The Pursuit of Effective Catalysis for C-C and C-N Cross-Coupling under Mild Conditions

by

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ABSTRACT

Homogeneous transition metal-catalysis has had a great impact on the synthesis of organic molecules in recent years. The selective mono-arylation of small molecules, a class of reactions predominantly achieved via transition metal-catalyzed cross-coupling reactions, is an important transformation for converting commercially available, abundant materials into value added products. Major advancements have been made with palladium-catalysis in mono-arylation reactions with such abundant stock materials as acetone and ammonia as well as other related compounds. Notwithstanding the utility of palladium in these challenging transformations, it has become desirable to move towards more cost efficient and abundant metals for catalysis. Nickel is significantly less expensive than palladium and shows the potential to provide similar or superior reactivity.

The palladium-catalyzed mono-α-arylation of acetone has been conducted at room temperature for the first time. Acetone is the smallest and simplest ketone which makes it a challenging substrate for selective mono-arylation methodologies. Palladium/JosiPhos mixtures have allowed the scope of reactivity to expand to include many (hetero)aryl halides.

Ammonia is produced on a large scale and is an ideal building block for organic synthesis. Selective mono-arylation of ammonia has been accomplished through use of palladium-catalysis. Moving to nickel catalysis has allowed for the development of the new DalPhos ligand, PAd-DalPhos, which is capable of facilitating nickel-catalyzed mono-arylation of ammonia and challenging primary amine coupling-partners under mild conditions with a large substrate scope. The nickel/PAd-DalPhos catalyst system has also made possible the first mono-arylation of ammonia employing arylmesylate coupling partners. Mono-arylation of primary amines can be achieved at room temperature using many (hetero)aryl (pseudo)halides and including chemoselective reactivity. Mono-arylation of primary amides and lactams employing nickel-catalysis was made possible for the first time.

Nickel is capable of reactivity beyond what has been demonstrated with palladium in transition metal-catalyzed cross-coupling. Nickel has shown the ability to utilize unique electrophiles in amination reactions such as carbamates, sulfamates, and pivalates which are largely inaccessible to palladium catalysis. These electrophiles were used for the first time in amination reactions with ammonia and primary alkyl amines.

LIST OF ABBREVIATIONS AND SYMBOLS USED

α alpha position – first carbon adjacent to heteroatom or specified functional group

β beta position – second carbon adjacent to heteroatom or specified functional group

δ chemical shift

κ hapticity - kappa (non-contiguous donor atoms)

1-Ad 1-adamantyl

Ar aryl

BHA Buchwald-Hartwig amination

BINAP 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene

cat. catalytic or catalyst

CgPH cage phosphine (1,3,5,7-tetramethyl-2,4,8-trioxaphosphaadamantane)

CPME cyclopentyl methyl ether

d doublet

dba dibenzylideneacetone

DG   directing group

DCM dichloromethane

DPPF   1,1′-ferrocenediyl-bis(diphenylphosphine)

ESI electrospray ionization

GC gas chromatography

GP general procedure

h hour(s)

(Het)   hetero atom containing aryl ring

HRMS high-resolution mass spectrometry

i.d. internal diameter

$J_{XX'}$ coupling constant between atom X and atom X'

L neutral 2-electron donor ligand

M mega or mol/L or molecular ion

m multiplet

NHC N-heterocyclic carbene

NMR nuclear magnetic resonance

PTFE poly(tetrafluoroethylene)

py   pyridine

q quartet

rt room temperature

s singlet

SGE scientific glass engineering

t triplet

TLC thin layer chromatography

Trt trityl protecting group (triphenylmethyl)

X halide substituent or anionic ligand

ACKNOWLEDGMENTS

CHAPTER 1 Introduction

1.1 General Introduction: Concept of Catalysis

Synthetic chemistry is based upon the ability to create chemical bonds in the most efficient possible manner. Bonds in starting materials are broken and new bonds are formed in the course of a given reaction, requiring energy in the process. One approach taken in trying to promote a challenging chemical reaction involves providing a surplus of energy via high pressures, and/or temperatures, or by using very reactive reagents, but these brute force methods are often not selective. Lower energy and more selective paths to these same products can be found through the use of catalysts. A catalyst is a substance which enhances the rate of a reaction without being consumed by the reaction.[1] Nature has a way of conducting such reactions through the use of biological catalysts called enzymes. Many of the reactions that take place in the human body would not be feasible if it were not for enzymes. For example, a glucose molecule outside of the body under ambient conditions will not be oxidized readily. However, inside human cells glucose can be oxidized efficiently by enzymes and the energy released can be used by the body (Figure 1-1).[2]

$$C_6H_{12}O_6 + 6O_2 \xrightarrow{\text{Enzymatic processes}} 6CO_2 + 6H_2O \quad \triangle G° = 2870 \text{ kJ/mol}$$
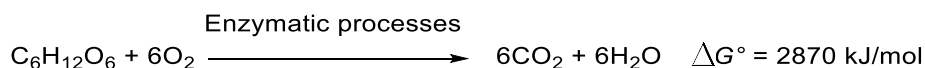
Figure 1-1: Glucose is oxidized in human cells by enzymes.

Most enzymes have a complex chemical structure, but upon stripping the enzyme down to the active site only, a unit remains.[3] While enzymes are extremely efficient catalysts,

they have evolved to act on very specific substrates and often cannot catalyze the same transformations on a wide variety of molecules.[2] From years of study of nature's example, tunable, robust synthetic catalysts have been identified that can bring about a plethora of chemical reactions. There are many types of chemical catalysts including, but not restricted to: simple acids and bases to main group organic molecules; and transition metal complexes. The last of these will be the focus of this thesis.

The two major conceptual categories of catalysis are heterogeneous and homogeneous catalysis. Heterogeneous catalysts act on reactants that are in a different phase, usually a solid catalyst in a liquid or gaseous medium. Heterogeneous catalysts are used widely in industry due to their high thermal stability and ease of purification of products. The Haber-Bosch process, for example, employs an iron-based heterogeneous catalyst to combine hydrogen and nitrogen gas in the production of ammonia. The catalyst is sturdy enough to survive the intense reaction conditions (150-250 bar, 300-550 °C)[4] and easy to separate from the gaseous reactants and products.

Homogeneous catalysts on the other hand are those that work in the same phase as the reactants. Unlike heterogeneous catalysts such as those used in the Haber-Bosch process (layers of iron oxides on alumina support),[4] which do not have a precise active site, homogeneous catalysts have a well-defined active site where they interact with the reactants. This allows chemists to systematically and logically design molecular catalysts that are easier to characterize and modify than their heterogeneous counterparts; due to being in the same phase as the reactants, such catalysts are also often capable of operating under more mild conditions. Appreciation of catalyst reactive sites and mild, homogeneous reaction conditions make it easier to direct studies to help propose mechanisms of reaction,

which in turn aid in the development of better catalysts.[5] Among the many types of homogeneous catalysts, transition metal complexes are catalysts that are of a particularly modular nature, making them simple to design and modify for use in varied synthetic applications. Moreover, the redox capabilities of the late transition metals in particular provide unique opportunities to promote challenging substrate transformations involving the breaking of otherwise robust reactant bonds. Homogeneous transition metal catalysis is the focus of the research detailed herein.

1.2 Development of Homogeneous Transition Metal Catalysts

As mentioned above, enzymes and non-transition metal chemical catalysts can be very useful for a wide variety of chemical transformations. However, when faced with difficult reactant bond activations such as unactivated C-H and C-X (where X is a halide or pseudohalide) bonds, transition metal catalysts typically offer optimal activity. The utility of transition metal catalysis has risen to prominence in recent years as illustrated by the Nobel Prizes in 2001, 2005, and 2010. In 2001 the Nobel Prize was awarded to Ryoji Noyori, William S. Knowles, and K. Barry Sharpless for their development of enantioselective catalysis.[6] In 2005 the prestigious award was given to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock for the development of the metathesis method in organic synthesis.[7] Briefly, Schrock and Grubbs catalysts are molybdenum and ruthenium metal complexes, respectively, that are capable of breaking and reconstructing C-C double bonds (Figure 1-2). This remarkable transformation and related variants such as ring opening/closing metathesis polymerization are exceptionally useful in the polymer

industry and serve to highlight the importance of C=C bond forming reactions in organic synthesis. It is worthy of mention here that the breakthrough achievements featured in these pioneering reports were in variably connected to innovations in the design of ancillary ligands to support catalytically active metal centers in terms of providing stability for the catalyst and aiding in achieving selectivity.
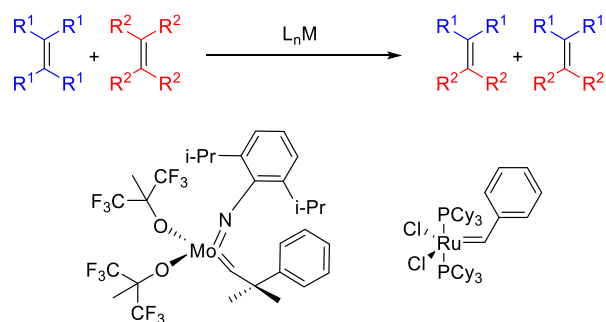
Figure 1-2: Generic, metathesis reaction scheme with a representative Schrock molybdenum catalyst and Grubbs generation-one ruthenium catalyst.

In 2010 the Nobel Prize was awarded to three chemists for developments in palladium-catalyzed C-C bond formation, Akira Suzuki, Richard F. Heck, and Ei-ichi Negishi. Given the relevance of palladium-catalyzed cross-coupling to this thesis research, a brief historical development of such reactions is provided below.

1.2.1 Palladium-Catalyzed Cross-coupling

In 1901 Ullmann and Bielecki demonstrated that transition metal-mediated C-C bond formation was possible by way of the homo-coupling of 1-bromo-2-nitrobenzene using excess copper (Figure 1-3a).[8]

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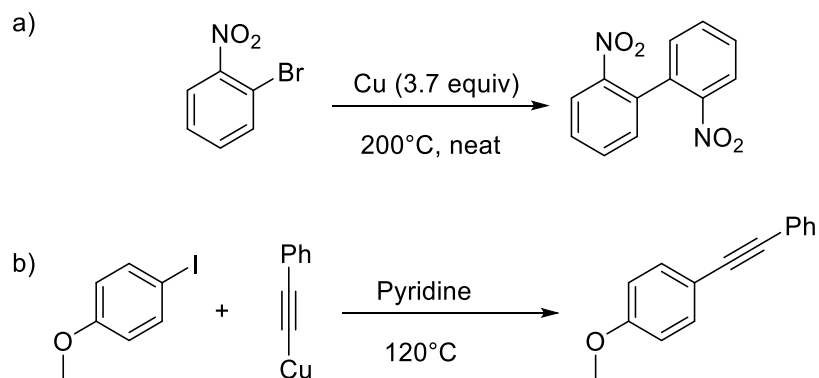
Figure 1-3: a) Ullmann homo-coupling. b) The Castro-Stephens reaction.

This reaction, even with such forcing conditions, no doubt stimulated researchers to further probe the possibility of using transition metals to form C-C bonds. With time, reactions capable of employing different coupling partners were developed, such as the Castro-Stephens reaction (Figure 1-3b).[9] Eventually transition metal-mediated reactions were brought into the catalytic realm and stoichiometric amounts of copper were beginning to be replaced by sub-stoichiometric amounts of palladium. The most prominent of these reactions were brought to light in the 1970s by the groups of Suzuki, Negishi, and Heck (Figure 1-4).[10] The Suzuki reaction joins organic groups together by forming a C-C bond, between sp^3 and sp^2 or sp hybridized carbons originating from an organoboron reagent and an electrophile typically involving a C-X bond, where X was typically bromine or iodine in the early development of the chemistry. Negishi reactions are very similar, but they employ zinc-based organometallic reagents. The generic mechanism for Suzuki and Negishi reactions are shown in the top cycle of Figure 1-4.
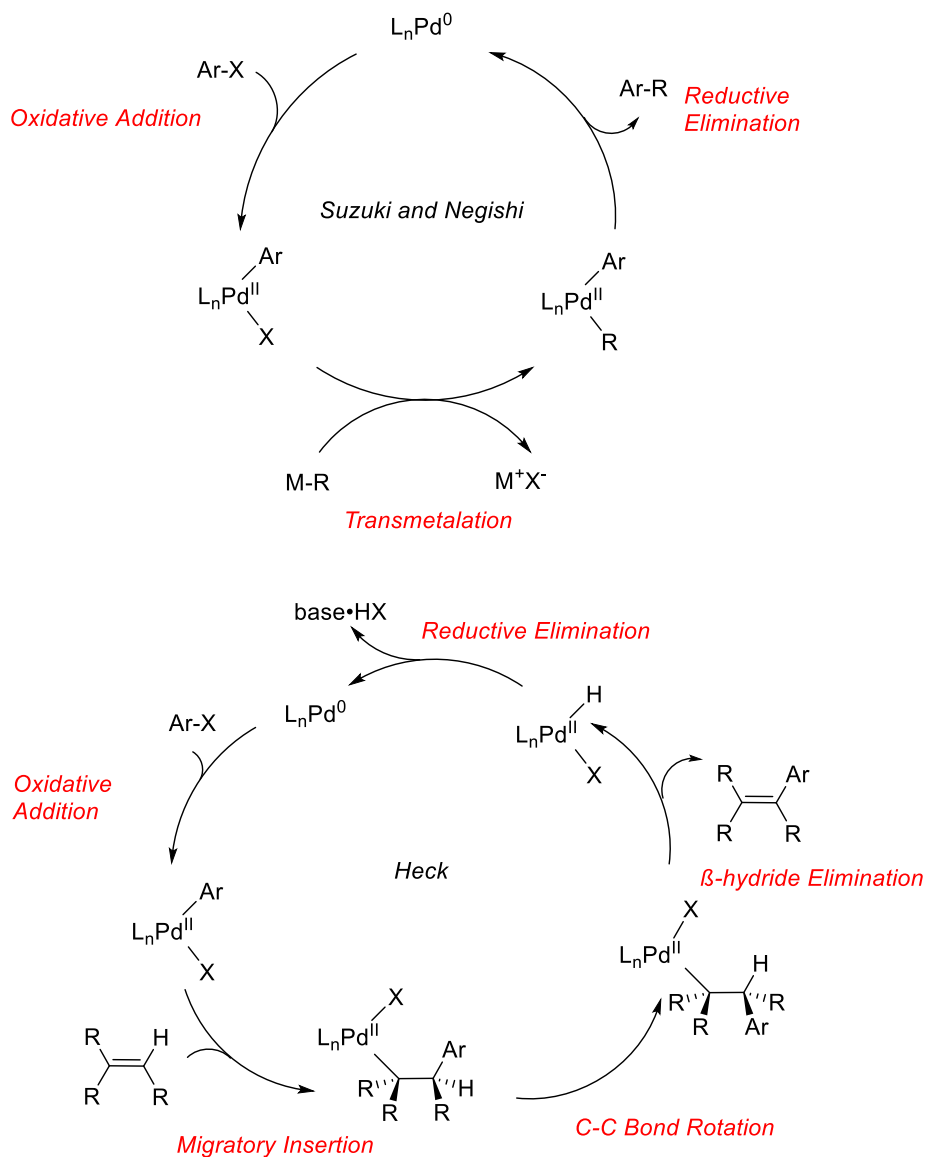
Figure 1-4: The general catalytic cycles of palladium-catalyzed Suzuki, Negishi and Heck reactions; the oxidation state of palladium is shown to emphasize the redox changes involved.

The first step beyond catalyst activation is the oxidative addition of the carbon-halide bond to ligated Pd(0) species. Transmetalation then occurs from a secondary metal, boron or zinc, to transfer the second organic group to palladium and release a metal halide salt. The final step of the mechanism is reductive elimination which forms the new C-C bond to make the product and regenerate the catalyst to continue the cycle. The Heck reaction is

used to combine two sp^2 hybridized carbons, which can be aryl or alkenyl groups as seen in the bottom cycle of Figure 1-4. The oxidative addition is the first step in this mechanism as well, but is followed by a migratory insertion of the alkenyl coupling partner rather than a transmetalation step. Upon bond rotation the hydrogen and palladium will be on the same side of the incipient double bond. The double bond of the alkene product is formed by β-hydride elimination leaving only the halogen and a hydride on palladium, which are reductively eliminated as an acid that is removed from the reaction by an added base. These reaction mechanisms are conceptually related to many other named palladium and nickel-catalyzed processes. Among the other C-C bond forming reactions that were being developed in the 1970s was the α-arylation reaction, first described by Semmelhack and co-workers.[11] The full utility of α-arylation would be realized in the late 1990s by the groups of Buchwald, Hartwig and Miura.[12]

1.3 Development of Efficient α-Arylation of Ketones

The potential applicability of metal-catalyzed α-arylation of ketones is demonstrated by the many organic compounds featuring the α-carbonyl moiety in current and potential pharmaceutical intermediates[13] such as estrogen receptor modulators,[14] benzazepines,[15] and analogs of rimonabant, an anti-obesity drug,[16] to name a few. A practical and efficient palladium-catalyzed synthesis of benzyl ketones was developed in 1997 independently by Buchwald, Hartwig and Miura.[12] These were the first examples of α-arylation of ketones that did not involve the use of a pre-formed enolate made with stoichiometric amounts of secondary metal. The choice of ancillary ligand is particularly important in α-arylation

chemistry in terms of obtaining generally active and selective catalysts, as seen in the reports of Buchwald[12a] and Hartwig[12b] who use BINAP variants (**L1-1**) and 1,1'-bis(di-o-tolylphosphino)ferrocene (**L1-2**) respectively (Figure 1-5 a and b). A common feature of these successful ancillary ligands is the presence of sterically demanding and chelating phosphorus-based donors.

a) R = Ph (**L1-1a**), o-tolyl (**L1-1b**) b) **L1-2** c) R = 1-Ad (**L1-3a**), o-tolyl (**L1-3b**)
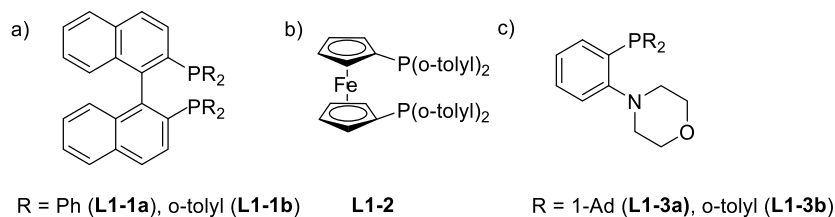
Figure 1-5: Ligands used in α-arylation chemistry. a) BINAP variants, b) Ferrocenyl variant, DPPF c) DalPhos variants.

As mentioned in Section 1.2, ancillary ligands help to stabilize the catalyst, promote key elementary reaction steps, and aid in achieving selectivity. The mechanism of α-arylation chemistry, shown in Figure 1-6, begins with the typical oxidative addition. The phosphine donors add electron density to the metal center making it easier to reduce the carbon-halide bond via oxidative addition. After oxidative addition occurs, the ketone coordinates to the metal and can be deprotonated by the base. Bulky ancillary ligands help at this stage to prevent β-hydride elimination of the enolate where possible. Once both organic fragments are attached to the metal, the large volume of the ligands eases the process of reductive elimination because it will result in the release of steric strain. There can exist an equilibrium between the Pd-O and Pd-C species before reductive elimination occurs which can be the rate limiting step.[13] Bis(phosphine) ligands enforce the cis orientation of the substrate ligands and favour the Pd-C species which both aid reductive elimination.[18]
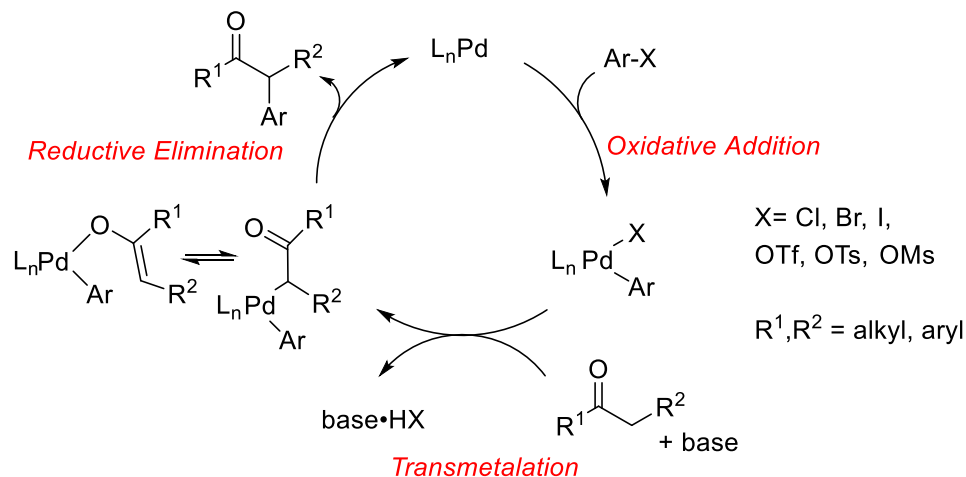
Figure 1-6: The general catalytic cycle of the palladium-catalyzed α-arylation of ketones.

Advancements in α-arylation chemistry have been made by the Stradiotto group. With the development of the DalPhos ligands, one of the most difficult ketone substrates for mono-α-arylation, acetone, was employed for the first time.[17] Difficulty arises in mono-α-arylation of ketones in part due to the fact that the sought-after product benzyl ketones contain acidic α-hydrogens, thus making the product a better substrate than the starting ketone and therefore more able to undergo further α-arylation leading to unwanted polyarylation. This challenge is even greater with acetone compared to other ketones since there is no other group on the ketone to increase the steric hindrance of the product as an indirect means of discouraging polyarylation, and to encourage reductive elimination of the $L_nPd(aryl)(CH_2C(O)Me)$ intermediate. Addressing this challenge requires ligands with extreme bulk such as Mor-DalPhos (**L1-3a**, Figure 1-5), which has two 1-adamantyl groups attached to the phosphorus. As mentioned above, the product of a mono-α-arylation reaction with acetone is a methyl benzyl ketone, which is capable of being arylated further. However, because acetone is a cheap, volatile solvent it can be used in great excess to

statistically favour reaction with acetone over the benzyl product ketone as a means of further promoting selectivity for mono-α-arylation. This leading report by the Stradiotto group,[17] in the mono-α-arylation of acetone, also shows a good example of the balance between steric bulk and electron richness in ligand design. The Mor-DalPhos ligand with adamantyl groups was unable to result in satisfactory yields with certain electron-poor aromatic coupling partners. It was suspected that the reductive elimination step was hindered because the acetone enolate intermediate complex was too electron-rich.[18] Upon replacement of the P(1-Ad)$_2$ group with a P(o-tolyl)$_2$ group (**L1-3b**, Figure 1-5), which is still fairly bulky, but less basic, the catalytic products were formed in excellent yields. Indeed, this example suggests that reductive elimination is the rate limiting step of the mechanism rather than oxidative addition for such substrates. Electron rich ligands such as alkyl phosphines aid oxidative addition by donating electron density to the metal making it more inclined to become oxidized. However, the same ligand property discourages reductive elimination, thus inhibiting turnover to form the product and regenerate the catalyst. By changing the adamantyl (alkyl) groups on Mor-DalPhos to tolyl (aryl) groups, reductive elimination can be promoted while not unduly inhibiting oxidative addition for such "activated" electron-poor coupling partners. This illustrates the delicate balance between favouring oxidative addition and reductive elimination when designing ligands for this chemistry. The above example also highlights the importance of being able to easily modify a ligand to suit particularly difficult substrates, if needed. Further advancements have been made by Stradiotto and co-workers to incorporate the use of aryl mesylates as the electrophilic coupling partner in mono-α-arylation of acetone,[19] and most recently

arising from this thesis research, the development of the room temperature mono-α-arylation of acetone.

1.3.1 Mono-α-Arylation of Acetone at Room Temperature

Prior to this thesis research, performing mono-α-arylation of acetone at room temperature was an unknown and highly sought-after reaction. After investigation of different catalyst systems, a JosiPhos-based catalyst system (Figure 1-7) that proved capable of enabling transformations of (hetero)aryl halides in the mono-α-arylation of acetone at room temperature, was identified. The development of this room temperature chemistry is the subject of Chapter 2 of this document.
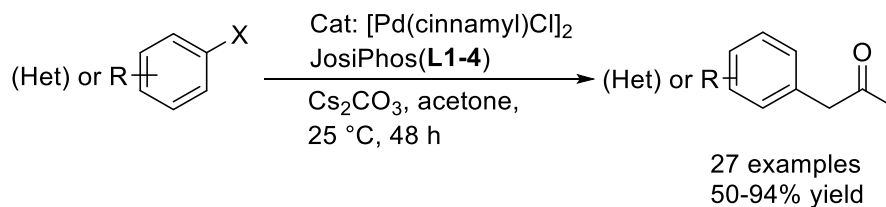
Figure 1-7: Room temperature mono-α-arylation of acetone.

While C-C bond formation is important in the field of synthetic chemistry, these are of course not the only important bonds. Palladium is also capable of catalyzing many types of C-N, C-O, C-P, C-S, and C-F bond-forming reactions. There have been great advances in C-N bond forming reactions in particular in recent years, with the development of the Buchwald-Hartwig amination (BHA) reaction.

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1.4 Buchwald-Hartwig Amination (BHA)

Buchwald-Hartwig amination, (BHA) developed contemporaneously by the groups of Buchwald and Hartwig, is the palladium-catalyzed cross-coupling of N-H substrates and (hetero)aryl (pseudo)halides to afford amine derivatives. Previous to the development of BHA the synthesis of aryl amines was primarily limited to organic methodology such as the nitration of arenes by electrophilic aromatic substitution followed by reduction to an aniline, nucleophilic aromatic substitution through a benzyne intermediate, or copper mediated Ullmann type procedures.[20] Early precursors to BHA required use of tin amines, which resulted in stoichiometric amounts of toxic tin waste.[21] Buchwald also pursued a pathway to aryl amines using an established aminoborane route,[22] inspired by the Suzuki C-C bond forming reaction. However it was during the development of this process that Buchwald and Hartwig independently established the arylation of amines using unactivated secondary amines and aryl halides, which today is referred to as BHA.[22-23] The initial catalytic systems were limited in scope, allowing for the conversion of only secondary amines with a few variations. With time, the research groups of Buchwald, Hartwig, and others would go on to develop the reaction to encompass a wide range of aryl and amine coupling partners.[24]

The mechanism of BHA resembles the other palladium-catalyzed reactions discussed in this chapter (Figure 1-8). Oxidative addition of a palladium(0) species to a carbon-(pseudo)halide bond begins the cycle. This is followed by coordination of an amine and subsequent deprotonation of the coordinated amine by a base. The formed palladium amido intermediate may be three- or four-coordinate depending on the binding nature of the

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ligand. Production of the amine through reductive elimination regenerates the palladium(0) catalyst to repeat the cycle.[23] Many factors influence the reaction such as ligand, palladium source, base, solvent, and temperature, which will be discussed below briefly.
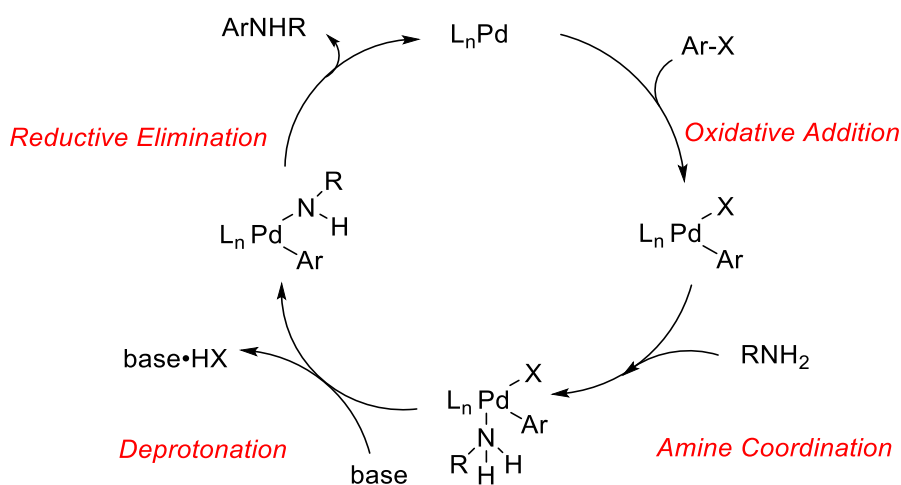
Figure 1-8: The general catalytic cycle of Buchwald-Hartwig amination.

The original reports on BHA by Buchwald and Hartwig each involved the use of tri(*o*-tolyl)phosphine as the ligand, but there have since been many more sophisticated ligands developed, leading to greatly expanded reaction scope. Hartwig typically uses bisphosphine ligands such as the ferrocene-based JosiPhos ligand family developed by Solvias (Figure 1-9a). Buchwald developed an array of dialkyl biarylphosphine ligands that can be modified in an effort to address particular reactivity challenges (Figure 1-9b). Other ligands and catalysts have been developed for use in challenging BHA chemistry such as Mor-DalPhos, BippyPhos, PEPPSI, and cataCXium® A, by the groups of Stradiotto,[24g] Singer,[25] Organ,[26] and Beller,[27] respectively (Figure 1-9). As with ketone α-arylation (Section 1.3), the electron donating ability and steric bulk of the ancillary ligand are important factors to aid the processes of oxidative addition and reductive elimination. While electron-rich phosphines ease the process of oxidative addition, they can hinder

C(sp^2)-N reductive elimination by stabilizing the palladium amido complex intermediate. Employing bulky ligands can compensate for this effect by causing release of steric strain upon reductive elimination. Bulky ligands also help protect the phosphine from oxidation, discourage diarylation, prevent cyclometalation and encourage the formation of what are thought to be catalytically active mono-ligated palladium species.[28] Given the inherently more sterically demanding nature of bidentate ligands verses monodentate ligands, the former became a popular choice in ligand development as shown in Figure 1-9. Indeed, there are data to suggest that seemingly monodentate ligands such as **L1-5** and **L1-6** can coordinate in a bidentate manner via the ipso carbon of the second lower aryl ring.[29]
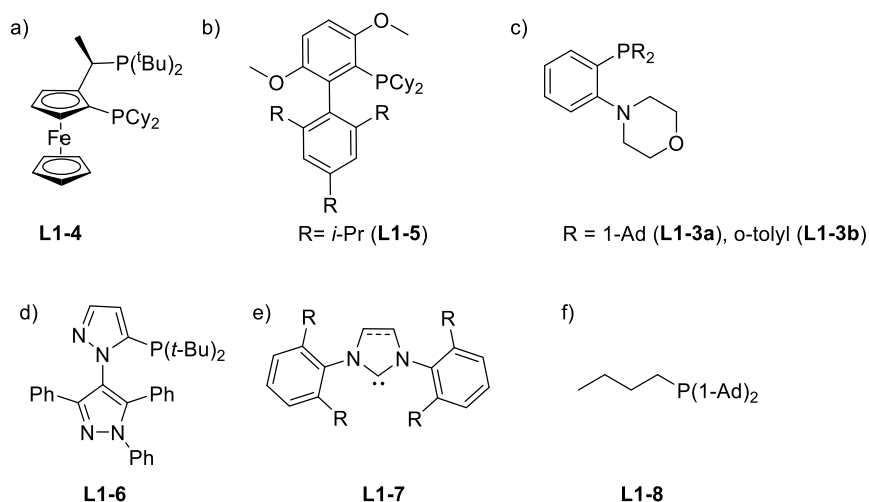
Figure 1-9: Some important ligand classes in Buchwald-Hartwig amination. a) JosiPhos CyPF-*t*Bu, b) BrettPhos, c) Mor-DalPhos variants, d) BippyPhos, e) Generic NHC ligand, f) CataCXium® A.

Another important factor for successful BHA chemistry is the choice of palladium source/pre-catalyst. Palladium must connect to the ancillary ligand and be in a zero oxidation state before the catalytic cycle can begin. Ligand and metal are typically added in a 1:1 ratio, but the presence of extra ligand has been shown to help stabilize the catalyst

especially for long reactions, presumably by rescuing palladium from off-cycle decomposition processes.[30] Palladium acetate is an attractive choice of source material because it is relatively cheap and readily available; however, the main drawback being that it is a source of palladium(2+), which requires reduction to palladium(0) by either an added reducing agent or some of the ancillary phosphine ligand. An alternative approach is to add a palladium(0) source directly such as bis(dibenzylideneacetone)palladium(0) (Pd(dba$_2$)) or a palladium complex in which the ligand is already attached (i.e. a pre-catalyst).

Solvent is most important with respect to solubility of the reagents, as all reaction components must be in the same phase for homogeneous catalysis to occur. The use of non-polar solvents is advantageous to help precipitate the by-product halide salt, while polar solvents can sometimes provide shorter reaction times.[31] The concentration of the catalyst and/or the substrates in the solvent can have a strong impact on reaction yields due to differing reaction rates, and varying solubility.[32] Indeed, in the context of BHA reactions, in particular, the concentration can help favour or discourage di-arylation of primary amines.

Using stronger or weaker base can also affect the success of amination reactions. The use of stronger bases typically gives shorter reaction times, but such bases may participate in side reactions, have lower functional group tolerance and lead to lower selectivity. The weaker bases essentially have the opposite advantages and disadvantages being longer reaction times, but higher functional group tolerance to groups such as ketones, nitro groups and esters.[32b] They can also enable the use of aryl sulfonates as electrophilic substrates.[19, 33]

Finally, temperature is a factor that influences not only the rate of a reaction, but also catalyst stability. While it is generally desirable to change the above parameters to allow aminations to occur at room temperature, elevated temperature may be required for certain substrates to react. Similarly, some substrates may give better yields with reduced rates and increased selectivity, at room temperature,[34] particularly when you want obtain mono-arylated products selectively in BHA of ammonia and primary amines.[24g, 24i, 35]

1.4.1 Buchwald-Hartwig Amination of Ammonia

As with the mono-α-arylation of acetone, the use of ammonia, the smallest and simplest N-H substrate, can present exceptional challenges in BHA. Ammonia is a highly desired coupling partner due to its abundance and the utility of the product anilines in pharmaceutical, agrochemical and conjugated organic[36] materials. Ammonia presents similar problems to acetone in that it is a small molecule offering no steric hindrance to aid the process of reductive elimination; the practical need to use excess ammonia can also lead to catalyst inhibition via ancillary ligand displacement. Product selectivity can become an issue since the resulting aniline is an excellent substrate for BHA, leading to di-arylation and even tri-arylation products. The solution to these problems came from the identification of ancillary ligands that could resist displacement, encourage reductive elimination and favour reacting with ammonia over the product aniline. The successful use of the Solvias JosiPhos (CyPF-*t*Bu, **L1-4**) ligand was reported by Shen and Hartwig in 2006, and represented the first ligand capable of BHA employing excess ammonia as the amine coupling partner.[37] Since this initial work, improvements have been made by

Hartwig, Stradiotto, Buchwald and others.[24a, 24b, 24d, 24e, 24i] Stradiotto and co-workers showed the first example of ammonia mono-arylation at room temperature employing DalPhos ligands.[24g]

1.4.2 Moving from Palladium to Nickel Catalysis in Amine Arylation and Beyond

There has been a recent trend in the field of organometallic chemistry of moving toward first row transition metals, due to the depleting natural abundance of the platinum group metals. Nickel is over 1000 times cheaper than palladium and is also a privileged metal in many cross-coupling reactions.[38] Ironically, nickel was once considered more versatile than palladium in the early days of cross-coupling chemistry, prior to the discoveries of Suzuki, Negishi, and Heck.[39] For the reasons above, recent advances in amine arylation employing (hetero)aryl chlorides involve the use of nickel in place of palladium;[33, 40] notwithstanding the utility of copper-catalyzed C-N cross-coupling, aryl chlorides are typically not compatible substrates. Amination methods employing nickel catalysis have been reported already[40a, 41] and will no doubt continue to flourish in the coming years. Stradiotto and co-workers have presented the first nickel catalyst capable of mono-arylation of ammonia utilizing a JosiPhos ligand, CyPF-Cy (**L1-9**).[42] Hartwig and co-workers independently reported a similar catalyst system employing another JosiPhos ligand variant for the amination of aryl chlorides with ammonia and ammonium salts.[40b] While these catalyst systems employ nickel as a cheap transition metal, the JosiPhos ligands used are quite expensive and not consistent with the idea of a more affordable amination method. The Stradiotto group envisioned a simple bisphosphine ligand for

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nickel-catalyzed amine mono-arylation in general. An ideal ligand would be well suited to the reaction profile of nickel: inexpensive, have trivial preparation, and a modular synthesis that could be easily modified to suit different amination reactions as needed. In this pursuit, a new member of the DalPhos ligand family was developed called PAd-DalPhos (**L1-10**). The PAd name is derived from the 1,3,5,7-tetramethyl-2,4,8-trioxaphosphaadamantane group as will be shown herein this thesis. PAd-DalPhos generally fits the criteria listed above. Furthermore, an air-stable pre-catalyst with PAd-DalPhos was sought to enable the end user to perform transformations without the need of a glovebox. Additional benefits of a nickel pre-catalyst include reduced reaction times and expanded substrate scope, as noted in Buchwald's report of an air-stable nickel pre-catalyst.[33] A pre-catalyst was thus developed using PAd-DalPhos to generate (PAd-DalPhos)Ni(o-tolyl)Cl (**C1-1**), which is air-stable and provided superior reactivity compared to analogues mixtures of ligand and Ni(COD)$_2$[43] (Figure 1-10).
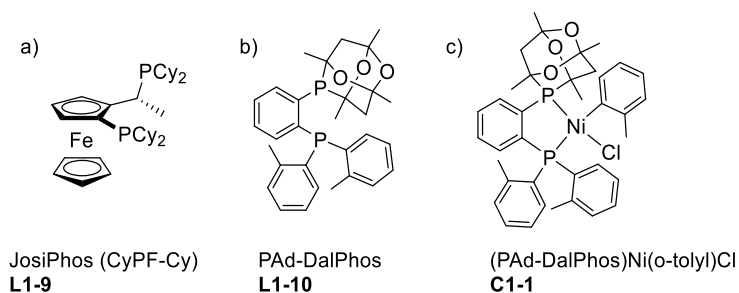
Figure 1-10: a) JosiPhos (CyPF-Cy) b) PAd-DalPhos c) (PAd-DalPhos)Ni(o-tolyl)Cl.

While ammonia is an important reaction partner, primary and secondary amines are still of interest to the synthetic community. Useful nickel-catalyzed amination of primary amines has been reported by Hartwig and co-workers.[40a] However, there exists significant room for improvement in terms of reaction conditions and substrate scope. Developing the PAd-

DalPhos ligand (**L1-10**) and exploring its scope of reactivity was a large undertaking involving the entire Stradiotto research group. The development of the scope of reactivity using primary and secondary amines was the thesis author's contribution to this work. Using the air-stable **C1-1** catalyst system primary amine arylation employing aryl chloride, bromide, tosylate and mesylate (hetero)aryl electrophiles and linear, branched and aryl amines with chemoselective examples was achieved. The vast majority of the scope was accomplished at room temperature and required no more than 0.1 excess of the amine coupling partner (Fig1-11). While exploration of ammonia reactivity was conducted primarily by other group members, the author was able to extend the **C1-1** system to include the first mono-arylation of ammonia using aryl mesylate electrophiles.
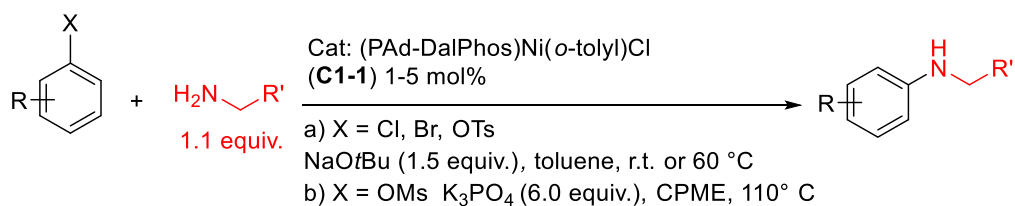
Figure 1-11: Mono-arylation of primary amines under unprecedented mild conditions.

Chapter 3 of this document will describe the use of the **C1-1** pre-catalyst system to explore reactions with ammonia and primary amines, as outlined above. Building on this work, there is considerable interest in the exploration of other nucleophiles and electrophiles outside of these, such as amide nucleophiles and other classes of pseudohalides.

1.4.3 Exploring Amides as *N*-Nucleophiles and Phenol-Derived Electrophiles

Given the success of **C1-1** in amination chemistry it was logical to further explore the capabilities of the PAd-DalPhos catalyst system in C(sp^2)-N cross coupling. Nickel catalysis has employed amides in many methodologies in recent years including transamidations[44] and cleavage of the amide C(sp^2)-N bond to produce esters,[45] diaryl ketones[46] and biphenyl products.[47] Amides have been used as nucleophiles in C(sp^2)-N cross-coupling with palladium catalysts,[48] but *N*-arylation of amides with nickel remained an outstanding challenge. In collaboration with another graduate student in the group, Chris Lavoie, the **C1-1** catalyst system was extended to include primary amides and lactams as the nitrogen coupling partners in nickel-catalyzed C(sp^2)-N cross-coupling (Figure 1-12). The author's contribution to the work focused primarily on the use of pseudohalide electrophiles in this project. This work is presented in Chapter 4.
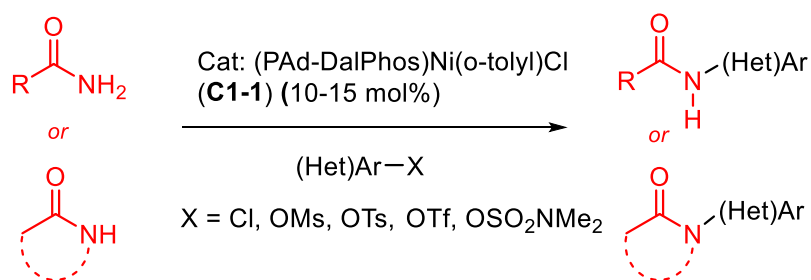
Figure 1-12: Arylation of primary amides and lactams using **C1-1** with (pseudo)halide electrophiles.

The most common electrophiles in cross-coupling are halogens and sulfonates (triflates, tosylates and mesylates). However, there are other classes of pseudohalides less commonly used. Carbamates and sulfamates are used as directing groups in ortho metalation[49]

reactions and other transformations[50] and of course it would be synthetically useful to utilize these functional groups additionally as electrophiles. Carbamates and sulfamates can be used as electrophiles in cross-coupling with secondary amines as demonstrated by Garg.[51] Chatani and co-workers have shown that, under similar conditions, related pivalates can be used as electrophiles with secondary amines.[41p] There was, however, no catalyst system which employed ammonia or primary amines with these electrophiles in this context. One facet of this thesis research involved exploring the use of carbamates, sulfamates, and pivalates in nickel-catalyzed amination of ammonia and primary amines. This work is presented in Chapter 5 utilizing JosiPhos ligands. (Figure 1-13)
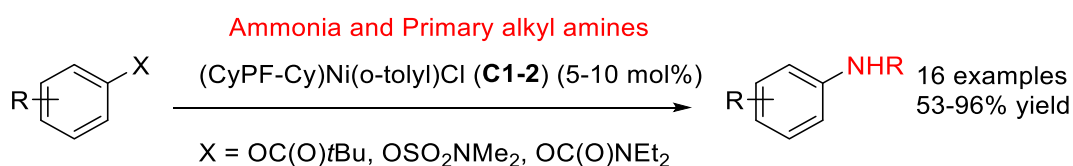
Figure 1-13: Amination of aryl pivalates, sulfamates, and carbamates with ammonia and primary amines.

CHAPTER 2 Palladium-Catalyzed Mono-α-Arylation of Acetone at Room Temperature

2.1 Contributions

This chapter describes the development of the first room temperature mono-α-arylation of acetone. This project was conducted in collaboration with Alicia J. Chisholm and Breanna K. V. Hargreaves who assisted in the late-stage optimization and isolation of some cross-coupling products. The author's contributions consist of the initial discovery of room temperature catalysis, optimization of the catalyst and reaction conditions, isolation of the product substrate scope, and characterization of all reported compounds. This work has been published (*Chem. Eur. J.* **2015**, *21*, 11006 – 11009).

2.2 Introduction

As discussed in the introductory chapter (Section 1.3), the α-arylation of ketones was developed just after the disclosure of alternative C-C bond forming reactions by Suzuki, Negishi, and Heck.[39] Following the establishment of protocols that did not require the use of enolates, reported independently by Buchwald, Hartwig, and Miura,[12] many other breakthroughs soon followed. Advancements in the mono-α-arylation of ketones include the first use of acetone by Stradiotto and co-workers,[17] as well as the incorporation of sulfonate electrophiles as coupling partners with acetone by Stradiotto[17, 19] and Ackermann.[52] Interestingly, Hartwig observed the presence of phenyl-propan-2-one in

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BHA reactions when acetone was used as a solvent, but no yield was reported.[53] This perhaps motivated attempts to employ acetone as a ketone in mono-α-arylation reactions. The successful use of the Mor-DalPhos ligand (**L1-3a**) in this chemistry,[17] inspired the use of other κ²-P,N ligands in catalytic systems for the mono-α-arylation of acetone.[54] Although pre-formed acetone enolates have been arylated in reports prior to the work of Stradiotto and co-workers mentioned above,[17] these approaches each depend on the use of toxic tin reagents, silyl enol ethers, microwave-assistance and/or other additives[55] resulting in low substrate scope and poor functional group tolerance given the harsh reaction conditions employed. While the mono-α-arylation of ketones is synthetically useful, the products of the mono-α-arylation of acetone, phenyl-2-propanone and its derivatives, in particular hold promise in the synthesis of biologically active molecules. For example, these benzyl ketones can be used in the synthesis of tetrahydro-4(1*H*)-pyridinones (Figure 2-1), which have shown antimicrobial activity against tuberculosis.[56] Other pyridinone derivatives display anticancer,[57] anticonvulsant,[58] and anti-inflammatory[59] properties.
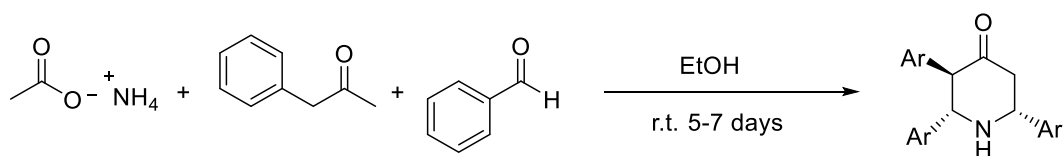
Figure 2-1: 1-Phenyl-propan-2-one in the synthesis of tetrahydro-4(1*H*)-pyridinones.

An important challenge regarding the mono-α-arylation of acetone is the need to identify catalysts that enable such transformations to be conducted at room temperature. Room temperature reactions are operationally simple, lower the environmental impact of the reaction, and can allow for greater variation in substrate scope compared to the heated

counterpart. While the use of acetone as both the ketone reactant and solvent is attractive in the synthesis of 1-(hetero)aryl-propan-2-one derivatives, each of the catalyst systems reported for acetone mono-α-arylation prior to the work presented herein, employ reaction temperatures (≥ 80 ºC, in some cases using a co-solvent) that exceed the boiling point of acetone (56 ºC). As such, the identification of alternative catalysts that are capable of promoting such transformations at room temperature would represent an important advance. Indeed, it is worthy of mention that while progress has been made with regard to the development of myriad palladium-catalyzed room temperature transformations using relatively inexpensive and abundant (hetero)aryl chloride reaction partners,[24g, 24i, 60] related examples of room temperature ketone mono-α-arylation chemistry are limited to four table entries involving (NHC)Pd-catalyzed transformations of propriophenone (41-75%).[61] The inherent challenge of achieving the mono-α-arylation of acetone at room temperature include room temperature oxidative addition of the aryl electrophile, as well as C-C reductive elimination involving a rather sterically unencumbered $L_nPd(aryl)(enolate)$ intermediate. As alluded to above, ancillary ligand choice is key to promoting such elementary steps. Described below is research related toward the development of the first room temperature mono-α-arylation reaction employing acetone.

2.3 Results and Discussion

Initial efforts to identify a catalyst system for the palladium-catalyzed mono-α-arylation of acetone at room temperature focused on the use of [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos

under conditions similar to those that were employed with success at 90 °C,[17] with the exception of using higher catalyst loading and a longer reaction time (Figure 2-2).
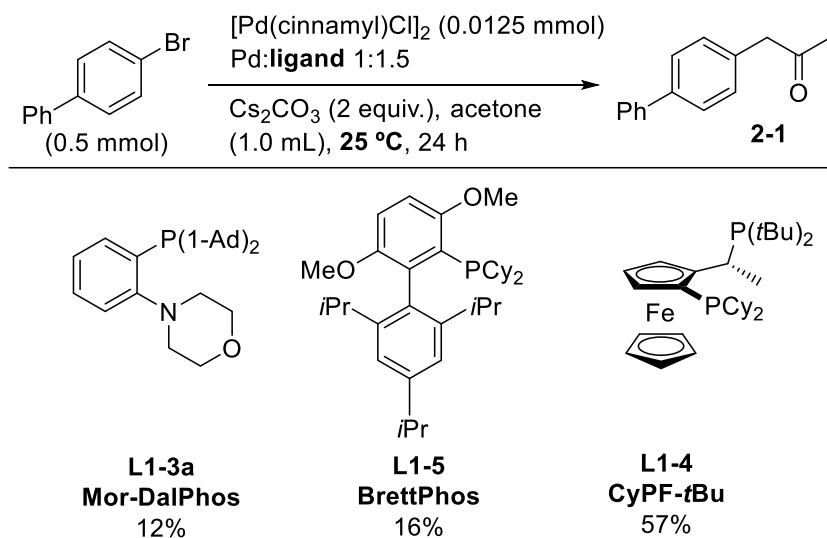
Figure 2-2: Ligand screen for the palladium-catalyzed mono-α-arylation of acetone at room temperature (yields of isolated **2-1** reported).

Poor results were obtained in the test reaction with 4-biphenyl bromide, affording **2-1** in 12% isolated yield. Similarly poor results were obtained when using BrettPhos (**L1-5**, 16%), a ligand developed by the Buchwald group that has proven to be effective in other classes of challenging mono-arylation reactions conducted at room temperature.[62] Reports from the Hartwig group have established the utility of the Solvias CyPF-*t*Bu JosiPhos (**L1-4**) ligand variant in otherwise difficult palladium-catalyzed ammonia mono-arylation reactions conducted at elevated temperatures,[24a, 37] as well as in room temperature C–S cross-couplings.[60f] Given the similar conceptual challenges presented by acetone mono-α-arylation chemistry, [Pd(cinnamyl)Cl]₂/CyPF-*t*Bu mixtures were evaluated in room temperature α-arylation reactions with acetone. The use of this catalyst system enabled the formation of **2-1** in 57% isolated yield under the conditions outlined in Figure 2-2.

Extending the reaction time from 24 to 48 h while employing 7.5 mol% Pd allowed for the isolation of **2-1** in 87% yield from 4-biphenyl bromide. Having identified the [Pd(cinnamyl)Cl] $_2$/CyPF-tBu catalyst system as being effective for the room temperature mono-α-arylation of acetone with 4-biphenyl bromide (7.5 mol% Pd), the scope of reactivity with substituted aryl chlorides, bromides, and iodides (Figure 2-3) was explored. Employing 4-biphenyl chloride as a coupling partner under analogous conditions afforded **2-1** in 88% isolated yield. A selection of para-substituted 4-chlorobiphenyl derivatives featuring methyl, trifluoromethyl, methoxy, or cyano substituents was also accommodated under these conditions (**2-2**–**2-5**, 50–69%), although increased catalyst loadings proved beneficial (10 mol% Pd; **2-3**–**2-5**, 71–86%). A series of ortho-, meta- and para-substituted halogenated anisoles proved to be effective substrates (**2-6**–**2-8**, 64–83%), as did 4-chloro-3-methylanisole (**2-9**, 78%) and 2-bromobiphenyl (**2-10**, 70%). Halogenated xylene (**2-11**, 60%; **2-12**, 80%), fluorobenzene (**2-13**, 62%), styrene (**2-14**, 64%), and napthyl (**2-15**, 57%; **2-16**, 77%) derivatives were also accommodated.
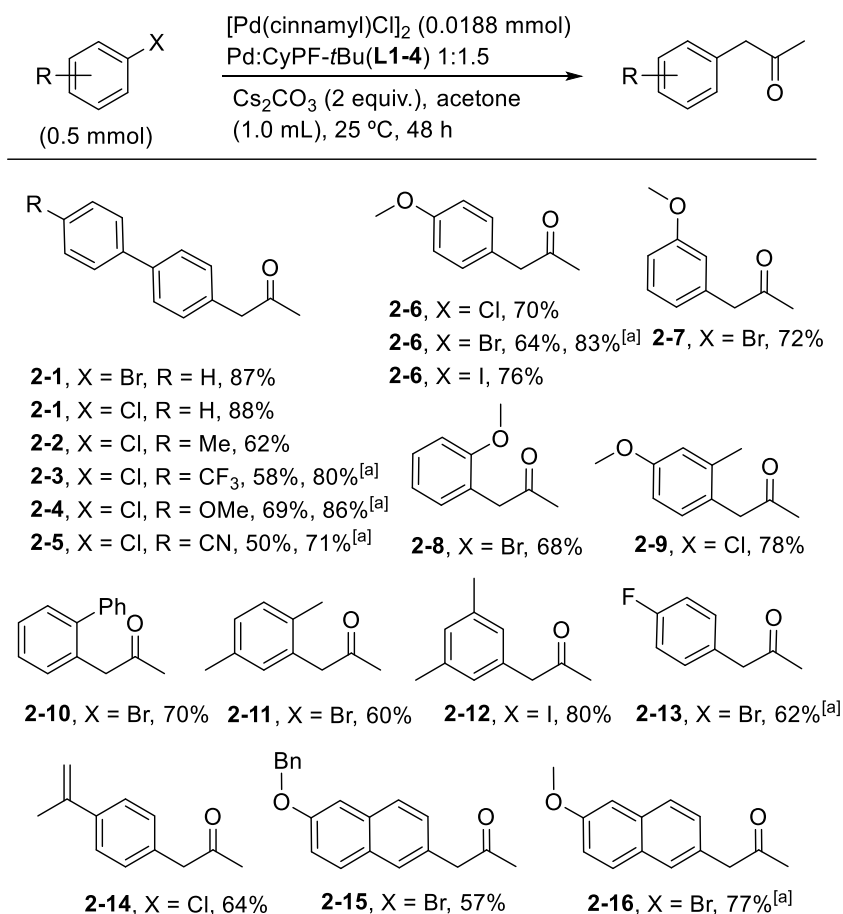
Figure 2-3: Scope of palladium-catalyzed mono-α-arylation of acetone employing substituted aryl halides (yields of isolated products reported). [a] Using 0.025 mmol [Pd(cinnamyl)Cl]$_2$.

Given the ubiquity of heterocyclic motifs in medicinal, biological, and natural products chemistry, it was desirable to pursue compatibility of electrophilic coupling partners featuring such functionality in the mono-α-arylation of acetone at room temperature using the [Pd(cinnamyl)Cl]$_2$/CyPF-tBu catalyst system (Figure 2-4). It is worthy of mention that while selected transformations of heterocycle-containing substrates have been featured in past reports on palladium-catalyzed acetone mono-α-arylation conducted at elevated temperature,[17, 19, 52, 54, 63] such coupling partners have for the most part been overlooked in this chemistry prior to the work detailed herein. In this context, it

is noteworthy that substituted pyrrole (**2-17**), pyridine (**2-18**, **2-19**), isoquinoline (**2-20**),

quinoline (**2-21**, **2-22**), quinaldine (**2-23**), (benzo)thiophene (**2-24**, **2-25**), benzothiazole (**2-26**), and benzodioxole (**2-27**) coupling partners functioned well in this newly developed

room temperature acetone mono-α-arylation chemistry (Figure 2-4, 51-94%).
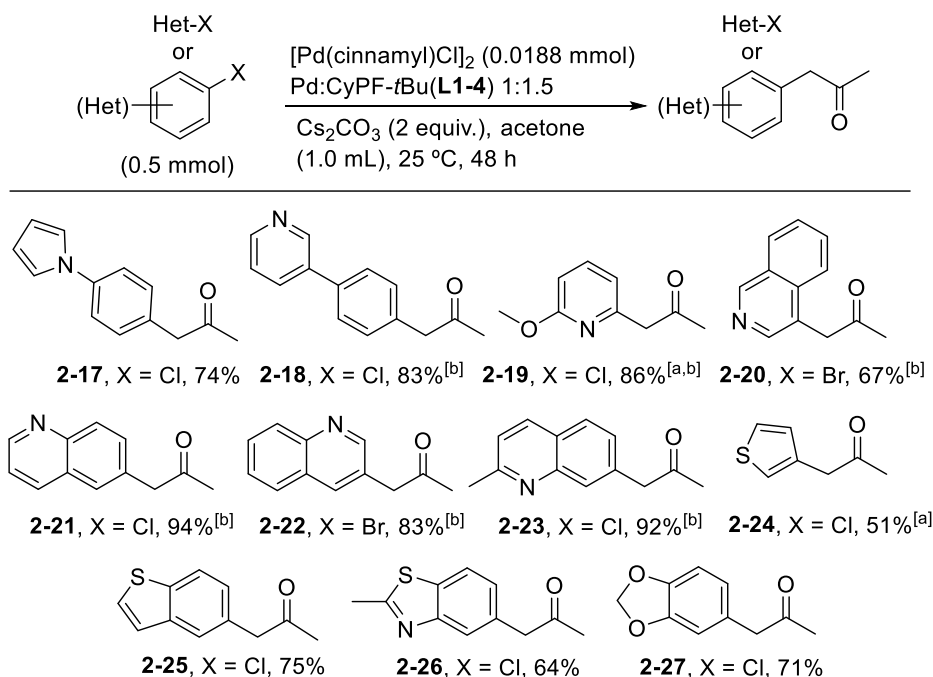
Figure 2-4: Scope of palladium-catalyzed mono-α-arylation of acetone employing aryl halides featuring heterocyclic functionality (yields of isolated products reported). [a] Using 0.025 mmol [Pd(cinnamyl)Cl]₂. [b] Isolated as the hydrochloride salt.

While the room-temperature mono-α-arylation chemistry described above was

conducted exclusively using acetone as the nucleophilic reaction partner, proof-of-

principle experiments confirmed that other (hetero)aryl methyl ketone substrates can also

be employed (Figure 2-5). In test cross-couplings with acetophenone, heteroaryl chlorides

featuring benzothiophene (**2-28**, 67%), benzothiazole (**2-29**, 95%), and quinoline (**2-30**,

88%) core structures each proved to be suitable substrates. The incorporation of

heterocyclic functionality into both of the reaction partners also proved to be feasible, as

evidenced by the successful room temperature cross-coupling of 5-chloro-benzo[*b*]thiophene with each of 2-acetylthiophene and 2-acetylfuran to afford **2-31** (82%) and **2-32** (53%), respectively.
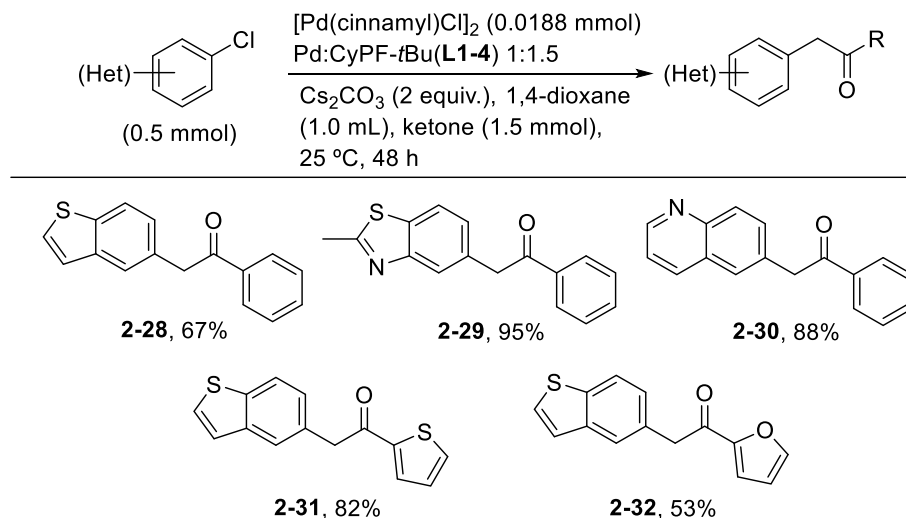
Figure 2-5: Palladium-catalyzed mono-α-arylations of (hetero)aryl methyl ketone substrates (yields of isolated products reported).

2.4 Ineffective Applications of the Developed Mono-α-Arylation Methodology

Although the mono-α-arylation of acetone at room temperature was generally successful, not all of the envisioned applications and research goals were accomplished. The sections below describe unsuccessful catalyst optimizations, substrate scope, and one-pot synthesis.

2.4.1 Exploring JosiPhos Pre-catalysts for Mono-α-Arylation of Acetone at Room Temperature

As mentioned in Section 1.4.2, binding the ligand to the metal prior to exposure to substrates in the form of a pre-catalyst may have advantages, such as shorter reaction time, higher yields, or reactivity under more mild conditions. After the JosiPhos (**L1-4**) ligand in Figure 2-2 was identified as the superior ligand in room temperature cross-coupling of acetone, attempts were made to synthesize a ligand metal pre-catalyst complex capable of higher performance compared to adding a palladium source and **L1-4** separately. Three pre-catalysts were prepared, isolated, and tested in the reaction as shown in Figure 2-6. **C2-1a** and **C2-1b** were previously studied by Hartwing[64] and resemble oxidative addition intermediates in the catalytic cycle. **C2-1b** contains a methoxy group in the ortho position to sterically favour reductive elimination. **C2-1c** was modeled after the (Mor-DalPhos)Pd(cinnamyl)Cl pre-catalyst developed by Stradiotto[24i] for the room temperature mono-arylation of ammonia.
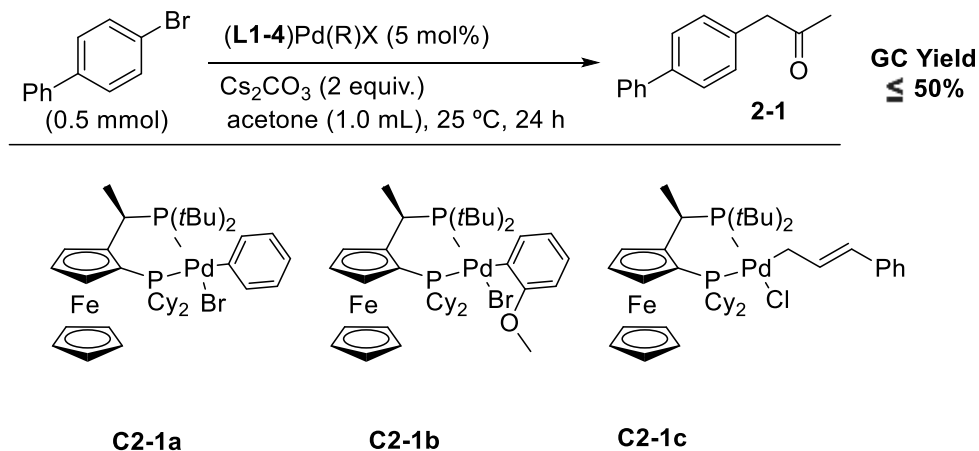
Figure 2-6: JosiPhos palladium pre-catalyst screen for the mono-α-arylation of acetone at room temperature.

Unfortunately, none of the pre-catalysts described gave better yields than [Pd(cinnamyl)Cl]$_2$/CyPF-tBu under the conditions of Figure 2-6 (only 50% conversion to desired product by GC). Catalyst activation of the [Pd(cinnamyl)Cl]$_2$ dimer must be facile since these oxidative addition complexes don't give any benefit compared to the combination of [Pd(cinnamyl)Cl]$_2$/CyPF-tBu. It was decided that continuing with commercially available combination of [Pd(cinnamyl)Cl]$_2$ and CyPF-tBu (**L1-4**) would be more attractive to end users than a pre-catalyst requiring more synthetic steps which delivered no benefit.

2.4.2 Unsuccessful Coupling Partners for Mono-α-Arylation

Although the methodology described was successful in mono arylating acetone and select aryl ketones with (hetero)aryl halides, there were substrates that did not generate product or gave unsubstantial yields.
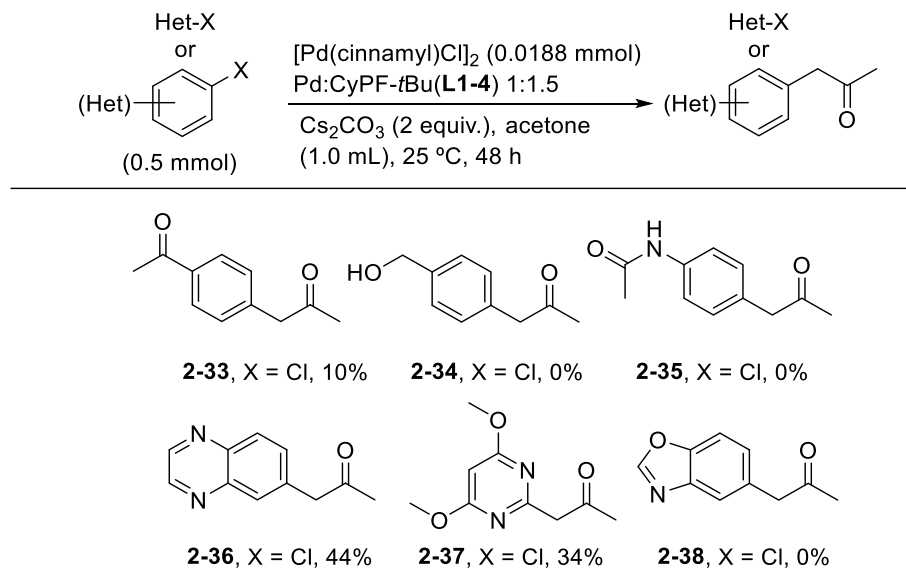
Figure 2-7: Examples of electrophile coupling partners that failed in the mono-α-arylation of acetone at room temperature (yields of isolated products reported).

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Selected substrates that were unsuccessful for the mono-α-arylation of acetone are shown in Figure 2-7. Product **2-33** would be the result of a chemoselective reaction in which mono-α-arylation of acetone is preferred over the coupling to acetophenone. Given the excess of acetone present in the reaction, coupling to acetone would be statistically favoured, making this type of selectivity possible; however, a small impure amount of the desired coupling product was isolated implying that the reaction was not selective. Compounds **2-34** and **2-35** represent chemoselective reactions in which the catalyst system prefers mono-α-arylation of acetone over C-O coupling and *N*-arylation of a secondary amide respectively. However, no turnover was observed on the basis of GC data for these coupling partners. It is possible that the oxygen on the benzyl alcohol moiety or the secondary amide moiety could bind to the metal at some stage of the cycle forming a very stable, but non-catalytically active complex. As shown in Section 2.3, many heteroaryl halides were successful coupling partners in this reaction, but products **2-36** – **2-38** were unable to be synthesized in synthetically useful yields. Compounds **2-36** and **2-37** containing quinoxaline and pyrimidine respectively are popular substructures in pharmaceutical compounds.[65] Higher yields may have been achieved by going to higher temperatures, but would not be consistent with the goal of developing and reporting a room temperature methodology. The substrate corresponding to **2-38** gave many products on the basis of GC data and isolation was not attempted. The arylation of (benzo)oxazoles via palladium-catalyzed C-H activation is known.[66] Undesired reactions at the methylene proton present in this compound may have been competitive with the reaction between acetone and the aryl chloride moiety.

It was desirable to extend the electrophile scope to include leaving groups beyond halides such as phenol-derived electrophiles. Figure 2-8 shows the successful use of 4-biphenyl toluenesulfonate as an electrophile for mono-α-arylation of acetone; however, this reaction required heating to 40 °C to obtain a useful yield and gave no turnover at room temperature.
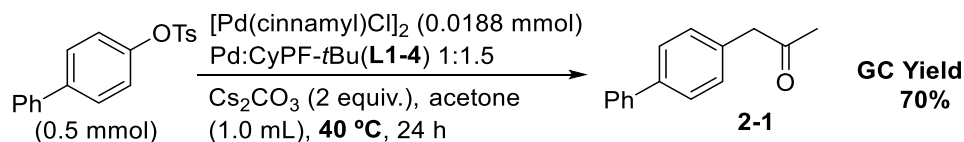
Figure 2-8: 4-Biphenyl toluenesulfonate in mono-α-arylation of acetone at room temperature.

Despite success in substituting aryl methyl ketones for acetone in this methodology, alkyl methyl ketones were not successfully employed as substrates. As illustrated in Figure 2-9, the alkyl methyl ketones employed in the test reaction gave little or no conversion of starting materials, even when paired with an electrophile that was high yielding with acetone and aryl methyl ketones. The methyl protons on aryl methyl ketones would be expected to be more acidic than the analogous protons on alkyl methyl ketones, which may be related to the observed difference in reactivity between the two types of ketone. Perhaps alkyl methyl ketones containing an electron withdrawing fluorocarbon chain would be activated toward activity, but this was not pursued.
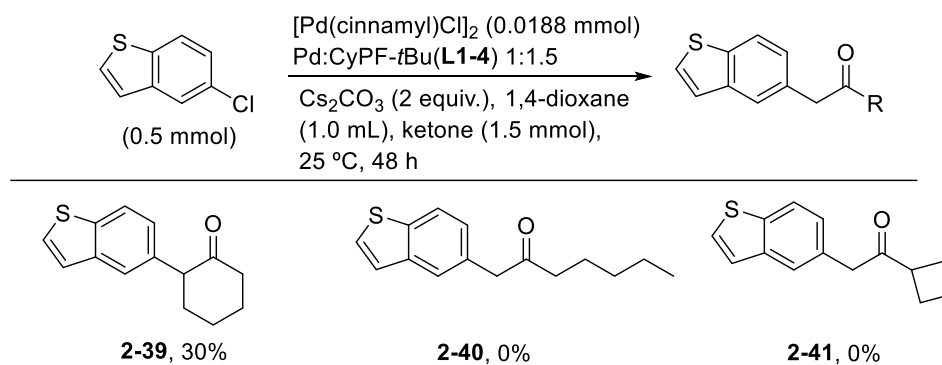
Figure 2-9: Alkyl methyl ketones in room temperature mono-α-arylation (yields of isolated products reported).

2.4.3 Unsuccessful One-pot Synthesis of Methyl-benzofurans

Benzofurans are a common scaffold in pharmaceuticals such as anti-tumor agents,[67] and calcium channel blockers,[68] as well as natural products.[69] Burch and co-workers reported the synthesis of substituted benzofurans through palladium-catalyzed arylation of ketones followed by condensation of benzyl ketones with ortho phenols.[70] It seemed possible to use the methodology described in this chapter to synthesize methyl benzofurans from acetone and ortho halophenols at room temperature, similar to the synthesis of indoles from acetone and amines described by Stradiotto.[63] The standard reaction conditions would be applied to aryl halides with a phenol or protected phenol in the ortho position, followed by the addition of excess trifluoracetic acid to promote the condensation reaction producing the benzofuran product.[70] In the cases of products derived from **2-44** and **2-45**, it was envisioned that the acid would also remove the protecting group in one step (Figure 2-10).
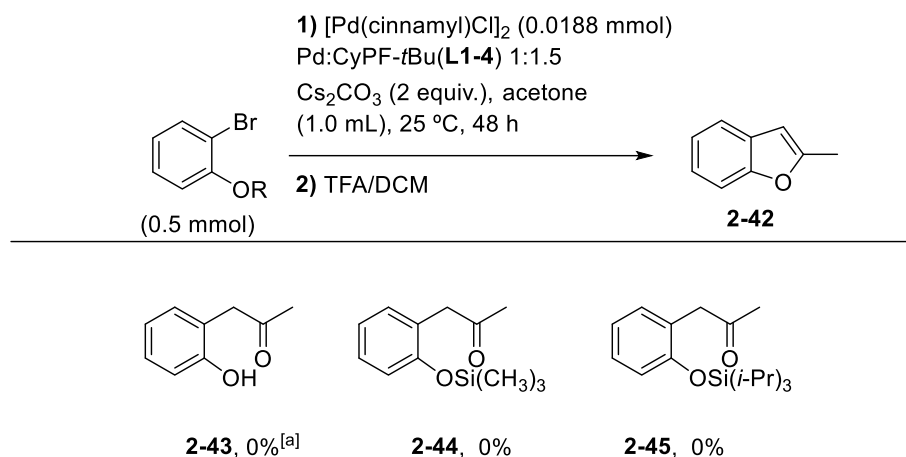
Figure 2-10: Attempted synthesis of benzofurans via room temperature mono-α-arylation of acetone (yields on the basis of GC data reported). [a] Three equivalents of Cs_2CO_3 were used.

The mono-α-arylation step of the reaction was not successful with these substrates. The synthesis of compound **2-43** was attempted under the standard conditions with an extra equivalent of base to account for competing phenol deprotonation. The oxygen of the phenol may have coordinated to the metal, thus inhibiting catalysis. The analogous phenol protected mono-α-arylation products **2-44** and **2-45** were not successfully formed either, but this may be due to increased steric bulk in the ortho position. The trimethylsilyl and triisopropylsilyl groups of **2-44** and **2-45** respectively are much larger than previous tolerated ortho methyl ester (**2-8**), methyl (**2-9**, **2-11**), and phenyl (**2-10**) groups discussed in Section 2.3.

2.5 Conclusions

In conclusion, the identified [Pd(cinnamyl)Cl]$_2$/JosiPhos(**L1-4**) catalyst system has enabled the first examples of acetone mono-α-arylation chemistry conducted at room temperature. The established substrate scope encompasses (hetero)aryl chlorides, bromides, and iodides featuring or lacking ortho-substitution, and comprising a range of substituents (e.g. methoxy, phenoxy, cyano, fluoro, trifluoromethyl, alkenyl) and heterocyclic structures (e.g. pyrrole, pyridine, isoquinoline, quinolone, quinaldine, (benzo)thiophene, benzothiazole, benzodioxole). Preliminary experimentation confirmed that other (hetero)aryl methyl ketones can also be accommodated in such room temperature mono-α-arylation chemistry. The established substrate scope is notable in that it is very extensive, and represents the first room temperature ketone mono-α-arylations employing a structurally diverse set of (hetero)aryl chlorides. Since the completion of this work, important advancements in mono-α-arylation of acetone have occurred. Notably, the Kwong group has developed indolylphosphine ligands for the mono-α-arylation of acetone which was able to tolerate aniline, acetophenone, amide, and indole functional groups.[71] Separately these indolylphosphine ligands have enabled the transformation to be completed at remarkably low loadings of palladium (less than 0.5 mol%).[72] Most recently Kwong and co-workers developed a one-pot synthesis of very sterically hindered 2,6-disubsituted benzyl ketones via palladium-catalyzed mono-α-arylation of acetone followed by activation of the ortho C-H bond(s) through cooperative catalysis of palladium and norbornene.[73] These important advancements are, however, all accomplished at elevated

temperature. The work described here is still the only catalyst system capable of mono-α-arylation of acetone at room temperature.

2.6 Experimental

2.6.1 General Considerations and Procedures

General Considerations. Unless otherwise stated, all reactions were set up inside a nitrogen-filled inert atmosphere glovebox and worked up in air using benchtop procedures. Distilled acetone was degassed via three repeated freeze-pump-thaw cycles, and was stored over activated 4 Å molecular sieves for a minimum of 12 hours prior to use. 1,4-Dioxane was dried over Na/benzophenone followed by distillation under an atmosphere of nitrogen. All other reagents, solvents and materials were used as received from commercial sources. Flash column chromatography was carried out using Silicycle SiliaFlash 60 silica (particle size 40–63 mm; 230–400 mesh) or using neutral alumina (150 mesh; Brockmann-III; activated), as indicated. All ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 K in CDCl$_3$ or D$_2$O. Chemical shifts are expressed in parts per million (ppm) using the residual solvent signal H$_2$O (^{1}H 4.69 ppm, ^{13}C externally referenced) or CHCl$_3$ (^{1}H 7.26 ppm, ^{13}C 71.4 ppm) as an internal reference. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All coupling constants (J) are reported in Hertz (Hz). In some cases fewer than expected independent ^{13}C NMR resonances were observed despite prolonged acquisition times. Mass spectra were obtained using ion trap (ESI) instruments operating in positive mode, and GC data were obtained on an instrument

equipped with a SGE BP-5 column (30 m, 0.25 mm i.d.). In the following experimental descriptions "**L1-4**" refers to the ligand variant CyPF-*t*Bu.

General Catalytic Procedure for the Alpha Arylation of Acetone with Aryl Halides (GP2-1). Unless specified otherwise in the text, $[Pd(\eta^1\text{-cinnamyl})Cl]_2$ (13.0 mg, 0.025 mmol), (*R*)-1-[(*S*)-2-(dicyclohexylphosphino)ferrocenyl]-ethyl-di-tert-butylphosphine (**L1-4**) (42.0 mg, 0.075 mmol), Cs_2CO_3 (326 mg, 1 mmol), aryl halide (0.5 mmol), and acetone (1.0 mL, 0.5 M concentration) were added to a screw-capped vial containing a small magnetic stir bar. The vial was sealed with a cap containing a PTFE septum, and left to stir vigorously for 48 hours at room temperature. The reaction progress was monitored qualitatively by use of GC methods. The crude reaction mixture was dissolved in ethyl acetate or dichloromethane (10 mL) and poured onto brine (10 mL); 1 M HCl (10 mL) was added subsequently to the mixture. The layers were separated and the aqueous layer was extracted with ethyl acetate or dichloromethane (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 use of column chromatography over alumina or silica.

General Catalytic Procedure for the Alpha Arylation of Acetone with Pyridinyl Aryl Halides (GP2-2). Unless specified otherwise in the text, $[Pd(\eta^1\text{-cinnamyl})Cl]_2$ (13.0 mg, 0.025 mmol), (*R*)-1-[(*S*)-2-(dicyclohexylphosphino)ferrocenyl]-ethyl-di-tert-butylphosphine (**L1-4**) (42.0 mg, 0.075 mmol), Cs_2CO_3 (326 mg, 1 mmol), pyridinyl aryl halide (0.5 mmol), and acetone (1.0 mL, 0.5 M concentration) were added to a screw-capped vial containing a small magnetic stir bar. The vial was sealed with a cap containing a PTFE septum, and left to stir vigorously for 48 hours at room temperature. The crude

reaction mixture was dissolved in dichloromethane (10 mL) and poured onto a mixture of brine (10 mL) and 1 M HCl (10 mL). The layers were separated and the organic layer was extracted with distilled water (2 x 10 mL). The aqueous fractions were combined and an excess of sodium carbonate was added. The aqueous layer was then extracted with dichloromethane (3 x 10 mL). The organic layers were combined and concentrated under reduced pressure to remove the volatile solvent. 2 M HCl in diethyl ether (8.0 mL, 2 equivalents) was then added to the organic residue causing precipitation of the HCl salt of the target compound. The diethyl ether was then removed under reduced pressure allowing for isolation of the product·HCl salt.

General Catalytic Procedure for the Alpha Arylation of Ketones with Aryl Halides (GP2-3). Unless specified otherwise in the text, $[Pd(\eta^1\text{-cinnamyl})Cl]_2$ (13.0 mg, 0.025 mmol), (*R*)-1-[(*S*)-2-(dicyclohexylphosphino)ferrocenyl]-ethyl-di-tert-butylphosphine (**L1-4**) (42.0 mg, 0.075 mmol), Cs_2CO_3 (326 mg, 1 mmol), aryl halide (0.5 mmol), ketone (1.5 mmol), and 1-4,dioxane (1.0 mL, 0.5 M concentration) were added to a screw-capped vial containing a small magnetic stir bar. The vial was sealed with a cap containing a PTFE septum, and left to stir vigorously for 48 hours at room temperature. The reaction progress was monitored qualitatively by use of GC methods. The crude reaction mixture was dissolved in ethyl acetate or dichloromethane (10 mL) and poured onto brine (10 mL). The layers were separated and the aqueous 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 use of column chromatography over alumina or silica.
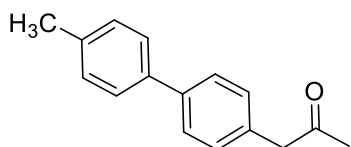
2.6.2 Synthesis and Characterization Data

1-Biphenyl-4-yl-propan-2-one (2-1)
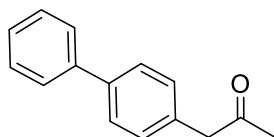
Following **GP2-1**, (0.50 mmol 4-chlorobiphenyl, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a yellow oil (88%). A 10% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.63-7.60 (m, 4H), 7.50-7.46 (m, 2H), 7.40-7.37 (m, 1H), 7.33-7.30 (m, 2H), 3.80 (s, 2H), 2.23 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 206.2, 140.9, 140.2, 133.4, 130.1, 129.0, 127.7, 127.5, 127.3, 51.1, 29.3; Spectral data are in agreement with the literature.[19] Following **GP2-1** using 4-bromobiphenyl (0.50 mmol, 7.5% Pd and 11.25% **L1-4** were used) the title compound was isolated as a yellow oil (87%) and spectral data are in agreement.[19]

1-(4'-Methyl-biphenyl-4-yl)-propan-2-one (2-2)

Following **GP2-1**, (0.50 mmol 4-chloro-4'-methyl-biphenyl, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a yellow oil (62%). A 15% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.60 (d, J = 7.8 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.30-7.28 (m, 4H),

3.77 (s, 2H), 2.43 (s, 3H), 2.23 (s, 3H); $^{13}C\{^1H\}$ NMR (125.8 MHz, CDCl$_3$): δ 206.4, 140.3, 138.2, 137.4, 133.2, 130.0, 129.7, 127.5, 127.1, 50.9, 29.6, 21.3; HRMS *m/z* ESI$^+$ found 247.1093 [M+Na]$^+$ calculated for C$_{16}$H$_{16}$NaO 247.1099.
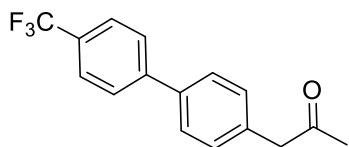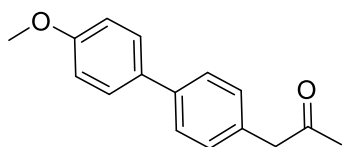
1-(4'-Trifluoromethyl-biphenyl-4-yl)-propan-2-one (2-3)

Following **GP2-1**, (0.50 mmol 4-chloro-4'-trifluoromethyl-biphenyl, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as an off white solid (58%). A 15% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^1H NMR (500 MHz, CDCl$_3$): δ 7.72 (m, 4H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 3.81 (s, 2H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR (125.8 MHz, CDCl$_3$): δ 206.1, 144.5, 138.9, 134.5, 130.3, 127.8, 127.6, 126.0, 123.4, 50.5, 29.3. Spectral data are consistent with the literature.[19] Following **GP2-1** using 4-chloro-4'-trifluoromethyl-biphenyl (0.50 mmol, 10% Pd and 15% **L1-4** were used) the title compound was isolated as an off white solid (80%) and spectral data are in agreement.[19]
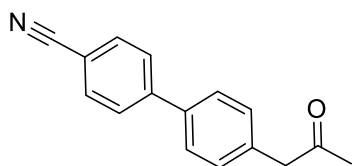
1-(4'-Methoxy-biphenyl-4-yl)-propan-2-one (2-4)

Following **GP2-1**, (0.50 mmol 4-chloro-4'-methoxy-biphenyl, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as an off white solid (69%). A 15% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^1H NMR

(500 MHz, CDCl$_3$): δ 7.57-7.55 (m, 4H), 7.30-7.28 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 3.77 (s, 2H), 2.23 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 206.8, 159.5, 140.0, 133.6, 132.9, 130.0, 128.3, 127.3, 114.5, 55.5, 50.5, 29.9; HRMS m/z ESI$^+$ found 263.1043 [M+Na]$^+$ calculated for C$_{16}$H$_{16}$NaO$_2$ 263.1048. Following **GP2-1** using 4-Chloro-4'-methoxy-biphenyl (0.50 mmol, 10% Pd and 15% **L1-4** were used) the title compound was isolated as an off white solid (86%) and spectral data are in agreement.

4'-(2-Oxo-propyl)-biphenyl-4-carbonitrile (2-5)

Following **GP2-1**, (0.50 mmol 4'-chloro-biphenyl-4-carbonitrile, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as an off white solid (50%). A 40% MTBE/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.77-7.70 (m, 4H), 7.61 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 3.82 (s, 2H), 2.26 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 205.5, 145.5, 138.4, 135.0, 132.8, 130.4, 127.8, 127.7, 119.0, 111.3, 50.6, 29.3; Spectral data are in agreement with the literature.[19] Following **GP2-1** using 4'-chloro-biphenyl-4-carbonitrile (0.50 mmol, 10% Pd and 15% **L1-4** were used) the title compound was isolated as an off white solid (71%) and spectral data are in agreement.[19]
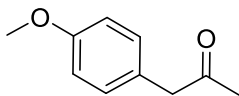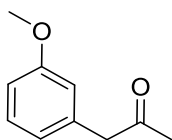
1-(4-Methoxy-phenyl)-propan-2-one (2-6)

Following **GP2-1**, (0.80 mmol 1-chloro-4-methoxy-benzene, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a colourless oil (70%). A 5% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.16 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 3.84 (s, 3H), 3.67 (s, 2H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 207.0, 158.9, 130.6, 126.5, 114.4, 55.5, 50.4, 29.3; Spectral data are in agreement with the literature.[19] Following **GP2-1** using 1-bromo-4-methoxy-benzene (0.80 mmol, 7.5% Pd and 11.25% **L1-4** were used) the title compound was isolated as a colourless oil (64%). Following **GP2-1** using 1-bromo-4-methoxy-benzene (0.80 mmol, 10% Pd and 15% **L1-4** were used) the title compound was isolated as a colourless oil (83%). Following **GP2-1** using 1-iodo-4-methoxy-benzene (0.80 mmol, 7.5% Pd and 11.25% **L1-4** were used) the title compound was isolated as a colourless oil (76%). In all cases the spectral data were in agreement with the title compound and literature.[19]

1-(3-Methoxy-phenyl)-propan-2-one (2-7)

Following **GP2-1**, (0.80 mmol 1-bromo-3-methoxy-benzene, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a yellow oil (72%). A 10% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR

(500 MHz, CDCl$_3$): δ 7.30-7.26 (m, 1H), 6.85-6.78 (m, 3H), 3.82 (s, 3H), 3.71 (s, 2H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 206.3, 160.0, 135.9, 129.9, 121.9, 115.2, 112.6, 55.3, 51.3, 29.3. Spectral data are in agreement with the literature.[17]
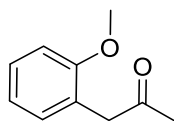
1-(2-Methoxy-phenyl)-propan-2-one (2-8)

Following **GP2-1**, (0.80 mmol 1-bromo-2-methoxy-benzene, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a yellow oil (68%). A 20% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.29-7.26 (m, 1H), 7.15-7.14 (m, 1H), 6.96-6.89 (m, 2H), 3.83 (s, 3H), 3.69 (s, 2H), 2.15 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 207.0, 157.5, 131.2, 128.7, 123.8, 120.8, 110.6, 55.5, 45.6, 29.3. Spectral data are in agreement with the literature.[52]

1-(4-Methoxy-2-methyl-phenyl)-propan-2-one (2-9)

Following **GP2-1**, (0.80 mmol 1-chloro-4-methoxy-2-methyl-benzene, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a yellow oil (78%). A 5% ethyl acetate/hexanes eluent system was use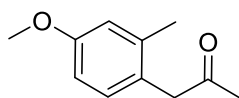d for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.03-7.00 (m, 2H), 6.83-6.81 (m, 1H), 3.85 (s, 3H), 3.63 (s, 2H), 2.24 (s, 3H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 207.3, 157.1, 131.9,

127.8, 127.2, 126.1, 110.4, 55.6, 50.4, 29.3, 16.4. Spectral data are in agreement with the literature.[17]

1-Biphenyl-2-yl-propan-2-one (2-10)
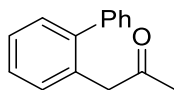
Following **GP2-1**, (0.50 mmol 2-bromobiphenyl, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a yellow oil (70%). A 5% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.46-7.43 (m, 2H), 7.42-7.37 (m, 3H), 7.33-7.32 (m, 1H), 7.30-7.27 (m, 3H), 3.74 (s, 2H), 2.03 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 206.1, 142.7, 141.5, 132.4, 130.8, 130.4, 129.3, 128.5, 127.9, 127.4, 127.3, 48.6, 29.6; HRMS *m/z* ESI$^+$ found 233.0937 [M+Na]$^+$ calculated for C$_{15}$H$_{14}$NaO 233.0942.
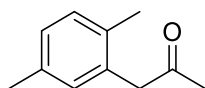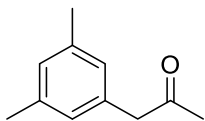
1-(2,5-Dimethylphenyl)-propan-2-one (2-11)

Following **GP2-1**, (0.80 mmol 2-bromo-1,4-dimethylbenzene, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a yellow oil (60%). A 5% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.12-7.10 (m, 1H), 7.04-7.03 (m, 1H), 6.99 (s, 1H), 3.71 (s, 2H), 2.34 (s, 3H), 2.24 (s, 3H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 206.7, 136.0, 133.8, 133.2, 131.3, 130.6, 128.3, 49.3, 29.5, 21.1, 19.4. Spectral data are in agreement with the literature.[17]

**1-(3,5-Dimethyl-phenyl)-propan-2-one (2-12)**

Following **GP2-1**, (0.80 mmol 1-iodo-3,5-dimethyl-benzene, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a yellow oil (80%). A 5% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.95 (s, 1H), 6.86 (s, 2H), 3.65 (s, 2H), 2.34 (s, 6H), 2.18 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 207.3, 138.5, 134.3, 128.9, 127.4, 51.2, 29.4, 21.4; HRMS *m/z* ESI$^+$ found 185.0937 [M+Na]$^+$ calculated for C$_{11}$H$_{14}$NaO 185.0942.

1-(4-Fluoro-phenyl)-propan-2-one (2-13)
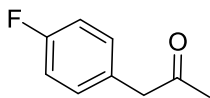
Following **GP2-1**, (0.80 mmol 1-bromo-4-fluoro-benzene, 10% Pd and 15% **L1-4** were used) the title product was isolated as a colourless oil (62%). A 10% to 5% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.21-7.18 (m, 2H), 7.08-7.04 (m, 2H), 3.71 (s, 2H), 2.18 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 206.2, 163.2 (d, J_{CF} = 231.2 Hz), 131.2 (d, J_{CF} = 8.0 Hz), 130.2, 115.8 (d, J_{CF} = 21.4 Hz), 50.2, 29.5. Spectral data are in agreement with the literature.[74]

1-(4-Isopropenyl-phenyl)-propan-2-one (2-14)

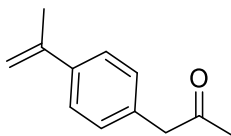
Following **GP2-1**, (0.80 mmol 1-chloro-4-isopropenyl-benzene, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a colourless oil (64%). A 100% dichloromethane eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.49-7.47 (m, 2H), 7.22-7.20 (m, 2H), 5.41 (s, 1H), 5.12-5.11 (m, 1H), 3.73 (s, 2H), 2.20 (s, 3H), 2.18 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 206.7, 143.2, 140.5, 133.8, 129.7, 126.3, 112.9, 51.1, 29.7, 22.2. Spectral data are in agreement with the literature.[17]

1-(6-Benzyloxy-naphthalen-2-yl)-propan-2-one (2-15)
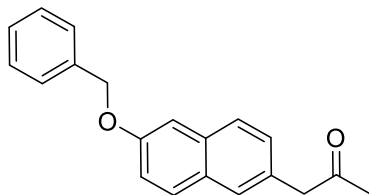
Following **GP2-1**, (0.50 mmol 2-benzyloxy-6-bromo-naphthalene, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a yellow solid (57%). A 20% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.76-7.73 (m, 2H), 7.64 (s, 1H), 7.53-7.52 (m, 2H), 7.46-7.43 (m, 3H), 7.40-7.38 (m, 1H), 7.33-7.25 (m, 2H), 5.22 (s, 2H), 3.85 (s, 2H), 2.21 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 206.9, 157.1, 137.1, 133.8, 129.8, 129.4, 128.9, 128.3, 128.2, 127.8, 127.6, 119.7, 107.4, 70.3 51.3, 29.5; HRMS *m/z* ESI$^+$ found 313.1199 [M+Na]$^+$ calculated for C$_{20}$H$_{18}$NaO$_2$ 313.1204.

1-(6-Methoxy-naphthalen-2-yl)-propan-2-one (2-16)
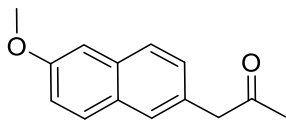
Following **GP2-1**, (0.50 mmol 2-bromo-6-methoxy-naphthalene, 10% Pd and 15% **L1-4** were used) the title product was isolated as a yellow solid (77%). An 8% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.76-7.72 (m, 2H), 7.64 (s, 1H), 7.33-7.31 (m, 1H), 7.20-7.16 (m, 2H), 3.96 (s, 3H), 3.85 (s, 2H), 2.21 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 206.9, 157.9, 133.8, 129.7, 129.3, 128.2, 128.1, 127.5, 119.3, 105.9, 55.5 51.3, 29.5; HRMS *m/z* ESI$^+$ found 237.0886 [M+Na]$^+$ calculated for C$_{14}$H$_{14}$NaO$_2$ 237.0891.
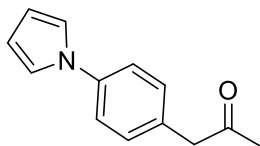
1-(4-Pyrrol-1-yl-phenyl)-propan-2-one (2-17)

Following **GP2-1**, (0.80 mmol 1-(4-chlorophenyl)-1*H*-pyrrole, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a faint pink oil (74%). A 100% dichloromethane eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.41-7.40 (m, 2H), 7.30-7.28 (m, 2H), 7.12-7.21 (m, 2H), 7.39-7.38 (m, 2H), 3.78 (s, 2H), 2.24 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 206.1, 140.1, 131.7, 130.8, 121.0, 119.5, 110.7, 50.4, 29.6. Spectral data are in agreement with the literature.[17]

3-[4-(2-Oxo-propyl)-phenyl]-pyridinium chloride (2-18)

Following **GP2-2**, (0.50 mmol 3-(4-chlorophenyl)-pyridine, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as orange solid (83%). ^{1}H NMR (500 MHz, D$_2$O): δ 9.01 (s, 1H), 8.81 (d, J = 8.3 Hz, 1H), 8.71 (d, J = 5.6 Hz, 1H), 8.10 - 8.07 (m, 1H), 7.73 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 4.00 (s, 2H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, D$_2$O): δ 213.5, 144.5, 140.0, 139.5, 136.4, 132.4, 131.0, 127.6, 127.3, 49.4, 29.2; HRMS m/z ESI$^+$ found 212.1070. [M+H]$^+$ calculated for C$_{14}$H$_{14}$NO 212.1075.

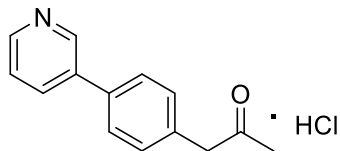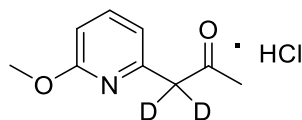**2-Methoxy-6-(2-oxo-propyl)-pyridinium chloride (2-19)**

Following **GP2-2**, (0.50 mmol 2-chloro-6-methoxy-pyridine, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as orange solid (86%). ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.32 (t, J = 8.3 Hz, 1H), 7.34 (d, J = 8.9 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 2.33 (on the basis of HMBC data), 4.13 (s, 3H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 208.3, 162.0, 148.6, 147.0, 119.7, 108.6, 58.2, 46.8 (on the basis of HMBC data, below), 29.6; HRMS m/z ESI$^+$ found 166.0863 [M+H]$^+$ calculated for C$_9$H$_{12}$NO$_2$ 166.0868.

4-(2-Oxo-propyl)-isoquinolinium chloride (2-20)

Following **GP2-2**, (0.50 mmol 4-bromoisoquinoline, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as brown solid (67%). ^{1}H NMR (500 MHz, D$_2$O): δ 9.54 (s, 1H), 8.46-8.41 (m, 1H), 8.35 (s, 1H), 8.20-8.17 (m, 1H), 8.09-8.08 (m, 1H), 8.01-8.00 (m, 1H), 4.59 (s, 2H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, D$_2$O): δ 210.4, 146.4, 137.2, 131.4, 131.2, 131.0, 127.2, 124.1, 43.5, 30.2; HRMS *m/z* ESI$^+$ found 186.0913 [M+H]$^+$ calculated for C$_{12}$H$_{12}$NO 186.0919.

6-(2-Oxo-propyl)-quinolinium chloride (2-21)
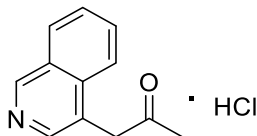

Following **GP2-2**, (0.50 mmol 6-chloroquinoline, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as orange solid (94%). ^{1}H NMR (500 MHz, D$_2$O): δ 9.05-9.04 (m, 2H), 8.16-8.14 (m, 1H), 8.06 (s, 1H), 8.03-8.00 (m, 1H), 7.94-7.93 (m, 1H), 4.23 (s, 2H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, D$_2$O): δ 212.0, 147.3, 137.3, 136.9, 129.7, 129.1, 121.9, 121.8, 120.4, 120.3, 49.2, 29.4; HRMS *m/z* ESI$^+$ found 186.0913 [M+H]$^+$ calculated for C$_{12}$H$_{12}$NO 186.0919.

