CHEMOSELECTIVE SUZUKI-MIYAURA CROSS-COUPLING OF SUBSTRATES CONTAINING AN ARYL AND A SECONDARY BENZYLIC BORONIC ESTER

by

Marieke Naomi Hutchinson

A thesis submitted to the Department of Chemistry

In conformity with the requirements for

the degree of Masters of Science

Queen's University

Kingston, Ontario, Canada

(October, 2012)

Abstract

The Suzuki-Miyaura cross-coupling reaction has become extremely important in the area of industry and academia. The ability to cleanly cross-couple aryl, alkyl, or alkenyl boronic acids/esters with aryl, alkyl, or alkenyl halides to generate new C-C bonds has proven to be a versatile tool towards the synthesis of complex molecules. Over the past three decades, there has been an array of developments and accomplishments in this area of research including the joint awarding of the 2010 Nobel Prize in Chemistry to Suzuki, Heck, and Negishi.

Our group published the first successful example of the cross-coupling of chiral secondary benzylic boronic esters. The key components in this reaction were the incorporation of silver oxide and excess triphenyl phosphine. Silver oxide was required for the transmetallation step to occur. Remarkably, the reaction was not only effective for the coupling of these challenging substrates; it was also selective for the branched benzylic species in the presence of a linear alkyl boronic ester.

In order to further probe the selectivity of the aforementioned cross-coupling reaction, we have prepared a substrate that incorporates both an aryl and a secondary benzylic boronic ester. Since the secondary benzylic boronic ester requires specialized conditions for the cross-coupling to proceed, we have been able to employ this reaction to introduce two different substituents in place of the boron groups based solely on reaction conditions. Herein, we discuss the optimization and successful chemoselective/iterative Suzuki-Miyaura cross-coupling of a substrate that incorporates both an aryl and a

secondary benzylic boronic ester without the need of protecting groups on the boron atoms.

Acknowledgements

Over the past two years, Kingston has been a beautiful place to call my home away from home. Not only have I had a lot of rewarding experiences but also have had the pleasure of building great relationships.

First of all, I would like to thank my supervisor Dr. Cathleen Crudden for her support and guidance on my project. Dr. Crudden provided insight towards my project and was always there to give me a push in the right direction when research was discouraging. Along with Dr. Crudden came the support of the Crudden Group. The Crudden Group has consisted of an array of talented people whom I have had the pleasure to work with on a daily basis. Thanks to all of you for brightening my days and keeping life interesting. This graduate work has been enhanced by your support, advice, friendships, and laughter.

Before the Crudden Group there was the Fagnou Group. In June 2009, I began my graduate studies with Dr. Keith Fagnou. The Fagnou Group was filled with friendly, aspiring, and intelligent students, some of whom I have continued communication with. However, unpredicted events occurred in November 2009 that led to the death of Dr. Fagnou. His loss was not only devastating to the ones closest to him, but also to the scientific world. Even though this was a challenging situation, I feel honored that I got the chance to work with such an inspired, scholarly, and genuine person like Dr. Fagnou. The knowledge, publication, and skills I acquired from my experience at the University of Ottawa prepared me further for attaining a Master's in Chemistry. The joint chairs of the chemistry department at the University of Ottawa were extremely accommodating

during the transition to a new research group. A special mention to my amazing roommates in Ottawa, Jasmine and Danielle, who welcomed and supported me with love and hugs, as well as a huge thanks to Brett and Alex for housing me during a mold infestation in my apartment.

Where would one be without their friends and family? This degree requires a tremendous thanks to all of you as well. If you are actually reading this, then you are most definitely a friend, feel free to stop after this page. Thanks to all of you who listened to me ramble on about chemistry even though your eyes glazed over when I talked about it, I just ignored this fact and kept rambling. Thanks for the support, love, hugs, dancing, laughter, adventures, conversation, prayers… this list could continue into a thesis within itself. Geneva House = Awesome. Thanks Kyle MacDonald, roommate extraordinaire. Most recently, I would like to send a shout out to the amazing girls at 45 Park Street; thanks for the hugs, support, and fun this September. You are all so very awesome and I love you.

Thanks Mom and Dad, you are my foundation. Thanks for taking care of my loved four-footed friend, Ms. Jasmine Caramel (Jazz). Your visit this June was timely, as well as the home cooked freezer meals that have kept me well-nourished during thesis writing. This thesis may not have been written if Dad hadn't persistently asked, since this past February, "How is your thesis coming? Are you done yet?".

I would like to dedicate my thesis to my Nan, the late Lillian Beaton. Ever since I was born, you supported my dreams and were one of the best grandmothers a girl could have. Every day you inspire me to be a better and stronger person. I will always love you with all my heart.

Table of Contents

List of Figures

List of Schemes

List of Tables

Abbreviations

9-BBN = 9-borabicyclo[3.3.1]nonane

Ac = acetyl

acac = acetylacetone

Alk = alkyl

Ar = aryl

BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

B:L = branched to linear ratio

Bu = butyl

C-C = carbon-carbon

COD = 1,5- cyclooctadiene

Cp = cyclopentyldienyl

Cy = cyclohexyl

dan = 1,8-diaminonaphthalene

dba = dibenzylidene acetone

DFT = density functional theory

DIOP = (−)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

DMB = dimethoxybenzene

DME = dimethoxyethane

dppb = 1,4-bis(diphenylphosphino)butane

dppe = 1,2-bis(diphenylphosphino)ethane

dppf = 1,2-bis(diphenylphosphino)ferrocene

EDG = electron donating groupEt_2O = diethyl ether

EtOH = ethanol

EWG = electron withdrawing group

FTIR = Fourier Transform Infrared Spectroscopy

GC-MS = gas chromatography – mass spectrometry

HBCat = catecholborane

HBpin = pinacolborane

HRMS = High Resolution Mass Spectroscopy

IR = Infrared

L = ligand

Me = methyl

MIDA = *N*-methyliminodiacetic acid

NMR = nuclear magnetic resonance

Nu = nucleophile OMs = mesylate

OTf = triflate

OTs = tosylate

Ph = phenyl

PPh_3 = triphenyl phosphine

q = quartet

rbf = round bottom flask

R, X, Y, Z = proton or variable organic group

SFC = supercritical fluid chromatography

Sia = siamyl

SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl

SPS = Solvent purification system

^{t}Bu = tert butyl

THF = tetrahydrofuran

Tol = toluene

XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Chapter 1

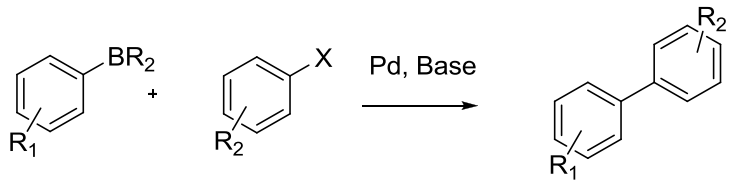
Introduction: The Suzuki-Miyaura reaction

1.1 Introduction

In the past few decades, transition metal catalysts have been employed to accomplish one of the most synthetically important processes, the formation of C-C bonds.[1] The development of these methodologies rests in the soul of organic chemistry. Over the years, unique discoveries have been made concerning the coupling of sp-, sp^2-, and sp^3–hybridized carbon nucleophiles with aryl or alkenyl electrophiles having the structure C(sp^2) –X where X represents a leaving group (X = I, Br, Cl, OMs, OTf, or N_2; Ms = methanesulfonyl, Tf = trifluoromethanesulfonyl).[2] These types of C-C bond transformations, called "cross couplings", have not only been shown to be extremely pertinent to a large variety of industrial syntheses of fine chemicals, pharmaceutically active compounds, and agricultural chemicals, but also towards the synthesis of natural products.[2] In particular, the Suzuki-Miyaura reaction has proven to be one of the most prominent reactions used towards the generation of new C-C bonds. This was exemplified by its inclusion in the 2010 Nobel Prize.[3]

The Suzuki-Miyaura reaction involves the palladium catalyzed cross-coupling of an organoborane or boronic acid species with an organic electrophile (*Scheme 1.1*).[4,5] The mechanism of the Suzuki-Miyaura reaction occurs in the following sequence, oxidative

addition of the aryl halide, followed by transmetalation of the arylboron species, and reductive elimination to yield the desired product and regenerate the active Pd^0 catalyst.[6]



Scheme 0-1. The Pd-catalyzed Suzuki-Miyaura cross-coupling between an aryl organoboron and an aryl halide to afford an unsymmetrical biaryl species. The organoboron coupling partner can be an aryl borane, boronic acid, or boronic ester.

1.1.1 Organoboron Compounds

Boronic acids are organic compounds consisting of a trivalent boron moiety that possesses one alkyl substituent along with two hydroxyl groups. This gives the boronic acid a trigonal planar geometry therefore causing the boron atom to be sp^2-hybridized. Due to the electron deficient nature of the boron atom, it contains an empty p-orbital which is able to accept electron density from neighbouring atomsHowever, these types of compounds are not naturally occurring and are derived synthetically from a primary source of boron such as boric acid, which is synthesized through acidification of borax with carbon dioxide.[7] In 1860, Frankland reported the first synthesis of boronic acids. The synthesis was performed by reacting diethylzinc with triethylborate yielding the highly air sensitive triethylborane which in turn oxidized to form ethylboronic acid.[8]

Boronic acids result from the second oxidation of boranes while borinic acids are formed by the first oxidation. The third oxidation of boranes creates boric acid. As a

borane becomes more oxidized there is a very noticeable increase in its inherent stability to atmospheric oxidation. Another class of organoboranes is boronic esters; one method for preparing these boronic acid derivatives is by dehydration of boric acid with alcohols (*Figure 1-1*).[7]

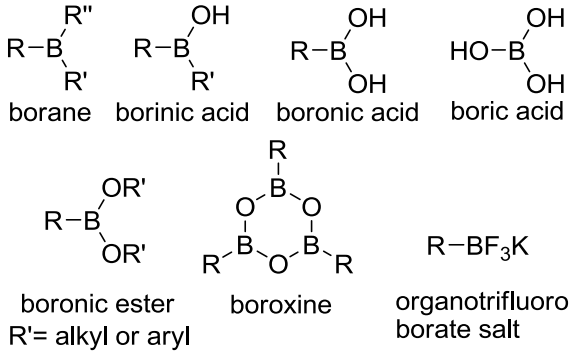


Figure 0-1. The different types of organoborane compounds.

Furthermore, the unique properties of boronic acids cause them to be extremely attractive synthetic intermediates. Not only are they mild Lewis acids but they have a significantly mitigated reactivity profile compared to other organometallics, are highly air stable, and can be easily handled. Due to their low toxicity they can also be classified as "green" compounds.[7]

One of the most useful reactions for boronic acids has been the Suzuki-Miyaura reaction. This type of reaction is successful regardless of the hydrated state of the boronic acid i.e.: free boronic acid or boronic anhydride (*Figure 1-1*). However, the oligomeric anhydride may lead to complications in reaction analysis and purification. Boronic ester and organotrifluoroborate derivatives have become popular in recent years as preferred

synthetic derivatives because they are more easily handled and purified, less air sensitive, and do not form boronic anhydrides.[7]

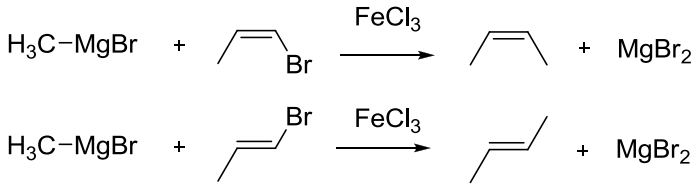
1.2 Organometallic Reagents For Transition Metal Catalysis

1.2.1 Grignard Reagents

One of the greatest advancements in organic chemistry has been the discovery of organometallic carbanion reagents. The nucleophilic nature of carbanions allows for the generation of new C-C bonds, highlighting their importance to the field of organic chemistry. Research has been focused for over a century on developing carbanion compounds and further understanding their stability and reactivity.[9]

Two types of important organometallic derivatives containing electropositive metals are organolithium and organomagnesium reagents. Organolithium compounds are generated through lithium-halide exchange while organomagnesium reagents are synthesized via insertion into the carbon-halide bond.[9] The latter are referred to as Grignard reagents and were first discovered by Victor Grignard in 1900.[10] Following this remarkable accomplishment, Victor Grignard was awarded the Nobel Prize in Chemistry in 1912.[10] The success of these Grignard reagents was not only due to their wide applicability to the fields of organic and organometallic chemistry but also to the ease and efficiency of their synthesis.[11]

In the 1960's and 1970's, research had been focused on the reactions of organo-lithium and –magnesium reagents in the presence of both stoichiometric and catalytic amounts of copper halides. However, these types of reactions were limited to sp^2- or sp-carbons. The early 70's are recognized for the discovery of the transition metal-catalyzed cross-coupling reaction of Grignard reagents with sp^2- or sp- carbons.[12] Precedence for this catalyzed cross-coupling was reported by Kochi and Tamura in 1971.[13] They published the iron catalyzed cross-coupling between 1-alkenyl bromides with Grignard reagents to afford the desired product with retention of configuration (*Scheme 1-2*).[13]

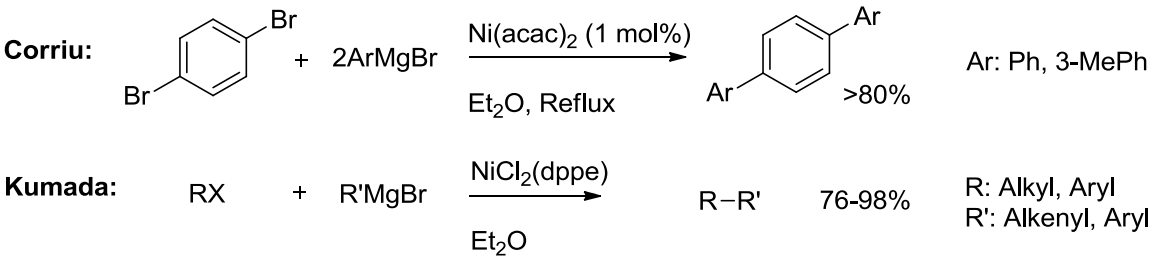


Scheme 0-2. The stereoselective iron-catalyzed cross-coupling between Grignard reagents and 1-alkenyl bromides.

During their studies into the cross-coupling reactions of alkyl halide with Grignard reagents, Kochi and Tamura described several different types of catalyst systems.[14,15] Silver mediated cross-coupling only gave the desired product when both the alkyl groups were the same, making this effectively a homo-coupling rather than a cross-coupling. In contrast, when the cross-coupling was attempted with copper(I) high yields were only obtained from primary alkyl halides.[14,15]

Following this, further advancements were made independently by Corriu[16] and Kumada[17]. They reported the nickel-catalyzed reaction of Grignard reagents with a

variety of 1-alkenyl and aryl bromides and chlorides (*Scheme 1-3*). In the case of Corriu's report, the catalyst system was nickel(II) acetylacetonate and they were able to obtain yields >80% when *p*-bromobenzene was employed.[16] Kumada and coworkers performed their cross-couplings in the presence of a nickel-phosphine complex, where bidentate bisphosphine gave the highest catalytic activity, with yields up to 98%.[17]



Scheme 0-3. The Ni-catalyzed cross-coupling reaction of Grignard reagents with a variety of 1-alkenyl and aryl bromides and chlorides as reported by Corriu (top) and Kumada (bottom).

In the preceding years, there were numerous independent contributions to the historical evolution of the cross-coupling field. Another key component that greatly impacted this methodology was the mechanistic proposal by Kumada and coworkers.[17] They stated that the cross-coupling between Grignard reagents and aryl chlorides occurred through a catalytic pathway initiated by oxidative addition followed by transmetallation, and concluded with reductive elimination.[17] Due to these discoveries, a new tactic for C-C bond formation was set into motion igniting the development of a significant organometallic field, metal-catalyzed cross-coupling.[17]

Subsequently, metal catalyzed cross-coupling reactions were further developed to incorporate other types of transition metal catalysts as well as organometallic reagents.

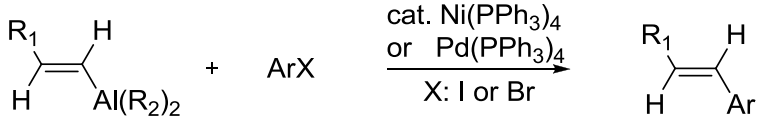
Even though the use of organo-lithium and –magnesium reagents had been fairly established, there were multiple issues that had surfaced with these reagents stemming from their high reactivity. Their highly reactive nature resulted in complications and limitations affecting either functional group tolerance or causing inevitable halogen-metal exchange leading to the undesired homocoupled product. The nickel-catalyzed cross-coupling of Grignard reagents was also prone to stereochemical scrambling of both the starting materials and metals.[12] Grignard reagents and organolithiums also lacked the ability to directly substitute with aryl, alkenyl, and alkynyl halides.

Up to this point, there had been a lack of success towards the direct and selective cross-coupling between alkenyl metals and alkenyl halides in cases where the incorporated alkenyl groups were different. It was concluded that alkenyl metals consisting of main group elements lacked the ability to efficiently undergo stereospecific cross-couplings with alkenyl halides.[18] However, it is noteworthy to add that the reaction between alkenyl cuprates with alkenyl halides had seen some promise even though it had lacked development. In 1975, Posner published a review highlighting cross-coupling reactions of organocopper reagents. The extensive review featured only a single example of alkenyl-alkenyl cross-coupling with the desired product obtained in 27% yield and no discussion as to whether homocoupled products were observed.[19]

1.2.2 From Organoaluminum to Organoboron Reagents

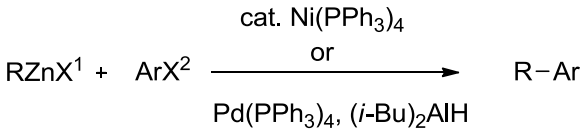
Negishi showed that various organometallic reagents could be synthesized containing less electropositive metals such as, Zn, Cd, B, Al, Si, Sn, and Zr.[20] These types of organometallic reagents could be prepared through hydrometalation reactions across C-C double and triple bonds; in the cases of B, Al, Si, Sn and Zr, it was possible to generate stereo- and regiodefined alkenyl metal compounds. It is known in the literature that organometallic compounds incorporating the metals listed above, in comparison to Li and Mg containing organometallics, are far more compatible with a variety of electrophiles, such as esters, amides, nitriles, and nitro compounds.[20]

Following this discovery, in 1976 Negishi reported the first example of Ni- and Pd-catalyzed cross coupling reactions incorporating non-Grignard reagents.[18,21] They reported an efficient route towards the general and selective Ni- and Pd-catalyzed cross-coupling of alkenylalanines with alkenyl halides to afford the desired highly stereospecific conjugated (E,E)- and (E,Z)-dienes in yields up to 82% (*Scheme 1-4*).[18] When the reaction was catalyzed by Pd, in each case the product was obtained with high stereospecificity (≥97%) and homocoupled product were formed in insignificant amounts (<2%). In contrast, when the cross-coupling was catalyzed by nickel, the stereospecificity was decreased and in some cases homocoupled products were obtained in >5%. Therefore, this confirmed that Pd was the more efficient catalyst for this transformation.[18]



Scheme 0-4. The Ni- or Pd-catalyzed cross-coupling of an alkenylalanine with an aryl halide.

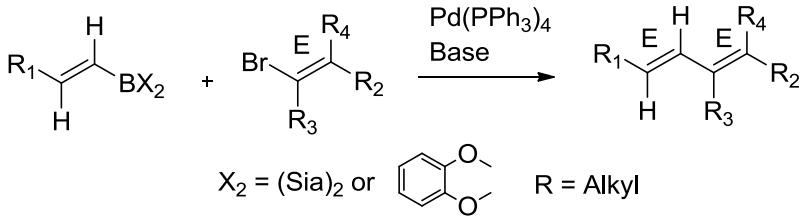
Subsequently, in 1977 Negishi reported that organozinc reagents ore readily cross-coupled with aryl bromides and iodides in the presence of Pd- or Ni-catalyzst systems (*Scheme 1-5*).[22,23] This provided the chemistry world with a general and mild protocol for cleanly synthesizing unsymmetrical biaryls and diarylmethanes in high yields. This reaction is now known as the Negishi reaction. As a result, Negishi became one of the recipients of the Nobel Prize in Chemistry in 2010.[22,23]



R = Ar or $ArCH_2$; X^1 = Br, Cl or Ar; X^2 = Br or I

Scheme 0-5. General schematic for the Negishi cross-coupling of an organozinc substrate with an aryl halide.

In 1979, elaborate investigations by Suzuki, Miyaura et al. lead to the origin of the Suzuki-Miyaura reaction.[24] They reported the first stereoselective Pd-catalyzed cross-coupling between aryl halides and alkenyl boranes with yields ≥99% (*Scheme 1-6*).[24] This reaction lead to the synthesis of highly stereo- and regiospecific conjugated dienes from organoboranes. It was also discovered that a key component towards the success of this reaction was exogenous base.[24]



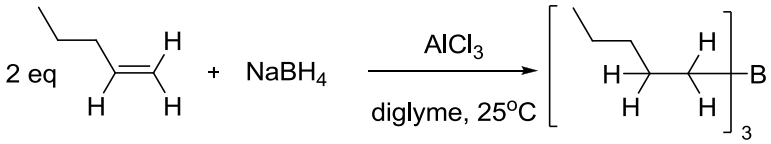
Scheme 0-6. The first example of Suzuki-Miyaura cross-coupling involving alkenyl boranes with alkenyl bromides.

1.3 Hydroboration

One of the most valuable synthetic tools in organic chemistry has been the hydroboration of alkenes and alkynes.[25] The organoboranes produced are both environmentally friendly and can be easily converted to a variety of organic compounds. Hydroboration can be performed with or without the use of transition metal catalysis.[25] More recently, asymmetric hydroboration has been accomplished affording optically active boron compounds. These enantioenriched compounds have become attractive moieties in organic synthesis.[25]

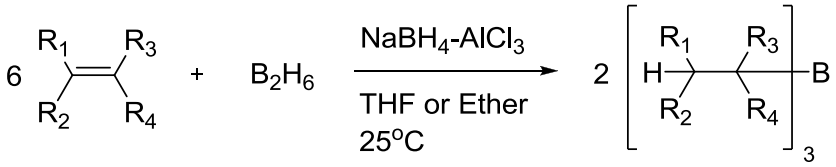
Even though it was known that organoboranes could be synthesized through a slow reaction between diboranes and either aliphatic olefins[26] or styrene[27]; more efficient conditions were not discovered until research performed by Herbert Brown.[28] While analyzing the reducing strength of $NaBH_4$, it was observed that ethyl oleate consumed three equivalents of hydride instead of the standard two equivalents required for an ester reduction. These findings were investigated and it was concluded that the H-B bond was

adding to the double bond to yield the corresponding organoborane.[28] In 1956, Brown and Subba reported that trialkylboranes could be readily synthesized by reacting $NaBH_4$ in diglyme in the presence of $AlCl_3$ (*Scheme 1-7*).[28]



Scheme 0-7. The hydroboration of *n*-pentene with sodium borohydride in the presence of aluminum chloride in diglyme.

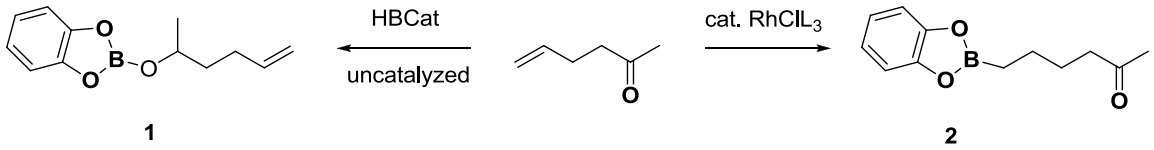
Through further analysis, Brown and Subba found that diborane (B_2H_6) would efficiently add to olefins at room temperature in the presence of the sodium-borohydride-aluminum chloride reagent when solvated by organic ethers (*Scheme 1-8*). [29] Surprisingly, the addition of the diborane across the C-C double bond was found to be anti-Markovnikov; where the boron atom added to the less substituted carbon. These remarkable discoveries expanded the scope of hydroboration, paving the road towards a valuable and attractive area in organic chemistry.[30]



Scheme 0-8. The hydroboration of olefins with diborane in the presence of the sodium-borohydride-aluminum chloride reagent.

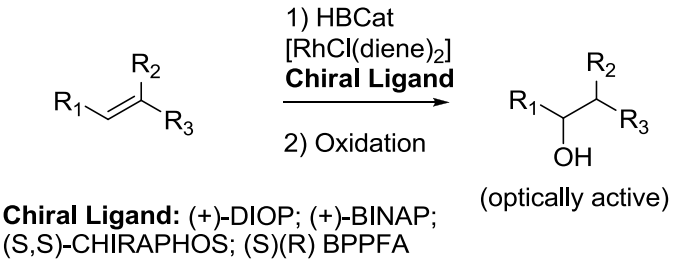
In 1985, Männig and Nöth expanded upon the area of hydroboration with their report featuring the first metal-catalyzed hydroboration.[31] They were able to perform the

hydroboration of alkenes and alkynes with catecholborane (HBCat), a considerably less active borane reagent, in the presence of rhodium catalysts to afford the desired alkylborane. They observed that this reagent reacted chemoselectivity since when 5-hexen-2-one was reacted with HBCat in the presence of the rhodium catalyst they obtained the alkyl boronic ester **2**. This is in contrast with the uncatalyzed reaction where addition of the H-B bond occurrs across the ketone group to yield **1** (*Scheme 1-9*).[31]



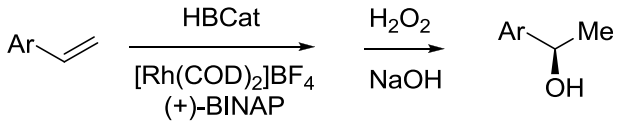
Scheme 0-9. The chemoselectivity observed with HBCat in the rhodium catalyzed versus uncatalyzed reaction.

1988 marked the emergence of catalytic asymmetric hydroborations, which were published in parallel by Burgess[32] and Suzuki[33]. They reported the rhodium-catalyzed hydroboration of 1,1- and 1,2-disubstitued alkenes to yield optically active organoboranes (*Scheme 1-10*). The catalyst systems were prepared via mixing the chiral phosphine with $[RhCl(diene)]_2$.[32,33]



Scheme 0-10. The catalytic asymmetric hydroboration of olefins with HBCat in the presence of a rhodium catalyst.

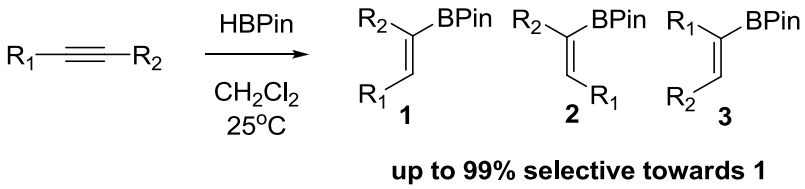
In 1989, Hayashi et al. reported the novel asymmetric synthesis of optically active 1-arylalkanols.[34] This was achieved by the asymmetric hydroboration of styrene derivatives with catecholborane in the presence of a rhodium catalyst incorporating the chiral ligand BINAP yielding the desired product in enantiometric excesses of ≥90 and regioselectivities of approximately 99:1 (*Scheme 1-11*). It was observed that by the use of specific cationic phosphine-rhodium catalysts the regiochemistry of the hydroboration of styrene derivatives becomes inverted in comparision to uncatalyzed hydroborations.[34]



Scheme 0-11. The rhodium-catalyzed asymmetric hydroboration of styrene derivatives and subsequent oxidation to yield the desired optically active arylalkanols.

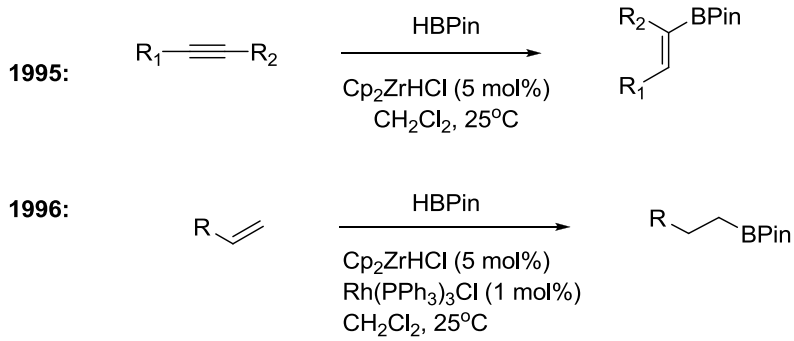
HBCat was found to be an important component for the metal-catalyzed hydroboration of alkenes. This was due to the ability of the oxygen atoms attached to boron to decrease the rate of the competitive uncatalyzed reaction. Unfortunately, HBCat is known to be difficult to handle and due to the lack of steric hindrance around the boron atom this causes it to be more readily prone to hydrolysis and decomposition. A viable alternative became pinacolboranes because not only did they exhibit higher air and thermal stability but the pinacol boronic esters produced through hydroboration can often be purified via column chromatography.[35]

Knochel et al. reported the first hydroboration by using pinacolborane (HBPin), they observed that this reagent was easily added to alkynes with regio- and stereoselectivity (*Scheme 1-12*).[36]



Scheme 0-12. The regio- and stereoselectivity of the hydroboration of alkynes with HBPin.[36]

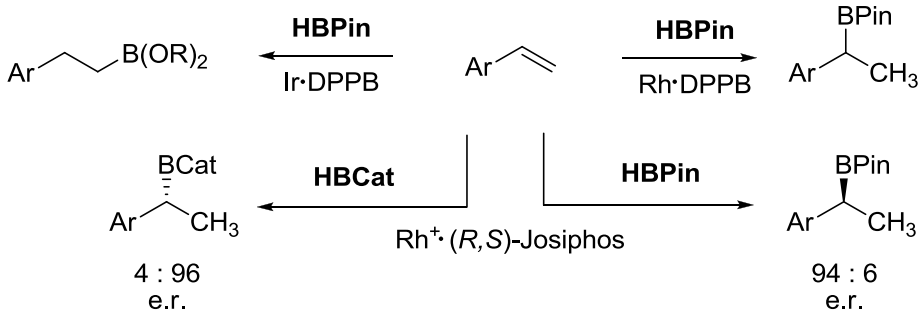
In 1995, Pereira et al. reported the hydroboration of alkynes with HBPin in the presence of $HZrCp_2Cl$ to afford the highly syn selective and regioselective products (*Scheme 1-13*).[37] Subsequently, they observed that the same catalyst system could be employed to hydroborate alkenes with HBPin to yield the desired terminal boronic esters.[38]



Scheme 0-13. The catalyzed hydroboration of alkynes and alkenes with HBPin.

More recently, our group reported the Rh-catalyzed hydroboration of vinyl arenes at 25°C with HBPin to yield the corresponding branched boronic esters in high enantio-

and regioselectivities.[35] It is noteworthy that in the presence of an iridium catalyst the linear boronic ester is favored in >98% selectivity. By employing HBCat inverted stereochemistry is observed in the products obtained (*Scheme 1-14*).[35]



Scheme 0-14. The regio- and enantiocontrol in the hydroboration of vinyl arenes with HBPin.

1.4 Mechanism of The Suzuki-Miyaura Reaction

1.4.1 General Catalytic Cycle

The general mechanism of the Suzuki-Miyaura catalytic cycle incorporates three intricate steps: oxidative addition, transmetallation, and reductive elimination. The active ligated Pd^0 species oxidatively adds into the arylhalide bond, this is followed by the transmetallation of the arylboron species, and concluded by reductive elimination to yield the desired biaryl compound while regenerating the active Pd^0 species (*Figure 1-2*).[6] It is noteworthy to indicate that the active palladium species is Pd^0 and the presence of base is necessary for the reactions success. These aspects and more will be discussed more in-depth later in the thesis.

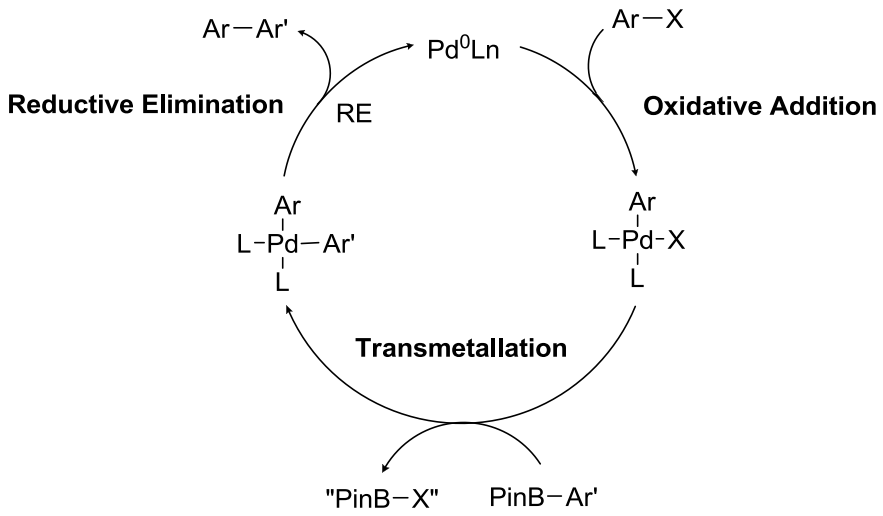


Figure 0-2. The general catalytic cycle for Suzuki-Miyaura cross-coupling between two sp^2-hybridized partners.

1.4.2 Phosphine Ligand Developments

The year 1998 marked the emergence of monodentate, bulky, and electron-rich dialkylbiarylphosphines.[39] These types of ligands have seen important applications towards such transformations as Pd-catalyzed cross coupling reactions.[40] They are readily available commercially or through a direct one pot synthesis approach.[41] Their properties make them valuable commodity for organic synthesis: a) crystalline materials, b) highly thermally stable, and c) commercially available. Their easily tunable steric and electronic properties are also significant attributes.[40]

One of the next key goals in the Suzuki-Miyaura cross-coupling was to expand the scope to include aryl chlorides, which are considerably less reactive but more

desirable because they are cheaper.[42] In 1998, Fu et al. showed one of the first examples of Pd-catalyzed Suzuki-Miyaura cross-coupling between an unactivated aryl chloride and phenylboronic acid employing commercially available trialkylphosphines such as $P(^tBu)_3$ and PCy_3.[42]

Another example of phosphine ligands that provide efficient catalysts for Suzuki-Miyaura cross-coupling reactions are ferrocenyl dialkylphosphines. These ligands are readily available through a two-step synthesis.[43]

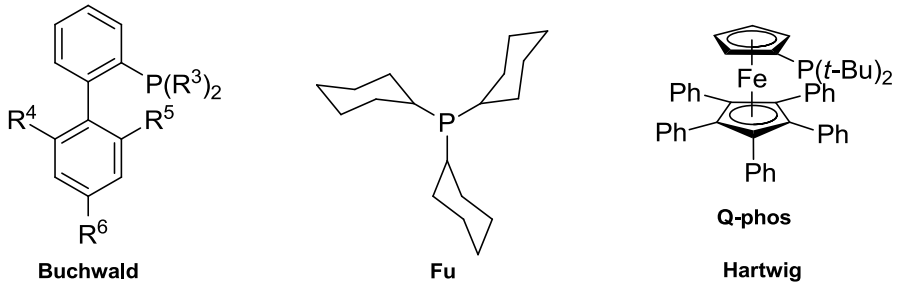


Figure 0-3. Different examples of phosphine ligands.

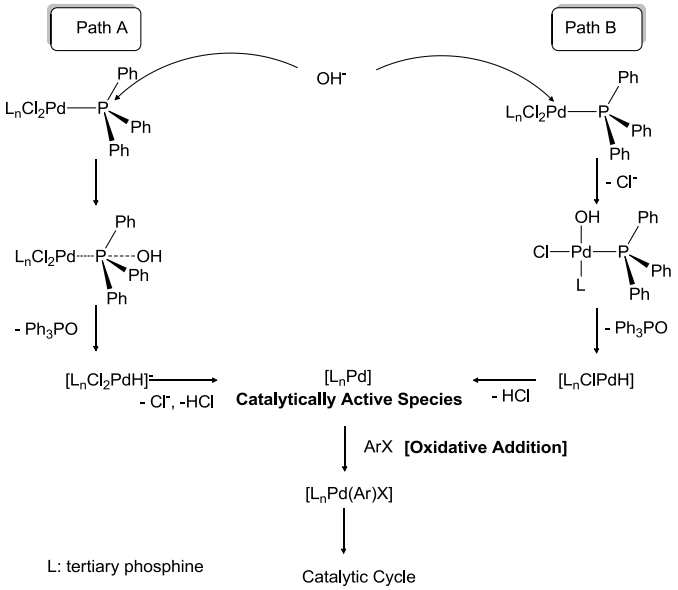
1.4.3 Formation of the Active Pd-Catalyst

Given that the typical conditions for Suzuki-Miyaura cross-coupling reaction are not extremely oxidizing, the most common catalysts used are zero-valent Pd(0) or divalent Pd(II). The active catalyst species is palladium(0) and in 1993 the *in situ* reduction of divalent Pd(II) to Pd(0) was studied in-depth by Grushin and Alper.[44] Even though their studies focused on the Pd-catalyzed carbonylation of haloarenes, the results are also relevant for other Pd-catalyzed processes, such as the Heck arylation,

carbonylation of organic halides, and a variety of cross-coupling reactions, specifically the Suzuki-Miyaura reaction.[44]

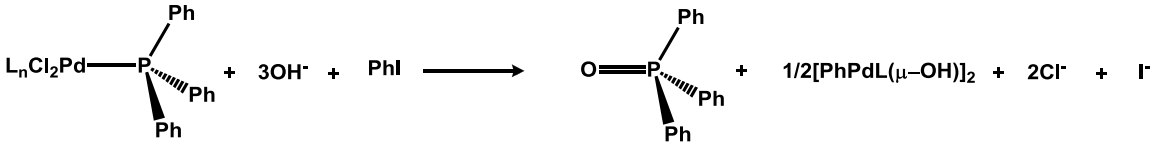
Grushin and Alper proposed two possible mechanisms, **Path A** and **Path B**, for the *in situ* generation of the active Pd(0) species (*Scheme 1-15*).[44] **Path A** is initiated by a nucleophilic attack from the hydroxide ion to the electron-deficient phosphorus atom coordinated to Pd. Following this, the phosphine becomes oxidized and dissociates as triphenylphosphine oxide producing the anionic palladium hydride, $[LPd(H)Cl_2]^-$. By elimination of Cl^- and HCl, the active catalytic species PdL_n is generated.[44]

Path B begins with ligand exchange of a chloride with a hydroxyl group through hydroxide attack at the Pd center. This is followed by the generation and dissociation of triphenylphosphine oxide and finally elimination of HCl to generate the active catalytic species PdL_n.[44]



Scheme 0-15. The two proposed pathways for the *in situ* generation of the active Pd(0) catalyst species.

They concluded that the mechanism was best represented by **Path B** since when a chiral phosphine was employed the resulting phosphine retained its configuration. This suggested that the mechanism did not include an S_N2-type attack at the phosphine center (*Scheme 1-16*).[44]



Scheme 0-16. This proves the validity of **Path B** because the chiral phosphine retains configuration.

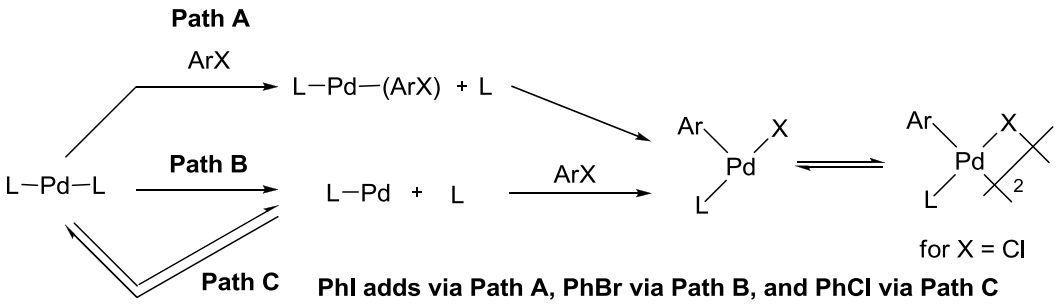
1.4.4 Oxidative Addition

The first step in the Suzuki-Miyaura catalytic cycle is the oxidative addition. Since it is a fundamental step in many types of cross-coupling reactions, there has been considerable focus on the details of this step. The reactivity of the ArX species, involved in the oxidative addition step, decreases in the order I > OTf > Br >> Cl. The ArX species becomes more activated with the incoorperation of an electron-withdrawing group (EWG) versus an electron-donating group (EDG). This is due to the electron-rich nature of the palladium complex that oxidatively inserts into the ArX bond.[6] The majority of reports are in agreement that the active species involved in oxidative addition is either a coordinatively unsaturated Pd(0) species that is monoligated (PdL) or diligated (PdL_2).[45]

Even though the products of this step are usually well characterized, the mechanism of this step is inconclusive. The different mechanisms that have been proposed either involve a concerted two-electron or a series of steps initiated by a single-electron transfer between the zerovalent metal center and the organic compound.[46]

In 1990, Amatore et al. reported on the oxidative addition step involving substituted iodobenzenes when $Pd(PPh_3)_4$ was the catalyst. Their results showed that PhI oxidatively added to a Pd(0) complex with only two phosphines, namely $Pd(PPh_3)_2$.[46]

In 2004, Barrios-Landeros and Hartwig performed the first study comparing the mechanisms involved in the oxidative addition step when the aryl halide was either iodo-, bromo-, or chloroarenes, the same catalyst system was used in each case, [Pd(Q-phos-tol)$_2$].[47] They concluded that the mechanism of oxidative addition was different depending on whether the halide was iodo, bromo, or chloro. In the case of PhI the mechanism involved an associative displacement of a phosphine ligand. When PhBr was employed the mechanism occurred via a rate-limiting dissociation of phosphine. Finally, for the addition of PhCl the mechanism followed a reversible dissociation of phosphine and subsequent rate-limiting oxidative addition (*Scheme 1-17*).[47]



Scheme 0-17. The mechanism of oxidative addition in the case of PhI, PhBr, and PhCl.

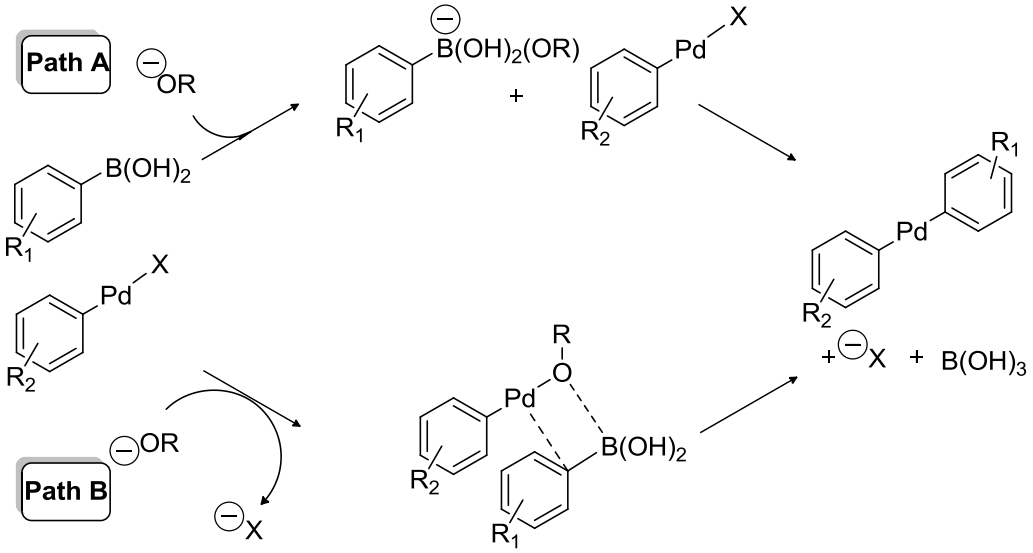
Following this, DFT calculations performed by Lam et al. showed how the electronic effect of ArX influenced the mechanism of oxidative addition to Pd(0) bisphosphine complexes bearing monodentate ligands.[45] Their results agree with the experimental data that ArBr and ArCl follow a dissociative monophosphine pathway because they are less susceptible to oxidative addition. Since oxidative addition is highly favored in the case of ArI especially those incorporating EWGs, the bisphosphine pathway plays an important role. They also showed that for substituted ArBr and ArCl substrates, whether the substitutent was an EWG or EDG had no effect on the preferred monophosphine pathway.[45] However, for the case of unsubstituted ArIs there was a competition between monophosphine and bisphosphone pathways, preferring the former, while substituted ArI showed a switch in preference. EWGs lead to a bisphosphine pathway in contrast to EDGs, which followed a monophosphine pathway. The authors concluded that when ArBr or ArCl were employed bulky or hemilabile ligands should be used because these ligands promote the monoligand pathway. In the case of ArI, they suggested that less bulky ligands should be used, especially when the ArI contains an EWG.[45]

1.4.5 Transmetallation and Role of the Base

In 2005, Maseras and coworkers performed a computational study on the role of the base in the Suzuki-Miyaura cross-coupling reaction.[48] They reported that the

transmetallation step showed an increased energy barrier without the addition of base. This was in agreement with the initial statement by Suzuki in 1979, that base was a necessary component in this cross-coupling reaction.[24]

Maseras and coworkers proposed two plausible mechanisms for the transmetallation step: **Path A** and **Path B**.[48] **Path A** is initiated by the formation of a boronate species via binding of the base to the boronic acid. This is then followed by transmetallation of the aryl group from the boronate species to the palladium center. It was noted that the energy profile obtained for **Path A** was quite smooth, indicating that this pathway was a good candidate for the mechanism of transmetallation. **Path B** involves the coordination of a hydroxyl group to the palladium center leading to transmetallation occuring between the oxo-Pd complex and the boronic acid. Even though **Path B** was observed to be energetically favorable via calculations, it may not be the most reliable due to the possibility of large quantities of oxidized phosphine ligand leading to catalyst destruction (*Scheme 1-18*).[48]



Scheme 0-18. The two plausible mechanisms for the transmetallation step, Path A and Path B.

