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IRIDIUM CATALYZED AROMATIC BORYLATION
AND ITS APPLICATIONS IN
ONE–POT PREPARATIONS OF SUBSTITUTED
AROMATIC BUILDING BLOCKS

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Ghayoor Abbas Chotana

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IRIDIUM CATALYZED AROMATIC BORYLATION AND ITS APPLICATIONS IN ONE–POT PREPARATIONS OF SUBSTITUTED AROMATIC BUILDING BLOCKS

BY

Ghayoor Abbas Chotana

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ABSTRACT

IRIDIUM CATALYZED AROMATIC BORYLATION AND ITS APPLICATIONS IN ONE–POT PREPARATIONS OF SUBSTITUTED AROMATIC BUILDING BLOCKS

By

Ghayoor Abbas Chotana

Selective functionalization of hydrocarbons represents one of the most challenging problems in homogeneous and heterogeneous catalysis. During the last decade, iridium catalyzed aromatic borylation has emerged as one of the most convenient methodologies for the regioselective functionalization of aromatic as well as heteroaromatic hydrocarbons. The most striking feature of this new tool available to the synthetic chemist is that the regioselectivities are governed by sterics, and hence, are complementary to those found in electrophillic aromatic substitution or directed *ortho* metalation. This unique feature allows for the synthesis of new aromatic building blocks, which were previously either unknown or difficult to synthesize. Another useful feature of this new methodology is the tolerance to several common functional groups such as halogens, esters, amides etc.

Iridium catalyzed borylation *ortho* to substituents other than H is typically hindered. Evaluation of steric effects of several substituents showed that CN is one of the smallest substituents. Since regioselectivities in Ir catalyzed borylation are controlled by sterics, we reasoned that borylations *ortho* to CN, an electronic *meta* director, should be possible. As a test, we examined several 4-substituted benzonitriles and found good *ortho* selectivity for several substrates. Regioselectivities greater than 99% were obtained for bulkier substituents such as ester, amine, acetanilide and trifluoromethyl. These borylations were the first general examples of *ortho*-functionalization of 4-benzonitriles.

This contrasts with *meta*-functionalizations, which have been known for more than a century.

Good to high regioselectivities were observed in mono- and di-borylation of a variety of substituted thiophenes. The BPin group was found to survive during electrophillic aromatic bromination reactions. Poor regioselectivities observed with d^{t}bpy ligand were improved by using bis-oxazoline derived ligands.

Since Ir catalyzed borylations leave aryl halogen (Cl, Br, and I) bonds intact, it might be useful if chemo–selective cross couplings can be accomplished at the halide positions while retaining the boronate functionality. We have found that under anhydrous basic conditions, cross coupling reactions such as amination, Sonogashira coupling, and C–S coupling can be carried out on the C–halogen bond, while keeping the C–B bond completely intact. The resulting amino boronate esters, aryl alkynyl boronate esters, and aromatic thio ether boronate esters are all new compounds and are difficult to synthesize by any other rout.

5-Coordinate, 16-electron, bi-dentate ligated iridium tris-boryl complexes have been proposed to be the active catalysts in the iridium catalyzed aromatic borylation. Our attempts to synthesize the proposed active catalysts using various bidentate ligands is presented, ultimately culminating in the successful synthesis of couple of (bis-phosphine)Ir(BPin)$_3$ complexes, which are the first examples of stable, 16-electron, iridium tris-boryl complexes. The complex (d^{t}ppe)Ir(BPin)$_3$ borylates aromatic compounds at room temperature.

To my beloved mother

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I am very thankful to Prof. Milton Rudolph Smith III for his guidance during my PhD and for giving me an opportunity to work on one of the most exciting chemistry of present time. I have learned so many things from him, all of which are not possible to list here. The most important one is to accept challenges and complete targets on time with unmatched levels of excellence. He can convert any raw grad student, like me, into gold with his hard work. I am also very thankful to him for his patience on my mistakes.

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LIST OF SYMBOLS AND ABBREVIATIONS

Ar	aryl
BCat	catecholatoboryl ($-BO_2C_6H_4$)
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, η^5-$C_5(CH_3)_5$
°C	degree Celcius
d	doublet
d^{t}bpy	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
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
HBPin	pinacolborane
Hz	Hertz
Ind	indenyl (C_9H_7)
IR	infrared
J	coupling constant
kcal	kilocalorie
LDA	lithium-di-isopropylamide
m	multiplet
m	*meta*
n	normal (straight chain hydrocarbon)
Me	methyl
MesH	mesitylenyl
min	minutes
mL	milliliters
mmol	millimole
mol	mole
NMR	nuclear magnetic resonance
o	*ortho*
OMe	methoxy (OCH_3)

p	*para*
Pd	palladium catalyst
Ph	phenyl
PMe_3	trimethyl phosphine
^iPr	*iso*-propyl
q	quartet
s	singlet
t	triplet
THF	tetrahydrofuran
TIPS	tri-isopropylsilyl
TNT	trinitrotoluene
TONs	turn over numbers
TPy	tetra-2-pyridinylpyrazine
δ	delta, ppm for NMR spectroscopy
η^n	hepticity of ligand
μL	microlitres

CHAPTER 1

Introduction

C–H Bond Activation and Functionalization of Hydrocarbons

Selective C–H bond activation of unreactive hydrocarbons, and subsequent functionalization to useful products, represents one of the most challenging problems in homogeneous and heterogeneous catalysis. Such transformations will assist the synthetic organic chemist to design new retrosynthetic approaches towards complex molecule synthesis. They could also result in synthesis of new and interesting compounds with potential applications in wide areas of research ranging from pharmaceutical to material sciences.

C–H activation refers to the binding of a hydrocarbon C–H bond to the metal center, normally by cleavage of the bond by oxidative addition (Eq 1.1).

$$L_nM + R\text{–}H \rightleftharpoons L_nM(R\text{–}H) \rightleftharpoons L_nM(R)(H) \qquad (1.1)$$

Functionalization, in contrast, involves replacement of a C–H hydrogen by an organic functional group G (Eq 1.2).

$$C\text{–}H \longrightarrow C\text{–}G \qquad (1.2)$$

In order to catalyze the functionalization of C–H bonds by a transition metal complex; the initial activation step shown in Eq. 1 should be followed by a secondary functionalization step. Functionalization has proved to be more difficult than the activation step, and a common reaction of alkyl hydride complexes is the reverse of Eq 1.1, which reforms the alkane. The requirement to carry out functionalization with good chemo-, regio-, stereo-, and enantioselectivity has further increased the challenges associated with catalytic transformations.

Hydrocarbons are some of the least reactive organic compounds. Their lack of reactivity is attributed to high bond energies of C–H bonds (typically 90-104 kcal/mol), very low acidity/basicity, and low bond polarity. Since hydrocarbons are the most abundant organic raw material available, there is huge interest in their selective functionalization.

Non-transition metal based approaches for hydrocarbon functionalization include electrophillic aromatic substitution,[1] directed *ortho* metalation/electrophillic addition,[2] free radical reactions,[3] and superacid mediated transformations.[4] Less explored but potentially highly useful areas include metathesis reactions of C–H and B–H bonds,[5] and reactions of unactivated C–H bonds with dioxiranes.[6] The uncatalyzed reactions typically give functionalization at the most substituted carbon atom (except for the free radical benzylic activation) often with limited selectivity.

In the past three decades, a variety of transition metal catalysts have been developed for the functionalization of C–H bonds. These new powerful methods can transform the C–H bond into C–C, C–O, C–N, C–B, C–Si, or C–halogen bonds.[7] Most of these reactions involve insertion of a low valent transition metal into the least hindered C–H bond, and are often highly selective.

Although all of these catalysts promote the same general transformations (C–H → C–G), they can operate within two very different mechanistic manifolds. Sanford has termed these two mechanisms as 'inner-sphere' and 'outer-sphere' mechanisms.[7] Alternative terminology, introduced by Crabtree, labels these mechanisms 'organometallic' and 'coordination' respectively.[8]

Inner-sphere Mechanism

The 'inner-sphere' C–H bond functionalization mechanism involves two discrete steps:

(i) cleavage of a C–H bond to afford a transition metal alkyl/aryl species and

(ii) functionalization of the nascent C–M bond with either an external reagent or at the metal center (Eq 1.3).

$$\text{C–H} + \text{cat. [M]} \xrightarrow{\text{(i) C-H cleavage}} \text{C–[M]} \xrightarrow{\text{(ii) Functionalization}} \text{C–G} \qquad (1.3)$$

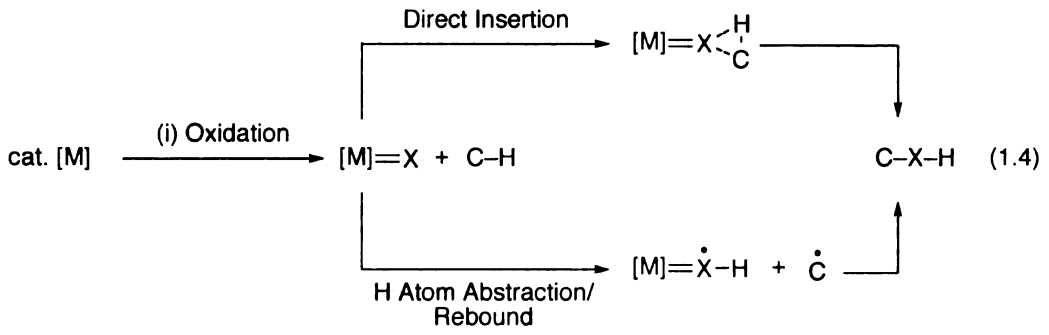
The key distinguishing feature of this mechanism is the formation of a discrete organometallic intermediate, and the structural and electronic requirements of this intermediate dictate the regio- and stereo selectivity of functionalization. These transformations often proceed with high selectivity for the less sterically hindered C–H bonds of a molecule; however, other factors, including the ligand environment at the metal center and the mechanism of the C–H bond cleavage step, can also influence selectivity in these systems.

Outer-sphere Mechanism

The 'outer-sphere mechanism' for C–H bond functionalization mimics biological oxidation reactions catalyzed by enzymes such as cytochrome P450 and methane monooxygenase (MMO). These processes proceed via

(i) formation of a high oxidation state metal complex containing an activated ligand X (typically a metal oxo–, imido–, or carbene species) followed by

(ii) reaction of ligand X with a C–H bond. This latter step can proceed by either direct insertion or H–atom abstraction/radical rebound (Eq 1.4).



The key distinguishing feature of the outer-sphere mechanism is that the alkane/arene substrate does not interact directly with the transition metal center but instead reacts with a coordinated ligand. These transformations involve build up of radical and/or cationic character at carbon, and therefore typically show high selectivity for weaker C–H bonds (e.g. those that are benzylic, allylic, 3°, or α to heteroatoms).

Arenes are often more reactive than alkanes in C–H bond cleavage reactions, in spite of greater strength of arene vs. alkane C–H bonds. Arenes are more reactive kinetically, probably because the arene C–H bond is less hindered and metal can interact with the ring prior to C–H cleavage, and more stable thermodynamically, because of the stronger aryl vs. alkyl C–M bonds in the product.

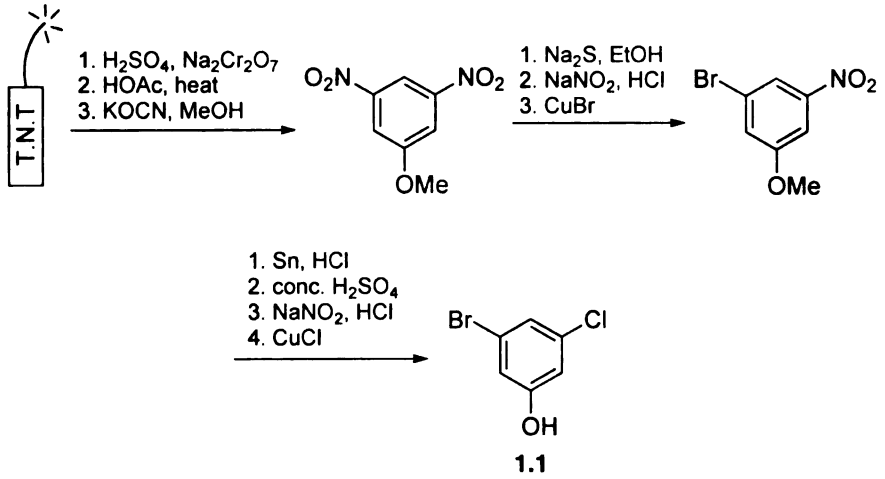
Functionalization of Aromatic Hydrocarbons

In 1825 Faraday reported that benzene and nitric acid react,[1] but Mitscherlich was the first to determine that nitrobenzene was the product in 1834.[9] In the intervening years, electrophillic aromatic substitution (EAS) has evolved as the workhorse for aromatic functionalization.

The regioselectivities for electrophillic aromatic substitution are governed by the number, type, and relative placement of substituents in the aromatic system, and that substituents typically fall into two classes[10]: (i) *ortho*, *para*-directors that typically

activate the aromatic system to electrophillic substitution and (ii) *meta*-directors that operate by virtue of *ortho*, *para* deactivation.

The major limitation of electrophillic aromatic substitution is its inability to prepare diverse *meta* substituted aromatics. For example, it took ten steps starting from TNT to prepare a relatively simple phenol[11] (Figure 1.1).



1.1

Figure 1.1. Synthesis of a *meta*-substituted phenol by electrophillic aromatic substitution.

Nucleophilic aromatic substitution is another approach for aromatic functionalization, however requirement of harsh basic conditions limits its wide applicability. Wittig in 1938[12] and Gilman in 1939[13] reported 'Directed *ortho* metalation' methodology for aromatic functionalization (Figure 1.2). Although it has proved to be a very useful technique, the functional groups must not react with organolithium reagents.

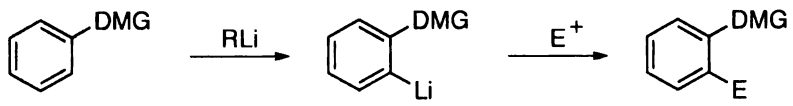


Figure 1.2. Aromatic functionalization via directed *ortho* metalation.

Organoboron Compounds

Organoboron compounds are synthetically valuable intermediates. The C–B bond of an organoboron compound can easily be transformed into a variety of functional groups.[14] Organoboron compounds have also been extensively used in cross-coupling reactions.[15] Although trialkylboranes are air/moisture sensitive, the oxygenated organoboranes are air/moisture stable and can be easily handled. The di-oxygenated organoboranes, called boronic acids or boronic esters, are the most commonly used organoboranes. The carbon attached to boron in organoboranes has a partial negative charge making these compounds as 'shelf stable carbanions'.[16]

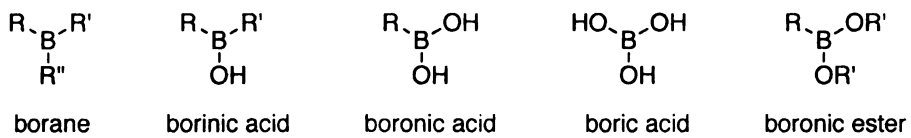


Figure 1.3. Oxygenated organoboron compounds.

Synthesis of Alkyl and Alkenyl Boranes

Organoboranes were first synthesized by Frankland in 1860 by the reaction of dialkylzinc and trialkoxyborane[17-19] (Figure 1.4).

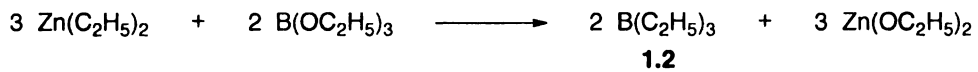


Figure 1.4. Preparation of the first organoborane compound, **1.2**.

The discovery of Grignard reagents led to the development of more versatile synthesis based on the reaction of these reagents with borontrifluoride etherate or alkoxyboranes.[20] However prior formation of reactive organometallics limited the use of this route.

Another possible route was the reaction of hydrocarbons with diborane. Early studies indicated that alkenes reacted with diborane at high temperature to form trialkyl boranes.[21] In 1957, Brown and Subba Rao reported that in the presence of organic ethers, diborane could be added to olefins with remarkable ease and speed at room temperature to form the corresponding organoboranes in high yield (Figure 1.5).[22] Similarly, alkenyl boranes were prepared by hydroboration of alkynes.

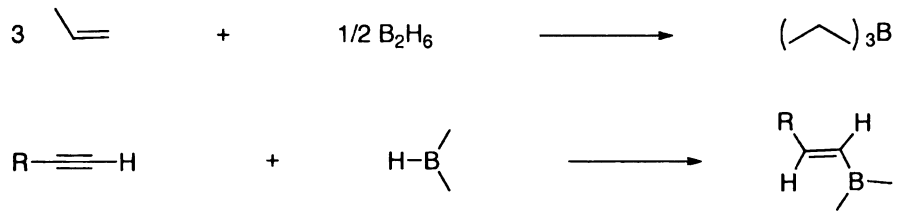


Figure 1.5. Hydroboration of alkenes and alkynes.

The resulting aliphatic boranes were extensively employed in organic syntheses resulting in the 1979 Nobel Prize being awarded to H. C Brown (shared with G. Wittig). Mannig and Noth reported the first examples of transition metal catalyzed hydroboration in 1985.[23] The chemo-, regio-, and stereoselectivities of metal catalyzed reactions were generally found to be complementary to those of uncatalyzed reaction.

Synthesis of Aromatic Boronates

Aryl boronic acids and esters are the most popular and widely used organoboranes. Their popularity in medicinal chemistry is due in large part to their role as cross-coupling partners for the synthesis of biaryl units, which are present in structure of several pharmaceutical drugs.

As oppose to the preparation of alkenyl boranes via hydroboration of alkynes, aromatic boranes cannot be easily prepared by hydroboration since benzyne intermediates

would be required. Thus aromatic boronate esters have been traditionally prepared in three steps by (1) halogenation (2) conversion of aryl halide to Grignard reagent (3) reaction of Grignard reagent with trialkyl borate to yield aryl boronate esters (Figure 1.6).[24]

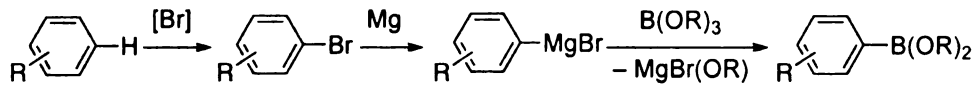


Figure 1.6. Traditional route for the synthesis of aryl boronic acids.

Directed *ortho* metalation (D*o*M) followed by trapping the resulting aryl lithium reagent with trialkylborates has also been used to prepare aryl boronic acids (Figure 1.7).[16,25,26] However this methodology suffers from the disadvantage of the need to use cryogenic conditions. The use of aryl magnesium/lithium reagents also limits functional group compatibility.

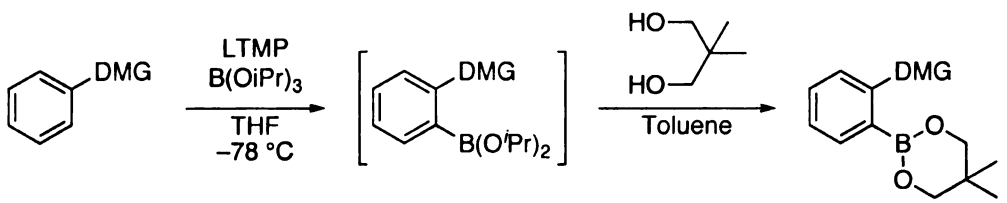


Figure 1.7. Synthesis of aryl boronic esters via directed *ortho* metalation.

One of the earliest methods for the preparation of aryl boronic acids involved the reactions between diaryl mercury compounds and boron trihalide. Since organomercurial compounds are toxic, this reaction has remained unpopular. In search of other reagents for this reaction, alkyl/aryl silanes and stannanes were found to undergo easily transmetallation with boron tribromide (Figure 1.8).[27]

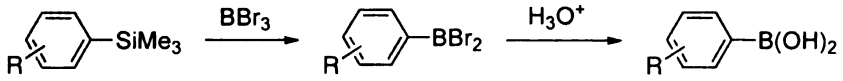
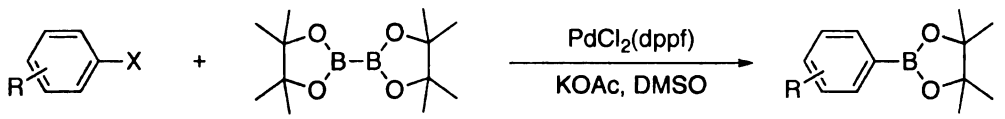


Figure 1.8. Synthesis of aryl boronic acids from trialkyl aryl silanes.

Transition Metal Catalyzed Aromatic C–B Bond Formation

In 1995, Miyaura et al. reported the palladium catalyzed direct conversion of aryl halides to arylboronate esters (Figure 1.9).[28] This methodology bypassed the need to generate aryl magnesium/lithium reagents from aryl halides, and hence increased the functional group tolerances during the preparation of aryl boronic esters.



1.3

Figure 1.9. Palladium catalyzed borylation of aryl halides.

In 2000, Strongin and Willis reported a palladium catalyzed coupling of aryl diazonium tetrafluoroborate salts with bis(pinacolato)diboron to synthesize aryl boronic esters (Figure 1.10).[29] The reaction proceeded under mild reaction conditions in the absence of a base to afford various functionalized arylboronic esters including haloarylboronic esters.

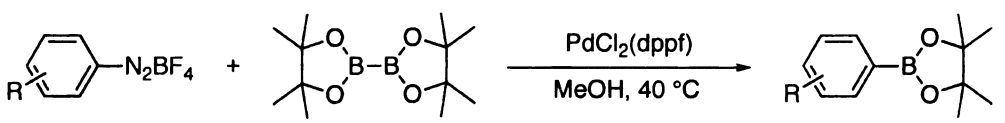


Figure 1.10. Palladium catalyzed borylation of aryl diazonium tetrafluoroborate salts.

Transition metal catalyzed cycloaddition of alkynyl boronate esters with diynes has also been utilized for the preparation of aryl boronic esters (Figure 1.11).[30-32]

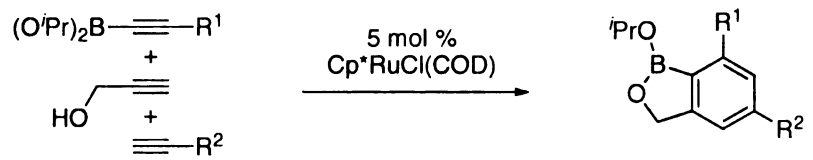


Figure 1.11. Synthesis of aryl boronic esters via cycloaddition of alkynyl boronate esters with diynes.

Since huge feedstocks of aromatic and heteroaromatic hydrocarbons are easily available, direct conversion of aromatic C–H bond to the C–B bond would be the ideal approach for the synthesis of aryl boronic esters (Figure 1.12).

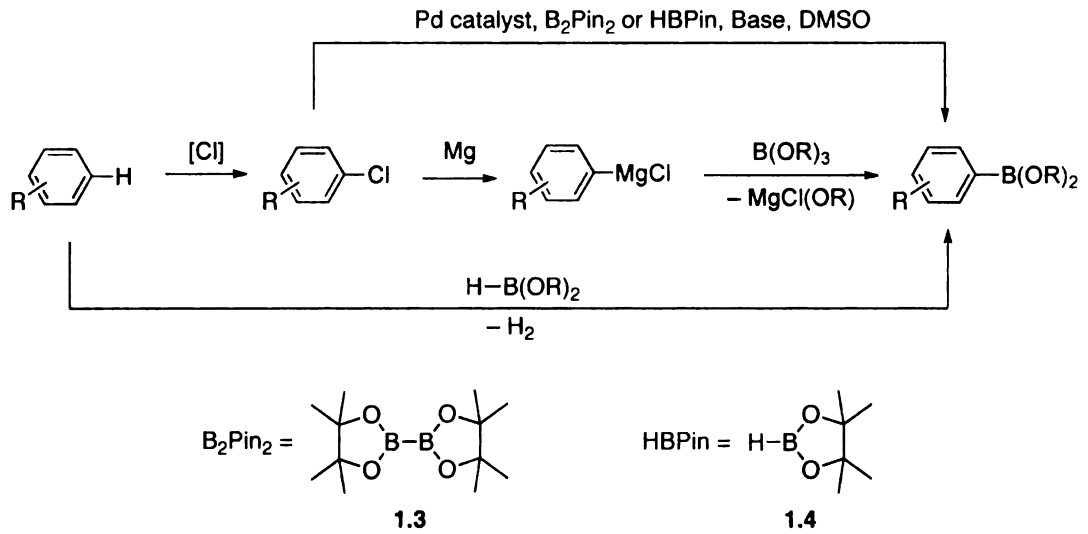


Figure 1.12. Different routes for the preparation of aryl boronic esters.

Uncatalyzed C–H Bond Borylation Reactions

In 1948, Hurd reported that at elevated temperatures, diborane reacts with several hydrocarbons such as alkenes, alkynes, paraffins, and benzene.[21] Benzene underwent substitution reaction to form phenylboron compounds, which upon alkaline workup gave phenylboronic acid. These reactions were carried out in stainless steel vessels and hence they might not be truly uncatalyzed.

Koster and Rotermund discovered in 1960 that pyrolysis of triorganoboranes yielded bicycloorganoborane **1.5**, alkene, and molecular hydrogen (Figure 1.13).[33] A four-centered mechanism was proposed for the observed cleavage of C–H and the formation of C–B bonds (Scheme 1.1).

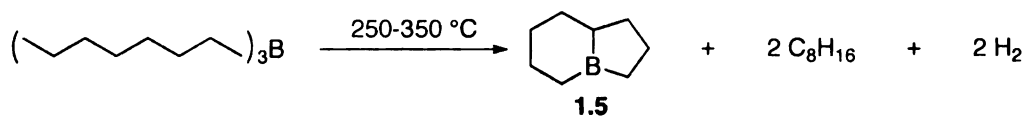
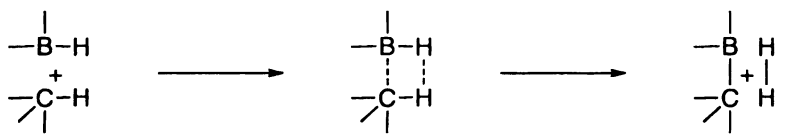


Figure 1.13. Pyrolysis of tri-*n*-octylborane.

Scheme 1.1. The four-centered mechanism of C–H/B–H dehydrogenation reactions.



Knochel observed similar intramolecular C–H activations of *tert*-butyl and phenyl groups in organoboranes in solutions.[34] Relatively small activation barriers (≤ 30 kcal mol^{-1}) have been predicted for intermolecular dehydrogenation reactions between borane and hydrocarbons that occur via four-centered transition states.[5]

Transition Metal Mediated Aromatic C–H Activation/Borylation

In 1995, Hartwig et al. reported the stoichiometric functionalization of arenes and alkenes by $(CO)_5Mn(BCat)$ (**1.6**), $(CO)_5MRe(BCat)$ (**1.7**), and $CpFe(CO)_2(BCat)$ (**1.8**) under photochemical conditions (Figure 1.14).[35]

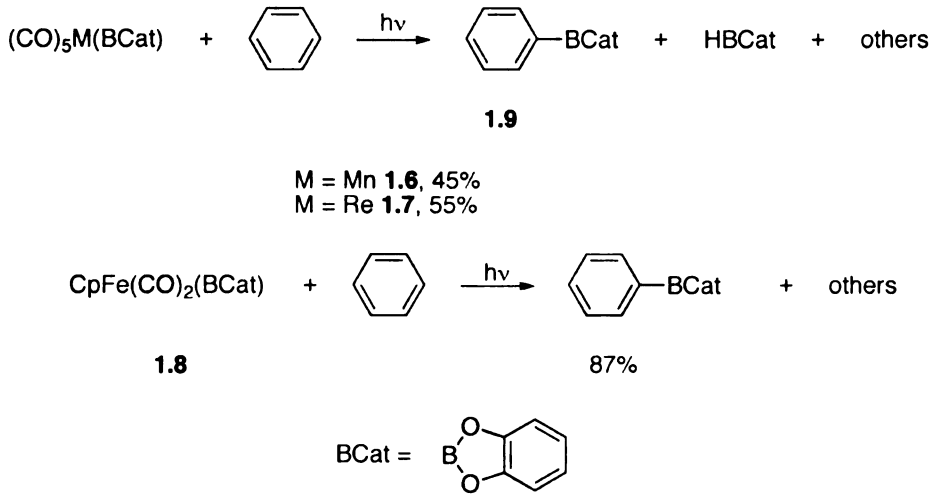


Figure 1.14. Transition metal mediated photochemical aromatic borylation.

Hartwig et al. also examined the photochemical stoichiometric reactions of $CpFe(CO)_2(BCat)$ (**1.8**) in a mono-substituted arene solvents.[36] They observed the formation of only *meta*- and *para*-substituted arylboronate esters except anisole, which showed substantial amounts of *ortho*-substituted product (Table 1.1).

Table 1.1. Ratio of product isomers from reaction of $CpFe(CO)_2(BCat)$ with C_6H_5X.

X	*o*	*m*	*p*
Me	–	1.1	1.0
OMe	1.0	1.6	1.1
Cl	–	1.5	1.0
CF_3	–	1.5	1.0
NMe_2	–	1.0	8.0

Transition Metal Catalyzed Aromatic C–H Activation/Borylation

In 1994, Rablen and Hartwig reported calculation of B–H and B–C bond dissociation energies for a series of borane reagents.[37,38] From the established thermochemical and computational data, the reaction in Eq 1.5 was calculated to be essentially thermoneutral.[39] Hence, catalysis should be thermodynamically feasible.

$$CH_4 + HBCat \rightleftharpoons CH_3BCat + H_2 \; ; \; \Delta H° = +1.1 \text{ kcal/mol} \qquad (1.5)$$

The first catalytic, thermal aromatic borylation was reported by Iverson and Smith in 1999 by using Cp*Ir(PMe_3)(H)(BPin) (**1.10**) as a precatlyst (Figure 1.15).[39] With about 3 TON, this was also the first demonstration of catalytic viability of Eq. 1.5.

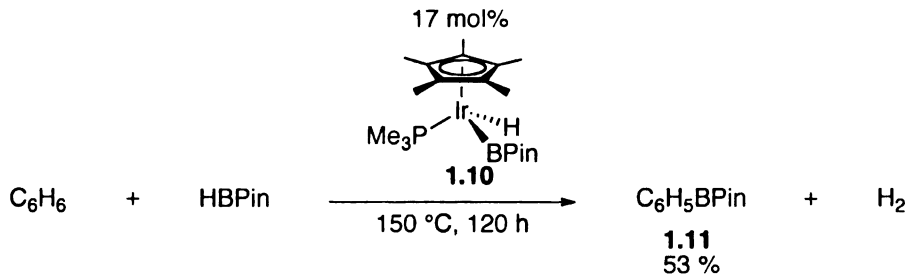


Figure 1.15. First transition metal catalyzed aromatic C–H activation/borylation.

In 2000, Hartwig et al. reported that the rhodium complex Cp*Rh(η^4-C_6Me_6) (**1.12**) catalyzes the formation of linear alkyl boranes from alkanes and borane reagents under thermal conditions (Figure 1.16).[40]

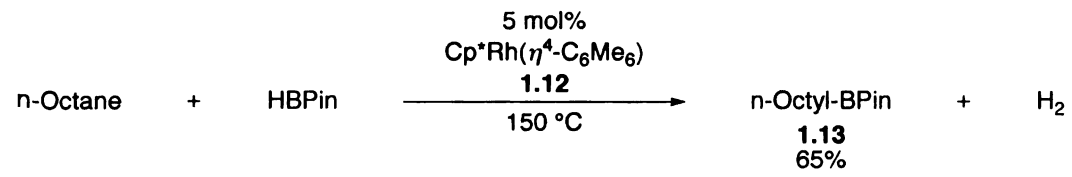


Figure 1.16. Thermal, catalytic, regiospecific functionalization of n-octane.

Cho and Smith in 2000 reported thermal catalytic borylations of substituted arenes using $Cp^*Ir(PMe_3)(H)(BPin)$ (**1.10**) or $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ (**1.12**).[41] Regioselectivities in this new catalytic aromatic borylation protocol were governed by sterics and hence were complementary to the traditional electrophillic aromatic substitution chemistry. For example, borylation of toluene gave a 2:1 statistical mixture of *m*- and *p*-C_6H_4MeBPin (Figure 1.17). 1,3-di-substituted arene was selectively functionalized on the 5-position (Figure 1.18). Heterocyclic substrate such as 2,6-di-methylpyridine was selectively borylated at the 4-position. Several functional groups including heteroatom substituents were tolerated. Iridium catalyst **1.10** was more selective for aromatic C–H activation vs. benzylic or C–F activation as compared to the rhodium catalyst **1.12**. Electron deficient arenes were more reactive than electron rich ones. Borylation of C_6D_6 with HBPin in the presence of *m*-C_6H_4Me(BPin) (**1.14b**) did not isomerize *m*-C_6H_4Me(BPin) or reduced it to toluene, indicating that the isomer distribution was kinetically determined.

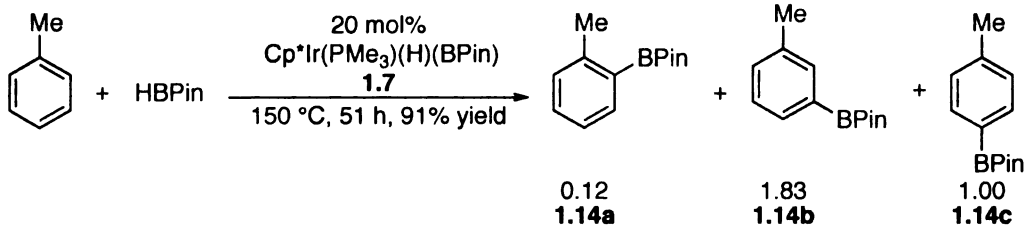
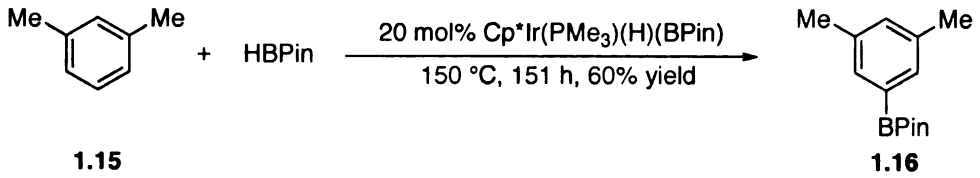


Figure 1.17. Statistical product distribution in sterically directed catalytic thermal borylation of mono substituted arene.



1.15 **1.16**

Figure 1.18. Regioselective borylation of 1,3-substituted arene.

Tse and Smith showed in 2001 that catalytic borylation could also be performed by using stoichiometric arenes in an inert solvent like cyclohexane.[42] Several 1,3-substituted arenes were selectively borylated on the 5-position using Cp*Rh(η^4-C_6Me_6) (**1.12**) precatalyst. 1,2-di-methoxybenzene was selectively borylated on the 4-position. TIPS protected pyrrole was selectively borylated on the 3-position. Attempted borylation of *m*-di-chlorobenzene resulted in the formation mixture of products, including those from dechlorination, indicating the incompatibility of halogenated arenes with rhodium precatalyst **1.12**.

Since iridium-based catalysts were more selective for aromatic C–H activation vs. the rhodium-based catalyst, detailed study of the iridium system was required in order to improve the turnover numbers. Mechanistic studies by Smith and co-workers[43] revealed that the active catalysts in the form of iridium phosphine species were generated by Cp* loss from Cp*Ir(PMe)$_3$(H)(BPin) (**1.10**). Active catalysts could also be generated by a combination of (Ind)Ir(COD) (**1.17**) and phosphine ligands. Commercially available precatalyst such as [Ir(COD)Cl]$_2$ (**1.18**) were also effective. Chelating phosphine substantially increased catalytic activity and TONs as high as 4500 were obtained with 1,2-bis-(dimethylphosphino)-ethane (dmpe) (**1.19**). This catalyst was highly selective for aromatic C–H bond activation as compared to aromatic C–Halogen or benzylic C–H

activation (Figure 1.19). Several functional groups including C–Halogen bonds were tolerated. A mechanism involving $Ir^{III/V}$ cycle was proposed (Figure 1.20).

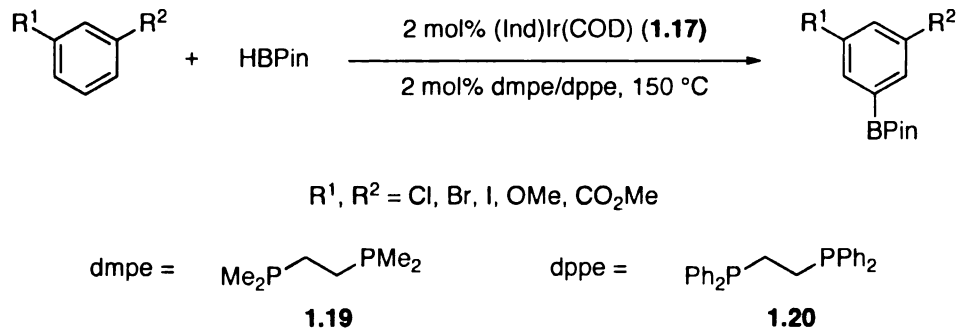


Figure 1.19. Improved catalysts for aromatic C–H activation/borylation.

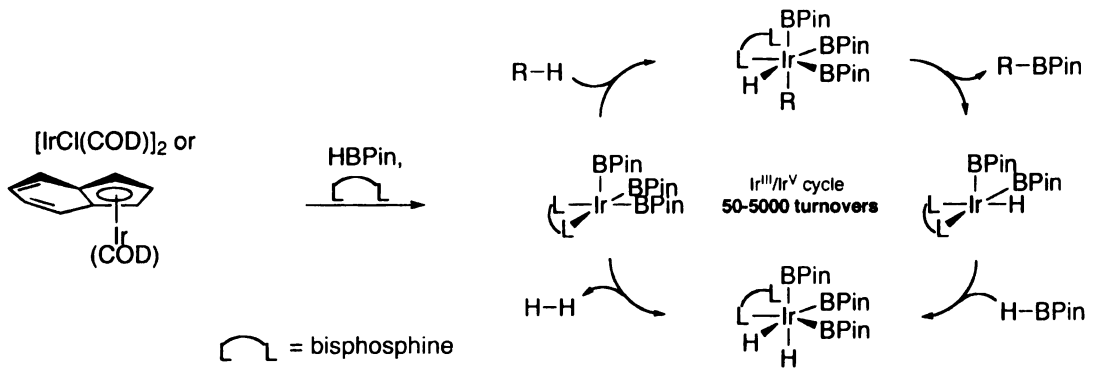


Figure 1.20. Catalytic cycle for iridium catalyzed aromatic C–H activation/borylation.

Shortly after Smith's report, Hartwig and coworkers showed that a combination of $[Ir(COD)Cl]_2$ (**1.18**) and 2,2`-bipyridine (**1.22**) could also catalyze aromatic borylation (Figure 1.21).[44] Regioselectivities and functional group tolerance in this system were similar to the one reported by Smith.[41,43]

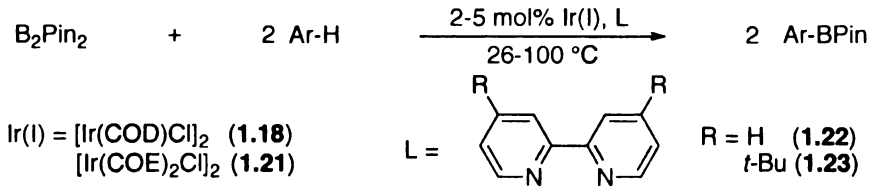


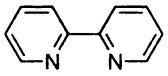
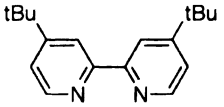
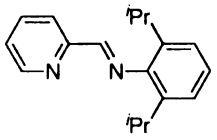
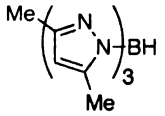
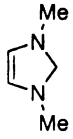
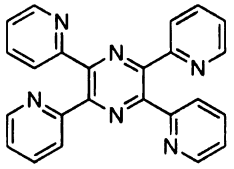
Figure 1.21. Ir/bpy catalyzed aromatic C–H activation/borylation.

In the same year, Miyaura and Hartwig reported catalyst system consisting of $[Ir(OMe)(COD)]_2$ (**1.24**), 4,4′-di-*t*-butyl-2,2′-bipyridine (dtbpy) (**1.23**), and B_2Pin_2 (**1.3**) to be effective for borylation of several electron deficient arenes at room temperature.[45] The reaction could also be carried out with HBPin[46] (**1.4**) and the substrate scope was expanded to simple heteroaromatics.[47,48]

A detailed mechanistic study was reported by Hartwig in 2005 where $[Ir(dtbpy)(COE)(BPin)_3]$ (**1.25**) was identified as the resting state of catalyst.[49] Kinetic studies showed that the active catalyst is generated by the reversible dissociation of COE, and the resulting reactive intermediate $[Ir(dtbpy)(BPin)_3]$ 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. TONs were increased up to 25,000.

Several reports have since appeared in literature where other precatlyst/ligand combinations have also been shown to carry out aromatic borylation. Chart 1.1 summarizes different types of catalysts/ligands systems which have been employed in aromatic C–H borylation.

Chart 1.1. Different catalysts systems used for aromatic borylation.

Entry	Inventor	Year	Precatalyst	Ligand
1	Smith[39]	1999	$Cp^*Ir(PMe_3)(H)(BPin)$	–
2	Smith[41]	2000	$Cp^*Rh(C_6Me_6)$	–
3	Marder[50]	2001	$[RhCl(P^iPr_3)_2(N_2)]$	–
4	Smith[43]	2002	(Ind)Ir(COD) or $[Ir(COD)Cl]_2$	Me_2P–PMe_2 or Ph_2P–PPh_2
5	Hartwig/Miyaura[44]	2002	$[Ir(COD)Cl]_2$	bpy = 
6	Miyaura/Hartwig[45]	2002	$[Ir(OMe)(COD)]_2$	dtbpy = 
7	Nishida/Tagata[53]	2004	$[Ir(COD)Cl]_2$	
8	Hartwig/Miyaura[49]	2005	$[Ir(dtbpy)(COE)(BPin)_3]$	–
9	Murata[55]	2006	$[Rh(COD)Cl]_2$ or $[Ir(COD)Cl]_2$	
10	Herrmann[56]	2006	$[Rh(COD)Cl]_2$ or $[Ir(COD)Cl]_2$	
11	Yinghuai[57]	2007	$[Ir(-o\text{-}O\text{-}C_6H_4\text{-}CH{=}N\text{-}CH_2Ph)(COD)]$	

Marder et al. showed in 2001 that [RhCl(P^iPr_3)$_2$(N_2)] (**1.26**) was an efficient catalyst for the borylation of aromatic and benzylic C–H bonds with HBPin.[50] This catalyst system was highly selective for benzylic functionalization of toluene, *p*-xylene, and mesitylene. DFT calculations at B3PW91 level indicated that [Rh($^iPr_3$)$_2$(H)] is the active species which oxidatively add to the C–H bond leading to an η^3-benzyl complex which is the key to determining the unusual benzylic regioselectivity.[51] Ishiyama and Miyaura reported in 2001 that 10% Pd/C was an effective catalyst for benzylic borylation of alkyl benzenes.[52]

Nishida and Tagata reported that a combination of [IrCl(COD)]$_2$ precatalyst and 2,6-diisopropyl-*N*-(2-pyridylmethylene)-aniline (**1.27**) ligand was effective for aromatic borylation at 80 °C.[53] *n*-Octane was a suitable solvent for several substrates while DME was better for indole. The yields tended to improve with smaller amounts of catalyst.

Beller et al. studied the selective borylation of arene C–H vs. benzylic C–H bonds in *o*-xylene.[54] Using [Ir(COD)Cl]$_2$ with 8 equiv of bpy, they observed exclusive aromatic C–H borylation on the 4-position. In contrast, use of [Rh(COD)(acac)] (**1.28**) or [Rh(COD)Cl]$_2$ (**1.29**) with bpy resulted in selective benzylic borylation. Simple heteroaromatic substrates were also borylated on positions adjacent to the heteroatom.

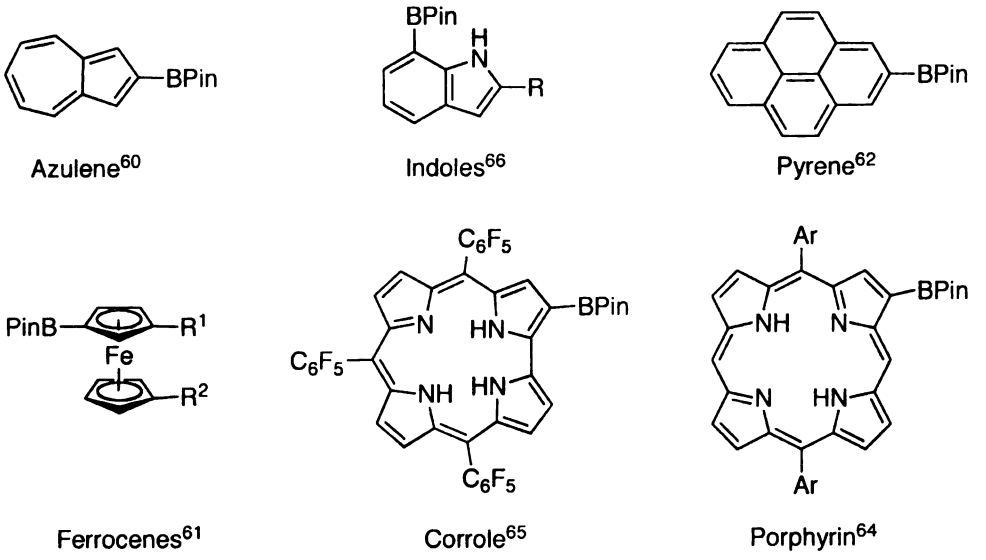
Murata has shown that hydrotris(pyrazolyl)borate complexes of rhodium and iridium can catalyze aromatic borylation around 100-120 °C.[55] The presence of heteroatom functional groups did not interfere with the outcome of iridium catalyzed reaction, however the rhodium system lacked this wide applicability.

Herrmann et al. have reported that bis-(*N*-heterocyclic)-carbene complexes of iridium (I) show significant catalytic performance in the direct borylation of arenes.[56] Halogenated benzenes including iodobenzene were found to be borylated at 40 °C in 9-12 h with 89-100% GC yields.

Yinghuai et al. have reported iridium (I) salicylaldiminato-cyclooctadiene complexes as reusable catalysts for C–H bond borylation of arenes with B_2Pin_2.[57] Among the several ligands tested, *tetra*-2-pyridinylpyrazine (TPy) was found to be the best ligand for this system. Catalytic performance was enhanced when a solvent mixture of dichloromethane and the ionic liquid, tributyltetradecylphosphonium dodecylbenzenesulfonate (TBPD) was used. In borylation of monosubstituted arenes, the ratios of *meta*- to *para*-isomers in the products ranged from 1.5:1 for toluene to 1.1:1 for anisole. The preference for *para*-substitution could further be enhanced by the use of ionic liquid as solvent. The yields were better for electron deficient arenes than those for electron rich arenes.

Mkhalid et al. have shown that the ligand dtbpy (**1.23**) used in aromatic borylation can itself be borylated when used in excess.[58] Although cycloalkene ligands are present in commonly used iridium borylation precatalysts, Olsson and Szabo have reported that catalytic borylation of unactivated cycloalkenes took place under the typical aromatic borylation conditions.[59]

The substrate scope of iridium catalyzed aromatic borylation has been extended to other aromatic systems (Figure 1.22). Kurotobi et al. have shown that iridium-catalyzed borylation introduces the boryl substituent at the 2-position of azulene, a position difficult to functionalize by other means.[60] Plenio et al. utilized iridium catalyzed borylation for the synthesis of borylated ferrocenes and half sandwich compounds.[61] Coventry et al. have reported the selective borylation in polycyclic aromatics such as naphthalene, pyrene, and perylene.[62] Complex systems such as meso-arylporphyrins,[63] functionalized porphyrins,[64] and corrole[65] have also been borylated. More recently, Smith et al. have described the regioselective borylation of 2-substituted indoles on the 7-position.[66] Lo et al. also observed identical reactivity/selectivity for 2-substituted indoles.[67]



Azulene[60] Indoles[66] Pyrene[62]

Ferrocenes[61] Corrole[65] Porphyrin[64]

Figure 1.22. Regioselective borylation in some complex aromatic systems.

The intermediate boronate ester can further be utilized without isolation. For example, Holmes et al. reported a one-pot protocol for borylation/Suzuki coupling of 1,3-di-substituted arenes.[68] Maleczka and co-workers showed that intermediate boronic ester can be oxidized without isolation to synthesize previously unknown/difficult to synthesize phenols.[69] Shi et al. have used the intermediate boronate esters to synthesize deuterium labeled aromatics.[70] Hartwig has reported that the intermediate boronic ester can be converted to aryl trifluoroborates/aryl boronic acids[71] and aryl halides.[72] The boronic ester can also sequentially be transformed to anilines/aryl ethers after conversion to boronic acids,[73] The atom diversity introduced via boronate esters is shown in Figure 1.23.

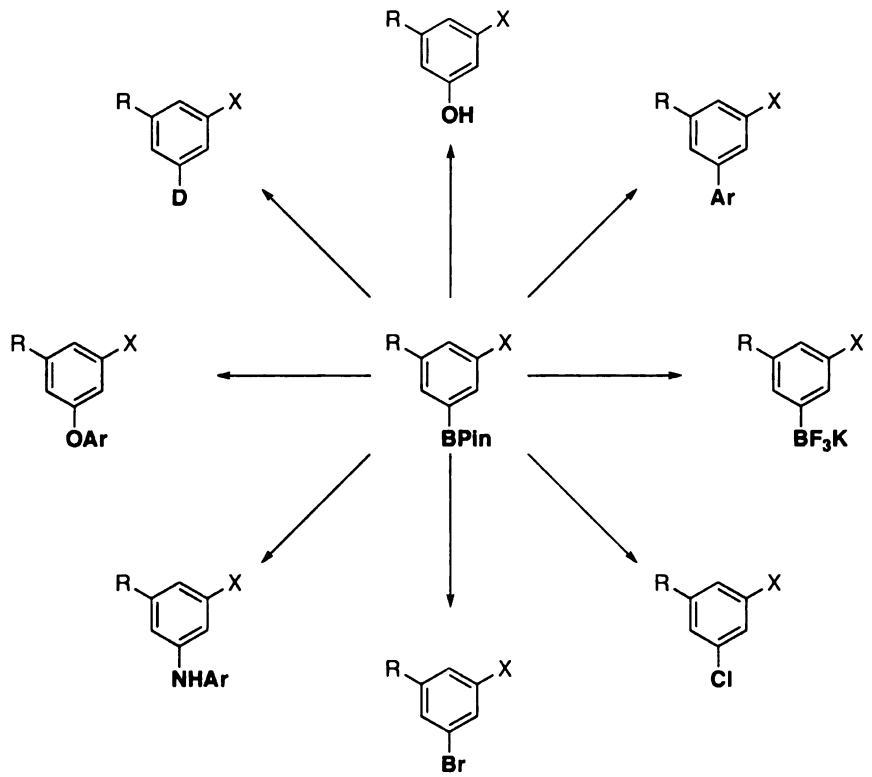


Figure 1.23. Diverse functional groups introduced via boronate ester.

Cross-Coupling Reactions

Transition metal catalyzed cross coupling reactions of organometals represent the most widely applicable organic skeleton construction method discovered and developed over the past several decades, allowing the synthetic chemists to synthesize practically almost all types of organic compounds.[74,75]

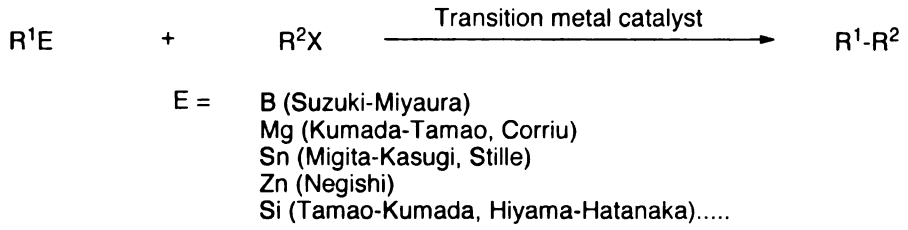


Figure 1.24. Metal catalyzed cross-coupling reactions.

Unlike Grignard reagents, organoboron compounds are air and water stable. The C–B bond in organoboranes is highly covalent, thus limiting the use of organoboranes reagents in ionic reactions. Low reactivity of organoboranes can be overcome by coordination of a negatively charged base to the boron atom to make it tetra-coordinate.

In 1979, Miyaura and Suzuki reported the first example of cross-coupling reaction involving organoboron compounds.[76] Several advantages including tolerance of a broad variety of functional groups, non toxic and mild reaction conditions, air and water stability of reagents, and easy separation of inorganic boron compounds, has made the Suzuki reaction as the reaction of choice for the construction of aryl-aryl bonds.

During the past decade, extensive research has been carried out by Buchwald & Hartwig groups to extend the cross-coupling chemistry to C–Heteroatom couplings such as C–N and C–O bond forming reactions.[77,78] Transition metal catalyzed arylations of amines and alcohols now have become the preferred method for the preparation of aryl amines and aryl ethers

The catalytic cycle for all these reactions typically consists of oxidative addition, transmetallation/insertion, and reductive elimination steps.

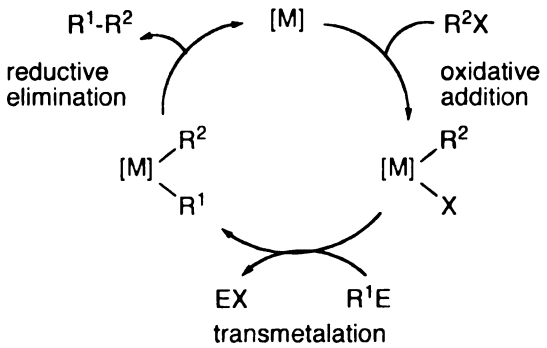


Figure 1.25. General catalytic cycle for cross-coupling reactions.

The reaction between aryl/alkenyl halides and alkynes to synthesize internal alkynes, firstly introduced by Sonogashira,[79] is another highly useful cross coupling reaction.

This thesis will describe our efforts to extend the scope and applications of iridium catalyzed aromatic borylations. Chapter 2 describes the regioselective borylation *ortho* to cyano groups in 4-substituted benzonitriles. Synthesis of a variety of substituted borylated thiophenes are discussed in Chapter 3. Efforts to improve regioselectivities in iridium catalyzed aromatic borylations by ligand modification are presented in Chapter 4.

Since aromatic C–Halogen bonds survive during iridium catalyzed aromatic borylation; we became interested if it is possible to carry out selective cross coupling on the C–Halogen bond, subsequent to borylation step, while keeping the BPin group intact. Our efforts in this regard to synthesize aromatic amino boronate esters, aromatic alkynyl boronate esters, and aromatic thioether boronate esters are presented in Chapter 5 and 6.

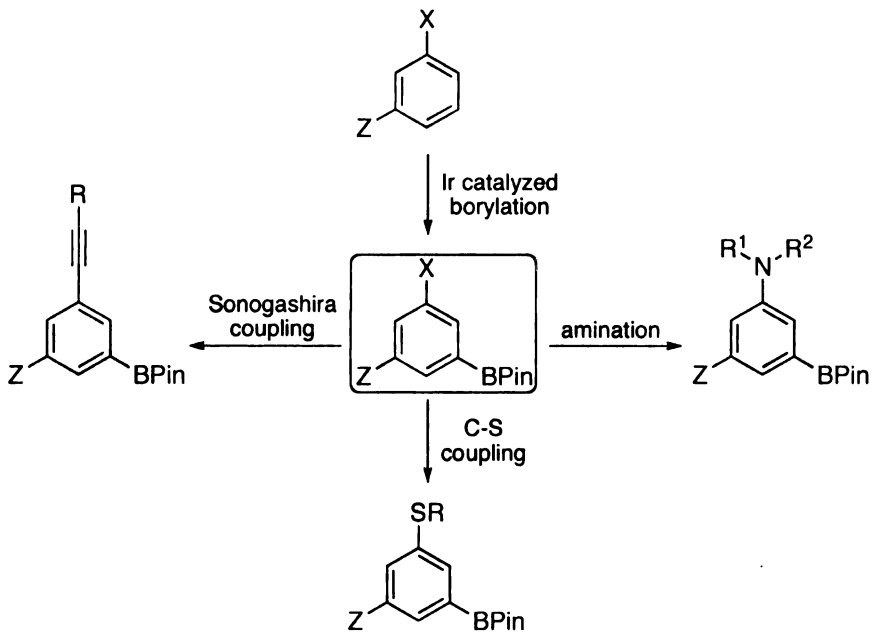


Figure 1.26. One-pot borylation/cross-coupling reactions.

5-Coordinate, 16-electron, bi-dentate ligated iridium tris-boryl complexes have been proposed to be the active catalysts in the iridium catalyzed aromatic borylation. From mechanistic studies, the support for these intermediates is strong, but 5-coordinate complexes have eluded isolation. Preparation and reactions of some 5-coordinate, iridium tris-boryl complexes are described in Chapter 7.

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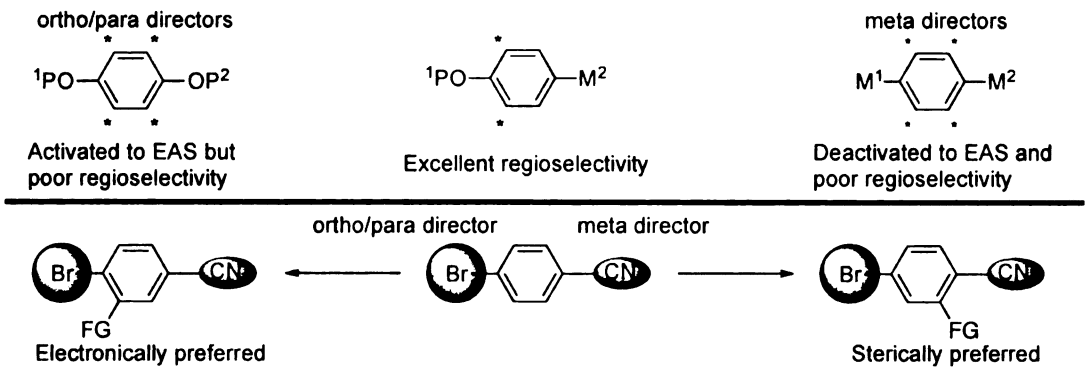
CHAPTER 2

Sterically Directed Functionalization of Aromatic C–H Bonds: Selective Borylation *ortho* to Cyano Groups in Arenes and Heterocycles

Introduction

Aromatic hydrocarbons are fundamental chemical building blocks, and their reactivity is a cornerstone of organic chemistry. Their utility derives largely from the regiochemical fidelity embodied in electrophilic aromatic substitutions.[1] While steric effects can influence electrophilic aromatic substitution, electronic effects typically dominate. For electrophilic aromatic substitution (EAS) reactions, substituents on aromatic rings fall into two classes: *ortho*, *para* directors and *meta* directors. When directing groups are positioned to work in concert, regioselectivity can be complete as in the classic example of nitration at the 3-postion of 4-bromobenzonitrile (Scheme 2.1, electronically preferred product, FG = NO_2).[2] For most di-substituted benzenes, EAS does not usually offer well-defined regiochemical outcomes. For example, two of the three possible arrangements of directing groups in 1,4-substituted benzenes give poor regioselectivity (Scheme 2.1).

Scheme 2.1. Regiochemical trends in electrophilic aromatic substitution for 1,4-substituted benzenes.



For the functionalization at positions *meta* to *ortho*, *para* directors and/or *ortho* to *meta* directors, alternate methods to electrophilic aromatic substitutions are required. In the case of certain *meta* directing substituents, directed *ortho* metalation (D*o*M) constitutes a powerful method for functionalization at the adjacent positions, provided that the substituent is a sufficiently strong directed metalation group (DMG).[3] For di-substituted benzenes, the regioselectivity of D*o*M depends on the positions of the substituents and their ranking in the DMG hierarchy. 1,3-Subsituted benzenes can often be derivatized selectively at the 2-position because DMG's can act in concert to direct metalation.

In contrast, DMG's can compete in 1,2- and 1,4-substituted benzenes. Therefore high regioselectivities are typically realized when there is a substantial difference in relative DMG powers. For example, while D*o*M protocols can be effective for functionalizing *ortho* to cyano groups in simple aromatic nitriles,[4,5] the presence of other groups can subvert the selectivity. Sometimes the regiochemical outcome is unexpected. For instance, competitive 2,5-dilithiation of 4-bromobenzonitrile occurs with LDA[6] and

deprotonation at the 3-position has been reported with the hindered phosphazene base, P_4-*t*-Bu,[7] even though the DMG ranking of CN is greater than Br. Prior to the publication of results described in this chapter, there were no documented transformations of 4-bromobenzonitrile that were selective for the 2-position[8,9] (See page 46 for work published afterwards). Moreover, examples of functionalization at the 2-position in other 4-substituted benzonitriles are limited, and there are no general approaches toward this end.[10-12] This is unfortunate because aryl nitriles have a rich chemistry, and are particularly useful entries into heterocyclic systems.[13,14]

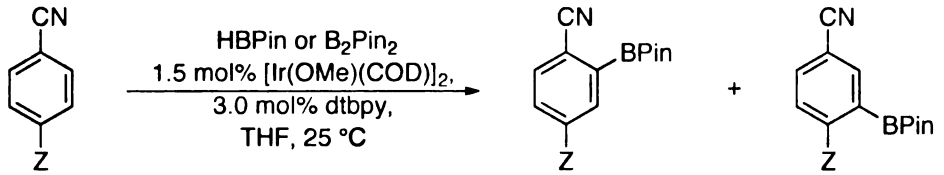
An alternate strategy for functionalizing benzonitriles that can potentially complement electrophilic aromatic substitutions and D*o*M's is to differentiate positions based on steric effects (Scheme 2.1). Since the first report by Ittel and co-workers in 1976,[15] there have been several reports of transition metal mediated C–H activations where steric, not electronic, effects are the overriding factors in regioselection. More recently, significant progress has been made in coupling C–H activation with subsequent transformations of the nascent M–C bond to design new catalytic processes.[16] Since 1999, we,[17-20] and others,[21-26] have been particularly interested in utilizing Ir–catalyzed borylations of arenes to tap the unique regioselectivities available to sterically directed C–H activations. We reasoned that borylation *ortho* to nitrile groups should be possible for appropriate substrates since the cyano group is only slightly larger than fluoride (vide infra). Our initial attempts to borylate benzonitriles with pinacolborane (HBPin) using Ir phosphine systems at elevated temperatures gave complex mixtures due to competitive reduction of the nitrile. More active Ir catalysts developed by Hartwig, Ishiyama, and Miyaura overcome this problem. These Ir dipyridyl catalysts operate at room

temperature, and examples have been reported showing that the nitrile group is compatible with the borylation conditions.[24,25] However, data is available for only three substrates, none of which addressed our regiochemical hypothesis. Herein, we describe results for the borylations *ortho* to cyano groups of benzonitriles.

Results

We first examined borylations of 4-substituted benzonitriles. As most substrates were poorly soluble in saturated hydrocarbons, borylations were typically carried out in THF solvent using the catalyst constituted from a 1:2 ratio of $[Ir(OMe)(COD)]_2$ (**1.24**) and dtbpy (**1.23**) as indicated in Scheme 2.2. The results for monoborylation reactions are given in Table 2.1. The reaction times roughly correspond to relative reactivities and yields are for isolated products with respect to the limiting reagent. Either HBPin (**1.4**) or B_2Pin_2 (**1.3**) can be used with shorter reaction times required for the latter reagent. For entries 1-3, 5-7, and 11, diborylation can be significant when the benzonitrile is the limiting reagent. For these substrates, a benzonitrile:borane reagent ratio of 4:1 was used to minimize diborylation.

