1-1-2012

Palladium-Catalyzed Borylation And Cross-Coupling Of Aryl And Heteroaryl Halides Utilizing Dibora Derivatives

Sarah Little Jane Trice
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Abstract
ABSTRACT

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Sarah Little Jane Trice

Professor Gary A. Molander

Although much current research focuses on developing new boron reagents and identifying robust catalytic systems for the cross-coupling of these reagents, the fundamental preparations of the nucleophilic partners (i.e., boronic acids and derivatives) has been studied to a lesser extent. Most current methods to access boronic acids are indirect and require harsh conditions or expensive reagents. Therefore, we sought to provide a simple, efficient, and direct synthesis of arylboronic acids. Utilizing aryl halides and an underutilized reagent, tetrahydroxydiboron B2(OH)4, we developed a palladium-catalyzed method that now provides access to boronic acids in high yield. The method eliminates the necessity to employ the extremely wasteful and most commonly used source of boron, bis(pinacolato)diboron.

The first method developed focused on the borylation of the less expensive and more commercially available aryl chlorides. We demonstrated that most functional groups are well tolerated under the mild reaction conditions, providing the corresponding trifluoroborate in good to excellent yield for most subtrates. We also demonstrated that the crude boronic acid could be easily and efficiently converted to a myriad of boronate esters. The method was later extended to include aryl and heteroaryls bromides, chlorides, and triflates.

We went on to demonstrate that we could achieve similar results with the synthetic precursor to B2(OH)4, tetrakis(dimethylamino)diboron.

We also demonstrated that we could perform a one-pot, two-step borylation/Suzuki cross-coupling reaction.

And Finally, through the use of ethylene glycol as an additive to the borylation reaction with B2(OH)4, we were able to access heteroaryl substrates that were difficult to obtain in good yield with our optimized methods. Using this strategy, we were able to access one-pot borylation/Suzuki cross-coupled products between two heteroaryls in high yield.

Degree Type
Dissertation

Degree Name
Doctor of Philosophy (PhD)

Graduate Group
Chemistry

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A DISSERTATION

In

Chemistry

Presented to the Faculties of the University of Pennsylvania in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

2012

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PALLADIUM-CATALYZED BORYLATION AND CROSS-COUPLING OF ARYL AND HETEROARYL HALIDES UTILIZING DIBORA DERIVATIVES

To my Grandmother Margaret, who always told me to "look it up!"

ACKNOWLEDGEMENTS

I would first like to thank my advisor, Dr. Molander, who took a chance on taking me into his lab. His guidance and freedom allowed me to grow into the scientist I have become today and for that I am very grateful.

I would also like to thank my committee members, Patrick Walsh, Marisa Kozlowski, and Donna Huryn for their encouragement during my three short years under their care. Each one of them offered invaluable advice that helped guide me through my journey.

I would like to thank all of the past and present Molander group members. I learned a lot from each and every one of them. Interestingly, the most important things I took away from my experiences with them had little to do with chemistry and more about people and growing up. I would like to extend a special thank you to Dr. Steven Kennedy for his enthusiasm for SCIENCE! Throughout our time together we accomplished a lot and produced truly beautiful work and for that I am eternally grateful. I would also like to thank Livia Cavalcanti for reminding me to sing and to follow my heart. Dee and Andreea, I thank them for being themselves and never wavering. A special thanks goes to Rosaura Padilla for being a true friend from the beginning to the end. Ro will always be in my fondest memories of graduate school.

I had the great pleasure of mentoring an undergraduate student, Melvin Lim in my last year as a graduate student. Melvin taught me how to guide a student through the process of discovery and showed me that the most talented people merely need a gentle

hand along the way.

I would also like to thank Madeleine Jouillé for her kindness and support. I look forward to many more dinners and glasses of wine on her balcony.

I am very grateful for the Wharton School and my professors there that offered me a new perspective on the world and my place in it. My time spent in the classes at Wharton will become an essential piece to my success as I re-enter the business world at Merck. I would also like to thank the members of my Wharton Crew. The many miles on the river taught me about teamwork, dedication, and how to have fun and work hard at the same time.

I would not have been able to accomplish my doctoral degree without the support of Dr. Joseph Vacca. His belief in my talent and drive are what allowed me to pursue my dream of graduate school. I will never forget his kindness and guidance. I would also like to thank all of the past and present members of Merck Medicinal Chemistry, especially Pablo DeLeon for his constant cheering from the sidelines and for showcasing my methods to the department. He is truly an innovator.

Finally, I would like to thank my family, whose unwavering support helped me to stay on the path to follow my dreams. I would like to especially thank my grandparents for their love of learning. They instilled in me the desire to always find the answer and to never stop learning. I thank my mother for taking my education seriously and for teaching me take care of myself. Her sacrifices and constant support helped make me into the strong and confident woman I am today. Lastly, I would like to thank Jourdan. Without his love and support I may not have made it through this.

ABSTRACT

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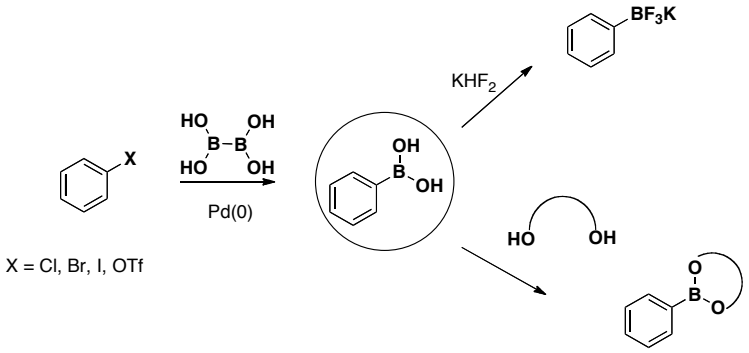

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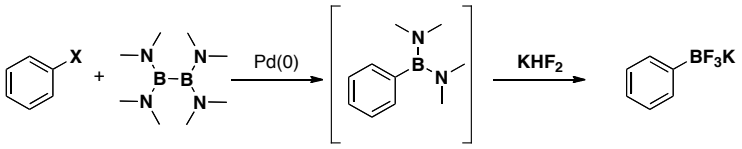

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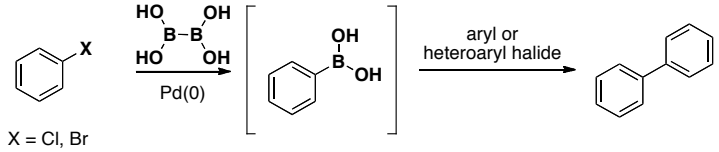

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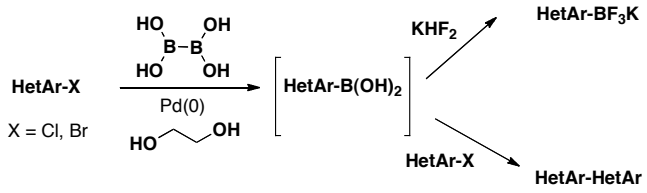

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LIST OF ABBREVIATIONS

δ	Chemical shift in parts per million
°C	Degrees Celcius
^{11}B	Boron nuclear magnetic resonance
^{13}C	Carbon nuclear magnetic resonance
^{19}F	Fluorine nuclear magnetic resonance
^{1}H	Proton nuclear magnetic resonance
aq	Aqueous
Ad	Adamantyl
AmPhos	Bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II)
BBA	Bis-boronic acid
BBr_3	Boron tribromide
biph	Biphenyl
BisPin, B_2Pin_2	Bis(pinacolato)diboron
$B(NMe_2)_3$	Dimethylaminoborane
br	Broad
$BrB(NMe_2)_2$	Bromobis(dimethylamino)boron
BrettPhos	2-(Dicyclohexylphosphino)-3,6-dimethoxy-2'-4'-6'-tri-*i*-propyl-1,1'-biphenyl
DTBPF	[1,1′-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II)
CH_2Cl_2	Dichloromethane

COD	1,5-Cyclooctadiene
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
DAN	1,8-Diaminonapthalene
DavePhos	2-Dicyclohexylphosphino-2′-(N,N-dimethylamino)biphenyl
dba	Dibenzylideneacetone
DMA	Dimethylacetamide
DMSO	Dimethylsulfoxide
Dppf	1,1′Bis(diphenylphosphino)ferrocene
Et	Ethyl
Et_3N	Triethylamine
EtOH	Ethanol
equiv	Equivalent(s)
G	Directing group
g	Gas
g	Gram
h	Hour(s)
HBPin	Pinacol borane
HPLC	High performance liquid chromatography
i	*iso*
Ir	Iridium

JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
k_n	Reaction rate constant
KOAc	Potassium acetate
Li	Lithium
M	Molar
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
Mg	Magnesium
MIDA	*N*-Methyliminodiacetic acid
min	Minutes
mL	Mililiter
NaO*t*-Bu	Sodium *tert*-butoxide
n-BuOH	Butanol
NMR	Nuclear magnetic resonance
o/n	Overnight
OMe	Methoxy
OMs	Mesylate
OTf	Triflate
p	para
Pd	Palladium
Ph	Phenyl
Pr	Propyl

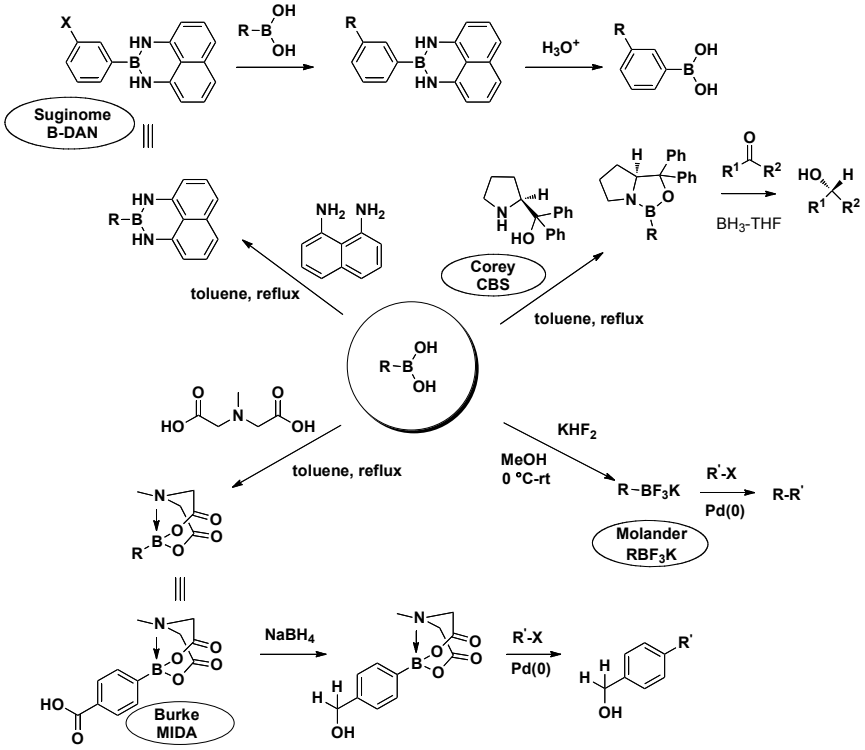
PTS	*p*-Toluenesulfonic acid
QPhos	1,2,3,4,5-Pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene
rt	Room temperature
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
SMC	Suzuki-Miyaura cross-coupling
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
t-amylOH	2-Methyl-2-butanol
t-Bu	*tert*-Butyl
t-BuOH	*tert*-Butanol
Tetrakis, $B_2(NMe_2)_4$	Tetrakis(dimethylamino)diboron
TsOH	*p*-Toluenesulfonic acid
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
XPhos-Pd-G1	XPhos precatalyst, first generation
XPhos-Pd-G2	XPhos precatalyst, second generation

Chapter 1. Overview of the Borylation of Aryl Halides Providing Ultimate Access to Boronic Acids

1.1 Introduction

Aryl boronic acids are key players in many reactions including 1,2-additions to carbonyl compounds,[1] 1,4-conjugate additions,[2] the Petasis-borono Mannich reaction,[3] the Chan-Lam coupling,[4] and the ever increasingly utilized Suzuki-Miyaura cross-coupling (SMC) reaction.[5,6] In addition to the direct use of boronic acids in reactions, they are often converted to other very useful reagents (Scheme 1.1). For example, the Burke group protects the boronic acid with *N*-methyliminodiacetic acid (MIDA), allowing functional group manipulation and subsequent cross-coupling.[7] Similarly Suginome protects a halide containing boronic acid with 1,8-diaminonaphthalene (B-DAN reagent).[8] The B-DAN group inhibits the boron moiety from reacting during the subsequent cross-coupling of the halide. After acid hydrolysis, the now deprotected boronic acid can undergo its own cross-coupling, providing ter-aryl compounds. Corey makes use of boronic acids en route to the very useful CBS reagent utilized in the asymmetric reduction of ketones.[9]

Scheme 1.1 Common Transformations of Boronic Acids



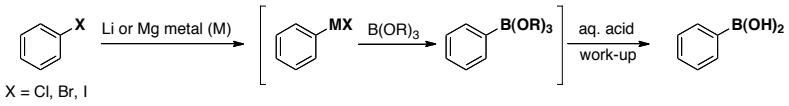
Interestingly, despite its widespread applicability and utility, very little effort has been focused on the synthesis of the boronic acid itself. Most groups, academic and industrial alike, still largely rely upon the commercial availability of the boronic acid. If the desired boronic acid is too expensive, or not commercially available, then a borylating method must be chosen to provide access to it.

1.2 Methods of Arylboronic Acid Synthesis: Metal/Halogen Exchange

The method most commonly employed en route to boronic acids is through metal/halogen exchange. The reaction utilizes aryl halides, lithium (Li) or magnesium (Mg) metals, and trialkylboranes [$B(OR)_3$] at low temperatures followed by an aqueous

acidic work-up (Equation1.1).[10,11]

Equation 1.1 Use of Metal/Halogen Exchange to Synthesize Boronic Acids



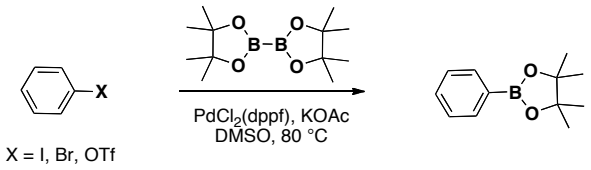
Although very useful, this method has several limitations. For example, low temperatures are required (-78 °C for Li with increases to -10 °C for Mg) while the trialkylborate is reacting with the organometallic intermediate. This low temperature is reported to help circumvent the formation of undesired side-products such as borinic acids and boranes.[10,11] Also, the method suffers from functional group incompatibility such that esters, nitriles, amines, alcohols and halide-containing alkyl groups cannot be used as they, too, will undergo transformations under the reaction conditions.

1.3 Miyaura Borylation of Aryl Halides and Pseudo Halides Utilizing Bis(pinacolato)diboron

Between 1995 and 1997, Miyaura et al. published the first palladium-catalyzed borylation of aryl bromides, iodides, and triflates, revolutionizing modern synthetic organic chemistry.[12,13] For the first time, pinacol boronate esters could be prepared without the use of harsh organometallic reagents, allowing access to numerous arylboron derivatives possessing sensitive functional groups that could not be realized through metal/halogen exchange. The method made use of bis(pinacolato)diboron (B_2Pin_2), $PdCl_2$(dppf), KOAc, in DMSO at 80 °C, providing the pinacol boronate ester in good

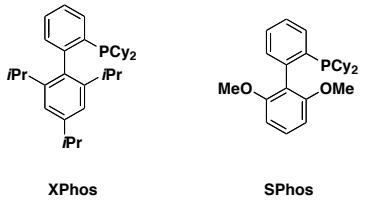
yield after column chromatography (Equation1.2).

Equation 1.2



Since Miyaura's seminal publication, others have contributed to expanding the scope further. For example, in 2007 Buchwald et al. were the first to demonstrate that aryl chlorides could efficiently undergo borylation.[14] Key to the success of this coupling was the use of newly developed dialkylphosphinobiphenyl ligands. The bulky nature of the ligand aids in the formation of the highly active LPd^0 complex, which is more reactive than the corresponding L_2Pd species (Figure 1.1).[15]

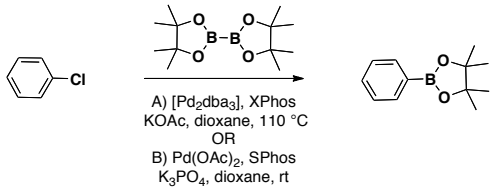
Figure 1.1 Dialkylphosphinobiphenyl Ligands XPhos and SPhos



The general method of Buchwald employed [Pd_2dba_3], XPhos, B_2Pin_2, and KOAc in dioxane at 110 °C. High temperatures were required to achieve high yields with reaction times ranging from 30 min to 5 h. Interestingly, when $Pd(OAc)_2$, K_3PO_4, and SPhos were

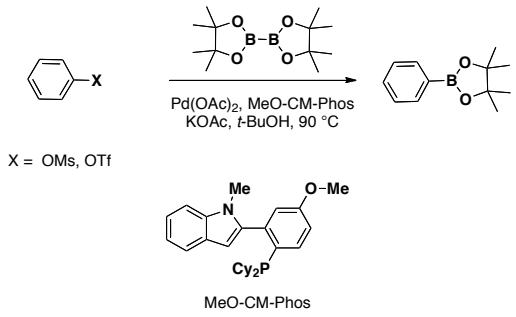
used instead of KOAc, [Pd_2dba_3], and XPhos, the borylation was carried out at room temperature. However, longer reactions times (24-48 h) were required (Equation1.3).

Equation 1.3



In 2011, Chow et al. described the Miyaura borylation of aryl mesylates and tosylates (Ar-OMs and Ar-OTs, respectively). Their method relied on the use of a newly designed catalyst MeO-CM-Phos along with $Pd(OAc)_2$, KOAc, and B_2Pin_2 in *t*-BuOH at 90 °C. They did not report the borylation of aryl halides under these reaction conditions (Equation 1.4).[16]

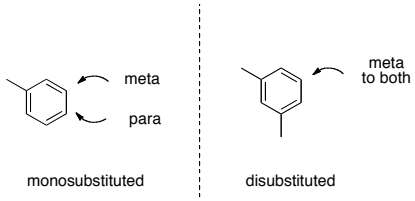
Equation 1.4



1.4 C-H Activation and Directed Metalation Utilizing Bis(pinacolato)diboron and Pinacolborane

Over the past 15 years, developments have been made allowing the use of C-H activation or directed metalation to construct C-B bonds.[17] These methods eliminate the need for halide-containing aryl substrates, and instead rely upon steric factors or directing groups to control regioselectivity. For either method, the most efficient catalyst system used in multiple methods is generated from iridium (Ir) catalysts, specifically $[Ir(OMe)(COD)]_2$ and $[Ir(COD)Cl]_2$, coupled with substituted bipyridyl ligands (such as di-*tert*-butylbipyridyl, dtbpy), B_2Pin_2 or pinacolborane (HBPin) in inert solvents (e.g. hexane, THF).[18,19] In the case of C-H activation, studies have demonstrated that borylation occurs preferentially at C-H bonds located in the meta- or para- position, while it does not occur at the more sterically hindered *ortho* position in substituted arenes.[19] There is also believed to be a weak electronic effect that aids in directing borylation to occur at these more electron-poor positions (Figure 1.2).[19]

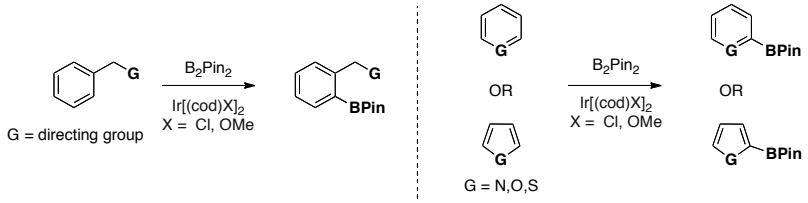
Figure 1.2 Borylation Patterns in C-H Activation



By contrast, directed metalation, as the name implies, requires the use of a directing group. This directing group can either be a substituent on the arene such as an

ester,[20] dimethylsilane,[21] or located in the ring itself in the form of a heteratom (N, O, S) within a heteroaryl system (Figure 1.3).[17] The latter allows the selective borylation at the 2-position of heteroaryl substrates through coordination of the metal center with the heteroatom (Figure 1.3).[22]

Figure 1.3 Use of a Directing Group for Borylation



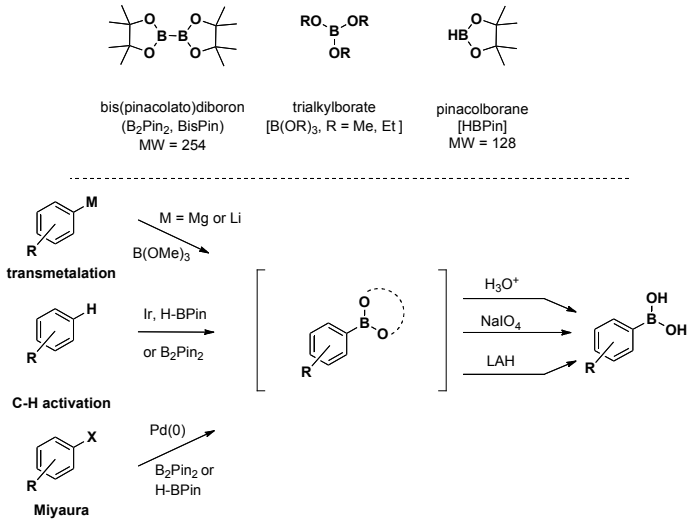
Although C-H activation has advanced at a rapid pace over the last 15 years, there are certain limitations that still remain, making it less attractive than the two aforementioned methods. For example, regioselectivity is controlled by steric factors or requires the use of a directing group, severely limiting the substrate scope. Additionally, iridium is one of the rarest metals in the world, making it an extremely expensive and potentially limited natural resource.

1.5 Hydrolysis of Common Boronate Esters to Obtain Boronic Acids

As described above, all methods currently used to access boronic acids utilize a boron source [B_2Pin_2, HBPin, $B(OR)_3$] that affords the corresponding product as a boronate ester. Therefore, to obtain the boronic acid, an additional step is required. Current ways to achieve this step include a two-step hydrolysis,[23-26] oxidation,[27-30]

reduction,[31] or transesterification.[32] All of these methods are intrinsically inefficient both in terms of atom economy and step economy. Additionally, they employ harsh reaction conditions ($NaIO_4$, diethanolamine, aq HCl, LAH, BBr_3), or require the use of excess polymer-supported boronic acid (Scheme 1.2).[32-34]

Scheme 1.2 Borylating Methods with Boron Sources Requiring Further Deprotection Methods to Obtain the Boronic Acid



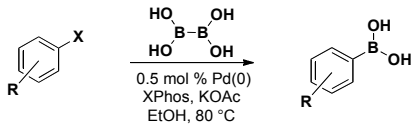
In most cases reported in the literature, the borylating reagent of choice en route to boronic acids is B_2Pin_2 (Scheme 1.2) because of its bench and thermal stability, relative ease of use, and high performance in borylation reactions. However, by modern standards, B_2Pin_2 is an extremely wasteful reagent, and dramatically reduces the overall efficiency of discovery and synthesis in both academic and industrial pursuits. Pinacol makes up >90% of the mass of B_2Pin_2. As it is not an integral component of the final

desired boronic acid partner and is typically removed, pinacol serves as an unwanted byproduct of current borylation reactions. With greater than 10 tons of B_2Pin_2 being produced annually, it is estimated that over 9 tons of pinacol are being used and disposed of needlessly each year.[35] In addition to the unnecessary generation of waste, if the boronic acid is required, once synthesized, the resulting pinacol boronates are often challenging to hydrolyze with the current methods. Even more problematic is the finding that pinacol, once released, is notoriously difficult to remove from reaction mixtures. Laborious extraction or distillation techniques are therefore required that further detract from the overall efficiency of the process.[34,36,37]

1.6 New Methods of Miyaura Borylation

Recently, we described a method that utilizes a relatively underutilized boron reagent in the chemical literature, tetrahydroxydiboron (diboronic acid, bis-boronic acid, BBA).[38] Through the use of BBA, boronic acids can be obtained directly without the need to perform a second deprotection step as required in all methods currently used (Equation1.5). The method is efficiently performed at low palladium catalyst loading (0.5 mol %) with XPhos and KOAc in EtOH at 80 °C.

Equation 1.5



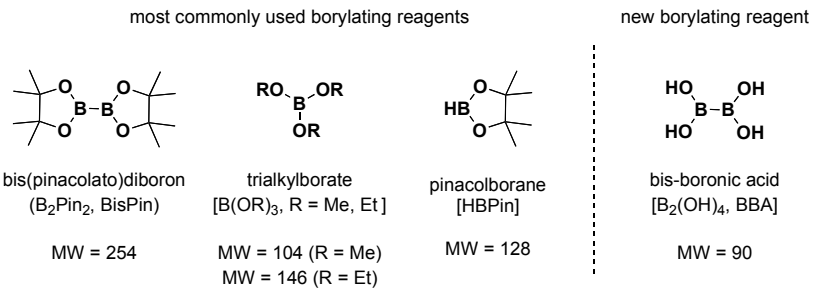
It should be noted that in 1999, a patent was granted to two researchers claiming the direct boronic acid synthesis of aryl iodides and bromides with multiple palladium sources, solvents, bases, and BBA.[39] They did not report isolated yields, and instead identified products through LCMS or GC analysis. Interestingly, they never published their work in the peer-reviewed chemical literature.

1.7 Conclusions

Arylboronic acids have emerged as increasingly important reagents in modern synthetic organic chemistry. However, few research efforts have been focused on the synthesis of this key player used in many synthetically useful transformations. Many boronic acids are commercially available; however, the most sought after and complex ones are typically expensive. Additionally, custom boronic acids, such as would be desired for drug discovery, often have to be synthesized. The most commonly used methods to synthesize boronic include metal/halogen exchange, C-H activation, and the palladium-catalyzed Miyaura borylation. These methods all require the use of B_2Pin_2, HBPin, or $B(OR)_3$ followed by a second deprotection step that can be tedious and detrimental to the overall yield (Figure 1.4). Most methods to make boronic acids utilize B_2Pin_2, which is an extremely wasteful reagent as only 20% of the mass of this material

ends up in the final boronic acid product. Recently, we reported a new method that makes use of BBA, and represents a much more atom economical method to carry out Miyaura borylation reactions (Figure 1.4). Through the use of BBA, boronic acids can be obtained directly, eliminating the need to perform laborious deprotection steps.

Figure 1.4 Old and New Borylating Reagents



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Chapter 2. Bis-Boronic Acid

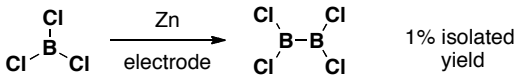
2.1 The Synthetic History of Bis-Boronic Acid

The history of bis-boronic acid (BBA) began in 1925 with the first reported synthesis of tetrachlorodiboron (B_2Cl_4) from boron trichloride (BCl_3) by Stock, Moore, and Schlesinger. Their method consisted of:

> "striking an arc across zinc electrodes immersed in liquid boron trichloride."

They reported a 1% yield with roughly 90% purity (Equation 2.1).[1]

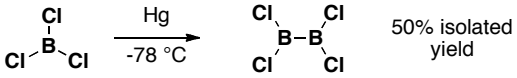
Equation 2.1



In 1949, three researchers from the University of Chicago, Wartik and Moore, in the laboratory of Schlesinger, reported a method seeking to improve upon that previously reported:

> "much better results have been obtained by passing gaseous BCl_3 at 1 to 2 mm. through a glow discharge established between mercury electrodes. The mercurous chloride and other non-volatile products remain. The volatile material is passed through a -78.5 °C trap which retains the tetrachlorodiborine" (Equation 2.2.).[2]

Equation 2.2

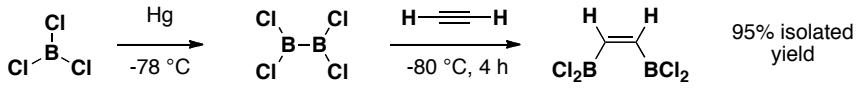


Over the course of the next five years, this team of researchers worked to improve the method. Although they could not avoid the use of mercury or electrodes they applied a process:

> "making it almost automatic, with the result that 5-10 g of the desired compound may be produced per week with very little attention.[3]"

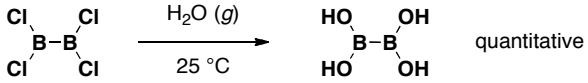
Published in an article directly preceding the account of this improved method, Dr. Schlesinger went on to demonstrate the addition of B_2Cl_4 across an alkyne. The method was presented in the literature as way to provide access to organoboron compounds (Equation 2.3).[4]

Equation 2.3



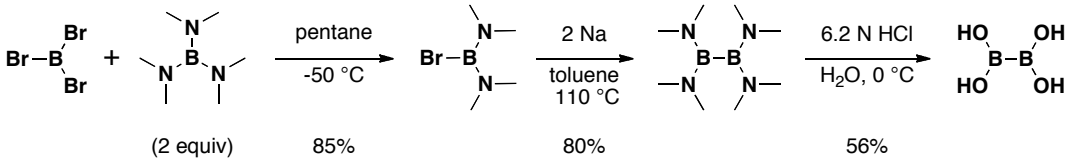
This result sparked immense interest in the synthetic community, and diboron compounds began to appear more frequently in the literature. Just one year later in 1955, Wartik and Moore reported the synthesis of BBA for the first time. Their method consisted of passing water vapor over B_2Cl_4 at room temperature (Equation 2.4).[5] Interestingly, they reported that they were not interested in BBA, but instead its decomposition product, boron monoxide.

Equation 2.4



In 1960, building upon the research of Wartik, Moore, and Schlesinger,[3] McKlosky and Brotherton of the Borax Chemical Company reported the first synthesis of tetrakis(dimethylamino)diboron [tetrakis, $B_2(NMe_2)_2$]. They reacted boron tribromide (BBr_3) and tris-(dimethylamino)-borane [$B(NMe_2)_3$] in pentane at reduced temperatures, affording bromobis(dimethylamino)boron $BrB(NMe_2)_2$ in 85% yield (Equation 2.5).[6] They then reacted $BrB(NMe_2)_2$ in toluene with molten sodium yielding tetrakis after distillation in 80% yield. One year later, in 1961, they went on to reported the synthesis of BBA from tetrakis and dilute aqueous acid (Equation 2.5).[7] Borax filed, and was later awarded a patent on the process in 1964 (Equation 2.5).[8]

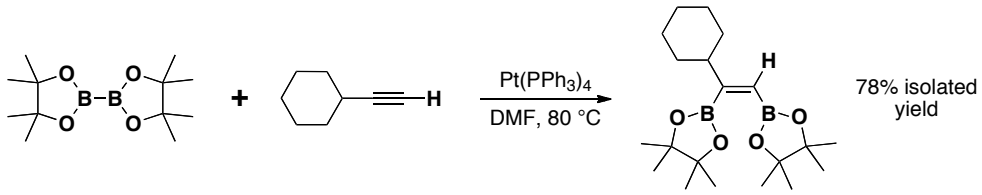
Equation 2.5



After the seminal publication and patent on the synthesis of BBA were reported in the 1960s, it essentially disappeared from the chemical literature. Twenty years later in 1984, the first synthesis of B_2Pin_2 was reported by Noth.[9] In 1993, Miyaura was the first to demonstrate the synthetic utility of B_2Pin_2 through the development of a platinum catalyzed diboration of alkynes (Equation 2.6).[10] Miyaura's method was a vast

improvement upon the previous work of Schlesinger in that B_2Pin_2 was reported to be a far more stable borylating source in comparison to B_2Cl_4, leading to compounds that could be isolated more readily.[4] Since Miyaura's publication, B_2Pin_2 became the borylating reagent of choice in modern synthetic organic chemistry and has largely remained so.

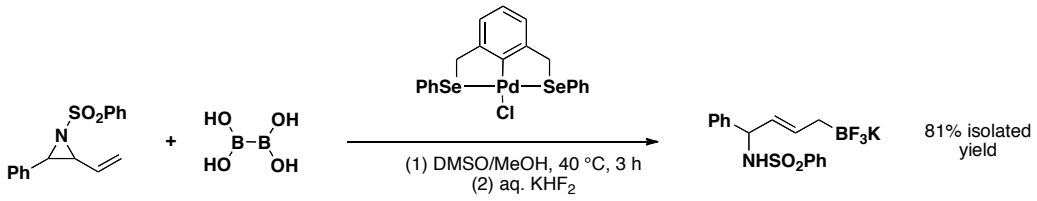
Equation 2.6



2.2 First Applications of Bis-Boronic Acid in the Chemical Literature

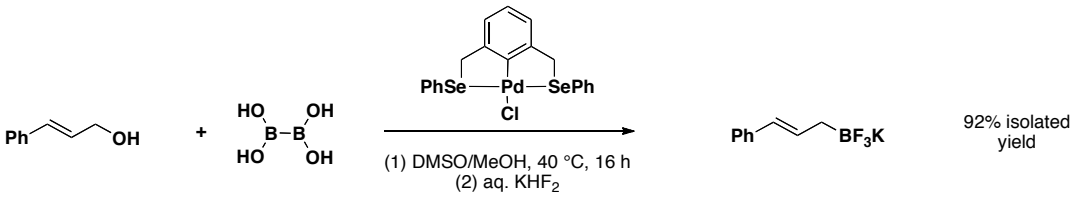
Nearly four decades after the first synthesis of BBA was reported by McKlosky, Brotherton, and Boone,[7] it re-emerged in the literature largely through the efforts of a research group at the University of Stockholm, Sweden. In 2005, Szabó et al. provided access to allylic boronic acids by reacting either vinyl cyclopropanes, or vinyl aziridines and allyl acetates in the presence of BBA and palladium pincer complexes.[11] When the allylic boronic acid products were concentrated in solvent or in the absence of solvent, they underwent complete decomposition. To enable isolation of the resulting allylborons, the boronic acid intermediates were directly converted to the corresponding trifluoroborates (Equation 2.7).

Equation 2.7



In 2006, a similar method was devised to convert allylic alcohols into the corresponding boronic acids.[12] The method tolerates a variety of substitution patterns, including branched and linear alcohols with high regioselectivity. Key to the success of the reaction was low reaction temperatures (20-40 °C) as allyl hydroxyl boronates can readily undergo hydroxyl boronate elimination to give the corresponding 1,3-diene. The boronic acid products were similarly immediately converted to the corresponding trifluoroborates in order to preserve the C-B bond (Equation 2.8).

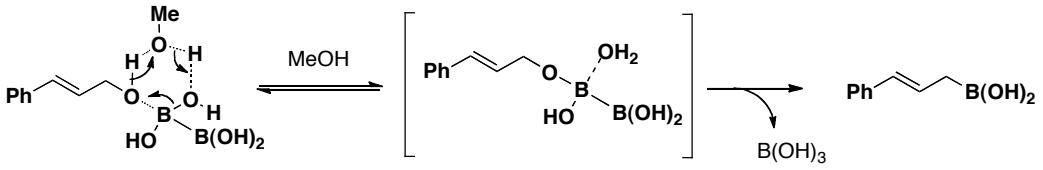
Equation 2.8



Additionally, they found that the mixture of DMSO/MeOH as solvent was key to enhanced solubility, aiding in the attainment of high yields and reasonable reaction times. They further propose that the mechanism of the borylation occurs through a 6-membered transition structure between BBA, the allylic alcohol, and a molecule of MeOH. Through this mechanism it was proposed that MeOH makes the hydroxyl group a better leaving

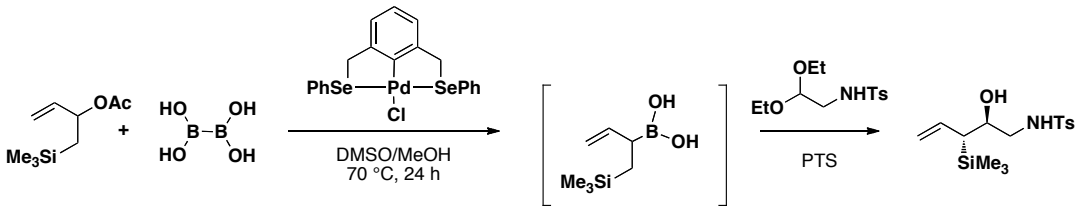
group through the formation of water, and that the coordination of this water molecule helps the subsequent cleavage of the B-B bond leading to the product (Equation 2.9).

Equation 2.9



In 2008, Szabó extended the method to the one-pot synthesis of α-amino acids and homoallyl alcohols from allylic alcohol, amine, aldehyde, and ketone starting materials. Excellent regio- and stereoselectivity was achieved over the two-step process and provided the products in good to excellent yield for all substrates reported (Equation 2.10).

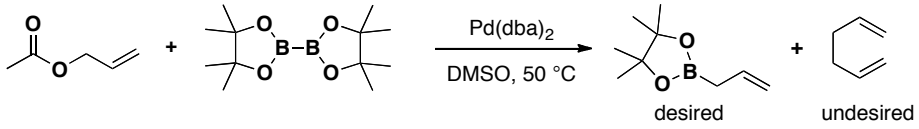
Equation 2.10



Despite the enormous utility of the aforementioned reactions developed by Szabo, neither BBA nor the palladium pincer complexes were commercially available, greatly inhibiting their use in the broader synthetic community. Because of this limitation, the

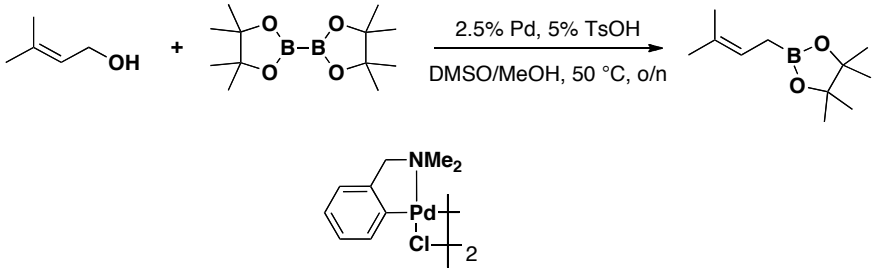
most common method used to access allyl boronates remained one developed by Miyaura a decade earlier and involved the reaction of allylic acetates or carbonates with B_2Pin_2 and $Pd(dba)_2$.[13] Unfortunately, a large drawback to this method is dimerization, affording 1,5-dienes that can compete with the desired pathway (Equation 2.11). This undesired side-product not only consumes the starting material, but inhibits product formation through complexation with the metal catalyst.

Equation 2.11



To provide a more reasonable solution to the poor availability of BBA and the palladium pincer complexes, and to provide a way to avoid formation of 1,5-dienes using the Miyaura method, Szabo developed a new process with commercially available B_2Pin_2 and di-μ-chlorobis{2-[(dimethylamino)methyl]phenyl-C,N}dipalladium(II) (Equation 2.12). With this new method in place, BBA disappeared once more from the chemical literature.

Equation 2.12

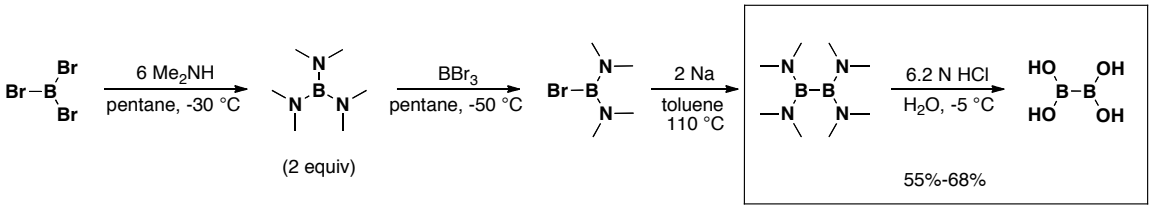


di-μ-chlorobis {2-[(dimethylamino)methyl]
phenyl-C,N} dipalladium(II)

2.3 Synthesis of Bis-Boronic Acid

At the onset of our endeavor to provide a direct method of attaining arylboronic acids through the use of BBA, it was still not commercially available, and therefore its synthesis was required. The robust synthesis of BBA developed by McKlosky, Brotherton, and Boone[7] later become the general route to synthesize B_2Pin_2, differing only in the last step, and therefore a very reliable synthesis is available.[14] Thankfully tetrakis(dimethylamino)diborane (tetrakis), the precursor to BBA, was generously supplied to our lab allowing us to focus solely on the optimization of the hydrolysis. The final optimized method required the cooling of water to -1 °C followed by addition of tetrakis dropwise, being careful to constantly maintain the temperature. Then 6.2 N HCl was added dropwise at the rate at which the internal temperature could be maintained at -5 °C. If the temperature ever rose more than 2-3 degrees, there was an immediate exotherm, and only boric acid was recovered. Key to the success of the reaction was the maintenance of the internal temperature of the reaction.

Scheme 2.1 Synthesis of BBA



The reaction was run on increasing large scale, with the final synthesis performed starting with 20 g of tetrakis. Even though BBA was still not commercially available during substrate scope exploration, it was synthesized on industrial scale and provided to us to facilitate our method development.[15]

2.4 Conclusions

The synthesis of BBA came to fruition largely through the research efforts of a handful of scientist in the late 1940s to the early 1960s. Upon the synthesis of BBA by McKloskey, Brotherton, and Boone in 1961, it largely disappeared from the chemical literature, only to re-emerge at the turn of the twenty-first century. Szabó was the first to demonstrate the synthetic utility of BBA through its use with palladium pincer catalysts to synthesize allyl boronic acids in high yield and excellent regio- and stereocontrol. His method represented a great improvement to older, more inefficient methods. However, beacuase BBA and the pincer complexes were not commercially available, the method went relatively unused. Szabó later went on to developed a modified version of his method that utilized a commercially available palladium source and B_2Pin_2.

At the start of our research, BBA was still not commercially available, and so its

synthesis was required. The synthesis of BBA largely remained unchanged from that reported by McKloskey, Brotherton, and Boone. The synthesis is the same as that of B_2Pin_2, differing only in the last step, providing a reliable synthetic pathway to follow. The synthesis, however is laborious, dangerous, and in our hands low yielding. With the donation of first tetrakis and then BBA to our laboratory, the pace of discovery greatly improved. Currently, largely because of our research efforts, BBA is now commercially available.

2.5 References

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(15) BBA was synthesized and generously provided to us by BASF.

Chapter 3: The Synthesis of Boronic Acids from Aryl Halides and Pseudo Halides Utilizing BBA

3.1 Introduction

The palladium-catalyzed Suzuki-Miyaura cross-coupling (SMC) reaction has become one of the most widely applied methods for C-C bond construction in current synthetic organic chemistry.[1,2] The ability to synthesize custom boronic acids using methods such as metal/halogen exchange, C-H activation, and the Miyaura borylation have provided the synthetic community reliable access to a wealth of biologically active and structurally diverse biaryl motifs.[3] Most research efforts surrounding the SMC reaction have focused on improving the scope of the reaction through identification of new metal/ligand components. Little research however, has been focused on improving the process of boronic acid synthesis.

3.2 Method Development of the Palladium-Catalyzed Direct Boronic Acid Synthesis Utilizing BBA

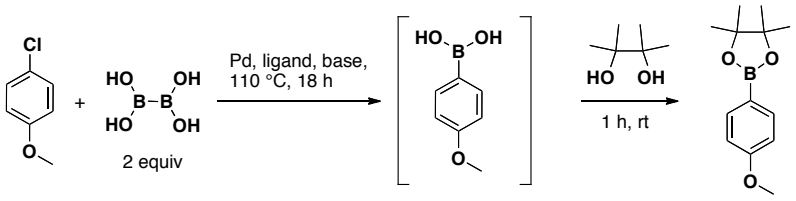
The palladium-catalyzed Miyaura borylation remains the most functionally group tolerant and operationally straightforward means to access boronic acids.[4,5] Therefore, any new method in their synthesis would have to be an improvement on this existing process. Clearly, one major improvement would be the removal of pinacol from the most commonly used borylating reagent bis(pinacolato)diboron (B_2Pin_2). This would allow direct access to the boronic acid and needless waste generation in the form of pinacol could be avoided. Further, the use of B_2Pin_2 for the Miyarua borylation most often

requires refluxing temperatures in ethereal solvents like 1,4-dioxane or THF, so a new process that would avoid these conditions would be desired. Additionally, any process that would afford the boronic after simple work-up and avoid the necessity to perform column chromatography followed by a laborious deprotection step would minimize waste and research efforts.

3.2.1 Method Development: High Throughput Experimentation

To find optimal conditions for the palladium-catalyzed borylation of aryl halides, we utilized microscale high throughput experimentation (HTE) through collaboration with Merck Research Laboratories. This technique makes use of a 96-well reaction plate, allowing parallel synthesis under an inert atmosphere. The reactions are efficiently run on 10 μmol scale, mimicking that of a bench-scale reaction. We began our studies with aryl chlorides because of their inexpensive nature and commercial availability compared to their iodo– and bromo–counterparts. We rationalized that starting with 4-chloroanisole would provide a reasonable test substrate as its electron-rich nature deactivates it toward borylation. Based upon current Miyaura borylating precedents found in the literature, an initial screen was designed looking at a variety of solvents (0.1 M), palladium sources (2.5 mol %), ligands, and bases (3 equiv) at 110 °C for 18 h. (Table 3.1). At the end of the 18 h reaction period, pinacol was added to convert any boronic acid to the boronate ester for ease in product identification. Product formation was monitored through the use of HPLC analysis against 4,4'-di-*tert*-butylbiphenyl as an internal standard.

Table 3.1 First HTE Screen with 4-Chloroanisole



Pd (2.5 mol %)	ligand	solvent (0.1 M)	base (3 equiv)
$Pd(OAc)_2$ $Pd(dba)_3$	RuPhos XPhos SPhos DTBPF	DMA toluene CPME CH_3CN	Et_3N KOAc

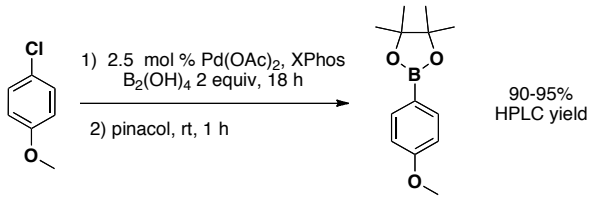
The first HTE screen provided the desired product in roughly 25% yield as compared to internal standard by HPLC analysis. This screen demonstrated that Pd(II) was a superior source of catalyst, as $Pd(OAc)_2$ clearly outperformed $Pd(dba)_3$. Both RuPhos and XPhos ligands led to the highest amounts of product, and polar DMA was the only suitable solvent tested. In terms of base, both an organic (Et_3N) and inorganic base (KOAc) provided product. With these results in hand, a second screen was designed incorporating more palladium sources, ligands, alcohol solvents, and bases (Table 3.2).

Table 3.2 Second HTE Screen

Pd (2.5 mol %)	ligand	solvent (0.1 M)	base (3 equiv)
$Pd(OAc)_2$ Pd_2dba_3 $[Pd(allyl)Cl]_2$ $Pd(acac)_2$	DavePhos RuPhos XPhos *t*Bu_3P-HBF_4 QPhos JohnPhos SPhos Me_4-*t*Bu-XPhos Ad_2PBu BrettPhos AmPhos	*t*-amylOH DMA MeCN *n*BuOH	1,8-diazabicyclo-[5.4.0]-undec-7-ene Et_3N 1,2,2,6,6-pentamethylpipiridine DABCO 1,1,3,3-tetramethylguanidine *i*Pr_2NEt KOAc, anhydrous NH_4OAc

In the second 96-reaction screen, the addition of alcohol solvents dramatically increased the yield, with the best performing combinations affording nearly 70% yield as compared to internal standard. $Pd(OAc)_2$ continued to be the best catalyst with both XPhos and Ad_2PBu (CatCXium A) ligands providing good results while KOAc and Et_3N were the most effective bases. A third screen was performed to assess the effect of differing BBA equivalents (1.5 equiv versus 2.0), inclusion of more alcohol solvents (*i*-PrOH and EtOH) while comparing the two ligands XPhos and Ad_2PBu (CataCXium A). The combination of 2.5 mol % $Pd(OAc)_2$ with XPhos and either Et_3N or KOAc in isopropanol (*i*-PrOH) or EtOH with 2 equivalents of BBA provided improved yields between 80-85%. With these semi-optimized reaction conditions in hand, we then focused the final screen on solvent concentration, ligand to catalyst ratio and temperatures, while maintaining the use of $Pd(OAc)_2$, XPhos and BBA amounts as determined in the third screen (Table 3.3).

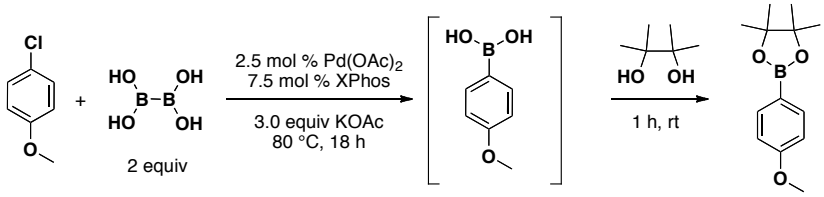
Table 3.3 Final HTE Screen



ligand : catalyst	solvent	concentration	base	equiv	temperature
1:1 2:1 3:1	*i*-PrOH	0.1 M 0.3 M	KOAc	1.5 3.0	65 °C 80 °C 105 °C
	EtOH	0.1 M 0.3 M	Et_3N	1.5 3.0	

Based upon the final HTE screen, optimized reaction conditions included the use of EtOH, as it led to lower amounts of protodeboronation than *i*-PrOH. When EtOH was employed as solvent, KOAc (3 equiv) was a better base and therefore was chosen. The rest of the components included $Pd(OAc)_2$ (2.5 mol %), 7.5 mol % XPhos (3:1 ligand to catalyst ratio), and 2 equiv BBA for 18 hours at 80 °C (Equation 3.1).

Equation 3.1



3.2.2 Bench Scale-Up with Optimized HTE Conditions

With these optimized conditions, the first attempt at scaling-up the reaction in the laboratory was undertaken. Much to our disappointment, the results were not reproducible, and the reaction did not lead to the formation of any product. Upon further analysis by ^{11}B NMR studies, it was determined that $Pd(OAc)_2$ [and thus Pd(II)] very rapidly decomposes BBA to boric acid when dissolved in EtOH (Figures 3.1-3.3). Note that there is a small amount of boric acid in the BBA (Figure 3.2) as this is the decomposition product that occurs slowly over time with bench storage.

Figure 3.1 ^{11}B NMR Spectrum of Boric Acid (10 mg) Dissolved in EtOH (1 mL)

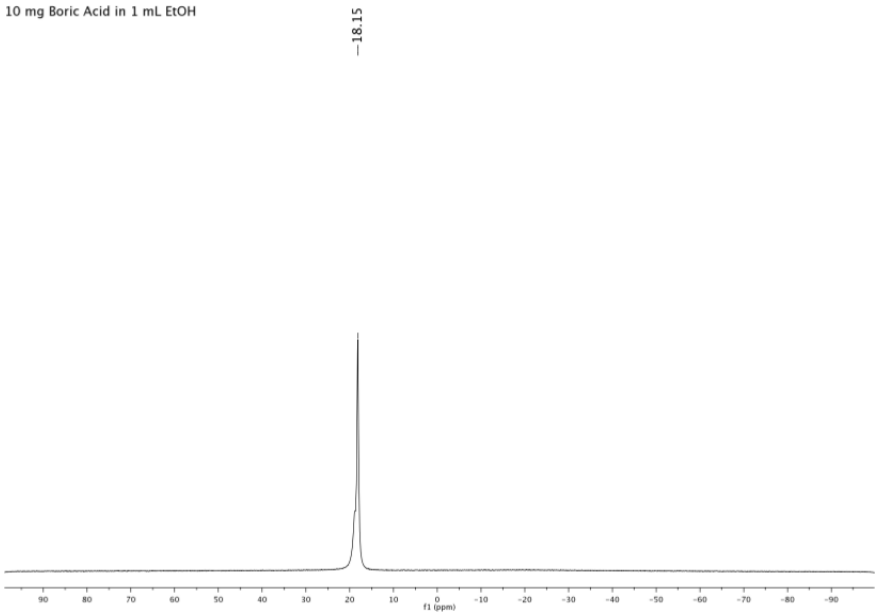


Figure 3.2 ^{11}B NMR Spectrum of BBA (10 mg) Dissolved in EtOH (1 mL)

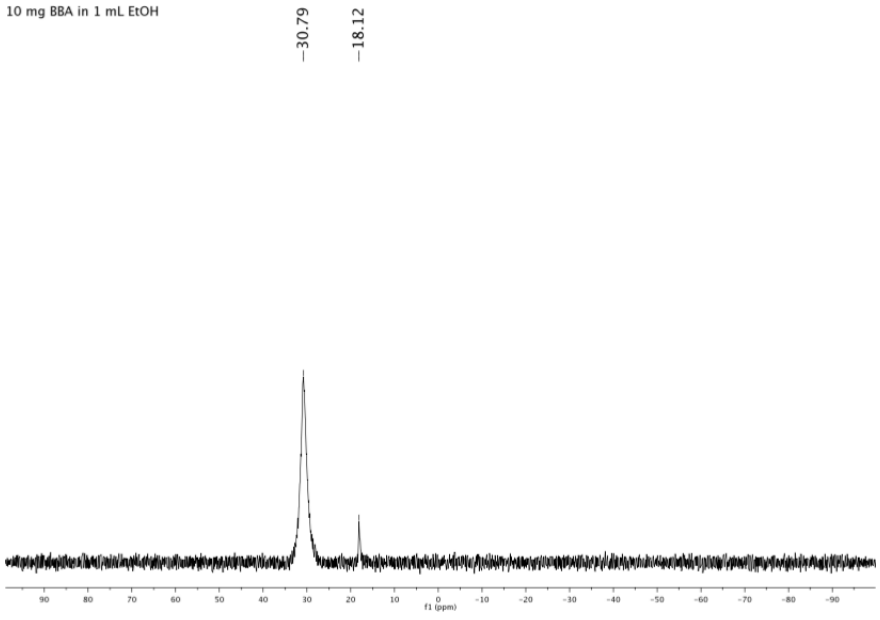
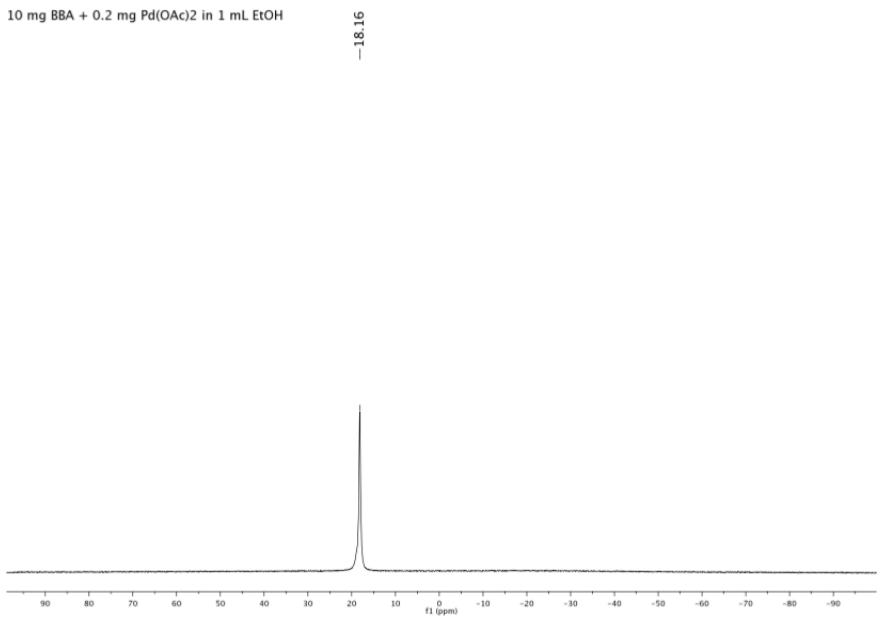


Figure 3.3 ^{11}B NMR Spectrum of BBA (10 mg) Dissolved in EtOH (1 mL) in the Presence of $Pd(OAc)_2$ (0.2 mg) for 15 Minutes. Complete Decomposition of BBA to Boric Acid.

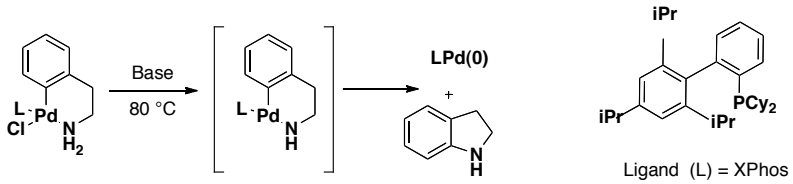


To elucidate the reason for the difference between the microscale HTE and bench method, every step in the screening process was carefully analyzed. One of the timesaving elements of HTE is the use of stock solutions to dose small amounts of catalyst, ligand, and base to the 96-well plate effectively in a consistent manner via a multichannel pipette. Typically, the solvents required to solubilize these components fully are not the solvents being screened and thus their removal is required. Indeed for our purposes, the ligands, catalyst, and bases were dosed to the plate in this manner, and the solvent was removed under high vacuum using a Genovac. During this process it was hypothesized that Pd(II) underwent the requisite reduction in the presence of ligand and base, such that Pd(0) was formed in the process (Equation 3.2).

Equation 3.2

Further probing experiments revealed that the active ligated Pd(0) catalyst could effectively be preformed by heating the Pd(II) source, ligand, and KOAc together for 1 h at 65 ºC in EtOH before the addition of BBA and the aryl chloride. This preformation greatly reduced the decomposition of BBA and thus confirmed the requirement of the preformation of the Pd(0) catalyst (aging at elevated temperatures in the presence of the ligand and base) to provide a sufficiently stable system for the reaction to occur. In light of this discovery, we returned to screening to ensure that we had the most efficient system. During this process, we tested a new "pre-activated", bench-stable catalyst reported by Buchwald that undergoes rapid transformation to the active Pd(0) species in the presence of catalytic amounts of strong base (NaO*t*-Bu) at elevated temperatures (Equation 3.3).[6] The catalyst, as shown in Equation 3.3 with L = XPhos, has since been named XPhos-Pd-G1 (XPhos ligated palladium-precatalyst, first generation).

Equation 3.3

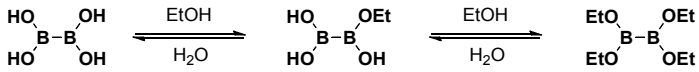


Use of this catalyst allowed the borylation to occur in an operationally simplified

manner, as there was no requirement to preactivate the catalyst through separate heating in EtOH with ligand and base. XPhos-Pd-G1 also proved to be a more efficient catalyst as 1 mol % Pd was found to be sufficient as opposed to 2.5 mol % when $Pd(OAc)_2$ was used. Further, BBA amounts could be reduced from 2 equivalents to 1.5 equivalents without a loss in yield. This preactivated catalyst was later commercialized and conveniently comes with the XPhos ligand (amongst others) already incorporated into the molecule.[6] It is currently available under the name XPhos-Pd-G1.

It is also hypothesized that the use of alcohol solvents, most notably ethanol, was optimal for solubility, stability, and reactivity, as BBA is most likely in equilibrium with various ethyl esters, providing some similarity to B_2Pin_2 (Equation 3.4). Although original screening conditions used anhydrous EtOH, further experiments showed that this was unnecessary, so going forward non-anhydrous, thoroughly degassed (nitrogen, 1 h) 200 proof EtOH was used.

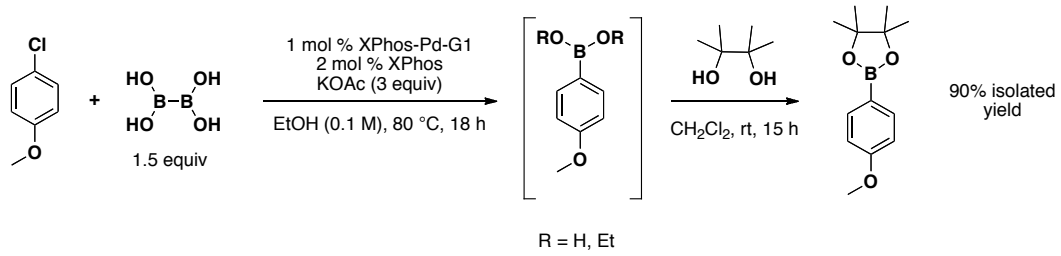
Equation 3.4



With screening complete and a stable system in place, optimized reaction conditions were achieved. As XPhos-Pd-G1 and all other reagents are bench stable, they are simply weighed on a bench top balance, the vessel sealed (with a cap fitted for a microwave reaction flask), purged with N_2, followed by the addition of EtOH. To provide full proof-of-concept, the reaction was run on scale (1.5 mmol), converted to the pinacol

ester, and purified by flash chromatography, providing the corresponding product in 90% isolated yield (Equation 3.5).

Equation 3.5

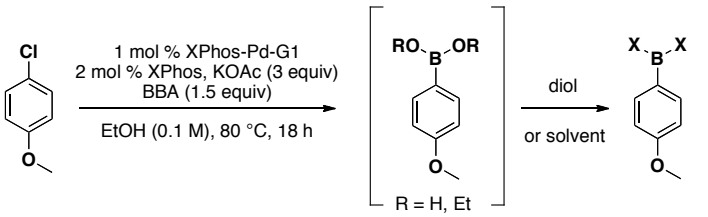


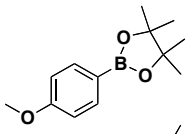
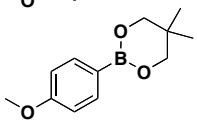
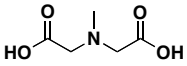
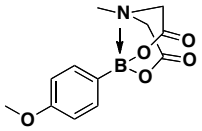
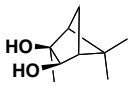
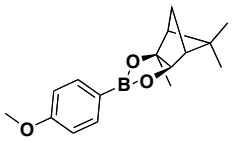
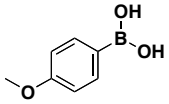
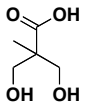
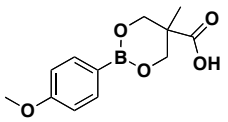
3.3 Results and Discussion

3.3.1 Palladium-Catalyzed Borylation of Aryl Chlorides with XPhos-Pd-G1

Utilizing the optimized protocol, a diverse set of boronate esters were synthesized. After acidic work-up, the crude mixture was taken up in CH_2Cl_2, the diol was added, and the reaction was stirred at room temperature for 15 h. All esters were isolated in good to excellent yield (Table 3.4). The boronic acid could also be easily isolated in good yield after work-up and a hexanes wash of the resulting solid (Table 3.4, entry 5).

Table 3.4 Palladium-Catalyzed Miyaura Borylation of 4-Chloroanisole and Their Conversion to Boronate Esters or Isolation of the Boronic Acid

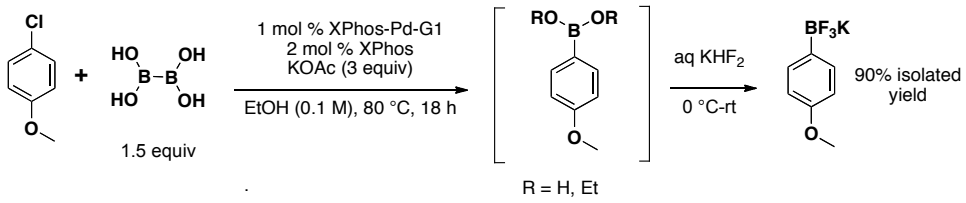


entry	diol/solvent	product	isolated yield (%)
1			90
2			87
3			90
4			72
5	hexanes wash		82
6			72

We next turned our attention to exploring the substrate scope of the reaction. It is important to note that although we demonstrated the isolation of the boronic acid product (Table 3.4, entry 5), it was often difficult to obtain the pure crystalline form of these materials without some loss in yield. This loss in yield did not accurately quantify the

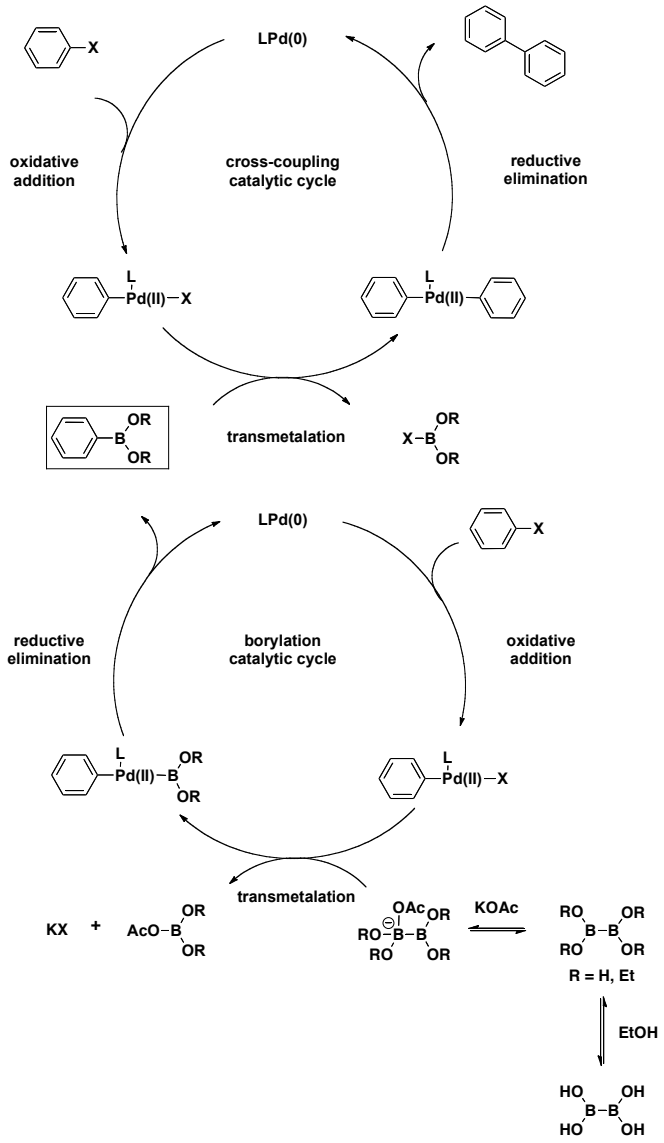
reaction conversion, as was the purpose of the study. Thus, crude boronic acids were immediately converted to the corresponding trifluoroborate after filtration of the reaction mixture through Celite and solvent removal. As demonstrated in Equation 3.6, the trifluoroborate of 4-chloroanisole was obtained in 90% yield after Soxhlet extraction, while the boronic acid isolation resulted in a lower yield of 82% (Table 3.4, entry 5). In addition to improved yields, conversion to the crystalline trifluoroborate also preserves the C-B bond during prolonged periods of bench storage.

Equation 3.6



As previously mentioned, the reaction was optimized on 4-chloroanisole through HTE. It was concluded at that time that 1.5 equivalents of BBA was sufficient for the successful borylation of aryl chlorides However, when 1.5 equivalents was used as the general procedure on a wide range of aryl chlorides, a significant amount of the homocoupled product was observed in some substrates. This can mechanistically be rationalized by the recognition that the oxidative addition complex, once formed, can undergo a transmetalation with either BBA or the rapidly forming boronic acid. Thus, the two catalytic cycles are in competition, and without sufficient BBA in the system, homocoupling will ensue (Scheme 3.1).

Scheme 3.1 Competing Catalytic Cycles

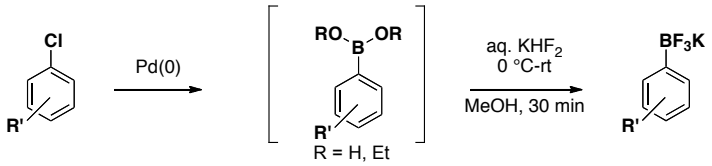


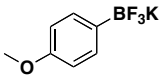
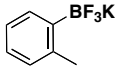
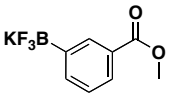
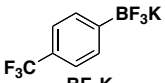
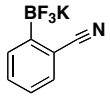
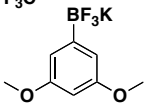
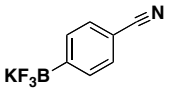
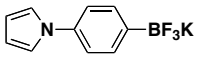
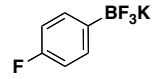
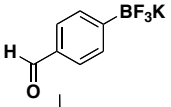
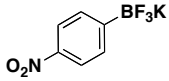
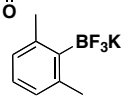
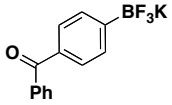
If, however, sufficient BBA is supplied to the catalytic cycle, the oxidative addition complex should preferentially react with BBA over the boronic acid. This is, in fact, what was experimentally observed. When three equivalents of BBA were utilized, yields improved, sometimes on the order of 20%. Indeed, the use of excess borylating

agent is not unique to this method, and is quite common in reactions wherein B_2Pin_2 is employed.[4]

The scope of the palladium-catalyzed borylation of aryl chlorides is outlined in Table 3.5 with two general procedures; one employing 1.5 equivalents of BBA for those substrates that performed well under those conditions (Table 3.5, general method[a]) and one that utilized 3.0 equivalents of BBA to reduce homocoupling and therefore improve the overall yield (Table 3.5, general method[c]).

Table 3.5 Borylation of Aryl Chlorides Utilizing 1.5 or 3.0 Equivalents of BBA and their Conversion to Trifluoroborates



entry	product	isolated yield (%)	entry	product	isolated yield (%)
1		90[a], 92[b]	8		75[c]
2		76[a]	9		82[c]
3		24[a]	10		92[c]
4		57[c]	11		84[a]
5		87[c]	12		80[c]
6		58[c]	13		50[c]
7		90[c]	14		65[c,d]
			15		45[c,e]

[a] General conditions: 1 mol % XPhos-Pd-G1, 2 mol % XPhos, 1 mol % NaO*t*-Bu, 3 equiv KOAc, 1.5 equiv BBA, EtOH (0.1 M), 80 °C, 18 h. [b] 6 mmol scale reaction. [c] 3.0 equiv BBA. [d] 3 mol % XPhos-Pd-G1, 50 °C, 24 h, [e] 5 mol % XPhos-Pd-G1, 50 °C, 48 h

Overall, the method is functional group tolerant, providing good to excellent yields of the trifluoroborates. In general, aryl rings substituted with electron-rich functional groups (Table 3.5, entries 10 and 11) fared better than those with electron withdrawing groups (Table 3.5, entries 2, 3, 4 and 6) consistent with Stille's observation that strongly electron-withdrawing groups such as nitro groups can promote reductive

dehalogenation.[7] Systems substituted in the *ortho*-position led to good yields (entry 8), and impressively the hindered 2,6-disubstituted aryl chlorides also cross-couple well (entry 13). The latter compares favorably to the only other related Miyaura borylations of similarly hindered systems, employing aryl bromides or iodides with high catalyst loads (5-10 mol %) and 2.2 – 3 equivalents of B_2Pin_2 or pinacolborane.[8]

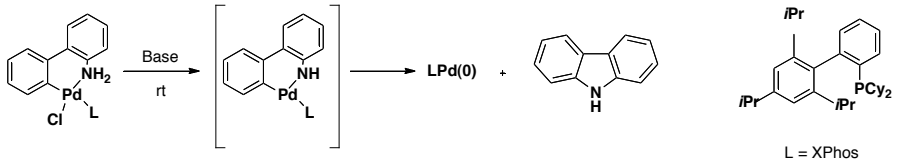
Heteroaryls proved more difficult to borylate under these reaction conditions and require higher catalyst loading (3-5 mol %) and longer reaction times of 24-48 h (Table 3.5, entries 14 and 15). Additionally, the reactions must be performed at reduced temperatures (50 °C) to eliminate the homocoupling of the formed boronic acid with the starting chloride. This side reaction was observed to occur rapidly at temperatures over 80 °C even at low catalyst loads. Initial optimization of the heteroaryl borylation reaction was carried out with 3-chlorothiophene (Table 3.5, entry 14). When the optimized method was applied to other heteroaromatic systems, it did not provide sufficient yields, and thus further work in this area was required.

Early in this study, we also examined the borylation of 4-bromo- and 4-iodoanisole, subjecting them to the identical conditions optimized for 4-chloroanisole utilizing 1.5 equivalents of BBA, 1 mol % XPhos-Pd-G1 at 80 °C in EtOH (0.1 M) for 18 h. We observed significant amounts of homocoupled and halide-reduction product. It was determined at this early stage that the method may not be general to all aryl halides, as the reaction had been optimized for aryl chlorides. Further studies would be required of these systems.

3.3.2 Palladium-Catalyzed Borylation of Aryl Bromides with XPhos-Pd-G2

Shortly after the completion of the aforementioned study of the Miyaura borylation of aryl chlorides utilizing XPhos-Pd-G1, we began studies to explore the borylation of aryl bromides to understand more completely the reactivity differences encountered as compared to their chloride counterparts. Coinciding with this study was a publication by Buchwald et al. that disclosed the synthesis and application of a second generation XPhos preformed catalyst XPhos-Pd-G2 (Equation 3.7).[9] As discussed by Buchwald, this improved catalyst allows rapid formation of the requisite Pd(0) species at room temperature with weak base (such as KOAc), eliminating the need for additional strong base (NaO*t*-Bu).

Equation 3.7

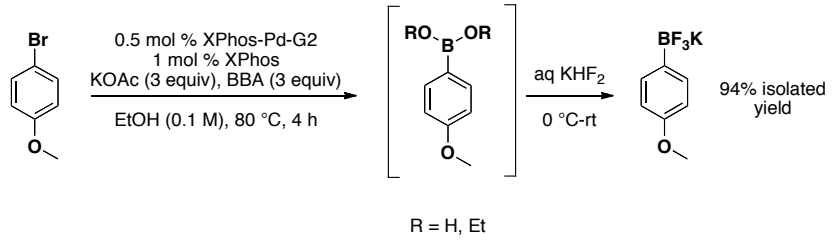


We included this catalyst in our HTE screens along with a myriad of G2-type preformed catalysts made available to use through our collaboration with the Merck Research Laboratories. Much to our delight, the XPhos-Pd-G2 catalyst performed exceptionally well, providing excellent conversion of 4-bromoanisole to the corresponding boronic acid (and subsequently the pinacol boronate for HPLC analysis).

Reaction conditions with XPhos-Pd-G2 required only small modifications in that with this more active catalyst, the palladium required was reduced by half, to 0.5 mol %

compared to the 1 mol % utilized with XPhos-Pd-G1, and as the 3:1 ligand to catalyst ratio was still superior to all others screened, the molar equivalents of XPhos could also be reduced to 1 mol % from 2 mol %. As with the previous method, the use of anhydrous EtOH is unnecessary, and as all reagents are air stable, there is no requirement to employ the use of a glove box. Also, due to the low pKa of the aminobiphenyl, the need to use a catalytic amount of NaO-*t*Bu was eliminated. It is with this improved protocol that the optimized reaction conditions were scaled up at the bench, providing the trifluoroborate in 94% isolated yield (Equation 3.8).

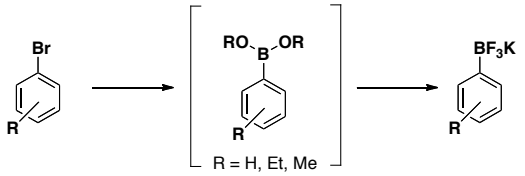
Equation 3.8

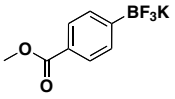
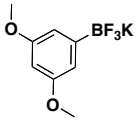
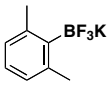
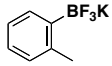
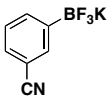
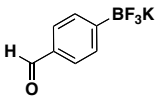
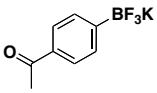
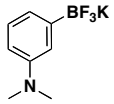
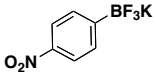
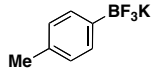
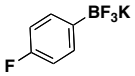
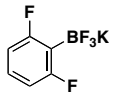
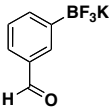
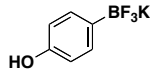
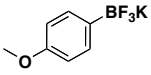
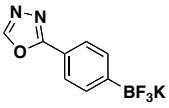
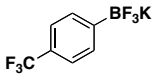
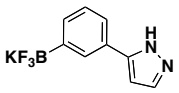


With proof of concept established, exploration of the full scope of the borylation of aryl bromides with the improved Pd-XPhos-G2 began (Table 3.6). Again, to fully demonstrate the efficiency of the method, all substrates were converted to their corresponding trifluoroborate after aqueous work-up. During the course of the synthesis of the first few substrates, we quickly noticed a very distinct color change, with the reaction going from colorless to a bright orange. Most curiously, we subjected the reaction to GC analysis and determined that the change occurs only when the all of the starting material has been consumed. We were pleased by this result, as we now had a

visual indicator at completion of the reaction, making the execution of the method even easier to facilitate.

Table 3.6 Borylation of Aryl Bromides Utlizing XPhos-Pd-G2 and their Conversion to Trifluoroborates



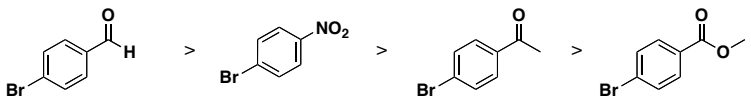
entry	product	time (h)	% isolated yield	entry	product	time (h)	% isolated yield
1		3	93	10		4	98
2		5	42	11		9	80
3		5	94	12		4	75[b]
4		2	95	13		3.5	94
5		4	64	14		2.5	90[c]
6		4	95	15		5.5	0
7		3	87[a,c]	16		1	98[c]
8		4	94	17		2	34[c]
9		3	88	18		4	79[c]

General conditions: 0.5 mol % XPhos-Pd-G2, 1 mol % XPhos, 3.0 equiv KOAc, 3.0 equiv $B_2(OH)_4$, EtOH (0.1 M) 80 ˚C for time indicated. [a] From the acetonide. [b] 0.1 M MeOH. [c] Compound synthesized by Dr. Steven Kennedy.

As outlined in Table 3.6, the method tolerates a wide range of functional groups

with most products isolated in good to excellent yield. However, there exist some limitations with the method. For example, aryl rings substituted with a ketone, nitro, or aldehyde functional group led to a mixture of the trifluoroborate (Table 3.6, entries 4, 5, and 12, respectively). Upon closer examination, it was discovered that a certain percentage of these substrates were undergoing a reduction to afford the corresponding alcohol or amine (Table 3.7). We found that the amount of reduction can be slightly reduced by running the reaction in MeOH (Table 3.6, entry 12).

Table 3.7 Comparisons of Hydride Reduction Products of Aldehyde, Nitro, and Ketone Functional Groups

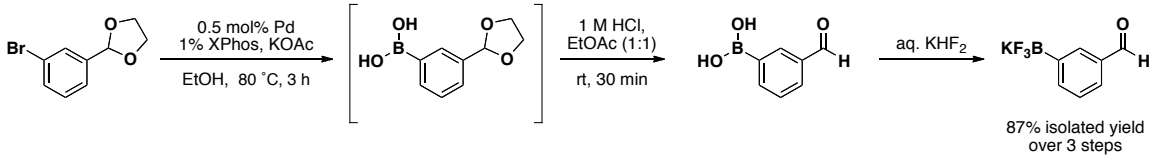


% reduction	30%	20%	9%	0%
combined yield	75%	65%	86%	95%

Because of their highly reactive nature, the aldehyde and nitro functional groups undergo the largest amount of reduction, while the less electrophilic ketone leads to very little of the secondary alcohol. The ester does not undergo any reduction because of the resonance stabilization afforded by the adjacent oxygen. As aldehydes are key functional groups often employed in the construction of more complex molecules, we attempted to offer a suitable solution to this limitation. We found that through the convenient use of an acetonide, the aldehyde can be obtained in 87% yield over three steps after simple

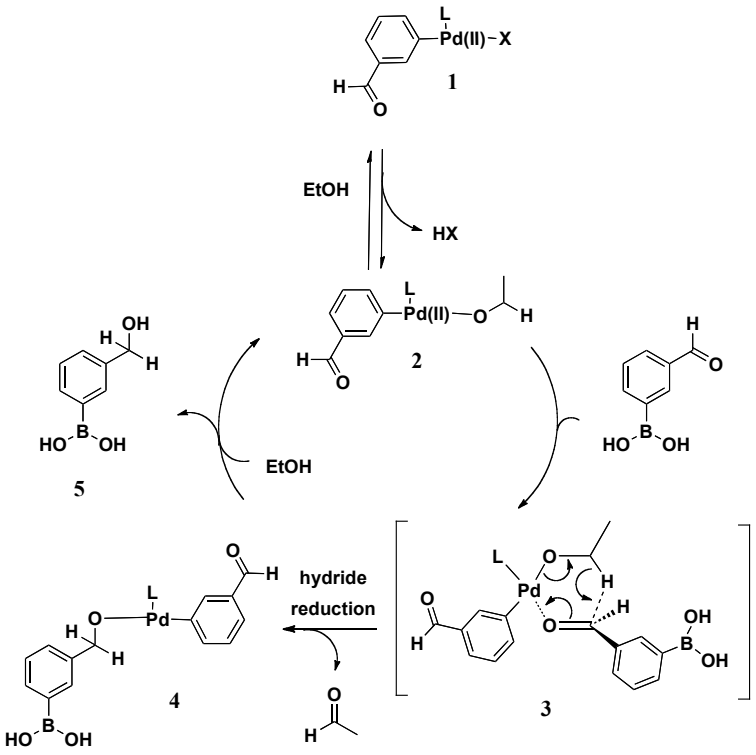
deprotection of the boronic acid intermediate before converting to the trifluoroborate (Scheme 3.2).

Scheme 3.2 Use of Acetonide to Provide Aldehyde-Containing Aryl Trifluoroborates



The mechanism of the reduction is believed to occur through a six-membered transition state structure, much like the metal catalyzed Meerwein-Ponndorf-Verley reduction.[10]

Scheme 3.3 Proposed Mechanism of the Palladium-Catalyzed Hydride Reduction



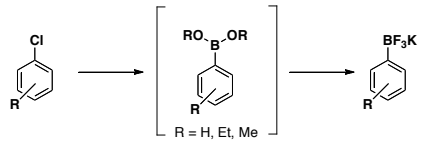
After the oxidative addition, complex **1** is in equilibrium with **2**, with alcoholysis

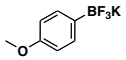
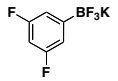
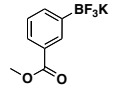
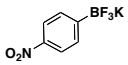
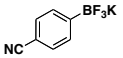
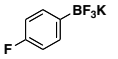
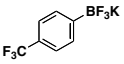
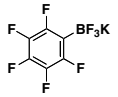
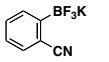
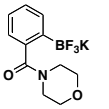
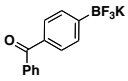
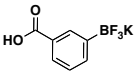
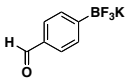
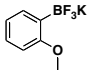
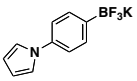
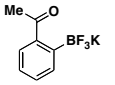
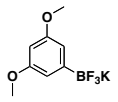
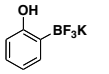
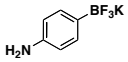
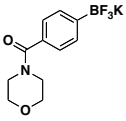
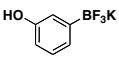
occurring selectively at the Pd-X bond.[11,12] Acting as a Lewis acid, complex **2** coordinates with the oxygen of the aldehyde carbonyl, delivering hydride via a six-membered transition structure represented by complex **3**. The subsequent hydride reduction affords complex **4**, which after alcoholysis with EtOH, provides the reduced aldehyde **5** regenerates catalytically active **2**.

3.3.3 Palladium-Catalyzed Borylation of Aryl Chlorides with XPhos-Pd-G2

As we now had an improved catalyst system, XPhos-Pd-G2, we revisited the aryl chlorides to fully explore the scope. The results are outlined in Table 3.8. In general, functional groups are well tolerated, and good to excellent yields are obtained after aqueous work-up and treatment with KHF_2. For comparison, the yields obtained with XPhos-Pd-G1 are given to demonstrate that in all cases, XPhos-Pd-G2 performed as well as, or in many cases, better than XPhos-Pd-G1 in the conversion (Table 3.8, entries[b]).

Table 3.8 Borylation of Aryl Chlorides Utilizing XPhos-Pd-G2, Their Conversion to Trifluoroborates, and Yield Comparison to XPhos-Pd-G1



entry	product	time (h)	% isolated yield	entry	product	time (h)	% isolated yield
1		2	93, 95[a], 90[b]	13		1.5	77[c]
2		2.5	97, 76[b]	14		2	64, 58[b]
3		1	81, 57[b]	15		4.5	53, 50[b]
4		2.5	98[c], 80[b,]	16		3.5	95, 75[b]
5		2.5	91[c], 82[b], 88[d]	17		2	0
6		1	27[c], 24[b]	18		6	64[c,e]
7		4	13	19		1.25	91[c,e], 90[b]
8		5	44[c]	20		20	80[c,e], 80[b]
9		1.5	66[c]	21		1	86[c], 84[b]
10		2	15[c,e]	22		2	99[c], 92[b]
11		1.5	17	23		2	68[c]
12		1.5	81[c]	24		2	98[c]

General conditions: 0.5 mol % XPhos-Pd-G2, 1 mol % XPhos, 3.0 equiv KOAc, 3.0 equiv $B_2(OH)_4$, EtOH (0.1 M), 80 ˚C for time indicated. [a] (1) 0.5 mol % of $Pd(OAc)_2$, 1.5 mol % of XPhos, 3.0 equiv KOAc, 80 ˚C in 3 mL EtOH for 20 min. (2) 3.0 equiv $B_2(OH)_4$ dissolved in 12 mL of EtOH, 4-chloroanisole, 80 ˚C for 1 h. [b] Yield from previous method with XPhos-Pd-G1 as catalyst. [c] Compound synthesized by Dr. Steven Kenndy. [d] 12 mmol reaction run with 0.1 mol % XPhos-Pd-G2, 0.2 mol % of XPhos, 3 equiv of KOAc, 3 equiv of $B_2(OH)_4$, EtOH (0.5 M) at 80 ˚C for 3 h. [e] MeOH used as solvent.

The reaction is scalable, as it was efficiently run on 12 mmol. In fact, scaling allowed a dramatic reduction in both palladium (from 0.5 mol % to 0.1 mol %) and solvent (from 0.1 M in EtOH to 0.5 M) with almost no decrease in yield (Table 3.8, entry 5[d]). Although not as operationally simple, the reaction can also be run with less expensive $Pd(OAc)_2$ (Table 3.8, entry 1[a]). In this modified protocol, before the addition of the pre-dissolved BBA (in EtOH) and substrate, 0.5 mol % of $Pd(OAc)_2$, 1.5 mol % of XPhos, and KOAc (3 equiv) are stirred in EtOH for 20 min at 80 °C. This sequence allows the requisite preactivation of the catalyst by reduction of Pd(II) to Pd(0), before the BBA and substrate are added.

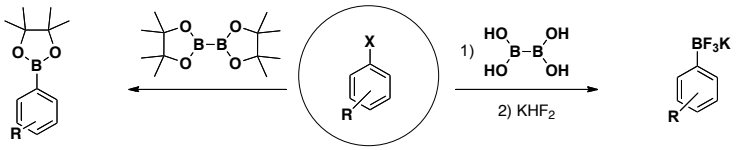
Substrates hindered by substitution (mono- or disubstituted at the *ortho*-positions) result in good to excellent yields (Table 3.8 entries 15 and 16). However, substrates with electron-withdrawing groups in the *ortho*-position represent the only major limitation of the method, leading to poor yields and/or mixtures of products (Table 3.8 entries 6, 7, 10 and 18). It was confirmed that these low yields are not due to protodeboronation by KHF_2, as quenching the reactions with pinacol led to the observation of equally low yields. Interestingly, a deprotected alcohol in the *ortho*-position also affords the product in the low yield of 17% (Table 3.8, entry 11), while a methyl ether in the *ortho*-position leads to the respectable yield of 66% (Table 3.8, entry 9). This observation if not unique to this method, and has been seen in similar attempts utilizing pinacolborane for the borylation of an aryl halide with electron withdrawing groups in the *ortho*-position.[13] Even though the reactions are run in EtOH, transesterification only occurs with a methyl ester in the *ortho*-position (Table 3.8, entry 18). Transesterification can be avoided by swapping

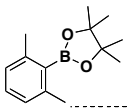
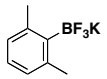
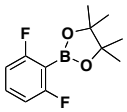
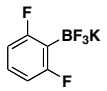
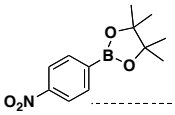
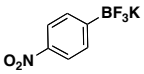
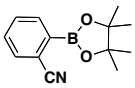
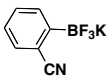
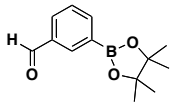
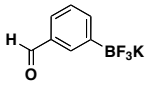
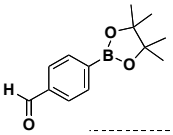
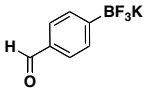
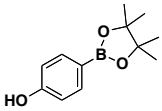
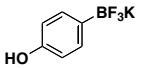
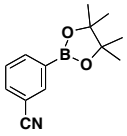
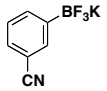
MeOH for EtOH, with no apparent loss in yield. As seen with aryl bromides, varying amounts of palladium-catalyzed hydride reduction were observed with ketones, nitro groups, and aldehydes. Again, employing MeOH as solvent instead of EtOH decreased the amount of reduction. The aryl chlorides also conveniently undergo a very distinct color change from colorless to bright yellow upon the consumption of the starting chloride.

3.3.4 Comparison of Miyaura Borylation Methods Utilizing Either BBA or B_2Pin_2

The Miyaura borylation with BBA in general works very well across a wide range of functional groups. In direct comparison to methods that access compounds with the same functional groups but utilize B_2Pin_2, our method holds up well and provides comparable yields in 80% of the case studies.[4,14-22] However, there is some overlap with the methods where one or the other outperforms. For example, sterically hindered substrates fare better when B_2Pin_2 is employed, as well as those containing nitro groups (Table 3.9, entries 1A-3B).[16,18] Further, if an electron-withdrawing substituent is required in the *ortho*-position, B_2Pin_2 is reported to provide modest yields, while this remains one of the major limitations of our method with BBA (Table 3.9, entry 4A/B).[13,16] In addition, unless aldehydes are protected, as in the case of the acetonide (Table 3.9, entry 5B, from the acetonide versus 6B without protection), B_2Pin_2 should be used, as palladium-hydride reduction does not occur in ethereal solvents, which are the standard (Table 3.9, entries 5A and 6A).[19] However, in the case of unprotected alcohols and cyano-containing substrates, BBA outperforms B_2Pin_2 (Table 3.9, entries 7B and 8B).[19,22]

Table 3.9 Comparison of Borylation Methods with Functionalized Substrates

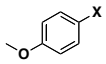
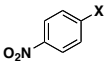
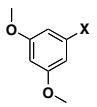


entry	product	% isolated yield	% isolated yield	product	entry
1A		96	42		1B
2A		72	0		2B
3A		86	64		3B
4A		72	27		4B
5A		65	87		5B
6A		80	75		6B 30% reduced
7A		85	98		7B
8A		81	94		8B

3.3.5 Reaction Kinetics and Known Mechanisms of Borylation

Not only is the color change convenient for the facilitation of the borylation of aryl bromides and chlorides, it also allowed us to monitor the rate of the reactions carefully.[23] This careful observation over time led to the discovery that aryl chlorides, in every instance tested, undergo the borylation faster than their bromide or iodo counterparts (Tables 3.6, 3.8, and 3.10).

Table 3.10 Rate Comparisons of Chlorides and Bromides Undergoing Borylation with XPhos-Pd-G2

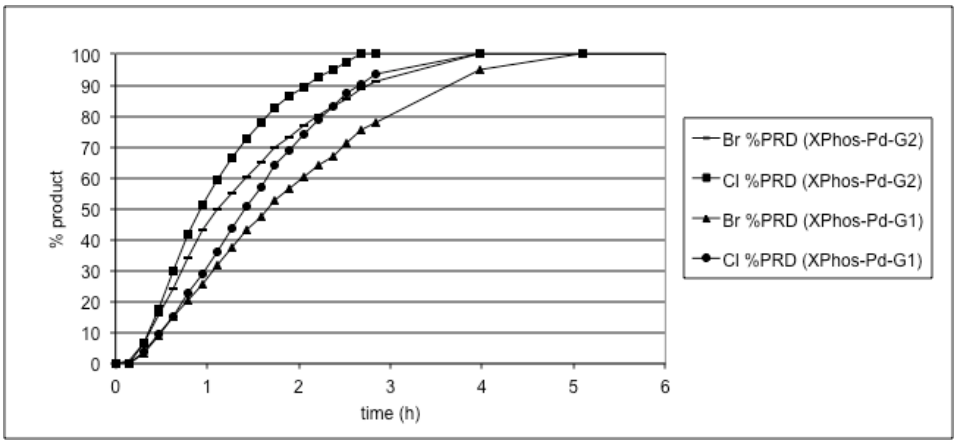
entry	X = Cl reaction time (h)	% isolated yield	substrate	X = Br reaction time (h)	% isolated yield	X = I reaction time (h)	% isolated yield
1	2	93		4	94	7	73
2	3.5	95		9	80		
3	2	64 7% reduction		4	64 20% reduction		
4	2.5	98		4	95		
5	2	99		4	98		

In general, the difference in rate did not significantly impact the yield of the isolated trifluoroborate. However, in the case of the nitro-substituted aryl halide (Table 3.10, entry 3), although the overall yield was 64% for both the chloride and the bromide,

the increased reaction time for the bromide led to significantly more of the palladium-catalyzed reduction (7% verses 20%). The *ortho*-methyl substituted bromide also suffered from a longer reaction time as it resulted in 15% less product than its chloride counterpart (Table 3.10, entry 2). As expected based upon this trend, 4-iodoanisole did not perform as well as its chloro- and bromo counterparts. In fact, the reaction did not even go to full conversion after reacting for 7 hours, and the precipitation of palladium black was observed in the reaction mixture (Table 3.10, entry 1).

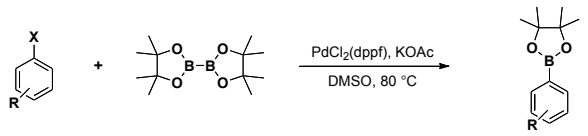
The same reactivity trend was seen with XPhos-Pd-G1. Head-to-head kinetics studies revealed that 4-chloroanisole goes to completion faster than 4-bromoanisole regardless of whether XPhos-Pd-G2 or XPhos-Pd-G1 is employed. In agreement with Buchwald's observations, XPhos-Pd-G2 performs the reaction at a higher rate for both the chloro and bromo species (Figure 3.4), leading to overall faster reaction times than XPhos-Pd-G1.[9]

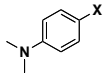
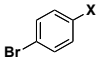
Figure 3.4 Kinetics Data of 4-Bromo- and 4-Chloroanisole with Both XPhos-Pd-G1 and XPhos-Pd-G2



The borylation rate for aryl halides with XPhos-Pd-G2 was therefore determined to be ArCl > ArBr > ArI. This is in direct contrast of that observed by Miyaura in his report on the palladium-catalyzed borylation of aryl iodides and bromides with B_2Pin_2, where he determined the rate order of I > Br.[17] In fact, it was found that aryl bromides underwent the borylation at significantly slower rates than the corresponding iodides (Table 3.11).

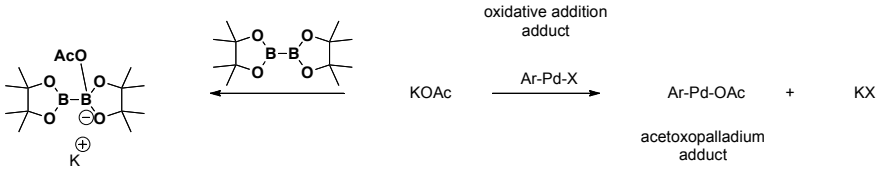
Table 3.11 Comparison of the Rate of Borylation of Aryl Bromides and Iodides Observed by Miyaura



entry	X = I reaction time (h)	% isolated yield	substrate	X = Br reaction time (h)	% isolated yield
1	2	82		24	69
2	6	90		24	23
3	1	86		2	86

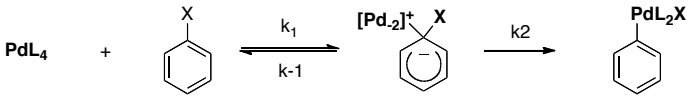
Entry 1 of Table 3.11 provides a direct comparison of this observed reverse rate order, with 4-bromoanisole requiring 24 h to go to completion compared to that of 4-iodoanisole, which required only 2 h. Based upon these observations, Miyaura proposed that KOAc can play a duel role in the reaction; it can either facilitate the transmetalation by undergoing an anion exchange with the oxidative addition adduct, or it can react with B_2Pin_2, increasing its nucleophilicity to boron (Equation 3.9)

Equation 3.9



Miyaura went on to isolate the acetoxopalladium adduct and demonstrated that in the presence of B_2Pin_2 in C_6D_6 it afforded the aryl pinacol boronate ester in 67% yield. Additionally, treatment of B_2Pin_2 with KOAc in DMSO resulted in no shift in the ^{11}B NMR, providing further evidence for the preferential formation of the acetoxopalladium adduct. This result was later confirmed by Buchwald et al. with detailed computational analysis studies.[4] Based upon these experiments, Miyaura proposed that the oxidative addition of the aryl halide is the rate-determining step. Oxidative addition of aryl halides to group 8 metals has been studied in detail. It is believed to be analogous to nucleophilic aromatic substitution in that the effect of the halide (i.e., its leaving group capacity) dictates the C-X bond breakage such that k_2 is rate determining (Equation 3.10).[24]

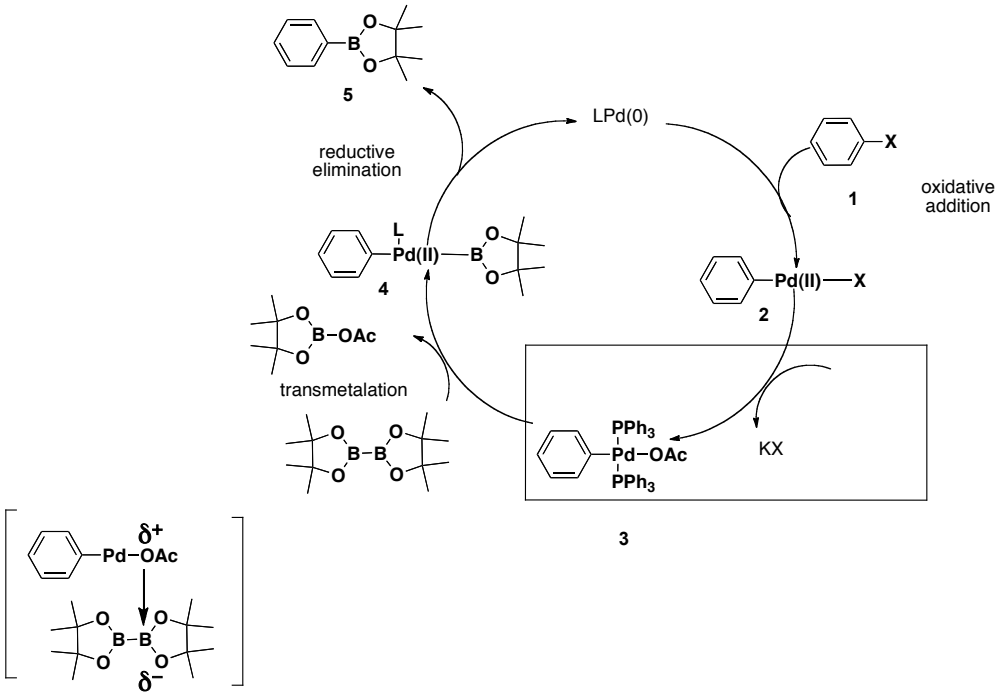
Equation 3.10



The catalytic cycle of the palladium-catalyzed borylation proposed by Miyaura is shown in Scheme 3.4.[17] After the oxidative addition of the aryl halide 1 to Pd(0), an anion exchange occurs, providing the acetoxopalladium adduct **3**. Miyaura attributes the high reactivity between organoboron species (in this case B_2Pin_2) and oxopalladium

complex **3** to the high oxophilicity of boron, coupled with the Pd-O bond that consists of a soft acid, hard base combination. Further evidence of this premise was supported by kinetic studies of the transmetalation process, which showed that coordination of the alkoxide to boron occurs first. This binding activates the boron species toward the metathesis of the organoboron species to palladium resulting in complex **4**.[25] Reductive elimination leads to the formation of the arylboronate species **5**.

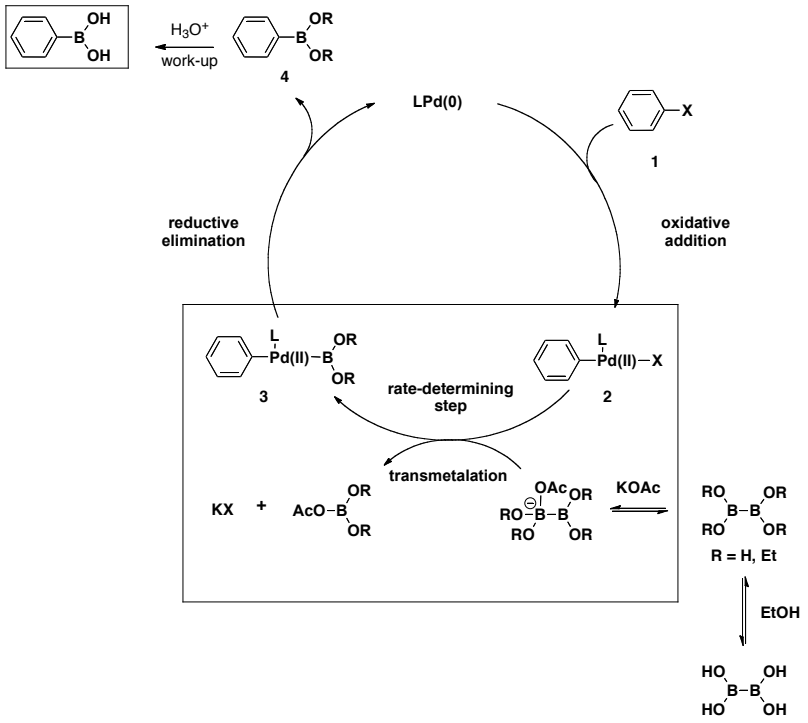
Scheme 3.4 Proposed Catalytic Cycle of the Borylation of Aryl Iodides and Bromides by Miyaura et al.



3.3.6 Proposed Mechanism of Borylation with XPhos-Pd-G1 and XPhos-Pd-G2

Because of the reverse rate order of our system compared to that of Miyaura in the borylation of aryl halides, it is clear that the reaction occurs through a different mechanism. Careful analysis of every step of the catalytic process shows clearly that oxidative addition is not the rate determining step, as it has been demonstrated that the rate of oxidative addition with Pd(0) and aryl halides is ArI > ArBr > ArCl.[24] Although this rate order is most certainly occurring at the oxidative addition, it is fast in comparison to the actual rate-determining step of the reaction. Also, it is unlikely that the anion exchange is occurring, forming the acetoxopalladium species as proposed by Miyaura. This would result in the same rate order he observed, as this adduct would be identical regardless of the starting halide. Based upon our observations, we propose that the rate-determining step of the reaction is therefore the transmetalation of the oxidative addition species **2** and BBA (or its ester where R = Et), and is driven by the inherent reactivity of the Pd-X bond (Scheme 3.5). Although we cannot experimentally confirm the formation of the activated boronate species of BBA, it is likely that it exists in equilibrium in some transient amount. Further, because of recent studies in the area, it is most likely that the role of the base in this mechanism is to act as an activating agent,[26-28] rather than undergo anion exchange with the oxidative addition adduct as proposed by both Miyaura and Buchwald.[4,17]

Scheme 3.5 Proposed Mechanism of Borylation with BBA and XPhos-Pd-G1 and XPhos-Pd-G2



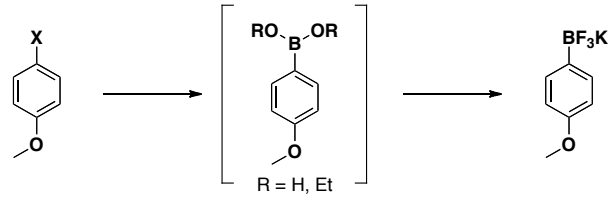
This rate order has also been observed by Buchwald et al. in their SMC reactions utilizing XPhos-Pd-G2 as catalyst wherein transmetalation was experimentally determined to be the rate-determining step.[9] The same trend also holds for the palladium-catalyzed Stille coupling reactions where relative rates have been ascribed to the electrophilicity of the intermediate organopalladium halides, which depend critically on the electronegativity of the halide component.[24] Further studies performed in our laboratory demonstrated that the rate of the reaction of both 4-bromo- and 4-chloroanisole were decelerated with the addition of increasing amounts of bromide (in the

form of *n*-Bu_4NBr) to the reaction mixtures. The effect was more pronounced with 4-bromoanisole than with 4-chloroanisole, providing further evidence in support of our mechanistic hypothesis.

3.3.7 Electrophile Scope

The general borylation was also examined with other aryl electrophiles (Table 3.12). As previously mentioned above, 4-iodoanisole reacted slower and in lower yield than its chloro- and bromo counterparts. Starting material remained even after 7 hours of reaction time, and palladium black precipitated from the reaction mixture. Aryl triflates borylate in excellent yield with reaction times resembling those of the 4-chloroanisole, which is most likely a result of the similarities in electronegativity between a chloride and triflate. Mesylates however, failed to give rise to any product.

Table 3.12 Electrophile Scope of the XPhos-Pd-G2 Catalyzed Borylation with BBA



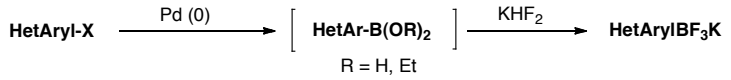
entry	X	time	% isolated yield
1	Cl	2	93
2	Br	4	94
3	I	7	73
4	OMs	16	0
5	OTf	2	99[a]

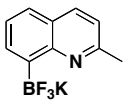
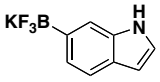
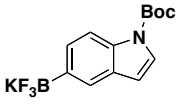
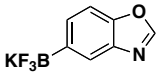
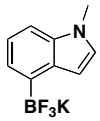
General conditions: 0.5 mol % XPhos-Pd-G2, 1 mol % XPhos, 3.0 equiv KOAc, 3.0 equiv $B_2(OH)_4$, EtOH (0.1 M), 80 ˚C for time indicated. [a] Compound synthesized by Dr. Steven Kennedy.

3.3.8 Borylation of Heteroaryl Halides using BBA, XPhos-Pd-G2, and a New Catalyst System

Applying the aforementioned general method of borylation utilizing BBA and XPhos-Pd-G2 in EtOH was efficient in systems where the halide was in the ring adjacent to the heteroatom (Table 3.13), providing good to excellent yields of the corresponding trifluoroborate.

Table 3.13 Borylation of Heteroaryl Halides Utilizing BBA and XPhos-Pd-G2



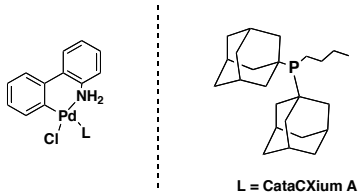
entry	X	time (h)	product	% isolated yield
1	Cl	2		52
2	Br	1.5		78[a]
5	Br	2		93[a]
7	Cl	1.5		81[a]
8	Br	5		80

General conditions: 0.5 mol % XPhos-Pd-G2, 1 mol % XPhos, 3 equiv KOAc, 3.0 equiv of $B_2(OH)_4$, EtOH (0.1 M), 80 °C for time indicated. [a] Compound synthesized by Dr. Steven Kennedy.

However, when the method was applied to systems in which the heteroatom was in the same ring as the halide, reaction times were long and low yields resulted, even when more catalyst was applied. Therefore, we returned to HTE to screen a variety of preformed catalysts, ligand to catalyst ratios, solvents, and temperatures. The most efficient method required the use of newly developed catalyst provided to us through our collaboration with the Merck Research Laboratories. This new system still makes use of the second generation aminobiphenyl precatalyst scaffold, but incorporates cataCXium A

as the ligand (Figure 3.5).

