IRIDIUM CATALYZED C–H ACTIVATION/BORYLATION OF AROMATIC/
HETEROAROMATIC SUBSTRATES AND ITS APPLICATION IN SMALL
MOLECULE SYNTHESIS

By

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ABSTRACT

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Catalytic transformation of carbon-hydrogen bonds to other functional groups represents a long-standing challenge in homogeneous and heterogeneous catalysis. The Ir-catalyzed C–H activation/borylation has emerged as a useful method for synthesizing various aryl and heteroaryl boronic esters with regiochemistry complimentary to traditional methods and tolerant of various functional groups. The steric dominance of C–H activation/borylation has allowed for the synthesis of new aromatic building blocks which were previously unaccessible or hard to synthesize.

The compatibility with Boc protecting groups allows for manipulating the regioselectivities for Ir-catalyzed borylations of nitrogen heterocycles. In addition, Ir-catalyzed borylations of protected amino acids are shown to be feasible for the first time, which augurs favorably for similar functionalizations of peptides. This work also established heat as a clean agent for Boc deprotection of BPin substituted heteroarenes.

The halogen tolerance that is a hallmark of Ir C–H borylation makes it trivial to construct building blocks possessing halogen and boronate ester functionality. This unique feature of C–H borylation in combination with Suzuki coupling has allowed the synthesis of 2,3-diaryl and 3,5-diaryl thiophenes. DuP 697 a COX-2 inhibitor was synthesized in 5-steps with an overall 42% yield.

Even though protolytic deborylation is an undesired side reaction in most coupling reactions, it was used to our advantage on diborylated substrates. C–H activation/borylation coupled with deborylation has proved to be powerful method in synthesizing pinacol boronic esters, with regiochemistry complementary to the previously known methods and tolerant of a variety of functional groups. The mildness and stereospecificity of the reactions has allowed us to use deuteration and deborylation on advanced molecules like pharmaceuticals.

N-Methyliminodiacetic acid protection has been used to attenuate the reactivity of the diboron compounds. It has allowed us to desymmetrize diboron compounds generated from Ir-catalyzed C–H activation/borylation and Miyaura borylation. The selective coupling of BPin leaving the BMIDA intact allows for the iterative cross-coupling. The utility of these substrates with two or more reaction sites in multi transformations has been demonstrated. This allows for the synthesis of complex organic molecules from simple building blocks.

To my beloved parents

ACKNOWLEDGMENTS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF SYMBOLS AND ABBREVIATIONS

Ar   aryl

BCat   catecholatoboryl ($-BO_2C_6H_4$)

Boc   *tert*-butoxycarbonyl

BPin   pinacolatoboryl ($-BO_2C_6H_{12}$)

B_2Pin_2 bis-pinacolato-di-boron ($C_{12}H_{24}B_2O_4$)

bpy   bi-pyridyl

COD   1,5-cyclooctadiene

COE   cyclooctene

conc   concentrated

Cp*   pentamethylcyclopentadienyl

^{o}C   degree Celcius

d   doublet

dtbpy   di-*tert*-butyl-bi-pyridyl

dd   doublet of doublet

DFT   density functional theory

DMG   directed metalation group

dmpe   1,2-bis-(dimethylphosphino)-ethane

D*o*M   directed *ortho* metalation

dppe   1,2-bis-(diphenylphosphino)-ethane

dppf   1,1'-bis-(diphenylphosphino)-ferrocene

DuP	DuPont
EAS	electrophilic aromatic substitution
Eq	equation
equiv	equivalent
GC	gas chromatography
GC-FID	gas chromatography-flame ionization detector
GC-MS	gas chromatography-mass spectroscopy
h	hour
HBDan	1,8-napthalenediaminatoborane
HBPin	pinacolborane
Hz	Hertz
Ind	indenyl (C_9H_7)
Ir	iridium
IR	infrared
J	coupling constant
kcal	kilocalorie
LDA	lithium-di-isopropylamide
m	multiplet
m	*meta*
n	normal (straight chain hydrocarbon)
Me	methyl
MIDA	*N*-methyliminodiacetic acid
min	minute

mL	milliliter
mmol	millimole
mol	mole
MTBE	methyl-*tert*-butyl ether
NMR	nuclear magnetic resonance
o	*ortho*
OMe	methoxy (OCH_3)
p	*para*
Pd	palladium
PMe_3	trimethyl phosphine
^{i}Pr	*iso*-propyl
q	quartet
s	singlet
t	triplet
THF	tetrahydrofuran
TIPS	tri-isopropylsilyl
TONs	turn over numbers
TPy	tetra-2-pyridinylpyrazine
δ	delta, ppm for NMR spectroscopy
μL	microlitre

CHAPTER 1

Introduction

C-H Activation and Functionalization of Aromatic and Heteroaromatic Compounds

The catalytic transformation of carbon-hydrogen bonds to other functional groups represents a long-standing challenge in homogeneous and heterogeneous catalysis as C-H bonds are the most ubiquitous chemical linkages in Nature. It has been a topic of great interest as hydrocarbons make up a large fraction of the world's supply of petroleum products and the possibility of using this inexpensive source of C_nH_m compounds to make practical organic molecules is a serious economic driving force. Unfortunately, the inert nature of C-H bonds towards many organic transformations makes this objective a challenge. The lack of reactivity of hydrocarbon C-H bonds can be attributed to their high bond dissociation energies (typically 90-104 kcal/mol), lack of polarity and very low acidity or basicity. Despite the fact that C-H bonds are difficult to cleave, functionalization of C-H bonds especially sp^2 C-H bonds is known.

Since its inception in 1825, when Faraday[1] reported that benzene and nitric acid react, but Mitscherlich[2] was the first to determine that nitrobenzene was the product in 1834, electrophilic aromatic substitution (EAS) has evolved as a preferred method for elaborating aromatic systems. The number, type and relative placement of substituents govern regioselectivities for EAS in the aromatic system. Substituents fall under two categories,[3] *ortho/para*-directors that activate the aromatic system towards electrophilic substitution and *meta*-directors that operate by virtue of *ortho/para* deactivation. The major limitation of EAS is the lack of regioselectivity in substitution. Figure 1.1 shows

the nine possible combinations of disubstituted benzene possessing *ortho/para* and/or *meta*-directors and only one of the nine combinations offer efficient regioselectivity towards electrophilic aromatic substitution. A specific example is the nitration of anisole,[4] which results in a mixture of *ortho* and *para* substituted products with essentially no preference for the *meta* substitution.
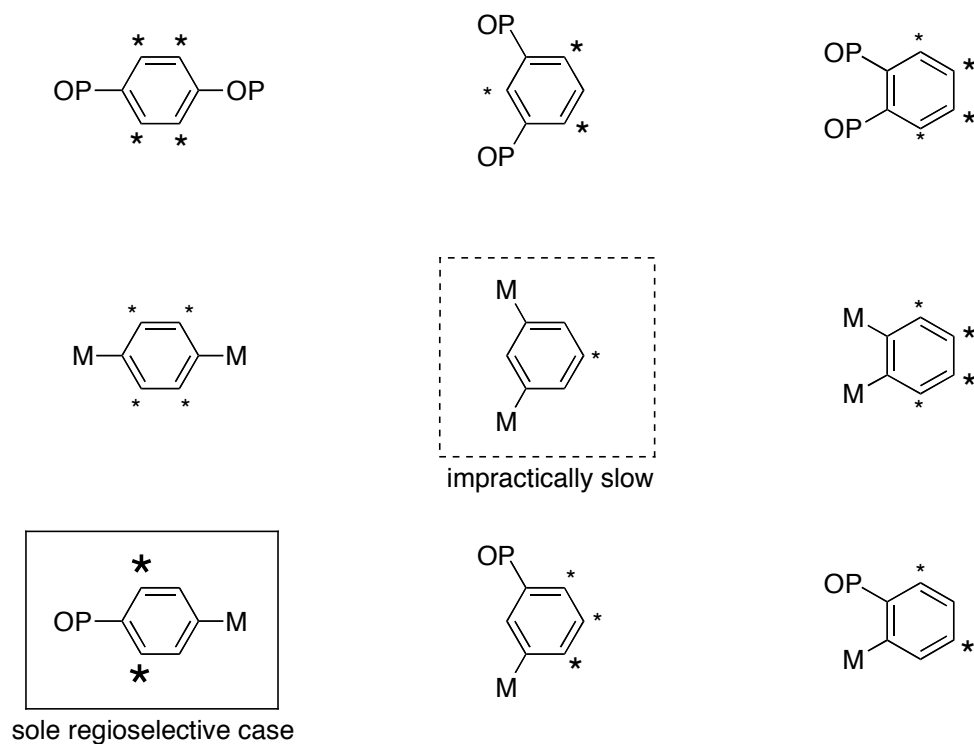
Figure 1.1 Regioselectivities for EAS of disubstituted benzenes possessing *ortho/para* and/or *meta*-directors. The relative rates at specific C-H positions are indicated by the size of the asterisks. Cases enclosed in boxes indicate single isomer selectivities.

Overcoming some of the limitations of EAS is the directed *ortho* metallation (D*o*M) discovered by Gilman[5] and Wittig[6] whom independently found that *n*-BuLi selectively deprotonates ortho to the methoxy group in anisole. The availability of several lithium reagents and efforts from several research groups have provided stimulus in

accelerating the pace of application of this methodology.[7] This research has allowed in including a variety of functional groups such as tertiary amines, fluorides, carbamates, protected phenols, carbonates and amides, together called the directed metalation groups (DMGs), that interact directly with the lithium reagent effecting metalation ortho to the substituent. Several groups that are *meta*-directing in EAS are strong DMGs, providing *ortho*-functionalization that complements EAS. Selectivity in D*o*M of arenes with two DMGs is high when the DMGs are meta to each other. Whereas in the case of 1,2 and 1,4-substituted benzenes the regioselectivity depends on the strength of the DMGs (Figure 1.2).
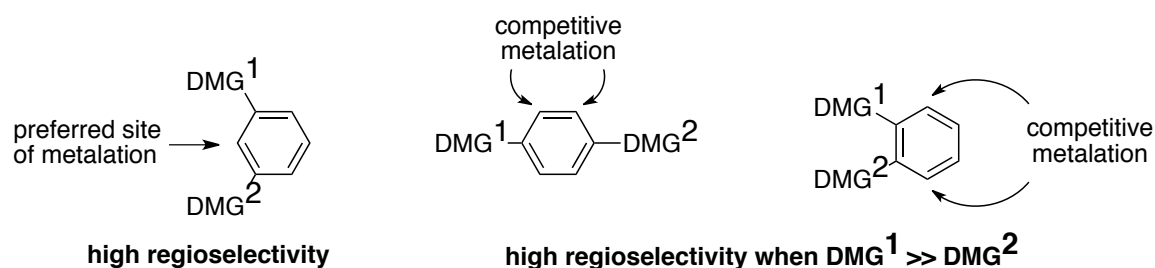
Figure 1.2 Regiochemical outcomes for the D*o*M of three possible isomers of benzene bearing two different DMG groups.

Despite its success, D*o*M has limitations. The most significant being the stoichiometric strong base required to effect the deprotonation. The presence of heavier halogens can result in transmetallation in preference to deprotonation, giving mixtures of products. Finally, many D*o*M protocols require cryogenic cooling.

Transition metal mediated C-H functionalization

Chatt and Davidson in 1965 first demonstrated metal insertion into a C-H bond.[8] Bis(dimethylphosphino)ethane complexes of Ruthenium were shown to oxidatively add

naphthalene and the Ru-H bond in the napthyl complex is formed by attack at the 2-position in naphthalene (Scheme 1.1). Similar, Fe napthylhydride complex was used by Ittel in 1976,[9] to report an important observation when this complex was dissolved in excess of toluene (Scheme 1.2). This complex was capable to activate the aryl C-H bonds in toluene, giving a statistical mixture of *meta* and *para*-tolyl complexes with no indication of the *ortho*-tolyl isomer. This reaction was the first proof that regioselectivity in transition metal mediated C-H activation is sterically directed and is substantially different than those seen in EAS and other aromatic substitutions.

Scheme 1.1 Oxidative addition of naphthalene C-H bonds to $Ru(dmpe)_2$.
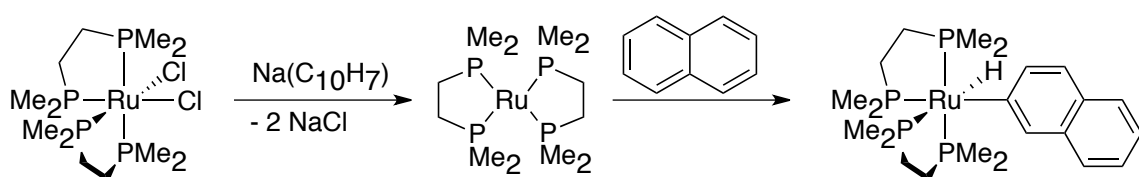
Scheme 1.2 Sterically directed C-H activation of toluene.
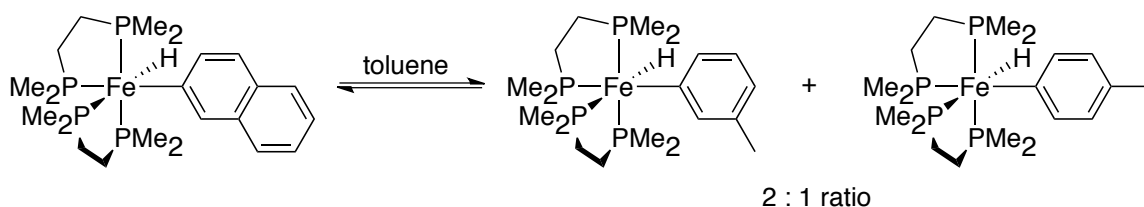
Discoveries in the intervening decade brought tremendous insight from the mechanistic studies of transition metal insertions to C-H bonds. In order to catalyze the functionalization of C–H bonds by a transition metal complex, the initial activation step should be followed by a secondary functionalization step. It became clear that activation of C-H bonds is not the real challenge and that functionalization has proved to be more difficult than the activation step. In 1986, Jones and Kosar reported a Ru-catalyzed C-H

bond activation for the synthesis of indole (Scheme 1.3).[10] They have shown

Ru(dmpe)$_2$H$_2$ can undergo intramolecular isocyanide insertion into a Ru-C bond that

arises from the C-H oxidative addition of 2,6-xylyl isocyanide generating 7-methyl

indole.

Scheme 1.3 Catalytic cycle for 7-methylindole synthesis via Ru-catalyzed C-H

activation.

CN−Aryl

[Ru]

[Ru]−C≡N−

C-H activation

[Ru] = Ru(Me$_2$PCH$_2$CH$_2$PMe$_2$)$_2$

[Ru]

[Ru]
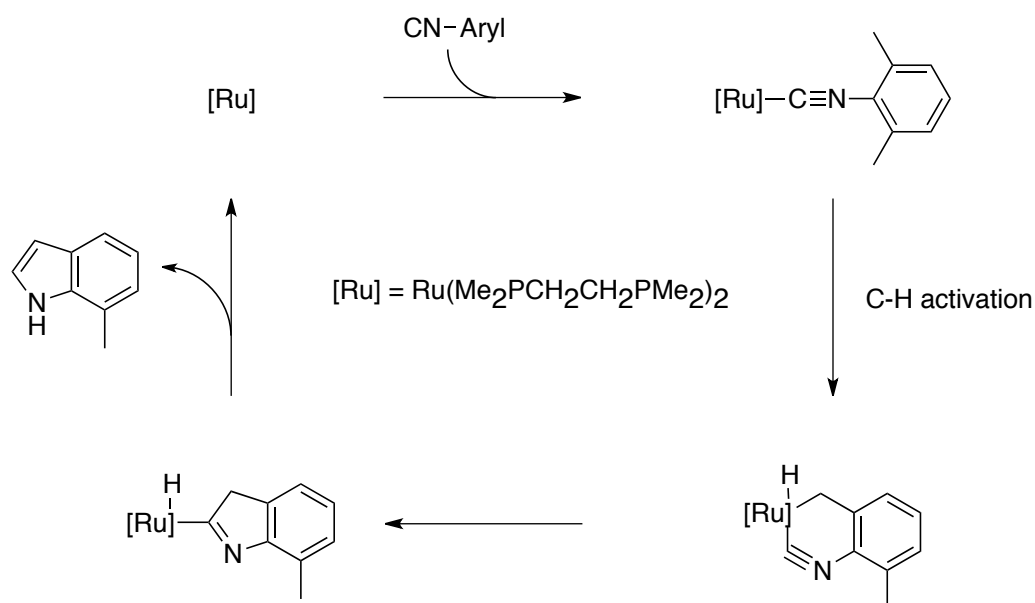
The next important contribution in C-H functionalization was the early report by

Berry and co-workers.[11] They have demonstrated the Rh-catalyzed dehydrogenative

coupling of arenes and triethylsilane, generating arylsilanes (Scheme 1.4). This

intermolecular silylation is in accordance with Ittel's observation of sterically directed

insertion into aromatic C-H bonds and is enhanced by electron withdrawing substitutents.

While the requirement for a sacrificial olefin is a minor setback, the limited substrate

scope is the primary drawback to Berry's chemistry.

Scheme 1.4 Rh-catalyzed dehydrogenative coupling for arylsilanes.
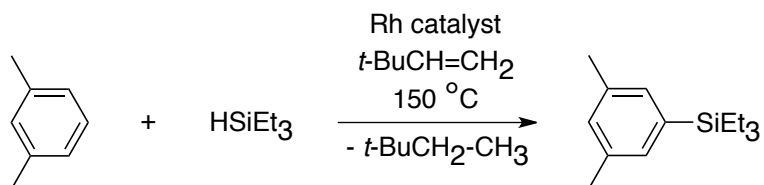
Studies concerning the fundamental properties and reaction chemistry of transition metal boryl complexes have been initiated since early 1990's. Transition metal-ligand covalent bond energies are important in understanding the catalysis. However, there have been few data available for boranes and no thermochemical data for transition metal boryl complexes until 1994. The theoretical estimation of B-H and B-C bond enthalpies reported by Rablen and Hartwig[12] gave conviction in organoborane synthesis *via* direct borylation of unsubstituted hydrocarbons. From the established thermochemical and computational data of borane reagents, the reaction in Scheme 1.5 is essentially thermoneutral.[13] Moreover, from the calculated BDE's for B-H, C-H, and B-C bonds synthesis of aryl boronic esters directly from boranes and arenes should be thermodynamically feasible.

Scheme 1.5 Thermodynamics of methane borylation with $HB(OR)_2$.

$$CH_4 \;+\; HB(OR)_2 \longrightarrow CH_3B(OR)_2 \;+\; H_2 \;\;;\;\; \Delta\, BDE = \text{-1 kcal/mol}$$

$$104\, \frac{kcal}{mol} \qquad 110\, \frac{kcal}{mol} \qquad\qquad 111\, \frac{kcal}{mol} \qquad 104\, \frac{kcal}{mol}$$
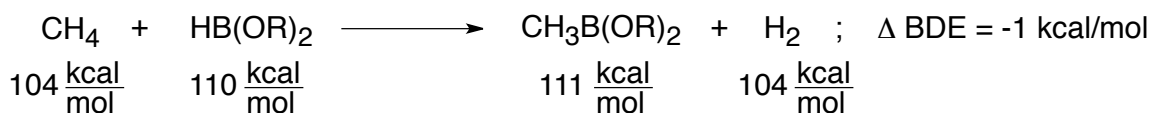
The versatility of organoboron compounds in organic chemistry renders them attractive targets for synthesis. For example, palladium catalyzed cross-coupling reactions of boronic acids or esters with aryl halides have become the most important method for the synthesis of biaryls.[14] In addition to their role in cross coupling reactions,

aryl boronic acids and esters are used for the preparation of phenols,[15] deuterated aryls,[16] aryl amines,[17] aryl ethers,[17,18] aryl halides,[19,20] potassium aryltrifluoroborates[21] and arylnitriles[22] (Figure 1.3).
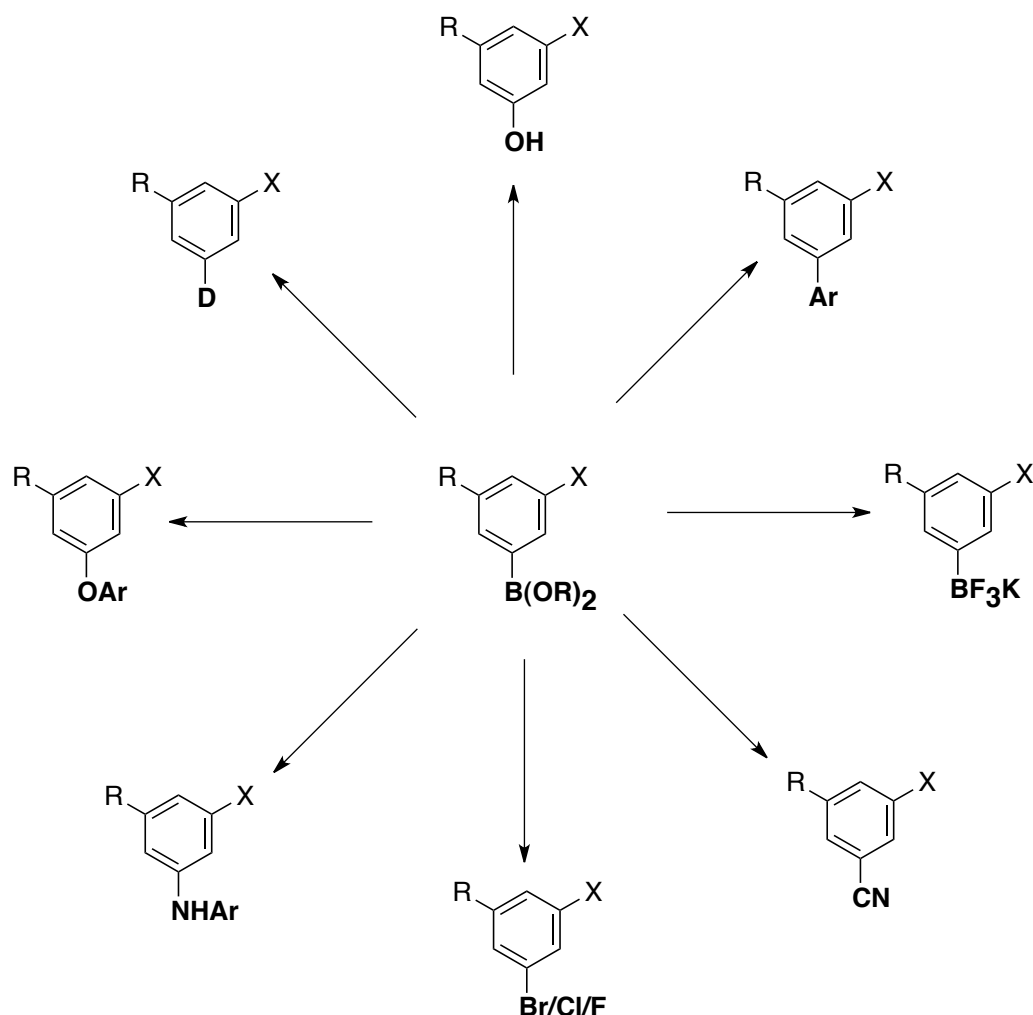
Figure 1.3 Various functional groups introduced via boronic acids and esters.

The arylboron reagents are traditionally prepared from the corresponding halide via Grignard or lithiate formation, reaction with a trialkyl borate followed by hydrolytic workup.[23] More direct route has been developed by Miyaura et al.[24] where the generation of Grignard and lithium reagents is avoided by using palladium catalysts to

effect the desired transformation from borane reagents and halogenated arenes (Scheme 1.6). While these methods can be high yielding, they rely on the availability or accessibility of an appropriately substituted aryl halide, which are typically derived from the corresponding arene via electrophilic aromatic substitution with the inherent limitations in selectivity. Thus, shorter routes that avoid the undesirable halogenated intermediates would be attractive.

Scheme 1.6 Different routes for the preparation of aryl boronic esters.
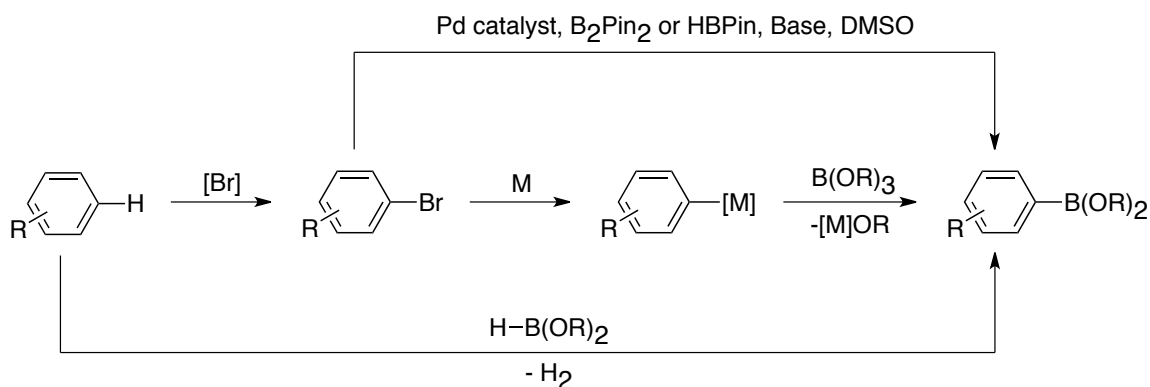
Directed *ortho* metalation followed by trapping the resulting aryl lithium reagent with trialkylborates has also been used to prepare aryl boron derivatives without the need for halogenation (Scheme 1.7).[25,26] However this method can suffer from the aforementioned limitations of D*o*M.

Scheme 1.7 Aryl boronic esters via directed *ortho* metalation
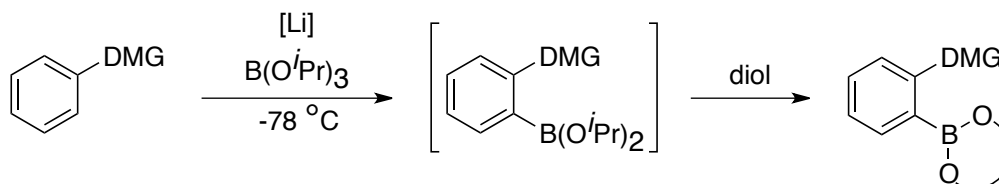
The direct borylation of non-activated C-H bonds was first described using alkanes. Initial stoichiometric reactions were followed by catalytic protocols reported by

Hartwig and coworkers.[28,29,30] In 1995, Hartwig et al.[28] reported a photochemical functionalization of arenes and alkenes with $(CO)_5Mn(BCat)$, $(CO)_5Re(BCat)$ and $CpFe(CO)_2(BCat)$ (Scheme 1.8). They have also seen that $Cp^*Fe(CO)_2(BCat')$ (Cp^* = C_5Me_5, Cat' = $1,2-O_2C_6H_2-3,5-(CH_3)_2$), $Cp^*Ru(CO)_2(BCat')$ and $Cp^*W(CO)_2(BCat')$ can undergo photochemical reaction with alkanes to give alkylboronate esters with functionalization of alkane exclusively at the terminal position.[29] Later on they developed the borylation of non-activated hydrocarbons using catalytic amounts of metal complexes.[30]

Scheme 1.8 Transition metal mediated photochemical borylation.
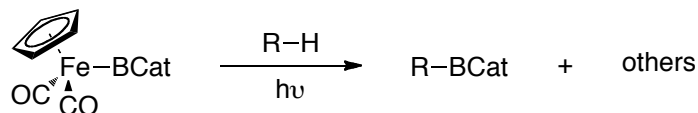
Fundamental studies on hydrocarbon activation by $Cp^*M(PMe_3)(H)_2$ (M = Rh, Ir) were described by Bergman[27,31] and Jones[32] and they have thoroughly studied the hydrocarbon oxidative addition leading to M-C bonds. As the formation of B-C bond is essentially thermoneutral, our group started studying formation of B-C bonds from M-C bonds in complexes of the type $Cp^*M(PMe_3)(H)(R)$ (M = Rh, Ir; R = H, alkyl, aryl, BPin). In 1999, our group reported the first catalytic, thermal aromatic borylation using $Cp^*Ir(PMe_3)(H)(BPin)$ as a precatalyst (Scheme 1.9).[33] With about 3 TON, this was the first demonstration of catalytic viability in C-H activation/borylation.

Scheme 1.9 First thermal catalytic aromatic borylation.

$$C_6H_6 \quad + \quad HBPin \quad \xrightarrow[\text{150 °C, 120 h}]{\text{17 mol\%}} \quad C_6H_5BPin \quad + \quad H_2$$

53% yield
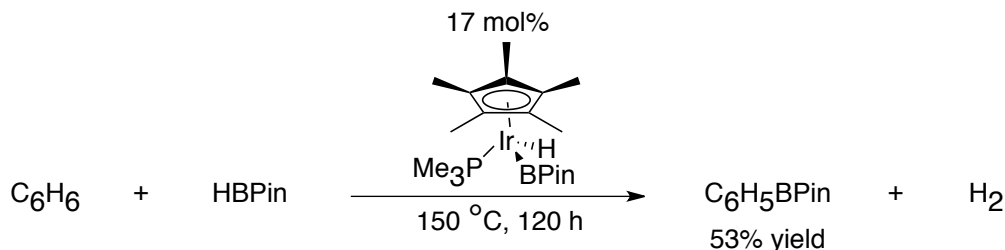
In 2000, Hartwig and co-workers reported a rhodium catalyst $Cp*Rh(\eta^4\text{-}C_6Me_6)$

that thermally catalyzes the regioselective borylation of alkanes and benzene with higher

turnover numbers.[34] This report has prompted our group to perform a comparitive study

of the $Cp*Ir(PMe_3)(H)(BPin)$ and $Cp*Rh(\eta^4\text{-}C_6Me_6)$ system (Scheme 1.10).[35] The Ir

system was more selective for the aromatic C-H bonds in the presence of weaker benzylic

C-H and aryl C-F bonds as compared to the Rh system. This report also established that

the regioselectivities were governed by sterics and were complementary to electrophilic

aromatic substitution and directed *ortho* metalation. For example, the borylation of

anisole gave a mixture of *ortho*/*meta*/*para* isomers (0.08:4.06:1.00) with *meta*-isomer

being the major product, which is complementary to EAS and D*o*M. It was also

determined that electron deficient arenes were more reactive, which was similar to

Berry's arene silation.

Scheme 1.10 Selectivities for Ir and Rh-catalyzed borylations.

[Ir]	97%	3%
[Rh]	87%	13%

[Ir]	96%	4%
[Rh]	84%	16%
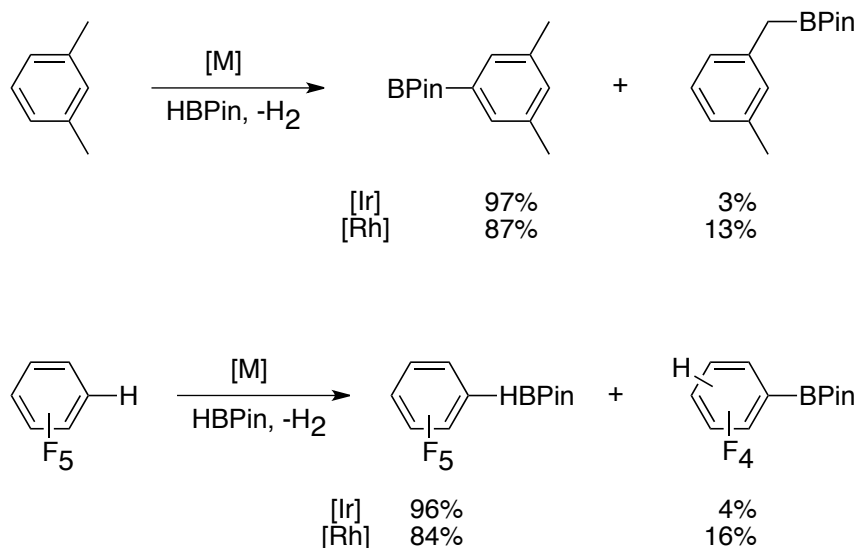
The catalytic C-H borylation can also be performed in an inert solvent using stoichiometric arenes. Our group in 2001 has shown Cp*Rh(η^4-C$_6$Me$_6$) precatalyst can selectively borylate 1,2- and 1,3-substituted arenes at the 4- and 5-position respectively.[36] The borylation of TIPS protected pyrrole was selective for the less hindered 3-position. The incompatibility of carbon-halogen bonds and nitriles was a major limitation of these Rh-precatalysts.

As the Ir-catalysts were more selective, detailed studies were performed to improve the catalyst turnover numbers. Mechanistic studies by our group[37] revealed that the active catalyst was generated by Cp* loss from Cp*Ir(PMe$_3$)(H)(BPin) and not by PMe$_3$ dissociation. Other combinations of iridium precursors and ligands generate more active catalysts for aromatic C-H borylations. Based on the trisboryl complexes by Marder, our group reported a combination of (Ind)Ir(COD) and phosphine ligands as catalysts for the borylation of arenes with HBPin (Scheme 1.11). Commercially available

11

precatalyst [Ir(COD)Cl]$_2$ was also effective. Chelating phosphines, 1,2-bis(dimethylphosphino)ethane (dmpe) and 1,2-bis(diphenylphosphino)ethane (dppe), increased the catalytic activity and turnover numbers to 4500. This catalyst system was highly selective for aromatic C-H bond activation even in the presence of C-Halogen and benzylic C-H bonds. We proposed a catalytic cycle involving Ir^{III}/Ir^{V} intermediates (Scheme 1.12). This mechanism was later supported by Sakaki's[38] computational studies and Hartwig's[39] mechanistic study in a closely related system.

Scheme 1.11 Improved catalysts for aromatic C-H activation/borylation.
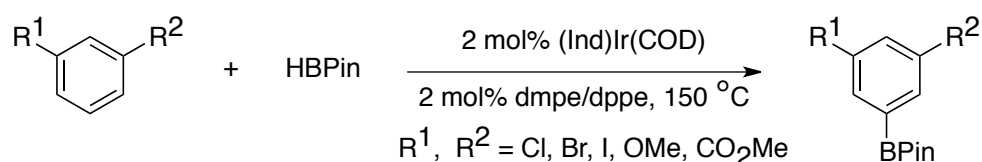
Scheme 1.12 Catalytic cycle for Ir-catalyzed aromatic C-H activation/borylation.
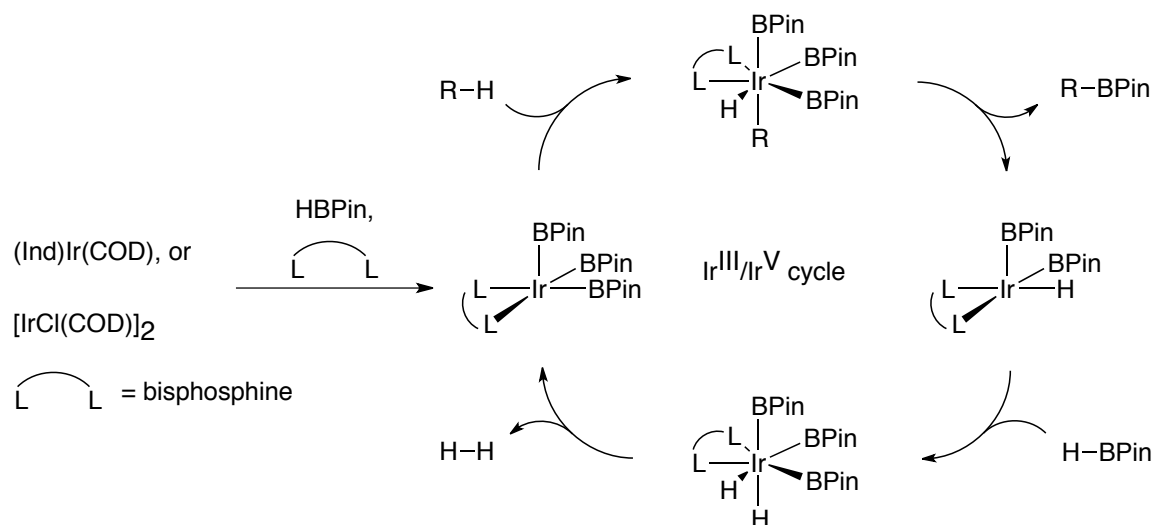
Subsequent to our groups report in 2002, Ishiyama, Miyaura, Hartwig and co-workers[40] reported the borylation of arenes catalyzed by iridium complexes of bipyridine (bpy) and di-*tert*-butylbipyridine (dtbpy). These systems catalyzed borylations of arenes

and heteroarenes at room temperature to 80 $^\circ$C. In the presence of [Ir(OMe)(COD)]$_2$ and dtbpy,[41] a variety of arenes reacted with B$_2$Pin$_2$ at room temperature to obtain regioselectivities and substrate scope similar to the ones reported by our group. The reaction could also be carried out with HBPin[42] and the substrate scope was expanded to simple heteroaromatics.[43,44] These catalyst systems were highly reactive with TONs reaching 25,000 in some cases. In 2005, Hartwig reported a detailed mechanistic study where [Ir(dtbpy)(COE)(BPin)$_3$] was identified as the resting state of catalyst.[39] Kinetic studies revealed the active catalyst is generated by the reversible dissociation of the COE and the 16-electron [Ir(dtbpy)(BPin)$_3$] cleaves the arene C–H bond in the rate determining step. Ir$^{I/III}$ cycle was ruled out and Ir$^{III/V}$ cycle was identified to be consistent with experimental results.

Several research groups reported aromatic borylations with other precatalyst/ligand combinations. In 2004, Nishida and Tagata[45] described the borylation of arenes and heteroarenes catalyzed by [Ir(COD)Cl]$_2$ and 2,6-diisopropyl-*N*-(2-pyridylmethylene)-aniline in *n*-octane or DME. Murata and co-workers in 2006,[46] reported the reaction of arenes with HBPin catalyzed by hydrotris(pyrazolyl)borate complexes of Rhodium and Iridium at 100-120 $^\circ$C. Also in 2006, Herrmann and co-workers[47] reported bis-(*N*-heterocyclic)-carbene iridium complex catalyzed the borylation of arenes with HBPin. Halogenated benzenes including iodobenzene were

found to be borylated at 40 °C in 9-12 h with 89-100% GC yields. In 2007, Yinghuai et al.[48] reported iridium (I) salicylaldiminato-cyclooctadiene complexes and additives such as bpy, *tetra*-2-pyridinylpyrazine (TPy) and PPh$_3$ served as reusable catalysts for C–H bond borylation of arenes with B$_2$Pin$_2$. The yields were higher when the reactions were conducted in a solvent mixture of ionic liquid and dichloromethane.