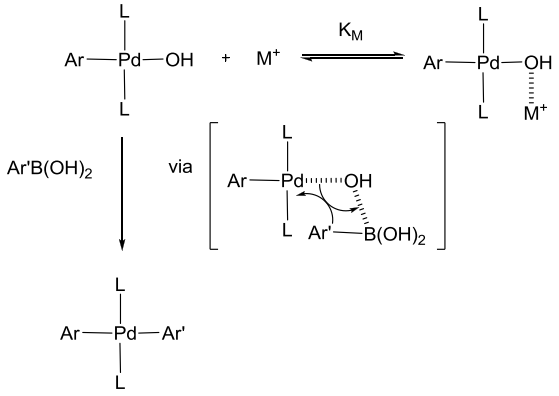
Schimt et al., reported kinetic data that was in agreement with **Path B**.[49] There results showed that transmetallation occurs between a neutral phenyl boronic acid in the presence of a Pd complex incoorperating an anionic base moiety.[49]

Following this in 2011, Carrow and Hartwig reported kinetic data that also supported the preference towards **Path B** for the transmetallation step.[50] They discussed that the transmetallation between *trans*-$Ar^1Pd(OH)L_2$ and boronic acid would occur more readily due to the following: the amount of palladium halide versus palladium hydroxo complexes is analogous, the amount of boronic acid versus trihydroxyborate is analogous, and the rate of transmetallation between the palladium hydroxo complex and aryl boronic acid is several orders of magnitude higher than that of the palladium halide complex with the trihydroxyborate species. Their results provided the first example of a quantitative analysis of the two plausible mechanisms of transmetallation including populations of reactants. However, it is noteworthy that these results cannot be

generalized towards all metal-ligand systems and there may be competition between **Path A** if a stronger base were employed.[50]

Subsequently, kinetic studies performed by Amatore et al. revealed the unprecedented triple role of the base in the catalytic cycle.[51] The first two roles were observed to have a positive effect on the catalytic cycle, 1) formation of the reactive intermediate *trans*-$Ar^1Pd(OH)L_2$ (L=PPh_3) involved in the transmetallation with $Ar^2B(OH)_2$ and 2) acceleration of the reductive elimination from *trans*-$Ar^1PdAr^2L_2$. The third role negatively affected the transmetallation step, 3) involved the formation of the intrinsically unreactive aryl borate $Ar^2B(OH)_3$.[51]

Recently, Amatore and coworkers published another kinetic study focusing on the effect of the countercations of anionic bases in the key transmetallation step.[52] Interestingly, the cations were observed to decrease the rate of the transmetallation step in the following decreasing reactivity order: $n$$Bu_4NOH$ > KOH > CsOH > NaOH. This effect is due to the complexation of the hydroxo ligand in the $Ar^1Pd(OH)L_2$ with the countercation M^+ (*Scheme 1-19*).[52]



Scheme 0-19. The competitive countercation (M^+ = Na^+, K^+, and Cs^+) complexation mechanism.

Originally, the mechanism for the transmetallation/reductive elimination step was studied with the use of nBu$_4$NOH as the base. This has been expanded to other types of bases such as acetates and carbonates.[52] Acetates were observed to be inefficient bases for Suzuki-Miyaura reactions involving $Ar^2B(OH)_2$. Even though they reacted with *trans*-$Ar^1Pd(OH)L_2$ to form *trans*-$Ar^1Pd(OAc)L_2$, this species did not successfully transmetallate with $Ar^2B(OH)_2$.[52]

The reactivity of carbonates was observed to increase upon the addition of water; however the reaction still occurred at a slower rate in comparision to when nBu$_4$NOH was used at the same concentration.[52] The mechanism of transmetallation is similar in both cases and proceeds through the formation of the reactive *trans*-$Ar^1Pd(OH)L_2$. The reaction time is slower in the case of the carbonates due to the lower concentration of hydroxide ions, which are formed by the reaction between water and carbonate. This reduces the efficiency of both the transmetallation and reductive elimination step.[52]

1.4.6 Reductive Elimination

The Suzuki-Miyaura cross-coupling reaction is concluded by a reductive elimination reaction. During this step the desired Ar-Ar^1 coupling product is obtained and the active Pd^0 complex is regenerated. In order for reductive elimination to occur the aryl groups bound to the metal center must be cis to one another. The rate of reductive elimination is highly dependent upon the steric and electronic effects of the ancillary

ligands. Both experimental and theoretical studies are in agreement that ligands with a decreased donating ability will cause the reductive elimination step to be increased.[53]

The reductive elimination step is also favored when the leaving group is highly σ-donating and the ligand trans to this organic group is a weaker donor. Moravskiy and Stille reported that prior dissociation of a ligand, forming a tricoordinate Pd(0) complex, may be required for the reductive elimintation to proceed.[54]

Phosphine ligands have been noted to have a critical effect on the rate of the reductive elimination step. It has been proposed that the steric effects of bulky ancillary ligands, L, increase the rate. Due to the steric bulk of the ligands and their increased dissociation energy; it is also proposed that the reductive elimination step would proceed via a three coordinate metal complex ultimately enhancing reactivity.[55] The rate is also seen to increase by the use of phosphine ligands that are poor electron donors. In the case of chelating diphosphine ligands increased rates are obtained with increased bite angles.[55]

Recently, Fairlamb et al. reported on the nature of π-acidic alkene ligands and there effect on Pd-catalyzed cross-couplings.[56] In their study, they focused on dibenzylidieneacetone (dba) and related ligands. They observed that these ligands have an inverse effect on the oxidative addition step in comparison to reductive elimination. Due to the π-acidic nature of this ligand, it withdraws electron density away from the Pd-center (*Figure 1-4*). Therefore this causes the rate of reductive elimination to be more accelerated in comparison to the rate of oxidative addition. Even though this causes an antagonist effect on the oxidative addition step, this can be seen as a more positive outcome. By decreasing the rate of oxidative addition this not only allows the rate to be

more similar to subsequent steps, such as transmetallation, but it also decreases the concentration of Pd(II) which would in turn lower the possibility of side products, ie homocoupled.[56]

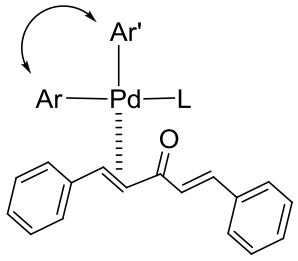


Figure 0-4. The effect of the π-acidic ligand dibenzylideneacetone on palladium.

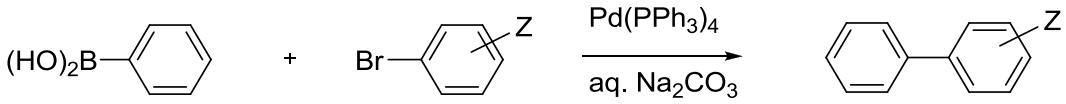
1.5 Developments of the Suzuki-Miyaura Reaction

1.5.1 Suzuki-Miyaura Cross-Coupling of sp^2-hybridized Partners

The Suzuki-Miyaura reaction has become one of the most influential reactions on organic synthesis.[4] Since the development of cross-coupling reactions many chemical-based companies have greatly benefited. These types of transformations allow for a more simplified route towards the synthesis of novel structures and have thus attracted pharmaceutical, agrochemical, and even material based industries. By comparison, prior to the 1980s the majority of synthesis of pharmaceuticals was based from natural products and their analogues whereas upon the installment of cross-coupling reactions the number of top selling drugs incorporating biaryl systems increased exponentially in 2007.[4]

Over the past three decades, thousands of reports have been published based on further modifying and developing the Suzuki-Miyaura reaction.[4] Along with a tremendous variety of reaction conditions, recent focus has been towards expanding the range of organic nucleophiles (aryl-, heteroaryl-, alkenyl-, primary- and secondary- alkyl) and nucleofuges (iodides, bromides, chlorides).[4]

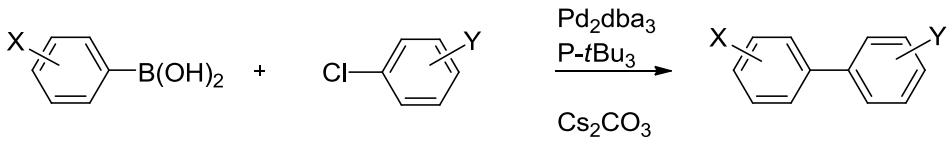
As previously stated, due to the research pioneered by Akira Suzuki and Norio Miyaura the Suzuki-Miyaura reaction was discovered in 1979.[24] Subsequently, in 1981 they reported the first palladium catalyzed cross-coupling between an arylboronic acid and an aryl halide.[57] They cross coupled phenyl boronic acid with a variety of aryl halides yielding the desired biaryl product in a range from 40-94% (*Scheme 1-20*).[57]



Scheme 0-20. The first example of Suzuki-Miyaura cross-coupling between an aryl boronic acid and an aryl halide.

One of the earlier limitations was the lack of conditions that would facilitate the efficient cross-coupling between an organoboron species with an electron-neutral or electron-rich aryl chlorides.[42] This was an area of interest due to the increasing commercial availability and decreased cost of aryl chlorides in comparison to iodides or bromides and the fact that the Suzuki-Miyaura cross-coupling of electron-neutral or electron-poor aryl chlorides give the desired cross-coupling product in yields <50%.[42]

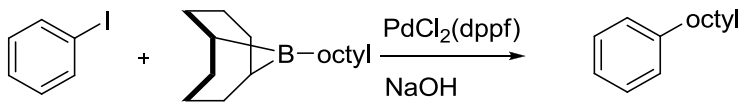
In 1998, Fu reported conditions in which a variety of aryl chlorides could be coupled with aryl boronic acids yielding the desired biaryl product from 82-92%.[42] The catalyst system employed in their study was $[Pd_2dba_3]$/P*t*-Bu_3 and the base was Cs_2CO_3. (*Scheme 1-21*).[42] They proposed that the steric bulk and electron-richness of the P-*t*Bu_3 ligand allowed for this cross-coupling of phenyl boronic acids and aryl chlorides to occur.[42]



Scheme 0-21. The Suzuki-Miyaura cross-coupling involving unactivated aryl chlorides.

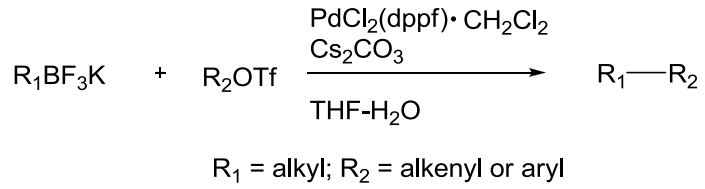
1.5.2 Suzuki-Miyaura Cross-Coupling of Primary sp^3-hybridized Organoboron Substrates

The first example of the coupling of sp^3-hybridized primary organoboron compounds was reported by Suzuki et al. in 1989.[58] They showed that β-alkyl-9-borabicyclo[3.3.l]nonanes (β-alkyl-9-BBN) could be cross-coupled with 1-halo-1-alkenes or aryl halides in the presence of $PdCl_2$(dppf) and bases such as sodium hydroxide, potassium carbonate, and phosphate (*Scheme 1-22*).[58]



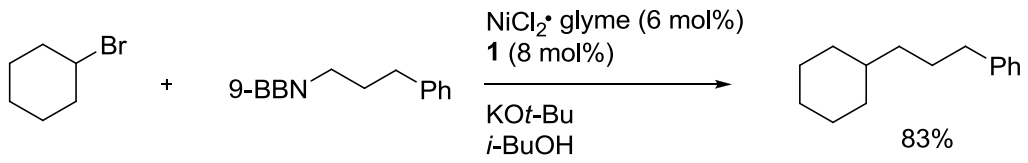
Scheme 0-22. The Pd-catalyzed cross-coupling of β-octyl-9-BBN with iodobenzene.

In 2001, Molander and coworkers reported the first efficient Suzuki-Miyaura cross-coupling of alkyltrifluoroborates with a variety of aryl or 1-alkenyl triflates (*Scheme 1-23*).[59] These substrates were seen to be viable alternatives to boronic acids due to their increased nucleophilicity and air stability.[59]



Scheme 0-23. The Suzuki-Miyaura cross-coupling of alkyltrifluoroborates with aryl or alkenyl triflates in the presence of palladium.

Up to this point, research towards the Suzuki-Miyaura cross-coupling of unactivated secondary electrophiles involved alkenyl or aryl boron compounds; an advantageous approach would be to progress towards coupling these substrates with alkylboranes. In 2007, Fu et al. accomplished Suzuki-Miyaura cross-coupling between alkylboranes and unactivated secondary alkyl electrophiles.[60] They screened a wide variety of catalyst systems and arrived to the conclusion that 1,2-diamines afford efficient catalysts for this transformation. By employing *N,N'*-dimethyl-1,2-cyclohexanediamine in the presence of $NiCl_2$·glyme they successfully cross-coupled a variety of β-alkyl-9-BBN with secondary alkylbromides (*Scheme 1-24*).[60]

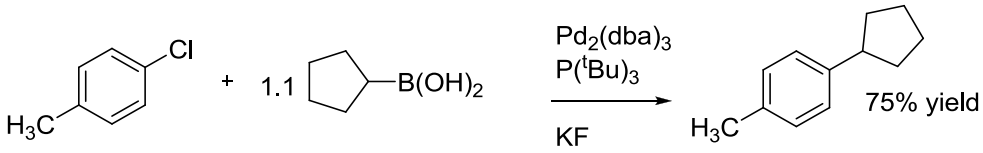


1 = trans-N, N'-dimethyl-1,2-cyclohexanediamine

Scheme 0-24. The Ni-catalyzed Suzuki-Miyaura cross-coupling of unactivated alkyl bromides with β-alkyl-9-BBN in the presence of **1**.

1.5.3 Suzuki-Miyaura Cross-Coupling of Secondary sp^3-hybridized Organoboron Substrates

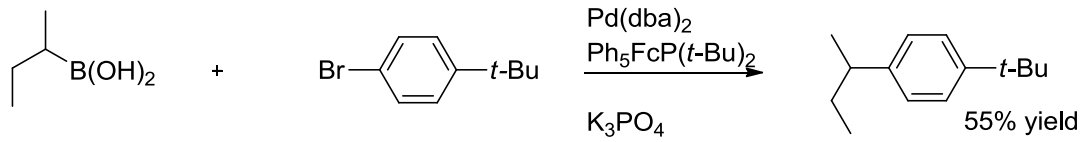
The first example of Suzuki-Miyaura cross-coupling of secondary organoboron species was accomplished by Fu et al. in 2000.[61] They highlighted an example of the Pd-catalyzed cross-coupling of cyclopentylboronic acid with *p*-methylchlorobenzene in the presence of KF (*Scheme 1-25*).[61]



Scheme 0-25. The palladium catalyzed cross-couplng of cyclopentylboronic acid with an unactivated aryl chloride.

This was followed by the cross-coupling of *sec*-butylboronic acid with *p-tert*-butylbromobenzene reported by Hartwig et al. (*Scheme 1-26*).[43] This reaction resulted in a mixture consisting of both the desired product and the undesired isomerized *n*-butylated derivative.[43] In the case of cyclopentylboronic acid, due to the symmetry of this substrate

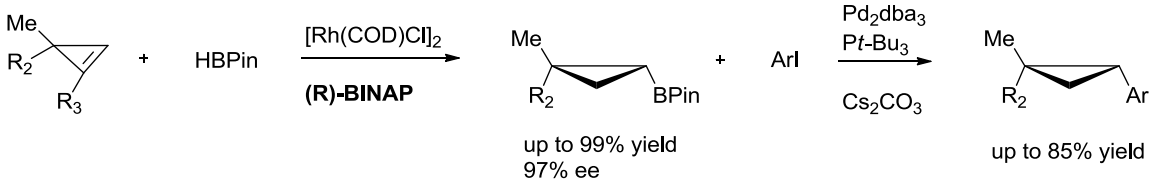
this isomerization is invisible.[61] Unfortunately, neither of these reports discussed how to overcome the challenge involved in the cross-coupling of secondary organometallics.[43]



Scheme 0-26. The palladium catalyzed cross-coupling of sec-butyl boronic acid with an aryl bromide.

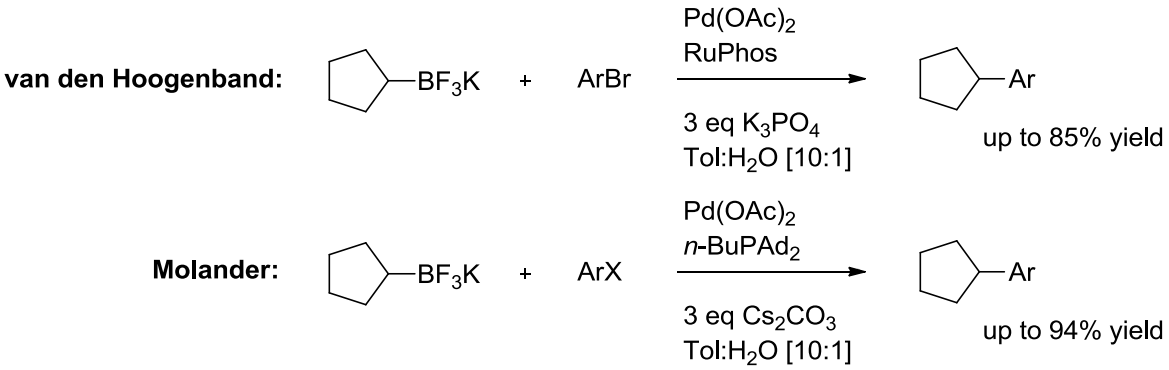
In 2003, Gevorgyan et al. reported the first rhodium-catalyzed protocol for the synthesis of stereodefinied cyclopropyl boron derivatives.[62] Therein, they described the rhodium-catalyzed asymmetric hydroboration of cyclopropenes affording cyclopropyl boron derivatives that were both highly diastereo- and enantioselective. Previously, these types of boron compounds were prepared through the use of expensive stoichiometric amounts of chiral auxiliaries.[62]

In order for these stereodefined cyclopropyl boronic ester derivatives to undergo Suzuki-Miyaura cross-coupling, they had to switch to the boronic acid derivatives. Following this, they performed cross-coupling of cis cyclopropyl boronic acids with a variety of vinyl and aryl iodides to obtain the desired cis trisubstituted cyclopropane moieties in good yields (*Scheme 1-27*).[62]



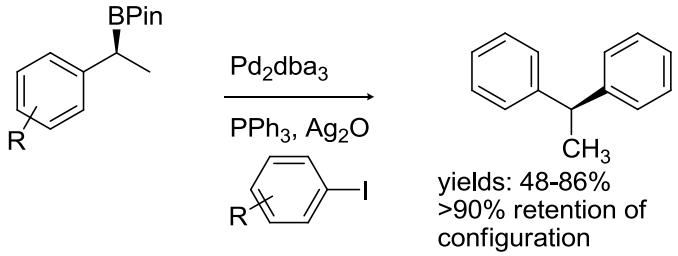
Scheme 0-27. The rhodium-catalyzed asymmetric hydroboration of cyclopropenes and subsequent Suzuki-Miyaura cross-coupling with an aryl iodide.

The difficulties in cross-coupling C(sp^3)-B bonds arises from two key steps in the catalytic cycle: transmetallation and reductive elimination. In the case of secondary organometallics, transmetallation is more challenging and reductive elimination becomes competitive with β-hydride elimination. By combining both organotrifluoroborates, and monoligating, electron-rich ligands these issues can be suppressed. Organotrifluoroborates have been known to resist proto-deboronation, increasing transmetallation, and mono-ligating electron rich ligands enhance the rate of reductive elimination relative to β-hydride elimination.[5] These two issues were focused on in parallel publications by Molander et al.[5] and van den Hoogenband et al.[63] They both employed organotrifluoroborates as well as electron-rich monoligated phosphine ligands. However, in certain cases there was still some isomerization via β-hydride elimination (*Scheme 1-28*).[5,63]



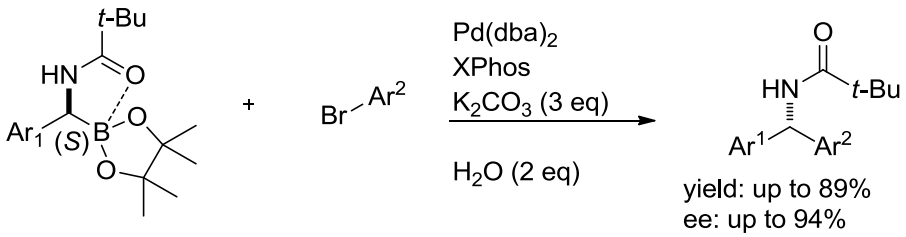
Scheme 0-28. The Pd-catalyzed cross-coupling of cyclopentyl alkyltrifluoroborate with an aryl halide.

Recently, our group demonstrated the first example of enantiospecific cross-coupling of a secondary boronic ester, an organoboron derivative that consists of a C(sp^3)-B bond, with a variety of aryl iodides.[64] Key factors for the success of the reaction include the use of silver oxide as the base, and the presence of excess phosphine. Silver oxide is believed to act as an accelerator for the transmetallation step of the Pd catalytic cycle (*Scheme 1-29*). The role of excess phosphine remains to be elucidated. The reaction was also discovered to be highly selective towards the branched boronic ester in the presence of the linear boronic ester.[64]



Scheme 0-29. The first example of enantiospecific cross-coupling of secondary boronic esters with a variety of aryl iodides.[64]

Following this, in 2010 Suginome and coworkers described the cross-coupling of chiral α-(acylamino)benzyl boronic esters with inversion of configuration.[65] They were capable of efficiently cross-coupling these chiral substrates with a variety of both aryl bromides and chlorides to afford diarylmethanamine compounds in high yield and high enantiomeric excess (*Scheme 1-30*).[65]



Scheme 0-30. The Pd-catalyzed cross-coupling of α-(acylamino)benzyl boronic esters with a variety of aryl bromides with inversion of configuration.

In 2012, greater insight into the chemoselectivity of the Pd/Ag_2O-mediated cross-coupling of secondary benzylic boronic esters was described in a publication from our group.[66] A variety of alkyl boronic esters were subjected to the cross-coupling conditions featured in *Scheme 1-29*, and it was observed that only allylic or benzylic boronic esters were reactive (*Figure 1-5*). An exception to this was compound **C**, indicating that sterics hindered the reactions success.[66]

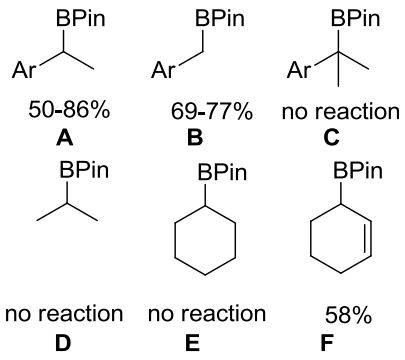
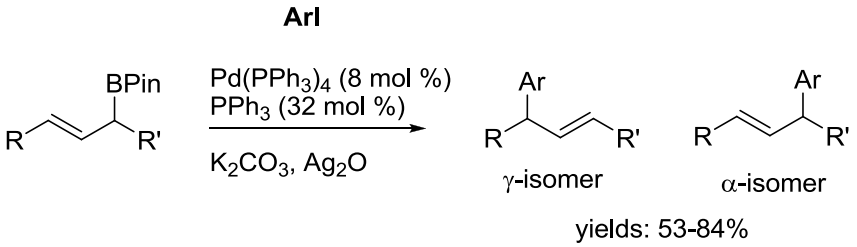


Figure 0-5. The reactivity of a variety of boronic ester substrates with *p*-iodoacetophenone under our standard Pd/Ag_2O conditions.[66]

The same publication described the first protocol for the regioselective Pd-catalyzed cross-coupling of racemic secondary allylic boronic esters with a variety of aryl iodides (*Scheme 1-31*).[66] In most cases, the coupling proceeded with high selectivity for the γ-isomer over α-isomer regardless of the aryl iodide. However, it was determined that sterics and possibly electronic factors were affecting the selectivity. When the substituent on the boron-bearing carbon was a smaller alkyl chain than that on the alkene, a 50:50 mixture of isomers was observed. However, by placing the phenyl substituent on the olefin side instead of the boron-bearing carbon, there was a switch in the selectivity to the α-isomer over γ-isomer.[66]



Scheme 0-31. The first protocol for the Pd-catalyzed cross-coupling of allylic boronic esters with a variety if aryl iodides in the presence of Ag_2O.[66]

1.6 Research Objectives

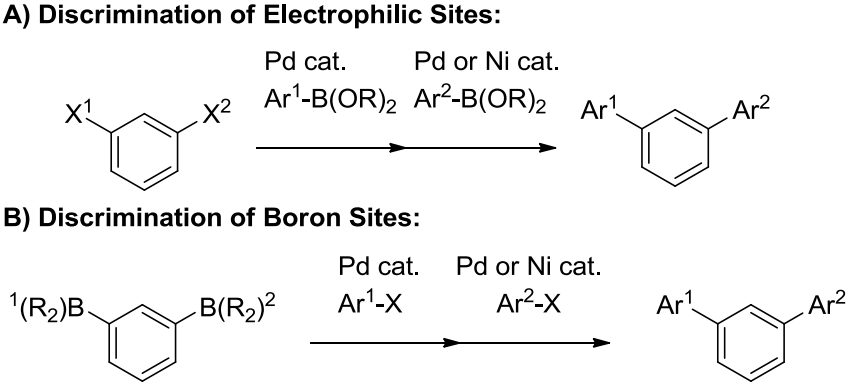
As previously stated, in 2009 the Crudden group developed the first conditions for Suzuki-Miyaura cross-couplings of chiral secondary benzylic boronic esters with a variety of aryl iodides to afford the desired compounds with retention of configuration.[64] The goal of this thesis is to further examine the selectivity of the secondary benzylic boronic ester cross-coupling reaction. This will be done by preparing a substrate that incorporates both an aryl boronic ester as well as a secondary benzylic boronic ester. Since the secondary benzylic boronic ester requires specialized conditions for the coupling to proceed, two different substituents can hopefully be introduced in place of the boron groups based solely on the reaction conditions, without the need for any protecting groups on boron.

Chapter 2

Chemoselective Suzuki-Miyaura Cross-Coupling

2.1 Introduction

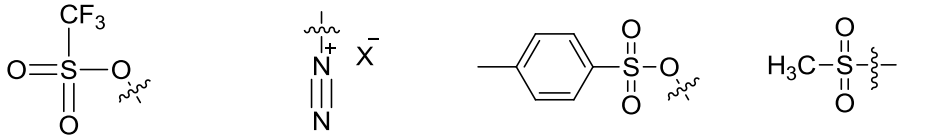
Recently, there has been increasing interest in utilizing the Suzuki-Miyaura reaction to prepare complex molecules by performing iterative cross-couplings with substrates containing two or more possible reactive sites.[67] The strategy with respect to these selective cross-couplings has been to develop a route in which the multiple reactive sites can be discriminated from one another. In order to accomplish this, the reactivity of either the two electrophilic sites (*Scheme 2-1, A*) or the boron reagents must be differentiated (*Scheme 2-1, B*).[67]



Scheme 2-1. Iterative Suzuki-Miyaura cross-coupling.[67]

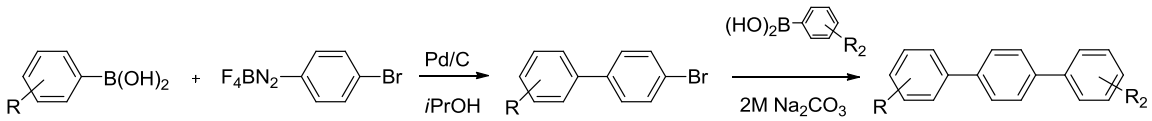
Discrimination between the electrophilic sites has proven to be the simplest approach for successive Suzuki-Miyaura cross-coupling. This is due to vast contrast in

the reactivity of aryl halides (I > Br >> Cl) and pseudo halides (such as triflates, tosylates, mesylates, and diazonium salts) (*Scheme 2-2*).[67]



Scheme 2-2. Examples of pseudohalides.

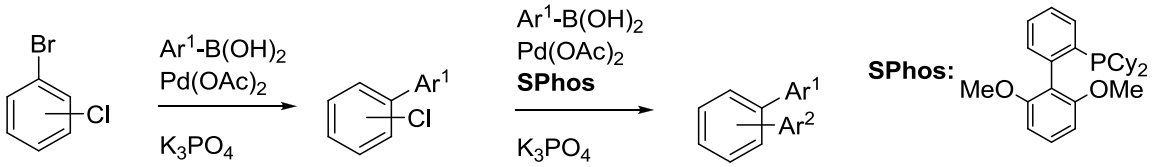
In 2007, Taylor and Felpin described the one-pot chemoselective Suzuki-Miyaura cross-coupling of phenyl boronic acid derivatives with *p*-bromobenzenediazonium tetrafluoroborate salt.[68] Due to the increased reactivity of the diazonium functional group, they were able to chemoselectively couple at the diazonium site in the presence of Pd(0)/C and *i*PrOH. Upon completion of this step, they added 2M Na_2CO_3 along with an aryl boronic acid to the reaction pot to yield the desired triaryl unsymmetrical terphenyl substrates (*Scheme 2-3*).[68]



Scheme 2-3. The one-pot chemoselective Suzuki-Miyaura cross-coupling of a *p*-bromobenzenediazonium tetrafluoroborate salt with an aryl boronic acid.

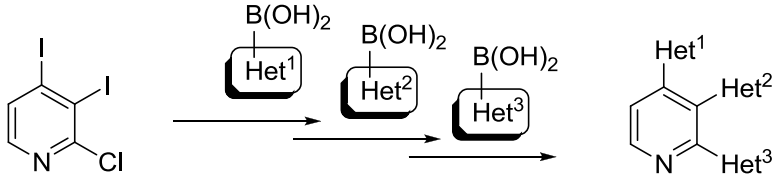
Following this, Hii and coworkers reported an efficient protocol for the cross-coupling of chloro-bromobenzenes with a variety of arylboronic acids.[69] They achieved the first coupling at the bromine site in the presence $Pd(OAc)_2$ and K_3PO_4 at room temperature. Coupling of the resulting diarylchloro substrate was performed at elevated

temperatures in the presence of 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos). This afforded the desired terphenyl compounds in moderate to high yields (*Scheme 2-4*).[69]



Scheme 2-4. The synthesis of terphenyls via iterative Suzuki-Miyaura cross-coupling of chloro-bromobenzenes.

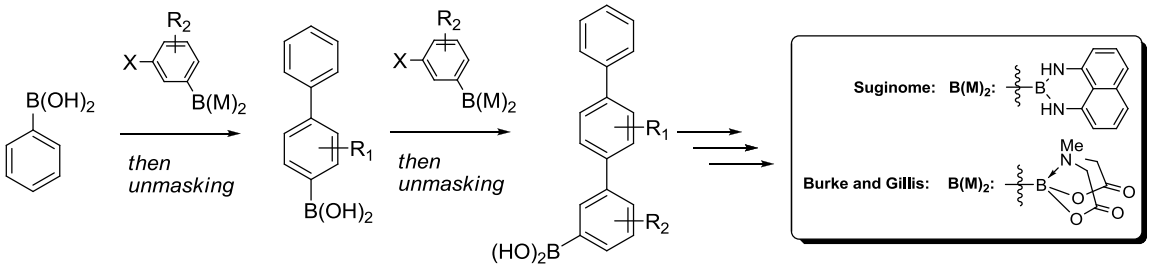
In 2010, Bryce and coworkers published the sequential iterative cross-coupling of 2-chloro-3,4-diiodopyridine with a variety of arylboronic acids to yield the desired 2,3,4-triheteroarylpyridine compounds (*Scheme 2-5*).[70]



Scheme 2-5. The synthesis of triheteroarylpyridine substrates through sequential iterative Suzuki-Miyaura cross-coupling.

Another route that makes iterative cross-coupling possible uses differentially functionalized boron substituents where one is deactivated towards coupling. The challenge in this approach is the development of a boron reagent that is unreactive under standard conditions but can be converted into a reactive species under mild conditions.[67] In 2007, Suginome and coworkers established a "boron-masking" strategy.[71] This was

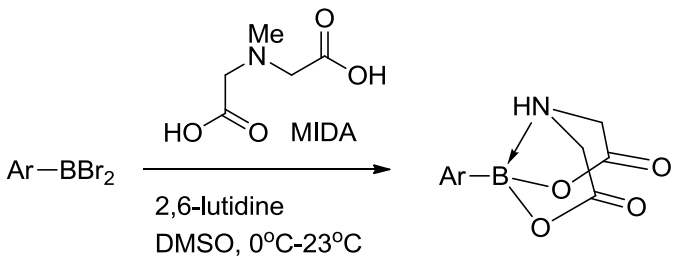
accomplished by protecting the boronic acid with 1,8-diaminonaphthalene (resulting in a B(dan) substituent) by simply refluxing both reagents in toluene followed by azeotropic removal of water.[71] The diaminoboron substituent is unreactive towards Pd-catalyzed cross-coupling due to the decreased Lewis acidity at the boron center via π-electron donation of the nitrogen atoms.[67] Therefore, the first Suzuki-Miyaura cross-coupling reaction will take place between an aryl boronic acid and an aryl halide containing a masked boron reagent. Subsequently, the boron atom can be unmasked in the presence of aqueous acid to afford the boronic acid. The cross-coupling can then be repeated (*Scheme 2-6*). This strategy highlights the potential for limitless iterative cross-coupling for the synthesis of complex oligoarenes.[71-73]



Scheme 2-6. The iterative cross-coupling via a boron masking approach towards the synthesis of multi-aryl compounds.

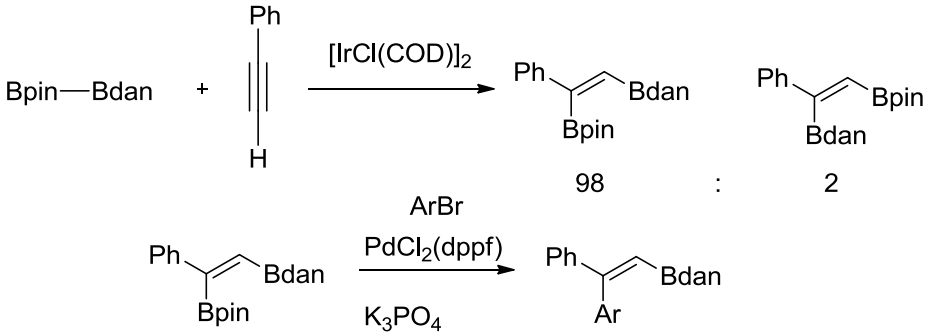
Shortly thereafter, a similar methodology was reported by Gillis and Burke.[74] They employed *N*-methyliminodiacetic acid (MIDA) as the boron masking reagent. The protected boron-containing compound is protected by reacting MIDA with a dibromo borane in the presence of 2,6-lutidine from 0-23 ^{o}C (*Scheme 2-7*). In the case of MIDA, the Lewis acidity of the boron atom is reduced due to the rehybridization of the boron atom from sp^2- to sp^3-hybridized therefore decreasing its activity towards

transmetallation. The successive cross-coupling approach is then complementary to that of Suginome and coworkers (*Scheme 2-6*). However, the MIDA protecting group is base sensitive therefore anhydrous conditions must be employed.[67]



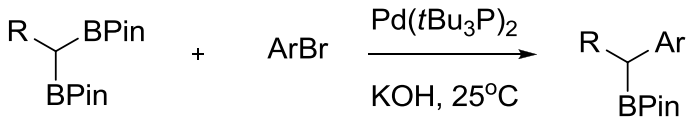
Scheme 2-7. Protection of boron with MIDA.[74]

Subsequently, in 2010 Suginome et al. performed the efficient diboration of phenylacetylene using the unsymmetrical diboron "(pin)B-B(dan)" featured in *Scheme 2-8*.[75] In the presence of $[IrCl(COD)]_2$ the transformation yielded the desired product in high regioselectivities. With this substrate in hand, they perform a selective cross-coupling at the pinacol boronic ester site with a variety of aryl bromides (*Scheme 2-8*). The B(dan) could then be removed via aqueous acid, allowing for successive cross-coupling to occur.[75]



Scheme 2-8. The diboration of phenyl acetylene followed by chemoselective Suzuki-Miyaura cross-coupling.

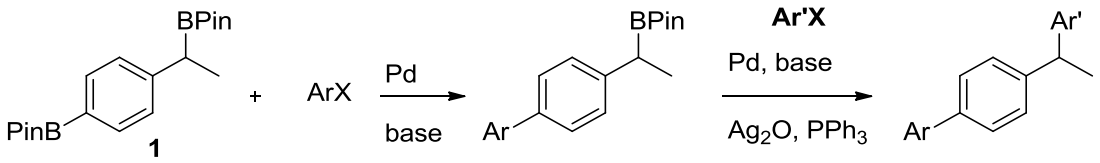
In 2010, Shibata et al. reported the regio- and chemoselective Suzuki-Miyaura cross-coupling of 1,1-diborylalkanes with a variety of aryl halides at room temperature.[76] Interestingly, the presence of the second boron group on the same carbon activated the first one towards coupling (*Scheme 2-9*).[76] Thus once the first coupling is completed the remaining boron group is unreactive.



Scheme 2-9. The regio- and chemoselective cross-coupling of 1,1-diborylalkanes.

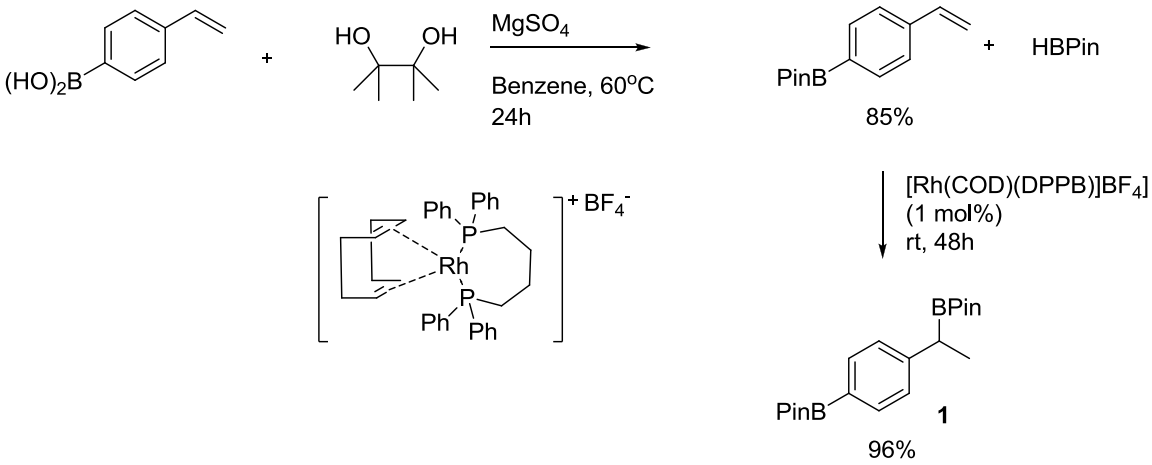
2.2 Chemoselective Suzuki-Miyaura Cross-Coupling of a Substrate Containing Both an Aryl and Secondary Benzylic Boronic Ester

In 2009, the Crudden group developed the first Suzuki-Miyaura procotol for the cross-coupling of secondary benzylic boronic esters with a variety of aryl iodides.[64] In order to cross-couple these boron substrates, specialized conditions were required. It was observed that both Ag_2O and excess PPh_3 were required for the reaction to succeed.[64] In the absence of Ag_2O, it was observed that the boronic ester didn't transmetallate. Thus we designed a substrate incorporating both an aryl and a secondary benzylic boronic ester. Therefore, if we are successful at coupling the C(sp^2)-B bond in the presence of the C(sp^3)-B bond then we should be able to accomplish a chemoselective coupling without the need for the use of protecting groups (*Scheme 2-10*).



Scheme 2-10. The proposed strategy for the chemoselective Suzuki-Miyaura cross-coupling of a substrate containing both an aryl and a secondary benzylic boronic ester.

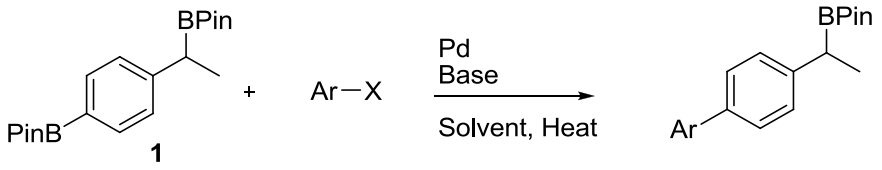
The synthesis of the desired boronic ester **1** was accomplished by reacting 4-vinylbenzene boronic acid with pinacol to afford the pinacol boronic ester. Upon subsequent Rh-catalyzed hydroboration of the double bond, the branched boronic pinacol ester site was generated (*Scheme 2-11*).



Scheme 2-11. The synthesis of the desired substrate that consists of both an aryl and a secondary alkyl boronic ester.

2.2.1 Suzuki-Miyaura Cross-Coupling at the C(sp^2)-B Bond

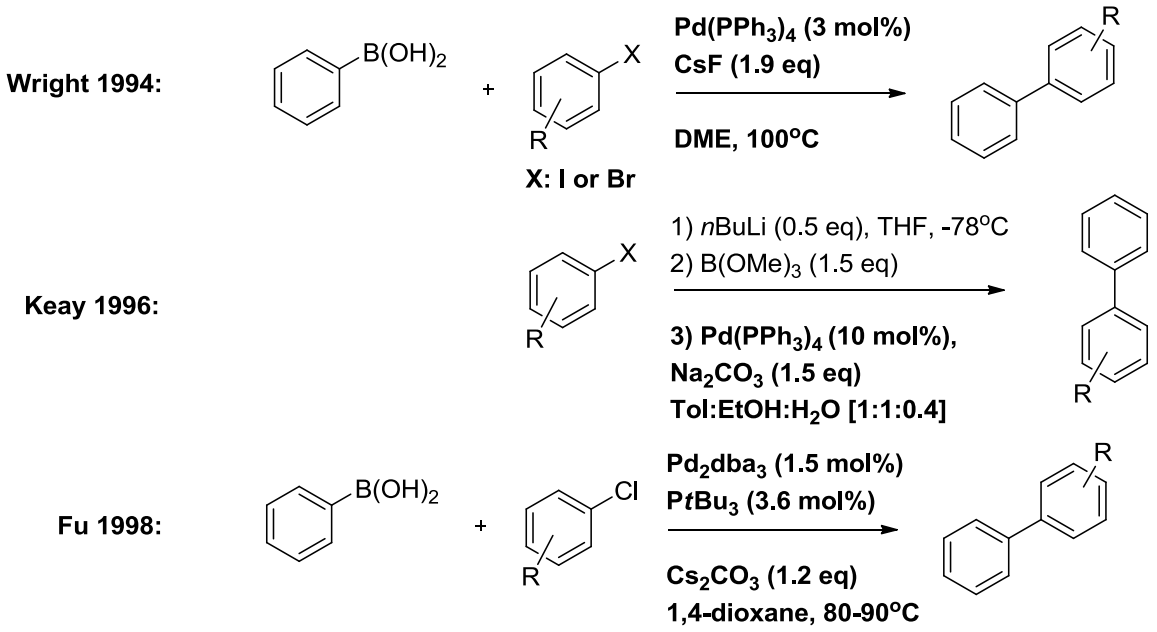
The first step was to accomplish cross-coupling selectively at the C(sp^2)-B bond of **1** (*Scheme 2-12*). C(sp^2)-B bonds are more reactive than C(sp^3) due to the presence of pi-bonding. This allows C(sp^2)-B bonds to more readily transmetallate due to an increased nucleophilicity. Over the past three decades there has been a vast amount of research focused on Suzuki-Miyaura cross-coupling reactions between C(sp^2)-B bonds, however, it is also essential that the coupling conditions be mild enough to prevent decomposition of the benzylic C(sp^3)-B bond.



