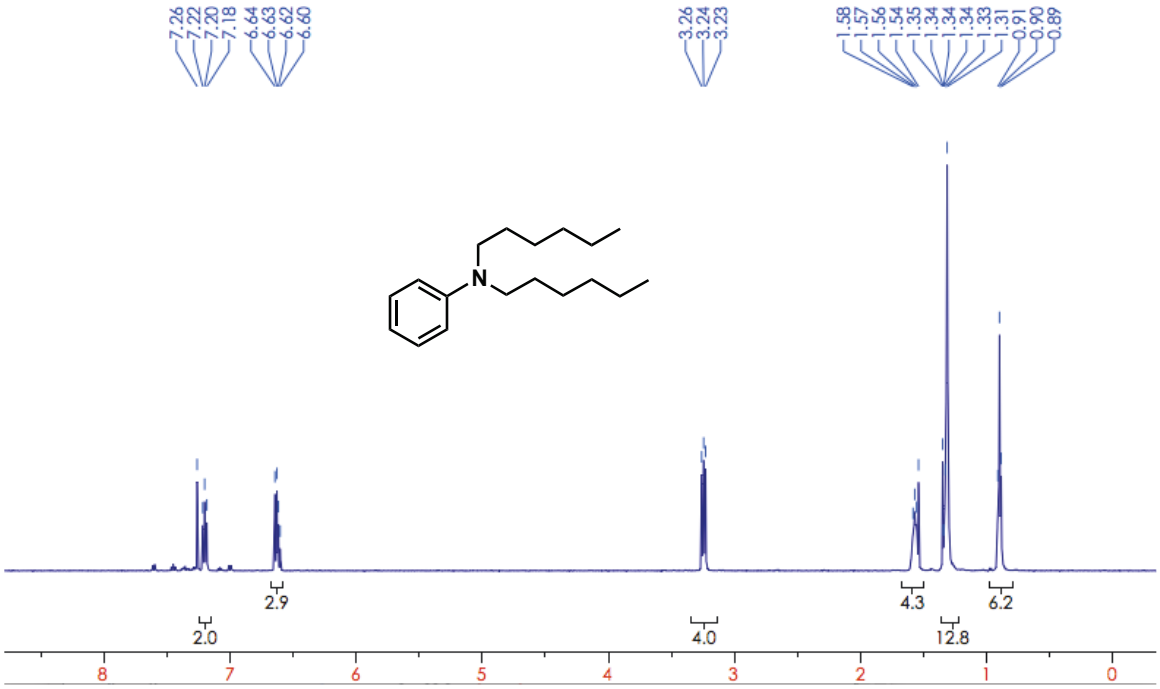
^{1}H NMR of **3-54**, (DMSO-*d6*, 500 MHz, 300 K)



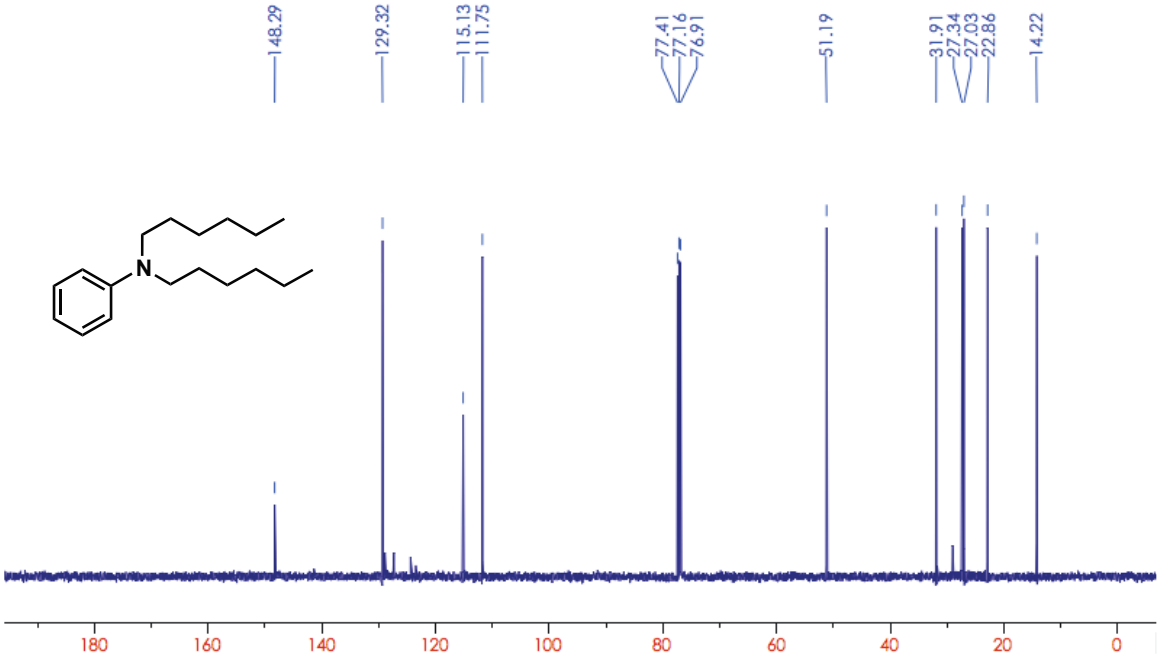
^{13}C{^{1}H} NMR of **3-54**, (DMSO-*d6*, 125.8 MHz, 300 K)



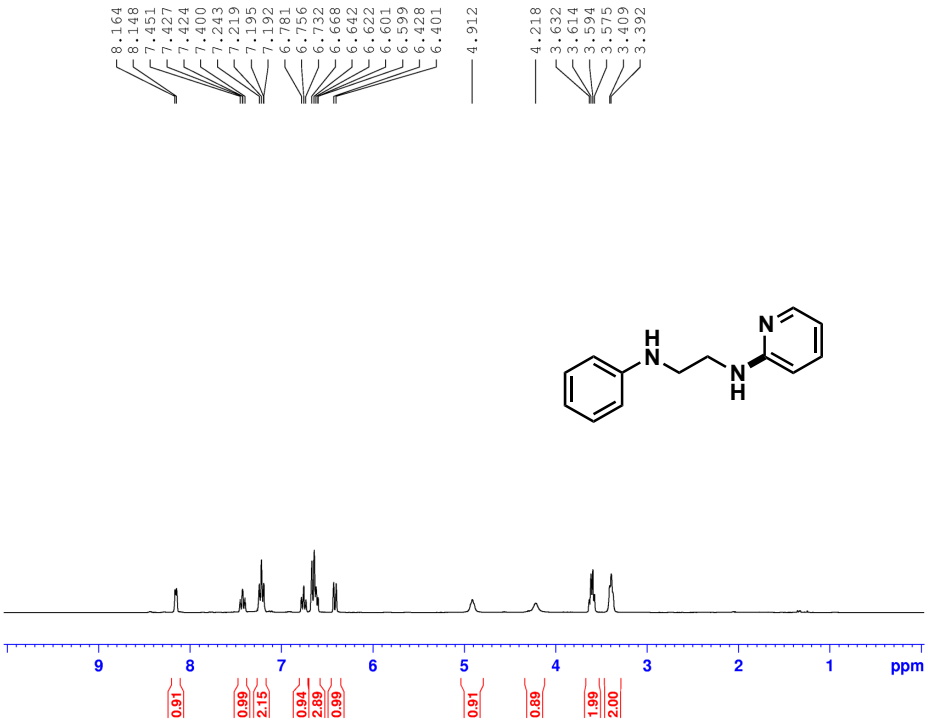
^{1}H NMR of **3-55**, ($CDCl_3$, 500 MHz, 300 K)



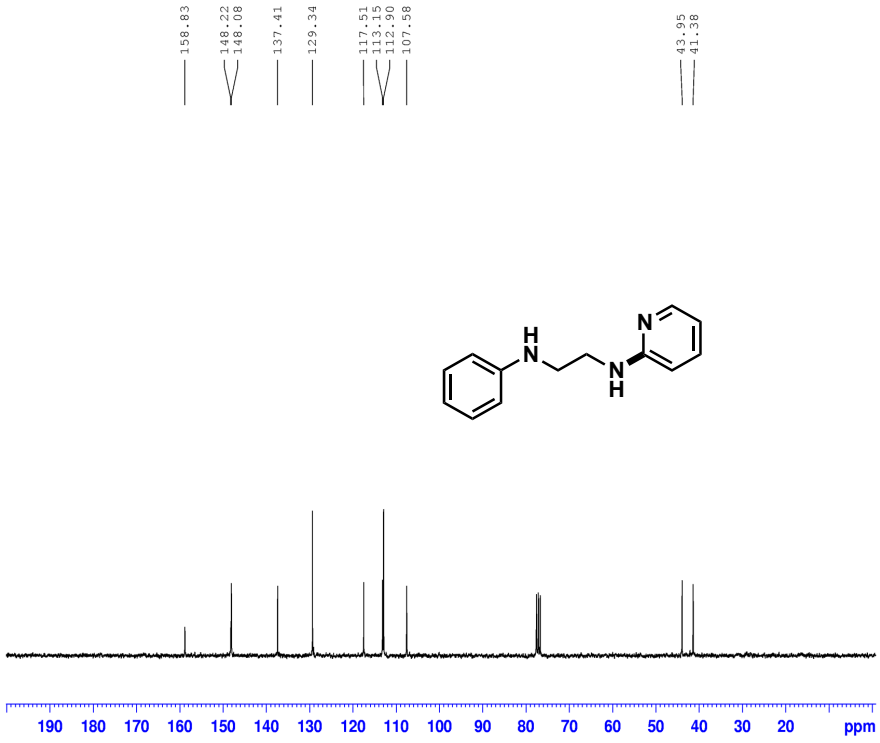
^{13}C{^{1}H} NMR of **3-55**, ($CDCl_3$, 125.8 MHz, 300 K)