In all of the above examples of C-H borylation only HBPin and B$_2$Pin$_2$ have been used. In 2009, Suginome and Iwadate[49] reported the borylation of arenes with 1,8-napthalenediaminatoborane (HBDan) catalyzed by iridium (Scheme 1.13). Highest yields were obtained when electron rich and electron poor arenes as solvents were allowed to react with HBDan in the presence of [Ir(OMe)(COD)]$_2$ and dppe at 80 °C.

Scheme 1.13 HBDan as the boron source in Ir-catalyzed C-H activation/borylation.
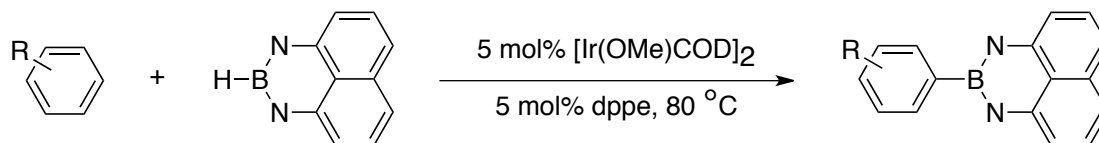
Directed *ortho*-borylation

C-H activation/borylation is sterically directed and functionalization occurs away from the substitutents. Efforts have been made to alter the selectivity by installing directing groups and altering the ligands employed. In 2008, Hartwig and co-workers[50] described *ortho*-borylation of arenes by installing dialkyl hydrosilyl group as a directing group. The reaction was catalyzed by the combination of [Ir(COD)Cl]$_2$ and dtbpy,

including benzylic hydrosilanes, silylated phenols and silylated *N*-alkyl anilines (Scheme 1.14).

Very recently, Ishiyama, Miyaura and co-workers[51] have reported the *ortho*-directed borylation of methylbenzoates using B_2Pin_2. A monodentate phosphine ligand, with strong electron withdrawing aryl groups $(3,5\text{-}(CF_3)_2C_6H_3)_3P$, in combination with $[Ir(OMe)(COD)]_2$ was selective in effecting the *ortho*-borylation at 80 °C in octane (Scheme 1.15).

Scheme 1.14 Silyl-directed *ortho*-borylation of arenes.
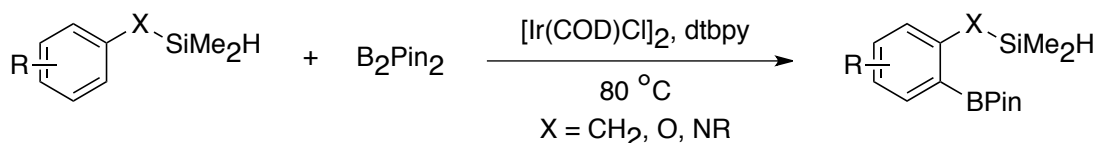
Scheme 1.15 *ortho* C-H borylation of benzoate esters.
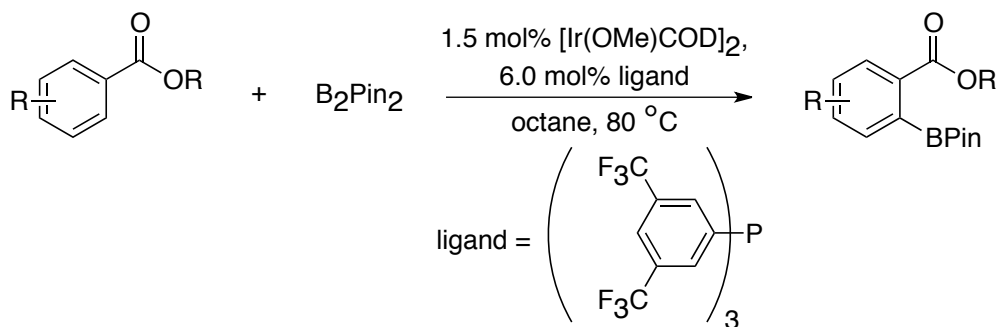
In 2009, Sawamura and co-workers[52] reported that a silica-supported monodentate, electron-rich and compact phosphine ligand (Silica-SMAP) in combination with $[Ir(OMe)(COD)]_2$ resulted in ortho-directed borylation of methyl benzoates using B_2Pin_2 (Scheme 1.16). This was the first example of a supported catalyst for arene borylation and the reaction occurred under mild conditions with excellent yields and

15

selectivities. Not only CO_2Me but also CO_2Et, $CO_2{}^tBu$, $CONMe_2$, SO_3Me, $CH(O(CH_2)_3O)$ and OMOM afforded the same *ortho* selectivity. Even the chlorine atom served as a directing group, thus expanding the scope and utility of iridium catalyzed *ortho*-directed borylation of arene C-H bonds.

Scheme 1.16 Silica-supported Iridium complexes for *ortho*-directed borylation.
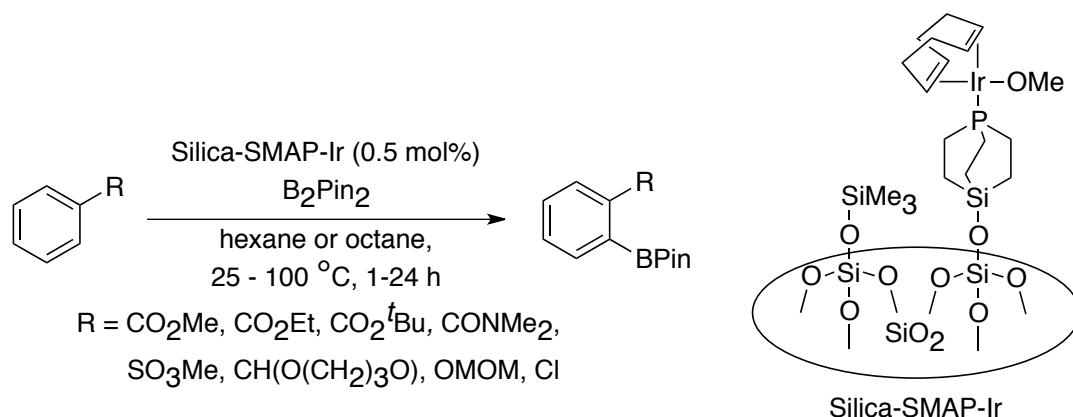
C-H Borylation of Heteroarenes

Heteroarenes are an important class of compounds found in a vast majority of biologically active molecules. Several research groups have investigated the Ir-catalyzed C-H borylation of heteroarenes.[41-44,53-56] In contrast to arenes, the regioselectivities for aromatic heterocycles depend on the position and hybridizations of the heteroatoms they contain, and are typically more reactive than their arene counterparts. Ishiyama, Miyaura and Hartwig have shown that the parent heterocycles pyrrole, thiophene, furan, indole, benzofuran and benzothiophene borylate selectively at the 2-position, adjacent to the heteroatom (Figure 1.4).[43] Reactions with excess of borane reagent produced 2,5-diborylated products in the case of pyrrole, thiophene, furan[43] and predominantly 2,7-

diborylated products in the case of indole and benzofuran.[54] In contrast to the

aforementioned heterocycles, whose heteroatoms are sp^3-hybridized, functionalization at

C-H positions adjacent to the N in pyridines and other sp^2-hybridized nitrogen containing

heterocycles is difficult to achieve. The borylation of pyridine resulted in a mixture of 3-

and 4-borylated products, whereas quinoline borylates exclusively at the 3-position.

Chapters 2 - 4 describe the C-H borylation of heteroarenes in more detail.

E = NH, O, S   3-BPin : 4-BPin ~ 2:1

(a)   (b)
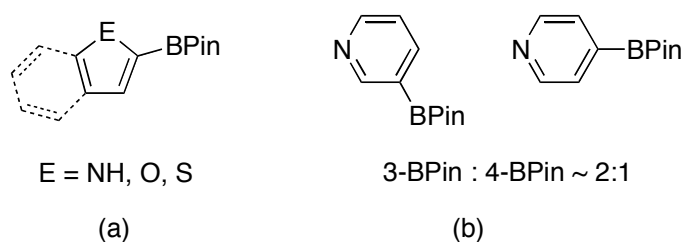
Figure 1.4 Borylation regioselectivities in heterocyclic systems reflecting (a) preference

for C-H functionalization adjacent to sp^3-hybridized heteroatoms and (b) aversion to

borylation at C-H sites flanking sp^2-hybridized nitrogen.

The presence of electronic effects on relative reactivities of arenes in Ir-catalyzed

borylation of C-H bonds has been noted since the earlier reports.[35] To better understand

these effects and the regioselectivities in heteroarenes, our group in collaboration with

Professor Dan Singleton at Texas A&M performed a unified experimental and

computational investigation of the Ir-mediated process. The experiment and theory favor

a model of C-H borylation where significant proton transfer character exists in the

transition state (Figure 1.5).[57] This explains the accelerated borylation rates in

pyrrole/thiophene/furan and the selective functionalization of C-H positions flanking the

heteroatoms in indole/benzofuran/benzothiophene, whose pK_as are relatively low making

them more reactive.
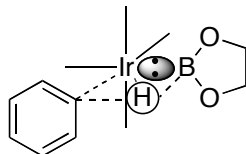
Figure 1.5 Transition state proton transfer to filled Ir–B bond.

Applications of C-H borylation

The high yields and high selectivity of C-H activation/borylation have been

exploited in the elaboration of arenes and heteroarenes and in the total synthesis of

rhazinicine,[58] SM-130686[59] and 5-(2-pyrenyl)-2′-deoxyuridine.[60] It has also been used

in the synthesis of macromolecules[61] and to prepare ligands for transition metal

complexes.[62] Several one-pot methods for the synthesis of organic compounds via Ir-

catalyzed C-H activation/borylation have been reported. The mildness of the conditions

has allowed the one-pot reactions of the crude boronate esters without removal of the

residual Ir-catalysts (Figure 1.3).

Our group reported a one-pot protocol for borylation/Suzuki coupling of 1,3-di-

substituted arenes.[37] We have shown that intermediate boronic ester can be oxidized

without isolation to obtain phenols,[63] which are previously difficult to synthesize by

traditional methods. Hartwig and co-workers have utilized this methodology and have

reported one-pot sequences for the conversion of arenes to aryl bromides,[64] aryl

18

chlorides,[64] arylamines,[65] arylethers,[65] enantioenriched diarylmethylamines,[66] arylboronic acids,[67] potassium aryltrifluoroborates[67] and aryl nitriles.[68]

A hallmark of Ir-catalyzed aromatic borylation is its tolerance of halogen substituents, which can be exploited in selective cross-coupling subsequent to borylation step, while keeping the BPin group intact (Scheme 1.17). Our group has shown that these halogens can participate in Pd-catalyzed amination reactions allowing for a one-pot aromatic borylation/amination route to a variety of amino-substituted arylboronic esters.[69] Our group also developed a procedure for the synthesis of 5-substituted-3-amidophenols,[70] through a sequence of C-H activation borylation/amidation/oxidation without isolation of any intermediate arenes. Dr. Chotana from our group has shown that C-S coupling and Sonogashira coupling can be affected at the halide terminus after borylation, generating aromatic thioether boronate esters and aromatic alkynyl boronate esters respectively.[71]

Scheme 1.17 One-pot borylation/cross-coupling reactions.
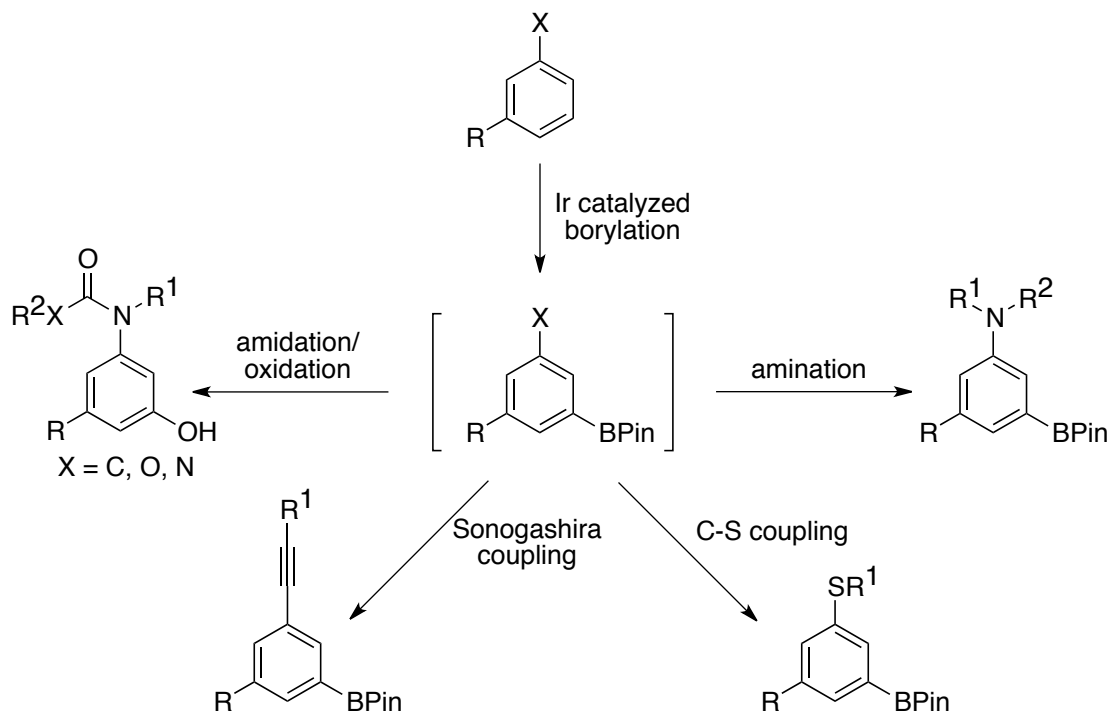
This thesis will describe our efforts to extend the scope and applications of iridium catalyzed aromatic borylations. Chapter 2 describes the regioselective borylation of Boc-protected heterocycles and aminoacids. The application of C-H activation/borylation in small molecule synthesis has been demonstrated by the synthesis of DuP-697 in Chapter 3. Chapter 4 describes the utility of combining C-H borylation with proteo deborylation in synthesizing new regioisomers. The recent development in the masking groups for boron reagents has prompted us to apply the boron masking technology on C-H borylation products, generating diboron compounds that are differentially protected. The usage of differentially ligated diboron reagents is shown in Chapter 5.

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CHAPTER 2

Boc Groups as Protectors and Directors for Ir-Catalyzed C–H Borylation of

Heterocycles

2.1 Introduction

Heterocycles are an important class of compounds existing in a variety of natural products. Of these are the nitrogen containing heterocycles like pyrroles,[1a] imidazoles,[1b] pyrazoles,[1c] indoles[1d] and azaindoles.[1e,f] Synthesis of substituted heterocycles can either be accomplished by constructing the ring from other substrates or functionalization of the existing ring. Direct functionalization of nitrogen containing heterocycles can lead to rapid access to materials that are cumbersome to prepare by classical methods. Ir-catalyzed borylation of C–H bonds is a new methodology for functionalizing aromatic and heteroaromatic hydrocarbons.[2] There are many methodological advances that highlight the efficacy of this process in synthesis.[3] Unlike traditional methods, the formation of C–B bond is imparted directly from more readily available C–H bonds. For aromatic substrates, steric effects dictate the regioselectivity, giving access to regiochemistry that is difficult to obtain using traditional synthetic methods. While for heterocyclic substrates, the origins of regioselectivity are less apparent, it has been shown monoborylation of pyrroles and indoles occurs adjacent to the heteroatom functionalizing the 2-position.

We had previously shown that the borylation regioselectivity for pyrrole can be shifted to the 3-position if the nitrogen is protected with a triisopropylsilyl (TIPS) group,[4] implying again that C-H activation/borylation is a sterically driven process and it can be

translated into heteroaromatics (Scheme 2.1). Following our report Miyaura and co-workers reported the borylation of *N*-triisopropylsilyl pyrrole and *N*-triisopropylsilyl indole with B_2Pin_2 in the presence of $[Ir(COD)Cl]_2$ and dtbpy to yield 3-borylated products (Scheme 2.2).[5] Unfortunately, trimethylsilyl protection, the more economical alternative, was impractical as the N–Si bond is prone to hydrolysis. For general synthetic utility, we sought an economical and robust protecting group to impart regioselectivity that TIPS protection provided. The compatibility of amides in aromatic borylations suggested that *tert*-butoxycarbonyl (Boc) protecting groups might be inert. If so, we envisioned that Boc compatibility might also facilitate borylations of appropriately protected natural and unnatural aromatic amino acids. Our results are described herein.

Scheme 2.1 Rh-catalyzed C-H activation/borylation of **2.1a**
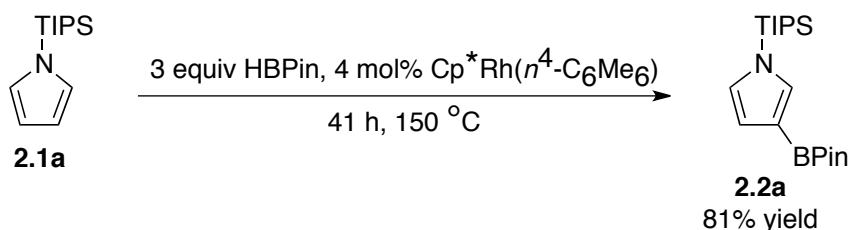
Scheme 2.2 Ir-catalyzed C-H activation/borylation of N-TIPS heterocycles
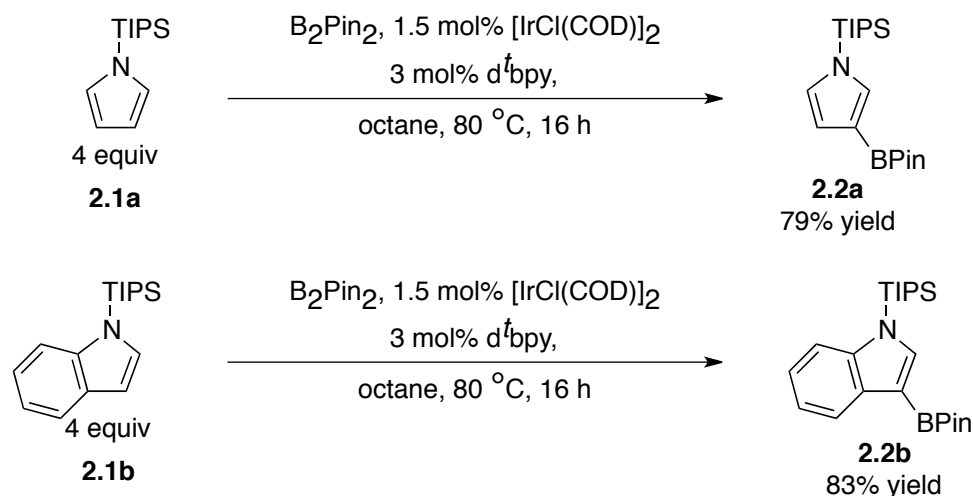
2.2 C-H activation/borylation of Boc-protected heterocycles.

N-Boc-pyrrole was the logical starting substrate for comparing Boc and TIPS protecting groups. The traditional synthesis of 3-BPin-N-Boc pyrrole is a 4-step sequence starting from N-triisopropyl pyrrole, involving bromination, deprotection of TIPS, Boc-protection and Miyaura borylation affording the product in 30% yield (Scheme 2.3).[6] Unlike the traditional method, we were pleased to find that C-H activation/borylation of N-Boc pyrrole proceeded smoothly with effectively complete regioselectivity for the 3-position in 90% yield. The yields are reproducible and scale reasonably well. For example, 100 g of the N-Boc pyrrole and 1.25 equiv of pinacolborane (HBPin) afford the product in 85% yield using an Ir catalyst loading of 0.5 mol% (Scheme 2.4). While this work was in progress Gaunt and co-workers reported borylation of *N*-Boc-pyrrole under microwave conditions.[7] They have used this methodology in the synthesis of rhazinicine, a member of the rhazinilams family of natural products that mimic the cellular effects of pacitaxel.

Scheme 2.3 Traditional route to the synthesis of **2.4a**

TIPS	1. NBS, THF
	2. TBAF, THF
2.1a	3. Boc$_2$O, DMAP, CH$_3$CN
	4. HBPin, 3 mol% PdCl$_2$(CH$_3$CN)$_2$,
	9 mol% S-Phos, NEt$_3$, toluene, 80 $^\circ$C

2.4a

30% yield
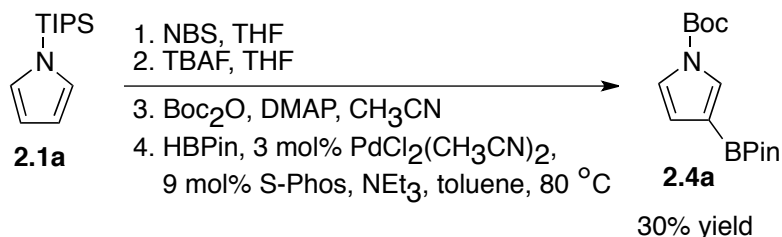
Scheme 2.4 C-H activation/borylation for the synthesis of **2.4a**
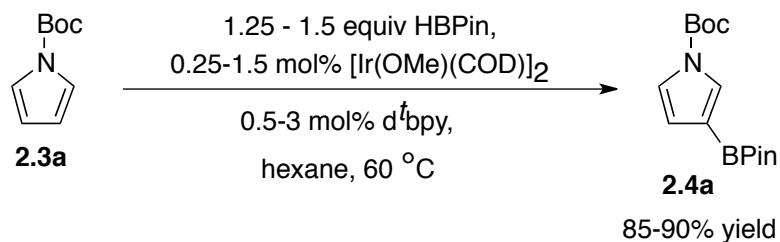
N-Boc compatibility is reasonably general as indicated by the other entries in Table 2.1. 2-Substituted pyrroles are known to borylate selectively at the 5-position yielding 2,5-substituted pyrroles. Alkyl and ester functionality is tolerated during the borylation conditions. To see whether the steric direction could be translated to substituted pyrroles the borylation of *N*-Boc-2-substituted pyrroles was attempted. The borylation proceeded smoothly affording the anticipated borylated product in good yield. This Boc protection methodology has allowed us to synthesize 2,4-substituted pyrroles. In addition to substituted pyrroles (entries 1 and 2), *N*-Boc-indole (entry 3) and *N*-Boc-7-azaindole (entry 4) afford acceptable yields of 3-borylated products. The outcome for *N*-Boc-7-azaindole reflects a preference for the 3-position of a 5-membered nitrogen heterocycle over sterically accessible sites in the 6-membered N-heterocyclic moiety. A second borylation of *N*-Boc-7-azaindole proceeds selectively at the 5-position (entry 5), presumably because C5 is less hindered than C4.[8]

The yield for *N*-Boc-6-azaindole was low and the *N*-Boc-imidazole reacted slowly (entry 7). In the latter case, rate diminution from N3 coordination to Ir is compounded by that fact that borylations adjacent to sp^2-hybridized N are difficult. For *N*-Boc-imidazole, approximately 90% conversion was achieved but extensive decomposition occurred on workup. A stable imidazole analog can be isolated in good yield if the more robust
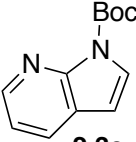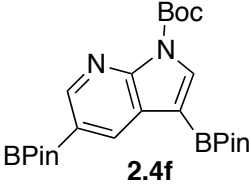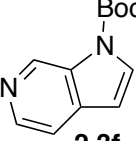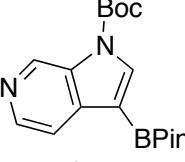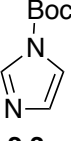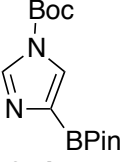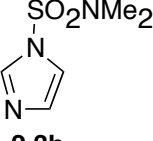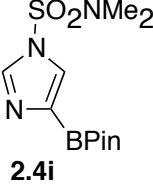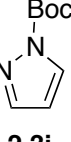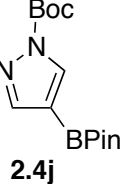
dimethylsulfonamide protecting group is used (entry 8). Entry 9 shows that *N*-Boc pyrazole affords the 4-borylated product, whereas borylation of *N*-methyl pyrazole gives the 5-borylated isomer as the major species.[9]

Table 2.1 Borylation of *N*-Boc-Protected Heterocycles[a]
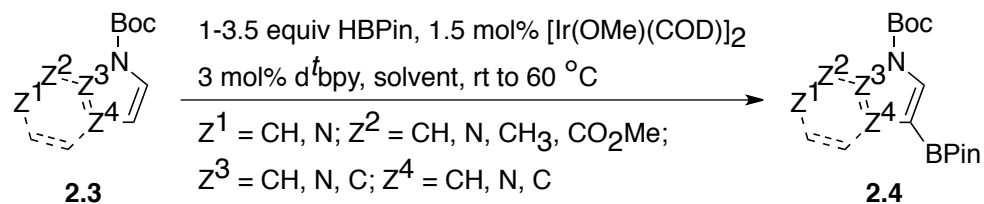
1-3.5 equiv HBPin, 1.5 mol% [Ir(OMe)(COD)]$_2$

3 mol% d^{t}bpy, solvent, rt to 60 °C

Z^1 = CH, N; Z^2 = CH, N, CH$_3$, CO$_2$Me;

Z^3 = CH, N, C; Z^4 = CH, N, C

2.3 → **2.4**

entry	substrate	conditions	product	% yield
1	**2.3b** (H$_3$C-, Boc)	THF, 60 °C, 6 h	**2.4b** (BPin)	82
2	**2.3c** (MeO$_2$C-, Boc)	n-hexane, rt, 5 h	**2.4c** (BPin)	75
3	**2.3d** (Boc-indole)	n-hexane, 60 °C, 8 h	**2.4d** (BPin)	65
4	**2.3e** (Boc-7-azaindole)	n-hexane, rt, 5 h	**2.4e** (BPin)	56

Table 2.1 (cont'd).

entry	substrate	conditions	product	% yield
5[b,c]	**2.3e**	n-hexane, rt, 96 h	**2.4f**	54
6[c]	**2.3f**	THF, 55 °C, 20 h	**2.4g**	14
7	**2.3g**	THF, 60 °C, 6 h	**2.4h**	--[d]
8[e]	**2.3h**	Et$_2$O, rt, 65 h	**2.4i**	82
9	**2.3i**	n-pentane, rt, 1.5 h	**2.4j**	76

[a]See experimental for details. [b]3.5 equiv HBPin used. [c]3.0 mol% [Ir(OMe)(COD)]$_2$, 6.0 mol% dtbpy used. [d]Approximately 90% conversion achieved, but the product decomposed on attempted isolation. [e]B$_2$Pin$_2$ (1.0 equiv) was the borylating agent.

2.3 Aminoacids in C-H activation/borylation

N-Boc amino acids are a very important class of Boc-protected compounds for consideration. As shown in Table 2.2, *N*-Boc aromatic and heteroaromatic amino acids are suitable substrates. The regioselectivities are substrate dependent and follow the

patterns established for arenes and heterocycles. For example, protected phenylalanine gives a mixture of products arising from *m*- and *p*-borylation with significant diborylation of the *m*-product. When the aromatic or heteroaromatic group is predisposed to regioselective borylation, conversion and yields improve dramatically as illustrated for entries 3 and 4. The Boc protected 2-thienylalanine methyl ester behaves the same as 2-substituted thiophenes. By adjusting the stoichiometry of the borane added the 2-thienylalanine could be either monoborylated at the 5-position (Table 2.2, entry 4) or diborylated at the 3,5-position (Table 2.2, entry 5). The final two entries in Table 2.2 show the indole nucleus of protected tryptophan can be mono or diborylated. The conversions for the tryptophan substrate were poorer than for the other amino acids in Table 2, and preparation of the monoborylated compound (entry 6) was complicated by competing diborylation. Nevertheless, the pure monoborylated compound could be obtained. By comparison, the 2,7-diborylated product (entry 7) was more readily isolated. To evaluate stereospecificity, both D and L isomers of *N*-Boc tryptophan methyl ester were borylated in separate experiments. In each case, none of the opposite enantiomer could be detected by chiral HPLC analysis.

Table 2.2 Borylation of *N*-Boc protected amino acids[a]
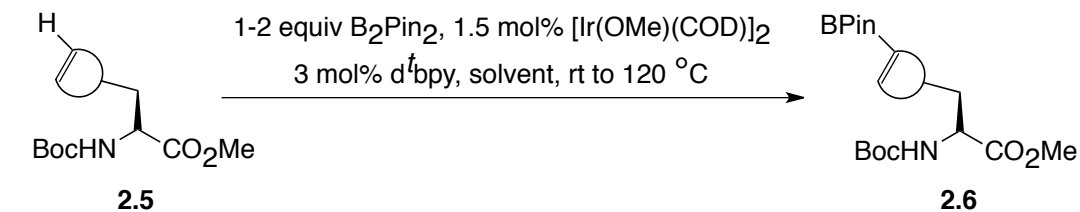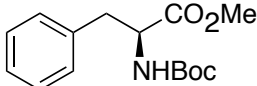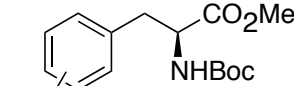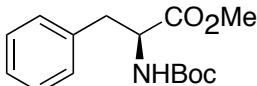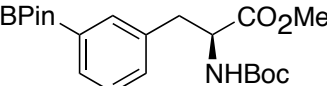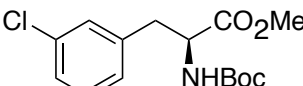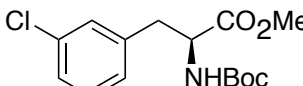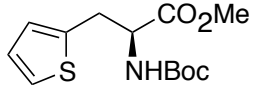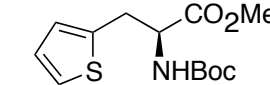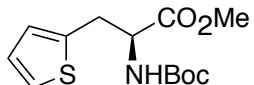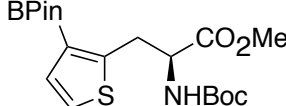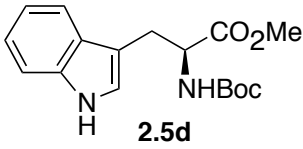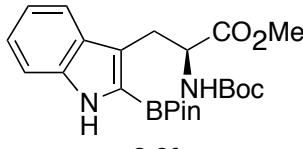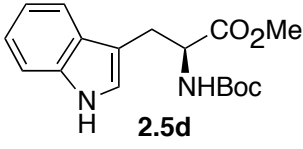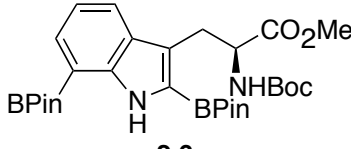
entry	substrate	conditions	product	% yield
1[b,c]	**2.5a**	CyH, 120 °C, 30 min	**2.6a**	26
2[c]	**2.5a**	CyH, 120 °C, 1 h	**2.6b**	18
3	**2.5b**	CyH, 120 °C, 20 min	**2.6c**	85
4	**2.5c**	MTBE, rt, 40 min	**2.6d**	84
5	**2.5c**	MTBE, rt, 72 h	**2.6e**	76

Table 2.2 (cont'd).

entry	substrate	conditions	product	% yield
6[d]	2.5d	MTBE, rt, 45 min	2.6f	43
7[e]	2.5d	MTBE, rt, 19 h	2.6g	54

[a]See experimental for details. [b]38% conversion. [c]Reaction performed under microwave irradiation. [d]63% based on recovered starting material. [e]2.0 equiv B_2Pin_2 used.

2.4 One-pot borylation/Suzuki-Miyaura coupling

We, and others, have developed one-pot processes where Ir-catalyzed borylations are followed by one or more chemical transformations.[3] To assess the potential for using the *N*-Boc protected substrates in one-pot processes, one elaboration of *N*-Boc pyrrole was examined. We chose the elegant chemistry developed by Buchwald and Billingsley for the C–C cross-coupling step, and targeted compound **2.7a** for a direct comparison to their work (Scheme 2.5).[6] When the identical reaction conditions for the C—C coupling step were incorporated as the second step in a one-pot synthesis from *N*-Boc pyrrole, biheterocycle **2.7a** was obtained in considerably lower yield than the 51% yield they reported when starting from pure **2.4a**. However, increasing the coupling reaction time from 12 to 48 h afforded **2.7a** in 76% isolated yield. Buchwald and Billingsley's route to **2.7a** used a conventional synthesis of **2.4a** (Scheme 2.3), which was prepared from pyrrole in multiple steps that include protection group swapping. Using pyrrole as the

common starting material, C–H borylation gives **2.7a** in 72% yield[10] (Scheme 2.5), which is significantly better than the 15% yield obtained by the conventional route.[6]

Unlike one pot C–H borylation/C–C coupling the yield of **2.7a** could be increased to 85% starting from pure **2.4a** (Scheme 2.6). The increase in yield could be attributed to lowered proteodeborylation when starting from pure **2.4a**.

Scheme 2.5 One-pot borylation/C–C cross-coupling of *N*-Boc pyrrole with 3-chlorothiophene.
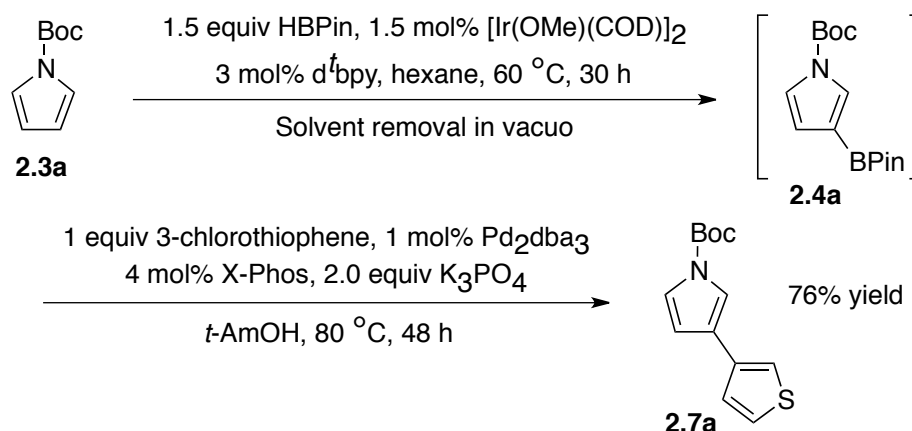
Scheme 2.6 Suzuki cross-coupling of pure **2.4a** with 3-chlorothiophene
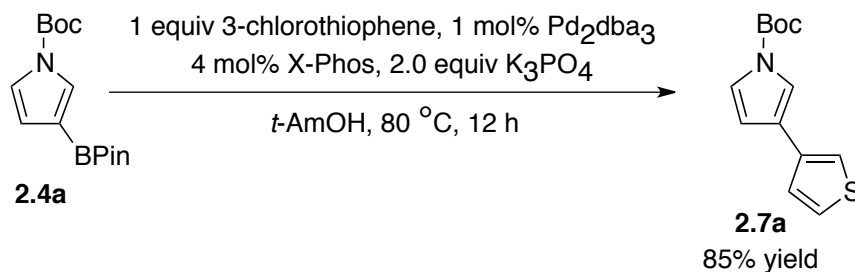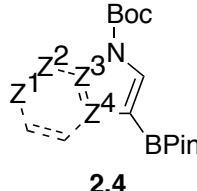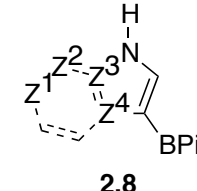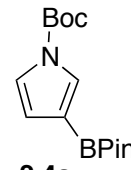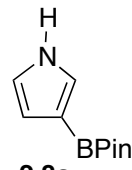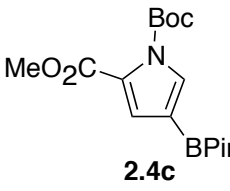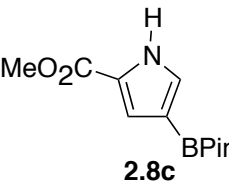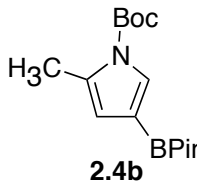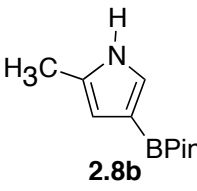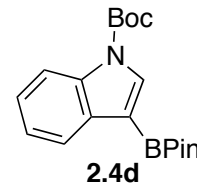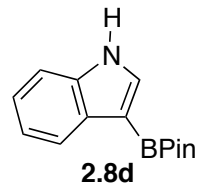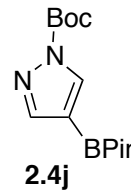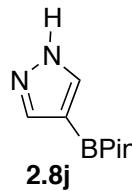
2.5 Boc-deprotection of products in Table 2.1

While it may be desirable to remove the Boc group after the boronate ester has been further transformed, there could be advantages to removing the Boc group while leaving the C–B bond intact. Of the known procedures for Boc removal,[11] standard

36

protocols were effective for deprotecting the amino acid borylation products in Table 2.2, but most methods for deprotecting *N*-Boc heterocycles in Table 2.1 were unsatisfactory. Deprotection of **2.4a** was investigated. Attempts to deprotect the Boc-group with HCl, CF_3COOH resulted in unidentifiable decomposition products and TBAF was ineffective. Treatment with NaOMe was successful in deprotection to yield 42% of the desired product. However, the deprotection yield varied significantly when done on a 2 g scale. Nevertheless, the Boc group could be cleaved thermally (Table 2.3).[12] This reagent free deprotection is not only economical but also is in strong accordance with the principles 1 and 8, prevent waste and avoid using solvents, of green chemistry.[13] Significantly, the products in Table 2.3 are regioisomers of the compounds that are obtained by borylating the unprotected heterocycles. The thermal deprotection of the azaindole products in Table 2.1 failed. Nonetheless **2.4e** was deprotected using CF_3COOH/CH_2Cl_2 in 55% isolated yield (Scheme 2.7).