Figure 3.5 Second Generation Palladium-Preformed Catalyst Scaffold with CataCXium A Ligand Attached

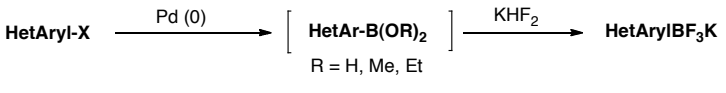


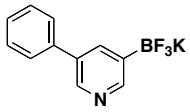
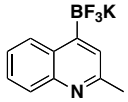
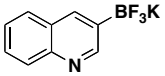
Use of this system required a higher catalyst load (5 mol %) but did not require the use of excess ligand, so the ligand to catalyst ratio was 1:1, lower reaction temperatures (50 °C), and DIEA (3 equiv) as base. Additionally, MeOH was found to be a superior solvent to EtOH, and the reaction performed better when more concentrated (0.2 M). Upon applying the system to a wide variety of heteroaryls, we found that the method was limited in scope and only worked well on systems that resembled the substrate used in screening (Table 3.14, entry 1). This finding, however, does not appear to be unique to this method. A thorough literature search of heteroaryl boronates synthesized with B_2Pin_2 or H-BPin revealed two trends: either the method reported was found for one functionalized heteroaryl,[29-40] or only a few examples were synthesized under reaction conditions considered to be a "general" methods procedure.[5,16,20,21,41-44]

Also noteworthy is that the heteroaryls examined in this search are among just a handful of heteroaryl borylated products that can be found in the literature. Additionally,

there is no publication dedicated solely to the Miyaura borylation of heteroaryls using B_2Pin_2. Our research observations, coupled with the literature results, provide evidence that a general method for the borylation of heteroaryls remains elusive, and that each substrate or general class of substrates may need to be treated on a case-by-case basis. However, as demonstrated by Table 3.14, discovery of a method to borylate a particular substrate or class can most likely be achieved rapidly through HTE.

Table 3.14 Borylation of Heteroaryl Halides Utilizing BBA and a New Catalyst System



entry	X	time (h)	product	% isolated yield
1	Br	1		64
2	Cl	1.5		47
3	Br	5		68

5.0 mol % cataCXium A precatalyst, 3 equiv *i*Pr_2NEt, 3.0 equiv of $B_2(OH)_4$, MeOH (0.2 M), 50 °C for time indicated.

Through making the trifluoroborate of these substrates (Table 3.14), we observed a mixture of the internal and potassium trifluoroborate salt. To quantify the yield of the reaction more accurately, all three substrates were subjected to a one-pot, two-step

borylation/Suzuki reaction, which is the subject of chapter 5, and details will further be discussed there.

3.4 Conclusions

Our research efforts have been directed toward the replacement of B_2Pin_2 with the more atom economical BBA in the palladium-catalyzed Miyaura borylation of aryl halides. We began our studies with the less expensive and more commercially available aryl chlorides making use of HTE to find a set of high-yielding reaction conditions quickly. Upon scale up in the laboratory, it was determined that preformation of the Pd(0) catalyst is required for the success of the reaction, as facile decomposition of BBA occurs in the presence of Pd(II) species. A newly reported preformed catalyst XPhos-Pd-G1 simplified the physical operation in that all reagents could be added to the reaction vessel at the same time, negating a two-step process that involved premixing the catalyst, ligand, and base to form the requisite Pd(0) species effectively. The method is run efficiently with environmentally benign ethanol as solvent in low catalyst loads (1 mol %) and reduced temperatures (80 °C). Further, as all the reagents are air-stable, the use of a glovebox is avoided. To represent the yields of the method and to preserve the fragile C-B bond, all intermediate boronic acids were quickly and efficiently converted to the trifluoroborates in good to excellent yield.

Shortly after the publication of our method with XPhos-Pd-G1, a new catalyst was published that proved even more effective at performing the borylation. Utilizing the second-generation preformed catalyst Pd-XPhos-G2, catalyst loads could be reduced by

half to 0.5 mol % with all other parameters remaining the same. The method resulted in higher yields for all aryl chlorides previously prepared with XPhos-Pd-G1 and was extended to aryl bromides, resulting in good to excellent yields of the corresponding trifluoroborates. Of great surprise and delight was the finding that upon the consumption of starting material, the borylation reactions change color, with aryl bromides turning bright orange, and aryl chlorides turning bright yellow. This observation of color change allowed us to monitor the rate of the reaction and revealed that the rate order of borylation is ArCl > ArBr > ArI. This order is in stark contrast to that observed by Miyaura in which he observed ArI >> ArBr in his seminal borylation with B_2Pin_2. Based upon our observations and further experiments, a new mechanism was set forth, proposing that transmetalation is in fact the rate-determining step of the reaction as opposed to the oxidative addition proposed by Miyaura. The method was also successfully extended to include heteroaryl halides, but remains limited in scope even through the use of a new catalyst system.

3.5 Experimental

Reagents: All reactions were carried out under an atmosphere of argon. Ethanol (200 proof) was thoroughly degassed with nitrogen directly before use. All aryl chlorides, XPhos-Pd-G1 and XPhos were purchased from commercial sources and used as received. XPhos-Pd-G2 was supplied by Dr. Mathew Tudge of the Merck Research Laboratories and used as received. KOAc and K_2CO_3 were dried in an oven overnight before use. All reagents (with exception of the aryl chlorides), were stored in a bench-top desiccator.

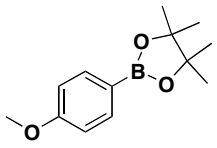
Tetrahydroxydiboron was synthesized[45,46] according to literature procedures prior to receiving it from BASF.

Analytical Methods: All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, ^{11}B NMR (when applicable), ^{19}F NMR (when applicable), IR spectroscopy, high-resolution mass spectrometry, and melting point determination (for solids). All known compounds were characterized by ^{1}H NMR and ^{13}C NMR and compared to literature values. ^{1}H, ^{13}C, ^{11}B, and ^{19}F were recorded at 500 MHz, 125.8 MHz, 128.4 MHz, and 470.8 MHz, respectively. Melting points are uncorrected.

General Experimental Procedure for the Palladium-Catalyzed Borylation of 4-Chloroanisole and its Conversion to Boronate Esters Utilizing XPhos-Pd-G1:

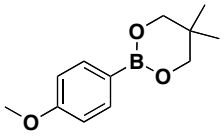
To an oven-dried glass vessel capable of being sealed with a Teflon cap (for microwave vials) was added XPhos-Pd-G1 (7.38 mg, 0.01 mmol), XPhos (9.52 mg, 0.02 mmol), tetrahydroxydiboron, (133.5 mg, 1.5 mmol), KOAc (294 mg, 3 mmol), and NaO*t*-Bu (1 mg, 0.01 mmol). The vessel was sealed and then evacuated and backfilled with N_2 (process was repeated three times). EtOH (10 mL degassed) was added via syringe followed by the addition of 4-chloroanisole (1.052 mmol) in a similar manner. The reaction was then heated to 80 ºC for 18 h. The reaction was cooled to rt then filtered through a thin pad of Celite (eluting with 100 mL EtOAc) and concentrated. To the crude concentrated reaction was added in equal parts 1 M aqueous HCl and EtOAc (25 mL each). This mixture was stirred 30 min before being added to a separatory funnel. The

aqueous layer was removed, and the organic layer was washed once with brine. The organic layer was collected, and the combined aqueous layers were further extracted with EtOAc (3 x 10 mL). The combined organics were dried (Na_2SO_4) and then concentrated under reduced pressure. The crude mixture was taken up in CH_2Cl_2, the corresponding diol was added (1.35 mmol), and the crude reaction was allowed to stir at rt. At completion of the reaction (as monitored by ^{11}B NMR in the reaction solvent), the reaction was concentrated, and the desired compound was purified by column chromatography, eluting with a gradient of EtOAc/hexane unless otherwise indicated.

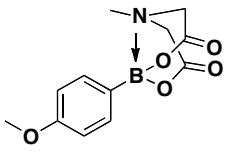


2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.[47]

Following the general procedure, a mixture of 4-chloroanisole (75 mg, 64 μL, 0.526 mmol), tetrahydroxydiboron (71 mg, 0.79 mmol), XPhos (4.75 mg, 0.1 mmol), XPhos-Pd-G1 (3.9 mg, 0.00526 mmol), KOAc (155 mg, 1.58 mmol), and NaO*t*-Bu (0.5 mg, 0.005 mmol) was heated to 80 ºC for 18 h. After acidic work-up, the crude reaction was taken up in CH_2Cl_2, pinacol (55 mg, 0.47 mmol) was added, and the reaction was allowed to stir overnight at rt. The crude product was purified via flash chromatography on silica gel (0-5% EtOAc/hexane) to provide the title compound in 90% yield (111 mg) as a colorless oil. Spectral data in accordance with that of published results. ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H), 1.35 (d, J = 4.5 Hz, 12H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 162.1, 136.4, 113.2, 83.5, 54.9, 24.8.

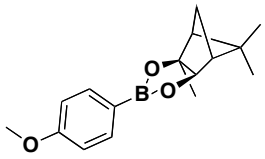


2-(4-Methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane.[47] Following the general procedure, a mixture of 4-chloroanisole (150 mg, 128 μL, 1.052 mmol), tetrahydroxydiboron (141 mg, 1.58 mmol), XPhos (10 mg, 0.02 mmol), XPhos-Pd-G1 (7.4 mg, 0.01 mmol), KOAc (310 mg, 3.16 mmol), and NaO*t*-Bu (1.0 mg, 0.01 mmol) was heated to 80 ºC for 18 h. After acidic work-up, the crude reaction was taken up in CH_2Cl_2, 2,2-dimethylpropane-1,3-diol (98 mg, 0.95 mmol) was added, and the reaction was allowed to stir overnight at rt. The crude product was purified via flash chromatography on silica gel (0-5% EtOAc/hexane) to provide the title compound in 87% yield (202.5mg) as a colorless oil. Spectral data in accordance with that of published results. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 3.83 (s, 3H), 3.76 (s, 4H), 1.03 (s, 6H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 161.9, 135.7, 113.3, 72.4, 55.2, 32.0, 22.1.



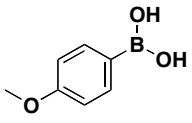
2-(4-Methoxyphenyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione. Following the general procedure, a mixture of 4-chloroanisole (410 mg, 350 μL, 2.87 mmol), tetrahydroxydiboron (387 mg, 4.3 mmol), XPhos (27 mg, 0.057 mmol), XPhos-Pd-G1 (21.2 mg, 0.0287 mmol), KOAc (845 mg, 8.61 mmol), and NaO*t*-Bu (2.75 mg, 0.0287 mmol) was heated to 80 ºC for 18 h. After acidic work-up, the crude reaction was taken up in a 0.5 M (95:5 toluene:DMSO) solution, and *N*-methylaminodiacetic acid (440 mg, 3 mmol) was added. The reaction was fitted with a toluene-filled Dean-Stark

trap with an attached reflux condenser and heated at reflux for 14 h. The crude reaction was concentrated until a chunky, wet solid was obtained. This solid was suspended in acetone (3 mL) and then Et_2O was added in 5 mL portions (25 mL total), precipitating the solid. The solid was filtered, rinsed with Et_2O (5 mL), and dried overnight to provide the title compound in 85% yield (642 mg) as a gray powder,[4] mp: >220 °C. ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.35 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 4.30 (d, J = 17.2 Hz, 2H), 4.07 (d, J = 17.2 Hz, 2H), 3.75 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (125.8 MHz, d_6-DMSO) δ 169.8, 160.3, 134.1, 113.7, 62.0, 55.2, 47.8. ^{11}B NMR (128.4 MHz, d_6-DMSO) δ 10.5. IR (KBr) 2960, 1764, 1324, 1217. HRMS (ES-) calcd. for $C_{12}H_{13}BNO_5$ (M-H) 262.0965 found 262.0887.

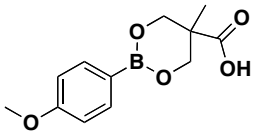


(3a*S*,4*S*,6*R*,6a*R*)-2-(4-Methoxyphenyl)-3a,5,5-trimethyltetrahydro-3a*H*-4,6-methanocyclopenta[*d*][1,3,2]dioxaborole. Following the general procedure, a mixture of 4-chloroanisole (150 mg, 128 μL, 1.052 mmol), tetrahydroxydiboron (141 mg, 1.58 mmol), XPhos (10 mg, 0.021 mmol), XPhos-Pd-G1 (7.4 mg, 0.01 mmol), KOAc (310 mg, 3.16 mmol), and NaO*t*-Bu (1.0 mg, 0.01 mmol) was heated to 80 ºC for 18 h. After acidic work-up, the crude reaction was taken up in CH_2Cl_2, (1*S*,2*S*,3*R*,4*R*)-2,5,5-trimethylbicyclo[2.1.1]hexane-2,3-diol (148 mg, 0.95 mmol) was added, and the reaction was allowed to stir overnight at rt. The crude product was purified via flash chromatography on silica gel (0-5% EtOAc/hexane) to provide the title compound in 75% yield (216 mg) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.76 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.45 – 4.39 (m, 1H), 3.83 (s, 3H), 2.41 (ddd, *J* = 11.2, 7.1, 2.1 Hz, 1H), 2.26 – 2.18 (m, 1H), 2.14 (t, *J* = 5.5 Hz, 1H), 1.99 – 1.89 (m, 2H), 1.47 (s, 3H), 1.31 (s, 3H), 1.23 (t, *J* = 8.7 Hz, 1H), 0.89 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 136.5, 113.4, 86.1, 78.2, 55.1, 51.5, 39.6, 38.2, 35.7, 28.7, 27.1, 26.5, 24.1. ^{11}B NMR (128.4 MHz, $CDCl_3$) δ 29.7. IR (neat) 2915, 1605, 1249**.** HRMS (ES+) calcd. for $C_{17}H_{24}BO_3$ (M+H) 287.1740, found 287.1819.



(4-Methoxyphenyl)boronic acid.[47] Following the general procedure, a mixture of 4-chloroanisole (214 mg, 182 μL, 1.5 mmol), tetrahydroxydiboron (201 mg, 2.25 mmol), XPhos (14.3 mg, 0.03 mmol), XPhos-Pd-G1 (11.08 mg, 0.015 mmol), KOAc (442 mg, 4.5 mmol), and NaO*t*-Bu (1.44 mg, 0.015 mmol) was heated to 80 ºC for 18 h. After acidic work-up, the crude reaction was concentrated and dried overnight. The crude boronic acid was washed with hexane to afford the title compound in 82% yield (187 mg) as a white solid. Spectral data in accordance with that of published results. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.9 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 163.3, 137.7, 113.7, 55.3.



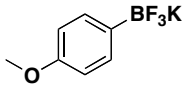
2-(4-Methoxyphenyl)-5-methyl-1,3,2-dioxaborinane-5-carboxylic Acid. Following the general procedure, a mixture of 4-chloroanisole (214 mg, 182 μL, 1.5 mmol), tetrahydroxydiboron (201 mg, 2.25 mmol), XPhos (14.3 mg, 0.03 mmol),

XPhos-Pd-G1 (11.08 mg, 0.015 mmol), KOAc (442 mg, 4.5 mmol), and NaO*t*-Bu (1.44 mg, 0.015 mmol) was heated to 80 ºC for 18 h. After acidic work-up, the crude reaction was taken up in CH_2Cl_2, 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoic acid (250 mg, 1.86 mmol) was added, and the reaction was allowed to stir overnight at rt. To the concentrated crude reaction was added Et_2O (10 mL) until a white solid precipitated out. The solid was filtered off, the reaction was concentrated, and the process was repeated until no additional precipitate was observed. The combined solids were dried overnight to provide the title compound in 72% yield (270 mg) as white free-flowing, low-melting powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.2 Hz, 2H), 4.42 (d, *J* = 11.0 Hz, 2H), 3.90 (d, *J* = 11.0 Hz, 2H), 3.82 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 179.2, 161.9, 135.7, 113.2, 99.9, 67.5, 55.1, 43.9, 18.2. ^{11}B NMR (128.4 MHz, d_6-DMSO) δ 26.3. IR (KBr) 2912, 1693, 1252, 1178. HRMS (CI+) calcd. for $C_{12}H_{16}BO_5$ 251.1013 (M+H), found 251.1091.

General Experimental Procedure for the Palladium-Catalyzed Borylation of Aryl Chlorides Utilizing XPhos-Pd-G1 and Their Conversion to Trifluoroborates:

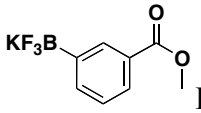
To an oven dried glass vessel capable of being sealed with a Teflon cap (for microwave vials) was added XPhos-Pd-G1 (14.8 mg, 20 μmol), XPhos (19 mg, 40 μmol), tetrahydroxydiboron (270 mg, 3 mmol), KOAc (590 mg, 6 mmol), and NaO*t*-Bu (2 mg, 20 μmol). The vessel was sealed and then evacuated and backfilled with N_2 (process was repeated three times). EtOH (20 mL degassed) was added via syringe followed by the addition of the chloride (2 mmol) in a similar manner (solid chlorides were added with

the other solid reagents before sealing). The reaction was then heated to 80 ºC for 18 h. The reaction was cooled to rt then filtered through a thin pad of Celite (eluting with 100 mL EtOAc), and concentrated. The concentrated crude reaction (unless otherwise indicated) was taken up in MeOH (~15 mL or enough to make a free-flowing solution) and cooled to 0 ºC. To this cooled mixture was added 3.5 equivalents of a 4.5 M aqueous KHF_2 solution, and the reaction was stirred for 10 min at 0 ºC before removing the bath and allowing the mixture to stir at rt for 20 min (or until the conversion to the corresponding trifluoroborate was achieved as determined by ^{11}B NMR). After conversion, the mixture was concentrated under reduced pressure, and then further dried under high vacuum overnight to remove any traces of water. The compound was purified with continuous Soxhlet extraction (overnight) with acetone (100 mL). The collected solvent was concentrated and then dissolved in a minimal volume of acetone (~3 mL). The addition of Et_2O (~25 mL) led to the precipitation of the desired product. The collected solid was washed with Et_2O. Further purification (to remove small organic or boron containing impurities) could be realized via trituration of the solid with Et_2O.

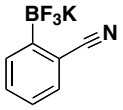


Potassium 4-Methoxyphenyl-trifluoroborate.[48] Following the general procedure, a mixture of 4-chloroanisole (855 mg, 730 μL, 6 mmol), tetrahydroxydiboron (804 mg, 9 mmol), XPhos (57.2 mg, 0.12 mmol), XPhos-Pd-G1 (44.28 mg, 0.06 mmol), KOAc (1.76 g, 18 mmol), and NaO*t*-Bu (5.76 mg, 0.06 mmol) was heated to 80 ºC for 18 h. The title compound was obtained as a white solid in 92% yield (1.18 g). Spectral data in accordance with that of published results. ^1H NMR (500 MHz, d_6-DMSO) δ 7.22 (d, J = 8.2 Hz, 2H), 6.66 (d, J = 8.1 Hz, 2H), 3.51 (s, 3H). ^{13}C NMR (125.8 MHz, d_6-DMSO) δ

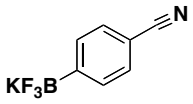
157.6, 132.6, 112.2, 54.9.



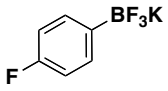
Potassium (3-(Methoxycarbonyl)phenyl)trifluoroborate. Following the general procedure, a mixture of methyl 3-chlorobenzoate (341 mg, 278 μL, 2 mmol), tetrahydroxydiboron (270 mg, 3 mmol), XPhos (19 mg, 40 μmol), XPhos-Pd-G1 (14.8 mg, 20 μmol), KOAc (590 mg, 6 mmol), and NaO*t*-Bu (2 mg, 20 μmol) was heated to 80 ºC for 18 h. The title compound was obtained as a white solid in 76% yield (369 mg). mp: >220 °C. ^{1}H NMR (500 MHz, d_6-DMSO) δ 8.00 (s, 1H), 7.67 (d, J = 6.7 Hz, 1H), 7.58 (d, J = 6.9 Hz, 1H), 7.24 (t, J = 7.4 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (125.8 MHz, d_6-DMSO) δ 167.9, 136.7, 132.7, 127.9, 126.9, 126.5, 51.9. ^{11}B NMR (128.4 MHz, d_6-DMSO) δ 1.3. ^{19}F NMR (470.8 MHz, d_6-DMSO) δ -139.69. IR (KBr) 1721, 1560, 1188**.** HRMS (ES-) calcd. for $C_8H_7BF_3O_2$ (M-K) 203.0491, found 203.0491.



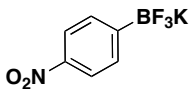
Potassium (2-Cyanophenyl)trifluoroborate. Following the general procedure, a mixture of 2-chlorobenzonitrile (275 mg, 2 mmol), tetrahydroxydiboron (270 mg, 3 mmol), XPhos (19 mg, 40 μmol), XPhos-Pd-G1 (14.8 mg, 20 μmol), KOAc (590 mg, 6 mmol), and NaO*t*-Bu (2 mg, 20 μmol) was heated to 80 ºC for 18 h. The title compound was obtained as an inseparable mixture of the trifluoroborate and the protodeboronated product. As a result, reasonable spectra for this compound could not be obtained.



Potassium (4-Cyanophenyl)trifluoroborate. Following the general procedure, a mixture of 4-chlorobenzonitrile (206 mg, 1.5 mmol), tetrahydroxydiboron (403 mg, 4.5 mmol), XPhos (14.8 mg, 30 μmol), XPhos-Pd-G1 (11.08 mg, 15 μmol), KOAc (442 mg, 4.5 mmol), and NaO*t*-Bu (1.44 mg, 15 μmol) was heated to 80 ºC for 18 h. The concentrated crude reaction was taken up in MeOH (15 mL) and 6.5 equiv (2.2 mL) of a 4.5 M aqueous KHF_2 solution was added. The title compound was obtained as a white solid in 57% yield (180 mg). mp: >220 °C. ^{1}H NMR (500 MHz, d_6-acetone) δ 7.62 (s, 2H), 7.45 (s, 2H). ^{13}C NMR (125.8 MHz, d_6-DMSO) δ 132.6, 130.6, 120.6, 108.3. IR (KBr) 2232, 1566. HRMS (ES-) calcd. for $C_7H_4BF_3N$ (M-K) 170.0389, found 170.0389.

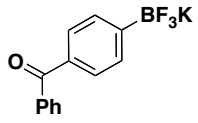


Potassium (4-Fluorophenyl)trifluoroborate.[48] Following the general procedure, a mixture of 1-chloro-4-fluorobenzene (261 mg, 213 μL, 2 mmol), tetrahydroxydiboron (270 mg, 3 mmol), XPhos (19 mg, 40 μmol), XPhos-Pd-G1 (14.8 mg, 20 μmol), KOAc (590 mg, 6 mmol), and NaO*t*-Bu (2 mg, 20 μmol) was heated to 80 ºC for 18 h. The title compound was obtained as a white solid in 80% yield (209 mg). Spectral data in accordance with that of published results. ^{1}H NMR (500 MHz, d_6-acetone) δ 7.42 (s, 2H), 6.78 (t, J = 8.5 Hz, 2H). ^{13}C NMR (125.8 MHz, d_6-DMSO) δ 161.9, 160.0, 132.8 (d, J = 5.9 Hz), 112.7 (d, J = 18.4 Hz)



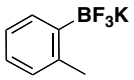
Potassium (4- Nitrophenyl)trifluoroborate. Following

the general procedure, a mixture of 1-chloro-4-nitrobenzene (236 mg, 1.5 mmol), tetrahydroxydiboron (403 mg, 4.5 mmol), XPhos (14.8 mg, 30 μmol), XPhos-Pd-G1 (11.08 mg, 15 μmol), KOAc (442 mg, 4.5 mmol), and NaO*t*-Bu (1.44 mg, 15 μmol) was heated to 80 ºC for 4 h. The concentrated crude reaction was taken up in MeOH (15 mL) and 6.5 equiv (2.2 mL) of a 4.5 M aqueous KHF_2 solution was added. The title compound was obtained as a light yellow solid in 58% yield (200 mg). mp: >220 °C. ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.96 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H). ^{13}C NMR (125.8 MHz, d_6-DMSO) δ 146.2, 132.5, 121.5. ^{11}B NMR (128.4 MHz, d_6-DMSO) δ 2.7. ^{19}F NMR (470.8 MHz, d_6-DMSO) δ -140.21. IR (KBr) 1514, 1359**.** HRMS (ES-) calcd. for $C_6H_4BF_3NO_2$ (M-K) 190.0287, found 190.0287.

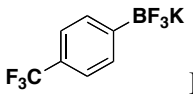


Potassium (4-Benzoylphenyl)trifluoroborate. Following the general procedure, a mixture of (4-chlorophenyl)(phenyl)methanone (433 mg, 2 mmol), tetrahydroxydiboron (540 mg, 6 mmol), XPhos (14.8 mg, 40 μmol), XPhos-Pd-G1 (11.08 mg, 20 μmol), KOAc (590 mg, 6 mmol), and NaO*t*-Bu (2 mg, 20 μmol) was heated to 80 ºC for 18 h. The concentrated crude reaction was taken up in MeOH (15 mL) and 6.5 equiv (2.2 mL) of a 4.5 M aqueous KHF_2 solution was added. After precipitation with ether, the solid was taken up in CH_3CN (20 mL) and oven-dried K_2CO_3 (970 mg, 7 mmol) and stirred overnight. The mixture was concentrated then the desired compound was obtained via hot filtration with acetone (3 x 20 mL). The title compound was obtained as a white solid in 90% yield (518 mg) as a mixture of the ketone (84%) and

hydrate (16%). mp: >220 °C. ^{1}H NMR (500 MHz, d_6-acetone) δ 7.71 (d, J = 7.2 Hz, 2H), 7.60 (d, J = 7.6 Hz, 2H), 7.57 – 7.54 (m, 1H), 7.54 (s, 2H), 7.49 (t, J = 7.5 Hz, 2H). ^{13}C NMR (125.8 MHz, d_6-DMSO) δ 196.9, 138.5, 132.5, 131.8, 129.9, 128.9, 128.6, 128.3. ^{11}B NMR (128.4 MHz, d_6-DMSO) δ 2.1. ^{19}F NMR (470.8 MHz, d_6-DMSO) δ -138.80, -139.83. IR (KBr) 1654**.** HRMS (ES-) calcd. for $C_{13}H_9BF_3O$ (M-K) 249.0699, found 249.0684.



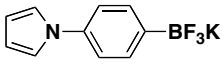
Potassium o-Tolyltrifluoroborate.[48] Following the general procedure, a mixture of 1-chloro-2-methylbenzene (190 mg, 176 μL, 1.5 mmol), tetrahydroxydiboron (403 mg, 4.5 mmol), XPhos (14.8 mg, 30 μmol), XPhos-Pd-G1 (11.08 mg, 15 μmol), KOAc (442 mg, 4.5 mmol), and NaO*t*-Bu (1.44 mg, 15 μmol) was heated to 80 ºC for 18 h. The concentrated crude reaction was taken up in MeOH (15 mL) and 6.5 equiv (2.2 mL) of a 4.5 M aqueous KHF_2 solution was added. The title compound was obtained as a white solid in 75% yield (222 mg). Spectral data in accordance with that of published results. ^{1}H NMR (500 MHz, d_6-acetone) δ 7.47 (d, J = 6.8 Hz, 1H), 6.96 – 6.86 (m, 3H), 2.39 (s, 3H). ^{13}C NMR (125.8 MHz, d_6-acetone) δ 140.9, 131.8, 128.2, 125.2, 123.2, 21.2.



Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate.[48] Following the general procedure, a mixture of 1-chloro-4-(trifluoromethyl)benzene (271 mg, 210 μL, 1.5 mmol), tetrahydroxydiboron (403 mg, 4.5 mmol), XPhos (14.8 mg, 30 μmol),

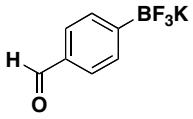
XPhos-Pd-G1 (11.08 mg, 15 μmol), KOAc (442 mg, 4.5 mmol), and NaO*t*-Bu (1.44 mg, 15 μmol) was heated to 80 ºC for 18 h. The concentrated crude reaction was taken up in MeOH (15 mL) and 6.5 equiv (2.2 mL) of a 4.5 M aqueous KHF_2 solution was added. The title compound was obtained as an off-white solid in 82% yield (310 mg). Spectral data in accordance with that of published results. ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.52 (d, J = 7.5 Hz, 2H), 7.41 (d, J = 7.6 Hz, 2H).

Potassium (3,5-Dimethoxyphenyltrifluoroborate.[44] Following the general procedure, a mixture of 1-chloro-3,5-dimethoxybenzene (345 mg, 2 mmol), tetrahydroxydiboron (270 mg, 3 mmol), XPhos (19 mg, 40 μmol), XPhos-Pd-G1 (14.8 mg, 20 μmol), KOAc (590 mg, 6 mmol), and NaO*t*-Bu (2 mg, 20 μmol) was heated to 80 ºC for 18 h. The title compound was obtained as a white solid in 92% yield (445 mg). Spectral data in accordance with that of published results. ^{1}H NMR (500 MHz, d_6-DMSO) δ 6.48 (s, 2H), 6.14 (s, 1H), 3.66 (s, 6H). ^{13}C NMR (125.8 MHz, d_6-DMSO) δ 159.3, 108.8, 99.7, 97.8, 54.7.



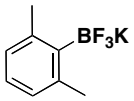
Potassium (4-(1H-Pyrrol-1-yl)phenyltrifluoroborate. Following the general procedure, a mixture of 1-(4-chlorophenyl)-1H-pyrrole (355 mg, 2 mmol), tetrahydroxydiboron (270 mg, 3 mmol), XPhos (19 mg, 40 μmol), XPhos-Pd-G1 (14.8 mg, 20 μmol), KOAc (590 mg, 6 mmol), and NaO*t*-Bu (2 mg, 20 μmol) was heated to 80 ºC for 18 h. The title compound was obtained as an off-white solid in 84% yield (314

mg). mp: >220 °C. ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.39 (d, J = 7.6 Hz, 2H), 7.25 (dd, J = 8.0 Hz, 5.2, 4H), 6.20 (d, J = 1.9 Hz, 2H). ^{13}C NMR (125.8 MHz, d_6-DMSO) δ 137.6, 132.3, 118.7, 117.7, 109.6. ^{11}B NMR (128.4 MHz, d_6-DMSO) δ 1.7. ^{19}F NMR (470.8 MHz, d_6-DMSO) δ -138.98. IR (KBr) 1604, 1328. HRMS (ES-) calcd. for $C_{10}H_8BF_3N$ (M-K) 210.0702, found 210.0702.

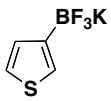


Potassium (4-Formylphenyl)trifluoroborate.[48] Following general procedure B, a mixture of 1-chloro-2-methylbenzene (190 mg, 176 μL, 1.5 mmol), tetrahydroxydiboron (403 mg, 4.5 mmol), XPhos (14.8 mg, 30 μmol), XPhos-Pd-G1 (11.08 mg, 15 μmol), KOAc (442 mg, 4.5 mmol), and NaO*t*-Bu (1.44 mg, 15 μmol) was heated to 80 ºC for 18 h. The reaction was cooled to rt then filtered through a thin pad of Celite (eluting with 100 mL EtOAc) and concentrated. To the crude concentrated reaction was added in equal parts 1 M aqueous HCl and EtOAc (20 mL each). This mixture was stirred 20 min before being added to a separatory funnel. The aqueous layer was removed, and the organic layer was washed once with brine. The organic layer was collected and the combined aqueous layers were further extracted with EtOAc (3 x 10 mL). The combined organics were dried (Na_2SO_4) and then concentrated under reduced pressure. The concentrated crude reaction was taken up in MeOH (15 mL) and 3 equiv (1 mL) of a 4.5 M aqueous KHF_2 solution was added. After precipitation with Et_2O, the solid taken up in CH_3CN (15 mL) and 3.5 equiv oven-dried K_2CO_3 (725 mg, 5.25 mmol) was added and the reaction stirred overnight. The mixture was concentrated then the

desired compound was obtained via hot filtration with acetone (3 x 20 mL). The title compound was obtained as an off-white solid in 80% yield (258 mg) as a mixture of the aldehyde (83%) and alcohol (17%). Spectral data in accordance with that of published results. ^{1}H NMR (500 MHz, d_6-DMSO) δ 10.37 (s, 1H), 8.14 (d, J = 7.3 Hz, 2H), 8.10 (d, J = 7.6 Hz, 2H). ^{13}C NMR (125.8 MHz, d_6-acetone) δ 193.5, 128.5, 125.8, 65.4. mp: >220 °C. IR (KBr) 1686. HRMS (ES-) calcd. for $C_7H_5BF_3O$ (M-K) 173.0386, found 173.0386.



Potassium (2,6-Dimethylphenyl)trifluoroborate.[48] Following the general procedure, a mixture of 2-chloro-1,3-dimethylbenzene (211 mg, 199 μL, 1.5 mmol), tetrahydroxydiboron (403 mg, 4.5 mmol), XPhos (14.8 mg, 30 μmol), XPhos-Pd-G1 (11.08 mg, 15 μmol), KOAc (442 mg, 4.5 mmol), and NaO*t*-Bu (1.44 mg, 15 μmol) was heated to 80 ºC for 18 h. The concentrated crude reaction was taken up in MeOH (15 mL) and 6.5 equiv (2.2 mL) of a 4.5 M aqueous KHF_2 solution was added. The title compound was obtained as a white solid in 50% yield (160 mg). Spectral data in accordance with that of published results. ^{1}H NMR (500 MHz, d_6-DMSO) δ 6.77 (t, J = 7.3 Hz, 1H), 6.68 (d, J = 7.2 Hz, 2H), 2.31 (s, 6H). ^{13}C NMR (125.8 MHz, d_6-DMSO) δ 140.9, 126.5, 124.5, 23.3, 23.3.

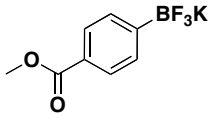


Potassium Thiophen-3-yltrifluoroborate.[48] Following the general procedure, a mixture of 3-chlorothiophene (178 mg, 140 μL, 1.5 mmol), tetrahydroxydiboron (403

mg, 4.5 mmol), XPhos (44.4 mg, 90 μmol), XPhos-Pd-G1 (33.24 mg, 45 μmol), KOAc (442 mg, 4.5 mmol), and NaO*t*-Bu (4.32 mg, 45 μmol) was heated to 50 ºC for 24 h. The concentrated crude reaction was taken up in MeOH (15 mL) and 6.5 equiv (2.2 mL) of a 4.5 M aqueous KHF_2 solution was added. The title compound was obtained as a white solid in 65% yield (185 mg). Spectral data in accordance with that of published results. ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.17 (s, 1H), 7.00 (s, 2H). ^{13}C NMR (125.8 MHz, d_6-DMSO) δ 131.9, 124.2, 122.5.

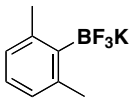
General Experimental Procedure for the Palladium-Catalyzed Borylation of Aryl and Heteroaryl Halides Utilizing XPhos-Pd-G2 and Their Conversion to Trifluoroborates: To an oven dried glass vessel capable of being sealed with a Teflon cap (for microwave vials) was added XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), $B_2(OH)_4$ (405 mg, 4.5 mmol), and KOAc (441 mg, 4.5 mmol). The vessel was sealed and then evacuated and backfilled with Ar (process was repeated four times). EtOH (15 mL degassed) was added via syringe followed by the addition of the halide (1.5 mmol) in a similar manner (solid halides were added with the other solid reagents before sealing). The reaction was then heated to 80 ºC (in a preheated oil bath) until the starting material was consumed (as monitored by GC). The reaction was cooled to rt then filtered through a thin pad of Celite (eluting with 5 x 10 mL of EtOAc), and concentrated. The crude reaction was dissolved in EtOAc (10 mL) and then transferred to a separatory funnel followed by the addition of H_2O (10 mL). The layers were separated and the organic layer was washed once with brine. The combined aqueous layers were further

extracted with EtOAc (3 x 5 mL). The combined organics were dried (Na_2SO_4) and concentrated. The concentrated crude reaction (unless otherwise indicated) was taken up in MeOH (~15 mL or enough to make a free-flowing solution) and cooled to 0 ºC. To this cooled mixture was added 4.5 equivalents of a 4.5 M aqueous KHF_2 solution (1 mL), and the reaction was stirred for 10 min at 0 ºC before removing the bath and allowing the mixture to stir at rt for 20 min (or until the conversion to the corresponding trifluoroborate was achieved as determined by ^{11}B NMR). The resulting mixture was then concentrated and then lyophilized overnight to remove any traces of water. The compound was purified with continuous Soxhlet extraction (overnight) with acetone (150 mL). The collected solvent filtered through a thin pad of Celite, rinsed with hot acetone (3 x 5 mL) then concentrated until a minimal volume of acetone remained (~3 mL). The addition of Et_2O (~25 mL) led to the precipitation of the desired product. The collected solid was washed with Et_2O. Further purification (to remove small organic or boron containing impurities) could be realized via trituration of the solid with Et_2O.

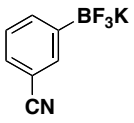


Potassium (4-(Methoxycarbonyl)phenyl)trifluoroborate. Following the general procedure, a mixture of methyl 4-bromobenzoate (322 mg, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 3 h. The title compound was obtained as a white solid in 93% yield (337 mg). Spectral data were in accordance with those of a commercially available sample. mp > 225 ºC. ^1H

NMR (500 MHz, acetone-d_6) δ 7.76 (d, J = 7.4 Hz, 2H), 7.58 (d, J = 7.3 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 167.7, 132.0, 127.8, 127.0, 52.2. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.5 (m). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -141.1.

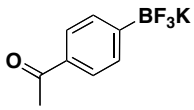


Potassium (2,6-Dimethylphenyl)trifluoroborate.[49] Following the general procedure, a mixture of 2-bromo-1,3-dimethylbenzene (277.6 mg, 200 μL, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 5 h. The title compound was obtained as a white solid in 42% yield (132 mg). Spectral data were in accordance with those of published results. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 6.80 – 6.74 (m, 1H), 6.70 (d, J = 7.2 Hz, 2H), 2.36 (s, 6H). ^{13}C NMR (125.8 MHz, acetone-d_6) δ 141.6, 126.8, 124.9, 22.9 (d, J = 2.52 Hz). ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.6 (q, J = 59 Hz). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -132.3.

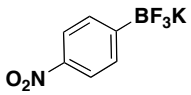


Potassium (3-Cyanophenyl)trifluoroborate. Following the general procedure, a mixture of 3-bromobenzonitrile (273 mg, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 5 h. The title compound was obtained as a white solid in 94% yield (296 mg). Spectral data were in accordance with those of a commercially available sample. . mp = 175 °C dec. ^{1}H NMR (500 MHz,

acetone-d_6) δ 7.75 (s, 2H), 7.41 (d, J = 7.5 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H). ^{13}C NMR (125.8 MHz, acetone-d_6) δ 136.3, 135.3, 128.8, 127.3, 120.3, 110.2. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.4 (q, J = 51 Hz). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -141.9.

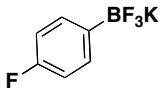


Potassium (4-Acetylphenyl)trifluoroborate.[50] Following the general procedure, a mixture of 1-(4-bromophenyl)ethanone (298.5 mg, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 2 h. The title compound was obtained as a white solid in 95% yield (323 mg) as a mixture of the ketone (86%) and palladium-hydride reduced (alcohol) product (9%). Spectral data were in accordance with those of a commercially available sample. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.73 (d, J = 7.6 Hz, 2H), 7.58 (d, J = 7.5 Hz, 2H), 2.49 (s, 3H). ^{13}C NMR (125.8 MHz, DMSO- d_6) δ 198.8, 134.9, 132.0, 126.9, 27.1. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.9 (m). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -141.

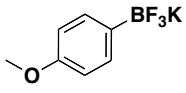


Potassium (4-Nitrophenyl)trifluoroborate.[49] Following the general procedure, a mixture of 1-bromo-4-nitrobenzene (303 mg, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 4 h. The title compound was obtained as a light reddish-brown solid in 64% yield (220 mg) as a

mixture of the nitro (45%) and palladium-hydride reduced (aniline) product (20%). Spectral data were in accordance with those of published results. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.97 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 7.7 Hz, 2H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 146.4, 132.7, 121.8. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.2 (q, J = 50.5 Hz). ^{19}F NMR (282 MHz, acetone-d_6) δ -144.1.

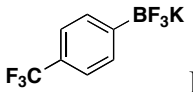


Potassium (4-Fluorophenyl)trifluoroborate.[49] Following the general procedure, a mixture of 1-bromo-4-fluorobenzene (262 mg, 165 μL, 1.5 mmol XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 4 h. The title compound was obtained as a white solid in 95% yield (288 mg). Spectral data were in accordance with those of published results. mp = 210 °C dec. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.45 (t, J = 7.2 Hz, 2H), 6.81 (t, J = 9.0 Hz, 2H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 162.4, 160.6, 133.4 (d, J = 6.3 Hz), 113.26 (d, J = 17.6 Hz). ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.9 (q, J = 54 Hz). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -141.9, -120.6.

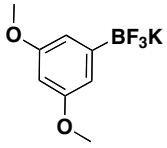


Potassium 4-Methoxyphenyl-trifluoroborate.[49] Following the general procedure, a mixture of 4-bromoanisole (214 mg, 182 μL, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 4 h. The title

compound was obtained as a white solid in 94% yield (289 mg). Spectral data were in accordance with those of published results. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.37 (d, J = 8.1 Hz, 2H), 6.67 (d, J = 8.1 Hz, 2H), 3.69 (s, 3H). ^{13}C NMR (125.8 MHz, acetone-d_6) δ 158.0, 132.7, 111.9, 54.2. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.3 (m). ^{19}F NMR (282 MHz, acetone-d_6) δ -141.8.

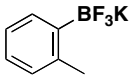


Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate.[49] Following the general procedure, a mixture of 1-bromo-4-(trifluoromethyl)benzene (337 mg, 210 μL, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 3 h. The title compound was obtained as an off-white solid in 88% yield (332 mg). Spectral data were in accordance with those of published results. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.64 (d, J = 7.6 Hz, 2H), 7.39 (d, J = 7.8, Hz 2H). ^{13}C NMR (125.8 MHz, acetone-d_6) δ 132.1, 127.1, 126.9, 126.6, 124.4, 122.8. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.5 (q, J = 51.8 Hz). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -143.3, -62.4.

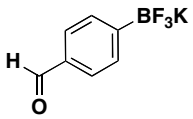


Potassium (3,5-Dimethoxyphenyl)trifluoroborate.[49] Following the general procedure, a mixture of 1-bromo-3,5-dimethoxybenzene (326 mg, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5

mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 4 h. The title compound was obtained as an off-white solid in 98% yield (375 mg). Spectral data were in accordance with those of published results. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 6.66 (s, 2H), 6.16 (t, J = 2.3 Hz, 1H), 3.68 (s, 6H). ^{13}C NMR (125.8 MHz, acetone-d_6) δ 159.9, 109.1, 97.9, 54.3. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.9 (m). ^{19}F NMR (338.8 MHz, DMSO-d_6) δ -142.5.

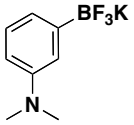


Potassium o-Tolyltrifluoroborate.[49] Following the general procedure, a mixture of 1-bromo-2-methylbenzene (256 mg, 180 μL, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 9 h. The title compound was obtained as an off-white solid in 80% yield (239 mg). Spectral data were in accordance with those of published results. . mp = 215 °C dec. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.46 (d, J = 6.7 Hz, 1H), 6.95 – 6.81 (m, 3H), 2.38 (s, 3H). ^{13}C NMR (125.8 MHz, acetone-d_6) δ 141.1, 132.1, 128.3, 125.2, 123.4, 21.4. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 1.6 (q, J = 57 Hz). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -140.5.

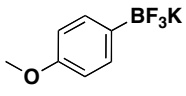


Potassium (4-Formylphenyl)trifluoroborate.[49] Following the general procedure, a mixture of 4-bromobenzaldehyde (277 mg, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$

(405 mg, 4.5 mmol), was heated to 80 ºC in MeOH (15 mL) for 4 h. The title compound was obtained as a white solid in 75% yield (240 mg) as a mixture of the aldehyde (45%) and palladium-hydride reduced (alcohol) product (30%). A reasonable spectra could not be obtained.

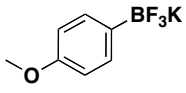


(3-(Dimethylamino)phenyl)trifluoroborate. Following the general procedure, a mixture of 4-bromobenzaldehyde (277 mg, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 3.5 h. After the standard workup (using sat. aq $NaHCO_3$ solution instead of H_2O during the aqueous workup), the title compound was obtained as a pale pink solid in 94% yield (320 mg). mp 185–187 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 6.99 (s, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.0 Hz, 1H), 6.52 – 6.47 (m, 1H), 2.83 (s, 6H). ^{13}C NMR (125.8 MHz, acetone-d_6) δ 150.0, 126.9, 121.4, 121.4, 117.2, 117.2, 110.9, 40.6. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.1. ^{19}F NMR (282 MHz, acetone-d_6) δ -142.2. IR (dry film): 1597, 1217. HRMS (ES-) calcd. for $C_8H_{10}BF_3N$: 188.0888 (M-K), found 188.0876.

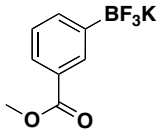


Potassium 4-Methoxyphenyl-trifluoroborate.[49] Following the general procedure, a mixture of 4-chloroanisole (214 mg, 183 μL, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and

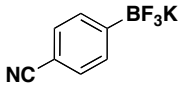
$B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 2 h. The title compound was obtained as a white solid in 93% yield (298 mg). Spectral data were in accordance with those of published results. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.37 (d, J = 7.8 Hz, 2H), 6.67 (d, J = 7.9 Hz, 2H), 3.69 (s, 3H). ^{13}C NMR (125.8 MHz, acetone-d_6) δ 158.0, 132.7, 111.9, 54.2. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.43 – 4.03 (m). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -141.7.



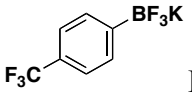
Potassium 4-Methoxyphenyl-trifluoroborate.[49] A mixture of $Pd(OAc)_2$ (1.68 mg, 7.5 μmol), XPhos (10.71 mg, 22.5 μmol), and KOAc (441 mg, 4.5 mmol) was heated to 80 ºC in EtOH (3 mL) for 20 min. The reaction was cooled to rt, a needle attached to a manifold under argon was inserted into the septa and 4-chloroanisole (214 mg, 183 μL, 1.5 mmol) was added neat via syringe followed by the addition of a solution of $B_2(OH)_4$ (405 mg, 4.5 mmol) in EtOH (12 mL). The needle was removed, and the reaction was heated to 80 ºC for an additional 1 h. See the general procedure for work-up. The title compound was obtained as a white solid in 95% yield (306 mg). Spectral data were in accordance with those of published results. mp > 225 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.21 (d, J = 7.4 Hz, 2H), 6.65 (d, J = 7.5 Hz, 2H), 3.65 (s, 3H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 157.8, 132.9, 112.5, 55.1. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.40 – 4.01 (m). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -141.8.



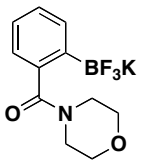
Potassium (3-(Methoxycarbonyl)phenyl)trifluoroborate.[49] Following the general procedure, a mixture of methyl 3-chlorobenzoate (256 mg, 208 μL, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 2.5 h. The title compound was obtained as a white solid in 97% yield (351 mg). Spectral data were in accordance with those of published results. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 8.23 (s, 1H), 7.74 (t, J = 7.4 Hz, 2H), 7.24 (t, J = 7.4 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 167.9, 136.8, 132.8, 127.9, 126.9, 126.5, 52.1. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.02 – 3.61 (m). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -143.2.



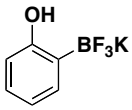
Potassium (4-Cyanophenyl)trifluoroborate.[49] Following the general procedure, a mixture of 4-chlorobenzonitrile (206 mg, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 1 h. The title compound was obtained as a white solid in 81% yield (255 mg). Spectral data were in accordance with those of published results. mp > 225 ºC**.** ^{1}H NMR (500 MHz, acetone-d_6) δ 7.65 (d, J = 7.6 Hz, 2H), 7.48 (d, J = 7.7 Hz, 2H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 132.5, 130.4, 120.5, 108.1. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.64 – 3.25 (m). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -143.9.



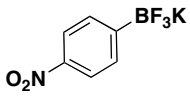
Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate.[49] Following the general procedure, a mixture of 1-chloro-4-(trifluoromethyl)benzene (2.166 g, 1.6 mL, 12 mmol), $B_2(OH)_4$ (3.24 g, 36 mmol), XPhos (11.42 mg, 0.024 mmol), XPhos-Pd-G2 (9.43 mg, 0.012 mmol), and KOAc (3.5 g, 36 mmol) was heated to 80 ºC in EtOH (24 mL) for 3 h. The title compound was obtained as an off-white solid in 88% yield (2.6 g). Spectral data were in accordance with those of published results. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.64 (d, J = 7.5 Hz, 2H), 7.40 (d, J = 7.5 Hz, 2H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 175.0, 132.31, 126.9, 126.8, 126.6, 126.4, 126.1, 124.6, 123.4, 123.34. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.7. ^{19}F NMR (338.8 MHz, acetone-d_6) δ -62.2, -142.8.



Potassium 2-(Morpholine-4-carbonyl)phenyl-trifluoroborate. Following the general procedure, a mixture of (2-chlorophenyl)(morpholino)methanone (338 mg, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 4 h. The title compound was obtained as a white solid in 13% yield (58 mg). The title compound was obtained as an inseparable mixture of the trifluoroborate and the protodeboronated product. As a result, reasonable spectra for this compound could not be obtained.

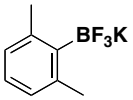


2-Hydroxyphenyltrifluoroborate.[51] Following the general procedure, a mixture of 2-chlorophenol (193 mg, 155 μL, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 1.5 h. The title compound was obtained as a white solid in 17% yield (50 mg). Spectral data were in accordance with those of published results. mp = 195 °C dec. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.50 (dd, J = 11.3 Hz, 1H), 7.28 (s, 1H), 6.88 (t, J = 7.4 Hz, 1H), 6.58 (t, J = 7.1 Hz, 1H), 6.50 (d, J = 7.9 Hz, 1H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 159.9, 133.5, 127.5, 118.9, 113.8. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.0 (q, J = 56 Hz). ^{19}F NMR (338.8 MHz, DMSO-d_6) δ -137.3.

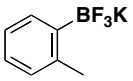


Potassium (4-Nitrophenyl)trifluoroborate.[49] Following the general procedure, a mixture of 1-chloro-4-nitrobenzene (236 mg, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 2 h. The title compound was obtained as a light reddish-brown solid in 64% yield (220 mg). Spectral data were in accordance with those of published results. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 8.00 (d, J = 8.1 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 146.3, 132.6, 121.7. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.9 (m). ^{19}F

NMR (338.8 MHz, acetone-d_6) δ -138.9.

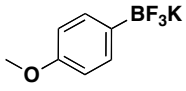


Potassium (2,6-Dimethylphenyl)trifluoroborate.[49] Following the general procedure, a mixture of 2-chloro-1,3-dimethylbenzene (211 mg, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 4.5 h. The title compound was obtained as a white solid in 53% yield (167 mg). Spectral data were in accordance with those of published results. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 6.82 – 6.77 (m, 1H), 6.72 (d, J = 7.3 Hz, 2H), 2.41 (s, 6H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 141.4, 126.9, 124.9, 23.8 (d, J = 2.52 Hz). ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.7 (q, J = 59 Hz). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -132.4.

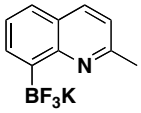


Potassium *o*-Tolyltrifluoroborate.[49] Following the general procedure, a mixture of 1-chloro-2-methylbenzene (190 mg, 176 μL, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 3.5 h. After the standard workup (using sat. aq. $NaHCO_3$ solution instead of H_2O during the aqueous workup), the title compound was obtained as a white solid in 95% yield (281 mg). Spectral data were in accordance with those of published results. mp = 210 °C dec. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.29 (s, 1H), 6.96 – 6.79 (m, 3H), 2.26 (s, 3H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 140.9, 132.0 (d, J = 2.52 Hz), 128.6, 125.5, 123.8, 22.1. ^{11}B NMR (128.4

MHz, acetone-d_6) δ 4.2 (q, J = 56 Hz). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -140.5.

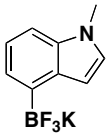


Potassium 4-Methoxyphenyl-trifluoroborate.[49] Following the general procedure, a mixture of 4-iodoanisole (351 mg, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 7 h. The title compound was obtained as a white solid in 73% yield (234 mg). Spectral data were in accordance with those published. mp > 225 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.25 (d, J = 8.1 Hz, 2H), 6.68 (d, J = 8.0 Hz, 2H), 3.66 (s, 3H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 157.4, 132.4, 111.9, 54.6. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.4 – 4.0 (m). ^{19}F NMR (339 MHz, acetone-d_6) δ -140.9.



Potassium (2-Methylquinolin-8-yl)trifluoroborate. Following the general procedure, a mixture of 8-chloro-2-methylquinoline (266 mg, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 2 h. The title compound was obtained as a yellow solid in 52% yield (194 mg). mp > 225 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 8.05 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 6.5 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.33 (t, J = 7.3 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 2.70 (s, 3H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 156.4, 151.7, 136.7, 133.4, 126.3, 126.2, 125.3, 120.9, 25.7. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.9. ^{19}F NMR (282 MHz, acetone-d_6) δ -138.8. IR

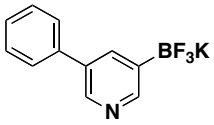
(dry film): 2924, 2340. HRMS (ES-) calcd. for $C_{10}H_8BF_3N$: 210.0696 (M-K), found 210.0702.



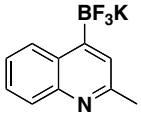
Potassium (2-Methylquinolin-8-yl)trifluoroborate. Following the general procedure, a mixture of 4-chloro-1-methyl-1H-indole (315 mg, 216 μL, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 5 h. The title compound was obtained as a peach-colored solid in 80% yield (285 mg). mp > 225 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.17 (d, J = 6.7 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 7.4 Hz, 1H), 6.94 (d, J = 3.0 Hz, 1H), 6.71 (s, 1H), 3.71 (s, 3H). ^{13}C NMR (125.8 MHz, DMSO) δ 136.1, 132.2, 127.2, 122.2 (d, J = 2.52 Hz), 120.7, 106.7, 104.1, 32.8. ^{19}F NMR (282 MHz, acetone-d_6) δ -139.9. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.09. IR (dry film): 2348, 1514. HRMS (ES-) calcd. for $C_9H_8BF_3N$: 198.07029 (M-K), found 198.0702.

General Experimental Procedure for the Palladium-Catalyzed Borylation of Heteroaryl Halides Utilizing Aminobiphenyl Prcatalyst Scaffold Containing CataCXium A and Their Conversion to Trifluoroborates: To an oven dried glass vessel capable of being sealed with a Teflon cap (for microwave vials) was added CataCXium A palladium(II) biphenyl preformed catalyst, CataCXium A-Pd-G2 (50 mg, 75 μmol) and $B_2(OH)_4$ (405 mg, 4.5 mmol). The vessel was sealed and then evacuated and backfilled with Ar (process was repeated four times). MeOH (7.5 mL, degassed) was

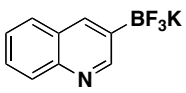
added via syringe followed by the addition of the halide (1.5 mmol) and DIEA (784 μL, 4.5 mmol) in a similar manner (solid halides were added with the other solid reagents before sealing). The reaction was then heated to 50 ºC until the starting material was consumed (as monitored by GC). The reaction was cooled to rt then filtered through a thin pad of Celite (eluting with 5 x 10 mL EtOAc), and concentrated. The crude reaction was dissolved in EtOAc (10 mL) and then transferred to a separatory funnel followed by the addition of sat. $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (3 x 5 mL). The combined organics were dried (Na_2SO_4) and concentrated. The concentrated crude reaction (unless otherwise indicated) was taken up in MeOH (~15 mL or enough to make a free-flowing solution) and cooled to 0 ºC. To this cooled mixture was added 4.5 equivalents of a 4.5 M aq KHF_2 solution (1 mL), and the reaction was stirred for 10 min at 0 ºC before removing the bath and allowing the mixture to stir at rt for 20 min (or until the conversion to the corresponding trifluoroborate was achieved as determined by ^{11}B NMR). The resulting mixture was then concentrated and then lyophilized overnight to remove any traces of water. The compound was purified with continuous Soxhlet extraction (overnight) with acetone (150 mL). The collected solvent was filtered through a thin pad of Celite, rinsed with hot acetone (3 x 5 mL) then concentrated until a minimal volume of acetone remained (~3 mL). The addition of Et_2O (~25 mL) led to the precipitation of the desired product. The collected solid was washed with Et_2O. Further purification (to remove small organic or boron containing impurities) could be realized via trituration of the solid with Et_2O.



Potassium (5-Phenylpyridin-3-yl)trifluoroborate. Following the general procedure, 3-bromo-5-phenylpyridine (351 mg, 1.5 mmol), CataCXium A-Pd-G2 (50 mg, 75 μmol), DIEA (581 mg, 785 μL, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 50 ºC in MeOH (7.5 mL) for 1 h. After the standard workup (using sat. aq. $NaHCO_3$ solution instead of H_2O during the aqueous workup), the title compound was obtained as an off-white solid in 64% yield (238 mg) as a mixture of the trifluoroborate and internal salt. As such, reasonable NMR spectra could not be obtained and the compound was subjected to a two-step, one-pot borylation/Suzuki reaction (Chapter 5).



Potassium (2-Methylquinolin-4-yl)trifluoroborate. Following the general procedure, a mixture of 4-chloroquinalidine (266 mg, 302 μL, 1.5 mmol), CataCXium A-Pd-G2 (50 mg, 75 μmol), DIEA (581 mg, 785 μL, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 50 ºC in MeOH (7.5 mL) for 1.5 h. The title compound was obtained as a white solid in 47% yield (175 mg) as a mixture of the trifluoroborate and internal salt. As such, reasonable NMR spectra could not be obtained, and the compound was subjected to a two-step, one-pot borylation/Suzuki reaction (Chapter 5).



Potassium (Quinolin-3-yl)trifluoroborate. Following the general procedure, a mixture of 3-bromoquinoline (312 mg, 202 μL, 1.5 mmol), CataCXium A-

Pd-G2 (50 mg, 75 μmol), DIEA (581 mg, 785 μL, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 50 ºC in MeOH (7.5 mL) for 5 h. The title compound was obtained as a white solid in 78% yield (275 mg) as a mixture of the trifluoroborate and internal salt. As such, reasonable NMR spectra could not be obtained and the compound was subjected to a two-step, one-pot borylation/Suzuki reaction (Chapter 5).

Kinetics Experiements:

Time course studies were run under general reaction conditions provided above and from previously described experimentals[49] on 0.5 mmol scale at 80 ˚C over the course of 4 h. A Chemspeed SLT 100 removed 30 μL aliquots t(0) and every 15 min thereafter. Samples were quenched into MeCN (700 μL) with 6 equiv of pinacol. At the completion of the reaction, the diluted samples were analyzed by HPLC.

Inhibitory Experiments:

Bromide ion inhibitory experiments studies were run under general reaction conditions (vide supra) on 0.5 mmol scale at 80 ˚C over the course of 5 h. To the corresponding reactions were added 1, 5, or 10 equiv of tetra-*n*-butylammonuim bromide (TBAB). A Chemspeed SLT 100 removed 30 uL aliquots t(0) every 5 minutes for 1 h, then samples were removed every 10 min for 2 h thereafter. Samples were quenched into MeCN (700 μL) with 6 equiv of pinacol. At the completion of the reaction, the diluted samples were analyzed by HPLC.

3.6 References

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Chapter 4. Palladium-Catalyzed Borylation of Aryl Halides and Pseudohalides Utilizing Tetrakis(dimethylamino)diboron

4.1 Introduction

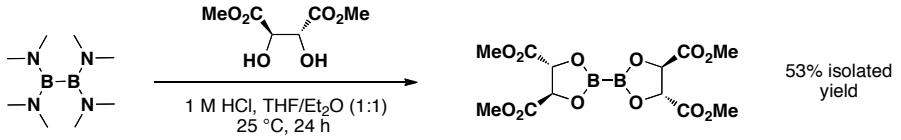
The availability of dibora compounds has enabled discovery most notably in the area of metal catalyzed reactions. Until recently, little effort has gone into utilizing dibora species other than the most commonly used bis(pinacolato)diboron (B_2Pin_2). We have contributed largely in this area by developing convenient and efficient methods utilizing BBA. Tetrakis(dimethylamino)diboron (tetrakis) is the common synthetic precursor to both bis-boronic acid (BBA) and B_2Pin_2. Through its use, we have developed a new and efficient method of palladium-catalyzed borylation.

4.2 History of the Synthetic Uses of Tetrakis(dimethylamino)diboron

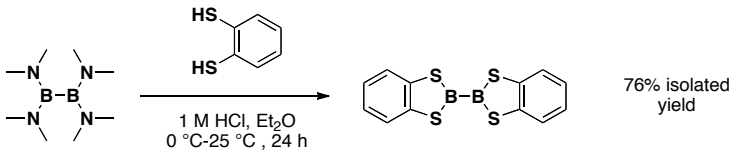
Since the first synthesis of tetrakis by Brotherton and McKloskey of the Borax Chemical Company in 1960,[1] tetrakis has appeared in the chemical literature as a precursor to other dibora derivatives including tetralkoxydiborons,[2-6] tetralkyldiborons,[7] bi(dithiol)catecholates,[8] and tetra(amino)diboron derivatives.[9] One of the first of these conversions was the synthesis of BBA in 1961 by Brotherton and co-workers[10] as a part of their ongoing study toward the synthesis of boron monoxide, amongst other compounds. Nearly five decades later, the synthesis of tetrakis has remained relatively unchanged. Because of its high thermal stability, ready availability from the Wurtz coupling of $BrB(NMe_2)_2$,[11] and high-yielding conversions, tetrakis has remained the reagent of choice en route to diverse dibora species. Illustrations of its use are outlined in

Equations 4.1-4.3.[5,6,8]

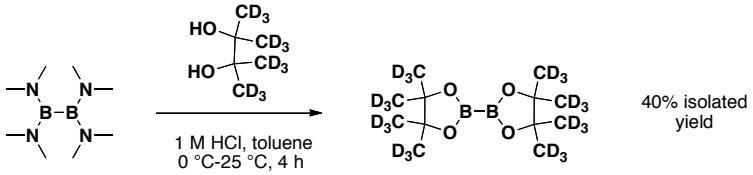
Equation 4.1



Equation 4.2

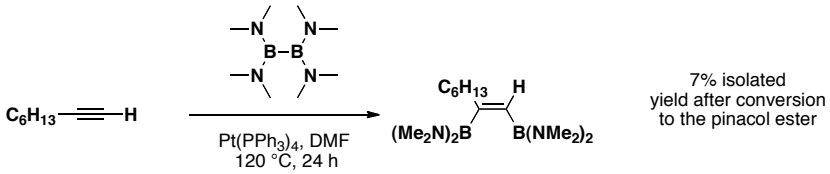


Equation 4.3

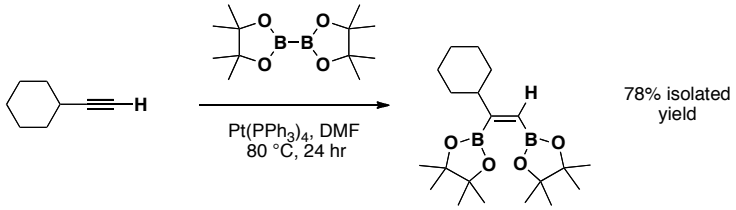


A decade after the first report on the synthesis of B_2Pin_2 from tetrakis in 1984,[12] Suzuki and Miyaura worked to develop a general method of bis-borylation across alkynes. They experimented with two dibora derivatives, B_2Pin_2 and its precursor, tetrakis.[13] In the presence of Pt(0), B_2Pin_2 far out-performed tetrakis during a 24 hour reaction time. In fact, only a 7% yield was reported when tetrakis (Equation 4.4) was utilized (83% unreacted tetrakis observed even at 120 °C) compared with a yield of 78% with B_2Pin_2 (Equation 4.5). Because of these results, tetrakis was abandoned as a possible reagent, and the method was optimized with B_2Pin_2.

Equation 4.4

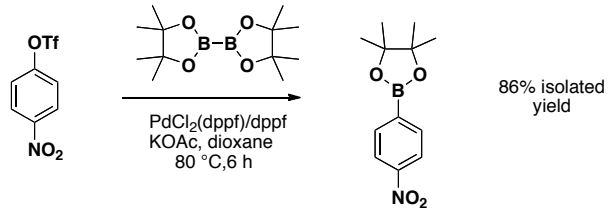


Equation 4.5

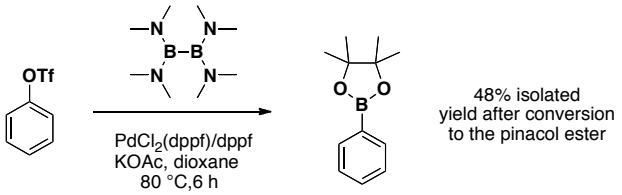


Suzuki and Miyaura did not lose all hope of tetrakis however, and attempted to use it again one year later in their method development of palladium-catalyzed borylation of aryl triflates.[14] Again, they reported unsatisfactory yields and long reaction times as compared to B_2Pin_2 (Equation 4.6), abandoning tetrakis once and for all as an effective borylating reagent (Equation 4.7).

Equation 4.6



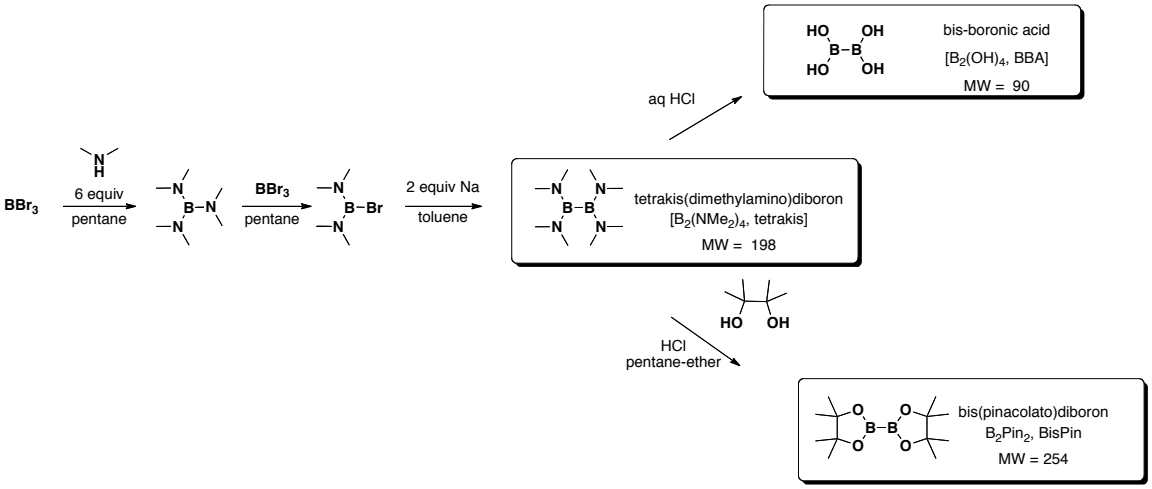
Equation 4.7



4.3 Method Development of the Use of Tetrakis as a General Borylating Reagent

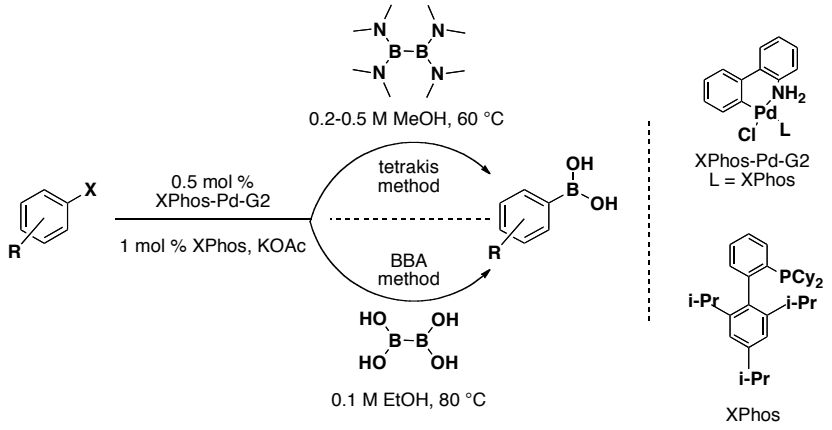
After completing an exploration of the scope of the palladium-catalyzed borylation of aryl halides utilizing BBA,[15] we were interested to see if we could go one-step backward, utilizing tetrakis as a borylating agent. As the sequence for the synthesis of BBA is shared with that of B_2Pin_2 up to the common precursor tetrakis,[10,16] such a method would remove the necessity to convert tetrakis into BBA or B_2Pin_2, reducing both time and chemical waste (Scheme 4.1).

Scheme 4.1 Syntheses of BBA and B_2Pin_2 from Shared Precursor Tetrakis



Returning to HTE, a high-yielding method was quickly identified. The best conditions required only slight modifications to our optimized method using BBA and XPhos-Pd-G2. The same low catalyst load of 0.5 mol % with 1.0 mol % of XPhos (3:1 ligand/catalyst) is used as well as 3 equivalents of KOAc. And although the BBA method is performed in EtOH, the method with tetrakis produces higher yields when run in MeOH. Aside from the fact that BBA is a solid and tetrakis is a liquid, operationally speaking, the set-up of the reactions is identical. As all reagents used are air stable, the solids are first weighed on a bench top balance. The vessel is then sealed and placed under an atmosphere of argon. Degassed MeOH is added to the reaction via syringe, followed by tetrakis in a similar manner. The mixture is then heated for the time required (Scheme 4.2).

Scheme 4.2 Comparison of Borylating Methods Utilizing BBA or Tetrakis



When BBA was used in our previous method, a very distinct color change occurred, indicating the completion of the reaction. Although a color change is observed

with tetrakis, it is slightly less distinct with some substrates, and therefore a GC analysis is performed to confirm consumption of starting material. As in our method with BBA, we found it difficult to obtain the pure crystalline form of the boronic acid without some loss in yield. Therefore, all crude boronic acids were conveniently converted to the corresponding trifluoroborates. This transformation also preserves the C-B bond more effectively if the compounds are to be stored on the bench top for prolonged periods of time.

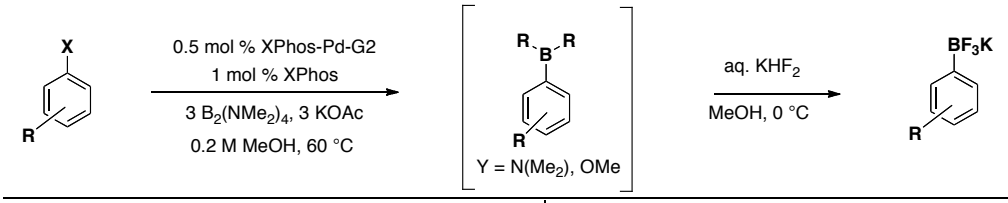
4.4 Results and Discussion

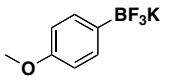
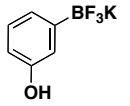
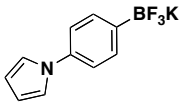
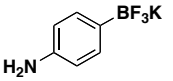
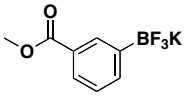
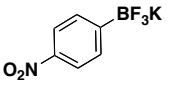
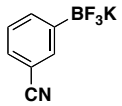
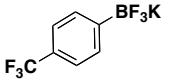
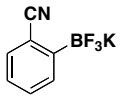
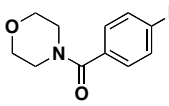
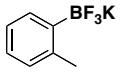
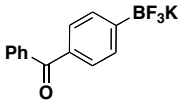
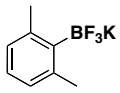
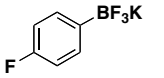
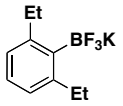
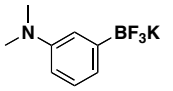
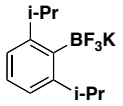
4.4.1 Palladium-Catalyzed Borylation of Aryl Chlorides and Bromides with Tetrakis

The scope of the borylation of aryl chlorides and bromides is outlined in Table 4.1. As seen in our previous methods, the boronic acid is obtained in a lower yield of 85% versus that of its trifluoroborate counterpart (97% yield, Table 4.1, entries 8 and 8[g]). As we sought to demonstrate the efficiency of the current method and to preserve the sensitive C-B bond, all crude boronic acids were converted directly to the more stable trifluoroborate salts. The method tolerates a wide range of functional groups, providing most trifluoroborates in good to excellent yield. It should also be noted that increasing the solvent concentration from 0.2 M MeOH to 0.5 M did not appear to affect the yield in the substrates attempted (Table 4.1, entries 1[a] and 8[a]). Based upon our current understanding of the borylation mechanism, dimethylamine gas is released upon conversion of tetrakis into the methyl ester. As the reaction is run in a sealed vessel under the general conditions, there is a build up of pressure in the form of dimethylamine gas. To determine

whether the pressure if dimethylamine was critical to the success of the reaction, a reaction was performed in a round bottom flask fitted with a reflux condenser. There was no apparent difference in carrying out the reaction under these conditions (Table 4.1, entry 2[c]). The reaction can also be efficiently scaled to 10 mmol with no loss in yield (Table 4.1, entry 5[e]).

Table 4.1 Synthesis of Trifluoroborates Utilizing Tetrakis and XPhos-Pd-G2



entry	X	product	time (h)	% isolated yield	entry	X	product	time (h)	% isolated yield
1	Cl		5	94, 94[a], 93[b]	10	Cl		5	84[d], 97[b]
2	Cl		3	96, 86[b], 93[c]	11	Br		5	96[d,h], 87[b,h]
3	Cl		7	39[d], 68[b]	12	Br		3	84, 97[b]
4	Br		3.5	56, 64[b]	13	Br		6	91, 94[b]
5	Cl		2.5	97, 91[b], 98[d,e]	14	Br		7	4[d], 27[b]
6	Cl		5.5	85, 81[b]	15	Br		26	75, 80[b]
7	Cl		2.5	92[d], 91[b]	16	Cl		22	81[d], 53[b]
8	Cl		3	97, 98[a] 98[b], 87[f], 85[g]	17	Cl		22	43[d]
9	Br		6		18	Cl		22	0[d]

General conditions: 0.5 mol % XPhos-Pd-G2, 1.0 mol % XPhos, 3.0 equiv KOAc, 3.0 equiv $B_2(NMe_2)_4$, MeOH (0.2 M), 60 ˚C for time indicated. [a] 0.5 M MeOH. [b] Yield from previous method with $B_2(OH)_4$ as boron source. [c] Reaction run in a round bottom flask with reflux condenser under argon. [d] Compound synthesized by Dr. Steven Kennedy. [e] 10 mmol reaction run under general reaction conditions. [f] (1) 5.0 mol % of $Pd(OAc)_2$, 10 mol % of XPhos, 3.0 equiv of KOAc, 60 ˚C in 2 mL MeOH for 20 min. (2) 3.0 equiv of $B_2(NMe_2)_4$ dissolved in 5.5 mL of MeOH, 1-chloro-4-fluorobenzene, 60 ˚C for time indicated. [g] Yield of isolated boronic acid. [h] From the acetonide.

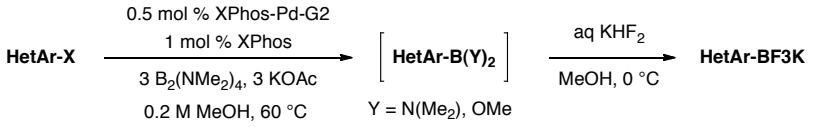
Although not as operationally simple, the less expensive $Pd(OAc)_2$ can be used in place of XPhos-Pd-G2, providing the 4-fluorophenyltrifluoroborate in 87% yield (Table 4.1, entry 8[f]). Tetrakis appears in our hands to be more stable to the borylation reaction conditions than BBA, but preconversion of $Pd(OAc)_2$ to Pd(0) or the use of the preformed Pd-XPhos-G2 still provides far superior conversion to product than reactions using $Pd(OAc)_2$ directly. Preformation to Pd(0) is adequately achieved by heating $Pd(OAc)_2$ with XPhos and KOAc in MeOH for 30 min at 60 °C before addition of tetrakis and the aryl halide.

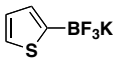
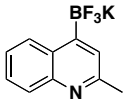
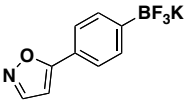
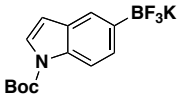
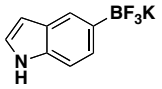
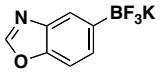
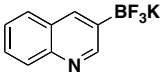
For comparison, yields of trifluoroborates obtained through the use of BBA are also included in Table 4.1 (denoted with superscript b).[15] In general, yields are comparable across both synthetic platforms (Table 4.1, entries 1, 6-9, 13, and 15). In a few instances, BBA provides yields 10% or above that of tetrakis (Table 4.1, entries 3, 4, 10, and 12). Noteworthy are the cases where tetrakis significantly outperforms BBA (Table 4.1, entries 2, 5, and 11), with the 2,6-dimethylphenyltrifluoroborate (Table 1, entry 16) providing the most impressive example of reactivity differences. Even the 2,6-diethylphenyltrifluoroborate was obtained in a reasonable yield of 43% (Table 4.1, entry 17). The complementary nature of the two methods now provides more synthetic options for the borylation of aryl halides.

4.4.2 Palladium-Catalyzed Borylation of Heteroaryl Chlorides and Bromides with Tetrakis

The method was also extended to heteroaryl halides, further demonstrating that certain substrates provide superior results employing one method over the other (yields of trifluoroborates obtained from our method utilizing BBA and XPhos-Pd-G2 are also included in the Table, denoted with superscript b). For example, both the isoxazole- and benzoxazole-substituted phenyltrifluoroborates are obtained in superior yield when BBA is used as the borylating source (Table 4.2, entries 4 and 7). However, tetrakis can be utilized to afford 3-thienyltrifluoroborate, a material that could not be accessed in the previously developed BBA method. With respect to the indoles synthesized, the use of a Boc protecting group provides significantly higher yields than when it is not used (Table 4.2, entries 5 and 6), with tetrakis providing good to excellent results for both. Most noteworthy when comparing methods is the significant difference in catalyst load when borylating heteroaryl compounds (Table 4.2, entries 3 and 5). When using BBA, 5 mol % palladium was required employing cataCXium A as ligand. With tetrakis, a 10-fold decrease in catalyst loading could be achieved (0.5 mol %) with XPhos-Pd-G2.

Table 4.2 Synthesis of Trifluoroborates from Heteroaryl Chlorides or Bromides



entry	X	product	time (h)	% isolated Yield
1	Cl		6	45[a]
2	Cl		5	5[a]
3	Cl		11	58, 47[b]
4	Br		5.5	37[a], 85[b]
5	Br		4.5	96[a], 93[b]
6	Br		6	70[a]
7	Cl		5	36[a], 81[b]
8	Br		5	64[a], 68[b]

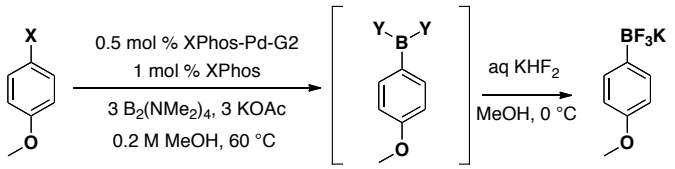
General conditions: 0.5 mol % XPhos-Pd-G2, 1.0 mol % XPhos, 3.0 equiv KOAc, 3.0 equiv $B_2(NMe_2)_4$, MeOH (0.2 M), 60 ˚C for time indicated. [a] Compound synthesized by Dr. Steven Kennedy. [b] Yield from previous method with $B_2(OH)_4$ as boron source.

4.4.3 Comparison in the Reactivity of Aryl Halides and Pseudohalides Utlilizing Tetrakis or BBA

Finally, we explored the scope of electrophilic partners that could be utilized in the reaction, using 4-substituted anisoles for direct comparison. The bromo, chloro, and

triflate-substituted anisole all performed well with either borylation method. Iodides, however, provide the best results with BBA as the borylating agent (Table 4.3).

Table 4.3 Electrophile Scope Utilizing Tetrakis as Borylating Source



Y = $N(Me_2)$, OMe

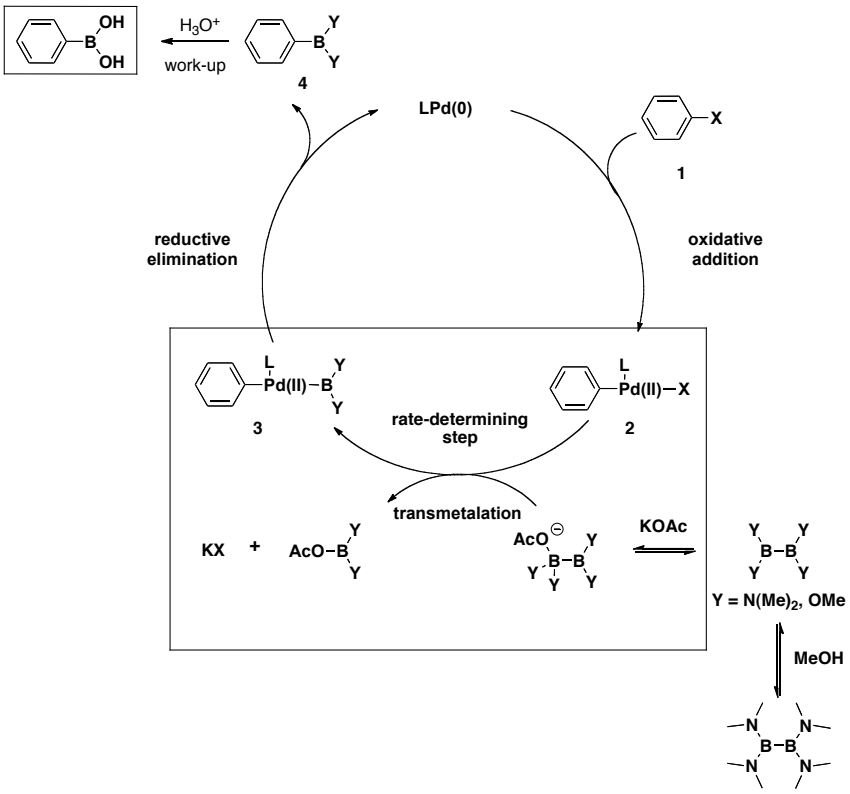
entry	X	time (h)	% isolated yield
1	Cl	5	94, 93[a]
2	Br	5	87, 94[a]
3	I	9	51, 73[a]
4	OTf	6.5	98, 99[a]

General conditions: 0.5 mol % XPhos-Pd-G2, 1.0 mol % XPhos, 3.0 equiv KOAc, 3.0 equiv of $B_2(NMe_2)_4$, MeOH (0.2 M), 60 ˚C for time indicated. [a] Yield from previous method with $B_2(OH)_4$ as boron source.

4.5 Mechanistic Considerations

Although the differences in reaction time are not as pronounced in the borylating method utilizing tetrakis, we believe the same mechanism is at work as described for the borylation of aryl halides utilizing BBA as the borylating agent. As 4-iodanisole reacts far slower than either 4-bromo- or 4-chloroanisole counterparts, the transmetalation is the proposed rate determining step of the reaction with the rate order ArCl > ArBr > ArI (Scheme 4.3).

Scheme 4.3 Proposed Mechanism of Boronic Acid Synthesis with Tetrakis



We have also been able to observe the transformation of tetrakis into the ester adduct experimentally by ^{11}B NMR through comparison of a neat sample of tetrakis (Figure 4.1, $\delta = 37.86$) to that of a sample where tetrakis was allowed to stir in MeOH for 15 minutes at room temperature (Figure 4.2, $\delta = 30.72$). The peak at 3.86 in Figure 4.2 is hypothesized to be the borate intermediate wherein the boron has a formal negative charge before conversion to the methyl ester.

Figure 4.1 Neat Tetrakis at Room Temperature (δ = 37.86 ppm)

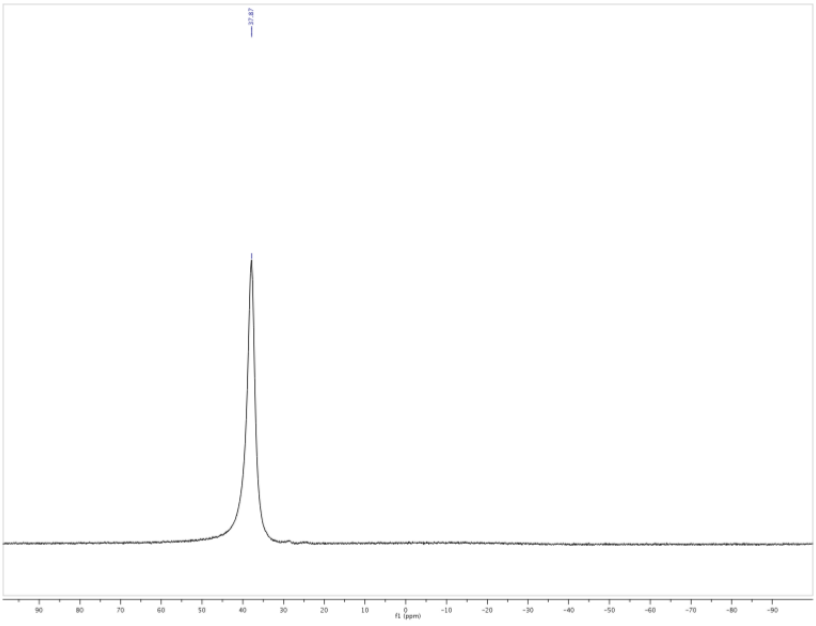
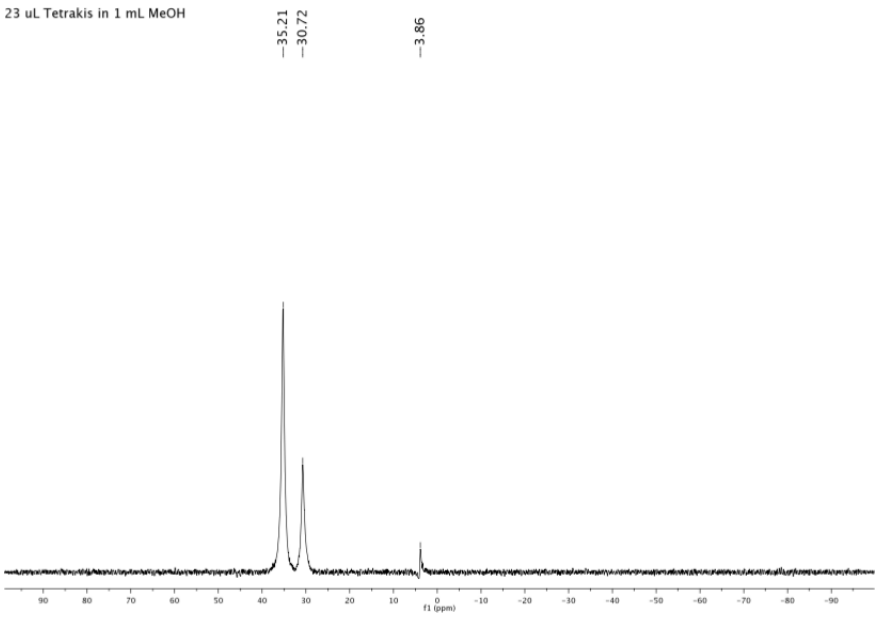


Figure 4.2 Tetrakis Stirred in MeOH at Room Temperature for 15 minutes (Tetrakis δ = 35.11 and its conversion to the Methyl Ester δ = 30.72)



4.6 Conclusions

We have demonstrated for the first time that tetrakis can be efficiently used in the palladium-catalyzed direct borylation of aryl and heteroaryl halides. The method tolerates a wide range of functional groups, providing the corresponding trifluoroborates in good to excellent yields. As tetrakis is the common precursor to both BBA and B_2Pin_2, the novel method represents an even more atom economical and efficient approach to previously reported methods utilizing BBA or other derivatives. However, the methods are complementary, and in some cases superior results can be obtained when one borylating agent (BBA or tetrakis) is used instead of the other. Also, because BBA is a solid and tetrakis is a liquid, there is now a choice of dosing method if desired. All reagents in the method are easily handled outside of a glovebox, and degassed MeOH is used. Low catalyst loads, low temperatures, and high solvent concentrations provide an efficient and easy to use method for borylation.

4.7 Experimental

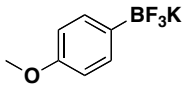
Reagents: All reactions were carried out under an atmosphere of argon. Methanol (anhydrous) was thoroughly degassed (1 h) with argon directly before use. All aryl halides, XPhos-Pd-G2, and XPhos were purchased from commercial sources and used as received. KOAc was dried in an oven overnight before use. All reagents (with the exception of the aryl halides) were stored in a bench-top desiccator. Tetrakis(dimethylamino)diboron was distilled (104 °C, 0.5 torr) and thoroughly degassed with argon before storing in a glovebox and put under argon atmosphere before

each use.

Analytical Methods: All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, ^{11}B NMR (when applicable), ^{19}F NMR, IR spectroscopy, high-resolution mass spectrometry, and melting point determination (for solids). All known compounds were characterized by ^{1}H NMR, ^{13}C NMR, ^{11}B NMR, and ^{19}F NMR and compared to literature values. ^{1}H, ^{13}C, ^{11}B, and ^{19}F were recorded at 500 MHz, 125.8 MHz, 128.4 MHz, 282 (or 338.8) MHz, respectively. Melting points are uncorrected.

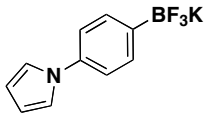
General Procedure for the Palladium-Catalyzed Borylation of Aryl and Heteroaryl Halides Utlizing Tetrakis and their Conversion to Trifluoroborates. To an oven dried glass vessel capable of being sealed with a Teflon cap (for microwave vials) was added XPhos-Pd-G2 preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), and KOAc (441 mg, 4.5 mmol). The vessel was sealed and then evacuated and backfilled with argon (process was repeated four times). MeOH (7.5 mL degassed) was added via syringe followed by the addition of the halide (1.5 mmol) in a similar manner (solid halides were added with the other solid reagents before sealing). Tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol) was added dropwise, and the reaction mixture was allowed to stir at rt for 5 min. The reaction was then added to a preheated oil bath warmed to 60 ºC and heated at this temperature until the starting material was consumed (as monitored by GC). The reaction was cooled to rt then filtered through a thin pad of Celite (eluting with 5 x 10 mL of EtOAc), and concentrated. The crude reaction was dissolved in EtOAc (10 mL) and then transferred to a separatory

funnel followed by the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the organic layer was washed once with brine. The combined aqueous layers were further extracted with EtOAc (3 x 5 mL). The combined organics were dried (Na_2SO_4) and concentrated. The concentrated crude reaction (unless otherwise indicated) was taken up in MeOH (~15 mL or enough to make a free-flowing solution) and cooled to 0 ºC. To this cooled mixture was added 4.5 equivalents of a 4.5 M aqueous KHF_2 solution (1 mL), and the reaction was stirred for 10 min at 0 ºC before removing the bath and allowing the mixture to stir at rt for 20 min (or until the conversion to the corresponding trifluoroborate was achieved as determined by ^{11}B NMR). The resulting mixture was then concentrated and then lyophilized overnight to remove any traces of water. The compound was purified with continuous Soxhlet extraction (overnight) with acetone (150 mL). The collected solvent was filtered through a thin pad of Celite, rinsed with hot acetone (3 x 5 mL), and concentrated until a minimal volume of acetone remained (~3 mL). The addition of Et_2O (~25 mL) led to the precipitation of the desired product. The collected solid was washed with Et_2O. Further purification (to remove small organic or boron containing impurities) could be realized via trituration of the solid with Et_2O.

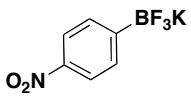


Potassium 4-Methoxyphenyl-trifluoroborate.[17] Following the general procedure, a mixture of 4-chloroanisole (214 mg, 183 μL, 1.5 mmol), XPhos-Pd-G2 preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and tetrakis(dimethylamino)diboron (890 mg,

1.03 mL, 4.5 mmol), was heated to 60 ºC in MeOH (7.5 mL) for 5 h. The title compound was obtained as a white solid in 94% yield (302 mg). mp > 225 ºC. Spectral data were in accordance with those of published results. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.22 (d, J = 7.9 Hz, 2H), 6.65 (d, J = 7.8 Hz, 2H), 3.66 (s, 3H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 157.8, 132.9, 112.5, 55.1. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.2 (m). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -141.8.

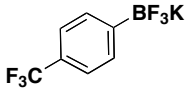


Potassium 4-(1H-Pyrrol-1-yl)phenyl-trifluoroborate.[17] Following the general procedure, a mixture of 1-(4-chlorophenyl)-1H-pyrrole (267 mg, 1.5 mmol), XPhos-Pd-G2 preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol), was heated to 60 ºC in MeOH (7.5 mL) for 3 h. The title compound was obtained as a white solid in 96% yield (358 mg). Spectral data were in accordance with those published. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.57 (d, J = 7.9 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.15 (t, J = 2.1 Hz, 2H), 6.22 (t, J = 2.1 Hz, 2H). ^{13}C NMR (125.8 MHz, acetone-d_6) δ 139.4, 133.6, 119.6, 119.0, 110.3. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.1. ^{19}F NMR (282 MHz, acetone-d_6) δ -141.7.

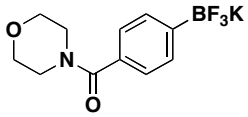


Potassium (4-Nitrophenyl)trifluoroborate.[17] Following the general procedure, a mixture of 1-bromo-4-nitrobenzene (303 mg, 1.5 mmol), XPhos-Pd-G2

preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol), was heated to 60 ºC in MeOH (7.5 mL) for 3.5 h. The title compound was obtained as a light reddish-brown solid in 56% yield (192 mg). Spectral data were in accordance with those of published results. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.97 (d, J = 7.7 Hz, 2H), 7.68 (d, J = 7.4 Hz, 2H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 146.4, 132.8, 121.8. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.4 (q, J = 50.5 Hz). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -143.9.

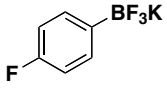


Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate.[17] Following the general procedure, a mixture of 4-trifluoromethylchlorobenzene (200 μL, 1.5 mmol), XPhos-Pd-G2 preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol), was heated to 60 ºC in MeOH (7.5 mL) for 2.5 h. The title compound was obtained as a white solid in 97% yield (365 mg). Spectral data were in accordance with those published. mp > 225 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.51 (d, J = 7.4 Hz, 2H), 7.40 (d, J = 7.5 Hz, 2H). ^{13}C NMR (125.8 Hz, DMSO-d_6) δ 132.3, 132.3, 126.8, 126.6, 126.3, 124.6, 123.4, 123.3, 100.1. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.8 (m). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -62.5, -143.3.



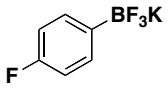
Potassium 4-(Morpholine-4-carbonyl)phenyl-trifluoroborate.[18]

Following the general procedure, a mixture of (4-chlorophenyl)(morpholino)methanone (340 mg, 1.5 mmol), XPhos-Pd-G2 preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol), was heated to 60 ºC in MeOH (7.5 mL) for 5.5 h. The title compound was obtained as a white solid in 85% yield (380 mg). Spectral data were in accordance with those published. mp > 225 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.36 (d, J = 7.5 Hz, 2H), 7.12 (d, J = 7.4 Hz, 2H), 3.56 (s, 8H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 170.9, 132.7, 131.7, 131.7, 125.7, 66.8. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.8 (m). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -143.1.

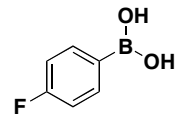


Potassium (4-Fluoropheny)trifluoroborate.[17] Following the general procedure, a mixture of 1-chloro-4-fluorobenzene (196 mg, 159 μL, 1.5 mmol), XPhos-Pd-G2 preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol), was heated to 60 ºC in MeOH (7.5 mL) for 3 h. The title compound was obtained as a white solid in 97% yield (295 mg). Spectral data were in accordance with those published. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.46 (t, J = 7.1 Hz, 2H), 6.82 (t, J = 8.9 Hz, 2H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 162.5, 160.6, 133.4 (d, J = 5.5 Hz), 113.3 (d, J = 18.4 Hz). ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.0 (q, J = 53 Hz). ^{19}F NMR (338.8

MHz, acetone-d_6) δ -120.4, -142.4.

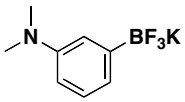


Potassium (4-Fluoropheny)trifluoroborate.[17] Following general procedure A, a mixture of $Pd(OAc)_2$ (16.8 mg, 75 μmol), XPhos (107 mg, 225 μmol), and KOAc (441 mg, 4.5 mmol) was heated in MeOH (2 mL) at 60 ºC for 30 min. The reaction was cooled to rt, a needle attached to a manifold under argon was inserted into the septa, and 1-chloro-4-fluorobenzene (196 mg, 159 μL, 1.5 mmol) was added neat via syringe followed by the dropwise addition of tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol) in a solution of MeOH (5.5 mL) The needle was removed and the reaction was heated to 60 ºC for an additional 2.5 h. See general procedure for work-up. The title compound was obtained as a white solid in 87% yield (263 mg). Spectral data were in accordance with those published. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.45 (t, J = 6.9 Hz, 2H), 6.81 (t, J = 8.9 Hz, 2H). ^{13}C NMR (125.8 MHz, acetone-d_6) δ 162.9, 160.9, 133.3 (d, J = 5.14 Hz), 112.8 (d, J = 19.27 Hz). ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.0 (q, J = 51 Hz). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -119.9, -142.1.



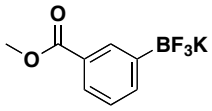
(4-Fluorophenyl)boronic Acid.[17] Following the general procedure, a mixture of 1-chloro-4-fluorobenzene (196 mg, 159 μL, 1.5 mmol), XPhos-Pd-G2 preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol), was heated to

60 ºC in MeOH (7.5 mL) for 2.5 h**.** The reaction was cooled to rt and filtered through a pad of Celite, rinsing with EtOAc (3 x 10 mL). After concentrating the reaction to dryness, EtOAc (10 mL) and 1 M HCl (10 mL) was added and the reaction was stirred at rt for 30 min. The mixture was then added to a separatory funnel and the aq layer was removed. The organic layer was washed with brine, and the combined aqueous layers were extracted with EtOAc (3 x 10 mL). The combined organics were dried (Na_2SO_4) and concentrated under vacuum. The crude boronic acid was then lyophilized overnight to remove any remaining water. To the dried solid was added hexanes (15 mL) and the slurry was sonicated (~ 1 min), affording a white solid that was filtered and rinsed with hexanes (10 mL). The title compound was obtained as a white solid in 85% yield (~90% pure, 178 mg). Spectral data were in accordance with those published. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.89 (t, J = 7.0 Hz, 2H), 7.16 (t, J = 8.6 Hz, 2H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 165.1, 163.2, 136.2, 114.8. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 29.1 (m).

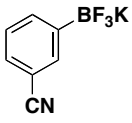


(3-(Dimethylamino)phenyl)trifluoroborate.[15] Following the general procedure, a mixture of 4-bromobenzaldehyde (277 mg, 1.5 mmol), XPhos-Pd-G2 preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol), was heated to 60 ºC in MeOH (7.5 mL) for 6 h. The title compound was obtained as a white solid in 90% yield (306 mg). mp > 225 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 8.20 (s, 1H), 7.71

(t, J = 7.1 Hz, 2H), 7.20 (t, J = 7.4 Hz, 2H), 3.81 (s, 6H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 168.1, 136.9, 132.9, 132.9, 128.1, 127.1, 126.7, 52.2).[11]B NMR (128.4 MHz, acetone-d_6) δ 3.8 (m). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -143.2.

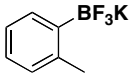


Potassium (3-(Methoxycarbonyl)phenyl)trifluoroborate.[17] Following the general procedure, a mixture of methyl 3-bromobenzoate (323 mg, 1.5 mmol), XPhos-Pd-G2 preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol), was heated to 60 ºC in MeOH (7.5 mL) for 3 h. The title compound was obtained as a white solid in 84% yield (216 mg). mp > 225 ºC. Spectral data were in accordance with those of published results. ^{1}H NMR (500 MHz, acetone-d_6) δ 8.20 (s, 1H), 7.71 (t, J = 7.3 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 3.81, (s, 3H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 168.1, 136.9, 132.1, 128.1, 127.1, 126.7, 52.2. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.9. ^{19}F NMR (338.8 MHz, acetone-d_6) δ -143.2.

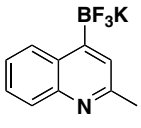


Potassium (3-Cyanophenyl)trifluoroborate.[15] Following the general procedure, a mixture of 3-bromobenzonitrile (273 mg, 1.5 mmol), XPhos-Pd-G2 preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol), was heated to 60 ºC in MeOH (7.5 mL) for 6 h. The title compound was obtained as a white solid in

91% yield (286 mg). Spectral data were in accordance with those of a commercially available sample. mp = 200 – 201 ºC. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.72 – 7.56 (m, 2H), 7.50 (d, J = 7.4 Hz, 1H), 7.32 (t, J = 7.4 Hz, 1H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 136.1, 134.7, 129.0, 127.5, 120.3, 109.4. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 0.7 (q, J = 49.5 Hz). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -143.8.

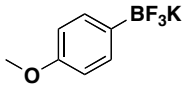


Potassium o-Tolyltrifluoroborate.[17] Following the general procedure, a mixture of 1-bromo-2-methylbenzene (256 mg, 180 μL, 1.5 mmol), XPhos-Pd-G2 preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol), was heated to 60 ºC in MeOH (7.5 mL) for 26 h. The title compound was obtained as an off-white solid in 75% yield (224 mg). Spectral data were in accordance with those of published results. mp 210-213 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.46 (d, J = 6.1 Hz, 1H), 6.88 (d, J = 13.0 Hz, 3H), 2.38 (s, 3H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 141.1, 132.2, 128.8, 125.6, 123.9, 22.3. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.3 (q, J = 57.6 Hz). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -140.6.

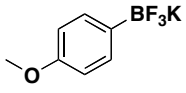


Potassium (2-Methylquinolin-4-yl)trifluoroborate. Following general procedure B, a mixture of 4-chloroquinalidine (266 mg, 302 μL, 1.5 mmol), XPhos-Pd-G2 preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol), was

heated to 60 ºC in MeOH (7.5 mL) for 11 h. The title compound was obtained as a white solid in 58% yield (218 mg) as a mixture of the trifluoroborate and internal salt. As such, reasonable NMR spectra could not be obtained.

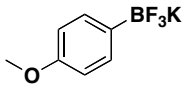


Potassium 4-Methoxyphenyl-trifluoroborate.[17] Following the general procedure, a mixture of 4-bromoanisole (280 mg, 187 μL, 1.5 mmol), XPhos-Pd-G2 preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol), was heated to 60 ºC in MeOH (7.5 mL) for 5 h. The title compound was obtained as a white solid in 87% yield (279 mg). Spectral data were in accordance with those of published results. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.37 (d, J = 7.7 Hz, 2H), 6.67 (d, J = 7.8 Hz, 2H), 3.69 (s, 3H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 157.8, 132.9, 112.5, 55.1.^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.3 (m). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -141.8.



Potassium 4-Methoxyphenyl-trifluoroborate.[17] Following the general procedure, a mixture of 4-iodoanisole (349 mg, 1.5 mmol), XPhos-Pd-G2 preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol), was heated to 60 ºC in MeOH (7.5 mL) for 9 h. The title compound was obtained as a white solid in 51% yield (163 mg). Spectral data were in accordance with those of published results. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.37 (d, J = 7.2 Hz, 2H), 6.67 (d, J = 7.2 Hz, 2H), 3.69 (s, 3H).^{13}C NMR (125.8 MHz, DMSO-d_6) δ 157.8, 132.8, 112.5, 55.1. ^{11}B

NMR (128.4 MHz, acetone-d_6) δ 4.3 (m). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -141.8.



Potassium 4-Methoxyphenyl-trifluoroborate.[17] Following the general procedure, a mixture 4-methoxyphenyl trifluoromethanesulfonate (384 mg, 271 μL, 1.5 mmol), XPhos-Pd-G2 preformed catalyst (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), and tetrakis(dimethylamino)diboron (890 mg, 1.03 mL, 4.5 mmol), was heated to 60 ºC in MeOH (7.5 mL) for 6.5 h. The title compound was obtained as a white solid in 98% yield (314 mg). Spectral data were in accordance with those of published results. mp > 225 ºC. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.37 (d, J = 7.5 Hz, 2H), 6.67 (d, J = 7.6 Hz, 2H), 3.69 (s, 3H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 157.8, 132.8, 112.5, 55.1. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.3 (m). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -141.8.

4.8 References

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Chapter 5. Palladium-Catalyzed Two-Step, One-Pot Borylation/Suzuki Cross-Coupling Reaction Utilizing Bis-Boronic Acid

5.1 Introduction

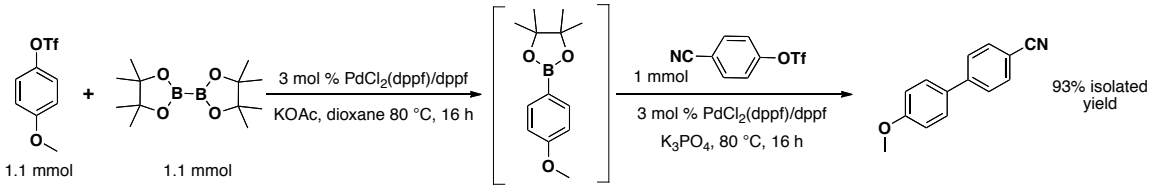
The Suzuki-Miyaura cross-coupling of boronic acids with organic halides is one of the most widely applied methods in current synthetic organic chemistry.[1,2] Since the first report of the palladium-catalyzed cross-coupling between an aryl halide and an arylboronic acid by Suzuki and Miyaura in 1981,[3] it has emerged as a functional group tolerant method, providing reliable and efficient access to structurally diverse biaryl motifs.[4] It is for these reasons that it remains one of the most important methods of choice for C-C bond formation in industrial and academic groups alike. Fueled by the commercial availability of numerous organic halides, boronic acids, and the constant development of improved catalyst systems,[5,6] rather intense research efforts continue in this area.