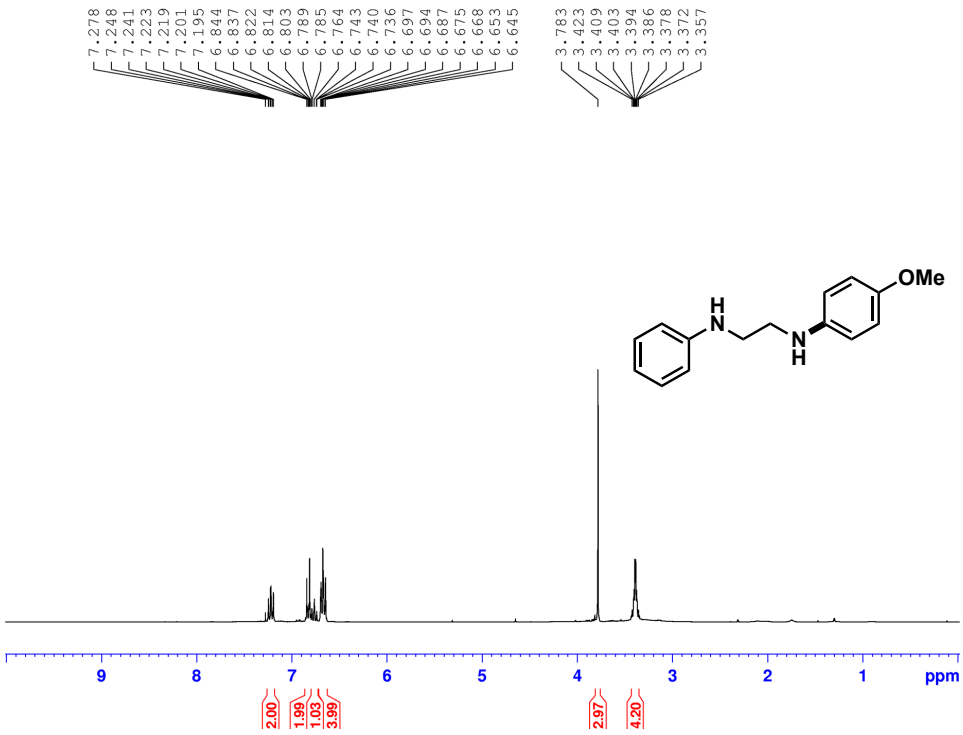
^{1}H NMR of **3-66**, (CDCl$_3$, 500 MHz, 300 K)



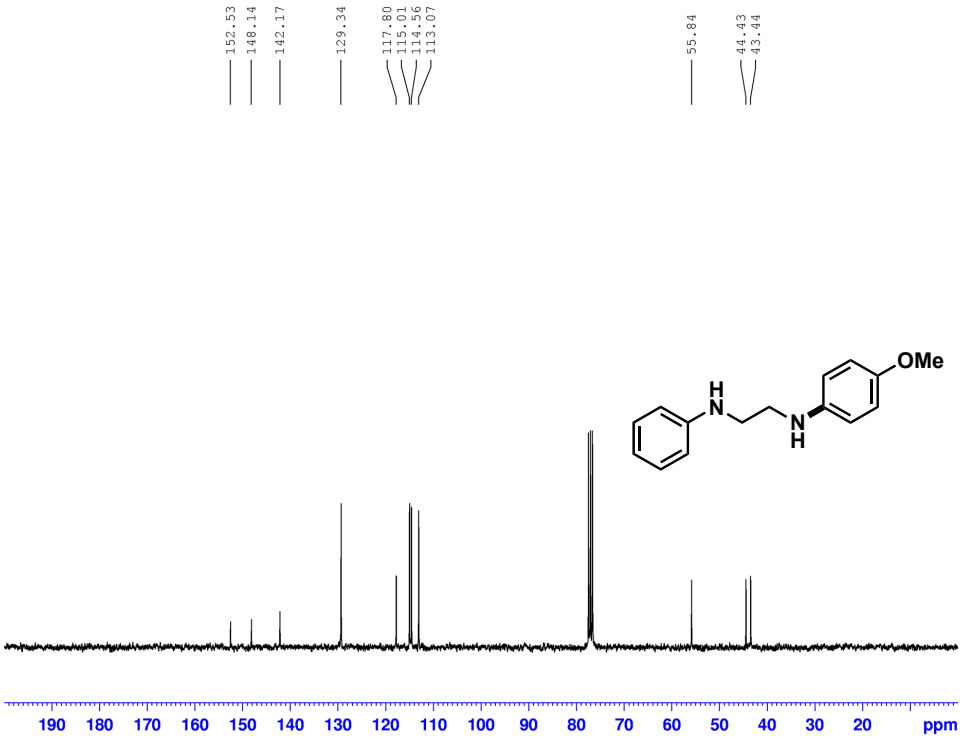
^{13}C{^{1}H} NMR of **3-66**, (CDCl$_3$, 125.8 MHz, 300 K)



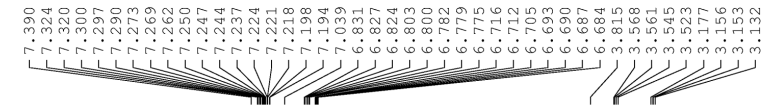
^{1}H NMR of **3-68**, ($CDCl_3$, 500 MHz, 300 K)

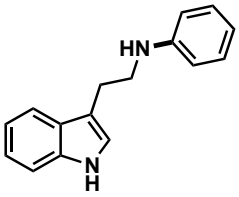


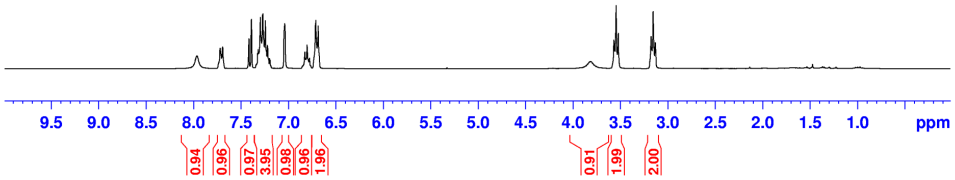
^{13}C{^{1}H} NMR of **3-68**, ($CDCl_3$, 125.8 MHz, 300 K)



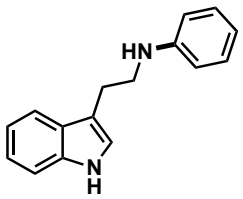
^{1}H NMR of **3-71**, ($CDCl_3$, 300 MHz, 300 K)

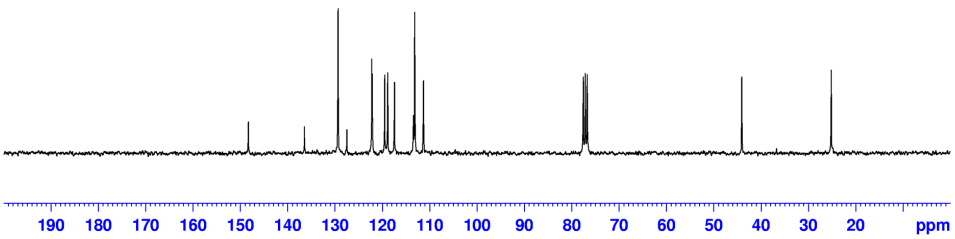




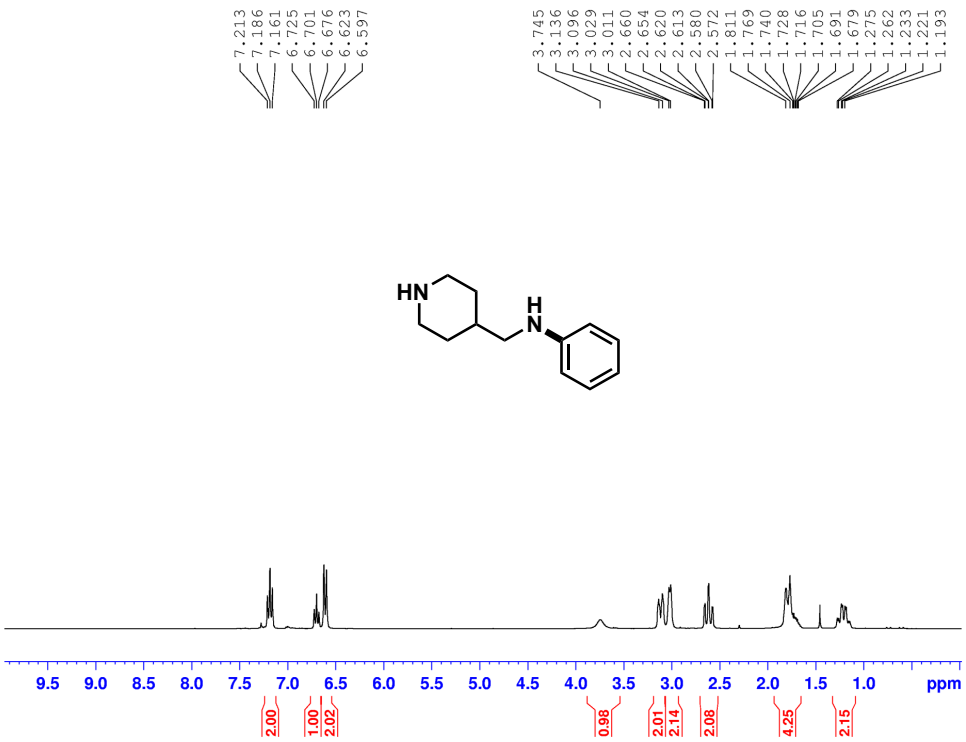


^{13}C{^{1}H} NMR of **3-71**, ($CDCl_3$, 75.4 MHz, 300 K)