Scheme 2.2. Catalytic borylation of 4-substituted benzonitriles.



2.x **2.xa** **2.xb**

Table 2.1. Regioselectivities for borylation of 4-substituted benzonitriles according to Scheme 2.2.

Entry	Z	Borane (equiv)	Time (h)	% yield	**%2.xa:%2.xb**
1	F	HBPin (0.25)	8	71	11:89 (8:92) **(2.1a:2.1b)**
2	Cl	HBPin (0.25)	36	76	80:20 (81:19) **(2.2a:2.2b)**
3	Br	HBPin (0.25)	48	73	95:5 (97:3) **(2.3a:2.3b)**
4	I	B_2Pin_2 (1.0)	40	70	>99:1 (>99:1) **(2.4a:2.4b)**
5	Me	HBPin (0.25)	72	64	94:6 (92:8) **(2.5a:2.5b)**
6	OMe	HBPin (0.25)	24	65	67:33 (67:33) **(2.6a:2.6b)**
7	SMe	B_2Pin_2 (0.25)	18	55	90:10 (87:13) **(2.7a:2.7b)**
8	NMe_2	B_2Pin_2 (1.0)	72	58	>99:1 (>99:1) **(2.8a:2.8b)**
9	CO_2Me	B_2Pin_2 (0.8)	48	65	>99:1 (>99:1) **(2.9a:2.9b)**
10	NHAc	B_2Pin_2 (1.6)	18	62	>99:1 (>99:1) **(2.10a:2.10b)**
11	CF_3	HBPin (0.25)	24	68	>99:1 (>99:1) **(2.11a:2.11b)**

Isomer ratios for isolated products are in parentheses.

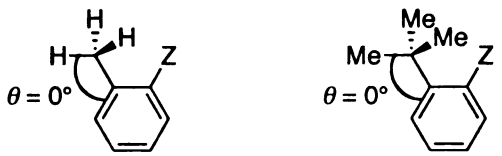
For 4-halobenzonitriles, the extent of borylation at the 3-position (isomer **b**) diminishes in the order F > Cl > Br > I. This trend is consistent with the ordering of steric

energies for substituents on a benzene ring F < CN < Cl < Br < I (vide infra). However, the regioselectivities are also consistent with the thermodynamic ordering of *ortho*-C–H acidities is F > CN > Cl from the literature.[27,28] Thus, rationalization of the regiochemical outcome is shackled with the age-old dilemma of definitively separating steric and electronic effects. Nevertheless, a compelling case can be made for steric directing effects as outlined below.

There are several approaches for evaluating steric effects.[29] Following a course recommended by Ingold,[30] Taft developed a parameter, *Es*, to account for steric effects on hydrolysis and esterification rates of *o*-benzoate esters.[31] It was later shown that *Es* values could be quantitatively related to van der Waals radii,[32] and values have been calculated for substituents absent in Taft's original work.[33] Dubois later revised Taft's definition, introducing the Taft-Dubois steric paramater, *E′s*.[34] Despite their demonstrated utility, *Es* and *E′s* values are nonetheless empirical and the database of values is still limited. Alternatively, the energy difference between equatorial and axial conformers of monosubstituted cyclohexanes (the *A* value) has been invoked as a measure of steric effects.[35] Although the equatorial site is indeed favored from a steric standpoint, cyclohexane conformational energies are not immune to electronic effects. Hence, *A* values are poor predictors of steric differences for electronically disparate substituents. For our purposes, although there is no *E′s* value in the literature for CN, the *Es* value that is typically quoted places CN between F and Cl, which seems reasonable.[36] Unfortunately, the value does not appear in the primary literature that is cited.[33] *A* values are of little help as the value for CN is lower than that of F,[37] and general agreement between *A* and *Es* values is poor.

Calculations of steric energies have been addressed using modern computational methods. We felt that a good, albeit crude, model for our purposes was that employed by Fujita and co-workers for evaluating the steric effects in the acid-catalyzed hydrolysis of *o*-benzamides.[38,39] In essence, their approach involves calculating the difference in enthalpies for 2-substituted toluenes and *tert*-butylbenzenes relative to toluene and *tert*-butylbenzene to extract steric enthalpies, denoted as $\Delta\Delta Hs(Z)$, for substituents Z, relative to hydrogen. For consistency, the dihedral angles for the methyl and *tert*-butyl groups were constrained as shown in Chart 2.1.[38] Since CN and other substituents in Table 2.1 were not included in the previous report, we recalculated the series.[40] Table 2.2 lists these $\Delta\Delta Hs(Z)$ values along with calculated and experimental ratios of 2- and 3-borylated benzonitriles.[41]

Chart 2.1



Z-Me

Z-*t*-Bu

$$\Delta\Delta H_s(Z) = [\Delta H_f°(Z\text{-}t\text{-}Bu) - \Delta H_f°(H\text{-}t\text{-}Bu)] - [\Delta H_f°(Z\text{-}Me) - \Delta H_f°(H\text{-}Me)]$$

Table 2.2. Calculated steric enthalpies ($\Delta\Delta H_s$) for *o*-benzene substituents Z and isomer ratios for borylation.[a]

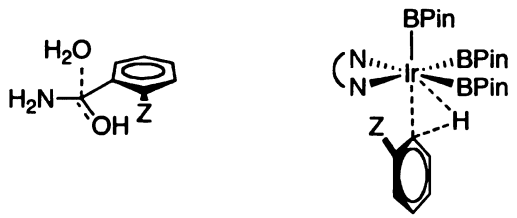
Z	$\Delta\Delta H_s(Z)$ Kcal/mol^{-1}	%**a**:%**b** calc[b]	%**a**:%**b** observed[c]
H	0	–	–
CN	3.211	–	–
F	1.535	6:94	8:92
Cl	4.133	83:17	81:19
Br	5.405	98:2	97:3
I	7.759	>99:1	>99:1
CH_3	5.532	98:2	92:8
OMe	2.013	31:69	67:33[d]
SMe	3.682	66:34	87:13[d]
NMe_2	5.039	96:4	>99:1
CO_2Me	4.856	94:6	>99:1
NHAc	5.166	96:4	>99:1
CF_3	8.845	>99:1	>99:1

[a]$\Delta\Delta H_s(Z)$ values computed according to the method in ref. 38. [b]Ref. 40. [c]GC-FID ratios from Table 2.1. [d]Isomer ratio was determind by NMR integration.

Agreement between the calculated and experimental isomer ratios is surprisingly good. The halide data correlates best, while selectivities for CO_2Me, NMe_2, and NHAc substituents are better than the calculated values. To gauge whether aromatic borylation is likely to be more sensitive to steric effects, it is instructive to consider putative

transition states for acid-catalyzed hydrolysis of an *o*-benzamide (**X**) and Ir-catalyzed C–H activation (**Y**) in Chart 2.2.

Chart 2.2



X **Y**

First, transition state **X** more closely resembles the steric model in Chart 2.1 from which $\Delta\Delta Hs(Z)$ values are calculated. Moreover, transition state **Y** should be more sensitive to the sterics of Z because an Ir–C bond ultimately forms *ortho* to Z, whereas attack by the less hindered water molecule is one carbon removed in transition state **X**.

The poorest agreement between calculated and observed isomer ratios in Table 2.2 is for Z = OMe, where the borylation is favored at the more hindered position. Although this could simply result from inherent deficiencies in the model, there is reason to believe electronic effects contribute to the regioselectivity. Specifically, while borylation of benzonitrile (**2.12**) gives a nearly statistical 2.15:1 ratio of *meta* to *para* isomers (Figure 2.1), anisole (**2.13**) borylation favors the *meta* isomer 4:1 (Figure 2.2). After taking statistics into account, this corresponds to a 2:1 preference for *meta* vs. *para* borylation.[18] Given that CN and OMe groups are nearly isosteric, the identical 2:1 preference for borylation *meta* to OMe may have electronic origins.

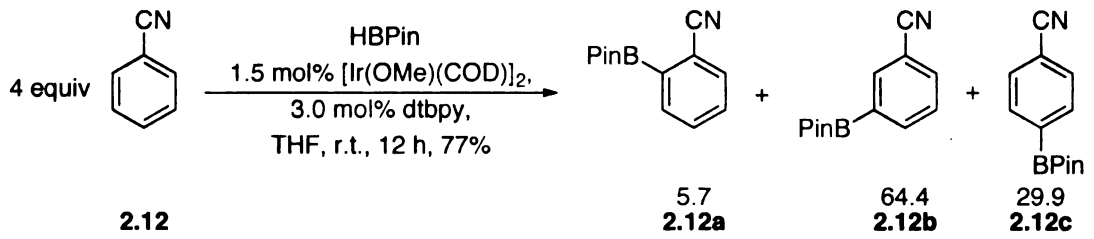


Figure 2.1. Product distribution in catalytic borylation of benzonitrile.

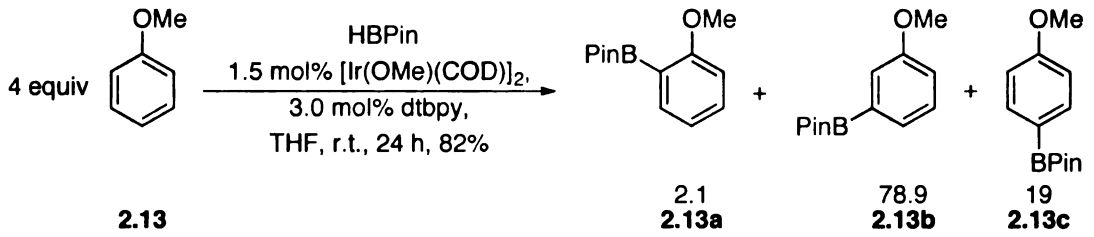
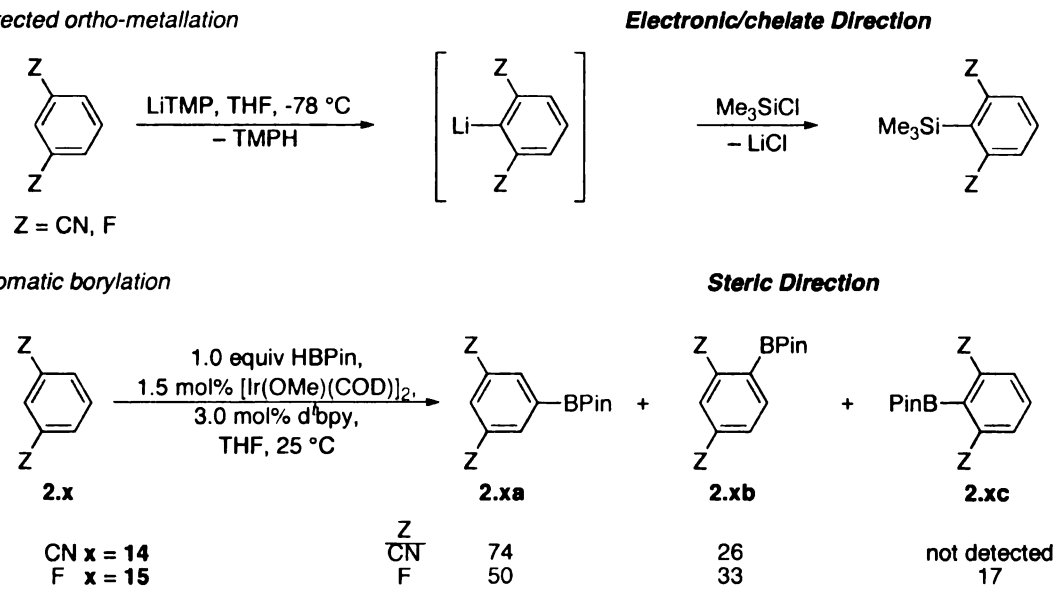


Figure 2.2. Product distribution in catalytic borylation of anisole.

To strengthen what is a circumstantial case for sterics overriding electronics in borylations of 4-benzonitriles, we turned to 1,3-di-subsituted CN and F benzenes, where C–H bonds flanked by 0-2 *ortho* hydrogens are present. Under D*o*M conditions, 1,3-dicyano and 1,3-difluorbenzene are known to react selectively at the 2-position as shown in Scheme 2.3.[42,43] If selectivities of Ir catalyzed borylations of CN and F substituted arenes are sterically directed, the propensity for borylation in the 1,3-disubstituted benzenes should follow the order 5- > 4- > 2-. As indicated in Scheme 2.3, this is indeed the case. Furthermore, only 1,3-difluorobenzene exhibits significant borylation at the 2-position (**2.15c**), consistent with the lower steric requirement for F relative to CN. Murai has invoked CN to Ru p-bonding to account for selective C–H activation *ortho* to CN.[44] However, from the data in Scheme 2.3, the borylation *ortho* to H vs. CN is favored by a factor of 5.7 in the present system. Thus, sterically directed regioselectivity is the only satisfactory explanation for the regiochemistry in these

borylations. Based on these results and the data in Table 2.2, we favor steric directing effects to account for the selectivities in Table 2.1.

Scheme 2.3.



Additional features of the reactions in Table 2.1 merit comment. First, the 2-borylated products for entries 2-5 and 6-11 are new compounds. In fact, 4-F-2-BPinC_6H_3CN (**2.1a**),[45] 4-MeO-2-BPinC_6H_3CN (**2.6a**),[46] and 4-MeO-3-BPinC_6H_3CN (**2.6b**)[47] are the only reported 2,4-benzonitriles with BPin group at the 2-position. Moreover, introduction of the BPin group using other methods, such as Miyaura's cross-coupling reactions of alkoxydiboron reagents and aryl halides, are inconvenient because access to the 2-halogenated compounds is extremely limited.[48] Entries 8-10 highlight the complementary nature of sterically directed borylations to DoM protocols, where hydrogens *ortho* to amine, ester, and amide groups react preferentially.[49,50] Thus, aromatic borylation provides the most general approach to elaborating the 2 positions of 4-substituted benzonitriles. Lastly, it should be noted that

entries 7 and 10 are the first examples of functional group tolerance for SMe and NHAc substituents, respectively, in Ir-catalyzed C–H borylations.

After the publication of results described in this chapter, Kristensen et al. and co-workers reported a directed *ortho* metalation route for the introduction of boronic ester group on the 2-position in 4-substituted benzonitriles when the 4-substituent is OMe, CF_3, F, Cl, and Br (Figure 2.3).[51] Regioselectivities similar to described in this chapter were observed (however they did not examine the regioselectivity for 4-ester substituted benzonitrile, for which our system is highly selective for functionalization ortho to the cyano group).

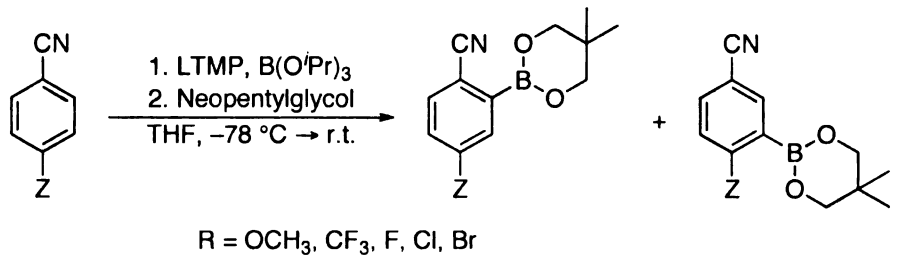
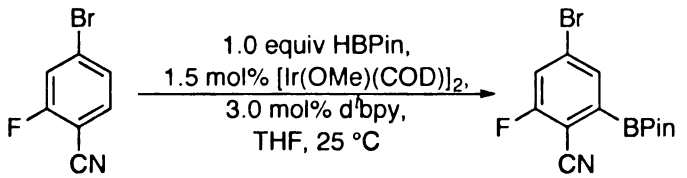


Figure 2.3. Directed *ortho* metalation for the preparation of 2-borylated benzonitriles.

Zhu et al. have used the borylation procedure described in this chapter to synthesize 4-NMe_2-2-$BPinC_6H_3CN$ (**2.8a**) and its corresponding boronic acid.[52] They found these compounds to be selective fluorescent sensors for saccharides and fluoride ion.

The regioselectivities in Table 2.2 are not necessarily limited to di-substituted benzenes. In addition to diborylation of 4-benzonitriles (vide infra), we also note that 4-bromo-2-fluorobenzonitrile is borylated according to Eq 2.1, affording a 5:95 ratio of 5- and 6-borylated products (**2.16b** and **2.16a** respectively). This is a particularly attractive reaction because 1,2-benzisoxazoles and other heterocycles can be obtained by

substitution of fluoride followed by ring-forming condensation with the cyano group.[53] Similarly, borylation of 3,4-dichlorobenzonitrile yields the 5- and 6-borylated isomers in a 20:80 ratio (**2.17b** and **2.17a** respectively). For both substrates, the selectivity for borylation ortho to CN vs. halide is virtually identical to that for the corresponding 4-halobenzonitriles in Table 2.1.

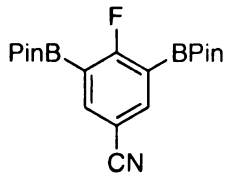
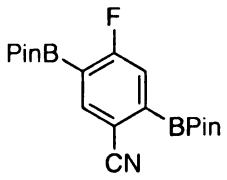
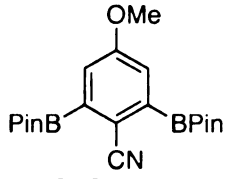
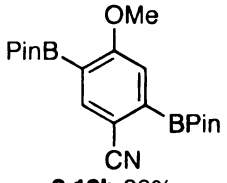
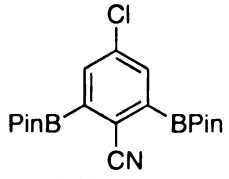
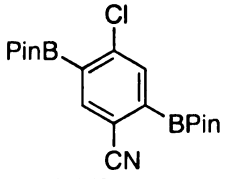
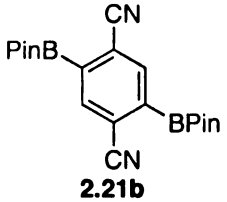
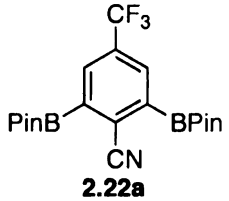


(**2.16a**) 85% yield,
95% isomeric purity

(2.1)

In order to avoid diborylation, excess arene was used for several entries in Table 2.1. We were curious as to how efficiently the diborylated products could be formed and whether compounds with isomeric purities sufficiently high as to be synthetically useful could be obtained. The reactions were typically run in THF with a 4:1 ratio of HBPin to arene at twice the catalyst loading for monoborylation. The results are given in Table 2.3.

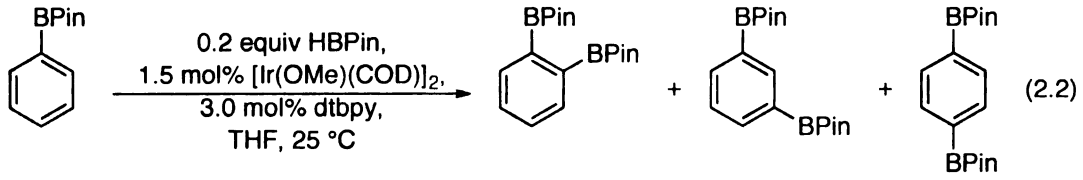
Table 2.3. Diborylation of 4-substituted benzonitriles.

Z[a]	%yield	Time (h)	Products[b]		
F	92	24	 **2.18a** 54% (86%)	+	 **2.18b** 46% (14%)
OMe[c]	81	48	 **2.19a** 20% (33%)	+	 **2.19b** 80% (60%)
Cl	82	48	 **2.20a** 20% (56%)	+	 **2.20b** 80% (44%)
CN	71[d]	20	–		 **2.21b**
CF_3	83	36	 **2.22a**		–

[a]Unless otherwise noted, all reactions were run in THF solution at 25 °C with 4.0 equiv HBPin and 6 mol% [Ir]. [b]Isomer distribution determind by GC-FID. Calculated values using the selectivities in Table 2.1 (ref 54) are shown in parantheses. [c]Reaction run at 60 °C. [d]Isolated as a single isomer after recrystallization from 93:7 mixture of 2,5- and 2,6-borylated isomers.

Unlike the situation for 4-bromo-2-fluorobenzonitrile and 3,4-di-chlorobenzonitrile, the observed distribution of isomers is much different than a

simple extrapolation of selectivities from Table 2.1 predicts.[54] In all cases the extent of 2,5-diborylation (isomer **b**) is significantly higher than expected, except for Z = CF_3 where borylation ortho to CF_3 is likely prohibitive. The data suggest that the BPin group has a directing role. To answer this question, we examined the regioselectivity for PhBPin borylation in THF under similar reaction conditions (Eq 2.2). The reaction was examined at low conversion to avoid skewing the data by borylation of *m*-$C_6H_4(BPin)_2$.[55] The *para* to *meta* ratio is 1.8:1, significantly greater than the 1:2 statistical ratio. This translates to a 3.6:1 selectivity for *para* vs. *meta* borylation after statistical corrections. While we are reluctant to speculate on the origins of this selectivity, BPin clearly has a *para* directing effect that likely contributes to the regioselectivities in Table 2.3. Lastly, it should be noted that single isomers of diborylated products can readily be obtained for Z = CN, or CF_3.

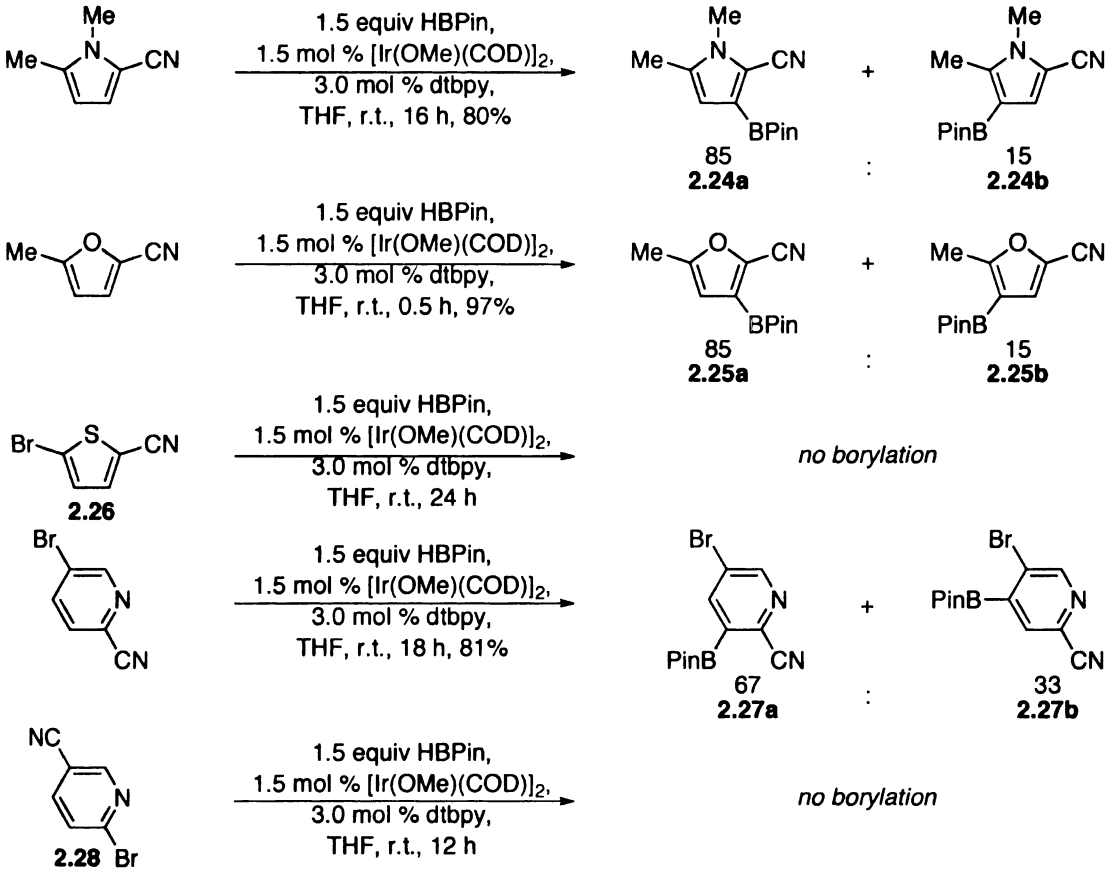


Undetected **2.23a** | 36 **2.23b** | 64 **2.23c**

We have also examined a limited number of heteroaromatic compounds to assess whether the regioselectivities found for arenes will translate to other substrates (Scheme 2.4). Borylation of 1,5-dimethyl-2-pyrrolecarbonitrile gives an 85:15 ratio of two regioisomers with the major isomer arising from borylation adjacent to the cyano group. Similarly, 5-methyl-2-furonitrile also borylates predominantly adjacent to the cyano group to give an 85:15 ratio of two borylated isomers. Borylation of 2-bromo-5-cyanothiophene was unsuccessful. Since the steric interactions between

adjacent positions diminish as aromatic rings contract, the decline in selectivity for the 5-membered heterocycles is not surprising. Two isomeric cyanopyridines were also examined. 5-bromo-2-cyanopyridine undergoes borylation to afford an isomer mixture. While borylation *ortho* to CN accounts for the major product, the degree of borylation *ortho* to Br is substantially higher than that found for 4-bromobenzonitrile. Somewhat surprisingly, 2-bromo-5-cyanopyridine gave no borylation products. Since halogen substituted aromatic heterocycles tend to be more reactive than their carbocyclic counterparts, side reactions that deactivate catalytically active species may be occuring.

Scheme 2.4.



Conclusions

In summary, the steric directing effects that govern the regioselectivities in Ir catalyzed borylations of aromatic and heteroaromatic compounds enable functionalization of C–H bonds adjacent to cyano groups, when these positions are the least hindered sites in the substrate. The regioselectivities for borylations complement those found in electrophilic aromatic substitutions and certain D*o*M's, and several relatively simple borylated products have been prepared for the first time. Diborylations of 4-benzonitriles favor *para*-disposed BPin groups when borylation at the 5-position is possible. While it appears that similar trends in regioselectivities can be extended to borylations of heteroaromatic nitriles, the substrate scope is narrower and the regioselectivity is poorer than for carbocyclic aromatic substrates. We are currently focusing on improving regioselectivities by modifying the Ir ligands, as well as sterically differentiating other aromatic substituents.

Experimental Details and Spectroscopic Data

Materials

Pinacolborane (HBPin) and bis(η^4-1,5-cyclooctadiene)-di-μ-methoxy-diiridium(I) $[Ir(OMe)(COD)]_2$ were prepared per literature procedures.[56,57] Bis(pinacolato)diboron (B_2Pin_2) was purchased from Callery Chemical Company and was used without purification. Tris(dibenzylidineacetone)dipalladium(0) (Pd_2dba_3) was purchased from Strem. 4,4′-Di-*t*-butyl-2,2′-bipyridine (dtbpy), tricyclohexylphosphine, and potassium acetate were purchased from Aldrich. 1-Bromo-3,5-difluorobenzene, 2-bromo-1,3-difluorobenzene, 1-bromo-2,4-difluorobenzene, and 4-iodobenzonitrile were purchased from Alfa Aesar. 4-Bromobenzonitrile and 4-methoxybenzonitrile were purchased from Lancaster Synthesis. 2-Bromo-4-methylbenzonitrile was purchased from Trans World Chemicals. 5-Bromo-2-cyanopyridine and 2-bromo-5-cyanopyridine were purchased from Matrix Scientific. All other benzonitriles were purchased from Aldrich. All substrates were purified before use. Solid substrates were sublimed under vacuum. 5-Methyl-2-furonitrile and 5-bromothiophene-2-carbonitrile were passed through activated alumina. 1,4-Dioxane and *n*-hexane were refluxed over sodium, distilled, and degassed. Tetrahydrofuran was used from a dry still packed with activated alumina. Silica gel (230-400 Mesh) was purchased from EM Science™.

General Methods

All reactions were monitored by a Varian CP-3800 GC-FID (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, 20 min.; 1.8 mL/min flow rate. 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. ^{11}B spectra were recorded on a Varian VXR-300 operating at 96.29 MHz and were referenced to neat $BF_3 \cdot Et_2O$ as the external standard. ^{19}F spectra were recorded on a Varian Inova-300 operating at 282.36 MHz and were referenced to neat $CFCl_3$ as the external standard. All coupling constants are apparent *J* values measured at the indicated field strengths. All 1-dimensional NOE experiments were obtained using the Varian implementation of the DPFGSE-NOE experiment[58] (hereafter termed NOESY1D). 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). High-resolution mass spectra were obtained at the Michigan State University Mass Spectrometry Service Center with a JOEL-AX505 mass spectrometer (resolution 7000). Melting points were measured on a MEL-TEMP® capillary melting apparatus and are uncorrected.

Note: The general methods describes here also corresponds to Chapters 3-7.

General Procedure

Unless otherwise specified, all reactions were carried out in THF solutions with 3 mol % [Ir] at 25 °C in 20 mL vials in a glove box under a nitrogen atmosphere. Substrates which gave a significant amount of both isomers were borylated employing an excess of benzonitrile to minimize diborylation (General procedure A), otherwise, excess borane was employed (General procedure B). The major isomer for the borylation of 4-methylbenzonitrile was identified by preparing an authentic sample using a slightly modified literature procedure.[59] The regioisomers in all other cases were assigned by NMR spectroscopy (^{13}C for substrates which have fluorine, while gHMBC and NOESY1D were used for substrates without fluorine). Ratios of the major versus minor isomer were determined in the crude reaction mixtures. Yields are based on the limiting reagent.

General Procedure A (Borane as limiting reactant)

In a glove box, a 20 mL vial, equipped with a magnetic stirring bar, was charged with $[Ir(OMe)(COD)]_2$ (5 mg, 7.5 10^{-3} mmol, 3 mol % Ir), 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) (4 mg, 1.5 10^{-2} mmol, 3 mol %), and pinacolborane (HBPin) (73 μL, 64 mg, 0.5 mmol, 1 equiv). These reagents were dissolved in 2 mL of THF, the corresponding benzonitrile (2.00 mmol, 4.00 equiv) was added, and the mixture was stirred at room temperature until the reaction was judged complete by GC-FID. Solvent was removed under reduced pressure. The crude material was dissolved in CH_2Cl_2 and passed through a plug of silica gel to remove metal byproducts. Kugelrohr distillation gave analytically pure samples.

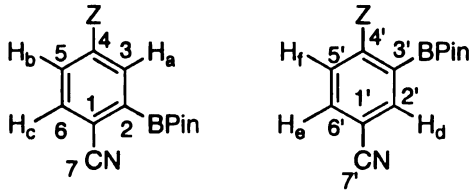
General Procedure B (Benzonitrile as limiting reactant)

In a glove box, a 20 mL vial, equipped with a magnetic stirring bar, was charged with $[Ir(OMe)(COD)]_2$ (10 mg, 1.5 10^{-2} mmol, 3 mol % Ir), dtbpy (8 mg, 3.0 10^{-2} mmol, 3 mol %), and excess HBPin or B_2Pin_2 (1.1 to 3.2 equiv of boron). These reagents were dissolved in 3 mL of THF, the corresponding benzonitrile (1 mmol, 1 equiv) was added, and the mixture was stirred at room temperature until the reaction was judged complete by GC-FID. Solvent was removed under reduced pressure. The crude material was dissolved in CH_2Cl_2 and passed through a plug of silica gel to furnish the desired borylated product.

General Procedure C (Diborylation)

In a glove box, a 20 mL vial, equipped with a magnetic stirring bar, was charged with $[Ir(OMe)(COD)]_2$ (20 mg, 0.03 mmol, 6 mol % Ir), dtbpy (16 mg, 0.06 mmol, 6 mol %), and excess HBPin (4.00 equivalent of boron). These reagents were dissolved in 3 mL of THF, the corresponding benzonitrile (1 mmol, 1 equiv) was added, and the mixture was stirred at room temperature until the reaction was judged complete by GC-FID. Solvent was removed under reduced pressure. The crude material was dissolved in CH_2Cl_2 and passed through a plug of silica gel to furnish the desired borylated product.

Regioisomer assignment by NMR spectroscopy



Isomer **a** Isomer **b**

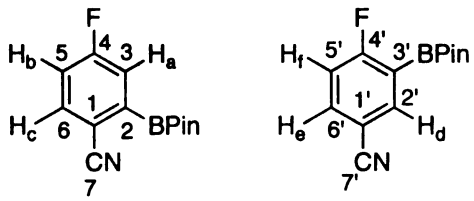
From gHMBC NMR experiments, the two regioisomers for the borylation of 4-substituted benzonitriles can be distinguished unambiguously. In Isomer **a**, carbon atoms represented as C1 and C4 on the benzene ring, as well as C7 (nitrile carbon) are the three quaternary carbon atoms in the 100-170 ppm region (quaternary carbon C2 is typically not observed due to broadening from and coupling with boron). These three quaternary carbon atoms should show cross peaks due to long range H–C couplings ($^3J_{C\text{-}H}$), which can be observed using gHMBC spectroscopy. In the gHMBC spectrum, carbon atoms C4 and C7 should show one cross peak each to proton Hc, whereas carbon atom C1 should show two cross peaks to protons Ha and Hb. Therefore the resulting number of cross peaks for C1, C4, and C7 should be 2, 1, and 1, respectively.

In Isomer **b**, carbon atoms represented as C1′, C4′, on the benzene ring, as well as C7′ (nitrile carbon) are the three quaternary carbon atoms in the 100-170 ppm region (quaternary carbon C3′ is typically not observed due to broadening from and coupling with boron). These three quaternary carbon atoms should show cross peaks due to long range H-C couplings ($^3J_{C\text{-}H}$). In the gHMBC spectrum, carbon atoms C4′ and C7′ should show two cross peaks each, to protons Hd and He, whereas carbon atom C1′ should show only one cross peak to proton Hf. Therefore the resulting number of cross peaks for C1′, C4′, and C7′ should be 1, 2, and 2, respectively. Hence isomers **a** and **b** can be unambiguously assigned from gHMBC data.

For isomer **a**, with proton H_c unambiguously assigned by gHMBC, Ha and Hb can be assigned from their multiplicities. Proton Ha appears as a doublet, coupled to proton Hb with $J \approx 2$-3 Hz. Proton Hb appears as a doublet of doublets due to coupling to protons Ha and Hc. Carbon atoms C3, C5, and C6 were then assigned from the correlations in the gHMQC spectra. Carbon atom C7 (nitrile carbon) usually appears around δ 119. Depending on the substituent, carbon atom C4 was usually found shifted downfield around δ 130-170 (except in 4-iodobenzonitrile for which it appears around δ 100). Carbon atom C1 is shifted upfield, and was usually found around δ 100-115. Similarly, all the carbons of isomer **b** can be assigned.

In the five membered heterocycles, the $^4J_{H\text{-}H}$ coupling was used together with gHMBC and NOESY1D spectroscopy to identify the major isomer. Regioisomers in the fluorine containing benzonitriles were assigned by ^{13}C spectroscopy (with the help of the fact that the boron bearing carbon is not observed due to broadening from and coupling with boron). In case of monoborylation of 1,3-di-cyanobenzene, and diborylation of 4-substituted benzonitriles, ^1H NMR spectroscopy was employed to assign the major and minor isomers.

Table 2.1, Entry 1. Borylation of 4-fluorobenzonitrile (2.1a + 2.1b).

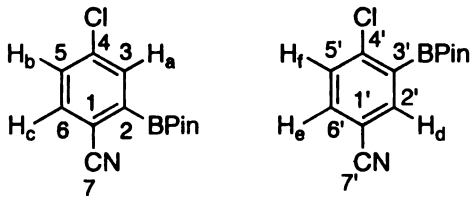


11 **2.1a** 89 **2.1b**

General procedure A was applied to 4-fluorobenzonitrile (242 mg, 2.00 mmol, 4.00 equiv) and HBPin (73 μL, 64 mg, 0.5 mmol, 1 equiv) with a reaction time of 8 h. The ratio of the two isomers in the crude reaction mixture by GC-FID was 11:89. Kugelrohr distillation furnished a mixture of the two isomeric borylated products (89 mg, 72% yield) as a white solid. The ratio of the two isomers in the isolated product by GC-FID was 8:92. ^{13}C NMR spectroscopy was used to assign the major isomer as 4-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzonitrile. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (**2.1a**) 7.67 (dd, J = 8.8 Hz, $^{4}J_{H\text{-}F}$ = 4.9 Hz, 1 H, Hc), 7.52 (dd, $^{3}J_{H\text{-}F}$ = 8.5 Hz, J = 2.9 Hz, 1 H, Ha), 7.17 (dt, J = 8.3, 2.9 Hz, 1 H, Hb) 1.34 (br s, 12 H, 4 CH_3 of BPin), (**2.1b**) 8.04 (dd, $^{4}J_{H\text{-}F}$ = 5.4 Hz, J = 2.2 Hz, 1 H, Hd), 7.7 (ddd, J = 8.5, 2.2 Hz, $^{4}J_{H\text{-}F}$ = 4.9 Hz, 1 H, He), 7.1 (t, J = 8.5 Hz, 1 H, Hf), 1.32 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**2.1a**) 164.2 (d, $^{1}J_{C\text{-}F}$ = 257.1 Hz, C4), 135.9 (d, $^{3}J_{C\text{-}F}$ = 8.8 Hz, C6), 122.8 (d, $^{2}J_{C\text{-}F}$ = 21.0 Hz, C3), 118.5 (d, $^{2}J_{C\text{-}F}$ = 22.2 Hz, C5), 118.1 (nitrile C7), 113.1 (C1), 85.1 (2 C), 24.7 (4 CH_3 of BPin), (**2.1b**) 169.0 (d, $^{1}J_{C\text{-}F}$ = 261.3 Hz, C4′), 141.6 (d, $^{3}J_{C\text{-}F}$ = 9.6 Hz, C2′), 137.0 (d, $^{3}J_{C\text{-}F}$ = 10.5 Hz, C6′), 117.9 (nitrile C7′), 116.7 (d, $^{2}J_{C\text{-}F}$ = 25.6 Hz, C5′), 108.2 (d, $^{4}J_{C\text{-}F}$ = 3.8 Hz, C1′), 84.5 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.92; ^{19}F NMR ($CDCl_3$, 282 MHz): δ (**2.1b**) – 92.62 (m), (**2.1a**) –104.84 (m); FT-IR (neat) $\tilde{\nu}$: 3076, 2982, 2934, 2231, 1608, 1487,

1429, 1412, 1373, 1350, 1236, 1143, 1070, 964, 852, 835, 571 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**2.1a**) M^+ 247 (29), 232 (97), 206 (100), 189 (74), 148 (97), 121 (25), (**2.1b**) M^+ 247 (26), 232 (100), 205 (12), 188 (20); Anal. Calcd for $C_{13}H_{15}BFNO_2$: C, 63.20; H, 6.12; N, 5.67. Found: C, 63.52; H, 6.20; N, 5.56; HRMS (EI): *m/z* 247.1171 [(M^+); $C_{13}H_{15}BFNO_2$: 247.1180].

Table 2.1, Entry 2. Borylation of 4-chlorobenzonitrile (2.2a + 2.2b).

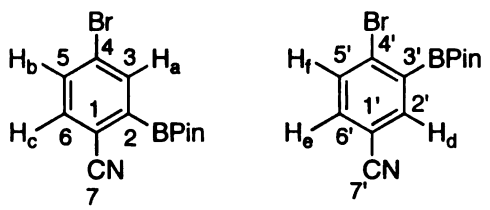


80 **2.2a** 20 **2.2b**

General procedure A was applied to 4-chlorobenzonitrile (550 mg, 4.00 mmol, 4.00 equiv) and HBPin (145 μL, 128 mg, 1 mmol) with a reaction time of 36 h. The ratio of the two isomers in the crude reaction mixture by GC-FID was 80:20. Kugelrohr distillation furnished a mixture of the two isomeric borylated products (200 mg, 76%, yield) as a white solid. The ratio of the two isomers in the isolated product by GC-FID was 81:19. gHMBC spectroscopy was used to assign the major isomer as 4-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzonitrile. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**2.2a**) 7.80 (d, J = 2.2 Hz, 1 H, Ha), 7.57 (d, J = 8.3 Hz, 1 H, Hc), 7.45 (dd, J = 8.3, 2.2 Hz, 1 H, Hb), 1.33 (br s, 12 H, 4 CH_3 of BPin), (**2.2b**) 7.94 (d, J = 2.2 Hz, 1 H, Hd), 7.56 (dd, J = 8.3, 2.2 Hz, 1 H, H_e), 7.41 (d, J = 8.3 Hz, 1 H, Hf), 1.32 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ (**2.2a**) 138.5 (C4), 135.8 (C3), 134.5 (C6), 131.2 (C5), 118.0 (nitrile C7), 115.3 (C1), 85.0 (2 C), 24.6 (4 CH_3 of BPin), (**2.2b**) 144.5 (C4′), 140.1 (C2′), 134.6 (C6′), 130.2 (C5′), 117.8 (nitrile C7′), 110.2 (C1′), 84.7 (2

C), 24.6 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.59; FT-IR (neat) $\tilde{\nu}$: 2982, 2228, 1587, 1554, 1479, 1402, 1373, 1333, 1271, 1215, 1169, 1144, 1103, 1065, 1042, 965, 870, 847, 831 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**2.2a**) M^+ 263 (24), 248 (65), 222 (100), 205 (31), 164(32), 137 (11), (**2.2b**) M^+ 263 (1), 248 (27), 228 (100), 186 (60), 164 (15), 142 (6); Anal. Calcd for $C_{13}H_{15}BClNO_2$: C, 59.25; H, 5.74; N, 5.32. Found: C, 58.90; H, 5.74; N, 5.10.

Table 2.1, Entry 3. Borylation of 4-bromobenzonitrile (2.3a + 2.3b).

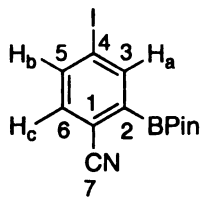


95 **2.3a** 5 **2.3b**

General procedure A was applied to 4-bromobenzonitrile (364 mg, 2.00 mmol, 4 equiv) and HBPin (73 μL, 64 mg, 0.5 mmol) with a reaction time of 48 h. The ratio of the two isomers in the crude reaction mixture by GC-FID was 95:5. Kugelrohr distillation furnished a mixture of the two isomeric borylated products (112 mg, 73% yield) as a white solid. The ratio of the two isomers in the isolated product by GC-FID was 97:3. gHMBC spectroscopy was used to assign the major isomer as 4-bromo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzonitrile. ^1H NMR ($CDCl_3$, 500 MHz): δ (**2.3a**) 7.97 (d, J = 2.0 Hz, 1 H, Ha), 7.62 (dd, J = 8.3, 2.0 Hz, 1 H, Hb), 7.50 (d, J = 8.3 Hz, 1 H, Hc), 1.33 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ (**2.3a**) 138.8 (C3), 134.5 (C6), 134.2 (C5), 127.1 (C4), 118.1 (nitrile C7), 115.8 (C1), 85.0 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.92; FT-IR (neat): $\tilde{\nu}$: 2980, 2228, 1582, 1551, 1480, 1416, 1399, 1373, 1335, 1271, 1144, 1084, 1069, 963, 862, 841, 763,

673 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 307 (16), 292 (51), 266 (100), 251 (45), 228 (17), 170 (15); Anal. Calcd for $C_{13}H_{15}BBrNO_2$: C, 50.70; H, 4.91; N, 4.55. Found: C, 50.29; H, 4.75; N, 4.57; HRMS (EI): *m/z* 307.0376 [(M^+); Calcd for $C_{13}H_{15}BBrNO_2$: 307.0379].

Table 2.1, Entry 4. 4-iodo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (2.4a).

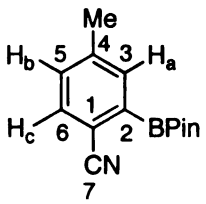


2.4a

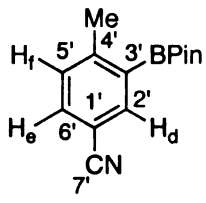
General procedure B was applied to 4-iodobenzonitrile (229 mg, 1 mmol, 1 equivalent) and B_2Pin_2 (254 mg, 1.00 mmol, 2.00 equivalents of boron) with a reaction time of 40 h. Only one isomer was observed in crude reaction mixture by GC-FID and by ^1H NMR spectroscopy. Solvent was removed under reduced pressure, and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford the single pure isomer (255 mg, 71% yield, mp 77-79 °C) as a white solid. gHMBC spectroscopy was used to assign the single isomer as 4-iodo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)benzonitrile. ^1H NMR ($CDCl_3$, 500 MHz): δ (**2.4a**) 8.19 (d, J = 2.0 Hz, 1 H, Ha), 7.85 (dd, J = 8.3, 2.0 Hz, 1 H, Hb), 7.36 (d, J = 8.3 Hz, 1 H, Hc), 1.34 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ (**2.4a**) 144.6 (C3), 140.1 (C5), 134.3 (C6), 118.3 (nitrile C7), 116.3 (C1), 99.8 (C4), 85.1 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.77; FT-IR (neat) $\tilde{\nu}$: 2980, 2228, 1576, 1545, 1480, 1414, 1395, 1374, 1335, 1271, 1140, 1071, 963, 859, 839, 826, 673 cm^{-1}; GC-MS (EI) *m/z* (% relative

intensity): M^+ 355 (42), 340 (75), 314 (100), 297 (72), 256 (77), 228 (11); Anal. Calcd for $C_{13}H_{15}BINO_2$: C, 43.99; H, 4.26; N, 3.95. Found: C, 44.17; H, 4.44; N, 3.88.

Table 2.1, Entry 5. Borylation of 4-methylbenzonitrile (2.5a + 2.5b).



94
2.5a



6
2.5b

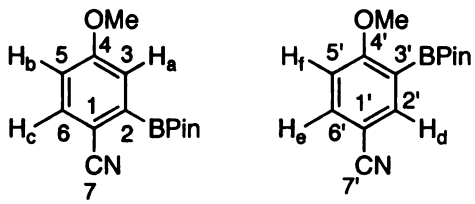
General procedure A was applied to 4-methylbenzonitrile (468 mg, 4.00 mmol) and HBPin (145 μL, 128 mg, 1 mmol) using 6 mol % [Ir] with a reaction time of 72 h. The ratio of the two isomers in the crude reaction mixture by GC-FID was 94:6. Kugelrohr distillation furnished a mixture of the two isomeric borylated products (156 mg, 64% yield) as colorless oil which solidified on standing. The ratio of the two isomers in the isolated product by GC-FID was 92:8. The major isomer was assigned as 4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzonitrile by the NOESY1D spectrum and by preparing an authentic sample using a slightly modified literature procedure.[59] ^{1}H NMR ($CDCl_3$, 500 MHz): δ (**2.5a**) 7.67 (br s, 1 H, Ha), 7.57 (d, J = 7.9 Hz, 1 H, Hb or Hc), 7.30 (d, J = 7.9 Hz, 1 H, Hb or Hc), 2.38(s, 3 H), 1.36 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**2.5a**) 142.2 (C4), 136.5, 133.4, 131.8 (C3, C5 and C6), 119.2 (nitrile C7), 114.2 (C1), 84.7 (2 C), 24.8 (4 CH_3 of BPin), 21.5 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.36; FT-IR (neat) $\tilde{\nu}$: 2980, 2932, 2226, 1603, 1491, 1447, 1408, 1391, 1381, 1373, 1346, 1265, 1213, 1140, 1069, 965, 853, 828, 675, 661 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 243 (46), 228 (70), 202 (100), 185 (52), 144 (92), 117 (25); Anal. Calcd for $C_{14}H_{18}BNO_2$: C, 69.17; H, 7.46; N, 5.76.

Found: C, 68.74; H, 7.64; N, 5.62; HRMS (EI): *m/z* 243.1425 [(M^+); Calcd for $C_{14}H_{18}BNO_2$: 243.1431].

Preparation of an authentic sample of 4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzonitrile (2.5a).

In a glove box, a 100 mL schlenk flask, equipped with a magnetic stirring bar, was charged with $Pd_2(dba)_3$ (14 mg, 0.015 mmol, 3 mol % Pd) and tricyclohexylphosphine (PCy_3, 20 mg, 0.072 mmol, 7.2 mol %). Dioxane (6 mL) was added and the resulting mixture was stirred for 30 minutes at room temperature. B_2Pin_2 (280 mg, 1.1 mmol), KOAc (147 mg, 1.5 mmol), and 2-bromo-4-methylbenzonitrile (196 mg, 1 mmol) were added successively. The schlenk flask was brought to a schlenk line. A condenser was attached, and the flask was flushed with nitrogen. The reaction mixture was stirred at 80 °C for 12 h. The mixture was treated with water (5 mL), and the product was extracted with ether, washed with brine, and dried over $MgSO_4$. Kugelrohr distillation furnished the desired product (151 mg, 62% yield) as a colorless oil. Its spectral data matched the major isomer (**2.5A**) obtained from the catalytic borylation of 4-methylbenzonitrile described earlier.

Table 2.1, Entry 6. Borylation of 4-methoxylbenzonitrile (2.6a + 2.6b).

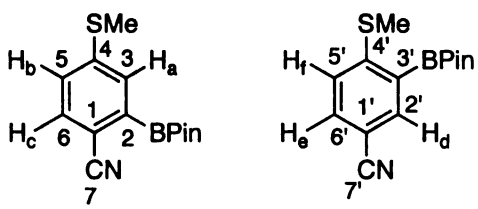


67 **2.6a** 33 **2.6b**

General procedure A was applied to 4-methoxybenzonitrile (266 mg, 2.00 mmol, 4.00 equiv) and HBPin (73 μL, 64 mg, 0.5 mmol) with a reaction time of 24 h. The ratio

of the two isomers in the crude reaction mixture by ^{1}H NMR spectroscopy was 67:33. Kugelrohr distillation furnished a mixture of the two isomeric borylated products (84 mg, 65% yield) as colorless oil. The ratio of the two isomers in the isolated product by ^{1}H NMR spectroscopy was 67:33. The NOESY1D and gHMBC spectra were used to assign the major isomer as 4-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzonitrile. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (**2.6a**) 7.59 (d, J = 8.5 Hz, 1 H, Hc), 7.31 (d, J = 2.9 Hz, 1 H, Ha), 6.97 (dd, J = 8.5, 2.9 Hz, 1 H, Hb), 3.84 (s, 3 H), 1.35 (br s, 12 H, 4 CH_3 of BPin), (**2.6b**) 7.93 (d, J = 2.4 Hz, 1 H, Hd), 7.65 (dd, J = 8.8, 2.4 Hz, 1 H, He), 6.87 (d, J = 8.8 Hz, 1 H, Hf), 3.85 (s, 3 H), 1.32 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**2.6a**) 161.7 (C4), 135.3 (C6), 120.6 (C3), 119.3 (nitrile C7), 117.0 (C5), 108.8 (C1), 84.8 (2 C), 55.5 (OCH_3), 24.73 (4 CH_3 of BPin), (**2.6b**) 166.9 (C4′), 140.9 (C2′), 136.6 (C6′), 119.2 (nitrile C7′), 110.7 (C5′), 103.6 (C1′), 84.1 (2 C), 55.5 (OCH_3), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.50; FT-IR (neat) $\tilde{\nu}$: 2980, 2942, 2842, 2224, 1601, 1493, 1466, 1449, 1424, 1412, 1373, 1345, 1271, 1238, 1144, 1060, 1030, 965, 853, 830 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 259 (100), 244 (61), 232 (9), 216 (73), 201 (65), 186 (25), 174 (20), 160 (79); HRMS (EI): *m/z* 259.1383 [(M^+); Calcd for $C_{14}H_{18}BNO_3$: 259.1380].

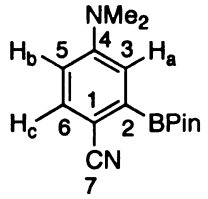
Table 2.1, Entry 7. Borylation of 4-thiometylbenzonitrile (2.7a + 2.7b).



90 **2.7a** 10 **2.7b**

General procedure A was applied to 4-thiomethylbenzonitrile (298 mg, 2.00 mmol, 2.00 equivalents) and B_2Pin_2 (127 mg, 0.5 mmol, 1 equivalent of boron) at 80 °C with a reaction time of 18 h. The ratio of the two isomers in the crude reaction mixture by ^1H NMR spectroscopy was 90:10. Kugelrohr distillation gave a fraction (155 mg) containing two isomers along with small amount of d^{t}bpy. Passing a CH_2Cl_2 solution of that fraction through a plug of silica furnished a mixture of two isomeric borylated products (150 mg, 55% yield) as a white solid. The ratio of the two isomers in the isolated product by ^1H NMR spectroscopy was 87:13. The NOESY1D and gHMBC spectra were used to assign the major isomer as 4-thiomethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzonitrile. ^1H NMR ($CDCl_3$, 500 MHz): δ (**2.7a**) 7.63 (d, J = 2.0 Hz, 1 H, Ha), 7.54 (d, J = 8.3 Hz, 1 H, Hc), 7.27 (dd, J = 8.3, 2.0 Hz, 1 H, Hb), 2.48 (s, 3 H), 1.35 (br s, 12 H, 4 CH_3 of BPin), (**2.7b**) 7.92 (d, J = 2.0 Hz, 1 H, Hd), 7.56 (dd, J = 8.3, 2.0 Hz, 1 H, He), 7.14 (d, J = 8.3 Hz, 1 H, Hf), 2.44 (s, 3 H), 1.34 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ (**2.7a**) 144.7 (C4), 133.4 (C6), 132.2 (C3), 127.1 (C5), 119.1 (nitrile C7), 112.4 (C1), 84.8 (2 C), 24.7 (4 CH_3 of BPin), 14.61 (SCH_3), (**2.7b**) 152.7 (C4′), 139.3 (C2′), 134.1 (C6′), 122.9 (C5′), 119.0 (nitrile C7′), 106.7 (C1′), 84.6 (2 C), 24.7 (4 CH_3 of BPin), 15.0 (SCH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.27; FT-IR (neat) $\tilde{\nu}$: 2980, 2928, 2224, 1584, 1547, 1483, 1397, 1381, 1373, 1345, 1269, 1213, 1167, 1142, 1107, 1059, 963, 871, 847, 825, 769, 741, 669 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 275 (100), 260 (26), 232 (41), 217 (46), 202 (9), 190 (10), 175 (54); Anal. Calcd for $C_{14}H_{18}BNO_2S$: C, 61.11; H, 6.59; N, 5.09. Found: C, 61.24; H, 6.95; N, 5.05; HRMS (EI): *m/z* 275.1157 [(M^+); Calcd for $C_{14}H_{18}BNO_2S$: 275.1151].

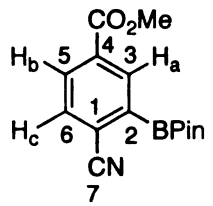
Table 2.1, Entry 8. 4-(Dimethylamino)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (2.8a).



2.8a

General procedure B was applied to 4-dimethylaminobenzonitrile (146 mg, 1 mmol, 1 equivalent) and B_2Pin_2 (254 mg, 1.00 mmol, 2.00 equivalents of boron) using 6 mol % [Ir] with a reaction time of 72 h. Only one isomer was observed in the crude reaction mixture by GC-FID and by ^{1}H NMR spectroscopy. Solvent was removed under reduced pressure, and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford the single pure isomer (180 mg, 66% yield, mp 110-111 °C) as a white solid. The NOESY1D and gHMBC spectra were used to assign the single isomer as 4-dimethylamino-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)benzonitrile. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**2.8a**) 7.48 (d, J = 8.8 Hz, 1 H, Hc), 7.04 (d, J = 2.9 Hz, 1 H, Ha), 6.67 (dd, J = 8.8, 2.9 Hz, 1 H, Hb), 3.01(s, 6 H), 1.35 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ (**2.8a**) 151.4 (C4), 134.8 (C6), 120.7 (nitrile C7), 118.1 (C3), 113.2 (C5), 102.3 (C1), 84.5 (2 C), 39.9 (CH_3), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.5; FT-IR (neat) $\tilde{\nu}$: 2980, 2932, 2815, 2213, 1597, 1553, 1508, 1485, 1429, 1416, 1374, 1337, 1271, 1230, 1169, 1144, 1053, 968, 847, 816 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 272 (100), 257 (7), 229 (11), 214 (11), 189 (6), 173 (23); Anal. Calcd for $C_{15}H_{21}BN_2O_2$: C, 66.2; H, 7.78; N, 10.29. Found: C, 66.54; H, 7.76; N, 10.06.

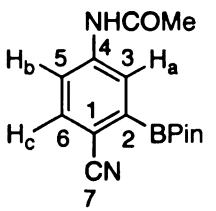
Table 2.1, Entry 9. Methyl 4-cyano-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (2.9a).



2.9a

General procedure B was applied to methyl 4-cyanobenzoate (161 mg, 1 mmol, 1 equivalent) and B_2Pin_2 (203 mg, 0.80 mmol, 1.60 equivalents of boron) with a reaction time of 48 h. Only one isomer was observed in the crude reaction mixture by GC-FID and by ^1H NMR spectroscopy. Solvent was removed under reduced pressure, and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford the single pure isomer (190 mg, 66% yield, mp 136-137 °C) as a white solid. The NOESY1D and gHMBC spectra were used to assign the single isomer as methyl 4-cyano-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)benzoate. ^1H NMR ($CDCl_3$, 300 MHz): δ (**2.9a**) 8.49 (d, J = 1.7 Hz, 1 H, Ha), 8.14 (dd, J = 8.1, 1.9 Hz, 1 H, Hb), 7.75 (d, J = 8.1 Hz, 1 H, Hc), 3.93 (s, 3 H), 1.37 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 75 MHz): δ (**2.9a**) 165.6 (C=O), 136.6 (C3), 133.4 (C6), 132.7 (C4), 131.9 (C5), 121.1 (C1), 118.1 (nitrile C7), 85.1 (2 C), 52.6 (CH_3), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.1; FT-IR (neat) $\tilde{\nu}$: 2980, 2954, 2230, 1721, 1603, 1487, 1410, 1375, 1337, 1279, 1251, 1144, 1115, 1069, 976, 851, 770, 654 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 287 (5), 272 (32), 256 (20), 244 (100), 229 (18), 188 (26), 156 (14); Anal. Calcd for $C_{15}H_{18}BNO_4$: C, 62.75; H, 6.32; N, 4.88. Found: C, 62.33; H, 6.26; N, 4.79. HRMS (EI): *m/z* 287.1327 [(M^+); Calcd for $C_{15}H_{18}BNO_4$: 287.1329].

Table 2.1, Entry 10. *N*-(4-cyano-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (2.10a).

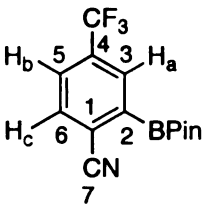


2.10a

General procedure B was applied to 4′-cyanoacetanilide (160 mg, 1 mmol, 1 equivalent) and B_2Pin_2 (406 mg, 1.60 mmol, 3.20 equivalents of boron) using 8 mol % [Ir] with a reaction time of 18 h. One borylated isomer was observed in the crude reaction mixture by GC-FID and by ^{1}H NMR spectroscopy along with a small amount of borylated/reduced (reduction of carbonyl group to CH_2) as a side product. Solvent was removed under reduced pressure. Column chromatography (ether, R_f 0.5) gave a mixture of the desired product and pinacol (239 mg). Kugelrohr distillation furnished the desired product (177 mg, 62% yield, mp 178-180 °C) as a white solid. The gHMBC spectrum was used to assign the single isomer as 4′-cyano-3′-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-acetanilide. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (**2.10a**) 7.99 (dd, J = 8.3, 2.0 Hz, 1 H, Hb), 7.85 (s, 1 H, N-H), 7.77 (d, J = 2.4 Hz, 1 H, Ha), 7.63 (d, J = 8.3 Hz, 1 H, Hc), 2.18 (s, 3 H), 1.32 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ (**2.10a**) 168.8 (C=O), 141.1 (C4), 134.7 (C6), 125.9 (C3), 121.5 (C5), 119 (nitrile C7), 111.6 (C1), 84.8 (2 C), 24.7 (4 CH_3 of BPin), 24.6 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.52; FT-IR (neat) $\tilde{\nu}$: 3319, 3104, 2980, 2934, 2225, 1701, 1678, 1601, 1578, 1532, 1497, 1416, 1373, 1344, 1302, 1258, 1140, 1063, 965, 853, 800, 743, 675 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 286 (100), 271 (18), 253 (32), 244 (89), 228 (68), 201

(42), 187 (68), 158 (13), 144 (58); HRMS (EI): *m/z* 286.1493 [(M^+); Calcd for $C_{15}H_{19}BN_2O_3$: 286.1489].

Table 2.1, Entry 11. 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)benzonitrile (2.11a).

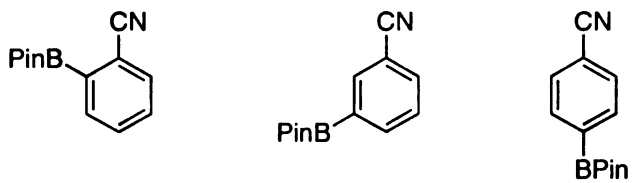


2.11a

General procedure B was applied to 4-(trifluoromethyl)-benzonitrile (171 mg, 1 mmol, 1 equiv) and HBPin (175 μL, 154 mg, 1.20 mmol) in *n*-hexane (3 mL) with a reaction time of 12 h. One monoborylated product and one diborylated product were observed in the crude reaction mixture by GC-FID (90:10). Solvent was removed under reduced pressure. The crude mixture was eluted with CH_2Cl_2 through a plug of silica gel. Sublimation furnished the desired single monoborylated product (203 mg, 68% yield, mp 79-80 °C) as a white solid. ^{13}C NMR spectroscopy was used to assign the single isomer as 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)benzonitrile. ^1H NMR ($CDCl_3$, 500 MHz): δ (**2.11a**) 8.12 (s, 1 H, Ha), 7.81 (d, J = 7.8 Hz, 1 H, Hb or Hc), 7.76 (d, J = 7.8 Hz, 1 H, Hb or Hc), 1.38 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ (**2.11a**) 133.7 (C6), 133.3 (q, $^2J_{C\text{-}F}$ = 33.2 Hz, C4), 132.5 (q, $^3J_{C\text{-}F}$ = 2.1 Hz, C3), 127.8 (q, $^3J_{C\text{-}F}$ = 3.3 Hz, C5), 122.1 (q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 120.7 (C1), 117.6 (nitrile C7), 85.3 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.03; ^{19}F NMR ($CDCl_3$, 282 MHz): δ –63.4; FT-IR (neat) $\tilde{\nu}$: 2982, 2234, 1613, 1574, 1423, 1354, 1306, 1271, 1175, 1142, 1082, 1065, 965, 878, 849, 675 cm^{-1}; LRMS (% rel. int.):

m/e 297 M^+ (23), 282 (100), 256 (81), 239 (27), 198 (19), 171 (10); HRMS (EI): *m/z* 297.1144 [(M^+); Calcd for $C_{14}H_{15}BF_3NO_2$: 297.1148].

Borylation of benzonitrile (2.12a + 2.12b + 2.12c).