With all of the advances, the Suzuki-Miyaura cross-coupling reaction still suffers a major limitation in that it relies upon the direct use of boronic acids. Although many boronic acids are commercially available, they can be very expensive and decompose with storage over time, often requiring at least 1.2 equivalents (with regard to the organic halide) in a typical Suzuki-Miyaura Cross-Coupling reaction.[7,8] Additionally, if the boronic acid is not commercially available, its synthesis is required, adding additional, often lengthy, steps to the research process.[9-18]

5.2 Two-Step, One-Pot Miyaura Borylation/Suzuki Coupling Reactions

Over the last 15 years, progress has been made to circumvent some of the limitations of the Suzuki-Miyaura cross-coupling reaction with the advent of one-pot Miyaura borylation/Suzuki cross-coupling reactions. The first reported system by Miyaura in 1997 utilized two organotriflates and bis(pinacolato)diboron (B_2Pin_2) in refluxing dioxane. The method required the synthesis of excess boronate and a second addition of catalyst to facilitate the cross-coupling in high yield. However, it demonstrated for the first time that the need to isolate or purchase a boronic acid could be eliminated. Instead, the method allows the coupling of two aryl triflates in a simple and efficient manner (Equation 5.1).[12]

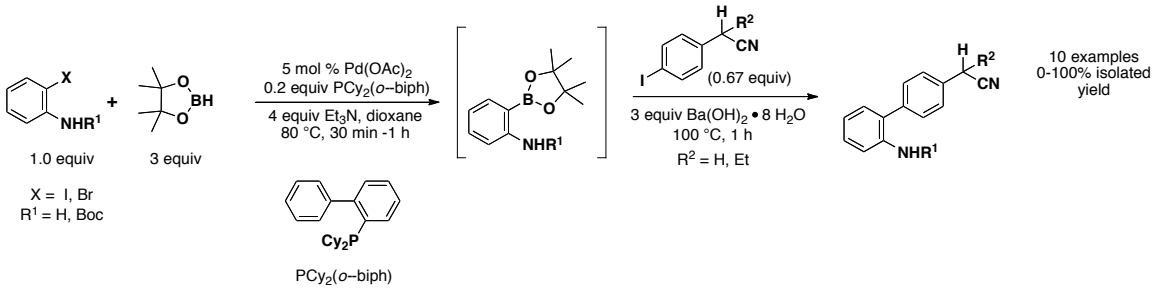
Equation 5.1



Since Miyaura's seminal paper in 1997, other groups have followed with improvements on the process. In 2000 and 2002 Boudain et al. extended the method to include aryl iodides and bromides with the more atom economical pinacolborane (H-BPin). This improved method eliminated the need to add additional catalyst in the second step but required 5 mol % of a palladium catalyst and dioxane at elevated temperatures, was limited in scope, and still required an excess of the boronate ester coupling partner

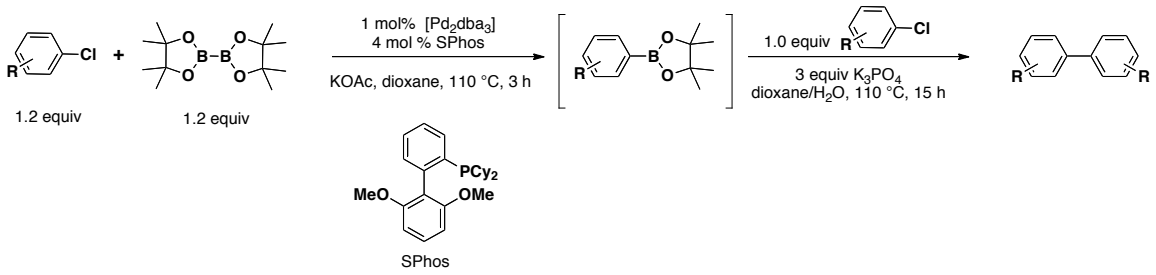
(Equation 5.2).[19,20]

Equation 5.2



The next major advance came in 2007 when Buchwald et al. successfully demonstrated the first general Miyaura borylation of aryl chlorides. In the same paper, they went on to show that the method could be extended to a one-pot Miyaura borylation/Suzuki cross-coupling reaction between two aryl chlorides. The one-pot method made use of B_2Pin_2 with efficient catalyst loads of 1 mol %, but required the use of excess boronate ester in refluxing dioxane (Equation 5.3).[21]

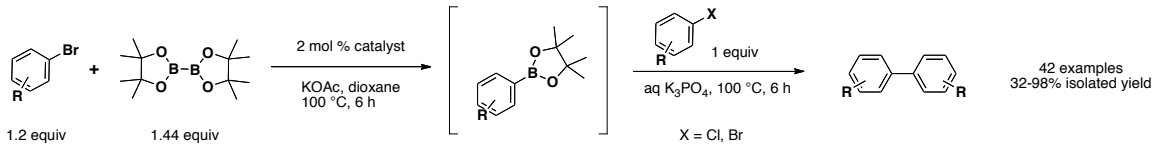
Equation 5.3



More recently, Wang et al. demonstrated that aryl- and heteroaryl bromides and chlorides could be used efficiently in the one-pot process when utilizing B_2Pin_2. However, the catalyst system developed is currently not commercially available and still requires the use of refluxing dioxane. In addition, there are no examples of aryl chlorides

undergoing the borylation reaction, and therefore they can only be used in the second step. Further, the method still requires that the boron coupling component be synthesized in excess (Equation 5.4).[22]

Equation 5.4



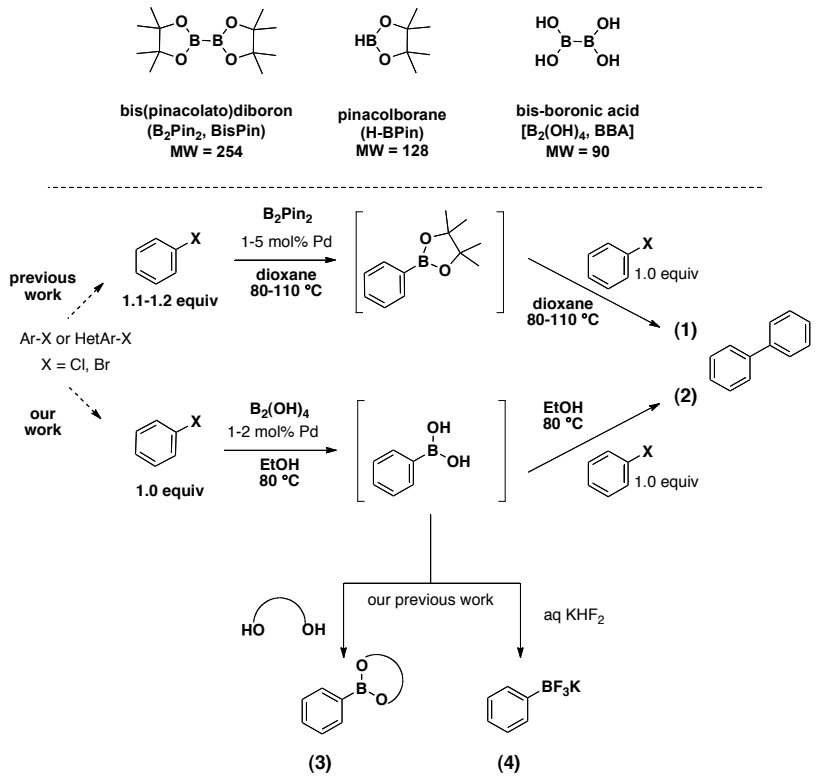
Overall, the one-pot Miyaura borylation/Suzuki cross-coupling is a very efficient method. The fact that boronic acids no longer have to be purchased or isolated, coupled with the ease of synthetic strategy with just reacting two aryl halides (or pseudohalides), make this method very attractive. However, although significant progress has been made, many disadvantages remain: 1) Current protocols make use of the atom inefficient bis(pinacolato)diboron or its derivatives to make the boronate ester. 2) The synthesis of excess boronate ester is required with respect to the second aryl halide. 3) High temperatures are utilized in solvents that are not environmentally sound (dioxane, DMF, toluene). 4) High catalyst loads are employed or a second loading of catalyst is required to facilitate the Suzuki reaction in the second step. 5) Some catalyst systems used are not commercially available.

5.3 Results and Discussion

In previous chapters, the full scope of the borylation of aryl and heteroaryl electrophiles (bromides, chlorides, iodides, and triflates) utilizing the bench stable and

atom economical bis-boronic acid to access boronic acids and derivatives directly was described (Scheme 1, Equations 3 and 4).[23,24] Early in the development of these methods we also briefly demonstrated that the boronic acid obtained after borylation efficiently undergoes the two-step, one-pot borylation/cross-coupling reaction providing biaryl products in good to excellent yield without the need to synthesize excess boronic acid. Instead, the method allowed the use of both halides in equimolar amounts (Scheme 5.1, Equation 2).[23] Additionally, the reactions were run in environmentally benign EtOH at reduced temperatures of 80 °C. With the extremely reactive preformed palladium catalysts (XPhos-Pd-G1/G2), low loads could be efficiently realized without the need to re-charge the system for the second step. Our method, therefore, in whole or in part, represents an improvement of current methods to access biaryl species utilizing a one-pot Miyaura borylation/Suzuki cross-coupling reaction sequence (Scheme 5.1, Equations 1 and 2).

Scheme 5.1 Diboron Reagents. Comparison of Current and Newly Developed One-Pot Miyaura Borylation/Suzuki Cross-Coupling Reaction Methods

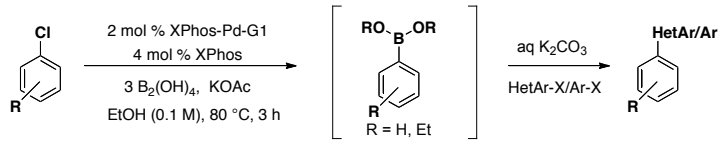


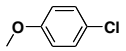
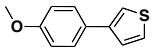
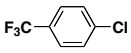
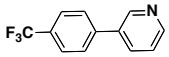
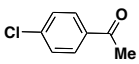
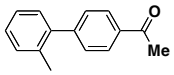
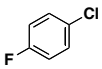
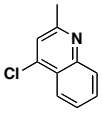
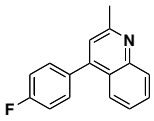
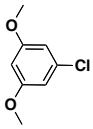
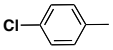
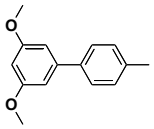
5.3.1 One-Pot Miyaura Borylation/Suzuki Cross-Coupling Reactions of Aryl Chlorides Utilizing XPhos-Pd-G1

In our first account of the one-pot Miyaura borylation/Suzuki cross-coupling reaction utilizing BBA, we made use of the XPhos-Pd-G1 catalyst, as it was the only preformed catalyst available at the time.[5,23] To facilitate the two-step reaction, the catalyst load was increased (from the requisite 1 mol % for the borylation only) to 2 mol %, with 4 mol % XPhos, KOAc (3 equiv), in EtOH at 80 °C. Similar to our borylation utilizing

XPhos-Pd-G1, three equivalents of BBA were required to minimize the formation of side-products. We were pleased to find that the use of stronger base (K_2CO_3) in the second step acts both to decompose any remaining BBA into boric acid and to facilitate the cross-coupling of the newly formed boronic acid with the subsequently added second aryl halide. As this work was included in our first account of the use of BBA, the substrate scope was limited to aryl chlorides, with few examples demonstrated as we sought only to provide proof-of-concept of the synthetic utility of BBA (Table 5.1).[23]

Table 5.1 First One-Pot, Two-Step Borylation/Coupling Reactions Utilizing BBA and XPhos-Pd-G1



entry	first chloride	second chloride	product	isolated yield (%)
1				85
2				90
3				63
4				60
5				55

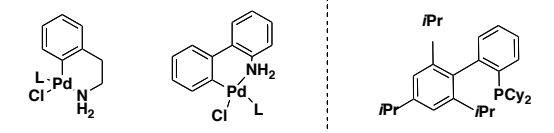
General conditions: a) 2 mol % XPhos-Pd-G1, 4 mol % XPhos, 3.0 equiv KOAc, 3.0 equiv $B_2(OH)_4$, EtOH (0.1 M), 80 ˚C, 3 h. b) 1.8 M K_2CO_3 (3 equiv), second aryl or heteroaryl halide (1 equiv), 80 ˚C, 15 h.

5.3.2 One-Pot Miyaura Borylation/Suzuki Cross-Coupling Reactions of Aryl Chlorides and Bromides Utilizing BBA and XPhos-Pd-G2

As mentioned above, in our first report of the one-pot Miyaura borylation/Suzuki cross-coupling reaction utilizing BBA, we made use of the first generation Buchwald preformed catalyst, XPhos-Pd-G1 with an efficient catalyst load of 2 mol % (Figure 5.1). As we successfully applied Buchwald's newly available second generation XPhos preformed catalyst, XPhos-Pd-G2, to the borylation of a variety of aryl and heteroaryl

electrophiles (Cl, Br, I, and triflate) we sought to explore the full scope of the one-pot Miyaura borylation/Suzuki cross-coupling reaction with this more reactive catalyst.[6] Through the use of XPhos-Pd-G2, we found that the effective catalyst load can be reduced by half (to 1 mol %) while still maintaining high yields.

Figure 5.1 First and Second Generation Buchwald Preformed Catalysts

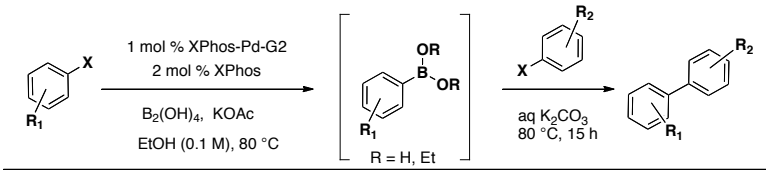


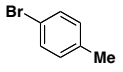
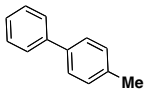
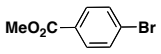
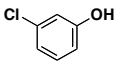
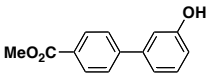
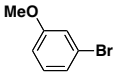
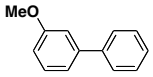
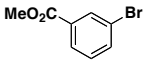
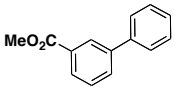
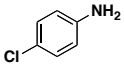
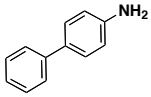
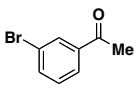
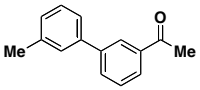
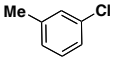
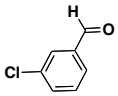
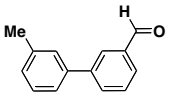
As all reagents are commercially available and bench stable, as with our previous methods, solids are simply weighed on a bench top balance and then placed under an inert atmosphere of argon before the addition of degassed, non-anhydrous EtOH. The reactions are then heated to 80 °C until the borylation is complete. As noted in our previous work with XPhos-Pd-G2, once all of the first halide has undergone borylation (and thus all of the starting material has been consumed), a readily observable color change occurs: aryl chlorides turn from colorless to yellow, and aryl bromides turn from colorless to orange. This signals that the second base (K_2CO_3), followed by the second halide, can now be added to the reaction. This visual cue greatly facilitates the ease by which the method is executed.

We began our exploration of the one-pot method by looking at simple aryl-aryl couplings to explore functional group compatibility (Table 5.2). In the first few substrates

synthesized, we utilized 1.3 equivalents of the second aryl halide (Table 5.2, entries 1-4). As we sought to provide a general method that did not rely on excessive use of either the boronic acid equivalent or the aryl halide component, we attempted the one-pot reaction with a 1:1 ratio of both halides (Table 5.2, entry 4) with no appreciable loss in yield. Going forward then, all reactions were carried out in this manner.

Table 5.2 Aryl-Aryl Two-Step, One-Pot Cross-Coupling Demonstrating Functional Group Tolerability



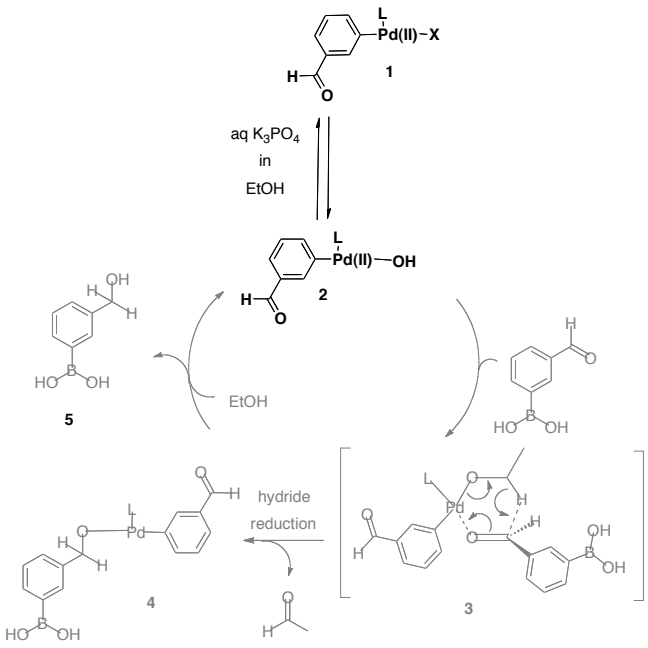
entry	first halide	time (h)	second halide	product	% isolated yield
1		2			83[a,b]
2		2			93[a,b,c]
3		2			94[a,b]
4		1.5			87(91)[a,b]
5		1			60[b]
6		1			79[b]
7		1			71

General conditions: a) 1 mol % XPhos-Pd-G2, 2 mol % XPhos, 3.0 equiv KOAc, 3.0 equiv $B_2(OH)_4$, EtOH (0.1 M), 80 °C for time indicated. b) 3 equiv 1.8 M K_2CO_3, 1 equiv second halide. 80 °C, 15 h. [a] 1.3 equiv second halide added in second step. [b] Compound synthesized by Dr. Steven Kennedy. [c] MeOH used as solvent.

Methyl esters perform well in the reaction (Table 5.2, entries 2 and 4) with minimal amounts (<5%) of transesterification with EtOH observed. This can, however, be completely avoided through the use of MeOH as solvent. Unprotected amines and

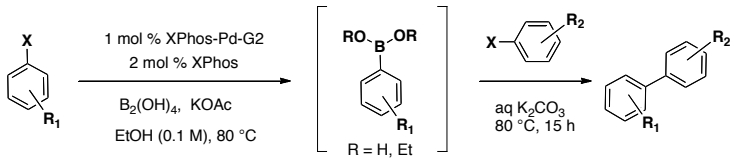
hydroxyl groups are well tolerated, leading to good to excellent yields after isolation of the cross-coupled product (Table 5.2, entries 2 and 5). We observe no α-arylation of ketones when used under these reaction conditions (Table 5.3, entry 4)[21] and no reduction of either the ketone or aldehyde as previously observed in the borylation and subsequent trifluoroborate isolation of aryl aldehydes and ketones.[23] This is very interesting as our studies conducted during the full scope exploration of the borylation clearly demonstrated that ketones, aldehydes, and nitro groups are susceptible to palladium-catalyzed hydride reduction. We believe that the use of strong base in the second step of the cross-coupling forms the Pd-OH species as proposed by Jutand et al. where R = H in complex **2** in Scheme 5.2.[25,26] Therefore, the use of strong base effectively shuts down the hydride reduction pathway (Scheme 5.2).

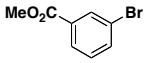
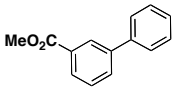
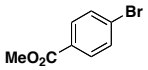
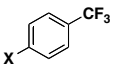
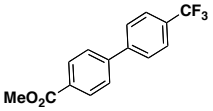
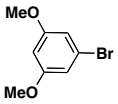
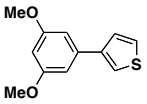
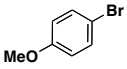
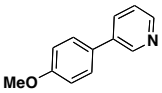
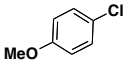
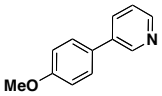
Scheme 5.2 Proposed Mechanism of the β-Hydride Elimination of the Alcoholysis Adduct



We next turned our attention to comparing the reactivities of aryl bromides and chlorides. As seen in Table 5.3, both aryl bromides and chlorides perform well, but chlorides consistently provide superior results when utilized in the second step. We believe this result is due to the character and therefore inherent reactivity of the Pd-X bond. Similar to the mechanism we proposed for the mechanism of borylation,[27] the transmetalation in this system is the rate-determining step in both mechanisms of coupling. Therefore, the more electronegative halide (Cl > Br) increases the electrophilicity of the organopalladium halide intermediate and escalates the rate at which this oxidative addition adduct undergoes transmetalation with the newly formed boronic acid (or BBA in the case of the borylation mechanism, Scheme 5.3).[6,24,28]

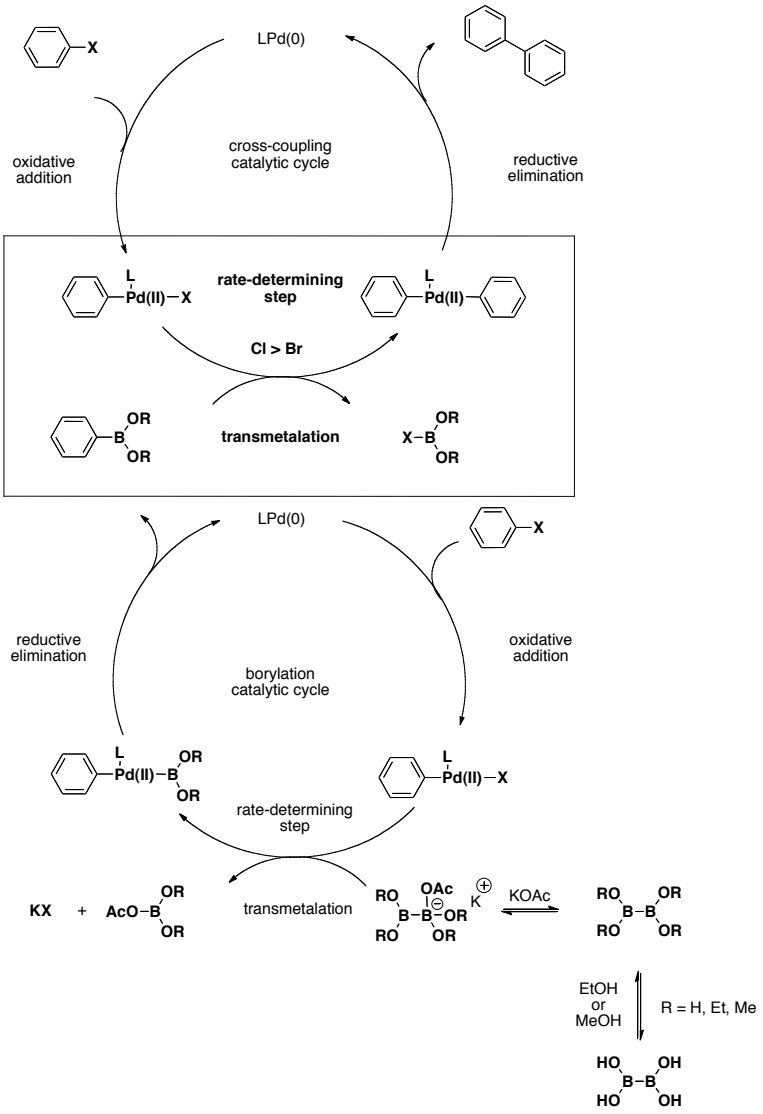
Table 5.3 Comparison of Borylation with Aryl Chlorides and Bromides Utilizing BBA and XPhos-Pd-G2



entry	first halide	time (h)	second halide	product	% isolated yield
1		1.5			Cl = 87[a] Br = 82[a]
2		2			Cl = 77 Br = 60
3		2.5			Cl = 62 Br = 51
4		2.5			Cl = 70 Br = 52
5		2			Cl = 82 Br = 80

General conditions: a) 1 mol % XPhos-Pd-G2, 2 mol % XPhos, 3.0 equiv KOAc, 3.0 equiv $B_2(OH)_4$, EtOH (0.1 M), 80 ˚C for time indicated. b) 3 equiv 1.8 M K_2CO_3. 1 equiv second halide. 80 ˚C, 15 h. [a] Compound synthesized by Dr. Steven Kennedy.

Scheme 5.3 Proposed Mechanisms of the Two-Step, One-Pot Borylation/Suzuki Reaction with BBA and XPhos-Pd-G2



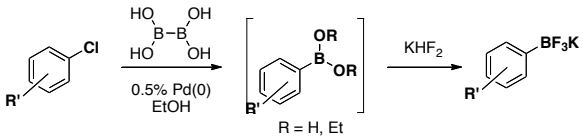
This increased rate of reaction with aryl chlorides in either step likely leads to less formation of undesirable side-products. It is of little surprise then, that the combination of an aryl chloride in the first step, coupled with a second aryl chloride in the second,

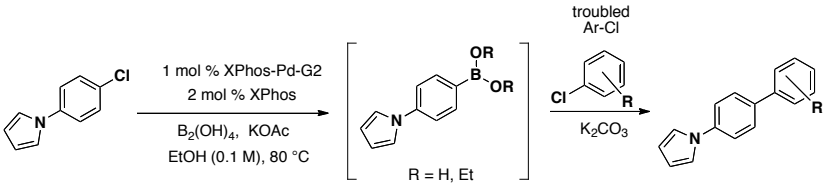
provides superior results to all other combinations (Table 5.3, entries 4 and 5). As aryl chlorides are currently less expensive, more abundant, and more diversely substituted than aryl bromides, this reactivity feature is especially useful. It should further be noted that this finding is in agreement with that proposed by Buchwald et al. in Suzuki/Miyaura cross-couplings with XPhos-Pd-G2, where they demonstrated that the rate order of transmetalation was ArCl > ArBr > ArI.[6]

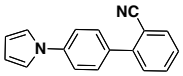
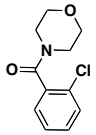
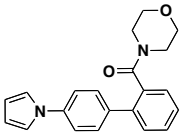
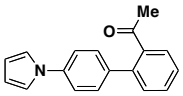
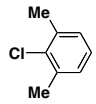
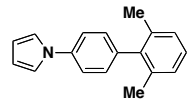
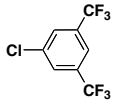
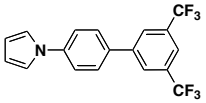
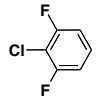
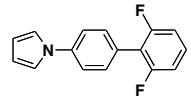
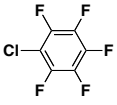
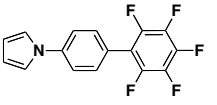
5.3.3 Use of the One-Pot Miyaura Borylation/Suzuki Cross-Coupling Reaction to Access Low-Yielding Borylation Substrates in Cross-Coupled Products

We next turned our attention to those substrates that provided low yields after borylation and subsequent conversion to the corresponding trifluoroborate in our previous studies (Table 5.4, Equation 5).[24] As these functional groups are desired in cross-coupled products, it was important to provide more efficient access to them. We surmised that even if they did not undergo the initial borylation in high yield, they should perform well as the second halide in the cross-coupling reaction. This was, in fact, observed. As outlined in Table 5.4, with the exception of entry 7, all substrates that provided low yields of the trifluoroborate provided good to excellent yields of the cross-coupled product when used in the second step. Most notable are entries 5 and 6, which afforded no borylated product but provided excellent yields of cross-coupled product.

Table 5.4 Aryl Chlorides Resulting in Low-Yielding Borylation used as the Second Partner in the One-Pot Miyaura Borylation/Suzuki Cross-Coupling Reaction





entry	troubled Ar-Cl	% isolated trifluoroborate yield	entry	reverse one-pot product	% isolated one-pot yield
1		27	1A		80[a]
2		13	2A		74[a]
3		15	3A		59
4		53	4A		57[a]
5		0	5A		94[a]
6		0	6A		86[a]
7		0	7A		< 1 GCMS[a]

General conditions for the one-pot sequence: a) 1 mol % XPhos-Pd-G2, 2 mol % XPhos, 3.0 equiv KOAc, 3.0 equiv $B_2(OH)_4$, EtOH (0.1 M), 80 ˚C for time indicated. b) 3 equiv 1.8 M K_2CO_3. 1 equiv second aryl chloride, 80 ˚C, 15 h. [a] Compound synthesized by Dr. Steven Kennedy.

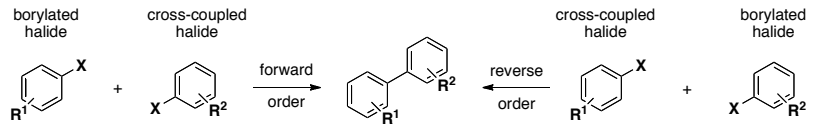
5.3.4 Reverse-Order Strategy in the One-Pot Miyaura Borylation/Suzuki Cross-Coupling Reaction Utilizing BBA and XPhos-Pd-G2

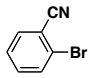
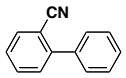
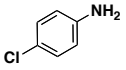
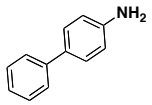
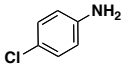
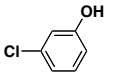
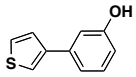
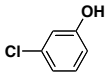
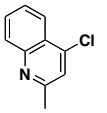
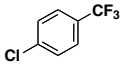
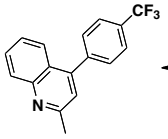
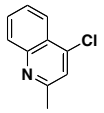
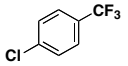
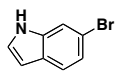
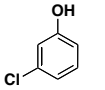
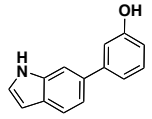
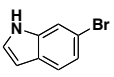
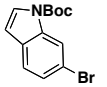
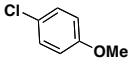
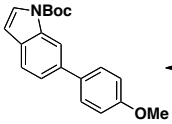
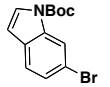
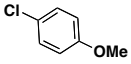
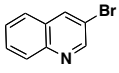
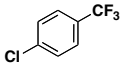
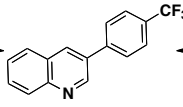
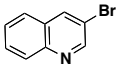
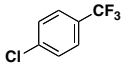
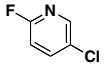
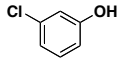
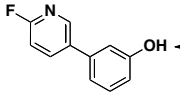
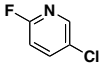
Because of the success encountered with the aforementioned strategy, its synthetic utility was explored still further. As mentioned above, one of the major advantages of the one-pot Miyaura Borylation/Suzuki cross-coupling reaction is the use of two aryl halides. This distinguishing feature therefore allows a choice in the order of addition when carrying out the reaction: which halide is borylated and which is used as the electrophile in the second step can easily be reversed. As demonstrated in Table 5.5, the order in which the halides are used can have a significant effect on the overall result of the reaction.

For example, some heteroarylboronic acids, once synthesized using our optimized method with the CataCXium A preformed precatalyst, readily decompose under the reaction conditions as evinced by the fact that the reaction goes to full conversion, but little to no product formation of the corresponding trifluoroborate is observed. Therefore, yields for products containing heteroaryls are typically better if the heteroaryl is used in the second step (Table 5.5, entries 3, 7, and 8). Interestingly, this is not always the case, as 4-chloroquinaldine provides superior yield when it is used to make the boronic acid (Table 5.5, entry 4). Both protected and unprotected indoles provide better results when they are used in the first step (Table 5.5, entries 5 and 6). Similarly, the unprotected amine performed better when used in the first step (Table 5.5, entry 2). If care is taken with respect to the order of addition, excellent yields can be obtained with most coupling partners. The results in Table 5.5 demonstrate the benefits of probing both combinations

on small scale to find the highest yielding order before scaling up the reaction.

Table 5.5 Reverse-Order Strategy Comparisons in the Cross-Coupling of Two Aryl Halides



entry	borylated halide	cross-coupled halide	% yield	product	% yield	cross-coupled halide	borylated halide
1			29[a] A		**69[a]** B		
2			60[a] A		**80[a]** B		
3			0[a,b] A		**91** B		
4			**63[b]** A		50 B		
5			**71[a]** A		15[a] B		
6			**85[a]** A		67[a] B		
7			60[b] A		**99[a]** B		
8			0[a,b] A		**96[a]** B		

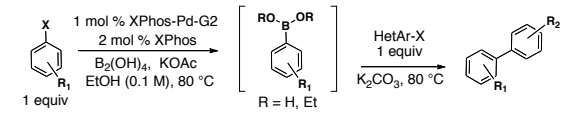
General conditions: a) 1 mol % XPhos-Pd-G2, 2 mol % XPhos, 3.0 equiv KOAc, 3.0 equiv $B_2(OH)_4$, EtOH (0.1 M), 80 ˚C for time indicated. b) 3 equiv 1.8 M K_2CO_3, 1 equiv second aryl halide. 80 ˚C, 15 h. [a] Compound synthesized by Dr. Steven Kennedy. [b] a) 5.0 mol % CataCXium A preformed catalyst, 3 equiv *i*-Pr_2NEt, 3.0 equiv $B_2(OH)_4$, MeOH (0.2 M), 50 ˚C for time indicated. b) 3 equiv 1 M K_3PO_4, 1 equiv second halide, 50 ˚C, 15 h.

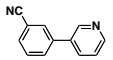
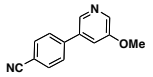
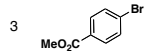
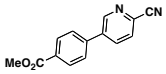
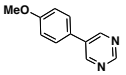
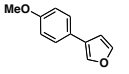
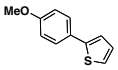
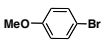
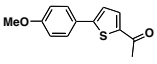
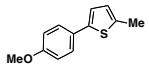
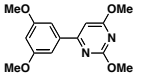
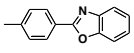
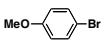
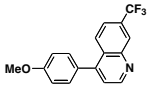
5.3.5 Utilization of Heteroaryls in the One-Pot Miyaura Borylation/Suzuki Cross-Coupling Reaction with BBA and XPhos-Pd-G2

We next turned our attention to exploring the scope of heteroaryl halides. As few heteroaryls perform exceptionally well (specifically those with the heteroatom in the same ring as the halide) under the general borylating conditions, we focused on their use as coupling partners in the second step. As outlined in Table 5.6, heteroaryl halides substituted at the 2-, 3-, and 4-position all undergo efficient cross-coupling. Pyridines substituted at the 3-position couple well with electron withdrawing, electron donating, and with no substitution at all (Table 5.6, entries 1-3). Similarly, 3-substituted pyrazines and furans provide good to excellent yields (Table 5.6 entries, 4 and 5). 2-Chlorothiophenes couple well (Table 5.6, entries 6-8) and even 2-benzoxazole provided reasonable yield over two steps (Table 5.6, entry 11). The 2-substituted pyrazine and pyridine provided modest yields (Table 5.6, entries 9 and 10) while the 4-chloroquinalidine coupled well, providing product in excellent yield (Table 5.6, entry 12). In a few cases where products were obtained in low yield using the general procedure, we found that the addition of 2 mmol of the heteroaryl halide in the second step (as compared to 1.5 equivalent so that the boronic acid and heteroaryl halide are 1:1) significantly increased the yield of the isolated product (Table 5.6, entries 2, 7-8). This is most likely a result of the protodehalogentation of the heteroaryl halide under the reaction conditions. This commonly observed side product occurs to different extents with heteroaryl halides depending on their substitution pattern in terms of both of functional groups and the halide. Finally, although we attempted the coupling of two heteroaryl

halides under these reaction conditions, products were only obtained in low yield. Therefore, the development of a method utilizing BBA to address this important area of research remains an active pursuit.

Table 5.6 Use of Substituted Heteroaryls as Electrophiles in the One-Pot Miyaura Borylation/Suzuki Cross-Coupling Reaction Utilizing BBA and XPhos-Pd-G2



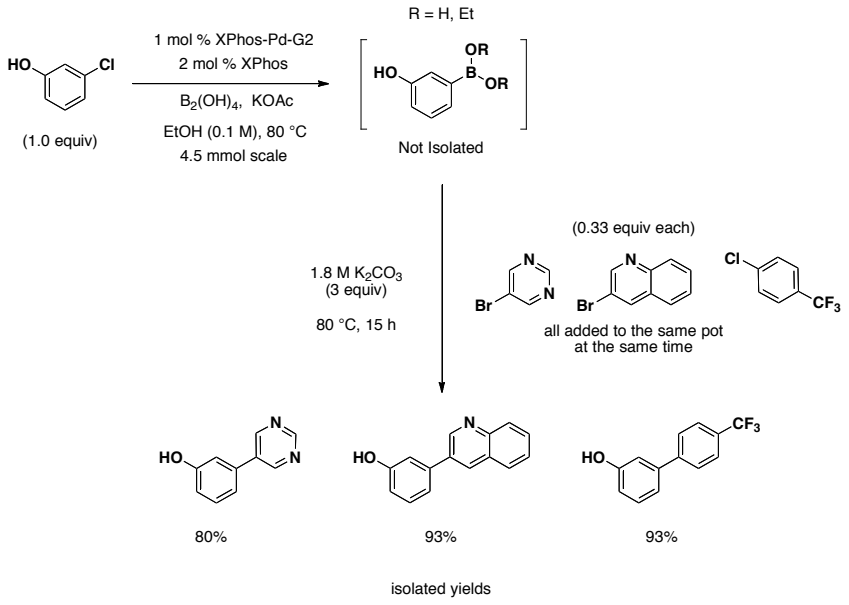
entry	aryl halide	time (h)	heteroaryl halide	product	isolated % yield
1		2			88
2		2			87[a], 57
3		2			73[b]
4		1.5			84
5		1.5			61
6		1.5			88
7		1.5			83[a], 63
8		1.5			67[a], 41
9		1			29
10		2			49[b]
11		1.5			32
12		1.5			81

General conditions: a) 1 mol % XPhos-Pd-G2, 2 mol % XPhos, 3.0 equiv KOAc, 3.0 equiv $B_2(OH)_4$, EtOH (0.1 M), 80 °C for time indicated. b) 3 equiv 1.8 M K_2CO_3, 1 equiv second halide. 80 °C, 15 h. [a] 1.3 equiv halide added in second step. [b] < 5% transesterification observed.

5.3.6 Other Useful Application of the One-Pot Miyaura Borylation/Suzuki Cross-Coupling Reaction with BBA: 3-in-1 Pot

We sought to demonstrate the power of this one-pot method further within the context of parallel synthesis. Being careful to choose substrates with polarity differences, an efficient borylation/3-in-1 pot Suzuki reaction can be efficiently performed, providing three distinct products in excellent yields after chromatography. As outlined in Scheme 5.4, the first halide undergoes the borylation, with subsequent addition of base and three aryl/heteroaryl halides in equimolar amounts affording the desired cross-coupled products. To the best our knowledge, this is the first time such a reaction has been demonstrated.[29]

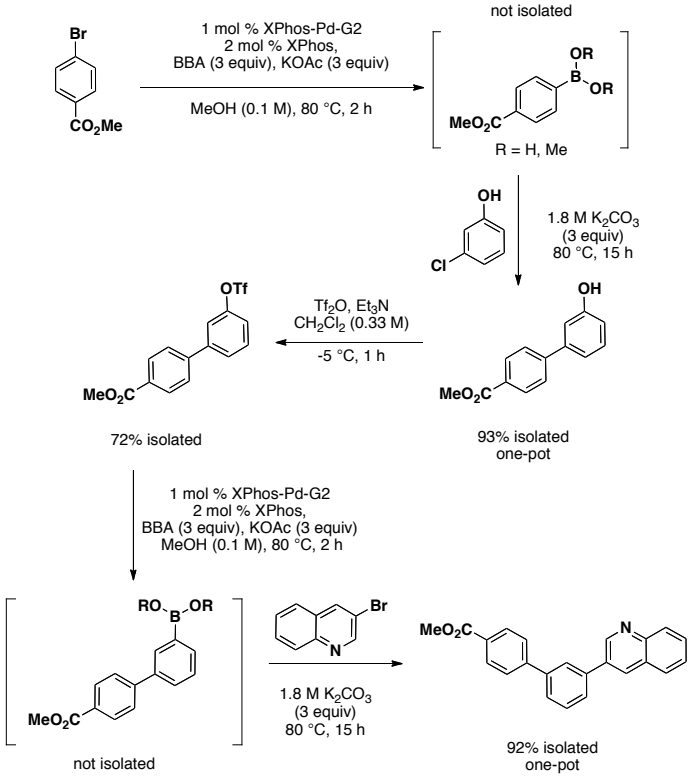
Scheme 5.4 Efficient Borylation/3-in-1 Pot Suzuki Reaction Utilizing BBA and XPhos-Pd-G2



5.3.7 Other Useful Application of the One-Pot One-Pot Miyaura Borylation/Suzuki Cross-Coupling Reaction with BBA: Teraryl Synthesis

Using that fact that triflates borylate in high yield under the general reaction conditions, they can essentially be used as a masked boronic acid or halide in a synthetic sequence in which an aryl halide exists in the same molecule. Using the strategy outlined in Scheme 5.5, the first cross-coupled product containing a hydroxyl group is isolated in the excellent yield of 94% after undergoing the two-step, one-pot Miyaura Borylation/Suzuki cross-coupling reaction with BBA and XPhos-Pd-G2. The alcohol moiety of this product is then converted to the triflate. This triflate product is then subjected to a second one-pot, two-step sequence. The final teraryl product was thus obtained in a combined yield of 62% over the 5-step sequence from simple aryl halides without ever purchasing or isolating a boronic acid.[29]

Scheme 5.5 Efficient Teraryl Synthesis Utilizing Alcohols as Masked Halides and Boronic Acids



5.4 Conclusions

The Suzuki-Miyaura reaction has emerged as one of the key transformations in modern synthetic organic chemistry. However, some undesirable aspects still remain, largely the requisite use of excess boronic acid to ensure efficient coupling. The advent of the two-step, one-pot borylation/Suzuki coupling reaction first demonstrated by Miyaura in 1997 and improved upon by other groups sought to help reduce this burden. Although advances were made, other reaction conditions, such as the use of B_2Pin_2 in the borylating step and refluxing ethereal solvents, still made these methods undesirable.

Through the use of BBA and the first and second generation Buchwald preformed catalysts, we have developed a method that allows the efficient coupling of two aryl halides in one-pot without the need to synthesize the boronic acid in excess. The user-friendly process uses environmentally benign ethanol, and the readily observable color change indicates when the strong base and second halide can be added.

Additional advances include a parallel-synthesis application wherein three distinct cross-coupled products can be obtained after the two-step sequence in high yield. Further, the method allows quick access to teraryl species without the need to purchase or isolate a boronic acid. The only current limitation to the method is the efficient coupling of two heteroaryl halides. Efforts remain ongoing in this area.

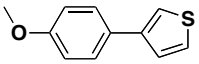
5.5 Experimental

Reagents: All reactions were carried out under an atmosphere of nitrogen or argon. Ethanol (non-anhydrous, 200 proof) was thoroughly degassed with argon directly before use. All aryl chlorides, XPhos-Pd-G1, XPhos-Pd-G2, and XPhos were purchased from commercial sources and used as received. KOAc and K_2CO_3 were dried in an oven overnight before use. All reagents (with the exception of the aryl chlorides), were stored in a bench-top desiccator. BBA was provided by BASF and used as received. The CataCXium A-Pd-G2 catalyst was synthesized and supplied by Dr. Mathew T. Tudge of the Merck Research Laboratories.

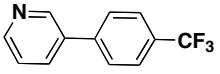
Analytical Methods: All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, high-resolution mass spectrometry, and melting point determination (for solids). All known compounds were characterized by ^{1}H NMR, ^{13}C NMR, and melting point determination and compared to literature values. ^{1}H and ^{13}C were recorded at 500 MHz and 125.8 MHz respectively. Melting points are uncorrected.

General Procedure for the Palladium-Catalyzed Borylation of Aryl Chlorides with XPhos-Pd-G1 and Their Suzuki Cross-Coupling with Aryl or Heteroaryl Chlorides. To an oven dried glass vessel capable of being sealed with a Teflon cap (for microwave vials) was added XPhos-Pd-G1 (27.6 mg, 37.5 μmol), XPhos (35.7 mg, 75 μmol), $B_2(OH)_4$ (402 mg, 4.5 mmol), KOAc (442 mg, 4.5 mmol), and NaO*t*-Bu (3.6 mg, 37.5 μmol). The vessel was sealed and then evacuated and backfilled with N_2 (process was repeated three times). EtOH (15 mL degassed) was added via syringe followed by the addition of the first chloride (1.5 mmol) in a similar manner (solid chlorides were added with the other solid reagents before sealing). The reaction was then heated to 80 ºC for 2 h, then a needle attached to a manifold under nitrogen was added to the septum and 3 equiv (2.5 mL, 4.5 mmol) of 1.8 M aqueous K_2CO_3 was added via syringe followed by the addition of the second aryl or heteroaryl chloride (1.5 mmol) in a similar manner (in a solution of 500 μL EtOH if solid). The nitrogen needle was removed, and the reaction was further heated to 80 ºC for 15 h. The reaction was cooled to rt then filtered through a thin pad of Celite (eluting with 100 mL EtOAc) and concentrated. The crude solid was extracted with EtOAc (3x 10 mL), the combined organics were dried (Na_2SO_4) and then

concentrated under reduced pressure. The desired compound was purified by column chromatography, eluting with EtOAc/hexane.

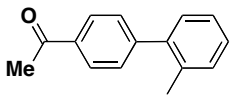


3-(4-Methoxyphenyl)thiophene. Following the general procedure, a mixture of 4-chloroanisole (214 mg, 182.5 μL, 1.5 mmol), tetrahydroxydiboron (202 mg, 2.25 mmol), XPhos (35.7 mg, 75 μmol), XPhos-Pd-G1 (27.6 mg, 37.5 μmol), KOAc (442 mg, 4.5 mmol), and NaO*t*-Bu (3.6 mg, 37.5 μmol) was heated to 80 ºC in EtOH for 2 h. At this point, a nitrogen needle was inserted and 3-chlorothiophene (177.87 mg, 140 μL, 1.5 mmol) and aq K_2CO_3 (1.8 M, 2.5 mL) were added via syringe. The crude product was purified via flash chromatography on silica gel (0-5% EtOAc/hexane) to provide the title compound in 85% yield (243 mg) as a white solid. mp: 122-125 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.9 Hz, 2H), 7.36 (d, *J* = 6.3 Hz, 3H), 6.95 (d, *J* = 7.9 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 158.9, 142.1, 128.9, 127.7, 126.4, 126.2, 119.0, 114.3, 55.4. IR (neat) 1606, 1503, 1248. HRMS (ES+) calcd. for $C_{11}H_{11}OS$ (M+H) 191.0452, found 191.0501.

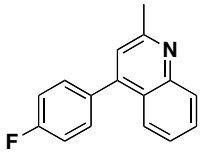


3-(4-(Trifluoromethyl)phenyl)pyridine. Following the general procedure, a mixture of 1-chloro-4-(trifluoromethyl)benzene (271 mg, 200 μL, 1.5 mmol), tetrahydroxydiboron (402 mg, 4.5 mmol), XPhos (35.7 mg, 75 μmol), XPhos-Pd-G1 (27.6 mg, 37.5 μmol), KOAc (442 mg, 4.5 mmol), and NaO*t*-Bu (3.6 mg, 37.5 μmol) was heated to 80 ºC in EtOH for 2 h. At this point, a nitrogen needle was inserted and 3-

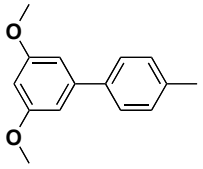
chloropyridine (170.25 mg, 143 μL, 1.5 mmol) and aq K_2CO_3 (1.8 M, 2.5 mL) were added via syringe. The crude product was purified via flash chromatography on silica gel (0-50% EtOAc/hexane) to provide the title compound in 90% yield (303 mg) as a yellow solid. mp: 65-68 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.66 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.75 (*d*, *J* = 7.4 Hz, 2H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.41 (s, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 149.5, 148.5, 135.4, 134.6, 130.5, 130.3, 130.2, 127.6, 126.2, 123.8. IR (neat) 1586, 1105. HRMS (ES+) calcd. for $C_{12}H_9F_3N$ (M+H) 224.0609, found 224.0687.



1-(2'-Methyl-[1,1'-biphenyl]-4-yl)ethanone. Following the general procedure, a mixture of 1-chloro-2-methylbenzene (189 mg, 175.3 μL, 1.5 mmol), tetrahydroxydiboron (402 mg, 4.5 mmol), XPhos (35.7 mg, 75 μmol), XPhos-Pd-G1 (27.6 mg, 37.5 μmol), KOAc (442 mg, 4.5 mmol), and NaO*t*-Bu (3.6 mg, 37.5 μmol) was heated to 80 ºC in EtOH for 2 h. At this point, a nitrogen needle was inserted and acetophenone (180 mg, 195 μL, 1.5 mmol) and aq K_2CO_3 (1.8 M, 2.5 mL) were added via syringe. The crude product was purified via flash chromatography on silica gel (0-5% EtOAc/hexane) to provide the title compound in 63% yield (198 mg) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.23 (m, 4H), 2.66 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 197.9, 147.1, 140.8, 135.7, 135.2, 130.6, 129.6, 129.6, 128.3, 128.0, 126.0, 26.7, 20.5. IR (neat) 3018, 1683, 1358, 1401. HRMS (ES+) calcd. for $C_{12}H_{15}O$ (M+H) 211.1045, found 211.1123.



4-(4-Fluorophenyl)-2-methylquinoline. Following the general procedure, a mixture 1-chloro-4-fluorobenzene (196 mg, 160 μL, 1.5 mmol), tetrahydroxydiboron (402 mg, 4.5 mmol), XPhos (35.7 mg, 75 μmol), XPhos-Pd-G1 (27.6 mg, 37.5 μmol), KOAc (442 mg, 4.5 mmol), and NaO*t*-Bu (3.6 mg, 37.5 μmol) was heated to 80 ºC in EtOH for 2 h. At this point, a nitrogen needle was inserted and 4-chloro-2-methylquinoline (266 mg, 302 μL, 1.5 mmol) and aq K_2CO_3 (1.8 M, 2.5 mL) were added via syringe. The crude product was purified via flash chromatography on silica gel (0-30% EtOAc/hexane) to provide the title compound in 60% yield (212 mg) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.71 – 7.66 (m, 1H), 7.47 – 7.41 (m, 3H), 7.20 (dd, *J* = 10.4, 6.9 Hz, 3H), 2.77 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 163.9, 161.9, 158.6, 148.5, 147.5, 134.2, 131.3 (d, *J* = 7.9 Hz), 129.3 (d, *J* = 34.0 Hz), 125.9, 125.4, 125.1, 122.3, 115.7 (d, *J* = 21.4 Hz), 25.4. IR (neat) 3064, 1606, 1498, 1413, 1224. HRMS (CI+) calcd. for $C_{16}H_{13}FN$ (M+H) 238.0954, found 238.1032.



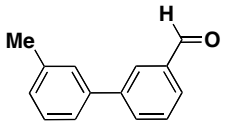
3,5-Dimethoxy-4'-methyl-1,1'-biphenyl. Following the general procedure, a mixture 1-chloro-3,5-dimethoxybenzene (244 mg, 1.41 mmol), tetrahydroxydiboron (380 mg, 4.23 mmol), XPhos (33.55 mg, 70.5 μmol), XPhos-Pd-

G1 (26 mg, 35 μmol), KOAc (414 mg, 4.23 mmol), and NaO*t*-Bu (3.36 mg, 35 μmol) was heated to 80 ºC in EtOH for 2 h. At this point, a nitrogen needle was inserted and 1-chloro-4-methylbenzene (178 mg, 166 μL, 1.41 mmol) and aq K_2CO_3. (1.8 M, 2.5 mL) were added via syringe. The crude product was purified via flash chromatography on silica gel (0-3% EtOAc/hexane) to provide the title compound in 55% yield (175 mg) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.7 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 2H), 6.72 (s, 2H), 6.45 (s, 1H), 3.83 (s, 6H), 2.39 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 183.2, 165.6, 160.5, 159.5, 151.6, 149.2, 127.4, 121.2, 77.5, 43.2. IR (neat) 2937, 2836, 1595, 1154. HRMS (CI+) calcd. for $C_{15}H_{17}O_2$ (M+H) 229.1150, found 229.1224.

General Procedure for the Palladium-Catalyzed Borylation of Aryl Halides and Their Suzuki Cross-Coupling with Aryl or Heteroaryl Halides.

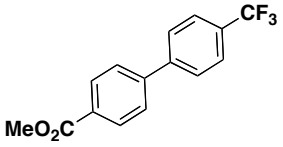
To an oven dried glass vessel capable of being sealed with a Teflon cap (for microwave vials) was added XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), tetrahydroxydiboron (405 mg, 4.5 mmol), and KOAc (441 mg, 4.5 mmol). The vessel was sealed and then evacuated and backfilled with Ar (process was repeated four times). EtOH (15 mL degassed) was added via syringe followed by the addition of the first halide (1.5 mmol) in a similar manner (solid halides were added with the other solid reagents before sealing). The reaction was then heated to 80 ºC for time indicated, then a needle attached to a manifold under argon was inserted into the septum, and 3 equivalents (2.5 mL, 4.5 mmol) of 1.8 M degassed aqueous K_2CO_3 was added via syringe followed by the addition of the second halide (1.5 mmol) in a similar manner (in a solution of 500

μL degassed EtOH or THF if solid). The manifold needle was removed, and the reaction was further heated to 80 ºC for 15 h. The reaction was cooled to rt, filtered through a thin pad of Celite (eluting with 100 mL EtOAc) and concentrated. The crude solid was extracted with EtOAc (3x 5 mL), the combined organics were dried (Na_2SO_4) and then concentrated under reduced pressure. The desired compound was purified by column chromatography, eluting with EtOAc/hexane unless otherwise indicated.



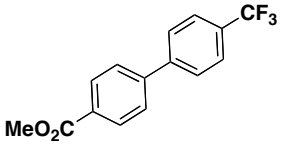
3'-Methyl-[1,1'-biphenyl]-3-carbaldehyde. Following the general procedure, a mixture of 3-chlorotoluene (190 mg, 177 μL, 1.5 mmol), XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), tetrahydroxydiboron (405 mg, 4.5 mmol), and KOAc (441 mg, 4.5 mmol) was heated to 80 ºC in EtOH for 1.5 h. Subsequently, a needle attached to a manifold under argon was added to the septum and 3 equiv (2.5 mL, 4.5 mmol) of 1.8 M degassed aqueous K_2CO_3 was added via syringe followed by 3-bromobenzaldehyde (185 mg, 176 μL, 1.5 mmol) in a similar manner. The manifold needle was removed, and the reaction was further heated to 80 ºC for 15 h. The crude product was purified via flash chromatography on silica gel (0-10% EtOAc/hexane) to provide the title compound as off-white crystals in 71% yield (210 mg). ^{1}H NMR Spectral data in accordance with those of published results. Prolonged storage on the bench led to decomposition and therefore a reasonable ^{13}C NMR spectra could not be obtained. Low melting solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.11 (t, J = 1.5, 1H), 7.91 – 7.82 (m, 2H), 7.62 (t, J = 7.6, 1H), 7.49 – 7.42 (m, 2H), 7.38

(t, J = 7.6, 1H), 7.23 (d, J = 7.5, 1H), 2.46 (s, 3H). IR (dry film): 3022, 1690, 1583, 753 cm^{-1}. HRMS (CI+) calcd. for $C_{14}H_{12}O$ (M+H) 197.0966, found 197.0964.



Methyl 4'-(Trifluoromethyl)-[1,1'-biphenyl]-4-carboxylate.[30]

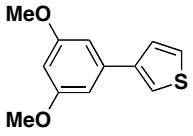
Following the general procedure, a mixture of methyl 4-bromobenzoate (322 mg, 1.5 mmol), XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), tetrahydroxydiboron (405 mg, 4.5 mmol), and KOAc (441 mg, 4.5 mmol) was heated to 80 ºC in EtOH for 2 h. Subsequently, a needle attached to a manifold under argon was inserted into the septum, and 3 equiv (2.5 mL, 4.5 mmol) of 1.8 M degassed aqueous K_2CO_3 was added via syringe followed by 1-bromo-4-(trifluoromethyl)benzene (337 mg, 210 μL, 1.5 mmol). The manifold needle was removed, and the reaction was further heated to 80 ºC for 15 h. The crude product was purified via flash chromatography on silica gel (0-5% EtOAc/hexane) to provide the title compound as a white solid in 60% yield (249 mg). Spectral data were in accordance with those of published results. mp 119-121 ºC**.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.2 Hz, 2H), 7.73 (s, 4H), 7.67 (d, J = 8.3 Hz, 2H), 3.96 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 166.9, 144.2, 143.7, 143.7, 130.4, 129.9, 127.8, 127.4, 126.1, 126.02 (q, J = 3.8) 52.4.



Methyl 4'-(Trifluoromethyl)-[1,1'-biphenyl]-4-carboxylate.[30]

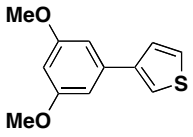
Following the general procedure, a mixture of methyl 4-bromobenzoate (322 mg, 1.5

mmol), XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), tetrahydroxydiboron (405 mg, 4.5 mmol), and KOAc (441 mg, 4.5 mmol) and was heated to 80 ºC for in EtOH 2 h. Subsequently, a needle attached to a manifold under argon was inserted into the septum, and 3 equiv (2.5 mL, 4.5 mmol) of 1.8 M degassed aqueous K_2CO_3 was added via syringe followed by 1-chloro-4-(trifluoromethyl)benzene (279 mg, 200 μL, 1.5 mmol). The manifold needle was removed, and the reaction was further heated to 80 ºC for 15 h. The crude product was purified via flash chromatography on silica gel (0-5% EtOAc/hexane) to provide the title compound as a white solid in 77% yield (323 mg). Spectral data were in accordance with those of published results. mp 118-120 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.3 Hz, 2H), 7.73 (s, 4H), 7.67 (d, J = 8.3 Hz, 2H), 3.96 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 166.90, 144.20, 143.67, 130.42, 130.38, 130.18, 129.95, 127.76, 127.40, 126.02 (q, J = 3.7), 52.40.

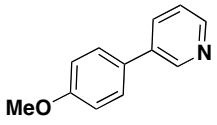


3-(3,5-Dimethoxyphenyl)thiophene. Following the general procedure, a mixture of 1-bromo-3,5-dimethoxybenzene (326 mg, 1.5 mmol), XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), tetrahydroxydiboron (405 mg, 4.5 mmol), and KOAc (441 mg, 4.5 mmol) was heated to 80 ºC for 2.5 h. Subsequently, a needle attached to a manifold under argon was inserted into the septum, and 3 equiv (2.5 mL, 4.5 mmol) of 1.8 M degassed aqueous K_2CO_3 was via syringe followed by 3-bromothiophene (245 mg, 140 μL, 1.5 mmol). The manifold needle was removed, and the reaction was further heated to 80 ºC for 15 h. The crude product was purified via flash

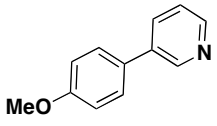
chromatography on silica gel (0-5% EtOAc/hexane) to provide the title compound as a yellow oil in 51% yield (170 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.39 – 7.35 (m, 2H), 6.75 (s, 2H), 6.43 (s, 1H), 3.84 (s, 6H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 161.2, 142.5, 138.0, 126.6, 126.3, 120.9, 105.0, 99.3, 55.6. IR (dry film): 3000, 1201, 838 cm^{-1}. HRMS (ES-) calcd. for $C_{12}H_{12}O_2S$ (M-H) 219.0558, found 219.0471.



3-(3,5-Dimethoxyphenyl)thiophene. Following the general procedure, a mixture of 1-bromo-3,5-dimethoxybenzene (326 mg, 1.5 mmol), XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), tetrahydroxydiboron (405 mg, 4.5 mmol), and KOAc (441 mg, 4.5 mmol) was heated to 80 ºC in EtOH for 2.5 h. Subsequently, a needle attached to a manifold under argon was inserted into the septum, and 3 equiv (2.5 mL, 4.5 mmol) of 1.8 M degassed aqueous K_2CO_3 was added via syringe followed by 3-chlorothiophene (178 mg, 140 μL, 1.5 mmol). The manifold needle was removed and the reaction was further heated to 80 ºC for 15 h. The crude product was purified via flash chromatography on silica gel (0-5% EtOAc/hexane) to provide the title compound as yellow oil in 62% yield (206 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.40 – 7.35 (m, 2H), 6.75 (s, 2H), 6.43 (s, 1H), 3.85 (s, 6H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 161.3, 142.5, 138.0, 126.7, 126.3, 120.9, 105.0, 99.3, 55.56. IR (dry film): 3000, 1203, 838 cm^{-1}. HRMS (CI+) calcd. for $C_{12}H_{11}O_2S$ (M+H) 221.0558, found 221.0638.

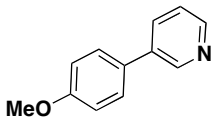


3-(4-Methoxyphenyl)pyridine.[31] Following the general procedure, a mixture of 4-bromoanisole (281 mg, 188 μL, 1.5 mmol), XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), tetrahydroxydiboron (405 mg, 4.5 mmol), and KOAc (441 mg, 4.5 mmol) was heated to 80 ºC in EtOH for 2.5 h. Subsequently, a needle attached to a manifold under argon was inserted into the septum and 3 equiv (2.5 mL, 4.5 mmol) of 1.8 M degassed aqueous K_2CO_3 was added via syringe followed by the addition of the 3-chloropyridine (170 mg, 143 μL, 1.5 mmol). The manifold needle was removed, and the reaction was further heated to 80 ºC for 15 h. The crude product was purified via flash chromatography on silica gel (0-50% EtOAc/hexane) to provide the title compound as a pale yellow solid in 70% yield (194 mg). Spectral data were in accordance with those of published results. mp 64-66 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (d, *J* = 1.7 Hz, 1H), 8.55 (d, *J* = 3.9 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.33 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.9, 148.1, 148.0, 136.4, 134.0, 130.4, 128.4, 123.7, 114.7, 55.5.



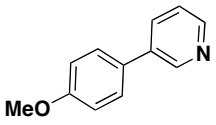
3-(4-Methoxyphenyl)pyridine.[31] Following the general procedure, a mixture of 4-bromoanisole (281 mg, 188 μL, 1.5 mmol), XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), tetrahydroxydiboron (405 mg, 4.5 mmol), and KOAc (441 mg, 4.5 mmol) was heated to 80 ºC in EtOH for 2.5 h. Subsequently, a

needle attached to a manifold under argon was inserted into the septum, and 3 equiv (2.5 mL, 4.5 mmol) of 1.8 M degassed aqueous K_2CO_3 was added via syringe followed by 3-bromopyridine (237 mg, 145 μL, 1.5 mmol). The manifold needle was removed, and the reaction was further heated to 80 ºC for 15 h. The crude product was purified via flash chromatography on silica gel (0-50% EtOAc/hexane) to provide the title compound as a pale yellow solid in 52% yield (144 mg). Spectral data were in accordance with those of published results. mp 64-66 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.55 (d, *J* = 4.6 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.33 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 2H), 3.86 (s, 4H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.9, 148.2, 148.0, 136.4, 133.9, 130.40, 128.4, 123.6, 114.7, 55.5.

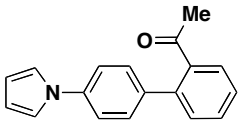


3-(4-Methoxyphenyl)pyridine.[31] Following the general procedure, a mixture of 4-chloroanisole (214 mg, 183 μL, 1.5 mmol), XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), tetrahydroxydiboron (405 mg, 4.5 mmol), and KOAc (441 mg, 4.5 mmol) was heated to 80 ºC in EtOH for 2 h. Subsequently, a needle attached to a manifold under argon was inserted into the septum, and 3 equiv (2.5 mL, 4.5 mmol) of 1.8 M degassed aqueous K_2CO_3 was added via syringe followed by 3-chloropyridine (170 mg, 143 μL, 1.5 mmol). The manifold needle was removed and the reaction was further heated to 80 ºC for 15 h. The crude product was purified via flash chromatography on silica gel (0-50% EtOAc/hexane) to provide the title compound as a pale yellow solid in 82% yield (229 mg). Spectral data were in accordance with those of

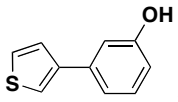
published results. mp 63-65 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (d, *J* = 1.9 Hz, 1H), 8.55 (d, *J* = 3.7 Hz, 1H), 7.83 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.34 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H).^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.9, 148.2, 148.0, 136.4, 134.0, 130.4, 128.4, 123.7, 114.7, 55.5.



3-(4-Methoxyphenyl)pyridine.[31] Following the general procedure, a mixture of 4-chloroanisole (214 mg, 183 μL, 1.5 mmol), XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), tetrahydroxydiboron (405 mg, 4.5 mmol), and KOAc (441 mg, 4.5 mmol) and heated to 80 ºC in EtOH for 2 h. Subsequently, a needle attached to a manifold under argon was inserted into the septum, and 3 equiv (2.5 mL, 4.5 mmol) of 1.8 M degassed aqueous K_2CO_3 was added via syringe followed by 3-bromopyridine (237 mg, 145 μL, 1.5 mmol). The manifold needle was removed, and the reaction was further heated to 80 ºC in EtOH for 15 h. The crude product was purified via flash chromatography on silica gel (0-50% EtOAc/hexane) to provide the title compound as a pale yellow solid in 80% yield (223 mg). Spectral data were in accordance with those of published results. mp 63-65 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (d, *J* = 1.7 Hz, 1H), 8.55 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.85-7.82 (m, 1 H), 7.54 – 7.48 (m, 2H), 7.35-7.33 (m, 1 H), 7.03 – 6.97 (m, 2H), 3.85 (s, 3H).^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.9, 148.1, 148.0, 136.4, 133.9, 130.4, 128.4, 123.6, 114.7, 55.5.

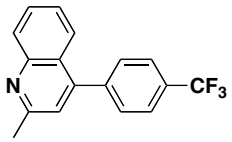


1-(4'-(1*H*-Pyrrol-1-yl)-[1,1'-biphenyl]-2-yl)ethanone. Following the general procedure, a mixture of 1-(4-chlorophenyl)-1*H*-pyrrole (190 mg, 177 μL, 1.5 mmol), XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), tetrahydroxydiboron (405 mg, 4.5 mmol), and KOAc (441 mg, 4.5 mmol) and heated to 80 ºC in EtOH for 1.5 h. Subsequently, a needle attached to a manifold under argon was inserted into the septum, and 3 equiv (2.5 mL, 4.5 mmol) of 1.8 M degassed aqueous K_2CO_3 was added via syringe followed by 2-chloroacetophenone (232 mg, 195 μL, 1.5 mmol) in a similar manner. The manifold needle was removed, and the reaction was further heated to 80 ºC in for 15 h. The crude product was purified via flash chromatography on silica gel (0-10% EtOAc/hexane) to provide the title compound as a yellow solid in 59% yield (230 mg). mp 119-121 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.52 (m, 2H), 7.49 – 7.44 (m, 3H), 7.41 (m, 3H), 7.16 (t, *J* = 2.2 Hz, 2H), 6.39 (t, *J* = 2.2 Hz, 2H), 2.12 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 204.7, 140.9, 140.5, 139.7, 138.1, 131.0, 130.4, 130.2, 128.2, 127.8, 120.5, 119.3, 110.9, 30.7. IR (dry film): 2977, 1673, 1613, 833, 761 cm^{-1}. HRMS (CI+) calcd. for $C_{18}H_{16}NO$ (M+H) 262.115, found 262.122.



3-(Thiophen-3-yl)phenol. Following the general procedure, a mixture of 3-chlorophenol (193 mg, 158 μL, 1.5 mmol), XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), tetrahydroxydiboron (405 mg, 4.5 mmol), and KOAc (441 mg, 4.5

mmol) and heated to 80 ºC in EtOH for 1.5 h. Subsequently, a needle attached to a manifold under argon was inserted into the septum, and 3 equiv (2.5 mL, 4.5 mmol) of 1.8 M degassed aqueous K_2CO_3 was added via syringe followed by 3-chlorothiophene (178 mg, 140 μL, 1.5 mmol) in a similar manner. The manifold needle was removed, and the reaction was further heated to 80 ºC for 15 h. The crude product was purified via flash chromatography on silica gel (0-10% EtOAc/hexane) to provide the title compound as off-white crystals in 91% yield (240 mg). mp 95-97 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, J = 2.8, 1.4 Hz, 1H), 7.38-7.28 (m, 2H), 7.20-7.19 (m, 1H), 7.10 – 7.08 (m, 1H), 6.80 – 6.75 (m, 1H), 4.75 (s, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$)δ155.95, 142.0, 137.7, 130.2, 126.5, 126.4, 120.8, 119.3, 114.2, 113.5. IR (dry film): 2365, 1581, 1219, 769 cm^{-1}. HRMS (CI+) calcd. for $C_{10}H_8OS$ (M+H) 177.029, found 177.037.



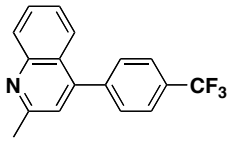
2-Methyl-4-(4-(trifluoromethyl)phenyl)quinolone.[24] Following the general procedure, a mixture of 1-chloro-4-(trifluoromethyl)benzene (271 mg, 200 μL, 1.5 mmol), XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), tetrahydroxydiboron (405 mg, 4.5 mmol), and KOAc (441 mg, 4.5 mmol) was heated to 80 ºC in EtOH for 1 h. Subsequently, a needle attached to a manifold under argon was inserted into the septum, and 3 equiv (2.5 mL, 4.5 mmol) of 1.8 M degassed aqueous K_2CO_3 was added via syringe followed by 4-chloroquinalidine (312 mg, 202 μL, 1.5 mmol). The manifold needle was removed, and the reaction was further heated to 80 ºC for 15 h. The crude product was purified via flash chromatography on silica gel (0-5%

MeOH/CH_2Cl_2) to provide the title compound as a white solid in 50% yield (215 mg). Spectral data were in accordance with those of published results. mp 105-107 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 7.7 Hz, 2H), 7.77 – 7.69 (m, 2H), 7.62 (d, *J* = 7.7 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.23 (s, 1H), 2.80 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 158.7, 148.5, 147.1, 141.9, 130.8, 130.6, 130.0, 129.8, 129.4, 126.3, 125.63 (q, *J* = 3.8), 125.24, 124.8, 122.3, 25.5.

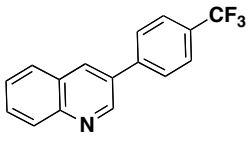
General Procedure for the Palladium-Catalyzed Borylation of Heteroaryl Halides and their Suzuki Coupling with Aryl Halides.

To an oven dried glass vessel capable of being sealed with a Teflon cap (for microwave vials) was added CataCXiumA-Pd-G2 (50 mg, 75 μmol) and $B_2(OH)_4$ (405 mg, 4.5 mmol). The vessel was sealed and then evacuated and backfilled with Ar (process was repeated four times). MeOH (7.5 mL, degassed) was added via syringe followed by the addition of the halide (1.5 mmol) and *i*-Pr_2NEt (784 μL, 4.5 mmol) in a similar manner (solid halides were added with the other solid reagents before sealing). The reaction was then heated to 50 ºC until the starting material was consumed (as monitored by GC). Subsequently, a needle attached to a manifold under argon was inserted into the septum and 3 equiv (4.5 mL, 4.5 mmol) of 1.0 M degassed aqueous K_3PO_4 was added via syringe followed by the second halide (1.5 mmol) in a similar manner (in a solution of 500 μL degassed EtOH or THF if solid). The manifold needle was removed, and the reaction was further heated to 50 ºC for 15 h. The reaction was cooled to rt, filtered through a thin pad of Celite (eluting with 5 x 10 mL EtOAc) and concentrated. The crude solid was

extracted with EtOAc (3x 5 mL), the combined organics were dried (Na_2SO_4) and then concentrated under reduced pressure. The desired compound was purified by column chromatography, eluting with EtOAc/hexane unless otherwise indicated.



2-Methyl-4-(4-(trifluoromethyl)phenyl)quinolone.[24] Following general procedure B, a mixture of 4-chloroquinalidine (312 mg, 202 μL, 1.5 mmol), CataCXiumA-Pd-G2 (50 mg, 75 μmol), *i*-Pr_2NEt (581 mg, 785 μL, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), were heated to 50 ºC in MeOH (7.5 mL) for 1.5 h. Subsequently, a needle attached to a manifold under argon was inserted into the septum, and 3 equiv (4.5 mL, 4.5 mmol) of 1.0 M degassed aqueous K_3PO_4 was added via syringe followed by 1-chloro-4-(trifluoromethyl)benzene (271 mg, 200 μL, 1.5 mmol). The manifold needle was removed, and the reaction was further heated to 50 ºC for 15 h. The crude product was purified via flash chromatography on silica gel (0-5% MeOH/CH_2Cl_2) to provide the title compound as off-white crystals in 63% yield (275 mg). Spectral data were in accordance with those of published results. mp 104-106 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.78 – 7.70 (m, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.23 (s, 1H), 2.80 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 158.7, 148.5, 147.1, 141.9, 131.1, 130.8, 130.6, 130.3, 130.0, 129.7, 129.4, 126.3, 125.65 (q, *J* = 3.7), 122.3, 25.5.



3-(4-(Trifluoromethyl)phenyl)quinolone.[24] Following the general procedure, 3-bromo-5-phenylpyridine (351 mg, 1.5 mmol), CataCXiumA-Pd-G2 (50 mg, 75 μmol), *i*-Pr_2NEt (581 mg, 785 μL, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 50 ºC in MeOH (7.5 mL) for 5 h. Subsequently, a needle attached to a manifold under argon was inserted into the septum, and 3 equiv (4.5 mL, 4.5 mmol) of 1.0 M degassed aqueous K_3PO_4 was added via syringe followed by 1-chloro-4-(trifluoromethyl)benzene (271 mg, 200 μL, 1.5 mmol). The manifold needle was removed, and the reaction was further heated to 50 ºC for 15 h. The crude product was purified via flash chromatography on silica gel (0-10% EtOAc/hexane) to provide the title compound as a pale yellow solid in 60% yield (245 mg). mp = 135-137 °C**.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (d, *J* = 2.2 Hz, 1H), 8.34 (d, *J* = 1.7 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.85 – 7.81 (m, 2H), 7.81 – 7.75 (m, 3H), 7.62 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 149.6, 147.9, 141.6, 133.9, 132.6, 130.5, 130.1, 129.5, 128.3, 127.9, 127.8, 127.5, 126.3 (q, *J* = 3.8), 125.4, 123.2, 100.1. IR (dry film): 2912, 2365. HRMS (ES+) calcd. for $C_{16}H_{10}F_3N$: 274.0844 (M+H), found 274.0857.

5.6 References

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Chapter 6. The Use of Ethylene Glycol in the Palladium-Catalyzed Borylation and Two-Step, One-Pot Borylation/Cross-Coupling of Heteroaryl Halides Utilizing BBA and XPhos-Pd-G2

6.1 Introduction

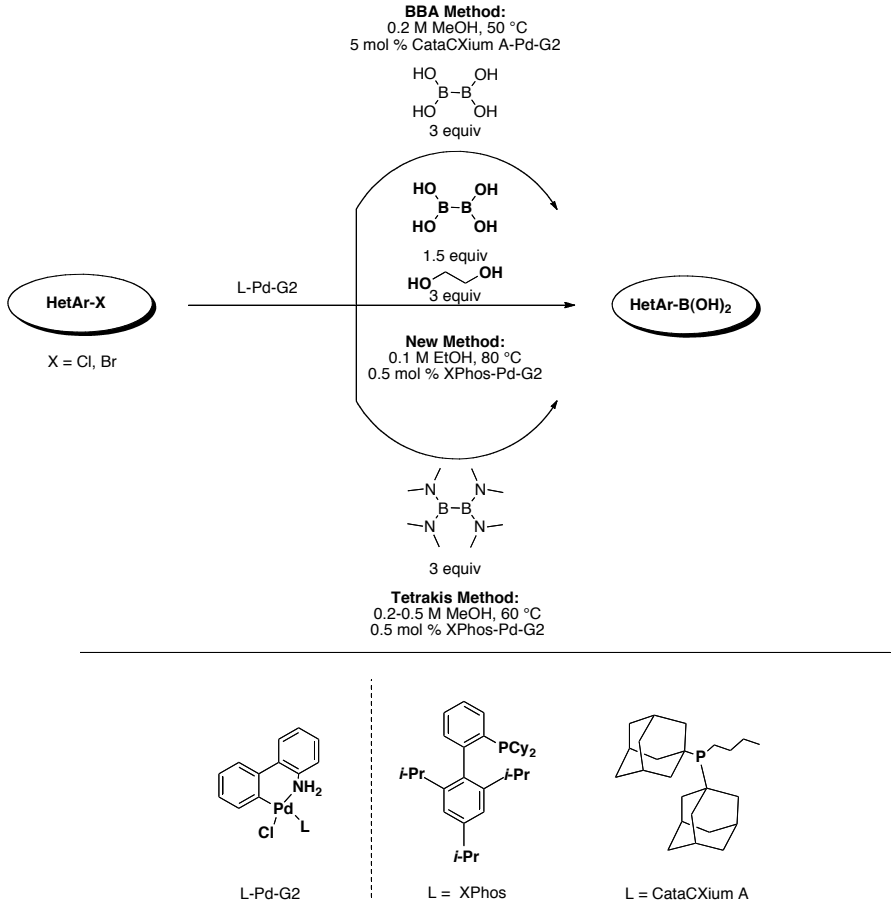
During our development of the palladium-catalyzed borylation of aryl halides, we discovered that heteroaryls and some aryl halides were only obtained in low to moderate yields, with many providing no product whatsoever.[1,2] Although some small improvements were made through the use of tetrakis as the source of boron, the substrate scope was still greatly limited. In an effort to provide access to these synthetically useful substrates, we developed a new method utilizing ethylene glycol, which appears in the early stages of discovery to provide access to previously low yielding substrates in excellent yield. Further, we are for the first time able to isolate cross-coupled products between two heteroaryls in high yield.

6.2 Results and Discussion

The aforementioned method was developed quickly, requiring only small modifications to our optimized method of borylation utilizing BBA and XPhos-Pd-G2. We were delighted that through the use of ethylene glycol, the amount of BBA could effectively be reduced by half to 1.5 equivalents, providing a far more efficient system for the borylation of aryl and heteroaryl halides. Through screening we found that ethylene glycol could be dosed in equimolar amounts with respect to the amount of boron in the reaction, and therefore 3.0 equivalents are used. Similar to our method utilizing

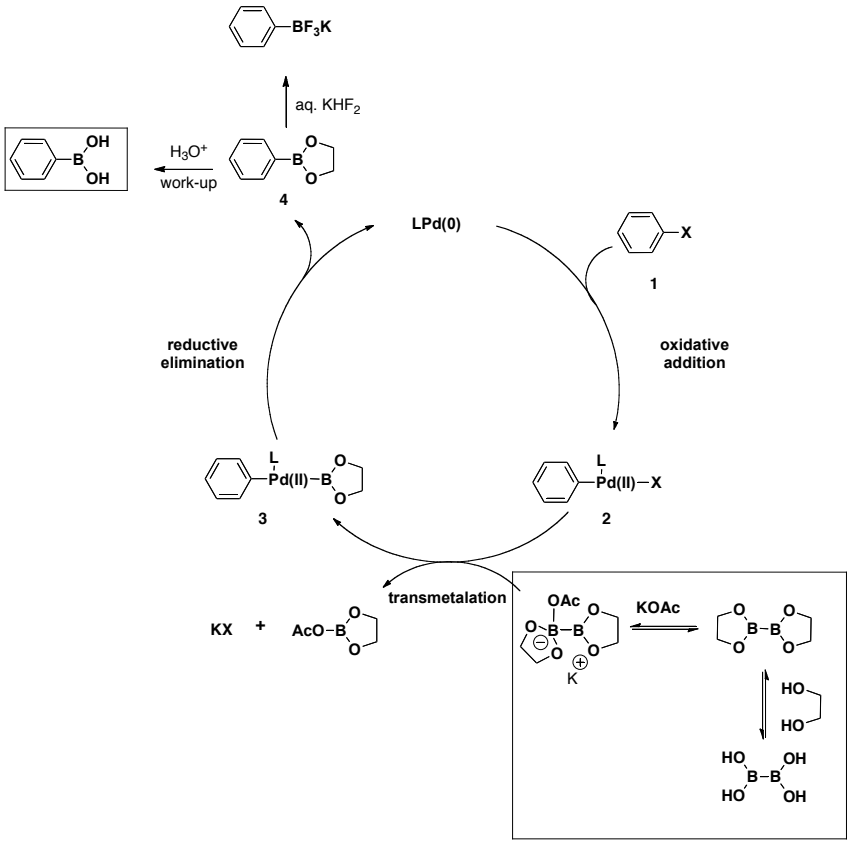
tetrakis, heteroaryl halides can now be borylated with 0.5 mol % XPhos-Pd-G2, as opposed to 5 mol % second generation aminobiphenyl preformed catalyst with CataXCium A as the ligand, (CataCXium A-Pd-G2, Figure 6.1). Additionally, ethanol is still the most efficient solvent at 80 °C. The useful color change observed in our previous method is also observed with aryl chlorides and bromides, changing the reaction mixtures from colorless to yellow and orange, respectively.

Figure 6.1 Comparison of All Optimized Methods for the Borylation of Heteroaryl Halides



As some aryl and heteroarylboronic acids are relatively unstable,[3,4] we rationalized that through the use of ethylene glycol, the intermediate boron species is more stable than the corresponding boronic acid after its formation. This stability, similar to that observed with pinacol boronate esters, allows more of the desired species to survive under the reaction conditions for the requisite reaction time. This phenomenon ultimately provides the trifluoroborate in higher isolated yield than previously observed with our methods. As reaction times are markedly decreased with the ethylene glycol additive, we propose that the BBA is first converted to the corresponding boronate and this species (or its activated borate counterpart) enters the catalytic cycle (Scheme 6.1).

Scheme 6.1 Proposed Catalytic Cycle of Borylation Utilizing Ethylene Glycol, BBA, and XPhos-Pd-G2

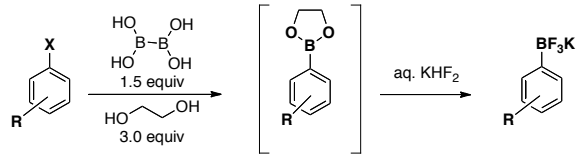


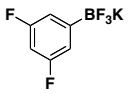
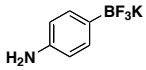
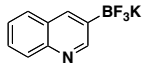
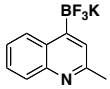
6.2.1 Improved Yields of the Borylation of Heteroaryl and Aryl Halides Utilizing Ethylene Glycol, BBA, and XPhos-Pd-G2

As mentioned previously, using the improved method, we were able to obtain substrates in improved yield that were borylated in poor to moderate yield using either the optimized BBA or tetrakis methods. For example, the yield of the highly electron-withdrawing 3,5-difluorobenzene saw a modest increase with the new method (Table 6.1, entry 1), while the yield of the electron donating 4-substituted aniline increased

substantially as compared to both previous BBA and tetrakis methods (Table 6.1, entry 2). We were especially pleased to see the increase in yield of the 3-bromoquinoline and 3-chlorothiophene derivatives, up from modest yields with the previous methods to excellent isolated yields under the improved set of conditions (Table 6.1, entries 3 and 5). However, not all yields improved, as 4-chloroquinaldine dropped in yield with respect to the tetrakis method and an only modest improvement was seen from the previous BBA method (Table 6.1, entry 4).[2]

Table 6.1 Yields of Trifluoroborates with a New Method Employing Ethylene Glycol as Compared to the First BBA and Tetrakis Methods



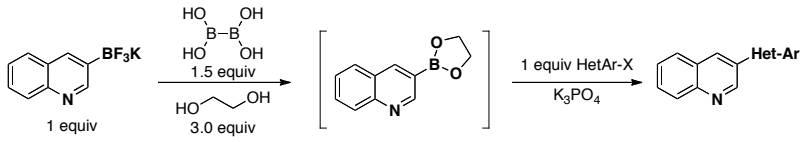
entry	X	product	improved method time (% yield)	first BBA method time (% yield)[a]	tetrakis method time (% yield)[b]
1	Cl		20 min (80)	1.5 h (77)	0
2	Cl		2 h (82)	2 h (68)	7 h (39)
3	Br		20 min (92)	1 h (68)	5 h (64)
4	Cl		30 min (52)	1.5 h (47)	11 h (58)
5	Cl		3.5 h (80)	0	45

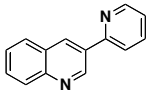
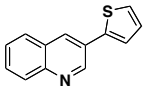
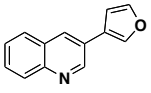
General reaction conditions: 0.5 mol % XPhos-Pd-G2, 1.0 mol % XPhos, 1.5 equiv $B_2(OH)_4$, 3 equiv ethylene glycol, 3 equiv KOAc, EtOH (0.1 M), 80 °C for time indicated. [a]Yield employing BBA general method: 0.5 mol % XPhos-Pd-G2, 1.0 mol % XPhos, 3 equiv $B_2(OH)_4$, 3 equiv KOAc, EtOH (0.1 M), 80 °C for time indicated. [b] Yield employing tetrakis general method: 0.5 mol % XPhos-Pd-G2, 1.0 mol % XPhos, 3 equiv tetrakis, 3 equiv KOAc, MeOH (0.2 M), 60 °C for time indicated

6.2.2 Two-Step, One-Pot Borylation/Suzuki Reactions of Two Heteroaryl Halides

With the new method employing ethylene glycol, we were able for the first time to cross-couple two heteroaryl halides efficiently in high yield. Wang et al. recently published a method utilizing a two-step, one-pot borylation/coupling reaction with B_2Pin_2 and a cyclopalladated ferrocenylimine. Although that method represented a great advance in this area of research, it is limited to the coupling of two pyridine derivatives, relies upon the use of dioxane at 100 °C, and still requires generation of the boronic acid in excess before the cross-coupling with the second pyridine derivative.[5] As outlined in Table 6.2, a variety of heteroaryl halides were efficiently cross-coupled with 3-bromoquinoline, providing excellent isolated yields over two steps.

Table 6.2 Isolated Yields of the Two-Step, One-Pot Borylation/Coupling Reaction Between Two Heteroaryl Halides with BBA, Ethylene Glycol, and XPhos-Pd-G2



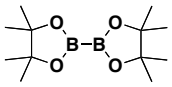
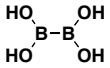
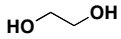
entry	second heteroaryl halide	product	% isolated yield
1			95%
2			88%
3			84%

General reaction conditions: (1) 1 mol % XPhos-Pd-G2, 2 mol % XPhos, 1.5 equiv $B_2(OH)_4$, 3 equiv ethylene glycol, 3 equiv KOAc ,EtOH (0.1 M), 80 °C for time indicated. (2) 1 equiv HetAr-X, 3 equiv 1 M K_3PO_4.

6.2.3 Method Considerations

The improved method utilizing ethylene glycol and BBA has several advantages over those previously developed utilizing BBA alone or employing B_2Pin_2. First, comparing the price of BBA and B_2Pin_2 on a cost-per-mole basis, BBA is half that of B_2Pin_2. When one takes into account that roughly 90% of B_2Pin_2 is pinacol, and therefore most likely removed prior to use, this cost difference is startling (Table 6.3).[6]

Table 6.3 Cost Comparisons of Borylating Reagents and Additives

reagent	structure	molecular weight	cost per mole[a]
B_2Pin_2		254	$ 2,650
BBA		90	$ 1,276
pinacol		118	$ 80
ethylene glycol		62	$ 3.50

[a] Prices based upon the largest quantity of reagent sold by Aldrich (not including bulk ordering)

Next, considering that the number of BBA equivalents are effectively reduced by 50 % with the ethylene glycol additive, the cost-per-reaction decreases dramatically,[7] even after taking into account the added cost of ethylene glycol (Table 6.4).

Table 6.4 Cost of a Reaction Performed on 1 Mole Scale Based Upon Method and Source of Boron Employed

method optimized with:	boron source equivalents	cost/reaction 1 mole scale
B_2Pin_2	3.0	$ 7,815
BBA	3.0	$ 3,828
BBA & ethylene glycol	1.5	$ 1,921[a]

[a] Price includes cost of 3 moles of ethylene glycol

In addition to the reduced cost realized with the new method, ethylene glycol is far easier to remove during the work-up of the reaction, as it is water-soluble. Pinacol on the other hand, is notoriously difficult to remove from the reaction mixture even after work-up and hydrolysis to the boronic acid or conversion to the trifluoroborate.[8-10] As such, pinacol is often found as an impurity in the final, desired product.

With all of the benefits of the new method, there are a few disadvantages. For example, the ethylene glycol ester of BBA believed to be the active reagent is far less atom economical than BBA alone. Further, the metabolites of ethylene are toxic, making the method less environmentally sound than using BBA alone.

6.3 Conclusions

Throughout the course of our method development to replace B_2Pin_2 with the more atom economical BBA in the borylation of aryl halides, we were never able to obtain heteroaryltrifluoroborates in high yield. Although we had great success utilizing

heteroaryls as the second partner in the one-pot, two-step borylation/coupling reaction, the method was limited to the incorporation of only one heteroaryl in the final cross-coupled product. A new method, still in the early stages of discovery, appears to solve many of the problems associated with our previous work. We can now access heteroaryl trifluoroborates in high yield and efficiently cross-couple two heteroaryl halides in the two-step, one-pot borylation/Suzuki reaction. Through the simple addition of ethylene glycol to the system, the amount of BBA can be reduced by 50% to 1.5 equivalents. All of these results provide great anticipation of what the final scope will encompass.

6.4 Experimental

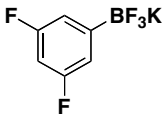
Reagents: All reactions were carried out under an atmosphere of argon. Ethanol (200 proof, non-anhydrous) and ethylene glycol (placed over activated sieves) were thoroughly degassed (1 h) with argon directly before use. All aryl halides were purchased from commercial sources and used as received. KOAc, K_3PO_4, and K_2CO_3 were dried in an oven overnight before use. All reagents (with the exception of the aryl halides) were stored in a bench-top desiccator. Bis-boronic acid was provided by BASF. The XPhos-Pd-G2 is now available from commercial sources.

Analytical Methods: All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, ^{11}B NMR (when applicable), ^{19}F NMR (when applicable), IR spectroscopy, high-resolution mass spectrometry, and melting point determination (for solids). All known compounds were characterized by ^{1}H NMR and ^{13}C NMR and compared to literature values. ^{1}H, ^{13}C, ^{11}B, and ^{19}F were recorded at 500 MHz, 125.8 MHz, 128.4 MHz, and

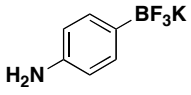
470.8 MHz, respectively. Melting points are uncorrected.

General Procedure for the Palladium-Catalyzed Borylation of Heteroaryl Halides with Ethylene Glycol Additive and Their Conversion to Trifluoroborates. To an oven dried glass vessel capable of being sealed with a Teflon cap (for microwave vials) was added XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), $B_2(OH)_4$ (203 mg, 2.25 mmol), and KOAc (441 mg, 4.5 mmol). The vessel was sealed and then evacuated and backfilled with Ar (process was repeated four times). EtOH (15 mL, degassed) was added via syringe followed by the addition of ethylene glycol (280 mg, 250 μL, 4.5 mmol) and the halide (1.5 mmol) in a similar manner (solid halides were added with the other solid reagents before sealing). The reaction was then heated to 80 ºC until the starting material was consumed (as monitored by color change and GC). The reaction was cooled to rt then filtered through a thin pad of Celite (eluting with 5 x 10 mL of EtOAc), and concentrated. The crude reaction was dissolved in EtOAc (10 mL) and then transferred to a separatory funnel and H_2O was added (10 mL). The layers were separated and the organic layer was washed once with brine (5 mL). The combined aqueous layers were further extracted with EtOAc (3 x 5 mL). The combined organics were dried (Na_2SO_4) and concentrated. The concentrated crude reaction was taken up in MeOH (~15 mL or enough to make a free-flowing solution) and cooled to 0 ºC. To this cooled mixture was added 4.5 equivalents of a 4.5 M aqueous KHF_2 solution (1 mL), and the reaction was stirred for 10 min at 0 ºC before removing the bath and allowing the mixture to stir at rt for 20 min (or until the conversion to the corresponding trifluoroborate was

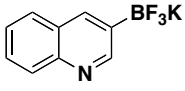
achieved as determined by ^{11}B NMR). The resulting mixture was concentrated and then lyophilized overnight to remove any traces of water. The compound was purified with continuous Soxhlet extraction (overnight) with acetone (150 mL). The collected solvent was filtered through a thin pad of Celite, rinsed with hot acetone (3 x 5 mL) then concentrated until a minimal volume of acetone remained (~3 mL). The addition of Et_2O (~25 mL) led to the precipitation of the desired product. The collected solid was washed with Et_2O. Further purification (to remove small organic or boron containing impurities) could be realized via trituration of the solid with Et_2O.



Potassium (3,5-Difluorophenyl)trifluoroborate.[2] Following the general procedure, 1-chloro-3,5-difluorobenzene (223 mg, 168 μL, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), ethylene glycol (280 mg, 250 μL, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 20 min. The title compound was obtained as a white solid in 80% yield (265 mg) as a white solid. Spectral data were in accordance with those of published results. mp: < 225 °C. ^1H NMR (500 MHz, acetone-d_6) δ 6.97 (d, J = 5.7 Hz, 2H), 6.59 – 6.47 (m, 1H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 162.4 (dd, J = 243 Hz), 113.4 (d, J = 15.4 Hz), 100.6 (d, J = 25.5 Hz). ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.4 (m). ^{19}F NMR (338.8 MHz, acetone-d_6) δ - 114.9, - 143.2.

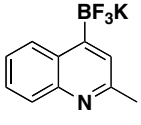


Potassium (4-Aminophenyl)trifluoroborate.[2] Following the general procedure, a 4-chloroaniline (191 mg, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), ethylene glycol (280 mg, 250 μL, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 2 h. The title compound was obtained in 82% yield (244 m**g)** as an off-white solid. Spectral data were in accordance with those of published results. mp: < 225 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.19 (d, J = 7.4 Hz, 2H), 6.45 (d, J = 7.5 Hz, 2H), 3.96 (s, 2H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 146.0, 132.5, 113.5. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 4.1 (m). ^{19}F NMR (338.8 MHz, acetone-d_6) δ – 141.5.

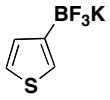


Potassium (Quinolin-3-yl)trifluoroborate.[11] Following the general procedure, 3-bromoquinoline (312 mg, 204 μL, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), ethylene glycol (280 mg, 250 μL, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 20 min. The title compound was obtained in 92% yield (324 mg) as a pale yellow solid. Spectral data were in accordance with those of published results. mp: < 225 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 9.02 (s, 1H), 8.18 (s, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 6.9 Hz, 1H), 7.40 (t, J = 7.0 Hz, 1H)**.** ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 155.8, 147.3, 138.0, 129.1, 128.7, 128.2, 127.9, 125.7. ^{11}B NMR (128.4 MHz, acetone-d_6) δ 3.5 (q, J = 49.6 Hz). ^{19}F NMR (338.8 MHz, acetone-d_6) δ –

141.9.

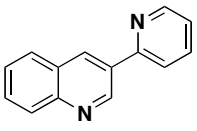


Potassium (2-Methylquinolin-4-yl)trifluoroborate. Following the general procedure, 4-chloroquinaldine (266 mg, 302 μL, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), ethylene glycol (280 mg, 250 μL, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 30 min. The title compound was obtained in 52% yield (194 mg) as an inseparable mixture of the internal salt and the trifluoroborate. Therefore, reasonable spectra could not be obtained.



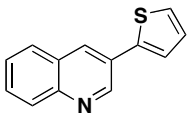
Potassium Thiophen-3-yltrifluoroborate.[2] Following the general procedure, 3-chlorothiophene (178 mg, 139 μL, 1.5 mmol), XPhos-Pd-G2 (5.89 mg, 7.5 μmol), XPhos (7.14 mg, 15 μmol), KOAc (441 mg, 4.5 mmol), ethylene glycol (280 mg, 250 μL, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol), was heated to 80 ºC in EtOH (15 mL) for 3.5 h. The title compound was obtained in 80% yield (227 mg) as an off-white solid. Spectral data were in accordance with those of published results. mp: < 225 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.16 (s, 1H), 6.99 (s, 1H), 6.97 (d, J = 4.6 Hz, 1H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 132.5, 124.9, 123.2. ^{11}B NMR (128.4 MHz, acetone-d_6) 3.1 (q, J = 52.6 Hz). ^{19}F NMR (338.8 MHz, acetone-d_6) δ -138.6.

General procedure for the Palladium-Catalyzed Borylation of Heteroaryl Halides with Ethylene Glycol Additive and their Suzuki Cross-Coupling with Heteroaryl Halides. To an oven dried glass vessel capable of being sealed with a Teflon cap (for microwave vials) was added XPhos-Pd-G2 (11.78 mg, 15 μmol), X-Phos (14.28 mg, 30 μmol), $B_2(OH)_4$ (203 mg, 2.25 mmol), and KOAc (441 mg, 4.5 mmol). The vessel was sealed and then evacuated and backfilled with Ar (process was repeated four times). EtOH (15 mL, degassed) was added via syringe followed by ethylene glycol (250 μL, 4.5 mmol) and the halide (1.5 mmol) in a similar manner (solid halides were added with the other solid reagents before sealing). The reaction was then heated to 80 ºC until the starting material was consumed (as monitored by GC). Subsequently, a needle attached to a manifold under argon was inserted into the septum, and 3 equiv (4.5 mL, 4.5 mmol) of 1.0 M degassed aqueous K_3PO_4 was added via syringe followed by the second halide (1.5 mmol) in a similar manner (in a solution of 500 μL degassed EtOH or THF if solid). The manifold needle was removed, and the reaction was further heated to 80 ºC for 15 h. The reaction was cooled to rt, filtered through a thin pad of Celite (eluting with 5 x 10 mL EtOAc) and concentrated. The crude solid was extracted with EtOAc (3x 5 mL) using saturated $NaHCO_3$ in place of water. The combined organics were dried (Na_2SO_4) and then concentrated under reduced pressure. The desired compound was purified by column chromatography, eluting with EtOAc/hexane unless otherwise indicated.



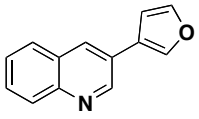
3-(Pyridin-2-yl)quinoline. Following the general procedure, a mixture of

3-bromoquinoline (312 mg, 204 μL, 1.5 mmol), XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), KOAc (441 mg, 4.5 mmol), ethylene glycol (280 mg, 250 μL, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol) was heated to 80 ºC for 20 min. Subsequently, a needle attached to a manifold under argon was inserted into the septum, and 3 equiv (4.5 mL, 4.5 mmol) of 1.0 M degassed aqueous K_3PO_4 was added via syringe followed by 2-chloropyridine (170 mg, 143 μL, 1.5 mmol). The manifold needle was removed, and the reaction was further heated to 80 ºC for 15 h. The crude product was purified via flash chromatography on silica gel (0-100% EtOAc/hexane) to provide the title compound in 95% yield (293 mg) as a light yellow solid. mp: 97-100 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (s, 1H), 8.77 (d, J = 5.2 Hz, 2H), 8.15 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.74 (t, J = 7.7 Hz, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.33 – 7.29 (m, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 154.9, 150.3, 149.4, 148.4, 137.2, 134.0, 132.0, 130.1, 129.4, 128.7, 128.0, 127.2, 122.9, 120.9. IR (neat) 3054, 1589, 1095. HRMS (ES+) calcd. for $C_{14}H_{11}N_2$ (M+H) 207.0922, found 207.0922.



3-(Thiophen-2-yl)quinolone. Following the general procedure, a mixture of 3-bromoquinoline (312 mg, 204 μL, 1.5 mmol), XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), KOAc (441 mg, 4.5 mmol), ethylene glycol (280 mg, 250 μL, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol) was heated to 80 ºC for 20 min. Subsequently, a needle attached to a manifold under argon was inserted into the septum,

and 3 equiv (4.5 mL, 4.5 mmol) of 1.0 M degassed aqueous K_3PO_4 was added via syringe followed by 2-chlorothiophene (178 mg, 140 μL, 1.5 mmol). The manifold needle was removed, and the reaction was further heated to 80 ºC for 15 h. The crude product was purified via flash chromatography on silica gel (0-100% EtOAc/hexane) to provide the title compound in 88% yield (280 mg) as a yellow solid. mp: 70-73 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (d, *J* = 2.0 Hz, 1H), 8.28 (s, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.70 (t, *J* = 7.0 Hz, 1H), 7.57 (t, *J* = 7.1 Hz, 1H), 7.51 (d, *J* = 2.6 Hz, 1H), 7.41 (d, *J* = 4.2 Hz, 1H), 7.22 – 7.14 (m, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 148.7, 147.4, 140.9, 131.5, 129.5, 128.6, 128.1, 127.9, 127.7, 127.4, 126.3, 124.6. IR (neat) 3066, 1492. HRMS (CI+) calcd. for $C_{13}H_9NS$ 211.0456, found 211.0461.



3-(Furan-3-yl)quinolone. Following the general procedure, a mixture of 3-bromoquinoline (312 mg, 204 μL, 1.5 mmol), XPhos-Pd-G2 (11.78 mg, 15 μmol), XPhos (14.28 mg, 30 μmol), KOAc (441 mg, 4.5 mmol), ethylene glycol (280 mg, 250 μL, 4.5 mmol), and $B_2(OH)_4$ (405 mg, 4.5 mmol) was heated to 80 ºC for 20 min. Subsequently, a needle attached to a manifold under argon was inserted into the septum, and 3 equiv (4.5 mL, 4.5 mmol) of 1.0 M degassed aqueous K_3PO_4 was added via syringe followed by 3-bromofurnan (220 mg, 135 μL, 1.5 mmol). The manifold needle was removed, and the reaction was further heated to 80 ºC for 15 h. The crude product was purified via flash chromatography on silica gel (0-100% EtOAc/hexane) to provide the title in 84% yield (246 mg) as a yellow solid. mp: 86-89 °C. ^{1}H NMR (500 MHz, $CDCl_3$)

δ 9.08 (d, *J* = 1.9 Hz, 1H), 8.16 (s, 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.91 (s, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.68 (t, *J* = 7.0 Hz, 1H), 7.60 – 7.52 (m, 2H), 6.84 (s, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 149.1, 147.3, 144.4, 139.3, 131.5, 129.4, 129.3, 128.3, 127.8, 127.2, 125.8, 123.6, 108.8. IR (neat) 3346, 1617. HRMS (CI+) calcd. for $C_{13}H_9NO$ 195.0684, found 195.0682.

6.5 References

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(6) Prices based upon the largest quantity of reagent sold by Aldrich (not including bulk ordering).