3-(2-Oxo-propyl)-quinolinium chloride (2-22)

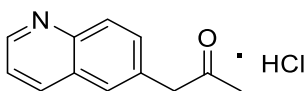
Following **GP2-2**, (0.50 mmol 3-bromoquinoline, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as orange solid (83%). ^{1}H NMR (500 MHz, D$_2$O): δ 8.94 (s, 1H), 8.87 (s, 1H), 8.22-7817 (m, 2H), 8.12-8.08 (m, 1H), 7.94-7.91 (m, 1H), 4.36 (s, 2H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, D$_2$O): δ 210.4, 147.9, 145.5, 136.7, 134.9, 130.1, 128.9, 128.8, 128.6, 120.2, 45.9, 29.2; HRMS m/z ESI$^+$ found 186.0913 [M+H]$^+$ calculated for C$_{12}$H$_{12}$NO 186.0919.
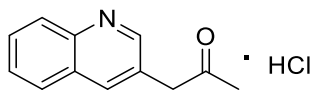
2-Methyl-7-(2-oxo-propyl)-quinolinium chloride (2-23)
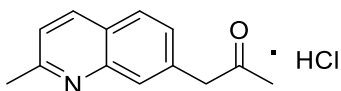
Following **GP2-2**, (0.50 mmol 7-chloro-2-methyl-quinoline, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as orange solid (92%). ^{1}H NMR (500 MHz, D$_2$O): δ 8.86 (d, J = 9.5 Hz, 1H), 8.14 (d, J = 9.5 Hz, 1H), 7.88 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 6.6 Hz, 1H), 4.25 (s, 2H), 2.93 (s, 3H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, D$_2$O): δ 211.7, 157.7, 146.2, 141.2, 137.5, 131.4, 129.0, 126.1, 123.1, 120.1 49.7, 29.5, 20.1; HRMS m/z ESI$^+$ found 200.1070 [M+H]$^+$ calculated for C$_{13}$H$_{14}$NO 200.1075.

1-Thiophen-3-yl-propan-2-one (2-24)
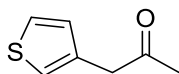
Following **GP2-1**, (0.80 mmol 3-chlorothiophene, 10% Pd and 15% **L1-4** were used) the title product was isolated as yellow oil (51%). A 5% ethyl acetate/hexanes eluent system

was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.35-7.34 (m, 1H), 7.14-7.13 (m, 1H), 7.01-7.00 (m, 1H), 3.77 (s, 2H), 2.20 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 205.8, 133.9, 128.4, 126.1, 123.0, 45.5, 29.6. Spectral data are in agreement with the literature.[75]

1-Benzo[b]thiophen-5-yl-propan-2-one (2-25)
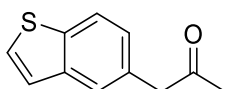
Following **GP2-1**, (0.50 mmol 5-chloro-benzo[*b*]thiophene, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as yellow solid (75%). A 5% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.89 (d, *J* = 8.3 Hz, 1H), 7.71 (s, 1H), 7.49 (d, *J* = 5.4 Hz, 1H), 7.35 (d, *J* = 5.4 Hz, 1H), 7.23-7.22 (m, 1H), 3.85 (s, 2H), 2.21 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 207.2, 140.4, 138.9, 130.6, 127.3, 125.9, 124.5, 123.9, 123.0, 51.2, 29.5; HRMS *m/z* ESI$^+$ found 213.0345 [M+Na]$^+$ calculated for C$_{11}$H$_{10}$NaOS 213.0350.

1-(2-Methyl-benzothiazol-5-yl)-propan-2-one (2-26)

Following **GP2-1**, (0.50 mmol 5-chloro-2-methyl-benzothiazole, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as yellow oil (64%). A 30% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.83-7.81 (m, 2H), 7.24-7.22 (m, 1H), 3.87 (s, 2H), 2.88 (s, 3H), 2.22 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 206.2, 167.9, 154.1, 134.7, 132.5,

126.3, 123.4, 121.8, 51.0, 29.5, 20.4; HRMS *m/z* ESI[+] found 288.0454 [M+Na][+] calculated for $C_{11}H_{11}NNaOS$ 288.0459.

1-Benzo[1,3]dioxol-5-yl-propan-2-one (2-27)
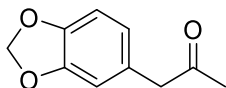
Following **GP2-1**, (0.50 mmol 5-chloro-benzo[1,3]dioxole, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as yellow oil (71%). A 10% ethyl acetate/hexanes eluent system was used for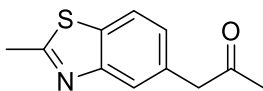 column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl3): δ 6.81-6.80 (m, 1H), 6.72.-6.71 (m, 1H), 6.69-6.67 (m, 1H), 5.98 (s, 2H), 3.63 (s, 2H), 2.18 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl3): δ 206.7, 148.1, 146.9, 128.1, 122.7, 110.0, 108.7, 101.3, 50.8, 29.3. Spectral data are consistent with the literature.[19]

2-Benzo[*b*]thiophen-5-yl-1-phenyl-ethanone (2-28)
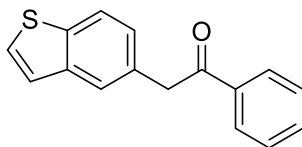
Following **GP2-3**, (0.50 mmol 5-chloro-benzo[*b*]thiophene, 1.5 mmol acetophenone, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a yellow solid (67%). A 50% dichloromethane/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl3): δ 8.08 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.77 (s, 1H), 7.62-7.58 (m, 1H), 7.51-7.46 (m, 3H), 7.33-7.30 (m, 2H), 4.45 (s, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl3): δ 198.0, 140.3, 138.7, 136.9, 133.4, 130.9, 128.9, 127.1, 126.1, 124.6, 124.0, 123.9, 45.8; HRMS *m/z* ESI[+] found 253.0682 [M+H][+] calculated for $C_{16}H_{13}OS$ 253.0687.

2-(2-Methyl-benzothiazol-5-yl)-1-phenyl-ethanone (2-29)
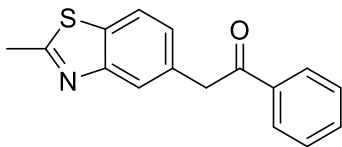
Following **GP2-3**, (0.50 mmol 5-chloro-2-methyl-benzothiazole, 1.5 mmol acetophenone, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a white solid (95%). A 25-15% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.08 (d, J = 7.5 Hz, 2H), 7.89 (s, 1H), 7.82-7.80 (m, 1H), 7.61-7.58 (m, 1H), 7.51-7.48 (m, 2H), 7.32-7.30 (m, 1H), 4.46 (s, 2H), 2.87 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 197.6, 167.9, 153.9, 136.7, 134.4, 133.5, 133.0, 128.9, 128.8, 126.6, 123.4, 121.7, 45.6, 20.4; HRMS m/z ESI$^+$ found 268.0791 [M+H]$^+$ calculated for C$_{16}$H$_{14}$NOS 268.0796.

1-Phenyl-2-quinolin-6-yl-ethanone (2-30)
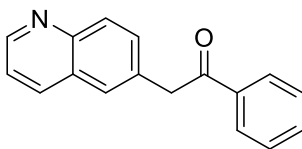
Following **GP2-3**, (0.50 mmol 6-chloroquinoline, 1.5 mmol acetophenone, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as white powder (88%). A 40% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.93-8.92 (m, 1H), 8.15-8.08 (m, 4H), 7.74 (s, 1H), 7.68-7.66 (m, 1H), 7.63-7.60 (m, 1H), 7.53-7.50 (m, 2H), 7.42-7.40 (m, 1H), 4.56 (s, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 197.9, 150.5, 147.8, 136.8, 136.0, 133.6, 133.2, 131.6, 130.0,

129.0, 128.8, 128.5, 128.2, 121.5, 45.8; HRMS *m/z* ESI⁺ found 248.1070 [M+H]⁺ calculated for $C_{17}H_{14}NO$ 248.1075.

2-Benzo[*b*]thiophen-5-yl-1-thiophen-2-yl-ethanone (2-31)
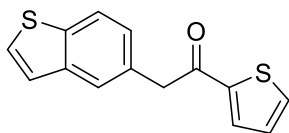
Following **GP2-3**, (0.50 mmol 5-chloro-benzo[*b*]thiophene, 1.5 mmol 1-thiophen-2-yl-ethanone, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a pale yellow solid (82%). A 50% dichloromethane/hexanes eluent system was used for column chromatography on silica gel. ¹H NMR (500 MHz, CDCl₃): δ 7.88 (d, *J* = 8.3 Hz, 1H), 7.84-7.83 (m, 1H), 7.80 (s, 1H), 7.68 (d, *J* = 4.5 Hz, 1H), 7.48 (d, *J* = 5.6 Hz, 1H), 7.34-7.33 (m, 2H), 7.17-7.15 (m, 1H), 4.35 (s, 2H); ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ 190.8, 144.1, 140.3, 138.8, 134.3, 133.0, 130.7, 128.4, 127.2, 126.0, 124.5, 124.0, 122.9, 46.8; HRMS *m/z* ESI⁺ found 259.0246 [M+H]⁺ calculated for $C_{14}H_{11}OS_2$ 259.0251.

**2-Benzo[*b*]thiophen-5-yl-1-furan-2-yl-ethanone (2-32)**
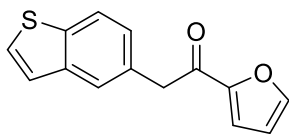
Following **GP2-3**, (0.50 mmol 5-chloro-benzo[*b*]thiophene, 1.5 mmol 1-furan-2-yl-ethanone, 7.5% Pd and 11.25% **L1-4** were used) the title product was isolated as a pale yellow solid (53%). A 70% dichloromethane/hexanes eluent system was used for column chromatography on silica gel. ¹H NMR (500 MHz, CDCl₃): δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.80 (s, 1H), 7.64 (s, 1H), 7.47-7.46 (m, 1H), 7.35-7.33 (m, 2H), 7.28-7.27 (m, 1H), 6.57-7.56 (m, 1H), 4.28 (s, 2H); ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ 186.7, 152.4, 146.5, 140.0,

138.5, 130.1, 128.5, 126.9, 124.4, 123.7, 122.6, 117.8, 112.4, 45.3; HRMS *m/z* ESI⁺ found

243.0474 [M+H]⁺ calculated for $C_{14}H_{11}O_2S$ 243.0480.

CHAPTER 3 Nickel-Catalyzed Amine Arylation

3.1 Contributions

This chapter describes the development of the first nickel-catalyzed mono-arylation of ammonia followed by the successful development of a new DalPhos ligand for improved mono-arylation of ammonia and primary amines with examples of room temperature activity. These projects were both conducted in collaboration with other members of the Stradiotto group. Post-doctoral fellow Dr. Andrey Borzenko established the catalyst system for the first nickel-catalyzed mono-arylation of ammonia using JosiPhos (**L1-9**) and Ni(COD)$_2$, and developed the majority of the substrate scope of the reaction alongside graduate student Nick L. Rotta-Loria. The author developed related reactions employing ammonia gas. In the second project discussed herein, Chris M. Lavoie developed the PAd-DalPhos Ligand (**L1-10**) and corresponding pre-catalyst (**C1-1**), and participated in the development of the scope of reactivity with ammonia alongside Dr. Andrey Borzenko, Nick L. Rotta-Loria, and Ryan S. Sawatzky. The author explored the substrate scope employing primary amine nucleophiles, and the scope of aryl mesylates using ammonia and primary amine nucleophiles. Ryan S. Sawatzky also isolated arylated primary amine products under microwave conditions using primary amine salts. Alicia J. Chisholm and Breanna K. V. Hargreaves assisted in the isolation of some ammonia and primary amine products. The contributions of each author are noted in the text and are mentioned when relevant throughout the chapter. The first nickel-catalyzed mono-arylation of ammonia work has been published in Angewandte Chemie (*Angew. Chem. Int. Ed.* **2015**, *54*, 3768–

3772) and the development of PAd-DalPhos for nickel-catalyzed aminations has been published in Nature Comunications (*Nat. Comm.* **2016**, *7*, 11073).

3.2 Introduction

Palladium-catalyzed arylation of N-H substrates (BHA) represents the current state-of-the-art in modern metal-catalyzed $C(sp^2)$-N bond formation.[22-23] BHA has evolved to encompass a wide scope of aryl halide coupling partners varying from those that are electron-rich, electron-poor, sterically hindered and heterocyclic, as well as the use of base-sensitive substrates.[62] The amine coupling partner scope has also expanded considerably since the initial development of BHA protocols, with transformations of ammonia,[24g, 37] hydrazine,[76] and chemoselective transformations such as the preference of primary amines over secondary amines being established.[24j, 62] BHA has been used as a key synthetic step in the synthesis of biologically important molecules, with indoles,[77] benzodiazepines,[24c] and natural products,[78] representing selected recent reports involving ammonia mono-arylation. However, as discussed in Section 1.4.2, the relatively rare nature of palladium, and the fact that numerous palladium-catalyzed reactions are now conducted on industrial scales[79] has resulted in a shift in focus of organometallic chemists to seek reactivity of the more abundant first-row transition metals, including for amine arylation.

Copper was one of the earliest metals used in cross coupling chemistry[8, 39] and is an attractive target for use as a cheap and abundant source of metal catalyst. However, copper catalyst systems in amine arylation have been studied in detail, and while they have shown

utility with aryl iodides and bromides they have a very limited scope with unactivated aryl chlorides.[80] There is a wider inventory of aryl chlorides commercially available compared to the other halogens, making them more desirable to use[81] and custom aryl chlorides can be easier to synthesize.[82] Relative to palladium, copper is much less suitable for amine arylation in terms of selectivity and substrate scope. Another first-row transition metal candidate for the replacement of palladium in amine arylation is nickel. Being over 1000 times cheaper than palladium, nickel is not only more economical for large scale reactions, but is also an excellent transition metal catalyst in its own right as shown by nickel-catalyzed Negishi,[10b] Suzuki,[83] and other challenging cross coupling reactions.[38] Nickel has shown promise in amine arylation since the early years of the field. The first example of nickel-catalyzed amine arylation was reported in 1997 by Wolfe and Buchwald.[41c] The work features a respectable scope of primary and secondary amines with aryl chlorides and employs relatively simple DPPF or phenanthroline-ligated nickel catalysts.[41c] While this report clearly represents an apparent breakthrough in first row transition metal-catalyzed C-N cross coupling, it seems that it was unappreciated at the time. In fact, the Buchwald research group would not again investigate the use of nickel in amine arylation for years to come. The Stradiotto group began to explore the use of nickel catalysis for amination recently, and much of this work is described in this chapter including the first nickel-catalyzed mono-arylation of ammonia and the development and application of PAd-DalPhos (**L1-10**), the most successful ligand employed in nickel-catalyzed arylation of nitrogen coupling partners, to date.

3.2.1 The First Nickel-Catalyzed Mono-arylation of Ammonia

Ammonia is a cheap and abundant feed stock chemical produced on a large scale in excess of one hundred million tonnes per year.[84] Clearly using ammonia directly in synthesis would be an attractive economic pathway to value-added products. Employing ammonia in transition metal catalyzed cross-couplings can be challenging as described in the introductory chapter (Section 1.4.1), due to potential ligand displacement by ammonia, and given the propensity of uncontrolled diarylation. Hartwig and co-workers were the first to use ammonia gas in the synthesis of anilines via palladium catalysis. Mono-arylation of ammonia was made possible by use of the bidentate JosiPhos ligand CyPF*t*-Bu (**L1-4**). Given the synthetic utility of producing anilines from substituted aryl halides and ammonia, many reports soon followed from the groups of Hartwig,[24a] Buchwald,[24b, 24c, 85] Beller,[24e, 24f] and Stradiotto,[24h-j, 86] which served to further improve the methodology. These advancements were all made by using palladium catalysts, as in Hartwig's pioneering report. Nonetheless, it has become of great interest to synthetic chemists to perform transition metal catalyzed transformations such as the mono-arylation of ammonia with more Earth abundant first-row metals, given the benefits mentioned above.

The nickel-catalyzed mono-arylation of ammonia was first achieved by Stradiotto and co-workers, using a JosiPhos (**L1-9**) ligated catalyst (Figure 3-1) to complete the transformation either by using stock solutions of ammonia in organic solvent (thereby allowing for only a limited excess of ammonia to be employed) or by using ammonia gas. A contemporaneous report by Hartwig regarding similar transformations also appeared.[40b]
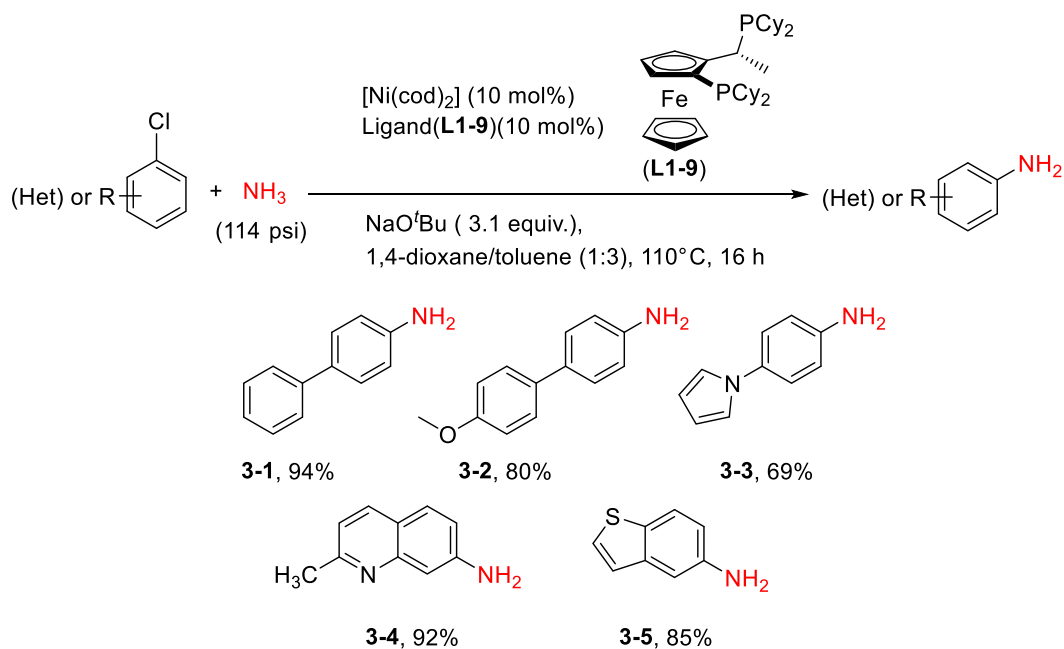
Figure 3-1: Proof-of-principal nickel-catalyzed ammonia mono-arylation reactions of aryl chlorides with ammonia gas (yields of isolated products reported).

While the use of ammonia stock solutions is convenient and operationally simple for use in small-scale laboratory syntheses, the use of ammonia gas would appear to be more scalable. The use of ammonia gas in BHA is limited to only two reports by the Hartwig group.[24a, 37] While the particular reason for this trend is unclear, it is possible that catalyst deactivation arising from ammonia-induced ancillary ligand dissociation may be problematic for some catalyst systems under high pressures of ammonia. As part of the development of a nickel catalyst capable of mono-arylation of ammonia, (**L1-9**/Ni(COD)$_2$) in combination with ammonia gas (114 psi initial pressure) was employed successfully in selected test reactions, affording the desired (hetero)biaryl (**3-1**, 94%; **3-2**, 80%; **3-3**, 69%), quinaldine (**3-4**, 92%), and benzothiophene (**3-5**, 85%) derivatives in high yields (Figure 3-1). These results are competitive with yields obtained using 0.5 M solutions of ammonia

in 1,4-dioxane in reactions conducted by group members Dr. Andrey Borzenko and Nick Rotta-Loria.[42]

3.2.2 Development of the PAd-DalPhos ligand for Nickel-catalyzed Amination

Although nickel is comparatively inexpensive versus palladium, the JosiPhos ligands (i.e. **L1-9**) used by the Stradiotto group in the first reported nickel-catalyzed mono-arylation of ammonia (Figure 3-1) are costly. Furthermore, while **L9-1** proved successful in the nickel-catalyzed mono-arylation of ammonia, it was observed that other ligands that performed well in the palladium cross-coupling of ammonia and aryl halides such as Mor-DalPhos[86] (**L1-3a**), BippyPhos[24j] (**L1-6**), and even structurally similar (CyPF-*t*Bu) (**L1-4**),[24a, 37] performed poorly when used with nickel.[42] Clearly the re-purposing of ligands developed with palladium will not be a universally effective strategy in developing nickel catalyst systems. In an effort to replace expensive JosiPhos ligands with simple modular ligands, the Stradiotto group was interested in designing a new ligand, capable of mediating the sought-after nickel-catalyzed mono-arylation of ammonia and other sought-after, yet challenging, cross-couplings. Ligands designed for palladium-catalyzed mono-arylation of ammonia are typically sterically hindered and electron-rich such as Mor-DalPhos, BrettPhos, BippyPhos, (Section 1.4). As discussed in Section 1.4, electron-rich ligands aid in the oxidative addition step of the catalytic cycle while the steric bulk of the ligand aids the reductive elimination step of the cycle. Given the higher propensity of nickel for $C(sp^2)$-Cl oxidative additions to Ni(0) versus Pd(0),[81a, 87] a sterically encumbered, and less

electron-rich ligand was envisioned. The 1,3,5,7-tetramethyl-2,4,8-trioxaphosphaadamantane, or cage phosphine (CgPH) had been used in ligands for palladium-catalyzed arylation of secondary amines, but was relatively under-explored in $C(sp^2)$-N cross-couplings.[88] The CgP group has roughly the steric profile of a di-tertbytl phosphine group and similar electronic properties to a $P(OR)_2$ group, [89] which met the criteria laid out above and thus was tested in multiple ligand structures. Chris Lavoie, a member of the Stradiotto group, synthesized multiple ligands containing the CgP fragment, leading to a new addition to the DalPhos ligand family, PAd-DalPhos (**L1-10**), which has a cheap, modular synthesis (Figure 3-2).
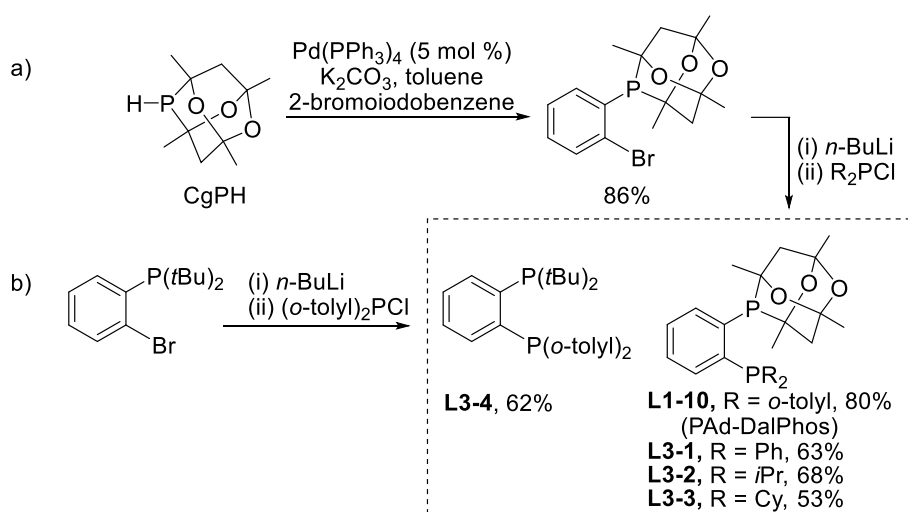
Figure 3-2: a) Synthesis of PAd-DalPhos and related ligands. b) Synthesis of **L3-4**, a close structural variant of PAd-DalPhos. (All synthesis by Chris Lavoie).

The CgPH can be P-C cross-coupled to 2-bromoiodobenzene using $Pd(PPh_3)_4$ using the conditions shown in Figure 3-2a. The CgP(o-bromophenyl) intermediate can than be reacted with *n*-BuLi and a chlorophosphine to produce ligand variants in a simple and efficient manner as demonstrated by the synthesis of **L3-1** – **L3-3** and **L1-10** (Figure 3-

2a). The synthesis of **L3-4** was carried out for comparison to PAd-DalPhos (**L1-10**) due to their similar steric profile (Figure 3-2b), but divergent electronic properties. PAd-DalPhos was superior to all other variants in the test reaction of mono-arylation of ammonia with 4-bromobiphenyl (yield of 90% estimated by GC).[43] Interestingly, if PAd-DalPhos is used with [Pd(cinnamyl)Cl]$_2$ instead of Ni(COD)$_2$ in the same test reaction there is minimal conversion to product (< 10% by GC) which supports the theory that PAd-DalPhos is apt for nickel catalysis.[43]

As mentioned in the introductory chapter (Section 1.4.2), it was desirable to move away from the air and moisture-sensitive, yet popular, nickel(0) source Ni(COD)$_2$,[41c, 90] and reap the benefits of a pre-catalyst. Moreover, the use of a pre-catalyst may improve reaction scope and yields by circumventing catalyst activation. While some air-stable nickel pre-catalysts have been developed previously, these often require an external reductant to bring nickel(0) into the catalytic cycle.[41a, 91] Hartwig and co-workers have developed a nickel(0) pre-catalyst (**C3-1**, Figure 3-3a) in their report on the first nickel-catalyzed amination of unactivated aryl chlorides with primary alphatic amines, but while this pre-catalyst provides high reactivity it is air and moisture sensitive.[40a]
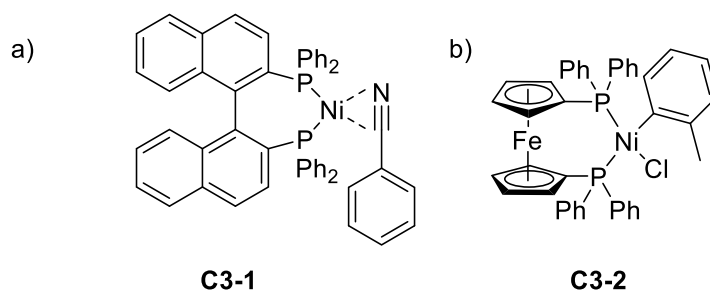

C3-1   **C3-2**

Figure 3-3: a) Hartwig's nickel pre-catalyst (**C3-1**). b) Buchwald's nickel pre-catalyst (**C3-2**).

Buchwald and co-workers have recently reported the development of an air-stable nickel pre-catalyst (Figure 3-3b, **C3-2**) for the amination of aryl chlorides and sulfonates with primary and secondary amines.[33] Pre-catalyst **C3-2** is an air-stable nickel(2+) complex that can be viewed as an oxidative addition intermediate in the catalytic cycle, which, can be synthesized from commercially available starting materials. The drawback to this type of oxidative addition complex pre-catalyst is that in catalysis the organic product will contain a percentage of the *o*-tolylamine equal to the amount of catalyst added, which further motivates low loading.[33] Research efforts in the Stradiotto group have focused on the development of air-stable pre-catalyst analogues of **C3-2**. Chris Lavoie prepared such a PAd-DalPhos nickel pre-catalyst (**C1-1**) (Figure 3-4) based on literature methods.[33, 38c]
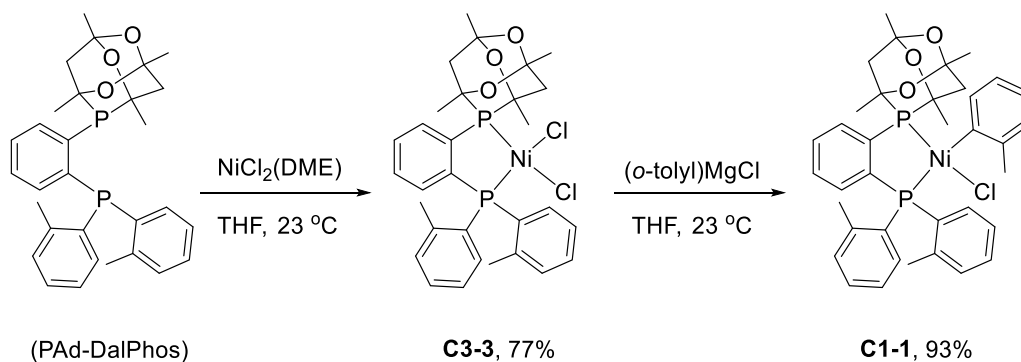

Figure 3-4: Synthesis of PAd-DalPhos based nickel pre-catalyst (**C1-1**).

The **C1-1** pre-catalyst was demonstrated to be air-stable by long term storage on the bench top before use and out-performed the analogous **L1-10**/Ni(COD)$_2$ combination in the mono-arylation of ammonia.[43] The useful performance and air-stability of **C1-1** make it an attractive choice for end users and is now commercially available.

3.2.3 State-of-the-Art Primary Amine Arylation

To complement the work of others in the Stradiotto group regarding ammonia mono-arylation using **C1-1**, it was desirable to explore the full synthetic utility of this new pre-catalyst in nickel-catalyzed amination, specifically in the realm of N-H coupling partners beyond ammonia such as primary and secondary amines for amination of (hetero)aryl (pseudo)halides. Formation of C(sp^2)-N bonds with primary amines in this simple fashion allows access to an array of nitrogen-containing molecules with potential applications in pharmaceutical synthesise.[92] As mentioned above, Hartwig and co-workers have developed a BINAP nickel pre-catalyst (**C3-1,** Figure 3-3a) for mono-arylation of primary amines.[40a] Although this work represents an important breakthrough in amine mono-arylation catalysis using a first row metal, there is much research to be done. Hartwig employs 1-4 mol % loading of nickel which is impressive, but further lowering catalyst loading is a perpetual goal in this chemistry, especially when using an oxidative addition-style-pre-catalyst (see Section 3.2.2). Also, it is best to avoid the use of excess reagents such as the amine, not only to simplify purification procedures, but to also conserve potentially highly valuable amine coupling partners. Conducting nickel-catalyzed amine mono-arylation reactions at room temperature is also highly desirable; as discussed in Section 2.2, room temperature reactions are operationally simple and may provide tolerance to a wider variety of (pseudo)aryl (hetero)halides and amine coupling partners. Reactivity of secondary amines as well as primary and secondary anilines should also be addressed further within the realm of nickel-catalyzed amination. The scope of aryl chlorides that have been employed in literature reports to date is impressive; however,

electron-rich aryl halides are problematic and require higher catalyst loading. Aryl bromides were also investigated mechanistically in Hartwig's report,[40a] but, as the authors mention, the scope of aryl bromides with nickel-catalyzed amine arylation is limited. There are also very few examples of sulfonate electrophiles used in nickel-catalyzed amination.[33] Chemoselective examples between primary and secondary amines are also desirable and should be further explored. Research efforts directed toward employing **C1-1** in addressing some of these challenges in nickel-catalyzed C(sp^2)-N cross-coupling is outlined in the following sections.

3.3 Results and Discussion

The initial goal in developing the substrate scope of arylation of primary amines with **C1-1**, was to improve upon the state-of-the-art methodology described above. Through optimization of the reaction parameters, conditions were found that met the desired criteria. Catalyst loading was kept relatively low (1-5 mol%) throughout the investigation of substrate scope and only 10% excess of the amine coupling partner was required for successful aminations. While some substrates required elevated temperatures to react, the vast majority of mono-arylation reactions were carried out at room temperature, a notable advantage compared to other nickel amination catalysts.[40a]

Compared to the initial screening reaction conditions for **C1-1** using ammonia, it was found that when employing primary amines, the amount of base could be halved from 3 to 1.5 equivalents, and the dioxane co-solvent was unnecessary, affording the conditions shown in Figure 3-5.
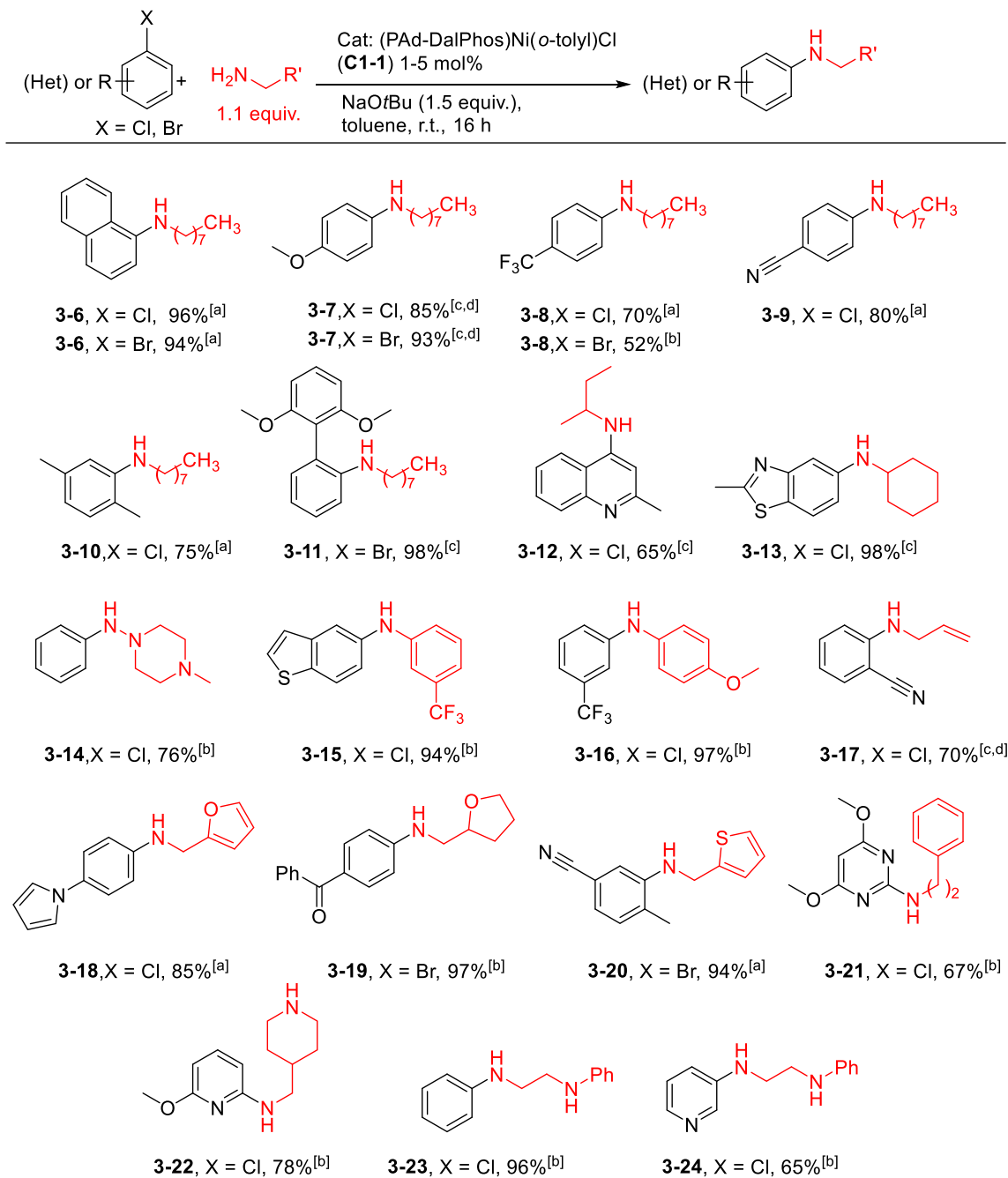
Figure 3-5: Scope of mono-arylation of primary amines employing **C1-1** and substituted (hetero)aryl chlorides and bromides (yields of isolated products reported). [a] Using 1 mol% **C1-1**. [b] Using 3 mol% **C1-1**. [c] Using 5 mol% **C1-1**. [d] Reaction conducted at 60 °C.

With these reaction conditions in hand the functional group tolerance of **C1-1** was evaluated by reacting aryl halides containing various functional groups with a simple amine substrate — octylamine. The catalyst was capable of tolerating electrophiles featuring electron-neutral (**3-6**) electron-donating (**3-7**) and electron-withdrawing (**3-8**, **3-9**) functional groups with both chloride and bromide leaving groups. It was noted that some electron-rich electrophiles required heating to 60 °C to produce products such as **3-7**, in keeping with the more challenging oxidative addition expected for such substances. Sterically hindered electrophiles were accommodated in products **3-10** and **3-11**. Beyond this initial survey with octylamine, further amine and (hetero)aryl halide combinations were explored. Branched primary alkylamines and anilines were successfully employed in the reaction scope with (hetero)aryl halides as shown by products **3-12** to **3-16** including a hydrazine derivative (**3-14**). Compound **3-17** is derived from an electrophile containing potentially coordinating nitrile group in the ortho position, and required heating to 60 °C to obtain a synthetically useful yield. Reactions producing products **3-18** to **3-20** employed amine coupling partners containing heterocycles without difficulty. 2-Chloro-4,6-dimethoxypyrimidine is a quite activated coupling partner, which could be prone to diarylation; however, the mono-arylation product (**3-21**) was achieved selectively. The uncatalyzed version of this reaction was performed as well, which confirmed that product **3-21** did not arise from an S_NAr background reaction. The preferred arylation of a primary alkylamine fragment in the presence of contending secondary amine groups by use of **C1-1** was demonstrated in the chemoselective formation of **3-22** to **3-24**. These transformations are in keeping with the observation that secondary dialkylamines (for

example, morpholine) are generally not suitable substrates for **C1-1** under the conditions outlined in Figure 3-5.

Given that **C1-1** was designed for the mono-arylation of ammonia, the smallest N-H coupling partner, it was desirable to explore reactivity with small amine coupling partners which are often challenging for the same reasons as ammonia. Figure 3-6 presents the application of mono-arylation methodology using **C1-1** to small amines methyl and dimethyl amine.
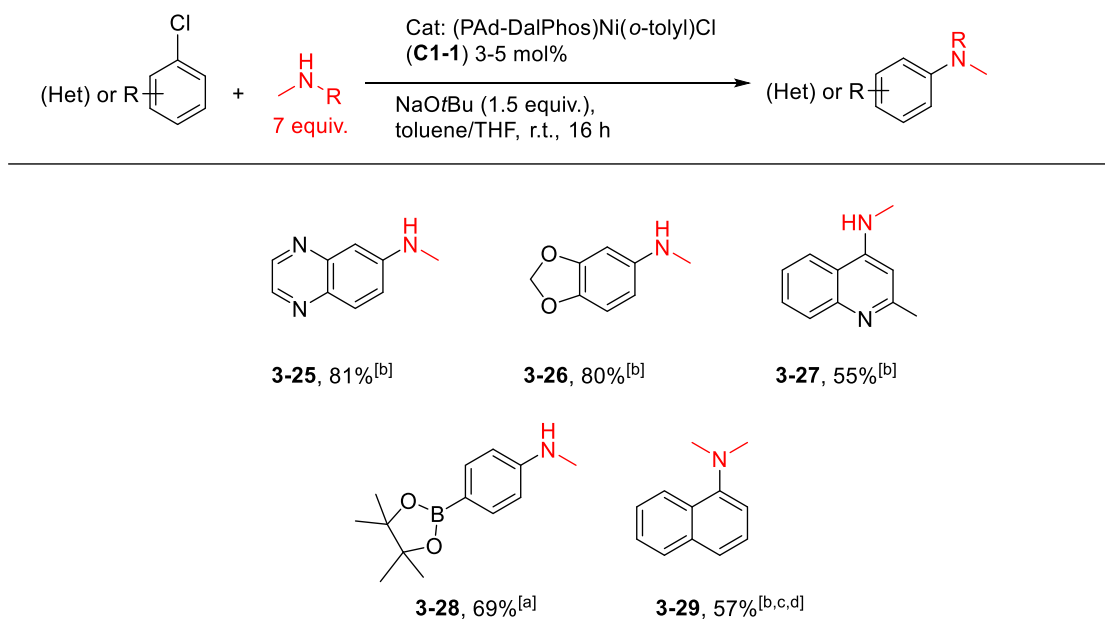

Figure 3-6: Mono-arylation of methyl and dimethyl amine employing **C1-1** and substituted (hetero)aryl chlorides (yields of isolated products reported). [a] Using 3 mol% **C1-1**. [b] Using 5 mol% **C1-1**. [c] Using 3 equivalents of amine. [d] Reaction conducted at 110 °C.

These inexpensive amine coupling partners are commercially available in stock solutions and thus were used in excess to favour mono-arylation, as is practiced with ammonia. Heteroaromatic scaffolds were well tolerated in coupling reactions with methyl amine including quinoxoline (**3-25**), dioxole (**3-26**), and quinaldine (**3-27**). The formation of the

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pinacolborane derivative **3-28** demonstrates the feasibility of conducting $C(sp^2)$–N cross-couplings employing **C1-1** in the presence of a potentially reactive pinacolborane moiety, which may be exploited subsequently in an orthogonal cross-coupling step. Lastly, the conditions described could be applied to dimethyl amine to afford product **3-29**, which is the only dialkyl secondary amine in the demonstrated reaction scope. The successful, although challenging (reaction temperature 110 °C, Figure 3-6), coupling of dimethyl amine is likely owed to its small size, which may enable it to fit into the relatively encumbered catalytically active site where other secondary amines cannot. It should be mentioned that fellow group member Ryan Sawatzky had success employing methyl and ethyl amine salts under microwave conditions with **C1-1**.

(Hetero)aryl chlorides and bromides were excellent substrates under the reaction conditions, but as mentioned in Section 3.2.3, phenol-derived pseudohalides also represent useful coupling partners and were previously under-explored in nickel-catalyzed amination.[33, 40a, 41c] Gratifyingly, tosylates could be converted to aryl amine products using **C1-1** without raising the temperature or otherwise adapting the reaction conditions (Figure 3-7).
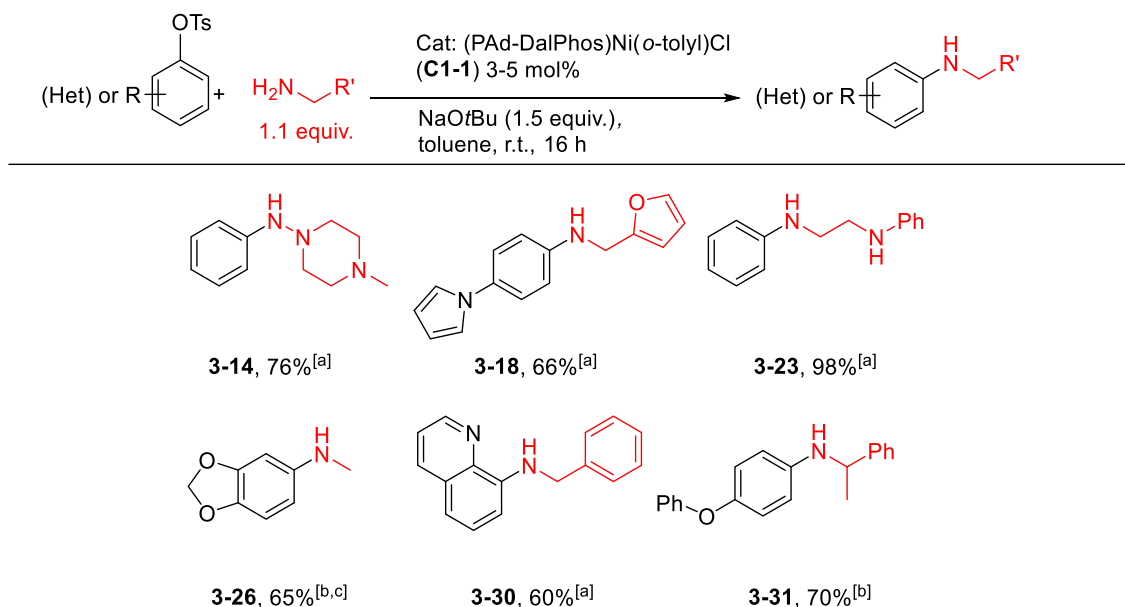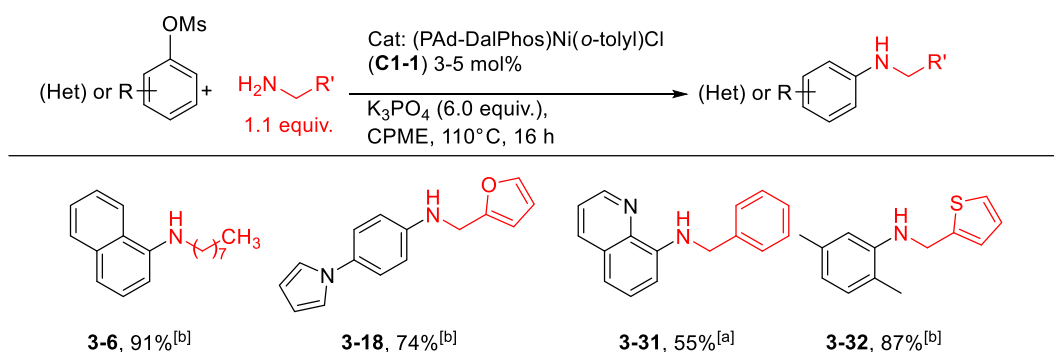
Figure 3-7: Mono-arylation primary amines employing **C1-1** and substituted (hetero)aryl tosylates (yields of isolated products reported). [a] Using 3 mol% **C1-1**. [b] Using 5 mol% **C1-1**. [c] Using 7 equivalents of amine.

Aryl tosylates were employed in a manner that mirrors the scope achieved with arylhalides; (hetero)aryl tosylate (**3-30**) and aryl tosylates containing heterocyclic addenda (**3-18**, **3-26**) were possible. Amine coupling partners included small (**3-26**), linear (**3-23**), branched (**3-14**, **3-31**), and heterocyclic containing (**3-18**) amines as well as a hydrazine derivative (**3-14**) and a primary amine containing a potentially competitive secondary amine fragment (**3-23**). In an effort to evaluate whether C(sp^2)–N cross-couplings employing **C1-1** and chiral amines could be conducted without racemization,[93] the room temperature cross-coupling of racemic and separately enantiopure α-methylbenzylamine leading to **3-31** was conducted; ^{1}H NMR analysis, employing a europium chiral shift reagent, of the **3-31** product thus formed indicated the absence of racemization when using enantiopure α-methylbenzyl amine, which could be important information to end users.

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Aryl mesylates are another pseudohalide of interest in $C(sp^2)$-N cross-coupling which was evaluated in this work. Aryl mesylate substrates are enticing due to the benefits over other pseudohalides since they are more atom-economical than analogous tosylates and more stable than analogous triflates.[94] The by-product, upon aqueous workup, of cross-coupling reactions using aryl mesylates is methanesulfonic acid, which is part of the natural sulfur cycle and can be subject to biodegradation.[95] Figure 3-8 shows the successful scope for (hetero)aryl mesylates aminated using **C1-1**.

Figure 3-8: Mono-arylation primary amines employing **C1-1** and substituted (hetero)aryl mesylates (yields of isolated products reported). [a] Using 3 mol% **C1-1**. [b] Using 5 mol% **C1-1**.

The conditions required for amination of (hetero)aryl mesylates are more forcing than those previously established for the other electrophiles employed. These conditions were adapted from a report by the Buchwald group disclosing amination of aryl mesylates (two examples) with anilines.[33] The examples in Figure 3-8 are the only (hetero)aryl mesylates aminated with primary alkylamines aside from one earlier report by Stradiotto and co-workers using a palladium catalyst.[19]

While other members of the group explored the scope of reactivity of **C1-1** with ammonia employing aryl halides and other aryl pseudohalides, the mono-arylation of ammonia using aryl mesylates was addressed as a separate challenge and this research is

presented here. **C1-1** was capable of mono-arylation of ammonia employing (hetero)aryl
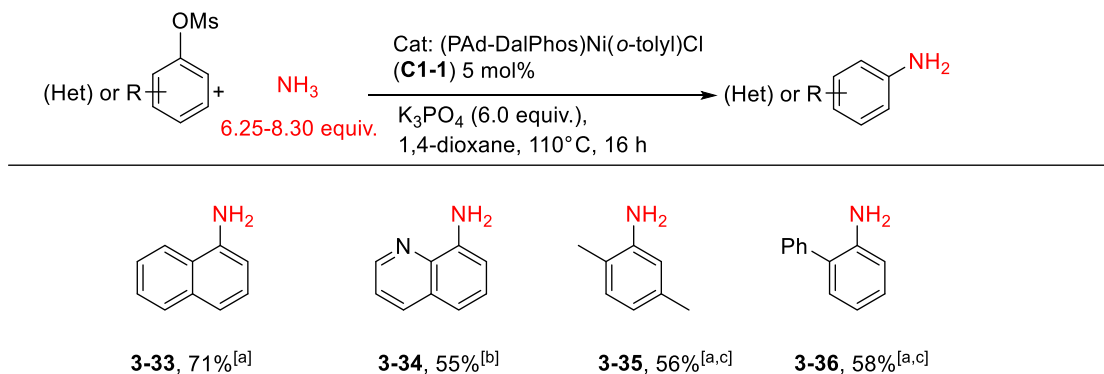
mesylates shown in Figure 3-9.

Figure 3-9: Mono-arylation of ammonia employing **C1-1** and substituted (hetero)aryl mesylates (yields of isolated products reported). [a] Using 8.30 equivalents of ammonia. [b] Using 6.25 equivalents of ammonia. [c] Yield determined on the basis of NMR integration using ferrocene as an internal standard.

The conditions employed in Figure 3-9 are, like those used for the mono-arylation of

primary amines using aryl mesylates (Figure 3-8), rather forcing. A great excess of

ammonia was required to achieve synthetically useful yields for most substrates and only

aryl mesylates with ortho substitution were accommodated in substantial yield.

Nonetheless, this is the only catalyst of any type known to complete this transformation.

3.4 Ineffective Applications of the Developed Mono-Arylation Methodology

Although the mono-arylation of primary amines using **C1-1** was generally successful,

not all of the envisioned applications and research goals were accomplished. The sections

below describe unsuccessful substrate scope with regards to the (hetero)aryl (pseudo)halide

and amine coupling partners.

3.4.1 Unsuccessful Coupling Partners for Mono-Arylation

During the initial survey of electrophile coupling partners in reactions with octylamine, there were aryl chlorides bearing certain functional groups that were not tolerated by **C1-1**. As shown in the top row of Figure 3-10 compounds **3-37** to **3-40** could not be produced by the coupling reaction of octylamine and various aryl chlorides.
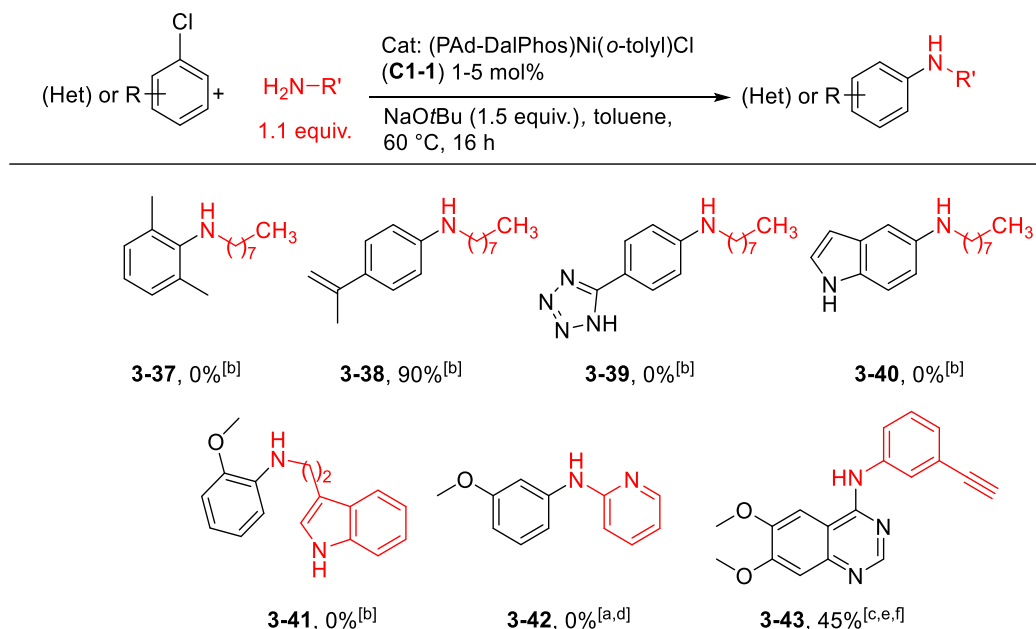
Figure 3-10: Examples of primary amine and aryl chloride coupling partners unable to be coupled using **C1-1** (yields on the basis of GC data reported). [a] Using 1 mol% **C1-1**. [b] Using 3 mol% **C1-1**. [c] Using 10 mol% **C1-1**. [d] Reaction conducted at room temperature. [e] Reaction conducted at 110 °C. [f] Isolated yield.

Despite the ability of **C1-1** to tolerate sterically hindered aryl chlorides with one group in the ortho position (compounds **3-10**, **3-11**), diortho substituted electrophiles such as 2,6-dimethylchlorobenzne gave no conversion to the corresponding product **3-37**, even at

elevated temperature (60°C). It was thought that amination reactions could be performed under the conditions above in the presence of alkenes, due to the formation of a single new product observed by GC data in attempts to synthesize compound **3-38**. However, several attempts to isolate the product **3-38** failed and only non-characterizable material was obtained, suggesting the product seen in the GC data was not the desired product. Compounds **3-39**, **3-40**, and **3-41** represent chemoselective amination products in which **C1-1** would prefer to react with primary amines over tetrazole and indoles respectively; however, no conversion of the starting materials was observed for these reactions. The (hetero)aryl chlorides corresponding to products **3-41** to **3-43** could be coupled to octylamine in high yield, but could not be used with the amines depicted in Figure 3-10. Employing 2-aminopyridine to generate product **3-42** was not possible under standard conditions (1 mol% **C1-1** at room temperature). Perhaps having the basic nitrogen of the pyridine ring in such close proximity to reacting amine allowed for the formation of a stable nickel complex, thus inhibiting catalysis. Successful synthesis of compound **3-43** would not only showcase the ability of **C1-1** to tolerate highly functionalized heteroaryl chlorides and terminal alkynes, but this molecule is also the core of Erlotinib, an anti-cancer drug.[96] Under forcing conditions (10 mol% **C1-1** at 110 °C) product **3-43** could be isolated in 45% yield. Further optimization of this reaction was not pursued due to the poor yield of **3-43** obtained from already forcing conditions, and the fact that Erlotinib and derivatives can be prepared more efficiently in high yields using metal free conditions.[97]

3.4.2 Unsuccessful Arylation of Secondary Amines

As mentioned previously, dimethyl amine was the only secondary alkylamine successfully arylated by use of **C1-1** (compound **3-29**, Figure 3-6). A variety of larger secondary amine coupling partners were assessed with an activated electrophile, but showed no conversion to the desired products (Figure 3-11).
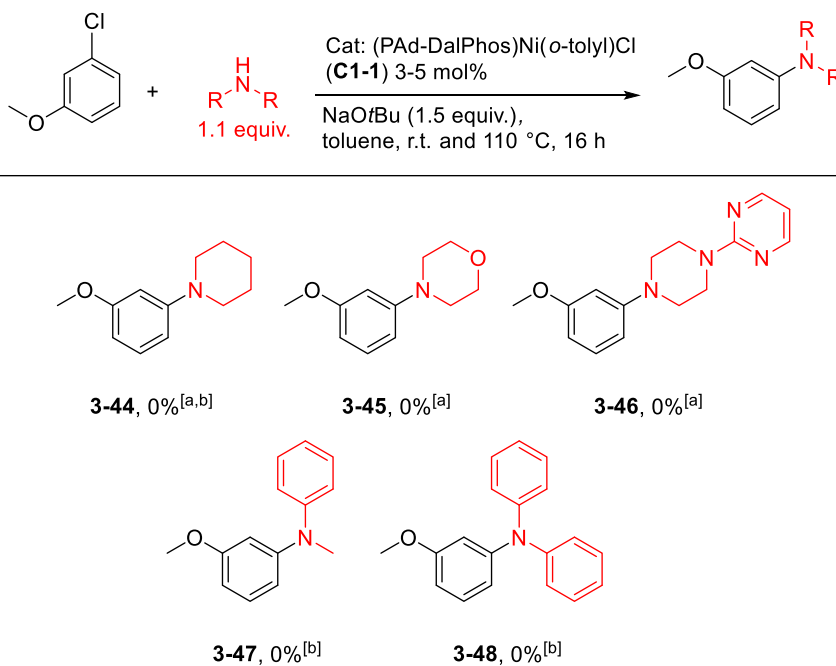
Figure 3-11: Examples of secondary amine coupling partners that could not be arylated by **C1-1** (yields on the basis of GC data reported). [a] Using 3 mol% **C1-1**. [b] Using 5 mol% **C1-1**.

Cyclic dialkyl, aryl alkyl, and diaryl secondary amines all failed to provide any conversion under the standard conditions and at elevated temperatures (110 °C). Interestingly, Dr. Andrey Borzenko was able to achieve modest yields with indole, azaindole and carbazole under forcing conditions (3 equivalents of sodium *tert*-butoxide, and 110°C). While these coupling partners are classified as secondary amines, they are planar and have a much

higher N-H acidity than the secondary alkylamines. It is possible that arylation of azoles is accomplished by a separate mechanism. In Section 1.4 the accepted mechanism of Buchwald-Hartwig amination describes the amine binding to the metal which causes the N-H acidity to rise allowing the deprotonation by the base. In the case of azoles, the N-H acidity is great enough that the base can deprotonate it without the aid of the metal catalyst. When the larger amines are already deprotonated, perhaps coordination to the metal is easier, thus allowing the cross-coupling to proceed. Further optimization and attempts to generate arylated secondary amine products were not persued. Nickel-catalyzed arylation of secondary amines has been known since Buchwald's pioneering report[41c] and other excellent nickel catalyst systems have been developed since[33, 41l, 98] including work from the Stradiotto group employing DPEPhos.[99]

3.4.3 Unsuccessful Amination of Five-membered (Hetero)aryl Electrophiles

Five-membered heterocycles are common fragments in pharmaceutical compounds,[100] but can be difficult in $C(sp^2)$-N cross-coupling reactions.[101] Use of five-membered (hetero)aryl halides in palladium-catalyzed $C(sp^2)$-N cross-coupling has been achieved by Buchwald and co-workers for the arylation of primary amines, secondary amines, anilines,[101a, 102] and amides.[103] Attempts were made to utilize five-membered rings as electrophiles in nickel-catalyzed amination with **C1-1** as outlined in Figure 3-12.
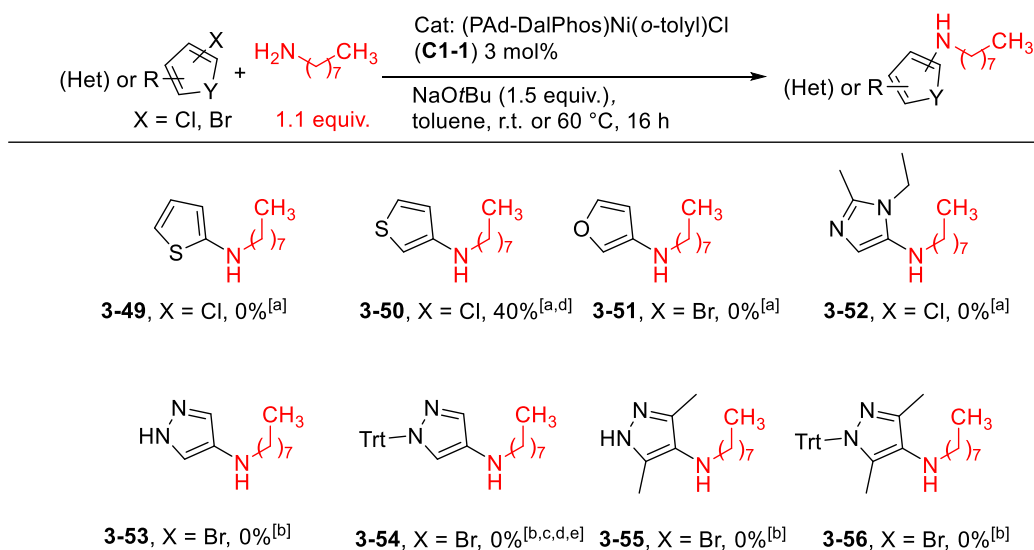
Figure 3-12: Examples of unsuccessful five-membered heteroaryl electrophile coupling partners in mono-arylation of octylamine using **C1-1** (yields on the basis of GC data reported). [a] room temperature. [b] Reaction conducted at 60 °C. [c] Reaction conducted at 110 °C. [d] Separate trials using lithium *tert*-butoxide and lithium bis(trimethylsilyl)amide instead of sodium *tert*-butoxide. [e] Separate trials using sodium hydride and cesium carbonate instead of sodium *tert*-butoxide.

Efforts to aminate several of these electrophiles with octylamine were unsuccessful. Halo thiophene (**3-49**, **3-50**), furan (**3-51**), and imidazole (**3-52**) substrates were subjected to the standard conditions at room temperature, but only 3-chlorothiophene gave any conversion. The yield of product **3-50** was not improved by changing the base to lithium *tert*-butoxide or lithium bis(trimethylsilyl)amide. Bromopyrazoles were also assessed in this amination methodology. Dimethyl substituted pyrazoles are regarded to be far more resistant to degradation compared to their unsubsituted counterparts. However, given the failure of **C1-1** to aminate other dimethyl substituted electrophiles, as discussed in Section 3.4.1, unsubstituted pyrazoles (**3-53** and **3-54**) were evaluated as well as dimethyl substituted pyrazoles (**3-55** and **3-56**). Similar reasoning was behind the evaluation of pyrazoles with (**3-54** and **3-56**) and without (**3-53** and **3-55**) the trityl protecting group. The trityl group is

quite bulky and may hinder the access of the substrate to the catalyst active site, but it also may prevent the free N-H (possibly deprotonated) from coordinating to the metal and inhibiting catalysis. In all cases the pyrazoles were shown to be unsuitable substrates for **C1-1** under the conditions shown (3 mol% of **C1-1** at 60 °C). Synthesis of compound **3-54** was attempted again separately with several different bases at 110 °C to no avail. It is unclear why five-membered (hetero)aryl halides coupling partners are so challenging for **C1-1**.

3.5 Conclusions

In conclusion, the pre-catalyst **C1-1**, featuring the sterically demanding and relatively electron-poor bisphosphine ancillary ligand **L1-9** (PAd-DalPhos), enables the first reports of nickel-catalyzed mono-arylation of primary alkylamines at room temperature. The demonstrated substrate scope contains a wide variety of primary amine and (hetero)aryl (pseudo)halide coupling partners employed under unprecedented mild conditions, with 29 examples of room temperature reactions and with only 0.1 excess equivalents of the amine coupling partner employed. The **C1-1** pre-catalyst has enabled examples of mono-arylation of ammonia involving (hetero)aryl mesylates, for which no capable catalyst system of any type had been described previously. Development of **C1-1** contributes towards the identification of high-performing nickel catalysts for use in synthetically important cross-coupling applications, and provides an alternative to the use of precious metals such as palladium.

Since the publication of this work there have been other effective methods to obtain arylated primary amine products reported. Nickel-catalyzed arylation of primary and secondary alkylamines using 4,4′-Di-*tert*-butyl-2,2′-dipyridyl ligand and electrochemistry was reported by Baran and co-workers.[104] This report demonstrates a diverse scope of coupling partners and contains some room temperature examples. Buchwald and MacMillan have recently published a nickel photo-catalyzed method which requires no ligand.[105] Primary amines, secondary amines, and anilines can be arylated with (hetero)aryl bromides and iodides including many complex drug like molecules demonstrated by co-workers at Merck. Methods complementary to mono-arylation for the acquisition of arylated amine products using nickel catalysis have also been reported recently such as the alkylation of anilines using alcohols as substrates by Banerjee and co-workers.[106]

3.6 Experimental

3.6.1 General Considerations and Procedures

General considerations. Unless otherwise stated, all reactions were set up inside a nitrogen-filled inert atmosphere glovebox, and were worked up in air using benchtop procedures. Toluene was deoxygenated by sparging with nitrogen followed by passage through a double column solvent purification system packed with alumina and copper-Q5 reactant, and storage over activated 4 Å molecular sieves. Cyclopentyl methyl ether (CPME) was degassed by use of three repeated freeze–pump–thaw cycles and was stored over activated 4Å molecular sieves. All other reagents, solvents and materials were used

as received from commercial sources. Flash column chromatography was carried out using Silicycle SiliaFlash 60 silica (particle size 40–63 mm; 230–400 mesh) or using neutral alumina (150 mesh; Brockmann-III; activated), as indicated. All ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 K in CDCl$_3$ with chemical shifts expressed in parts per million (p.p.m.) using the residual CHCl$_3$ solvent signal (^{1}H, 7.26 p.p.m.; ^{13}C, 71.4 p.p.m.) as an internal reference. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, with all coupling constants (J) reported in Hertz (Hz). In some cases, fewer than expected independent ^{13}C NMR resonances were observed despite prolonged acquisition times. Mass spectra were obtained using ion trap (ESI) instruments operating in positive mode, and GC data were obtained on an instrument equipped with a SGE BP-5 column (30 m, 0.25 mm i.d.). Pre-catalyst C1-1 was synthesized following a literature procedure.[43] Aryl mesylates and Aryl tosylates were synthesized following a literature procedure.[107]

General Catalytic Procedure for the Amination of Aryl Halides with Primary Amines (GP3-1). Unless specified otherwise in the text, PAd-DalPhosNi(o-tol)Cl (**C1-1**) (10.3 mg, 0.015 mmol, 3 mol%), NaOtBu (72.3 mg, 0.75 mmol, 1.5 equivalents), (psedo)aryl halide (0.5 mmol, 1.0 eq), amine (0.55 mmol, 1.1 equivalents) and toluene (4.67 mL) were added to a screw-capped vial containing a small magnetic stir bar. The vial was sealed with a cap containing a PTFE septum, and left to stir vigorously for 16 hours at room temperature. The reaction progress was monitored qualitatively by use of GC methods. The crude reaction mixture was dissolved in ethyl acetate (10 mL) and poured onto brine (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic fractions were combined, dried over Na$_2$SO$_4$ and concentrated under

reduced pressure. The crude residue was purified by use of column chromatography over alumina or silica.

General Catalytic Procedure for the Amination of Aryl Halides with Methyl and Dimethylamine (GP3-2). Unless specified otherwise in the text, PAd-DalPhosNi(*o*-tol)Cl (**C1-1**) (17.2 mg, 0.025 mmol, 5 mol%), NaO*t*Bu (72.3 mg, 0.75 mmol, 1.5 equivalents), (psedo)aryl halide (0.5 mmol, 1.0 equivalents), followed by the addition of amine as a 2M amine solution in THF (1.75 mL, 3.5 mmol, 7.0 equivalents) were added to a screw-capped vial containing a small magnetic stir bar. The vial was sealed with a cap containing a PTFE septum, and left to stir vigorously for 16 hours at room temperature. The reaction progress was monitored qualitatively by use of GC methods. The crude reaction mixture was dissolved in ethyl acetate (10 mL) and poured onto brine (10 mL). The layers were separated and the aqueous 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 use of column chromatography over alumina or silica.

General Catalytic Procedure for the Amination of Aryl Mesylates with Primary Amines (GP3-3). Unless specified otherwise in the text, PAd-DalPhosNi(*o*-tol)Cl (**C1-1**) (17.2 mg, 0.025 mmol 5 mol%), K_3PO_4 (636.8 mg, 3 mmol, 6.0 equivalents), aryl mesylate (0.5 mmol, 1.0 equivalents), amine (0.55 mmol, 1.1 equivalents) and CPME (2.00 mL) were added to a screw-capped vial containing a small magnetic stir bar. The vial was sealed with a cap containing a PTFE septum, and left to stir vigorously for 16 hours at 110°C. The reaction progress was monitored qualitatively by use of GC methods. The crude reaction mixture was dissolved in ethyl acetate (10 mL) and poured onto brine (10 mL). The layers were separated and the aqueous 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 use of column chromatography over alumina or silica.

General Catalytic Procedure for the Amination of Aryl Mesylates with Primary Amines (GP3-4). Unless specified otherwise in the text, PAd-DalPhosNi(*o*-tol)Cl (**C1-1**) (4.14 mg, 0.006 mmol, 5 mol%), K_3PO_4 (152.8 mg, 0.72 mmol, 6.0 equivalents), aryl mesylate (0.12 mmol, 1.0 equivalents), followed by the addition of NH_3 as a 0.5 M Ammonia solution in 1,4-dioxane (1.5 mL, 0.75 mmol, 6.25 eq) were added to a screw-capped vial containing a small magnetic stir bar. The vial was sealed with a cap containing a PTFE septum, and left to stir vigorously for 16 hours at 110°C. The reaction progress was monitored qualitatively by use of GC methods. The crude reaction mixture was dissolved in ethyl acetate (10 mL) and poured onto brine (10 mL). The layers were separated and the aqueous 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 use of column chromatography over alumina or silica.

3.6.2 Synthesis and Characterization Data

N-(1-naphthyl)-Octylamine (3-6)
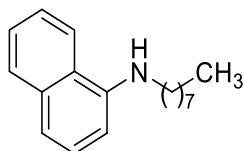

Following **GP3-1**: (0.50 mmol 1-chloro-naphthylene, 0.55 mmol octylamine, 1 mol% **C1-1**) the title product was isolated as a yellow oil in 96% yield. A 1% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.85-7.82 (m, 2H), 7.50-7.45 (m, 2H), 7.41-7.38 (m, 1H), 7.30-7.26 (m, 1H), 6.66 (d, J = 8.5 Hz, 1H), 4.35 (br s, 1H), 3.32-3.30 (m, 2H), 1.85-1.80 (m, 2H), 1.57-1.51 (m, 2H), 1.45-1.35 (m, 8H) 0.96 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 143.9, 134.6, 128.9, 126.9, 125.9, 124.8, 123.6, 120.0, 117.4, 104.5, 44.6, 32.3, 29.7, 29.6, 27.6, 22.9, 14.4; Following **GP3-1** the title product was isolated as a yellow oil in 94% yield from the corresponding bromide). Following **GP3-3** the title product was isolated as a yellow oil in 91% yield from the corresponding mesylate, 5 mol% **C1-1**) A 2% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. Spectral data are consistent with the literature.[108]

4-Methoxy-N-octylaniline (3-7)
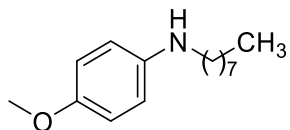
Following **GP3-1**: (0.50 mmol 4-chloroanisole, 0.55 mmol octylamine, 5 mol% **C1-1**, stirred at 60 °C) the title product was isolated as a dark yellow oil in 85% yield. A 5% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel.
^{1}H NMR (300 MHz, CDCl$_3$): δ 6.82-6.79 (m, 2H), 6.62-6.58 (m, 2H), 3.77 (s, 3H), 3.35 (br s, 1H), 3.11-3.06 (m, 2H), 1.67-1.58 (m, 2H), 1.46-1.31 (m, 10H), 0.91 (t, J = 11.3 Hz, 3H); ^{13}C{^{1}H} NMR (75.5 MHz, CDCl$_3$): δ 152.0, 143.0, 114.9, 114.0, 55.9, 45.0, 31.8, 29.7, 29.4, 29.3, 27.2, 22.7, 14.1; Following **GP3-1** the title product was isolated as a dark yellow oil in 93% yield from the corresponding bromide, 5 mol% **C1-1** stirred at 60°C). Spectral data are in agreement with the literature.[40a]

N-Octyl-4-(trifluoromethyl)anilinie (3-8)
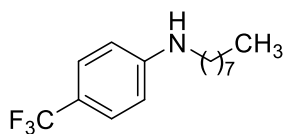
Following **GP3-1**: (0.50 mmol 1-chloro-4-(trifluoromethyl)benzene, 0.55 mmol octylamine, 1 mol% **C1-1**) the title product was isolated as a yellow oil in 70% yield. A 1% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.44-7.42 (m, 2H), 6.63-6.61 (m, 2H), 3.97 (br s, 1H), 3.19-3.15 (m, 2H), 1.69-1.64 (m, 2H), 1.47-1.42 (m, 2H), 1.37-1.32 (m, 8H), 0.93 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 151.1, 126.8 (d, J_{CF} = 3.7 Hz), 126.4 (d, J_{CF} = 269 Hz), 118.8 (d, J_{CF} = 38.4 Hz), 112.0, 43.8, 32.1, 29.6, 29.5, 29.4, 27.4, 22.8, 14.3 Following **GP3-1** the title product was isolated as a yellow oil in 52% yield from the corresponding bromide, 3 mol% **C1-1**). Spectral data are in agreement with the literature.[40a]

4-(Octylamino)benzonitrile (3-9)
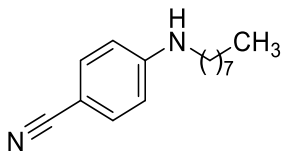
Following **GP3-1**: (0.50 mmol 4-chlorobenzonitrile, 0.55 mmol octylamine, 1 mol% **C1-1**) the title product was isolated as a yellow solid in 80% yield. A 5% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.46-7.44 (m, 2H), 6.58-6.56 (m, 2H), 4.18 (br s, 1H), 3.19-3.15 (m, 2H), 1.69-1.63 (m, 2H), 1.46-1.40 (m, 2H), 1.38-1.32 (m, 8H), 0.92 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 151.6, 133.9, 130.1, 120.8, 112.3, 98.7, 43.5, 32.0, 29.5, 29.4, 27.3, 22.9, 14.3; Spectral data are in agreement with the literature.[40a]

2,5-Dimethyl-*N*-octylaniline (3-10)
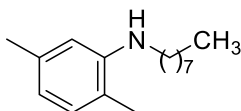
Following **GP3-1**: (0.50 mmol 2-chloro-1,4-dimethylbenzene, 0.55 mmol octylamine, 1 mol% **C1-1**) the title product was isolated as a yellow oil in 75% yield. A 1% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.98-6.96 (m, 1H), 6.51-6.48 (m, 2H), 3.43 (br s, 1H), 3.18 (t, J = 6.6 Hz, 2H), 2.34 (s, 3H), 2.13 (s, 3H), 1.74-1.68 (m, 2H), 1.50-1.44 (m, 2H), 1.38-1.34 (m, 8H), 0.94 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 146.6, 136.9, 130.1, 118.9, 117.5, 110.8, 44.3, 32.6, 29.9, 29.7, 29.5, 27.4, 22.9, 21.9, 17.3, 14.4; Spectral data are in agreement with the literature.[40a]

2',6'-dimethoxy-*N*-octylamine (3-11)
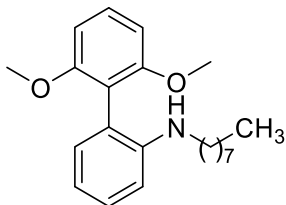
Following **GP3-1**: (0.50 mmol 2′-bromo-2,6-dimethoxybiphenyl, 0.55 mmol octylamine, 5 mol% **C1-1**) the title product was isolated as a light brown oil in 98% yield. A 0% to 5% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.34 (t, J = 8.4 Hz, 1H), 7.29-7.23 (m, 1H), 7.04-7.01 (m, 1H), 6.80-6.74. (m, 2H), 6.70 (s, 1H), 6.68 (s, 1H), 3.74 (s, 6H), 3.47 (br s, 1H), 3.14-3.09 (m, 2H), 1.56-1.46 (m, 2H), 1.34-1.27 (m, 10H), 0.92-0.88 (m, 3H); ^{13}C{^{1}H} NMR (75.5 MHz, CDCl$_3$): δ 158.4, 146.5, 131.2, 129.1, 128.5, 120.0, 116.4, 116.0, 110.5, 104.3, 56.0, 44.2, 31.9, 29.4, 29.3, 29.2, 27.0, 22.6, 14.1; HRMS *m/z* ESI$^+$ found 342.2428 [M+H]$^+$ calculated for C$_{22}$H$_{32}$NO$_2$ 342.2433.

***Sec*-Butyl-(2-methyl-quinolin-4-yl)amine (3-12)**
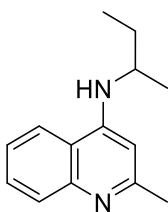
Following **GP3-1**: (0.50 mmol 4-chloroquinaldine, 0.55 mmol *sec*-butylamine, 5 mol% **C1-1**, stirred at 25 °C) the title product was isolated as a white solid in 65% yield. A 1% trimethylamine, 39% hexane, 60% ethyl acetate eluent system was used for column chromatography on silica gel. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.93-7.90 (m, 1H), 7.69-7.65 (m, 1H), 7.63-7.58 (m, 1H), 7.40-7.35 (m, 1H), 6.35 (br s, 1H), 4.74-4.72 (m, 1H),

3.74-3.60 (m, 1H), 2.64 (s, 3H), 1.83-1.59 (m, 2H), 1.34 (d, J = 6.8 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (125.8 MHz, CDCl$_3$): δ 159.8, 149.0, 148.8, 129.6, 129.2, 123.9, 119.1, 117.6, 99.4, 49.7, 29.7, 26.1, 20.1, 10.6; HRMS m/z ESI$^+$ found 215.1543 [M+H]$^+$ calculated for C$_{14}$H$_{19}$N$_2$ 215.1548.

Cyclohexyl-(2-methyl-benzothiazol-5-yl)-amine (3-13)
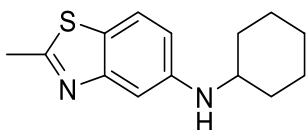
Following **GP3-1**: (0.50 mmol 5-chloro-2-methylbenzothiazole, 0.55 cyclohexylamine, 5 mol% **C1-1**, stirred at 25 °C) the title product was isolated as a white solid in 98% yield. A 15% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^1H NMR (500 MHz, CDCl$_3$): δ 7.55 (d, J = 8.5 Hz, 1H), 7.12-7.18 (m, 1H), 6.70-6.68 (m, 1H), 3.66 (br s, 1H), 3.37-3.32 (m, 1H), 2.81 (s, 3H), 2.17-2.14 (m, 2H), 1.84-1.78 (m, 2H), 1.73-1.68 (m, 1H), 1.47-1.39 (m, 2H) 1.32-1.18 (m, 3H); $^{13}C\{^1H\}$ NMR (125.8 MHz, CDCl$_3$): δ 167.6, 155.4, 146.7, 123.8, 121.7, 114.1, 104.8, 52.4, 33.5, 26.2, 25.3, 20.3; HRMS m/z ESI$^+$ found 247.1263 [M+H]$^+$ calculated for C$_{14}$H$_{19}$N$_2$S 247.1269.

4-methyl-*N*-phenylpiperazin-1-amine, (3-14)
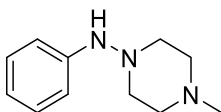
Following **GP3-1**: (0.50 mmol chlorobenzene, 5.5 mmol 4-methyl-1-piperazinamine, 3 mol% **C1-1**, stirred at 25 °C) the title product was isolated as a white solid in 76% yield. A 1% triethylamine, 2% methanol, 97% ethyl acetate eluent system was used for column chromatography on silica gel. ^1H NMR (500 MHz, CDCl$_3$): δ 7.24-7.21 (m, 2H), 6.94-

6.92 (m, 2H), 6.84-6.80 (m, 1H), 4.38 (br s, 1H), 2.82 (s, 4H), 2.60 (s, 4H), 2.37 (s, 3H);

^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 147.7, 129.4, 119.7, 113.9, 56.0, 55.4.3, 46.0;

Following **GP3-1**: (3 mol% **C1-1**) the title product was isolated as a dark yellow oil in

76% yield from the corresponding tosylate. Spectral data are in agreement with the

literature.[19]

Benzo[b]thiophen-5-yl-(3-trifluoromethyl-phenyl)- amine (3-15)
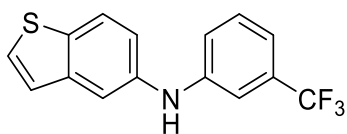
Following **GP3-1**: (0.50 mmol 5-chlorobenzothiophene, 0.55 mmol 3-(trifluoride)aniline,

3 mol% **C1-1**, stirred at 25 °C) the title product was isolated as a green crystalline solid in

94% yield. A 100% hexane to 5% ethyl acetate/hexanes eluent system was used for column

chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.86 (d, J = 8.6 Hz, 1H),

7.62-7.61 (m, 1H), 7.52 (d, J = 5.4 Hz, 1H), 7.39-7.36 (m, 1H), 7.29-7.28 (m, 2H), 7.23-

7.21 (m, 1H), 7.19-7.15 (m, 2H), 5.90 (br s, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ

145.0, 140.8, 138.6, 134.4, 132.0, 131.7, 129.9, 127.8, 123.5, 123.4, 119.2, 118.8, 116.6,

114.1, 112.7 (q, J_{CF} = 30.4 Hz); HRMS m/z ESI$^+$ found 294.0559 [M+H]$^+$ calculated for

C$_{15}$H$_{11}$F$_3$NS 294.0564.

(4-Methoxy-phenyl)-(3-trifluoromethyl-phenyl)- amine (3-16)
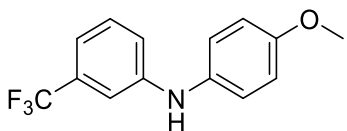
Following **GP3-1**: (0.50 mmol 3-chlorobenzotrifluoride, 0.55 mmol 4-methoxyaniline, 3

mol% **C1-1**, stirred at 25 °C) the title product was isolated as a black oil in 97% yield. A

10% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.33-7.32 (m, 1H), 7.14-7.11 (m, 3H), 7.08-7.06 (m, 1H), 7.05-7.03 (m, 1H), 6.95-6.93 (m, 2H), 5.65 (br s, 1H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 156.5, 146.3, 134.6, 130.0, 123.8, 118.1, 115.9, 115.2, 111.6, 55.8; Spectral data are in agreement with the literature.[109]

2-Allylamino-benzonitrile (3-17)
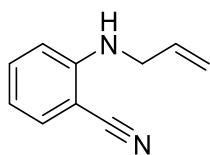
Following **GP3-1**: (0.12 mmol 2-chloro-benzonitrile, 0.132 mmol allylamine, 5 mol% **C1-1**, stirred at 60 °C) the title product was isolated as a yellow oil in 70% yield. A 30% DCM/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.44-7.39 (m, 2H), 6.74-6.68 (m, 2H), 5.99-5.92 (m, 1H), 5.36-5.32 (m, 1H), 5.27-5.25 (m, 1H), 4.77 (br s, 1H), 3.92-3.90 (m, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 150.3, 134.4, 134.0, 132.9, 118.1, 117.3, 116.9, 111.2, 96.1, 46.2; Spectral data are consistent with the literature.[110]

Furan-2-ylmethyl-(4-pyrrol-1-yl-phenyl)-amine (3-18)
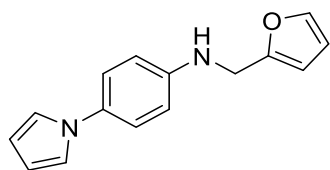
Following **GP3-1**: (0.50 mmol 1-(4-chlorophenyl)-1H-pyrrole, 0.55 mmol furfurylamine, 1 mol% **C1-1**, stirred at 25 °C) the title product was isolated as white solid in 85% yield. A 100% hexane to 5% ethyl acetate/hexanes eluent system was used for column

chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.42-7.41 (m, 1H), 7.27-7.24 (m, 2H), 7.01-6.99 (m, 2H), 6.76-6.73 (m, 2H), 6.38-6.37 (m, 1H), 6.34-6.33 (m, 2H), 6.30-6.29 (m, 1H), 4.38 (s, 2H), 4.11 (br s, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 152.7, 146.1, 142.3, 132.8, 122.7, 120.1, 114.0, 110.7, 109.7, 107.3, 41.9; Following **GP3-1**: (3 mol% **C1-1**) the title product was isolated as a white solid in 66% yield from the corresponding tosylate. A 10% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. Following **GP3-3**: (5 mol% **C1-1**) the title product was isolated as a white solid in 74% yield from the corresponding mesylate. A 10% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. HRMS m/z ESI$^+$ found 239.1179 [M+H]$^+$ calculated for C$_{15}$H$_{15}$N$_2$O 239.1184.

Phenyl-{4-[(tetrahydro-furan-2-ylmethyl)- amino]-phenyl}-methanone (3-19)
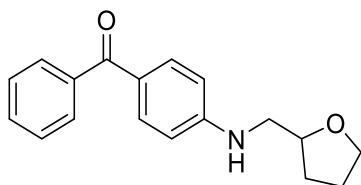
Following **GP3-1**: (0.50 mmol 4-benzophenone, 0.55 mmol tetrhydrofurfurylamine, 3 mol% **C1-1**, stirred at 25 °C) the title product was isolated as a yellow oil in 97% yield. A 10% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.78-7.74 (m, 4H), 7.57-7.54 (m, 1H), 7.50-7.47 (m, 2H), 6.65-6.63 (m, 2H), 4.64 (br s, 1H), 4.20-4.17 (m, 1H), 3.97-3.92 (m, 1H), 3.86-3.82 (m, 1H), 3.41-3.39 (m, 1H), 3.23-3.18 (m, 1H), 2.13-2.06 (m, 1H), 2.01-1.95 (m, 2H), 1.73-1.66 (m, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 152.2, 139.2, 132.9, 131.1, 129.4, 128.0, 126.2, 111.8, 68.4, 47.3, 29.1, 25.8; HRMS m/z ESI$^+$ found 304.1308 [M+Na]$^+$ calculated for C$_{18}$H$_{19}$NNaO$_2$ 304.1313

4-Methyl-3-[(thiophen-2-ylmethyl)-amino]-benzonitrile (3-20)
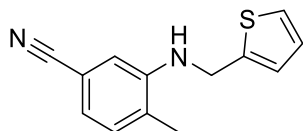
Following **GP3-1**: (0.50 mmol 3-bromo-4-methylbenzonitrile, 0.55 mmol 2-thiophenemethylamine, 1 mol% **C1-1**, stirred at 25 °C) the title product was isolated as a yellow solid in 94% yield. An 8% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.29-7.27 (m, 1H), 7.16-7.13 (m, 1H), 7.07-7.05 (m, 1H), 7.03-6.98 (m, 2H), 6.88-6.87 (m, 1H), 4.58 (d, J = 5.6 Hz, 2H), 2.22 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 146.1, 141.7, 130.9, 127.9, 127.4, 125.8, 125.3, 121.8, 120.1, 112.7, 110.9, 43.4, 18.0; HRMS m/z ESI$^+$ found 251.0613 [M+Na]$^+$ calculated for C$_{13}$H$_{12}$N$_2$NaS 251.0619.

(4,6-Dimethoxy-pyrimidin-2-yl)-phenethyl-amine (3-21)
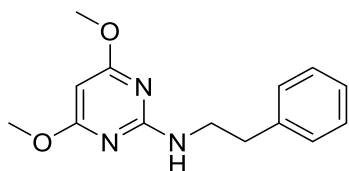
Following **GP3-1**: (0.50 mmol 2-chloro-4,6-dimethoxypyrimidine, 0.55 mmol phenethylamine, 3 mol% **C1-1**, stirred at 25 °C) the title product was isolated as a white solid in 67% yield. A 5% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.36-7.30 (m, 2H), 7.27-7.21 (m, 2H), 5.43 (s, 1H), 4.96 (br s, 1H), 3.87 (s, 6H), 3.72-3.65 (m, 2H), 2.93 (t, J = 12.0 Hz, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 172.2, 161.7, 139.4, 128.8, 128.5,

78.7, 53.5, 42.8, 36.0; HRMS m/z ESI$^+$ found 260.1394 [M+H]$^+$ calculated for $C_{14}H_{18}N_3O_2$ 260.1399.

(6-Methoxy-pyridin-2-yl)-piperidin-4-ylmethyl-amine (3-22)
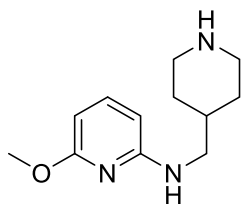
Following **GP3-1**: (0.50 mmol 2-chloro-6-methoxypyridine, 0.55 mmol 4-(aminomethyl)piperidine, 3 mol% **C1-1**, stirred at 25 °C) the title product was isolated as a clear solid in 78% yields. The reaction mixture was cooled and filtered through a short plug of alumina and washed with ethyl acetate (50 mL) and the product was collected with methanol (40 mL). After concentrating the methanol solution under reduced pressure, the crude product was purified by washing with cold hexanes (3 x 5 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.34 (t, J = 8.0 Hz 1H), 6.04 (d, J = 7.8 Hz 1H), 5.95 (d, J = 8.0 Hz 1H), 4.53-4.49 (m, 1H), 4.04 (s, 2H), 3.85 (s, 3H), 3.39-3.35 (m, 2H), 3.26-3.21 (m, 2H), 2.81-2.72 (m, 2H), 1.94-1.87 (m, 2H), 1.59-1.45 (m, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 163.9, 157.9, 140.3, 98.1, 97.5, 53.4, 47.6, 45.0, 35.6, 28.6; HRMS m/z ESI$^+$ found 222.1601 [M+H]$^+$ calculated for $C_{12}H_{20}N_3O$ 222.1606.

***N,N'*-Diphenyl-ethane-1,2-diamine (3-23)**
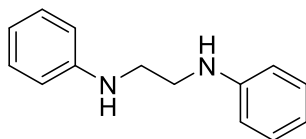
Following **GP3-1**: (0.50 mmol chlorobenzene, 0.55 mmol *N*-phenylethylenediamine, 3 mol% **C1-1**, stirred at 25 °C) the title product was isolated as a white solid in 96% yield.

The reaction mixture was cooled and filtered through a short plug of silica on Celite and washed with dichloromethane (40 mL). After concentrating the so-formed mixture under reduced pressure, the crude product was purified by washing with cold hexanes (3 x 5 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.26-7.21 (m, 4H), 6.80-6.75 (m, 2H), 6.70-6.68 (m, 4H), 3.88 (s, 2H), 3.43 (s, 4H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 148.0, 129.3, 117.8, 113.0, 43.3; Following **GP3-1**: (3 mol% **C1-1**) the title product was isolated as a white solid in 98% yield from the corresponding tosylate. Spectral data are consistent with the literature.[24j]

N^1-Phenyl-N^2 -(pyridin-3-yl)ethane-1,2-diamine (3-24)
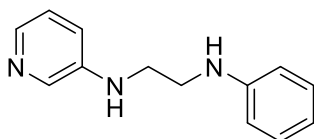
Following **GP3-1**: (0.50 mmol 3-chloropyridine, 0.55 mmol *N*-phenylethylenediamine, 3 mol% **C1-1**, stirred at 25 °C) the title product was isolated as a pale yellow oil in 65% yield. The reaction mixture was cooled and filtered through a short plug of silica on Celite and washed with dichloromethane (40 mL). After concentrating the so-formed mixture under reduced pressure, the crude product was purified by washing with cold hexanes (3 x 5 mL). ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.10-8.08 (m, 1H), 8.03-8.01 (m, 1H), 7.28-7.19 (m, 2H), 7.14-7.09 (m, 1H), 6.94-6.91 (m, 1H), 6.80-6.75 (m, 1H) 6.70-6.68 (m, 2H), 3.99 (br s, 1H), 3.88 (br s, 1H), 3.44 (s, 4H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 147.8, 144.0, 139.2, 136.3, 129.4, 123.7, 118.7, 118.0, 113.1, 43.1, 42.9; Spectral data are consistent with the literature.[111]

Methyl-quinoxalin-6-yl-amine (3-25)
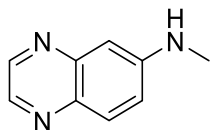
Following **GP3-2**: (0.60 mmol 6-chloroquinoxaline, 4.2 mmol methylamine, 5 mol% **C1-1**, stirred at 25 °C, 0.085M concentration of aryl halide) the title product was isolated as a neon yellow solid in 81% yield. A 60% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.68 (d, J = 2.2 Hz, 1H), 8.54 (d, J = 2.0 Hz, 1H), 7.88 (d, J = 9.1 Hz, 1H), 7.17-7.15 (m, 1H), 7.00-6.99 (m, 1H), 4.31 (br s, 1H), 3.04 (d, J = 5.2 Hz, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 145.7, 145.0, 143.4, 140.4, 138.2, 130.1, 122.0, 103.3, 30.5; Spectral data are in agreement with the literature.[112]

Benzo[1,3]dioxol-5-yl-methyl-amine (3-26)
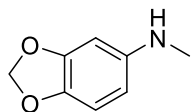
Following **GP3-2**: (0.60 mmol 5-chloro-1,3-benzodioxole, 4.2 mmol methylamine, 5 mol% **C1-1**, stirred at 25 °C) the title product was isolated as a dark yellow oil in 80% yield. A 12% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.72 (d, J = 8.3 Hz, 1H), 6.29 (d, J = 2.4 Hz, 1H), 6.09-6.07 (m, 1H), 5.89 (s, 2H), 3.51 (br s, 1H), 2.83 (m, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 147.2, 145.3, 139.6, 108.6, 103.8, 100.5, 95.6, 31.7; Following **GP3-1**: (5 mol% **C1-1**) the title product was isolated as a dark yellow oil in 65% yield from the corresponding tosylate. A 60% dichloromethane/hexanes eluent system was used for

column chromatography on silica gel. Spectral data are in agreement with the literature.[19]

Methyl-(2-methyl-quinolin-4-yl)amine (3-27)
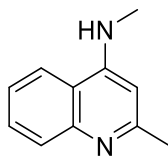
Following **GP3-2**: (0.50 mmol 4-chloroquinaldine, 3.5 mmol methylamine, 5 mol% **C1-1**, stirred at 25 °C) the title product was isolated as a white solid in 55% yield. A 2% trimethylamine, 38% hexane, 60% ethyl acetate eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.97-7.95 (m, 1H), 7.70-7.68 (m, 1H), 7.65-7.61 (m, 1H), 7.42-7.38 (m, 1H), 6.38 (s, 1H), 5.00 (br s, 1H), 3.09 (d, J = 5.0 Hz 3H), 2.67 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 159.9, 150.8, 148.4, 129.5, 129.2, 124.1, 119.2, 117.6, 99.0, 30.3, 26.0; Spectral data are in agreement with the literature.[113]

4-(_N_-Methylamino)phenylboronic acid pinacol ester (3-28)
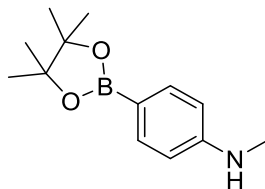
Following **GP3-2**: (0.24 mmol 4-chlorophenylboronic acid pinacol ester, 1.68 mmol methyl amine, 3 mol% **C1-1**) the title product was isolated as a clear colourless oil in 69% yield. A 10% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.70-7.68 (m, 2H), 6.63-6.61 (m, 2H), 3.96 (br s, 1H), 2.89-2.88 (m, 3H), 1.37-1.36 (s, 12H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 152.0,

136.5, 111.7, 83.4, 30.5, 25.1; HRMS m/z ESI$^+$ found 234.1660 [M+H]$^+$ calculated for $C_{13}H_{21}BNO_2$ 234.1665.

1-(*N,N*-dimethylamino)naphthalene (3-29)
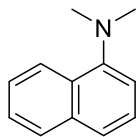
Following **GP3-2**: (0.60 mmol 1-chloronaphthylene, 1.8 mmol dimethylamine, 5 mol% **C1-1**, stirred at 110 °C) the title product was isolated as a brown liquid in 57% yield. A 2% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.29-8.27 (m, 1H), 7.87-7.84 (m, 1H), 7.57-7.48 (m, 3H), 7.46-7.40 (m, 1H), 7.13-7.10 (m, 1H), 2.95-2.94 (m, 6H); ^{13}C{^{1}H} NMR (75.5 MHz, CDCl$_3$): δ 145.7, 145.0, 143.4, 140.4, 138.2, 130.1, 122.0, 103.3, 30.5; Spectral data are in agreement with the literature.[114]

Benzyl-quinolin-8-yl-amine (3-30)
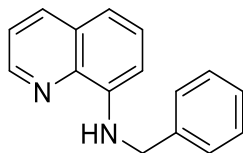

Following **GP3-1**: (0.50 mmol toluene-4-sulfonic acid quinolin-8-yl ester, 0.55 mmol Benzylamine, 3 mol% **C1-1**, stirred at 25 °C) the title product was isolated as a yellow oil in 60% yield. A 5% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.77-8.76 (m, 1H), 8.12-8.10 (m, 1H), 7.50-7.48 (m, 2H), 7.43-7.30 (m, 5H), 7.11-7.10 (m, 1H), 6.70-6.69 (m, 1H), 6.55 (br s, 1H), 4.61-4.60 (m, 2H); ^{13}C{^{1}H} NMR (75.5 MHz, CDCl$_3$): δ 159.8,

149.0, 148.8, 129.6, 129.2, 123.9, 119.1, 117.6, 99.4, 49.7, 29.7, 26.1, 20.1, 10.6;

Following **GP3-3**: (3 mol% **C1-1**) the title product was isolated as a yellow oil in 55%

yield from the corresponding mesylate. Spectral data are consistent with the literature.[115]

(4-Phenoxy-phenyl)-(1-phenyl-ethyl)-amine (3-31)
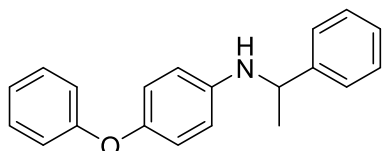
Following **GP3-1**: (0.50 mmol toluene-4-sulfonic acid 4-phenoxy-phenyl ester, 0.55

mmol alpha-methylbenzylamine, 5 mol% **C1-1**) the title product was isolated as a yellow

oil in 70% yield. A 5% ethyl acetate/hexanes eluent system was used for column

chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.43-7.41 (m, 2H), 7.39-

7.36 (m, 2H), 7.31-7.26 (m, 3H), 7.04-7.01 (m, 2H), 6.94-6.92 (m, 2H), 6.86-6.84 (m,

2H), 6.56-6.53 (m, 2H), 4.51 (q, J = 13.4 Hz, 1H), 4.04 (br s, 1H), 1.58 (d, J = 6.7 Hz,

3H); ^{13}C{^{1}H} NMR (75.5 MHz, CDCl$_3$): δ 159.0, 147.9, 145.2, 144.0, 129.4, 128.7,

126.9, 125.9, 121.9, 121.0, 117.2, 114.2, 54.0, 25.1; Spectral data are consistent with the

literature.[116] In an effort to evaluate whether such cross-couplings could be conducted

with retention of stereochemistry within the α-methylbenzylamine substrate, the cross-

coupling reaction was repeated using (*S*)-(−)-α-methylbenzylamine. In each case, the

product **3-31** formed from the racemic and separately the enantiopure α-

methylbenzylamine starting material was dissolved in CDCl$_3$ (0.6 mL) and treated with

europium tris[(heptafluoropropylhydroxymethylene)-(+)-camphorate] (ca. 8-10 mg); the

^{1}H NMR spectrum of each mixture was then obtained. Notably, the ^{1}H NMR spectrum of

3-31 synthesized from racemic α-methylbenzylamine displayed two equal-intensity

methyl resonances (doublets), in keeping with the racemic nature of the α-methylbenzylamine starting material. In contrast, only a single doublet methyl resonance was observed in the case of **3-31** prepared from (S)-(−)-α-methylbenzylamine under analogous conditions. These observations provide qualitative confirmation that racemization of the (S)-(−)-α- methylbenzylamine starting material under cross-coupling conditions leading to **3-31** does not occur.