Table 2.3 Thermal deprotection of *N*-Boc protected borylation products from Table 2.1[a]

entry	substrate	conditions	product	% yield
1	2.4a	180 °C, 35 min	2.8a	80
2	2.4c	180 °C, 18 min	2.8c	76
3	2.4b	140 °C, 16 h	2.8b	72
4	2.4d	180 °C, 45 min	2.8d	64
5	2.4j	180 °C, 5 min	2.8j	72

[a]*N*-Boc protected substrates were placed in a flask and heated in air.

Scheme 2.7 Deprotection of **2.4e** with CF$_3$COOH
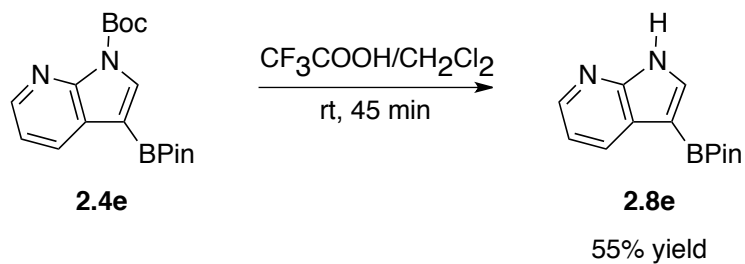
2.6 Conclusions

In summary, compatibility with Boc protecting groups allows for manipulating the regioselectivities for Ir-catalyzed borylations of nitrogen heterocycles. In addition, Ir-catalyzed borylations of protected amino acids are shown to be feasible for the first time, which augurs favorably for similar functionalizations of peptides. Importantly, this work also establishes heat as a clean agent for Boc deprotection of BPin substituted heteroarenes.

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BIBLIOGRAPHY

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CHAPTER 3

C-H Activation/borylation in small molecule synthesis - DuP 697

3.1 Introduction

Iridium catalyzed C-H activation/borylation is emerging as a versatile synthetic methodology for organic chemistry.[1] Our group and others have demonstrated how C-H activation/borylation coupled with other transformations can be exploited in the synthesis of some previously inaccessible or hard to access compounds.[2,3] Applications of the sequence of C-H borylation and cross-coupling have been reported in the total synthesis of rhazinicine,[4a] SM-130686[4b] and 5-(2-pyrenyl)-2′-deoxyuridine.[4c] It has also been used in the synthesis of macromolecules[4d] and to prepare ligands for transition metal complexes.[4e] We have recently described the application of C-H activation/borylation for the elaboration of thiophenes.[1f] Thiophenes are an important class of heterocyclic compounds with applications in the design of advanced materials to the treatment of various diseases. In particular, 2,3-diarylthiophenes have been shown to selectively inhibit the cycloxygenase-2 (COX-2) enzyme,[5] which is induced during inflammatory conditions. DuP 697 **(3.1)** is one of the earliest members of this tricyclic class of inhibitors and it is moderately selective for COX-2. Although its unacceptably long half-life led to its withdrawal during phase I clinical trials, it was a forbearer to successful selective COX-2 inhibitors like Celebrex[TM]. Thus, DuP 697 provides an intriguing backdrop for honing synthetic strategies for drug development.

3.1 DuP 697   Celebrex^{TM}
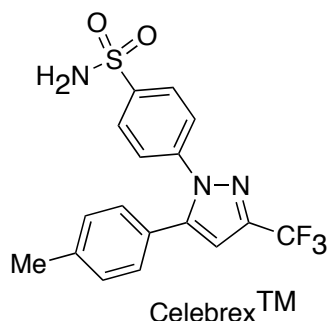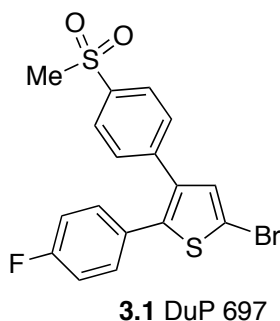
3.2 Previous/Early synthesis of DuP-697

The first published synthesis of DuP 697 (Scheme 3.1) was linear and involved construction of the thiophene ring from appropriate starting materials. It is interesting that a literature search of 2-bromothiophenes that bear cyclic substituents at the 4 and 5-positions yields only 56 compounds, 28 of which have been the subject of biological studies. The route in Scheme 3.1 likely contributes to this dearth of structural diversity for the following reasons. First, a linear sequence where the critical 4- and 5- substituents of the thiophene nucleus are installed in the first steps is not attractive for QSAR studies. Second, Friedel-Crafts acylation and oxidation steps employed in the synthesis are relatively harsh and limit the scope of substituents that can be accommodated.

To overcome some of these limitations, a second approach to diarylthiophenes (Scheme 3.2) related to **3.1** was devised, which entailed a series of alternating brominations and Suzuki couplings.[5d] This route was an improvement, but an even more attractive strategy would utilize a building block possessing all of functionality required for the couplings that introduce the 4 and 5-subsitutents. Herein, we show how C-H activation/borylation makes such an approach to **3.1** and its analogues possible.

Scheme 3.1 Original Synthesis Of DuP 697
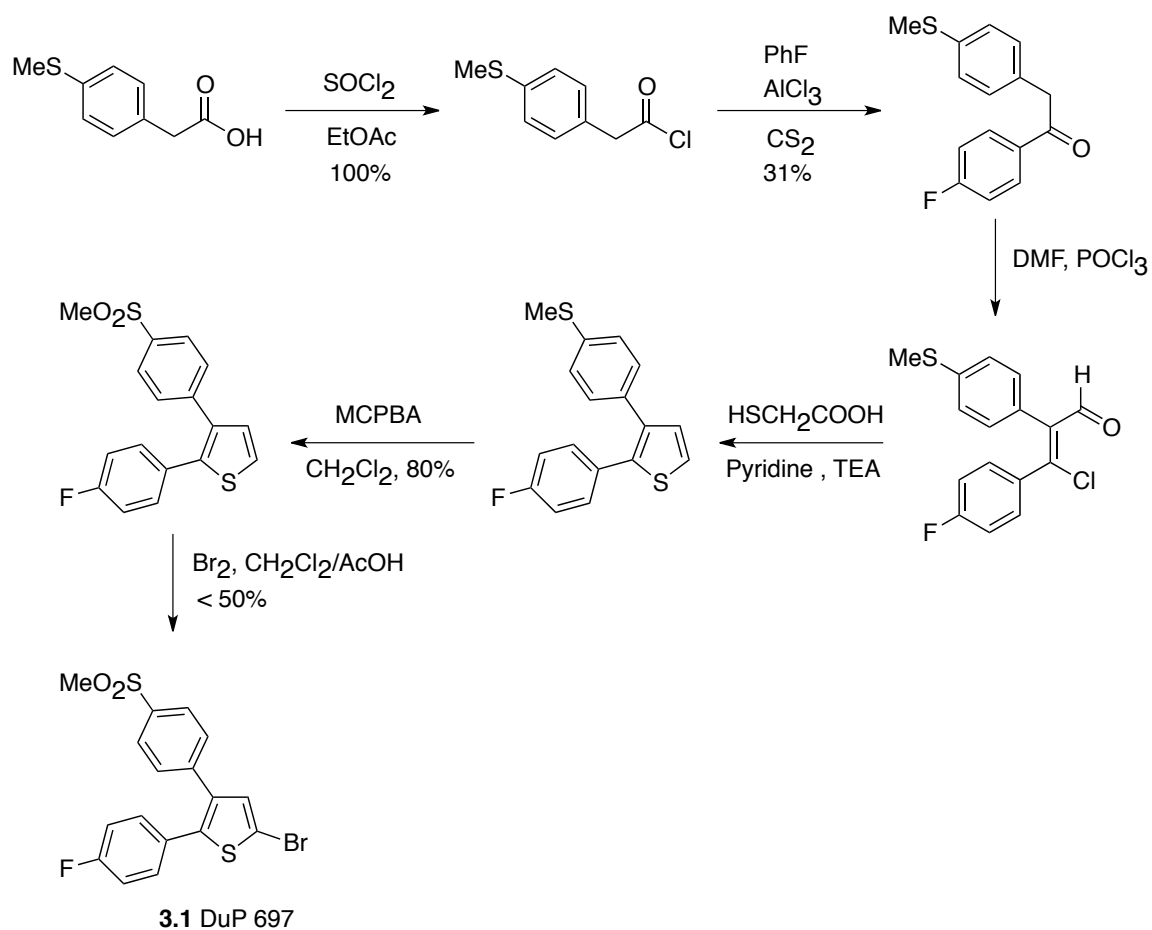
3.1 DuP 697

Scheme 3.2 Suzuki Approach to DuP 697
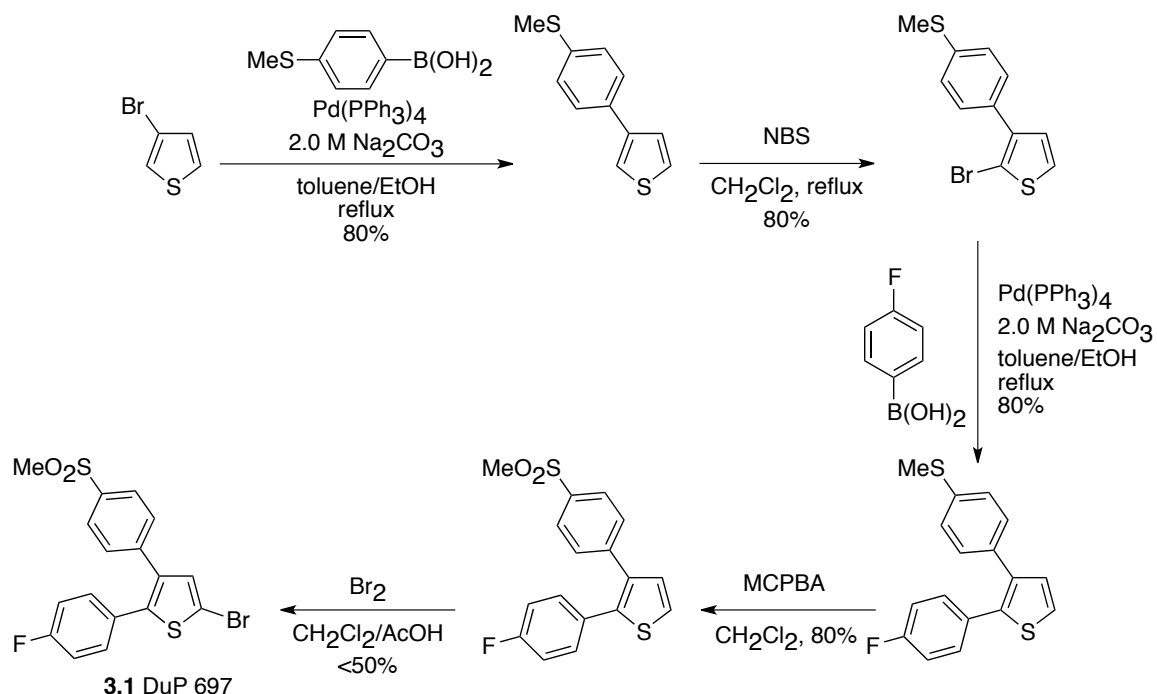
3.1 DuP 697

3.3 Our Synthesis of DuP 697

Aryl boronate esters are versatile synthetic intermediates that are widely used in the construction of carbon–carbon and carbon-heteroatom bonds, and Ir-catalyzed borylation of C-H bonds provides a convenient way to access them. We have previously reported that TMS group can be tolerated in Ir-catalyzed borylation of thiophene C-H bonds. The key player in our approach to **3.1** and its analogs (Scheme 3.3) is compound **3.2**, which is obtained from Ir-catalyzed C–H borylation of 2-chloro-5-trimethylsilylthiophene. Because C–H borylations are sensitive to steric effects, the selectivity for the C–H bond at the 3-position is excellent. The BPin and Cl groups serve as Suzuki coupling sites for elaborating the thiophene core, and the trimethylsilyl substituent is transformed to Br in the final step. Before attempting the synthesis a few questions came to mind, can the BPin be selectively coupled in the presence of chloride.

How easy is the chloride to couple considering the low reactivity and steric bulk of the 3-aryl group. How selective is the bromodesilylation.

Scheme 3.3 Retrosynthesis of DuP 697 and its analogs.
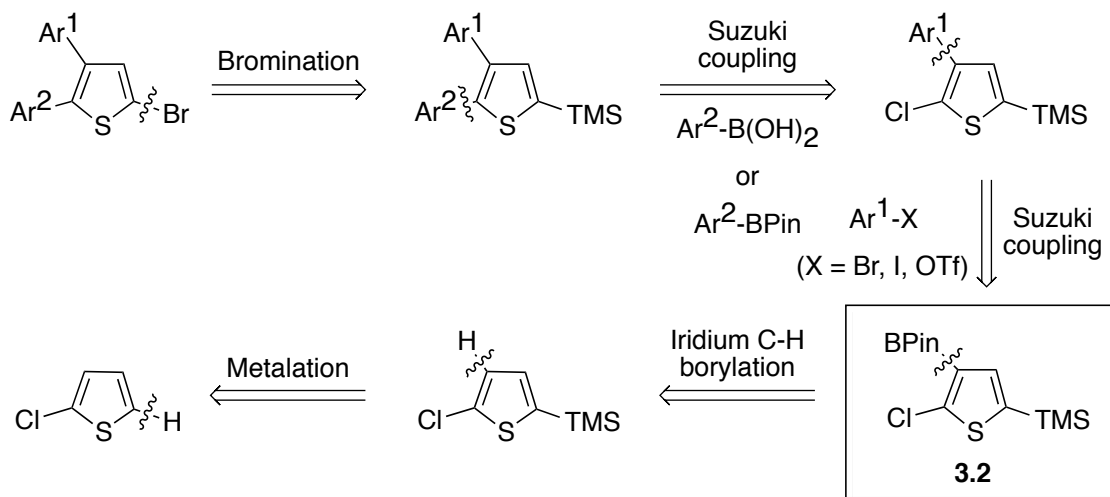
Deprotonation at the 5-position of 2-chlorothiophene, followed by trapping with TMSCl generated 2-chloro-5-trimethylsilylthiophene **3.3** (Scheme 3.4).[6] Unsymmetrical 2,5-disubstituted thiophenes borylate preferentially ortho to the least bulky substituent. When the steric demands of the two substituents are sufficiently different, as in the case of 2-chloro-5-trimethylsilylthiophene, a single monoborylated product can be obtained in 93% yield (Scheme 3.5). With all of the substituents in place, the synthesis of DuP 697 and its analogues was attempted.

Scheme 3.4 Synthesis of 2-chloro-5-trimethylsilyl thiophene **(3.3)**
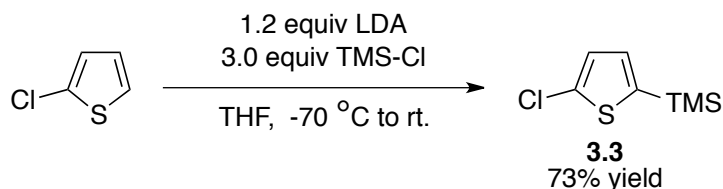
Scheme 3.5 C-H activation/borylation of 2-chloro-5-trimethylsilylthiophene **3.3**
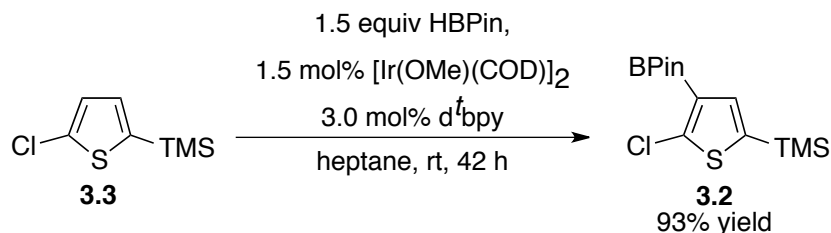
Suzuki Coupling of 3.2

One of the important features of Ir-catalyzed borylations is their ability to tolerate one-pot reactions where subsequent transformations of the crude boronate esters can be accomplished without removing the residual Ir catalysts. The one-pot C-H borylation/Suzuki-Miyaura cross-coupling of **3.3** with 3-bromotoluene was accomplished by Dr. Chotana generating the 3-arylated thiophene **3.4a** in 61% yield.[1f] The low yield in this one-pot protocol was due to competitive protolytic deborylation. To improve the yield of this Suzuki-Miyaura cross-coupling, the reaction was performed with isolated **3.2**. The cross-coupled product **3.4a** was isolated in 85% yield, with an overall yield of 79% over two steps (Scheme 3.6).

Scheme 3.6 Suzuki Coupling of **3.2** with 3-bromotoluene
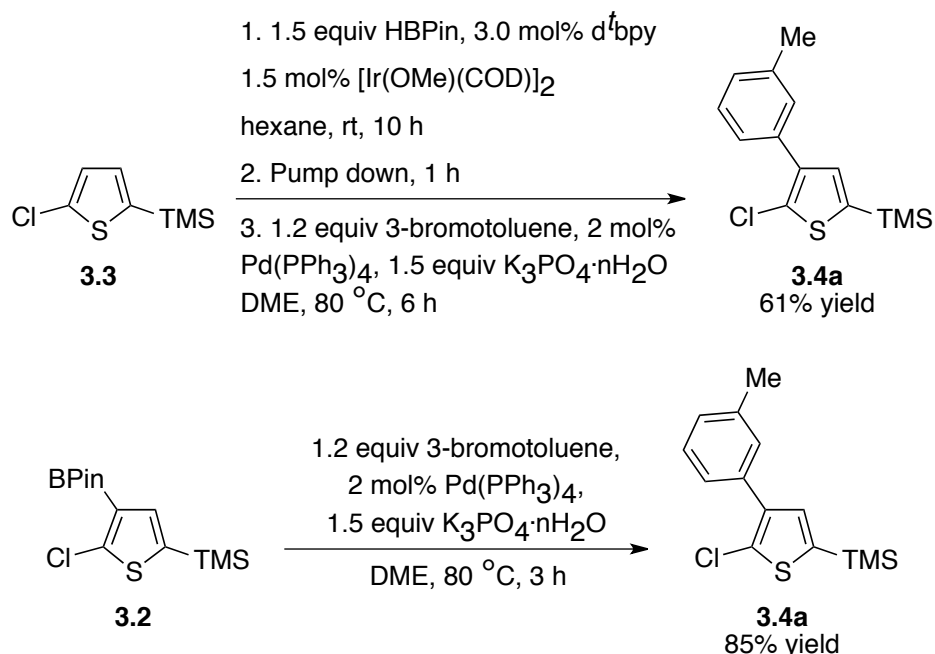
With these Suzuki conditions the cross-coupling of **3.2** with 4-bromo thioanisole (Table 3.1, entry 1) and 4-bromophenyl methyl sulfone (Table 3.1, entry 2) was attempted. Protolytic deborylation was the major issue in both cases. In the case of 4-bromophenyl methyl sulfone coupling there was >99% deborylation. Using Pd(II) instead of Pd(0) was the solution to this problem. 2 mol% of $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ was effective in cross-coupling, minimizing deborylation. Even though deborylation was minimized, dechlorination was an issue in the cross-coupling of **3.2** with 4-bromo thioanisole in the presence of $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ (table 3.1, entry 3). Nonetheless, the desired 4-bromophenyl methyl sulfone was coupled efficiently with **3.2** to isolate the product **3.4b** in 87% yield (table 3.1, entry 4). There was no evidence for Suzuki coupling polymerization, indicating that the chloride in **3.2** does not compete with the aryl bromide partner.

Table 3.1 Suzuki Coupling of **3.2** with 4-substituted bromobenzene
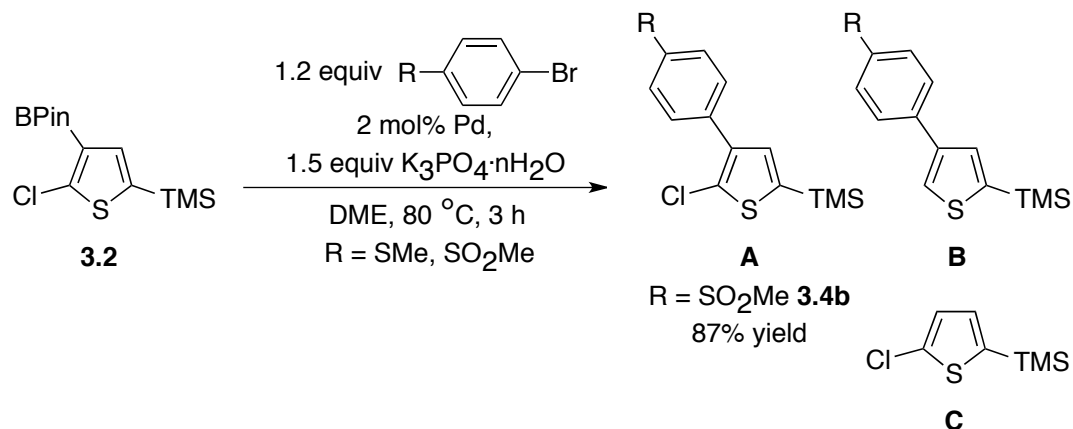
Entry	R	Pd-source	A	B	C
1	SCH$_3$	Pd(PPh$_3$)$_4$	81.1	-	18.9
2	SO$_2$CH$_3$	Pd(PPh$_3$)$_4$	<1	-	>99
3	SCH$_3$	PdCl$_2$·dppf·CH$_2$Cl$_2$	62.5	35.4	2.1
4	SO$_2$CH$_3$	PdCl$_2$·dppf·CH$_2$Cl$_2$	87.7	-	12.3

Attempts to optimize this reaction i.e. minimize deborylation were unsuccessful (Scheme 3.7). Use of DME and water as solvent mixture was fatal leading to 92% deborylation. The usage of anhydrous K$_3$PO$_4$ was unfruitful with only 2% conversion after 18h.

Scheme 3.7 Optimization of **3.2** Suzuki coupling with 4-bromophenyl methyl sulfone
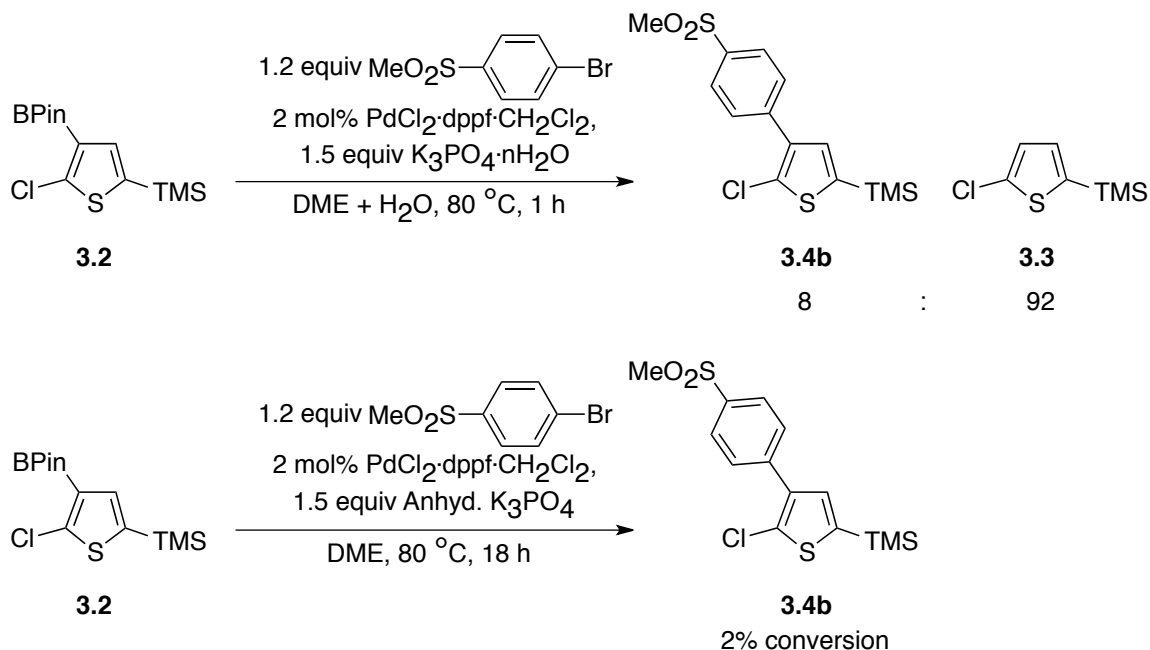
Suzuki coupling of 3.4b

With 3-aryl thiophene **3.4b** in hand the Suzuki coupling at chloride terminus was attempted. For many years a major limitation of palladium-catalyzed coupling processes has been the poor reactivity of aryl chlorides. Until recently, nearly all reports of palladium-catalyzed couplings described the use of organic bromides, iodides and triflates as substrates, despite the fact that, among the halides, chlorides are the most useful single class of substrates, because of their low cost and wider diversity of available compounds. Unfortunately, chlorides were generally unreactive under the conditions employed to couple bromides, iodides and triflates. The low reactivity of the chlorides has been attributed to their high bond dissociation energies, which leads to reluctance by aryl chlorides to oxidatively add to Pd^0 centers, a critical initial step in palladium-catalyzed coupling reactions. Since 1998, a lot of progress has been done towards

51

achieving this goal and catalysts based on bulky, electron-rich phosphanes and carbenes have displayed exceptional reactivity with broad substrate scope.[7] Buchwald's   biaryl monophosphine ligands facilitate the coupling of heteroaryl chlorides as well as hindered aryl and heteroaryl halides. With the conditions developed by Billingsley and Buchwald for the construction of carbon-carbon bonds, the Suzuki-Miyaura coupling of **3.4b** was attempted.[8] A catalyst system derived from Pd$_2$dba$_3$ and XPhos was highly active and efficient in coupling compound **3.4b** with 4-florophenylboronic acid (Scheme 3.8), yielding the desired 2,3-diaryl thiophene **3.5** in 85% yield.

Scheme 3.8 Suzuki coupling of **3.4b** to yield **3.5**
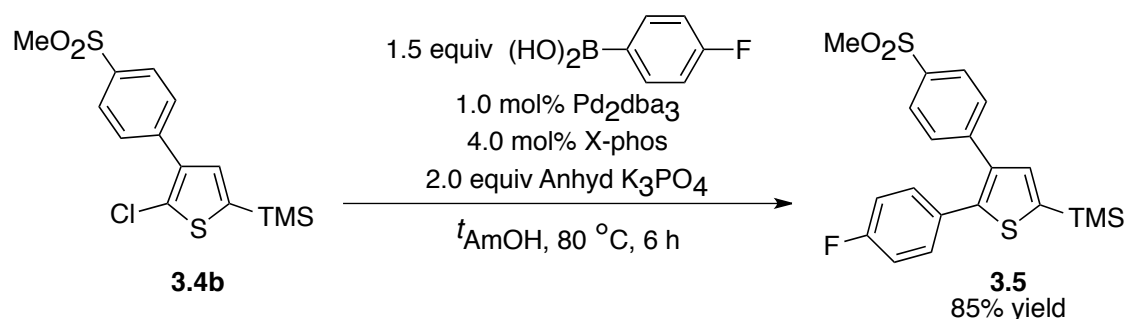
Desilylative bromination of 3.5

N-Bromosuccinimide in acetonitrile has been shown to be a mild and regiospecific brominating agent.[9a] It also has been successfully used in the ipso-desilylative bromination of aromatics.[9b] We have previously shown that NBS in acetonitrile was selective for C-Si bond i.e. desilylative bromination in the presence of other aryl C-H bonds.[1f] With these conditions the bromination of **3.5** was attempted. 1.0 equiv of NBS in acetonitrile at room temperature was effective in transforming the C-Si bond to the C-Br bond (Scheme 3.9) generating DuP 697 (**3.1**) in 87% yield. Based on

the success of this method and in collaboration with Dr. Maleczka's group we were able to create a variety of DuP 697 analogues,[2e] which would be hard to synthesize by previously known methods.

Scheme 3.9 Desilylative bromination of **3.5**

3.5

1.0 equiv NBS
———————————→
CH_3CN, rt, 12 h

3.1 DuP 697
87% yield
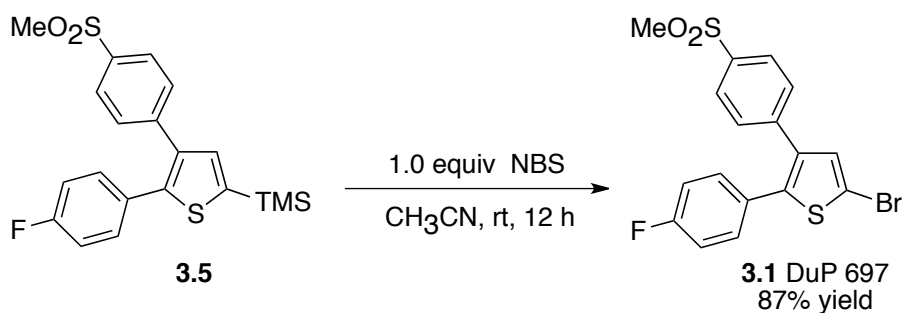
Synthesis of 3,5-diarylthiophenes

The 3-aryl thiophene **3.4a** generated from the Suzuki coupling of **3.2** with 3-bromobenzene was subjected to desilylative bromination using the same conditions as above. The so formed 5-bromo-2,3-disubstituted thiophene **3.6** was subjected to Suzuki coupling to yield 3,5-diaryl thiophene **3.7** (Scheme 3.10).

Scheme 3.10 Synthesis of 3,5-diarylthiophenes
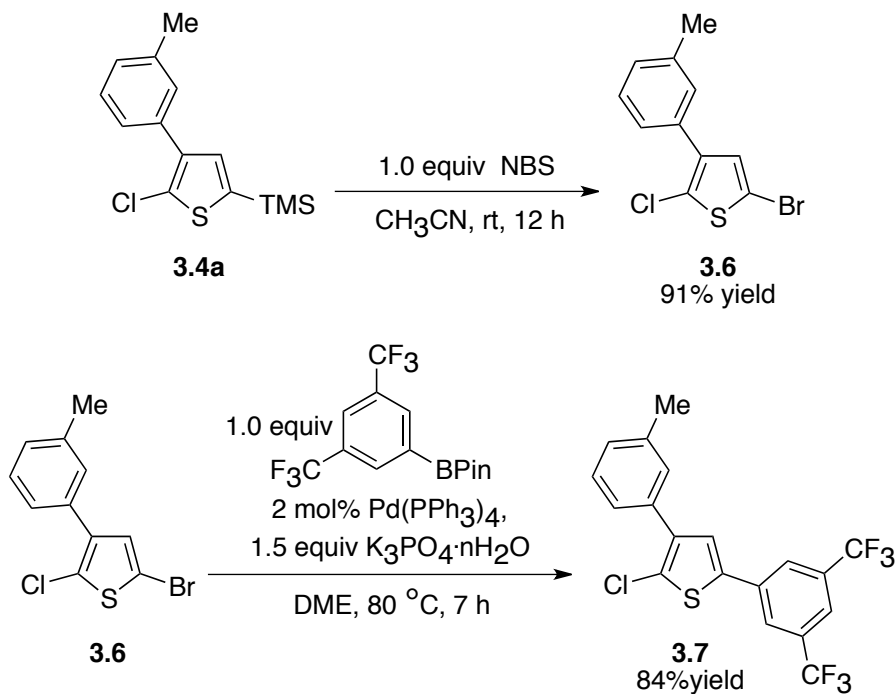
Conclusions

In conclusion, the DuP 697 family of COX-2 inhibitors serves as a backdrop for demonstrating the synthetic flexibility that can result when Ir-catalyzed C–H borylation is married to Suzuki cross-couplings. The halogen tolerance that is a hallmark of Ir C–H borylation makes it trivial to construct compound **3.2**, a building block possessing halogen and boronate ester functionality. This plays directly to one of the strengths of the Suzuki cross–coupling—its exquisite chemoselectivity for halogen functional groups. This feature makes **3.2** a versatile core for efficiently preparing a range of 2,3-diaryl thiophenes and 3,5-diaryl thiophenes.

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BIBLIOGRAPHY

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CHAPTER 4

Diborylation/deborylation for new regioisomers

4.1 Introduction

Boronic acids are highly versatile coupling reagents but their limited stability and incompatibility with many synthetic reagents have resulted in the development of many important surrogates.[1] One major limitation of boronic acids is protolytic deborylation, which requires the use of more than 1.0 equivalent in coupling reactions for better conversions. Even though protolytic deborylation is an undesired side reaction in most coupling reactions, it can be used to our advantage as shown in this chapter. Protolytic deborylation of organoboron compounds is a well-known process, but the method has been restricted to the utilization of boronic acids. Arylboronic acids can be readily deborylated in highly acidic or basic aqueous solutions[2] and metal-catalyzed[3] protodeborylation of boronic acids is also well known (Scheme 4.1). It was shown that arylboronic acids could also be protodeborylated thermally by prolonged heating in refluxing etheral solvents.[4]

Scheme 4.1 Deborylation of boronic acids
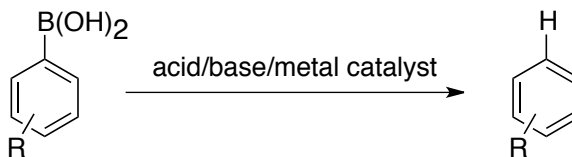
Unlike boronic acids, boronic esters are stable and compatible with a variety of reagents. Beyond the traditional synthesis of pinacol boronic esters, the recent development of C-H activation/borylation has allowed the synthesis of pinacol boronic esters with regioselectivity dominated by sterics.[5] This method is not only

complementary in regioselectivity to the existing methods but also could tolerate a variety of functional groups. Our group and others have shown that arenes and heteroarenes can be regioselectively borylated to obtain C-B bonds which were previously unaccessible or hard to access. It was shown that by adjusting the stoichiometry of the borane added, the heterocycle can either be monoborylated or diborylated.[5c,d,f] The monoborylated products are synthetically useful and have been used in a variety of transformations,[5a,6] but it was the diborylated compounds whose synthetic utility was limited. Our approach to overcome this problem was to selectively deborylate one of the borons to give regioisomers of the monoborylated product. This approach of functionalizing the less reactive bond via difunctionalization and selective mono defunctionalization is known (Scheme 4.2). Even though pinacol boronic esters are less reactive due to the reduced Lewis acidity of the boron center, they have been used in a variety of transformations, but a reliable method for the protolytic deborylation of pinacol boronic esters is still lacking.

Scheme 4.2 Difunctionalization/defunctionalization for less reactive bond functionalization.
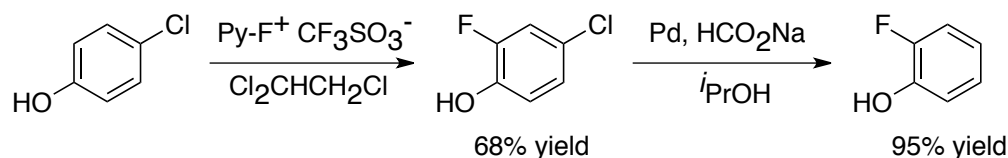
A previous study conducted by Dr. Feng Shi in Professor Maleczka's lab involved the deuteration of pinacol boronic esters generated via C-H activation/borylation.[7] To seek out conditions for the deuteriolysis of aryl boronic esters they investigated a variety of conditions on commercially available 3,4-dichlorophenylboronic acid pinacol ester

(Table 4.1). The desired deutero deborylation reaction proved to be unexpectedly difficult. Entries 1 and 2 shows that either an acid or tertiary amine base respectively failed to give the desired deuteration product even at temperatures as high as 150 ^{o}C. Even though an oxygen base or cesium fluoride could progress the deutero deborylation, full conversion could not be obtained even after extended periods of heating. Fortunately, crude 3,4-dichlororphenylboronic acid pinacol ester generated from borylation of 1,2 – dichlorobenzene gave full conversion to the corresponding deuterium-labelled product within 1 h at 150 ^{o}C using D_2O in THF. It was previously known, that iridium-catalyzes the addition of aryl boronic acids to electron-deficient alkenes or dienes.[8] The two Ir precatalysts (Table 4.1, entries 9,10) that were known to promote C-H activation/borylation were successful in deutero deborylation. Surprisingly, $(d^tbpy)Ir(coe)(BPin)_3$ (Table 4.1, entry 11), the catalyst resting state during borylation was a poor promoter for the deborylation although a significant conversion of 47% was observed. Crabtree's catalyst, previously known to effect H/D exchange, was also capable of deutero deborylation (Table 4.1, entry 12). We wondered whether we can implement Feng's work with diborylation to synthesize regioisomers of monoborylation. The results are described herein.

4.2 Diborylation/Deborylation of thiophenes

The increasing importance for organo boron compounds with new regioselectivity prompted us to explore the possibility of C-H activation/diborylation coupled with deborylation. Thiophenes are an important class of 5-membered heterocycles with applications in the design of advanced materials to the treatment of various diseases.

Table 4.1 Catalyst promoted deutero deborylation conditions.[7]
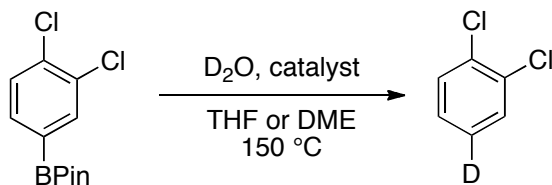
Entry	Catalyst (equiv)	Time (h)	%Conversion[d]
1[a]	Ac$_2$O (0.5)	2	Trace
2[a]	DABCO (1.1)	5	Trace
3[a]	NaOH (0.11)	2	26
4[a]	NaOH (1.1)	2	59
5[a]	NaOMe (2.2)	1	61
6[a]	NaOMe (2.2)	5	76
7[a,c]	CsF (1.1)	4	55
8[b]	Crude borylation mixture (0.02)	0.5	100
9[b]	(Ind)Ir(COD) (0.02)	0.5	95
10[b]	[Ir(OMe)(COD)]$_2$ (0.01)	0.5	98

Table 4.1 (cont'd).

11^b	(d^{t}bpy)Ir(COE)(BPin)$_3$ (0.02)	0.5	47
12^b	[Ir(PCy$_3$)(py)(COD)][PF$_6$] (0.02)	0.5	100

[a]Reactions were run in 0.5 mmol scale in 0.25 mL D$_2$O (~23 equiv) and 2 mL DME. [b] Reactions were run in 1 mmol scale in 0.5 mL D$_2$O (~23 equiv) and 3-4 mL solvent, arbitrarily for 30 min. [c]1 h at 150 °C followed by 3 h at 160 °C. [d]GC area ratio calibrated with corresponding non-deuterated compound.