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Appendix A1. ^{1}H, ^{13}C, ^{11}B, and ^{19}F Spectra Relevant to Chapter 3

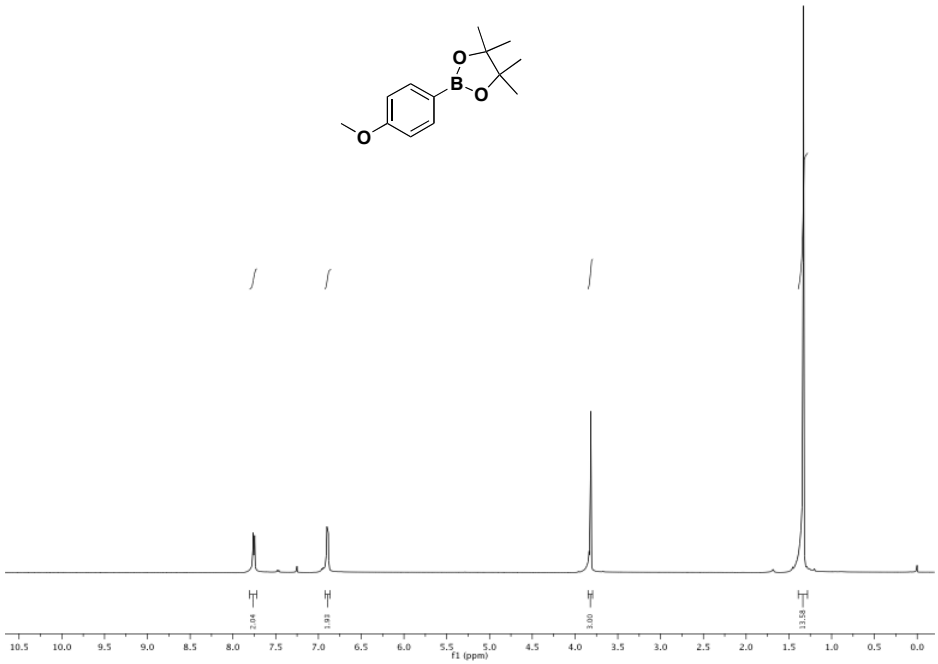

Figure A1.1 ^{1}H NMR Spectra (500 MHz, $CDCl_3$), 2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

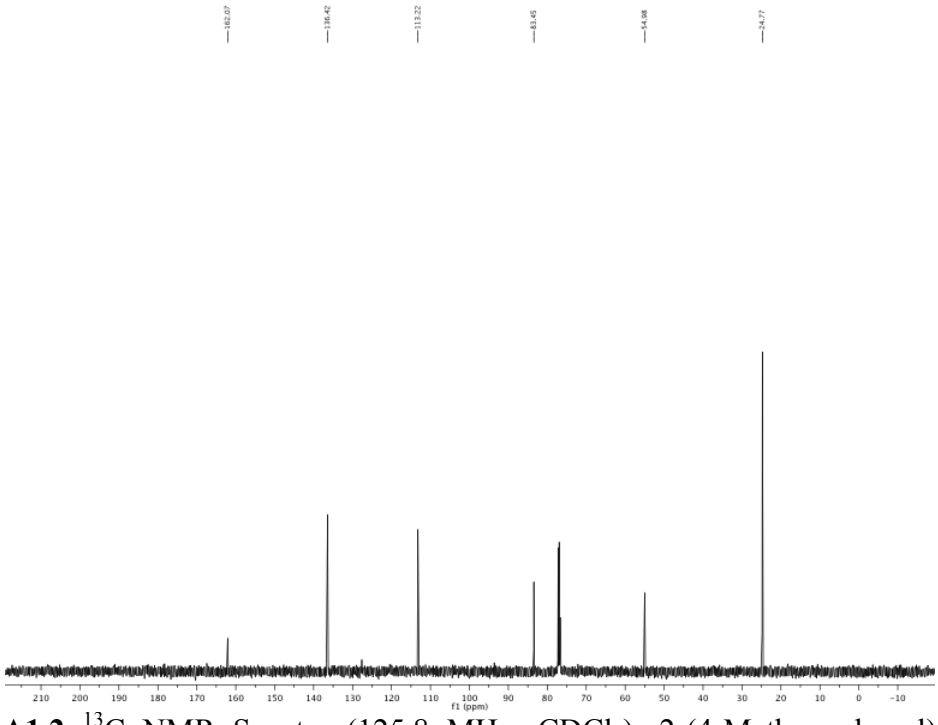

Figure A1.2 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$), 2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

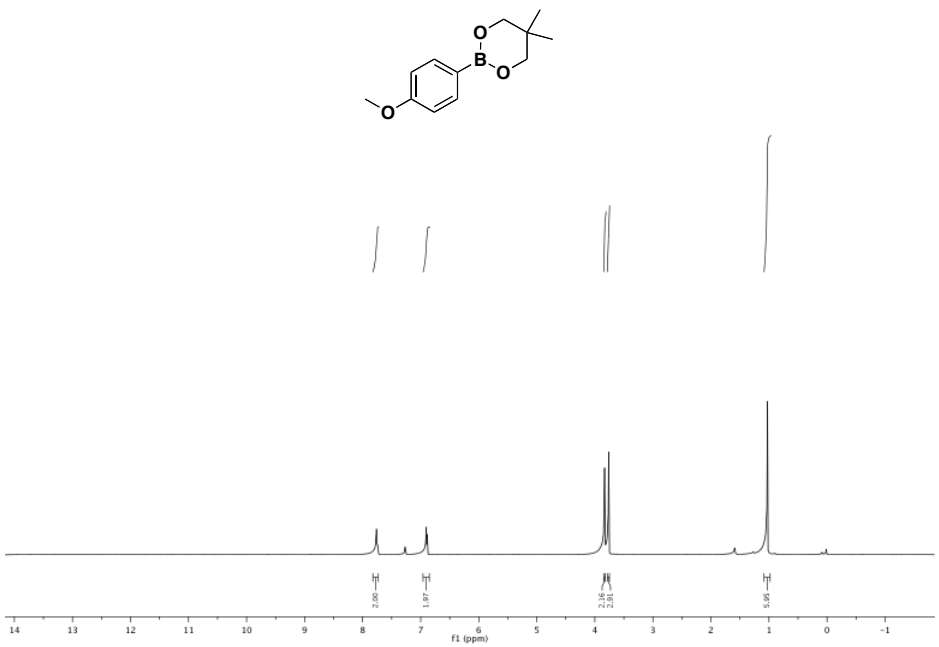

Figure A1.3 ^{1}H NMR Spectra (500 MHz, $CDCl_3$), (2-(4-Methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane

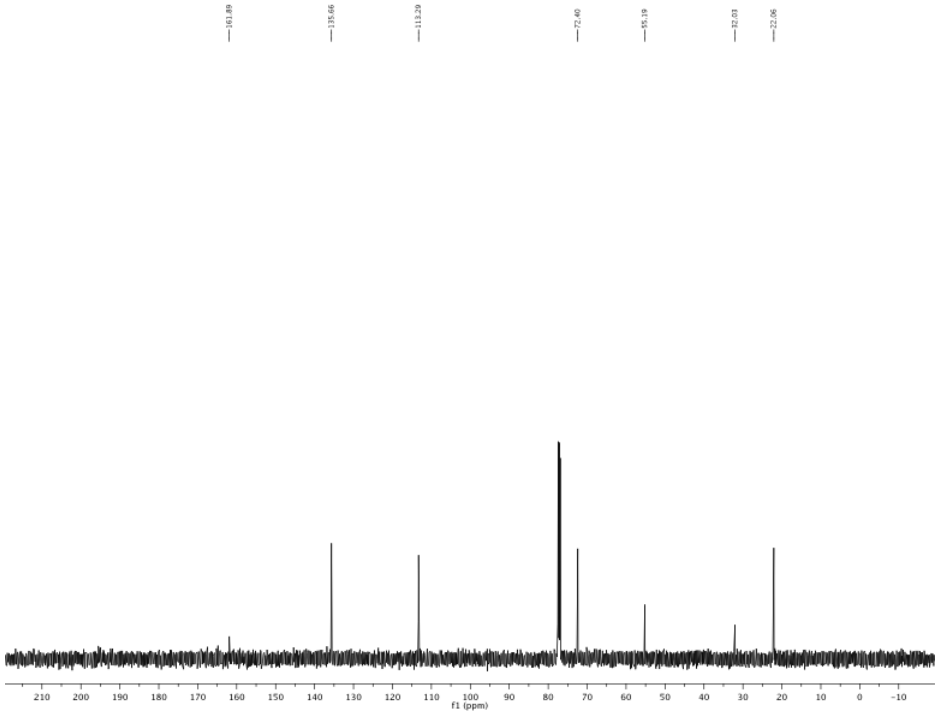

Figure A1.4 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$), (2-(4-Methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane

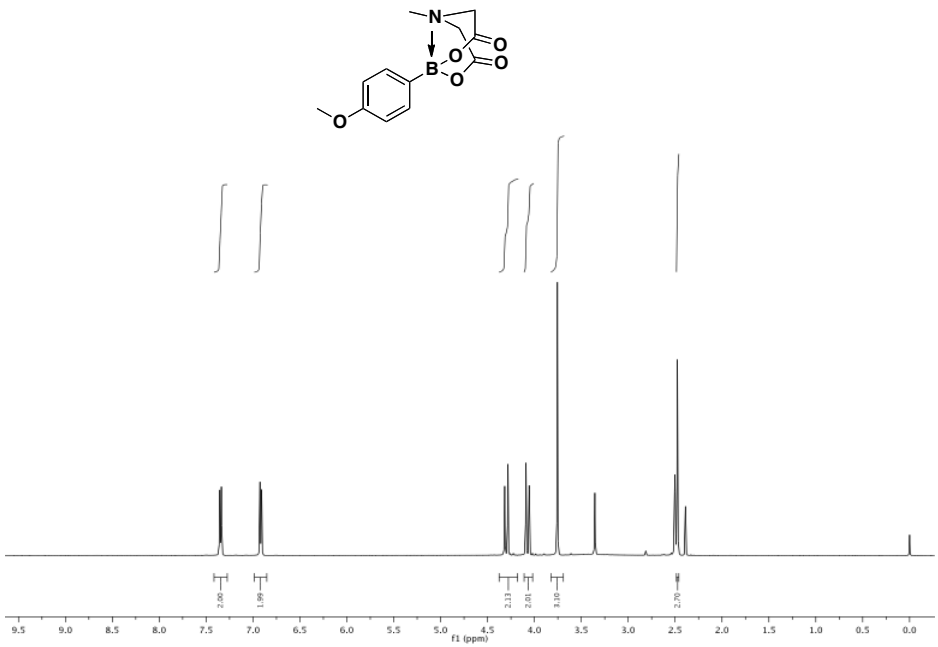

Figure A1.5 ^{1}H NMR Spectra (500 MHz, d_6-DMSO), 2-(4-Methoxyphenyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione

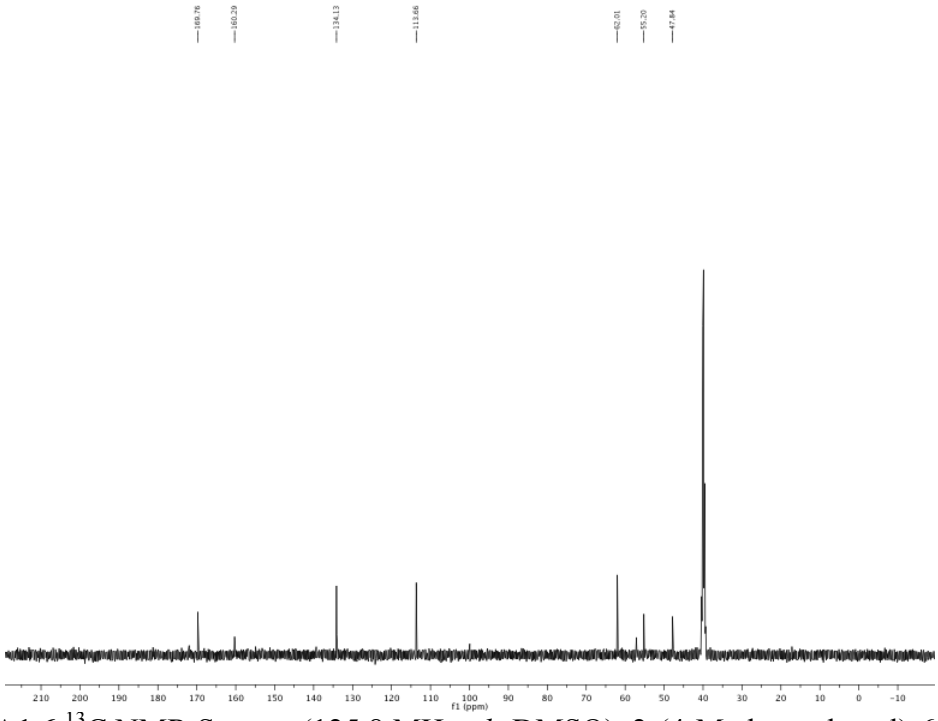

Figure A1.6 ^{13}C NMR Spectra (125.8 MHz, d_6-DMSO), 2-(4-Methoxyphenyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione

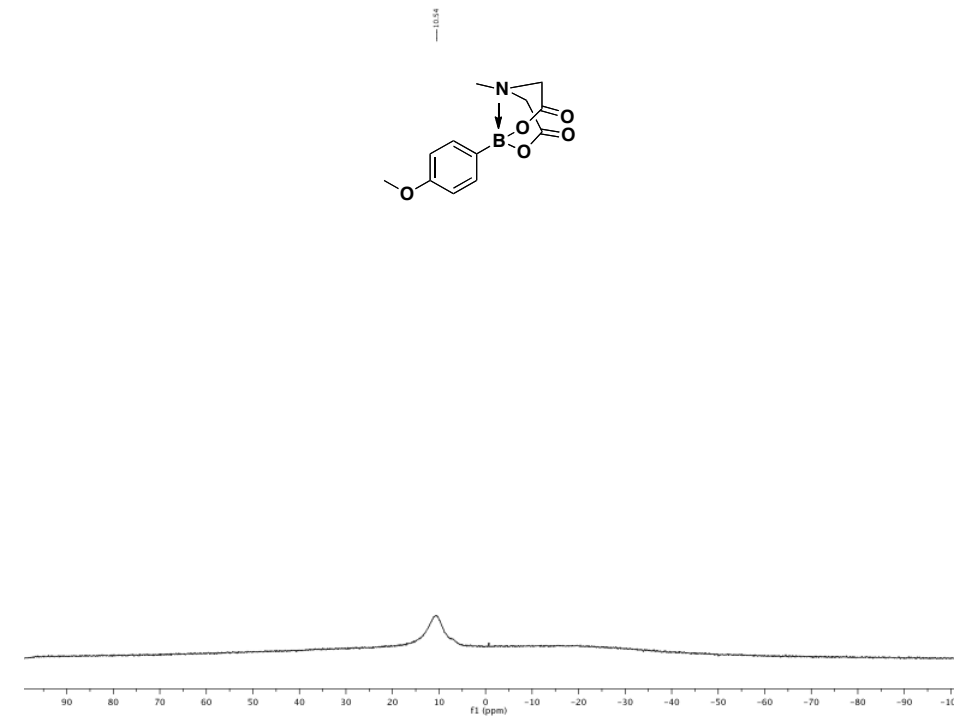

Figure A1.7 ^{11}B NMR Spectra (128.4 MHz, d_6-DMSO), 2-(4-Methoxyphenyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione

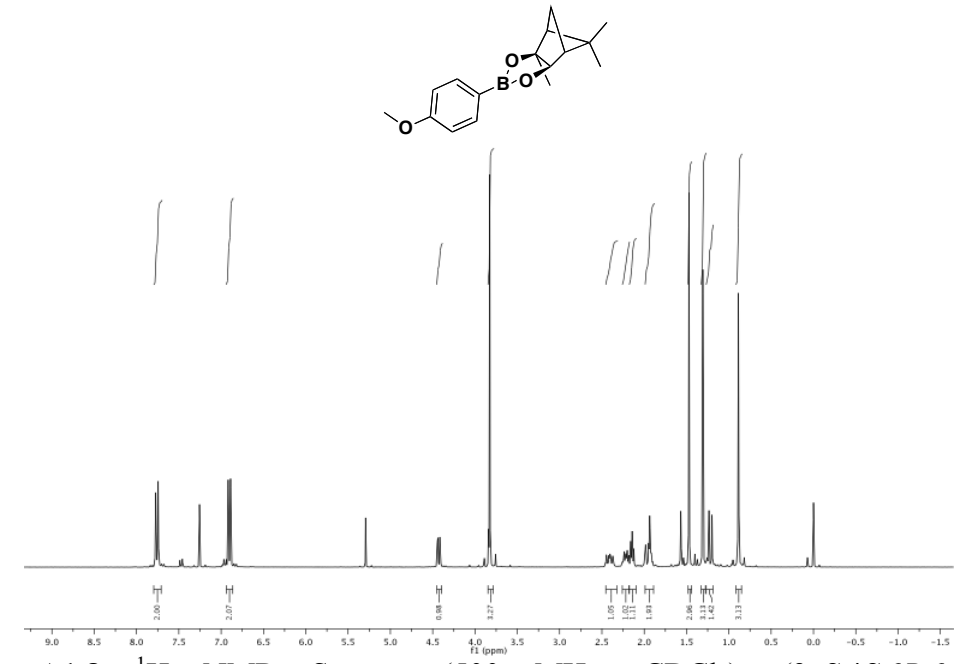

Figure A1.8 ^{1}H NMR Spectra (500 MHz, $CDCl_3$), (3a*S*,4*S*,6*R*,6a*R*)-2-(4-Methoxyphenyl)-3a,5,5-trimethyltetrahydro-3a*H*-4,6-methanocyclopenta[*d*][1,3,2]dioxaborole

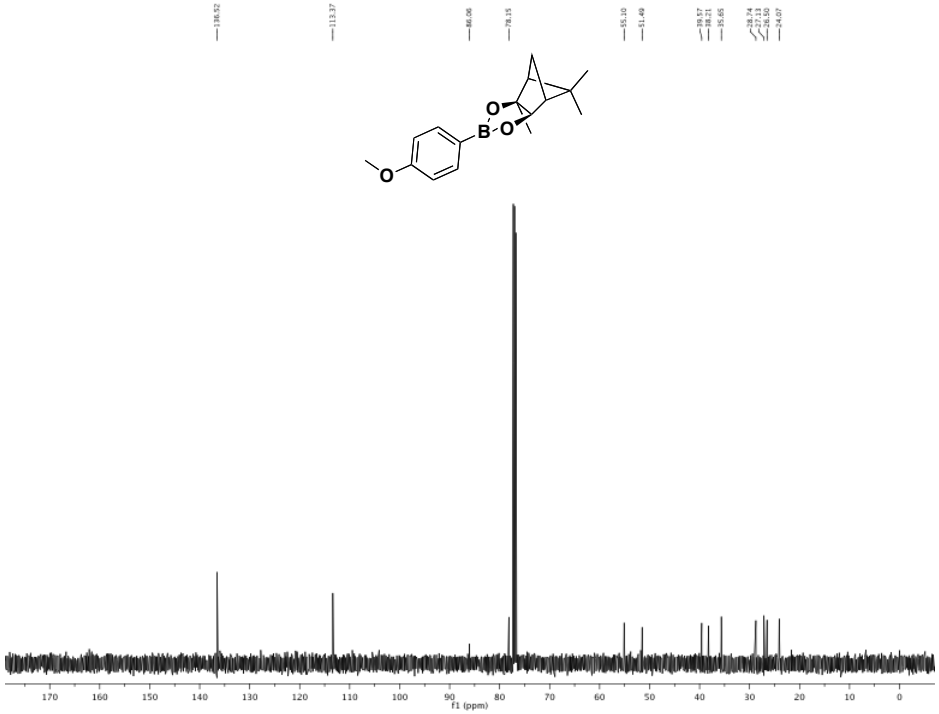

Figure A1.9 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$), (3a*S*,4*S*,6*R*,6a*R*)-2-(4-Methoxyphenyl)-3a,5,5-trimethyltetrahydro-3a*H*-4,6-methanocyclopenta[*d*][1,3,2]dioxaborole

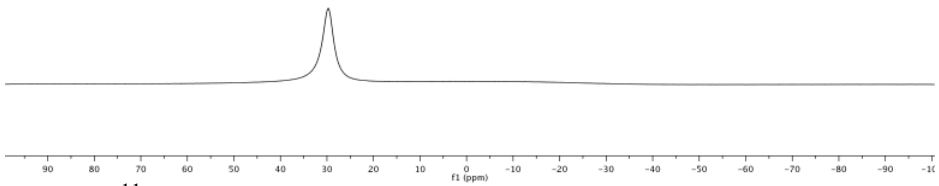

Figure A1.10 ^{11}B NMR Spectra (128.4 MHz, $CDCl_3$), (3a*S*,4*S*,6*R*,6a*R*)-2-(4-Methoxyphenyl)-3a,5,5-trimethyltetrahydro-3a*H*-4,6-methanocyclopenta[*d*][1,3,2]dioxaborole

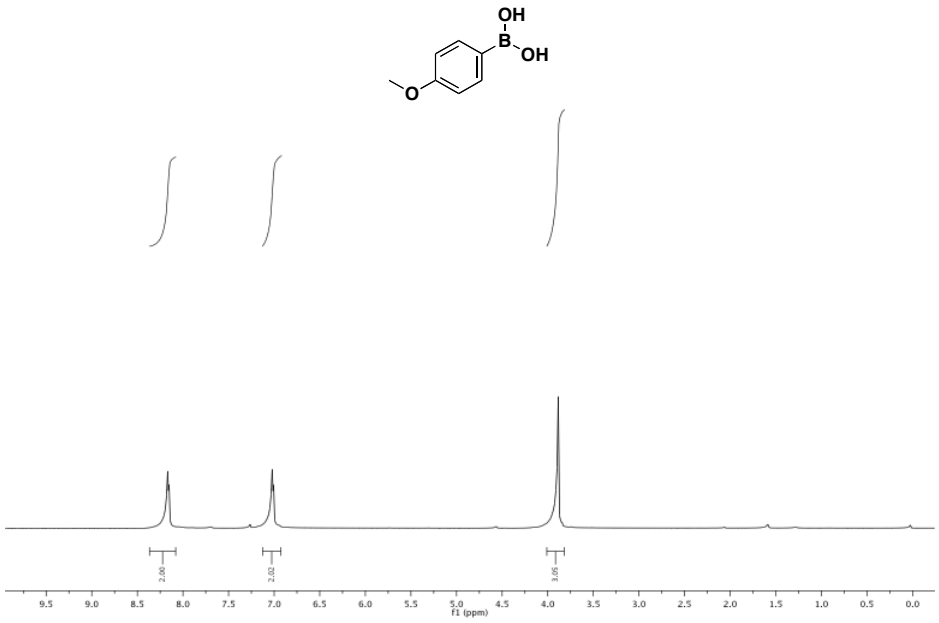

Figure A1.11 ^{1}H NMR Spectra (500 MHz, $CDCl_3$), (4-Methoxyphenyl)boronic acid

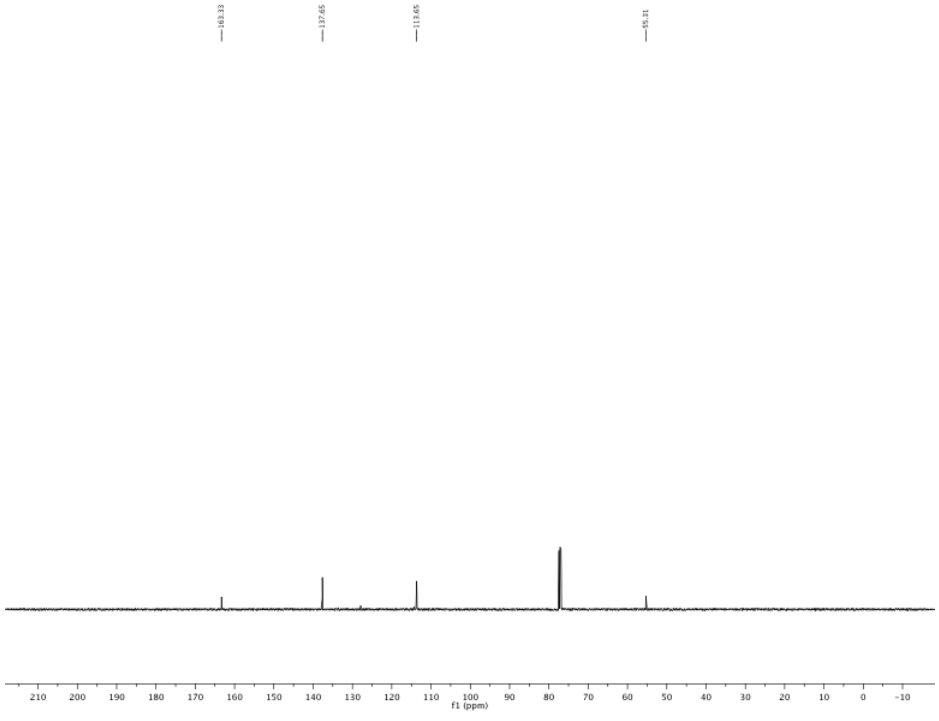

Figure A1.12 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$), (4-Methoxyphenyl)boronic acid

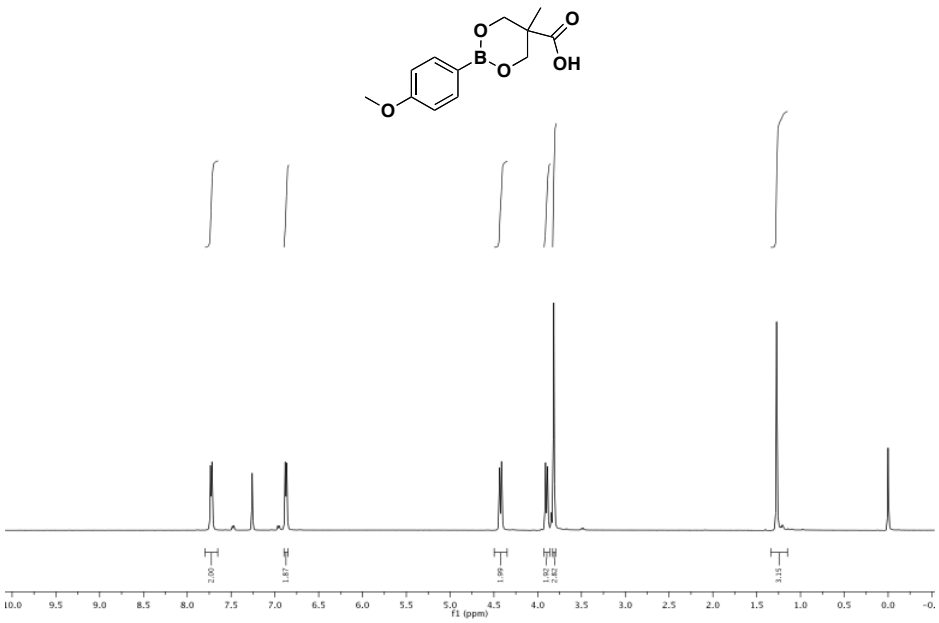

Figure A1.13 ^{1}H NMR Spectra (500 MHz, $CDCl_3$), 2-(4-Methoxyphenyl)-5-methyl-1,3,2-dioxaborinane-5-carboxylic acid

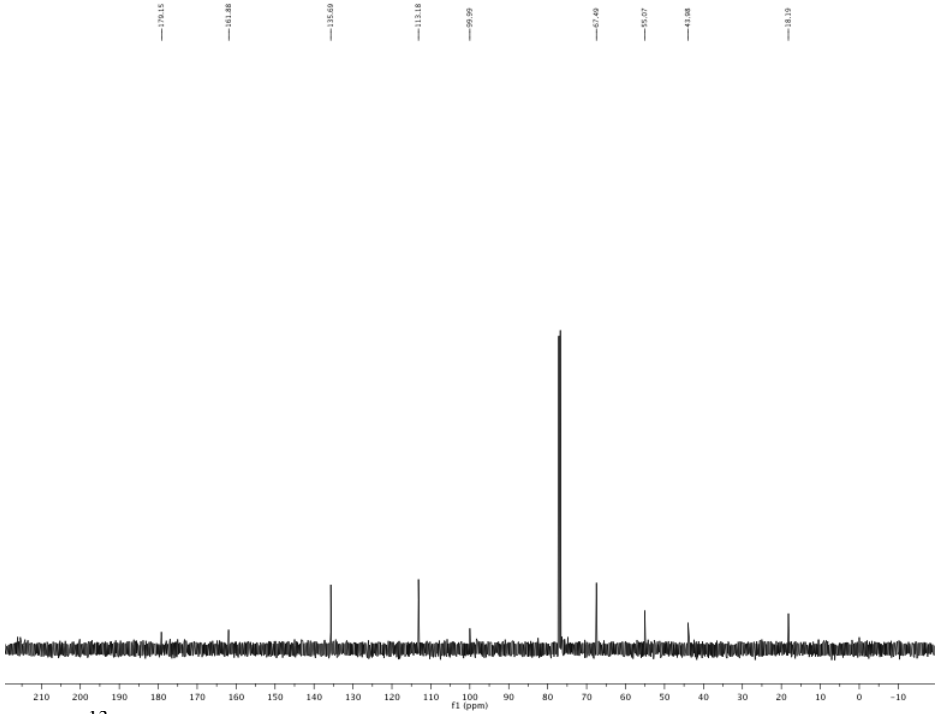

Figure A1.14 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$), 2-(4-Methoxyphenyl)-5-methyl-1,3,2-dioxaborinane-5-carboxylic acid

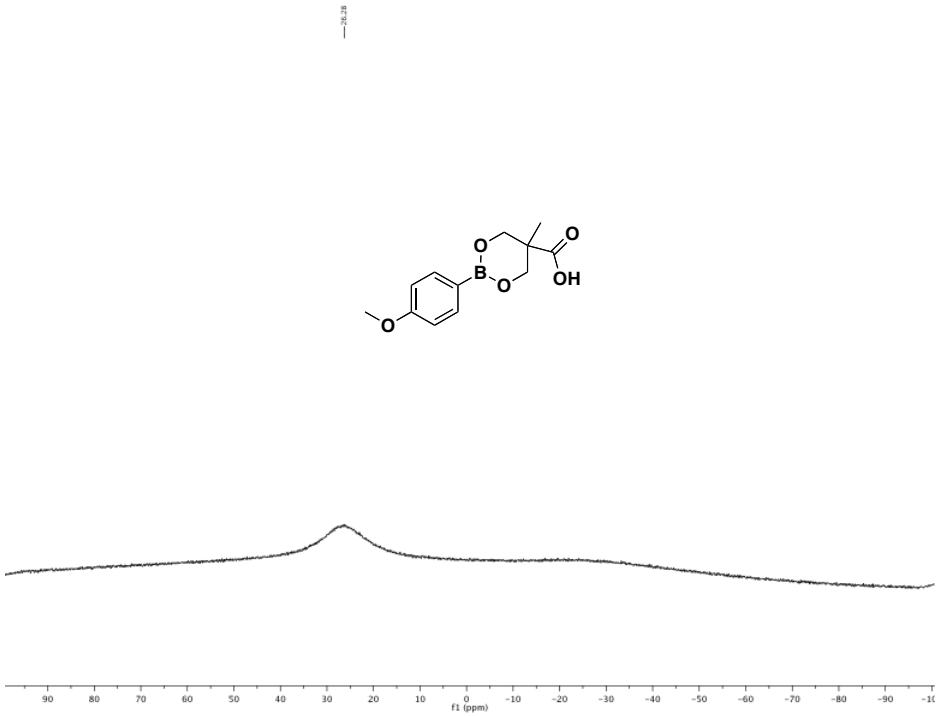

Figure A1.15 ^{11}B NMR Spectra (128.4 MHz d_6-DMSO), 2-(4-Methoxyphenyl)-5-methyl-1,3,2-dioxaborinane-5-carboxylic acid

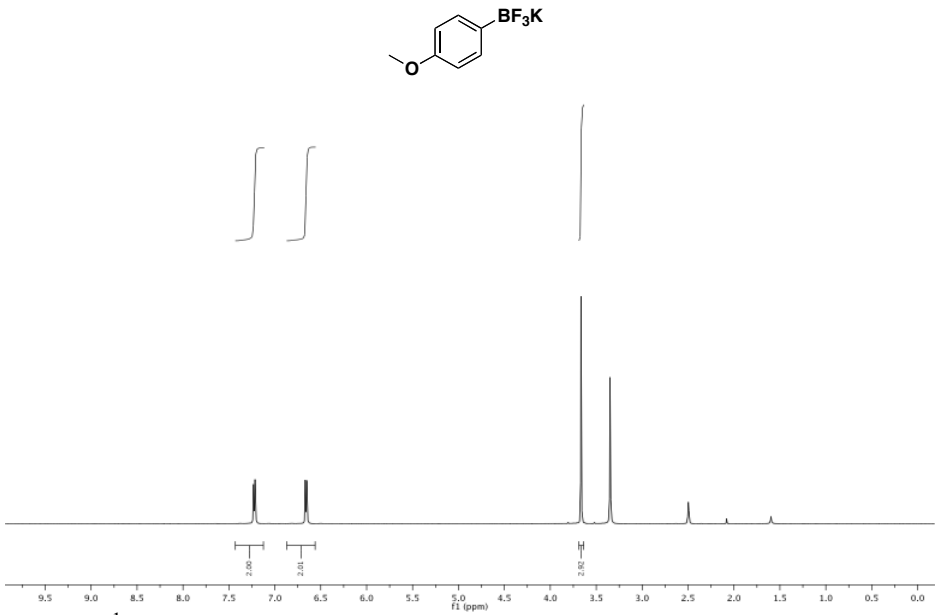

Figure A1.16 ^{1}H NMR Spectra (500 MHz, d_6-DMSO), Potassium 4-Methoxy-trifluoroborate

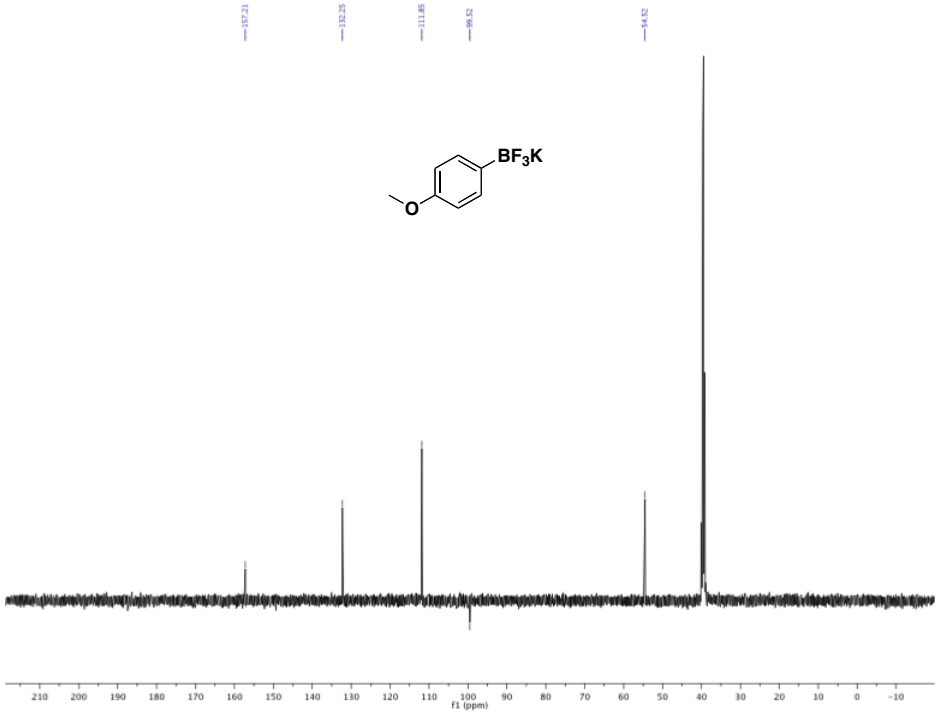

Figure A1.17 ^{13}C NMR Spectra (125.8 MHz, d_6-DMSO), Potassium 4-Methoxy-trifluoroborate

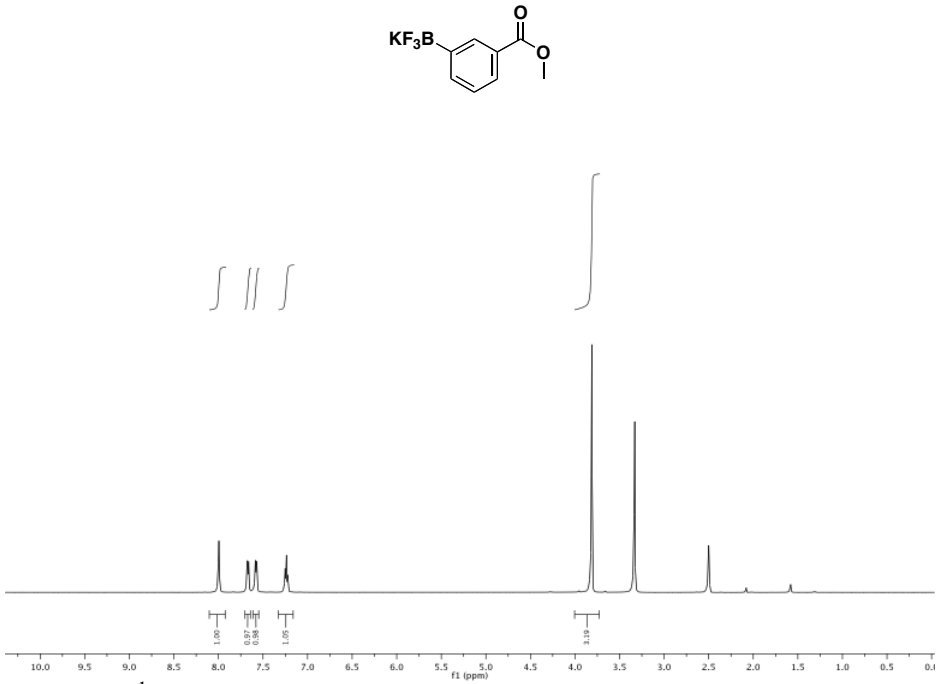

Figure A1.18 ^{1}H NMR Spectra (500 MHz, d_6-DMSO), Potassium (3-(Methoxycarbonyl)phenyl)trifluoroborate

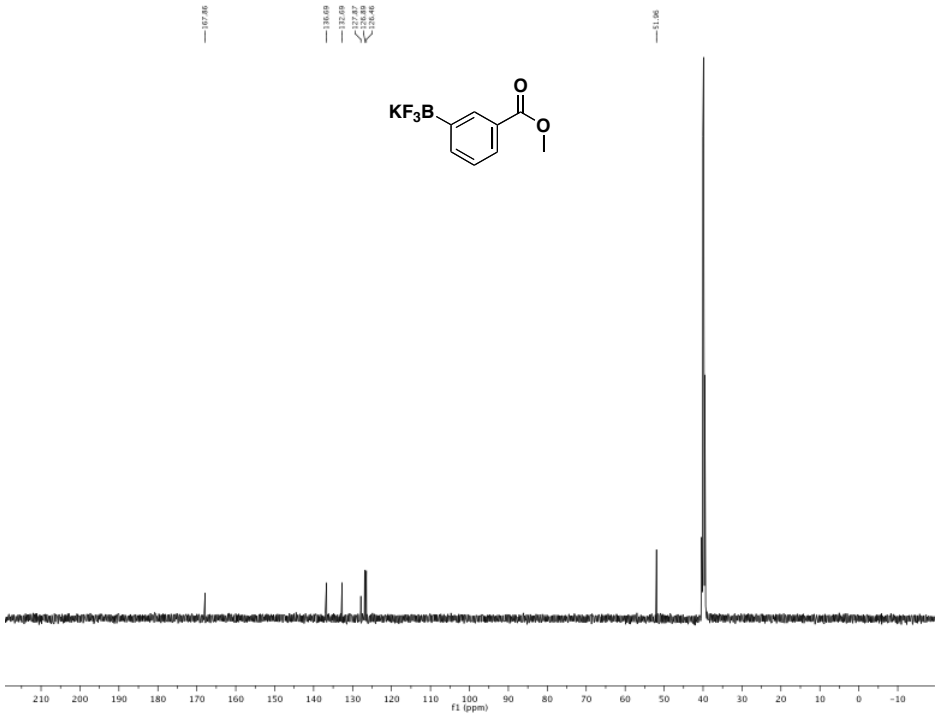

Figure A1.19 ^{13}C NMR Spectra (125.8 MHz, d_6-DMSO), Potassium (3-(Methoxycarbonyl)phenyl)trifluoroborate

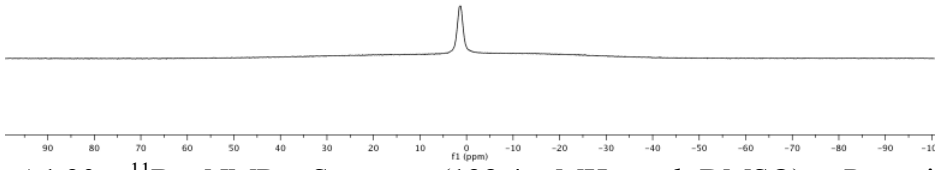

Figure A1.20 ^{11}B NMR Spectra (128.4 MHz, d_6-DMSO), Potassium (3-(Methoxycarbonyl)phenyl)trifluoroborate

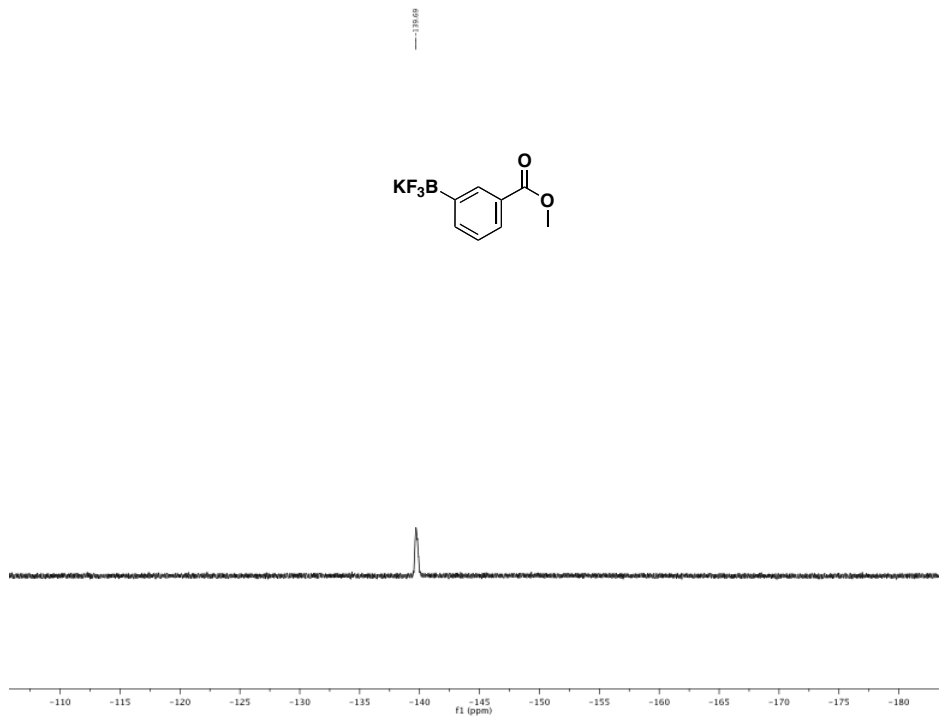

Figure A1.21 ^{19}F NMR Spectra (470.8 MHz, d_6-DMSO), Potassium (3-(Methoxycarbonyl)phenyl)trifluoroborate

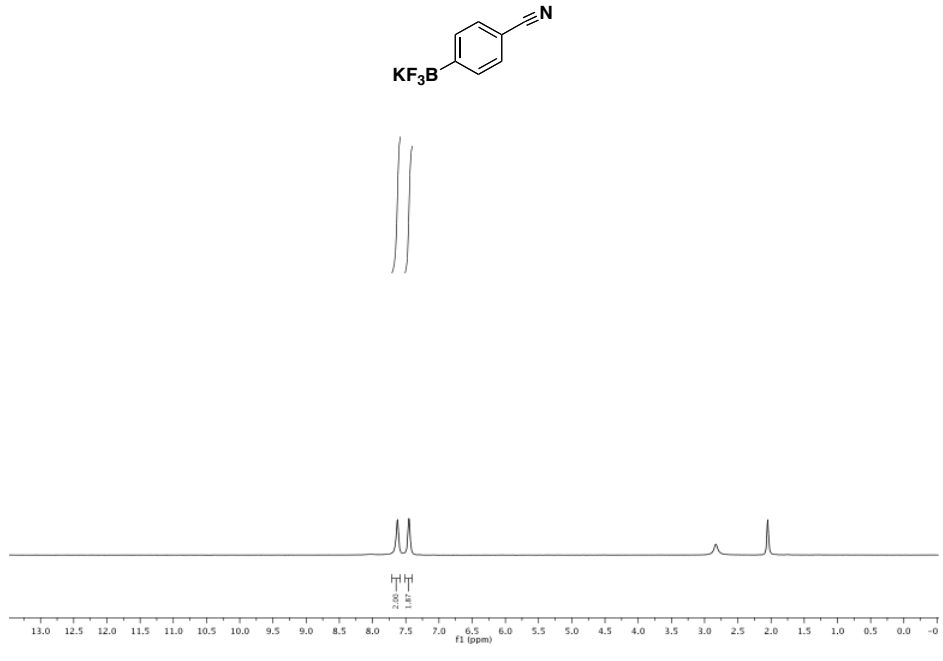

Figure A1.22 ^{1}H NMR Spectra (500 MHz, d_6-Acetone), Potassium (2-Cyanophenyl)trifluoroborate

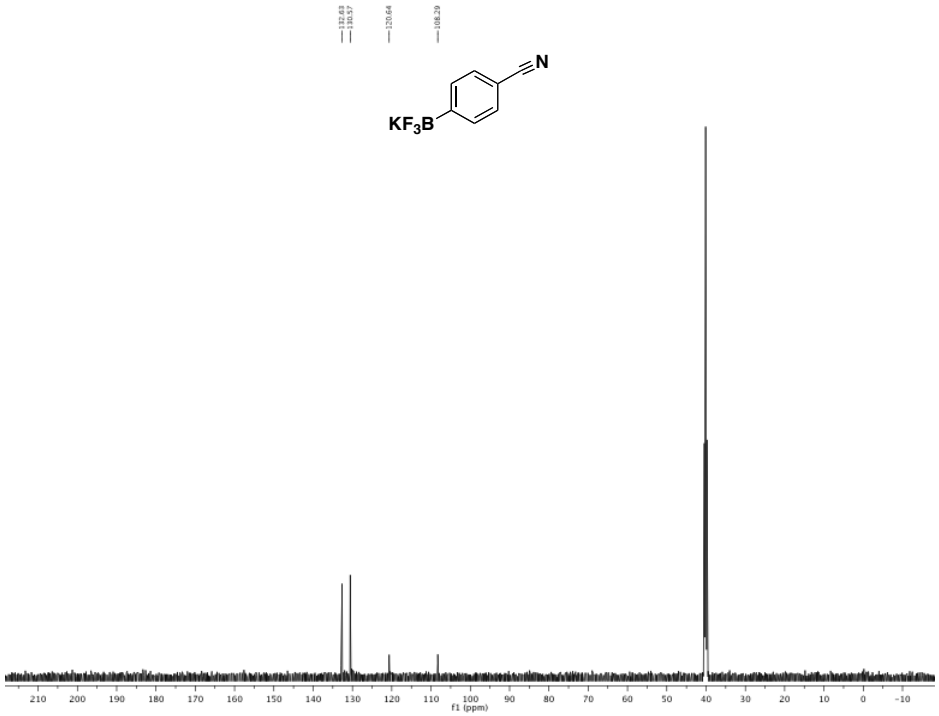

Figure A1.23 ^{13}C NMR Spectra (125.8 MHz, d_6-DMSO), Potassium (2-Cyanophenyl)trifluoroborate

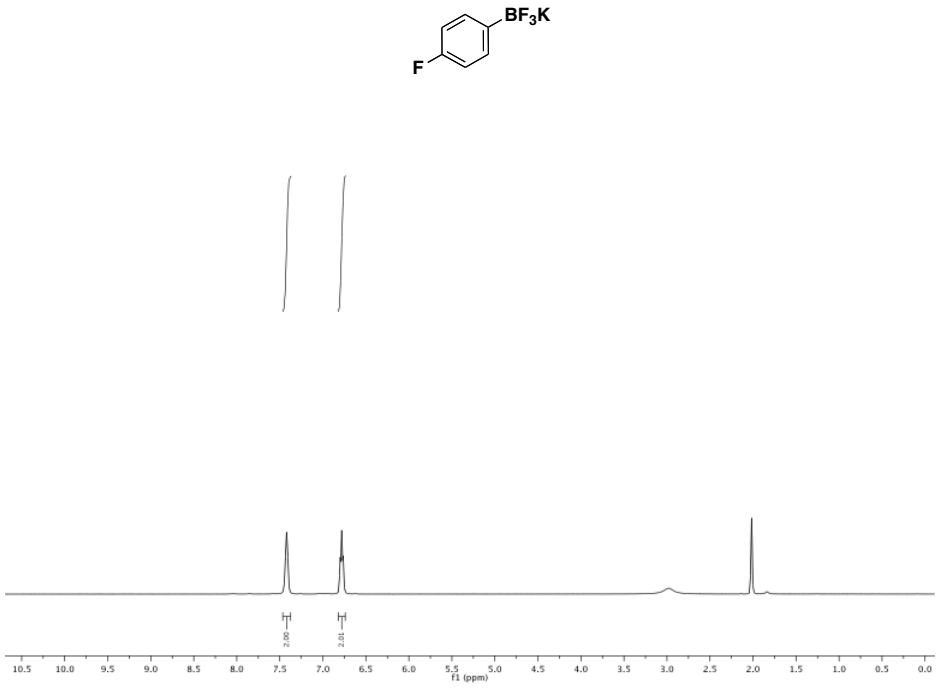

Figure A1.24 ^{1}H NMR Spectra (500 MHz, d_6-Acetone), Potassium (4-Fluorophenyl)trifluoroborate

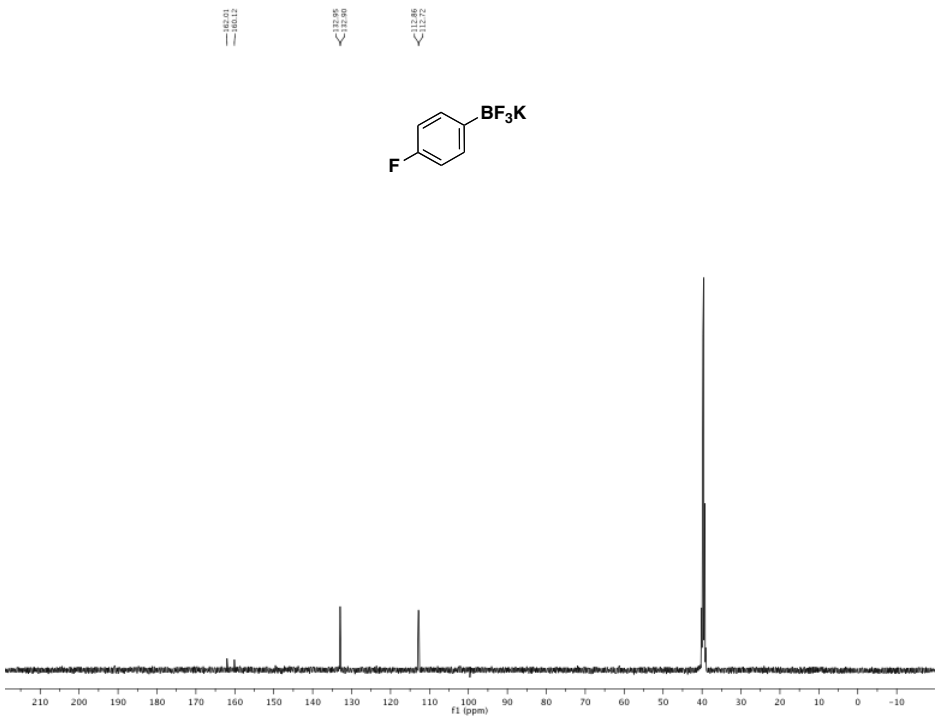

Figure A1.25 ^{13}C NMR Spectra (125.8 MHz, d_6-DMSO), Potassium (4-Fluorophenyl)trifluoroborate

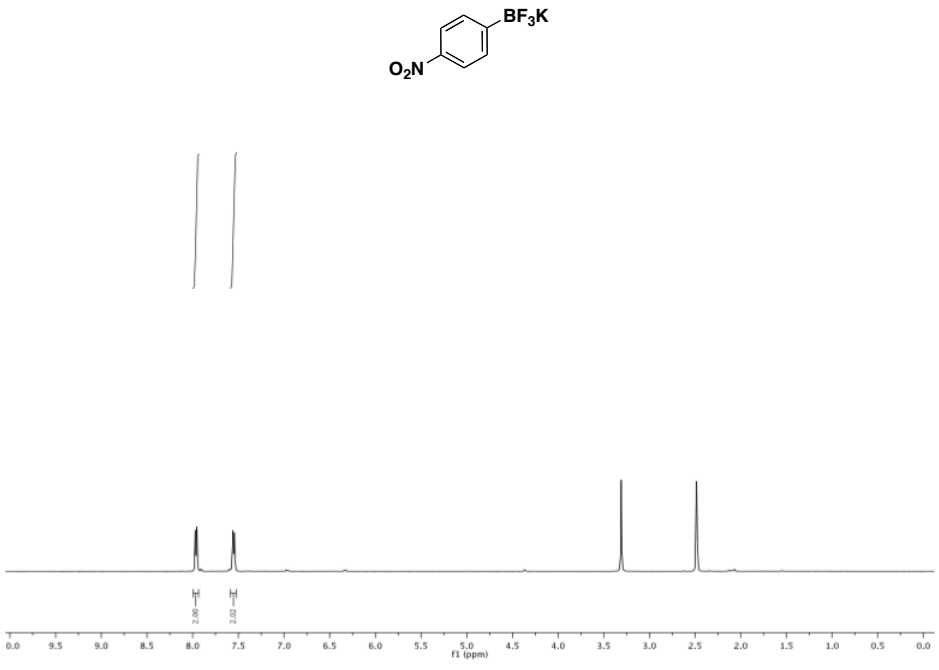

Figure A1.26 ^{1}H NMR Spectra (500 MHz, d_6-DMSO), Potassium (4-Nitrophenyl)trifluoroborate

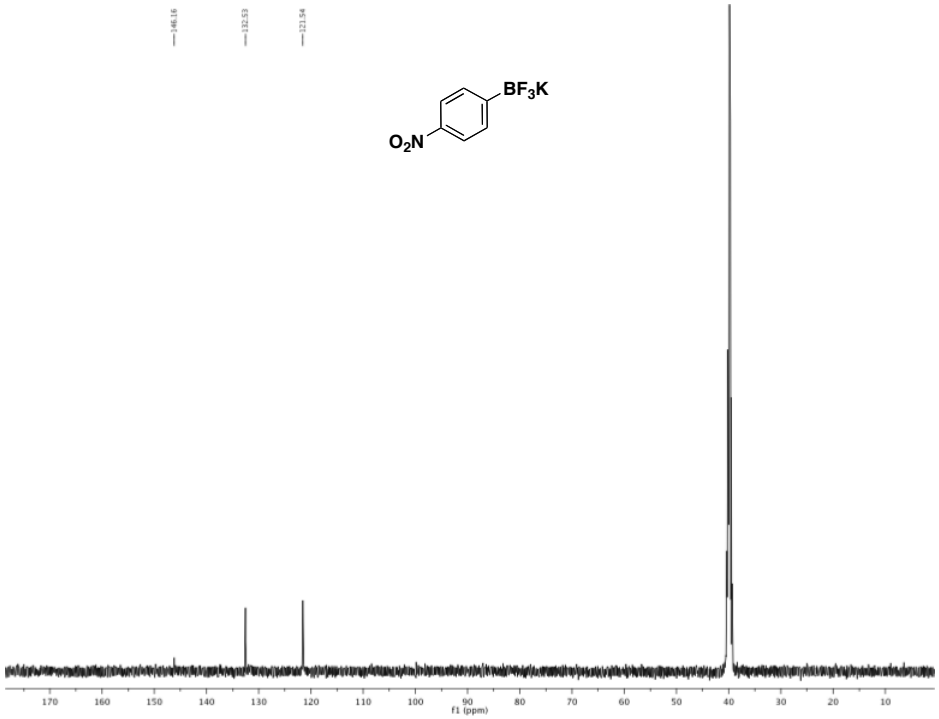

Figure A1.27 ^{13}C NMR Spectra (125.8 MHz, d_6-DMSO), Potassium (4-Nitrophenyl)trifluoroborate

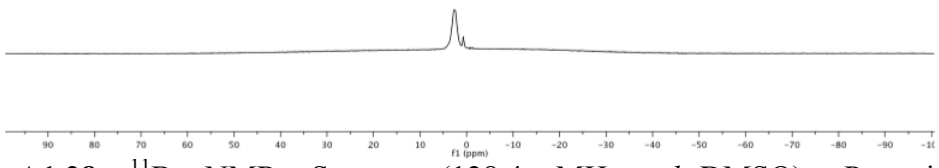

Figure A1.28 ^{11}B NMR Spectra (128.4 MHz, d_6-DMSO), Potassium (4-Nitrophenyl)trifluoroborate

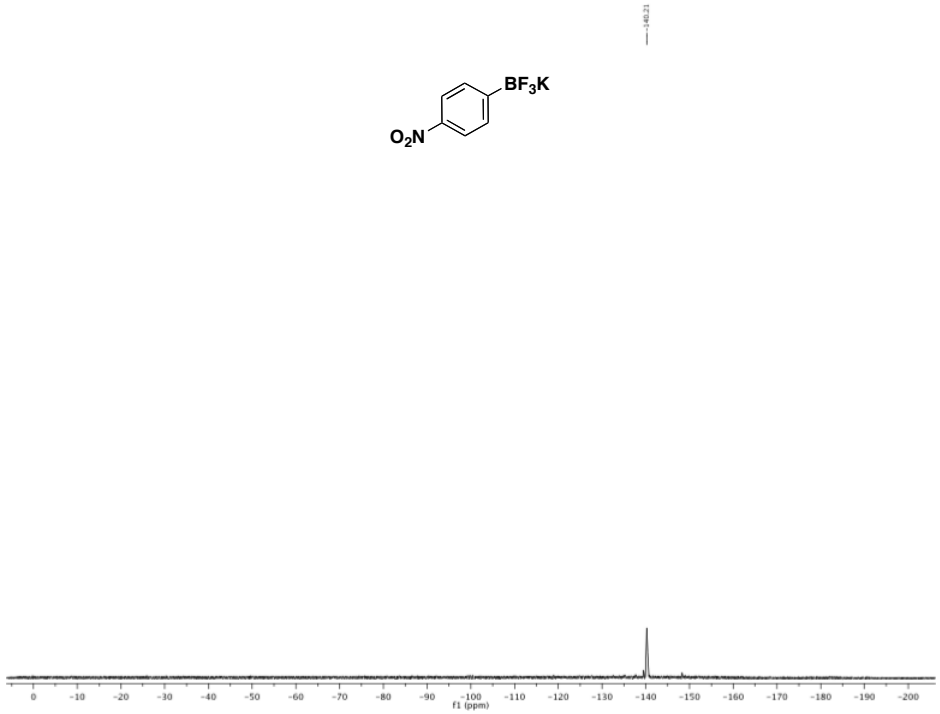

Figure A1.29 ^{19}F NMR Spectra (470.8 MHz, d_6-DMSO), Potassium (4-Nitrophenyl)trifluoroborate

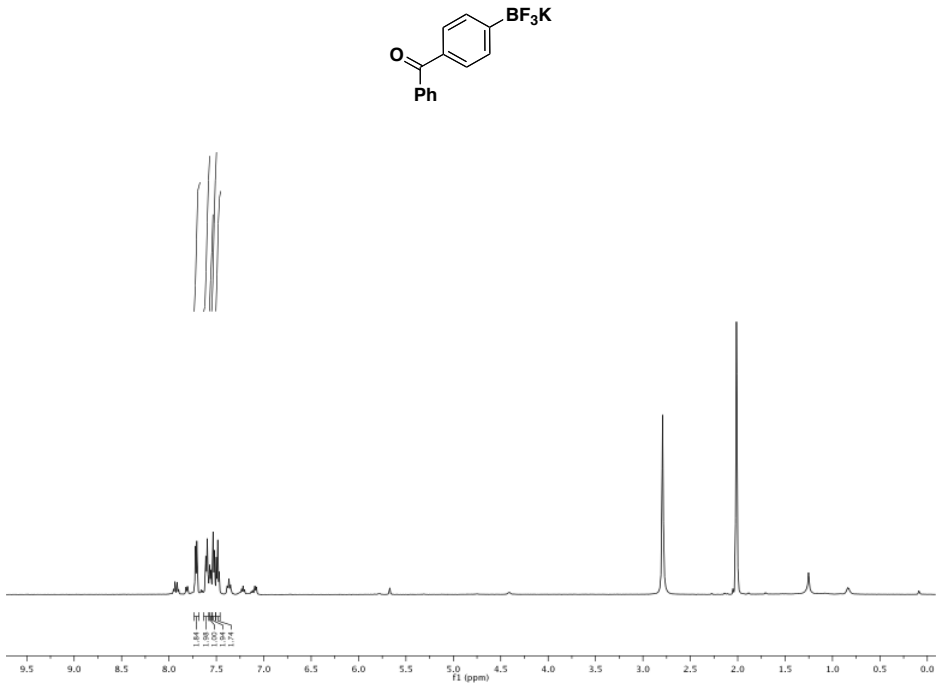

Figure A1.30 ^{1}H NMR Spectra (500 MHz, d_6-Acetone), Potassium (4-Benzoylphenyl)trifluoroborate

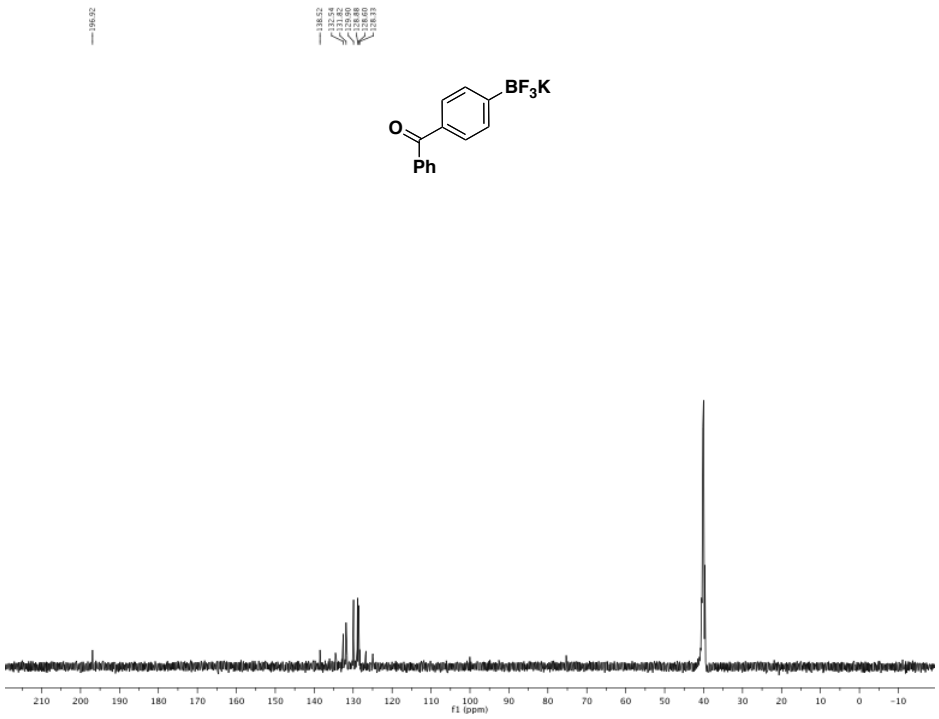

Figure A1.31 ^{13}C NMR Spectra (125.8 MHz, d_6-DMSO), Potassium (4-Benzoylphenyl)trifluoroborate

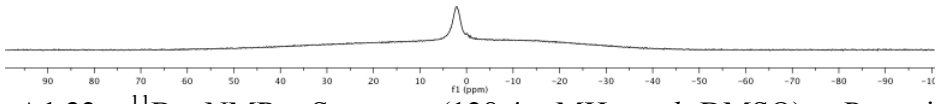

Figure A1.32 ^{11}B NMR Spectra (128.4 MHz, d_6-DMSO), Potassium (4-Benzoylphenyl)trifluoroborate

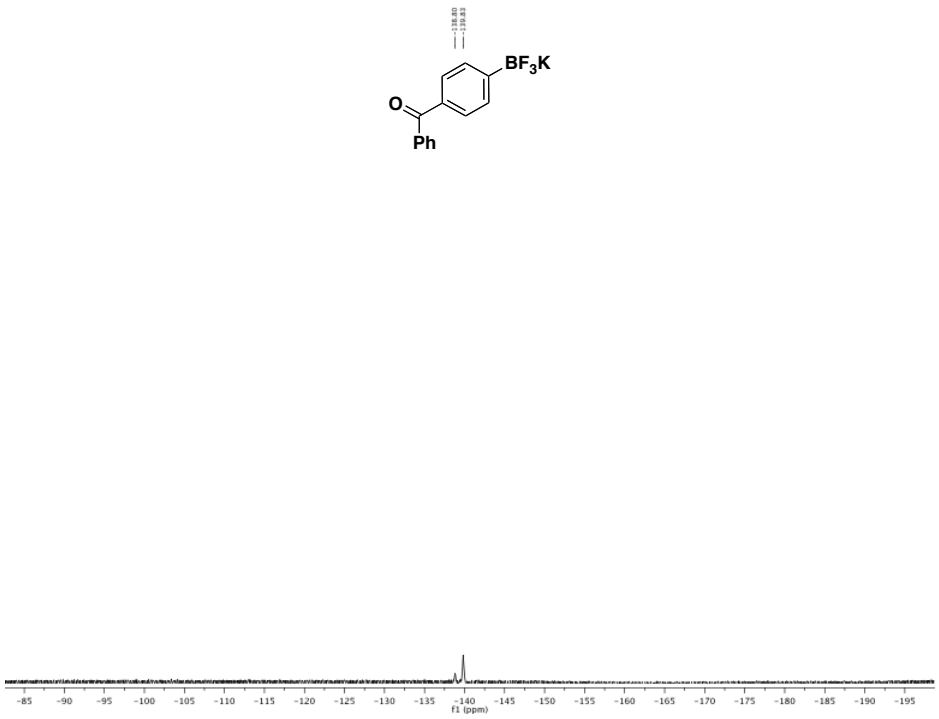

Figure A1.33 ^{19}F NMR Spectra (470.8 MHz, d_6-DMSO), Potassium (4-Benzoylphenyl)trifluoroborate

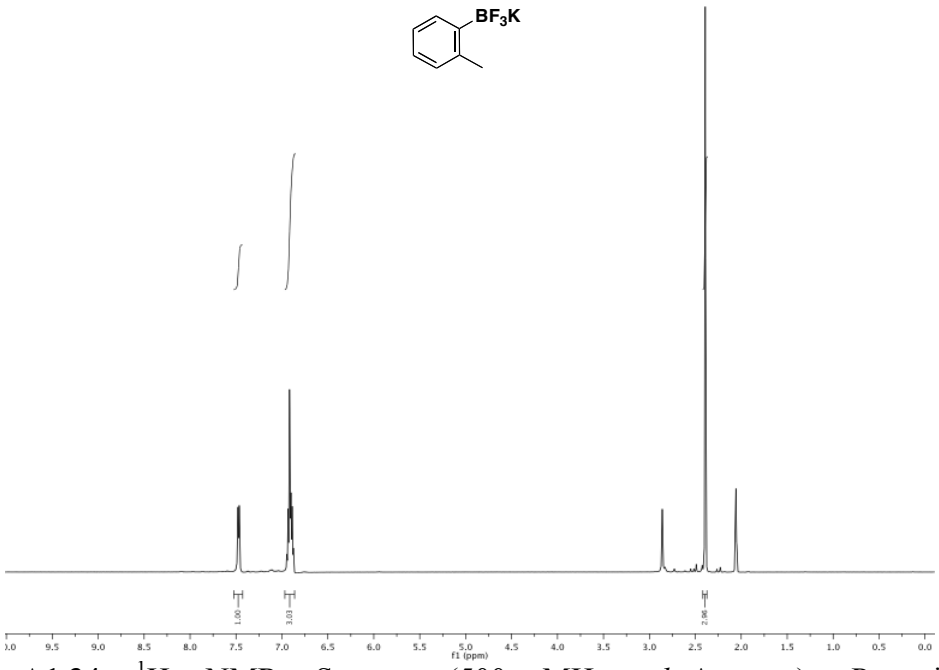

Figure A1.34 ^{1}H NMR Spectra (500 MHz, d_6-Acetone), Potassium o-Tolyltrifluoroborate

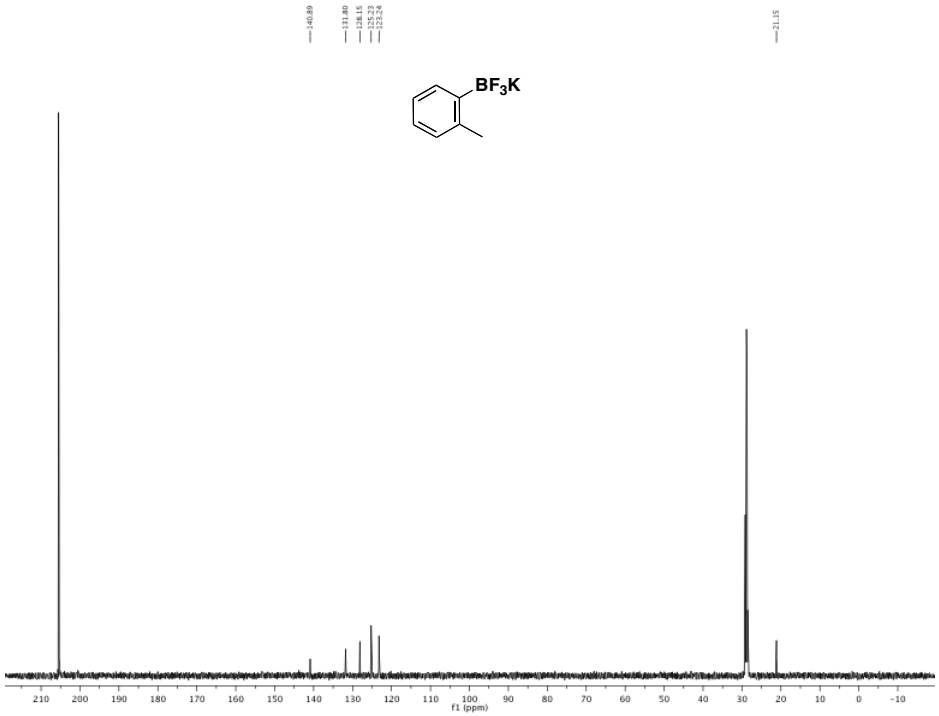

Figure A1.35 ^{13}C NMR Spectra (125.8 MHz, d_6-Acetone) Potassium o-Tolyltrifluoroborate

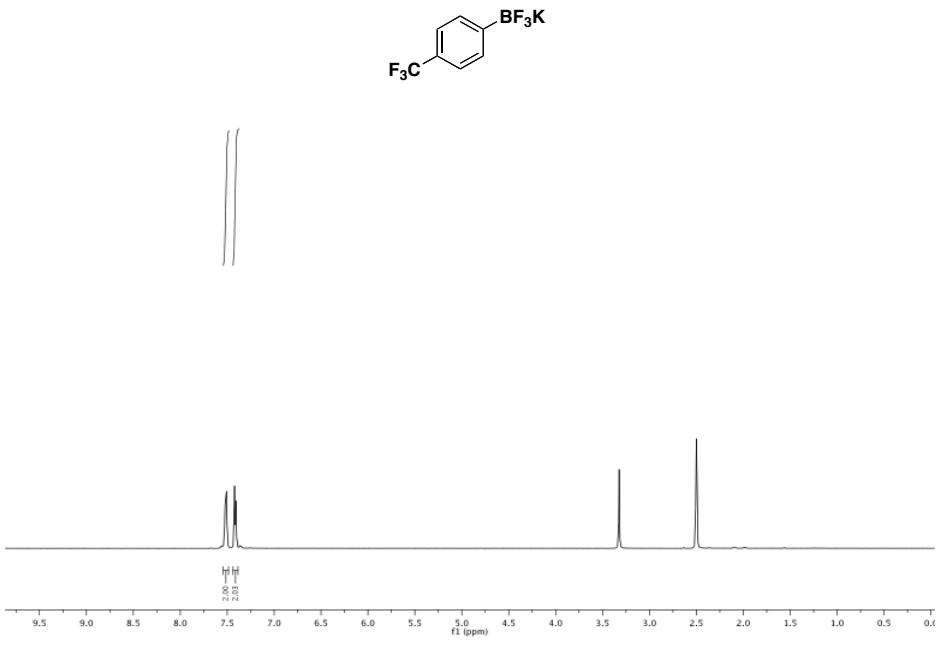

Figure A1.36 ^{1}H NMR Spectra (500 MHz, d_6-DMSO), Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate

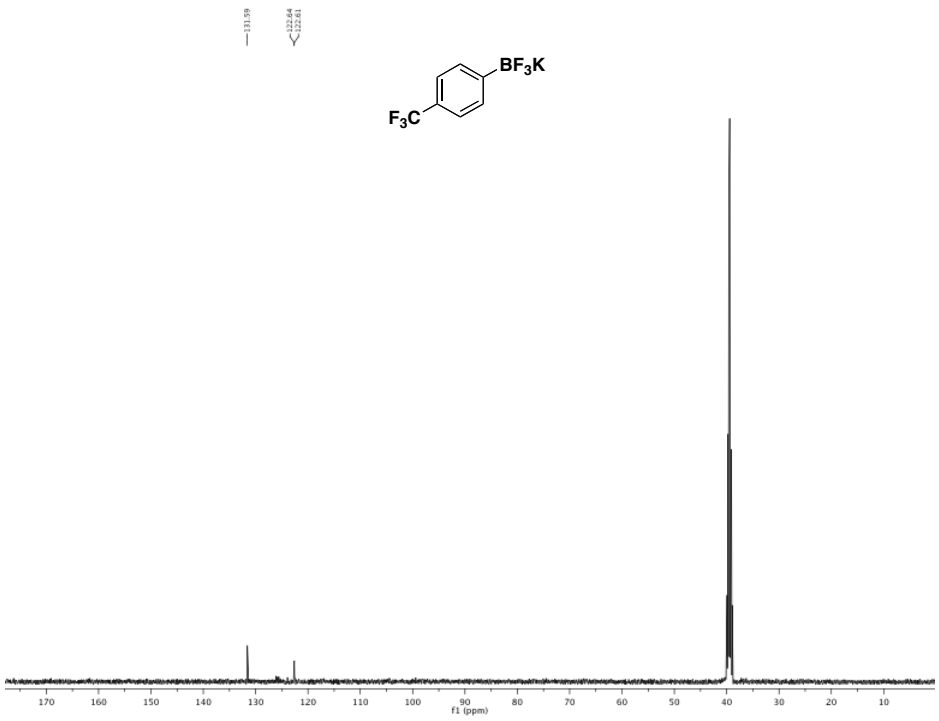

Figure A1.37 ^{13}C NMR Spectra (125.8 MHz, d_6-DMSO), Potassium (4-(trifluoromethyl)phenyl)trifluoroborate

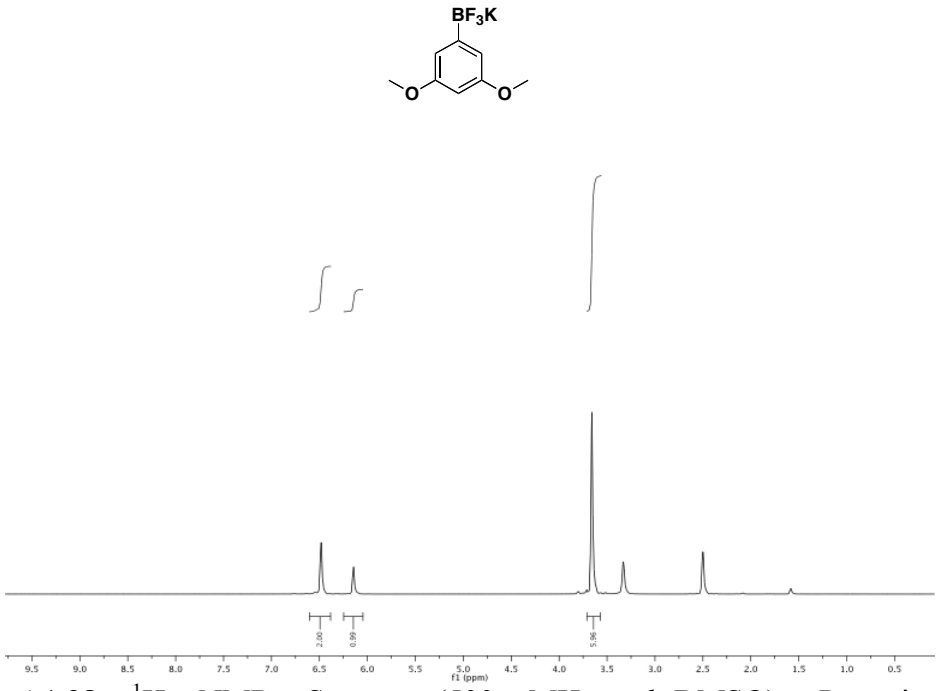

Figure A1.38 ^{1}H NMR Spectra (500 MHz, d_6-DMSO), Potassium (3,5-Dimethoxyphenyltrifluoroborate

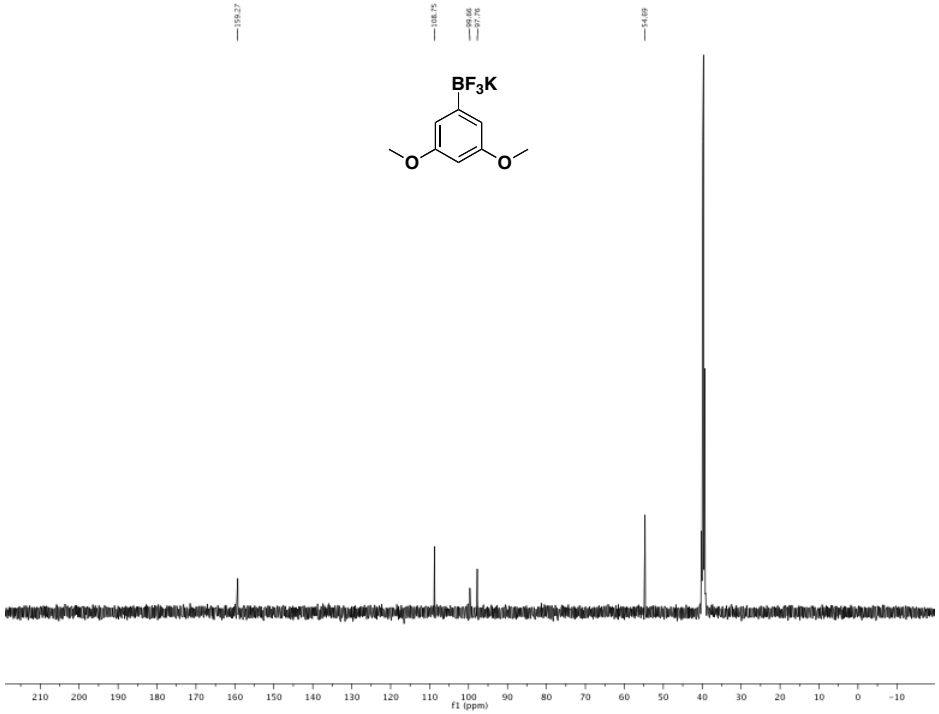

Figure A1.39 ^{13}C NMR Spectra (125.8 MHz, d_6-DMSO), Potassium (3,5-Dimethoxyphenyltrifluoroborate

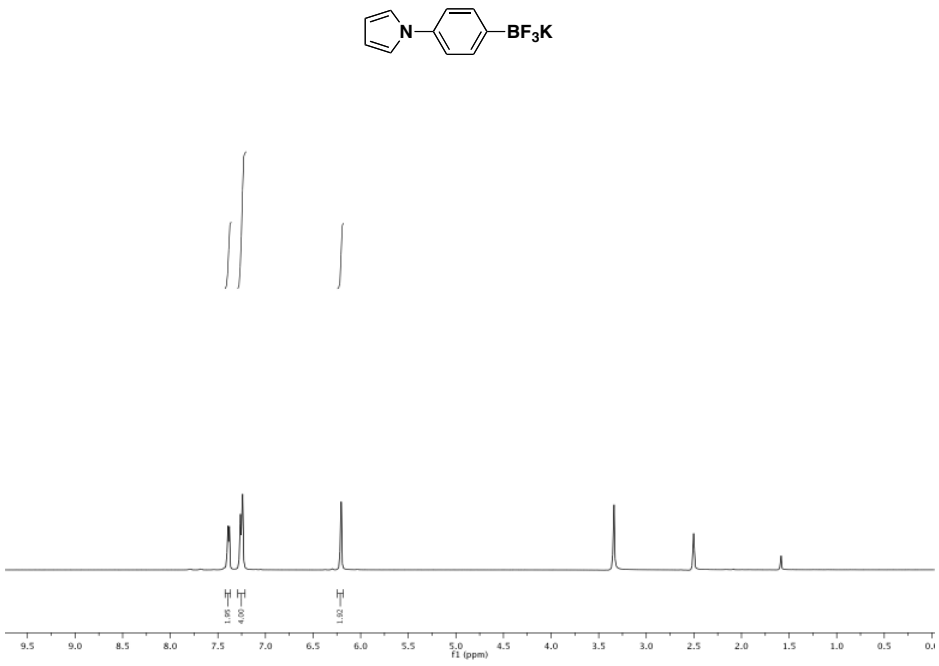

Figure A1.40 ^{1}H NMR Spectra (500 MHz, d_6-DMSO), Potassium (4-(1H-Pyrrol-1-yl)phenyltrifluoroborate

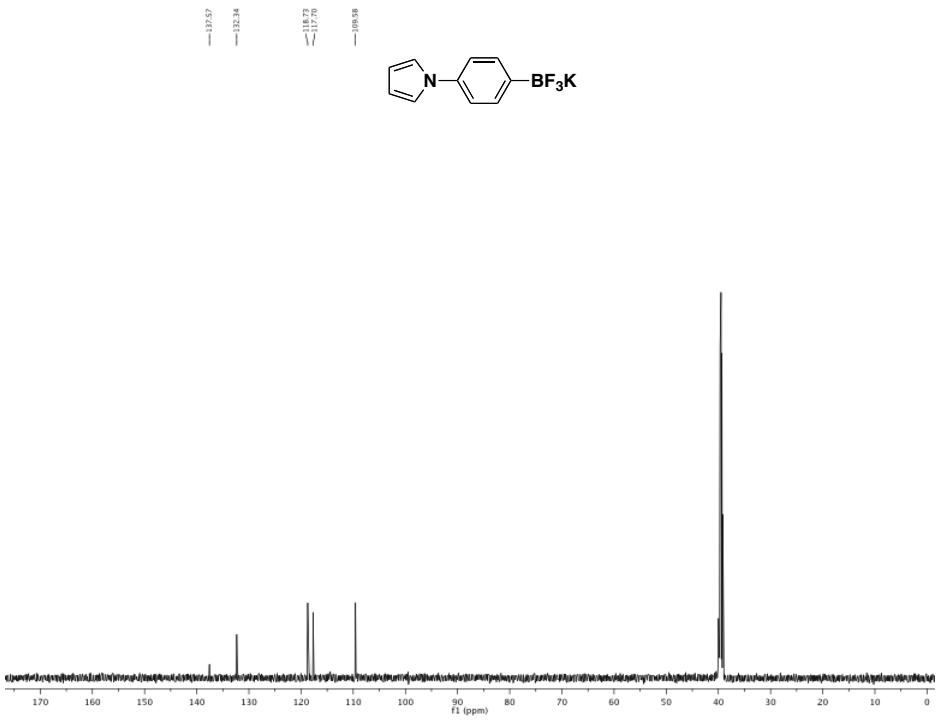

Figure A1.41 ^{13}C NMR Spectra (125.8 MHz, d_6-DMSO), Potassium (4-(1H-Pyrrol-1-yl)phenyltrifluoroborate

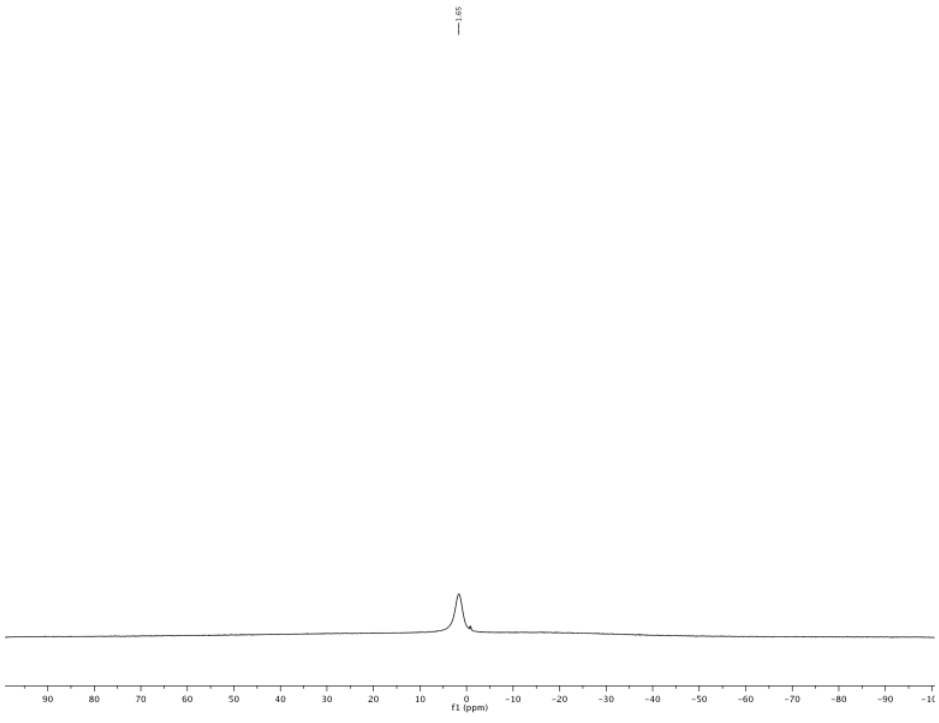

Figure A1.42 ^{11}B NMR Spectra (128.4 MHz, d_6-DMSO), Potassium (4-(1H-Pyrrol-1-yl)phenyltrifluoroborate

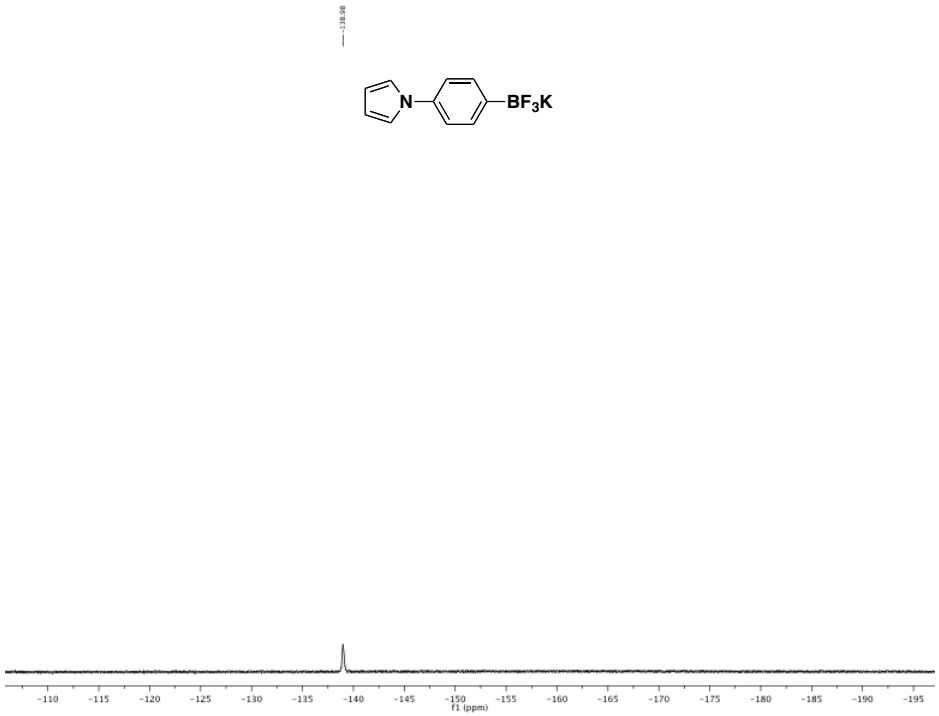

Figure A1.43 ^{19}F NMR Spectra (470.8 MHz, d_6-DMSO), Potassium (4-(1H-Pyrrol-1-yl)phenyltrifluoroborate

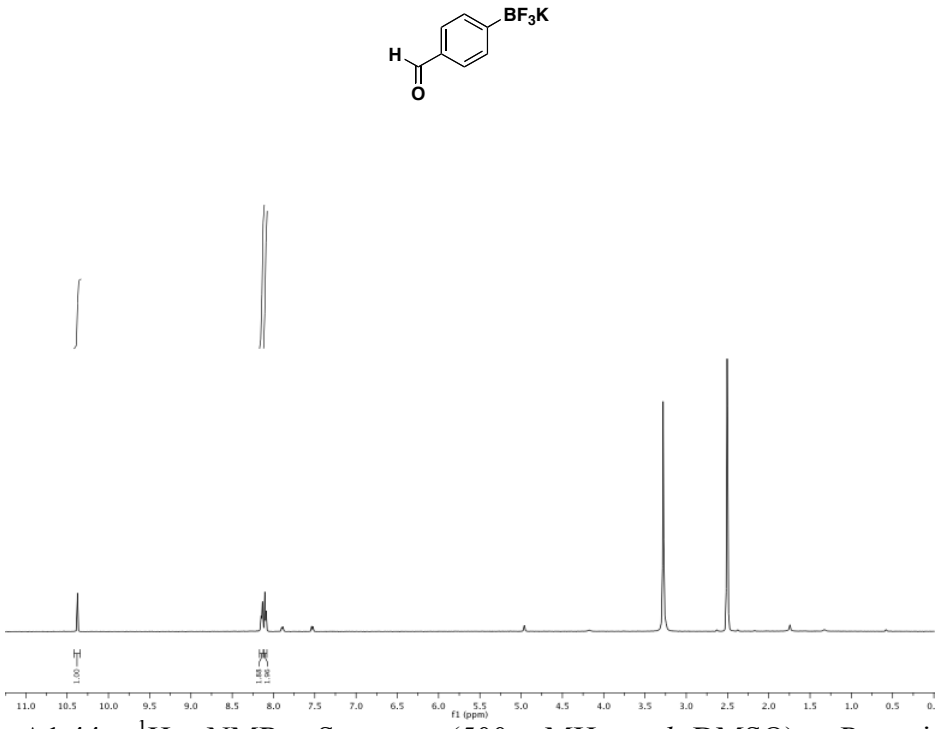

Figure A1.44 ^{1}H NMR Spectra (500 MHz, d_6-DMSO), Potassium (4-Formylphenyl)trifluoroborate

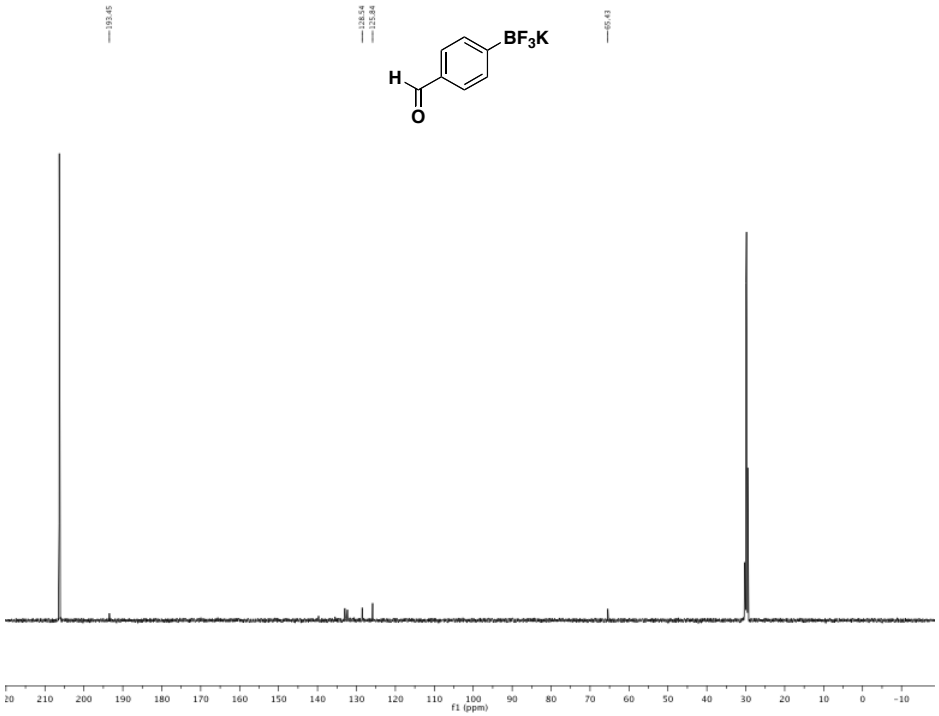

Figure A1.45 ^{13}C NMR Spectra (500 MHz, d_6-Acetone), Potassium (4-Formylphenyl)trifluoroborate

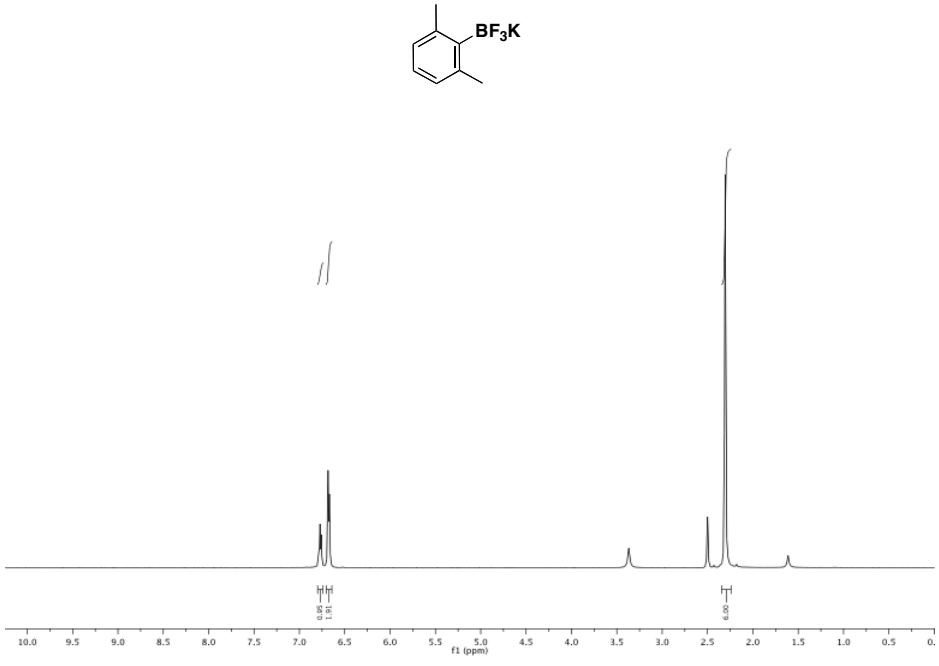

Figure A1.46 ^{1}H NMR Spectra (500 MHz, d_6-DMSO), Potassium (2,6-Dimethylphenyl)trifluoroborate

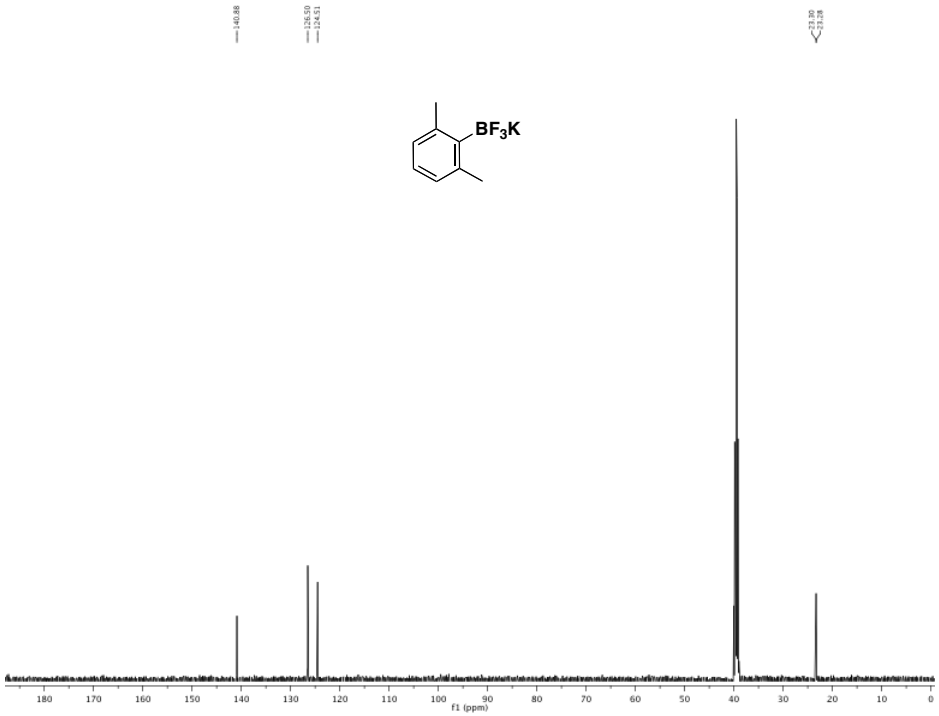

Figure A1.47 ^{13}C NMR Spectra (125.8 MHz, d_6-DMSO), Potassium (2,6-Dimethylphenyl)trifluoroborate

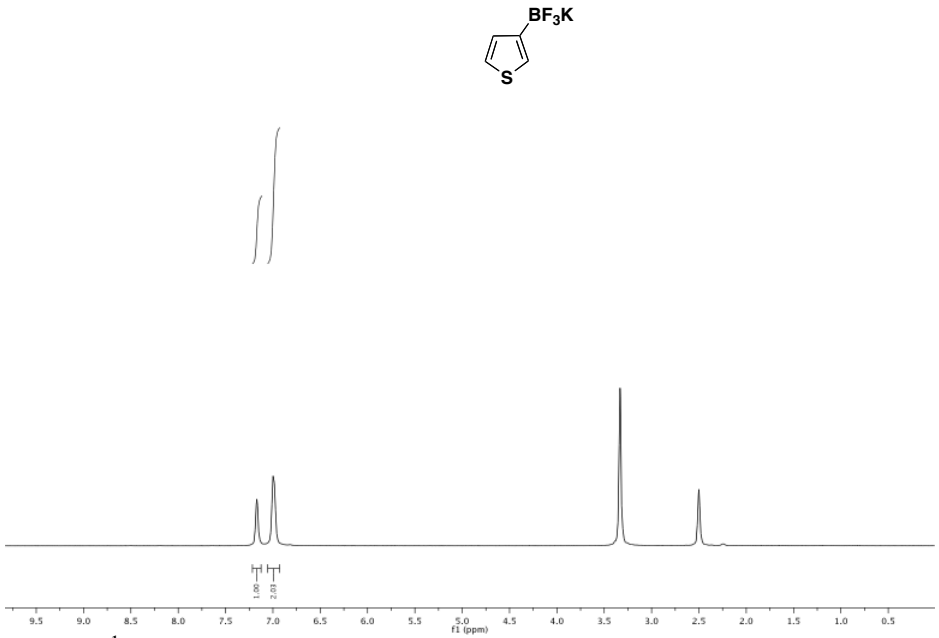

Figure A1.48 ^{1}H NMR Spectra (500 MHz, d_6-DMSO), Potassium Thiophen-3-yltrifluoroborate

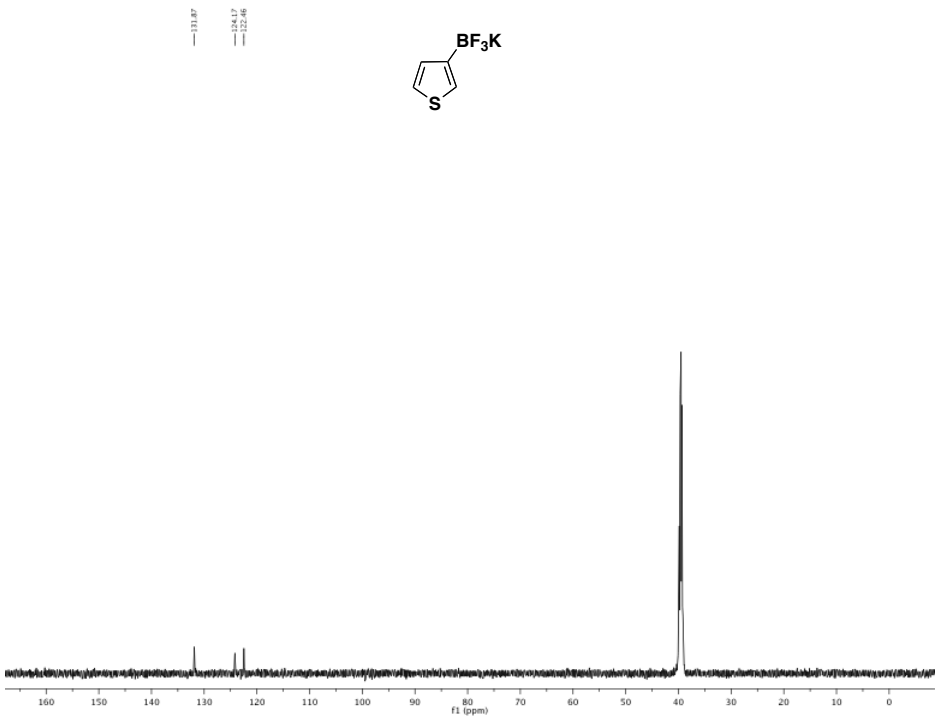

Figure A1.49 ^{13}C NMR Spectra (125.8 MHz, d_6-DMSO), Potassium Thiophen-3-yltrifluoroborate

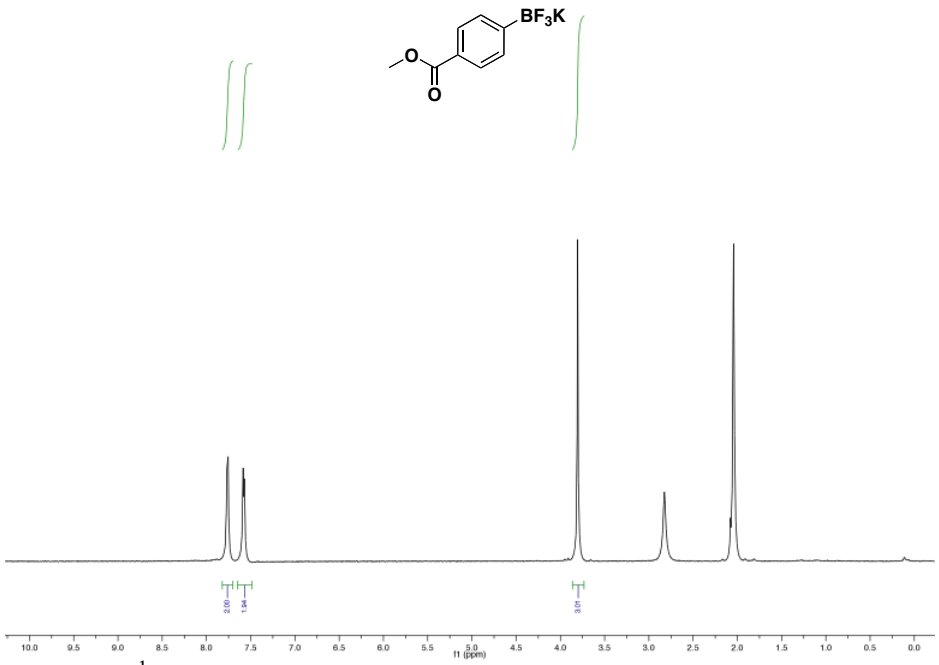

Figure A1.50 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (4-(Methoxycarbonyl)phenyl)trifluoroborate

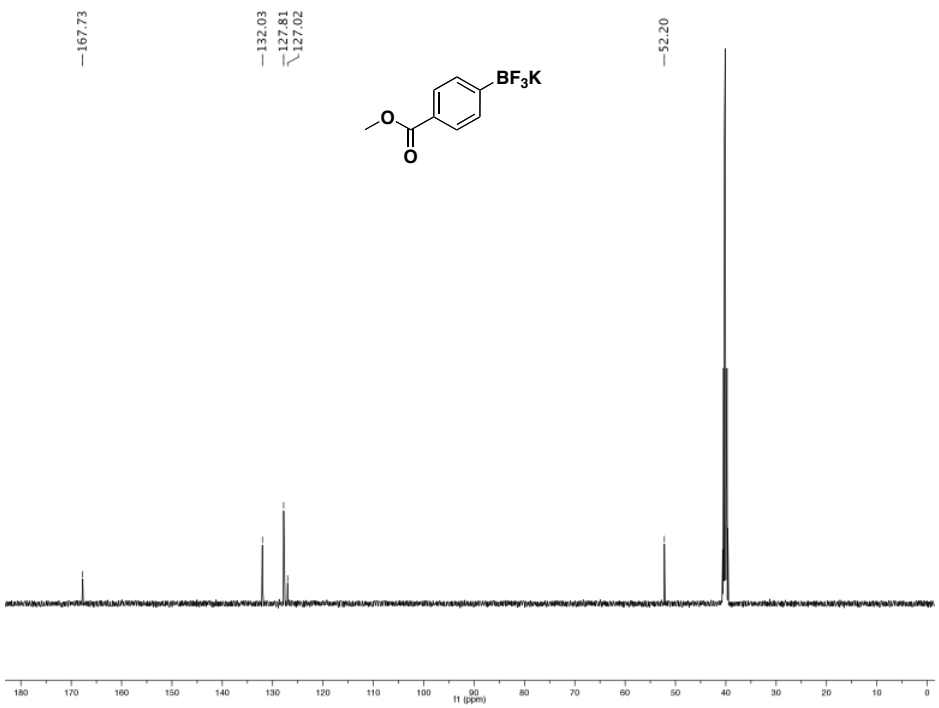

Figure A1.51 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (4-(Methoxycarbonyl)phenyl)trifluoroborate

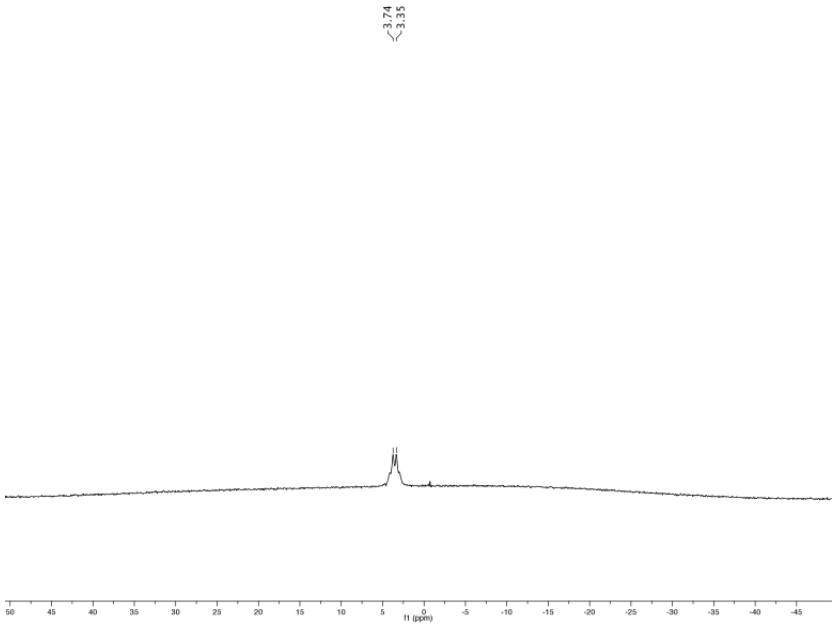

Figure A1.52 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (4-(Methoxycarbonyl)phenyl)trifluoroborate

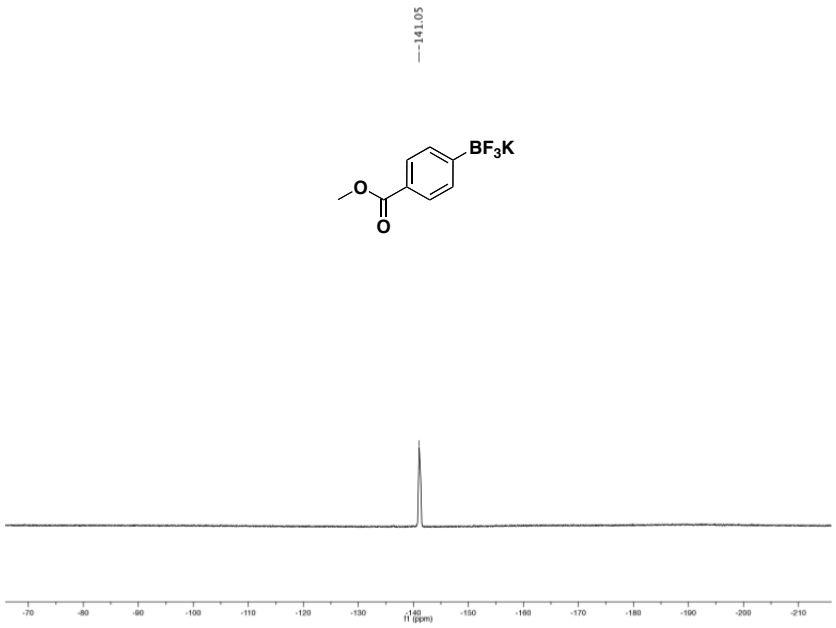

Figure A1.53 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (4-(Methoxycarbonyl)phenyl)trifluoroborate

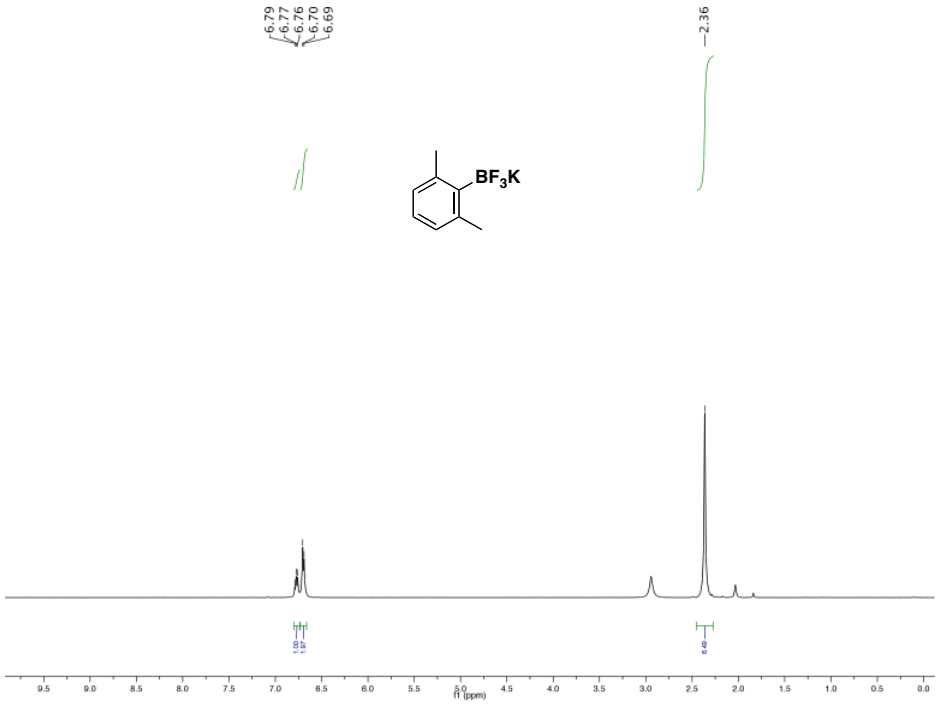

Figure A1.54 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (2,6-Dimethylphenyl)trifluoroborate

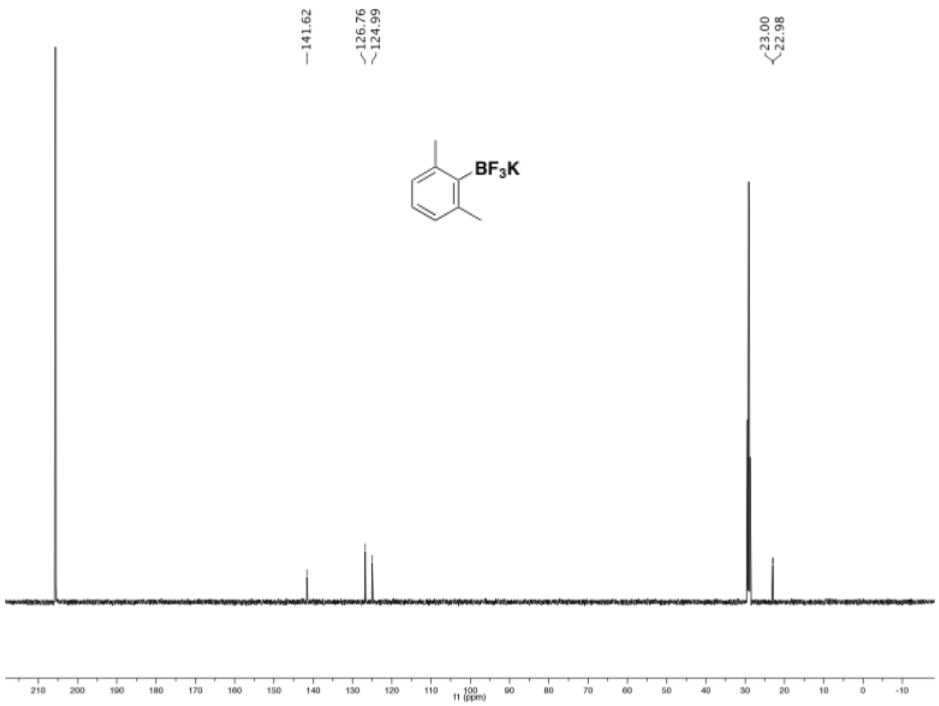

Figure A1.55 ^{13}C NMR Spectra (125.8 MHz, acetone-d_6) Potassium (2,6-Dimethylphenyl)trifluoroborate

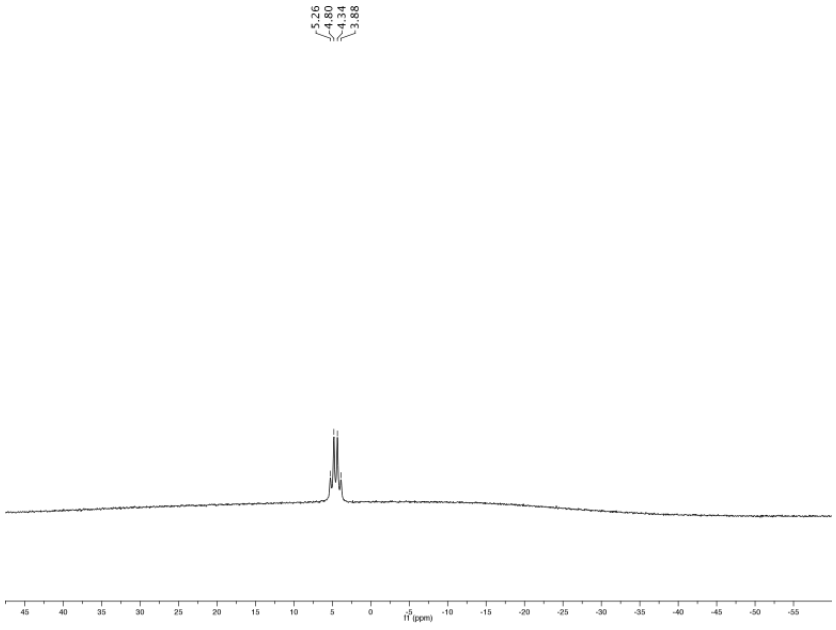

Figure A1.56 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (2,6-Dimethylphenyl)trifluoroborate