(2,5-Dimethyl-phenyl)-thiophen-2-ylmethyl-amine (3-32)
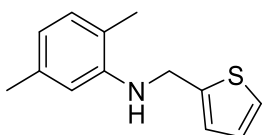
Following **GP3-3**: (0.50 mmol methane sulfonic acid 2,5-dimethyl-phenyl ester, 0.55 mmol 2-thiophenemethylamine, 5 mol% **C1-1**) the title product was isolated as a yellow oil in 87% yield. A 5% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.29-7.28 (m, 1H), 7.10-7.08 (m, 1H), 7.04-7.01 (m, 2H), 6.59-6.58 (m, 2H), 4.60 (s, 2H), 3.86 (br s, 1H), 2.34 (s, 3H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 145.7, 143.3, 137.0, 130.2, 127.1, 125.3, 124.8, 119.5, 118.5, 111.3, 43.7, 21.8, 17.3; HRMS *m/z* ESI$^+$ found 218.0998 [M+H]$^+$ calculated for C$_{13}$H$_{16}$NS 218.1003.

Naphthalen-1-amine (3-33)
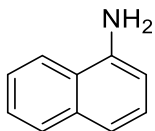
Following **GP3-4** (0.50 mmol methane sulfonic acid naphthalen-1-yl ester, 4.15 mmol ammonia, 5 mol% **C1-1**) the title compound was isolated in 71% yield from the

corresponding mesylate. A 5% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.88-7.84 (m, 2H), 7.51-7.49 (m, 2H), 7.36-7.29 (m, 2H), 6.82 (m, 1H), 4,17 (br s, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 142.3, 134.6, 128.8, 126.5, 126.0, 125.1, 123.9, 121.0, 109.1. Spectral data are consistent with the literature.[42]

Quinolin-8-ylamine (3-34)
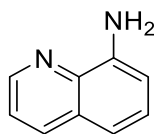
Following **GP3-4**: (0.50 mmol methane-4-sulfonic acid quinolin-8-yl ester, 3.125 mmol ammonia, 5 mol% **C1-1**) the title compound was isolated in 53% yield from the corresponding mesylate. A 50% DCM/hexanes to 10% NEt$_3$/hexanes eluent system was used for column chromatography on silica gel followed by an acidic work up with ethyl acetate 1 M HCl$_{(aq)}$ and distilled water. The organic fractions were combined, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to yield as a orange oil in 53% yield. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.81-8.79 (m, 1H), 8.11-8.10 (m, 1H), 7.41-7.36 (m, 2H), 7.20-7.18 (m, 1H), 6.98-6.96 (m, 1H), 5.02 (br s, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 147.6, 144.2, 138.7, 136.2, 129.1, 127.6, 121.5, 116.3, 110.2; Spectral data are in agreement with the literature.[117]

2,5-Dimethylaniline (3-35)
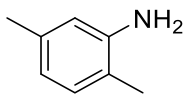
Following **GP3-4**: (0.12 mmol methanesulfonic acid 2,5-dimethyl-phenyl ester, 1.0 mmol ammonia, 5 mol% **C1-1**) the title product was made in 56% yield on the basis of NMR integration using ferrocene as an internal standard.

[1,1'-Biphenyl]-2-amine (3-36)
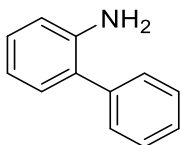
Following **GP3-4**: (0.12 mmol methanesulfonic acid biphenyl-2-yl ester, 1.0 mmol ammonia, 5 mol% **C1-1**) the title product was made in 58% yield on the basis of NMR integration using ferrocene as an internal standard.

CHAPTER 4 Nickel-Catalyzed Mono-Arylation of Amides

4.1 Contributions

This chapter describes the development of the first nickel-catalyzed *N*-arylation of amides using **C1-1**. This project was conducted in collaboration with Chris M. Lavoie who was responsible for the initial discovery, ligand screen, control reactions, initial optimization, and isolation of cross-coupling products with primary amides and aryl halides. The author's contributions consist of further optimization of the catalyst and reaction conditions utilizing pseudohalide coupling partners, isolation of derived cross-coupling products with primary amides and lactams, and characterization of reported compounds herein. The contributions of each author are noted in the text and are mentioned when relevant throughout the chapter. This work is published (*Chem. Eur. J.* **2016**, *22*, 18752–18755).

4.2 Introduction

The aryl amide organic fragment can be found in many biologically active molecules including synthetic drugs[65c, 118] and natural products.[119] Due to their abundant presence in such important molecules there has been much interest in synthesizing aryl amides. The earliest synthetic pathways to these products were developed by Goldberg in his adaptation of the Ullmann reaction using copper[120] and there have been many improvements on this classical reaction.[80, 121] Following the discovery of palladium-catalyzed arylation of

lactams by Shakespeare[48g] further advancements were made to widen the scope of the reaction[24j, 32a, 48b-d, 121a, 121b] including the use of difficult electrophiles such as aryl mesylates[48e] and five-membered heterocycles.[103] Amides can be particularly difficult nucleophiles compared to primary and secondary amines due to their ability to coordinate with nitrogen and oxygen to the metal center and inhibit catalysis.[122] While the current state-of-the-art amide arylation requires palladium and copper catalysis, there are many benefits to moving toward protocols using nickel catalysis as described in Section 3.2.

As described in Chapter 3, nickel-catalyst **C1-1** proved effective in amination reactions employing ammonia, primary amine, aniline, and azole nucleophiles. It was of interest to further explore the utility of **C1-1** in cross-coupling reactions within the realm of C(sp^2)-N bond formation and nickel-catalyzed amidation had not yet been addressed.

A current major research area in nickel catalysis is activation of amides via C-N oxidative addition (Figure 4-1).
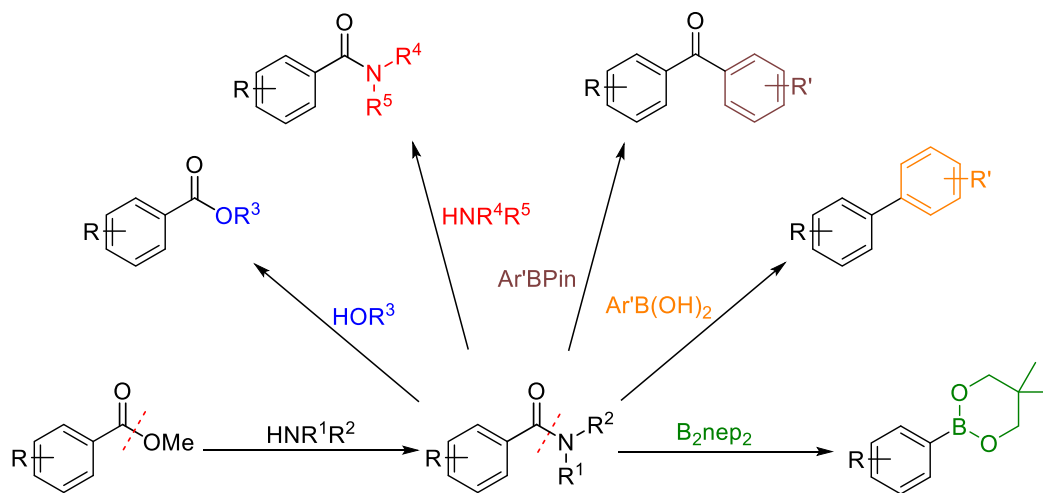
Figure 4-1: Examples of nickel-catalyzed transformations of twisted amides to provide various organic products.

Nickel is capable of C-N bond cleavage when this bond is sufficiently unstable, which is dependent on the groups the nitrogen is bearing,[123] typically benzyl and/or *tert*-butyloxycarbonyl (Boc). Work in this area includes many remarkable nickel-catalyzed transformations utilizing these "twisted" amides. The amides can be generated from esters[124] or used to produce new esters.[45] New amides can be produced as well via transamidation.[44] Through coupling with organoboronates it is possible to produce diaryl ketones,[46] or bi-aryl Suzuki type products through C-N bond cleavage followed by CO deinsertion.[47] Organoborane products can also be formed by a similar route through reaction with diboron compounds (Figure 4-1).[125] Despite all the successful work with amides in nickel catalysis, the *N*-arylation of amides was an unknown transformation prior the work herein.

4.3 Results and Discussion

The initial catalyst screening and optimization for the nickel-catalyzed amidation of aryl halides was conducted by graduate student Chris Lavoie. Several ligands that had proven successful in palladium-catalyzed amidation featured in the reports mentioned above, were screened for reactivity in nickel-catalyzed amidation. However, PAd-DalPhos was found to be superior. Several base and solvent combinations were found to be useful in the amidation reaction employing **C1-1**, and these needed to be optimized empirically for given substrate combinations. Separate optimization was required for the use of pseudohalide electrophiles; this is outlined in Figure 4-2.
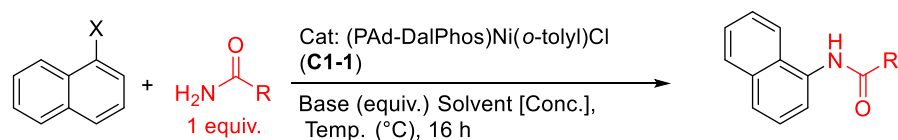
Entry #	Cat. (mol%)	X	R	Base (equiv.)	Solvent [Conc.]	Temp. (°C)	GC yield
1	5	OMs	CH_3	Cs_2CO_3 (1.5)	1,4-dioxane [0.12]	80	35%
2	5	OTs	CH_3	Cs_2CO_3 (1.5)	1,4-dioxane [0.12]	80	15%
3	10	OMs	CH_3	Cs_2CO_3 (1.5)	1,4-dioxane [0.12]	110	25%
4	10	OTs	CH_3	Cs_2CO_3 (1.5)	1,4-dioxane [0.12]	110	25%
5	10	OTs	CH_3	Cs_2CO_3 (6)	1,4-dioxane [0.12]	110	50%
6	10	OTs	CH_3	Cs_2CO_3 (6)	tBuOH [0.12]	110	60%
7	5	OTs	CH_3	NaOtBu (1.5)	toluene [0.06]	90	0%
8	5	OTs	py	NaOtBu (1.5)	toluene [0.12]	90	85%
9	5	OTs	py	NaOtBu (1.5)	toluene [0.06]	90	95%
10	5	OMs	py	K_3PO_4 (1.5)	tBuOH [0.12]	90	55%
11	5	OMs	py	K_3PO_4 (6)	tBuOH [0.12]	90	10%
12	5	OMs	py	K_3PO_4 (1.5)	tBuOH [0.06]	90	55%
13	5	OMs	py	K_3PO_4 (1.5)	1,4-dioxane [0.06]	90	70%
14	5	OMs	py	K_3PO_4 (1.5)	toluene [0.06]	90	80%
15	5	OTs	py	K_3PO_4 (1.5)	toluene [0.06]	90	60%
16	5	OTf	py	K_3PO_4 (1.5)	toluene [0.06]	90	50%
17	5	$OS(O)_2N(CH_3)_3$	py	K_3PO_4 (1.5)	toluene [0.06]	90	80%
18	5	OTs	py	K_3PO_4 (3)	toluene [0.06]	90	60%
19	5	OTf	py	K_3PO_4 (3)	toluene [0.06]	90	100%
20	5	$OS(O)_2N(CH_3)_3$	py	K_3PO_4 (3)	toluene [0.06]	90	100%
21	5	OTs	CH_3	K_3PO_4 (3)	toluene [0.06]	90	100%

Figure 4-2: Optimization of nickel-catalyzed amidation of pseudohalides including OTs, OMs, OTf, and $OS(O)_2N(CH_3)_2$ using **C1-1** (yields on the basis of GC data rounded to the nearest 5% reported). Concentrations in mol/L with respect to aryl pseudohalide.

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Initial catalyst screening efforts were conducted using cesium carbonate and 1,4-dioxane at 80 °C, since these conditions functioned well for some aryl halides. The reaction partners chosen were a relatively simplistic amide (acetamide) and 1-naphthyl mesylate and tosylate (entries 1 and 2). As shown in Figure 4-2, these conditions resulted in minimal conversation to the desired product and increasing the catalyst loading to 10 mol% and the temperature to 110 °C did not provide satisfactory improvement (entries 3 and 4). Increasing the equivalents of base to 6, in 1,4-dioxane and separately in *tert*-butanol, resulted in much higher yields, but still not full conversion of the simple reaction partners (entries 5 and 6). Sodium *tert*-butoxide and toluene were investigated next and showed no turnover to the desired product (entry 7) when using acetamide. However, when the amide coupling partner was changed to nicotinamide, nearly full conversion was achieved (entries 8 and 9), suggesting a difference in reactivity between alkyl and aryl amides. While these conditions would be tolerable for the aryl tosylate electrophiles, new conditions would need to be found to employ base-sensitive pseudohalides such as mesylates and triflates. Continuing with nicotinamide as the amide coupling partner, weak base conditions were sought for aryl mesylate electrophiles. Entries 10-12 show reactions employing potassium phosphate and *tert*-butanol at various equivalents and concentrations that were found previously to be favorable in aminations employing aryl mesylates.[19] Although these conditions provided some fair yields, large amounts of phenol were detected on the basis of GC analysis. Much higher yields were found by switching to aprotic solvents 1,4-dioxane and toluene in entries 13 and 14, respectively. Conditions from entry 14 were then applied to 1-naphthyl tosylate, triflate and sulfamate in entries 15, 16, and 17, respectively, resulting in decent yields of the target product. Increasing the base loading to 3 equivalents

of potassium phosphate resulted in greatly improved yields for all but the 1-naphthyl tosylate reaction (entries 18-20). When acetamide was employed under the same conditions, 1-naphthyl tosylate gave full conversion to the aryl amide product (entry 21). The conditions described in entries 18-21 were in general considered to be suitable, but further optimization was required for specific substrate combinations with respect to the concentration, amount of base, and catalyst loading.

Successful examples of amidation of activated (hetero)aryl (pseudo)halides using **C1-1** are shown in Figure 4-3.
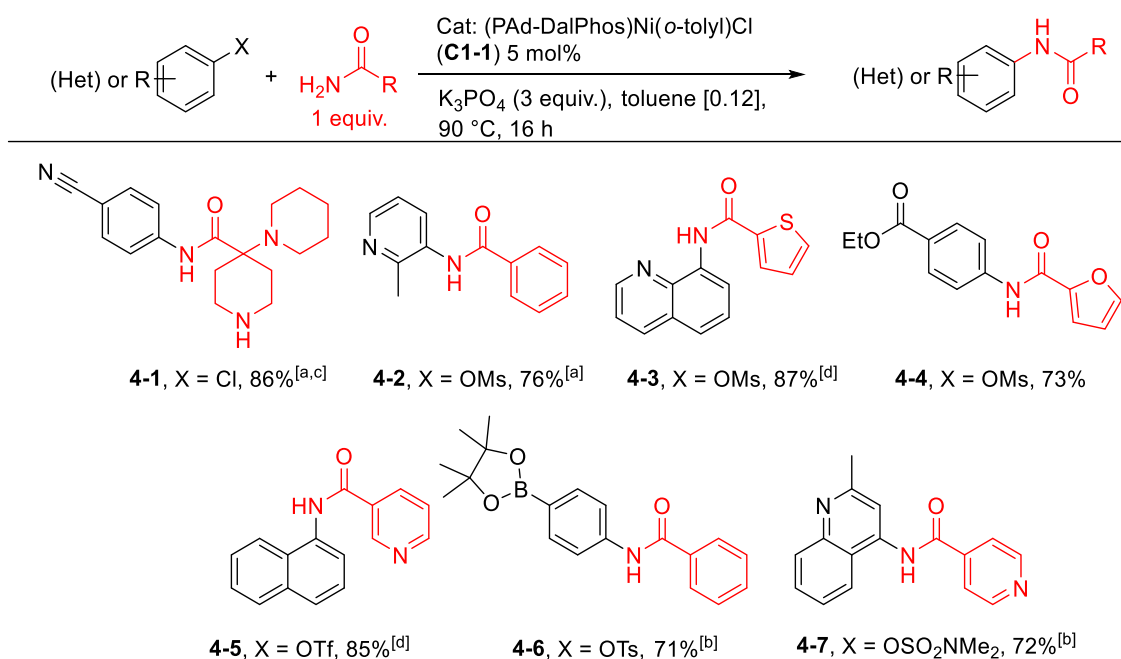
Figure 4-3: Amidation of (hetero)aryl (pseudo)halides with primary amides using **C1-1** (yields of isolated products reported). [a] Using 15 mol% **C1-1**. [b] Using 10 mol% **C1-1**. [c] Using 1.5 equivalents of potassium phosphate. [d] Using 0.06 M with respect to the aryl (pseudo)halide.

Under the conditions shown in Figure 4-3, many electrophiles can be employed for amidation using **C1-1** such as chloride (**4-1**), mesylate (**4-2**, **4-3**, **4-4**), triflate (**4-5**), tosylate

(4-6), and sulfamate (4-7). Heteroaryl functionality could be tolerated in both reaction partners (4-2, 4-3, 4-4, 4-7). Notably, the transformation can be completed in the presence of an unprotected secondary amine, as evidenced by the ability of **C1-1** to react exclusively with the primary amide to yield product **4-1**, which is the core of an anti-psychotic drug pipamperone.[126] The boronic pinacol ester moiety of compound **4-6** is also retained during the amidation reaction and can be used in later transformations.

Although acyclic secondary amides were not accommodated in the scope of reactivity by **C1-1**, lactams could be arylated in good yield using the described protocol in Figure 4-4.
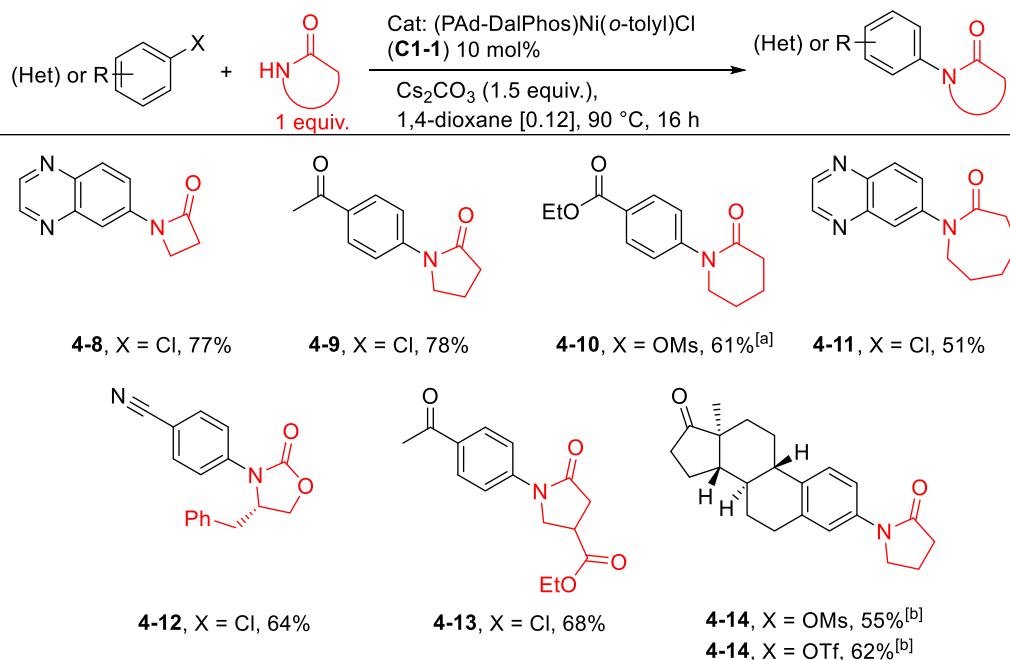
Figure 4-4: Arylation of lactams with (hetero)aryl (pseudo)halides using **C1-1** (yields of isolated products reported). [a] Using potassium phosphate (1.5 equivalents) and toluene [0.12]. [b] Using 15 mol% **C1-1**, potassium phosphate (3 equivalents) and toluene [0.12].

Lactams generally required higher catalyst loading than the primary amides; however, lactams of ring sizes from 4-7 were arylated in modest yields (**4-8**, **4-9**, **4-10**, **4-11**).

Interesting examples include arylation of a commonly used Evans auxiliary (**4-12**), and another lactam with substitution on the lactam ring (**4-13**). Racemization of the chiral oxazolidone (**4-12**) did not occur as evidenced by ^{1}H NMR analysis, employing a europium chiral shift reagent. Pseudohalide electrophiles were also compatible with lactams as shown by the formation of products **4-10** and **4-14**, which contains the biologically active molecule estrone, generated from the corresponding mesylate and triflate.

4.4 Ineffective Applications of the Developed Amidation Methodology

As discussed above the reaction conditions for the *N*-arylation of primary amides using **C1-1** were often substrate dependent. The scope of reactivity in the electrophile contains only electron-neutral and electron-withdrawing (activated) functional groups. Electrophiles containing electron-donating groups, such as 4-chloroanisole, could not be tolerated. Due to the temperamental nature of the reaction conditions, some of the envisioned applications and research goals were not accomplished. The sections below describe unsuccessful substrate scope with regards to the amide coupling partner and the unsuccessful synthesis of pharmaceutical compounds containing an aryl amide fragment.

4.4.1 Unsuccessful Amide Coupling Partners

Many amide coupling partners were unsuitable substrates for use in cross-coupling reactions with **C1-1** under a variety of reaction conditions. Figure 4-5 shows several amides that could not be cross-coupled successfully, even when paired with typically facile electrophile coupling partners.
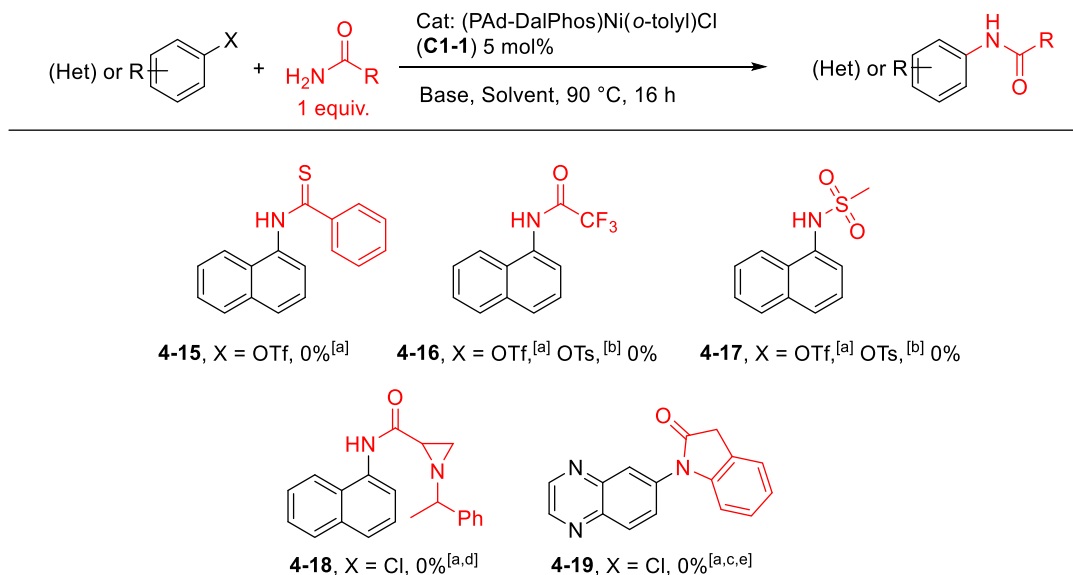
Figure 4-5: Unsuccessful arylation of amides with (hetero)aryl (pseudo)halides using **C1-1** (yields on the basis of GC data reported). [a] Using potassium phosphate (3 equivalents) and toluene [0.12]. [b] Using sodium *tert*-butoxide (1.5 equivalents) and toluene [0.12]. [c] Using cesium carbonate (1.5 equivalents) and 1,4-dioxane [0.12]. [d] Using 10 mol%. [e] Using 15 mol%.

Thiobenzamide is a close structural analog of benzamide, which was a favorable coupling partner in this methodology. When exchanging the oxygen of benzamide for sulfur the reaction proved infeasible under the conditions described (Figure 4-5). As mentioned in the introduction, amides are capable of binding to the metal center in a κ^2 fashion through the nitrogen and oxygen. Perhaps the sulfur atom in thiobenzamide binds more strongly

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with the catalyst than the oxygen of benzamide, preventing the formation of product **4-15**. Trifluoroacetamide is another amide coupling partner could not be arylated under the conditions in Figure 4-5 despite being structurally similar to acetamide, which was employed successfully. The fluorine atoms on trifluoroacetamide make the nitrogen less nucleophilic than that of acetamide. Amides are generally considered weak nucleophiles[48d] and trifluoroacetamide may be past the threshold of minimum nucleophilicity needed for binding to nickel that **C1-1** is able to tolerate. Product **4-17** could not be produced from methanesulfonamide. Both triflate and tosylate electrophiles failed when paired with methanesulfonamide. Perhaps methanesulfonamide is too hindered by its oxygen groups to undergo arylation with **C1-1**. Product **4-18** would be derived from (1-α-methylbenzyl)aziridine-2-carboxamide. The GC data obtained for reactions conducted with this amide coupling partner show small amounts of many different products, and isolation was not attempted. This may suggest that the aziridine functional group may not be compatible with **C1-1** or the reaction conditions required for successful amidation reactivity might cause the aziridine ring to open, preventing appreciable accumulation of product **4-18**. Although lactams (Figure 4-4) and indoles[43] were successful coupling partners for **C1-1**, indolone could not be arylated to give product **4-19** under conditions shown in Figure 4-5.

4.4.2 Unsuccessful Synthesis of Imatinib and Amsacrine using Amidation Methodology

It has been mentioned often throughout this thesis that the developed methodologies may find applications in the pharmaceutical industry given the ubiquity of $C(sp^2)$-N bonds in many pharmaceutical compounds.[36b, 92] It was desirable to demonstrate the ability of **C1-1** to catalyze a $C(sp^2)$-N bond forming reaction in a commercial drug molecule to showcase its applicability. Imatinib and Amsacrine are both anti-cancer compounds[65c, 127] used in leukemia treatment (Figure 4-6).
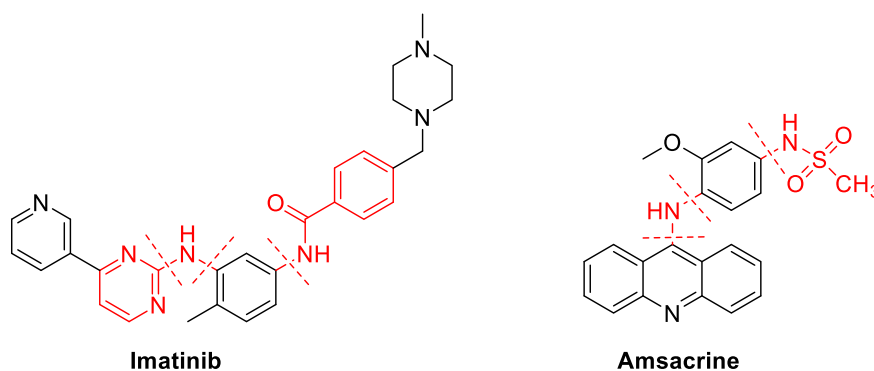
Figure 4-6: Structures of pharmaceutical compounds Imatinib and Amsacrine.

There are multiple $C(sp^2)$-N bonds that could potentially be formed by **C1-1** using the protocols for mono-arylation of ammonia, primary amines (anilines in this case), and amides in these molecules. In both structures **C1-1** would need to perform one $C(sp^2)$-N bond forming reaction on an aryl ring containing another potential electrophilic site. Imatinib would require amination or amidation of one leaving group selectively over another in the meta position, while Amsacrine would require tolerance of a leaving group in the para position. Due to the variety of reaction conditions found in the amidation

methodology (Section 4-3), which often differed based on leaving group, it was thought that perhaps selectivity between two different leaving groups could be achieved. Figure 4-7 illustrates the attempts to perform C(sp^2)-N cross-coupling in the presence of another leaving group with **C1-1**.

Entry #	*position* X	Nucleophile	Base (equiv.)	Temp. (°C)	GC yield
1	*meta* OH	benzamide	NaOtBu (1.5)	90	0%
2	*meta* OTf	benzamide	K$_3$PO$_4$ (3)	90	0%
3	*meta* OTs	benzamide	K$_3$PO$_4$ (1.5)	90	0%
4	*meta* OTs	benzamide	NaOtBu(1.5)	90	0%
5	*meta* OTs	aniline	NaOtBu (1.5)	25	0%
6	*meta* OTs	aniline	K$_3$PO$_4$ (1.5)	50	0%
7	*meta* Br	2-aminopyrimidine	NaOtBu (1.5)	25	0%
8	*meta* OTs	2-aminopyrimidine	K$_3$PO$_4$ (1.5)	25	0%
9	*para* OMs	methanesulfonamide	K$_3$PO$_4$ (1.5)	90	0%
10	*para* OS(O)$_2$NMe$_2$	methanesulfonamide	K$_3$PO$_4$ (1.5)	90	0%

Figure 4-7: Reaction conditions used in the attempt to selectively form a C(sp^2)-N bond in the presence of a second leaving group (yields on the basis of GC data reported).

An initial attempt was made to tolerate a phenol which could be later converted to a pseudohalide for the second cross-coupling (entry 1). No conversion of the starting material was observed on the basis of the GC data. This may be due to inhibition of catalysis caused by the phenol oxygen binding to nickel. In the hopes of amidating the triflate or tosylate preferentially to the chloride, reactions were performed using the conditions in entries 2 and 3 respectively. Conditions in entry 4 were employed to favour

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the amidation of the chloride over the tosylate. After these conditions failed to produce any conversion of the starting materials another approach was taken. Entries 5 and 6 describe conditions to aminate one electrophile in the presence of another with aniline. Reaction conditions used in the previous chapter for the amination of chlorides and tosylates are used here in entry 5, but once again no conversion of the starting material was observed. 2-Aminopyrimidine, a closer analog to the amine coupling partner that would be required in the synthesis of imatinib, was employed under similar conditions (entries 7 and 8) with 1-bromo-3-chlorobenzene and (3-chlorophenyl)para-toluenesulfonate leading to no conversion of starting material in both cases. As mentioned in Section 4.4.1 methanesulfonamide could not be coupled to 1-naphthyl chloride, but attempts were made to couple methanesulfonamide to less hindered electrophiles in entries 9 and 10. These reactions were conducted to determine if an amidation reaction could be carried out in the presence of another electrophile in the para position. No conversion of the starting materials was observed for these reactions as well. It is unclear if the methanesulfonamide, the second electrophilic site, or both are problematic. Substrates featuring a chloride para to a pseudohalide may cause the two groups to deactivate one another. As mentioned above, 4-chloroanisole could not be amidated using **C1-1**. (4-Chlorophenyl)methanesulfonate (entry 9) and (4-chlorophenyl)dimethanesulfamate (entry 10) may behave similarly to 4-chloroanisole.

4.5 Conclusions

In conclusion, the scope of reactivity of **C1-1** was expanded to include primary amides and lactams as N-H coupling partners in the realm of C(sp^2)-N bond forming reactions. A diverse scope of arylated amide products can be derived from a variety of electrophile coupling partners including aryl chlorides, tosylates, mesylates, triflates, and sulfamates. **C1-1** was capable of performing the amidation reaction in the presence of potentially competing functional groups such as a secondary alkylamine and pinacol boronic ester. The amidation reactions described in this chapter using **C1-1** represent the first nickel-catalyzed *N*-arylation of amides, which complements other work in the field such as nickel-catalyzed activation of amide C-N bonds discussed in the introduction of this chapter. Chris Lavoie conducted control reactions to confirm **C1-1** does not undergo unwanted C-N activation[128] under reported optimum conditions.[46]

While **C1-1** remains the only nickel catalyst reported to date for *N*-arylation of amides, advancements have been made with other first row transition metals such as copper. Schmitt and co-works reported a copper-catalyzed Ullmann type procedure for the arylation of amides, carbamates, and azoles using water as the solvent.[129] A copper-catalyzed C(sp^2)-N bond forming reaction utilizing arylsilanes as electrophile coupling partners and primary amines, amides and lactams as the nucleophile coupling partners has been published by Hartwig and co-workers.[130] This protocol enables C(sp^2)-N bond formation in the presence of aryl chlorides, which could be utilized in syntheses requiring two cross-coupling reactions on the same aryl ring. Sterically hindered amides and sterically hindered diortho-substituted electrophiles that could not be accommodated by

use of **C1-1**, can be cross-coupled in a copper-catalyzed procedure reported by Muñiz and co-workers.[131]

4.6 Experimental

4.6.1 General Considerations and Procedures

General Considerations. All reactions were set up inside a nitrogen-filled, inert atmosphere glovebox (unless otherwise indicated) and isolated under standard benchtop conditions. Toluene used in the glovebox was deoxygenated by purging with nitrogen followed by passage through a double column solvent purification system equipped with one alumina-packed column and one column packed with copper-Q5 reactant. 1,4-Dioxane used in the glovebox was deoxygenated by purging with nitrogen followed by storage over activated 4 Å molecular sieves for 48 h. **tert**-butanol was dried over CaH_2 followed by distillation under an atmosphere of nitrogen. All solvents used within the glovebox were stored over activated 4 Å molecular sieves. All other reagents, solvents and materials were used as received from commercial sources. Flash column chromatography was carried out using Silicycle SiliaFlash 60 silica (particle size 40–63 mm; 230–400 mesh) or using neutral alumina (150 mesh; Brockmann-III; activated), as indicated. All ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 K. Chemical shifts are expressed in parts per million (ppm) using the solvent signal CD_3CN (^{1}H 1.94 ppm, ^{13}C 1.32 and 118.3 ppm) or DMSO-d_6 (^{1}H 2.50 ppm, ^{13}C 39.5 ppm) as an internal reference. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; 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. Mass spectra were obtained using ion trap (ESI) instruments operating in positive mode, and GC data were obtained on an instrument equipped with a SGE BP-5 column (30 m, 0.25 mm i.d.). Pre-catalyst C1-1 was synthesized following a literature procedure.[43] Aryl mesylates and Aryl tosylates were synthesized following a literature procedure.[107] Aryl triflates were synthesized following a literature procedure.[132] Aryl sulfamates were synthesized following a literature procedure.[133]

General Catalytic Procedure for the N-Arylation of Amides and Lactams with Aryl (pseudo)Halides (GP4-1). In a nitrogen-filled glovebox, pre-catalyst **C1-1** (5-15 mol %), aryl (pseudo)halide (1.0 equivalents), base (1.5 equivalents), and amide or lactam (1.0-1.1 equivalents) were added to a screw-capped vial containing a magnetic stir bar, followed by the addition of either toluene, 1,4-dioxane or *tert*-butanol. 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 to 90 °C for 18 h with magnetic stirring. The vial was then removed from the heating block and left to cool to ambient temperature. The reaction progress was monitored qualitatively by use of GC methods. The crude reaction mixture was dissolved in ethyl acetate (10 mL) and poured onto brine (10 mL). The layers were separated and the aqueous 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 use of column chromatography over alumina or silica.

4.6.2 Synthesis and Characterization Data

[1,4']Bipiperidinyl-4'-carboxylic acid (4-cyano-phenyl)-amide (4-1)
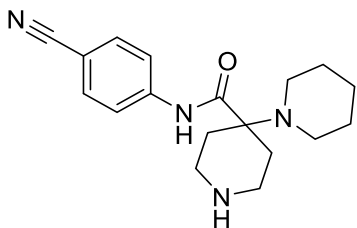
Following **GP4-1**: (0.50 mmol 4-chlorobenzonitrile, 0.50 mmol (1,4′-bipiperidine)-4′-carboxamide, 15 mol% **C1-1**, K$_3$PO$_4$ and toluene ([ArCl] = 0.12 M)) the title product was isolated as a white solid in 86% y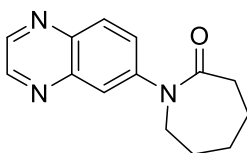ield. A 5% methanol/ethyl acetate eluent system was used for column chromatography on alumina. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 9.63 (br s, 1H), 7.91-7.88 (m, 2H), 7.77-7.75 (m, 2H), 2.88-2.84 (m, 2H), 2.65-2.60 (m, 2H), 2.52-2.46 (m, 4H), 1.94-1.91 (m, 2H), 1.69-1.64 (m, 2H), 1.55-1.50 (m, 4H), 1.39-1.38 (m, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 173.3, 143.1, 132.9, 120.1, 119.0, 104.9, 65.4, 47.0, 42.9, 30.1, 26.4, 24.6; *m/z* ESI$^+$ found 313.2023 [M+H]$^+$ calculated for C$_{18}$H$_{25}$N$_4$O 313.2028.

N-(2-Methyl-3-pyridinyl)benzamide (4-2)
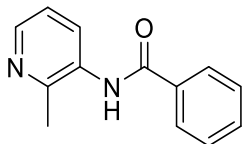
Following **GP4-1**: (0.50 mmol methanesulfonic acid 2-methyl-pyridin-3-yl ester, 0.50 mmol Benzamide, 15 mol% **C1-1**, K$_3$PO$_4$ (3.0 equivalents) and toluene ([ArOMs] = 0.12 M)) the title product was isolated as a a pale yellow solid in 76% yield. A 100% DCM to 40% DCM/ethyl acetate eluent system was used for column chromatography on silica gel.

^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.04 (br s, 1H), 8.36-8.35 (m, 1H), 8.01-7.99 (m, 2H), 7.78-7.76 (m, 1H), 7.64-7.61 (m,1H), 7.57-7.54 (m, 2H) 7.30-7.28 (m, 1H) 2.46 (s, 3H);^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 165.5, 153.8, 146.1, 134.1, 133.8, 132.4, 131.7, 128.4, 127.6, 121.3, 21.0; m/z ESI$^+$ found 213.1022 [M+H]$^+$ calculated for C$_{13}$H$_{13}$N$_2$O 213.1028.

N-(Quinolin-8-yl)thiophenecarboxamide (4-3)
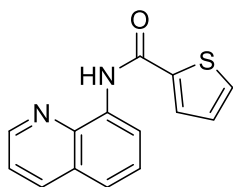
Following **GP4-1**: (0.50 mmol methane -4-sulfonic acid quinolin-8-yl ester, 0.50 mmol 2-Thiophenecarboxamide, 5 mol% **C1-1**, K$_3$PO$_4$ and toluene ([ArOMs] = 0.06 M)) the title product was isolated as a white solid in 87% yield. A 10% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.55 (br. s, 1H), 9.00-8.99 (m, 1H), 8.61-8.60 (m, 1H), 8.49-8.47 (m, 1H), 8.01-8.00 (m, 1H), 7.96-7.95 (m, 1H), 7.77-7.76 (m, 1H), 7.71-7.65 (m, 2H), 7.31-7.29 (m, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 159.3, 149.2, 139.1, 138.3, 136.7, 133.7, 132.3, 129.2, 128.5, 127.8, 127.0, 122.5, 122.3, 117.0; m/z ESI$^+$ found 277.0406 [M+Na]$^+$ calculated for C$_{14}$H$_{10}$N$_2$NaOS 277.0412.

4-[(2-furanylcarbonyl)amino]-ethyl ester benzoic acid (4-4)
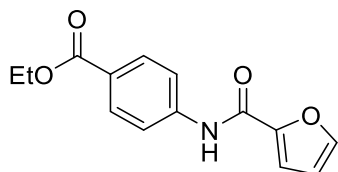
Following **GP4-1**: (0.50 mmol 4-methanesulfonyloxy-benzoic acid ethyl ester, 0.50 mmol furan-2-caroxylic acid amide, 5 mol% **C1-1**, K$_3$PO$_4$ (3.0 equivalents) and toluene

([ArOMs] = 0.12 M)) the title product was isolated as a white solid in 73% yield. A 100% DCM eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.47 (br. s, 1H), 7.98-7.92 (m, 5H), 7.41-7.40 (m, 1H), 6.74-6.73 (m, 1H), 4.31(q, J = 7.1 Hz, 2H) 1.33 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 165.3, 156.4, 147.1, 146.1, 143.0, 130.0, 124.6, 119.5, 115.4, 112.2, 60.4, 14.2; m/z ESI$^+$ found 282.0737 [M+Na]$^+$ calculated for $C_{14}H_{13}NNaO_4$ 282.0742.

N-1-naphthalenyl-3-pyridinecarboxamide (4-5)
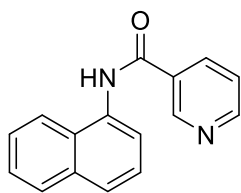
Following **GP4-1**: (0.50 mmol trifluoro-methanesulfonic acid napthalen-1-yl ester, 0.50 mmol nicotinamide, 5 mol% **C1-1**, K_3PO_4 (3.0 equivalents) and toluene ([ArOTf] = 0.06 M)) the title product was isolated as a white solid in 85% yield. A 100% ethyl acetate eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.62 (br. s, 1H), 9.26 (s, 1H), 8.82 (dd, J = 4.8, 1.4 Hz, 1H), 8.44 (d, J = 7.9 Hz, 1H), 8.06-8.04 (m, 1H), 8.01-7.99 (m, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.66-7.56 (m, 5H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 164.7, 152.2, 148.8, 135.5, 133.7, 133.4, 130.3, 130.1, 128.9, 128.0, 126.4, 126.1, 126.0, 125.5, 123.8, 123.5, 123.3; m/z ESI$^+$ found 271.0842 [M+Na]$^+$ calculated for $C_{16}H_{12}N_2NaO$ 271.0847.

N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-benzamide (4-6)
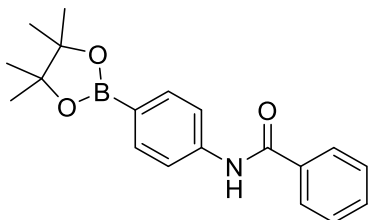
Following **GP4-1**: (0.30 mmol toluene-4-sulfonic acid4-(4,4,5,5-tetramethyl-[1,3,2]dioaborolan-2-yl)-phenyl ester, 0.30 mmol benzamide, 10 mol% **C1-1**, K$_3$PO$_4$ (3.0 equivalents) and toluene ([ArOTs] = 0.12 M)) the title product was isolated as an off-white solid in 71% yield. A 15% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.35 (br. s, 1H), 7.97-7.96 (m, 2H), 7.84-7.82 (m, 2H), 7.67-7.66 (m, 2H), 7.62-7.60 (m, 1H). 7.56-7.53 (m, 2H), 1.31 (s, 12H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 165.7, 142.0, 135.1, 134.8, 131.6, 128.3, 127.7, 119.2, 83.4, 24.7. *m/z* ESI$^+$ found 346.1585 [M+Na]$^+$ calculated for C$_{19}$H$_{22}$ BNNaO$_3$ 346.1590.

N-(2-methyl-4-quinolinyl)- 4-Pyridinecarboxamide (4-7)
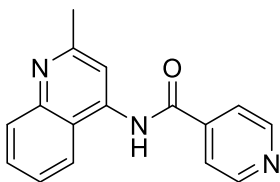
Following **GP4-1**: (0.375 mmol dimethyl-sulfonic acid 2-methyl-quinolin-4-yl ester, 0.375 mmol isonicotinamide, 10 mol% **C1-1**, K$_3$PO$_4$ (3.0 equivalents) and toluene ([ArOSO$_2$N(Me)$_2$] = 0.12 M)) the title product was isolated as an off-white solid in 72% yield. A 100% ethyl acetate to 5% methanol/ethyl acetate eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 10.84 (br. s,

1H), 8.85-8.84 (m, 2H), 8.21-8.20 (m, 1H), 7.99-7.95 (m, 3H), 7.84 (s, 1H), 7.77-7.74 (m, 1H), 7.58-7.55 (m, 1H), 2.68 (s, 3H); $^{13}C\{^1H\}$ NMR (125.8 MHz, DMSO-d_6): δ 165.2, 158.9, 150.3, 148.3, 141.3, 129.6, 128.5, 125.2, 123.0, 121.8, 120.9, 115.7, 25.0; m/z ESI$^+$ found 264.1131 [M+H]$^+$ calculated for $C_{16}H_{14}N_3O$ 264.1137.

1-Quinoxalin-6-yl-azetidin-2-one (4-8)
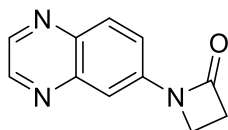
Following **GP4-1**: (0.50 mmol 6-chloro-quinoxaline, 0.50 mmol 2-Azetidinone, 10 mol% **C1-1**, Cs_2CO_3 and 1,4-dioxane ([ArCl] = 0.12 M)) the title product was isolated as a bright yellow solid in 77% yield. A 100% ethyl acetate eluent system was used for column chromatography on silica gel. ^1H NMR (500.1 MHz, DMSO-d_6): δ 8.92-8.91 (m, 1H), 8.85-8.84 (m, 1H), 8.13-8.11 (m, 1H), 8.07-8.05 (m, 1H), 7.80-7.79 (m, 1H), 3.83 (t, J = 4.7 Hz, 2H), 3.21 (t, J = 4.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (125.8 MHz, DMSO-d_6): δ 165.5, 146.3, 144.0, 143.0, 139.5, 139.2, 130.5, 120.7, 111.8, 38.5, 36.2; m/z ESI$^+$ found 222.0638 [M+Na]$^+$ calculated for $C_{11}H_9N_3NaO$ 222.0643.

1-(4-acetylphenyl)-2-pyrrolidinone (4-9)
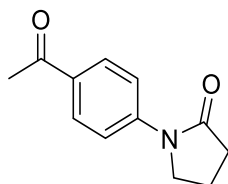
Following **GP4-1**: (0.50 mmol 4-chloro-acetophenone, 0.50 mmol 2-Pyrrolidinone, 10 mol% **C1-1**, Cs_2CO_3 and 1,4-dioxane ([ArCl] = 0.12 M)) the title product was isolated as an off-white solid in 78% yield. A 70% ethyl acetate/hexanes eluent system was used for

column chromatography on silica gel. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 7.99-7.97 (m, 2H), 7.83-7.82 (m, 2H), 3.90 (t, J = 7.1 Hz, 2H), 2.57-2.54 (m, 5H), 2.12-2.06 (m, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, CD$_3$CN): δ 196.6, 174.6, 143.6, 131.9, 129.1, 118.3, 47.9, 32.4, 26.4, 17.2. Spectral data are consistent with the literature.[134]

Ethyl 4-(2-oxo-1-piperidinyl)benzoate (4-10)
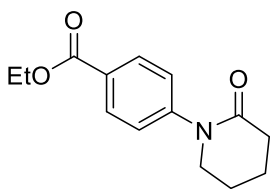
Following **GP4-1**: (0.50 mmol 4-methanesulfonyloxy-benzoic acid ethyl ester, 0.50 mmol δ-valerolactam, 10 mol% **C1-1**, K$_3$PO$_4$ and toluene ([ArOMs] = 0.12 M)) the title product was isolated as a yellow solid in 61% yield. A 100% DCM to 100% ethyl acetate eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 7.96-7.95 (m, 2H), 7.48-7.46 (m, 2H), 4.32 (q, J = 7.1, 2H), 3.67 (t, J = 5.7 Hz, 2H), 2.44 (t, J = 6.5 Hz, 2H), 1.90-1.84 (m, 4H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 169.1, 165.2, 147.7, 129.5, 126.8, 125.6, 60.6, 50.2, 32.7, 22.8, 20.7, 14.1. Spectral data are consistent with the literature.[121a]

1-Quinoxalin-6-yl-azetpan-2-one (4-11)

Following **GP4-1**: (0.50 mmol 6-chloro-quinoxaline, 0.50 mmol ε-caprolactam, 10 mol% **C1-1**, Cs$_2$CO$_3$ and 1,4-dioxane ([ArCl] = 0.12 M)) the title product was isolated as an off-

white solid in 51% yield. A 100% ethyl acetate to 10% methanol/ethyl acetate eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 8.95-8.94 (m, 1H), 8.93-8.92 (m, 1H), 8.08-8.06 (m, 1H), 7.91-7.90 (m, 1H), 7.81-7.78 (m, 1H), 3.94-3.93 (m, 2H), 2.71-2.69 (m, 2H), 1.84-1.76 (m, 6H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 174.7, 145.8, 145.7, 145.2, 142.4, 140.3, 129.9, 128.8, 124.0, 51.9, 37.0, 28.9, 28.3, 22.9; m/z ESI$^+$ found 264.1107 [M+Na]$^+$ calculated for C$_{14}$H$_{15}$N$_3$NaO 264.1113.

4-[(4S)-2-Oxo-4-(phenylmethyl)-3-oxazolidinyl]benzonitrile (4-12)
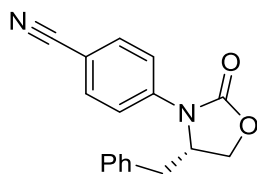
Following **GP4-1**: (0.50 mmol 4-chlorobenzonitrile, 0.50 mmol (4S)-4-benzyl-1,3-oxazolidin-2-one, 10 mol% **C1-1**, Cs$_2$CO$_3$ and 1,4-dioxane ([ArCl] = 0.12 M)) the title product was isolated as a white solid in 64% yield. A 100% DCM to 1% methanol/DCM eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 7.92-7.86 (m, 4H), 7.31-7.23 (m, 3H), 7.20-7.18 (m, 2H), 5.07-5.02 (m, 1H), 4.45-4.42 (m, 1H) 4.27-4.24 (m, 1H), 3.02-2.98 (m, 1H), 2.93-2.88 (m, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 154.3, 141.3, 135.3, 133.3, 129.5, 128.4, 126.9, 120.1, 118.8, 105.8, 65.9, 55.1, 36.0; Spectral data are consistent with the literature.[135] In an effort to evaluate whether such cross-couplings could be conducted with retention of stereochemistry within the (4S)-4-benzyl-1,3-oxazolidin-2-one substrate, the isolated product of the cross-coupling reaction was dissolved in DMSO-d_6 and treated with europium tris[-(heptafluoropropylhydroxymethylene)-(+)-camphorate] (ca. 8-10 mg); the

^{1}H NMR spectrum of was obtained and only a single methine resonance was observed in the case of **4-12** prepared from (4S)-4-benzyl-1,3-oxazolidin-2-one. This observation suggests that racemization of the (4S)-4-benzyl-1,3-oxazolidin-2-one starting material under cross-coupling conditions leading to **4-12** does not occur.

1-(4-acetylphenyl)-5-oxo-pyrrolidine-3-carboxylic acid ethyl ester (4-13)
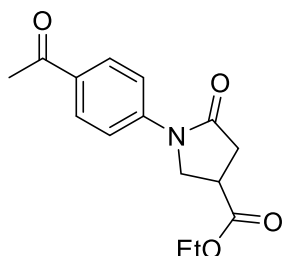
Following **GP4-1**: (0.50 mmol 4-chloro-acetophenone, 0.50 mmol Ethyl 5-oxopyrrolidine-3-carboxylate, 10 mol% **C1-1**, Cs$_2$CO$_3$ and 1,4-dioxane ([ArCl] = 0.12 M)) the title product was isolated as a white solid in 68% yield. A 10% to 50% to 70% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 8.00-7.97 (m, 2H), 7.84-7.81 (m, 2H), 4.19-4.13 (m, 3H), 4.06-4.02 (m, 1H), 3.52-3.45 (m, 1H), 2.88-2.76 (m, 2H), 2.56 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 196.6, 172.5, 172.3, 143.0, 132.2, 129.1, 118.5, 60.8, 49.7, 35.1, 34.9, 26.5, 14.0; m/z ESI$^+$ found 298.1050 [M+Na]$^+$ calculated for C$_{15}$H$_{17}$NNaO$_4$ 298.1055.

1-(13-Methyl-17-oxo-7, 8, 9, 11, 12, 13, 14, 15, 16, 17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)-pyrrolidin-2-one (4-14)
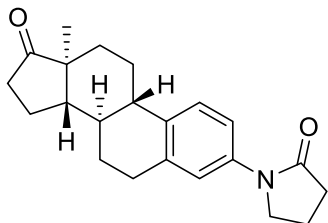
Following **GP4-1**: (0.12 mmol methanesulfonic acid 13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decarhydro-6*H*-cyclopenta[a]phenanthrene-3-yl ester, 0.12 mmol 2-Pyrrolidinone, 15 mol% **C1-1**, K_3PO_4 (3.0 equivalents) and toluene ([ArOMs] = 0.12 M)) the title product was isolated as a white solid in 55% yield. A 50% to 60% ethyl acetate/ hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 7.41-7.39 (m, 1H), 7.34-7.33 (m, 1H), 7.28-7.26 (m, 1H), 3.83-3.76 (m, 2H), 2.87-2.84 (m, 2H), 2.48-2.38 (m, 4H), 2.26-2.23 (m, 1H), 2.12-2.196 (m, 5H), 1.79-1.77 (m, 1H) 1.61-1.48 (m, 3H) 1.43-1.37 (m, 3H), 0.84 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, DMSO-d_6): δ 219.5, 173.4, 137.2, 136.4, 135.3, 125.3, 119.7, 117.1, 49.6, 48.1, 47.3, 43.6, 37.6, 35.3, 32.2, 31.3, 29.1, 26.0, 25.3, 21.1, 17.4, 13.5; *m/z* ESI$^+$ found 360.1934 [M+Na]$^+$ calculated for $C_{22}H_{27}NNaO_2$ 360.1939. Following **GP4-1**: The title compound was synthesized from the corresponding aryl triflate in 62% yield.

CHAPTER 5 Nickel-Catalyzed Amination of Aryl Carbamates, Sulfamate, and Pivalates

5.1 Contributions

This chapter describes the development of the first nickel-catalyzed amination of aryl carbamates, sulfamates, and pivalates with ammonia and primary alkylamines using **C1-2**. The author's contributions consist of the initial discovery, ligand screen, optimization of reaction conditions, and isolation of all cross-coupling products. This work has been published (*Synlett* **2017***, 28,* 1652–1656).

5.2 Introduction

Phenol-derived pseudohalides are useful coupling partners in many cross-coupling applications, including C-N bond formation as discussed in earlier chapters. Pseudohalides can be synthesized easily and often require trivial purification.[136] The wide inventory of commercially available phenols can provide access to many electrophiles including biologically important molecules such as estrone or tocopherol that may not be available as corresponding aryl halides.[137] As mentioned in Section 3.2.2 nickel has a higher propensity for $C(sp^2)$-Cl oxidative additions to Ni(0) versus Pd(0),[81a, 87] and pseudohalide $C(sp^2)$-O bonds are typically have more difficulty undergoing oxidative addition relative to aryl halides,[138] making nickel well suited for

reactivity with pseudohalide coupling partners. As described in previous chapters, **C1-1** is capable of effecting transformations of phenol-derived sulfonate coupling partners such as tosylates, mesylates, and triflates with ammonia, primary amine, and amide nucleophiles. These pseudohalides can, however, also be employed in palladium-catalyzed C(sp^2)-N cross-couplings.[19, 48e, 62, 137] There are other classes of phenol-derived pseudohalides that can be utilized with nickel that are much less compatible with palladium.[139] Carbamates, sulfamates, and pivalates shown in Figure 5-1 have been used as electrophiles within nickel catalysis[139] and represent an area in which nickel can access new reactivity beyond established palladium catalyst systems.
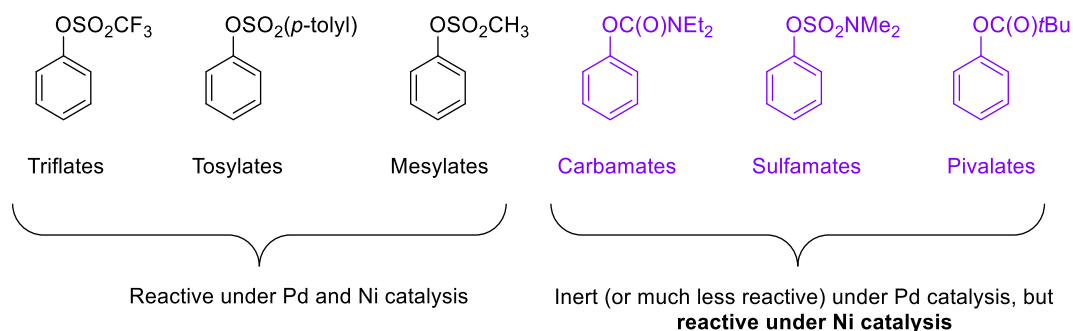
Figure 5-1: Examples of pseudohalides reactive under palladium catalysis versus pseudohalides inert under palladium catalysis.[139]

   The carbamate and sulfamate functional groups are particularly attractive in that such pseudohalides can function as directing groups for other transformations, including electrophilic aromatic substitution, directed ortho metalation,[49a, 49c, 50a, 140] cine substitution,[50b] and other C-H activations.[50c, 141] The opportunity to further utilize these functional groups as electrophiles in amination cross-coupling has not been overlooked. Nickel-catalyzed amination of aryl sulfamates with anilines (2 examples) appear in a

report from the Buchwald group[33] and one example of an amidation of an aryl sulfamate

using **C1-1** by the Stradiotto group[128] (Chapter 4). Figure 5-2a illustrates the use of

carbamates and sulfamates more widely as electrophiles in the arylation of secondary

amines by Garg and co-workers.[51, 142] In a similar fashion Chatani and co-workers have

employed nickel-catalysis to aminate related aryl pivalates with secondary amines

(Figure 5-2b).[143]

a) Garg & co-workers. *Org. Lett.* **2012**, *14*, 4182

R⦵—X + HNR$_2$ → [NiCl$_2$ (DME), SIPr•HCl, Ph-B(pin), NaO*t*Bu, 1,4-dioxane, 80 °C] → R⦵—NR$_2$

X = OC(O)NEt$_2$
X = OSO$_2$NMe$_2$

40 examples
40- 98% yield

b) Chatani & co-workers. *Angew. Chem. Int. Ed.* **2010**, *49*, 2929

R⦵—X + HNR$_2$ → [Ni(COD)$_2$, IPr•HCl, NaO*t*Bu, toluene, 80 °C] → R⦵—NR$_2$

X = OC(O)*t*Bu

20 examples
56- 99% yield

c) *This Work*

R⦵—X + H$_2$NR → [(CyPF-Cy)Ni(o-tolyl)Cl (**C1-2**) (5-10 mol%), Base, Solvent, r.t -110 °C] → R⦵—NHR

X = OC(O)NEt$_2$ R = H, Alkyl
X = OSO$_2$NMe$_2$
X = OC(O)*t*Bu

16 exampes
53-96% yield

Figure 5-2: a) Previous work with amination of aryl carbamates and sulfamates with secondary amines.[51] b) Previous work with amination of aryl pivalates with secondary amines.[143] c) Amination of aryl carbamates, sulfamates, and pivalates with ammonia and primary alkylamines.

Aside from two examples using octylamine and hexylamine with 1-

dimethanesulfamatenaphthylene by Ackermann and co-workers,[144] primary alkylamines

have not been used with these electrophiles. While the use of benzophenone imine as an ammonia surrogate with such electrophiles has been reported recently,[41y] prior to the work presented in this chapter no catalyst system (palladium, nickel, or other) using ammonia directly with these electrophiles has been reported. The work herein describes the successful application of the air-stable pre-catalyst (CyPFCy)Ni(o-tolyl)Cl (**C1-2**) in developing new C(sp^2)–N cross-couplings of ammonia or primary alkylamines with (hetero)aryl carbamates, sulfamates, or pivalates (Figure 5-2c).

5.3 Results and Discussion

Conditions from literature reports of amination of carbamates with secondary amines (Figure 5-2a)[51] were modified and employed in initial screening of pre-catalysts for mono-arylation of ammonia. 1-Naphthylcarbamate was found to be a successful substrate for Garg and co-workers[51] in the arylation of secondary amines and thus was chosen for screening with ammonia (Figure 5-3).
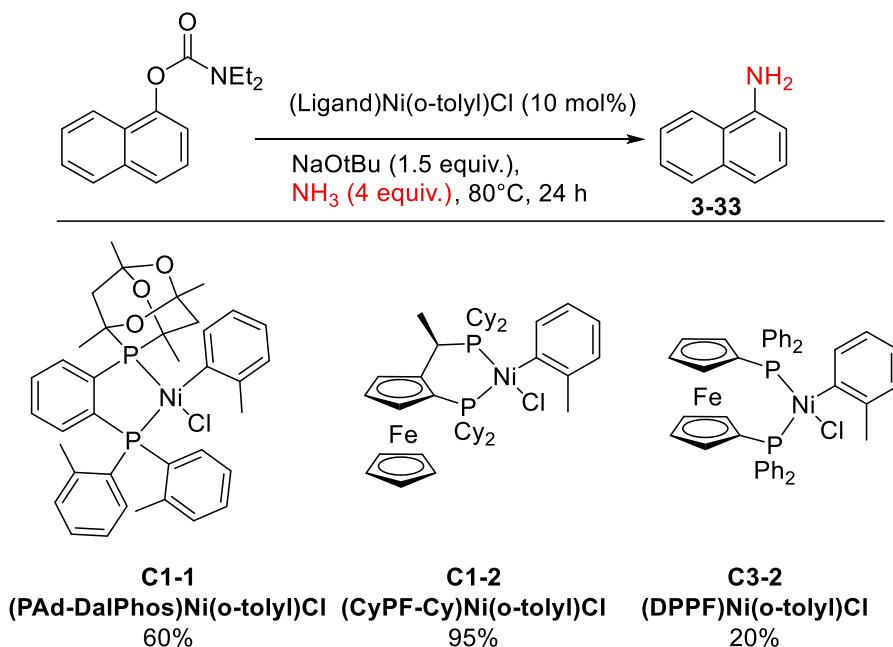
Figure 5-3: Pre-catalyst screen for the nickel-catalyzed mono-arylation of ammonia (estimated conversion to **3-33** on the basis of GC data reported).

The three pre-catalysts chosen for the initial screening were all successful in nickel-catalyzed amination reactions. As described in previous chapters, **C1-1** has proven successful in mono-arylations of ammonia and primary amines employing (hetero)aryl (pseudo)halides. The JosiPhos nickel pre-catalyst **C1-2** is based on the JosiPhos (**L1-9**) ligand that was successfully used in the first report of nickel-catalyzed mono-arylation of ammonia.[42] Lastly, **C3-2** is the nickel pre-catalyst reported by Buchwald and co-workers to be successful in arylation of anilines with (hetero)aryl pseudohalides.[33] As shown in Figure 5-3, **C1-2** performed best in the test reaction employed, providing high conversion to product **3-33**. Given the variety of JosiPhos ligands available, a ligand screen was performed to evaluate the efficacy of other JosiPhos ligand variants in this reaction. Figure 5-4 shows the JosiPhos ligands screened for the mono-arylation of ammonia using 1-naphthylcarbamate.
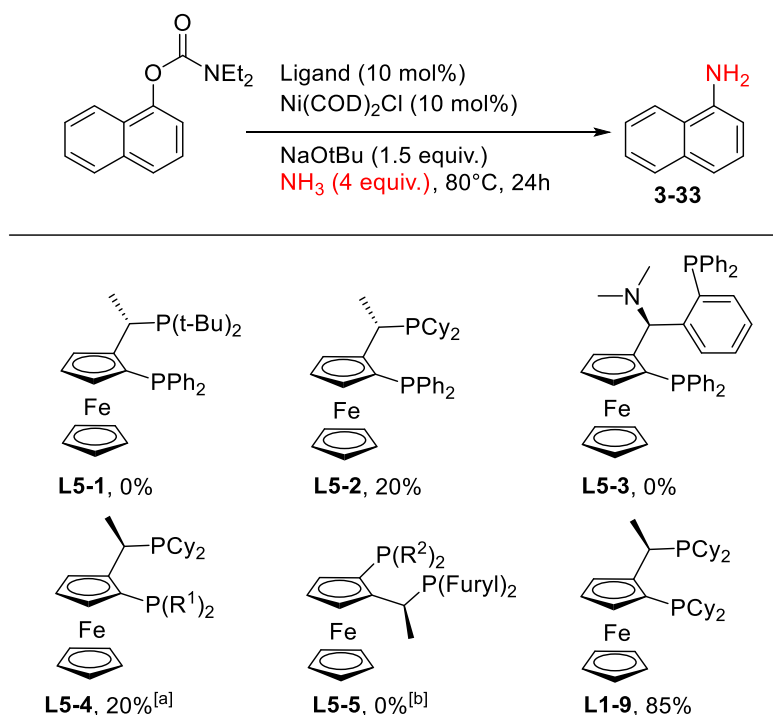
Figure 5-4: Screen of JosiPhos ligands for mono-arylation of ammonia with aryl carbamates. (estimated conversion to **3-33** on the basis of GC data reported). [a] R^1 = 3,5-bis(trifluoromethyl)phenyl. [b] R^2 = 3,5-methylphenyl.

Surprisingly, ligand **L5-1**, which was found to be optimal amongst the ligands surveyed by Green and Hartwig[40b] in their report on the nickel-catalyzed mono-arylation of ammonia employing (hetero)aryl halides, proved completely ineffective. Further derivatives including those with combinations of cyclohexyl and (substituted)aryl groups, on phosphorus (**L5-2**, **L5-3** and **L5-4**) as well as those bearing furyl and xylyl substitution (**L5-5**), performed in an unsatisfactory manner, despite showing success in the first study of ammonia mono-arylation using (hetero)aryl halides.[42] However, in returning to CyPF-Cy (**L1-9**), the ligand featured in the optimal pre-catalyst identified in Figure 5-3, high conversion (85%) to the target aniline **3-33** was achieved. Having identified **C1-2** as being a useful pre-catalyst for the conversion of 1-naphthylcarbamate into **3-33**, the scope of

reactivity was examined. Gratifyingly, ammonia mono-arylation employing (hetero)aryl sulfamates and carbamates leading to the products in Figure 5-5 was achieved.
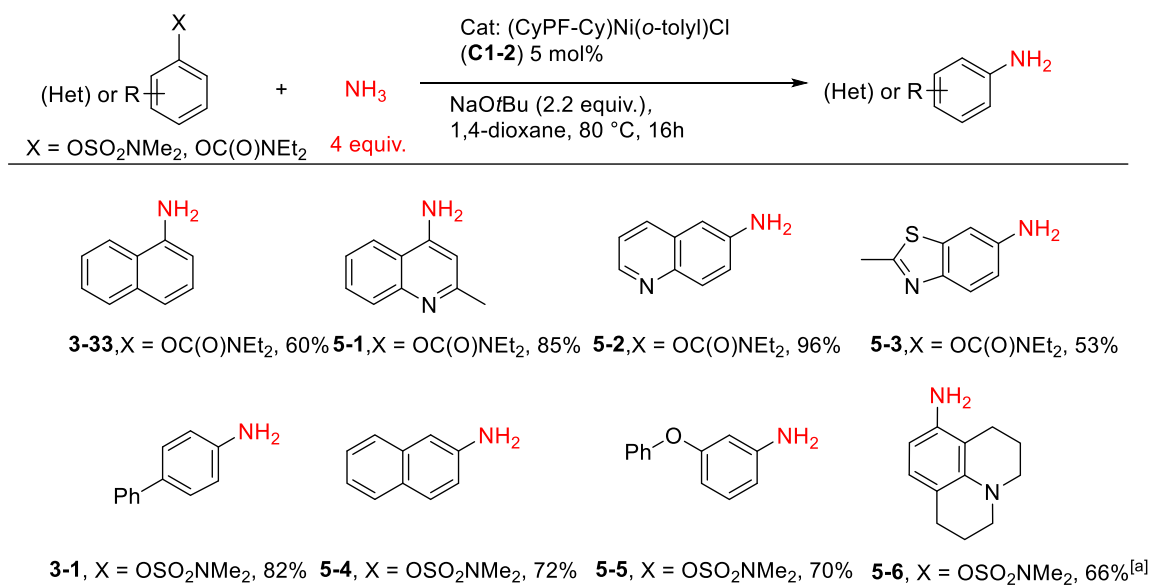
Figure 5-5: Mono-arylation of ammonia with aryl carbamates and sulfamates employing **C1-2** (yields of isolated products reported). [a] Using 7.5 mol% **C1-2**.

Substrates featuring ortho, meta, para, and/or trisubstitution were each tolerated, as were heterocyclic species based on quinaldine (**5-1**), quinoline (**5-2**), benzothiazole, and (**5-3**) julolidine (**5-6**). By comparison, efforts to extend such cross-couplings to analogous pivalate electrophiles were unsuccessful, affording only phenol under various conditions.

Given the utility of secondary *N*-alkyl aniline derivatives,[145] there is considerable interest in the development of catalyst systems that effect the *N*-arylation of primary alkylamines. On this basis, and knowing that the mono-arylation of primary alkylamines shares some of the same challenges associated with ammonia mono-arylation, **C1-2** applied was in C(sp^2)-N cross-couplings of primary alkylamines employing (hetero)aryl sulfamates and carbamates (Figure 5-6).
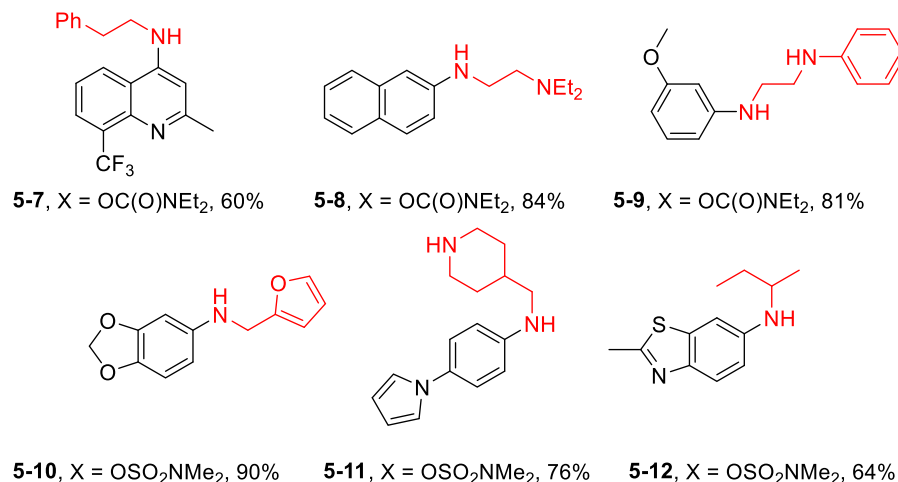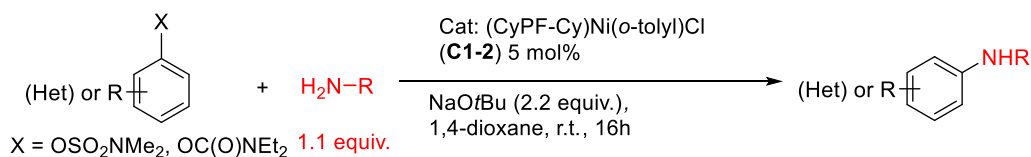
Figure 5-6: Mono-arylation primary alkylamines with aryl carbamates and sulfamates employing **C1-2** (yields of isolated products reported).

Sulfamates and carbamates were successfully coupled to primary alkylamines under the same conditions as used with ammonia, with the exception that the primary amines can undergo arylation at room temperature. The successful scope of sulfamates and carbamates contains heteroaryl and heterocyclic functionality including quinaldine (**5-7**), benzodioxol (**5-10**), pyrrole (**5-11**), and benzothiazole (**5-12**). A range of primary amine coupling partners were employed. Examples encompass linear (**5-7**, **5-8**) and branched (**5-12**) amines, as well as amines containing heteroaryl moieties (**5-10**). Primary amines can be cross-coupled in the presence of alkyl and aryl secondary amines (**5-9**, **5-11**), as well as potentially chelating diamines (**5-8**, **5-9**).

Whereas pivalates were found to be incompatible with ammonia mono-arylation chemistry using **C1-2** under a range of conditions, reaction conditions were identified leading to success in C(sp^2)–N cross-couplings with primary alkylamines (Figure 5-7).
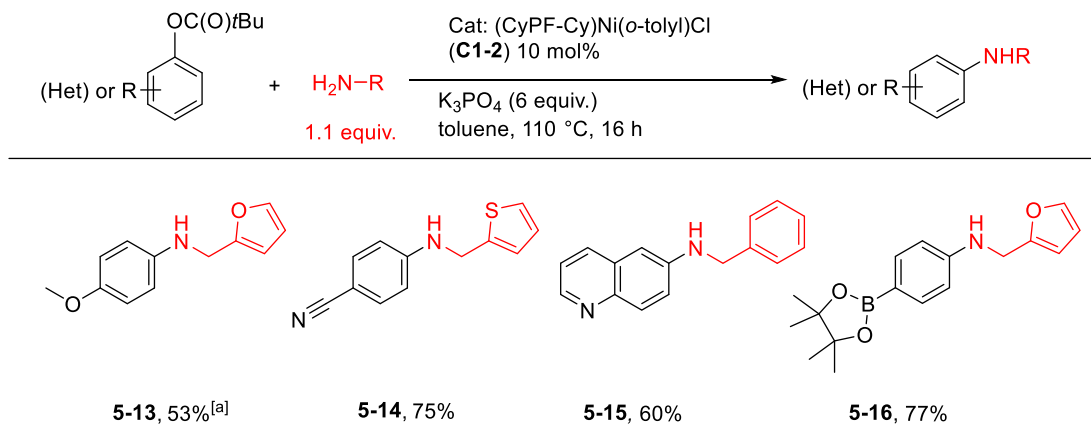
Figure 5-7: Mono-arylation primary alkylamines with aryl pivalates employing **C1-2** (yields of isolated products reported). [a] Using 2.2 equivalents of sodium *tert*-butoxide.

The use of toluene in place of 1,4-dioxane, and substitution of potassium phosphate for sodium *tert*-butoxide, each independently reduced phenol formation when using (hetero)aryl pivalate coupling partners. With these experimental modifications, and employing somewhat forcing conditions (10 mol% **C1-2**, 110 °C), electron-rich, electron-poor, and heteroaryl pivalates were accommodated, affording products **5-13** to **5-16** in synthetically useful yields (Figure 5-7) with tolerance of methoxy (**5-13**), cyano (**5-14**), quinolyl (**5-15**), and pinacol boron (BPin) moieties (**5-16**). The successful formation of **5-16** from the corresponding pivalate suggests that **C1-2** may be employed in sequential and chemoselective amination–Suzuki transformations.

5.4 Ineffective Applications of the Pseudohalide Amination Methodology

Although the mono-arylation of ammonia and primary alkylamines using **C1-2** was successful in allowing the production of aniline and amine products presented above, not all of the envisioned applications and research goals were accomplished. As discussed in introduction Section 5.2, carbamates and sulfamates are used in other transformations as directing groups. Efforts were made to demonstrate the utility of the amination methodology through a one-pot reaction consisting of a C-H activation assisted by the pseudohalide directing group, followed by an amination reaction catalyzed by **C1-2**, using the same pseudohalide as an electrophile. Before a one-pot reaction was attempted, borylated aryl pseudohalides were synthesised according to methods previously reported[141] and evaluated as possible substrates for the arylation of primary amines (Figure 5-8).

5-17, X = OC(O)NEt$_2$, R = furyl, 0%
5-18, X = OC(O)NEt$_2$, R = (CH$_2$)$_6$CH$_3$, 0%[a]
5-17, X = OC(O)tBu, R = furyl, 20%[b,c]
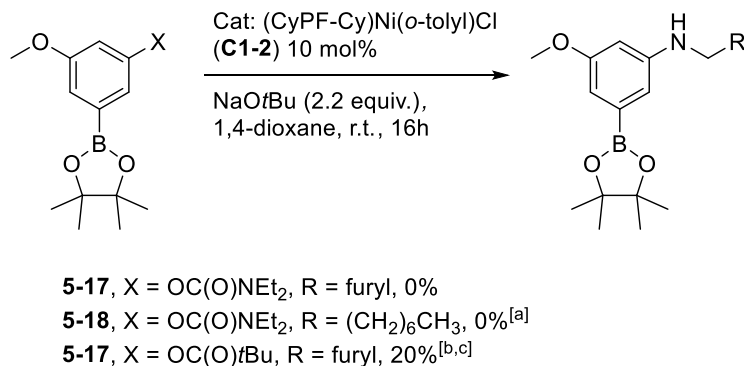
Figure 5-8: Amination of an aryl carbamate and pivalate containing meta pinacol borane substituent using **C1-2**. (yields on the basis of GC data reported). [a] Reaction conducted at 80 °C. [b] Reaction conducted at 110 °C. [c] Using 6 equivalents of potassium phosphate and toluene.

Unfortunately, attempts to aminate these materials were not successful. Under standard conditions optimized for amination of aryl carbamates with primary amines no product **5-17** was observed on the basis of GC analysis. The GC data did indicate that 50% of the starting borylated aryl carbamate had been converted to (3-methoxypheny)-carbamate. Despite the ability of **C1-2** to tolerate a boron pinacol ester in the para position (compound **5-16**, Figure 5-7) it would appear that the presence of the meta methoxy and carbamate groups somehow activate the boronic ester towards reactivity with **C1-2**. Upon increasing the temperature and switching the amine coupling partner from furfuryl amine to octylamine, no improvement was observed. Many different new products were observed by GC analysis and isolation was not attempted. Using the analogous aryl pivalate and amination conditions optimized for aryl pivalates resulted in only 20% of what may be the desired product, but most of the staring material remained unconverted, and product isolation was not pursued.

5.5 Conclusions

In summary, a protocol for C(sp^2)–N cross-couplings of ammonia or primary alkylamines with (hetero)aryl sulfamates, carbamates, or pivalates has been successfully developed. The chemistry makes use of the air-stable pre-catalyst (CyPF-Cy)Ni(o-tolyl)Cl (**C1-2**), and tolerates a broad spectrum of heterocyclic functionality within both reaction partners, as well as ether (**5-5**, **5-9**, **5-13**), nitrile (**5-14**), pyrrole (**5-11**), trifluoromethyl (**5-7**), and boronic ester substituents (**5-16**). The transformations documented herein are notable in that they represent the first cross-couplings of ammonia

with (hetero)aryl sulfamate and carbamate electrophiles and the first cross-couplings of primary alkylamines with pivalate and carbamate electrophiles, including rare examples of nickel-catalyzed room-temperature $C(sp^2)$–N cross-couplings of primary alkylamines. Currently there is only one other literature report by Schranck and Tlili describing the nickel-catalyzed amination aryl carbamate electrophiles, which uses ammonia and primary amine salts, and employs a nickel pre-catalyst based on **L1-9**.[146] The methodology reported herein represents a valuable addition to the field of cross-coupling chemistry, by providing new pathways for exploiting these interesting electrophiles in chemical synthesis. Furthermore, the new reactivity established by use of **C1-2** herein highlights the ability of appropriately ligated nickel-based catalysts to provide inroads to useful reactivity manifolds that cannot be accessed by use of palladium-based catalyst systems.

5.6 Experimental

5.6.1 General Considerations and Procedures

General Considerations. All reactions were set up inside a nitrogen-filled, inert atmosphere glovebox and isolated under standard benchtop conditions. 1,4-Dioxane used in the glovebox was deoxygenated by purging with nitrogen followed by storage over activated 4 Å molecular sieves for 48 h. All solvents used within the glovebox were stored over activated 4 Å molecular sieves. All other reagents, solvents and materials were used as received from commercial sources. Flash column chromatography was carried out using

Silicycle SiliaFlash 60 silica (particle size 40–63 mm; 230–400 mesh) or using neutral alumina (150 mesh; Brockmann-III; activated), as indicated. All ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 K. Chemical shifts are expressed in parts per million (ppm) using the solvent signal CDCl$_3$ (^{1}H 7.26 ppm, CHCl$_3$; ^{13}C 77.2 ppm, CDCl$_3$) as an internal reference. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; 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. Mass spectra were obtained using ion trap (ESI) instruments operating in positive mode, and GC data were obtained on an instrument equipped with a SGE BP-5 column (30 m, 0.25 mm i.d.). Pre-catalysts **C1-1**,[43] **C1-2**,[35] **C3-2**,[33] were each prepared by using literature procedures. Aryl sulfamates and aryl carbamates were synthesized following a literature procedure.[133] Aryl pivalates were synthesized following a literature procedure.[147]

Preparation of 2-Methylquinolin-4-yl diethylcarbamate
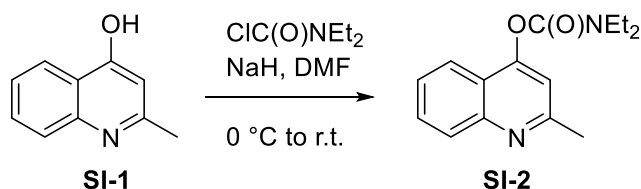
Using a protocol adapted from a literature procedure,[133] a Schlenk flask was charged with NaH (0.0792 g, 1.98 mmol, 1.2 equivalents, 60% dispersion in oil), and cooled to 0 ºC. Then a solution of 4-hydroxy-2-methylquinoline (0.263 g, 1.65 mmol, 1 equivalents) in DMF (7.3 mL) was added dropwise via syringe to the NaH. The resulting solution was warmed to r.t. for 10 min, and then cooled to 0 ºC. A solution of diethyl carbamoyl chloride

(0.250 mL, 1.98 mmol, 1.2 equivalents) in DMF (2 mL) was then added dropwise via cannula to the reaction vessel. The reaction was warmed to r.t., allowed to stir for 16 h, and then quenched with several drops of water. The reaction mixture was poured into a separatory-funnel containing an aqueous solution of 5% LiCl (30 mL). 5 manual separatory-funnel extractions were done in series using an aqueous solution of 5% LiCl as the aqueous phase and dichloromethane as the organic phase. The organic layers were combined and the solvent was removed under reduced pressure. The solid material was dissolved in Et_2O (50 mL) and H_2O (15 mL), and transferred to a separatory funnel. The layers were separated, and the organic layer was washed with 1 M KOH (15 mL), then H_2O (15 mL). The combined aqueous layers were extracted with Et_2O (3x20 mL). The combined organic layers were then washed with brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography 50% ethyl acetate/hexanes to yield carbamate **SI-2** as a white solid (0.393 g, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07-8.04 (m, 1H), 7.97-7.94 (m, 1H), 7.73-7.68 (m, 1H), 7.54-7.48 (m, 1H), 7.31 (s, 1H), 3.60 (q, $J = 7.1$, 2H), 3.48 (q, $J = 7.1$, 2H), 2.76 (s, 3H) 1.39 (t, $J = 7.1$, 3H), 1.29 (t, $J = 7.1$, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 160.1, 152.9, 130.0, 128.9, 124.3, 121.3, 113.8, 113.0, 106.1, 42.8, 42.5, 25.8, 14.7, 13.5. *m/z* ESI$^+$ found 259.1441 [M+H]$^+$ calculated for $C_{15}H_{19}N_2 O_2$ 259.1441.

Procedure for Catalyst Screening. In a nitrogen-filled glovebox, Ni(COD)$_2$ (3.3 mg, 0.012 mmol, 0.1 equivalents), ligand (0.012 mmol, 0.1 equivalents), 1-chloronaphthylene (29.2 mg, 0.12 mmol, 1.0 equivalents), NaOtBu (25.4 mg, 0.26 mmol, 2.2 equivalents), and NH$_3$ (0.5 M solution in 1,4-dioxane, 0.96 mL, 0.48 mmol, 4 equivalents) were added to a screw-capped glass vial containing a magnetic stir bar. 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 to 80 °C, at which point magnetic stirring was initiated. After 24 h, calibrated GC analysis of reaction aliquots was used to estimate the consumption of and percentage of product (**3-33**) formed. Pre-catalyst screening was conducted by using an identical protocol, where **C1-1**, **C1-2**, and **C3-2** (0.1 equivalents) were individually used in place of added Ni(COD)$_2$ and ligand.

General Catalytic Procedure for the mono-arylation of Ammonia (GP5-1). In a nitrogen-filled glovebox, pre-catalyst **C1-2** (5-7.5 mol %), (hetero)aryl pseudohalide (1.0 equivalents), base (2.2 equivalents), and NH$_3$ (0.5 M solution in 1,4-dioxane, 0.96 mL, 0.48 mmol, 4 equivalents) were added to a screw-capped vial containing a magnetic stir bar. 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 to 80 °C, at which point magnetic stirring was initiated. After 16 h, the vial was then removed from the heating block and was allowed to cool to ambient temperature. The crude product was purified by flash-column chromatography to afford the purified product.

General Catalytic Procedure for the mono-arylation of Primary Alkylamines (GP5-2). A protocol analogous to that employed in ammonia monoarylation was employed, using **C1-2** (5-10 mol%), base (2.2 or 6.0 equivalents, as specified), primary alkylamine (1.1 equivalents), and solvent (toluene or 1,4-dioxane, as specified), with reactions conducted at 25 °C unless otherwise specified (aryl pivalates stirred at 110 °C).

5.6.2 Synthesis and Characterization Data

Biphenyl-4-ylamine, (3-1)
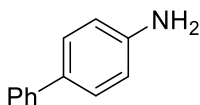
Following **GP5-1**: (0.60 mmol dimethyl-sulfamic acid biphenyl-4-yl ester, 2.4 mmol ammonia, 5 mol% **C1-2**, NaO^{t}Bu (2.2 equivalents) ([ArOSO$_2$N(Me)$_2$] = 0.125 M))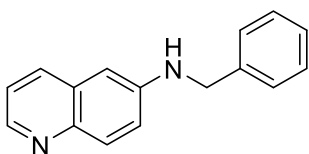 the title product was isolated as a brown solid in 82% yield. A 10% to 15% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 7.58-7.56 (m, 2H), 7.46-7.41 (m, 4H), 7.32-7.30 (m, 1H), 6.81-6.79 (m, 2H), 3.75 (br. s, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 146.0, 141.4, 131.8, 128.9, 128.2, 126.6, 126.5, 115.6. This compound was shown earlier in chapter 3, but was synthesized by this procedure. Spectral data are in agreement with the literature.[43]

Naphthalen-1-ylamine, (3-33)
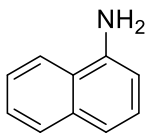
Following **GP5-1**: (0.60 mmol diethyl-carbamic acid naphthalen-1-yl ester, 2.4 mmol ammonia, 5 mol% **C1-2**, NaO^{t}Bu (2.2 equivalents) ([ArOCON(Et)$_2$] = 0.125 M)) the title product was isolated as a brown oil in 60% yield. A 10% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 7.88-7.83 (m, 2H), 7.52-7.48 (m, 2H), 7.37-7.31 (m, 2H), 6.84-6.82 (m, 1H), 4.23 (br. s,

2H); $^{13}C\{^1H\}$ NMR (125.8 MHz, CDCl$_3$): δ 142.2, 134.6, 128.8, 126.5, 126.1, 125.1, 123.9, 121.0, 119.3, 110.0. Spectral data are in agreement with the literature.[42]

2-methyl-4-Quinolinamine, (5-1)
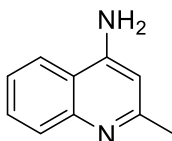
Following **GP5-1**: (0.60 mmol diethyl-carbamic acid 2-methyl-quinolin-4-yl ester, 2.4 mmol ammonia, 5 mol% **C1-2**, NaO^{t}Bu (2.2 equivalents) ([ArOCON(Et)$_2$] = 0.125 M)) the title product was isolated as a yellow solid in 85% yield. A 70% ethyl acetate, 20% hexanes, 10% diisopropylamine eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 7.98-7.96 (m, 1H), 7.76-7.74 (m, 1H), 7.68-7.65 (m, 1H), 7.45-7.42 (m, 1H), 6.56 (s, 1H), 4.65 (br. s, 2H), 2.64 (s, 3H); $^{13}C\{^1H\}$ NMR (125.8 MHz, CDCl$_3$): δ 159.5, 149.8, 148.7, 129.6, 129.2, 124.3, 120.2, 117.6, 104.2, 25.5. Spectral data are agreement with the literature.[43]

6-Quinolinamine, (5-2)
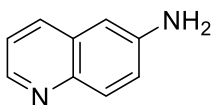
Following **GP5-1**: (0.70 mmol diethyl-carbamic acid quinoline-6-yl ester, 2.8 mmol ammonia, 5 mol% **C1-2**, NaO^{t}Bu (2.2 equivalents) ([ArOCON(Et)$_2$] = 0.125 M)) the title product was isolated as a yellow solid in 96% yield. A 45% ethyl acetate, 45% hexanes, 10% triethylamine eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 8.70-8.69 (m, 1H), 7.95-7.92 (m, 2H), 7.32-7.29 (m, 1H), 7.21-7.18 (m, 1H), 6.94-6.93 (m, 1H), 3.98 (br. s, 2H); $^{13}C\{^1H\}$ NMR (125.8 MHz,

CDCl$_3$): δ 147.1, 144.8, 143.8, 133.9, 130.9, 130.0, 121.7, 121.6, 107.7. Spectral data are in agreement with the literature.[42]

2-methyl-6-Benzothiazolamine, (5-3)
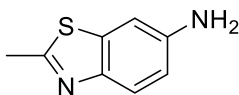
Following **GP5-1**: (0.60 mmol diethyl carbamic acid 2-methyl-benzothiazol-6-yl ester, 2.4 mmol ammonia, 5 mol% **C1-2**, NaO^{t}Bu (2.2 equivalents) ([ArOCON(Et)$_2$] = 0.125 M)) the title product was isolated as a brown solid in 53% yield. A 49.5% ethyl acetate 49.5% hexanes 1% diisopropylamine eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 7.75-7.73 (m, 1H), 7.10-7.09 (m, 1H), 6.84-6.82 (m, 1H), 3.80 (br. s, 2H), 2.79 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 162.8, 147.1, 144.2, 137.5, 123.0, 115.4, 106.1, 20.0. Spectral data are in agreement with the literature.[148]

Naphthalen-2-ylamine, (5-4)
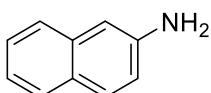
Following **GP5-1**: (0.60 mmol dimethyl-sulfamic acid napthalen-2-yl ester, 2.4 mmol ammonia, 5 mol% **C1-2**, NaO^{t}Bu (2.2 equivalents) ([ArOSO$_2$N(Me)$_2$] = 0.125 M)) the title product was isolated as a brown solid in 72% yield. A 10% to 15% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 7.74-7.69 (m, 2H), 7.64-7.62 (m, 1H), 7.41-7.38 (m, 1H), 7.28-7.24 (m, 1H), 7.03-7.02 (m, 1H), 7.00-6.98 (m, 1H), 3.87 (br. s, 2H); ^{13}C{^{1}H} NMR (125.8 MHz,

CDCl$_3$): δ 144.3, 135.2, 129.4, 128.2, 127.9, 126.6, 126.0, 122.7, 118.4, 108.8. Spectral data are in agreement with the literature.[43]

3-phenoxy-Benzenamine, (5-5)
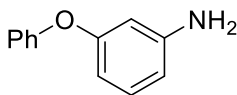
Following **GP5-1**: (0.60 mmol dimethyl-sulfamic acid 3-phenoxy-phenyl ester, 2.4 mmol ammonia, 5 mol% **C1-2**, NaO^{t}Bu (2.2 equivalents) ([ArOSO$_2$N(Me)$_2$] = 0.125 M)) the title product was isolated as a yellow oil in 70% yield. A 50% DCM/hexanes to 10% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 7.39-7.35 (m, 2H), 7.15-7.11 (m, 2H), 7.07-7.05 (m, 2H), 6.47-6.43 (m, 2H), 6.37-6.36 (m, 1H), 3.71 (br. s, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 158.7, 157.4, 148.2, 130.5, 129.8, 123.4, 119.3, 110.3, 109.1, 105.7. Spectral data are in consistent with the literature.[149]

2,3,6,7-tetrahydro-1H,5H-Benzo[ij]quinolizin-8-amine, (5-6)
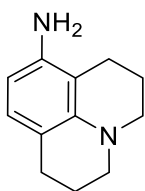
Following **GP5-1**: (0.12 mmol dimethyl-sulfamic acid 2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinoline-8-yl ester, 0.48 mmol ammonia, 7.5 mol% **C1-2**, NaO^{t}Bu (2.2 equivalents) ([ArOSO$_2$N(Me)$_2$] = 0.125 M)) the title product was isolated as a brown oil in 66% yield. A 20% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 6.70 (d, J = 7.9 Hz 1H),

6.09 (d, J = 7.9 Hz 1H), 3.43 (br. s, 2H), 3.13-3.09 (m, 4H), 2.75-2.72 (m, 2H), 2.55-2.52 (m, 2H), 2.10-2.05 (m, 2H), 2.02-1.98 (m, 2H); $^{13}C\{^1H\}$ NMR (125.8 MHz, CDCl$_3$): δ 144.0, 142.7, 127.2, 113.0, 107.1, 104.5, 50.7, 49.7, 27.5, 22.8, 22.5, 22.2. m/z ESI$^+$ found 188.1386 [M+H]$^+$ calculated for C$_{12}$H$_{17}$N$_2$ 188.1392.

Phenethyl-(8-trifluoromethyl-quinolin-4-yl)-amine, (5-7)
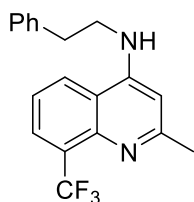
Following **GP5-2**: (0.40 mmol diethyl carbamic acid 2-methyl-8-trifluoromethyl-quinolin-4-yl ester, 0.44 mmol phenethylamine, 5 mol% **C1-2**, NaO^{t}Bu (2.2 equivalents), 1,4-dioxane ([ArOCON(Et)$_2$] = 0.125 M)) the title product was isolated as a yellow oil in 60% yield. A 10% ethyl acetate/hexanes eluent system was used for column chromatography on alumina. ^1H NMR (500.1 MHz, CDCl$_3$): δ 7.98-7.96 (m, 1H), 7.75-7.73 (m, 1H), 7.41-7.30 (m, 6H), 6.48 (s, 1H), 4.95 (br. s, 1H), 3.63-3.61 (m, 2H), 3.10-3.08 (m, 2H), 2.69 (s, 3H); $^{13}C\{^1H\}$ NMR (125.8 MHz, CDCl$_3$): δ 160.9, 149.3, 145.6, 138.6, 129.1, 128.9, 127.5 (q, J_{CF} = 6 Hz) 127.1, 125.8, 123.6, 123.5, 122.3, 118.3, 100.1, 44.3, 35.0, 26.6. m/z ESI$^+$ found 331.1417 [M+H]$^+$ calculated for C$_{19}$H$_{18}$F$_3$N$_2$ 331.1422.

N, N-Diethyl-N'-naphthalen-2-yl-ethane-1,2-diamine, (5-8)
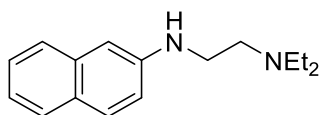
Following **GP5-2**: (0.30 mmol diethyl-carbamic acid napthalen-2-yl ester, 0.33 mmol 2-

Diethylaminoethylamine, 5 mol% **C1-2**, NaO^{t}Bu (2.2 equivalents), 1,4-dioxane ([ArOCON(Et)$_2$] = 0.125 M)) the title product was isolated as a yellow oil in 84% yield. A 20% ethyl acetate/hexanes eluent system was used for column chromatography on alumina. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 7.71-7.69 (m, 1H), 7.67-7.64 (m, 2H), 7.40-7.37 (m, 1H), 7.23-7.20 (m, 1H), 6.98-6.96 (m, 1H), 6.85-6.84 (m, 1H), 4.58 (br. s, 1H), 3.29-3.27 (s, 2H). 2.81-2.79 (m, 4H), 1.09 (t, J = 7.1 Hz 6H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 146.6, 135.5, 129.0, 127.8, 127.7, 126.4, 126.1, 122.0, 118.5, 104.6, 51.7, 46.9, 41.5, 12.0. m/z ESI$^+$ found 243.1856 [M+H]$^+$ calculated for C$_{16}$H$_{23}$ N$_2$ 243.1861.

N^1-(3-methoxyphenyl)-N^2-phenyl-1,2-Ethanediamine, (5-9)
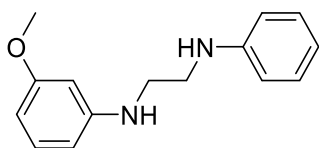
Following **GP5-2**: (0.50 mmol diethyl-carbamic acid 3-methoxy-phenyl ester, 0.55 mmol N-phenylethylenediamine, 5 mol% **C1-2**, NaO^{t}Bu (2.2 equivalents), 1,4-dioxane ([ArOCON(Et)$_2$] = 0.125 M)) the title product was isolated as a yellow oil in 81% yield. A 20% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 7.24-7.21 (m, 2H), 7.14-7.11 (m, 1H), 6.79-6.76 (m, 1H), 6.70-6.68 (m, 2H), 6.35-6.33 (m, 1H), 6.31-6.29 (m, 1H), 6.25-6.24 (m, 1H), 3.90 (br. s, 2H), 3.81 (s, 3H), 3.43 (s, 4H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 161.1, 149.7, 148.2, 130.3, 129.6, 118.1, 113.3, 106.4, 103.2, 99.3, 55.3, 43.6. m/z ESI$^+$ found 243.1492 [M+H]$^+$ calculated for C$_{15}$H$_{19}$N$_2$O 243.1497.

3,4-(Methylenedioxy)-*N*-furfurylaniline, (5-10)
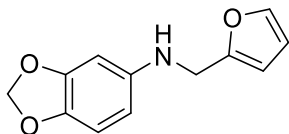
Following **GP5-2**: (0.50 mmol dimethyl-sulfamic acid benzo[1,3]dioxol-5-yl ester, 0.55 mmol furfurylamine, 5 mol% **C1-2**, NaO^{t}Bu (2.2 equivalents), 1,4-dioxane ([ArOSO$_2$N(Me)$_2$] = 0.125 M)) the title product was isolated as a yellow oil in 90% yield. A 10% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 7.40-7.39 (m, 1H), 6.70-6.69 (m, 1H), 6.36-6.34 (m, 2H), 6.26-6.25 (m, 1H), 6.16-6.14 (m, 1H), 5.89 (s, 2H), 4.29 (s, 2H), 3.84 (br. s, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 153.0, 148.6, 143.6, 142.1, 140.3, 110.5, 108.8, 107.2, 105.2, 100.9, 96.7, 42.7. Spectral data are in agreement with the literature.[150]

Piperidin-4-ylmethyl-(4-pyrrol-1-yl-phenyl)-amine, (5-11)
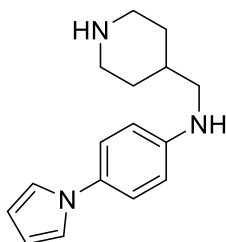
Following **GP5-2**: (0.50 mmol dimethyl-sulfamic acid 4-pyrrol-1-yl-phenyl ester, 0.55 mmol 4-(aminomethyl) piperidine, 5 mol% **C1-2**, NaO^{t}Bu (2.2 equivalents), 1,4-dioxane ([ArOSO$_2$N(Me)$_2$] = 0.125 M)) the title product was isolated as a white solid in 76% yield. A 100% ethyl acetate to 10%Methanol/DCM eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 7.24-7.22 (m, 2H), 7.00-6.99 (m, 2H), 6.67-6.65 (m, 2H), 6.33-6.32 (m, 2H), 3.80 (br. s, 1H), 3.19-3.16 (m, 2H),

3.08-3.06 (m, 2H), 2.70-2.64 (m, 2H), 2.16 (br. s, 1H), 1.81-1.74 (m, 3H), 1.32-1.24 (m, 2H); $^{13}C\{^1H\}$ NMR (125.8 MHz, CDCl$_3$): δ 146.9, 132.0, 122.8, 120.0, 113.2, 109.5, 50.7, 46.6, 36.4, 31.7. *m/z* ESI$^+$ found 256.1808 [M+H]$^+$ calculated for C$_{16}$H$_{22}$N$_3$ 256.1814.