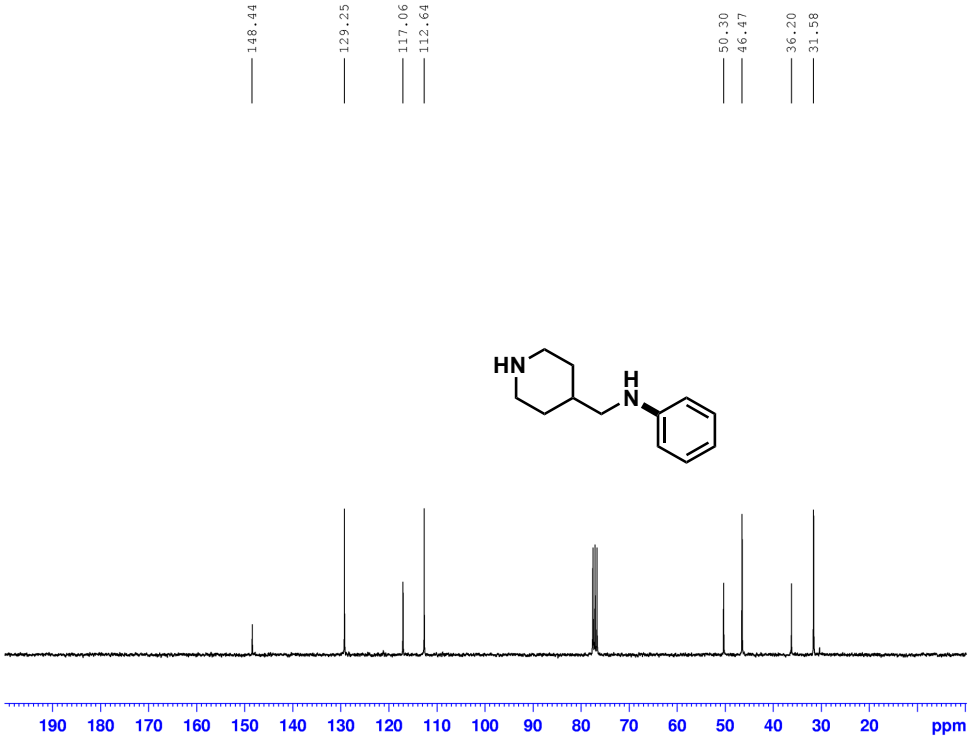




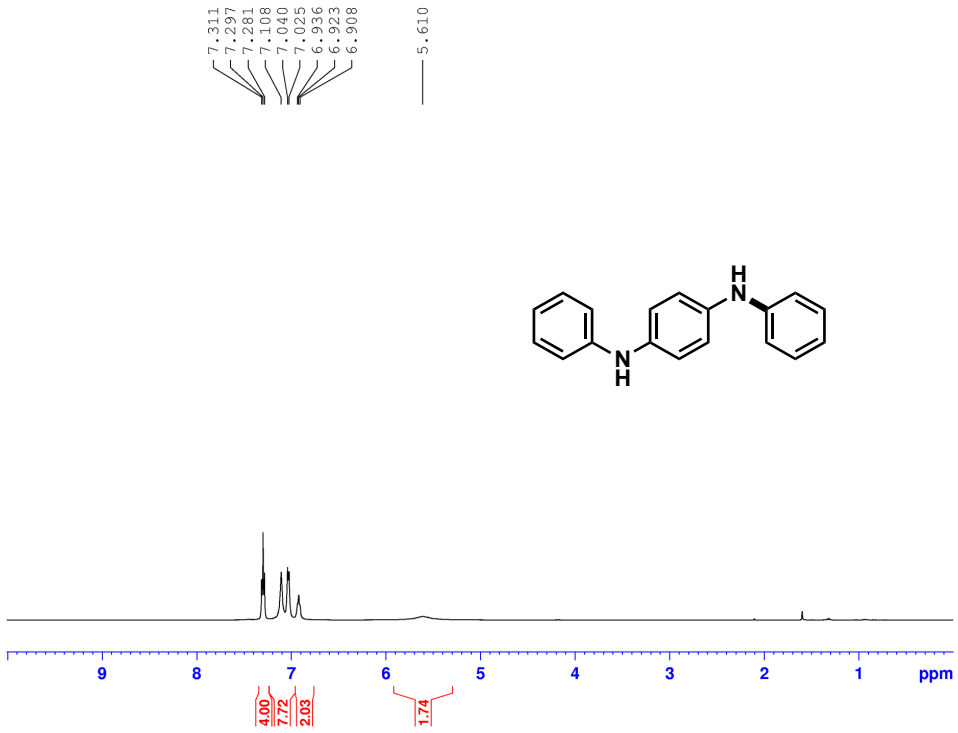
^{1}H NMR of **3-74**, ($CDCl_3$, 300 MHz, 300 K)



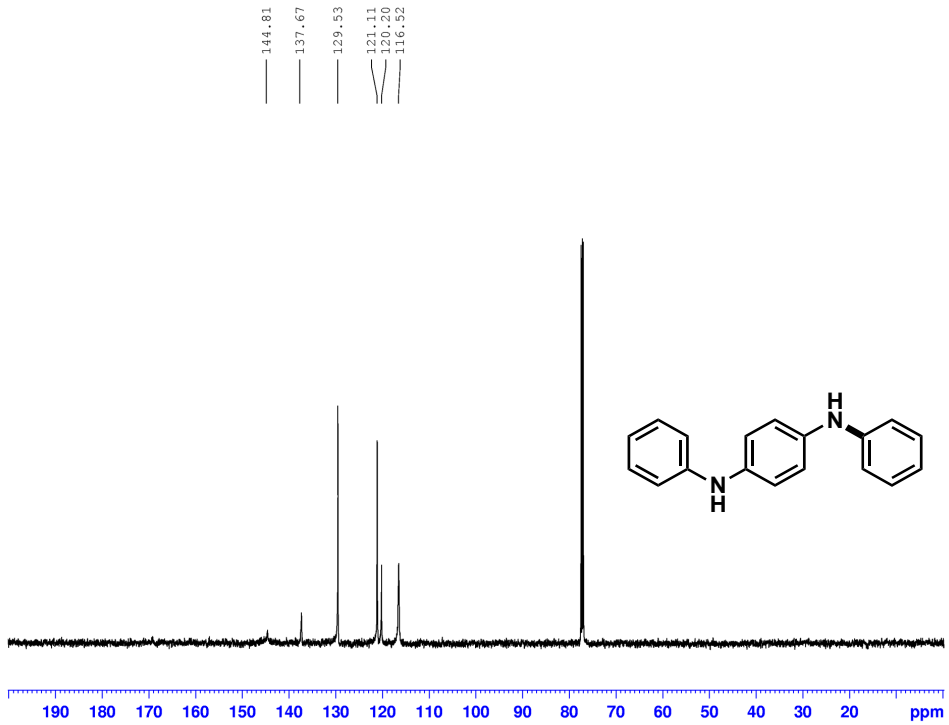
^{13}C{^{1}H} NMR of **3-74**, ($CDCl_3$, 75.4 MHz, 300 K)



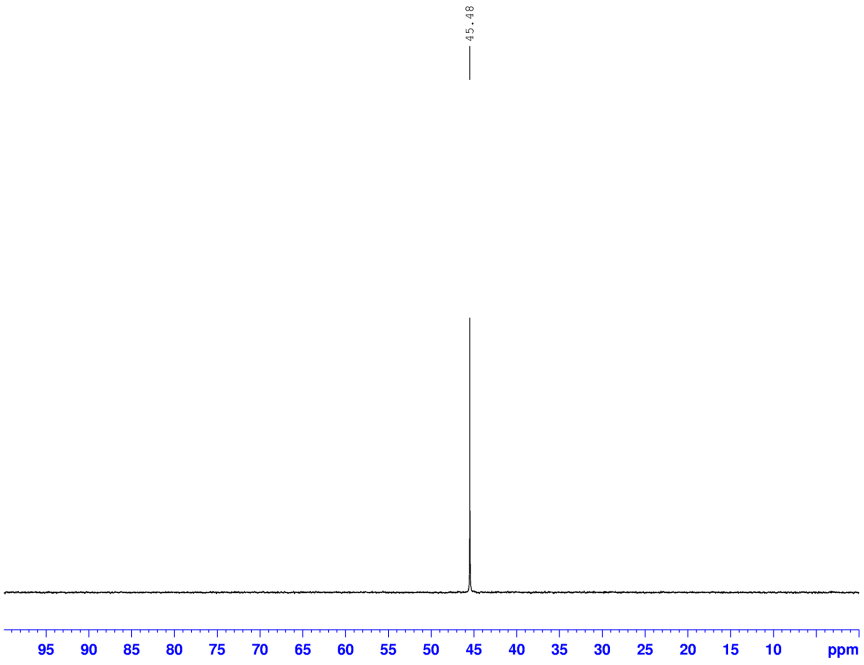
^{1}H NMR of **3-75**, ($CDCl_3$, 500 MHz, 300 K)