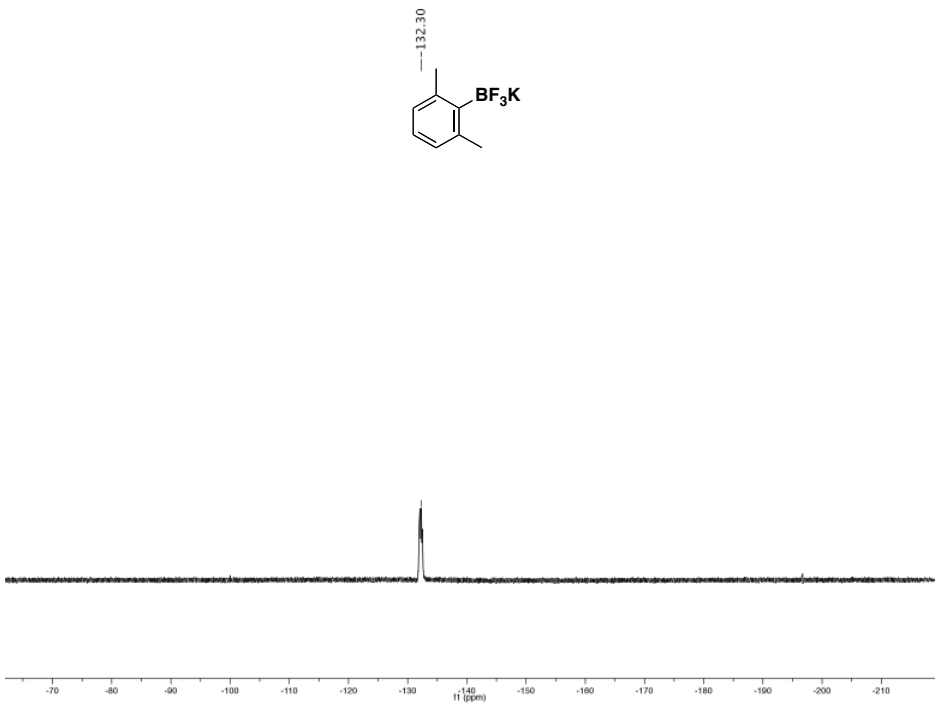

Figure A1.57 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (2,6-Dimethylphenyl)trifluoroborate

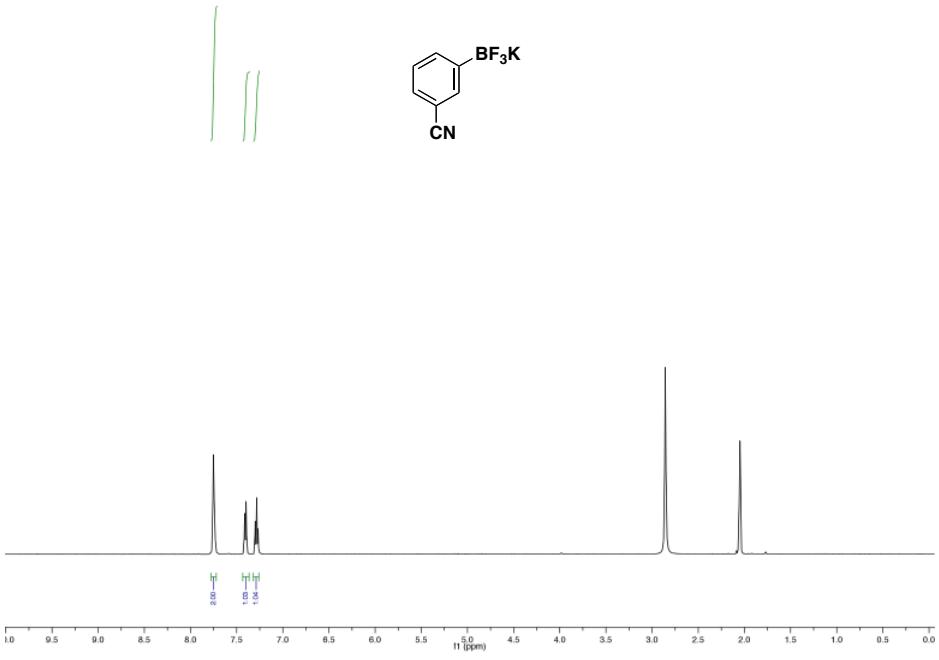

Figure A1.58 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (3-Cyanophenyl)trifluoroborate

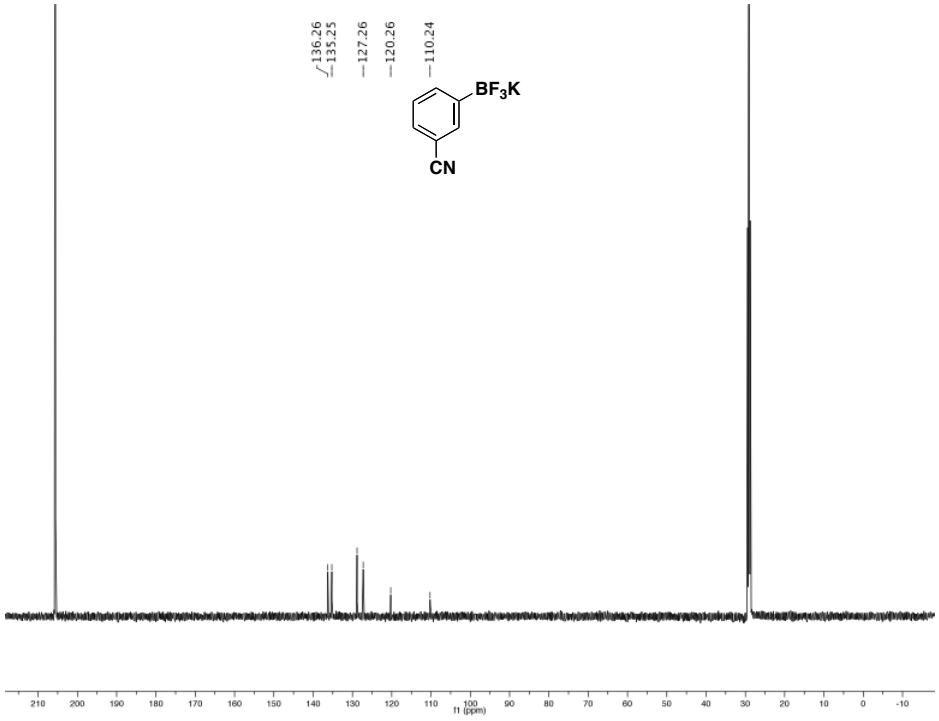

Figure A1.59 ^{13}C NMR Spectra (125.8 MHz, acetone-d_6) Potassium (3-Cyanophenyl)trifluoroborate

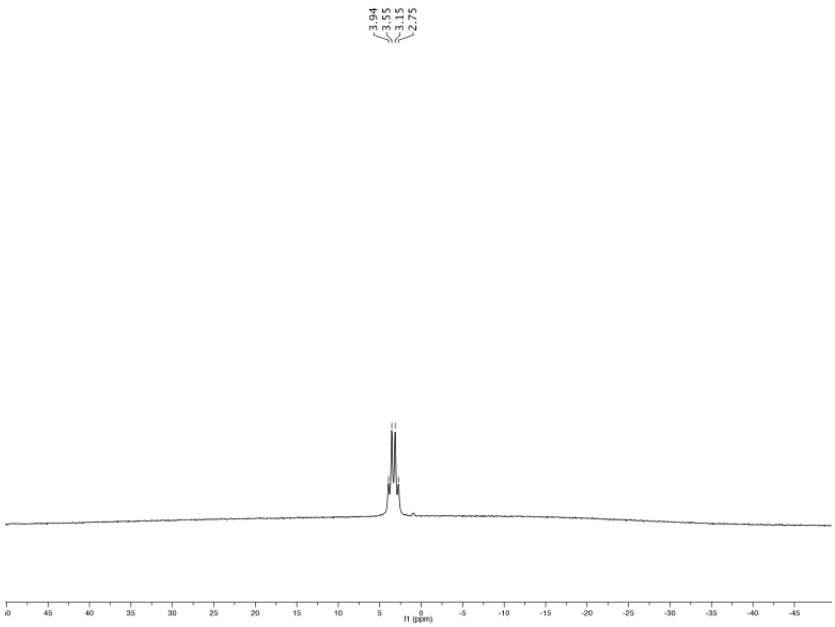

Figure A1.60 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (3-Cyanophenyl)trifluoroborate

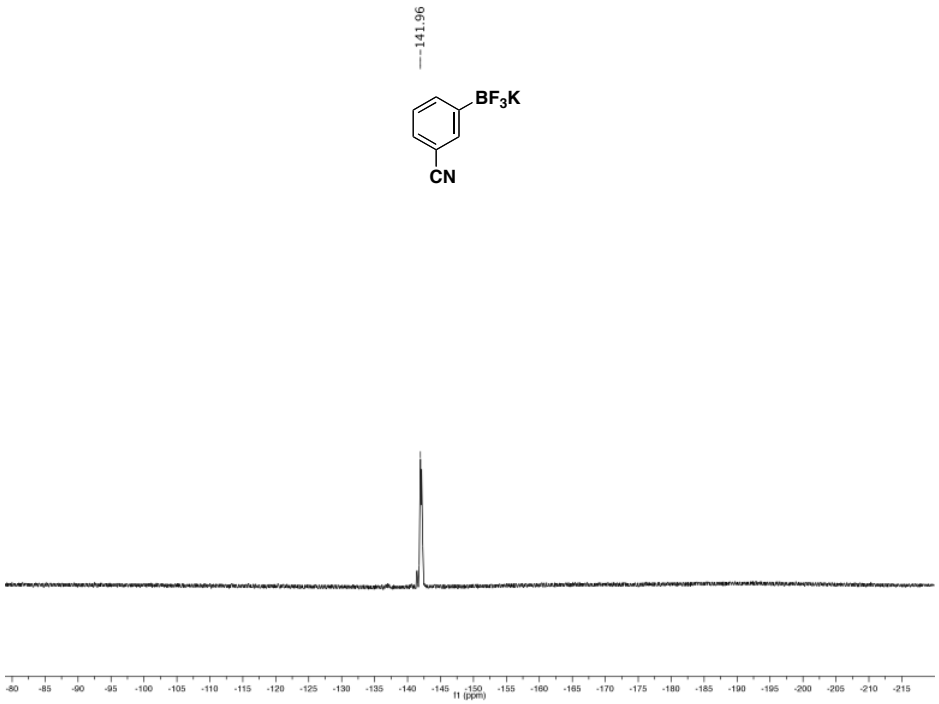

Figure A1.61 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (3-Cyanophenyl)trifluoroborate

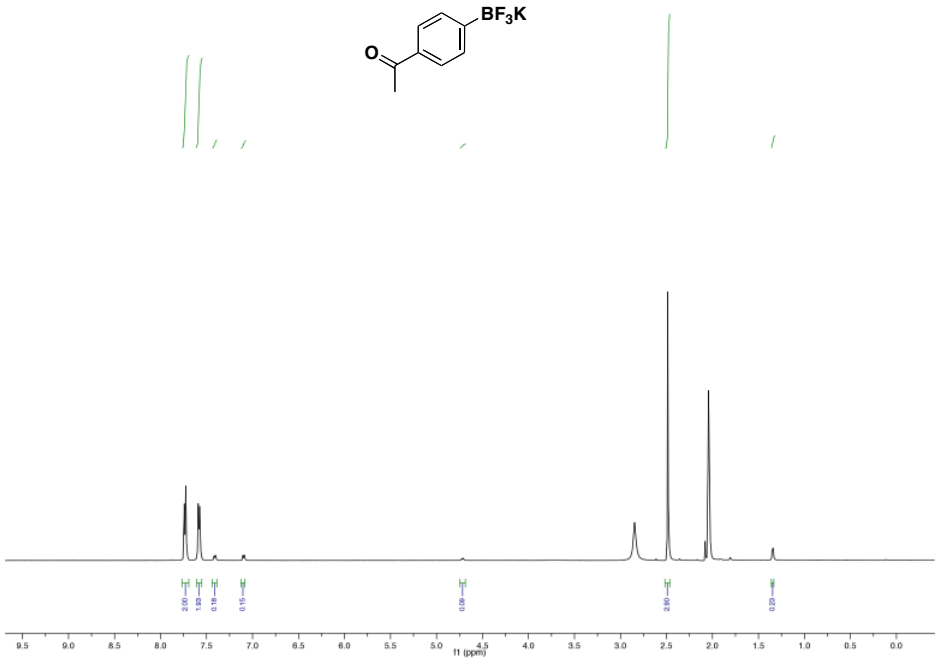

Figure A1.62 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (4-Acetylphenyl)trifluoroborate

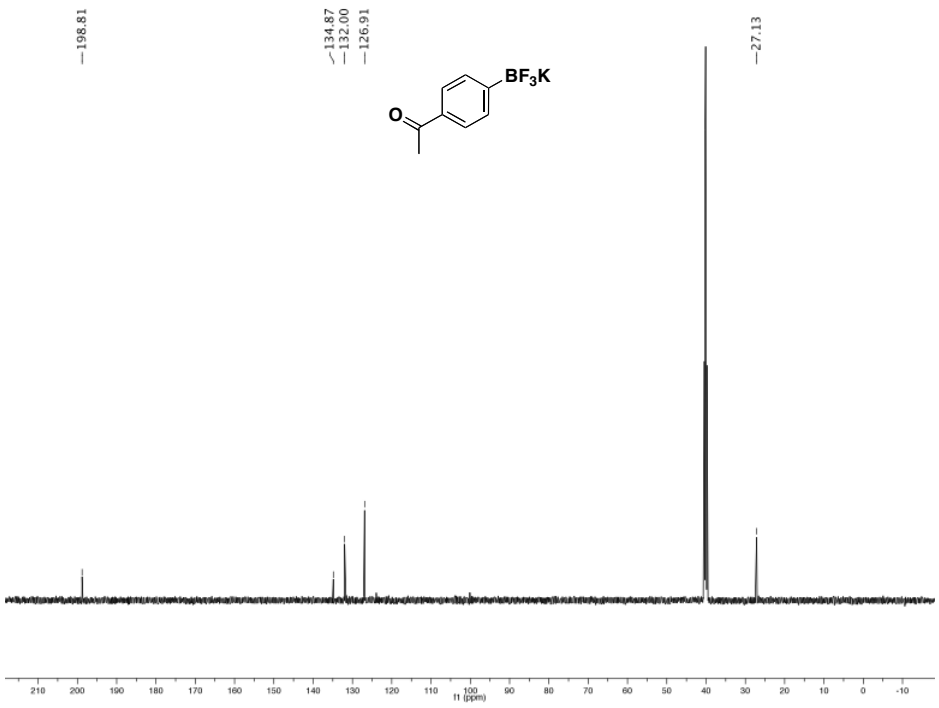

Figure A1.63 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (4-Acetylphenyl)trifluoroborate

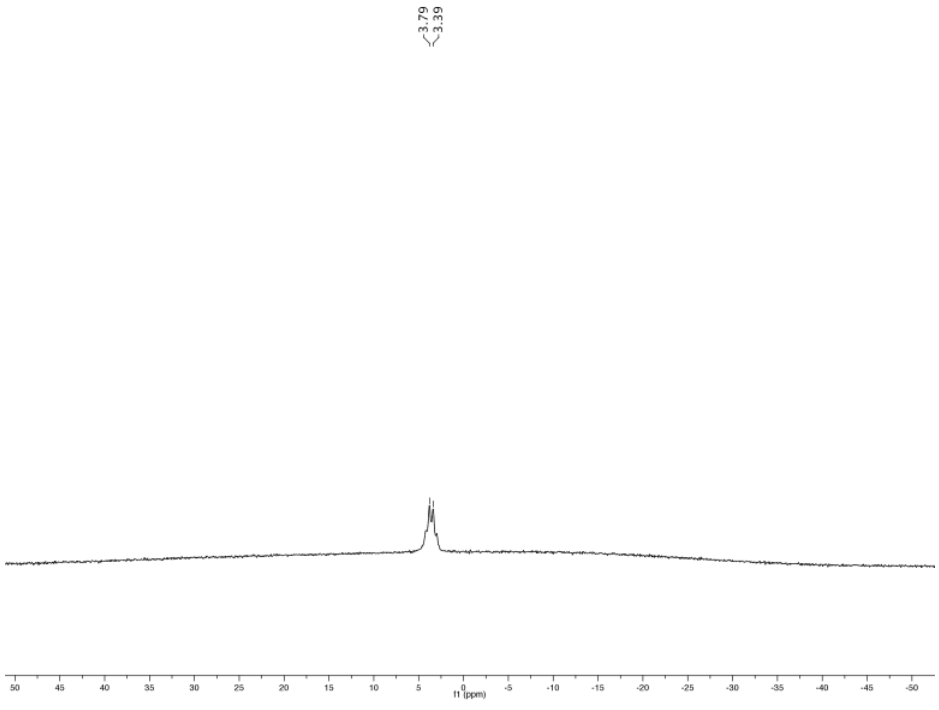

Figure A1.64 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (4-Acetylphenyl)trifluoroborate

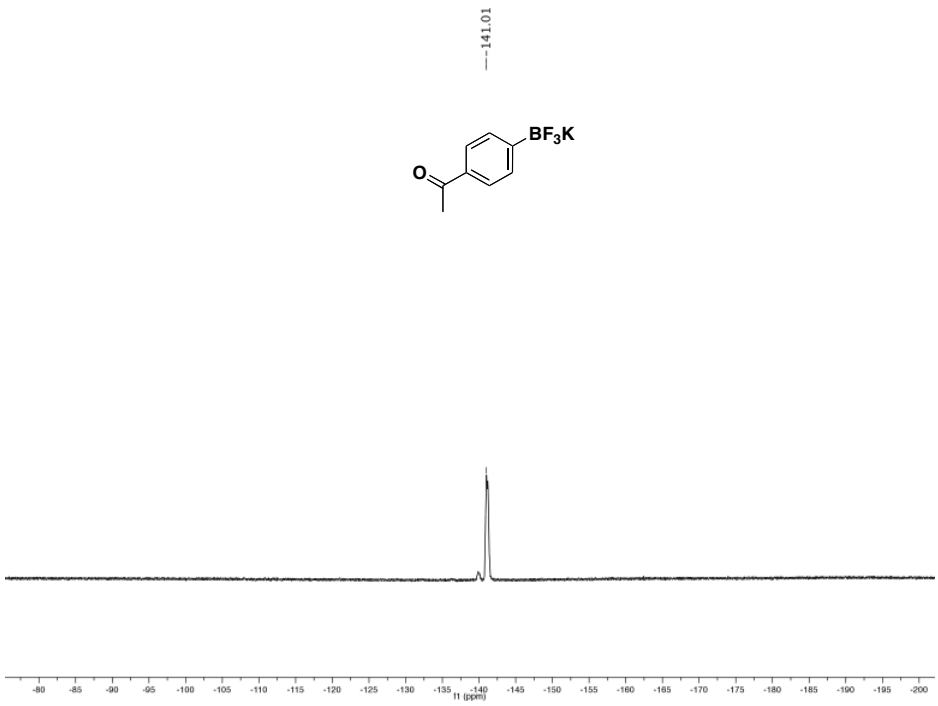

Figure A1.65 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (4-Acetylphenyl)trifluoroborate

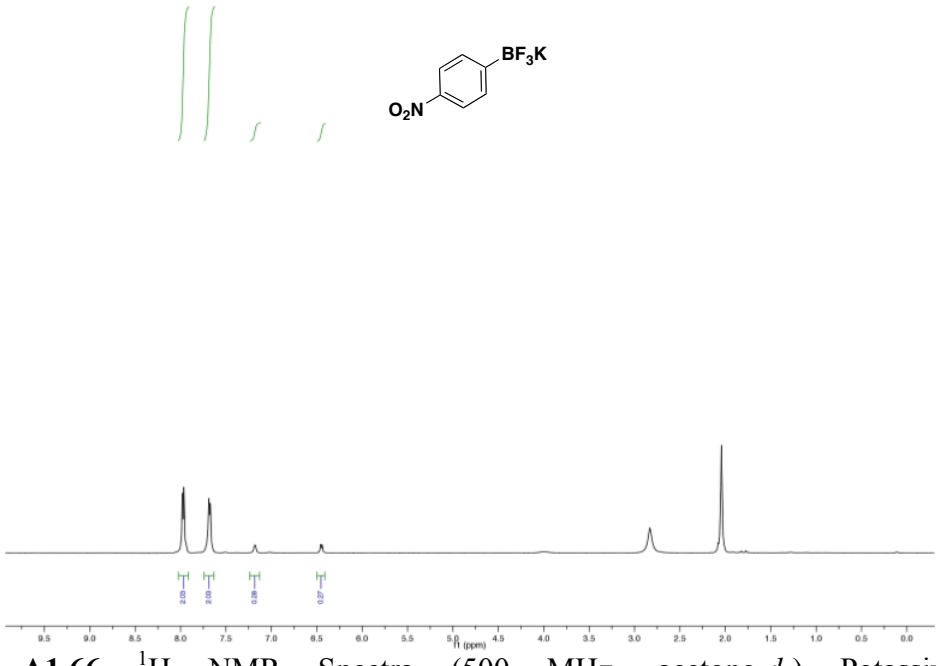

Figure A1.66 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (4-Nitrophenyl)trifluoroborate

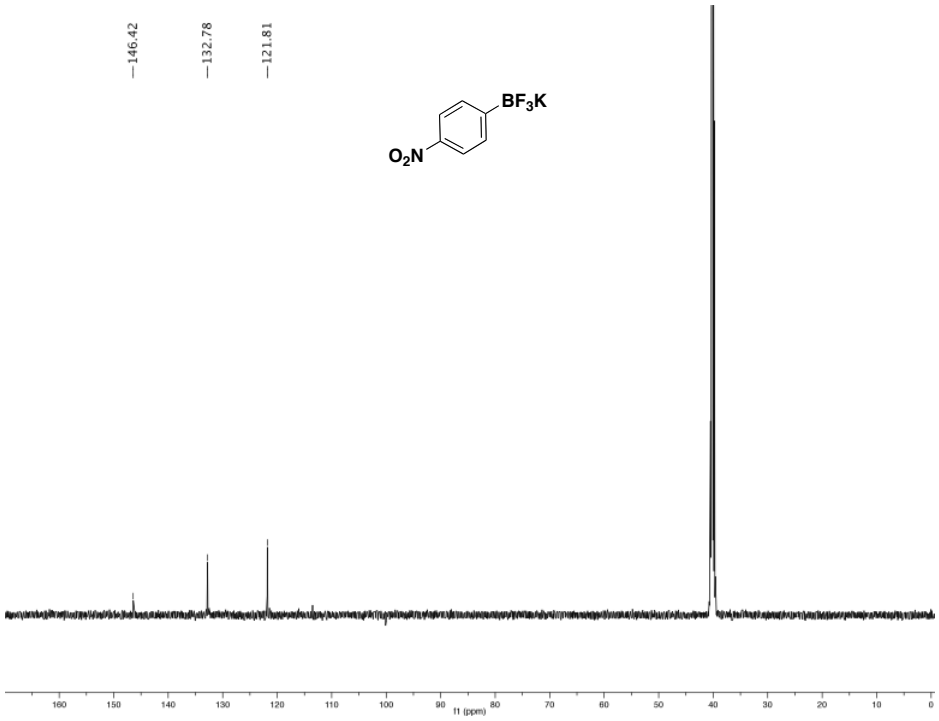

Figure A1.67 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (4-Nitrophenyl)trifluoroborate

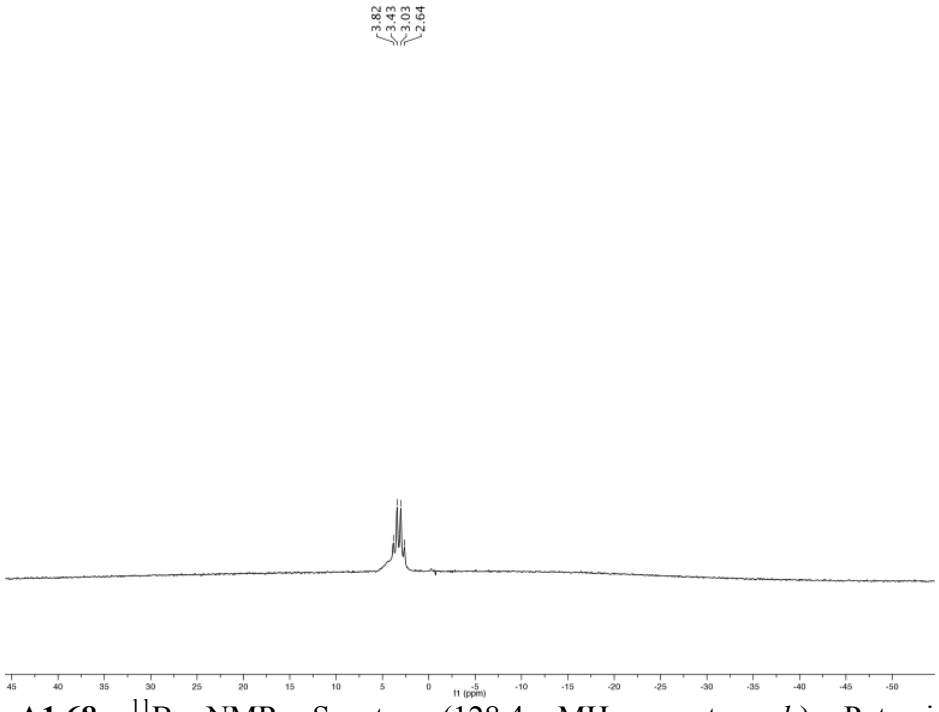

Figure A1.68 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (4-Nitrophenyl)trifluoroborate

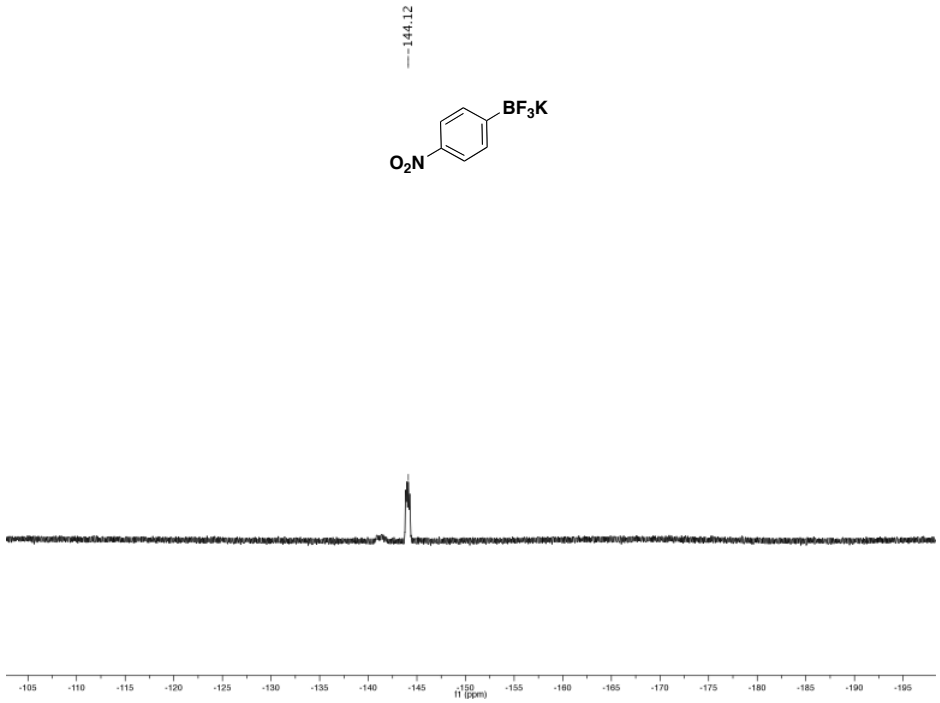

Figure A1.69 ^{19}F NMR Spectra (282 MHz, acetone-d_6) Potassium (4-Nitrophenyl)trifluoroborate

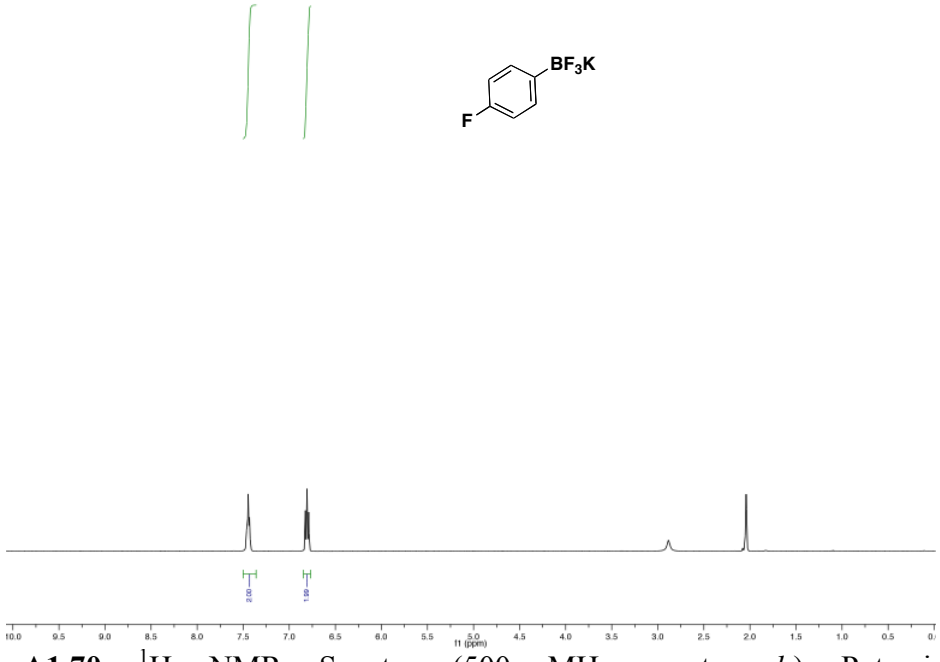

Figure A1.70 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (4-Fluorophenyl)trifluoroborate

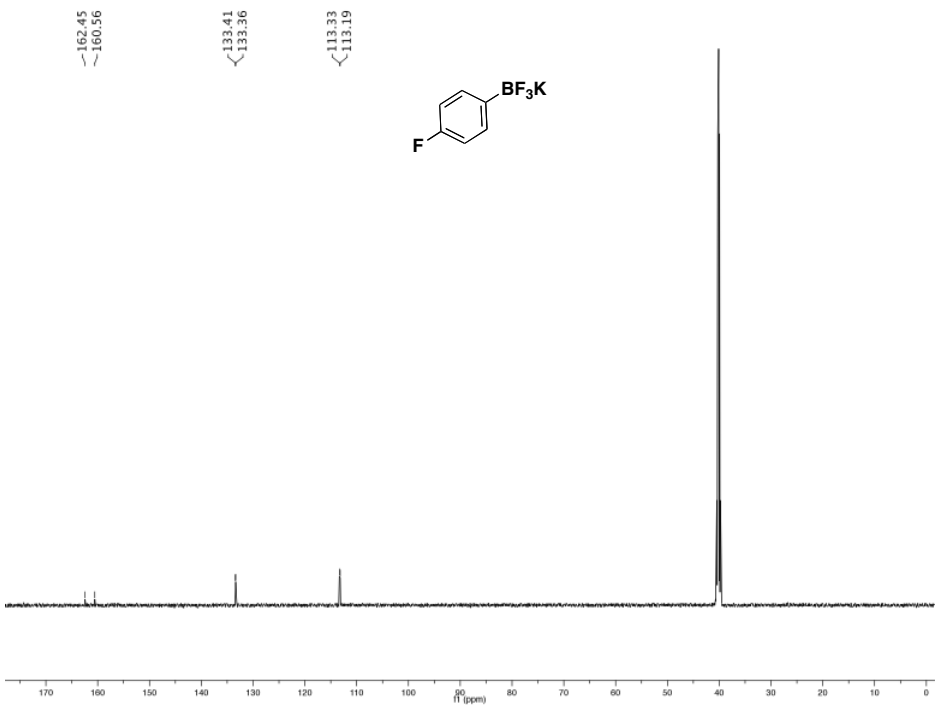

Figure A1.71 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (4-Fluorophenyl)trifluoroborate

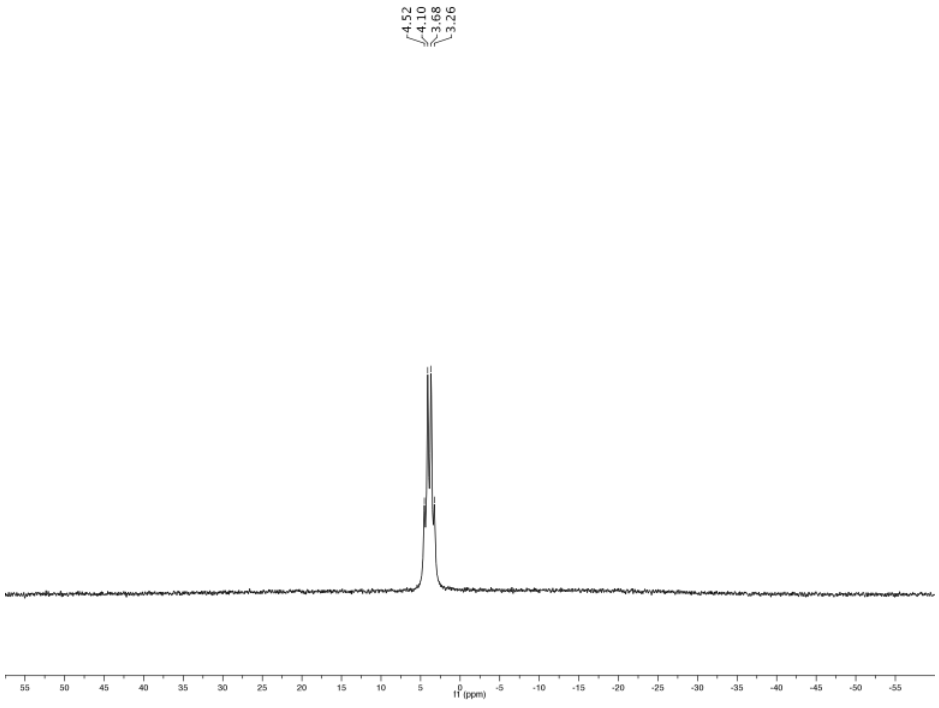

Figure A1.72 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (4-Fluorophenyl)trifluoroborate

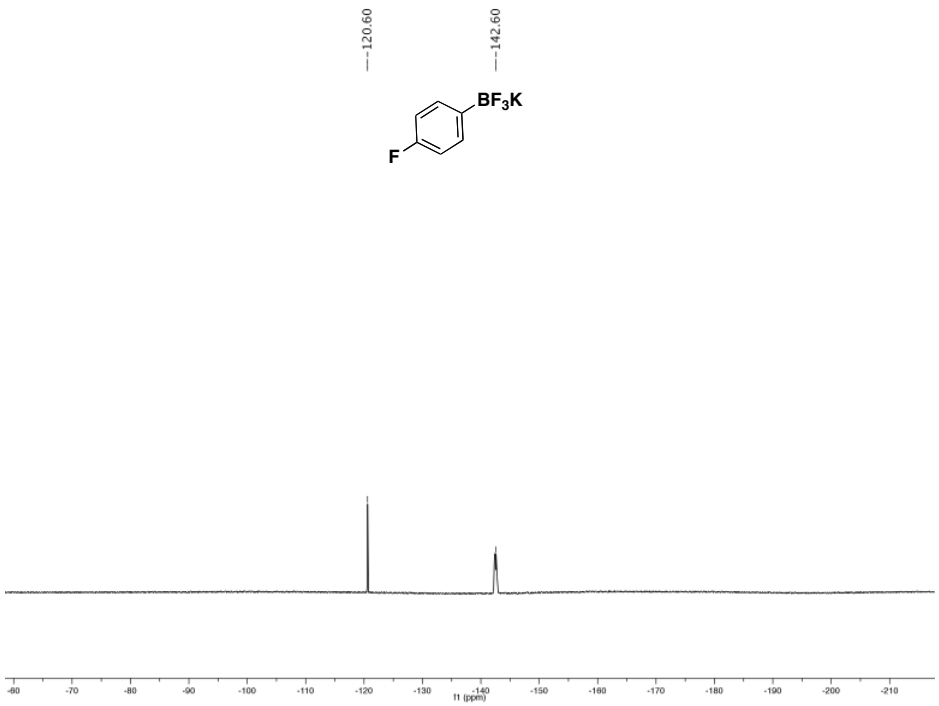

Figure A1.73 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (4-Fluorophenyl)trifluoroborate

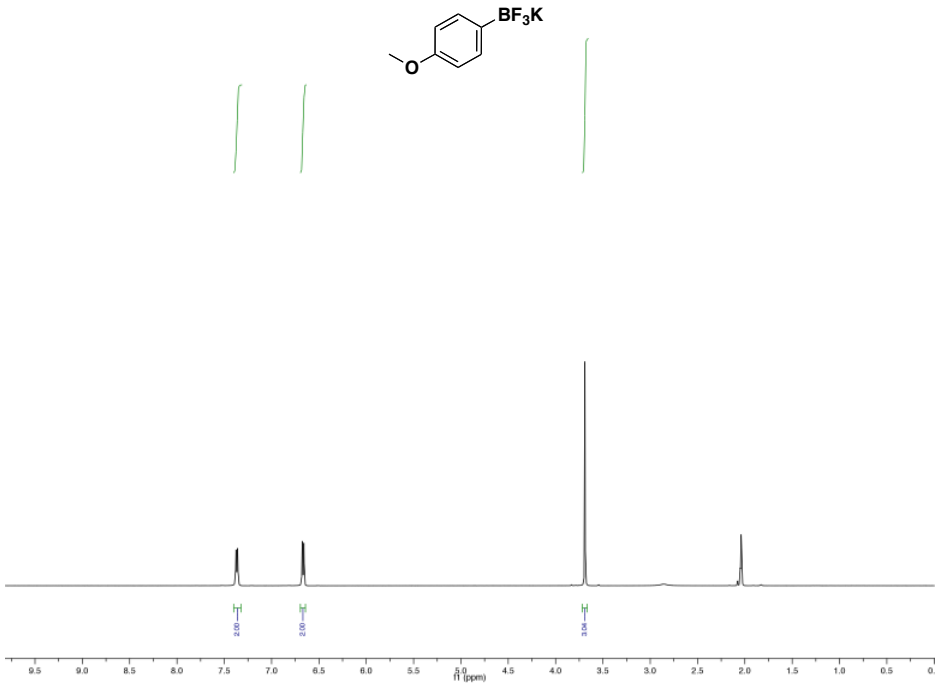

Figure A1.74 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

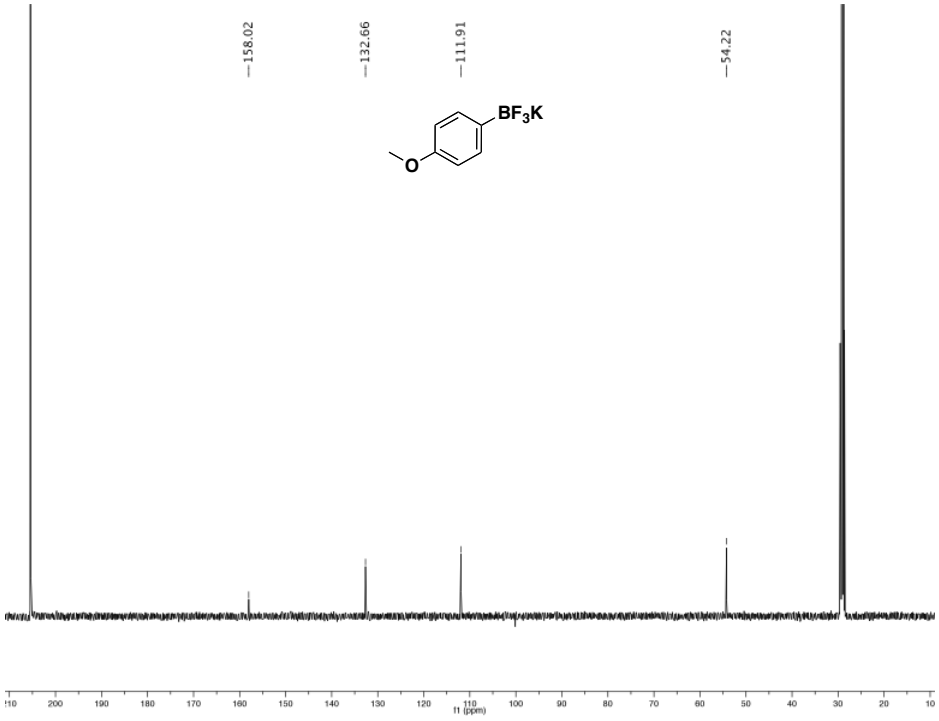

Figure A1.75 ^{13}C NMR Spectra (125.8 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

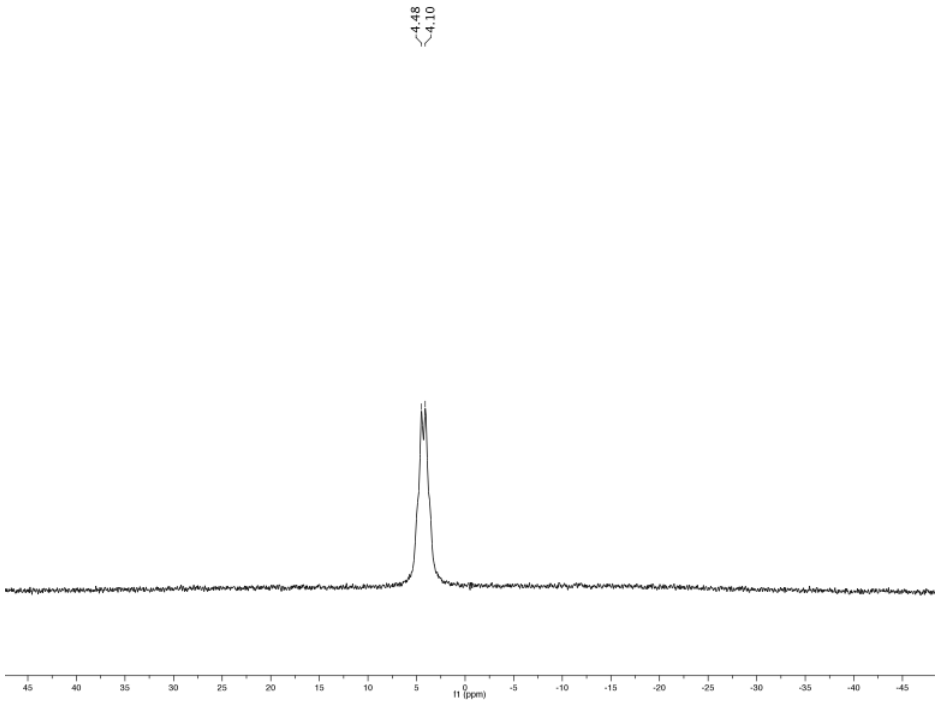

Figure A1.76 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

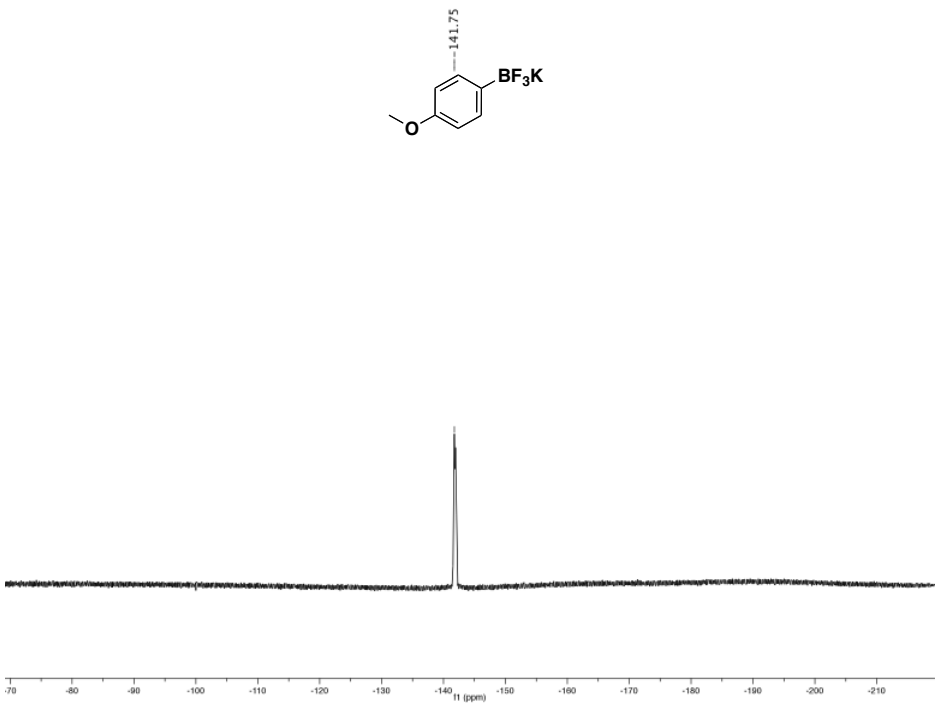

Figure A1.77 ^{19}F NMR Spectra (282 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

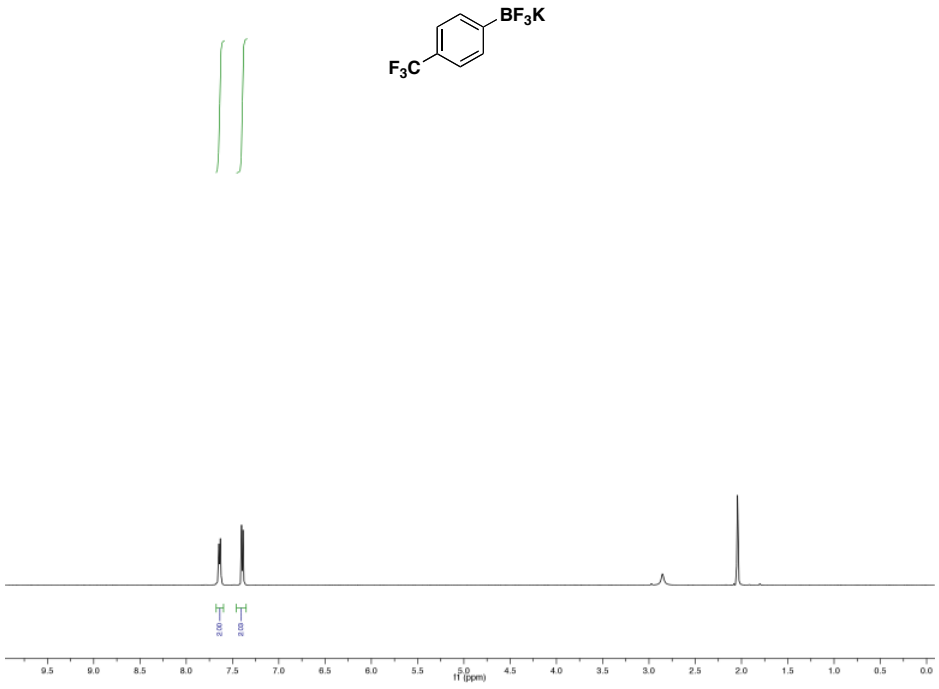

Figure A1.78 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate

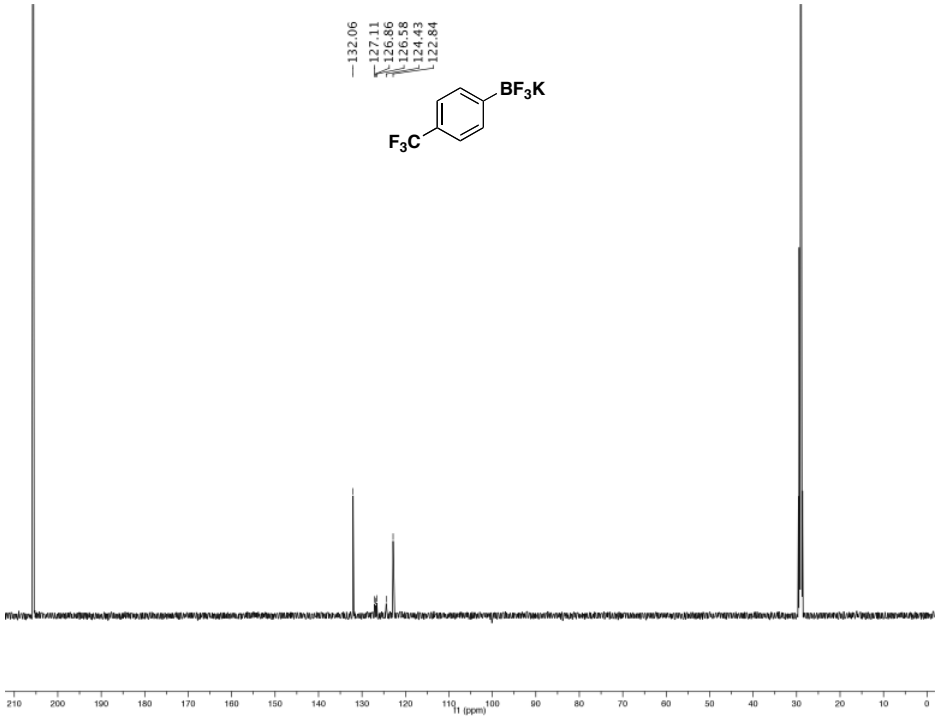

Figure A1.79 ^{13}C NMR Spectra (500 MHz, acetone-d_6) Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate

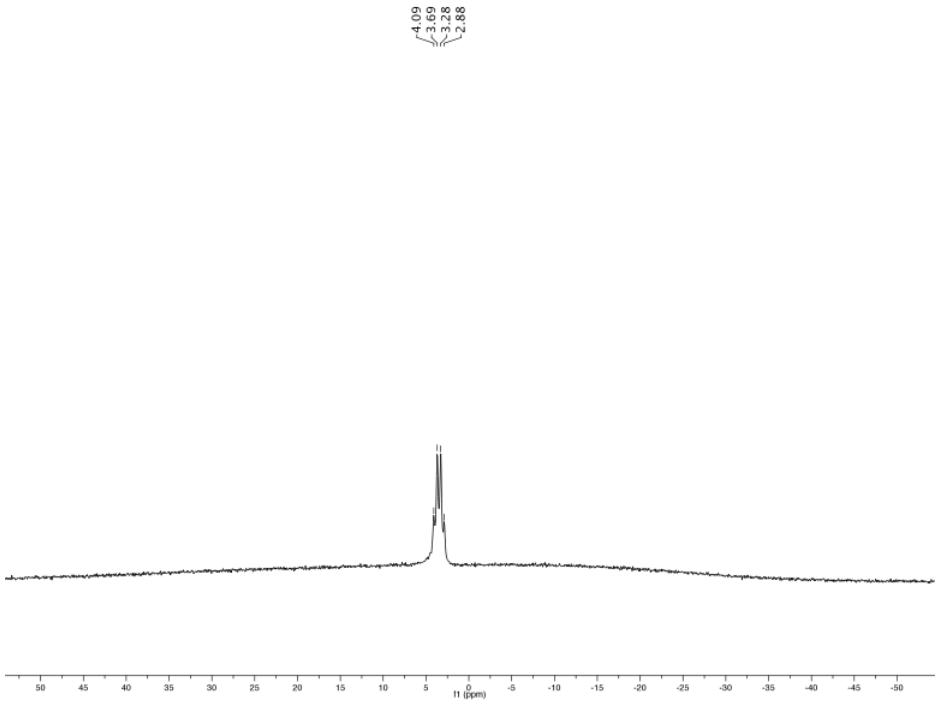

Figure A1.80 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate

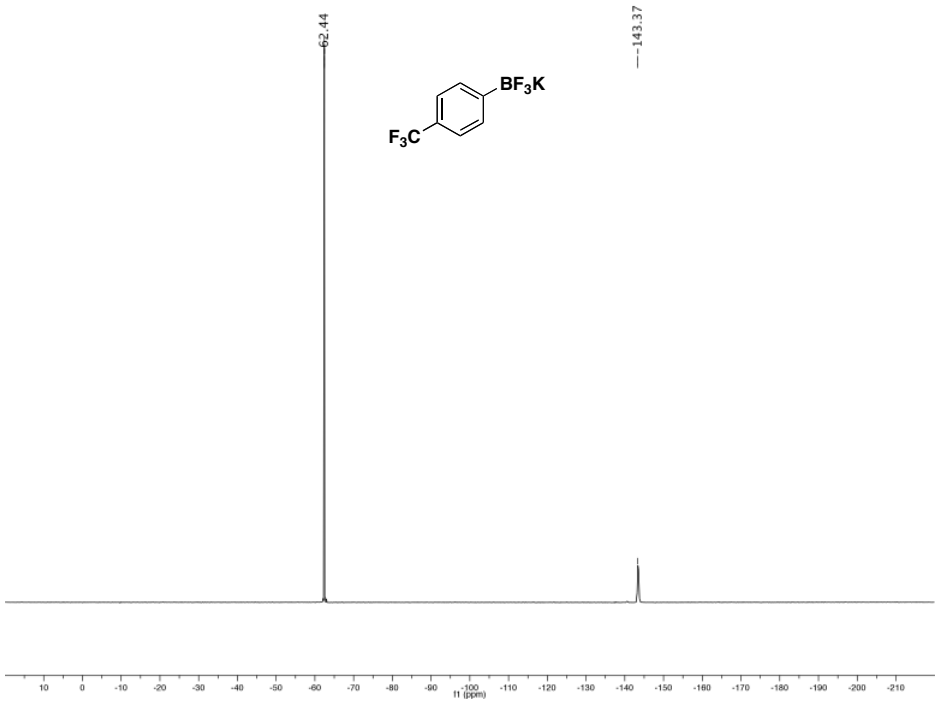

Figure A1.81 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate

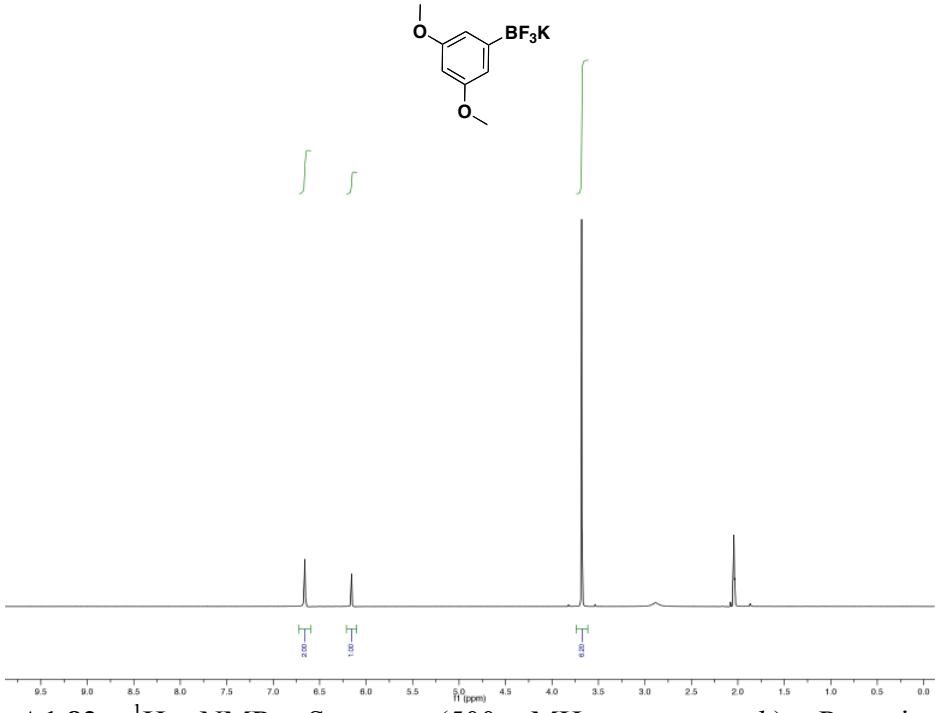

Figure A1.82 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (3,5-Dimethoxyphenyl)trifluoroborate

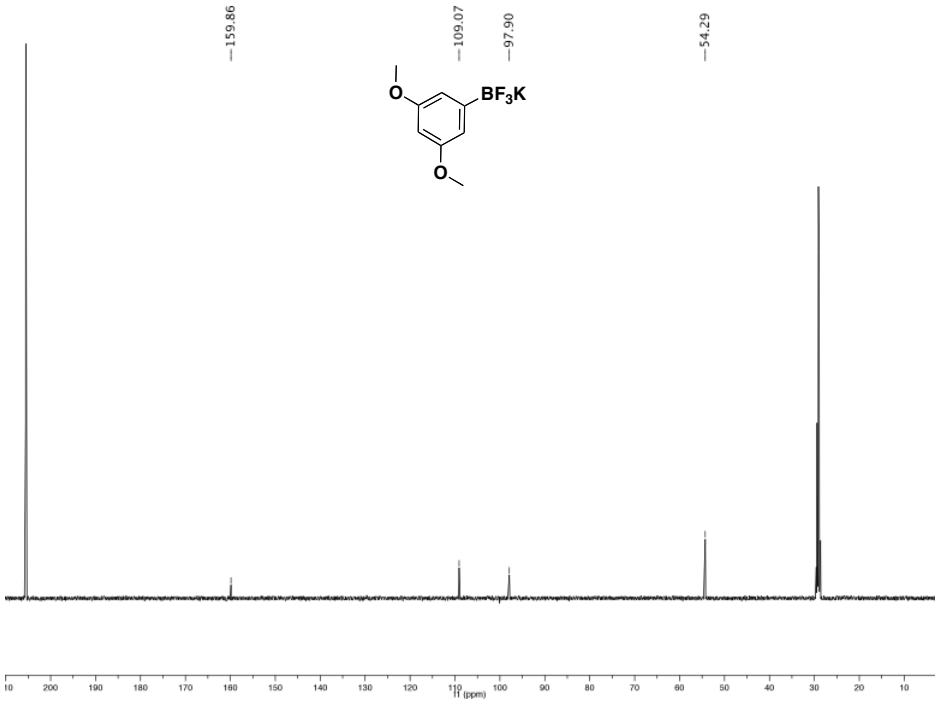

Figure A1.83 ^{13}C NMR Spectra (125.8 MHz, acetone-d_6) Potassium (3,5-Dimethoxyphenyl)trifluoroborate

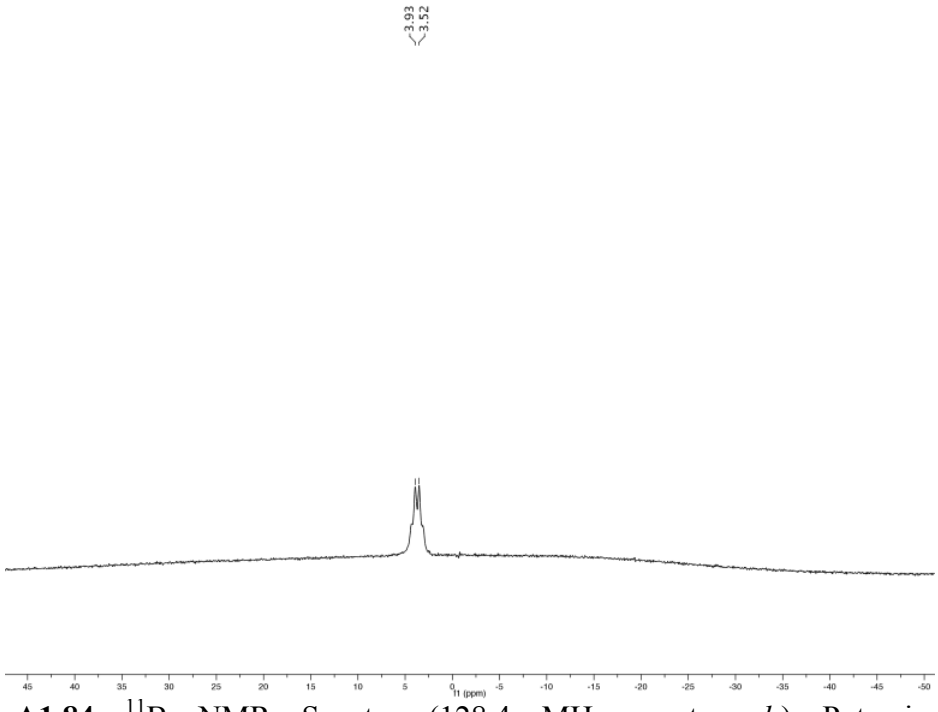

Figure A1.84 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (3,5-Dimethoxyphenyl)trifluoroborate

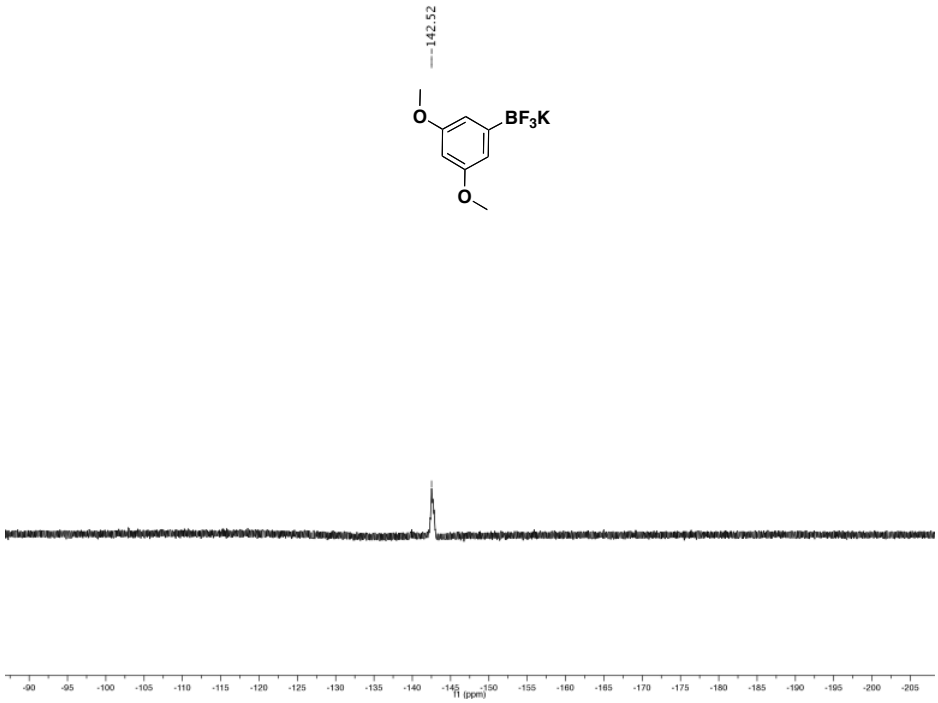

Figure A1.85 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (3,5-Dimethoxyphenyl)trifluoroborate

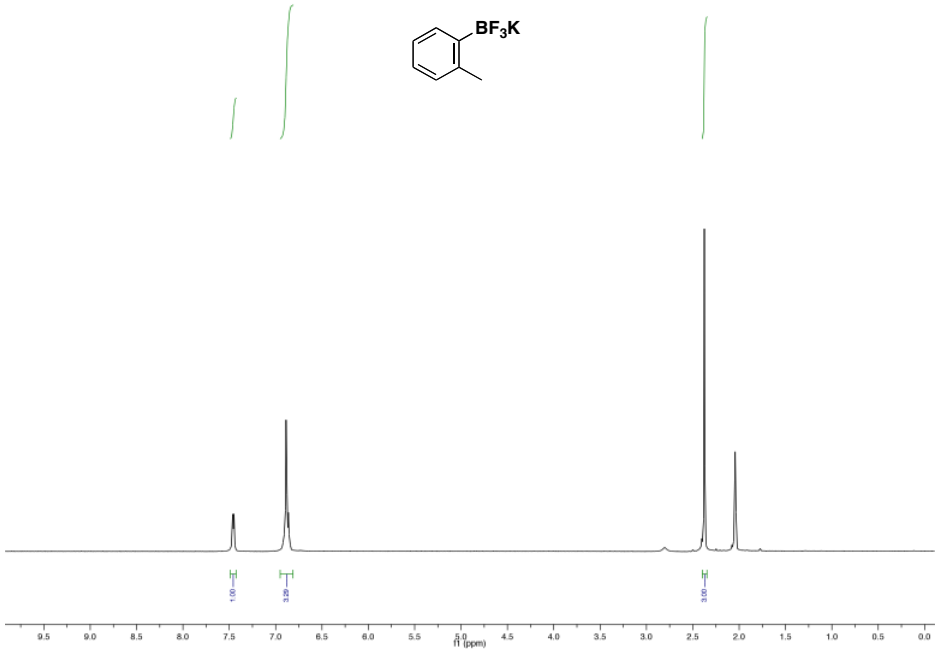

Figure A1.86 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium *o*-Tolyltrifluoroborate

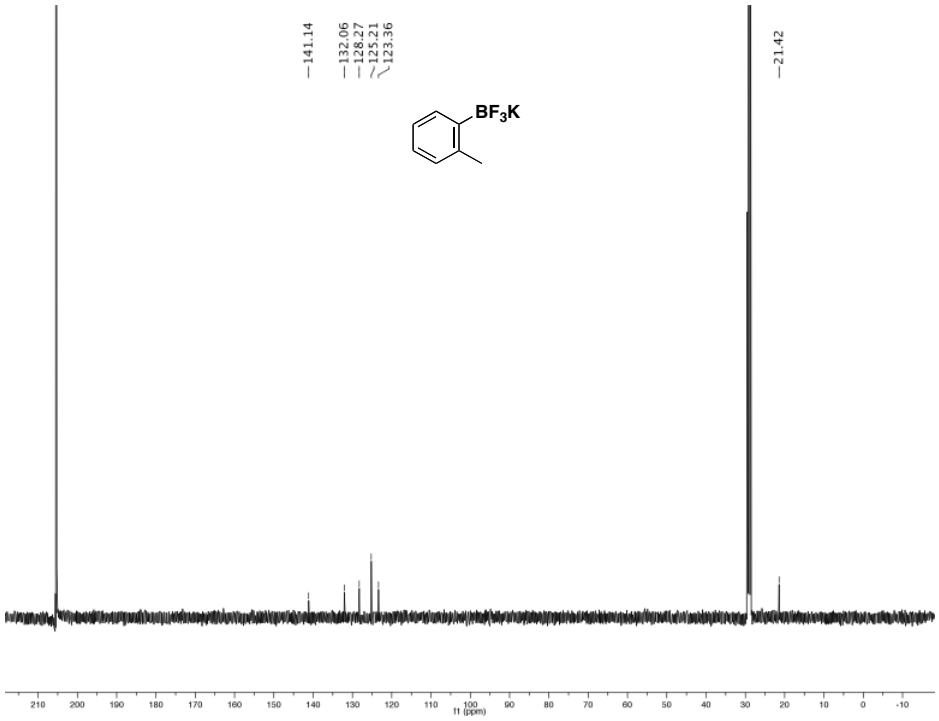

Figure A1.87 ^{13}C NMR Spectra (125.8 MHz, acetone-d_6) Potassium *o*-Tolyltrifluoroborate

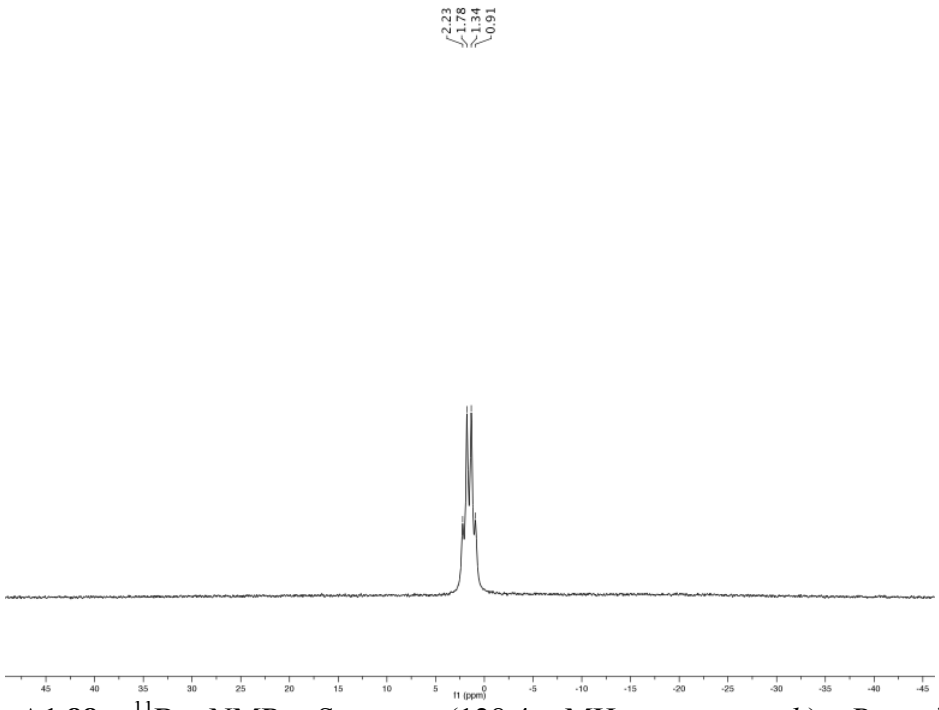

Figure A1.88 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium *o*-Tolyltrifluoroborate

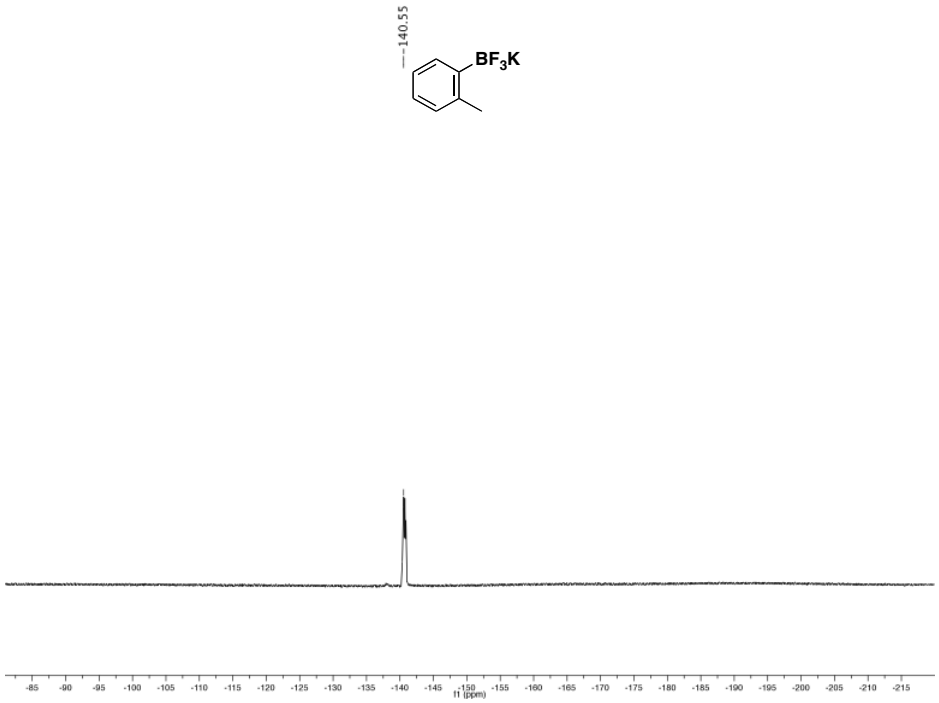

Figure A1.89 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium *o*-Tolyltrifluoroborate

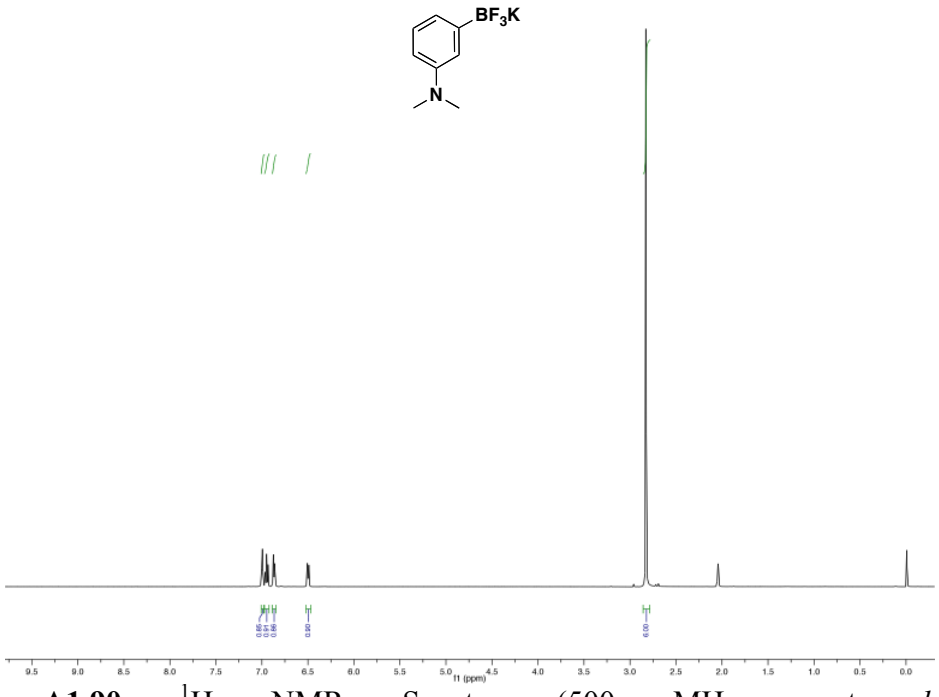

Figure A1.90 ^{1}H NMR Spectra (500 MHz, acetone-d_6) (3-(Dimethylamino)phenyl)trifluoroborate

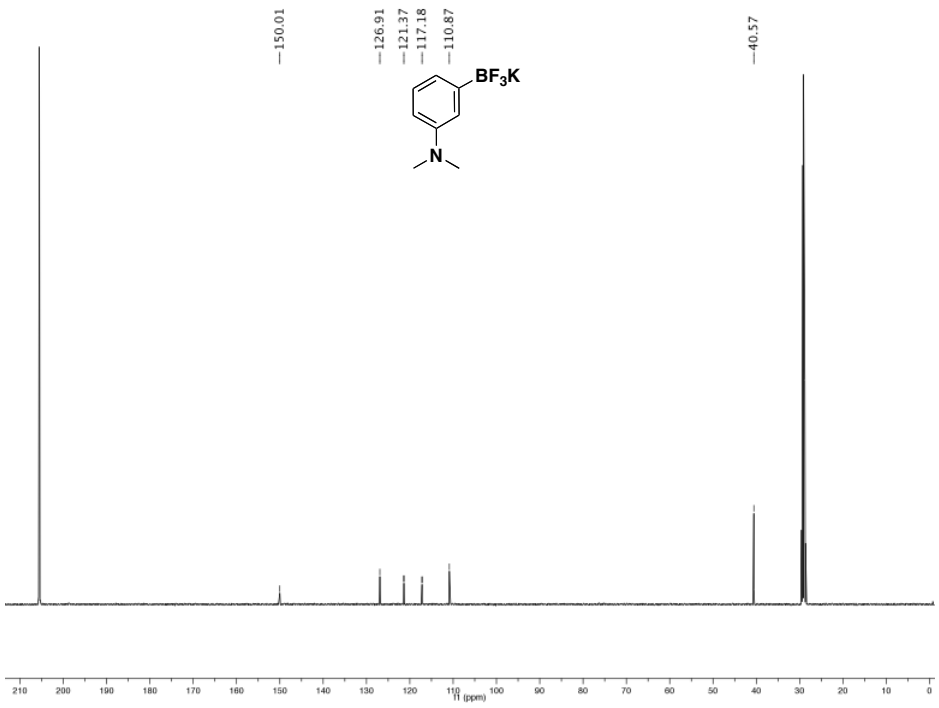

Figure A1.91 ^{13}C NMR Spectra (125.8 MHz, acetone-d_6) (3-(Dimethylamino)phenyl)trifluoroborate

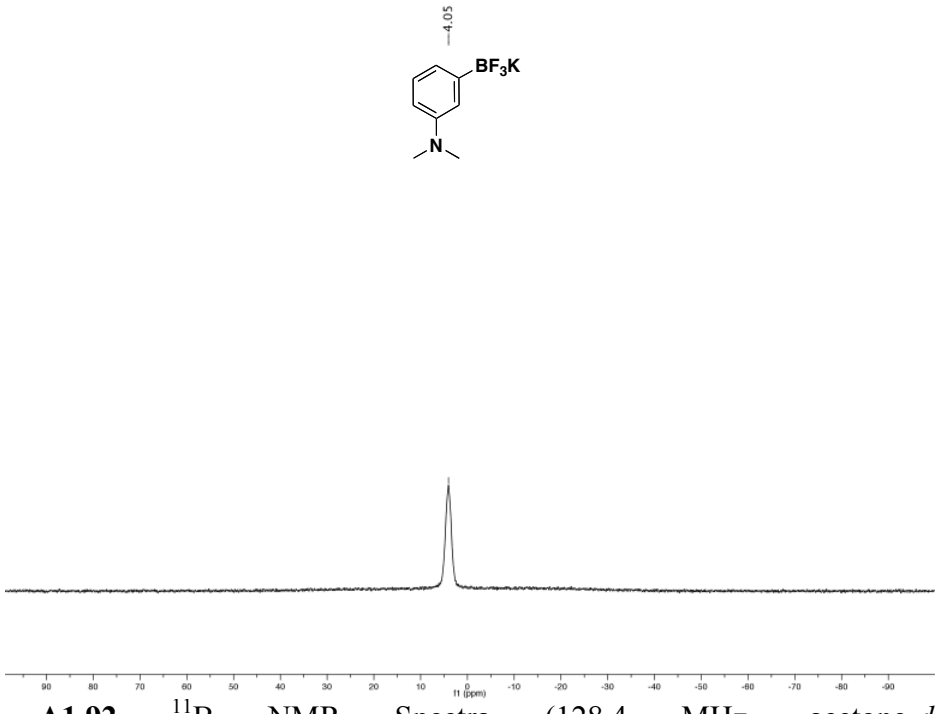

Figure A1.92 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) (3-(Dimethylamino)phenyl)trifluoroborate

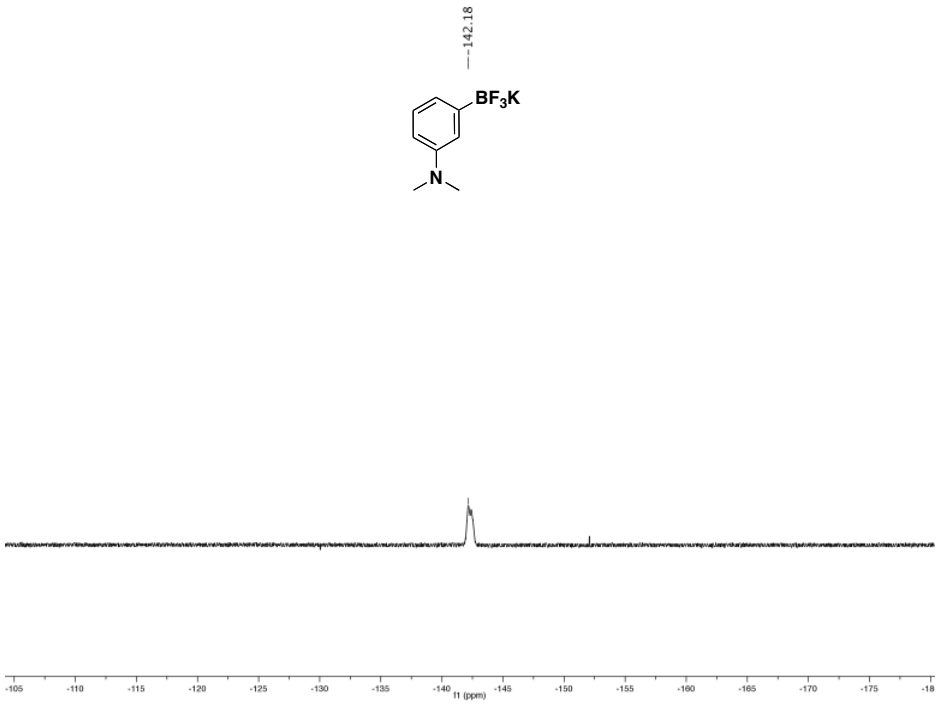

Figure A1.93 ^{19}F NMR Spectra (282 MHz, acetone-d_6) (3-(Dimethylamino)phenyl)trifluoroborate

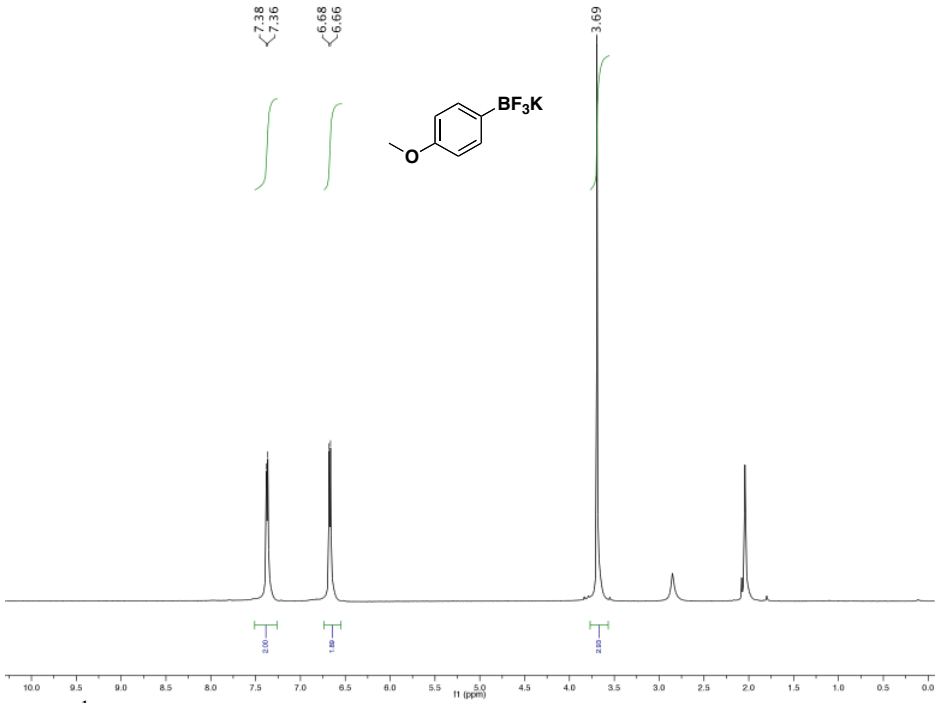

Figure A1.94 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

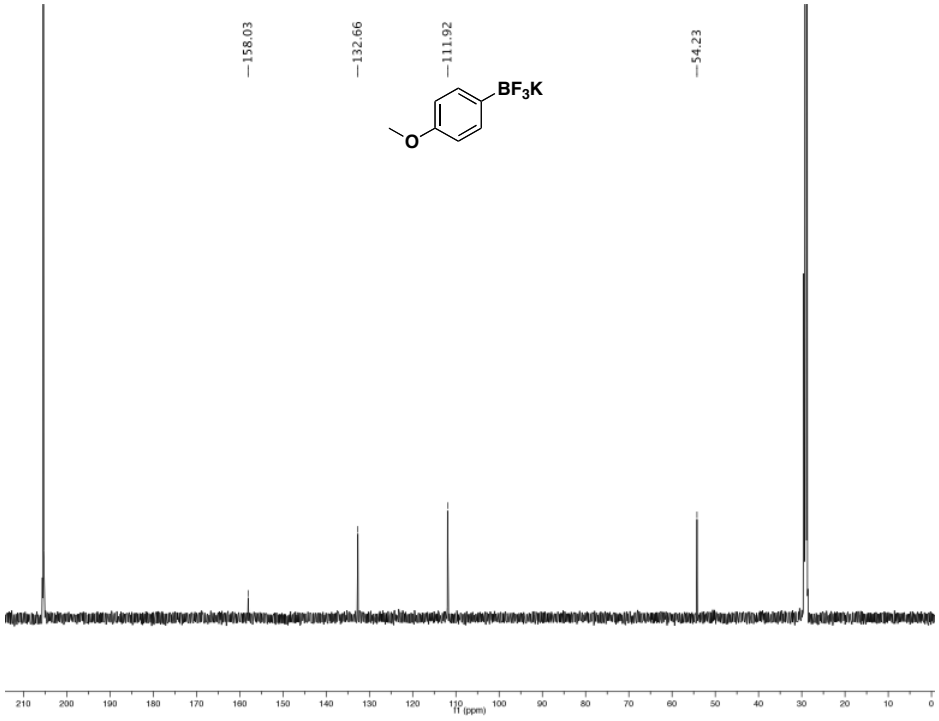

Figure A1.95 ^{13}C NMR Spectra (125.8 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

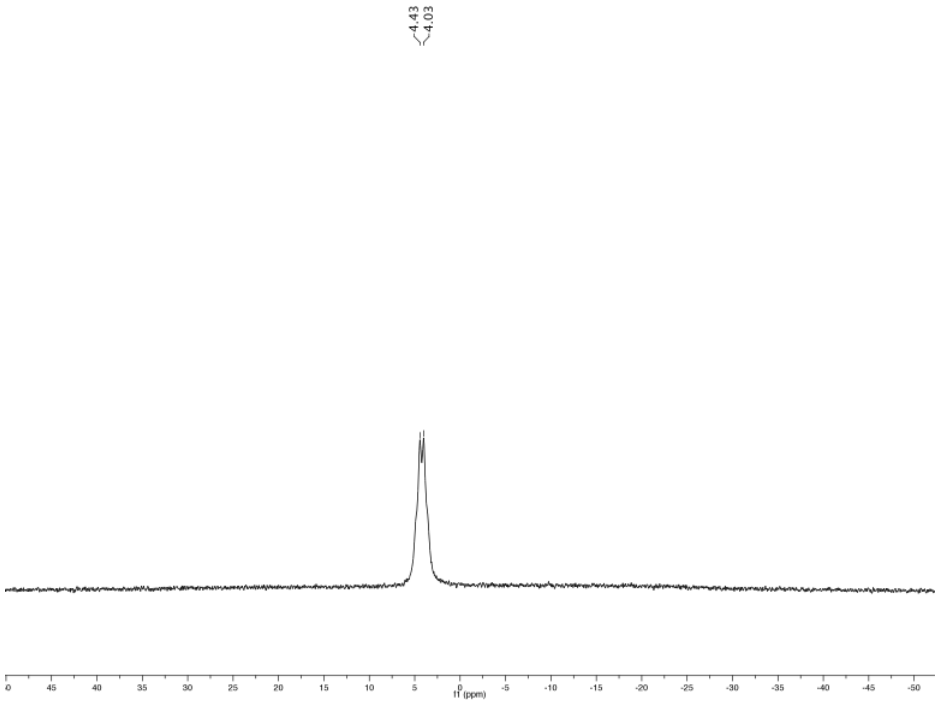

Figure A1.96 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

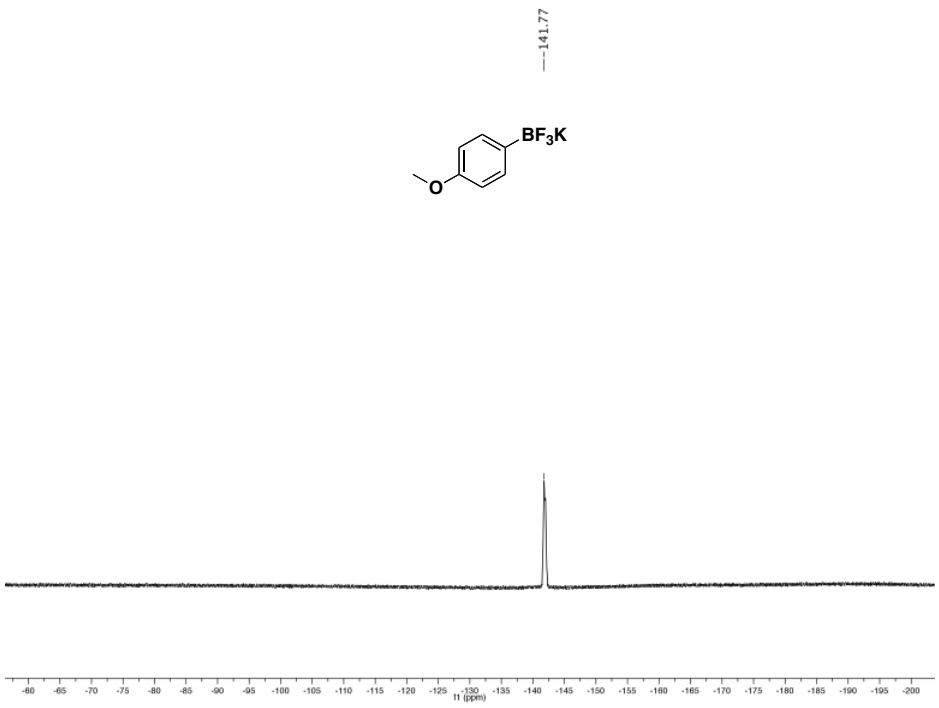

Figure A1.97 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

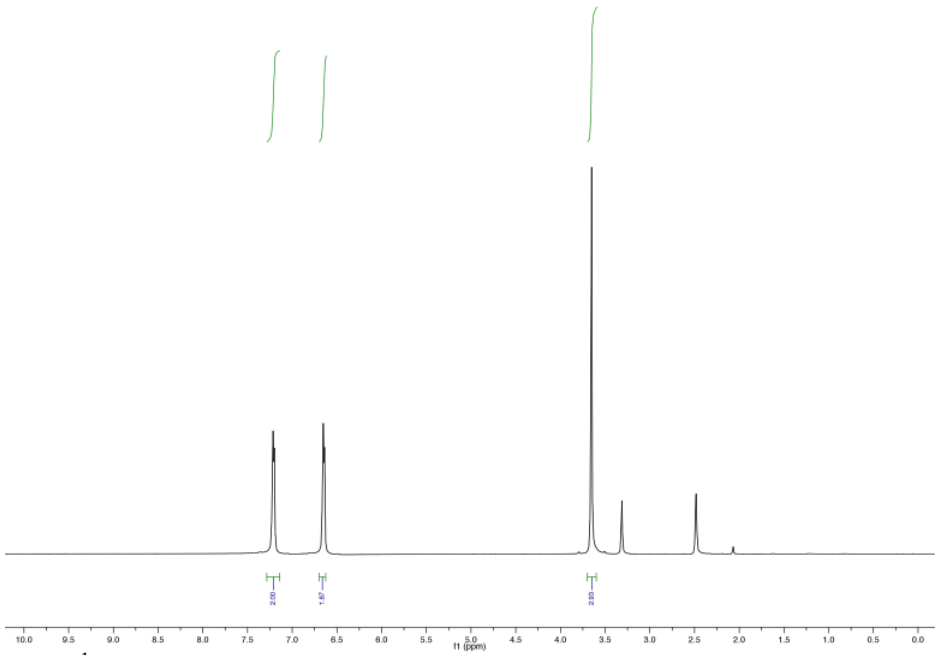

Figure A1.98 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

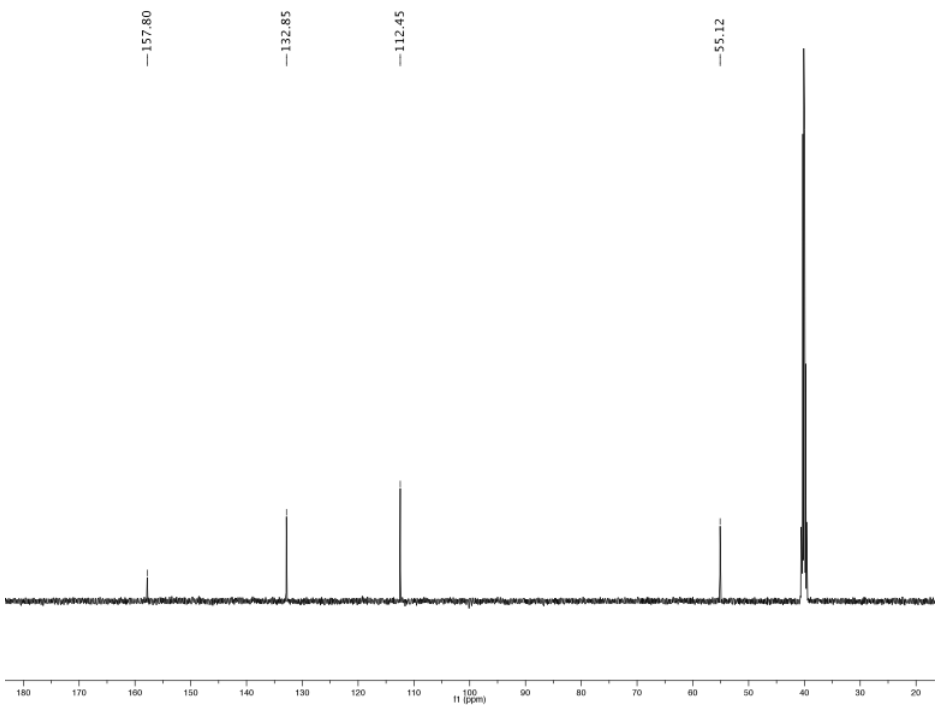

Figure A1.99 ^{13}C NMR Spectra (125.8 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

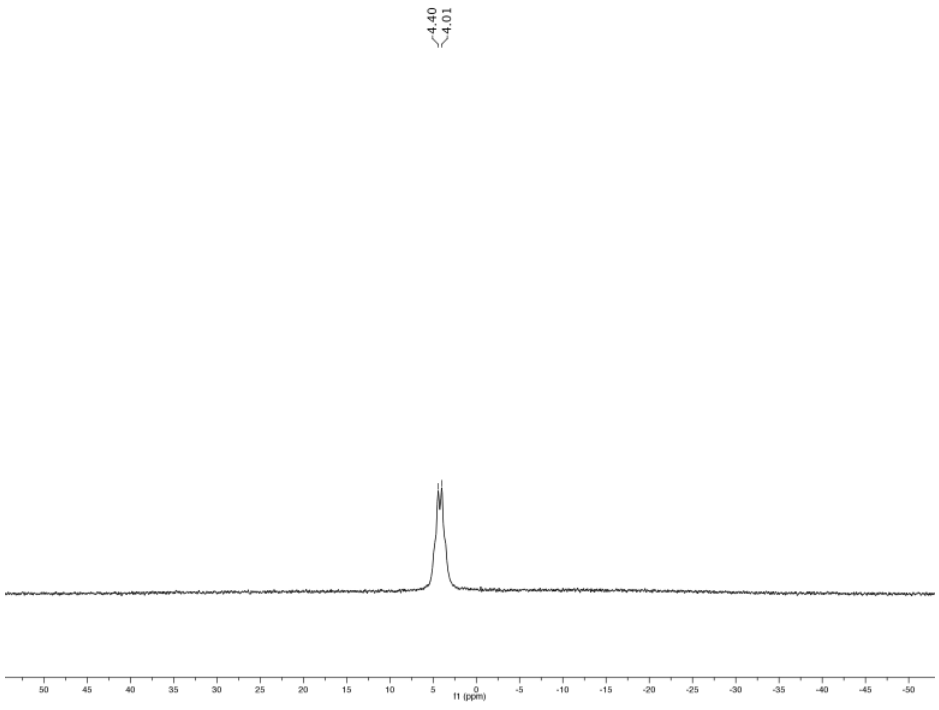

Figure A1.100 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

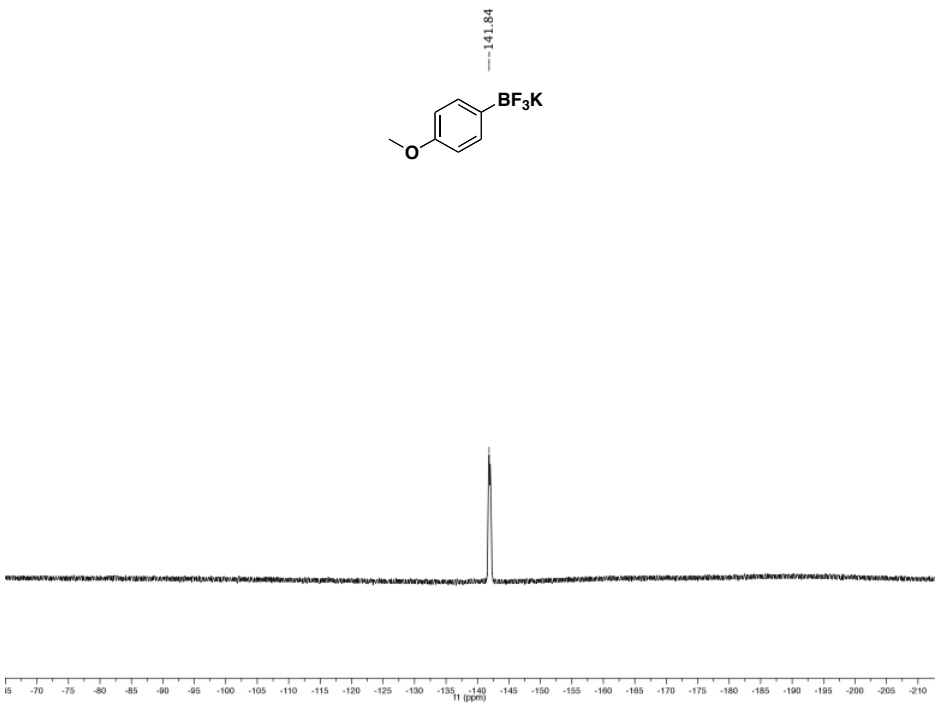

Figure A1.101 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

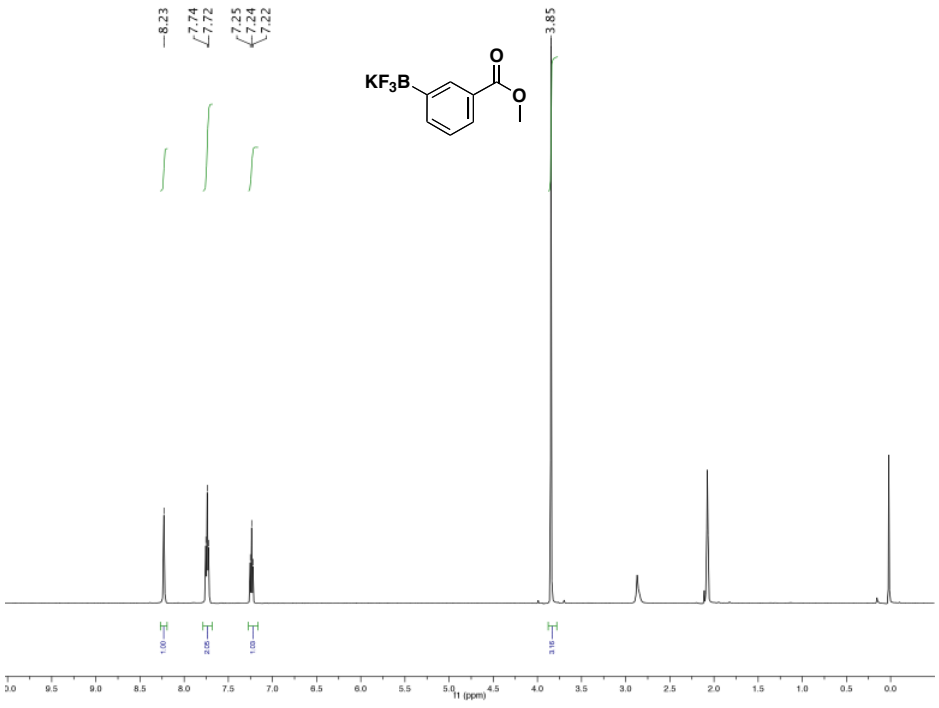

Figure A1.102 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (3-(Methoxycarbonyl)phenyl)trifluoroborate

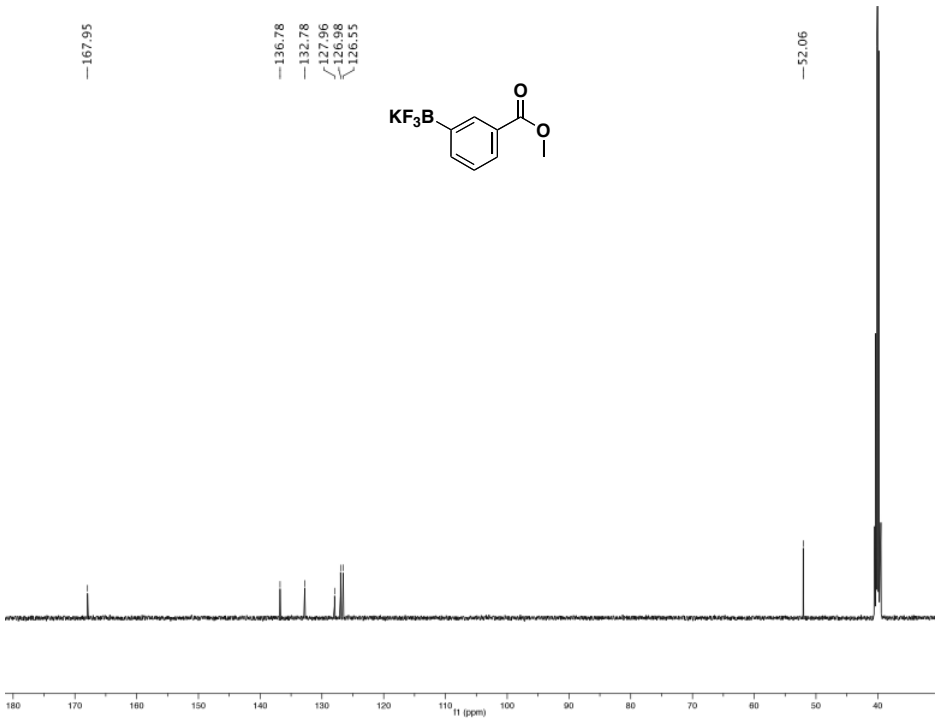

Figure A1.103 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (3-(Methoxycarbonyl)phenyl)trifluoroborate

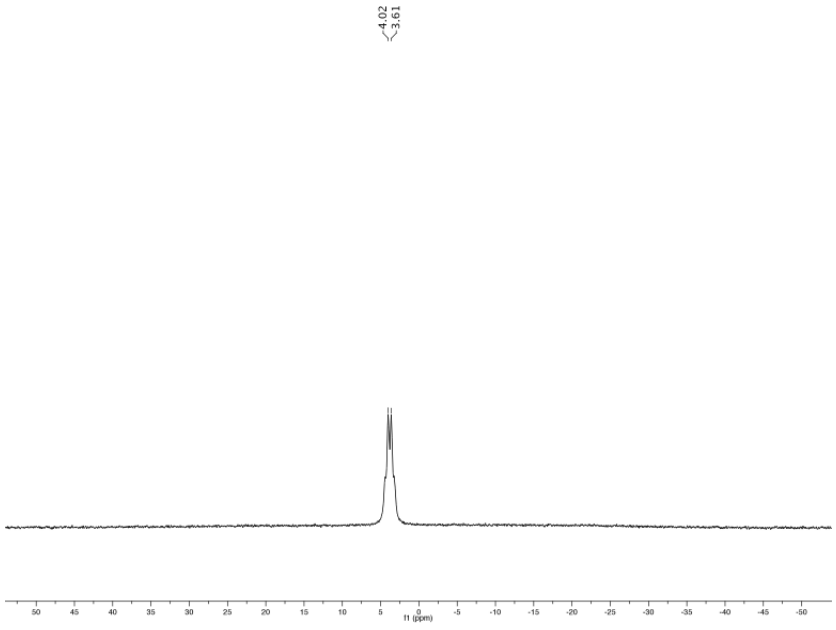

Figure A1.104 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (3-(Methoxycarbonyl)phenyl)trifluoroborate

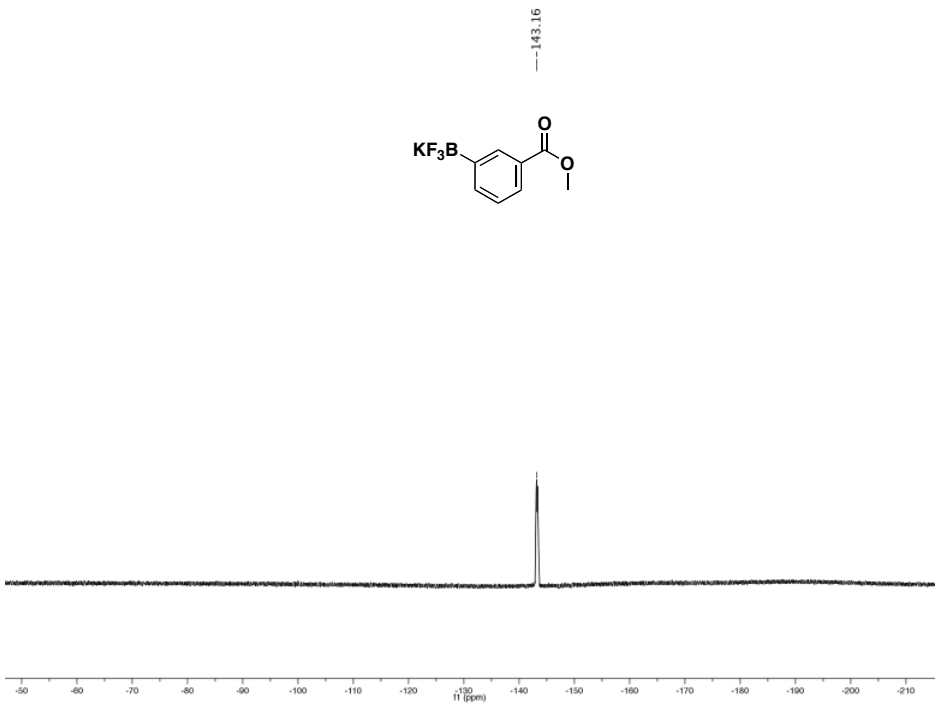

Figure A1.105 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (3-(Methoxycarbonyl)phenyl)trifluoroborate

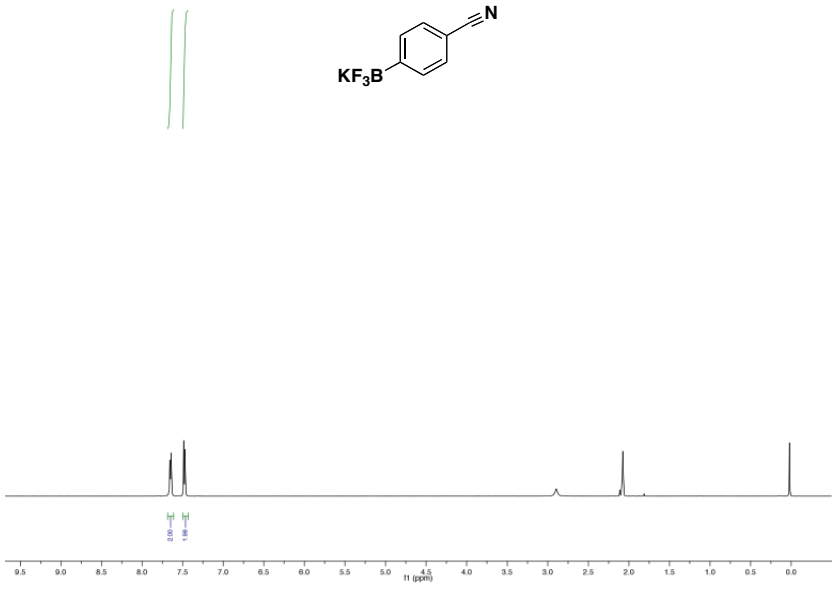

Figure A1.106 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (4-Cyanophenyl)trifluoroborate

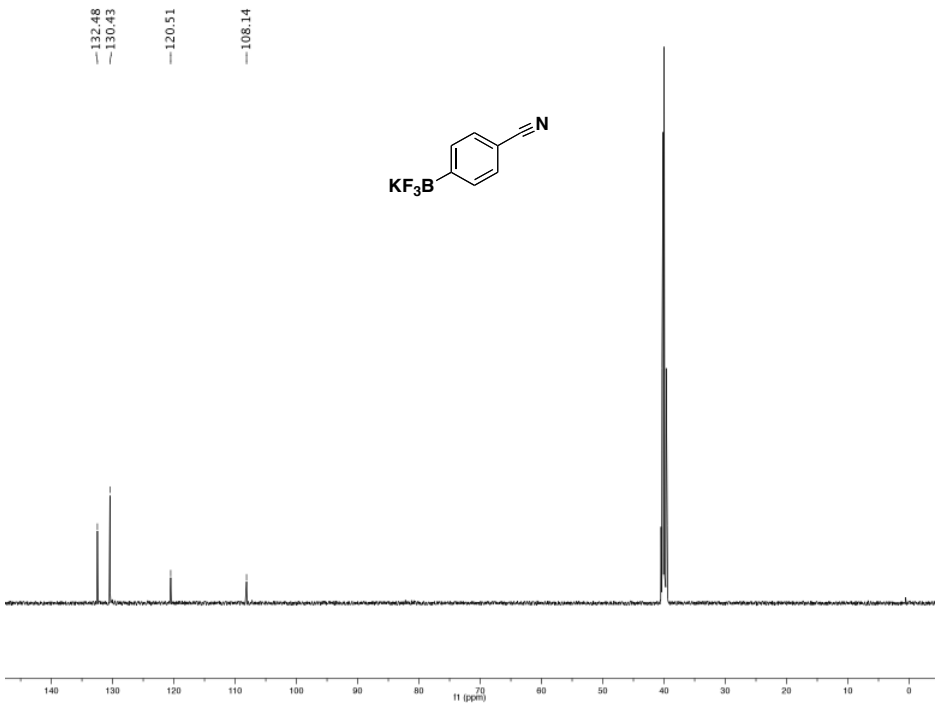

Figure A1.107 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (4-Cyanophenyl)trifluoroborate