2-methyl-*N*-(1-methylpropyl)-6-Benzothiazolamine, (5-12)
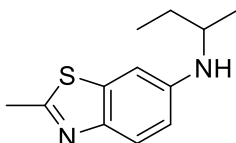
Following **GP5-2**: (0.50 mmol dimethyl-sulfamic acid 2-methyl-benzothiazol-6-yl ester, 0.55 mmol *sec*-butylamine, 5 mol% **C1-2**, NaO^{t}Bu (2.2 equivalents), 1,4-dioxane ([ArOSO$_2$N(Me)$_2$] = 0.125 M)) the title product was isolated as a yellow oil in 64% yield. A 20% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 7.72-7.71 (m, 1H), 6.95-6.94 (m, 1H), 6.73-6.71 (m, 1H), 3.61 (br. s, 1H), 3.47-3.43 (m, 1H), 2.78 (s, 3H), 1.71-1.63 (m, 1H), 1.59-1.50 (m, 1H), 1.24 (d, *J* =6.3 Hz, 3H), 1.01 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (125.8 MHz, CDCl$_3$): δ 161.7, 145.8, 145.7, 137.9, 122.9, 114.5, 102.8, 50.5, 29.8, 20.4, 20.0, 10.6. *m/z* ESI$^+$ found 221.1107 [M+H]$^+$ calculated for C$_{12}$H$_{17}$N$_2$S 221.1112.

Furan-2-ylmethyl-(4-methoyxy-phenyl)-amine, (5-13)
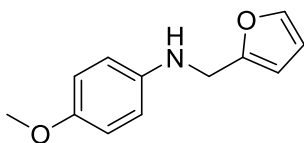
Following **GP5-2**: (0.50 mmol pivalic acid 4-methoxy-phenyl ester, 0.55 mmol furfurylamine, 10 mol% **C1-2**, NaO^{t}Bu (2.2 equivalents), toluene ([ArOCO^{t}Bu] = 0.12 M), stirred at 110 °C) the title product was isolated as a yellow oil in 53% yield. A 10% ethyl

acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 7.40-7.39 (m, 1H), 6.84-6.81 (m, 2H), 6.70-6.68 (m, 2H), 6.36-6.35 (m, 1H), 6.26-6.25 (m, 1H), 4.31 (s, 2H), 3.85 (br. s, 1H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 153.2, 152.8, 142.1, 142.0, 115.1, 114.9, 110.5, 107.1, 56.0, 42.7. Spectral data are in agreement with the literature.[35]

4-[(Thiophen-2-ylmethyl)-amino]-benzonitrile, (5-14)
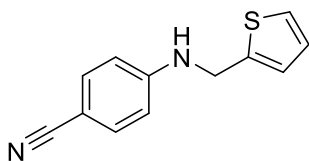
Following **GP5-2**: (0.50 mmol pivalic acid 4-cyano-phenyl ester, 0.55 mmol 2-thiophenemethylamine, 10 mol% **C1-2**, K$_3$PO$_4$ (6.0 equivalents), toluene ([ArOCO^{t}Bu] = 0.08 M), stirred at 110 °C) the title product was isolated as a yellow solid in 75% yield. A 10% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 7.51-7.49 (m, 2H), 7.29-7.28 (m, 1H), 7.08-7.07 (m, 1H), 7.02-7.00 (m, 1H), 6.77-6.76 (m, 2H), 5.09 (br. s, 1H), 4.60 (s, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 150.3, 140.8, 134.0, 133.7, 127.3, 126.1, 125.5, 120.3, 113.3, 43.1. *m/z* ESI$^+$ found 237.0457 [M+Na]$^+$ calculated for C$_{12}$H$_{10}$N$_2$NaS 237.0457.

Benzyl-quinolin-6-yl-amine, (5-15)

Following **GP5-2**: (0.50 mmol pivalic acid quinoline-6-yl ester, 0.55 mmol benzylamine, 10 mol% **C1-2**, K$_3$PO$_4$ (6.0 equivalents), toluene ([ArOCO^{t}Bu] = 0.08 M), stirred at 110

°C) the title product was isolated as a yellow solid in 60% yield. A 50% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 8.63-8.62 (m, 1H), 8.17-8.16 (m, 1H), 8.09-8.08 (m, 1H), 7.45-7.40 (m, 5H), 7.36-7.33 (m, 2H), 6.79-6.78 (m, 1H), 4.66 (br. s, 1H), 4.50 (s, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 146.4, 145.6, 142.6, 138.8, 134.8, 131.3, 130.4, 129.9, 129.0, 127.7, 122.0, 121.5, 103.4, 48.5. *m/z* ESI$^+$ found 235.1230 [M+H]$^+$ calculated for C$_{16}$H$_{15}$N$_2$ 235.1230.

Furan-2-ylmethyl-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolane-2-yl)-phenyl]-amine, **(5-16)**
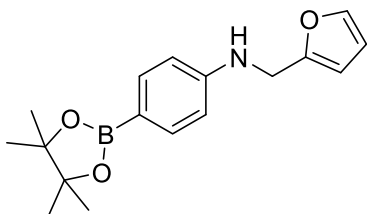
Following **GP5-2**: (0.40 mmol pivalic acid 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolane-2-yl)-phenyl ester, 0.44 mmol furfurylamine, 10 mol% **C1-2**, K$_3$PO$_4$ (6.0 equivalents), toluene ([ArOCO^{t}Bu] = 0.08 M), stirred at 110 °C) the title product was isolated as a yellow oil in 77% yield. A 5% to 10% ethyl acetate/hexanes eluent system was used for column chromatography on silica gel. ^{1}H NMR (500.1 MHz, CDCl$_3$): δ 7.72-7.70 (m, 2H), 7.38-7.37 (m, 1H), 6.83-6.81 (m, 2H), 6.34-6.33 (m, 2H), 4.89 (br. s, 1H), 4.41 (s, 2H), 1.36 (s, 12H); ^{13}C{^{1}H} NMR (125.8 MHz, CDCl$_3$): δ 142.5, 136.5, 136.1, 114.0, 110.7, 108.3, 83.6, 42.2, 27.4, 25.1. *m/z* ESI$^+$ found 300.1766 [M+H]$^+$ calculated for C$_{17}$H$_{23}$BNO$_3$ 300.1766.

CHAPTER 6 Conclusions and Future Work

6.1 Introduction

The previous chapters describe the success of the JosiPhos and DalPhos ligand families in metal catalyzed C-C and C-N cross-coupling reactions, with a focus on the latter. While there are still advancements to be made in palladium-catalyzed cross-coupling, such as the topic of Chapter 2 (mono-α-arylation of acetone at room temperature), the field of nickel-catalyzed cross-coupling is rapidly growing and will likely be the future of these transformations. Presented in this document are some of the first examples of challenging nickel-catalyzed $C(sp^2)$-N bond forming reactions, such as the room temperature mono-arylation of primary alkylamines (Chapter 3), *N*-arylation of amides and lactams (Chapter 4), and amination of aryl carbamates, sulfamates, and pivalates with ammonia and primary amines (Chapter 5). However, this field is still expanding. There are many limitations to address in the current methodologies and new reactivity to be discovered. In the sections below a summary and new potential areas to explore are presented with respect to each previous the themes of chapters 2-5.

6.2 Mono-α-Arylation of Acetone

The mono-α-arylation acetone at room temperature was an important improvement made possible by use of a JosiPhos (**L1-4**) and palladium catalyst system. The JosiPhos

ligand family were employed in asymmetric hydrogenations in years past[151] and later found use in achiral transformations such as BHA[152] and α-arylation. The JosiPhos ligands therefore are not fully utilized in the mono-α-arylation acetone due to their unnecessary enantiopurity, which is wasteful given their costly nature. A potential application of this transformation could be a variation of the reaction to produce enatio-enriched products from acetone. The benzyl ketone products shown in Chapter 2 could be arylated a second time to produce diaryl benzyl ketones with different aryl groups (Figure 6-1a). Alpha substituted alkyl ketones could be transformed with this methodology into chiral benzyl ketones as well. Initial efforts could begin with a screen of JosiPhos ligands employing simple substrates such as propiophenone derivatives to find conditions that will accommodate the larger substrate class (Figure 6-1b).
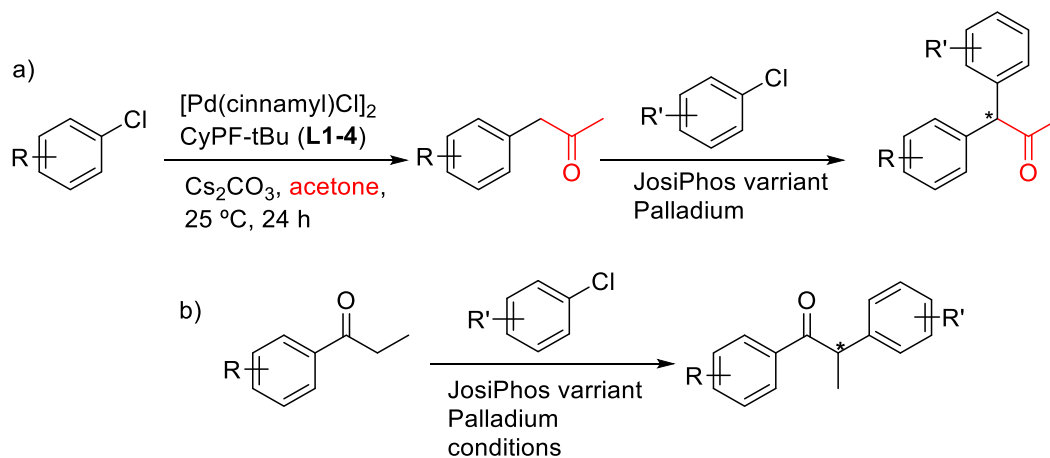
Figure 6-1: Potential applications of chiral JosiPhos ligands in mono-α-arylation chemistry.

Beyond palladium and JosiPhos, an obvious future advancement for the mono-α-arylation of acetone would be to develop a nickel-catalyzed protocol to harvest the benefits of nickel catalysis described in Chapter 1 and 3. Although Hartwig has made an impactful

contribution in this area through the development of nickel-catalyzed α-arylation of ketones,[153] all of the work with acetone has been with palladium. As discussed in Section 2.4.2, aryl tosylates were not used because they required elevated temperatures to produce the desired products. As shown in Chapters 3 and 5, nickel-catalysts are capable of accomidating tosylates and other pseudohalides in room temperature aminations with both DalPhos and JosiPhos ligands respectively.

The application of the mono-α-arylation of acetone methodology in the synthesis of benzofurans was unsuccessful (Section 2.4.3). A major factor in this failure is likely the inability of the JosiPhos catalyst to tolerate very large ortho substituents. A possible solution to this would be to use a smaller phenol protecting group such as a methyl ester to generate derivatives of product **2-8** (Section 2.3). Given that the current system can tolerate a methoxy group in the ortho position, it may be possible to demethylate under mild conditions[154] to the corresponding phenol and continue the proposed benzofuran synthesis (Figure 6-2). A separate approach, more consistent with the idea of developing a nickel-catalyzed protocol, would be to move away from JosiPhos ligands to ligands with an easier, modular synthesis such as PAd-DalPhos. Buchwald was very successful with this approach in palladium chemistry in the development of different biarylphosphine ligands suited for different tasks.[32b] One ligand variant could be used to obtain the benzyl ketone products while a second ligand could be developed for the benzofuran synthesis (Figure 6-2).
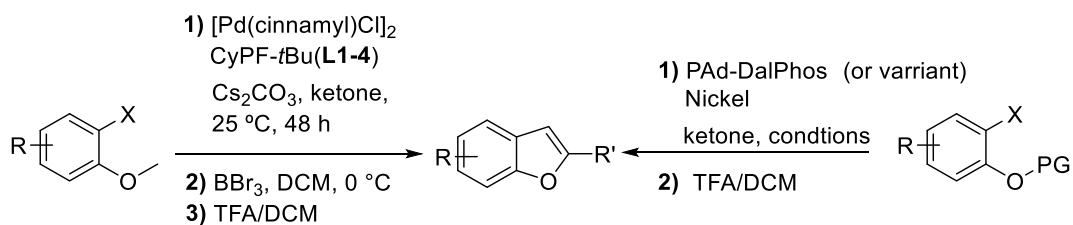
Figure 6-2: New potential synthesis of benzofurans via room temperature mono-α-arylation of acetone.

New ligand variants can also be used to tolerate different functional groups as was done with Mor-DalPhos (Section 1.3).[17] A separate ligand could be developed to address the lack of electrophiles with electron-withdrawing substituents in the scope of mono-α-arylation of acetone at room temperature.

6.3 Nickel-Catalyzed Amination

The (PAd-DalPhos)Ni(o-tolyl)Cl (**C1-1**) pre-catalyst can accommodate a wide scope of coupling partners in amination reactions as described in Chapter 3. However, there are still limitations to be addressed. The inability of **C1-1** to tolerate five-membered ring electrophiles is unfortunate given their potential utility as synthons in many biologically active molecules.[100] Five-membered rings present different steric and electronic properties than six-membered rings. To begin to address this issue, stoichiometric amination reactions could be performed in an effort to analyze the catalyst and reactants after being exposed to the reaction conditions. Another limitation of **C1-1** was its inability to employ di-ortho substituted electrophiles with six or five-membered rings. Mechanistic investigations could also aid in the design of ligands to accommodate more sterically

hindered coupling partners such as these. PAd-DalPhos was designed to perform ammonia mono-aryaltion reactions, which requires it to be sterically encumbering to discourage unwanted polyarylation. However, the same steric profile is detrimental when employing bulky coupling partners. In combination with experimental ligand synthesis, reductive elimination complexes could be modeled computationally to help suggest ligand variants that might be able to accommodate large coupling partners. The steric profile of the ligand was considered an important factor in palladium-catalyzed amination of five-membered rings as well. This type of study would contribute to work to further elucidate the mechanism of nickel-catalyzed amination with PAd-DalPhos ligands, which has began and is ongoing in the Stradiotto group.[155] It may be possible to synthesize a PAd-DalPhos variant that is tailored for aminations with sterically congested coupling partners such as 1,6-dimethylchlorobenzene and others. Derivatizing PAd-DalPhos for specific applications in nickel-catalyzed amination has already been successful in the mono-arylation of cyclopropylamine.[156]

6.4 Nickel-Catalyzed Amidation

The (PAd-DalPhos)Ni(o-tolyl)Cl (**C1-1**) catalyst was employed in the first examples of nickel-catalyzed *N*-arylations of primary amines and lactams. However, there is still much research to be done on this challenging transformation. The scope of coupling partners used in the nickel-catalyzed amidation with **C1-1** was limited compared to the demonstrated scope of amination and it was not possible to perform the amidation reactions at room temperature. One potential problem in metal catalyzed amidation is the ability of

the amide coupling partners to bind in a κ^2 fashion to the metal center as noted with palladium.[122] Attempts to isolate a PAd-DalPhos nickel amidate complex from a stoichiometric reaction might be an appropriate staring point (Figure 6-3).
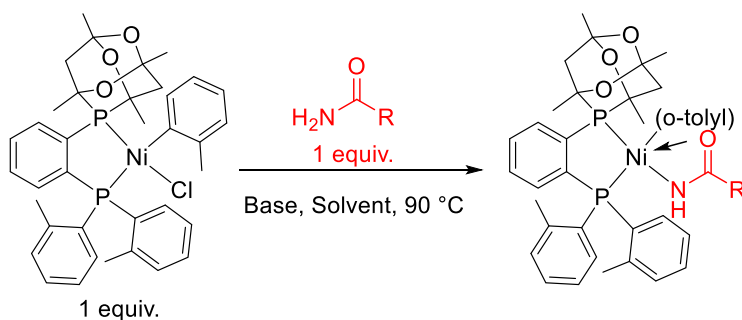
Figure 6-3: Proposed synthesis of PAd-DalPhos amidate complex.

From knowledge of the interactions of amides with the PAd-DalPhos nickel complex it may be possible to design a new ligand or variant of PAd-DalPhos that could give rise to a more active catalyst. Simply changing the pre-catalyst may affect reactivity as well. The ortho tolyl group on the nickel center is aminated by the amine nucleophile upon catalyst activation to produce an ortho tolyl aniline compound in the same percentage as the amount of pre-catalyst used. There are very few examples of ortho substituted electrophiles employed in the scope because they were difficult coupling partners (Section 4.3). This suggests that the initial oxidative addition of the ortho tolyl halide is difficult. The coordination of the amide to a complex bearing a hindered ortho tolyl ligand may also be difficult and could account for lack of reactivity with certain amide coupling partners. Schranck and co-workers use a similar catalyst to **C1-2** substituting the ortho tolyl fragment is with a para cyano aryl fragment.[146] 4-Chlorobenzonitrile was an excellent substrate in amidation reactions using **C1-1** and perhaps a pre-catalyst based on this moiety (**C6-1**) would be a more active catalyst (Figure 6-4).

C6-1
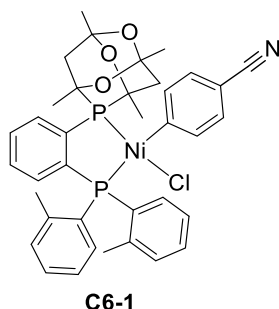
Figure 6-4: New potential PAd-DalPhos pre-catalyst (PAd-DalPhos)Ni(p-benzonitrile)Cl.

A previous strategy in palladium-catalyzed arylation of secondary amides includes the development of a cationic palladium catalyst by using aryl triflate and nonaflate electrophiles to accommodate the weak nucleophilicity of secondary amides.[48d] Similar strategies could be used with nickel to develop an amidation catalyst with a wider scope of reactivity. Furthermore, a more active catalyst may be capable of room temperature reactivity to allow the tolerance of more functional groups. For example, the amide containing an aziridine ring discussed in Section 4.4.1 seems to degrade under the reaction conditions (90 °C), but at room temperature arylation of such amide coupling partners might be possible. Buchwald and co-workers have disclosed several reports on the palladium-catalyzed amidation reaction[24j, 32a, 48b-e, 121a, 121b] [103] and there will likely be much future research building on this initial work with nickel.

6.5 Nickel-Catalyzed Amination of Aryl Carbamates, Sulfamates, and Pivalates.

The successful amination aryl carbamates, sulfamates, and pivalates with ammonia and primary alkylamines represents an important advancement for nickel catalysis.

Utilization of these electrophiles creates a synthetic pathway to aniline products that cannot be accessed by use of palladium catalysis. One of the most attractive features of these leaving groups is their ability to function as directing groups in other transformations, as discussed in Section 5.1. Unfortunately, attempts to harness the directing group and electrophile capabilities of these groups in the same molecule were ineffective in the work presented herein. In the reactions that were attempted in Section 5.4 some important observations can be made. In the case of the carbamate there seems to be undesired Suzuki reactivity where the boronic ester is cleaved and replaced with a proton as observed by GC analysis. The analogous compound using the pivalate as a directing group provided potentially 20% of the desired amination product and no deborylated material was observed. A new catalyst might be able to increase this yield to a more synthetically useful amount. As mentioned earlier the JosiPhos ligands are expensive and difficult to modify, while PAd-DalPhos has a more modular synthesis. In the initial test reaction (PAd-DalPhos)Ni(o-tolyl)Cl (**C1-1**) gave an inferior yield of 1-aminonaphthalene to (CyPF-Cy)Ni(o-tolyl)Cl (**C1-2**) (60% to 95% respectively), but was not a completely futile reaction. PAd-DalPhos or a derivative may be capable of tolerating the meta boronic ester in aminations of aryl carbamates and pivalates (Figure 6-5).
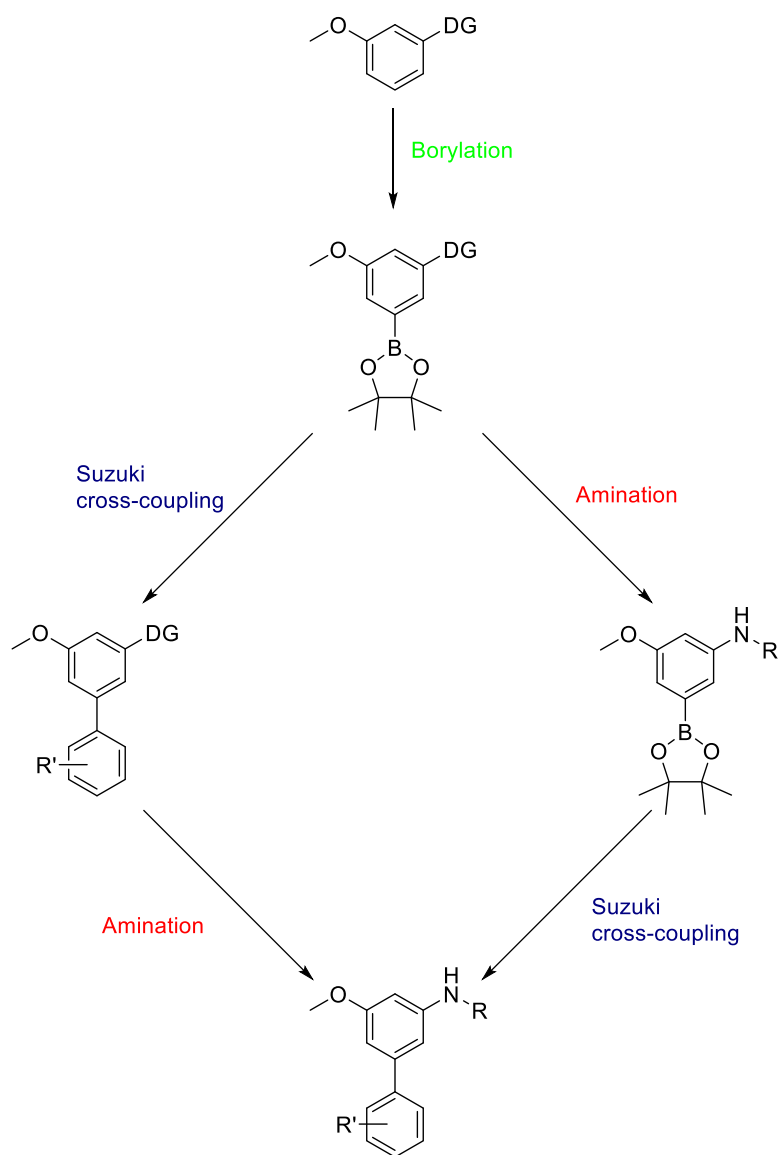
Figure 6-5: Proposed nickel-catalyzed amination and Suzuki reactions with JosiPhos or PAd-DalPhos ligands.

The deborylation reaction with **C1-2** should also not be ignored. There is potential to utilize these catalysts further and develop a nickel Suzuki catalyst system based on JosiPhos or PAd-DalPhos ligand variants (Figure 6-5). If the rates of each of these reactions were matched appropriately, there is potential for the development of one-pot reaction protocols.

References

[1]   J. E. McMurry, Fay, R. C., *General Chemistry: Atoms First*, Pearson Education Inc. , Upper Saddle River, New Jersey **2010**.

[2]   R. H. Garret, and Grisham, C. M. , *Biochemistry* 4ed., University of Virginia, Boston, MA, **2010**.

[3]   M. L. Zastrow, F. A. PeacockAnna, J. A. Stuckey, V. L. Pecoraro, *Nat. Chem.* **2012**, *4*, 118-123.

[4]   M. Appl, in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH **2000**.

[5]   J. F. Hartwig, University Science Books, Sausalito, California, **2010**.

[6]   a) R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008-2022; b) W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1998-2007.

[7]   a) R. R. Schrock, *Angew. Chem. Int. Ed.* **2006**, *45*, 3748-3759; b) Y. Chauvin, *Angew. Chem. Int. Ed.* **2006**, *45*, 3740-3747; c) R. H. Grubbs, *Angew. Chem. Int. Ed.* **2006**, *45*, 3760-3765.

[8]   F. Ullmann, J. Bielecki, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2174-2185.

[9]   R. D. Stephens, C. E. Castro, *J. Org. Chem.* **1963**, *28*, 3313-3315.

[10]   a) N. Miyaura, A. Suzuki, *J. Chem. Soc. Chem. Commun.* **1979**, 866-867; b) S. Baba, E. Negishi, *J. Am. Chem. Soc.* **1976**, *98*, 6729-6731; c) R. F. Heck, J. P. Nolley, *J. Org. Chem.* **1972**, *37*, 2320-2322.

[11]   M. F. Semmelhack, P. M. Helquist, L. D. Jones, *J. Am. Chem. Soc.* **1971**, *93*, 5908-5910.

[12]   a) M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 11108-11109; b) B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 12382-12383; c) T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Angew. Chem. Int. Ed.* **1997**, *36*, 1740-1742.

[13]   C. C. C. Johansson, T. J. Colacot, *Angew. Chem. Int. Ed.* **2010**, *49*, 676-707.

[14]   A. Kamada, A. Sasaki, N. Kitazawa, T. Okabe, K. Nara, S. Hamaoka, S. Araki, H. Hagiwara, *Chem. Pharm. Bull.* **2004**, *52*, 79-88.

[15]   H. A. K. A. El-Aal, A. A. Khalaf, *Aust. J. Chem.* **2013**, *66*, 635-645.

[16]   M. Ślusarczyk, W. M. De Borggraeve, G. Hoornaert, F. Deroose, J. T. M. Linders, *Eur. J. Org. Chem.* **2008**, *2008*, 1350-1357.

[17] K. D. Hesp, R. J. Lundgren, M. Stradiotto, *J. Am. Chem. Soc.* **2011**, *133*, 5194-5197.

[18] D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 5816-5817.

[19] P. G. Alsabeh, M. Stradiotto, *Angew. Chem. Int. Ed.* **2013**, *52*, 7242-7246.

[20] a) R. G. R. Bacon, H. A. O. Hill, *Quarterly Reviews, Chemical Society* **1965**, *19*, 95-125; b) J. Lindley, *Tetrahedron* **1984**, *40*, 1433-1456; c) H. B. Goodbrand, N.-X. Hu, *J. Org. Chem.* **1999**, *64*, 670-674.

[21] M. Kosugi, M. Kameyama, T. Migita, *Chem. Lett.* **1983**, *12*, 927-928.

[22] A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem. Int. Ed. Engl* **1995**, *34*, 1348-1350.

[23] J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609-3612.

[24] a) G. D. Vo, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 11049-11061; b) D. S. Surry, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 10354-10355; c) D. Tsvelikhovsky, S. L. Buchwald, *J. Am. Chem. Soc.* **2011**, *133*, 14228-14231; d) C. W. Cheung, D. S. Surry, S. L. Buchwald, *Org. Lett.* **2013**, *15*, 3734-3737; e) T. Schulz, C. Torborg, S. Enthaler, B. Schäffner, A. Dumrath, A. Spannenberg, H. Neumann, A. Börner, M. Beller, *Chem. Eur. J.* **2009**, *15*, 4528-4533; f) A. Dumrath, C. Lübbe, H. Neumann, R. Jackstell, M. Beller, *Chem. Eur. J.* **2011**, *17*, 9599-9604; g) R. J. Lundgren, B. D. Peters, P. G. Alsabeh, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 4071-4074; h) P. G. Alsabeh, R. J. Lundgren, L. E. Longobardi, M. Stradiotto, *Chem. Commun.* **2011**, *47*, 6936-6938; i) P. G. Alsabeh, R. J. Lundgren, R. McDonald, C. C. C. Johansson Seechurn, T. J. Colacot, M. Stradiotto, *Chem. Eur. J.* **2013**, *19*, 2131-2141; j) S. M. Crawford, C. B. Lavery, M. Stradiotto, *Chem. Eur. J.* **2013**, *19*, 16760-16771.

[25] G. J. Withbroe, R. A. Singer, J. E. Sieser, *Org. Process Res. Dev.* **2008**, *12*, 480-489.

[26] C. Valente, M. Pompeo, M. Sayah, M. G. Organ, *Org. Process Res. Dev.* **2014**, *18*, 559-559.

[27] A. Tewari, M. Hein, A. Zapf, M. Beller, *Tetrahedron* **2005**, *61*, 9705-9709.

[28] D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 6338-6361.

[29] T. J. Maimone, P. J. Milner, T. Kinzel, Y. Zhang, M. K. Takase, S. L. Buchwald, *J. Am. Chem. Soc.* **2011**, *133*, 18106-18109.

[30] B. P. Fors, N. R. Davis, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 5766-5768.

[31] S. R. Stauffer, M. A. Steinbeiser, *Tetrahedron Lett.* **2005**, *46*, 2571-2575.

[32] a) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653-6655; b) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27-50.

[33] N. H. Park, G. Teverovskiy, S. L. Buchwald, *Org. Lett.* **2014**, *16*, 220-223.

[34] I. T. Raheem, S. N. Goodman, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 706-707.

[35] J. S. K. Clark, C. M. Lavoie, P. M. MacQueen, M. J. Ferguson, M. Stradiotto, *Organometallics* **2016**, *35*, 3248-3254.

[36] a) M. Liang, J. Chen, *Chem. Soc. Rev.* **2013**, *42*, 3453-3488; b) S. A. Lawrence, *Amines: Synthesis, Properties and Applications*, Cambridge University Press, Cambridge, **2006**; c) A. G. MacDiarmid, *Angew. Chem. Int. Ed.* **2001**, *40*, 2581-2590.

[37] Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 10028-10029.

[38] a) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2010**, *111*, 1346-1416; b) T. Mesganaw, N. K. Garg, *Org. Process Res. Dev.* **2012**, *17*, 29-39; c) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299-309.

[39] C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085.

[40] a) S. Ge, R. A. Green, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 1617-1627; b) R. A. Green, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2015**, *54*, 3768-3772.

[41] a) L. Hie, S. D. Ramgren, T. Mesganaw, N. K. Garg, *Org. Lett.* **2012**, *14*, 4182-4185; b) A. R. Martin, Y. Makida, S. Meiries, A. M. Z. Slawin, S. P. Nolan, *Organometallics* **2013**, *32*, 6265-6270; c) J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 6054-6058; d) E. Brenner, R. Schneider, Y. Fort, *Tetrahedron Lett.* **2000**, *41*, 2881-2884; e) C. Desmarets, R. Schneider, Y. Fort, *Tetrahedron Lett.* **2000**, *41*, 2875-2879; f) B. H. Lipshutz, H. Ueda, *Angew. Chem.*

Int. Ed. **2000**, *39*, 4492-4494; g) C. Desmarets, R. Schneider, Y. Fort, *Tetrahedron Lett.* **2001**, *42*, 247-250; h) R. Omar-Amrani, A. Thomas, E. Brenner, R. Schneider, Y. Fort, *Org. Lett.* **2003**, *5*, 2311-2314; i) R. A. Kelly, III, N. M. Scott, S. Diez-Gonzalez, E. D. Stevens, S. P. Nolan, *Organometallics* **2005**, *24*, 3442-3447; j) C. Chen, L.-M. Yang, *J. Org. Chem.* **2007**, *72*, 6324-6327; k) K. Matsubara, K. Ueno, Y. Koga, K. Hara, *J. Org. Chem.* **2007**, *72*, 5069-5076; l) G. Manolikakes, A. Gavryushin, P. Knochel, *J. Org. Chem.* **2008**, *73*, 1429-1434; m) C.-Y. Gao, X. Cao, L.-M. Yang, *Org. Biomol. Chem.* **2009**, *7*, 3922-3925; n) M. Tobisu, T. Shimasaki, N. Chatani, *Chem. Lett.* **2009**, *38*, 710-711; o) L. Ackermann, R. Sandmann, W. Song, *Org. Lett.* **2011**, *13*, 1784-1786; p) T. Shimasaki, M. Tobisu, N. Chatani, *Angew. Chem. Int. Ed.* **2010**, *49*, 2929-2932; q) J.-H. Huang, L.-M. Yang, *Org. Lett.* **2011**, *13*, 3750-3753; r) T. Mesganaw, A. L. Silberstein, S. D. Ramgren, N. F. F. Nathel, X. Hong, P. Liu, N. K. Garg, *Chem Sci* **2011**, *2*, 1766-1771; s) S. D. Ramgren, A. L. Silberstein, Y. Yang, N. K. Garg, *Angew. Chem. Int. Ed.* **2011**, *50*, 2171-2173; t) M. J. Iglesias, J. F. Blandez, M. R. Fructos, A. Prieto, E. Alvarez, T. R. Belderrain, M. C. Nicasio, *Organometallics* **2012**, *31*, 6312-6316; u) M. Tobisu, A. Yasutome, K. Yamakawa, T. Shimasaki, N. Chatani, *Tetrahedron* **2012**, *68*, 5157-5161; v) S. S. Kampmann, A. N. Sobolev, G. A. Koutsantonis, S. G. Stewart, *Adv. Synth. Catal.* **2014**, *356*, 1967-1973; w) R. A. Green, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2015**, 3768–3772; x) N. H. Park, G. Teverovskiy, S. L. Buchwald, *Org. Lett.* **2013**, *16*, 220-223; y) H. Yue, L. Guo, X. Liu, M. Rueping, *Org. Lett.* **2017**, *19*, 1788-1791; z) H. Yue, L. Guo, H.-H. Liao, Y. Cai, C. Zhu, M. Rueping, *Angew. Chem. Int. Ed.* **2017**, *56*, 4282-4285; aa) M. Tobisu, N. Chatani, *Acc. Chem. Res.* **2015**, *48*, 1717-1726.

[42]   A. Borzenko, N. L. Rotta-Loria, P. M. MacQueen, C. M. Lavoie, R. McDonald, M. Stradiotto, *Angew. Chem. Int. Ed.* **2015**, *54*, 3773-3777.

[43]   C. M. Lavoie, P. M. MacQueen, N. L. Rotta-Loria, R. S. Sawatzky, A. Borzenko, A. J. Chisholm, B. K. V. Hargreaves, R. McDonald, M. J. Ferguson, M. Stradiotto, *Nat. Commun.* **2016**, *7*, 11073.

[44]   E. L. Baker, M. M. Yamano, Y. Zhou, S. M. Anthony, N. K. Garg, **2016**, *7*, 11554.

[45]   L. Hie, N. F. Fine Nathel, T. K. Shah, E. L. Baker, X. Hong, Y.-F. Yang, P. Liu, K. N. Houk, N. K. Garg, *Nature* **2015**, *524*, 79-83.

[46]   N. A. Weires, E. L. Baker, N. K. Garg, **2016**, *8*, 75.

[47]   S. Shi, G. Meng, M. Szostak, *Angew. Chem. Int. Ed.* **2016**, *55*, 6959-6963.

[48]   a) J. Yin, S. L. Buchwald, *Org. Lett.* **2000**, *2*, 1101-1104; b) J. Yin, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 6043-6048; c) B. P. Fors, K. Dooleweerdt, Q. Zeng, S. L. Buchwald, *Tetrahedron* **2009**, *65*, 6576-6583; d) J. D. Hicks, A. M. Hyde, A. M. Cuezva, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 16720-16734; e) K. Dooleweerdt, B. P. Fors, S. L. Buchwald, *Org. Lett.* **2010**, *12*, 2350-2353; f) P. J. Manley, M. T. Bilodeau, *Org. Lett.* **2004**, *6*, 2433-2435; g) W. C. Shakespeare, *Tetrahedron Lett.* **1999**, *40*, 2035-2038.

[49]   a) K. Groom, S. M. S. Hussain, J. Morin, C. Nilewski, T. Rantanen, V. Snieckus, *Org. Lett.* **2014**, *16*, 2378-2381; b) C. Schneider, E. Broda, V. Snieckus, *Org. Lett.* **2011**, *13*, 3588-3591; c) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879-933.

[50]   a) X. Zhao, C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 5837-5844; b) T. Mesganaw, N. F. Fine Nathel, N. K. Garg, *Org. Lett.* **2012**, *14*, 2918-2921; c) K. Yamazaki, S. Kawamorita, H. Ohmiya, M. Sawamura, *Org. Lett.* **2010**, *12*, 3978-3981.

[51]   L. Hie, S. D. Ramgren, T. Mesganaw, N. K. Garg, *Org. Lett.* **2012**, *14*, 4182-4185.

[52]   L. Ackermann, V. P. Mehta, *Chem. Eur. J.* **2012**, *18*, 10230-10233.

[53]   D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234-245.

[54]   a) C. Gäbler, M. Korb, D. Schaarschmidt, A. Hildebrandt, H. Lang, *Adv. Synth. Catal.* **2014**, *356*, 2979-2983; b) P. Li, B. Lü, C. Fu, S. Ma, *Adv. Synth. Catal.* **2013**, *355*, 1255-1259.

[55]   a) H. R. Chobanian, P. Liu, M. D. Chioda, Y. Guo, L. S. Lin, *Tetrahedron Lett.* **2007**, *48*, 1213-1216; b) P. Liu, T. J. Lanza Jr, J. P. Jewell, C. P. Jones, W. K. Hagmann, L. S. Lin, *Tetrahedron Lett.* **2003**, *44*, 8869-8871.

[56]   V. P. A. Raja, S. Perumal, P. Yogeeswari, D. Sriram, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3881-3884.

[57]   I. Baracu, V. Dobre, I. Niculescu-Duvaz, *J. Prakt. Chem.* **1985**, *327*, 667-674.

[58]   P. A. Reddy, K. E. Woodward, S. M. McIlheran, B. C. H. Hsiang, T. N. Latifi, M. W. Hill, S. M. Rothman, J. A. Ferrendelli, D. F. Covey, *J. Med. Chem.* **1997**, *40*, 44-49.

[59]   A. Ranise, S. Schenone, O. Bruno, F. Bondavalli, W. Filippelli, G. Falcone, B. Rivaldi, *Il Farmaco* **2001**, *56*, 647-657.

[60]   a) A. F. Littke, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 6989-7000; b) G. Adjabeng, T. Brenstrum, J. Wilson, C. Frampton, A. Robertson, J. Hillhouse, J. McNulty, A. Capretta, *Org. Lett.* **2003**, *5*, 953-955; c) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696; d) N. Marion, O. Navarro, J. G. Mei, E. D. Stevens, N. M. Scott, S. P. Nolan, *J. Am. Chem. Soc.* **2006**, *128*, 4101-4111; e) O. Navarro, N. Marion, J. G. Mei, S. P. Nolan, *Chem. Eur. J.* **2006**, *12*, 5142-5148; f) E. Alvaro, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 7858-7868; g) C. Han, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 7532-7533; h) A. G. Sergeev, T. Schulz, C. Torborg, A. Spannenberg, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 7595-7599; i) M. Pompeo, R. D. Froese, N. Hadei, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 11354-11357; j) G.-p. Lu, C. Cai, B. H. Lipshutz, *Green Chem.* **2013**, *15*, 105; k) C. A. Wheaton, J.-P. J. Bow, M. Stradiotto, *Organometallics* **2013**, *32*, 6148-6161; l) J. L. Farmer, M. Pompeo, A. J. Lough, M. G. Organ, *Chem. Eur. J.* **2014**, *20*, 15790-15798; m) M. Pompeo, J. L. Farmer, R. D. Froese, M. G. Organ, *Angew. Chem. Int. Ed.* **2014**, *53*, 3223-3226; n) J. Zhang, A. Bellomo, N. Trongsiriwat, T. Jia, P. J. Carroll, S. D. Dreher, M. T. Tudge, H. Yin, J. R. Robinson, E. J. Schelter, P. J. Walsh, *J. Am. Chem. Soc.* **2014**, *136*, 6276-6287.

[61]   R. Singh, S. P. Nolan, *J. Organomet. Chem.* **2005**, *690*, 5832-5840.

[62]   B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *Journal of the American Chemical Society* **2008**, *130*, 13552-13554.

[63]   N. L. Rotta-Loria, A. Borzenko, P. G. Alsabeh, C. B. Lavery, M. Stradiotto, *Adv. Synth. Catal.* **2015**, *357*, 100-106.

[64]   J. L. Klinkenberg, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 11830-11833.

[65]   a) P. Rebelli, J. R. Yerrabelly, B. K. Yalamanchili, R. Kommera, V. R. Ghojala, K. R. Bairy, *Org. Process Res. Dev.* **2013**, *17*, 1021-1026; b) N. C. Niphade, K. M.

Jagtap, C. T. Gaikawad, M. N. Jachak, V. T. Mathad, *Org. Process Res. Dev.* **2011**, *15*, 1382-1387; c) J. C. Yang, D. Niu, B. P. Karsten, F. Lima, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 2531-2535; d) S. A. Munk, D. A. Harcourt, P. N. Arasasingham, J. A. Burke, A. B. Kharlamb, C. A. Manlapaz, E. U. Padillo, D. Roberts, E. Runde, L. Williams, L. A. Wheeler, M. E. Garst, *J. Med. Chem.* **1997**, *40*, 18-23.

[66]   a) L. Yang, J. Yuan, P. Mao, Q. Guo, *RSC Advances* **2015**, *5*, 107601-107607; b) F. Shibahara, E. Yamaguchi, T. Murai, *Chem. Commun.* **2010**, *46*, 2471-2473.

[67]   A. Gangjee, R. Devraj, J. J. McGuire, R. L. Kisliuk, *J. Med. Chem.* **1995**, *38*, 3798-3805.

[68]   A. P. Kozikowski, D. Ma, L. Du, N. E. Lewin, P. M. Blumberg, *J. Am. Chem. Soc.* **1995**, *117*, 6666-6672.

[69]   a) A. D. Patil, A. J. Freyer, L. Killmer, P. Offen, B. Carte, A. J. Jurewicz, R. K. Johnson, *Tetrahedron* **1997**, *53*, 5047-5060; b) B. Bowden, E. Ritchie, W. Taylor, *Aust. J. Chem.* **1972**, *25*, 2659-2669.

[70]   C. Eidamshaus, J. D. Burch, *Org. Lett.* **2008**, *10*, 4211-4214.

[71]   W. C. Fu, C. M. So, W. K. Chow, O. Y. Yuen, F. Y. Kwong, *Org. Lett.* **2015**, *17*, 4612-4615.

[72]   W. C. Fu, Z. Zhou, F. Y. Kwong, *Organometallics* **2016**, *35*, 1553-1558.

[73]   W. C. Fu, B. Zheng, Q. Zhao, W. T. K. Chan, F. Y. Kwong, *Org. Lett.* **2017**, *19*, 4335-4338.

[74]   C. He, S. Guo, L. Huang, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 8273-8275.

[75]   J. Kaschel, T. F. Schneider, P. Schirmer, C. Maaß, D. Stalke, D. B. Werz, *Eur. J. Org. Chem.* **2013**, *2013*, 4539-4551.

[76]   a) R. J. Lundgren, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 8686-8690; b) A. DeAngelis, D.-H. Wang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 3434-3437.

[77]   P. G. Alsabeh, R. J. Lundgren, L. E. Longobardi, M. Stradiotto, *Chem. Commun.* **2011**, *47*, 6936-6938.

[78]   P. N. Carlsen, T. J. Mann, A. H. Hoveyda, A. J. Frontier, *Angew. Chem. Int. Ed.* **2014**, *53*, 9334-9338.

[79]   M. Balasubramanian, in *Tetrahedron Organic Chemistry Series, Vol. Volume 26* (Eds.: L. Jie Jack, W. G. Gordon), Elsevier, **2007**, pp. 587-620.

[80]   D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450-1460.

[81]   a) V. V. Grushin, H. Alper, *Chem. Rev.* **1994**, *94*, 1047-1062; b) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176-4211.

[82]   T. D. Sheppard, *Org. Biomol. Chem.* **2009**, *7*, 1043-1052.

[83]   J. D. Shields, D. T. Ahneman, T. J. A. Graham, A. G. Doyle, *Org. Lett.* **2014**, *16*, 142-145.

[84]   M. Appl, Wiley-VCH, **1999**.

[85]   C. W. Cheung, D. S. Surry, S. L. Buchwald, *Org. Lett.* **2013**, *15*, 3734-3737.

[86]   R. J. Lundgren, B. D. Peters, P. G. Alsabeh, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 4071-4074.

[87]   a) M. Hidai, T. Kashiwagi, T. Ikeuchi, Y. Uchida, *J. Organomet. Chem.* **1971**, *30*, 279-282; b) A. Morvillo, A. Turco, *J. Organomet. Chem.* **1981**, *208*, 103-113; c) T. T. Tsou, J. K. Kochi, *J. Am. Chem. Soc.* **1979**, *101*, 6319-6332; d) F. Maseras, I. Funes, D. Nelson, *Chem. Eur. J.*, *23*, 16728-16733.

[88]   D. Gerristma, T. Brenstrum, J. McNulty, A. Capretta, *Tetrahedron Lett.* **2004**, *45*, 8319-8321.

[89]   P. G. Pringle, M. B. Smith, *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis.*, John Wiley & Sons Ltd., **2012**.

[90]   S. Ge, J. F. Hartwig, *J. Am. Chem. Soc.* **2011**, *133*, 16330-16333.

[91]   E. Brenner, Y. Fort, *Tetrahedron Lett.* **1998**, *39*, 5359-5362.

[92]   a) T. Wang, M. L. Goodall, P. Gonzales, M. Sepulveda, K. R. Martin, S. Gately, J. P. MacKeigan, *J. Med. Chem.* **2015**, *58*, 3025-3035; b) M. S. Evans, G. B. Maglinger, A. M. Fletcher, S. R. Johnson, *Neuropharmacology* **2016**, *101*, 179-187.

[93]   S. Wagaw, R. A. Rennels, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 8451-8458.

[94]   R. H. Munday, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 2754-2755.

[95]   a) S. C. Baker, D. P. Kelly, J. C. Murrell, *Nature* **1991**, *350*, 627; b) M. C. Wilkinson, *Org. Lett.* **2011**, *13*, 2232-2235.

[96]   A. Z. Dudek, K. L. Kmak, J. Koopmeiners, M. Keshtgarpour, *Lung Cancer* **2006**, *51*, 89-96.

[97]   D. K. Waiker, C. Karthikeyan, V. Poongavanam, J. Kongsted, O. Lozach, L. Meijer, P. Trivedi, *Biorg. Med. Chem.* **2014**, *22*, 1909-1915.

[98]   a) J. Li, Z.-X. Wang, *Org. Lett.* **2017**, *19*, 3723-3726; b) M. J. Iglesias, J. F. Blandez, M. R. Fructos, A. Prieto, E. Álvarez, T. R. Belderrain, M. C. Nicasio, *Organometallics* **2012**, *31*, 6312-6316.

[99]   R. S. Sawatzky, M. J. Ferguson, M. Stradiotto, *Synlett* **2017**, *28*, 1586-1591.

[100]   a) T. E. Long, J. T. Williams, *Expert Opinion on Investigational Drugs* **2014**, *23*, 1375-1387; b) R. Leurs, R. A. Bakker, H. Timmerman, I. J. P. de Esch, *Nature Reviews Drug Discovery* **2005**, *4*, 107.

[101]   a) D. Maiti, B. P. Fors, J. L. Henderson, Y. Nakamura, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 57-68; b) M. W. Hooper, J. F. Hartwig, *Organometallics* **2003**, *22*, 3394-3403.

[102]   a) M. Su, N. Hoshiya, S. L. Buchwald, *Org. Lett.* **2014**, *16*, 832-835; b) M. D. Charles, P. Schultz, S. L. Buchwald, *Org. Lett.* **2005**, *7*, 3965-3968.

[103]   M. Su, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2012**, *51*, 4710-4713.

[104]   C. Li, Y. Kawamata, H. Nakamura, J. C. Vantourout, Z. Liu, Q. Hou, D. Bao, J. T. Starr, J. Chen, M. Yan, P. S. Baran, *Angew. Chem. Int. Ed.* **2017**, *56*, 13088-13093.

[105]   E. B. Corcoran, M. T. Pirnot, S. Lin, S. D. Dreher, D. A. DiRocco, I. W. Davies, S. L. Buchwald, D. W. C. MacMillan, *Science* **2016**, *353*, 279-283.

[106]   M. Vellakkaran, K. Singh, D. Banerjee, *ACS Catalysis* **2017**, 8152-8158.

[107]   D. A. Wilson, C. J. Wilson, C. Moldoveanu, A.-M. Resmerita, P. Corcoran, L. M. Hoang, B. M. Rosen, V. Percec, *J. Am. Chem. Soc.* **2010**, *132*, 1800-1801.

[108]   Q. Shen, T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 6586-6596.

[109]   Y. Zhang, V. César, G. Storch, N. Lugan, G. Lavigne, *Angew. Chem. Int. Ed.* **2014**, *53*, 6482-6486.

[110]   P. I. Kitov, D. F. Vinals, S. Ng, K. F. Tjhung, R. Derda, *J. Am. Chem. Soc.* **2014**, *136*, 8149-8152.

[111] B. J. Tardiff, R. McDonald, M. J. Ferguson, M. Stradiotto, *J. Org. Chem.* **2012**, *77*, 1056-1071.

[112] R. A. Green, J. F. Hartwig, *Org. Lett.* **2014**, *16*, 4388-4391.

[113] S. C. Teguh, N. Klonis, S. Duffy, L. Lucantoni, V. M. Avery, C. A. Hutton, J. B. Baell, L. Tilley, *J. Med. Chem.* **2013**, *56*, 6200-6215.

[114] R. S. Lewis, M. F. Wisthoff, J. Grissmerson, W. J. Chain, *Org. Lett.* **2014**, *16*, 3832-3835.

[115] Y. Du, S. Oishi, S. Saito, *Chem. Eur. J.* **2011**, *17*, 12262-12267.

[116] X.-Y. Liu, C.-M. Che, *Org. Lett.* **2009**, *11*, 4204-4207.

[117] S. Voth, J. W. Hollett, J. A. McCubbin, *J. Org. Chem.* **2015**, *80*, 2545-2553.

[118] a) E. N. Koini, P. Papazafiri, A. Vassilopoulos, M. Koufaki, Z. Horváth, I. Koncz, L. Virág, G. J. Papp, A. Varró, T. Calogeropoulou, *J. Med. Chem.* **2009**, *52*, 2328-2340; b) T. Tsunoda, A. Yamazaki, T. Mase, S. Sakamoto, *Org. Process Res. Dev.* **2005**, *9*, 593-598.

[119] a) Z.-B. Jiang, X.-H. Meng, B.-Y. Jiang, C.-G. Zhu, Q.-L. Guo, S.-J. Wang, S. Lin, J.-G. Shi, *Chin. Chem. Lett.* **2015**, *26*, 653-656; b) M. R. Stephen, M. T. Rahman, V. V. N. P. B. Tiruveedhula, G. O. Fonseca, J. R. Deschamps, J. M. Cook, *Chem. Eur. J.* **2017**, *23*, 15805-15819.

[120] I. Goldberg, *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691-1692.

[121] a) A. Klapars, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 7421-7428; b) E. R. Strieter, D. G. Blackmond, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4120-4121; c) M. Rovira, M. Soler, I. Güell, M.-Z. Wang, L. Gómez, X. Ribas, *J. Org. Chem.* **2016**, *81*, 7315-7325; d) S.-K. Kang, S.-H. Lee, D. Lee, *Synlett* **2000**, *2000*, 1022-1024.

[122] K.-i. Fujita, M. Yamashita, F. Puschmann, M. M. Alvarez-Falcon, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 9044-9045.

[123] V. Pace, W. Holzer, G. Meng, S. Shi, R. Lalancette, R. Szostak, M. Szostak, *Chem. Eur. J.* **2016**, *22*, 14494-14498.

[124] L. Hie, N. F. Fine Nathel, X. Hong, Y.-F. Yang, K. N. Houk, N. K. Garg, *Angew. Chem. Int. Ed.* **2016**, *55*, 2810-2814.

[125] J. Hu, Y. Zhao, J. Liu, Y. Zhang, Z. Shi, *Angew. Chem.* **2016**, *128*, 8860-8864.

[126] A. Leyva-Pérez, J. R. Cabrero-Antonino, P. Rubio-Marqués, S. I. Al-Resayes, A. Corma, *ACS Catalysis* **2014**, *4*, 722-731.

[127] I. González-Sánchez, J. D. Solano, M. A. Loza-Mejía, S. Olvera-Vázquez, R. Rodríguez-Sotres, J. Morán, A. Lira-Rocha, M. A. Cerbón, *Eur. J. Med. Chem.* **2011**, *46*, 2102-2108.

[128] C. M. Lavoie, P. M. MacQueen, M. Stradiotto, *Chem. Eur. J.* **2016**, *22*, 18752-18755.

[129] M. Bollenbach, P. G. V. Aquino, J. X. de Araújo-Júnior, J.-J. Bourguignon, F. Bihel, C. Salomé, P. Wagner, M. Schmitt, *Chem. Eur. J.* **2017**, *23*, 13676-13683.

[130] J. Morstein, E. D. Kalkman, C. Cheng, J. F. Hartwig, *Org. Lett.* **2016**, *18*, 5244-5247.

[131] N. Lucchetti, M. Scalone, S. Fantasia, K. Muñiz, *Angew. Chem. Int. Ed.* **2016**, *55*, 13335-13339.

[132] F. Y. Kwong, C. W. Lai, M. Yu, Y. Tian, K. S. Chan, *Tetrahedron* **2003**, *59*, 10295-10305.

[133] K. W. Quasdorf, M. Riener, K. V. Petrova, N. K. Garg, *J. Am. Chem. Soc.* **2009**, *131*, 17748-17749.

[134] Y.-J. Chen, H.-H. Chen, *Org. Lett.* **2006**, *8*, 5609-5612.

[135] A. J. DeAngelis, P. G. Gildner, R. Chow, T. J. Colacot, *J. Org. Chem.* **2015**, *80*, 6794-6813.

[136] a) M. B. M. Reddy, M. A. Pasha, *Phosphorus, Sulfur, and Silicon and the Related Elements* **2011**, *186*, 1867-1875; b) X. Lei, A. Jalla, M. A. Abou Shama, J. M. Stafford, B. Cao, *Synthesis* **2015**, *47*, 2578-2585.

[137] H. G. Lee, P. J. Milner, S. L. Buchwald, *Org. Lett.* **2013**, *15*, 5602-5605.

[138] S. Bajo, G. Laidlaw, A. R. Kennedy, S. Sproules, D. J. Nelson, *Organometallics* **2017**, *36*, 1662-1672.

[139] M. Tobisu, N. Chatani, *Top. Curr. Chem.* **2016**, *374*, 41.

[140] a) J. Fässler, J. A. McCubbin, A. Roglans, T. Kimachi, J. W. Hollett, R. W. Kunz, M. Tinkl, Y. Zhang, R. Wang, M. Campbell, V. Snieckus, *J. Org. Chem* **2015**, *80*, 3368-3386; b) K. W. Quasdorf, A. Antoft-Finch, P. Liu, A. L. Silberstein, A. Komaromi, T. Blackburn, S. D. Ramgren, K. N. Houk, V. Snieckus, N. K. Garg, *J.*

Am. Chem. Soc. **2011**, *133*, 6352-6363; c) A. Antoft-Finch, T. Blackburn, V. Snieckus, *J. Am. Chem. Soc.* **2009**, *131*, 17750-17752; d) R. B. Bedford, R. L. Webster, C. J. Mitchell, *Org. Biomol. Chem.* **2009**, *7*, 4853-4857.

[141] T. E. Hurst, T. K. Macklin, M. Becker, E. Hartmann, W. Kügel, J.-C. Parisienne-La Salle, A. S. Batsanov, T. B. Marder, V. Snieckus, *Chem. Eur. J.* **2010**, *16*, 8155-8161.

[142] a) J. E. Dander, N. A. Weires, N. K. Garg, *Org. Lett.* **2016**, *18*, 3934-3936; b) N. F. F. Nathel, J. Kim, L. Hie, X. Jiang, N. K. Garg, *ACS Catal.* **2014**, *4*, 3289-3293; c) S. D. Ramgren, A. L. Silberstein, Y. Yang, N. K. Garg, *Angew. Chem. Int. Ed.* **2011**, *50*, 2171-2173.

[143] T. Shimasaki, M. Tobisu, N. Chatani, *Angew. Chem. Int. Ed.* **2010**, *49*, 2929-2932.

[144] L. Ackermann, R. Sandmann, W. Song, *Org. Lett.* **2011**, *13*, 1784-1786.

[145] P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564-12649.

[146] J. Schranck, P. Furer, V. Hartmann, A. Tlili, *Eur. J. Org. Chem.* **2017**, *2017*, 3496-3500.

[147] K. W. Quasdorf, X. Tian, N. K. Garg, *J. Am. Chem. Soc.* **2008**, *130*, 14422-14423.

[148] A. J. MacNair, M.-M. Tran, J. E. Nelson, G. U. Sloan, A. Ironmonger, S. P. Thomas, *Org. Biomol. Chem.* **2014**, *12*, 5082-5088.

[149] S. Yang, C. Wu, H. Zhou, Y. Yang, Y. Zhao, C. Wang, W. Yang, J. Xu, *Adv. Synth. Catal.* **2013**, *355*, 53-58.

[150] F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 793-796.

[151] H.-U. Blaser, W. Brieden, B. Pugin, F. Spindler, M. Studer, A. Togni, *Top. Catal.* **2002**, *19*, 3-16.

[152] Q. Shen, S. Shekhar, J. P. Stambuli, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2005**, *44*, 1371-1375.

[153] X. Liao, Z. Weng, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 195-200.

[154] I. Ryu, H. Matsubara, S. Yasuda, H. Nakamura, D. P. Curran, *J. Am. Chem. Soc.* **2002**, *124*, 12946-12947.

[155] C. M. Lavoie, R. McDonald, E. R. Johnson, M. Stradiotto, *Adv. Synth. Catal.* **2017**, *359*, 2972-2980.

[156]   J. P. Tassone, P. M. MacQueen, C. M. Lavoie, M. J. Ferguson, R. McDonald, M.
Stradiotto, *ACS Catalysis* **2017**, *7*, 6048-6059.

Appendix Representative NMR Spectra

Below are ^{1}H NMR and ^{13}C{^{1}H} NMR spectra of the compounds from the experimental section of each chapter.

^{1}H NMR Spectrum of 1-Biphenyl-4-yl-propan-2-one, **2-1** (CDCl$_3$, 500.1 MHz)
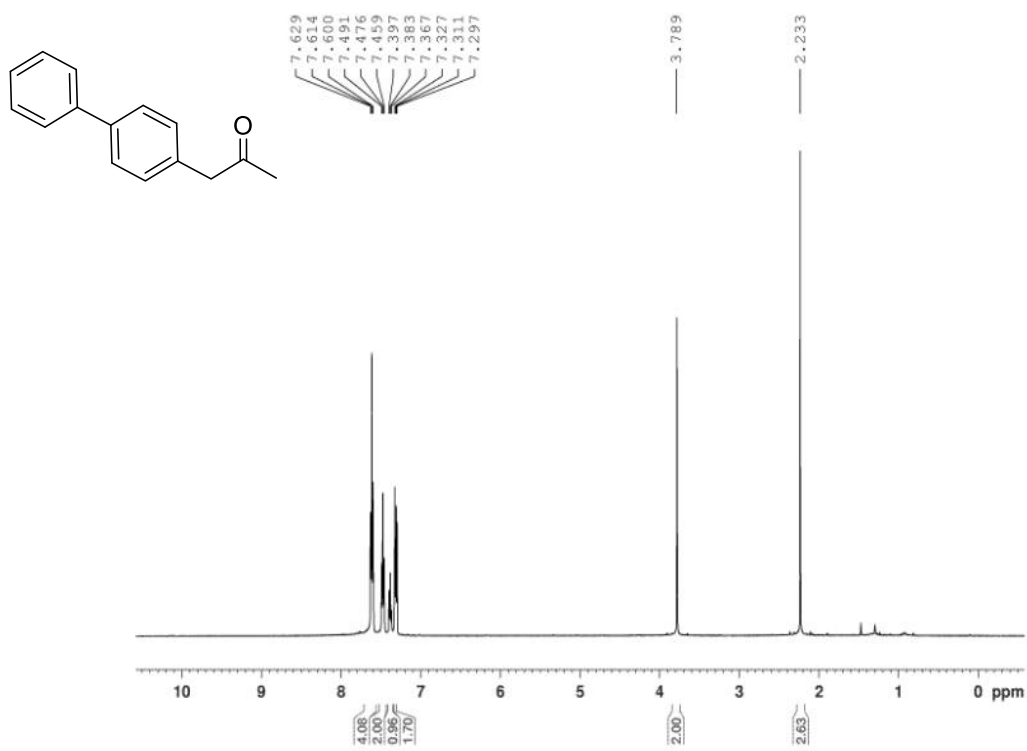
^{13}C{^{1}H} NMR Spectrum of 1-Biphenyl-4-yl-propan-2-one, **2-1** (CDCl$_3$, 125.8 MHz)
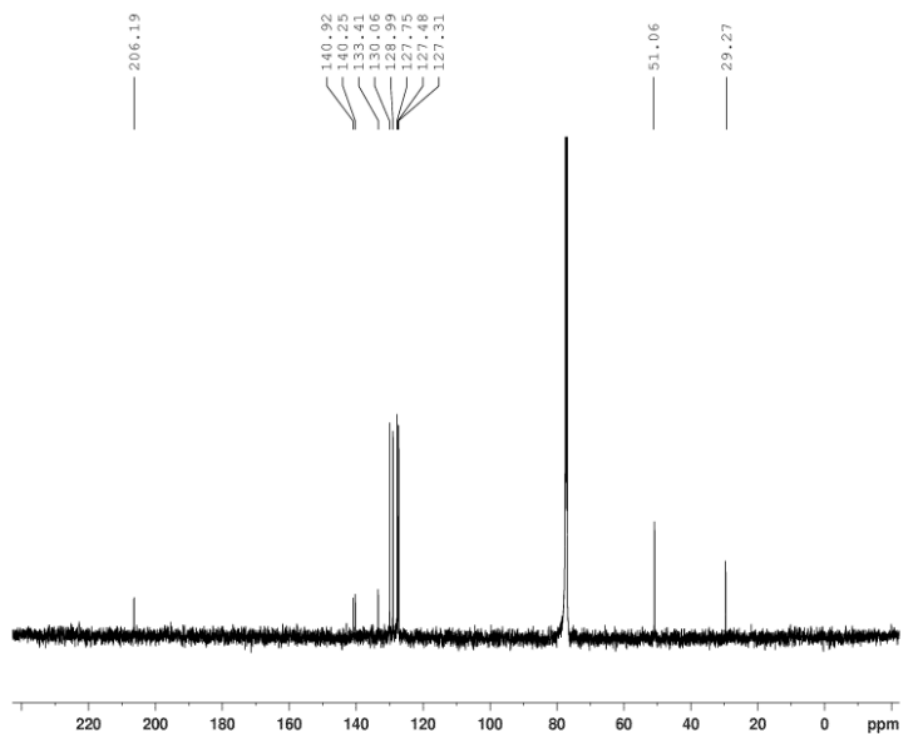
^{1}H NMR Spectrum of 1-(4'-Methyl-biphenyl-4-yl)-propan-2-one, **2-2** (CDCl$_3$, 500.1 MHz)
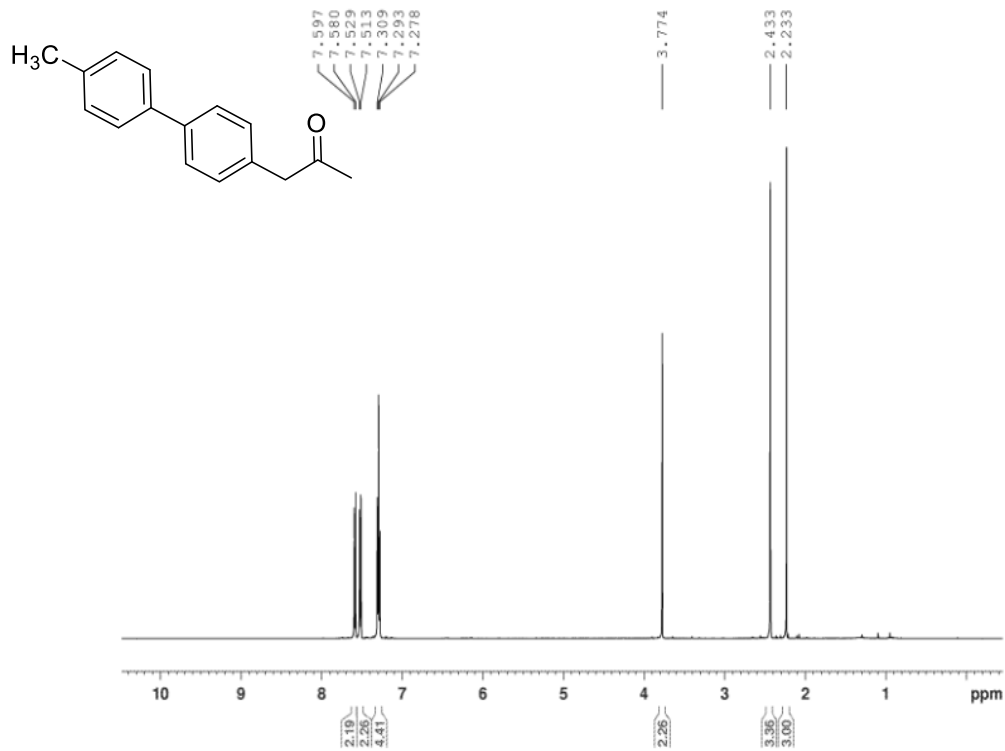
^{13}C{^{1}H} NMR Spectrum of 1-(4'-Methyl-biphenyl-4-yl)-propan-2-one, **2-2** (CDCl$_3$, 125.8 MHz)
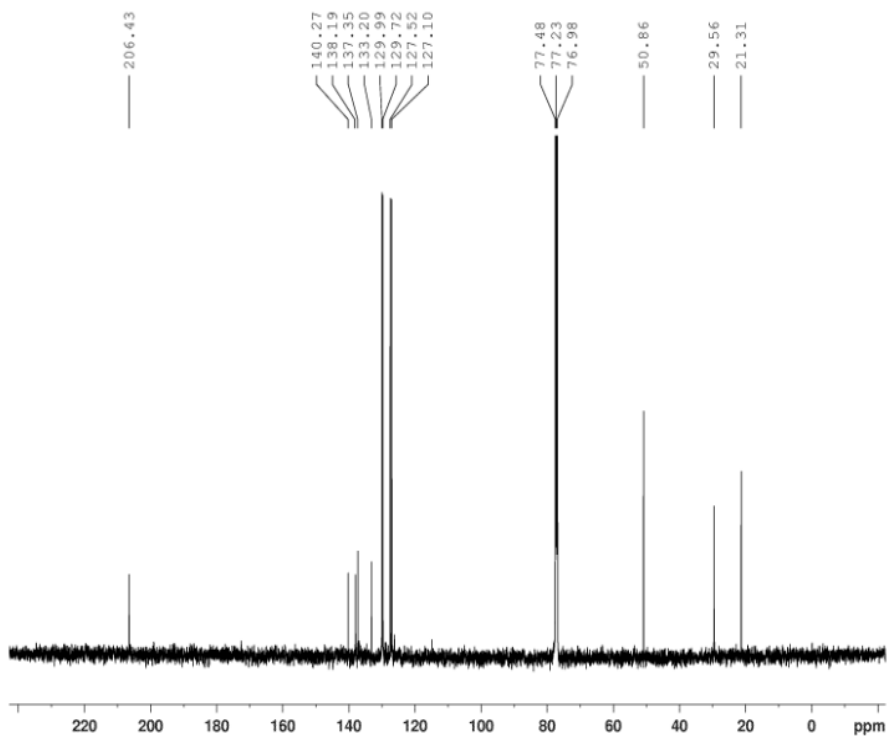
^{1}H NMR Spectrum of 1-(4'-Trifluoromethyl-biphenyl-4-yl)-propan-2-one, **2-3** (CDCl$_3$, 500.1 MHz)

^{13}C{^{1}H} NMR Spectrum of 1-(4'-Trifluoromethyl-biphenyl-4-yl)-propan-2-one, **2-3** (CDCl$_3$, 125.8 MHz)
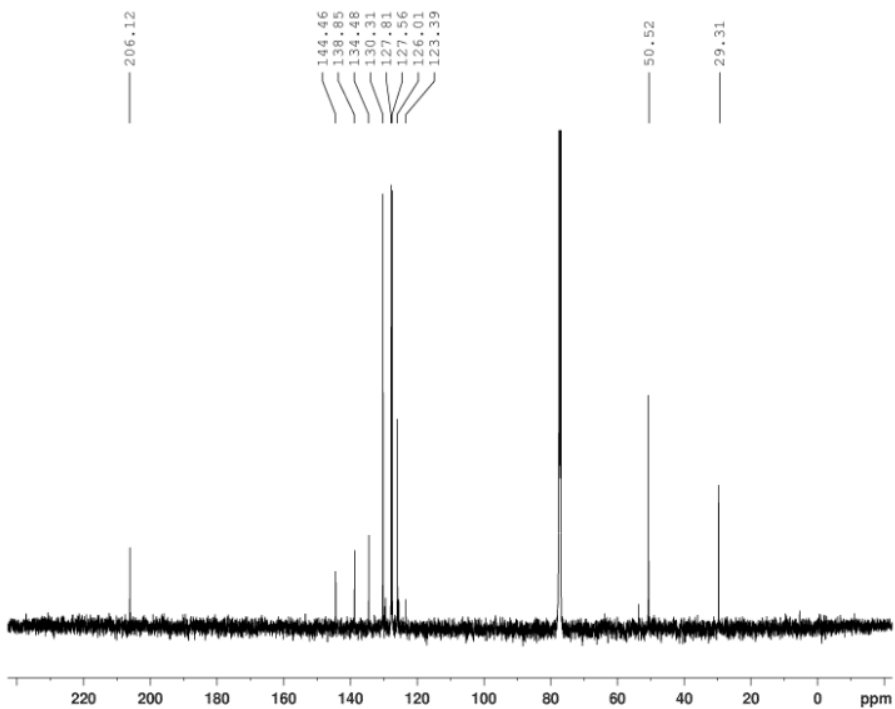
^{1}H NMR Spectrum of 1-(4'-Methoxy-biphenyl-4-yl)-propan-2-one, **2-4** (CDCl₃, 500.1 MHz)
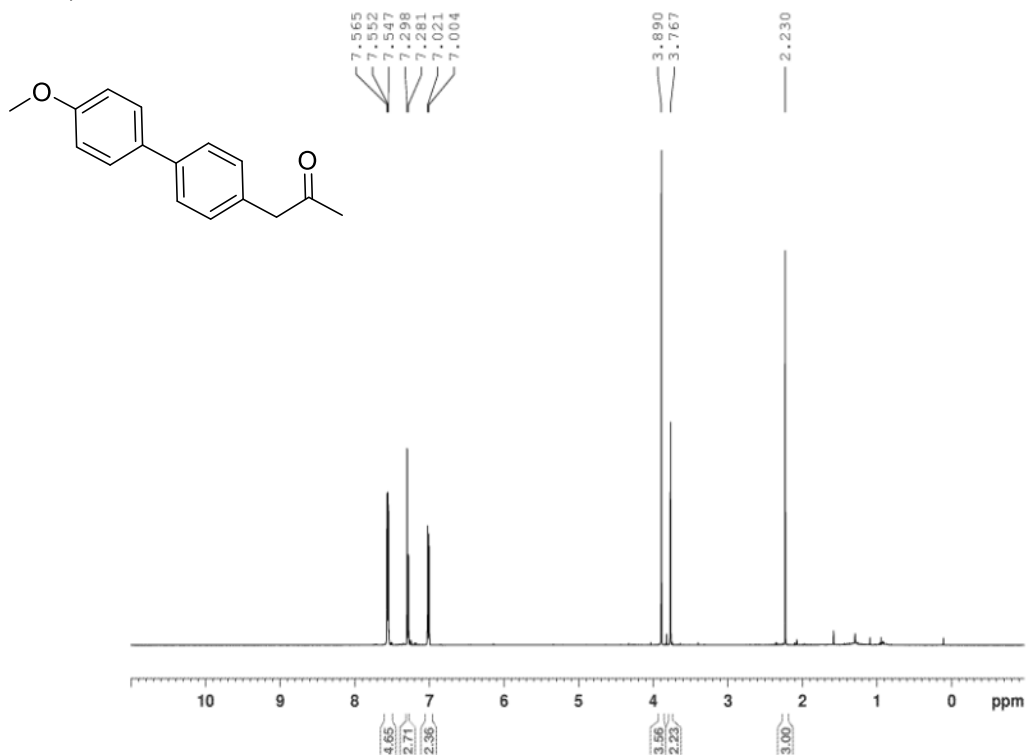
^{13}C{^{1}H} NMR Spectrum of 1-(4'-Methoxy-biphenyl-4-yl)-propan-2-one, **2-4** (CDCl₃, 125.8 MHz)
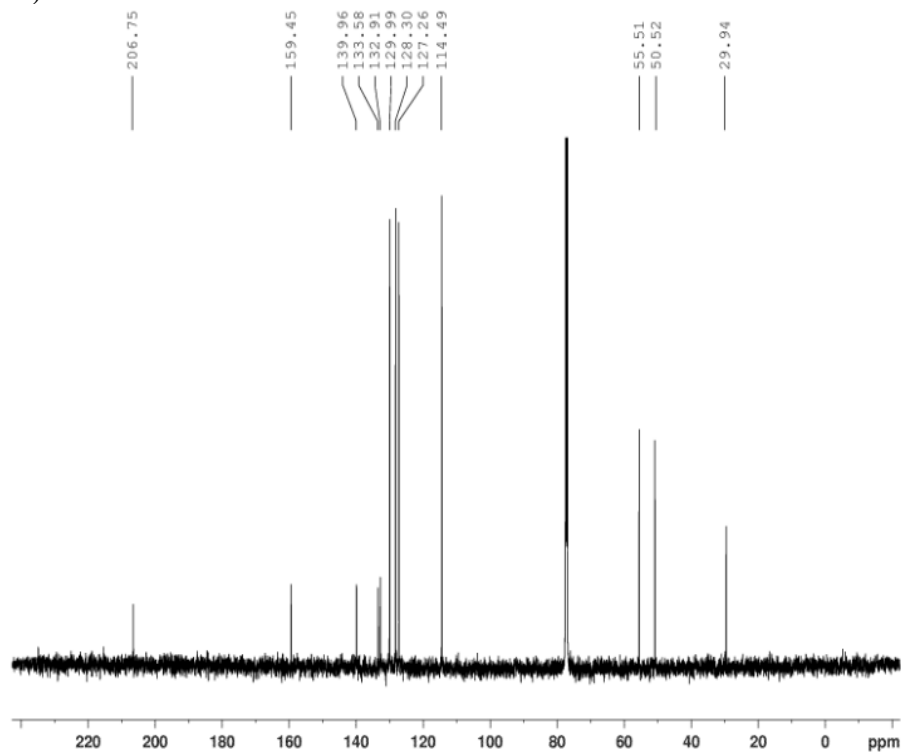
^{1}H NMR Spectrum of 4'-(2-Oxo-propyl)-biphenyl-4-carbonitrile, **2-5** (CDCl$_3$, 500.1 MHz)
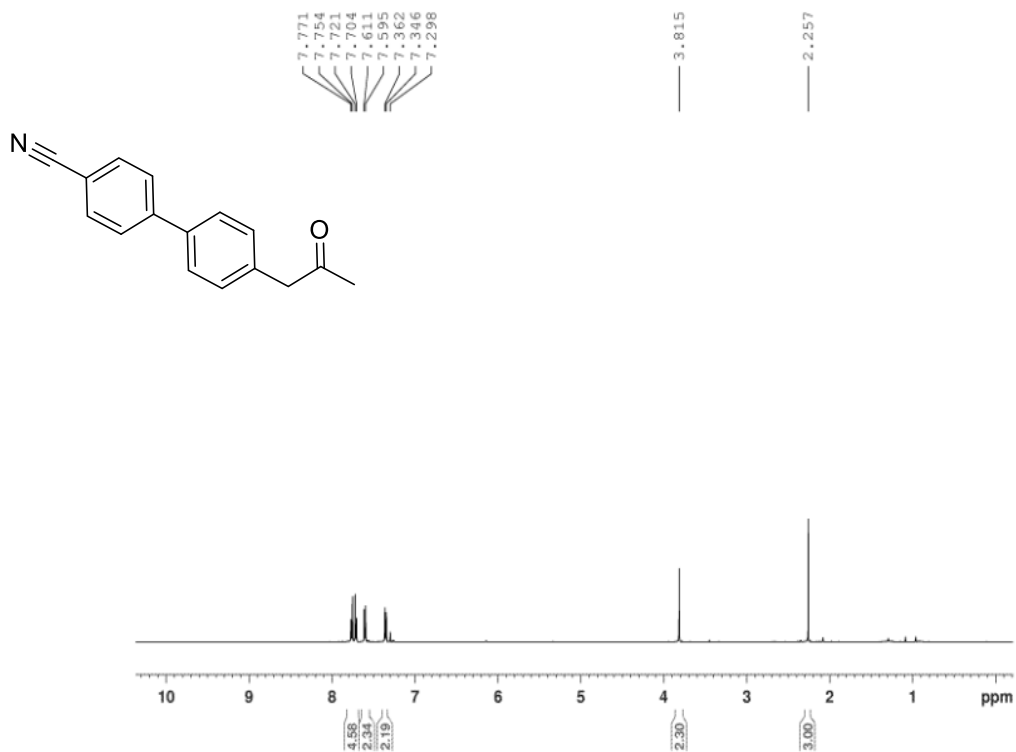
^{13}C{^{1}H} NMR Spectrum of 4'-(2-Oxo-propyl)-biphenyl-4-carbonitrile, **2-5** (CDCl$_3$, 125.8 MHz)
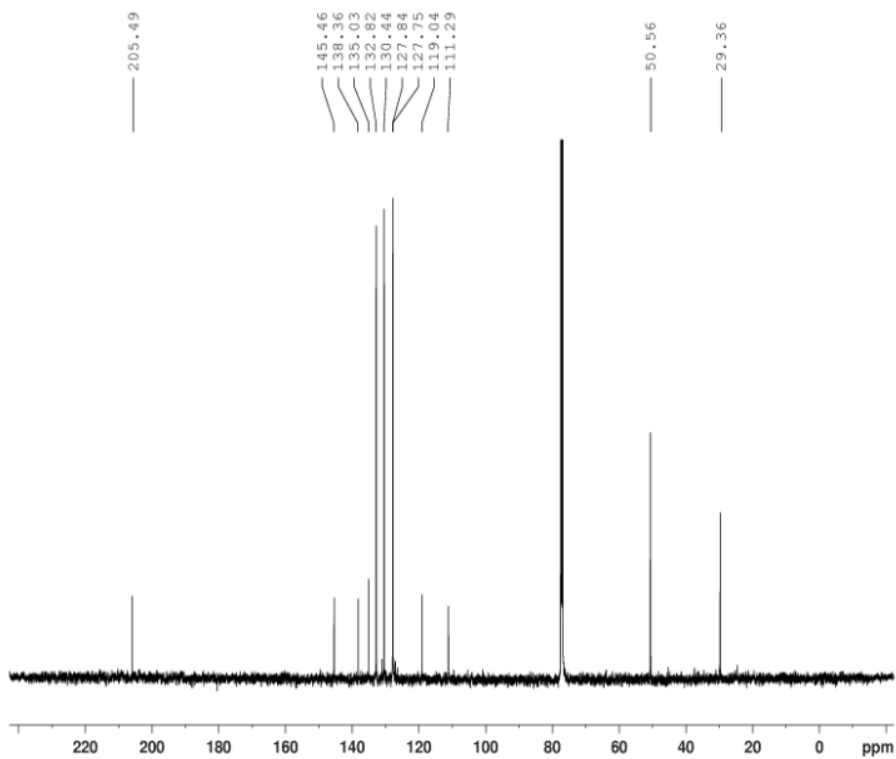
¹H NMR Spectrum of 1-(4-Methoxy-phenyl)-propan-2-one, **2-6** (CDCl₃, 500.1 MHz)
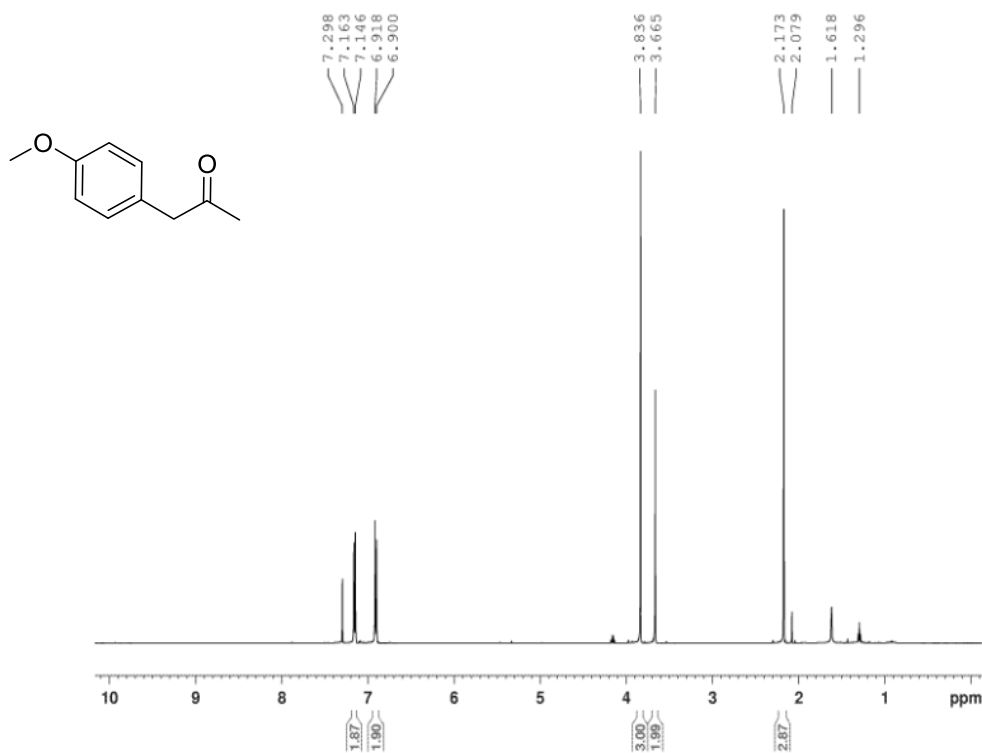
¹³C{¹H} NMR Spectrum of 1-(4-Methoxy-phenyl)-propan-2-one, **2-6** (CDCl₃, 125.8 MHz)
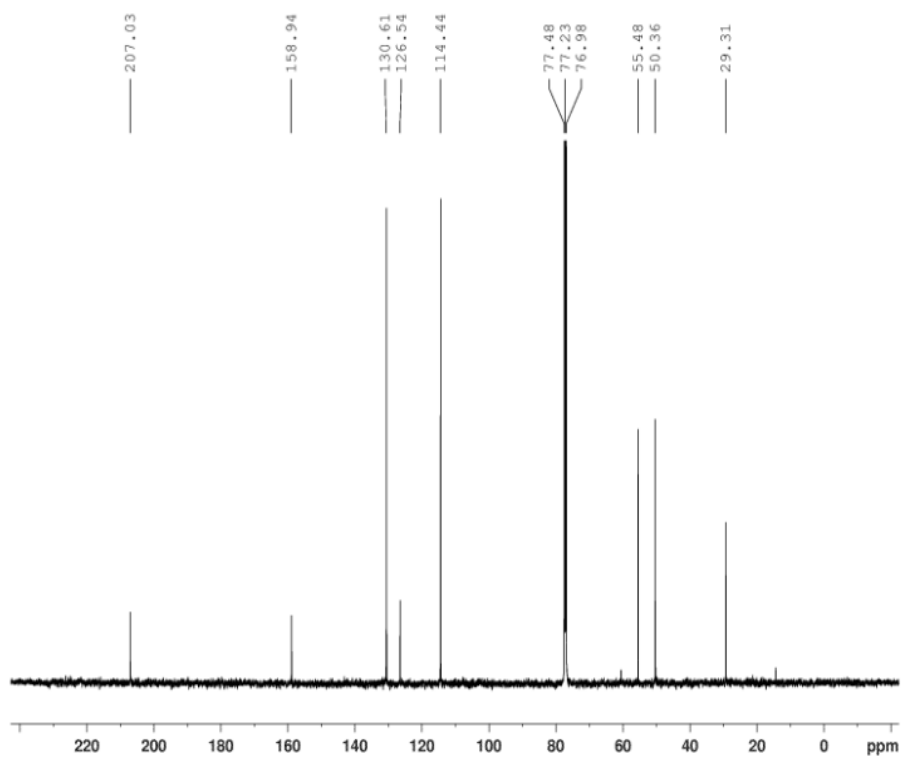
¹H NMR Spectrum of 1-(3-Methoxy-phenyl)-propan-2-one, **2-7** (CDCl₃, 500.1 MHz)
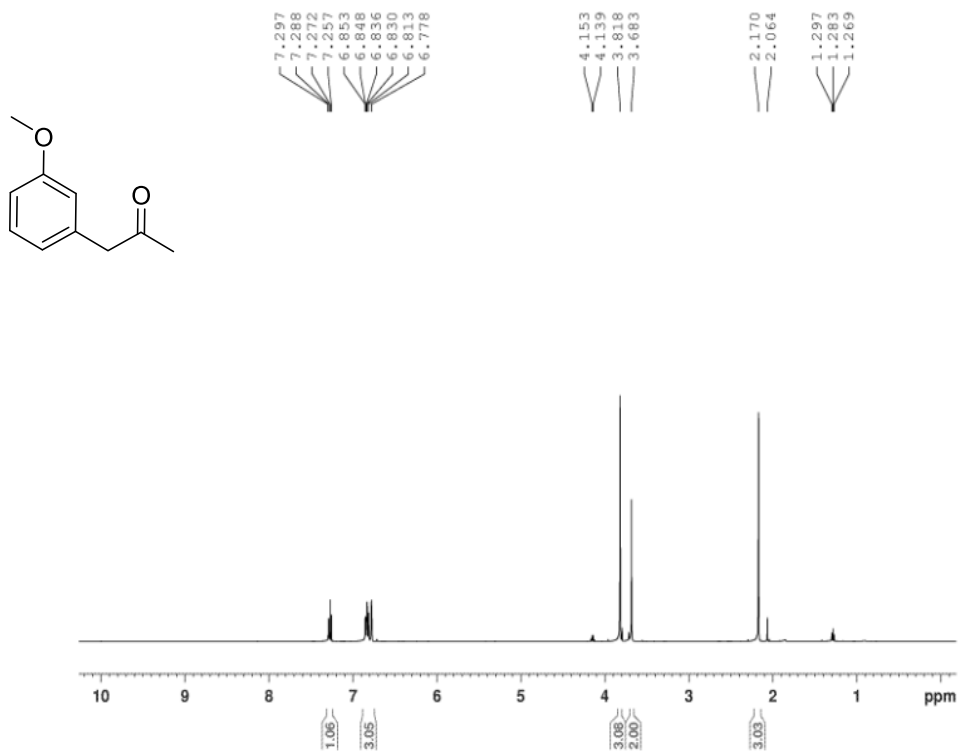
¹³C{¹H} NMR Spectrum of 1-(3-Methoxy-phenyl)-propan-2-one, **2-7** (CDCl₃, 125.8 MHz)
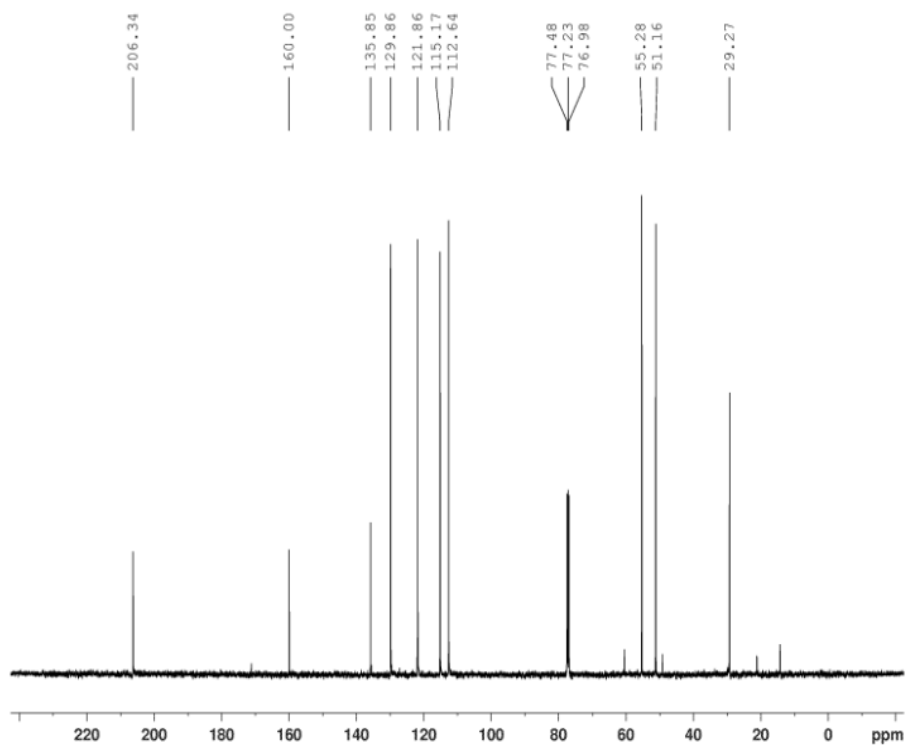
^{1}H NMR Spectrum of 1-(2-Methoxy-phenyl)-propan-2-one, **2-8** (CDCl$_3$, 500.1 MHz)
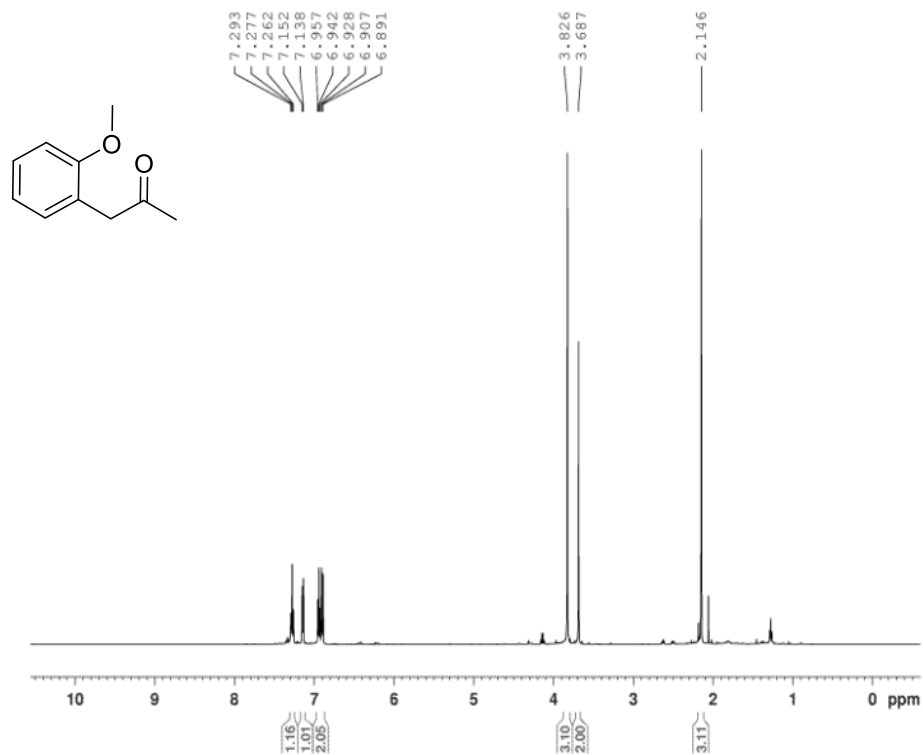
^{13}C{^{1}H} NMR Spectrum of 1-(2-Methoxy-phenyl)-propan-2-one, **2-8** (CDCl$_3$, 125.8 MHz)
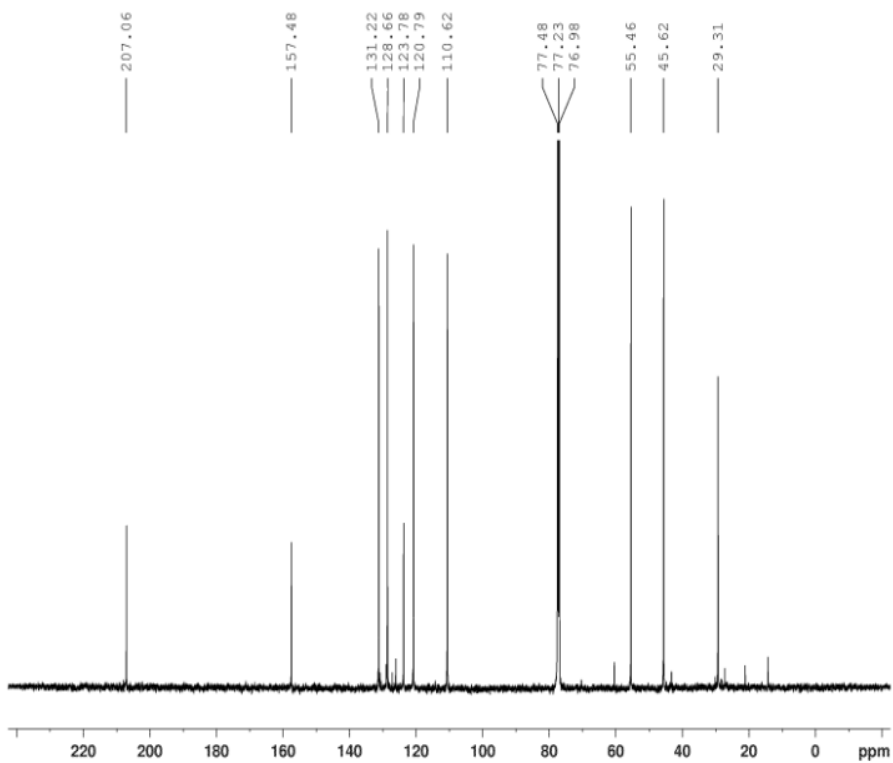
¹H NMR Spectrum of 1-(4-Methoxy-2-methyl-phenyl)-propan-2-one, **2-9** (CDCl₃, 500.1 MHz)
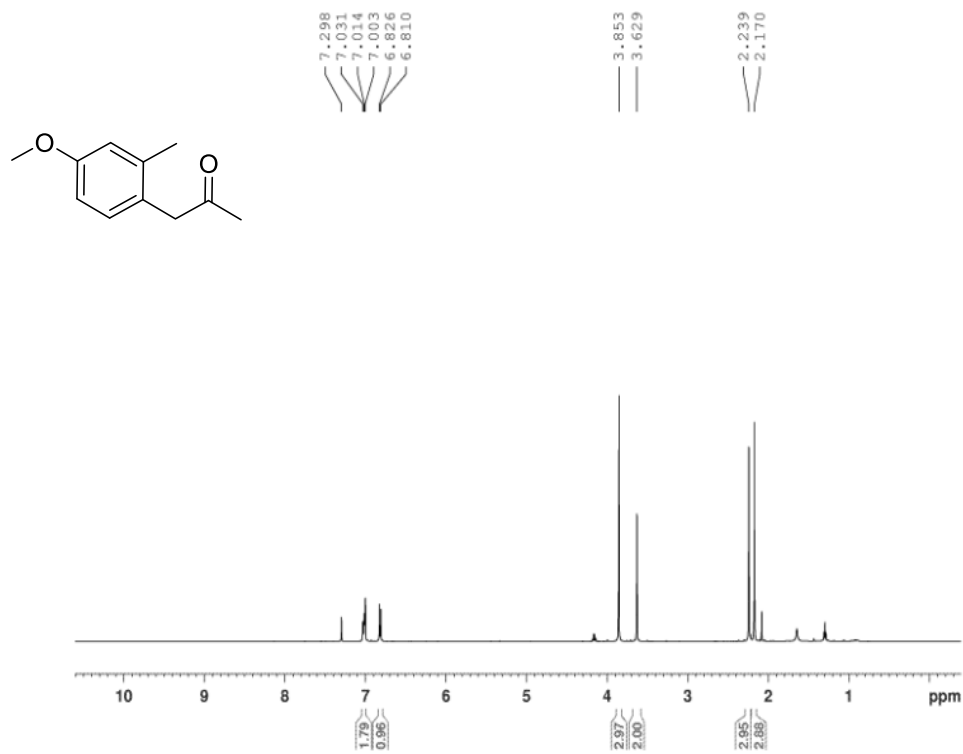
¹³C{¹H} NMR Spectrum of 1-(4-Methoxy-2-methyl-phenyl)-propan-2-one, **2-9** (CDCl₃, 125.8 MHz)
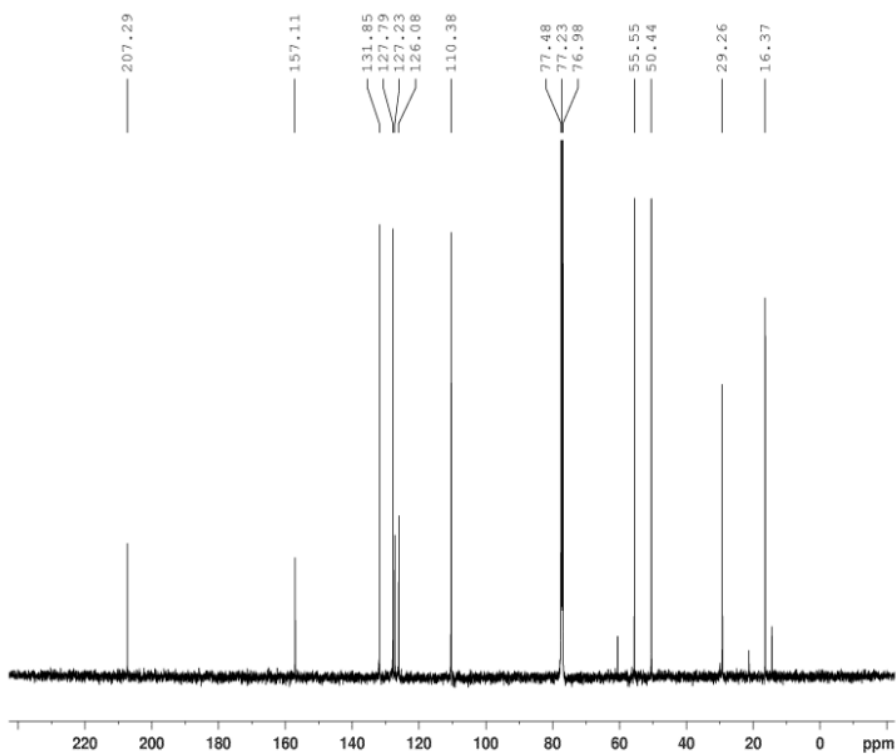
¹H NMR Spectrum of 1-Biphenyl-2-yl-propan-2-one, **2-10** (CDCl₃, 500.1 MHz)
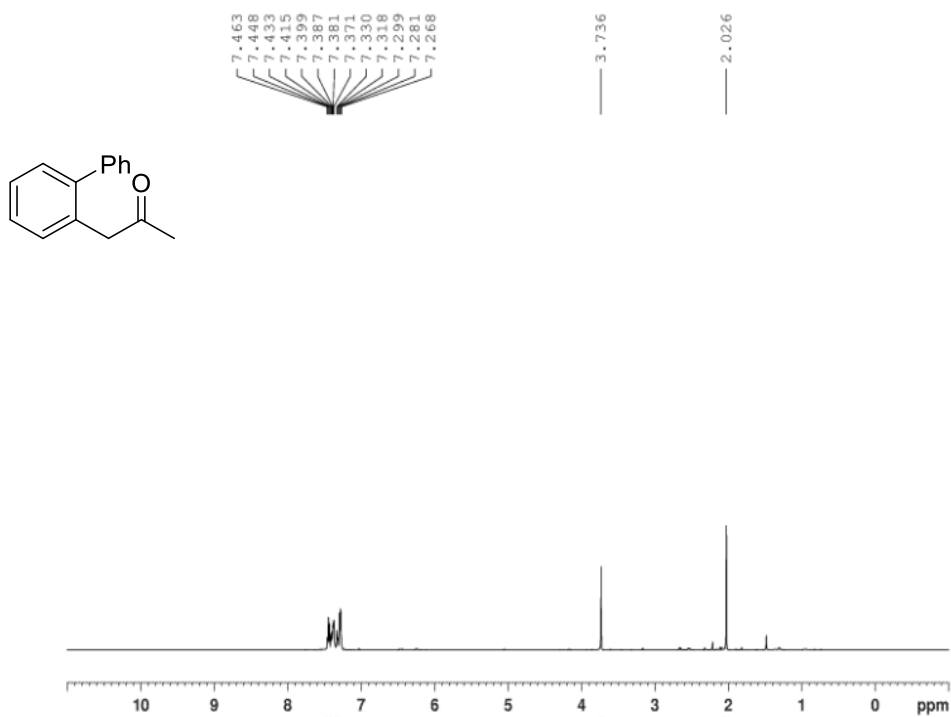
¹³C{¹H} NMR Spectrum of 1-Biphenyl-2-yl-propan-2-one, **2-10** (CDCl₃, 125.8 MHz)
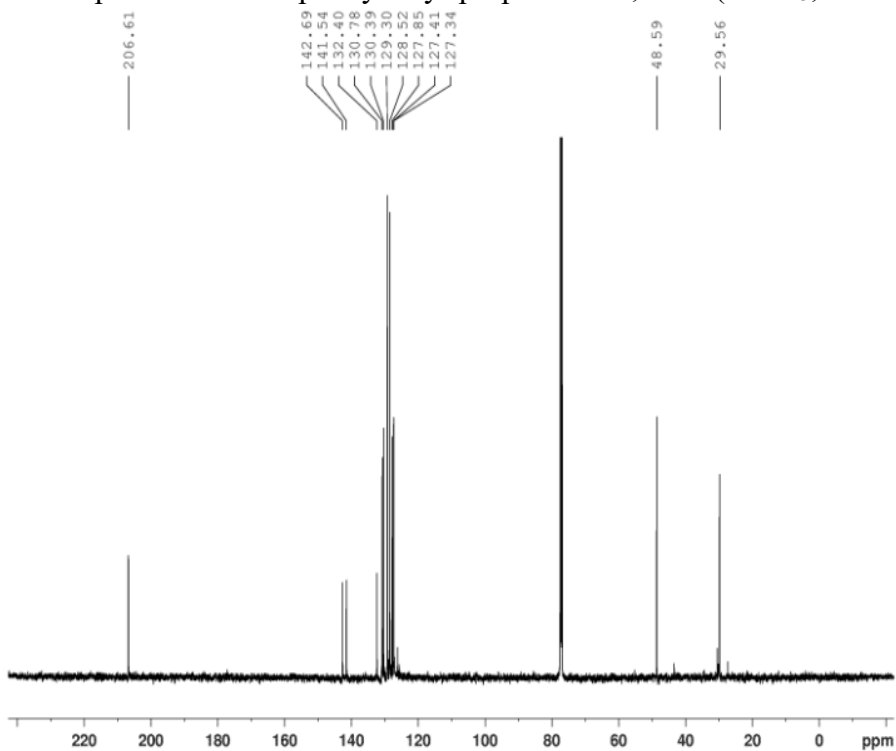
¹H NMR Spectrum of 1-(2,5-Dimethyl-phenyl)-propan-2-one, **2-11** (CDCl₃, 500.1 MHz)
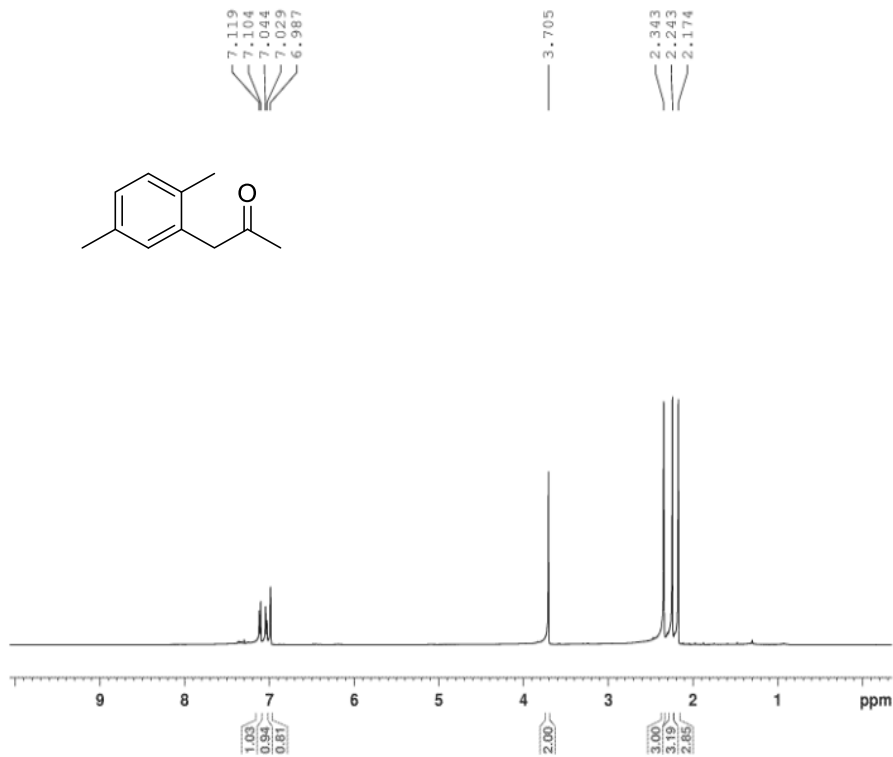
¹³C{¹H} NMR Spectrum of 1-(2,5-Dimethyl-phenyl)-propan-2-one, **2-11** (CDCl₃, 125.8 MHz)
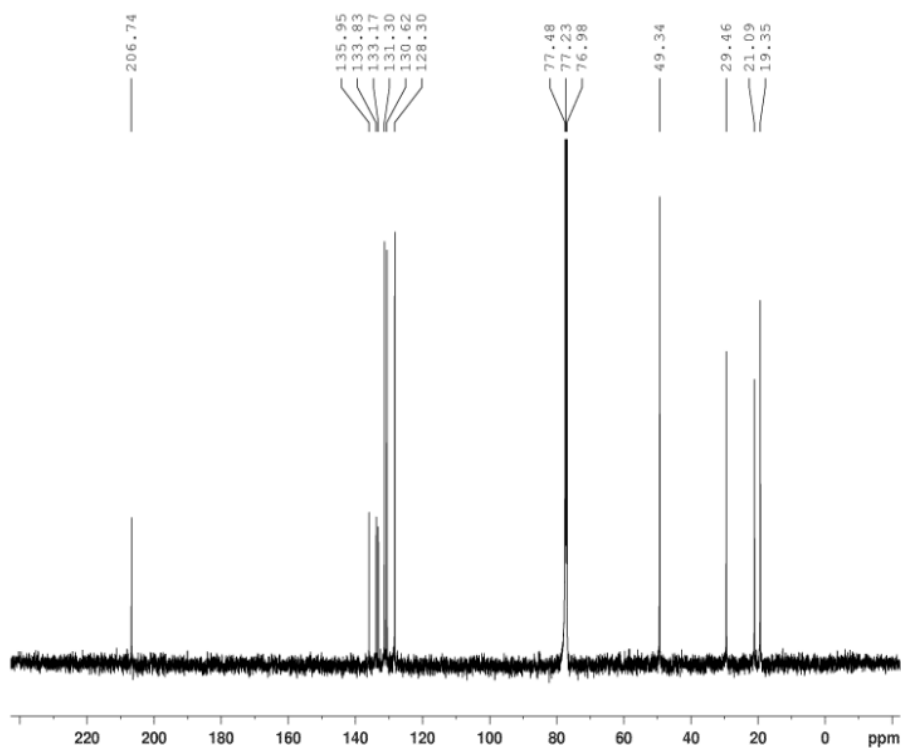
¹H NMR Spectrum of 1-(3,5-Dimethyl-phenyl)-propan-2-one, **2-12** (CDCl₃, 500.1 MHz)
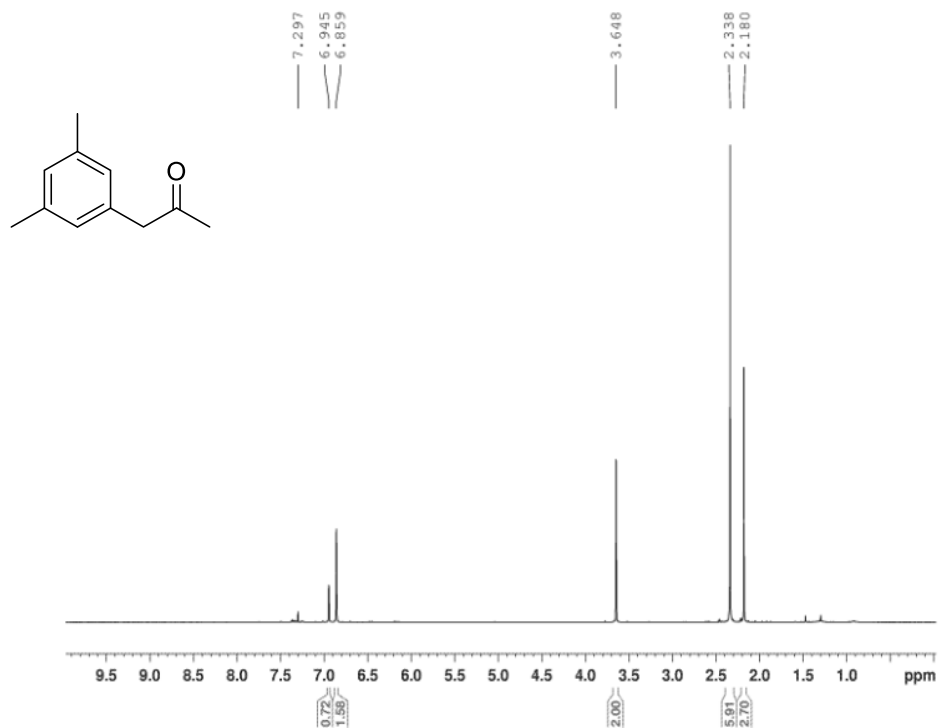
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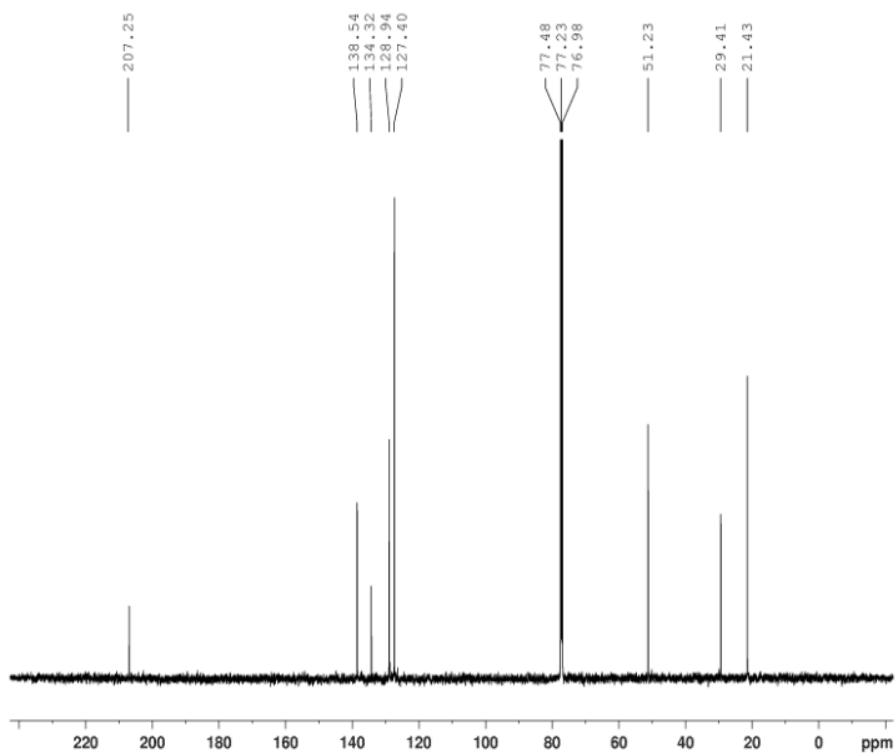
¹H NMR Spectrum of 1-(4-Fluoro-phenyl)-propan-2-one, **2-13** (CDCl₃, 500.1 MHz)
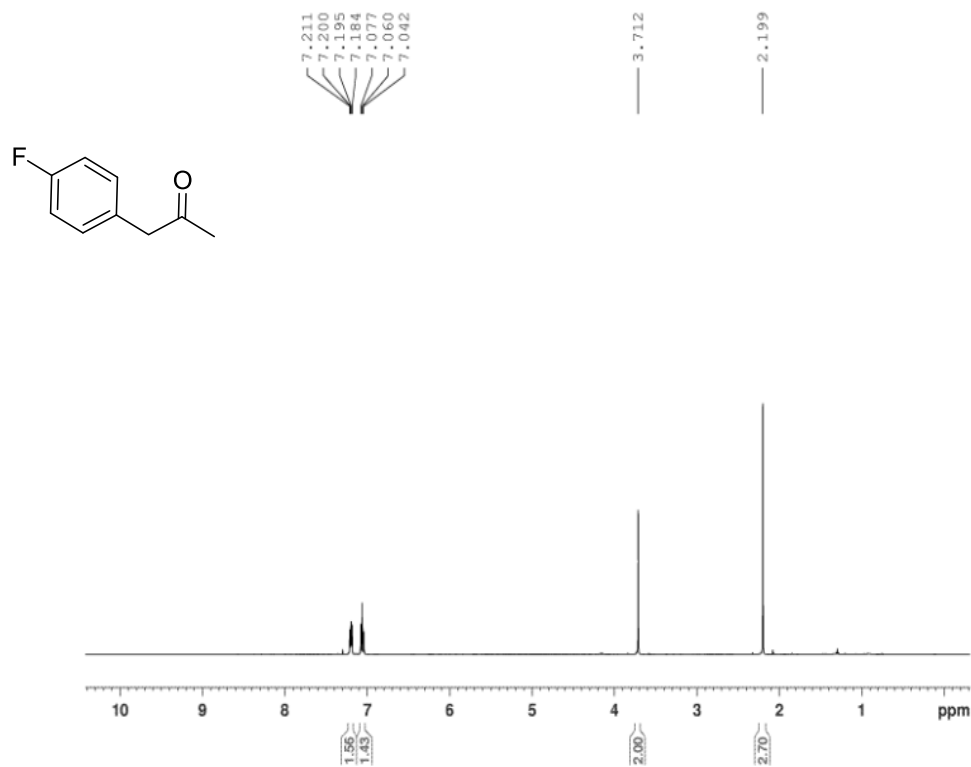
¹³C{¹H} NMR Spectrum of 1-(4-Fluoro-phenyl)-propan-2-one, **2-13** (CDCl₃, 125.8 MHz)
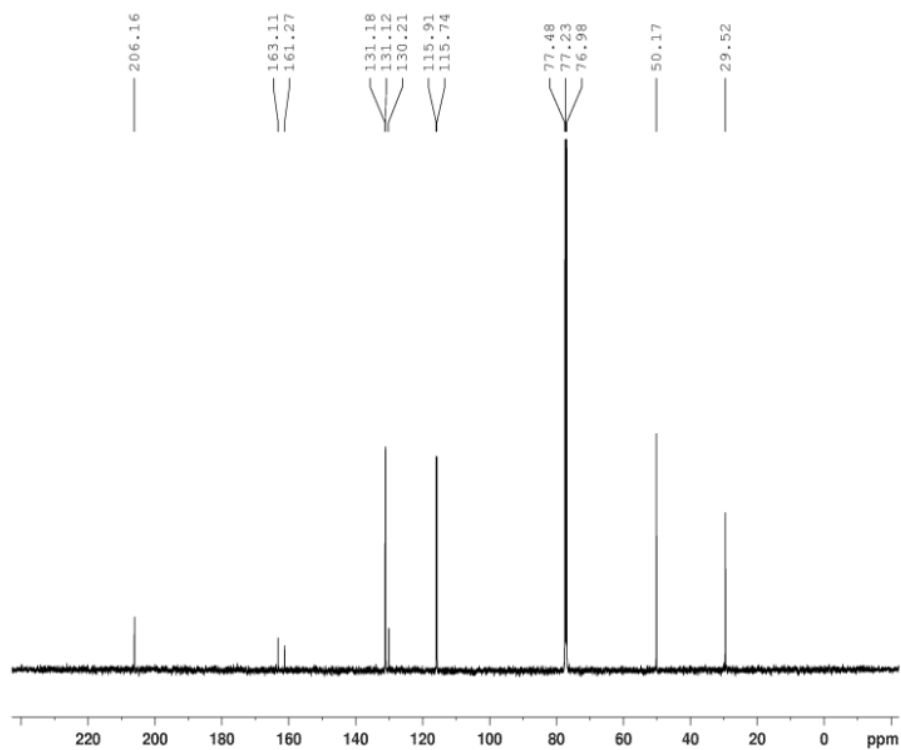
¹H NMR Spectrum of 1-(4-Isopropenyl-phenyl)-propan-2-one, **2-14** (CDCl₃, 500.1 MHz)