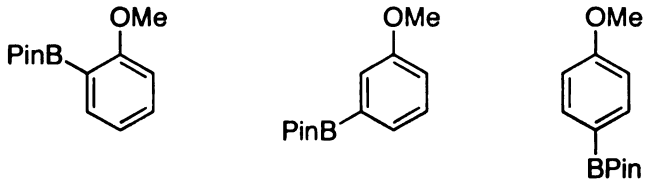


5.7 **2.12a** 64.4 **2.12b** 29.9 **2.12c**

General procedure A was applied to benzonitrile (412 mg, 4 mmol, 4 equiv) and HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) with a reaction time of 12 h. The ratio of the three isomers in the crude reaction mixture by GC-FID was 5.7:64.4:29.9. Solvent and excess substrate were removed under reduced pressure. The crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford a mixture of the three isomeric borylated products (176 mg, 77% combined yield) as a white solid. ^{1}H NMR, gCOSY, and gHMBC spectroscopy were used to assign the major isomer as 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)benzonitrile. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**2.12b**-*meta* isomer) 8.07-8.05 (br s, 1 H), 7.98 (td, J = 7.5, 1.2 Hz, 1 H), 7.71-7.67 (m, 1 H), 7.44 (dt, J = 7.5, 0.7 Hz, 1 H), 1.32 (br s, 12 H, 4 CH_3 of BPin), (**2.12c**-*para* isomer) 7.87-7.84 (m, 2 H), 7.62-7.59 (m, 2 H), 1.32 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ (**2.12b**-*meta* isomer) 138.7 (CH), 138.3 (CH), 134.3 (CH), 128.3 (CH), 118.7 (C), 112 (C), 84.4 (2 C), 24.8 (4 CH_3 of BPin), (**2.12c**-*para* isomer) 135 (CH), 131 (CH), 118.7 (C), 114.4 (C), 84.7 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 31.2; FT-IR (neat) $\tilde{\nu}$: 3063, 2980, 2934, 2230, 1603, 1483, 1398, 1360, 1329, 1271, 1143, 1088, 964, 880, 849, 700, 653 cm^{-1}; GC-MS (EI) *m/z* (% relative

intensity): (**2.12b**-*meta* isomer) M^+ 229 (11), 230 M^{+1} (29), 214 (100), 186 (10), 143 (44), (**2.12c**-*para* isomer) M^+ 229 (5), 230 M^{+1} (14), 186 (9), 143 (41); HRMS (EI): *m/z* 229.1271 [(M^+); Calcd for $C_{13}H_{16}BNO_2$: 229.1274].

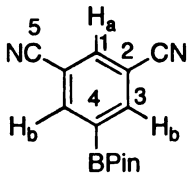
Borylation of anisole (2.13a + 2.13b + 2.13c).



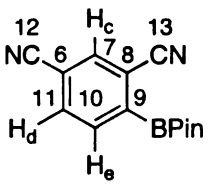
2.1 **2.13a** | 78.9 **2.13b** | 19 **2.13c**

General procedure A was applied to anisole (432 mg, 4.00 mmol, 4 equiv) and HBPin (145 μL, 128 mg, 1 mmol) with a reaction time of 24 h. The ratio of the three isomers in the crude reaction mixture by GC was 2.1:78.9:19. Solvent and excess substrate were removed under reduced pressure. The crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford a mixture of the three isomeric borylated products (193 mg, 82% combined yield) as colorless oil. ^{1}H NMR spectroscopy was used to assign the major isomer as 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)anisole. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**2.13b**/*meta* isomer) 7.40-7.25 (m, 3 H), 7.00 (m, 1 H), 3.82 (s, 3 H), 1.33 (br s, 12 H, 4 CH_3 of BPin), (**2.13c**/*para* isomer) 7.75-7.72 (m, 2 H), 6.89-6.86 (m, 2 H), 3.81 (s, 3 H), 1.32 (br s, 12 H, 4 CH_3 of BPin). The spectra were in agreement with those described in the literature.[18]

Borylation of 1,3-dicyanobenzene (2.14a + 2.14b).



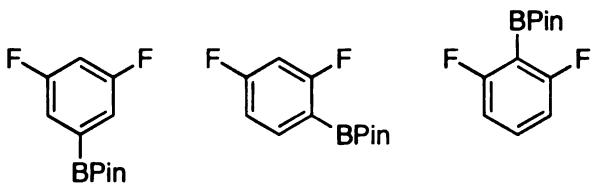
74
2.14a



26
2.14b

General procedure A was applied to 1,3-dicyanobenzene (256 mg, 2.00 mmol, 4.00 equiv) and HBPin (73 μL, 64 mg, 0.5 mmol) with a reaction time of 12 h. The ratio of the two isomers in the crude reaction mixture by ^{1}H NMR spectroscopy was 74:26. Kugelrohr distillation furnished a mixture of the two isomeric borylated products (79 mg, 62% yield) as a white solid. The ratio of the two isomers in the isolated product by ^{1}H NMR spectroscopy was 77:23. ^{1}H NMR spectroscopy was used to assign the major isomer as 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isophthalonitrile. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**2.14a**) 8.24 (d, J = 1.7 Hz, 2 H, Hb), 7.96 (t, J = 1.7 Hz, 1 H, Ha), 1.33 (br s, 12 H, 4 CH_3 of BPin), (**2.14b**) 7.99 (d, J = 7.8 Hz, 1 H, He), 7.92 (d, J = 1.4 Hz, 1 H, Hc), 7.80 (dd, J = 7.8, 1.4 Hz, 1 H, Hd), 1.36 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H}($CDCl_3$, 125 MHz): δ (**2.14a**) 141.8 (CH, C3), 137.1 (CH, C1), 116.7 (C, nitrile C5), 113.5 (C, C2), 85.2 (2 C), 24.8 (4 CH_3 of BPin), (**2.14b**) 136.6 (CH), 136.1 (CH), 134.4, (CH), 118.6 (C), 116.8 (C), 116.7 (C), 115.3 (C), 85.5 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.03; FT-IR (neat) $\tilde{\nu}$: 3073, 2982, 2237, 1595, 1418, 1398, 1374, 1339, 1233, 1215, 1169, 1144, 1129, 1064, 966, 897, 849, 698 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 254 (7), 239 (100), 211 (15), 196 (4), 168 (43), 155 (7); Anal. Calcd for $C_{14}H_{15}BN_2O_2$: C, 66.18; H, 5.95; N, 11.02. Found: C, 66; H, 6.02; N, 10.81.

Borylation of 1,3-difluorobenzene (2.15a + 2.15b + 2.15c).



50 **2.15a** 33 **2.15b** 17 **2.15c**

General procedure A was applied to 1,3-fluorobenzene (228 mg, 2.00 mmol, 4 equiv) and HBPin (73 μL, 64 mg, 0.5 mmol, 1 equiv) with a reaction time of 1 h. The ratio of the three isomers in the crude reaction mixture by GC-FID was 50:33:17, with GC-FID retention time of 7.92, 8.17, and 8.35 minutes respectively. ^{13}C NMR spectroscopy and authentic sample preparation were used for making regioisomeric assignments. Authentic samples of each isomer were synthesized using a slightly modified literature procedure.[59]

Preparation of authentic samples of borylated 1,3-difluorobenzenes.

In a glove box, a 100 mL schlenk flask, equipped with a magnetic stirring bar, was charged with $Pd_2(dba)_3$ (14 mg, 0.015 mmol, 3 mol% Pd) and tricyclohexylphosphine (PCy_3, 20 mg, 0.072 mmol, 7.2 mol%). Dioxane (6 mL) was added and the resulting mixture was stirred for 30 minutes at room temperature. B_2Pin_2 (280 mg, 1.1 mmol), KOAc (147 mg, 1.5 mmol), and the corresponding bromo substituted 1,3-difluorobenzene (193 mg, 1 mmol) were added successively. The schlenk flask was brought to a schlenk line. A condenser was attached, and the flask was flushed with nitrogen. The reaction mixture was stirred at 80 °C for 12 h. The mixture was treated with water (5 mL), and the product was extracted with ether, washed with brine, and

dried over $MgSO_4$. Crude material was eluted with CH_2Cl_2 through a plug of silica gel to afford the desired product. Characterization data for each isomer is described below.

2-(3,5-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.15a).

161 mg (67% yield, mp 47-48 °C); GC-FID retention time 7.92 minute; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28-7.24 (m, 2 H), 6.85 (tt, $^2J_{H\text{-}F}$ = 9.1 Hz, $^4J_{H\text{-}H}$ = 2.5 Hz, 1 H), 1.32 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 162.7 (dd, $^1J_{C\text{-}F}$ = 249.8 Hz, $^3J_{C\text{-}F}$ = 12.1 Hz, C), 116.8 (m, 2 CH), 106.5 (t, $^2J_{C\text{-}F}$ = 25.2 Hz, CH), 84.4 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 31.1; ^{19}F NMR ($CDCl_3$, 282 MHz): δ –110.8 (m); FT-IR (neat) $\tilde{\nu}$: 2924, 2853, 1367, 1259, 1022, 800 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 240 (16), 225 (100), 197 (13), 154 (58); Anal. Calcd for $C_{12}H_{15}BF_2O_2$: C, 60.04; H, 6.30. Found: C, 59.94; H, 6.31; HRMS (EI): *m/z* 240.1139 [(M^+); Calcd for $C_{12}H_{15}BF_2O_2$: 240.1133].

2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.15b).

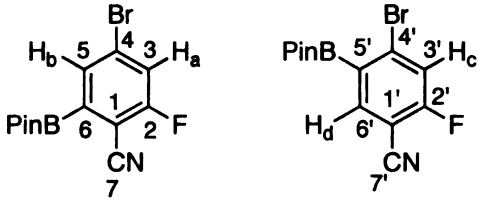
170 mg (71% yield, mp 39-40 °C); GC-FID retention time 8.17 minute; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74-7.66 (m, 1 H), 6.88-6.81 (m, 1 H), 6.78-6.71 (m, 1 H), 1.33 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 168.5 (dd, $^1J_{C\text{-}F}$ = 175.8 Hz, $^3J_{C\text{-}F}$ = 12.1 Hz, C), 165.2 (dd, $^1J_{C\text{-}F}$ = 174.7 Hz, $^3J_{C\text{-}F}$ = 12.1 Hz, C), 138.2 (t, $^3J_{C\text{-}F}$ = 10.1 Hz, CH), 111.1 (dd, $^2J_{C\text{-}F}$ = 20.1 Hz, $^4J_{C\text{-}F}$ = 3.5 Hz, CH), 103.7 (dd, $^2J_{C\text{-}F}$ = 27.9 Hz, $^2J_{C\text{-}F}$ = 24.4 Hz, CH), 84.0 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.7; ^{19}F NMR ($CDCl_3$, 282 MHz): δ –105.2 (m), -98.6 (m); FT-IR (neat) $\tilde{\nu}$: 3074, 2982, 2934, 1614, 1593, 1421, 1387, 1356, 1331, 1263, 1143, 1107, 1070, 960, 856, 733, 652, 576 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 240 (51), 225 (100), 197 (9), 181 (45),

141 (65); Anal. Calcd for $C_{12}H_{15}BF_2O_2$: C, 60.04; H, 6.30. Found: C, 59.71; H, 6.26; HRMS (FAB): *m/z* 240.1134 [(M^+); Calcd for $C_{12}H_{15}BF_2O_2$: 240.1133].

2-(2,6-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.15c).

172 mg (72% yield, mp 50-51 °C); GC-FID retention time 8.35 minute; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38-7.28 (m, 1 H), 6.86-6.77 (m, 2 H), 1.36 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 166.7 (dd, $^1J_{C\text{-}F}$ = 250.3 Hz, $^3J_{C\text{-}F}$ = 13.1 Hz, C), 132.9 (t, $^3J_{C\text{-}F}$ = 10.3 Hz, CH), 111.2-110.8 (m, 2 CH), 84.3 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.6; ^{19}F NMR ($CDCl_3$, 282 MHz): δ –100.6 (m); FT-IR (neat) $\tilde{\nu}$: 2988, 2930, 1626, 1458, 1383, 1354, 1334, 1138, 1095, 1053, 985, 850, 825, 792, 671, 559 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 240 (26), 225 (100), 197 (5), 181 (68); Anal. Calcd for $C_{12}H_{15}BF_2O_2$: C, 60.04; H, 6.30. Found: C, 60.02; H, 6.42.

Borylation of 2-fluoro-4-bromobenzonitrile (2.16a + 2.16b).

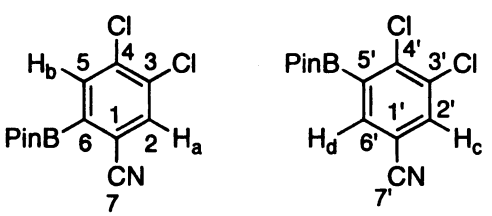


95 **2.16a** 5 **2.16b**

General procedure B was applied to 2-fluoro-4-bromobenzonitrile (200 mg, 1 mmol, 1 equivalent) and HBPin (290 μL, 256 mg, 2.00 mmol, 2.00 equiv) with a reaction time of 9 h. The ratio of the two monoborylated isomers in the crude reaction mixture by ^{1}H NMR spectroscopy was 95:5. A small amount of diborylated product was also observed. Solvent was removed under reduced pressure, and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel. Sublimation afforded a mixture of two isomeric

borylated products (278 mg, 85% combined yield) as a white solid. The ratio of the two monoborylated isomers in the isolated product by ^{1}H NMR spectroscopy was 95:5. ^{1}H NMR spectroscopy were used to assign the major isomer as 2-fluoro-4-bromo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)benzonitrile. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (**2.16a**) 7.77 (d, J = 1.7 Hz, 1 H, Hb), 7.44 (dd, $^2J_{H\text{-}F}$ = 8.3 Hz, J = 1.7 Hz, 1 H, Ha), 1.35 (br s, 12 H, 4 CH_3 of BPin), (**2.16b**) 7.90 (d, $^3J_{H\text{-}F}$ = 7.5 Hz, 1 H, Hd), 7.42 (d, $^2J_{H\text{-}F}$ = 8.5 Hz, 1 H, Hc), 1.35 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ (**2.16a**) 163.3 (d, $^1J_{C\text{-}F}$ =262.8 Hz, C, C2), 134.6 (d, $^4J_{C\text{-}F}$ = 4 Hz, CH, C5), 127.8 (d, $^3J_{C\text{-}F}$ = 8 Hz, C, C4), 122 (d, $^2J_{C\text{-}F}$ = 23 Hz, CH, C3), 112.9 (nitrile, C, C7), 104.6 (d, $^2J_{C\text{-}F}$ = 14.1 Hz, C, C1), 85.4 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.94; ^{19}F NMR ($CDCl_3$, 282 MHz): δ (**2.16a**) -103.9 (d, J = 7.9 Hz); FT-IR (neat) $\tilde{\nu}$: 3086, 2986, 2934, 2237, 1590, 1557, 1462, 1408, 1375, 1358, 1329, 1140, 972, 985, 880, 843, 742, 665 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 325 (15), 310 (37), 284 (67), 267 (34), 246 (31), 226 (57); Anal. Calcd for $C_{13}H_{14}BBrFNO_2$: C, 47.90; H, 4.33; N, 4.3. Found: C, 48.15, H, 4.28; N, 4.16.

Borylation of 3,4-dichlorobenzonitrile (2.17a + 2.17b).

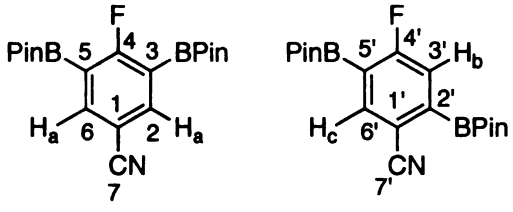


80 **2.17a** 20 **2.17b**

General procedure B was applied to 3,4-dichlorobenzonitrile (172 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equivalent) with a reaction time of 18 h. The ratio of the two monoborylated isomers in the crude reaction mixture by ^{1}H

NMR spectroscopy was 80:20. Solvent was removed under reduced pressure and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford a mixture of two isomeric borylated products (265 mg, 89% combined) as a white solid. The ratio of the two monoborylated isomers in the isolated product by ^1H NMR spectroscopy was 81:19. ^1H NMR spectroscopy was used to assign the major isomer as 4,5-dichloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)benzonitrile. ^1H NMR ($CDCl_3$, 500 MHz): δ (**2.17a**) 7.92 (s, 1 H), 7.73 (s, 1 H), 1.35 (br s, 12 H, 4 CH_3 of BPin), (**2.17b**) 7.84 (d, J = 2 Hz, 1 H), 7.74 (d, J = 2 Hz, 1 H), 1.35 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ (**2.17a**) 137.7 (CH), 137.1 (C), 135.8 (C), 134.8 (CH), 116.9 (C), 116.6 (C), 85.3 (2 C), 24.7 (4 CH_3 of BPin), (**2.17b**) 142.7 (C), 137.6 (CH), 135 (CH), 134.3 (C), 116.8 (C), 111.3 (C), 85 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.9; FT-IR (neat) $\tilde{\nu}$: 2982, 2234, 1580, 1535, 1472, 1383, 1342, 1304, 1142, 1084, 964, 910, 850, 669 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**2.17a**) M^+ 297 (22), 282 (60), 256 (100), 239 (48), 198 (41), (**2.17b**) M^+ 297 (1), 282 (28), 262 (100), 220 (80); Anal. Calcd for $C_{13}H_{14}BCl_2NO_2$: C, 52.40; H, 4.74; N, 4.70. Found: C, 52.42; H, 4.79; N, 4.55; HRMS (EI): *m/z* 297.0500 [(M^+); Calcd for $C_{13}H_{14}BCl_2NO_2$: 297.0495].

Table 2.3, Entry 1. Diborylation of 4-fluorobenzonitrile (2.18a + 2.18b).

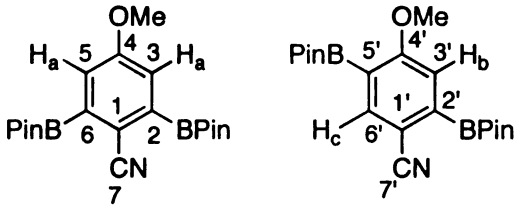


54 **2.18a** 46 **2.18b**

General procedure C was applied to 4-fluorobenzonitrile (121 mg, 1 mmol, 1 equiv) and HBPin (580 μL, 512 mg, 4.00 mmol, 4.00 equiv) with a reaction time of 24 h.

The ratio of the two isomers in the crude reaction mixture by ^{1}H NMR spectroscopy was 54:46. Solvent was removed under reduced pressure, and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford a mixture of two isomeric diborylated products (343 mg, 92% combined yield) as a white solid. The ratio of the two diborylated isomers in the isolated product by ^{1}H NMR spectroscopy was 53:47. ^{1}H, ^{13}C NMR and gHMBC spectroscopy were used to assign the major isomer as 4-fuoro-3,5-bis-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)benzonitrile. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (**2.18a**) 8.1 (d, $^4J_{H\text{-}F}$ = 4.9 Hz, 2 H, Ha), 1.28 (br s, 24 H, 8 CH_3 of BPin), (**2.18b**) 8.04 (d, $^4J_{H\text{-}F}$ = 5.4 Hz, 1 H, Hc), 7.46 (d, $^3J_{H\text{-}F}$ = 8.8 Hz, 1 H, Hb), 1.32 (br s, 12 H, 4 CH_3 of BPin), 1.31 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**2.18a**) 172 (d, $^1J_{C\text{-}F}$ = 266 Hz, C4), 143.9 (d, $^3J_{C\text{-}F}$ = 10.9 Hz, C2), 117.9 (nitrile C), 108 (d, $^4J_{C\text{-}F}$ = 3.6 Hz, C1), 84.4 (4 C), 24.7 (8 CH_3 of BPin), (**2.18b**) 168.1 (d, $^1J_{C\text{-}F}$ = 261.4 Hz, C4′), 142.6 (d, $^3J_{C\text{-}F}$ = 8.8 Hz, C6′), 122.6 (d, $^2J_{C\text{-}F}$ = 23.8 Hz, C3′), 118.1 (nitrile C7′), 112.6 (d, $^4J_{C\text{-}F}$ = 3.6 Hz, C1′), 85 (2 C), 84.5 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.8; ^{19}F NMR ($CDCl_3$, 282 MHz): δ (**2.18a**) –81.8 (m), (**2.18b**) –94.9 (m); FT-IR (neat) $\tilde{\nu}$: 2980, 2934, 2232, 1599, 1497, 1437, 1414, 1373, 1334, 1267, 1215, 1142, 1095, 966, 889, 848, 584 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**2.18a**) M^+ 373 (4), 358 (59), 353 (100), 315 (22), 253 (45), (**2.18b**) 373 M^+ (32), 358 (68), 331 (100), 315 (53), 274 (39); Anal. Calcd for $C_{19}H_{26}B_2FNO_4$: C, 61.17; H, 7.03; N, 3.75. Found: C, 61.37,; H, 6.83; N, 3.82.

Table 2.3, Entry 2. Diborylation of 4-methoxybenzonitrile(2.19a + 2.19b).

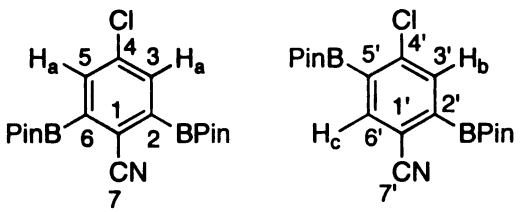


20 **2.19a** 80 **2.19b**

General procedure C was applied to 4-methoxybenzonitrile (133 mg, 1 mmol, 1 equiv) and HBPin (580 μL, 512 mg, 4.00 mmol, 4.00 equivalent) at 60 °C for 48 h. The ratio of the two diborylated isomers in the crude reaction mixture by ^{1}H NMR spectroscopy was 80:20. Solvent was removed under reduced pressure, and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford a mixture of two isomeric diborylated products (310 mg, 81% combined yield) as a white solid. The ratio of the two diborylated isomers in the isolated product by ^{1}H NMR spectroscopy was 80:20. ^{1}H NMR and gHMBC spectroscopy were used to assign the major isomer as 4-methoxy-2,5-bis-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)benzonitrile. ^{1}H NMR (C_6D_6, 500 MHz): δ (**2.19a**) 7.61 (s, 2H, Ha), 3.08 (s, 3H), 1.11 (br s, 24 H, 8 CH_3 of BPin), (**2.19b**) 8.42 (s, 1 H, Hc), 7.36 (s, 1 H, Hb), 3.20 (s, 3 H), 1.10 (br s, 12 H, 4 CH_3 of BPin), 1.06 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} (C_6D_6, 125 MHz): δ (**2.19a**) 160.8 (C4), 123.4 (C3), 118.6 (nitrile C7), 114.9 (C1), 84.6 (4 C), 24.8 (8 CH_3 of BPin), (**2.19b**) 166.3 (C4′), 143.1 (C6′), 137.4 (br, C2′), 122.1 (br, C5′), 119.32 (nitrile, C7′), 117.36 (C3′), 110.1 (C1′), 84.8 (2 C), 83.8 (2 C), 24.79 (4 CH_3 of BPin), 24.76 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.90; FT-IR (neat) $\tilde{\nu}$: 2980, 2936, 2224, 1601, 1503, 1398, 1373, 1337, 1244, 1142, 1094, 964, 858 cm^{-1}; GC-MS (EI) *m/z* (% relative

intensity): M^+ 385 (100), 370 (63), 343 (98), 327 (53), 286 (41); Anal. Calcd for $C_{20}H_{29}B_2NO_5$: C, 62.38; H, 7.59; N, 3.64. Found: C, 62.36; H, 7.41; N, 3.69.

Table 2.3, Entry 3. Diborylation of 4-chlorobenzonitrile (2.20a + 2.20b).

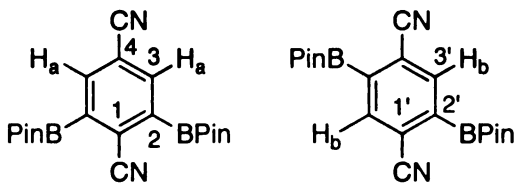


20 **2.20a** 80 **2.20b**

General procedure C was applied to 4-chlorobenzonitrile (138 mg, 1 mmol, 1 equiv) and HBPin (580 μL, 512 mg, 4 mmol, 4 equivalent) with a reaction time of 48 h. The ratio of the two diborylated isomers in the crude reaction mixture by GC-FID was 80:20. Solvent was removed under reduced pressure, and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford a mixture of two isomeric diborylated products (320 mg, 82% combined yield) as a white solid. The ratio of the two diborylated isomers in the isolated product by GC-FID was 80:20. ^{1}H NMR and gHMBC spectroscopy were used to assign the major isomer as 4-chloro-2,5-bis-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)benzonitrile. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (**2.20a**) 7.83 (s, 2 H, Ha), 1.349 (br s, 24 H, 8 CH_3 of BPin), (**2.20b**) 7.97 (s, 1 H), 7.80 (s, 1 H), 1.35 (br s, 12 H, 4 CH_3 of BPin), 1.34 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**2.20a**) 137.7 (C4), 137.3 (C3), 119.7(C1), 117.6 (nitrile C7), 85.04 (4 C), 24.7 (8 CH_3 of BPin), (**2.20b**) 143.6 (C4′), 141.2 (C6′), 136.5 (C3′), 118.2 (nitrile, C7′), 114.8 (C1′), 85.1 (2 C), 84.8 (2 C), 24.7 (8 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.25; FT-IR (neat) $\tilde{\nu}$: 2980, 2230, 1591, 1383, 1341, 1269, 1142, 1122, 1088, 962, 855 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**2.20a**) M^+ 389 (36),

374 (64), 348 (23), 290 (53), 248 (49), 207 (100), (**2.20b**) M^+ 389 (30), 374 (57), 354 (100), 347 (88), 331 (39), 312 (37), 290 (35); Anal. Calcd for $C_{19}H_{26}B_2ClNO_4$: C, 58.59; H, 6.73; N, 3.6. Found: C, 58.27, H, 6.78; N, 3.41; HRMS (EI): *m/z* 389.1746 [(M^+); Calcd for $C_{19}H_{26}B_2ClNO_4$: 389.1736].

Table 2.3, Entry 4. Diborylation of 1,4-dicyanobenzene (2.21a + 2.21b).

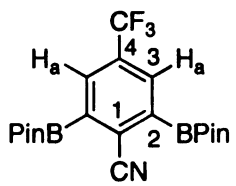


7 **2.21a** 93 **2.21b**

General procedure C was applied to 1,4-dicyanobenzene (128 mg, 1 mmol, 1 equiv) and HBPin (580 μL, 512 mg, 4.00 mmol, 4.00 equivalent) with a reaction time of 20 h. The ratio of the two diborylated isomers in the crude reaction mixture by GC-FID was 93:7. Solvent was removed under reduced pressure. Crystallization from THF/pentane gave the major isomer (270 mg, 71% yield, mp 242-245 °C) as a white solid. ^{13}C NMR spectroscopy were used to assign the major isomer as 2,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)terephthalonitrile. ^1H NMR ($CDCl_3$, 500 MHz): δ (**2.21a**) 8.15 (s, 2H,), 1.37 (br s, 24 H, 8 CH_3 of BPin), (**2.21b**) 8.16 (s, 2 H), 1.37 (br s, 24 H, 8 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 75 MHz): δ (**2.21b**) 140.1 (C3′, 2 CH), 135.4 (br, C2′, 2 C), 120.1 (C1′, 2 C), 117.4 (nitrile, 2 C), 85.4 (4 C), 24.7 (8 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.16; FT-IR (neat) $\tilde{\nu}$: 2984, 2230, 1497, 1416, 1391, 1347, 1287, 1267, 1169, 1140, 1100, 962, 927, 855, 814, 711, 598 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**2.21b**) M^+ 380 (35), 365 (69) , 339 (100), 322 (69), 281

(46); Anal. Calcd for $C_{20}H_{26}B_2N_2O_4$: C, 63.21; H, 6.90; N, 7.37. Found: C, 63.39, H, 7.19; N, 7.02.

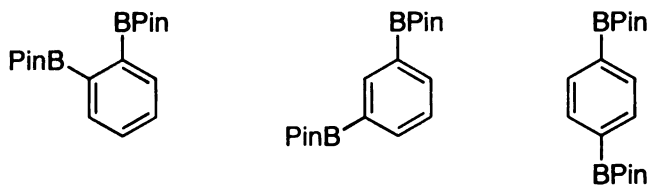
Table 2.3, Entry 5. 2,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)benzonitrile (2.22a).



2.22a

General procedure C was applied to 4-(trifluoromethyl)-benzonitrile (171 mg, 1 mmol, 1 equiv) and HBPin (580 μL, 512 mg, 4.00 mmol, 4.00 equivalent) with a reaction time of 36 h. Solvent was removed under reduced pressure, and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford single diborylated isomer (350 mg, 83% yield) as a white solid. ^{13}C NMR spectroscopy were used to assign the single isomer as 2,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)-benzonitrile. ^1H NMR ($CDCl_3$, 300 MHz): δ (**2.22a**) 8.12 (s, 2 H), 1.37 (br s, 24 H, 8 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 75 MHz): δ (**2.22a**) 133.9 (q, $^3J_{C\text{-}F}$ = 3 Hz, C3), 132 (q, $^2J_{C\text{-}F}$ = 32.2 Hz, C4), 125 (nitrile, C), 123.3 (q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 117.1 (C1), 85.2 (2 C), 24.7 (8 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.14; ^{19}F NMR ($CDCl_3$, 282 MHz): δ –63.3; FT-IR (neat) $\tilde{\nu}$: 2982, 2936, 2234, 1582, 1469, 1431, 1383, 1373, 1334, 1319, 1290, 1269, 1245, 1140, 1080, 966, 883, 846, 690 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 423 (45), 408 (100), 382 (36), 324 (45), 282 (62); Anal. Calcd for $C_{20}H_{26}B_2F_3NO_4$: C, 56.78; H, 6.19; N, 3.31. Found: C, 56.81; H, 5.92; N, 3.29; HRMS (EI): *m/z* 423.1999 [(M^+); Calcd for $C_{20}H_{26}B_2F_3NO_4$: 423.2000].

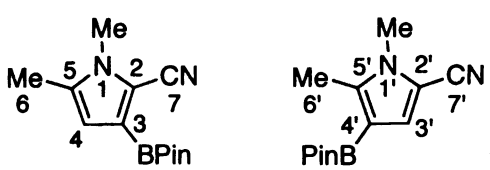
Borylation of PhBPin (2.23a + 2.23b + 2.23c).



0 **2.23a** 35.4 **2.23b** 64.6 **2.23c**

General procedure B was applied to benzene (78 mg, 1 mmol, 1 equiv) and HBPin (175 μL, 153.6 mg, 1.20 mmol, 1.20 equivalents) with a reaction time of 24 h. The first equivalent of borane generates PhBPin in situ and the remaining 0.2 equivalents give the two diborylated isomers. PhBPin and the two diborylated isomers were present at the end of reaction. The GC-FID ratio of the two diborylated isomers was 64.6:35.4. A mixture of the two diborylated isomers was isolated (51 mg). ^{1}H NMR spectroscopy was used to assign the major isomer as 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)benzene. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**2.23b**/*meta* isomer) 8.25 (d, J = 1 Hz, 1 H), 7.88 (dd, J = 7.3, 1.5 Hz, 2 H), 7.35 (td, J = 7.3, 1 Hz, 1 H), 1.31 (s, 24 H, 8 CH_3 of BPin), (**2.23c**/*para* isomer) 7.78 (s, 4 H), 1.32 (s, 24 H, 8 CH_3 of BPin). The spectra were in agreement with those described in the literature.[60]

Borylation of 1,5-dimethyl-2-pyrrolecarbonitrile (2.24a + 2.24b).

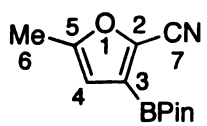


85 **2.24a** 15 **2.24b**

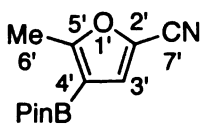
General procedure B was applied to 1,5-dimethyl-2-pyrrolecarbonitrile (240 mg, 2 mmol, 1 equiv) and HBPin (435 μL, 384 mg, 3.00 mmol, 1.50 equivalents) with a

reaction time of 16 h. The ratio of the two isomers in the crude reaction mixture by GC-FID was 85:15. Solvent was removed under reduced pressure, and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford a mixture of two isomeric borylated products (394 mg, 80% combined yield) as a white solid. The ratio of the two isomers in the isolated product by GC-FID was 82:18. The NOESY1D and gHMBC spectra were used to assign the major isomer as 1,5-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-2-pyrrolecarbonitrile. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**2.24a**) 6.21 (d, $^4J_{H\text{-}H}$ = 0.7 Hz, 1 H, pyrrol ring H), 3.63 (s, 3 H, NCH_3), 2.21 (d, $^4J_{H\text{-}H}$ = 0.7 Hz, 3 H, CH_3 on pyrrol ring), 1.30 (br s, 12 H, 4 CH_3 of BPin), (**2.24b**) 7.03 (s, 1 H, pyrrol ring H), 3.6 (s, 3 H, NCH_3), 2.41 (s, 3 H, CH_3 on pyrrol ring), 1.27 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**2.24a**) 135.4 (C5), 114 (C4), 113.8 (nitrile C7), 109.6 (C2), 83.0 (2 C), 32.0 (NCH_3), 24.3 (4 CH_3 of BPin), 11.8 (CH_3), (**2.24b**) 143.9 (C5′), 125.2 (C3′), 113.7 (nitrile C7′), 103.8 (C2′), 82.6 (2 C), 31.8 (NCH_3), 24.4 (4 CH_3 of BPin), 11.9 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 32.75; FT-IR (neat) $\tilde{\nu}$: 2980. 2934, 2735, 1561, 1501, 1441, 1408, 1390, 1379, 1371, 1313, 1262, 1187, 1167, 1144, 1111, 1017, 860, 835, 708 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**2.24a**) M^+ 246 (100), 231 (19), 203 (12), 189 (16), 160 (13), 146 (20), (**2.24b**) M^+ 246 (100), 231 (20), 189 (51), 160 (21), 146 (43); Anal. Calcd for $C_{13}H_{19}BN_2O_2$: C, 63.44; H, 7.78; N, 11.38. Found: C, 63.34; H, 7.78; N, 11.34.

Borylation of 5-methyl-2-furonitrile (2.25a + 2.25b).



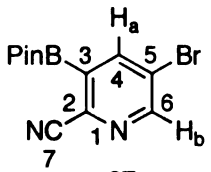
85
2.25a



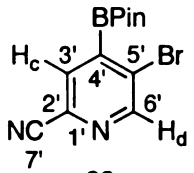
15
2.25b

General procedure B was applied to 5-methyl-2-furonitrile (210 uL, 214 mg, 2 mmol, 1 equiv) and HBPin (435 μL, 384 mg, 3.00 mmol, 1.50 equivalents) with a reaction time of 0.5 h. The ratio of the two isomers in the crude reaction mixture by GC-FID was 85:15. Solvent was removed under reduced pressure, and the crude mixture was eluted with CH_2Cl_2 through a plug of silica gel to afford a mixture of two isomeric borylated products (456 mg, 97% combined yield) as a white solid. The ratio of the two isomers in the isolated product by GC was 90:10. The NOESY1D and gHMBC spectra were used to assign the major isomer as 5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-2-furonitrile. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**2.25a**) 6.23 (d, $^4J_{H\text{-}H}$ = 1.0 Hz, 1 H, furan ring H), 2.29 (d, $^4J_{H\text{-}H}$ = 1.0 Hz, 3 H, CH_3 on furan ring), 1.27 (br s, 12H, 4 CH_3 of BPin), (**2.25b**) 7.12 (s, 1 H, furan ring H), 2.46 (s, 3 H, CH_3 on furan ring), 1.25 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ (**2.25a**) 157.6 (C5), 130.4 (C2), 111.9 (nitrile C7), 111.5 (C4), 84.3 (2 C), 24.6 (4 CH_3 of BPin), 13.4 (CH_3), (**2.25b**) 167 (C5′), 127.4 (C3′), 124.1 (C2′), 111.7 (nitrile C7′), 83.8 (2 C), 24.7 (4 CH_3 of BPin), 14.2 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.9; FT-IR (neat) $\tilde{\nu}$: 2982, 2934, 1595, 1543, 1446, 1428, 1408, 1392, 1381, 1373, 1335, 1302, 1228, 1169, 1143, 1043, 963, 855, 804, 712 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**2.25a**) M^+ 233 (89), 218 (42), 203 (20), 190 (64), 175 (59), 149 (100), 134 (47), (**2.25b**) M^+ 233 (100), 218 (81), 191 (54), 175 (62), 149 (53), 133 (63); Anal. Calcd for $C_{12}H_{16}BNO_3$: C, 61.84; H, 6.92; N, 6.01. Found: C, 62.25; H, 7.0; N, 5.80.

Borylation of 5-bromo-2-cyanopyridine (2.27a + 2.27b).



67
2.27a



33
2.27b

General procedure B was applied to 5-bromo-2-cyanopyridine (183 mg, 1 mmol, 1 equiv) and HBPin (290 μL, 256 mg, 2.00 mmol, 2.00 equiv) with a reaction time of 18 h. The ratio of the two isomers in the crude reaction mixture by ^{1}H NMR spectroscopy was 67:33. Kugelrohr distillation furnished a mixture of the two isomeric borylated products (253.5 mg, 81% combined) as a white solid. The ratio of the two isomers in the isolated product by ^{1}H NMR spectroscopy was 64:36. ^{1}H NMR and gHMBC spectroscopy were used to assign the major isomer as 5-bromo-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-2-cyanopyridine. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**2.27a**) 8.76 (d, J = 2.4 Hz, 1 H, Hb), 8.28 (d, J = 2.4 Hz, 1 H, Ha), 1.37 (br s, 12 H, 4 CH_3 of BPin), (**2.27b**) 8.76 (s, 1 H, Hd), 7.85 (s, 1 H, Hc), 1.36 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ (**2.27a**) 153.6 (C6), 145.8 (C4), 136.1 (C2), 124.4 (C5), 116.6 (nitrile C7), 85.7 (2 C), 24.8 (4 CH_3 of BPin), (**2.27b**) 153.1 (C6′), 134.5 (C3′), 131.4 (C2′), 130.1 (C5′), 116.7 (nitrile C7′), 85.6 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.5; FT-IR (neat) $\tilde{\nu}$: 3048, 2979, 2244, 1566, 1539, 1416, 1383, 1342, 1318, 1269, 1142, 1069, 1026, 964, 872, 847, 771 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**2.27a**) M^+ 308 (41), 310 (M^{2+} 37), 293 (95), 267 (96), 250 (65), 229 (34), 209 (42), (**2.27b**) M^+ 308 (7), 293 (33), 267 (17), 229 (100), 187 (91); Anal. Calcd for $C_{12}H_{14}BBrN_2O_2$: C, 46.65; H, 4.57; N, 9.07. Found: C, 46.52; H, 4.48; N, 8.76.

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(8) The deprotonation at the 2-position of 4-bromobenzonitrile is cited as an unpublished result in ref. 7.

(9) Alternatively, the nitrile group could be converted to a DMG, such as an amide or ester. Subsequent DoM and reformation of the nitrile group could give 2-substituted nitriles.

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(55) The experiment in Eq 2.2 was performed through the reaction of benzene with 1.2 equivalents of HBPin in thf in the presence of Ir catalyst. The first equivalent of borane generates PhBPin in situ and the remaining 0.2 equivalents give the diborylated isomers.

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CHAPTER 3

Iridium Catalyzed Borylation of Substituted Thiophenes

Introduction

Thiophenes are an important class of five membered heterocycles. Substituted thiophenes have found applications in several research areas such as natural product synthesis, drug design, and material science.[1] Apart from ring closure protocols, direct functionalizations of thiophene nucleus by electrophillic aromatic substitution, halogen-metal exchange, and directed *ortho* metalation have traditionally been used to synthesize poly-substituted thiophenes. These methods have certain limitations. Electrophillic substitution usually takes place at the 2- and/or 5-position and is also affected by the presence of a directing group, while the metalation approaches have limited functional group tolerances.

Organoboranes are versatile organic intermediates. They have extensively been employed in Suzuki cross-coupling reactions.[2] The C-B bond has also been used to introduce a wide variety of functional groups by substitution reactions.[3] Apart from their use as nucleophillic coupling partner in the Suzuki reaction, thiopheneboronic acids and esters have also been used in diverse areas of research including organic electronics,[4-6] preparation of radiolabeled compounds,[7] as inhibitors,[8] polymers,[9] and sensing materials.[10]

Thiophene boronic acids have traditionally been prepared from organomagnesium or lithium reagents. 2-Thiopheneboronic acid was firstly prepared by Krause and Pomeranz in 1932 by the reaction of 2-thienylmagnesium bromide with boron trifluoride.[11] Later, Johnson et al. replaced boron trifluoride with trialkyl borate.[12] In

1957, 3-thiopheneboronic acid was prepared from 3-thienylmagnesium bromide and trialkyl borate.[13] Due to the requirement of pregeneration of organometallic reagents under cryogenic conditions, this methodology had limited functional group tolerance. Transition metal catalyzed borylation of aryl and heteroaryl halides, introduced by Miyaura in 1995, allowed the presence of broad range of functional groups.[14-17] However, a C–Halogen bond was still a prerequisite for introduction of boronic acid functionality.

In 1999, Iverson and Smith reported the first thermal catalytic aromatic C–H activation borylation.[18] This method bypassed the need of C–Halogen bond for the formation of C-B bond. The selectivity and activity of the catalyst system has been improved over the years.[19-23] Now this system has become one of the most convenient methodology for the selective, direct C–H functionalization of aromatic hydrocarbons. Sterically governed regioselectivities in this protocol are complementary to those found in electrophillic aromatic substitution[24] and directed *ortho* metalation[25,26] approaches. Apart from aromatics, five and six membered heterocycles can also be borylated.

The application of this new methodology to the heteroaromatic systems was firstly demonstrated by Cho and Smith in 2000,[19] when 2,6-di-methylpyridine was regioselectively borylated on the 4-position. In 2001, Tse and Smith reported that *N*-TIPS-pyrrole, a five membered heterocycle, could be selectively borylated on the 3-position.[21] With more improved catalysts, selective C–H borylation of halogenated heteroaromatic substrates was also achieved.[20] In 2002, Miyaura and Hartwig reported that five membered heterocycles could be selectively borylated on the 2-position.[27] In 2005, we showed that 2,5-di-substituted five membered heterocycles could be borylated on the 3-position.[28] Borylation in more complex systems such as corrole[29] and

porphyrins[30] has also been reported. In 2006, we have reported the regioselective borylation of 2-substituted indoles and benzofuran on the 7-position.[31]

Considering the importance and need for the ready availability of polyfunctionalized thiophenes, we decided to study the iridium catalyzed C–H borylation of substituted thiophenes. Herein, we describe our results on the borylation of mono-, di-, and tri-substituted thiophenes.

Results and Discussion

2-Substituted thiophenes were borylated with Pinacolborane (HBPin) using 3 mol % $[Ir(OMe)COD]_2$/dtbpy catalyst loading at room temperature (Scheme 3.1). Typically, borylation was complete within 1 h and the 5-borylated products were isolated in 82-97% yields (Table 3.1). Apart from common functionalities in iridium catalyzed borylation such as ester, alkoxy, chloro, and iodo, additional functional group tolerance to acyl (COMe), and trimethylsilyl (TMS) groups was also observed. 2,3-Di-halo-substituted thiophene (Table 1, entry 7) was also cleanly borylated under these conditions.

Scheme 3.1. Monoborylation of 2-substituted thiophenes.

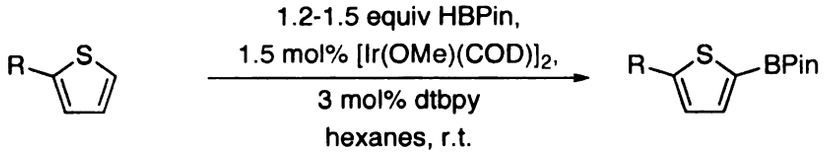
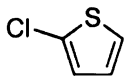
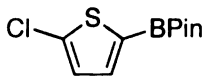
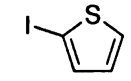
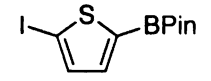
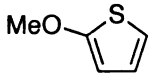
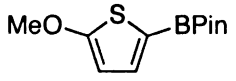
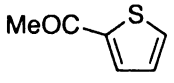
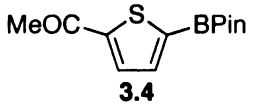
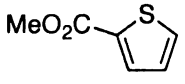
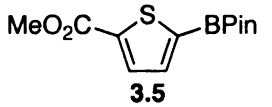
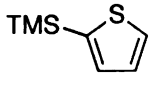
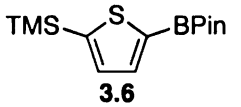
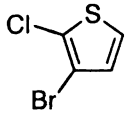
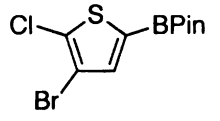


Table 3.1. Monoborylation of 2-substituted thiophenes according to scheme 3.1.

Entry	Thiophene	HBPin equiv	Time (h)	Product	%yield
1		1.2	0.25	 **3.1**	97
2		1.5	1	 **3.2**	92
3		1.2	1	 **3.3**	82
4		1.2	0.5	 **3.4**	85
5		1.5	0.5	 **3.5**	94
6		1.5	0.5	 **3.6**	93
7		1.5	0.20	 **3.7**	78

The case becomes slightly complicated for 3-substituted thiophenes since there are two open positions adjacent to the heteroatom that can potentially be borylated as shown in Scheme 3.2. The regioselectivities observed in monoborylation of 3-substituted thiophenes are shown in Table 3.2.

Scheme 3.2. Monoborylation of 3-substituted thiophenes.

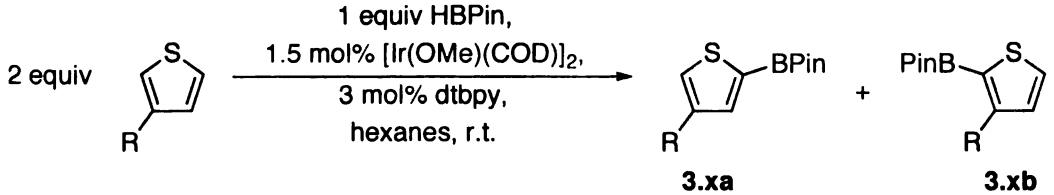
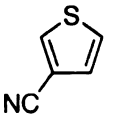
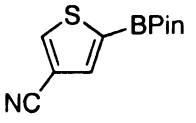
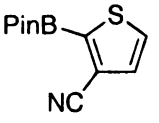
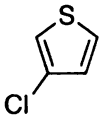
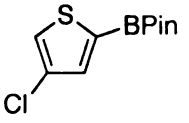
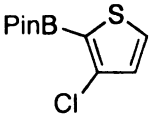
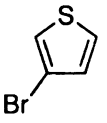
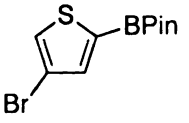
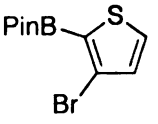
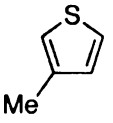
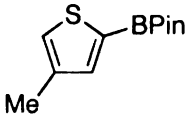
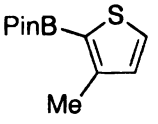
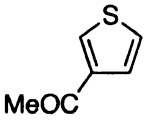
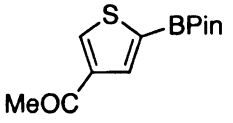
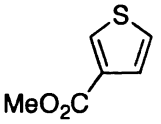
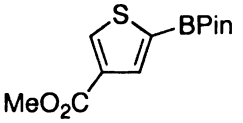
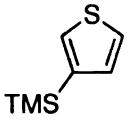
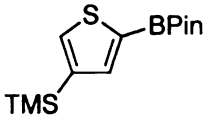
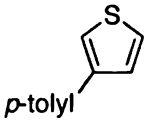
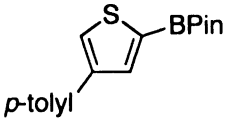
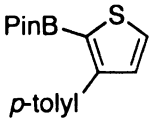


Table 3.2. Monoborylation of 3-substituted thiophenes according to scheme 3.2.

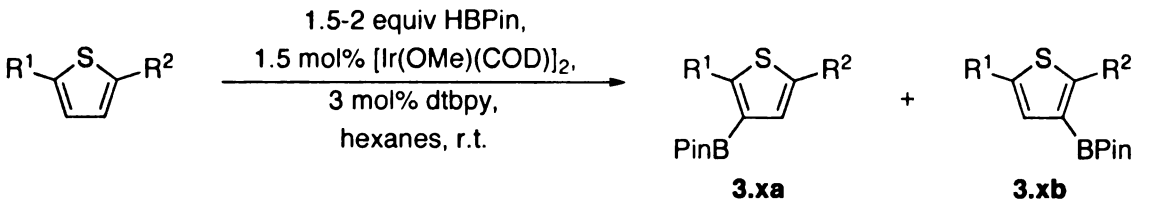
Entry	Thiophene	Products **a**	**b**	Isomer Ratio **3.xa** : **3.xb**	%yield
1		 **3.8a**	 **3.8b**	47 : 53	54
2		 **3.9a**	 **3.9b**	78 : 22	66
3		 **3.10a**	 **3.10b**	89 : 11	72
4		 **3.11a**	 **3.11b**	89 : 11	67
5		 **3.12a**	–	> 99 : 1	82
6		 **3.13a**	–	> 99 : 1	95
7		 **3.14a**	–	> 99 : 1	79
8		 **3.15a**	 **3.15b**	97 : 3	74

For smaller substituents such as chloro, bromo, and methyl, mixtures of two borylated regioisomers were observed. The major product observed for these substrates was the 5-borylated isomer (**3.xa**). The presence of small amounts of borylated isomer at the 2-position indicates that the steric effects of *ortho* substituents decrease for 5-membered rings relative to 6-membered rings.

In the case of 3-cyanothiophene, the ratio of 5- and 2-boryalted isomers was 47:53 respectively. This was surprising as we expected 5-borylated isomer to be the major product. One possible explanation could be that the electron withdrawing inductive effect of the 3-cyano group on the 2-position makes its C–H bond more activated as compared to the 5-position. The small steric demand of the cyano group and wider bond angles in a 5-membered ring may also facilitate borylation at the 2-position. Christophersen has reported the preparation of the 2-borylated isomer by Pd catalyzed borylation of 2-bromo-3-cyanothiophene.[15] In their case, although the borylated product was formed in 45% yield based on NMR, all attempts to isolate the product failed due to complete deborylation during aqueous workup. No such deborylation was observed in our case and the product mixture was isolated in 54% yield.

For sterically bulky substituents, such as ester, acyl, and trimethylsilyl (TMS), a single monoborylated isomer was observed. 3-Phenyl substitution also gives 97% regioselectivity for the 5-borylated isomer without borylation of the phenyl ring. Good to excellent regioselectivities for the 5-position in 3-substituted thiophenes observed here are consistent with sterically directed aromatic borylation and silylation.[32]

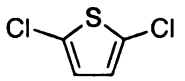
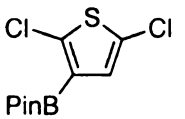
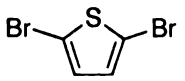
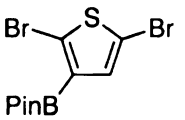
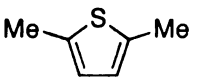
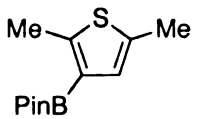
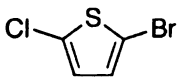
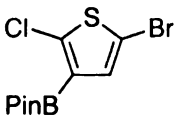
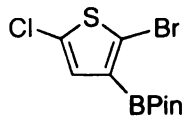
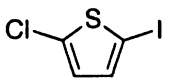
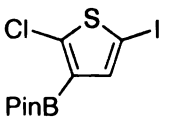
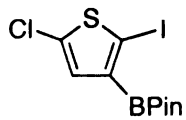
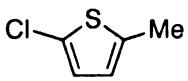
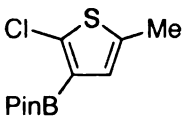
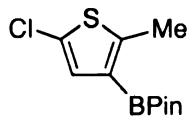
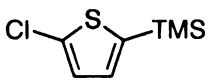
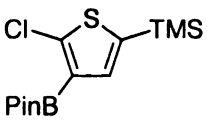
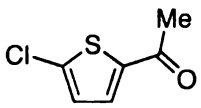
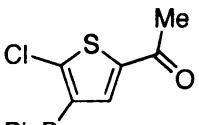
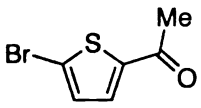
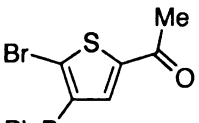
Scheme 3.3. Monoborylation of 2,5-di-substituted thiophenes.



3.xa **3.xb**

Next we examined the borylation of 2,5-di-substituted thiophenes (Scheme 3.3 and Table 3.3). There is only one borylated product regioisomer possible for symmetrical substrates. Complications were observed for electron-deficient as well as electron-rich thiophenes for different reasons. Borylation of 2,5-di-chlorothiophene slows down after initial rapid conversion, accompanied by precipitation of brown particles suggesting the decomposition of catalyst. Nevertheless the conversion was complete in 20 h and the product was isolated in 86% yield. The borylation of 2,5-di-bromothiophene was more problematic, and only 89% conversion of the substrate was observed after 48 h at room temperature with 9 mol% [Ir] catalyst loadings. The monoborylated product was isolated in 56% yield. The reason for reduced catalytic activity after rapid initial conversion could be that the C–halogen bonds in these cases are weak, and may compete with the desired C–H activation. Attempted catalytic borylation of electron-rich 2,5-di-methylthiophene using the [Ir(OMe)(COD)]/dtbpy system at room temperature was also very slow. Reduced activity due to electron rich behavior in this case was over come by using (Ind)Ir(COD)/dmpe system at 150 °C and the monoborylated product was isolated in 97% yield.

Table 3.3. Monoborylation of 2,5-di-substituted thiophenes according to scheme 3.3.

Entry	Thiophene	%[Ir]	Time (h)	Products a	Products b	Isomer Ratio **3.xa** : **3.xb**	%yield
1		3	20	 **3.16**	–	–	86
2		9	48	 **3.17**	–	–	56
3		2	16	 **3.18**	–	–	97
4		6	28	 **3.19a**	 **3.19b**	67 : 33	87
5		3	20	 **3.20a**	 **3.20b**	85 : 15	89
6		3	18	 **3.21a**	 **3.21b**	70 : 30	86
7		3	6	 **3.22a**	–	> 99 : 1	93
8		3	12	 **3.23a**	–	–	–
9		3	12	 **3.24a**	–	–	–

Unsymmetrical 2,5-disubstituted thiophenes yielded regioisomeric mixtures of two monoborylated products (Table 3.3). The borylation takes place preferentially *ortho* to the less bulky substituents. 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. Attempted borylations of 2-chloro-5-acetyl thiophene and 2-bromo-5-acetyl thiophene were unsuccessful and the reactions usually stopped after ~10% conversion. It is worthwhile to mention here that borylation in small 5-membered heteroaromatic substrate such as 2-acetyl-5-methyl-furan went to full conversion in 16 h (with 97:3 regioselectivity).

High regioselectivity of borylation for 2-chloro-5-trimethylsilylthiophene prompted us to examine the diborylation of 2-substituted thiophenes. We reasoned that since the BPin group attached to the 5-position via monoborylation is significantly bulkier than the 2-substituent, the second borylation should regioselectively take place at the 3-position. Indeed, diborylation of several 2-substituted thiophenes was found to be highly regioselective (Scheme 3.4 and Table 3.4).

Scheme 3.4. Diborylation of 2-substituted thiophenes.

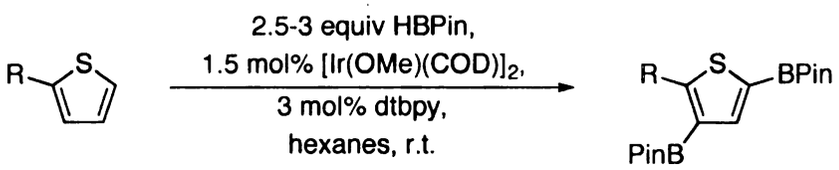
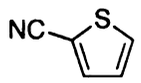
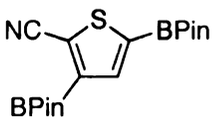
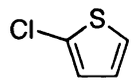
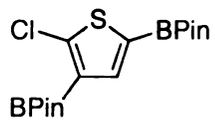
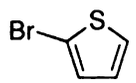
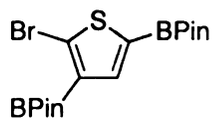
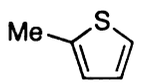
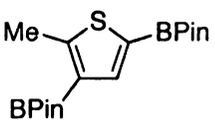
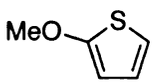
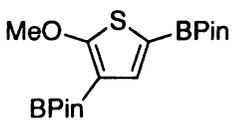
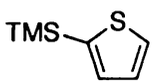
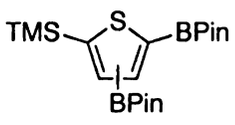
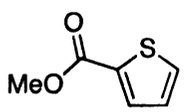
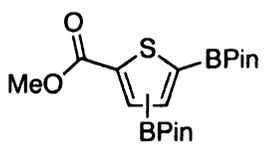


Table 3.4. Diborylation of 2-substituted thiophenes according to scheme 3.4.

Entry	Thiophene	HBPin equiv	Time (h)	Product	%yield
1		3	1	 **3.25**	88
2		2.5	12	 **3.26**	85
3		2.5	12	 **3.27**	92
4		3	72	 **3.28**	90
5		3	48	 **3.29**	89
6		3	72	 **3.30a + 3.30b**	–
7		3	36	 **3.31a + 3.31b**	–

The two boronic ester groups in these 3,5-diborylated thiophenes are chemically different. It might be possible that various C-B bond transformations, such as protolytic deborylation, fluorination, chlorination, bromination, iodination, cyanation, sulfonation,

Suzuki coupling etc., could selectively be carried out on the 5-BPin group, leading to new 3-BPin thiophene boronic esters as single regioisomers.

In the cases of 2-methyl thiophene and 2-methoxy thiophene, small amounts (1.5-1.6% by GC-FID) of a minor diborylated isomer were also observed. The GC-FID retention times of these minor diborylated isomers were different from those observed for diborylated products derived from 3-methyl/methoxy substituted thiophenes. Therefore the minor diborylated isomers observed for 2-methyl/methoxy substituted thiophenes could either be 4,5-diborylated or methyl/methoxy borylated products.

Attempted diborylation of 2-trimethylsilyl thiophene resulted in only 12% diborylation (by GC-FID) after 72 h at 60 °C. Similarly, attempted diborylation of methyl-2-thiophene carboxylate resulted in only 7% diborylation (mixture of two isomers in 63:37 ratio by GC-FID) after 36 h at room temperature. These results suggest that diborylation of 2-substituted thiophenes is only feasible when the 2-substituent is relatively small. It is important to mention here that diborylation in small 5-membered heterocyclic substrate such as methyl-2-furan-carboxylate did went to full conversion at room temperature in 24 h to give two regioisomeric diborylated products. Hence borylation *ortho* to bulky substituents such as BPin and ester is feasible in furans.

3-Substituted thiophenes can also be diborylated at 2- and 5-positions when the 3-substituent is nitrile, chloro, bromo, methyl, and *p*-tolyl (Scheme 3.5 and Table 3.5). 3-Trimethylsilyl thiophene went to only 18% diborylation after 48 h at 60 °C, while attempted borylation of 3-acetyl thiophene with 3 equivalents of HBPin resulted in reduction of the carbonyl group during diborylation.

It is worthwhile to note that during attempted diborylation of 2- and 3-trimethylsilyl thiophenes, formation of small amounts of B_2Pin_2 was observed from HBPin. Since the C–H activation step during these attempted diborylations is highly inhibited due to sterics; the side reaction of dehydrodimerization of HBPin becomes significant. Marder has also observed the dehydrodimerization of HBPin to B_2Pin_2 during benzylic borylation using $[RhCl(P^iPr_3)_2(N_2)]$ precursor catalyst.[33]

Scheme 3.5. Diborylation of 3-substituted thiophenes.

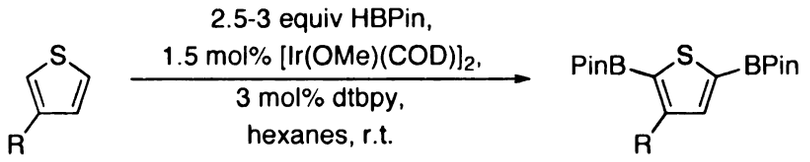
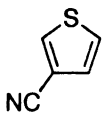
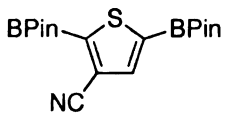
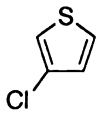
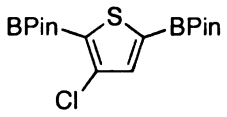
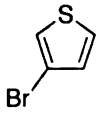
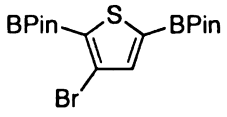
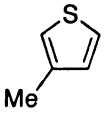
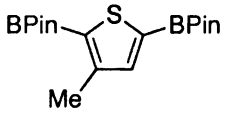
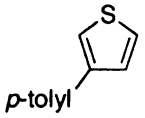
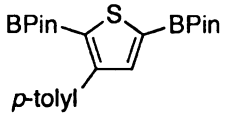
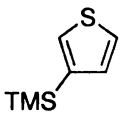
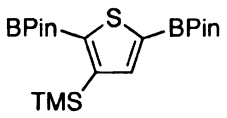
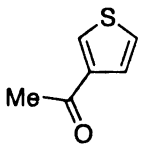
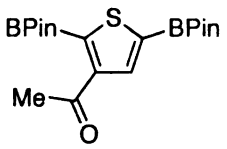


Table 3.5. Diborylation of 3-substituted thiophenes according to scheme 3.5.

Entry	Thiophene	HBPin equiv	Time (h)	Product		%yield
1		2.5	0.5		**3.32**	85
2		2.5	1		**3.33**	91
3		2.5	1		**3.34**	95
4		3	6		**3.35**	77
5		2.3	16		**3.36**	61
6		3	48		**3.37**	–
7		3	24		**3.38**	–

In 2,3,5-tri substituted thiophenes the 4-position is locked between two *ortho* substituents. Since the bond angles in 5-membered heterocycles are wider than those in 6-memebered rings, we thought that the 4-position in 2,3,5-tri substituted thiophenes might be accessible for borylation. However, only about 2% borylation was observed for 3-bromo-2,5-di-methylthiophene (**3.39**) under room temperature conditions using $[Ir(OMe)(COD)]_2$ and dtbpy. The outcome was the same with (Ind)Ir(COD) and dmpe at

150 °C. Apart from steric hindrance for borylation, the electron-rich nature of 3-bromo-2,5-di-methylthiophene could also be responsible for this low reactivity. Borylation of 3-bromo-2,5-di-chlorothiophene (**3.40**), an electron deficient substrate, was attempted using $[Ir(OMe)(COD)]_2$ and dtbpy at room temperature. The borylation stalled after about 5% conversion. The borylation of this substrate was also tested using (Ind)Ir(COD) and dmpe at 150 °C. The result was surprising as the single product obtained in 73% isolated yield was found to be 3-bromo-2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-thiophene **3.7** (Figure 3.1).

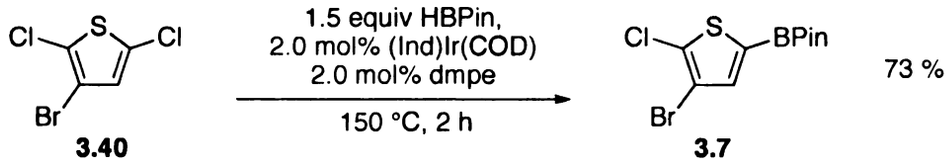


Figure 3.1. Attempted borylation of 3-bromo-2,5-di-chloro thiophene.

The product obtained here was found to be identical to one obtained by borylation of 3-bromo-2-chloro thiophene (Table 1, entry 7). The result was interesting for several reasons. Firstly, instead of a C–H bond, a C–Cl bond is activated by the Iridium catalyst. Secondly, the C–Cl bond was activated in preference to the C–Br bond. Finally, of the two C–Cl bonds, the sterically more accessible chloride was selectively substituted.