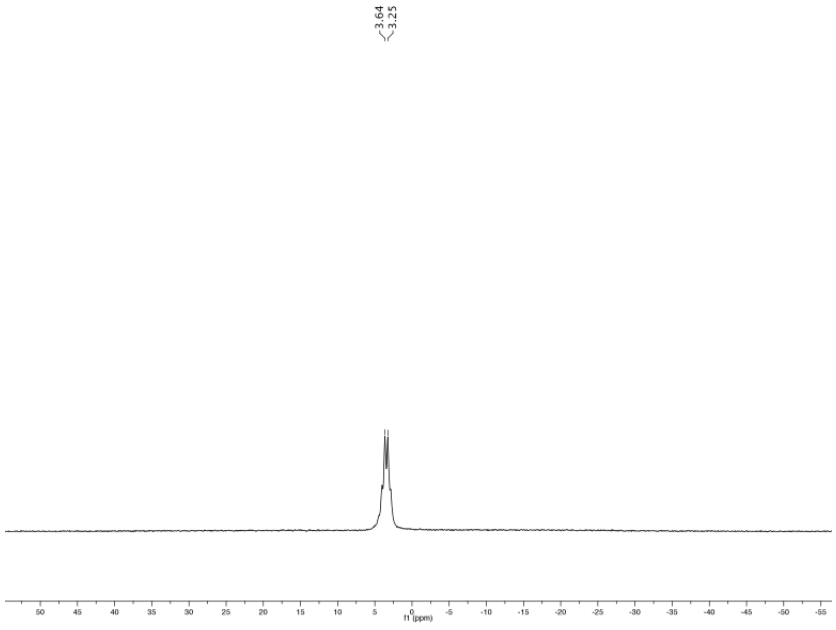

Figure A1.108 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (4-Cyanophenyl)trifluoroborate

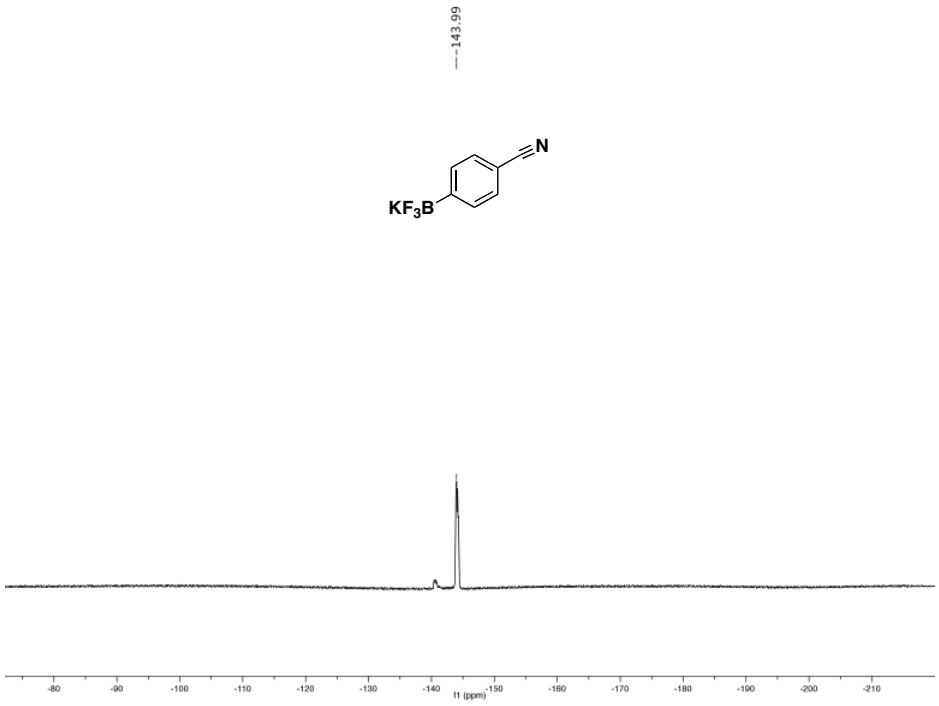

Figure A1.109 ^{19}F NMR Spectra 338.8 MHz, acetone-d_6) Potassium (4-Cyanophenyl)trifluoroborate

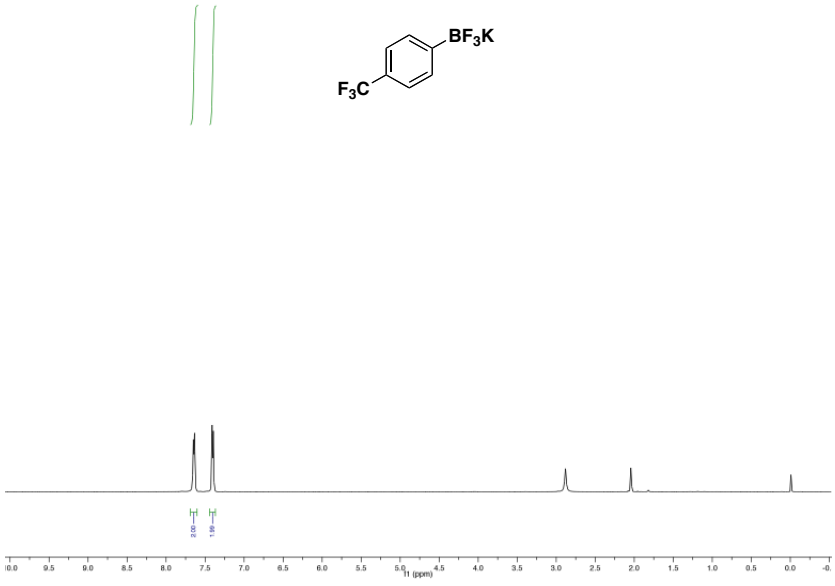

Figure A1.110 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate

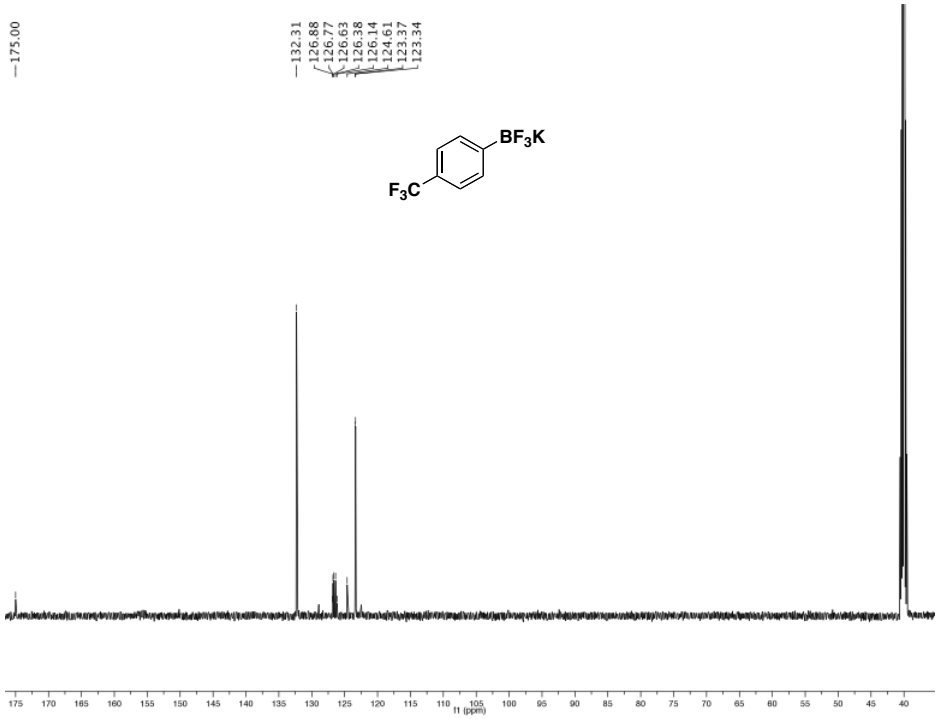

Figure A1.111 ^{13}C NMR Spectra (125.8 Hz, DMSO-d_6) Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate

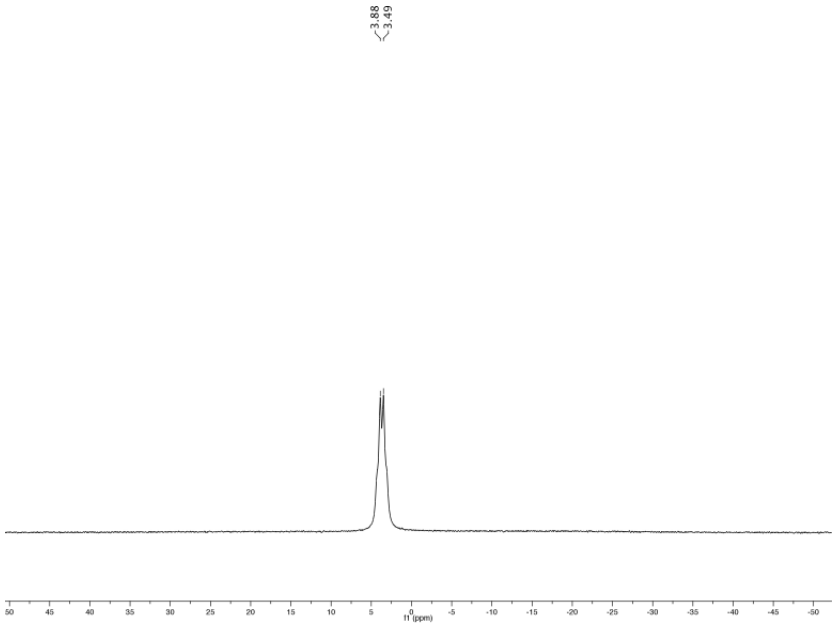

Figure A1.112 ^{11}B NMR (128.4 MHz, acetone-d_6) Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate

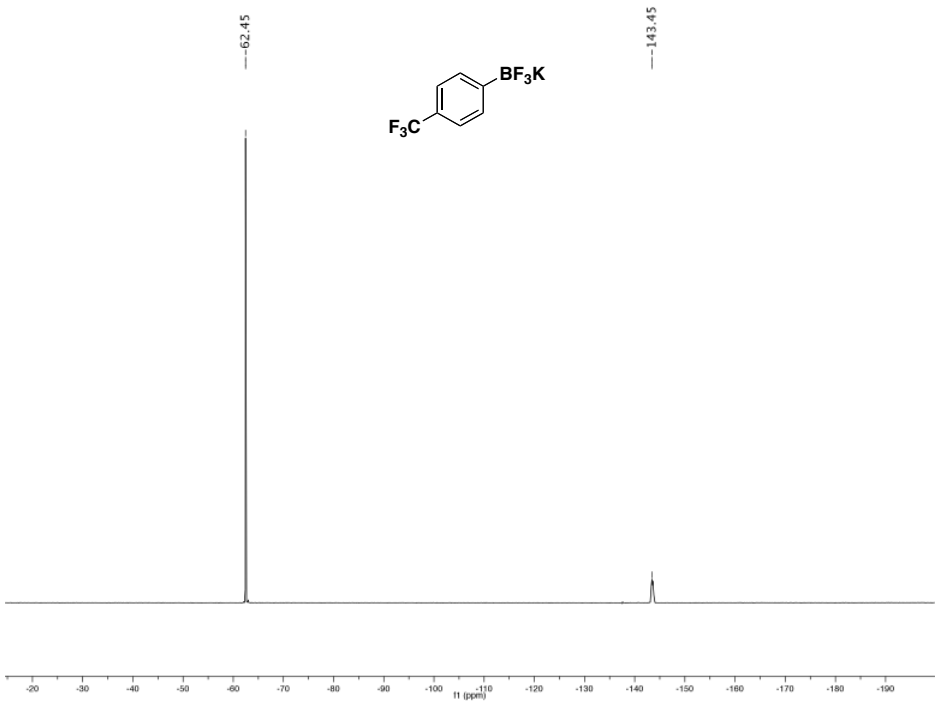

Figure A1.113 ^{19}F NMR (282 MHz, acetone-d_6) Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate

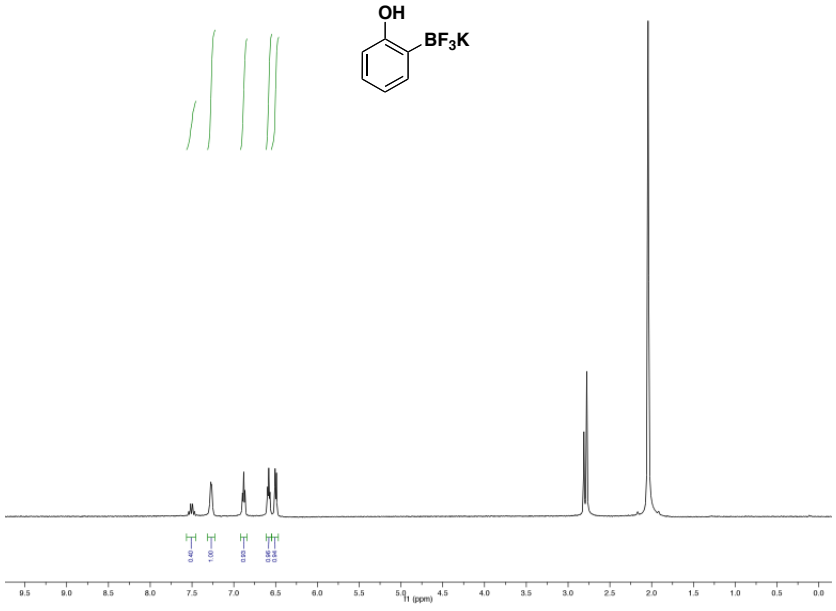

Figure A1.114 ^{1}H NMR Spectra (500 MHz, acetone-d_6) 2-Hydroxyphenyltrifluoroborate

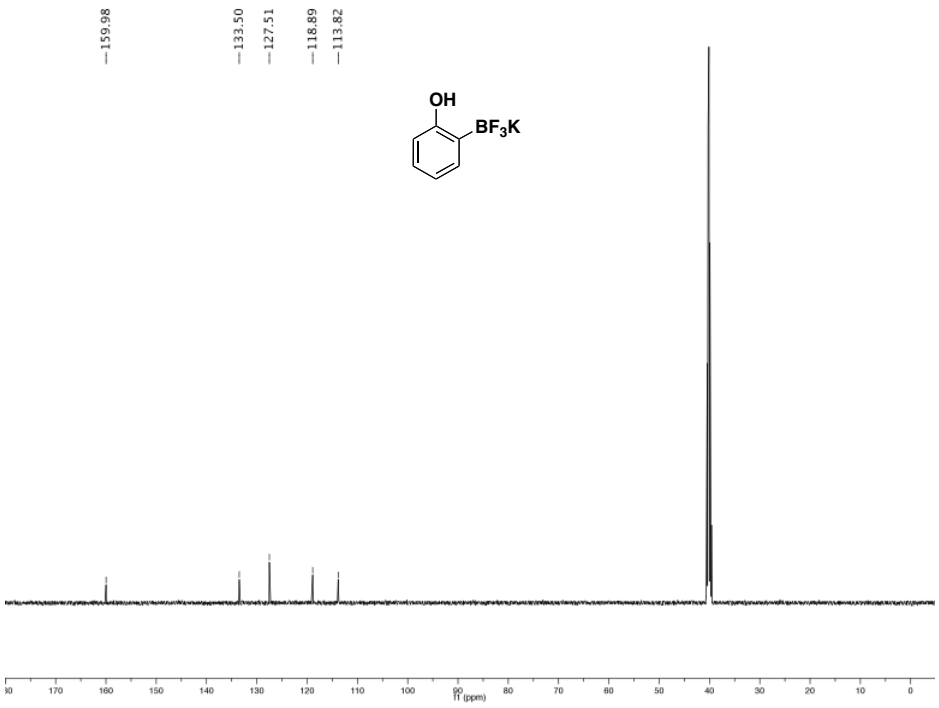

Figure A1.115 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) 2-Hydroxyphenyltrifluoroborate

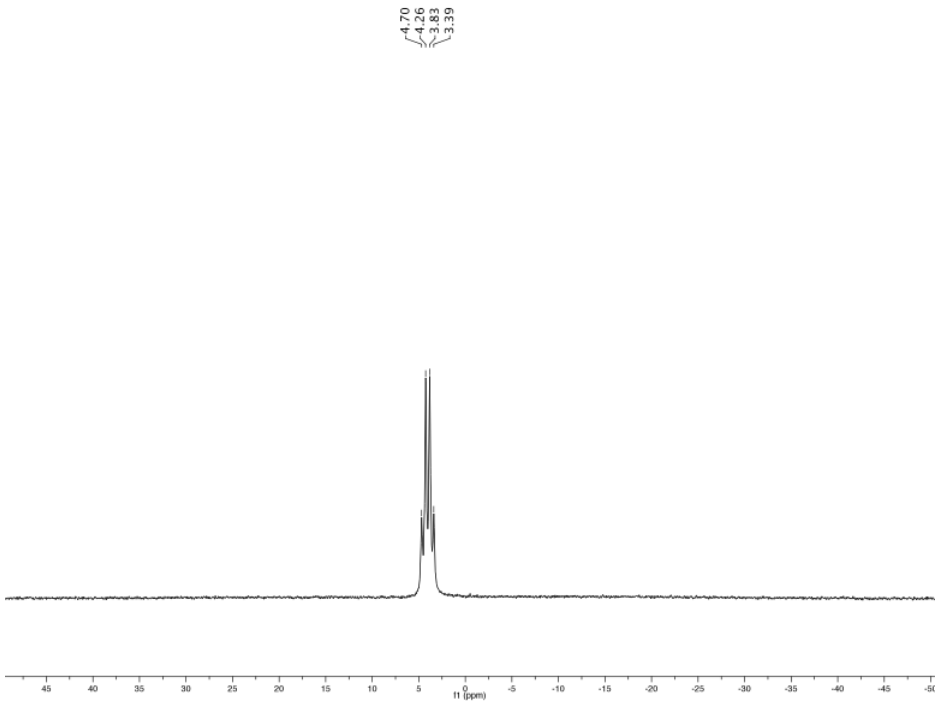

Figure A1.116 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) 2-Hydroxyphenyltrifluoroborate

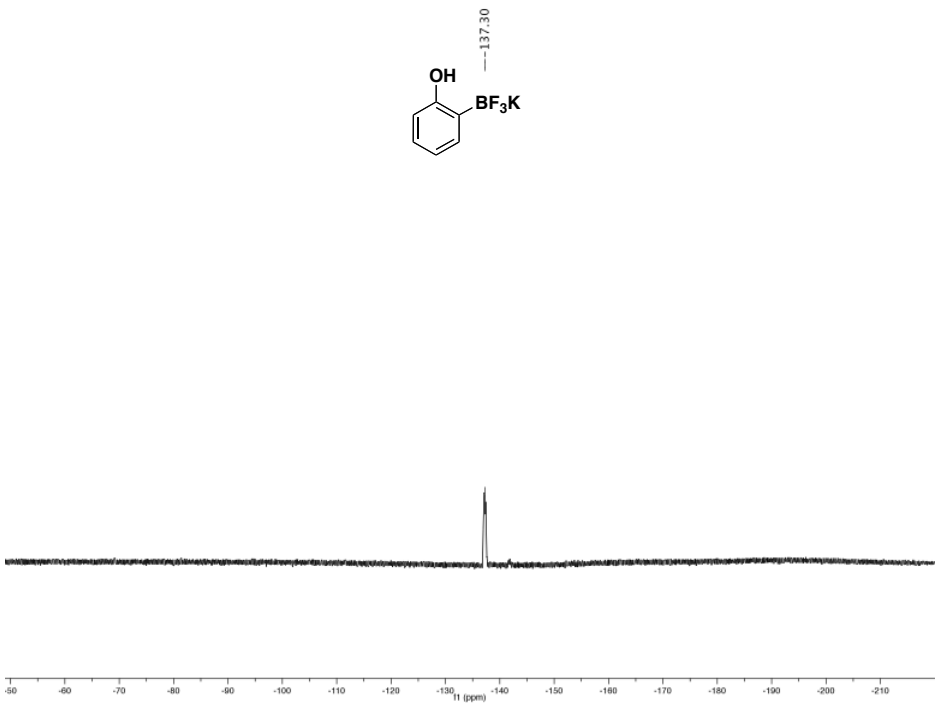

Figure A1.117 ^{19}F NMR Spectra (338.8 MHz, DMSO-d_6) 2-Hydroxyphenyltrifluoroborate

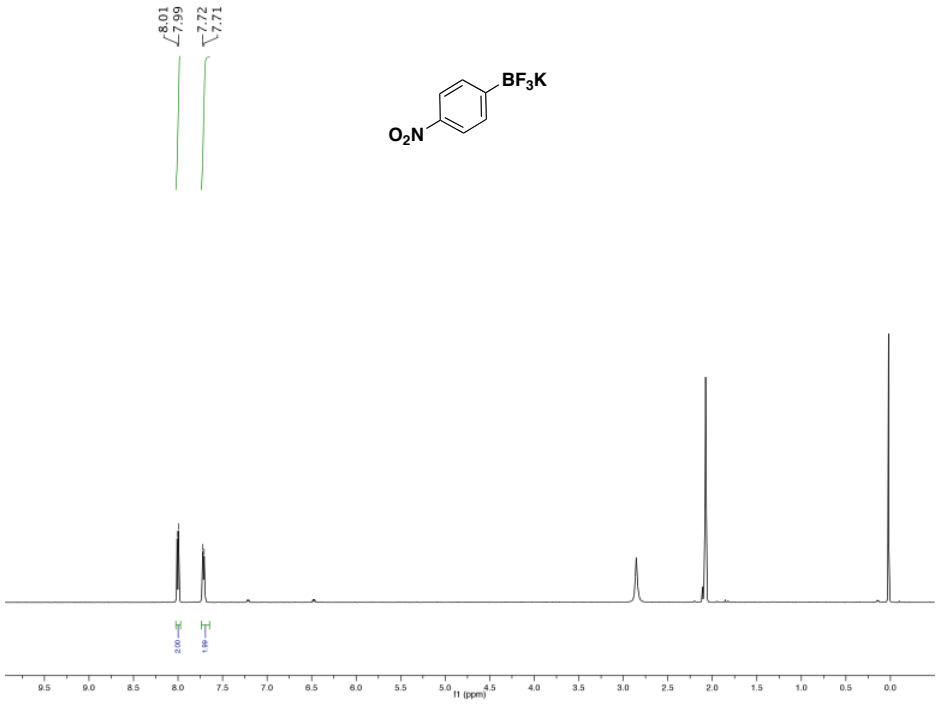

Figure A1.118 ^{1}H NMR (500 MHz, acetone-d_6) Potassium (4-Nitrophenyl)trifluoroborate

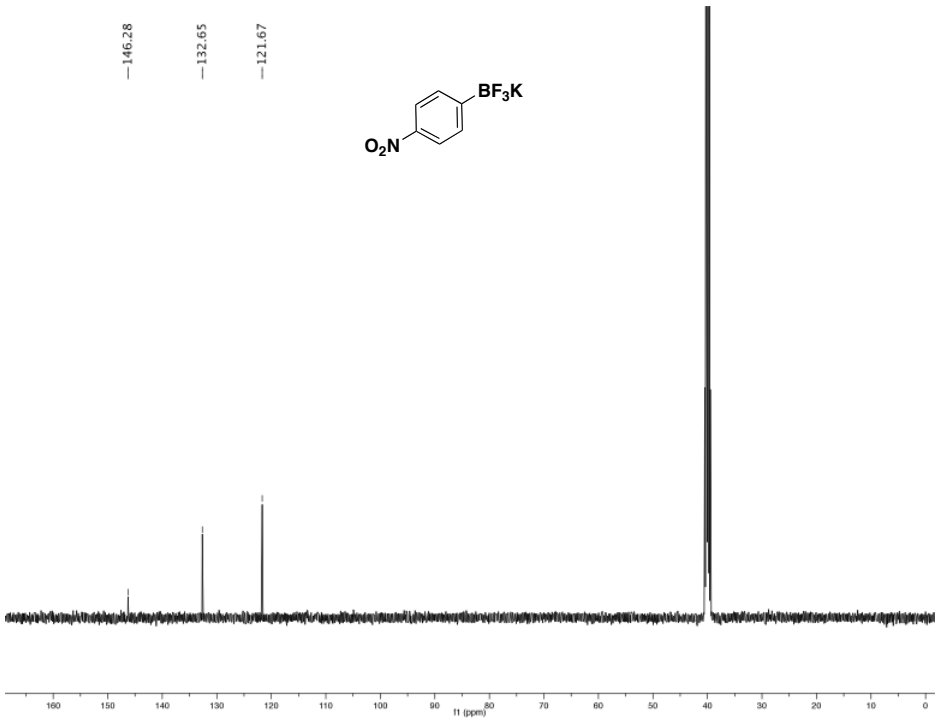

Figure A1.119 ^{13}C NMR (125.8 MHz, DMSO-d_6) Potassium (4-Nitrophenyl)trifluoroborate

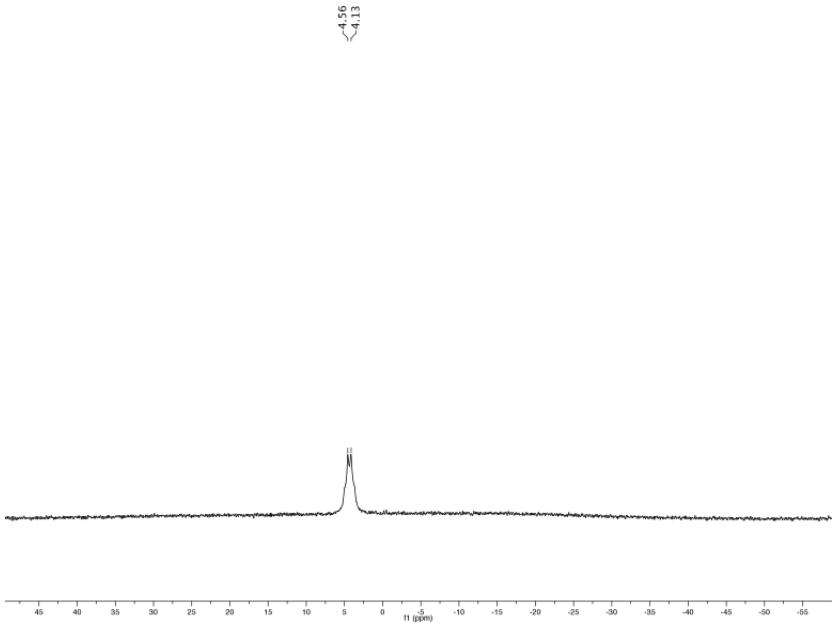

Figure A1.120 ^{11}B NMR (128.4 MHz, acetone-d_6) Potassium (4-Nitrophenyl)trifluoroborate

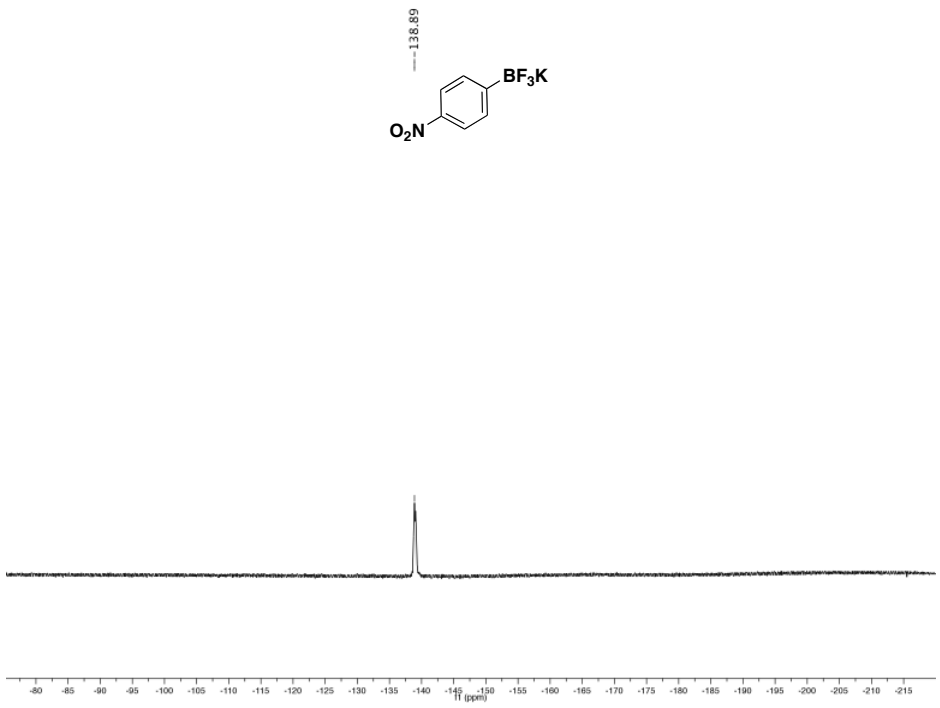

Figure A1.121 ^{19}F NMR (338.8 MHz, acetone-d_6) Potassium (4-Nitrophenyl)trifluoroborate

Figure A1.122 ^{1}H NMR (500 MHz, acetone-d_6) (2,6-Dimethylphenyl)trifluoroborate

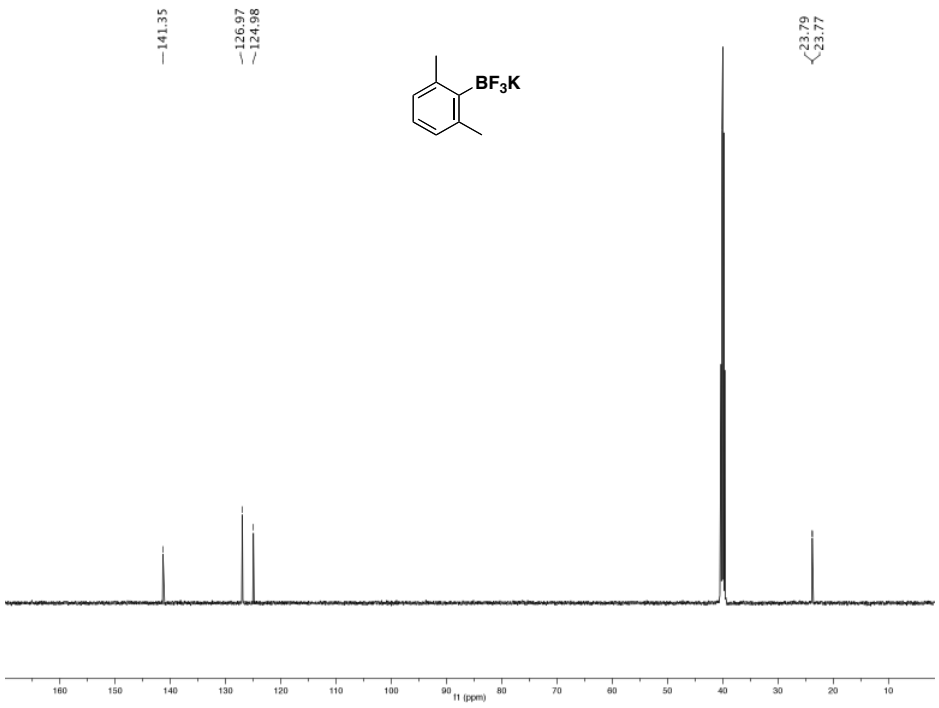

Figure A1.123 ^{13}C NMR (125.8 MHz, DMSO-d_6) (2,6-Dimethylphenyl)trifluoroborate

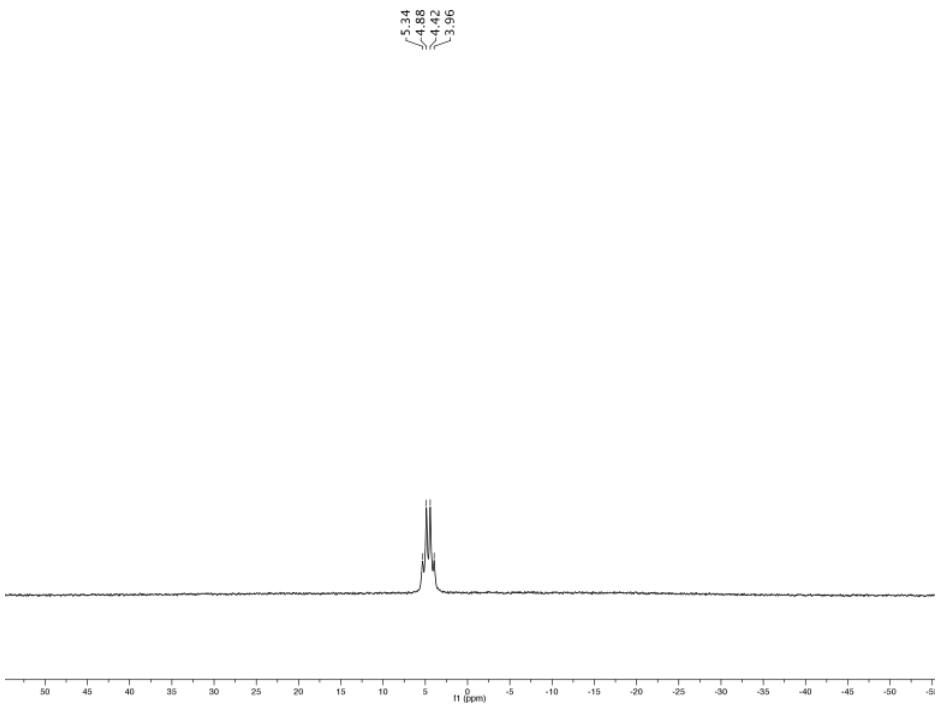

Figure A1.124 ^{11}B NMR (128.4 MHz, acetone-d_6) (2,6-Dimethylphenyl)trifluoroborate

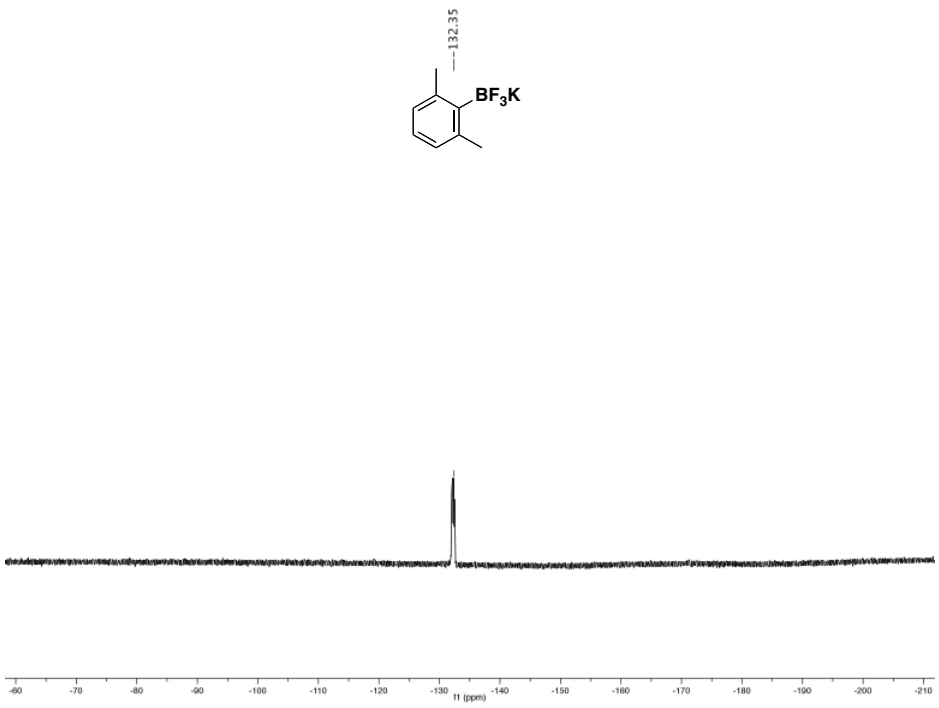

Figure A1.125 ^{19}F NMR (338.8 MHz, acetone-d_6) (2,6-Dimethylphenyl)trifluoroborate

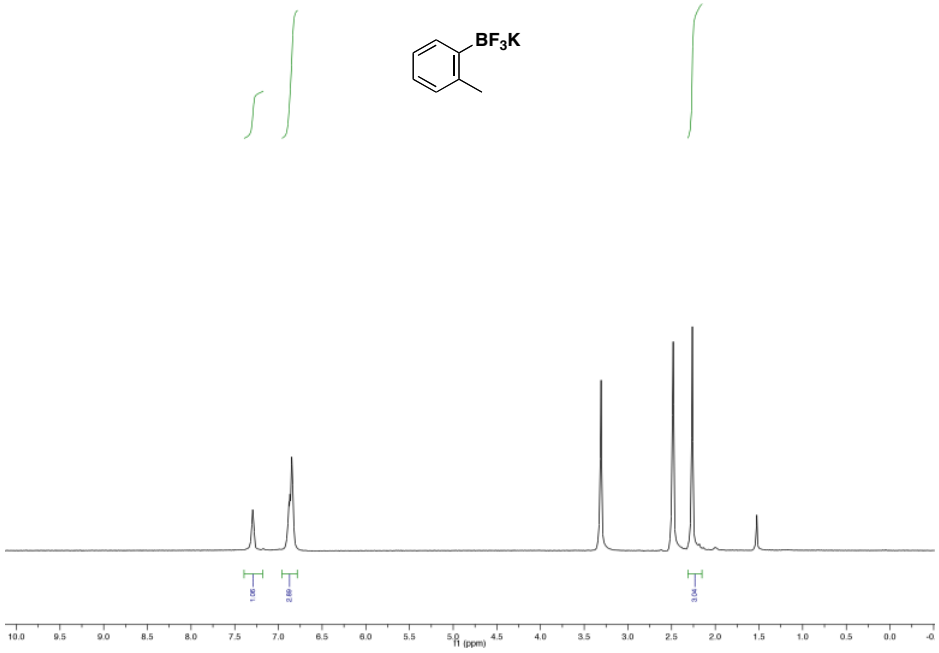

Figure A1.126 ^{1}H NMR (500 MHz, DMSO-d_6) Potassium *o*-Tolyltrifluoroborate

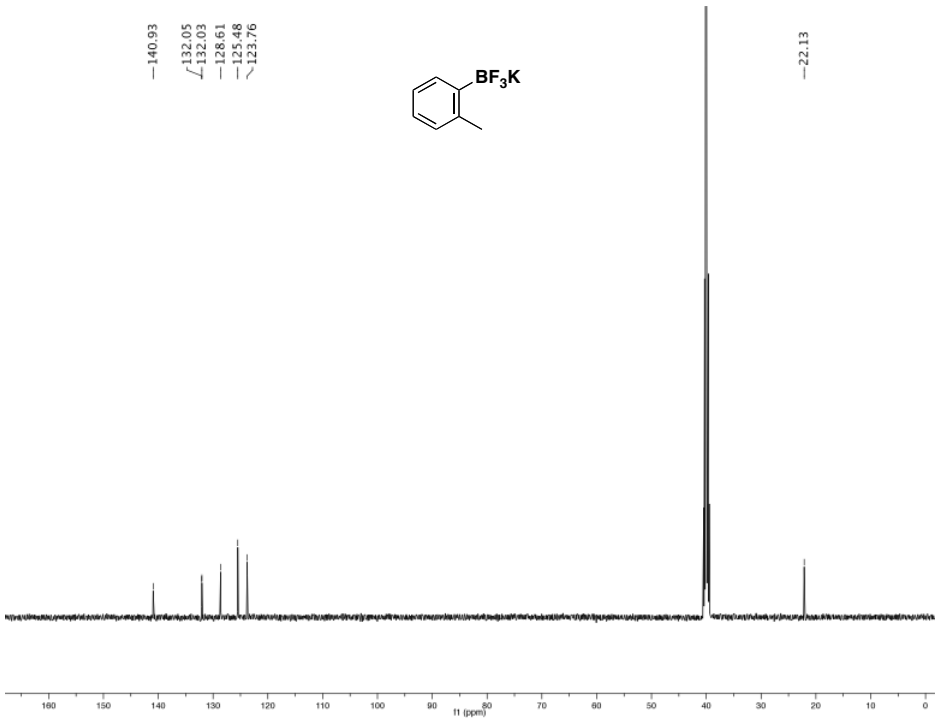

Figure A1.127 ^{13}C NMR 125.8 MHz, DMSO-d_6) Potassium *o*-Tolyltrifluoroborate

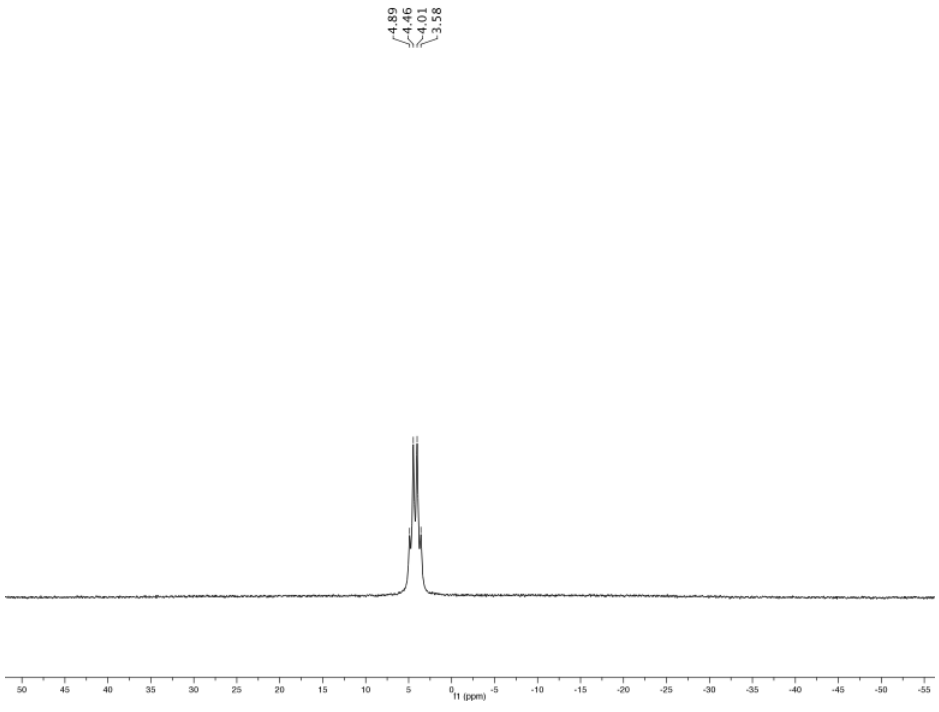

Figure A1.128 ^{11}B NMR (128.4 MHz, acetone-d_6) Potassium *o*-Tolyltrifluoroborate

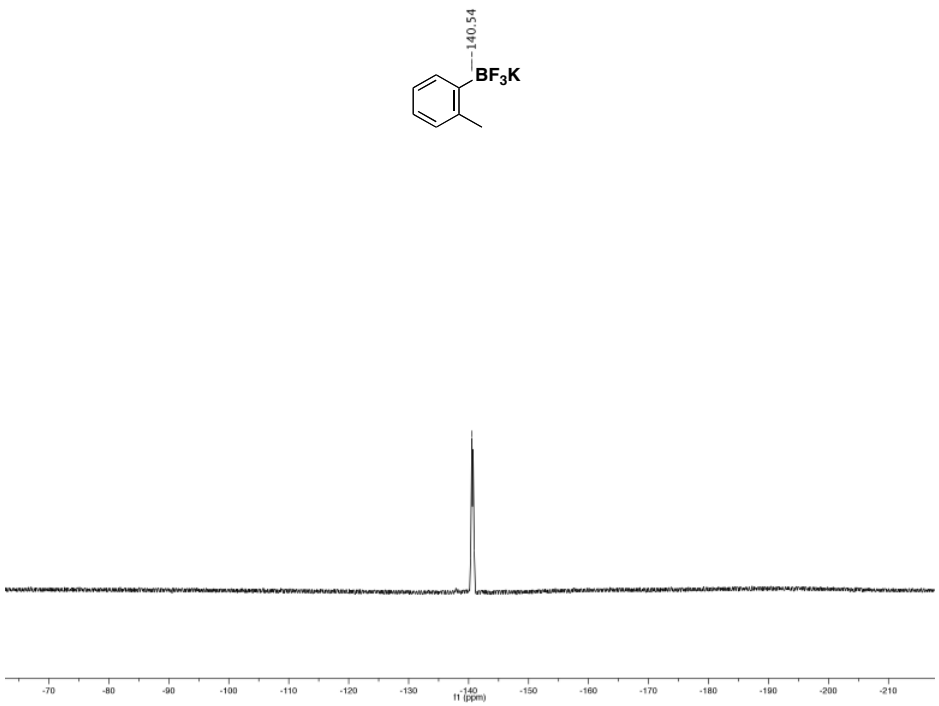

Figure A1.129 ^{19}F NMR (338.8 MHz, acetone-d_6) Potassium *o*-Tolyltrifluoroborate

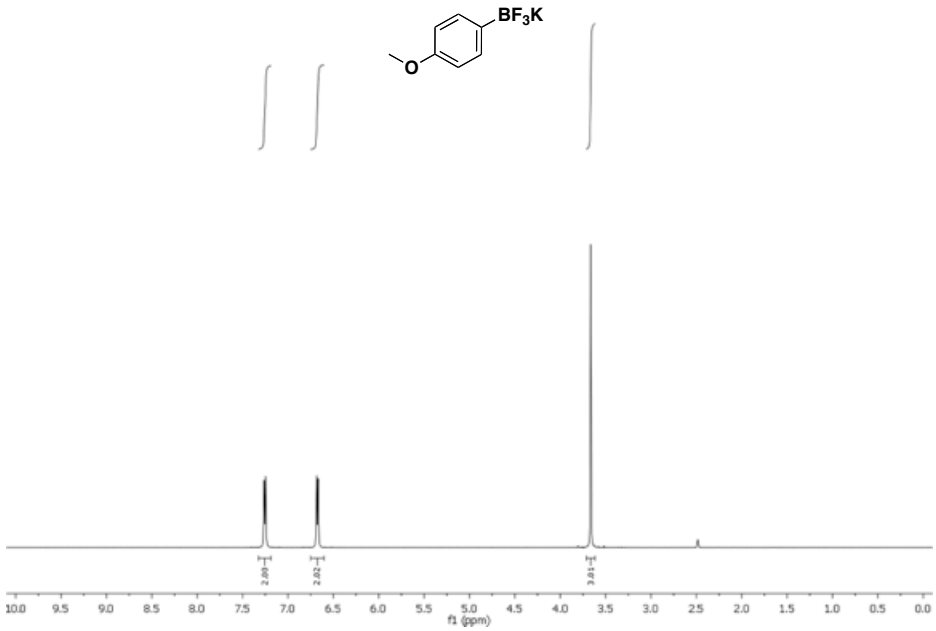

Figure A1.130 ^{1}H NMR Spectra (500 MHz, DMSO-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

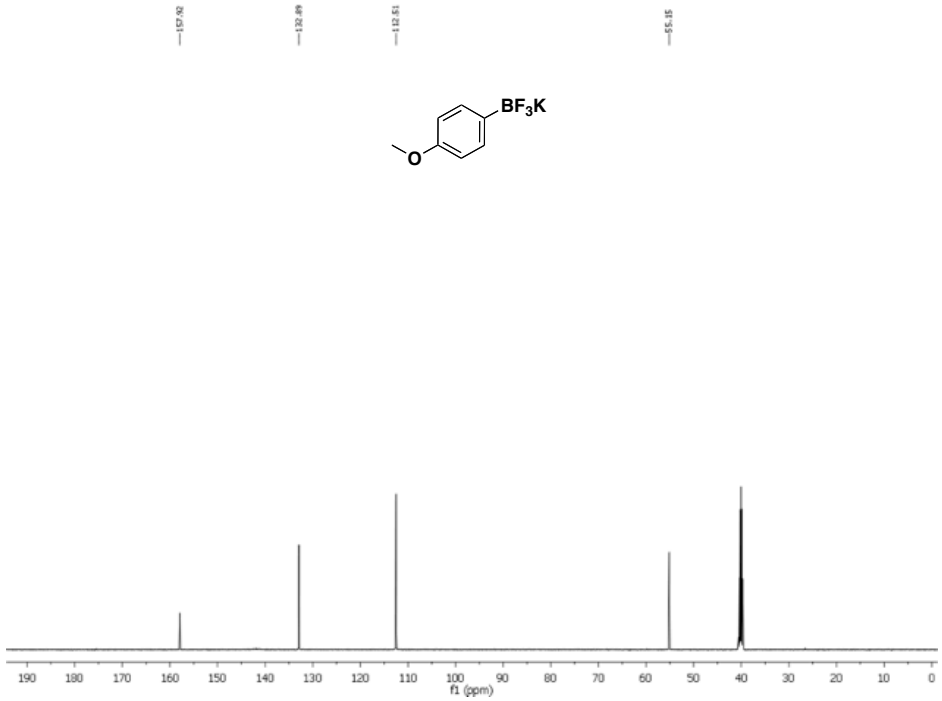

Figure A1.131 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

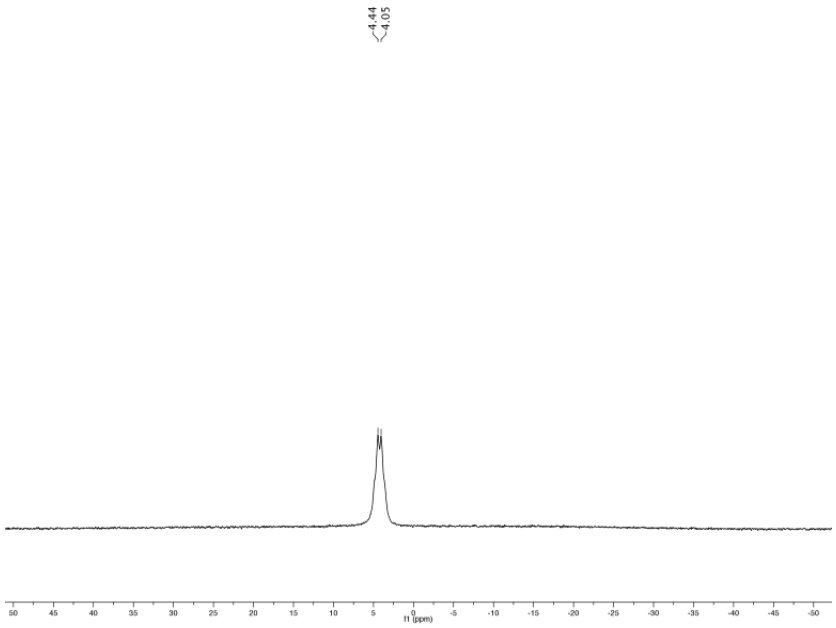

Figure A1.132 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

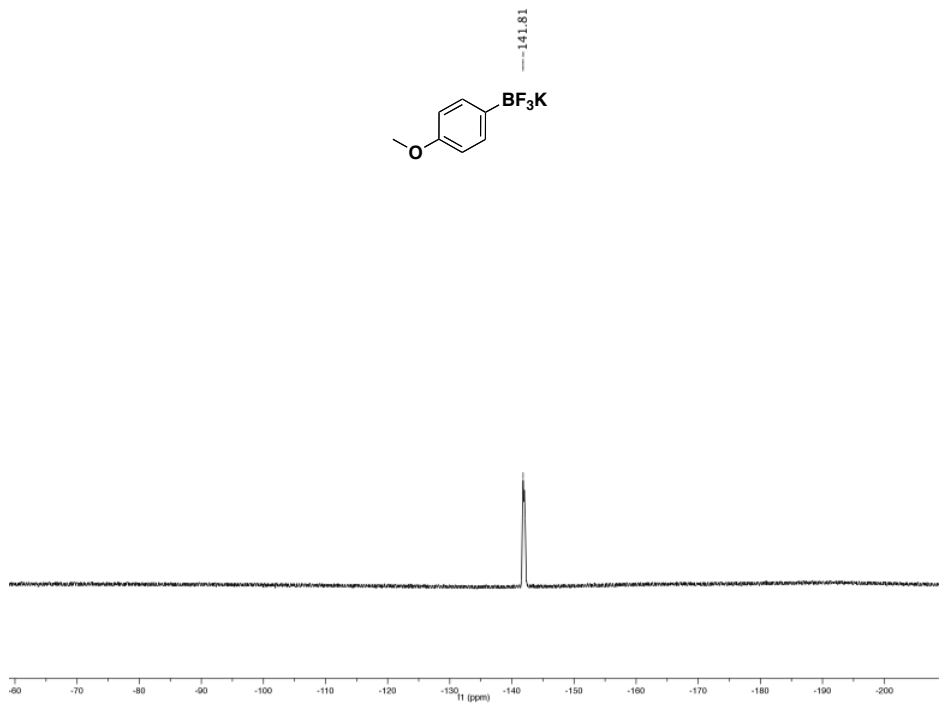

Figure A1.133 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

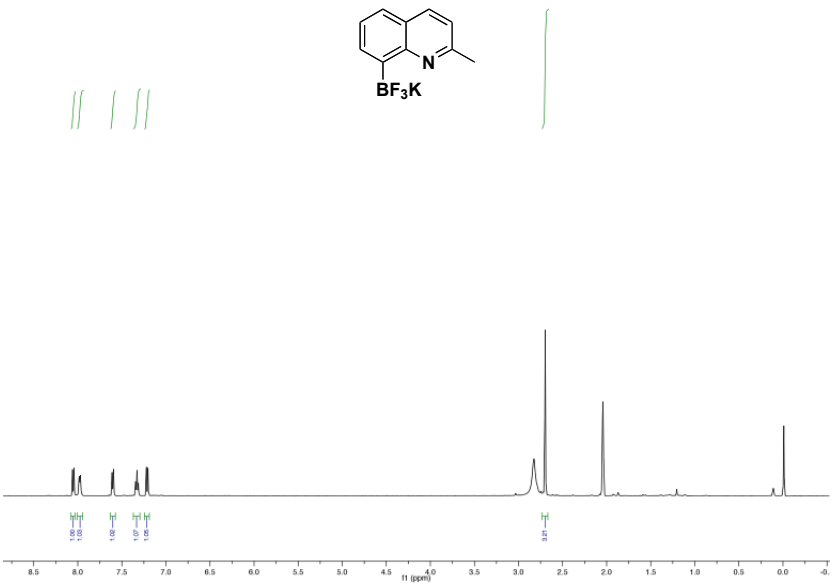

Figure A1.134 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (2-Methylquinolin-8-yl)trifluoroborate

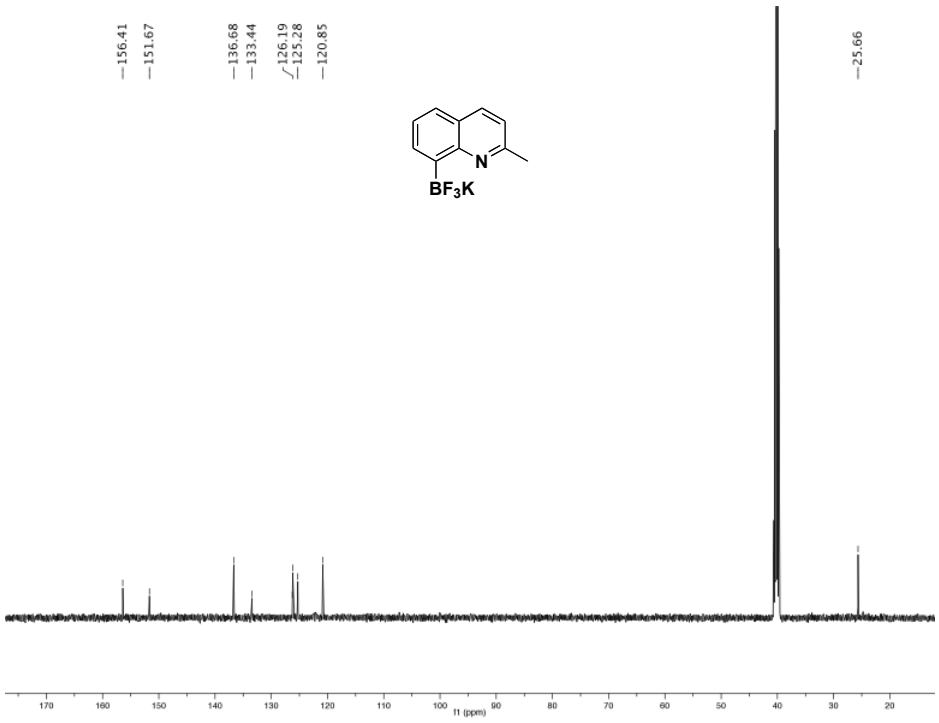

Figure A1.135 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (2-Methylquinolin-8-yl)trifluoroborate

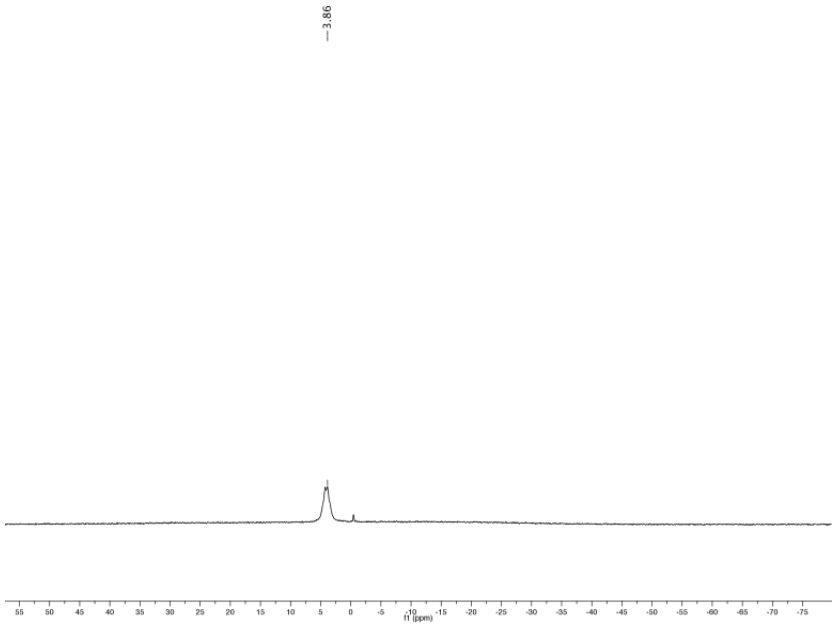

Figure A1.136 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (2-Methylquinolin-8-yl)trifluoroborate

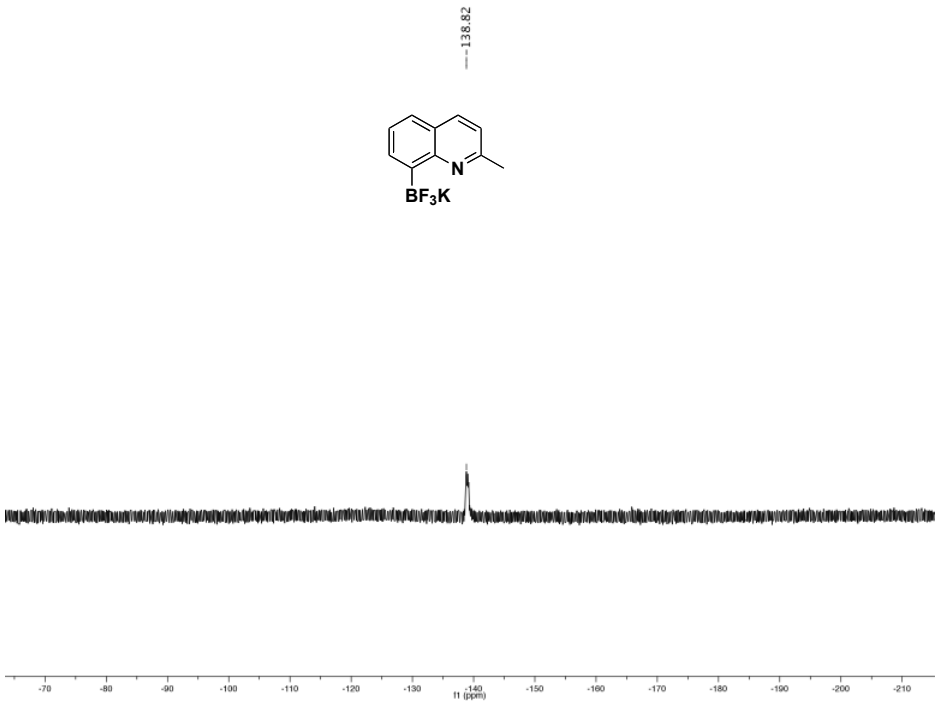

Figure A1.137 ^{19}F NMR Spectra (282 MHz, acetone-d_6) Potassium (2-Methylquinolin-8-yl)trifluoroborate

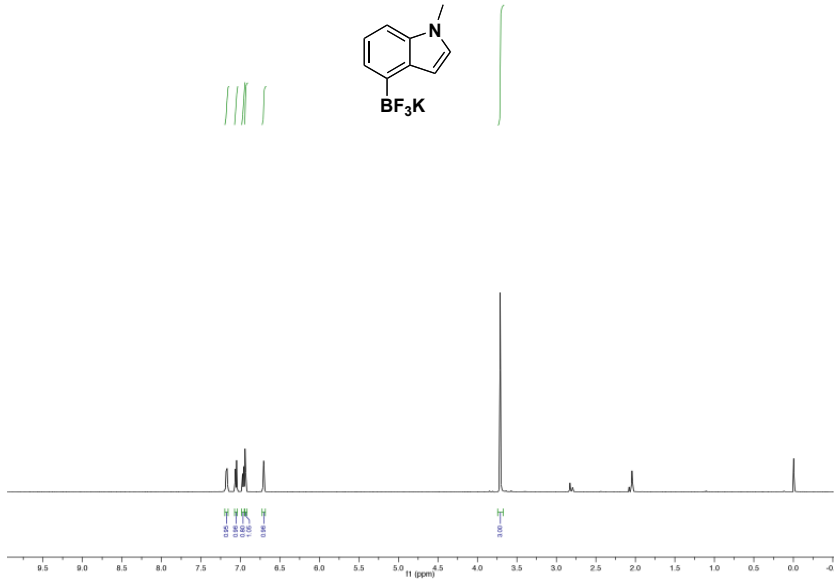

Figure A1.138 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (2-Methylquinolin-8-yl)trifluoroborate

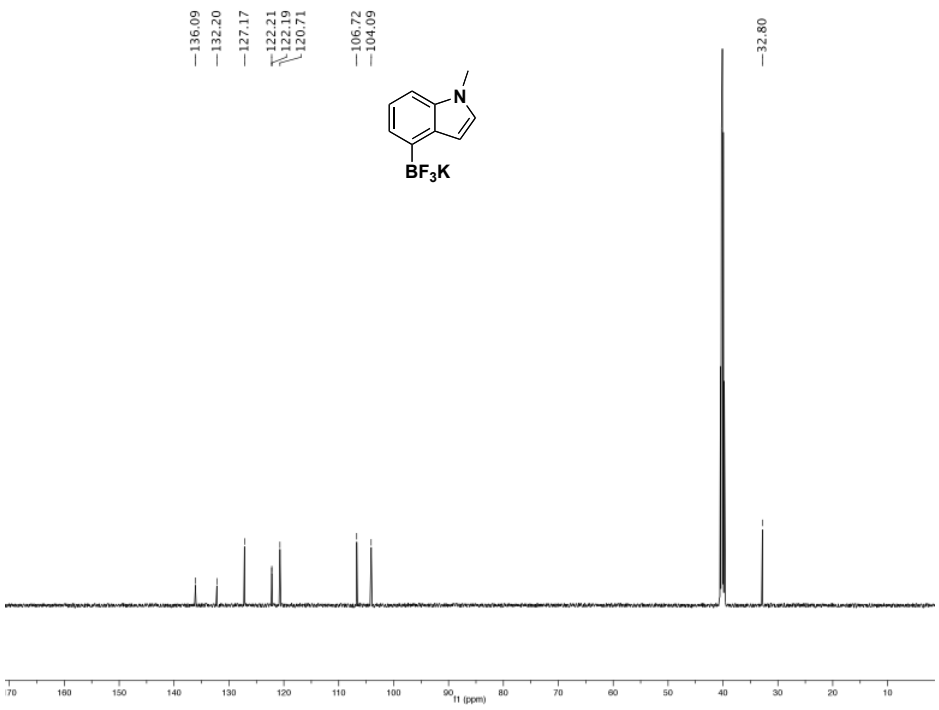

Figure A1.139 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (2-Methylquinolin-8-yl)trifluoroborate

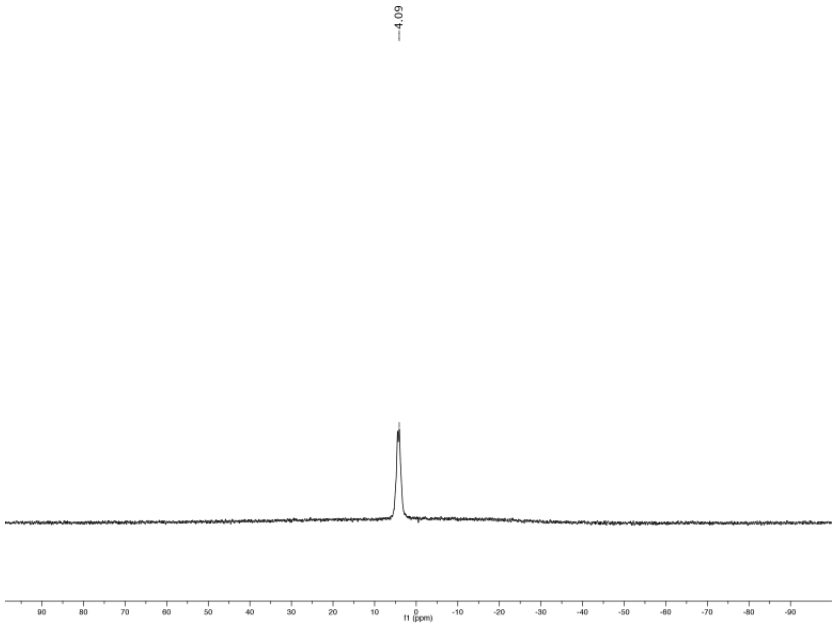

Figure A1.140 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (2-Methylquinolin-8-yl)trifluoroborate

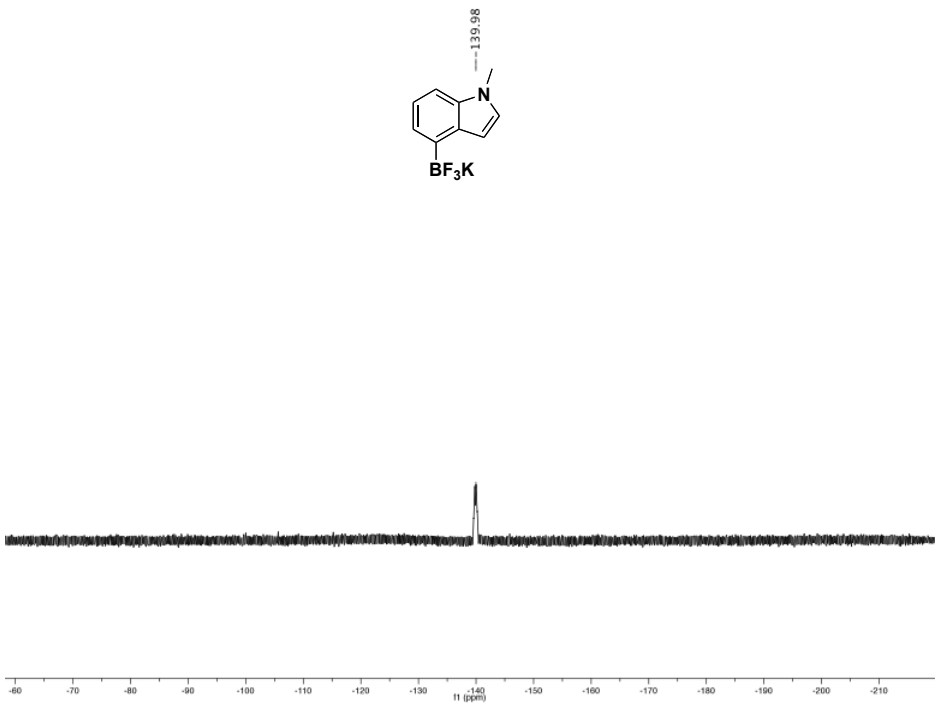

Figure A1.141 ^{19}F NMR Spectra (282 MHz, acetone-d_6) Potassium (2-Methylquinolin-8-yl)trifluoroborate

Appendix A2. ^{1}H, ^{13}C, ^{11}B, and ^{19}F Spectra Relevant to Chapter 4

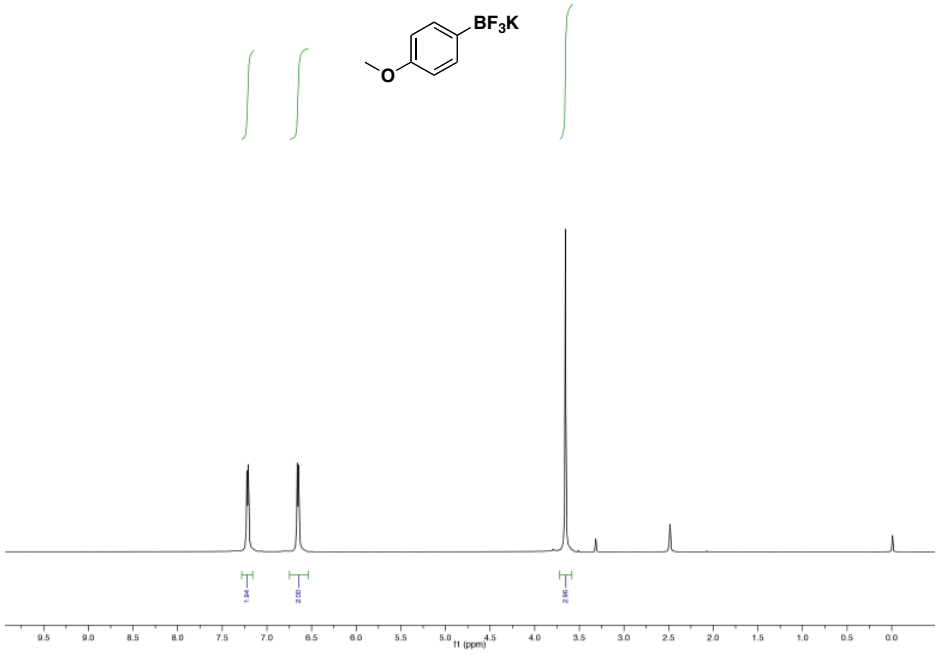

Figure A2.1 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

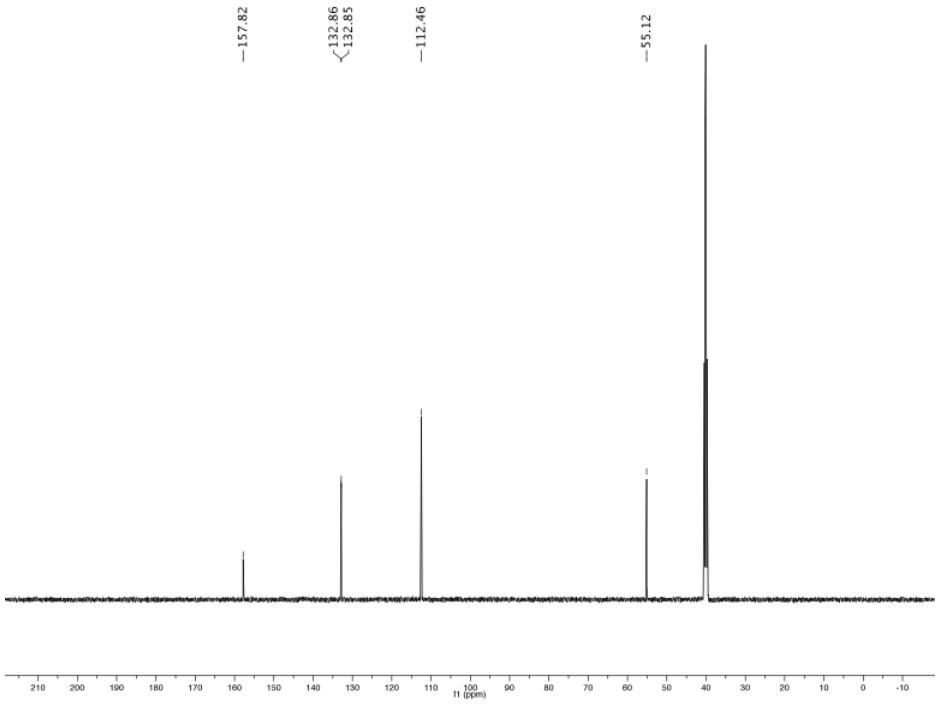

Figure A2.2 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

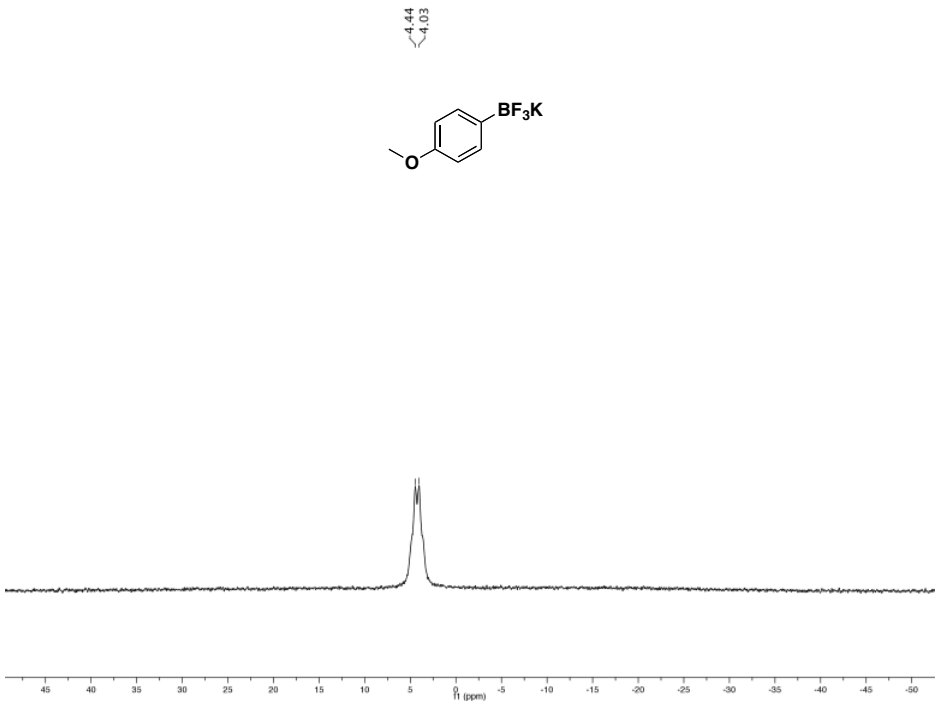

Figure A2.3 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

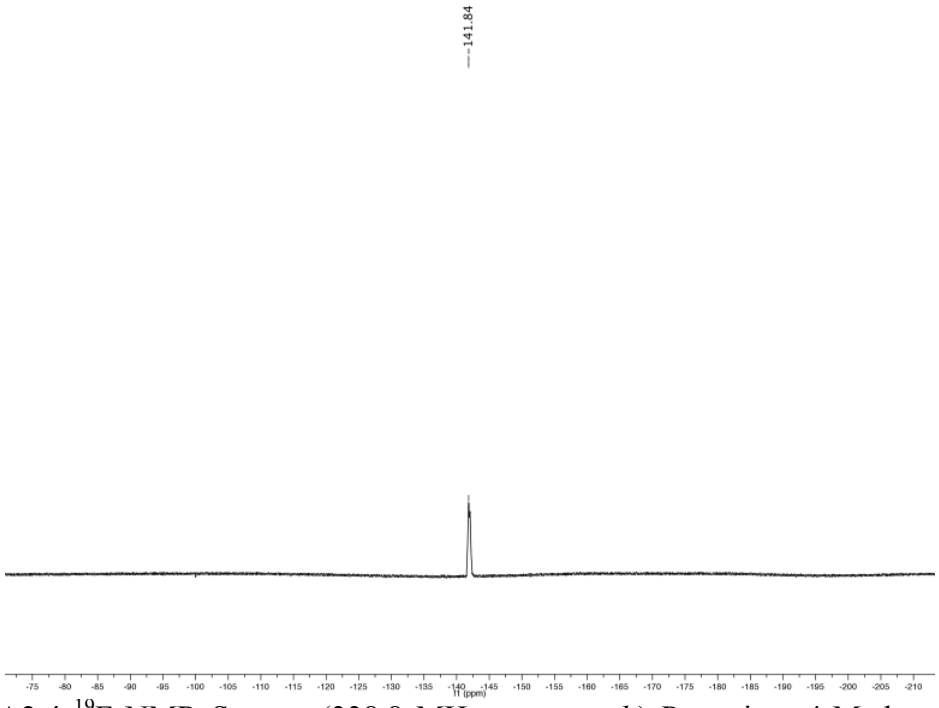

Figure A2.4 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

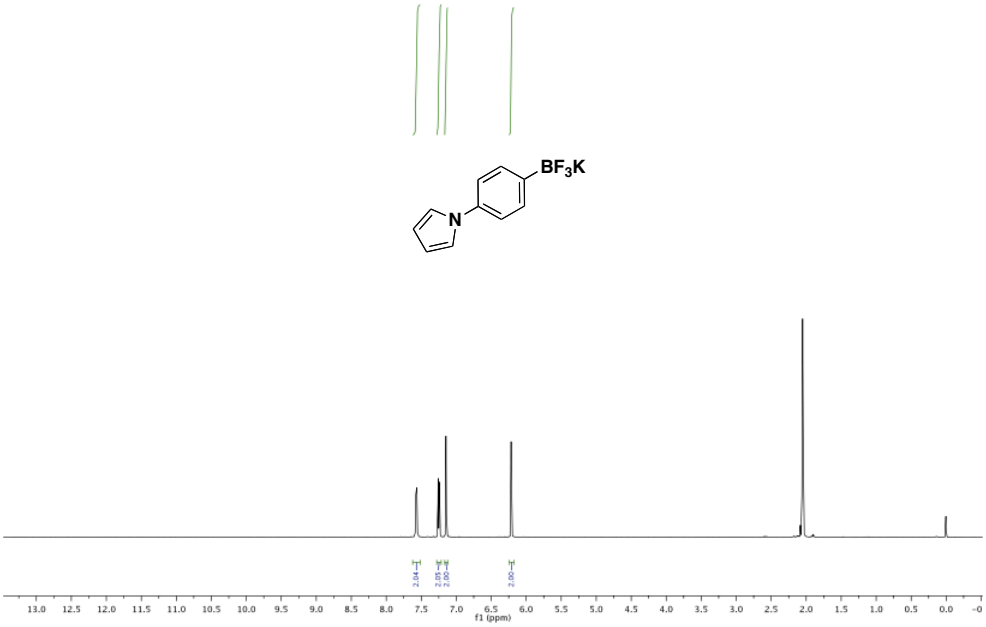

Figure A2.5 ^{1}H NMR Spectra (500 MHz, DMSO-d_6) Potassium 4-(1H-Pyrrol-1-yl)phenyl-trifluoroborate

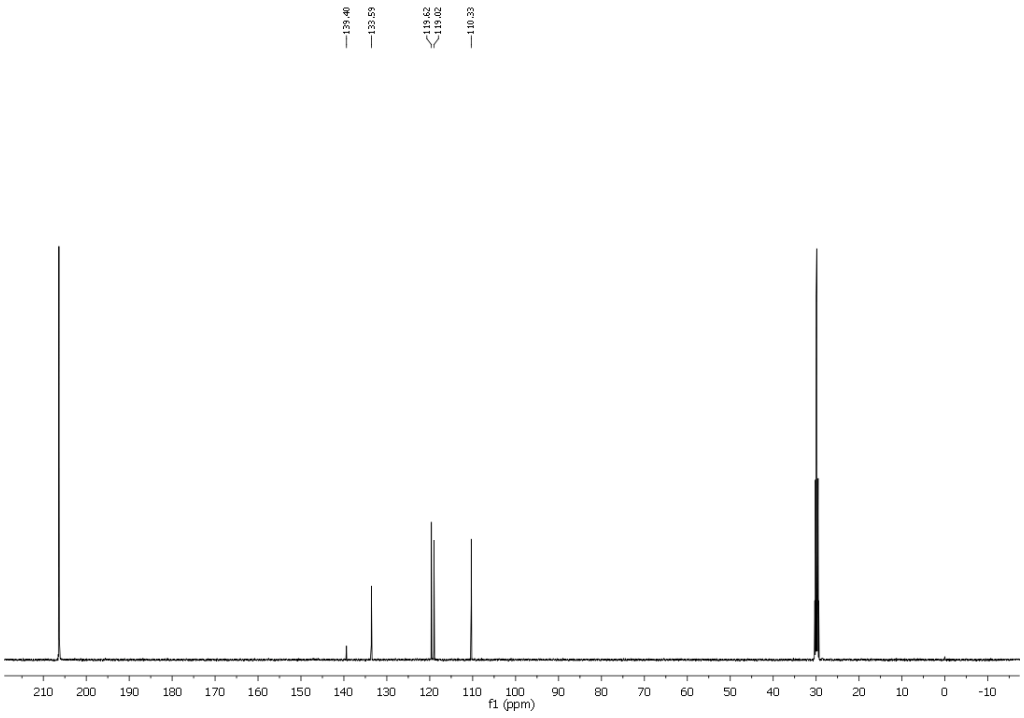

Figure A2.6 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium 4-(1H-Pyrrol-1-yl)phenyl-trifluoroborate

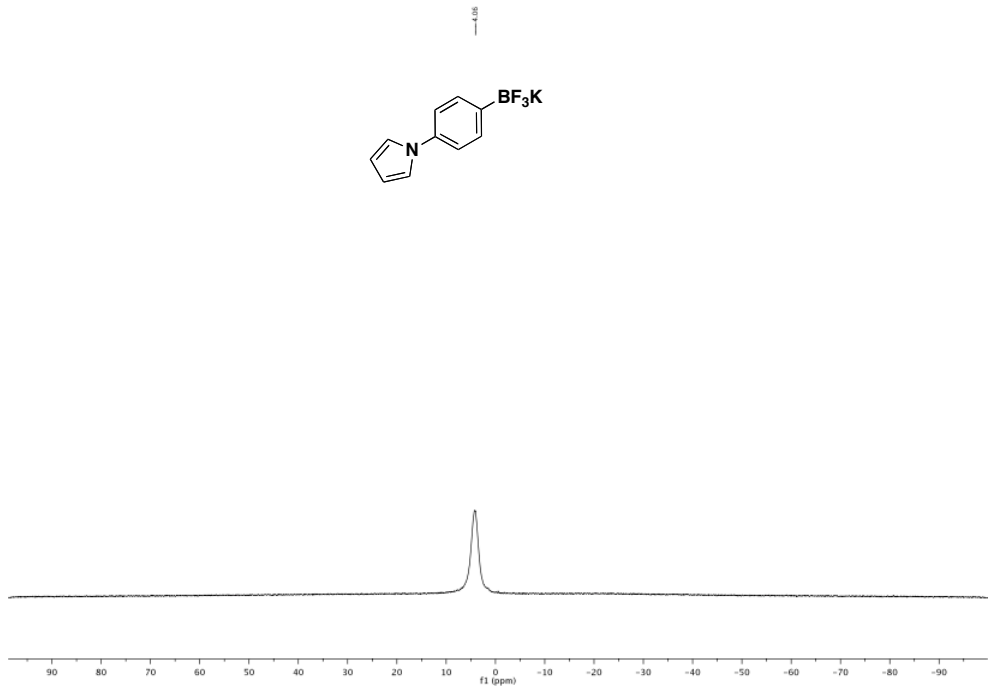

Figure A2.7 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium 4-(1H-Pyrrol-1-yl)phenyl-trifluoroborate

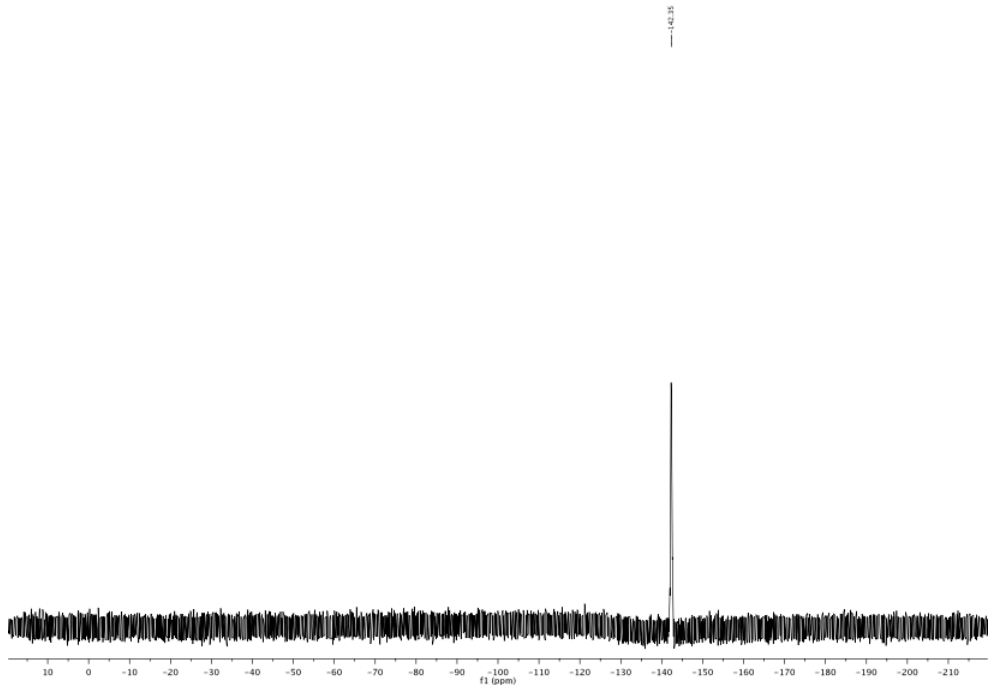

Figure A2.8 ^{19}F NMR Spectra (282 MHz, acetone-d_6) Potassium 4-(1H-Pyrrol-1-yl)phenyl-trifluoroborate

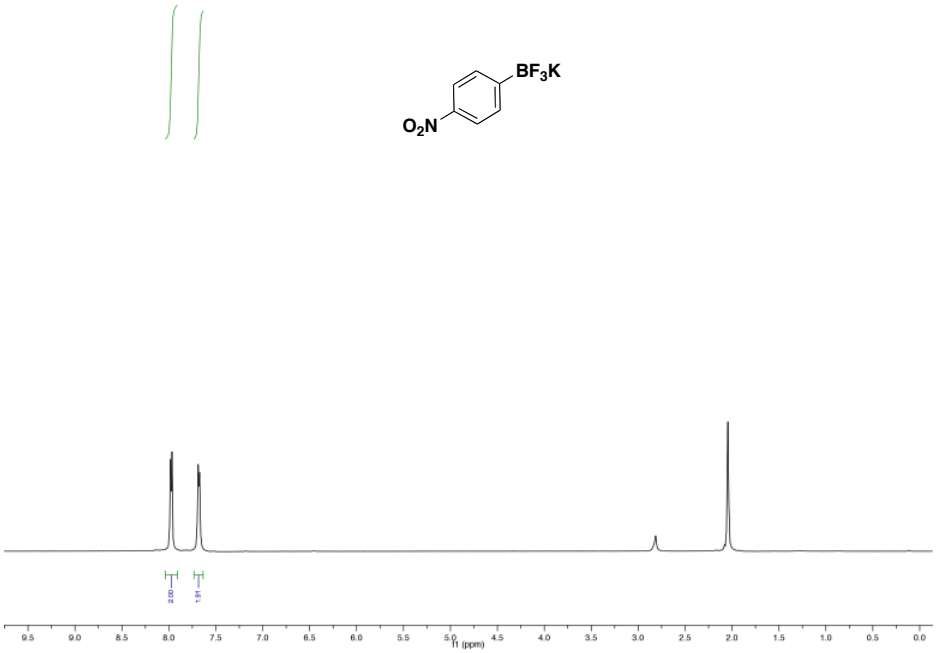

Figure A2.9 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (4-Nitrophenyl)trifluoroborate

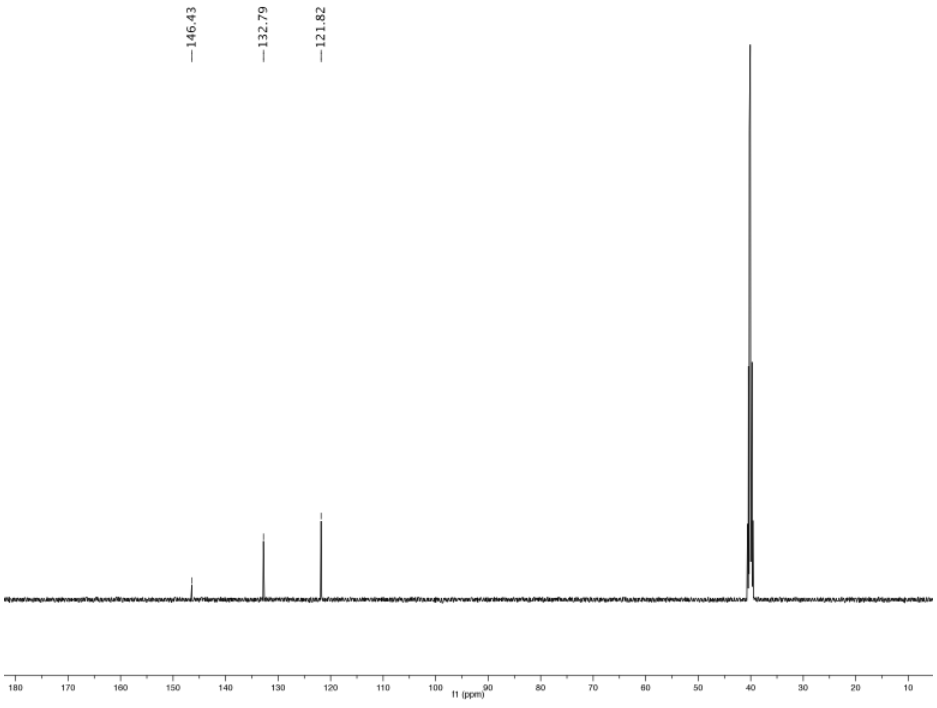

Figure A2.10 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (4-Nitrophenyl)trifluoroborate

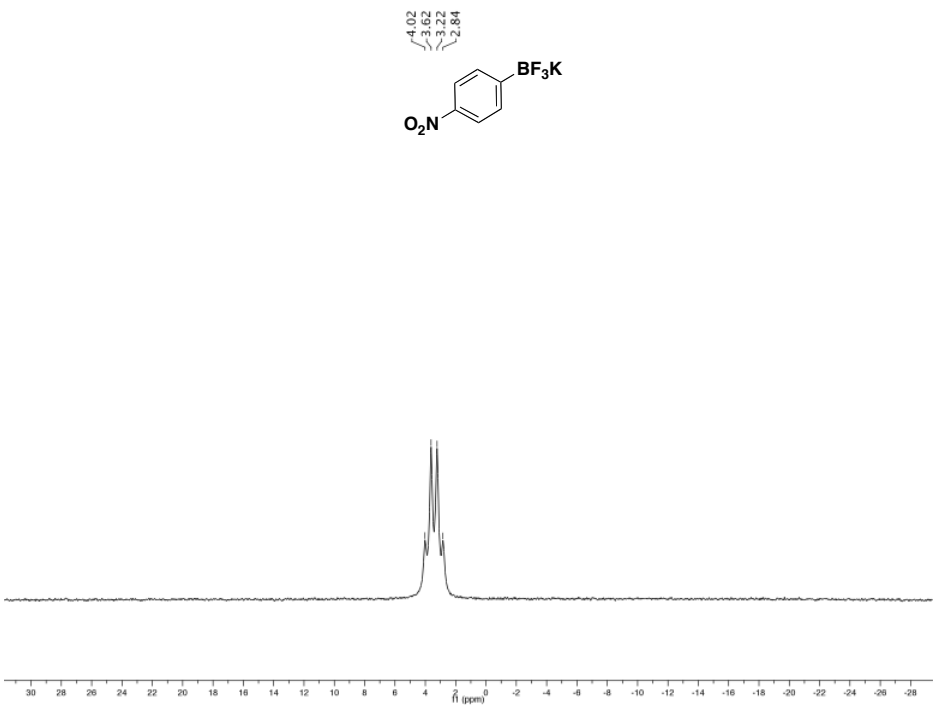

Figure A2.11 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (4-Nitrophenyl)trifluoroborate

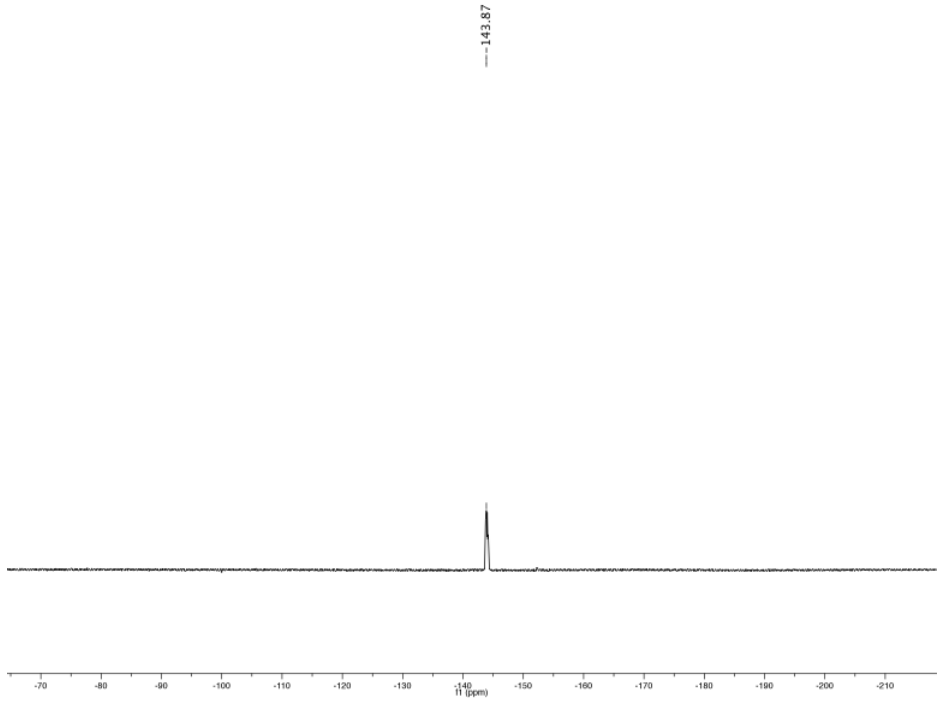

Figure A2.12 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (4-Nitrophenyl)trifluoroborate

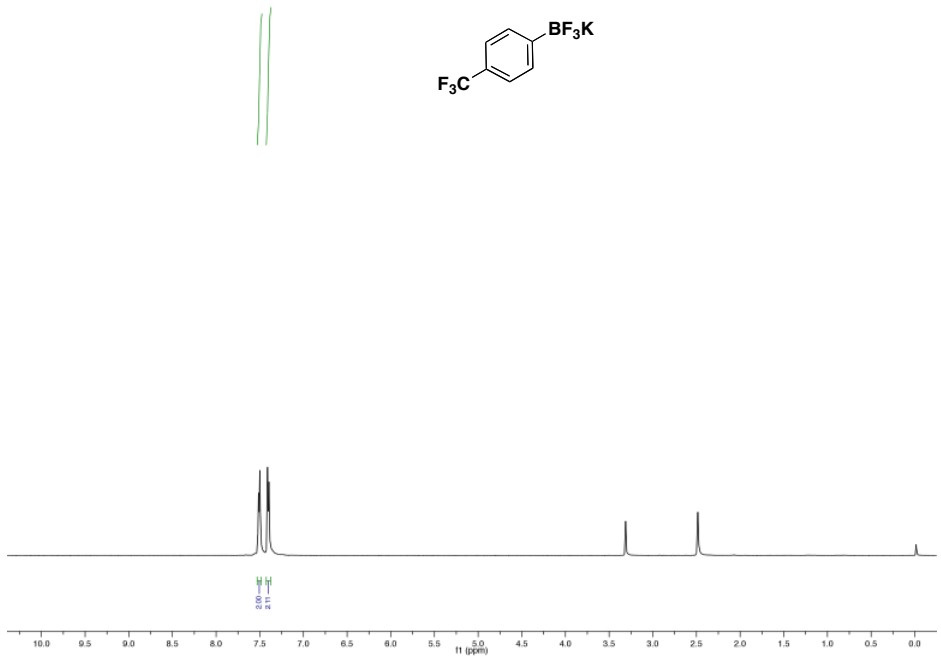

Figure A2.13 ^{1}H NMR Spectra (500 MHz, DMSO-d_6) Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate

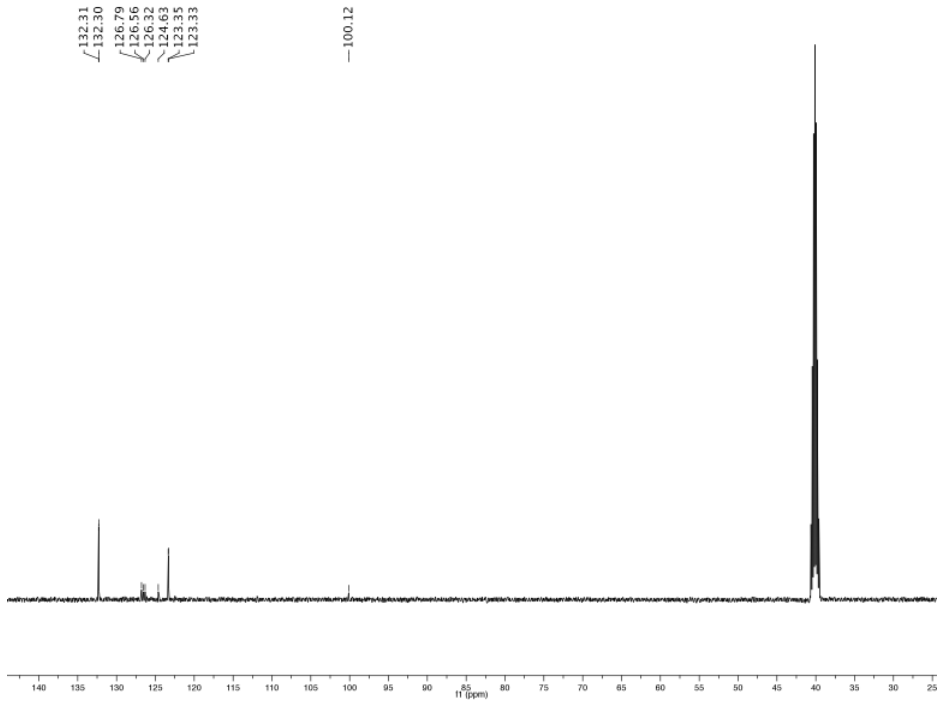

Figure A2.14 ^{13}C NMR Spectra (125.8 Hz, DMSO-d_6) Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate

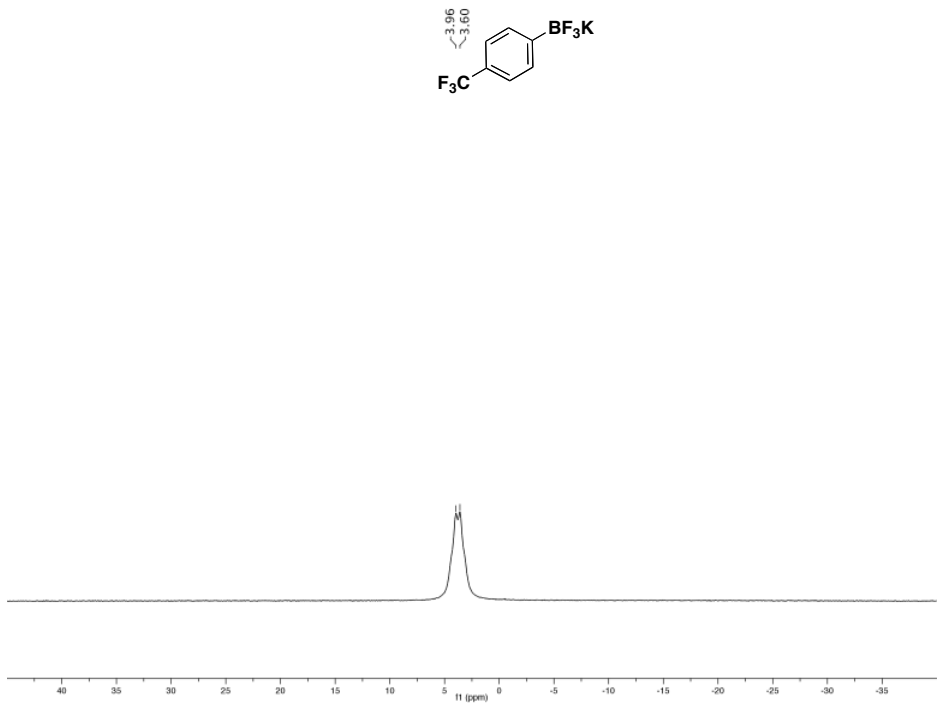

Figure A2.15 ^{11}B NMR (128.4 MHz, acetone-d_6) Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate

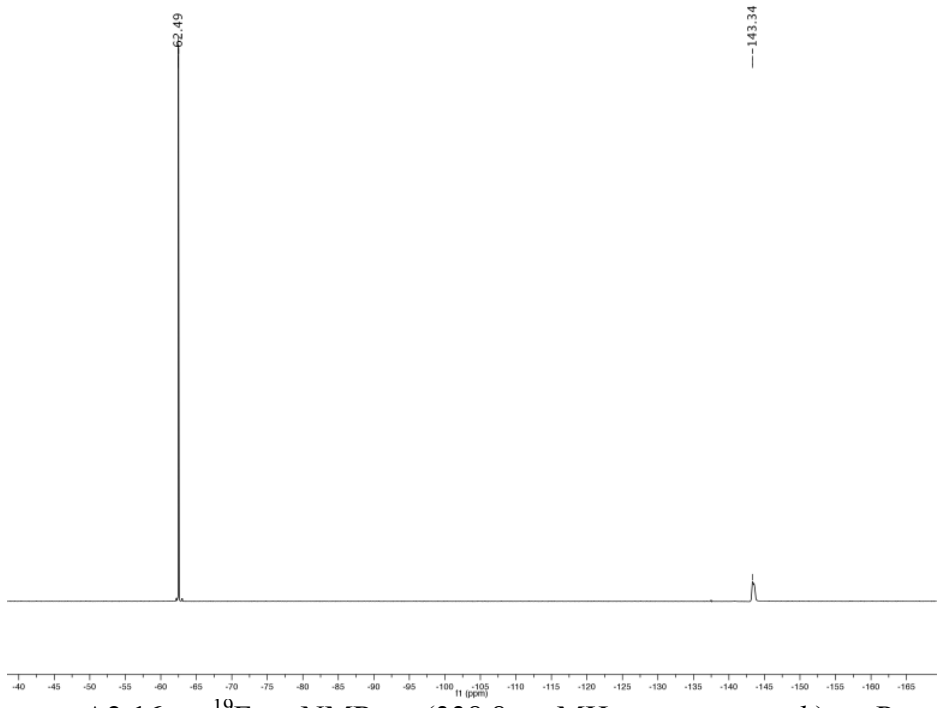

Figure A2.16 ^{19}F NMR (338.8 MHz, acetone-d_6) Potassium (4-(Trifluoromethyl)phenyl)trifluoroborate

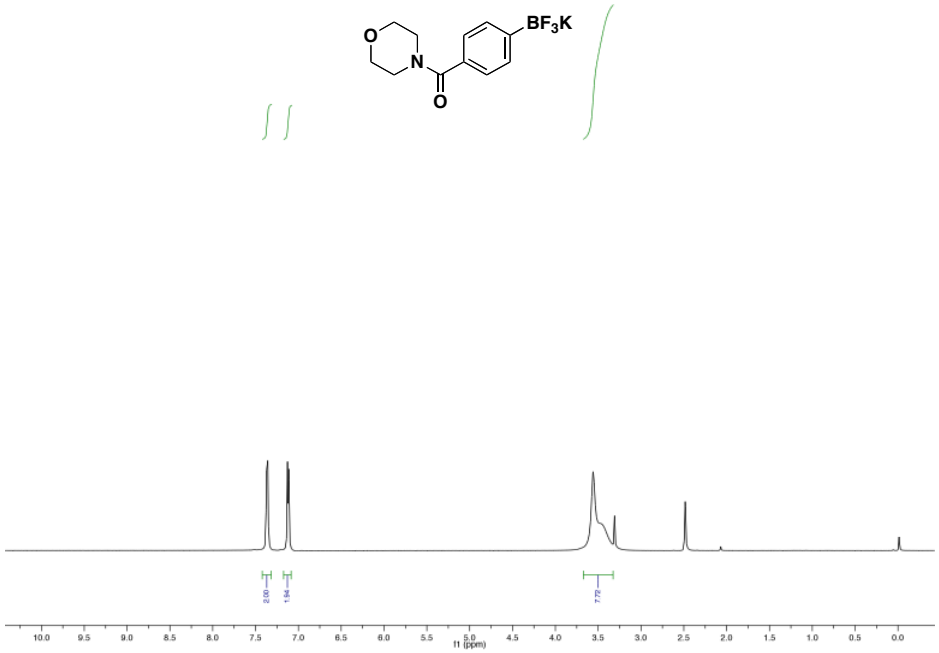

Figure A2.17 ^{1}H NMR Spectra (500 MHz, DMSO-d_6) Potassium 4-(Morpholine-4-carbonyl)phenyl-trifluoroborate

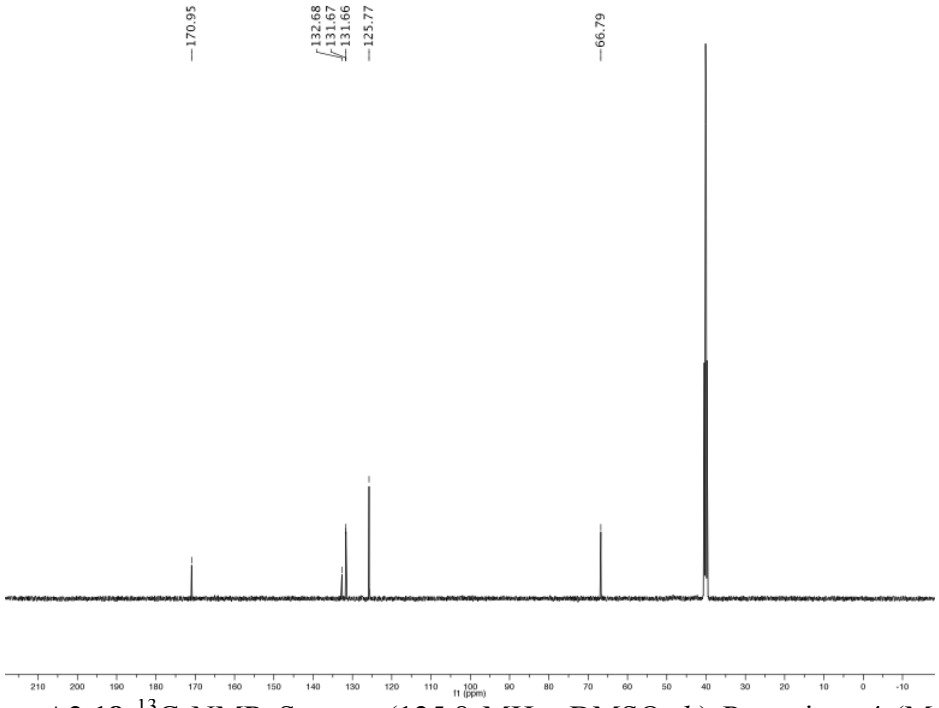

Figure A2.18 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium 4-(Morpholine-4-carbonyl)phenyl-trifluoroborate