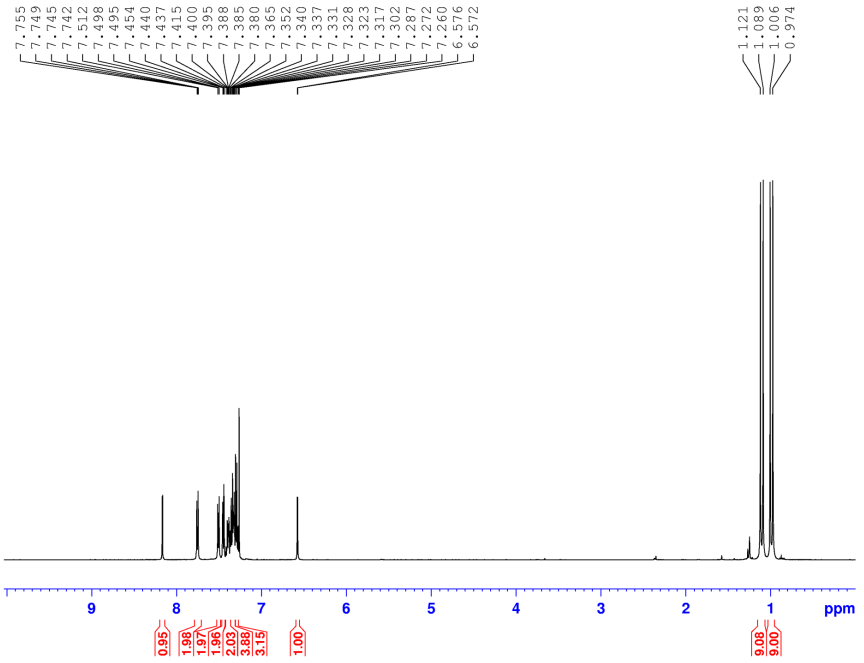
^{13}C{^{1}H} NMR of **3-75**, ($CDCl_3$, 125.8 MHz, 300 K)



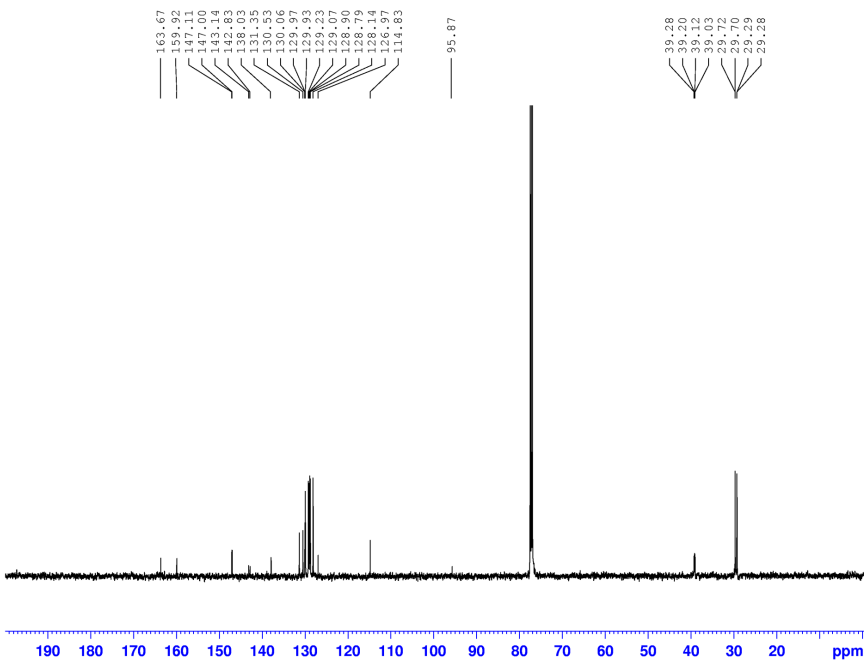
^{31}P NMR of **C1** ($CDCl_3$, 202 MHz, 300 K)



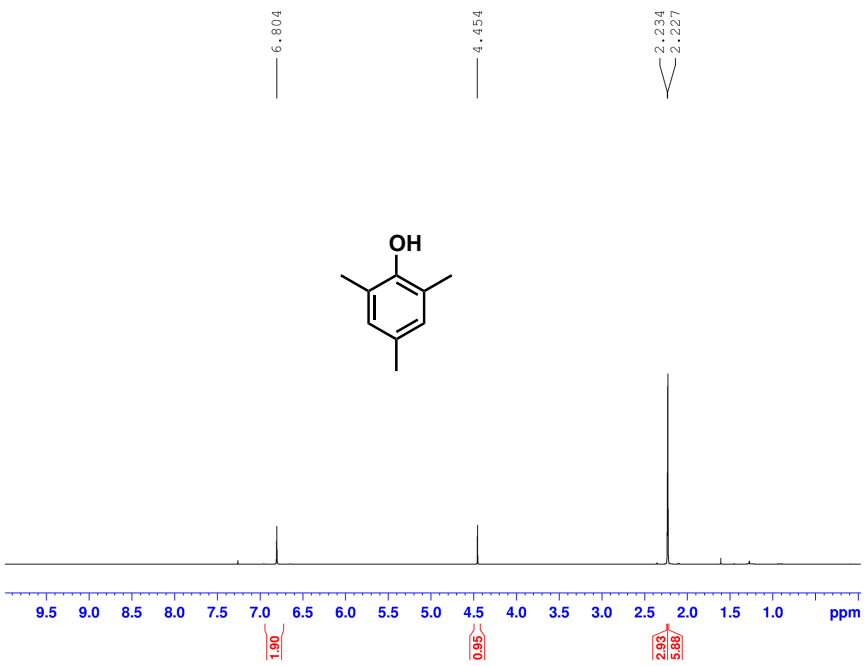
^{1}H NMR of **C1** ($CDCl_3$, 500 MHz, 300 K)



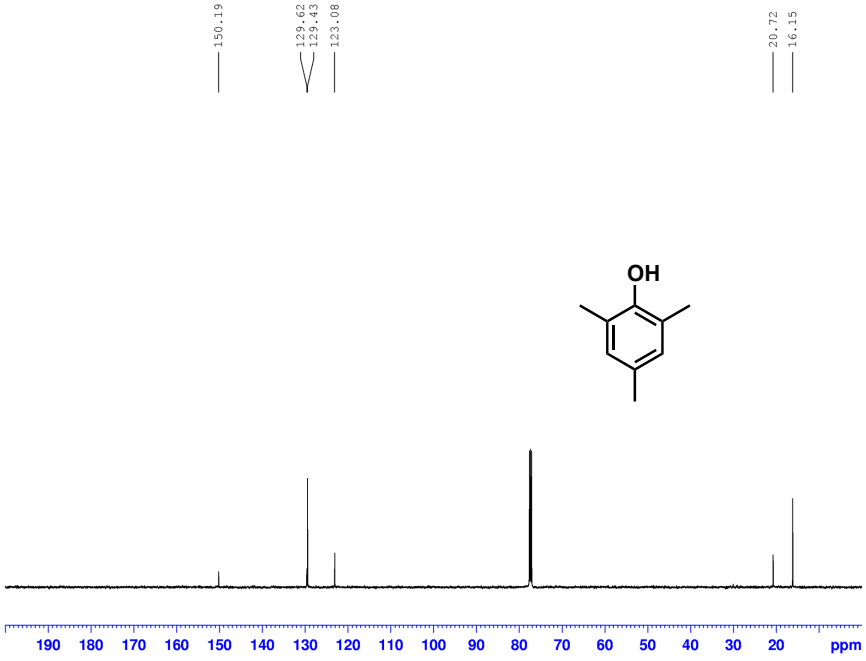
$^{13}C\{^{1}H\}$ NMR of **C1** ($CDCl_3$, 125.8 MHz, 300 K)



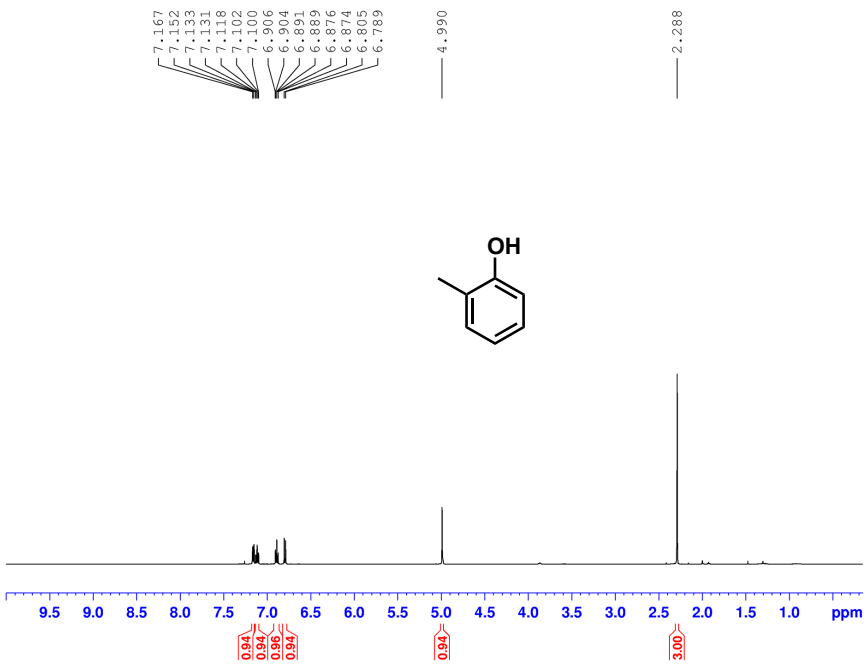
^{1}H NMR of **4-1** ($CDCl_3$, 500 MHz, 300 K)



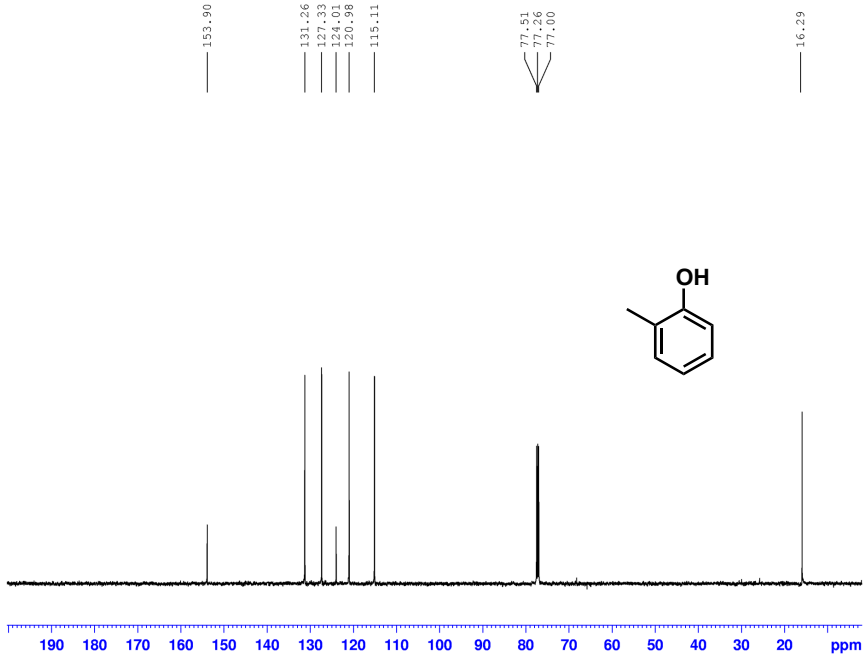
^{13}C{^{1}H} NMR of **4-1** ($CDCl_3$, 125.8 MHz, 300 K)