At least two pathways could account for the observed product. The first involves oxidative addition of C–Cl bond followed by reductive elimination of C–B bond. Another possibility is first reduction of C–Cl bond to C–H bond followed by rapid borylation. The mechanism of this reaction needs to be fully investigated.

Since 2,3,5-trisubstituted thiophenes could not be borylated to synthesize tetra-substituted thiophenes, we looked for other possible routes for the desired final

product. Borylation of 2,5-di substituted thiophene (Table 3.3) followed by bromination could also give the desired product. Although electrophillic aromatic C–H bromination of aryl boronic esters (to synthesize brominated aryl boronic esters) is unknown, there are examples where aryl/heteroaryl boronic acid have been brominated.[13,34,35] We were successful in brominating 2,5-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-thiophene (**3.18**) using one equivalent of Br_2 in $CHCl_3$ and the mono brominated product 3-bromo-2,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-thiophene (**3.41**) was isolated in 82% yield (Figure 3.2). Slight excess of bromine results in the bromination of methyl groups (without any displacement of the BPin group) and hence should be avoided.

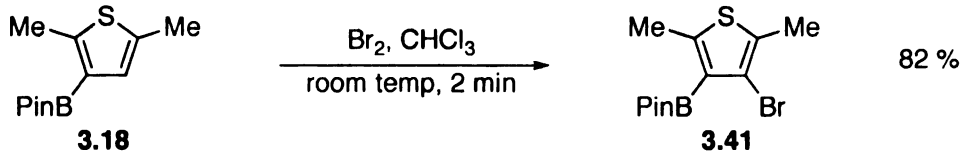
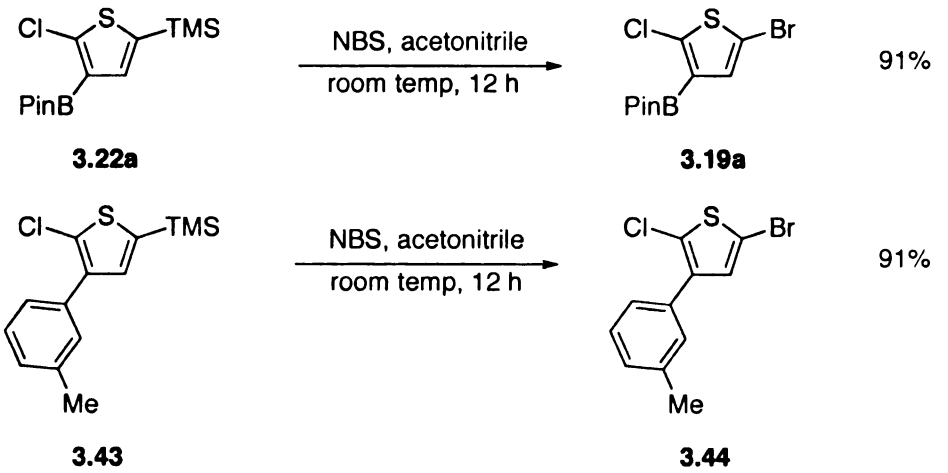


Figure 3.2. Bromination of thiophene boronic ester.

Attempted bromination of 2,5-di-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-thiophene (**3.16**) with Br_2 in $CHCl_3$ was ineffective even after 24 h at 100 °C. Bromination with NBS in acetonitrile[36] resulted in mixture of products including BPin substitution with Br (**3.40**) along with the desired C–H brominated product (**3.42**).

During our search for different routes for the desired tetra-substituted thiophene product of this substrate, we found that the 2-trimethylsilyl group can easily be replaced with Br using NBS in acetonitrile (Figure 3.3).



3.22a **3.19a** **3.43** **3.44**

Figure 3.3. Substitution of trimethylsilyl group with bromine.

As mentioned earlier, catalytic borylation of 2-chloro-5-bromothiophene gave a mixture of 3- and 4-borylated isomers in 67:33 ratio (**3.19a** and **3.19b**, Table 3.3). Pure 3-borylated isomer **3.19a** can be obtained by bromination of 2-chloro-3-BPin-5-trimethylsilylthiophene **3.22a** in 91% yield as shown in Figure 3.3. Trimethylsilyl group in 2-chloro-3-BPin-5-trimethylsilylthiophene **3.22a** was selectively substituted with bromine under these conditions while keeping the BPin group completely intact.

The intermediate thiophene boronic esters can be employed in subsequent Suzuki coupling without isolation as shown in Figure 3.4.

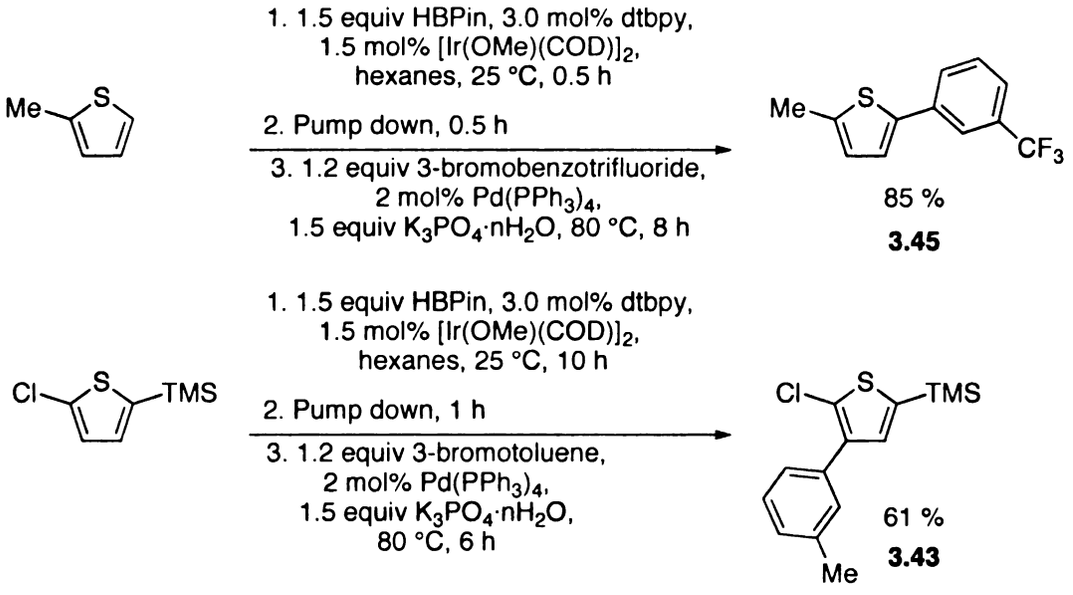


Figure 3.4. One-pot borylation Suzuki coupling of thiophenes.

Conclusion

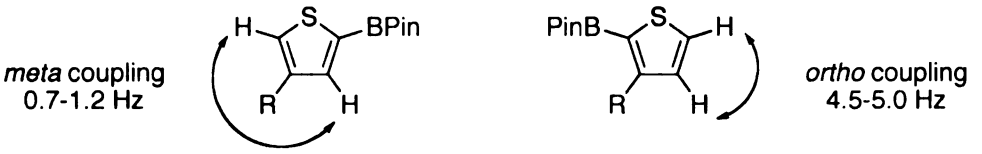
In conclusion, a variety of borylated di-, tri-, and tetra-substituted thiophenes have been prepared by iridium catalyzed aromatic borylation. Under appropriate conditions, selective electrophillic aromatic C–H bromination can be carried out on the thiophene boronic esters. Further studies regarding Suzuki coupling with heteroaryl halides, borylation of Suzuki coupled thiophenes, and electrophillic aromatic substitution (bromination, nitration, etc) of aryl/heteroaryl boronic esters needs to be extensively explored.

Experimental Details and Spectroscopic Data

Materials

Bis(η^4-1,5-cyclooctadiene)-di-μ-methoxy-diiridium(I) [Ir(OMe)(COD)]$_2$ and (η^5-indenyl)(cyclooctadiene)iridium(I) {(Ind)Ir(COD)} were prepared per the literature procedures.[37,38] Pinacolborane (HBPin) was generously supplied by BASF and was distilled before use. All commercially available chemicals were purified before use. Solid substrates were sublimed under vacuum. Liquid substrates were distilled before use. *n*-Hexane was refluxed over sodium, distilled, and degassed. Dimethoxy ethane (DME), ether, and tetrahydrofuran were obtained from dry stills packed with activated alumina and degassed before use. Silica gel (230-400 Mesh) was purchased from EMD™.

Regioisomer assignment of borylation products by ^{1}H NMR spectroscopy.



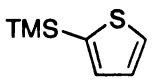
a **b**

From the ^{1}H NMR coupling constant *J*, the two regioisomer products obtained by the borylation of 3-substituted thiophenes can be distinguished unambiguously. In case of the 2,4-borylated product, the value of the four-bond (*meta*) coupling constant $^4J_{H-H}$ is usually around 0.7-1.2 Hz. While in case of the 2,3-borylated product, the value of the three-bond (*ortho*) coupling constant $^3J_{H-H}$ is usually around 4.5-5.0 Hz. Since these two ranges of coupling constants are quite far apart, the two regioisomers can easily be distinguished by the value of ^{1}H NMR coupling constant.

The regioisomeric assignments of borylated products of unsymmetrical 2,5-di-substituted thiophenes are based on ^{1}H NMR chemical shifts of the methine protons.

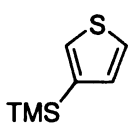
Syntheses of Substrates

a. 2-Trimethylsilylthiophene.



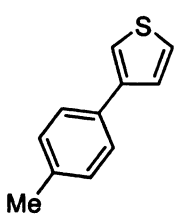
2-Trimethylsilylthiophene was prepared per the literature procedure.[39] The product was isolated as colorless oil (31-33 °C at 0.01 mm Hg, 2.62 g, 56% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.58 (dd, J = 4.6, 0.8 Hz, 1 H), 7.25 (dd, J = 3.3, 0.8 Hz, 1 H), 7.17 (dd, J = 4.6, 3.3, Hz, 1 H), 0.31 (s, 9 H, CH_3 of TMS); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 140.1 (C), 133.9 (CH), 130.4 (CH), 128.1 (CH), -0.01 (3 CH_3 of TMS).

b. 3-Trimethylsilylthiophene.



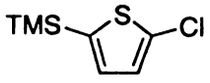
3-Trimethylsilylthiophene was prepared per the literature procedure.[40] The product was isolated as colorless oil (34 °C at 0.01 mm Hg, 1.77 g, 57% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42 (dd, J = 2.6, 1.1 Hz, 1 H), 7.38 (dd, J = 4.8, 2.6 Hz, 1 H), 7.17 (dd, J = 4.8, 1.1 Hz, 1 H), 0.25 (s, 9 H, CH_3 of TMS); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 141.2 (C), 131.39 (CH), 131.37 (CH), 125.6 (CH), –0.6 (3 CH_3 of TMS).

c. 3-*p*-Tolylthiophene.



3-*p*-Tolylthiophene was prepared by the Suzuki coupling of 3-bromothiophene and *p*-tolylboronic acid.[41] The product was isolated as a white solid (629 mg, 90% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47-7.50 (m, 2 H), 7.39-7.40 (m, 1 H), 7.37-7.36 (m, 2 H), 7.20-7.19 (m, 2 H), 2.36 (s, 3 H); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 142.3 (C), 136.8 (C), 133.1 (C), 129.4 (CH), 126.3 (2 CH), 126.0 (CH), 119.6 (CH), 21.1 (CH_3).

d. 2-Chloro-5trimethylsilylthiophene.



2-Chloro-5-trimethylsilylthiophene was prepared by following the literature procedure for the synthesis of 2-bromo-5-trimethylsilylthiophene.[42] The product was isolated as colorless oil (56-57 °C at 0.01 mm Hg, 2.61 g, 69% 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 (C), 134.5 (C), 133.3 (CH), 127.4 (CH), -0.3 (3 CH_3 of TMS); FT-IR (neat) $\tilde{\nu}$: 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 $C_7H_{11}ClSSi$: C, 44.07; H, 5.81. Found: C, 43.59; H, 5.90; HRMS (EI): *m/z* 190.0036 [M^+; Calcd for $C_7H_{11}ClSSi$: 190.0039].

Catalytic Borylation of Substituted Thiophenes

Borylation using d^{t}bpy Ligand

General Procedure A (Monoborylation with heteroaromatic substrate as the limiting reactant)

The [Ir] catalyst was generated by a modified literature protocol,[43] 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 (1.5 to 2 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 d^{t}bpy 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 scintillation vial 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 scintillation vial. Substituted thiophene (1 mmol, 1 equiv) was added to the scintillation vial. The reaction was stirred at room temperature and was monitored by GC-FID/MS. After completion of the reaction, the volatile materials were removed on a rotary evaporator. The crude material was dissolved in CH_2Cl_2 and passed through a short plug of silica to afford the corresponding borylated product.

General Procedure B (Monoborylation with HBPin as the limiting reactant)

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%). HBPin (1 mmol, 1 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 the 20 mL scintillation vial 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 scintillation vial. Excess 3-substituted thiophene (2-4 equiv) was added to the scintillation vial. The reaction was stirred at room temperature and was monitored by GC-FID/MS. After completion of the reaction, the volatile materials were removed on a rotary evaporator. The crude material was dissolved in CH_2Cl_2 and passed through a short plug of silica to afford the corresponding borylated isomeric mixture.

General Procedure C (Diborylation)

General procedure A was applied with 2.5-3 equivalents of HBPin.

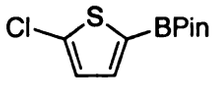
Borylation with Phosphine Ligand

General Procedure D

In a glove box, (Ind)Ir(COD) (8.3 mg, 0.02 mmol, 2.00 mol% Ir) and dmpe (3 mg, 0.02 mmol, 2.00 mol%) were weighed in two separate test tubes. HBPin (218 μL, 190 mg, 1.50 mmol, 1.50 equiv) was added to the dmpe test tube and the resulting solution was than mixed with (Ind)Ir(COD). This catalyst solution was added to a Schlenk flask equipped with a magnetic stirring bar. Substituted thiophene (1 mmol, 1 equiv) was added to the Schlenk flask. The Schlenk flask was closed, brought out of the glove box, and was heated at 150 °C in an oil bath. 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 dissolved in CH_2Cl_2 and passed through a short plug of silica to afford the corresponding borylated product.

Table 3.1. Monoborylation of 2-substituted thiophenes

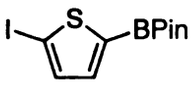
Table 3.1, Entry 1. 2-(5-chlorothiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.1).



3.1

The general procedure A was applied to 2-chlorothiophene (184 μL, 236 mg, 2 mmol, 1 equiv) and HBPin (348 μL, 307 mg, 2.40 mmol, 1.20 equiv) for 15 minutes. The product was isolated as colorless oil (476 mg, 97% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37 (d, J = 3.7 Hz, 1 H), 6.95 (d, J = 3.7 Hz, 1 H), 1.31 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 136.8 (C), 136.7 (CH), 127.6 (CH), 84.3 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.8; FT-IR (neat) $\tilde{\nu}$: 2980, 2932, 1530, 1433, 1352, 1334, 1282, 1271, 1142, 1035, 852, 804, 663 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 244 (100), 229 (17), 201 (21), 184 (17) 158 (12); Anal. Calcd for $C_{10}H_{14}BClO_2S$: C, 49.11; H, 5.77. Found: C, 49.12; H, 5.98.

Table 3.1, Entry 2. 2-(5-iodothiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.2).

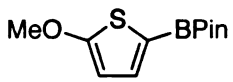


3.2

The general procedure A was applied to 2-iodothiophene (111 μL, 210 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 1 h. The product was isolated as a white solid (310 mg, 92% yield, mp 48-49 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27 (d, J = 3.5 Hz, 1 H), 7.25 (d, J = 3.5 Hz, 1 H), 1.31 (br s, 12

H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ 138.5 (CH), 138.3 (CH), 84.3 (2 C), 81.5 (C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.7; FT-IR (neat) $\tilde{\nu}_{max}$: 2978, 2932, 1522, 1418, 1314, 1267, 1142, 1064, 1018, 853, 663 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 336 (100), 321 (13), 250 (6), 236 (14), 209 (12), 167 (43); Anal. Calcd for $C_{10}H_{14}BIO_2S$: C, 35.75; H, 4.20. Found: C, 36.04; H, 4.24.

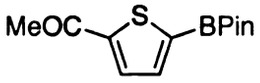
Table 3.1, Entry 3. 2-(5-methoxythiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.3).



3.3

The general procedure A was applied to 2-methoxythiophene (202 μL, 228 mg, 2 mmol, 1 equiv) and HBPin (348 μL, 307 mg, 2.40 mmol, 1.20 equiv) for 1 h. The product was isolated as colorless oil (395 mg, 82% yield). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.31 (d, J = 3.8 Hz, 1 H), 6.28 (d, J = 3.8 Hz, 1 H), 3.89 (s, 3 H, OCH_3), 1.31 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ 172.8 (C), 136.5 (CH), 106.1 (CH), 83.8 (2 C), 60.4 (OCH_3), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.0; FT-IR (neat) $\tilde{\nu}$: 3084, 2978, 2934, 2870, 1549, 1483, 1423, 1365, 1302, 1213, 1143, 989, 854, 781, 684, 661 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 240 (100), 225 (5), 197 (12), 180 (18); Anal. Calcd for $C_{11}H_{17}BO_3S$: C, 55.02; H, 7.14. Found: C, 54.72; H, 7.60.

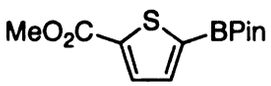
Table 3.1, Entry 4. 1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)ethanone (3.4).



3.4

The general procedure A was applied to 2-acetylthiophene (108 μL, 126 mg, 1 mmol, 1 equiv) and HBPin (175 μL, 154 mg, 1.20 mmol, 1.20 equiv) for 0.5 h. The product was isolated as a white solid (213 mg, 85% yield, mp 64-66 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 (d, J = 3.8 Hz, 1 H), 7.54 (d, J = 3.8 Hz, 1 H), 2.53 (s, 3 H, $COCH_3$), 1.31 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 190.6 (C=O), 149.4 (C), 137.2 (CH), 132.6 (CH), 84.6 (2 C), 27.4 ($COCH_3$), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.2; FT-IR (neat) $\tilde{\nu}$: 2980, 2934, 1669, 1520, 1348, 1288, 1267, 1142, 1020, 852, 667 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 252 (77), 237 (100), 209 (15), 195 (8), 179 (5), 166 (33), 153 (14) 137 (12) 109 (6); Anal. Calcd for $C_{12}H_{17}BO_3S$: C, 57.16; H, 6.80. Found: C, 56.88; H, 7.06.

Table 3.1, Entry 5. Methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (3.5).

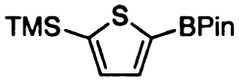


3.5

The general procedure A was applied to methyl-2-thiophenecarboxylate (116 μL, 142 mg, 1 mmol, 1 equiv) and HBPin (192 μL, 218 mg, 1.50 mmol, 1.50 equiv) for 0.5 h. The product was isolated as a white solid (252 mg, 94% yield, mp 114-117 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.79 (d, J = 3.7 Hz, 1 H), 7.53 (d, J = 3.7 Hz, 1 H), 3.87 (s, 3 H,

CO_2CH_3), 1.33 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR $\{^1H\}$ ($CDCl_3$, 125 MHz): δ 162.6 (C=O), 139.4 (C), 136.9 (CH), 133.9 (CH), 84.6 (2 C), 52.2 (CO_2CH_3), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.1; FT-IR (neat) $\tilde{\nu}$: 2970, 1719, 1527, 1354, 1248, 1145, 1097, 852, 832, 752, 665 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 268 (71), 253 (91), 237 (56), 182 (100); Anal. Calcd for $C_{12}H_{17}BO_4S$: C, 53.75; H, 6.39. Found: C, 53.44; H, 6.44.

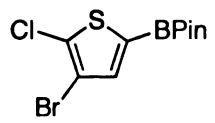
Table 3.1, Entry 6. Trimethyl(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)silane (3.6).



3.6

The general procedure A was applied to 2-trimethylsilylthiophene (312 mg, 2 mmol, 1 equiv) and HBPin (435 μL, 384 mg, 3.00 mmol, 1.50 equiv) for 0.5 h. The product was isolated as a white solid (523 mg, 93% yield, mp 61-62 °C). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.67 (d, J = 3.3 Hz, 1 H), 7.31 (d, J = 3.3 Hz, 1 H), 1.32 (br s, 12 H, 4 CH_3 of BPin), 0.30 (s, 9 H, 3 CH_3 of TMS); ^{13}C NMR $\{^1H\}$ ($CDCl_3$, 75 MHz): δ 148.4 (C), 137.8 (CH), 135.0 (CH), 84.0 (2 C), 24.8 (4 CH_3 of BPin), –0.1 (3 CH_3 of TMS); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.6; FT-IR (neat) $\tilde{\nu}$: 3054, 2980, 2957, 1514, 1435, 1346, 1331, 1259, 1250, 1142, 1072, 981, 841, 821, 758, 699 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 282 (14), 267 (100), 239 (31), 167 (8); Anal. Calcd for $C_{13}H_{23}BO_2SSi$: C, 55.31; H, 8.21. Found: C, 54.85; H, 8.74; HRMS (EI): *m/z* 282.1285 [(M^+); Calcd for $C_{13}H_{23}BO_2SSi$: 282.1281].

Table 3.1, Entry 7. 2-(4-bromo-5-chlorothiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.7).



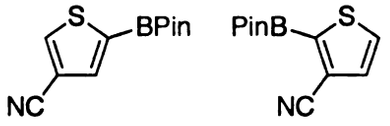
3.7

The general procedure A was applied to 2-chloro-3-bromothiophene (110 μL, 197 mg, 1 mmol, 1 equiv) and HBPin (192 μL, 218 mg, 1.50 mmol, 1.50 equiv) for 10 minutes. The product was isolated as a white solid (253 mg, 78% yield, mp 60-61°C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38 (s, 1 H), 1.30 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 138.9 (CH), 133.2 (C), 112.0 (C), 84.6 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.5; FT-IR (neat) $\tilde{\nu}$: 2980, 2932, 1523, 1425, 1340, 1267, 1142, 1041, 852, 661 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 324 (100), 322 (73), 309 (45), 281 (26), 264 (29), 243 (38); Anal. Calcd for $C_{10}H_{13}BBrClO_2S$: C, 37.13; H, 4.05. Found: C, 37.20; H, 4.16.

Note: Attempted borylation of 2,5-dichloro-3-bromothiophene with borylation procedure D also gave the same product where C-Cl bond was borylated and the single monoborylated product was isolated in 73% yield (see attempted monoborylation of tri-substituted thiophene). Only one of the two C-Cl bonds is activated with chemoselectivity greater than 99%. The NMR data matched with the borylated product of 2-chloro-3-bromothiophene as described above.

Table 3.2. Monoborylation of 3-substituted thiophenes

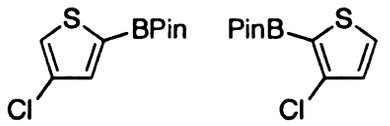
Table 3.2, Entry 1. Borylation of 3-cyanothiophene (3.8a + 3.8b).



47 **3.8a** 53 **3.8b**

The general procedure B was applied to 3-cyanothiophene (182 μL, 218 mg, 2.00 mmol, 2.00 equiv) and HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) for 1 h. The ratio of two monoborylated products at the end of reaction was 47:53 by GC-FID. The monoborylated product mixture was isolated as a white solid (126 mg, 54% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**3.8a**) 8.13 (d, J = 1.2 Hz, 1 H), 7.75 (d, J = 1.2 Hz, 1 H), 1.33 (br s, 12 H, 4 CH_3 of BPin), (**3.8b**) 7.62 (d, J = 4.9 Hz, 1 H), 7.38 (d, J = 4.9 Hz, 1 H), 1.36 (br s, 12 H, CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**3.8a**) 140.8 (CH), 138.1 (CH), 114.7 (C), 111.9 (C), 85.1 (2 C), 24.7 (4 CH_3 of BPin), (**3.8b**) 132.7 (CH), 131.3 (CH), 118.2 (C), 115.1 (C), 84.8 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.6; FT-IR (neat) $\tilde{\nu}$: 2980, 2231, 1429, 1319, 1142, 1039, 850, 628 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**3.8a**) M^+ 235 (7), 220 (100), 192 (9), 149 (37), 136 (15), (**3.8b**) M^{+1} 236 (100), 220 (78), 194 (51), 178 (33), 149 (36), 136 (31); Anal. Calcd for $C_{11}H_{14}BNO_2S$: C, 56.19; H, 6.00; N, 5.96. Found: C, 55.74; H, 5.99; N, 6.00.

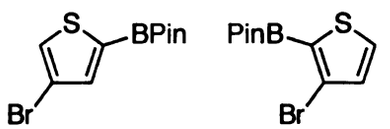
Table 3.2, Entry 2. Borylation of 3-chlorothiophene (3.9a + 3.9b).



78 **3.9a** 22 **3.9b**

The general procedure B was applied to 3-chlorothiophene (186 μL, 237 mg, 2.00 mmol, 2.00 equiv) and HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) for 1 h. The ratio of two monoborylated products at the end of reaction was 78:22 by GC-FID. The monoborylated product mixture was isolated as a white solid (160 mg, 66% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**3.9a**) 7.43 (d, J = 1.0 Hz, 1 H), 7.35 (d, J = 1.0 Hz, 1 H), 1.32 (br s, 12 H, 4 CH_3 of BPin), (**3.9b**) 7.51 (d, J = 5.0 Hz, 1 H), 7.01 (d, J = 5.0 Hz, 1 H), 1.34 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**3.9a**) 136.9 (CH), 131.8 (C), 126.7 (CH), 84.4 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.0; FT-IR (neat) $\tilde{\nu}$: 3107, 2980, 2932, 1522, 1421, 1356, 1336, 1142, 1026, 854, 665cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 244 (100), 246 (38), 231 (15), 229 (38), 209 (24), 158 (27); Anal. Calcd for $C_{10}H_{14}BClO_2S$: C, 49.11; H, 5.77. Found: C, 49.33; H, 5.81.

Table 3.2, Entry 3. Borylation of 3-bromothiophene (3.10a + 3.10b).

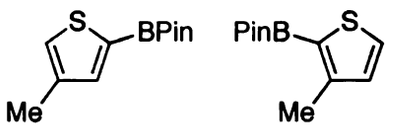


89 **3.10a** 11 **3.10b**

The general procedure B was applied to 3-bromothiophene (190 μL, 326 mg, 2.00 mmol, 2.00 equiv) and HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) for 1 h. The ratio of

two monoborylated products at the end of reaction was 89:11 by GC-FID. The monoborylated product mixture was isolated as a white solid (209 mg, 72% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**3.10a**) 7.49 (d, J = 1.2 Hz, 1 H), 7.46 (d, J = 1.2 Hz, 1 H), 1.32 (br s, 12 H, 4 CH_3 of BPin), (**3.10b**) 7.48 (d, J = 5.0 Hz, 1 H), 7.08 (d, J = 5.0 Hz, 1 H), 1.34 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**3.10a**) 139.3 (CH), 129.5 (CH), 111.2 (C), 84.4 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.0; FT-IR (neat) $\tilde{\nu}$: 2980, 1518, 1415, 1350, 1143, 1026, 852, 665 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**3.10a**) M^+ 289 (51), 290 (98), 288 (100), 275 (61), 273 (55), 247 (18), 245 (21), 230 (19) 204 (41), (**3.10b**) M^+ 289 (13), 290 (25), 288 (27), 275 (10), 273 (9), 209 (100), 189 (11), 167 (67); Anal. Calcd for $C_{10}H_{14}BBrO_2S$: C, 41.56; H, 4.88. Found: C, 41.74; H, 4.88.

Table 3.2, Entry 4. Borylation of 3-methylthiophene (3.11a + 3.11b).

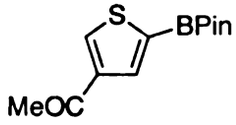


89 **3.11a** 11 **3.11b**

The general procedure B was applied to 3-methylthiophene (194 μL, 196 mg, 2.00 mmol, 2.00 equiv) and HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) for 1 h. The ratio of two monoborylated products at the end of reaction was 89:11 by GC-FID. The monoborylated product mixture was isolated as colorless oil (150 mg, 67% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**3.11a**) 7.42 (d, J = 0.7 Hz, 1 H), 7.17 (t, J = 1.1 Hz, 1 H), 2.27 (d, J = 0.5 Hz, 1 H), 1.32 (br s, 12 H, 4 CH_3 of BPin), (**3.11b**) 7.46 (d, J = 4.6 Hz, 1 H), 6.95 (d, J = 4.6 Hz, 1 H), 2.47 (s, 1 H), 1.30 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**3.11a**) 139.4 (CH), 138.9 (C), 128.0 (CH), 83.9 (2 C), 24.7

(4 CH_3 of BPin), 14.9 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.5; FT-IR (neat) $\tilde{\nu}$: 2978, 2930, 1550, 1441, 1371, 1327, 1302, 1271, 1143, 1028, 962, 854 665 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**3.11a**) M^+ 224 (100), 209 (27), 181 (18), 138 (44), (**3.11b**) M^+ 224 (100), 209 (68), 167 (64), 138 (54), 124 (61); Anal. Calcd for $C_{11}H_{17}BO_2S$: C, 58.95; H, 7.65. Found: C, 58.65; H, 8.09.

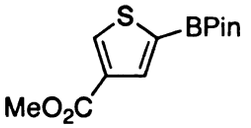
Table 3.2, Entry 5. 1-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-3-yl)ethanone (3.12a).



3.12a

The general procedure A was applied to 3-acetylthiophene (126 mg, 1 mmol, 1 equiv) and HBPin (174 μL, 154 mg, 1.20 mmol, 1.20 equiv) for 15 minutes. The product was isolated as colorless oil (206 mg, 82% yield). ^1H NMR ($CDCl_3$, 500 MHz): δ 8.26 (d, J = 1.1 Hz, 1 H), 8.00 (d, J = 1.1 Hz, 1 H), 2.50 (s, 3 H, $COCH_3$) 1.32 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ 192.0 (C=O), 143.8 (C), 138.1 (CH), 137.0 (CH), 84.5 (2 C), 27.8 ($COCH_3$), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.2; FT-IR (neat) $\tilde{\nu}$: 3098, 2980, 2934, 1680, 1530, 1448, 1381, 1373, 1340, 1305, 1215, 1143, 1024, 850, 667 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 252 (21), 237 (55), 209 (100), 195 (9), 153 (22), 137 (19); Anal. Calcd for $C_{12}H_{17}BO_3S$: C, 57.16; H, 6.80. Found: C, 56.77; H, 7.19.

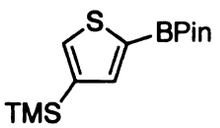
Table 3.2, Entry 6. Methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-3-carboxylate (3.13a).



3.13a

The general procedure A was applied to methyl 3-thiophenecarboxylate (121 μL, 142 mg, 1 mmol, 1 equiv) and HBPin (174 μL, 154 mg, 1.20 mmol, 1.20 equiv) for 1 h. The product was isolated as a white solid (256 mg, 95% yield, mp 84-85 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.31 (d, J = 1.0 Hz, 1 H), 8.01 (d, J = 1.0 Hz, 1 H), 3.84 (s, 3 H, CO_2CH_3) 1.33 (br s, 12 H, CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 163.1 (C=O), 138.8 (CH), 137.9 (CH), 134.9 (C), 84.4 (2 C), 51.6 (CO_2CH_3), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.4; FT-IR (neat) $\tilde{\nu}$: 3107, 2980, 2951, 1722, 1537, 1458, 1431, 1388, 1373, 1336, 1307, 1224, 1143, 1024, 987, 852, 752, 667 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 268 (65), 253 (100), 237 (22), 225 (39), 211 (29), 193 (12), 182 (45), 169 (41), 137 (27); Anal. Calcd for $C_{12}H_{17}BO_4S$: C, 53.75; H, 6.39. Found: C, 53.54; H, 6.66.

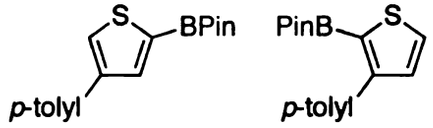
Table 3.2, Entry 7. Trimethyl(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-3-yl)silane (3.14a).



3.14a

The general procedure A was applied to 3-trimethylsilylthiophene (156 mg, 1 mmol, 1 equiv) and HBPin (174 μL, 154 mg, 1.20 mmol, 1.20 equiv) for 30 minutes. The product was isolated as a white solid (222 mg, 79% yield, mp 87-89 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71 (d, J = 1.0 Hz, 1 H), 7.69 (d, J = 1.0 Hz, 1 H), 1.33 (br s, 12 H, 4 CH_3 of BPin), 0.24 (s, 9 H, 3 CH_3 of TMS); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 142.4 (C), 141.9 (CH), 138.4 (CH), 83.8 (2 C), 24.6 (4 CH_3 of BPin), –0.6 (3 CH_3 of TMS); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.5; FT-IR (neat) $\tilde{\nu}$: 2980, 2955, 1510, 1410, 1325, 1263, 1250, 1143, 1105, 1028, 902, 852, 839, 754, 667 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 282 (7), 267 (100), 239 (2), 167 (7); Anal. Calcd for $C_{13}H_{23}BO_2SSi$: C, 55.31; H, 8.21. Found: C, 54.68; H, 8.47; HRMS (EI): *m/z* 282.1283 [(M^+); Calcd for $C_{13}H_{23}BO_2SSi$: 282.1281].

Table 3.2, Entry 8. Borylation of 3-*p*-tolylthiophene (3.15a + 3.15b).



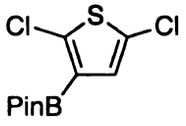
97 **3.15a** 3 **3.15b**

The general procedure B was applied to 3-*p*-tolylthiophene (192 mg, 1.1 mmol, 1.1 equiv) and HBPin (145 μL, 128 mg, 1.00 mmol, 1.00 equiv) for 1 h. The ratio of two monoborylated isomers at the end of reaction was 97:3 by GC-FID. The product was isolated as colorless oil (223 mg, 74 % yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.91 (d, J = 1.2 Hz, 1 H), 7.68 (d, J = 1.2 Hz, 1 H), 7.48-7.52 (m, 2 H), 7.17-7.20 (m, 2 H), 2.35 (s, 3 H, CH_3) 1.36 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 143.8 (C), 136.8 (C), 136.2 (CH), 132.9 (C), 129.5 (CH), 126.9 (CH), 126.4 (CH), 84.2 (2 C), 24.8 (4 CH_3 of BPin), 21.1 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.4; FT-IR (neat) $\tilde{\nu}$: 3090,

2978, 2928, 1547, 1441, 1379, 1371, 1329, 1311, 1269, 1143, 1026, 850, 819, 771, 667 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 300 (100), 285 (12), 214 (12); Anal. Calcd for $C_{17}H_{21}BO_2S$: C, 68.01; H, 7.05. Found: C, 68.54; H, 6.97; HRMS (EI): *m/z* 300.1360 [(M^+); Calcd for $C_{17}H_{21}BO_2S$: 300.1355].

Table 3.3. Monoborylation of 2,5-di-substituted thiophenes

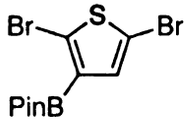
Table 3.3, Entry 1. 2-(2,5-Dichlorothiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.16).



3.16

The general procedure A was applied to 2-5-di-chlorothiophene (107 μL, 153 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 20 h. The product was isolated as a white solid (240 mg, 86% yield, mp 35-36 °C). ^1H NMR ($CDCl_3$, 500 MHz): δ 6.94 (s, 1 H), 1.30 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ 137.1 (C), 131.1 (CH), 126.2 (C), 84.0 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.5; FT-IR (neat) $\tilde{\nu}$: 2980, 1535, 1437, 1371, 1313, 1263, 1142, 1032, 966, 889, 848, 692 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 278 (100), 280 (68), 263 (32), 265 (22), 243 M-35 (79), 245 (30), 201 (51); Anal. Calcd for $C_{10}H_{13}BCl_2O_2S$: C, 43.05; H, 4.70. Found: C, 43.26; H, 4.74.

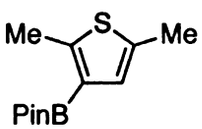
Table 3.3, Entry 2. 2-(2,5-Dibromothiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.17).



3.17

The general procedure A was applied to 2-5-di-bromothiophene (113 μL, 142 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) with 6 mol % [Ir] catalyst loading for 36 h. Additional 3 mol % [Ir] catalyst and 1 equiv of HBPin was added at this stage and the reaction was run for 12 more h at room temperature. The ratio of the starting material to product after 48 h was 11:89. The product was isolated as a white solid (206 mg, 56% yield, mp 72-73 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.09 (s, 1 H), 1.31 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 135.8 (CH), 121.9 (C), 110.9 (C), 84.0 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.5; FT-IR (neat) $\tilde{\nu}$: 2978, 1525, 1365, 1307, 1248, 1143, 991, 962, 883, 848, 690 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 368 (100), 370 (51), 366 (52), 353 (18), 287 (56), 289 (59), 268 (28), 208 (77), 166 (69); Calcd for $C_{10}H_{13}BBr_2O_2S$: C, 32.65; H, 3.56. Found: C, 32.92; H, 3.57.

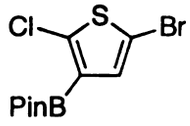
Table 3.3, Entry 3. 2-(2,5-Dimethylthiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.18).



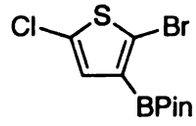
3.18

The general procedure D was applied to 2-5-di-methylthiophene (228 μL, 224 mg, 2 mmol, 1 equiv) and neat HBPin (435 μL, 384 mg, 3.00 mmol, 1.50 equiv) for 16 h at 150 °C. The product was isolated as a colorless semi solid (460 mg, 97% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.81 (d, J = 1.2 Hz, 1 H), 2.59 (s, 3 H, CH_3), 2.38 (d, J = 0.4 Hz, 3 H, CH_3), 1.30 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 150.8 (C), 136.1 (C), 130.7 (CH), 83.0 (2 C), 24.8 (4 CH_3 of BPin), 15.6 (CH_3), 14.7 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.3; FT-IR (neat) $\tilde{\nu}$: 2978, 2924, 1493, 1394, 1304, 1265, 1145, 868, 700 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 238 (100), 223 (8), 181 (37); Anal. Calcd for $C_{12}H_{19}BO_2S$: C, 60.52; H, 8.04. Found: C, 60.62; H, 8.18.

Table 3.3, Entry 4. Borylation of 2-bromo-5-chlorothiophene (3.19a + 3.19b).



67
3.19a



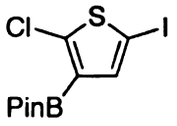
33
3.19b

The general procedure A was applied to 2-bromo-5-chlorothiophene (110 μL, 197 mg, 1 mmol, 1 equiv) and HBPin (290 μL, 256 mg, 2.00 mmol, 2.00 equiv) with 3% [Ir] catalyst loading for 8 h. Additional 3 % [Ir] and 0.5 equiv of HBPin was added and the reaction was run for 20 more h at room temperature. The ratio of the two monoborylated products at the end of reaction was 67:33 by GC-FID. The monoborylated product mixture was isolated as a white solid (281 mg, 87% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (**3.19a**) 7.10 (s, 1 H), 1.30 (br s, 12 H, 4 CH_3 of BPin), (**3.19b**) 6.94 (s, 1 H), 1.30 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**3.19a**) 139.6 (C), 134.9 (CH), 108.3 (C), 84.0 (2C), 24.8 (4 CH_3 of BPin), (**3.19b**) 132.0 (CH), 128.9 (C), 119.5

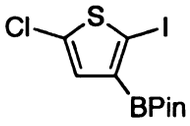
(C), 84.1 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.5; FT-IR (neat) $\tilde{\nu}$: 2980, 1527, 1427, 1371, 1253, 1140, 1028, 962, 848, 693 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): **(3.19a)** M^+ 324 (100), 322 (78), 289 (67), 287 (64), 208 (40), 166 (34), **(3.19b)** M^+ 324 (89), 322 (69), 309 (23), 245 (41), 243 (99), 203 (43), 201 (100), 166 (50); Anal. Calcd for $C_{10}H_{13}BBrClO_2S$: C, 37.13; H, 4.05. Found: C, 37.25; H, 4.05.

Note: The data for the pure major isomer **3.19a** is described in the bromination section of this supporting information.

Table 3.3, Entry 5. Borylation of 2-chloro-5-iodothiophene (3.20a + 3.20b).



85
3.20a

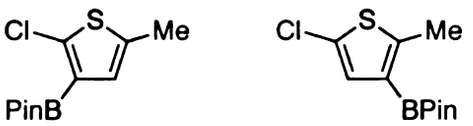


15
3.20b

The general procedure A was applied to 2-chloro-5-iodothiophene (122 mg, 0.5 mmol, 1 equiv) and HBPin (109 μL, 96 mg, 0.75 mmol, 1.50 equiv) for 20 h. The ratio of two monoborylated products at the end of reaction was 85:15 by GC-FID. The monoborylated product mixture was isolated as a white solid (165 mg, 89% yield). ^1H NMR ($CDCl_3$, 300 MHz): δ **(3.20a)** 7.31 (s, 1 H), 1.30 (br s, 12 H, 4 CH_3 of BPin), **(3.20b)** 6.87 (s, 1 H), 1.31 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ **(3.20a)** 143.4 (C), 142.3 (CH), 84.0 (2 C), 69.3 (C), 24.8 (4 CH_3 of BPin), **(3.20b)** 132.8 (CH), 84.2 (2 C), 81.1 (C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.3; FT-IR (neat) $\tilde{\nu}$: 2978, 1523, 1414, 1371, 1248, 1140, 1024, 966, 881, 848 690 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): **(3.20a)** M^+ 370 (100), 355 (13), 335 (29), 270 (25), 208 (15), 166 (11), **(3.20b)** M^+ 370 (100), 355 (10), 270 (24), 243 (13),

201 (32), 166 (21); Anal. Calcd for $C_{10}H_{13}BIClO_2S$: C, 32.42; H, 3.54. Found: C, 32.58; H, 3.38.

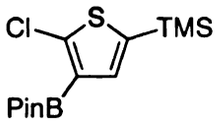
Table 3.3, Entry 6. Borylation of 2-chloro-5-methylthiophene (3.21a + 3.21b).



70 **3.21a** 30 **3.21b**

The general procedure A was applied to 2-chloro-5-methylthiophene (133 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 18 h. The ratio of two monoborylated products at the end of reaction was 70:30 by GC-FID. The monoborylated product mixture was isolated as a colorless semi solid (221 mg, 86% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**3.21a**) 6.77 (q, J = 1.2 Hz, 1 H), 2.35 (d, J = 1.2 Hz, 3 H, CH_3), 1.31 (br s, 12 H, 4 CH_3 of BPin), (**3.21b**) 6.95 (s, 1 H), 2.60 (s, 3 H, CH_3), 1.28 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**3.21a**) 137.4 (C), 137.0 (C), 130.1 (CH), 83.6 (2 C), 24.8 (4 CH_3 of BPin), 14.9 (CH_3), (**3.21b**) 151.1 (C), 131.6 (CH), 125.4 (C), 83.4 (2 C), 24.8 (4 CH_3 of BPin), 15.7 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.1; FT-IR (neat) $\tilde{\nu}$: 2980, 2926, 1556, 1475, 1390, 1371, 1309, 1257, 1143, 1026, 966, 898, 850, 696 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**3.21a**) 258 M^+ (100), 243 (17), 223 (51), 181 (36), 153 (37) (**3.21b**) 258 M^+ (100), 243 (18), 223 (7), 201 (93), 172 (23); Anal. Calcd for $C_{11}H_{16}BClO_2S$: C, 51.10; H, 6.24. Found: C, 51.66; H, 6.58; HRMS (EI): *m/z* 258.0653 [(M^+); Calcd for $C_{11}H_{16}BClO_2S$: 258.06526].

Table 3.3, Entry 7. (5-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)trimethylsilane (3.22a).



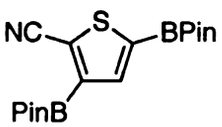
3.22a

The general procedure A was applied to 2-chloro-5-trimethylsilylthiophene (382 mg, 2 mmol, 1 equiv) and HBPin (435 μL, 384 mg, 3.00 mmol, 1.50 equiv) for 6 h. The single monoborylated product was isolated as a solid (589 mg, 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 (C), 139.42 (CH), 139.37 (C), 83.7 (2 C), 24.8 (4 CH_3 of BPin), –0.24 (3 CH_3 of TMS); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.1; FT-IR (neat) $\tilde{\nu}$: 2980, 1525, 1415, 1363, 1307, 1253, 1238, 1143, 993, 841, 758, 696 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity) 316 (33), 301 (100), 281 (6), 201 (15): M^+; Anal. Calcd for $C_{13}H_{22}BClO_2SSi$: C, 49.30; H, 7.00; Found: C, 49.16; H, 7.16.

Diborylation

Table 3.4. Diborylation of 2-substituted thiophenes

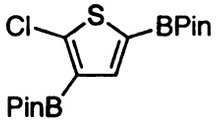
Table 3.4, Entry 1. 3,5-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carbonitrile (3.25).



3.25

The general procedure C was applied to 2-cyanoothiophene (94 μL, 109 mg, 1 mmol, 1 equiv) and HBPin (435 μL, 384 mg, 3.00 mmol, 3.00 equiv) for 1 h. The single diborylated product was isolated as a white solid (317 mg, 88% yield, mp 132-133 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (s, 1 H), 1.33 (br s, 12 H, CH_3 of BPin), 1.31 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 143.1 (CH), 123.2 (C), 114.3 (C), 84.8 (2 C), 84.6 (2 C), 24.8 (4 CH_3 of BPin), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.6; FT-IR (neat) $\tilde{\nu}$: 2980, 2934, 2220, 1531, 1458, 1373, 1319, 1138, 1030, 966, 848, 667 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 361 (73), 346 (53), 320 (100), 303 (31), 275 (24), 262 (29); Anal. Calcd for $C_{17}H_{25}B_2NO_4S$: C, 56.55; H, 6.98; Found: C, 56.45; H, 7.16.

Table 3.4, Entry 2. 2,2'-(5-Chlorothiophene-2,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (3.26).

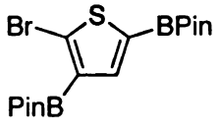


3.26

The general procedure C was applied to 2-chlorothiophene (92 μL, 118 mg, 1 mmol, 1 equiv) and HBPin (363 μL, 320 mg, 2.50 mmol, 2.50 equiv) for 12 h. The single diborylated product was isolated as a white solid (315 mg, 85% yield, mp 130-131 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.72 (s, 1 H), 1.30 (br s, 12 H, 4 CH_3 of BPin), 1.29 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 146.3 (C), 143.6 (CH), 84.2 (2 C), 83.8 (2 C), 24.8 (4 CH_3 of BPin), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.0; FT-IR (neat) $\tilde{\nu}$: 2976, 2928, 1539, 1456, 1371, 1340, 1309, 1140, 1042, 964, 851, 665 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 370 (100), 372 (40), 355 (46), 335

(85), 313 (21), 285 (39), 227 (52); Anal. Calcd for $C_{16}H_{25}B_2ClO_4S$: C, 51.87; H, 6.80; Found: C, 51.69; H, 7.00.

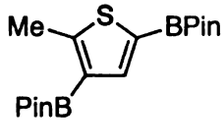
Table 3.4, Entry 3. 2,2'-(5-Bromothiophene-2,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (3.27).



3.27

The general procedure C was applied to 2-bromothiophene (97 μL, 163 mg, 1 mmol, 1 equiv) and HBPin (363 μL, 320 mg, 2.50 mmol, 2.50 equiv) for 12 h. The single diborylated product was isolated as a white solid (381 mg, 92% yield, mp 116-118 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 (s, 1 H), 1.30 (br s, 12 H, 4 CH_3 of BPin), 1.29 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 144.3 (CH), 129.3 (C), 84.2 (2 C), 83.8 (2 C), 24.8 (4 CH_3 of BPin), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.9; FT-IR (neat) $\tilde{\nu}$: 2978, 1537, 1452, 1327, 1140, 1026, 964, 850, 665 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 414 (100), 416 (97), 401 (22), 335 (71); Anal. Calcd for $C_{16}H_{25}B_2BrO_4S$: C, 46.31; H, 6.07; Found: C, 46.39; H, 6.06.

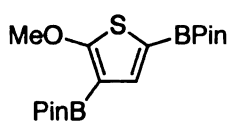
Table 3.4, Entry 4. 2,2'-(5-Methylthiophene-2,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (3.28).



3.28

The general procedure C was applied to 2-methylthiophene (97 μL, 98 mg, 1 mmol, 1 equiv) and HBPin (435 μL, 384 mg, 3.00 mmol, 3.00 equiv) for 72 h. The ratio of the two isomeric monoborylated products at the end of reaction was 98.5:1.5 by GC-FID (The GC-FID retention time of the minor diborylated isomer was different from the retention time of the single diborylated product of 3-methylthiophene). The product was isolated as a white solid (316 mg, 90% yield, mp 127-129 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.81 (s, 1 H), 2.68 (s, 3 H, CH_3), 1.29 (br s, 12 H, 4 CH_3 of BPin), 1.28 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 159.6 (C), 144.9 (CH), 83.8 (2 C), 83.2 (2 C), 24.9 (4 CH_3 of BPin), 24.7 (4 CH_3 of BPin), 15.9 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.5; FT-IR (neat) $\tilde{\nu}$: 2976, 1541, 1475, 1323, 1138, 1012, 844 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 350 (87), 335 (32), 293 (100), 264 (45), 250 (38); Anal. Calcd for $C_{17}H_{28}B_2O_4S$: C, 58.32; H, 8.06; Found: C, 57.96; H, 7.81.

Table 3.4, Entry 5. 2,2'-(5-Methoxythiophene-2,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (3.29).



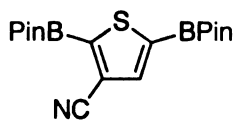
3.29

The general procedure C was applied to 2-methoxythiophene (101 μL, 114 mg, 1 mmol, 1 equiv) and HBPin (435 μL, 384 mg, 3.00 mmol, 3.00 equiv) for 48 h. The ratio of the two isomeric monoborylated products at the end of reaction was 98.6:1.4 by GC-FID (The GC-FID retention time of the minor diborylated isomer was different from the retention time of the single diborylated product of 3-methoxythiophene). The product was isolated as a white solid (324 mg, 89% yield, mp 110-112 °C). ^{1}H NMR ($CDCl_3$, 500

MHz): δ 7.68 (s, 1 H), 3.98 (s, 3 H, OCH_3), 1.282 (br s, 12 H, 4 CH_3 of BPin), 1.280 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ 181.5 (C), 143.8 (CH), 83.7 (2 C), 83.2 (2 C), 61.8 (OCH_3), 24.8 (4 CH_3 of BPin), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.3; FT-IR (neat) $\tilde{\nu}$: 2978, 1549, 1481, 1334, 1140, 1022, 968, 852, 663 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 366 (100), 352 (10), 324 (5), 282 (11), 250 (13); Anal. Calcd for $C_{17}H_{28}B_2O_5S$: C, 55.77; H, 7.71; Found: C, 55.41; H, 7.56.

Table 3.5. Diborylation of 3-substituted thiophenes

Table 3.5, Entry 1. 2,5-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-3-carbonitrile (3.32).

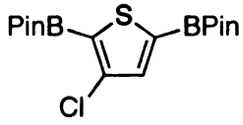


3.32

The general procedure C was applied to 3-cyanothiophene (91 μL, 109 mg, 1 mmol, 1 equiv) and HBPin (363 μL, 320 mg, 2.50 mmol, 2.50 equiv) for 0.5 h. The single diborylated product was isolated as a white solid (306 mg, 85% yield, mp 139 °C). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.80 (s, 1 H), 1.34 (br s, 12 H, 4 CH_3 of BPin), 1.31 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ 140.3 (CH), 118.8 (C), 115.2 (C), 85.1 (2 C), 84.8 (2 C), 24.7 (8 CH_3 of 2 BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.8; FT-IR (neat) $\tilde{\nu}$: 2980, 2936, 2230, 1525, 1373, 1269, 1138, 1055, 962, 850, 667 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 361 (70), 346 (45), 331 (28), 320 (100), 304 (80), 275 (39), 262 (51); Anal. Calcd for $C_{17}H_{25}B_2NO_4S$: C, 56.55; H, 6.98; Found: C,

55.78; H, 6.96; HRMS (FAB): *m/z* 362.1778 [(M^{+1}); Calcd for $C_{17}H_{26}B_2NO_4S$: 362.1768].

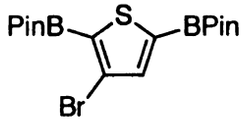
Table 3.5, Entry 2. 2,2'-(3-Chlorothiophene-2,5-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (3.33).



3.33

The general procedure C was applied to 3-chlorothiophene (93 μL, 118 mg, 1 mmol, 1 equiv) and HBPin (363 μL, 320 mg, 2.50 mmol, 2.50 equiv) for 1 h. The single diborylated product was isolated as a white solid (337 mg, 91% yield, mp 112-114 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45 (s, 1 H), 1.32 (br s, 12 H, 4 CH_3 of BPin), 1.30 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 138.3 (CH), 134.7 (C), 84.5 (2 C), 84.3 (2 C), 24.73 (4 CH_3 of BPin), 24.72 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.1; FT-IR (neat) $\tilde{\nu}$: 2980, 1516, 1383, 1348, 1307, 1140, 1041, 958, 853, 669 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 370 (57), 355 (38), 335 (100), 285 (40); Anal. Calcd for $C_{16}H_{25}B_2ClO_4S$: C, 51.87; H, 6.80; Found: C, 51.86; H, 6.88.

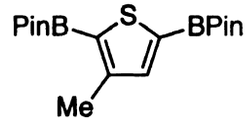
Table 3.5, Entry 3. 2,2'-(3-Bromothiophene-2,5-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (3.34).



3.34

The general procedure C was applied to 3-bromothiophene (95 μL, 163 mg, 1 mmol, 1 equiv) and HBPin (363 μL, 320 mg, 2.50 mmol, 2.50 equiv) for 1 h. The single diborylated product was isolated as a white solid (396 mg, 95% yield, mp 96-98 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.52 (s, 1 H), 1.32 (br s, 12 H, 4 CH_3 of BPin), 1.30 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 141.2 (CH), 119.9 (C), 84.5 (2 C), 84.3 (2 C), 24.73 (4 CH_3 of BPin), 24.71 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.9; FT-IR (neat) $\tilde{\nu}$: 2978, 1510, 1344, 1304, 1269, 1140, 1039, 958, 853, 667 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 415 (33), 416 (51), 414 (52), 401 (15), 399 (11), 335 (100), 249 (20), 193 (31); Anal. Calcd for $C_{16}H_{25}B_2BrO_4S$: C, 46.31; H, 6.07; Found: C, 46.32; H, 6.16.

Table 3.5, Entry 4. 2,2'-(3-Methylthiophene-2,5-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (3.35).

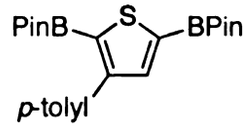


3.35

The general procedure C was applied to 3-methylthiophene (97 μL, 98 mg, 1 mmol, 1 equiv) and HBPin (435 μL, 384 mg, 3.00 mmol, 3.00 equiv) for 6 h. The product was isolated as a white solid (268 mg, 77% yield, mp 128-129 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43 (s, 1 H), 2.43 (s, 3 H, CH_3), 1.303 (br s, 12 H, 4 CH_3 of BPin), 1.302 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 149.3 (C), 140.6 (CH), 84.0 (2 C), 83.6 (2 C), 24.8 (4 CH_3 of BPin), 24.7 (4 CH_3 of BPin), 15.6 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.2; FT-IR (neat) $\tilde{\nu}$: 2978, 2932, 1537, 1387, 1373, 1332, 1311, 1290, 1267, 1140, 1060, 962, 854, 680, 669 cm^{-1}; GC-MS (EI) *m/z* (% relative

intensity): M^+ 350 (100), 335 (26), 292 (22), 264 (96) 250 (29); Anal. Calcd for $C_{17}H_{28}B_2O_4S$: C, 58.32; H, 8.06; Found: C, 58.34; H, 8.45.

Table 3.5, Entry 5. 2,2'-(3-*p*-Tolylthiophene-2,5-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (3.36).

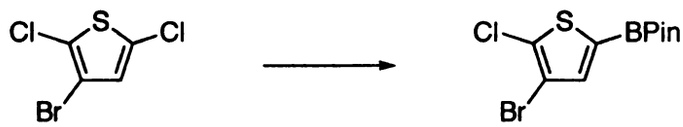


3.36

The general procedure C was applied to 3-*p*-tolylthiophene (174 mg, 1 mmol, 1 equiv) and HBPin (333 μL, 294 mg, 2.30 mmol, 2.30 equiv) for 16 hr. The product was isolated as colorless oil (260 mg, 61% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.73 (s, 1 H), 7.42-7.45 (m, 2 H), 7.12-7.15 (m, 2 H), 2.36 (s, 3 H, CH_3), 1.32 (br s, 12 H, 4 CH_3 of BPin), 1.27 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 152.2 (C), 139.6 (CH), 136.7 (C), 133.8 (C), 128.9 (2 CH), 128.4 (2 CH), 84.1 (2 C), 83.9 (2 C), 24.7 (4 CH_3 of BPin), 24.5 (4 CH_3 of BPin), 21.2 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.8; FT-IR (neat) $\tilde{\nu}$: 2978, 2932, 1537, 1473, 1373, 1331, 1309, 1261, 1140, 1037, 958, 854, 819, 669 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 426 (100), 340 (9), 310 (9); HRMS (FAB): *m/z* 426.2213 [(M^+); Calcd for $C_{23}H_{32}B_2O_4S$: 426.2207].

Attempted borylation of tri-substituted thiophene.

Borylation of 2-5-di-chloro-3-bromo-thiophene.



3.40 **3.7**

The general procedure D was applied to 2-5-di-chloro-3-bromo-thiophene (**3.40**) (232 mg, 1 mmol, 1 equiv) and neat HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 2 h at 150 °C. The product **3.7** was isolated as a colorless solid (233 mg, 73% yield). The spectroscopic data of this product matched with the data of borylated product obtained from 2-chloro-3-bromo-thiophene as described earlier.

Bromination

a. 2-(4-Bromo-2,5-dimethylthiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.41).

3.18 **3.41**

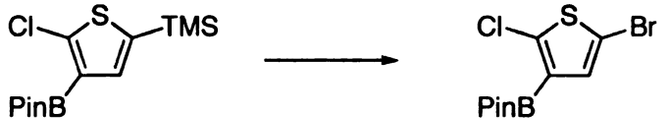
2-(2,5-dimethylthiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3.18**) (238 mg, 1 mmol, 1 equiv) was dissolved in 2 mL of $CHCl_3$ in a 20 mL scintillation vial equipped with a magnetic stirring bar. Bromine (160 mg, 1 mmol, 1 equiv, dissolved in 2 mL of $CHCl_3$) was added drop-wise during two minutes. The reaction was then quenched with water. The product was extracted with CH_2Cl_2 (3 × 20 mL) and dried over $MgSO_4$. Column chromatography (hexane/CH_2Cl_2 1:1, R_f 0.7) furnished the desired product as a white solid (260 mg, 82%, mp 55-56 °C). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.54 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 1.32 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ 147.9 (C), 131.2 (C), 113.1 (C), 83.5 (2 C), 24.8 (4 CH_3 of BPin), 16.2 (CH_3), 14.5 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.5; FT-IR (neat) $\tilde{\nu}$: 2978, 2922, 1537, 1377, 1315, 1234, 1143, 852 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 317 (46), 318

(84), 316 (81), 303 (11) 301 (10), 261 (100), 259 (99), 237 927), 195 (38), 180 (41); Anal. Calcd for $C_{12}H_{18}BBrO_2S$: C, 45.46; H, 5.72. Found: C, 45.54; H, 5.91.

General Procedure E (Substitution of TMS with Br)

TMS group was replaced with Bromine by employing the literature conditions used for aromatic bromination.[8] Substrate (1 mmol, 1 equiv) was added to a 20 mL scintillation vial equipped with a magnetic stirring bar. N-bromosuccinamide (1 mmol, 1 equiv) was added in to the vial. Acetonitrile (3-5 mL) was also added to the vial. The reaction mixture was stirred at room temperature and was monitored by GC-FID/MS. After the completion of the reaction, the volatile materials were removed on a rotary evaporator and the crude product was passed through a short silica plug to afford the brominated product.

b. 2-(5-Bromo-2-chlorothiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.19a).

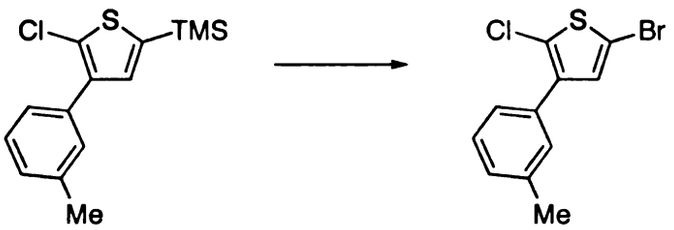


3.22a **3.19a**

The general procedure E was applied to (5-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)trimethylsilane **3.22a** (317 mg, 1 mmol) for 12 h. The product was isolated as a white solid (295 mg, 91%, mp 51-53 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.10 (s, 1 H), 1.30 (br s, 12 H, CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 139.6 (C), 134.9 (CH), 108.3 (C), 84.1 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.5; FT-IR (neat) $\tilde{\nu}$: 2978, 1530, 1427, 1373, 1311, 1253, 1142, 1028, 962, 848, 883, 848, 692 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 323 (48),

324 (100), 322 (81), 309 (21), 307 (14), 289 (38), 287 (36) 208 (23), 166 (22); Anal. Calcd for $C_{10}H_{13}BBrClO_2S$: C, 37.13; H, 4.05; Found: C, 37.25; H, 4.19.

c. 5-Bromo-2-chloro-3-*m*-tolylthiophene (3.44).

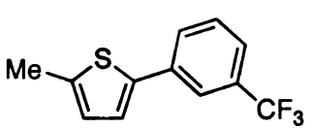


3.43 **3.44**

The general procedure E was applied to (5-chloro-4-*m*-tolylthiophen-2-yl)trimethylsilane (**3.43**) (280 mg, 1 mmol) for 12 h. The product 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, CH_3); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 139.3 (C), 138.2 (C), 133.1 (C), 131.2 (CH), 129.1 (CH), 128.8 (CH), 128.4 (CH), 125.5 (CH), 124.0 (C), 108.3 (C), 21.4 (CH_3); FT-IR (neat) $\tilde{\nu}$: 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 $C_{11}H_9BrClS$: C, 45.94; H, 2.80; Found: C, 45.96; H, 2.79.

One-Pot borylation/Suzuki coupling of substituted thiophenes

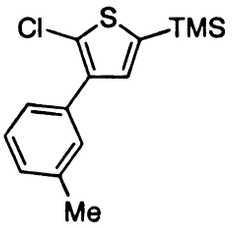
a. 2-Methyl-5-(3-(trifluoromethyl)phenyl)thiophene (3.45).