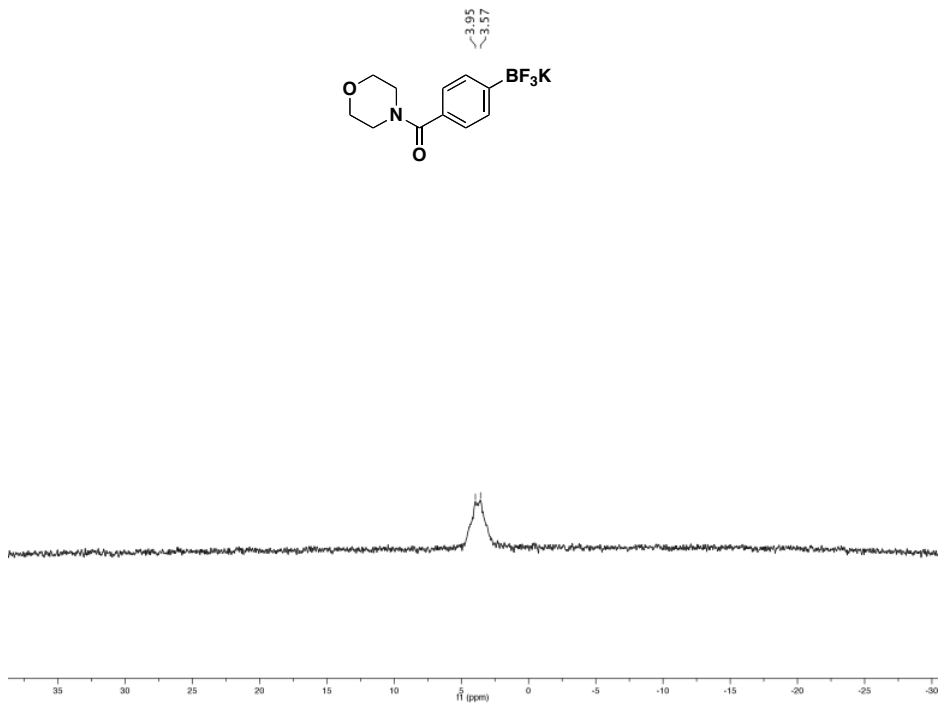

Figure A2.19 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium 4-(Morpholine-4-carbonyl)phenyl-trifluoroborate

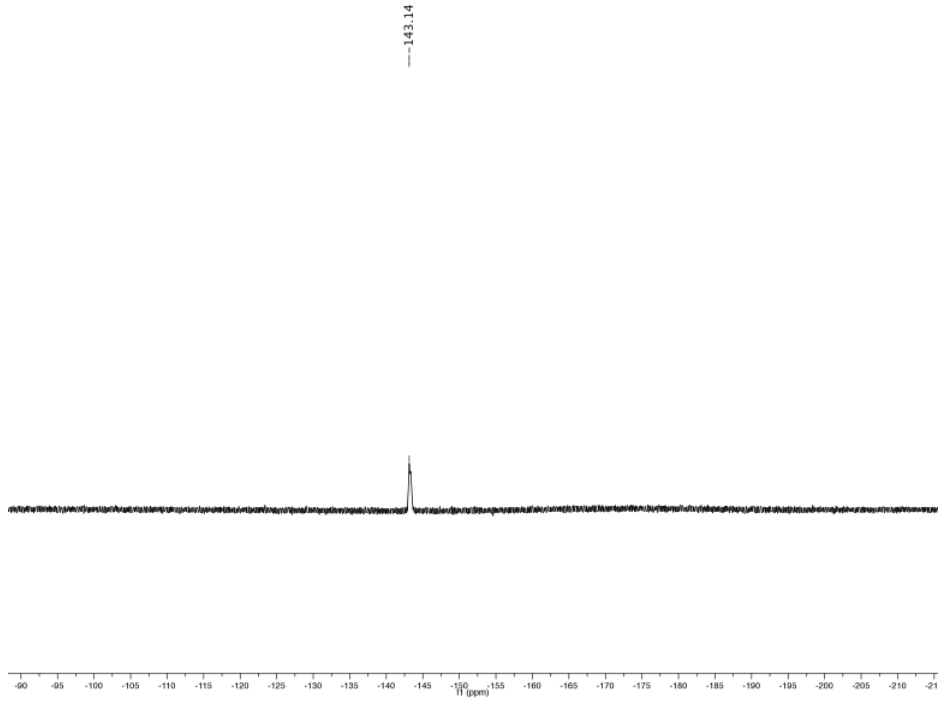

Figure A2.20 ^{19}F NMR Spectra (338.8 MHz, DMSO-d_6) Potassium 4-(Morpholine-4-carbonyl)phenyl-trifluoroborate

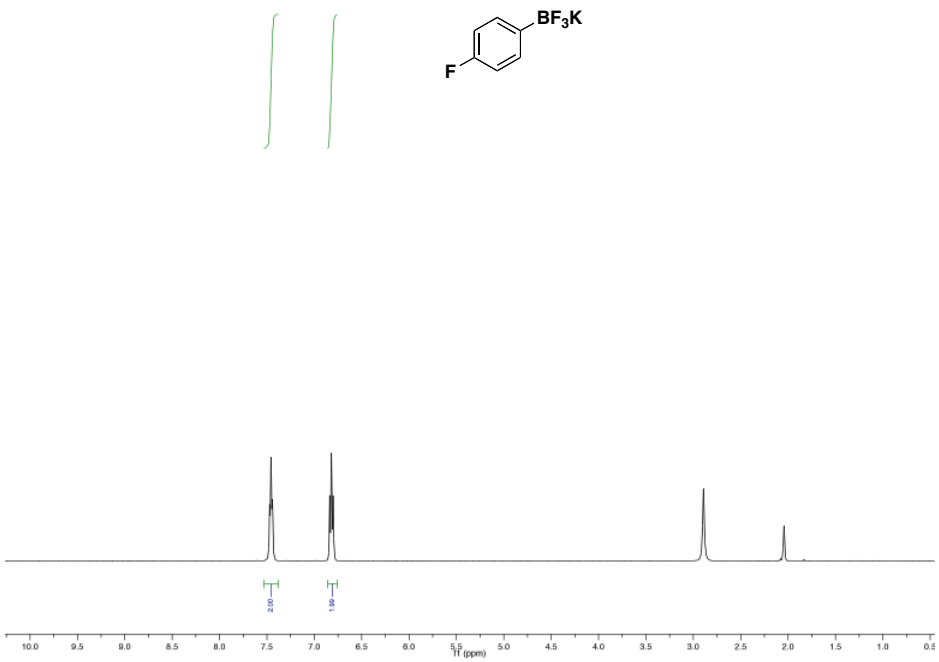

Figure A2.21 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (4-Fluorophenyl)trifluoroborate

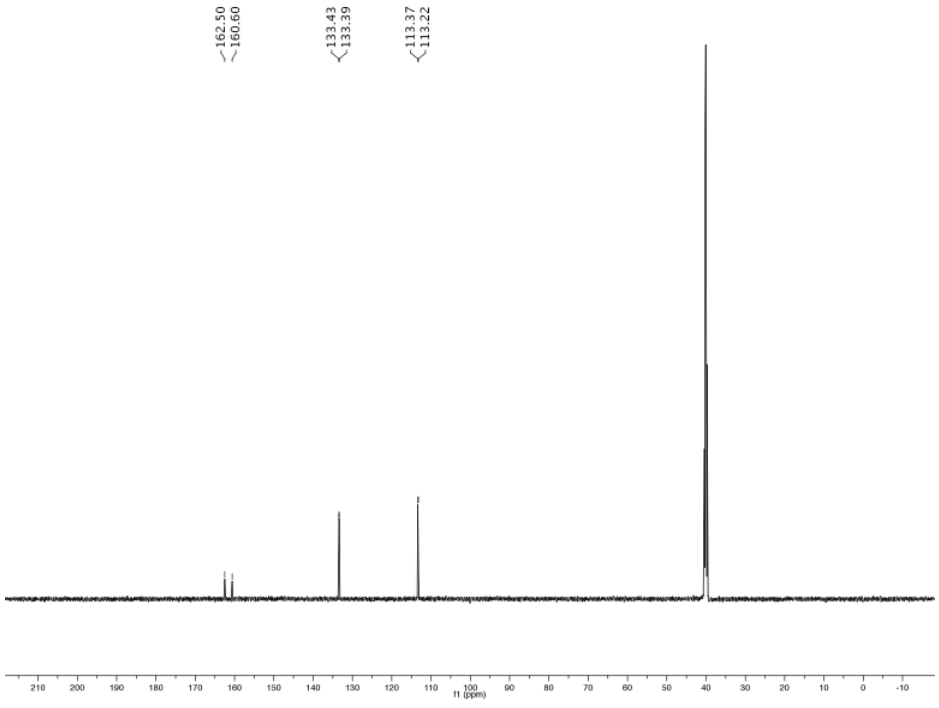

Figure A2.22 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (4-Fluorophenyl)trifluoroborate

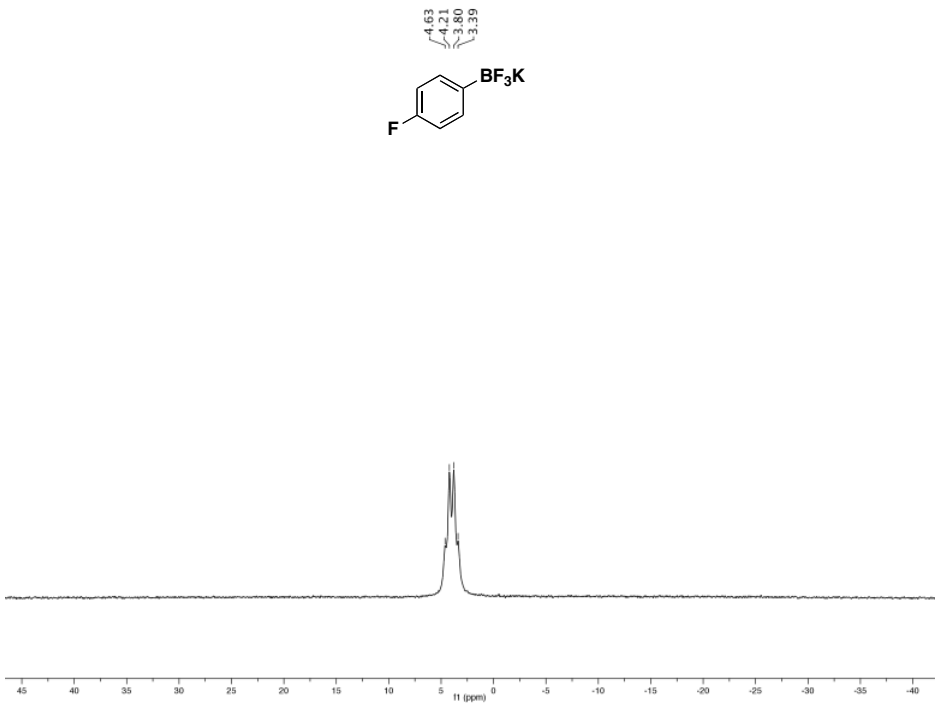

Figure A2.23 ^{11}B NMR (128.4 MHz, acetone-d_6) Potassium (4-Fluorophenyl)trifluoroborate

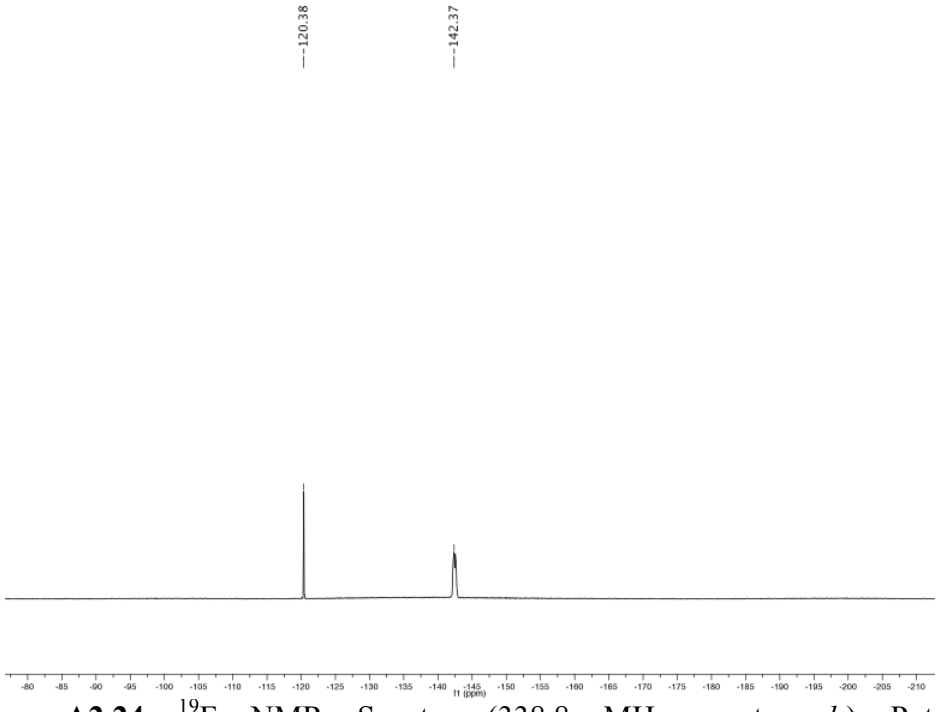

Figure A2.24 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (4-Fluorophenyl)trifluoroborate

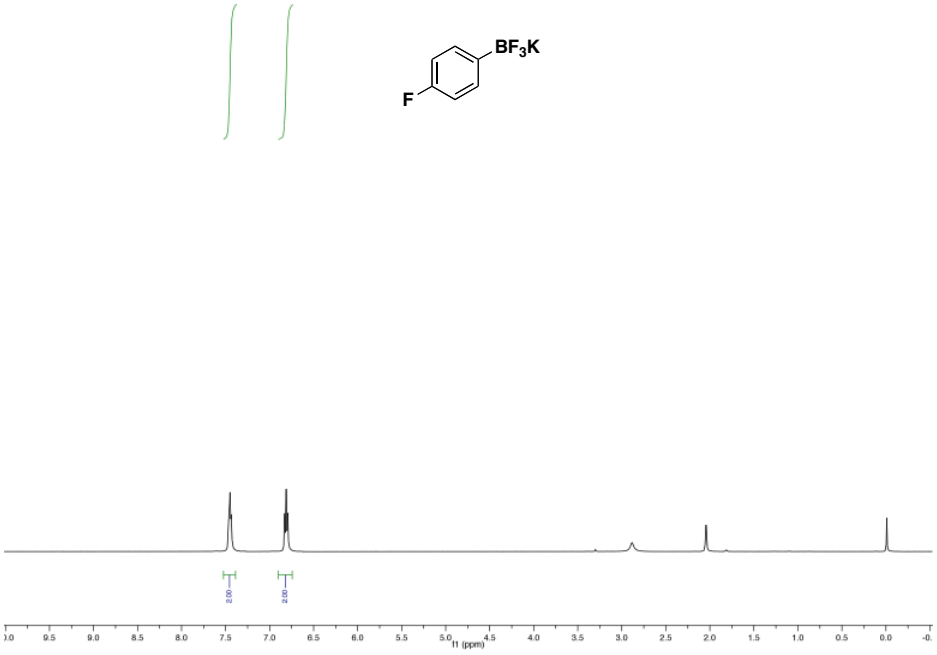

Figure A2.25 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (4-Fluorophenyl)trifluoroborate

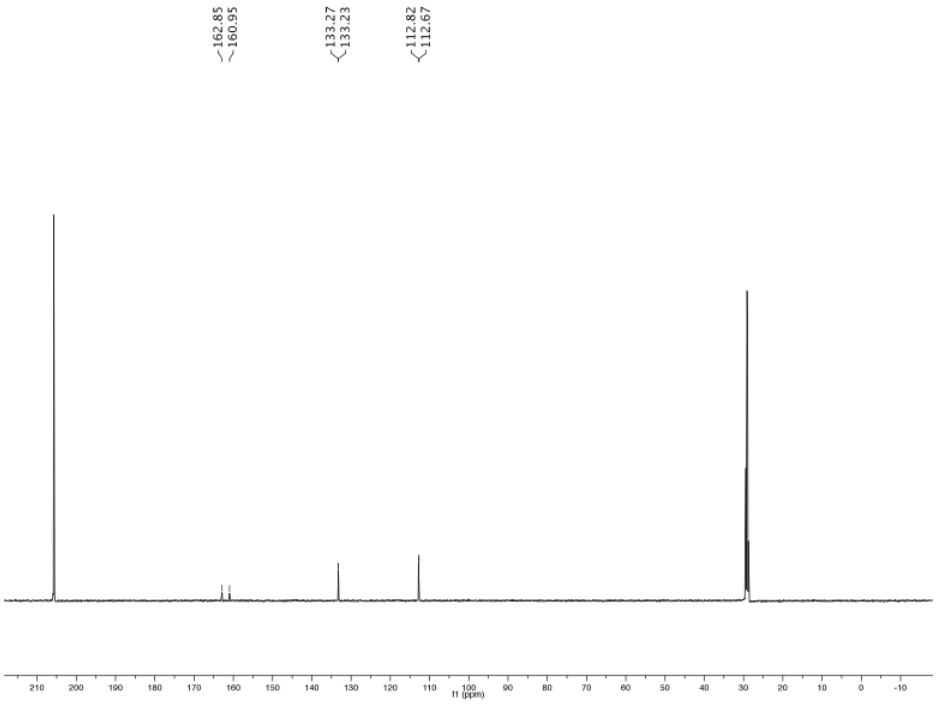

Figure A2.26 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (4-Fluorophenyl)trifluoroborate

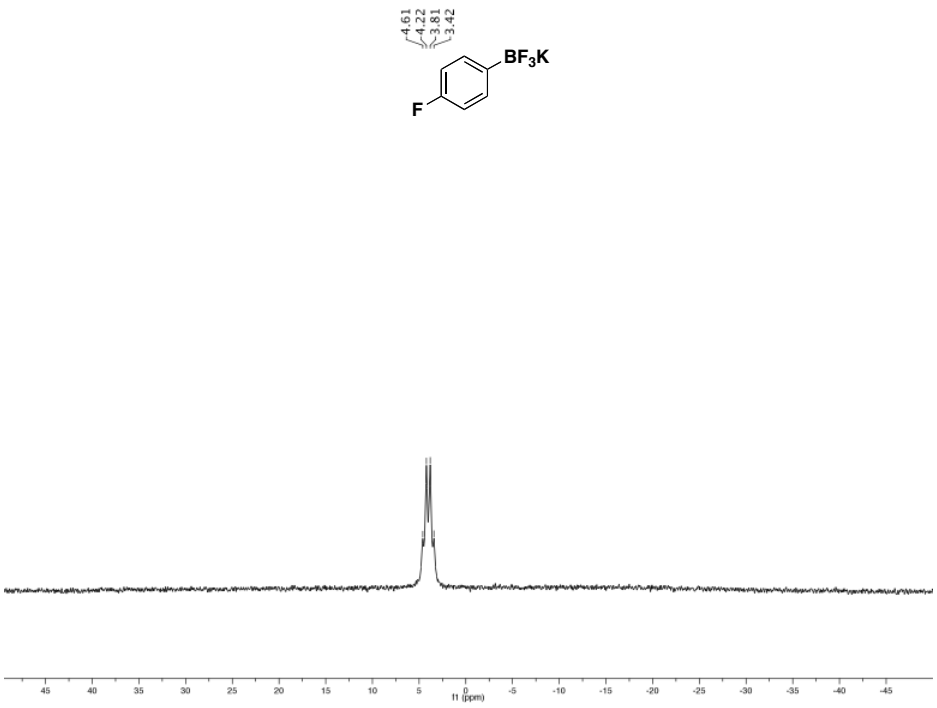

Figure A2.27 ^{11}B NMR (128.4 MHz, acetone-d_6) Potassium (4-Fluorophenyl)trifluoroborate

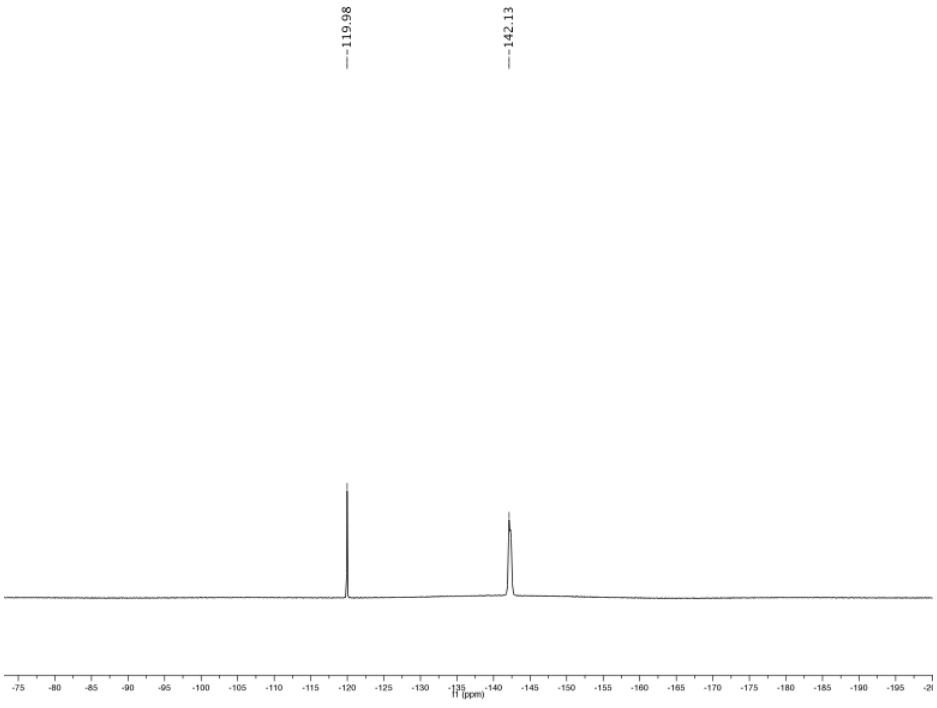

Figure A2.28 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (4-Fluorophenyl)trifluoroborate

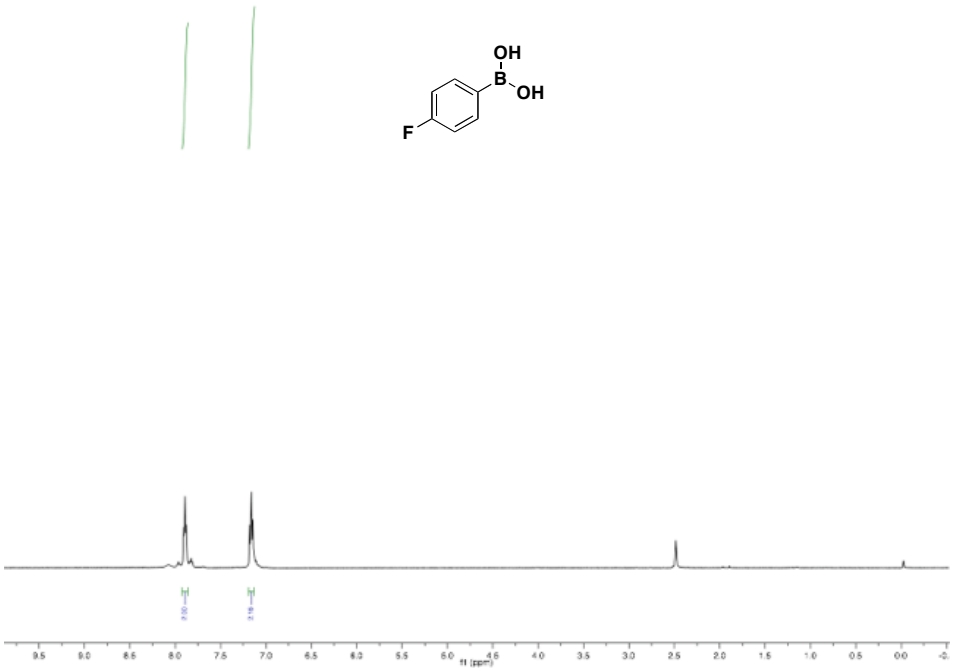

Figure A2.29 ^{1}H NMR Spectra (500 MHz, acetone-d_6) (4-Fluorophenyl)boronic acid

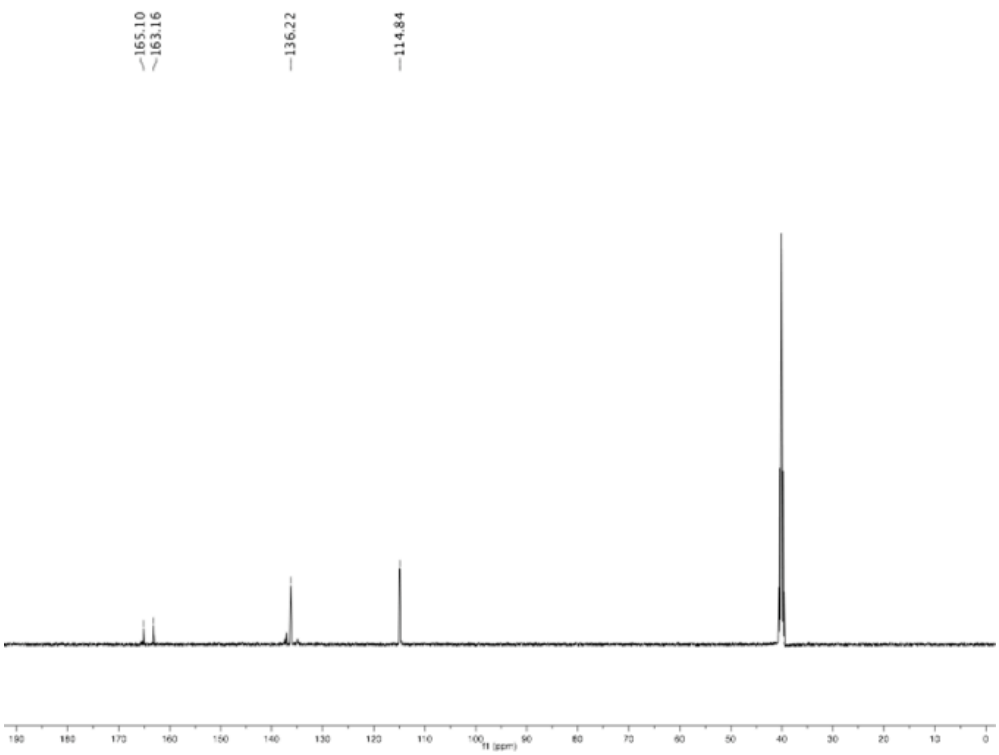

Figure A2.30 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) (4-Fluorophenyl)boronic acid

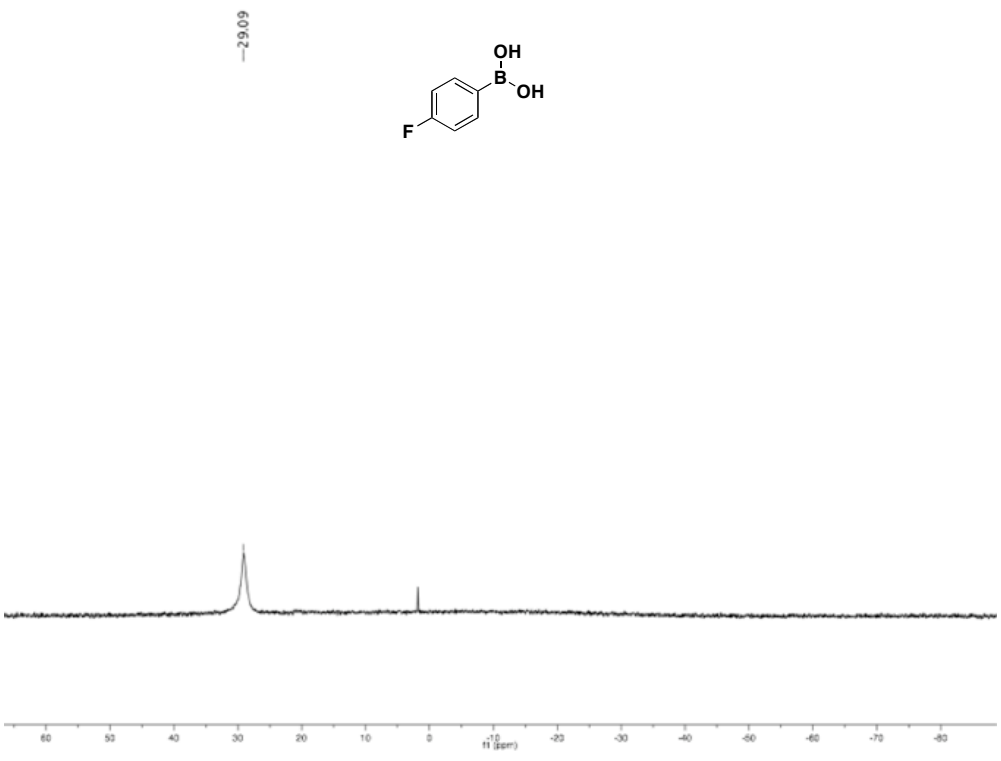

Figure A2.31 ^{11}B NMR (128.4 MHz, acetone-d_6) (4-Fluorophenyl)boronic acid

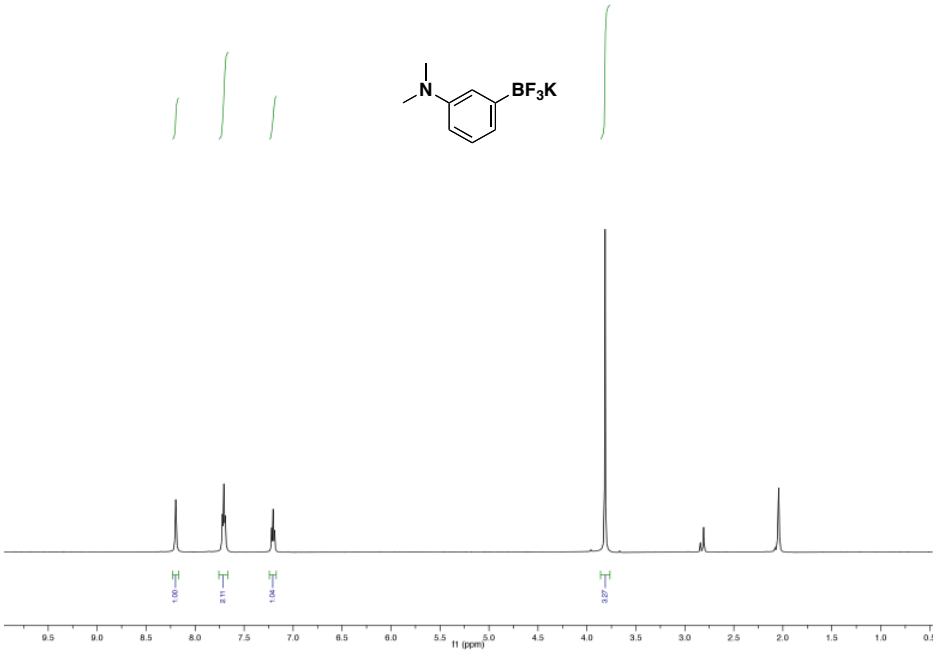

Figure A2.32 ^{1}H NMR Spectra (500 MHz, acetone-d_6) (3-(Dimethylamino)phenyl)trifluoroborate

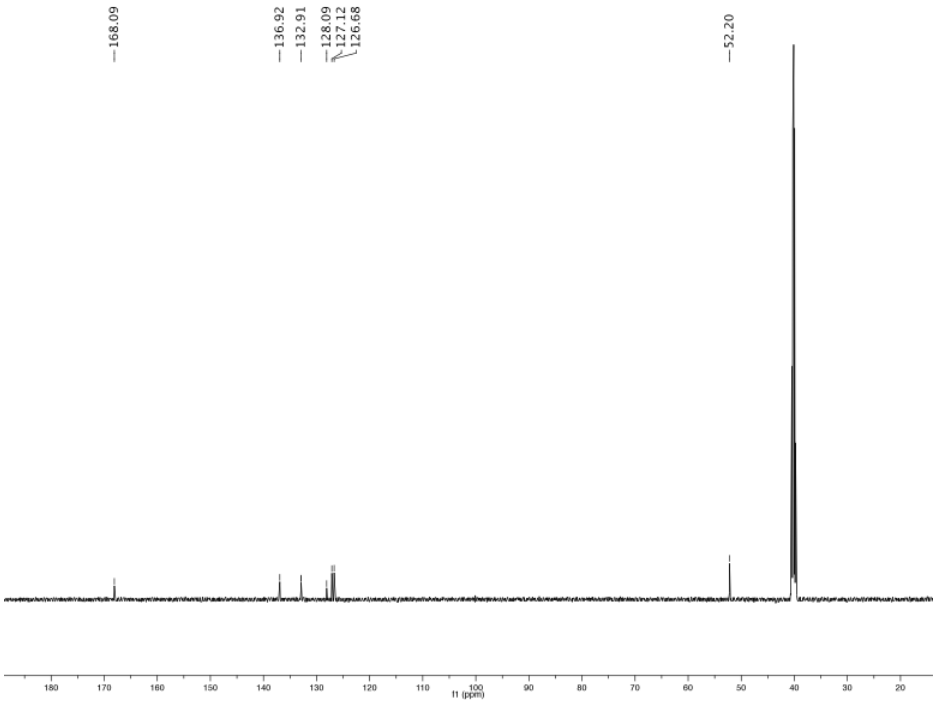

Figure A2.33 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) (3-(Dimethylamino)phenyl)trifluoroborate

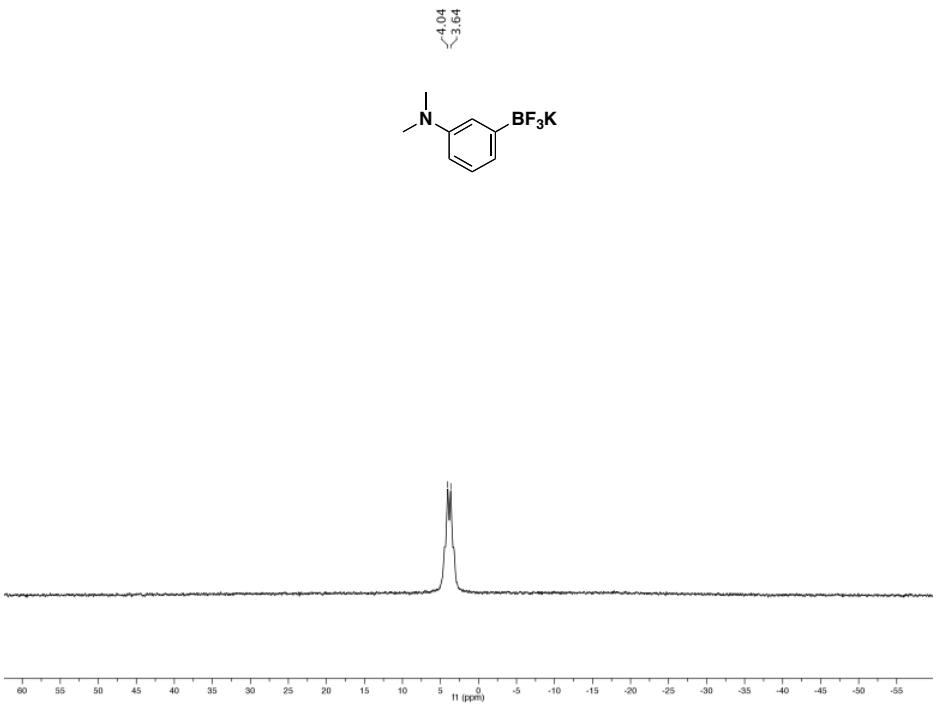

Figure A2.34 ^{11}B NMR (128.4 MHz, acetone-d_6) (3-(Dimethylamino)phenyl)trifluoroborate

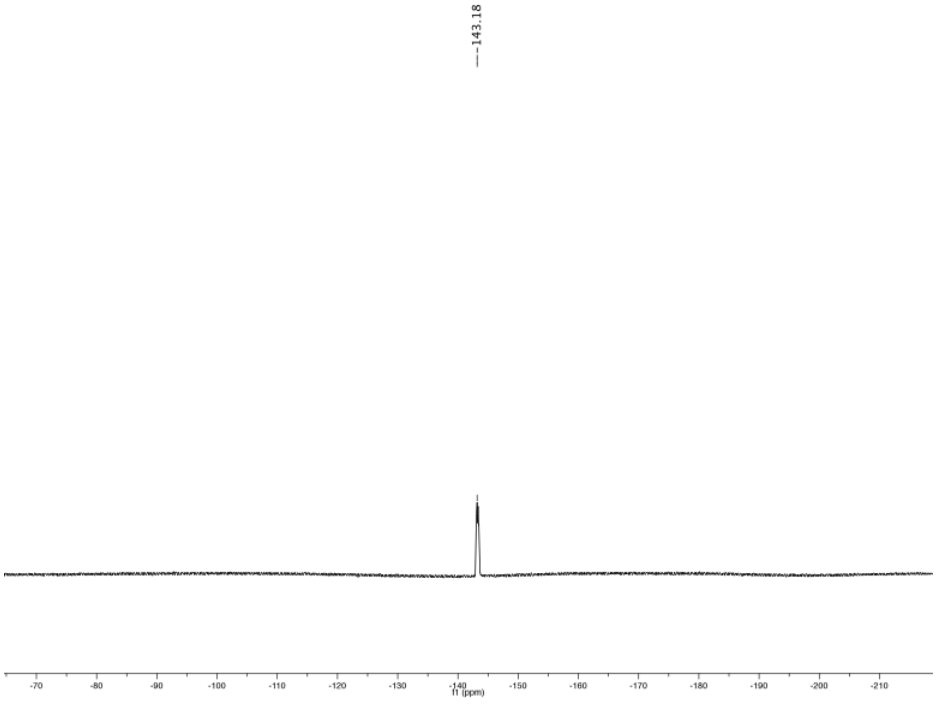

Figure A2.35 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) (3-(Dimethylamino)phenyl)trifluoroborate

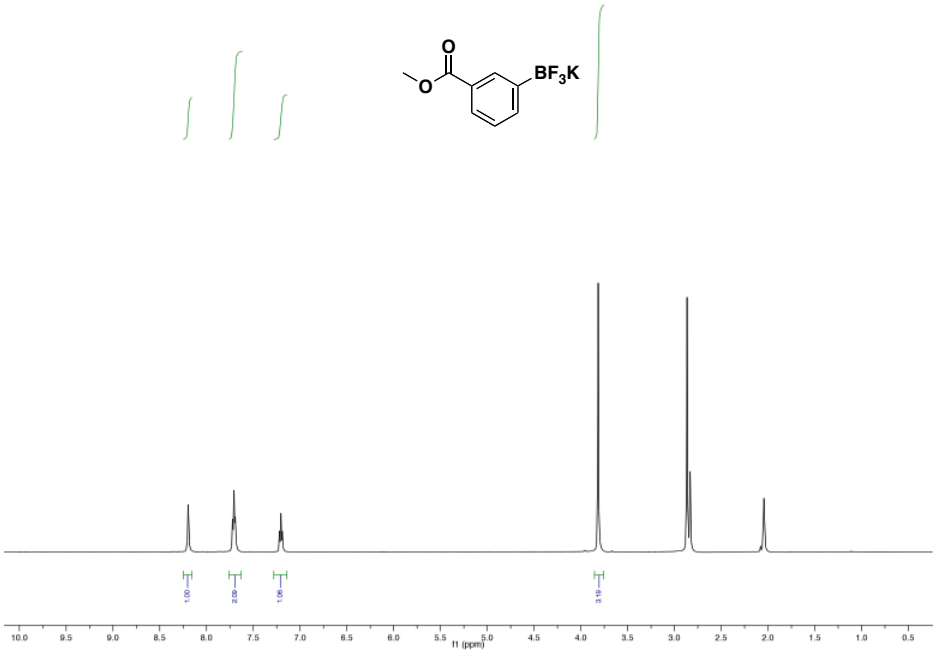

Figure A2.36 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (3-(Methoxycarbonyl)phenyl)trifluoroborate

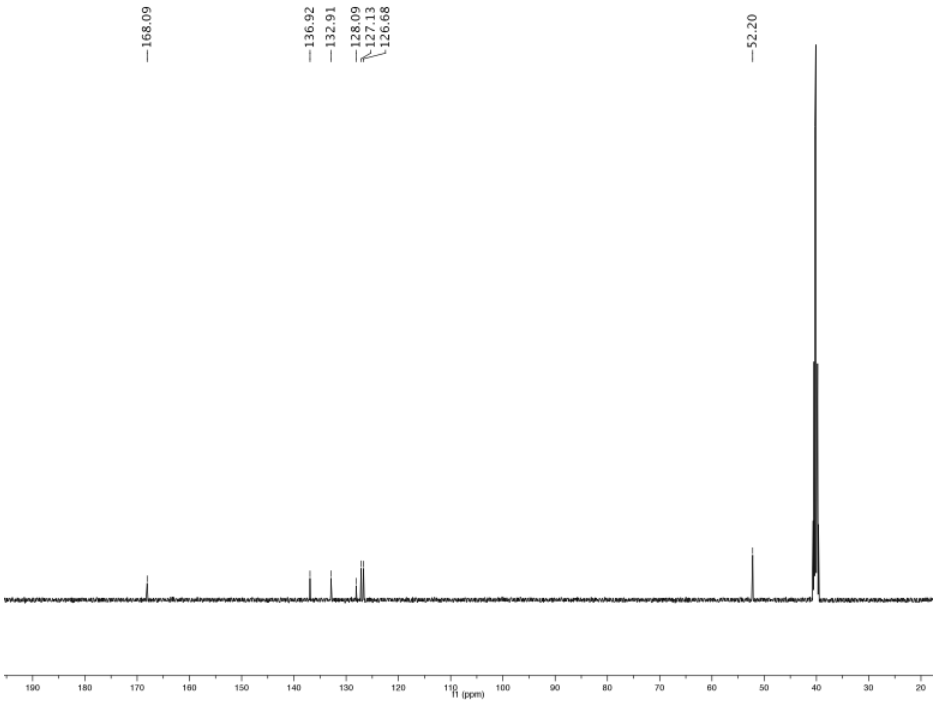

Figure A2.37 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (3-(Methoxycarbonyl)phenyl)trifluoroborate

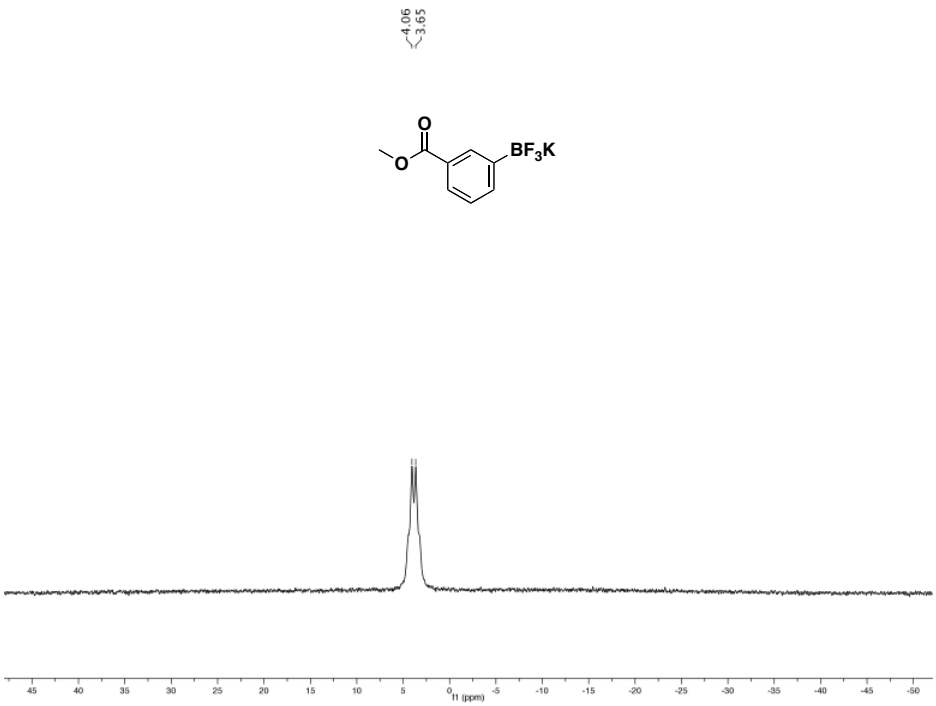

Figure A2.38 ^{11}B NMR (128.4 MHz, acetone-d_6) Potassium (3-(Methoxycarbonyl)phenyl)trifluoroborate

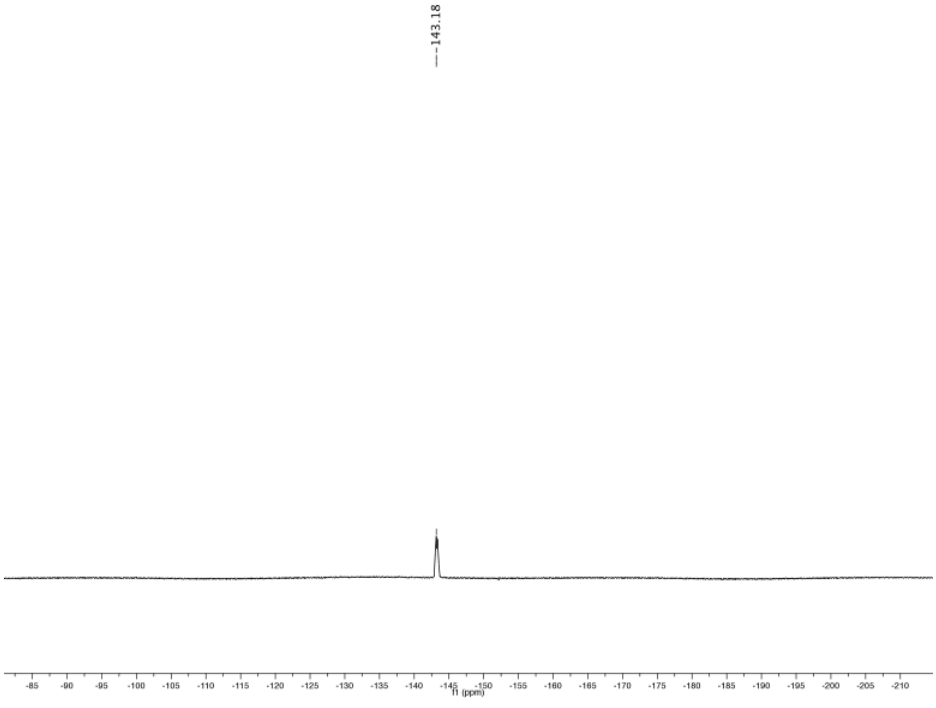

Figure A2.39 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (3-(Methoxycarbonyl)phenyl)trifluoroborate

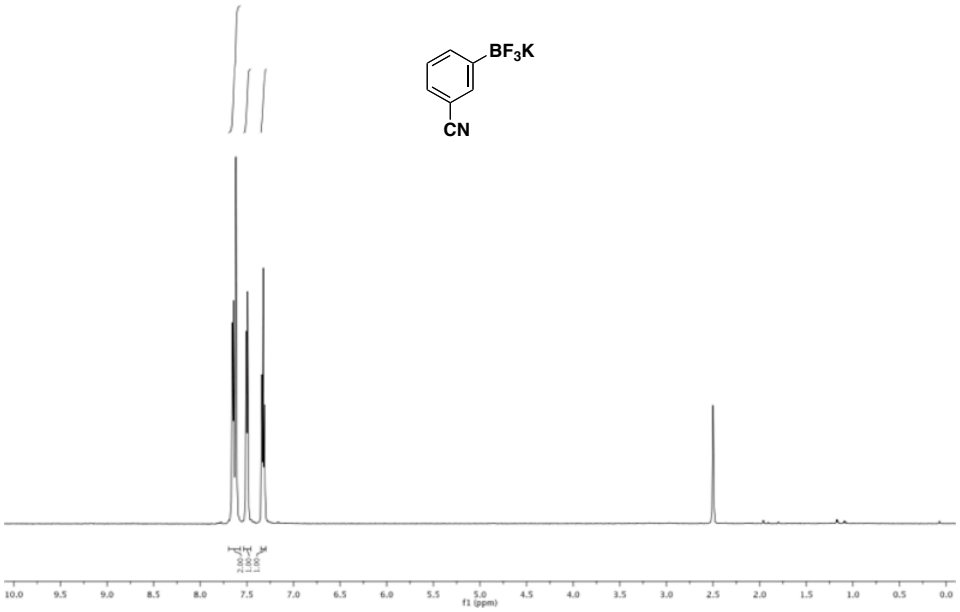

Figure A2.40 ^{1}H NMR Spectra (500 MHz, DMSO-d_6) Potassium (3-Cyanophenyl)trifluoroborate

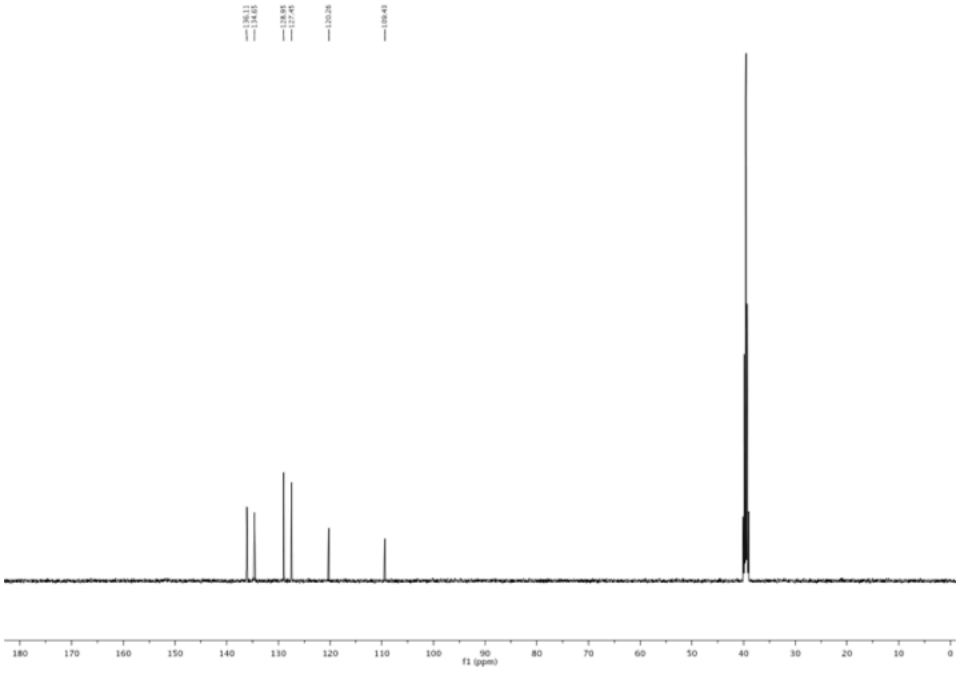

Figure A2.41 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (3-Cyanophenyl)trifluoroborate

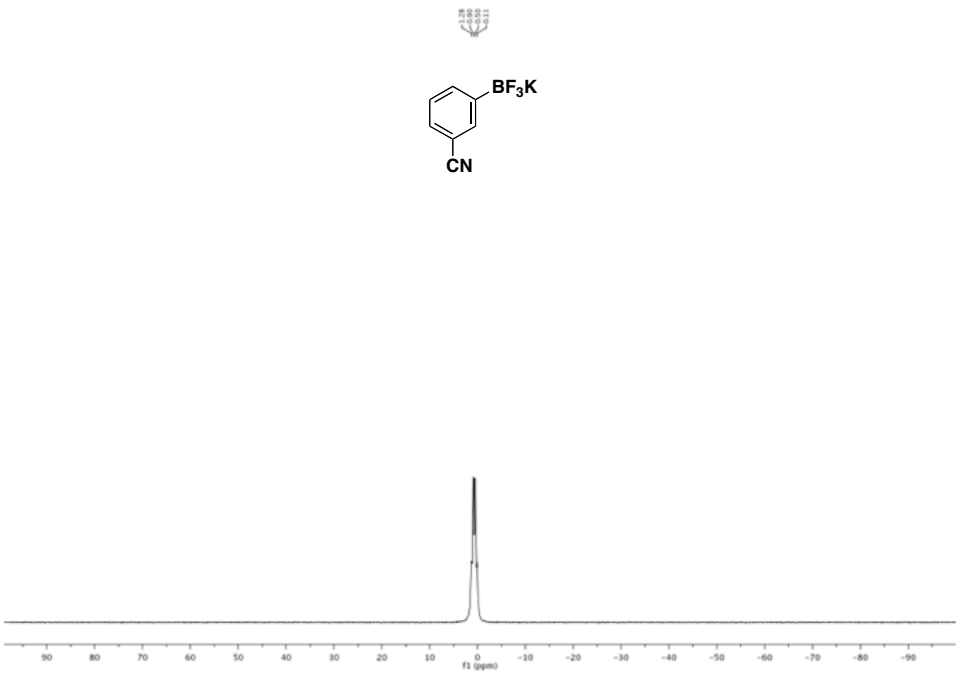

Figure A2.42 ^{11}B NMR (128.4 MHz, acetone-d_6) Potassium (3-Cyanophenyl)trifluoroborate

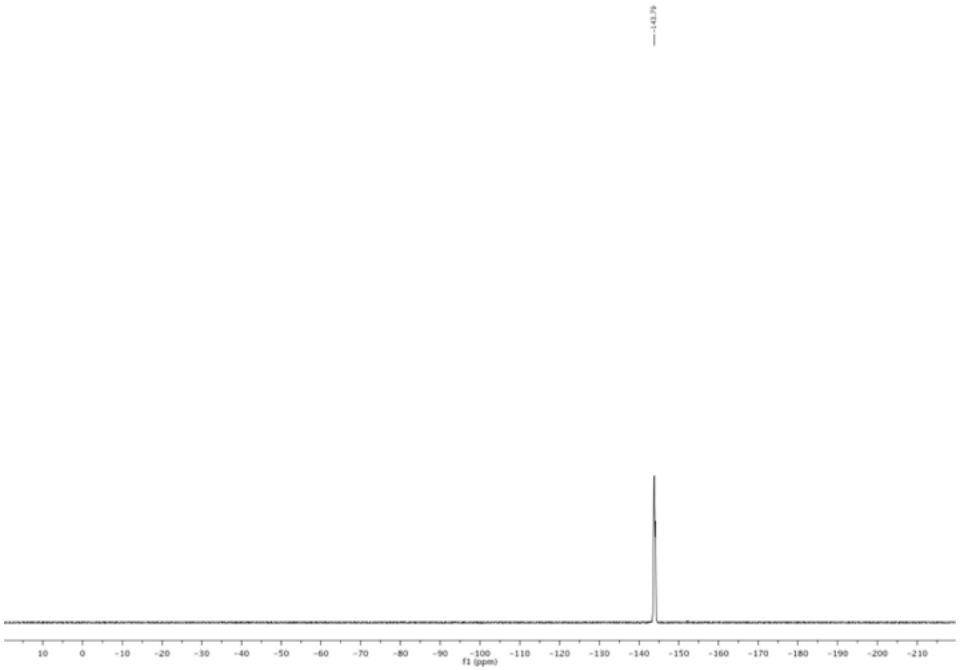

Figure A2.43 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (3-Cyanophenyl)trifluoroborate

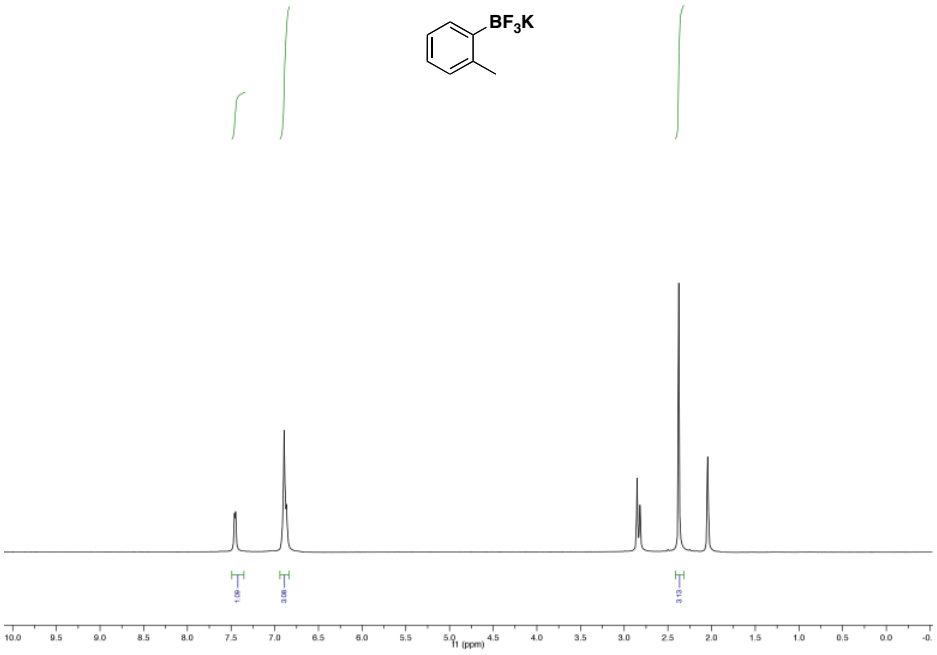

Figure A2.44 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium o-Tolyltrifluoroborate

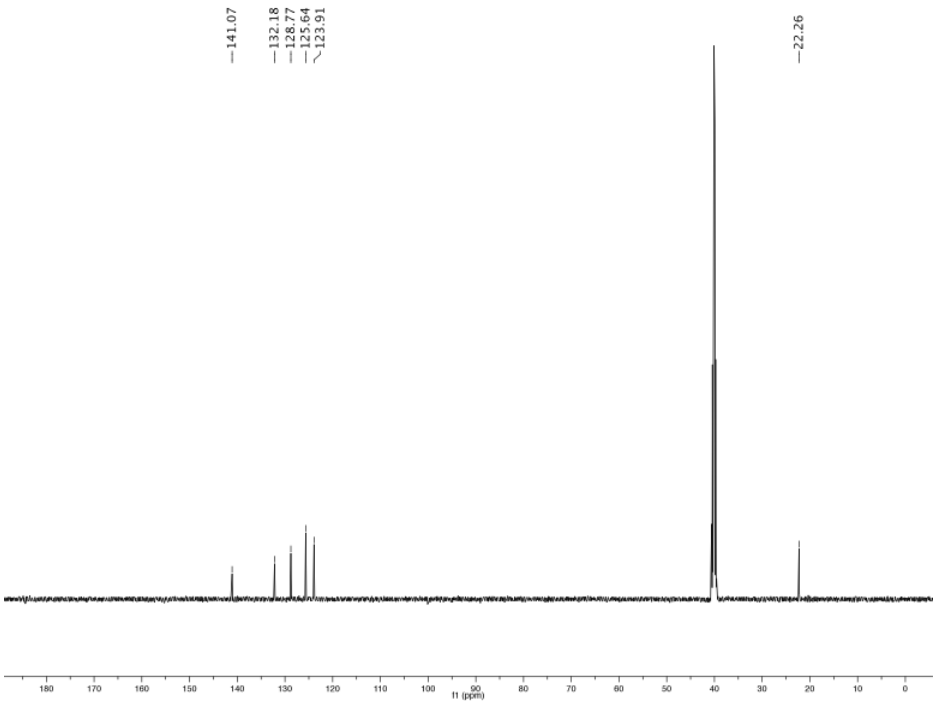

Figure A2.45 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium o-Tolyltrifluoroborate

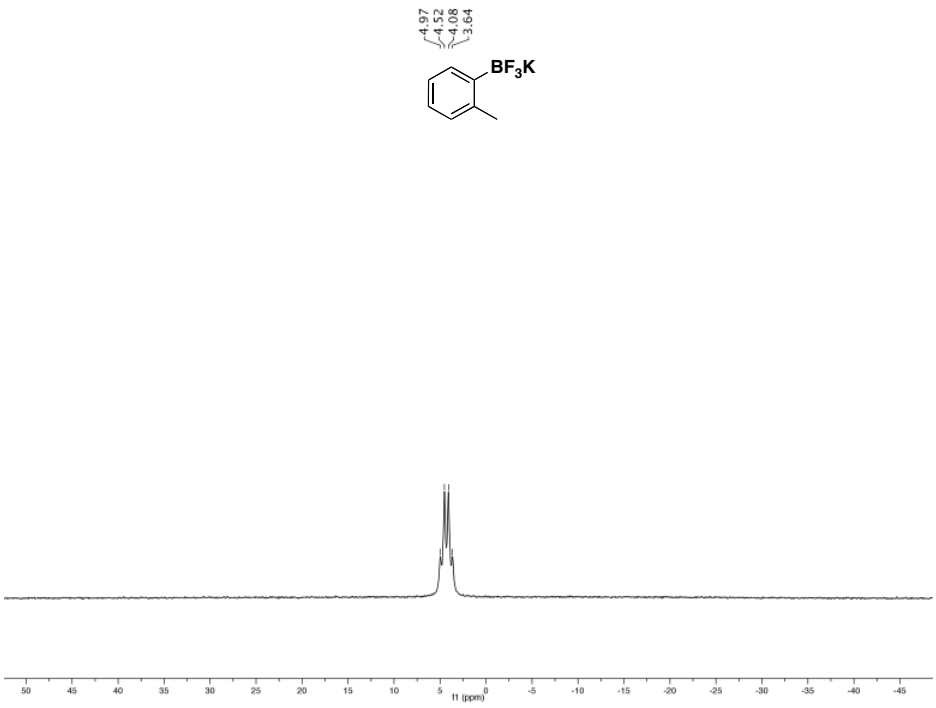

Figure A2.46 ^{11}B NMR (128.4 MHz, acetone-d_6) Potassium o-Tolyltrifluoroborate

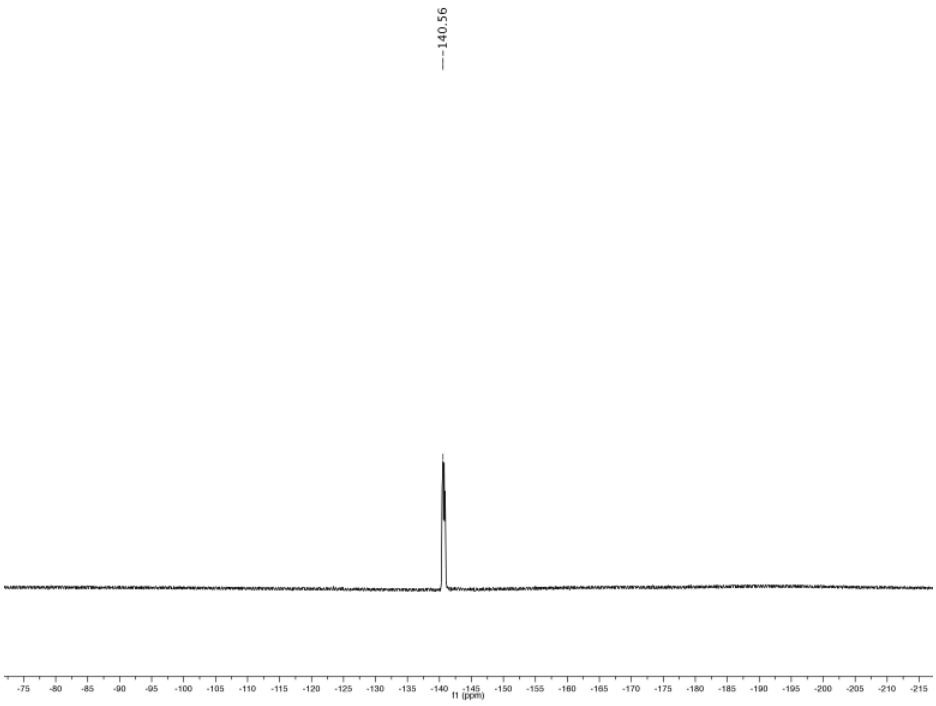

Figure A2.47 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium o-Tolyltrifluoroborate

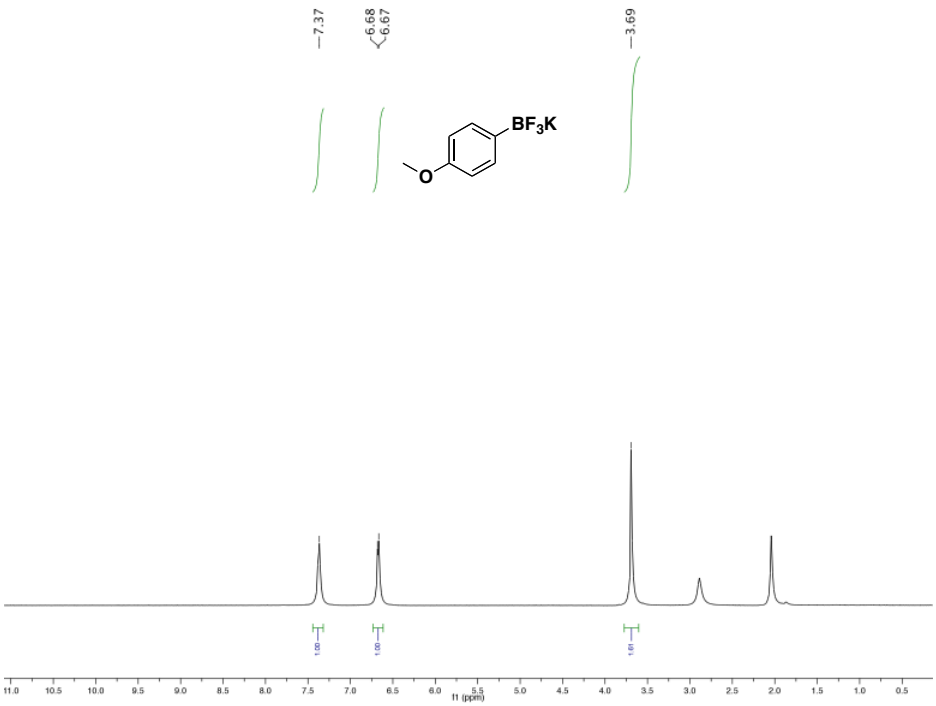

Figure A2.48 ^{1}H NMR Spectra (500 MHz, DMSO-d_6) Potassium 4-Methoxyphenyl-trifluoroborate (from the bromide)

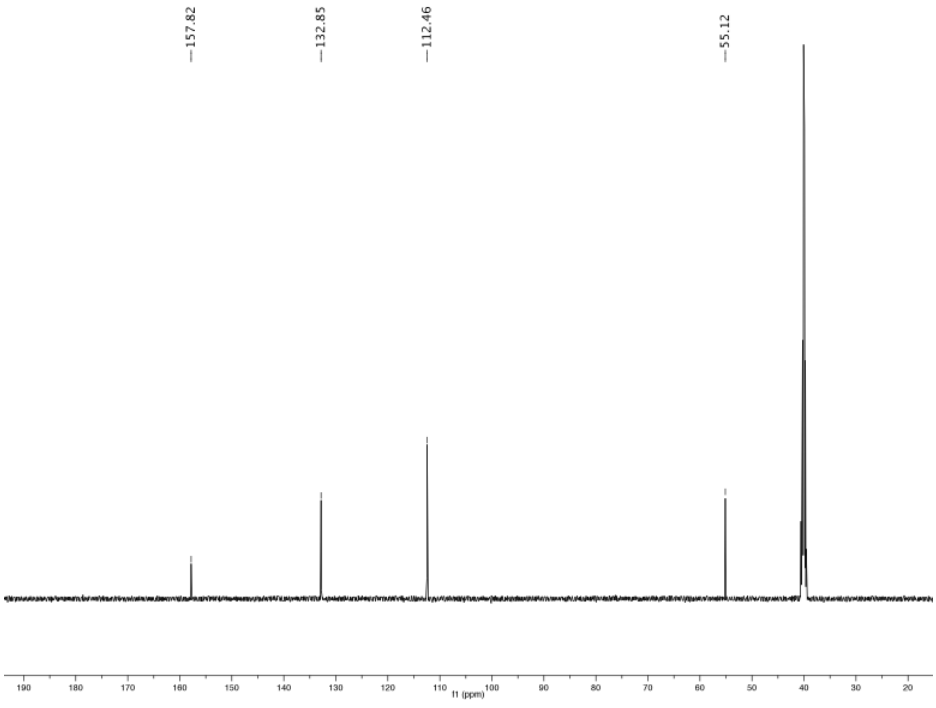

Figure A2.49 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

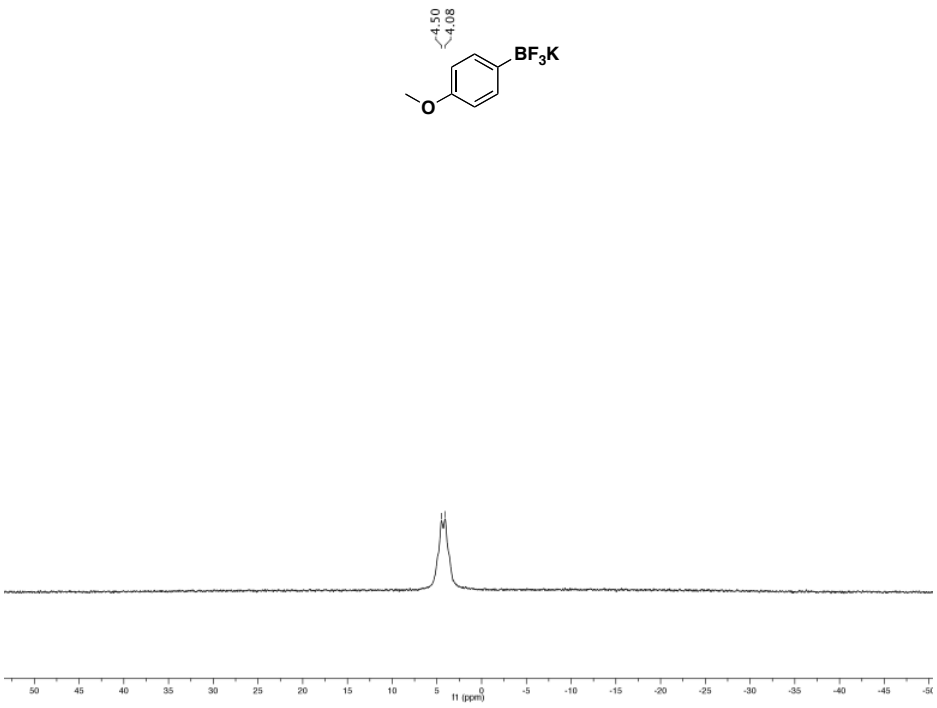

Figure A2.50 ^{11}B NMR (128.4 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

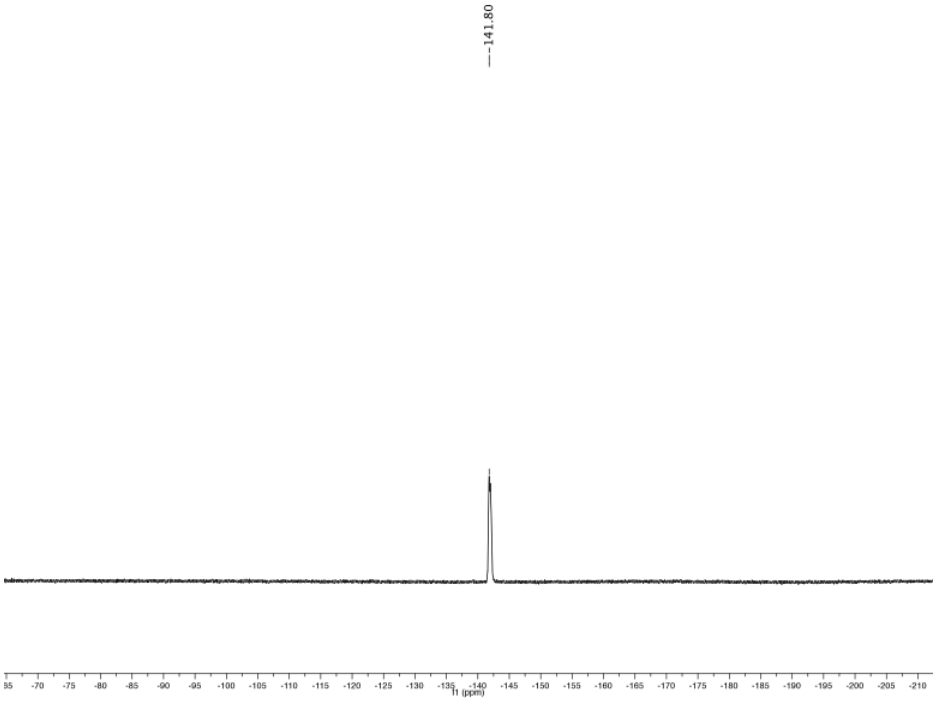

Figure A2.51 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

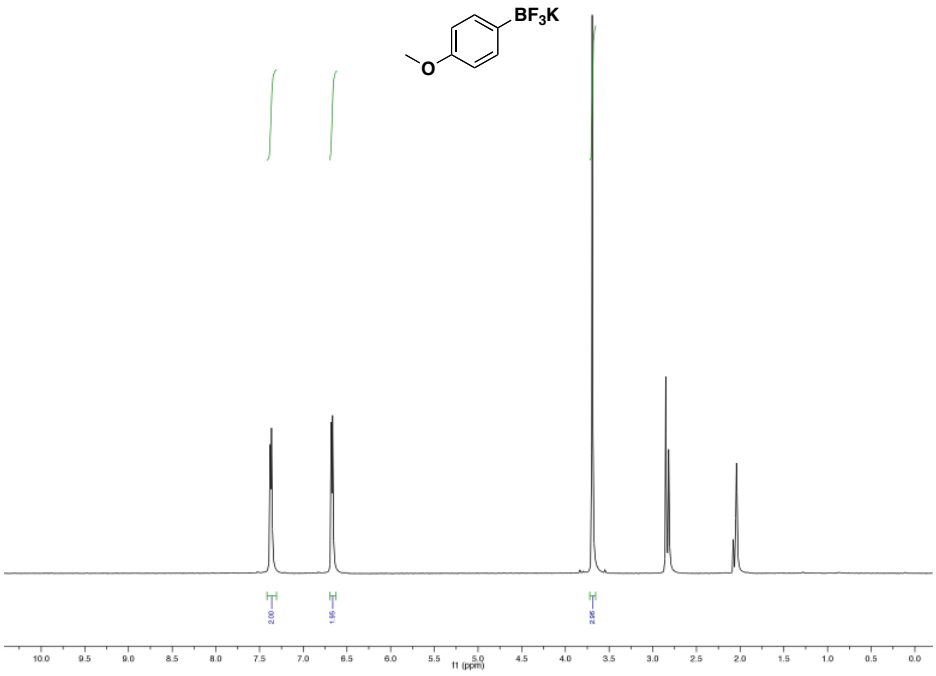

Figure A2.52 ^{1}H NMR Spectra (500 MHz, Acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate (from the iodide)

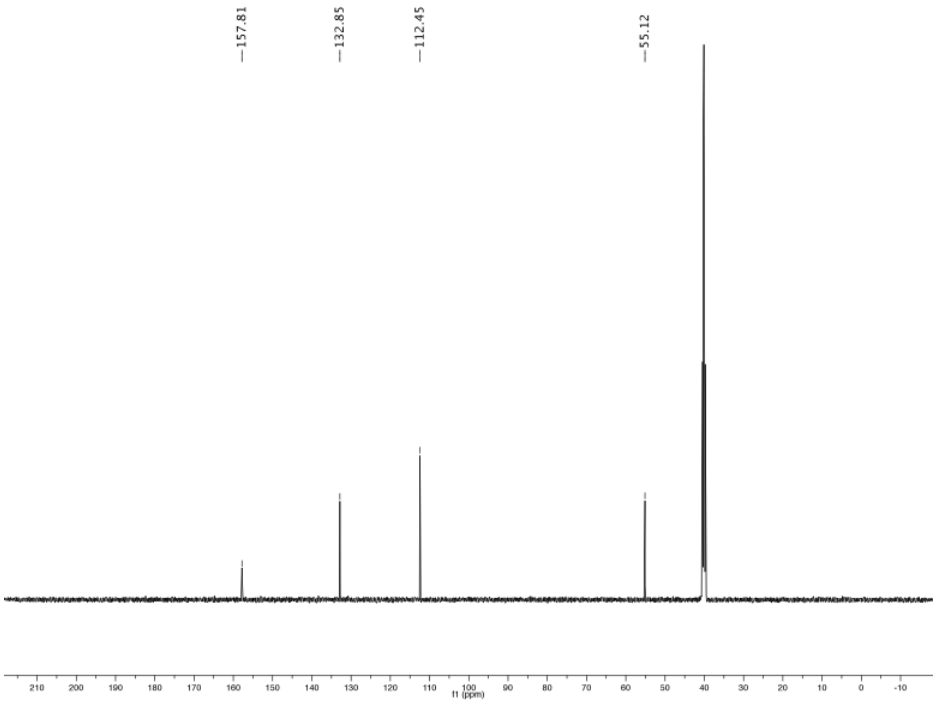

Figure A2.53 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

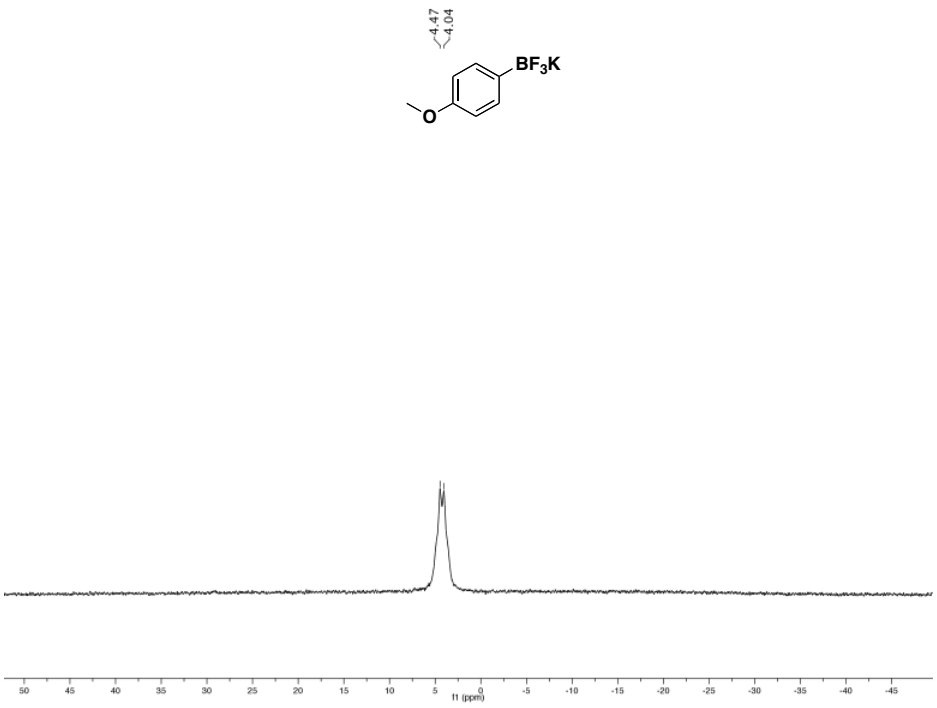

Figure A2.54 ^{11}B NMR (128.4 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

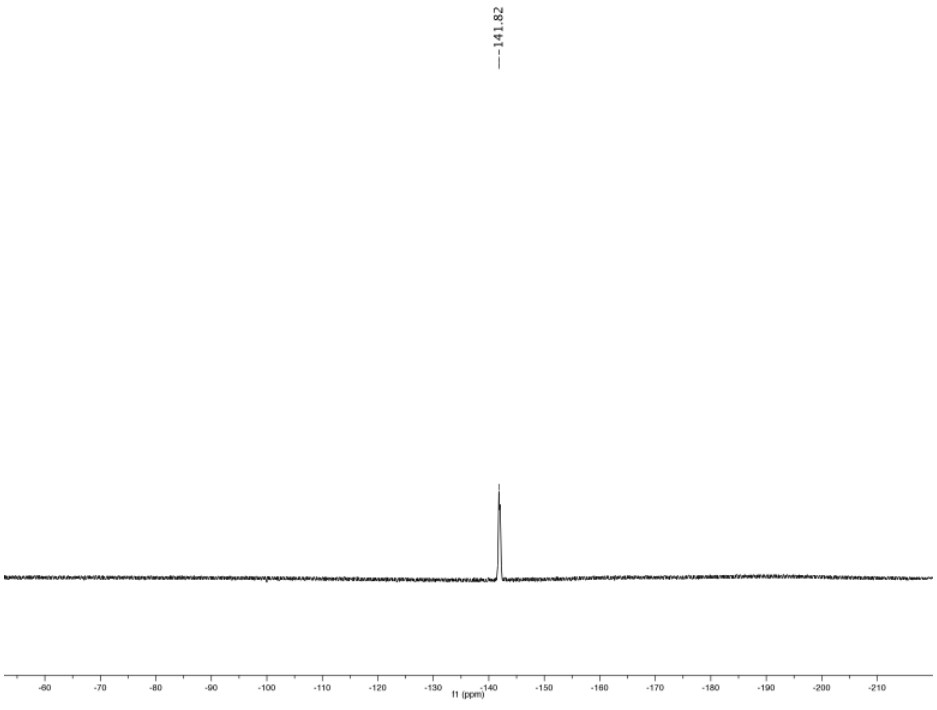

Figure A2.55 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

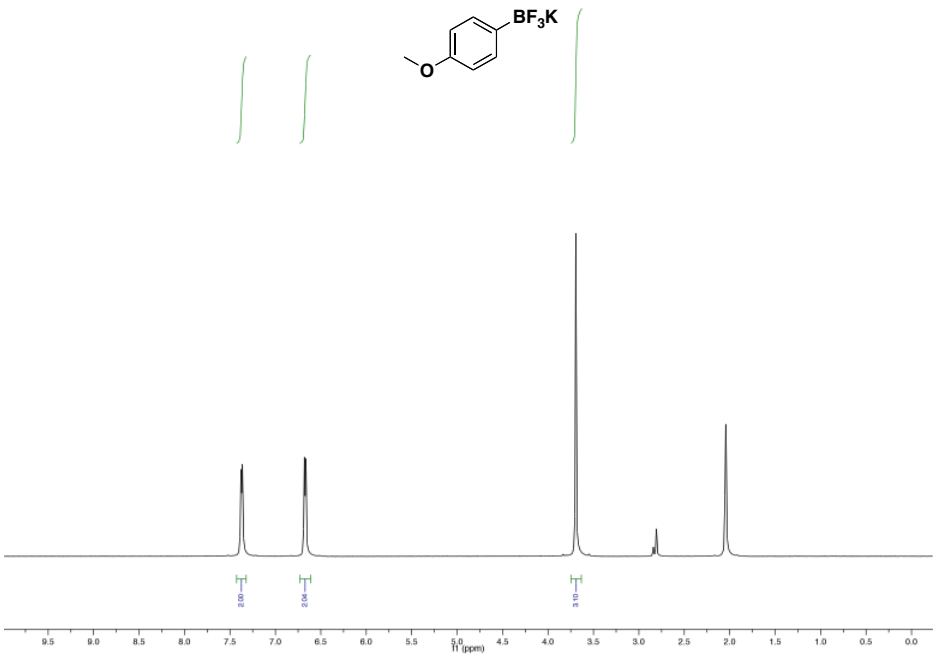

Figure A2.56 ^{1}H NMR Spectra (500 MHz, DMSO-d_6) Potassium 4-Methoxyphenyl-trifluoroborate (from the triflate)

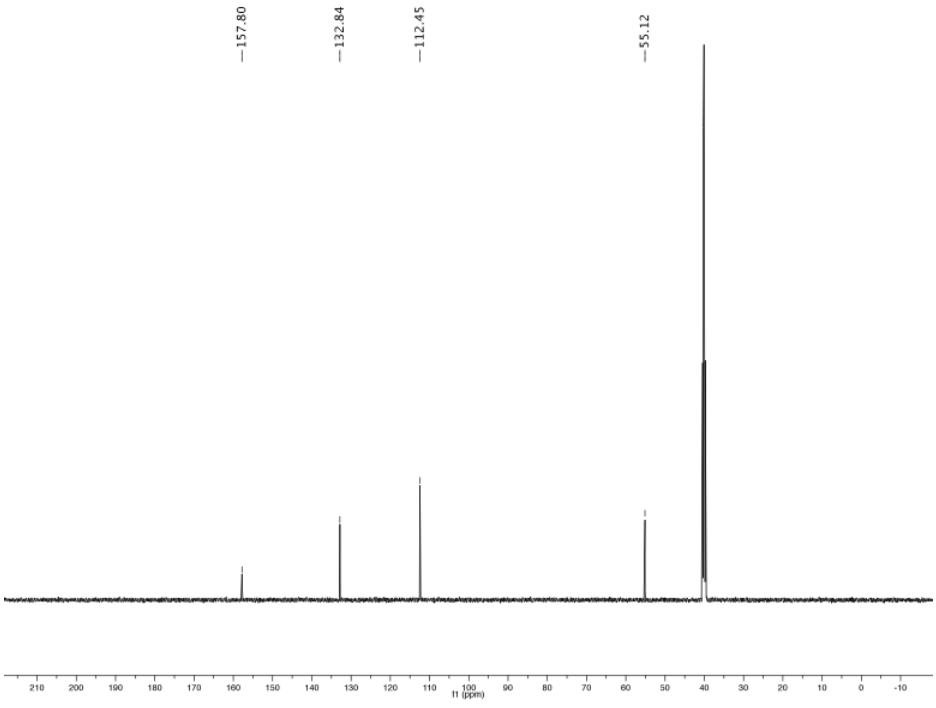

Figure A2.57 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

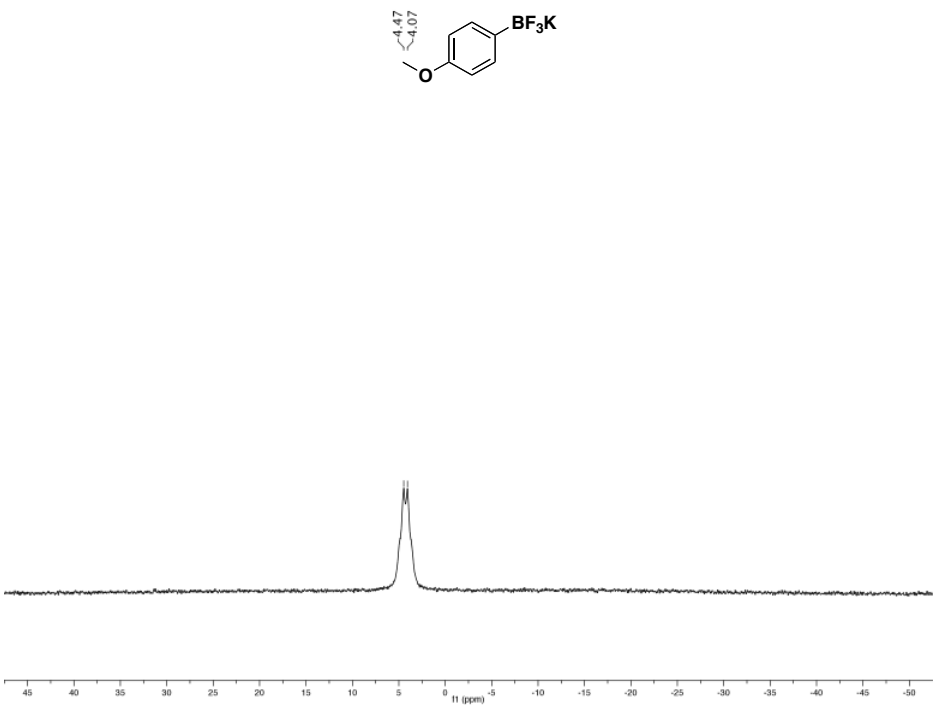

Figure A2.58 ^{11}B NMR (128.4 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

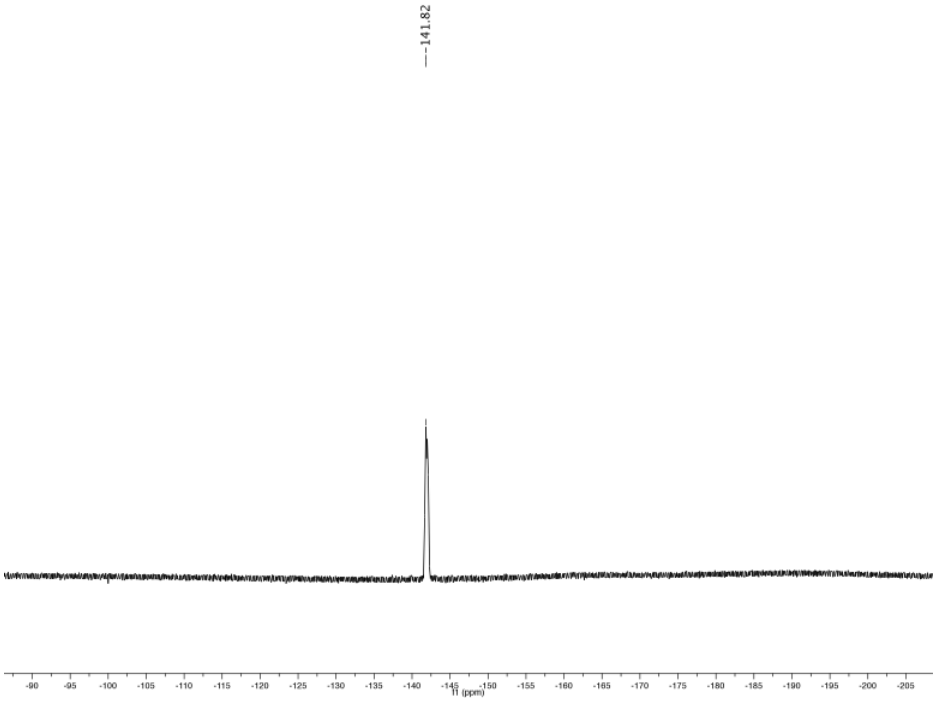

Figure A2.59 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium 4-Methoxyphenyl-trifluoroborate

Appendix A3. ^{1}H, ^{13}C, ^{11}B, and ^{19}F Spectra Relevant to Chapter 5

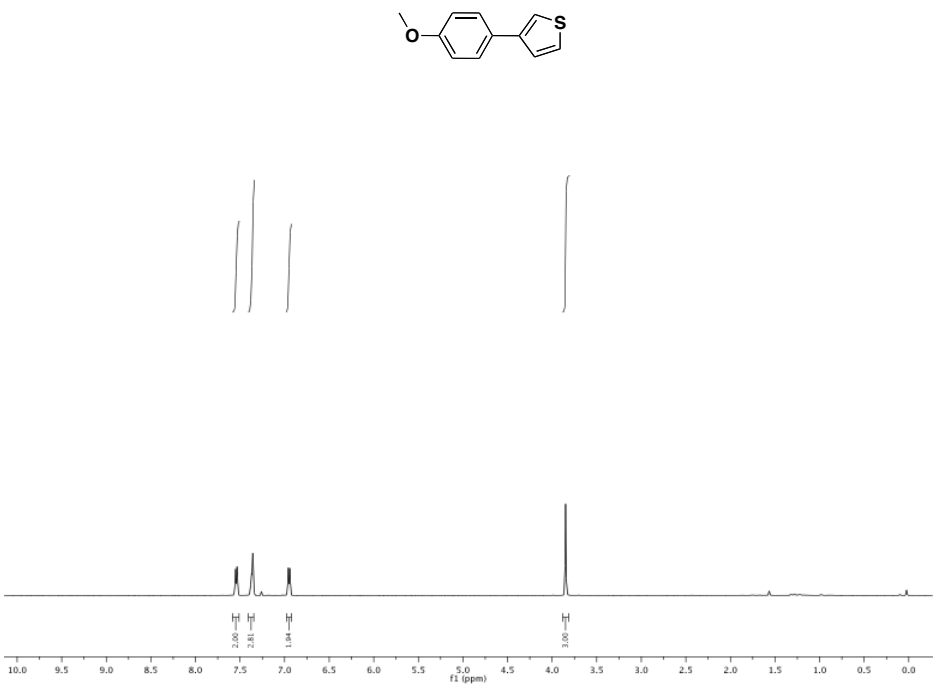

Figure A3.1 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 3-(4-Methoxyphenyl)thiophene

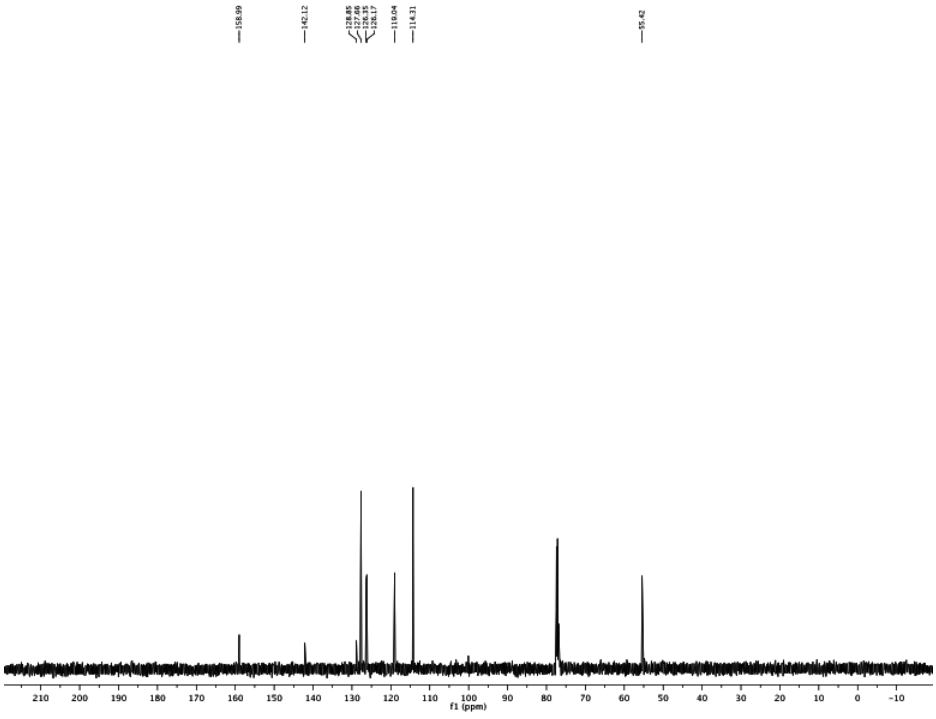

Figure A3.2 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) 3-(4-Methoxyphenyl)thiophene

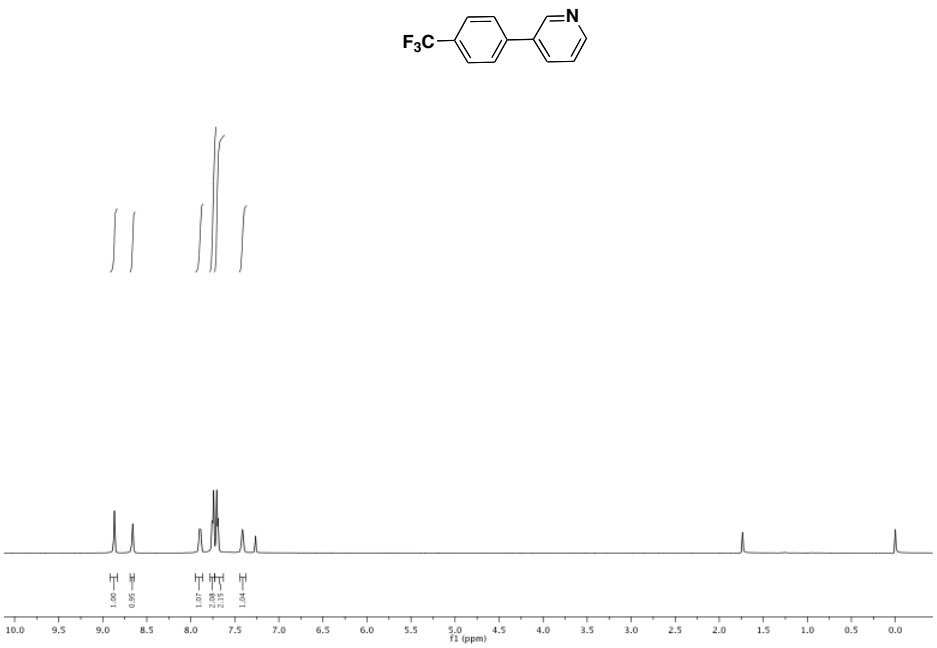

Figure A3.3 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 3-(4-(Trifluoromethyl)phenyl)pyridine

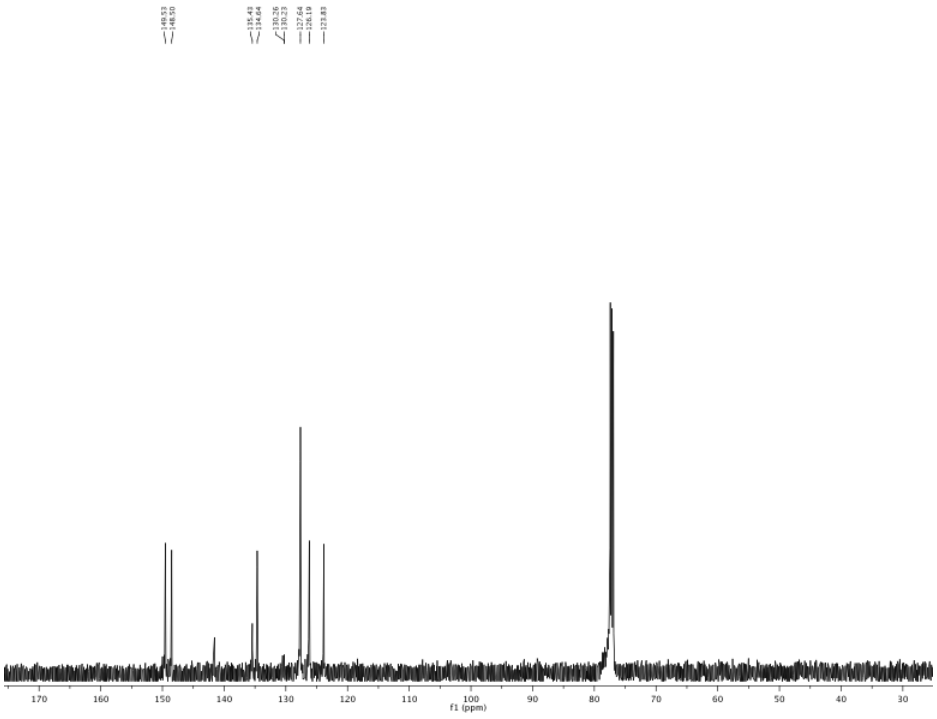

Figure A3.4 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$), 3-(4-(Trifluoromethyl)phenyl)pyridine

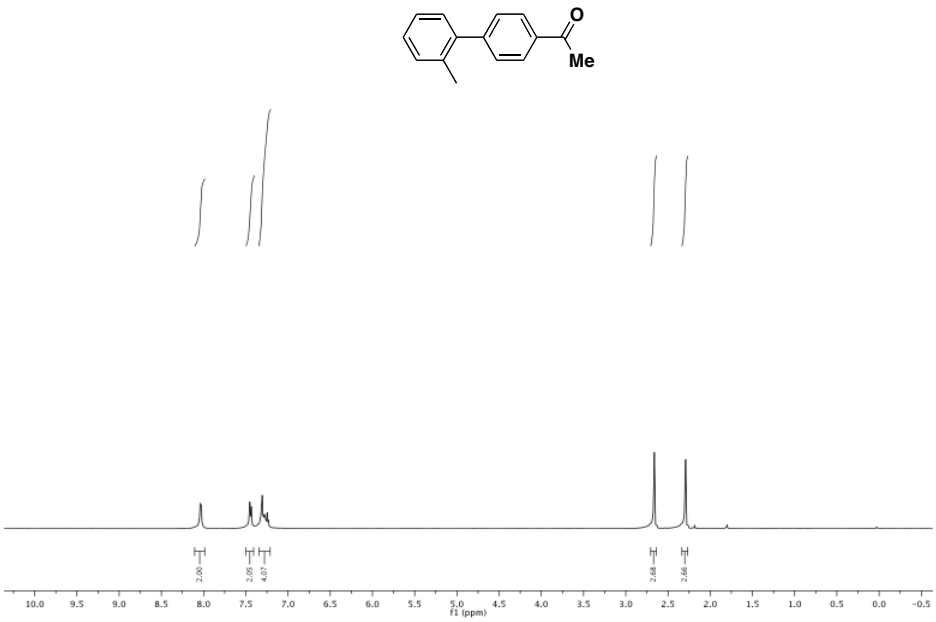

Figure A3.5 ^{1}H NMR Spectra (500 MHz, $CDCl_3$), 1-(2'-Methyl-[1,1'-biphenyl]-4-yl)ethanone

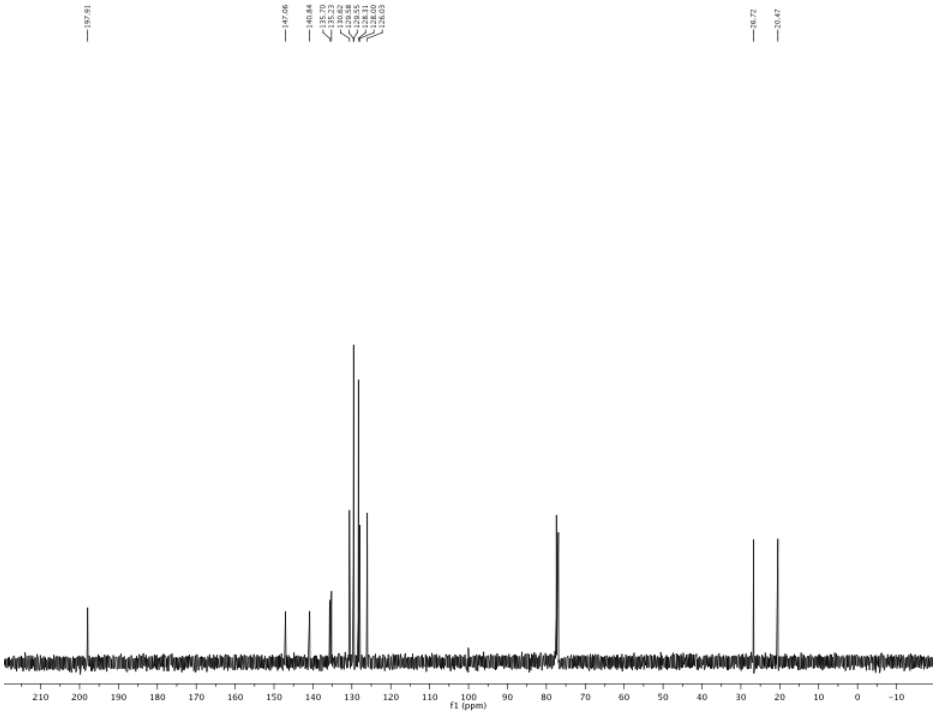

Figure A3.6 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$), 1-(2'-Methyl-[1,1'-biphenyl]-4-yl)ethanone

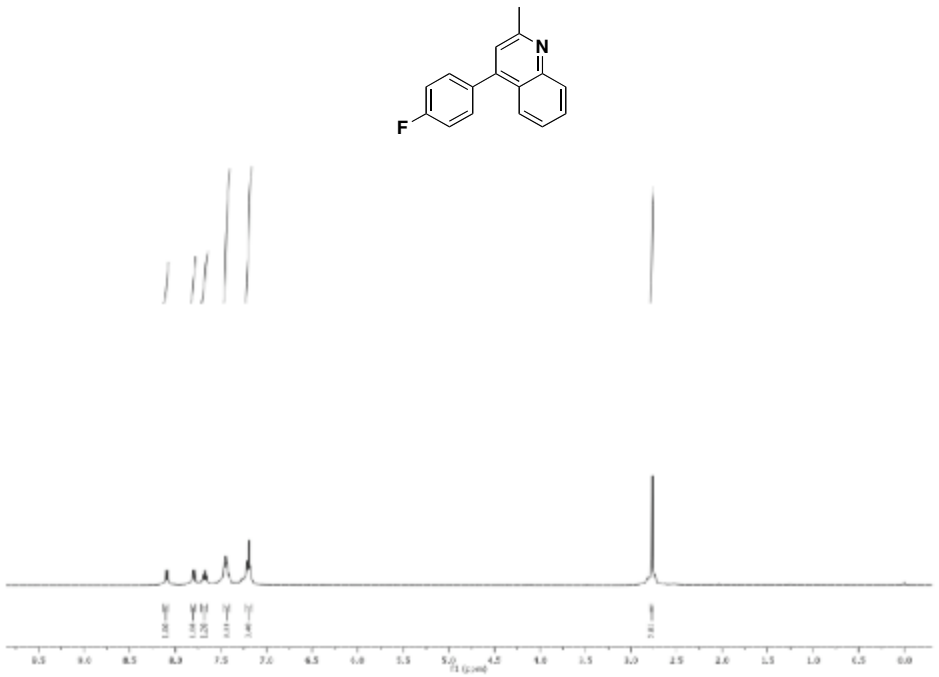

Figure A3.7 ^{1}H NMR Spectra (500 MHz, $CDCl_3$), 4-(4-Fluorophenyl)-2-methylquinoline

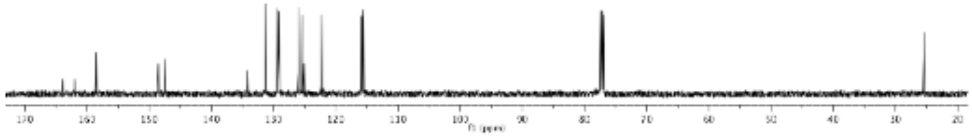

Figure A3.8 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$), 4-(4-Fluorophenyl)-2-methylquinoline

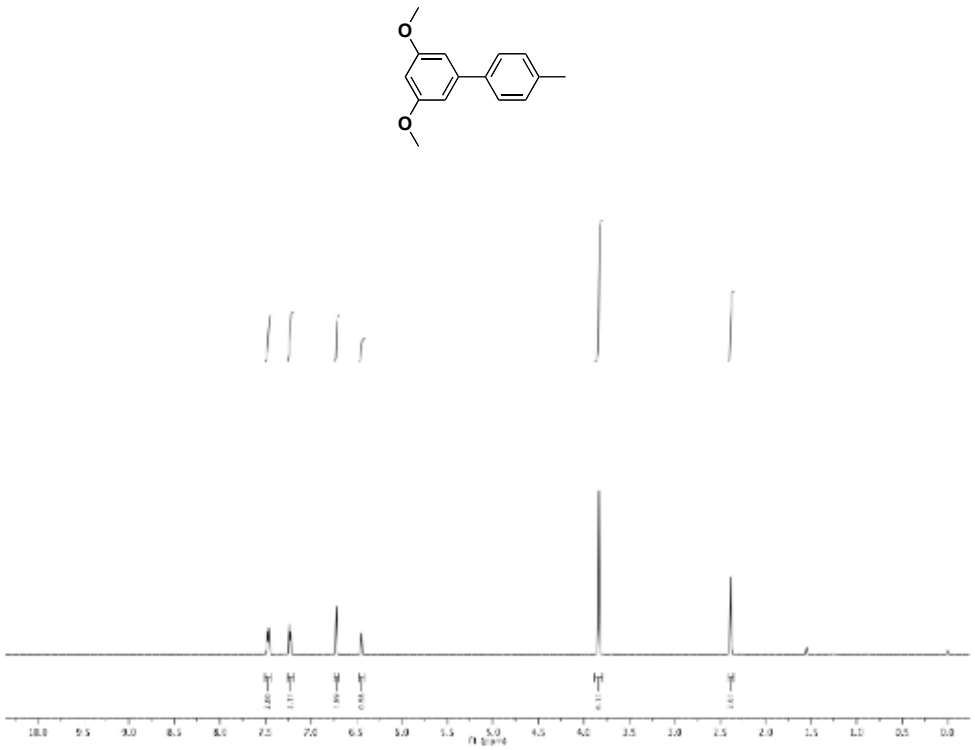

Figure A3.9 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 3,5-Dimethoxy-4'-methyl-1,1'-biphenyl

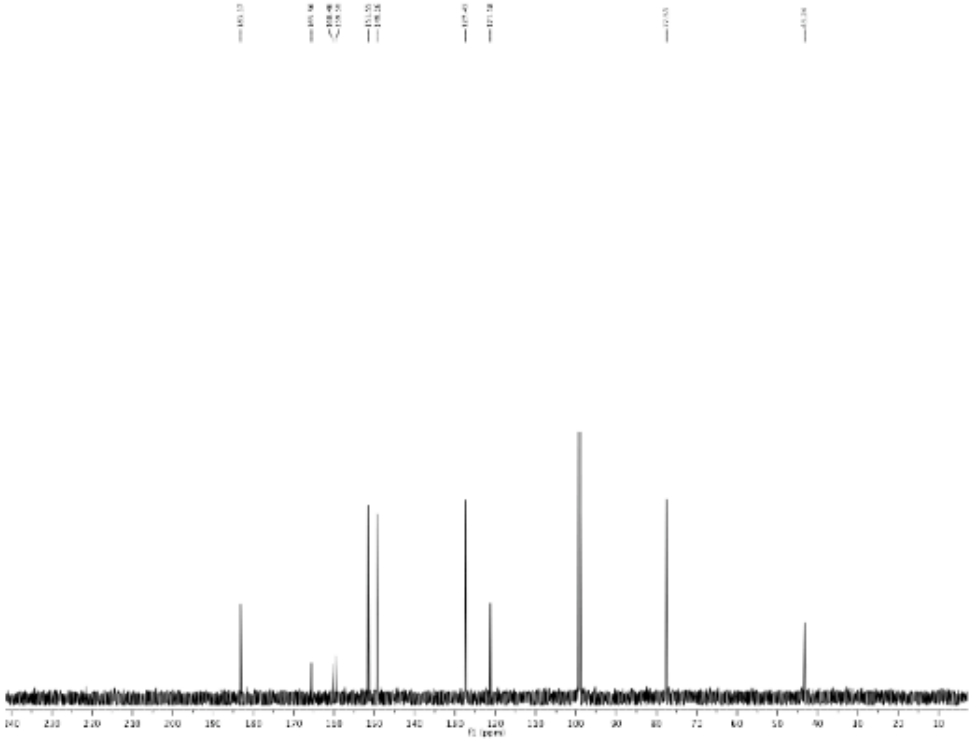

Figure A3.10 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) 3,5-Dimethoxy-4'-methyl-1,1'-biphenyl

