TELESCOPING C–H BORYLATIONS WITH PHOTOREDOX AND IMIDAZOLYLSULFONATE CHEMISTRY: A WAY TO AVOID HALOAROMATICS AND POTENTIALLY GENOTOXIC IMPURITIES IN SUZUKI REACTIONS.

By

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ABSTRACT

TELESCOPING C–H BORYLATIONS WITH PHOTOREDOX AND IMIDAZOLYLSULFONATE CHEMISTRY: A WAY TO AVOID HALOAROMATICS AND POTENTIALLY GENOTOXIC IMPURITIES IN SUZUKI REACTIONS

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Cross-coupling reactions are a mainstay of drug candidate synthesis. Owing to this prominence, the American Chemical Society's Green Chemistry Institute's Pharmaceutical Roundtable deemed cross-couplings that avoid halogenated aromatics (C–H activation) as their top aspirational reaction. To meet this aspiration, we have worked to develop iridium-catalyzed C–H borylations as a practical approach for directly converting arenes and heterocycles into nucleophilic cross-coupling partners. This chemistry not only obviates the need for halogens in the preparation of aryl and heteroarylboronic esters, but with hydrogen gas as the only stoichiometric byproduct of these chemoselective reactions, we and others have shown that Ir catalyzed borylations can be combined with other chemical events enabling a multitude of one-pot processes. Among these telescoped reaction sequences, we established C–H borylation/oxidations as a novel route to phenols, including phenols that often bear otherwise difficult to access contra-electronic substitution patterns.

Herein we discuss the development and further advancement of the scope and green features of this chemistry by performing in situ oxidation of the boron under photoredox conditions. Furthermore, as phenols can be readily converted to sulfonates, we have expanded the reach of iridium-catalyzed borylations and use C–H activation to eliminate the need for halogenated cross-coupling electrophiles. Thus we have developed a one-pot C–H borylation/ photoredox oxidation/ sulfonation sequence. In recognition of the potential safety-genotoxicity

issues related to triflates, mesylates and tosylates this sequence was built so as to enable the generation of imidazolylsulfonates ($ArOSO_2Im$) as the final cross-coupling electrophile. We also telescoped sequence that does not conclude with the imidazolylsulfonate formation. Rather the final aim was the establishment of a one-pot sequence that joins the efficiency of C–H borylation with the environmentally friendly aspects of photoredox chemistry and the safety features of imidazolylsulfonates. Namely we have established a one-pot C–H borylation/photoredox oxidation/ imidazolylsulfonation/ Suzuki coupling sequence.

In the second part of this dissertation, the use of high-throughput experimentation for the discovery of cheap, readily available catalytic systems, namely bismuth(III) acetate and silver oxide for selective deborylation of polyborylated substrates will be discussed. Bismuth (III) acetate is a safe, inexpensive, and selective facilitator of sequential protodeboronations, which when used in conjunction with Ir-catalyzed borylations allows access to a diversity of borylated indoles. The versatility of combining Ir-catalyzed borylations with Bi(III)-catalyzed protodeboronation is demonstrated by selectively converting 6-fluoroindole into products with Bpin groups at the 4-, 5-, 7-, 2,7-, 4,7-, 3,5-, and 2,4,7- positions and the late-stage functionalization of sumatriptan. Further elaboration of the reactivity of $Bi(OAc)_3$ for heteroarene substrates and Ag_2O for arene substrates including deborylation/deuteration studies are discussed.

Ir-catalyzed C-H borylations of aromatic compounds often allowed achieving the kinetically favored product. Herein a procedure to achieve reversibility in the catalytic borylation was studied with excess borylating agents and higher catalyst loads to obtain a novel thermodynamic borylated product, which cannot be obtained under usual Ir-catalyzed borylation methods.

I dedicate this dissertation to my loving parents, Damayanthi and Sarath, my wonderful brother Jaliya, my sister Indeewari and my adorable niece Nayeli for their continuous love, support and encouragement.

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KEY TO ABBREVIATIONS

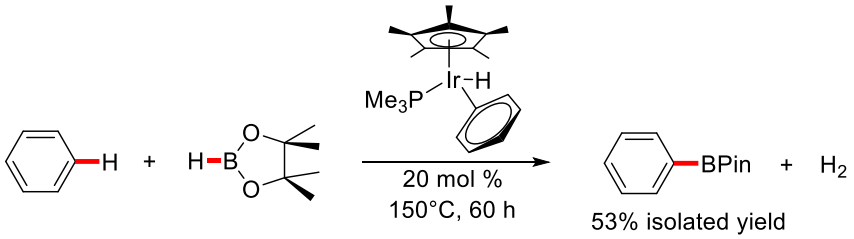
ACS	American Chemical Society
B_2Pin_2	bis(pinacolato)diboron
Boc	butoxycarbonyl
Bu	butyl
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloromethane
Cp	cyclopentadienyl
Cod	1,5-cyclooctadiene
coe	cyclooctene
Cy	cyclohexyl
DMG	directed metallating group
DMAc	N,N-dimethylacetamide
DMF	N,N-dimethylformamide
dtbpy	4-4’-di-*tert*-butyl-2-2’-bipyridine
equiv	equivalents
ESI	electrospray ionization
Et	ethyl
GCI	Green Chemistry Institute
h	hour
HBPin	pinacol borane
HRMS	high-resolution mass spectrometry

mg	milligrams
mL	milliliter
mmol	millimole
mp	melting point
N_2	nitrogen
NMP	N-methyl pyrrolidinone
NMR	nuclear magnetic resonance
Pd	palladium
$PdCl_2(PPh_3)_2$	dichlorobis(triphenylphosphine)palladium(II)
$Pd(OAc)_2$	palladium acetate
$Pd(PPh_3)_4$	palladium tetrakis(triphenylphosphine)
ppm	parts per million
rt	room temperature
$Ru(bpy)_3Cl_2$	tris(2,2′-bipyridyl)dichlororuthenium(II)
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	tetramethylphenanthroline

CHAPTER 1. INTRODUCTION

1.1. Ir-catalyzed C–H activation/borylation.

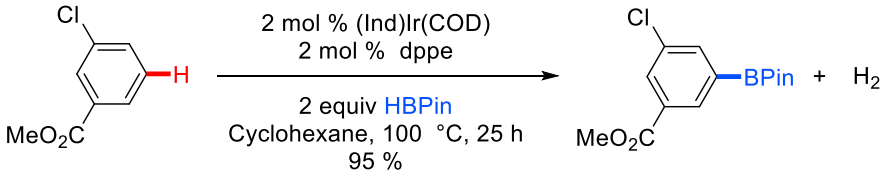
C–H activation/borylation[1] is a type of C–H activation[2] method that converts unactivated C–H bonds to C–B bonds. This transformation is thermodynamically favored and often carried out with the use of transition metals like Re, Rh, Ru, Ir and Pd.[3] In 1999, Smith and Iverson reported the first thermal catalytic aromatic C–H activation/borylation reaction using Cp*Ir(PMe_3)Bpin(H) catalyst in the presence of HBpin, (pin = pinacolate) as boron source at 150 °C with 3 turnovers (Scheme 1.1). While the initial TONs (turn over numbers) were low, this was the first example of thermal, catalytic C–H activation/borylation of an arene.[4]



Scheme 1.1: First thermal catalytic borylation of benzene

Development of this process[4,5] reached a milestone in 2002, when the Smith group introduced the use of 2 mol % (Ind)Ir(COD) precatalyst in combination with bisphosphine ligands (usually dppe or dmpe) to affect the borylation of unactivated arenes and heteroarenes with pinacolborane (HBPin) (Scheme 2).[6] The optimized process was high yielding, functional group tolerant (alkyl, halo-, carboxy, alkoxy-, and protected amino), and efficient. The regiochemistry of the reactions were dictated by sterics and not electronics. As a consequence, 1,3-substituted arenes gave only 5-boryl or meta products, even when both the 1- and 3-substituents were ortho, para directing.

Further, the reactions were inherently clean as they could often be run without solvent and always occurred with hydrogen being the primary byproduct formed in stoichiometric amounts.

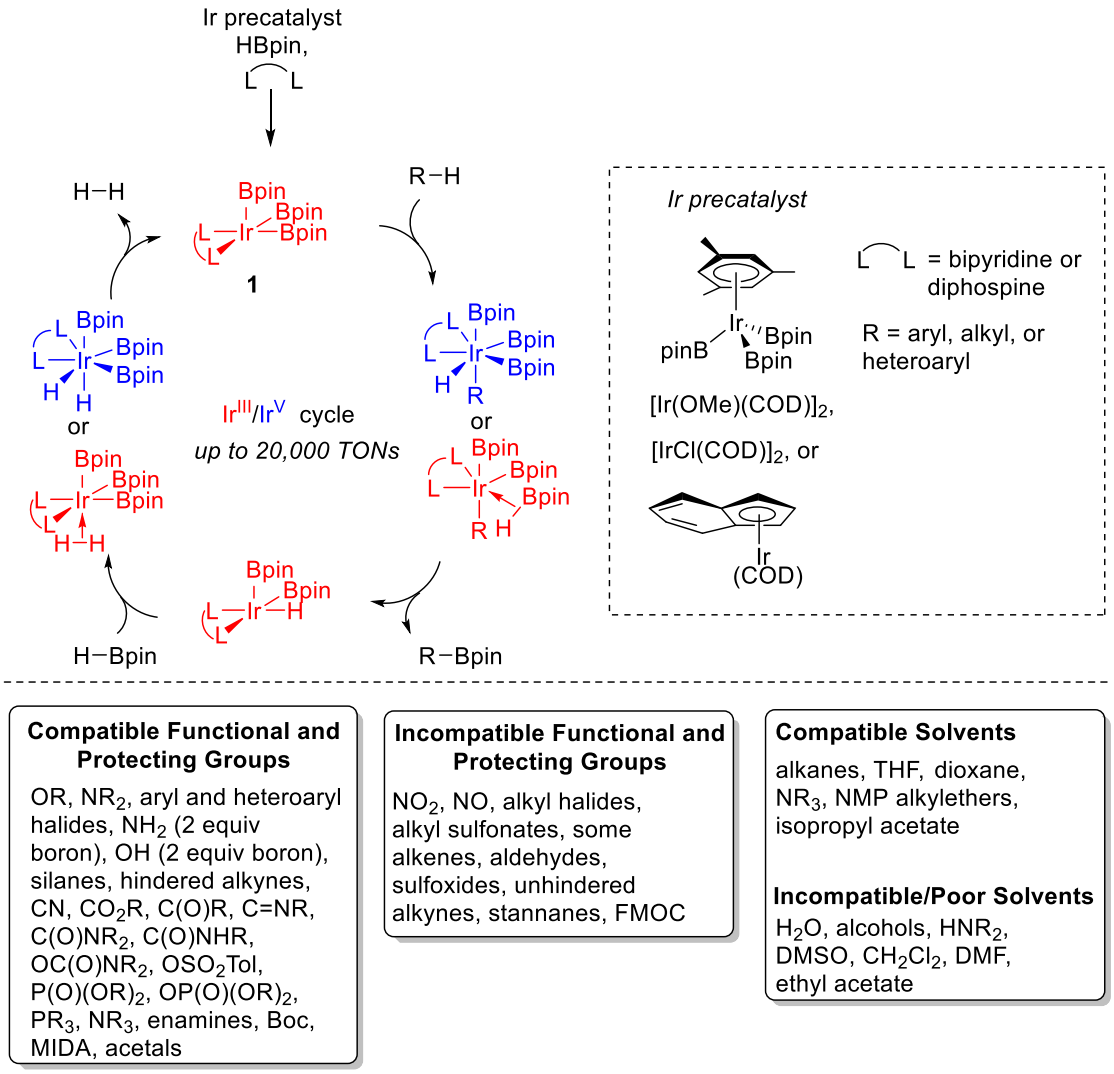


Scheme 1.2: Example of a C–H activation/borylation catalyzed by (Ind)Ir(COD)-dppe.

Hartwig and coworkers later showed that the precatalyst $[Ir(OMe)COD]_2$ in combination with a bipyridine ligand 4-4'-di-tert-butyl-2,2'-bipyridine (dtbpy), using bispinacolatodiboron (B_2Pin_2) as boron source, could affect borylation reaction at room temperature.[7] Ever since the early disclosures of the Smith group in 1999 there has been a significant advancement around the C–H activation/borylation was reported by Smith,[8] Hartwig, Ishiyama and Miyaura groups[9] and others[10]. While most catalysts use Ir, recent work shows that Pt[11] and earth-abundant metals[12] can be effective in this reaction, and "metal-free" examples have also been developed.[13] In many regards the catalysts complement the Ir chemistry.[12a,9]

The catalytic cycle for Ir catalyzed C–H activation/borylation has been proposed to operate via a Ir(III)/Ir(V) catalytic species as shown in the Scheme 1.3.[6,9g] First, the oxidative addition of B_2Pin_2 or HBPin to an Ir(I) precatalyst species in the presence of a donor ligand, typically bidentate, generate the active trisboryl Ir(III) active catalyst. Ir(I) compounds have been found to be proficient precatalysts include (Ind)Ir(COD), $[Ir(COD)Cl]_2$ and $[Ir(OMe)COD]_2$ and bidentate ligands such as dmpe, dtbpy, or dppe (1,2-bis(diphenylphosphino)ethane) have been employed. The most commonly used system is $[Ir(OMe)COD]_2$ with dtbpy, where the active catalyst is generated in-situ. Oxidative addition of the substrate to the trisboryl Ir(III)

intermediate gives an Ir(V) species. As reported by Maleczka, Singleton and Smith,[8f] experimental and theoretical data suggest that significant proton transfer character exist in the C–H activation transition state. Reductive elimination of the RBPin product and subsequent oxdative addition by B_2Pin_2 or HBPin to the resulting bisborylIr(III) complex gives an 18e- Ir(V) intermediate. Reductive elimination of HBPin or H_2 regenerates the active trisboryl iridium(III) catalyst.

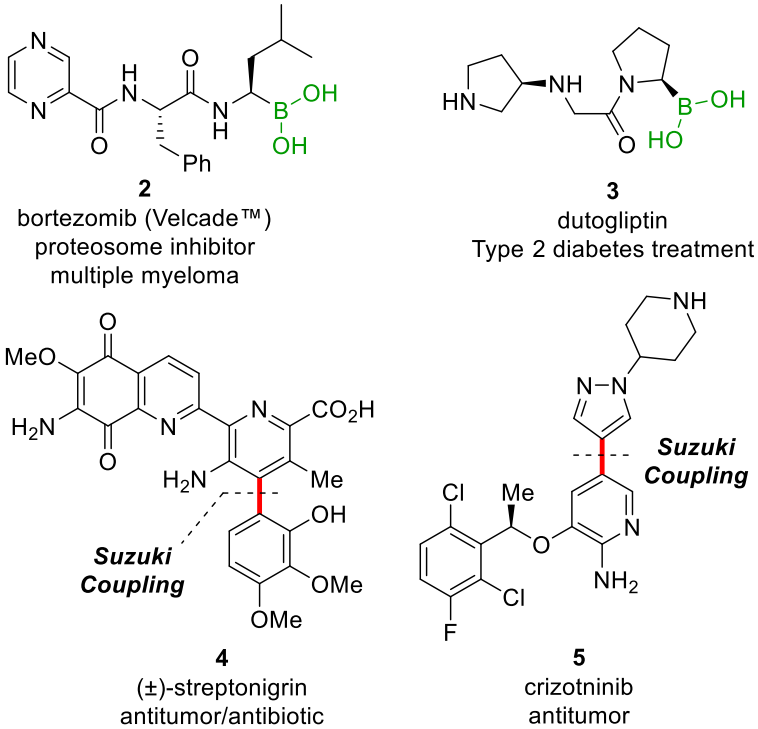


Scheme 1.3: Proposed catalytic cycle of Ir-catalyzed C–H activation/borylation.

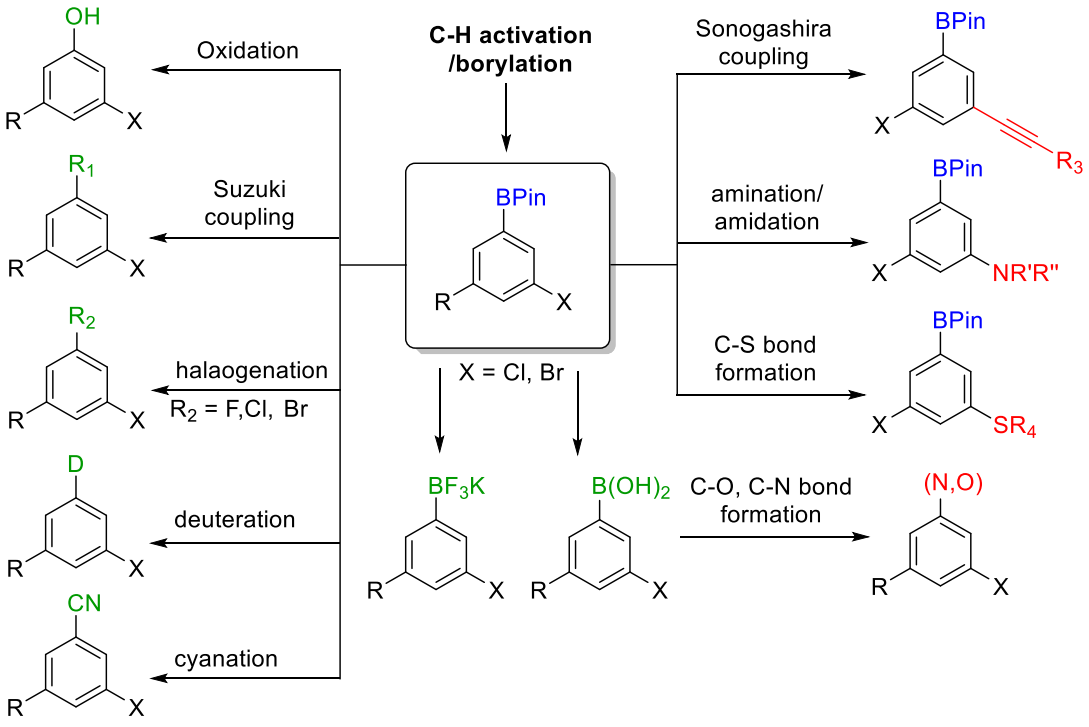
1.2. Synthetic value of Ir-catalyzed C–H activation/borylation.

Organoboron compounds are privileged synthons for constructing C–C and C–heteroatom bonds under mild conditions, and development of their synthetic transformations continues to flourish.[14] Synthesis of arylboronates are usually carried either via Grignard or lithiate formation, reaction with trialkyl borate followed by hydrolytic work up or via direct cross coupling of halides to the boronate, developed independently by Miyaura and Masuda.[1,15] Complementary to these methods of synthesis direct Ir catalyzed C–H activation/borylation provides access to these synthetically valuable compounds without depending on the accessibility of the corresponding halides or organometallics.

Figure 1.1: Examples of boron-containing drug candidates, and APIs that are prepared by Suzuki couplings.



Further, complementary to electrophilic aromatic substitution and functional group-directed metalation chemistries that are governed by electronics, Ir catalyzed C–H activation/borylation displays a regioselectivity that is mainly directed by sterics, as opposed to electronics. This C–H activation/borylation, therefore, operates largely outside of the electronic manifold and allows for the construction of the previously difficult to access arylboronic esters. Moreover, in a testament to the mildness of these borylations, halogens, esters, alkoxy groups, nitriles, amines, amides, sterocenters, etc. are well tolerated. The reactions are also highly atom economical with H_2 being the only stoichiometric byproduct. It worth noting that some functional groups (ex: nitro, alkyl halides, aldehydes, sulfoxides etc.) are not tolerated under these catalytic conditions and further improvements in such regard would to be advantageous (scheme 1.3).[8,9,10]



Scheme 1.4: Synthetic utility of borylated arenes

Organoboron species are useful building blocks for pharmaceuticals and other compounds of interest to the biomedical community. Not only organoboron containing drugs have been developed (**2** and **3**, see Figure 1),[16] their use as starting materials for a wide array of transformations is well established. In particular, the Suzuki-Miyaura coupling of boronic acids or esters with sp_2 halides is a common, mild, and versatile method for constructing C–C bonds.[17] (See Figure 1 for some recent examples of drug candidates prepared by way of a Suzuki reaction). These compounds can also be developed further to form carbon oxygen, [18] halogen, [19] nitrile, [20]nitrogen[18c],[21] aryl[6,22] and other carbon-carbon[17] bonds (Scheme 1.4). In addition to being able to manipulate the BPin, effort has been placed into pursuing C–halogen couplings while keeping the BPin intact. A halide containing borylated compounds can be subjected to Sonogashira coupling, amidation, amination or a C-S bond forming reaction at the halide position (Scheme 1.4). Further, hydrogen being the only byproduct Ir catalyzed C–H activation/borylation proceeds with remarkable cleanness and hence is amenable one-pot transformation. For example one-pot borylation/oxidation,[18] borylation/amination[8e] and borylation/Suzuki[6,22] reactions were previously reported. Further expansion of these methodologies and Ir catalyzed C–H activation/borylation/deborylation-deuteration methodologies with be discussed in the chapter 2,3, and 4.

REFERENCES

REFERENCES

1. Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931.

2. (a) Crabtree, R. H. *J. Chem. Soc., Dalton Trans* **2001**, 2437–2450. (b) Goldberg, K. I.; Goldman, A. S., *Activation and Functionalization of C-H Bonds*. American Chemical Society : Distributed by Oxford University Press:Washington, DC, 2004.

3. Ishiyama, T.; Miyaura, N. J. *Organomet. Chem*. **200**3, *680*, 3–11.

4. Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.*, **1999**, *121*, 7696 – 7697.

5. Tse, M. K., Cho, J. Y. and Smith, M. R. *Org. Lett.* **2001,** *3* (18), 2831-2833.

6. Cho, J. Y., Tse, M. K., Holmes, D., Maleczka, R. E. and Smith, M. R. *Science* **2002,** *295* (5553), 305-308.

7. Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc*. **2002**, *124*, 390–391.

8. (a) Maleczka, R. E., Jr.; Shi, F.; Holmes, D.; Smith, M. R., III *J. Am. Chem. Soc.* **2003**, *125*, 7792–7793. (b) Chotana, G. A.; Rak, M. A.; Smith, M. R., III *J. Am. Chem. Soc.* **2005**, *127*, 10539–10544. (c) Holmes, D.; Chotana, G. A.; Maleczka, R. E.; Smith, M. R. *Org. Lett.* **2006**, *8*, 1407–1410. (d) Paul, S.; Chotana, G. A.; Holmes, D.; Reichle, R. C.; Maleczka, R. E., Jr.; Smith, M. R., III *J. Am. Chem. Soc.* **2006**, *128*, 15552–15553. (e) Shi, F.; Smith, M. R., III; Maleczka, R. E., Jr. *Org. Lett.* **2006**, *8*, 1411–1414. (f) Chotana, G. A.; Kallepalli, V. A.; Maleczka, R. E., Jr.; Smith, M. R., III *Tetrahedron* **2008**, *64*, 6103– 6114. (g) Chotana, G. A.; Vanchura, B. A., II; Tse, M. K.; Staples, R. J.; Maleczka, R. E., Jr.; Smith, M. R., III *Chem. Commun.* **2009**, 5731–5733. (h) Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E., Jr.; Smith, M. R., III *J. Org. Chem.* **2009**, *74*, 9199–9201. (i) Vanchura, B. A., II; Preshlock, S. M.; Roosen, P. C.; Kallepalli, V. A.; Staples, R. J.; Maleczka, R. E., Jr.; Singleton, D. A.; Smith, M. R., III *Chem. Commun.* **2010**, *46*, 7724–7726. (j) Preshlock, S. M.; Plattner, D. L.; Maligres, P. E.; Krska, S. W.; Maleczka Jr., R. E.; Smith, M. R., III. *Angew. Chem. Int. Ed*., **2013**, *52*, 12915 – 12919. (k) Preshlock, S. M.; Ghaffari, B.; Maligres, P. E.; Krska, S. W.; Maleczka Jr., R. E.; Smith, M. R., III. *J. Am. Chem. Soc.*, **2013**, *135*, 7572 – 7582. (l) Jayasundara, C. R. K.; Unold, J. M.; Oppenheimer, J.; Smith, M. R., III; Maleczka Jr., R. E. *Org. Lett.*, **2014,** *16*, 6072 – 6075. (n) Ghaffari, B.; Preshlock, S. M.; Plattner, D. L.; Staples, R. J.; Maligres, P. E.; Krska, S. W.; Maleczka Jr., R. E.; Smith, M. R., III. *J. Am. Chem. Soc*., **2014**, *136*, 14345 – 14348.

9. (a) Waltz, K. M.; Muhoro, C. N.; Hartwig, J. F. *Organometallics* **1999**, *18*, 3383–3393. (b) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056–3058. (c) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390–391. (d) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura,

N. *Tetrahedron Lett.* **2002**, *43*, 5649–5651. (e) Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N. *Chem. Commun.* **2003**, 2924–2925. (f) Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal.* **2003**, *345*, 1103–1106. (g) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263–14278. (h) Ishiyama, T.; Miyaura, N. *Pure Appl. Chem.* **2006**, *78*, 1369–1375. (i) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434–15435. (j) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757–760. (k) Tzschucke, C. C.; Murphy, J. M.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 761–764. (l) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534–7535. (m) Simmons, E. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 17092–17095. (n) Liskey, C. W.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 11389–11391.(o) Roosen, P. C.; Kallepalli, V. A.; Chattopadhyay, B.; Maleczka, R. E., Jr.; Singleton, D. A; Smith, M. R., III. *J. Am. Chem. Soc.* **2012**, *134*, 11350 – 11353.(p) Cho, S. H.; Hartwig, J. F. *Chem. Sci.*, **2014**, *5*, 694 – 698. (b) Cho, S. H.; Hartwig, J. F. *J. Am. Chem. Soc.*, **2013**, *135*, 8157 – 8160. (q) XLarsen, M. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4287-4299.(r) Larsen, M. A.; Cho, S. H.; Hartwig, J. F. *J. Am. Chem. Soc.*, **2016**, *138*, 762 – 765.

10. (a) Coventry, D. N.; Batsanov, A. S.; Goeta, A. E.; Howard, J. A. K.; Marder, T. B.; Perutz, R. N. *Chem. Commun.* **2005**, 2172–2174. (b) Mkhalid, I. A. I.; Coventry, D. N.; Albesa- Jove, D.; Batsanov, A. S.; Howard, J. A. K.; Perutz, R. N.; Marder, T. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 489–491. (c) Hamasaka, G.; Ochida, A.; Hara, K.; Sawamura, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5381–5383. (d) Harrisson, P.; Morris, J.; Marder, T. B.; Steel, P. G. *Org. Lett.* **2009**, *11*, 3586–3589. (e) Harrisson, P.; Morris, J.; Steel, P. G.; Marder, T. B. *Synlett* **2009**, 147,150. (f) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058–5059. (g) Ros, A.; Fernandez, R.; Lassaletta, J. M. *Chem. Soc. Rev.*, **2014**, *43*, 3229 – 3243. (h) Kawamorita, S.; Miyazaki, T.; Ohmiya, H.; Iwai, T.; Sawamura, M. *J. Am. Chem. Soc.*, **2011**, *133*, 19310 – 19313. (i) Iwai, T.; Harada, T.; Hara, K.; Sawamura, M. *Angew. Chem. Int. Ed.*, **2013**, *52*, 12322 – 12326.

11. Furukawa, T.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2015**, *137*, 12211-12214.

12. (a) J. V.; Semproni, S. P.; Chirik, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 4133-4136. (b) Mazzacano, T. J.; Mankad, N. P. *J. Am. Chem. Soc.* **2013**, *135*, 17258-17261. (c) Yan, G. B.; Jiang, Y. B.; Kuang, C. X.; Wang, S. A.; Liu, H. C.; Zhang, Y.; Wang, J. B. *Chem. Commun.* **2010**, *46*, 3170-3172. (d) Dombray, T.; Werncke, C. G.; Jiang, S.; Grellier, M.; Vendier, L.; Bontemps, S.; Sortais, J.-B.; Sabo-Etienne, S.; Darcel, C. *J. Am. Chem. Soc.* **2015**, *137*, 4062-4065. (e) Furukawa, T.; Tobisu, M.; Chatani, N. *Chem. Commun.* **2015**, *51*, 6508-6511.

13. (a) Cazorla, C.; De Vries, T. S.; Vedejs, E. *Org. Lett.* **2013**, *15*, 984-987. (b) Del Grosso, A.; Singleton, P. J.; Muryn, C. A.; Ingleson, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 2102-2106.

14. Fernández, E.; Whiting, A. *Synthesis and Application of Organoboron Compounds*; Springer International Publishing: Cham, Switzerland, 2015.

15. (a) Ishiyama, T.; Murata, M.; Miyuara, N. *J. Org. Chem.* **1995**, *60*, 7508-7510. (b) Ishiyama, T; Miyuara, N. *J. Organomet. Chem.* **2000**, *611*, 392-402. (c) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164.

16. (a) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177-2250. (b) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027-3043. (c) Scorei, R. I.; Popa, R. *Anti-Cancer Agents in Medicinal Chemistry- Anti-Cancer Agents)* **2010**, *10*, 346-351.

17. a) Miyaura, N. and Suzuki, A. *Chem. Rev.* **1995,** *95* (7), 2457-2483. b) Suzuki, A. *J. Organomet. Chem.* **1999,** *576* (1-2), 147-168. (c) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412-443. (d) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis-Stuttgart* **2004**, 2419-2440. (e) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633-9695. (f) Biajoli, A. F. P.; Schwalm, C. S.; Limberger, J.; Claudino, T. S.; Monteiro, A. L. *J. Braz. Chem. Soc.* **2014**, *25*, 2186-2214.

18. (a) Maleczka, R. E., Jr.; Shi, F.; Holmes, D.; Smith, M. R., III *J. Am. Chem. Soc.* **2003**, *125*, 7792. (b) Shi, F.; Smith, M. R., III; Maleczka, R. E., Jr. *Org. Lett.* **2006**, *8*, 1411. (c) Tzschucke, C. C.; Murphy, J. M.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 761. (d) Norberg, M. A.; Smith, M. R., III; Maleczka, R. E., Jr. *Synthesis* **2011**, 857.

19. (a) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860. (b) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.

20. (a) Liskey, C. W.; Liao, X. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 11389

21. (a) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757

22. (a) Kallepalli, V. A.; Sanchez, L.; Li, H.; Gesmundo, N. J.; Turton, C. L.; Maleczka, R. E., Jr.; Smith, M. R., III *Heterocycles* **2010**, *80*, 1429-1448.

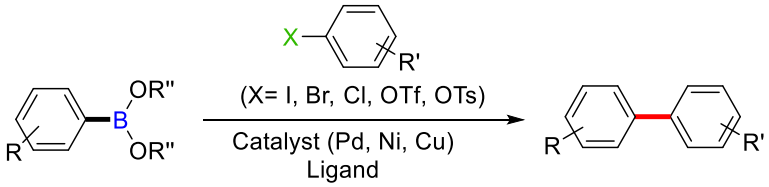
CHAPTER 2: TELESCOPING C–H BORYLATIONS WITH PHOTOREDOX AND IMIDAZOLYLSULFONATE CHEMISTRY: A WAY TO AVOID HALOAROMATICS AND POTENTIALLY GENOTOXIC IMPURITIES IN SUZUKI REACTIONS

2.1. Introduction

In 2005, the American Chemical Society's (ACS), Green Chemistry Institute (GCI)[1] teamed with several leading global pharmaceutical corporations, namely, AstraZeneca, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Pfizer, and Schering–Plough to form the GCI Pharmaceutical Roundtable (ACS GCIPR)[2] to catalyze the implementation of green chemistry and green engineering in the global pharmaceutical industry. Two years later, Roundtable chemists published a list of research areas that they deemed key to advancing green drug discovery, development, and production.[3] Owing in part to the extensive use of cross-coupling reactions by the pharmaceutical industry as well as various environmental problems associated with the production and use of aryl halides, ***cross-couplings that avoid the use of haloaromatics (C–H activation)*** topped their list of aspirational reactions. The Pharmaceutical Roundtable's interest in cross-couplings that avoid the preparation of haloaromatics rests in part on the industry's reliance on cross-coupling reactions to construct C–C bonds.[3] For example, it was found that more than 75% of pharmaceuticals in phase III clinical trials, as well as those already on the market contain at least one aryl or heteroaryl group.[3] Furthermore, a great number of the aryl groups, especially phenyls, are incorporated into the active pharmaceutical ingredients preassembled.[3,4] Recent advances in metal-catalysed crosscoupling reactions to form new C-C bonds have greatly facilitated the versatility of incorporating aryls for medicinal chemistry.[3]

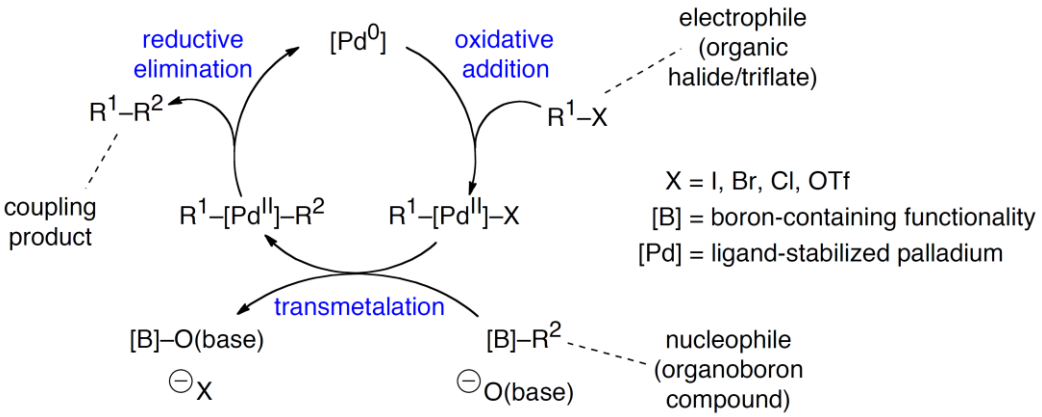
There are several methods that have been utilized for the construction of aryl-aryl bonds, ranging from the classic Ullmann[5] reaction to cross-couplings such as the Pd-catalyzed Heck,[6]

Hiyama,[7] Kumada-Corriu,[8] Negishi,[9] Suzuki-Miyaura,[10] Sonogashira,[11] and Stille[12] reactions. Recognizing the tremendous impact of cross-couplings in organic synthesis, the 2010 Nobel Prize in Chemistry was awarded jointly to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki "for Palladium-catalyzed cross-couplings in organic synthesis".[13] Amoung these methods, the Palladium-catalyzed coupling of a boronic acid or ester with an aryl halide or psuedohalide, termed the Suzuki-Miyaura reaction (Scheme 2.1), has emerged as the method of choice for aryl-aryl bond formation. The Suzuki reaction, like all Pd-catalyzed cross coupling processes, has a



Scheme 2.1: Suzuki-Miyaura reaction.

sequence where it take place in three main steps: (I) oxidative addition of the aryl halide R^1X to a Pd^0 complex $[Pd^0Ln]$ to afford $[R^1Pd^{II}X]$, (II) transmetalation, where this complex then reacts with the arylboronic acid $R^2B(OH)_2$ to form $[R^1Pd^{II}R^2]$ and (III) reductive elimination, which generates the coupling product R^1-R^2 and the Pd^0 catalyst (Scheme 2.2). [10e]

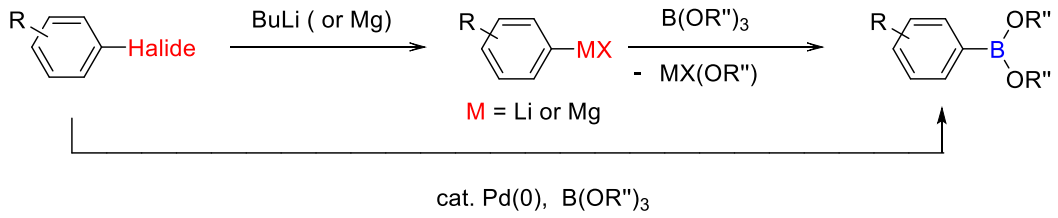


Scheme 2.2: The Suzuki coupling catalytic cycle.

Today, the Suzuki reaction is routinely applied in high-throughput screening for drug discovery, in the final steps of convergent natural product syntheses, and in the synthesis of conjugated organic materials.[14] This widespread use is mainly due to the mild reaction conditions, making the Suzuki reaction tolerant of diverse functionalities.[10] Furthermore, the stability, ease of handling, and low toxicity of the organoboron coupling partners make this coupling ideal for the preparation of highly functionalized molecules that can be used in one-pot strategies.[10] Infact, a recent study on the different reactions used in the pursuit of drug candidates by leading pharmaceutical industries revealed that the most commonly used reaction in C-C bond formation was the Suzuki-Miyaura cross-coupling reaction, accounting for 40% of all such reactions.[15]

Despite their wide use, Suzuki-Miyaura reactions are not without shortcomings. Of particular concern is the aryl halide intensive nature of these reactions. Indeed, not only do halogenated aromatics traditionally serve as Suzuki-Miyaura reaction electrophiles, but they also routinely serve as starting materials for preparing the corresponding aryl boronates, either via Grignard or lithiate formation, reaction with a trialkyl borate followed by hydrolytic workup[16] or

via direct cross coupling of halide to the boronate, developed independently by Miyaura and Masuda (Scheme 1.3).[17,18]



Scheme 2.3: Routes for the formation of aryl boronates via aryl halides.

Problems associated with aryl halides range from inherent toxicity issues[19] to difficulties often encountered during their preparation, especially when the sought-after substrates bear contraelectronic substitution patterns. This point was made by Carey, et al. who in their 2006 analysis of reactions used for pharma's preparation of 128 drug candidates wrote: *"A number have synthetically challenging substitution patterns and are hence very expensive (or) are often very difficult to produce. New methods for the synthesis of these difficult substitution patterns would be welcomed."* [4]

Developing green Suzuki reactions that avoid the preparation of haloaromatics

Fully cognizant of the problems associated with haloroaromatics and thus the need to "Green Up" the Suzuki reaction, we approached the problem by:

1. Investigating a new class of non-halogenated Suzuki electrophiles.

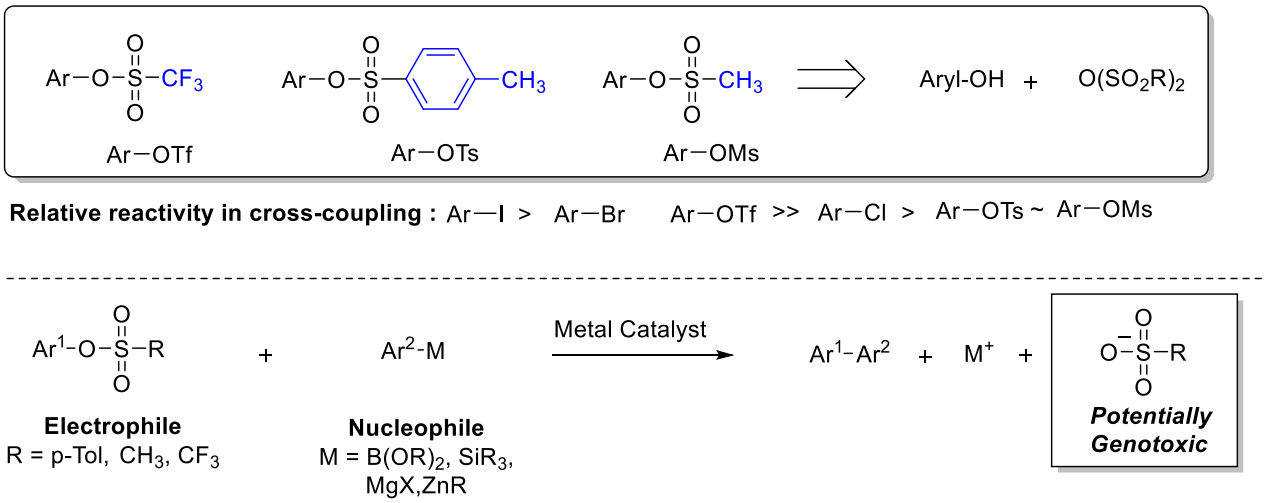
2. Advancing our C-H activation approach to boronic esters.

3. Developing a one-pot C-H activation/borylation/Suzuki with imidazolylsulfonates.

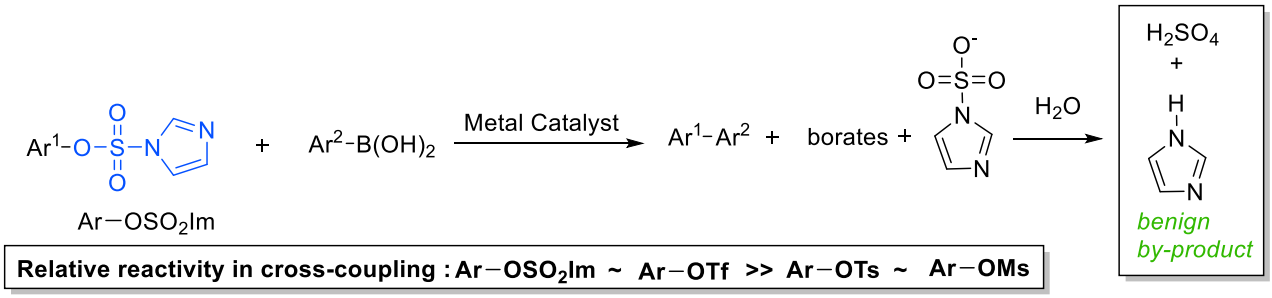
2.2. Investigating a new class of non-halogenated Suzuki electrophiles: Imidazozylsulfonates as halide free electrophiles

With respect to the electrophile, aryl triflates,[20] tosylates[21] and mesylates[22] have long been employed as alternatives to aryl halides. However, self-destruction of the cross-coupling byproduct of these electrophiles tosylic, methanesulfonic, and triflic acids form potential genotoxic impurities (PGIs) (Scheme 2.4, 2.5).[23]

In the presence of water, imidazolesulfonic acid hydrolyzes to produce imidazole and sulfuric acid eliminating the potential of forming alkyl or aryl genotoxic sulfonates from residual sulfonic acid. Because of this, Albaneze-Walker and co-workers examined the use of imidazolylsulfonates as alternative electrophilies in palladium-catalyzed coupling reactions (Scheme 2.6).[24]

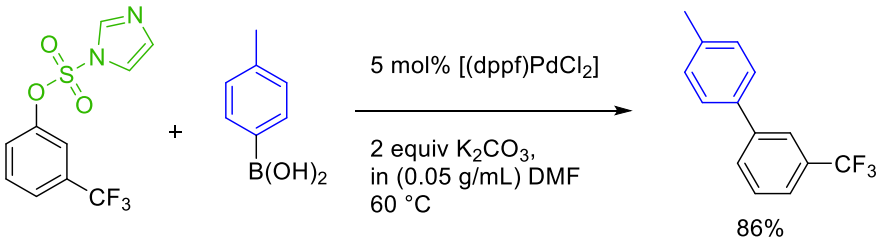


Scheme 2.4: Degradation of post-coupling byproducts.



Scheme 2.5: Degradation of imidazolesulfonic acid.

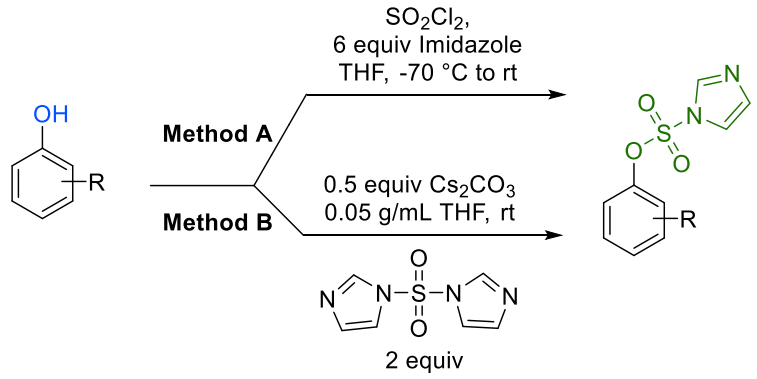
They showed that imidazolylsulfonates act as fully competent electrophilic coupling partners in Suzuki-Miyaura and Negishi type palladium-mediated couplings.[24] Further it was found that imidazolylsulfonates show several advantages over the traditional C-O electrophiles: They are greener than aryl triflates, aryl tosylates and mesylates. They show a markedly improved reactivity over aryl tosylates and mesylates and showed improved stability, handling properties, and cost over aryl triflates. Additionally, they are phenol derivatives and thus eliminate the need for haloaromatics



Scheme 2.6: Example of imidazolylsulfonates in Suzuki-Miyaura reaction.

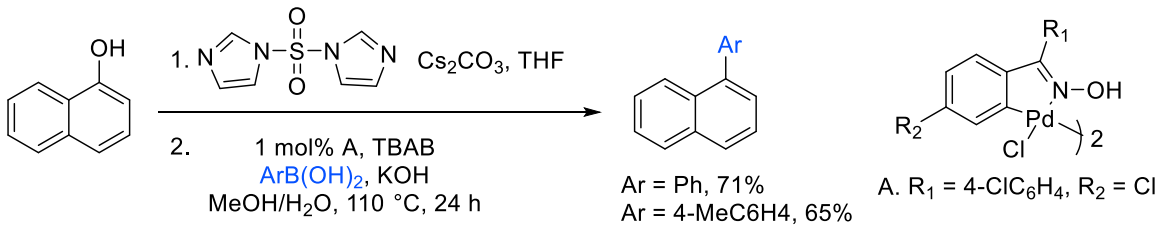
A key benefit of phenol-derived electrophiles is the ready accessibility of these substrates and most notably, oxygenation on the aromatic ring can be used to introduce additional substituents thus allowing access to a wider substrate scope. [25,26] Several methods were investigated for the preparation of aryl imidazolylsulfonates. Albaneze-Walker and co-workers showed that (Scheme

2.7, Method B) was effective for electron-rich phenols[24] while later in 2010, Shirbin and co-workers used (Scheme 2.7, Method A) with electron-poor phenol.[27]



Scheme 2.7: Preparation of aryl imidazolylsulfonates.

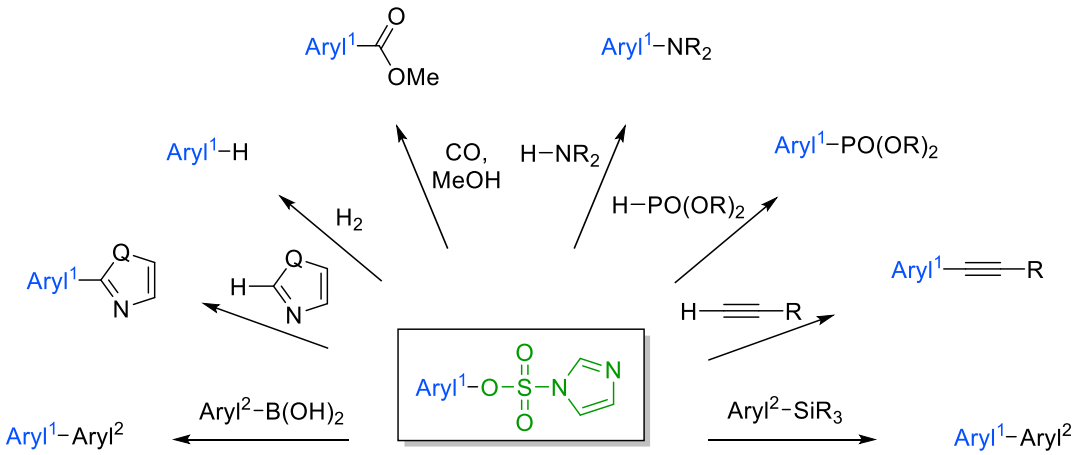
In 2010, Shirbin and co-workers developed a protocol allowing for the use of aryl imidazolylsulfonates in Sonogashira and Hiyama reactions providing environmentally-benign syntheses of arylacetylenes and biaryls.[27]



Scheme 2.8: Recent Examples for the use of aryl imidazolylsulfonates in Suzuki reaction.

In 2011 Cívicos and co-workers showed that one-pot sulfonation/Suzuki cross-coupling sequence of 1-naphthol with phenyl- and 4-tolylboronic acids (Scheme 2.8).[28] Thus, with its wide applicability, there have been considerable efforts into improving the use of imidazolylsulfonates in cross coupling reactions. Subsequent to the Albaneze-Walker report, examples have been disclosed where imidazolylsulfonate electrophiles were used successfully in other Suzuki cross-coupling reactions, Buchwald-Hartwig type C–N bond-

forming reactions[29], C–H arylations[30], synthesis of arylphosphonates[31], and Sonogashira and Hiyama cross-coupling reactions (Scheme 2.9).[32]



Scheme 2.9: Current metal-catalyzed cross-couplings employing imidazolylsulfonates electrophiles

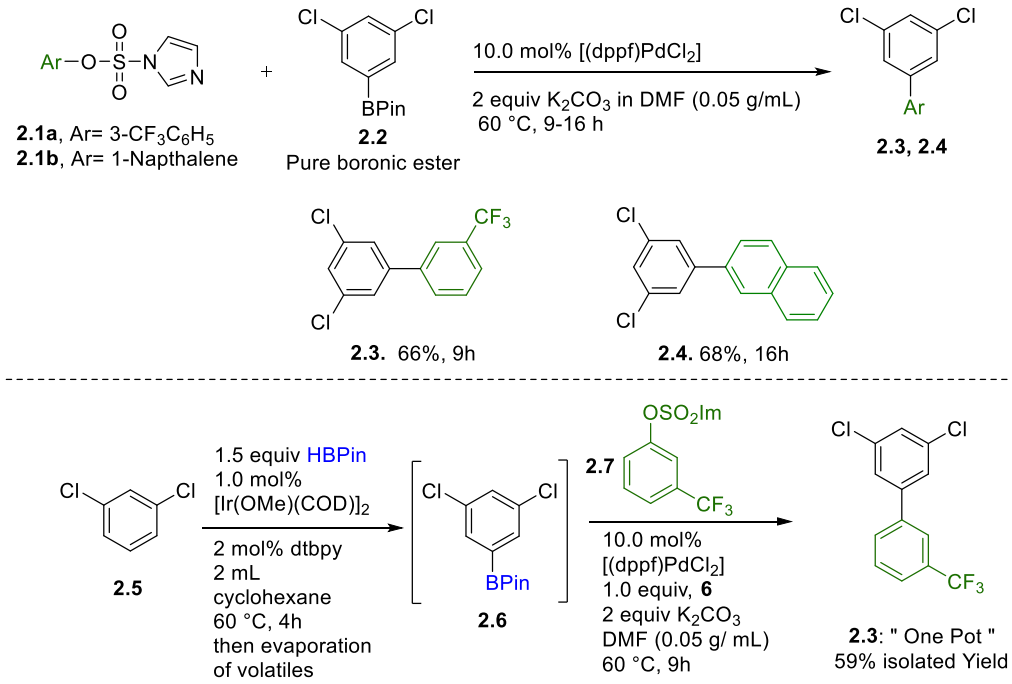
Advancing C-H activation approach to boronic esters.