3.45

The general borylation procedure A was applied to 2-methylthiophene (484 μL, 491 mg, 5 mmol, 1 equiv) and HBPin (870 μL, 768 mg, 6.00 mmol, 1.20 equiv) in a Schlenk flask for 0.5 h. The reaction mixture was pumped down under high vacuum for 0.5 h to remove the volatile materials. $Pd(PPh_3)_4$ (116 mg, 0.10 mmol, 2 mol%), 3-bromo-benzotrifluoride (837 μL, 1350 mg, 6.00 mmol, 1.2 equiv), and DME (6 mL) were added to the Schlenk flask inside the glove box. The Schlenk flask was then brought out of the glove box and attached to a Schlenk line. $K_3PO_4 \cdot nH_2O$ (1592 mg, 1.50 equiv) was added under N_2 counter flow to the Schlenk flask. The flask was stoppered and the mixture was heated at 80 °C for 8 h. The flask was cooled down to room temperature and 20 mL of water were added to the reaction mixture. The reaction mixture was extracted with ether (3 × 20 mL). The combined ether extractions were washed with brine (20 mL), followed by water (10 mL), dried over $MgSO_4$ before being concentrated under reduced pressure on a rotary evaporator. Column chromatography (hexanes, R_f 0.5) furnished the product as white semi solid (1026 mg, 85% yield). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.77 (t, J = 0.8 Hz, 1 H), 7.68 (d, J = 7.6 Hz, 1 H), 7.42-7.48 (m, 2 H), 7.15 (d, J = 3.5 Hz, 1 H), 6.73-6.75 (m, 1 H), 2.51 (s, 3 H, CH_3); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ 140.7 (C), 140.1 (C), 135.5 (C), 131.2 (q, $^2J_{C\text{-}F}$ = 32.6 Hz, C), 129.3 (CH), 128.5 (CH), 126.4 (CH), 124.1 (q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 124.0 (CH), 123.4 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, CH), 122.0 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, CH), 15.4 (CH_3); FT-IR (neat) $\tilde{\nu}$: 3073, 2922, 2865, 1497, 1340, 1325, 1165, 1126, 1074, 790, 694 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 242 (100), 223 (4), 173 (6); Anal. Calcd for $C_{12}H_9F_3S$: C, 59.49; H, 3.74; Found: C, 59.38; H, 3.56.

b. (5-Chloro-4-*m*-tolylthiophen-2-yl)trimethylsilane (3.43).



3.43

The general borylation procedure A was applied to 2-chloro-5-trimethylsilylthiophene (382 mg, 2 mmol, 1 equiv) and HBPin (435 μL, 384 mg, 3.00 mmol, 1.50 equiv) in a Schlenk flask for 10 h. The reaction mixture was pumped down under high vacuum for 1 h to remove the volatile materials. $Pd(PPh_3)_4$ (46 mg, 2 mol %), 3-bromo-toluene (291 μL, 410 mg, 2.40 mmol, 1.2 equiv), and DME (3 mL) were added to the Schlenk flask inside the glove box. The Schlenk flask was then brought out of the glove box and attached to a Schlenk line. $K_3PO_4 \cdot nH_2O$ (637 mg, 1.50 equiv) was added under N_2 counter flow to the Schlenk flask. The flask was stoppered and the mixture was heated at 80 °C for 6 h. The flask was cooled down to room temperature and 10 mL of water were added to the reaction mixture. The reaction mixture was extracted with ether (3 × 10 mL). The combined ether extractions were washed with brine (10 mL), followed by water (10 mL), dried over $MgSO_4$ before being concentrated under reduced pressure on a rotary evaporator. Column chromatography (hexanes, R_f 0.5) furnished the product as a colorless liquid (369 mg, 66% yield). ^1H 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 $\{^1H\}$ ($CDCl_3$, 75 MHz): δ 139.6 (C), 138.2 (C), 138.0 (C), 135.3 (CH), 134.3 (C), 129.3 (C), 129.1 (CH), 128.29 (CH), 128.27 (CH), 125.6 (CH), 21.5 (CH_3), –0.3 (3 CH_3 of TMS); FT-IR (neat) $\tilde{\nu}$: 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.

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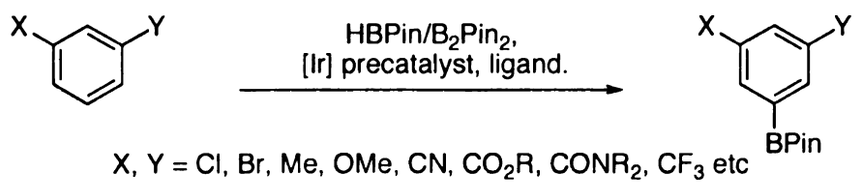
CHAPTER 4

Bisoxazoline Ligands in Iridium Catalyzed Aromatic C-H Activation/ Borylation

Introduction

Selective functionalization of hydrocarbons represents one of the most challenging problems in homogeneous and heterogeneous catalysis. Recently transition metal catalyzed selective C–H activation-functionalization into valuable functional groups such as C–O, C–N, C–Halogen bonds has emerged as a useful tool for this purpose.[1] In 1999, Iverson and Smith reported the first thermal catalytic aromatic C–H activation borylation.[2] Since then, iridium catalyzed aromatic borylation has emerged as the most convenient methodology for the regioselective functionalization of aromatic and heteroaromatic hydrocarbons.[3-19] Several common functional groups such as halogens, ester, amide, nitrile, etc. are tolerated in this methodology. However, the most striking feature of this new tool available to the synthetic chemist is that the regioselectivities are governed by sterics.[3,5,7,11] Hence, C–H borylations complement electrophillic aromatic substitutions[20] and directed *ortho* metalations.[21,22] Excellent selectivity is generally observed in 1,3-di-substituted arenes, which are borylated at the 5-position (Scheme 4.1). This unique feature allows for the synthesis of new aromatic building blocks, which were previously either unknown or difficult to synthesize.[6,7,19]

Scheme 4.1. Regioselective iridium catalyzed aromatic borylation.



Since the first report of this reaction by our group in 1999, the main focus of research in this field has been to improve the selectivity (for aromatic C–H bond activation vs. aromatic C–Halogen or benzylic C–H bond activation) and activity of the catalyst system. Several ligands have been employed for this purpose. These include phosphines such as dmpe or dppe,[5] bpy/dtbpy,[11] pyridine-imine,[23] tris(pyrazolyl)boarte,[24] carbenes,[25] and salicylaldimine.[26] However no attempt has been made to improve the regioselectivities when mixtures of regioisomers are obtained.

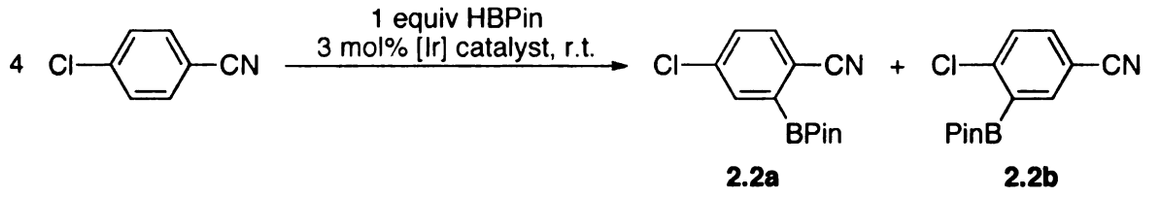
Borylations of 1,3- and symmetric 1,2-di-subsituted benzenes are the most selective since both substrate classes have C-H sites whose flanking carbon-substituents are hydrogen. Borylation of symmetric 1,4-substituted benzene also results in a single regioisomer. However, borylations of unsymmetric 1,4-/1,2-di-substituted benzenes, and 2,5-di-substituted 5-membered heterocycles are more varied in their outcomes.

Good selectivity in borylation of unsymmetric 1,4-substituted benzenes can be observed when the steric demands of the two substituents are quite different. For example, when one of the two substituents in 1,4-substituted benzene is either F or CN, high selectivity for borylation *ortho* to these substituents is feasible.[6,7] In case of CN, we have reported that although greater than 99% selectivity is possible when the second substituent is large such as ester, amide, iodo, or trifluoromethyl; the selectivity decreases when the second substituent has steric demand smaller such as to bromo or methyl. Selectivities are also decreased in going from 1,4-di-substituted arene to 2,5-di-substituted 5-membered heterocycles (with identical substituents) due to the opening of bond angle.[7] We became interested to determine if it is possible to improve the differentiation between the two substituents on the arene based on their sterics.

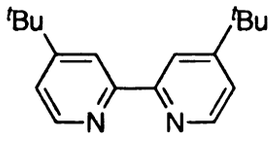
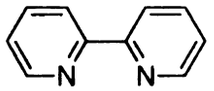
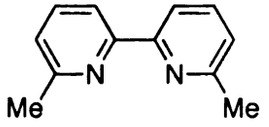
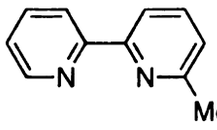
Results and Discussion

4-Chloro benzonitrile was chosen as a test substrate as its borylation using dtbpy ligand gives an 80:20 mixture of two regioisomers as shown in Scheme 4.2.[7] Since regioselectivities in iridium-catalyzed borylation are governed by sterics, we conjectured that increasing the steric bulk on the ligand closer to the iridium metal center might improve the selectivity. Borylation using 6,6`-di-methyl-bipyridyl ligand **4.1** was very slow and the selectivity was almost identical to that for dtbpy. Probably the presence of two methyl groups has halted the catalytic activity. Reducing the steric bulk to only one Me group in 6`-methyl-bipyridyl **4.2** also did not improve the selectivity under these conditions.

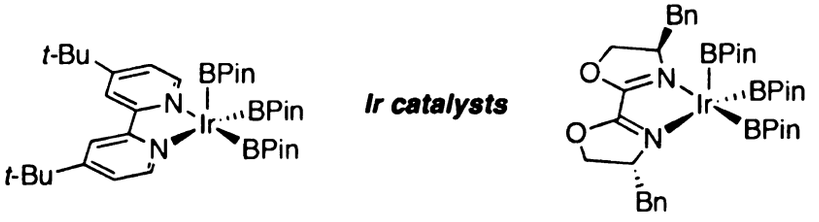
Scheme 4.2. Regioselectivity in borylation of 4-chloro benzonitrile.



2.2a **2.2b**

Ligand		2.2a	2.2b	Time
	**1.23**	80	20	48 h complete
	**1.22**	80	20	48 h complete
	**4.1**	81	19	48 h, ~ 3% conversion
	**4.2**	77	23	48 h, ~ 10% conversion

The observed no effect in regioselectivities upon modifying the bpy based ligand can be understood by examining the proposed active catalyst in this reaction. The proposed active catalysts in the iridium catalyzed aromatic borylation are 5-coordinate, 16 electron, bi-dentate ligated iridium tris-boryl complexes such as **4.3** shown in Figure 4.1.[5,16]



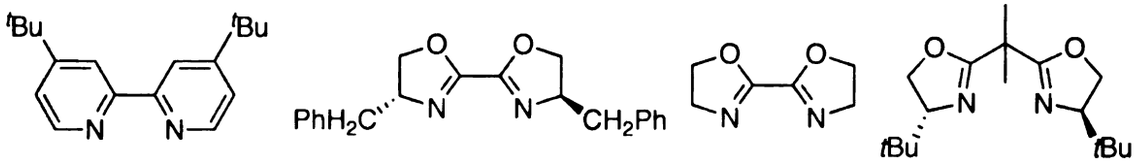
4.3 **4.4**

Figure 4.1. Proposed iridium catalysts for aromatic borylation.

The incoming arene substrate approaches from the bottom of the proposed complex. From Figure 4.1, it is clear that the presence of methyl groups on the 6-position of bipyridine derived ligand will only increase the steric bulk in the plane of bpy ligand and will not assist in differentiating between the two substituents on the incoming arene substrate. During our early studies on different ligands for aromatic borylation, we noticed that di-imine type ligands, derived from the condensation of bi-napthyl-di-amine and appropriate ketone, were effective for aromatic borylation at elevated temperatures. Considering the apparent similarity in bpy and di-ketimine type ligands, we looked for other ligands that contain the di-imine core but on which the steric bulk can be varied above and/or below the plane of the ligand. Substituted bis-oxazoline ligands fulfill both of these requirements. The 2-substituent in a bis-oxazoline type ligand will be above or below the plane of ligand as it is on an sp^3 hybridized carbon. As shown in Figure 4.1, one of the 2-substituent on the bis-oxazoline ligand in the proposed active catalyst **4.4**

should be pointing towards the incoming substrate, which might result in better differentiation between the two substituents on the arene ring.

Although bis-oxazoline derived ligands have extensively been employed in several types of reactions, they have not been tested in aromatic borylation. We decided to investigate borylation of aromatic substrates using these ligands (Figure 4.2).



1.23 **4.5** **4.6** **4.7**

Figure 4.2. Bidentate di-imine based ligands used for aromatic borylation.

Borylation of 3-chlorobenzotrifluoride was attempted with 2,2′-bis[(4S)-4-benzyl-2-oxazoline] (**4.5**). To our delight, the reaction was complete in 48 h at room temperature using 3 mol % **4.5**/[Ir(OMe)COD]$_2$, and the borylated product was isolated in 82% yield (Figure 4.3).

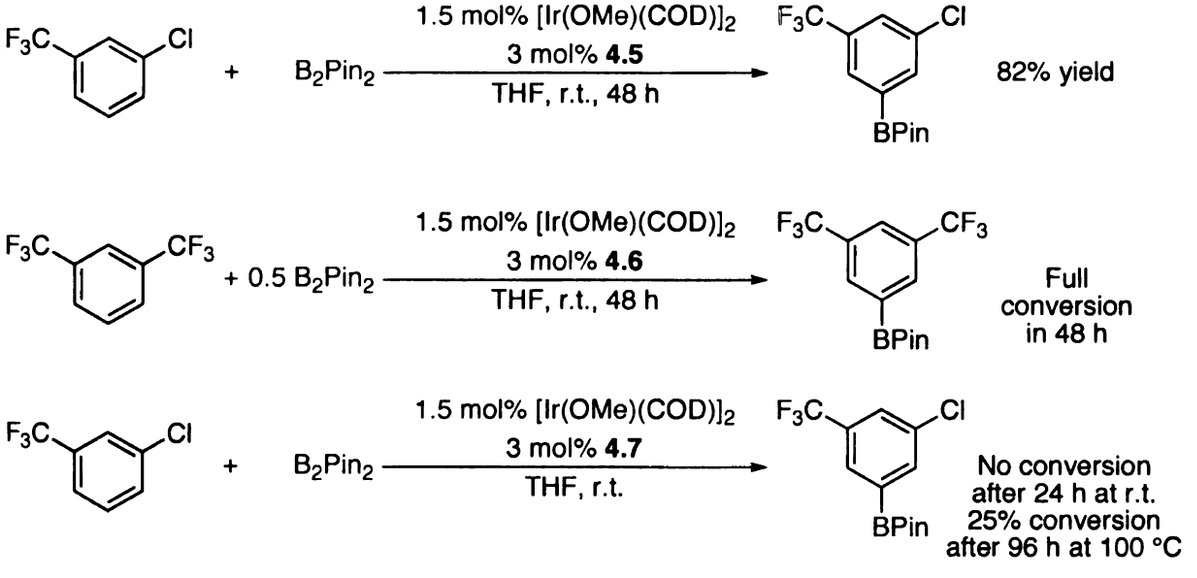


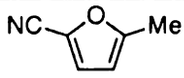
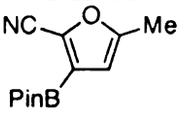
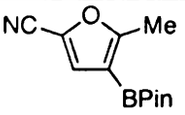
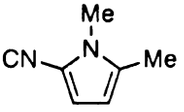
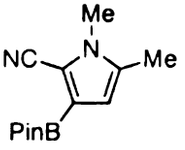
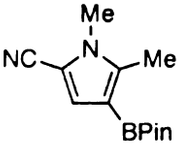
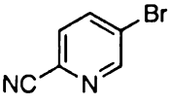
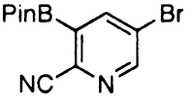
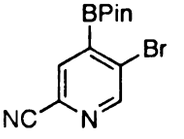
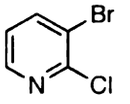
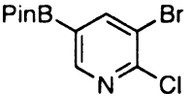
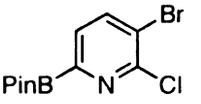
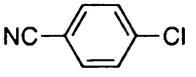
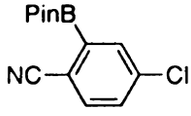
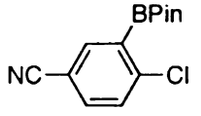
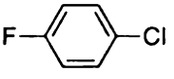
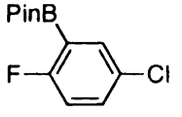
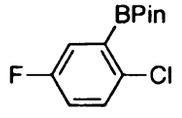
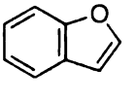
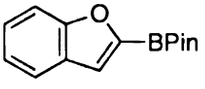
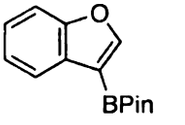
Figure 4.3. Aromatic borylation with bisoxazoline ligands.

Borylation was also possible with unsubstituted 2,2′-bis(2-oxazoline) (**4.6**). The reaction time for heteroaromatic substrates was even less than that for aromatic substrates. Increasing the carbon backbone in 2,2-isopropylidene-bis(4-*tert*-butyl-2-oxazoline) (**4.7**) was not helpful as no catalytic borylation of 3–chlorobenzotrifluoride was observed at room temperature. This indicated the importance of appropriate bite angle for better catalytic activity. It is worthwhile to mention that in the above mentioned reactions, the catalyst was not pre-generated by first mixing $[Ir(OMe)(COD)]_2$ with HBPin, which may have resulted in low activity. Still, these results were encouraging, as only bpy based ligands were previously known to catalyze aromatic borylation at ambient temperatures.

Borylation of 4-chlorobenzonitrile was attempted and we were pleased to observe that the regioselectivity was improved from 80:20 with **1.23** to 93:7 using **4.5**. Unsubstituted bisoxazoline ligand **4.6** gave selectivity of 84:16 under these conditions. It seems that the presence of benzyl groups on the 2-position in **4.5** (vs. **4.6**) is helpful in differentiating the two substituents on the arene substrate.

We next examined borylation of other substrates where mixtures of regioisomers were observed. The results are presented in Table 4.1. For reference the regioselectivities using dtbpy ligand are also included.

Table 4.1. Borylation regioselectivities for **4.5** vs. dtbpy (**1.23**).[a]

Entry	Substrate	Products **a**	Products **b**	**4.5** Ratio **a** : **b** %yield, Time (h), Boron equiv	**1.23** Ratio **a** : **b** %yield, Time (h), Boron equiv
1		 **2.25a**	 **2.25b**	> 99:1[b] 96, (2) 1.5	85:15 95, (0.5) 1.5
2		 **2.24a**	 **2.24b**	97:3[b] 66, (72)[c] 3	85:15 80, (16) 1.5
3		 **2.27a**	 **2.27b**	93:7[b] 85, (6) 1.5	67:33 81, (18) 2
4		 **4.8a**	 **4.8b**	75:25[d] 79, (64)[e] 1.5	87:13[d] –[f], (16) 1.5
5[g]		 **2.2a**	 **2.2b**	93:7[b] 60, (36) 0.25	80:20 76, (36) 0.25
6[g]		 **4.9a**	 **4.9b**	99.4:0.6[h] 83, (6) 0.25	97.2:2.8[h] 68, (4) 0.25
7		 **4.10A**	 **4.10B**	> 99.4:0.6[i] 93, (1) 1.2	97.5:2.5[i] 82, (0.5) 1.2

[a]Unless otherwise noted, all reaction were carried out at room temperature with 3 mol% [Ir]/**4.5** catalyst loading and 1.2-1.5 equiv of HBPin. Yields are based on substrate. Ratios were determined by GC-FID in crude reaction mixture upon completeion of reaction. [b]Regioisomer assignment is based on ref. 7. [c]Reaction was run by pre generating the catalystusing 0.2 equiv HBPin, 3 mol% $[ir(OMe)(COD)]_2$, and 6 mol% **4.5**. 1 equiv of B_2Pin_2 was used as the boron source. About 80% conversion was observed after 48 h at r.t., after which additional 1.5 mol% $[ir(OMe)(COD)]_2$, 3 mol% **4.5**, and 1 equiv HBPin were added. Reaction was complete after 72 h.[d]See experimental section for regioismer assgnment by 2D NMR. [e]Reaction started with 3 mol% $[Ir(OMe)(COD)]_2$, 3 mol% **4.5** and 1.5 equiv HBPin. After 30 h, additional 1.5 mol% $[Ir(OMe)(COD)]_2$ was added and the reaction was complete after 64 h. [f]Reaction went to full conversion, however no attempt was made to isolate the product. [g]Yields are based on HBPin. [h]Regioisomer assgnment of major isomer is based on ^{13}C NMR. [i]Regioismer assgnment is based on ref. 12 and 10.

Borylation of unsymmetric 2-cyano-5-methyl furan was found to be highly selective with greater than 99% regioselectivity for functionalization adjacent to smaller cyano group. This selectivity was much better than that for **1.23**, which was 85:15.[7] Although borylation of 2-cyano-5-methyl furan with **4.5** was complete in less than 2 h, borylation of more electron rich substrate, 2-cyano-1,5-di-methyl-pyrrole, with this ligand was very sluggish at room temperature. Here 9 mol% [Ir]/**4.5** was required for full conversion in 64 h. Despite its low reactivity, **4.5** was more selective (97:3) as compare to **1.23** (85:15).[7]

For 2-cyano-4-bromopyridine, where the two substituents are *para* to each other, the regioselectivity was found to be 93:7 using **4.5**. This selectivity was much better than that for dtbpy, which was 67:33.[7] The selectivity for this substrate using **4.6** was 78:22. This indicates that the presence of benzyl groups on the bisoxazoline ligand results in better steric differentiation between the bromo and cyano substituents in the substrate. Similar selectivities for borylation of 4-chlorobenzonitrile and 2-cyano-4-bromopyridine using **4.5** indicate a slight electronic preference for borylation at the 4-position of pyridine.

It has been reported that the borylation of unsubstituted pyridine takes place at 3- and 4-positions with statistical 67:33 selectivity.[12] The absence of any borylation at the 2-position is considered to be due to the possible adduct formation between pyridine and borane (however the ^{11}B NMR indicates no interaction between HBPin and pyridine). As a consequence, borylation of 3-substituted or 2,3-di-substituted pyridine should selectively take place at the 5-position. Surprisingly, borylation of 2-chloro-3-bromopyridine with [Ir]/dtbpy catalyst system gave a mixture of two

regioisomers. While the major isomer was the 5-borylated product, 2D NMR analysis showed that the minor isomer was 6-borylated product. The result was surprising since iridium catalyzed borylation on the 2-position of pyridine, when 3- and 4-positions are available for C–H borylation, is unprecedented.[27] With **4.5** the selectivity was even better for the 2-position and the monoborylated product mixture (75:25) was isolated in 79% yield. The formation of the 5-borylated product as the major isomer, even though the 2-position is more electronically favored (in the absence of any steric hindrance via adduct formation) hints the participation of more than one catalytically active species. Isomeric purities of the monoborylated products for entries 6 and 7 were increased up to 99.4% using **4.5**.

Monoborylation of 1-methylpyrazole with dtbpy gave a mixture of 5- and 4-borylated regioisomers with 90:10 selectivity (Figure 4.4). Surprisingly, the regioselectivity using **4.5** was also identical. Considering that bulky benzyl groups in **4.5** may be causing hindrance for borylation next to the NMe group, we tested the unsubstituted **4.6** for this substrate. Indeed the selectivity was improved to 97:3 with **4.9**.

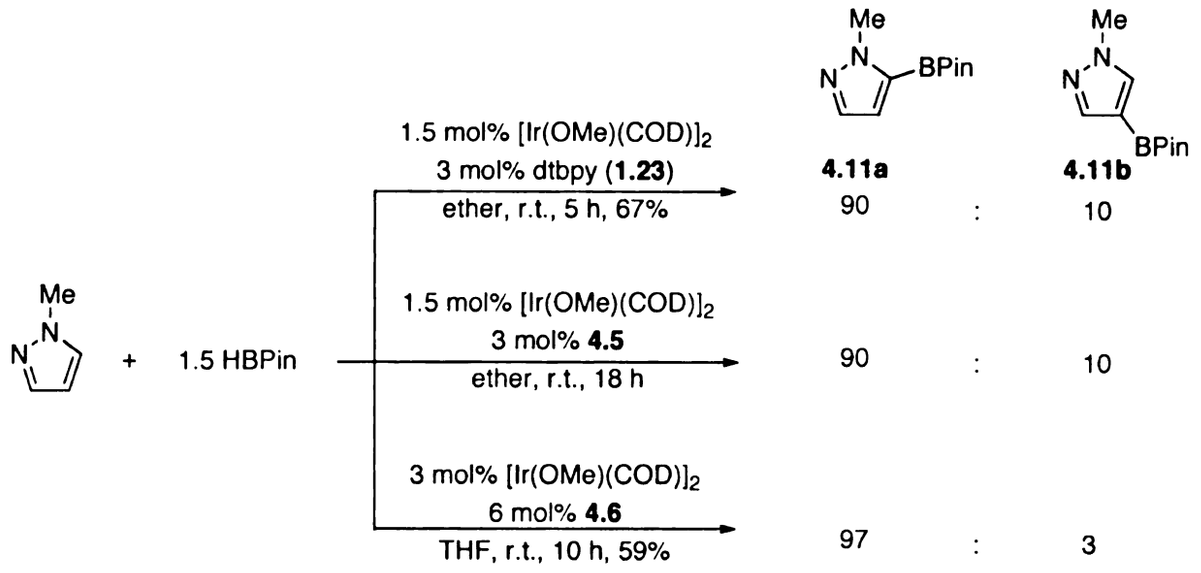


Figure 4.4. Regioselectivities for monoborylation of 1-methylpyrazole.

Monoborylation of 3-substituted thiophenes also give mixtures of 2- or 5-monoborylated regioisomers when the 3-substituent is sterically less bulky (e.g. Me, Cl, Br, CN). We therefore also studied these substrates to see if any improvement in regioselectivity is possible with ligand **4.5** (Scheme 4.3). Our results for these substrates are shown in Table 4.2.

For 3-cyanothiophene, the selectivity with dtbpy (**1.23**) was 47:53. This was not the sterically preferred out come, and was an exception to the general observation that the regioselectivities in Ir catalyzed borylation are governed by sterics. The combination of electronic activation and very small size of the cyano group may be the reason for the slight preference for borylation on the 2-position in this case. Using **4.5,** the regioselectivity was improved to 38:62. It seems that the bisoxazoline ligand **4.5** is more selective for borylation *ortho* to the cyano group. At the same time, we thought that presence of bulky benzyl groups in **4.5** might be shifting the borylation away from the

2-position to the 5-position. Hence borylation using unsubstituted ligand **4.6** was attempted, and indeed the selectivity was improved to 14:86 in favor of the 2-position.

Scheme 4.3. Monoborylation of 3-substituted thiophenes with **4.5**.

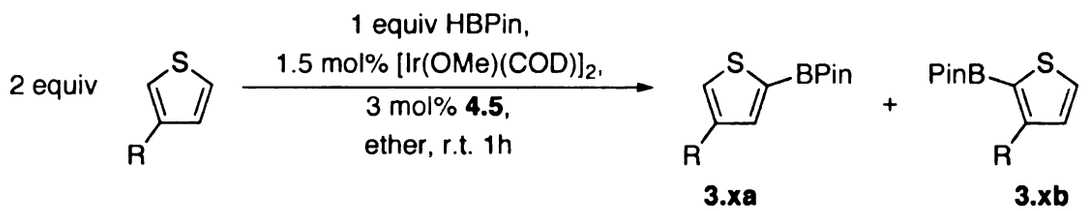
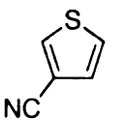
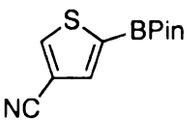
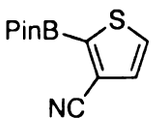
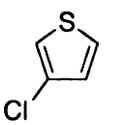
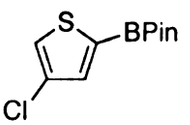
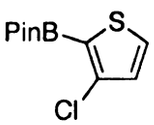
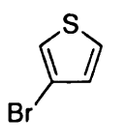
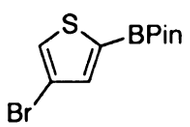
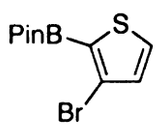
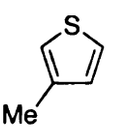
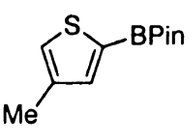
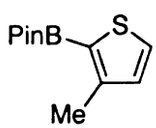


Table 4.2. Comparison of regioselectivities for monoborylation of 3-substituted thiophenes with **4.5** and **1.23** according to scheme 4.3.[a]

Entry	Substrate	Products a	Products b	**4.5** **3.xa : 3.xb** %yield	**1.23** **3.xa : 3.xb** %yield
1[b]		 **3.8a**	 **3.8b**	38:62 62	47:53 54
2[c]		 **3.9a**	 **3.9b**	86:14 66	78:22 66
3		 **3.10a**	 **3.10b**	94:6 63	89:11 72
4		 **3.11a**	 **3.11b**	93:7 68	89:11 67

[a]All reactions were carried out under conditions described in Scheme 4.3. Regioisomeric ratios were determined by GC-FID. Regioisomeric assigments are based on ^{1}H NMR. [b]Regioselectivity using **4.6** was 14:86 with 59% yield. [c]Ratio determined by ^{1}H NMR.

When the 3-substituent is Cl, Br, or Me, the major monoborylated isomer is the 5-borylated isomer with **1.23**, consistent with sterically directed borylation. For these substrates the regioselectivities were further slightly improved with **4.5**.

2,5-substituted thiophenes also give a mixture of regioisomers when the 2- and 5-substituents are not identical (Scheme 4.4). The two regioisomers can easily be identified by the ^{1}H NMR chemical shifts of the methine protons in the borylated products. The major product is the isomer where borylation takes place next to the sterically less demanding substituent. Our results for some of these substrates are shown in Table 4.3.

Scheme 4.4. Monoborylation of 2,5-di-substituted thiophenes with **4.5**.

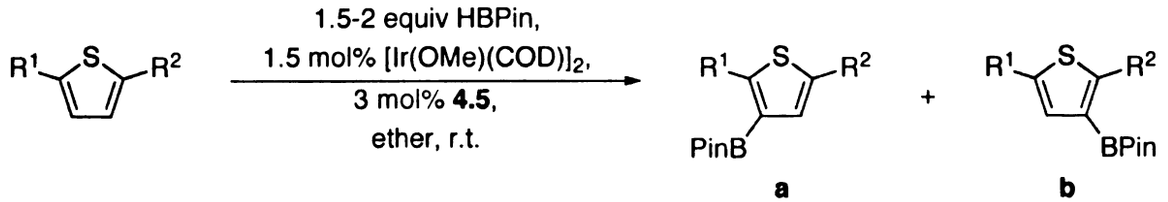
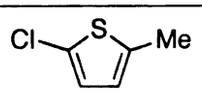
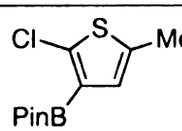
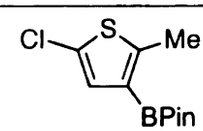
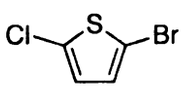
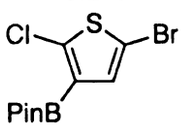
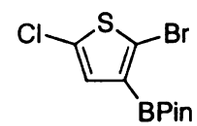
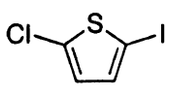
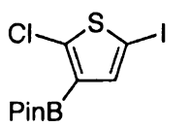
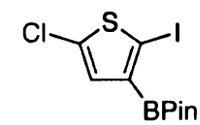
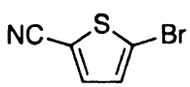
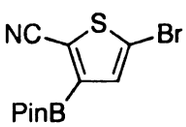
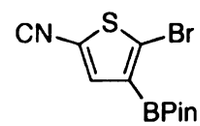
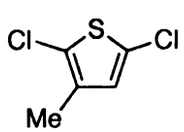
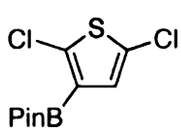
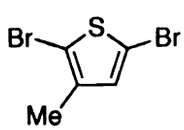
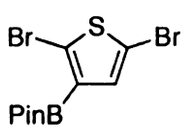


Table 4.3. Borylation of 2,5-substituted thiophenes according to scheme 4.4.

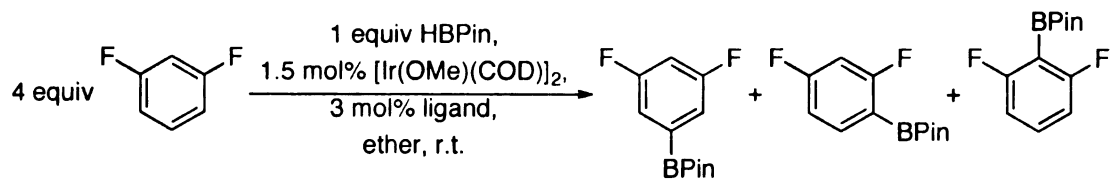
Entry	Substrate	Products **a**	Products **b**	**4.5** **a** : **b** % [Ir], Time (h) Boron equiv %yield	**1.23** **a** : **b** % [Ir], Time (h) Boron equiv %yield
1		 **3.21a**	 **3.21b**	85:15 3, (36) 1.5 82	70:30 3, (18) 1.5 86
2		 **3.19a**	 **3.19b**	72:28 3, (3) 1.5 87	67:33 6, (28) 2 87
3		 **3.20a**	 **3.20b**	92:8 3, (16) 1.5 89	85:15 3, (20) 1.5 89
4		 **2.26a**	 **2.26b**	> 98:2 6, (16) 1.5 90	–[a]
5		 **3.16**	–	– 3, (6) 1.5 84	– 3, (20) 1.5 86
6		 **3.17**	–	– 3, (6) 1.5 90	– 9, (48) 2.5 56

[a]Stoichiometric i.e. ~3% conversion by GC-FID was observed when the borylation was attempted with **1.23** in THF.

For 2-chloro-5-methyl-thiophene, the selectivity was improved from 70:30 with dtbpy to 85:15 with **4.5**. Since Me and Br are of similar size, we expected a similar increase for 2-chloro-5-bromo-thiophene. However the use of **4.5** caused only slight increase in selectivity for this substrate. Presumably electronic factors may also have contributed in improvement of selectivity in the case of 2-chloro-5-methyl-thiophene. A more significant improvement in regioselectivity was also observed for 2-chloro-5-iodo-thiophene.

Despite the slight increase in selectivity for 2-chloro-5-bromo-thiophene, we noticed that the reaction was complete in only 3 h with 3 mol% [Ir]/**4.5** as compare to 28 h with 6 mol% [Ir]/dtbpy. Longer reaction time with dtbpy ligand is probably due to the activation of weak C-Halogen bond in this case which results in catalyst deactivation. This result prompted us to test borylation of 2-cyano-5-bromo-thiophene, a substrate whose catalytic borylation was not feasible with dtbpy ligand.[7] Indeed the catalytic borylation of 2-cyano-5-bromo-thiophene was found to be possible with **4.5** and the borylated product was isolated in 90% yield. Similarly, use of **4.5** resulted in reduced reaction times/catalyst loadings for borylation of 2,5-di-bromo and 2,5-di-chloro thiophenes (Entries 5 and 6).

Scheme 4.5. Monoborylation of 1,3-di-fluorobenzene with ligands **1.23**, **4.5**, and **4.6**.



2.15a **2.15b** **2.15c**

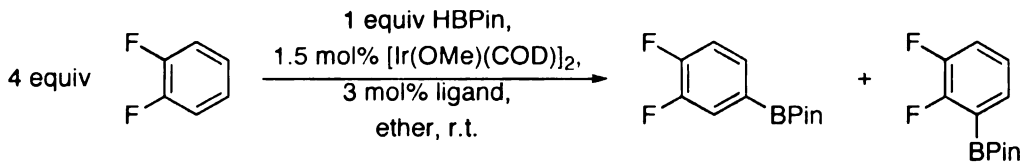
Table 4.4. GC-FID ratios of monoborylated products of 1,3-di-fluorobenzene according to scheme 4.5.

			Regioisomers		
Entry	Ligand	Time (h)	**2.15a**	**2.15b**	**2.15c**
1	**1.23**	16	48	31	21
2	**4.5**	36	22	21	57
3	**4.6**	36	5	12	83

Regioisomeric assignments were made by comparing the GC-FID retention times of the products in the crude reaction mixture with those for authentic samples.

Fluorine has a very small steric demand, allowing boryltaion *ortho* to F substituents in arenes. Monoborylation of 1,3-di-fluorobenzene was examined with ligands **1.23**, **4.5** and **4.6** (Scheme 4.5). The observed regioisomer distribution is shown in Table 4.4. The major monoborylated product with **1.23** was the 5-borylated isomer, in accordance with the sterically directed aromatic borylation. However, the major regioisomer with **4.6** was **2.15c**, indicating the preference for bisoxazoline type ligands to borylate *ortho* to the fluoro group. Interestingly, the presence of benzyl groups in **4.5** directed borylation away from the fluorine substituents.

Scheme 4.6. Monoborylation of 1,2-di-fluorobenzene with ligands **1.23**, **4.5**, and **4.6**.



4.12a **4.12b**

Table 4.5. GC-FID ratios of monoborylated products of 1,2-di-fluorobenzene according to scheme 4.6.

			Regioisomers	
Entry	Ligand	Time (h)	**4.12a**	**4.12b**
1	**1.23**	16	37	63
2	**4.5**	36	18	82
3[a]	**4.6**	36	9	91

Regioisomeric assignments was made by comparing the GC-FID retention time of the products in the crude reaction mixture with that for an authentic sample of **4.12a.** [a]Product mixture from a reaction in THF for 48 h at room temperature using 3 mol% [Ir]/**4.6**, 1 equiv HBPin, and 2 equiv of arene substrate was isolated in 31% yield.

For monoborylation of 1,2-difluorobenzene (Scheme 4.6), all three ligands tested here were more selective for borylation *ortho* to the fluoro substituent. The best selectivity was observed with **4.6**. The origin for the preference of borylation *ortho* to F vs. H is not clear at this point. The results described here are preliminary, and hence, detail work including regioisomeric distribution with other ligands such as dmpe/dppe, investigation of other fluorinated aromatics along with isolated yields needs to be carried out in order to develop a better understanding (of borylation of fluorinated substrates).

Conclusions

In conclusion, bisoxazoline type ligands are effective in iridium-catalyzed borylation. Heteroaromatic substrates and activated aromatics can easily be borylated at room temperature. Several cases were noticed where bisoxazoline derived ligands **4.5** and **4.6** gave better regioselectivity as compare to dtbpy. **4.5** was also more effective than dtbpy for borylation of 2,5-di-halo substituted thiophenes. Generally, the presence of bulky group on the 2-position of bisoxazoline ligand resulted in improved steric differentiation of the substituents in the substrate. However the exact origin of difference in borylation regioselectivities observed with bisoxazoline type ligands vs. dtbpy is not clear at this point.

Experimental Details and Spectroscopic Data

Materials

All substrates were purified before use. Solid substrates were sublimed under vacuum and liquid substrates were purified by distillation. Bis(η^4-1,5-cyclooctadiene)-di-μ-methoxy-diiridium(I) $[Ir(OMe)(COD)]_2$ was prepared per the literature procedure.[28] Pinacolborane (HBPin) was generously supplied by BASF and was distilled before use. Ether and tetrahydrofuran (THF) were obtained from a dry still packed with activated alumina and degassed before use. Silica gel (230-400 Mesh) was purchased from EMD™.

General Borylation Procedures

General Procedure A

In a glove box, a 20 mL scintillation vial equipped with a magnetic stirring bar, was charged with 2,2'-bis[(4S)-4-benzyl-2-oxazoline] (9.6 mg, 0.03 mmol, 3 mol%) (**4.5**). Ether (1 mL) was added to the scintillation vial in order to dissolve the ligand. $[Ir(OMe)(COD)]_2$ (10 mg, 0.015 mmol, 3 mol% Ir) was weighed in a test tube. HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) or B_2Pin_2 (256 mg, 1.00 mmol, 1 equiv), and ether (1 mL) were added to the $[Ir(OMe)(COD)]_2$ containing test tube. The resulting solution was transferred to the 20 mL scintillation vial. Additional ether (1 mL) was used to wash the test tube and the washings were transferred to the scintillation vial. Substrate (1 mmol, 1 equiv) was then added to the scintillation vial and the reaction mixture was stirred at room 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 dissolved in CH_2Cl_2 and passed through a short plug of silica to afford the corresponding borylated product.

General Procedure B (Borane as limiting reactant)

In a glove box, a 20 mL scintillation vial equipped with a magnetic stirring bar, was charged with 2,2′-bis[(4S)-4-benzyl-2-oxazoline] (9.6 mg, 0.03 mmol, 3 mol%). (**4.5**). Ether (1 mL) was added to the scintillation vial in order to dissolve the ligand. $[Ir(OMe)(COD)]_2$ (10 mg, 0.015 mmol, 3 mol% Ir) was weighed in a test tube. HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) and ether (1 mL) were added to the $[Ir(OMe)(COD)]_2$ containing test tube. The resulting solution was transferred to the 20 mL scintillation vial. Additional ether (1 mL) was used to wash the test tube and the washings were transferred to the scintillation vial. Substrate (2.00 mmol, 2.00 equiv) was then added to the scintillation vial and the reaction mixture was stirred at room 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 dissolved in CH_2Cl_2. Unreacted starting material was recovered by eluting with hexanes through a short plug of silica. Eluting with CH_2Cl_2 afforded the corresponding borylated product.

General Procedure C

The general procedure A was applied using 2,2′-bis(2-oxazoline) (**4.6**) as the ligand.

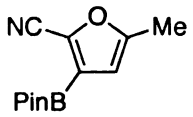
General Procedure D

The general procedure A was applied using dtbpy (**1.23**) as the ligand and hexanes as the solvent.

General Procedure E

The general procedure B was applied using dtbpy as the ligand and hexanes as the solvent.

Table 4.1, Entry 1. 5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carbonitrile (2.25a).

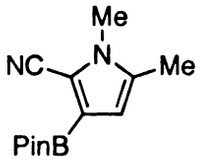


2.25a

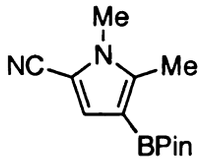
The general procedure A was applied to 2-cyano-5-methylfuran (105 μL, 107 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 2 h. Only one regioisomer was observed by GC-FID. The borylated product was isolated as a white solid (225 mg, 96% yield, mp 89 °C) with >99% isomeric purity by ^{1}H NMR. Regiochemical assignment is based on ref. 7. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.24 (q, J = 1.0 Hz, 1 H), 2.31 (d, J = 1.0 Hz, 3 H, CH_3), 1.30 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 157.7 (C), 130.5 (C), 112.0 (C), 111.5 (CH), 84.4 (2 C), 24.7 (CH_3, 4 CH_3 of BPin), 13.5 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.9; FT-IR (neat) $\tilde{\nu}$: 2984, 2936, 2224, 1541, 1406, 1373, 1331, 1300, 1147, 1041, 854, 817, 709 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^{+1} 234 (100), 233 (98), 218 (23), 203 (16), 190 (41), 175 (23); HRMS (FAB): *m/z* 234.1305 [(M^{+1}); Calcd for $C_{12}H_{17}BNO_3$: 234.1302].

Borylation with Procedure D with 1.5 equiv HBPin for 0.5 h gave two regioisomers in ratio 85:15 with 95% (221 mg) yield.[7]

Table 4.1, Entry 2. Borylation of 2-cyano-1,5-di-methylpyrrole.



97
2.24a

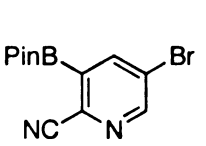


3
2.24b

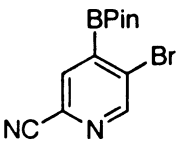
Borylation of 2-cyano-1,5-di-methylpyrrole (120 mg, 1 mmol, 1 equiv) with B_2Pin_2 (254 mg, 1.00 mmol, 2.00 equiv of Boron) was started after pre-generating the catalyst using 3 mol% $[Ir(OMe)(COD)]_2$, HBPin (26 mg, 0.20 mmol, 0.20 equiv), and 6 mol% of **4.5**. After 48 h at room temperature, about 80% conversion of the starting material was observed. Additional 3 mol% [Ir]/**4.5** and 1 equiv of HBPin was added and the reaction was run for 24 more h at room temperature. The ratio of two monoborylated regioisomers at the end of reaction was 97:3 by GC-FID. Regiochemical assignment is based on ref. 7. The borylated product was isolated as a white solid (163 mg, 66% yield, mp 130-131 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**2.24a**) 6.22 (d, J = 0.7 Hz, 1 H), 3.62 (s, 3 H, NCH_3), 2.21 (d, J = 0.7 Hz, 3 H, CH_3), 1.29 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**2.24a**) 135.6 (C), 114.5 (CH), 114.3 (C), 110.3 (C), 83.6 (2 C), 32.4 (NCH_3), 24.8 (CH_3, 4 CH_3 of BPin), 12.2 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.9; FT-IR (neat) $\tilde{\nu}$: 2978, 2215, 1562, 1500, 1408, 1311, 1260, 1142, 1016, 707 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 246 (100), 231 (35), 189 (32), 160 (25), 146 (58); HRMS (EI): *m/z* 246.1539 [(M^+); Calcd for $C_{13}H_{19}BN_2O_2$: 246.1540].

Borylation with Procedure D with 1.5 equiv HBPin for 16 h gave two regioisomers in ratio 85:15 with 80% yield.[7]

Table 4.1, Entry 3. Borylation of 2-cyano-5-bromopyridine (2.27a + 2.27b).



93
2.27a



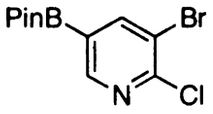
7
2.27b

The general procedure A was applied to 2-cyano-5-bromopyridine (183 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 6 h. The ratio of two monoborylated regioisomers at the end of reaction was 93:7 by GC-FID. Regiochemical assignment is based on ref. 7. Kugelrohr distillation gave mixture of monoborylated products as a white solid (263 mg, 85% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**2.27a**) 8.76 (d, J = 2.4 Hz, 1 H), 8.28 (d, J = 2.4 Hz, 1 H), 1.37 (br s, 12 H, CH_3 of BPin), (**2.27b**) 8.76 (s, 1 H), 7.85 (s, 1 H), 1.36 (br s, 12 H, CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ (**2.27a**) 153.6 (CH), 145.8 (CH), 136.1 (C), 124.4 (C), 116.6 (C, nitrile), 85.7 (2 C), 24.8 (CH_3, 4 CH_3 of BPin), (**2.27b**) 153.1 (CH), 134.5 (CH), 131.4 (C), 130.1 (C), 116.7 (C, nitrile), 85.6 (2 C), 24.8 (CH_3, 4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.5; FT-IR (neat) $\tilde{\nu}$: 3048, 2979, 2244, 1566, 1539, 1416, 1383, 1342, 1318, 1269, 1142, 1069, 1026, 964, 872, 847, 771 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**2.27a**) 308 M^+ (41), 310 (M^{2+} 37), 293 (95), 267 (96), 250 (65), 229 (34), 209 (42), (**2.27b**) 308 M^+ (7), 293 (33), 267 (17), 229 (100), 187 (91); Anal. Calcd for $C_{12}H_{14}BBrN_2O_2$: C, 46.65; H, 4.57; N, 9.07. Found: C, 46.52; H, 4.48; N, 8.76.

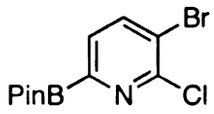
The ratio of the two regioisomers with Procedure C for 6 h was 78:22 with 78% yield.

The ratio of the two regioisomers with Procedure D with 2 equiv HBPin for 18 h was 67:33 with 81% yield.[7]

Table 4.1, Entry 4. Borylation of 2-chloro-3-bromopyridine (4.8a + 4.8b).



75
4.8a



25
4.8b

The general procedure A was applied to 2-chloro-3-bromopyridine (192 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) with 3% [Ir]/**4.5** catalyst loading for 30 h. At that stage, additional 1.5 mol% $[Ir(OMe)(COD)]_2$ was added and the reaction was stirred for 34 more hour. The ratio of the two monoborylated regioisomers at the end of reaction (total 64 h) was 75:25 by GC-FID. Kugelrohr distillation gave mixture of monoborylated products as a white solid (252 mg, 79% yield). NMR spectroscopy (gHMQC and gHMBC) was used to assign the regiochemistry of the minor isomer as described in the following section. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**4.8a**) 8.57 (d, J = 2 Hz, 1 H), 8.22 (d, J = 2 Hz, 1 H), 1.29 (br s, 12 H, 4 CH_3 of BPin), (**4.8b**) 7.86 (d, J = 7.8 Hz, 1 H), 7.54 (d, J = 7.8 Hz, 1 H), 1.31 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**4.8a**) 153.4 (CH), 153.2 (C), 147.9 (CH), 120.1 (C), 84.7 (2 C), 24.7 (CH_3, 4 CH_3 of BPin), (**4.8b**) 151.3 (C), 140.9 (CH), 130.0 (CH), 122.7 (C), 85.0 (2 C), 24.7 (CH_3, 4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.4; FT-IR (neat) $\tilde{\nu}$: 3040, 2980, 2932, 1576, 1344, 1142, 1037, 844, 733, 675 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**4.8a**) 318 M^{+1} (85), 317 M^+ (24), 319 M^{+2} (45), 304 (47), 302 (37), 276 (9), 262 (16), (**4.8b**) 319 M^{+2} (80), M^+ 317 (66), 304 (33), 302 (28), 284 (21), 282 (17), 263 (87), 261 (67), 238 (10), 220 (38), 218 (34); Anal. Calcd for $C_{11}H_{14}BBrClNO_2$: C, 41.49; H, 4.43; N, 4.40. Found: C, 41.63; H, 4.51; N, 8.22.

The ratio of two regioisomers with Procedure D for 16 h was 87:13.

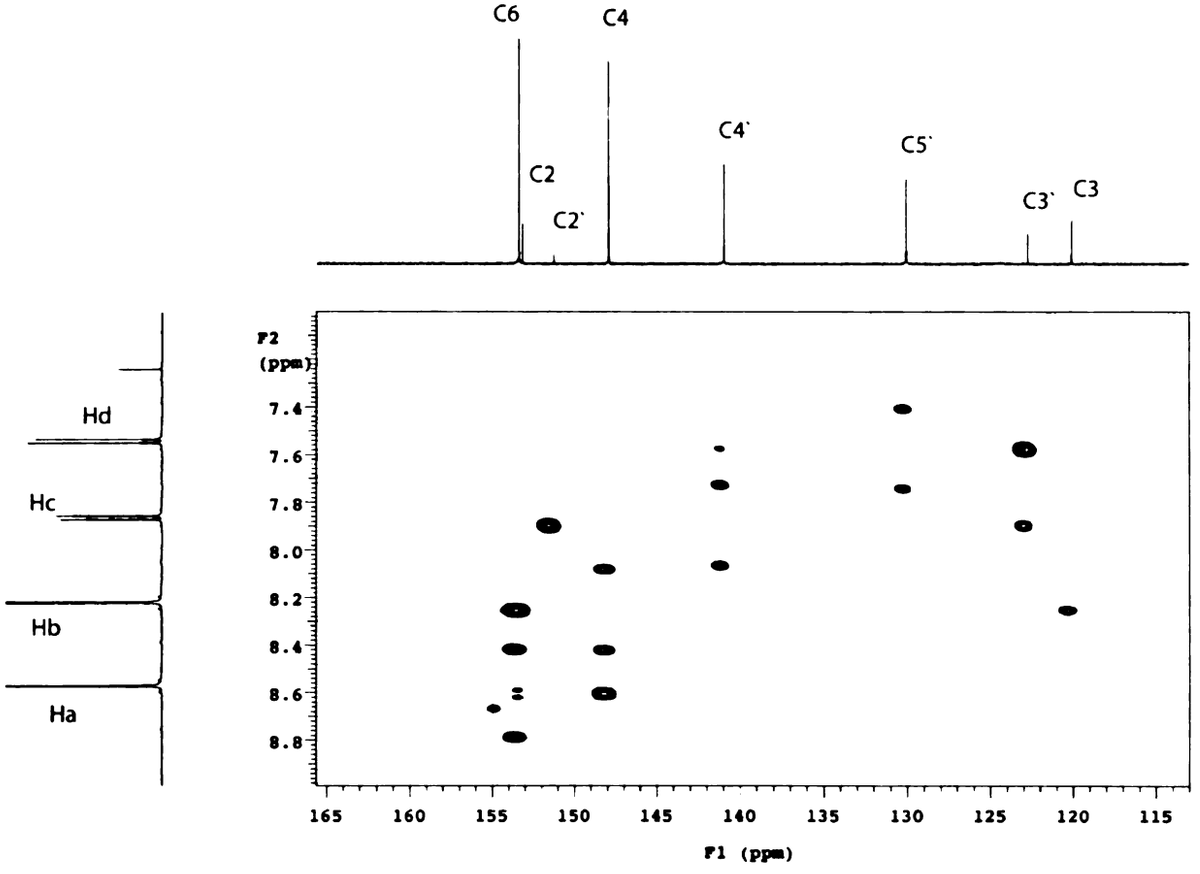
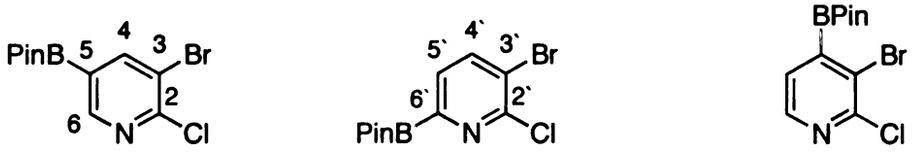


Figure 4.5. gHMBC spectrum of product mixture of 4.8a and 4.8b.

Regiochemical assignment of 4.8a and 4.8b.



75
4.8a

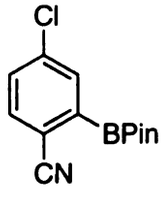
25
4.8b

not detected
4.8c

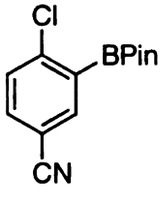
^{1}H NMR of the product mixture showed that the value of the coupling constant *J* between the two protons of the major regioisomer is 2.0 Hz. This data unambiguously assign the major isomer as **4.8a**. The value of the coupling constant *J* between the two protons of the minor regioisomer is 7.8 Hz. This can either be for the 4-borylated (**4.8c**) or 6-borylated (**4.8b**) product. Quaternary carbon atoms, C3 and C3`, attached to Br in

major and minor isomer respectively can easily be identified as they appear most up-field (Figure 5). Similarly, carbon atoms, C2 and C2`, attached to Cl in major and minor isomer respectively can also be easily identified as they are the deshielded quaternary carbons above 150 ppm. Carbon C2` showed a strong 3-bond cross peak in the gHMBC spectrum to proton Hc, to which carbon C3` also showed a week 2-bond cross peak. This can only be true if proton Hc is on carbon C4`, thereby ruling out the possibility of 4-borylated product, and hence unambiguously assigning the regiochemistry of the minor isomer as being 6-borylated product. The minor regioisomer also does not show any methine (CH) carbon above 150 ppm in the ^{13}C NMR spectrum, which should be the case for the carbon C6 of **4.8c**. The chemical shifts of the remaining carbons and their corresponding cross-peaks in the gHMBC spectrum are also in accordance of this assignment.

Table 4.1, Entry 5. Borylation of 4-chlorobenzonitrile (2.2a + 2.2b).



93
2.2a



7
2.2b

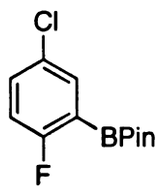
General procedure B was applied to 4-chlorobenzonitrile (550 mg, 4.00 mmol, 4.00 equiv) and HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) for 36 h. The ratio of two monoborylated regioisomers at the end of reaction was 93:7 by GC-FID. Regiochemical assignment is based on ref. 7. Kugelrohr distillation furnished the borylated product mixture as a white solid (158 mg, 60% yield). ^1H NMR ($CDCl_3$, 300 MHz): δ (**2.2a**) 7.80 (d, J = 2.2 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.45 (dd, J = 8.3, 2.2 Hz, 1H), 1.33 (br s,

12H, 4 CH_3 of BPin), (**2.2b**) 7.94 (d, J = 2.2 Hz, 1H), 7.56 (dd, J = 8.3, 2.2 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 1.32 (br s, 12H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 75 MHz): δ (**2.2a**) 138.5 (C), 135.8 (CH), 134.5 (CH), 131.2 (CH), 118.0 (C nitrile), 115.3 (C), 85.0 (2 C), 24.6 (CH_3, 4 CH_3 of BPin), (**2.2b**) 144.5 (C), 140.1 (CH), 134.6 (CH), 130.2 (CH), 117.8 (C nitrile), 110.2 (C), 84.7 (2 C), 24.6 (CH_3, 4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.6; FT-IR (neat) $\tilde{\nu}$: 2982, 2228, 1587, 1554, 1479, 1402, 1373, 1333, 1271, 1215, 1169, 1144, 1103, 1065, 1042, 965, 870, 847, 831 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**2.2a**) 263 M^+ (24), 248 (65), 222 (100), 205 (31), 164(32), 137 (11), (**2.2b**) 263 M^+ (1), 248 (27), 228 (100), 186 (60), 164 (15), 142 (6); Anal. Calcd for $C_{13}H_{15}BClNO_2$: C, 59.25; H, 5.74; N, 5.32. Found: C, 58.90; H, 5.74; N, 5.10.

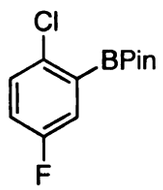
The ratio of two regioisomers with Procedure C was 84:16.

The ratio of two regioisomers with Procedure E was 80:20[7] with 76% yield.

Table 4.1, Entry 6. 2-(5-chloro-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.9a).



99.4
4.9a



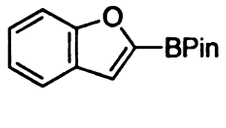
0.6
4.9b

General procedure B was applied to 4-fluorochlorobenzene (350 μL, 522 mg, 4.00 mmol, 4.00 equiv) and HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) for 6 h. The ratio of two monoborylated regioisomers at the end of reaction was 99.4:0.6 by GC-FID. Regiochemical assignment of the major product is based on the C–F coupling information in the ^{13}C NMR (with the help of the fact that the boron bearing carbon is not

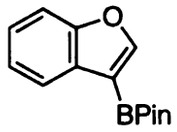
observed due to broadening from and coupling with boron). The GC-FID peak area for **4.9b** was decreased in going from ligand **1.23** to **4.5**. The borylated product was isolated as a white solid (213 mg, 83% yield, mp 75-76 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (**4.9a**) 7.66 (dd, J = 4.9, 2.9 Hz, 1H), 7.32-7.36 (m, 1 H), 6.96 (t, J = 8.3 Hz, 1H), 1.33 (br s, 12H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ (**4.9a**) 165.5 (d, $^{1}J_{C\text{-}F}$ = 252 Hz, C), 136.2 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz, CH), 133.0 (d, $^{3}J_{C\text{-}F}$ = 9.1 Hz, CH), 128.9 (s, C), 116.8 (d, $^{2}J_{C\text{-}F}$ = 26.2 Hz, CH), 84.2 (2 C), 24.8 (CH_3, 4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.6; ^{19}F NMR ($CDCl_3$, 282 MHz): δ –105.8; FT-IR (neat) $\tilde{\nu}$: 2982, 1610, 1485, 1408, 1338, 1267, 1221, 1143, 1099, 1070, 964, 875, 850, 821, 682, 640 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**4.9a**) 256 M^+ (80), 241 (100), 213 (17), 196 (73), 179 (20), 152 (74); Anal. Calcd for $C_{12}H_{15}BClFO_2$: C, 56.19; H, 5.89. Found: C, 56.26; H, 5.89.

The ratio of two regioisomers with Procedure E was 97.2:2.8 with 68% yield.

Table 4.1, Entry 7. 2-(benzofuran-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.10a).



99.4
4.10a



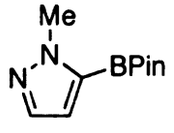
0.6
4.10b

The general procedure A was applied to benzofuran (108 μL, 118 mg, 1 mmol, 1 equiv) and HBPin (175 μL, 154 mg, 1.20 mmol, 1.20 equiv) for 1 h. The ratio of two monoborylated regioisomers at the end of reaction was 99.4:0.6 by GC-FID. Regiochemical assignment is based on ref. 12 and 10. The GC-FID peak area for **4.10b** was decreased in going from ligand **1.23** to **4.5**. The borylated product was isolated as a

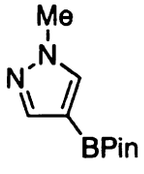
white solid (227 mg, 93% yield, mp 86-87 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.58-7.62 (m, 1 H), 7.55 (dd, J = 8.3, 0.7 Hz, 1 H), 7.38 (d, J = 1.0 Hz, 1 H), 7.28-7.34 (m, 1 H), 7.20 (dt, J = 7.8 Hz, 1.0 Hz, 1 H), 1.36 (s, 12 H, CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 157.5 (C), 127.5 (C), 125.9 (CH), 122.7 (CH), 121.8 (CH), 119.5 (CH), 111.9 (CH), 84.6 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.1; FT-IR (neat) $\tilde{\nu}$: 3065, 2991, 2978, 2936, 1566, 1361, 1327, 1138, 1068, 962, 852, 831, 819, 756, 748, 692 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 244 (52), 245 (9), 243 (14), 229 (11), 201 (100), 159 (16), 158 (17), 144 (19); Anal. Calcd for $C_{14}H_{17}BO_3$: C, 68.89; H, 7.02. Found: C, 68.82; H, 7.35.

Borylation with Procedure D gave two regioisomers in ratio 97.5:2.5 with 82% yield.[10,12,23]

1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole 94.11a).



97
4.11a



3
4.11b

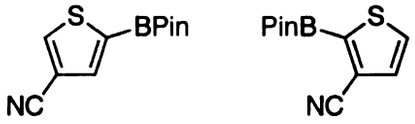
The general procedure C was applied to 1-methylpyrazole (82 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) with 6% [Ir] catalyst loading for 10 h. The ratio of two monoborylated regioisomers at the end of reaction was 97:3 by GC-FID. Regiochemical assignment is based on coupling information in the ^{1}H NMR. Kugelrohr distillation afforded the borylated product was isolated as a white solid (122 mg, 59% yield, mp 62-63 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**4.11a**) 7.46 (d, J = 2.0 Hz, 1 H), 6.69 (d, J = 2.0 Hz, 1 H), 4.06 (s, 3 H, CH_3), 1.31 (br s, 12 H, 4 CH_3 of BPin);

^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ (**4.11a**) 138.3 (CH), 115.8 (CH), 84.1 (2 C), 39.3 (CH_3), 24.8 (CH_3, 4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 27.7; FT-IR (neat) $\tilde{\nu}$: 2982, 1529, 1350, 1331, 1288, 1250, 1143, 1105, 1012, 854, 798, 704 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^{+1} 209 (100), 193 (2), 165 (3), 122 (6); HRMS (EI): *m/z* 209.1464 [(M^{+1}); Calcd for $C_{10}H_{18}BN_2O_2$: 209.1461].

Borylation with Procedure A with 3 equiv HBPin and 6 mol% [Ir] catalyst for 18 h gave two regioisomers in ratio 89:11.

Borylation with Procedure D with 1.5 equiv HBPin for 5 h gave two regioisomers in ratio 90:10 with 67% yield.

Table 4.2, Entry 1. Borylation of 3-cyanothiophene (3.8a + 3.8b).