Scheme 2-12. General schematic for the Pd-catalyzed cross-coupling at the aryl boronic ester site of **1** with an aryl halide.

From the literature, we chose three different types of conditions that showed efficient Suzuki-Miyaura cross-coupling between a C(sp^2)-B bond and aryl halides, and subjected compound **1** to these conditions (*Scheme 2-13*). In 1994, Wright et al. reported the Pd-catalyzed cross-coupling of phenyl boronic acid with a variety of aryl bromides in the presence of cesium fluoride to afford the desired product in up to ≥99% yield.[77] Following this, Keay et al. published the *in situ* Pd-catalyzed cross-coupling of an aryl boronic ester moiety with a variety of aryl bromides and iodides in the presence of

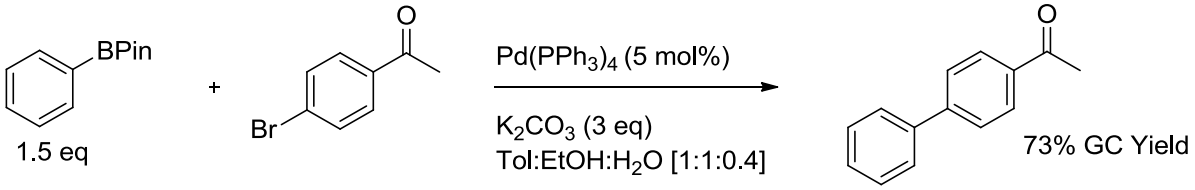
Na_2CO_3 using the solvent system mixture 1:1:0.4 toluene-ethanol-water.[78] The third publication of interest was reported by Fu and coworkers in 1998.[42] Herein, they describe the Pd-catalyzed cross-coupling of phenyl boronic acid with a variety of aryl chlorides in the presence of Cs_2CO_3. They utilized what is now known as the Fu catalyst system, Pd_2dba_3/P*t*Bu_3.[42]



Scheme 2-13. A variety of Suzuki-Miyaura cross-coupling conditions reported in the literature.[42,77,78]

Instead of submitting our desired substrate to the three different conditions listed above, we first tested a less expensive derivative, phenyl boronic ester. We found that the most successful conditions for the cross-coupling of phenyl boronic ester were the ones described by Keay et al., yielding the desired biaryl product in a 71% GC yield.[78] By lowering the palladium loading to 5 mol% and switching the base to three equivalents of K_2CO_3 we found that the yield remained approximately the same, 73% GC yield. We

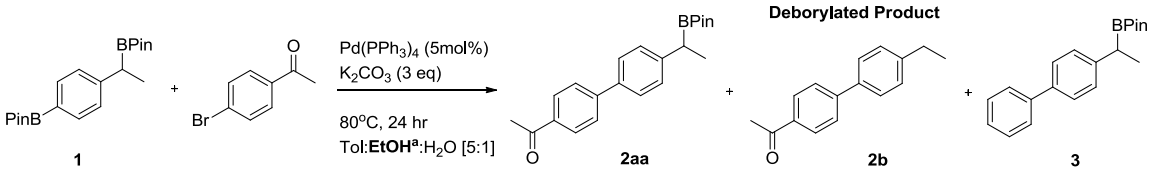
chose to continue with these optimized conditions, as the lower the palladium loading was more attractive for the cross-coupling reaction (*Scheme 2-14*).[78]



Scheme 2-14. The Pd-catalyzed cross-coupling between phenyl boronic ester and bromo-acetophenone under conditions reported by Keay et al.[78]

Following this, we employed our desired substrate under the conditions described in *Scheme 2-14*. However, only the deborylated version of our desired product **2b** was observed in high conversion by GC-MS (*Table 2-1*, entry 1). By the removal of ethanol from the solvent system, we were able to obtain the desired substrate **2aa** in 80% isolated yield (*Table 2-1, entry 2*). Another important observation made was that by changing the equivalents of reaction to 1:1, the yield remained the same. Since our boronic ester **1** is a more expensive reagent this change to the reaction conditions was beneficial.

Table 2-1. The chemoselective cross-coupling between the aryl site and bromoacetophenone yielding the desired product **2aa** and undesired deborylated product **2b**.



Entry	Solvent	Yield of 2aa[a] (%)	Yield of 2b[a] (%)	Yield of 3[a] (%)
1	Tol:EtOH:H_2O [1:1:0.4]	0	High Conversion[b]	0
2	Tol:H_2O [1:0.2]	80	0	13

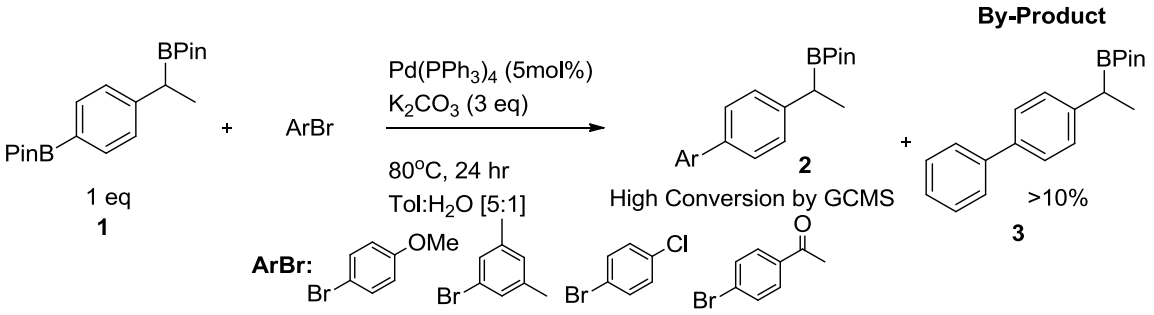
[a]NMR yield calculated by using DMB as the internal standard. [b]High conversion by GC-MS.

Notably, the reaction was completely chemoselective for coupling at the C(sp^2)-B bond and was successfully applied for a variety of aryl bromides. No traces of the secondary benzylic coupling were observed under these conditions.

These optimal conditions allowed us to determine that a key component for effective cross-coupling at the aryl site was water. The addition of water might help to solubilize the base and provide for a more facile transmetallation.[52]

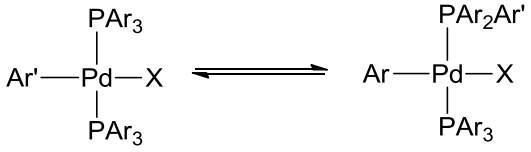
The next step was to expand the scope of the coupling at the C(sp^2)-B bond. Several aryl bromides were cross-coupled with **1**. Even though the reactions showed high conversion to product by GC-MS, it was unexpectedly difficult to isolate the desired product in pure form. Upon further analysis, the identity of trace by-product was determined to be the phenylated derivative **3** (*Scheme 2-15*). The formation of this by-

product was caused by activation of the C-P bond in triphenyl phosphine, and exchange of this phenyl group with the aryl group attached to palladium, which is known as catalyst scrambling.[79] Not only did this cause a decrease in the yields but it hindered the purification of our desired products.



Scheme 2-15. The determined identity of a by-product believed to be formed through scrambling of the catalyst system.

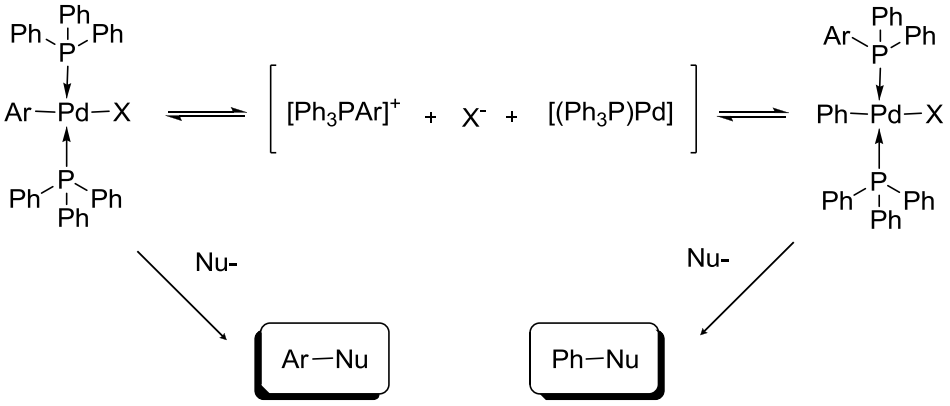
The by-product formation, due to catalyst scrambling, has been previously reported in the literature.[79] Grushin reported that this type of aryl/aryl exchange can occur with the following complexes, $[(Ph_3P)_2Pd(Ar)I]$, $[(Ph_3P)_2Pd(Ar)Br]$, and $[(Ph_3P)_2Pd(Ar)Cl$, at temperatures above 50°C (*Scheme 2-16*).[79]



Scheme 2-16. Catalyst scrambling due to aryl/aryl exchange.

The aryl/aryl exchange was reported to most likely occur via a tetraarylphosphonium intermediate involved in the C-P reductive elimination-oxidative

addition reaction sequence (*Scheme 2-17*). Due to this type of exchange, the desired product becomes contaminated by a by-product of similar structure. Efforts have been made towards suppressing or eliminating the production of this undesired product. Grushin reported ways to suppress the Ph/Ar exchange reactions of $[(Ph_3P)_2Pd(Ar)X]$ (X = I, Br, Cl, F and HF_2) including conducting the reaction in a low polarity solvent system in the presence of the following: extra phosphine ligand, extra aryl halide source, or increased Pd-catalyst concentration.[79]

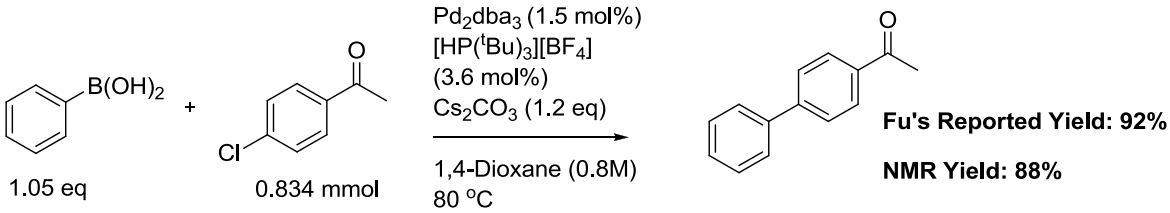


Scheme 2-17. Catalyst scrambling caused through an aryl/aryl exchange mechanism.

Several variations of the optimized reaction conditions were employed as suggested by Grushin et al.[79] Using our previous conditions, featured in *Scheme 2-15*, the following changes were performed: the equivalents of aryl bromide were doubled with or without doubling the concentration of palladium, the equivalents of the boronic ester substrate **1** were increased to 1.5, and excess triphenylphosphine was added to the reaction system. However, in all cases not only was the formation of the undesired by-product observed by GCMS but there was a notable decrease in the conversion to the

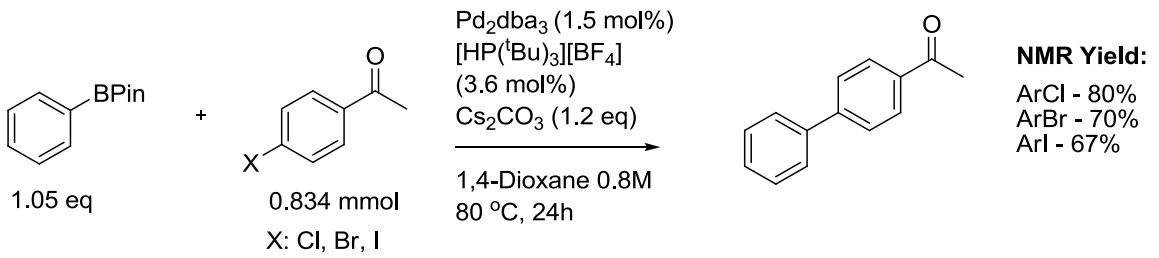
desired product. Since we were unable to decrease by-product formation with this catalyst system, we decided to revisit the Fu catalyst system (Pd_2dba_3/P*t*Bu_3), which does not require a triaryl phosphine. In the past decade, this catalyst system has received interest due to its high efficiency toward the cross-coupling of a wide variety of organoboron compounds in the presence of various types of aryl halides.

Subsequently, we realized the highly hygroscopic nature of the boronic acids/esters, which explains our previous issues in reproducing results published by Fu et al. in 1998.[42] We circumvented this issue via drying our substrates containing boronic acids/esters in a desiccator overnight in the presence of P_2O_5. We were than able to reproduce the results mentioned in this publication. By reacting phenyl boronic acid with chloroacetophenone under Fu's optimal conditions we obtained the desired biaryl species in 88% NMR yield (*Scheme 2-18*).[42]



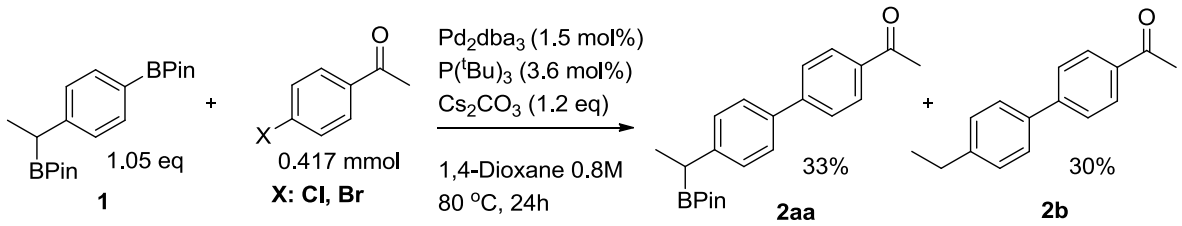
Scheme 2-18. The cross-coupling of phenyl boronic acid with chloro-acetophenone under the conditions reported by Fu et al.[61]

Subsequently, we submitted phenyl boronic ester to these conditions in the presence of iodo-, bromo-, and chloroacetophenone affording the desired biaryl compound in 67, 70, and 80% yields, respectively (*Scheme 2-19*).



Scheme 2-19. The cross-coupling of phenyl boronic ester with chloro-, bromo-, and iodoacetophenone.

When we employed our boronic ester **1** under the conditions previously discussed by Fu, to our surprise we observed the formation of our desired product **2aa** as well as the deborylated product **2b** (*Scheme 2-20*).

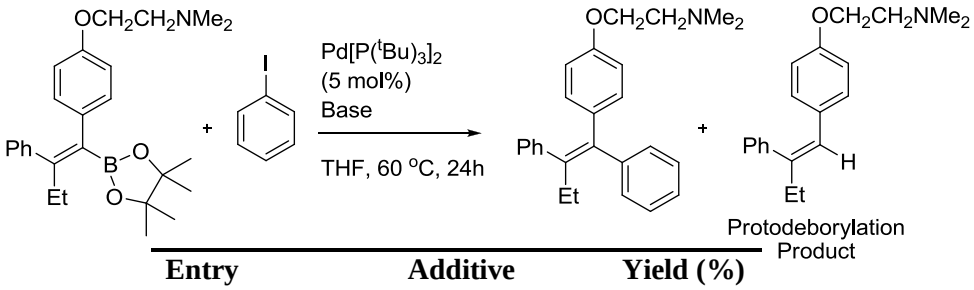


Scheme 2-20. The Suzuki-Miyaura cross-coupling between boronic ester **1** and aryl halide under conditions reported by Fu et al.[42]

The first parameter we decided to optimize was the reaction time. By shortening the length of the reaction we hoped that we could avoid the undesired protodeborylation from occurring. However, when the reaction was monitored after 15 minutes it was observed that both **2aa** and **2b** were being formed simultaneously. Therefore, altering the

reaction time was not feasable. In 2004, Yoshida et al. published the successful regio- and stereospecific Suzuki-Miyaura cross coupling of an alkenyl pinacol boronic ester with a variety of aryl iodides in yields ranging from 42-99%.[80] These conditions were variant of original Fu work.[42] However, by pairing $Pd[P(^tBu)_3]_2$ with Cs_2CO_3 the desired product was obtained in only 54% yield and 16% of the starting reagent was protodeborylated (*Table 2-2, entry 1*). Through optimization the Yoshida group discovered that changing the additive to 3 equivalents of water along with 3 equivalents of NaOH, yielded the desired compound in 98% (*Table 2-2, entry 4*). It was proposed that the addition of water and NaOH, could lead to the generation of an Ar-Pd-OH intermediate, which is suggested to be more active towards transmetallation.[80]

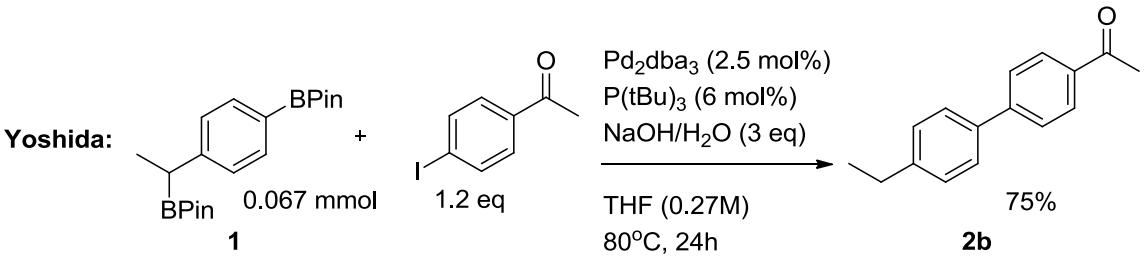
Table 2-2. The optimization of the Pd-catalyzed conditions proposed by Yoshida et al.[80]



Entry	Additive	Yield (%)
1	Cs_2CO_3	54, 16[a]
2	Cs_2CO_3/H_2O	85
3	NaOH	80
4	$NaOH/H_2O$	98

[a]yield of protodeborylation.

Thus we employed $NaOH/H_2O$ as the base/additive instead of Cs_2CO_3. A reaction was set-up with substrate **1** utilizing conditions described in the report by Yoshida et al.[80] However, only the protodeborylation product **2b** was formed in 75% yield (*Scheme 2-21*).



Scheme 2-21. The attempted Suzuki-Miyaura conditions leading to the formation of solely the protodeborylation product **2b**.

Optimizing the conditions reported by Yoshida et al.,[80] we began by examining the effect of the base, starting with KOAc, KF, and K_3PO_4. When the base used was KOAc there was no reaction (*entry 1, Table 2-3*). In the case of KF and K_3PO_4, **2b** was observed to form in approximately quantitative yield (*entry 2 and 3, Table 2-3*).

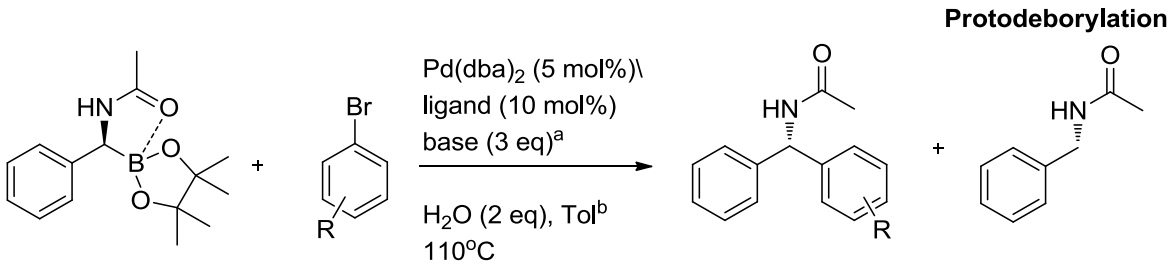
Table 2-3. Optimization of the base within the conditions reported by Yoshida et al.

Entry	Base	Yield of 2aa[a] (%)	Yield of 2b[a] (%)
1	KOAc	No Reaction	
2	KF	0	>99
3	K_3PO_4	0	>99

[a]NMR yield calculated using dimethoxybenzene (DMB) as the internal standard.

Suginome and coworkers also discussed the issue of protodeborylation in their 2010 publication.[65] In this paper they described the first Suzuki-Miyaura cross-coupling

of a chiral alkyl boronic ester resulting in an inversion of stereochemistry (*Scheme 2-22*). This report provided insight with regards to the protodeborylation because their alkyl boronic ester system was similar in structure to our secondary benzylic boronic ester. During preliminary screening, Suginome noted that the rate of formation of the protodeborylation product was slower in toluene than 1,4-dioxane. While employing the Fu-type catalyst system, Pd/P(^{t}Bu)$_3$, the protodeborylated product was observed when the



base was K_2CO_3. However, by switching the base to KF no protodeborylation was observed.[65]

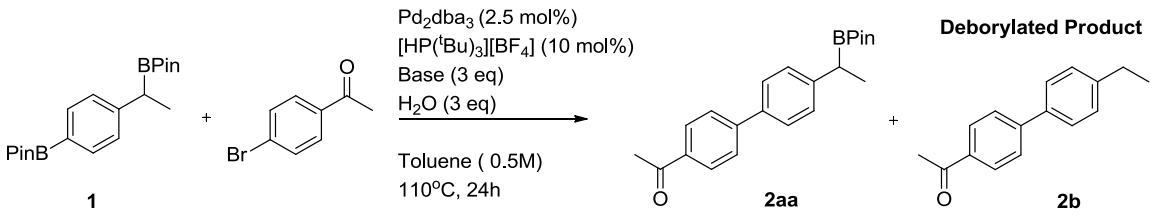
[a] when KF was used there was no observed protodeborylation.
[b]rate of protodeborylation was slower in toluene than 1,4-dioxane.

Scheme 2-22. The Suzuki-Miyaura cross-coupling of α-(acylamino)benzylboronic esters with a variety of aryl bromides to yield the desired diarylmethanamine in high yields with inversion of configuration.

By following the Suginome conditions[65], promising results were observed. No deborylation was observed, although the desired product was obtained in a 35% NMR yield. It was encouraging that even though the yield was low, there was no formation of any by-products caused through catalyst scrambling or protodeborylation (*Table 2-4, entry 6*).

Since the conditions reported by Suginome et al. showed promising results, we then began optimizing these conditions. Our first focus was base optimization and we employed the following bases: Cs_2CO_3, KOH, NaOH, Na_2CO_3, KF, and K_2CO_3. When the base was Cs_2CO_3 and KOH, the reaction resulted in almost complete conversion to **2b** (*Table 2-4, entry 1 and 2*). By removing water from the system we attempted KOH and NaOH, this resulted in a mixture of products (*Table 2-4, entry 3 and 4*). When Na_2CO_3 and KF were employed **2aa** was formed in low yield without the formation of **2b** (*Table 2-4, entry 5 and 6*). However, to our satisfaction, when K_2CO_3 was used the NMR yield of **2aa** increased to 79% (*Table 2-4, entry 7*) along with 21% formation of the undesired compound **2b**.

Table 2-4. Optimization of the base within the conditions reported by Suginome et al.



Entry	Base	Yield of 2aa[a] (%)	Yield of 2b[a] (%)
1	Cs_2CO_3	0	96
2	KOH	5	95
3	KOH[b]	21	67
4	NaOH[b]	29	59
5	Na_2CO_3	28	0
6	KF	35	0
7	K_2CO_3	79	21

[a]NMR yield calculated using DMB as the internal standard. [b]The reaction was run without water.

As in the previous case, it was concluded that both products were being produced simultaneously. It was also later discovered that the result from *entry 3* from *Table 3*-3 was difficult to reproduce, causing an inconsistency with our previous results. We then considered the publication by Shibata et al. in 2010 (*Scheme 2-9*).[76] Their reactions were performed at room temperature and the C(sp^3)-B bond, which is essentially equivalent to the one present in our substrate, remained intact under the conditions. This led us to infer that perhaps the elevated reaction temperatures in our system were causing protodeborylation to occur.[76, 76]

In fact, by lowering the temperature of the system not only were we able to obtain reproducible results, but an increase in the yield of the desired substrate was observed. By decreasing the temperature to 80^{o}C we were able to reproduce the result of 80:20 **2aa**:**2b** (*Table 2-4, entry 1*). When the temperature was decreased to 60^{o}C, we finally obtained our desired product in 95% NMR yield (*Table 2-4, entry 2*). No reaction was observed at room temperature (*Table 2-4, entry 3*).

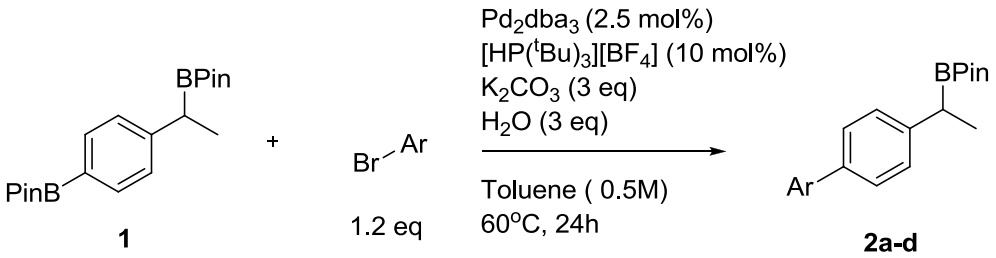
Table 2-5. Variation of the temperature for the cross-coupling of substrate **1** with bromo acetophenone.

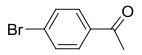
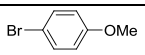
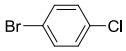
Entry	Temp. (^{o}C)	Yield of 2aa[a] (%)	Yield of 2b[a] (%)
1	80	82	18
2	60	95	5
3	25	No Reaction	

Reaction Conditions: Pd_2dba_3 (2.5 mol%), [HP(^{t}Bu)$_3$][BF4] (10 mol%), K_2CO_3 (3 eq), H_2O (3 eq) heated for 24 hours. [a]NMR yield calculated by using DMB as the internal standard.

Upon the discovery of successful conditions for the selective Suzuki-Miyaura cross-coupling at the C(sp^2)-B bond of our substrate **1**, we immediately began to expand the scope of this transformation. We were able to chemoselectively cross-couple at the aryl site with a variety of aryl bromides to obtain yields ranging from 95-99% by NMR, without loss of the C-B bond (*Table 2-5*).

Table 2-6. The expanded scope of the Pd-catalyzed cross-coupling at the aryl boronic ester site.



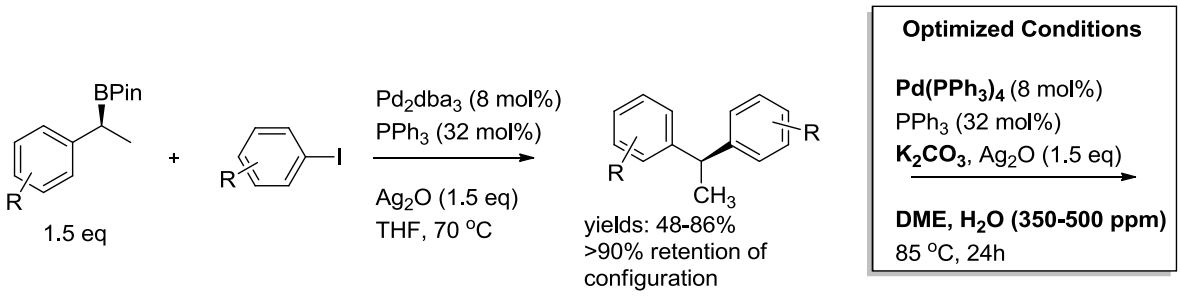
ArBr	Label	Yield (%)
	**2aa**	88[a] (95)[b]
	**2ab**	76[c] (96)
	**2ac**	(>99)
	**2ad**	67[d] (>99)

[a]Isolated yield. [b]NMR yields with internal standard as DMB. [b]The reaction was run at 10 times the scale and product was isolated. [c]The reaction was run at 15.5 times the scale and product was isolated.

2.2.2 Suzuki-Miyaura Cross-Coupling at the Secondary Alkyl Boronic Ester Site

As previously stated, the Crudden group established the first protocol for the Suzuki-Miyaura Pd-catalyzed cross-coupling of secondary benzylic boronic esters in the presence of Ag_2O and excess PPh_3.[64] More recently the conditions have been further modified. By the addition of 1.5 equivalents of K_2CO_3 to the system the stereoretention was observed to increase to 98% ee.[81] It was also noteworthy that aryl bromides become viable, although low yielding, candidates for this transformation upon the presence of K_2CO_3.[82]

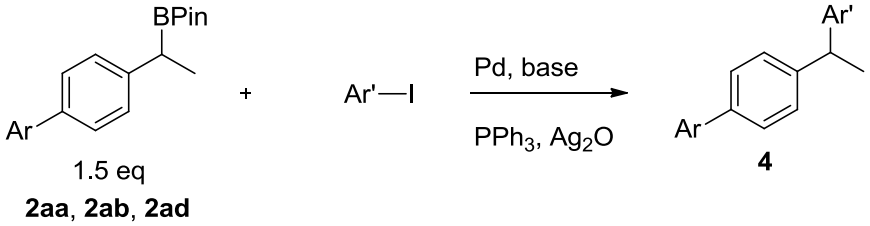
The addition of water to the reaction system was also analyzed. It was observed that a minimal concentration of water, 350-500 ppm, is likely required in order for the reaction to proceed (*Scheme 2-23*). It was observed that the reaction performance decreases upon the inclusion of molecular sieves that were used to remove adventitious water from THF. However, when water was used as co-solvent instead of an additive yields suffered dramatically.[82]



Scheme 2-23. The optimized conditions for the Suzuki-Miyaura cross-coupling of secondary boronic ester substrate.

The next step in our proposed chemoselective Suzuki-Miyaura cross-coupling of **1** was to cross-couple at the secondary alkyl site of compounds **2aa**, **2ab**, and **2ad**. Since

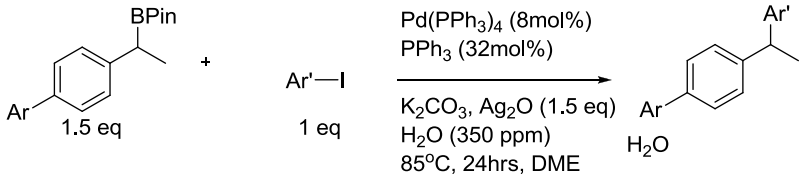
the conditions for this step have been previously optimized[82] we began with these conditions.

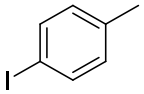
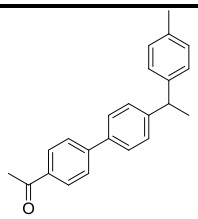
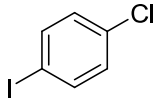
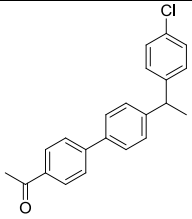
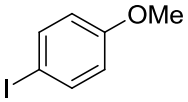
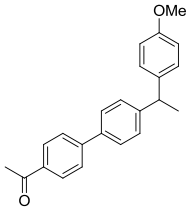
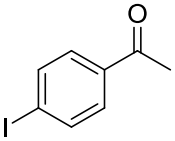
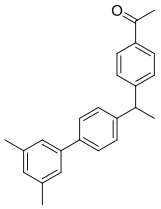


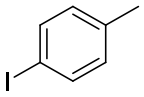
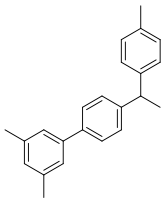
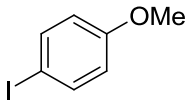
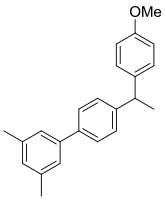
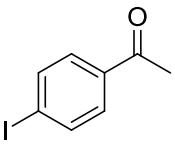
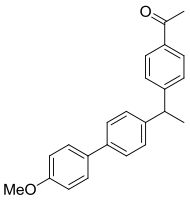
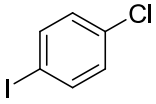
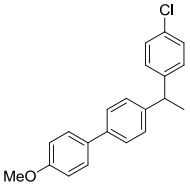
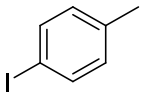
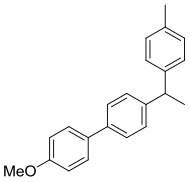
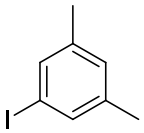
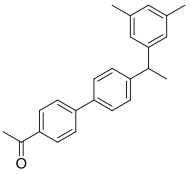
Scheme 2-24. General schematic for the Pd-catalyzed cross-coupling at the alkyl boronic ester site of **2aa, 2ab, 2ad** with an aryl iodide.

Using conditions developed by our group[64,81] we were able to successfully perform the Pd-catalyzed cross-coupling of the benzylic boronic esters **2aa**, **2ab**, and **2ad** with several aryl iodides in the presence of Ag_2O and excess PPh_3 to afford the desired triaryl species in yields ranging from 49-76% (*Table 2-6*). It should be noted that yields were consistently higher in the presence of 350 ppm water.

Table 2-7. The Suzuki-Miyaura cross-coupling of secondary benzylic boronic ester substrates **2aa**, **2ab**, and **2ad** with a variety of aryl iodides.



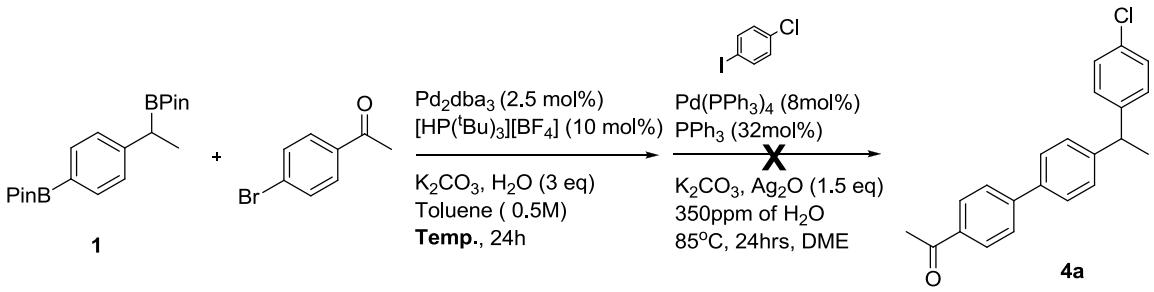
ArBPin	Ar'I	Ar-Ar'	Label	Yield[a] (%)
2aa			**4a**	50[b], 71
2aa			**4b**	57[b], 66
2aa			**4c**	56
2ad			**4d**	71, (67)[c]

2ad			**4e**	76
2ad			**4f**	62
2ab			**4g**	59
2ab			**4h**	53
2ab			**4i**	49
2aa			**4j**	32[b]

[a]NMR yields were calculated by the use of DMB as an internal standard. [b]Reaction performed in the absence of H_2O. [c]Isolated yield.

2.2.3 Attempted One-Pot Iterative Cross-Coupling of Boronic Ester Substrate 1

In order to analyze the efficiency of our chemoselective cross-coupling of **1**, we had previously attempted to accomplish both cross-couplings in one-pot. This was performed by first preparing the cross-coupling at the C(sp^2)-B bond. After 24 hours, the reagents for the cross-coupling at the secondary benzylic site were prepared in the glovebox and sealed with a Teflon cap. The reaction mixture from the aryl cross-coupling reaction was then injected into the vial containing the reagent for the alkyl cross-coupling step. After an additional 24 hours, the reaction mixture was analyzed by GCMS. Unfortunately, the final product **4a** was not observed (*Scheme 2-25*). This reaction is proposed to not succeed in a one-pot set-up due to the differences between the reaction conditions from each cross-coupling step. The secondary benzylic cross-coupling step is extremely sensitive; it has been observed that by increasing the concentration of water or base results in decreased yield or no reaction. Therefore, it was not a surprise that the one-pot attempt did not succeed. Further optimization was not performed for the one-pot reaction.



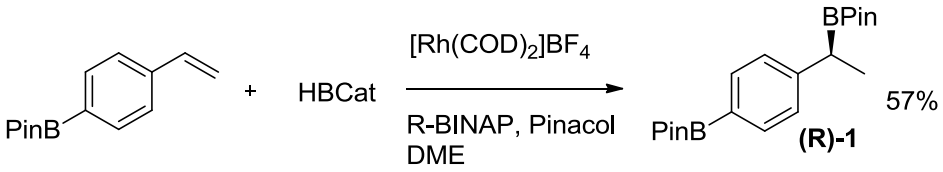
Scheme 2-25. Attempted one-pot iterative cross-coupling of boronic ester substrate **1**.

2.3 Conclusions and Future Work

We have been able to circumvent the following two issues which caused by-product formation: aryl/aryl exchange due to a catalyst system resulting in the formation of by-product **3**, and deborylation yielding the by-product **2b**. The former issue was resolved by switching the catalyst system, and deborylation was suppressed by lowering the reaction temperature. Subsequently, we discovered optimal conditions to afford the cross-coupling of our desired substrate **1** selectively at the aryl boronic ester site obtaining compounds **2a-d** in NMR yields ranging from 95-99%. Upon isolation of the products from the first cross coupling, **2aa**, **2ab**, and **2ad**, we then performed cross-coupling at the secondary benzylic alkyl site with NMR yields ranging from 49-76%.

Further research will begin with the isolation/purification of the racemic compounds from the cross-coupling at the secondary alkyl site, **4a-i**. This will be followed by the repeating the chemoselective Suzuki-Miyaura cross-coupling described above with our enantioenriched substrate **(R)-1**. The enantiomeric excess of the final isolated triaryl product will then be analyzed by SFC.

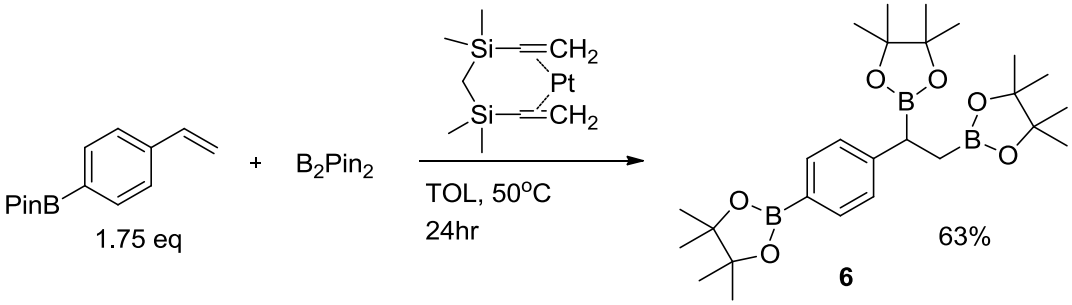
We have been able to synthesize the enantioenriched version of our substrate **(R)-1**. This was accomplished via the rhodium-catalyzed hydroboration of 4-vinylbenzene boronic acid in the presence of R-BINAP to yield our desired product in 57% (*Scheme 2-26*). The procedure was obtained from a reported published by Crudden et al. in 2004.[35]



Scheme 2-26. The synthesis of the enantioenriched version of our desired substrate.[35]

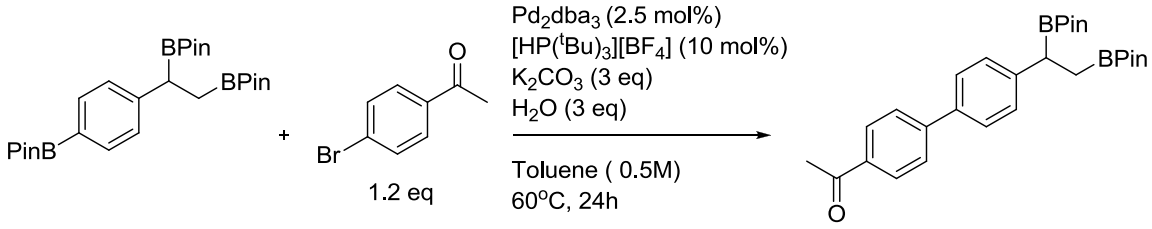
However, the oxidation of **(R)-1** posed difficulties due to the C(sp^2)-B bond. Therefore, the enantiomeric excess of this reagent was not calculated. Work is currently in progress to calculate the enantiomeric excess of the compounds isolated from the cross-coupling at the C(sp^2)-B bond of **(R)-1** with a variety of aryl bromide.

Upon completion of this project, the next direction of interest would be to cross-couple a substrate that incorporates an aryl boronic ester, a secondary benzylic boronic ester, and a linear alkyl boronic ester. We have already been able to successfully synthesize this substrate of interest, **6**, in 63%. This was completed via Pt-catalyzed diboration of 4-vinyl pinacol boronic ester to afford **6** (*Scheme 2-27*). The conditions were modified from a previously published procedure by Miyaura et al. in 1997.[83]



Scheme 2-27. Synthesis of substrate **6**.

However, preliminary results have suggested the complications of chemoselective cross-coupling of this substrate. Due to the third boronic ester, this creates another site at which protodeborylation can occur. This is an issue that may need to be resolved through optimization of the conditions for the cross-coupling at the C(sp^2)-B bond (*Scheme 2-28*).



***Unverifiable mixture of starting material, desired product, as well as potentially deborylated and coupled products at the linear site.

Scheme 2-28. Preliminary attempt at the chemoselective cross-coupling at the C(sp^2)-B bond on the substrate **5**.

Chapter 3
Experimental

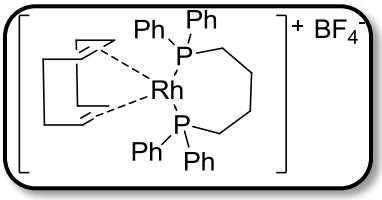
3.1 General Considerations

All cross-coupling reactions were set-up in a nitrogen filled glovebox. The solvents utilized in these reactions were purified either by literature procedures[84] via a solvent still apparatus or an alumina-dried purification system (Innovative Technologies SPS). They were then degassed by a minimum of three freeze-pump-thaw cycles and stored in the glovebox over 4 Å molecular sieves or a combination of sieves and Al_2O_3. If necessary, reagents used were purified via literature procedure[84] and degassed by the procedure discussed above. Any compounds containing boronic esters or acids were dried in a vacuum sealed desiccator with P_2O_5 over night and stored in the glovebox fridge under -20^{o}C. All bases used in cross-coupling were ground and dried in a vacuum sealed desiccator with P_2O_5 over night before use. Pd_2dba_3, $Pd(PPh_3)_4$, $[Rh(cod)_2]BF_4$, and Ag_2O were used in the glovebox as purchased from Aldrich, Strem, and Acros, respectively. Thin Layer Chromatography was performed on aluminum backed silica plates and visualized by UV (254, 365 nm), the indicators utilized to stain were phosphomolybdic acid, permanganate, and 2,4-dinitrophenylhydrazine. Column chromatography was performed by using flash grade silica (Silicycle, 40-63 μm particle size, 60 Å porosity) and reagent grade solvents. All GC-MS spectra were obtained using an Agilent Technologies 5975CVL-MSD (triple axis detector), the capillary measures 30m by 250 μm by 0.25μm nominal, 250 inlet, splitless detector. NMR spectroscopy was performed

on four Bruker Advance machines: 300 MHz, 400 MHz, 500 MHz, and 600 MHz, as indicated. High Resolution Mass Spectroscopy (HRMS) was performed on the Voyager DE STR MALDI TOF instrument. All infrared spectra were obtained using a Varion 640 Fourier Transform Infrared Spectrometer (FTIR). Pinacolborane (HBPin) and cathecolborane (HBCat) were distilled under reduced pressure and stored in the glovebox below -20^{o}C. When ^{11}B NMR and ^{31}P NMR were performed on the manual 400 and 500 MHz Bruker Advance machines, the external boron and phosphine standards used were neat BF_3-OEt_2 and 30% phosphoric acid, respectively, these were run in their own NMR tube. The external standard peaks appear in indicated NMR spectra, this is because the first scan of the NMR spectrum was run with the external standard, the NMR spectrum was then calibrated, and the NMR experiment was continued with the sample of interest.