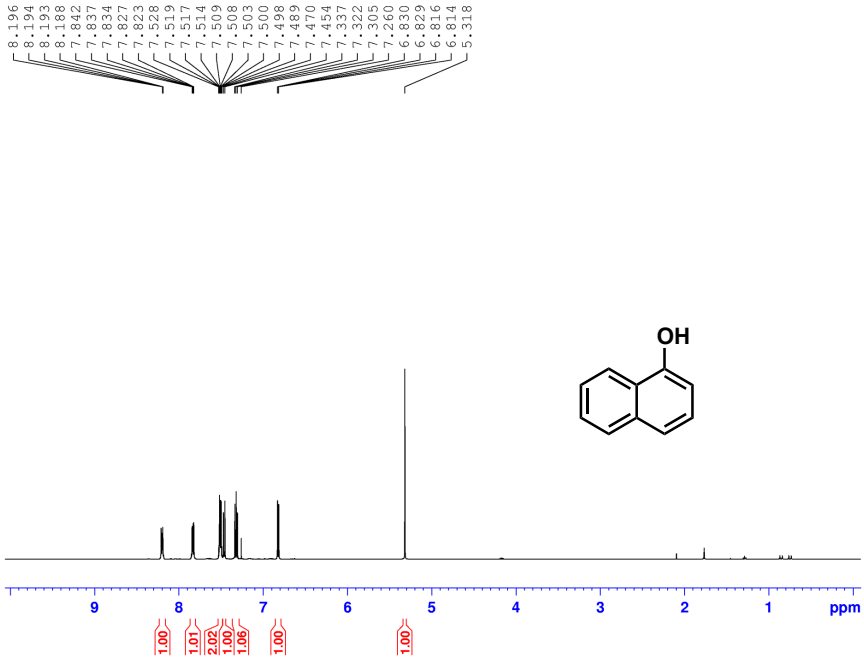
^{1}H NMR of **4-3** ($CDCl_3$, 500 MHz, 300 K)



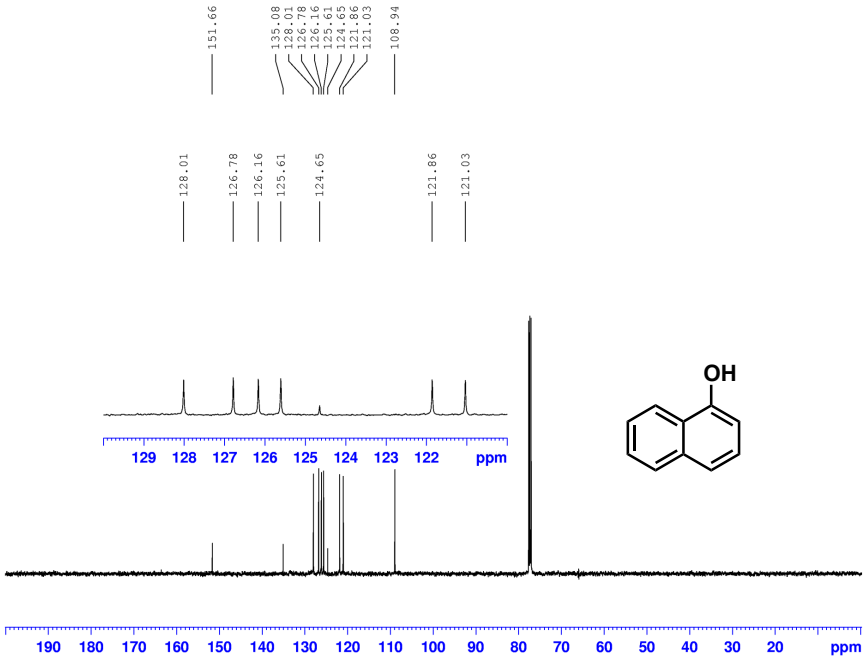
^{13}C{^{1}H} NMR of **4-3** ($CDCl_3$, 125.8 MHz, 300 K)



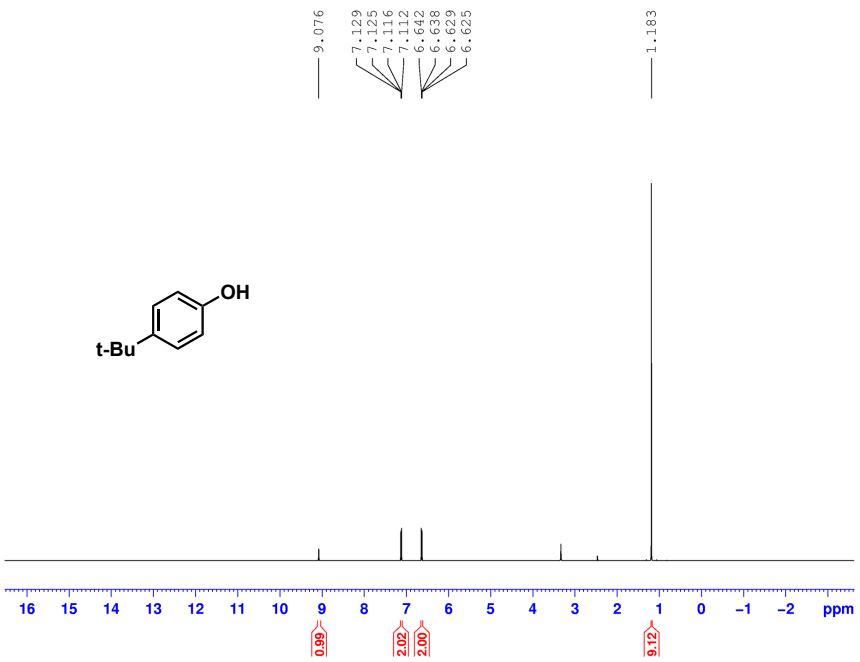
^{1}H NMR of **4-6** ($CDCl_3$, 500 MHz, 300 K)



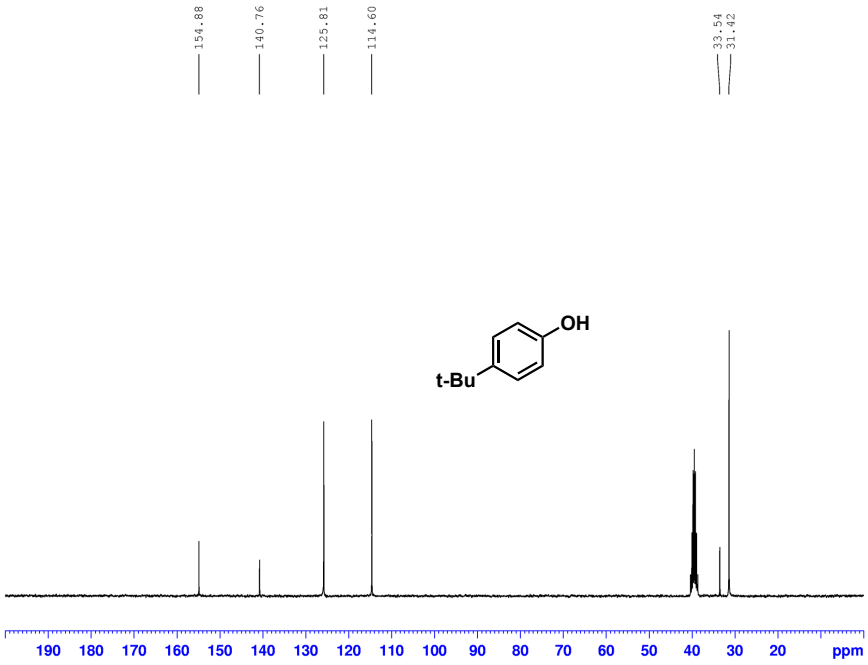
^{13}C{^{1}H} NMR of **4-6** ($CDCl_3$, 125.8 MHz, 300 K)



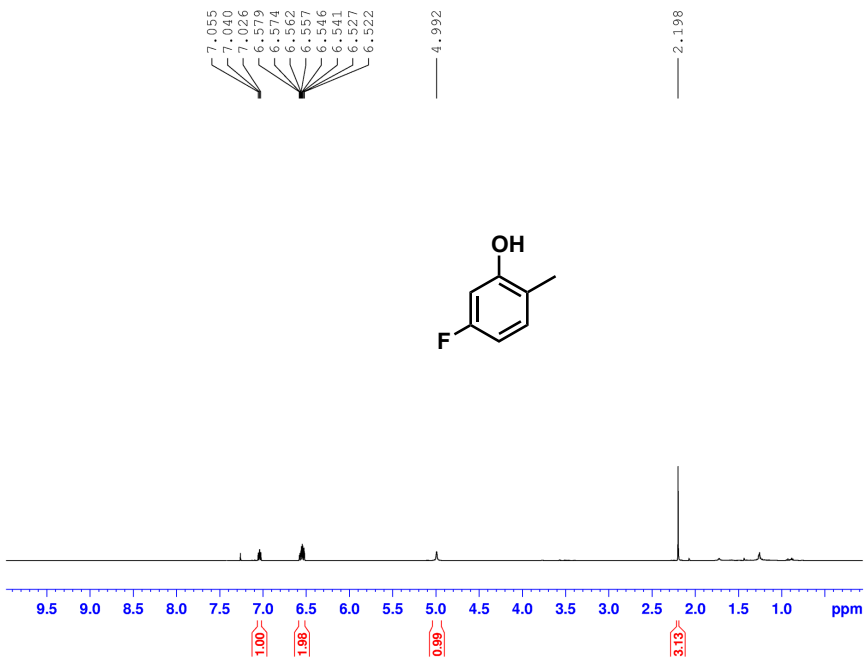
^{1}H NMR of **4-9** (DMSO-*d6*, 500 MHz, 300 K)