7.487
7.470
7.215
7.198

5.405
5.120
5.118
5.115

3.726

2.195
2.184

10   9   8   7   6   5   4   3   2   1   0   ppm

1.96
1.92

1.06
1.06

2.00

2.86
2.99
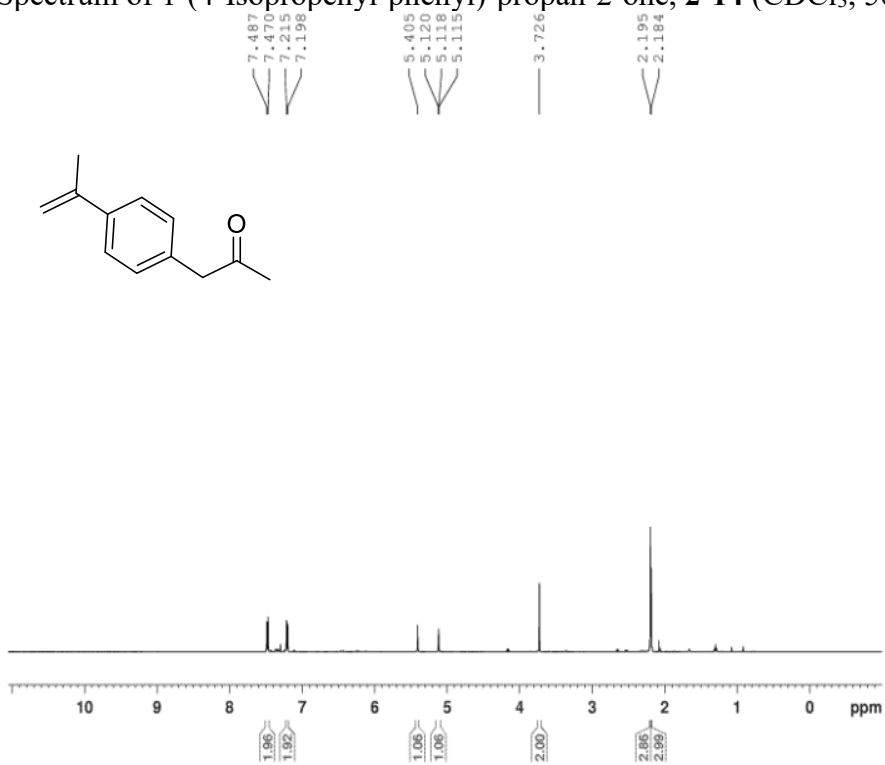
¹³C{¹H} NMR Spectrum of 1-(4-Isopropenyl-phenyl)-propan-2-one, **2-14** (CDCl₃, 125.8 MHz)

206.72

143.23
140.51
133.80
129.71
126.33

112.86

77.74
77.48
77.23

51.10

29.71
22.20

220   200   180   160   140   120   100   80   60   40   20   0   ppm

189
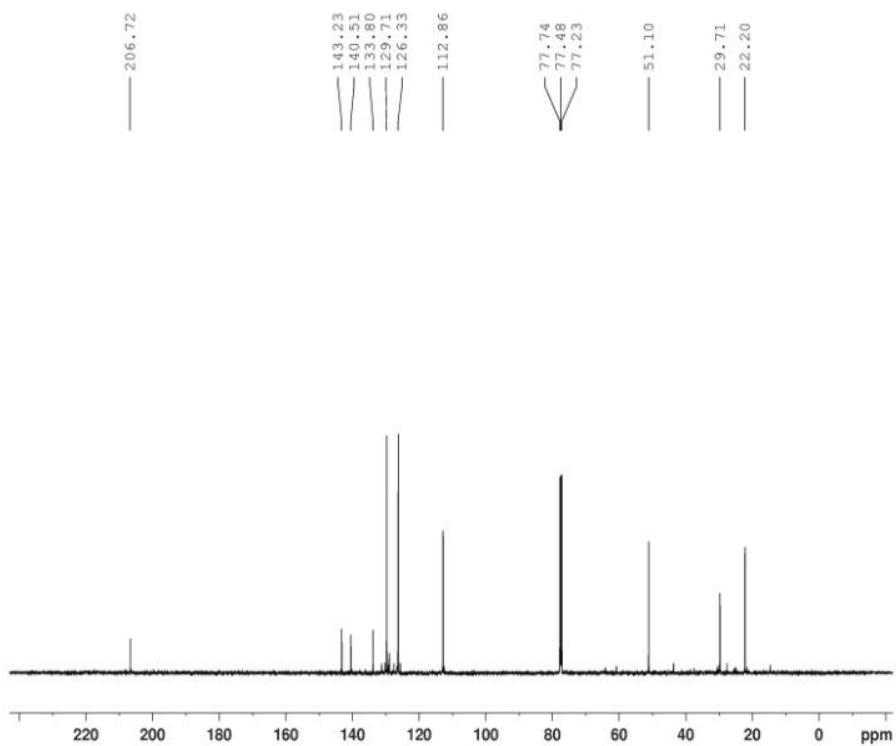
¹H NMR Spectrum of 1-(6-Benzyloxy-naphthalen-2-yl)-propan-2-one, **2-15** (CDCl₃, 500.1 MHz)
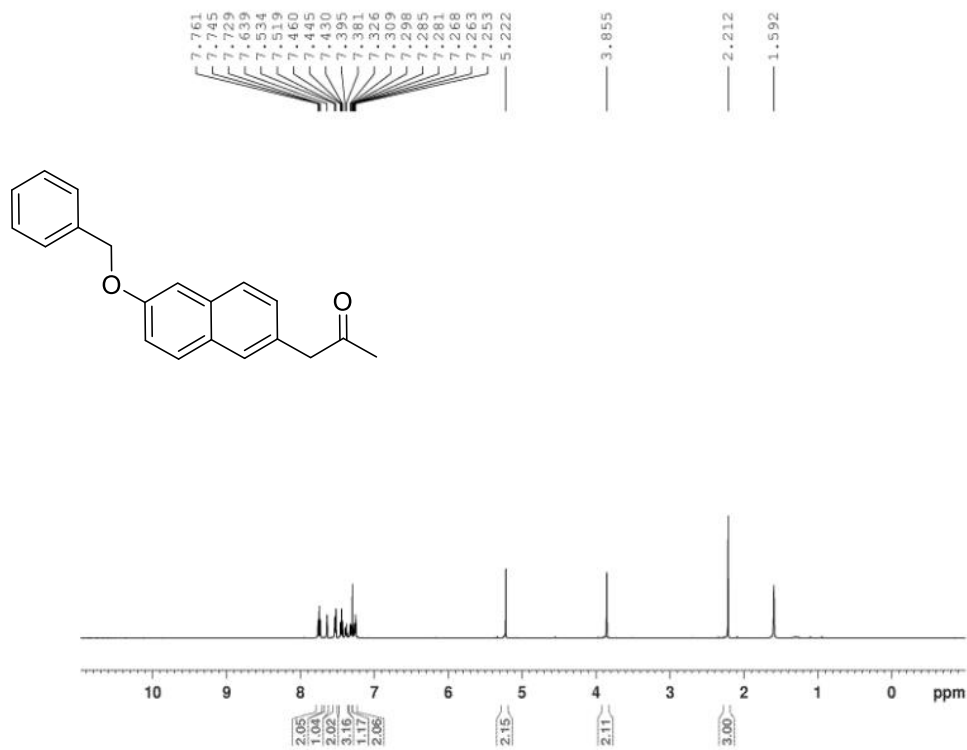
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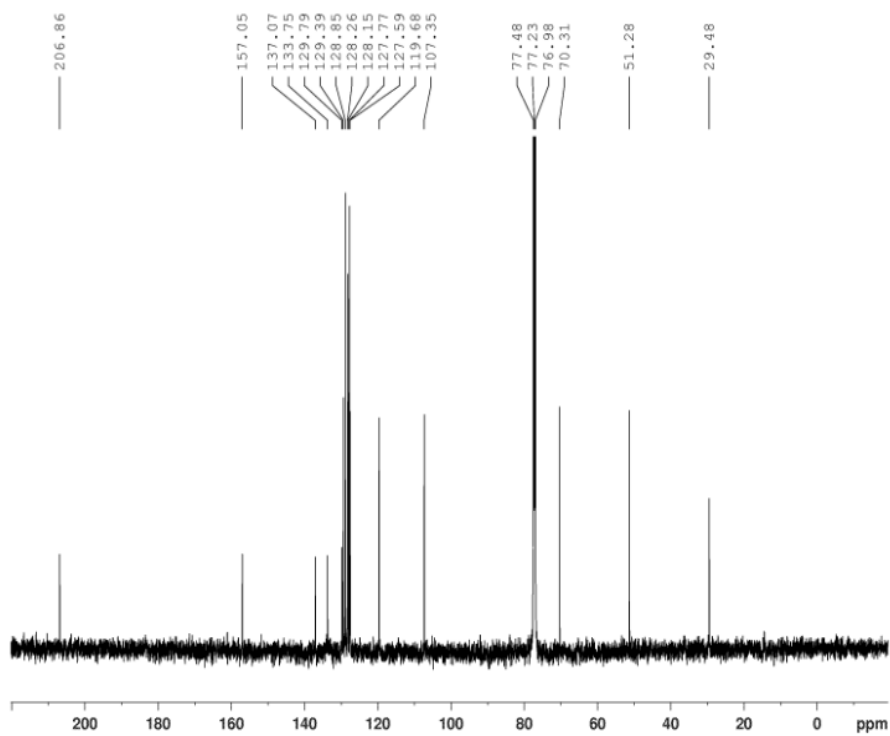
^{1}H NMR Spectrum of 1-(6-Methoxy-naphthalen-2-yl)-propan-2-one, **2-16** (CDCl$_3$, 500.1 MHz)
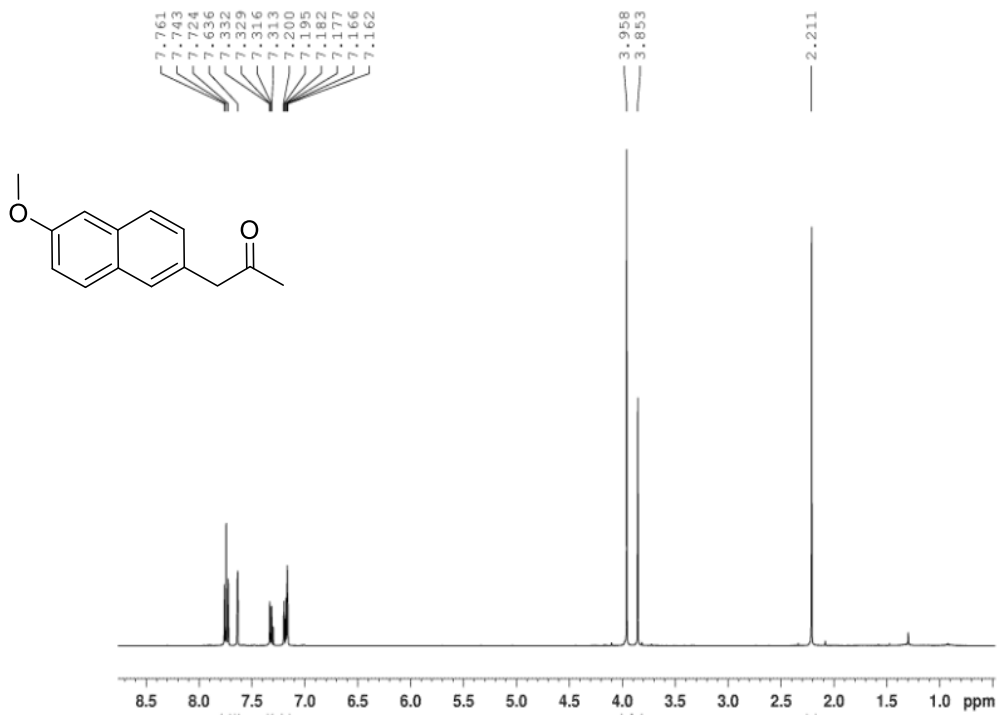
^{13}C{^{1}H} NMR Spectrum of 1-(6-Methoxy-naphthalen-2-yl)-propan-2-one, **2-16** (CDCl$_3$, 125.8 MHz)
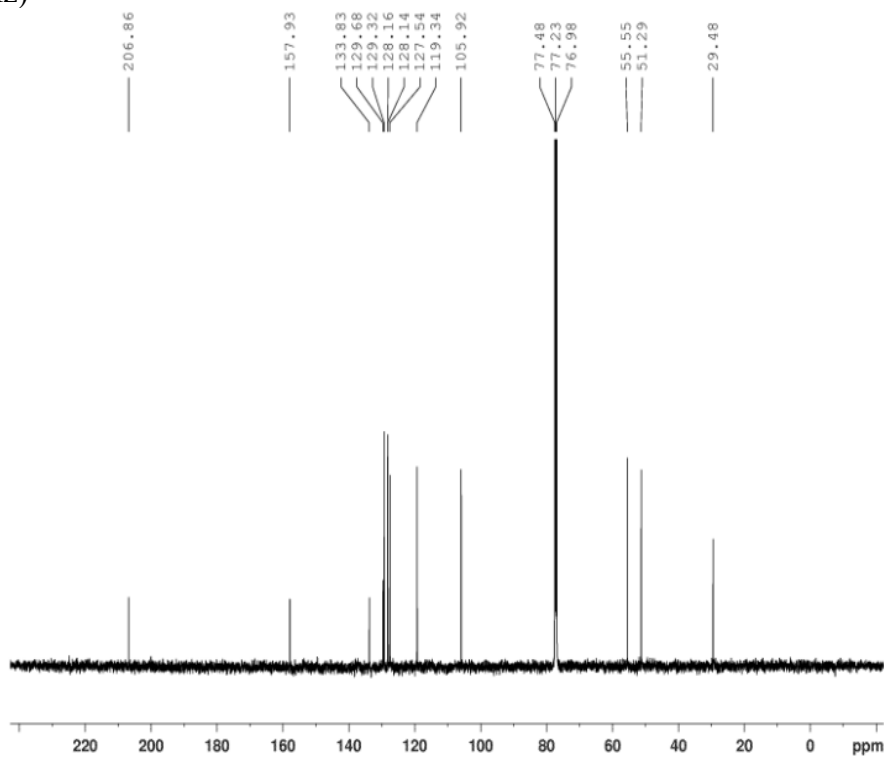
^{1}H NMR Spectrum of 1-(4-Pyrrol-1-yl-phenyl)-propan-2-one, **2-17** (CDCl$_3$, 500.1 MHz)
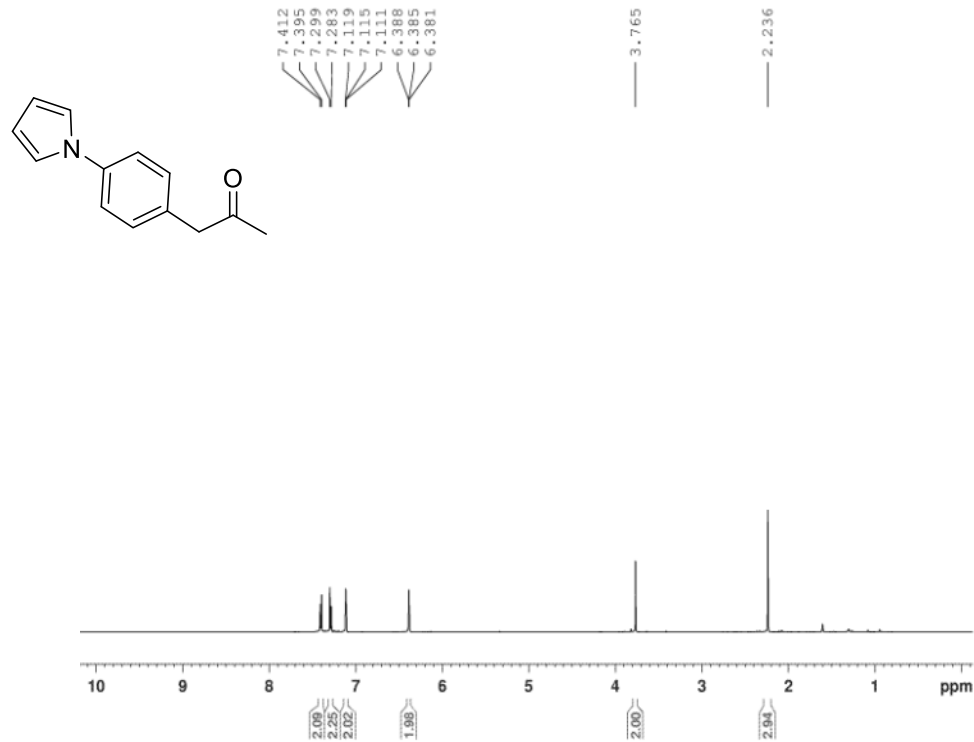
^{13}C{^{1}H} NMR Spectrum of 1-(4-Pyrrol-1-yl-phenyl)-propan-2-one, **2-17** (CDCl$_3$, 125.8 MHz)
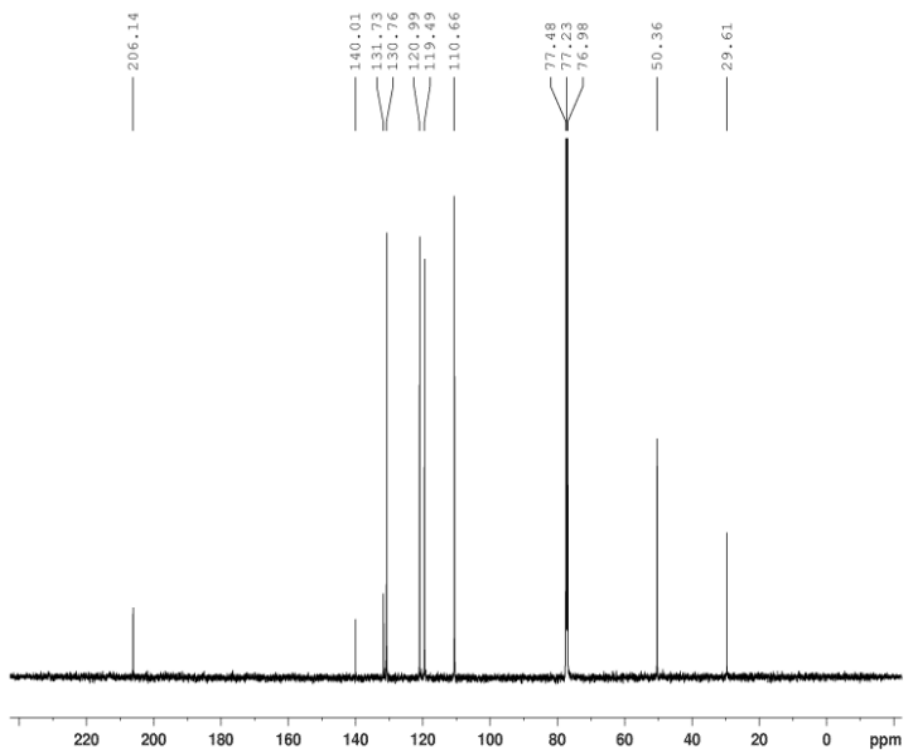
¹H NMR Spectrum of 3-[4-(2-Oxo-propyl)-phenyl]-pyridinium chloride, **2-18** (D₂O, 500.1 MHz)
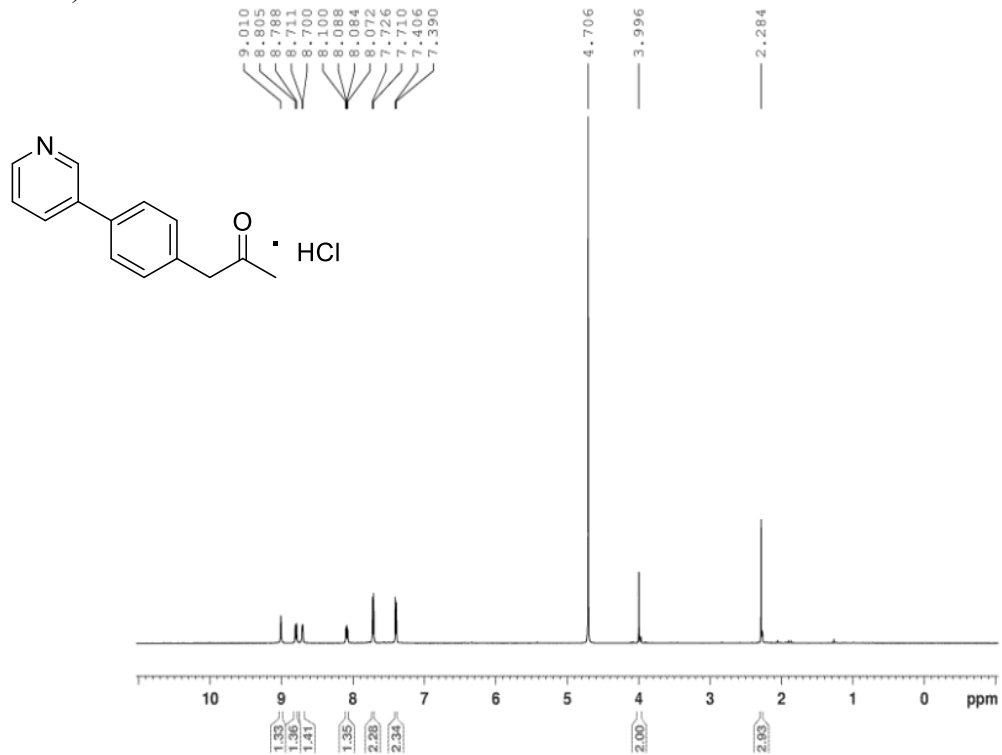
¹³C{¹H} NMR Spectrum of 3-[4-(2-Oxo-propyl)-phenyl]-pyridinium chloride, **2-18** (D₂O, 125.8 MHz)
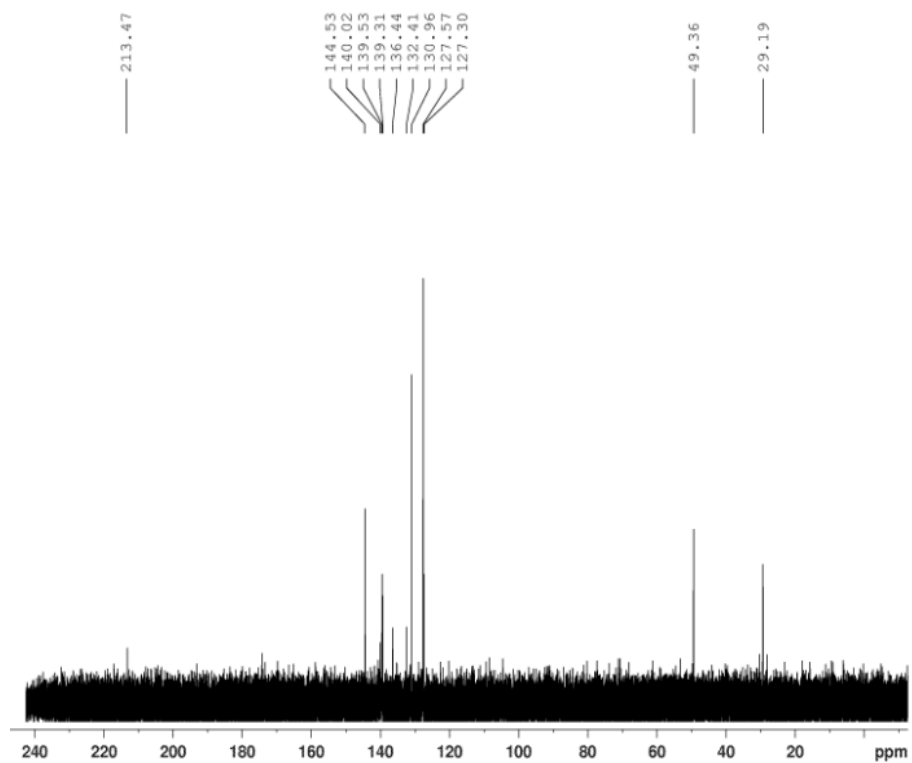
^{1}H NMR Spectrum of 2-Methoxy-6-(2-oxo-propyl)-pyridinium chloride, **19** (D$_2$O, 500.1 MHz)
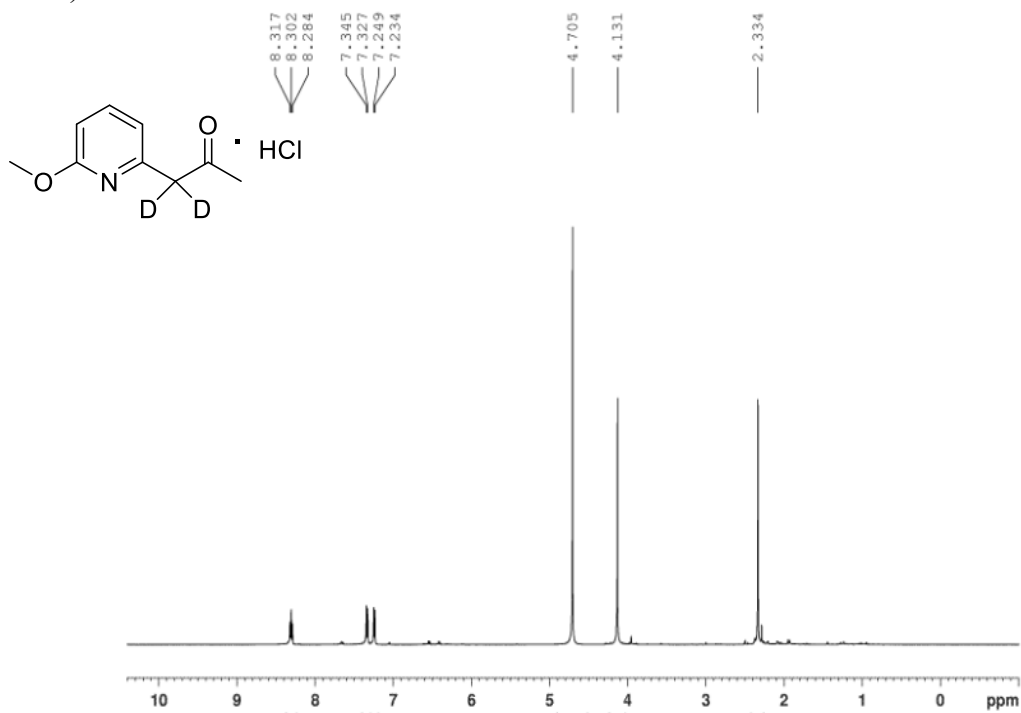
^{13}C{^{1}H} NMR Spectrum of 2-Methoxy-6-(2-oxo-propyl)-pyridinium chloride, **2-19** (D$_2$O, 125.8 MHz)
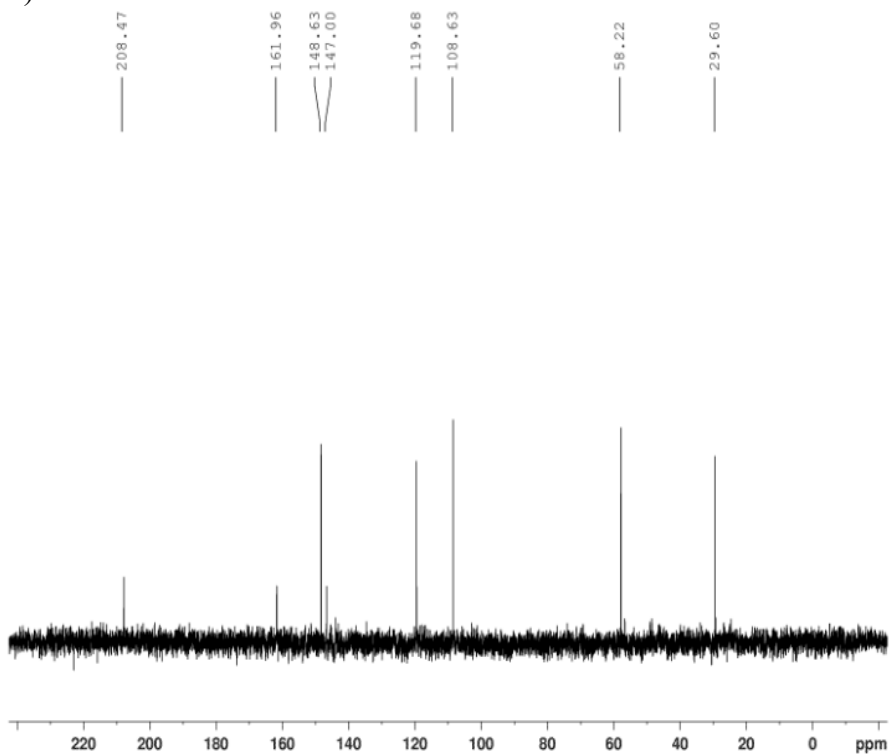
¹H -¹³C HMBC NMR Spectrum of 2-Methoxy-6-(2-oxo-propyl)-pyridinium chloride, **2-19** (D₂O, 125.8 MHz)
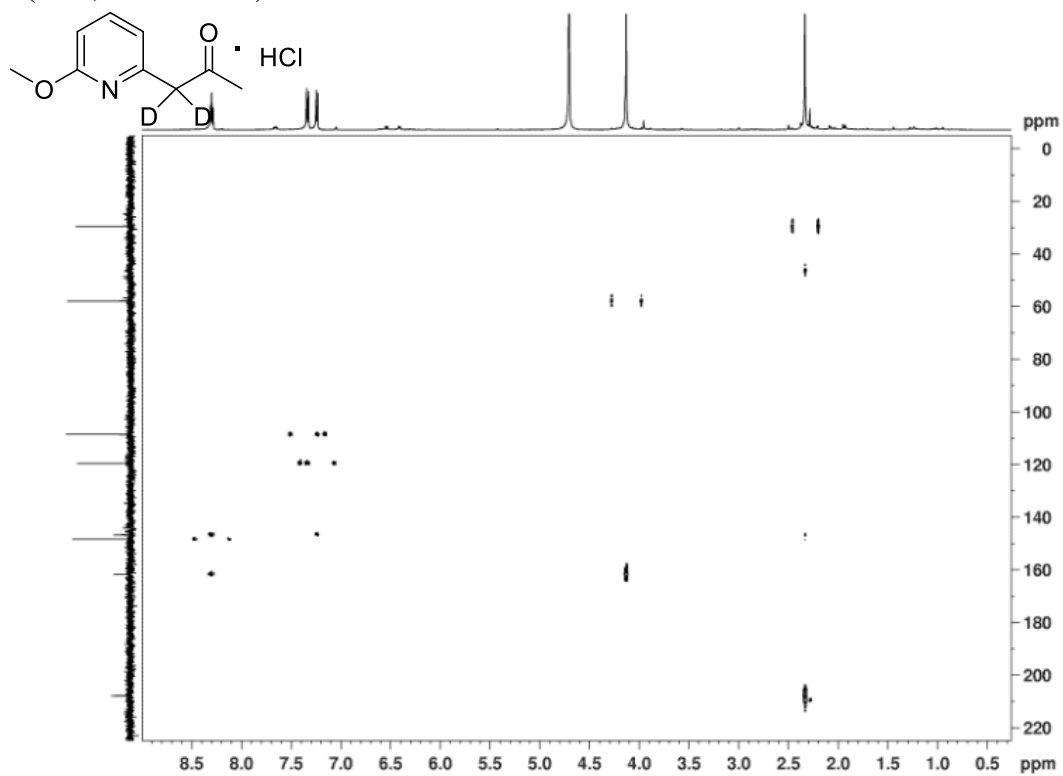
^{1}H NMR Spectrum of 4-(2-Oxo-propyl)-isoquinolinium chloride, **2-20** (D$_2$O, 500.1 MHz)
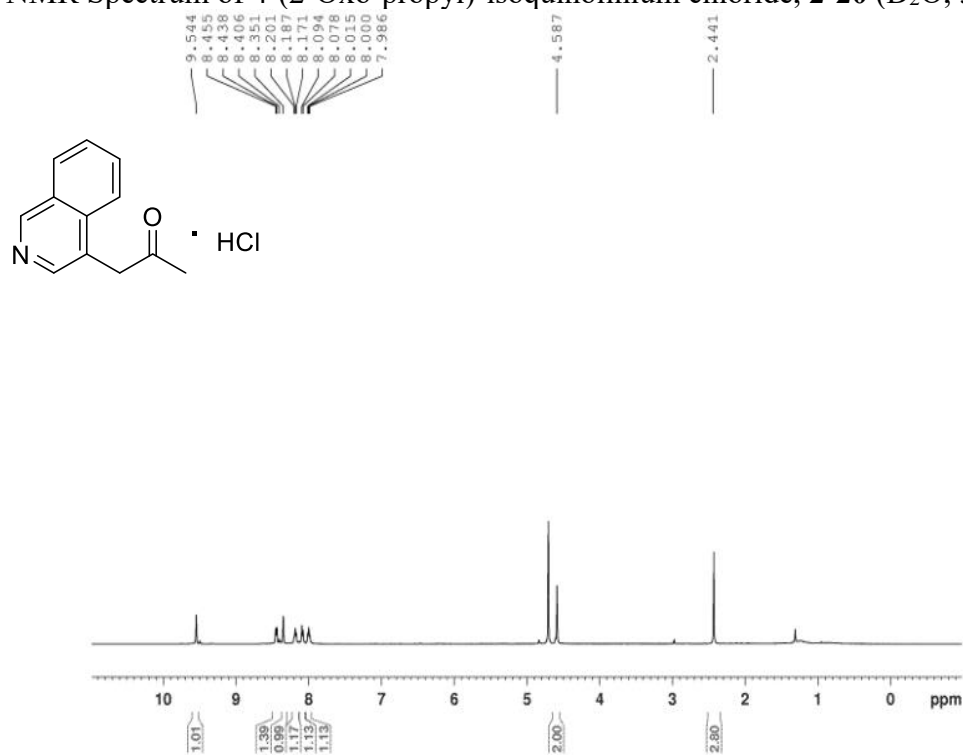
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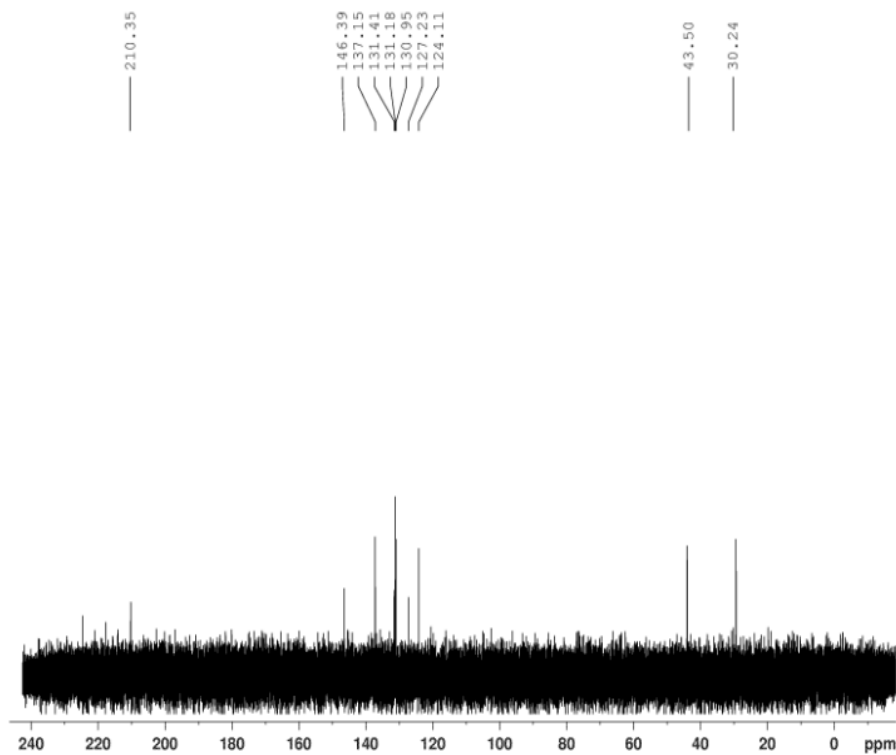
¹H NMR Spectrum of 6-(2-Oxo-propyl)-quinolinium chloride, **2-21** (D₂O, 500.1 MHz)
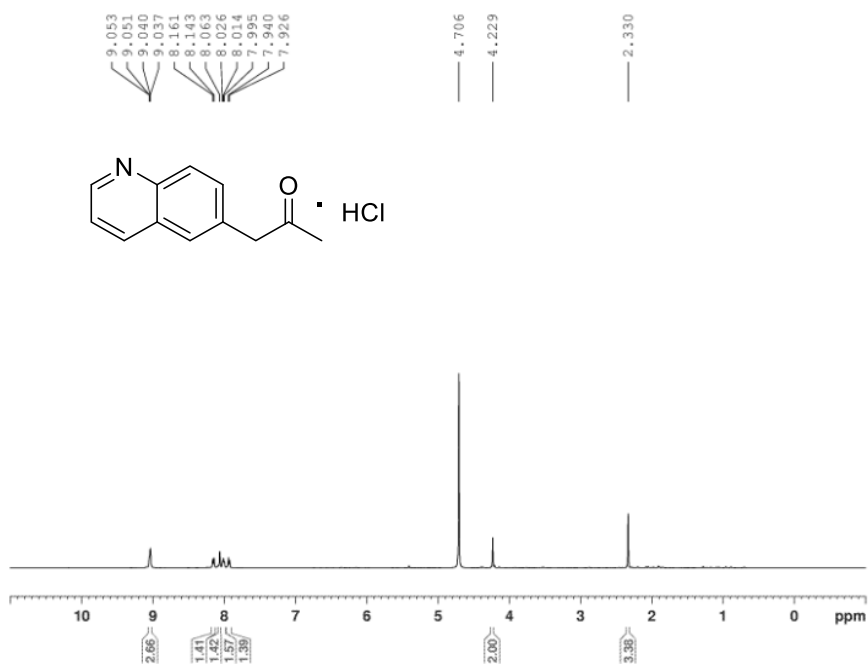
¹³C{¹H} NMR Spectrum of 6-(2-Oxo-propyl)-quinolinium chloride, **2-21** (D₂O, 125.8 MHz)
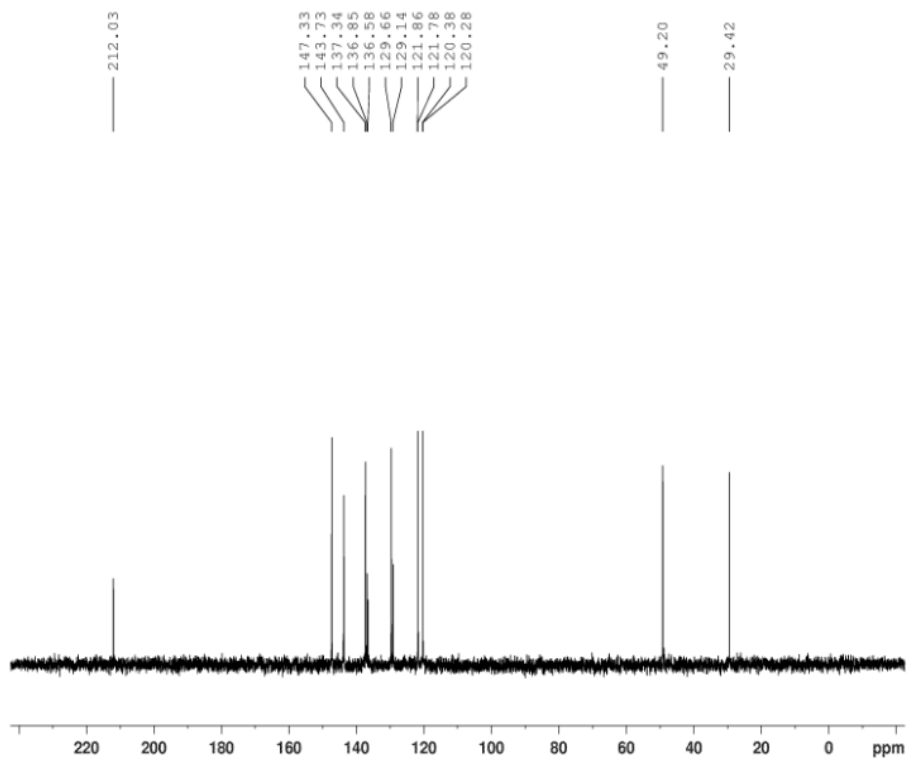
^{1}H NMR Spectrum of 3-(2-Oxo-propyl)-quinolinium chloride, **2-22** (D$_2$O, 500.1 MHz)
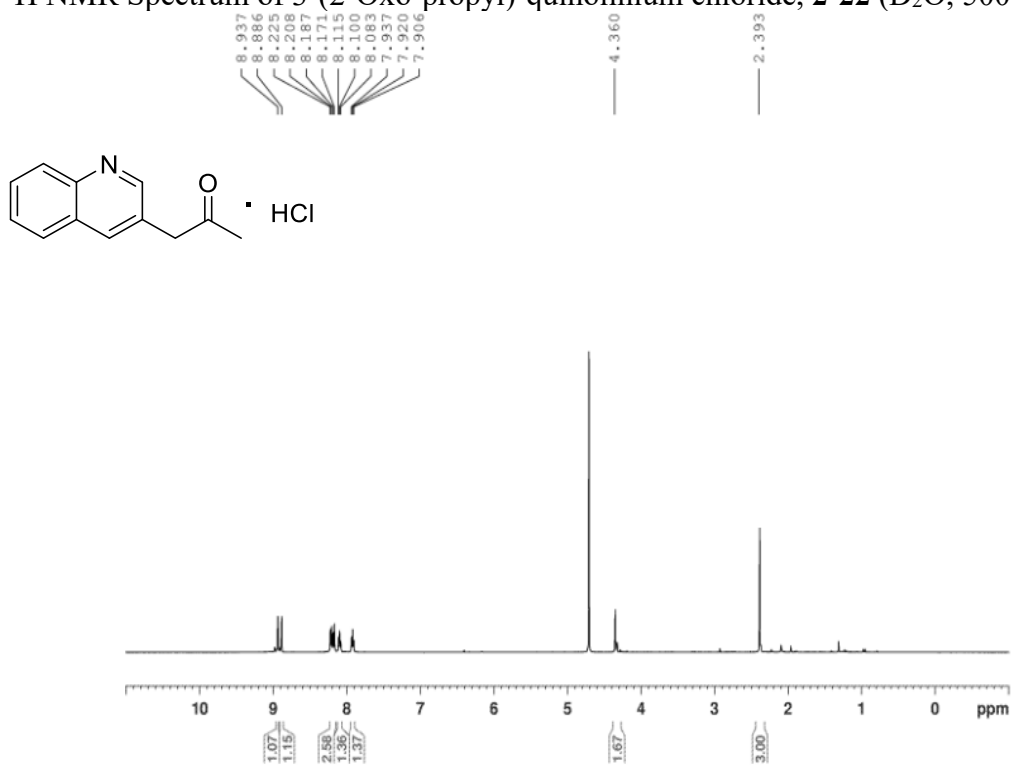
^{13}C{^{1}H} NMR Spectrum of 3-(2-Oxo-propyl)-quinolinium chloride, **2-22** (D$_2$O, 125.8 MHz)
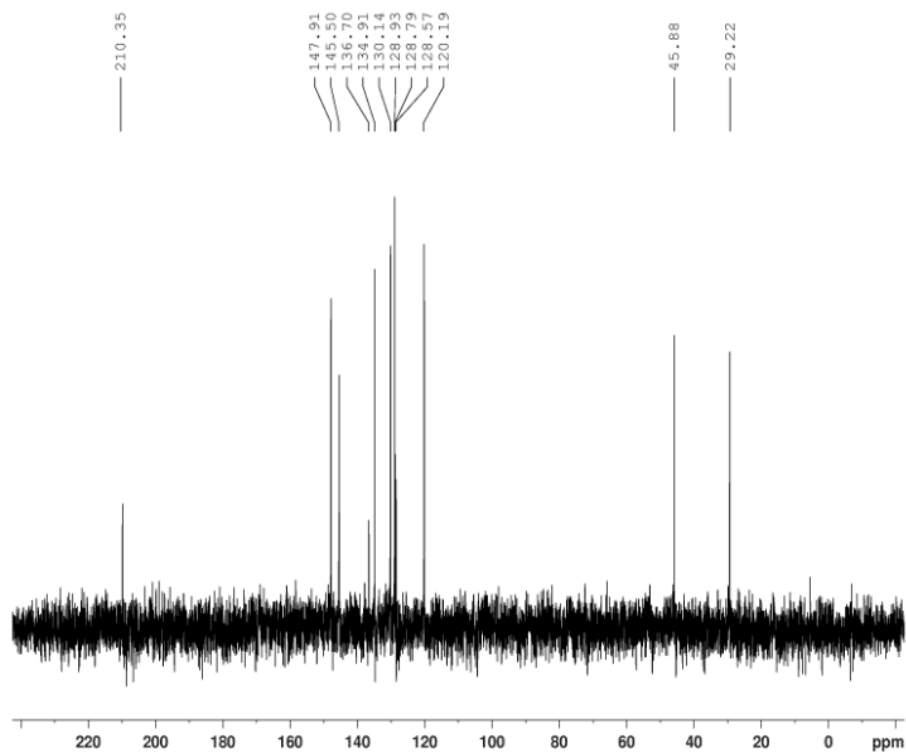
¹H NMR Spectrum of 2-Methyl-7-(2-oxo-propyl)-quinolinium chloride, **2-23** (D₂O, 500.1 MHz)

¹³C{¹H} NMR Spectrum of 2-Methyl-7-(2-oxo-propyl)-quinolinium chloride, **2-23** (D₂O, 125.8 MHz)
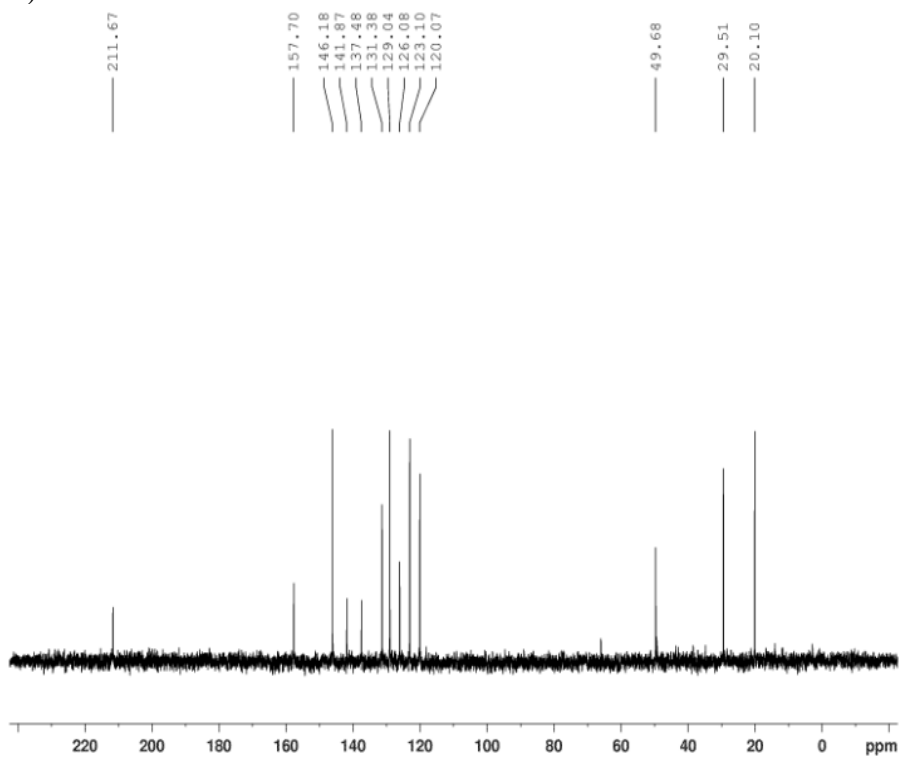
¹H NMR Spectrum of 1-Thiophen-3-yl-propan-2-one, **2-24** (CDCl₃, 500.1 MHz)

7.353
7.347
7.343
7.337
7.141
7.138
7.008
6.997

3.765

2.204

10   9   8   7   6   5   4   3   2   1   0   ppm

0.67
0.51
0.75

2.00

2.94
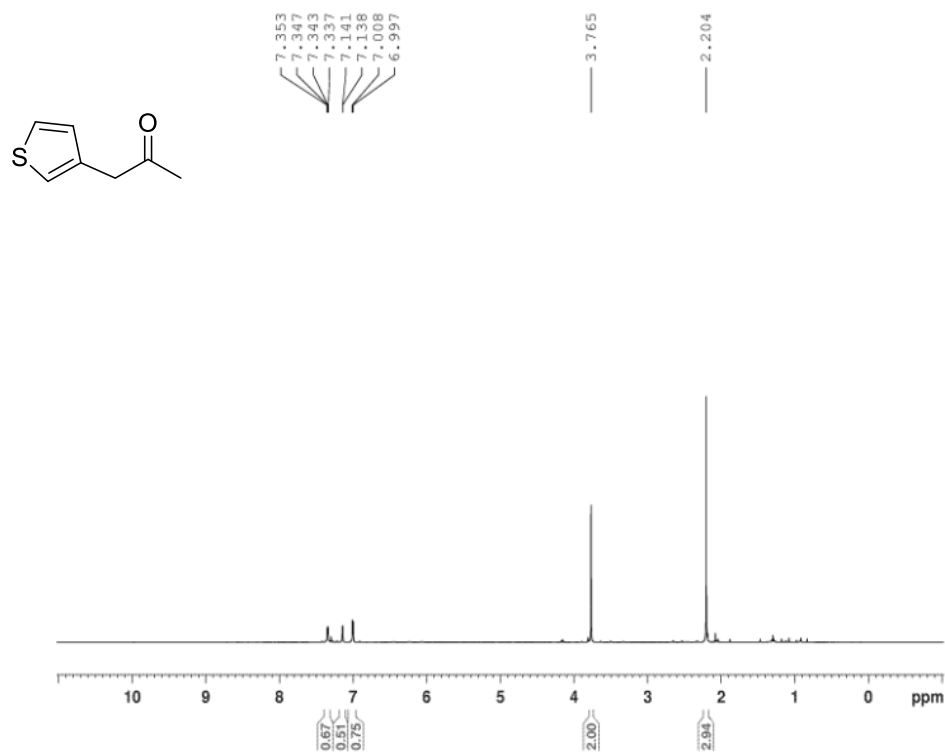
¹³C{¹H} NMR Spectrum of 1-Thiophen-3-yl-propan-2-one, **2-24** (CDCl₃, 125.8 MHz)

205.77

133.89
128.43
126.11
122.98

45.53

29.60

220   200   180   160   140   120   100   80   60   40   20   0   ppm
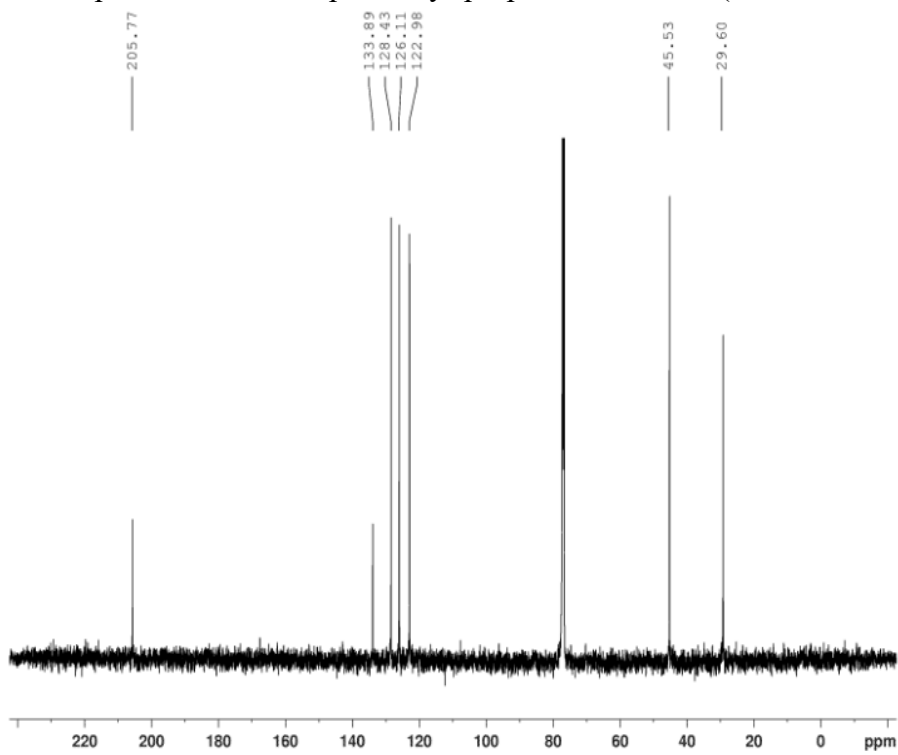
¹H NMR Spectrum of 1-Benzo[*b*]thiophen-5-yl-propan-2-one, **2-25** (CDCl₃, 500.1 MHz)
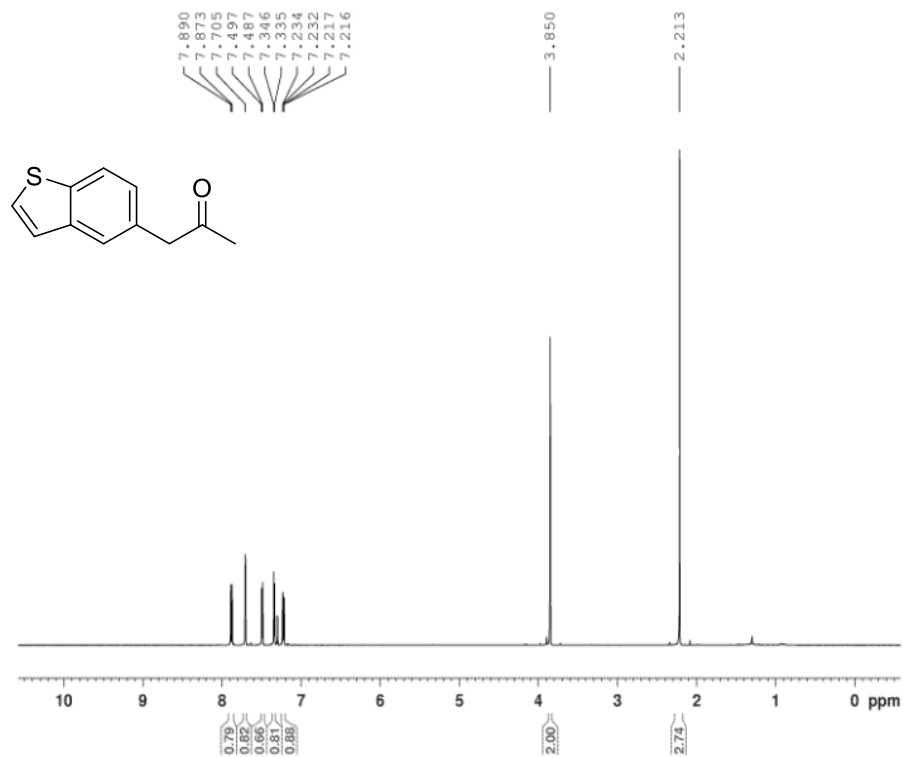
¹³C{¹H} NMR Spectrum of 1-Benzo[*b*]thiophen-5-yl-propan-2-one, **2-25** (CDCl₃, 125.8 MHz)
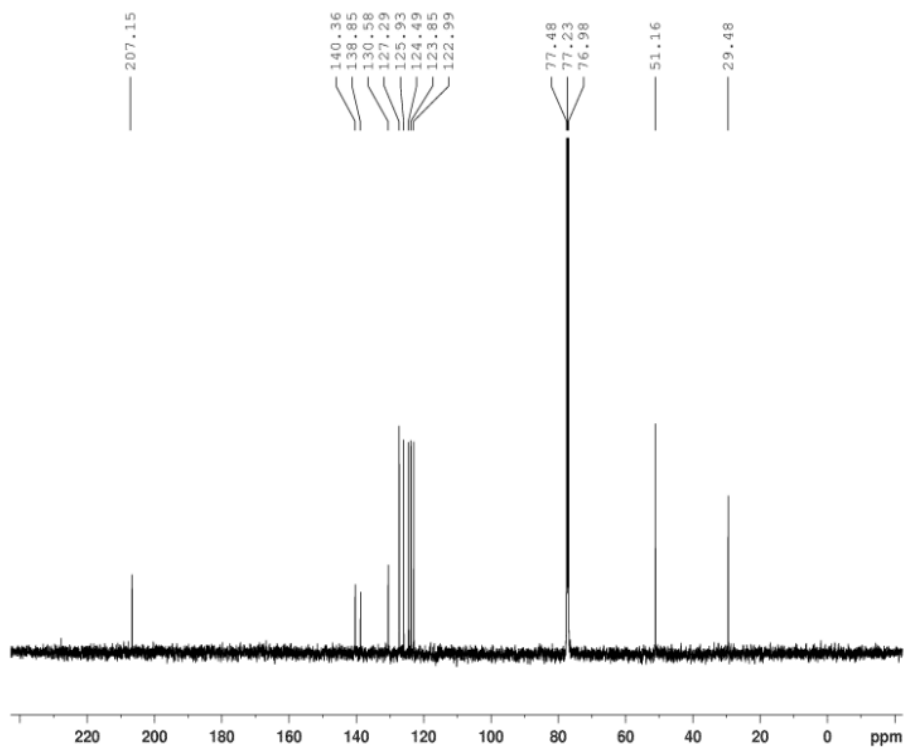
¹H NMR Spectrum of 1-(2-Methyl-benzothiazol-5-yl)-propan-2-one, **2-26** (CDCl₃, 500.1 MHz)

¹³C{¹H} NMR Spectrum of 1-(2-Methyl-benzothiazol-5-yl)-propan-2-one, **2-26** (CDCl₃, 125.8 MHz)
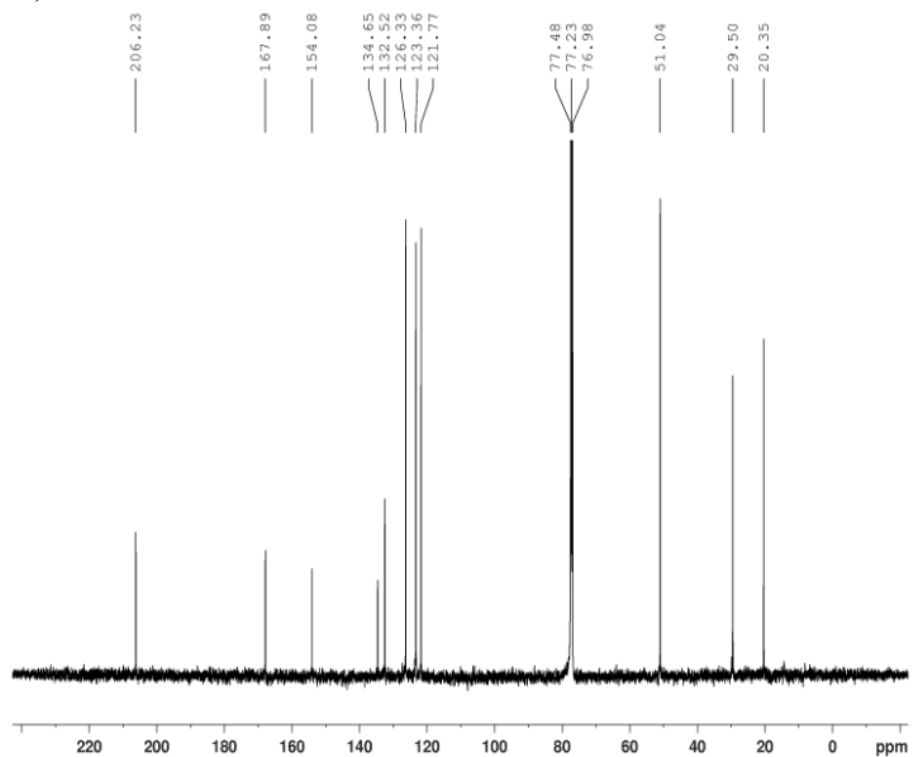
¹H NMR Spectrum of 1-Benzo[1,3]dioxol-5-yl-propan-2-one, **2-27** (CDCl₃, 500.1 MHz)

^{1}H NMR Spectrum of 1-Benzo[1,3]dioxol-5-yl-propan-2-one, **2-27** (CDCl$_3$, 500.1 MHz)

^{13}C{^{1}H} NMR Spectrum of 1-Benzo[1,3]dioxol-5-yl-propan-2-one, **2-27** (CDCl$_3$, 125.8 MHz)
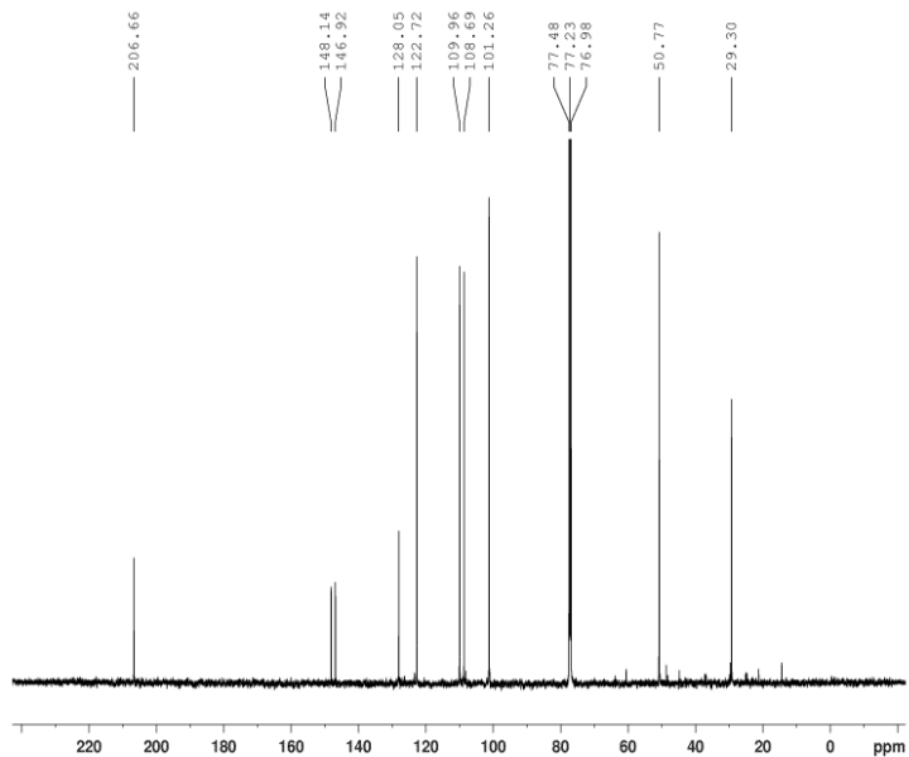
^{1}H NMR Spectrum of 2-Benzo[*b*]thiophen-5-yl-1-phenyl-ethanone, **2-28** (CDCl$_3$, 500.1 MHz)
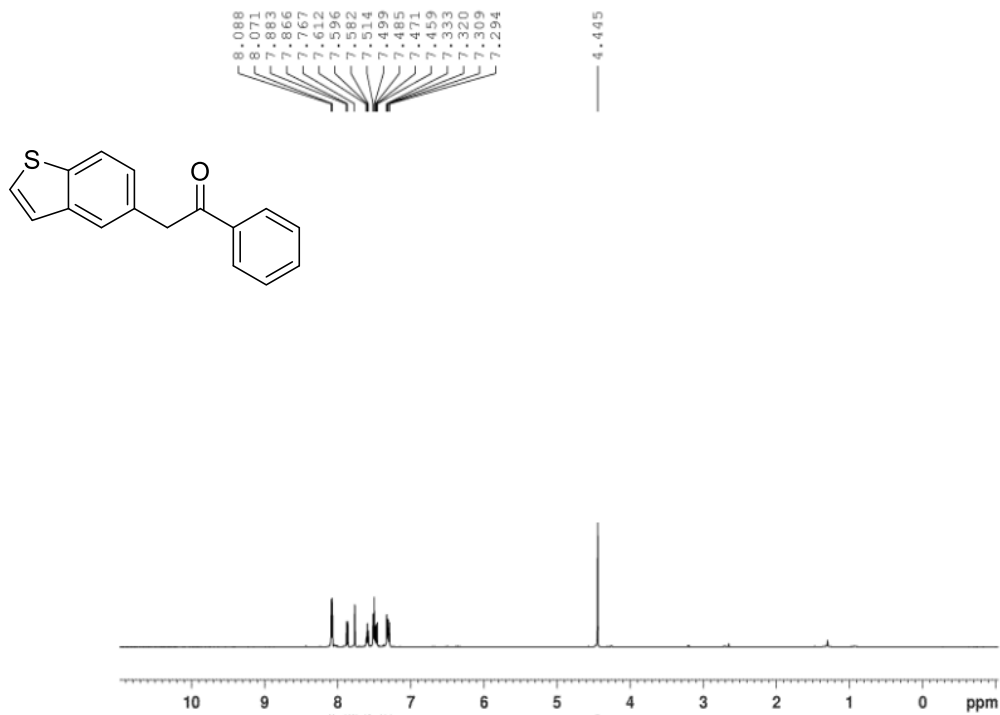
^{13}C{^{1}H} NMR Spectrum of 2-Benzo[*b*]thiophen-5-yl-1-phenyl-ethanone, **2-28** (CDCl$_3$, 125.8 MHz)
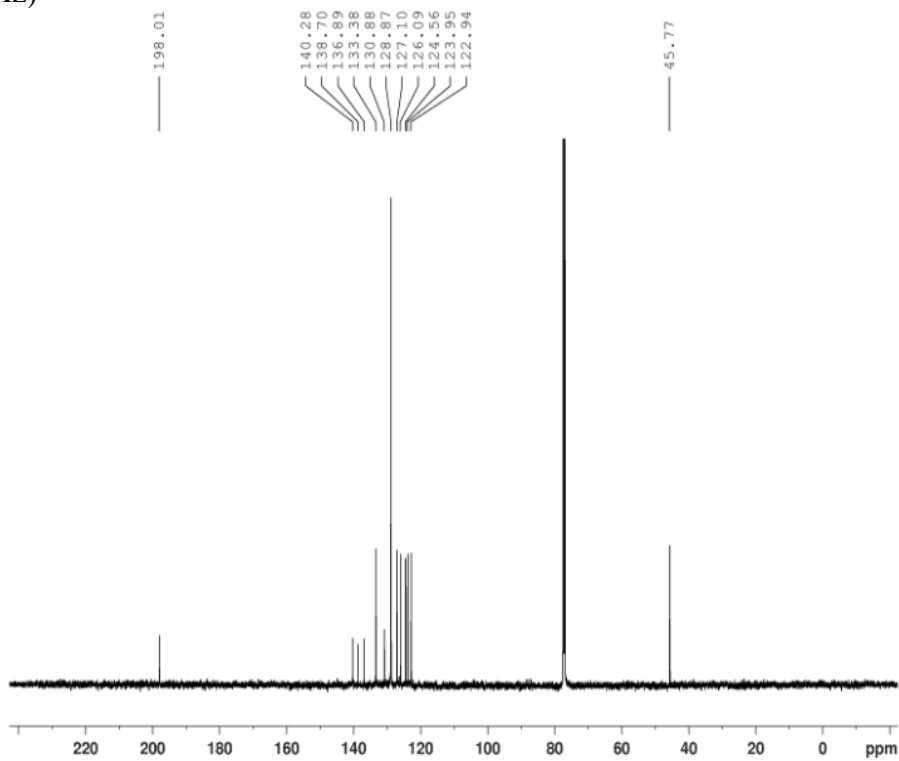
^{1}H NMR Spectrum of 2-(2-Methyl-benzothiazol-5-yl)-1-phenyl-ethanone, **2-29** (CDCl$_3$, 500.1 MHz)

^{13}C{^{1}H} NMR Spectrum of 2-(2-Methyl-benzothiazol-5-yl)-1-phenyl-ethanone, **2-29** (CDCl$_3$, 125.8 MHz)
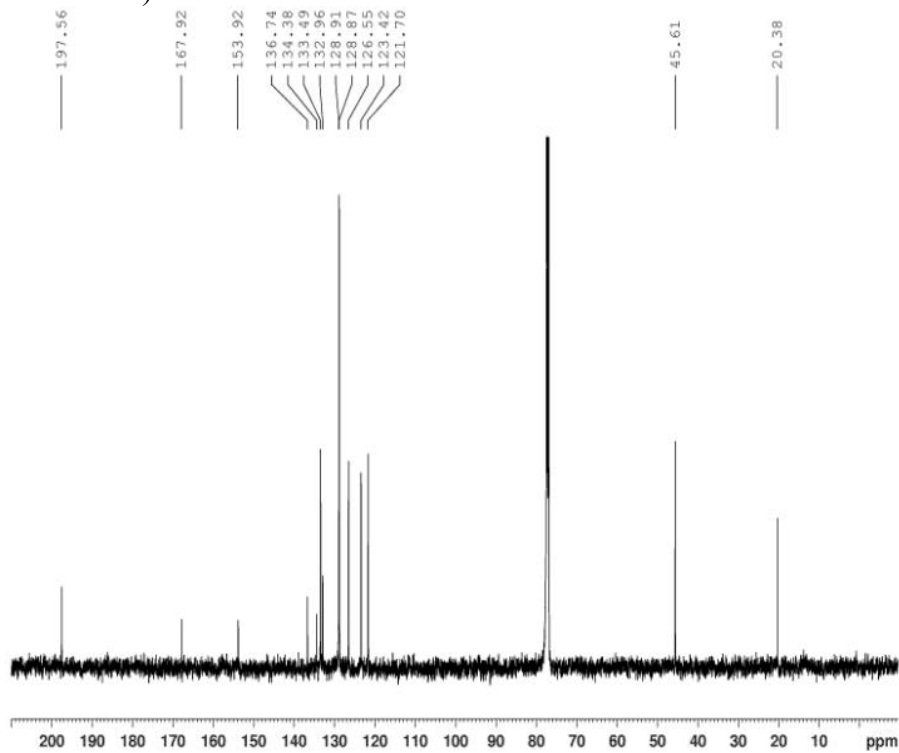
¹H NMR Spectrum of 1-Phenyl-2-quinolin-6-yl-ethanone, **2-30** (CDCl₃, 500.1 MHz)
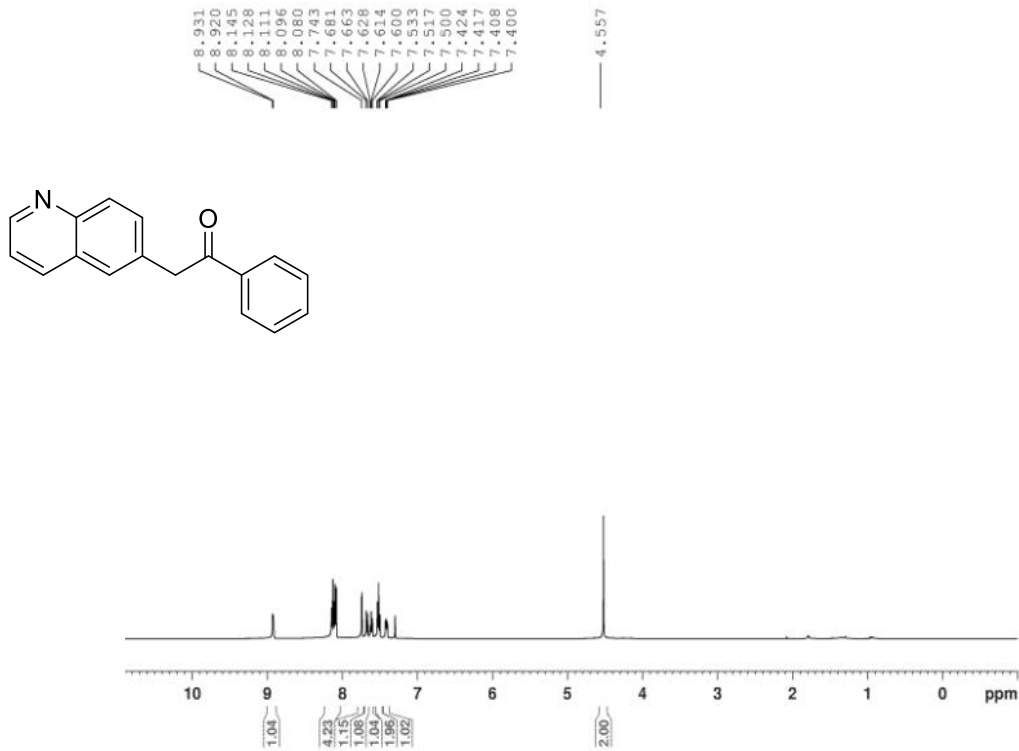
¹³C{¹H} NMR Spectrum of 1-Phenyl-2-quinolin-6-yl-ethanone, **2-30** (CDCl₃, 125.8 MHz)
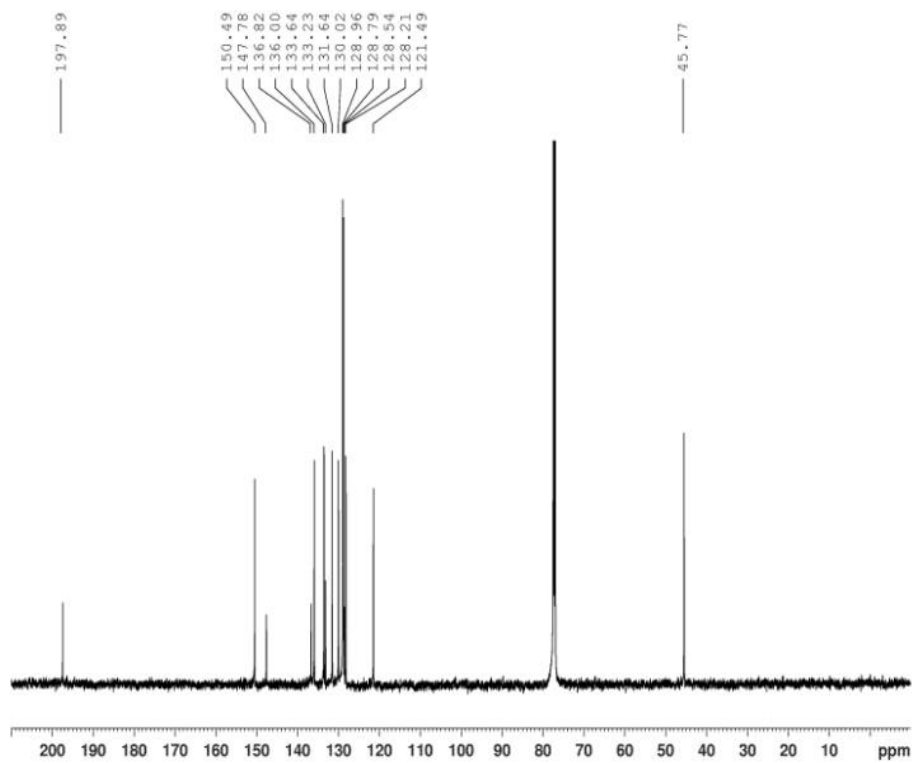
¹H NMR Spectrum of 2-Benzo[*b*]thiophen-5-yl-1-thiophen-2-yl-ethanone, **2-31** (CDCl₃, 500.1 MHz)
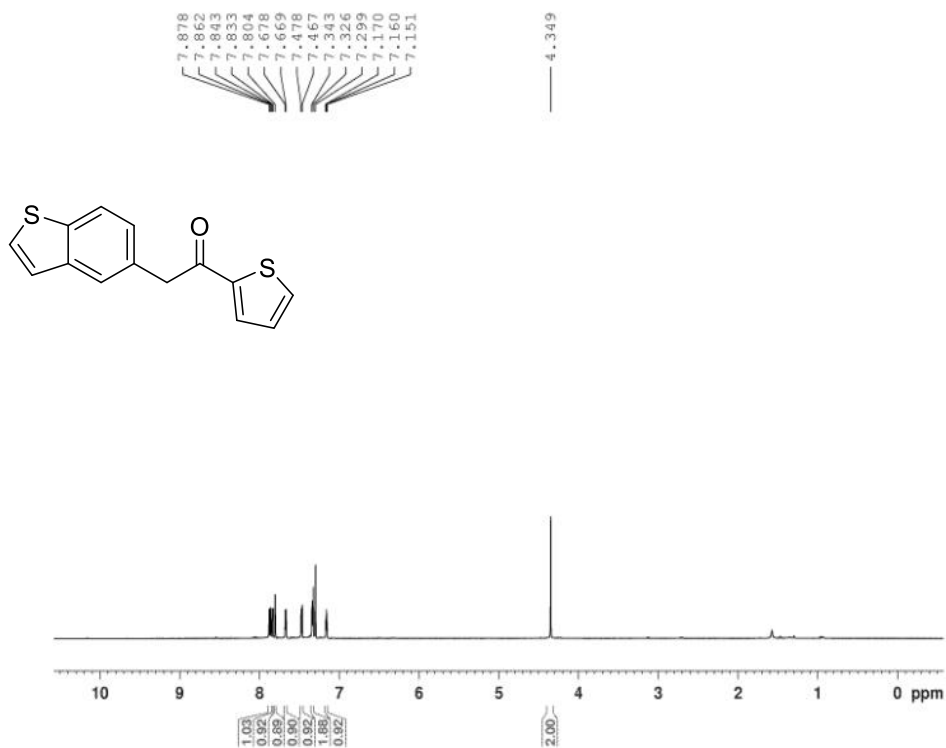
¹³C{¹H} NMR Spectrum of 2-Benzo[*b*]thiophen-5-yl-1-thiophen-2-yl-ethanone, **2-31** (CDCl₃, 125.8 MHz)
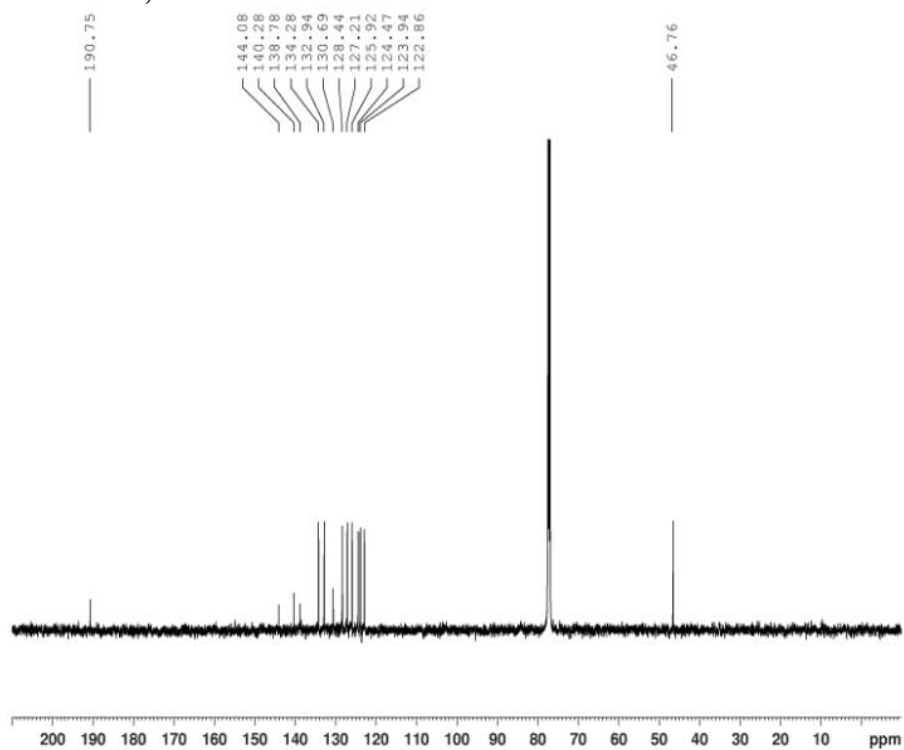
¹H NMR Spectrum of 2-Benzo[*b*]thiophen-5-yl-1-furan-2-yl-ethanone, **2-32** (CDCl₃, 500.1 MHz)