As for the nucleophile, Ir-catalyzed C–H borylations have proven very effective at the direct generation of aryl and heteroarylboronic esters from non-halogenated substrates[33]. Such reactions operate best with electron deficient arenes and their regiochemical outcomes are typically driven by sterics and not the electronic nature of preexisting substituents. This has allowed researchers to access arene substitution patterns that can be difficult to achieve by way of traditional electrophilc and nucleophilic aromatic substitutions. More recent work on Ir-catalyzed C–H borylations have focused on the development of methods that afford ortho borylations, improve reactivity toward electron rich arenes, and make use of polyborylations to enable access to an ever-growing number of C–H derived aryl and heteroarylboronates.

Herein we describe the marriage of Ir-catalyzed C–H borylations with imidazolylsulfonate chemistry as a means to carry out cross-couplings without the need to use haloaromatics as either the electrophile or the precursor to the ncleophile. Furthermore, we report on our efforts to develop a telescoped C–H borylation-oxidation-imidazolylsulfonate formation-Suzuki coupling sequence**.**

2.3. Results and Discussion

Our individual experiences with imidazolylsulfonates and Ir-catalyzed C–H borylations had several points in common. The functional group tolerance of catalytic C–H borylations combined with hydrogen gas being the only stoichiometric by-product of these reactions has allowed C–H borylations to be developed into several one-pot protocols including C–H activation-borylation-Suzuki cross-couplings[33c] and C–H activation-borylation-oxidations to generate phenols[33d]. Imidazolylsulfonates are prepared from phenols and as previously mentioned are good Suzuki coupling partners. Building from these areas of overlap, we set out to develop protocols that combine the use, and advantages, of imidazolylsulfonates and Ir-catalyzed C–H borylations. The initial report by Albaneze-Walker and co-workers[24] of imidazolylsulfonate cross couplings demonstrated the use of arylboronic acids as the nucleophilic partner. Thus we first established conditions to simply couple imidazolylsulfonates with arylboronic esters. Initial Suzuki cross-coupling studies were carried out with imidazolylsulfonate derivatives under conditions, which worked well with arylboronic acids. The cross-coupling of compounds **2.1** with boronic ester **2.2** was initially performed using catalyst (dppf)$PdCl_2$ and K_2CO_3 in DMF at 60 °C (Scheme 2.10, **2.3** and **2.4**). As depicted in Scheme 2.10, cross-coupling was successful for an arylboronic ester affording **2.3** and **2.4** with 66% and 68% isolated yield respectively.



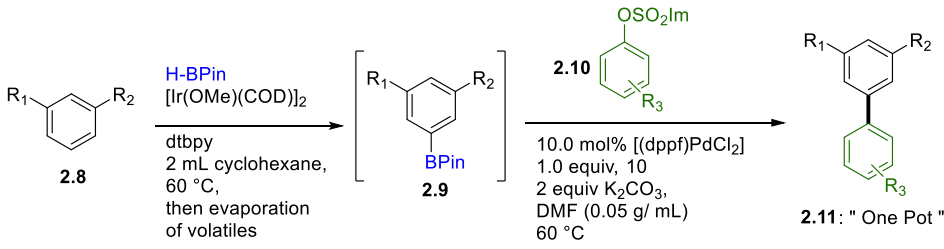
Scheme 2.10: Cross-coupling of Boronic Esters with Imidazolylsulfonates

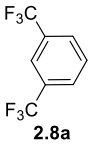
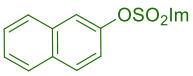
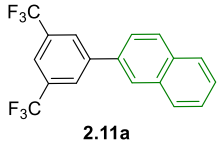
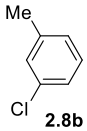
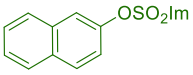
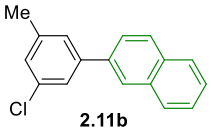
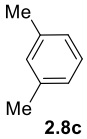
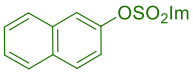
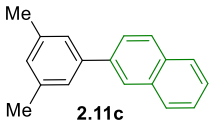
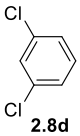
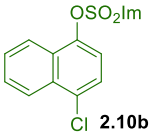
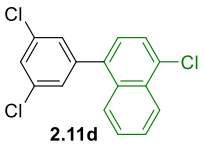
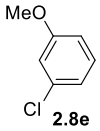
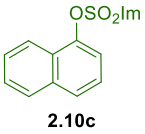
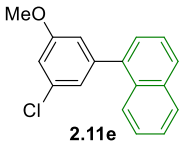
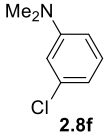
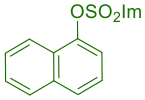
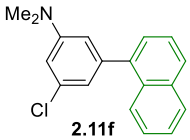
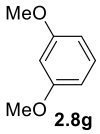
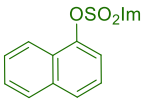
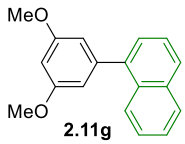
Having established that boronic esters are competent coupling partners for imidazolylsulfonates, we explored a one-pot C–H activation/borylation/Suzuki sequence. We knew from past work that the spent Ir and other sub-stoichiometric byproducts did not interfere with one-pot C–H activation/borylation/Suzuki cross-couplings with arylhalides.[33c] While these earlier results were encouraging, they did not necessarily assure success with imidazolylsulfonate coupling partners. Thus, while our overall goal was to eliminate the use of haloaromatics, we thought it best to establish the applicability of one-pot C–H activation/borylation/Suzuki coupling with imidazolylsulfonates by employing arenes that had shown to be highly active and selective in past borylations and that has been used in previous one-pot procedures. For these reasons (and despite the fact that making polychlorinated biphenyls is not green chemistry!), we chose 1,3-dichlorobenzene (**2.5**) as our starting arene (Scheme 2.10). Upon complete borylation of **2.5**, the volatiles were removed *in vacuo* and K_2CO_3 in DMF along with imidazolylsulfonate **2.7** was

added to the pot. The reaction mixture was degassed, followed by addition of 10 mol % (dppf)$PdCl_2$. The reaction mixture was heated to 60 °C and the cross-coupling proceeded under nitrogen to afford the desired biaryl product 3,5-dichloro-3'-(trifluoromethyl)-1,1'-biphenyl, **2.3** in 59% isolated yield. In practice, the one pot procedure tended to give slightly lower yields when compared with the ability of an imidazolylsulfonate to serve as an electrophile in the one-pot Ir-catalyzed borylation/Suzuki confirmed a series of biaryls were generated in this way (Table 2.1).

As referred to earlier, the regiochemistry of C–H borylations tends to be sterically driven. This allows for the facile synthesis of *meta*-disubstituted arylboronic esters when starting with 1,3-disubstituted arenes. This regioselectivity combined with good chemoselectivity of the entire process, meant that the biaryls from these one-pot processes were generally formed as a single product and in good yield. While the electron-withdrawing or donating ability of the arene substituents do not impact the regiochemical outcome, substituent electronics plays a significant role in borylation rates. Such rate effects were on display in the one-pot reaction sequences.

Table 2.1: One-pot C-H Activation/Borylation/Suzuki Coupling of Disubstituted Arenes.[a]



Entry	Arene	Imidazolylsulfonate	Product	T (h)	Yield (%)b
1.	 **2.8a**	 **2.10a**	 **2.11a**	16	68
2.	 **2.8b**	 **2.10a**	 **2.11b**	36	72
3.	 **2.8c**	 **2.10a**	 **2.11c**	14	82
4.	 **2.8d**	 **2.10b**	 **2.11d**	16	48
5.	 **2.8e**	 **2.10c**	 **2.11e**	14	74
6.	 **2.8f**	 **2.10c**	 **2.11f**	6	62
7.	 **2.8g**	 **2.10c**	 **2.11g**	16	72

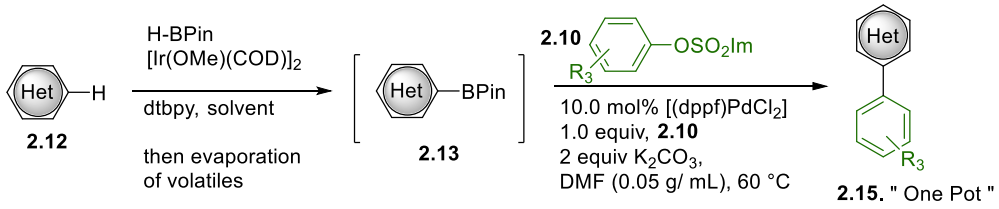
[a]Reaction Conditions: Borylation: For Entry 1; 1.5 equiv HBPin, 2 mol% $[Ir(OMe)(COD)]_2$, 3 mol% dtbpy, cyclohexane, 60 °C, 1h. For Entry 2; 2.0 equiv HBPin, 3 mol% $[Ir(OMe)(COD)]_2$, 6 mol% dtbpy, solvent, 60 °C, THF, 24 h. For Entry 3; 1.0 equiv B_2Pin_2, 1 mol% $[Ir(OMe)(COD)]_2$, 2 mol% TMP, THF, 80 °C, 4 h. For Entry 4; 1.5 equiv HBPin, 1 mol% $[Ir(OMe)(COD)]_2$, 2 mol% dtbpy, cyclohexane, 60 °C, 4 h. For Entry 5,6; 1.1 equiv B_2Pin_2, 1.5 mol% $[Ir(OMe)(COD)]_2$, 3 mol% dtbpy, THF, 80 °C, 12 h. . For Entry 7; 1.1 equiv B_2Pin_2, 1.0 mol% $[Ir(OMe)(COD)]_2$, 2 mol% TMP, THF, 80 °C, 4 h unless otherwise noted. Suzuki: see the reaction scheme in Table 1. For Entry 3,5 & 6 used DMF/H_2O (10:1) and for Entry 7 used DMAc/H_2O (10:1) [b] Isolated yields

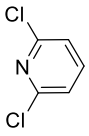
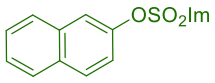
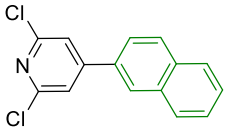
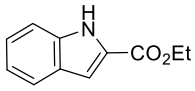
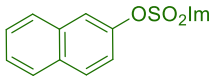
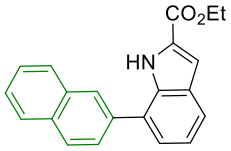
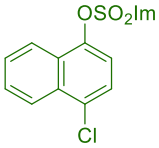
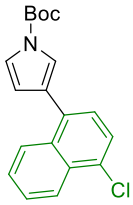
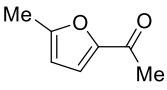
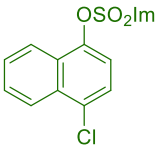
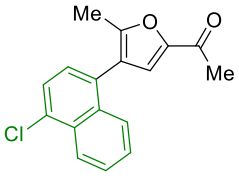
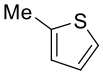
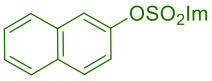
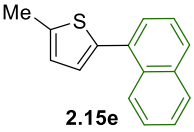
For example, the one-pot process starting with electron deficient 1,3-bis(trifluoromethyl)benzene **2.8a** was effective and relatively fast, giving the corresponding biaryl in good yield (Table 2.1, Entry 1). Tandem coupling of the boronic ester of *m*-chlorotoluene, **2.8b** with imidazolylsulfonate of naphthalene-2-ol (**2.10a**) gave the desired chlorobiphenyl in 72% yield, but required relatively long borylation and coupling time (Table 2.1, Entry 2). Further for the Suzuki coupling of m-xylene, **2.8c** with imidazolylsulfonate (**2.10a**) (Table 2.1, Entry 3) the standard conditions were attempted first, but were only obtained 40% conversion at 60 °C for 40 h. Several modifications to the standard cross-coupling procedure were attempted, and to our delight addition of water (DMF/H_2O 10:1) with raising the temperature to 80 °C, was resulted with 82% isolated yield. This modified cross coupling condition was then employed in the cross-coupling of other electron rich arene intermediates like of **2.8e** and **2.8f** with imidazolylsulfonate **2.9c** to obtain **2.11e** and **2.11f** cross-coupled product with good yields. Moreover, for entry 7, 1,3-dimethoxybenzene (**2.8g**), since electron richness of the arene it was more difficult to borylate than electron poor arenes, the standard borylation conditions with dtbpy (4-4'-di-*tert*-butyl-2-2'-bipyridine) as the ligand did not borylate to completion. After changing ligands to TMP (tetramethylphenanthroline) and raising the temperature to 80 °C, the borylation finally went to complete conversion as judged by ^{1}H NMR. The corresponding cross-coupling was then carried out with switching the solvent to a combination of DMAc (N,N-dimethylacetamide) and water (instead of using DMF), raising the temperature to 80 °C from 60 °C and adding a slight excess of imidazolyl sulfonate (1.2 equivalents) gave improved results, and finally gave consistent 90% conversions and greater than 70% isolated yields of the product. It appears that in addition to being sluggish for the borylation, this substrate was also difficult for the Suzuki coupling. In spite of the difficulties, we proved that optimization of the cross-coupling could

still result in excellent conversions and isolated yields. Further, it was shown that both electron deficient and electron rich arenes can undergo borylation/cross-coupling in a one-pot fashion. It is worth noting that under these conditions, no Pd catalyzed cross-coupling was observed with the chloro-functionality. This advantage allows generation of substrates that can be further elaborated.

The facile and flexible construction of aryl heteroaromatics is important owing to their potential as therapeutics[34]. Borylation of pyridine gives low to moderate yields of the 3- and 4-borylated pyridine[35], which limits its use in the one-pot coupling. The low yield may be attributable to partial catalyst deactivation due to coordination of the pyridine nitrogen. Indeed, when the pyridine nitrogen is sterically encumbered, as in 2,6-dichloropyridine (**2.12a**) exclusive 4-borylated product was obtained. Despite this, first attempts to use 2,6-dichloropyridine in the one-pot coupling with the imidazolylsulfonate of naphthalene-2-ol (**2.10a**) were unsuccessful, with very sluggish reactivity observed in the cross-coupling[36]. Although we had deemed an anhydrous protocol preferable for future one-pot sequences, our previous Pd-catalyzed cross-couplings with imidazolylsulfonates responded well to aqueous solvent mixtures. Here too, it was found that replacing DMF with 3:1 DME: H_2O as the solvent allow for a more efficient coupling of 2,6-dichloro-4-BPin-pyridine (Table 2.2, Entry 1).

Table 2.2: One pot C-H Activation/Borylation/Suzuki Coupling of Heteroarenes.[a]



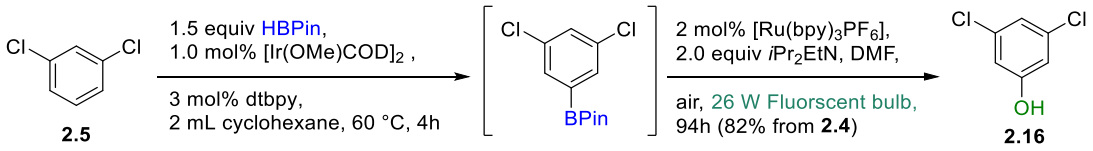
Entry	Arene	Imidazolylsulfonate	Product	T (h)[b]	Yield (%)[c]
1.[d]	 **2.12a**	 **2.10a**	 **2.15a**	16	42
2.	 **2.12b**	 **2.10a**	 **2.15b**	16	57
3.	 **2.12c**	 **2.10b**	 **2.15c**	16	67
4.	 **2.12d**	 **2.10b**	 **2.15d**	20	49
5.	 **2.12e**	 **2.10a**	 **2.15e**	6	62

[a]Reaction Conditions: Borylation: For Entries 1 and 2; 1.5 equiv HBPin, 3 mol% [Ir(OMe)(COD)]2 , 6 mol% dtbpy, 60 °C, 1 h THF and 3 h in hexane in respectively. For Entries 3 and 4; 1.5 equiv HBPin, 1.5 mol% [Ir(OMe)(COD)]2 , 3 mol% dtbpy, 60 °C, cyclohexane, 2 h and 1h respectively, unless otherwise noted. [b]Suzuki Time. [c]Yields represent isolated yields, unless otherwise noted. [d]Solvent DMF:H2O; 3:1 for the Suzuki coupling.

2-Subtituted indoles borylate at C7[37] and when subjected to our one-pot coupling with imidazolylsulfonate of naphthalene-2-ol (**2.10a**) afforded the 7-arylated product, **2.15a** in 57% isolated yield (Table 2, Entry 2). The readily available N-Boc-pyrrole underwent borylation to give 3-BPin-N-Boc-pyrrole[38], which when reacted crude with the imidazolylsulfonate of 4-chloronaphthalen-1-ol (**2.10b**) allowed for the directed synthesis of **15c** in 58% overall yield (Table 2, Entry 3). 2-Acetyl-5-methylfuran could be arylated ortho to the methyl substituent (49% overall yield)[33,39] while 2-methyl thiophene borylated[33i] and then arylated at the C5 position in 52% yield.

2.3.1. One-pot C–H activation/borylation/photoredox oxidation:

Having demonstrated the viability of a one-pot C-H activation borylation/Suzuki coupling with the use of imidazolylsulfonates as the electrophiles, we next set out to explore the possibility of a one-pot imidazolylsulfonate synthesis that employs crude phenol mixtures generated in a one-pot C–H activation/borylation/oxidation. Similar to Suzuki work, this chemistry would build from prior experience, as we had previously established one-pot C–H activation/borylation/oxidation protocols. In these early examples, aqueous oxone and later H_2O_2[40] were used to oxidize crude boronates to phenols. These methods work well when the desired end product was the phenol. However, the salt stream from the spent oxone and the impact aqueous conditions would have on our long term plan to follow up the oxidation with an in situ imidazolylsulfonate formation. Furthermore our long-term plan was to combine in situ imidazolylsulfonate formation with the same-pot Suzuki. That final step also had the potential of being compromised by left over oxidant acting on the Suzuki boronate.



Scheme 2.11: First example for the C–H activation/borylation/oxidation with photoredox catalysis.

The above-cited potential incompatibilities with oxone and H_2O_2, coupled with the general desire to incorporate new green chemistry into our methods led us to an investigation of photoredox chemistry as a method for the oxidation of the crude C–H borylation products. Jørgensen and Xiao and co-workers[41] showed the possibility of oxidative hydroxylation of aryl boronic acids using photoredox catalysis with visible light and using oxygen from the atmosphere as an oxidant. Such an oxidation method is not only environmentally benign, but voided the potential problems of unreacted oxidant and/or aqueous conditions. While they showed one example of a boronic ester, the rest of the substrates tested were boronic acids. Moreover, DMF, which we shown to be a compatible solvent in the one-pot C–H borylation/Suzuki with imidazolylsulfonate, is a suitable solvent for this chemistry and that the $Ru(bpy)_3Cl_2$ photoredox catalyst system would be inert through the Suzuki-Miyaura cross-coupling reaction suggested that we could adapt photoredox oxidation to our one-pot protocol . As before, 1,3-dichlorobenzene (**2.5**) was chosen as an initial substrate owing to our knowledge of its performance in the first generation of our C–H activation/borylation/oxidation chemistry. Thus our plan was to evaluate these conditions against a sweep of arenes and heteroarenes. We were please when preliminary results revealed that this photoredox catalysis oxidation method is compatible with our borylation conditions. As illustrated in Scheme 2.11, photoredox of the crude boronate from **2.5** under 2 mol % $[Ru(bpy)_3PF_6]$ catalysis and florescent lighting was immediately successful giving 82% yield of 3,5-dichlorphenol (**2.16**). To the best of our

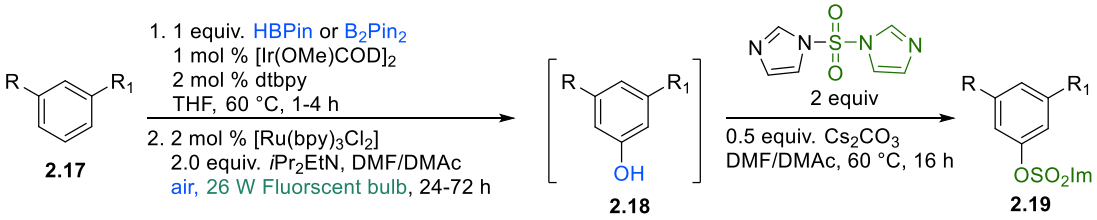
knowledge this is the first example of C–H activation/borylation/oxidation using photoredox catalysis to transform the boronic ester group to a hydroxyl group.

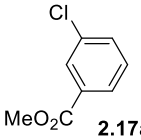
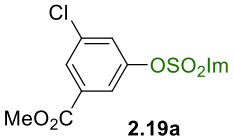
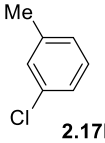
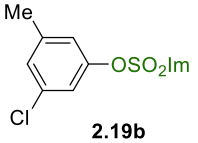
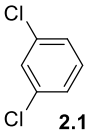
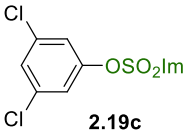
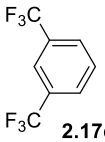
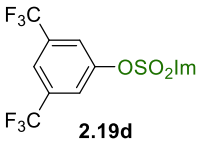
2.3.2. One-pot C–H activation/borylation/photoredox oxidation/imidazolylsulfonate formation

Although the incorporation of photoredox into this sequence demanded a solvent swap and long oxidation times, we proceeded to the next goal of converting the crude phenols into their imidazolylsulfonates. The idea was to follow up the oxidation step with the introduction of 1,1'-sulfonyldiimidazole and associated reagents into the reaction mixture to generate imidazolylsulfonates. In doing so, we wanted to employ substrates with electronically varied functional groups so as to test the reactivity and chemoselectivity of the photoredox oxidations. Methyl 3-chlorobenzoate was the first substrate explored (Table 2.3).[42] In tandem fashion, we subjected Methyl 3-chlorobenzoate to the borylation/photoredox oxidation conditions and then when simply adding sulfonyl diimidazole and solid Cs_2CO_3 to the reaction crude enabled the formation of the corresponding imidazolylsulfonate after heating at 60 °C for 16 hours. The isolated yield of this one-pot process was 44% yield over the three steps for an average yield of 76% per step. The other substrates that were screened performed as well or better with up to 65% overall yield (i.e. an average of 87% per step) being observed for Entry 3. Not only has the one-pot process tolerated diverse functionalities but also shown good reactivity towards both electron rich and poor arenes. Given our earlier described advantage of using aqueous DMAc in the one-pot C–H borylation/Suzuki sequence, we were pleased that, in addition to DMF, DMAc was also a suitable solvent for the photoredox and imidazolylsulfonate forming steps. For example, based on our findings, it appears that whichever amide solvent you use makes little

difference because the phenol of Methyl 3-chlorobenzoate (**2.18a**) was isolated in 72% yield from the reaction in DMAc and 67% yield from the reaction in DMF.

Table 2.3: One-pot C-H Activation/Borylation/Oxidation/Imidazolylsulfonation of Disubstituted Arenes

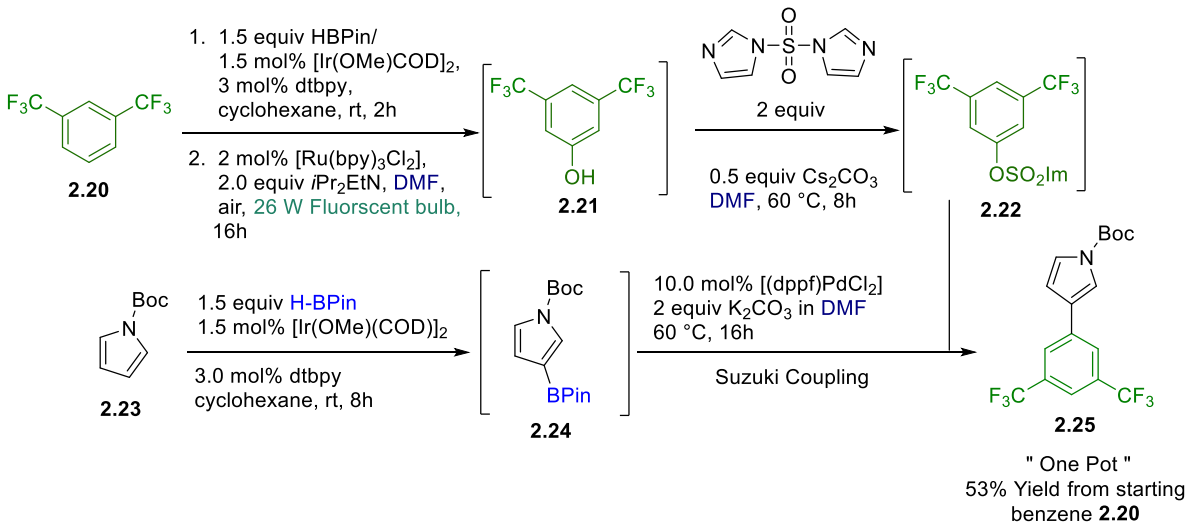


Entry	Arene	Imidazolyl Sulfonate	Yield[a]
1[b]	 **2.17a**	 **2.19a**	44%
2	 **2.17b**	 **2.19b**	44%
3[b]	 **2.17c**	 **2.19c**	65%
4	 **2.17d**	 **2.19d**	56%

[a] Isolated Yields.
[b] 1.5 equivalents of HBpin used.
[c] 1.5 mol % of $[Ir(OMe)COD]_2$ and 3 mol % dtbpy were used.

2.3.3. One-pot C–H borylation/photoredox/oxidation/imidazolylsulfonation/Suzuki coupling sequence.

Having established the individual reactions needed, we next set out to execute a fully telescoped one-pot C–H borylation/photoredox oxidation/imidazolylsulfonation/Suzuki coupling sequence.



Scheme 2.12: One-pot C–H borylation/photoredox oxidation/ imidazolylsulfonation / Suzuki coupling sequence.

In tandem fashion, first C–H activation/borylation/oxidation of unactivated arene 1,3-bis-trifluormethylbenzene, **2.20** was carried out from previously established methodology comprising photoredox oxidation of the boronic ester that was resulted from Ir catalalyzed C–H activation/borylation (Scheme 2.12). Then to the crude reaction mixture containing phenol **2.21** in DMF was added 1,1'-sulfonyldiimidazole and Cs_2CO_3 and heated at 60 °C for 8 hours to synthesize the imidazolylsulfonate **2.22**. The reactions were monitored by GC-MS analysis to confirm the synthesis of the desired product as well as to check for complete conversion of the starting crude material. In a separate reaction vessel, the Ir-catalyzed C–H borylation of N-Boc-pyrrole **2.23** generated boronic ester **2.24** and the volatiles were removed *in vacuo*. Then the crude imidazolylsulfonate **2.22**, in DMF was added to the unpurified boronic ester **2.24** along

with K_2CO_3 .The reaction mixture was degassed, followed by addition of 10 mol % (dppf)$PdCl_2$ and was heated to 60 °C and the cross-coupling proceeded under nitrogen to afford the desired biaryl product, **2.25** in 53% isolated yield based on the unactivated arene 1,3-bis-trifluormethylbenzene **2.20**. This also represent an average yield of 85% for each step from the 1,3-bis-trifluormethylbenzene.

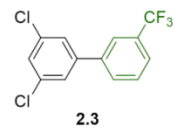
This telescoped sequences validates our hypotheses that Ir-catalyzed C–H borylations combined with photoredox chemistry and the employment of imidazolylsulfonates fully allows for cross-couplings that avoid the use of haloaromatics.

2.4. Conclusion

In conclusion, we have demonstrated that haloaromatics can be avoided entirely in both the nucleophilic and the electrophilic cross-coupling partners in a C–H borylation/photoredox oxidation/imidazolylsulfonation/Suzuki coupling sequence. The development of this telescoped sequence led to a novel use of photoredox chemistry. From a practical standpoint, this approach eliminates the expense, hazardous waste, and time required for isolation, purification of intermediate boronic esters, phenols, and imidazolylsulfonates. Lastly, by employing imidazolylsulfonates the presence of potentially genotoxic byproducts in the final product is significantly minimized.

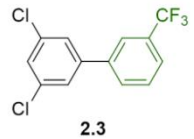
APPENDIX

^{1}H-NMR, 500 MHz, $CDCl_3$



2.3

^{13}C-NMR, 126 MHz, $CDCl_3$



2.3

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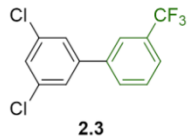
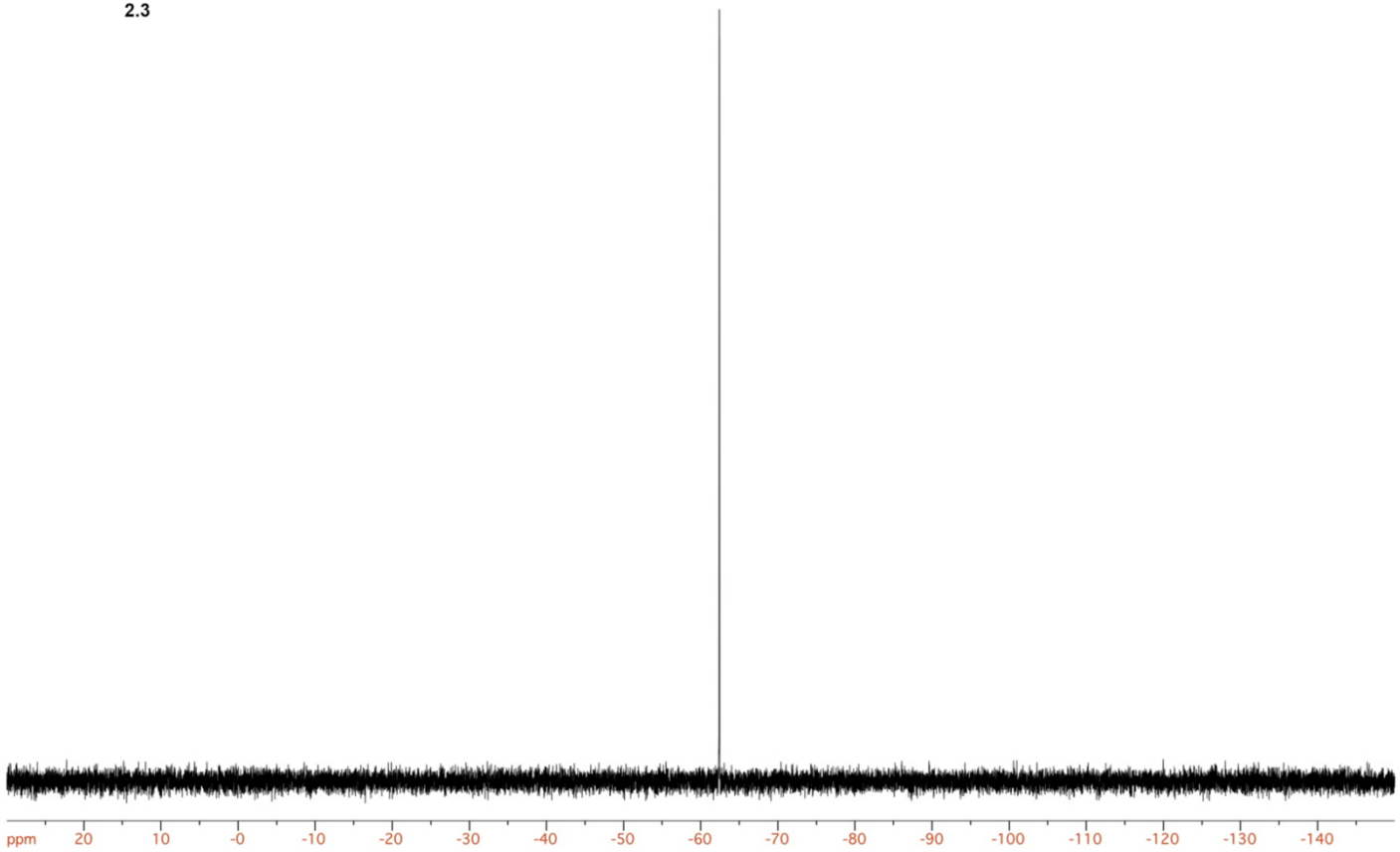


2.3



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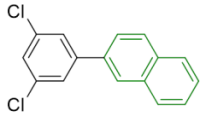

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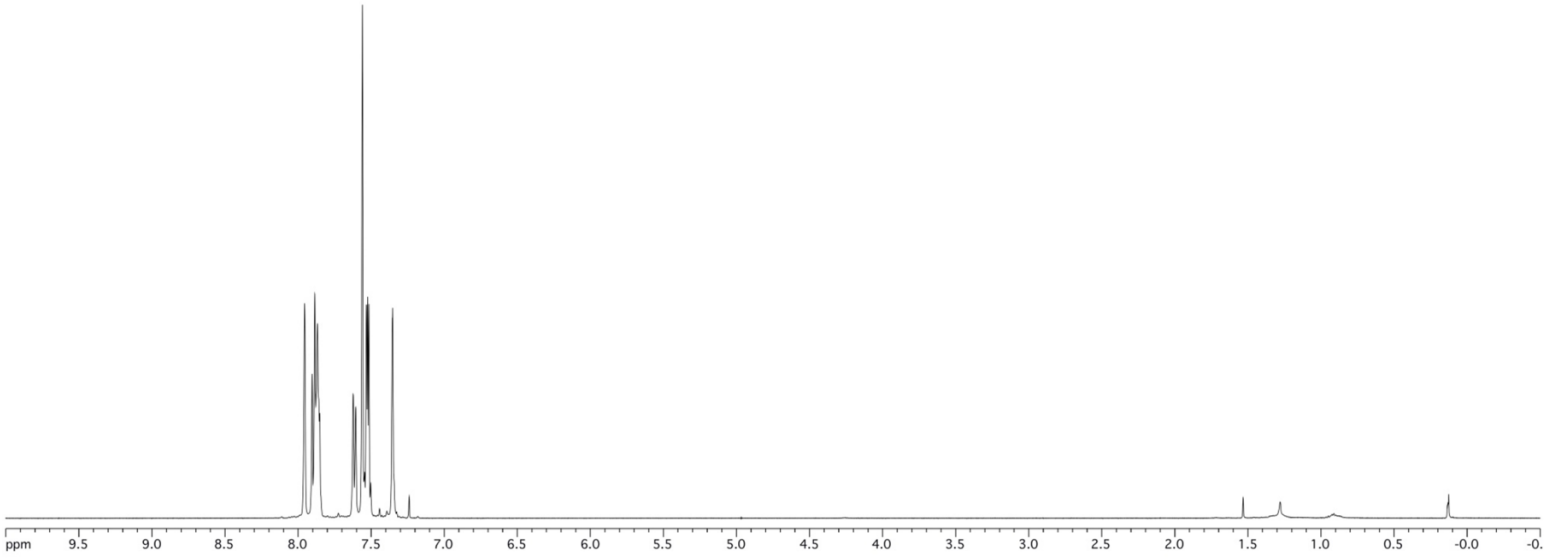

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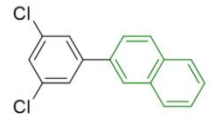

2.4

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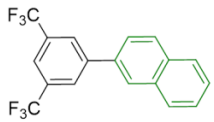
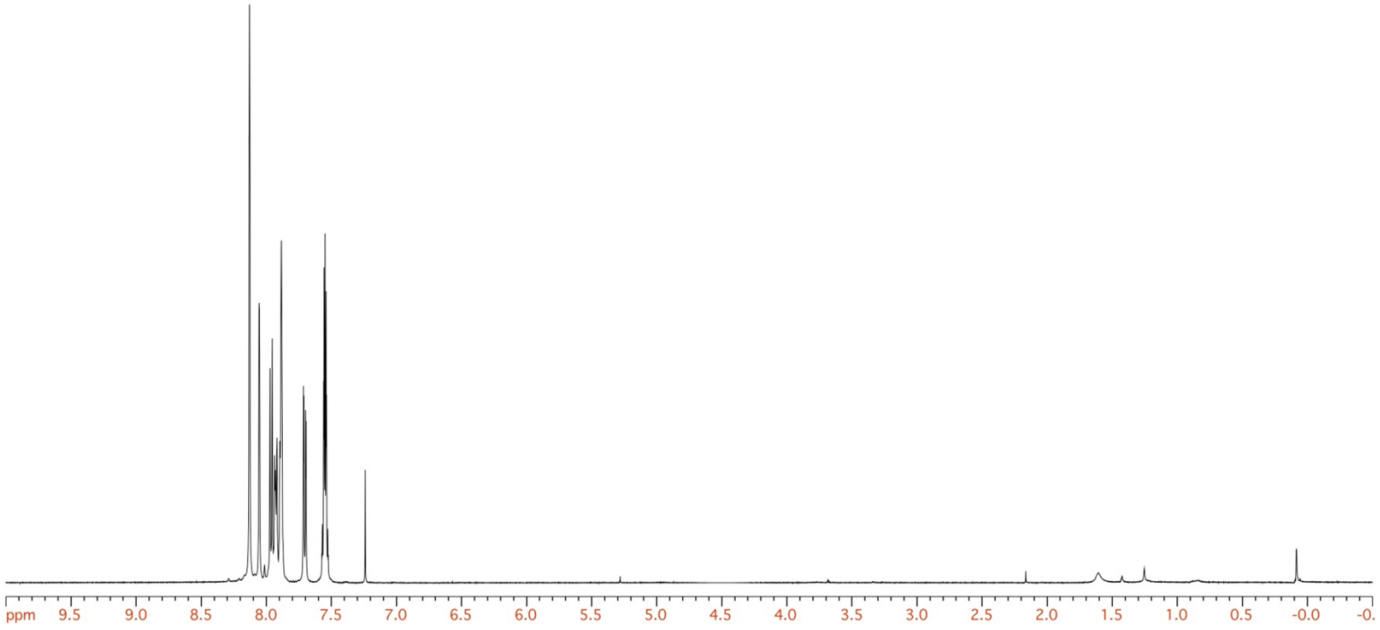


2.11a



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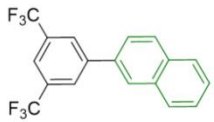

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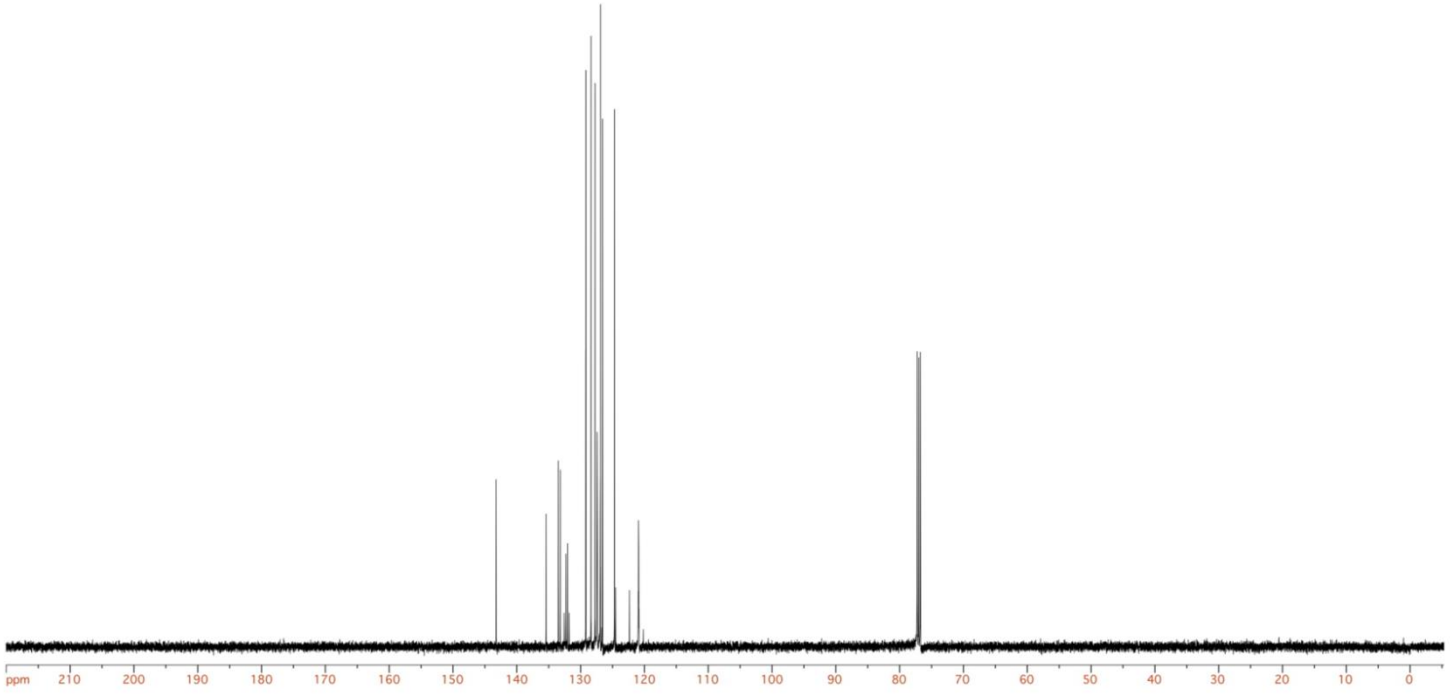

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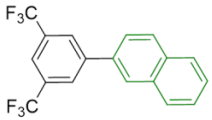

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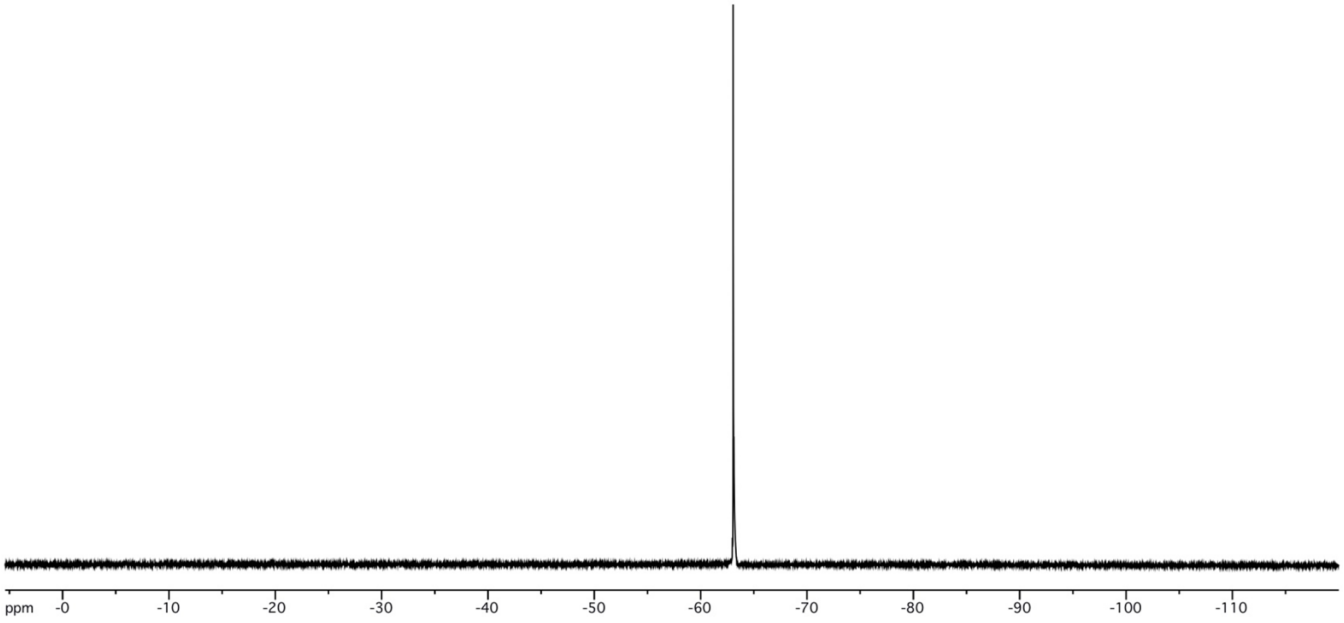

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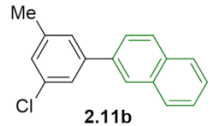

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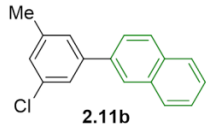

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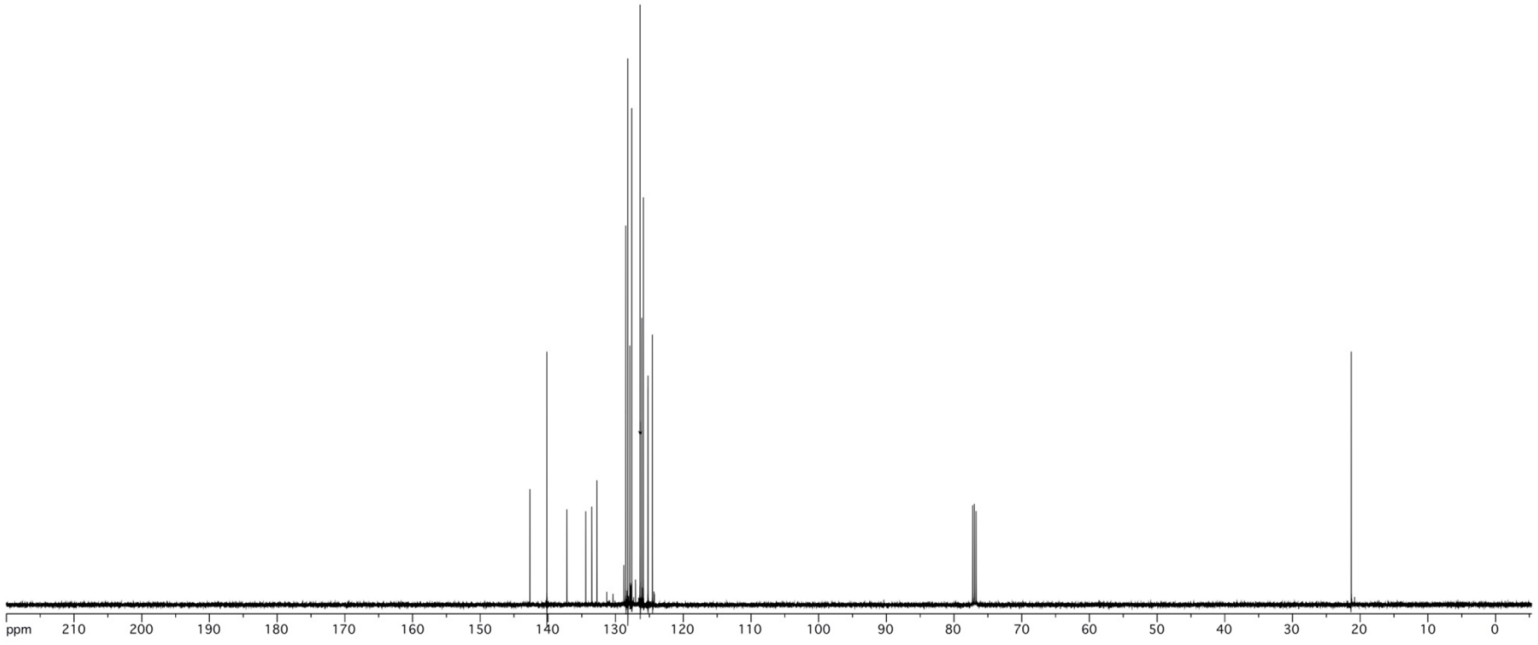

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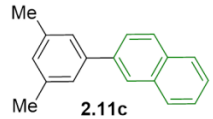

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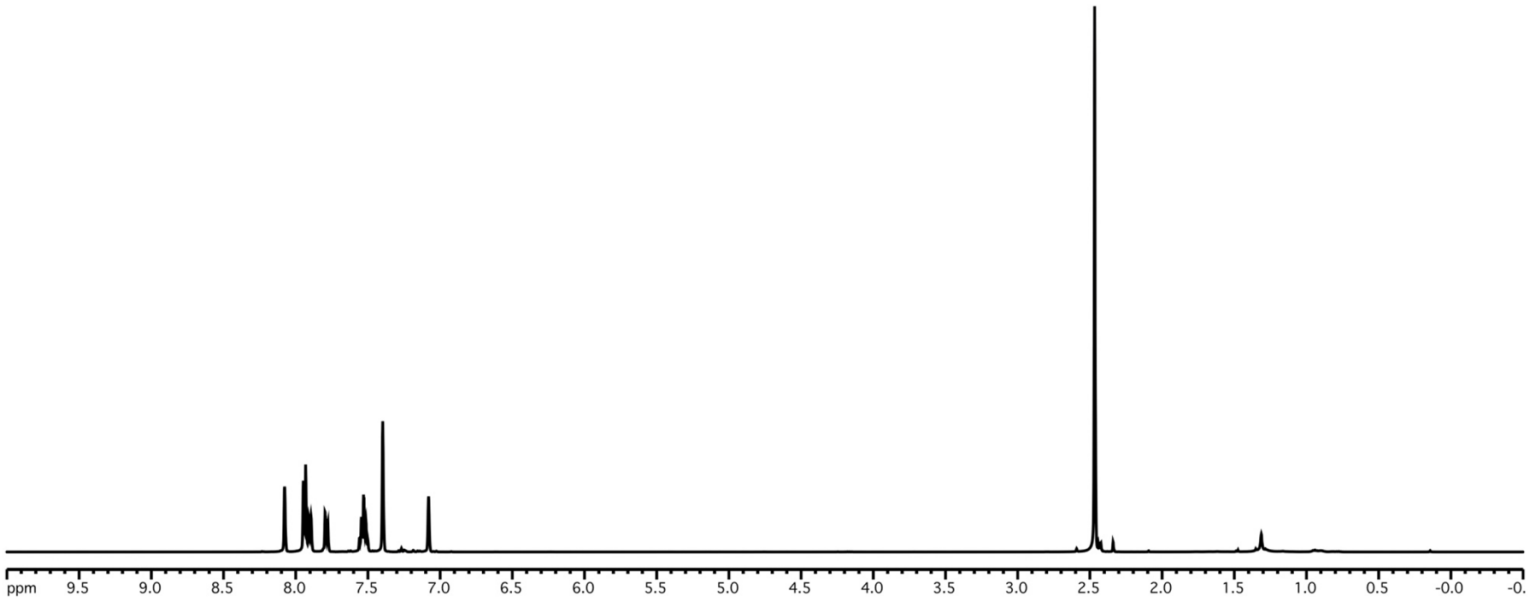

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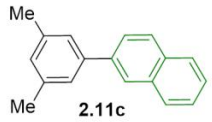