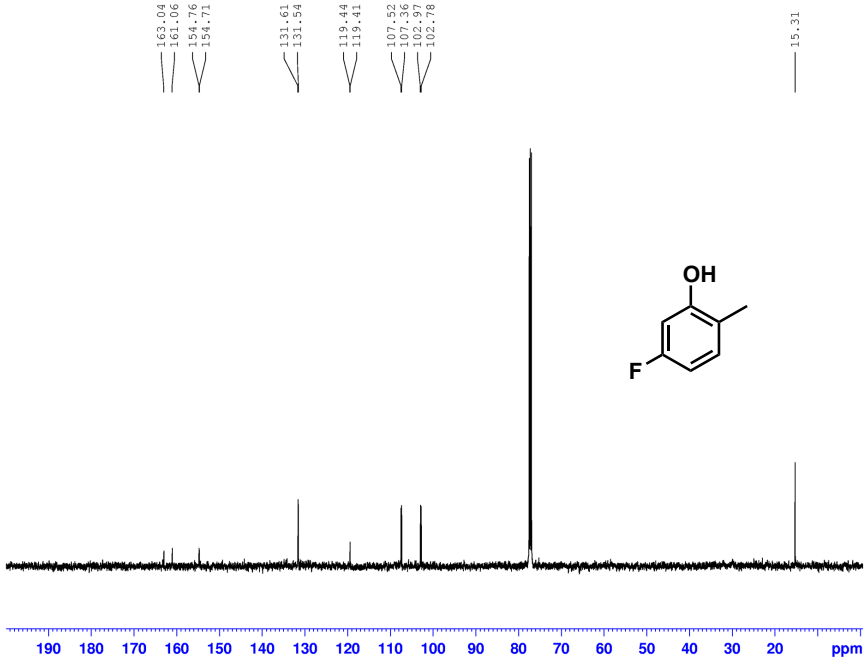
^{13}C{^{1}H} NMR of **4-9** (DMSO-*d6*, 125.8 MHz, 300 K)



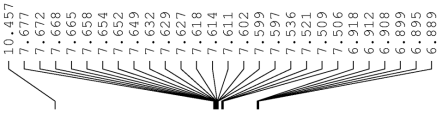
^{1}H NMR of **4-12** ($CDCl_3$, 500 MHz, 300 K)

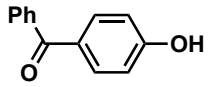


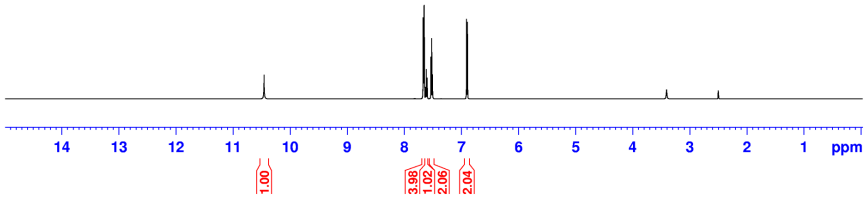
^{13}C{^{1}H} NMR of **4-12** ($CDCl_3$, 125.8 MHz, 300 K)



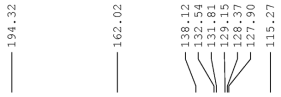
^{1}H NMR of **4-15** (DMSO-*d6*, 500 MHz, 300 K)

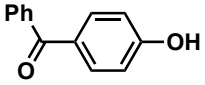


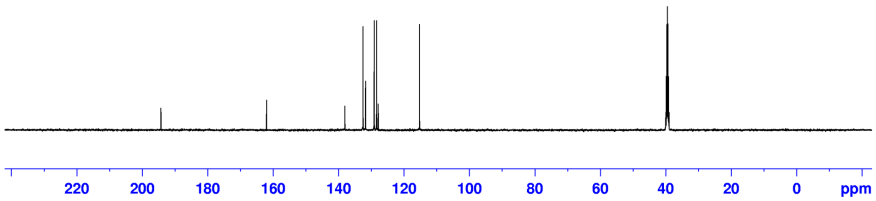




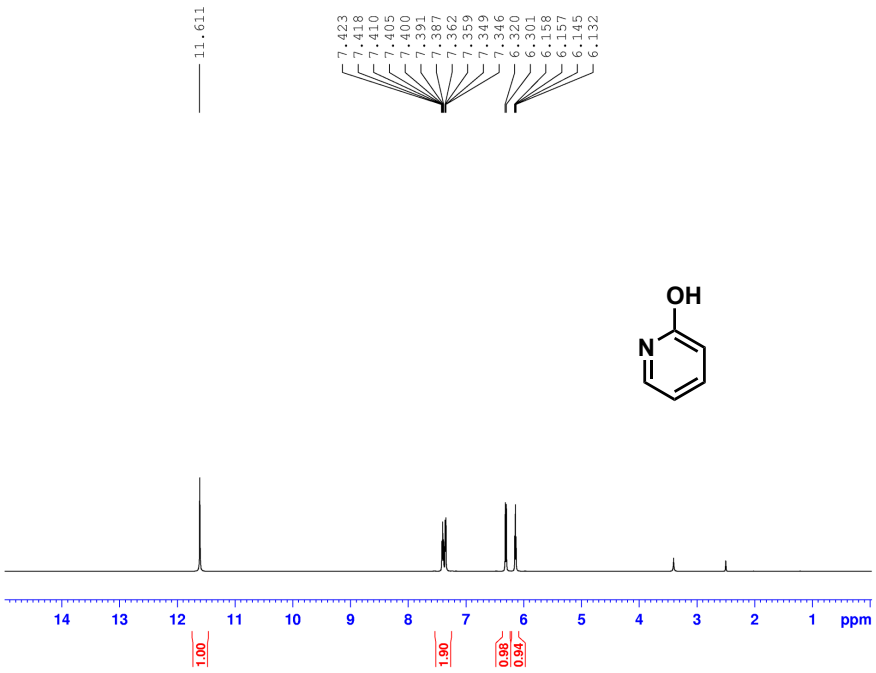
^{13}C{^{1}H} NMR of **4-15** (DMSO-*d6*, 125.8 MHz, 300 K)



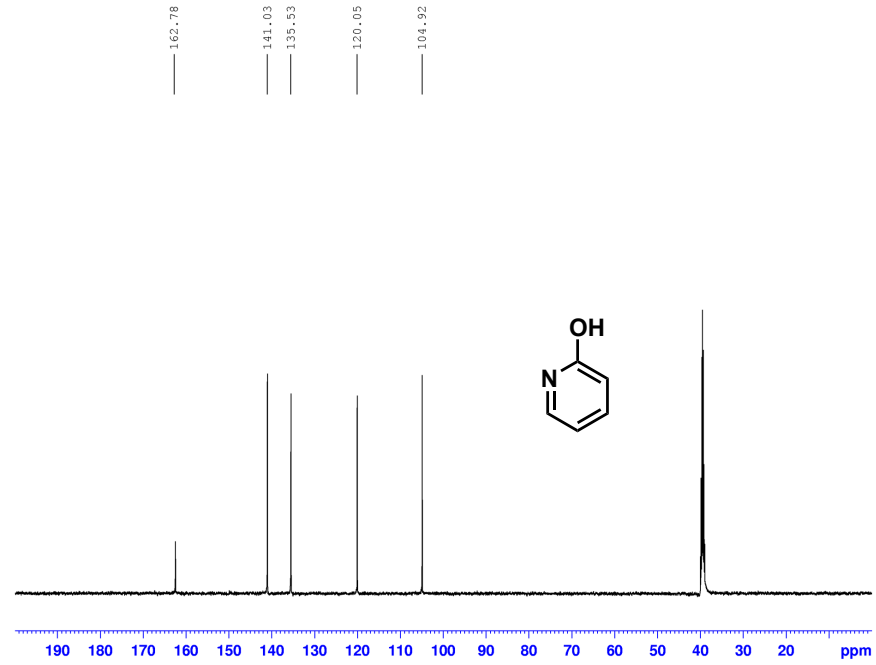




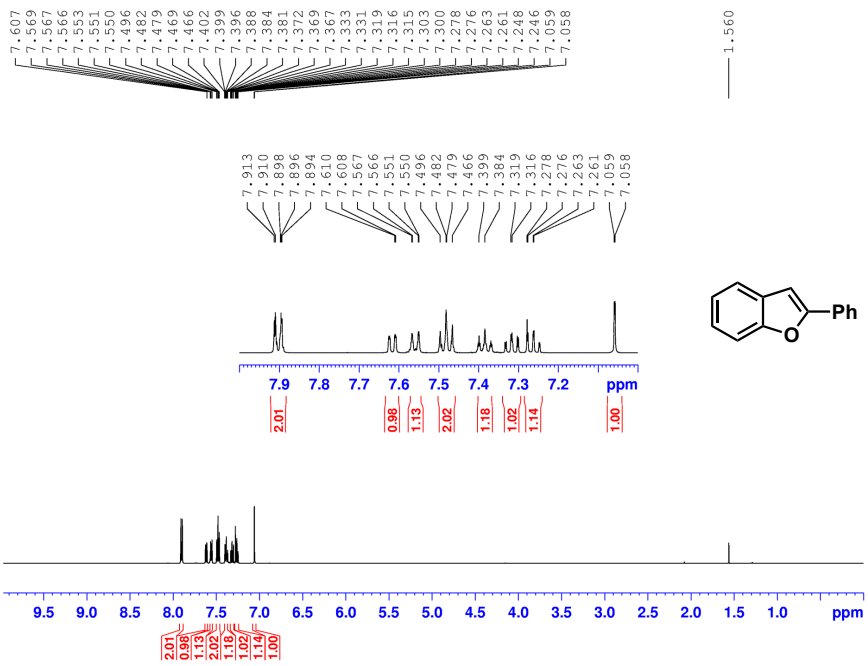
^{1}H NMR of **4-17** (DMSO-*d6*, 500 MHz, 300 K)