7.871
7.854
7.804
7.640
7.472
7.462
7.345
7.335
7.325
7.277
7.271
6.573
6.569
6.567

4.276

0.98
0.93
0.97
0.97
2.06
0.97

0.95

2.00
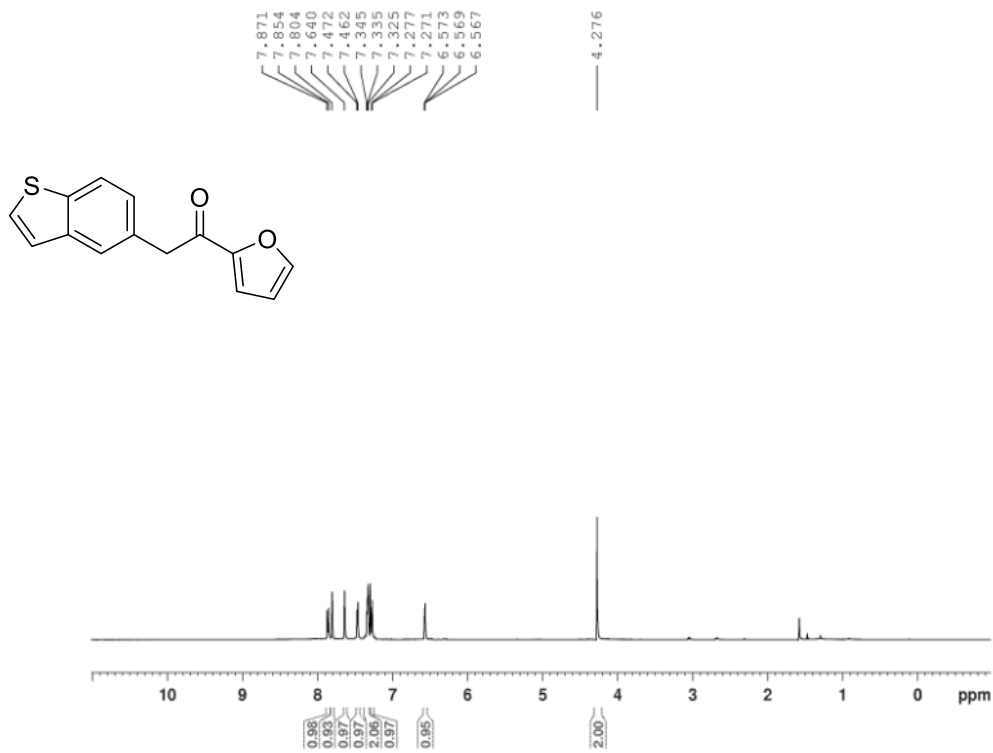
¹³C{¹H} NMR Spectrum of 2-Benzo[*b*]thiophen-5-yl-1-furan-2-yl-ethanone, **2-32** (CDCl₃, 125.8 MHz)

186.66

152.44
146.53
140.02
138.53
130.10
128.48
126.86
125.82
124.35
123.66
122.59
117.84
112.39

45.29
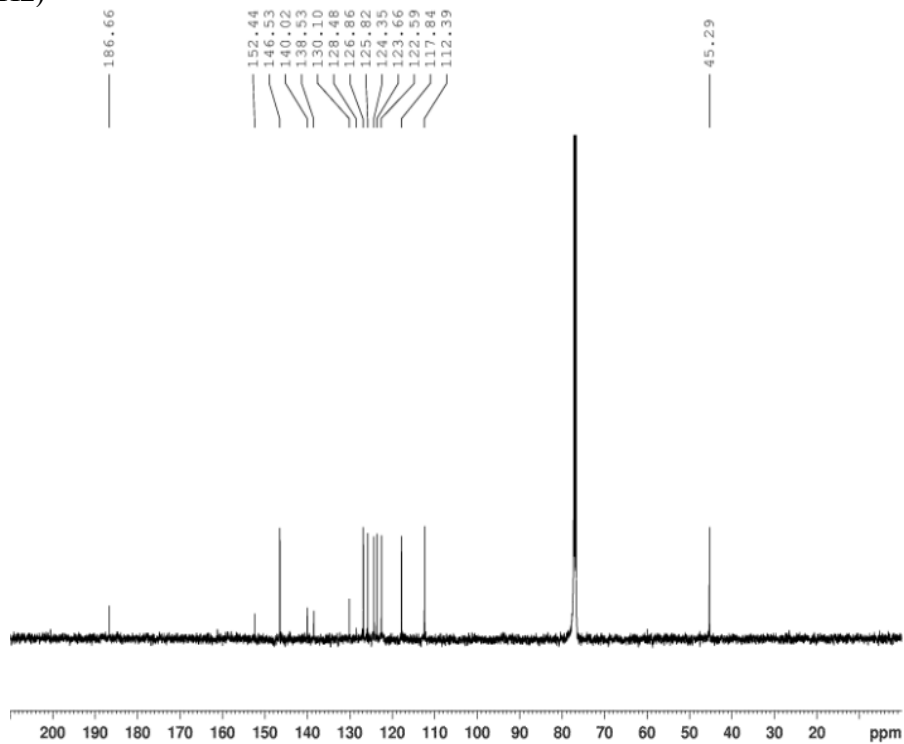
^{1}H NMR Spectrum of *N*-(1-naphthyl)-Octylamine, **3-6** (CDCl$_3$, 500.1 MHz)
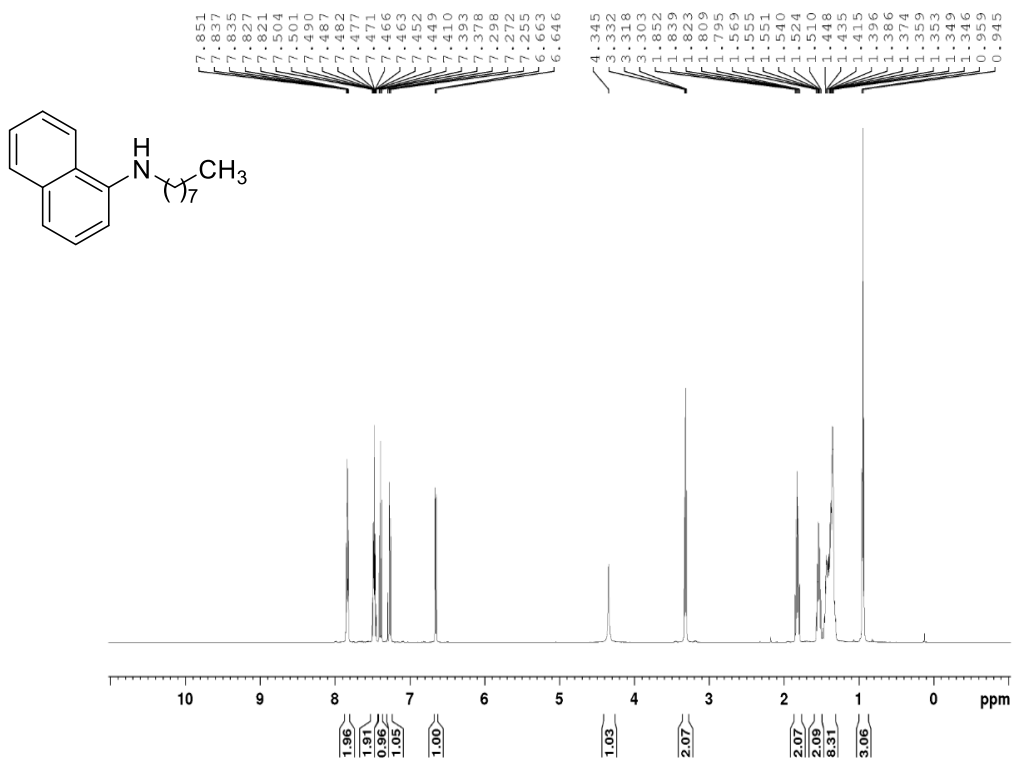
^{13}C{^{1}H} NMR Spectrum of *N*-(1-naphthyl)-Octylamine, **3-6** (CDCl$_3$, 125.8 MHz)

209
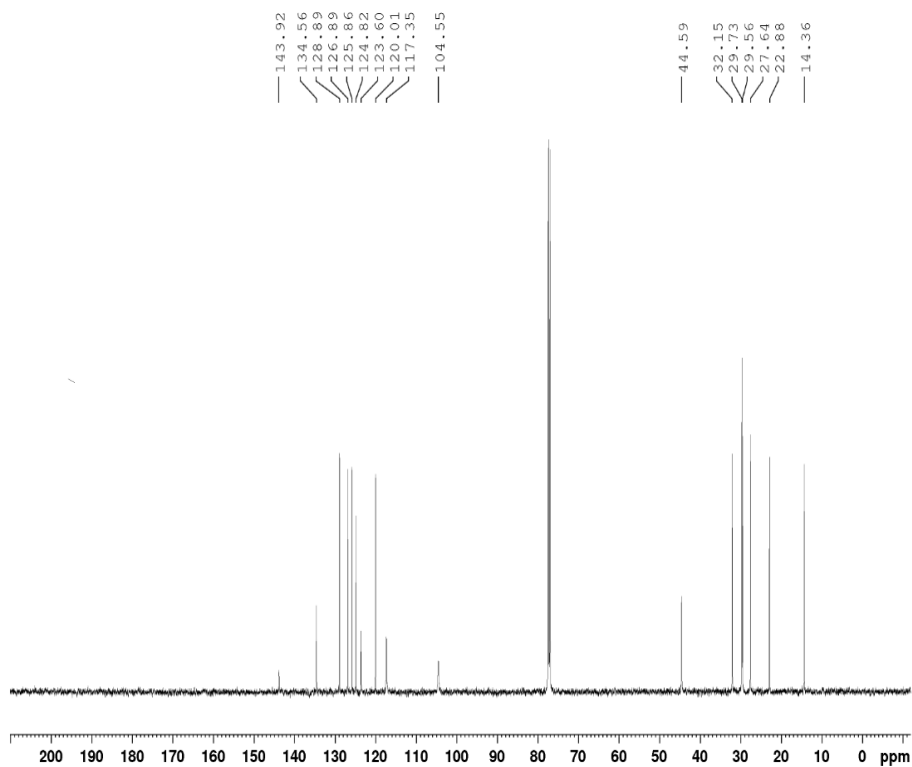
¹H NMR Spectrum of 4-Methoxy-*N*-octylaniline, **3-7** (CDCl₃, 300.1 MHz)
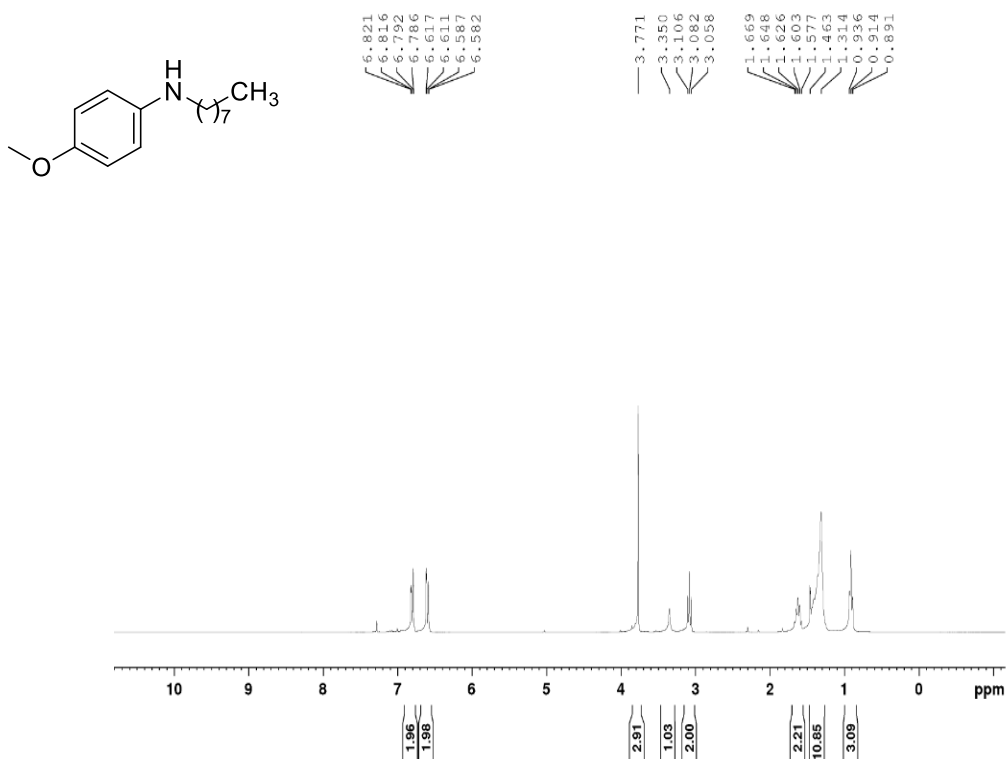
¹³C{¹H} NMR Spectrum of 4-Methoxy-*N*-octylaniline, **3-7** (CDCl₃, 125.8 MHz)

210
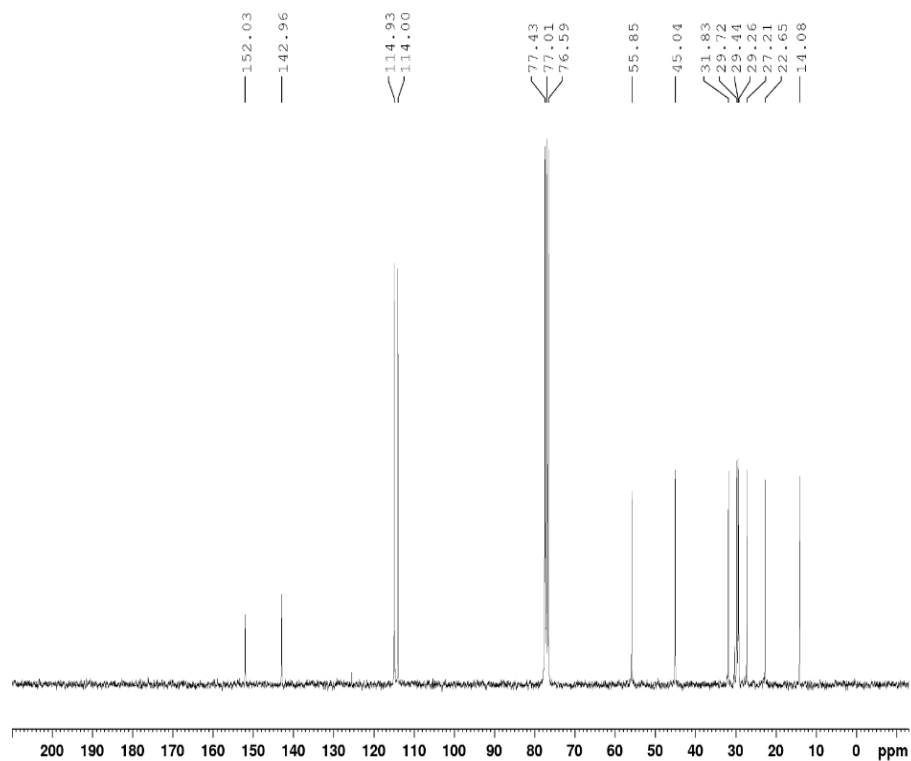
¹H NMR Spectrum of *N*-Octyl-4-(trifluoromethyl)anilinie, **3-8** (CDCl₃, 500.1 MHz)
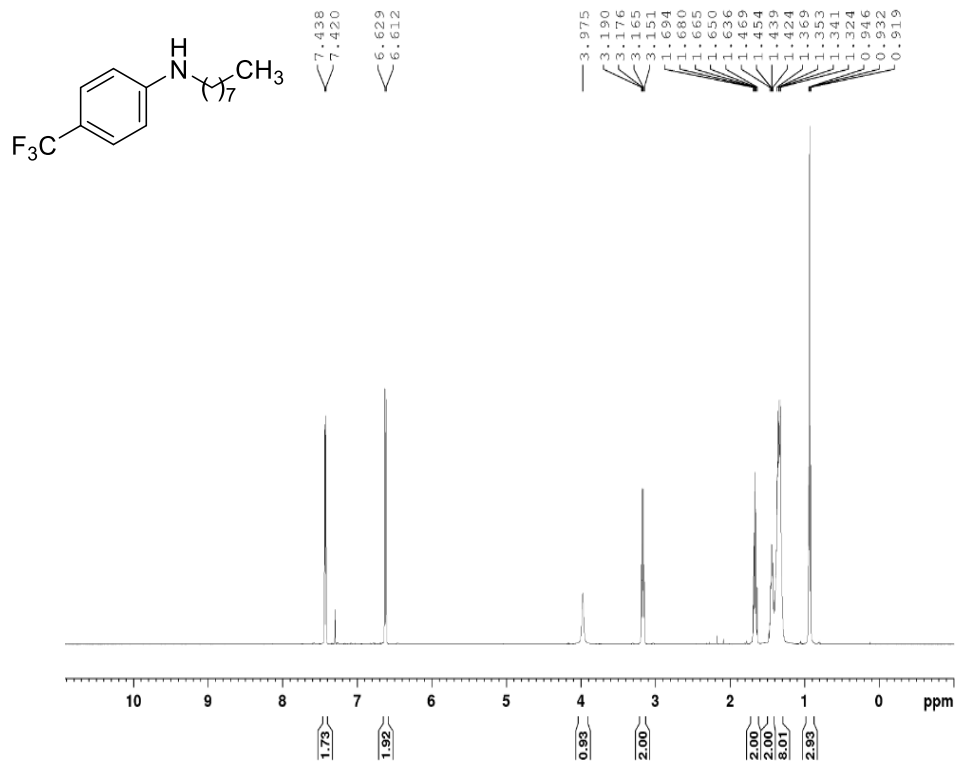
¹³C{¹H} NMR Spectrum of *N*-Octyl-4-(trifluoromethyl)anilinie, **3-8** (CDCl₃, 125.8 MHz)
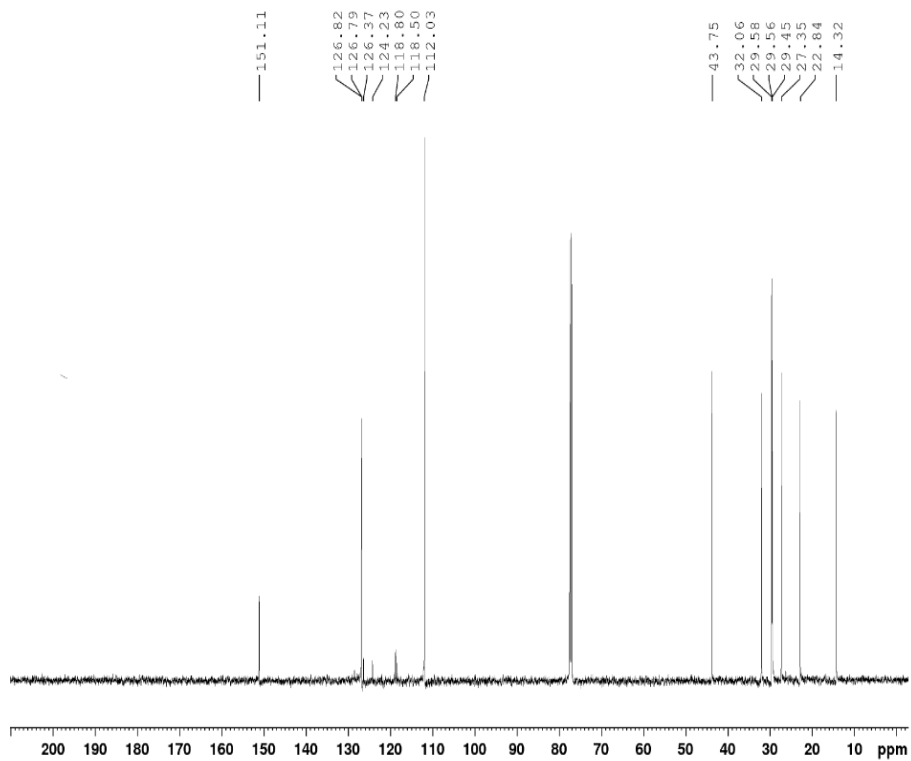
¹H NMR Spectrum of 4-(Octylamino)benzonitrile, **3-9** (CDCl₃, 500.1 MHz)
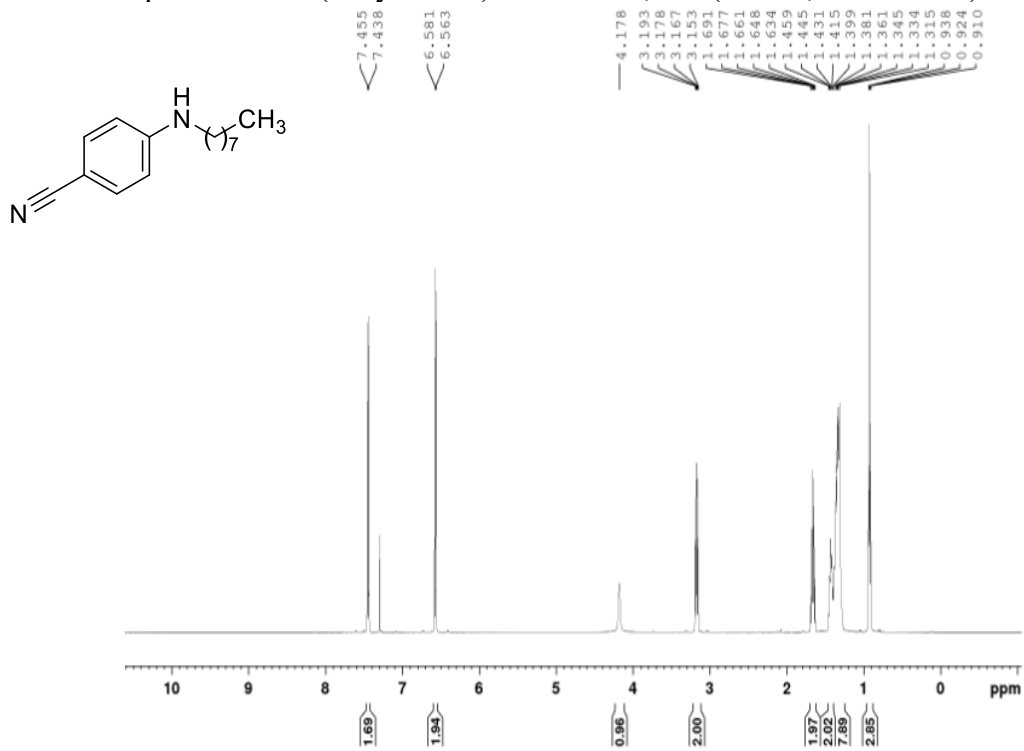
¹³C{¹H} NMR Spectrum of 4-(Octylamino)benzonitrile, **3-9** (CDCl₃, 125.8 MHz)
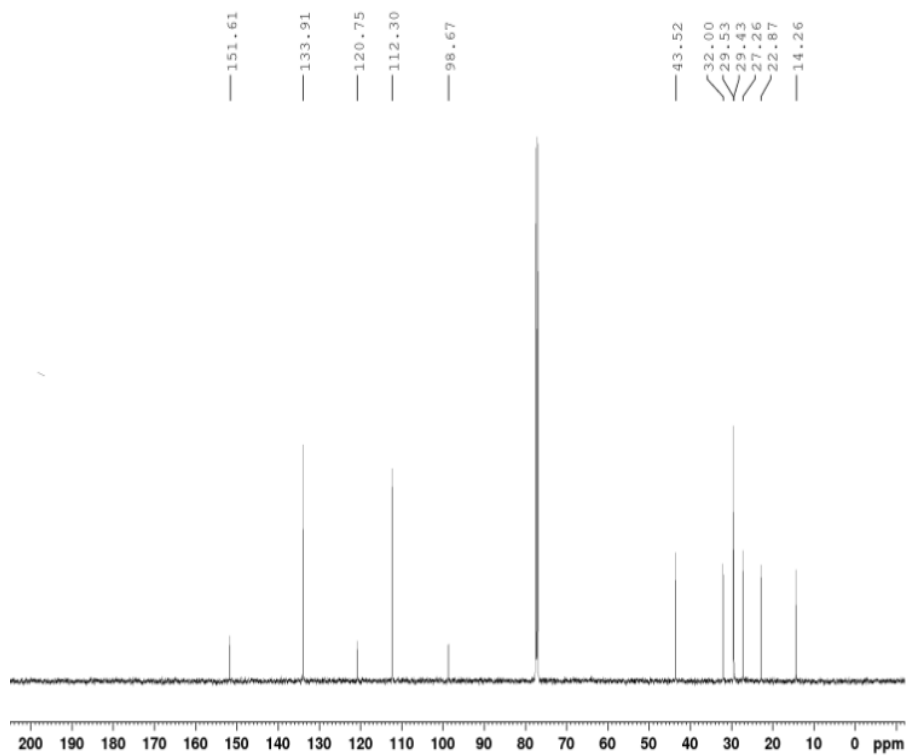
¹H NMR Spectrum of 2,5-Dimethyl-*N*-octylaniline, **3-10** (CDCl₃, 500.1 MHz)
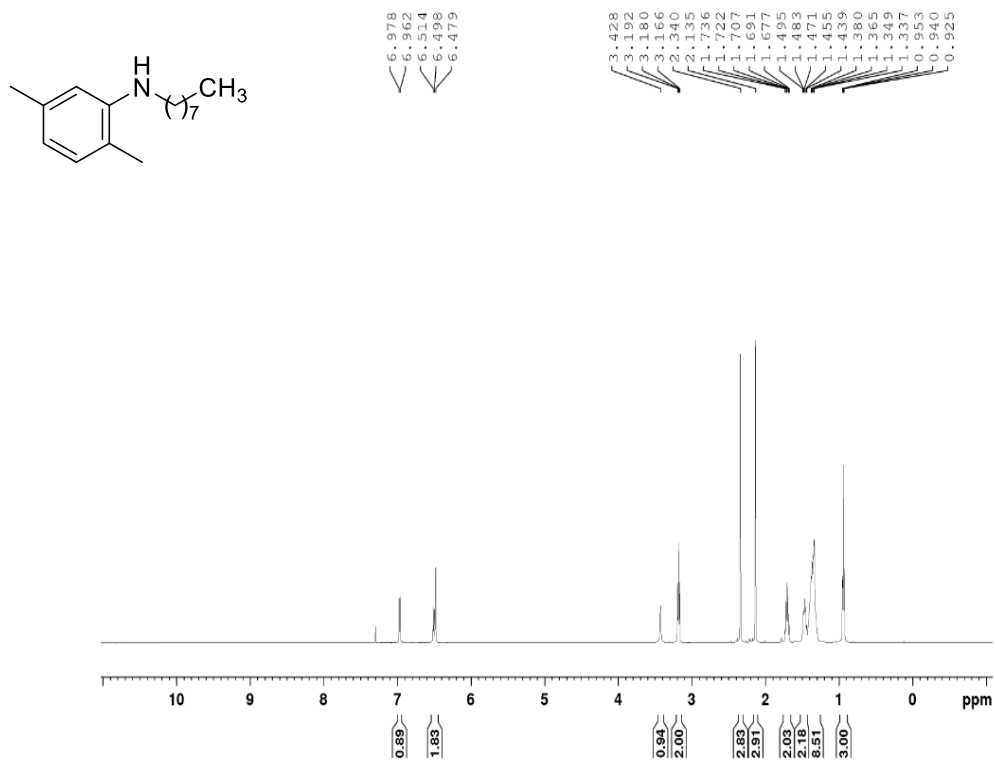
¹³C{¹H} NMR Spectrum of 2,5-Dimethyl-*N*-octylaniline, **3-10** (CDCl₃, 125.8 MHz)
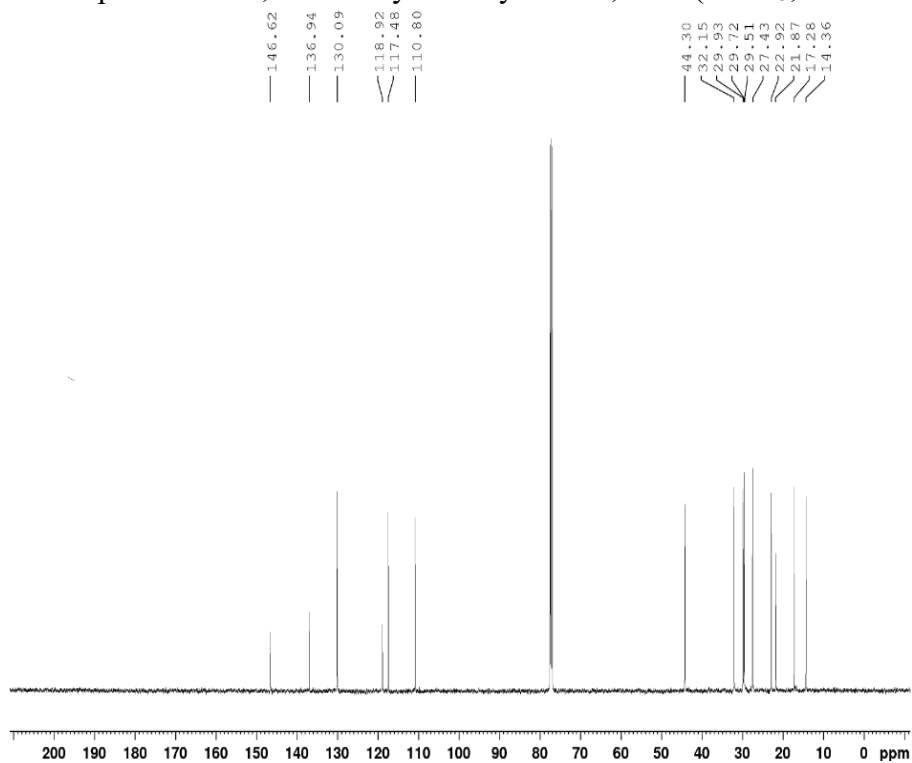
¹H NMR Spectrum of 2',6'-dimethoxy-*N*-octylamine, **3-11** (CDCl₃, 300.1 MHz)
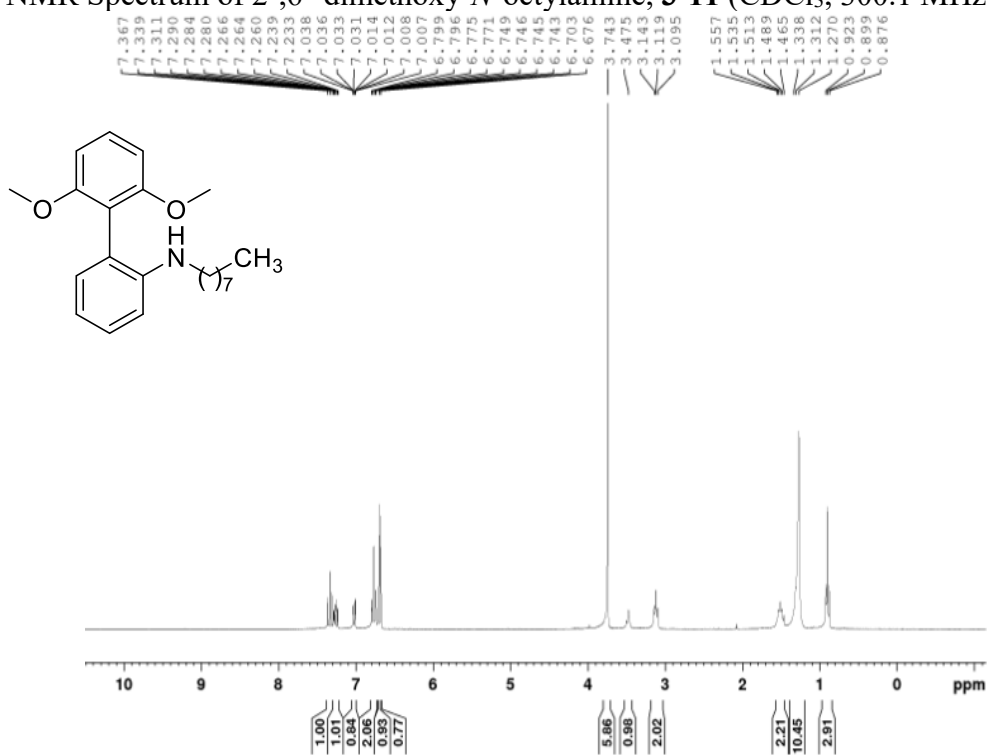
¹³C{¹H} NMR Spectrum of 2',6'-dimethoxy-*N*-octylamine, **3-11** (CDCl₃, 75.5 MHz)
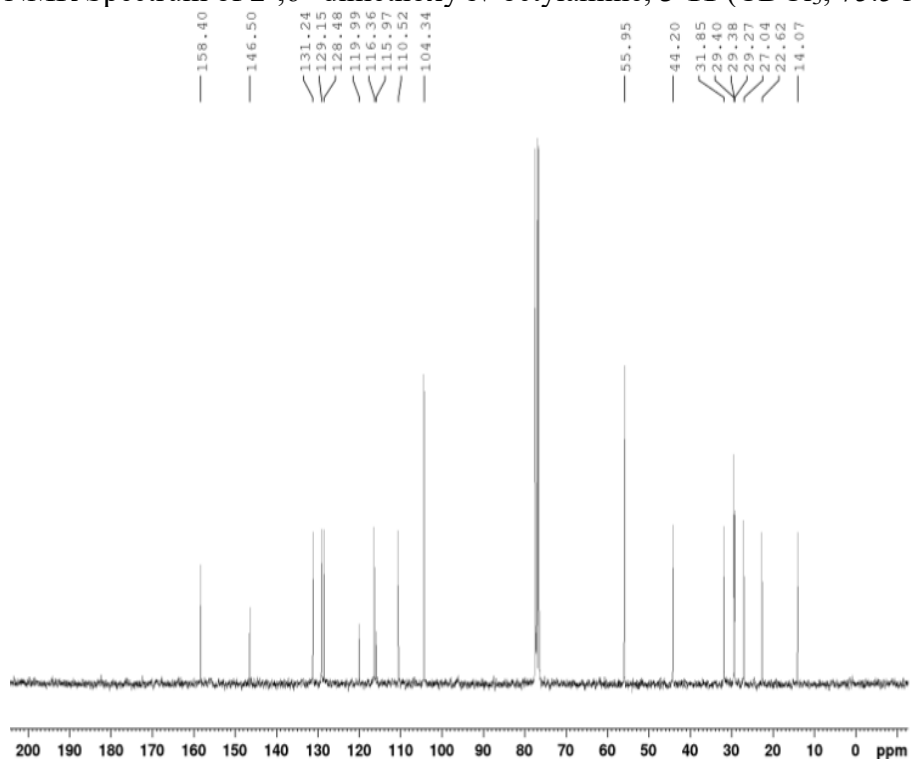
^{1}H NMR Spectrum of *Sec*- Butyl-(2-methyl-quinolin-4-yl)amine, **3-12** (CDCl$_3$, 500.1 MHz)
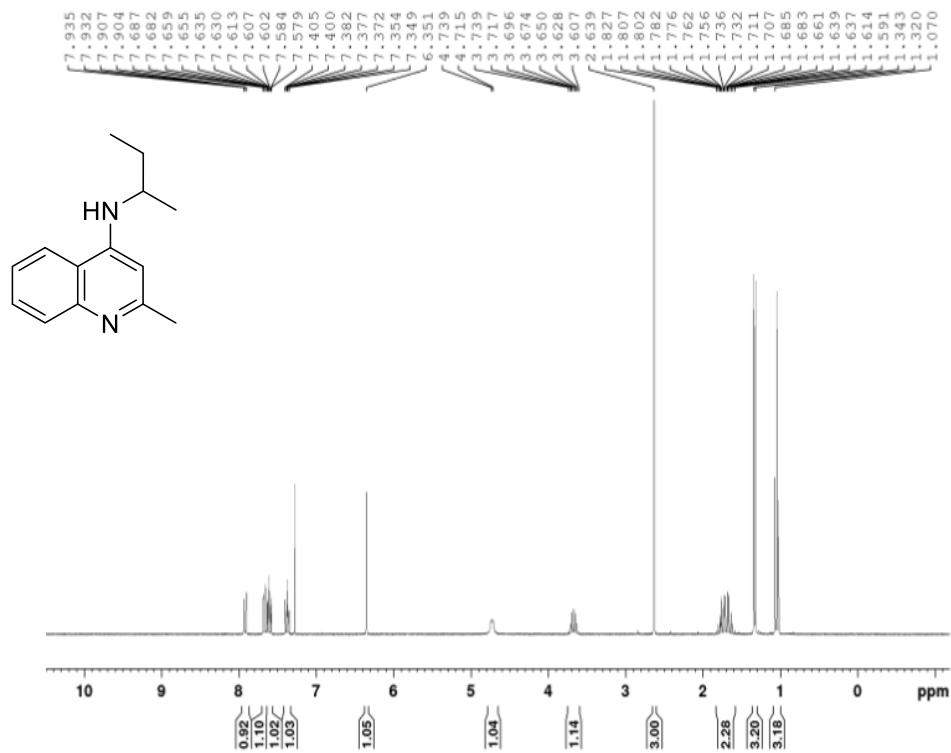
^{13}C{^{1}H} NMR Spectrum of *Sec*- Butyl-(2-methyl-quinolin-4-yl)amine, **3-12** (CDCl$_3$, 125.8 MHz)
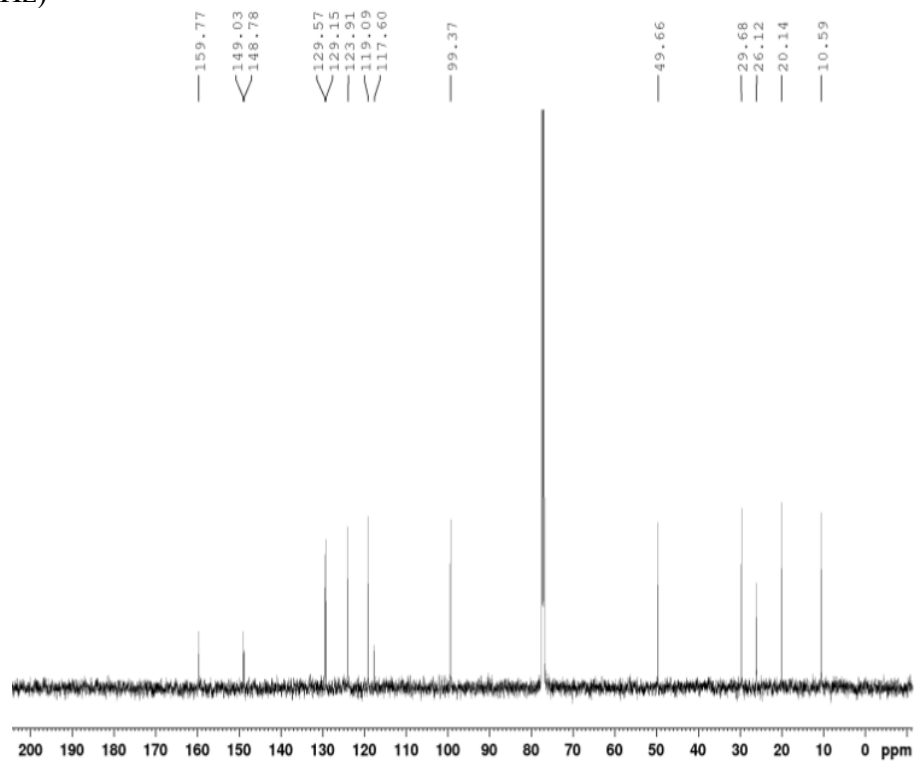
¹H NMR Spectrum of Cyclohexyl-(2-methyl-benzothiazol-5-yl)-amine, **3-13** (CDCl₃, 500.1 MHz)

^{1}H NMR Spectrum of Cyclohexyl-(2-methyl-benzothiazol-5-yl)-amine, **3-13** (CDCl$_3$, 500.1 MHz)
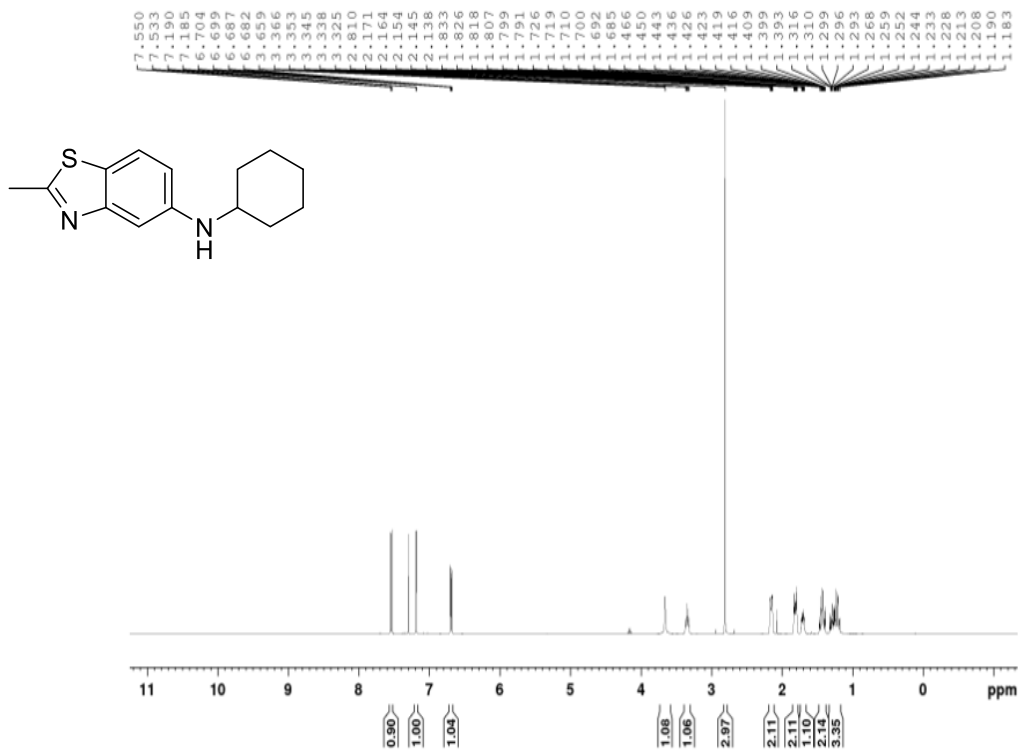
^{13}C{^{1}H} NMR Spectrum of Cyclohexyl-(2-methyl-benzothiazol-5-yl)-amine, **3-13** (CDCl$_3$, 125.8 MHz)
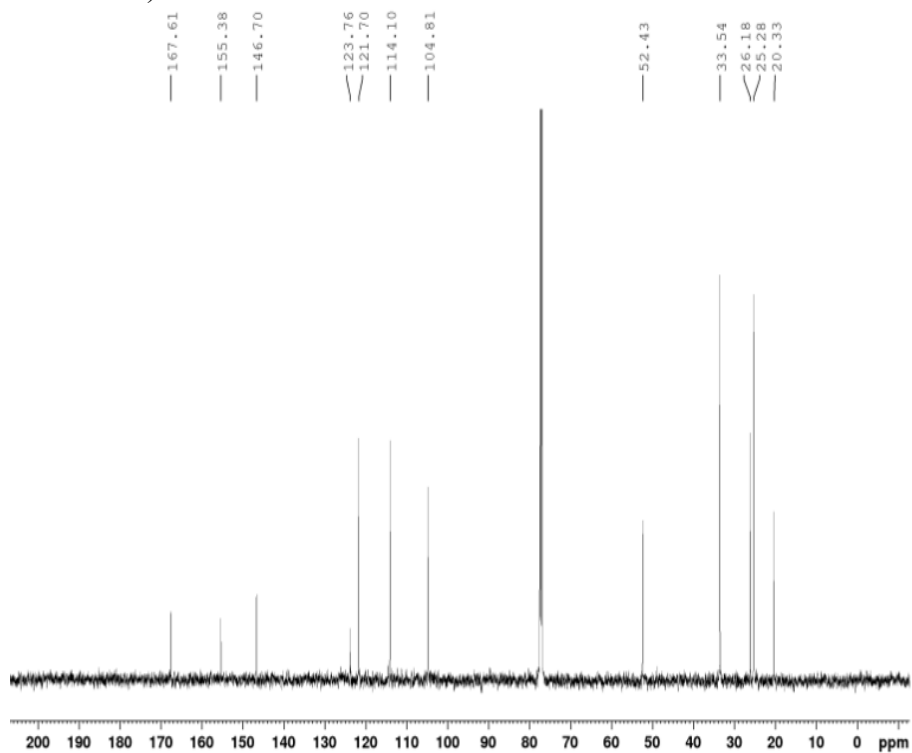
^{1}H NMR Spectrum of 4-methyl-N-phenylpiperazin-1-amine, **3-14** (CDCl$_3$, 500.0 MHz)
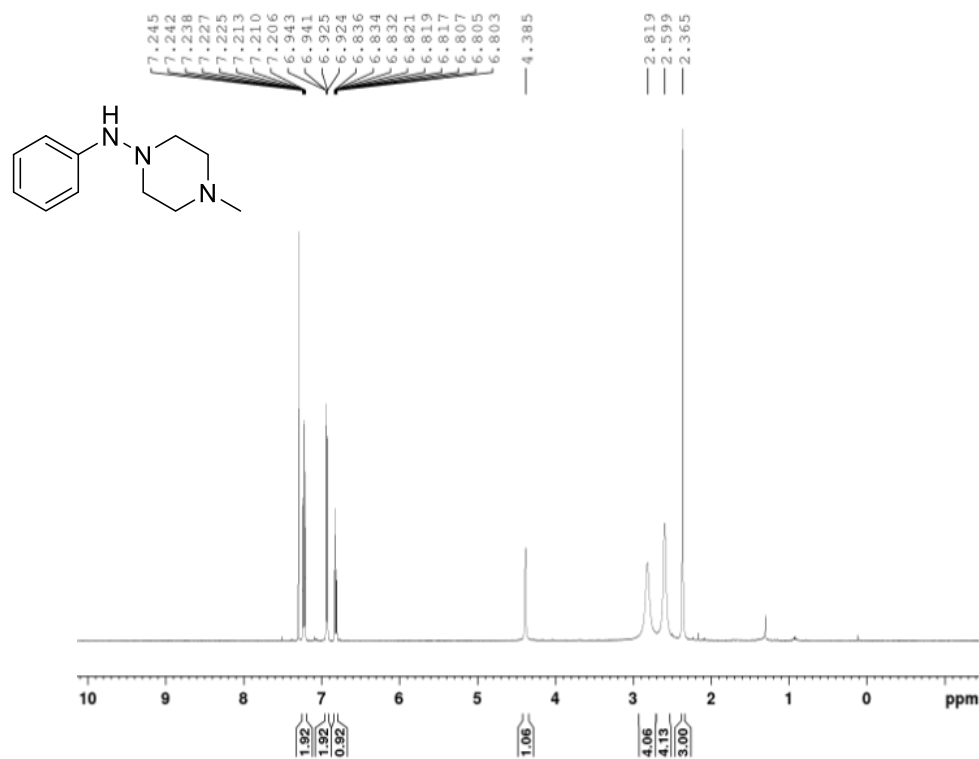
^{13}C{^{1}H} NMR Spectrum of 4-methyl-N-phenylpiperazin-1-amine, **3-14** (CDCl$_3$, 125.8 MHz)
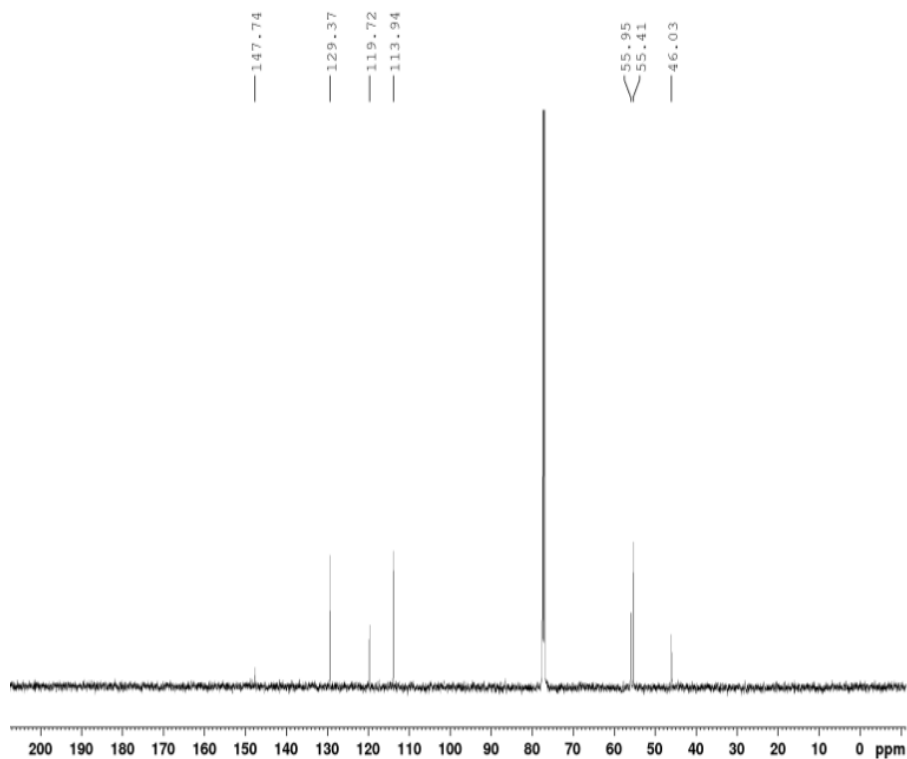
¹H NMR Spectrum of Benzo[*b*]thiophen-5-yl-(3-trifluoromethyl-phenyl)- amine, **3-15** (CDCl₃, 500.1 MHz)
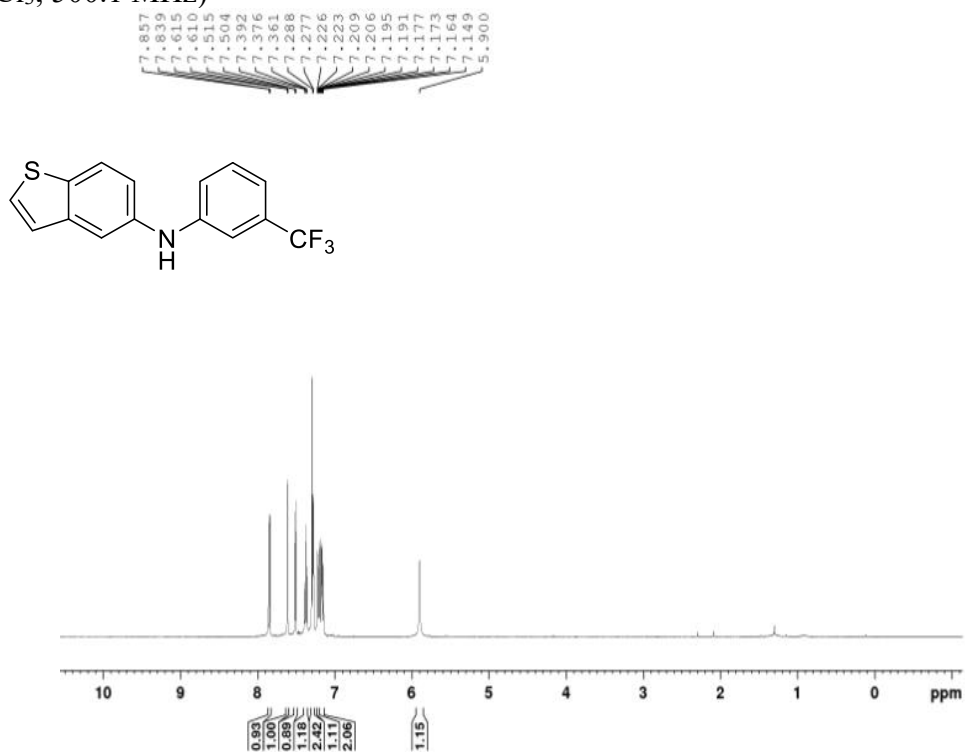
¹³C{¹H} NMR Spectrum of Benzo[*b*]thiophen-5-yl-(3-trifluoromethyl-phenyl)- amine, **3-15** (CDCl₃, 125.8 MHz)

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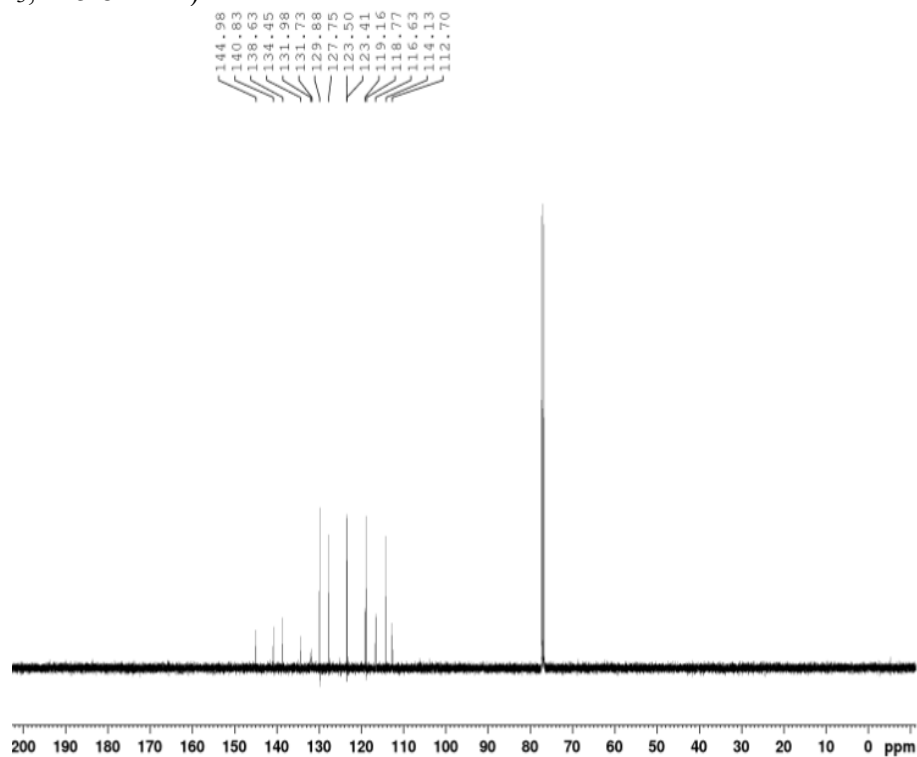
¹H NMR Spectrum of (4-Methoxy-phenyl)-(3-trifluoromethyl-phenyl)- amine, **3-16** (CDCl₃, 500.1 MHz)
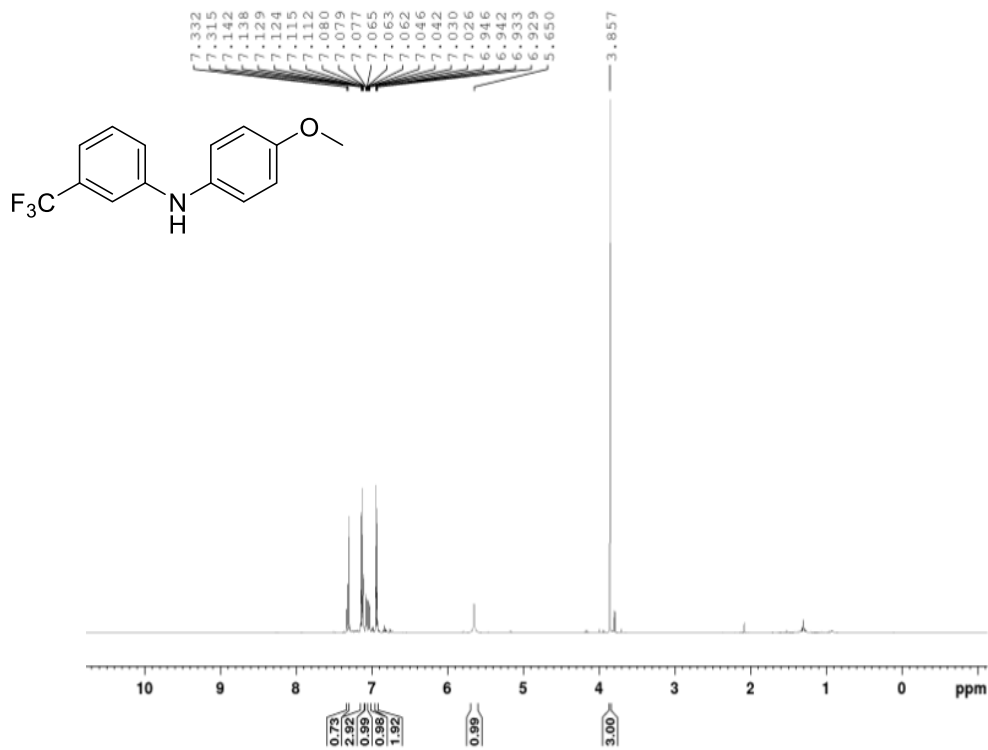
¹³C{¹H} NMR Spectrum of (4-Methoxy-phenyl)-(3-trifluoromethyl-phenyl)- amine, **3-16** (CDCl₃, 125.8 MHz)
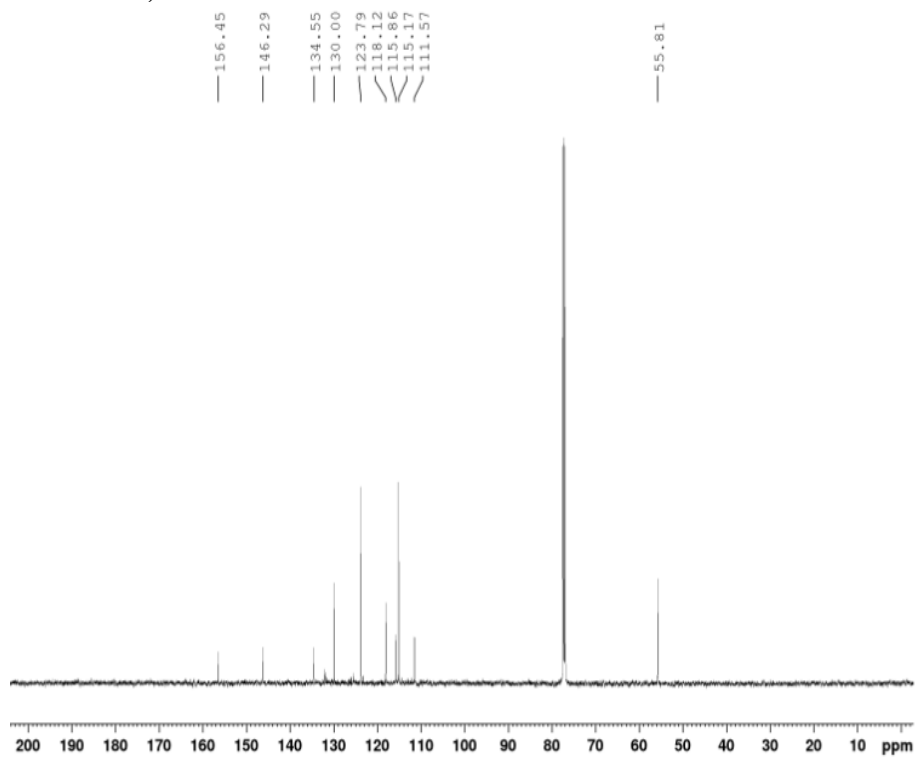
¹H NMR Spectrum of 2-Allylamino-benzonitrile, **3-17** (CDCl₃, 500.1 MHz)

^{1}H NMR Spectrum of 2-Allylamino-benzonitrile, **3-17** (CDCl$_3$, 500.1 MHz)
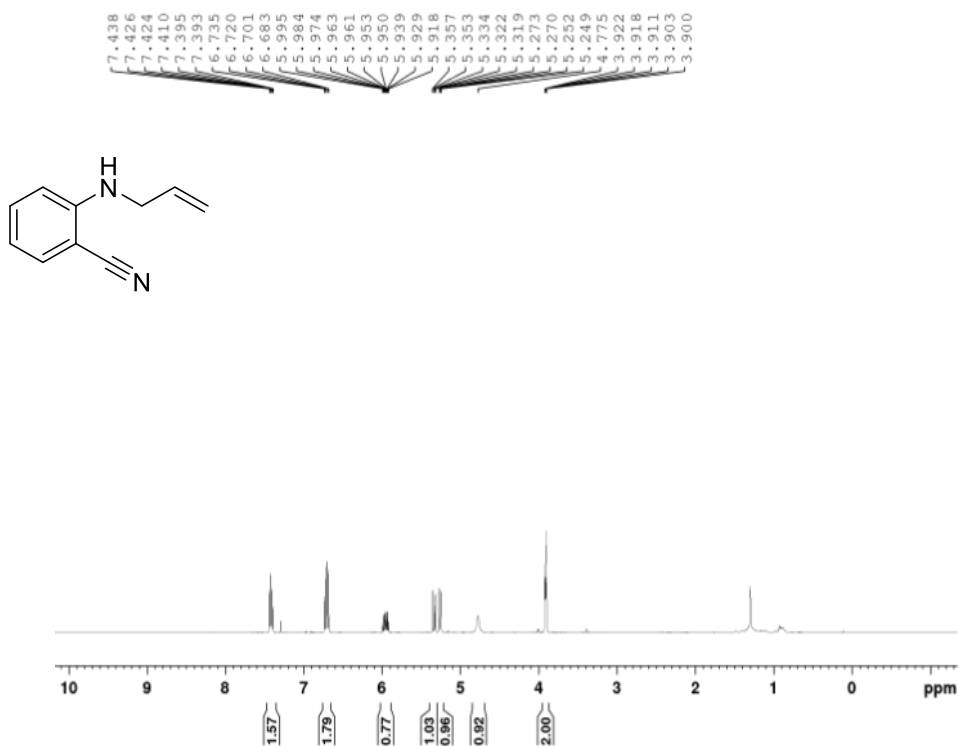
^{13}C{^{1}H} NMR Spectrum of 2-Allylamino-benzonitrile, **3-17** (CDCl$_3$, 125.8 MHz)
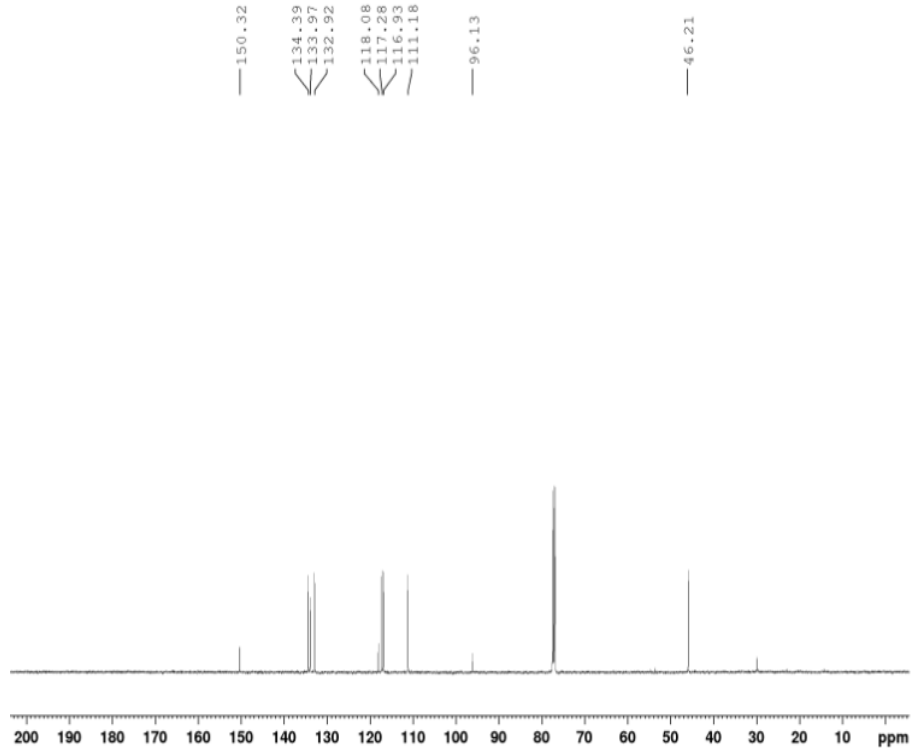
^{1}H NMR Spectrum of Furan-2-ylmethyl-(4-pyrrol-1-yl-phenyl)-amine, **3-18** (CDCl$_3$, 500.1 MHz)
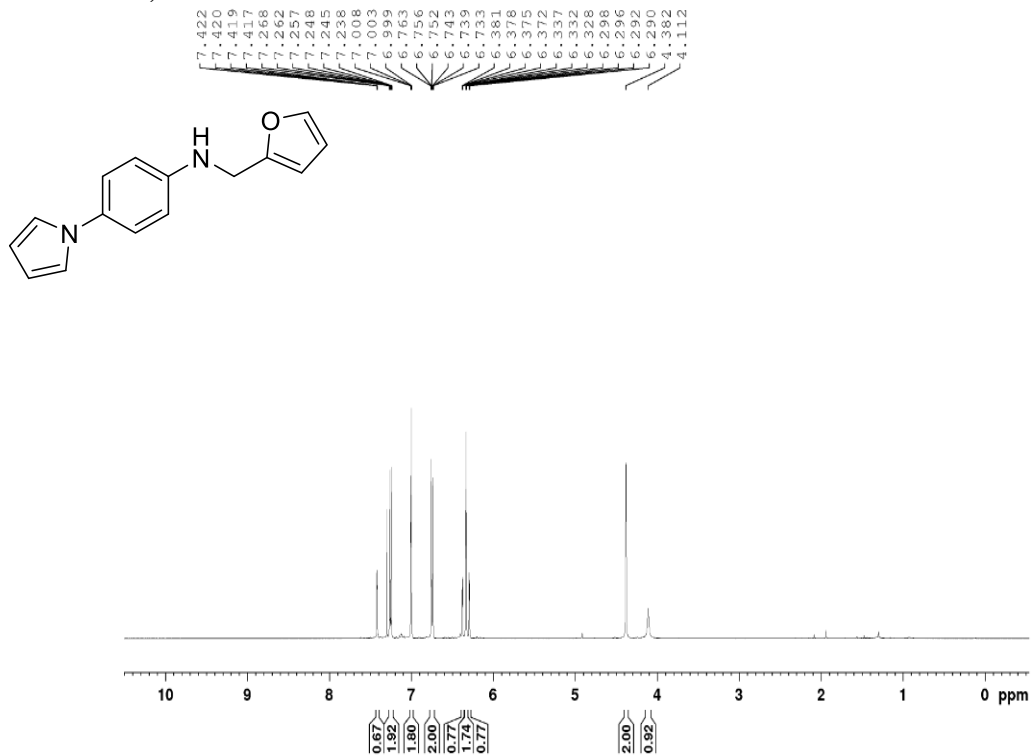
^{13}C{^{1}H} NMR Spectrum of Furan-2-ylmethyl-(4-pyrrol-1-yl-phenyl)-amine, **3-18** (CDCl$_3$, 125.8 MHz)
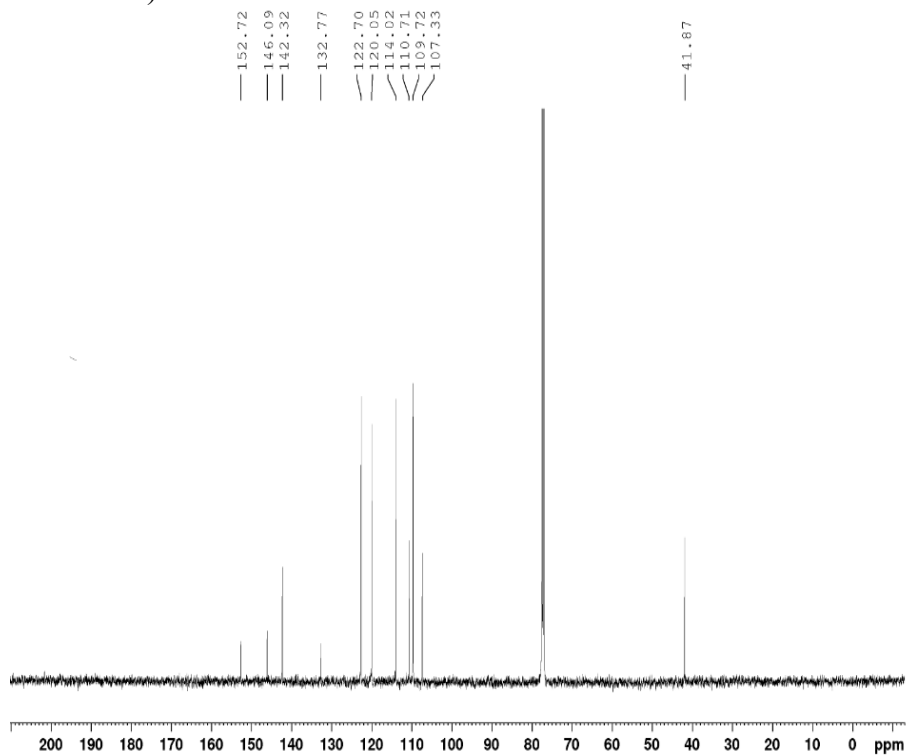
¹H NMR Spectrum of Phenyl-{4-[(tetrahydro-furan-2-ylmethyl)- amino]-phenyl}-methanone, **3-19** (CDCl₃, 500.1 MHz)
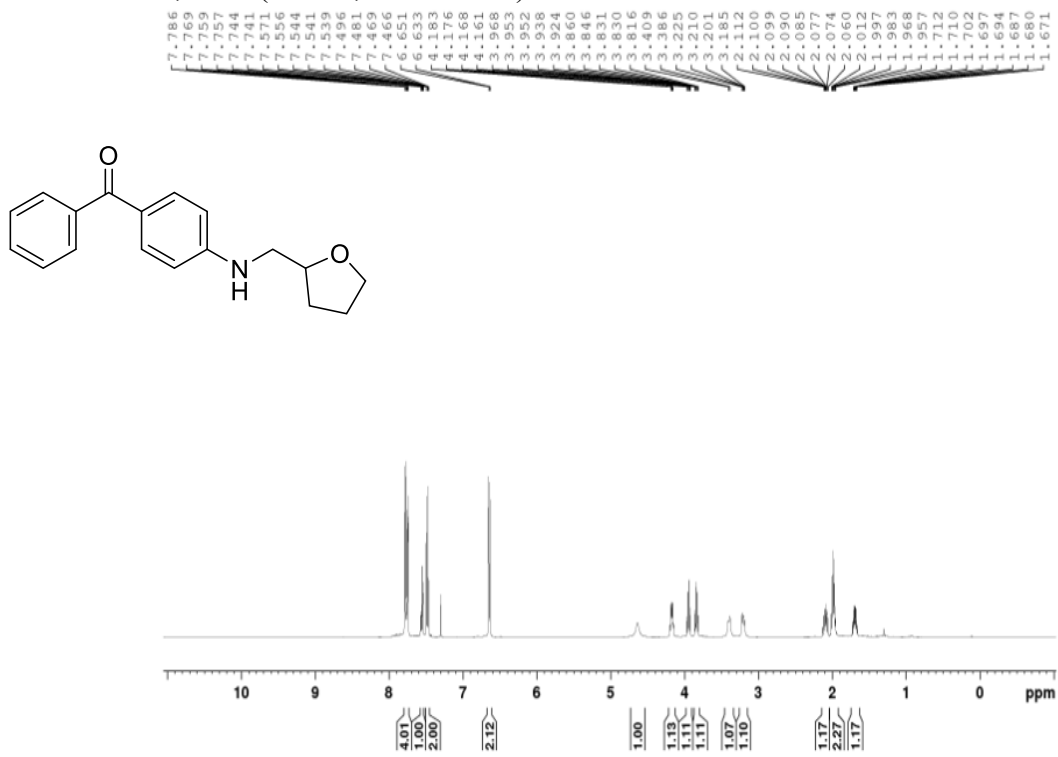
¹³C{¹H} NMR Spectrum of Phenyl-{4-[(tetrahydro-furan-2-ylmethyl)- amino]-phenyl}-methanone, **3-19** (CDCl₃, 125.8 MHz)
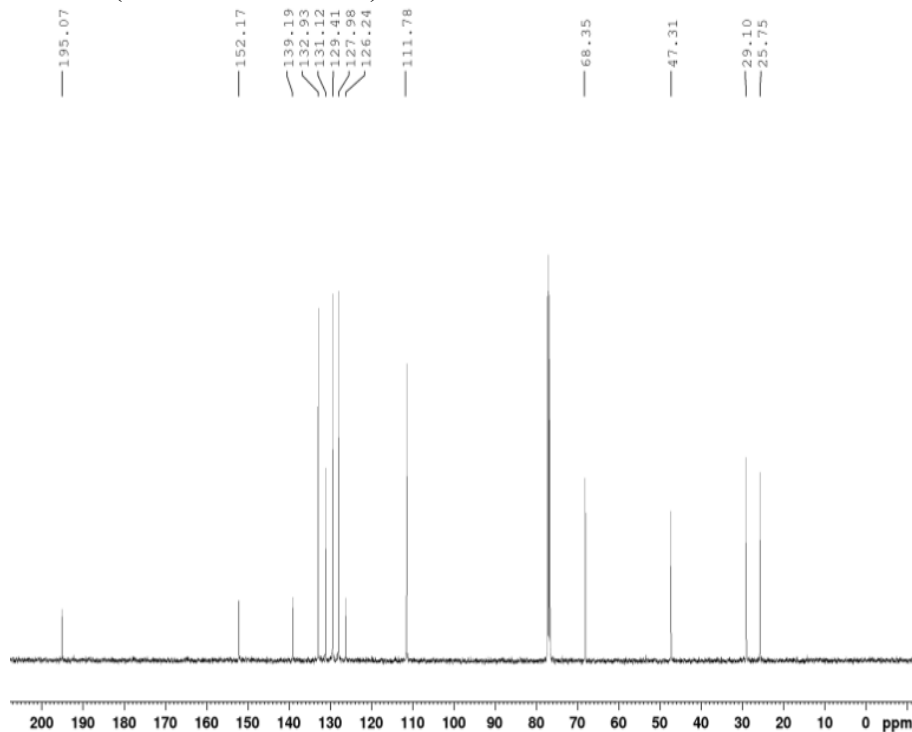
¹H NMR Spectrum of 4-Methyl-3-[(thiophen-2-ylmethyl)-amino]-benzonitrile, **3-20** (CDCl₃, 300.1 MHz)
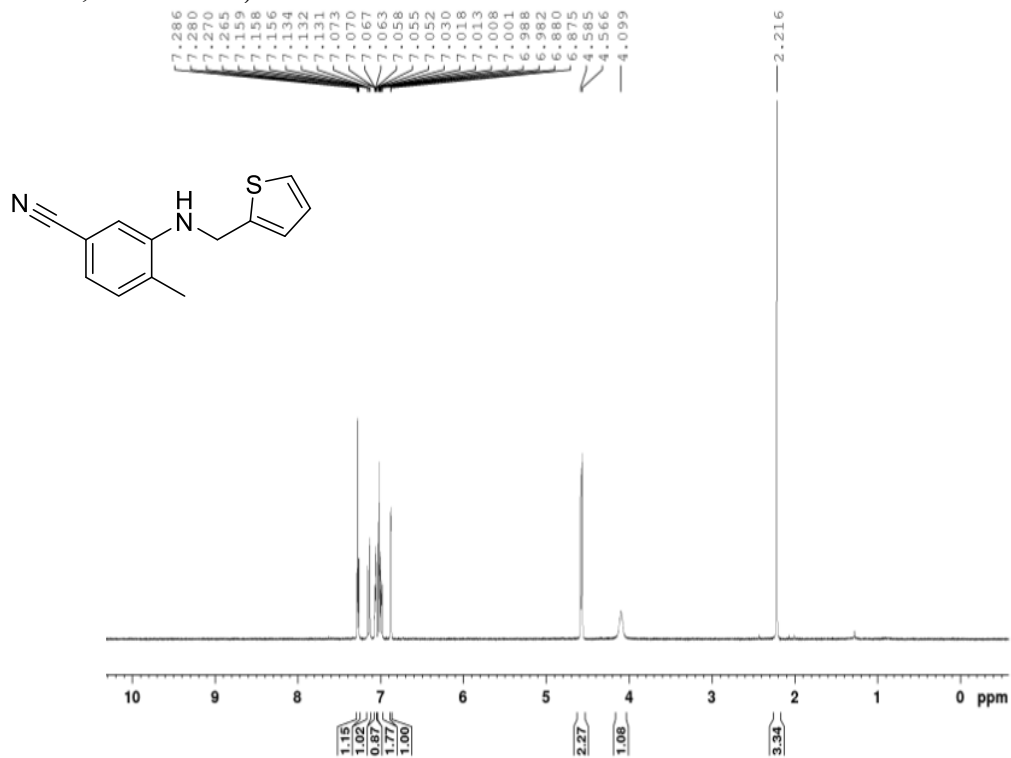
¹³C{¹H} NMR Spectrum of 4-Methyl-3-[(thiophen-2-ylmethyl)-amino]-benzonitrile, **3-20** (CDCl₃, 125.8 MHz)
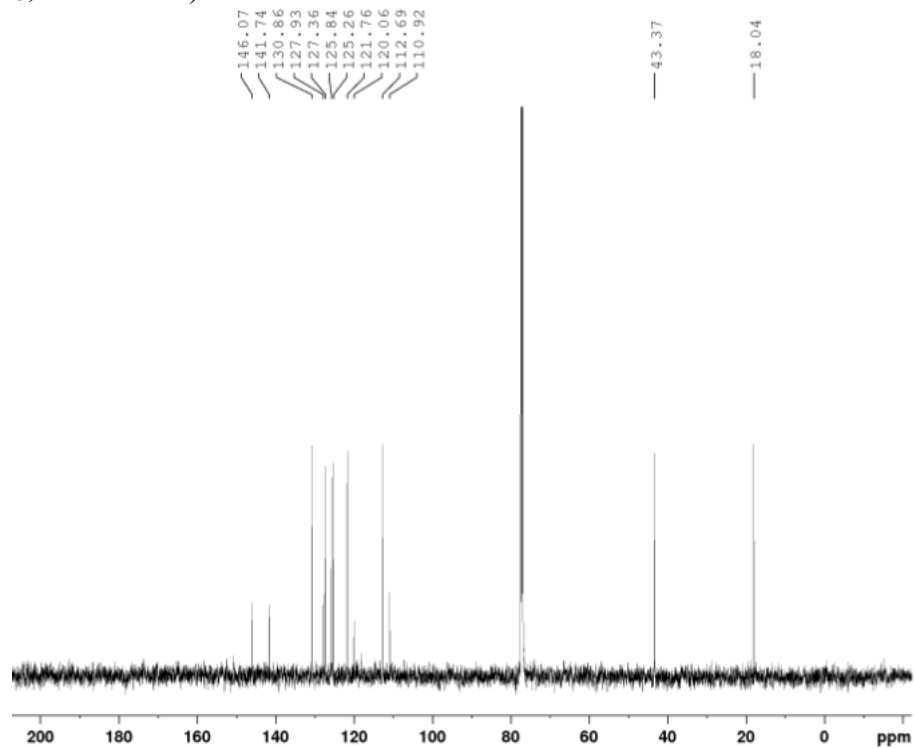
¹H NMR Spectrum of (4,6-Dimethoxy-pyrimidin-2-yl)-phenethyl-amine, **3-21** (CDCl₃, 500.1 MHz)
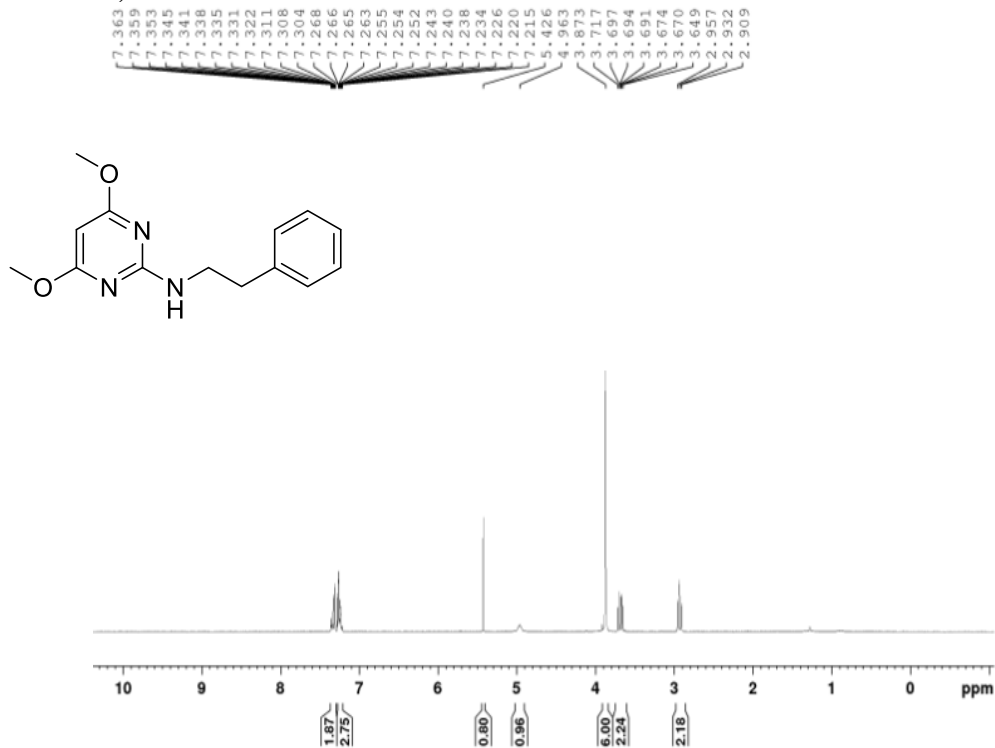
¹³C{¹H} NMR Spectrum of (4,6-Dimethoxy-pyrimidin-2-yl)-phenethyl-amine, **3-21** (CDCl₃, 125.8 MHz)
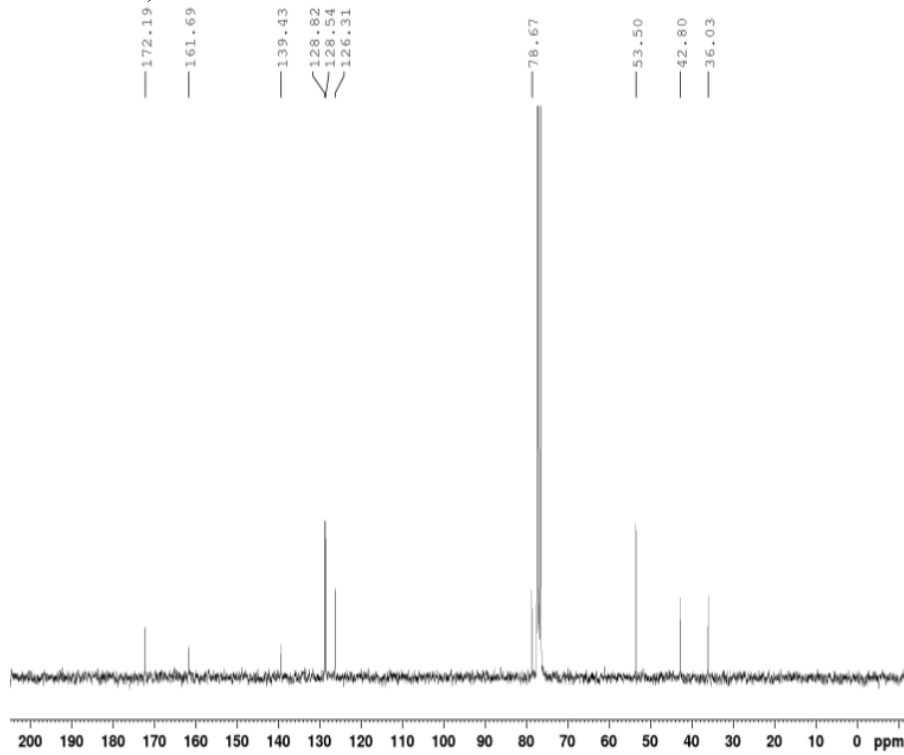
¹H NMR Spectrum of (6-Methoxy-pyridin-2-yl)-piperidin-4-ylmethyl-amine, **3-22** (CDCl₃, 300.1 MHz)
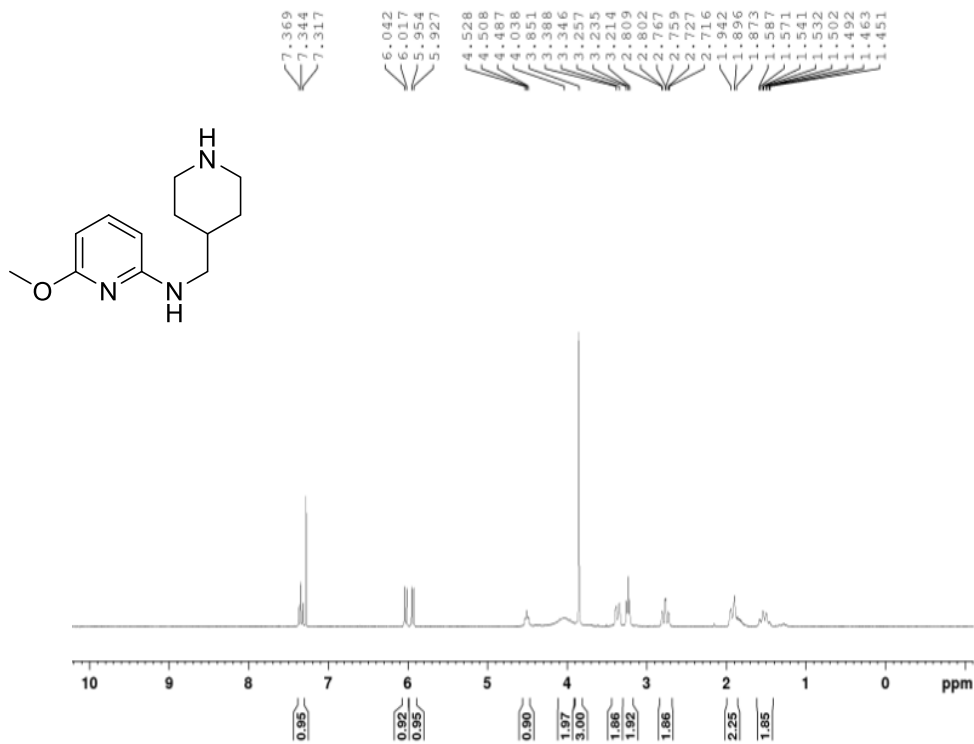
¹³C{¹H} NMR Spectrum of (6-Methoxy-pyridin-2-yl)-piperidin-4-ylmethyl-amine, **3-22** (CDCl₃, 125.8 MHz)
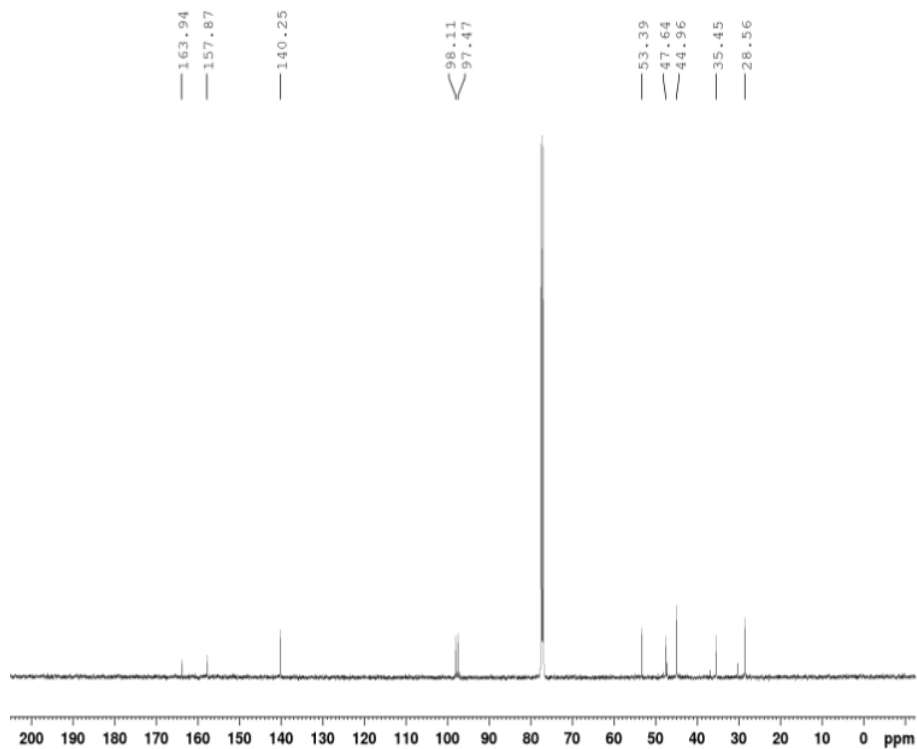
^{1}H NMR Spectrum of *N,N'*-Diphenyl-ethane-1,2-diamine, **3-23** (CDCl$_3$, 300.1 MHz)
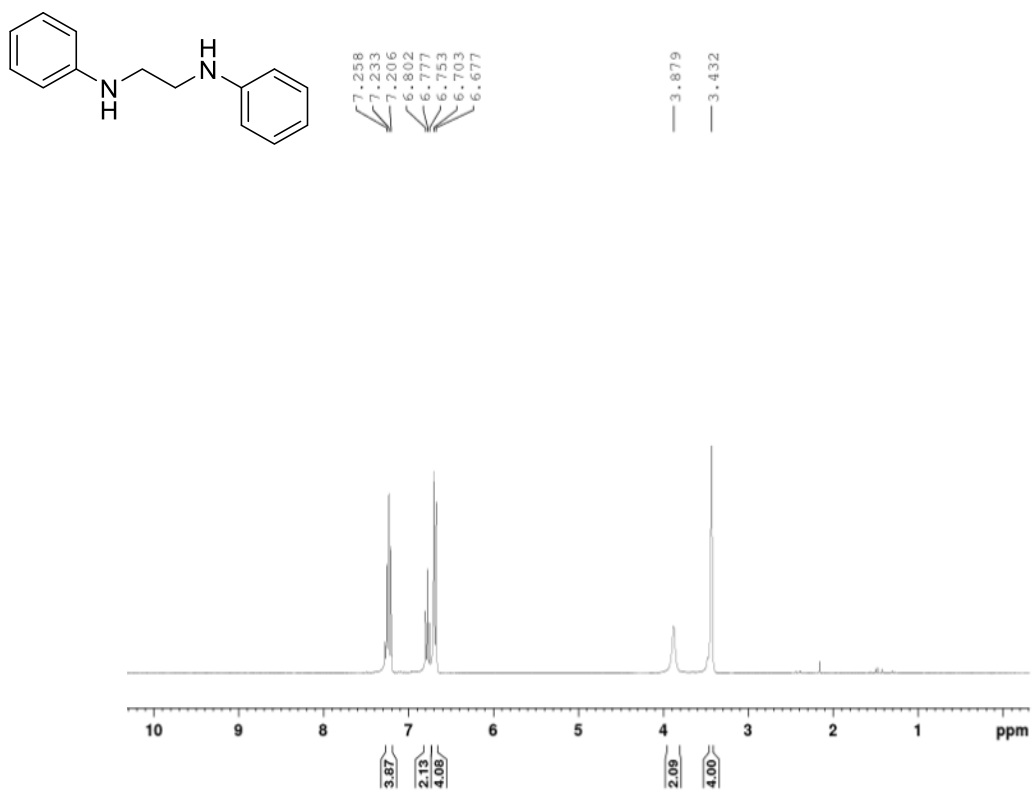
^{13}C{^{1}H} NMR Spectrum of *N,N'*-Diphenyl-ethane-1,2-diamine, **3-23** (CDCl$_3$, 125.8 MHz)
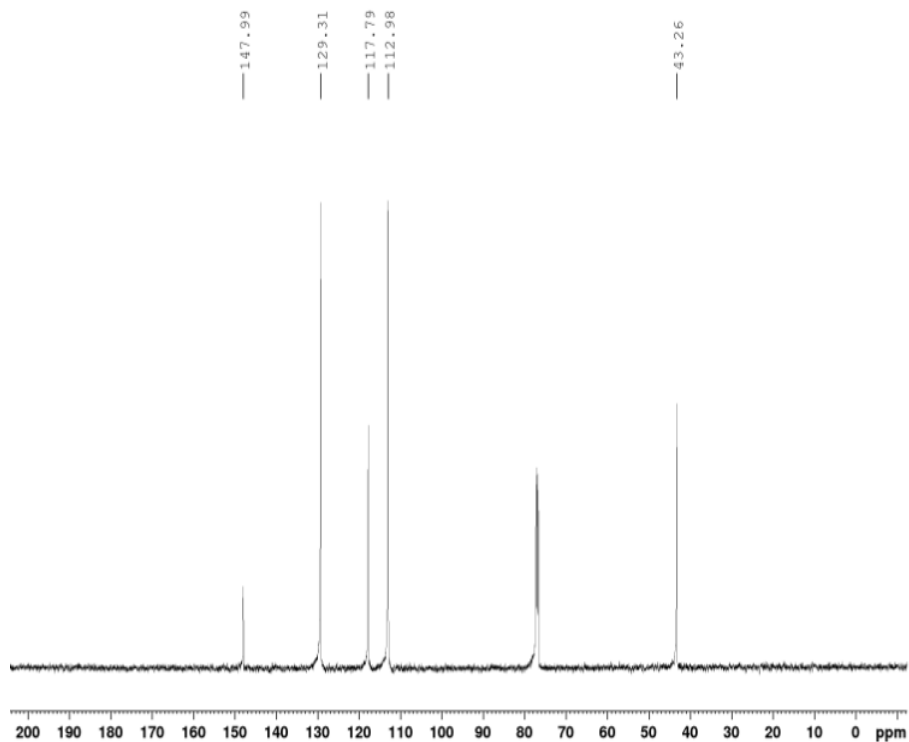
^{1}H NMR Spectrum of N^1-Phenyl-N^2-(pyridin-3-yl)ethane-1,2-diamine, **3-24** (CDCl$_3$, 300.1 MHz)
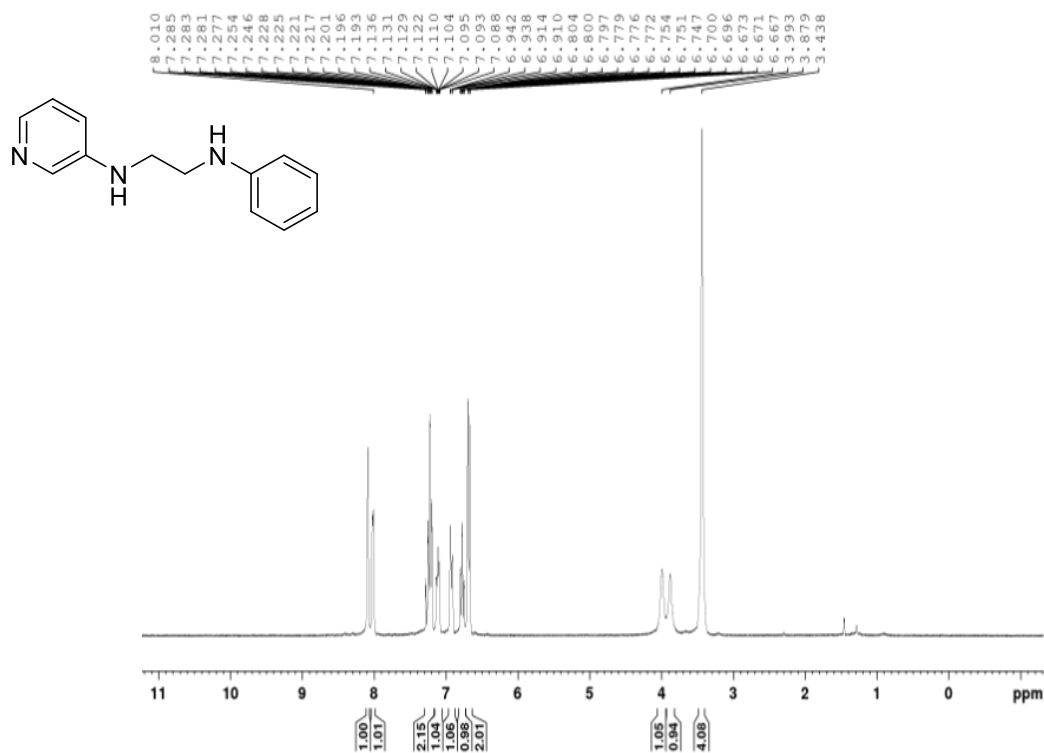
^{13}C{^{1}H} NMR Spectrum of N^1-Phenyl-N^2-(pyridin-3-yl)ethane-1,2-diamine, **3-24** (CDCl$_3$, 125.8 MHz)
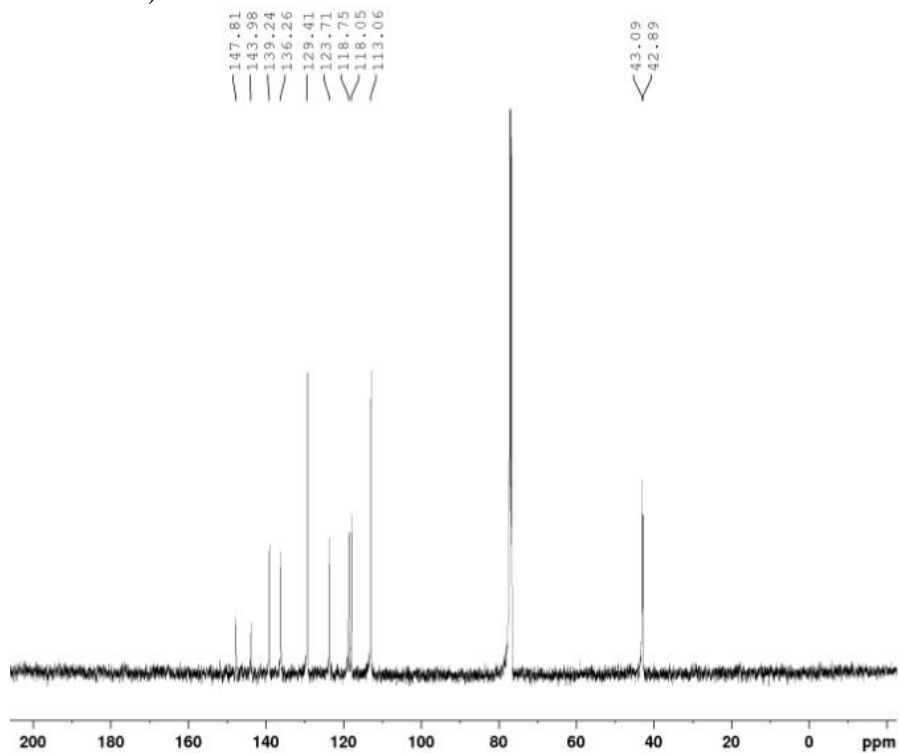
¹H NMR Spectrum of Methyl-quinoxalin-6-yl-amine, **3-25** (CDCl₃, 500.1 MHz)
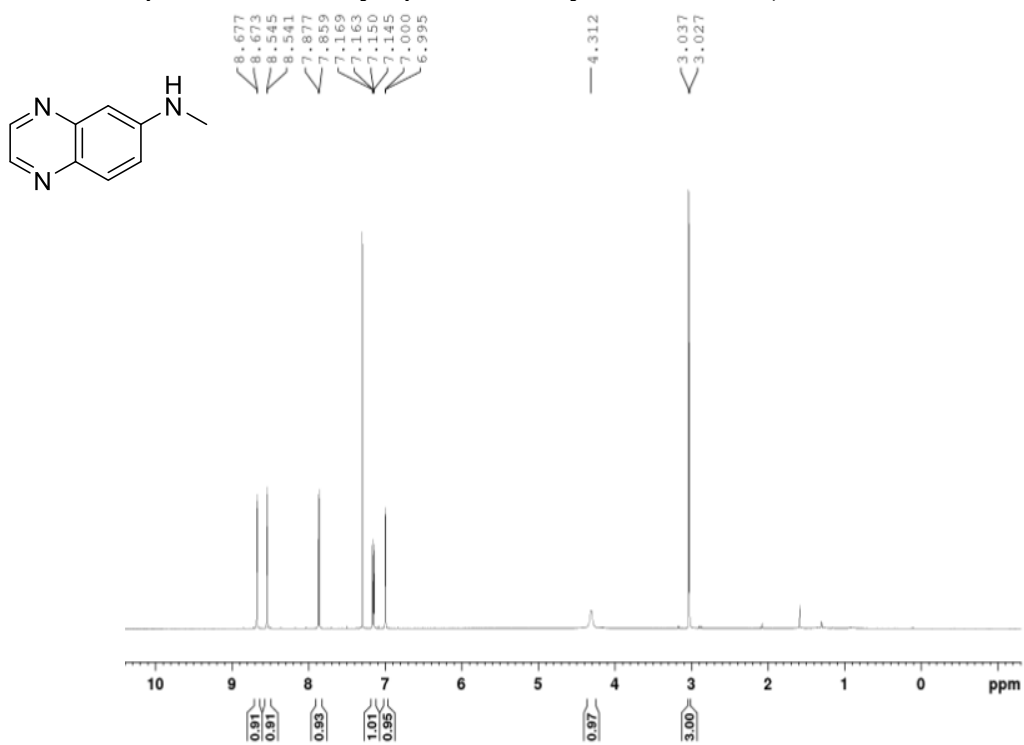
¹³C{¹H} NMR Spectrum of Methyl-quinoxalin-6-yl-amine, **3-25** (CDCl₃, 125.8 MHz)