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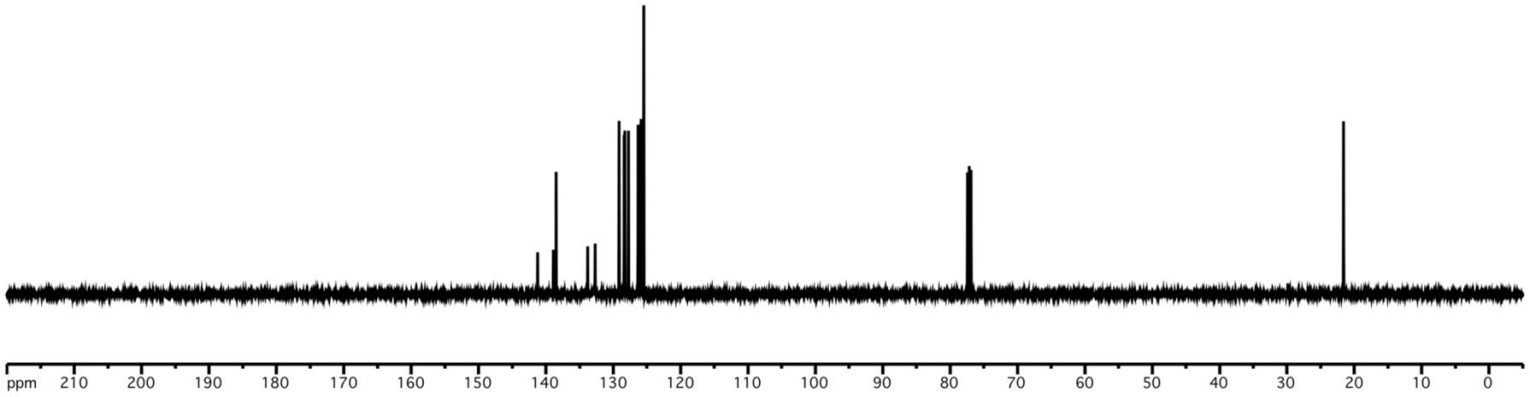

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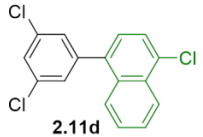

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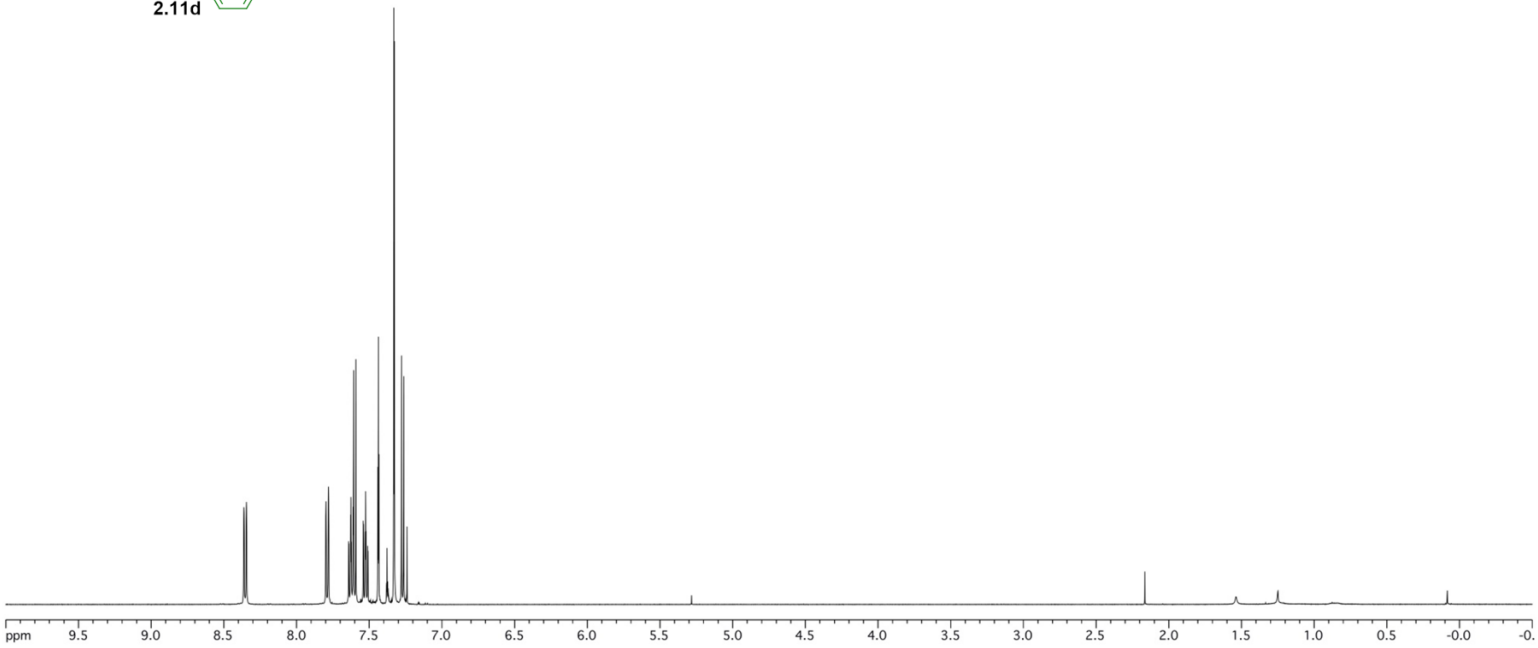

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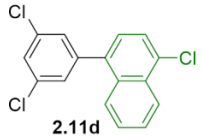
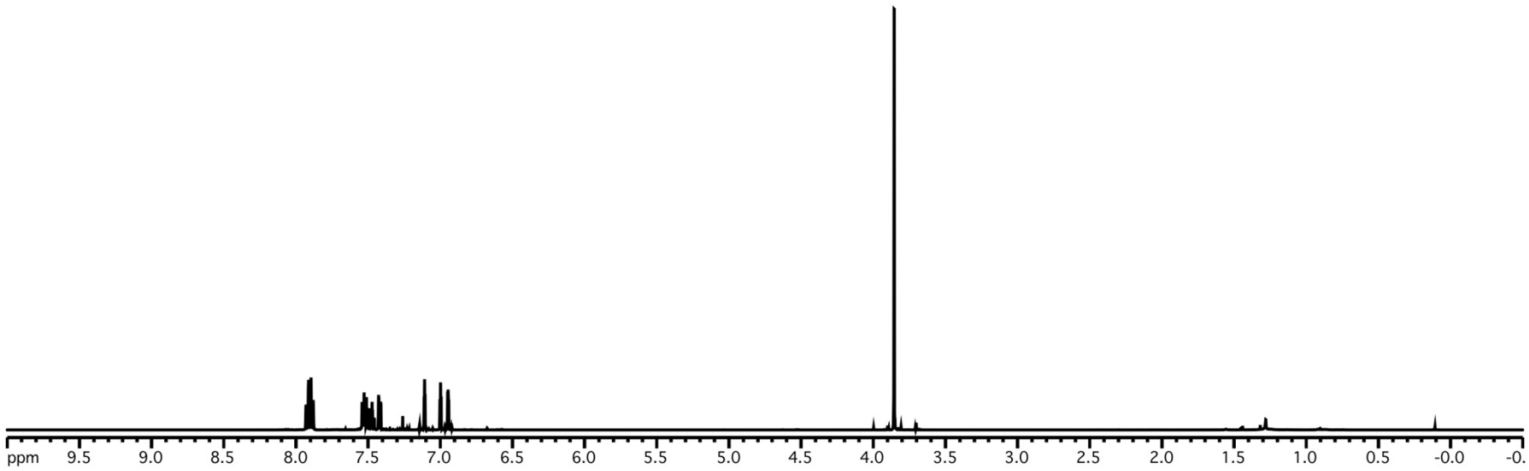


2.11d

^{1}H-NMR, 500 MHz, $CDCl_3$

2.11e



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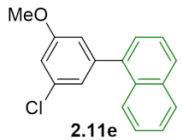

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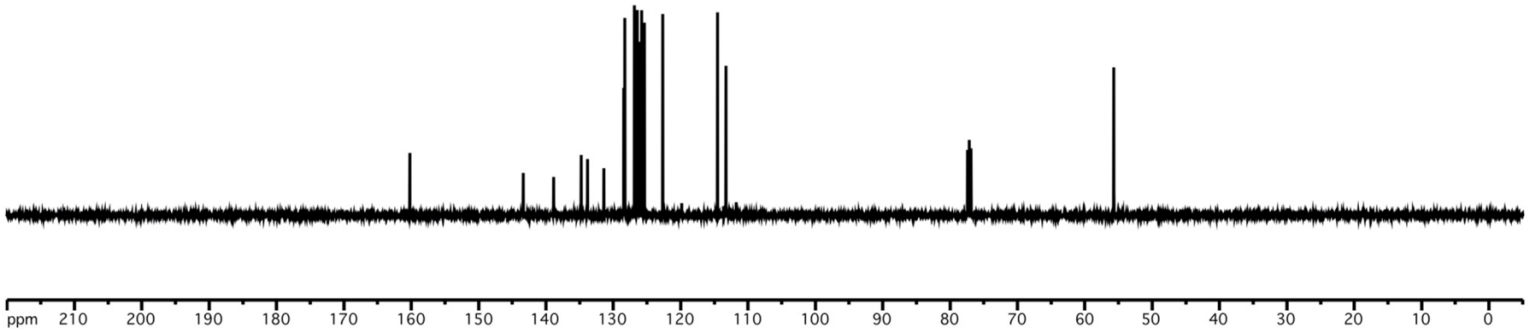

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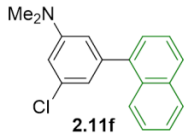

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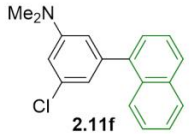

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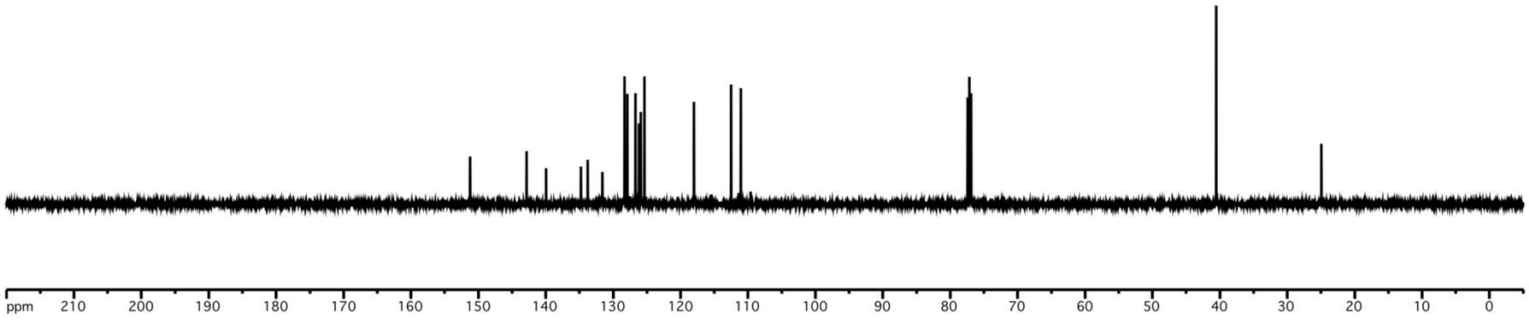

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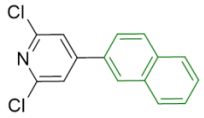

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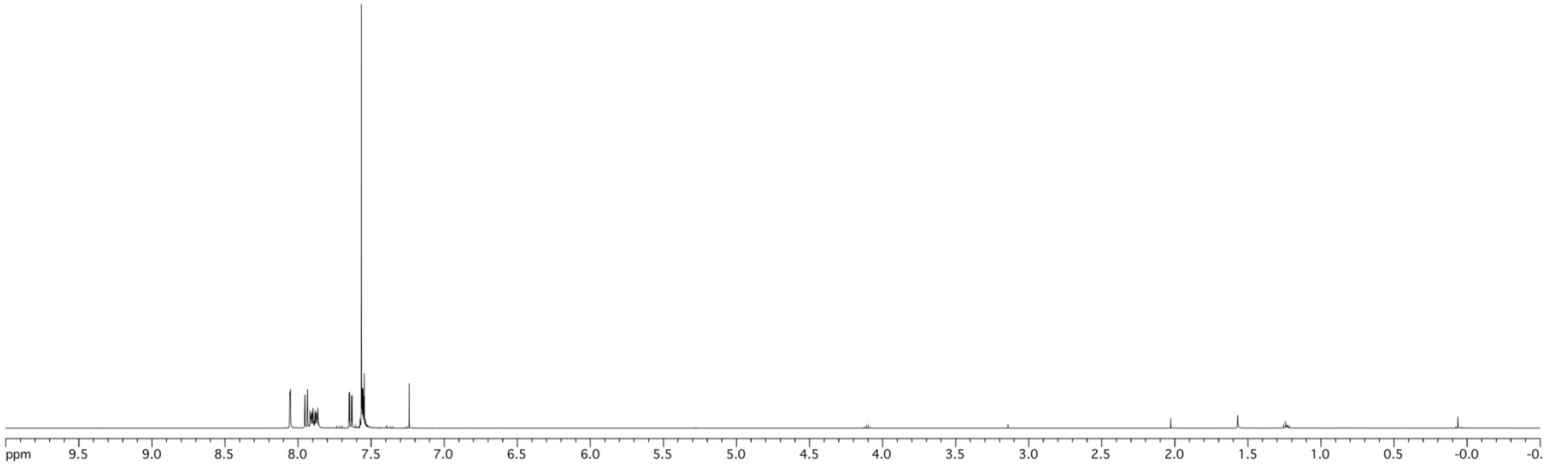

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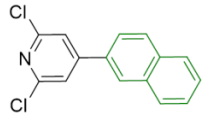

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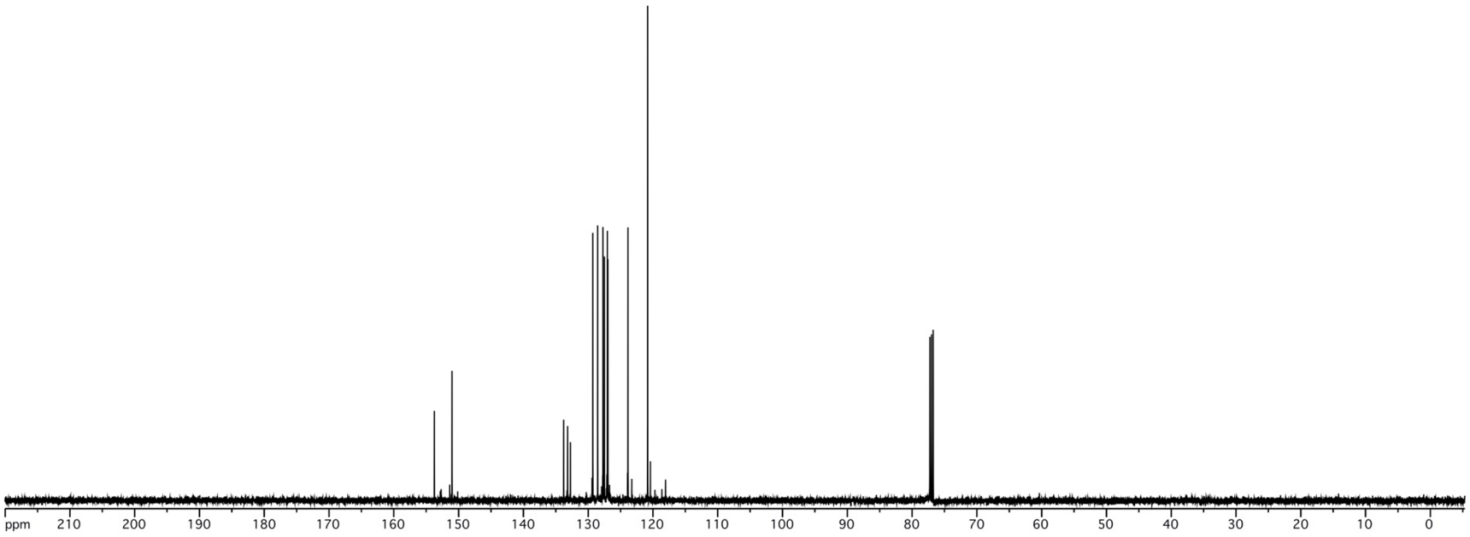

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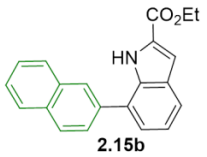

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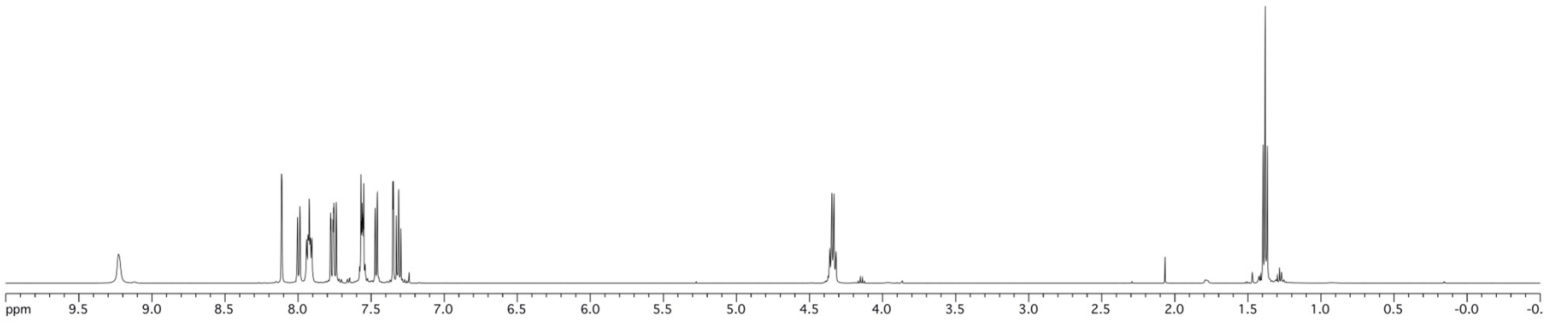

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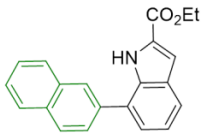

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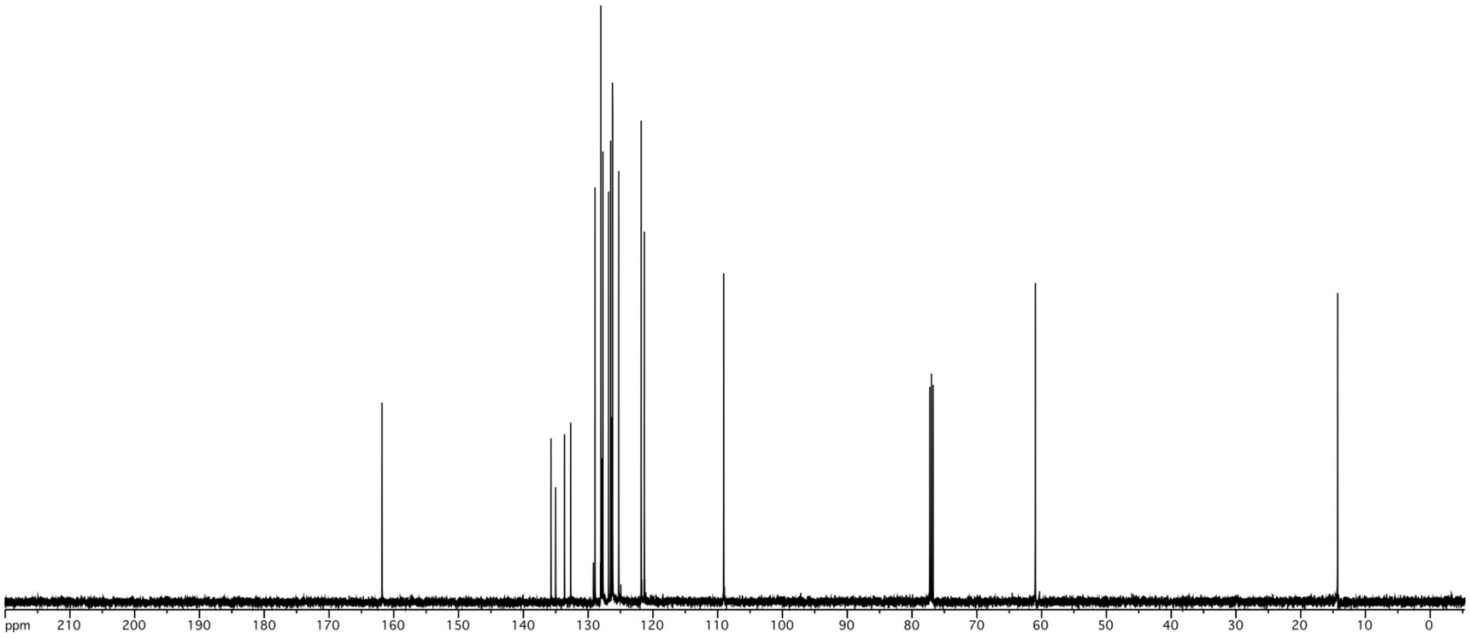

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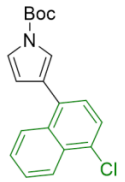

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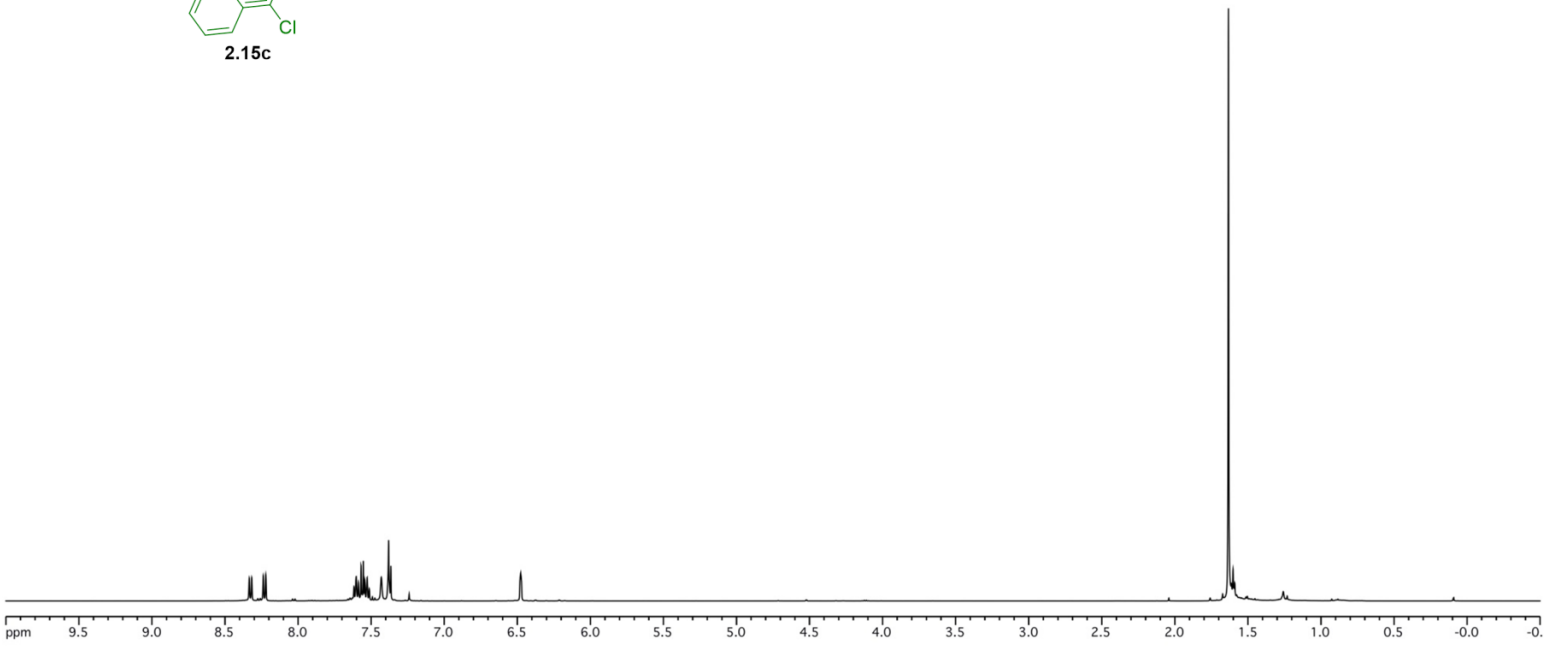

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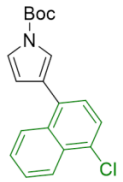

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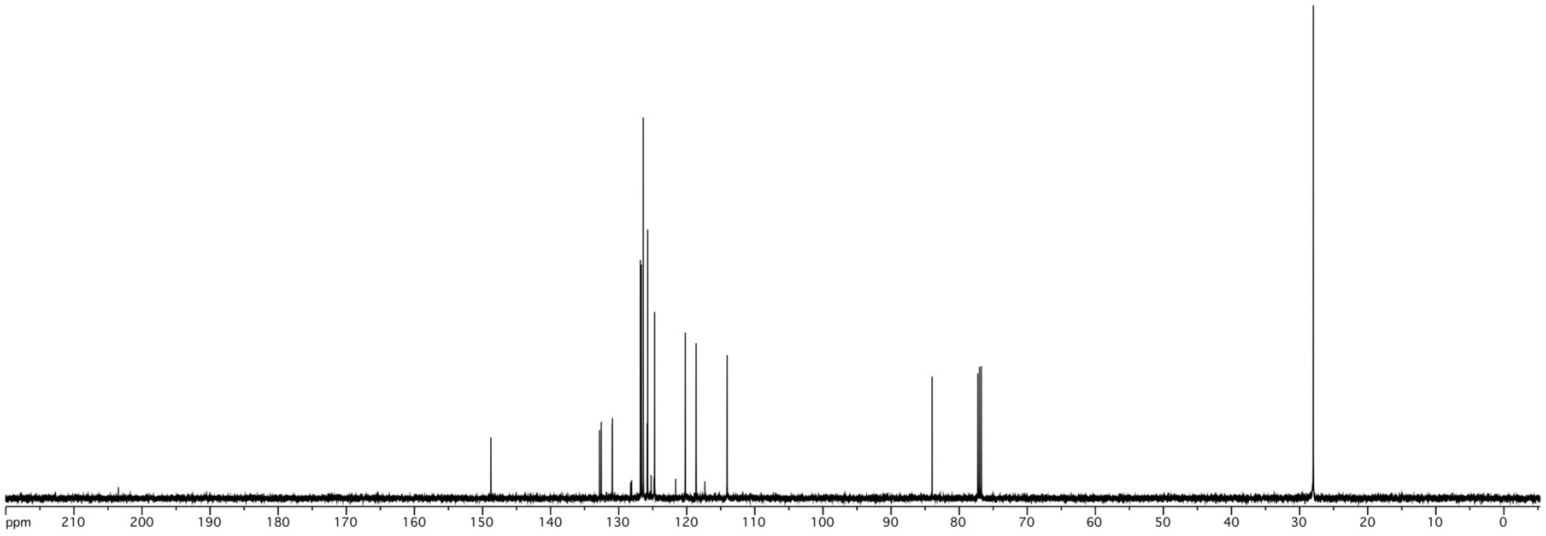

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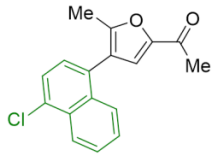

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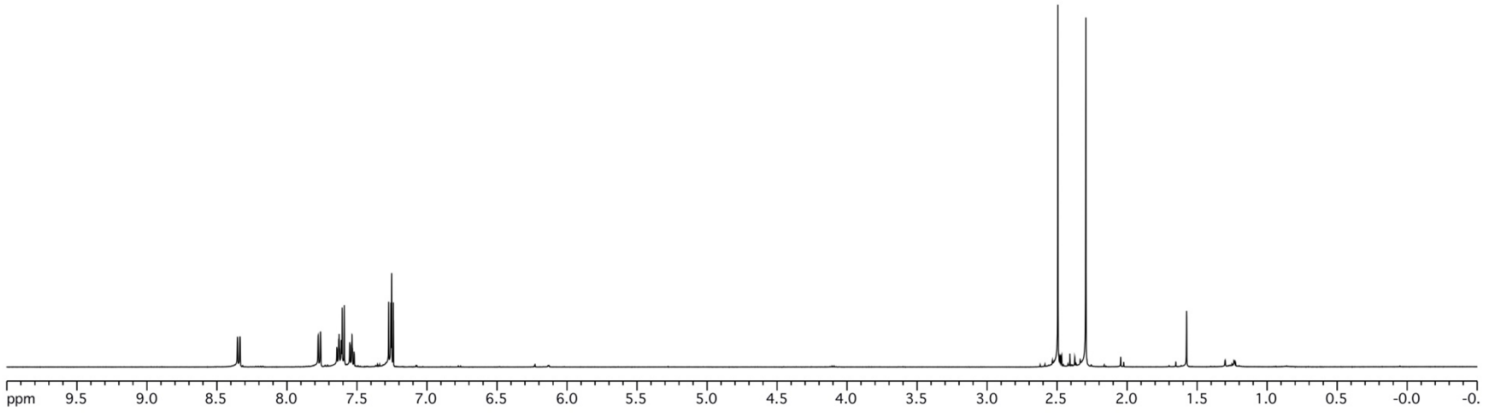

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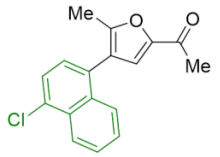

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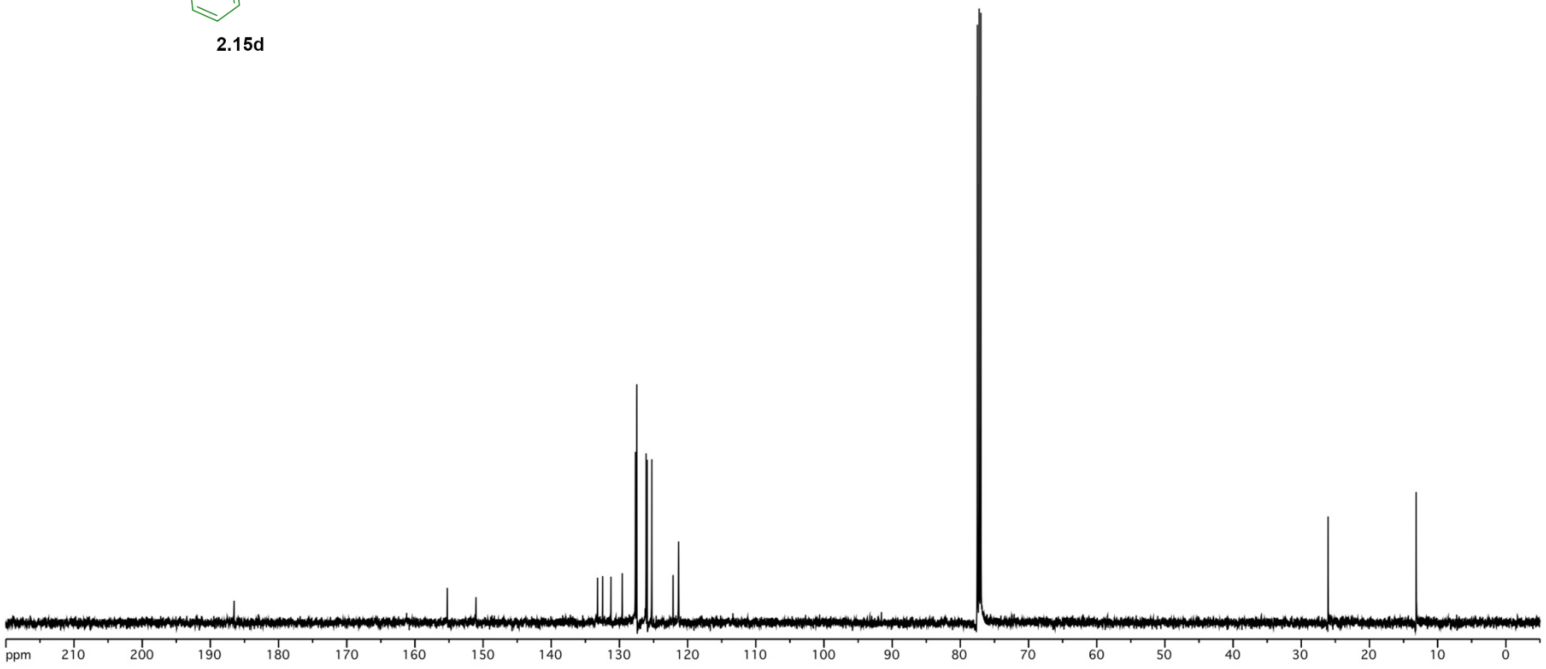

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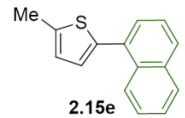

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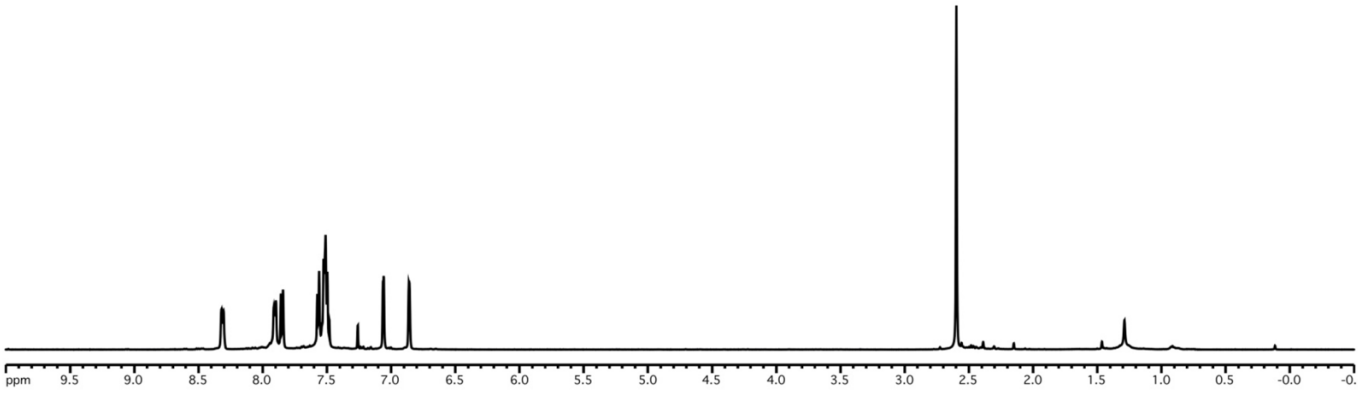

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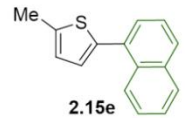

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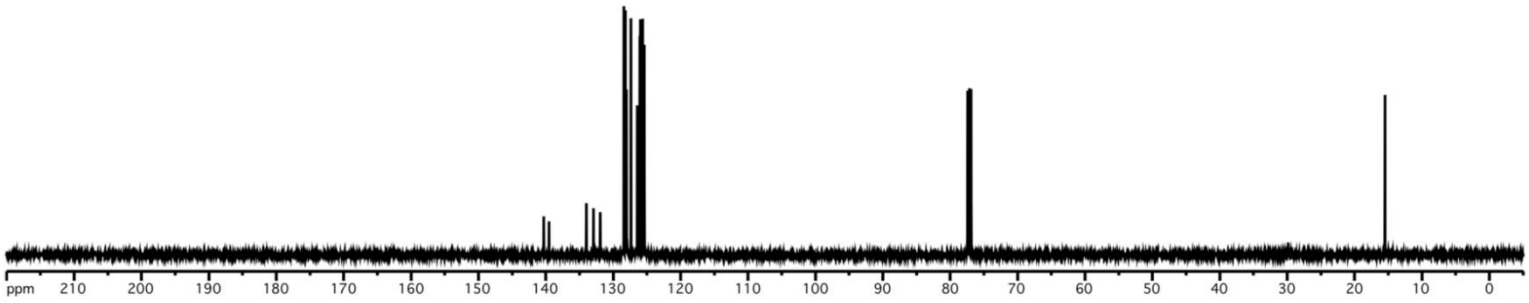

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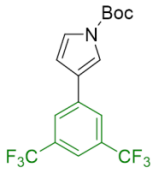

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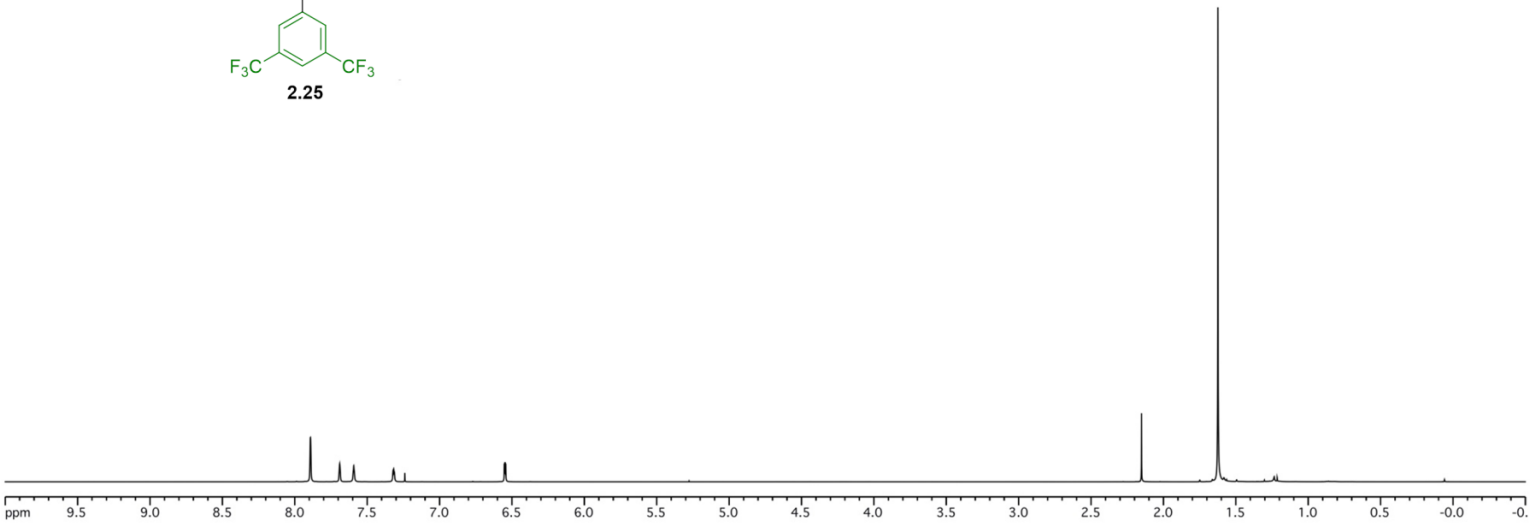


REFERENCES

REFERENCES

1. http://www.greenchemistryinstitute.org.

2. http://www.chemistry.org/greenchemistryinstitute/pharma_roundtable.html.

3. Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaksh, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.

4. Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem*. **2006**, *4*, 2337–2347. See also: Dugger, R. W.; Ragan, J. A.; Ripin, D. H. B. *Org. Process Res. Dev*. **2005**, *9*, 253–258.

5. a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382; b) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853; c) Ullmann, F.; Sponagel, P. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2211. d) Ullmann, F.; Illgen, E. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 380.

6. a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. b) Heck, R. F. Palladium Reagents; Academic Press: London, 1990.

7. Hiyama, T.; Shirakawa, *E. Top. Curr. Chem.* **2002**, *219*, 61.

8. a) Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545. b) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669. c) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc.*, *Chem. Commun*. **1972**, 144. d) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.

9. a)Negishi, E. I. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233. b)Negishi, E. I. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1598.

10. (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979,** *20***,** 3437. (b) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866.
For recent reviews on the Suzuki–Miyaura reaction, see:
c) Han F-S.; *Chem Soc Rev.* **2013,** *42*, 5270. d) Rossi, R.; Bellina, F.; Lessi, M. *Tetrahedron.* **2011**, *67*, 6969; e) Polshettwar, V.; Decottignes, A.; Len, C.; Fihri, A. *ChemSusChem*. **2010**, *3*. 502; f) Martin, R.; Buchwald, S. L.; *Acc. Chem. Res.* **2008**, *41*, 1462; g) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron*. **2008**, *64*, 3047; h) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275; i) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal*. **2006**, *348*, 609; j) Suzuki, A. *Chem. Commun.* **2005**, 4759; k) Nicolau, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem.* **2005**, *117*, 4516 ; l) Bellina, F.; Carpita A.; Rossi, R. *Synthesis.* **2004**, 2419; m) Tyrrel E.; Brookes, P. *Synthesis.* **2004**, 469; n) Suzuki, A. The Suzuki Reaction with Arylboron Compounds in Arene Chemistry. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley–VCH Verlag GmbH&Co. KGaA: Weinheim, Germany, 2002; pp 53. o) Kotha, S.; Lahiri, K.; Kashinath, D. Tetrahedron. **2002**, *58*, 9633. p) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. q)

Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. r) Stanforth, S. P. *Tetrahedron*. **1998**, *54*, 263. s) Miyaura, N.; Suzuki, *A. Chem. Rev.* **1995**, *9*5, 245.

11. Sonogashira, K. J. *Organomet. Chem.* **2002**, *653*, 46.

12. Stille, J. K. *Angew. Chem., Int. Ed.* **1986**, *25*, 508.

13. http://nobelprize.org/nobel_prizes/chemistry/laureates/2010/ index.html.

14. a) Chemler, S. R.; Danishefsky, S. J.; *Org. Lett.* **2000**, *2*, 2695. b) Schlüter, A. D. *J. Polym. Sci. A* **2001**, *39*, 1533. c) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177**.**

15. Roughley, S. D.; Jordan, A. M., *J. Med. Chem*. **2011**, *54*, 3451.

16. See, among others; a) Gerrard, W. *The Chemistry of Boron*: Academic; New York, 1961. b) Muetterties, E. L. *The Chemistry of Boron and its Compounds*; Wiley: NewYork, 1967. c) Matteson, D. S. *The Chemistry of the Metal-Carbon Bond*; Hartley, F., Patai, S.. Eds.; Wiley: New York, 1987; Vol. 4, p 307 d) Matteson, D. S.; Liedtke, J. D. *J. Am. Chem. Soc*. **1965**, *87*, 1526.

17. a) Ishiyama, T.; Murata, M.; Miyuara, N. *J. Org. Chem.* **1995**, *60*, 7508-7510. b) Ishiyama, T; Miyuara, N. *J. Organomet. Chem.* **2000**, *611*, 392-402. c) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164.

18. Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

19. Chen, G.; Bunce, N. J.; *Environ Toxicol.* **2004**, *19*, 480.

20. a) Fernández-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F**.** *J. Am. Chem. Soc.* **2006,** *128***,** 2180; b) Zhang, L.; Meng, T.; Fan, R.; Wu, J**.** *J. Org. Chem.* **2007,** *72***,** 7279. c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020; d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644; e) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158; f) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393.

21. a) Percec, V.; Bae, J. Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060. b) Percec, V.; Bae, J. Y.; Zhao, M. Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 176; c) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552. d) Kobayashi, Y.; Mizojiri, R. *Tetrahedron Lett.* **1996**, *37*, 8531; e) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc*. **2008**, *130*, 2754.

22. (a) Wu, J.; Liao, Y.; Yang, Z. *J. Org. Chem.* **2001**, *66*, 3642; (b) Fu, X. Y.; Zhang, S. Y.; Yin, J. G.; Schumacher, D. P. *Tetrahedron Lett.* **2002**, *43*, 6673; (c) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993; (d) Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 13848; (e) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369; (f) Klapars,

A.; Campos, K. R.; Chen, C. Y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185; (g) Tang, Z. Y.; Hu, Q. S. *J. Am. Chem. Soc.* **2004**, *126*, 3058; (h) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818; (i) Zhang, L.; Meng, T.; Wu, J. *J. Org. Chem.* **2007**, *72*, 9346; (j) Wu, J.; Zhu, Q.; Wang, L.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 670. k) So C. M.; Kwong, F. Y. *Chem Soc Rev.* **2011**, *40*, 4963 .

23. (a) Glowienke, S.; Frieauff, W.; Allmendinger, T.; Martus, H.-J.; Suter, W.; Mueller, L. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis.* **2005,** *581***,** 23; (b) David J, S.; *Regul. Toxicol. Pharm.* **2006,** *45***,** 79.

24. Albaneze-Walker, J.; Raju, R.; Vance, J. A.; Goodman, A. J.; Reeder, M. R.; Liao, J.; Maust, M. T.; Irish, P.; Andrews, D. R. *Org. Lett*. **2009**, *11*, 1463.

25. Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346.

26. Luo, Y.; Wu, J. *Organometallics*. **2009**, *28*, 6823.

27. Shirbin, S. J.; Boughton, B. A.; Zammit, S. C.; Zanatta, S. D.; Marcuccio, S. M.; Hutton, C. A.; Williams, S. J.; *Tetrahedron Lett.* **2010**, *51*, 2971.

28. a) Cívicos, J. F.; Gholinejad, M.; Alonso, D. A.; Nájera, C.; *Chem Lett.* **2011**, *40*, 907.b) Cívicos, J. F.; Alonso, D. A,; Nájera, C.; *Adv. Synth. Catal.* **2012**, *354*, 2771.

29. (a) Ackermann, L., Sandmann, R. and Song, W. Org. Lett. 2011, 13, 1784-1786. (b)Brachet, E., Hamze, A., Peyrat, J.-F., Brion, J.-D. and Alami, M. Org. Lett. 2010, 12, 4042-4045. (c) Treguier, B., Hamze, A., Provot, O., Brion, J.-D. and Alami, M. Tetrahedron Lett. 2009, 50, 6549-6552.

30. Ackermann, L.; Barfuesser, S.; Pospech, *J. Org. Lett.* **2010**, *12*, 724-726.

31. Luo, Y. and Wu, J. Organometallics 2009, 28, 6823-6826.

32. Shirbin, S. J., Boughton, B. A., Zammit, S. C., Zanatta, S. D., Marcuccio, S. M., Hutton, C. A. and Williams, S. J. Tetrahedron Lett. 2010, 51, 2971-2974.

33. a) Cho, J.-Y.; Iverson, C. N.; Smith, M. R., III *J. Am. Chem. Soc.* **2000**, *122*, 12868. (b) Tse, M. K.; Cho, J.-Y.; Smith, M. R., III *Org. Lett.* **2001**, *3*, 2831. (c) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science,* **2002**, *295*, 305. (d) Maleczka, R. E., Jr.; Shi, F.; Holmes, D.; Smith, M. R., III *J. Am. Chem. Soc.* **2003**, *125*, 7792. (e) Chotana, G. A.; Rak, M. A.; Smith, M. R., III *J. Am. Chem. Soc.* **2005**, *127*, 10539–10544. (f) Holmes, D.; Chotana, G. A.; Maleczka, R. E.; Smith, M. R. *Org. Lett.* **2006**, *8*, 1407–1410. (g) Paul, S.; Chotana, G. A.; Holmes, D.; Reichle, R. C.; Maleczka, R. E., Jr.; Smith, M. R., III *J. Am. Chem. Soc.* **2006**, *128*, 15552. (h) Shi, F.;Smith, M. R., III; Maleczka, R. E., Jr. *Org. Lett.* **2006**, *8*, 1411. (i) Chotana, G. A.; Kallepalli, V. A.; Maleczka, R. E., Jr.; Smith, M. R., III *Tetrahedron*, **2008**, *64*,

6103. (j) Chotana, G. A.; Vanchura, B. A., II; Tse, M. K.; Staples, R. J. Maleczka, R. E., Jr.; Smith, M. R., III *Chem. Commun.* **2009**, 5731. (k) Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E., Jr.; Smith, M. R., III *J. Org. Chem.* **2009**, *74*, 9199. (l) Vanchura, B. A., II; Preshlock, S. M.; Roosen, P. C.; Kallepalli, V. A.; Staples, R. J.; Maleczka, R. E., Jr.; Singleton, D. A.; Smith, M. R., III *Chem. Commun.* **2010**, *46*, 7724.

34. a) Wermuth, C. G.; Contreras, J. M.; Pinto, J.; Guilbaud, P.; Rival, Y.; Bourguignon, J. J. *Acta Pharmaceutica Hungarica*. **1996**, S3-S8. (b) Contreras, J. M.; Rival, Y.; Chayer, S.; Wermuth, C. G. *J. Med. Chem.* **1999**, *42*, 730. Otsubo, T.; Aso, Y.; Takimiya, K. J. Mater. Chem.

35. Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002,** *43*,5649.

36. Tarce amount of Suzuki cross-coupled product was observed in GC-FID and GC-MS.

37. Paul, S.; Chotana, G. A.; Holmes, D.; Reichle, R. C.; Maleczka, R. E., Jr.; Smith, M. R., III *J. Am. Chem. Soc.* **2006**, *128*, 15552.

38. Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E., Jr.; Smith, M. R., III *J. Org. Chem.* **2009**, *74*, 9199.

39. (a) Maleczka, R. E., Jr.; Shi, F.; Holmes, D.; Smith, M. R., III. *J. Am. Chem. Soc.* **2003**, *125*, 7792–7793. (b) Shi, F.; Smith, M. R., III; Maleczka, R. E., Jr. *Org. Lett.* **2006**, *8*, 1411–1414. (c) Norberg, A. M.; Smith, M. R., III; Maleczka, R. E., Jr. *Synthesis* **2011**, 857–859.

40. Sasaki, I.; Taguchi, J.; Hiraki, S.; Hajime, I.; Ishiyama, T.; *Chem. Eur. J.* **2015**, *21*,9236.

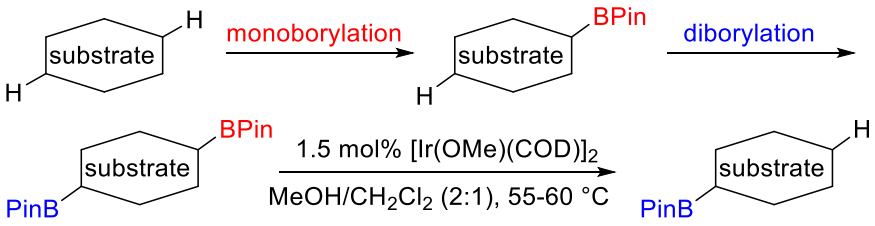
41. Zou, Y.-Q.; Chen, J.-R.; Liu, X.-P.; Lu, L.-Q.; Davis, R. L.; Jørgensen, K.A.; Xiao. W. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 3.

42. Our manuscript on this is in preparation, also see; Baker, Aaron. Organometallic Chemistry Pertaining to Main Group Elements Silicon, Germanium, Tin, and Boron. Ph.D.Thesis, Michigan State University, East Lansing, 2016.