3.2 Chemoselective Suzuki-Miyaura Cross-Coupling at the C(sp^2)-B Bond

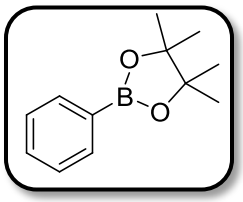
Synthesis of catalyst for hydroboration, [Rh(cod)(DPPB)]BF_4:



In a nitrogen filled glovebox, a solution of 1,4-bis(diphenylphosphino)butane (DPPB) (0.14 mmol, 59.7 mg) in 5 mL of tetrahydrofuran (THF) was added to a solution of [Rh(cod)$_2$]BF_4 (0.14 mmol, 56.8 mg) in 5 mL of THF. The reaction mixture was stirred overnight.[85] Subsequently, the THF was decanted and the resulting orange solid was dissolved in a minimal amount of dichloromethane (DCM), the vial diluted

with THF and stored at glovebox temperature. Upon crystallization, the solvent was decanted and the crystals were allowed to dry within the glovebox atmosphere. The desired catalyst was isolated in 67% yield (0.089 mmol, 67.2 mg). **^{1}H-NMR:** (500 MHz, CD_2Cl_2) δ 7.60-7.52 (m, 20H) [PPh_2], 4.44 (br s, 4 H) [olefinic H of cod], 2.43 (br s, 4 H) [P-CH_2 of DPPB], 2.32-2.19 (m, 8 H) [alkyl H of cod], 1.67-1.63 (m, 4 H) [CH_2 of DPPB] **^{13}C-NMR:** (125 MHz, CD_2Cl_2): δ 133.8 [phenyl], 133.7 [phenyl], 133.7 [phenyl], 132.1 [phenyl], 129.9 [phenyl], 129.9 [phenyl], 129.8 [phenyl], 101.2 [olefinic C of cod], 68.3 [C-P of DPPB], 30.9 [CH_2 DPPB], 26.2 [alkyl C of cod], 25.3 [alkyl C of cod] **^{31}P-NMR:** (200 MHz, CD_2Cl_2) δ 24.9 (d, J_{Rh-P} = 143.5 Hz). The external standard used was 30% phosphoric acid; appearing as a singlet at 0.0 ppm. CAS: 79255-71-3[86]

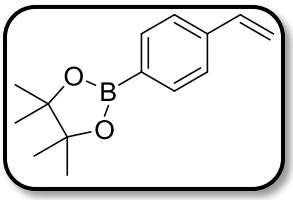
Synthesis of 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane:



Phenyl boronic acid (9.78 mmol, 1.19 g), pinacol (12.2 mmol, 1.43 g), and $MgSO_4$ (9.99 mmol, 1.20 g) were stirred in 60 mL of benzene, from the bottle, at room temperature. After 24 hours, the reaction mixture was filtered and the solvent was removed by rotovap. Upon gradient column chromatography (20:1-10:1 Hex:EtOAc), the desired phenyl boronic ester was isolated in 70% yield (6.86 mmol, 1.40 g). **^{1}H-NMR:** (300 MHz, $CDCl_3$) δ 7.82-7.79 (m, 2 H) [phenyl], 7.49-7.43 (m, 1 H) [phenyl], 7.39-7.34 (m, 2 H) [phenyl], 1.35 (s, 12 H) [CH_3-BPin] **^{13}C-NMR:** (100 MHz, $CDCl_3$) δ 134.7 [phenyl], 131.2 [phenyl], 127.7 [phenyl], 83.8 [C-B phenyl], 24.9 [CH_3 of BPin] **^{11}B-NMR:** (160 MHz, $CDCl_3$) δ 31. The

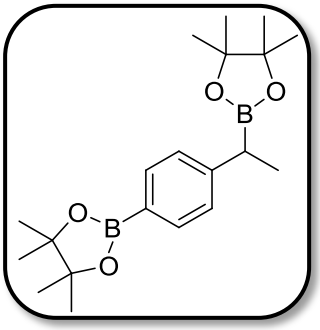
automatic 400 NMR machine was used in this case, no standard was required. CAS: 24388-23-6[87]

This matches with the CAS spectra*Synthesis of 4,4,5,5-tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane:*



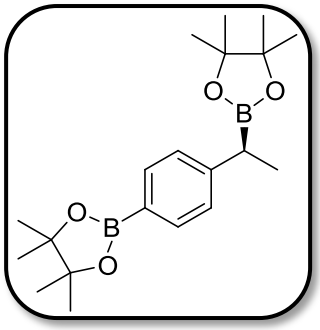
In a dried rbf, 4-vinylbenzeneboronic acid (0.0180 mol, 2.66 g) was dissolved in 60 mL of benzene, from the bottle, at 60 ^{o}C. Following this, pinacol (0.0216 mol, 2.55 g) and $MgSO_4$ (0.0184 mol, 2.21 g) were added and the reaction mixture was stirred at 60 ^{o}C for 24 hours. The resulting solution was filtered and solvent was removed via rotary evaporation. The desired product was isolated by column chromatography (5:1 Hex:EtOAc) as a colorless oil in 85% yield (0.0153 mol, 3.53 g). **^{1}H-NMR:** (400 MHz, $CDCl_3$): δ 7.80 (d, 2 H, *J* = 7.7 Hz) [phenyl], 7.43 (d, 2 H, *J* = 7.7 Hz) [phenyl], 6.75 (dd, 1 H, *J* = 10.9, 17.6 Hz) [olefinic CH], 5.85 (d, 1 H, *J* = 17.6 Hz) [olefinic CH_2], 5.33 (d, 1 H, *J* = 10.9 Hz) [olefinic CH_2], 1.39 (s, 12 H) [CH_3-BPin] **^{13}C-NMR:** (100 MHz) δ 140.2 [phenyl], 136.8 [phenyl], 135.0 [phenyl], 125.5 [phenyl], 114.8 [olefinic CH], 83.7 [olefinic CH_2], 24.8 [CH_3-BPin] **^{11}B-NMR:** (160 MHz) δ 31. CAS: 870004-04-9[88] The external standard used was BF_3-OEt_2; appearing as a singlet at 0.0 ppm.

*Synthesis of racemic 4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl-1,3,2-dioxaborolane (**1**):*



In a nitrogen filled glovebox, [Rh(cod)(DPPB)][BF_4] (0.044 mmol, 32 mg) and 4,4,5,5-tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane (4.4 mmol, 1.0 g) were dissolved in 2 mL of THF, distilled and deoxygenated. A solution of HBPin (5.28 mmol, 676 mg) in 1 mL of THF was transferred to the previous mixture. The resulting solution was capped and stirred at glove box temperature for 48 hours. Subsequently, solvent was removed via rotary evaporation and the desired compound was isolated as a white solid in 85% yield (3.75 mmol, 1.34 g) by column chromatography (10:1 Hex:EtOAc). **^{1}H-NMR:** (400 MHz, $CDCl_3$) δ 7.71 (d, 2 H, *J* = 8.1 Hz) [phenyl], 7.23 (d, 2 H, *J* = 7.9 Hz) [phenyl], 2.45 (q, 1 H, *J* = 7.4 Hz) [CH benzylic], 1.33 (s, 15 H) [3H = CH_3 alkyl, 12H = BPin-CH_3], 1.19 (s, 6 H) [BPin-CH_3], 1.18 (s, 6 H) [BPin-CH_3] **^{13}C-NMR:** (100 MHz, $CDCl_3$) δ 148.5 [phenyl], 134.8 [phenyl], 127.2 [phenyl], 83.5 [C-B phenyl], 83.3 [O-C(CH_3)$_2$ of pinacol], 24.8 [B-CH benzylic], 24.6 [BPin-CH_3], 16.7 [CH_3 alkyl] **^{11}B-NMR:** (160 MHz, $CDCl_3$) δ 33. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{20}H_{32}B_2O_4$) *m/z* 358.2487; found 358.2491. The automatic 400 NMR machine was used in this case, no standard was required.

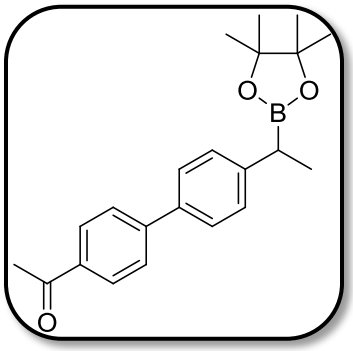
*Synthesis of (**R**)-4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl-1,3,2-dioxaborolane (**R-1**):*



In a nitrogen filled glovebox, $[Rh(COD)_2][BF_4]$ (0.0570 mmol, 23.1 mg) and R-BINAP (0.068 mmol, 42 mg) were combined in an oven dried Schlenk tube with 4 mL of dimethoxyethane (DME), distilled and deoxygenated, and stirred for 10 minutes. Subsequently, 4,4,5,5-tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane (2.62 mmol, 603 mg) was added to the stirred solution. In a separate oven dried rbf, HBCat was dissolved in 2 mL of DME. The Schlenk tube and rbf were removed from the glovebox, attached to a schlenk line, and opened to a stream of argon. The flasks were then cooled below -69^{o}C and the HBCat solution was cannula transferred to the Schlenk tube. The reaction was maintained below -69 ^{o}C for 5 hours. Following this, pinacol (4.43 mmol, 1.02 g), from the glovebox, was added to the Schlenk tube through a stream of argon. The reaction was stirred overnight and allowed to warm to room temperature. Subsequently, the desired product was isolated as a white solid via column chromatography (20:1 Hex: EtOAc) in 57 % yield (1.48 mmol, 530 mg). Oxidation of this substrate was unsuccessful. Therefore, enantiomeric excess was calculated on the products isolated from the coupling at the C(sp^2)-B bond of **(R)-1**. **^{1}H-NMR:** (40 0MHz, $CDCl_3$) δ 7.71 (d, 2 H, *J* = 8.0 Hz) [phenyl], 7.23 (d, 2 H, *J* = 8.0 Hz) [phenyl], 2.45 (q, 1 H, *J* = 7.4 Hz) [CH benzylic], 1.33 (s, 15 H) [3H = CH_3 alkyl; 12H = CH_3-BPin], 1.19 (s, 6 H) [CH_3-BPin], 1.18 (s, 6 H) [CH_3-BPin] **^{13}C-NMR:** (100 MHz,

$CDCl_3$) δ 148.6 [phenyl], 134.9 [phenyl], 127.3 [phenyl], 83.5 [C-B phenyl], 83.3 [O-$C(CH_3)_2$ of pinacol], 24.8 [B-CH benzylic], 24.6 [CH_3-BPin],16.8 [CH_3 alkyl]. **^{11}B-NMR:** (160 MHz, $CDCl_3$) δ 34. The automatic 400 NMR machine was used in this case, no standard was required.

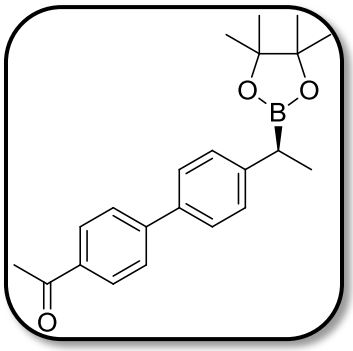
*Synthesis of substrate **2aa**:*



In a nitrogen filled glove box, 4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl)-1,3,2-dioxaborolane (0.050 mmol, 17.9 mg), 4-bromoacetophenone (0.060 mmol, 11.9 mg), K_2CO_3 (0.15 mmol, 20.7 mg), $Pd_2(dba)_3$ (0.00125 mmol, 1.1 mg, 2.5 mol%), and PPh_3 (0.0050 mmol, 1.5 mg) were weighed into an oven dried vial and 0.1 mL of toluene, purified by the SPS and degassed, was added. The vial was sealed with a black cap fitted with a Teflon septum. The vial was removed from the glovebox and immediately sealed with Teflon and electrical tape. H_2O (0.15 mmol, 2.7 µL), which had been purged separately with argon for 15-30 mins, was then added to the reaction vial via glass syringe. The top of the cap was filled with Teflon tape and sealed with electrical tape. Subsequently, the reaction mixture was stirred vigorously at 60 ^oC for 24 hours. The solution was then filtered through celite and eluted with Et_2O. The yield was determined via 400 MHz NMR spectroscopy with dimethoxybenzene (DMB) (0.0446 mmol, 6.16 mg) as the internal standard and determined to be 95%. When the reaction was run at 5

times the scale, the desired compound was isolated by gradient column chromatography (20:1-10:1 Hex:EtOAc) in 88% yield (0.22 mmol, 78.1 mg) as a pale yellow solid. **^{1}H-NMR:** (400 MHz, $CDCl_3$) δ 8.01 (d, 2 H, *J* = 8.3 Hz) [phenyl], 7.68 (d, 2 H, *J* = 8.3 Hz) [phenyl], 7.55 (d, 2 H, *J* = 8.2 Hz) [phenyl], 7.33 (d, 2 H, *J*= 8.2 Hz) [phenyl], 2.63 (s, 3 H) [CH_3 acetyl], 2.50 (q, 1 H, *J* = 7.4 Hz) [CH benzylic], 1.38 (d, 3 H, *J* = 7.5 Hz) [alkyl CH_3], 1.23 (s, 6 H) [CH_3 of BPin], 1.22 (s, 6 H) [CH_3 of BPin] **^{13}C-NMR:** (100 MHz, $CDCl_3$) δ 197.7 [acetyl C=O], 145.8 [phenyl], 145.5 [phenyl], 136.5 [phenyl], 135.5 [phenyl], 128.8 [phenyl], 128.4 [phenyl], 127.1 [phenyl], 126.9 [phenyl], 83.4 [O-$C(CH_3)_2$ of pinacol], 29.7 [CH_3 of acetyl], 26.6 [B-CH benzylic], 24.6 [CH_3-BPin], 17.0 [CH_3 alkyl] **^{11}B-NMR:** (160 MHz, $CDCl_3$) δ 34. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{22}H_{27}BO_3$) *m/z* 350.2053; found 350.2047. **IR (ν_{max}/cm^{-1}):** 2984 (m), 2935 (m), 2235 (m), 1677 (s), 1270 (s). The automatic 400 NMR machine was used in this case, no standard was required.

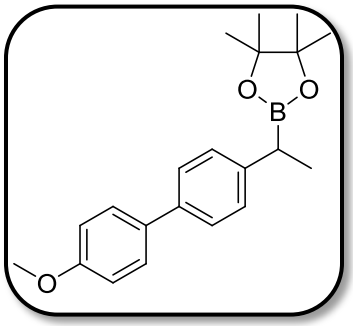
*Synthesis of substrate **(R)-2aa**:*



In a nitrogen filled glove box, (R)-4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl)-1,3,2-dioxaborolane (0.50 mmol, 179.1 mg), 4-bromoacetophenone (0.60 mmol, 119.4 mg), K_2CO_3 (1.5 mmol, 207.3 mg), $Pd_2(dba)_3$ (0.0125 mmol, 11.5 mg, 2.5 mol%), and PPh_3 (0.050 mmol, 14.5 mg) were weighed into an oven dried vial and 1 mL

of toluene, purified by the SPS and degassed, was added. The vial was sealed with a black cap fitted with a Teflon septum. The vial was removed from the glovebox and immediately sealed with Teflon and electrical tape. H_2O (1.5 mmol, 27 µL), which had been purged separately with argon for 15-30 mins, was then added to the reaction vial via glass syringe. The top of the cap was filled with Teflon tape and sealed with electrical tape. Subsequently, the reaction mixture was stirred vigorously at 60 ^oC for 24 hours. The solution was then filtered through Celite and eluted with Et_2O. The desired product was isolated by gradient column chromatography (20:1-10:1 Hex:EtOAc) as a pale yellow solid in 37% yield (0.19 mmol, 65 mg). **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 8.01 (d, 2 H, *J* = 8.2 Hz) [phenyl], 7.68 (d, 2 H, *J* = 8.3 Hz) [phenyl], 7.55 (d, 2 H, *J* = 8.1 Hz) [phenyl], 7.33 (d, 2 H, *J* = 8.1 Hz) [phenyl], 2.62 (s, 3H) [acetyl CH_3], 2.50 (q, 1 H, *J* = 7.4 Hz) [CH benzylic], 1.38 (d, 3 H, *J* = 7.5 Hz) [CH_3 alkyl], 1.23 (s, 6 H) [CH_3-BPin], 1.22 (s, 6 H) [CH_3-BPin]. **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 197.7 [acetyl C=O], 145.8 [phenyl], 145.5 [phenyl], 136.5 [phenyl], 135.4 [phenyl], 128.8 [phenyl], 128.4 [phenyl], 127.1 [phenyl], 126.8 [phenyl], 83.4 [O-$C(CH_3)_2$ of pinacol], 26.6 [B-CH benzylic], 24.6 [CH_3-BPin], 17.0 [CH_3 alkyl] **^{11}B NMR:** (160 MHz, $CDCl_3$) δ 33. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{22}H_{27}BO_3$) *m/z* 350.2053; found 350.2066. **IR (ν_{max}/cm^{-1}):** 2978 (s), 2249 (m), 1678 (s), 1269 (s). The external standard used was BF_3-OEt_2; appearing as a singlet at 0.0 ppm.

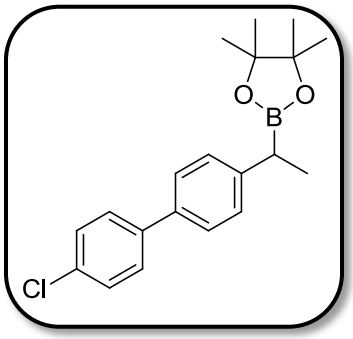
*Synthesis of compound **2ab**:*



In a nitrogen filled glove box, 4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl)-1,3,2-dioxaborolane (0.050 mmol, 17.9 mg), 1-bromo-4-methoxybenzene (0.060 mmol, 11.3 mg), K_2CO_3 (0.15 mmol, 20.7 mg), $Pd_2(dba)_3$ (0.00125 mmol, 1.2 mg, 2.5 mol%), and PPh_3 (0.0050 mmol, 1.5 mg) were weighed into an oven dried vial and 0.1 mL of toluene, purified by the SPS and degassed, was added. The vial was sealed with a black cap fitted with a Teflon septum. The vial was removed from the glovebox and immediately sealed with Teflon and electrical tape. H_2O (0.15 mmol, 2.7 µL), which had been purged separately with argon for 15-30 mins, was then added to the reaction vial via glass syringe. The top of the cap was filled with Teflon tape and sealed with electrical tape. Subsequently, the reaction mixture was stirred vigorously at 60 ^oC for 24 hours. The solution was then filtered through Celite and eluted with Et_2O. The yield was determined via 500 MHz NMR spectroscopy with DMB (0.0412 mmol, 5.69 mg) as the internal standard and determined to be 94%. At 10 times the scale described above the compound was isolated by gradient column chromatography (40:1-20:1 Hex:EtOAc) as a pale yellow solid in 76% yield (0.38 mmol, 130 mg). **^{1}H-NMR:** (400 MHz, $CDCl_3$) δ 7.54 (d, 2 H, *J* = 8.7 Hz) [phenyl], 7.48 (d, 2 H, *J* = 8.2 Hz) [phenyl], 7.29 (d, 2 H, *J* = 8.0 Hz) [phenyl], 6.98 (d, 2 H, *J* = 8.7 Hz) [phenyl], 3.87 (s, 3 H) [OMe], 2.49 (q, 1 H, *J* = 7.5 Hz) [CH benzylic], 1.39 (d, 3 H, *J* = 7.5 Hz) [CH_3 alkyl], 1.26 (s, 6 H) [CH_3- BPin], 1.24

(s, 6 H) [CH_3- BPin] **^{13}C-NMR:** (100 MHz, $CDCl_3$) δ 158.8 [MeO-C phenyl], 143.5 [phenyl], 137.5 [phenyl], 133.9 [phenyl], 128.1 [phenyl], 127.9 [phenyl], 126.6 [phenyl], 114.1 [phenyl], 83.3 [O-C(CH_3)$_2$ of pinacol], 55.3 [OMe], 24.6 [CH_3-BPin], 17.1 [CH_3 alkyl] **^{11}B-NMR:** (160 MHz, $CDCl_3$) δ 33. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{21}H_{27}BO_3$) *m/z* 338.2053; found 338.2046. **IR (ν_{max}/cm^{-1}):** 2971 (s), 2930 (s), 2251 (m), 1248 (s), 1143 (s). The external standard used was BF_3-OEt_2; appearing as a singlet at 0.0 ppm.

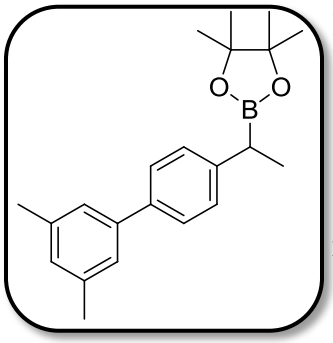
*Synthesis of substrate **2ac***



In a nitrogen filled glove box, 4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl)-1,3,2-dioxaborolane (0.10 mmol, 35.8 mg), 1-bromo-4-methoxybenzene (0.12 mmol, 23.9 mg), K_2CO_3 (0.30 mmol, 41.5 mg), $Pd_2(dba)_3$ (0.0025 mmol, 2.3 mg, 2.5 mol%), and PPh_3 (0.010 mmol, 2.9 mg) were weighed into an oven dried vial and 0.2 mL of toluene, purified by the SPS and degassed, was added. The vial was sealed with a black cap fitted with a Teflon septum. The vial was removed from the glovebox and immediately sealed with Teflon and electrical tape. H_2O (0.30 mmol, 5.4 µL), which had been purged separately with argon for 15-30 mins, was then added to the reaction vial via glass syringe. The top of the cap was filled with Teflon tape and sealed with electrical tape. Subsequently, the reaction mixture was stirred vigorously at 60 ^oC for 24 hours. The

solution was then filtered through celite and eluted with Et_2O. The yield was determined via 500 MHz NMR spectroscopy with DMB (0.0795 mmol, 10.99 mg) as the internal standard and determined to be 99%. **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ 7.52 (d, 2 H, *J* = 8.2 Hz) [phenyl], 7.48 (d, 2 H, *J* = 7.9 Hz) [phenyl], 7.31 (d, 2 H, *J* = 7.9 Hz) [phenyl], 7.27 (d, 2H, *J* = 7.1 Hz) [phenyl], 2.50 (q, 1 H, *J* = 7.3 Hz) [CH benzylic], 1.38 (d, 3 H, *J* = 7.5 Hz) [CH_3 alkyl], 1.25 (s, 6 H) [CH_3-BPin], 1.24 (s, 6 H) [CH_3-BPin].

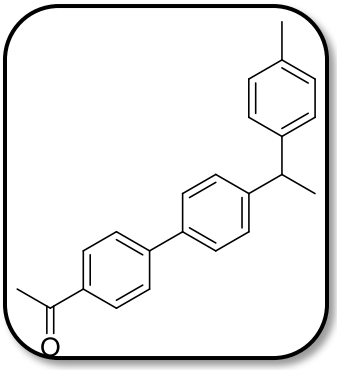
*Synthesis of compound **2ad**:*



In a nitrogen filled glove box, 4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl)-1,3,2-dioxaborolane (0.05 mmol, 17.9 mg), 1-bromo-4-methoxybenzene (0.06 mmol, 11.1 mg), K_2CO_3 (0.15 mmol, 20.7 mg), $Pd_2(dba)_3$ (0.00125 mmol, 1.2 mg, 2.5 mol%), and PPh_3 (0.005 mmol, 1.5 mg) were weighed into an oven dried vial and 0.1 mL of toluene, purified by the SPS and degassed, was added. The vial was sealed with a black cap fitted with a Teflon septum. The vial was removed from the glovebox and immediately sealed with Teflon and electrical tape. H_2O (0.15 mmol, 2.7 µL), which had been purged separately with argon for 15-30 mins, was then added to the reaction vial via glass syringe. The top of the cap was filled with Teflon tape and sealed with electrical tape. Subsequently, the reaction mixture was stirred vigorously at 60 ^oC for 24 hours. The solution was then filtered through Celite and eluted with Et_2O. The yield was determined

via 500 MHz NMR with DMB (0.0384 mmol, 5.31 mg) as the internal standard and determined to be 99%. At 15.5 times the scale described above, the compound was isolated by gradient column chromatography (40:1-20:1 Hex:EtOAc) as a viscous oil in 67% yield (0.52 mmol, 174 mg). **^{1}H-NMR:** (400 MHz, $CDCl_3$) δ 7.50 (d, 2 H, *J* = 8.1 Hz) [phenyl], 7.29 (d, 2 H, *J* = 7.9 Hz) [phenyl], 7.23 (s, 2 H) [phenyl], 6.98 (s, 1 H) [phenyl], 2.50 (q, 1 H, *J* = 7.5 Hz) [CH benzylic], 2.39 (s, 6H) [CH_3 of phenyl], 1.39 (d, 3 H, *J* = 7.5 Hz) [CH_3 benzylic], 1.25 (s, 6 H) [CH_3-BPin], 1.24 (s, 6 H) [CH_3- BPin] **^{13}C-NMR:** (100 MHz, $CDCl_3$) δ 144.4 [phenyl], 141.9 [phenyl], 138.3 [phenyl], 129.4 [phenyl], 128.8 [phenyl], 127.5 [phenyl], 125.0 [phenyl], 98.8 [phenyl], 83.3 [O-$C(CH_3)_2$ of pinacol], 25.0 [CH_3-BPin], 21.9 [CH_3 of phenyl], 17.5 [CH_3 alkyl] **^{11}B-NMR:** (160 MHz, $CDCl_3$) δ 33. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{21}H_{27}BO_3$) *m/z* 336.2261; found 336.2253. **IR (ν_{max}/cm^{-1}):** 2979 (s), 2366 (m), 2253 (m), 1444 (m), 1153 (m). The external standard used was BF_3-OEt_2; appearing as a singlet at 0.0 ppm.

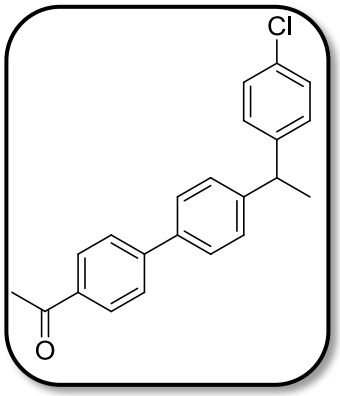
*Synthesis of substrate **4a**:*



In a nitrogen filled glovebox, **2aa** (0.11 mmol, 39.4 mg), 4-iodotoluene (0.075 mmol, 16.4 mg), Ag_2O (0.11 mmol, 25.5 mg), K_2CO_3 (0.11 mmol, 15.2 mg), $Pd(PPh_3)_4$ (0.0060 mmol, 6.9 mg), and PPh_3 (0.024 mmol, 6.3 mg) were weighed into an oven dried vial and 1.73 mL of DME, distilled and deoxygenated. Teflon tape was wrapped around the top of the vial and then the vial was

sealed with a black cap fitted with a Teflon septum. In a separate vial, 180 mg of DME was added. Both vials were removed from the glovebox and immediately sealed with Teflon and electrical tape. H_2O (0.15 mmol, 10.5 µL), which had been purged separately with argon for 15-30 mins, was then added to the vial containing DME via glass syringe. Subsequently, 10.5 µL from the H_2O:DME solution was added to the reaction mixture. The top of the cap was filled with Teflon tape and sealed with electrical tape. Subsequently, the reaction mixture was stirred vigorously at 85 ^oC for 24 hours. The solution was then filtered through Celite and eluted with Et_2O. The yield was determined via 500 MHz NMR spectroscopy with DMB (0.0543 mmol, 7.51 mg) as the internal standard and determined to be 72%. **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ 8.02 (d, 2 H, *J* = 8.3 Hz) [phenyl], 7.56 (d, 4 H, *J* = 8.3 Hz) [phenyl], 7.33 (d, 2 H, *J* = 8.0 Hz) [phenyl], 7.16 (d, 2 H, *J* = 8.2 Hz) [phenyl], 7.13 (d, 2 H, *J* = 8.1 Hz) [phenyl], 4.18 (q, 1 H, *J* = 7.2 Hz) [CH benzylic], 2.64 (s, 3 H) [CH_3 of acetyl], 2.33 (s, 3 H) [CH_3 of phenyl], 1.68 (d, 3 H, *J* = 7.2 Hz) [CH_3-BPin].

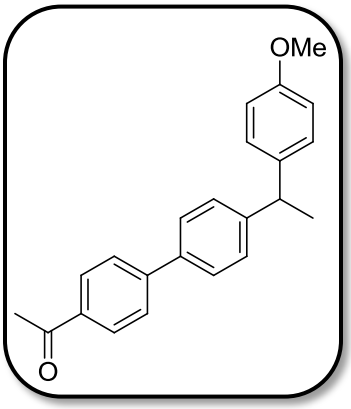
*Synthesis of **4b**:*



In a nitrogen filled glovebox, **2aa** (0.075 mmol, 26.9 mg), 4-chloro-iodobenzene (0.050 mmol, 11.9 mg), Ag_2O (0.075 mmol, 17.4 mg), K_2CO_3 (0.075 mmol, 10.4 mg), $Pd(PPh_3)_4$ (0.0040 mmol, 4.6 mg), and PPh_3 (0.016 mmol, 4.2 mg) were weighed into an oven dried vial and 1.15 mL of DME,

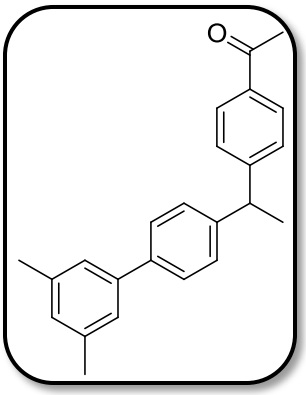
distilled and deoxygenated. Teflon tape was wrapped around the top of the vial and then the vial was sealed with a black cap fitted with a Teflon septum. In a separate vial, 120 mg of DME was added. Both vials were removed from the glovebox and immediately sealed with Teflon and electrical tape. H_2O (0.15 mmol, 7 µL), which had been purged separately with argon for 15-30 mins, was then added to the vial containing DME via glass syringe. Subsequently, 7 µL from the H_2O:DME solution was added to the reaction mixture. The top of the cap was filled with Teflon tape and sealed with electrical tape. Subsequently, the reaction mixture was stirred vigorously at 85 ^oC for 24 hours. The solution was then filtered through Celite and eluted with Et_2O. The yield was determined via 500 MHz NMR spectroscopy with DMB (0.0404 mmol, 5.58 mg) as the internal standard and determined to be 70%. **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ 8.04 (d, 2 H, *J* = 8.3 Hz) [phenyl], 7.68 (d, 2 H, *J* = 8.3 Hz) [phenyl], 7.58 (d, 2 H, *J* = 8.2 Hz) [phenyl], 7.32 (d, 2 H, *J* = 8.2 Hz) [phenyl], 7.29 (d, 2 H, *J* = 8.6 Hz) [phenyl], 7.20 (d, 2 H, *J* = 8.4 Hz) [phenyl], 4.20 (q, 1 H, *J* = 7.2 Hz) [CH benzylic], 2.65 (s, 3 H) [CH_3 of acetyl], 1.68 (d, 3 H, *J* = 7.2 Hz) [CH_3 alkyl].

*Synthesis of **4c**:*



In a nitrogen filled glovebox, **2aa** (0.075 mmol, 26.9 mg), 4-methoxy-iodobenzene (0.050 mmol, 11.7 mg), Ag_2O (0.075 mmol, 17.4 mg), K_2CO_3 (0.075 mmol, 10.37mg), $Pd(PPh_3)_4$ (0.0040 mmol, 4.6 mg), and PPh_3 (0.016 mmol, 4.2 mg) were weighed into an oven dried vial and 1.15 mL of DME, distilled and deoxygenated. Teflon tape was wrapped around the top of the vial and then the vial was sealed with a black cap fitted with a Teflon septum. In a separate vial, 120 mg of DME was added. Both vials were removed from the glovebox and immediately sealed with Teflon and electrical tape. H_2O (0.15 mmol, 7.35 µL), which had been purged separately with argon for 15-30 mins, was then added to the vial containing DME via glass syringe. Subsequently, 7.35 µL from the H_2O:DME solution was added to the reaction mixture. The top of the cap was filled with Teflon tape and sealed with electrical tape. Subsequently, the reaction mixture was stirred vigorously at 85 ^oC for 24 hours. The solution was then filtered through Celite and eluted with Et_2O. The yield was determined via 500MHz NMR spectroscopy with DMB (0.0379 mmol, 5.24 mg) as the internal standard and determined to be 63%. **^{1}H-NMR:** (400 MHz, $CDCl_3$) δ 7.94 (d, 2 H, *J* = 8.6 Hz) [phenyl], 7.93 (d, 2 H, *J* = 8.6 Hz) [phenyl], 7.40 (d, 2 H, *J* = 7.6 Hz) [phenyl], 7.39 (d, 2 H, *J* = 7.6 Hz) [phenyl], 7.23 (d, 2 H, *J* = 8.1 Hz) [phenyl], 7.09 (d, 2 H, *J* = 8.5 Hz) [phenyl], 4.08 (q, 1 H, *J* = 7.2 Hz) [CH benzylic], 3.71 (s, 3 H) [OMe], 3.47 (s, 3 H) [CH_3 acetyl], 1.58 (d, 3 H, *J* = 7.2 Hz) [CH_3 alkyl].

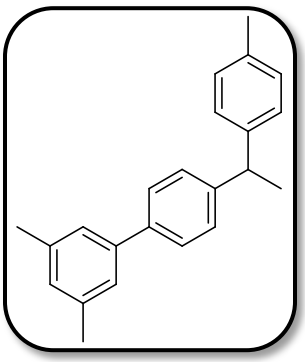
*Synthesis of **4d**:*



In a nitrogen filled glovebox, **2ad** (0.11 mmol, 37.0 mg), 4-iodoacetophenone (0.073 mmol, 18.0 mg), Ag_2O (0.11 mmol, 25.5 mg), K_2CO_3 (0.075 mmol, 15.2 mg), $Pd(PPh_3)_4$ (0.0059 mmol, 6.8 mg), and PPh_3 (0.024 mmol, 6.2 mg) were weighed into an oven dried vial and 1.68 mL of DME, distilled and deoxygenated. Teflon tape was wrapped around the top of the vial and then the vial was sealed with a black cap fitted with a Teflon septum. In a separate vial, 165 mg of DME was added. Both vials were removed from the glovebox and immediately sealed with Teflon and electrical tape. H_2O (0.15 mmol, 10.5 µL), which had been purged separately with argon for 15-30 mins, was then added to the vial containing DME via glass syringe. Subsequently, 10.5 µL from the H_2O:DME solution was added to the reaction mixture. The top of the cap was filled with Teflon tape and sealed with electrical tape. Subsequently, the reaction mixture was stirred vigorously at 85 ^oC for 24 hours. The solution was then filtered through Celite and eluted with Et_2O. The yield was determined via 500 MHz NMR spectroscopy with DMB (0.0730 mmol, 10.08 mg) as the internal standard and determined to be 68%. The desired product was isolated by gradient column chromatography (20:1-10:1 Hex:EtOAc) to yield a pale yellow solid in 67% yield (0.049 mmol, 16 mg). **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.92 (d, 2 H, *J* = 8.3 Hz) [phenyl], 7.52 (d, 2 H, *J* = 8.2 Hz) [phenyl], 7.37 (d, 2 H, *J* = 8.2 Hz) [phenyl], 7.28 (d, 2H, *J* = 8.0 Hz) [phenyl], 7.20 (s, 2 H) [phenyl], 7.00 (s, 1 H) [phenyl],

4.27 (q, 1 H, *J* = 7.2 Hz) [CH benzylic], 2.60 (s, 3 H) [CH_3 acetyl], 2.39 (s, 6 H) [CH_3 of phenyl], 1.72 (d, 3 Hz, *J* = 7.2 Hz) [CH_3 alkyl]. **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 197.8 [acetyl C=O], 152.0 [phenyl], 144.2 [phenyl], 142.7 [phenyl], 140.8 [phenyl], 139.6 [phenyl], 138.2 [phenyl], 135.2 [phenyl], 128.8 [phenyl], 128.6 [phenyl], 127.8 [phenyl], 127.3 [phenyl], 125.0 [phenyl], 44.5 [CH benzylic], 29.7 [CH_3 of acetyl], 26.6 [CH_3 of aryl], 21.4 [CH_3 alkyl]. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{24}H_{24}O$) *m/z* 328.1827; found 328.1839. **IR (ν_{max}/cm^{-1}):** 2962 (s), 2849 (m), 2255 (m), 1680 (s), 1270 (m).

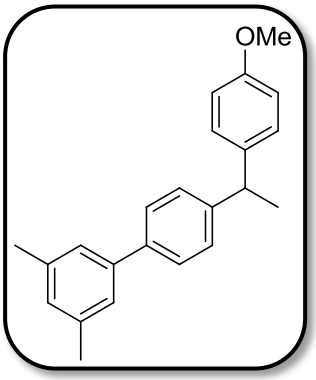
*Synthesis of **4e**:*



In a nitrogen filled glovebox, **2ad** (0.11 mmol, 37.0 mg), 4-iodoacetophenone (0.073 mmol, 15.9 mg), Ag_2O (0.11 mmol, 25.5 mg), K_2CO_3 (0.075 mmol, 15.2 mg), $Pd(PPh_3)_4$ (0.0059 mmol, 6.8 mg), and PPh_3 (0.024 mmol, 6.2 mg) were weighed into an oven dried vial and 1.68 mL of DME, distilled and deoxygenated. Teflon tape was wrapped around the top of the vial and then the vial was sealed with a black cap fitted with a Teflon septum. In a separate vial, 165 mg of DME was added. Both vials were removed from the glovebox and immediately sealed with Teflon and electrical tape. H_2O (0.15 mmol, 10.5 µL), which had been purged separately with argon for 15-30 mins, was then added to the vial containing DME via glass syringe. Subsequently, 10.5 µL from the H_2O:DME solution was added to the reaction mixture. The top of the cap was filled with Teflon tape and sealed with electrical tape.

Subsequently, the reaction mixture was stirred vigorously at 85 ^{o}C for 24 hours. Total concentration of H_2O within the reaction mixture was approximately 350 ppm. The solution was then filtered through Celite and eluted with Et_2O. The yield was determined via 500 MHz NMR spectroscopy with DMB (0.0729 mmol, 10.07 mg) as the internal standard and determined to be 73%. **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ 7.71 (d, 2 H, *J* = 7.1 Hz) [phenyl], 7.29 (d, 2 H, *J* = 7.1 Hz) [phenyl], 7.20 (s, 2 H) [phenyl], 7.17 (d, 2 H, *J* = 8.1 Hz) [phenyl], 7.13 (d, 2 H, *J* = 8.0 Hz) [phenyl], 6.99 (s, 1 H) [phenyl], 4.17 (q, 1 H, *J* = 7.2 Hz) [CH benzylic], 2.38 (s, 6 H) [CH_3 of phenyl], 2.34 (s, 3 H) [CH_3 of phenyl], 1.67 (d, 3 H, *J* = 7.2 Hz) [CH_3 alkyl].

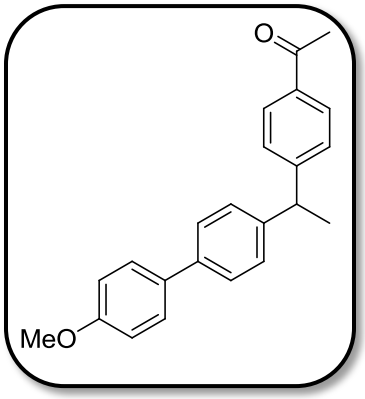
*Synthesis of **4f**:*



In a nitrogen filled glovebox, **2ad** (0.11 mmol, 37.0 mg), 4-methoxy iodobenzene (0.073 mmol, 17.0 mg), Ag_2O (0.11 mmol, 25.5 mg), K_2CO_3 (0.075 mmol, 15.2 mg), $Pd(PPh_3)_4$ (0.0059 mmol, 6.8 mg), and PPh_3 (0.024 mmol, 6.2 mg) were weighed into an oven dried vial and 1.68 mL of DME, distilled and deoxygenated. Teflon tape was wrapped around the top of the vial and then the vial was sealed with a black cap fitted with a Teflon septum. In a separate vial, 165 mg of DME was added. Both vials were removed from the glovebox and immediately sealed with Teflon and electrical tape. H_2O (0.15 mmol, 10.5 µL), which had been purged separately with argon for 15-30 mins, was then added to the vial containing DME via

glass syringe. Subsequently, 10.5 µL from the H_2O:DME solution was added to the reaction mixture. The top of the cap was filled with Teflon tape and sealed with electrical tape. Subsequently, the reaction mixture was stirred vigorously at 85 ^oC for 24 hours. Total concentration of H_2O within the reaction mixture was approximately 350 ppm. The solution was then filtered through Celite and eluted with Et_2O. The yield was determined via 500 MHz NMR spectroscopy with DMB (0.0773 mmol, 10.68 mg) as the internal standard and determined to be 70%. **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ 7.71 (d, 3 H, *J* = 8.0 Hz) [phenyl], 7.69 (d, 3 H, *J* = 7.9 Hz) [phenyl], 7.28 (d, 3 H, *J* = 8.1 Hz) [phenyl], 7.20 (s, 3 H) [phenyl], 4.16 (q, 1 H, *J* = 7.2 Hz) [CH benzylic], 3.80 (s, 3 H) [OMe], 2.38 (s, 6 H) [CH_3 of phenyl], 1.67 (d, 3 H, *J* = 7.2 Hz) [CH_3 alkyl].

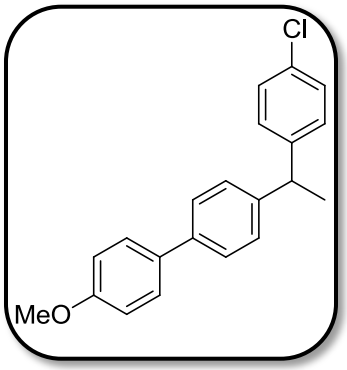
*Synthesis of **4g**:*



In a nitrogen filled glovebox, **2ab** (0.075 mmol, 25.4 mg), 4-iodoacetophenone (0.050 mmol, 12.3 mg), Ag_2O (0.075 mmol, 17.4 mg), K_2CO_3 (0.075 mmol, 10.4 mg), $Pd(PPh_3)_4$ (0.0040 mmol, 4.6 mg), and PPh_3 (0.016 mmol, 4.2 mg) were weighed into an oven dried vial and 1.15 mL of DME, distilled and deoxygenated. Teflon tape was wrapped around the top of the vial and then the vial was sealed with a black cap fitted with a Teflon septum. In a separate vial, 120 mg of DME was added. Both vials were removed from the glovebox and immediately sealed with Teflon and electrical tape. H_2O (0.15 mmol, 7

μL), which had been purged separately with argon for 15-30 mins, was then added to the vial containing DME via glass syringe. Subsequently, 7 μL from the H_2O:DME solution was added to the reaction mixture. The top of the cap was filled with Teflon tape and sealed with electrical tape. Subsequently, the reaction mixture was stirred vigorously at 85 ^oC for 24 hours. The solution was then filtered through Celite and eluted with Et_2O. The yield was determined via 500 MHz NMR spectroscopy with DMB (0.0557 mmol, 7.70 mg) as the internal standard and determined to be 56%. **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ 7.92 (d, 2 H, *J* = 8.2 Hz) [phenyl], 7.56 (d, 4 H, *J* = 7.6 Hz) [phenyl], 7.37 (d, 2 H, *J* = 8.2 Hz) [phenyl], 7.27 (d, 2 H, *J* = 9.1 Hz) [phenyl], 6.98 (d, 2 H, *J* = 8.7 Hz) [phenyl], 4.26 (q, 1 H, *J* = 7.2 Hz) [CH benzylic], 3.57 (s, 3 H) [OMe], 2.59 (s, 3 H) [acetyl CH_3], 1.71 (d, 3 H, *J* = 7.2 Hz) [CH_3 alkyl].

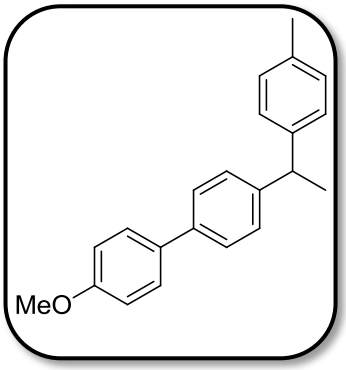
*Synthesis of **4h**:*



In a nitrogen filled glovebox, **2ab** (0.075 mmol, 25.4 mg), 4-iodotoluene (0.050 mmol, 10.9 mg), Ag_2O (0.075 mmol, 17.4 mg), K_2CO_3 (0.075 mmol, 10.37mg), $Pd(PPh_3)_4$ (0.0040 mmol, 4.6 mg), and PPh_3 (0.016 mmol, 4.2 mg) were weighed into an oven dried vial and 1.15 mL of DME, distilled and deoxygenated. Teflon tape was wrapped around the top of the vial and then the vial was sealed with a black cap fitted with a Teflon septum. In a separate vial, 120 mg of DME was added. Both vials were removed from the glovebox and immediately sealed with

Teflon and electrical tape. H_2O (0.15 mmol, 7 µL), which had been purged separately with argon for 15-30 mins, was then added to the vial containing DME via glass syringe. Subsequently, 7 µL from the H_2O:DME solution was added to the reaction mixture. The top of the cap was filled with Teflon tape and sealed with electrical tape. Subsequently, the reaction mixture was stirred vigorously at 85 ^oC for 24 hours. The solution was then filtered through Celite and eluted with Et_2O. he yield was determined via 500 MHz NMR spectroscopy with DMB (0.0863 mmol, 11.93 mg) as the internal standard and determined to be 60%. **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ 7.56 (d, 4 H, *J* = 7.3 Hz) [phenyl], 7.28 (d, 2 H, *J* = 8.4 Hz) [phenyl], 7.25 (d, 2 H, *J* = 8.2 Hz) [phenyl], 7.20 (d, 2 H *J* = 8.4 Hz, 2H) [phenyl], 6.98 (d, 2 H, *J* = 8.8 Hz) [phenyl], 4.17 (q, 1 H, *J* = 7.2 Hz) [CH benzylic], 3.86 (s, 3H) [OMe], 1.66 (d, 3 H, *J* = 7.2 Hz) [CH_3 alkyl].