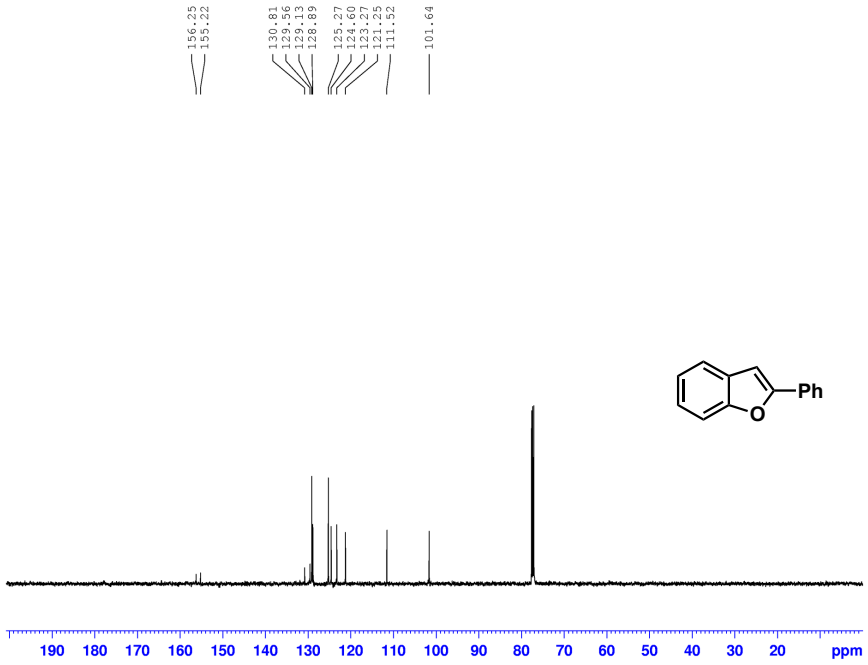
^{13}C{^{1}H} NMR of **4-17** (DMSO-*d6*, 125.8 MHz, 300 K)



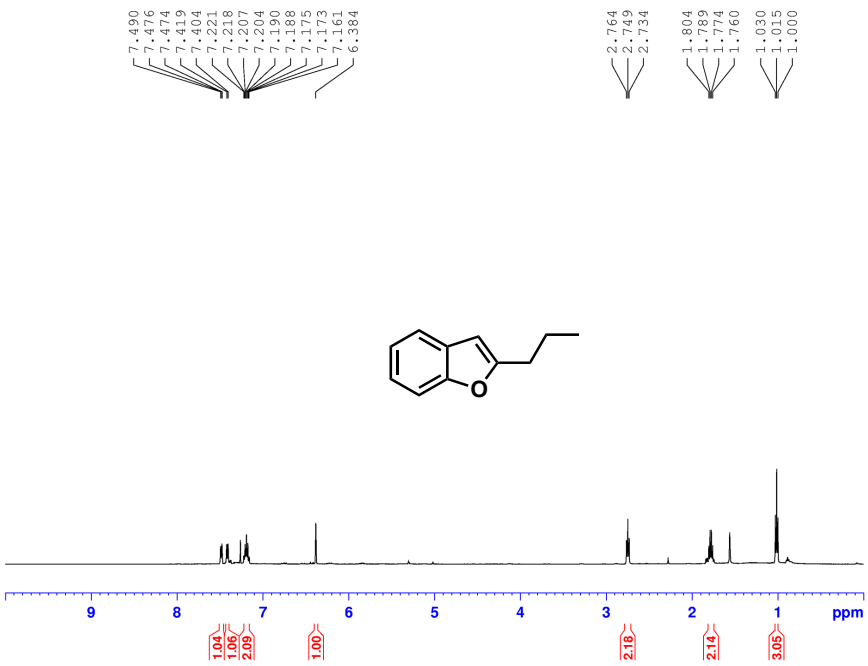
^{1}H NMR of **4-18** ($CDCl_3$, 500 MHz, 300 K)



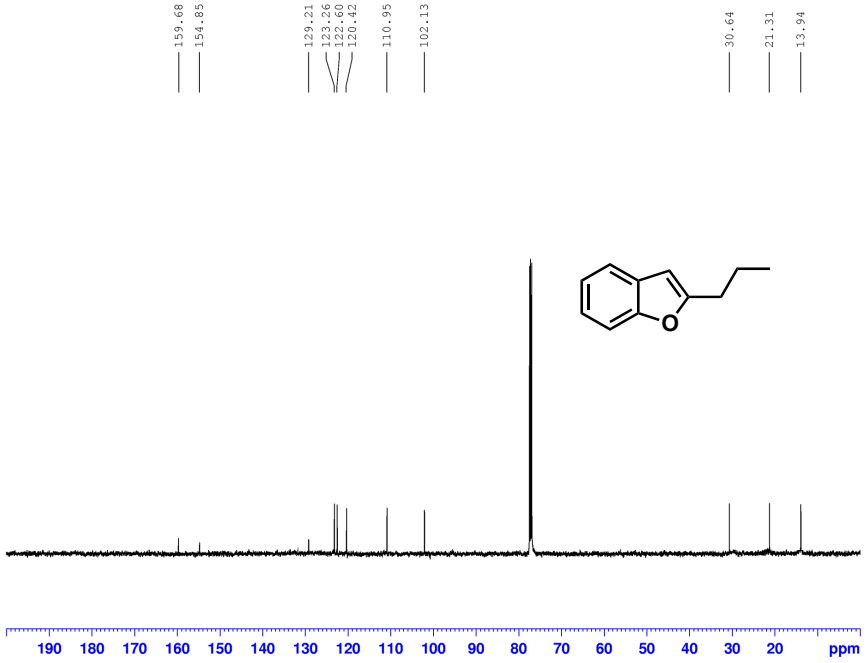
^{13}C{^{1}H} NMR of **4-18** ($CDCl_3$, 125.8 MHz, 300 K)



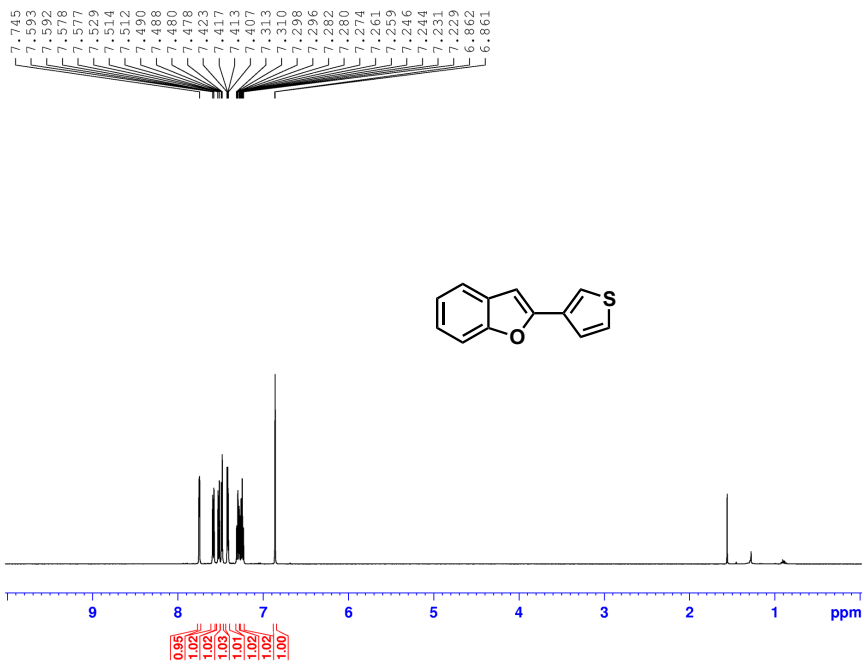
^{1}H NMR of **4-21** ($CDCl_3$, 500 MHz, 300 K)



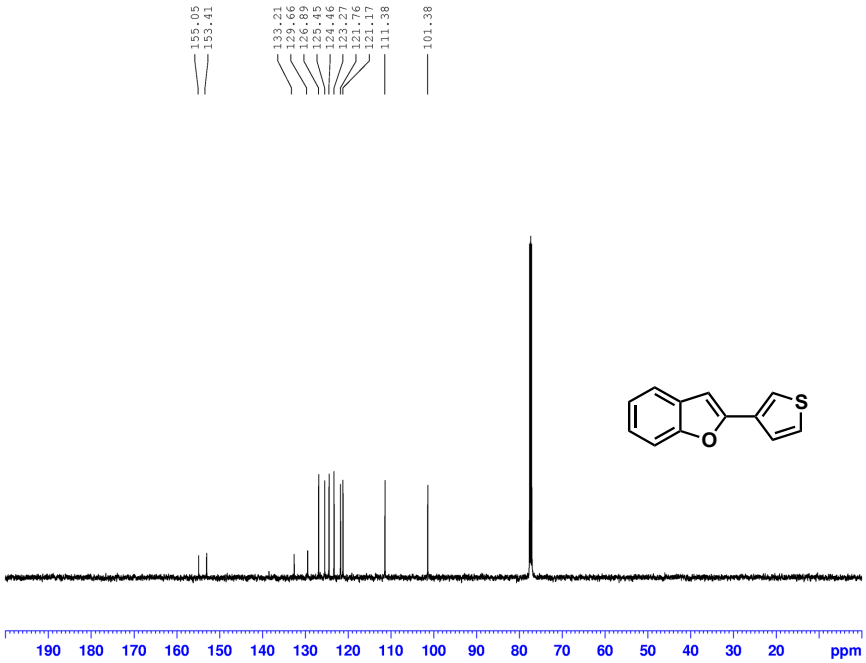
^{13}C{^{1}H} NMR of **4-21** ($CDCl_3$, 125.8 MHz, 300 K)