38 **3.8a** 62 **3.8b**

The general procedure B was applied to 3-cyanothiophene (182 μL, 218 mg, 2.00 mmol, 2.00 equiv) and HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) for 1 h. The ratio of two monoborylated regioisomers at the end of reaction was 38:62 by GC-FID. The monoborylated product mixture was isolated as a white solid (145 mg, 62% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**3.8a**) 7.62 (d, J = 4.9 Hz, 1 H), 7.38 (d, J = 4.9 Hz, 1 H), 1.36 (br s, 12 H, 4 CH_3 of BPin), (**3.8b**) 8.13 (d, J = 1.2 Hz, 1 H), 7.75 (d, J = 1.2 Hz, 1 H), 1.33 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**3.8a**) 132.7 (CH), 131.4 (CH), 118.3 (C), 115.2 (C), 84.9 (2 C), 24.7 (4 CH_3 of BPin), (**3.8b**) 140.8 (CH), 138.1 (CH), 114.7 (C), 111.9 (C), 85.1 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.6; FT-IR (neat) $\tilde{\nu}$: 2980, 2231, 1429, 1319, 1142, 1039, 850, 628

cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**3.8a**) M^{+1} 236 (100), 220 (78), 194 (51), 178 (33), 149 (36), 136 (31), (**3.8b**) M^{+} 235 (7), 220 (100), 192 (9), 149 (37), 136 (15); Anal. Calcd for $C_{11}H_{14}BNO_2S$: C, 56.19; H, 6.0; N, 5.96. Found: C, 55.74; H, 5.99; N, 6.0.

The ratio of two regioisomers with Procedure C was 14:86 with 59% yield.

The ratio of two regioisomers with Procedure E was 47:53 with 54% yield.

Table 4.2, Entry 2. Borylation of 3-chlorothiophene (3.9a + 3.9b).

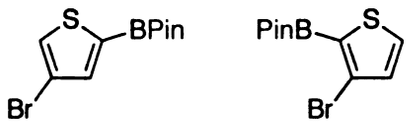
86
3.9a

14
3.9b

The general procedure B was applied to 3-chlorothiophene (186 μL, 237 mg, 2.00 mmol, 2.00 equiv) and HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) for 1 h. The ratio of two monoborylated regioisomers at the end of reaction was 86:14 by ^1H NMR. The monoborylated product mixture was isolated as a white solid (161 mg, 66% yield). ^1H NMR ($CDCl_3$, 300 MHz): δ (**3.9a**) 7.43 (d, J = 1.0 Hz, 1 H), 7.35 (d, J = 1.0 Hz, 1 H), 1.32 (br s, 12 H, 4 CH_3 of BPin), (**3.9b**) 7.51 (d, J = 5.0 Hz, 1 H), 7.01 (d, J = 5.0 Hz, 1 H), 1.34 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ (**3.9a**) 136.9 (CH), 131.8 (C), 126.7 (CH), 84.4 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.0; FT-IR (neat) $\tilde{\nu}$: 3107, 2980, 2932, 1522, 1421, 1356, 1336, 1142, 1026, 854, 665cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^{+} 244 (100), 246 (38), 231 (15), 229 (38), 209 (24), 158 (27); Anal. Calcd for $C_{10}H_{14}BClO_2S$: C, 49.11; H, 5.77. Found: C, 49.33; H, 5.81.

The ratio of two regioisomers with Procedure E was 78:22 with 66% yield.

Table 4.2, Entry 3. Borylation of 3-bromothiophene (3.10a + 3.10b).

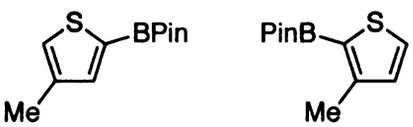


94 **3.10a** 6 **3.10b**

The general procedure B was applied to 3-bromothiophene (190 μL, 326 mg, 2.00 mmol, 2.00 equiv) and HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) for 1 h. The ratio of two monoborylated regioisomers at the end of reaction was 94:6 by GC-FID. The monoborylated product mixture was isolated as a white solid (182 mg, 63% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**3.10a**) 7.49 (d, J = 1.2 Hz, 1 H), 7.46 (d, J = 1.2 Hz, 1 H), 1.32 (br s, 12 H, 4 CH_3 of BPin), (**3.10b**) 7.48 (d, J = 5.0 Hz, 1 H), 7.08 (d, J = 5.0 Hz, 1 H), 1.34 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**3.10a**) 139.3 (CH), 129.5 (CH), 111.2 (C), 84.4 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.0; FT-IR (neat) $\tilde{\nu}$: 2980, 1518, 1415, 1350, 1143, 1026, 852, 665 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**3.10a**) M^+ 289 (51), 290 (98), 288 (100), 275 (61), 273 (55), 247 (18), 245 (21), 230 (19) 204 (41), (**3.10b**) M^+ 289 (13), 290 (25), 288 (27), 275 (10), 273 (9), 209 (100), 189 (11), 167 (67); Anal. Calcd for $C_{10}H_{14}BBrO_2S$: C, 41.56; H, 4.88. Found: C, 41.74; H, 4.88.

The ratio of two regioisomers with Procedure E was 89:11 with 72% yield.

Table 4.2, Entry 4. Borylation of 3-methylthiophene (3.11a + 3.11b).

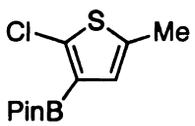


93 **3.11a** 7 **3.11b**

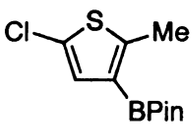
The general procedure B was applied to 3-methylthiophene (194 μL, 196 mg, 2.00 mmol, 2.00 equiv) and HBPin (145 μL, 128 mg, 1 mmol, 1 equiv) for 1 h. The ratio of two monoborylated regioisomers at the end of reaction was 93:7 by GC-FID. The monoborylated product mixture was isolated as a white solid (153 mg, 68% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**3.10a**) 7.42 (d, J = 0.7 Hz, 1 H), 7.17 (t, J = 1.1 Hz, 1 H), 2.27 (d J = 0.5 Hz, 1 H), 1.32 (br s, 12 H, 4 CH_3 of BPin), (**3.10b**) 7.46 (d, J = 4.6 Hz, 1 H), 6.95 (d, J = 4.6 Hz, 1 H), 2.47 (s, 1 H), 1.30 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ (**3.10a**) 139.4 (CH), 138.9 (C), 128.0 (CH), 83.9 (2 C), 24.7 (4 CH_3 of BPin), 14.9 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.5; FT-IR (neat) $\tilde{\nu}$: 2978, 2930, 1550, 1441, 1371, 1327, 1302, 1271, 1143, 1028, 962, 854 665 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**3.10a**) M^+ 224 (100), 209 (27), 181 (18), 138 (44), (**3.10b**) M^+ 224 (100), 209 (68), 167 (64), 138 (54), 124 (61); Anal. Calcd for $C_{11}H_{17}BO_2S$: C, 58.95; H, 7.65. Found: C, 58.65; H, 8.09.

The ratio of two regioisomers with Procedure E was 89:11 with 67% yield.

Table 4.3, Entry 1. Borylation of 2-chloro-5-methylthiophene (3.21a + 3.21b).



85
3.21a



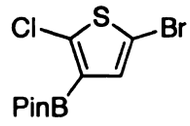
15
3.21b

The general procedure A was applied to 2-chloro-5-methylthiophene (133 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 36 h. The ratio of two monoborylated regioisomers at the end of reaction was 85:15 by GC-FID. The monoborylated product mixture was isolated as a colorless semi solid (210 mg, 82% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ (**3.21a**) 6.77 (q, J = 1.2 Hz, 1 H), 2.35 (d, J = 1.2

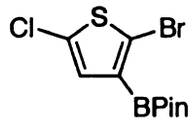
Hz, 3 H, CH_3), 1.31 (br s, 12 H, 4 CH_3 of BPin), (**3.21b**) 6.95 (s, 1 H), 2.60 (s, 3 H, CH_3), 1.28 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR $\{^1H\}$ ($CDCl_3$, 125 MHz): δ (**3.21a**) 137.4 (C), 137.0 (C), 130.1 (CH), 83.6 (2 C), 24.8 (4 CH_3 of BPin), 14.9 (CH_3), (**3.21b**) 151.1 (C), 131.6 (CH), 125.4 (C), 83.4 (2 C), 24.8 (4 CH_3 of BPin), 15.7 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.1; FT-IR (neat) $\tilde{\nu}$: 2980, 2926, 1556, 1475, 1390, 1371, 1309, 1257, 1143, 1026, 966, 898, 850, 696 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**3.21a**) 258 M^+ (100), 243 (17), 223 (51), 181 (36), 153 (37) (**3.21b**) 258 M^+ (100), 243 (18), 223 (7), 201 (93), 172 (23); Anal. Calcd for $C_{11}H_{16}BClO_2S$: C, 51.10; H, 6.24. Found: C, 51.66; H, 6.58; HRMS (EI): *m/z* 258.0653 [(M^+); Calcd for $C_{11}H_{16}BClO_2S$: 258.06526].

The ratio of two regioisomers with Procedure D was 70:30 with 86% yield.

Table 4.3, Entry 2. Borylation of 2-bromo-5-chlorothiophene (3.19a + 3.19b).



72
3.19a



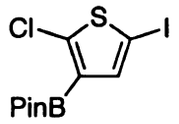
28
3.19b

The general procedure A was applied to 2-bromo-5-chlorothiophene (110 μL, 197 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 3 h. The ratio of two monoborylated regioisomers at the end of reaction was 72:28 by GC-FID. The monoborylated product mixture was isolated as a white solid (281 mg, 87% yield). ^1H NMR ($CDCl_3$, 500 MHz): δ (**3.19a**)) 7.10 (s, 1 H), 1.30 (br s, 12 H, 4 CH_3 of BPin), (**3.19b**) 6.94 (s, 1 H), 1.30 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR $\{^1H\}$ ($CDCl_3$, 125 MHz): δ (**3.19a**) 139.6 (C), 134.9 (CH), 108.3 (C), 84.0 (2C), 24.8 (4 CH_3 of BPin), (**3.19b**) 132.0 (CH), 128.9 (C), 119.5 (C), 84.1 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.5; FT-IR (neat) $\tilde{\nu}$: 2980, 1527, 1427, 1371, 1253, 1140, 1028,

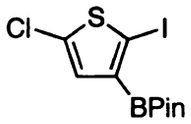
962, 848, 693 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**3.19a**) M^+ 324 (100), 322 (78), 289 (67), 287 (64), 208 (40), 166 (34), (**3.19b**) M^+ 324 (89), 322 (69), 309 (23), 245 (41), 243 (99), 203 (43), 201 (100), 166 (50); Anal. Calcd for $C_{10}H_{13}BBrClO_2S$: C, 37.13; H, 4.05. Found: C, 37.25; H, 4.05.

Borylation of 2-bromo-5-chlorothiophene using Procedure D was not complete after 8 h at 3% [Ir] catalyst loading. Additional 3 % [Ir] and 0.5 equiv of HBPin was added and the reaction was run for 20 more h at room temperature. The ratio of two monoborylated regioisomers at the end of reaction was 67:33 by GC-FID. The product was isolated in 87% (281 mg) yield.

Table 4.3, Entry 3. Borylation of 2-chloro-5-iodothiophene (3.20a + 3.20b).



92
3.20a



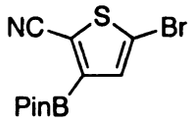
8
3.20b

The general procedure A was applied to 2-chloro-5-iodothiophene (245 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 16 h. The ratio of two monoborylated regioisomers at the end of reaction was 92:8 by GC-FID. The monoborylated product mixture was isolated as a white solid (330 mg, 89% yield). ^1H NMR ($CDCl_3$, 300 MHz): δ (**3.20a**) 7.31 (s, 1 H), 1.30 (br s, 12 H, 4 CH_3 of BPin), (**3.20b**) 6.87 (s, 1 H), 1.31 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ (**3.20a**) 143.4 (C), 142.3 (CH), 84.0 (2 C), 69.3 (C), 24.8 (4 CH_3 of BPin), (**3.20b**) 132.8 (CH), 84.2 (2 C), 81.1 (C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.3; FT-IR (neat) $\tilde{\nu}$: 2978, 1523, 1414, 1371, 1248, 1140, 1024, 966, 881, 848 690 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): (**3.20a**) M^+ 370 (100), 355 (13), 335

(29), 270 (25), 208 (15), 166 (11), (**3.20b**) M^+ 370 (100), 355 (10), 270 (24), 243 (13), 201 (32), 166 (21); Anal. Calcd for $C_{10}H_{13}BIClO_2S$: C, 32.42; H, 3.54. Found: C, 32.58; H, 3.38.

The ratio of two regioisomers with Procedure D was 85:15 with 89% yield.

Table 4.3, Entry 4. 5-bromo-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carbonitrile (2.26a).

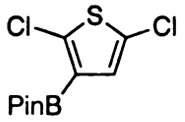


>98
2.26a

The general procedure A was applied to 2-bromo-5-cyanothiophene (111 μL, 188 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 2.00 mmol, 1.50 equiv) with 3% [Ir] catalyst loading for 8 h. Additional 3 % [Ir] catalyst and 0.5 equiv of HBPin was added at this stage and the reaction was run for 8 more h at room temperature. The borylated product was isolated as a white solid (284 mg, 90% yield, mp 98-100 °C) with >98% isomeric purity by GC-FID. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30 (s, 1 H), 1.30 (br s, 12 H, CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 136.0 (CH), 119.1 (C), 118.8 (C), 113.1 (C), 84.9 (2 C), 24.7 (CH_3, 4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.0; FT-IR (neat) $\tilde{\nu}$: 2980, 2218, 1520, 1408, 1332, 1255, 1143, 1132, 964, 891, 846, 696 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 315 (100), 313 (97), 314 (59), 300 (32), 298 (30), 272 (85), 257 (47), 255 (48), 229 (22), 192 (76); Anal. Calcd for $C_{11}H_{13}BBrNO_2S$: C, 42.07; H, 4.17; N, 4.46. Found: C, 42.32; H, 4.11; N, 4.50.

It was not possible to borylate this substrate using Procedure D.[7]

Table 4.3, Entry 5. 2-(2,5-dichlorothiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

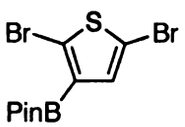


3.16

The general procedure A was applied to 2-5-dichlorothiophene (107 μL, 153 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 6 h. The product was isolated as a white solid (233 mg, 84% yield, mp 35-36 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.94 (s, 1 H), 1.30 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 137.1 (C), 131.1 (CH), 126.2 (C), 84.0 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.5; FT-IR (neat) $\tilde{\nu}$: 2980, 1535, 1437, 1371, 1313, 1263, 1142, 1032, 966, 889, 848, 692 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 278 (100), 280 (68), 263 (32), 265 (22), 243 M-35 (79), 245 (30), 201 (51); Anal. Calcd for $C_{10}H_{13}BCl_2O_2S$: C, 43.05; H, 4.70. Found: C, 43.26; H, 4.74.

Borylation of 2,5-dichlorothiophene using Procedure D took 20 h for full conversion at 3% [Ir] catalyst loading. The product was isolated in 86% (240 mg) isolated yield.

Table 4.3, Entry 6. 2-(2,5-dibromothiophen-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

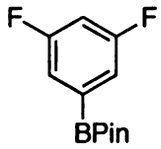


3.17

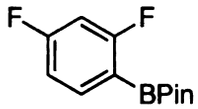
The general procedure A was applied to 2-5-dibromothiophene (113 μL, 142 mg, 1 mmol, 1 equiv) and HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 6 h. The product was isolated as a white solid (331 mg, 90% yield, mp 72-73 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.09 (s, 1 H), 1.31 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 135.8 (CH), 121.9 (C), 110.9 (C), 84.0 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 28.5; FT-IR (neat) $\tilde{\nu}$: 2978, 1525, 1365, 1307, 1248, 1143, 991, 962, 883, 848, 690 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 368 (100), 370 (51), 366 (52), 353 (18), 287 (56), 289 (59), 268 (28), 208 (77), 166 (69); Calcd for $C_{10}H_{13}BBr_2O_2S$: C, 32.65; H, 3.56. Found: C, 32.92; H, 3.57.

Borylation of 2,5-bromothiophene using Procedure D was not complete after 36 h at 6% [Ir] catalyst loading. Additional 3 % [Ir] and 1 equiv of HBPin was added and the reaction was run for 12 more h at room temperature. The ratio of the starting material to product after 48 h was 11:89. The product was isolated in 56% (206 mg) yield.

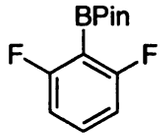
Table 4.4. Borylation of 1,3-di-fluorobenzene (2.15a + 2.15b + 2.15c).



22
2.15a



21
2.15b



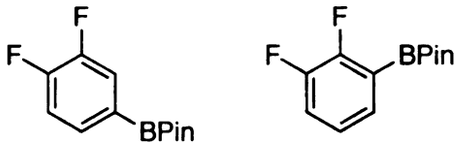
57
2.15c

The general procedure B was applied to 1,3-di-fluorobenzene (394 μL, 456 mg, 4 mmol, 4 equiv) and HBPin (145 μL, 128 mg, 1.00 mmol, 1.00 equiv) for 36 h. The ratio of three monoborylated regioisomers at the end of reaction was 22:21:57 by GC-FID.[29]

The ratio of the two regioisomers with Procedure C was 5:12:83.

The ratio of the three regioisomers with Procedure E was 48:31:21.

Table 4.5. Borylation of 1,2-di-fluorobenzene (4.12a + 4.12b).



18 **4.12a** 82 **4.12b**

The general procedure B was applied to 1,2-di-fluorobenzene (394 μL, 456 mg, 4 mmol, 4 equiv) and HBPin (145 μL, 128 mg, 1.00 mmol, 1.00 equiv) for 36 h. The ratio of two monoborylated regioisomers at the end of reaction was 18:82 by GC-FID. Regiochemical assignment is based on comparison with the GC-FID retention times of the two isomers, 8.15 and 8.48 minute for **4.12a** and **4.12b** respectively, with that of an authentic sample of **4.12a** prepared from the Pd catalyzed borylation of 4-bromo-1,2-di-fluorobenzene as described below.

The ratio of the two regioisomers with Procedure C was 9:91.

The ratio of the two regioisomers with Procedure E was 37:63.

Preparation of authentic sample of 2-(3,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.12a).

In a glove box, a 100 mL schlenk flask, equipped with a magnetic stirring bar, was charged with $Pd_2(dba)_3$ (14 mg, 0.015 mmol, 3 mol% Pd) and tricyclohexylphosphine (PCy_3, 20 mg, 0.072 mmol, 7.2 mol%). Dioxane (6 mL) was added and the resulting mixture was stirred for 30 minutes at room temperature. B_2Pin_2 (280 mg, 1.1 mmol), KOAc (147 mg, 1.5 mmol), and 4-bromo-1,2-di-fluorobenzene (193 mg, 1 mmol) were added successively. The schlenk flask was brought to a schlenk line. A condenser was attached, and the flask was flushed with nitrogen. The reaction mixture

was stirred at 80 °C for 2 h. The mixture was treated with water (10 mL), and the product was extracted with ether, washed with brine, and dried over $MgSO_4$. Crude material was eluted with CH_2Cl_2 through a plug of silica gel to afford the desired product (157 mg, 65% yield) as light yellow oil; GC-FID retention time 8.15 minute; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47-7.59 (m, 2 H), 7.07-7.16 (m, 1 H), 1.31 (s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 152.8 (dd, $^1J_{C\text{-}F}$ = 252 Hz, $^3J_{C\text{-}F}$ = 12.1 Hz, C), 149.7 (dd, $^1J_{C\text{-}F}$ = 248 Hz, $^3J_{C\text{-}F}$ = 12.1 Hz, C), 131.3 (m, CH), 123.2 (d, $^2J_{C\text{-}F}$ = 15.1 Hz, CH), 116.9 (d, $^2J_{C\text{-}F}$ = 16.1 Hz, CH), 84.0 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 31.1; ^{19}F NMR ($CDCl_3$, 282 MHz): δ –133.9 (m), –139.5 (m); FT-IR (neat) $\tilde{\nu}$: 2980, 1614, 1520, 1417, 1361, 1273, 1197, 1145, 1116, 964, 920, 854, 763, 677 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 240 (7), 225 (100), 197 (7), 154 (28); Anal. Calcd for $C_{12}H_{15}BF_2O_2$: C, 60.04; H, 6.30. Found: C, 60.06; H, 6.21; HRMS (EI): *m/z* 240.1132 [(M^+); Calcd for $C_{12}H_{15}BF_2O_2$: 240.1133].

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CHAPTER 5

One-Pot Borylation/Amination Reactions:

Synthesis of Arylamine Boronate Esters from Halogenated Arenes

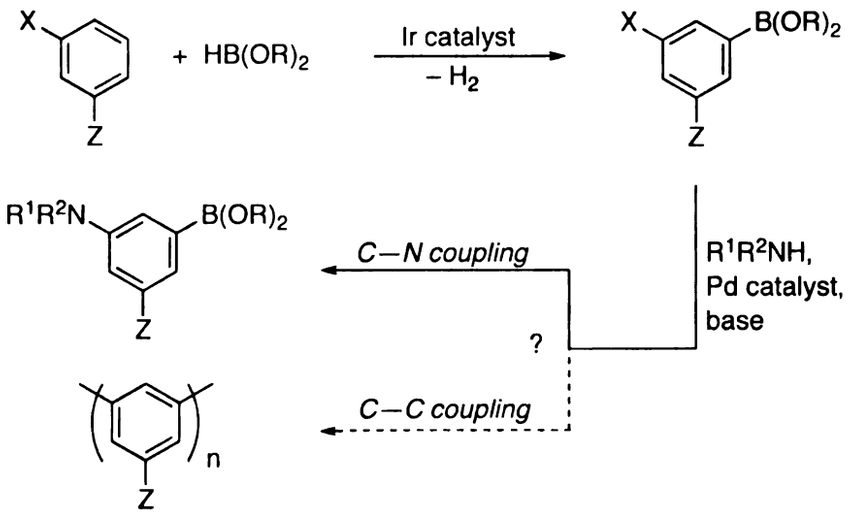
Introduction

Metal-catalyzed halide substitution reactions have enhanced the synthetic utility of halogenated aromatic compounds. Noteworthy examples include C–C,[1,2] C–N, and C–O[3-5] bond-forming reactions, which are predominantly Pd-mediated processes.[6] Because the scope of these transformations is tied to commercial availability of halogenated compounds, processes that enable functionalization at non-halogen sites can augment the substrate pool. In this regard, Ir catalyzed borylation reactions are particularly intriguing because C–H bonds in halogenated aromatic systems can be converted selectively to C–B bonds.[7-10] We, and others, have shown that this selectivity enables one-pot elaborations of aryl halides to phenols, when the boronic ester is oxidized,[11] or to biaryls and polyaromatics when the nascent arylboronate ester is subjected to subsequent Pd mediated C–C coupling.[7,10,12]

These results suggest that other metal catalyzed transformations of crude arylboronate esters produced from Ir-catalyzed aromatic borylations might be possible. In this chapter we describe a one-pot borylation/amination protocol where aryl halides can be converted to C-borylated anilines. In addition to requiring that the Pd catalyzed reaction operates without interference from Ir species that remain after borylation, realization of the tandem catalytic process hinges on the successful differentiation between C–N and C–C couplings with an aryl halide when amines and boronic esters are present in the reaction milieu.

Cross-couplings of aryl boron reagents or amines with aryl halides constitute two of the most important reactions for aryl halides. These reactions are typically facilitated by Pd catalysts in the presence of stoichiometric quantities of base. Given the similar reaction conditions for C–C and C–N couplings, attempted catalytic amination of the halogenated arylboronate ester in Scheme 5.1 could produce an aryl amine if C–N coupling is favored, polyaromatic products if C–C coupling dominates, or a mixture of these products if C–N and C–C formation is competitive.

Scheme 5.1. Possible outcomes for a one-pot borylation/amination sequence.

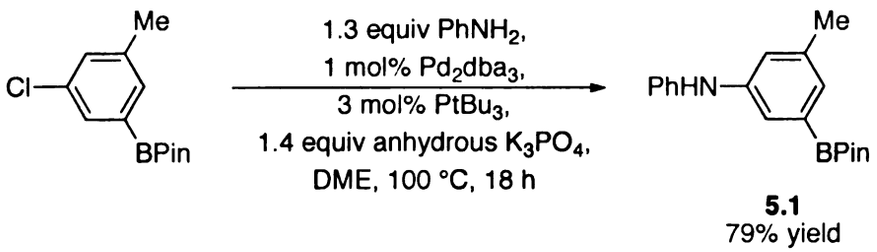


In terms of literature precedent, the prospects for selective amination according to Scheme 5.1 were bleak. As well as we are aware, there are no examples where C–B bonds survive during Pd–catalyzed amination conditions. Moreover, there are numerous examples where cross couplings of arylboronic acids[13-16] and esters[17] are accomplished in the presence of primary and secondary amines. However, our examinations of one-pot aromatic borylation/C–C coupling of arenes offered a ray of hope for the amination pathway in Scheme 5.1. Specifically, we found that Suzuki-Miyaura cross-couplings of pinacolate esters of arylboronic acids were typically slower than reactions of the

arylboronic acids themselves.[18] Moreover, the rates of C–C couplings for pinacol boronate esters further diminish when the reactions are carried out under anhydrous conditions. Since virtually all examples of B–C/C–X cross-couplings of substrates with amine functionality involve boronic acids or boronate esters in the presence of either water or hydroxide, we reasoned that the combination of an aprotic base and an anhydrous, aprotic solvent offered the best chance for realizing C–N in lieu of C–C coupling.

Results and Discussion

After an initial attempt of the one-pot reaction sequence failed, we explored aminations of the purified borylation product of 3-chlorotoluene. To our delight, selective C–N coupling was found using anhydrous K_3PO_4 as the base according to Eq 1. Returning to the one-pot sequence, we examined the effects of the Ir and Pd precatalysts, base, and solvent on yields for the "one-pot" sequence in Scheme 5.2. The results are tabulated in Table 5.1.



5.1
79% yield

(5.1)

Scheme 5.2. One-pot borylation/amination of 3-chlorotoluene.

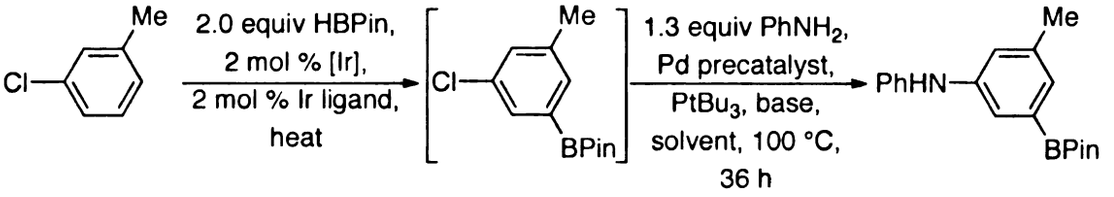


Table 5.1. Effects of Ir and Pd precatalyst, base, and solvent on one-pot borylation/amination of 3-chlorotoluene according to scheme 5.2.

Entry	Ir precatalyst	Ir Ligand	Borylation Conditions	Pd Precatalyst	Base	Solvent	GC-yield[a]
1	(Ind)Ir(COD)	dmpe	150 °C, 18 h	Pd_2dba_3	K_3PO_4	DME	93
2	(Ind)Ir(COD)	dppe	150 °C, 18 h	Pd_2dba_3	K_3PO_4	DME	89
3	(Ind)Ir(COD)	dtbpy	100 °C, 18 h	Pd_2dba_3	K_3PO_4	DME	87
4	$[Ir(OMe)(COD)]_2$	dtbpy	80 °C, 24 h	Pd_2dba_3	K_3PO_4	DME	87
5	(Ind)Ir(COD)	dmpe	150 °C, 18 h	Pd_2dba_3	$K_3PO_4 \cdot nH_2O$	DME	0
6	(Ind)Ir(COD)	dmpe	150 °C, 18 h	Pd_2dba_3	Cs_2CO_3	DME	88
7	(Ind)Ir(COD)	dmpe	150 °C, 18 h	Pd_2dba_3	NaOtBu	DME	18
8	(Ind)Ir(COD)	dmpe	150 °C, 18 h	Pd_2dba_3	KOtBu	DME	10
9	(Ind)Ir(COD)	dmpe	150 °C, 18 h	Pd_2dba_3	K_3PO_4	Dioxane	85
10	(Ind)Ir(COD)	dmpe	150 °C, 18 h	Pd_2dba_3	K_3PO_4	Toluene	84
11	(Ind)Ir(COD)	dmpe	150 °C, 18 h	$Pd(OAc)_2$	K_3PO_4	DME	56

[a]GC-yields based upon starting arene as an average of three runs.

Entries 1–4 examine the effects of the Ir source and the Ir ligand. While room temperature borylations are prohibitively slow for 3-chlorotoluene, the borylations could be carried out at 80 °C when the Ir ligand was 4,4′-di-*tert*-butyl-2,2′-bipyridyl (dtbpy). The best yields of the borylated aryl amine were obtained when borylations were carried out using the (Ind)Ir(COD)/1,2-bis(dimethylphosphino)ethane (dmpe) Ir precatalyst/ligand formulation. In all cases, conversion of 3-chlorotoluene to the intermediate boronate ester was complete. Hence, the variations in yields for entries 1-4 likely arise from the efficiencies of the amination step.

Entries 1 and 5-8 illustrate the effects of the base on the amination step. K_3PO_4 and Cs_2CO_3 are both effective, whereas NaOtBu and KOtBu gave very low yields of the amino boronate ester. Entry 5 shows the deleterious effects of water as the amino boronate ester is not detected when $K_3PO_4 \cdot nH_2O$ is the base. In contrast to NaOtBu and KOtBu, where predominance of the intermediate boronate ester indicates that conversion to the amino boronate is simply slow, with $K_3PO_4 \cdot nH_2O$ the intermediate boronate ester is completely consumed. Entries 1, 9, and 10 show that the amination step is moderately sensitive to variations in the solvent, with DME giving superior results. Lastly, entries 1 and 11 illustrate the effect of the Pd precatalyst with Pd_2dba_3 being superior to $Pd(OAc)_2$, the principle difference being significant generation of the deborylated aryl amine for the latter Pd precatalyst.

Armed with the results from Table 5.1, we examined the scope of the borylation/amination sequence for various 3-substituted halobenzenes for which borylation at the 5-position predominates. The general conditions in Scheme 5.3 were used and the results are listed in Table 5.2.

Scheme 5.3. Preparation of 1,3,5-arylamino boronate esters by one-pot borylation/amination of arylhalides.

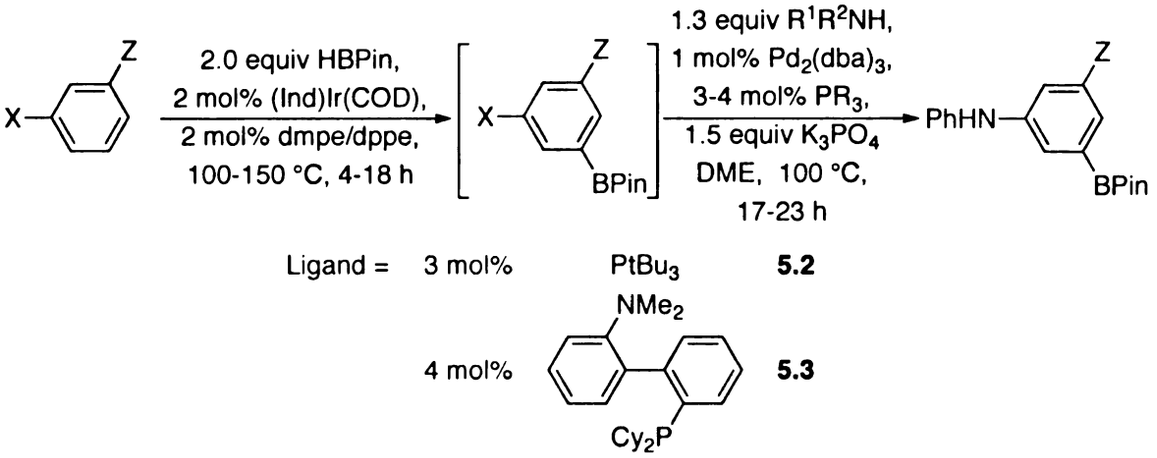


Table 5.2. Preparation of 1,3,5-arylamino boronate esters according to scheme 5.3.

Entry	Z	X	Borylation Conditions			Amination Conditions			Product	%yield
			Ligand	Temp	Time (h)	Amine	Ligand	Time (h)		
1	Me	Cl	dmpe	150 °C	8	$PhNH_2$	**5.2**	19	**5.1**	75
2	Me	Cl	dmpe	150 °C	16	morpholine	**5.2**	22	**5.4**	73
3	Me	Cl	dmpe	150 °C	17	PhNMeH	**5.3**	16	**5.5**	83
4	Me	Cl	dmpe	150 °C	17	Bu_2NH	**5.2**	23	**5.6**	50
5	Me	Br	dmpe	150 °C	8	$PhNH_2$	**5.2**	19	**5.1**	63
6	CO_2Me	Cl	dppe	100 °C	17	$PhNH_2$	**5.2**	16	**5.7**	47
7	CF_3	Cl	dppe	100 °C	4	$PhNH_2$	**5.3**	18	**5.8**	71
8[a]	CF_3	Cl	dppe	100 °C	4	mlorpholine	**5.3**	17	**5.9**	49
9	CF_3	Cl	dmpe	150 °C	4	PhNMeH	**5.2**	23	**5.10**	65
10	OMe	Cl	dmpe	150 °C	12	$PhNH_2$	**5.3**	17	**5.11**	63
11	NMe_2	Cl	dmpe	150 °C	18	$PhNH_2$	**5.3**	17	**5.12**	73

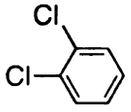
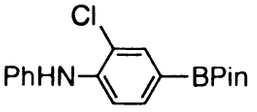
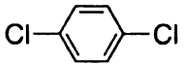
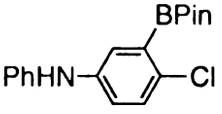
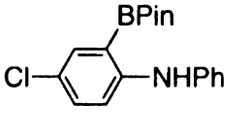
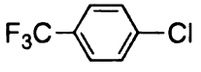
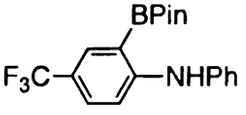
[a]Suzuki product ~ 20% was also observed by GC-FID.

The isolated yields for the reactions in Table 5.2, based on the starting aryl halide, range from 47-83% with an average yield of 64%. This average corresponds to an 80% yield for the individual steps, assuming that the borylation and amination yields are identical. When the pure aryl boronate ester derived from borylation of 3-chlorotolene was isolated and subsequently aminated with aniline, the product in entry 1 was isolated in 60% overall yield based on 3-chlorotoluene, compared to the 75% yield obtained for the one-pot reaction. Thus, higher isolated yields are realized in the one-pot tandem reactions where isolation and purification of the intermediate aryl halide boronate esters are avoided.[19]

Entries 1-4, examine the effect of varying the amine on aminations of the borylation product of 3-chlorotoluene. The yields for aniline, morpholine, and N-methylaniline are excellent, while amination with dibutylamine gave a significantly lower yield of the 3-amino boronate ester. Entries 1, 6, 7, 10, and 11 show the effect of varying the Z substituent in Scheme 3. Electron withdrawing substituents give lower yields of the 3-amino boronate esters. Since electron withdrawing substituents on aryl boronic acids accelerate Suzuki-Miyaura cross-couplings, competition from this side reaction may contribute to the lower yields for electron deficient aryl chlorides. Consistent with this notion, small quantities of aminated biaryls that arise from Suzuki-Miyaura coupling can be detected in the crude reaction mixture for entry 8.

Examples of 2 and 4-substituted halogenated benzenes that react with a high degree of regioselectivity are more limited. Nevertheless, the results from one-pot borylation/amination reactions using these substrates suggest that extensions beyond the regiochemistries in Table 5.2 are possible.

Table 5.3. One-pot borylation/amination of *ortho* and *para*-substituted chlorobenzenes.[a]

Entry	Aryl halide	Product	% yield
1		 19 : 1 **5.14a** **5.14b**	46
2[b]		 **5.15a**  **5.15b** ~ 10% GC-yield. Two regioisomers observed in 7:1 ratio by GC-FID.	0
3		 7 **5.16**	45

[a]See experimental details for specific reaction conditions. [b]The intermediate boronate ester was isolated.

Because unsymmetrical *o*-disubstituted benzenes typically exhibit poor borylation regioselectivities, the only 2-substituted halogenated benzene examined is *o*-dichlorobenzene. Regioselective borylation at the 4-position affords an intermediate boronate ester where the chloride positions are chemically distinct. Thus, synthetic utility depends on high regioselectivity in the amination step. Fortunately, the BPin group exerts a directing effect that, regardless of its origins (i.e. steric or electronic), responds to variations in the Pd phosphine ligand. While good regioselectivity is found for $PtBu_3$ (2:1) and 2-dicyclohexylphosphino-2'-dimethylamino-1,1'-biphenyl (6:1), 2-(dicyclohexyl phosphino)biphenyl (**5.13**) gave superior results affording a 19:1 ratio of two regioisomers by GC-FID. 2D NMR spectroscopy (gHMBC) showed that the major

product was the one where amination took place on the chloride *para* to the BPin group (see experimental details). With the exception of regioselective amination at the 2-position of 2,3-dichloropyridine,[20] regioselectivities of this type have not been previously reported.

p-Dichlorobenzene similarly affords a single monoborylated product where the chloride positions are also chemically distinct. For this substrate, a two-fold excess of arene is required to minimize diborylation. Consequently, the intermediate boronate ester was isolated. In contrast to the one pot reaction for *o*-dichlorobenzene, subsequent amination of this boronate ester with aniline was less efficient, less regioselective, and deborylation was also observed. Attempts to isolate the pure amino boronate esters were unsuccessful.

When the 4-subtituent in 4-substituted chlorobenzenes is sufficiently large, borylation at the 2-position predominates. For example, 4-(trifluoromethyl)-chlorobenzene affords a 95:5 ratio of 2 and 3-monoborylated products respectively. The major regioisomer can easily be identified from the C–F coupling information in the ^{13}C NMR (with the help of the fact that the boron bearing carbon is not observed due to broadening from and coupling with boron). Subsequent amination of the crude reaction mixture with aniline and isolation gives isomerically pure 2-borylated amine. As was the case for *p*-dichlorobenzene, approximately 20% of the intermediate boronate ester suffers deborylation, suggesting that this may be a general problem for aminations of chlorides ortho to BPin groups.

Conclusions

In summary, one pot borylation/amination provides an efficient protocol for preparing the 1,3,5-arylamino boronate esters from 3-substituted aryl halides. The one pot sequence can be extended to *ortho* and *para*– substituted chlorobenzenes. In the case of dichlorobenzenes, a highly regioselective substitution has been observed *para* to the BPin group in the boronate ester derived from the borylation of *o*-dichlorobenzene. The key feature that enables the one-pot sequence is preference of C–N over C–C coupling when a primary or secondary amine, a pinacolate boron ester, and an aryl halide are subjected to Pd coupling conditions where anhydrous K_3PO_4 is the requisite base.[2,21,24] We are presently evaluating the generality and pursuing applications of this selectivity.[25]

Experimental Details and Spectroscopic Data

Materials

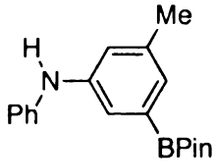
All commercially available chemicals were used as received or purified as described. Aryl halides were refluxed over CaH_2, distilled, and degassed. Aniline, *N*-methylaniline, dibutylamine, and morpholine were refluxed over KOH, distilled, and degassed. Methyl-3-chlorobenzoate was stirred over 4Å molecular sieves and then passed through activated alumina before use. Pinacolborane (HBPin) was stirred over PPh_3 overnight, vacuum transferred into an air free flask and brought into the glove box. 4,4′-Di-*tert*-butyl-2,2′-bipyridine (dtbpy) was sublimed before use. (η^5-Indenyl)(cyclooctadiene)iridium {(Ind)Ir(COD)} and bis(η^4-1,5-cyclooctadiene)-di-μ-methoxy-diiridium(I) $[Ir(OMe)(COD)]_2$ were prepared per literature procedures.[26,27] Anhydrous potassium phosphate was obtained by heating hydrated potassium phosphate at 150 °C under vacuum for 7 days. Ethylene glycol dimethyl ether (DME) and *n*-hexane were refluxed over sodium, distilled, and degassed. Silica gel (60 Å, 230-400 Mesh) was used for column chromatography.

General Procedure

In a dry box, aryl halide (2 mmol, 1 equiv), HBPin (580 μL, 512 mg, 4.00 mmol, 2.00 equiv), (Ind)Ir(COD) (17 mg, 0.04 mmol, 2.0 mol%) and dmpe (6 mg, 0.04 mmol, 2 mol%) or dppe (16 mg, 0.04 mmol, 2 mol%) were transferred into a thick-walled air-free flask equipped with a magnetic stirring bar. The flask was sealed, removed from the glove box, and stirred at 150 °C (dmpe) or 100 °C (dppe) until the reaction was judged complete by GC-FID. The reaction mixture was allowed to cool to room temperature and subsequently placed under vacuum for 1-2 h. The thick walled flask was brought into the

dry box and anhydrous K_3PO_4 (594 mg, 2.8 mmol, 1.4 equiv), Pd_2dba_3 (18 mg, 0.02 mmol, 1 mol %), $PtBu_3$ (12 mg, 0.06 mmol, 3 mol%), 2-dicyclohexylphosphino-2′-(*N*,*N*-di-methylamino)biphenyl (32 mg, 0.08 mmol, 4 mol%) or 2-(dicyclohexylphosphino)biphenyl (28 mg, 0.08 mmol, 4 mol%), amine (2.4-2.6 mmol, 1.2-1.3 equiv) and DME (3mL) were added. The flask was then sealed, removed from the dry box and stirred at 100 °C until the reaction was judged complete by GC-FID. After completion, the reaction mixture was extracted three times with ether. The combined organics were washed with brine followed by water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was then subjected to column chromatography.

Table 5.2, Entry 1. *N*-Phenyl-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-aniline (5.1).

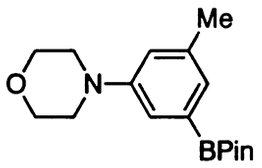


5.1

The general procedure was applied to 3-chlorotoluene (253 mg, 2 mmol). The borylation step was carried out neat with HBPin (580 μL, 512 mg, 4.00 mmol, 2.00 equiv) and dmpe (6 mg, 0.04 mmol, 2 mol%) at 150 °C for 8 h. The amination step was then carried out using $PtBu_3$ (12 mg, 0.06 mmol, 3 mol%) and aniline (224 mg, 2.40 mmol, 1.20 equiv) at 100 °C for 19 h. Column chromatography (hexanes/CH_2Cl_2 2:3) furnished the desired product (463 mg, 75% yield, mp 100 °C) as a light yellow oil, which solidified on standing. ^{1}H NMR (C_6D_6, 500 MHz) δ 7.64 (br s, 2 H), 7.07-7.03 (m, 2 H), 6.92-6.89 (m, 2 H), 6.86 (br s, 1 H), 6.77-6.74 (m, 1 H), 5.05 (br s, 1 H), 2.11 (s, 3

H), 1.13 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} (C_6D_6, 125 MHz) δ 144.0 (C), 143.0 (C), 138.4 (C), 129.5 (CH), 129.2 (CH), 122.5 (CH), 122.2 (CH), 120.7 (CH), 117.8 (CH), 83.7 (C), 24.94 (4 CH_3 of BPin), 21.34 (CH_3); ^{11}B NMR (C_6D_6, 96 Hz) δ 29.1; FT-IR (NaCl) $\tilde{\nu}$: 3393, 3365 (sh), 3036, 2979, 2926, 2867, 1590, 1518, 1497, 1470, 1410, 1368, 1312, 1271, 1237, 1215, 1167, 1144, 1117, 1031, 1019, 967, 911, 853, 745, 712, 698, 668 cm^{-1} GC-MS (EI) *m/z* (% relative intensity): M^+ 309 (100), 294 (2), 250 (3), 236 (7), 209 (27), 193 (14), 167 (11), 147 (5). Anal. Calcd for $C_{19}H_{24}BO_2N$: C, 73.80; H, 7.82; N, 4.53. Found: C, 73.82; H, 7.94; N, 4.43.

Table 5.2, Entry 2. 3-(*N*-morpholino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-toluene (5.2).

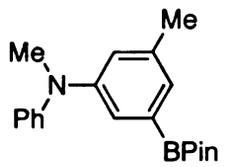


5.4

The general procedure was applied to 3-chlorotoluene (253 mg, 2 mmol). The borylation step was carried out neat with HBPin (580 μL, 512 mg, 4.00 mmol, 2.00 equiv) and dmpe (6 mg, 0.04 mmol, 2 mol%) at 150 °C for 16 h. The amination step was then carried out using $PtBu_3$ (12 mg, 0.06 mmol, 3 mol%) and morpholine (209 mg, 2.4 mmol, 1.2 equiv) at 100 °C for 22 h. Column chromatography (hexanes/EtOAc 2:1) furnished the desired product (445 mg, 73.4% yield) as a light yellow oil. ^1H NMR (C_6D_6, 500 MHz) δ 7.64 (s, 1 H), 7.54 (d, J = 2.4 Hz, 1 H), 6.68 (s, 1H), 3.51 (t, J = 4.8 Hz, 4 H), 2.74 (t, J = 4.8 Hz, 4 H), 2.22 (d, J = 0.4 Hz, 3 H), 1.16 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} (C_6D_6, 125 MHz) δ 151.5 (C), 138.0 (C), 128.3 (CH), 120.1 (CH), 120.0 (CH), 83.6 (C), 67.0 (CH_2), 49.6 (CH_2), 25.0 (4 CH_3 of BPin), 21.7 (CH_3); ^{11}B NMR δ

28.8. FT-IR (NaCl) $\tilde{\nu}$: 2977, 2921, 2855, 2820, 1590, 1470, 1441, 1387, 1372, 1316, 1271, 1242, 1188, 1165, 1146, 1123, 1013, 967, 853, 708 cm^{-1}; GC MS (EI) m/z (% relative intensity): M^+ 303 (100), 288 (4), 272 (6), 258 (5), 245 (41), 203 (7), 187 (6), 172 (10), 159 (35), 145 (70), 131 (8), 117 (27), 91 (13), 65 (7), 57 (10); Anal. Calcd for $C_{17}H_{26}BNO_3$: C, 67.34; H, 8.64; N, 4.62. Found: C, 67.28; H, 8.56; N, 4.55.

Table 5.2, Entry 3. *N*-Methyl-*N*-phenyl-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-aniline (5.5).

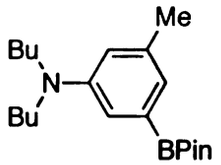


5.5

The general procedure was applied to 3-chlorotoluene (127 mg, 1 mmol). The borylation step was carried out neat with HBPin (290 μL, 256 mg, 2.00 mmol, 2.00 equiv) and dmpe (3 mg, 0.02 mmol, 2 mol%) at 150 °C for 17 h. The amination step was then carried out using 2-dicyclohexylphosphino-2′-(*N*,*N*-di-methylamino)biphenyl (16 mg, 0.04 mmol, 4 mol%) and *N*-methylaniline (139 mg, 1.30 mmol, 1.30 equiv) at 100 °C for 16 h. Column chromatography (hexanes/ether 4:1) furnished the desired product (270 mg, 83.4% yield) as a light yellow oil which solidified on standing. Analytically pure material was obtained by sublimation (140 °C at 0.05 mm Hg), mp 69-71 °C. ^{1}H NMR (C_6D_6, 300 MHz) δ 7.82 (d, J = 2.0 Hz, 1 H), 7.73 (d, J = 0.7 Hz, 1 H), 7.12-7.05 (m, 2 H), 7.00 (m, 1 H), 6.95-6.90 (m, 2 H), 6.82-6.76 (m, 1 H), 2.94 (s, 3 H), 2.07 (m, 3 H), 1.11 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} (C_6D_6, 125 MHz) δ 149.8 (C), 149.2 (C), 138.5 (C), 130.4 (CH), 129.4 (CH), 126.4 (CH), 125.8 (CH), 120.6 (CH), 119.5 (CH), 83.7 (C), 40.2 (CH_3), 25.0 (4 CH_3 of BPin), 21.3 (CH_3); ^{11}B NMR δ 26.4; FT-IR

(neat) $\tilde{\nu}$: 3038, 2978, 2928, 1599, 1585, 1498, 1435, 1383, 1370, 1315, 1250, 1192, 1146, 1117, 1094, 966, 905, 853, 752, 712, 698 cm^{-1}; GC MS (EI) m/z (% relative intensity): M^+ 323 (100), 222 (7). Anal. Calcd for $C_{20}H_{26}BNO_2$: C, 74.32; H, 8.11; N, 4.33. Found: C, 74.42; H, 7.81; N, 4.27.

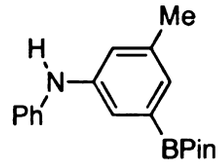
Table 5.2, Entry 4. *N-N*-Di-*n*-butyl-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-aniline (5.6).



5.6

The general procedure was applied to 3-chlorotoluene (127 mg, 1 mmol). The borylation step was carried out neat with HBPin (290 μL, 256 mg, 2.00 mmol, 2.00 equiv) and dmpe (3 mg, 0.02 mmol, 2 mol%) at 150 °C for 17 h. The amination step was then carried out using $PtBu_3$ (6 mg, 0.03 mmol, 3 mol%) and dibutylamine (155 mg, 1.20 mmol, 1.2 equiv) at 100 °C for 23 h. Column chromatography (hexanes/ether 12:1) furnished the desired product (174 mg, 50.2% yield) as a light yellow oil. ^1H NMR (C_6D_6, 500 MHz) δ 7.51-7.49 (m, 2 H), 6.74 (br s, 1 H), 3.14-3.10 (t, J = 7.8 Hz, 4 H), 2.28 (s, 3 H), 1.43-1.49 (m, 4 H), 1.18-1.11 {m, 16 H; methyls in BPin and methylenes in butyls ($-CH_2-CH_2-CH_3)_2$ }, 0.81-0.78 (t, J = 7.8 Hz, 6 H); ^{13}C NMR {^1H} (C_6D_6, 125 MHz) δ 148.5 (C), 138.0 (C), 124.4 (CH), 117.0 (CH), 116.8 (CH), 83.4 (C), 50.9 (CH_2), 29.9 (CH_2), 25.0 (4 CH_3 of BPin), 22.0 (CH_3), 20.6 (CH_2), 14.1 (CH_3); ^{11}B NMR δ 37.2; FT-IR (neat) $\tilde{\nu}$: 2959, 2932, 2874, 1591, 1443, 1402, 1370, 1310, 1273, 1190, 1146, 853, 710 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 345 (20), 302 (100), 260 (32). Anal. Calcd for $C_{21}H_{36}BNO_2$: C, 73.04; H, 10.51; N, 4.06. Found: C, 72.91; H, 10.91; N, 3.82.

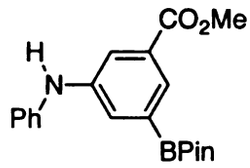
Table 5.2, Entry 5. *N*-Phenyl-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-aniline (5.1).



5.1

The general procedure was applied to 3-bromotoluene (342 mg, 2 mmol). The borylation step was carried out neat with HBPin (580 μL, 512 mg, 4.00 mmol, 2.00 equiv) and dmpe (6 mg, 0.04 mmol, 2 mol%) at 150 °C for 8 h. The amination step was then carried out using $PtBu_3$ (12 mg, 0.06 mmol, 3 mol%) and aniline (224 mg, 2.40 mmol, 1.20 equiv) at 100 °C for 19 h. Column chromatography (hexanes/CH_2Cl_2 2:3) furnished the desired product (389 mg, 63% yield) as light yellow oil.

Table 5.2, Entry 6. Methyl-3-(phenylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzoate (5.7).

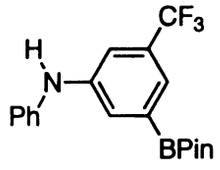


5.7

The general procedure was applied to methyl-3-chlorobenzoate (341 mg, 2 mmol). The borylation step was carried out neat with HBPin (580 μL, 512.0 mg, 4.00 mmol, 2.00 equiv) and dppe (16 mg, 0.04 mmol, 2 mol%) at 100 °C for 17 h. The amination step was then carried out using $PtBu_3$ (12 mg, 0.06 mmol, 3 mol%) and aniline (224 mg, 2.4 mmol, 2.4 equiv) at 100 °C for 16 h. Column chromatography (CH_2Cl_2/ether 30:1) furnished the desired product (335 mg, 47.4%, yield, mp 154-155

°C) as a creamy solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.99 (dd, J = 1.6, 1.0 Hz, 1 H), 7.84 (dd, J = 2.6, 1.6 Hz, 1 H), 7.61 (dd, J = 2.6, 1.0 Hz, 1 H), 7.29-7.25 (m, 2 H), 7.07-7.05 (m, 2 H), 6.96-6.93 (tt, J = 7.3, 1.2, 1.1 Hz, 1 H), 5.77 (br s, 1 H), 3.87 (s, 3 H), 1.32 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz) δ 167.13 (C), 143.0 (C), 142.6 (C), 130.8 (C), 129.5 (CH), 128.2 (CH), 128.1 (CH), 121.5 (CH), 120.6 (CH), 118.1 (CH), 84.1 (C), 52.0 (CH_3), 24.8 (4 CH_3 of BPin); ^{11}B NMR (C_6D_6, 96 Hz) δ 27.8; FT-IR (KBr) $\tilde{\nu}$: 3368, 3042, 3019, 2992, 2977, 2952, 1701, 1593, 1534, 1499, 1466, 1437, 1426, 1418, 1379, 1325, 1308, 1289, 1260, 1219, 1167, 1146, 1123, 1030, 1011, 992, 970, 940, 884, 851, 774, 754, 704, 696, 671, 585 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 353 (100), 338 (3), 322 (4), 253 (17), 236 (12), 220 (6), 194 (39), 167 (22), 77 (13), 59 (10). Anal. Calcd for $C_{20}H_{24}BO_4N$: C, 68.01; H, 6.85; N, 3.97. Found: C, 68.21; H, 6.86; N, 3.93.

Table 5.2, Entry 7. *N*-Phenyl-3-(trifluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-aniline (5.8).

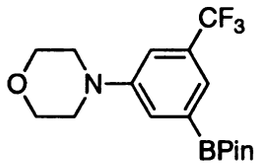


5.8

The general procedure was applied to 3-chloro-benzotrifluoride (361 mg, 2 mmol). The borylation step was carried out neat with HBPin (400 mg, 3.10 mmol, 1.55 equiv) and dppe (16 mg, 0.04 mmol, 2 mol%) at 100 °C for 4 h. The amination step was then carried out using 2-dicyclohexylphosphino-2′-(*N*,*N*-di-methylamino)biphenyl (32 mg, 0.08 mmol, 4 mol%) and aniline (224 mg, 2.40 mmol, 1.2 equiv) at 100 °C for 18 h. Column chromatography (hexanes/CH_2Cl_2 2:3) furnished the desired product (518 mg,

71% yield, mp 83-85 °C) as a light yellow solid. ^{1}H NMR (C_6D_6, 500 MHz) δ 8.03 (d, J = 0.9 Hz, 1 H), 7.74 (d, J = 2.3 Hz, 1 H), 7.14-7.13 (m, 1 H), 7.02-6.99 (m, 2 H), 6.84-6.82 (m, 2 H), 6.79-6.76 (m, 1 H), 4.96 (br s, 1 H), 1.06 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} (C_6D_6, 125 MHz) δ 144.0 (C), 142.2 (C), 131.5 (q, $^2J_{C\text{-}F}$ = 32.1 Hz, C), 129.7 (CH), 126.4 (CH), 125.0 (q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 123.3 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, CH), 122.3 (CH), 118.9 (CH), 116.3 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, CH), 84.2 (C), 24.8 (4 CH_3 of BPin); ^{11}B NMR (C_6D_6, 96 Hz) δ 29.9; ^{19}F NMR (C_6D_6, 282 MHz) δ -62.7; FT-IR (NaCl) $\tilde{\nu}$: 3397, 3362, 3040, 2980, 2932, 2870, 1595, 1520, 1497, 1520, 1497, 1470, 1447, 1414, 1389, 1331, 1300, 1273, 1240, 1215, 1167, 1142, 1125, 1100, 1080, 1030, 996, 970, 953, 876, 851, 828, 760, 745, 710, 696, 689, 666 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 363 (100), 348 (5), 344 (4), 281 (5), 277 (11), 263 (45), 242 (5), 216 (14), 193 (9), 174 (7), 167 (9), 85 (9), 77 (13), 59 (10). Anal. Calcd for $C_{19}H_{21}BF_3N\ O_2$: C, 62.83; H, 5.83; N, 3.86. Found: C, 62.65; H, 5.55; N, 3.78; HRMS (EI): *m/z* 363.1607 [(M^+); Calcd for $C_{19}H_{21}BF_3NO_2$: 363.1617].

Table 5.2, Entry 8. 3-(*N*-morpholino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzotrifluoride (5.9).

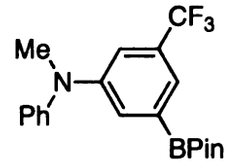


5.9

The general procedure was applied to 3-chloro-benzotrifluoride (361 mg, 2 mmol). The borylation step was carried out neat with HBPin (400 mg, 3.10 mmol, 1.55 equiv) and dppe (16 mg, 0.04 mmol, 2 mol%) at 100 °C for 18 h. The amination step was then carried out using 2-dicyclohexylphosphino-2′-(N,N-di-methylamino)biphenyl (36

mg, 0.08 mmol, 4 mol%) and morpholine (209 mg, 2.4 mmol, 1.2 equiv) at 100 °C for 17 h. Column chromatography (CH_2Cl_2/Ether 30:1) furnished the desired product (349.1 mg, 48.9% yield, mp 72 °C) as a light yellow waxy solid. ^1H NMR (C_6D_6, 500 MHz) δ 7.98 (s, 1 H), 7.58 (d, J = 2.4 Hz, 1 H), 7.06 (s, 1 H), 3.36 (t, J = 4.8 Hz, 4 H), 2.52 (t, J = 4.8 HZ, 4 H), 1.12 (4 CH_3 of BPin); ^{13}C NMR {^1H} (C_6D_6, 125 MHz) δ 151.4 (C), 131.3 (q, $^2J_{C\text{-}F}$ = 31 Hz, C), 125.4 (q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 125.2 (CH), 122.4 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, CH), 114.5 (q, $^3J_{C\text{-}F}$ = 3.1 Hz, CH), 84.2 (C), 66.6 (CH_2), 48.4 (CH_2), 24.9 (4 CH_3 of BPin); ^{19}F NMR (C_6D_6, 282 MHz) δ -62.3; ^{11}B NMR (C_6D_6, 96 Hz) δ 28.1; FT-IR (NaCl) $\tilde{\nu}$: 2980, 2928, 2896, 2859, 2832, 1601, 1470, 1441, 1402, 1325, 1294, 1271, 1167, 1146, 1123, 994, 974, 961, 878, 847, 706, 687 cm^{-1}; GC MS (EI) m/z (% relative intensity): M^+ 357 (100), 342 (7), 299 (25), 284 (33), 256 (10), 228 (8), 213 (63), 199 (75), 171 (27), 142 (22), 85 (12), 59 (19); Anal. Calcd for $C_{17}H_{23}BF_3NO_3$: C, 57.17; H, 6.49; N, 3.92. Found: C, 57.36; H, 6.30; N, 3.99.

Table 5.2, Entry 9. *N*-methyl-*N*-phenyl-3-trifluoromethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)]-aniline (5.10).

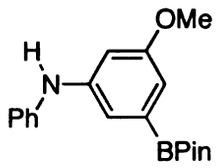


5.10

The general procedure was applied to 3-chloro-benzotrifluoride (181 mg, 1 mmol). The borylation step was carried out neat with HBPin (290 μL, 256 mg, 2.00 mmol, 2.0 equiv) and dmpe (3 mg, 0.02 mmol, 2 mol%) at 150 °C for 4 h. The amination step was then carried out using $PtBu_3$ (6 mg, 0.03 mmol, 3 mol%) and *N*-methyl-aniline (129 mg, 1.2 mmol, 1.2 equiv) at 100 °C for 22.5 h. Column chromatography

(hexanes/CH_2Cl_2 2:1) furnished the desired product (488 mg, 65% yield) as a light yellow waxy solid. ^{1}H NMR (C_6D_6, 500 MHz) δ 8.09 (m, 1 H), 7.82 (d, J = 2.5 Hz, 1 H), 7.34 (m, 1 H), 7.02-6.96 (m, 2 H), 6.86-6.77 (m, 3 H), 2.73 (s, 3 H), 1.05 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} (C_6D_6, 125 MHz) δ 149.4 (C), 148.4 (C), 131.5 (q, $^2J_{C\text{-}F}$ = 31.6 Hz, C), 129.8 (CH), 127.3 (CH), 125.2 (q, $^1J_{C\text{-}F}$ = 272.3 Hz, CF_3), 123.7 (CH), 123.3 (CH), 122.8 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, CH), 117.1 (q, $^3J_{C\text{-}F}$ = 3.0 Hz, CH), 84.1 (C), 39.8 (CH_3), 24.8 (4 CH_3 of BPin); ^{19}F NMR (C_6D_6, 282 MHz) δ –62.6; ^{11}B NMR (C_6D_6, 96 MHz) δ 30.3; FT-IR (neat) $\tilde{\nu}$: 2980, 2936, 1591, 1497, 1470, 1439, 1391, 1373, 1331, 1298, 1271, 1169, 1144, 1125, 1084, 966, 929, 872, 849, 710, 700, 687 cm^{-1}; GC MS (EI) m/z (% relative intensity): M^+ 377 (100). Anal. Calcd for $C_{20}H_{23}BF_3NO_2$: C, 63.68; H, 6.15; N, 3.71. Found: C, 64.03; H, 5.78; N, 3.49; HRMS (EI): *m/z* 377.1779 [(M^+); Calcd for $C_{20}H_{23}BF_3NO_2$: 377.1774].

Table 5.2, Entry 10. *N*-Phenyl-3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolyl-2-yl)-aniline (5.11).

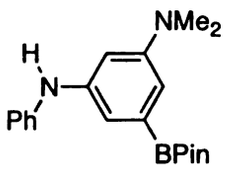


5.11

The general procedure was applied to 3-chloroanisole (285 mg, 2 mmol). The borylation step was carried out neat with HBPin (580 μL, 512 mg, 4.00 mmol, 2 equiv) and dmpe (6 mg, 0.04 mmol, 2 mol%) at 150 °C for 12 h. The amination step was then carried out using 2-dicyclohexylphosphino-2′-(*N*,*N*-di-methylamino)biphenyl (32 mg, 0.08 mmol, 4 mol%) and aniline (242 mg, 2.60 mmol, 1.30 equiv) at 100 °C for 17 h. Column chromatography (pentane/ether 4:1) furnished the desired product (405.5 mg,

62.4% yield) as a light yellow waxy solid. ^{1}H NMR (C_6D_6, 300 MHz) δ 7.46 (d, J = 2.0 Hz, 1 H), 7.37 (d, J = 2.4 Hz, 1 H), 7.05-7.00 (m, 2 H), 6.92-6.89 (m, 2 H), 6.81-6.79 (t, J =2.4 Hz, 1 H), 6.78-6.73 (m, 1 H), 5.19 (br s, 1 H), 3.33 (s, 3 H), 1.12 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} (C_6D_6, 75 MHz) δ 160.9 (C), 144.6 (C), 143.5 (C), 129.5 (CH), 121.1 (CH), 118.2 (CH), 117.7 (CH), 111.9 (CH), 107.7 (CH), 83.8 (C), 54.8 (CH_3), 24.9 (4 CH_3 of BPin); ^{11}B NMR (C_6D_6, 96 MHz) δ 31.8; FT-IR (neat) $\tilde{\nu}$: 3360, 2978, 1588, 1497, 1437, 1373, 1310, 1246, 1194, 1163, 1144, 1057, 970, 909, 853, 743, 699 cm^{-1}; GC MS (EI) m/z (% relative intensity): M^+ 325 (100), 225 (7); Anal. Calcd for $C_{19}H_{24}BNO_3$: C, 70.17, H, 7.44, N, 4.31. Found: C, 69.85, H, 6.68, N, 4.50. HRMS (EI): *m/z* 325.1857 [(M^+); Calcd for $C_{19}H_{24}BNO_3$: 325.2154].