*Synthesis of **4i**:*

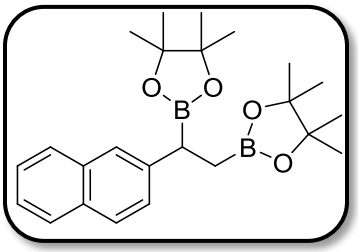


In a nitrogen filled glovebox, **2ab** (0.124 mmol, 41.8 mg), 1-chloro-4-iodobenzene (0.083 mmol, 18.0 mg), Ag_2O (0.124 mmol, 28.7 mg), K_2CO_3 (0.124 mmol, 17.1 mg), $Pd(PPh_3)_4$ (0.00664 mmol, 7.7 mg), and PPh_3 (0.0266 mmol, 7.0 mg) were weighed into an oven dried vial and 1.91 mL of DME, distilled and deoxygenated. Teflon tape was wrapped around the top of the vial and then the vial was sealed with a black cap fitted with a Teflon septum. In a separate vial, 200

mg of DME was added. Both vials were removed from the glovebox and immediately sealed with Teflon and electrical tape. H_2O (0.15 mmol, 12.3 µL), which had been purged separately with argon for 15-30 mins, was then added to the vial containing DME via glass syringe. Subsequently, 12.3 µl from the H_2O:DME solution was added to the reaction mixture. The top of the cap was filled with Teflon tape and sealed with electrical tape. Subsequently, the reaction mixture was stirred vigorously at 85 ^oC for 24 hours. The solution was then filtered through Celite and eluted with Et_2O. The yield was determined via 500 MHz NMR spectroscopy with DMB (0.0423 mmol, 5.84 mg) as the internal standard and determined to be 61%. **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ 7.56 (d, 2 H, *J* = 7.5 Hz) [phenyl], 7.56 (d, 2 H, *J* = 7.4 Hz) [phenyl], 7.28 (d, 2 H, *J* = 8.1 Hz) [phenyl], 7.17 (d, 2 H, *J* = 8.1 Hz) [phenyl], 7.13 (d, 2H, *J* = 7.9 Hz) [phenyl], 6.97 (d, 2 H, *J* = 8.8 Hz) [phenyl], 4.17 (q, 1 H, *J* = 7.2 Hz) [CH benzylic], 3.85 (s, 3 H) [OMe], 2.33 (s, 3 H) [CH_3 of phenyl], 1.67 (d, 3 H, *J* = 7.2 Hz) [CH_3 alkyl].

3.3 The Chemoselective Suzuki-Miyaura Cross-Coupling of a Substrate Containing Both a Secondary and Primary Alkyl Boronic Ester.

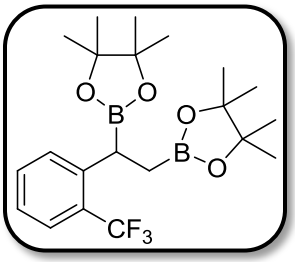
Synthesis of 2,2'-[1-[Naphthalene]-1,2-ethanediyl]bis[4,4,5,5-tetramethyl-1,3,2-dioxaborolane]:



Bis(pinacolato) diboron (0.500 mmol, 127 mg) was weighed in a vial and sealed with a septum. The vial was purged with argon for 15 minutes. Following this, bis(pinacolato) diboron was dissolved in toluene (2 mL), purified by the SPS and degassed. Platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex [solution in xylenes, (~2% Pt)] (0.335 mmol, 150 µL) and 2-vinyl naphthalene (0.875 mmol, 135 mg) were added to the solution vial via syringe. Subsequently, the septum was switched to a green teflon cap under a stream of argon, and the reaction was stirred at 50 ^{o}C for 24 hours. The desired product was isolated by column chromatography (10:1 Hex:EtOAc) in 22% yield (0.11 mmol, 45 mg). All reagents were placed in separate vials and purged with argon for 30 minutes except for toluene and bis(pinacolato) diboron which was purged for 15 minutes. **^{1}H-NMR:** (400 MHz, $CDCl_3$) δ 7.78-7.71 (m, 3H) [naphthalene], 7.66 (s, 1H) [naphthalene], 7.43-7.37 (m, 3H) [naphthalene], 2.71 (dd, 1H, *J* = 5.7, 10.9) [CH benzylic], 1.53-1.44 (m, 1H) [B-CH_2 alkyl], 1.21 (s, 13H) [1H = B-CH_2 alkyl; 12H = CH_3-BPin], 1.20 (s, 6H) [CH_3-BPin], 1.18 (s, 6H) [CH_3-BPin]. **^{13}C-NMR:** (100MHz, $CDCl_3$) δ 143.1 [phenyl], 133.8 [phenyl], 131.7 [phenyl], 127.5

[phenyl], 127.4 [phenyl], 125.5 [phenyl], 125.5 [phenyl], 124.6 [phenyl], 83.3 [O-$C(CH_3)_2$ of pinacol], 83.1 [O-$C(CH_3)_2$ of pinacol], 25.0 [B-CH benzylic], 24.7 [CH_3-BPin], 24.6 [CH_3-BPin], 24.5 [B-CH_2 alkyl] **^{11}B-NMR:** (160 MHz, $CDCl_3$) δ 34. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{24}H_{34}B_2O_4$) *m/z* 408.2643; found 408.2657. **IR (ν_{max}/cm^{-1}):** 2945 (s), 2870 (s), 2254 (m).

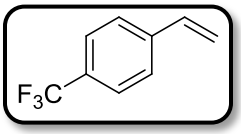
Synthesis of 2,2'-[1-[2-(trifluoromethyl)phenyl]-1,2-ethanediyl]bis[4,4,5,5-tetramethyl-1,3,2-dioxaborolane]:



Bis(pinacolato) diboron (0.500 mmol, 127 mg) was weighed in a vial and sealed with a septum. The vial was purged with argon for 15 minutes. Following this, bis(pinacolato) diboron was dissolved in toluene (2ml), purified by the SPS and degassed. Platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex [solution in xylenes, (~2% Pt)] (0.335 mmol, 150 µl) and 2-(trifluoromethyl)styrene (0.875 mmol, 128 µL) were added to the solution vial via syringe. Subsequently, the septum was switched to agreen teflon cap under a stream of argon, and the reaction was stirred at 50 ^{o}C for 24 hours. The desired product was isolated by column chromatography (10:1 Hex:EtOAc) in 40% yield (0.20 mmol, 85 mg). All reagents were placed in separate vials and purged with argon for 30 minutes except for toluene from the stilles and bis(pinacolato) diboron which was purged for 15 minutes. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (d, 1 H, J = 7.7 Hz) [phenyl], 7.42

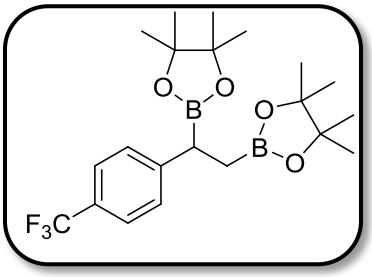
(d, 2 H, J = 3.8 Hz) [phenyl], 7.18 (dt, 1 H, J = 8.3, 4.0 Hz) [phenyl], 2.93 (dd, 1 H, J = 9.3, 6.5 Hz) [CH benzylic], 1.36 – 1.28 (m, 2H) [B-CH_2 alkyl], 1.20 (s, 6H) [CH_3-BPin], 1.18 (s, 12H) [CH_3-BPin], 1.16 (s, 6H) [CH_3-BPin] **^{13}C NMR:** (100 MHz, $CDCl_3$) δ 145.2 (q, J = 1.8 Hz) [phenyl C-CF_3], 131.5 [phenyl], 129.8 [phenyl], 127.8 [phenyl], 127.1 (q, J = 274 Hz) [CF_3], 125.6 (q, J = 15.9 Hz) [phenyl C *ortho* CF_3], 124.8 [phenyl], 83.4 [O-$C(CH_3)_2$ of pinacol], 83.1 [O-$C(CH_3)_2$ of pinacol], 29.7 [B-CH benzylic], 24.9 [B-CH benzylic], 24.6 [CH_3-BPin], 24.5 [B-CH_2 alkyl] **^{11}B NMR:** (160 MHz, $CDCl_3$) δ 33.4. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{22}H_{27}BO_3$) *m/z* 426.2361; found 426.2378. **IR (ν_{max}/cm^{-1}):** 2938 (s), 2866 (m), 2254 (m), 1316 (m).

Synthesis of substrate 4-(trifluoromethyl)styrene:



1,8-Diazabicyclo[5.4.0]undec-7-ene (13.2 mmol, 2.1 mL) was added to a refluxing solution of methyltriphenylphosphonium bromide (12.0 mmol, 4.3 g) in 60 mL of dichloromethane (DCM). After 30 minutes, a solution of 4-trifluoromethyl) benzaldehyde (6.00 mmol, 0.82 mL) dissolved in 18 mL of dichloromethane (DCM), from bottle, was added to the refluxing mixture and the reaction was refluxed for 2 hours. The resulting solution was extracted with H_2O and the solvent was removed via rotary evaporation. Unfortunately, the product was found to be extremely volatile and there was only enough collected for the subsequent diboration reaction affording a low crude yield of ~16% (0.96 mmol, 165.8 mg). CAS: 402-50-6[89]

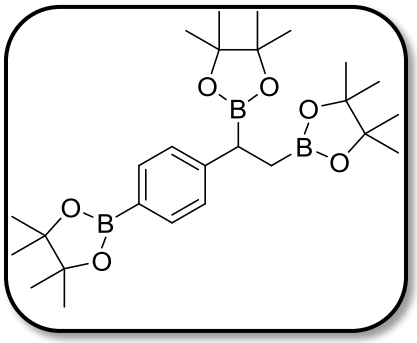
Synthesis of 2,2'-[1-[4-(Trifluoromethyl)phenyl]-1,2-ethanediyl]bis[4,4,5,5-tetramethyl-1,3,2-dioxaborolane]:



Bis(pinacolato) diboron (0.500 mmol, 127 mg) was weighed in a vial and sealed with a septum. The vial was purged with argon for 15 minutes. Following this, bis(pinacolato) diboron was dissolved in toluene (2 mL), purified by the SPS and degassed. Platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex [solution in xylenes, (~2% Pt)] (0.335 mmol, 150 µL) and crude 4-(trifluoromethyl)styrene (0.875 mmol, 130 µL) were added to the solution vial via syringe. Subsequently, the septum was switched to a green teflon cap under a stream of argon, and the reaction was stirred at 50 ^{o}C for 24 hours. The desired product was isolated by column chromatography (10:1 Hex:EtOAc) in 19% yield (0.096 mmol, 41 mg). All reagents were placed in separate vials and purged with Argon for 30 minutes except for toluene from the stilles and bis(pinacolato) diboron which was purged for 15 minutes. **^{1}H NMR**: (300 MHz, $CDCl_3$) δ 7.48 (d, 2 H, *J* = 8.1 Hz) [phenyl], 7.32 (d, 2 H, *J* = 7.6 Hz) [phenyl], 2.59 (dd, 1 H *J* = 10.6, 5.9 Hz, 1H) [CH benzylic], 1.43–1.30 (m, 2 H) [B-CH_2 alkyl], 1.20 (s, 6 H) [CH_3-BPin], 1.19 (s, 6 H) [CH_3-BPin], 1.19 (s, 6 H) [CH_3-BPin], 1.18 (s, 6 H) [CH_3-BPin]. CAS: 1198172-07-4[90]

3.4 The Chemoselective Suzuki-Miyaura Cross-Coupling of a Substrate Containing an Aryl, a Secondary Benzylic, and Primary Alkyl Boronic Ester.

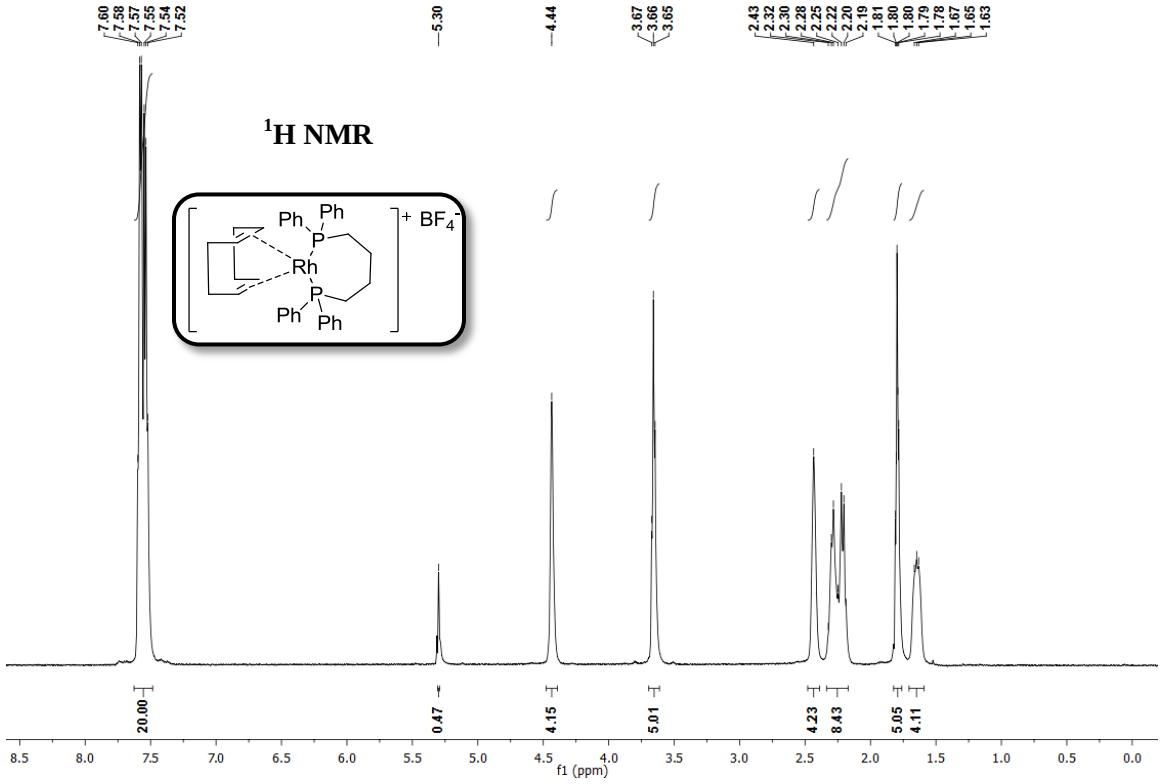
*Synthesis of substrate **6**:*



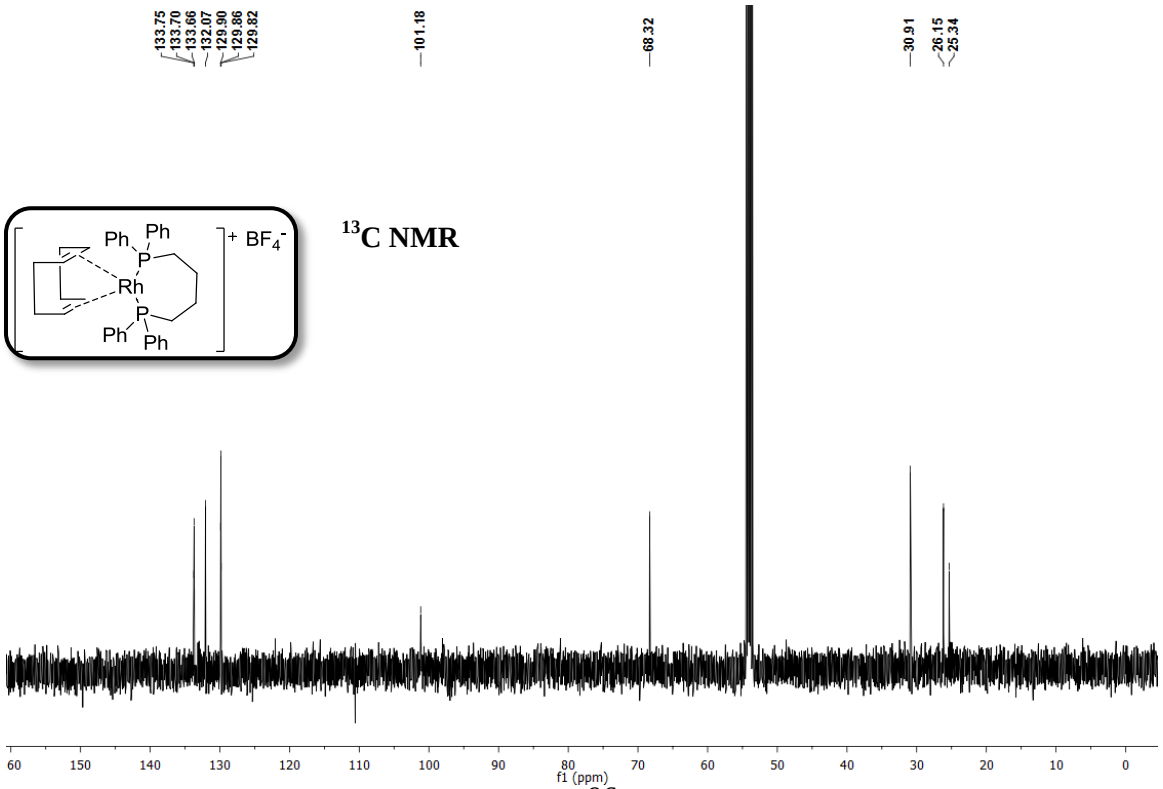
Bis(pinacolato) diboron (B_2Pin_2) (0.803 mmol, 204 mg) was weighed in a vial and sealed with a septum.Platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex [solution in xylenes, (~2% Pt)] (0.538 mmol, 240 µL) was weighed in a separate vial and sealed with a black cap fitted with a Teflon septum. The previous two vials were than purged with argon for 30 minutes. In a N_2 filled glovebox, 4,4,5,5-tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane (1.41 mmol, 322 mg) was weighed in a vial, dissolved in 3.2 mL of toluene, purified by the SPS and degassed, and sealed with a black cap fitted with a Teflon septum. This vial was removed from the glovebox and the solution was added to the vial containing B_2Pin_2 via syringe. Platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex solution in xylenes, (~2% Pt)] was then transferred to the reaction solution as well. Subsequently, the septum was switched to a green Teflon cap under a stream of argon, and the reaction was stirred at 50 ^{o}C for 48 hours. The desired product was isolated by column chromatography (10:1 Hex:EtOAc) in 63% yield (0.51 mmol, 245 mg). **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 7.68 (d, 2 H, *J* = 7.9 Hz) [phenyl], 7.23 (d, 2 H, *J* = 7.9 Hz) [phenyl], 2.54 (dd, 1 H, *J* = 11.1, 5.3 Hz) [CH benzylic], 1.41 (dd, 1 H, *J* = 15.7, 4.5 Hz) [B-CH_2 alkyl], 1.32 (s, 12 H) [CH_3-BPin],

1.21 (s, 12 H) [CH_3-BPin], 1.18 (s, 6 H) [CH_3-BPin], 1.16 (s, 6 H) [CH_3-BPin], 1.10 (dd, 1 H, J = 16.1, 5.4 Hz) [CH_2 alkyl] **^{13}C NMR:** (101 MHz, $CDCl_3$) δ 156.7 [phenyl], 149.1 [phenyl], 134.7 [phenyl], 127.4 [phenyl], 83.5 [O-C(CH_3)$_2$ of pinacol], 83.2 [O-C(CH_3)$_2$ of pinacol], 83.0 [O-C(CH_3)$_2$ of pinacol], 25.0 [B-CH benzylic], 24.9 [CH_3-BPin], 24.8 [CH_3-BPin], 24.7 [CH_3-BPin], 24.5 [B-CH_2 alkyl] **^{11}B NMR:** (160 MHz, $CDCl_3$) δ 34. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{22}H_{27}BO_3$) *m/z* 484.3339; found 484.3362. **IR (ν_{max}/cm^{-1}):** 2944 (s), 2666 (m), 2253 (m). The external standard used was BF_3-OEt_2; appearing as a singlet at 0.0 ppm.

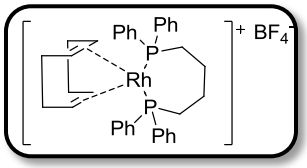
3.5 NMR Spectra



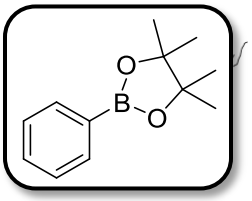
^{1}H NMR



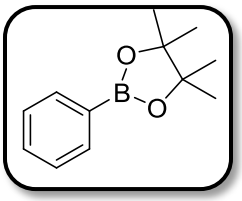
^{13}C NMR



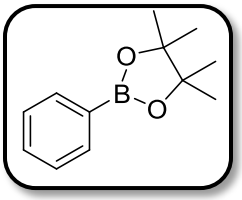
^{31}P NMR



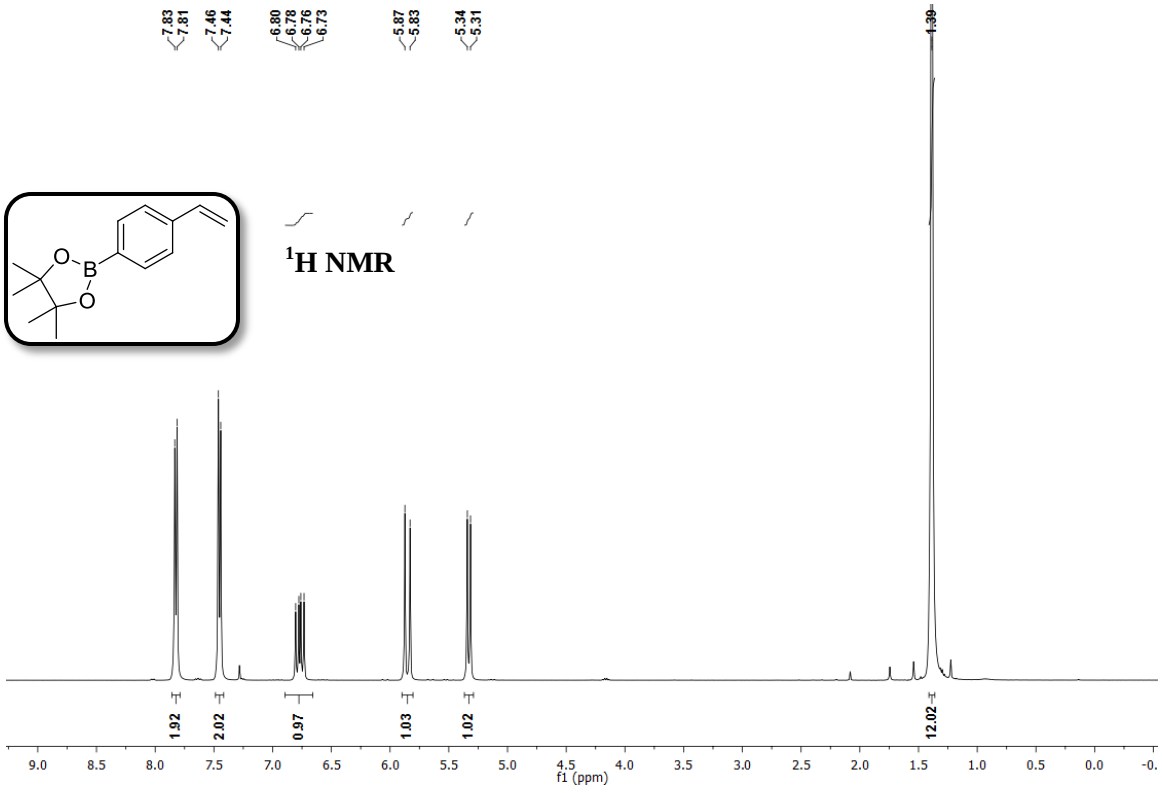
^{1}H NMR



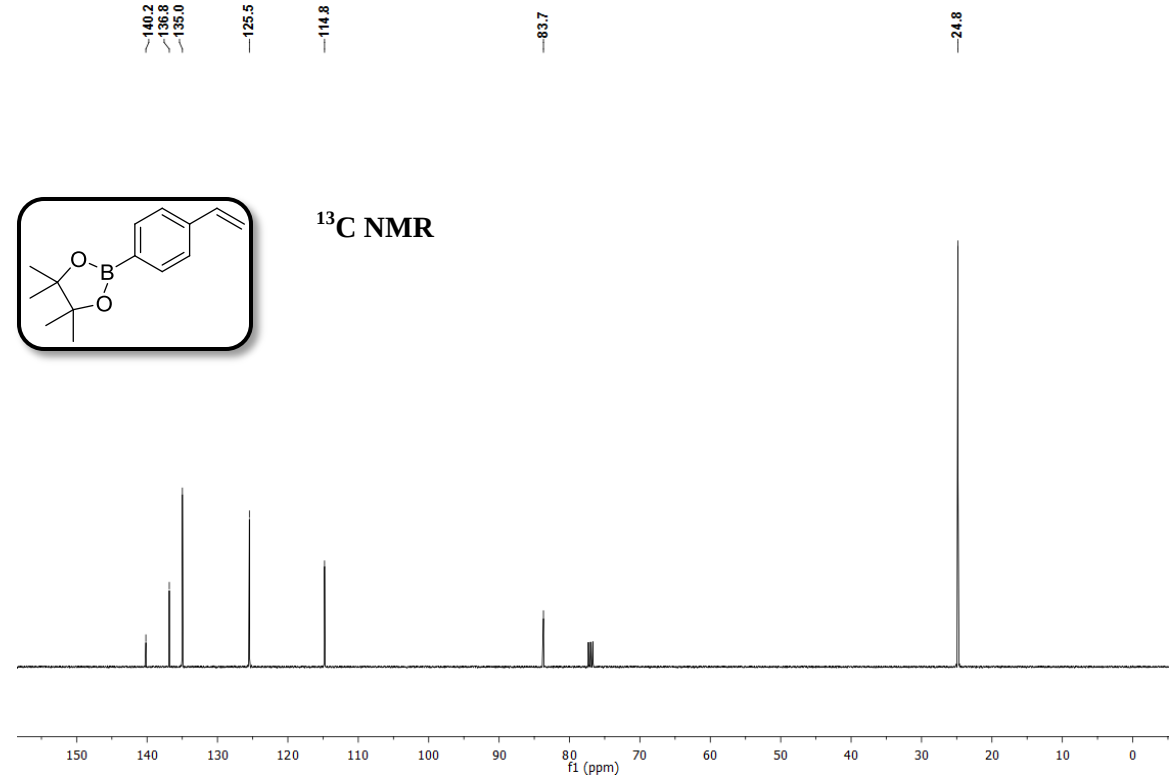
^{13}C NMR



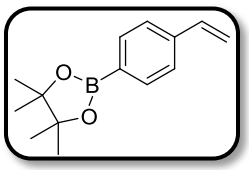
^{11}B NMR



^{1}H NMR

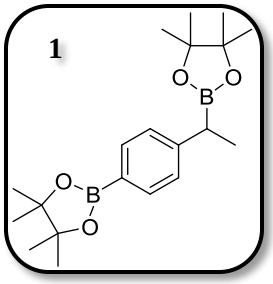


^{13}C NMR

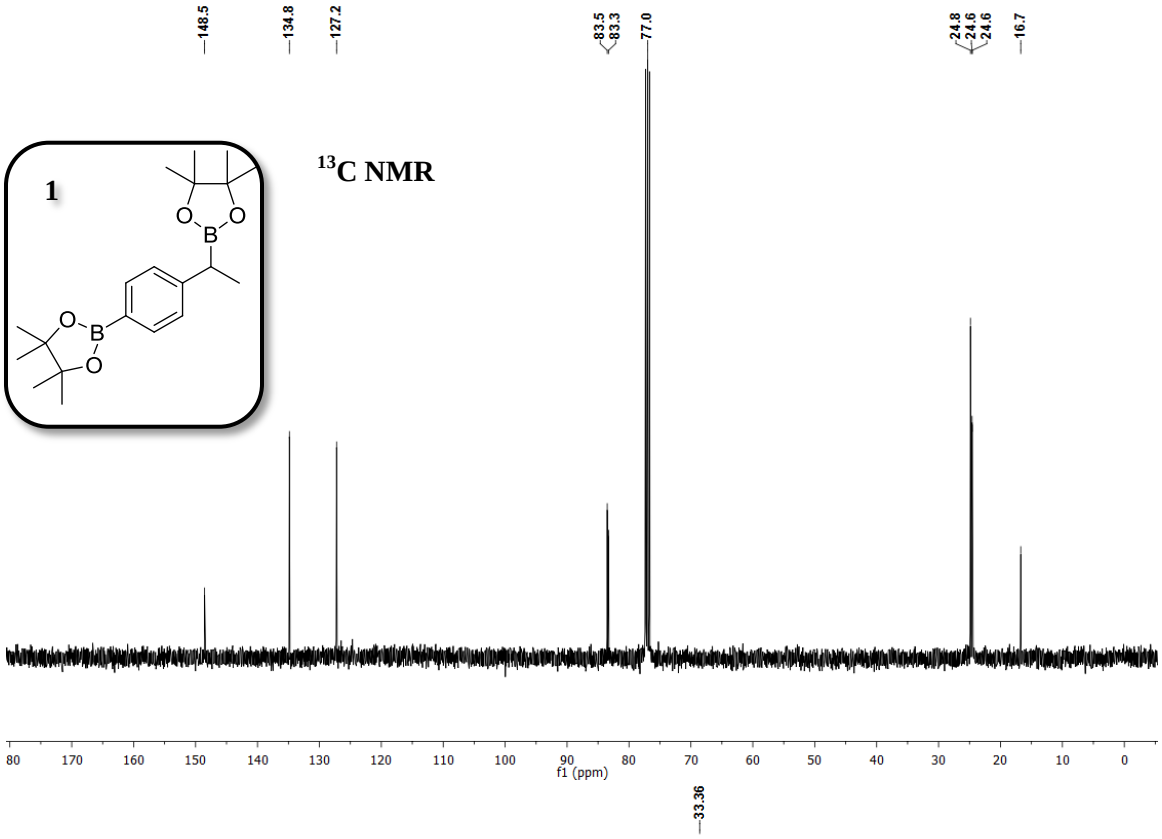


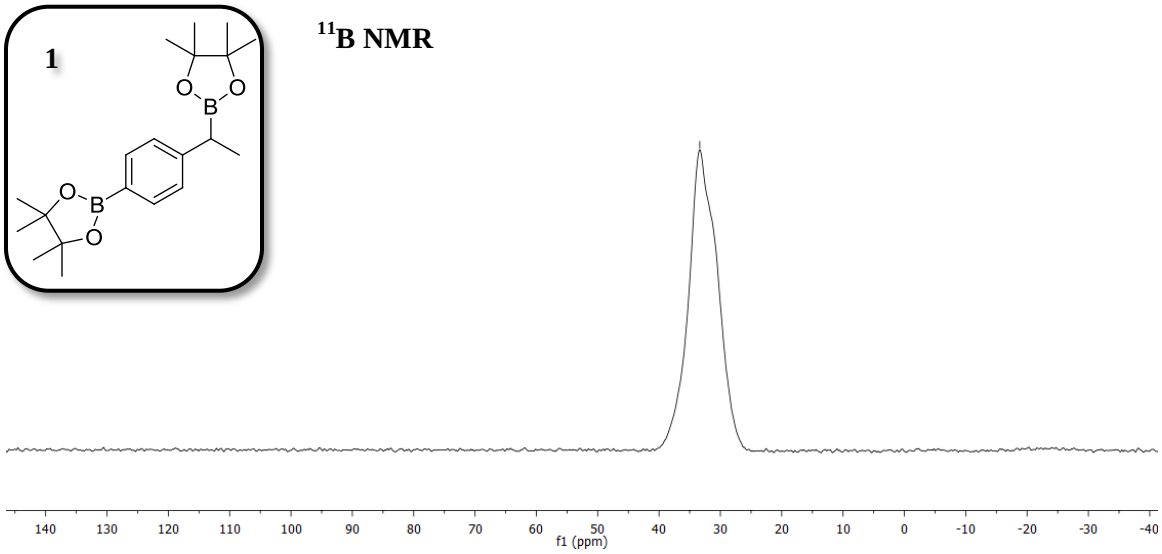
^{11}B NMR

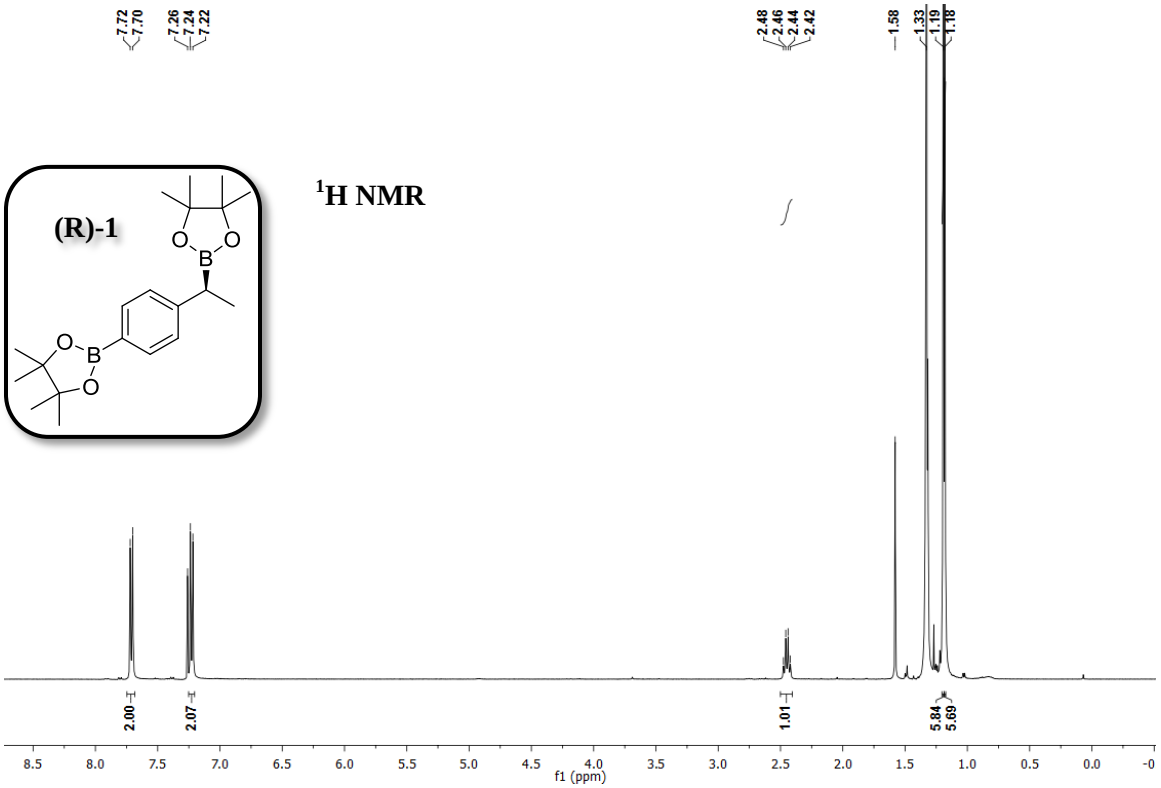
1

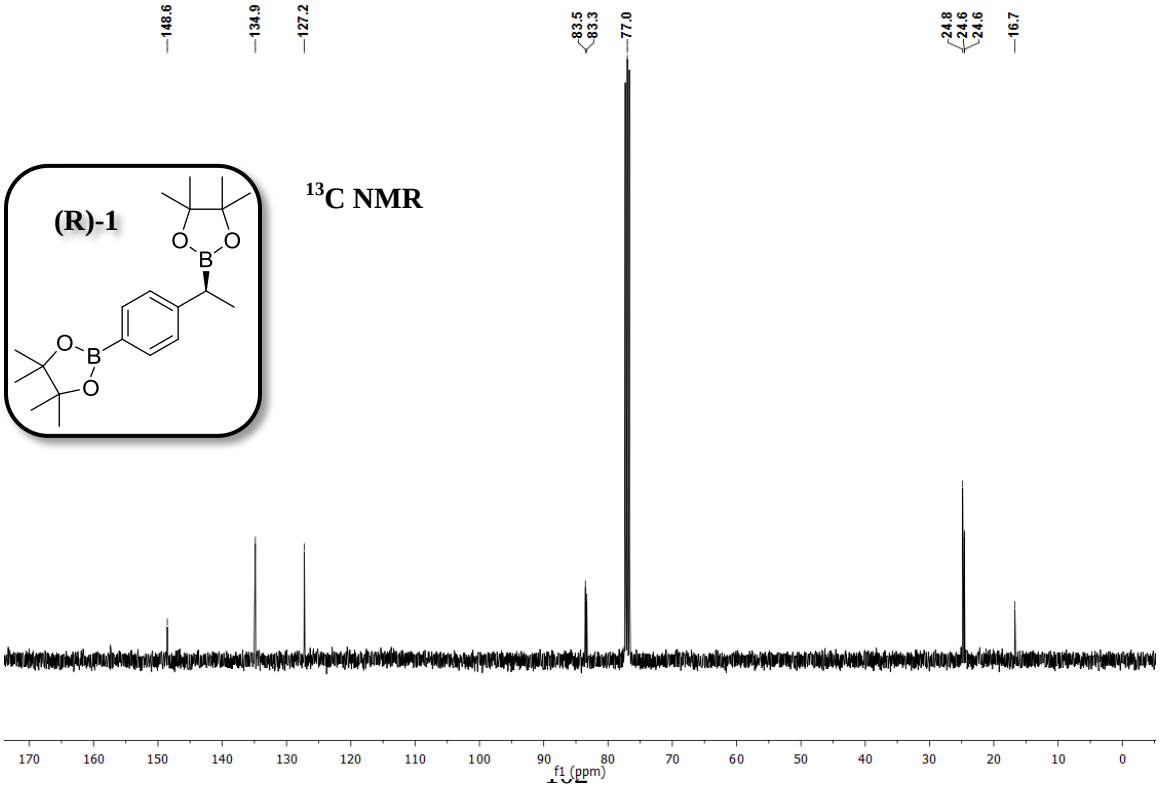


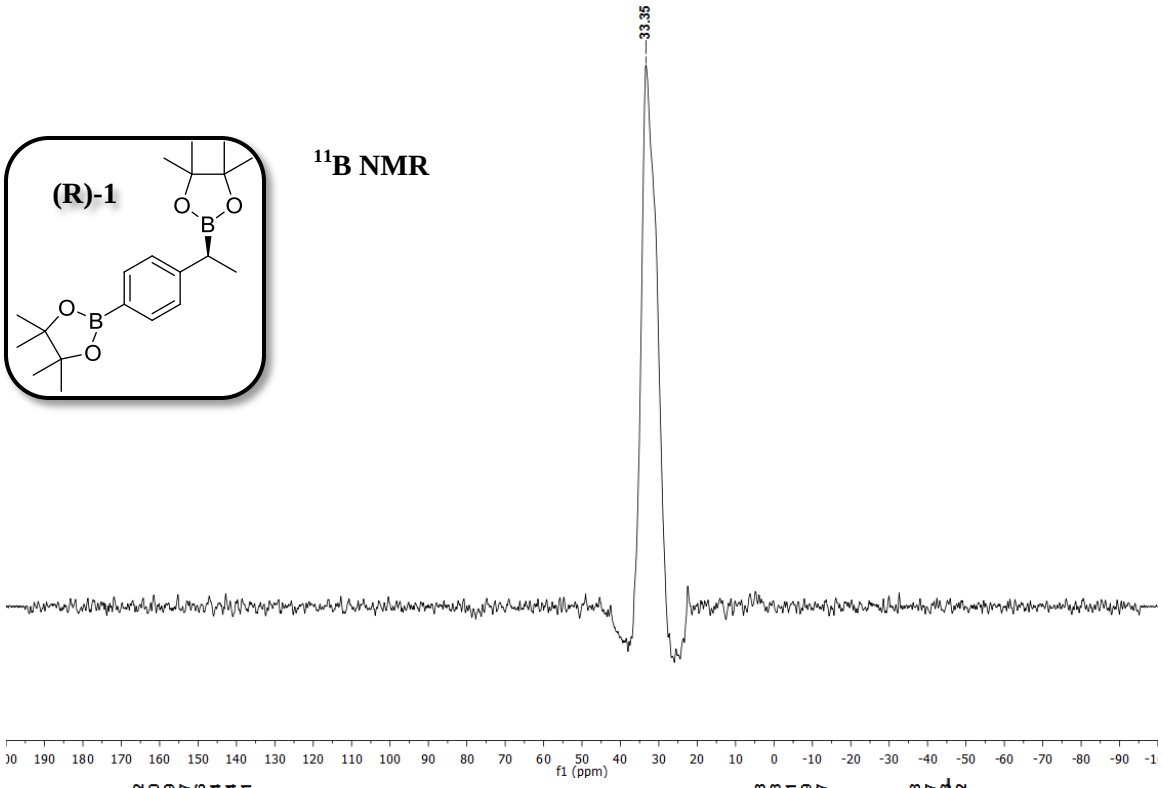
^{1}H NMR

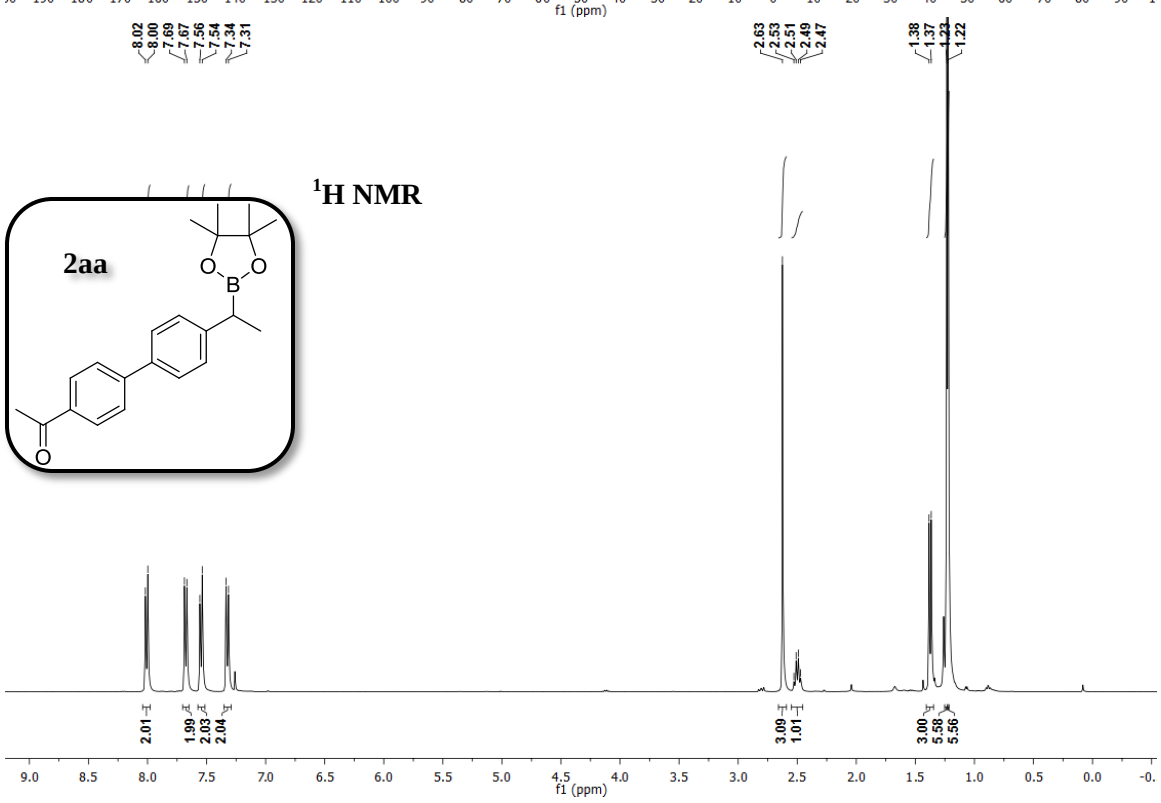

148.5
134.8
127.2
83.5
83.3
77.0
24.8
24.6
24.6
16.7
1
13C NMR
f1 (ppm)
33.36

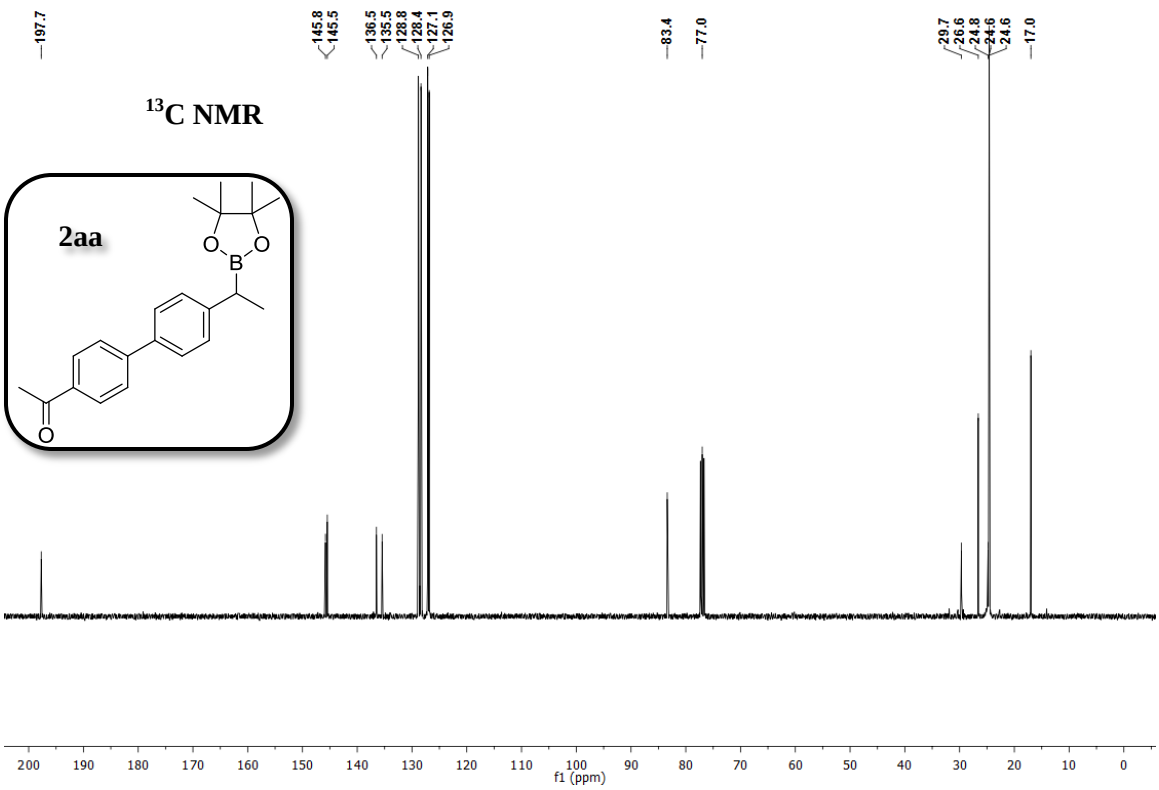

1
11B NMR
f1 (ppm)