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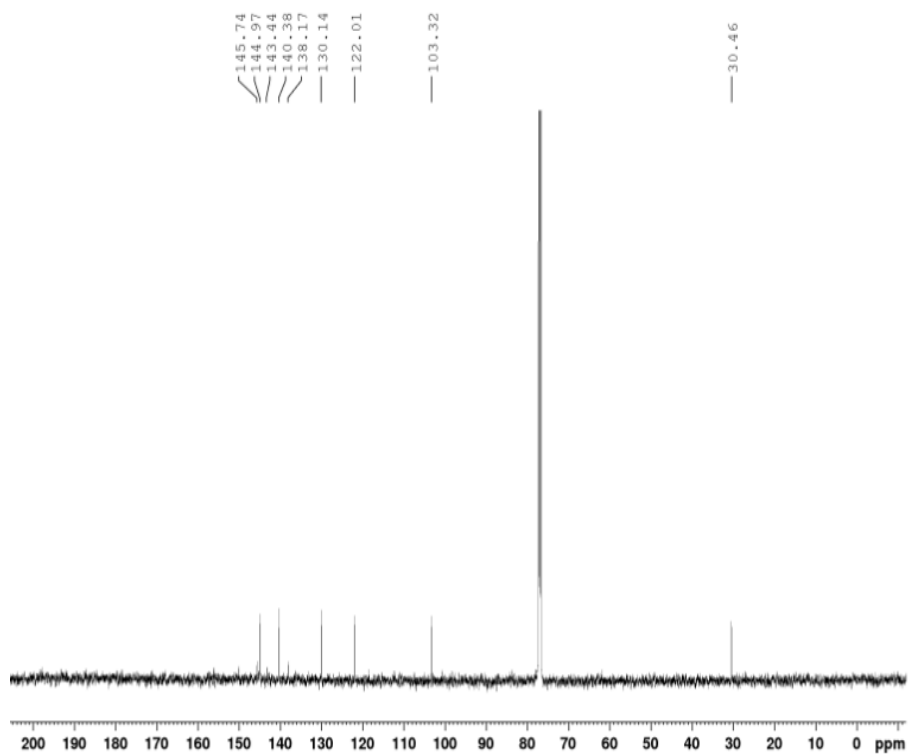
^{1}H NMR Spectrum of Benzo[1,3]dioxol-5-yl-methyl-amine, **3-26** (CDCl$_3$, 300.1 MHz)
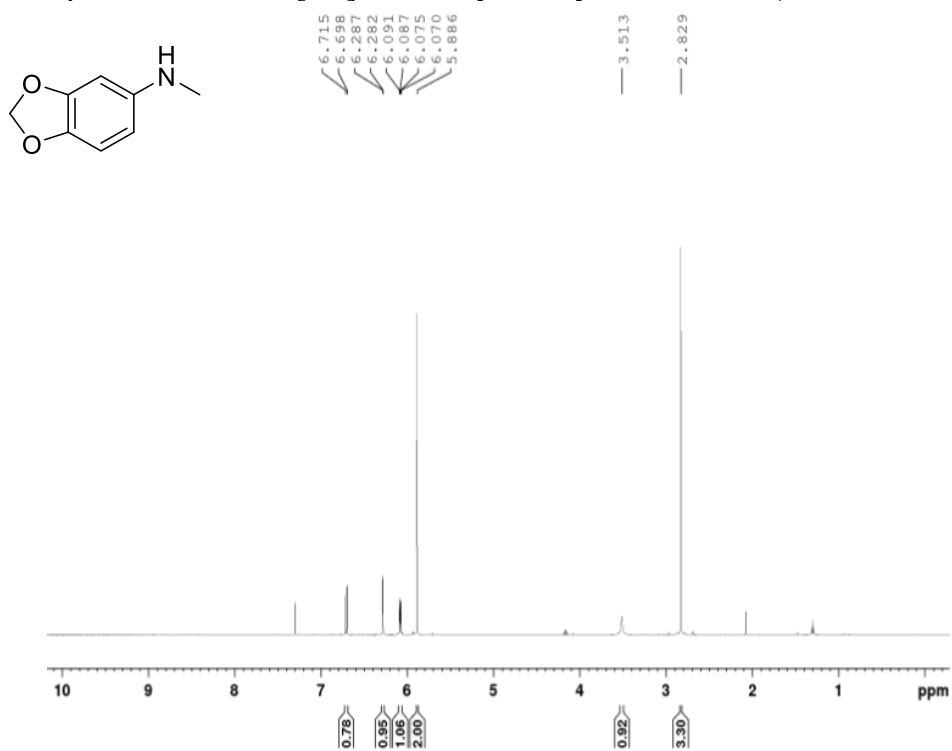
^{13}C{^{1}H} NMR Spectrum of Benzo[1,3]dioxol-5-yl-methyl-amine, **3-26** (CDCl$_3$, 125.8 MHz)
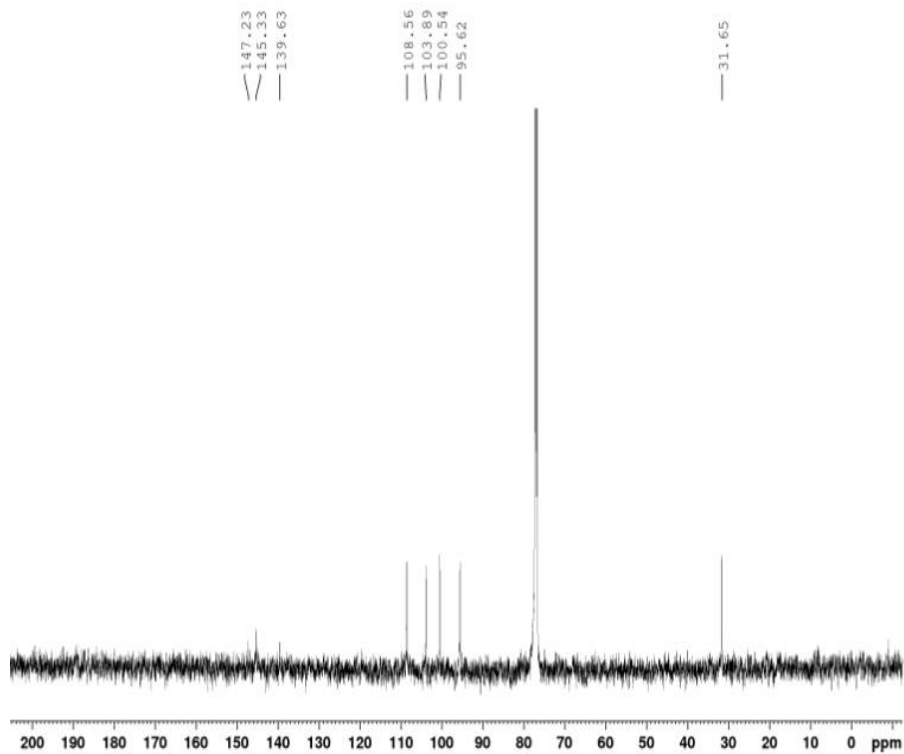
^{1}H NMR Spectrum of Methyl-(2-methyl-quinolin-4-yl)amine, **3-27** (CDCl$_3$, 500.1 MHz)
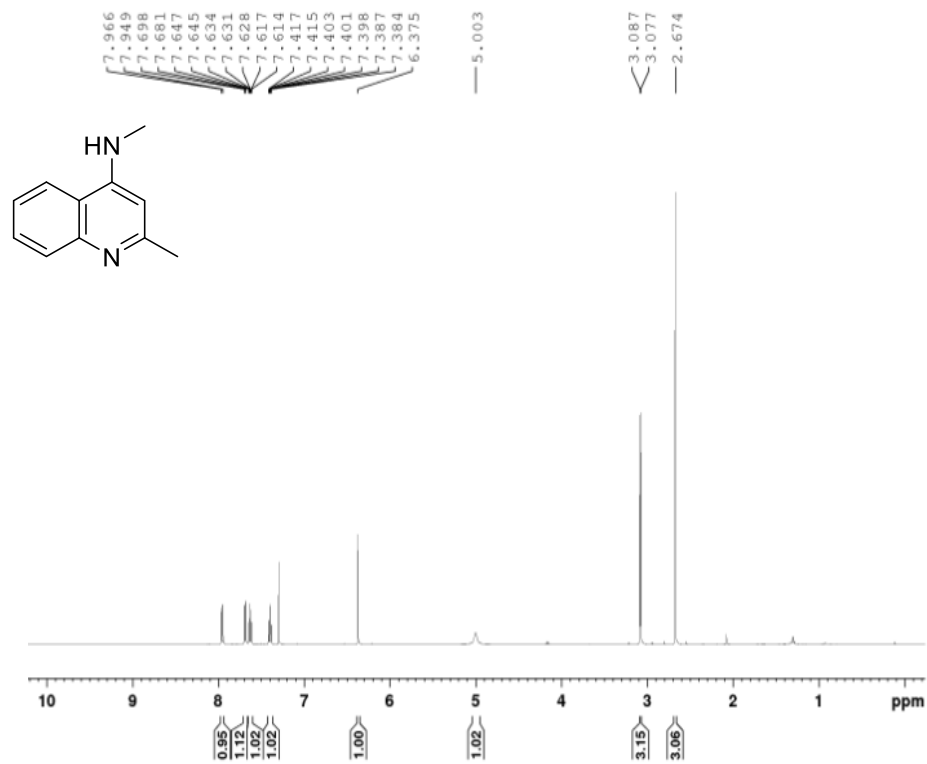
^{13}C{^{1}H} NMR Spectrum of Methyl-(2-methyl-quinolin-4-yl)amine, **3-27** (CDCl$_3$, 125.8 MHz)
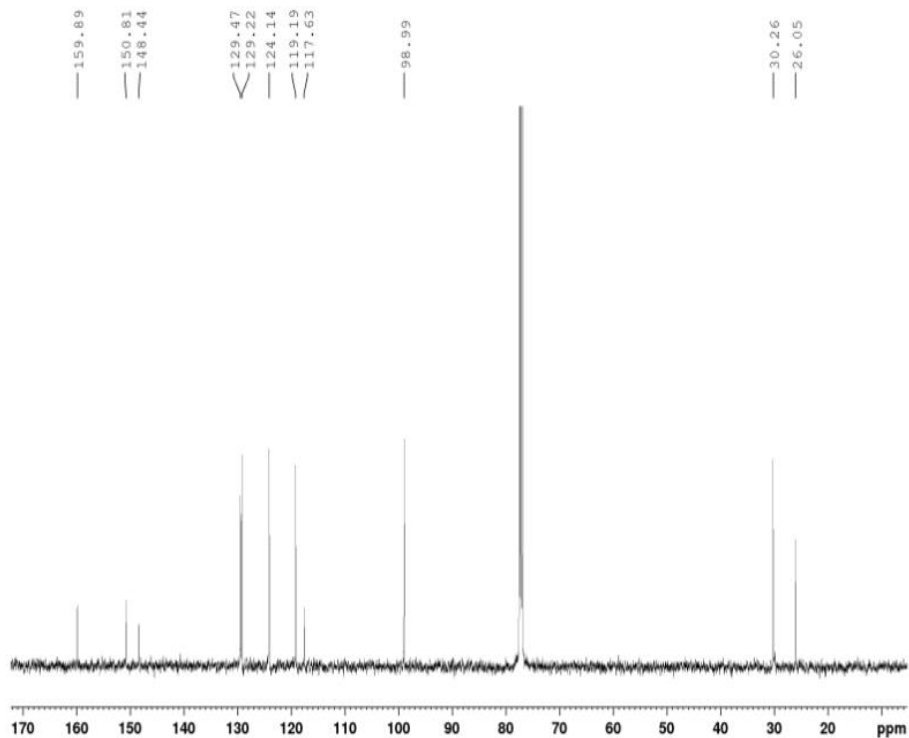
¹H NMR Spectrum of 4-(*N*-Methylamino)phenylboronic acid pinacol ester, **3-28** (CDCl₃, 500.1 MHz)
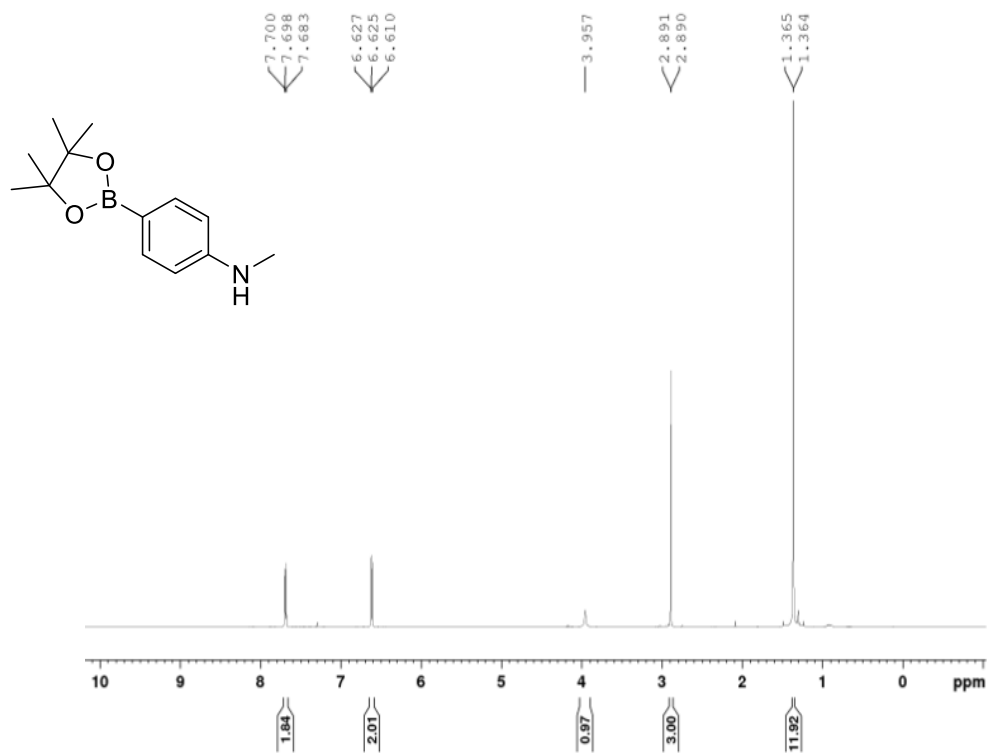
¹³C{¹H} NMR Spectrum of 4-(*N*-Methylamino)phenylboronic acid pinacol ester, **3-28** (CDCl₃, 125.8 MHz)
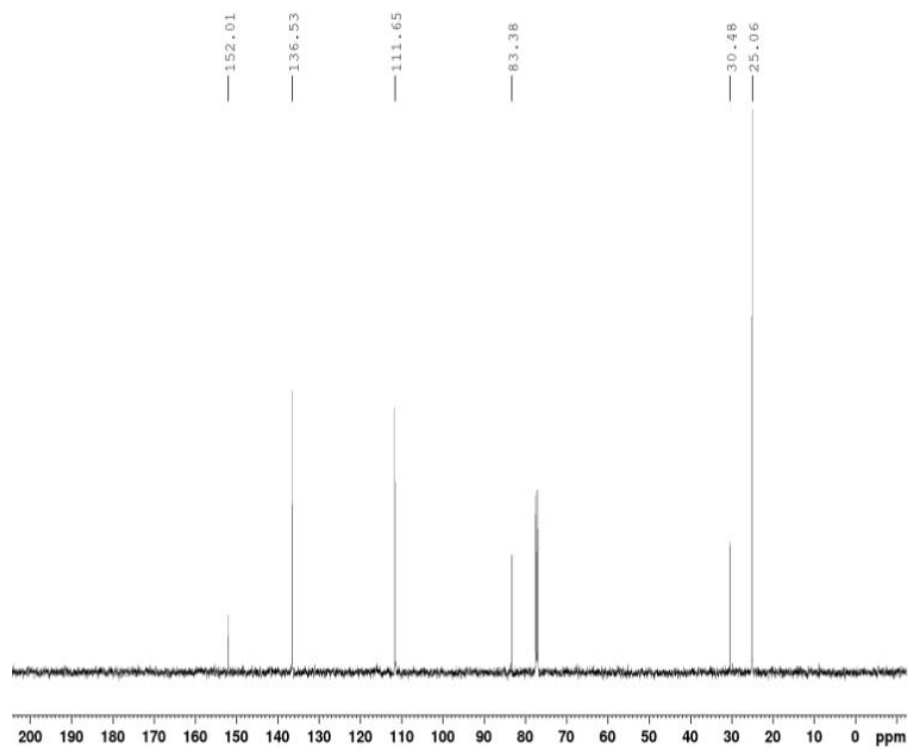
^{1}H NMR Spectrum of 1-(*N,N*-dimethylamino)naphthalene, **3-29** (CDCl$_3$, 300.1 MHz)
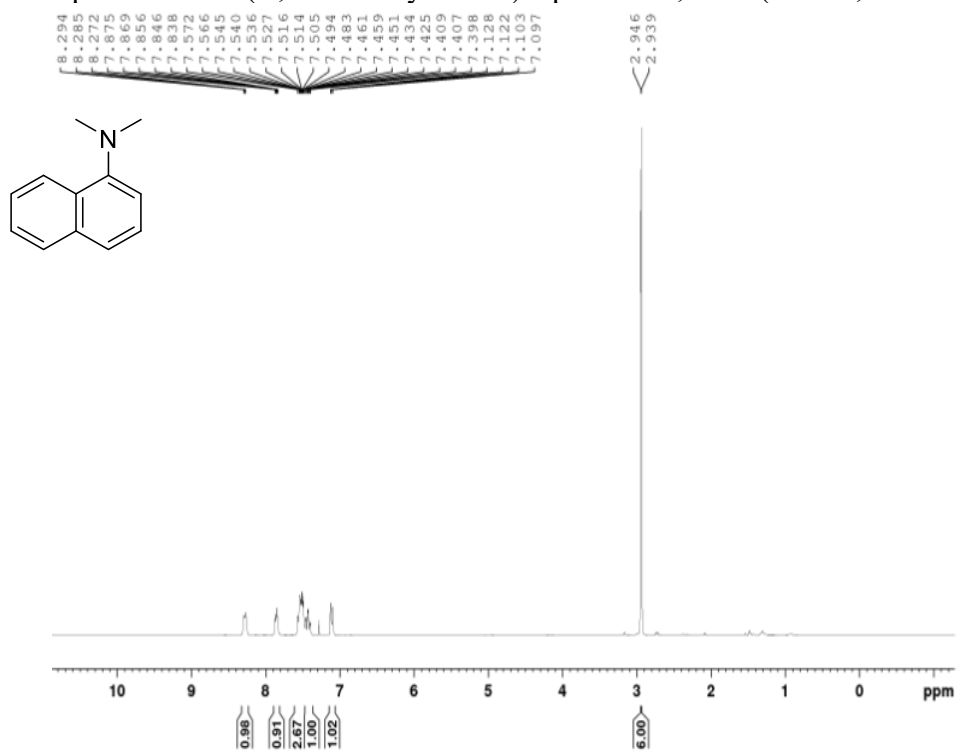
^{13}C{^{1}H} NMR Spectrum of 1-(*N,N*-dimethylamino)naphthalene, **3-29** (CDCl$_3$, 125.8 MHz)
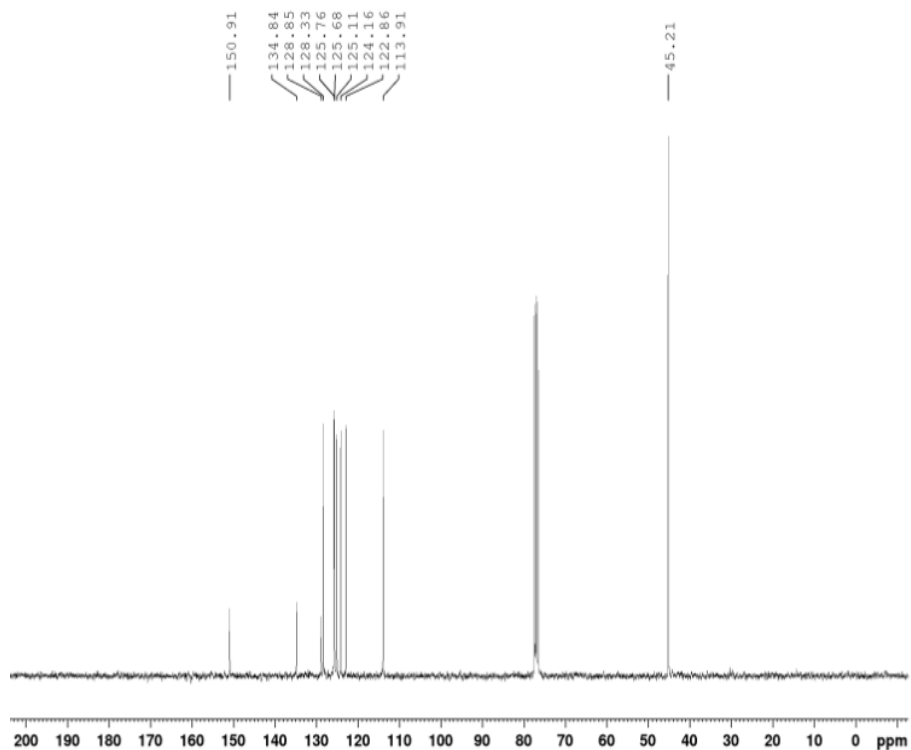
¹H NMR Spectrum of Benzyl-quinolin-8-yl-amine, **3-30** (CDCl₃, 300.1 MHz)

8.768
8.766
8.760
8.757
8.115
8.113
8.099
8.096
7.496
7.481
7.427
7.419
7.410
7.406
7.403
7.391
7.376
7.360
7.333
7.318
7.304
7.298
7.109
7.095
6.701
6.688
6.654
6.615
4.603

0.79
0.88
1.74
4.58
0.95
0.99
0.88
2.00

10   9   8   7   6   5   4   3   2   1   0   ppm
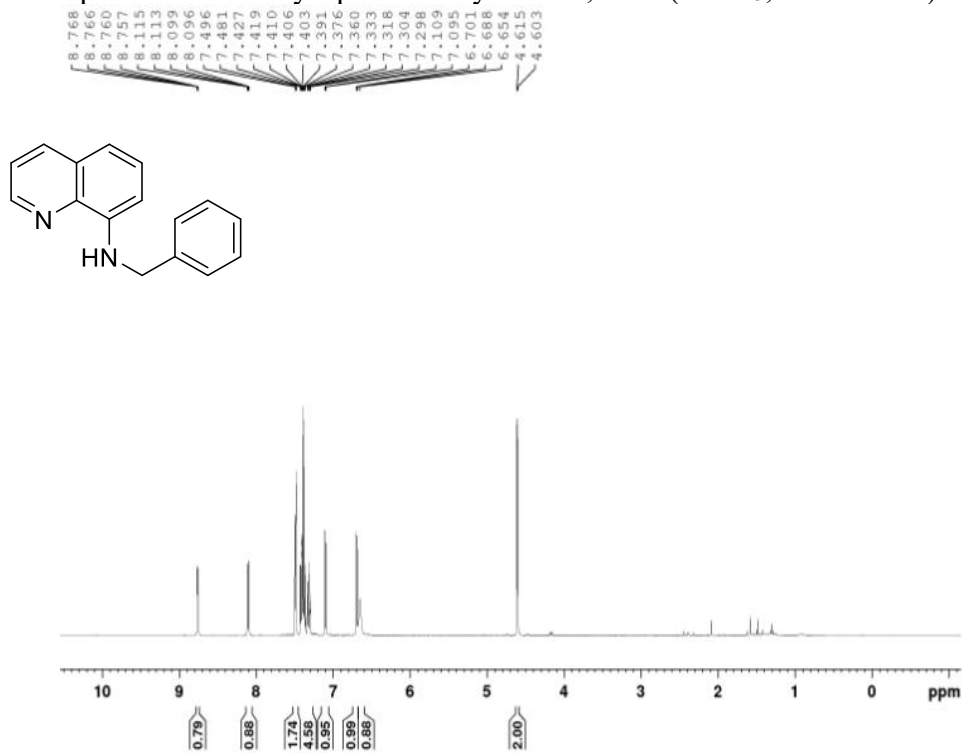
¹³C{¹H} NMR Spectrum of Benzyl-quinolin-8-yl-amine, **3-30** (CDCl₃, 75.5 MHz)

146.92
144.62
139.26
138.26
136.01
128.61
127.75
127.41
127.12
121.41
114.14
105.11

47.72

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

233
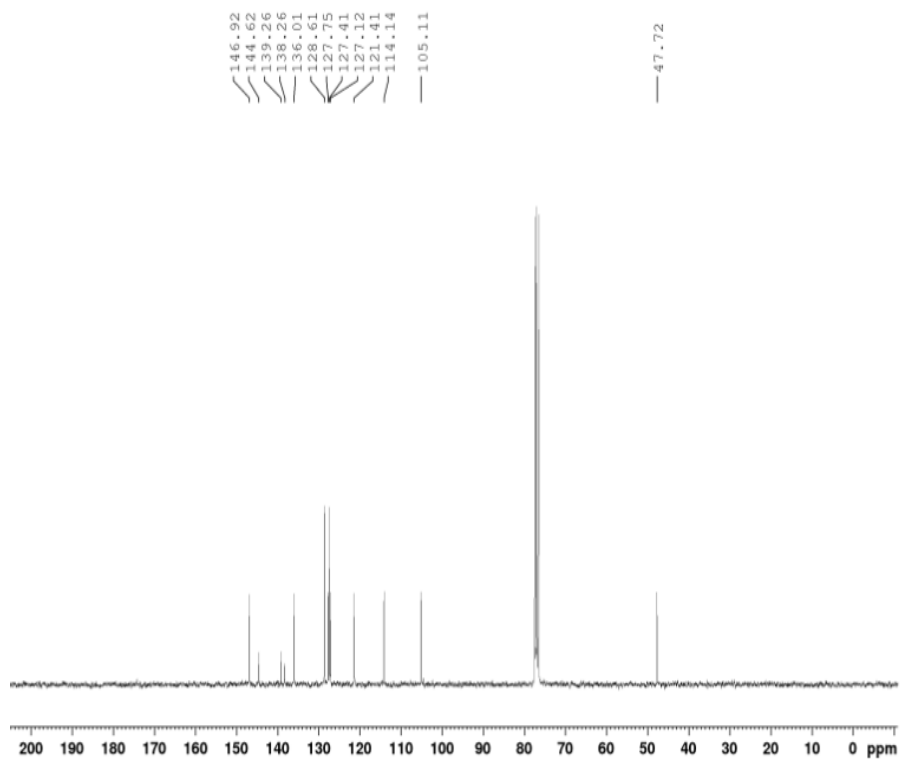
¹H NMR Spectrum of (4-Phenoxy-phenyl)-(1-phenyl-ethyl)-amine, **3-31** (CDCl₃, 300.1 MHz)
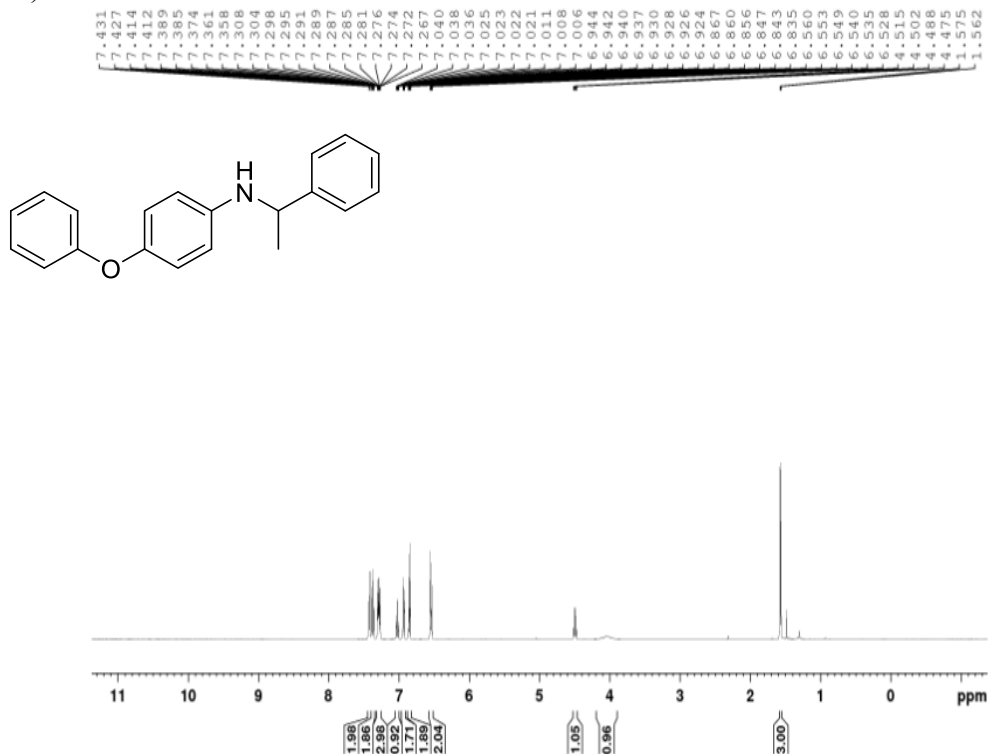
¹³C{¹H} NMR Spectrum of (4-Phenoxy-phenyl)-(1-phenyl-ethyl)-amine, **3-31** (CDCl₃, 75.5 MHz)
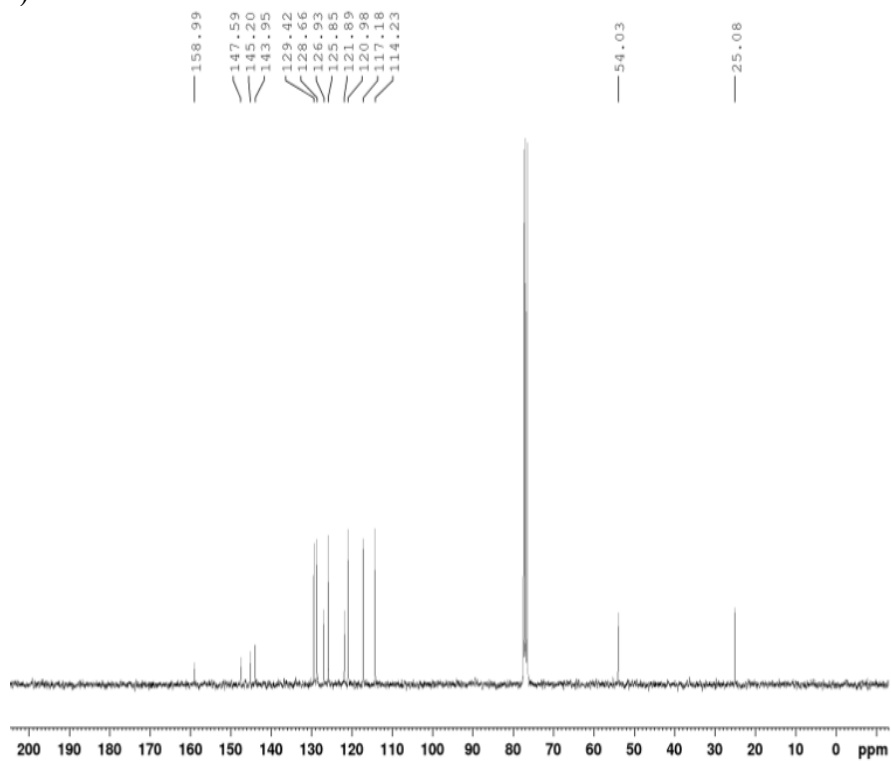
¹H NMR Spectrum of (2,5-Dimethyl-phenyl)-thiophen-2-ylmethyl-amine, **3-32** (CDCl₃, 500.1 MHz)
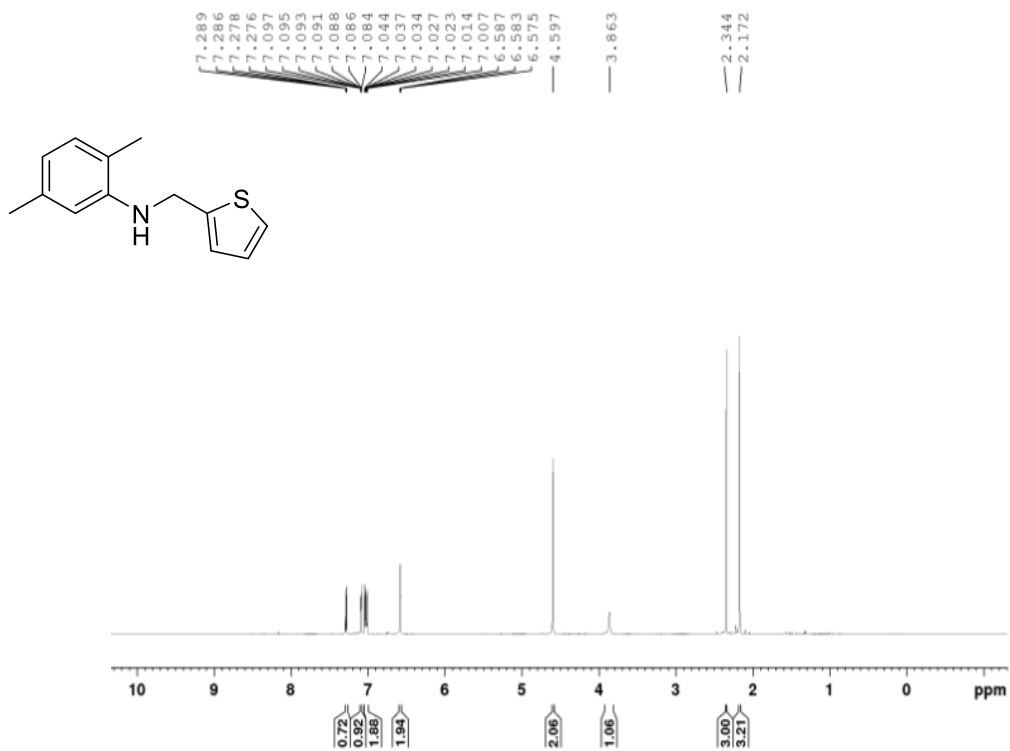
¹³C{¹H} NMR Spectrum of (2,5-Dimethyl-phenyl)-thiophen-2-ylmethyl-amine, **3-32** (CDCl₃, 125.8 MHz)
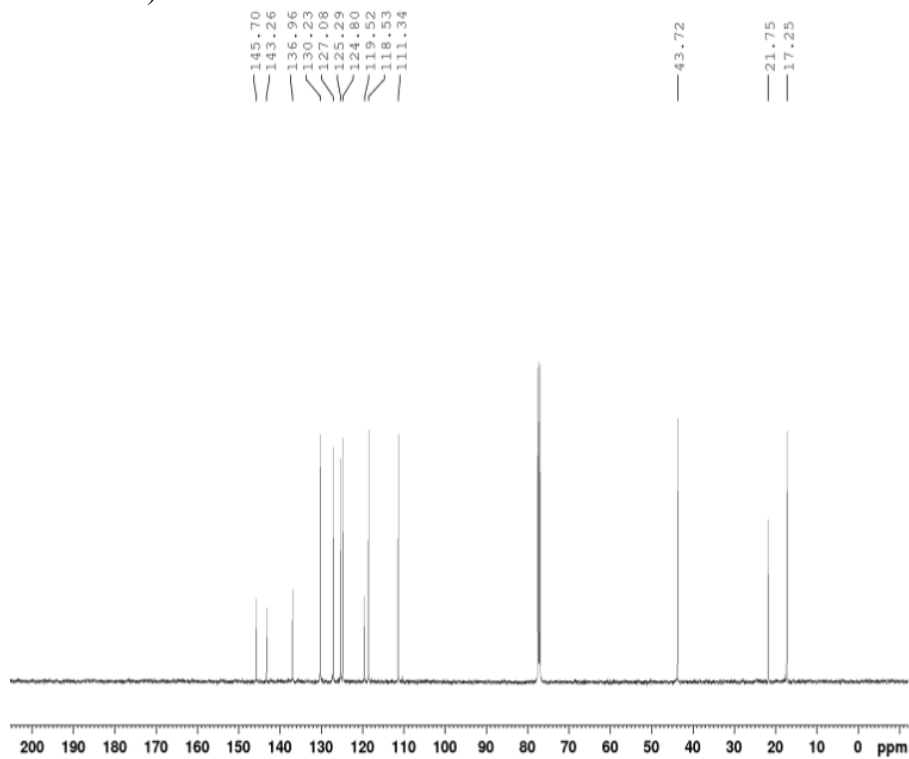
^{1}H NMR Spectrum of Naphthalen-1-ylamine, 3-33 (CDCl$_3$, 500.1 MHz)

7.877, 7.864, 7.858, 7.853, 7.846, 7.843, 7.838, 7.834, 7.516, 7.507, 7.502, 7.499, 7.496, 7.493, 7.488, 7.479, 7.371, 7.356, 7.345, 7.331, 7.314, 6.840, 6.826, 6.825

4.235

2.04 2.01 1.98 1.00 2.10
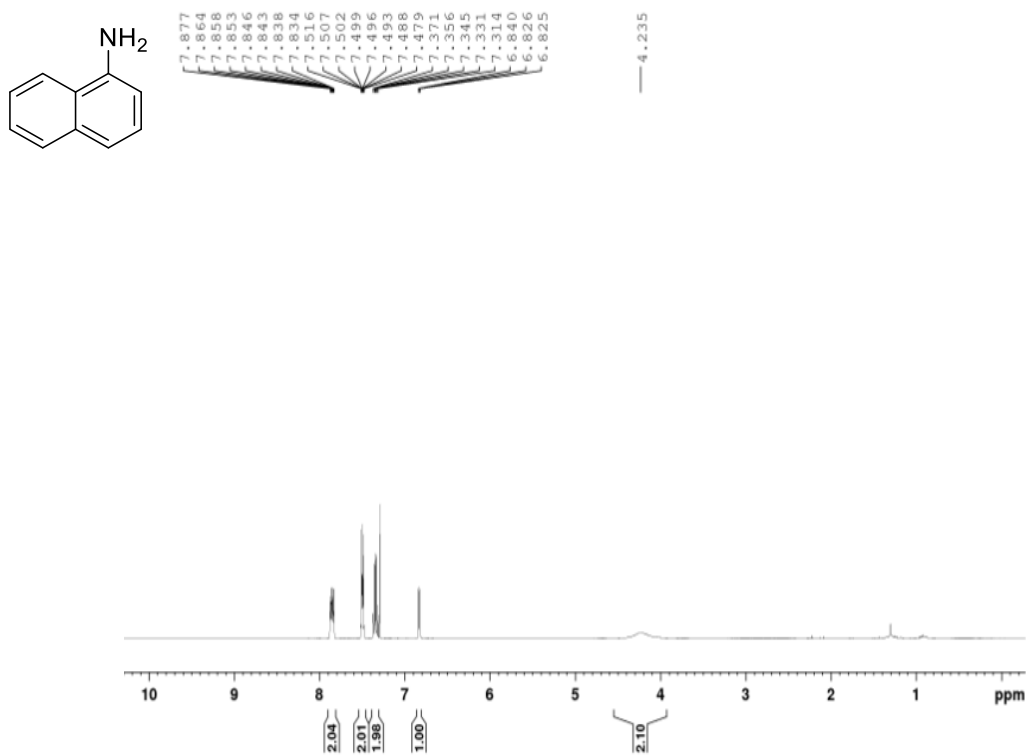
^{13}C{^{1}H} NMR Spectrum of Naphthalen-1-ylamine, 3-33 (CDCl$_3$, 125.8 MHz)

142.18, 134.63, 128.77, 126.53, 126.06, 125.09, 123.92, 120.99, 119.28, 109.98
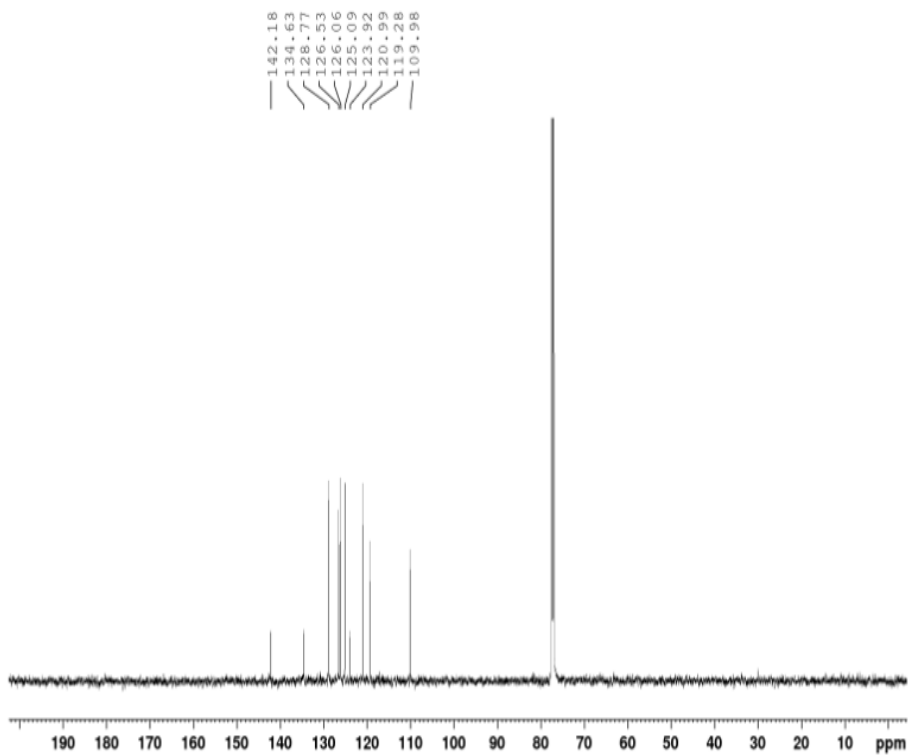
^{1}H NMR Spectrum of Quinolin-8-ylamine, **3-34** (CDCl$_3$, 500.1 MHz)
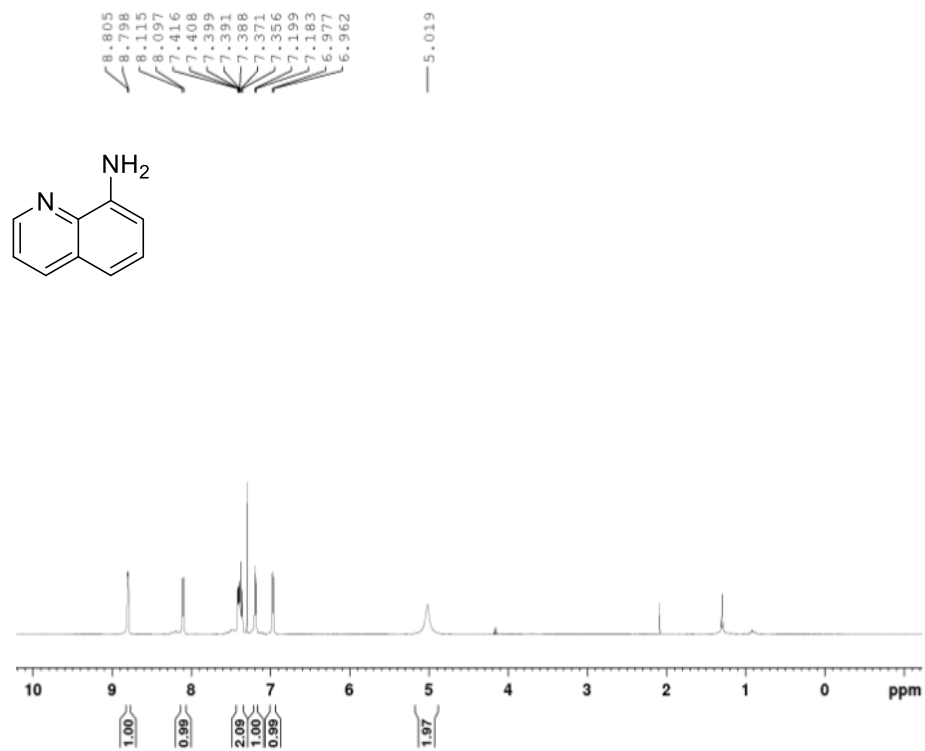
^{13}C{^{1}H} NMR Spectrum of Quinolin-8-ylamine, **3-34** (CDCl$_3$, 125.8 MHz)
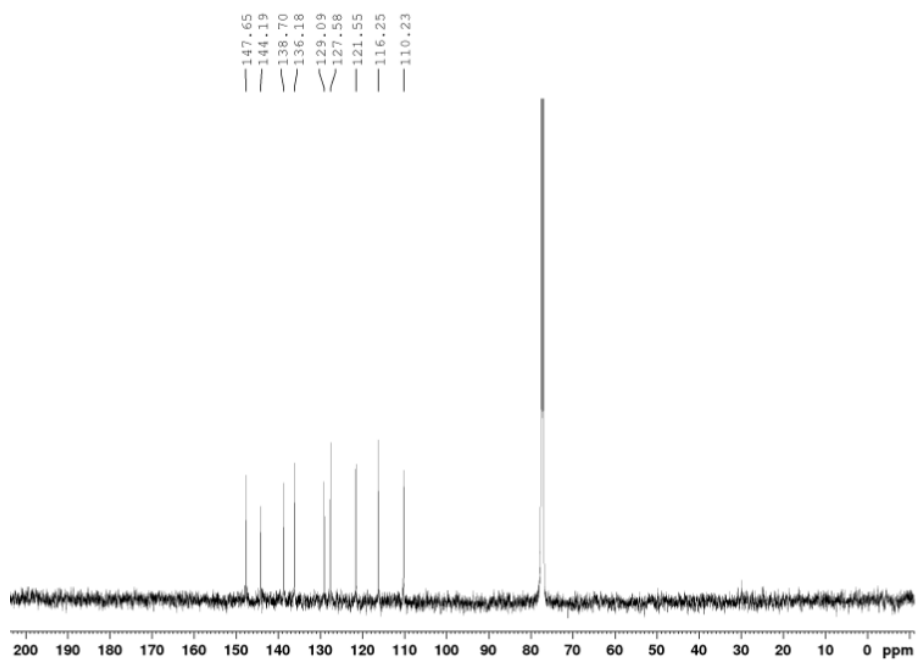
^{1}H NMR Spectrum of [1,4']Bipiperidinyl-4'-carboxylic acid (4-cyano-phenyl)-amide, **4-1** (DMSO-d_6, 500.1 MHz)
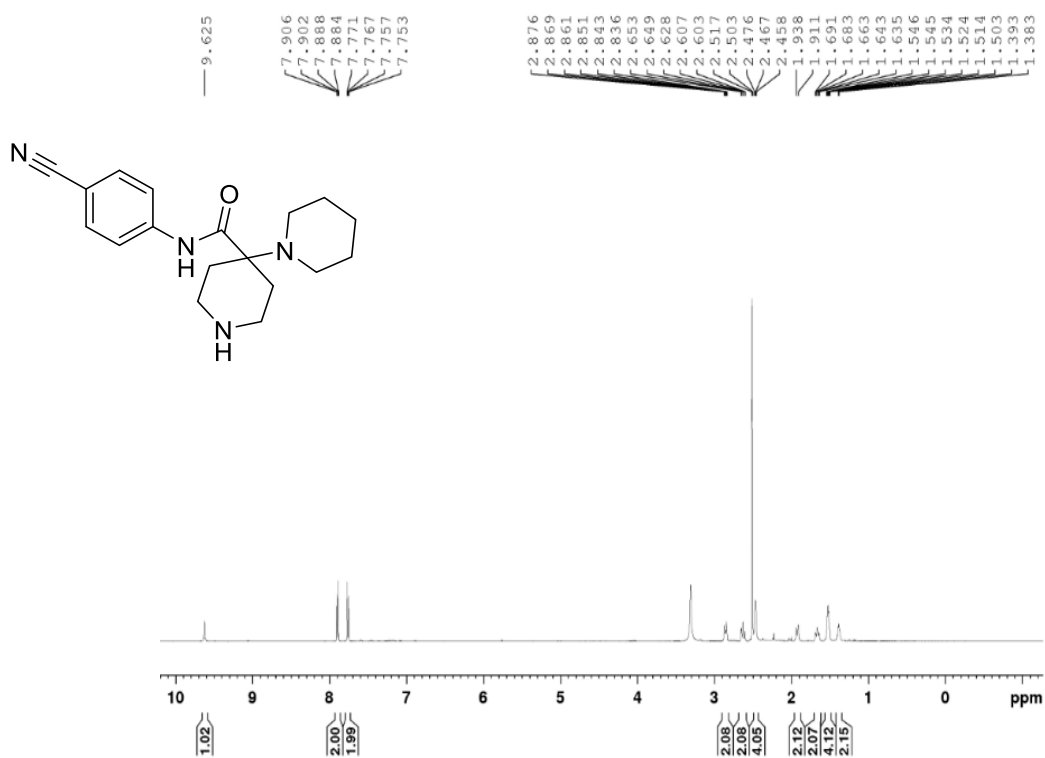
^{13}C{^{1}H} NMR Spectrum of [1,4']Bipiperidinyl-4'-carboxylic acid (4-cyano-phenyl)-amide, **2t** (DMSO-d_6, 125.8 MHz)
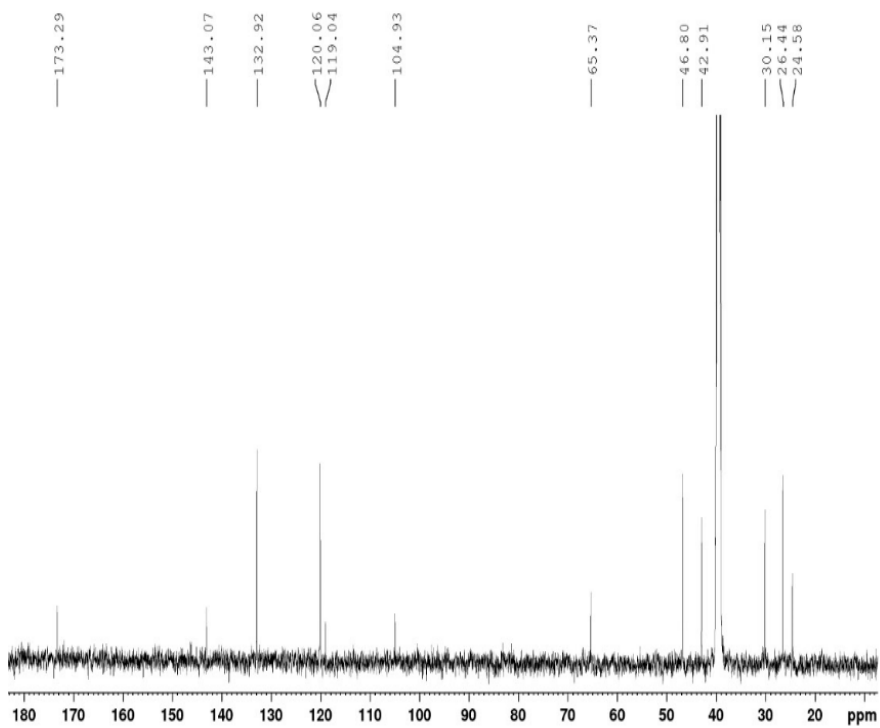
¹H NMR Spectrum of N-(2-Methyl-3-pyridinyl)benzamide, **4-2** (DMSO-*d*₆, 500.1 MHz)
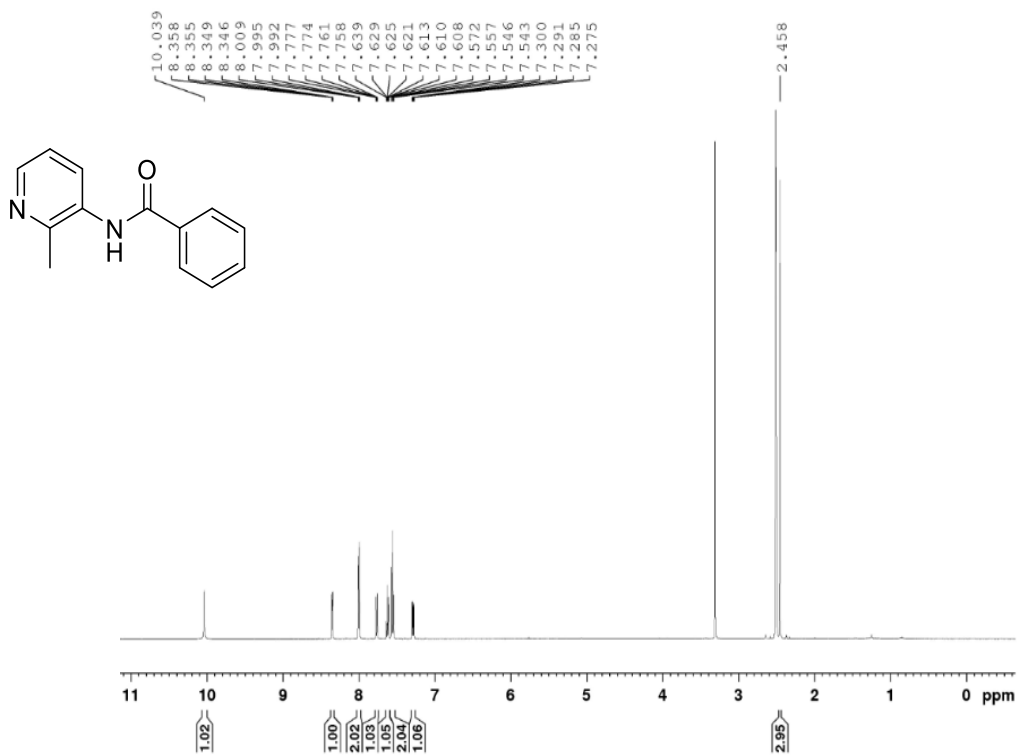
¹³C{¹H} NMR Spectrum of N-(2-Methyl-3-pyridinyl)benzamide, **4-2** (DMSO-*d*₆, 125.8 MHz)
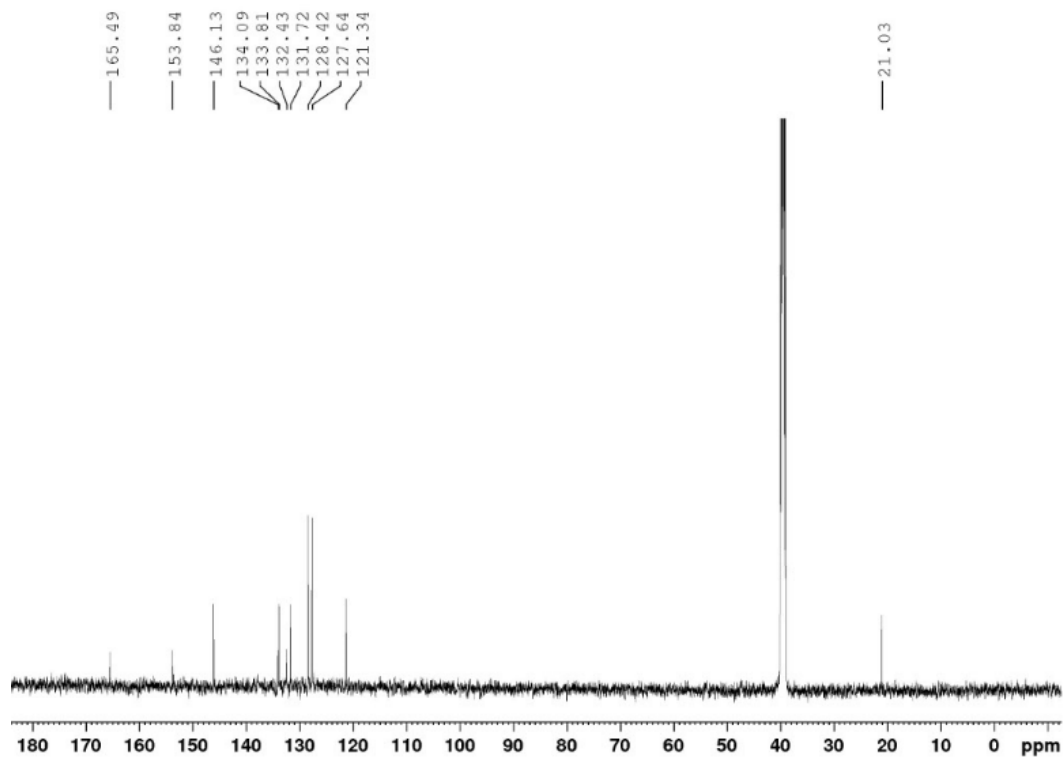
¹H NMR Spectrum of *N*-(Quinolin-8-yl)thiophenecarboxamide, **4-3** (DMSO-*d*₆ , 500.1 MHz)
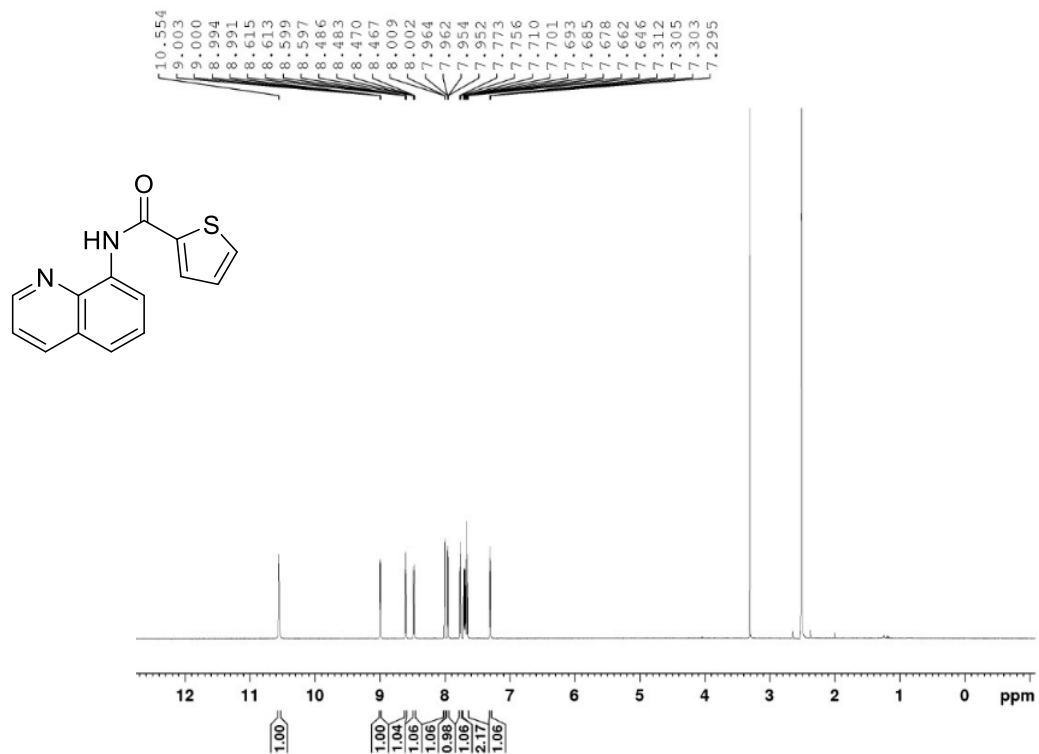
¹³C{¹H} NMR Spectrum of *N*-(Quinolin-8-yl)thiophenecarboxamide, **4-3** (DMSO-*d*₆ , 125.8 MHz)
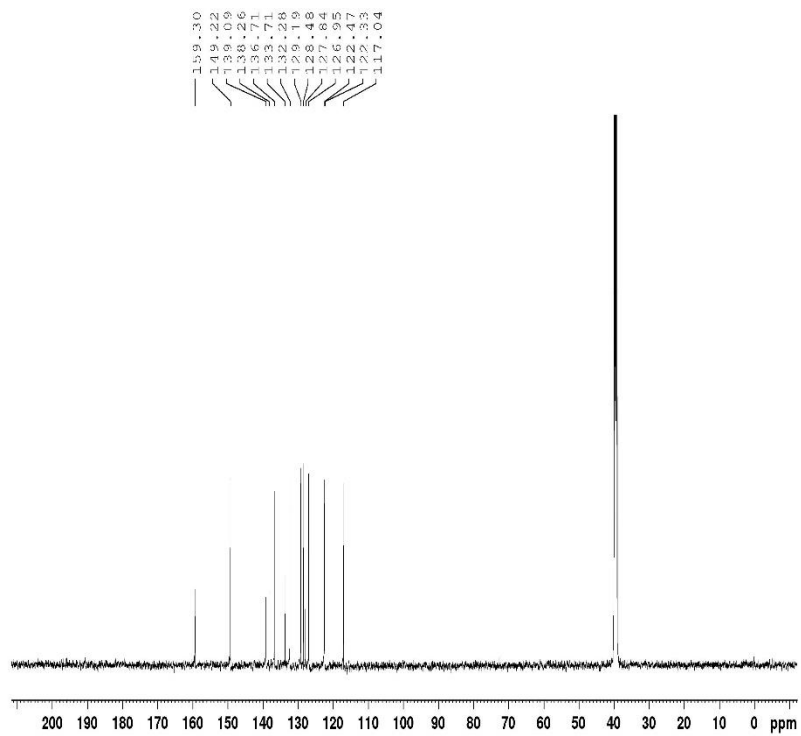
¹H NMR Spectrum of 4-[(2-furanylcarbonyl)amino]-ethyl ester benzoic acid, **4-4** (DMSO-d_6, 500.1 MHz)

¹³C{¹H} NMR Spectrum of 4-[(2-furanylcarbonyl)amino]-ethyl ester benzoic acid, **4-4** (DMSO-d_6, 125.8 MHz)
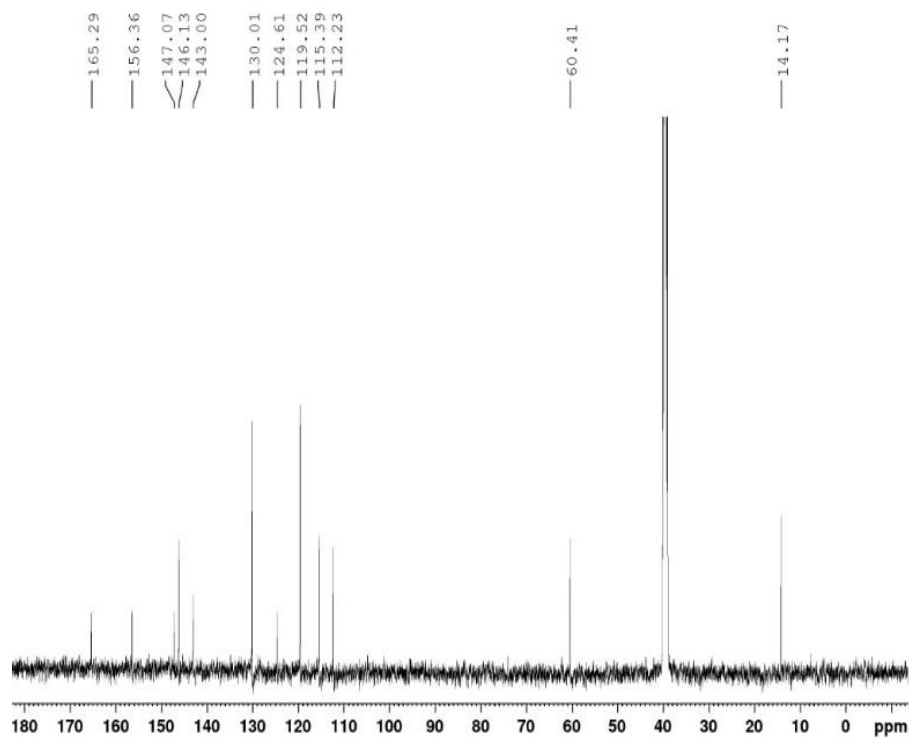
¹H NMR Spectrum of *N*-1-napthalenyl-3-pyridinecarboxamide, **4-5** (DMSO-*d*₆, 500.1 MHz)
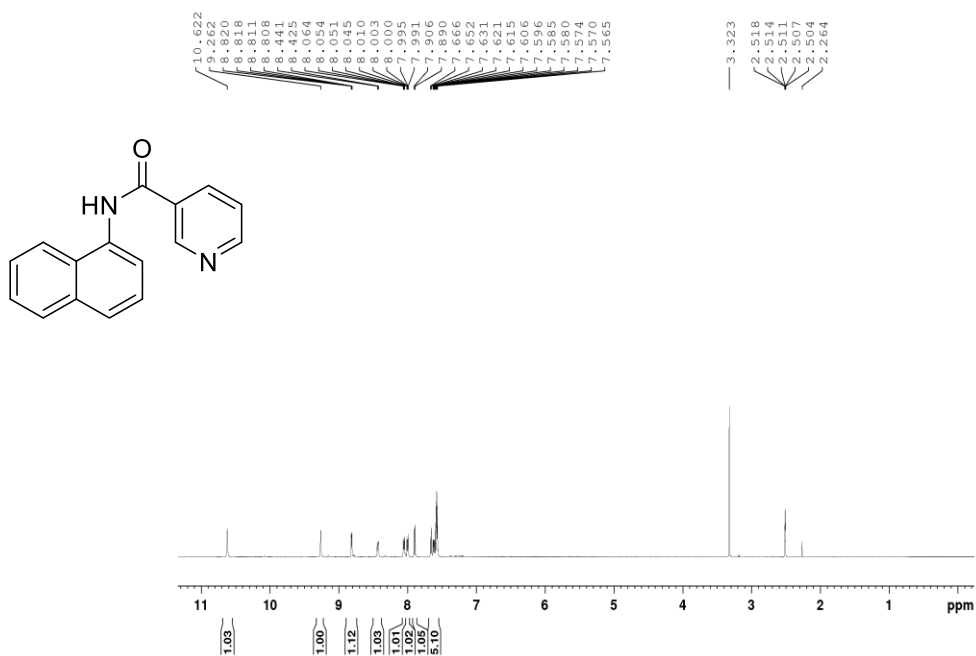
¹³C{¹H} NMR Spectrum of *N*-1-napthalenyl-3-pyridinecarboxamide, **2g** (DMSO-*d*₆, 125.8 MHz)
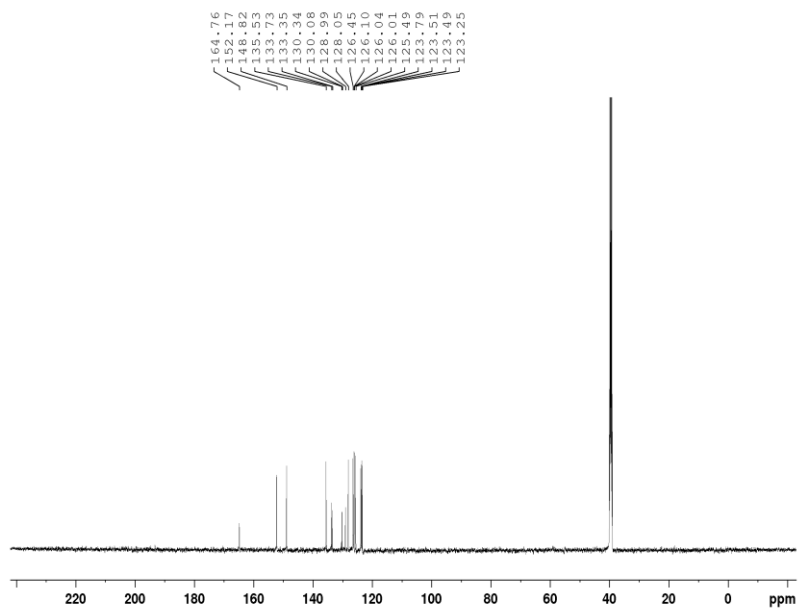
^{1}H NMR Spectrum of N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-benzamide, **4-6** (DMSO-d_6, 500.1 MHz)
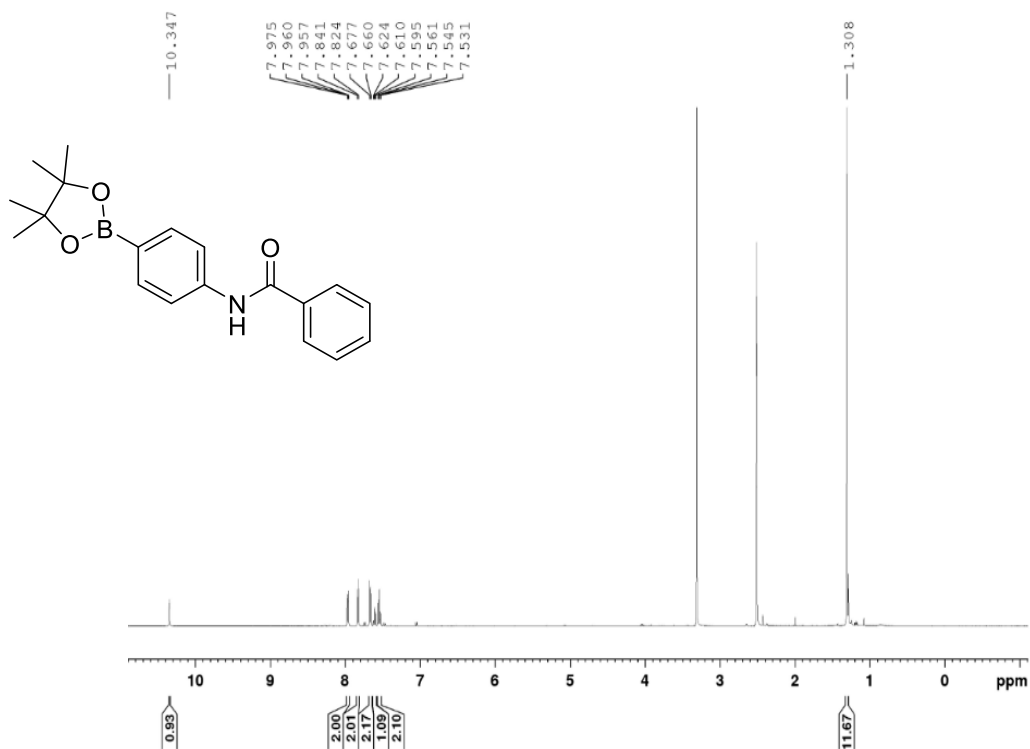
^{13}C{^{1}H} NMR Spectrum of N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-benzamide, **4-6** (DMSO-d_6, 125.8 MHz)

243
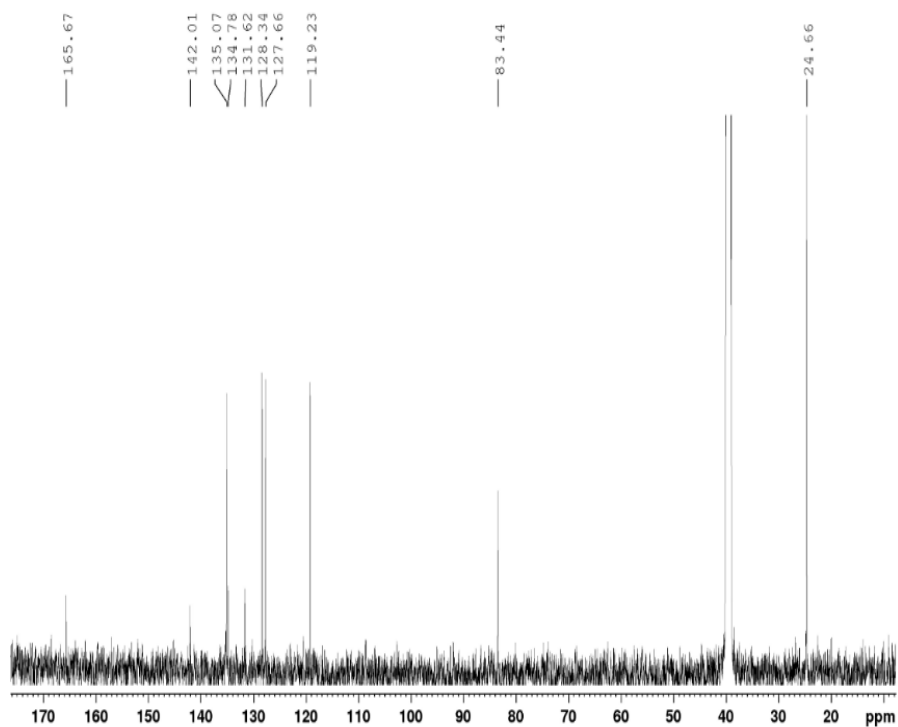
¹H NMR Spectrum of *N*-(2-methyl-4-quinolinyl)- 4-pyridinecarboxamide, **4-7** (DMSO-d₆, 500.1 MHz)
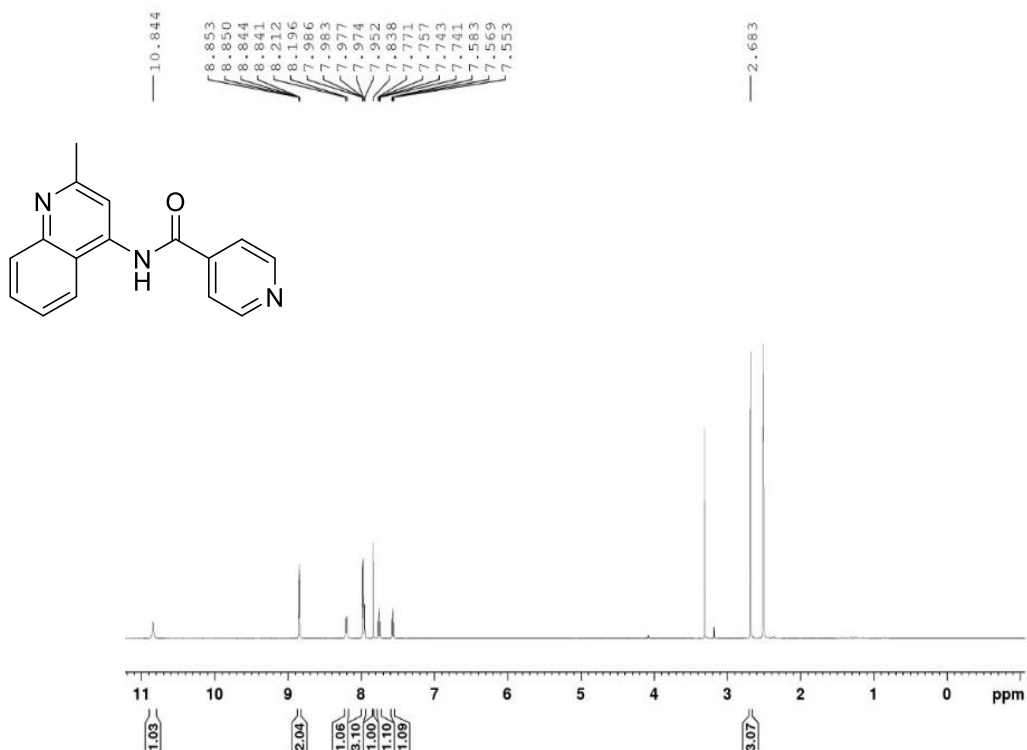
¹³C{¹H} NMR Spectrum of *N*-(2-methyl-4-quinolinyl)- 4-pyridinecarboxamide, **4-7** (DMSO-d₆, 125.8 MHz)

244
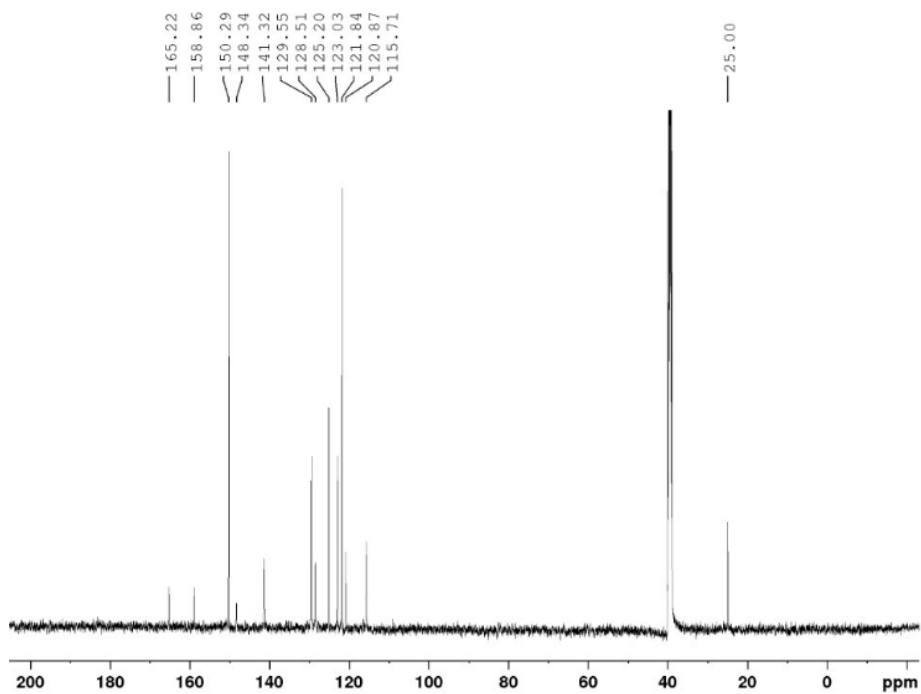
¹H NMR Spectrum of 1-Quinoxalin-6-yl-azetidin-2-one, **4-8** (DMSO-d_6, 500.1 MHz)
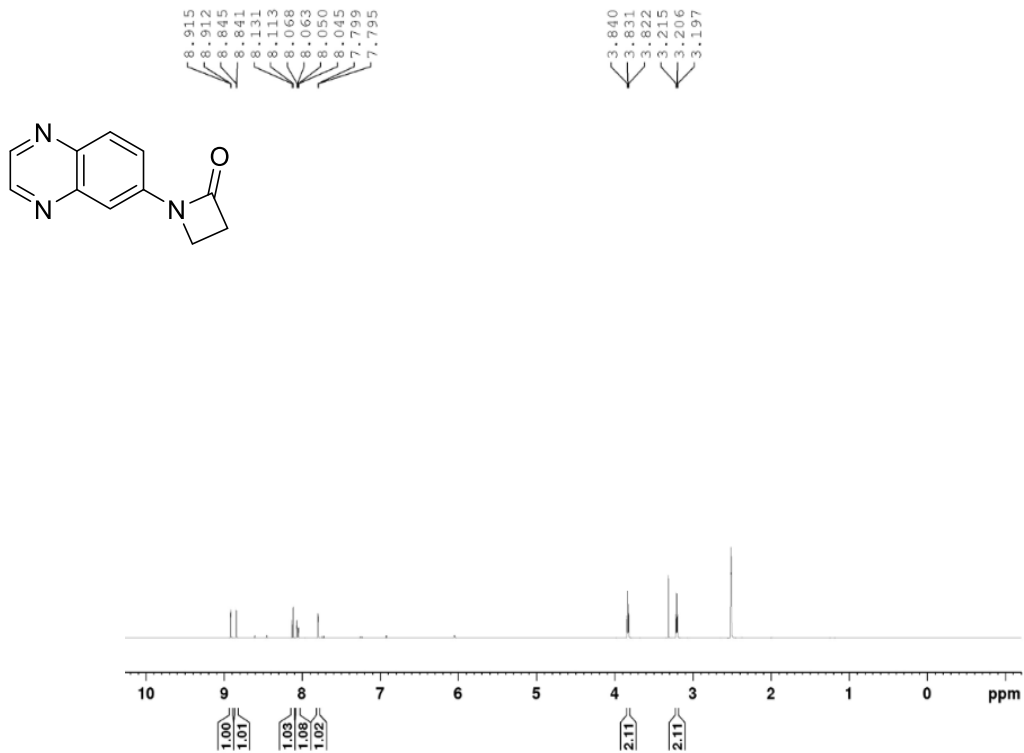
¹³C{¹H} NMR Spectrum of 1-Quinoxalin-6-yl-azetidin-2-one, **4-8** (DMSO-d_6, 125.8 MHz)

245
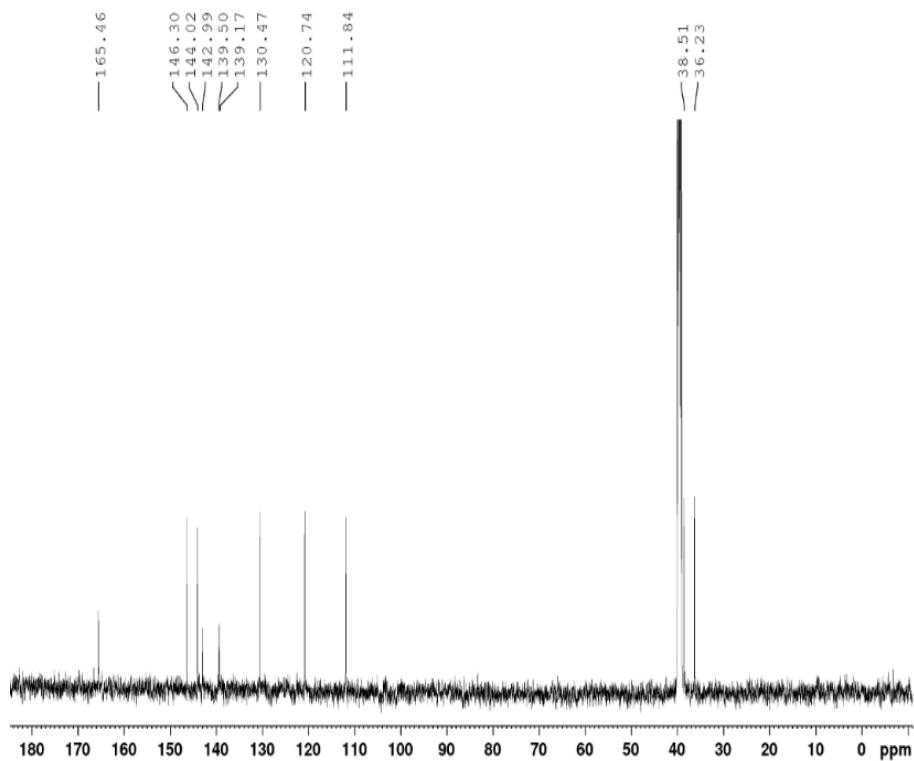
^{1}H NMR Spectrum of 1-(4-acetylphenyl)-2-pyrrolidinone, **4-9** (DMSO-d_6, 500.1 MHz)
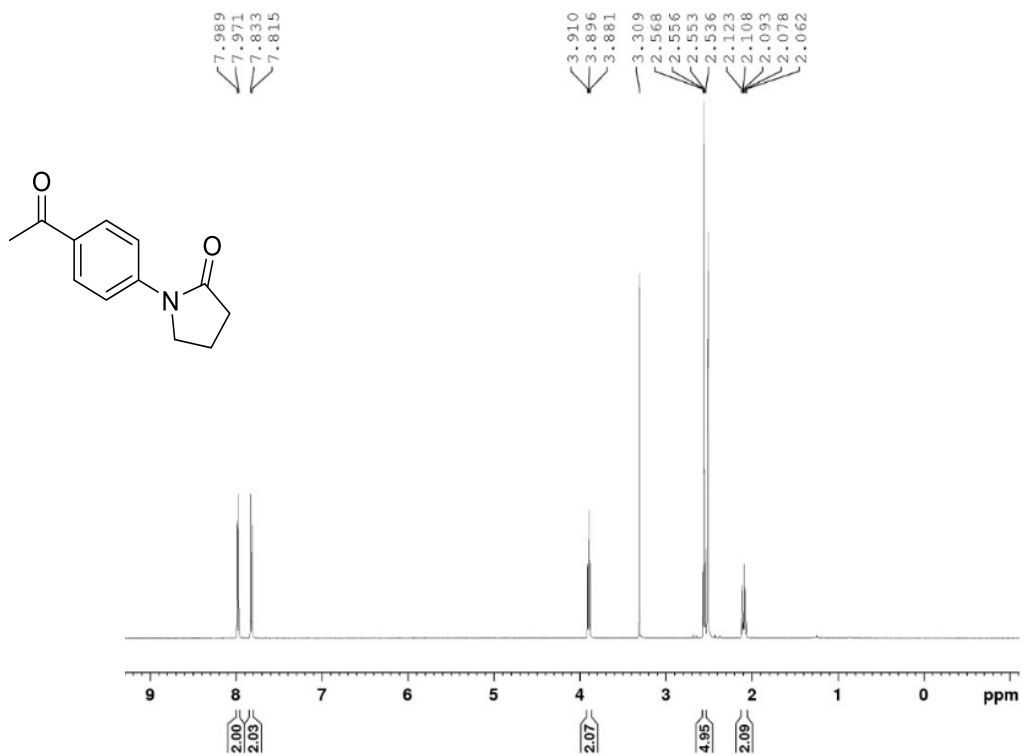
^{13}C{^{1}H} NMR Spectrum of 1-(4-acetylphenyl)-2-pyrrolidinone, **4-9** (DMSO-d_6, 125.8 MHz)

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¹H NMR Spectrum of Ethyl 4-(2-oxo-1-piperidinyl)benzoate, **4-10** (DMSO-*d*₆, 500.1 MHz)
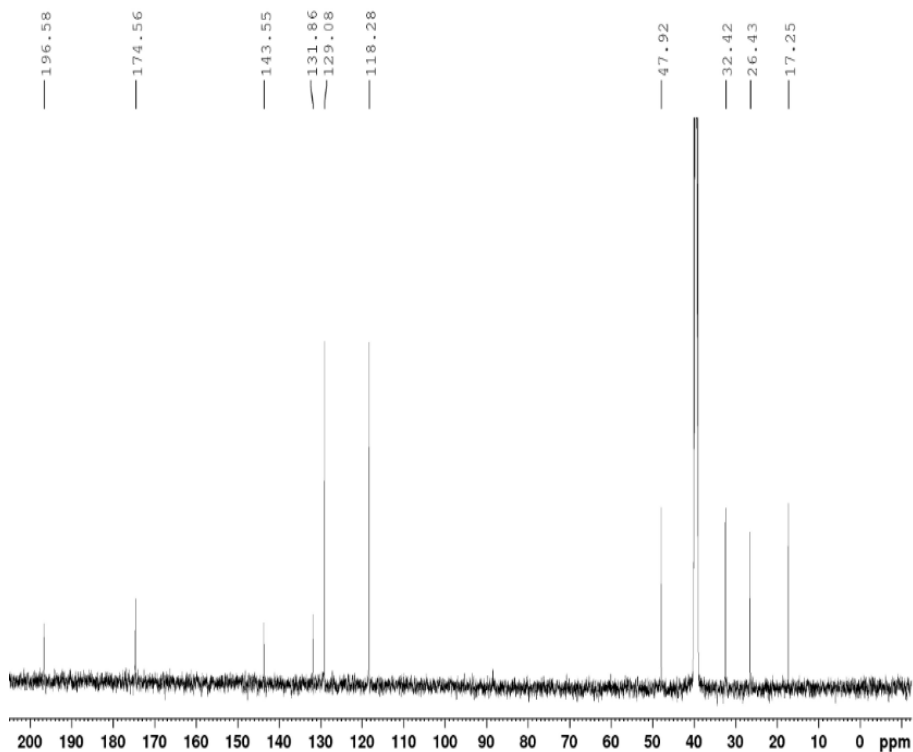
^{1}H NMR Spectrum of Ethyl 4-(2-oxo-1-piperidinyl)benzoate, **4-10** (DMSO-d_6, 500.1 MHz)
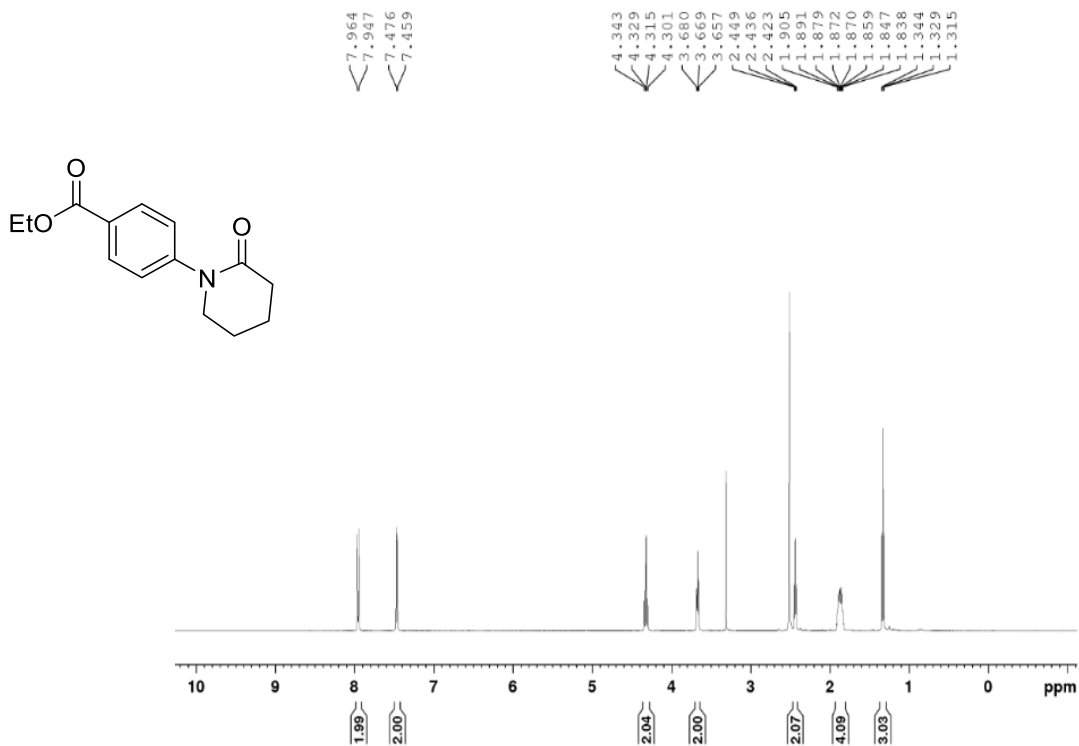
^{13}C{^{1}H} NMR Spectrum of Ethyl 4-(2-oxo-1-piperidinyl)benzoate, **4-11** (DMSO-d_6, 125.8 MHz)