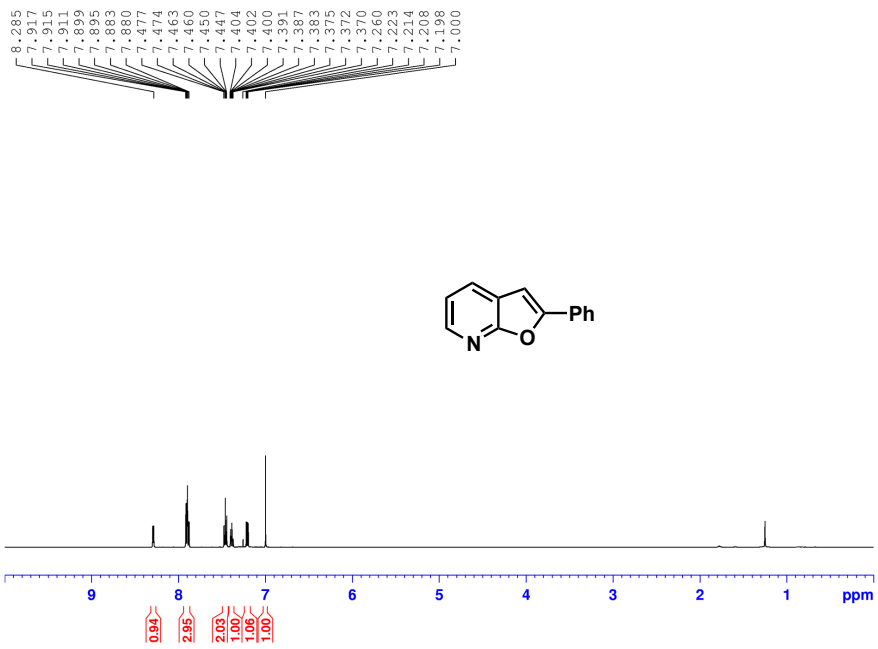
^{1}H NMR of **4-22** ($CDCl_3$, 500 MHz, 300 K)



^{13}C{^{1}H} NMR of **4-22** ($CDCl_3$, 125.8 MHz, 300 K)



^{1}H NMR of **4-24** ($CDCl_3$, 500 MHz, 300 K)



^{13}C{^{1}H} NMR of **4-24** ($CDCl_3$, 125.8 MHz, 300 K)

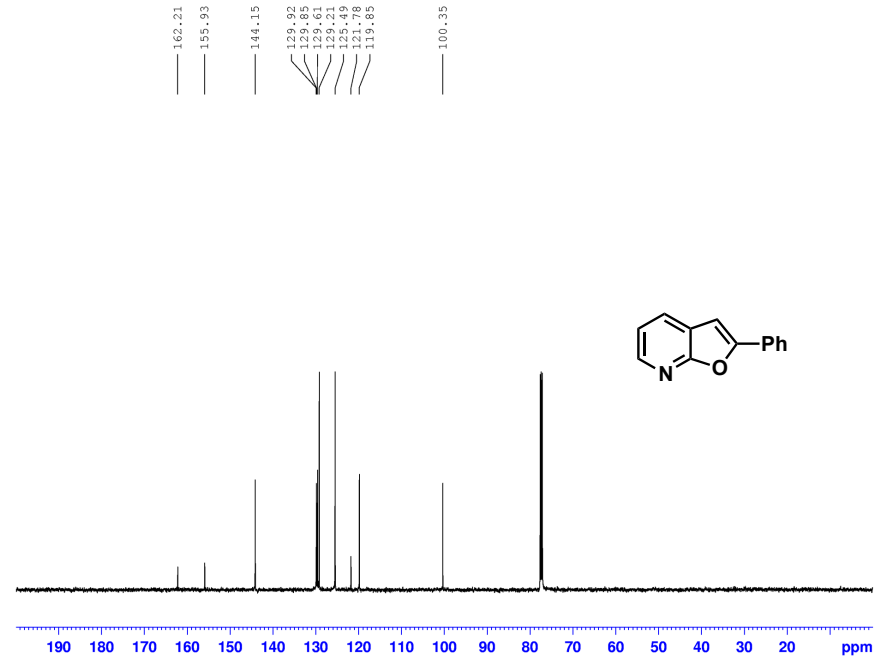


Table A–1. Crystallographic Experimental Details for **L1**.

A. Crystal Data	
formula	$C_{35}H_{55}OPSi$
formula weight	550.85
crystal dimensions (mm)	0.61 × 0.14 × 0.04
crystal system	orthorhombic
space group	*Pbca* (No. 61)
unit cell parameters[a]	
a (Å)	8.7730 (1)
b (Å)	23.8938 (4)
c (Å)	30.2150 (5)
V (Å^3)	6333.68 (17)
Z	8
ρ_{calcd} (g cm^{-3})	1.155
μ (mm^{-1})	1.306
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	graphite-monochromated Cu Kα (1.54178)
temperature (°C)	–100
scan type	ω scans (0.75°) (5 s exposures)
data collection 2θ limit (deg)	140.14
total data collected	40496 (-10 ≤ h ≤ 10, -29 ≤ k ≤ 29, -36 ≤ l ≤ 36)
independent reflections	5997 (R_{int} = 0.0463)
number of observed reflections (*NO*)	5393 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXD*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–97*[d])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9545–0.5046
data/restraints/parameters	5997 / 0 / 343
goodness-of-fit (S)[e] [all data]	1.035
final R indices[f]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0371
wR_2 [all data]	0.1057
largest difference peak and hole	0.569 and –0.284 e Å^{-3}

[a]Obtained from least-squares refinement of 9967 reflections with 5.84° < 2θ < 139.04°. [b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker. [c]Schneider, T. R.; Sheldrick, G. M. *Acta Crystallogr.* **2002**, *D58*, 1772-1779. [d]Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122. [e]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of

parameters varied; $w = [\sigma^2(F_o^2) + (0.0592P)^2 + 2.7697P]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$). [f] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table A–2. Crystallographic Experimental Details for **3-37**.

A. Crystal Data	
formula	$C_{12}H_{12}N_2O_2S$
formula weight	248.30
crystal dimensions (mm)	0.43 × 0.43 × 0.23
crystal system	Monoclinic
space group	P2(1)/c
unit cell parameters	
a (Å)	12.4987 (s)
b (Å)	9.0435 (2)
c (Å)	10.4311 (3)
V (Å^3)	1148.80 (5)
Z	4
ρ_{calcd} (g cm^{-3})	1.436
μ (mm^{-1})	0.272
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/APEX II CCD[a]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (K)	296(2)
data collection 2θ limit (deg)	27.53
total data collected	21707 (-16 ≤ h ≤ 16, -11 ≤ k ≤ 11, -13 ≤ l ≤ 13)
independent reflections	2633 (R_{int} = 0.0157)
structure solution method	direct methods (*SHELXS–97*[b])
refinement method	full-matrix least-squares on F^2 (*SHELXL–97*[b])
absorption correction method	Semi-empirical from equivalents
range of transmission factors	0.9405–0.8922
data/restraints/parameters	2633 / 0 / 162
goodness-of-fit (S)[e] [all data]	1.036
final R indices[f]	
$R_1[F_o^2 \geq 2\sigma(F_o^2)]$	0.0293
wR_2 [all data]	0.0802
largest difference peak and hole	0.388 and –0.360 e Å^{-3}

[a]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker [b]Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

Table A–3. Crystallographic Experimental Details for **C1**.

A. Crystal Data	
formula	$C_{32}H_{35}Cl_2N_4PPd$
formula weight	683.91
crystal dimensions (mm)	0.58 × 0.13 × 0.10
crystal system	orthorhombic
space group	$Pna2_1$ (No. 33)
unit cell parameters[a]	
a (Å)	18.6413 (7)
b (Å)	14.2255 (5)
c (Å)	11.4958 (4)
V (Å^3)	3048.48 (19)
Z	4
ρ_{calcd} (g cm^{-3})	1.490
μ (mm^{-1})	0.865
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/APEX II CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–100
scan type	ω scans (0.3°) (15 s exposures)
data collection 2θ limit (deg)	55.20
total data collected	26491 ($-24 \le h \le 24$, $-18 \le k \le 18$, $-14 \le l \le 14$)
independent reflections	7051 (R_{int} = 0.0249)
number of observed reflections (*NO*)	6684 [$F_o^2 \ge 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–97*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–97*[c])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9200–0.6338
data/restraints/parameters	7051 / 0 / 362
Flack absolute structure parameter[d]	–0.021(18)
goodness-of-fit (*S*)[e] [all data]	1.034
final *R* indices[f]	
$R_1[F_o^2 \ge 2\sigma(F_o^2)]$	0.0233
wR_2 [all data]	0.0595
largest difference peak and hole	0.600 and –0.426 e Å^{-3}

[a]Obtained from least-squares refinement of 9930 reflections with $4.36° < 2\theta < 48.82°$. [b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker [c]Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122. [d]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr.* **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G.

J. Appl. Cryst. **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration. [e]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0307P)^2 + 1.1964P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3)$. [f]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.