CHAPTER 3. DISCOVERY AND DEVELOPMENT OF NOVEL CATALYTIC SYSTEMS FOR SELECTIVE PROTODEBORONATION

3.1 Introduction

Catalytic C–H activation/borylation allows for the direct construction of aryl boronic esters which are very useful synthetic building blocks[1,2] from hydrocarbon feed stocks in a single step, obviating the need for prior functionalization (e.g. halogenation), pyrophoric reagents, cryogenic conditions, etc.[3] Owing to their mild, selective, and atom economical nature, Ir-catalyzed borylations, can be followed by subsequent chemical events to allow for variety of direct and one-pot processes. In this way, C–H activation/borylations have been combined with Suzuki[4] and other cross-couplings, aminations,[5] amidations,[6] etc. In the course of developing one-pot protocols for Ir-catalyzed C–H borylation and subsequent elaboration of the resulting organoboronate intermediates, our group recently disclosed Ir-catalyzed borylation/deborylation method that enables new regiochemical out comes (Scheme 3.1).[7]

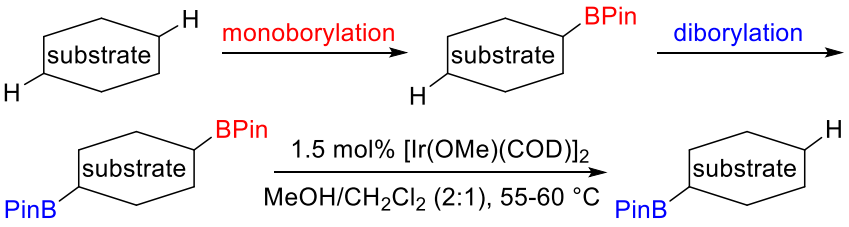


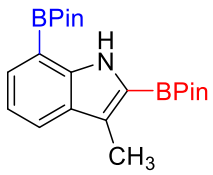
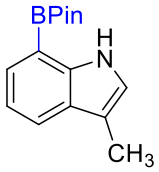
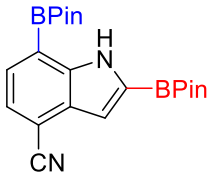
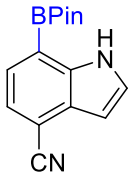
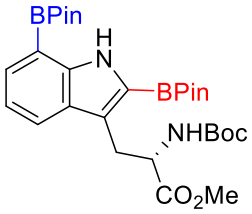
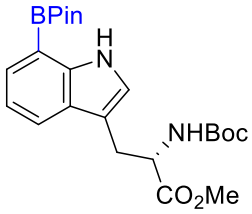
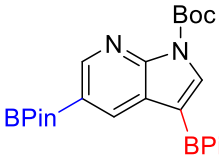
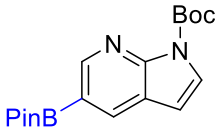
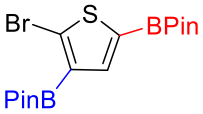
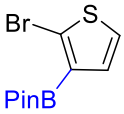
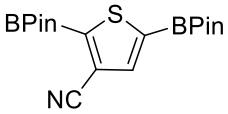
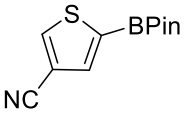
Scheme 3.1: Synthesis of monoborylated compounds via deborylation/deborylation

Ir-catalyzed C-H activation/borylations of arenes typically install Bpin with regioselectivities governed by sterics.[8] In addition, borylations of arenes and heterocycles occur under mild conditions and a number of important functional groups are tolerated. As shown in the Scheme 3.1 multiple borylations followed by selective deborylation of the first installed

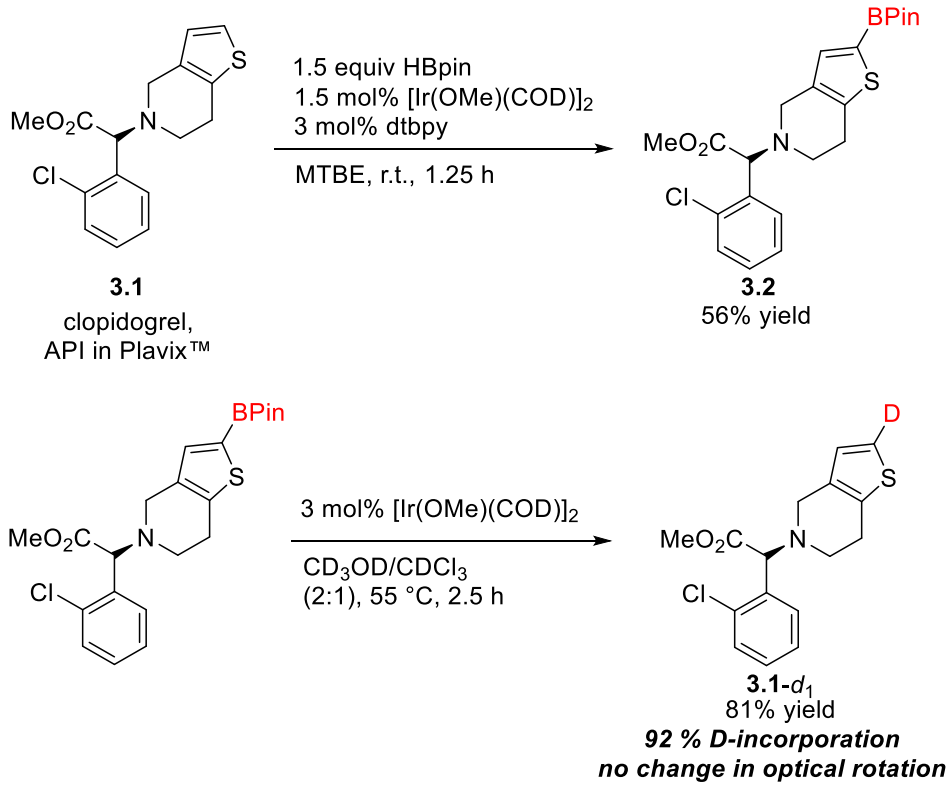
boron with 1.5 mol % catalyst loading of $[Ir(OMe)(COD)]_2$ in $MeOH/CH_2Cl_2$ at 55-60 °C. Deborylation of a number of diborylated heterocycles was examined and some of the results are shown in Table 3.1. For the indole substrates (entries 1-3), diborylation/deborylation affords the 7-borylated products, which have previously been prepared by a relay-directed reaction of N–silylated indoles, which are in turn prepared in a Ru-catalyzed reaction from the parent indole and a disilane.[9] After Ir-catalyzed C–H borylation, the silane deprotection yields the 7-borylated product. Diborylation/deborylation obviates the need for N-protection/deprotection. Entries 3 and 4 utilize Boc protected compounds and demonstrate that, as is the case for Ir-catalyzed C–H borylation, Boc protecting groups are compatible with Ir-catalyzed deborylation. Diborylation/deborylation of 2-halogenated thiophenes provide unique halogenated building blocks. Synthesis of these compounds by lithiation would not be feasible because halogenated heteroaryl lithium compounds undergo "halogen dance" rearrangements.[10] The fact that 3- or 5-boryalted isomers of 2-halogenated thiophenes can be accessed is a testament to the mild conditions of these Ir-catalyzed processes. As indicated above the data reflect that the relative reactivities in deborylation reactions parallel the reactivities of the parent arenes towards borylation so that in cases where sequential diborylation is observed, the products deborylate selectively at the position that was the first site of borylation. Due to the mirror in relatives reactivities of borylation and deborylation a different regioisomeric product is observed than that of the product of direct C–H borylation. This is a major advantage of this deborylation/deborylation technique. Also, our group has shown that mild deborylation could be accomplished in organic solvents, and subsequent deuterodeborylation of these molecules to produce labeling method with good functional group tolerance, and whose regioselectivity complements existing methods (Scheme 3.2)

Table 3.1 Synthesis of monoborylated compounds via deborylation/deborylation[7]



entry	diborylated compound	product	time,[b] yield
1			0.75 h, 68%
			1 h, 85%
3			2 h, 58%
4			4h, 49%
5[c]			10 h, 80%
6[d]			5 h, 58%

[a]Except as where noted reactions were carried out with pure diborylated starting materials. [b]Time refers to the deborylation step. [c]One-pot synthesis from starting thiophene. [d]Monoborylation of 3-cyanothiophene catalyzed by [IrOMe(COD]$_2$/dtbpy gives a 1.1:1 ratio of 2- and 5-borylated isomers.

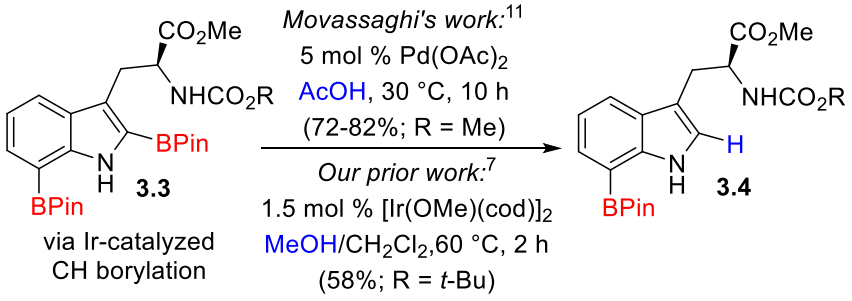


Scheme 3.2: Borylation/Deuterodeborylation of Clopidogrel

As shown in Scheme 3.2, Ir-catalyzed deuterodeborylation can be achieved at 55 °C in 2:1 $CD_3OD/CDCl_3$ with 92% deuteration at the 5-position of the thiophene ring of clopidogrel, the active ingredient of Plavix confirming, that the 5-position was the site of borylation. Also compared to unlabeled clopidogrel, the 5-deuterated clopidogrel showed no loss of optical rotation. This showcase that the conditions for C-H activation/borylation are sufficiently mild for late stage of advanced molecules like pharmaceuticals.

Recently, Movassaghi and co-workers[11] showed that the 2,7-diborylation of tryptophans, tryptamines, and 3-alkylindoles could be followed by in situ palladium-catalyzed C2-protodeboronation to selectively afford the C7-products (Scheme 3.3). From a strategic perspective borylation/protodeboronation sequence enables a streamlined approach to 7-

borylated indoles that are otherwise difficult to access without additional steps and/or prefunctionalization[12] We too had observed selective deborylations of a number of diborylated heterocycles, including several 2,7-diborylated indoles (Scheme 3.3). [7]



Scheme 3.3: Prior art

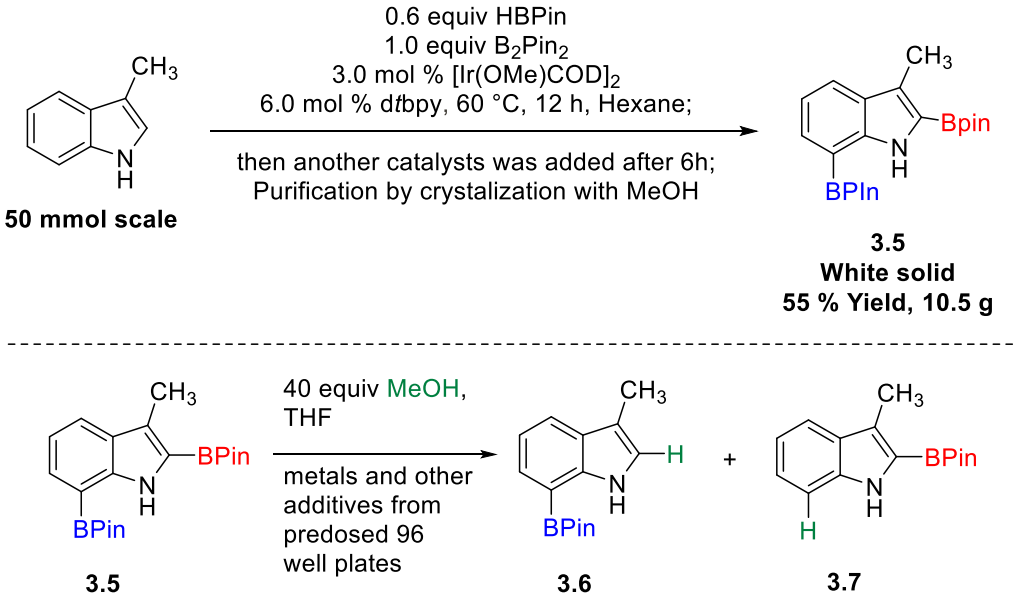
Though borylation/protodeboronation sequence enables several advantages as discussed this tactic may not seem "green" owing to the loss of atom economy. Moreover, the use of Ir metal in theses transformations seems to be less attractive with respect to cost effectiveness. Hence in an effort to expand borylation/protodeboronation methodology, we directed our studies towards discovering alternative catalytic systems or attractive additives that are earth abundant, cheap and mild, while also enhancing selectivity.

3.2. Investigation for novel catalytic systems for protodeboronation of boronic acids and esters via high-throughput experimentation (HTE) techniques.

3.2.1. Bismuth acetate catalyzed protodeboronation of boronic esters arenes and heteroarenes.

We began our quest for the search of alternative catalytic systems or attractive additives that are earth abundant and cheap for borylation/protodeboronation by selecting a model compound as shown in Scheme 3.4. While the regioselectivity of aromatic C–H borylations is mainly driven by steric effects, C–H acidity is a secondary driver.[13] The Ir-catalyzed borylation

of unprotected indoles such as 3-methylindole first installs a Bpin group at C2 and then upon further reaction at C7.[14] The grams scale synthesis of this diborylated product **3.5** is shown in Scheme 3.4. It should be noted that due to the steric demand, installing the Bpin at C2 position is challenged in 3-methylindole compared to than that of unsubituted bare indole. Scheme 3.4b shows the two possible outcomes when **3.5** subjected to protodeboronation. Selective deborylation at C2 over C7 gives **3.6** and complete deborylation will results in 3.7. In accord with our previous findings[7], the fact that the relative reactivities in Ir-catalyzed deborylation reactions parallel to the reactivities of the parent arenes towards borylation hinted that in cases where sequential diborylation is observed, the products would deborylate selectively at the position that was the first site of borylation. So the deborylation is to follow with regard to the Bpin moiety: "first Bpin in - first Bpin out". Moreover, as borylation at C3 substituted indoles are challenged, we assumed that it will translate into a challenging deborylation. Hence it is safe to assume that any additives or catalysts that we might discover will provide us a greater selectivity towards the deborylation of the Bpin at C2.

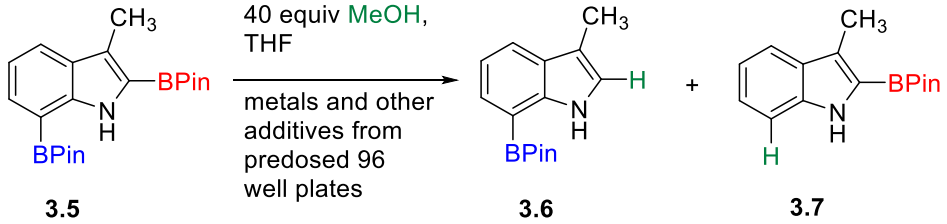


Scheme 3.4: Discovery of Bi catalyzed protodeboronations

Initial forays toward the investigation were propelled by the idea of using High Throughput Experimentation (HTE), which enables screening of 96-well plates that are pre-dosed with intriguing metal salts and additives. These pre-dosed plates were comprised with 95 different components that we envisioned would facilitate protodeboronation and also with an empty well that serves as the control. The metal salts and additives (2 μmol of additives in wells C03, C05, C12 and from E02 to F02, and 5 μmol of the rest of the additives) that were chosen are displayed in Figure 3.1. The (3-methyl-2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole) **3.5** (10 μmol/reaction) and 1,3,5-tri-tertbutylbenzene (1 μmol/reaction) (used as an internal standard to quantify the reaction) were dosed together into the reaction vials in THF (100 μL). Then 40 equiv of MeOH was added to all the reactions. The reactions were then sealed and stirred at 25 ^{o}C for 4h inside the glove box. Then 10 μL of the reactions was measured into a 96-well plate LC block and were diluted with 600 μL of acetonitrile. The 96-well plate LC block was then sealed with a silicon-rubber storage mat, and the reactions were analyzed using standard reverse-phase HPLC (see the experimental).

The outcome of the experiment is summarized in Figure 3.2a and 3.2b. As expected, the control well (A01), which contains no additive, showed no product formation. It is important to note here that in the course of the HPLC analysis we have observed boronic acid adduct formation. Further analysis suggested it to be an artifact generated by the hydrolysis of Bpin moiety during the HPLC run rather than a product formed during the deborylation. Despite the apparent unreactivity of many metal salts and additives after 4 hours at 25 ^{o}C, product **3.6** was formed in significant quantities with $Bi(OTf)_3$. Other metal salts of Cu, Ag, Zn, Ga and Sc also showed some reactivity.

Figure 3.1: 96 well plate catalyst screen for protodeboronation



	1	2	3	4	5	6	7	8	9	10	11	12
A	Control	LiCl	NaF	NaBr	NaI	NaCN	Na TFA	Na TCA	$NaBF_4$	NaOTs	Na2SO3	Na_2S_2O3
B	Na_2SO_4	KCl	CsF	CsCl	$V(acac)_2$	$CrCl_2$	$MnCl_2$	$FeCl_2$	$FeCl_3$	Fe (II) acac	Fe (III) acac	$Co(acac)_2$
C	$Co(acac)_3$	NiF_2	$NiBr_2$ /DME	Ni (II) acac	(PPh_3) $NiCl_2$	CuCl	$CuCl_2$	CuBr	CuI	Cu (II) (acac)	(1,10-phenan)Br_2 Cu II	Cp_2ZrCl_2
D	Mo(acac)	$Pd(OAc)_2$	Pd $(Cl)_2$dppf DCM	$Pd_2(dba)_3$	Ag_2O	AgOTf	AuCl	$AuCl_3$	Mg 325 mesh	Al 200 mesh	Cu <75 micron	Zn 100 mesh
E	Pd black	$Mg(OTf)_2$	$Ca(OTf)_2$	$Sc(OTf)_3$	$Zn(OTf)_2$	$Ga(OTf)_3$	$Y(OTf)_3$	$In(OTf)_3$	Sn (II) OTf_2	$La(OTf)_3$	$Sm(OTf)_3$	$Yb(OTf)_3$
F	$Hf(OTf)_3$	$BiOTf_3$	Boron oxide	$Al(OiPr)_3$	$Ti(OMe)_4$	$CeCl_3$	$ZnCl_2$	$K2CO_3$	$KHCO_3$	KOAc	$K3PO_4$	2,2-diphenyl ethylamine
G	proton sponge	4-phenylpy	oxalic acid	BSA	citric acid	3-phenyl propanoic acid	Bu_4NBr	$NaBH_4$	$PhI(OAc)_2$	CAN	oxone	AIBN
H	BHT	18-Crown-6	4A, MS	diamine	aminoalcohol	TPP	dppf	CataXCium A	X phos	salen	phenantroline	BINOL

Conditions: 10 μmol substrate, 100 μL THF, 40 equiv of each MeOH Standard: 0.1 equiv of 1,3,5-tri-tertbutylbenzene

Figure 3.2a: Metal Screen for Deborylation at 25 °C, 4 h (From A1:D12)

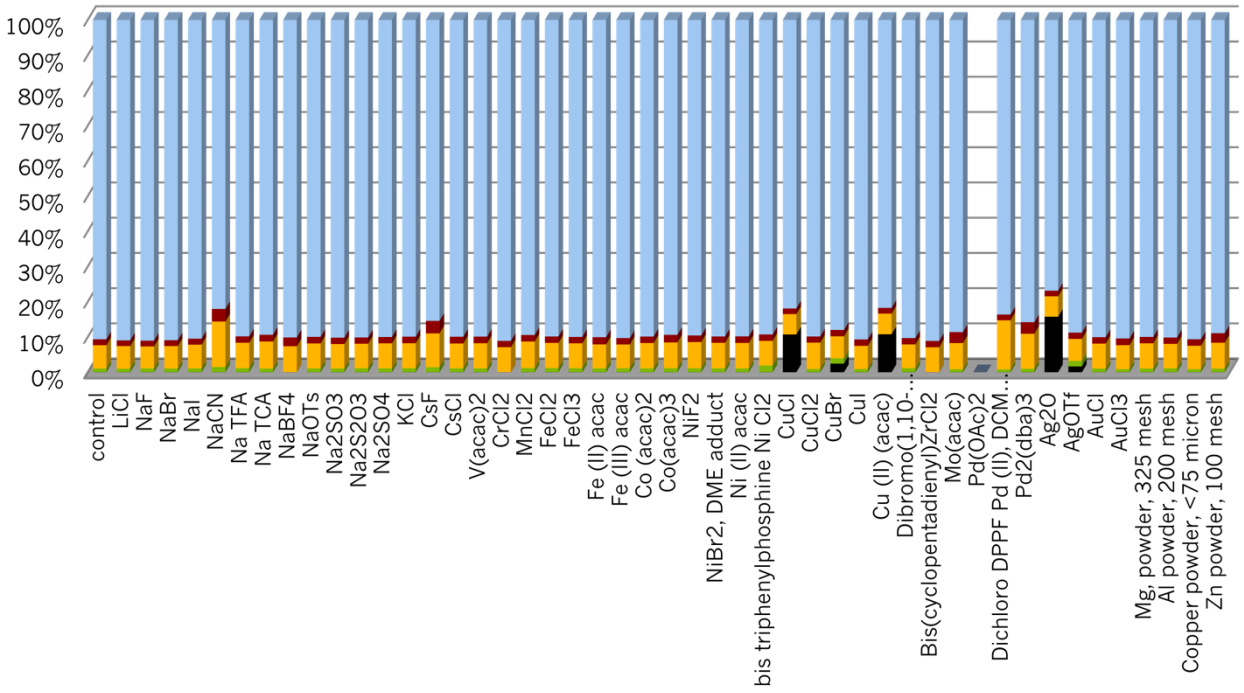


Figure 3.2b: Metal Screen for Deborylation at 25 °C, 4 h (From E1:H12)

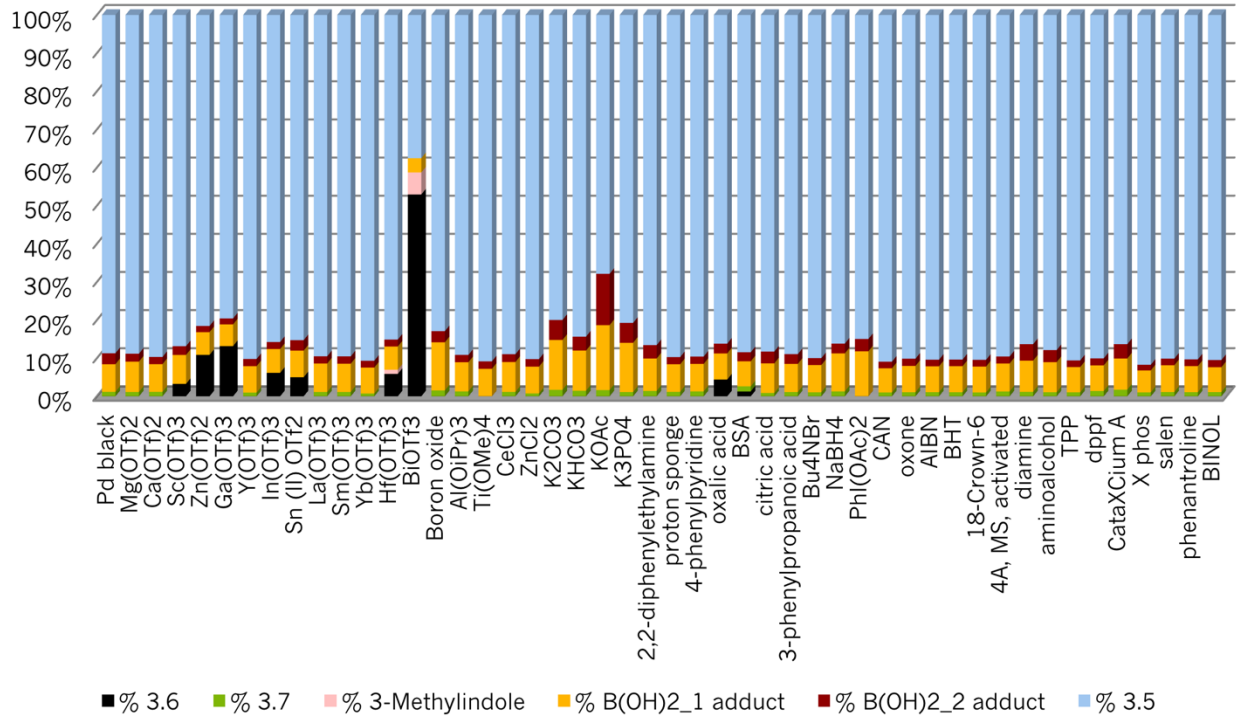


Figure 3.3a: Metal Screen for Deborylation at 40 °C, 16 h (From A1:D12)

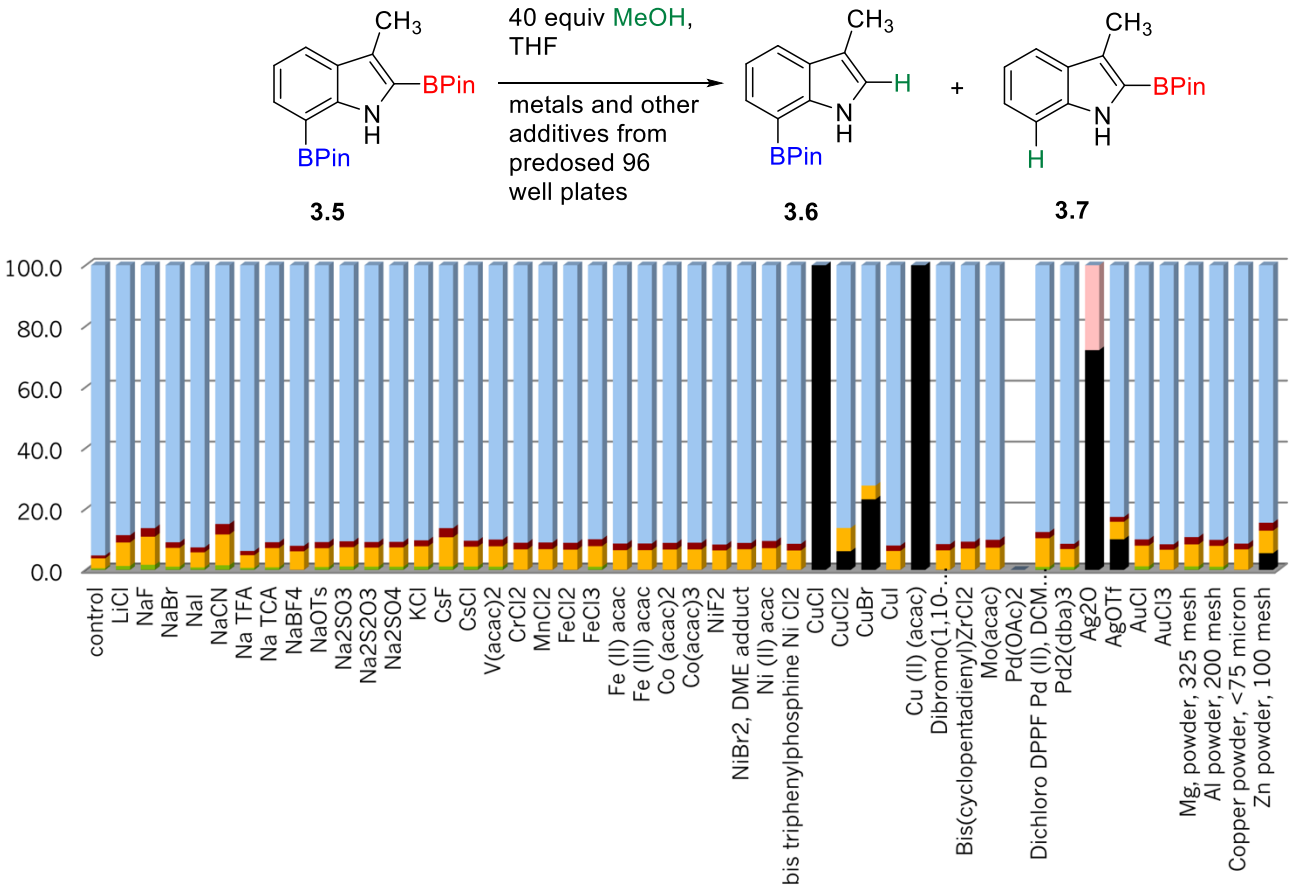
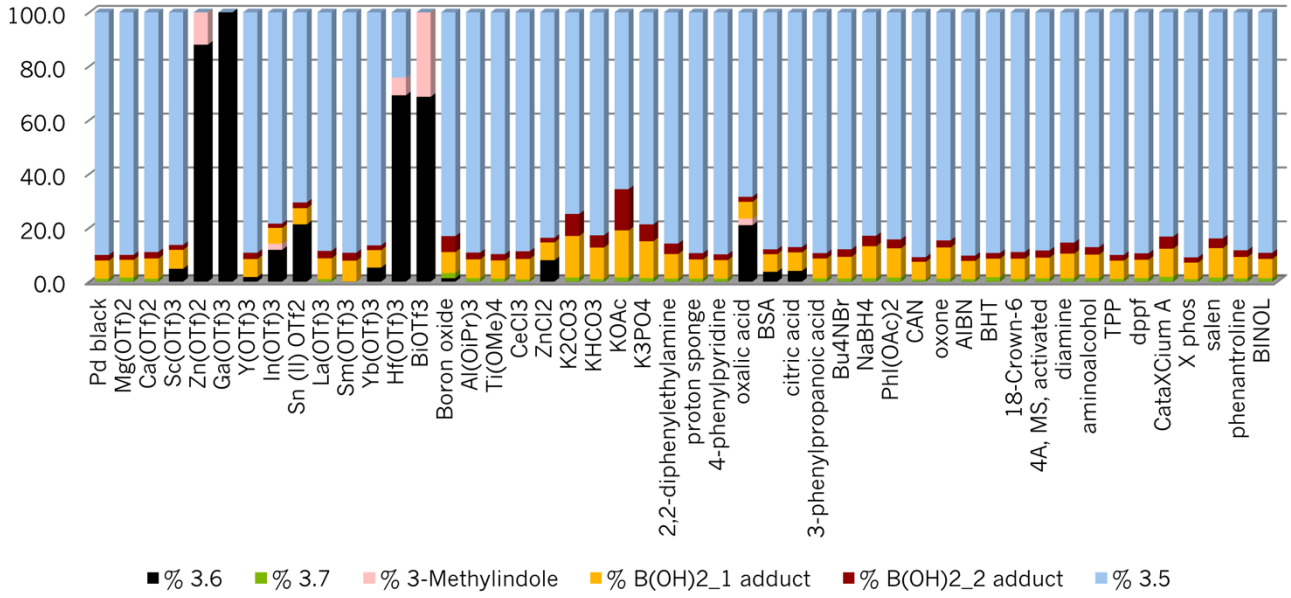


Figure 3.3b: Metal Screen for Deborylation at 40 °C, 16 h (From E1:H12)

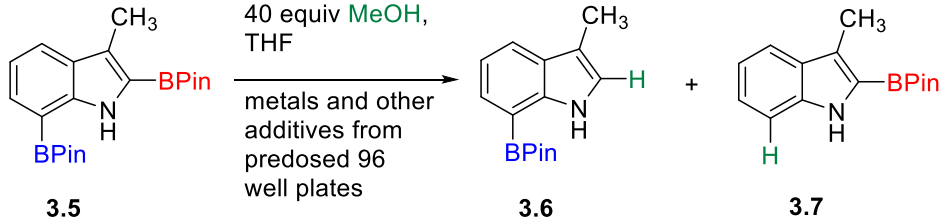


To assess the effect from higher reaction times and temperatures we then extended the study by heating the platform at 40 ^{o}C for 16 hours and then by analyzing the well plate by previously stated analytical methods (Figure 3.3a and 3.3b). Interestingly upon heating the reaction progressed well towards the desired product with CuCl, $Cu(acac)_2$, Ag_2O and with the triflates of Zn, Ga, and Hf. Remarkably, it was further shown that with regards to $Bi(OTf)_3$ despite given more reaction time and heating the amount 3-methylindole (generated from complete deborylation of **3.5**) generated was low comparted to than that of Ag_2O which only showed about 10% of **3.6** at room temperature. Pivotal to the success of this endeavor towards better and much selective catalyst to replace Ir based catalytic system was the discovery of this Bi based metal salt. Not only it was active at room temperature but at higher temperatures and even at longer reaction times it showcased a notable selectivity towards the protodeboronation of the Bpin at the C2 position of the indole compared to Bpin at C7 position. Additionally, this result demonstrates that Bi-mediated deborylations still follows the 'first Bpin in - first Bpin out' trend that we have previously observed.[7]

Knowing we have a one good hit, $Bi(OTf)_3$ for selective deborylation at C2 and few salts that might work out: we continued our endeavor towards further elaboration of the key metal salts based on Bi, Ag, Zn, Cu, Sc, Hf, and Fe shown in Figure 3.4. The additives (5 μmol) were dosed into the 96-well reactor vial as solutions or well-stirred slurries in MeOH. Slurries were dosed using a single-tip pipettor with the sampling tip cut to allow free flow of the slurry. Plates of these additives were dosed in advance of the reaction, the solvent was removed by evacuation on a GeneVac and the plates were stored in the glovebox. The (3-methyl-2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole) **3.5** (10 μmol/reaction) and 1,3,5-tri-tertbutylbenzene (1 μmol/reaction) (used as an internal standard to quantify the reaction) were

dosed together into the reaction vials in THF (100 μL) for wells from A1:D9 and in DMF (100 μL) for wells E1:H9. Then 40 equiv of MeOH was added to all wells. The reaction wells were then sealed and the contents stirred at 25 ^{o}C for 4 h inside a glove box. Then 10 μL of the reaction mixtures were measured into 96-well plate liquid-chromatography (LC) block and were diluted with 600 μL of acetonitrile. The 96-well plate LC block was then sealed with a silicon-rubber storage mat, and the reactions were analyzed using standard reverse-phase HPLC (see the experimental). In this study we were envisioning to see how the reactivity changes with respect to the solvent as well as from the metal. The data obtained from this experiment after statistical treatments are summarized in Figure 3.5a and 3.5b. We were quite elated to obtain several hits that proved the hypothesis of selecting catalytic systems based on hits from previous experimental outcomes. Moreover, these results demonstrate that there is a clear solvent effect. As shown in Figure 3.5a THF seems to be the favorable solvent overall considering that it has enhanced the reactivity of many catalytic systems. For example, rare earth metal triflates of Sc, Ti, Ga, Y and Hf showed no reactivity in DMF, but were active in THF. Like many lanthanide triflates that promote reaction with their lewis acidic properties, theses triflates showed diminished activity in coordinating solvents like DMF. Further, CuCl and $Cu(MeCN)_4PF_6$, which showed trace amounts in THF, were more active in DMF probably due to enhance solubility. With the knowledge of activity towards protodeboronation with $Bi(OTf)_3$, we investigated other bismuth salts, like $BiCl_3$, $Bi(OTf)_3$, $Bi(OAc)_3$, BiF_3 and $BiOClO_4$.

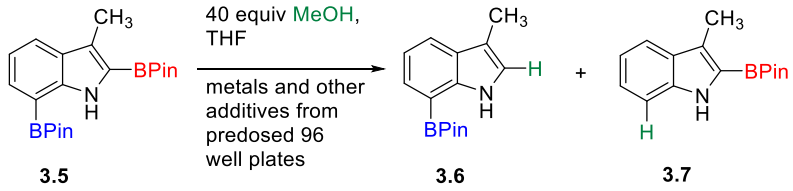
Figure 3.4: Additional Metal Screen for Deborylation and Solvent Effect.



3.5 **3.6** **3.7**

	1	2	3	4	5	6	7	8	9	10	11	12
A	Control	$Sc(OTf)_3$	$Cp_2Ti(OTf)_2$	$TiCl_3$	VCl_3	$Fe(OTf)_2$	$Fe(NO_3)_3$	$CoCl_2$	$Co(NO_3)_2$	$Ni(OTf)_2$	CuCl	$CuCl_2$
B	$Cu(OTf)_2$	$Cu(MeCN)_4\ PF_6$	$Zn(OTf)_2$	$Ga(OTf)_3$	$Ga(ClO_4)_3$	$Y(OTf)_3$	YCl_3	$ZrCl_4$	$RuCl_3$	$PdBr_2$	Ag_2O	AgOTf
C	$(nBu_4N)_2Ag_2I_4$	$Cd(OAc)_2$	$Cd(ClO_4)_2$	$InCl_3$	$In(OTf)_3$	$SnCl_2$	$Sn(OTf)_2$	SbF_3	$HfCl_4$	$Hf(OTf)_4$	$W(CO)_6$	$PbCl_2$
D	$BiCl_3$	$Bi(OTf)_3$	$Bi(NO_3)_3$	$Bi(OAc)_3$	BiF_3	$BiOClO_4$	$Sb(OAc)_3$	$Ce(OTf)_4$	Oxalic Acid			
E	Control	$Sc(OTf)_3$	$Cp_2Ti(OTf)_2$	$TiCl_3$	VCl3	$Fe(OTf)_2$	$Fe(NO_3)_3$	$CoCl_2$	Co(NO3)2	$Ni(OTf)_2$	CuCl	$CuCl_2$
F	$Cu(OTf)_2$	$Cu(MeCN)_4\ PF_6$	$Zn(OTf)_2$	$Ga(OTf)_3$	Ga(ClO4)3	$Y(OTf)_3$	YCl_3	$ZrCl_4$	RuCl3	$PdBr_2$	Ag_2O	AgOTf
G	$(nBu_4N)_2Ag_2I_4$	$Cd(OAc)_2$	$Cd(ClO_4)_2$	$InCl_3$	In(OTf)3	$SnCl_2$	$Sn(OTf)_2$	SbF_3	HfCl4	$Hf(OTf)_4$	$W(CO)_6$	$PbCl_2$
H	$BiCl_3$	$Bi(OTf)_3$	$Bi(NO_3)_3$	$Bi(OAc)_3$	BiF3	$BiOClO_4$	$Sb(OAc)_3$	$Ce(OTf)_4$	Oxalic Acid			

Figure 3.5a: Metal Screen for Deborylation at 25 °C, 4 h, THF (From A1:D9)



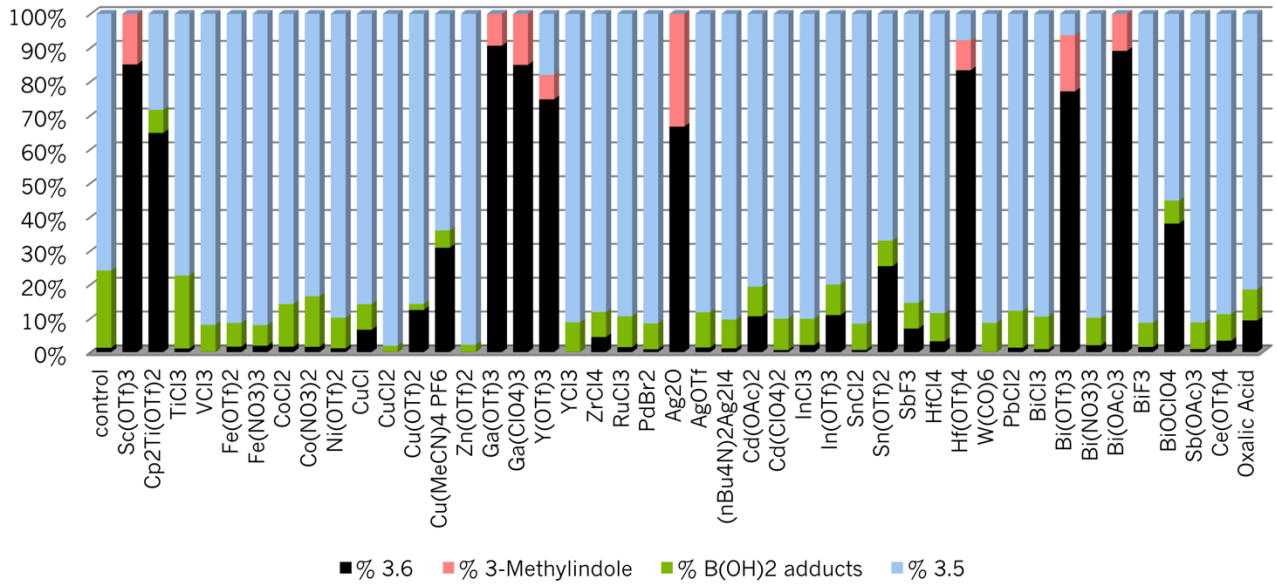
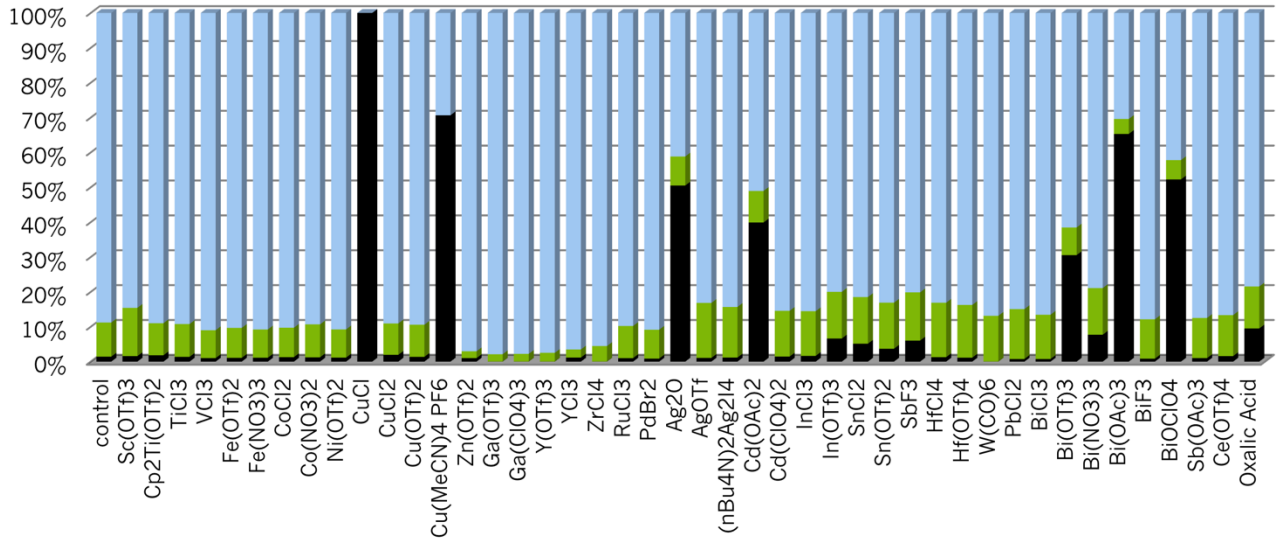
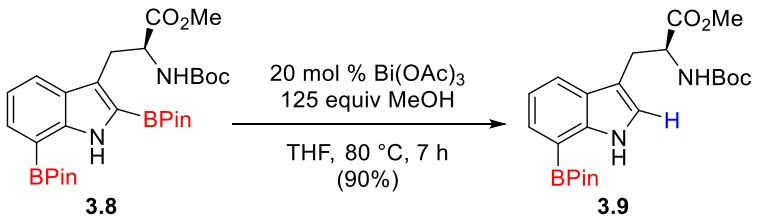


Figure 3.5b: Metal Screen for Deborylation at 25 °C, 4h, DMF (From E1:H9)



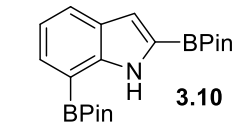
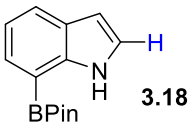
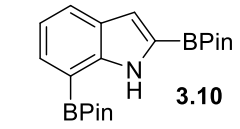
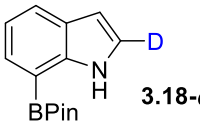
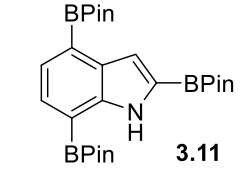
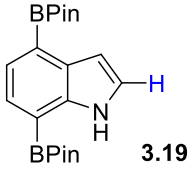
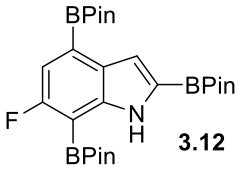
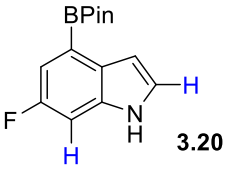
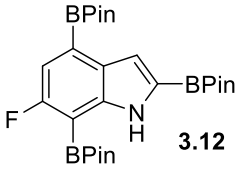
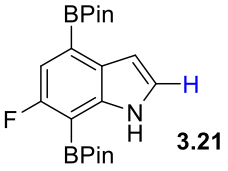
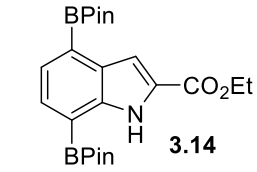
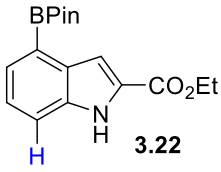
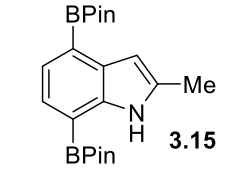
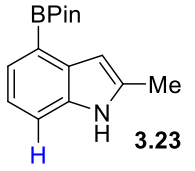
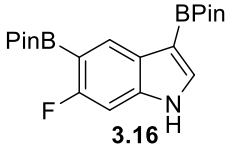
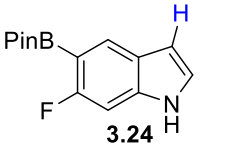
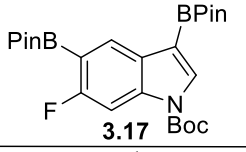
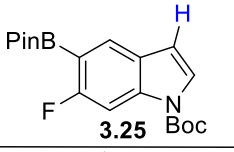
Notably, $Bi(OAc)_3$ resulted with complete conversion of **3.5** with less over deborylation product **3.7**, compared to than that of produced from $Bi(OTf)_3$. $Bi(OAc)_3$ demonstrated better reactivity and selectivity towards C2-Bpin deborylation compared to $Bi(OTf)_3$ (Figure 3.5a). Ag_2O generated about 35% of **3.7** which results from over deborylation. It is evident from the data that Ag_2O to be more reactive and hence showed poor selectivity, evident from the generation of 3-Methylindole about twice that was observed from $Bi(OTf)_3$ and $Bi(OAc)_3$. We were delighted to find out that several catalytic systems to be active for protodeboronation that includes rare earth metal triflates of Sc, Ti, Ga, Y and Hf which gained the attention in recent years for their catalytic activities[15] and also Ag_2O, $Bi(OTf)_3$ and $Bi(OAc)_3$. It is the goal of this outlook to allay the aforementioned catalytic systems to a more practical, environmentally friendly (green) and economical methodology that provides selective protodeboronation in a way similar to the previously described Ir- and Pd-catalyzed protodeboronations. Considering these factors in mind we set our eye for $Bi(OAc)_3$. A method that incorporates bismuth would be quite attractive since bismuth salts are earth abundant, less toxic, and orders of magnitude less expensive than the corresponding precious metal salts.[16] During the course of the studies with 20 mol% $Bi(OAc)_3$ in THF we also observed that whereas the conditions for deboronations with Ir[7] and Pd[8] call for an inert atmosphere, Bi-catalyzed deboronations can be run under air. Based on the above described HTE studies and given the advantages possess by $Bi(OAc)_3$ we finalized the conditions and further expand the study towards a broad substrate scope. We chose **3.8** as a starting point given it was employed prior in deborylations carried out by Ir and Pd based catalysts (Scheme 3.3). We subjected purified **3.8** to 20 mol % $Bi(OAc)_3$ in MeOH (127 equiv) and THF at 80 °C (sealed tube) for 7 h afforded 7-borylated **3.9** in 90% yield (Scheme 3.5). [17]



Scheme 3.5: $Bi(OAc)_3$ catalyzed protodeboronation of **3.8**

Examining first 2,7-diborylated indole (**3.10**), we found that heating this compound with 20 mol % $Bi(OAc)_3$ and 125 equiv of ACS grade MeOH in THF, afforded the 7-borylated indole (**3.18**) in 82% yield after 17 h (entry 1). Curiously, when we looked to deuterated **3.10**, the reaction was complete (83% isolated yield 87% deuterium incorporation[18,19]) after stirring with 60 equiv of 99.8% CD_3OD for 12 h at room temperature (entry 2). A closer look into these differences revealed that, as we had observed with some of the Ir-catalyzed debornations,[7] the grade of MeOH could significantly impact the reaction rate. For example, protodeboronation of **3.10** was complete in less than three hours when anhydrous MeOH that came in sealed bottles was employed. Notably, reactions with either grade of methanol were reproducible. To highlight the method's relative robustness and economy, we chose to continue our study with the lower grade methanol.[20] Under similar conditions, 2,4,7-triborylated indole (**3.11**) was monoprotodeboronated to afford 4,7-diborylated indole (**3.19**) in 75% yield (entry 3). Attempts at the selective C2/C7 diprotodeboronation of **3.11** were not successful. In contrast, 2,4,7-triborylated-6-fluoroindole (**3.12**) underwent clean diprotodeboronation to afford **3.20** in 80% yield (entry 4) when the amount of MeOH was increased. Monoprotodeboronation of **3.12** (entry 5) provided further indication that these reactions are in part substrate dependent, as relative to **3.11**, trisboylated **3.12** required less time and equivalents of methanol to achieve the selective deborylation of the Bpin at C2 in similar yields.

Table 3.2: $Bi(OAc)_3$ catalyzed protodeboronations

Entry	Starting Indole	Product	Conditions and Yield	
1	 **3.10**	 **3.18**	20 mol % $Bi(OAc)_3$, 125 equiv MeOH, THF, 80 °C, 17 h, 82%[a]	
2	 **3.10**	 **3.18-*d*$_1$**	20 mol % $Bi(OAc)_3$, 40 equiv CD_3OD, THF, 80 °C, 2.5 h, 83%[a]	
3	 **3.11**	 **3.19**	20 mol % $Bi(OAc)_3$, 125 equiv MeOH, THF, 80 °C, 17 h, 75%[a]	
4	 **3.12**	 **3.20**	20 mol % $Bi(OAc)_3$, 250 equiv MeOH, THF, 80 °C, 15 h, 80%[a]	
5	 **3.12**	 **3.21**	20 mol % $Bi(OAc)_3$, 60 equiv MeOH, THF, 80 °C, 5 h, 67%[a]	
6	 **3.14**	 **3.22**	40 mol % $Bi(OAc)_3$, 375 equiv MeOH, THF, 80 °C, 16 h, (54:9:41 **3.22**:**indole**:**3.14**)[b]	Ref 7 Ir-catalysis (33:67 **3.22**:**indole**)[b] Modified[d] Ir-catalysis[c] 54%[a] **3.22**, 13%[a] **indole**
7	 **3.15**	 **3.23**	40 mol % $Bi(OAc)_3$, 500 equiv MeOH, THF, 80 °C, 16 h, (52:5:43 **3.23**:**indole**:**3.15**)[b]	Ref 7 Ir-catalysis[c] 74%[a] (91:9 **3.23**:**3.15**)[b]
8	 **3.16**	 **3.24**	20 mol % $Bi(OAc)_3$, 50 equiv MeOH, THF, 80 °C, 3 h, 88%[a]	Ref 7 Ir-catalysis[c] 66%[a] (87:13 **3.24**:**indole**)[b]
9	 **3.17**	 **3.25**	40 mol % $Bi(OAc)_3$, 500 equiv MeOH, THF, 80 °C, 16 h, (no reaction)[b]	Ref 7 Ir-catalysis[c] 47%[a] (60:40 **25**:**indole**)[b]

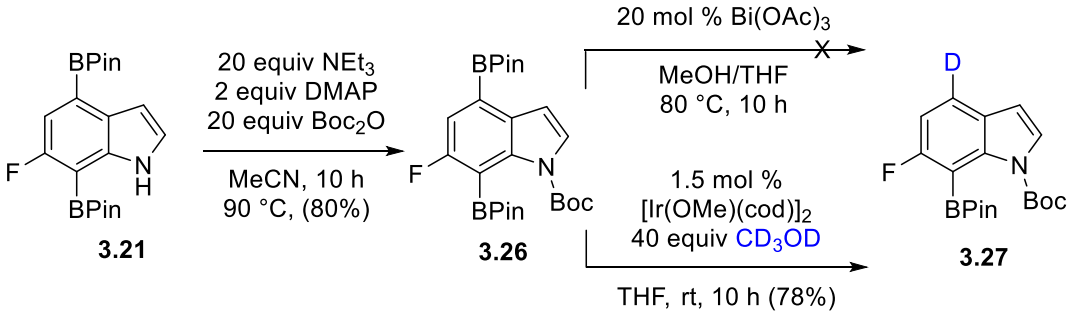
[a]Isolated yields. [b]Ratio determined by ^{1}H-NMR of the crude reaction mixture. [c]See Supporting Information for details.