Table 5.2, Entry 11. *N*-Phenyl-3-(*N,N*-dimethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-aniline (5.12).

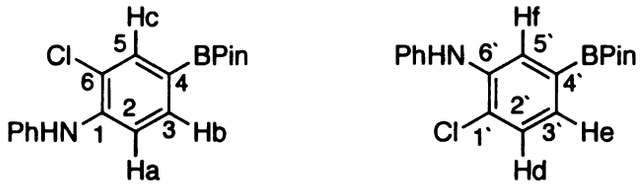


5.12

The general procedure was applied to 3-chloro-*N,N*-dimethyl aniline (312 mg, 2 mmol). The borylation step was carried out neat with HBPin (580 μL, 512.0 mg, 4.00 mmol) and dmpe (6 mg, 0.04 mmol, 2 mol%) at 150 °C for 18 h. The amination step was then carried out using 2-dicyclohexylphosphino-2′-(*N,N*-di-methylamino)biphenyl (32 mg, 0.08 mmol, 4 mol%) and aniline (242 mg, 2.6 mmol, 1.30 equiv) at 100 °C for 17 h. Column chromatography (pentane/THF 5:1) furnished the desired product (494 mg, 73% yield, mp 133-134 °C) as a white solid. ^{1}H NMR (C_6D_6, 300 MHz) δ 7.39 (d, J = 1.5 Hz, 1 H), 7.32 (d, J = 2.5 Hz, 1 H), 7.10-7.04 (m, 2 H), 6.98-6.94 (m, 2 H), 6.79-6.74 (m, 1

H), 6.55 (t, J = 2.3 Hz, 1 H), 5.15 (br s, 1 H), 2.52 (s, 6 H), 1.14 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} (C_6D_6, 75 MHz) δ 151.7 (C), 144.6 (C), 143.8 (C), 129.5 (CH), 120.3 (CH), 117.6 (CH), 114.8 (CH), 113.4 (CH), 106.6 (CH), 83.6 (C), 40.3 (CH_3), 24.9 (4 CH_3 of BPin); ^{11}B NMR (C_6D_6, 96 MHz) δ 32.03; FT-IR (neat) $\tilde{\nu}$: 3366, 3048, 2978, 2932, 2801, 1584, 1497, 1470, 1437, 1414, 1383, 1298, 1275, 1250, 1217, 1143, 1120, 1016, 968, 849, 754, 736, 708, 698 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 338 (100), 309 (7) 237 (5). Anal. Calcd for $C_{20}H_{27}BN_2O_2$: C, 71.02; H, 8.04; N, 8.28. Found: C, 71.05; H, 8.05; N, 8.25.

Table 5.3, Entry 1. *N*-Phenyl-2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-aniline (5.14a + 5.14b).



5.14a 93%

5.14b 7%

The general procedure was applied to 1,2-di-chlorobenzene (294 mg, 2 mmol). The borylation step was carried out neat with HBPin (435 mg, 3.00 mmol, 1.50 equiv) and dmpe (6 mg. 0.04 mmol, 2 mol%) at 100 °C for 4 h. The amination step was then carried out using 2-dicyclohexylphosphinobiphenyl (28 mg, 0.08 mmol, 4 mol%) and aniline (242 mg, 2.6 mmol, 1.30 equiv) at 100 °C for 24 h. The ratio of the two isomers in the crude reaction mixture by GC was 93:7. Column chromatography (hexane/CH_2Cl_2 1:2) furnished a mixture of two isomers (300 mg, 46% combined yield) as alight yellow oil. The ratio of the two isomers in the isolated mixture by GC was 95:5. The presence of two three-bond cross peaks from carbon C1 to protons Hb and Hc in the gHMBC

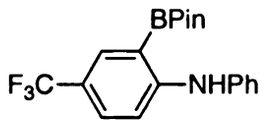
spectrum was used to assign the major isomer as *N*-phenyl-2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-aniline. ^{1}H NMR (C_6D_6, 500 MHz) δ (**5.14a**) 8.24 (d, J = 1.3 Hz, 1 H), 7.82 (dd, J = 8.2, 1.5 Hz, 1 H), 7.14 (d, J = 8.2 Hz, 1 H) 7.01-6.98 (m, 2 H), 6.84-6.81 (m, 1 H), 6.78-6.77 (m, 2 H), 6.08 (br s, 1 H), 1.11 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} (C_6D_6, 125 MHz) δ (**5.14a**)143.5 (C), 140.8 (C), 136.9 (CH), 134.8 (CH), 129.5 (CH), 123.5 (CH), 121.6 (CH), 120.9 (C), 114.2 (CH), 83.7 (C), 24.9 (4 CH_3 of BPin); ^{11}B NMR (C_6D_6, 96 MHz) δ 30.9; FT-IR (neat) $\tilde{\nu}$: 3407, 3050, 2978, 2930, 1593, 1524, 1499, 1470, 1431, 1354, 1265, 1221, 1144, 1098, 1049, 965, 882, 822, 752, 729, 694, 669 cm^{-1}; GC MS (EI) m/z (% relative intensity): M^+ 329 (100), 331 (35), 328 (27), 230 (13), 194 (10). Anal. Calcd for $C_{18}H_{21}BClNO_2$: C, 65.59; H, 6.42; N, 4.25. Found: C, 66.18; H, 6.88; N, 3.98. HRMS (EI): *m/z* 329.1355 [(M^+); Calcd for $C_{18}H_{21}BClNO_2$: 329.1354].

Table 5.3, Entry 2. Attempted amination of 2,5-di-chloro-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzene.

In a dry box, 2,5-di-chloro-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzene (273 mg, 1 mmol, 1 equiv), anhydrous K_3PO_4 (297 mg, 1.40 mmol, 1.40 equiv), Pd_2dba_3 (9 mg, 0.01 mmol, 1 mol%), 2-(dicyclohexylphosphino)biphenyl (14 mg, 0.04 mmol, 4 mol%), aniline (118 μL, 1.30 mmol, 1.30 equiv) and DME (3mL) were added. The flask was then sealed, removed from the dry box, stirred at 100 °C for 24 hr, and the reaction was monitored by GC-FID/MS. GC analysis after 24 hr showed 95% conversion of the starting boron pinacolate ester. The combined GC yield of two isomeric arylamine boronate esters was about 10%. GC ratio of two isomeric arylamine boronotae esters was 7:1. Deborylated aryl amine (approximately 3% by GC) was also observed along with

small amounts of Suzuki products. Attempted isolation was not successful and no clean arylamine boronate ester was isolated.

Table 5.3, Entry 3. *N*-Phenyl-4-(trifluoromethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-aniline (5.16).



5.16

The general procedure was applied to 4-chlorobenzotrifluoride (722 mg, 4.00 mmol, 2.00 equiv). The borylation step was carried out neat with HBPin (256 mg, 2 mmol, 1 equiv) and dmpe (6 mg, 0.04 mmol, 2 mol%) at 150 °C for 4 h. The ratio of the two borylated isomers by GC was 95:5. ^{13}C NMR spectroscopy was used to assign the major borylated isomer as 4-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzotrifluoride. The amination step was then carried out using 2-dicyclohexylphosphino-2′-(*N*,*N*-di-methylamino)biphenyl (32 mg, 0.08 mmol, 4 mol %) and aniline (242 mg, 2.60 mmol, 1.30 equiv) at 100 °C for 8 h. Column chromatography (hexane/CH_2Cl_2 2:1) furnished the desired product (329 mg, 45% yield) as a light yellow solid. Analytically pure material was obtained by recrystallization from benzene, mp 110-111 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.03 (br s, 1 H), 7.99 (d, J = 2 Hz, 1 H), 7.47 (dd, J = 8.8, 2.2 Hz, 1 H), 7.39-7.36 (m, 2 H), 7.26-7.24 (m, 2 H), 7.17 (d, J = 8.8 Hz, 1 H) 7.13-7.10 (m, 1 H), 1.39 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} (C_6D_6, 125 MHz) δ 154.0 (C), 141.3 (C), 135.0 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, CH), 130 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, CH), 129.8 (CH), 125.7 (q, $^1J_{C\text{-}F}$ = 270.4 Hz, CF_3), 123.8 (CH), 122.1 (CH), 120.0 (q, $^2J_{C\text{-}F}$ = 32.6 Hz, C), 112.5 (CH), 84.3 (C), 24.6 (4 CH_3 of BPin); ^{19}F NMR

(C_6D_6, 282 MHz) δ -61.4; ^{11}B NMR (C_6D_6, 96 MHz) δ 31.0; FT-IR (neat) $\tilde{\nu}$: 3380, 2982, 2936, 1620, 1597, 1584, 1499, 1480, 1368, 1316, 1269, 1246, 1167, 1144, 1111, 1078, 1065, 860, 754 cm^{-1}; GC MS (EI) m/z (% relative intensity): M^+ 363 (100), 344 (8), 306 (22) 263 (95). Anal. Calcd for $C_{19}H_{21}BF_3NO_2$: C, 62.83; H, 5.83; N, 3.86. Found: C, 62.98; H, 5.66; N, 3.90.

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CHAPTER 6

Part A: Synthesis of Borylated Aromatic Alkynes by One-Pot Borylation/Sonogashira Coupling

Introductions

Iridium catalyzed aromatic C–H activation/borylation, first reported by Iverson and Smith in 1999,[1] has emerged as one of the most convenient methodology for the regioselective functionalization of aromatics and heteroaromatics.[2-12] Because selectivities in iridium catalyzed borylation are determined by sterics as oppose to electronic effects, this new synthetic tool provides unique regioselectivities which are complementary to those found in electrophilic aromatic substitution[13] and directed *ortho* metalation.[14,15] An important feature of iridium-catalyzed borylation is the tolerance to a variety of functional groups such as halogens, ester, amide, acyl (in 5-membered heterocycles), and nitrile. However functional group tolerance to side chain alkene or unhindered alkyne has not been reported with present catalyst systems.

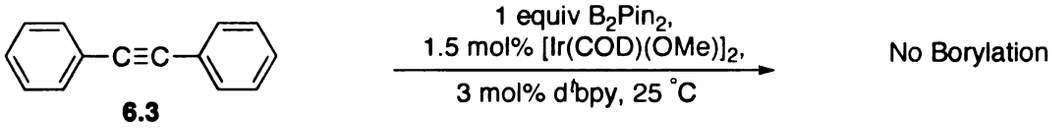
Borylated aromatic alkynes are usually intermediates in the synthesis of extensively conjugated polymeric materials.[16] Aromatic alkynyl boronate esters/acids have also found applications in diverse areas such as crystal engineering,[17] biological inhibition,[18] molecular sensing,[19] chirality and structural assignment,[20] etc. The boronic ester/acid functionality is usually introduced on the aromatic alkyne either by metalation[21,22] or by Pd catalyzed borylation of aromatic halides.[23] Direct C–H bond borylation will reduce the number of steps towards synthesis of borylated aromatic alkynes. This will also allow access to the unique regioselectivities associated with aromatic borylation in the target molecule. Further, reduction of alkyne to alkene will

provide access to aromatic alkenyl boronate esters. We therefore decided to investigate the potential tolerance of alkynyl group in iridium catalyzed aromatic borylation. Herein, we describe our results on attempted borylation of aromatic alkynes, and the synthesis of borylated aromatic alkynes by one-pot borylation/Sonogashira coupling.

Results and Discussion

Attempted borylation of phenyl acetylene (**6.1**) with $[Ir(OMe)(COD)]_2$/dtbpy catalyst system was unsuccessful. Considering that the terminal C–H bond in acetylene may be acidic enough (*p*Ka 25) towards $[Ir(OMe)(COD)]_2$, we examined 1-phenyl-1-propylene (**6.2**) and di-phenyl acetylene (**6.3**) for possible aromatic borylation. Neither of these underwent aromatic borylation with $[Ir(OMe)(COD)]_2$/dtbpy catalyst system (Scheme 6.1). Although these borylation were attempted without pre-generating the active catalyst, it is unlikely that the results will be different with pre-generation.

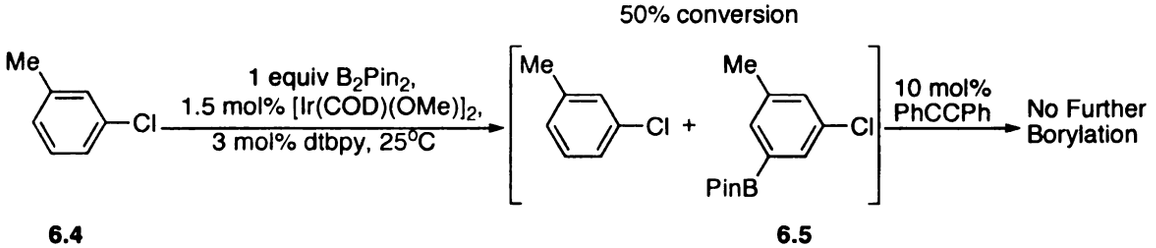
Scheme 6.1. Attempted borylation of di-phenyl acetylene.



6.3

It was also found that the addition of 10 mol% of diphenylacetylene halts the ongoing borylation of an otherwise suitable substrate as shown in Scheme 6.2.

Scheme 6.2. Borylation inhibition by aromatic alkyne.

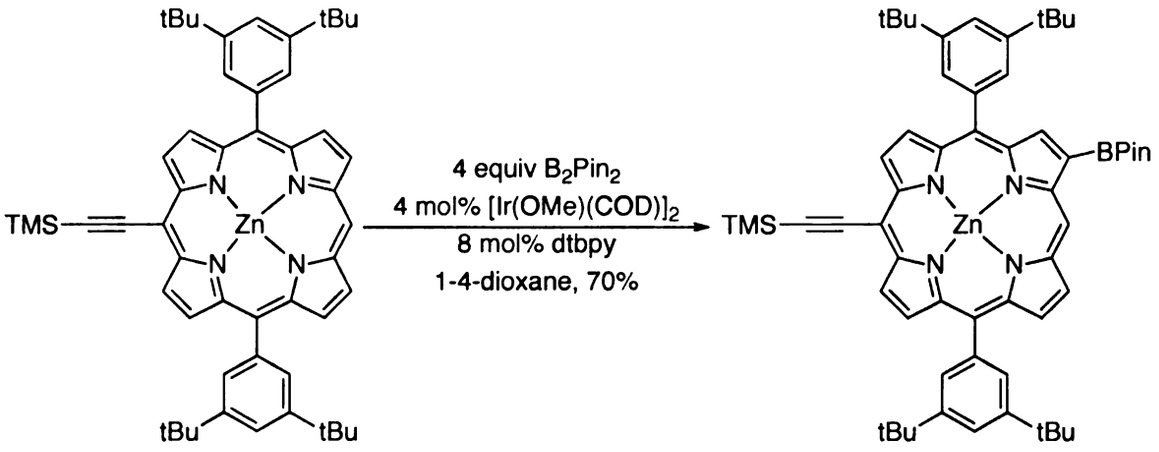


6.4 **6.5**

Attempted borylation of di-phenyl acetylene with (Ind)Ir(COD)/dmpe at 150 °C gave a mixture of products arising from hydrogenation, hydroboration, and catalytic borylation. These results suggest that alkynyl group binds tightly with the active borylation catalyst at room temperature, and at elevated temperatures the alkynyl group becomes a reactive partner.

During the course of this project, Hata et al. reported borylation of alkynylporphyrin **6.6** to synthesize borylated alkynylporphyrin **6.7** (Scheme 6.3).[24] It is likely that the presence of two bulky substituents on alkyne hinder its binding with the active [Ir] catalyst, thus allowing catalytic borylation to take place.

Scheme 6.3. Borylation of alkynylporphyrin.



6.6 **6.7**

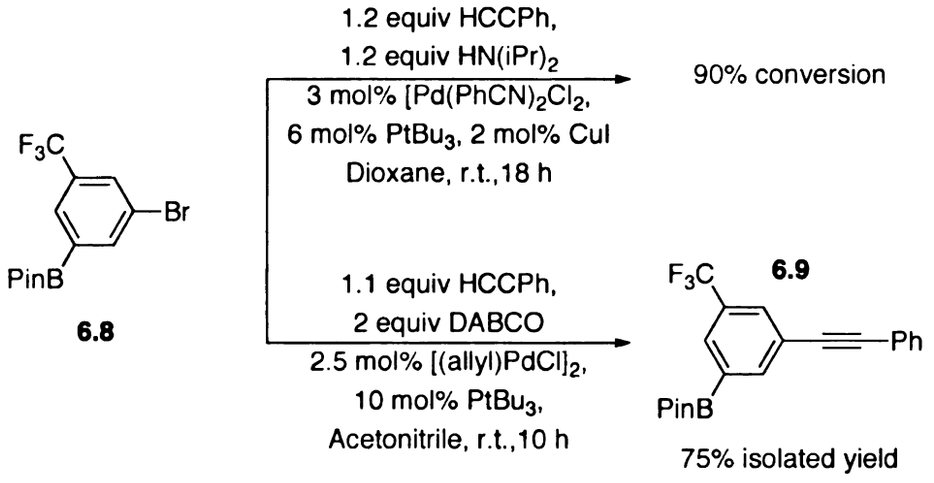
Our results on attempted borylation of unhindered aromatic alkynes prompted us to sought alternate routs for the synthesis of simple borylated aromatic alkynes. Our success in one-pot borylation/amination for the synthesis of aromatic aminoboronate esters had shown that under anhydrous conditions, the C–Halogen bond in a haloarylboronate ester could be selectively employed in C–N coupling while keeping the

C-B bond completely intact.[7,8] We therefore decided to test the viability of Sonogashira coupling[25,26] of haloarylboronate esters.

When this work was started, there were no examples of tolerance of boronic ester group during the Sonogashira reaction. Subsequent to our initial reports,[27,28] some reports have appeared where Sonogashira coupling has been carried out in the presence of boronic ester group.[18,19,29-31] Nevertheless, the direct introduction of boronic ester functionality by iridium catalyzed aromatic C–H activation along with its unique regioselectivities will have its own advantages.

3-Bromo-5-BPin-benzotrifluoride (**6.8**) was subjected to Sonogashira coupling as a test substrate (Scheme 6.4). Using Fu's conditions,[32] the Sonogashira coupling stopped after about 90% conversion of the substrate in 18 h, possibly due to the homocoupling of the phenyl acetylene. We were, however, pleased to observe the formation of the desired borylated aromatic alkyne without any significant deborylation. The presence of CuI co-catalyst during Sonogashira coupling can result in oxidative homocoupling of alkynes. Buchwald has shown that a copper co-catalyst may also inhibit Sonogashira coupling.[33] Shifting to copper free conditions reported by Soheili[34] resulted in full conversion of substrate in 10 h and the resulting borylated aromatic alkyne was isolated in 75% yield.

Scheme 6.4. Sonogashira coupling of 3-bromo-5-BPin-benzotrifluoride.



With this success, we moved to the one-pot sequence of borylation/Sonogashira coupling. We could envision at least two potential issues towards this approach. Firstly, residual iridium catalyst/ligand may affect the subsequent Sonogashira coupling. Secondly, iridium is known to catalyze the polymerization of aromatic alkynes.[35] 3-Bromobenzotrifluoride was borylated using (Ind)Ir(COD)/dmpe catalyst system and the intermediate boronate ester was then subjected to Sonogashira coupling without isolation. The coupling went smoothly without any interference from residual iridium catalyst/borylation by-products and the desired product was isolated in 64% yield. Other substrates were also utilized in this one-pot methodology. The general one-pot borylation/Sonogashira coupling sequence is shown in Scheme 6.5 and the yields of some borylated alkynes are presented in Table 6.1.

Scheme 6.5. One-pot borylation/Sonogashira coupling.

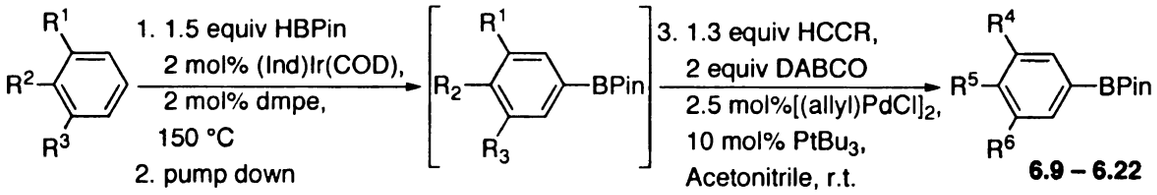


Table 6.1. Preparation of borylated aromatic alkynes by One-pot aromatic borylation/ Sonogashira coupling of aryl bromides according to scheme 6.5.

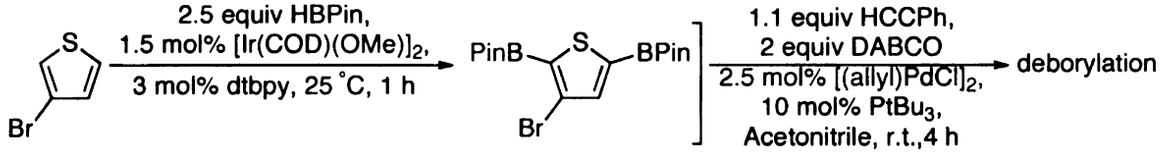
Entry	Substrate			Borylation Time (h)	Alkyne	Sonogashira Time (h)	Product			
	R^1	R^2	R^3				R^4	R^5	R^6	%yield
1	CF_3	H	Br	3	Ph—≡—H	5	CF_3	H	Ph—≡	64 (**6.9**)
2	Me	H	Br	12	Ph—≡—H	12	Me	H	Ph—≡	61 (**6.10**)
3	OMe	H	Br	16	Ph—≡—H	4	OMe	H	Ph—≡	52 (**6.11**)
4	NMe_2	H	Br	24	Ph—≡—H	20	NMe_2	H	Ph—≡	70 (**6.12**)
5	Cl	H	Br	12	Ph—≡—H	12	Cl	H	Ph—≡	37 (**6.13**)
6[b]	CN	H	Br	2	Ph—≡—H	2	CN	H	Ph—≡	52 (**6.14**)
7	Me	H	Br	12	TMS—≡—H	4	Me	H	TMS—≡	65 (**6.15**)
8	Cl	H	Br	4	TMS—≡—H	4	Cl	H	TMS—≡	59 (**6.16**)
9[b,c]	CN	H	Br	2	TMS—≡—H	2	CN	H	TMS—≡	47 (**6.17**)
10	Me	Me	Br	10	Ph—≡—H	18	Me	Me	Ph—≡	77 (**6.18**)
11	Me	Br	Me	4	Ph—≡—H	40	Me	Ph—≡	Me	70 (**6.19**)
12	Br	H	Br	8	TMS—≡—H	2	TMS—≡	H	TMS—≡	54 (**6.20**)
13	Br	Br	H	8	TMS—≡—H	2	TMS—≡	TMS—≡	H	57 (**6.21**)
14	Br	Br	H	4	Ph—≡—H	9	Ph—≡	Ph—≡	H	78 (**6.22**)

[a]See experimental section for specific details. [b]3 mol% $[Ir(OMe)(COD0]_2$/dtbpy was used for borylation. [c]Borylation was carried out with 0.6 equiv of B_2Pin_2.

Both electron rich as well as electron deficient aryl bromides were used as electrophiles. Phenyl acetylene and TMS acetylene were employed as the alkyne partner. Functional groups such as Cl, CN, and OMe were tolerated which can potentially be further elaborated. Entries 10 and 11 show that a hindered C–Br bond in a bromoaryl boronate ester can undergo selective Sonogashira coupling without any deborylation of the easily accessible C–B bond. Double Sonogashira coupling can be carried out starting from 1,3-di-bromobenzene (entry 12). Attempted mono-Sonogashira coupling on the intermediate boronic ester of 1,2-di-bromobenzene using 0.9 equiv of TMS-acetylene resulted in a 1:3 mixture of two regioisomers, however the di-Sonogashira product was the major species observed by GC-FID. The resulting borylated aromatic enediynes were isolated in good yields by using 2.2 equiv of alkyne (entries 13 and 14). It might be however possible to achieve good selectivity in mono-Sonogashira coupling, without forming the di-Sonogashira product, by using a less active catalyst system.

To expand the scope of this methodology to heteroaromatics, we examined the one-pot borylation/Sonogashira coupling of 3-bromothiophene as shown in Scheme 6.5. The diborylation was complete in 1 h, however upon subsequent Sonogashira coupling, extensive deborylation was observed.

Scheme 6.6. Attempted di-borylation Sonogashira coupling of 3-bromothiophene.



Considering that presence of iridium may have caused deborylation, we tested Sonogashira coupling on isolated 2-bromo-5-BPin-thiphene. Although the Sonogashira coupling was complete in 2 h, about 80% of the coupled product was deborylated. These results suggest that the presence of BPin functionality on the 2-position of thiophene does not survive Sonogashira conditions. Zheng[30] has also reported deborylation during microwave assisted Sonogashira coupling of 2-borylated heteroaromatics. It might be however possible to tolerate BPin group in heteroarenes on a position further away from the heteroatom (or with better catalysts).

In conclusion, we have developed an efficient one-pot aromatic C–H activation borylation/Sonogashira coupling protocol for the synthesis of borylated aromatic alkynes starting from simple aryl bromides. This methodology tolerates a variety of functional groups and several borylated alkynes were prepared in good to high yields. Further elaboration of these synthetically useful intermediates for possible applications in material sciences needs to be investigated. Extension of this methodology to heteroaromatic aryl halides, and inclusion of aryl chlorides as coupling partner will also be useful.

CHAPTER 6

Part B: Synthesis of Borylated Aromatic Thioethers by One-Pot Borylation/C–S Coupling

Introduction

Our success in one-pot borylation/cross coupling reactions of aryl halides to synthesize aromatic amino boronate esters[7] and aromatic alkynyl boronate esters prompted us to further expand the scope of one-pot methodology for the synthesis of multiply functionalized aromatic building blocks starting from simple aryl halides. We were particularly interested in C–S and C–O couplings since aromatic ethers/thioethers have a wide range of applications. Aromatic thio boronate esters and borylated aromatic ethers are usually prepared by metalation or by Miyaura's Pd catalyzed borylation[36] of aryl halides. Application of iridium catalyzed aromatic C–H activation/borylation for the incorporation of boronic ester group can reduce the number of steps towards the synthesis of these molecules. However the iridium catalyzed borylation of aromatic ethers is very slow due to the electron rich nature of substrate. Although there is one example of tolerance of SMe group during iridium catalyzed aromatic borylation,[6] less reactivity similar to aromatic ethers is expected in other aromatic thioethers.

Iridium catalyzed aromatic C–H activation/borylation of aryl halides followed by C–S/C–O coupling at the C–Halogen bond can be an alternate route for these compounds. There is no example in literature where a C–B bond survives during C–S/C–O bond forming reaction. Further the C–B bond has often been employed in the construction of C–S/C–O bond.[37,38] We were however optimistic that under anhydrous conditions, the

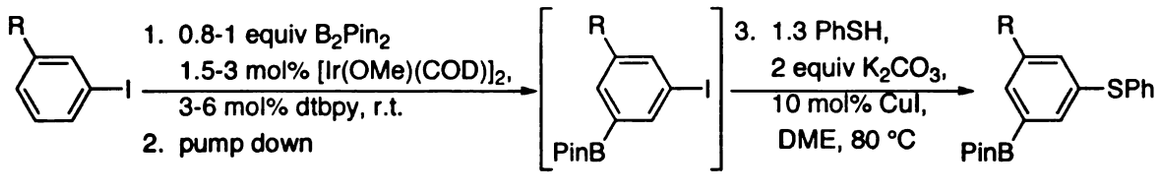
desired chemoselective transformation at the C–Halogen bond might be achieved while keeping the C–B bond completely intact.

Results and Discussion

As a first step, we subjected isolated boronic ester derived from 3-bromoiodobenzene to C–S coupling conditions reported by Buchwald.[39] Coupling with analytical grade thiophenol resulted in deborylation. However, with distilled thiophenol and 10 mol % CuI catalyst loading, the coupling went smoothly in DME solvent and the borylated thioether was isolated in 84% yield. Next, we examined the one-pot borylation/C–S coupling sequence starting from simple 3-substituted aryl iodides. We were delighted that newly formed C–B bond survived during the subsequent C–S coupling step. Also, the residual iridium catalyst/borylation by products did not cause any complication in the C–S coupling step. The general one-pot borylation/C–S coupling procedure is shown in Scheme 6.6. The isolated yields for borylated aromatic thioethers are shown in Table 6.2.

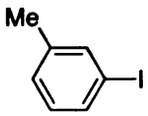
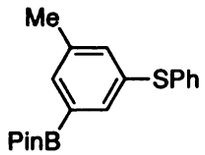
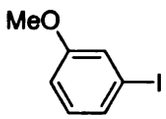
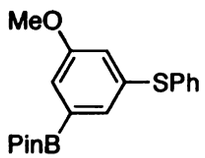
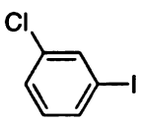
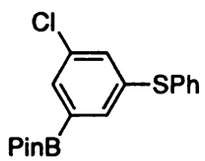
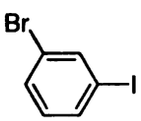
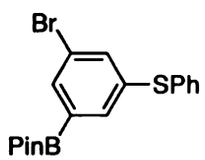
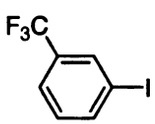
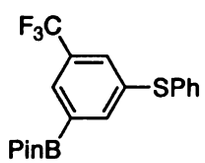
As per literature,[39] functional groups such as alkyl, alkoxy, Cl, Br, and CF_3 were tolerated under these conditions. However, we noticed that aliphatic sulfides, when used as coupling partners, were much less reactive under these conditions and the C-S coupling step was not complete even after one week at 80 °C.

Scheme 6.7. One-pot borylation/C-S coupling of aryl iodides.



R = Me, OMe, Cl, Br, CF_3 **6.23-6.27**

Table 6.2. Preparation of aromatic thioethers boronate esters by One-pot aromatic borylation/C–S coupling of aryliodides according to scheme 6.7.

Entry	Aryl Iodide	Borylation Time (h)	C–S Coupling Time (h)	Product	%yield
1[a]		48	36		73 **6.23**
2[a]		36	24		77 **6.24**
3[b]		12	24		43 **6.25**
4[b]		12	24		26 **6.26**
5[b]		12	24		71 **6.27**

a. 1 equiv of B_2Pin_2 and 6 mol% [Ir] was used. b. 0.8 equiv of B_2Pin_2 and 3 mol% [Ir] was used.

We have previously reported that aromatic borylation can be carried out in the presence of SMe functional group (Figure 6.1).[6] However, borylation on di-aryl substituted sulfides can potentially take place on both of the aromatic rings. In cases where borylation of only one of the two aryl rings is desired, one-pot borylation/C-S coupling sequence will provide the desired product as a single regioisomer.

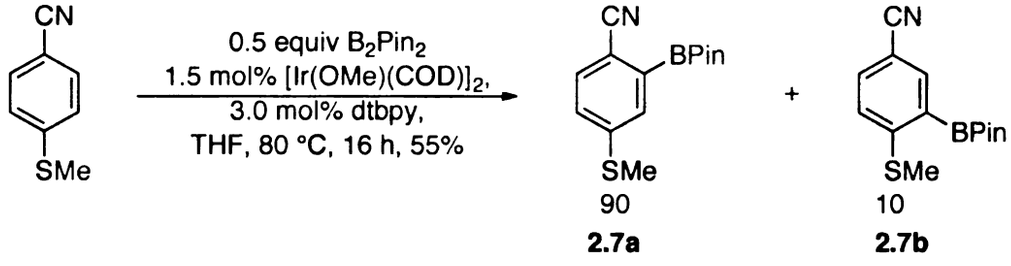


Figure 6.1. Functional group tolerence of SMe group in Ir catalyzed aromatic borylation.

Migita has reported the $Pd(PPh_3)_4$ catalyzed nucleophillic substitution of aryl bromides with thiolate anions using NaO^{t}Bu base (Eq 6.1).[40] Attempted C–S coupling of 3-bromo-5-BPin-toluene under these conditions resulted in a 50:50 mixture of the desired product along with the deborylated product. No C–S coupling was observed using the weaker base, K_2CO_3.

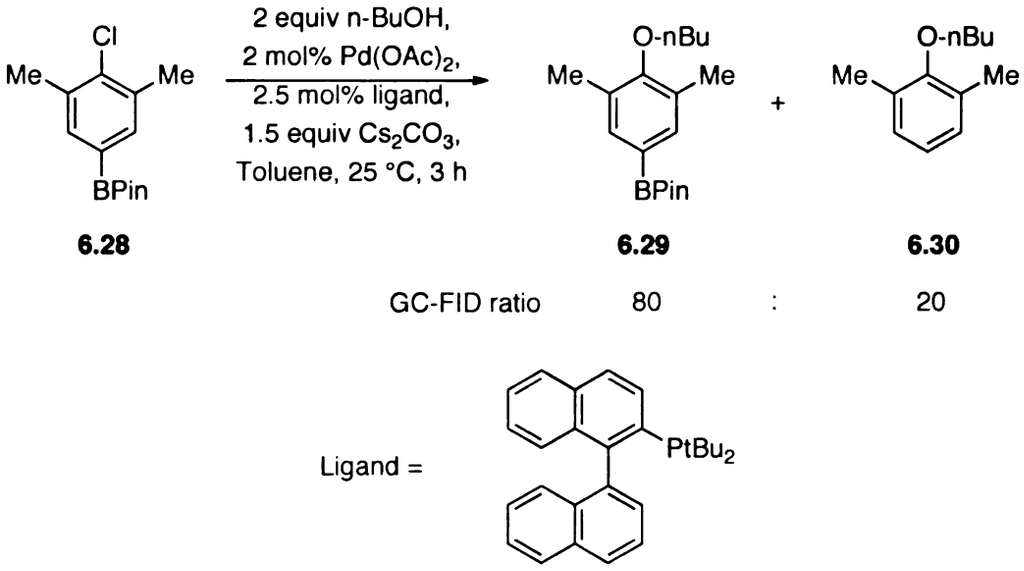
$$\text{ArX} + \text{RSH} \xrightarrow[8\ \text{mol\%}\ Pd(PPh_3)_4]{2\ \text{equiv}\ t\text{-BuONa}} \text{ArSR} \qquad (6.1)$$

In conclusion, one-pot borylation/C–S coupling is a convenient route for the synthesis of borylated aromatic thioethers.

Attempted C–O Coupling of Borylated Aryl Chloride.

Attempted C-O coupling[41] on an isolated hindered borylated aryl chloride met with much less success as significant deborylation was observed (Scheme 6.7). This is probably due to high tendency of the C-B bond to undergo transmetallation with (alkoxo)-Palladium (II) complexes.[42]

Scheme 6.7. Attempted C–O coupling of 2-chloro-5-BPin-*m*-xylene.



Formation of the desired product as the major species is promising. This suggests that the formaion of C–O bond is much faster as compared to the breaking of C–B bond. Use of a more active catalyst for C–O coupling, less n-BuOH, and more active aryl bromide in place of the aryl chloride, may result in clean C–O coupling without any deborylation. The present study was limited to a single substrate. Detailed studies of this reaction, along with differently substituted aryl halides as starting materials needs to be carried out.

Experimental Details and Spectroscopic Data Part A

Materials

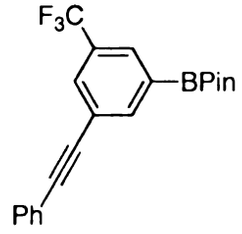
All commercially available chemicals were used as received or purified as described. Bis(η^4-1,5-cyclooctadiene)-di-μ-methoxy-diiridium(I) $[Ir(OMe)(COD)]_2$, (η^5-Indenyl)(cyclooctadiene)iridium {(Ind)Ir(COD)}, and Pinacolborane (HBPin) were prepared per the literature procedures.[43-45] 4,4′-Di-*t*-butyl-2,2′-bipyridine (dtbpy), bis(pinacolato)diboron (B_2Pin_2), and 3-bromobenzonitrile were sublimed before use. Liquid aryl bromides were refluxed over CaH_2, distilled, and degassed. Phenyl acetylene was distilled before use. Acetonitrile was distilled over activated molecular sieves. *n*-Hexane was refluxed over sodium, distilled, and degassed. Silica gel (230-400 Mesh) was purchased from EMD™.

General Procedure

In a glove box, (Ind)Ir(COD) (8 mg, 0.02 mmol, 2 mol% Ir), dmpe (3 mg, 0.02 mmol, 2 mol%), HBPin (256 mg, 2.0 mmol, 2 equiv), and aryl halide (1 mmol, 1 equiv) were transferred into a Schlenk flask equipped with a magnetic stirring bar. The flask was stoppered, removed from the glove box, and stirred at 150 °C until the borylation was judged complete by GC-FID/MS. The reaction mixture was allowed to cool to room temperature and subsequently placed under high vacuum for 1-2 h. The Schlenk flask was brought into the dry box and 1,4-diazabicyclo[2.2.2]octane [DABCO] (225 mg, 2 mmol, 1 equiv), allylpalladium chloride dimer (9 mg, 0.025 mmol, 2.5 mol%), $PtBu_3$ (20 mg, 0.1 mmol, 10 mol%), alkyne (1.1-1.3 mmol, 1.1-1.3 equiv) and acetonitrile (3mL) were added.[34] The flask was then stoppered, and stirred at room temperature until the Sonogashira coupling was judged complete by GC-FID. After completion, 10 mL of

water were added to the reaction mixture. The reaction mixture was extracted with ether (10 mL × 3). The combined ether extractions were washed with brine (10 mL), followed by water (10 mL), dried over $MgSO_4$ before being concentrated under reduced pressure on a rotary evaporator. The crude material was then subjected to column chromatography.

Table 6.1, Entry 1. 3-(Phenylethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzotrifluoride (6.9).

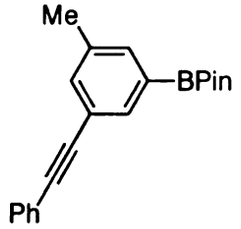


6.9

The general procedure was applied to 3-bromobenzotrifluoride (279 μL, 450 mg, 2 mmol, 1 equiv). The borylation step was carried out with HBPin (436 μL, 384 mg, 3.00 mmol, 1.50 equiv) for 3 h. The Sonogashira coupling step was carried out with phenyl acetylene (242 μL, 225 mg, 2.20 mmol, 1.1 equiv) for 5 h. Gradient column chromatography (pentane:dichloromethane 4:1 → pentane:dichloromethane 1:1) furnished the desired product as orange yellow oil, which solidified on standing (473 mg, 64% yield, mp 74-75 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.12 (br s, 1 H), 7.97-7.98 (m, 1 H), 7.83-7.84 (m, 1 H), 7.48-7.53 (m, 2 H), 7.32-7.36 (m, 3 H), 1.35 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 141.0 (CH), 131.7 (2 CH), 130.6 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, CH), 130.5 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, CH), 130.4 (q, $^2J_{C\text{-}F}$ = 31.6 Hz, C), 128.6 (CH), 128.4 (2 CH), 123.9 (q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 123.8 (C), 123.7 (C), 91.0 (C), 87.8 (C), 84.4 (2 C), 24.7 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.6; ^{19}F NMR ($CDCl_3$,

282 MHz) δ -63.0; FT-IR (neat) $\tilde{\nu}$: 2980, 1601, 1493, 1369, 1306, 1277, 1169, 1130, 966, 898, 871, 847, 756, 704, 688 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 372 (100), 357 (10), 286 (18), 272 (12); HRMS (FAB): *m/z* 372.1510 [(M^+); Calcd for $C_{21}H_{20}BF_3O_2$: 372.1508].

Table 6.1, Entry 2. 3-(Phenylethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-toluene (6.10).

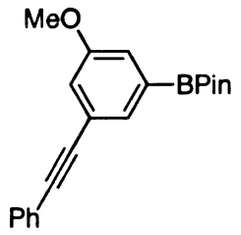


6.10

The general procedure was applied to 3-bromotoluene (122 μL, 171 mg, 1 mmol, 1 equiv). The borylation step was carried out with HBPin (290 μL, 256 mg, 2.00 mmol, 2.00 equiv) for 12 h. The Sonogashira coupling step was carried out with phenyl acetylene (121 μL, 112 mg, 1.10 mmol, 1.1 equiv) for 12 h. Column chromatography (pentane/dichloromethane 1:1, R_f 0.8) furnished the desired product as yellow oil, which solidified on standing (193 mg, 61% yield, mp 73-75 °C). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.80 (s, 1 H), 7.57-7.58 (m, 1 H), 7.47-7.50 (m, 2 H), 7.43-7.44 (m, 1 H), 7.30-7.34 (m, 3 H), 2.34 (s, 3 H), 1.34 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} ($CDCl_3$, 125 MHz): δ 137.3 (C), 135.3 (CH), 135.2 (CH), 134.7 (CH), 131.6 (2 CH), 128.3 (2 CH), 128.1 (CH), 123.6 (C), 122.8 (C), 89.6 (C), 89.1 (C), 83.9 (2 C), 24.9 (4 CH_3 of BPin), 21.0 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 31.7; FT-IR (neat) $\tilde{\nu}$: 2976, 1595, 1491, 1417, 1385, 1371, 1317, 1289, 1207, 1143, 966, 852, 756, 706, 690 cm^{-1}; GC-MS (EI) *m/z* (% relative

intensity): M^+ 318 (100), 304 (15), 233 (11), 219 (12); HRMS (FAB): *m/z* 318.1794 [(M^+); Calcd for $C_{21}H_{23}BO_2$: 318.1791].

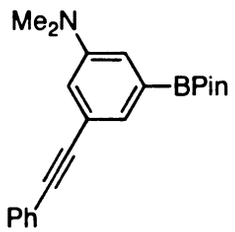
Table 6.1, Entry 3. 3-(Phenylethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-anisole (6.11).



6.11

The general procedure was applied to 3-bromoanisole (254 μL, 374 mg, 2 mmol, 1 equiv). The borylation step was carried out with HBPin (580 μL, 512 mg, 4.00 mmol, 2.00 equiv) for 16 h. The Sonogashira coupling step was carried out with phenyl acetylene (286 μL, 266 mg, 2.60 mmol, 1.3 equiv) for 4 h. Gradient column chromatography (hexanes/dichloromethane 1:1 → hexanes/dichloromethane 0:1) furnished the desired product as yellow oil (343 mg, 52% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.59 (dd, *J* = 1.5, 0.7 Hz, 1 H), 7.49-7.51 (m, 2 H), 7.31-7.33 (m, 3 H), 7.29 (dd, *J* = 2.7, 0.7 Hz, 1 H), 7.14 (dd, *J* = 2.7, 1.5, Hz, 1 H), 3.83 (s, 3 H), 1.34 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 158.9 (C), 131.6 (2 CH), 130.7 (CH), 128.3 (2 CH), 128.2 (CH), 123.9 (C), 123.3 (C), 119.8 (CH), 119.6 (CH), 89.22 (C), 89.20 (C), 84.0 (2 C), 55.4 (OCH_3), 24.9 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.6; FT-IR (neat) $\tilde{\nu}$: 2980, 1581, 1373, 1224, 1143, 1057, 966,850, 756, 704 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 334 (100), 319 (10), 276 (6), 248 (15), 234 (21); HRMS (FAB): *m/z* 334.1742 [(M^+); Calcd for $C_{21}H_{23}BO_3$: 334.1740].

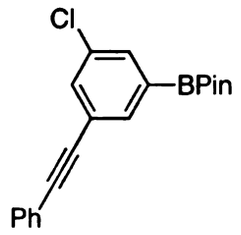
Table 6.1, Entry 4. *N,N*-Di-methyl-3-(phenylethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-aniline (6.12).



6.12

The general procedure was applied to *N,N*-dimethyl-3-bromoaniline (400 mg, 2 mmol, 1 equiv). The borylation step was carried out with HBPin (580 μL, 512 mg, 4.00 mmol, 2.00 equiv) for 24 h. The Sonogashira coupling step was carried out with phenyl acetylene (242 μL, 225 mg, 2.20 mmol, 1.1 equiv) for 20 h. Column chromatography (pentane/ether 4:1, R_f 0.5) furnished the desired product as yellow oil (488 mg, 70% yield). ^{1}H NMR (C_6D_6, 300 MHz): δ 8.02 (br s, 1 H), 7.50-7.53 (m, 2 H), 7.47 (d, J = 2.4 Hz, 1 H), 7.11 (dd, J = 2.6, 1.5 Hz, 1 H), 6.95-7.05 (m, 3 H), 2.42 (s, 6 H), 1.13 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} (C_6D_6, 75 MHz): δ 150.3 (C), 131.9 (2 CH), 128.5 (2 CH), 128.1 (CH), 127.5 (CH), 124.3 (C), 124.0 (C), 119.5 (CH), 118.4 (CH), 91.5 (C), 89.0 (C), 83.8 (2 C), 40.0 (2 CH_3), 25.0 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 31.0; FT-IR (neat) $\tilde{\nu}$: 2978, 2930, 2799, 1587, 1489, 1429, 1386, 1269, 1143, 1010, 966, 846, 756, 704, 690 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 347 (100), 289 (2), 247 (10); HRMS (FAB): *m/z* 347.2060 [(M^+); Calcd for $C_{22}H_{26}BNO_2$: 347.2057].

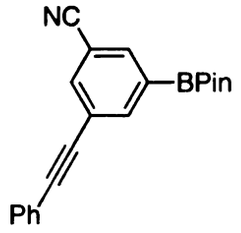
Table 6.1, Entry 5. 3-(Phenylethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-chlorobenzene (6.13).



6.13

The general procedure was applied to 3-bromochlorobenzene (118 μL, 191 mg, 1 mmol, 1 equiv). The borylation step was carried out with HBPin (290 μL, 256 mg, 2.00 mmol, 2.00 equiv) for 12 h. The Sonogashira coupling step was carried out with phenyl acetylene (121 μL, 112 mg, 1.10 mmol, 1.1 equiv) for 12 h. Column chromatography (pentane/dichloromethane 4:3, R_f 0.8) furnished the desired product as a light yellow solid (117 mg, 37% yield, mp 45-46 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.84 (dd, J = 1.6, 1.0 Hz, 1 H), 7.71 (dd, J = 2.2, 1.0 Hz, 1 H), 7.57 (dd, J = 2.2, 1.6 Hz, 1 H), 7.48-7.51 (m, 2 H), 7.32-7.34 (m, 3 H), 1.34 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 136.0 (CH), 134.2 (CH), 133.9 (C), 133.7 (CH), 131.7 (2 CH), 128.5 (CH), 128.4 (2 CH), 124.7 (C), 122.9 (C), 90.5 (C), 88.0 (C), 84.4 (2 C), 24.9 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.8; FT-IR (neat) $\tilde{\nu}$: 2978, 1562, 1412, 1356, 1142, 966, 862, 756, 700, 690 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 338 (100), 340(33), 324 (18), 280 (5), 252 (59); HRMS (FAB): *m/z* 338.1247 [(M^+); Calcd for $C_{20}H_{20}BClO_2$: 338.1245].

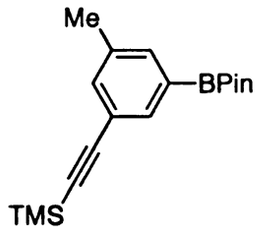
Table 6.1, Entry 6. 3-(Phenylethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzonitrile (6.14).



6.14

The general procedure was applied to 3-bromobenzonitrile (182 mg, 1 mmol, 1 equiv). The borylation step was carried out with HBPin (290 μL, 256 mg, 2.00 mmol, 2.00 equiv), $[Ir(OMe)(COD)]_2$ (10 mg, 0.015 mmol, 3 mol% Ir), and dtbpy (8 mg, 0.03 mmol, 3 mol%) at room temperature for 2 h. The Sonogashira coupling step was carried out with phenyl acetylene (121 μL, 112 mg, 1.10 mmol, 1.1 equiv) for 2 h. Column chromatography (dichloromethane, R_f 0.7) furnished the desired product as a light yellow solid (171 mg, 52% yield, mp 83-85 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.14 (dd, J = 1.7, 1.2 Hz, 1 H), 7.99 (dd, J = 1.7, 1.2 Hz, 1 H), 7.84 (t, J = 1.7 Hz, 1 H), 7.48-7.51 (m, 2 H), 7.33-7.38 (m, 3 H), 1.34 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 141.7 (CH), 137.4 (CH), 136.8 (CH), 131.7 (2 CH), 128.9 (CH), 128.4 (2 CH), 124.4 (C), 122.5 (C), 118.1 (C), 112.6 (C), 91.7 (C), 87.0 (C), 84.7 (2 C), 24.9 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 29.7; FT-IR (neat) $\tilde{\nu}$: 3061, 2980, 2932, 2231 (s), 2212 (w), 1589, 1491, 1415, 1377, 1329, 1298, 1143, 1122, 966, 897, 848, 756, 698, 690 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 329 (100), 314 (8), 244 (46), 230 (27); HRMS (FAB): *m/z* 330.1668 [(M^{+1}); Calcd for $C_{21}H_{21}BNO_2$: 330.1665].

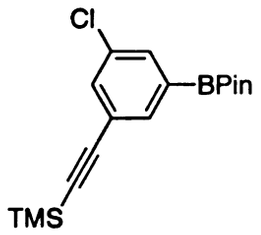
Table 6.1, Entry 7. 3-(Trimethylsilylethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-toluene (6.15).



6.15

The general procedure was applied to 3-bromotoluene (122 μL, 171 mg, 1 mmol, 1 equiv). The borylation step was carried out with HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 12 h. The Sonogashira coupling step was carried out with trimethylsilyl acetylene (156 μL, 108 mg, 1.10 mmol, 1.1 equiv) for 4 h. Column chromatography (pentane/ether 9:1, R_f 0.8) furnished the desired product as yellow oil (204 mg, 65% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73 (d, J = 0.5 Hz, 1 H), 7.54 (d, J = 0.7 Hz, 1 H), 7.36 (m, 1 H), 2.29 (s, 3 H), 1.32 (br s, 12 H, 4 CH_3 of BPin), 0.21 (s, 9 H, 3 CH_3 of TMS); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 137.1 (C), 135.6 (CH), 135.4 (CH), 135.0 (CH), 122.5 (C), 105.3 (C), 93.6 (C), 83.9 (2 C), 24.9 (4 CH_3 of BPin), 20.9 (CH_3), -0.02 (3 CH_3 of TMS); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.3; FT-IR (neat) $\tilde{\nu}$: 2978, 2154, 1591, 1383, 1365, 1248, 1145, 966, 848, 760, 706 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 314 (15), 299 (100), 199 (11); HRMS (FAB): *m/z* 314.1875 [(M^+); Calcd for $C_{18}H_{27}BO_2Si$: 314.1873].

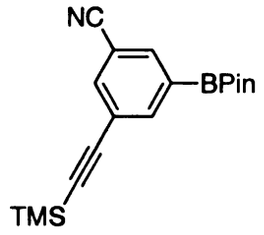
Table 6.1, Entry 8. 3-(Trimethylsilylethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-chlorobenzene (6.16).



6.16

The general procedure was applied to 3-bromochlorobenzene (118 μL, 191 mg, 1 mmol, 1 equiv). The borylation step was carried out with HBPin (218 μL, 192 mg, 1.50 mmol, 1.50 equiv) for 4 h. The Sonogashira coupling step was carried out with trimethylsilyl acetylene (184 μL, 128 mg, 1.30 mmol, 1.3 equiv) for 4 h. Gradient column chromatography (hexanes/dichloromethane 1:1 → hexanes/dichloromethane 0:1) furnished the desired product as yellow oil (196 mg, 59% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.76 (dd, J = 1.6, 1.0 Hz, 1 H), 7.68 (dd, J = 2.2, 1.0 Hz, 1 H), 7.49 (dd, J = 2.2, 1.6 Hz, 1 H), 1.31 (br s, 12 H, 4 CH_3 of BPin), 0.21 (s, 9 H, 3 CH_3 of TMS); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 136.3 (CH), 134.4 (CH), 134.0 (CH), 133.8 (C), 124.4 (C), 103.4 (C), 95.6 (C), 84.3 (2 C), 24.8 (4 CH_3 of BPin), -0.2 (3 CH_3 of TMS); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.7; FT-IR (neat) $\tilde{\nu}$: 2978, 2166, 1562, 1352, 1143, 966, 927, 844, 760, 702 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 334 (8), 320 (100), 219 (10); HRMS (FAB): *m/z* 335.1407 [(M^{+1}); Calcd for $C_{17}H_{25}BO_2SiCl$: 335.14055].

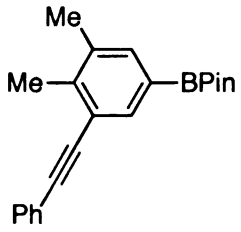
Table 6.1, Entry 9. 3-(Trimethylsilylethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzonitrile (6.17).



6.17

The general procedure was applied to 3-bromobenzonitrile (182 mg, 1 mmol, 1 equiv). The borylation step was carried out with B_2Pin_2 (153 mg, 0.60 mmol, 1.2 equiv of boron), $[Ir(OMe)(COD)]_2$ (10 mg, 0.015 mmol, 3 mol% Ir), and dtbpy (8 mg, 0.03 mmol, 3 mol%) at room temperature for 2 h. The Sonogashira coupling step was carried out with trimethylsilyl acetylene (156 μL, 108 mg, 1.10 mmol, 1.1 equiv) for 2 h. Column chromatography (pentane/ethylacetate 9:1, R_f 0.7) furnished the desired product as yellow oil (154 mg, 47% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.05 (dd, J = 1.7, 1.0 Hz, 1 H), 7.96 (dd, J = 1.7, 1.2 Hz, 1 H), 7.75 (t, J = 1.7 Hz, 1 H), 1.32 (br s, 12 H, 4 CH_3 of BPin), 0.21 (s, 9 H, 3 CH_3 of TMS); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 142.0 (CH), 137.6 (CH), 137.1 (CH), 124.1 (C), 117.9 (C), 112.3 (C), 102.3 (C), 97.1 (C), 84.7 (2 C), 24.8 (4 CH_3 of BPin), -0.3 (3 CH_3 of TMS); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.5; FT-IR (neat) $\tilde{\nu}$: 2961, 2235, 2158, 1589, 1369, 1250, 1143, 968, 954, 846, 760, 700 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 325 (3), 311 (100), 210 (3); HRMS (FAB): *m/z* 326.1748 [(M^{+1}); Calcd for $C_{18}H_{25}BO_2SiN$: 326.17477].

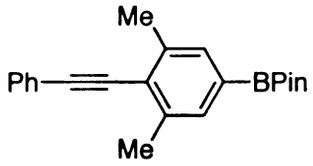
Table 6.1, Entry 10. 3-(Phenylethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-*o*-xylene (6.18).



6.18

The general procedure was applied to 3-bromo-*o*-xylene (136 μL, 185 mg, 1 mmol, 1 equiv). The borylation step was carried out with HBPin (290 μL, 256 mg, 2.00 mmol, 2.00 equiv) for 10 h. The Sonogashira coupling step was carried out with phenyl acetylene (143 μL, 132 mg, 1.30 mmol, 1.3 equiv) for 18 h. Column chromatography (pentane/dichloromethane 1:2, R_f 0.8) furnished the desired product as a yellow solid (255 mg, 77% yield, mp 104-105 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.88 (s, 1 H), 7.57 (s, 1 H), 7.51-7.54 (m, 2 H), 7.30-7.36 (m, 3 H), 2.50 (s, 3 H), 2.31 (s, 3 H), 1.35 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 141.7 (C), 136.5 (CH), 136.1 (C), 135.8 (CH), 131.4 (2 CH), 128.3 (2 CH), 127.9 (CH), 123.7 (C), 122.9 (C), 92.7 (C), 88.9 (C), 83.8 (2 C), 24.9 (4 CH_3 of BPin), 20.1 (CH_3), 17.7 (CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.9; FT-IR (neat) $\tilde{\nu}$: 2978, 1398, 1389, 1143, 966, 854, 756, 686 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 332 (100), 318 (14), 275 (6), 247 (8), 232 (20), 218 (12); HRMS (FAB): *m/z* 332.1948 [(M^+); Calcd for $C_{22}H_{25}BO_2$: 332.19477].

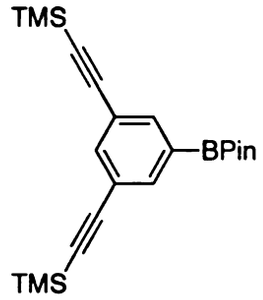
Table 6.1, Entry 11. 2-(Phenylethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-*m*-xylene (6.19).



6.19

The general procedure was applied to 2-bromo-*m*-xylene (134 μL, 185 mg, 1 mmol, 1 equiv). The borylation step was carried out with HBPin (290 μL, 256 mg, 2.00 mmol, 2.00 equiv) for 4 h. The Sonogashira coupling step was carried out with phenyl acetylene (143 μL, 132 mg, 1.30 mmol, 1.3 equiv) for 40 h. Gradient column chromatography (hexanes/dichloromethane 2:1 → hexanes:dichloromethane 0:1) furnished the desired product as yellow oil (233 mg, 70% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55-7.57 (m, 2 H), 7.54 (s, 2 H), 7.33-7.39 (m, 3 H), 2.53 (s, 3 H), 1.37 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 139.4 (2 C), 132.8 (2 CH), 131.4 (2 CH), 128.4 (CH), 128.2 (CH), 125.8 (C), 123.7 (C), 99.0 (C), 87.3 (C), 83.8 (2 C), 24.8 (4 CH_3 of BPin), 20.9 (2 CH_3); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 31.3; FT-IR (neat) $\tilde{\nu}$: 2978, 1606, 1385, 1365, 1315, 1238, 1143, 856, 756, 686 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 332 (100), 318 (5), 247 (22), 233 (16), 218 (9); HRMS (FAB): *m/z* 332.1950 [(M^+); Calcd for $C_{22}H_{25}BO_2$: 332.1948].

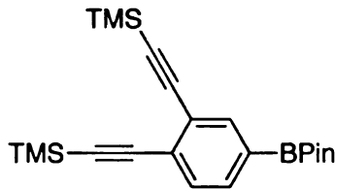
Table 6.1, Entry 12. 1,3-Bis-(trimethylsilylethynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzene (6.20).



6.20

The general procedure was applied to 1,3-di-bromobenzene (121 μL, 236 mg, 1 mmol, 1 equiv). The borylation step was carried out with HBPin (218 μL, 218 mg, 1.50 mmol, 1.50 equiv) for 8 h. The Sonogashira coupling step was carried out with trimethylsilyl acetylene (312 μL, 216 mg, 2.20 mmol, 2.2 equiv) for 2 h. Column chromatography (pentane/dichloromethane 2:1, R_f 0.7) furnished the desired product as yellow oil (212 mg, 54% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.82 (d, J = 1.7 Hz, 2 H), 7.62 (t, J = 1.7 Hz, 1 H), 1.30 (br s, 12 H, 4 CH_3 of BPin), 0.20 (s, 18 H, 6 CH_3 of 2 TMS); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 137.9 (2 CH), 137.4 (CH), 122.9 (2 C), 104.0 (C), 94.8 (C), 84.1 (2 C), 24.8 (4 CH_3 of BPin), -0.1 (6 CH_3 of 2 TMS); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.2; FT-IR (neat) $\tilde{\nu}$: 2961, 2899, 2154, 1583, 1412, 1371, 1250, 976, 844, 760, 702 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 396 (14), 382 (100), 282 (7); HRMS (FAB): *m/z* 396.2116 [(M^+); Calcd for $C_{22}H_{33}BO_2Si$: 396.2112].

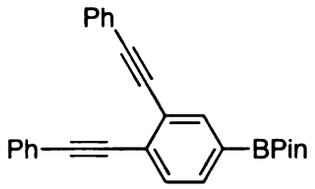
Table 6.1, Entry 13. 1,2-Bis-(trimethylsilylethynyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzene (6.21).



6.21

The general procedure was applied to 1,3-di-bromobenzene (121 μL, 236 mg, 1 mmol, 1 equiv). The borylation step was carried out with HBPin (218 μL, 218 mg, 1.50 mmol, 1.50 equiv) for 8 h. The Sonogashira coupling step was carried out with trimethylsilyl acetylene (340 μL, 236 mg, 2.40 mmol, 2.4 equiv) for 2 h. Column chromatography (pentane/dichloromethane 2:1, R_f 0.7) furnished the desired product as a light yellow solid (226 mg, 57% yield, mp 123-124 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89 (dd, J = 1.2, 0.6 Hz, 1 H), 7.62 (dd, J = 7.8, 1.2 Hz, 1 H), 7.41 (dd, J = 7.8, 0.6 Hz, 1 H), 1.31 (br s, 12 H, 4 CH_3 of BPin), 0.25 (s, 9 H, 3 CH_3 of 2 TMS), 0.23 (s, 9 H, 3 CH_3 of 2 TMS); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 138.7 (CH), 133.9 (CH), 131.4 (CH), 128.0 (C), 125.2 (C), 103.4 (C), 103.2 (C), 99.8 (C), 98.2 (C), 84.1 (2 C), 24.9 (4 CH_3 of BPin), 0.03 (3 CH_3 of 2 TMS), -0.01 (3 CH_3 of 2 TMS); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.8; FT-IR (neat) $\tilde{\nu}$: 2978, 2961, 2899, 2157, 1599, 1390, 1356, 1250, 964, 924, 844, 760, 684 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 396 (88), 381 (57), 339 (18), 282 (100); HRMS (FAB): *m/z* 396.2119 [(M^+); Calcd for $C_{22}H_{33}BO_2Si$: 396.2112].

Table 6.1, Entry 14. 1,2-Bis-(phenylethynyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzene (6.22).



6.22

The general procedure was applied to 1,2-di-bromobenzene (121 μL, 236 mg, 1 mmol, 1 equiv). The borylation step was carried out with HBPin (290 μL, 256 mg, 2.00 mmol, 2.00 equiv) for 4 h. The Sonogashira coupling step was carried out with phenyl acetylene (242 μL, 225 mg, 2.20 mmol, 2.2 equiv) for 9 h. Column chromatography (dichloromethane, R_f 0.8) furnished the desired product as yellow oil (313 mg, 78% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01 (d, J = 1.2 Hz, 1 H), 7.71 (dd, J = 7.6, 1.2 Hz, 1 H), 7.53-7.57 (m, 5 H), 7.31-7.33 (m, 6 H), 1.35 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 138.2 (CH), 133.9 (CH), 131.7 (2 CH), 131.6 (2 CH), 131.0 (CH), 128.5 (CH), 128.37 (2 CH), 128.34 (2 CH), 128.30 (CH), 128.1 (C), 125.3 (C), 123.5 (C), 123.2 (C), 94.8 (C), 93.5 (C), 88.6 (C), 88.4 (C), 84.1 (2 C), 24.9 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.1; FT-IR (neat) $\tilde{\nu}$: 3059, 2978, 2930, 2214, 1599, 1491, 1400, 1358, 1143, 1107, 964, 916, 854, 756, 688 cm^{-1}; MS (EI) *m/z* (% relative intensity): M^+ 404 (88), 389 (3), 318 (34), 304 (85), 276 (50); HRMS (FAB): *m/z* 404.1950 [(M^+); Calcd for $C_{28}H_{25}BO_2$: 404.1948].

Experimental Details and Spectroscopic Data Part B

Materials

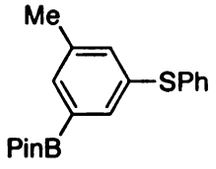
All commercially available chemicals were used as received or purified as described. 4,4′-Di-*tert*-butyl-2,2′-bipyridine (dtbpy) and Bis(pinacolato)diboron (B_2Pin_2) were sublimed before use. Aryl iodides were refluxed over CaH_2, distilled, and degassed. Benzenethiol was distilled before use. Anhydrous potassium carbonate and copper iodide were obtained by heating at 150 °C under vacuum for 7 days. Ethylene glycol dimethyl ether (DME) and *n*-hexane was refluxed over sodium, distilled, and degassed.