We have previously shown how iridium-catalyzed C-H borylation has been applied to various substituted thiophenes to synthesize polyfunctionalized thiophenes in good to excellent yields.[5f] 2-substituted thiophenes can be borylated selectively at the 5-position when treated with 1.0 - 1.5 equiv. of borane. Given excess borane, 2.5 - 3.0 equiv., 2-substituted thiophenes can be diborylated at the 3 and 5 positions generating 3,5-diborylated-2-substituted thiophenes (Scheme 4.3).[9]

Scheme 4.3 Borylation of 2-substituted thiophenes.
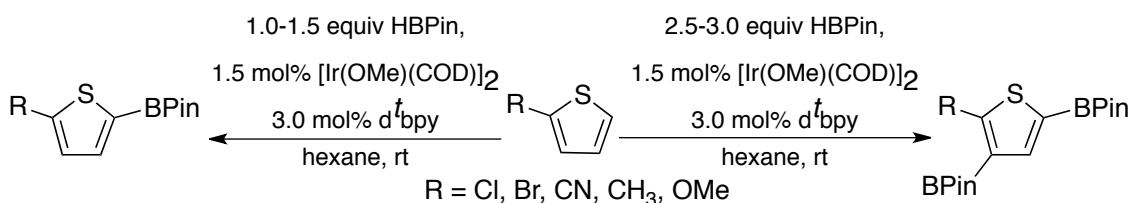
With no synthetic utility of these diborylated compounds reported, we investigated the possibility of deborylation to generate regioisomers of monoborylation i.e. 3-borylated-2-substituted thiophenes. 2,3-substituted thiophenes especially the 2,3-diaryl thiophenes have been shown to selectively inhibit COX-2 enzyme induced during inflammation.[10] This substitution is hard to synthesize by direct functionalization method

of C-H bonds. As the conditions reported by Dr. Feng Shi for deutero deborylation were harsh, milder conditions were explored and found that methanol in dichloromethane (2:1) at 55 ^{o}C was effective for protodeborylation. As mentioned previously the crude borylation mixture was effective in deborylation, has prompted us to perform a one-pot diborylation/deborylation of 2-substituted thiophenes. After the initial diborylation in hexane, the solvent was pumped off and the crude reaction mixture was subjected to deborylation at 55 ^{o}C in a mixture of CH_3OH/CH_2Cl_2 (2:1) (Scheme 4.4). The first boron to be introduced is the one to be readily deborylated giving 3-BPin-2-substituted thiophenes, regioisomers of monoborylation, in good yields (Table 4.2). The one-pot diborylation/deborylation of 2-chlorothiophene failed due to dideborylation, so the deborylation was performed on isolated diborylated product (Scheme 4.5) to yield the desired 2,3-substituted product (**4.3d**).

Scheme 4.4 One-pot diborylation/deborylation of 2-substituted thiophenes.
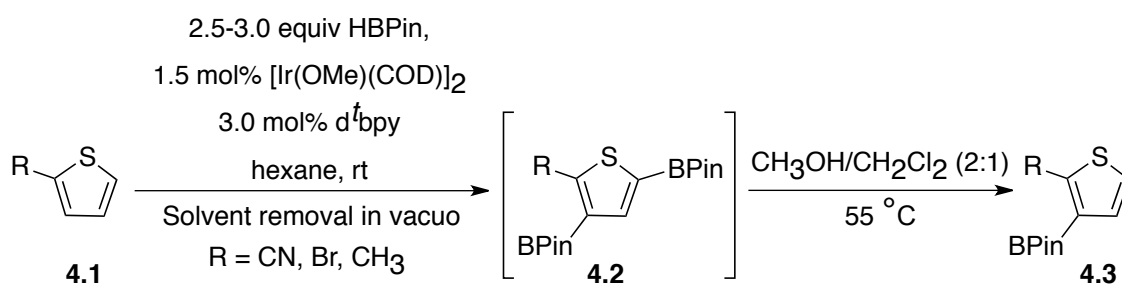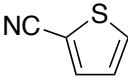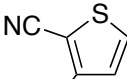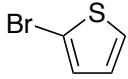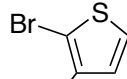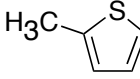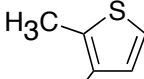
Table 4.2 Diborylation/deborylation of 2-substituted thiophenes according to Scheme 4.4.

entry	substrate	HBPin equiv	borylation time	deborylation time	product	% yield
1	NC—S (**4.1a**)	2.5	4 h	5.5 h	NC—S, BPin (**4.3a**)	75
2	Br—S (**4.1b**)	3.0	22 h	10 h	Br—S, BPin (**4.3b**)	80
3	H₃C—S (**4.1c**)	3.0	48 h	5 h	H₃C—S, BPin (**4.3c**)	72

Scheme 4.5 Deborylation of 3,5-diBPin-2-chlorothiophene (**4.2d**).

Cl—S—BPin, BPin (**4.2d**) → 1.5 mol% [Ir(OMe)(COD)]$_2$, CH$_3$OH/CH$_2$Cl$_2$ (2:1), 55 °C, 0.5 h → Cl—S, BPin (**4.3d**) 60% yield

Similar to 2-substituted thiophenes, 3-substituted thiophenes can be mono or diborylated by adjusting the stochiometry of the borane (Scheme 4.6).[5f,9a] The monoborylation product is usually a mixture of 2-BPin and 5-BPin isomers, unless the 3-substitutent is sterically bulky to block the 2-borylation, and diborylation gives the 2,5-diBPin compound. In the case of 3-cyanothiophene, a mixture of 2-BPin and 5-BPin isomers were formed in 1.13:1 ratio and isolated as a mixture. The diborylation of 3-

cyanothiophene forms the 2,5-diBPin-3-cyanothiophene (**4.2e**), which upon deborylation afforded the 5-BPin-3-cyanothiophene isomer (**4.3e**) (Scheme 4.7).

Scheme 4.6 Borylation of 3-substituted thiophenes.
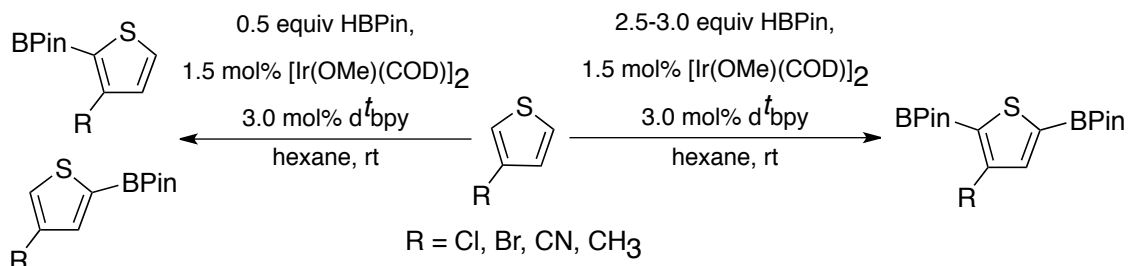
Scheme 4.7 Deborylation of 2,5-diBPin-3-cyanothiophene (**4.2e**).
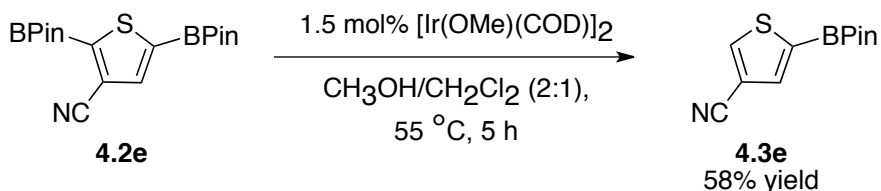
4.3 Diborylation and Deborylation of Indoles and N-Boc-7-Azaindole

Indoles are an important class of heterocycles with wide range of biological activities and hence they can act as lead compounds or key building blocks.[11] Direct functionalization of indoles would create a method for the synthesis of materials that are cumbersome to prepare by classical methods. Although C-2[12,13] and C-3[5g,14] functionalization of indole can be readily achieved due to greater reactivity of the azole ring, the functionalization of the benzenoid ring remains a challenging task. C-7 functionalized indoles exist in some natural products, such as 7-prenylindole,[15a] pyrrolophenanthridone alkaloids,[15b] asperazine,[15c] chloropeptin I[15d] and in drug discovery for interesting indole scaffolds like etodolac.[15e] Selective C-7 functionalization

65

of indoles typically requires a substitutent at the 2-position to block reactivity at that site

or a directing group or both (Scheme 4.8). The directed metalation approach by Snieckus

and co-workers[16] requires an amide protection of nitrogen and C-2 TMS protection for

functionalization at the 7-position. On the other hand our group reported the direct C-H

borylation of 2-substituted indoles without the need for a directing group on nitrogen.[5d]

Recently Hartwig and co-workers[17] reported the N-silyl directed C-H borylation of

indoles without the need for a substituent at the 2-position. Even though Hartwig's

procedure did not require blocking the 2-position, it still requires protection/deprotection

to achieve 7-BPin NH-indoles.

Scheme 4.8 C-7 functionalization of indoles.
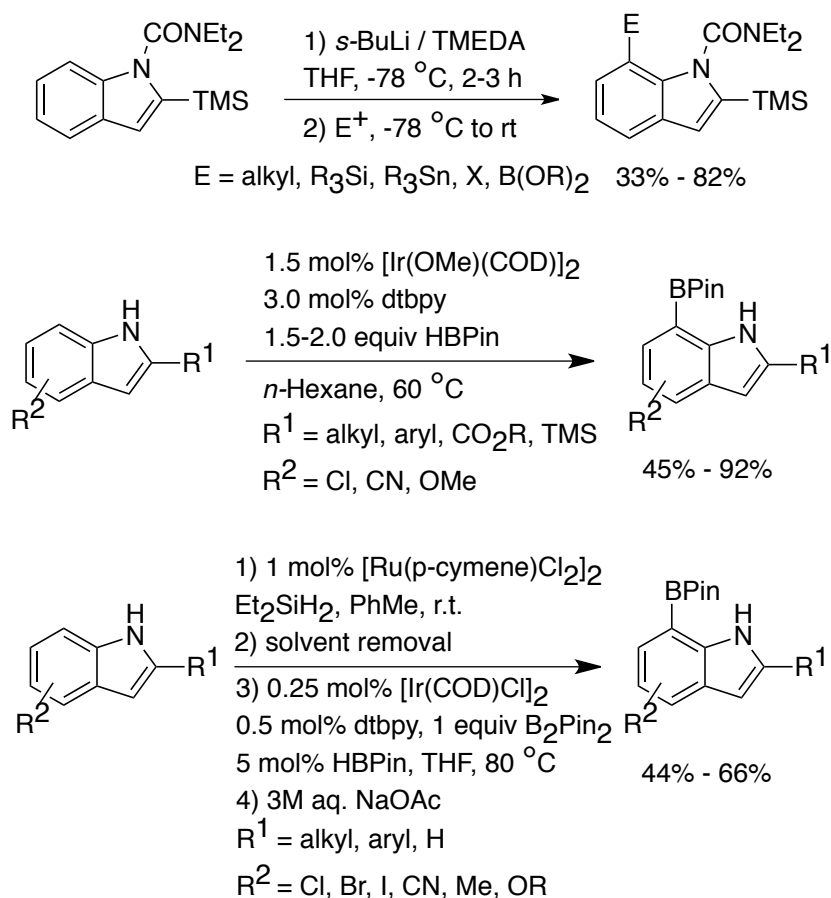
Reactions that functionalize the C-7 position without the need for a directing group or substituent at 2-position would be more attractive. Our group and others have shown that indoles can be monoborylated to give 2-BPin indoles or diborylated to give 2,7-diBPin indoles (Scheme 4.9).[5d,12] As seen for thiophene deborylation, the first boron to be introduced is most readily deborylated, the same was investigate with 2,7-diBPin indoles. Deborylation of the diBPin indoles was selective for 2-BPin giving the 7-BPin indoles (Table 4.3). Various substitutents such as methyl, nitrile and bromo at the 3, 4 and 5-positions were tolerated. The yields of diborylation/deborylation, over 2-steps, were higher when compared to the N-silyl directed borylation reported by Hartwig[17] (Scheme 4.10). The deborylation conditions are mild and have been used on diborylated tryptophan to yield 7-BPin tryptophan (Table 4.3, entry 4).

Scheme 4.9 Borylation of substituted indoles.

R = Br, CH$_3$, CN
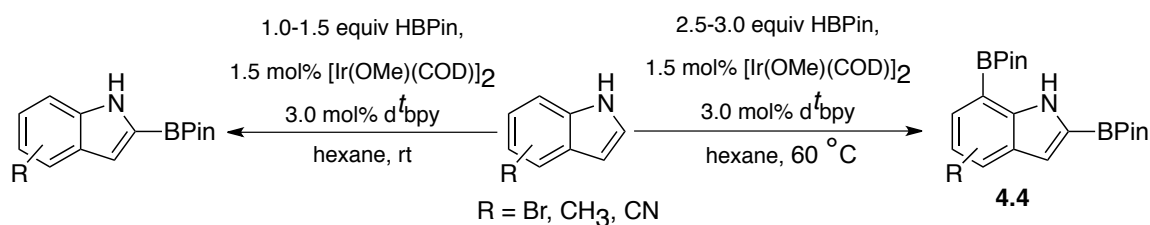
Scheme 4.10 Comparison of diborylation/deborylation with N-silyldirected borylation of indoles.

R^1 = CH$_3$ (61%)
= CN (45%)
= Br (55%)

R^1 = CH$_3$ (59%)
= CN (78%)
= Br (66%)
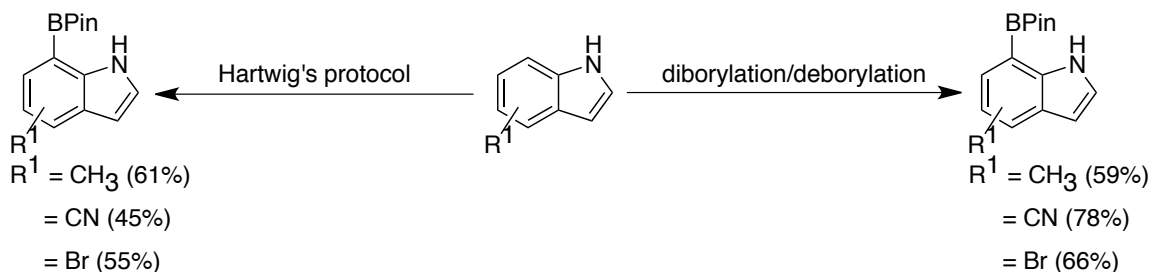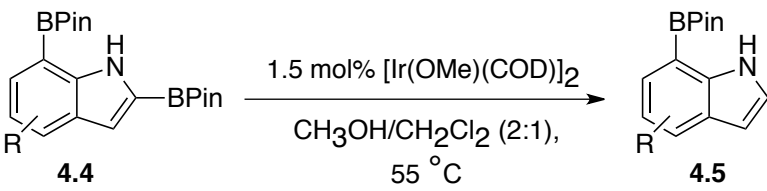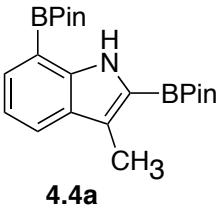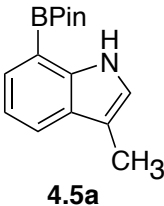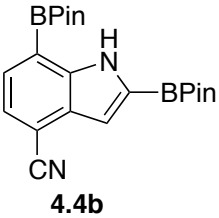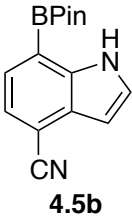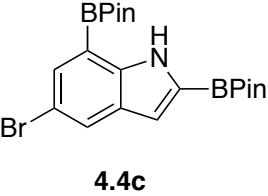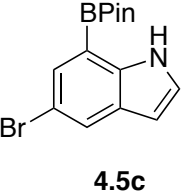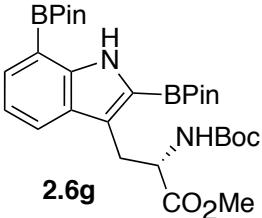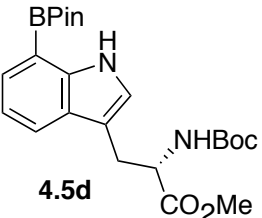
Table 4.3 Deborylation of 2,7-diBPin indoles (**4.4**).

entry	substrate	time	product	% yield
1	**4.4a**	72 h	**4.5a**	75
2	**4.4b**	1 h	**4.5b**	85
3	**4.4c**	1.75 h	**4.5c**	70
4	**2.6g**	2 h	**4.5d**	58

As shown in chapter-2, N-Boc-7-azaindole can be monoborylated to give 3-BPin-N-Boc-7-azaindole (**2.4e**) or diborylated to give 3,5-diBPin-N-Boc-7-azaindole (**2.4f**).[5g,9b] The diborylated product (**2.4f**) can be selectively deborylated at the 3-position giving the 5-BPin-N-Boc-7-azaindole (Scheme 4.11), a regioisomer of monoborylation.

Scheme 4.11 Deborylation of 3,5-diBPin-N-Boc-7-azaindole (**2.4f**).

2.4f

1.5 mol% [Ir(OMe)(COD)]$_2$

CH$_3$OH/CH$_2$Cl$_2$ (2:1),
55 $^\circ$C, 4 h

4.5e
49% yield
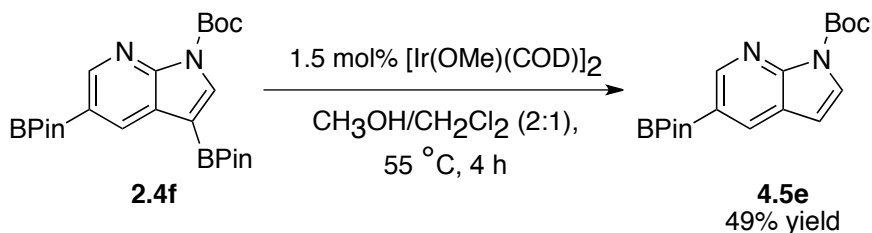
4.4 C-H Activation/Borylation, deuteration and deborylation of Clopidogrel

The mildness of C-H activation/borylation and deborylation conditions would allow their use in late synthetic stages and on advanced molecules like pharmaceuticals. To demonstrate this we have choosen Clopidogrel, the active ingredient of Plavix. Clopidogrel is an antiplatelet agent used to inhibit blood clots in coronary artery disease, peripheral vascular disease and cerebrovascular disease.[18]

Researchers have found that drug compounds incorporating deuterium isotope are more stable than their hydrogen equivalents and such deuterated drugs may be safer, longer lasting or more effective than their analogues.[19] Clopidogrel was selectively monoborylated next to the heteroatom, which upon deuteriolysis under the conditions shown in Scheme 4.12 affords deuterated clopidogrel. Functionalization at the distal end of the molecule in the presence of a more reactive proximal site is quite challenging. Clopidogrel was diborylated to a 1:1 mixture of regioisomers (Scheme 4.13) and when subjected to protolytic deborylation, can selectively deborylate at the proximal site leaving the distal end functionalized (Scheme 4.14).

Scheme 4.12 Monoborylation and deutero deborylation of clopidogrel.

4.6a

1.5 equiv HBPin,
1.5 mol% [Ir(OMe)(COD)]$_2$
3.0 mol% d^{t}bpy
MTBE, rt, 1 h 15 min

4.6b
56% yield

4.6b

3.0 mol% [Ir(OMe)(COD)]$_2$
CD$_3$OD + CDCl$_3$ (2:1), 55 °C
2 h 30 min

4.6c
81% yield
92 % D-incorporation
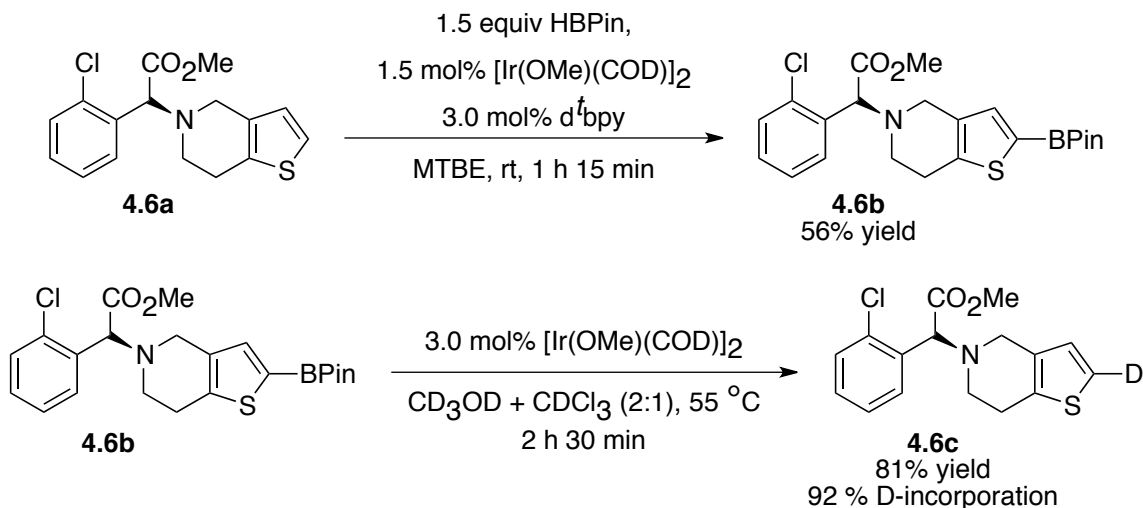
We have previously established that C-H activation/borylation is stereospecific and products are obtained with no loss of stereochemistry.[5g] To assess the same during deborylation, the monoborylated clopidogrel was subjected to protolytic deborylation and the product was compared with clopidogrel using optical rotation. There was no change in optical rotation between clopidogrel and the product obtained from deborylation.

Scheme 4.13 Diborylation of clopidogrel.

4.6a

3.0 equiv HBPin,
3.0 mol% [Ir(OMe)(COD)]$_2$
6.0 mol% d^{t}bpy
MTBE, rt, 30 h

4.6d

+

4.6e
77% yield (1:1)
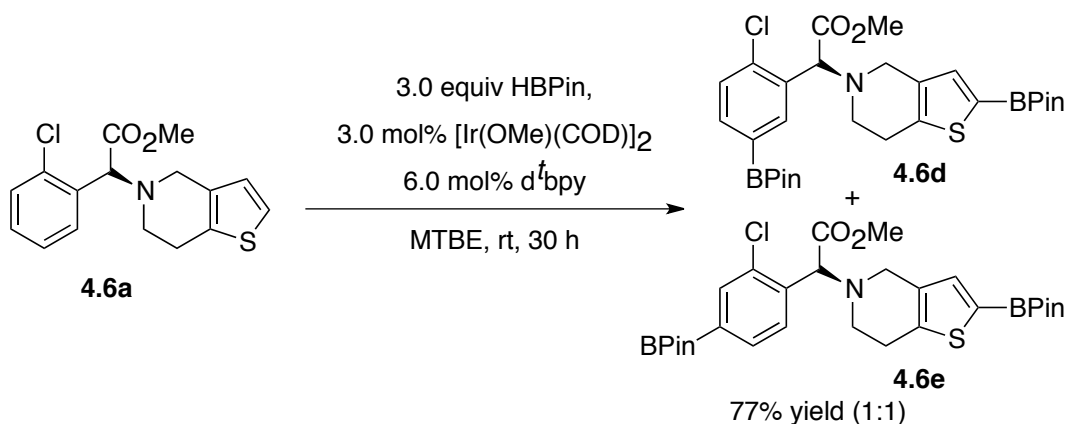
Scheme 4.14 Deborylation of diborylated clopidogrel.
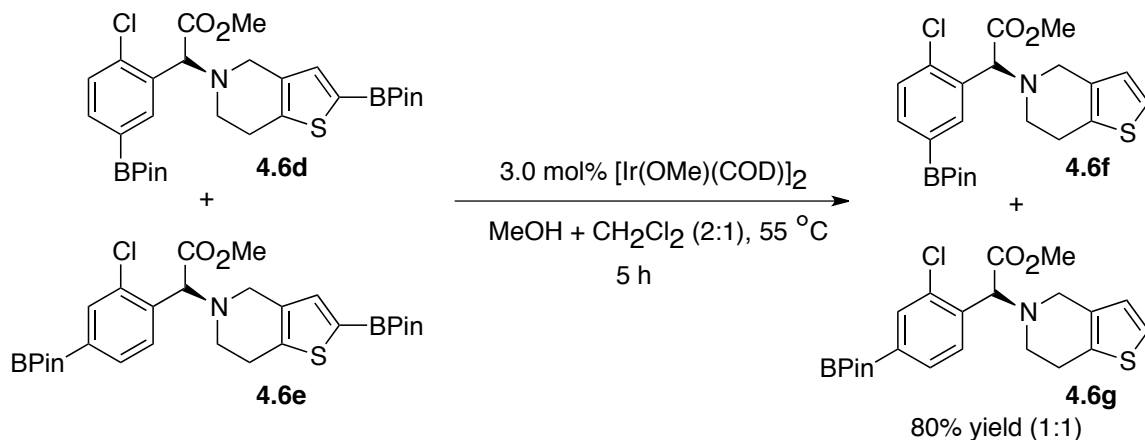
4.5 Reaction Mechanism

In terms of the reaction mechanism, we have not performed an in-depth investigation, but a putative catalytic cycle is given in Scheme 4.15. From Table 4.1 we have seen that Ir species without any added ligand is the active catalytic species and therefore a catalytic cycle different from the C-H borylation is possibly in play. It calls for an Ir(I) alkoxide as the active catalytic species. A subsequent transmetalation step is responsible for the cleavage of the C–B bond to generate the aryl Ir species. Protonolysis/deuteriolysis of this Ir-Ar bond affords the arene and regenerates the Ir alkoxide. Our major explanation that Ir(I), rather than Ir(III), is the catalytically active species is based on two reasons. For one, according to Table 1, Ir(I) species are better catalysts than Ir(III). For the other, this transmetalation is known for Ir-catalyzed reactions[8] and Ir(I) species are generally recognized as the active catalysts in these reactions.

Scheme 4.15 A putative mechanism for Ir-catalyzed deborylation.

Ar—D/H   Ir—OMe   Ar—BPin

MeOH/D   Ir—Ar   PinB—OMe
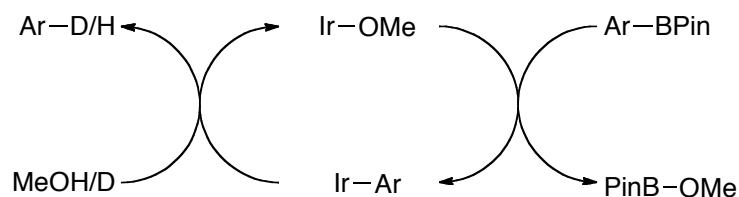
4.6 Conclusions

In conclusion C-H activation/borylation coupled with deborylation has proved to be powerful method in synthesizing pinacol boronic esters, with regiochemistry complementary to the previously known methods and tolerant of a variety of functional groups. The mildness and stereospecificity of the reactions has allowed us to use deuteration and deborylation on advanced molecules like pharmaceuticals.

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BIBLIOGRAPHY

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CHAPTER 5

Desymmetrization of Diborylated Substrates and Synthetic Applications

5.1 Introduction

Iterative cross-coupling of bifunctional arenes and heteroarenes have greatly facilitated the preparation of oligoarene-type polymers.[1] Efforts towards achieving this goal have influenced the preparation of some bifunctional organoboranes.[2-5] Organoboronic acid derivatives have been widely used in the palladium-mediated coupling with organic halides i.e. the Suzuki-Miyaura coupling, which has become one of the most powerful carbon-carbon bond forming methods in organic synthesis. The bifunctional organoborane can have C-halogen and C-B bonds in the same molecule[3a,4a,5a] or have two C-B bonds whose reactivity is tamed by the presence of different protecting groups.[3b,3d,4b,5b] The former has been reported where haloarylboronic acid derivatives (Scheme 5.1 and 5.2) have been used in iterative cross-coupling or other cross-coupling reactions. The mechanism of cross-coupling reactions requires the presence of a vacant and Lewis acidic p-orbital.[6] Ligands that contain strongly electron donating heteroatoms reduce the Lewis acidity of the boron and thereby inhibit the reactivity of organoboron compounds.[6a]

Suginome has used a boron masking strategy to attenuate the reactivity at boron centers (Scheme 5.1) rendering them temporarily inactive and allowing the use of bifunctional arenes in the iterative coupling reactions.[3a] For a masking group to be highly effective there are some requirements including (1) easy installation, (2) high stability

during coupling and isolation and (3) easy removal. Amino groups are considered good masking group for boron center, as they will donate their lone pairs into the vacant p-orbital of the boron atom, thus lowering the acidity significantly in comparison with their corresponding boronic acids. 1,8-Diaminonapthalene acts as the masking agent by forming a stable cyclic diaminoborane with haloarylboronic acids. The so formed haloarylboronamides were tolerant of iterative Suzuki-Miyaura cross-coupling and helped in the synthesis of teraryls, quarteraryls and quinquearyls.[3a]

Scheme 5.1 Suginome Boron masking strategy of bromoarylboronic acids.
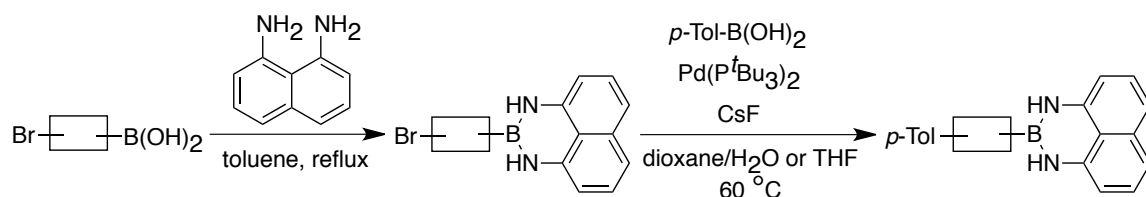
Another possibility for masking the boron center is to rehybridize the boron center from sp^2 to sp^3 via complexation through a trivalent ligand. Mancilla reported that N-methyliminodiacetic acid (MIDA) could be used as a protecting group for boronic acids and the so formed boronic esters have rigid bicyclic structures of strong intramolecular N–B coordination.[7] These boronic esters are highly stable but can be cleaved readily using relatively mild reagents, as the heteroatom boron bonds in tetrahedral adducts are predicted to be weaker than those in their tricoordinate counterparts. Two decades later, Burke reported the use of these highly stable MIDA boronate esters.[4] They have complexed a variety of aryl, heteroaryl, vinyl and alkyl haloboronic acids with MIDA to yield a series of B-protected bifunctional building blocks (Scheme 5.2). The utility of

77

these bifunctional building blocks has been demonstrated in the iterative Suzuki-Miyaura cross-coupling for small molecule natural products synthesis. The versatility of these bifunctional MIDA boronates as cross-coupling partner in Stille, Heck, Sonagashira, Miyaura borylation and Negishi coupling has been achieved at the bromide terminus without perturbing the MIDA boronate.[4b] MIDA boronate group is stable to a wide range of common synthetic reagents, which enables for the synthesis of complex boronic acids from simple organoborane starting materials.[4c]

Scheme 5.2 MIDA protected haloarylboronic acids.
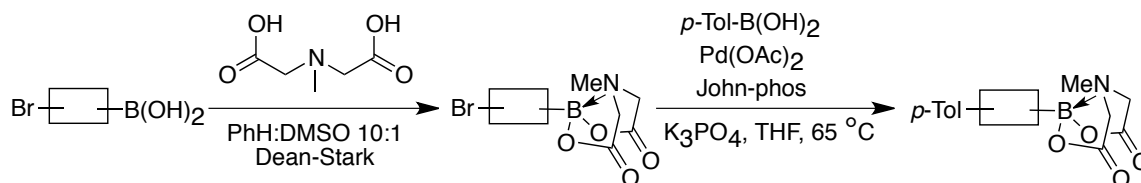
The widespread applications of arylboronic acids and aryl boronates in transition metal catalyzed reactions has led to increased demand for various boronic acids and esters. The traditional route to prepare aryl boron compounds via Grignard reagents and lithium reagents suffers from drawbacks like using rigorous anhydrous conditions and poor functional group compatibility. Overcoming some of these limitations, Miyaura reported a Pd-catalyzed direct conversion of aryl halides to aryl boronates.[8] A more economical and environmentally friendly method is the direct conversion of C-H bonds to C-B bonds and great efforts have been made towards this over the past decade. The Ir-catalyzed C-H activation/borylation has emerged as a useful method for synthesizing various aryl and heteroaryl boronic esters with regiochemistry complimentary to traditional methods and tolerant of various functional groups.[9] By adjusting the

stoichiometry of the borane added, some of the aryls and heteroaryls can be mono or diborylated.[9c,d,f] The synthetic utility of the monoborylated product has been well demonstrated in the conversion of C-B bonds to C-C, C-N, C-O and C-X bonds.[9a,10] It is the diborylated products whose synthetic utility is limited. As discussed in Chapter-4, the deborylation has allowed us to selectively cleave one of the C-B bonds generating regioisomers of monoborylation. A generally useful strategy would involve the boron-selective coupling of differentially ligated diboron reagents.

Suginome et al. has reported benzenediboronic acid derivatives (BPin-BDan), where the boronyl groups are differentially protected for orthogonal reactivity in cross-coupling reactions (Scheme 5.3).[3b] Our attempts to make similar BPin-BDan compounds based on pyrrole were unsuccessful as discussed later in the chapter.

Scheme 5.3 BPin-BDan compounds for orthogonal functionalization.
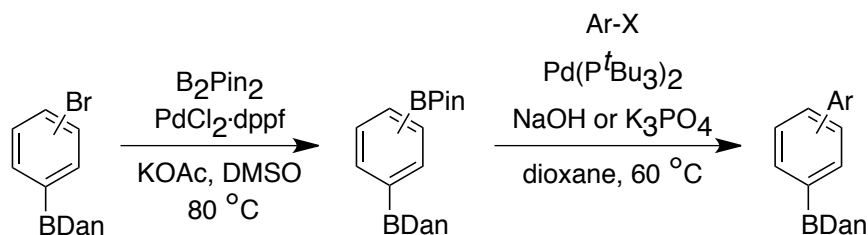
Burke et al. developed an alkenyl diboron compound, based on BPin-BMIDA ligands, which cross-couples selectively on the nature of the non-participating boron substituents (Scheme 5.4).[4b] Although the boron masking/unmasking strategy allows for the orthogonal reactivity of compounds bearing two nucleophilic coupling sites, it would be more beneficial if the unmasking stage could be skipped. Achieving this goal, Molander's group reported the orthogonal reactivity in boryl-substituted

organotrifluoroborates, where in the reactivity difference between organotrifluoroborates and trialkylboranes was exploited for multicomponent complex molecule synthesis (Scheme 5.5).[5b]

Scheme 5.4 Burke's trivalent protecting group for orthogonal functionalization.
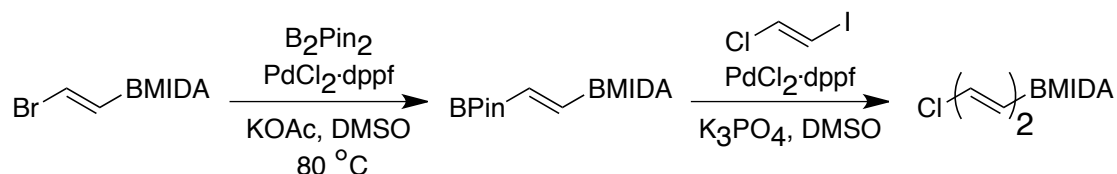
Scheme 5.5 Molander's one-pot hydroboration and orthogonal Suzuki-Miyaura coupling protocol.
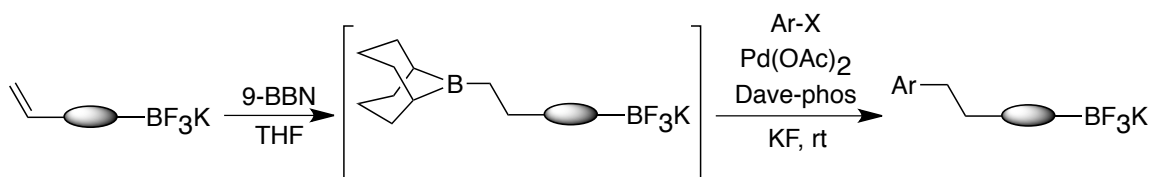
C–H activation/borylation has allowed us to access bispinacolboronic esters, where the boron sites are chemically equivalent. If these positions could be selectively transformed, C–H borylation would provide a simple protocol for desymmetrizing C–H bonds. Two approaches for preparing differentially ligated diborylated compounds are borylation/protection/borylation and diborylation/desymmetrization (Scheme 5.6). The former strategy has an additional step and the protecting group must be compatible with Ir-catalyzed borylation. The C-H activation/borylation of 2-BDan pyrrole with HBPin resulted in exchange of the diaminonapthalene group in 2-BDan pyrrole with the pinacolate group in HBPin and this occurred at a rate competitive with C-H borylation. Where as the C-H activation/borylation of 3-BPin pyrrole with HBDan resulted in dehydropolymerization of HBDan with no product formation. Both approaches require

selectivity for one of two symmetric sites. The borylation/protection/borylation route requires that diborylation be avoided in the first step, while the diborylation/desymmetrization strategy calls for a selective monoprotection of the symmetric diboronate. As indicated in Scheme 5.6, either strategy could also apply to symmetrical dihalides.