[d]3 mol % $[Ir(OMe)COD]_2$, 40 equiv. MeOH, THF at rt.

The protodeboronation of 4,7-diborylated-2-carboethoxy-indole **3.14** (entry 6) was instructive for comparing the synthetic efficiency of Bi vs. Ir-catalyzed deboronations. After 24 h at 80 °C, diborylatedindole **3.14** and 40 mol % $Bi(OAc)_3$ in MeOH/THF gave monoprotodeboronated **3.22** as the major product along with fully protodeboronated 2-carboethoxy-indole and unreacted **3.14** in a 54/9/41 ratio per NMR analysis of the crude reaction product. Our recently published Ir-mediated conditions of 2 h at 1.5 mol % $[Ir(OMe)COD]_2$ in 2:1 MeOH/CH_2Cl_2 at 60 °C,[7] performed worse giving the fully protodeboronated 2-carboethoxy-indole and **3.22** in a ratio of 67:33. However, Ir-catalysis in MeOH/THF (~1:6) at rt reacted best affording **3.22** in 54% isolated yield along with 13% 2-carboethoxy-indole. 4,7-Diborylated-2-methyindole **3.15** under the $Bi(OAc)_3$ conditions also afforded a 52/5/43 mixture of monoprotodeboronated **3.23** to 2-methylindole to **3.15** respectively. Indole **3.15** was another substrate where Ir-mediated protodeboronation proved superior, giving a 91/9 mixture of **3.23** and starting material **3.15** with **3.23** being isolated in 74% yield (entry 7). In their own accord 3,5-diborylated indoles (**3.16** and **3.17**) seems to be interesting and informative. Compound **3.16** was exclusively monoprotodeboronated at C3 by 20 mol % $Bi(OAc)_3$, in MeOH/THF after 3 h at 80 °C, affording **3.24** in 88% yield (entry 8). Deboronation of **3.16** under our published Ir-catalyzed protodeboronation conditions proved less selective. With Ir, the crude reaction product contained 13% of fully deboronated 6-fluoroindole and **3.24** was isolated in 66% yield. Attempts to optimize Ir-catalyzed deboronation of **3.16** never met with the selectivity observed with $Bi(OAc)_3$ unless the reaction was stopped prior to complete consumption of starting material.

In contrast to **3.16**, Boc-protected **3.17** failed to undergo any deboronation by the action of $Bi(OAc)_3$ (entry 9). Indole **3.17** was susceptible to Ir-catalyzed deboronation, but again those conditions proved too harsh, giving the N-Boc protected 6-fluoroindole as the major product

(21/79 **3.25**/N-Boc protected 6-fluoroindole in the crude reaction mixture). The ratio of **3.25**/N-Boc protected 6-fluoroindole improved to 60/40 (47% isolated yield of **3.25**) when the protodeboronation was run with 3 mol % Ir in MeOH/THF at room temperature for 10 h.

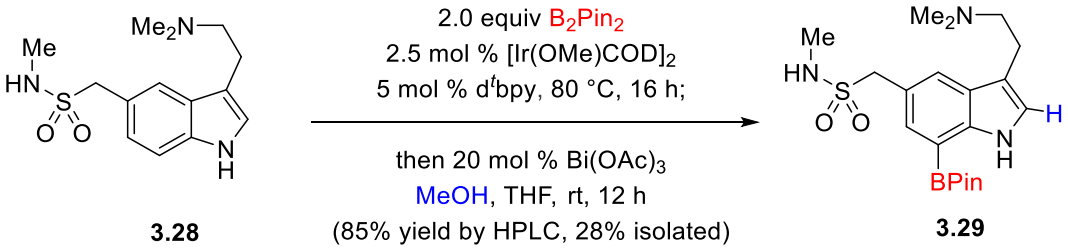


Scheme 3.6: Changing the sequence of protodeboronation

We further investigated the reactivity difference between unprotected and N-Boc-indoles as shown (Scheme 3.6). 4,7-Diborylated-6-fluoroindole **3.21** was converted to its Boc derivative (**3.26**) and then subjected to both the Bi and Ir deboronation conditions. Again, there was no reaction by $Bi(OAc)_3$. However, under the Ir-catalyzed protodeboronation conditions, using CD_3OD as the protic material, afforded the C4 deuterated product **3.27** in 78% yield. This result demonstrates that the general order of the first boron "on" being the first boron "off" in Ir-catalyzed deboronations can be altered subsequent to borylation by introducing nearby functionality that is sterically demanding.

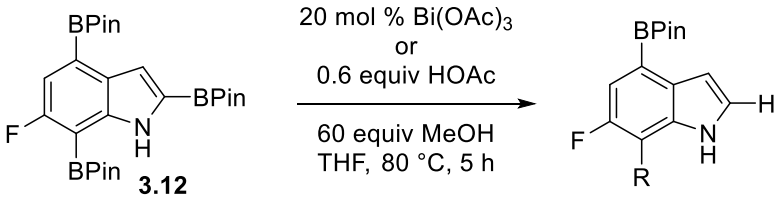
To demonstrate this chemistry in late-stage functionalization, we applied the one-pot diborylation/deboronation sequence to 5-HT receptor agonist sumatriptan (**3.28**) (Scheme 5). Thus indole **3.28** was thus converted to the 2,7-diborylated product. Selective $Bi(OAc)_3$ catalyzed deboronation of the crude product was then achieved in 85% yield by quantitative

HPLC. However, the highly polar nature of **3.29** coupled with the hydrolytic instability of the Bpin ester made purification a challenge and the isolated yield of **3.29** was only 28%.



Scheme 3.7: Functionalization of sumatriptan

Although the mechanism of these $Bi(OAc)_3$ mediated deboronations remains to be established, the above examples point to an interaction with the indole nitrogen as being important to achieving selectivity and gaining reactivity. Given Movassaghi and co-workers' Pd-catalyzed C2 protodeboronation of indoles with HOAc as the proton source,[8] we questioned if HOAc, either residual in the $Bi(OAc)_3$ or in situ generated, was playing a part in our bismuth-catalyzed protodeboronations. Towards this end, we examined the reactivity of diborylated **3.12** with 0.6 equiv of HOAc, which would correspond to the theoretical amount of acetic acid available from 20 mol % of $Bi(OAc)_3$ (Scheme 3.8). Under these conditions no protodebornation was observed. Increasing the amount of HOAc to 40 equiv had no effect as again only starting **3.12** was observed after 5 h at 80 °C. The next set of experiments was performed with free $Bi(OAc)_3$ that had been washed with CCl_4 until the washings showed no HOAc by NMR. Somewhat surprisingly, HOAc free $Bi(OAc)_3$ exhibited enhanced reactivity, as washed $Bi(OAc)_3$ afforded a 3:1 mixture of **3.21** and **3.20** while the same reaction with unwashed $Bi(OAc)_3$ gave no **3.20**. While not quantified, it appears that adventitious HOAc lowers the relative reactivity of the unwashed $Bi(OAc)_3$, perhaps by interfering with a putative Bi/indole nitrogen interaction.



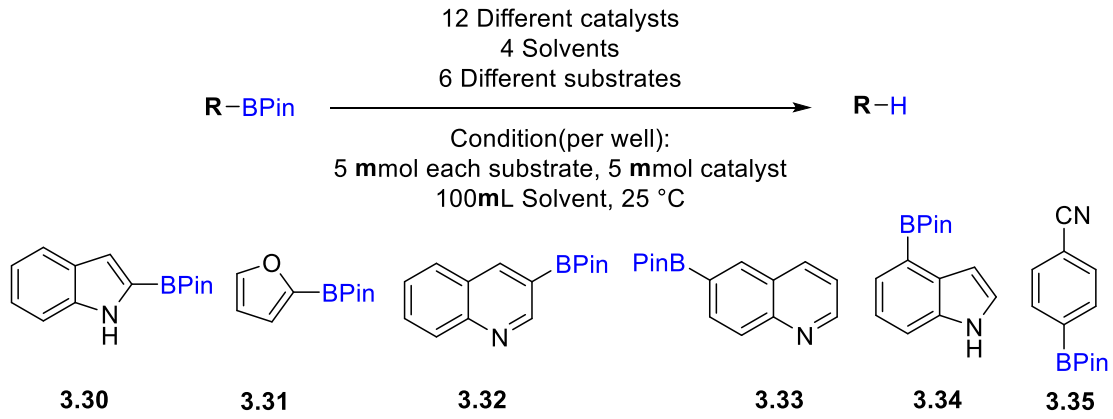
$Bi(OAc)_3$ "free" of HOAc: 90% 3:1 R = Bpin (**3.21**) / R= H (**3.20**)
$Bi(OAc)_3$ used "as is": 67% R = Bpin (**3.21**)
HOAc used in place of $Bi(OAc)_3$: no reaction

Scheme 3.8: Exploring the potential role of HOAc

In conclusion, bismuth acetate is a safe, shelf stable, inexpensive, and operationally simple alternative to Ir and Pd for the catalytic protodeboronations of indoles. Whereas the conditions for deboronations with Ir[8] and Pd[6] call for an inert atmosphere, Bi-catalyzed deboronations can be run under air. Furthermore, while reaction times are dependent on the grade of methanol employed, solvents need not be distilled or degassed. In general, sequential deboronations with $Bi(OAc)_3$ occur in the same order in which the Bpin groups are installed via Ir-catalyzed borylation. Relative to related methods, $Bi(OAc)_3$ tends to offer greater selectivity in protodeboronations of di- and triborylated indoles. Thus, by tuning the C–H borylation and deboronation conditions one can access a variety of boron substitution patterns from a single starting indole.

3.2.2. Silver oxide catalyzed protodeboronation of boronic esters arenes and heteroarenes.

We have established bismuth acetate as a safe and inexpensive alternative to Ir and Pd as a facilitator of catalytic deborylations primarily in indole substrates. In addition to $Bi(OAc)_3$, high throughput screening revealed few other metal salts that facilitates deborylation, including CuCl and Ag_2O. With this knowledge in hand we envisioned to expand this chemistry to other substrates, to determine the selectivity of protodeboronation and to give the end user grounding principles to determine the catalytic system that suits him/her based on the substrate class and selectivity that desired. Efforts were then directed to arrange a set of experiments as showed in Scheme 3.9.

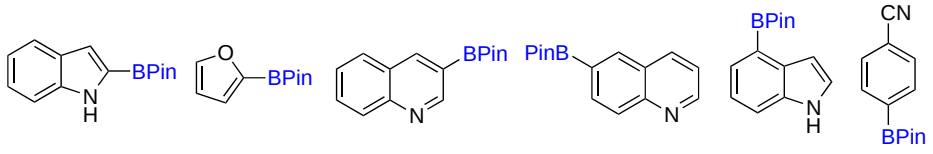


	Catalyst	Control	$Bi(OAc)_3$	$[Ir(OMe)COD]_2$	Ag_2O	$Bi(OTf)_3$	$Ga(ClO_4)_3$	$Hf(OTf)_4$	$Cu(OTf)_2$	CuCl	$Cu(MeCN)_4PF_6$	$Cd(OAc)_2$	$[Ir(COD)(PCy_3(py)]$
Solvent	Row/Col	1	2	3	4	5	6	7	8	9	10	11	12
THF	A												
NMP	B												
DMF	C												
Acetonitrile	D												

Scheme 3.9: HTE protodeborynation study on multiple substrates

The selection of these substrates are worthy of a comment. We anticipated that having the Bpin group in the aromatic ring side or heteroaromatic ring side with close proximity to the heteroatom could have an impact on the protodeboronation. Hence, two indoles were selected 3.30 and 3.34 where the Bpin is at 2- position and 4- position. Following the same pattern two quinolones were selected where Bpin are placed at 3 and 6 positions (3.32 and 3.33). We added 3.35 as reference to observe the reactivity with respect to heterocyclic boronic esters. Our study was mainly focused on three catalytic systems and their behavior towards the chosen substrates, $Bi(OAc)_3$, Ag_2O, and $[Ir(OMe)(COD)]_2$. The rest of the catalytic systems were employed based on previous screening data. The additives (5 μmol) were dosed into the well reactor vial as solutions or well-stirred slurries in MeOH. Slurries were dosed using a single-tip pipettor with the sampling tip cut to allow free flow of the slurry. Plates of these additives were dosed in advance of the reaction, the solvent was removed by evacuation on a GeneVac and the plates were stored in a glovebox. Then each starting substrates **3.30-3.35** (5 μmol/reaction) and 1,3,5-tri-tertbutylbenzene (1 μmol/reaction) (used as an internal standard to quantify the reaction) were dosed together into the reaction vials in appropriate solvent (THF, DMF, NMP and ACN: 100 μL). Then 40 equiv of MeOH was added to all the reactions. The reaction wells were then sealed and stirred at 25 ^{o}C for 3.5 h inside a glove box. Then 10 μL of the reaction mixtures were measured into a 96-well plate LC block and were diluted with 600 μL of acetonitrile. The 96-well plate LC block was then sealed with a silicon-rubber storage mat, and the reactions were analyzed using standard reverse-phase HPLC (see the experimental). This analysis generated substantial amount of data and for the discussion here only important and significant outcomes are summarized.

Table 3.3: Protodeboronations of selected heterocyclic boronic esters.



3.30 **3.31** **3.32** **3.33** **3.34** **3.35**

Entry		Catalyst	Solvent	% Deborylation of substrates[a] **3.30**	**3.32**	**3.33**	**3.34**	**3.35**
1	A:2	$Bi(OAc)_3$	THF	63				
2	B:2		NMP	28				
3	C:2		DMF	35				
4	D:2		ACN	84				
5	A:3	$[Ir(OMe)COD]_2$	THF	80	20	11		
6	B:3		NMP	73	32			
7	C:3		DMF	74	29			
8	D:3		ACN	89	41	20	20	
9	A:4	Ag_2O	THF	100	100	52	19	100
10	B:4		NMP	81	69			24
11	C:4		DMF	89	90			17
12	D:4		ACN	96	100	48	14	75

[a]Only %deborylation>10 % are showing here for simplicity.

Pivotal to the success of this experiment is providing conditions to compete each substrate for deborylation to monitor their relative rates towards each catalyst and condition. Hence the reactions were stopped prior to complete conversions. Interestingly 2-borylated furan **3.31** reacted much faster compared to the rest of the substrates with all catalytic systems and those the results are not included in the Table 3.3. Table 3.3 summarizes data for the catalytic systems that we were very fascinating with and some are worthy a comment. From a glance it is evident that 2-Bpin indole **3.30** is to be the most reactive and also active towards of $Bi(OAc)_3$, Ag_2O, and $[Ir(OMe)(COD)]_2$. Moreover, of focus on entries 1, 5 and 9 makes the activity increased from $Bi(OAc)_3$ 63% < $[Ir(OMe)(COD)]_2$ 80% < Ag_2O 100% in THF. A striking difference was noted with the **3.34** 4-Bpin Indole**,** which showed little or no reactivity towards $Bi(OAc)_3$ and with some reactivity for $[Ir(OMe)(COD)]_2$, 19% in THF for Ag_2O. This indicates

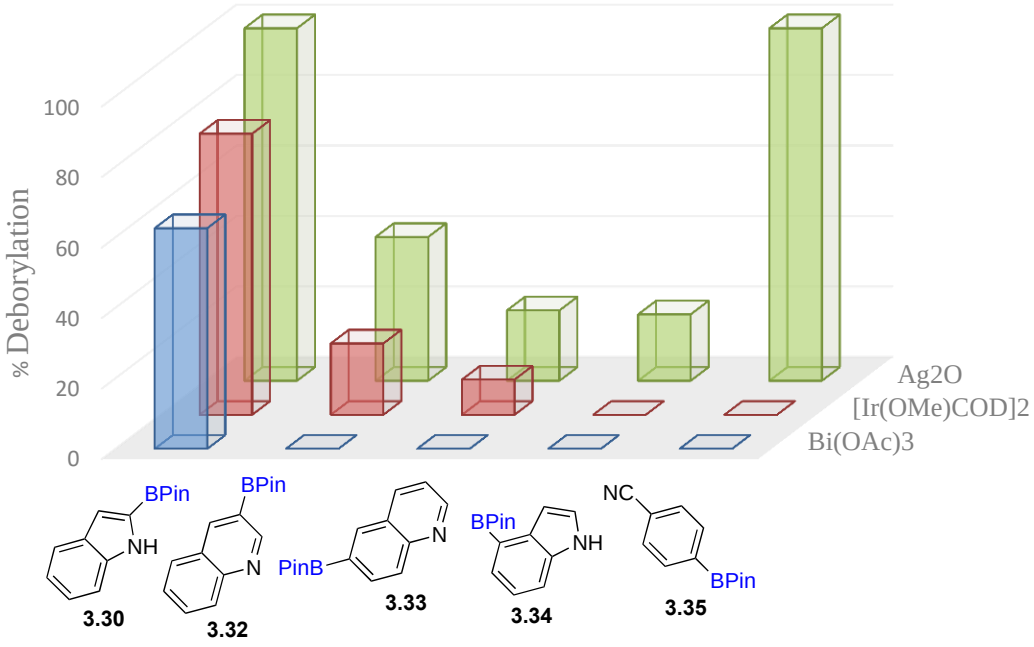
that protodeboronation to promote by having the Bpin in close proximity to a heteroatom. Similar observations were made with 3-Bpin quinoline **3.32** and 6-Bpin quinoline **3.33**. While both of these substrates were unresponsive towards $Bi(OAc)_3$ they showed high reactivity with silver oxide already100% product was observed for **3.32** and 52% with **3.33** in THF (entry 9). The percent of deborylation dropped by half (entry 9) in THF with Ag_2O when the position of the Bpin was changed from C3- to C6- in the quinoline ring system, confirming our hypothesis about having the boron close to heteroatoms for enhanced reactivity. Interestingly, with respect to the 4-cyanophenylboronic acid pincol ester **3.35** underwent protodeboronation with silver oxide and not with the other catalysts. We have observed[7] previously with prolong reaction time provided $[Ir(OMe)(COD)]_2$ to facilitates the deborylation of **3.35**.

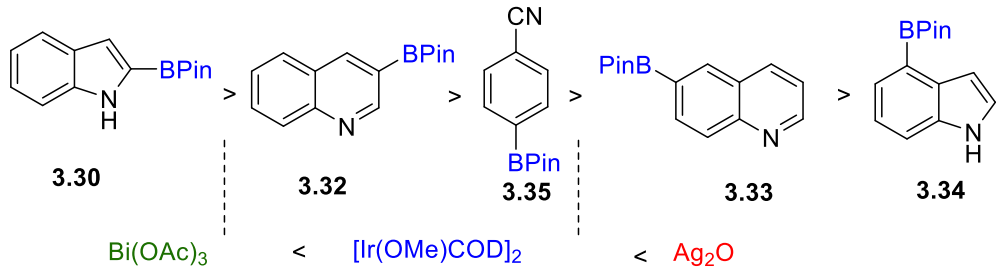
It should be noted that there is a solvent effect affiliated with the protodeboronation as evident from data show in Table 3.3. Particularly, with all three catalysts: $Bi(OAc)_3$, Ag_2O, and $[Ir(OMe)(COD)]_2$ 2-Bpin indole **3.30** shows more deborylation in THF and acetonitrile compared to NMP and DMF (entry 1-12). Further, 2-Bpin indole **3.30** showed very similar activity in THF and acetonitrile with Ag_2O, and $[Ir(OMe)(COD)]_2$ but acetonitrile seems to be better when it comes to $Bi(OAc)_3$. A closer look shows similar solvent trends with other substrates as well. Markedly, 4-cyanophenylboronic acid pincol ester **3.35** showed more deborylation in THF (100%, entry 9) and acetonitrile (75%, entry 12) compared to NMP (24%, entry 10) and DMF (17%, entry 11). A similar tendency was noted with **3.33** and **3.34** as well.

Data affirmed in Table 3.3 has further articulated and showcased in Figure 3.6. It remarkably showcases that when it comes to $Bi(OAc)_3$ as the catalyst of choice, that it will only work upon 2-Bpin indole and similar class of compounds which we have proven to work well as detailed in previous section. This data set give you the freedom to choose the catalyst of choice

based on the substrates we have it at hand. For instance, if we have a 2,7-diborylated indole substrate, utilizing Ag_2O may not be the best choice as it tends to react faster hence diminishing the selectivity of the deborylation. But, if it is the objective to obtain selective deborylation at 2-Bpin, look no further, you have hit the jackpot with $Bi(OAc)_3$.

Figure 3.6: Metal Screen for Deborylation of Heteroarene Boronic Esters: 25 ^{o}C, 3.5 h, THF.



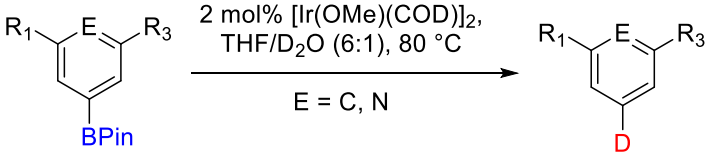


Scheme 3.10: Trend in protodeborynation

To obtain high degrees of deborylation, with lesser concern with selectivity the strategy should be to use Ag_2O. It seems to react with wide variety of substrates while the reactivity of $[Ir(OMe)(COD)]_2$ lies between Ag_2O itself and $Bi(OAc)_3$. The above facts can be summarized and depicted in Scheme 3.10. A general reactivity pattern of Ag> Ir> Bi in deborylating strength was observed. Previously we have established bismuth acetate as a safe and inexpensive alternative to Ir as a facilitator of catalytic deborylations and illustreared its usefulness with variety of indole based substrates.[17] Additionally, it is also envisoned to exploit silveroxide, a cheap alternative to Ir, as a deborylating/deuteration catalyst to afford noval deuterated product. A description of such a process is presented in the next section.

3.2.3. Silver oxide catalyzed deuterodeborylation of boronic esters arenes.

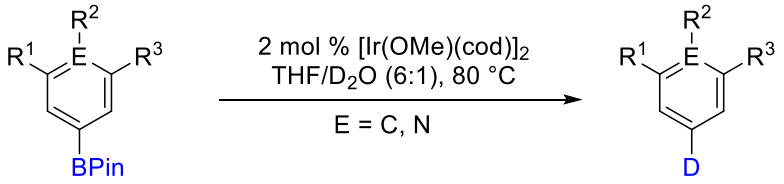
Recently, deuterated molecules have captured the attention of the scientific community as a new class of drug candidates.[21,22] Deuterium and tritium isotopic labeled compounds have long being incorporated as probes for spectroscopy, tools for reaction mechanisms investigation, pharmacokinetics and enzymology.[23] Out of the methods available for the synthesis of such compounds, traditional deuteration methods such as acid, base or transition metal promoted H/D exchange methods can suffer from harsh conditions, incomplete deuterium incorporation, or poor functional group compatibility,[24] although some transition metal catalysts exhibit remarkable activities.[25] Metal halogen exchange, followed by deuterolysis of the organometallic intermediate is another method of incorporating a deuterium in an aryl or heteroaryl ring, selectively.[23] Also, metal catalyzed deuterdecarboxylation method have been developed.[26] But these methods are not without shortcomings. They require pre-functionalization and limited to ortho deuterations.[23, 27,28] Our group recently outlined an alternative method for generating deuterated arenes and heteroarenes.[7] Pinacolboronate esters undergo selective deuterodeborylation in THF/D_2O (6:1 by volume) at 80 °C in the presence of 2 mol % $[Ir(OMe)(COD)]_2$ Scheme 3.11.

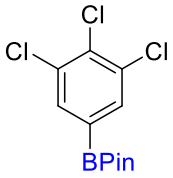
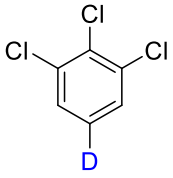
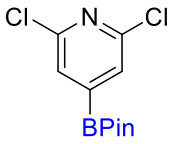
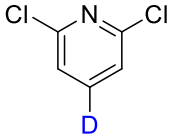
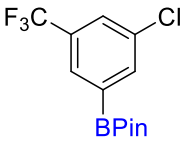
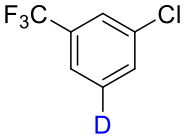
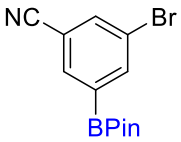
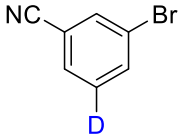
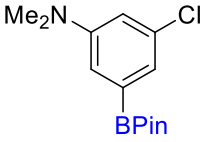
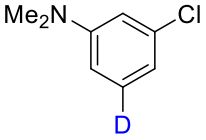
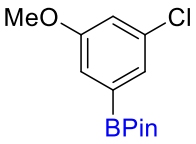
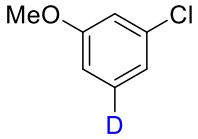


Scheme 3.11: Selective deuterodeborylation reactions

The results of deuterodeborylations are given in Table 2. GC analyses indicated clean conversion to products with lower yields in entries 3 and 4 resulting from loss on isolation. The relative reactivities in deborylation mirror the reactivities of the parent arenes towards borylation, with more electron deficient substrates being more reactive.

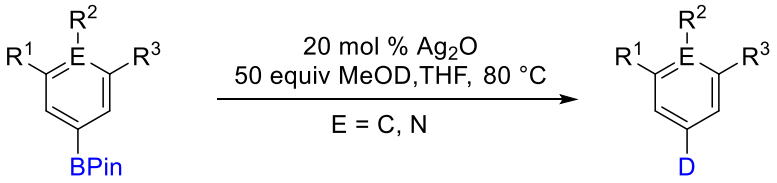
Table 3.4: Selective deuterodeborylation reactions

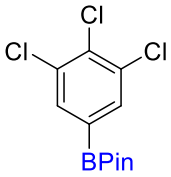
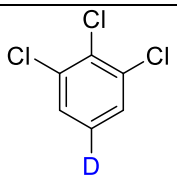
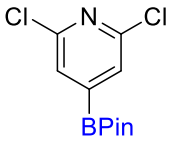
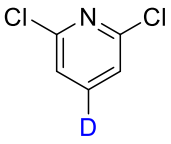
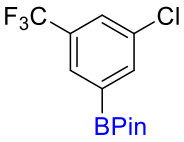
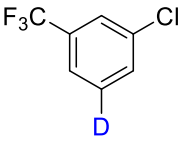
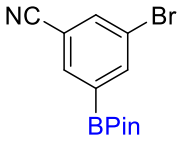
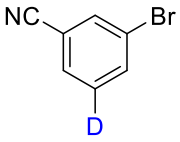
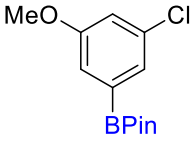
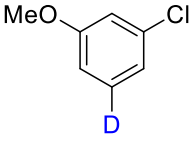
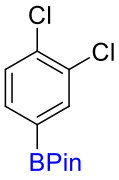
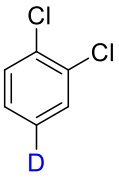


entry	arene	deuteration time	product	yield[b], %D[c]
1		2 h		80%, >98[d]
2		2 h		82%, 96
3		2 h		65%,[e] >98
4		2 h		60%, >98
5		4.5 h		74%, 96
6		3 h		74%, 93

[a]All reactions were run with 2 mmol of organoboronate, [{Ir(OMe)(COD)}] = 0.011 M. scale. [b]Isolated yields. [c]Determined by integration of ^{13}C NMR spectra;[d]~4% 4-deuterated product was observed due to ~4% 4-borylated isomer in the starting material. [e]Owing to product volatility, solvent impurities were present.

Table 3.5: Deuteration protocol for synthesizing deuterated aromatics with Ag_2O.[29]



entry	arene	deuteration time	product	yield, %D[c]
1		1 h		55%,[a] 98
2		1 h		40%,[a] 98
3		2.5 h		78%,[b] 99
4		3 h		60%,[a] 97
5		2 h		62%,[a] 96
6		3 h		91%,[b] 98

[a]Isolated yields. [b]Crude yields

During the course our study on alternative catalytic systems for Ir, for protodeboronations we discovered Ag_2O, which showed remarkable reactivity as compared to $[Ir(OMe)(COD)]_2$. As stipulated in the previous section Ag_2O, was active towards variety of substrate classes and

showed promising deborylations even at room temperature. Further, a general reactivity pattern of Ag> Ir> Bi in deborylating strength was observed. In a rationale to provide a pragmatic and economical alternative to Ir based deuterodeborylation we explored Ag_2O.[29] The borylated arene (1 mmol) was added 20 mol% Ag_2O, 0.1 mL D_2O and 0.5 mL dry THF. The flask was sealed and heated in an oil bath to 80 °C until the reaction was judged complete by TLC thin plate. Upon completion, the mixture was filtered through 1 mL silica gel, dried over $MgSO_4$ and evaporated. Column chromatography (5% ethyl acetate/hexane) afforded the products shown in Table 3.5. As noted, Ag-catalyzed deborylation can be utilized to isotopically label arenes. The overall reactions were clean, producing the deuterated arenes as the only aromatic products in high yields and with greater than 94% deuterium incorporation. Functional groups such as halogens, nitriles, amines and ethers were tolerated. It is important to note here that the Ag-catalyzed deborylation do not require an inert environment to set up the reactions as in the case of Ir-catalyzed deborylation, an added advantage of this novel method.

The Ag-catalyzed deborylations are not limited by substrate electronics. The mild conditions of Ag-catalyzed deuterodeborylation and deborylations could make applications to complex substrates. In summary, we have shown that Ag-catalyzed deuterodeborylation can be utilized to isotopically label unactivated C–H positions of arenes selectively.

REFERENCES

REFERENCES

1. Zhichkin, P. E.; Krasutsky, S. G.; Beer, C. M.; Rennells, W. M.; Lee, S. H.; Xiong, J. M. *Synthesis* **2011**, 1604–1608.

2. Reck, F.; Zhou, F.; Eyermann, C. J.; Kem, G.; Carcanague, D.; Ioannidis, G.; Illingworth, R.; Poon, G.; Gravestock, M. B. *J. Med. Chem.* **2007**, *50*, 4868–4881.

3. (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931. (b) Preshlock, S. M.; Ghaffari, B.; Maligres, P. E.; Krska, S. W.; Maleczka, R. E., Jr.; Smith M. R., III *J. Am. Chem. Soc*. **2013**, *135*, 7572–7582.

4. Cho, J. Y., Tse, M. K., Holmes, D., Maleczka, R. E., Jr. and Smith, M. R., III *Science*. **2002**, *295*, 305-308.

5. Holmes, D.; Chotana, G. A.; Maleczka, R. E., Jr.; Smith, M. R., III *Org. Lett.* **2006**, *8*, 1407 1410.

6. Shi, F.; Smith, M. R., III; Maleczka, R. E., Jr. *Org. Lett.* **2006**, *8*, 1411–1414.

7. Kallepalli, V. A.; Gore, K. A.; Shi, F.; Sanchez, L.; Chotana, G. A.; Miller, S. L.; Maleczka, R. E., Jr.; Smith, M. R., III *J. Org. Chem.* **2015**, *80*, 8341–8353.

8. (a) Vanchura, B. A., II; Preshlock, S. M.; Roosen, P. C. Kallepalli, V. A.; Staples, R. J.; Maleczka, R. E., Jr.; Singleton, D. A.; Smith, M. R., III *Chem. Commun.* **2010**, *46*, 7724–7726. (b) Tajuddin, H.; Harrisson, P.; Bitterlich, B.; Collings, J. C.; Sim, N.; Batsanov, A. S.; Cheung, M. S.; Kawamorita, S.; Maxwell, A. C.; Shukla, L.; Morris, J.; Lin, Z.; Marder, T. B.; Steel, P. G. *Chem. Sci.* **2012**, *3*, 3505–3514.
9. D. W. Robbins, T. A. Boebel and J. F. Hartwig, *J. Am. Chem. Soc.*, **2010**, *132*, 4068-4069.

10. M. Schnürch, M. Spina, A. F. Khan, M. D. Mihovilovic and P. Stanetty, *Chem. Soc. Rev.*, 2007, **36**, 1046-1057.

11. Loach, R. P.; Fenton, O. S.; Amaike, K.; Siegel, D. S.; Ozkal, E.; Movassaghi, M. *J. Org. Chem.* **2014**, *79*, 11254-11263.
12. For a recent selective synthesis of a monoborylated indazole by selective deborylation of a diborylated indazole using KOH see Sadler, S. A.; Hones, A. C.; Roberts, B.; Blakemore, D.; Marder, T. B.; Steel, P. G. *J. Org. Chem.* **2015**, *80*, 5308–5314.

13. (a) Vanchura, B. A., II; Preshlock, S. M.; Roosen, P. C. Kallepalli, V. A.; Staples, R. J.; Maleczka, R. E., Jr.; Singleton, D. A.; Smith, M. R., III *Chem. Commun.* **2010**, *46*, 7724–7726. (b) Tajuddin, H.; Harrisson, P.; Bitterlich, B.; Collings, J. C.; Sim, N.; Batsanov, A. S.; Cheung, M. S.; Kawamorita, S.; Maxwell, A. C.; Shukla, L.; Morris, J.; Lin, Z.; Marder, T. B.; Steel, P. G. *Chem. Sci.* **2012**, *3*, 3505–3514.

14. For representative examples see: (a) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649–5651. (b) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056–3058. (c) Ishiyama, T.; Takagi, J.; Nobuta, Y.; Miyaura, N. *Org. Synth*. **2005**, *82*, 126–133, (d) Paul, S.; Chotana, G. A.; Holmes, D.; Reichle, R. C.; Maleczka, R. E., Jr.; Smith, M. R., III *J. Am. Chem. Soc.* **2006**, *128*, 15552–15553. (e) Meyer, F.-M.; Liras, S.; Guzman-Perez, A.; Perreault, C.; Bian, J.; James, K. *Org. Lett*. **2010**, *12*, 3870–3873. (f) Homer, J. A.; Sperry, J. *Tetrahedron Lett.* **2014**, *55*, 5798–5800.

15. Kobayashi, H.; Sugiura, M.; Kitagawa, H.; Lam, W. *Chem. Rev.* **2002**, *102*, 2227−2302.

16. Mohan, R. *Nat. Chem.* **2010**, *2*, 336.

17. Shen, F.; Tyagarajan, S.; Perera, D.; Krska, S. W.; Maligres, P. E.; Smith, M. R., III; Maleczka, R. E., Jr.; *Org. Lett*. **2016**, *18*, 1554–1557.

18. 10% Deuterium incorporation was initially observed at C3. Washing with H_2O reprotonated this carbon.

19. The percent deuterium incorporation was determined by integration of the ^{1}H-NMR spectrum.

20. We suspect the protodeboronations are slowed by materials leaching from the plastic bottle and/or common MeOH impurities such as formaldehyde, DMAc, and dimethyl acetals of simple alkanones and/or alkanals (Guella, G.; Ascenzi, D.; Franceschi, P.; Tosi, P. *Rapid Commun. Mass Spectrom.* **2007**, *21*, 3337–3344).

21. Harbeson, S. L.; Tung, R. D. In *Annual Reports in Medicinal Chemistry*, Elsevier Academic Press Inc, San Diego: 2011, *46*, pp. 403-417.

22. Halford, B. *Chemical and Engineering news*. **2016**, *94*, 32-33.

23. Kohen, A.; Limbach, H. H. In *Isotope Effects in Chemistry and Biology*, CRC Press, Boca Raton: 2006.

24. Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. *Angew. Chem. Int. Ed.*, **2007**, *46*, 7744-7765.

25. Golden, J. T.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.*, **2001**, *123*, 5837-5838.

26. Grainger, R.; Nikmal, A.; Cornella, J.; Larrosa, I. *Org. Biomol. Chem.*, **2012**, *10*, 3172-3174.

27. Crabtree, R. H.; Holt, E. M.; Lavin, M.; Morehouse, S. M. *Inorg. Chem.*, **1985**, *24*, 1986 - 1992.

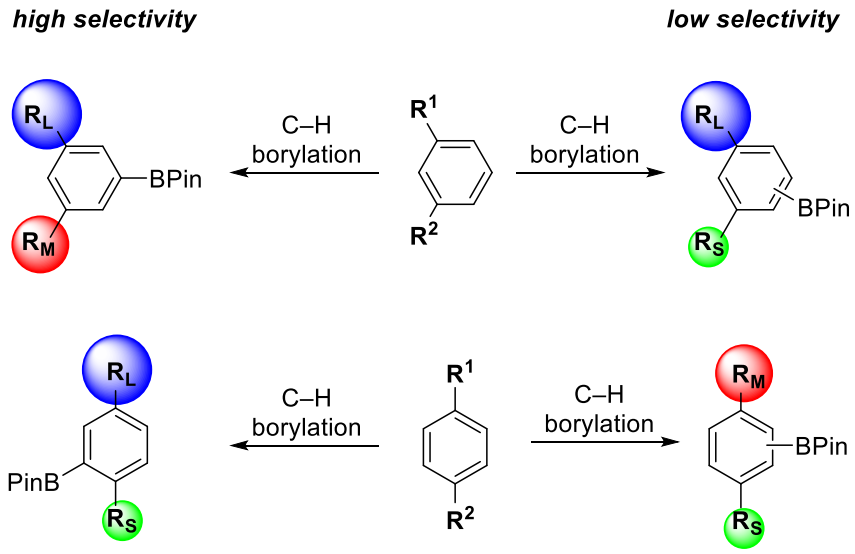
28. Beak, P.; Brown, R. A. *J. Org. Chem.*, **1982**, *47*, 34-46.

29. Our manuscript on this is in preparation and Shen, F. Discovery and the Development of Bismuth Salt Mediated Catalytic Deborylation and Allied Studies. MSc. Thesis, Michigan State University, East Lansing, 2015.

CHAPTER 4. REVERSIBILITY IN Ir-CATALYZED C–H POLYBORYLATION: A BORONIC ESTER DANCE.

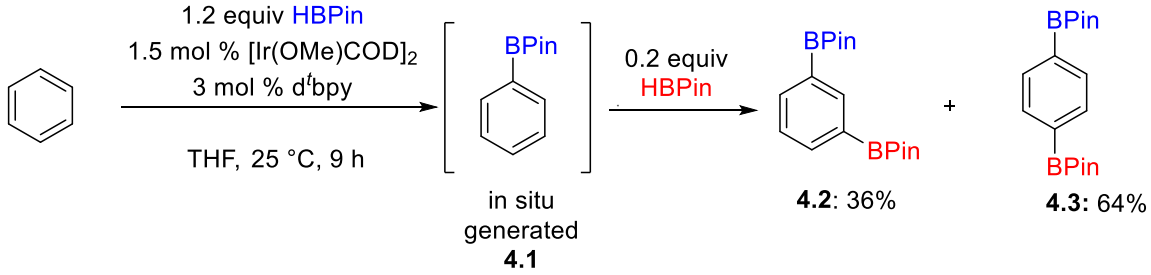
4.1 Introduction

Ir-catalyzed C–H activation/borylation was first reported in 1999.[1] Within two decades this methodology evolved into a synthetic protocol to install a boron group on a pre-functionalized benzene or heterocycle.[2] Ir-catalyzed C–H activation/borylation provides synthetic methodology for aryl and heteroaromatic substitution patterns that are difficult to achieve through traditional methods of electrophylic aromatic substitution (EAS) and directed ortho metallation (D*o*M). Moreover generating boronic esters by Ir-catalyzed C–H activation/borylation obviates the need for prior functionalization (e.g. halogenation), pyrophoric reagents, cryogenic conditions, etc. [3] Earlier studies have characterized many features of this methodology. The Ir-catalyzed C–H activation/borylation tolerates a wide variety of functionalities pre-installed on the aryl or heteroaryl substances. As demonstrated experimentally, steric effects govern the regioselectivity of the Ir-catalyzed C–H activation/borylation in most cases.[4] For example, 1,3-substituted benzenes show exclusive borylation at the sterically accessible meta position given the benzene substituents are sufficiently large to block functionalization of their ortho C–H bonds (Scheme 4.1). For 1,4-substituted benzenes, selective sterically directed C–H borylation can be achieved when the sterics of the substituents differ significantly. When it comes to monosubstituted benzene derivatives, borylation regiochemistry can be directed by the directing group effect of the substituent.



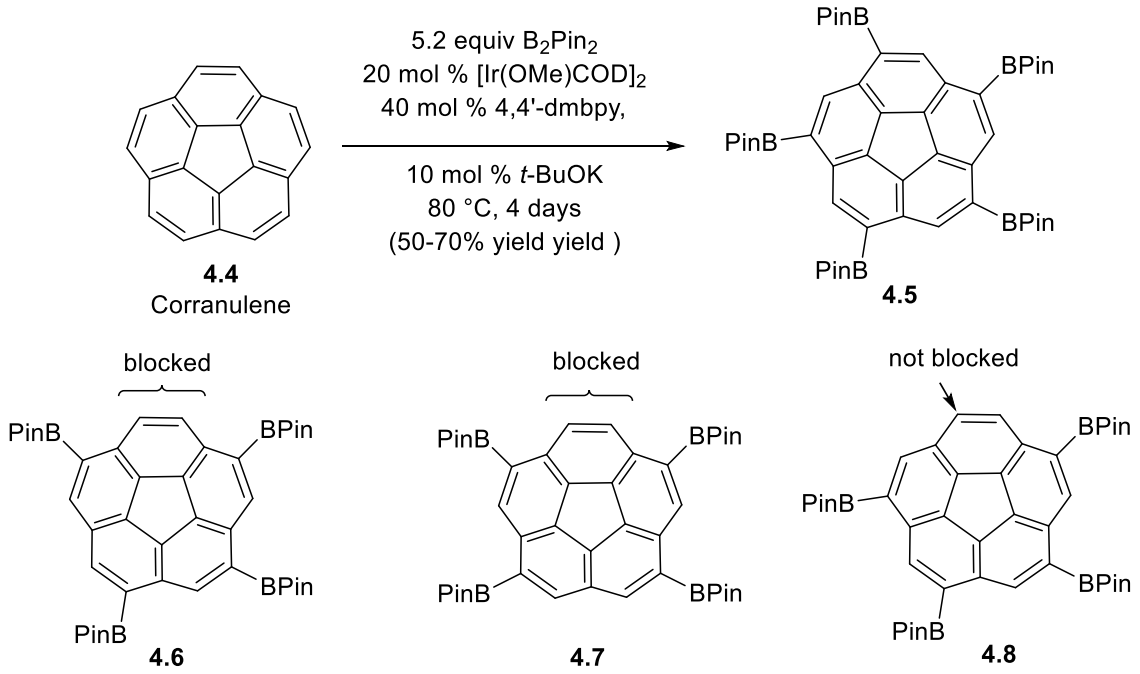
Scheme 4.1: Regioselecivity in Ir-catalyzed C–H activation/borylation

Our group previously established a directing role associated with BPin group.[5] When, benzene was reacted with 1.2 equiv of HBPin in THF in the presence of the Ir catalyst the first equivalent of borane generates PhBPin in situ, and the remaining 0.2 equiv gives the diborylated isomers as shown in Scheme 4.2. The reaction was examined at low conversion to avoid skewing the data by borylation of m-$C_6H_4(BPin)_2$. The para to meta ratio is 1.8:1, significantly greater than the 1:2 statistical ratios. This translates to a 3.6:1 selectivity for para vs meta borylation after statistical corrections. While the origins of this selectivity are not entirely clear, it has been both predicted computationally and proven experimentally that absent overriding steric effects Ir-catalyzed C–H activation/borylation favors more acidic C–H bonds.[5] Thus the electron withdrawing nature of the BPin group may be important in the observed para directing effect.



Scheme 4.2: Directing group effect of Bpin

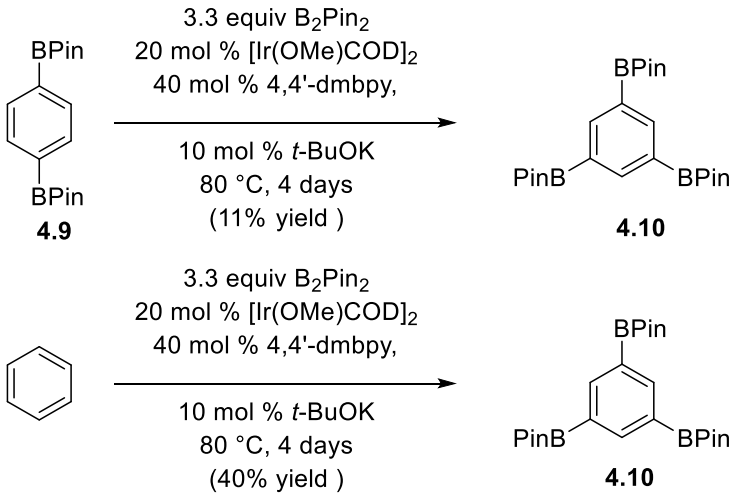
Recently, a report by Eliseeva and Scott [6] revealed the reversibility of Ir-catalyzed aromatic C–H borylations. Such reversibility could be achieved through the use of a relatively large amount of catalyst and ligand along with added *t* -BuOK, and an excess of B_2pin_2. Heating this combination of reagents and arene for a prolonged period provided a convenient method to prepare highly borylated compounds such as 1,3,5,7,9-*pentakis*(Bpin)corannulene **4.5**. (Scheme 4.2) and 1,3,5-*tris*(Bpin)-benzene **4.10** (Scheme 4.3). This finding is remarkable as under standard conditions, the direct borylation of corannulene with B_2pin_2, catalyzed by $[Ir(OMe)COD]_2$ in the presence of various bipyridyl ligands produces 1,3,5,7,9-*pentakis*(Bpin)corannulene (**4.5**), as a mixture with the two *tetrakis*(Bpin)corannulenes (**4.6** and **4.7**), The observed ratio of **4.5** /**4.6** /**4.7** was approximately 1:3:1. In this case, the large steric demand of each Bpin substituent precludes borylation not only in the ortho position on the same ring but also in the peri position on the adjacent ring (Scheme 4.3).



Scheme 4.3: Ir-catalyzed C–H polyborylation of Corranulene

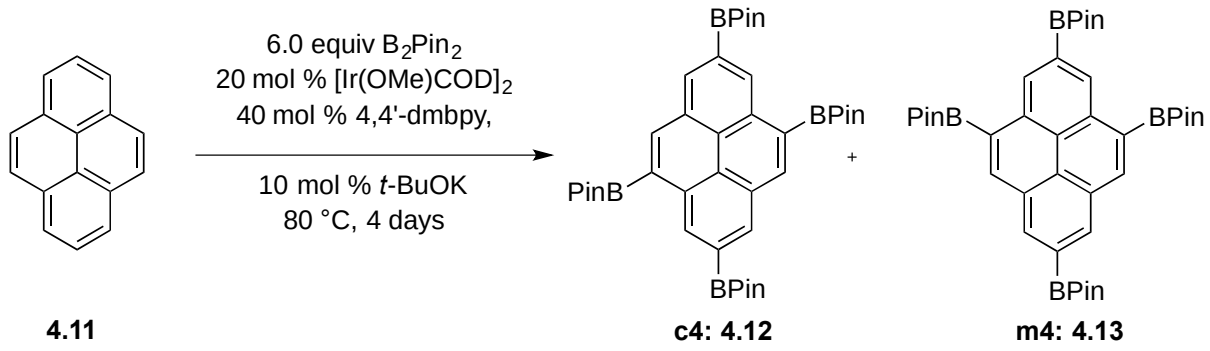
It is evident that in the Eliseeva and Scott work the polyborylation was pushed to the maximum capacity of Bpin's that could be incorporate into the corannulene. The buildup and subsequent disappearance of the "wrong" tetrakis(Bpin)-corannulenes **4.6** and **4.7** clearly indicates that these new conditions provide a kinetically accessible pathway for deborylation of these isomers back temporarily to the tris(Bpin)corannulene stage, thus, imparting a self-correction aspect to the synthesis of **4.5**. The main focus of Eliseeva and Scott's study was on the polyborylation of corannulene and the conditions (ligand, catalyst load, base and solvent) were accordingly optimized, they did further elaborate the reversibility of the Ir-catalyzed aromatic C–H borylation by applying the optimized conditions to benzene and 1,4-*bis*(Bpin)benzene **4.9** borylation (Scheme 4.4). Here they observed complete conversion of 1,4-*bis*(Bpin)benzene (**4.9**) and benzene to 1,3,5-*tris*(Bpin)benzene (**4.10**) under the reversible borylation conditions. By carrying out these reactions under high catalyst load, higher temperature, excess boron source

and longer time period that authors deemed “exhaustive borylation”, seems to have resulted with a new outcome to the typically observed borylation under normal kinetically controlled conditions as stated above Scheme 4.2.



Scheme 4.4: Ir-catalyzed C–H polyborylation of benzene and 1,4-*bis*(Bpin)benzene

Eliseeva and Scott state that this results could be the operation of a deborylation/reborylation “self-correction” process that repositions the Bpin substituents until a pattern that accommodates the maximum number of Bpin substituents is achieved. They further, extended the conditions that were optimized for the polyborylation of corranulene to the polyborylation of pyrene. Eliseeva and Scott stated that polyborylation of pyrene also to follow the deborylation/reborylation “self-correction” process to obtain 2,4,7,9-*tetrakis*(Bpin)pyrene c4-isomer **4.12** and none of the 2,4,7,10-*tetrakis*(Bpin)pyrene m4-isomer of **4.12**. The authors did not investigate the crude product directly after the reaction was finished, but instead followed a workup procedure including solvent removal and washing of the crude product with methanol, giving a white solid after filtration, which was almost pure **4.12**.