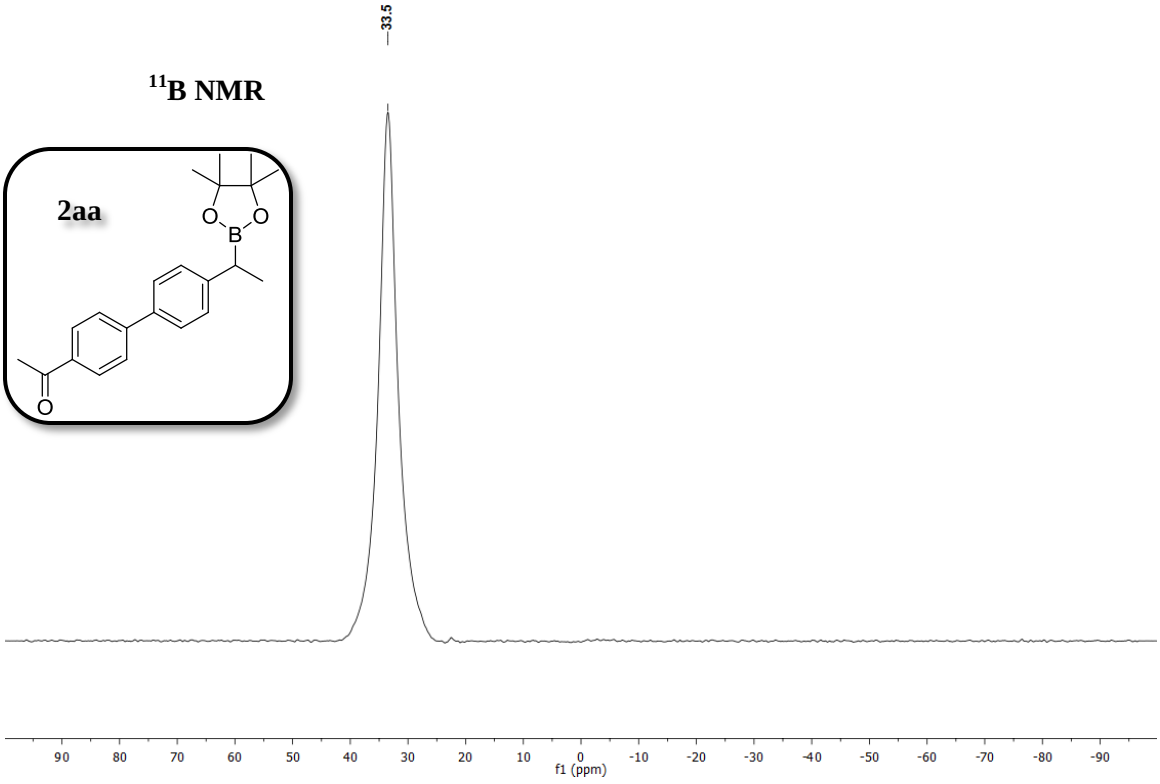

(R)-1
^{1}H NMR
7.72
7.70
7.26
7.24
7.22
2.48
2.46
2.44
2.42
1.58
1.33
1.19
1.18
2.00
2.07
1.01
5.84
5.69
f1 (ppm)

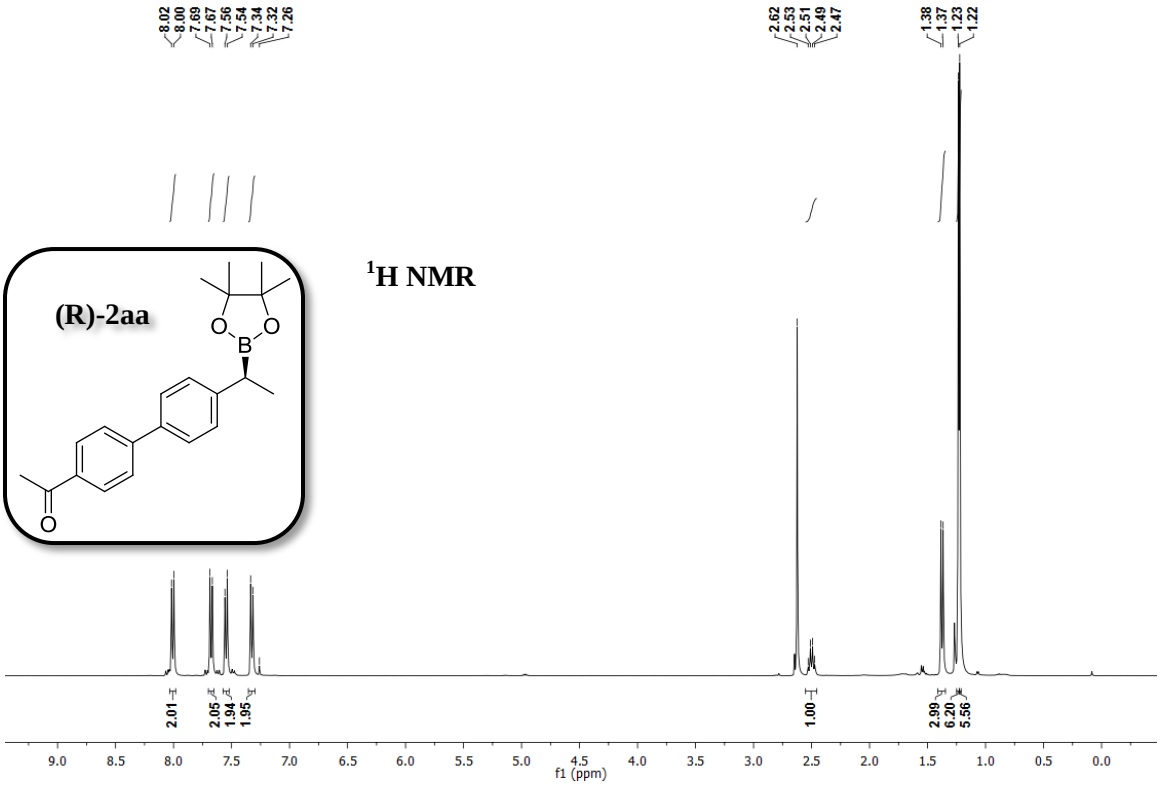

(R)-1
^{13}C NMR
148.6
134.9
127.2
83.5
83.3
77.0
24.8
24.6
24.6
16.7
f1 (ppm)

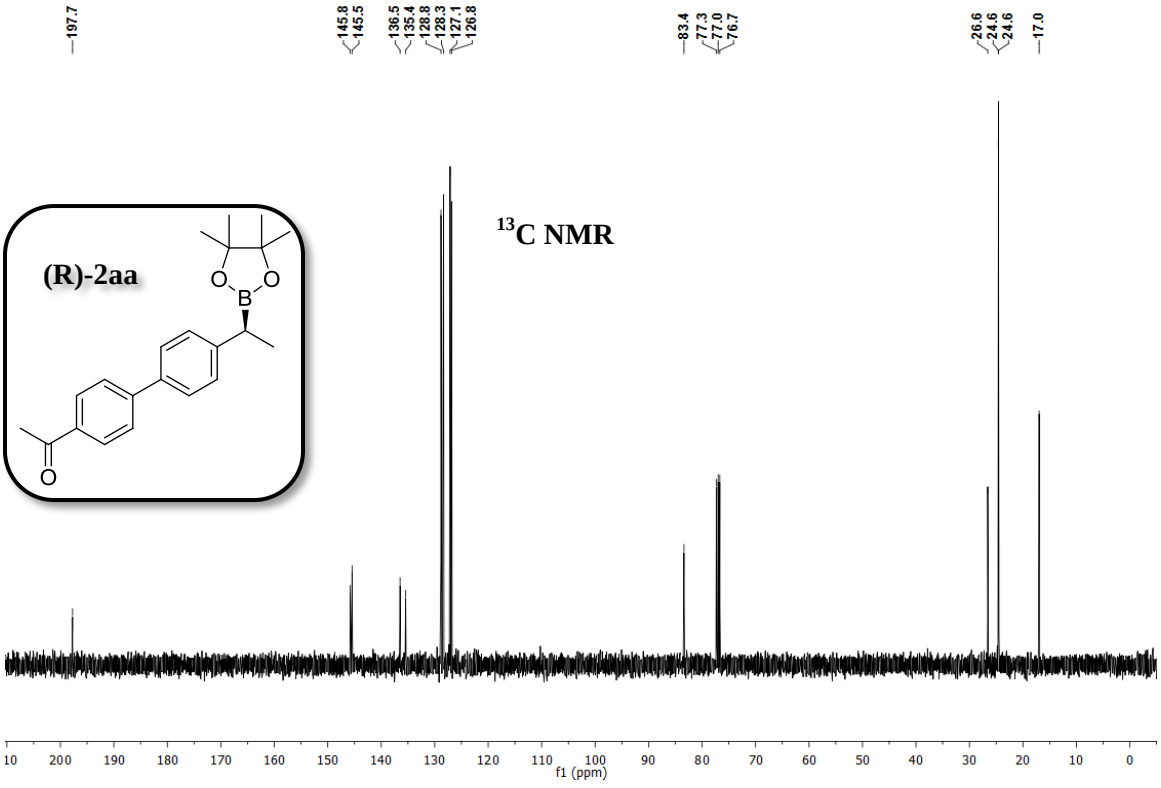

(R)-1
^{11}B NMR
33.35
f1 (ppm)

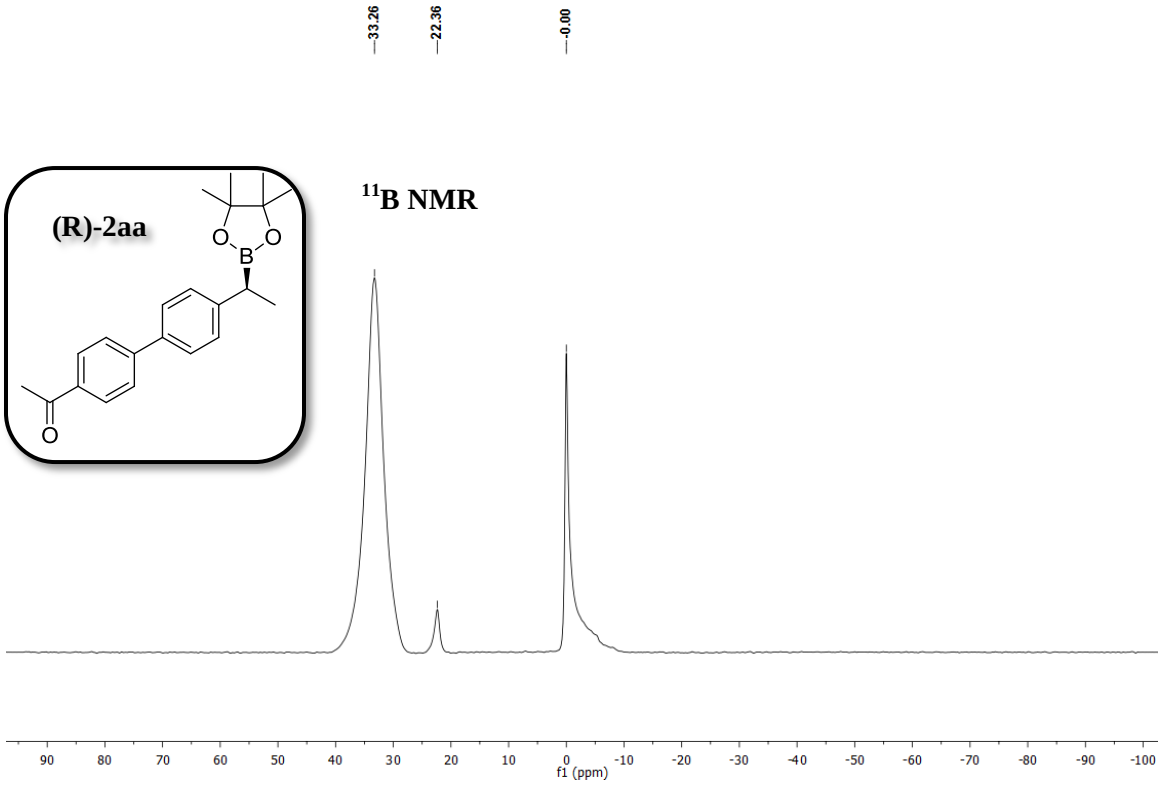

2aa
^{1}H NMR
8.02
8.00
7.69
7.67
7.56
7.54
7.34
7.31
2.63
2.53
2.51
2.49
2.47
1.38
1.37
1.23
1.22
2.01
1.99
2.03
2.04
3.09
1.01
3.00
5.58
5.56
f1 (ppm)

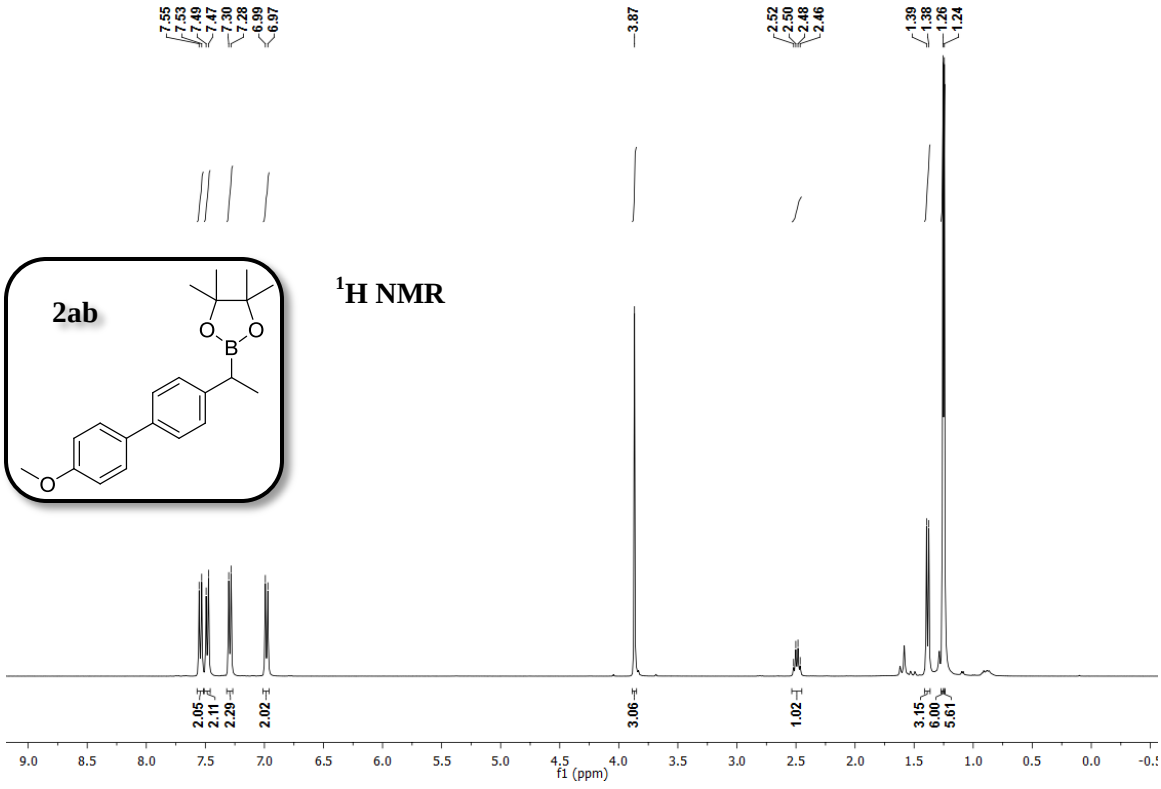

197.7
145.8
145.5
136.5
135.5
128.8
128.4
127.1
126.9
83.4
77.0
29.7
26.6
24.8
24.6
24.6
17.0
13C NMR
2aa
O
B
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

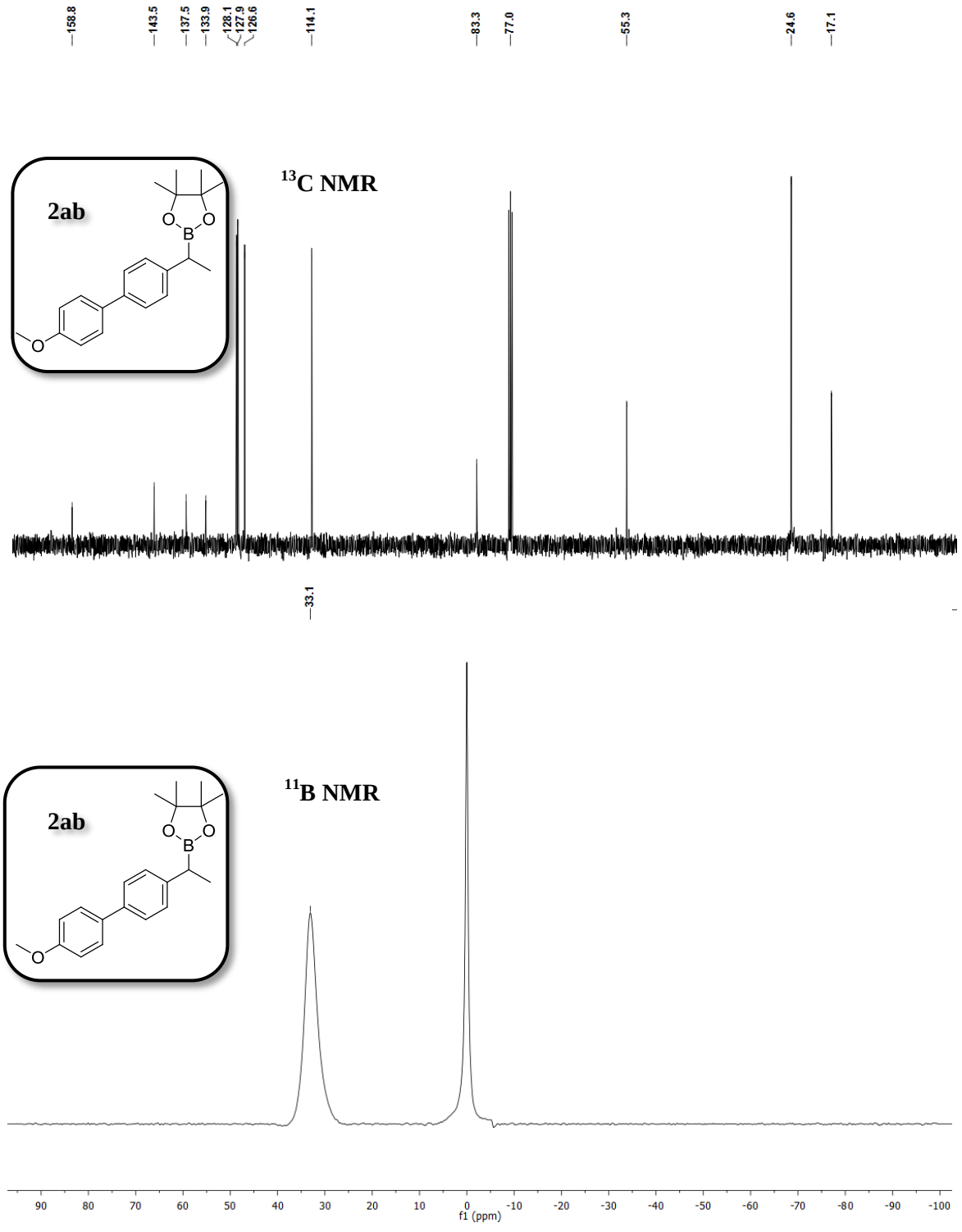

33.5
11B NMR
2aa
O
B
O
O
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90
f1 (ppm)

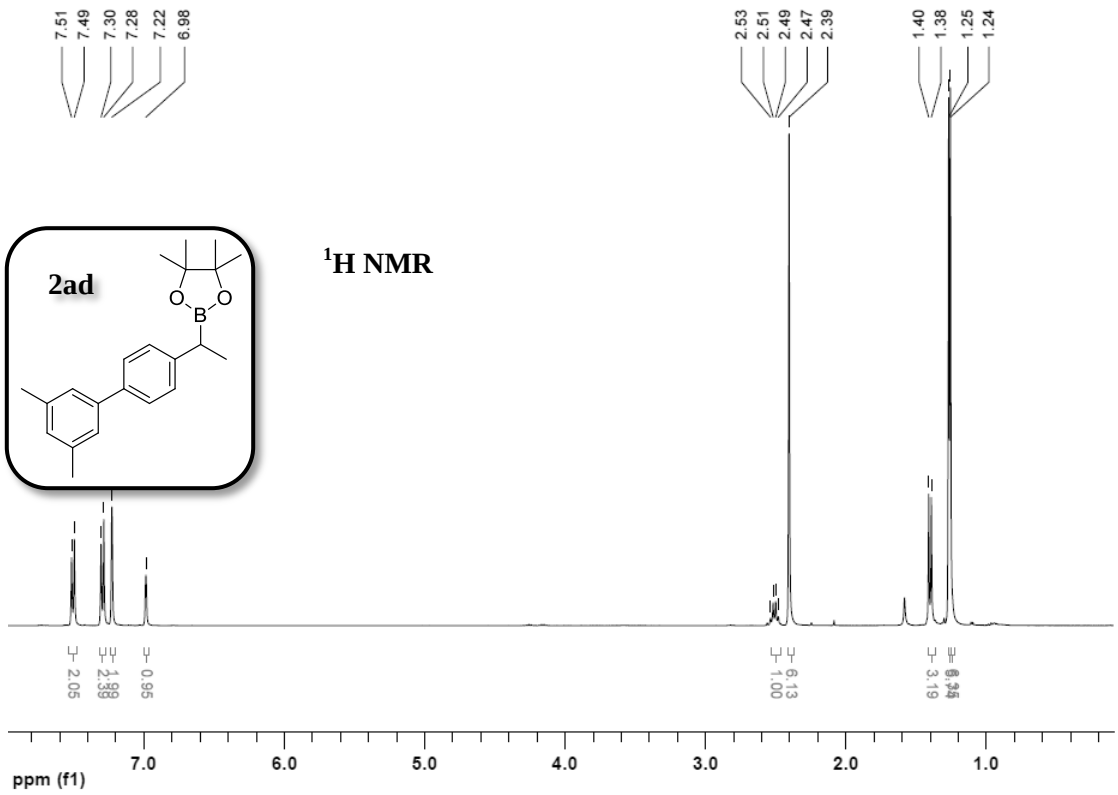

8.02
8.00
7.69
7.67
7.56
7.54
7.34
7.32
7.26
2.62
2.53
2.51
2.49
2.47
1.38
1.37
1.23
1.22
(R)-2aa
O
B
O
O
^{1}H NMR
2.01
2.05
1.94
1.95
1.00
2.99
6.20
5.56
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

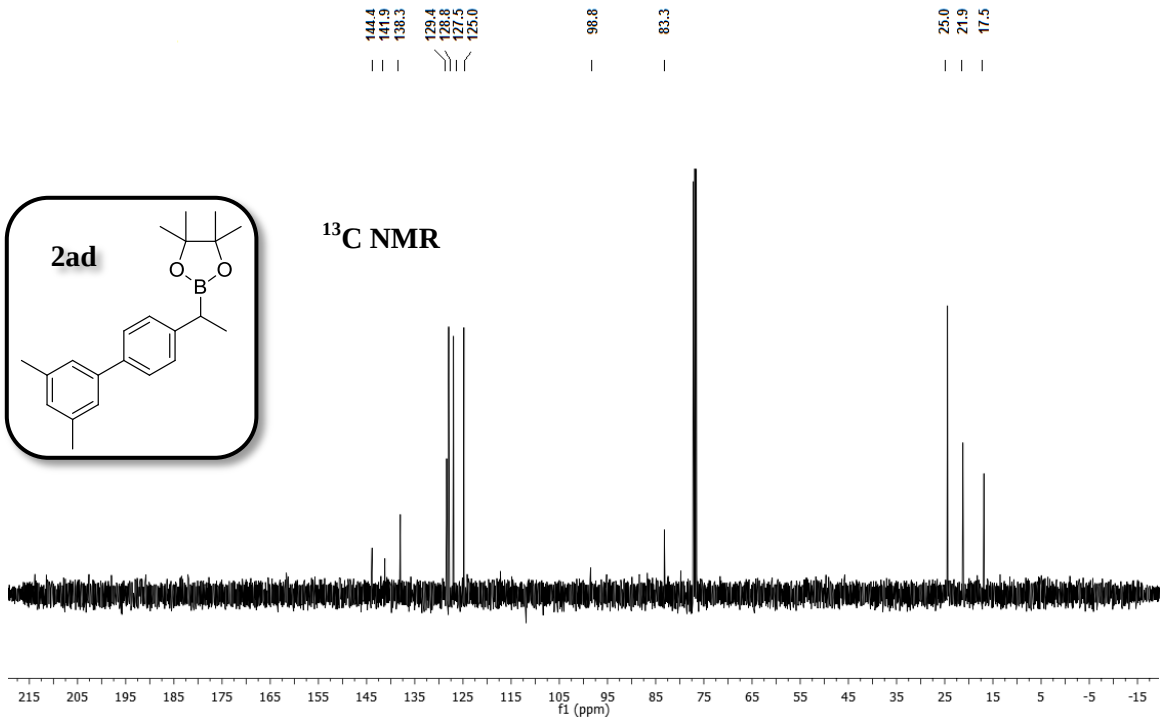

197.7
145.8
145.5
136.5
135.4
128.8
128.3
127.1
126.8
83.4
77.3
77.0
76.7
26.6
24.6
24.6
17.0
(R)-2aa
O
B
O
O
^{13}C NMR
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

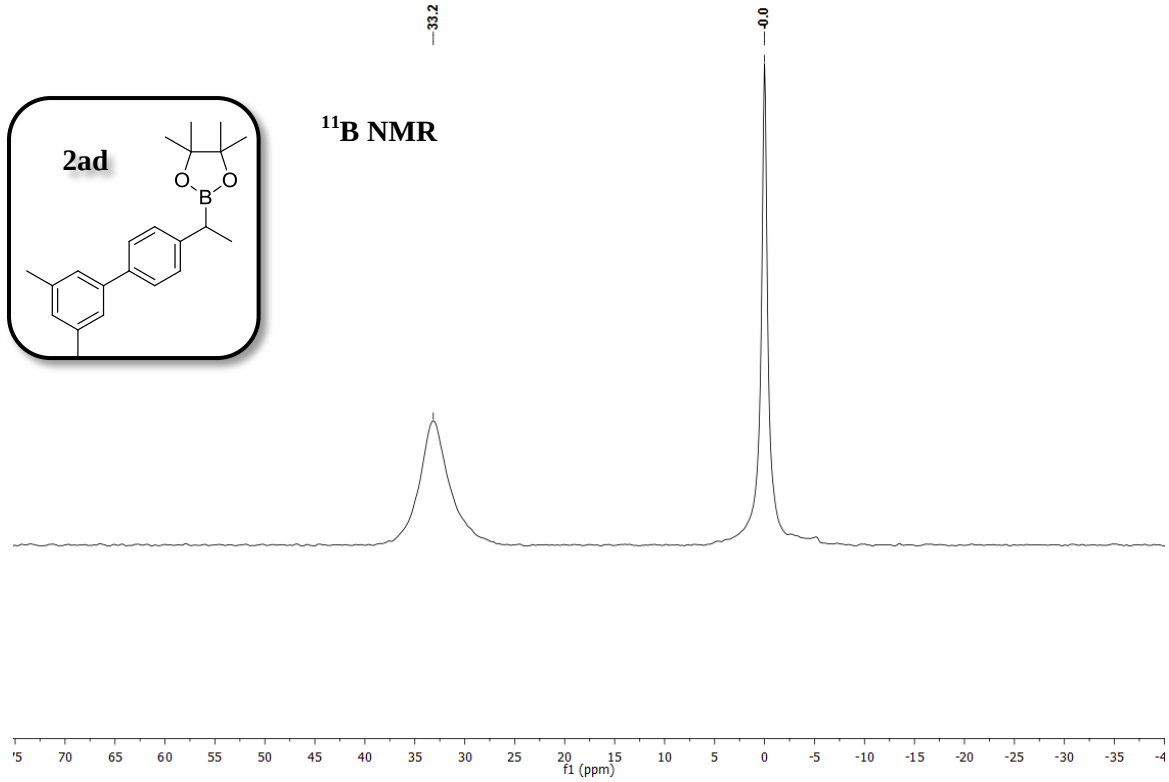

33.26
22.36
0.00
(R)-2aa
O
B
O
O
^{11}B NMR
f1 (ppm)

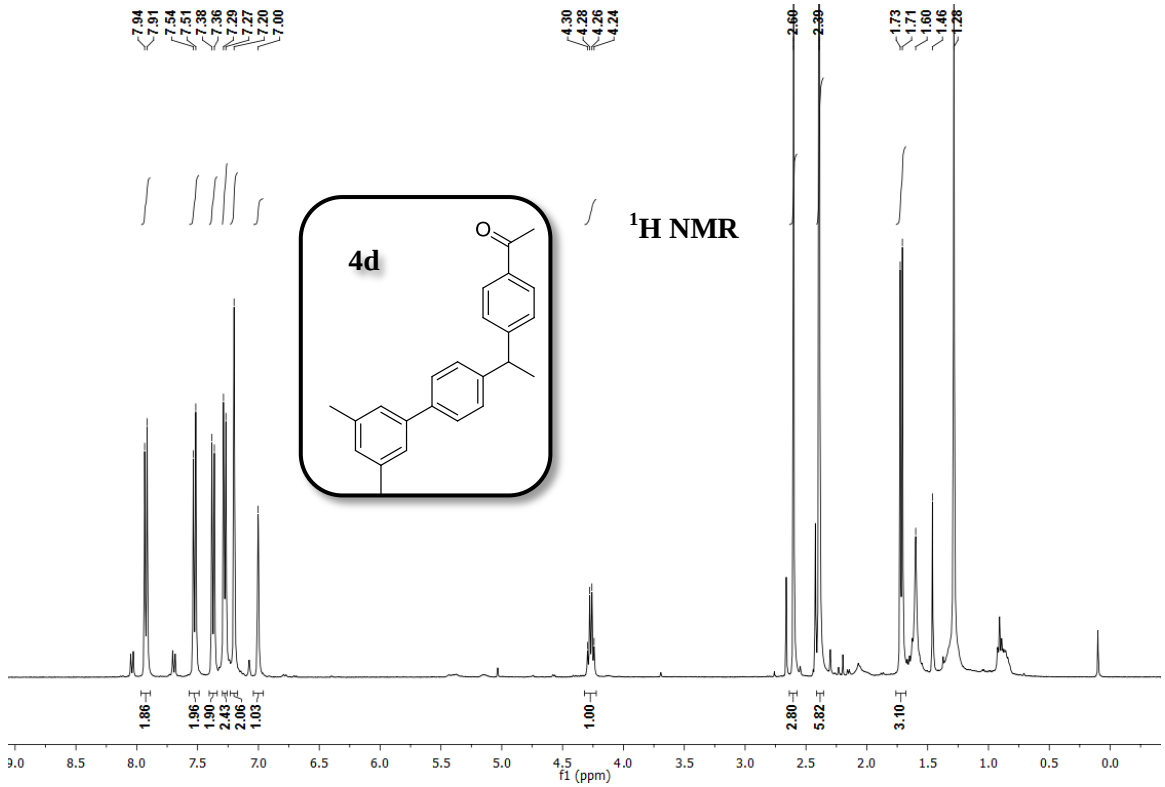

7.55
7.53
7.49
7.47
7.30
7.28
6.99
6.97
3.87
2.52
2.50
2.48
2.46
1.39
1.38
1.26
1.24
2ab
O
B
O
O
^{1}H NMR
2.05
2.11
2.29
2.02
3.06
1.02
3.15
6.00
5.61
f1 (ppm)

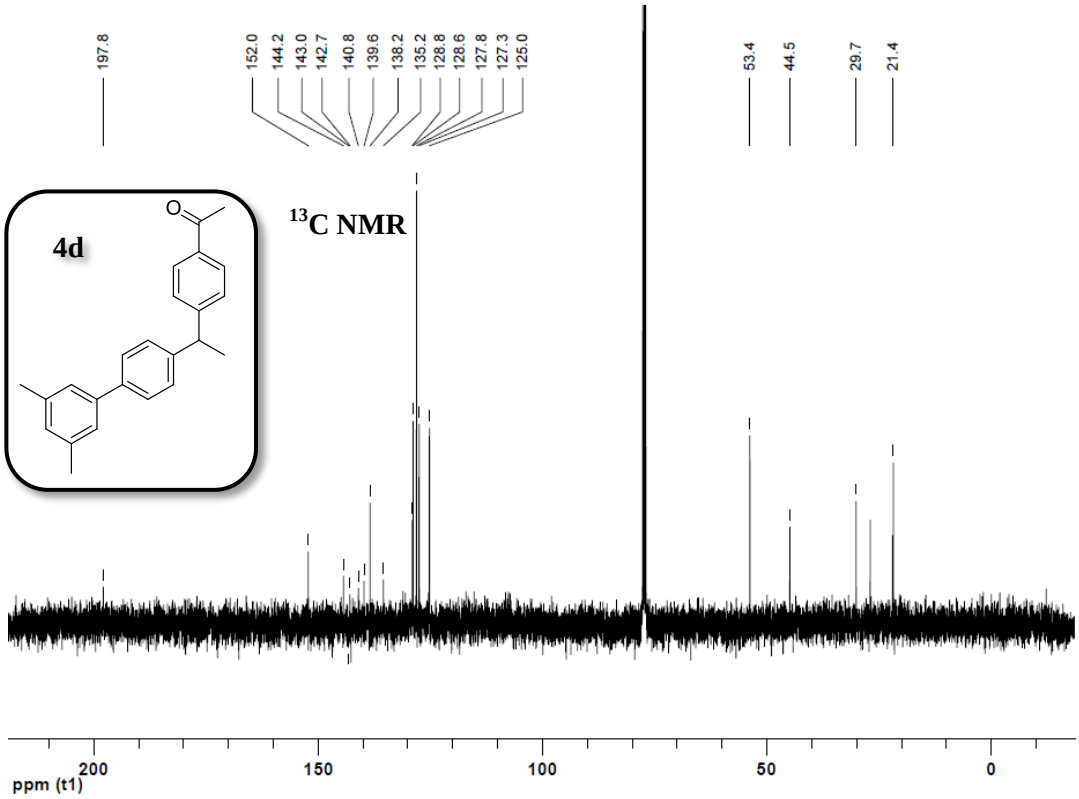

158.8
143.5
137.5
133.9
128.1
127.9
126.6
114.1
83.3
77.0
55.3
24.6
17.1
2ab
13C NMR
33.1
2ab
11B NMR
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
f1 (ppm)

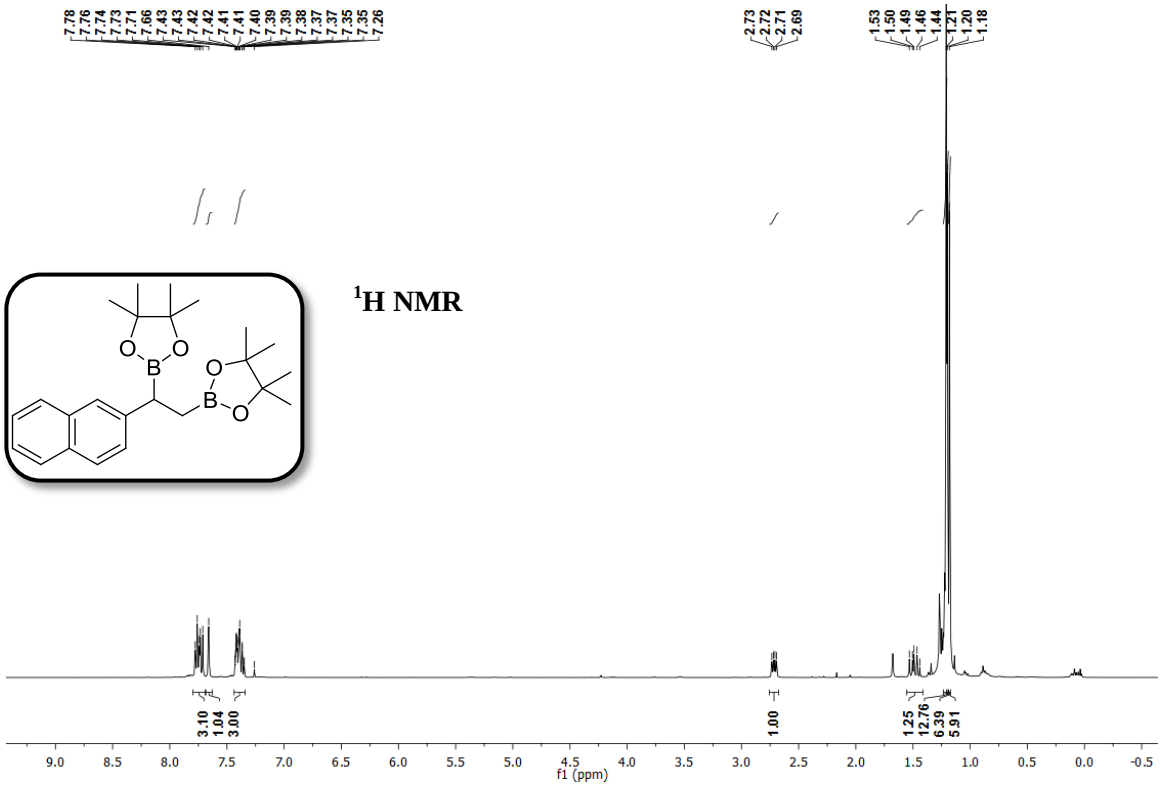

7.51
7.49
7.30
7.28
7.22
6.98
2.53
2.51
2.49
2.47
2.39
1.40
1.38
1.25
1.24
2ad
1H NMR
2.05
1.00
3.19
0.95
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

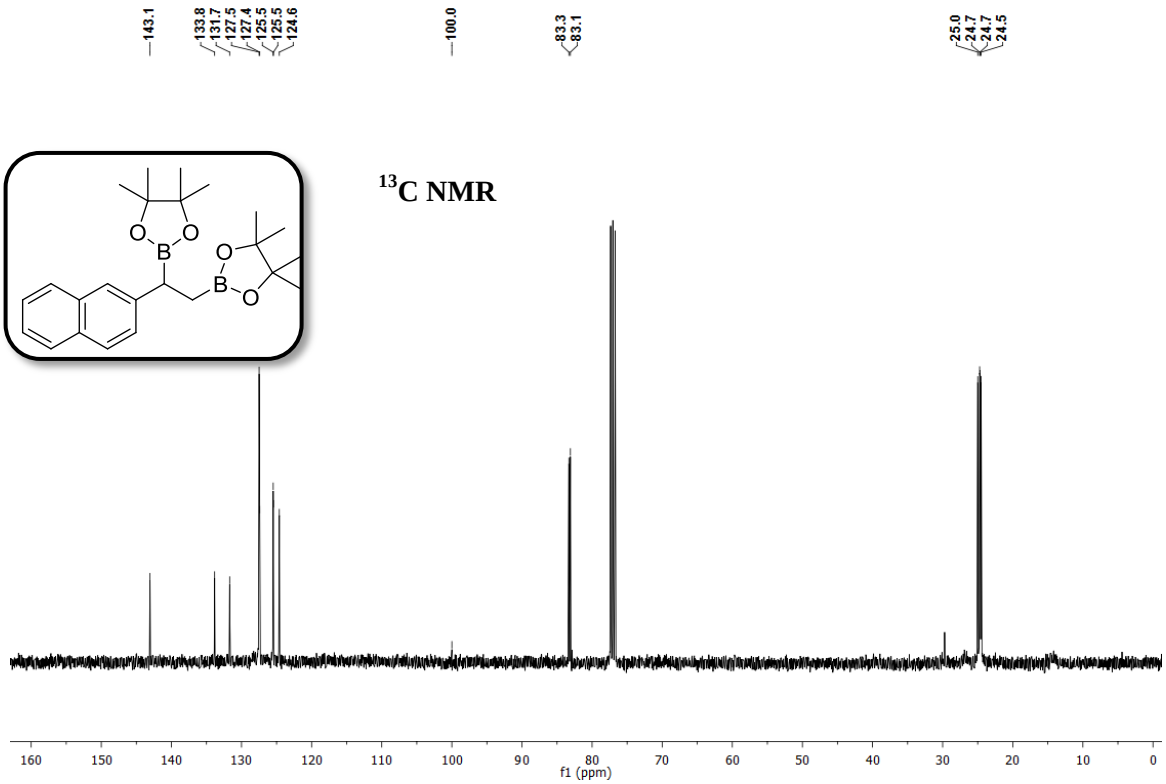

144.4
141.9
138.3
129.4
128.8
127.5
125.0
98.8
83.3
25.0
21.9
17.5
2ad
13C NMR
215
205
195
185
175
165
155
145
135
125
115
105
95
85
75
65
55
45
35
25
15
5
-5
-15
f1 (ppm)


2ad
^{11}B NMR
33.2
0.0
f1 (ppm)

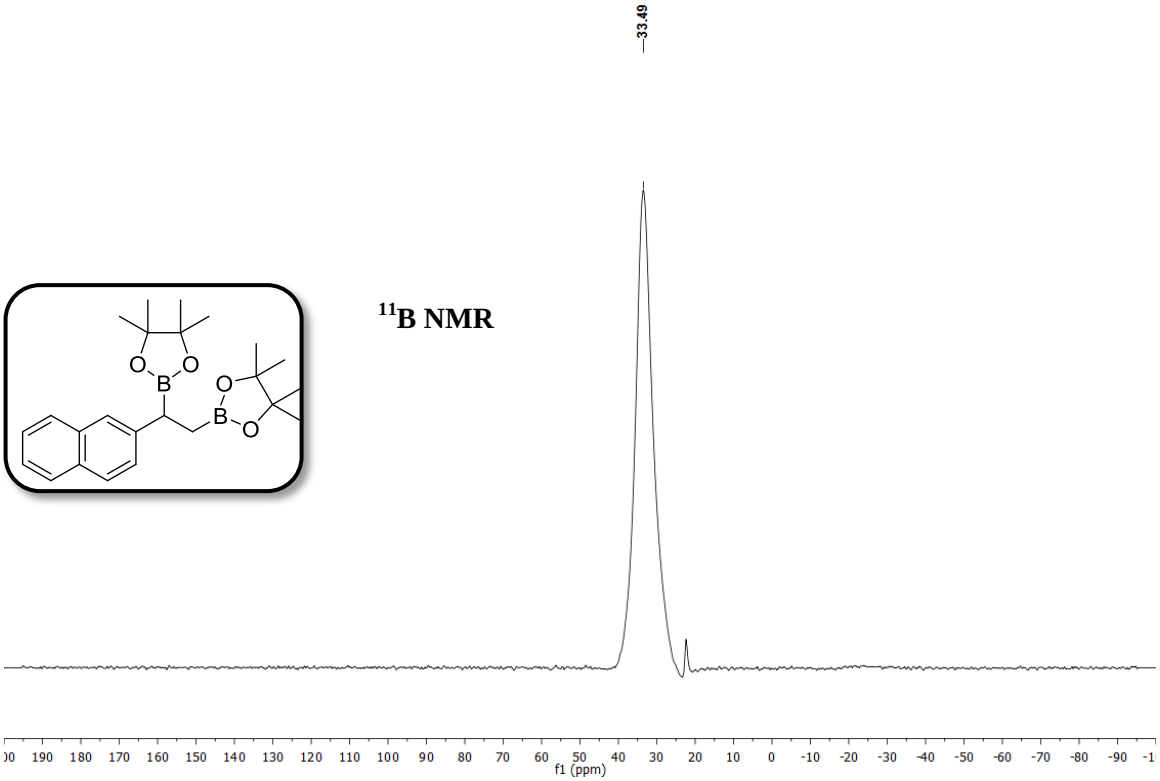

4d
^{1}H NMR
7.94
7.91
7.54
7.51
7.38
7.36
7.29
7.27
7.20
7.00
4.30
4.28
4.26
4.24
2.60
2.39
1.73
1.71
1.60
1.46
1.26
1.86
1.96
1.90
2.43
2.06
1.03
1.00
2.80
5.82
3.10
f1 (ppm)