247
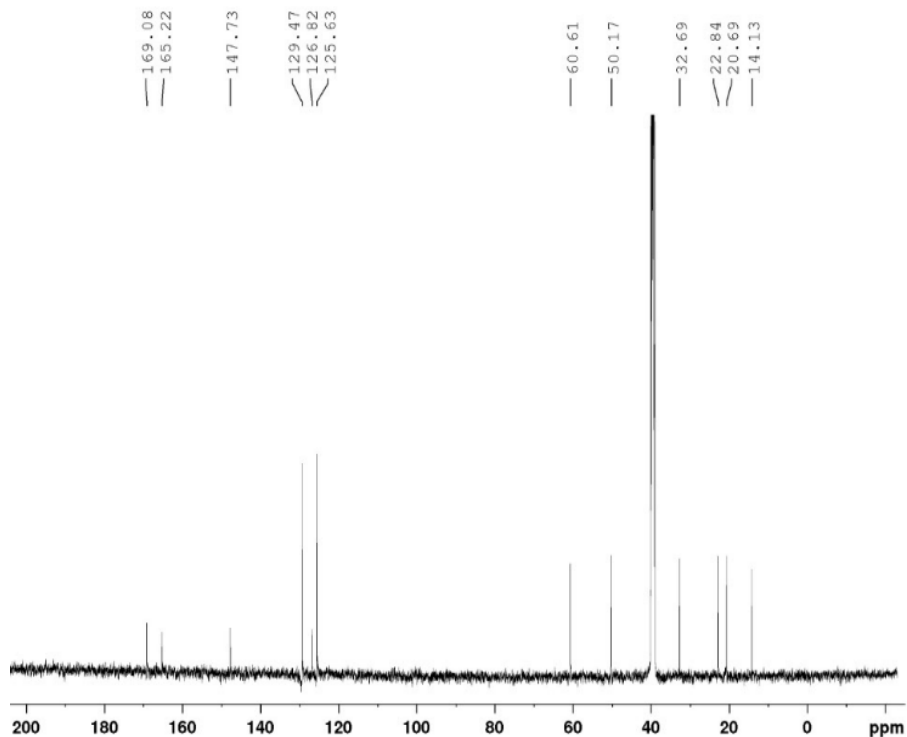
^{1}H NMR Spectrum of 1-Quinoxalin-6-yl-azetpan-2-one, **4-11** (DMSO-*d*$_6$, 500.1 MHz)
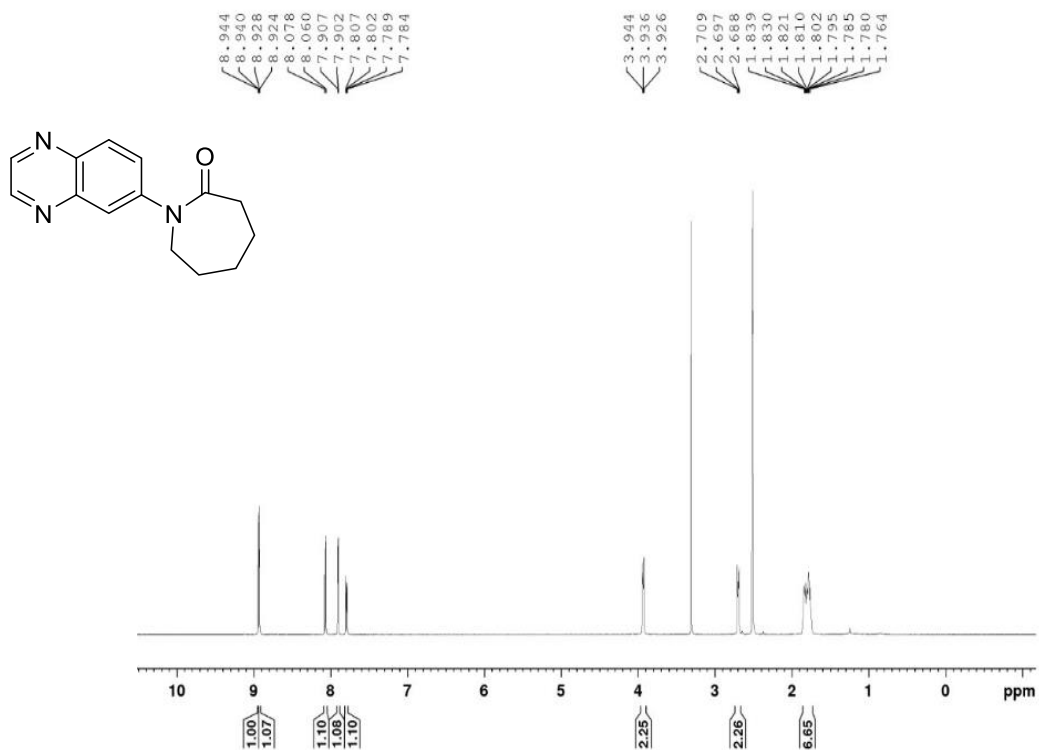
^{13}C{^{1}H} NMR Spectrum of 1-Quinoxalin-6-yl-azetpan-2-one, **4-11** (DMSO-*d*$_6$, 125.8 MHz)
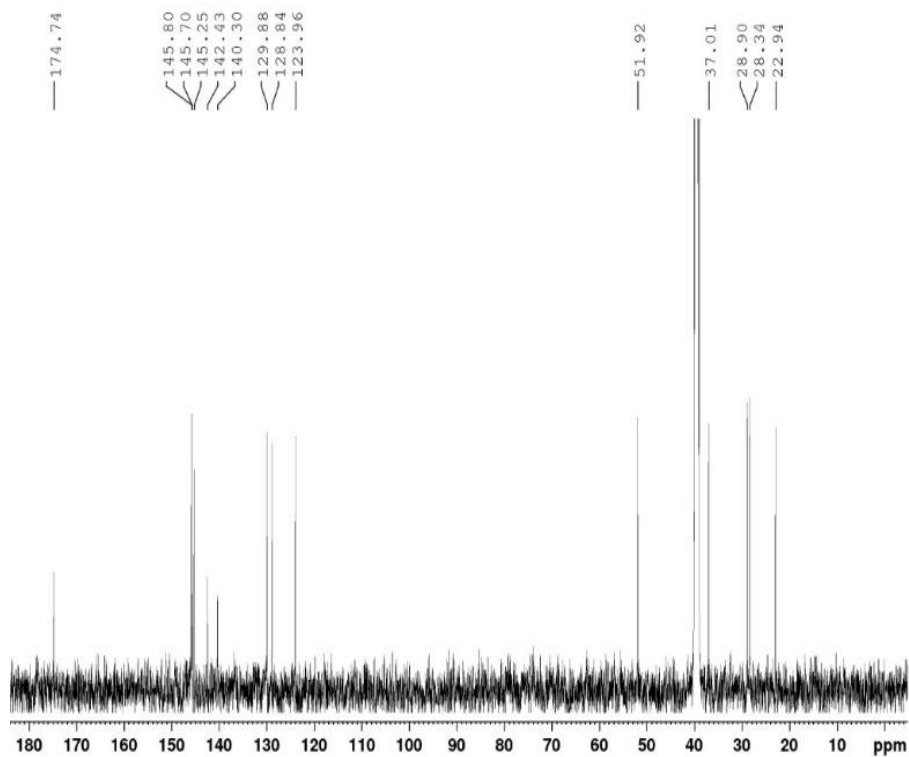
¹H NMR Spectrum of 4-[(4S)-2-Oxo-4-(phenylmethyl)-3-oxazolidinyl]benzonitrile, **4-12** (DMSO-d_6, 500.1 MHz)
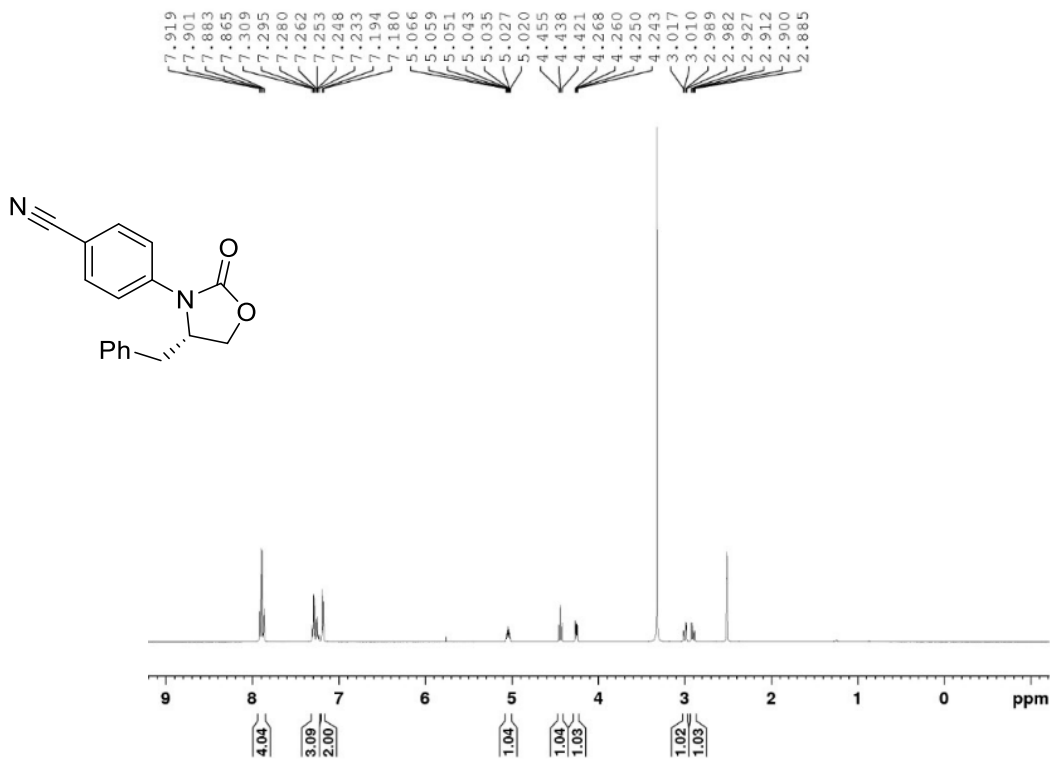
¹³C{¹H} NMR Spectrum of 4-[(4S)-2-Oxo-4-(phenylmethyl)-3-oxazolidinyl]benzonitrile, **4-12** (DMSO-d_6, 125.8 MHz)
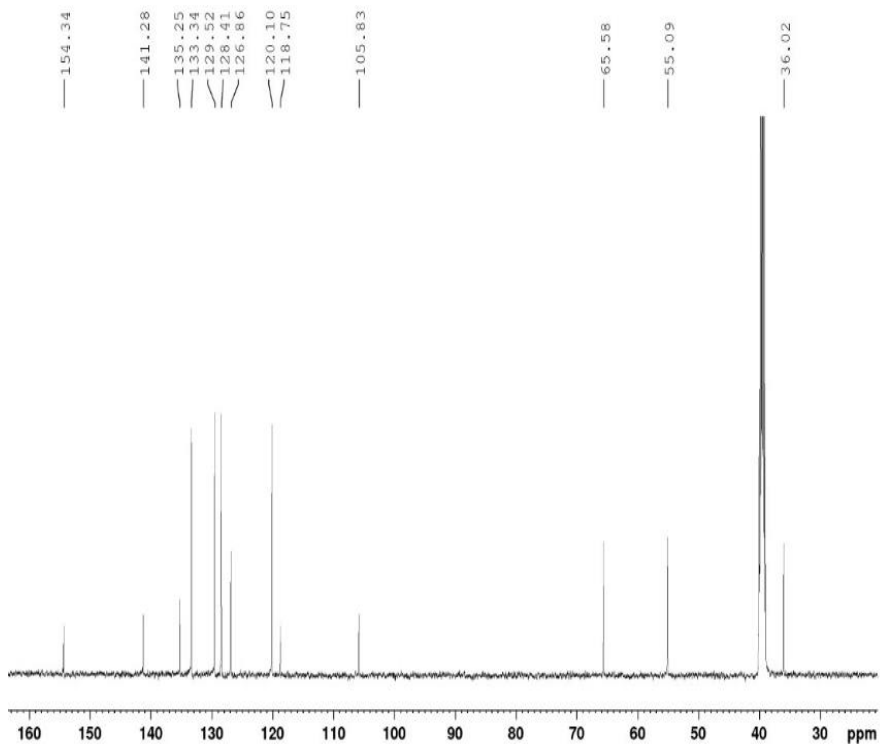
¹H NMR Spectrum of 1-(4-acetylphenyl)-5-oxo-pyrrolidine-3-carboxylic acid ethyl ester, **4-13** (DMSO-*d*₆, 500.1 MHz)
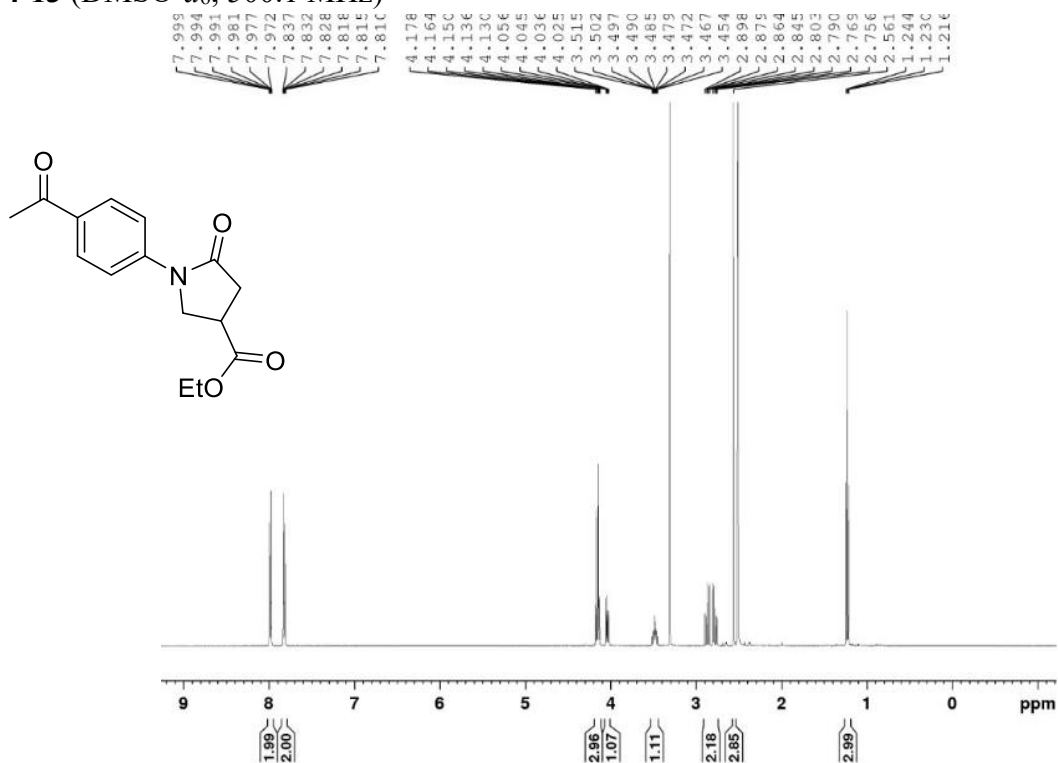
¹³C{¹H} NMR Spectrum of 1-(4-acetylphenyl)-5-oxo-pyrrolidine-3-carboxylic acid ethyl ester, **4-13** (DMSO-*d*₆, 125.8 MHz)
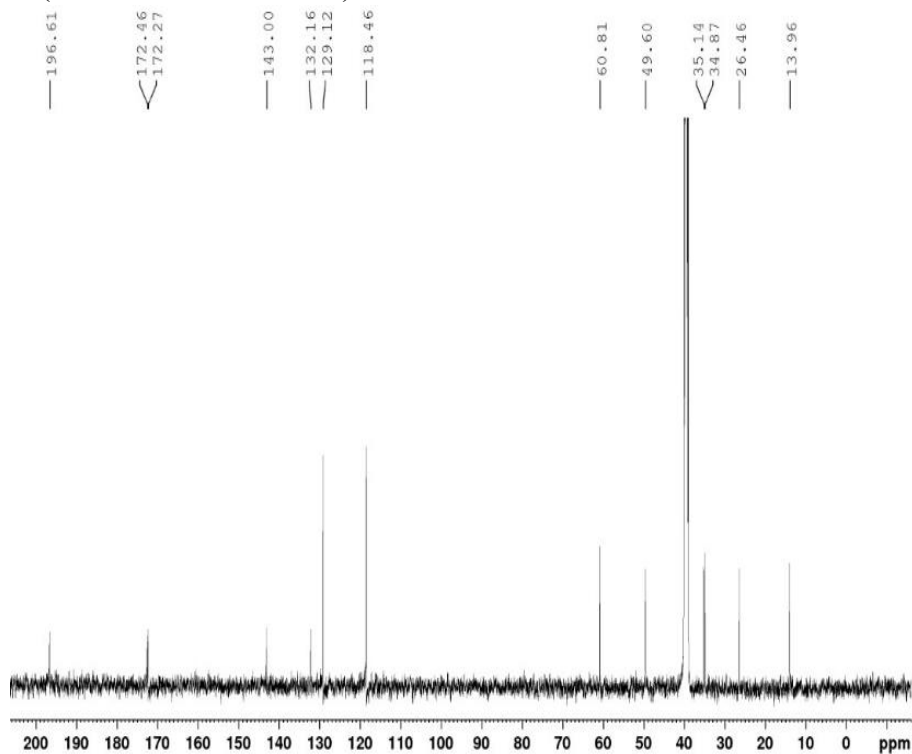
¹H NMR Spectrum of 1-(13-Methyl-17-oxo-7, 8, 9, 11, 12, 13, 14, 15, 16, 17-decahydro-6H- cyclopenta[a]phenanthren-3-yl)-pyrrolidin-2-one, **4-14** (DMSO-*d*₆, 500.1 MHz)
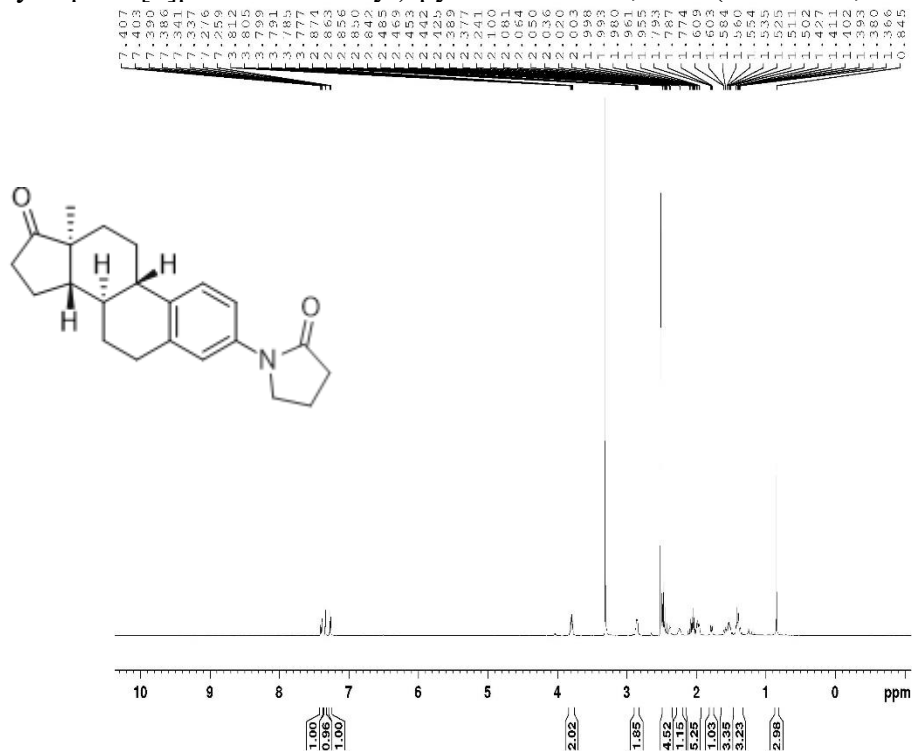
¹³C{¹H} NMR Spectrum of 1-(13-Methyl-17-oxo-7, 8, 9, 11, 12, 13, 14, 15, 16, 17-decahydro-6H- cyclopenta[a]phenanthren-3-yl)-pyrrolidin-2-one, **4-14** (DMSO-*d*₆, 125.8 MHz)
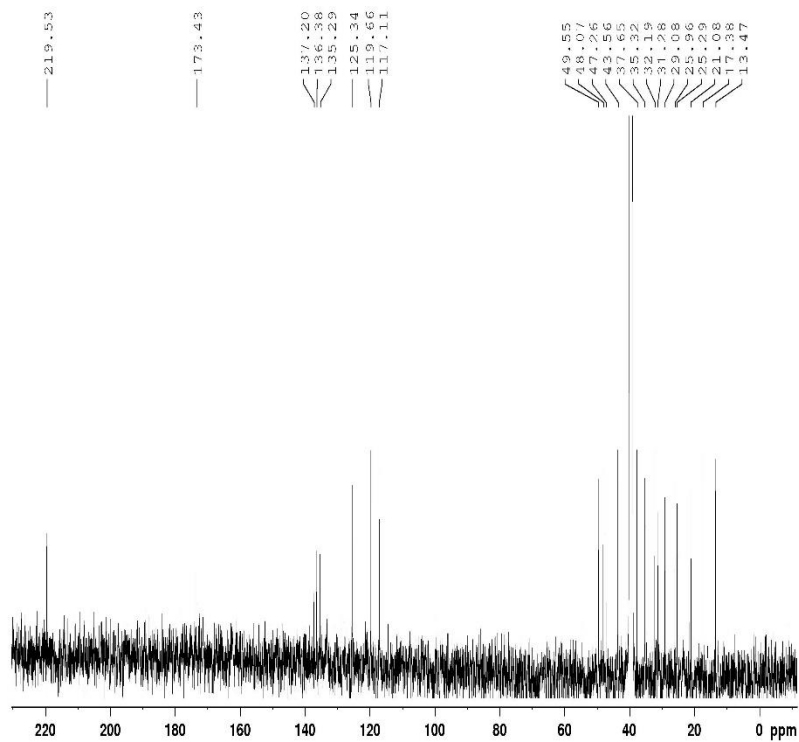
^{1}H NMR Spectrum of Biphenyl-4-ylamine, **3-1** (CDCl$_3$, 500.1 MHz)
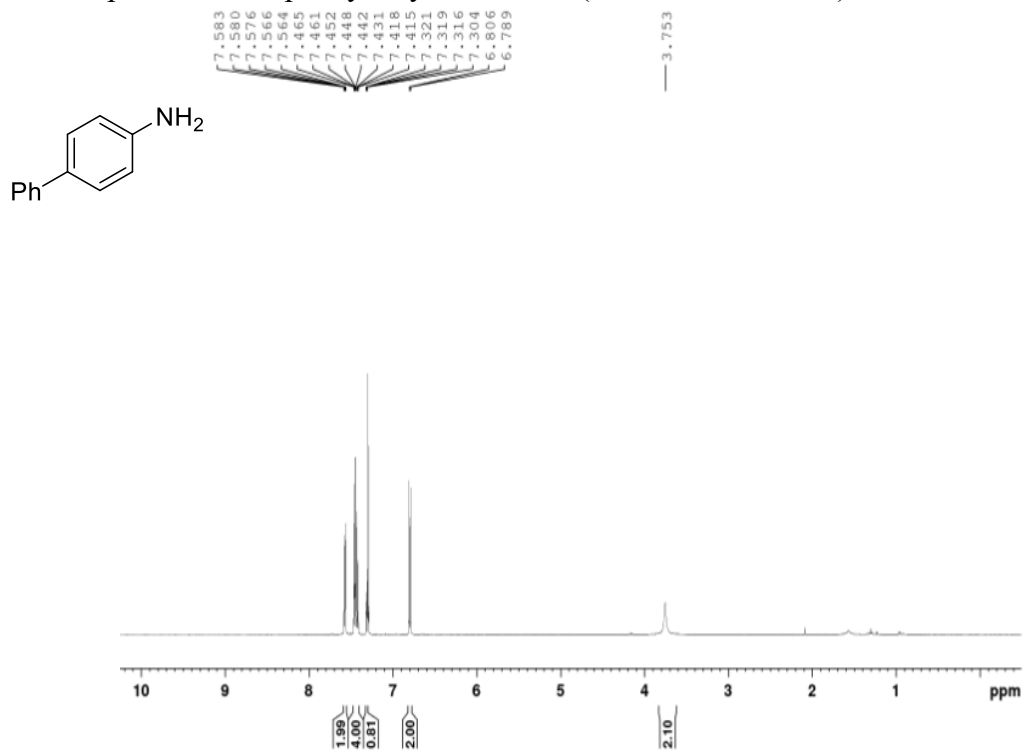
^{13}C{^{1}H} NMR Spectrum of Biphenyl-4-ylamine, **3-1** (CDCl$_3$, 125.8 MHz)
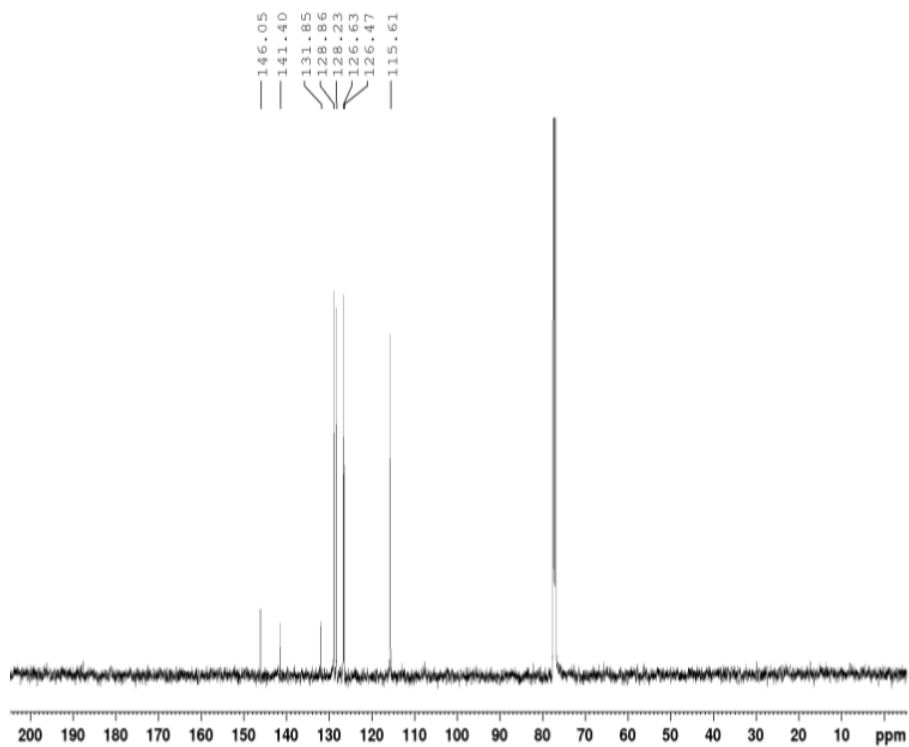
¹H NMR Spectrum of 2-methyl-4-Quinolinamine, **5-1** (CDCl₃, 500.1 MHz)
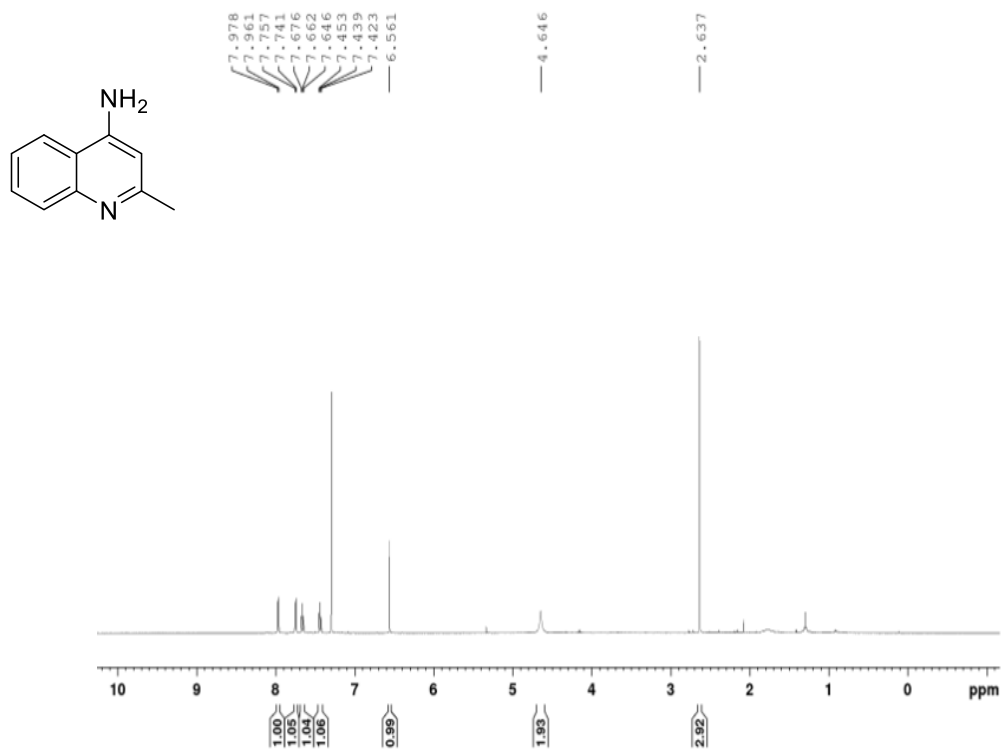
¹³C{¹H} NMR Spectrum of 2-methyl-4-Quinolinamine, **5-1** (CDCl₃, 125.8 MHz)
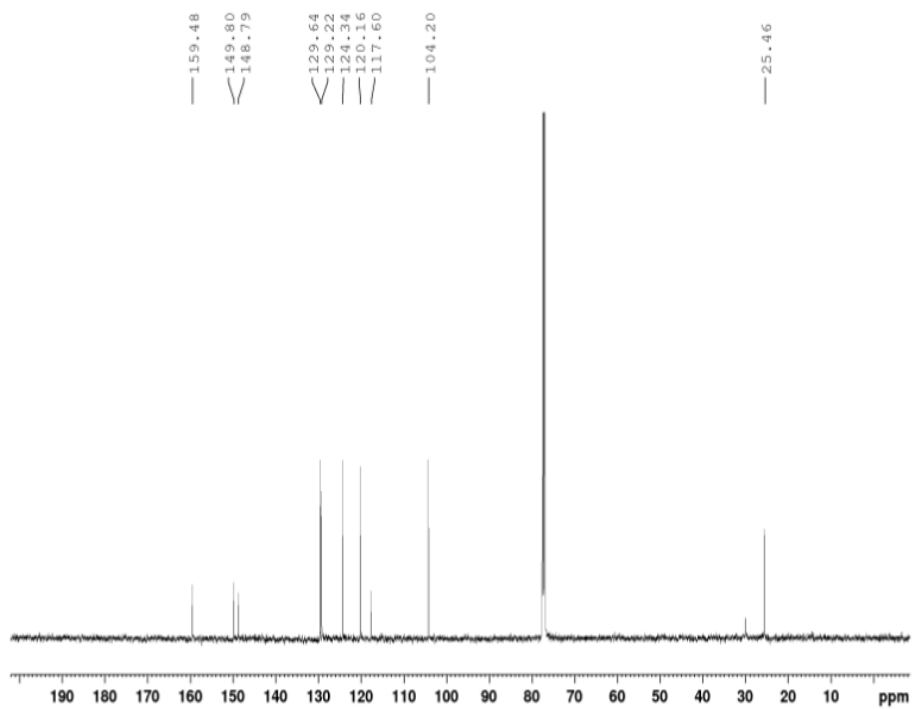
¹H NMR Spectrum of 6-Quinolinamine, **5-2** (CDCl₃, 500.1 MHz)
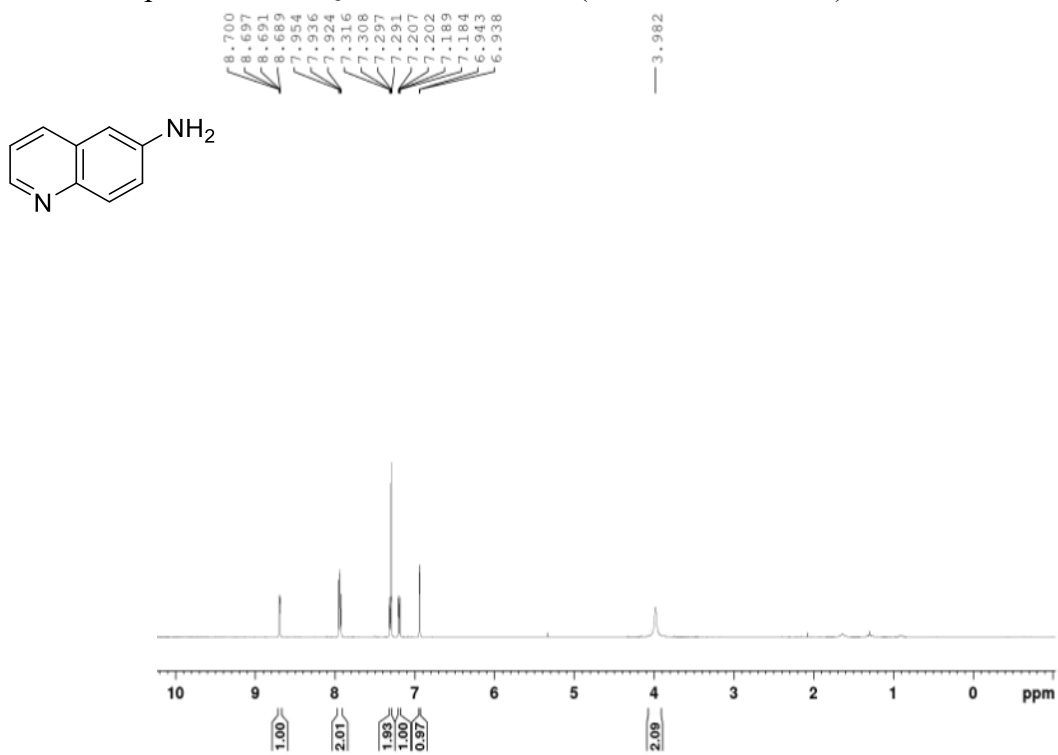
¹³C{¹H} NMR Spectrum of 6-Quinolinamine, **5-2** (CDCl₃, 125.8 MHz)
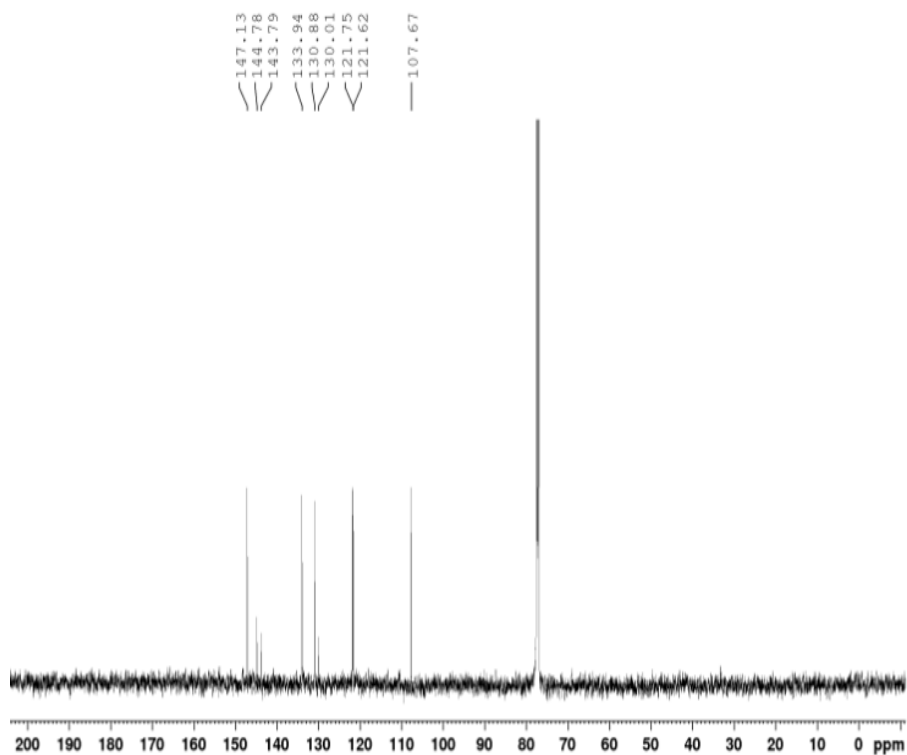
¹H NMR Spectrum of 2-methyl-6-Benzothiazolamine, **5-3** (CDCl₃, 500.1 MHz)
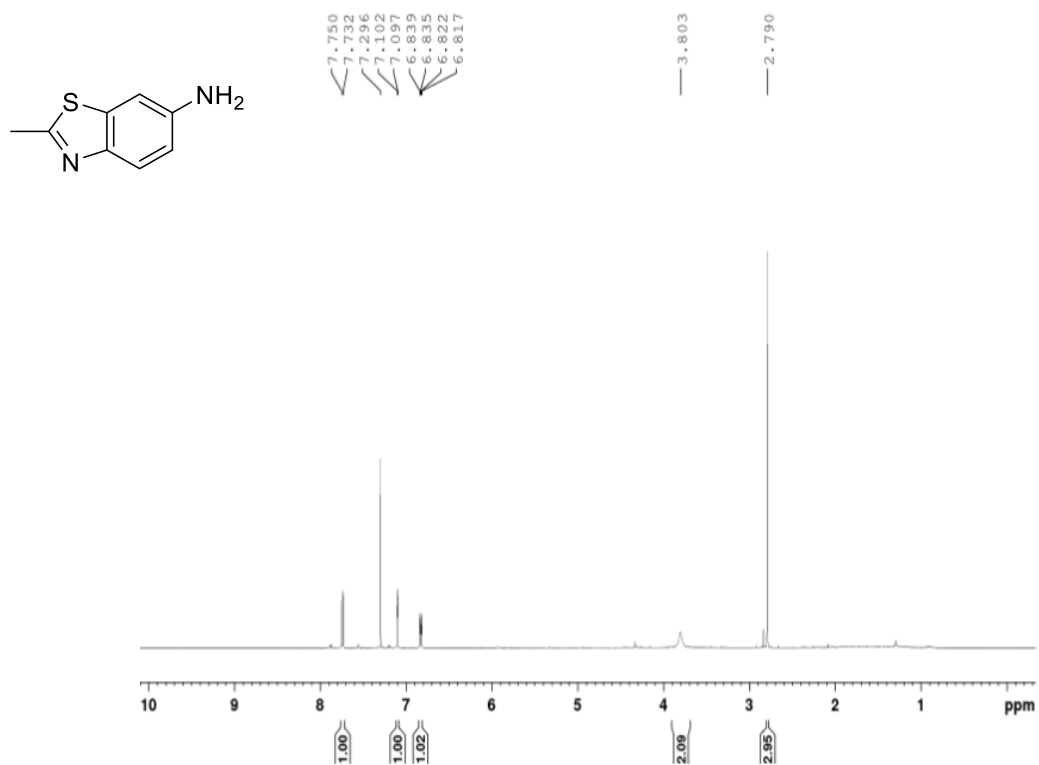
¹³C{¹H} NMR Spectrum of 2-methyl-6-Benzothiazolamine, **5-3** (CDCl₃, 125.8 MHz)
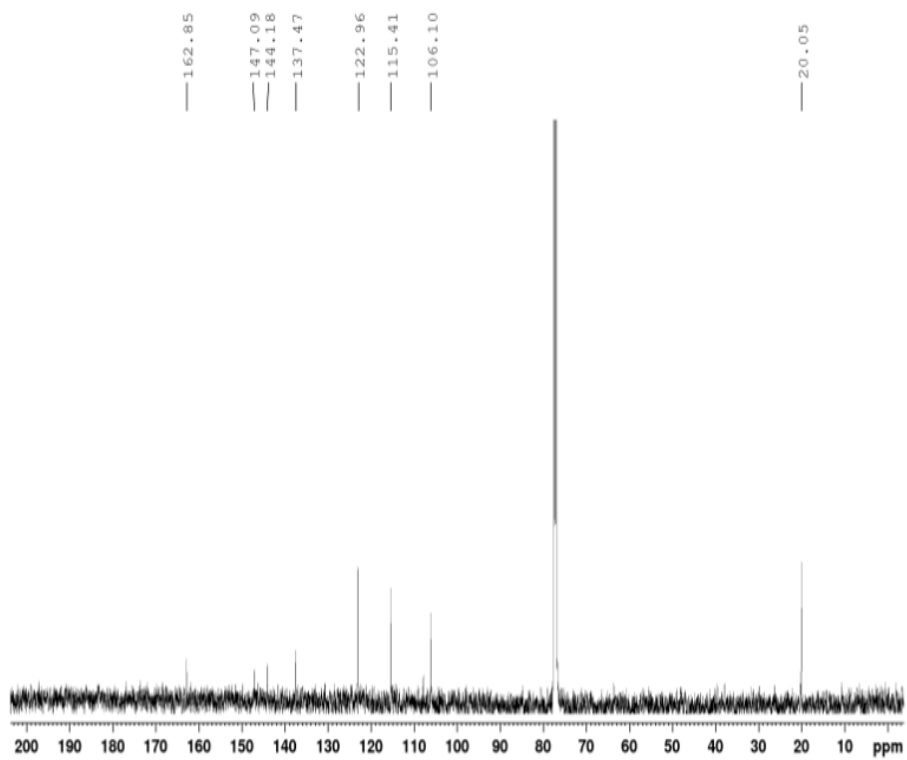
^{1}H NMR Spectrum of Naphthalen-2-ylamine, 5-4 (CDCl₃, 500.1 MHz)
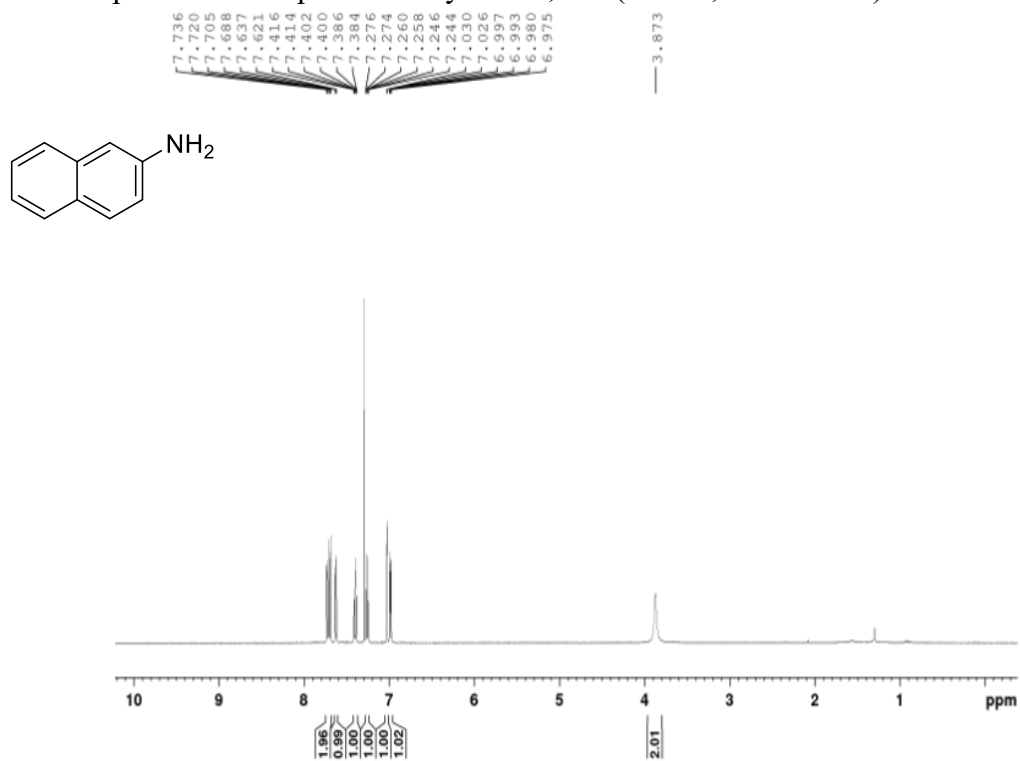
^{13}C{^{1}H} NMR Spectrum of Naphthalen-2-ylamine, 5-4 (CDCl₃, 125.8 MHz)

¹H NMR Spectrum of 3-phenoxy-Benzenamine, **5-5** (CDCl₃, 500.1 MHz)

Peaks (ppm): 7.379, 7.363, 7.347, 7.145, 7.129, 7.113, 7.071, 7.069, 7.054, 6.466, 6.463, 6.447, 6.429, 6.426, 6.372, 6.368, 6.363, 3.710

¹³C{¹H} NMR Spectrum of 3-phenoxy-Benzenamine, **5-5** (CDCl₃, 125.8 MHz)

Peaks (ppm): 158.67, 157.37, 148.20, 130.55, 129.84, 123.36, 119.31, 110.28, 109.11, 105.73

^{1}H NMR Spectrum of 3-phenoxy-Benzenamine, **5-5** (CDCl$_3$, 500.1 MHz)

Peak labels (ppm): 7.379, 7.363, 7.347, 7.145, 7.129, 7.113, 7.071, 7.069, 7.054, 6.466, 6.463, 6.447, 6.429, 6.426, 6.372, 6.368, 6.363, 3.710

Structure: Ph–O–(benzene ring)–NH$_2$

Integrations: 2.03, 2.03, 1.98, 1.97, 1.00, 2.10

^{13}C{^{1}H} NMR Spectrum of 3-phenoxy-Benzenamine, **5-5** (CDCl$_3$, 125.8 MHz)

Peak labels (ppm): 158.67, 157.37, 148.20, 130.55, 129.84, 123.36, 119.31, 110.28, 109.11, 105.73

¹H NMR Spectrum of 2,3,6,7-tetrahydro-1*H*,5*H*-Benzo[*ij*]quinolizin-8-amine, **5-6** (CDCl₃, 500.1 MHz)

^{1}H NMR Spectrum of 2,3,6,7-tetrahydro-1*H*,5*H*-Benzo[*ij*]quinolizin-8-amine, **5-6** (CDCl$_3$, 500.1 MHz)
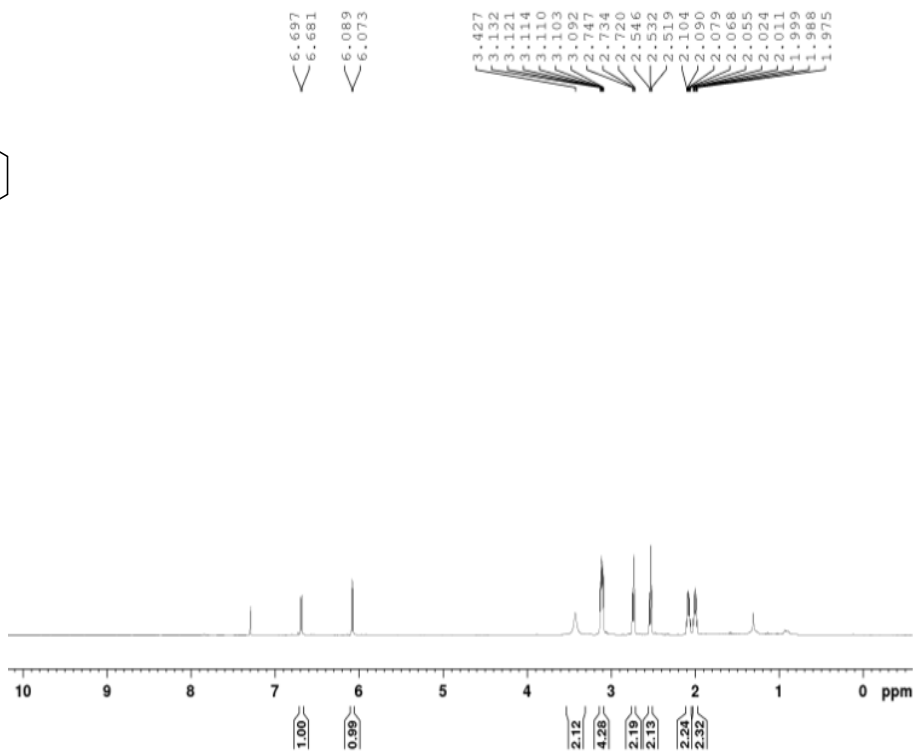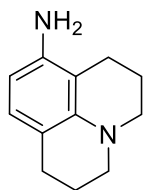
^{13}C{^{1}H} NMR Spectrum of 2,3,6,7-tetrahydro-1*H*,5*H*-Benzo[*ij*]quinolizin-8-amine, **5-6** (CDCl$_3$, 125.8 MHz)
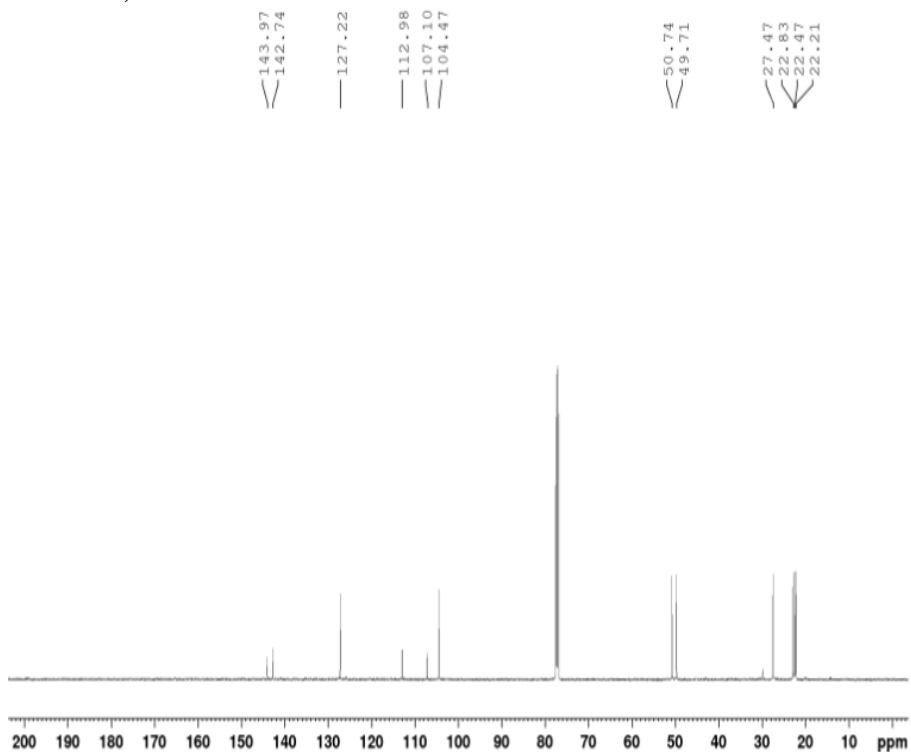
¹H NMR Spectrum of Phenethyl-(8-trifluoromethyl-quinolin-4-yl)-amine, **5-7** (CDCl₃, 500.1 MHz)
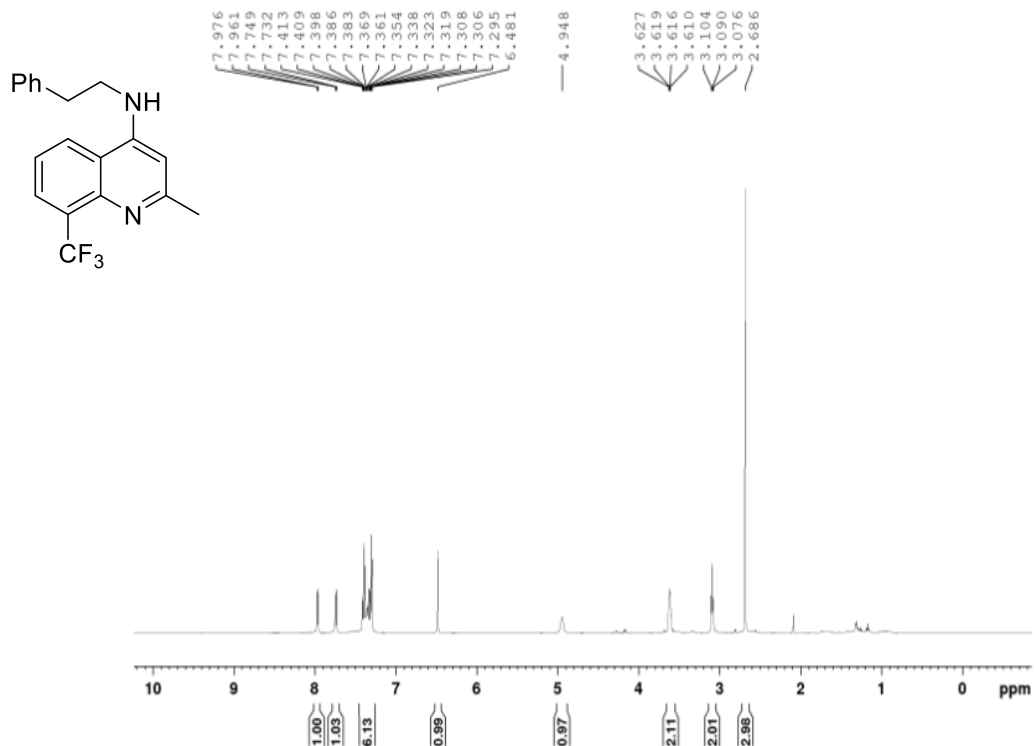
¹³C{¹H} NMR Spectrum of Phenethyl-(8-trifluoromethyl-quinolin-4-yl)-amine, **5-7** (CDCl₃, 125.8 MHz)

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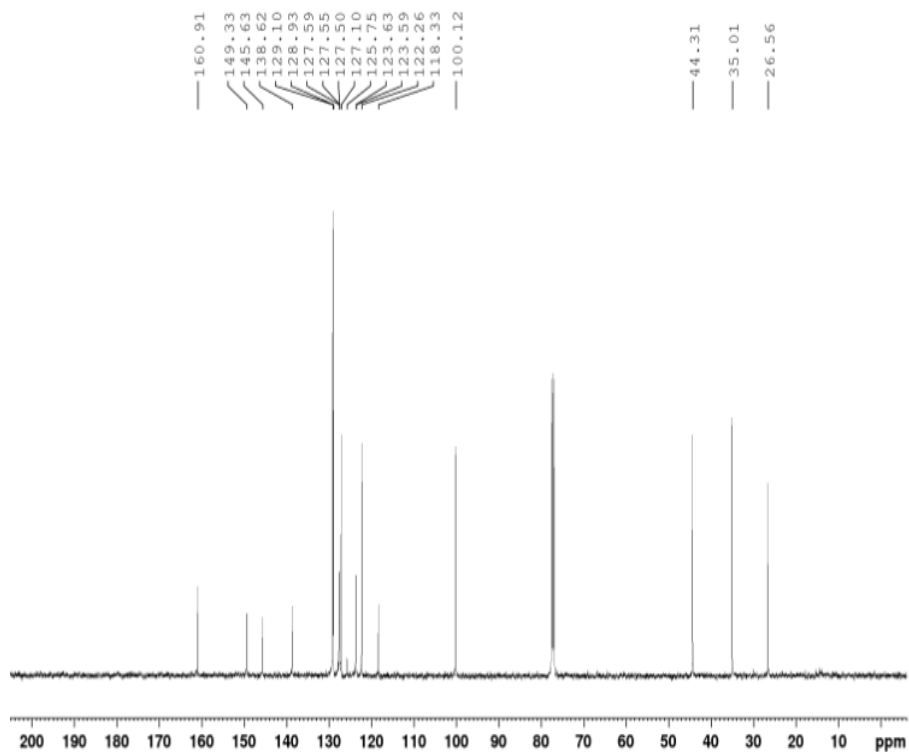
^{1}H NMR Spectrum of *N, N*-Diethyl-*N'*-naphthalen-2-yl-ethane-1,2-diamine, **5-8** (CDCl$_3$, 500.1 MHz)
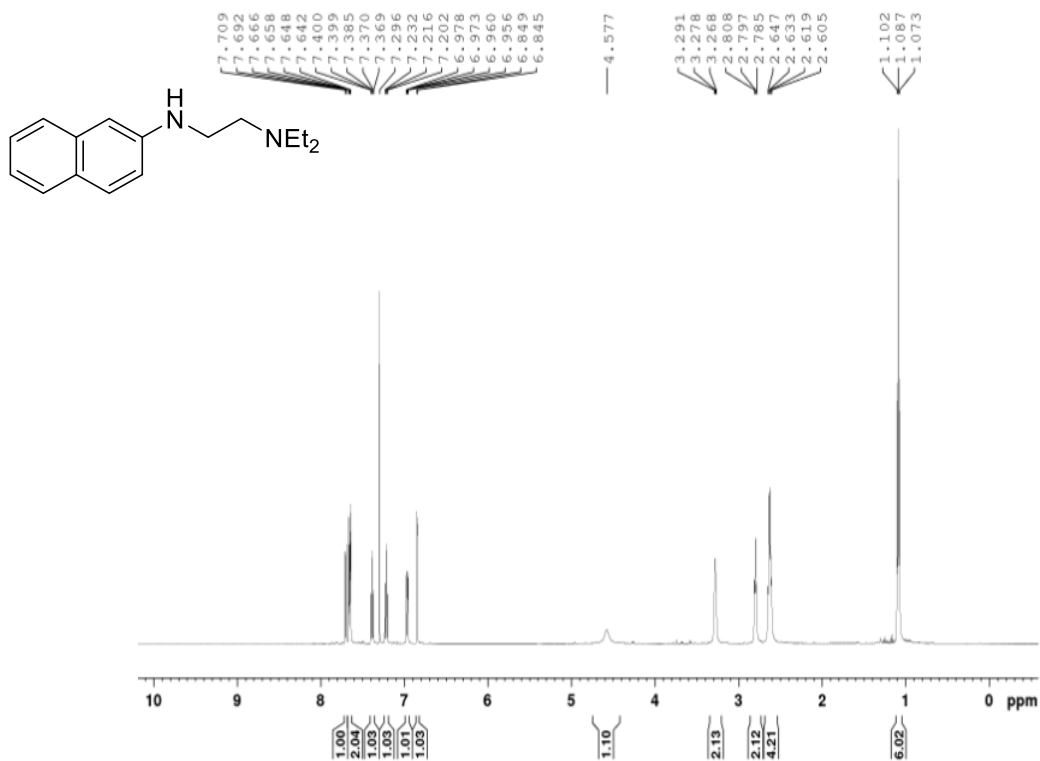
^{13}C{^{1}H} NMR Spectrum of *N, N*-Diethyl-*N'*-naphthalen-2-yl-ethane-1,2-diamine, **5-8** (CDCl$_3$, 125.8 MHz)
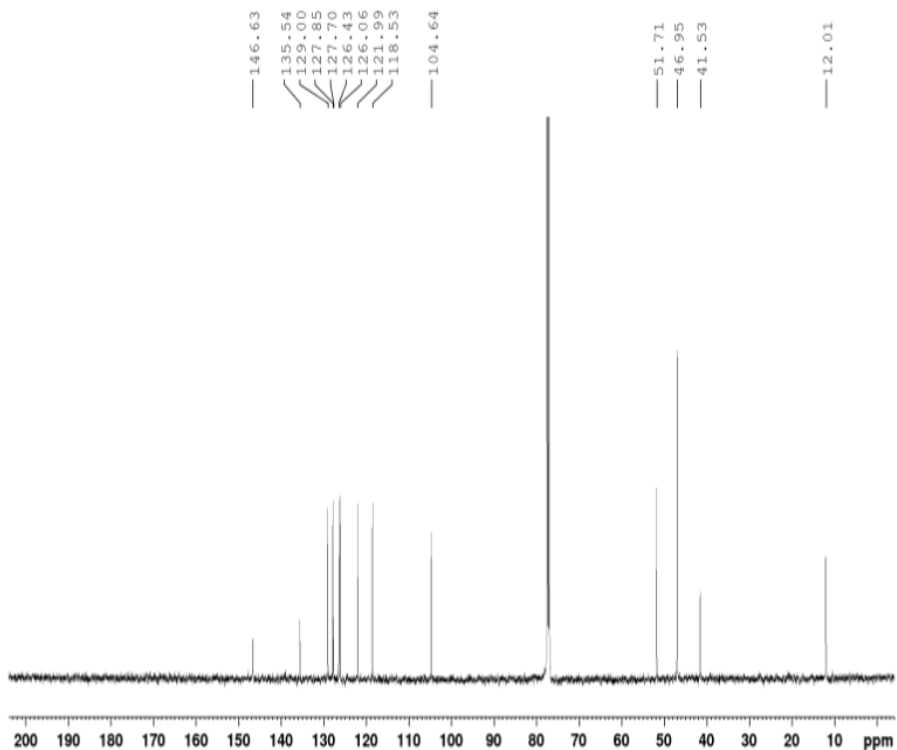
^{1}H NMR Spectrum of N^1-(3-methoxyphenyl) -N^2-phenyl-1,2-Ethanediamine, **5-9** (CDCl$_3$, 500.1 MHz)
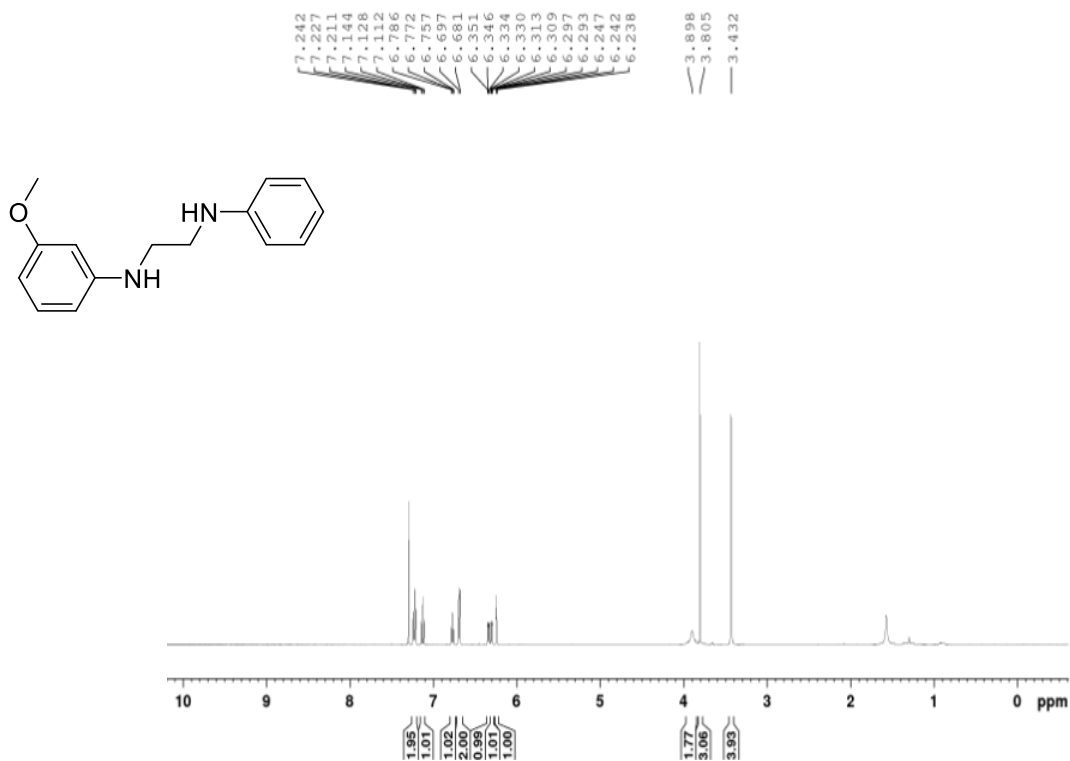
^{13}C{^{1}H} NMR Spectrum of N^1-(3-methoxyphenyl)-N^2-phenyl-1,2-Ethanediamine, **5-9** (CDCl$_3$, 125.8 MHz)
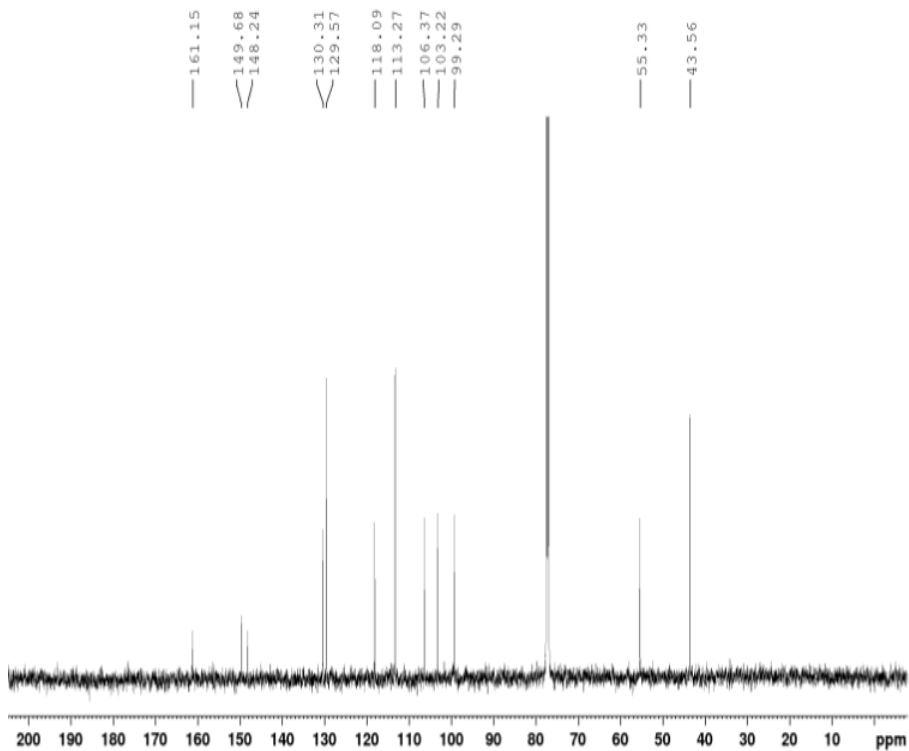
^{1}H NMR Spectrum of 3,4-(Methylenedioxy)-N-furfurylaniline, **5-10** (CDCl$_3$, 500.1 MHz)
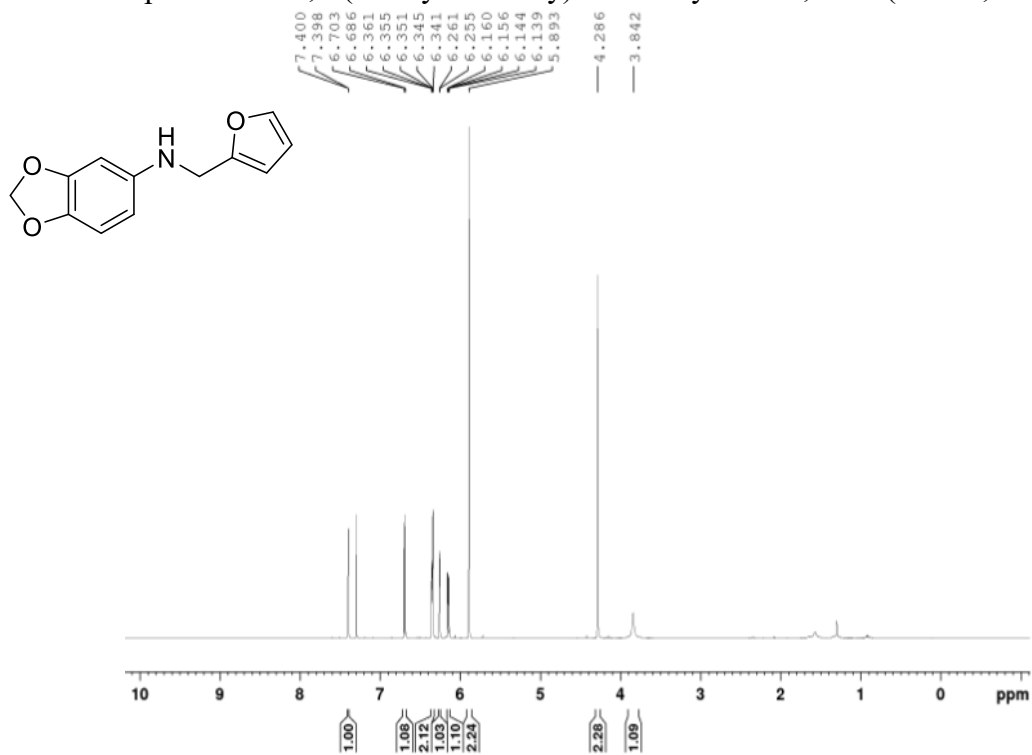
^{13}C{^{1}H} NMR Spectrum of 3,4-(Methylenedioxy)-N-furfurylaniline, **5-10** (CDCl$_3$, 125.8 MHz)
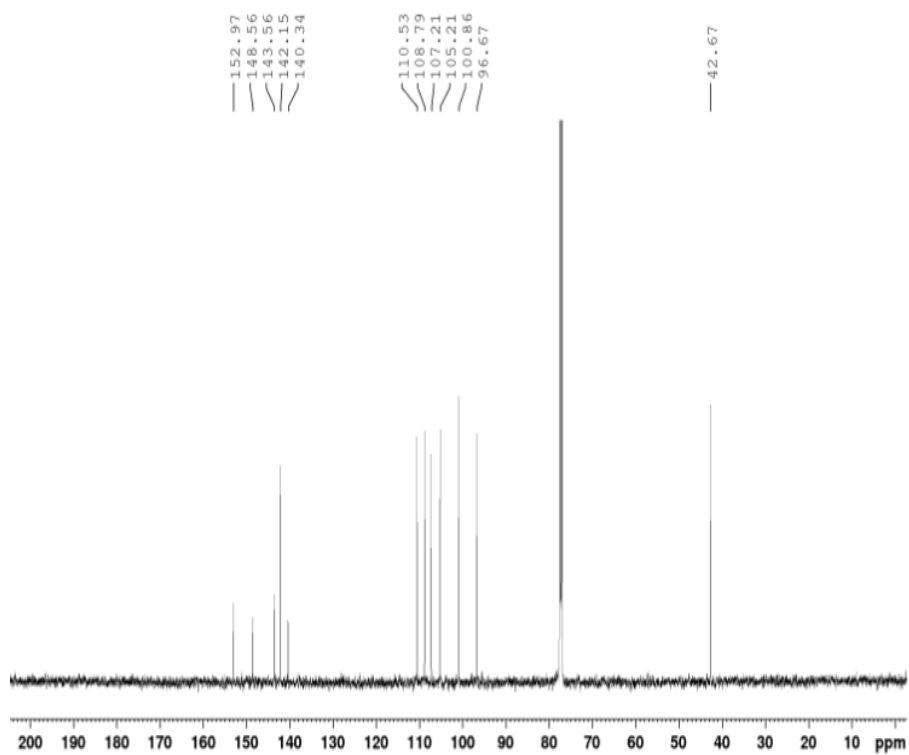
¹H NMR Spectrum of Piperidin-4-ylmethyl-(4-pyrrol-1-yl-phenyl)-amine, **5-11** (CDCl₃, 500.1 MHz)
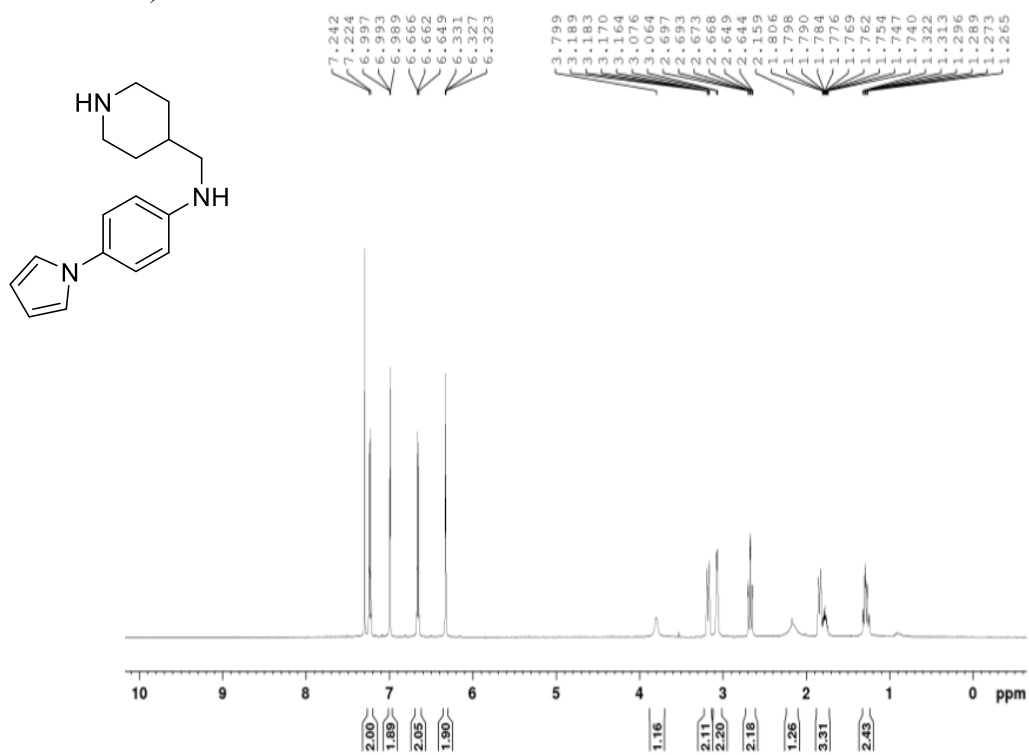
¹³C{¹H} NMR Spectrum of Piperidin-4-ylmethyl-(4-pyrrol-1-yl-phenyl)-amine, **5-11** (CDCl₃, 125.8 MHz)
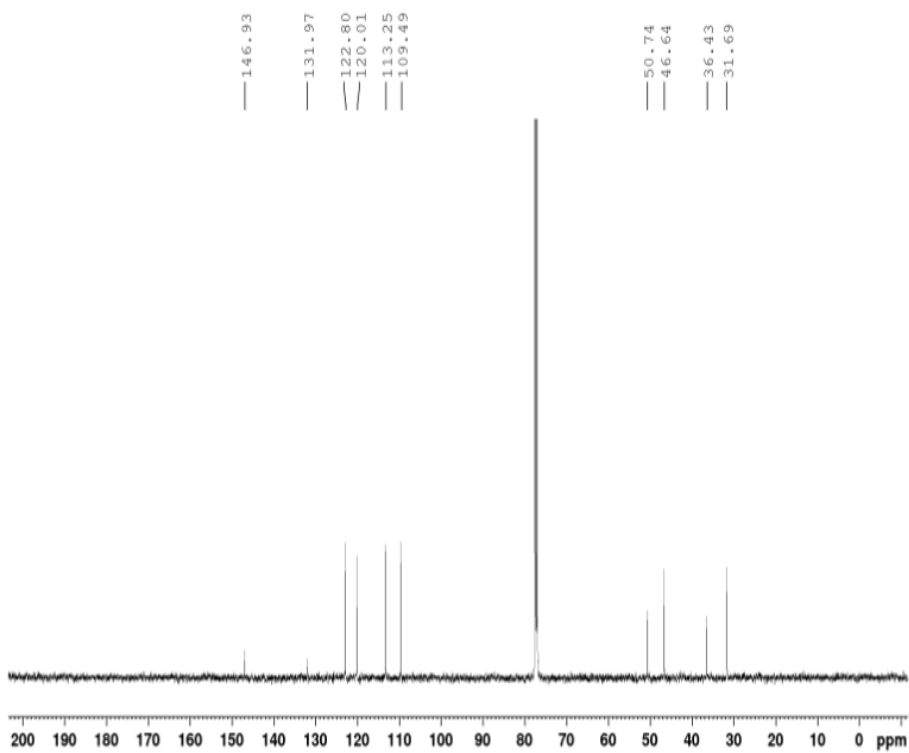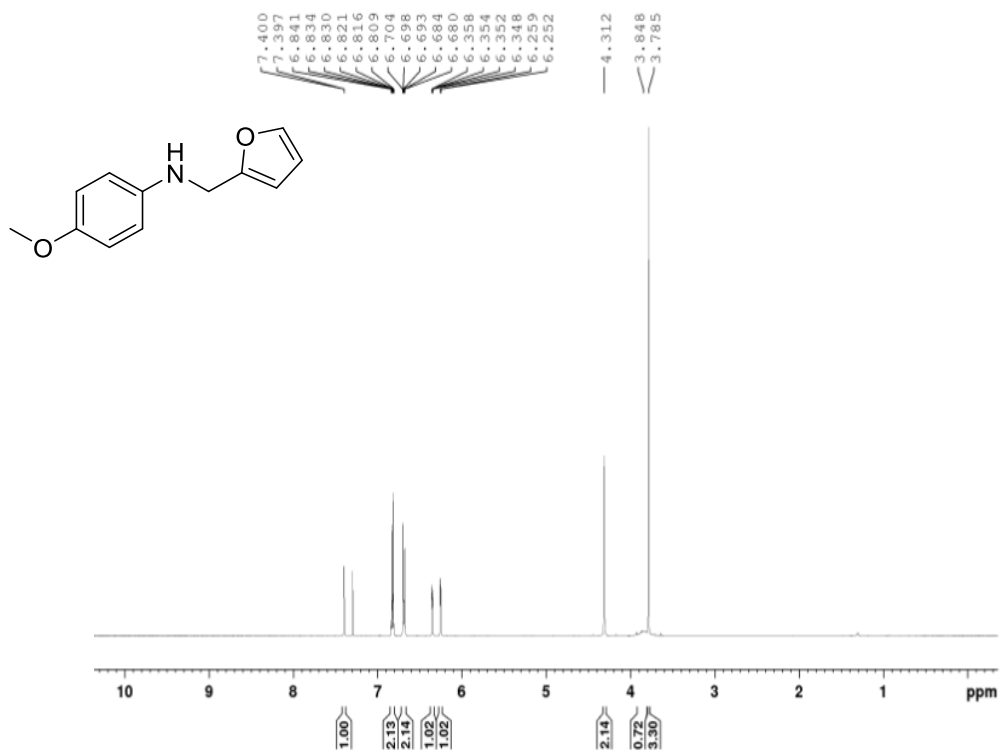
¹H NMR Spectrum of 2-methyl-*N*-(1-methylpropyl)-6-Benzothiazolamine, **5-12** (CDCl₃, 500.1 MHz)
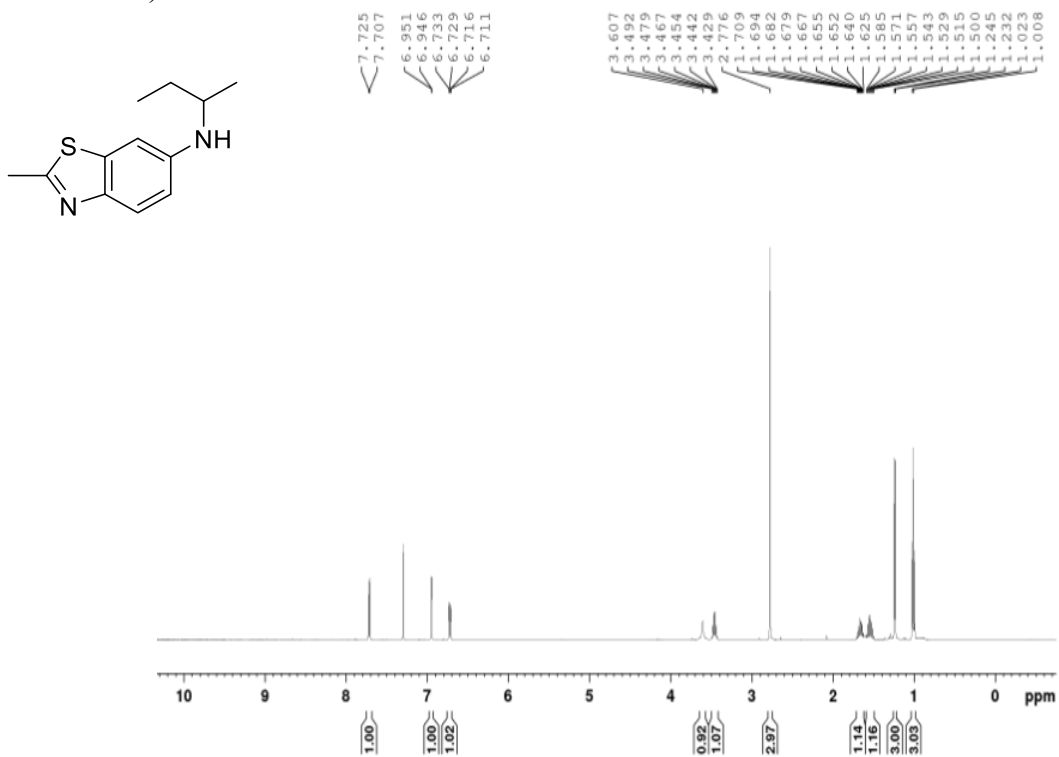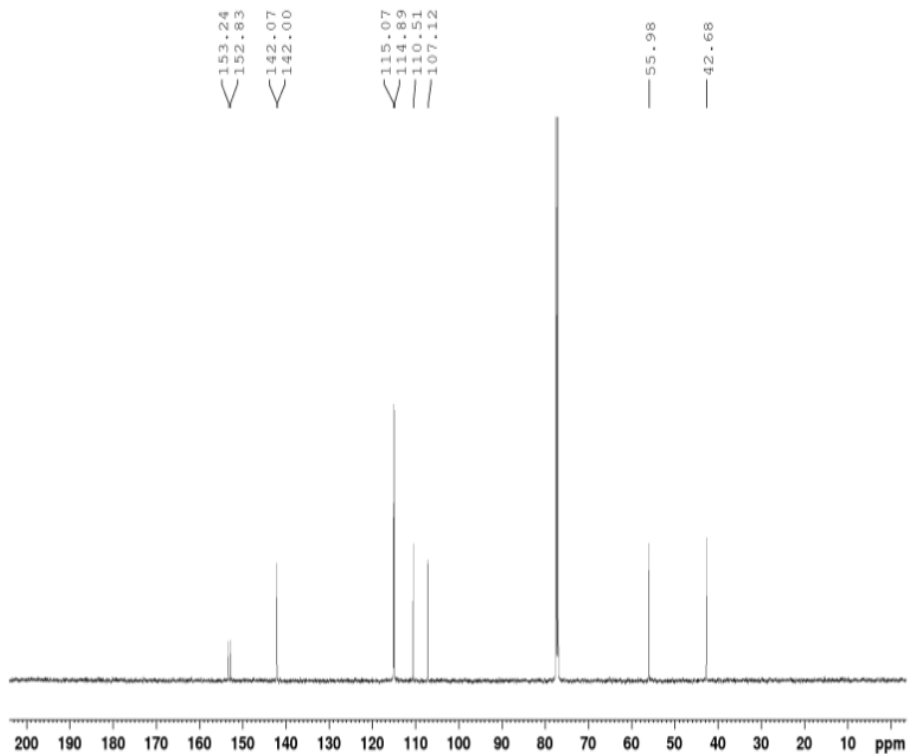

¹³C{¹H} NMR Spectrum of 2-methyl-*N*-(1-methylpropyl)-6-Benzothiazolamine, **5-12** (CDCl₃, 125.8 MHz)
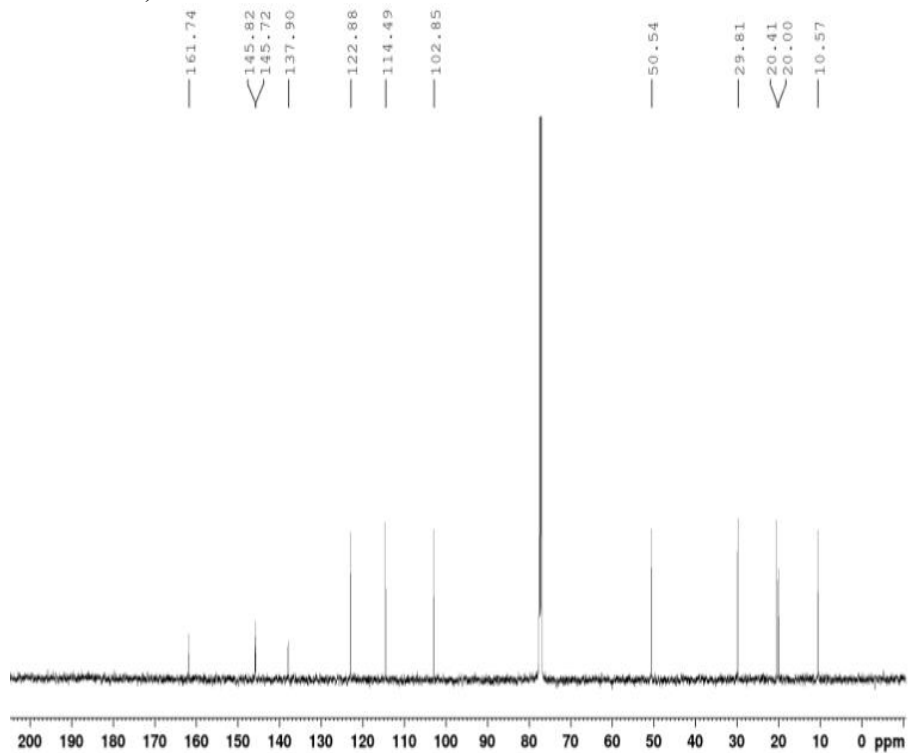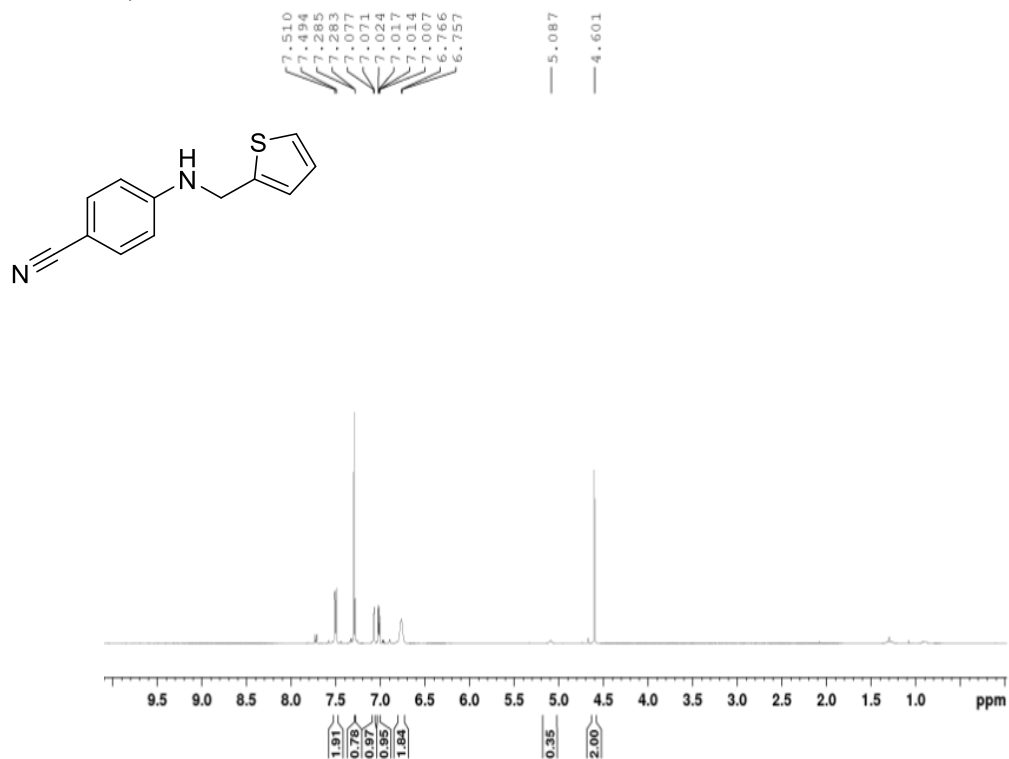
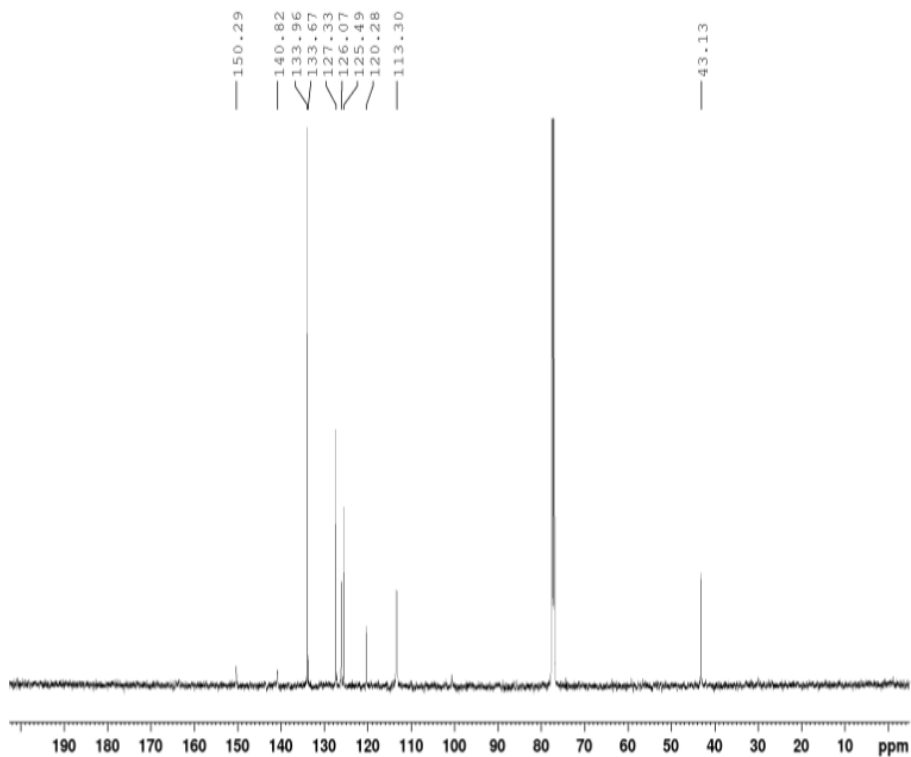^{1}H NMR Spectrum of Furan-2-ylmethyl-(4-methoyxy-phenyl)-amine, **5-13** (CDCl$_3$, 500.1 MHz)

^{13}C{^{1}H} NMR Spectrum of Furan-2-ylmethyl-(4-methoyxy-phenyl)-amine, **5-13** (CDCl$_3$, 125.8 MHz)

¹H NMR Spectrum of 4-[(Thiophen-2-ylmethyl)-amino]-benzonitrile, **5-14** (CDCl₃, 500.1 MHz)

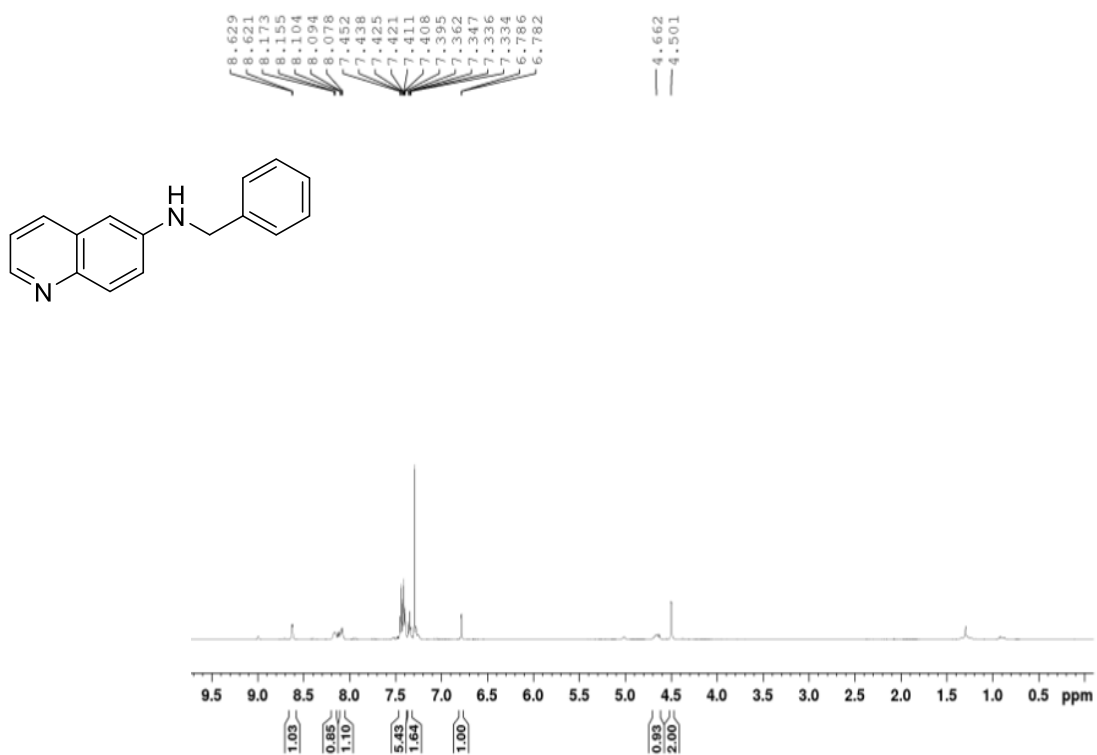¹³C{¹H} NMR Spectrum of 4-[(Thiophen-2-ylmethyl)-amino]-benzonitrile, **5-14** (CDCl₃, 125.8 MHz)

¹H NMR Spectrum of Benzyl-quinolin-6-yl-amine, **5-15** (CDCl₃, 500.1 MHz)

8.629
8.621
8.173
8.155
8.104
8.094
8.078
7.452
7.438
7.425
7.421
7.411
7.408
7.395
7.362
7.347
7.336
7.334
6.786
6.782

4.662
4.501

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

1.03 0.85 1.10 5.43 1.64 1.00 0.93 2.00

¹³C{¹H} NMR Spectrum of Benzyl-quinolin-6-yl-amine, **5-15** (CDCl₃, 125.8 MHz)
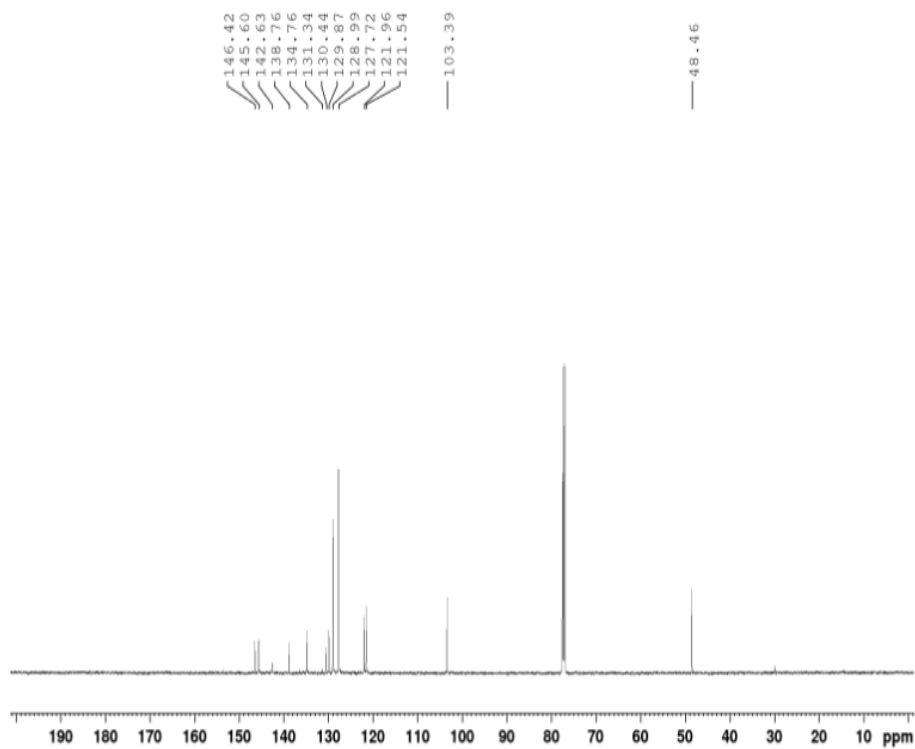
146.42
145.60
142.63
138.76
134.76
131.34
130.44
129.87
128.99
127.72
121.96
121.54

103.39

48.46

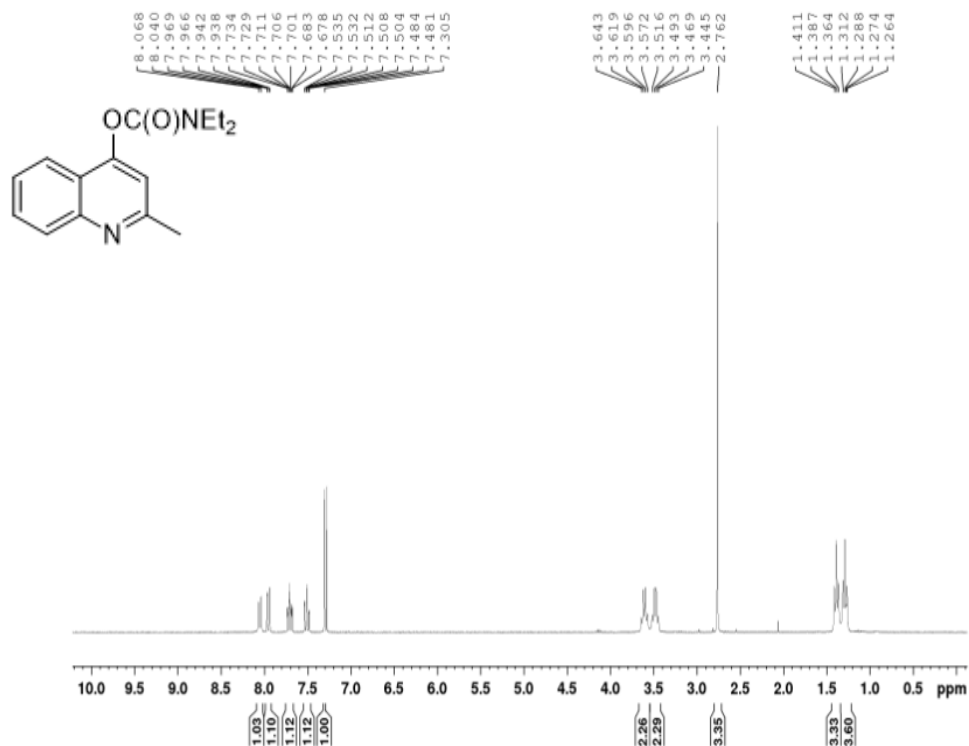190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

¹H NMR Spectrum of Furan-2-ylmethyl-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolane-2-yl)-phenyl]-amine, **5-16** (CDCl₃, 500.1 MHz)
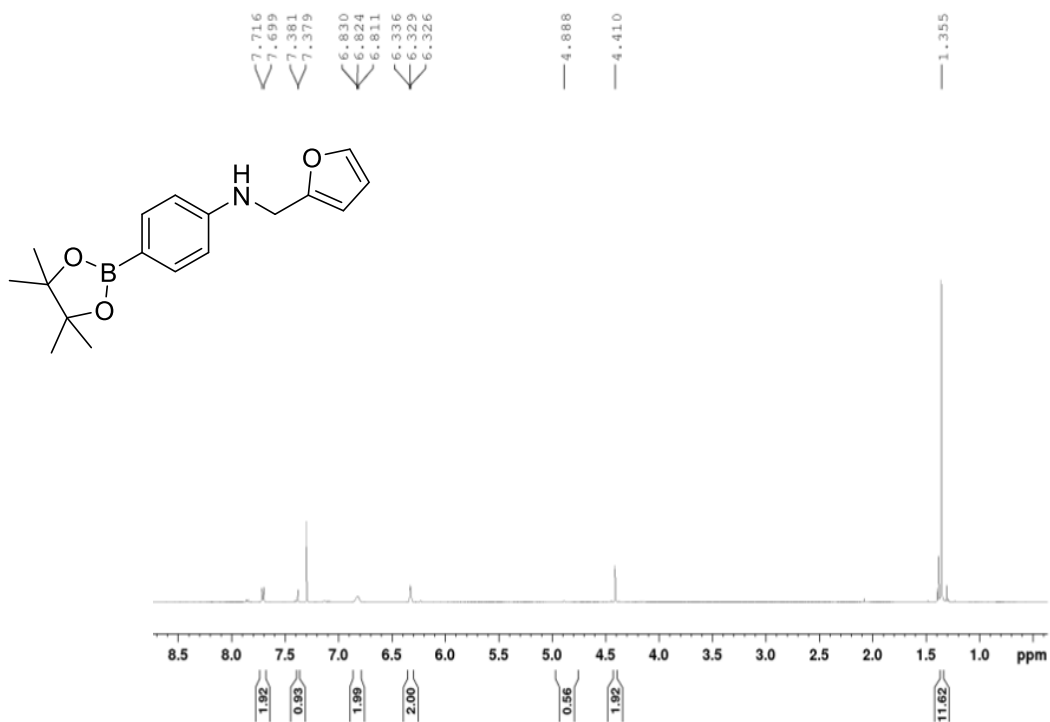
¹³C{¹H} NMR Spectrum of Furan-2-ylmethyl-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolane-2-yl)-phenyl]-amine, **5-16** (CDCl₃, 125.8 MHz)
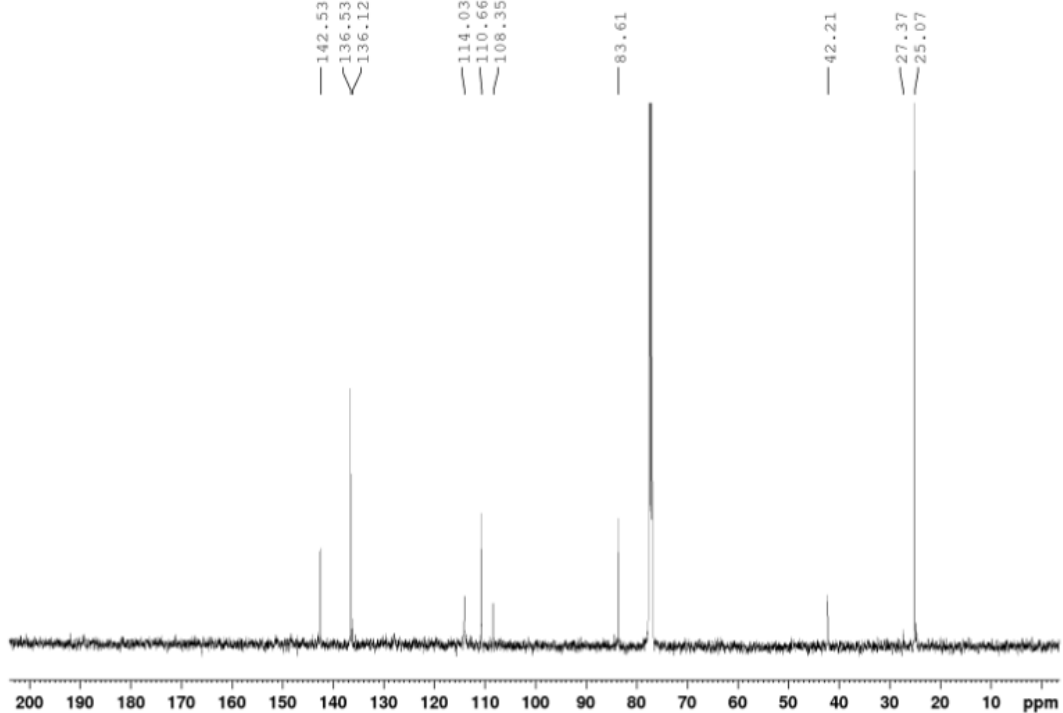
^{1}H NMR Spectrum of 2-Methylquinolin-4-yl diethylcarbamate, **SI-2** (CDCl$_3$, 500.1 MHz)

^{13}C{^{1}H} NMR Spectrum of 2-Methylquinolin-4-yl diethylcarbamate, **SI-2** (CDCl$_3$, 125.8 MHz)