4.11 **c4: 4.12** **m4: 4.13**

Scheme 4.5: Ir-catalyzed C–H polyborylation of **4.11**

Marder and co-workers[7] carried out further investigations in order to determine whether or not the reaction results in an equilibrium mixture of c4- : m4-isomers. They attempted to equilibrate pure c4- or m4-isomers (88% pure, vide infra) into a thermodynamic mixture of c4- and m4-isomers using the same conditions as those shown in Scheme 4.5. However, there was no change observed in either case; i.e., the c4-isomer was not converted to the m4-isomer, nor was the m4-isomer converted to the c4-isomer. This showed that the Ir-catalyzed (20 mol %) borylation of pyrene, at least at the 4- and 9/10-positions, is in fact not reversible, even in the presence of *t*-BuOK and large amounts of B_2pin_2. Thus, they concluded that that the c4- : m4-isomer ratios are determined by kinetic selectivity. It should be noted here that Marder and co-workers did confirm that the borylations of benzene, biphenyl, and corannulene are reversible.

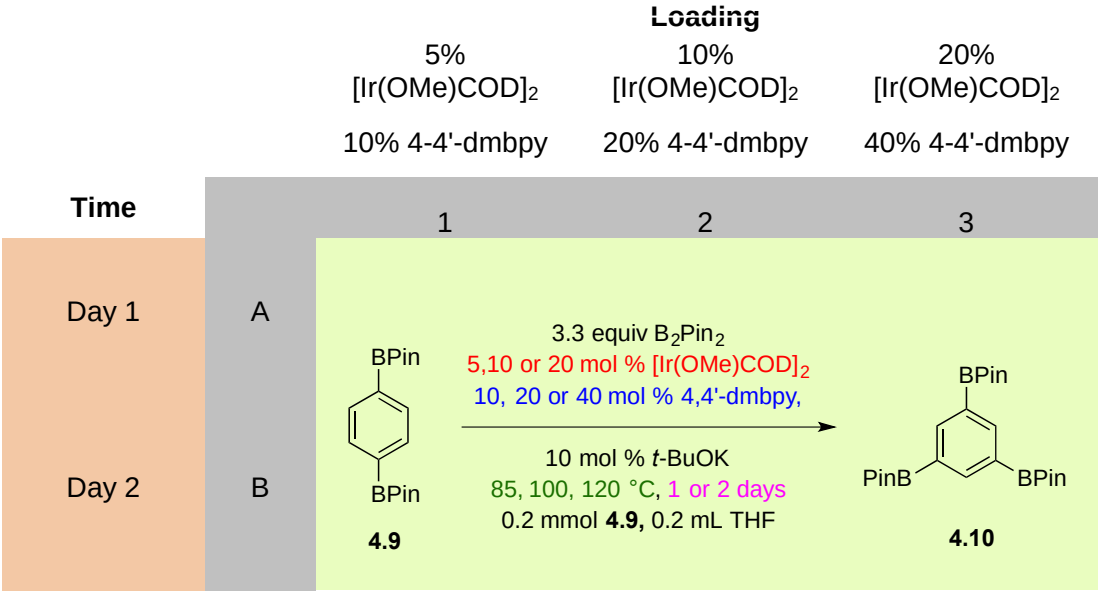
4.2 Optimization of the Ir-catalyzed C–H polyborylation towards 1,3,5-*tris*(Bpin)benzene.

Aside from the work described above, there was very little information available on the polyborylations of other benzene substrates. Eliseeva and Scott described the synthesis of 1,3,5-*tris*(Bpin)benzene (**4.10**) but they never optimized conditions for these substrates or expanded their studies to broaden the substrate scope or to determine the effect of EWG/EDG substitutions on reversibility or final regiochemical outcomes. Intrigued by these studies and the questions these studies evoked, we envisioned to dive deep in to the unchartered territory of polyboration of benzenes derivatives.

4.2.1. Effect of catalysts/ ligand load, reaction time and temperature on the Ir-catalyzed C–H polyborylation of 1,4-*bis*(Bpin)benzene.

To obtain further information regarding the effect of the catalyst/ligand load, temperature and reaction time for the synthesis of 1,3,5-*tris*(Bpin)benzene (**4.10**) from 1,4-*bis*(Bpin)benzene (**4.9**), we designed a set of HTE experiments shown in Figure 4.1. Considering the number of variables we were changing and also the fact that each of the setups shown had to run at three different temperatures, we envisioned to set up reactions using stock solutions of reagents. The reactions were carried out at 0.2 mmol scale of 1,4-*bis*(Bpin)benzene (**4.9**) in biotage microwave vials using THF as the solvent. 1,3,5-Methoxylbenzene, (IS) 0.1 mmol/reaction was used as an internal standard to quantify the reaction. The reactions were sealed and stirred at 85, 100 and 120 °C for 1 or 2 days after which the reactions were analyzed using standard reverse-phase HPLC (see the experimental section).

Figure 4.1: Ir-catalyzed C–H polyborylation of 1,4-*bis*(Bpin)benzen



This experiment yielded several intriguing results and some of the important trends will be highlighted herein. It was observed that there is a striking effect of the $[Ir(OMe)COD]_2$ catalyst and 4,4′ -dimethyl-2,2′ -bipyridine (dmbpy) loadings for the synthesis of 1,3,5-*tris*(Bpin)benzene (**4.10**) in THF (Figure 4.2a, 4.2b and 4.2c). Figure 4.2a depicts the HPLC chromatogram of the reactions with 5 mol % $[Ir(OMe)COD]_2$ and 10 mol % dmbpy at 120 °C for 1 day. As illustrated, with 5 mol% $[Ir(OMe)COD]_2$ none of the expected product (**4.10**) was observed. Interestingly, we did observe a new product with a retention time of 1.66 min that showed the same mass as of the desired product. To our delight we were able to isolate this compound and deduced it to be the 1,2,4-*tris*(Bpin)benzene (**4.14**). Compound **4.14** was isolated in 18% yield (Scheme 4.5).[8]

Figure 4.2a: 5 mol% $[Ir(OMe)COD]_2$, 10 mol% dmbpy, 120 ^{o}C, 1 day

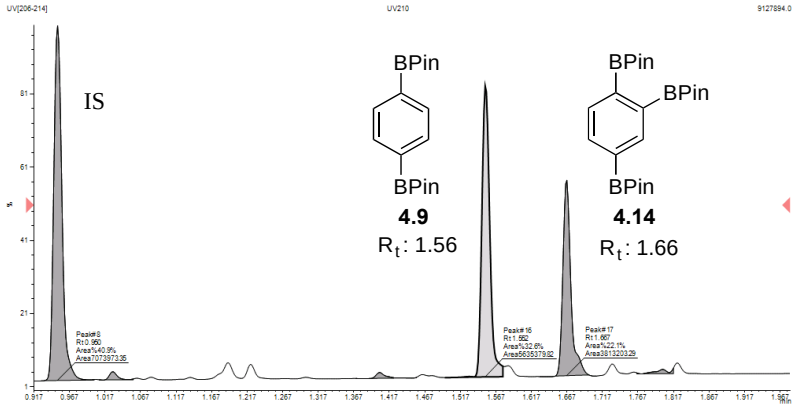


Figure 4.2b: 10 mol% $[Ir(OMe)COD]_2$, 20 mol% dmbpy, 120 ^{o}C, 1 day

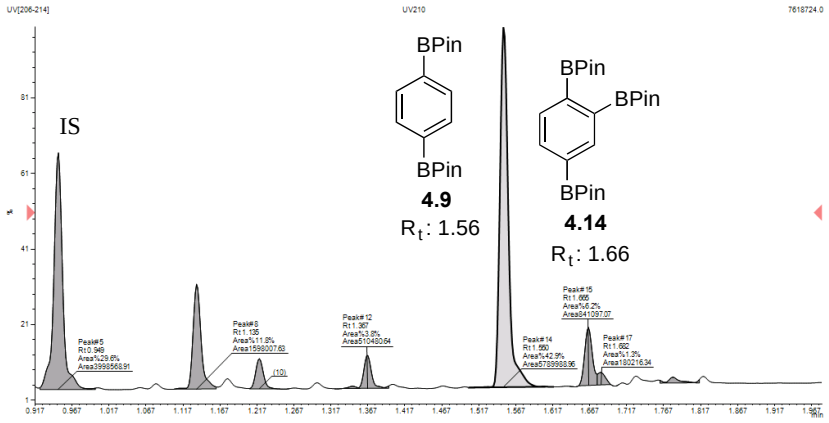
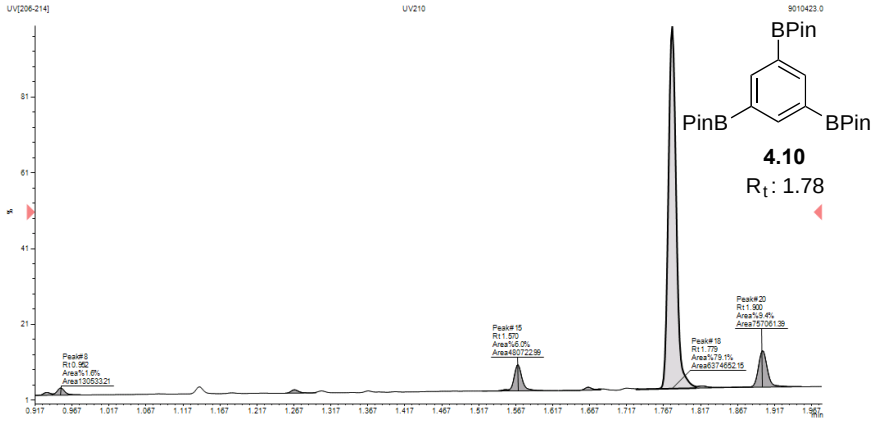
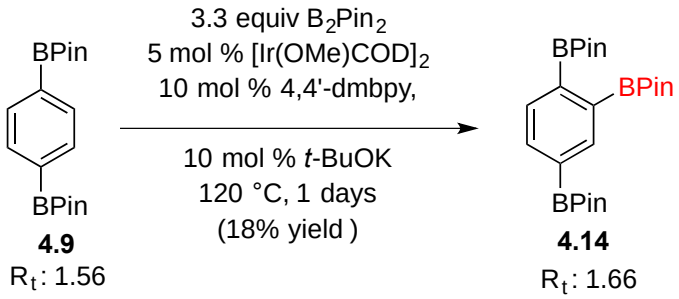


Figure 4.2c: 20 mol% $[Ir(OMe)COD]_2$, 40 mol% dmbpy, 120 ^{o}C, 1 day



It should be noted here that this observation and the isolation of 1,2,4-*tris*(Bpin)benzene (**4.14**) took us by surprise as to the best of our knowledge an installation of a Bpin ortho to another Bpin during Ir-catalyzed C–H activation/borylation had never been reported.[8]



Scheme 4.6: Ir-catalyzed C–H polyborylation of 1,4-*bis*(Bpin)benzene

Further analysis of the data obtained for the synthesis of **4.10** with 5 mol % $[Ir(OMe)COD]_2$ and 10 mol % dmbpy at 120 °C, are summarized in Table 4.1.

Table 4.1: Ir-catalyzed C–H polyborylation of 1,4-*bis*(Bpin)benzene

		Substrates % at each temperature [a,]					
		85 °C		100 °C		120 °C	
		4.9	**4.14**	**4.9**	**4.14**	**4.9**	**4.14**
1	Day 1	75	25	68	32	60	40
2	Day 2	86	14	70	30	63	37

[a]Reactions were carried out with 5 mol % $[Ir(OMe)COD]_2$ and 10 mol % 4-4'-dmbpy

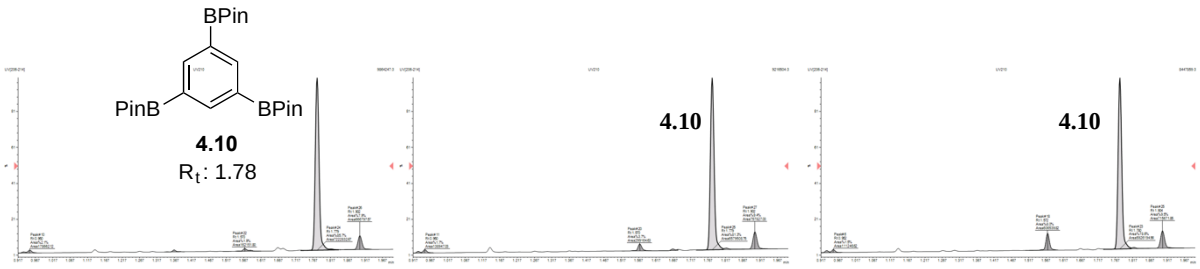
As noted earlier, none of the expected product (**4.10**) was observed regardless of the increment of temperature or reaction time. On the other hand, it is evident that the production of 1,2,4-*tris*(Bpin)benzene **4.14** increased with increment of the temperature, with yields of 25% at 85 °C and 40% at 120 °C (Entry 1). Interestingly, yields did not change significantly when the temperature was increased from 100 °C to 120 °C. Moreover, it was noted that running the reaction for 2 days was not advantageous (entry 2).

Figure 4.2b depicts the HPLC chromatogram of the reaction run with 10 mol % $[Ir(OMe)COD]_2$ and 20 mol % dmbpy at 120 °C for 1 day. Again, as illustrated, none of the expected product (**4.10**) was observed. Under these conditions though, the reaction was not clean and afforded a collection of unidentified products. To our surprise, it is evident that compared to reactions run with 5 mol % $[Ir(OMe)COD]_2$ the amount of 1,2,4-*tris*(Bpin)benzene **4.14** was also low. This observation is true for all the other reactions carried out with 10 mol % $[Ir(OMe)COD]_2$ catalyst load. During data analysis we observed that our added internal standard 1,3,5-methoxylbenzene decomposed under higher catalyst loads of Ir. Hence, more quantitative analysis was not possible. To our delight we observed full conversion of 1,4-*bis*(Bpin)benzene (**4.9**) to 1,3,5-*tris*(Bpin)benzene (**4.10**) with 20 mol % $[Ir(OMe)COD]_2$ and 40 mol % dmbpy (Figure 4.2c) at 85 ^{o}C for 1 day (see experimental section). Interestingly, this observation cut down the reaction time by 3 days compared what was reported by Scott *et.al*. In our view, this represents a significate advantage for the implementation of this methodology to other Ir-catalyzed C–H polyborylations. Moreover, this result demonstrates that it is necessary to start the reaction with a higher catalyst load (20 mol % $[Ir(OMe)COD]_2$, 40 mol % dmbpy) to even have a chance of getting to 1,3,5-*tris*(Bpin)benzene (**4.10**). It is clear from our observations that in order to obtain 1,3,5-*tris*(Bpin)benzene (**4.10**) that a borylation/deborylation process takes place, as

Scott *et.al*. claimed, to install the maximum number of Bpin groups. The formation of 1,2,4-*tris*(Bpin)benzene (**4.14**) at low catalyst load (5 mol % $[Ir(OMe)COD]_2$, 10 mol % dmbpy) and the halting of the reaction so as to stop any forward progress towards 1,3,5-*tris*(Bpin)benzene (**4.10**) even with higher temperatures and longer reaction times raises several questions. Does 1,2,4-*tris*(Bpin)benzene (**4.14**) act as an intermediate which undergoes deborylation to yield 1,3-*bis*(Bpin)benzene, which could reborylate to give 1,3,5-*tris*(Bpin)benzene (**4.10**) or is it immune to deborylation which leads to the observation at lower catalyst loads.

Further, with regards to the effect of temperature on this reaction as depicted in Figure 4.3, quantitative conversion of 1,4-*bis*(Bpin)benzene (**4.9**) to 1,3,5-*tris*(Bpin)benzene (**4.10**) observed even at 85 ^{o}C. This suggests that higher temperature like 120 ^{o}C to be not advantageous.

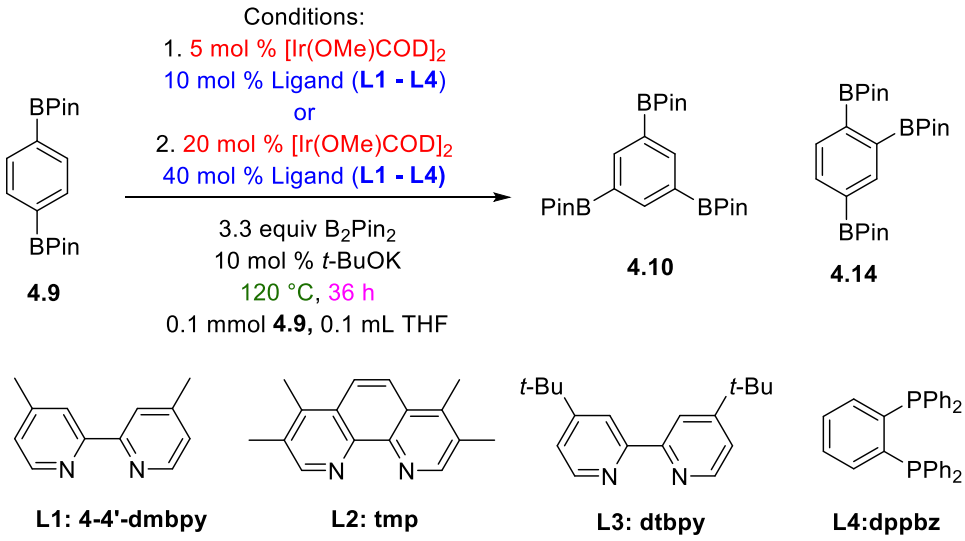
Figure 4.3: (a) 85 ^{o}C , (b) 100 ^{o}C (c) 120 ^{o}C at 20 mol % $[Ir(OMe)COD]_2$, 40 mol % dmbpy, 1 day



(a) 85 ^{o}C **(b)** 100 ^{o}C **(c)** 120 ^{o}C

4.2.2. Effect of ligand and base on the Ir-catalyzed C–H polyborylation of 1,4-*bis*(Bpin)benzene.

Encouraged by this preliminary result, we next investigated whether there is an effect from the ligand. The selected ligands are shown in Scheme 4.6. We carried out this set of experiments at two different catalyst loadings (5 mol% Ir dimer and 20 mol % Ir dimer) as we have previously observed a significant catalyst loading dependence for this transformation. The reactions were setup in HTE fashion with the use of stock solutions at 0.1 mmol scale with 0.1 mL THF as solvent and the data are summarized in the Table 4.7.



Scheme 4.7: Effect of ligand on Ir-catalyzed C–H polyborylation of 1,4-*bis*(Bpin)benzene

The borylation of **4.9** with B_2pin_2, catalyzed by $[Ir(OMe)COD]_2$, shows a strong dependence on the choice of ligand used. Borylations with 1,2-Bis(diphenylphosphino)benzene (dppbz) in THF at 120 °C did not give product for any combination of catalyst loadings. Phosphine ligands have been used in catalytic borylations prior but it is observed that the reactive catalytic system to be less active than the ones generated in situ with nitrogen chelate ligands.[3] The effects of the ligand

were dramatic with 3,4,7,8- tetramethyl-1,10-phenanthroline (tmp) outperforming 4,4′-di-tert-butyl-2,2′-bipyridine (dtbpy) and dmbpy. With the tmp ligand 65 % and 67 % of **4.10** was obtained at 5 mol% and 10 mol% Ir catalyst respectively and the higher catalyst load was not advantageous. If it the objective to obtain **4.14**, then the choice of ligand would be dmbpy at 5 mol % Ir catalyst loading. In contrast to dtbpy and dmbpy, the electron rich tmp ligand helps to generate more active electron-rich catalysts that drive the borytation, which is consistent with previously observed Ir catalyzed borylation methodologies. [3]

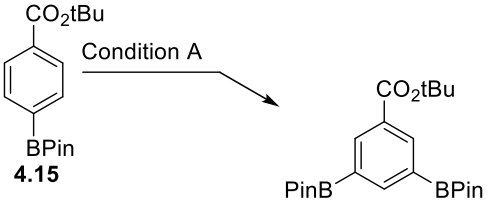
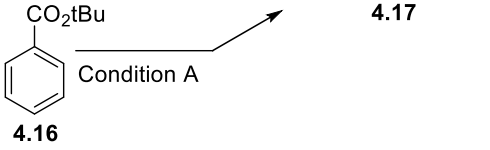
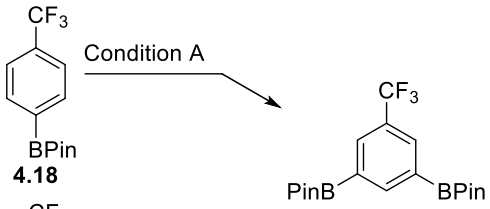
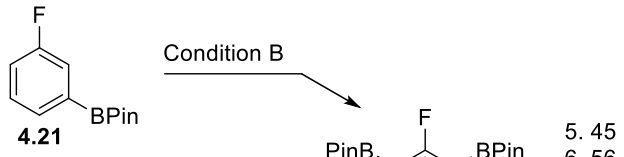
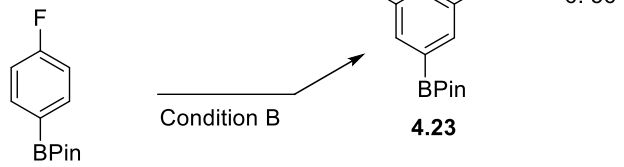
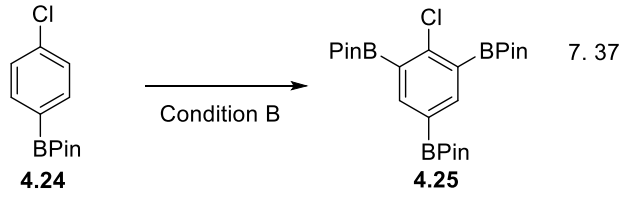
Table 4.2: Effect of ligand for Ir-catalyzed C–H polyborylation of 1,4-*bis*(Bpin)benzene

		Yield of **4.10** and **4.14** at each condition [a] (yields determined by HPLC)			
		Condition 1 5 mol % $[Ir(OMe)COD]_2$ 10 mol % Ligand (**L1 - L4**)		**Condition 2** 20 mol % $[Ir(OMe)COD]_2$ 40 mol % Ligand (**L1 - L4**)	
Entry	**Ligand**	**4.10**	**4.14**	**4.10**	**4.14**
1	**L1**: dmbpy	0	18	25	9
2	**L2**: tmp	65	3	67	0
3	**L3**: dtbpy	0	0	0	5
4	**L4**: dppbz	0	0	0	0

[a]Reactions condition 1: 5 mol% $[Ir(OMe)COD]_2$, 10 mol % tmp, THF at 120 °C, Reactions condition 2: 20 mol% $[Ir(OMe)COD]_2$, 40 mol % tmp, THF at 120 °C,

One other key part in this transformation of Ir-catalyzed C–H polyborylation of 1,4-*bis*(Bpin)benzene is the base. During the course of the studies of polyborylation of corannulene and pyrene, Eliseeva and Scott [6] revealed that there is a ligand specific base dependence for the reaction. They found out that the dmpby ligand works better in the in the presence of *t*–BuOK. But when 5,5´-dmbpy and dtbpy are used as the ligand, added base has little or no effect on the product distribution. Eliseeva and Scott suggested, the dmbpy ligand may be deprotonated by t-BuOK and thus become a stronger donor. It is important to note here that the base tmp was not utilized in the studies of Eliseeva and Scott and hence we were curious to see whether the use of *t*–BuOK is really necessary for this transformation. The borytation of 1,4-*bis*(Bpin)benzene (**4.9**) was carried out with 20 mol% $[Ir(OMe)COD]_2$, 40 mol% tmp, excess B_2pin_2 at 120 ^oC in THF with added *t*–BuOK and another one with no added *t*–BuOK. To our surprise almost quantitate conversions to the product 1,3,5-*tris*(Bpin)benzene (**4.10**) was observed in both with base and without and thus, the added base has no significant effect for this particular transformation. With the optimized conditions in hand, we then proceed to test the scope of the Ir-catalyzed C–H polyborylation with respect to other substituted benzene substrates. As shown in table 4.3, entry 1, 4-Bpin-*tert*-butylbenzoate (**4.15**) was subjected to reaction condition A (20 mol% $[Ir(OMe)COD]_2$, 40 mol % tmp, THF at 120 °C) to obtain 3,5-di(Bpin)*tert*-butylbenzoate (**4.17**) in 60 % isolated yield. Similarly, 4-Bpin-trifluoromethylbenzene (**4.18**) yielded 3,5-di(Bpin)-trifluoromethylbenzene (**4.19**) in 61 % yield (entry 3). These two examples suggest that as describe earlier that indeed a deborylation/borylation process is taking place in order to achieve the stable 3, 5-disubstituted boronic ester derivatives. Further, polyboryation of *tert*-butylbenzoate (**4.16**) and α,α,α-trifluorotoluene (**4.19**) also lead to the stable 3, 5- disubstituted boronic ester derivatives (entry 2 and entry 4).

Table 4.3: Ir-catalyzed C-H polyborylation of arenes

Entry	Substrate	Product	Yields[a]
1			1. 60
2			2. 79
3			3. 61
4			4. 58
5			5. 45
6			6. 56
7			7. 37

[a]Yields refer to spectroscopically pure products

Conditon A: 20 mol% $[Ir(OMe)COD]_2$, 40 mol % tmp, THF at 120 °C

Conditon B: 5 mol% $[Ir(OMe)COD]_2$, 10 mol % tmp, THF at 120 °C

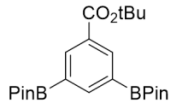
The Ir-catalyzed C–H activation/borylation is governed by steric effect and when a relatively large group like -CO_2tBu or -CF_3 is incorporated in the benzene ring, adding the incoming Bpin group ortho to the substitution is very unlikely (Scheme 4.1). In contrast, relatively small groups like fluorine allow the installation of another Bpin group ortho to the substitution as seen during the polyborylation of 3-Bpin-fluorobenzene (**4.21**) and 4-Bpin-fluorobenzene (**4.22**) (entry 5 and 6). Though it's not obvious to whether there is a deborylato/borylation process involved in the entry 6 as the product 2,4,6-tris(Bpin)fluorobenzene (**4.23)** could be simply resulted from borylation othro to fluorine group, the polyborylation of 3-Bpin-fluorobenzene (**4.21**) suggest otherwise. Moreover, polyborylation of 4-Bpin-chlorobenzene (**4.24**) (entry 6) was resulted with 2,4,6-tris(Bpin)chlorobenze (**4.25**).

4.3. Conclusion

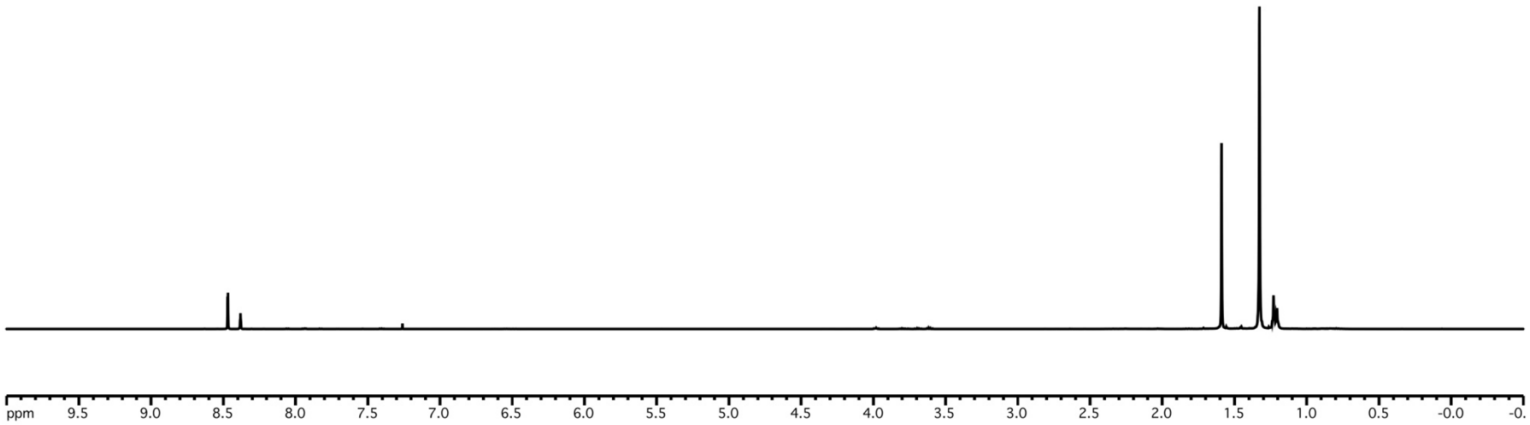
In conclusion, we have studied the polyborylation of aromatic arenes. The Ir catalysts facilitate reactions not only in the forward direction (e.g., borylation) but, inescapably, also in the reverse direction. In principle, therefore, all arene borylations should eventually lead to exhaustive borylation, even under the normal borylation conditions, if they are run long enough with an excess of borylating agent (Le Châtlier' s principle). The more exothermic the forward reaction, of course, the slower will be the reverse reaction. We also have found that despite the previous reports, a catalytic amount of base has no effect on the deborylation of arenes under the borylation conditions. Further, we have developed a method where it extends the capability of synthesizing novel boronic ester analogs that are hard or incapable to achieve from typical borylation conditions.

APPENDIX

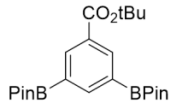
^{1}H-NMR, 500 MHz, $CDCl_3$



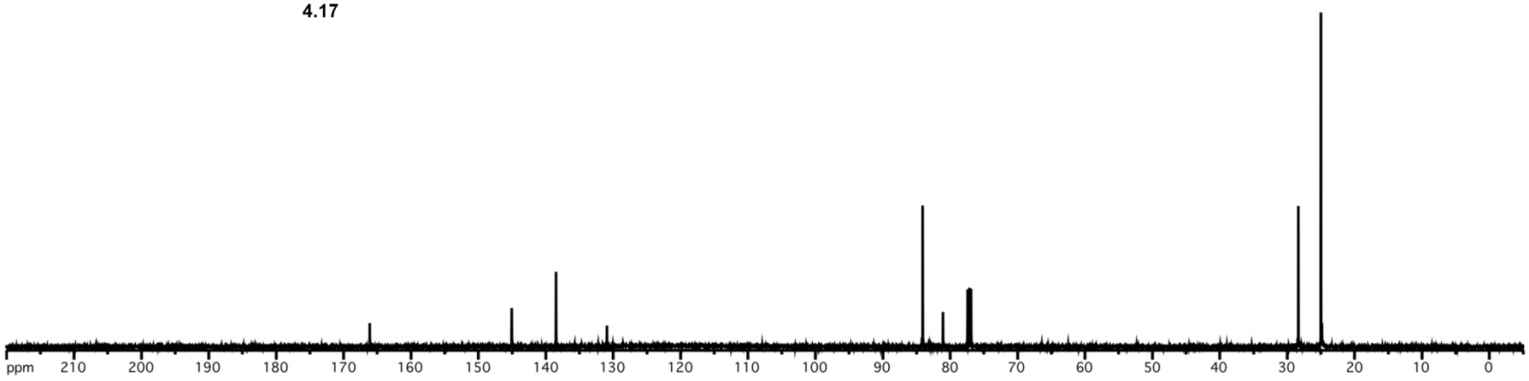
4.17



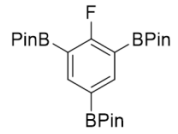
^{13}C-NMR, 126 MHz, $CDCl_3$



4.17

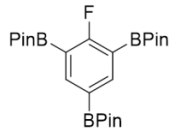


^{1}H-NMR, 500 MHz, $CDCl_3$



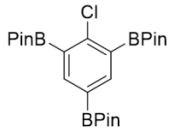
4.23

^{13}C-NMR, 126 MHz, $CDCl_3$

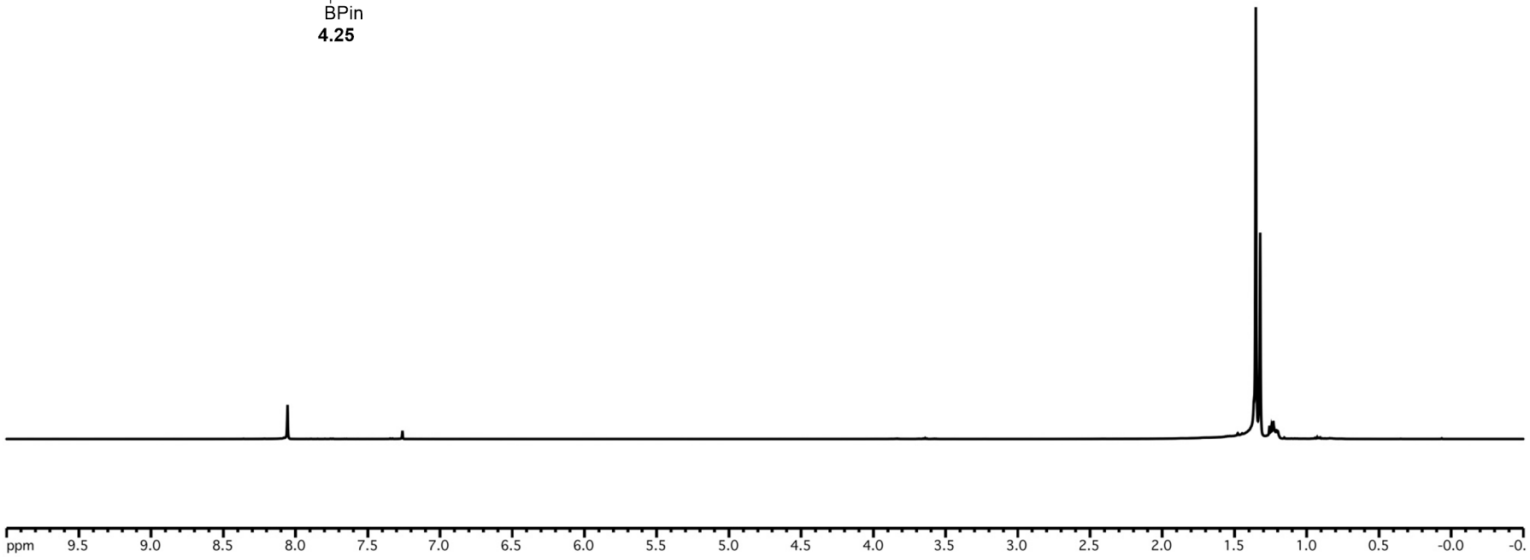


4.23

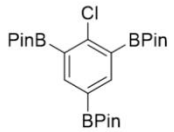
^{1}H-NMR, 500 MHz, $CDCl_3$



4.25



^{13}C-NMR, 126 MHz, $CDCl_3$



4.25

REFERENCES

REFERENCES

1. Iverson, C. N.; Smith, M. R. *J.Am.Chem.Soc*. **1999**, *121*, 7696-7697.

2. (a) Smith, M. R.; Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E. Jr. *Science* **2002**, *295*, 305–308. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390–391. (c) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931.

3. Preshlock, S. M.; Ghaffari, B.; Maligres, P. E.; Krska, S. W.; Maleczka, R. E., Jr.; Smith M. R., III *J. Am. Chem. Soc*. **2013**, *135*, 7572–7582.

4. (a) Chotana, G. A.; Rak, M. A.; Smith, M. R. *J. Am. Chem. Soc.* **2005**, *127*, 10539-10544. (b) Maleczka, R. E.; Shi, F.; Holmes, D.; Smith, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 7792-7793.

5. (a) Vanchura, B. A.; Preshlock, S. M.; Roosen, P. C.; Kallepalli, V. A.; Staples, R. J.; Maleczka, R. E.; Singleton, D. A.; Smith, M. R. *Chem. Commun.* **2010**, *46*, 7724-7726. (b) Tajuddin, H.; Harrisson, P.; Bitterlich, B.; Collings, J. C.; Sim, N.; Batsanov, A. S.; Cheung, M. S.; Kawamorita, S.; Maxwell, A. C.; Shukla, L.; Morris, J.; Lin, Z. Y.; Marder, T. B.; Steel, P. G. *Chem. Sci.* **2012**, *3*, 3505-3515.

6. Eliseeva, M. N.; Scott, L. T. *J. Am. Chem. Soc*. **2012**, *134*, 15169−15172.

7. Ji, L., Fucke, K., Bose, S. K., Marder. T. B. *J. Org. Chem*. **2015**, *80*, 661-665

8. The isolated product of 1,2,4-*tris*(Bpin)benzene contained 10% impurity of 1,4 *bis*(Bpin)benzene.

CHAPTER 5. EXPERIMENTAL

5.1. Experimental details for Chapter 2: Telescoping C–H Borylations with Photoredox and Imidazolylsulfonate Chemistry

General Materials and Methods

Catalytic reaction mixtures were prepared in a glove box. All reactions were carried out oven-dried glassware under an N_2 atmosphere, unless otherwise noted. HBPin was purchased from Aldrich, and further purified by stirring with PPh_3 to remove residual BH_3, and vacuum transferred at room temperature to give the borane as a clear viscous liquid. All solvents were reagent grade. Diethyl ether, cyclohexane and tetrahydrofuran (THF) were distilled from sodium/benzophenone under nitrogen atmosphere before use. Dimethylformamide (DMF) was treated with calcium hydride, distilled, and stored over freshly activated 4Å molecular sieves. Freeze-pump-thaw method was the preferred technique for solvent degassing. 1,3-Bis(trifluoromethyl)benzene and 1,3-dichlorobenzene were distilled, dried over 4Å sieves, and vacuum transferred to an air free flask. Unless otherwise specified all the imidazolylsulfonates used, were prepared by Dr. Jennifer Albaneze-Walker. 4,4′-Di-t-butyl-2,2′-bipyridine (d^{t}bpy) was purchased from Aldrich. $[Ir(OMe)(COD)]_2$ was prepared according to literature procedures.[1] Palladium catalyst $PdCl_2$(dppf) and Ruthenium catalyst $Ru(bpy)_3Cl_2$ were purchased from Aldrich and used as received. Column chromatography was performed on 60 Å silica gel (230–400 mesh). NMR spectra were recorded on Varian spectrometers: Inova-300 (300.11 MHz for ^{1}H and 75.47 MHz for ^{13}C and 96.29 MHz for ^{11}B), Varian VXR-500 (499.74 MHz for ^{1}H and 125.67 MHz for ^{13}C), Varian Unity-500-Plus (499.74 MHz for ^{1}H and 125.67 MHz for ^{13}C). ^{1}H and ^{13}C chemical shifts (in ppm) were referenced to residual solvent signals: $CDCl_3$ (δ 7.24 for ^{1}H and 77.0 for ^{13}C) and DMSO-d_6 (δ 2.49 for ^{1}H and 39.5 for ^{13}C). ^{11}B chemical shifts were

referenced to neat $BF_3.Et_2O$ (δ 0.0 ppm) as external standard. ^{19}F NMR was referenced to neat $CFCl_3$ as the external standard. Melting points were recorded on a MEL-TEMP® capillary melting point apparatus and are uncorrected. Low-resolution mass spectra were acquired using gas chromatography-mass spectrometry (GC-MS) on a HP 5890 series II GC coupled to a VG Trio-1 mass spectrometer operated in EI+ mode (70 eV). High-resolution mass spectra were acquired at the MSU Mass Spectrometry facility using a Waters GCT Premier GC/TOF instrument (EI, CI), a JEOL HX-110 double-focusing magnetic sector instrument (FAB), or a Waters QTOF Ultima mass spectrometer (APCI, ESI).

General Procedure for C–H Activation/Borylation (Procedure A).

Unless otherwise specified, all reactions followed this general procedure. The Ir-catalyst was generated by a modified literature protocol,[1] where in a glove box, a Schlenk flask, equipped with a magnetic stirring bar, was charged with the corresponding substrate (1 mmol, 1 equiv). Two separate test tubes were charged with $[Ir(OMe)(COD)]_2$ (10 mg, 0.015 mmol, 3 mol % Ir) and d^{t}bpy (8 mg, 0.03 mmol, 3 mol %). Excess HBPin/B_2Pin_2 (1.0 to 2 equiv) was added to the $[Ir(OMe)(COD)]_2$ containing test tube. Solvent (Cyclohexane/THF) (1 mL) was added to the d^{t}bpy containing test tube in order to dissolve the d^{t}bpy. The d^{t}bpy solution was then mixed with the $[Ir(OMe)(COD)]_2$ and HBPin//B_2Pin_2 mixture. After mixing for one minute, the resulting solution was transferred to the Schlenk flask. Additional solvent (1 mL) was used to wash the test tubes and the washings were transferred to the Schlenk flask. The flask was stoppered, brought out of the glove box, and attached to the Schlenk line in a fume hood. The Schlenk flask was placed under N_2 and the reaction was carried out at the specified temperature. NOTE, room temperature borylations were carried out inside the glove box after sealing the Schlenk flask. Unless otherwise specified, cyclohexane used as the solvent for borylations. The reaction was

monitored by GC-FID/MS. After completion of the reaction, the volatile materials were removed on a rotary evaporator.

General Procedure for Suzuki Coupling

Suzuki coupling with pure boronic esters (Procedure B).

A Schlenk flask was charged with imidazolylsulfonate (1 equiv), aryl boronic ester (1 equiv) and potassium carbonate (2 equiv) in DMF (0.05 g/mL). Then, the reaction mixture was degassed three times by freeze-pump-thaw degassing method. Next, (dppf)$PdCl_2$ catalyst (10 mol%) was added to the Schlenk flask under a nitrogen purge. Finally, the reaction was stirred at 60°C in an oil bath for 16 h and was cooled to room temperature and diluted with EtOAc and H_2O. The layers were separated and aqueous phase was washed with EtOAc (3X). The combined organic extracts were washed with water (3X), dried ($MgSO_4$), concentrated and purified by flash chromatography on silica provided the product.

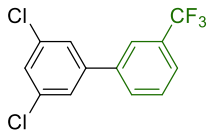
General Procedure for One-pot C–H acitivation/borylation Suzuki Coupling:

(Procedure C).

The borylation was carried out as given in general procedure for C–H Activation/Borylation. After completion of the reaction, the volatile materials were removed on a rotary evaporator. Then, the Schlenk flask was charged with imidazolylsulfonate (1 equiv) and potassium carbonate (2 equiv) in DMF (0.05 g/mL). The reaction mixture was degassed three times by freeze-pump-thaw degassing method. Next, (dppf)$PdCl_2$ catalyst (10 mol%) was added to the Schlenk flask under a nitrogen purge. Finally, the reaction was stirred at 60°C in an oil bath for 16 h and was cooled to room temperature and diluted with EtOAc and H_2O. The layers were separated and aqueous phase was washed with EtOAc (3X). The combined organic extracts were washed with

water (3X), dried ($MgSO_4$), and concentrated. Purification by flash chromatography on silica provided the products listed in Table 1 and Table 2.

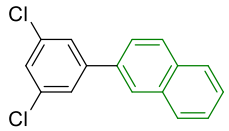
Experimental details for one-pot C–H acitivation/borylation Suzuki Coupling products.



2.3

3,5-dichloro-3'-(trifluoromethyl)-1,1'-biphenyl (2.3).

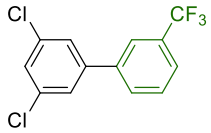
The general procedure B for Suzuki coupling was applied with the following amounts; 3-Trifluoromethylphenylimidazolesulfonate (292.3 mg, 1 mmol), 2-(3,5-dichlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (273.0 mg, 1 mmol), (dppf)$PdCl_2$ (73.2 mg, 0.10 mmol), K_2CO_3 (276.4 mg, 2 mmol) and DMF (5.5 mL). Suzuki reaction was carried out at 60 °C for 9 h. Column chromatography on silica eluting with a gradient of hexanes to 8:2 hexane/ EtOAc gave 192.7 mg (66.0 %) of 3,5-dichloro-3'-(trifluoromethyl)-1,1'-biphenyl as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38 (t, J = 1.8 Hz, 1H), 7.45 (s, 2H), 7.58-7.55 (m, 1H), 7.66-7.63 (m, 1H), 7.71-7.69 (m, 1H), 7.75 (td, J = 1.6, 0.8 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 122.81 (d, J = 272.5 Hz), 123.91 (q, J = 3.7 Hz), 125.14 (q, J = 3.7 Hz), 125.74, 127.97, 129.58, 130.37, 131.56 (q, J = 33.5 Hz), 135.60, 139.37, 142.67 (two Sp^2 C, overlapping with each other); FT-IR (neat) $\tilde{\nu}_{max}$: 3093, 2917, 1583, 1433, 1211, 1169, 1054, 936, 862, 810; ^{19}F NMR d -62.4 ; MS *m/z* (rel. int.) 290 (100), 271 (12), 221 (7), 201 (20), 152 (17).



2.4

1-(3,5-dichlorophenyl)naphthalene (2.4).

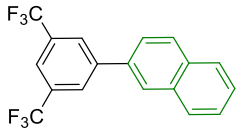
The general procedure B with the following amounts; Imidazole-1-sulfonatenapthalene (274.3 mg, 1 mmol), 2-(3,5-dichlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (273.0 mg, 1 mmol), (dppf)$PdCl_2$ (73.2 mg, 0.10 mmol), K_2CO_3 (276.4 mg, 2 mmol) and DMF (5.5 mL). Suzuki reaction was carried out at 60 °C for 16 h. Column chromatography on silica eluting with a gradient of hexanes to 8:2 hexane/ EtOAc gave 370 mg (68.0 %) of 1-(3,5-dichlorophenyl)naphthalene as a white solid. mp = 86 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, *J* = 1.3 Hz, 1H), 7.54-7.50 (m, 2H), 7.56 (s, 2H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.88 (m, 3H), 7.96 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 124.76, 125.80, 126.17, 126.57, 126.63, 127.14, 127.65, 128.28, 128.80, 133.00, 133.41, 135.30, 135.70, 144.04. HRMS (EI): *m/z* calculated for $C_{16}H_{10}Cl_2$ $[M]^+$ 272.0160, found 272.0150.



2.7

3,5-dichloro-3'-(trifluoromethyl)-1,1'-biphenyl (2.7) via one-pot C–H activation/borylation/ Suzuki sequence.

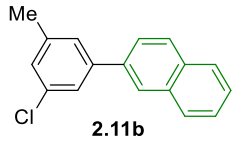
The general procedure for borylations (Procedure A) and one-pot C–H acitivation/borylation Suzuki coupling (Procedure C) with the following amounts: HBPin (217 μL, 1.5 mmol), $[Ir(OMe)(COD)]_2$ (6.6 mg, 0.01 mmol), d^tbpy (5.4 mg, 0.02 mmol), 1,3-dichlorobenzene (123 μL, 1.0 mmol), 3-Trifluoromethylphenylimidazolesulfonate (292.3 mg, 1 mmol), $(dppf)PdCl_2$ (73.17 mg, 0.10 mmol), K_2CO_3 (276.4 mg, 2 mmol) and DMF (5.5 mL). Borylation was carried out at 60 °C for 4 h and Suzuki reaction was run for 9 h at 60 °C. Column chromatography on silica eluting with a gradient of hexanes to 8:2 hexane/ EtOAc gave 172.0 mg (59.0 %) of 3,5-dichloro-3'-(trifluoromethyl)-1,1'-biphenyl as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (t, *J* = 1.9 Hz, 1H), 7.47 (d, *J* = 1.9 Hz, 2H), 7.61-7.58 (m, 1H), 7.69-7.67 (m, 1H), 7.73-7.71 (m, 1H), 7.79 (td, *J* = 1.6, 0.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 123.94 (q, *J* = 272.4 Hz), 124.13 (q, *J* = 3.4 Hz), 125.13 (q, *J* = 3.3 Hz), 125.72, 127.96, 129.57, 130.36, 131.52 (q, *J* = 32.5 Hz), 135.59, 139.34, 142.64 (two Sp^2 C, overlapping with each other). FT-IR (neat) $\tilde{\nu}_{max}$: 3093, 2917, 1583, 1433, 1211, 1169, 1054, 936, 862, 810; ^{19}F NMR -62.5; MS (% rel. int.): 290 (100), 271 (12), 221 (7), 201 (20), 152 (17).



2.11a

2-(3,5-bis(trifluoromethyl)phenyl)naphthalene (2.11a).

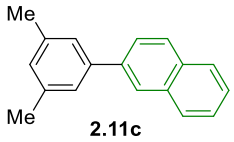
The general procedure for borylations (Procedure A) and one-pot C–H acitivation/borylation Suzuki coupling (Procedure C) with the following amounts: HBPin (217 μL, 1.5 mmol), $[Ir(OMe)(COD)]_2$ (13.2 mg, 0.02 mmol), d^tbpy (8.0 mg, 0.03 mmol), 1,3-Bis(trifluoromethyl)benzene (155 μL, 1.0 mmol), Imidazole-2-sulfonatenapthalene (274.3 mg, 1 mmol), (dppf)$PdCl_2$ (73.17 mg, 0.10 mmol), K_2CO_3 (276.4 mg, 2 mmol) and DMF (5.5 mL). Borylation was carried out at 60 °C for 1 h and Suzuki reaction was run for 16 h at 60 °C. Column chromatography on silica eluting with a gradient of hexanes to 8:2 hexane/ EtOAc gave 230.0 mg (68.0 %) of 2-(3,5-bis(trifluoromethyl)phenyl)naphthalene as a white solid: mp = 92-94 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.52 (m, 2H), 7.70 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.94-7.87 (m, 3H), 7.96 (d, *J* = 8.5 Hz, 1H), 8.05 (s, 1H), 8.13 (s, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 120.91 (septet, *J* = 3.8 Hz), 123.41 (q, *J* = 272.8 Hz), 124.67, 126.56, 126.89 (d, *J* = 3.1 Hz), 127.41-127.38 (m), 127.73, 128.35, 129.17, 132.17 (q, *J* = 33.2 Hz), 133.16, 133.47, 135.40, 143.22; FT-IR (neat) $\tilde{n}_{max}$: 3073, 2930, 1556, 1273, 1126, 1049, 825, 490; ^{19}F NMR: -63.05; HRMS (EI): *m/z* calculated for $C_{18}H_{10}F_6$ $[M]^+$ 340.0687, found 340.0694.



2.11b

2-(3-chloro-5-methylphenyl)naphthalene (2.11b).

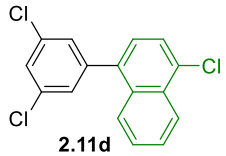
The general procedure for borylations (Procedure A) and one-pot C–H acitivation/borylation Suzuki coupling (Procedure C) with the following amounts: HBPin (290 μL, 2.0 mmol), $[Ir(OMe)(COD)]_2$ (19.8 mg, 0.03 mmol), d^tbpy (16.1mg, 0.06 mmol), 1-chloro-3-methylbenzene(119 μL, 1.0 mmol), imidazole-2-sulfonatenaphthalene (274.3 mg, 1 mmol), $(dppf)PdCl_2$ (73.17 mg, 0.10 mmol), K_2CO_3 (276.4 mg, 2 mmol) and DMF (5.5 mL). Borylation was carried out at 60 °C for 24 h in THF as the solvent and Suzuki reaction was run for 36 h at 60 °C. Column chromatography on silica eluting with a gradient of hexanes to 8:2 hexane/ EtOAc gave 182.0 mg (72.0 %) of 2-(3-chloro-5-methylphenyl)naphthalene as a white solid: mp = 78-80 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.43 (d, J = 0.6 Hz, 3H), 7.20 (ddd, J = 1.9, 1.4, 0.6 Hz, 1H), 7.40 (td, J = 1.5, 0.7 Hz, 1H), 7.54-7.49 (m, 3H), 7.69 (dd, J = 8.5, 1.9 Hz, 1H), 7.92-7.86 (m, 3H), 8.01 (d, J = 1.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.32, 124.55, 125.21, 125.89, 126.14, 126.37, 126.38, 127.61, 127.90, 128.19, 128.49, 132.75, 133.51, 134.40, 137.19, 140.15, 142.66; FT-IR (neat) $\tilde{\nu}_{max}$: 3039, 3026, 2987, 1944, 1511, 1434, 1273, 1158, 1025, 963; HRMS (EI): *m/z* calculated for $C_{17}H_{13}Cl$ $[M]^+$ 252.0706, found 252.0701.