Scheme 5.6 Two strategies for desymmetrizing aromatic hydrocarbons and dihalides.
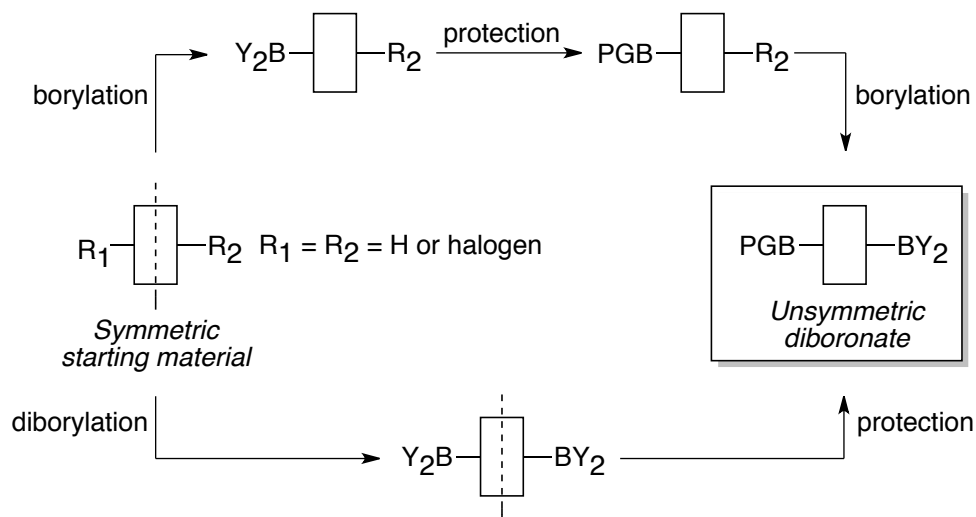
To evaluate the diborylation/protection route, the masking of bispinacolboronic esters with MIDA was attempted. Bala Ramanathan, a postdoc in our lab, was successful in desymmetrization of symmetrical bisboronic esters by selective mono MIDA protection giving BPin-BMIDA and BNeopentylglycolate-BMIDA compounds (Scheme 5.7). The reaction was performed using a three-fold excess of bisboronic esters with MIDA as the limiting reagent in DMSO:benzene = 2:3 at reflux. The excess bisboronic esters can be separated from the desired product and recycled, by washing the reaction mixture with a hydrocarbon solvent. The utility of these differentially ligated diboron reagents in selective couplings generating C-C, C-N, C-O and C-X bonds will be discussed.

Scheme 5.7 Desymmetrization of symmetrical bisboronic esters.

3.0 equiv

C$_6$H$_6$/DMSO, 120 °C, 14 h

5.1a
63% yield

5.1b
52% yield

5.1c
58% yield

5.1d
72% yield

5.1e
11% yield
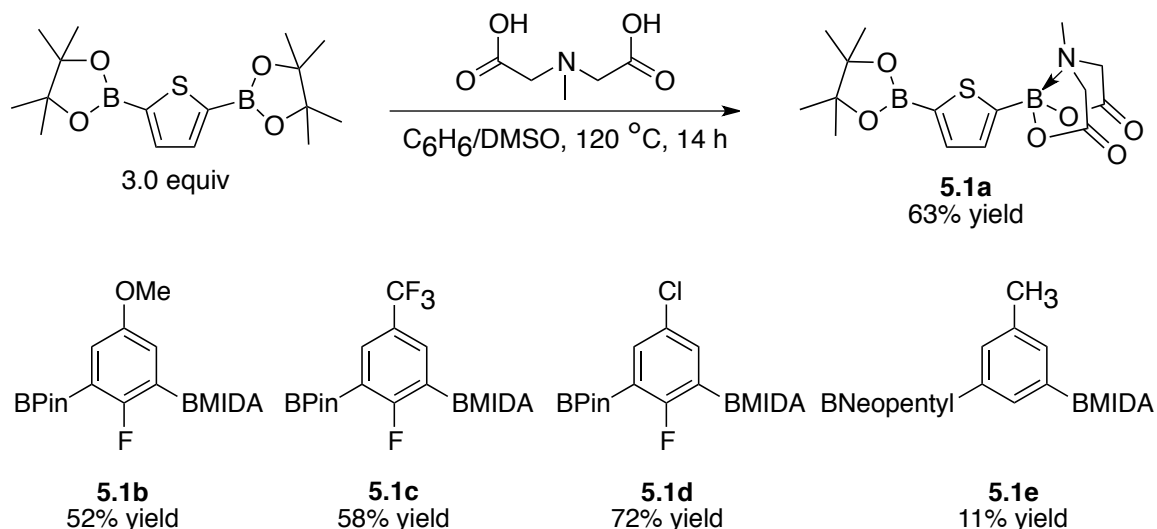
5.2 Suzuki-Miyaura Coupling of Aryl and Heteroaryl BPin-BMIDA compounds

Since its inception in 1979,[11] the Suzuki-Miyaura reaction has seen significant advancement and emerged as a successful method for C-C bond formation in complex molecule synthesis. After a decade of extensive efforts for the synthesis of active catalyst systems, synthetic chemists have focused their attention towards the successive Suzuki-Miyaura coupling reactions with substrates containing two or more reactive sites. The key to obtaining orthogonal functionalization through consecutive Suzuki-Miyaura coupling is to modulate the reactivity of the reaction sites. In an attempt to do so we have synthesized BPin-BMIDA compounds via C-H activation/borylation or Miyaura borylation. To demonstrate the selectivity of these substrates in the Suzuki-Miyaura reaction, **5.1a** was subjected to conditions suitable for coupling pinacol boronic esters and aryl bromides (Scheme 5.8).[10e] In spite of the base-sensitive nature of the MIDA protecting group, it was possible to perform a selective Suzuki-Miyaura coupling at the BPin terminus leaving the BMIDA intact.

As the conditions for Suzuki coupling in Scheme 5.8 were not optimal for coupling other aryl BPin-BMIDA compounds, different conditions were explored. It was shown by Burke that alkenyl BPin-BMIDA could be chemoselectively coupled at the BPin terminus using PdCl$_2$•dppf in DMSO.[4b] Using DMSO as solvent has proved to be successful in Suzuki coupling the aryl and heteroaryl BPin-BMIDA compounds in good yields (Table 5.1). Table 5.1 shows the various aryl BPin-BMIDA compounds employed in selective Suzuki-Miyaura cross-coupling. The diaryl products can be unmasked and employed in iterative cross-coupling.

Scheme 5.8 Suzuki-Miyaura coupling of **5.1a**
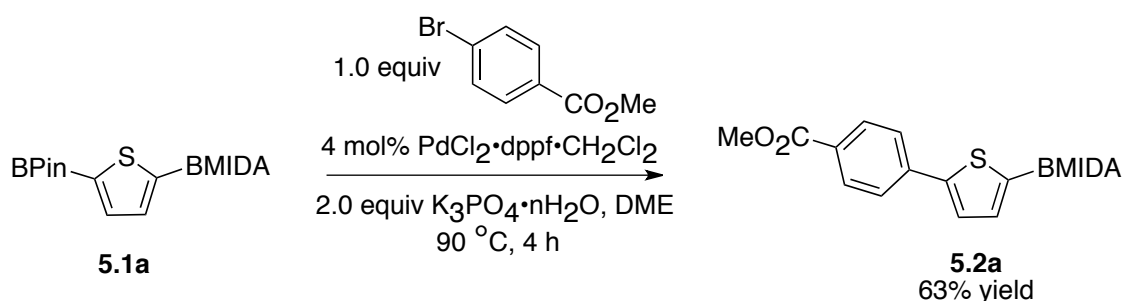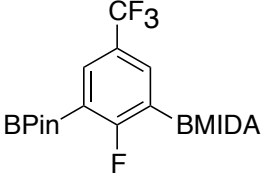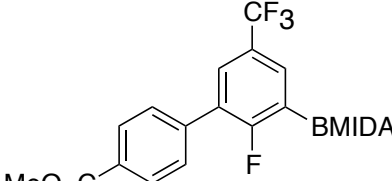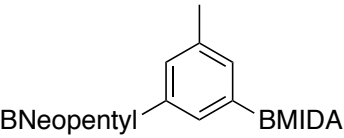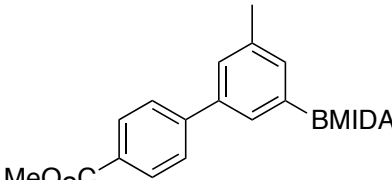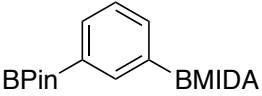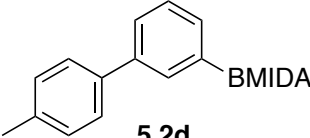
Table 5.1 Suzuki-Miyaura coupling of differentially ligated diboron compounds
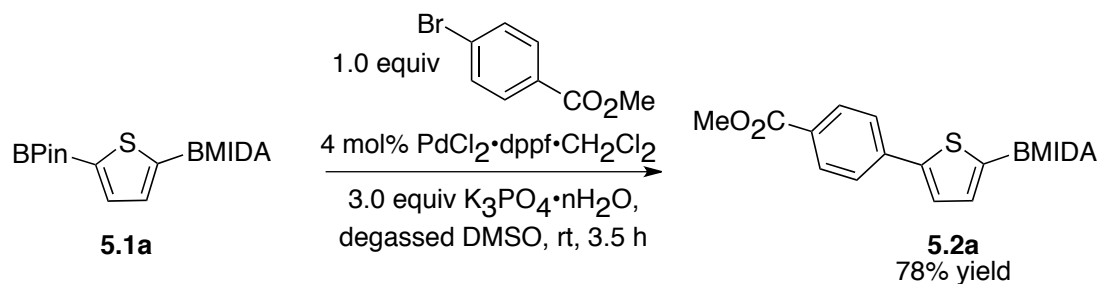
entry	substrate	product	time, % yield
1	**5.1c**	**5.2b**	6 h, 78%
2	**5.1e**	**5.2c**	6 h, 81%
3	**5.1f**	**5.2d**	3.5 h, 81%

5.3 Amination of BNeopentyl-BMIDA compounds

The increasing importance of Suzuki-Miyaura coupling in organic synthesis has brought about a diverse set of aryl and heteroaryl boronic acids and esters. Even though carbon-carbon bond formation from carbon-boron bonds is well established, the corresponding carbon-heteroatom bond formation has synthetic utility. Aryl amines and aryl ethers are ubiquitous and are available in a wide range of pharmaceuticals and agro

chemicals. Synthesis of aryl amines and aryl ethers is by classical Cu-mediated Ullmann reaction and Pd-catalyzed C-N bond formation of aryl halides developed by Buchwald and Hartwig.[12] These reactions suffered from harsh conditions and the use of expensive Pd-catalyst. Chan, Evan, and Lam devised Cu-catalyzed couplings where aryl boronic acids afford C-O, C-N, and C-S bonds when reacted with phenols, anilines and thiophenols respectively.[13] Since their discoveries, several research groups have made considerable progress in expanding this Cu-mediated cross-coupling methodology to include anhydrides of boronic acids (i.e. boroxines), as well as acyclic and cyclic boronic esters.[12] Chan and Lam have shown that neopentylglycolate boronic esters are more efficient than the corresponding pinacol boronic esters.[14] To investigate the C-N coupling using the differentially ligated diboron compounds, we used bifunctional BNeopentylglycolate-BMIDA compounds. Under the conditions reported by Chan and Lam $(Cu(OAc)_2/Pyridine/CH_2Cl_2/rt)$,[14] the coupling of BNeopentyl-BMIDA with benzimidazole failed to give any product.

In 2007, Hartwig et al. reported the sequential iridium-catalyzed borylation and copper-catalyzed coupling of arenes generating anilines and aryl ethers.[10d] Under modified conditions of their procedure, wherein 1.0 equiv of anhydrous $Cu(OAc)_2$ was used instead of 10 mol% of $Cu(OAc)_2 \cdot H_2O$. The modified conditions were ineffective in coupling benzimidazole, but were successful in coupling cyclohexyl amine. The coupling was selective for the BNeopentylglycolate terminus obtaining the desired product in moderate 48% yield (Scheme 5.9).

Scheme 5.9 Chemoselective Amination of BNeopentyl-BMIDA
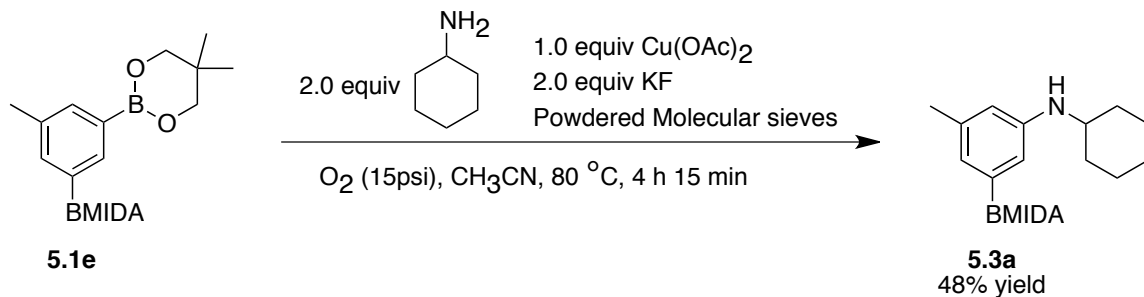
5.4 Halodeboronation of BPin-BMIDA compounds

Aryl halides are valuable synthetic intermediates that have been used in a variety of carbon-carbon and carbon-heteroatom bond formation. Even though a large number of aryl halides are commercially available, the regioselective introduction of halogen into advanced molecules can be quite challenging. Traditional routes of aromatic halogenation suffer from harsh conditions, which limits their applicability. Hence, milder and better halogenation routes have synthetic value. Arylboron compounds were known to halodeboronate regioselectively. N-halosuccinimides,[15a] dibromodimethylhydantoin,[15b] and chloramine T/NaBr[15c] have been employed for the conversion of arylboron compounds to aryl halides. In 2004, Huffman and co-workers[15d] reported the use of $CuBr_2$ for the conversion of phenols to aryl bromides via arylboronate esters. Unlike traditional routes C-H activation/borylation generates boronic esters based on sterics, which upon halodeboronation could generate aryl halides which were previously hard to access. Recently Hartwig's group reported a one-pot Ir-catalyzed C-H activation/borylation coupled with Cu(II) mediated halogenation to synthesize a variety of 3,5-disubstituted aryl bromides and chlorides.[10b] To demonstrate the potential of these

differentially ligated diboron compounds in various transformations, we investigated the possibility of selective halodeboronation of BPin-BMIDA compounds.

The halodeboronation of **5.1b** was attempted. Similar to Suzuki coupling and amination, the halodeboronation of the BPin terminus was anticipated leaving the BMIDA intact. Some of the previously known conditions for halodeboronation were explored. *N*-bromosuccinimide, which was previously known to effect ipso-halogenation of arylboronic acids was ineffective in halodeboronation of the boronic esters. Copper(II)bromide/chloride were unselective, giving a mixture of mono and dihalogenated products. In pursuit of conditions for selective halodeboronation, we found that NBS in the presence of $Cu(OAc)_2 \cdot H_2O$ was selective for BPin halodeboronation leaving the BMIDA intact. Optimized reaction conditions are shown in Scheme 5.10, which gave 80% yield of the desired product. Even under optimized reaction conditions there was 5-10% of protolytic deborylation seen. In an attempt to minimize the protolytic deborylation, the reaction was performed using anhydrous $Cu(OAc)_2$. There was no reaction under these conditions.

Scheme 5.10 Optimized conditions for chemoselective halodeboronation of **5.1b**.

5.1b

5.4a
80% yield
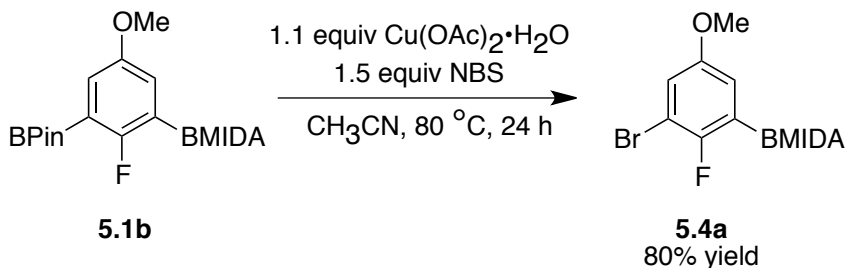
5.5 Sequential cross-coupling of diboron compounds

C-H activation/diborylation coupled with desymmetrization using the MIDA ligand has allowed us to access multifunctionalized arenes. The key to the application of

these substrates in the synthesis of complicated molecules is the multiple transformations that can be employed at the two or more reactive sites. The products obtained from selective Suzuki-Miyaura coupling, amination and halodeboronation can undergo a similar set of transformations at the BMIDA terminus or can undergo different transformations after MIDA deprotection. To illustrate the multiple transformations that can be effected at the multiple reaction sites, we have chosen compound **5.1d** that was obtained from C-H activation/diborylation followed by MIDA desymmetrization of 4-fluorochlorobenzene (Scheme 5.11). **5.1d** was subjected to chemoselective Suzuki-Miyaura coupling, under the conditions previously described, to obtain the biaryl **5.2e** in 84% yield (Scheme 5.12). Attempted Buchwald-Hartwig aminations at the chloride terminus of **5.2e** were unsuccessful. Therefore, an in-situ deprotection/oxidation of the BMIDA was used to obtain the desired phenol **5.5a** in 92% yield (Scheme 5.13).[16] This reaction illustrates the ease with which MIDA deprotection can be effected and employed in subsequent transformations of the in-situ generated boronic acid. Compound **5.5a** was then subjected to Buchwald-Hartwig amination, at the chloride terminus under the conditions reported by Biscoe et al.[17] The highly active palladacycle precatalyst was successful in making the C-N bond generating the desired amination product **5.6a** in 85% yield (Scheme 5.14). An overall yield of 66% over three steps was obtained.

Scheme 5.11 Synthesis of **5.1d** from 4-fluorochlorobenzene
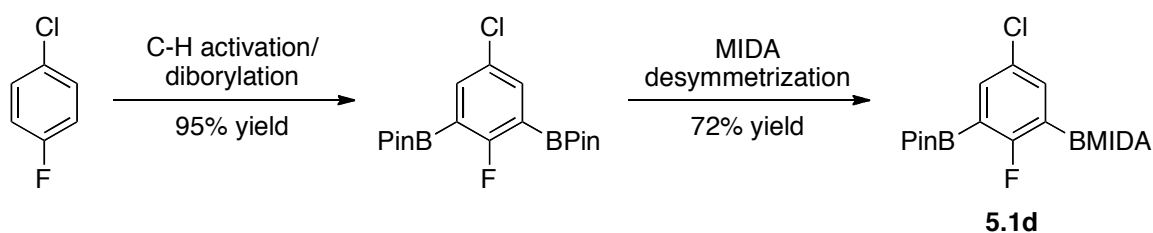
Scheme 5.12 Suzuki-Miyaura coupling of **5.1d**

5.1d

1.1 equiv

4 mol% PdCl$_2$·dppf·CH$_2$Cl$_2$

3.0 equiv K$_3$PO$_4$·nH$_2$O,
DMSO, rt, 10 h

5.2e
84% yield
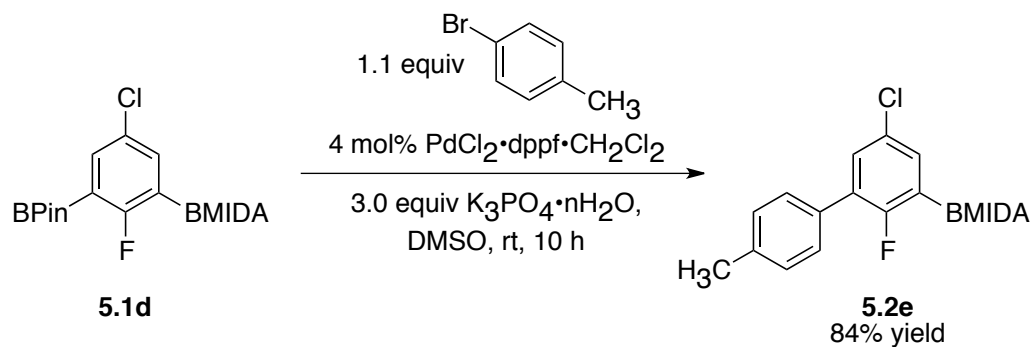
Scheme 5.13 Deprotection/oxidation of **5.2e**

5.2e

4.0 equiv NaOH, 3.0 equiv H$_2$O$_2$

THF, rt, 2 h

5.5a
92% yield
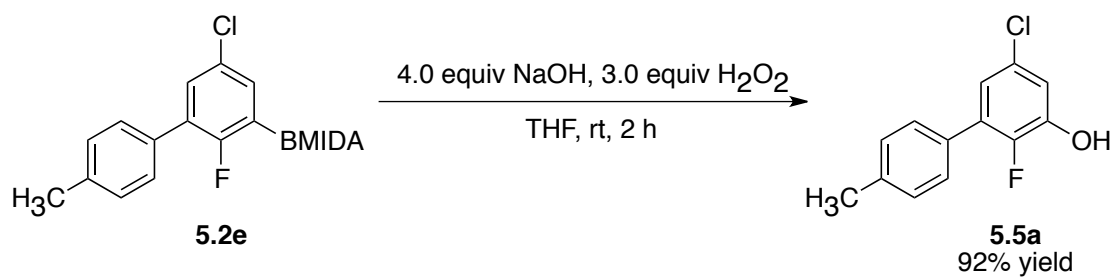
Scheme 5.14 Buchwald-Hartwig amination of **5.5a**

5.5a

1.5 equiv

2 mol%
PdPhosX

2.4 equiv LHMDS

p-dioxane, rt, 3 h

5.6a
85% yield
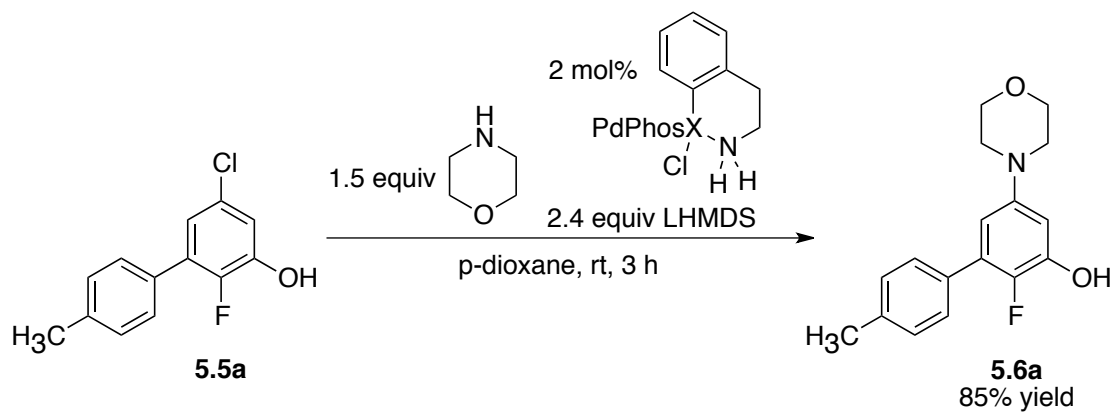
5.6 Conclusions

In conclusion we have shown how MIDA protection can be used to attenuate the reactivity of the diboron compounds. It has allowed us to desymmetrize diboron compounds generated from Ir-catalyzed C-H activation/borylation and Miyaura borylation. The selective coupling of BPin leaving the BMIDA intact allows for the iterative cross-coupling. The utility of these substrates with two or more reaction sites in multi transformations has been demonstrated. This allows for the synthesis of complex organic molecules from simple building blocks.

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CHAPTER 6

Experimental Details and Compound Characterization Data

6.1 Chapter-2. Experimental Details and Spectroscopic Data

6.1.1 Materials and Methods

Pinacolborane (HBPin) was generously supplied by BASF. Bis(η^4-1,5-cyclooctadiene)-di-μ-methoxy-diiridium(I) [Ir(OMe)(COD)]$_2$ was prepared per the literature procedure.[1] 4,4′-Di-t-butyl-2,2′-bipyridine (d^{t}bpy) was purchased from Aldrich. N-Boc pyrrole, N-Boc indole and Boc-L-phenylalanine methyl ester were purchased from Aldrich. Methyl-2-pyrrolecarboxylate and 7-azaindole were purchased from Aldrich and Boc-protected per literature procedure.[2] 2-Methylpyrrole and 6-azaindole were prepared per literature procedures[3] and Boc protected. L-Tryptophan was purchased from Chem-Impex International and protected per literature procedure.[4] All substrates were purified by column chromatography or passing through a plug of alumina. Pinacolborane (HBPin) was distilled before use. n-Hexane, cyclohexane and MTBE were refluxed over sodium, distilled, and degassed. Tetrahydrofuran was obtained from a dry still packed with activated alumina and degassed before use. Silica gel was purchased from EMD ^{TM} (230-400 Mesh).

All reactions were monitored by GC-FID (Varian CP-3800; column type: WCOT Fused silica 30m × 0.25mm ID coating CP-SIL 8 CB). GC-FID method: 70 °C, 2 min.; 20 °C/min, 9 min.; 250 °C, 10 or 20 min.; All reported yields are for isolated materials.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova-300 (300.11 and 75.47 MHz respectively), Varian VXR-500 or Varian Unity-500-Plus spectrometer (499.74 and 125.67 MHz respectively) and referenced to residual solvent signals (7.24 ppm and 77.0 ppm for CDCl$_3$, respectively). ^{11}B spectra were recorded on a Varian VXR-300 operating at 96.29 MHz and were referenced to neat BF$_3$•Et$_2$O as the external standard. All coupling constants are apparent J values measured at the indicated field strengths. All 2-dimensional experiments were run using z-axis pulse field gradients. Elemental analyses were performed at Michigan State University using a Perkin Elmer Series II 2400 CHNS/O Analyzer. GC-MS data were obtained using a Varian Saturn 2200 GC/MS (column type: WCOT Fused silica 30m × 0.25mm ID coating CP-SIL 8 CB). Melting points were measured on a MEL-TEMP$^{®}$ capillary melting apparatus and are uncorrected. Optical rotations were recorded on a Perkin Elmer Polarimeter 341 at the sodium D line. A Biotage Initiator microwave was used for the borylation of Boc-L-phenylalanine (Absorption level: Normal; Stir rate: 600 rpm).

6.1.2 General Procedure for Borylation

Unless otherwise specified, all reactions followed this general procedure. The Ir-catalyst was generated by a modified literature protocol,[5] where in a glove box, a Schlenk flask, equipped with a magnetic stirring bar, was charged with the corresponding substrate (1 mmol, 1 equiv). Two separate test tubes were charged with [Ir(OMe)(COD)]$_2$ (10 mg, 0.015 mmol, 3 mol % Ir) and dtbpy (8 mg, 0.03 mmol, 3 mol %). Excess HBPin (1.1 to 2 equiv) was added to the [Ir(OMe)(COD)]$_2$ containing test

tube. *n*-Hexane or THF (1 mL) was added to the dtbpy containing test tube in order to dissolve the dtbpy. The dtbpy solution was then mixed with the [Ir(OMe)(COD)]$_2$ and HBPin mixture. After mixing for one minute, the resulting solution was transferred to the Schlenk flask. Additional *n*-hexane or THF (2 × 1 mL) was used to wash the test tubes and the washings were transferred to the Schlenk flask. The flask was stoppered, brought out of the glove box, and attached to the Schlenk line in a fume hood. The Schlenk flask was placed under N$_2$ and the reaction was carried out at the specified temperature. The reaction was monitored by GC-FID/MS. After completion of the reaction, the volatile materials were removed on a rotary evaporator. The crude material was purified by column chromatography or dissolved in CH$_2$Cl$_2$ and passed through a plug of silica. Small amounts of impurities, if present, were removed by crystallization. Regiochemistry of the borylated products was assigned by NMR spectroscopy (^{1}H, ^{13}C, gCOSY, NOE).

Scheme 2.4 Borylation of *N*-Boc pyrrole (2.4a).

2.4a
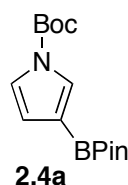
The general procedure was applied to *N*-Boc pyrrole **2.3a** (1.00 g, 6.00 mmol, 1 equiv) and HBPin (1088 μL, 960 mg, 7.50 mmol, 1.25 equiv) at 55 °C for 13 h. The product **2.4a** was isolated as a white solid (1.59 g, 90% yield, mp 83-85 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.61 (t, *J* = 1.7 Hz, 1 H), 7.23 (dd, *J* = 3.2, 2.1 Hz, 1H), 6.44 (dd, *J* = 3.2, 1.5 Hz, 1 H), 1.56 (br s, 9 H), 1.30 (br s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125

MHz): δ 148.6, 128.8, 120.7, 116.2, 83.8, 83.3, 28.0, 24.8; ^{11}B NMR (CDCl$_3$, 96 MHz):

δ 30.2; FT-IR (neat) $\tilde{v}_{max}$: 3150, 2980, 2934, 1748, 1563, 1491, 1372, 1329, 1292,

1217, 1183, 1144, 1067, 976, 936, 857, 775, 691 cm^{-1}; GC-MS (EI) *m/z* (% relative

intensity): M$^+$ 293 (13), 237 (55), 194 (39), 193 (35), 178 (76), 107 (100), 57 (14); Anal.

Calcd for C$_{15}$H$_{24}$BNO$_4$: C, 61.45; H, 8.25; N, 4.78. Found: C, 61.68; H, 8.53; N, 4.70.

Table 2.1, Entry 1: Borylation of *N*-Boc-2-methylpyrrole (2.4b).

2.4b
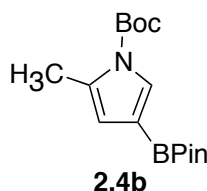
The general procedure was applied to *N*-Boc-2-methylpyrrole **2.3b** (181 mg, 1.00

mmol, 1 equiv) and HBPin (218 µL, 192 mg, 1.50 mmol, 1.50 equiv) at 60 °C for 6 h.

The product **2.4b** was isolated as a white solid (253 mg, 82% yield, mp 68-70 °C). [1]H

NMR (CDCl$_3$, 500 MHz): δ 7.57 (d, *J* = 2.0 Hz, 1 H), 6.15-6.14 (m, 1 H), 2.39 (d, 1.2

Hz, 3 H), 1.55 (br s, 9 H), 1.29 (br s, 12 H); ^{13}C NMR {[1]H} (CDCl$_3$, 125 MHz): δ 149.4,

132.5, 129.6, 115.9, 83.5, 83.2, 28.0, 24.7, 15.1; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 30.2;

FT-IR (neat) $\tilde{v}_{max}$: 2980, 2930, 1748, 1586, 1532, 1399, 1372, 1318, 1296, 1271, 1256,

1221, 1190, 1165, 1144, 1105, 1078, 970, 855, 774, 708, 691 cm^{-1}; GC-MS (EI) *m/z* (%

relative intensity): M$^+$ 307 (23), 251 (100), 207 (48), 192 (37), 121 (49), 57 (13); Anal.

Calcd for C$_{16}$H$_{26}$BNO$_4$: C, 62.56; H, 8.53; N, 4.56. Found: C, 62.58; H, 8.46; N, 4.46.

Table 2.1, Entry 2: Borylation of *N*-Boc-methyl-2-pyrrolecarboxylate (2.4c).

2.4c
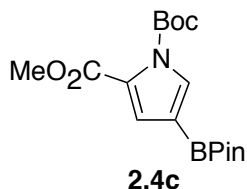
The general procedure was applied to *N*-Boc-methyl-2-pyrrole carboxylate **2.3c** (450 mg, 2.00 mmol, 1 equiv) and HBPin (348 μL, 307 mg, 2.40 mmol, 1.20 equiv) at room temperature for 5 h. The product **2.4c** was isolated as a white solid (524 mg, 75% yield, mp 109-110 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.65 (d, *J* = 1.7 Hz, 1 H), 7.08 (d, *J* = 1.7 Hz, 1 H), 3.79 (s, 3 H), 1.54 (br s, 9 H), 1.27 (br s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 161.1, 148.0, 134.7, 126.0, 125.6, 84.9, 83.5, 51.8, 27.6, 24.7; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 29.9; FT-IR (neat) $\tilde{\nu}_{max}$: 2980, 1755, 1730, 1570, 1483, 1435, 1391, 1373, 1314, 1283, 1252, 1213, 1142, 106, 970, 957, 851, 775, 760, 706, 689 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (M-100)$^+$ 251 (100), 236 (49), 208 (45), 165 (52), 152 (40), 151 (42), 120 (35), 94 (13); Anal. Calcd for C$_{17}$H$_{26}$BNO$_6$: C, 58.14; H, 7.46; N, 3.99. Found: C, 57.84; H, 7.68; N, 3.98.

Table 2.1, Entry 3: Borylation of *N*-Boc indole (2.4d).

2.4d

The general procedure was applied to *N*-Boc indole **2.3d** (1.09 g, 5.00 mmol, 1 equiv) and HBPin (1.45 mL, 1.28 g, 10.00 mmol, 2.00 equiv) at 60 °C for 8 h. The

product **2.4d** was isolated as a white solid (1.11 g, 65% yield, mp 100-102 °C). ^{1}H NMR

(CDCl$_3$, 500 MHz): δ 8.15 (d, *J*= 8.1 Hz, 1 H), 8.00 (s, 1 H), 7.98-7.96 (m, 1 H), 7.31-

7.23 (m, 2 H), 1.65 (br s, 9 H), 1.36 (br s, 12 H); ^{13}C NMR {[1]H} (CDCl$_3$, 125 MHz): δ

149.4, 136.1, 135.2, 133.5, 124.2, 122.9, 122.6, 114.9, 83.8, 83.3, 28.2, 24.9; ^{11}B NMR

(CDCl$_3$, 96 MHz): δ 30.4; FT-IR (neat) $\tilde{\nu}_{max}$: 3054, 2978, 2934, 1740, 1555, 1478,

1453, 1402, 1372, 1339, 1318, 1246, 1208, 1140, 1111, 1061, 986, 857, 766, 748 cm^{-1};

GC-MS (EI) *m/z* (% relative intensity): (M-100)$^+$ 243 (100), 228 (28), 157 (14), 143 (17);

Anal. Calcd for C$_{19}$H$_{26}$BNO$_4$: C, 66.49; H, 7.64; N, 4.08. Found: C, 66.70; H, 7.64; N,

3.95.

Table 2.1, Entry 4: Borylation of *N*-Boc-7-azaindole (2.4e).

2.4e
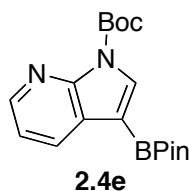
The general procedure was applied to *N*-Boc-7-azaindole **2.3e** (218 mg, 1.00

mmol, 1 equiv) and HBPin (160 μL, 141 mg, 1.10 mmol, 1.10 equiv) at room

temperature for 5 h. The product **2.4e** was isolated as a white solid (193 mg, 56% yield,

mp 115-117 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.45 (dd, *J* = 4.9, 1.7 Hz, 1 H), 8.21

(dd, *J* = 7.8, 1.7 Hz, 1 H), 8.01 (br s, 1 H), 7.17 (dd *J* = 7.8, 4.6 Hz, 1 H), 1.62 (br s, 9 H),

1.33 (br s, 12 H); ^{13}C NMR {[1]H} (CDCl$_3$, 125 MHz): δ 149.3, 147.6, 145.1, 135.4,

130.9, 126.1, 118.8, 84.3, 83.5, 28.1, 24.8; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 30.2; FT-IR

(neat) $\tilde{v}_{max}$: 2980, 2934, 1763, 1736, 1599, 1547, 1477, 1418, 1372, 1316, 1285, 1267, 1248, 1211, 1142, 1107, 1069, 984, 858, 775, 681 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (M-100)$^+$ 244 (100), 229 (38), 187 (35), 158 (37), 144 (46) 117 (11); Anal. Calcd for C$_{18}$H$_{25}$BN$_2$O$_4$: C, 62.81; H, 7.32; N, 8.14. Found: C, 63.18; H, 7.59; N, 8.09.

Table 2.1, Entry 5: Diborylation of *N*-Boc-7-azaindole (2.4f).
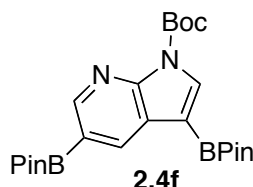
The general procedure was applied to *N*-Boc-7-azaindole **2.3e** (218 mg, 1.00 mmol, 1 equiv) and HBPin (508 μL, 448 mg, 3.50 mmol, 3.50 equiv) at room temperature for 96 h. The product **2.4f** from plug with CH$_2$Cl$_2$ was not pure, so recrystallized from CH$_2$Cl$_2$/hexane (1 : 2) as a pale yellow solid (253 mg, 54% yield, mp 176-178 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.82 (d, *J* = 1.7 Hz, 1 H), 8.54 (d, *J* = 1.5 Hz, 1 H), 8.01 (s, 1 H), 1.63 (br s, 9 H), 1.35-1.34 (2 overlapping singlets, 24 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 151.5, 151.1, 147.5, 137.4, 135.7, 125.2, 84.3, 83.9, 83.6, 28.1, 24.85, 24.84; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 30.9; FT-IR (neat) $\tilde{v}_{max}$: 2980, 2934, 1765, 1738, 1543, 1476, 1418, 1372, 1341, 1306, 1246, 1142, 853, 698 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (M-100)$^+$ 370 (100), 355 (13), 313 (10), 285 (45), 271

(14), 171 (10); Anal. Calcd for $C_{24}H_{36}B_2N_2O_6$: C, 61.31; H, 7.72; N, 5.96. Found: C, 61.55; H, 7.90; N, 6.03.

Table 2.1, Entry 6: Borylation of *N*-Boc-6-azaindole (2.4g).

2.4g
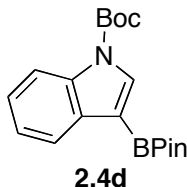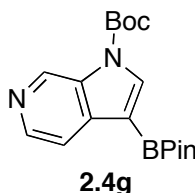
The general procedure was applied to *N*-Boc-6-azaindole **2.3f** (218 mg, 1.00 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) at 55 °C for 20 h (80% conversion). The product **2.4g** was isolated as a white solid (48 mg, 14% yield, mp 114-124 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.37 (br s, 1 H), 8.39 (d, J = 5.4 Hz, 1 H), 8.09 (br s, 1 H), 7.84 (dd, J = 5.4, 0.7 Hz, 1 H), 1.66 (br s, 9 H), 1.34 (br s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 148.6, 142.3, 139.3, 137.9, 137.2, 133.1, 117.1, 85.1, 83.6, 28.1, 24.9; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 30.0; FT-IR (neat) $\tilde{\nu}_{max}$: 3137, 2980, 2934, 1746, 1599, 1568, 1545, 1464, 1439, 1400, 1372, 1327, 1310, 1252, 1213, 1138, 1069, 1038, 857, 831, 735 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (M-100)$^{+}$ 244 (100), 229 (60), 207 (11), 158 (28), 144 (62), 118 (17), 91 (10); Anal. Calcd for $C_{18}H_{25}BN_2O_4$: C, 62.81; H, 7.32; N, 8.14. Found: C, 63.13; H, 7.72; N, 8.06.