197.8
152.0
144.2
143.0
142.7
140.8
139.6
138.2
135.2
128.8
128.6
127.8
127.3
125.0
53.4
44.5
29.7
21.4
4d
13C NMR
ppm (t1)
200
150
100
50
0

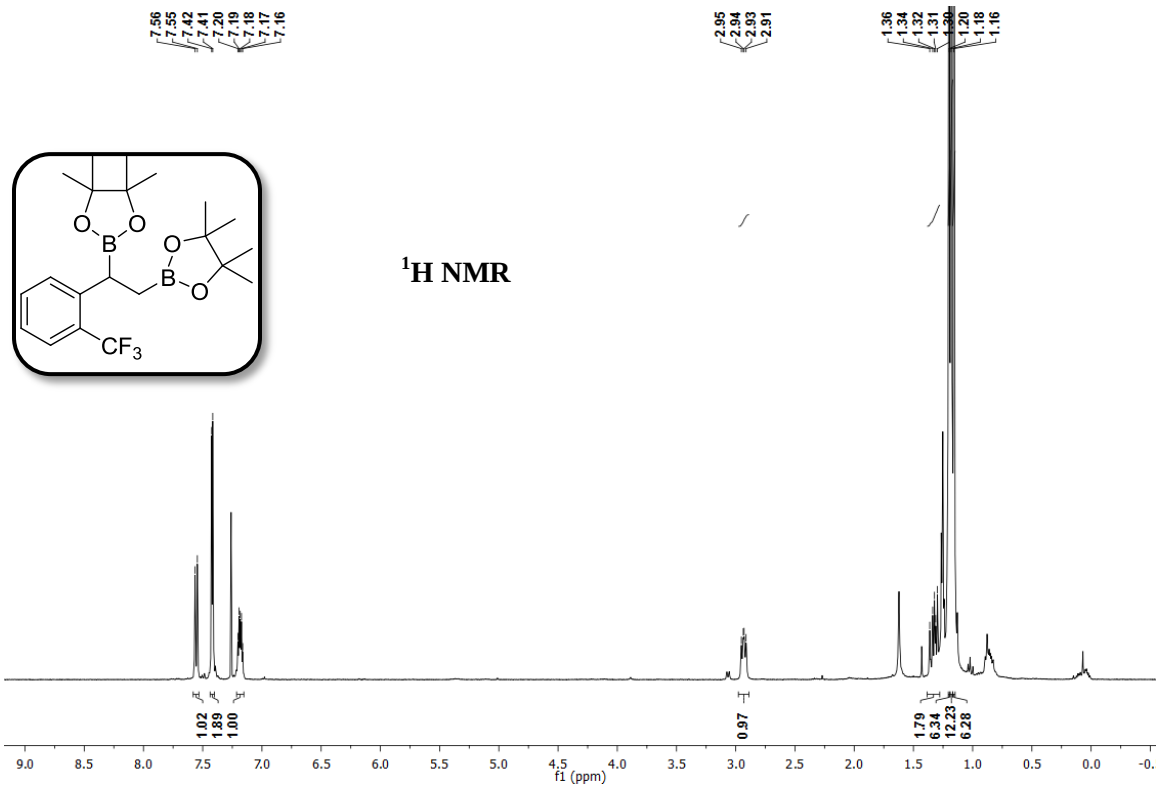

7.78
7.76
7.74
7.73
7.71
7.66
7.43
7.42
7.42
7.42
7.41
7.41
7.40
7.39
7.39
7.38
7.37
7.37
7.35
7.35
7.26
2.73
2.72
2.71
2.69
1.53
1.50
1.49
1.46
1.44
1.21
1.20
1.18
1H NMR
3.10
1.04
3.00
1.00
1.25
12.76
6.39
5.91
f1 (ppm)

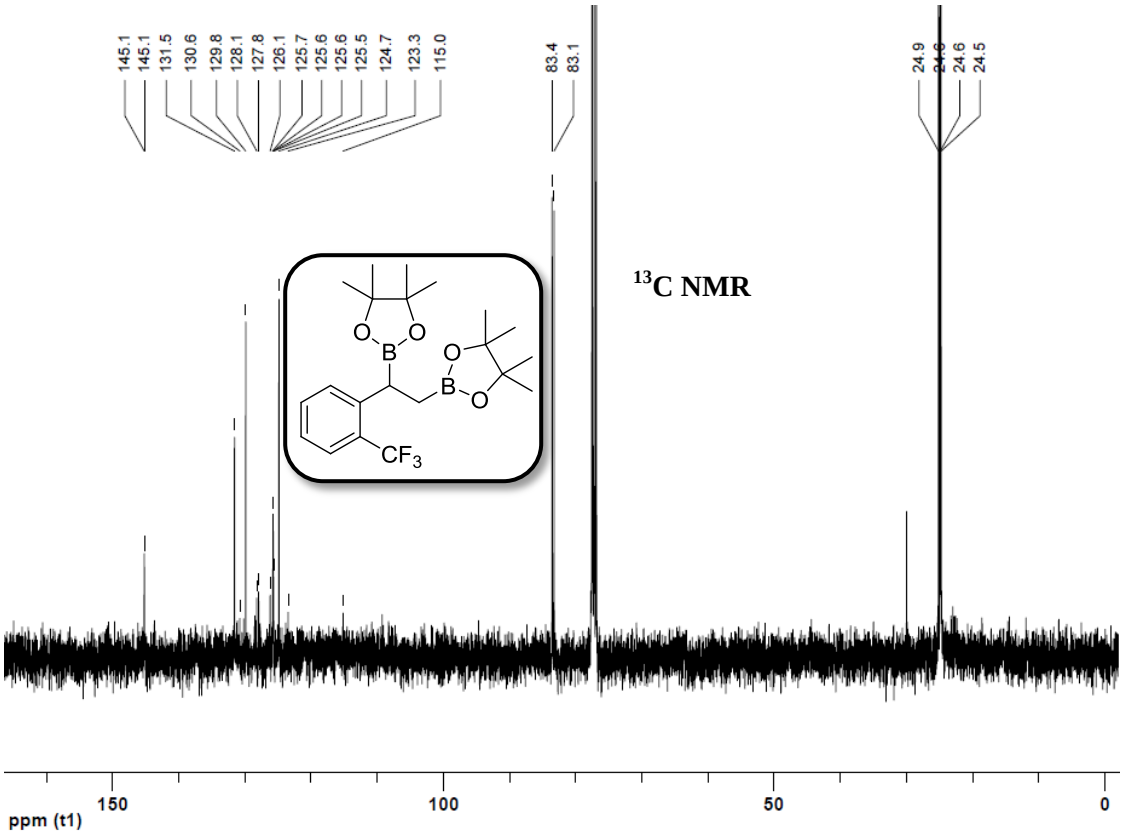


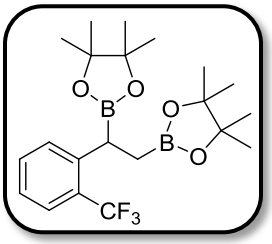
^{13}C NMR



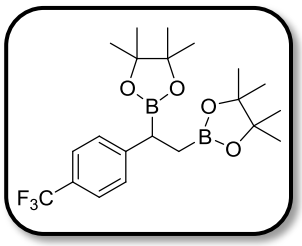
^{11}B NMR


7.56
7.55
7.42
7.41
7.20
7.19
7.18
7.17
7.16
2.95
2.94
2.93
2.91
1.36
1.34
1.32
1.31
1.20
1.18
1.16
O
B
O
O
B
O
CF3
1H NMR
1.02
1.89
1.00
0.97
1.79
6.34
12.23
6.28
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

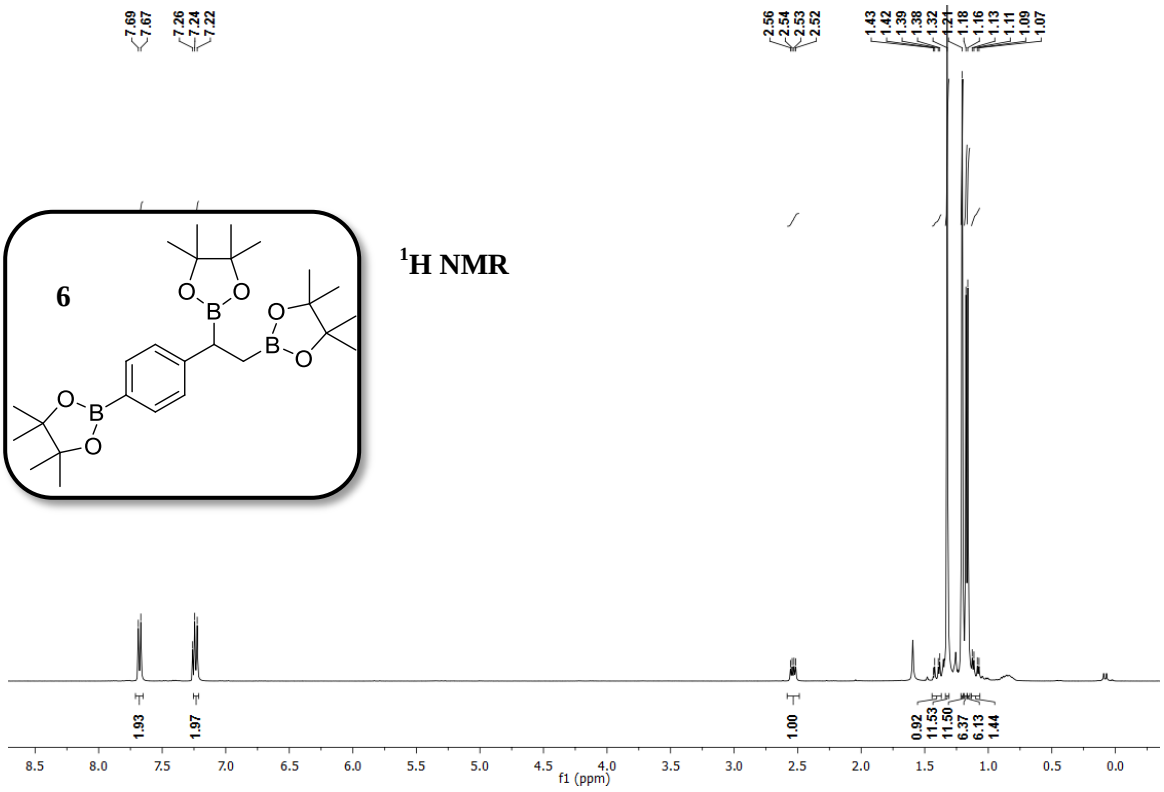

145.1
145.1
131.5
130.6
129.8
128.1
127.8
126.1
125.7
125.6
125.6
125.5
124.7
123.3
115.0
83.4
83.1
24.9
24.6
24.6
24.5
O
B
O
O
B
O
CF3
13C NMR
150
100
50
0
ppm (t1)

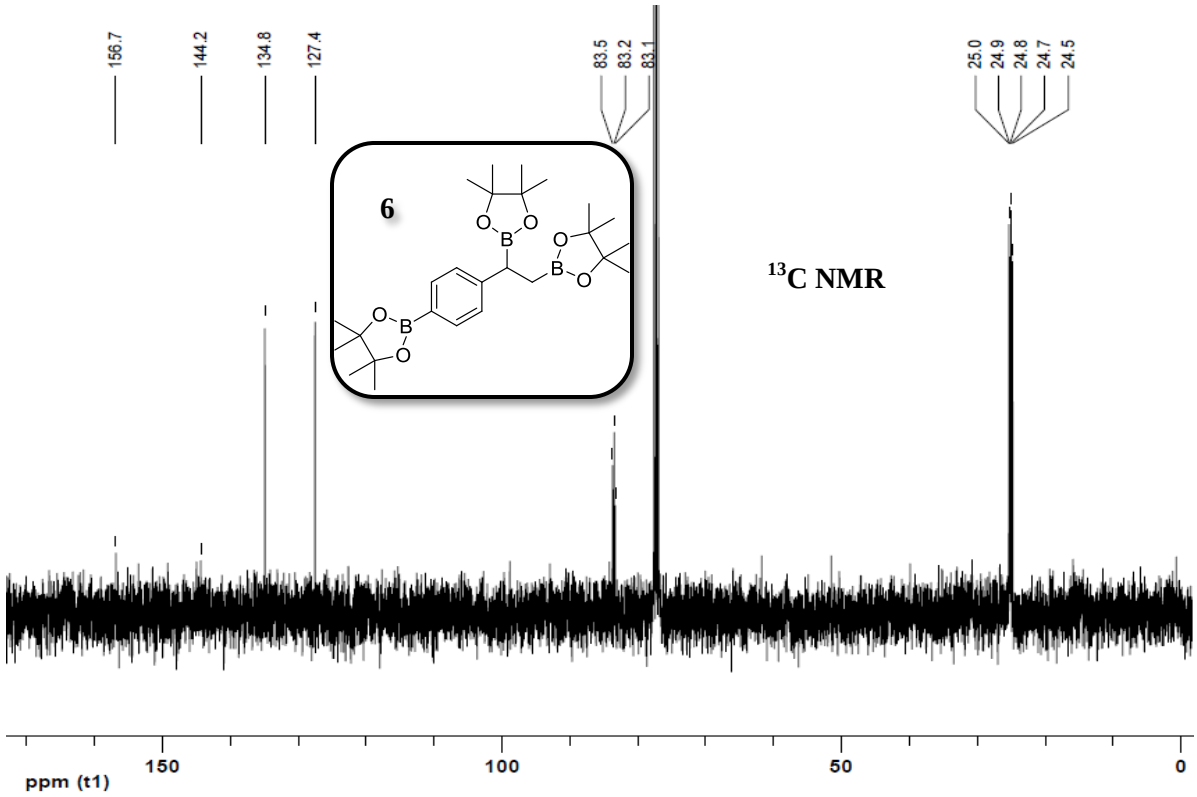


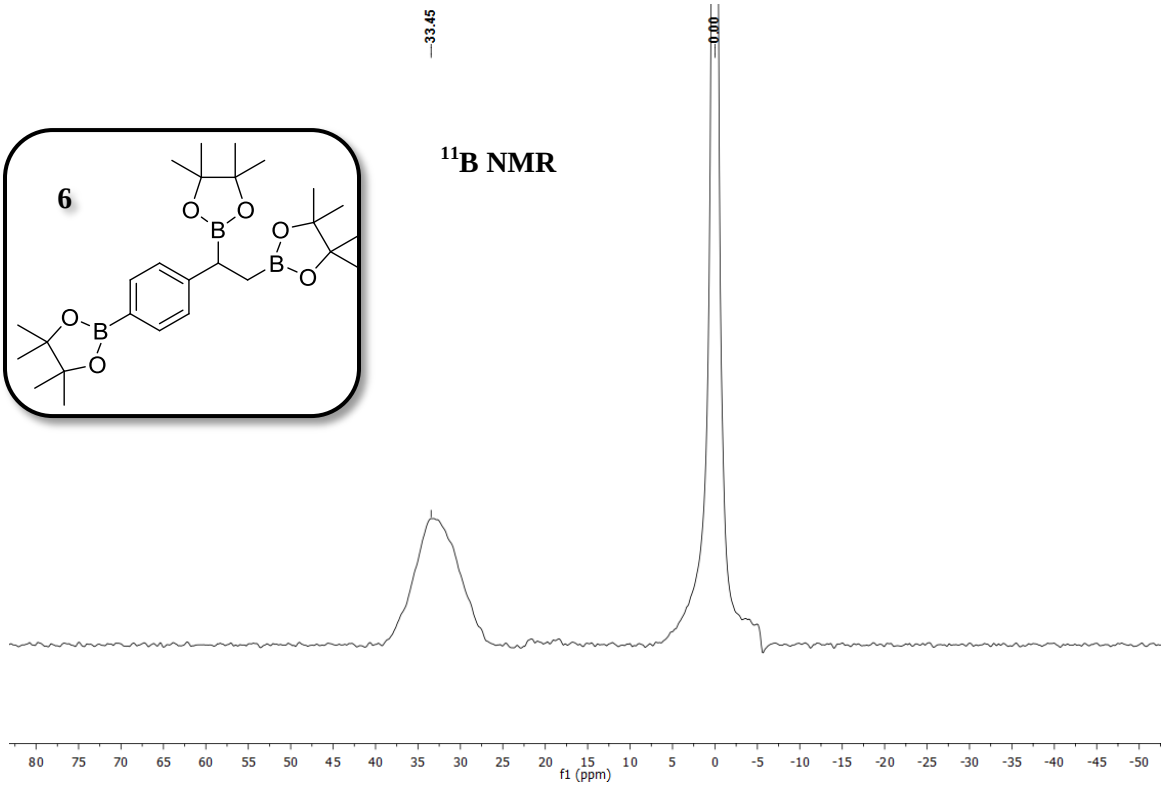
^{11}B NMR



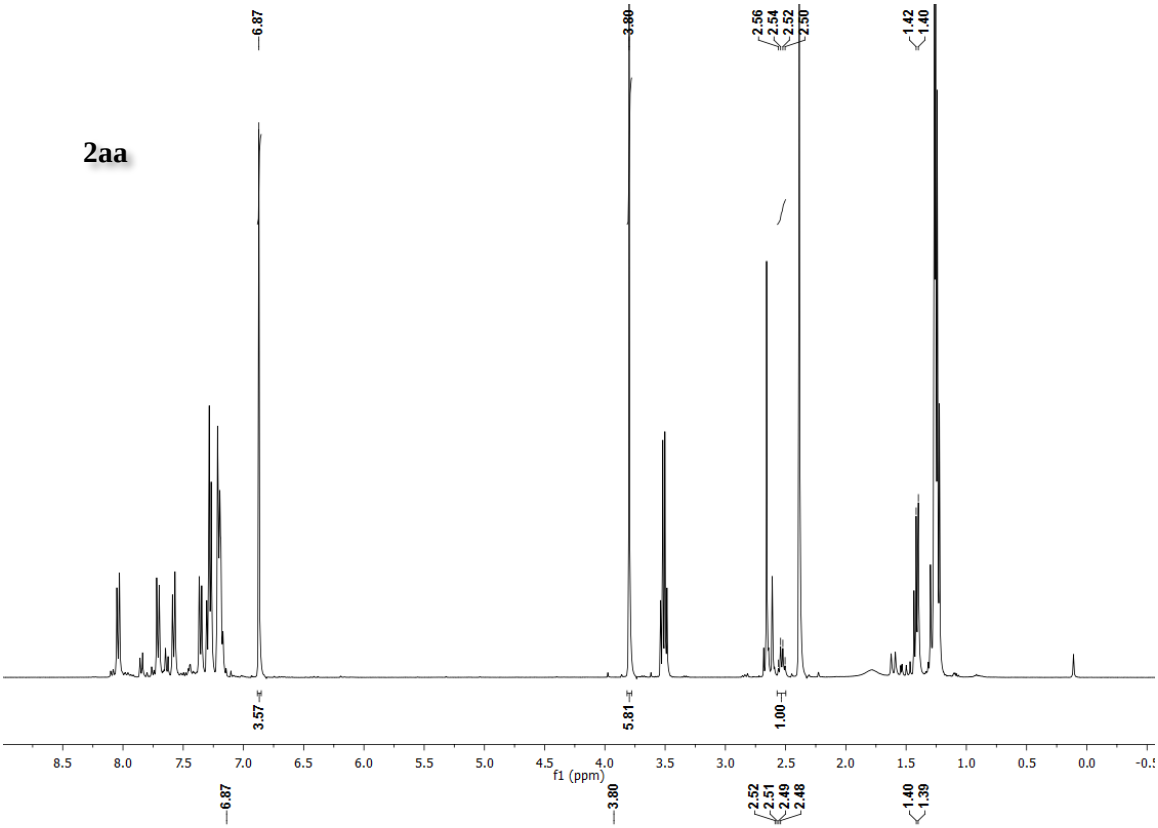
^{1}H NMR

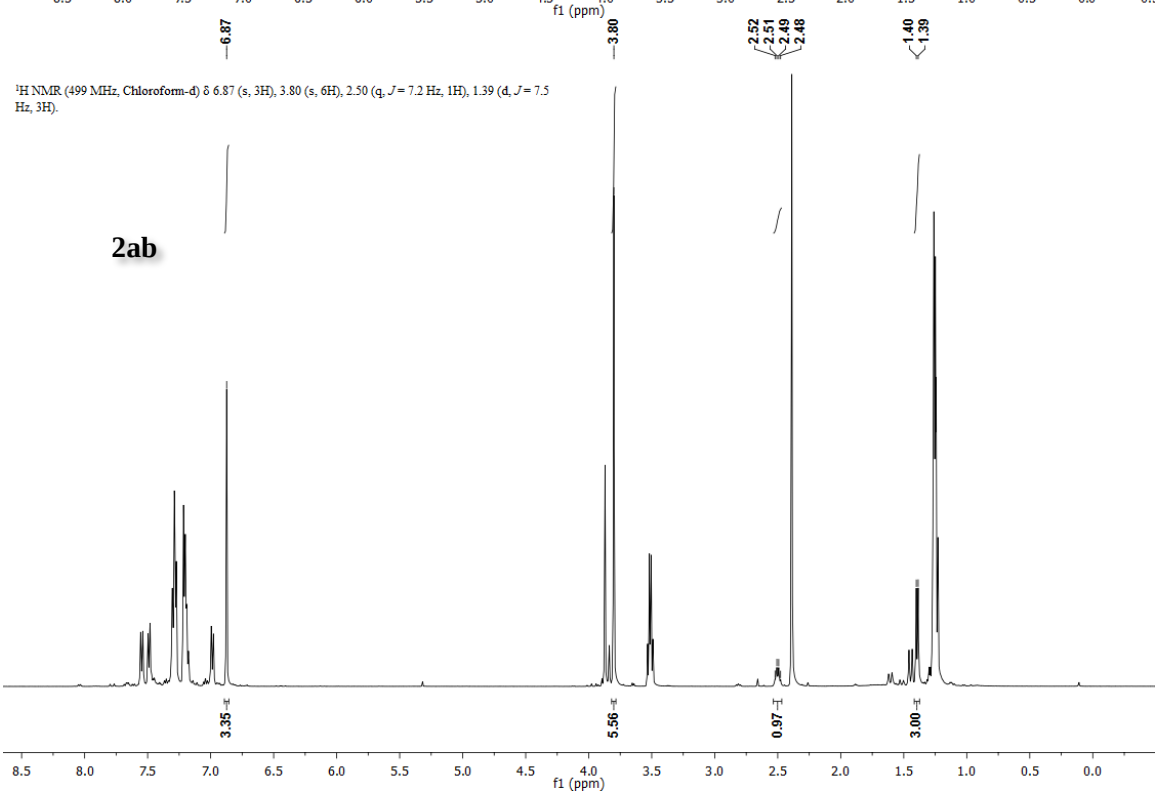

7.69
7.67
7.26
7.24
7.22
2.56
2.54
2.53
2.52
1.43
1.42
1.39
1.38
1.32
1.21
1.18
1.16
1.13
1.11
1.09
1.07
6
^{1}H NMR
1.93
1.97
1.00
0.92
11.53
11.50
6.37
6.13
1.44
f1 (ppm)


156.7
144.2
134.8
127.4
83.5
83.2
83.1
25.0
24.9
24.8
24.7
24.5
6
^{13}C NMR
ppm (t1)

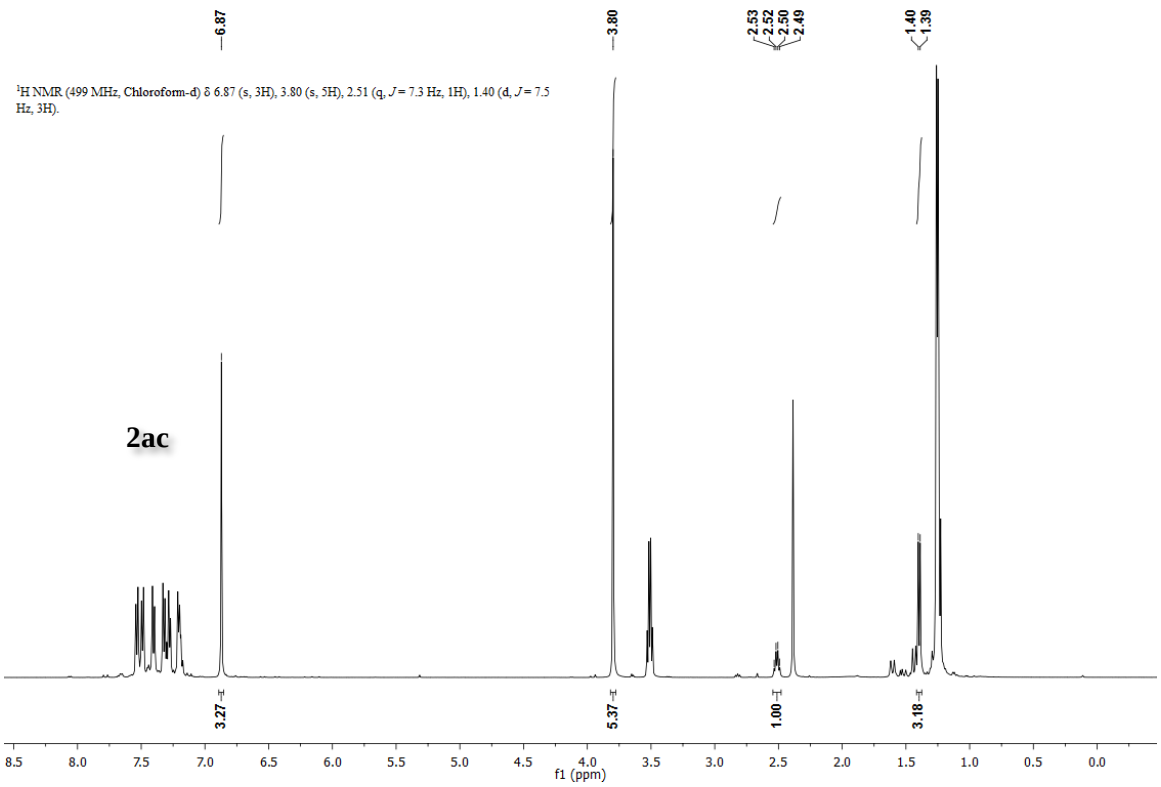

6
^{11}B NMR
33.45
0.00
80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50
f1 (ppm)

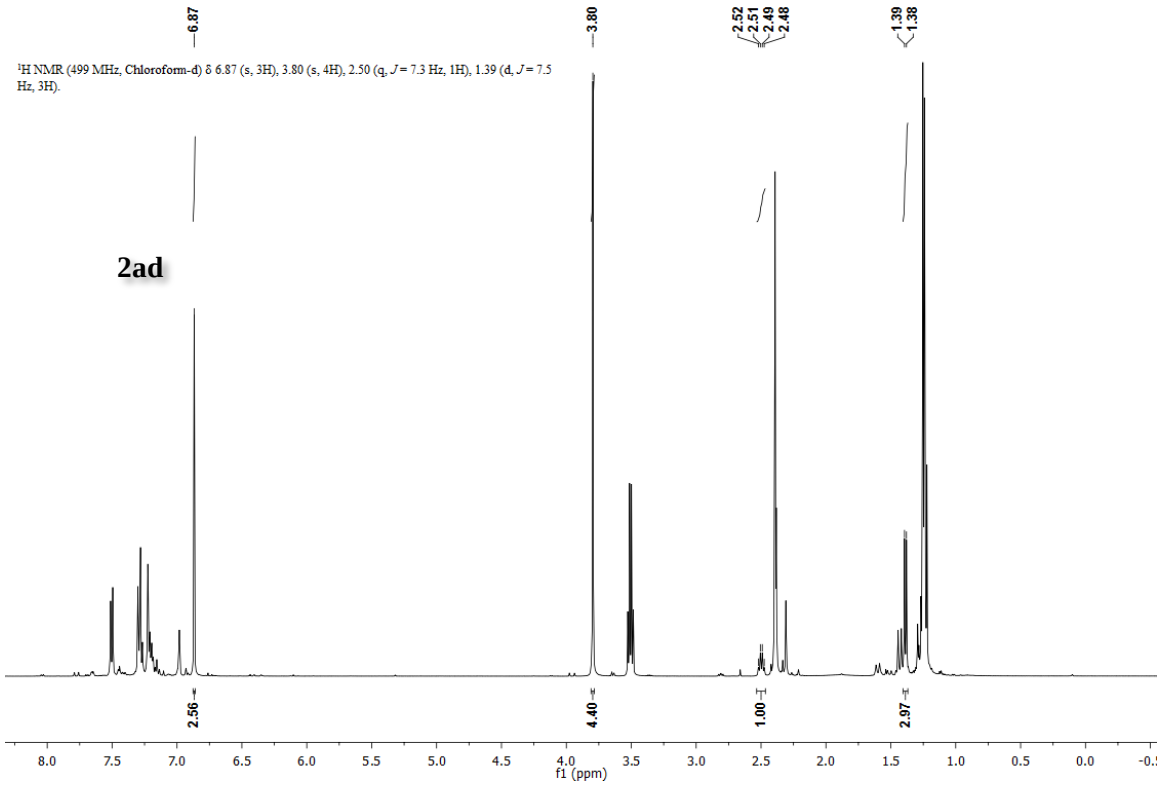
3.6 NMR Yield Data (^{1}H NMR)

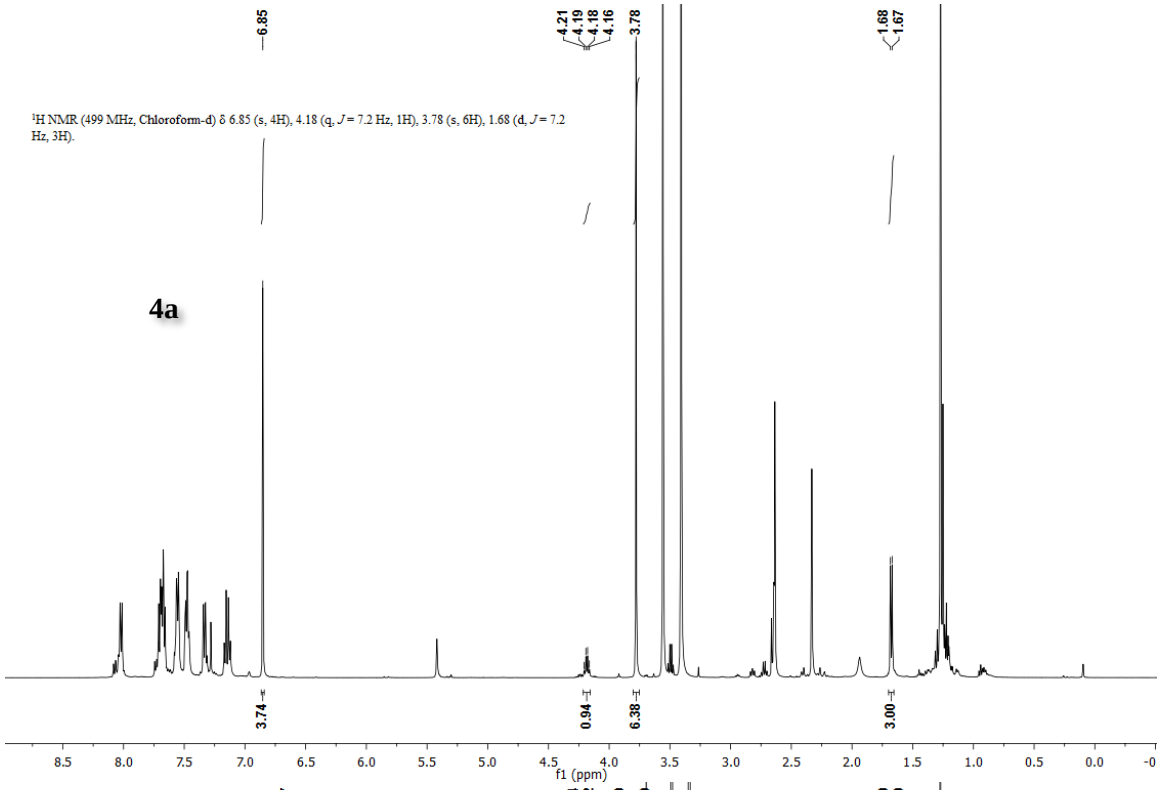


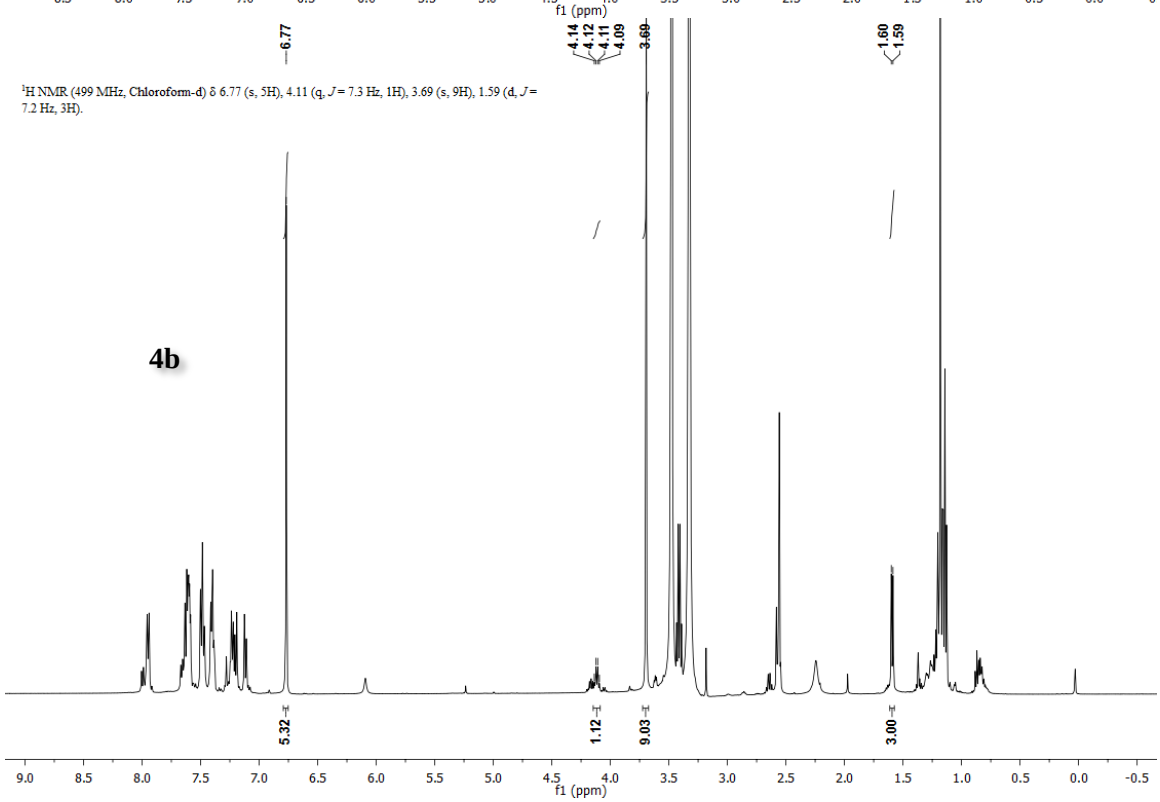


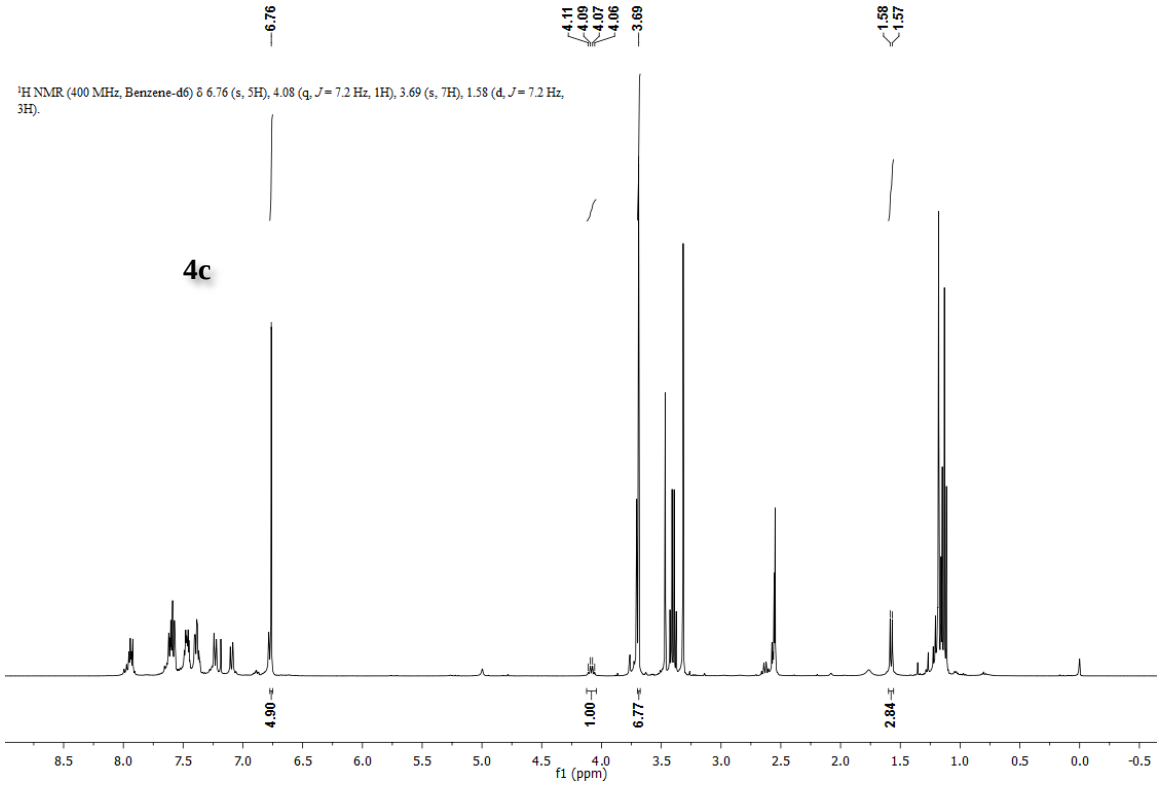
^{1}H NMR (499 MHz, Chloroform-d) δ 6.87 (s, 3H), 3.80 (s, 6H), 2.50 (q, J = 7.2 Hz, 1H), 1.39 (d, J = 7.5 Hz, 3H).