2.11c

2-(3,5-dimethylphenyl)naphthalene (2.11c).

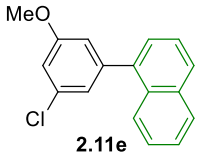
The general procedure for borylations (Procedure A) and one-pot C–H acitivation/borylation Suzuki coupling (Procedure C) with the following amounts: B_2Pin_2 (254 mg, 1.0 mmol), $[Ir(OMe)(COD)]_2$ (6.6 mg, 0.01 mmol), TMP (5.7 mg, 0.02 mmol), m-Xylene (123 μL, 1.0 mmol), imidazole-2-sulfonatenaphthalene (274.3 mg, 1 mmol), $(dppf)PdCl_2$ (73.17 mg, 0.10 mmol), K_2CO_3 (276.4 mg, 2 mmol) and DMF (5.5 mL)/H_2O (0.5 mL). Borylation was carried out at 80 °C for 4 h in THF (2 mL) as the solvent and Suzuki reaction was run for 14 h at 80 °C. Column chromatography on silica eluting with a gradient of hexanes to 8:2 hexane/ EtOAc gave 190.0 mg (82.0 %) of 2-(3,5-dimethylphenyl)naphthalene as a white solid: mp = 64 - 65 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.44 (s, 6H), 7.05 (s, 1H), 7.36 (s, 2H), 7.50 (quintetd, J = 7.5, 1.6 Hz, 2H), 7.76 (dd, J = 8.5, 1.8 Hz, 1H), 7.88-7.86 (m, 1H), 7.92-7.90 (m, 2H), 8.04 (d, J = 1.3 Hz, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 21.61, 125.47, 125.83, 125.87, 125.91, 126.32, 127.75, 128.29, 128.38, 129.14, 132.69, 133.80, 138.49, 138.90, 141.23.; FT-IR (neat) $\tilde{\nu}$max:3056, 3025, 2917, 2851, 1593, 1456, 1272, 820, 750, 699 HRMS (EI): *m/z* calculated for $C_{18}H_{16}[M+H]^+$ 233.130, found 233.131.



2.11d

1-chloro-4-(3,5-dichlorophenyl)naphthalene (11d).

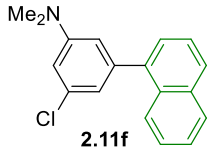
The general procedure for borylations (Procedure A) and one-pot C–H acitivation/borylation Suzuki coupling (Procedure C) with the following amounts: HBPin (217 μL, 1.5 mmol), $[Ir(OMe)(COD)]_2$ (6.6 mg, 0.01 mmol), d^{t}bpy (5.4 mg, 0.02 mmol), 1,3-dichlorobenzene (123 μL, 1.0 mmol), 1-((4-chloronaphthalen-1-yl)sulfonyl)-1*H*-imidazole (292.7 mg, 1 mmol), $(dppf)PdCl_2$ (73.17 mg, 0.10 mmol), K_2CO_3 (276.4 mg, 2 mmol) and DMF (5.5 mL). Borylation was carried out at 60 °C for 4 h and Suzuki reaction was run for 16 h at 60 °C. Column chromatography on silica eluting with hexanes gave 147.0 mg (48.0 %) of 1-chloro-4-(3,5-dichlorophenyl)naphthalene as a white solid: mp = 123 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 1.9 Hz, 2H), 7.44 (t, *J* = 1.9 Hz, 1H), 7.52 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.64-7.59 (m, 2H), 7.79 (d, *J* = 8.4 Hz, 1H), 8.35 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 124.92, 125.55, 125.81, 126.71, 127.20, 127.31, 127.66, 128.42, 130.87, 132.16, 132.49, 134.90, 136.61, 142.84; FT-IR (neat) $\tilde{\nu}_{max}$: 3068, 2974, 2736, 1698, 1573, 1464, 1389, 1235, 1130, 943, 896, 479; HRMS (EI): *m/z* calculated for $C_{16}H_9Cl_3$ $[M]^+$ 305.9770, found 305.9757.



2.11e

1-(3-chloro-5-methoxyphenyl)naphthalene (2.11e).

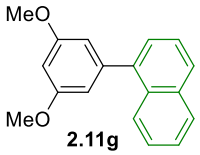
The general procedure for borylations (Procedure A) and one-pot C–H acitivation/borylation Suzuki coupling (Procedure C) with the following amounts: B_2Pin_2 (279.4 mg, 1.1 mmol), $[Ir(OMe)(COD)]_2$ (9.9 mg, 0.015 mmol), d^tbpy (8.0 mg, 0.03 mmol), 3-Chloroanisole (123 μL, 1.0 mmol), imidazole-1-sulfonatenaphthalene (274.3 mg, 1 mmol), $(dppf)PdCl_2$ (73.17 mg, 0.10 mmol), K_2CO_3 (276.4 mg, 2 mmol) and DMF (5.5 mL)/H_2O (0.5 mL). Borylation was carried out at 80 °C for 12 h in THF (2 mL) as the solvent and Suzuki reaction was run for 14 h at 60 °C. Column chromatography on silica eluting with a gradient of hexanes to 8:2 hexane/ EtOAc gave 198.0 mg (74.0 %) of 1-(3-chloro-5-methoxyphenyl)naphthalene as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.86 (s, 3H), 6.94 (dd, *J* = 2.3, 1.4 Hz, 1H), 7.00 (t, *J* = 2.1 Hz, 1H), 7.11 (t, *J* = 1.6 Hz, 1H), 7.42 (dd, *J* = 7.0, 1.2 Hz, 1H), 7.47 (ddd, *J* = 8.3, 6.8, 1.5 Hz, 1H), 7.54-7.50 (m, 2H), 7.93-7.88 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 55.70, 113.28, 114.53, 122.66, 125.39, 125.79, 126.06, 126.44, 126.88, 128.30, 128.45, 131.40, 133.83, 134.77, 138.86, 143.36, 160.20; FT-IR (neat) $\tilde{\nu}_{max}$:2994, 2934, 2831, 1565, 1220, 1048, 798, 774, 693; HRMS (EI): *m/z* calculated for $C_{17}H_{13}ClO[M+H]^+$ 269.071, found 269.072.



2.11f

3-chloro-N,N-dimethyl-5-(naphthalen-1-yl)aniline (2.11f).

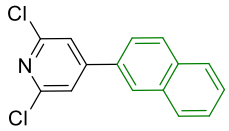
The general procedure for borylations (Procedure A) and one-pot C–H acitivation/borylation Suzuki coupling (Procedure C) with the following amounts: B_2Pin_2 (279.4 mg, 1.1 mmol), $[Ir(OMe)(COD)]_2$ (9.9 mg, 0.015 mmol), d^tbpy (8.0 mg, 0.03 mmol), 3-chloro-N,N-dimethylaniline (155.6 mg, 1.0 mmol), imidazole-1-sulfonatenaphthalene (274.3 mg, 1 mmol), $(dppf)PdCl_2$ (73.17 mg, 0.10 mmol), K_2CO_3 (276.4 mg, 2 mmol) and DMF (5.5 mL)/H_2O (0.5 mL). Borylation was carried out at 80 °C for 12 h in THF (2 mL) as the solvent and Suzuki reaction was run for 6 h at 60 °C. Column chromatography on silica eluting with a gradient of hexanes to 8:2 hexane/ EtOAc gave 174.7 mg (62.0 %) of 3-chloro-N,N-dimethyl-5-(naphthalen-1-yl)aniline as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.00 (s, 6H), 6.76 (d, *J* = 32.8 Hz, 2H), 6.86 (s, 1H), 7.44 (ddd, *J* = 14.5, 7.6, 1.1 Hz, 2H), 7.53-7.48 (m, 2H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.92 (dd, *J* = 14.9, 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 40.54, 111.06, 112.51, 118.02, 125.37, 125.91, 126.09, 126.19, 126.69, 127.91, 128.32, 131.60, 133.78, 134.79, 139.95, 142.84, 151.23; FT-IR (neat) $\tilde{\nu}_{max}$:3043, 2890, 2802, 1591, 1559, 1487, 1393, 1227, 961, 797, 775,693; HRMS (EI): *m/z* calculated for $C_{18}H_{16}ClN$ $[M+H]^+$ 282.103, found 282.104.



2.11g

1-(3,5-dimethoxyphenyl)naphthalene (2.11g).

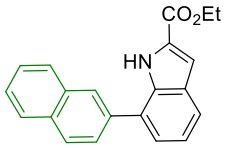
The general procedure for borylations (Procedure A) and one-pot C–H acitivation/borylation Suzuki coupling (Procedure C) with the following amounts: B_2Pin_2 (254 mg, 1.1 mmol), $[Ir(OMe)(COD)]_2$ (6.6 mg, 0.01 mmol), TMP (5.8 mg, 0.02 mmol), 1,3-dimethoxybenzene (0.12 mL,1.0 mmol), imidazole-1-sulfonatenaphthalene (328.8 mg, 1.2 mmol), $(dppf)PdCl_2$ (73.17 mg, 0.10 mmol), K_2CO_3 (276.4 mg, 2 mmol) and DMAc (5.0 mL)/H_2O (0.5 mL). Borylation was carried out at 80 °C for 4 h in THF (2 mL) as the solvent and Suzuki reaction was run for 16 h at 80 °C. Gradient column chromatography on silica eluting with hexanes to 7:3 hexane / CH_2Cl_2 as eluent gave 190 mg (72.0% yield) of known compound[2] 1-(3,5-dimethoxyphenyl)naphthalene as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.91 (s, 6H), 6.67 (t, *J* = 2.1 Hz 1H), 6.77 (d, *J* = 2.1 Hz, 2H), 7.55 (m, 4H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.97 (d, *J* = 7.9 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 55.5, 99.6, 108.3, 125.4, 125.9, 126.2, 127.9, 128.3, 131.6, 133.8, 140.3, 142.9, 160.7.



2.15a

2,6-dichloro-4-(naphthalen-2-yl)pyridine (2.15a).

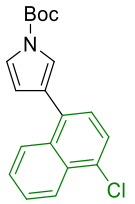
The general procedure for borylations (Procedure A) and one-pot C–H acitivation/borylation Suzuki coupling (Procedure C) with the following amounts: HBPin (217 μL, 1.5 mmol), $[Ir(OMe)(COD)]_2$ (19.8 mg, 0.03 mmol), d^tbpy (16.1mg, 0.06 mmol), 2,6-dichloropyridine (147 mg, 1.0 mmol), Imidazole-2-sulfonatenapthalene (274.3 mg, 1 mmol), $(dppf)PdCl_2$ (73.17 mg, 0.10 mmol), K_2CO_3 (276.4 mg, 2 mmol) and DMF (5.5 mL). Borylation was carried out at 60 °C for 1 h in THF as the solvent and Suzuki reaction was run for 16 h at 60 °C. Gradient column chromatography on silica eluting with 100 % hexanes to 8:2 hexane / EtOAc as eluent gave 115.1 mg (42.0 %) of 2-(3-chloro-5-methylphenyl)naphthalene as a white solid: mp = 144-145 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58-7.54 (m, 4H), 7.64 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.92-7.86 (m, 2H), 7.94 (d, *J* = 8.6 Hz, 1H), 8.05 (dd, *J* = 1.4, 0.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 120.82, 123.85, 126.95, 127.04, 127.50, 127.72, 128.53, 129.29, 132.75, 133.17, 133.78, 151.01, 153.74; FT-IR (neat) $\tilde{\nu}_{max}$: 3046, 2341, 1566, 1531, 1360, 1130, 976, 878, 790; HRMS (ESI): m/z calculated for $C_{15}H_{10}NCl_2$ $[M+H]^+$ 274.0190, found 274.0201.



2.15b

Ethyl 7-(naphthalen-2-yl)-1*H*-indole-2-carboxylate (2.15b).

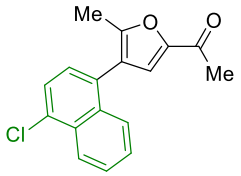
The general procedure for borylations (Procedure A) and one-pot C–H acitivation/borylation Suzuki coupling (Procedure C) with the following amounts: HBPin (217 μL, 1.5 mmol), $[Ir(OMe)(COD)]_2$ (19.8 mg, 0.03 mmol), d^{t}bpy (16.1mg, 0.06 mmol), Ethyl indole-2-carboxylate (189.2 mg, 1.0 mmol), Imidazole-2-sulfonatenapthalene (274.3 mg, 1 mmol), $(dppf)PdCl_2$ (73.17 mg, 0.10 mmol), K_2CO_3 (276.4 mg, 2 mmol) and DMF (5.5 mL). Borylation was carried out at 60 °C for 3 h in hexane as the solvent and Suzuki reaction was run for 16 h at 60 °C. Gradient column chromatography on silica eluting with 100 % hexanes to 8:2 hexane / EtOAc as eluent gave 180 mg (57.0 %) of Ethyl 7-(naphthalen-2-yl)-1*H*-indole-2-carboxylate as a white solid: mp = 125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (t, *J* = 7.1 Hz, 3H), 4.34 (q, *J* = 7.1 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 2.1 Hz, 1H), 7.46 (d, *J* = 7.1 Hz, 1H), 7.58-7.54 (m, 2H), 7.78-7.74 (m, 2H), 7.94-7.91 (m, 2H), 7.99 (d, *J* = 8.4 Hz, 1H), 8.11 (s, 1H), 9.23 (bs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.29, 60.96, 109.07, 121.32, 121.81, 125.28, 126.22, 126.24, 126.36, 126.52, 126.84, 127.72, 127.87, 128.03, 128.95, 132.69, 133.64, 135.02, 135.73, 161.81; FT-IR (neat) $\tilde{\nu}_{max}$: 3460, 2979, 1701, 1301, 1241, 1202, 1022, 823, 677; HRMS (ESI): m/z calculated for $C_{21}H_{17}NO_2$ $[M+H]^+$ 316.1338, found 316.1339.



2.15c

3-(4-chloronaphthyl)-N-Boc-pyrrole (2.15c).

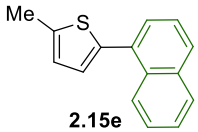
The general procedure for borylations (Procedure A) and one-pot C–H acitivation/borylation Suzuki coupling (Procedure C) with the following amounts: HBPin (217 μL, 1.5 mmol), $[Ir(OMe)(COD)]_2$ (10.0 mg, 0.015 mmol), d^tbpy (8.0 mg, 0.02 mmol), N-Boc-pyrrole (167 μL, 1.0 mmol), 1-((4-chloronaphthalen-1-yl)sulfonyl)-1*H*-imidazole (292.7 mg, 1 mmol), $(dppf)PdCl_2$ (73.17 mg, 0.10 mmol), K_2CO_3 (276.4 mg, 2 mmol) and DMF (5.5 mL). Borylation was carried out at 60 °C for 2 h and Suzuki reaction was run for 60 h at 60 °C. Gradient column chromatography on silica eluting with hexanes to 7:3 hexane / EtOAc as eluent gave 219.0 mg (67.0 %) of 3-(4-chloronaphthalen)-N-Boc-pyrrole as a slightly yellowish viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.63 (s, 9H), 6.48 (dd, *J* = 2.7, 1.3 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 2H), 7.43 (s, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.60 (dd, *J* = 8.0, 7.2 Hz, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 8.33 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 27.99, 83.98, 114.07, 118.63, 120.22, 124.71, 125.73, 125.82, 126.39, 126.67, 126.81, 130.92, 130.94, 132.56, 132.83, 148.77; FT-IR (neat) $\tilde{\nu}_{max}$: 3015, 2945, 1732, 1586, 1421, 1368, 1215, 1159, 890, 707; *MS (% rel. int.):* 227 (100), 191 (24), 165 (20), 151 (1), 96 (4), 83 (6), 63 (4).



2.15d

1-(4-(4-chloronaphthalen-1-yl)-5-methylfuran-2-yl)ethanone (2.15d).

The general procedure for borylations (Procedure A) and one-pot C–H acitivation/borylation Suzuki coupling (Procedure C) with the following amounts: HBPin (217 μL, 1.5 mmol), $[Ir(OMe)(COD)]_2$ (10.0 mg, 0.015 mmol), d^{t}bpy (8.0 mg, 0.02 mmol), 2-acetyl-5-methylfuran (116 μL, 1.0 mmol) and. , 1-((4-chloronaphthalen-1-yl)sulfonyl)-1*H*-imidazole (292.7 mg, 1 mmol), $(dppf)PdCl_2$ (73.17 mg, 0.10 mmol), K_2CO_3 (276.4 mg, 2 mmol) and DMF (5.5 mL). Borylation was carried out at 60 °C for 1 h in cyclohexane (2 mL) and Suzuki reaction was run for 20 h at 60 °C. Gradient column chromatography on silica eluting with hexanes to 7:3 hexane / EtOAc as eluent gave 139.5 mg (49.0 %) of 1-(4-(4-chloronaphthalen-1-yl)-5-methylfuran-2-yl)ethanone as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.29 (s, 2H), 2.49 (s, 2H), 7.25 (d, J = 0.5 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.54 (m, J = 1.2 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.63 (m, J = 1.3 Hz, 1H), 7.77 (dd, J = 8.4, 0.6 Hz, 1H), 8.34 (m, J = 0.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.15, 26.07, 121.32, 122.13, 125.26, 125.93, 126.08, 127.44, 127.46, 127.66, 129.59, 131.25, 132.47, 133.21, 151.04, 155.25, 186.52; FT-IR (neat) $\tilde{n}_{max}$: 3128, 2923, 2853, 1587, 1334, 1212, 1128, 1021, 957, 801, 610; HRMS (EI): *m/z* calculated for $C_{17}H_{13}O_2Cl$ $[M]^+$, 284.0604 found 284.0616.



2.15e

2-methyl-5-(naphthalen-1-yl)thiophene (2.15d).

The general procedure for borylations (Procedure A) and one-pot C–H acitivation/borylation Suzuki coupling (Procedure C) with the following amounts: HBPin (217 μL, 1.5 mmol), $[Ir(OMe)(COD)]_2$ (6.6 mg, 0.01 mmol), d^{t}bpy (8.0 mg, 0.02 mmol), 2-acetyl-5-methylfuran (116 μL, 1.0 mmol) and. , 1-((4-chloronaphthalen-1-yl)sulfonyl)-1*H*-imidazole (292.7 mg, 1 mmol), $(dppf)PdCl_2$ (73.17 mg, 0.10 mmol), K_2CO_3 (276.4 mg, 2 mmol) and DMF (5.5 mL)/ H_2O (0.5 mL). Borylation was carried out at 25 °C for 1 h in cyclohexane (2 mL) and Suzuki reaction was run for 6 h at 60 °C. Gradient column chromatography on silica eluting with hexanes to 7:3 hexane/ EtOAc as eluent gave 139.5 mg (62.0 %) of 2-methyl-5-(naphthalen-1-yl)thiophene as a colorless oil of known compound[3]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.60 (s, 3H), 6.86 (t, J = 1.0 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 7.51 (quintet, J = 7.1 Hz, 3H), 7.57 (d, J = 7.0 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.91 (t, J = 4.1 Hz, 1H), 8.32-8.30 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 15.48, 125.39, 125.63, 125.98, 126.05, 126.43, 127.38, 128.04, 128.20, 128.42, 131.93, 132.93, 133.99, 139.52, 140.31.

Experimental details for one-pot C–H activation/borylation/oxidation routes to imidazolylsulfonates and their direct incorporation into the one-pot borylation/Suzuki couplings.

General Procedure for C–H Activation/Borylation/Oxidation with Photoredox Catalysis (Procedure D).

First, the general procedure for C–H Activation/Borylation (Procedure A) was applied to the unactivated arene or heteroarene with relevant amounts. After completion of the reaction, the volatile materials were removed on a rotary evaporator. To a mixture of crude boronic ester (approximately 1 mmol, usually a dark orange or brown gel-like liquid or a solid), $Ru(bpy)_3Cl_2•6H_2O$ (15.0 mg, 0.02 mmol) in DMF (10.0 mL) was added *i*Pr_2NEt (350 μL, 2.0 mmol). The solution was stirred at room temperature adjacent to a 26-W compact fluorescent light bulb in open to air (without bubbling air). After boronic ester was completely consumed (monitored by GC-FID/MS and TLC analysis), the resulting crude phenol was used in next step without any purification.

General Procedure for Synthesis of Aryl Imidazolylsulfonates (Procedure E).

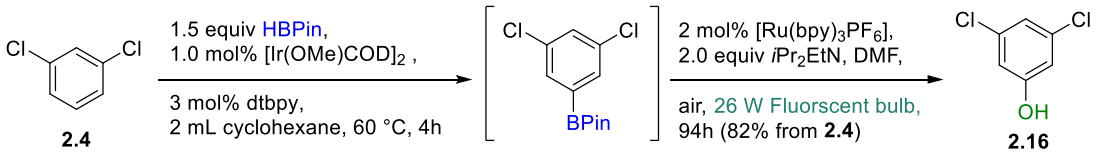
The flask containing the phenol substrate was charged with N-N'-sulfonyldiimidazole (396.4 mg, 2 mmol) and Cs_2CO_3 (162.9 mg, 0.5 mmol) in THF (0.05 g/mL). The reaction was stirred at room temperature (or at the specific temperature reported) and monitored by GC-FID/MS or TLC. After starting phenol was completely consumed the resulting crude imidazolylsulfonates was used in next step after removing the excess solvent *in vacuo*, without any purification.

Note: To obtain the purified imidazolylsulfonates following procedure has been used.

The reaction solution was concentrated and EtOAc was added and cooled to 0 ^{o}C and saturated aqueous NH_4Cl was added. The layers were separated and the aqueous layer was washed with EtOAc (3 X). The combined organic extracts were washed with water (2X), followed by brine (1 X), dried (Mg_2SO_4), and concentrated onto celite and purification by flash chromatography.

Experimental details for the C–H activation/borylation/oxidation with photoredox catalysis.

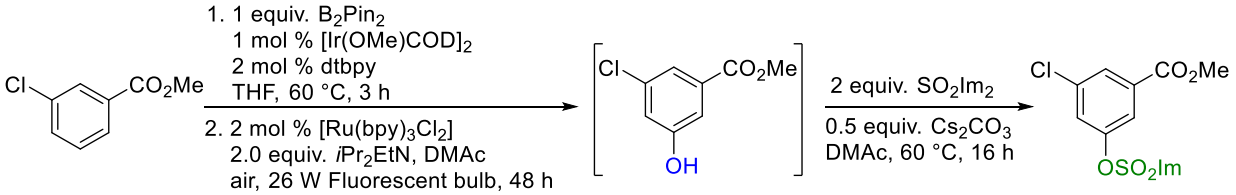
Preparation of 3,5-Dichlorophenol, **2.16**:



The general borylation procedure A was applied with the following amounts: HBPin (217 μL, 1.5 mmol), $[Ir(OMe)(COD)]_2$ (6.6 mg, 0.01 mmol), d^{t}bpy (5.4 mg, 0.02 mmol), 1,3-dichlorobenzene (123 μL, 1.0 mmol) and cyclohexane (2 mL). Borylation was carried out at 60 °C for 4 h. After completion of the reaction, the volatile materials were removed on a rotary evaporator. Then the general procedure E, photoredox catalyzed oxidation conditions were applied to the crude boronic ester with following amounts: $Ru(bpy)_3PF_6$ (16.5 mg, 0.02 mmol), *i*Pr_2NEt (350 μL, 2.0 mmol) and dry DMF (10.0 mL). Note: The $Ru(bpy)_3PF_6$ (provided by Ms. Daniela Rotondo, McCusker Group) catalyst was used instead of $Ru(bpy)_3Cl_2$•$6H_2O$. The reaction was monitored by GC-MS/FID and once it was completed, the reaction mixture was cooled to 0 ℃ and quenched carefully by aqueous solution of HCl (10%, 10 mL). The resultant mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (2 x 20 mL) and dried over Mg_2SO_4. After removal of the solvent in vacuum, the residue

was purified by FC (silica gel, EtOAc:PE = 1:5) to give the desired product **25** (134 mg, 82 %) as a colorless solid: mp = 66-68 °C (Aldrich 67-69 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.90 (s, 1H), 6.74 (d, *J* = 1.7 Hz, 2H), 6.94 (t, *J* = 1.8 Hz, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 114.53, 121.41, 135.47, 156.42.

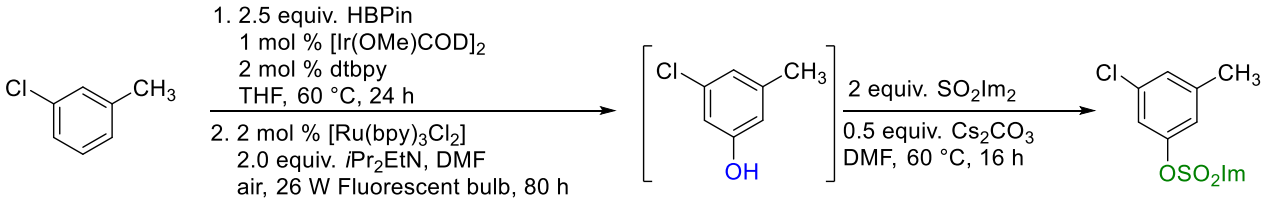
Synthesis of Imidazolylsulfonates[3b]



2.17a **2.18a** **2.19a**

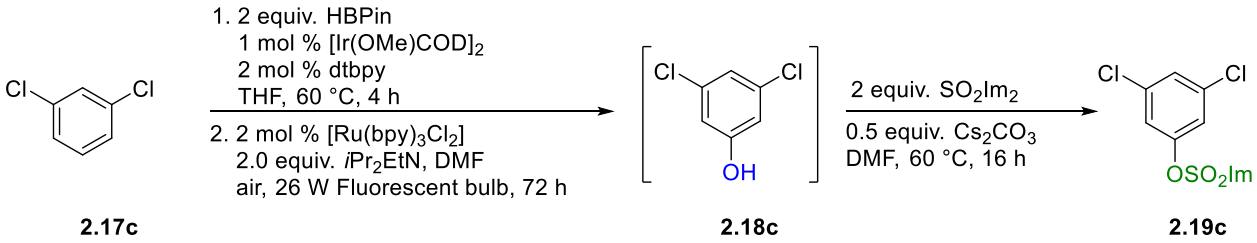
Methyl 3-(((1*H*-imidazol-1-yl)sulfonyl)oxy)-5-chlorobenzoate (2.19a): The general borylation Procedure 5A was applied with the following amounts: B_2Pin_2 (254 mg, 1 mmol, 1 equiv.), $[Ir(OMe)(COD)]_2$ (6.6 mg, 0.01 mmol, 1 mol %), dtbpy (5.4 mg, 0.02 mmol, 2 mol %), methyl 3-chlorobenzoate (0.12 mL, 1.0 mmol) and THF (2 mL). Borylation was carried out for 3 h at 60 °C. After completion of the reaction, the volatile materials were removed on a rotary evaporator. Crude boronic ester was transferred to a 100 mL round-bottom flask with the use of DMAc (10 mL), followed by addition of $Ru(bpy)_3Cl_2•6H_2O$ (15.0 mg, 0.02 mmol, 2 mol %), and iPr_2NEt (0.35 mL, 2.0 mmol, 2 equiv.). The solution was stirred at room temperature below a 26-W compact fluorescent light bulb open to air (without bubbling air). The reaction was monitored by GC-MS/FID and once it was completed (48 h), the crude reaction mixture was charged with N-N'-sulfonyldiimidazole (297.3 mg, 1.5 mmol, 1.5 equiv.) and Cs_2CO_3 (162.9 mg, 0.5 mmol, 0.5 equiv.) and stirred at 60 °C for 16 h. The reaction was cooled to room temperature and diluted with EtOAc and H_2O. The layers were separated and aqueous phase was washed with EtOAc (3x at 50 mL each). The combined organic extracts were washed with water (3x at 250 mL) and then

brine (100 mL), dried over $MgSO_4$, and concentrated to obtain the methyl 3-(((1*H*-imidazol-1-yl)sulfonyl)oxy)-5-chlorobenzoate. After removal of the solvent *in vacuo*, the residue was purified by FC (silica gel, hexanes:CH_2Cl_2 = 1:1) to give the desired product (140 mg, 44%) as a white solid (mp = 60-62 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.91 (s, 3H), 7.18 (m, 1H), 7.20 (s, 1H), 7.31 (d, *J* = 1.2 Hz, 1H), 7.48 (d, *J* = 1.2 Hz, 1H), 7.78 (s, 1H), 8.01 (s, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 53.0, 118.2, 120.8, 126.1, 130.0, 131.8, 133.6, 136.0, 137.4, 148.8, 163.9. IR: 3127, 1731, 1294 cm.$^{-1}$ HRMS (EI) m/z 316.998 $[M+1]^+$; calculated $[M+1]^+$ for $C_{11}H_9ClN_2O_5S^+$ 316.992.



3-chloro-5-methylphenyl 1*H*-imidazole-1-sulfonate (2.19b): The general borylation Procedure 5A was applied with the following amounts: HBPin (0.29 mL, 2.5 mmol, 2.5 equiv.), $[Ir(OMe)(COD)]_2$ (6.6 mg, 0.01 mmol, 1 mol %), dtbpy (5.4 mg, 0.02 mmol, 2 mol %), 3-chlorotoluene (0.12 mL, 1.0 mmol), and THF (2 mL). Borylation was carried out for 24 h at 60 °C. After completion of the reaction, the volatile materials were removed on a rotary evaporator. Crude boronic ester was transferred to a 100 mL round-bottom flask with the use of DMF (10 mL), followed by addition of $Ru(bpy)_3Cl_2$•$6H_2O$ (15.0 mg, 0.02 mmol, 2 mol %), and iPr_2NEt (0.35 mL, 2.0 mmol, 2 equiv.). The solution was stirred at room temperature below a 26-W compact fluorescent light bulb open to air (without bubbling air). The reaction was monitored by GC-MS/FID and once it was completed (80 h), the crude reaction mixture was charged with N-

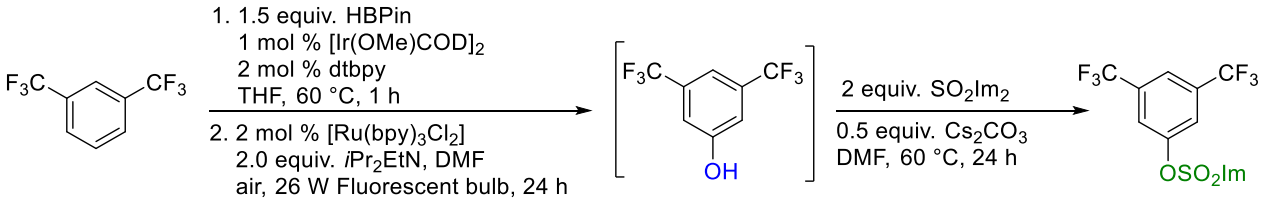
N'-sulfonyldiimidazole (396 mg, 2 mmol, 2 equiv.) and Cs_2CO_3 (162.9 mg, 0.5 mmol, 0.5 equiv.) and stirred at 60 °C for 16 h. The reaction then was cooled to room temperature and diluted with EtOAc and H_2O. The layers were separated and aqueous phase was washed with EtOAc (3x at 50 mL each). The combined organic extracts were washed with water (3x at 250 mL) and then brine (100 mL), dried over $MgSO_4$, and concentrated to obtain the 3-chloro-5-methylphenyl 1*H*-imidazole-1-sulfonate. After removal of the solvent *in vacuo*, the residue was purified by FC (silica gel, hexanes:CH_2Cl_2 = 1:1) to give the desired product (120 mg, 44%) as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.31 (s, 3H), 6.61 (s, 1H), 6.80 (s, 1H), 7.17 (s, 1H), 7.19 (s, 1H), 7.31 (s, 1H), 7.78 (s, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 21.0, 118.3, 119.0, 120.1, 129.6, 131.4, 135.1, 137.5, 142.1, 148.8. IR: 3131, 2926, 1605, 1580 cm.$^{-1}$ HRMS (EI) m/z 273.008 $[M+1]^+$; calculated $[M+1]^+$ for $C_{10}H_9ClN_2O_3S^+$ 273.002.



2.17c **2.18c** **2.19c**

3,5-dichlorophenyl 1*H*-imidazole-1-sulfonate (2.19c): The general borylation Procedure 5A was applied with the following amounts: HBPin (0.219 mL, 2 mmol, 2 equiv.), $[Ir(OMe)(COD)]_2$ (6.6 mg, 0.01 mmol, 1 mol %), dtbpy (5.8 mg, 0.02 mmol, 2 mol %), 1,3-dichlorobenzene (0.12 mL, 1.0 mmol), and THF (2 mL). Borylation was carried out for 4 h at 60 °C. After completion of the reaction, the volatile materials were removed on a rotary evaporator. Crude boronic ester was transferred to a 100 mL round-bottom flask with the use of DMF (10 mL), followed by addition of $Ru(bpy)_3Cl_2$•$6H_2O$ (15.0 mg, 0.02 mmol, 2 mol %), and iPr_2NEt

(0.35 mL, 2.0 mmol, 2 equiv.). The solution was stirred at room temperature below a 26-W compact fluorescent light bulb open to air (without bubbling air). The reaction was monitored by GC-MS/FID and once it was completed (72 h), the crude reaction mixture was charged with N-N'-sulfonyldiimidazole (396 mg, 2 mmol, 2 equiv.) and Cs_2CO_3 (162.9 mg, 0.5 mmol, 0.5 equiv.) and stirred at 60 °C for 16 h. The reaction was then cooled to room temperature and diluted with EtOAc and H_2O. The layers were separated and aqueous phase was washed with EtOAc (3x at 50 mL each). The combined organic extracts were washed with water (3x at 250 mL) and then brine (100 mL), dried over $MgSO_4$, and concentrated to obtain the 3,5-dichlorophenyl 1*H*-imidazole-1-sulfonate. After removal of the solvent *in vacuo*, the residue was purified by FC (silica gel, hexanes:CH_2Cl_2 = 1:1) to give the desired product (190 mg, 65%) as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.87 (s, 1H), 6.87 (s, 1H), 7.18 (s, 1H), 7.29 (s, 1H), 7.34 (s, 1H), 7.80 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 118.2, 120.6, 129.2, 131.8, 136.2, 137.4, 148.9. IR: 3131, 3091, 1583, 1433 cm.$^{-1}$ HRMS (EI) m/z 292.953 $[M+1]^+$; calculated $[M+1]^+$ for $C_9H_6Cl_2N_2O_3S^+$ 292.948.

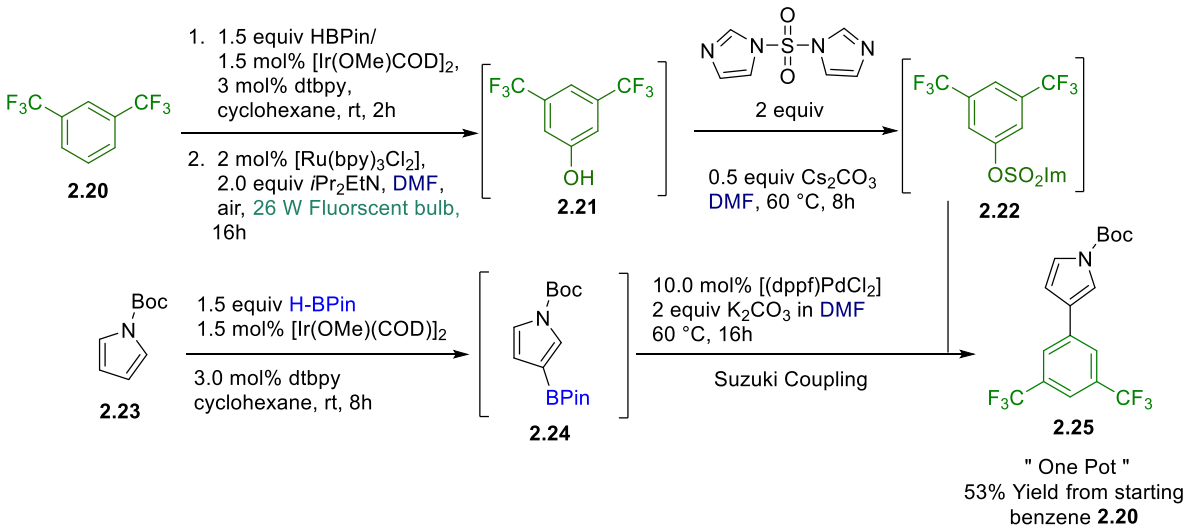


2.17d **2.18d** **2.19d**

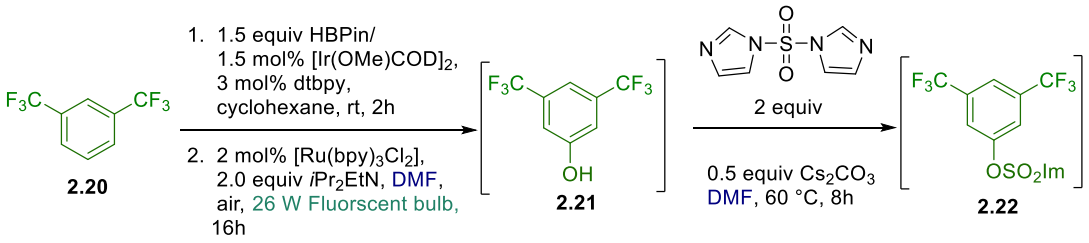
3,5-bis(trifluoromethyl)phenyl 1*H*-imidazole-1-sulfonate (2.19d): The general borylation Procedure 5A was applied with the following amounts: HBPin (0.217 mL, 1.5 mmol, 1.5 equiv.), $[Ir(OMe)(COD)]_2$ (6.6 mg, 0.01 mmol, 1 mol %), dtbpy (5.4 mg, 0.02 mmol, 2 mol %), methyl 3-chlorobenzoate (0.12 mL, 1.0 mmol), and THF (2 mL). Borylation was carried out for 1 h at 60

°C. After completion of the reaction, the volatile materials were removed on a rotary evaporator. Crude boronic ester was transferred to a 100 mL round-bottom flask with the use of DMF (10 mL), followed by addition of $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (15.0 mg, 0.02 mmol, 2 mol %), and iPr_2NEt (0.35 mL, 2.0 mmol, 2 equiv.). The solution was stirred at room temperature below a 26-W compact fluorescent light bulb open to air (without bubbling air). The reaction was monitored by GC-MS/FID and once it was completed (24 h), the crude reaction mixture was charged with N-N'-sulfonyldiimidazole (396 mg, 2 mmol, 2 equiv.) and Cs_2CO_3 (162.9 mg, 0.5 mmol, 0.5 equiv.) and stirred at 60 °C for 24 h. The reaction was then cooled to room temperature and diluted with EtOAc and H_2O. The layers were separated and aqueous phase was washed with EtOAc (3x at 50 mL each). The combined organic extracts were washed with water (3x at 250 mL) and then brine (100 mL), dried over $MgSO_4$, and concentrated to obtain the 3,5-bis(trifluoromethyl)phenyl 1*H*-imidazole-1-sulfonate. After removal of the solvent *in vacuo*, the residue was purified by FC (silica gel, hexanes: CH_2Cl_2 = 1:1) to give the desired product (200 mg, 56%) as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (s, 1H), 7.32 (s, 1H), 7.43 (s, 2H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 16.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 118.2, 120.9, 122.5 (m), 123.1, 132.0, 134.1 (q, *J* = 42 Hz), 137.3, 149.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ -63.3. IR: 3135, 3101, 1441, 1363 cm.$^{-1}$ HRMS (EI) m/z 361.005 $[M]^+$; calculated for $C_{11}H_6F_6N_2O_3S^+$ 361.000.

Experimental details for one-pot synthesis of 3-(3,5-bis(trifluoromethyl)phenyl)-N-Boc-pyrrole.



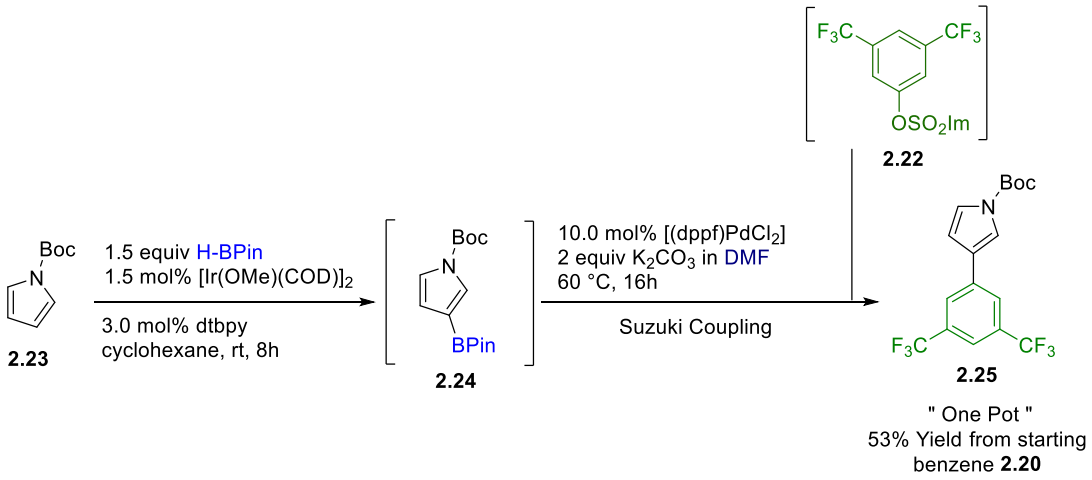
preparation of 3,5-bis(trifluoromethyl)phenylimidazolesulfonate, **2.22***:*



The general borylation procedure A was applied with the following amounts: HBPin (217 µL, 1.5 mmol), $[Ir(OMe)(COD)]_2$ (10.0 mg, 0.15 mmol), d^{t}bpy (8.0 mg, 0.03 mmol), 1,3-Bis(trifluoromethyl)benzene, **2.20** (155 µL, 1.0 mmol) and cyclohexane (2 mL). Borylation was carried out for 2 h. The reaction was monitored by GC-MS and TLC. After completion of the reaction, the volatile materials were removed on a rotary evaporator. Crude boronic ester was transferred to a 100 mL round-bottom flask with the use of DMF (10 mL), followed by addition of $Ru(bpy)_3Cl_2•6H_2O$ (15.0 mg, 0.02 mmol, 2 mol %), and iPr_2NEt (0.35 mL, 2.0 mmol, 2 equiv.). The reaction was carried out at room temperature adjacent to a 26-W compact fluorescent light bulb in open to air for 16 h, to obtain the crude phenol **2.21.** Next, the crude

reaction mixture was charged with N-N'-sulfonyldiimidazole (396.4 mg, 2 mmol) and Cs_2CO_3 (162.9 mg, 0.5 mmol) as given in procedure E and stirred at 60 °C to obtain the 3,5-bis(trifluoromethyl)phenylimidazolesulfonate **2.22** (reaction was monitored by GC-MS/FID). The crude material was used in next step, Suzuki reaction, without any purification.

preparation of 3-(3,5-bis(trifluoromethyl)phenyl)-N-Boc-pyrrole, **2.20**:



The general procedure for borylations (Procedure A) with the following amounts was followed: HBPin (217 μL, 1.5 mmol), $[Ir(OMe)(COD)]_2$ (10.0 mg, 0.15 mmol), d^tbpy (8.0 mg, 0.03 mmol), N-Boc-pyrrole**, 2.23** (167 μL, 1.0 mmol) and cyclohexane (2 mL). Borylation of **2.23** was carried out at room temperature for 8 h. After completion of the reaction, the volatile materials were removed on a rotary evaporator. Then the one-pot C–H acitivation/borylation Suzuki coupling (Procedure C) was applied to with the following amounts: $(dppf)PdCl_2$ (73.17 mg, 0.10 mmol) and K_2CO_3 (276.4 mg, 2 mmol). DMF from the previous reaction was used to transfer the crude 3,5- bis(trifluoromethyl)phenylimidazolesulfonate **2.22** to the Schlenk flask that contain the crude borylated material, **2.24.** (Note that the same DMF solvent is using from

previous two steps, without an addition of any new solvent) Suzuki reaction was carried out at 60 °C for 16 h (the reaction was monitored by GC-MS/FID). Then crude material after the subsequent work up was subjected to a gradient column chromatography on silica eluting with hexanes to 7:3 hexane / EtOAc as eluent gave 201.0 mg (53.0 %) of 3-(3,5-bis(trifluoromethyl)phenyl)-N-Boc-pyrrole as a slightly yellowish viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.62 (s, 9H), 6.55 (dd, *J* = 3.3, 1.8 Hz, 1H), 7.32 (dd, *J* = 3.1, 2.2 Hz, 1H), 7.59 (s, 1H), 7.69 (s, 1H), 7.89 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 27.96, 84.65, 109.83, 117.08, 119.85 (septet, *J* = 3.8 Hz), 121.74, 123.40 (q, *J* = 272.7 Hz), 125.21, 125.23, 131.99 (q, *J* = 33.1 Hz), 136.60, 148.38.; IR (neat) $\tilde{\nu}_{max}$: 2979, 2931, 1747, 1563, 1490, 1375, 1291, 1143, 1066, 973, 855, 780; ^{19}F NMR: -63.2 ; HRMS (ESI): m/z calculated for $C_{17}H_{16}F_6NO_2$ $[M+H]^+$ 380.1085, found 380.1084.

5.2. Experimental details for Chapter 3: Discovery and Development of Novel Catalytic Systems for Selective Protodeboronation

General Materials and Methods

Unless otherwise stated, the reported yields refer to chromatograph-ically and spectroscopically pure compounds. Pinacolborane (HBpin) and B_2pin_2 were generously supplied by BoroPharm, Inc. and used as received. Bis(η^4-1,5-cyclooctadiene)-di-μ-methoxy-diiridium(I) ([Ir(OMe)(cod)]$_2$), was prepared per a literature procedures.[1] 4,4′-Di-*t*-butyl-2,2′-bipyridine (dtbpy) was purchased from Aldrich. $IrCl_3$•$(H_2O)_x$ was purchased from Pressure Chemical Co. 2,7-Bis(Bpin)-*N*-Boc-L-tryptophan methyl ester was prepared according to a literature procedure.[2] All borylated starting substrates were purified by column chromatography prior to use. For all Ir-catalyzed reactions, tetrahydrofuran (THF) was obtained from a dry still packed with activated alumina and degassed before use. For all Bi-catalyzed deboronations, THF was reagent grade and used as received. Acetonitrile (MeCN), triethylamine (NEt_3), and dichloromethane (DCM) were reagent grade. Silica gel was (230-400 Mesh).

Reactions were monitored by thin layer chromatography on precoated silica gel plates (Merck), using UV light or phosphomolybdic acid stain for visualization. Column chromatography was performed on 60 Å silica gel (230–400 mesh). NMR spectra were recorded on Varian VXR-500, Varian Unity-500-Plus (499.74 MHz for ^{1}H and 125.67 MHz for ^{13}C) and Bruker 500 (500.13 MHz for ^{1}H and 125.77 MHz for ^{13}C) spectrometer. ^{1}H and ^{13}C chemical shifts (in ppm) were referenced to the residual protonated or natural abundance solvent signals.[3] ^{11}B spectra were recorded at 160.32 MHz. All coupling constants are apparent *J* values measured at the indicated field strengths. Melting points are uncorrected. High-resolution mass spectrum was acquired at the MSU Mass Spectrometry facility using a Waters GCT Premier GC/TOF instrument (in ESI

mode) (Waters Milford, MA) and at Merck (Rahway, NJ) using a Waters Xevo G2 QTof instrument (in ESI mode). Low-resolution mass spectra were performed at the Molecular Metabolism and Disease Collaborative Mass Spectrometry Core facility at MSU on a Thermo Scientific LTQ-Orbitap Velos using the Ion Trap analyzer in positive ionization mode by nano-ESI. HPLC assays were carried out using a C-18 reversed-phase column eluted with 0.1% H_3PO_4 (aq) and acetonitrile (ACN) monitoring the compounds at 210 nm and 320 nm.

General procedures

General borylation procedure with $[Ir(OMe)(COD)]_2$ and d^{t}bpy.

In a glove box, a 20 mL reaction vial, equipped with a magnetic stirring bar, was charged with the substrate. Two separate test tubes were charged with $[Ir(OMe)(COD)]_2$ (1 mol% Ir) and d^{t}bpy (1 mol%). THF (2 × 200 µL) 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 (2.8 x Ir mol %). After mixing for one minute, the resulting solution was transferred to the reaction vial. Additional THF (3 × 200 µL) was used to wash the test tubes and the washings were transferred to the reaction vial. The reaction vial was sealed, brought out of the glove box and the reaction was carried out at the specified temperature. After completion of the reaction, the mixture was passed through a silica plug to remove the dark brown red color. After further elution with DCM, the volatile materials were removed by rotary evaporation. The crude material was further purified by column chromatography.

General deboronation procedure with $Bi(OAc)_3$ and MeOH. A reaction vial equipped with a magnetic stirring bar was charged with substrate and $Bi(OAc)_3$ (20 mol %). The described MeOH and THF solvent mixture was added to the vial. The reaction vial was sealed and the reaction was carried out at the 80 °C. After completion of the reaction as judged by TLC, the

crude mixture was passed through a plug of celite and washed three times by ethyl acetate. After the volatile materials were removed by rotary evaporation the crude material was purified by column chromatography.

General deboronation procedure with $[Ir(OMe)(COD)]_2$ and MeOH.[4] A Schlenk flask equipped with a magnetic stirring bar was charged with substrate (1.0 mmol, 1.0 equiv) and $[Ir(OMe)(COD)]_2$ (10 mg, 0.015 mmol, 3 mol % Ir). The Schlenk flask was then evacuated and backfilled with nitrogen (this sequence was carried out two times). The solvent mixture (methanol/dichloromethane 2:1, 5 mL) was degassed by a freeze-pump-thaw method then added to the Schlenk flask and flushed under nitrogen twice as mentioned previously. The Schlenk flask was sealed and the reaction was carried out at the 60 °C. After completion of the reaction as judged by TLC, the volatile materials were removed by rotary evaporation. The crude material was purified by column chromatography.