Table 2.1, Entry 8: Borylation of *N,N*-dimethylimidazole-1-sulfonamide (2.4i).

2.4i
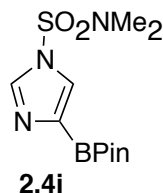
The general procedure was applied to *N,N*-dimethylimidazole-1-sulfonamide **2.3h** (175 mg, 1.00 mmol, 1 equiv) and B_2Pin_2 (254 mg, 1.00 mmol, 1 equiv) at room temperature for 65 h. The crude reaction mixture was washed with pentane, 3 mL portions, until the washings were colorless. The product **2.4i** was isolated as an off white solid (249 mg, 82% yield, mp 118-122 $^\circ$C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.95 (d, J = 1.2 Hz, 1 H), 7.66 (d, J = 1.2 Hz, 1 H), 2.83 (s, 6 H), 1.32 (br s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 137.9, 126.9, 84.2, 38.2, 24.8; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 29.0; FT-IR (neat) $\tilde{\nu}_{max}$: 2980, 2884, 1543, 1474, 1393, 1299, 1177, 1132, 1065, 966, 729 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): 301 (68), 300 (24), 286 (28), 202 (20), 193 (100), 192 (28), 149 (22), 135 (52), 109 (30), 108 (42), 95 (19), 43 (25); Anal. Calcd for C$_{11}$H$_{20}$BN$_3$O$_4$S: C, 43.87; H, 6.69; N, 13.95. Found: C, 44.03; H, 7.08; N, 14.12.

Table 2.1, Entry 9: Borylation of *N*-Boc pyrazole (2.4j).

2.4j
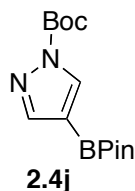
The general procedure was applied to *N*-Boc pyrazole **2.3i** (168 mg, 1.00 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.5 equiv) at room temperature for 90 min. The product **2.4j** was isolated as a pale yellow solid (223 mg, 76% yield, mp 84-86 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.34 (d, *J* = 0.7 Hz, 1 H), 7.88 (d, *J* = 0.6 Hz, 1H), 1.60 (br s, 9 H), 1.29 (br s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 148.6, 147.2, 137.7, 85.5, 83.8, 27.9, 24.7; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 29.2; FT-IR (neat) $\tilde{v}_{max}$: 2980, 1748, 1572, 1393, 1372, 1318, 1289, 1277, 1256, 1144, 1092, 982, 959, 857, 845, 772, 696 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (M-99)$^+$ 195 (88), 194 (25), 179 (100), 178 (25), 151 (8), 95 (35), 43 (12); Anal. Calcd for C$_{14}$H$_{23}$BN$_2$O$_4$: C, 57.16; H, 7.88; N, 9.52. Found: C, 57.56; H, 7.90; N, 9.75.

Table 2.2, Entry 1: Borylation of Boc-L-phenylalanine methyl ester (2.6a1, 2.6a2).
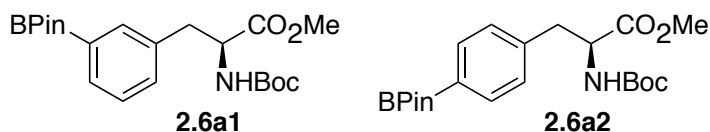
2.6a1   **2.6a2**

The general procedure was applied to Boc-L-phenylalanine methyl ester **2.5a** (140 mg, 0.50 mmol, 1 equiv) and B$_2$Pin$_2$ (127 mg, 0.50 mmol, 1.00 equiv) at 120 °C in a microwave for 0.5 h. Sample was taken after 0.5 h with a syringe, dissolved in CH$_2$Cl$_2$ and GC-FID was ran. There was 37.5% conversion by GC-FID and the ratio of starting material to meta isomer to para isomer to diborylated product was 62.5:27.0:5.6:4.9 by GC-FID of the crude reaction mixture. Column chromatography (hexanes/diethyl ether 75:25) furnished a mixture of the meta and para isomers as a thick liquid (53 mg, 26% yield) and unreacted starting material (47 mg). The ratio of the two isomers in the

isolated product by ^{1}H NMR was 71:29. gCosy NMR spectroscopy was used to assign

the major isomer as meta **2.6a1**. ^{1}H NMR (CDCl$_3$, 500 MHz): δ (major/*meta* isomer

2.6a1) 7.66-7.64 (d, *J*= 7.3 Hz, 1 H), 7.54 (s, 1 H), 7.28-7.25 (t, *J*= 7.5 Hz, 1 H), 7.20-

7.18 (d, *J*= 7.6 Hz, 1 H), 4.98-4.96 (d, *J*= 7.8 Hz, 1 H), 4.57-4.51 (m, 1 H), 3.68 (s, 3 H),

3.13-2.98 (m, 2 H), 1.38 (br s, 9 H), 1.30 (br s, 12 H), (minor/para isomer **2.6a2**) 7.71-

7.70 (d, *J*= 8.1 Hz, 2 H), 7.10-7.08 (d, *J*= 7.7 Hz, 2 H), 4.96-4.95 (d, *J*= 6.6 Hz, 1 H),

4.57-4.51 (m, 1 H), 3.66 (s, 3 H), 3.13-2.98 (m, 2 H), 1.38 (br s, 9 H), 1.30 (br s, 12 H);

^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ (major/*meta* isomer **2.6a1**) 172.3, 155.0, 135.8,

135.3, 133.4, 132, 127.9, 83.7, 79.8, 54.5, 52.1, 38.2, 28.2, 24.8, (minor/para isomer

2.6a2) 172.2, 155.0, 139.2, 135.0, 128.6, 83.7, 79.9, 54.3, 52.1, 38.4, 28.2, 24.9; ^{11}B

NMR (CDCl$_3$, 96 MHz): δ 31.2 ; FT-IR (neat) $\tilde{v}_{max}$: 3447, 3366, 2979, 2934, 1748,

1717, 1503, 1435, 1362, 1167, 1146, 1080, 857, 712 cm^{-1}.

Table 2.2, Entry 2: Diborylation of Boc-L-phenylalanine methyl ester (2.6b).
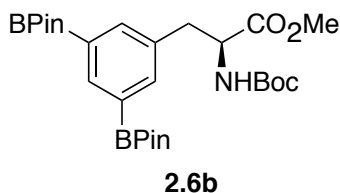
2.6b

The general procedure was applied to Boc-L-phenylalanine methyl ester **2.5a** (140

mg, 0.50 mmol, 1 equiv) and B$_2$Pin$_2$ (254 mg, 1.00 mmol, 2.00 equiv) at 120 $^\circ$C in a

microwave for 1.0 h. There was 88.5% conversion by GC-FID and the ratio of starting

material to meta isomer to para isomer to diborylated product was 11.5:29.9:19.1:39.5 by

GC-FID of the crude reaction mixture. Column chromatography (hexanes/diethyl ether

75:25) furnished the diborylated product **2.6b** as a white solid (48 mg, 18% yield, mp 69-79 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.13 (s, 1 H), 7.63 (s, 2 H), 4.94-4.92 (d, J= 7.7 Hz, 1 H), 4.53-4.50 (q, J= 6.5 Hz , 1 H), 3.69 (s, 3 H), 3.14-2.97 (m, 2 H), 1.40 (br s, 9 H), 1.31 (br s, 24 H); ^{13}C NMR {[1]H} (CDCl$_3$, 125 MHz): δ 172.4, 155.0, 139.9, 138.5, 134.6, 83.7, 79.8, 54.7, 52.1, 38.1, 28.3, 24.9; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 31.4; FT-IR (neat) $\tilde{v}_{max}$: 3447, 3366, 2979, 2934, 1746, 1719, 1599, 1503, 1453, 1393, 1327, 1167, 1144, 968, 847, 720 cm^{-1}; $[\alpha]^{20}_D$ +34.5 (*c* 0.4, CH$_2$Cl$_2$); Anal. Calcd for C$_{27}$H$_{43}$B$_2$NO$_8$: C, 61.04; H, 8.16; N, 2.64. Found: C, 60.99; H, 8.22; N, 2.50.

Table 2.2, Entry 3: Borylation of Boc-3-chloro-L-phenylalanine methyl ester (2.6c).

2.6c
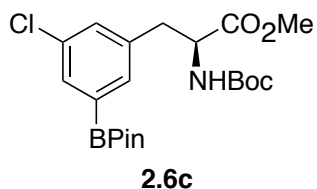
The general procedure was applied to Boc-3-chloro-L-phenylalanine methyl ester **2.5b** (314 mg, 1.00 mmol, 1 equiv) and B$_2$Pin$_2$ (305 mg, 1.20 mmol, 1.20 equiv) at 120 °C for 20 min. Passing the crude material through a silica plug (methylene chloride/diethyl ether 95:5) furnished the product **2.6c** as a pale yellow solid (376 mg, 85% yield, mp 86-89 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.63 (s, 1 H), 7.41 (s, 1 H), 7.17 (s, 1 H), 4.98-4.96 (d, J= 7.6 Hz, 1 H), 4.54-4.50 (ddd, J= 5.8, 6.2, 8.2 Hz, 1 H), 3.70 (s, 3 H), 3.12-2.95 (m, 2 H), 1.41 (br s, 9 H), 1.31 (br s, 12 H); ^{13}C NMR {[1]H} (CDCl$_3$, 125 MHz): δ 172.0, 154.9, 137.5, 133.9, 133.7, 133.1, 131.9, 84.1, 79.9, 54.3,

52.2, 37.7, 28.2, 24.8; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 30.5; FT-IR (neat) $\tilde{v}_{max}$: 3366,

2980, 1748, 1719, 1503, 1358, 1167, 1146, 860, 708 cm^{-1}; $[\alpha]^{20}_D$ +47.0 (*c* 0.3,

CH$_2$Cl$_2$); Anal. Calcd for C$_{21}$H$_{31}$BClNO$_6$: C, 57.36; H, 7.11; N, 3.19. Found: C, 57.20;

H, 7.50; N, 3.58.

Table 2.2, Entry 4: Borylation of Boc-L-2-thienylalanine methyl ester (2.6d).

2.6d
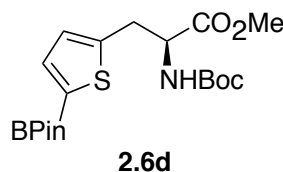
The general procedure was applied to Boc-L-2-thienylalanine methyl ester **2.5c**

(143 mg, 0.50 mmol, 1 equiv) and HBPin (128 mg, 1.00 mmol, 2 equiv) at room

temperature for 40 min. Passing the crude material through a silica plug (methylene

chloride/diethyl ether 95:5) furnished the product **2.6d** as a pale yellow gel (172 mg, 84%

yield). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.42 (d, *J*= 3.4 Hz, 1 H), 6.82 (d, *J*= 3.4 Hz, 1 H),

5.13-5.12 (d, *J*= 8.1 Hz, 1 H), 4.58-4.54 (m, 1 H), 3.70 (s, 3 H), 3.38 (d, *J*= 4.9 Hz, 2 H),

1.39 (s, 9 H), 1.28 (s, 12 H); ^{13}C NMR {[1]H} (CDCl$_3$, 75 MHz): δ 171.4, 154.9, 144.9,

137.4, 128.2, 83.9, 79.9, 54.1, 52.3, 32.5, 28.2, 24.6; ^{11}B NMR (CDCl$_3$, 96 MHz): δ

28.8; FT-IR (neat) $\tilde{v}_{max}$: 3363, 2978, 1747, 1717, 1472, 1358, 1165, 1144 cm^{-1}; $[\alpha]^{20}_D$

+45.3 (*c* 1.0, CH$_2$Cl$_2$); Anal. Calcd for C$_{19}$H$_{30}$BNO$_6$S: C, 55.48; H, 7.35; N, 3.41.

Found: C, 55.70; H, 7.00; N, 3.21.

**Table 2.2, Entry 5: Diborylation of Boc-L-2-thienylalanine methyl ester (2.6e).**

2.6e
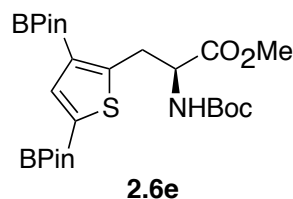
The general procedure was applied to Boc-L-2-thienylalanine methyl ester **2.5c** (285 mg, 1.00 mmol, 1 equiv) and HBPin (512 mg, 4.00 mmol, 4 equiv) at room temperature for 72 h. Passing the crude material through a silica plug (methylene chloride/diethyl ether 95:5) furnished the product **2.6e** as a pale yellow solid (410 mg, 76% yield, mp 59-66 °C). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.82 (s, 1 H), 5.79-5.77 (d, J= 7.8 Hz, 1 H), 4.43-4.36 (m, 1 H), 3.73 (s, 3 H), 3.38 (m, 2 H), 1.34 (s, 9 H), 1.32 (s, 6 H), 1.30 (s, 6 H), 1.28 (s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 75 MHz): δ 172.4, 157.5, 155.5, 144.5, 83.9, 83.8, 79.5, 55.8, 52.3, 31.9, 28.3, 24.9, 24.8, 24.7; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 29.1; FT-IR (neat) $\tilde{v}_{max}$: 3384, 2980, 2934, 1752, 1721, 1539, 1478, 1372, 1321, 1271, 1167, 1140 cm^{-1}; $[\alpha]^{20}_D$ +0.95 (c 1.0, CH$_2$Cl$_2$); HRMS (FAB+): m/z calculated for [C$_{25}$H$_{42}$B$_2$NO$_8$S]$^+$ 538.2822, found 538.2817.

Table 2.2, Entry 6: Monoborylation of Protected Tryptophan (2.6f).

2.6f
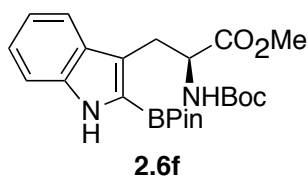
In a glove box, the Boc-L-tryptophan methyl ester **2.5d** (159 mg, 0.5 mmol, 1 equiv) was weighed in a 20 mL vial and dissolved in 10 mL of MTBE. Two separate test

tubes were charged with [Ir(OMe)(COD)]$_2$ (10 mg, 0.015 mmol, 6 mol % Ir) and d^{t}bpy

(8 mg, 0.03 mmol, 6 mol %). HBPin (15 μL, 0.2 equiv) was added to the

[Ir(OMe)(COD)]$_2$ test tube. HBPin was used to generate the active catalyst more

efficiently,[5] whereas B$_2$Pin$_2$ was used to avoid N-borylation and get better conversion.

Methyl *tert*-butyl ether (1 mL) was added to the dtbpy containing test tube in order to

dissolve the dtbpy. The dtbpy solution was then mixed with the [Ir(OMe)(COD)]$_2$ and

HBPin mixture. After mixing for one minute, the resulting solution was transferred to the

20 mL reaction vial containing the Boc-L-tryptophan methyl ester. Additional methyl

tert-butyl ether (2 × 1 mL) was used to wash the test tubes and the washings were

transferred to the reaction vial. B$_2$Pin$_2$ (127 mg, 0.5 mmol, 1 equiv) was weighed in a test

tube and was transferred to the reaction vial by dissolving in MTBE (5 mL). The reaction

vial was stirred at room temperature inside the glove box. The reaction was monitored by

TLC. The reaction was stopped after 45 minutes. Volatile materials were removed on a

rotary evaporator. The ratio of starting indole substrate to monoborylated product to

diborylated product was 0.42:1.0:0.05 by ^{1}H NMR of the crude reaction mixture. The

crude material was dissolved in CH$_2$Cl$_2$ (2 mL) and placed on a silica column. Column

chromatography (silica gel, hexanes/ethyl acetate 3:1, R$_f$ 0.3) gave three fractions. The

first fraction (13 mg) was a 1:1 mixture of mono and diborylated products. The second

fraction (95 mg, 43% yield based on starting indole used) was pure monoborylated

product. The third fraction was recovered unreacted starting indole substrate (50 mg).

The monoborylated product in the second fraction was obtained as a white solid (95 mg,

63% yield based on recovered starting indole, mp 183-185 °C). The monoborylated

product exists as 80:20 mixture of two amide rotamers at room temperature by ^{1}H NMR.

Different ^{1}H NMR peaks for the two amide rotamers coalesce at 70 °C in C_6D_6.

Regiochemistry of the monoborylated product was assigned by NMR spectroscopy. [1]H

NMR (CDCl$_3$, 300 MHz): δ 8.48 (br s, 1 H), 7.66 (d, $J = 8.1$ Hz, 1 H), 7.32 (d, $J = 8.1$

Hz, 1 H), 7.22 (dt, $J = 7.5$, 1.0 Hz, 1 H), 7.10 (dt, $J = 7.5$, 1.0 Hz, 1 H), 5.94 – 5.56 (d, $J =$

7.1 Hz, 1 H both rotamers), 4.32-4.38 (m, 1 H both rotamers), 3.71 (s, 3 H), 3.27-3.45 (m,

2H), 1.39 (br s, 6 H), 1.37 (br s, 6 H), 1.18-1.34 (br s, 9 H both rotamers); ^{13}C NMR

{[1]H} (CDCl$_3$, 75 MHz): δ 173.4, 155.6, 138.3, 128.0, 124.0, 123.3, 119.7, 119.5, 111.4,

84.5, 79.2, 55.2, 51.9, 28.3, 27.6, 24.9, 24.7; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 29.4; FT-IR

(neat) $\tilde{v}_{max}$: 3379, 2978, 1718, 1550, 1516, 1390, 1325, 1267, 1169, 1112, 856, 744 cm^{-1}; GC-MS (EI) m/z (% relative intensity): M$^+$ 444 (0.97), 370 (0.52), 344 (0.40), 327

(0.73), 285 (1.3), 256 (100), 155 (35.2); $[\alpha]^{20}_D$ -14.3 (c 0.7, CH$_2$Cl$_2$); Anal. Calcd for

C$_{23}$H$_{33}$BN$_2$O$_6$: C, 62.17; H, 7.49; N, 6.30. Found: C, 61.96; H, 7.53; N, 6.23; HRMS

(EI): m/z calculated for [C$_{23}$H$_{33}$BN$_2$O$_6$]$^+$ 444.2432, found 444.2433.

Table 2.2, Entry 7: Diborylation of Protected Tryptophan (2.6g)

2.6g
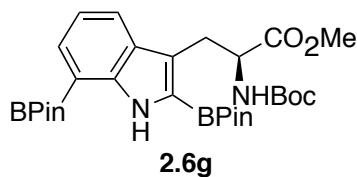
In a glove box, the Boc-L-tryptophan methyl ester **2.5d** (159 mg, 0.5 mmol, 1 equiv) and B_2Pin_2 (254 mg, 1.0 mmol, 2 equiv) was weighed in a 20 mL vial. Two separate test tubes were charged with $[Ir(OMe)(COD)]_2$ (10 mg, 0.015 mmol, 6 mol % Ir) and dtbpy (8 mg, 0.03 mmol, 6 mol %). HBPin (20 µL, 18 mg, 0.14 mmol, 0.28 equiv) along with 1 mL of methyl *tert*-butyl ether was added to the $[Ir(OMe)(COD)]_2$ test tube. Methyl *tert*-butyl ether (1 mL) was added to the dtbpy test tube in order to dissolve the dtbpy. The dtbpy solution was then mixed with the $[Ir(OMe)(COD)]_2$ and HBPin mixture. After mixing for one minute, the resulting solution was transferred to the 20 mL reaction vial containing indole substrate and B_2Pin_2. Additional methyl *tert*-butyl ether (1 mL) was used to wash the test tubes and the washings were transferred to the reaction vial. The reaction vial was stirred at room temperature inside the glove box for 19 h. At this point the volatile materials were removed and the crude material was purified via a gradient column (10% ethyl acetate/hexanes to 30% ethyl acetate/hexanes) on silica gel. The product was isolated as a white solid (153 mg, 54% yield, mp 88-94 °C). The diborylated product exists as 80:20 mixture of two amide rotamers at room temperature by ^{1}H NMR. Different ^{1}H NMR peaks for the two amide rotamers coalesce at 70 °C in C_6D_6. Regiochemistry of the diborylated product was assigned by NMR spectroscopy.

^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.21 (br s, 1H), 7.78-7.76 (d, *J* = 7.9 Hz, 1 H), 7.70-7.69 (d, *J* = 6.8 Hz, 1H), 7.13-7.10 (t, *J* = 7.8 Hz, 1H), 5.99-5.60 (d, *J*= 6.7 Hz, 1 H both rotamers), 4.34-4.30 (m, 1 H both rotamers), 3.70 (s, 3 H both rotamers), 3.43-3.30 (m, 2

H), 1.41 (br s, 6 H), 1.39 (br s, 18 H), 1.34 (br s, 9 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125

MHz): δ 173.5, 155.6, 142.9, 131.7, 126.8, 123.0, 122.9, 119.2, 84.3, 83.8, 79.2, 55.3,

52.1, 28.3, 27.2, 25.0, 24.9, 24.6; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 30.2; FT-IR (neat) $\tilde{v}$

max: 3453, 3391, 3056, 2980, 2934, 1754, 1719, 1551, 1514, 1497, 1441, 1416, 1391,

1368, 1337, 1294, 1207, 1167, 1136, 1101, 853, 683 cm^{-1}; $[\alpha]^{20}_D$ +11.1 (c 0.4,

CH$_2$Cl$_2$); Anal. Calcd for C$_{29}$H$_{44}$B$_2$N$_2$O$_8$: C, 61.08; H, 7.78; N, 4.91. Found: C, 61.02;

H, 8.15; N, 4.98.

Scheme 2.5 One-pot borylation/C-C cross-coupling reaction of 2.3a with 3-chlorothiophene (2.7a).

2.7a
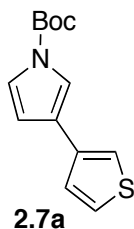
The general borylation procedure was applied to **2.3a** (167 μL, 167 mg, 1.00

mmol, 1 equiv) and HBPin (217 μL, 192 mg, 1.50 mmol, 1.50 equiv) at 60 °C for 30 h.

The GC-FID showed 100% consumption of the starting material. The reaction mixture

was pumped down under high vacuum for 2 h to remove the volatile materials. The

Schlenk flask was brought into the glove box, where Pd$_2$dba$_3$ (9.2 mg, 0.01 mmol),

XPhos[6] (19.1 mg, 0.04 mmol) and powdered, anhydrous K$_3$PO$_4$ (425 mg, 2.00 mmol,

2.0 equiv) were added. The Schlenk tube was sealed and brought out of the glove box.

The Schlenk tube was opened under argon and was capped with a rubber septum. The

Schlenk tube was then evacuated and backfilled with argon (this sequence was carried out two times). *t*-Amyl alcohol (2.00 mL) and 3-chlorothiophene (93 mL, 119 mg, 1.00 mmol, 1.0 equiv) were added via syringe through the septum. The septum was then replaced with a Teflon screwcap and flushed with argon twice as mentioned previously. The Schlenk tube was then sealed and heated at 80 °C for 48 h. At this point the reaction mixture was allowed to cool to room temperature. The reaction solution was then filtered through a thin pad of silica gel (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel (5% EtOAc/hexanes) to provide the Suzuki product as a pale yellow solid (189 mg, 76% yield, mp 49-51 °C). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.39 (t, *J* = 1.7 Hz, 1 H), 7.31 (dd, *J* = 4.9, 2.9 Hz, 1H), 7.27-7.23 (m, 3H), 6.44 (dd, *J* = 3.2, 1.7 Hz, 1 H), 1.60 (br s, 9 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 148.8, 135.6, 125.9, 123.2, 120.8, 118.6, 115.6, 110.8, 83.8, 27.9; FT-IR (neat) $\tilde{v}_{max}$: 3144, 3108, 2980, 2934, 1742, 1489, 1412, 1372, 1345, 1327, 1314, 1271, 1258, 1227, 1161, 1146, 1078, 974, 851, 770 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M$^+$ 249 (3), 193 (100), 149 (68), 148 (26), 121 (20), 57 (33); Anal. Calcd for C$_{13}$H$_{15}$NO$_2$S: C, 62.62; H, 6.06; N, 5.62. Found: C, 62.53; H, 5.99; N, 5.52.

Scheme 2.6 Suzuki cross-coupling of 2.4a with 3-chlorothiophene (2.7a).

2.7a
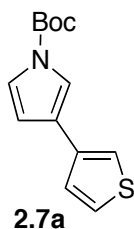
In a glove box, Schlenk flask equipped with a magnetic stirring bar, was charged with **2.4a** (293 mg, 1.00 mmol, 1.0 equiv), Pd_2dba_3 (9.2 mg, 0.01 mmol), XPhos[6] (19.1 mg, 0.04 mmol) and powdered, anhydrous K_3PO_4 (425 mg, 2.00 mmol, 2.0 equiv). The Schlenk tube was sealed and brought out of the glove box. The Schlenk tube was opened under argon and was capped with a rubber septum. The Schlenk tube was then evacuated and backfilled with argon (this sequence was carried out two times). *t*-Amyl alcohol (2.00 mL) and 3-chlorothiophene (93 μL, 119 mg, 1.00 mmol, 1.0 equiv) were added via syringe through the septum. The septum was then replaced with a Teflon screwcap and flushed with argon twice as mentioned previously. The Schlenk tube was then sealed and heated at 80 $^\circ$C for 12 h. At this point the reaction mixture was cooled to room temperature. The reaction solution was then filtered through a thin pad of silica gel (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel (5% EtOAc/hexanes) to provide the Suzuki product as a pale yellow solid (212 mg, 85% yield, mp 49-51 $^\circ$C).

6.1.3 General Procedure for Boc Deprotection

Unless otherwise specified, all reactions followed this general procedure.[7] A Schlenk flask, equipped with a magnetic stirring bar, was charged with the substrate and heated in air at specified temperature until bubbling ceases. The crude material was dissolved in CH_2Cl_2 and passed through a plug of silica. Evaporation of solvent afforded the product.

Table 2.3, Entry 1: Deprotection of 2.4a (2.8a).

2.8a
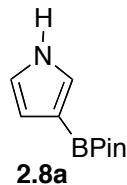
The general procedure for deprotection was applied to **2.4a** (2930 mg, 10.00 mmol) at 180 °C for 35 min. The product **2.8a** was isolated as a white solid (1548 mg, 80% yield, mp 102-104 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.61 (br s, 1 H), 7.23 (ddd, J =1.5, 1.7, 2.7 Hz, 1 H), 6.82 (dd, J =1.7, 2.5 Hz, 1 H), 6.55 (ddd, J =1.5, 2.5, 2.6 Hz, 1 H), 1.31 (br s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 127.0, 118.6, 113.8, 82.9, 24.8; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 30.6; FT-IR (neat) $\tilde{v}_{max}$: 3372, 3121, 2980, 2930, 1549, 1495, 1429, 1418, 1383, 1371, 1318, 1291, 1165, 1140, 1107, 966, 930, 860, 737, 691, 592 cm^{-1}; GC-MS (EI) m/z (% relative intensity): M$^+$ 193 (100), 178 (20), 150 (9), 107 (21); Anal. Calcd for C$_{10}$H$_{16}$BNO$_2$: C, 62.22; H, 8.35; N, 7.26. Found: C, 62.46; H, 8.35; N, 7.35.

Table 2.3, Entry 2: Deprotection of 2.4c (2.8c).

2.8c
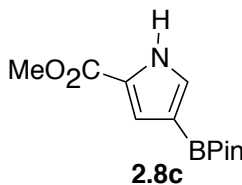
The general procedure for deprotection was applied to **2.4c** (150 mg, 0.43 mmol) at 180 °C for 18 min. The product **2.8c** was isolated as a white solid (82 mg, 76% yield, mp 133-135 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.42 (br s, 1 H), 7.32 (dd, J= 2.9, 1.5 Hz, 1

114

H), 7.22 (dd, J= 2.4, 1.5 Hz, 1 H), 3.82 (s, 3 H), 1.29 (br s, 12 H); ^{13}C NMR {^{1}H}

(CDCl$_3$, 125 MHz): δ 161.6, 130.9, 123.9, 121.2, 83.2, 51.5, 24.8; ^{11}B NMR (CDCl$_3$, 96

MHz): δ 30.2; FT-IR (neat) $\tilde{v}_{max}$: 3308, 2978, 1707, 1564, 1499, 1443, 1363, 1284,

1271, 1211, 1144, 1078, 968, 857, 772, 743, 691 cm^{-1}; GC-MS (EI) m/z (% relative

intensity): M^{+} 251 (100), 236 (25), 208 (29), 176 (18), 165 (27), 152 (7), 150 (8), 120 (9);

Anal. Calcd for C$_{12}$H$_{18}$BNO$_4$: C, 57.40; H, 7.23; N, 5.58. Found: C, 57.19; H, 7.37; N,

5.51.

Table 2.3, Entry 3: Deprotection of 2.4b (2.8b).

2.8b
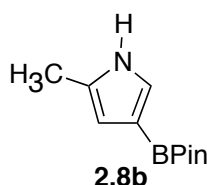
The general procedure for deprotection was applied to **2.4b** (100 mg, 0.33 mmol)

at 140 °C for 16 h. The product **2.8b** was isolated as a white solid (49 mg, 72% yield, mp

102-108 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.11 (br s, 1 H), 7.09 (dd, J = 2.4, 1.7 Hz, 1

H), 6.18-6.17 (m, 1 H), 2.25 (d, J = 0.7 Hz, 3 H), 1.29 (br s, 12 H); ^{13}C NMR {^{1}H}

(CDCl$_3$, 125 MHz): δ 128.6, 125.9, 111.2, 82.7, 24.8, 12.6; ^{11}B NMR (CDCl$_3$, 96 MHz):

δ 30.6; FT-IR (neat) $\tilde{v}_{max}$: 3362, 2977, 2926, 1582, 1522, 1458, 1391, 1374, 1291,

1212, 1148, 1130, 970, 943, 858, 816, 708, 691 cm^{-1}; GC-MS (EI) m/z (% relative

intensity): M$^+$ 207 (100), 192 (16), 121 (19), 106(13); Anal. Calcd for C$_{11}$H$_{18}$BNO$_2$: C, 63.80; H, 8.76; N, 6.76. Found: C, 63.80; H, 9.03; N, 6.59.

Table 2.3, Entry 4: Deprotection of 2.4d (2.8d)

2.8d

The general procedure for deprotection was applied to **2.4d** (1000 mg, 2.92 mmol) at 180 °C for 45 min. The product **2.8d** was isolated as a white solid (453 mg, 64% yield, mp 163-165 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.49 (br s, 1 H), 8.08-8.06 (m, 1 H), 7.61 (d, J= 2.5 Hz, 1 H), 7.36-7.34 (m, 1 H), 7.21-7.16 (m, 2 H), 1.37 (br s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 136.7, 133.9, 131.6, 122.5, 122.2, 120.5, 110.9, 82.9, 24.9; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 30.5; FT-IR (neat) $\tilde{\nu}_{max}$: 3413, 2980, 2932, 1484, 1458, 1439, 1335, 1138, 1032, 851,768, 743, 671 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M$^+$ 243 (100), 228 (49), 157 (24), 143 (48), 117 (16); Anal. Calcd for C$_{14}$H$_{18}$BNO$_2$: C, 69.17; H, 7.46; N, 5.76. Found: C, 69.40; H, 7.51; N, 5.73.
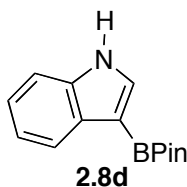
Table 2.3, Entry 5: Deprotection of 2.4j (2.8j).

2.8j
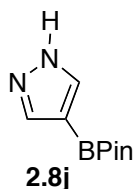
The general procedure for deprotection was applied to **2.4j** (294 mg, 1.00 mmol) at 180 °C for 5 min. The product **2.8j** was isolated as a pale yellow solid (140 mg, 72% yield, mp 147-149 °C). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 11.96 (br s, 1 H), 7.88 (s, 2H), 1.29 (br s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 140.2, 83.3, 24.7; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 29.7; FT-IR (neat) $\tilde{v}_{max}$: 3231, 2977, 1564, 1495, 1424, 1393, 1333, 1283, 1235, 1214, 1140, 978, 943, 857, 710, 696 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): 195 (79), 194 (21), 179 (100), 178 (25), 151 (8), 137 (10), 95 (35), 43 (15); Anal. Calcd for C$_9$H$_{15}$BN$_2$O$_2$: C, 55.71; H, 7.79; N, 14.44. Found: C, 55.67; H, 7.74; N, 14.61.

Scheme 2.7 Deprotection of 2.4e with CF$_3$COOH (2.8e)

2.8e
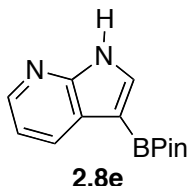
To a 250 mL RBF charged with a magnetic stir bar was added **2.4e** (1.03 g, 3 mmol) and 45 mL of dry CH$_2$Cl$_2$. To this was added 36 mL of trifluoroacetic acid and the reaction flask was capped with a glass stopper. The reaction was stirred at room temperature for 45 min. Quenched the reaction mixture with 150 mL Saturated Na$_2$CO$_3$ solution and extracted into 250 mL CH$_2$Cl$_2$. The organic layer was extracted with 150 mL each of water and brine. Organic layer was dried over anhydrous Na$_2$SO$_4$ and evaporated to afford the crude product. The crude product was washed with hexanes (4 x

12 mL) and recrystallized from CH_2Cl_2/hexanes. The product **2.8e** was isolated as a cream colored solid (404 mg, 55% yield). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 11.77 (br s, 1 H), 8.33-8.30 (m, 2 H), 7.84 (s, 1 H), 7.13 (dd, *J*= 7.8, 4.9 Hz, 1 H), 1.35 (br s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 150.0, 142.3, 134.9, 130.9, 124.4, 116.4, 82.9, 24.9; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 30.0; FT-IR (neat) $\tilde{v}_{max}$: 3289, 3079, 2983, 2969, 1523, 1435, 1418, 1391, 1370, 1331, 1316, 1280, 1266, 1144, 1118, 1109, 1009, 992, 853, 677 cm^{-1}; Anal. Calcd for $C_{13}H_{17}BN_2O_2$: C, 63.97; H, 7.02; N, 11.48. Found: C, 63.62; H, 7.29; N, 11.38.

6.2 Chapter-3. Experimental Details and Spectroscopic Data

6.2.1 Materials and Methods

Pinacolborane (HBPin) was supplied by BASF. Bis(η^4-1,5-cyclooctadiene)-di-*μ*-methoxy-diiridium(I) [Ir(OMe)(COD)]$_2$ was prepared per the literature procedure.[1] 4,4′-Di-*tert*-butyl-2,2′-bipyridine (dtbpy) was purchased from Aldrich. 4-Bromophenyl methyl sulfone and 4-fluorophenylboronic acid were purchased from Aldrich. All substrates were purified by column chromatography. Pinacolborane (HBPin) was distilled before use. *n*-Heptane and DME were refluxed over sodium benzophenone, distilled, and degassed. *t*-Amyl alcohol was distilled from magnesium turnings and stored over molecular sieves. Silica gel was purchased from EMD $^{™}$ (230-400 Mesh).

6.2.2 General Procedures

General Procedure A

In a glove box or outside, an air-free flask, equipped with a magnetic stirring bar, was put under nitrogen and charged with Pd (2 mol %) and substrate (1.00 mmol, 1 equiv). The aryl halide (1.20 mmol, 1.2 equiv) dissolved in DME (3.00 mL) was added to the flask followed by the addition of $K_3PO_4 \cdot nH_2O$ (320 mg, 1.50 mmol, 1.5 equiv). The flask was capped with a teflon screwcap, evacuated and backfilled with nitrogen (this sequence was carried out two times). The flask was then sealed and heated at 80 $^\circ$C for specified time. The reaction was monitored by GC-FID/MS. After completion of the reaction, the reaction mixture was allowed to cool to room temperature. The reaction solution was then filtered through a thin pad of silica gel (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel to provide the Suzuki product.

General Procedure B

In a glove box or outside, an air-free flask, equipped with a magnetic stirring bar, was put under nitrogen and charged with Pd_2dba_3 (9.2 mg, 0.01 mmol), XPhos (19.1 mg, 0.04 mmol) and powdered, anhydrous K_3PO_4 (425 mg, 2.00 mmol, 2.0 equiv).[6] The flask was sealed and brought out of the glove box. The flask was opened under nitrogen and aryl boronate (1.50 mmol, 1.5 equiv) was added. The flask was capped with a rubber septum, evacuated and backfilled with nitrogen (this sequence was carried out two times). The aryl halide (1.00 mmol, 1.0 equiv) dissolved in *t*-amyl alcohol (3.00 mL) was added via syringe through the septum. The septum was then replaced with a Teflon screwcap

and flushed with nitrogen twice as mentioned previously. The flask was then sealed and heated at 80 °C for the specified time. The reaction was monitored by GC-FID/MS. After completion of the reaction, the reaction mixture was allowed to cool to room temperature. The reaction solution was then filtered through a thin pad of silica gel (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified via flash chromatography on silica gel to provide the Suzuki product.

General Procedure for Desilylative Bromination

Substrate (1.00 mmol, 1.0 equiv) was added to a scintillation vial equipped with a magnetic stirring bar. N-Bromosuccinimide (1.00mmol, 1.0 equiv) was added to the vial along with 5 mL of acetonitrile.[8] The reaction mixture was stirred at room temperature and was monitored by GC-FID/MS. After completion of the reaction the volatiles were removed on a rotary evaporator and the crude product was passed through a short silica plug to afford the brominated product.