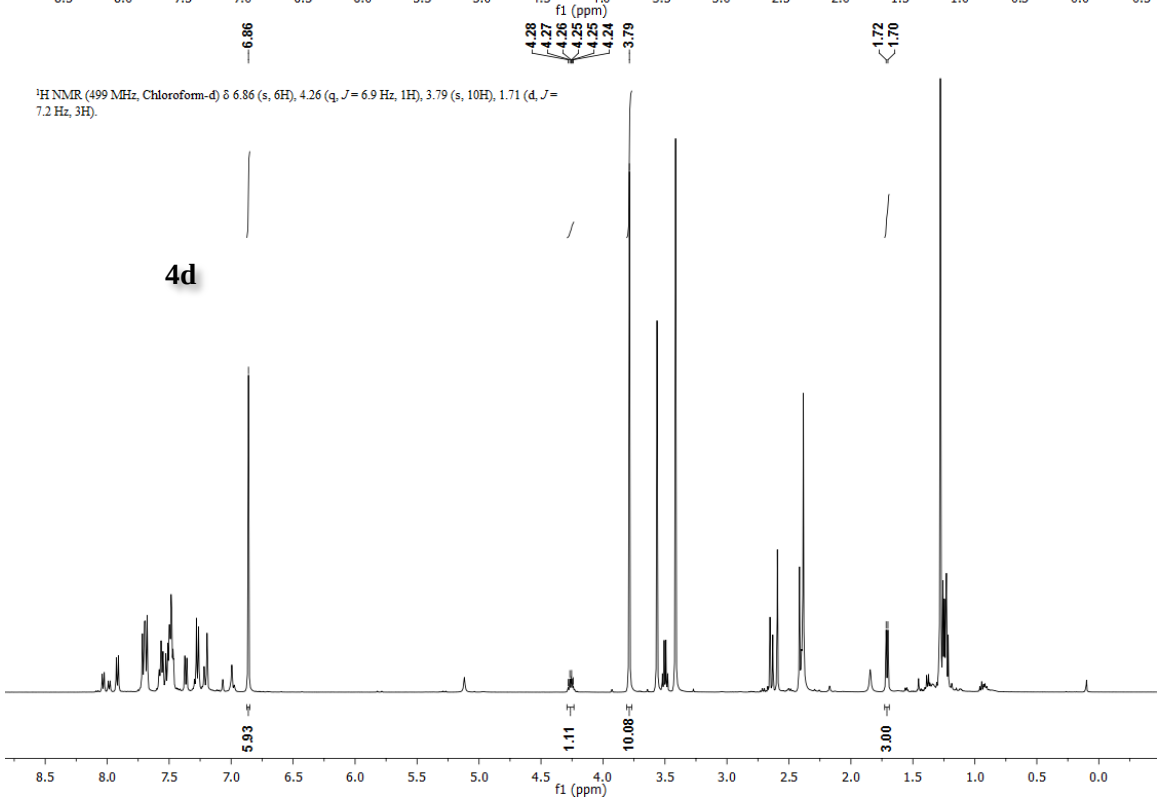

6.87
3.80
2.53
2.52
2.50
2.49
1.40
1.39
¹H NMR (499 MHz, Chloroform-d) δ 6.87 (s, 3H), 3.80 (s, 5H), 2.51 (q, J = 7.3 Hz, 1H), 1.40 (d, J = 7.5 Hz, 3H).
2ac
3.27
5.37
1.00
3.18
f1 (ppm)

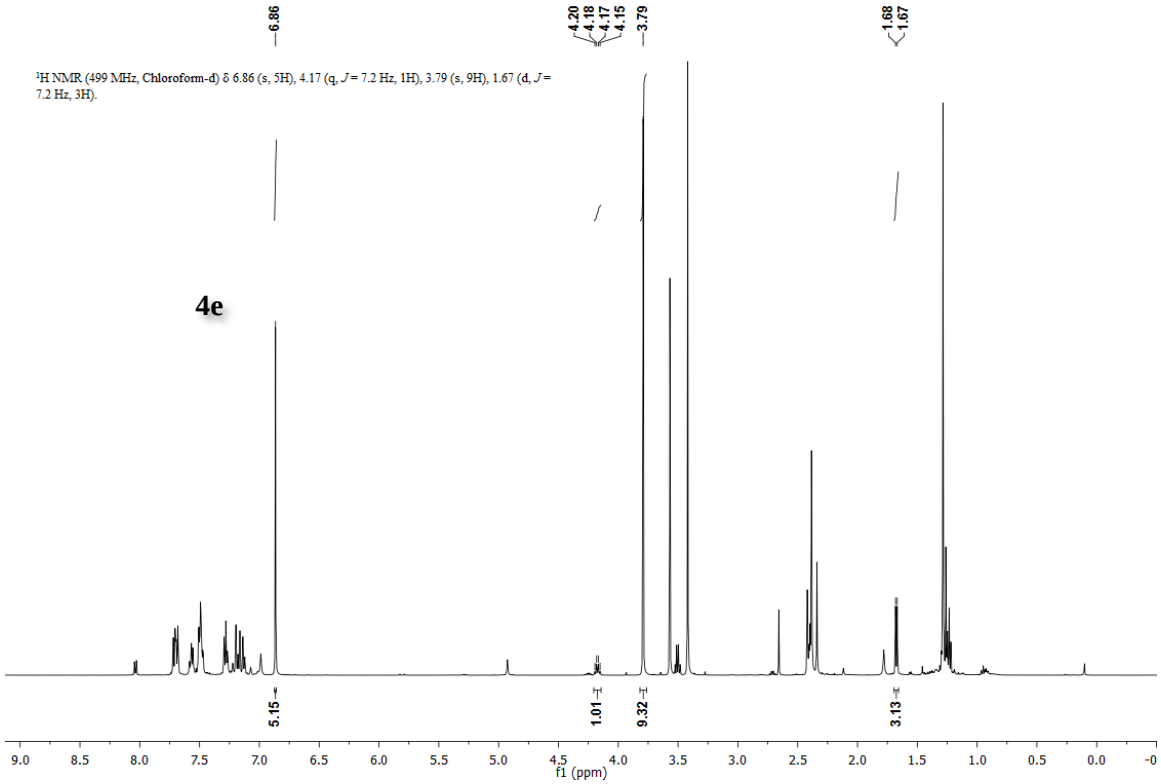

6.87
3.80
2.52
2.51
2.49
2.48
1.39
1.38
¹H NMR (499 MHz, Chloroform-d) δ 6.87 (s, 3H), 3.80 (s, 4H), 2.50 (q, J = 7.3 Hz, 1H), 1.39 (d, J = 7.5 Hz, 3H).
2ad
2.56
4.40
1.00
2.97
f1 (ppm)

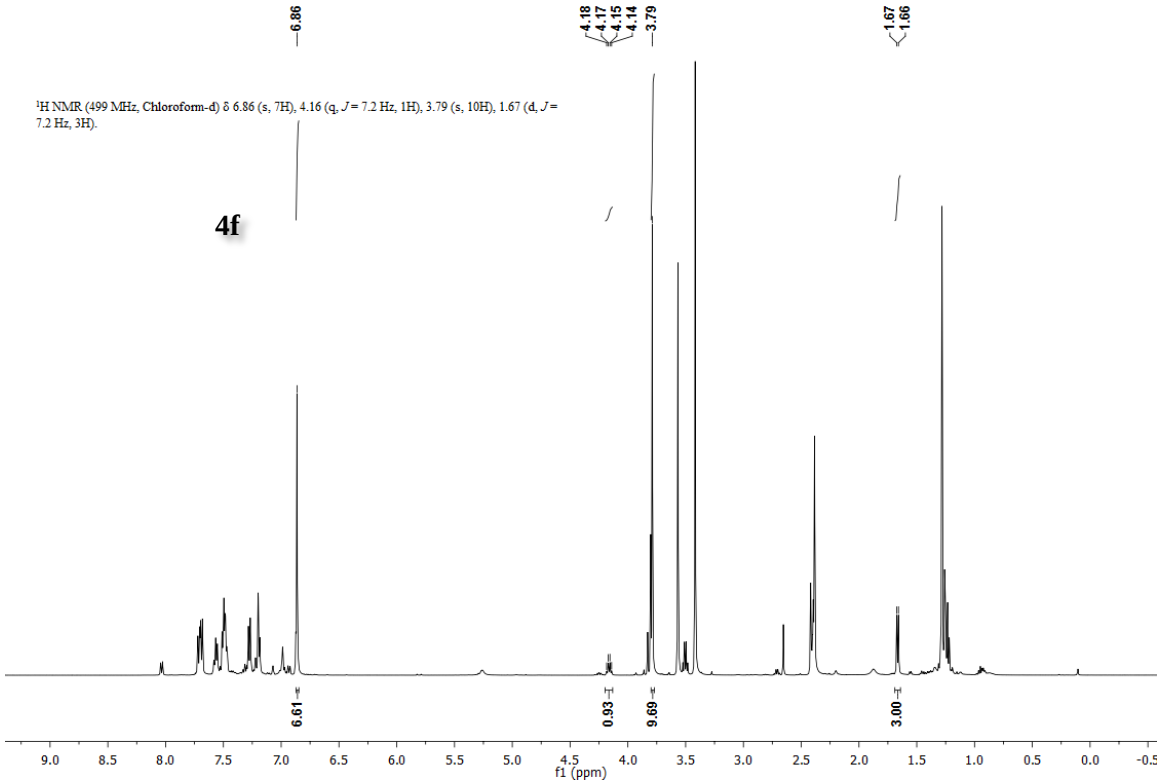

6.85
4.21
4.19
4.18
4.16
3.78
1.68
1.67
^{1}H NMR (499 MHz, Chloroform-d) δ 6.85 (s, 4H), 4.18 (q, J = 7.2 Hz, 1H), 3.78 (s, 6H), 1.68 (d, J = 7.2 Hz, 3H).
4a
3.74
0.94
6.38
3.00
f1 (ppm)

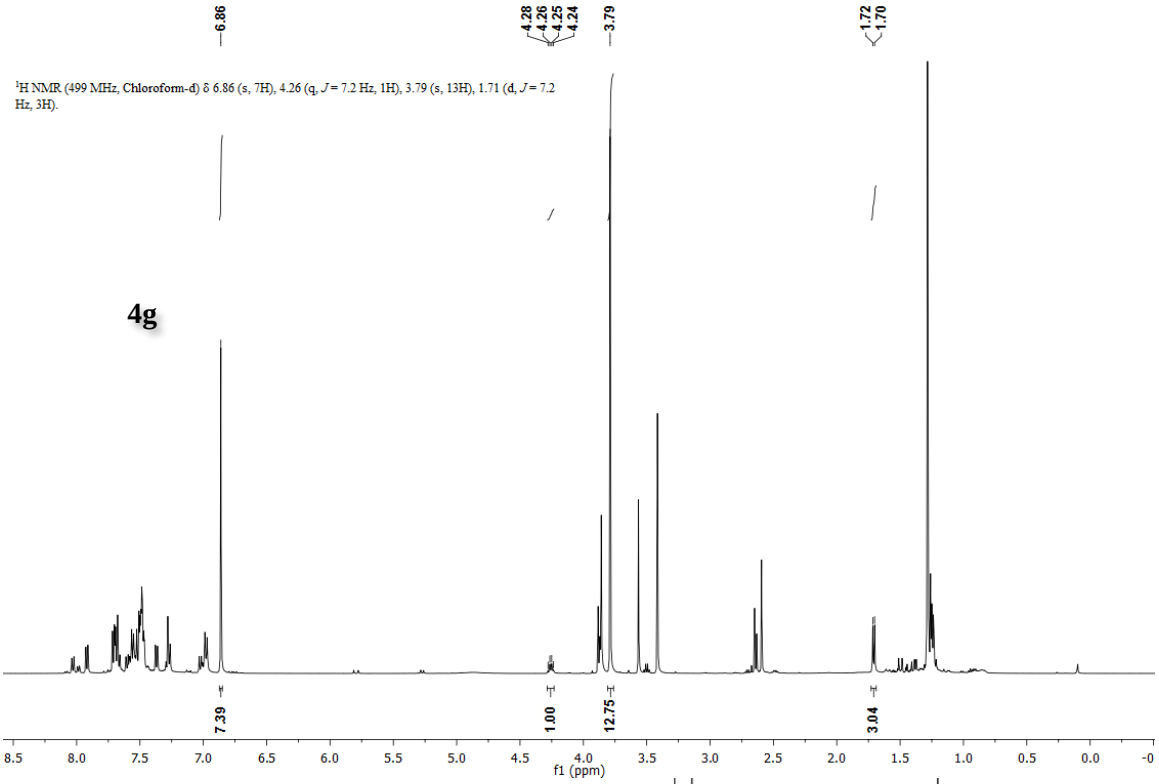

6.77
4.14
4.12
4.11
4.09
3.69
1.60
1.59
^{1}H NMR (499 MHz, Chloroform-d) δ 6.77 (s, 5H), 4.11 (q, J = 7.3 Hz, 1H), 3.69 (s, 9H), 1.59 (d, J = 7.2 Hz, 3H).
4b
5.32
1.12
9.03
3.00
f1 (ppm)

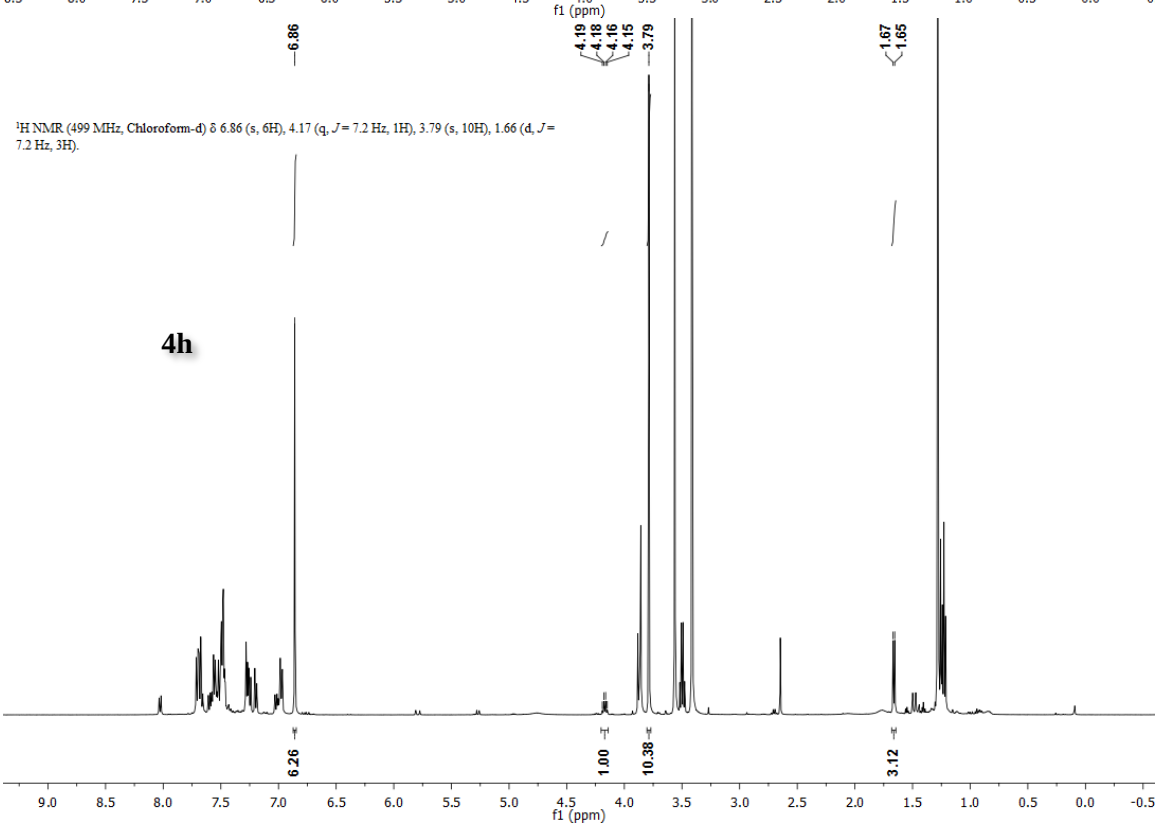

6.76
4.11
4.09
4.07
4.06
3.69
1.58
1.57
¹H NMR (400 MHz, Benzene-d6) δ 6.76 (s, 5H), 4.08 (q, J = 7.2 Hz, 1H), 3.69 (s, 7H), 1.58 (d, J = 7.2 Hz, 3H).
4c
4.90
1.00
6.77
2.84
f1 (ppm)

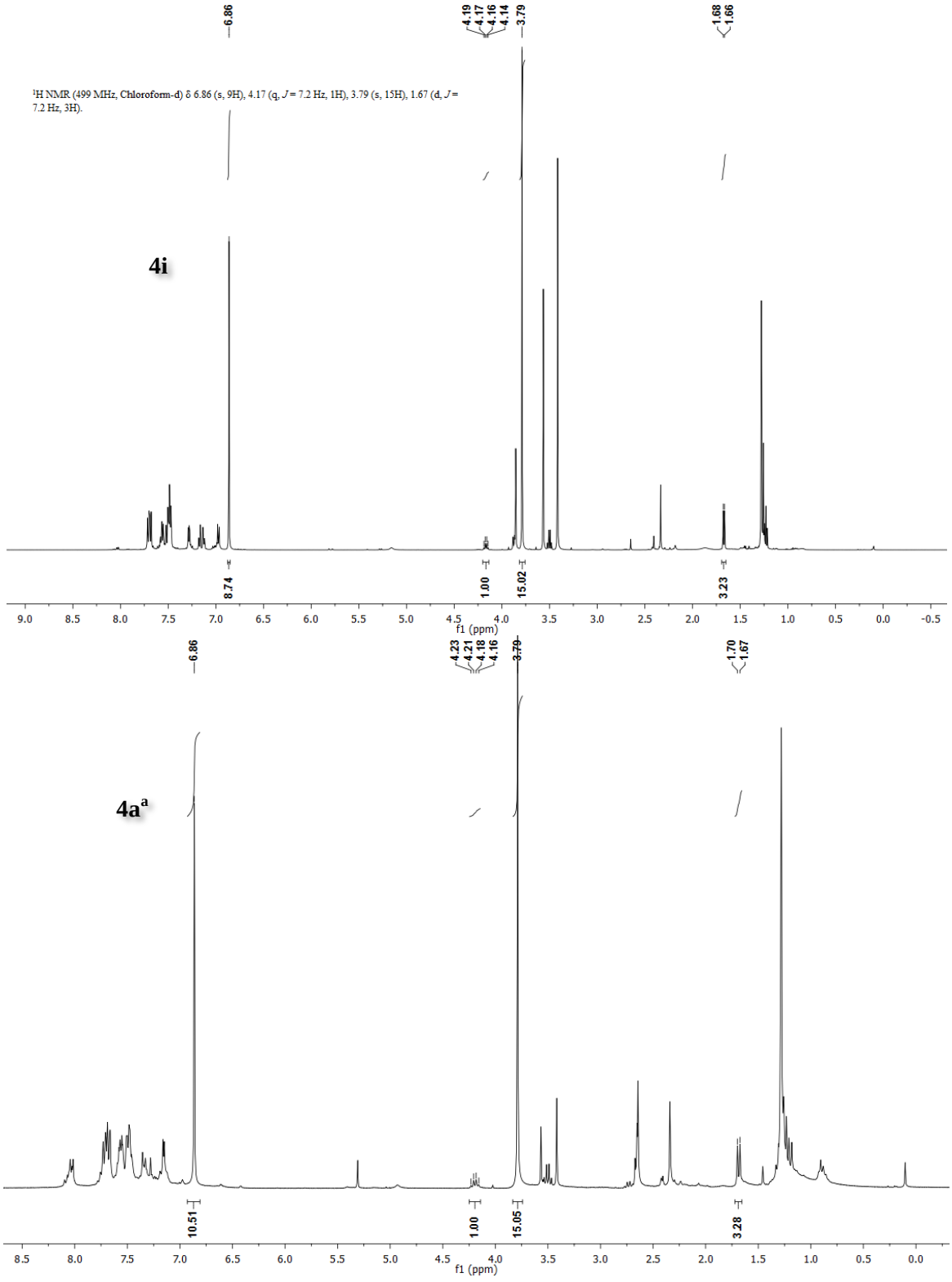

6.86
4.28
4.27
4.26
4.25
4.25
4.24
3.79
1.72
1.70
¹H NMR (499 MHz, Chloroform-d) δ 6.86 (s, 6H), 4.26 (q, J = 6.9 Hz, 1H), 3.79 (s, 10H), 1.71 (d, J = 7.2 Hz, 3H).
4d
5.93
1.11
10.08
3.00
f1 (ppm)

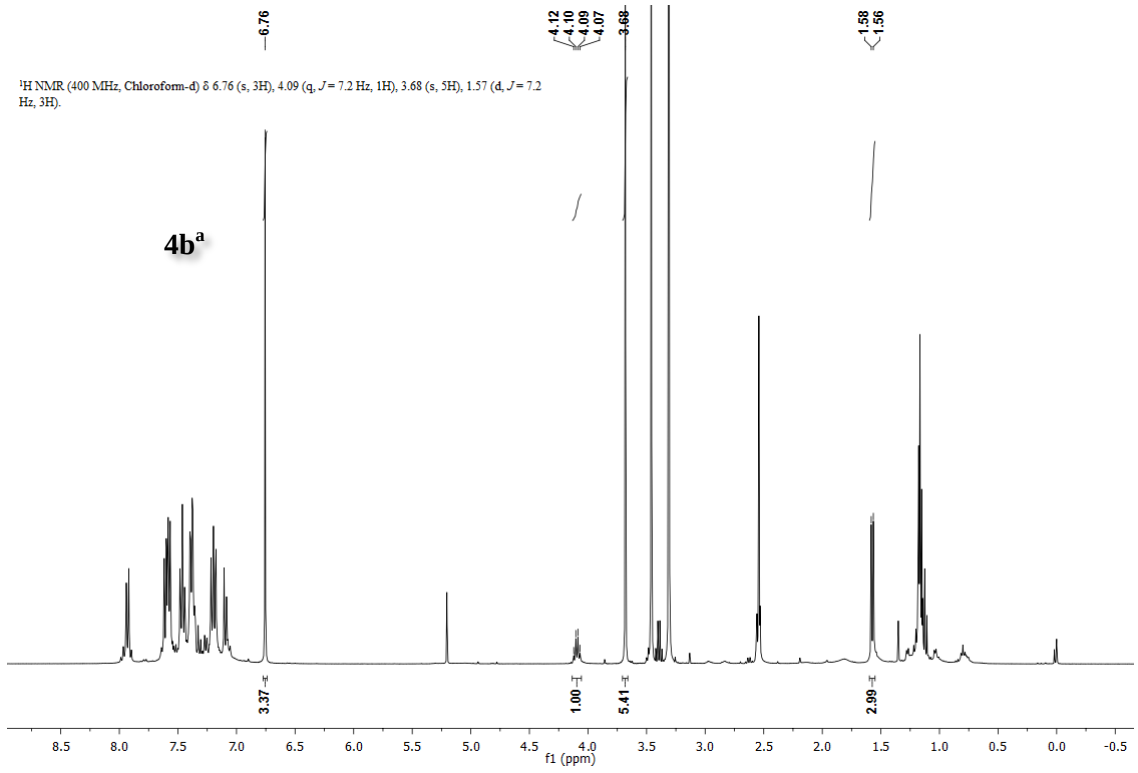

6.86
4.20
4.18
4.17
4.15
3.79
1.68
1.67
¹H NMR (499 MHz, Chloroform-d) δ 6.86 (s, 5H), 4.17 (q, J = 7.2 Hz, 1H), 3.79 (s, 9H), 1.67 (d, J = 7.2 Hz, 3H).
4e
5.15
1.01
9.32
3.13
f1 (ppm)

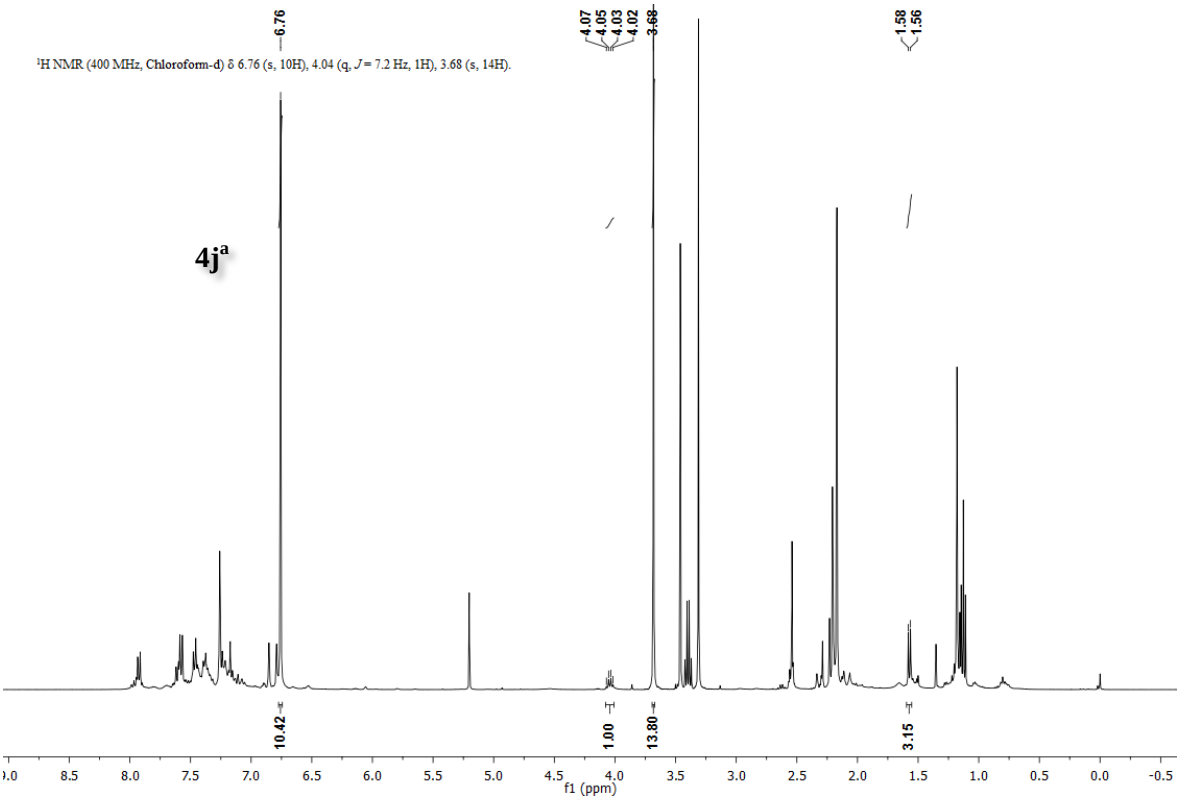

6.86
4.18
4.17
4.15
4.14
3.79
1.67
1.66
¹H NMR (499 MHz, Chloroform-d) δ 6.86 (s, 7H), 4.16 (q, J = 7.2 Hz, 1H), 3.79 (s, 10H), 1.67 (d, J = 7.2 Hz, 3H).
4f
6.61
0.93
9.69
3.00
f1 (ppm)


6.86
4.28
4.26
4.25
4.24
3.79
1.72
1.70
^{1}H NMR (499 MHz, Chloroform-d) δ 6.86 (s, 7H), 4.26 (q, J = 7.2 Hz, 1H), 3.79 (s, 13H), 1.71 (d, J = 7.2 Hz, 3H).
4g
7.39
1.00
12.75
3.04
f1 (ppm)


6.86
4.19
4.18
4.16
4.15
3.79
1.67
1.65
^{1}H NMR (499 MHz, Chloroform-d) δ 6.86 (s, 6H), 4.17 (q, J = 7.2 Hz, 1H), 3.79 (s, 10H), 1.66 (d, J = 7.2 Hz, 3H).
4h
6.26
1.00
10.38
3.12
f1 (ppm)


6.86
4.19
4.17
4.16
4.14
3.79
1.68
1.66
¹H NMR (499 MHz, Chloroform-d) δ 6.86 (s, 9H), 4.17 (q, J = 7.2 Hz, 1H), 3.79 (s, 15H), 1.67 (d, J = 7.2 Hz, 3H).
4i
8.74
1.00
15.02
3.23
f1 (ppm)
6.86
4.23
4.21
4.18
4.16
3.79
1.70
1.67
4a[a]
10.51
1.00
15.05
3.28
f1 (ppm)





[a]Reactios performed in the absence of H_2O.

References

(1) Fagnou, K.; Lautens, M. Rhodium-Catalyzed Carbon-Carbon Bond Forming Reactions of Organometallic Compounds. *Chem. Rev.* **2003**, *103*, 169-196.

(2) Rudolph, A.; Lautens, M. Secondary Alkyl Halides in Transition-Metal-Catalyzed Cross-Coupling Reactions. *Angew. Chem. Int. Ed.* **2009**, *48*, 2656-2670.

(3) Suzuki, A. Cross-Coupling Reactions Of Organoboranes: An Easy Way To Construct C-C Bonds (Nobel Lecture). *Angew. Chem. Int. Ed.* **2011**, *50*, 6722-6737.

(4) Molander, G. A.; Canturk, B. Organotrifluoroborates and Monocoordinated Palladium Complexes as Catalysts-A Perfect Combination for Suzuki–Miyaura Coupling. *Angew. Chem. Int. Ed.* **2009**, *48*, 9240-9261.

(5) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. Efficient Cross-Coupling of Secondary Alkyltrifluoroborates with Aryl Chlorides- Reaction Discovery Using Parallel Microscale Experimentation. *J. Am. Chem. Soc.* **2008**, *130*, 9257-9259.

(6) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457-2483.

(7) Hall, D. G. *Boronic Acids-Preparation, Applications in Organic Synthesis and Medicine;* John Wiley & Sons New York: 2005; pp 1-3.

(8) Frankland, E. XLVI. On a New Series of Organic Compounds Containing Boron. *J. Chem. Soc.* **1862**, *15*, 363-381.

(9) Carey, F. A.; Sundberg, R. J. *Carbanions and Other Carbon Nucleophiles;* Advanced Organic Chemistry; Springer US: 2007; pp 579-628.

(10) Grignard, V. Sur Quelques Nouvelles Combinaisons Organometallique du Magnesium et Leur Application a des Syntheses D'alcools et Hydrocarbures. *C. R. Acad. Sci. , Ser. Ilc: Chim.* **1900**, *130*, 1322-1324.

(11) Seyferth, D. The Grignard Reagents. *Organometallics* **2009**, *28*, 1598-1605.

(12) Kohei, T.; Miyaura, N. *Cross-Coupling Reactions : A Practical Guide;* Miyaura, N., Ed.; Springer: Berlin, 2002; pp 1-9.

(13) Tamura, M.; Kochi, J. K. Vinylation of Grignard Reagents. Catalysis by Iron. *J. Am. Chem. Soc.* **1971**, *93*, 1487-1489.

(14) Kochi, J. K.; Tamura, M. Alkylcopper(I) in the Coupling of Grignard Reagents with Alkyl Halides. *J. Am. Chem. Soc.* **1971**, *93*, 1485-1487.

(15) Tamura, M.; Kochi, J. K. Coupling of Grignard Reagents with Organic Halides. *Synthesis* **1971**, *6*, 303-305.

(16) Corriu, R. J. P.; Masse, J. P. Activation of Grignard Reagents by Transition-metal Complexes. A New and Simple Synthesis of *trans*-Stilbenes and Polyphenyls. *J. Chem. S. Chem. Commun.* **1972**, 144.

(17) Tamao, K.; Sumitani, K.; Kumada, M. Selective Carbon-Carbon Bond Formation by Cross-Coupling of Grignard Reagents with Organic Halides. Catalysis by Nickel-Phosphine Complexes. *J. Am. Chem. Soc.* **1972**, *94*, 4374-4376.

(18) Baba, S.; Negishi, E. A Novel Stereospecific Alkenyl-Alkenyl Cross-Coupling by a Palladium- or Nickel-Catalyzed Reaction of Alkenylalanes with Alkenyl Halides. *J. Am. Chem. Soc.* **1976**, *98*, 6729-6731.

(19) Posner, G. H. Substitution Reactions Using Organocopper Reagents. *Org. React.* **1975**, *22*, 253-400.

(20) Negishi, E. Palladium- or Nickel-Catalyzed Cross Coupling. A New Selective Method for Carbon-Carbon Bond Formation. *Acc. Chem. Res.* **1982**, *15*, 340-348.

(21) Negishi, E.; Baba, S. Novel Stereoselective Alkenyl-Aryl Coupling via Nickel-Catalysed Reaction of Alkenylanes with Aryl Halides. *J. C. S. Chem. Commun.* **1976**, 596-597.

(22) Negishi, E.; Van Horn, D. E. Selective Carbon-Carbon Bond Formation via Transition Metal Catalysis. 4. A Novel Approach to Cross-Coupling Exemplified by the Nickel-Catalyzed Reaction of Alkenylzirconium Derivatives with Aryl Halides. *J. Am. Chem. Soc.* **1977**, *99*, 3168-3170.

(23) Negishi, E.; King, A. O.; Okukado, N. Selective Carbon-Carbon Bond Formation via Transition Metal Catalysis. 3. A Highly Selective Synthesis of Unsymmetrical Biaryls and Diarylmethanes by the Nickel- or Palladium-Catalyzed Reaction of Aryl- and Benzylzinc Derivatives with Aryl Halides. *J. Org. Chem.* **1977**, *42*, 1821-1823.

(24) Miyaura, N.; Yamada, K.; Suzuki, A. A New Stereospecific Cross-Coupling by the Palladium-Catalyzed Reaction of 1-Alkenylboranes with 1-Alkenyl or 1-Alkynyl Halides. *Tetrahedron Lett.* **1979**, *20*, 3437-3440.

(25) Brown, H. C.; Rangaishenvi, M. V. Some Recent Applications of Hydroboration/Organoborane Chemistry to Heterocycles. *J. Heterocycl. Chem.* **1990**, *27*, 13-24.

(26) Whatley, A. T.; Pease, R. N. A Kinetic Study of the Diborane-Ethylene Reaction. *J. Am. Chem. Soc.* **1954**, *76*, 835-838.

(27) Stone, F. G. A.; Emeleus, H. J. The Reaction of Diborane with Some Alkene Oxides and Vinyl Compounds. *J. Chem. Soc.* **1950**, 2755-2759.

(28) Brown, H. C.; Rao, B. C. S. A New Technique for the Conversion of Olefins into Organoboranes and Related Alcohols. *J. Am. Chem. Soc.* **1956**, *78*, 5694-5695.

(29) Brown, H.; Rao, B. C. Hydroboration of Olefins. A Remarkably Fast Room-Temperature Addition of Diborane to Olefins. *J. Org. Chem.* **1957**, *22*, 1136-1137.

(30) Hargittai, B. H. C. Brown Centennial (1912–2004). *Struct Chem* **2012**, *23*, 939-941.

(31) Männig, D.; Nöth, H. Catalytic Hydroboration with Rhodium Complexes. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 878-879.

(32) Burgess, K.; Ohlmeyer, M. J. Enantioselective Hydroboration Mediated by Homochiral Rhodium Catalysts. *J. Org. Chem.* **1988**, *53*, 5178-5179.

(33) Sato, M.; Miyaura, N.; Suzuki, A. Rhodium(I)-Catalyzed Asymmetric Hydroboration of Alkenes with 1,3,2-Benzodioxaborole. *Tetrahedron Lett.* **1990**, *31*, 231-234.

(34) Hayashi, T.; Matsumoto, Y.; Ito, Y. Catalytic Asymmetric Hydroboration of Styrenes. *J. Am. Chem. Soc.* **1989**, *111*, 3426-3428.

(35) Crudden, C. M.; Hleba, Y. B.; Chen, A. C. Regio- and Enantiocontrol in the Room-Temperature Hydroboration of Vinyl Arenes with Pinacol Borane. *J. Am. Chem. Soc.* **2004**, *126*, 9200-9201.

(36) Tucker, C. E.; Davidson, J.; Knochel, P. Mild and Stereoselective Hydroborations of Functionalized Alkynes and Alkenes Using Pinacolborane. *J. Org. Chem.* **1992**, *57*, 3482-3485.

(37) Pereira, S.; Srebnik, M. Hydroboration of Alkynes with Pinacolborane Catalyzed by $HZrCp_2Cl$. *Organometallics* **1995**, *14*, 3127-3128.

(38) Pereira, S.; Srebnik, M. Transition Metal-Catalyzed Hydroboration of and CCl_4 Addition to Alkenes. *J. Am. Chem. Soc.* **1996**, *118*, 909-910.

(39) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. A Highly Active Catalyst for Palladium-Catalyzed Cross-Coupling Reactions: Room-Temperature Suzuki Couplings and Amination of Unactivated Aryl Chlorides. *J. Am. Chem. Soc.* **1998**, *120*, 9722-9723.

(40) Martin, R.; Buchwald, S. L. Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands. *Acc. Chem. Res.* **2008**, *41*, 1461-1473.

(41) Kaye, S.; Fox, J. M.; Hicks, F. A.; Buchwald, S. L. The Use of Catalytic Amounts of CuCl and Other Improvements in the Benzyne Route to Biphenyl-Based Phosphine Ligands. *Adv. Synth. Catal.* **2001**, *343*, 789-789-794.

(42) Littke, A. F.; Fu, G. C. A Convenient and General Method for Pd-Catalyzed Suzuki Cross-Couplings of Aryl Chlorides and Arylboronic Acids. *Angew. Chem. Int. Ed.* **1998**, *37*, 3387-3388.

(43) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. Air Stable, Sterically Hindered Ferrocenyl Dialkylphosphines for Palladium-Catalyzed C-C, C-N, and C-O Bond-Forming Cross-Couplings. *J. Org. Chem.* **2002**, *67*, 5553-5566.

(44) Grushin, V. V.; Alper, H. Alkali-Induced Disproportionation of Palladium(II) Tertiary Phosphine Complexes, $[L_2PdCl_2]$, to LO and Palladium(0). Key Intermediates in the Biphasic Carbonylation of ArX Catalyzed by $[L_2PdCl_2]$. *Organometallics* **1993**, *12*, 1890-1901.

(45) Lam, K. C.; Marder, T. B.; Lin, Z. DFT Studies on the Effect of the Nature of the Aryl Halide Y-C_6H_4-X on the Mechanism of Its Oxidative Addition to Pd^0L versus Pd^0L_2. *Organometallics* **2007**, *26*, 758-760.

(46) Amatore, C. A.; Pfluger, F. Mechanism of Oxidative Addition of Palladium(0) with Aromatic Iodides in Toluene, Monitored at Ultramicroelectrodes. *Organometallics* **1990**, *9*, 2276-2282.

(47) Barrios-Landeros, F.; Hartwig, J. F. Distinct Mechanisms for the Oxidative Addition of Chloro-, Bromo-, and Iodoarenes to a Bisphosphine Palladium(0) Complex with Hindered Ligands. *J. Am. Chem. Soc.* **2005**, *127*, 6944-6945.

(48) Braga, A. A. C.; Morgon, N. H.; Ujaque, G.; Maseras, F. Computational Characterization of the Role of the Base in the Suzuki-Miyaura Cross-Coupling Reaction. *J. Am. Chem. Soc.* **2005**, *127*, 9298-9307.

(49) Schmidt, A.; Kurokhtina, A.; Larina, E. Role of a base in Suzuki-Miyaura reaction. *Russ. J. of Gen. Chem.* **2011**, *81*, 1573-1574.

(50) Carrow, B. P.; Hartwig, J. F. Distinguishing Between Pathways for Transmetalation in Suzuki-Miyaura Reactions. *J. Am. Chem. Soc.* **2011**, *133*, 2116-2119.

(51) Amatore, C.; Jutand, A.; Le Duc, G. Kinetic Data for the Transmetalation/Reductive Elimination in Palladium-Catalyzed Suzuki–Miyaura Reactions: Unexpected Triple Role of Hydroxide Ions Used as Base. *Chem. Eur. J.***2011**, *17*, 2492-2503.

(52) Amatore, C.; Jutand, A.; Le Duc, G. Mechanistic Origin of Antagonist Effects of Usual Anionic Bases (OH^-, CO_3^{2-}) as Modulated by Their Countercations (Na^+, Cs^+, K^+) in Palladium-Catalyzed Suzuki-Miyaura Reactions. *Chem. Eur. J.* **2012**, *18*, 6616-6625.

(53) Sajith, P. K.; Suresh, C. H. Mechanisms of Reductive Eliminations in Square Planar Pd(II) Complexes: Nature of Eliminated Bonds and Role of trans Influence. *Inorg. Chem.* **2011**, *50*, 8085-8093.

(54) Moravskiy, A.; Stille, J. K. Mechanisms of 1,1-Reductive Elimination from Palladium: Elimination of Ethane from Dimethylpalladium(II) and Trimethylpalladium(IV). *J. Am. Chem. Soc.* **1981**, *103*, 4182-4186.

(55) García-Melchor, M.; Ujaque, G.; Maseras, F.; Lledós, A. Theoretical Evaluation of Phosphine Effects in Cross-Coupling Reactions. **2011**, *37*, 57-84.

(56) Fairlamb, I. J. S. π-Acidic Alkene Ligand Effects in Pd-catalysed Cross-Coupling Processes: Exploiting the Interaction of Dibenzylidene acetone (dba) and Related Ligands with Pd(0) and Pd(II). *Org. Biomol. Chem.* **2008**, *6*, 3645-3656.

(57) Suzuki, A.; Yanagi, T.; Miyaura, N. The Palladium-Catalyzed Cross-Coupling Reaction of Phenylboronic Acid with Haloarenes in the Presence of Bases. *Synth. Commun.* **1981**, 513-519.

(58) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Sato, M.; Suzuki, A. Palladium-Catalyzed Inter- and Intramolecular Cross-Coupling Reactions of B-alkyl-9-borabicyclo[3.3.1]nonane Derivatives with 1-halo-1-alkenes or Haloarenes. Syntheses of Functionalized Alkenes, Arenes, and Cycloalkenes via a Hydroboration-Coupling Sequence. *J. Am. Chem. Soc.* **1989**, *111*, 314-321.

(59) Molander, G.; Ito, T. Cross-Coupling Reactions of Potassium Alkyltrifluoroborates with Aryl and 1-Alkenyl Trifluoromethanesulfonates. *Org. Lett.* **2001**, *3*, 393-396.

(60) Saito, B.; Fu, G. C. Alkyl-Alkyl Suzuki Cross-Couplings of Unactivated Secondary Alkyl Halides at Room Temperature. *J. Am. Chem. Soc.* **2007**, *129*, 9602-9603.

(61) Littke, A. F.; Dai, C.; Fu, G. C. Versatile Catalysts for the Suzuki Cross-Coupling of Arylboronic Acids with Aryl and Vinyl Halides and Triflates under Mild Conditions. *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028.

(62) Rubina, M.; Rubin, M.; Gevorgyan, V. Catalytic Enantioselective Hydroboration of Cyclopropenes. *J. Am. Chem. Soc.* **2003**, *125*, 7198-7199.

(63) Hoogenband, A. v. d.; Lange, J. H. M.; Terpstra, J. W.; Koch, M.; Visser, G. M.; Visser, M.; Korstanje, T. J.; Jastrzebski, J. T. B. H. Ruphos-Mediated Suzuki Cross-Coupling of Secondary Alkyl Trifluoroborates. *Tetrahedron Lett.* **2008**, *49*, 4122-4124.

(64) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. Cross Coupling Reactions of Chiral Secondary Organoboronic Esters With Retention of Configuration. *J. Am. Chem. Soc.* **2009**, *131*, 5024-5025.

(65) Ohmura, T.; Awano, T.; Suginome, M. Stereospecific Suzuki-Miyaura Coupling of Chiral α-(Acylamino)benzylboronic Esters with Inversion of Configuration. *J. Am. Chem. Soc.* **2010**, *132*, 13191-13193.

(66) Glasspoole, B. W.; Ghozati, K.; Moir, J. W.; Crudden, C. M. Suzuki-Miyaura Cross-Couplings of Secondary Allylic Boronic Esters. *Chem. Commun.* **2012**, *48*, 1230-1232.

(67) Tobisu, M.; Chatani, N. Devising Boron Reagents for Orthogonal Functionalization through Suzuki–Miyaura Cross-Coupling. *Angew. Chem. Int. Ed.* **2009**, *48*, 3565-3568.

(68) Taylor, R. H.; Felpin, F. Suzuki-Miyaura Reactions of Arenediazonium Salts Catalyzed by Pd(0)/C. One-Pot Chemoselective Double Cross-Coupling Reactions. *Org. Lett.* **2007**, *9*, 2911-2914.

(69) Antelo Miguez, J. M.; Adrio, L. A.; Sousa-Pedrares, A.; Vila, J. M.; Hii, K. K. A Practical and General Synthesis of Unsymmetrical Terphenyls. *J. Org. Chem.* **2007**, *72*, 7771-7774.

(70) Daykin, L. M.; Siddle, J. S.; Ankers, A. L.; Batsanov, A. S.; Bryce, M. R. Iterative and Regioselective Cross-Couplings of 2-chloro-3,4-diiodopyridine Leading to 2,3,4-triheteroarylpyridines. *Tetrahedron* **2010**, *66*, 668-675.

(71) Noguchi, H.; Hojo, K.; Suginome, M. Boron-Masking Strategy for the Selective Synthesis of Oligoarenes via Iterative Suzuki-Miyaura Coupling. *J. Am. Chem. Soc.* **2007**, *129*, 758-759.

(72) Noguchi, H.; Shioda, T.; Chou, C.; Suginome, M. Differentially Protected Benzenediboronic Acids: Divalent Cross-Coupling Modules for the Efficient Synthesis of Boron-Substituted Oligoarenes. *Org. Lett.* **2008**, *10*, 377-380.

(73) Iwadate, N.; Suginome, M. Synthesis of B-Protected β-Styrylboronic Acids via Iridium-Catalyzed Hydroboration of Alkynes with 1,8-Naphthalenediaminatoborane Leading to Iterative Synthesis of Oligo(phenylenevinylene)s. *Org. Lett.* **2009**, *11*, 1899-1902.

(74) Gillis, E. P.; Burke, M. D. A Simple and Modular Strategy for Small Molecule Synthesis: Iterative Suzuki-Miyaura Coupling of B-Protected Haloboronic Acid Building Blocks. *J. Am. Chem. Soc.* **2007**, *129*, 6716-6717.

(75) Iwadate, N.; Suginome, M. Differentially Protected Diboron for Regioselective Diboration of Alkynes: Internal-Selective Cross-Coupling of 1-Alkene-1,2-diboronic Acid Derivatives. *J. Am. Chem. Soc.* **2010**, *132*, 2548-2549.

(76) Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. Chemoselective and Regiospecific Suzuki Coupling on a Multisubstituted sp^3-Carbon in 1,1-Diborylalkanes at Room Temperature. *J. Am. Chem. Soc.* **2010**, *132*, 11033-11035.

(77) Wright, S. W.; Hageman, D. L.; McClure, L. D. Fluoride-Mediated Boronic Acid Coupling Reactions. *J. Org. Chem.* **1994**, *59*, 6095-6097.

(78) Andersen, N. G.; Maddaford, S. P.; Keay, B. A. A Modified in Situ Suzuki Cross-Coupling of Haloarenes for the Preparation of C_2-Symmetric Biaryls. *J. Org. Chem.* **1996**, *61*, 9556-9559.

(79) Grushin, V. V. Thermal Stability, Decomposition Paths, and Ph/Ph Exchange Reactions of $[(Ph_3P)_2Pd(Ph)X]$ (X = I, Br, Cl, F, and HF_2). *Organometallics* **2000**, *19*, 1888-1900.

(80) Kamei, T.; Itami, K.; Yoshida, J. Catalytic Carbometalation/Cross-Coupling Sequence across Alkynyl(2-pyridyl)silanes Leading to a Diversity-Oriented Synthesis of Tamoxifen-Type Tetrasubstituted Olefins. *Adv. Synth. and Catal.* **2004**, *346*, 1824-1835.

(81) Oderinde, M. unpublished results.

(82) Glasspoole, B. W. The Chemoselective, Enantiospecific Cross-Coupling of Secondary Boronic Esters and the Stability of Mesoporous Silica Supports for Pd Catalysis, Queen's University, Ph.D Thesis, 2011.

(83) Ishiyama, T.; Yamamoto, M.; Miyaura, N. Diboration of Alkenes with Bis(pinacolato)diboron Catalysed by a Platinum(0) Complex. *Chem. Commun.* **1997**, 689-690.

(84) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals (4th Edition);* Elsevier: 1996; , pp 1-523.

(85) Cui, C.; Bonder, E. M.; Jäkle, F. Weakly Coordinating Amphiphilic Organoborate Block Copolymers. *J. Am. Chem. Soc.* **2010**, *132*, 1810-1812.

(86) Anderson, M. P.; Pignolet, L. H. Rhodium Complexes of 1,4-bis(diphenylphosphino)butane. Crystal and Molecular Structures of $[Rh(dppb)_2]BF_4 \cdot C_4H_{10}O$ and $[Rh(cod)(dppb)]BF_4$. *Inorg. Chem.* **1981**, *20*, 4101-4107.

(87) Clary, J. W.; Rettenmaier, T. J.; Snelling, R.; Bryks, W.; Banwell, J.; Wipke, W. T.; Singaram, B. Hydride as a Leaving Group in the Reaction of Pinacolborane with Halides under Ambient Grignard and Barbier Conditions. One-Pot Synthesis of Alkyl, Aryl, Heteroaryl, Vinyl, and Allyl Pinacolboronic Esters. *J. Org. Chem.* **2011**, *76*, 9602-9610.

(88) Qin, Y.; Sukul, V.; Pagakos, D.; Cui, C.; Jäkle, F. Preparation of Organoboron Block Copolymers via ATRP of Silicon and Boron-Functionalized Monomers. *Macromolecules* **2005**, *38*, 8987-8990.

(89) Okuma, K.; Sakai, O.; Shioji, K. Wittig Reaction by Using DBU as a Base. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1675-1676.

(90) Paptchikhine, A.; Cheruku, P.; Engman, M.; Andersson, P. G. Iridium-Catalyzed Enantioselective Hydrogenation of Vinyl Boronates. *Chem. Commun.* **2009**, 5996-5998.