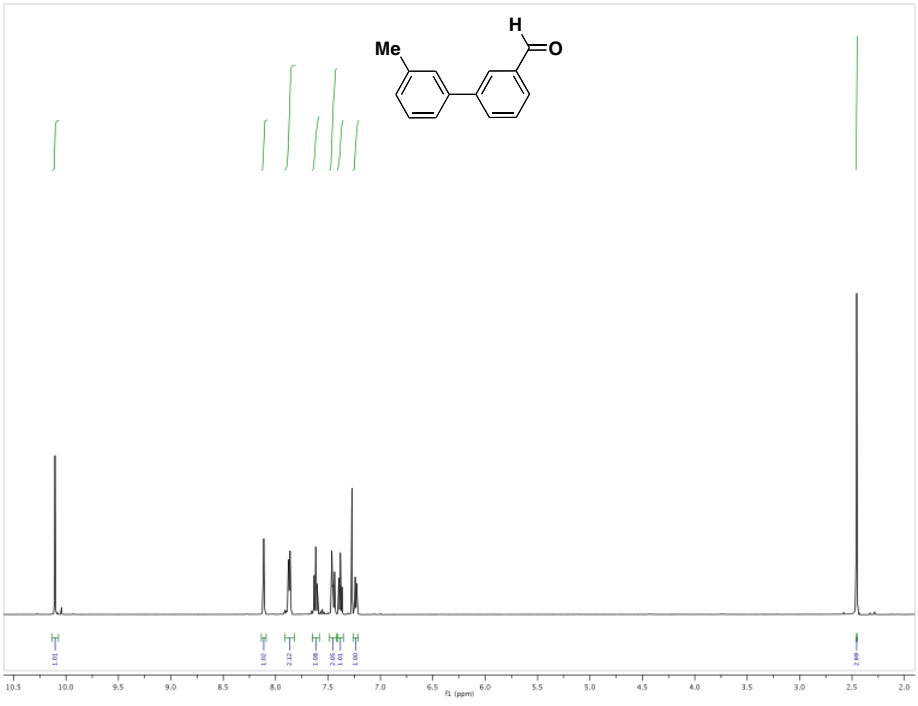

Figure A3.11 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 3'-Methyl-[1,1'-biphenyl]-3-carbaldehyde

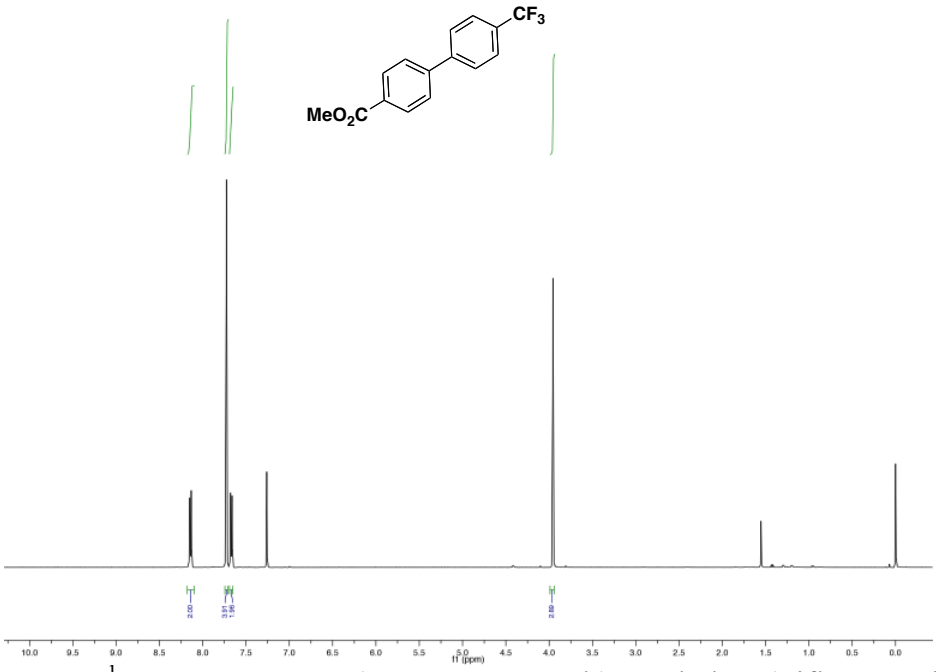

Figure A3.12 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) Methyl 4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylate (from the aryl chloride in the second step)

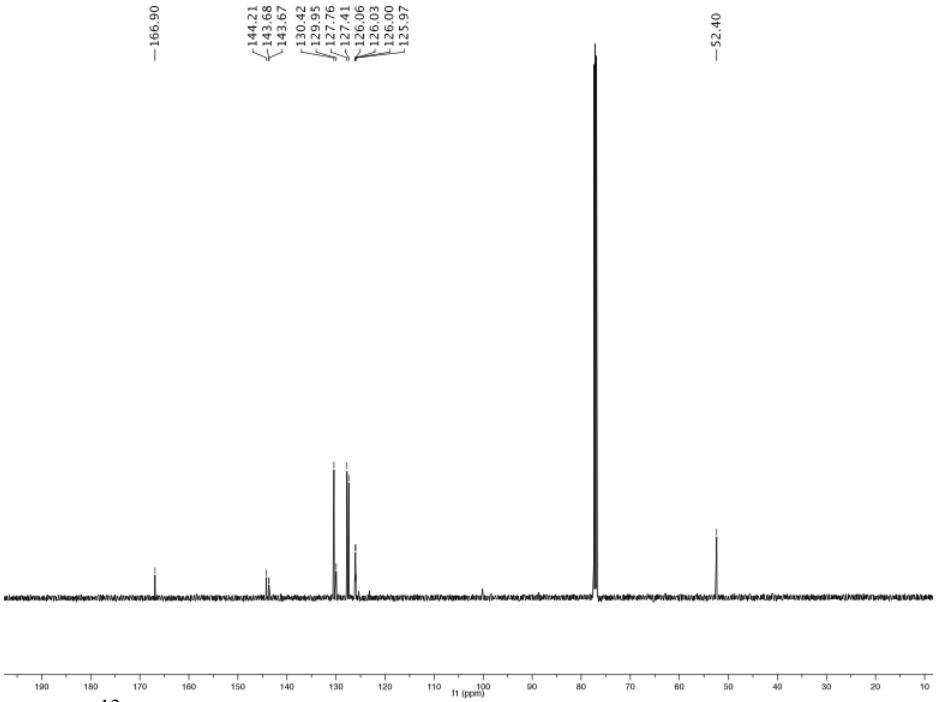

Figure A3.13 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) Methyl 4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylate (from the aryl chloride in the second step)

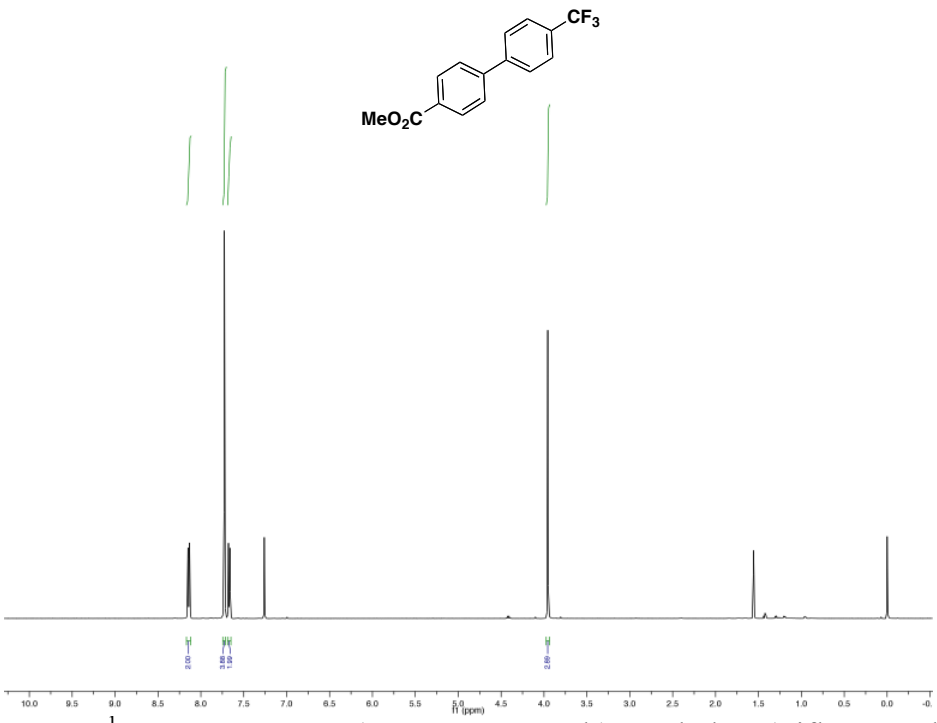

Figure A3.14 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) Methyl 4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylate (from the aryl bromide in the second step)

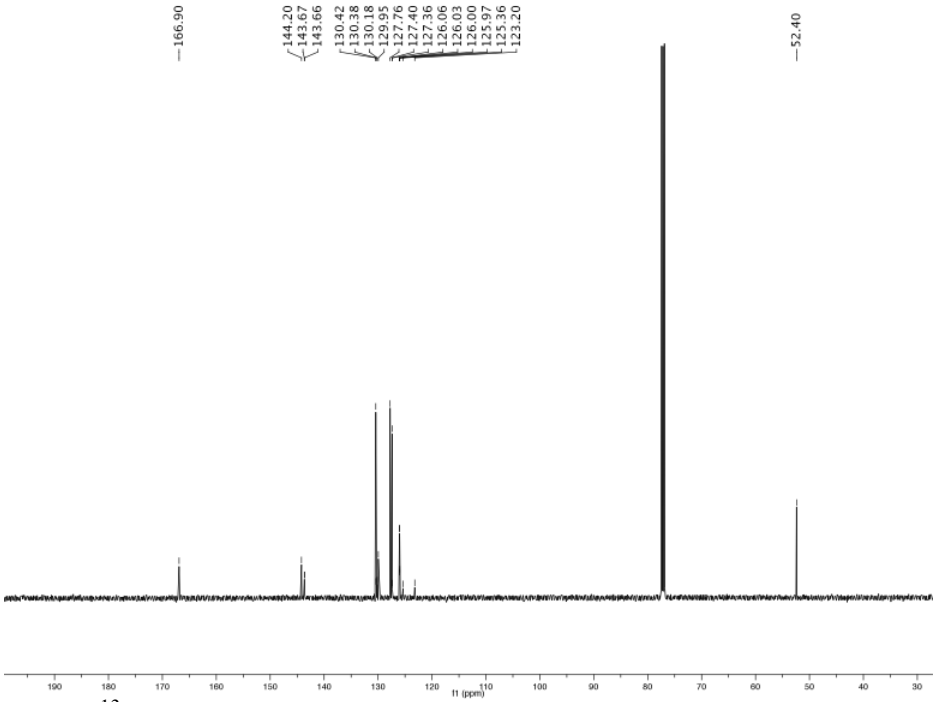

Figure A3.15 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) Methyl 4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylate (from the aryl bromide in the second step)

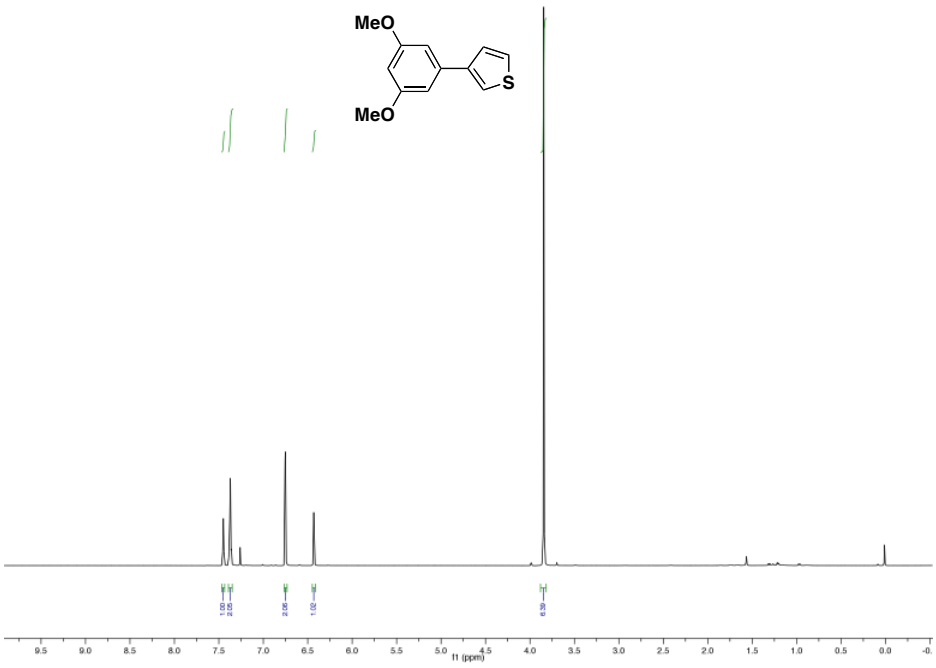

Figure A3.16 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 3-(3,5-Dimethoxyphenyl)thiophene (from the heteroaryl chloride in the second step)

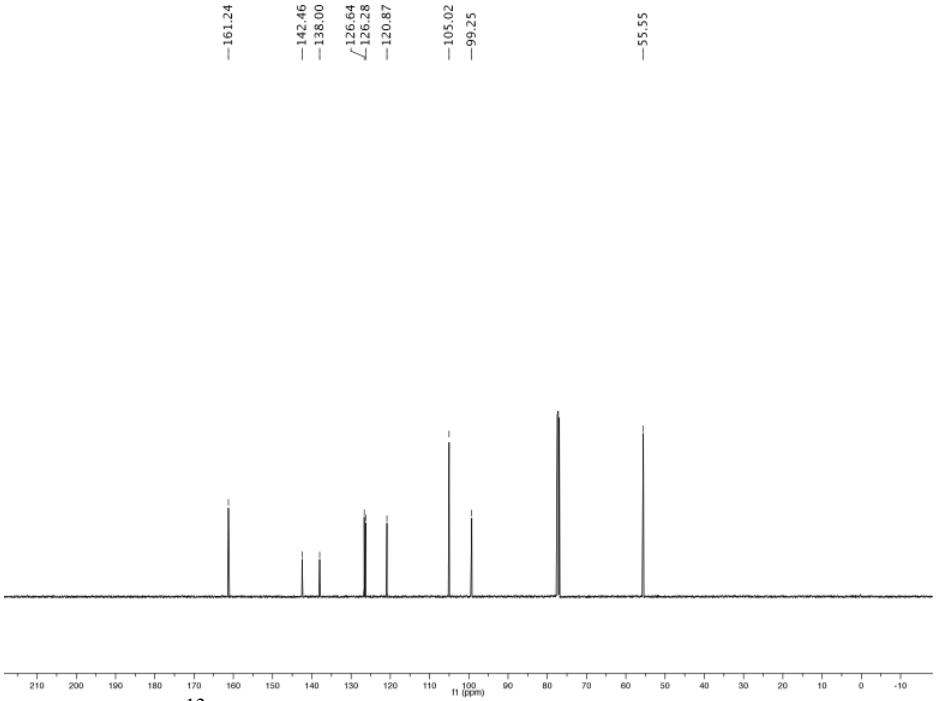

Figure A3.17 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) 3-(3,5-Dimethoxyphenyl)thiophene (from the heteroaryl chloride in the second step)

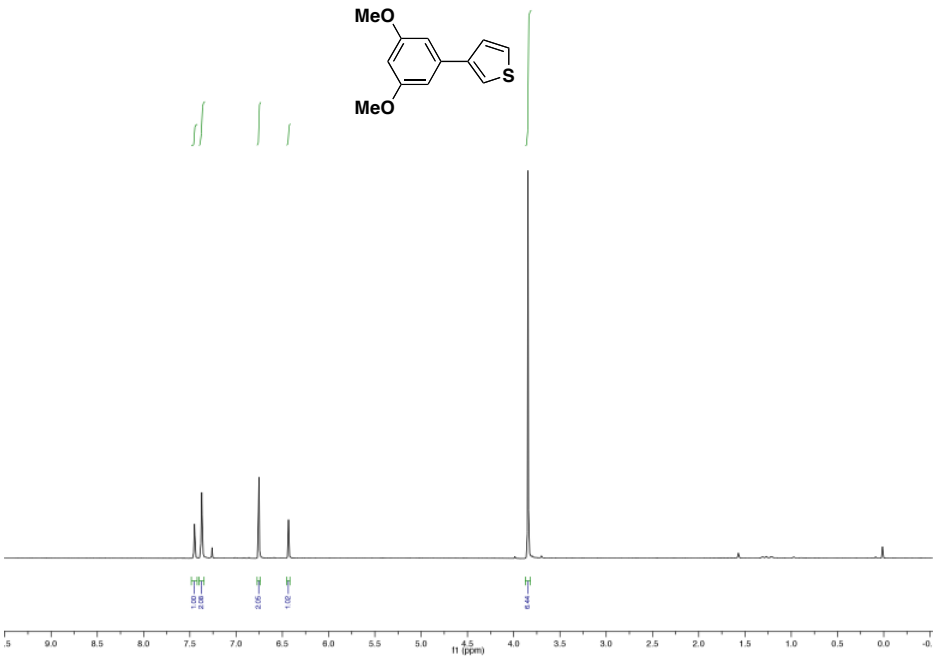

Figure A3.18 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 3-(3,5-Dimethoxyphenyl)thiophene (from the heteroaryl bromide in the second step)

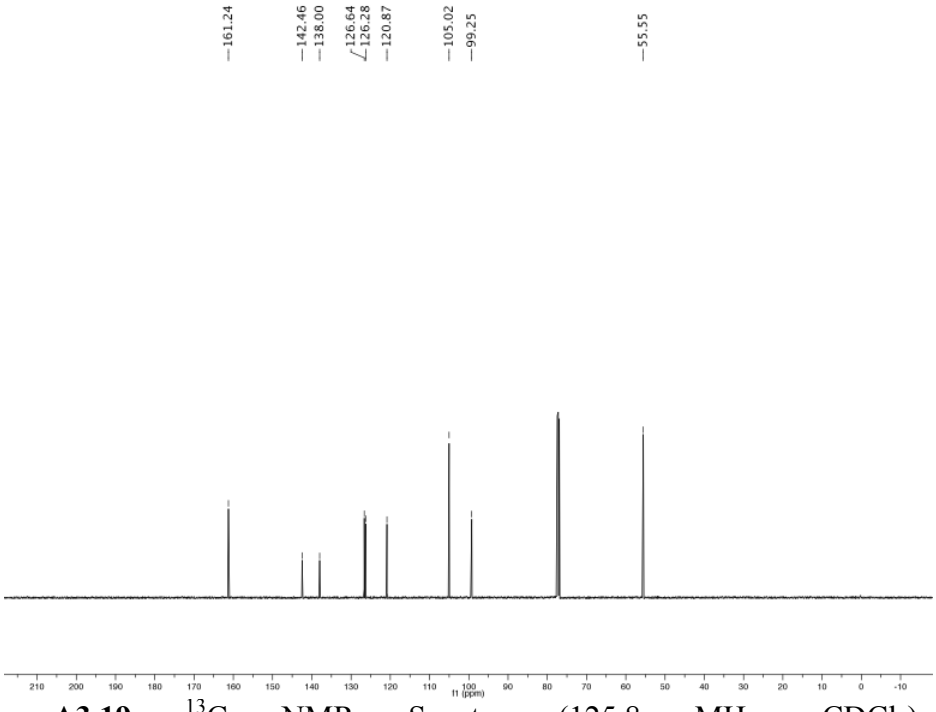

Figure A3.19 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) 3-(3,5-Dimethoxyphenyl)thiophene (from the heteroaryl bromide in the second step)

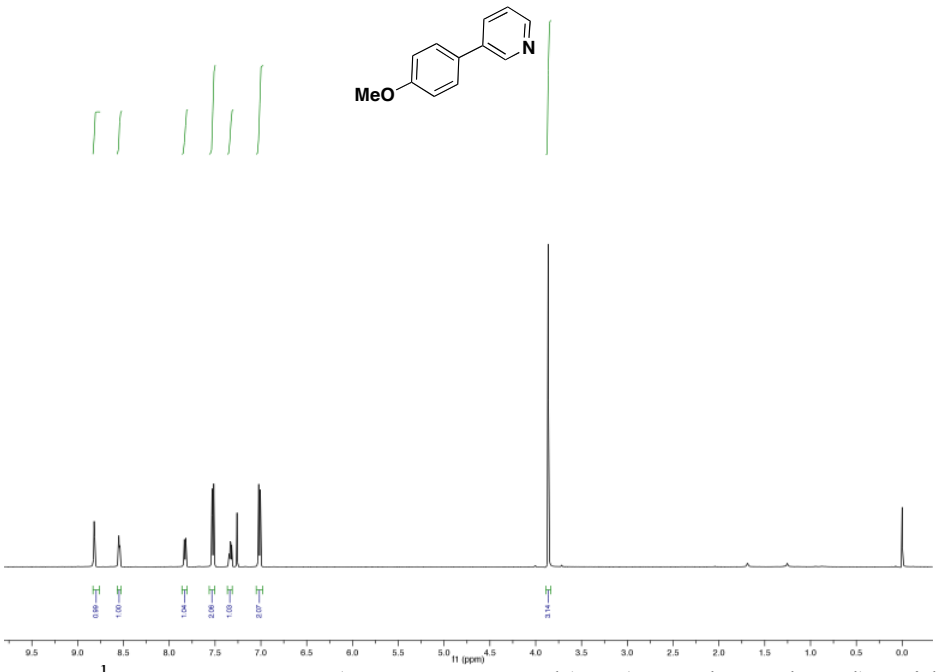

Figure A3.20 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 3-(4-Methoxyphenyl)pyridine (from the heteroaryl chloride in the second step)

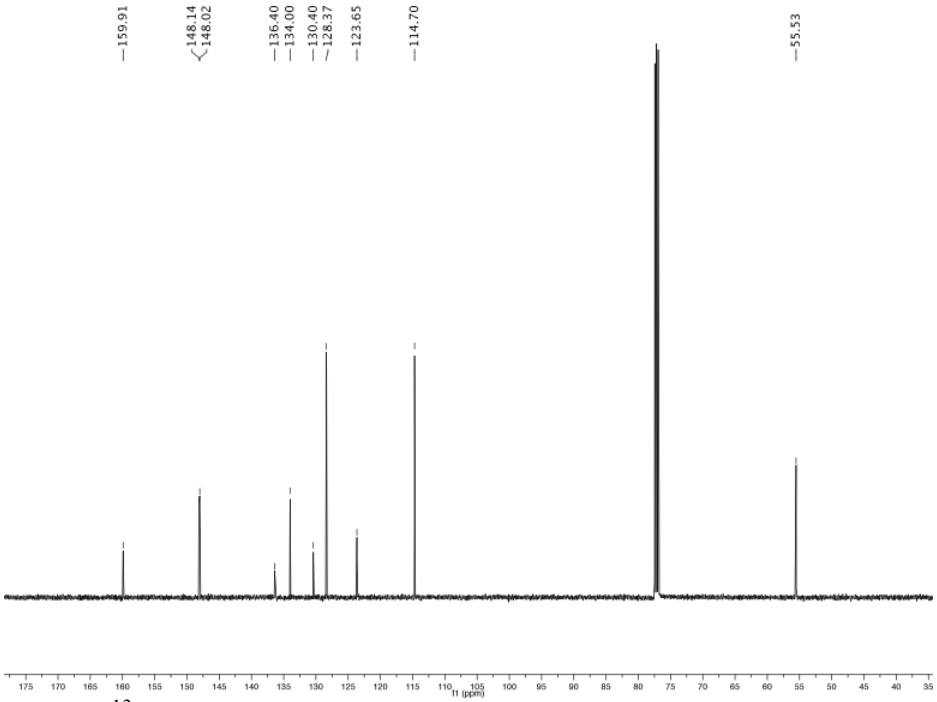

Figure A3.21 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) 3-(4-Methoxyphenyl)pyridine (from the heteroaryl chloride in the second step)

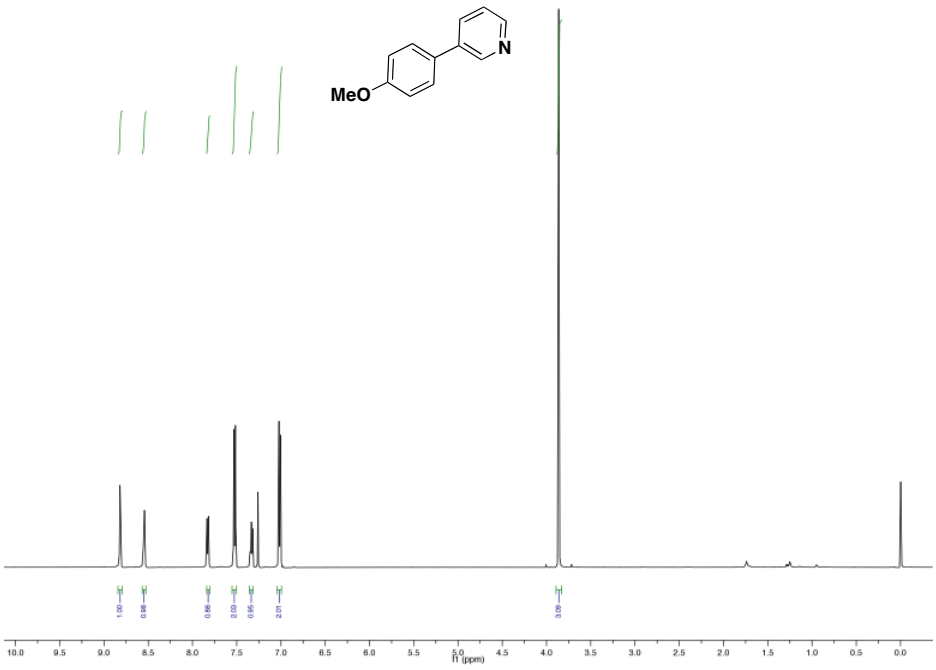

Figure A3.22 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 3-(4-Methoxyphenyl)pyridine (from the heteroaryl bromide in the second step)

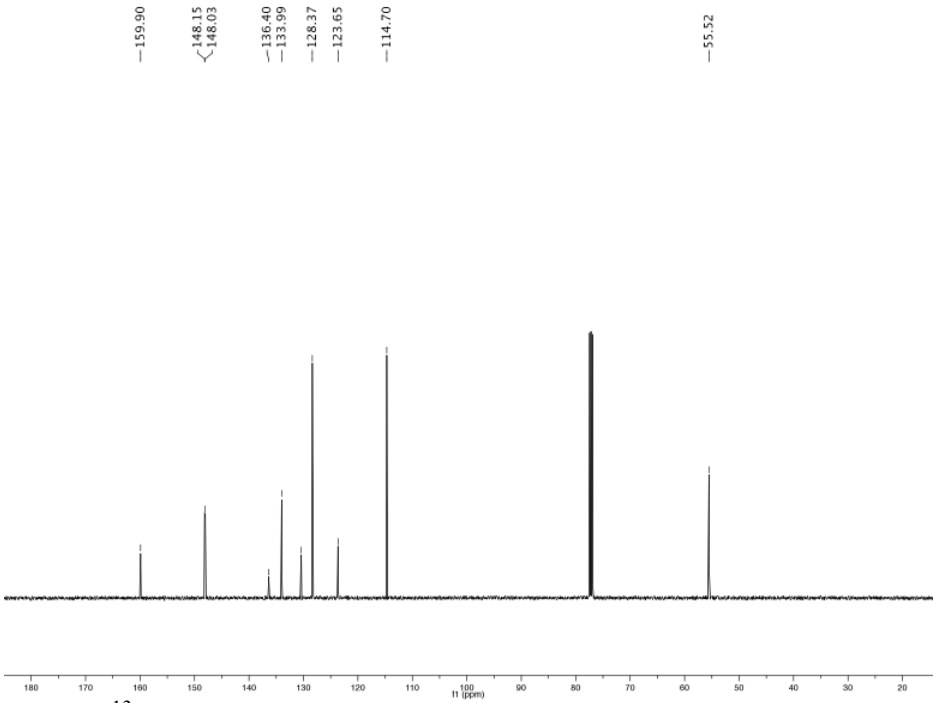

Figure A3.23 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) 3-(4-Methoxyphenyl)pyridine (from the heteroaryl bromide in the second step)

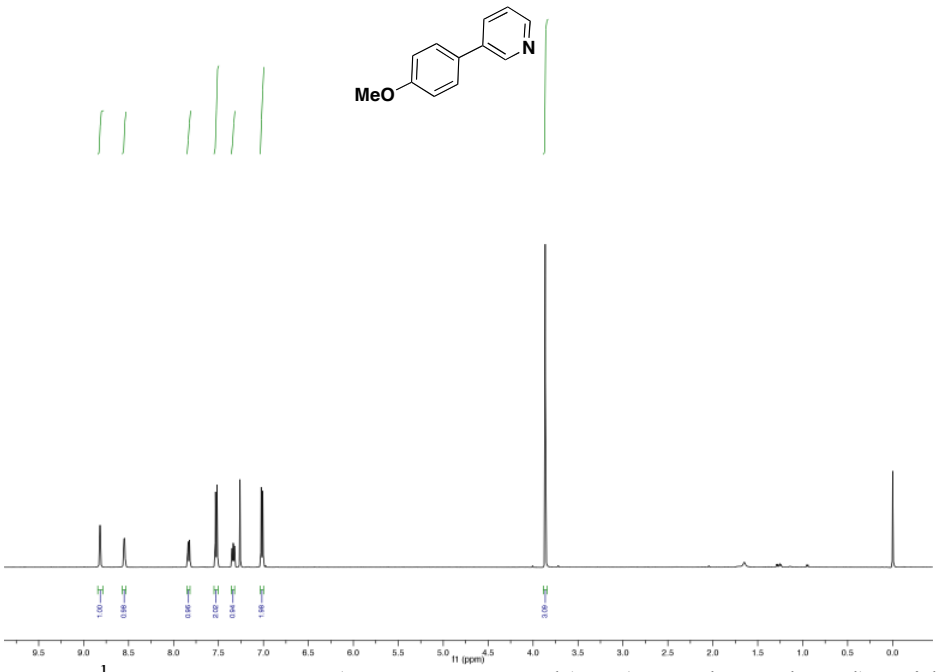

Figure A3.24 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 3-(4-Methoxyphenyl)pyridine (from the heteroaryl chloride in the second step)

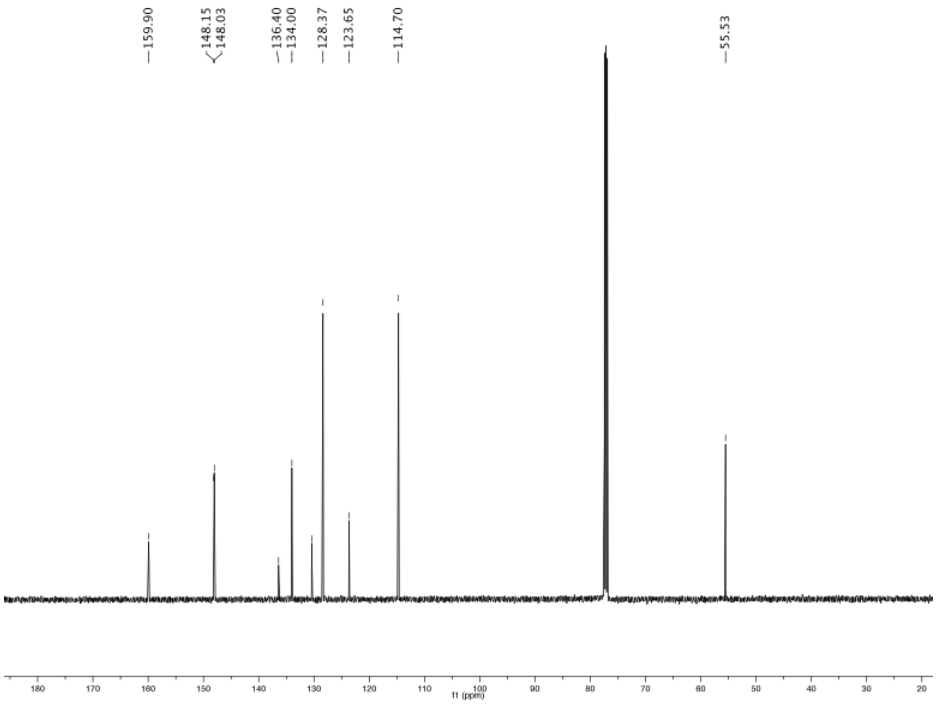

Figure A3.25 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) 3-(4-Methoxyphenyl)pyridine (from the heteroaryl chloride in the second step)

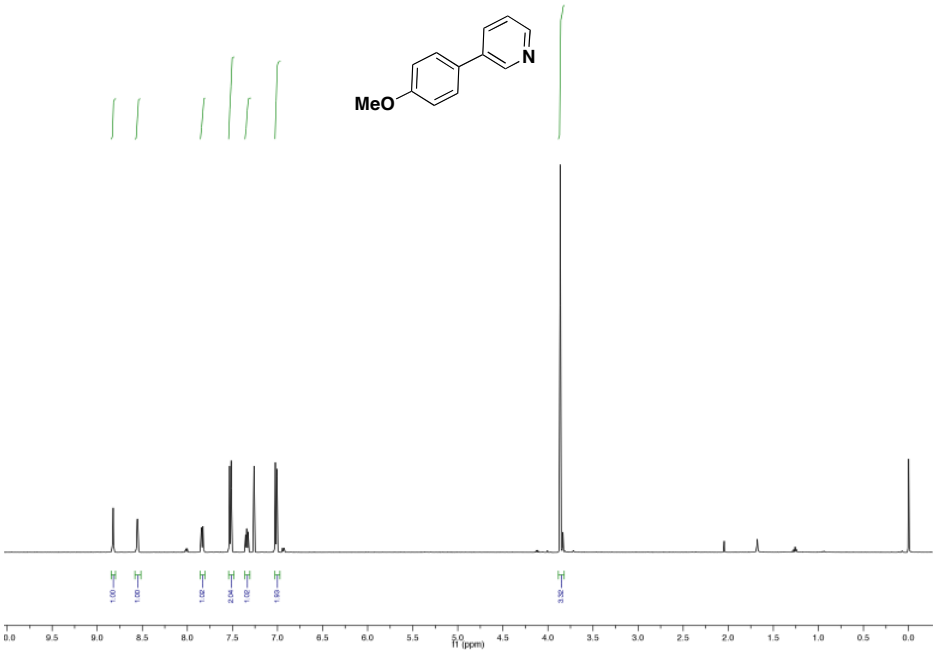

Figure A3.26 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 3-(4-Methoxyphenyl)pyridine (from the heteroaryl bromide in the second step)

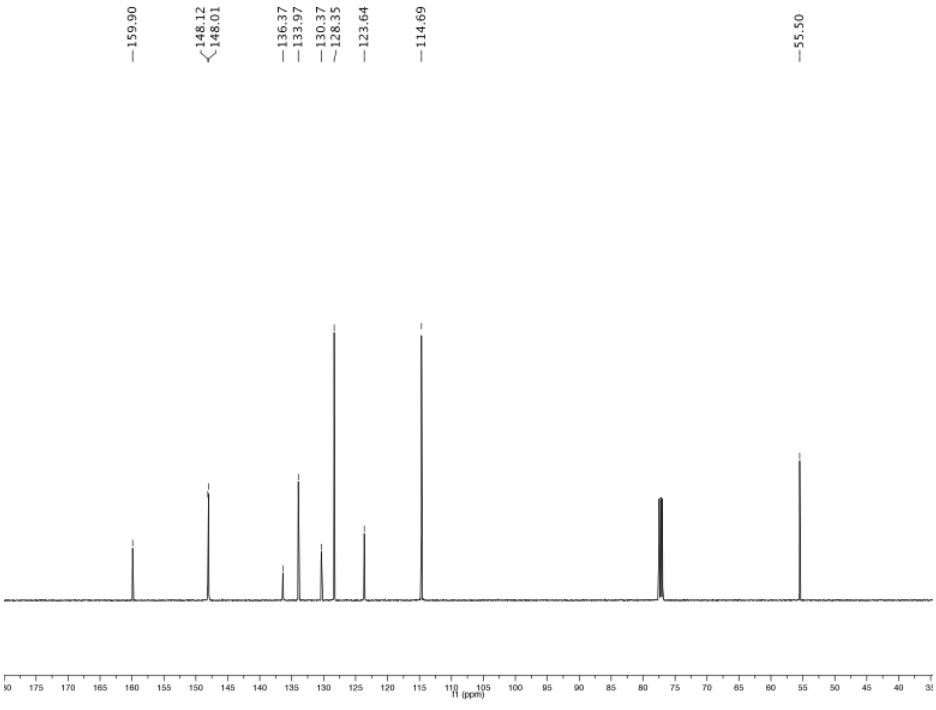

Figure A3.27 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) 3-(4-Methoxyphenyl)pyridine (from the heteroaryl bromide in the second step)

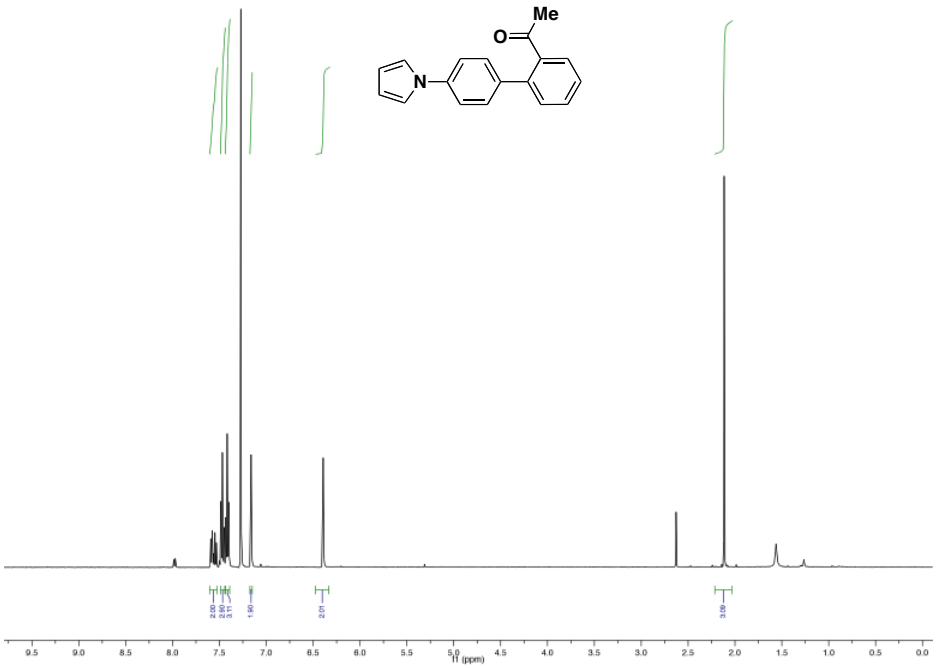

Figure A3.28 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 1-(4'-(1*H*-Pyrrol-1-yl)-[1,1'-biphenyl]-2-yl)ethanone

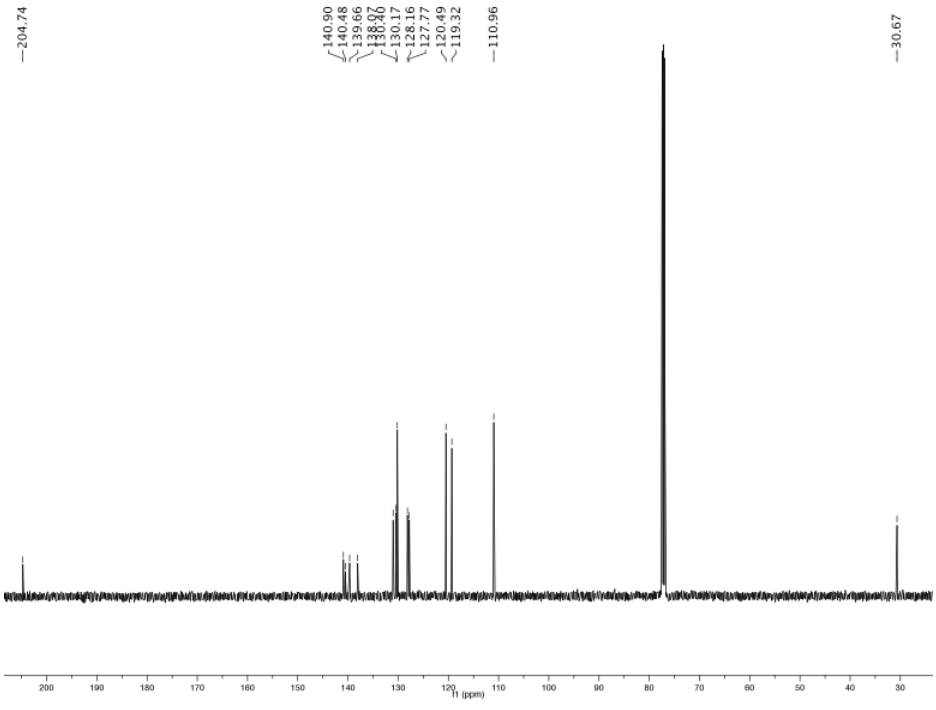

Figure A3.29 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) 1-(4'-(1*H*-Pyrrol-1-yl)-[1,1'-biphenyl]-2-yl)ethanone

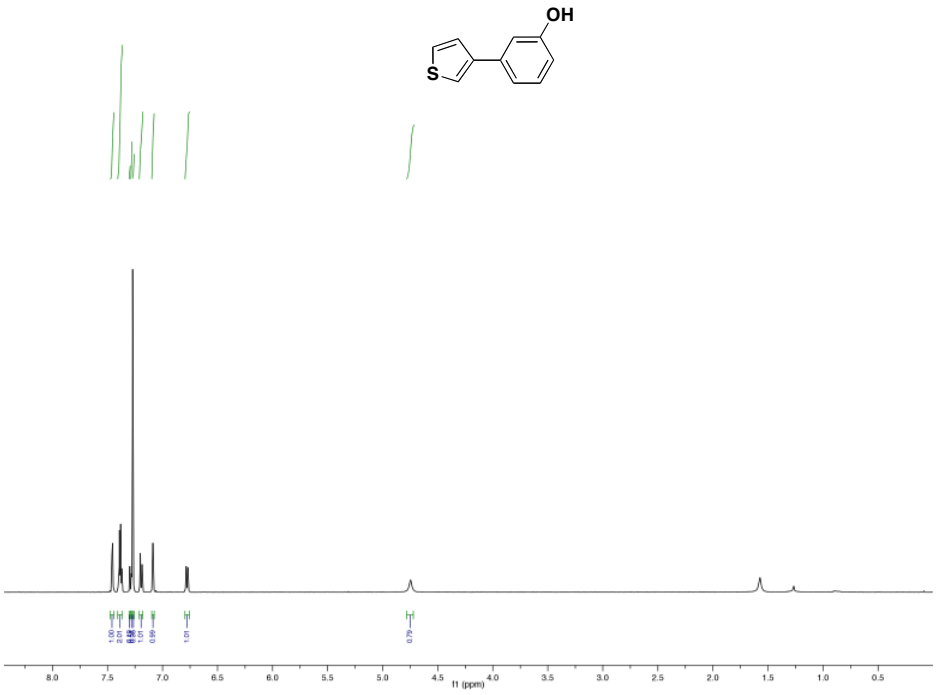

Figure A3.30 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 3-(Thiophen-3-yl)phenol (path B)

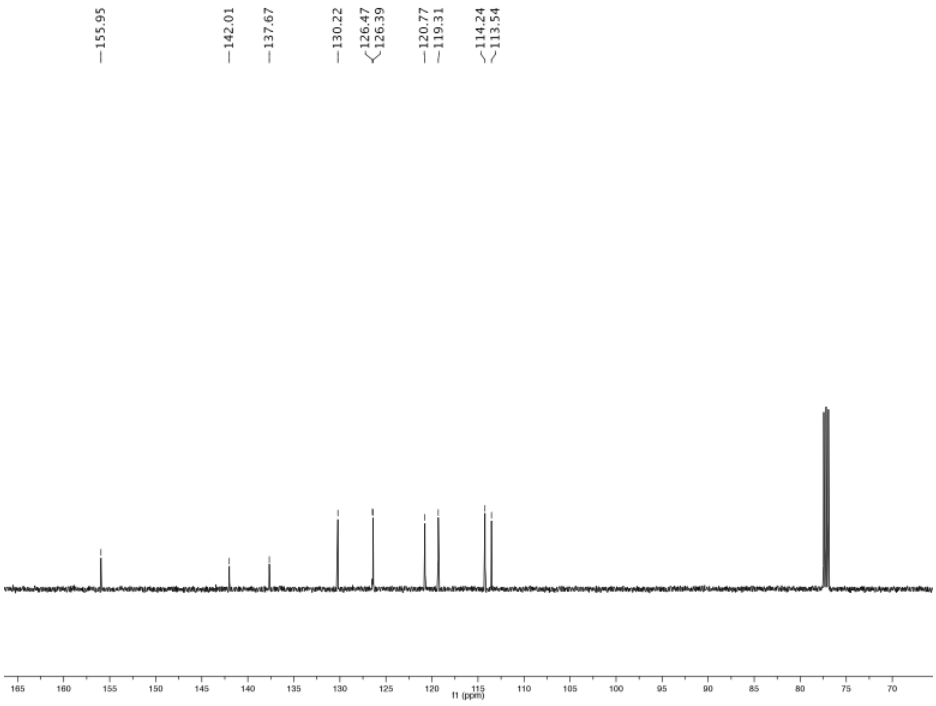

Figure A3.31 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) 3-(Thiophen-3-yl)phenol (path B)

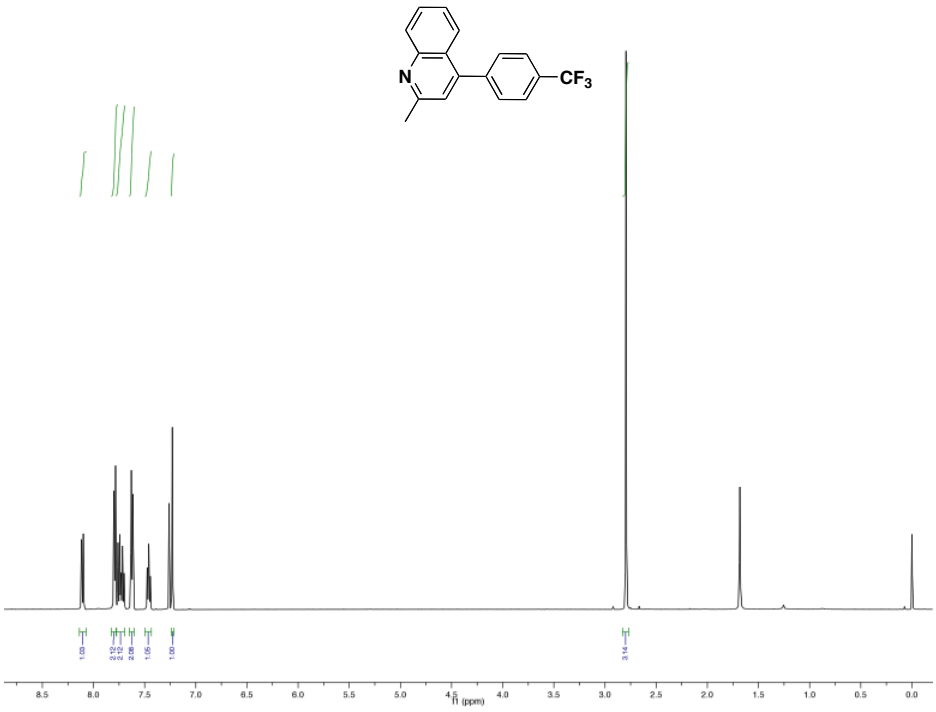

Figure A3.32 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 2-Methyl-4-(4-(trifluoromethyl)phenyl)quinolone (path A)

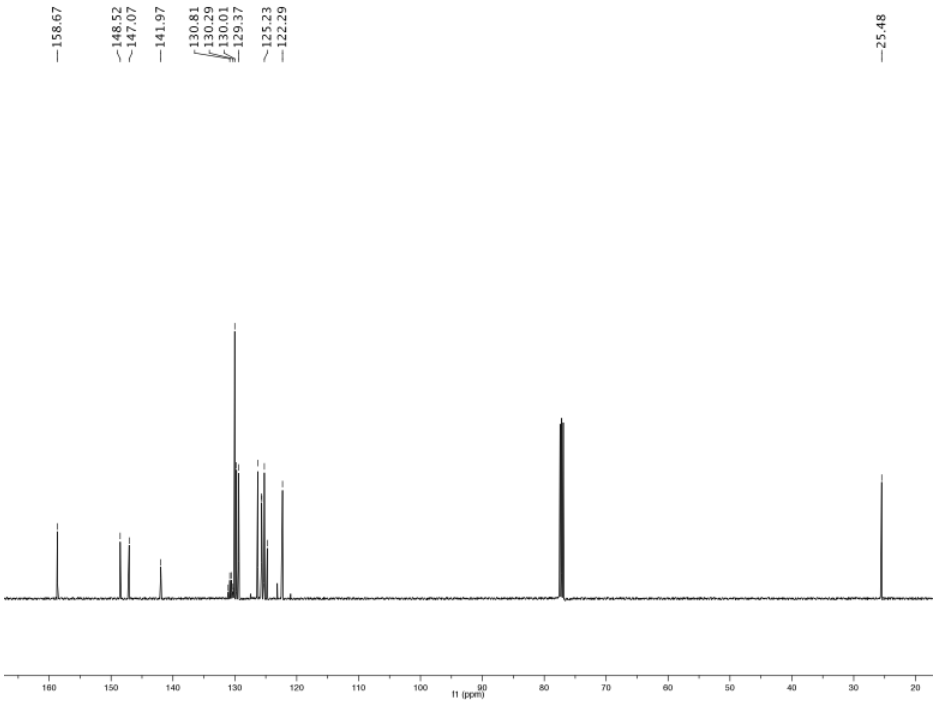

Figure A3.33 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) 2-Methyl-4-(4-(trifluoromethyl)phenyl)quinolone (path A)

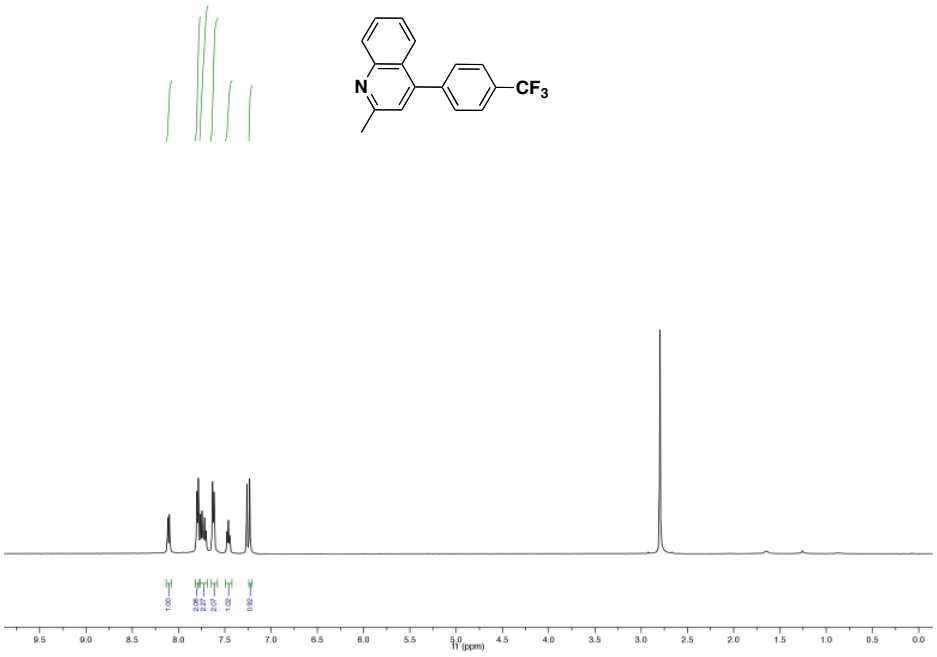

Figure A3.34 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 2-Methyl-4-(4-(trifluoromethyl)phenyl)quinolone (path B)

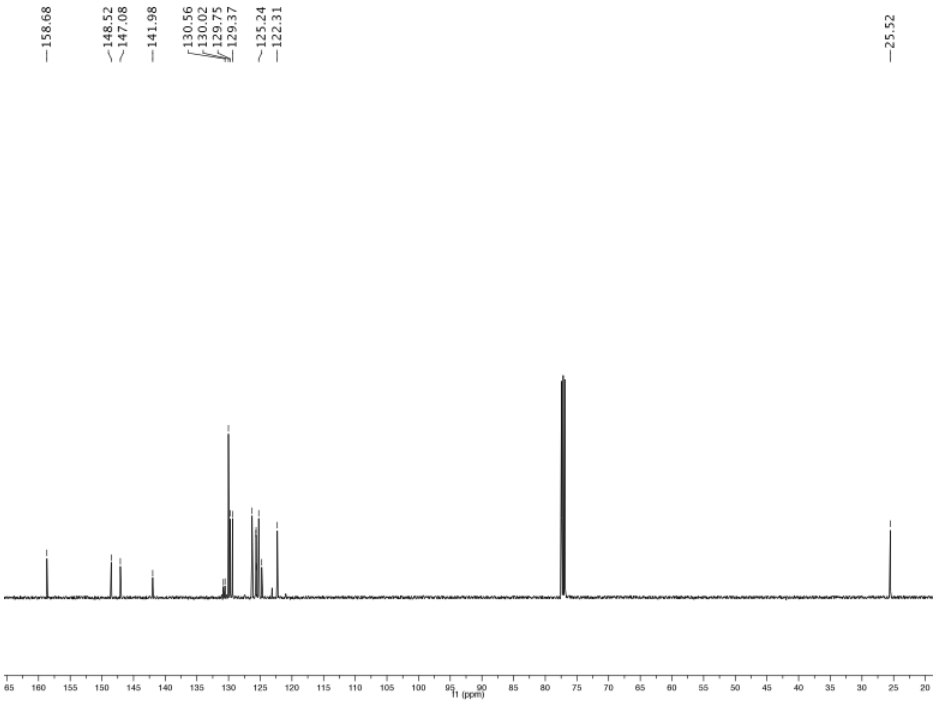

Figure A3.35 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) 2-Methyl-4-(4-(trifluoromethyl)phenyl)quinolone (path B)

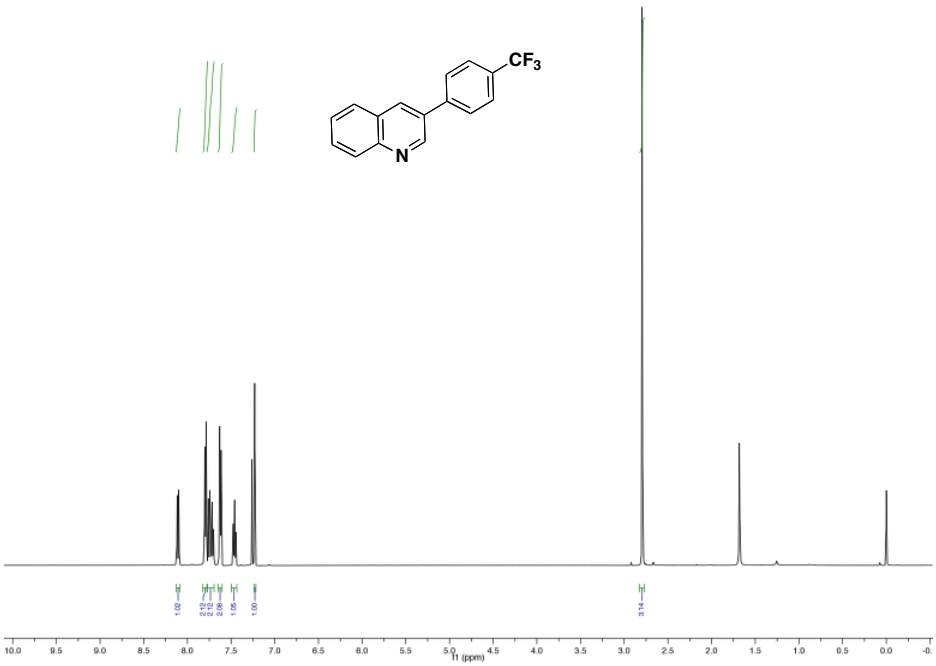

Figure A3.36 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 3-(4-(trifluoromethyl)phenyl)quinolone (path A)

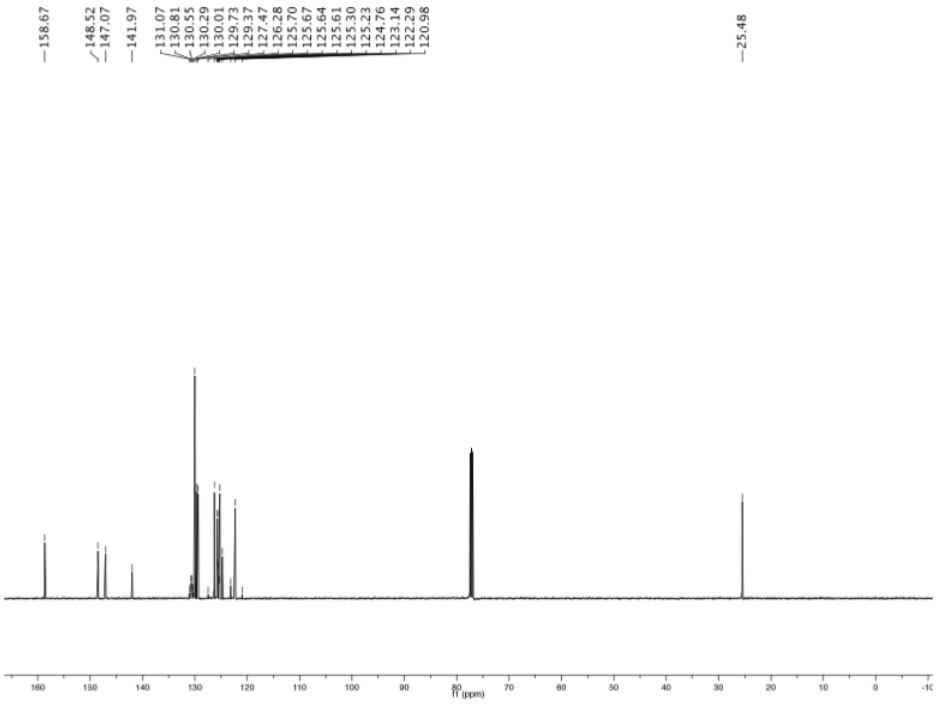

Figure A3.37 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) 3-(4-(trifluoromethyl)phenyl)quinolone (path A)

Appendix A4. ^{1}H, ^{13}C, ^{11}B, and ^{19}F Spectra Relevant to Chapter 6

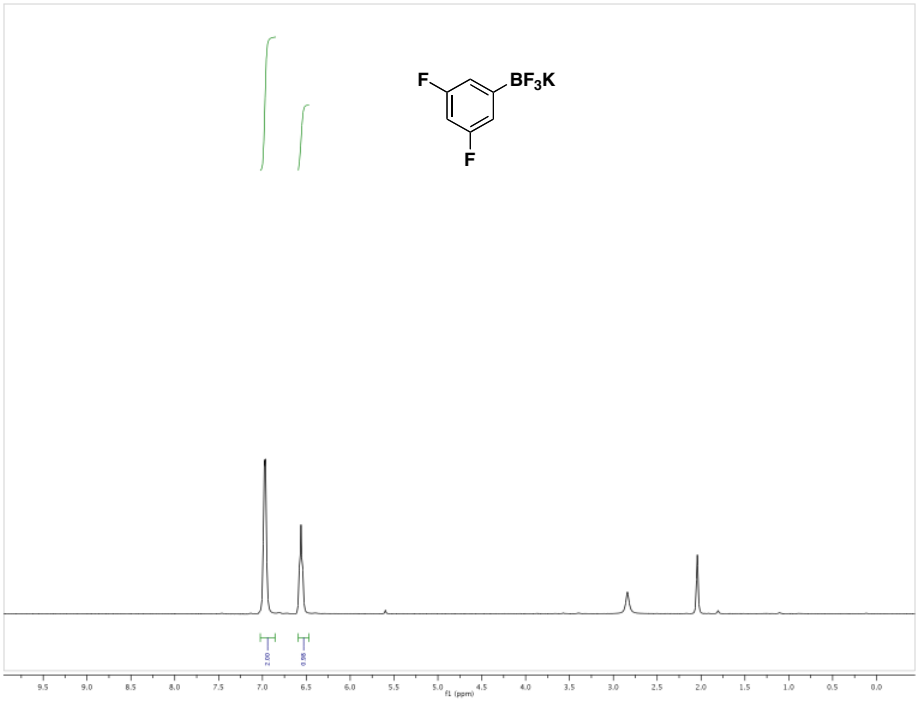

Figure A4.1 ^{1}H NMR Spectra (500 MHz, acetone-d_6**)** Potassium (3,5-Difluorophenyl)trifluoroborate

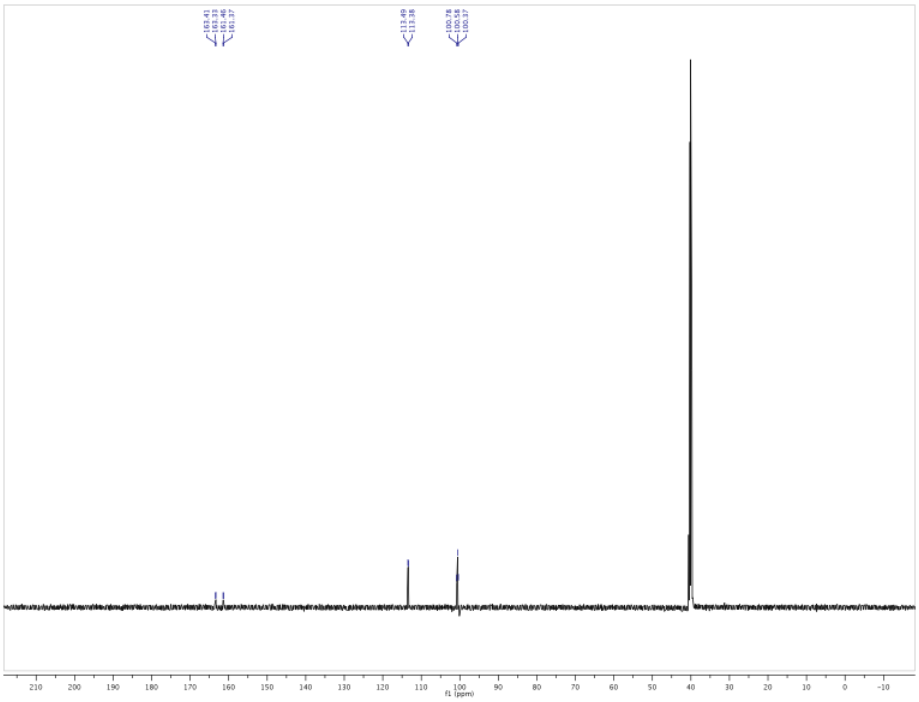

Figure A4.2 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (3,5-Difluorophenyl)trifluoroborate

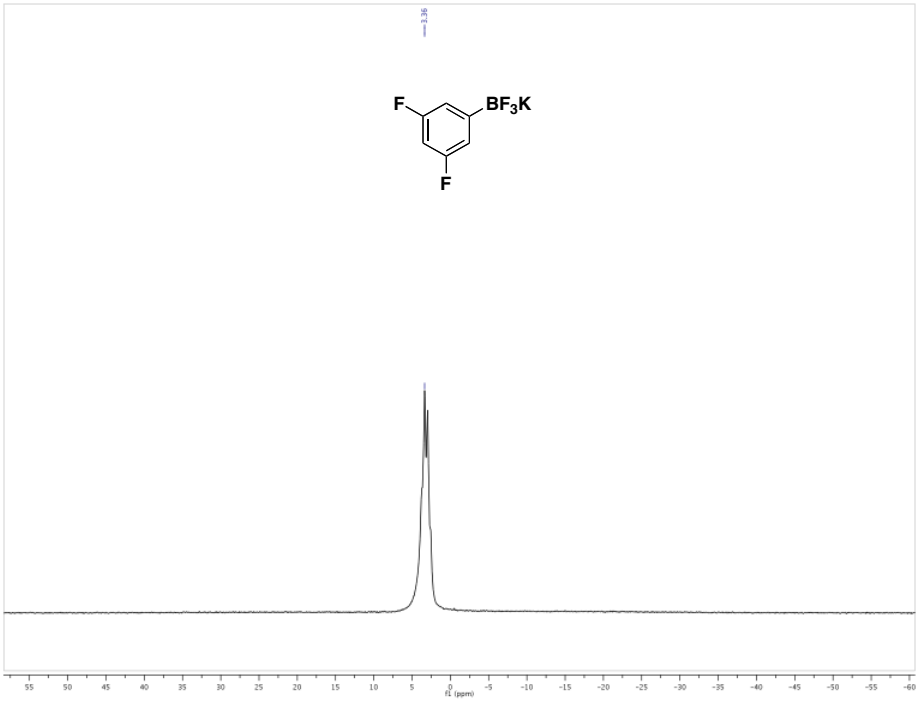

Figure A4.3 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (3,5-Difluorophenyl)trifluoroborate

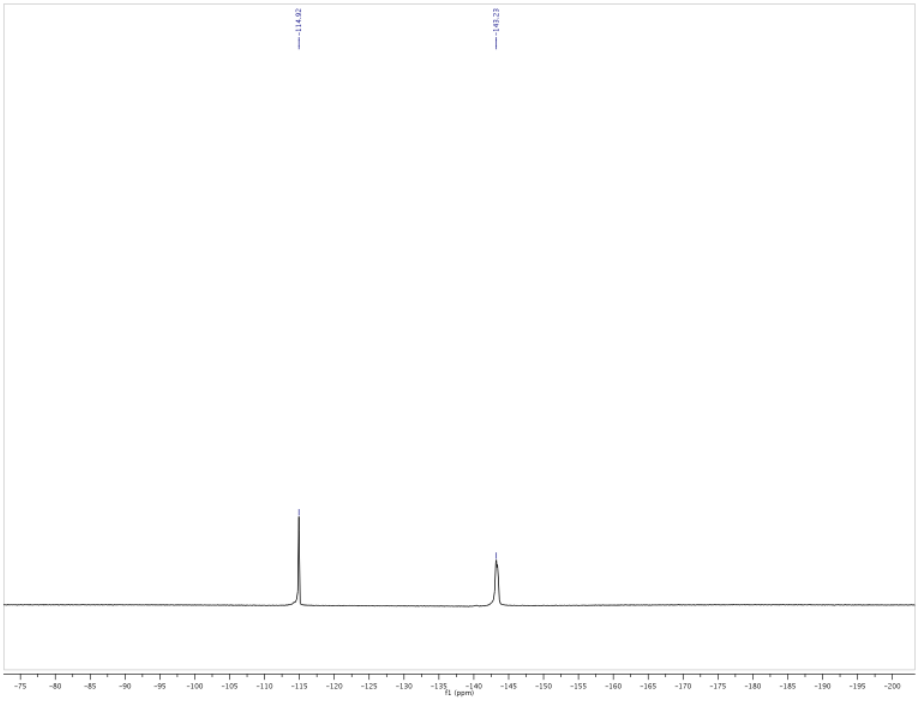

Figure A4.4 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (3,5-Difluorophenyl)trifluoroborate

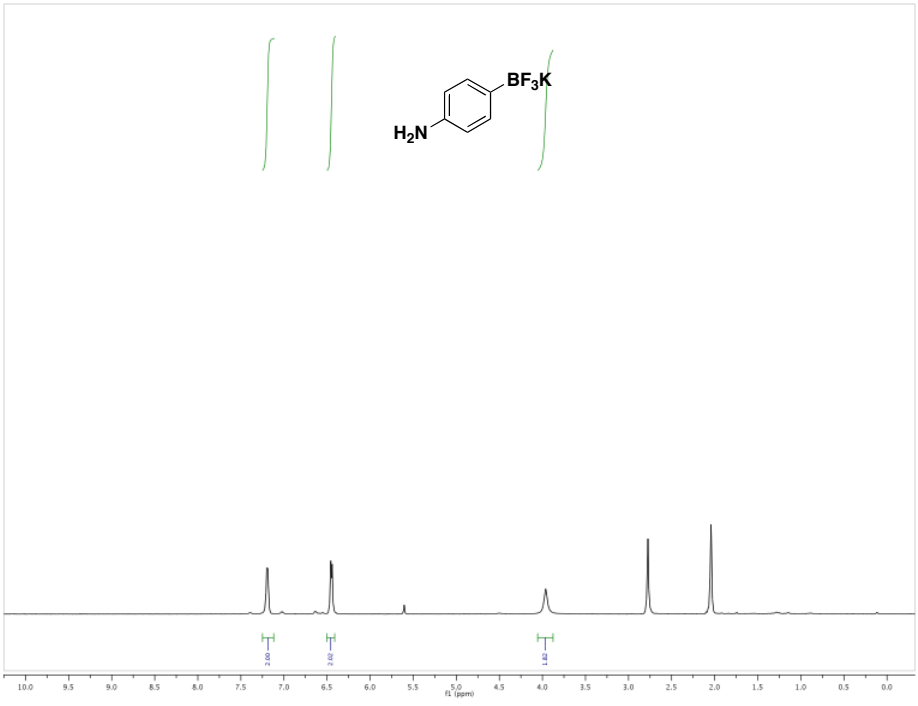

Figure A4.5 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (4-Aminophenyl)trifluoroborate

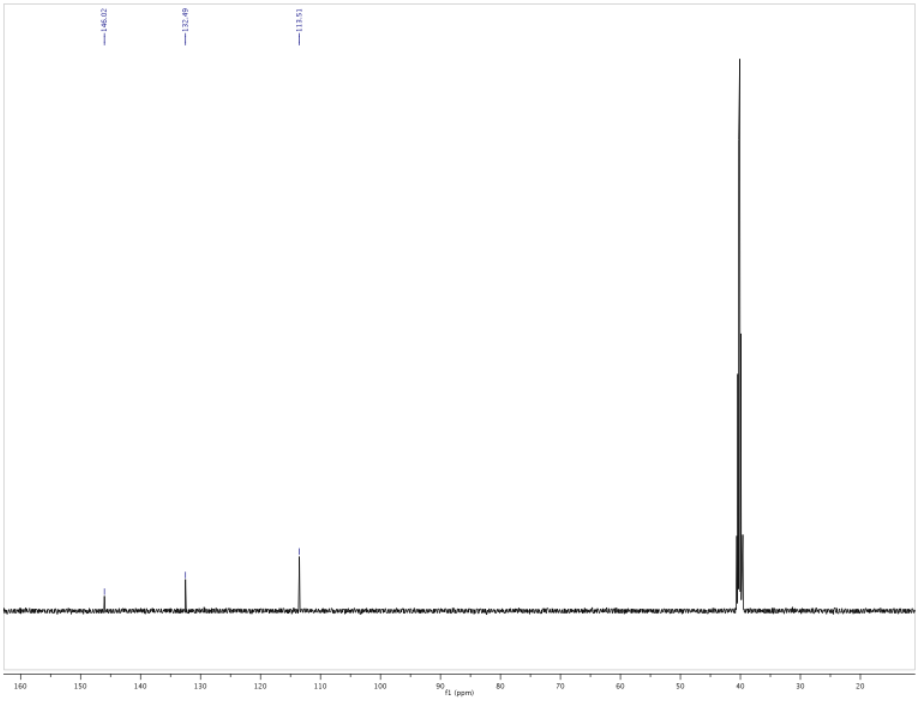

Figure A4.6 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (4-Aminophenyl)trifluoroborate

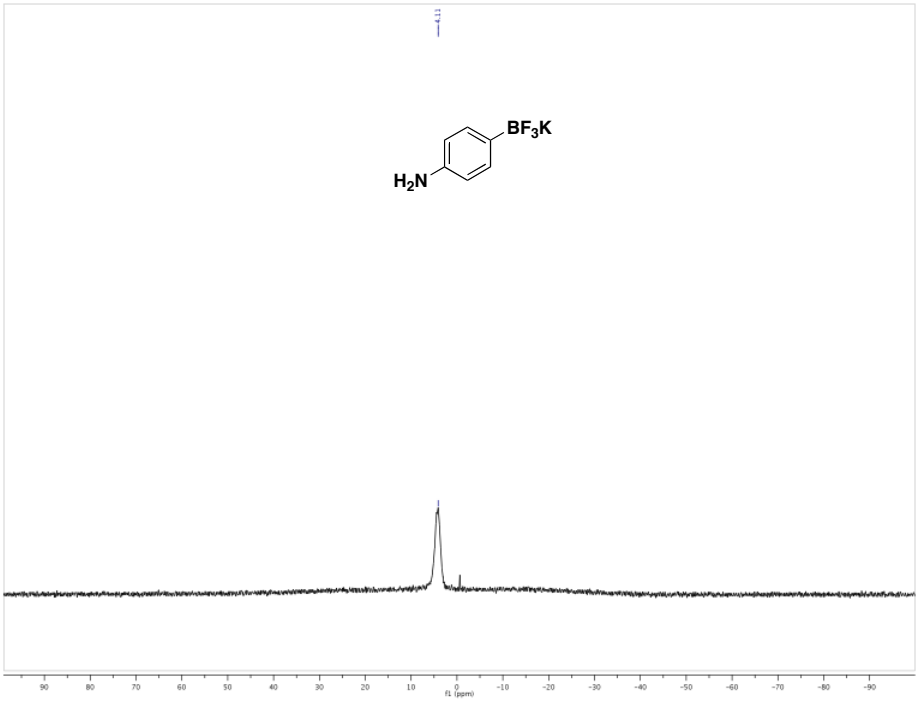

Figure A4.7 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (4-Aminophenyl)trifluoroborate

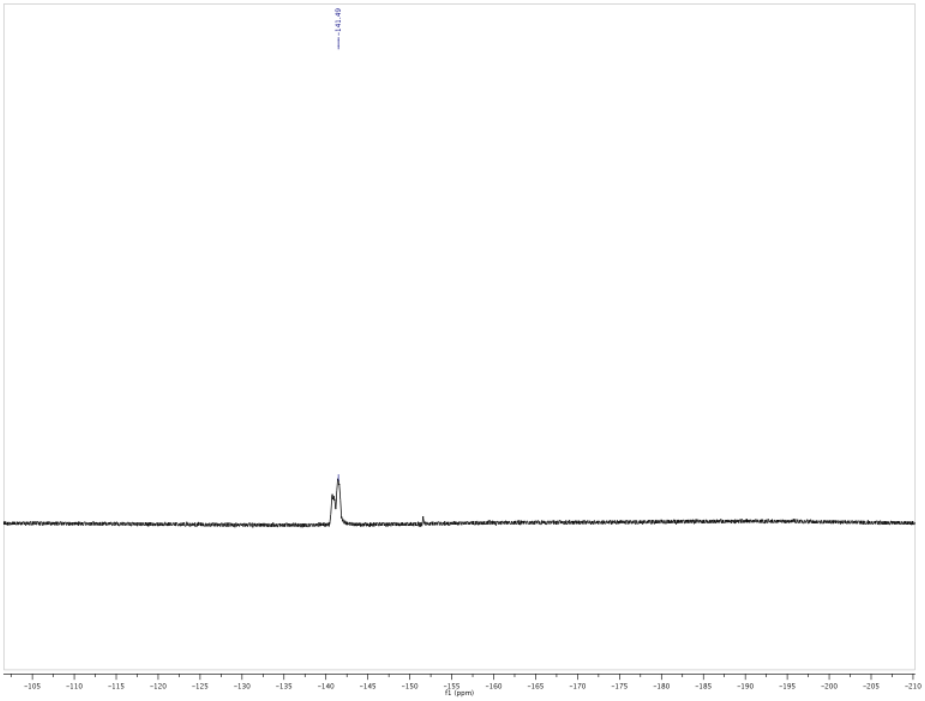

Figure A4.8 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (4-Aminophenyl)trifluoroborate

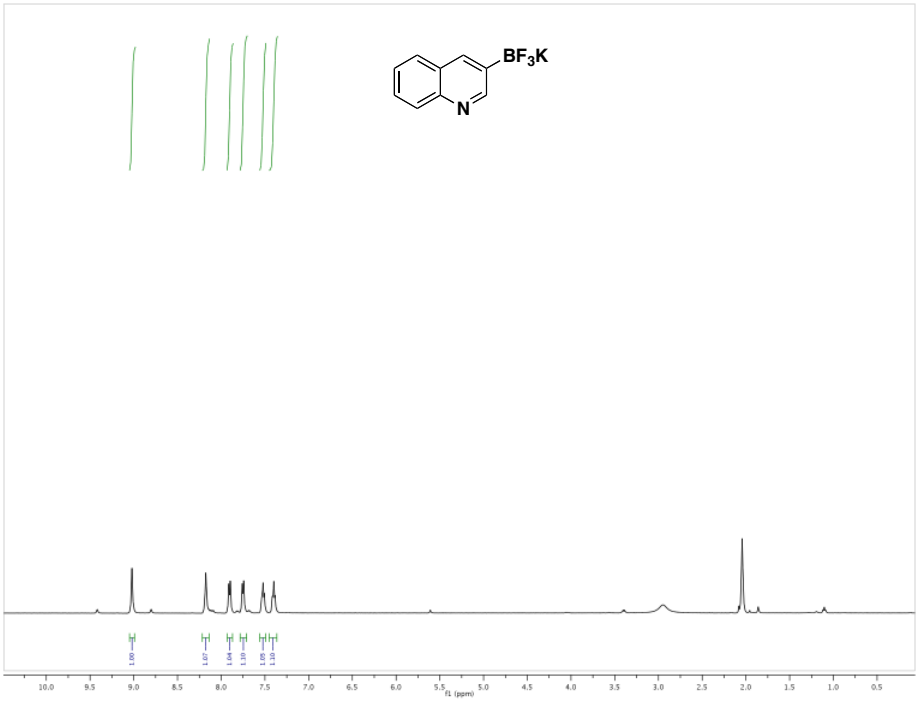

Figure A4.9 ^{1}H NMR Spectra (500 MHz, acetone-d_6) Potassium (Quinolin-3-yl)trifluoroborate

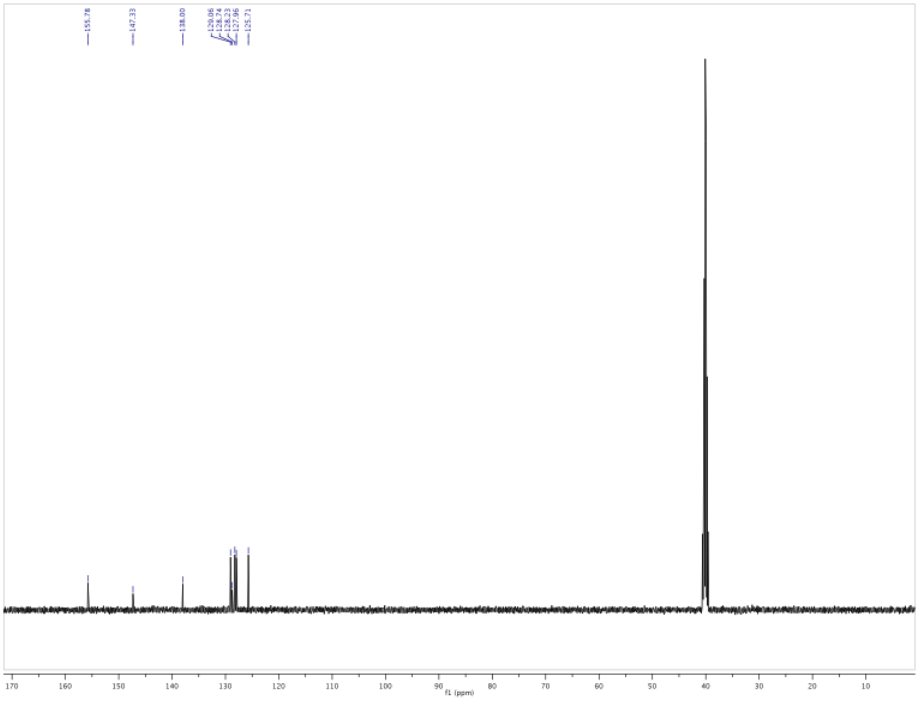

Figure A4.10 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium (Quinolin-3-yl)trifluoroborate

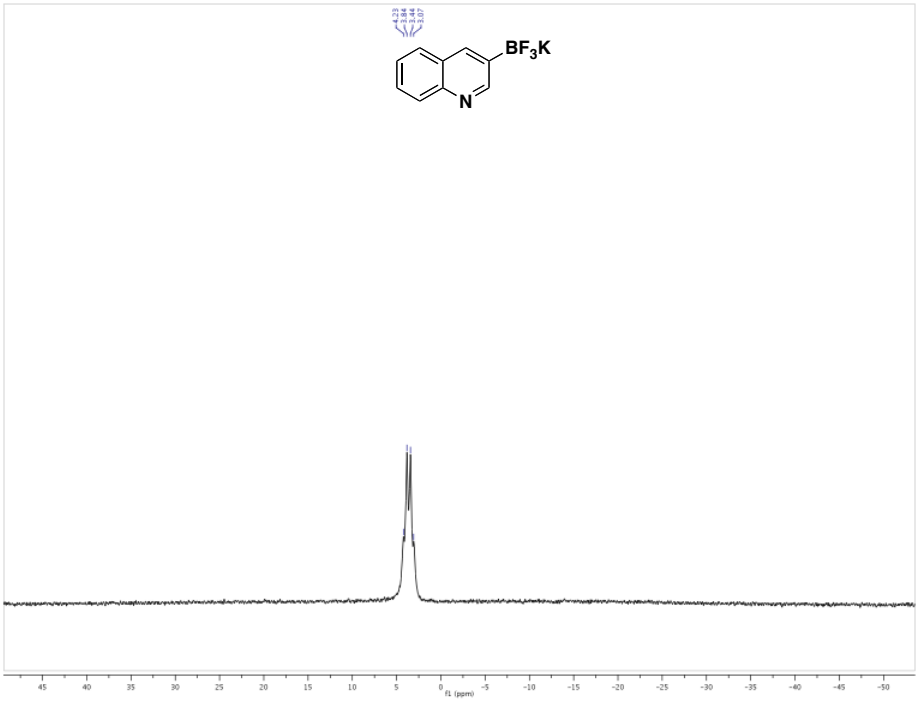

Figure A4.11 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium (Quinolin-3-yl)trifluoroborate

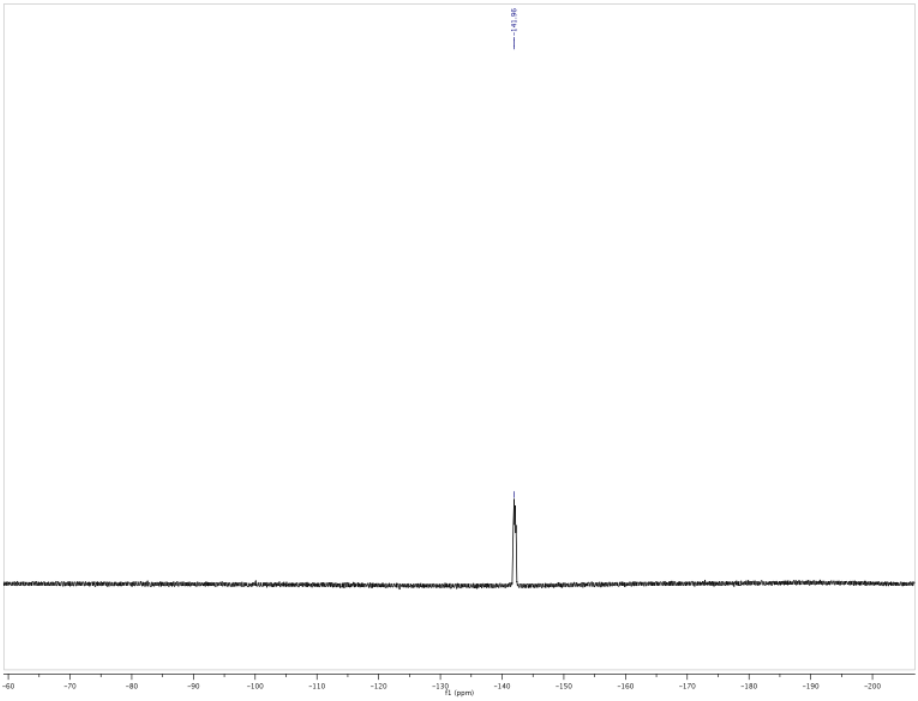

Figure A4.12 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium (Quinolin-3-yl)trifluoroborate

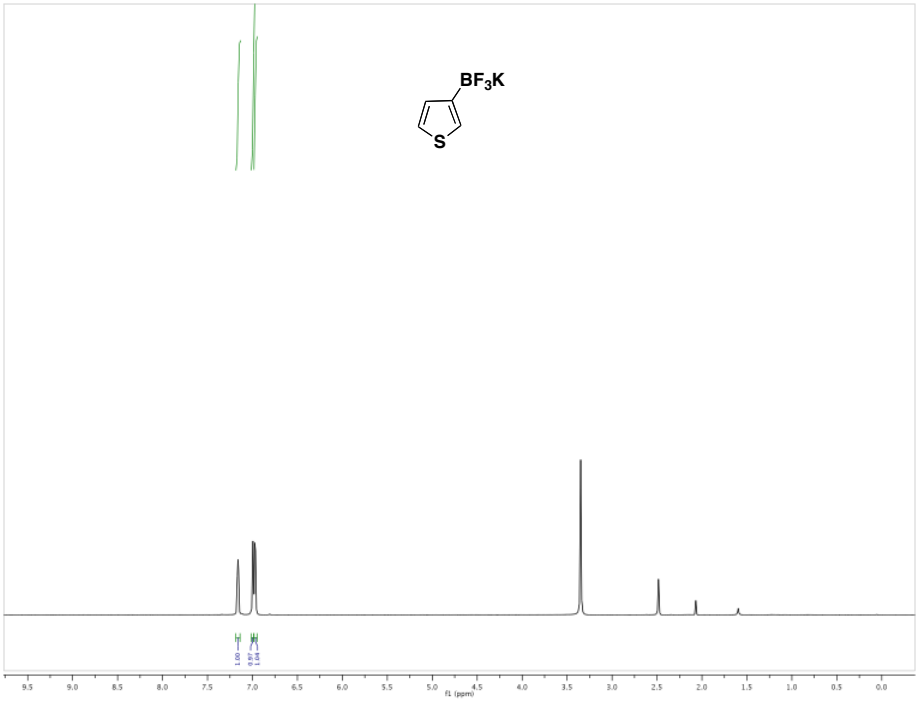

Figure A4.13 ^{1}H NMR Spectra (500 MHz, DMSO-d_6) Potassium Thiophen-3-yltrifluoroborate

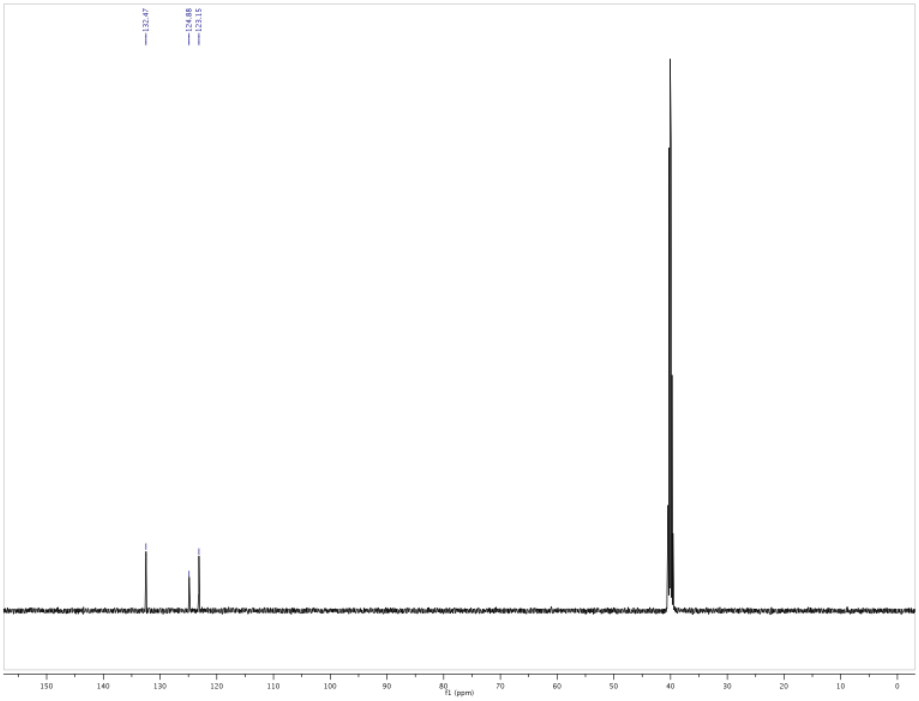

Figure A4.14 ^{13}C NMR Spectra (125.8 MHz, DMSO-d_6) Potassium Thiophen-3-yltrifluoroborate

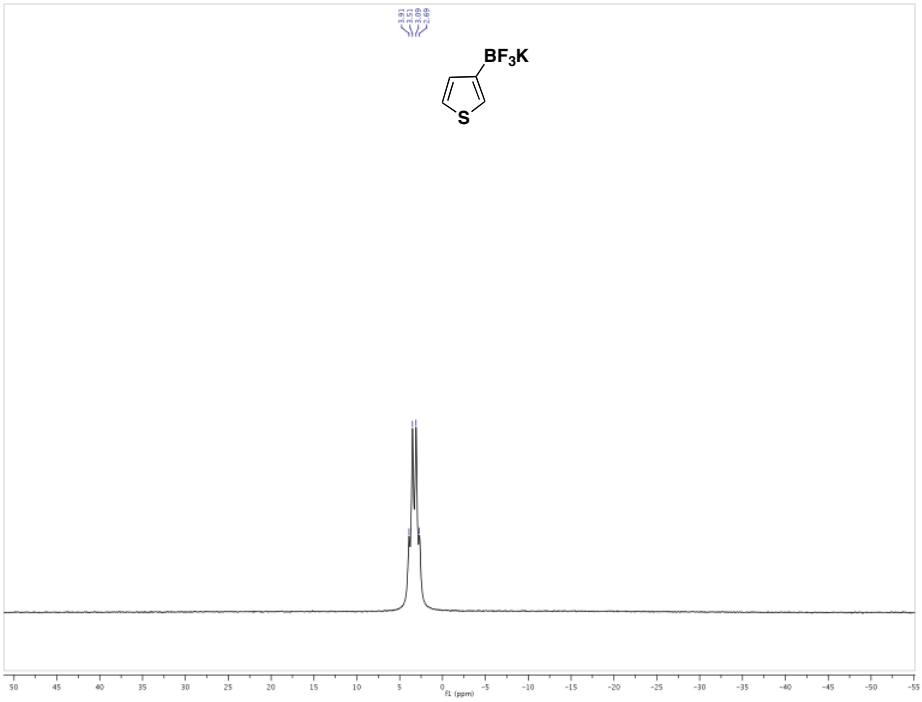

Figure A4.15 ^{11}B NMR Spectra (128.4 MHz, acetone-d_6) Potassium Thiophen-3-yltrifluoroborate

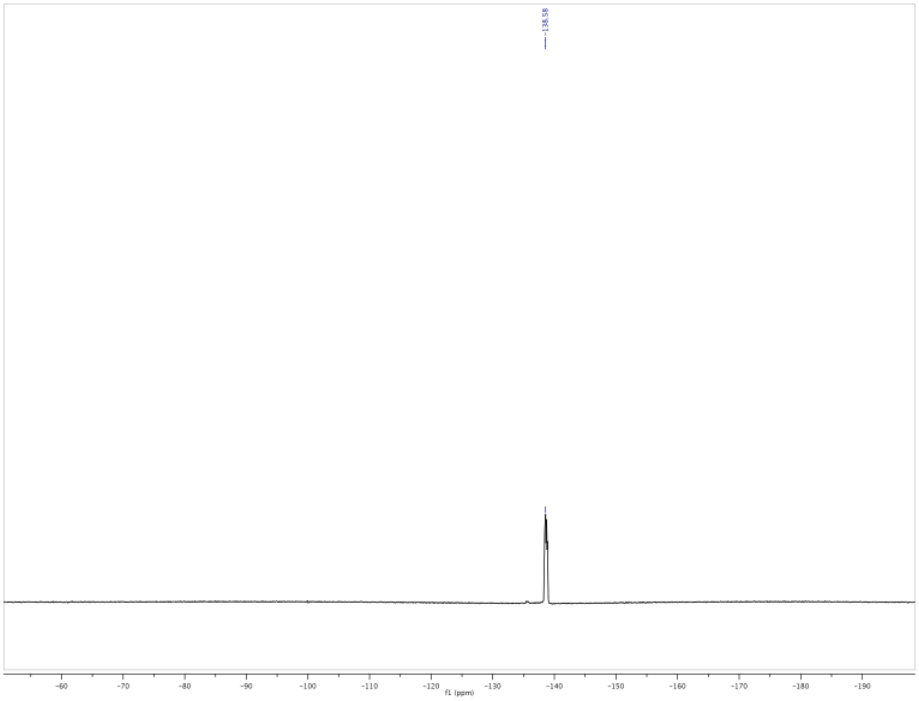

Figure A4.16 ^{19}F NMR Spectra (338.8 MHz, acetone-d_6) Potassium Thiophen-3-yltrifluoroborate

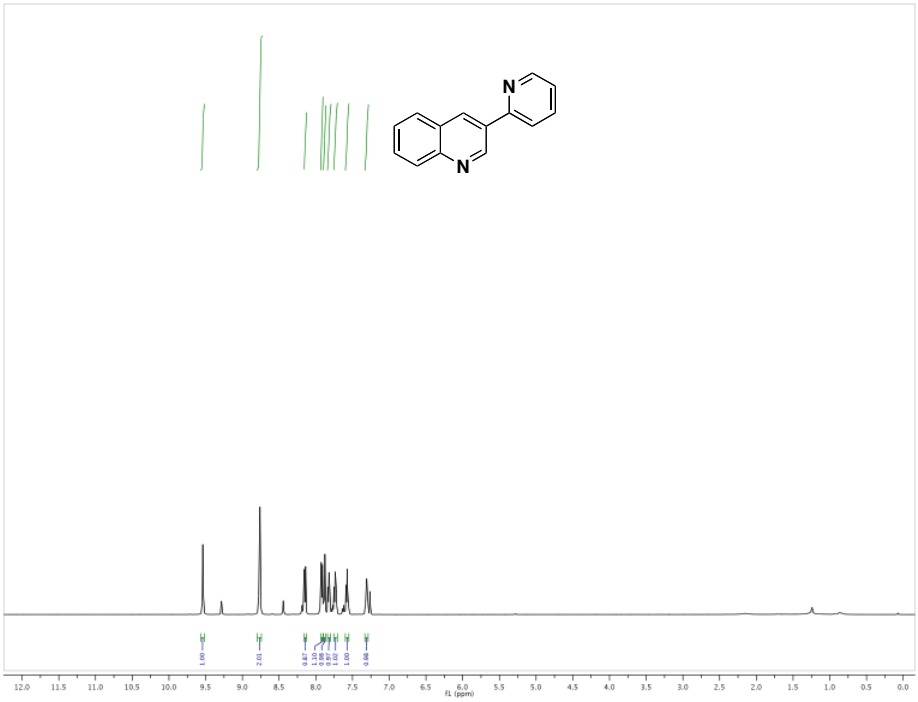

Figure A4.17 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 3-(Pyridin-2-yl)quinolone

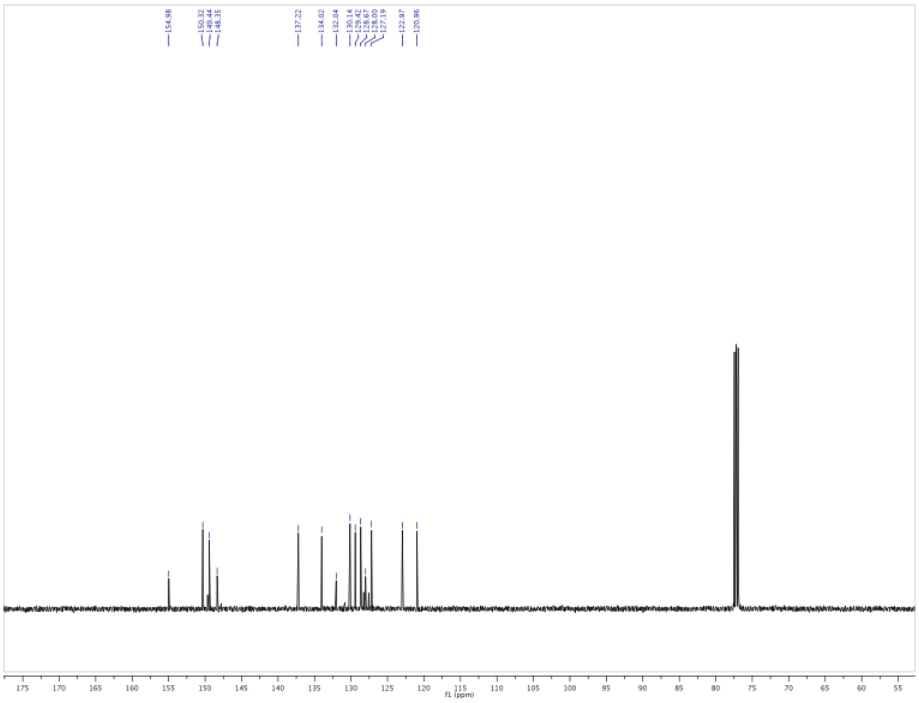

Figure A4.18 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) 3-(Pyridin-2-yl)quinolone

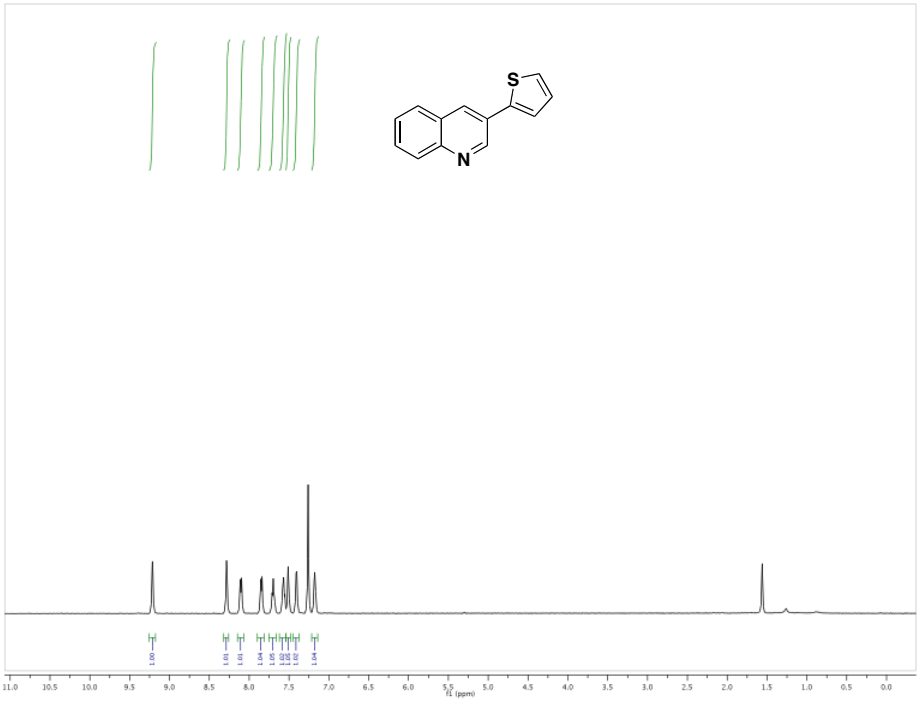

Figure A4.19 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 3-(Pyridin-2-yl)quinolone

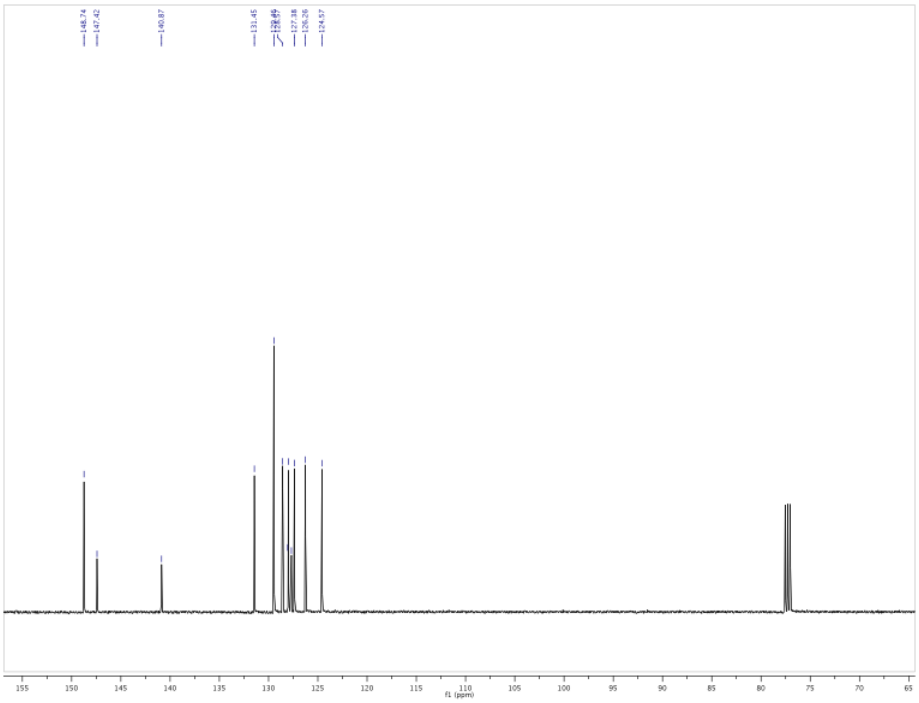

Figure A4.20 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$ 3-(Pyridin-2-yl)quinolone

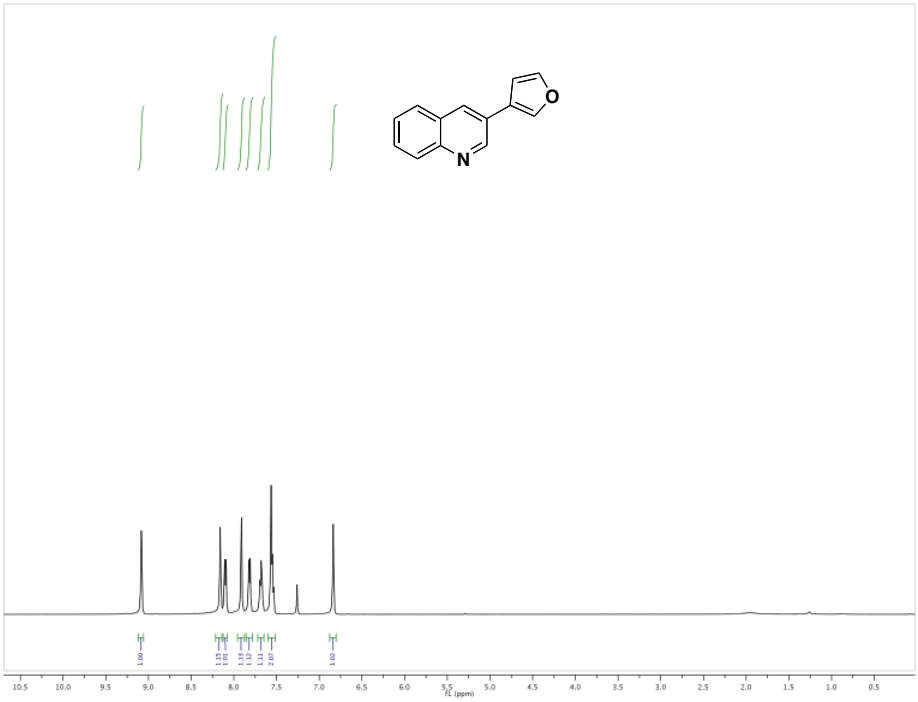

Figure A4.21 ^{1}H NMR Spectra (500 MHz, $CDCl_3$) 3-(Furan-3-yl)quinolone

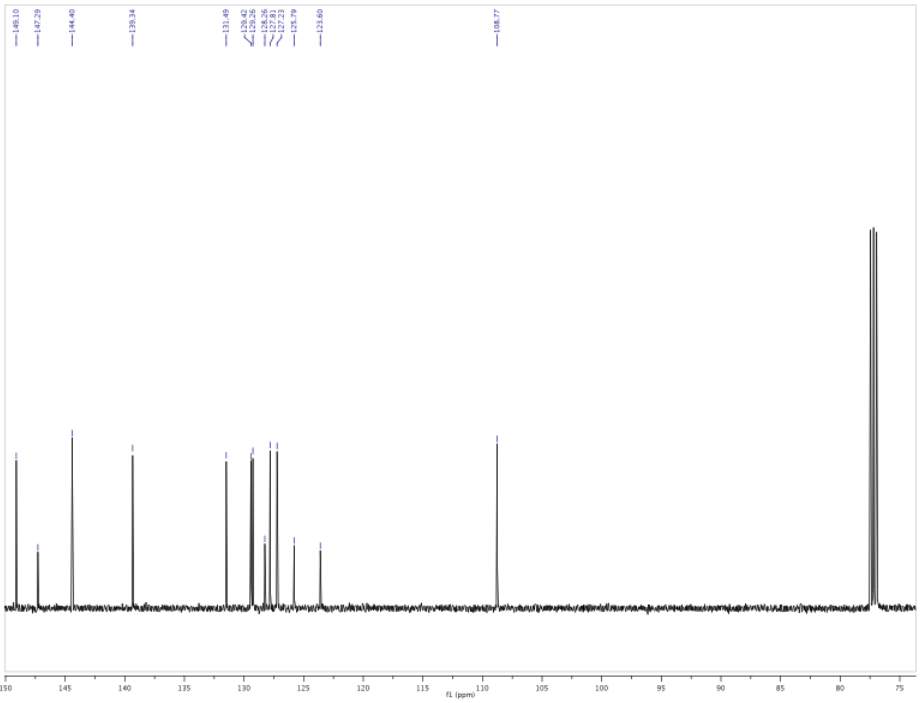

Figure A4.22 ^{13}C NMR Spectra (125.8 MHz, $CDCl_3$) 3-(Furan-3-yl)quinolone

ABOUT THE AUTHOR

Sarah Little Jane Trice was born in Phoenix, Arizona on September 10, 1981 to Arthur and Karen Husband. She grew up living in many Southwestern states including Colorado, Montana, and Utah. At age 10 she began studying the violin and was awarded a full music scholarship to Northern Arizona University in Flagstaff, Arizona in 2000.

After a few years studying music, she changed her major to chemistry on full academic scholarship. She graduated from Northern Arizona University *summa cum laude* with a degree in chemistry in 2005.

Shortly after graduation, Sarah joined the Medicinal Chemistry Department of the Merck Research Laboratories in West Point, PA. There, she began taking classes toward her PhD in chemistry at the University of Pennsylvania. After four years at the bench with Merck, Sarah was a granted a leave of absence and joined the Molander lab as a Merck Doctoral Fellow in the Fall of 2009.

While at the University of Pennsylvania, Sarah earned a Certificate of Business from the Wharton school. She also joined the Wharton Crew as both a sweep rower and coxswain. Sarah is now training to race as a scull rower. She plays and performs on her violin a small group of musicians, and sings whenever she can.

Sarah loves to travel and to meet new people from all corners of the world. She dreams one day of opening her own international restaurant, serving food inspired from all over the world. Upon graduation, Sarah will return to the Medicinal Chemistry Department of the Merck Research Laboratories.

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