General Procedure

In a glove box, a Schlenk flask, equipped with a magnetic stirring bar, was charged with the corresponding aryl iodide (2 mmol, 1 equiv). Two separate test tubes were charged with $[Ir(OMe)(COD)]_2$ (20 mg, 0.03 mmol, 3 mol% Ir) and dtbpy (16 mg, 0.06 mmol, 3 mol%). B_2Pin_2 (1.6-2.0 mmol, 0.8 to 1 equiv) was added to the $[Ir(OMe)(COD)]_2$ test tube. *n*-Hexane (2 mL) was added to the dtbpy containing test tube in order to dissolve the d'bpy. The dtbpy solution was then mixed with the $[Ir(OMe)(COD)]_2$ and B_2Pin_2 mixture. After mixing for one minute, the resulting solution was transferred to the Schlenk flask containing the aryl iodide. Additional *n*-hexane (1 mL) was used to wash the test tubes and the washings were transferred to the Schlenk flask. The flask was stoppered, and the reaction mixture was stirred at room temperature until the borylation was judged complete by GC-FID/MS. The reaction mixture was placed under high vacuum for 2 h to remove the volatile materials. Anhydrous K_3CO_3 (553 mg, 4 mmol, 2 equiv), CuI (40 mg, 0.2 mmol, 10mol%), benzenethiol (2.6 mmol, 1.3 equiv) and DME (3mL) were added.[39] The flask was then stoppered, removed from

the dry box and stirred at 80 °C in an oil bath until the reaction was judged complete by GC-FID. The flask was cooled down to room temperature and 10 mL of water were added to the reaction mixture. The reaction mixture was extracted with ether (10 mL × 3). The combined ether extractions were washed with brine (10 mL), followed by water (10 mL), dried over $MgSO_4$ before being concentrated under reduced pressure on a rotary evaporator. The crude material was then subjected to column chromatography. Isolated yields are not optimized.

Table 6.2, Entry 1. 2-(3-Methyl-5-(phenylthio)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl (6.23).

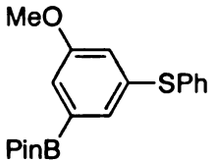


6.23

The general procedure was applied to 3-iodotoluene (436 mg, 256 μL, 2.00 mmol, 1 equiv). The borylation step was carried out with B_2Pin_2 (508 mg, 2.00 mmol, 1.00 equiv, 2.00 equiv of boron) and 6 mol% [Ir] at room temperature for 48 h. The C-S coupling step was carried out at 80 °C for 36 h. Column chromatography (pentane/dichloromethane 2:1) furnished the desired product as a white solid (477 mg, 73% yield, R_f = 0.5, mp 84-85 °C). ^{1}H NMR (C_6D_6, 300 MHz): δ 8.26 (br s, 1 H), 7.83 (br s, 1 H), 7.33-7.34 (m, 1 H), 7.27-7.31 (m, 2 H), 6.80-6.92 (m, 3 H), 1.94 (s, 3 H, CH_3), 1.07 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} (C_6D_6, 75 MHz): δ 138.8 (C), 137.4 (C), 136.3 (CH), 136.0 (CH), 135.4 (CH), 135.1 (C), 130.5 (2 CH), 129.3 (2 CH), 126.6 (CH), 83.8 (2 C), 24.8 (4 CH_3 of BPin), 20.9 (CH_3); ^{11}B NMR (C_6D_6, 96 MHz): δ

31.2; FT-IR (neat) $\tilde{\nu}$: 2978, 1352, 1317, 1213, 1143, 966, 858, 738, 708 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 326 (100), 312 (4), 240 (17), 226 (11); Anal. Calcd for $C_{19}H_{23}BO_2S$: C, 69.95; H, 7.10. Found: C, 69.54; H, 7.19.

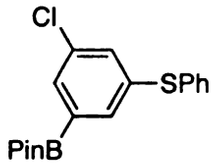
Table 6.2, Entry 2. 2-(3-Methoxy-5-(phenylthio)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl (6.24).



6.24

The general procedure was applied to 3-iodoanisole (468 mg, 239 μL, 2.00 mmol, 1 equiv). The borylation step was carried out with B_2Pin_2 (508 mg, 2.00 mmol, 1.00 equiv, 2.00 equiv of boron) and 6 mol% [Ir] at room temperature for 36 h. The C-S coupling step was carried out at 80 °C for 24 h. Column chromatography (pentane/ether 4:1) furnished the desired product as a white solid (525 mg, 77% yield, R_f = 0.7, mp 81-83 °C). ^1H NMR (C_6D_6, 300 MHz): δ 8.01 (br s, 1 H), 7.60 (br s, 1 H), 7.29-7.32 (m, 2 H), 7.17-7.18 (m, 1 H), 6.82-6.92 (m, 3 H), 3.16 (s, 3 H, CH_3), 1.07 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^1H} (C_6D_6, 75 MHz): δ 160.5 (C), 137.1 (C), 136.6 (C), 131.1 (2 CH), 130.8 (CH), 129.4 (2 CH), 126.9 (CH), 120.7 (CH), 119.1 (CH), 84.0 (2 C), 54.7 (OCH_3), 24.8 (4 CH_3 of BPin); ^{11}B NMR (C_6D_6, 96 MHz): δ 31.0; FT-IR (neat) $\tilde{\nu}$: 3060, 2978, 2934, 2835, 1570, 1469, 1446, 1350, 1255, 1230, 1143, 1101, 1051, 966, 858, 704 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 342 (100), 327 (5), 256 (13), 242 (12); Anal. Calcd for $C_{19}H_{23}BO_3S$: C, 66.68; H, 6.77. Found: C, 66.58; H, 7.02.

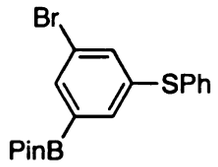
Table 6.2, Entry 3. 2-(3-Chloro-5-(phenylthio)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl (6.25).



6.25

The general procedure was applied to 3-iodochlorobenzene (477 mg, 250 μL, 2.00 mmol, 1 equiv). The borylation step was carried out with B_2Pin_2 (406 mg, 1.60 mmol, 0.80 equiv, 1.60 equiv of boron) at room temperature for 12 h. The C-S coupling step was carried out at 80 °C for 24 h. Gradient column chromatography (pentane:dichloromethane 4:1 → pentane:dichloromethane 1:1) furnished the desired product as a white solid (297 mg, 43% yield, mp 83-84 °C). ^{1}H NMR (C_6D_6, 300 MHz): δ 8.06 (dd, J = 1.8, 0.9 Hz, 1 H), 7.96 (dd, J = 2.0, 0.9 Hz, 1 H), 7.41 (t, J = 2.0 Hz, 1 H), 7.19-7.23 (m, 2 H), 6.83-6.87 (m, 3 H), 1.01 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 137.7 (C), 134.9 (CH), 134.7 (C), 134.6 (C), 133.0 (CH), 132.7 (CH), 131.5 (2 CH), 129.3 (2 CH), 127.5 (CH), 84.3 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR (C_6D_6, 96 MHz): δ 30.7; FT-IR (neat) $\tilde{\nu}$: 3061, 2980, 2932, 2835, 1552, 1342, 1143, 964, 871, 844, 792, 742, 700, 691 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 346 (100), 331 (9), 260 (31), 246 (14); Anal. Calcd for $C_{18}H_{20}BClO_2S$: C, 62.36; H, 5.81. Found: C, 62.13; H, 5.56.

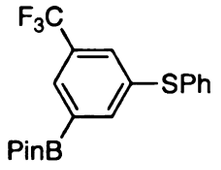
Table 6.2, Entry 4. 2-(3-Bromo-5-(phenylthio)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl (6.26).



6.26

The general procedure was applied to 3-iodobromobenzene (566 mg, 256 μL, 2.00 mmol, 1 equiv). The borylation step was carried out with B_2Pin_2 (406 mg, 1.60 mmol, 0.80 equiv, 1.60 equiv of boron) at room temperature for 12 h. The C-S coupling step was carried out at 80 °C for 24 h. Gradient column chromatography (pentane:dichloromethane 3:1 → pentane:dichloromethane 1:1) furnished the desired product as a white solid (204 mg, 26% yield, mp 105-106 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (dd, J = 1.9, 0.9 Hz, 1 H), 7.73 (dd, J = 1.8, 0.9 Hz, 1 H), 7.44 (t, J = 1.8 Hz, 1 H), 7.25-7.34 (m, 5 H), 1.31 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 137.8 (C), 135.9 (CH), 135.7 (CH), 135.4 (CH), 134.8 (C), 131.4 (2 CH), 129.4 (2 CH), 127.5 (CH), 123.0 (C), 84.3 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.8; FT-IR (neat) $\tilde{\nu}$: 2978, 1340, 1143, 964, 871, 843, 765, 741, 700 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 392 (100), 390 (99), 306 (27), 292 (16); Anal. Calcd for $C_{18}H_{20}BBrO_2S$: C, 55.27; H, 5.15. Found: C, 55.67; H, 5.06.

Table 6.2, Entry 5. 2-(3-trifluoromethyl-5-(phenylthio)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl (6.27).



6.27

The general procedure was applied to 3-iodobromobenzene (544 mg, 290 μL, 2.00 mmol, 1 equiv). The borylation step was carried out with B_2Pin_2 (406 mg, 1.60 mmol, 0.80 equiv, 1.60 equiv of boron) at room temperature for 12 h. The C-S coupling step was carried out at 80 °C for 24 h. Gradient column chromatography (pentane:dichloromethane 3:1 → pentane:dichloromethane 1:2) furnished the desired product as a white solid (537 mg, 71% yield, mp 87-88 °C). ^{1}H NMR (C_6D_6, 500 MHz): δ 8.25 (br s, 2 H), 7.70 (m, 1 H), 7.18-7.22 (m, 2 H), 6.83-6.87 (m, 3 H), 1.01 (br s, 12 H, 4 CH_3 of BPin); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 140.0 (CH), 137.1 (C), 134.4 (C), 131.5 (2 CH), 131.1 (q, $^2J_{C\text{-}F}$ = 32.2 Hz, C), 129.7 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, CH), 129.6 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, CH), 129.4 (2 CH), 127.7 (CH), 123.8 (q, $^1J_{C\text{-}F}$ = 273 Hz, CF_3), 84.4 (2 C), 24.8 (4 CH_3 of BPin); ^{11}B NMR (C_6D_6, 96 MHz): δ 30.7; ^{19}F NMR ($CDCl_3$, 282 MHz) δ -62.7; FT-IR (neat) $\tilde{\nu}$: 3063, 2980, 2934, 1603, 1365, 1331, 1294, 1271, 1169, 1130, 1099, 964, 875, 847, 748, 706, 686 cm^{-1}; GC-MS (EI) *m/z* (% relative intensity): M^+ 380 (100), 365 (6), 294 (11), 280 (12); Anal. Calcd for $C_{19}H_{20}BF_3O_2S$: C, 60.01; H, 5.30. Found: C, 60.02; H, 5.05.

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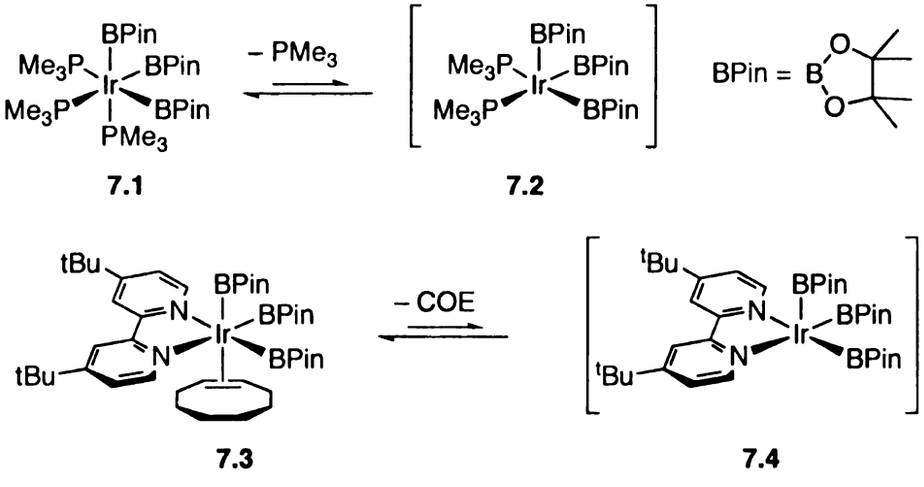
CHAPTER 7

Getting the Sterics Just Right: A Five-Coordinate Iridium Trisboryl Complex that Reacts with C–H bonds at Room Temperature

Introduction

In many transition metal catalyzed processes, ligand dissociation or some other rearrangement of the metal "catalyst" is required to generate the metal species that reacts with substrate(s) in the catalytic cycle. Such is the case for Ir-catalyzed borylations of C–H bonds, where the five-coordinate boryl complexes believed to be responsible for C–H functionalization have not been observed. The closest approach to the five-coordinate complexes in phosphine and dipyridyl ligated systems are the six-coordinate complexes **7.1**[1] and **7.2**.[2] While both of these compounds will borylate sp^2-hybridized C–H bonds, ligand dissociation precedes the key C–H interaction between the hydrocarbon and the Ir center.

Scheme 7.1. Generation of five-coordinate intermediates for C–H borylation.



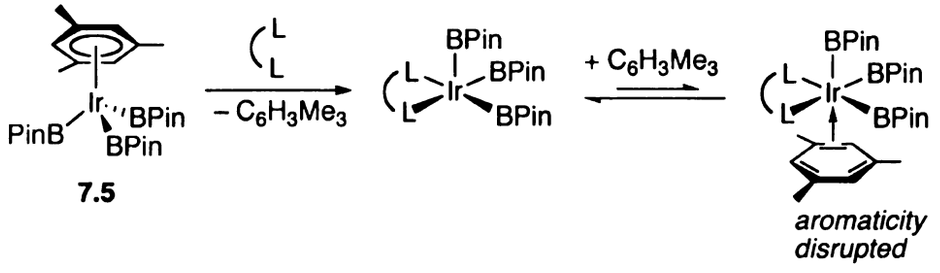
Because Ir-catalyzed borylations exhibit unusual chemo and regioselectivities, the reactivity of five-coordinate trisboryl complexes could offer important information

regarding the catalytic reaction. Ignoring the well-known maxim that true reactive intermediates are rarely isolable, we set out to prepare five-coordinate complexes that react directly with arenes and heterocycles. Herein we describe our results in this direction.

Results and Discussion

We expected that the choice of Ir starting material ligand would be critical to successful preparation of five-coordinate complexes. Since compound **7.3** retains an η^2-olefin from the starting material, we felt that displacement of an arene with a bidentate chelating ligand might yield the desired five-coordinate complexes since η^2-coordination of the expelled arene would carry the penalty of disrupting its aromaticity (Scheme 7.2). The mesitylene trisboryl complex, **7.5**, was selected as the starting material, since the mesitylene methyl groups block access to the arene sp^2 C–H bonds.

Scheme 7.2. Arene route to five-coordinate boryl complexes.



7.5 reacts with dmpe (1,2-bis(dimethylphosphino)ethane) to yield a new species, **7.6**. ^{31}P NMR spectra revealed two chemically inequivalent P environments at –11.1 and –50.9 ppm for **7.6** present in a 2:1 ratio respectively along with small amounts of an unidentified species (**7.7**) (Figure 7.1).

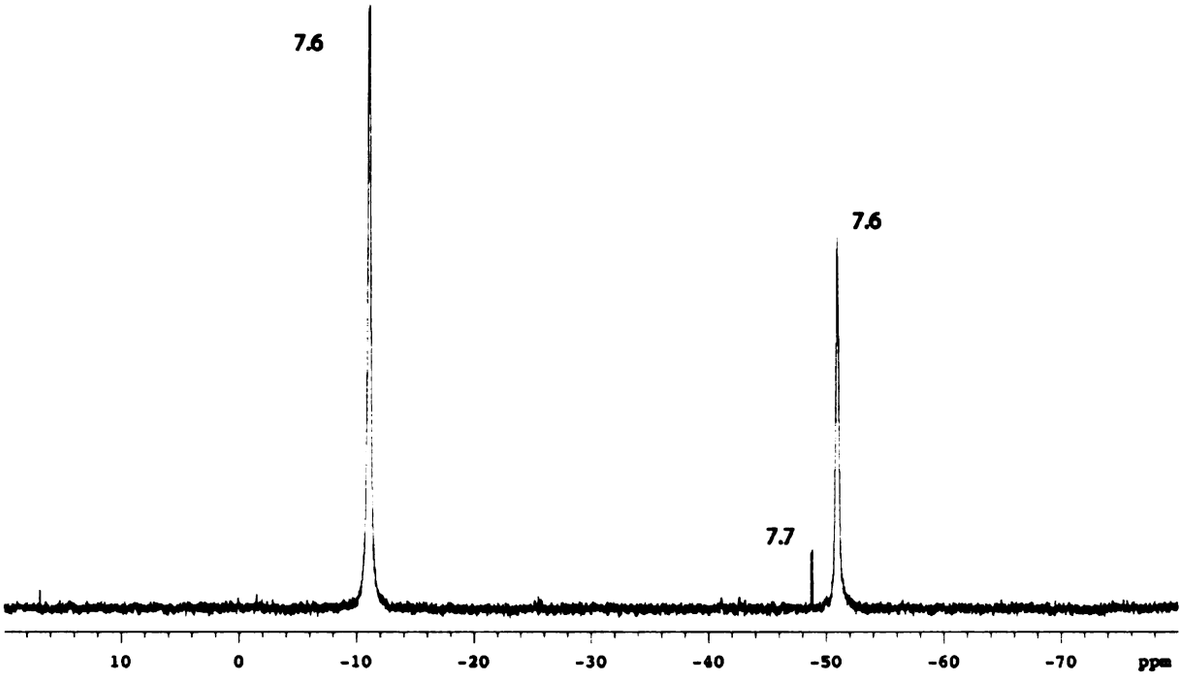
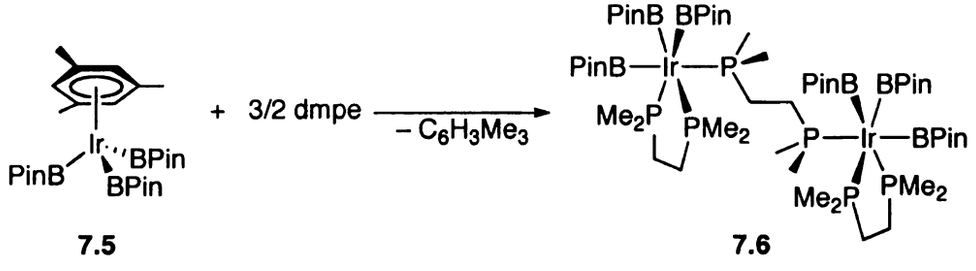


Figure 7.1. ^{31}P NMR of **7.6**, a small amount of an unknown compound **7.7** is also present.

The ^{31}P NMR signal of the unidentified product **7.7** appears as a doublet at –48.7 ppm (d, J = 23 Hz). Its chemical shift is very close to the unbound starting phosphine ligand. ^{1}H NMR spectra of crude reaction mixtures also showed that unreacted **7.5** was present in addition to resonances for **7.6** with the ratio 1:2 ratio of **7.5**:**7.6**. At this point, it was clear that **7.6** was a dinuclear species, which could be obtained in good yield by adjusting the stoichiometry (Eq 1).



7.5 **7.6** (7.1)

While catalytic borylation of 1,3-bis-trifluoromethylbenzene (**7.8**) is complete in 1 h at 150 °C with equimolar (4 mol%) loadings of **7.5** and dmpe, no conversion was observed with 2 mol% of pure dimer **7.6** under similar conditions (Figure 7.2). However borylation with 2 mol% **7.6** did go to full conversion after 48 h at 150 °C. Monitoring the reaction with 2 mol% **7.6** by ^{31}P NMR showed disappearance of peaks at –11.1 and –50.9 along with appearance of several new peaks during the first 24 h at 150 °C. Similarly with 4 mol% of **7.5** and 6 mol% dmpe, no borylation was observed after 6 h at 150°C, although borylation ultimately did complete after 48 h. These results are consistent with our previous observation that catalysis ceases abruptly when P:Ir ratios reach 3:1. The formation of **7.6** suggests that a significant portion of the Ir may be sequestered in an inactive form. Consequently, the efficiency of the active forms of Ir phosphine catalysts may have been significantly underestimated.

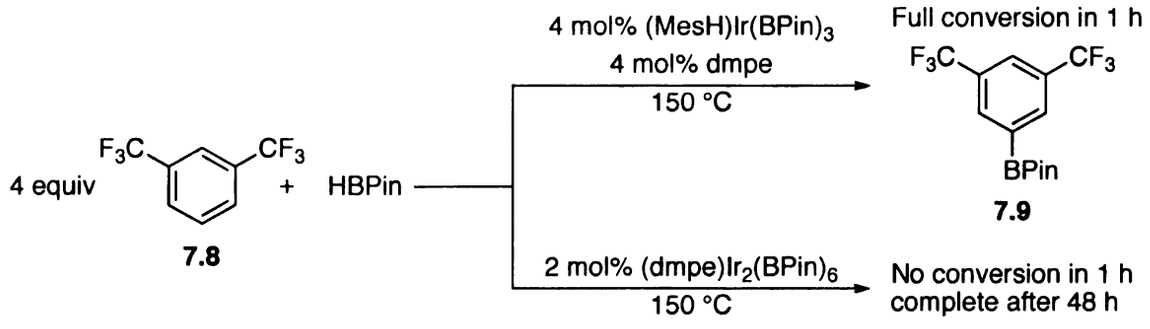
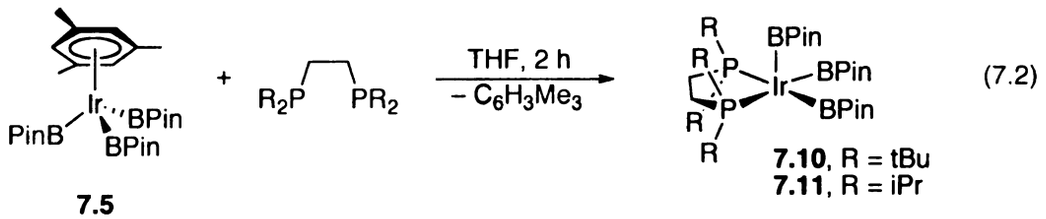


Figure 7.2. Borylation results of 1,3-bis-trifluoromethylbenzene.

The most obvious tact for preparing a five-coordinate complex is to increase the steric demands of the phosphine ligand. Indeed, **7.5** reacts cleanly with 1,2-bis(di-*tert*-butylphosphino)-ethane (dtbpe) in pentane in 36 h to afford a new complex, **7.10**. The reaction time was found to be much shorter (2 h) using THF as the solvent. The reaction can easily be monitored by the disappearance of signal for the

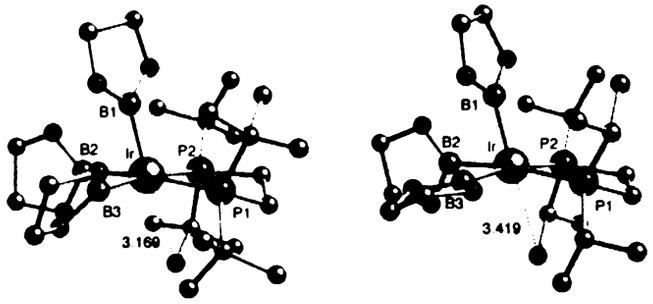
starting dtbpe ligand in ^{31}P NMR and appearance of a single new peak at 93 ppm. Pure product is obtained in quantitative yield after removing the THF solvent and mesitylene under vacuum. The ^{31}P NMR and ^{1}H NMR spectra of **7.10** are consistent with a five-coordinate structure (Eq 7.2). This was confirmed by X-ray crystallography and the structure of **7.10** is shown in Figure 7.3. The geometry about Ir is a distorted square pyramid. The Ir atom lies only 0.14 Å above the least-squares plane defined by the phosphorus and basal boron atoms. The apical boron atom shows the most pronounced distortion. The Ir–B1 vector is ~15° away from being normal to the basal plane, canting towards the boryl groups and away from the phosphine ligand. Unique boryl resonances cannot be discerned in low temperature ^{1}H NMR spectra (up to –80 in C_7D_8), indicating either isochronus chemical shifts or rapidly exchanging boryl environments. Similarly a single chemical shift for the *t*-Bu methyl groups were observed at –1.26 ppm (d, $^{3}J_{H-P}$ = 11.9 Hz) in C_7D_8.



7.5 (7.2)

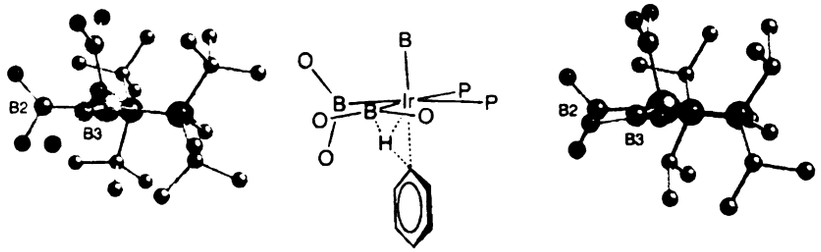
The structure of **7.10** differs from the most closely related boron compound, *trans*-$IrCl(BCat)_2(PEt_3)_2$ (Cat = catecholate),[3] which is a distorted trigonal bipyramid with trans axial phosphines. Given that many nominally five-coordinate d^6 transition metal structures are stabilized by agostic interactions from C–H bonds in their ligand periphery, we have examined this possibility for **7.10**. NMR and IR spectra lack the signatures associated with agostic C–H interactions, which is consistent with the solid state structure where the closest Ir–C distance of 3.169(9) Å falls outside the range of

2.65–2.94 Å for Ir compounds with bona fide agostic interactions, and is ~ 0.5 Å longer than the distances for five-coordinate Ir^{III} examples.



7.10 **7.11**

Figure 7.3. X-ray structures of compounds **7.10** and **7.11** with BPin methyl groups omitted. The black carbons are those with the closest Ir contacts. In both cases, the Ir–C distances are significantly longer than those in compounds with Ir C–H agostic interactions.



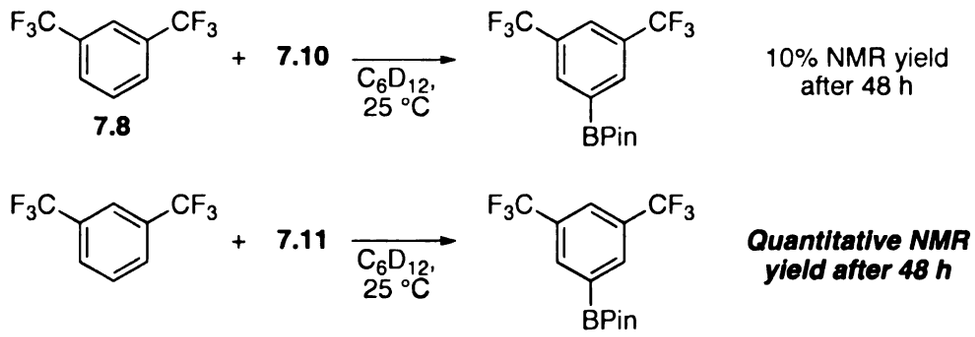
7.10 **7.12** **7.11**

Figure 7.4. A comparison of the orientation for the B3 boryl ligands in structures **7.10** and **7.11** with the qualitative transition state **7.12**. For compound **7.10**, rotation about the Ir–B bond is required to reach the transition state, whereas the boryl orientation in **7.11** is ideal for cleaving the arene C–H bond.

7.10 reacts only slowly with arenes at room temperature (Scheme 7.3). This is not surprising considering the crowded environment at the metal center (Figure 7.3) and is consistent with the low catalytic activity of in situ generated catalysts using dtbpe as the

chelating ligand. To ease the steric crowding at the Ir center, compound **7.11**, the isopropyl analog of **7.10**, was prepared in analogous fashion. The spectroscopic data and solid-state structure for **7.11** are similar to those for **7.10** (Figure 7.3). The closest Ir–C contact (3.419 Å) is even longer than that in **7.10**, reflecting a bona fide five-coordinate structure for **7.11**.

Scheme 7.3. Relative reactivity of 7.10 and 7.11 with 1,3-bis-trifluoromethylbenzene.



Relative to **7.10**, **7.11** is significantly more reactive at room temperature as the stoichiometric borylation with 1,3-bis-trifluoromethylbenzene **7.8** attests (Scheme 7.3). Stoichiometric reaction of **7.11** with 2-methylthiophene was also complete in 4 h at room temperature. This enhancement clearly arises from steric relief, and a comparison between the putative transition state for C–H functionalization, depicted by structure **7.12**, and structures **7.10** and **7.11** shows how a relatively subtle change in the ligand alters accessibility to the transition state (Figure 7.4). Computational studies show that the transition state for C–H scission is very late and is assisted by interaction arene hydrogen and one of the boryl ligands. For this to occur, the participating boryl ligand (B3 in structures **7.10** and **7.11**) must be oriented such that the boron p orbital is orthogonal to the basal plane of the square pyramid. Certainly, other factors will be important in determining relative rates, but access to the proper boryl orientation will be

critical. As seen in Figure 7.4, the dihedral angle θ between the plane defined by B3 and its oxygen atoms and the basal plane in **7.10** is considerable (θ = 48°), while the boryl plane in **7.11** is virtually coplanar with the basal plane (θ = 4°). Thus, transition state **7.12** should be readily accessible from structure **7.11**, while the boryl ligand in **7.10** must reorient for the boryl p orbital to be accessible.

Although both **7.10** and **7.11** stoichiometrically react with electron deficient arenes as well as with heteroaromatic substrates, neither of them catalyzed aromatic borylation at room temperature. It is worthwhile to mention here that both **7.10** and **7.11** are stable in C_6D_6 and C_7D_8 for several hours at room temperature, allowing their characterization in these solvents. However, both of these do catalyze benzene borylation at elevated temperatures (Figure 7.5). Again **7.11** is more reactive than **7.10** for borylation at elevated temperatures.

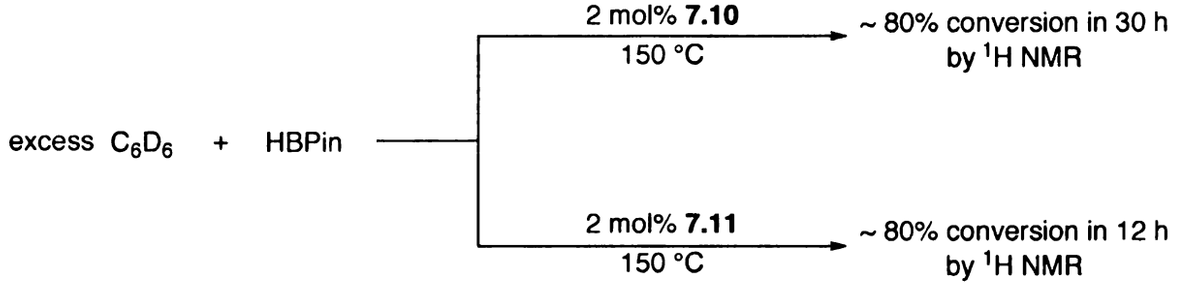
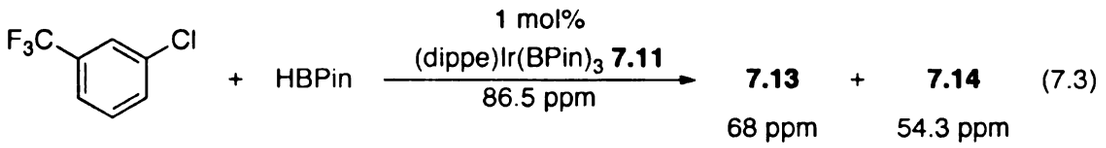


Figure 7.5. Catalytic aromatic borylation with 7.10 and 7.11 at 150 °C.

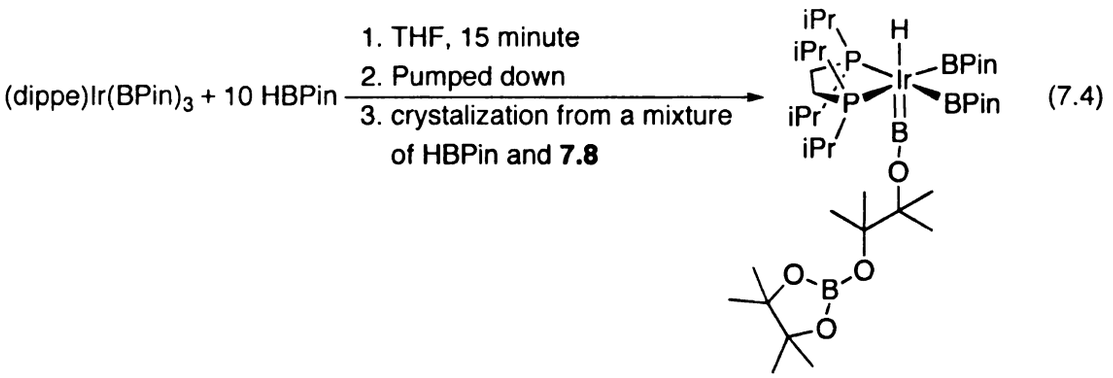
While attempted room temperature catalytic borylation with **7.11**, we noticed that the light yellow color of solution of **7.11** in THF immediately decolorized upon addition of HBPin (Eq 7.3). Although no aromatic borylation was observed in the initial room temperature ^{11}B NMR, the initial ^{31}P NMR showed absence of signal corresponding to **7.11** (86.5 ppm). The major product (~95%) in the initial ^{31}P NMR was at 68 ppm (**7.13**)

along with small amount of another peak (~5%) at 54 ppm (**7.14**). It was clear that **7.11** and excess (~4 equiv) HBPin react together, in the absence of arene substrate, to form these new species.



(7.3)

In an attempt to identify **7.13, 7.11** was reacted with 10 equiv of HBPin in THF for 15 minutes (Eq 7.4). After removal of solvent under vacuum, the crude product was crystallized from a mixture of HBPin and 1,3-bis-trifluoromethylbenzene (**7.8**). The crystal structure of product showed an iridium complex having almost linear Ir-B-O angle (170°), and a short Ir-B bond length (1.95 A), indicative of Ir-B double bond. Braunschweig has reported borylene complexes of Pt and some early transition metals.[4] However the present complex is the first one which has both boryl as well as borylene ligands. Another interesting feature is the breaking of a strong B–O bond at room temperature, although another B–O bond is formed at the same time to compensate for the loss in energy.



(7.4)

Considering the high reactivity of the five coordinate complex **7.11**, it was important to check the possibility of aliphatic borylation with this compound. Reaction of

7.11 with 25 equiv of HBPin in cyclohexane (C_6H_{12}) did not show any borylation by ^{11}B NMR after 6 h at 150 °C. Considering that cyclohexane has only secondary C–H bonds, and HBPin is a less reactive partner as compared to B_2Pin_2, we decided to test catalytic borylation of n-octane with B_2Pin_2. After heating a solution of B_2Pin_2 in n-octane at 80 °C for 1 h with 5 mol% **7.11**, small amounts of HBPin were observed by ^{11}B NMR, although no borylated octane was observed in the GC-FID. The source of hydride for the formation of HBPin is not clear. The hydride may come from the isopropyl methyl groups in phosphine ligand, the glass surface, or from another source. Upon heating at 150 °C for 24 h, the ^{11}B NMR showed complete consumption of B_2Pin_2. A peak around 30 ppm in the ^{11}B NMR indicated the formation of C-borylated product. A doublet was also observed due to the formation of HBPin. The GC-FID data showed formation of octyl-BPin (single regioisomer). No more conversion was observed upon further heating with the newly formed HBPin. Similarly, n-hexane and pentane were also borylated at 150 °C and single borylated regioisomers were observed by GC-FID.

Hartwig et al. have reported Rh, Ir, and Ru catalyzed aliphatic C-H borylation.[5,6] Their reported conditions for [Ir] catalyzed aliphatic borylation are much harsher than described in this chapter. With 10 mol% of Cp^*IrH_4 at 200 °C, yields for the borylation of n-octane never exceeded above 20%. However with 10 mol% $Cp^*Ir(C_2H_4)_2$, after 10 days at 200 °C, 58% yield was obtained, indicating that in situ generated HBPin is also used in borylation. They have observed high selectivity for terminal functionalization in straight chain hydrocarbons. It is therefore plausible to think that in the present case, the terminal C–H bond are borylated. Our results are very preliminary, and further research

including optimization of catalytic conditions, identification of regioisomers, isolation of products, screening of substrates etc, needs to be carried out.

Based on reactivity of **7.5** with dippe and dtbpe, we expected that 1,2-bis(diphenylphosphino)ethane (dppe) might also give a 5-coordinate complex as the sole product. However reaction of **7.5** with 1.5 equiv of dppe in THF solvent after 0.5 h showed three products by ^{31}P NMR (Figure 7.6).

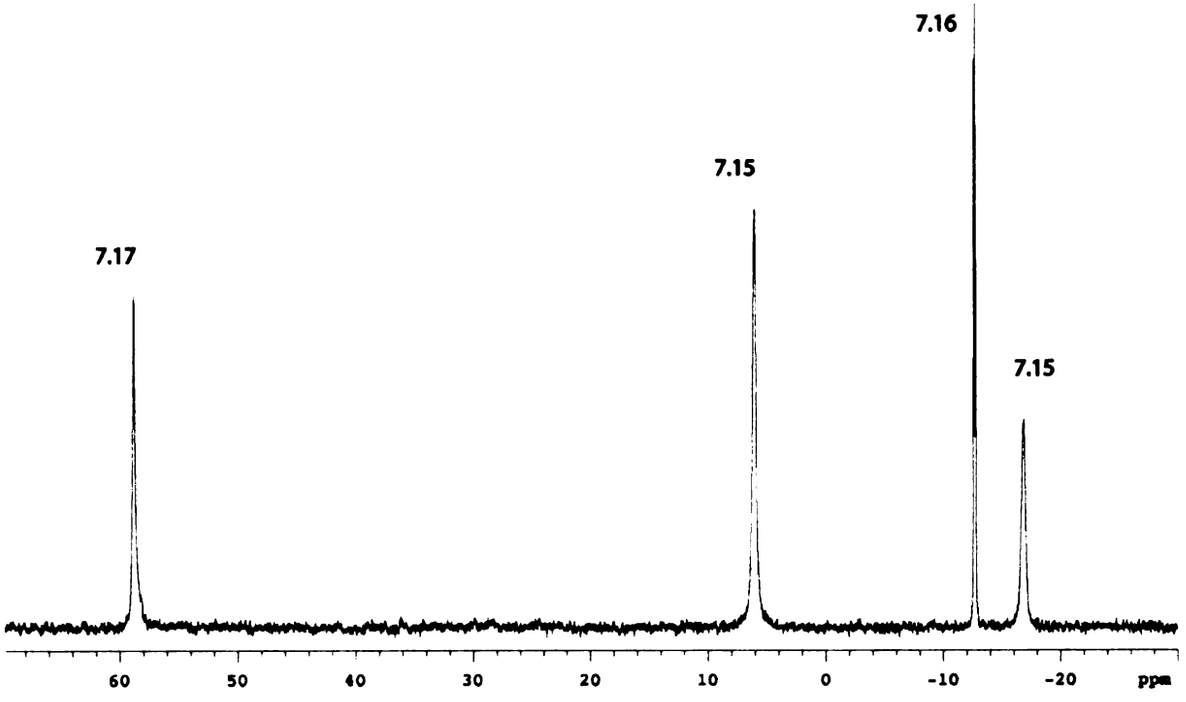


Figure 7.6. ^{31}P **NMR of crude reaction of dppe with 7.5.**

Two broad resonances in 2:1 ratio at 6.1 and −16.7 ppm respectively are tentatively assigned to the dimeric complex **7.15** (due to similarity with dmpe result). A doublet at −12.6 ppm (J = 31 Hz) for an unknown product **7.16** was also observed. The chemical shift of this doublet is very close to that for unbound dppe. These two results are similar to the reactivity of **7.5** with dmpe. Consistent with the downfield shifts for **7.10** (93 ppm) and **7.11** (86.5 ppm), another single resonance at 59 ppm was also

observed and was tentatively assigned to the monomeric complex **7.17** (See Figure 7.8). It seems that dppe ligand exhibit reactivities similar to both dmpe as well as dtbpe/dippe. No further attempt was made to isolate/fully characterize these products.

Apart from the less steric bulk of dmpe and dppe, ability to assess transoid conformation may also be responsible for the formation of dimeric complexes **7.6** and **7.15**. To restrict the possible formation of dimeric complex via assess to the transoid conformation, 1,2-bis(diphenylphosphino)benzene **7.18** was reacted with **7.5** in THF. To our surprise, about 94% product in the ^{31}P NMR (after 2 h at room temperature) belonged to a single down field resonance at 67.8 ppm (Figure 7.7), tentatively assigned to the monomeric complex **7.19** (Figure 7.8). Less than 6% area in the ^{31}P NMR belonged to small down field (relative to starting phosphine ligand which appears at −12.3 ppm) resonances at 33 and 39.5 ppm.

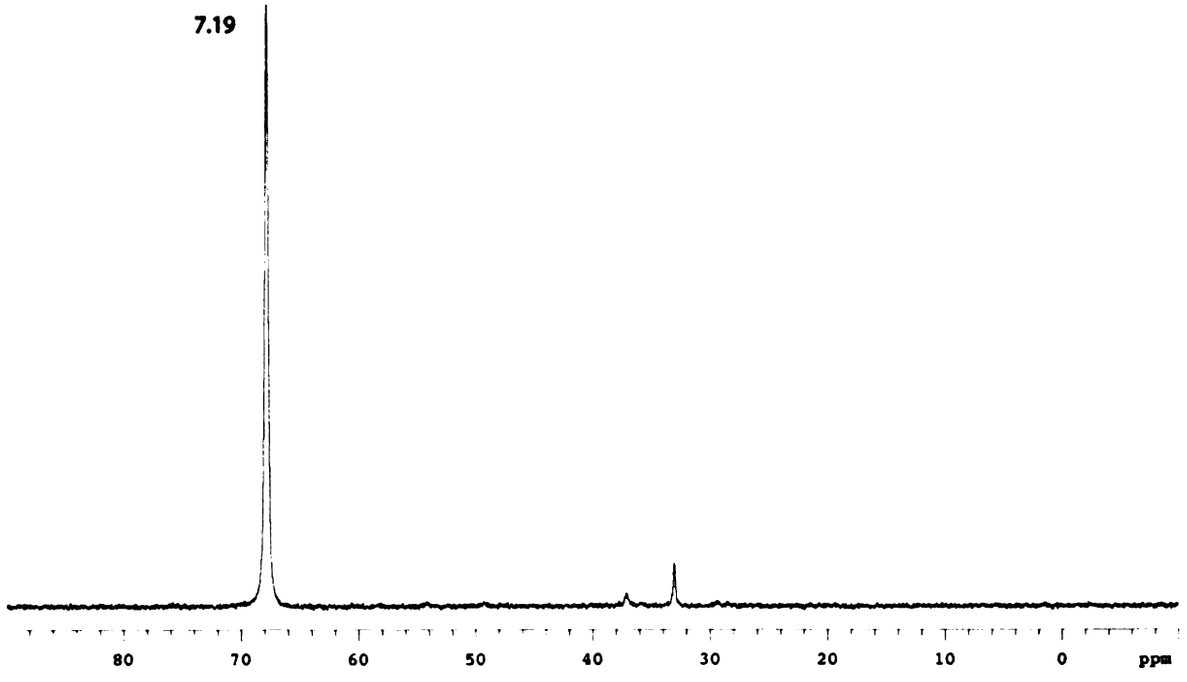
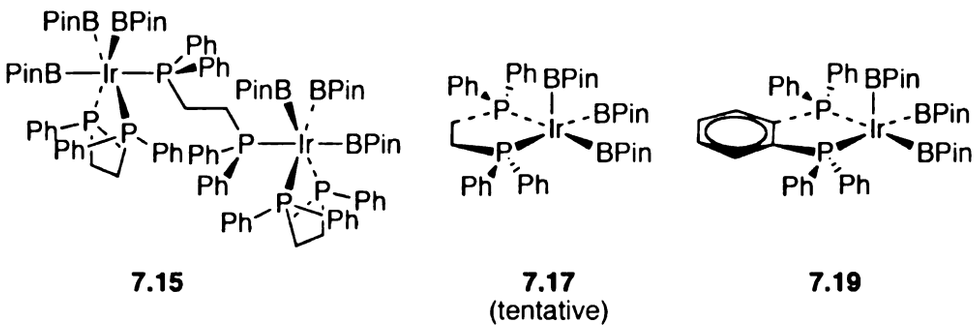


Figure 7.7. ^{31}P NMR of crude reaction of **7.18** with **7.5**.

Since both dppe and **7.18** have similar steric demands, formation of monomeric **7.19** in case of reaction of **7.5** with **7.18,** indicates that inability to assess transoid conformation disfavors dimer formation (or favor the monomeric complex formation) (Figure 7.8).



7.15 **7.17** (tentative) **7.19**

Figure 7.8. Proposed formulation of **7.15**, **7.17**, and **7.19** based on ^{31}P NMR data.

More interestingly, as opposed to **7.10** and **7.11,** which were stable in C_6D_6 for short periods of time, **7.19** reacts immediately with C_6D_6. Stoichiometric reaction of **7.19** with 1,3-bis-trifluoromethylbenzene was also instantaneous. One possible explanation for the enhanced reactivity of **7.19** relative to **7.11** could be the planer backbone of the phosphine ligand. Unfortunately, **7.19** is also not stable in other solvents (such as THF) for long periods of time to allow its crystallization. Due to this limitation, we were unable to get pure product for full characterization.

The enhanced reactivity of **7.19** prompted us to examine its catalytic activity at room temperature. As opposed to **7.11**, 1 mol% of **7.18** did catalyze the borylation of 3-chloro-benzotrifluoride at room temperature, although only 36% conversion was observed by GC-FID after 96 h (Figure 7.9). A combination of 0.5 mol% $[Ir(OMe)(COD)]_2$ and 1 mol% **7.18** also showed about 20% borylation of the same substrate after 96 h at room temperature. Despite low conversions, these are the first

examples where a phosphine-based ligand is shown to catalyze aromatic borylation at room temperature. It is worthwhile to mention here that in contrast to the reaction of HBPin with **7.11**, addition of HBPin to an orange solution of **7.19** in THF did not cause any immediate decolorization.

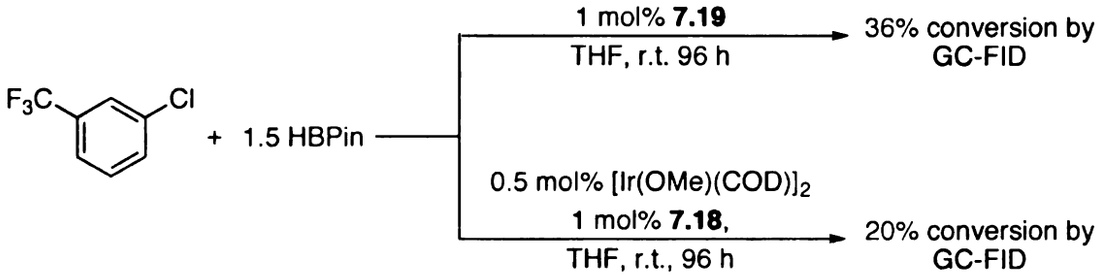


Figure 7.9. Room temperature catalytic borylation with **7.19**.

Conclusions

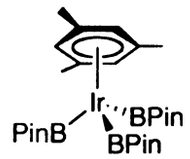
In summary, the steric influence of the chelating diphosphinoethane ligands has a dramatic effect on the structures and reactivities of the trisboryl complexes obtained by reactions with the arene complex **7.5**. It is interesting that even though equimolar solutions of **7.5** and dmpe are catalytically active for borylation, the major product **7.6** obtained by reaction of **7.5** and dmpe is inactive. Consequently, it is conceivable that the active catalytic species for the phosphine-supported catalysts are present in very low concentration. Significantly, the first five-coordinate boryl complexes that react with arenes at room temperature have been obtained by increasing the steric requirements of the phosphine substituents. Still further detailed investigation of several preliminary results described in this chapter needs to be carried out in order to uncover the secrets of borylation chemistry.

Experimental Details and Spectroscopic Data

General Methods

All commercially available chemicals were used as received unless otherwise indicated. Pinacolborane (HBPin containing 1% NEt_3) was generously supplied by BASF. (η^5-Indenyl)(cyclooctadiene)iridium (I) {(Ind)Ir(COD)} and bis-(di-*iso*-propylphosphino)-ethane (dtppe) were prepared per the literature procedure.[7,8] We are thankful to Prof. Gregory L. Hillhouse (University of Chicago) for a generous gift of bis-(di-*tert*-butylphosphino)-ethane (dtbpe). Mesitylene was refluxed over sodium, distilled, and degassed. Tetrahydrofuran was obtained from a dry still packed with activated alumina and degassed before use. All the experiments were carried out in a glove box under a nitrogen atmosphere or by using standard Schlenk techniques.

Synthesis of (η^6-MesH)Ir(BPin)$_3$ (7.5)

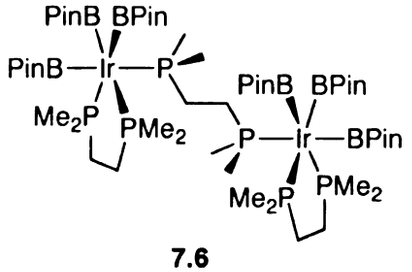


7.5

The literature prep[9] for the BCat analogue was modified to synthesize the (η^6-MesH)Ir(BPin)$_3$ (**7.5**). (Ind)Ir(COD) (1 g, 2.4 mmol, 1 equiv) and HBPin (3.5 mL, 3.1 g, 24 mmol, 10 equiv) were dissolved in 10 mL mesitylene in a Schlenk flask in a glove box. The flask was stoppered, brought out of the glove box, and heated in a 75 °C oil bath for 12 h. Mesitylene was removed under high vacuum to give a viscous dark brown oil. The crude mixture was then triturated with 2 mL of cold hexamethyldisiloxane and filtered to give a white solid (680 mg). Additional material (45 mg) was obtained upon filtering the concentrated filtrate. Combined yield (725 mg, 44%, mp 164-166 °Ç

dec). ^{1}H NMR (C_6D_6, 500 MHz): δ 5.62 (s, 3 H), 2.24 (s, 9 H, 3 CH_3), 1.33 (s, 36 H, 3 BPin); ^{13}C NMR {^{1}H} (C_6D_6, 500 MHz): δ 118.1 (C), 96.9 (CH), 81.0 (C), 25.7 (CH_3 of BPin), 19.7 (CH_3 of mesitylene); ^{11}B NMR (C_6D_6, 96 MHz): δ 33.2; Anal. Calcd for $C_{27}H_{48}IrB_2O_6$: C, 46.77; H, 6.98. Found: C, 47.13; H, 7.18.

Synthesis of $(dmpe)_3Ir_2(BPin)_6$ (7.6)

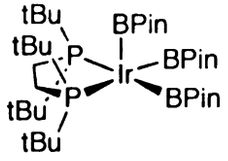


7.6

In a 20 mL vial, equipped with a magnetic stirring bar, (η^6-MesH)Ir(BPin)$_3$ (**7.5**) (174 mg, 0.25 mmol, 1 equiv) was dissolved in THF (1 mL). Bis-(di-methylphosphino)-ethane (dmpe) (57 mg, 0.37 mmol, 1.5 equiv) was weighed out in a test tube and was transferred to the reaction vial by dissolving in THF (1 mL × 2). The reaction was stirred at room temperature for 0.25 h. The crude reaction mixture was pumped down under high vacuum to remove volatiles. Small amounts (5-10% by ^{31}P NMR) of unknown product **7.7** was still present with this stoichiometry of dmpe and **7.5**, however ^{31}P NMR signal for **7.7** disappear after heating at 150 °C for 5-10 minutes in a 4:1 mixture of 1,3-bis-(trifluoromethyl)-benzene/HBPin (without appearance of any new peak in the ^{31}P NMR under these conditions). Upon cooling to room temperature, complex **7.6** crystallized as a white solid. ^{1}H NMR (C_6D_6, 500 MHz): δ 2.10 (s, 4 H), 1.82 (d, J = 9.2 Hz, 12 H), 1.68 (d, J = 6.7 Hz, 12 H), 1.38 (s, 24 H), 1.34 (d, overlapped with the BPin singlet, 8 H), 1.33 (s, 24 H), 1.29 (s, 24 H), 1.2-1.02 (br, 8 H); ^{11}B NMR (C_6D_6, 160

MHz): δ 37.3; ^{31}P NMR (C_6D_6, 202 MHz): δ -11.1 (s, 4 P), -50.9 (s, 2 P); Anal. Calcd for $C_{54}H_{120}Ir_2B_6O_{12}P_6$: C, 40.62; H, 7.58. Found: C, 40.81; H, 7.56.

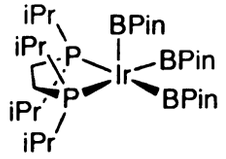
Synthesis of (dtbpe)Ir(BPin)$_3$ (7.10)



7.10

In a 20 mL vial, equipped with a magnetic stirring bar, (η^6-MesH)Ir(BPin)$_3$ (**7.5**) (174 mg, 0.25 mmol, 1 equiv) was dissolved in THF (1 mL). Bis-(di-*tert*-butylphosphino)-ethane (d^{t}bpe) (80 mg, 0.25 mmol, 1 equiv) was weighed out in a test tube and was transferred to the reaction vial by dissolving in THF (1 mL × 2). The reaction was stirred at room temperature for 2 h. ^{31}P NMR showed full consumption of the starting phosphine ligand and the appearance of a single new peak. The crude reaction mixture was pumped down under high vacuum to give the desired complex **7.10** as a light yellow solid (yield 220 mg, quantitative, mp 108-110 °C dec). ^{1}H NMR (C_7D_8, 500 MHz): δ 1.60-1.54 (m, 4 H), 1.35 (s, 36 H, 3 BPin), 1.25 (d, $^3J_{H-P}$ = 11.9 Hz, 36 H, 12 CH_3), ^{1}H NMR (C_6D_{12}, 500 MHz): δ 1.88-1.80 (m, 4 H), 1.28 (d, $^3J_{H-P}$ = 11.9 Hz, 36 H, 12 CH_3 of d^{t}bpe), 1.19 (s, 36 H, 12 CH_3 of 3 BPin); ^{13}C NMR {^{1}H} (C_7D_8, 125 MHz): δ 81.1 (s, 6 C), 37.14-37.05 (m, 4 C), 30.5 (s, 12 CH_3 of d^{t}bpe), 26.4 (s, 12 CH_3 of BPin), 25.50-25.28 (m, 2 CH_2); ^{11}B NMR (C_7D_8, 160 MHz): δ 34.7; ^{31}P NMR (C_7D_8, 202 MHz): δ 93.0; Anal. Calcd for $C_{36}H_{76}IrB_3O_6P_2$: C, 48.50; H, 8.59. Found: C, 48.53; H, 8.65.

Synthesis of (dippe)Ir(BPin)$_3$ (7.11)



7.11

In a 20 mL vial, equipped with a magnetic stirring bar, (η^6-MesH)Ir(BPin)$_3$ (**7.5**) (202 mg, 0.29 mmol, 1 equiv) was dissolved in THF (1 mL). Bis-(di-*iso*-propylylphosphino)-ethane (d^{i}ppe) (76 mg, 0.29 mmol, 1 equiv) was weighed out in a test tube and was transferred to the reaction vial by dissolving in THF (1 mL × 2). The reaction was stirred at room temperature for 2 h. ^{31}P NMR showed full consumption of the starting phosphine ligand and the appearance of a single new peak. The crude reaction mixture was pumped down under high vacuum to give the desired complex **7.11** as a yellow-orange solid (yield 242 mg, quantitative, mp 114-116 °C dec). ^{1}H NMR (C_7D_8, 500 MHz): δ 2.52-2.42 (m, 4 H), 1.41-1.38 (m, 4 H), 1.33 (s, 36 H, 3 BPin), 1.12-1.06 (m, 24 H), ^{1}H NMR (C_6D_{12}, 500 MHz): δ 2.56-2.44 (m, 4 H), 1.68-1.60 (m, 4 H), 1.15 (s, 36 H, 3 BPin), 1.17-1.01 (m, 24 H); ^{13}C NMR {^{1}H} (C_7D_8, 500 MHz): δ 80.8 (s, 6 C), 27.01-26.85 (m, 4 C), 26.1 (s, 12 CH_3 of BPin), 24.80-24.53 (m, 2 CH_2), 19.7 (s, 6 CH_3 of d^{i}ppe), 19.4 (s, 6 CH_3 of d^{i}ppe); ^{11}B NMR (C_7D_8, 160 MHz): δ 39.1; ^{31}P NMR (C_7D_8, 202 MHz): δ 86.5; Anal. Calcd for $C_{32}H_{68}IrB_3O_6P_2$: C, 46.00; H, 8.20. Found: C, 46.23; H, 8.76.

Stoichiometric borylation of 1,3-bis-trifluromethylbenzene with (dippe)Ir(BPin)$_3$

(dippe)Ir(BPin)$_3$ (**7.11**) (33 mg, 0.04 mmol, 1 equiv) was weighed out in a test tube and was transferred to a J. Young NMR tube using C_6D_{12} (175 μL × 4). 1,3-bis-trifluoromethylbenzene (6.2 μL, 0.04 mmol, 1 equiv) was syringed in to the J. Young NMR tube. 1,4-bis-trifluoromethylbenzene (6.2 μL, 0.04 mmol, 1 equiv) was also syringed in to the J. Young NMR tube as an internal standard. The J. Young NMR tube was capped and the reaction was monitored by ^{1}H, ^{31}P, and ^{11}B NMR. The NMR yield after 48 h at room temperature was 104%.

The analogous stoichiometric reaction of **7.11** with 2-methyl thiophene was complete in 4 h at room temperature.

Stoichiometric borylation of 1,3-bis-trifluromethylbenzene with (dtbpe)Ir(BPin)$_3$

(dtbpe)Ir(BPin)$_3$ (**7.10**) (36 mg, 0.04 mmol, 1 equiv) was weighed out in a test tube and was transferred to a J. Young NMR tube using C_6D_{12} (175 μL × 4). 1,3-bis-trifluoromethylbenzene (6.2 μL, 0.04 mmol, 1 equiv) was syringed in to the J. Young NMR tube. 1,4-bis-trifluoromethylbenzene (6.2 μL, 0.04 mmol, 1 equiv) was also syringed in to the J. Young NMR tube as an internal standard. The J. Young NMR tube was capped and the reaction was monitored by ^{1}H, ^{31}P, and ^{11}B NMR. The NMR yield after 48 h at room temperature was 10%.

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APPENDICES

Appendix A. Summary of preliminary crystal data and structure refinement for **7.6**.

Empirical formula	$C_{54}H_{120}B_6Ir_2O_{12}P_6$	
Formula weight	1596.58	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$Pca2_1$	
Unit cell dimensions	a = 31.795(6) Å	α= 90°.
	b = 10.407(2) Å	β= 90°.
	c = 22.943(5) Å	γ = 90°.
Volume	7592(3) $Å^3$	
Z	4	
Density (calculated)	1.397 Mg/m^3	
Absorption coefficient	3.677 mm^{-1}	
F(000)	3256	
Crystal size	0.18 x 0.16 x 0.12 mm^3	
Theta range for data collection	1.28 to 25.00°.	
Index ranges	-37<=h<=37, -12<=k<=12, -27<=l<=27	
Reflections collected	55026	
Independent reflections	13386 [R(int) = 0.2008]	
Completeness to theta = 25.00°	100.0 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	13386 / 1 / 758	
Goodness-of-fit on F^2	1.063	
Final R indices [I>2sigma(I)]	R1 = 0.0742, wR2 = 0.1508	
R indices (all data)	R1 = 0.1609, wR2 = 0.1855	
Absolute structure parameter	0.514(15)	
Largest diff. peak and hole	4.989 and -1.677 $e.Å^{-3}$	

Appendix A. Summary of crystal data and structure refinement for (dtbpe)Ir(BPin)$_3$ **7.10**.

Empirical formula	$C_{36}H_{76}B_3IrO_6P_2$	
Formula weight	891.54	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.651(4) Å	α= 73.82(3)°.
	b = 12.035(4) Å	β= 76.42(3)°.
	c = 17.151(4) Å	γ = 69.37(2)°.
Volume	2136.6(11) Å^3	
Z	2	
Density (calculated)	1.386 Mg/m^3	
Absorption coefficient	3.238 mm^{-1}	
F(000)	924	
Crystal size	0.40 x 0.22 x 0.18 mm^3	
Theta range for data collection	1.85 to 23.36°.	
Index ranges	-11<=h<=12, -8<=k<=13, -18<=l<=19	
Reflections collected	9677	
Independent reflections	6106 [R(int) = 0.0668]	
Completeness to theta = 23.36°	98.4 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6106 / 0 / 457	
Goodness-of-fit on F^2	1.031	
Final R indices [I>2sigma(I)]	R1 = 0.0581, wR2 = 0.1428	
R indices (all data)	R1 = 0.0653, wR2 = 0.1477	
Largest diff. peak and hole	4.276 and -4.159 e.Å^{-3}	

Summary of crystal data and structure refinement for (dippe)Ir(BPin)$_3$ **7.11**.

Empirical formula	C_{32} H_{68} B_3 Ir O_6 P_2	
Formula weight	835.43	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P $2_1/c$	
Unit cell dimensions	a = 17.821(4) Å	α= 90°.
	b = 12.668(3) Å	β= 104.80(3)°.
	c = 18.491(4) Å	γ = 90°.
Volume	4035.9(14) Å^3	
Z	4	
Density (calculated)	1.375 Mg/m^3	
Absorption coefficient	3.424 mm^{-1}	
F(000)	1720	
Crystal size	0.25 x 0.19 x 0.16 mm^3	
Theta range for data collection	1.97 to 23.31°.	
Index ranges	-19<=h<=19, -14<=k<=14, -20<=l<=20	
Reflections collected	34198	
Independent reflections	5816 [R(int) = 0.0803]	
Completeness to theta = 23.31°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5816 / 247 / 417	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0464, wR2 = 0.0999	
R indices (all data)	R1 = 0.0685, wR2 = 0.1097	
Largest diff. peak and hole	1.706 and -1.458 e.Å^{-3}	

Summary of crystal data and structure refinement for **7.18**.

Empirical formula	$C_{38}H_{80}B_4F_6IrO_8P_2$	
Formula weight	1076.40	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 12.6467(15) Å	α= 90°.
	b = 11.3423(13) Å	β= 93.481(2)°.
	c = 39.579(5) Å	γ = 90°.
Volume	5666.9(11) $Å^3$	
Z	4	
Density (calculated)	1.262 Mg/m^3	
Absorption coefficient	2.471 mm^{-1}	
F(000)	2212	
Crystal size	0.035 x 0.013 x 0.003 mm^3	
Theta range for data collection	1.66 to 29.20°.	
Index ranges	-16<=h<=17, -15<=k<=15, -52<=l<=51	
Reflections collected	67440	
Independent reflections	14253 [R(int) = 0.1050]	
Completeness to theta = 29.20°	92.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.828647	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	14253 / 18 / 693	
Goodness-of-fit on F^2	1.032	
Final R indices [I>2sigma(I)]	R1 = 0.0568, wR2 = 0.1125	
R indices (all data)	R1 = 0.1170, wR2 = 0.1357	
Largest diff. peak and hole	1.429 and -1.989 $e.Å^{-3}$	