Scheme 3.4 Synthesis of 2-chloro-5-trimethylsilyl thiophene (3.3)

3.3
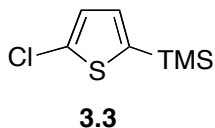
To a solution of *n*-butyllithium (69 mL, 124 mmol, 1.8 M in hexanes) in THF (100 mL) was added dropwise at -78 °C diisopropylamine (14.9 g, 20.5 mL, 147 mmol, 1.4 equiv). The mixture was warmed to 0 °C for 10 mins and then recooled to -78 °C. This solution was cannula transferred to a mixture of 2-chlorothiophene (12.5 g, 9.7 mL, 105 mmol, 1.0 equiv) and chlorotrimethylsilane (34.2 g, 40.3 mL, 315 mmol, 3.0 equiv)

at -78 °C. The solution was allowed to warm to room temperature and stirred at room temperature for 1 h. The reaction mixture was poured into 600 mL water with 10 mL 3 N HCl. The aqueous layer was extracted with 2x550 mL of diethylether. The organic layer was washed with saturated sodium bicarbonate and brine. After drying over anhydrous sodium sulfate the solvent was removed by rotary evaporation. Vacuum distillation (70 °C at 25 mm Hg) afforded the product **3.3** as colorless oil (14.7 g, 73% yield). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 6.98 (d, J = 3.5 Hz, 1 H), 6.93 (d, J = 3.5 Hz, 1 H), 0.27 (s, 9 H, CH$_3$ of TMS); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 140.2, 134.5, 133.3, 127.4, -0.3; FT-IR (neat) $\tilde{v}_{max}$: 2959, 1415, 1251, 1205, 1072, 964, 841 cm^{-1}; GC-MS (EI) m/z (% relative intensity): M^{+} 190 (34), 192 (13), 175 (100); Anal. Calcd for C$_7$H$_{11}$ClSSi: C, 44.07; H, 5.81. Found: C, 43.59; H, 5.90; HRMS (EI): m/z 190.0036 [M^{+}; Calcd for C$_7$H$_{11}$ClSSi: 190.0039].

Scheme 3.5 C-H activation/borylation of 2-chloro-5-trimethylsilylthiophene (3.2)

3.2
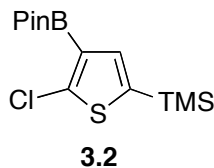
In a glove box, a 250 mL RB flask, equipped with a magnetic stirring bar, was charged with [Ir(OMe)(COD)]$_2$ (424 mg, 0.639 mmol, 3 mol % Ir) and 20 mL heptane. To this was added HBPin (9.3 mL, 8.2 g, 64 mmol 1.5 equiv) and the mixture was then stirred for 5mins. The d^{t}bpy (343 mg, 1.278 mmol, 3 mol %) dissolved in 20 mL of

heptane was added and the mixture was then stirred for 10 mins. 2-Chloro-5-trimethylsilyl thiophene **3.3** (8.1g, 43 mmol, 1 equiv) was added along with 60 mL more of heptane. The reaction was left to stir in the glove box for 42 h. The solvent was pumped off and the crude was passed through a plug of silica gel eluting with CH_2Cl_2. Evaporation of the solvent afforded the product **3.2** as a white solid (12.5 g, 93% yield, mp = 68–69 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26 (s, 1 H), 1.32 (br s, 12 H, 4 CH_3 of BPin), 0.26 (s, 9 H, 3 CH_3 of TMS); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 144.7, 139.42, 139.37, 83.7 (2 C), 24.8, –0.24; ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.1; FT-IR (neat) $\tilde{v}_{max}$: 2980, 1525, 1415, 1363, 1307, 1253, 1238, 1143, 993, 841, 758, 696 cm^{-1}; GC-MS (EI) m/z (% relative intensity) M$^+$ 316 (33), 301 (100), 281 (6), 201 (15); Anal. Calcd for $C_{13}H_{22}BClO_2SSi$: C, 49.30; H, 7.00; Found: C, 49.16; H, 7.16.

Scheme 3.6 Suzuki Coupling of 3.2 with 3-bromotoluene (3.4a)

3.4a
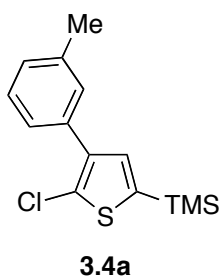
The general procedure A was applied to **3.2** (317 mg, 1.00 mmol, 1 equiv) with 3-bromotoluene (205 mg, 1.20 mmol, 1.20 equiv) and Pd(PPh$_3$)$_4$ (23 mg, 2 mol%) for 3 h. Column chromatography (hexanes, R$_f$ 0.5) furnished the product **3.4a** as a colorless liquid (239 mg, 85% yield). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.27-7.37 (m, 3 H), 7.13-

7.16 (m, 1 H), 7.12 (s, 1 H), 2.39 (s, 3 H, CH$_3$), 0.31 (s, 9 H, 3 CH$_3$ of TMS); ^{13}C-NMR

$\{^{1}$H$\}$ (CDCl$_3$, 75 MHz): δ 139.6, 138.2, 138.0, 135.3, 134.3, 129.3, 129.1, 128.29,

128.27, 125.6, 21.5, –0.3; FT-IR (neat) $\tilde{\nu}_{max}$: 3040, 2957, 2922, 1606, 1408, 1252, 993,

839, 781, 756, 700, 630 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^{+} 280 (49), 282

(19), 266 (100), 267 (48); Anal. Calcd for C$_{14}$H$_{17}$ClSSi: C, 59.86; H, 6.10; Found: C,

59.56; H, 6.21.

Table 3.1, Entry 4 Suzuki Coupling of 3.2 with 4-bromophenyl methyl sulfone (3.4b)

3.4b
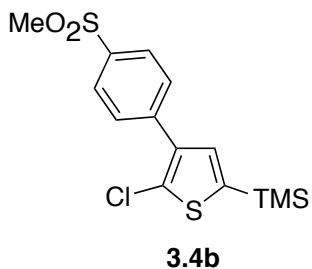
The general procedure A was applied to 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolane)-5-trimethylsilylthiophene **3.2** (1580 mg, 5.00 mmol, 1 equiv) with 4-

bromophenyl methyl sulfone (1410 mg, 6.00 mmol, 1.20 equiv) and PdCl$_2$·dppf·CH$_2$Cl$_2$

(82 mg, 0.10 mmol, 2 mol % Pd) for 1 h. Column chromatography (40% ethyl

acetate/hexanes, R$_f$ 0.6) furnished the product **3.4b** as a white solid (1511 mg, 87% yield,

mp 110-112 °C). ^{1}H-NMR (CDCl$_3$, 300 MHz): δ 7.98 (d, *J* = 8.5 Hz, 2 H), 7.75 (d, *J* =

8.8 Hz, 2 H), 7.14 (s, 1 H), 3.08 (s, 3 H), 0.32 (s, 9 H); ^{13}C-NMR $\{^{1}$H$\}$ (CDCl$_3$, 75

MHz): δ 139.8, 139.6, 139.2, 137.5, 134.4, 131.1, 129.3, 127.5, 44.5, –0.3; FT-IR (neat)

$\tilde{v}_{max}$ 3019, 2957, 1599, 1533, 1397, 1312, 1252, 1153, 1088, 991, 957, 839, 770 cm^{-1};

Anal. Calcd for $C_{14}H_{17}ClO_2S_2Si$: C, 48.75; H, 4.97; Found: C, 48.34; H, 5.36.

Scheme 3.8 Suzuki coupling of 3.4b to yield 3.5

3.5
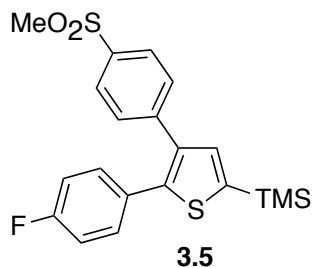
The general procedure B was applied to **3.4b** (690 mg, 2.00 mmol, 1 equiv) with 4-florophenylboronic acid (420 mg, 3.00 mmol, 1.50 equiv) for 6 h. Column chromatography (70% ether/hexanes, R$_f$ 0.5) furnished the product **3.5** as a light cream colored solid (689 mg, 85% yield, mp 141-143 °C). ^{1}H-NMR (CDCl$_3$, 300 MHz): δ 7.83 (d, J = 8.3 Hz, 2 H), 7.44 (d, J = 8.2 Hz, 2 H), 7.24 (s, 1 H), 7.21 (m, 2 H), 6.97 (m, 2 H), 3.05 (s, 3 H), 0.36 (s, 9 H); ^{13}C-NMR {^{1}H} (CDCl$_3$, 75 MHz): δ 162.5 (d, $^1J_{C\text{-}F}$ = 248.5 Hz), 144.7, 142.2, 140.4, 138.6, 137.4, 136.5, 130.9 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 129.8, 129.7 (d, $^4J_{C\text{-}F}$ = 3.6 Hz), 127.5, 115.8 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 44.5, –0.2; FT-IR (neat) $\tilde{v}_{max}$ 3065, 2957, 2930, 2897, 1599, 1537, 1506, 1314, 1252, 1235, 1154, 1094, 1001, 957, 833, 772 cm^{-1}; Anal. Calcd for $C_{20}H_{21}FO_2S_2Si$: C, 59.37; H, 5.23; Found: C, 58.47; H, 5.64.

HRMS (ESI+): *m/z* calculated for $[C_{20}H_{22}FO_2S_2Si]^+$ 405.0815, found 405.0816.

Scheme 3.9 Desilylative bromination of 3.5 (3.1)

3.1
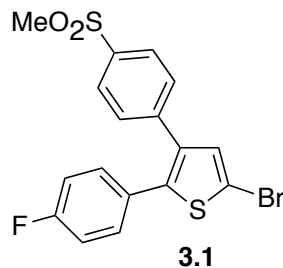
The general procedure for desilylative bromination was applied to **3.5** (404 mg, 1.00 mmol, 1 equiv) with NBS (178 mg, 1.00 mmol, 1 equiv) for 12 h. Silica plug with CH_2Cl_2 and washing the plug product with hexanes furnished the product **3.1** as a white solid (358 mg, 87% yield, mp 129-131 °C). ^{1}H-NMR (CDCl$_3$, 300 MHz): δ 7.82 (d, J = 8.7 Hz, 2 H), 7.37 (d, J = 8.7 Hz, 2 H), 7.16 (m, 2 H), 7.11 (s, 1 H), 6.98 (m, 2 H), 3.05 (s, 3 H); ^{13}C-NMR {^{1}H} (CDCl$_3$, 75 MHz): δ 162.7 (d, $^1J_{C\text{-}F}$ = 249.5 Hz), 140.8, 140.7, 139.2, 136.5, 132.2, 131.0 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 129.7, 128.5 (d, $^4J_{C\text{-}F}$ = 3.6 Hz), 127.6, 116.1 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 111.9, 44.4; FT-IR (neat) $\tilde{v}_{max}$ 3069, 2926, 1597, 1506, 1489, 1439, 1312, 1282, 1235, 1152, 1094, 983, 957, 860, 830, 772, 735, 681, 558, 544 cm^{-1}; Anal. Calcd for $C_{17}H_{12}BrFO_2S_2$: C, 49.64; H, 2.94; Found: C, 49.50; H, 3.06.

Scheme 3.10 Desilylative bromination of 3.4a (3.6)

3.6
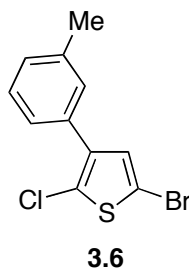
The general procedure for desilylative bromination was applied to **3.4a** (280 mg,

1 mmol) with NBS (178 mg, 1.00 mmol, 1 equiv) for 12 h. The product **3.6** was isolated

as a colorless liquid (261 mg, 91%). ^{1}H-NMR (CDCl$_3$, 300 MHz): δ 7.29-7.31 (m, 3 H),

7.15-7.18 (m, 1 H), 7.02 (s, 1 H), 2.38 (s, 3 H); ^{13}C-NMR {^{1}H} (CDCl$_3$, 75 MHz): δ

139.3, 138.2, 133.1, 131.2, 129.1, 128.8, 128.4, 125.5, 124.0, 108.3, 21.4; FT-IR (neat) $\tilde{\nu}$

max 3042, 2920, 2858, 1604, 1487, 1028, 972, 831, 789, 779, 700 cm^{-1}; GC-MS (EI) *m/z*

(% relative intensity): M$^+$ 287 (63), 288 (100), 290 (29), 287 (63), 251 (5), 171 (19);

Anal. Calcd for C$_{11}$H$_8$BrClS: C, 45.94; H, 2.80; Found: C, 45.96; H, 2.79.

Scheme 3.10 Suzuki coupling of 3.6 (3.7)
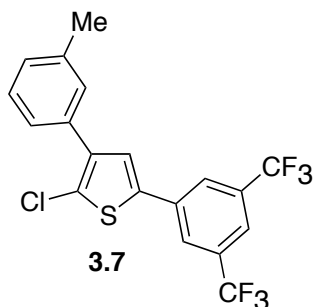
The general procedure A was applied to **3.6** (69 mg, 0.24 mmol, 1.0 equiv) with

1,3-bis-trifluoromethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)benzene (82 mg, 0.24

mmol, 1.0 equiv) and Pd(PPh$_3$)$_4$ (5.5 mg, 0.0048 mmol, 2 mol %) for 7 h. Column

chromatography (hexanes, R$_f$ 0.5) furnished the product **3.7** as a white solid (85 mg, 84%

yield, mp 77-79 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.94 (s, 2 H), 7.80 (s, 1 H), 7.41-

7.40 (m, 2H), 7.38 (s, 1 H), 7.37-7.33 (t, *J* = 7.8 Hz, 1H), 7.22-7.20 (d, *J* = 7.3 Hz, 1 H),

2.43 (s, 3 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 140.1, 138.3, 137.1, 135.6, 133.4,

132.6 (q, $^2J_{C\text{-}F}$ = 33.6 Hz), 129.1, 128.9, 128.5, 126.4, 126.2, 125.5, 125.2 (q, $^3J_{C\text{-}F}$ =

3.8 Hz), 123.1 (q, $^1J_{C-F}$ = 272.8 Hz), 121.1 (q, $^3J_{C-F}$ = 3.6 Hz), 21.4; FT-IR (neat) $\tilde{\nu}$

$_{max}$: 3048, 2926, 1618, 1474, 1433, 1369, 1330, 1279, 1227, 1181, 1136, 1109, 1011,

891, 845, 789, 698, 684 cm^{-1}; HRMS (FAB+): *m/z* calculated for [C$_{19}$H$_{11}$ClF$_6$S]$^+$

420.0177, found 420.0174.

6.3 Chapter-4. Experimental Details and Spectroscopic Data

6.3.1 Materials and Methods

The materials and methods are similar to the ones specified in 6.1.1.
Commercially available chemicals were purified before use. Solid substrates were
sublimed under vacuum. Liquid substrates were distilled before use. High-resolution
mass spectra were acquired at the Michigan State University Mass Spectrometry facility
using a Waters QTOF Ultima mass spectrometer equipped with an electrospray
ionization (ESI) source.

6.3.2 General Procedures

General Procedure for One-pot Diborylation/Deborylation

The Ir-catalyst was generated by a modified literature protocol,[5] where in a glove
box, two separate test tubes were charged with [Ir(OMe)(COD)]$_2$ (10 mg, 0.015 mmol, 3
mol% Ir) and dtbpy (8 mg, 0.03 mmol, 3 mol%). Excess HBPin (2.5 to 3 equiv.) was
added to the [Ir(OMe)(COD)]$_2$ test tube. *n*-Hexane (1 mL) was added to the d^{t}bpy
containing test tube in order to dissolve the dtbpy. The dtbpy solution was then mixed
with the [Ir(OMe)(COD)]$_2$ and HBPin mixture. After mixing for one minute, the
resulting solution was transferred to Schlenk flask equipped with a magnetic stirring bar.

Additional *n*-hexane (2 × 1 mL) was used to wash the test tubes and the washings were transferred to the Schlenk flask. Substituted thiophene (1 mmol, 1 equiv.) was added to the Schlenk flask. The reaction was stirred at room temperature and was monitored by GC-FID/MS. After completion of the reaction, the volatile materials were removed and 5 mL of CH_3OH/CH_2Cl_2 mixture (2:1) was added and heated at 55 $^\circ$C. The reaction was monitored by GC-FID/MS and after completion of the reaction, the volatile materials were removed on a rotary evaporator. The crude material was purified by column chromatography or dissolved in CH_2Cl_2 and passed through a plug of silica. Small amounts of impurities, if present, were removed by crystallization.

General Procedure for Borylation

Two separate test tubes were charged with $[Ir(OMe)(COD)]_2$ and dtbpy. Excess HBPin was added to the $[Ir(OMe)(COD)]_2$ test tube. In cases where B_2Pin_2 was used as the borylating agent, HBPin (3 x Ir mol%) was used to generate active catalyst. *n*-Hexane or cyclohexane or MTBE (1 mL) was added to the dtbpy containing test tube in order to dissolve the dtbpy. The dtbpy solution was then mixed with the $[Ir(OMe)(COD)]_2$ and HBPin mixture. After mixing for one minute, the resulting solution was transferred to Schlenk flask equipped with a magnetic stirring bar. Additional *n*-hexane or cyclohexane or MTBE (2 × 1 mL) was used to wash the test tubes and the washings were transferred to the Schlenk flask. Substrate (1 mmol, 1 equiv.) was added to the Schlenk flask. The flask was stoppered, brought out of the glove box, and attached to the Schlenk line in a fume hood. The Schlenk flask was placed under N_2 and the reaction was carried out at

the specified temperature. The reaction was monitored by GC-FID/MS. After completion of the reaction, the volatile materials were removed on a rotary evaporator. The crude material was purified by column chromatography or dissolved in CH_2Cl_2 and passed through a plug of silica.

General Procedure for Deborylation

A Schlenk flask equipped with a magnetic stirring bar and condensor was charged with substrate (1.0 mmol, 1.0 equiv) and [Ir(OMe)(COD)]$_2$ (10 mg, 0.015 mmol, 3 mol% Ir). The Schlenk flask was then evacuated and backfilled with nitrogen (this sequence was carried out two times). Solvent mixture (methanol/dichloromethane 2:1, 5 mL) was added to the Schlenk flask and flushed under nitrogen twice as mentioned previously. The Schlenk flask was placed under N_2 and the reaction was carried out at the specified temperature. The reaction was monitored by GC-FID/MS. After completion of the reaction, the volatile materials were removed on a rotary evaporator. The crude material was purified by column chromatography or dissolved in CH_2Cl_2 and passed through a plug of silica.

Table 4.2, Entry 1: One-pot synthesis of 4.3a

4.3a
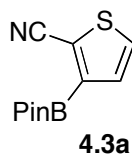
The general procedure for one-pot diborylation/deborylation was applied to 2-cyanothiophene **4.1a** (93 μL, 109 mg, 1.00 mmol, 1.00 equiv). The diborylation step was carried out with HBPin (363 μL, 320 mg, 2.50 mmol, 2.50 equiv) for 4 h. The

deborylation step was carried out for 5.5 h. Column chromatography (20% ethyl acetate/hexanes, R_f 0.6) furnished the product **4.3a** as a pale yellow solid (178 mg, 75% yield, mp 64-66 °C). ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.53 (d, J = 4.9 Hz, 1 H), 7.37 (d, J = 4.9 Hz, 1 H), 1.34 (s, 12 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 133.3, 131.5, 118.0, 114.3, 84.7, 24.8; ^{11}B NMR (CDCl$_3$, 96 MHz) δ 28.8; FT-IR (neat) $\tilde{v}_{max}$: 2980, 2939, 2220, 1520, 1402, 1381, 1373, 1314, 1271, 1140, 986, 908, 853, 841, 752, 691 cm^{-1}; HRMS (ESI+): (m/z) calculated for [M+H]$^+$ [C$_{11}$H$_{15}$BNO$_2$S]$^+$ 236.0917, found 236.0923.
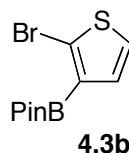
Table 4.2, Entry 2: One-pot synthesis of 4.3b

4.3b

The general procedure for one-pot diborylation/deborylation was applied to 2-bromothiophene **4.1b** (194 μL, 326 mg, 2.00 mmol, 1.00 equiv). The diborylation step was carried out with HBPin (870 μL, 768 mg, 6.00 mmol, 3.00 equiv) for 22 h. The deborylation step was carried out for 10 h. A silica plug with CH$_2$Cl$_2$ afforded the product **4.3b** as a pale yellow solid (460 mg, 80% yield, mp 48-50 °C). ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.17 (d, J = 5.4 Hz, 1 H), 7.12 (d, J = 5.4 Hz, 1 H), 1.32 (s, 12 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 133.3, 126.2, 122.5, 83.8, 24.8; ^{11}B NMR (CDCl$_3$, 96 MHz) δ 29.5; FT-IR (neat) $\tilde{v}_{max}$: 3104, 2978, 2930, 1524, 1428, 1415, 1388, 1366,

1306, 1272, 1140, 965, 896, 853, 675 cm^{-1}; HRMS (APCI+): (m/z) calculated for

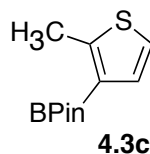[C$_{10}$H$_{15}$BBrO$_2$S]$^+$ 289.0069, found 289.0065.

Table 4.2, Entry 3: One-pot synthesis of 4.3c

4.3c

The general procedure for one-pot diborylation/deborylation was applied to 2-methylthiophene **4.1c** (194 μL, 196 mg, 2.00 mmol, 1.00 equiv). The diborylation step was carried out with HBPin (870 μL, 768 mg, 6.00 mmol, 3.00 equiv) for 48 h. The deborylation step was carried out for 5 h. Column chromatography (50% dichloromethane/hexanes, R$_f$ 0.5) furnished the product **4.3c** as a colorless oil (325 mg, 72% yield). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.20 (d, J = 5.1 Hz, 1 H), 7.02 (d, J = 5.1 Hz, 1 H), 2.69 (s, 3 H), 1.31 (s, 12 H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 152.5, 133.1, 121.9, 83.1, 24.9, 15.6; ^{11}B NMR (CDCl$_3$, 96 MHz) δ 29.8; FT-IR (neat) $\tilde{v}_{max}$: 2978, 2926, 1536, 1435, 1414, 1389, 1372, 1314, 1302, 1273, 1215, 1165, 1146, 1086, 1024, 963, 870, 679 cm^{-1}; HRMS (ESI+): (m/z) calculated for [M+H]+ [C$_{11}$H$_{18}$BO$_2$S]$^+$ 225.1121, found 225.1118.

Synthesis of 3,5-diBPin-2-chlorothiophene (4.2d).

4.2d
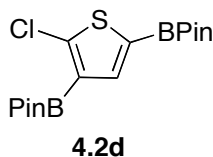
The general procedure for borylation was applied to 2-chlorothiophene (3.9 mL, 5 g, 42 mmol, 1 equiv), [Ir(OMe)(COD)]$_2$ (560 mg, 0.84 mmol, 4 mol% Ir), dtbpy (452 mg, 1.68 mmol, 4 mol%) and HBPin (18.4 mL, 16.2 g, 126 mmol, 3.00 equiv) in pentane at rt for 60 h. The crude reaction mixture was passed through a plug of silica gel eluting with CH$_2$Cl$_2$ to afford the diborylated product **4.2d** as a white solid (14.8 g, 95% yield, mp 129-131 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.72 (s, 1 H), 1.30 (s, 12 H), 1.29 (s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 146.3, 143.6, 84.2, 83.8, 24.8, 24.7; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 29.0; FT-IR (neat) $\tilde{v}_{max}$: 2976, 2928, 1539, 1456, 1371, 1340, 1309, 1140, 1042, 964, 851, 665 cm^{-1}; Anal. Calcd for C$_{16}$H$_{25}$B$_2$ClO$_4$S: C, 51.87; H, 6.80; Found: C, 51.69; H, 7.00.

Scheme 4.5 Deborylation of 3,5-diBPin-2-chlorothiophene (4.3d)

4.3d
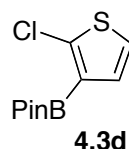
The general procedure for deborylation was applied to **4.2d** (185 mg, 0.50 mmol, 1 equiv) and [Ir(OMe)(COD)]$_2$ (5 mg, 0.0075 mmol, 3 mol% Ir) at 55 °C for 0.5 h. The crude reaction mixture was passed through a plug of silica gel eluting with CH$_2$Cl$_2$ to afford the product **4.3d** as an off white solid (73 mg, 60% yield, mp 27-29 °C). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.13 (d, J = 5.6 Hz, 1 H), 7.03 (d, J = 5.6 Hz, 1 H), 1.32 (s, 12 H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 140.1, 132.4, 123.3, 83.8, 24.8; ^{11}B NMR (CDCl$_3$, 96

MHz) δ 28.5; FT-IR (neat) $\tilde{\nu}_{max}$: 2980, 2939, 1528, 1431, 1420, 1391, 1372, 1310, 1273, 1213, 1167, 1142, 1088, 1024, 966, 899, 855, 833, 745, 675 cm^{-1}; HRMS (APCI+): (m/z) calculated for $[C_{10}H_{15}BClO_2S]^+$ 245.0574, found 245.0578.

Scheme 4.6 Synthesis of 2,5-diBPin-3-cyanothiophene (4.2e)

4.2e
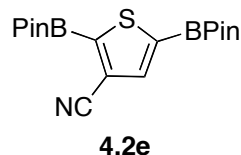
The general procedure for borylation was applied to 3-cyanothiophene (4.16 mL, 5 g, 46 mmol, 1 equiv), [Ir(OMe)(COD)]$_2$ (455 mg, 0.69 mmol, 3 mol% Ir), dtbpy (369 mg, 1.38 mmol, 3 mol%) and HBPin (16.6 mL, 14.7 g, 115 mmol, 2.50 equiv) in pentane at rt for 1.5 h. The crude reaction mixture was passed through a plug of silica gel eluting with CH$_2$Cl$_2$ to afford the diborylated product **4.2e** as a white solid (16.2 g, 98% yield, mp 138 - 140 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.80 (s, 1 H), 1.34 (s, 12 H), 1.31 (s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 140.3, 118.8, 115.2, 85.1, 84.8, 24.7; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 28.8; FT-IR (neat) $\tilde{\nu}_{max}$: 2980, 2936, 2230, 1525, 1373, 1269, 1138, 1055, 962, 850, 667 cm^{-1}; HRMS (FAB+): (m/z) calculated for C$_{17}$H$_{26}$B$_2$NO$_4$S: 362.1768, found 362.1778.

Scheme 4.7 Deborylation of 2,5-diBPin-3-cyanothiophene (4.3e)

4.3e
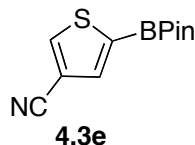
The general procedure for deborylation was applied to **4.2e** (361 mg, 1.00 mmol, 1 equiv) and [Ir(OMe)(COD)]$_2$ (10 mg, 0.015 mmol, 3 mol% Ir) at 55 °C for 5 h. The crude reaction mixture was passed through a plug of silica gel eluting with CH$_2$Cl$_2$. The volatiles were removed to afford the plug product. The plug product was washed with cold hexanes to furnish the product **4.3e** as a white solid (137 mg, 58% yield, mp 90-92 °C). ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.13 (d, J = 1.2 Hz, 1 H), 7.75 (d, J = 1.2 Hz, 1 H), 1.32 (s, 12 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 141.0, 138.2, 114.9, 111.8, 84.8, 24.7; ^{11}B NMR (CDCl$_3$, 96 MHz) δ 28.1; FT-IR (neat) $\tilde{v}_{max}$: 3100, 2979, 2931, 2227, 1542, 1437, 1386, 1355, 1303, 1264, 1138, 1025, 960, 880, 849, 661; cm^{-1}; HRMS (ESI+): (m/z) calculated for [M+H]$^+$ [C$_{11}$H$_{15}$BNO$_2$S]$^+$ 236.0917, found 236.0921.

Scheme 4.9 Synthesis of 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-3-methylindole (4.4a)

4.4a CH$_3$
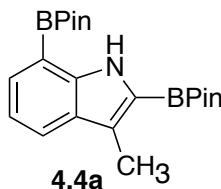
The general procedure for borylation was applied to 3-methylindole (393 mg, 3 mmol, 1 equiv), [Ir(OMe)(COD)]$_2$ (60 mg, 0.09 mmol, 6 mol% Ir), dtbpy (48 mg, 0.18

mmol, 6 mol%) and B_2Pin_2 (838 mg, 3.30 mmol, 1.1 equiv) in cyclohexane at 60 °C for 18 h. Column chromatography (50% dichloromethane/hexanes, R_f 0.8) furnished the diborylated product **4.4a** as a pale yellow solid (902 mg, 79% yield, mp 122-124 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.10 (s, 1 H), 7.76-7.70 (m, 2 H), 7.11 (dd, J = 7.8, 6.8 Hz, 1 H), 2.56 (s, 3 H), 1.41 (s, 12 H), 1.38 (s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 142.9, 131.2, 127.9, 124.2, 123.3, 118.4, 83.7, 83.5, 24.95, 24.88, 10.0; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 29.4; FT-IR (neat) $\tilde{\nu}_{max}$: 3458, 2979, 2931, 1599, 1554, 1416, 1369, 1319, 1282, 1264, 1140, 1104, 841, 682 cm^{-1}; HRMS (ESI+): (m/z) calculated for [M+H]$^+$ [C$_{21}$H$_{32}$B$_2$NO$_4$]$^+$ 384.2517, found 384.2520.

Scheme 4.9 Synthesis of 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-4-cyanoindole (4.4b)

4.4b
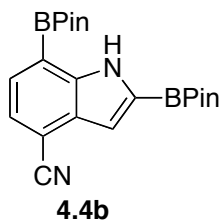
The general procedure for borylation was applied to 4-cyanoindole (142 mg, 1 mmol, 1 equiv), [Ir(OMe)(COD)]$_2$ (10 mg, 0.015 mmol, 3 mol% Ir), dtbpy (8 mg, 0.03 mmol, 3 mol%) and B_2Pin_2 (318 mg, 1.25 mmol, 1.25 equiv) in hexane at 60 °C for 16 h. The crude reaction mixture was passed through a plug of silica gel eluting with CH$_2$Cl$_2$ to afford the diborylated product **4.4b** as an off white solid (366 mg, 93% yield,

mp 158-160 °C). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 9.50 (s, 1 H), 7.67 (d, J = 7.3 Hz, 1 H),

7.42 (d, J = 7.3 Hz, 1 H), 7.29 (d, J = 2.0 Hz, 1 H), 1.40 (s, 12 H), 1.37 (s, 12 H); ^{13}C

NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 142.6, 129.9, 128.1, 124.4, 118.4, 112.0, 106.4, 85.5,

84.5, 24.9, 24.8; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 29.8; FT-IR (neat) $\tilde{v}_{max}$: 3445, 2980,

2936, 2218, 1545, 1373, 1332, 1296, 1142, 972, 852, 775, 704, 680 cm^{-1}; HRMS (EI+):

(m/z) calculated for [M+H]$^+$ [C$_{21}$H$_{28}$B$_2$N$_2$O$_4$]$^+$ 394.2235, found 394.2234.
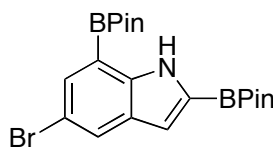
Scheme 4.9 Synthesis of 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-5-bromoindole (4.4c)

4.4c

The general procedure for borylation was applied to 5-bromoindole (392 mg, 2 mmol, 1 equiv), [Ir(OMe)(COD)]$_2$ (40 mg, 0.06 mmol, 6 mol% Ir), dtbpy (32 mg, 0.12 mmol, 6 mol%) and B$_2$Pin$_2$ (635 mg, 2.50 mmol, 1.25 equiv) in cyclohexane at 60 °C for 15 h. The crude reaction mixture was passed through a plug of silica gel eluting with CH$_2$Cl$_2$. The volatiles were removed to afford the diborylated product **4.4c** as an off white solid (838 mg, 94% yield, mp 138-140 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.30 (s, 1 H), 7.87 (d, J = 2.2 Hz, 1 H), 7.75 (d, J = 2.0 Hz, 1 H), 7.02 (d, J = 2.0 Hz, 1 H), 1.39 (s, 12 H), 1.36 (s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 141.6, 133.3, 129.2,

127.1, 113.0, 112.9, 84.21, 84.20, 24.9, 24.8; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 29.3; FT-IR

(neat) $\tilde{v}_{max}$: 3449, 2980, 2923, 1590, 1546, 1417, 1361, 1317, 1299, 1258, 1142, 970,

872, 852, 734, 701 cm^{-1}; HRMS (ESI+): (m/z) calculated for [M+H]$^{+}$

[C$_{20}$H$_{29}$B$_2$BrNO$_4$]$^{+}$ 448.1466, found 448.1472.

Table 4.3, Entry 1: Deborylation of 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-3-methylindole (4.5a)

4.5a
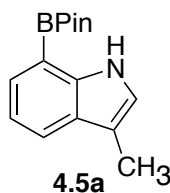
The general procedure for deborylation was applied to **4.4a** (192 mg, 0.50 mmol,

1 equiv) and [Ir(OMe)(COD)]$_2$ (5 mg, 0.0075 mmol, 3 mol% Ir) at 55 °C for 72 h.

Column chromatography (10% ethylacetate/hexanes, R$_f$ 0.4) furnished the product **4.5a**

as a thick liquid (96 mg, 75% yield). ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.93 (s, 1H), 7.69

(dd, J = 7.8, 1.0 Hz, 1 H), 7.63 (dd, J = 7.1, 1.0 Hz, 1 H), 7.11 (dd, J = 7.8, 7.1 Hz, 1 H),

7.00 (m, 1 H), 2.33 (d, J = 1.2 Hz, 3 H), 1.38 (s, 12 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ

141.4, 129.1, 127.2, 122.3, 121.5, 118.5, 111.0, 83.7, 25.0, 9.6; ^{11}B NMR (CDCl$_3$, 96

MHz) δ 31.6; FT-IR (neat) $\tilde{v}_{max}$: 3463, 2977, 2926, 2864, 1607, 1593, 1491, 1437,

1372, 1325, 1291, 1204, 1136, 1105, 1047, 966, 849, 752, 683 cm^{-1}; HRMS (ESI+):

(m/z) calculated for [C$_{15}$H$_{21}$BNO$_2$]$^{+}$ 258.1665, found 258.1668.

Table 4.3, Entry 2: Deborylation of 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-4-cyanoindole (4.5b)

4.5b
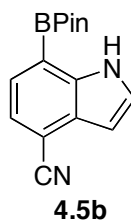
The general procedure for deborylation was applied to **4.4b** (197 mg, 0.50 mmol, 1 equiv) and [Ir(OMe)(COD)]$_2$ (5 mg, 0.0075 mmol, 3 mol% Ir) at 55 $^\circ$C for 1 h. A silica plug was run with CH$_2$Cl$_2$ and the product **4.5b** was isolated as a pale yellow solid (114 mg, 85% yield, mp 146-148 $^\circ$C). ^{1}H NMR (CDCl$_3$, 500 MHz) δ 9.44 (s, 1H), 7.63 (d, J = 7.3 Hz, 1 H), 7.45 (d, J = 7.3 Hz, 1 H), 7.41 (t, J = 3.2, 2.4 Hz, 1 H), 6.74 (dd, J = 3.2, 2.4 Hz, 1 H), 1.39 (s, 12 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 140.6, 128.3, 128.1, 126.8, 124.2, 118.7, 105.7, 101.1, 84.5, 24.9; ^{11}B NMR (CDCl$_3$, 96 MHz) δ 31.2; FT-IR (neat) $\tilde{v}_{max}$: 3389, 2980, 2228, 1603, 1508, 1401, 1373, 1337, 1310, 1207, 1142, 1109, 1080, 968, 887, 851, 822, 741, 681 cm^{-1}; HRMS (ESI+): (m/z) calculated for [C$_{15}$H$_{18}$BN$_2$O$_2$]$^+$ 269.1461, found 269.1462.

Table 4.3, Entry 3: Deborylation of 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-5-bromoindole (4.5c)

4.5c
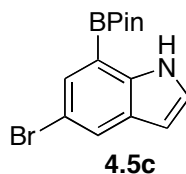
The general procedure for deborylation was applied to **4.4c** (224 mg, 0.50 mmol, 1 equiv) and [Ir(OMe)(COD)]$_2$ (5 mg, 0.0075 mmol, 3 mol% Ir) at 55 $^\circ$C for 1 h 45 min. Column chromatography (50% dichloromethane/hexanes, R$_f$ 0.7) furnished the desired product **4.5c** as an off white solid (134 mg, 83% yield, mp 130-132 $^\circ$C). ^{1}H NMR (CDCl$_3$, 500 MHz) δ 9.19 (s, 1H), 7.85 (d, J = 1.7 Hz, 1 H), 7.71 (d, J = 1.9 Hz, 1 H), 7.25 – 7.23 (m, 1 H), 6.47 – 6.46 (m, 1 H), 1.38 (s, 12 H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 139.5, 131.4, 128.8, 126.4, 125.3, 112.9, 101.6, 84.2, 24.9; ^{11}B NMR (CDCl$_3$, 96 MHz) δ 30.9; FT-IR (neat) $\tilde{v}_{max}$: 3447, 2978, 1599, 1507, 1454, 1420, 1391, 1368, 1327, 1310, 1294, 1273, 1181, 1167, 1142, 978, 864, 847, 731, 689, 677 cm^{-1}; HRMS (ESI+): (m/z) calculated for [C$_{14}$H$_{18}$BBrNO$_2$]$^+$ 322.0614, found 322.0617.

Table 4.3, Entry 4: Deborylation of 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-Boc-L-tryptophan methyl ester (4.5d)
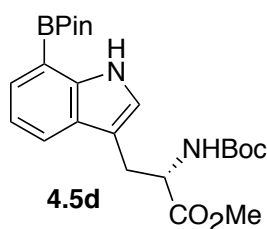
The general procedure for deborylation was applied to **2.6g** (150 mg, 0.26 mmol, 1 equiv) and [Ir(OMe)(COD)]$_2$ (2.6 mg, 0.0039 mmol, 3 mol% Ir) at rt for 2 h. Column chromatography (20% ethylacetate/hexanes, R$_f$ 0.4) furnished the product **4.5d** as a white solid (67 mg, 58% yield, mp 177-179 $^\circ$C). ^{1}H NMR (CDCl$_3$, 500 MHz) δ 9.12 (s, 1 H),

7.66 (d, $J = 8.1$ Hz, 1 H), 7.63 (d, $J = 7.1$ Hz, 1 H), 7.11 (dd, $J = 7.8, 7.1$ Hz, 1 H), 7.04

(s, 1 H), 5.05 (d, $J = 7.8$ Hz, 1 H), 4.63 – 4.61 (m, 1 H), 3.66 (s, 3 H), 3.29 (d, $J = 4.9$ Hz,

2 H), 1.41 (s, 9 H), 1.37 (s, 12 H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 172.7, 155.2, 141.3,

129.5, 126.6, 122.7, 122.3, 119.1, 109.6, 83.8, 79.7, 54.2, 52.2, 28.3, 27.9, 24.9; [11]B

NMR (CDCl$_3$, 96 MHz) δ 30.6; FT-IR (neat) $\tilde{\nu}_{max}$: 3453, 2981, 2919, 2853, 2252, 1742,

1708, 1599, 1492, 1437, 1373, 1331, 1167, 1135, 799, 735 cm^{-1}; $[\alpha]^{20}_D$ +39.3 (c 1.0,

CHCl$_3$); HRMS (ESI+): (m/z) calculated for $[C_{23}H_{34}BN_2O_6]^+$ 445.2510, found

445.2519.

Scheme 4.11 Deborylation of N-Boc-3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaboryl)-7-azaindole (4.5e)

4.5e
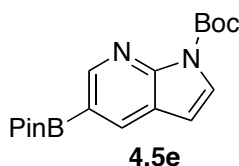
The general procedure for deborylation was applied to **2.4f** (235 mg, 0.50 mmol,

1 equiv) and [Ir(OMe)(COD)]$_2$ (5 mg, 0.0075 mmol, 3 mol% Ir) at 55 °C for 4 h.

Column chromatography (10% ether/dichloromethane, R$_f$ 0.4) furnished the product **4.5e**

as a white solid (84 mg, 49% yield, mp 95-98 °C). ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.82

(d, $J = 1.5$ Hz, 1 H), 8.26 (d, $J = 1.7$ Hz, 1 H), 7.58 (d, $J = 4.2$ Hz, 1 H), 6.46 (d, $J = 4.2$

Hz, 1 H), 1.64 (s, 9 H), 1.33 (s, 12 H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 151.3, 149.9,

147.8, 135.9, 126.4, 122.4, 104.7, 84.0, 83.9, 28.1, 24.8; ^{11}B NMR (CDCl$_3$, 96 MHz) δ

31.2; FT-IR (neat) $\tilde{v}_{max}$: 2980, 2935, 1759, 1733, 1606, 1562, 1535, 1478, 1358, 1319, 1251, 1150, 1102, 1028, 968, 856, 770, 734, 685 cm^{-1}; HRMS (ESI+): (m/z) calculated for $[C_{18}H_{26}BN_2O_4]^+$ 345.1986, found 345.1985.

Scheme 4.12 Monoborylation of Clopidogrel (4.6b)

4.6b
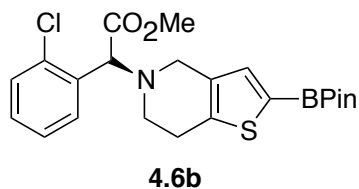
The general procedure for borylation was applied to clopidogrel **4.6a** (161 mg, 0.50 mmol, 1 equiv), [Ir(OMe)(COD)]$_2$ (5 mg, 0.0075 mmol, 3 mol% Ir), dtbpy (4 mg, 0.015 mmol, 3 mol%) and HBPin (109 μL, 96 mg, 0.75 mmol, 1.50 equiv) in methyl *tert*-butyl ether at rt for 1 h 15 min. Column chromatography (5% ether/dichloromethane, R_f 0.6) furnished the product **4.6b** as a sticky yellow precipitate (126 mg, 56% yield). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.66-7.64 (m, 1 H), 7.39-7.37 (m, 1 H), 7.28-7.22 (m, 2 H), 7.20 (s, 1 H), 4.89 (s, 1 H), 3.74 (d, *J*= 14.2 Hz, 1 H), 3.70 (s, 3 H), 3.63 (d, *J*= 14.2 Hz, 1 H), 2.89-2.85 (m, 4 H), 1.29 (s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 171.3, 141.2, 135.6, 135.0, 134.7, 133.9, 129.9, 129.8, 129.4, 127.1, 83.9, 67.7, 52.1, 50.5, 47.9, 25.9, 24.7; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 28.9; FT-IR (neat) $\tilde{v}_{max}$: 2978, 2950, 1752, 1478, 1378, 1333, 1267, 1214, 1167, 1143, 1037, 1014, 997, 853, 755, 732 cm^{-1}; $[\alpha]^{20}_D$ +28.0 (*c* 1.0, CHCl$_3$); HRMS (ESI+): (m/z) calculated for $[C_{22}H_{28}BClNO_4S]^+$ 448.1521, found 448.1523.

Scheme 4.12 Deutero deborylation of monoborylated Clopidogrel (4.6c)

4.6c
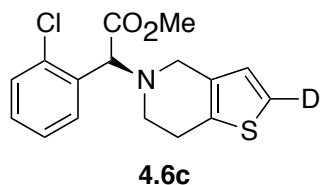
The general procedure for deborylation was applied to **4.6b** (112 mg, 0.25 mmol, 1 equiv) and [Ir(OMe)(COD)]$_2$ (5 mg, 0.0075 mmol, 6 mol% Ir) in 1.25 mL of CD$_3$OD/CDCl$_3$ (2:1) at 55 °C for 2 h 30 min. Column chromatography (5% ether/dichloromethane, R$_f$ 0.7) furnished the product **4.6c** as a thick pale yellow liquid (65 mg, 81% yield, 92% D-incorporation). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.69-7.66 (m, 1 H), 7.40-7.37 (m, 1 H), 7.28-7.23 (m, 2 H), 6.65 (s, 1 H), 4.89 (s, 1 H), 3.74 (d, J= 14.2 Hz, 1 H), 3.70 (s, 3 H), 3.61 (d, J= 14.4 Hz, 1 H), 2.89-2.85 (m, 4 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): δ 171.3, 134.6, 133.8, 133.2, 133.1, 129.9, 129.7, 129.4, 127.1, 125.0, 67.8, 52.1, 50.6, 48.2, 25.6, 25.5; FT-IR (neat) $\tilde{\nu}_{max}$: 2949, 2921, 2846, 2815, 1741, 1470, 1434, 1260, 1227, 1200, 1166, 1029, 755 cm^{-1}; [α]$^{20}_D$ +42.2 (c 0.7, CHCl$_3$); HRMS (ESI+): (m/z) calculated for [C$_{16}$^{1}H$_{16}$^{2}HClNO$_2$S]$^+$ 323.0731, found 323.0734.

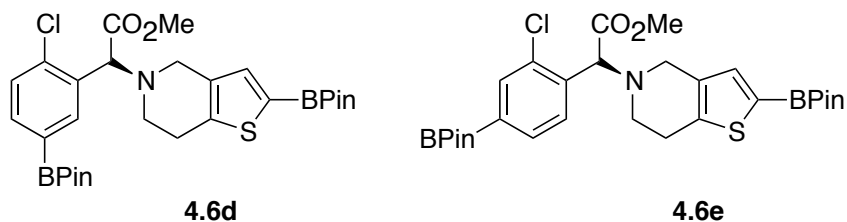**Scheme 4.13 Diborylation of Clopidogrel (4.6d/4.6e)**

4.6d   **4.6e**

The general procedure for borylation was applied to clopidogrel **4.6a** (322 mg, 1.00 mmol, 1 equiv), [Ir(OMe)(COD)]$_2$ (20 mg, 0.03 mmol, 6 mol% Ir), dtbpy (16 mg, 0.06 mmol, 6 mol%) and HBPin (435 µL, 384 mg, 3.00 mmol, 3.00 equiv) in methyl *tert*-butyl ether at rt for 30 h. Column chromatography (15% ether/dichloromethane, R$_f$ 0.4) furnished the product as a pale yellow solid in a 1:1 mixture of **4.6d** and **4.6e** (441 mg, 77% yield, mp 72-80 °C). ^{1}H NMR (CDCl$_3$, 500 MHz): **4.6d** δ 7.99 (d, *J*= 1.5 Hz, 1 H), 7.69-7.64 (m, 1 H), 7.37 (d, *J*= 7.8 Hz, 1 H), 7.21 (s, 1 H), 4.92 (s, 1 H), 3.74 (d, *J*= 14.2 Hz, 1 H), 3.70 (s, 3 H), 3.63 (d, *J*= 14.2 Hz, 1 H), 2.88-2.84 (m, 4 H), 1.30 (s, 12 H), 1.29 (s, 12 H); **4.6e** δ 7.81 (s, 1 H), 7.69-7.64 (m, 2 H), 7.19 (s, 1 H), 4.90 (s, 1 H), 3.76 (d, *J*= 14.2 Hz, 1 H), 3.68 (s, 3 H), 3.61 (d, *J*= 14.2 Hz, 1 H), 2.88-2.84 (m, 4 H), 1.32 (s, 12 H), 1.29 (s, 12 H); ^{13}C NMR {^{1}H} (CDCl$_3$, 125 MHz): **4.6d** δ 171.3, 141.3, 137.9, 136.2, 135.7, 135.1, 133.1, 129.2, 84.0, 83.8, 67.6, 52.1, 50.5, 47.7, 24.86, 24.85, 24.83, 24.7; **4.6e** δ 171.1, 141.2, 135.8, 135.6, 134.9, 134.5, 133.1, 129.3, 84.2, 83.9, 67.8, 52.1, 50.6, 47.9, 25.9, 24.82, 24.79, 24.7; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 28.6; FT-IR (neat) $\tilde{v}_{max}$: 2979, 2931, 1744, 1479, 1382, 1357, 1327, 1271, 1166, 1144, 1107, 1014, 855, 733 cm^{-1}; $[\alpha]^{20}_D$ +31.3 (*c* 1.0, CHCl$_3$); HRMS (ESI+): (m/z) calculated for [C$_{28}$H$_{39}$B$_2$ClNO$_6$S]$^+$ 574.2373, found 574.2381.

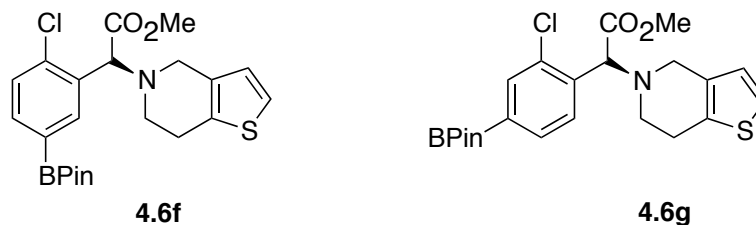**Scheme 4.13 Deborylation of diborylated Clopidogrel (4.6f/4.6g)**

4.6f   **4.6g**

The general procedure for deborylation was applied to **4.6d/4.6e** (144 mg, 0.25 mmol, 1 equiv) and [Ir(OMe)(COD)]$_2$ (5 mg, 0.0075 mmol, 6 mol% Ir) at 55 $^\circ$C for 5 h. Column chromatography (15% ether/dichloromethane, R$_f$ 0.6) furnished the product as a sticky yellow precipitate in a 1:1 mixture of **4.6f** and **4.6g** (89 mg, 80% yield). ^{1}H NMR (CDCl$_3$, 300 MHz): **4.6f** δ 8.03 (d, J= 1.5 Hz, 1 H), 7.66 (dd, J= 7.8, 1.5 Hz, 1 H), 7.38 (d, J= 8.1 Hz, 1 H), 7.04 (d, J= 5.1 Hz, 1 H), 6.66 (d, J= 5.1 Hz, 1 H), 4.91 (s, 1 H), 3.80 – 3.72 (m, 1 H), 3.71 (s, 3 H), 3.66 – 3.58 (m, 1 H), 2.88-2.85 (m, 4 H), 1.30 (s, 12 H); **4.6g** δ 7.82 (s, 1 H), 7.68-7.64 (m, 2 H), 7.03 (d, J= 5.1 Hz, 1 H), 6.64 (d, J= 5.1 Hz, 1 H), 4.90 (s, 1 H), 3.80 – 3.72 (m, 1 H), 3.69 (s, 3 H), 3.66 – 3.58 (m, 1 H), 2.88-2.85 (m, 4 H), 1.32 (s, 12 H); ^{13}C NMR {[1]H} (CDCl$_3$, 125 MHz): **4.6f** δ 171.3, 137.9, 136.2, 135.6, 133.4, 133.3, 133.1, 129.2, 125.3, 122.6, 84.0, 67.7, 52.1, 50.7, 48.0, 24.87, 24.85; **4.6g** δ 171.1, 136.5, 135.8, 134.5, 133.25, 133.21, 133.17, 129.4, 125.2, 122.7, 84.2, 67.9, 52.1, 50.7, 48.3, 24.83, 24.79; ^{11}B NMR (CDCl$_3$, 96 MHz): δ 29.9; FT-IR (neat) $\tilde{v}_{max}$: 2985, 2950, 2930, 1744, 1604, 1435, 1386, 1357, 1331, 1204, 1167, 1145, 964, 858, 736, 703, 681 cm^{-1}; [α]$^{20}_D$ +67.0 (c 0.7, CHCl$_3$); HRMS (ESI+): (m/z) calculated for [C$_{22}$H$_{28}$BClNO$_4$S]$^+$ 448.1521, found 448.1525.

6.4 Chapter-5. Experimental Details and Spectroscopic Data

6.4.1 Materials and Methods

All reactions, unless otherwise specified, were performed under an inert atmosphere of nitrogen. All commercially available reagents were used as received. [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II), [PdCl$_2$(dppf)], complex was purchased from CombiPhos Inc. Chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II), Cu(OAc)$_2$ were purchased from Aldrich. Thin layer chromatography was performed on 0.25 mm thick aluminum-backed silica gel plates purchased from Silicyle and 0.250 mm thick glass backed silica gel TLC plates with F-254 indicator obtained from Dynamic Absorbents Inc. Components were visualized with ultraviolet light (λ =254 nm) and with KMnO$_4$ stain, followed by heating, for the compounds that were UV inactive. Column chromatography was performed on Silia P-Flash silica gel. 1,4-Dioxane was refluxed over sodium/benzophenone ketyl, distilled, and degassed. Acetonitrile was obtained from a dry still packed with activated alumina and degassed before use.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova-300 (300.11 and 75.47 MHz respectively), Varian VXR-500 or Varian Unity-500-Plus spectrometer (499.74 and 125.67 MHz respectively) and referenced to residual solvent signals (7.24 ppm and 77.0 ppm for CDCl$_3$, respectively). ^{11}B spectra were recorded on a Varian VXR-300 operating at 96.29 MHz and were referenced to neat BF$_3$·Et$_2$O as the external standard. ^{19}F spectra were recorded on a Varian VXR-300 operating at 282.4 MHz and were

referenced to trichlorofluoromethane ($CFCl_3$) as the external standard. All coupling constants are apparent J values measured at the indicated field strengths. Melting points were measured on a MEL-TEMP® capillary melting point apparatus and are uncorrected.

High-resolution mass spectra were acquired at the Michigan State University Mass Spectrometry facility using a Waters QTOF Ultima mass spectrometer equipped with an electrospray ionization (ESI) source.

6.4.2 General Procedure for Suzuki Coupling

In a glove box or outside, a Schlenk flask equipped with a magnetic stir bar and nitrogen inlet was added substrate (0.50 mmol, 1 equiv) and $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ (0.02 mmol, 4 mol % Pd). To this was added aryl halide (0.50 mmol, 1 equiv) followed by the addition of $K_3PO_4 \cdot nH_2O$ (1.50 mmol, 3.0 equiv). The flask was capped with a rubber septum, evacuated and backfilled with nitrogen (this sequence was carried out three times). To this was added 5 mL of degassed DMSO and flushed with nitrogen twice as mentioned previously. The reaction was stirred at room temperature and monitored by NMR. Once the reaction is done, the reaction mixture was poured into 75 mL of EtOAc and extracted with 50 mL each of water and saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and the volatiles were removed under vacuum. The crude brown solid was dissolved in CH_3CN and absorbed onto 250 mg of Florisil. The free flowing powder was dry-loaded onto a plug of silica gel and flushed with copious amounts of Et_2O. The product was eluted with CH_3CN and the volatiles were removed under vacuum. The plug product was washed with ether to provide the Suzuki product.

Table 5.1 Suzuki-Miyaura coupling of 5.1a (5.2a)

5.2a
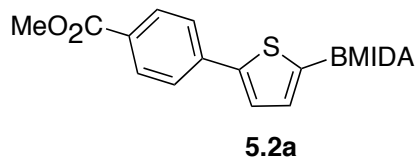
The general procedure for Suzuki coupling was applied to **5.1a** (183 mg, 0.50 mmol, 1 equiv) with methyl-4-bromobenzoate (108 mg, 0.50 mmol, 1 equiv) for 3.5 h. The product **5.2a** was isolated as a white solid (146 mg, 78% yield, mp 243-245 $^{\circ}$C). ^{1}H NMR (DMSO-d6, 500 MHz): δ 7.98 (d, J= 8.3 Hz, 2 H), 7.82 (d, J = 8.3 Hz, 2 H), 7.73 (d, J = 3.6 Hz, 1 H), 7.36 (d, J = 3.4 Hz, 1 H), 4.39 (d, J = 17.3 Hz, 2 H), 4.17 (d, J = 17.1 Hz, 2 H), 3.86 (s, 3 H), 2.67 (s, 3 H); ^{13}C NMR {^{1}H} (DMSO-d6, 125 MHz): δ 168.8, 165.8, 145.4, 138.1, 134.5, 130.0, 128.1, 126.7, 125.3, 61.5, 52.1, 47.5; ^{11}B NMR (DMSO-d6, 96 MHz): δ 10.6; FT-IR (neat) $\tilde{\nu}_{max}$: 3032, 2955, 1792, 1753, 1722, 1707, 1606, 1452, 1336, 1319, 1294, 1257, 1215, 1184, 1118, 1068, 1037, 987, 819, 808, 767 cm^{-1}; HRMS (ESI+): (m/z) calculated for $[C_{17}H_{17}BNO_6S]^{+}$ 374.0870, found 374.0875.

Table 5.1, Entry 1: Suzuki-Miyaura coupling of 5.1c (5.2b)

5.2b
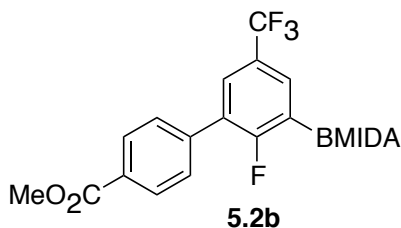
The general procedure for Suzuki coupling was applied to **5.1c** (445 mg, 1.0 mmol, 1 equiv) with methyl-4-bromobenzoate (215 mg, 1.0 mmol, 1 equiv) for 6 h. The product **5.2b** was isolated as a pale yellow solid (352 mg, 78% yield, mp 265-267 $^{\circ}$C).

^{1}H NMR (DMSO-d6, 500 MHz): δ 8.07 (d, *J*= 8.1 Hz, 2 H), 7.95 (d, *J* = 4.9 Hz, 1 H),

7.86 (s, 1 H), 7.79 (d, *J* = 7.6 Hz, 2 H), 4.48 (d, *J* = 17.3 Hz, 2 H), 4.19 (d, *J* = 17.3 Hz, 2

H), 3.89 (s, 3 H), 2.76 (s, 3 H); ^{13}C NMR {^{1}H} (DMSO-d6, 125 MHz): δ 168.9, 165.9,

164.0 (d, $^1J_{C-F}$ = 251.1 Hz), 138.5, 131.8 (m), 129.6 (d, $^3J_{C-F}$ = 2.5 Hz), 129.5 (m),

129.4, 129.3, 128.1 (d, $^2J_{C-F}$ = 17.8 Hz), 125.5 (dq, $^2J_{C-F}$ = 32.2 Hz, $^4J_{C-F}$ = 2.7 Hz),

123.9 (q, $^1J_{C-F}$ = 272.7 Hz), 62.8, 52.2, 47.9; ^{11}B NMR (DMSO-d6, 96 MHz): δ 9.8; ^{19}F

NMR (DMSO-d6, 282.4 MHz): δ -60.1, -104.7; FT-IR (neat) $\tilde{v}_{max}$: 3012, 2958, 1778,

1723, 1613, 1450, 1433, 1423, 1357, 1338, 1282, 1261, 1243, 1171, 1125, 1047, 1024,

896, 871, 862, 642 cm^{-1}; HRMS (ESI+): (m/z) calculated for [M+NH$_4$]$^+$

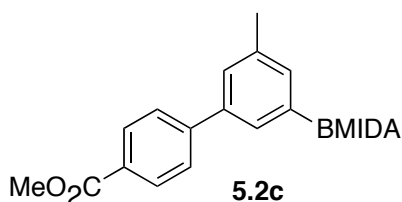[C$_{20}$H$_{20}$BF$_4$N$_2$O$_6$]$^+$ 471.1351, found 471.1351.

Table 5.1, Entry 2: Suzuki-Miyaura coupling of 5.1e (5.2c)

The general procedure for Suzuki coupling was applied to **5.1e** (180 mg, 0.50

mmol, 1 equiv) with methyl-4-bromobenzoate (108 mg, 0.50 mmol, 1 equiv) for 6 h. The

product **5.2c** was isolated as a pale yellow solid (155 mg, 81% yield, mp 248-250 °C).

^{1}H NMR (DMSO-d6, 500 MHz): δ 8.04 (d, *J*= 7.8 Hz, 2 H), 7.83 (d, *J*= 8.1 Hz, 2 H),

7.56 (s, 1 H), 7.54 (s, 1 H), 7.32 (s, 1 H), 4.36 (d, *J* = 17.3 Hz, 2 H), 4.17 (d, *J* = 17.1 Hz,

2 H), 3.88 (s, 3 H), 2.58 (s, 3 H), 2.40 (s, 3 H); ^{13}C NMR {^{1}H} (DMSO-d6, 125 MHz): δ

169.4, 166.1, 145.3, 138.2, 137.3, 133.2, 129.7, 128.3, 128.22, 128.18, 127.1, 61.9, 52.1, 47.8, 21.1; ^{11}B NMR (DMSO-d6, 96 MHz): δ 10.4; FT-IR (neat) $\tilde{v}_{max}$: 3008, 2957, 1769, 1722, 1608, 1454, 1436, 1393, 1377, 1333, 1286, 1247, 1215, 1182, 1091, 1045, 1025, 952, 849, 774, 746, 709 cm^{-1}; HRMS (ESI+): (m/z) calculated for $[M+NH_4]^+$ $[C_{20}H_{24}BN_2O_6]^+$ 399.1727, found 399.1732.

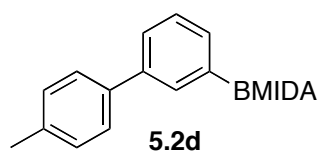**Table 5.1, Entry 3: Suzuki-Miyaura coupling of 5.1f (5.2d)**

5.2d

The general procedure for Suzuki coupling was applied to **5.1f** (180 mg, 0.50 mmol, 1 equiv) with 4-bromotoluene (85 mg, 0.50 mmol, 1 equiv) for 3 h 30 min. The product **5.2d** was isolated as an off white solid (131 mg, 81% yield, mp 246-249 °C). ^{1}H NMR (DMSO-d6, 500 MHz): δ 7.67 (s, 1 H), 7.62 (td, *J*= 7.3, 1.7 Hz, 1 H), 7.57 (d, *J*= 8.3 Hz, 2 H), 7.45-7.39 (m, 2H), 7.27 (d, *J*= 7.8 Hz, 2 H), 4.35 (d, *J* = 17.3 Hz, 2 H), 4.16 (d, *J* = 17.1 Hz, 2 H), 2.56 (s, 3 H), 2.34 (s, 3 H); ^{13}C NMR {^{1}H} (DMSO-d6, 125 MHz): δ 169.4, 139.3, 137.7, 136.5, 131.2, 130.5, 129.4, 128.2, 127.1, 126.7, 61.9, 47.7, 20.6; ^{11}B NMR (DMSO-d6, 96 MHz): δ 10.7; FT-IR (neat) $\tilde{v}_{max}$: 3018, 2955, 1766, 1456, 1336, 1291, 1244, 1203, 1097, 1055, 1035, 994, 860, 792, 708 cm^{-1}; HRMS (ESI+): (m/z) calculated for $[M+NH_4]^+$ $[C_{18}H_{22}BN_2O_4]^+$ 341.1673, found 341.1674.

Scheme 5.8 Chemoselective Amination of 5.1e (5.3a)

5.3a
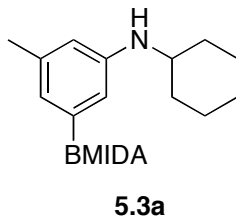
The reaction was setup in a glove box. A Schlenk flask, equipped with a magnetic stirring bar, was charged with **5.1e** (180 mg, 0.5 mmol, 1 equiv), Anhydrous Cu(OAc)$_2$ (91 mg, 0.5 mmol, 1 equiv), anhydrous KF (58 mg, 1.0 mmol, 2 equiv) and powdered 4 $^\circ$A molecular sieves (500 mg). To this mixture was added 5 mL of CH$_3$CN followed by the addition of cyclohexylamine (115 μL, 99 mg, 1.0 mmol, 2 equiv). The flask was capped, brought out of the box and put under vacuum. The flask was back filled with 15psi of O$_2$, capped and heated at 80 $^\circ$C for 4 h 30 min. The crude was filtered through a plug of silica gel flushing with CH$_3$CN. The CH$_3$CN layer was pump down and the plug product was purified by gradient column chromatography with Et$_2$O:CH$_3$CN 9:1 – 8:2 to yield product **5.3a** as a pale yellow solid (83 mg, 48% yield, mp 101-105 $^\circ$C). ^{1}H NMR (DMSO-d6, 500 MHz): δ 6.45 (s, 1 H), 6.37 (s, 1 H), 6.35 (s, 1 H), 5.14 (br s, 1 H), 4.42 (d, J = 17.1 Hz, 2 H), 4.12 (d, J = 17.1 Hz, 2 H), 3.16 (br s, 1H), 2.49 (s, 3 H), 2.18 (s, 3 H), 1.89 (dd, J = 12.9, 3.4 Hz, 2 H), 1.70 (dt, J = 13.4, 3.4 Hz, 2 H), 1.58 (dt, J = 12.7, 3.9 Hz, 1 H), 1.31 (qt, J = 12.5, 3.4 Hz, 2 H), 1.19 – 1.09 (m, 3 H); ^{13}C NMR {^{1}H} (DMSO-d6, 125 MHz): δ 169.4, 147.4, 136.9, 120.2, 114.2, 113.2, 61.5, 50.4, 47.4, 32.6, 25.6, 24.5, 21.5; ^{11}B NMR (DMSO-d6, 96 MHz): δ 11.7; FT-IR (neat) $\tilde{v}_{max}$: 3393,

2984, 2930, 2855, 1767, 1667, 1593, 1518, 1451, 1373, 1337, 1292, 1199, 1175, 1148, 1034, 961, 891, 835, 768, 710, 664 cm^{-1}; HRMS (ESI+): (m/z) calculated for [C$_{18}$H$_{26}$BN$_2$O$_4$]$^+$ 345.1986, found 345.1986.

Scheme 5.9 Chemoselective halodeboronation of 5.1b (5.4a)

5.4a
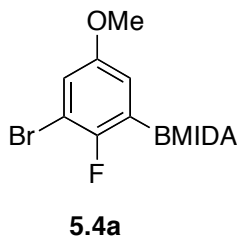
A Schlenk flask, equipped with a magnetic stirring bar, was charged with **5.1b** (102 mg, 0.25 mmol, 1 equiv), Cu(OAc)$_2$·H$_2$O (55 mg, 0.275 mmol, 1.1 equiv) and NBS (67 mg, 0.375 mmol, 1.5 equiv). The flask was capped with a rubber septum, evacuated and backfilled with nitrogen (this sequence was carried out three times). To this mixture was added 5 mL of degassed dry CH$_3$CN and flushed with nitrogen twice as mentioned previously. The flask was stoppered and the reaction was stirred at 80 °C for 24 h. Cooled the reaction to room temperature and poured into 75 mL of EtOAc. The organic layer was extracted with 50 mL each of water and saturated NaCl solution. The organic layer was dried over anhydrous Na$_2$SO$_4$ and the volatiles were removed under vacuum. The extraction product was purified by column chromatography with Et$_2$O:CH$_3$CN 9:1 to yield product **5.4a** as a white solid (72 mg, 80% yield, mp 174-176 °C). ^{1}H NMR (DMSO-d6, 500 MHz): δ 7.28 (dd, *J*= 5.6, 3.2 Hz, 1 H), 6.95 (dd, *J* = 4.4, 3.2 Hz, 1 H), 4.42 (d, *J* = 17.3 Hz, 2 H), 4.12 (d, *J* = 17.1 Hz, 2 H), 3.77 (s, 3 H), 2.65 (s, 3 H); ^{13}C

NMR {^{1}H} (DMSO-d6, 125 MHz): δ 168.9, 155.5 (d, $^4J_{C-F}$ = 2.0 Hz), 155.3 (d, $^1J_{C-F}$ =

234.2 Hz), 119.3 (d, $^3J_{C-F}$ = 8.1 Hz), 118.9, 108.3 (d, $^2J_{C-F}$ = 26.2 Hz), 62.5, 55.8, 47.6;

^{11}B NMR (DMSO-d6, 96 MHz): δ 11.5; ^{19}F NMR (DMSO-d6, 282.4 MHz): δ -112.4;

FT-IR (neat) $\tilde{v}_{max}$: 3014, 2965, 1771, 1570, 1456, 1433, 1406, 1337, 1290, 1265, 1204,

1130, 1036, 1018, 951, 897, 856, 758, 725, 704 cm^{-1}; HRMS (ESI+): (m/z) calculated for

$[C_{12}H_{13}BBrFNO_5]^+$ 360.0054, found 360.0059.

Scheme 5.10 Suzuki-Miyaura coupling of 5.1d (5.2e)

5.2e
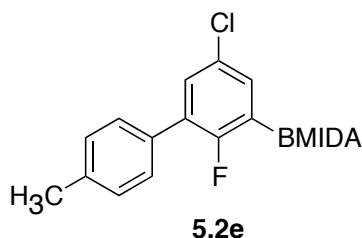
To a 50 mL Schlenk round bottom flask equipped with a magnetic stir bar was

added 4-bromotoluene (564 mg, 3.30 mmol, 1.1 equiv). To this mixture was added **5.1d**

(1234 mg, 3.0 mmol, 1 equiv), PdCl$_2$·dppf·CH$_2$Cl$_2$ (98 mg, 0.12 mmol, 4 mol % Pd) and

K$_3$PO$_4$·nH$_2$O (1908 mg, 9.0 mmol, 3.0 equiv). The flask was capped with a rubber

septum, evacuated and backfilled with nitrogen (this sequence was carried out three

times). To this mixture was added 30 mL of degassed DMSO and flushed with nitrogen

twice as mentioned previously. The reaction was stirred at room temperature for 10 h.

The reaction mixture was poured into 300 mL of EtOAc and extracted with 100 mL each

of water and saturated NaCl solution. The organic layer was dried over anhydrous

Na$_2$SO$_4$ and the volatiles were removed under vacuum. The brown solid was dissolved in

CH₃CN and passed through a plug of silica gel eluting with CH₃CN. Volatiles were removed under vacuum to yield a pale yellow solid. The pale yellow solid was washed with ether to give **5.2e** as an off white solid (943 mg, 84% yield, mp 206-208 °C). ^{1}H NMR (DMSO-d6, 500 MHz): δ 7.56 (dd, J = 6.8, 2.7 Hz, 1 H), 7.46 (d, J = 7.8 Hz, 2 H), 7.41 (dd, J = 4.4, 2.7 Hz, 1 H), 7.28 (d, J = 7.8 Hz, 2 H), 4.43 (d, J = 17.3 Hz, 2 H), 4.14 (d, J = 17.3 Hz, 2 H), 2.72 (s, 3 H), 2.35 (s, 3 H); ^{13}C NMR {^{1}H} (DMSO-d6, 125 MHz): δ 168.8, 160.6 (d, $^1J_{C-F}$ = 243.5 Hz), 137.7, 132.9 (d, $^3J_{C-F}$ = 9.7 Hz), 131.1 (d, $^3J_{C-F}$ = 4.6 Hz), 131.0, 130.0 (d, $^2J_{C-F}$ = 18.9 Hz), 129.1, 128.8 (d, $^4J_{C-F}$ = 2.8 Hz), 128.4 (d, $^4J_{C-F}$ = 2.5 Hz), 62.6, 47.7, 20.7; ^{11}B NMR (DMSO-d6, 96 MHz): δ 11.1; ^{19}F NMR (DMSO-d6, 282.4 MHz): δ -113.2; FT-IR (neat) $\tilde{\nu}_{max}$: 2995, 1744, 1451, 1428, 1410, 1337, 1294, 1271, 1238, 1192, 1127, 1042, 1001, 891, 862, 820, 685 cm^{-1}; HRMS (ESI+): (m/z) calculated for $[C_{18}H_{17}BClFNO_4]^+$ 376.0923, found 376.0928.

Scheme 5.11 Deprotection/oxidation of 5.2e (5.5a)

5.5a
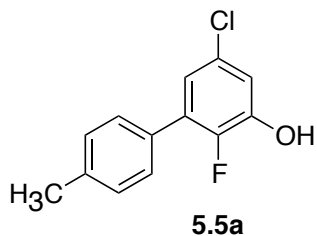
To a 100 mL round bottom flask equipped with a magnetic stir bar was added **5.2e** (750 mg, 2.0 mmol, 1.0 equiv) and THF (20 mL). To this was added 1.0 M NaOH (8 mL, 8.0 mmol, 4 equiv.) followed by the addition of 30% H_2O_2 (680 μL, 6.0 mmol, 3

equiv.). The reaction was stirred at room temperature for 2 h. The reaction was quenched

with sat. NaHSO$_3$ and extracted with 2x75 mL EtOAc. The EtOAc layer was washed

with 50 mL each of water and saturated NaCl solution. Dried the organic layer over

anhydrous Na$_2$SO$_4$ and the volatiles were removed under vacuum to obtain the product

5.5a as an off white solid (435 mg, 92% yield, mp 67-69 °C). ^{1}H NMR (DMSO-d6, 500

MHz): δ 10.45 (s, 1 H), 7.41 (d, J = 8.1 Hz, 2 H), 7.27 (d, J = 8.3 Hz, 2 H), 6.96 (dd, J =

7.1, 2.7 Hz, 1 H), 6.90 (dd, J = 5.9, 2.7 Hz, 1 H), 2.34 (s, 3 H); ^{13}C NMR {^{1}H} (DMSO-

d6, 125 MHz): δ 147.2 (d, $^1J_{C-F}$ = 242.6 Hz), 146.6 (d, $^2J_{C-F}$ = 14.3 Hz), 137.7, 131.2,

130.4 (d, $^2J_{C-F}$ = 12.4 Hz), 129.1, 128.5 (d, $^4J_{C-F}$ = 3.2 Hz), 127.7 (d, $^4J_{C-F}$ = 4.1 Hz),

119.1 (d, $^3J_{C-F}$ = 1.8 Hz), 116.1 (d, $^3J_{C-F}$ = 3.2 Hz), 20.7; ^{19}F NMR (DMSO-d6, 282.4

MHz): δ -143.4; FT-IR (neat) $\tilde{v}_{max}$: 3376, 2923, 1609, 1597, 1520, 1479, 1445, 1401,

1314, 1298, 1275, 1200, 1186, 1129, 938, 847, 810, 789, 729 cm^{-1}; HRMS (ESI-): (m/z)

calculated for [C$_{13}$H$_9$ClFO]$^-$ 235.0326, found 235.0324.

Scheme 5.12 Buchwald-Hartwig amination of 5.5a (5.6a)

5.6a
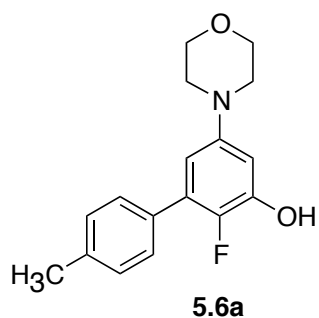
In a glove box, a 20 mL scintillation vial equipped with a magnetic stir bar was added **5.5a** (118 mg, 0.5 mmol, 1.0 equiv) and 1.0 M LiHMDS in THF (1.2 mL, 1.2 mmol, 2.4 equiv). To this was added chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II)[9] (7.4 mg, 0.01 mmol, 2 mol%) dissolved in 1.2 mL of 1,4-dioxane followed by the addition of morpholine (65 µL, 0.75 mmol, 1.5 equiv.). The vial was capped, stirred at room temperature for 3 h. The reaction mixture was brought out and poured into 60 mL of EtOAc, quenched with 20 mL of 1.0M HCl and extracted with 30 mL each of water and saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and the volatiles were removed under vacuum. The pale yellow solid was dissolved in THF and passed through a plug of silica gel eluting with CH_3CN. Volatiles were removed under vacuum to yield the product **5.6a** as a white solid (122 mg, 85% yield, mp 213-215 $^\circ$C). ^{1}H NMR (DMSO-d6, 500 MHz): δ 9.67 (s, 1 H), 7.40 (d, J = 7.8 Hz, 2 H), 7.24 (d, J = 7.8 Hz, 2 H), 6.50 (dd, J = 7.1, 2.9 Hz, 1 H), 6.36 (dd, J = 5.1, 2.9 Hz, 1 H), 3.72 (t, J = 4.4 Hz, 4 H), 3.03 (t, J = 4.4 Hz, 4 H), 2.34 (s, 3 H); ^{13}C NMR {[1]H} (DMSO-d6, 125 MHz): δ 147.6 (d, $^4J_{C\text{-}F}$ = 2.3 Hz), 145.5 (d, $^2J_{C\text{-}F}$ = 13.8 Hz), 142.6 (d, $^1J_{C\text{-}F}$ = 235.2 Hz), 136.8, 133.1, 128.9, 128.8 (d, $^2J_{C\text{-}F}$ = 11.1 Hz), 128.5 (d, $^4J_{C\text{-}F}$ = 2.8 Hz), 106.7, 104.0, 66.1, 48.9, 20.7; ^{19}F NMR (DMSO-d6, 282.4 MHz): δ -152.9; FT-IR (neat) $\tilde{v}_{max}$: 3202, 1603, 1516, 1487, 1451, 1383, 1265, 1190, 1169, 1107, 1001, 907, 907, 866, 855, 812, 745 cm^{-1}; HRMS (ESI+): (m/z) calculated for $[C_{17}H_{19}FNO_2]^+$ 288.1400, found 288.1404.

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