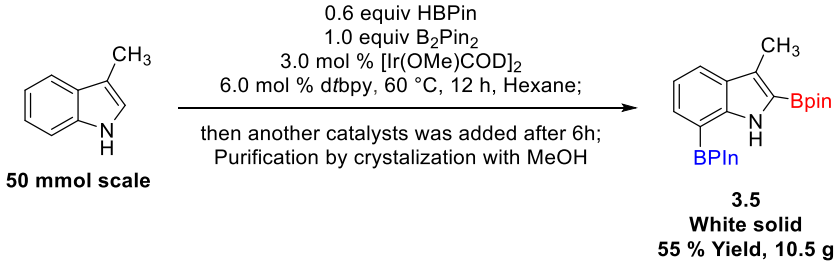
High-throughput Experimentation (HTE) Equipment, Materials and Methods:

Parallel synthesis was accomplished in an MBraun glove-box operating with a constant N_2-purge (oxygen typically <5 ppm). The experimental design was accomplished using Accelrys Library Studio. Screening reactions were carried out in Wheaton 250 μL vials (31 mm height x 5 mm diameter) in a 96-well plate aluminum reactor block with aluminum spacers (equipment available from Analytical Sales and Services). Liquid chemicals were dosed using multi-channel or single-channel pipettors. Solid chemicals were dosed as solutions or slurries in appropriate solvents. Undesired addition solvent was removed using a GeneVac system located inside the glovebox.The reactions were heated and stirred on a heating block with a tumble-stirrer (V&P Scientific) using 1.32 mm diameter x 1.57 mm length parylene stir bars. The tumble stirring mechanism helps to insure uniform stirring throughout the 96-well plate.

The reactions were sealed in the 96-well plate during reaction. Below each reactor vial in the aluminum 96-well plate was a 0.062 mm thick silicon-rubber gasket. Directly above the glass vial reactor tops was a Teflon perfluoroalkoxy copolymer resin sealing gasket and above that, two more 0.062 mm thick silicon-rubber gaskets. The entire assembly was compressed between an aluminum top and the reactor base with 9 evenly- placed screws.

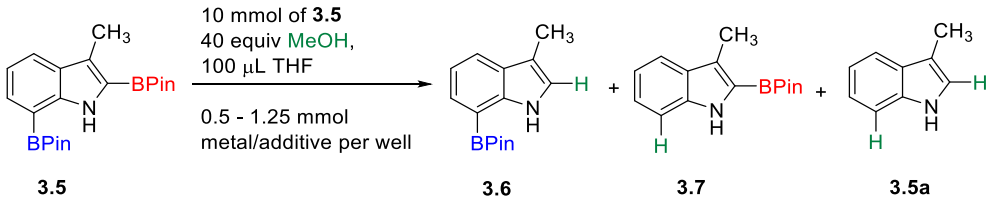
HTE Experiment 1. Deborylation reaction using the additive plate with substrate 3.5 (3-methyl-2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole).

Preperation of (3-methyl-2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole), 3.5.



In a glove box, a 40 mL reaction vial, equipped with a magnetic stirring bar, was charged with 3-methylindole (6.5 g, 50 mmol, 1 equiv) and B_2Pin_2 (12.7 g, 50 mmol, 1 equiv). Two separate test tubes were charged with $[Ir(OMe)(COD)]_2$ (1 g, 1.5 mmol, 6 mol % Ir) and d^{t}bpy (805.2 mg, 3 mmol, 6 mol %). HBpin (4.34 mL, 0.56 mmol, 0.6 equiv) was added to the $[Ir(OMe)(COD)]_2$ test tube. Hexane was added to the d^{t}bpy containing test tube in order to dissolve the d^{t}bpy. The d^{t}bpy solution was then mixed with the $[Ir(OMe)(COD)]_2$ and HBpin mixture. After mixing for 1 min, the resulting solution was transferred to the vial containing the indole substrate. Additional hexane (50 mL) was used to wash the test tubes and the washings were transferred to the vial. The vial was well sealed and stirred at 60 °C. After 6 h, another load of catalyst was added to drive the reaction to completion and the reaction was stirred for 12 h. After complete conversion of 3-methylindole the reaction mixture was passed through a silica

plug to remove the dark brown red color. After further elution with DCM, the volatile materials were removed by rotary evaporation. The crude residue was purified by crystallization with methanol. Indole **3.5** was isolated as a white solid (10.5 g, 55%, mp 163°C). Spectroscopic data is consistent with literature reports.[4] ^{1}H NMR and ^{13}C NMR match for the reported values. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 12H), 1.42 (s, 12H), 7.13-7.09 (m, 2H), 7.71 (dd, J = 7.0, 1.2 Hz, 1H), 7.79 (dt, J = 7.9, 1.0 Hz, 1H), 9.35 (s, 1H); ^{13}C-NMR (101 MHz, CDCl3): δ 24.98, 25.14, 76.84, 77.16, 77.48, 83.97, 84.15, 113.97, 119.46, 125.27, 127.45, 131.41, 143.29.



3.5 **3.6** **3.7** **3.5a**

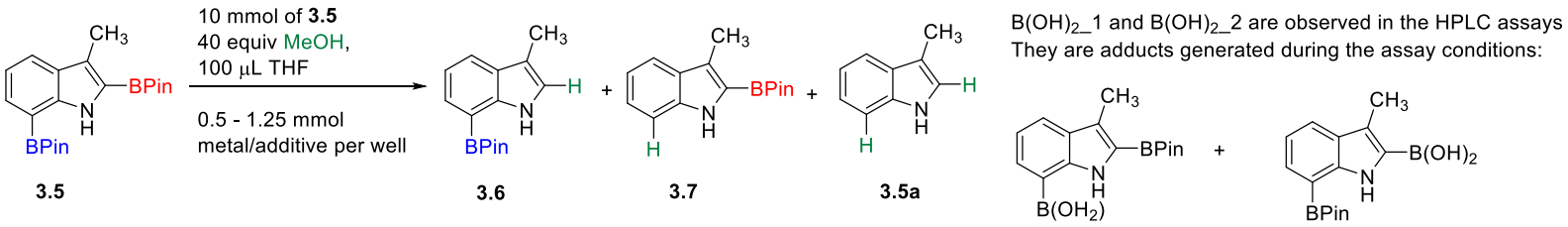
Preparation of Additive plates (Procedure A).

The following procedure is representative of the HTE reactions run in the chapter 3. The additives (0.5 µmol of additives in wells C03, C05, C12 and from E02 to F02, and 1.25 µmol of the rest of the additives) were dosed into the 96-well reactor vial as solutions or well-stirred slurries (10 or 25 µL of 0.05 M) in toluene or tetrahydrofuran (THF) depending upon the solubility of the additive. Slurries were dosed using a single-tip pipettor with the sampling tip cut to allow free flow of the slurry. Plates of these additives were dosed in advance of the reaction, the solvent was removed by evacuation on the GeneVac and the plates were stored in the glovebox.

Additive plate screening.

A parylene stir-bar was added to each vial of the additive plates. Then the (3-methyl-2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole) **3.5** (10 µmol/reaction) and 1,3,5-tri-tertbutylbenzene (1 µmol/reaction) (used as an internal standard to quantify the reaction) were

dosed together into the reaction vials in THF (100 μL). Then 40 equiv of MeOH was added to all the reactions. The reactions were then sealed and stirred at 25 ^{o}C for 4h. Then 10 μL of the reactions was measured into 96-well plate LC block and were diluted with 600 μL of acetonitrile. The 96-well plate LC block was then sealed with a silicon-rubber storage mat, and the reactions were analyzed using standard reverse-phase Agilent HPLC (see methods above).



	1	2	3	4	5	6	7	8	9	10	11	12
A	Control	LiCl	NaF	NaBr	NaI	NaCN	Na TFA	Na TCA	$NaBF_4$	NaOTs	Na2SO3	Na_2S_2O3
B	Na_2SO_4	KCl	CsF	CsCl	$V(acac)_2$	$CrCl_2$	$MnCl_2$	$FeCl_2$	$FeCl_3$	Fe (II) acac	Fe (III) acac	$Co(acac)_2$
C	$Co(acac)_3$	NiF_2	$NiBr_2$ /DME	Ni (II) acac	(PPh_3) $NiCl_2$	CuCl	$CuCl_2$	CuBr	CuI	Cu (II) (acac)	(1,10-phenan)Br_2 Cu II	Cp_2ZrCl_2
D	Mo(acac)	$Pd(OAc)_2$	Pd $(Cl)_2$dppf DCM	$Pd_2(dba)_3$	Ag_2O	AgOTf	AuCl	$AuCl_3$	Mg 325 mesh	Al 200 mesh	Cu <75 micron	Zn 100 mesh
E	Pd black	$Mg(OTf)_2$	$Ca(OTf)_2$	$Sc(OTf)_3$	$Zn(OTf)_2$	$Ga(OTf)_3$	$Y(OTf)_3$	$In(OTf)_3$	Sn (II) OTf_2	$La(OTf)_3$	$Sm(OTf)_3$	$Yb(OTf)_3$
F	$Hf(OTf)_3$	$BiOTf_3$	Boron oxide	$Al(OiPr)_3$	$Ti(OMe)_4$	$CeCl_3$	$ZnCl_2$	$K2CO_3$	$KHCO_3$	KOAc	$K3PO_4$	2,2-diphenyl ethylamine
G	proton sponge	4-phenylpy	oxalic acid	BSA	citric acid	3-phenyl propanoic acid	Bu_4NBr	$NaBH_4$	$PhI(OAc)_2$	CAN	oxone	AIBN
H	BHT	18-Crown-6	4A, MS	diamine	aminoalcohol	TPP	dppf	CataXCium A	X phos	salen	phenantroline	BINOL

The Additive plate**,** designed for rapid improvement of difficult chemistry transformations, has 95-different practical additives and one control reaction (Note: $B(OH)_2$_1 and $B(OH)_2$_2 are observed in the HPLC assays They are adducts generated during the assay conditions)

Table 5.1: Tabulated quantitative HPLC data for metal screen for deborylation at 25 ^{o}C, 4 h.

Well	Additive	% of 3.6	% of 3.6a	% of 3.5a	% $B(OH)_2$_1	% $B(OH)_2$_2	% of 3.5
A:1	Control	0	1.1	0	6.6	1.7	90.6
A:2	LiCl	0	1	0	6.4	1.6	91
A:3	NaF	0	1.1	0	6.3	1.6	91
A:4	NaBr	0	1.1	0	6.4	1.7	90.9
A:5	NaI	0	1.1	0	6.8	1.7	90.5
A:6	NaCN	0	1.5	0	12.9	3.6	82
A:7	NaTFA	0	1.2	0	7.2	1.8	89.8
A:8	NaTCA	0	1.1	0	7.7	1.9	89.4
A:9	$NaBF_4$	0	0	0	7.4	2.5	90.1
A:10	NaOTs	0	1.1	0	7.1	1.8	90
A:11	Na_2SO_3	0	1.1	0	7	1.8	90.2
A:12	$Na_2S_2O_3$	0	1.1	0	7	1.8	90.1
B:1	Na_2SO_4	0	1.1	0	7.1	1.8	90
B:2	KCl	0	1.2	0	7.1	1.8	89.9
B:3	CsF	0	1.4	0	9.6	3.5	85.4
B:4	CsCl	0	1.1	0	7.1	1.9	89.9
B:5	$V(acac)_2$	0	1.1	0	7.1	1.9	89.9
B:6	$CrCl_2$	0	0	0	7.1	1.8	91.1
B:7	$MnCl_2$	0	1.2	0	7.6	1.9	89.4
B:8	$FeCl_2$	0	1.2	0	7.2	1.8	89.8
B:9	$FeCl_3$	0	1.2	0	7.1	1.8	90
B:10	Fe (II) acac	0	1.1	0	6.8	2.1	90
B:11	Fe (III) acac	0	1.1	0	6.8	1.8	90.3

Table 5.1 (cont'd)

B:12	Co $(acac)_2$	0	1.1	0	7.2	1.8	89.9
C:1	$Co(acac)_3$	0	1.1	0	7.3	2.2	89.4
C:2	NiF_2	0	1.1	0	7.4	1.9	89.6
C:3	$NiBr_2$, DME adduct	0	1.1	0	7.3	1.8	89.8
C:4	Ni (II) acac	0	1.1	0	7.2	1.9	89.8
C:5	(Bis-triphenylphosphine) $NiCl_2$	0	1.9	0	7	1.8	89.3
C:6	CuCl	10.7	0	0	5.8	1.6	81.9
C:7	$CuCl_2$	0	0.9	0	7.5	1.8	89.8
C:8	CuBr	2.5	1.5	0	6.3	1.8	88
C:9	CuI	0	0.9	0	6.6	1.8	90.7
C:10	Cu (II) (acac)	10.8	0	0	5.9	1.6	81.7
C:11	Dibromo(1,10-phenanthroline)Cu(II)	0	1.1	0	6.8	1.8	90.3
C:12	Bis(cyclopentadienyl)$ZrCl_2$	0	0	0	7.1	1.8	91.1
D:1	Mo(acac)	0	0.9	0	7.4	3.1	88.6
D:2	$Pd(OAc)_2$	NA	NA	NA	NA	NA	NA
D:3	Dichloro DPPF Pd (II), DCM adduct	0	0.8	0	13.9	1.6	83.6
D:4	$Pd_2(dba)_3$	0	1	0	9.9	3.3	85.8
D:5	Ag_2O	15.8	0	0	5.8	1.6	76.9
D:6	AgOTf	1.7	1.6	0	6.3	1.8	88.7
D:7	AuCl	0	1.1	0	7.1	1.8	90
D:8	$AuCl_3$	0	0.9	0	6.8	1.9	90.4
D:9	Mg, powder, 325 mesh	0	1.1	0	7.2	1.8	90
D:10	Al powder, 200 mesh	0	1.1	0	7	1.8	90.1
D:11	Copper powder, <75 micron	0	0.9	0	6.6	1.8	90.6
D:12	Zn powder, 100 mesh	0	1	0	7.3	2.7	88.9

Table 5.1 (cont'd)

E:1	Pd black	0	1.2	0	7.3	2.9	88.7
E:2	$Mg(OTf)_2$	0	1.1	0	8	2.1	88.8
E:3	$Ca(OTf)_2$	0	1.2	0	7.3	1.9	89.7
E:4	$Sc(OTf)_3$	3.3	0	0	7.6	2.3	86.8
E:5	$Zn(OTf)_2$	10.9	0	0	6	1.6	81.6
E:6	$Ga(OTf)_3$	13.2	0	0	5.7	1.5	79.6
E:7	$Y(OTf)_3$	0	1	0	6.9	1.9	90.2
E:8	$In(OTf)_3$	6.2	0	0	6.2	1.8	85.8
E:9	Sn (II) OTf_2	5	0	0	7	2.7	85.3
E:10	$La(OTf)_3$	0	1.1	0	7.5	1.9	89.5
E:11	$Sm(OTf)_3$	0	1.1	0	7.4	1.9	89.5
E:12	$Yb(OTf)_3$	0	0.7	0	6.8	1.8	90.7
F:1	$Hf(OTf)_3$	5.9	0	1.1	6.1	1.8	85.1
F:2	$BiOTf_3$	52.9	0	5.8	3.7	0	37.6
F:3	Boron oxide	0	1.5	0	12.6	2.9	82.9
F:4	$Al(OiPr)_3$	0	1.3	0	7.6	1.9	89.1
F:5	$Ti(OMe)_4$	0	0	0	7.2	2	90.8
F:6	$CeCl_3$	0	1.2	0	7.8	2.1	89
F:7	$ZnCl_2$	0	0.8	0	7	2	90.2
F:8	$K2CO_3$	0	1.7	0	13.1	5.2	80
F:9	$KHCO_3$	0	1.5	0	10.5	3.7	84.3
F:10	KOAc	0	1.6	0	17	13.5	67.9
F:11	K_3PO_4	0	1.1	0	12.9	5.2	80.8
F:12	2,2-diphenylethylamine	0	1.4	0	8.5	3.5	86.6

Table 5.1 (cont'd)

G:1	proton sponge	0	1.2	0	7.2	1.9	89.7
G:2	4-phenylpyridine	0	1.3	0	7.2	1.9	89.6
G:3	oxalic acid	4.4	0	0	6.9	2.6	86.2
G:4	BSA	1.3	1.3	0	6.6	2.4	88.4
G:5	citric acid	0	0.9	0	7.8	3.1	88.3
G:6	3-phenylpropanoic acid	0	1.1	0	7.4	2.6	88.9
G:7	Bu_4NBr	0	1.1	0	7.2	1.8	90
G:8	$NaBH_4$	0	1.3	0	10	2.6	86.2
G:9	$PhI(OAc)_2$	0	0	0	11.8	3.2	85
G:10	CAN	0	1	0	6.3	1.7	90.9
G:11	oxone	0	1.1	0	6.9	1.9	90.1
G:12	AIBN	0	1.1	0	6.8	1.7	90.4
H:1	BHT	0	1.1	0	6.8	1.7	90.4
H:2	18-Crown-6	0	1	0	6.8	1.8	90.4
H:3	4A, MS, activated	0	1.3	0	7.3	1.8	89.6
H:4	diamine	0	1.2	0	8.2	4.3	86.3
H:5	aminoalcohol	0	1.1	0	7.9	3.2	87.9
H:6	TPP	0	1.1	0	6.6	1.7	90.6
H:7	dppf	0	1.4	0	6.7	1.8	90
H:8	CataXCium A	0	1.7	0	8.2	3.8	86.3
H:9	X phos	0	1	0	5.8	1.5	91.7
H:10	salen	0	1.1	0	7	1.7	90.1
H:11	phenantroline	0	1.1	0	6.8	1.8	90.3
H:12	BINOL	0	1.1	0	6.5	1.9	90.5

Table 5.2: Tabulated quantitative HPLC data for metal screen for deborylation at 40 ^{o}C, 16 h.

Well	Additive	% of 3.6	% of 3.6a	% of 3.5a	% $B(OH)_2$_1	% $B(OH)_2$_2	3.50%
A:1	Control	0.0	0.5	0.0	3.3	1.0	95.3
A:2	LiCl	0.0	1.3	0.0	7.7	2.4	88.6
A:3	NaF	0.0	1.7	0.0	9.2	2.8	86.3
A:4	NaBr	0.0	1.1	0.0	6.2	1.8	90.9
A:5	NaI	0.0	0.8	0.0	4.9	1.6	92.6
A:6	NaCN	0.0	1.5	0.0	10.1	3.4	84.9
A:7	NaTFA	0.0	0.6	0.0	4.2	1.4	93.8
A:8	NaTCA	0.0	0.8	0.0	6.3	1.9	90.9
A:9	$NaBF_4$	0.0	0.0	0.0	6.1	1.8	92.1
A:10	NaOTs	0.0	0.9	0.0	6.2	2.0	90.9
A:11	Na_2SO_3	0.0	1.1	0.0	6.3	1.9	90.6
A:12	$Na_2S_2O_3$	0.0	1.0	0.0	6.3	1.8	90.8
B:1	Na_2SO_4	0.0	1.0	0.0	6.3	1.8	90.8
B:2	KCl	0.0	1.1	0.0	6.6	2.0	90.3
B:3	CsF	0.0	1.1	0.0	9.6	3.0	86.3
B:4	CsCl	0.0	1.1	0.0	6.5	2.0	90.4
B:5	$V(acac)_2$	0.0	1.1	0.0	6.7	2.2	90.0
B:6	$CrCl_2$	0.0	0.0	0.0	6.8	2.2	91.1
B:7	$MnCl_2$	0.0	0.0	0.0	6.8	2.2	91.0
B:8	$FeCl_2$	0.0	0.0	0.0	6.7	2.3	91.1

Table 5.2 (cont'd)

B:9	$FeCl_3$	0.0	1.0	0.0	6.8	2.3	89.9
B:10	Fe (II) acac	0.0	0.0	0.0	6.5	2.2	91.3
B:11	Fe (III) acac	0.0	0.0	0.0	6.5	2.2	91.3
B:12	$Co(acac)_2$	0.0	0.0	0.0	6.7	2.2	91.1
C:1	$Co(acac)_3$	0.0	0.0	0.0	6.7	2.2	91.1
C:2	NiF_2	0.0	0.0	0.0	6.4	1.9	91.7
C:3	$NiBr_2$, DME adduct	0.0	0.0	0.0	6.8	2.1	91.1
C:4	Ni (II) acac	0.0	0.0	0.0	7.1	2.4	90.5
C:5	(Bis-triphenylphosphine) $NiCl_2$	0.0	0.0	0.0	6.4	2.2	91.4
C:6	CuCl	100.0	0.0	0.0	0.0	0.0	0.0
C:7	$CuCl_2$	6.1	0.0	0.0	7.6	0.0	86.2
C:8	CuBr	23.2	0.0	0.0	4.5	0.0	72.3
C:9	CuI	0.0	0.0	0.0	6.2	1.8	92.0
C:10	Cu (II) (acac)	100.0	0.0	0.0	0.0	0.0	0.0
C:11	Dibromo(1,10-phenanthroline)Cu(II)	0.0	0.0	0.0	6.4	2.0	91.5
C:12	Bis(cyclopentadienyl)$ZrCl_2$	0.0	0.0	0.0	7.0	2.3	90.7
D:1	Mo(acac)	0.0	0.0	0.0	7.3	2.6	90.1
D:2	$Pd(OAc)_2$	NA	NA	NA	NA	NA	NA
D:3	Dichloro DPPF Pd (II), DCM adduct	0.0	1.0	0.0	9.4	2.1	87.6
D:4	$Pd_2(dba)_3$	0.0	0.9	0.0	5.9	1.7	91.4
D:5	Ag_2O	72.2	0.0	27.8	0.0	0.0	0.0
D:6	AgOTf	10.0	0.0	0.0	5.8	1.6	82.6
D:7	AuCl	0.0	1.2	0.0	6.8	2.0	90.0
D:8	$AuCl_3$	0.0	0.0	0.0	6.6	1.8	91.6
D:9	Mg, powder, 325 mesh	0.0	1.1	0.0	7.2	2.4	89.2

Table 5.2 (cont'd)

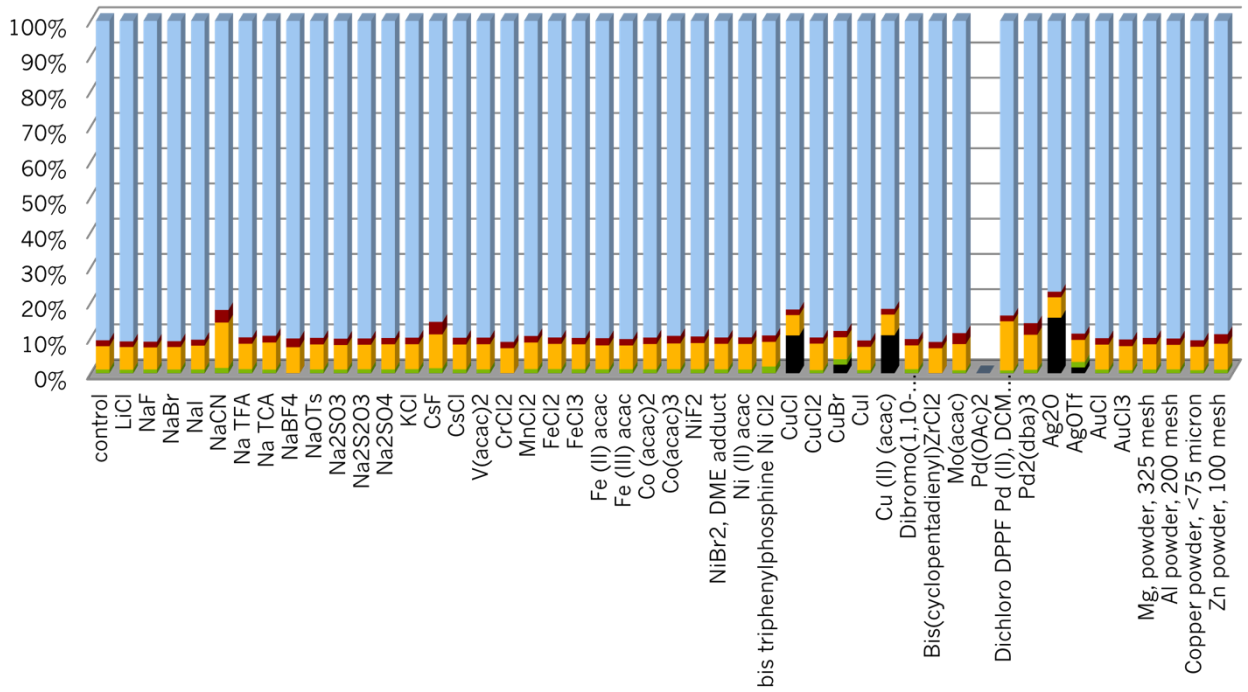
D:10	Al powder, 200 mesh	0.0	1.0	0.0	6.8	2.0	90.1
D:11	Copper powder, <75 micron	0.0	0.0	0.0	6.8	1.9	91.4
D:12	Zn powder, 100 mesh	5.5	0.0	0.0	7.4	2.6	84.5
E:1	Pd black	0.0	1.1	0.0	6.8	2.0	90.1
E:2	$Mg(OTf)_2$	0.0	1.5	0.0	6.6	1.8	90.1
E:3	$Ca(OTf)_2$	0.0	1.1	0.0	7.5	2.4	89.0
E:4	$Sc(OTf)_3$	4.8	0.0	0.0	7.0	1.8	86.4
E:5	$Zn(OTf)_2$	88.0	0.0	12.0	0.0	0.0	0.0
E:6	$Ga(OTf)_3$	100.0	0.0	0.0	0.0	0.0	0.0
E:7	$Y(OTf)_3$	1.7	0.0	0.0	6.7	2.3	89.3
E:8	$In(OTf)_3$	11.8	0.0	2.3	5.9	1.6	78.5
E:9	Sn (II) OTf_2	21.3	0.0	0.0	6.0	2.1	70.6
E:10	$La(OTf)_3$	0.0	0.9	0.0	7.7	2.8	88.6
E:11	$Sm(OTf)_3$	0.0	0.0	0.0	7.8	2.9	89.3
E:12	$Yb(OTf)_3$	5.2	0.0	0.0	6.5	1.8	86.5
F:1	$Hf(OTf)_3$	69.2	0.0	6.6	0.0	0.0	24.2
F:2	$BiOTf_3$	68.6	0.0	31.4	0.0	0.0	0.0
F:3	Boron oxide	1.3	1.9	0.0	7.8	5.9	83.1
F:4	$Al(OiPr)_3$	0.0	1.3	0.0	7.0	2.5	89.2
F:5	$Ti(OMe)_4$	0.0	1.1	0.0	6.7	2.3	89.8
F:6	$CeCl_3$	0.0	0.8	0.0	7.6	2.8	88.7
F:7	$ZnCl_2$	7.9	0.0	0.0	6.6	1.7	83.7
F:8	$K2CO_3$	0.0	1.5	0.0	15.4	8.2	74.9
F:9	$KHCO_3$	0.0	1.0	0.0	11.7	4.6	82.8

Table 5.2 (cont'd)

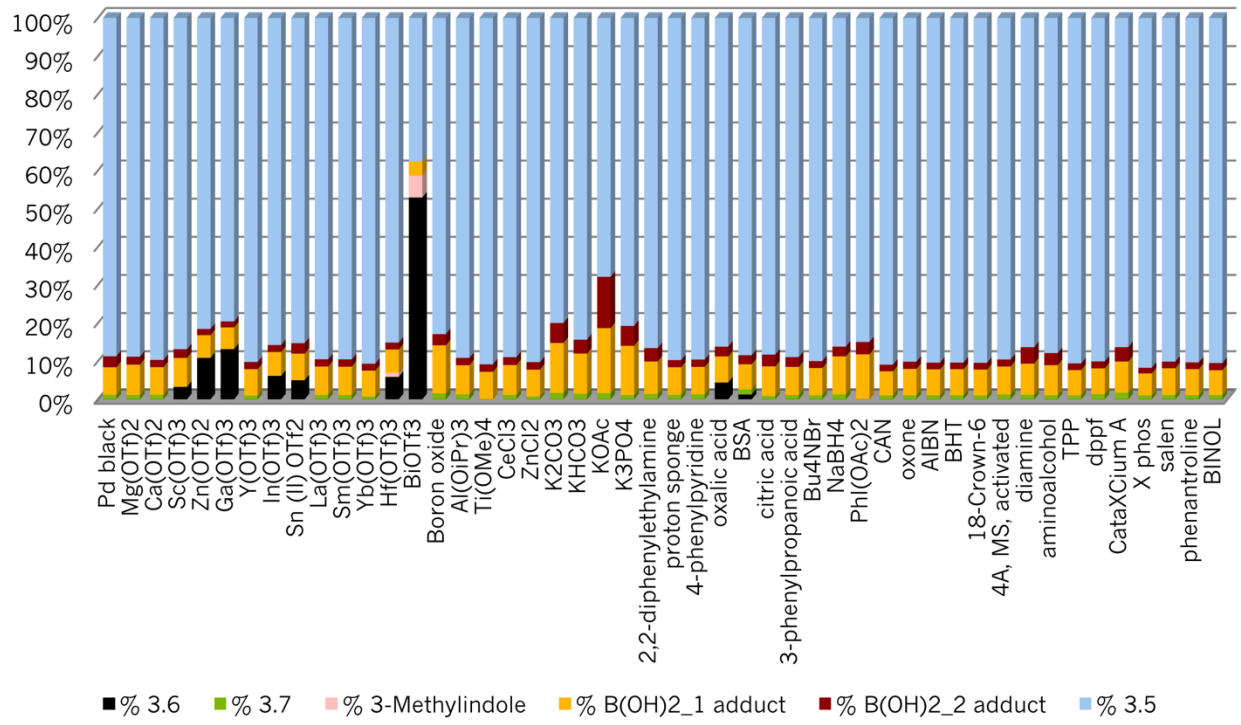
F:10	KOAc	0.0	1.5	0.0	17.5	15.3	65.7
F:11	K_3PO_4	0.0	1.3	0.0	13.7	6.2	78.7
F:12	2,2-diphenylethylamine	0.0	1.2	0.0	9.1	3.9	85.9
G:1	proton sponge	0.0	1.1	0.0	7.1	2.3	89.4
G:2	4-phenylpyridine	0.0	1.1	0.0	6.9	2.1	89.9
G:3	oxalic acid	21.0	0.0	2.4	6.2	1.9	68.5
G:4	BSA	3.7	0.0	0.0	6.5	1.8	88.0
G:5	citric acid	4.0	0.0	0.0	6.9	2.0	87.2
G:6	3-phenylpropanoic acid	0.0	1.2	0.0	7.4	2.0	89.4
G:7	Bu_4NBr	0.0	1.1	0.0	8.1	2.8	88.0
G:8	$NaBH_4$	0.0	1.3	0.0	11.9	3.9	83.0
G:9	$PhI(OAc)_2$	0.0	1.5	0.0	10.8	3.3	84.3
G:10	CAN	0.0	0.8	0.0	6.5	1.7	90.9
G:11	oxone	0.0	1.1	0.0	11.6	2.6	84.7
G:12	AIBN	0.0	1.0	0.0	6.7	2.0	90.3
H:1	BHT	0.0	1.7	0.0	6.9	2.1	89.4
H:2	18-Crown-6	0.0	1.0	0.0	7.5	2.4	89.0
H:3	4A, MS, activated	0.0	1.2	0.0	7.7	2.7	88.4
H:4	diamine	0.0	1.2	0.0	9.2	4.1	85.5
H:5	aminoalcohol	0.0	1.3	0.0	8.7	2.8	87.2
H:6	TPP	0.0	1.0	0.0	6.8	2.1	90.1
H:7	dppf	0.0	1.3	0.0	6.8	2.4	89.5
H:8	CataXCium A	0.0	1.8	0.0	10.4	4.5	83.3
H:9	X phos	0.0	1.0	0.0	6.1	2.0	91.0
H:10	salen	0.0	1.5	0.0	10.9	3.6	84.0
H:11	phenantroline	0.0	1.2	0.0	8.0	2.5	88.4

Table 5.2 (cont'd)							
H:12	BINOL	0.0	1.3	0.0	7.2	2.2	89.3

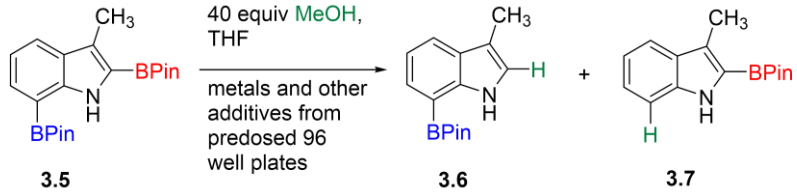
Metal Screen for Deborylation at 25 °C, 4h (From A1:D12)

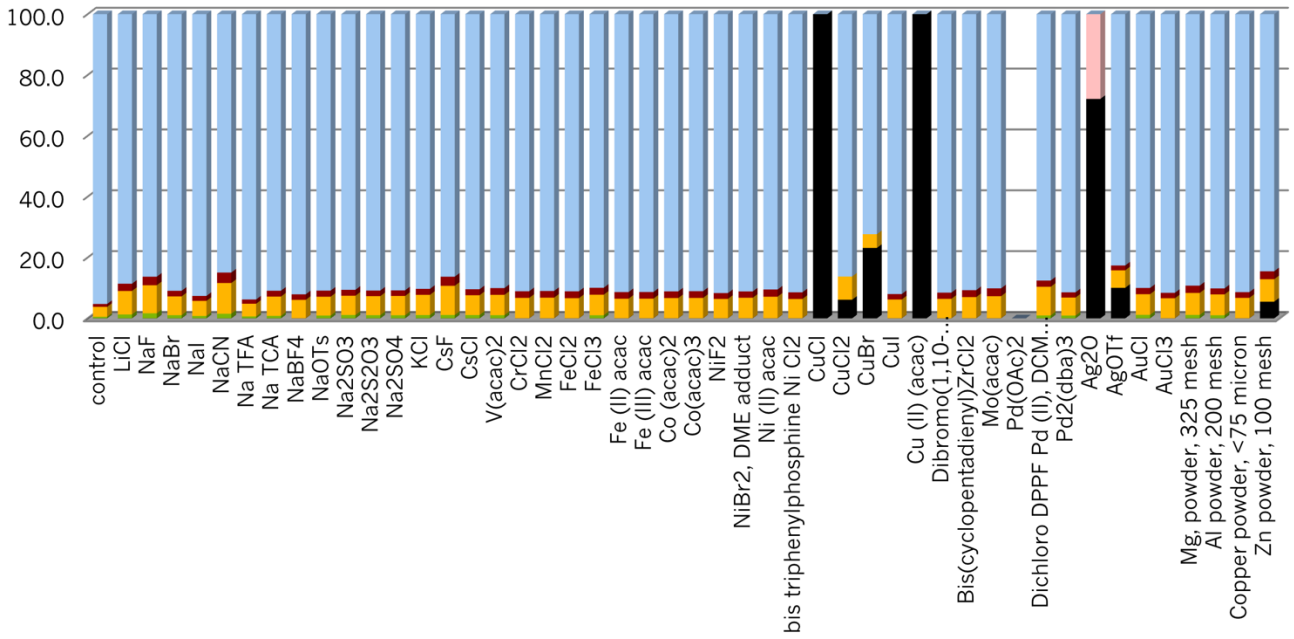


Metal Screen for Deborylation at 25 °C, 4h (From E1:H12)

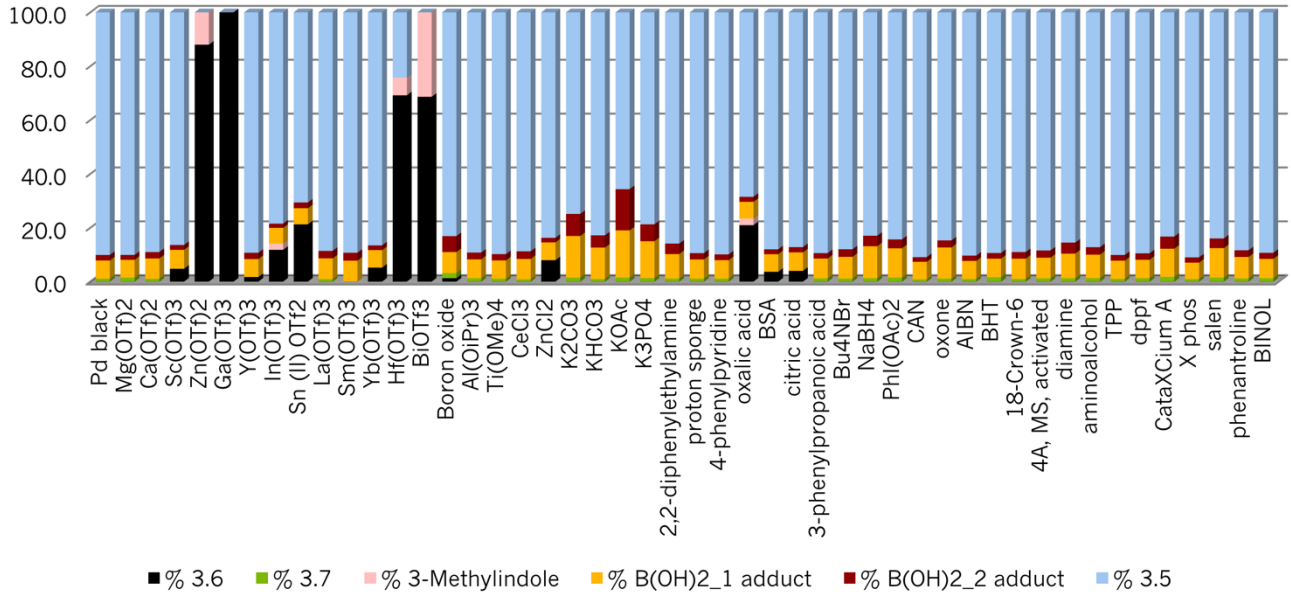


Metal Screen for Deborylation at 40 °C, 16h (From A1:D12)

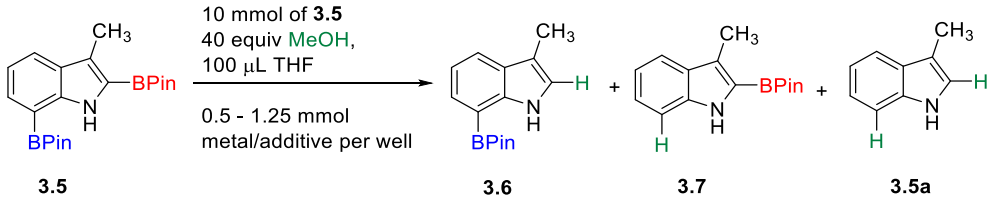




Metal Screen for Deborylation at 40 °C, 16h (From E1:H12)



HTE Experiment 2: Deborylation reaction using the modified additive plate with substrate 3.5 (3-methyl-2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole) .



Preparation of additive plates with new screening additives.

As given in the general procedure A, the additives (5 μmol of additives per well) were dosed into the 96-well reactor vial as solutions or well-stirred slurries (30 μL of 0.166 M) in MeOH. Slurries were dosed using a single-tip pipettor with the sampling tip cut to allow free flow of the slurry. Plates of these additives were dosed in advance of the reaction, the solvent was removed by evacuation on the GeneVac and the plates were stored in the glovebox. In this way 4 additives plates were produced. (Which contain two sets of Metal salts as shown Figure S4)

Additive plate screening.

A parylene stir-bar was added to each vial of the additive plates. Then the (3-methyl-2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole) 5 (10 μmol/reaction) and 1,3,5-tri-tertbutylbenzene (1 μmol/reaction) (used as an internal standard to quantify the reaction) were dosed together into the reaction vials in THF (100 μL) and the solvent was removed by evacuation on the GeneVac. Then THF (100 μL) was added for wells from A1 – D9 followed by DMF (100 μL) for wells E1 – H9. Finally 40 equiv of MeOH was added to all the reactions. The reactions were then sealed and stirred at 25 ^{o}C for 4h. Then 10 μL of the reactions was measured into 96-well plate LC block and were diluted with 600 μL of acetonitrile. The 96-well plate LC block was then sealed with a silicon-rubber storage mat, and the reactions were analyzed using standard reverse-phase Agilent HPLC (see methods above).

	1	2	3	4	5	6	7	8	9	10	11	12
A	control	Sc(OTf)3	$Cp_2Ti(OTf)2$	TiCl3	VCl3	Fe(OTf)2	Fe(NO3)3	CoCl2	Co(NO3)2	Ni(OTf)2	CuCl	CuCl2
B	Cu(OTf)2	Cu(MeCN)4 PF6	Zn(OTf)2	Ga(OTf)3	Ga(ClO4)3	Y(OTf)3	YCl3	ZrCl4	RuCl3	PdBr2	Ag2O	AgOTf
C	(nBu4N)2Ag2I4	Cd(OAc)2	Cd(ClO4)2	InCl3	In(OTf)3	SnCl2	Sn(OTf)2	SbF3	HfCl4	Hf(OTf)4	W(CO)6	PbCl2
D	BiCl3	Bi(OTf)3	Bi(NO3)3	Bi(OAc)3	BiF3	BiOClO4	Sb(OAc)3	Ce(OTf)4	Oxalic Acid			
E	control	Sc(OTf)3	$Cp_2Ti(OTf)2$	TiCl3	VCl3	Fe(OTf)2	Fe(NO3)3	CoCl2	Co(NO3)2	Ni(OTf)2	CuCl	CuCl2
F	Cu(OTf)2	Cu(MeCN)4 PF6	Zn(OTf)2	Ga(OTf)3	Ga(ClO4)3	Y(OTf)3	YCl3	ZrCl4	RuCl3	PdBr2	Ag2O	AgOTf
G	(nBu4N)2Ag2I4	Cd(OAc)2	Cd(ClO4)2	InCl3	In(OTf)3	SnCl2	Sn(OTf)2	SbF3	HfCl4	Hf(OTf)4	W(CO)6	PbCl2
H	BiCl3	Bi(OTf)3	Bi(NO3)3	Bi(OAc)3	BiF3	BiOClO4	Sb(OAc)3	Ce(OTf)4	Oxalic Acid			

The Additive plate with new metal salts.

Table 5.3: Tabulated quantitative HPLC data for metal screen for deborylation at 25 ^{o}C, 4 h. for HTE 2 experiment:

Location	Additive	% of 3.6	% 3.5a	% $B(OH)_2$_isomers	% 3.5
A:1	Control	1.3	0.0	22.8	75.9
A:2	$Sc(OTf)_3$	85.0	15.0	0.0	0.0
A:3	$Cp_2Ti(OTf)_2$	64.8	0.0	6.8	28.4
A:4	$TiCl_3$	1.1	0.0	21.6	77.4
A:5	VCl_3	0.0	0.0	8.1	91.9
A:6	$Fe(OTf)_2$	1.6	0.0	7.0	91.4
A:7	$Fe(NO_3)_3$	1.9	0.0	6.1	92.0
A:8	$CoCl_2$	1.6	0.0	12.6	85.8
A:9	$Co(NO_3)_2$	1.6	0.0	15.0	83.5
A:10	$Ni(OTf)_2$	1.1	0.0	9.0	89.9
A:11	CuCl	6.6	0.0	7.6	85.8
A:12	$CuCl_2$	0.0	0.0	1.9	98.1
B:1	$Cu(OTf)_2$	12.4	0.0	1.8	85.8
B:2	$Cu(MeCN)_4$ PF_6	30.8	0.0	5.1	64.0
B:3	$Zn(OTf)_2$	0.0	0.0	2.2	97.8
B:4	$Ga(OTf)_3$	90.6	9.4	0.0	0.0
B:5	$Ga(ClO_4)_3$	84.9	15.1	0.0	0.0
B:6	$Y(OTf)_3$	74.7	7.2	0.0	18.1
B:7	YCl_3	0.0	0.0	8.8	91.2
B:8	$ZrCl_4$	4.5	0.0	7.4	88.2
B:9	$RuCl_3$	1.5	0.0	9.1	89.4
B:10	$PdBr_2$	0.8	0.0	7.6	91.5
B:11	Ag_2O	66.6	33.4	0.0	0.0
B:12	AgOTf	1.4	0.0	10.4	88.2
C:1	$(nBu_4N)_2Ag_2I_4$	1.1	0.0	8.5	90.4
C:2	$Cd(OAc)_2$	10.6	0.0	8.7	80.7
C:3	$Cd(ClO_4)_2$	0.6	0.0	9.3	90.1
C:4	$InCl_3$	2.1	0.0	7.7	90.2
C:5	$In(OTf)_3$	10.9	0.0	9.0	80.0
C:6	$SnCl_2$	0.6	0.0	7.7	91.6
C:7	$Sn(OTf)_2$	25.4	0.0	7.6	67.0
C:8	SbF_3	7.0	0.0	7.6	85.5
C:9	$HfCl_4$	3.2	0.0	8.3	88.5
C:10	$Hf(OTf)_4$	83.3	8.9	0.0	7.8
C:11	$W(CO)_6$	0.0	0.0	8.6	91.4
C:12	$PbCl_2$	1.3	0.0	10.9	87.8

Table 5.3 (cont'd)

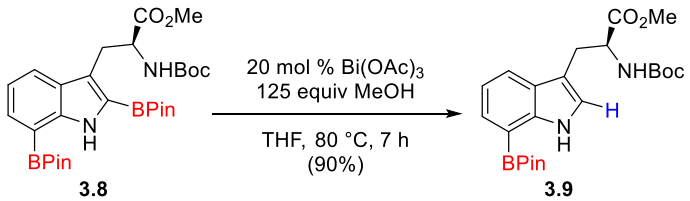
D:1	$BiCl_3$	0.9	0.0	9.6	89.5
D:2	$Bi(OTf)_3$	77.1	16.6	0.0	6.3
D:3	$Bi(NO_3)_3$	2.0	0.0	8.1	89.9
D:4	$Bi(OAc)_3$	89.0	11.0	0.0	0.0
D:5	BiF_3	1.5	0.0	7.1	91.4
D:6	$BiOClO_4$	38.0	0.0	6.8	55.2
D:7	$Sb(OAc)_3$	0.9	0.0	7.8	91.3
D:8	$Ce(OTf)_4$	3.4	0.0	7.8	88.8
D:9	Oxalic Acid	9.4	0.0	9.1	81.5
E:1	Control	1.4	0.0	9.8	88.8
E:2	$Sc(OTf)_3$	1.6	0.0	13.8	84.6
E:3	$Cp_2Ti(OTf)_2$	1.8	0.0	9.2	89.0
E:4	$TiCl_3$	1.4	0.0	9.4	89.2
E:5	VCl_3	1.0	0.0	8.0	91.0
E:6	$Fe(OTf)_2$	1.1	0.0	8.6	90.3
E:7	$Fe(NO_3)_3$	1.1	0.0	8.1	90.8
E:8	$CoCl_2$	1.3	0.0	8.4	90.3
E:9	$Co(NO_3)_2$	1.2	0.0	9.5	89.3
E:10	$Ni(OTf)_2$	1.2	0.0	8.1	90.8
E:11	CuCl	100.0	0.0	0.0	0.0
E:12	$CuCl_2$	1.9	0.0	9.0	89.1
F:1	$Cu(OTf)_2$	1.4	0.0	9.2	89.4
F:2	$Cu(MeCN)_4\ PF_6$	70.7	0.0	0.0	29.3
F:3	$Zn(OTf)_2$	1.0	0.0	2.0	97.0
F:4	$Ga(OTf)_3$	0.0	0.0	2.1	97.9
F:5	$Ga(ClO_4)_3$	0.0	0.0	2.2	97.8
F:6	$Y(OTf)_3$	0.0	0.0	2.5	97.5
F:7	YCl_3	1.2	0.0	2.3	96.5
F:8	$ZrCl_4$	0.0	0.0	4.5	95.5
F:9	$RuCl_3$	1.0	0.0	9.2	89.8
F:10	$PdBr_2$	0.9	0.0	8.3	90.8
F:11	Ag_2O	50.5	0.0	8.3	41.2
F:12	AgOTf	1.1	0.0	15.8	83.2
G:1	$(nBu_4N)_2Ag_2I_4$	1.2	0.0	14.5	84.3
G:2	$Cd(OAc)_2$	39.9	0.0	9.0	51.1
G:3	$Cd(ClO_4)_2$	1.5	0.0	13.1	85.4
G:4	$InCl_3$	1.6	0.0	12.8	85.5
G:5	$In(OTf)_3$	6.6	0.0	13.4	80.0
G:6	$SnCl_2$	5.1	0.0	13.4	81.5
G:7	$Sn(OTf)_2$	3.7	0.0	13.2	83.1

Table 5.3 (cont'd)					
G:8	SbF_3	6.0	0.0	13.8	80.1
G:9	$HfCl_4$	1.3	0.0	15.6	83.1
G:10	$Hf(OTf)_4$	1.1	0.0	15.1	83.7
G:11	$W(CO)_6$	0.0	0.0	13.1	86.9
G:12	$PbCl_2$	0.8	0.0	14.3	84.9
H:1	$BiCl_3$	0.8	0.0	12.7	86.6
H:2	$Bi(OTf)_3$	30.5	0.0	7.9	61.5
H:3	$Bi(NO_3)_3$	7.7	0.0	13.4	78.9
H:4	$Bi(OAc)_3$	65.3	0.0	4.3	30.4
H:5	BiF_3	0.8	0.0	11.3	87.9
H:6	$BiOClO_4$	52.2	0.0	5.5	42.2
H:7	$Sb(OAc)_3$	1.0	0.0	11.5	87.5
H:8	$Ce(OTf)_4$	1.6	0.0	11.7	86.7
H:9	Oxalic Acid	9.5	0.0	12.0	78.5

Experimental Details and Spectroscopic Data[5]

The experimental data are reported: (a) Shen, F.; Tyagarajan, S.; Perera, D.; Krska, S. W.; Maligres, P. E.; Smith, M. R., III; Maleczka, R. E., Jr.; *Org. Lett*. **2016**, *18*, 1554–1557. (b) Shen, F. carried out the experiments and also reported as Shen, F. Discovery and the Development of Bismuth Salt Mediated Catalytic Deborylation and Allied Studies. MSc. Thesis, Michigan State University, East Lansing, 2015.

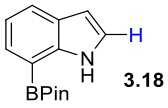
7-Bpin-Boc-L-tryptophan methyl ester (3.8) via Scheme 3.5.



The general Bi-catalyzed deboronation procedure was applied to 2,7-bis(Bpin)-Boc-L-tryptophan methyl ester **3.8** (39 mg, 0.068 mmol) and $Bi(OAc)_3$ (5.3 mg, 0.0137 mmol, 20 mol%) with a MeOH /THF solvent mixture (0.34 mL / 0.27 mL) at 80 °C for 7 h. The crude material was concentrated and purified by column chromatography (20% ethyl acetate/hexanes) on silica gel. The product (**2**) was isolated as white solid (27 mg, 90%, mp 177 °C). ^{1}H NMR (CD_3OD, 500 MHz) δ 9.13 (br s, 1 H), 7.67 (d, *J* = 7.8 Hz, 1 H), 7.64 (d, *J* = 6.8 Hz, 1 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 7.06 (s, 1 H), 5.06 (d, *J* = 7.8, 1 H), 4.64 (m, 1 H), 3.67 (s, 3 H), 3.31 (d, *J* = 4.9, 2 H), 1.43 (s, 9), 1.39 (s, 12 H); ^{13}C NMR (CD_3OD, 125 MHz) δ 172.7, 155.2, 141.3, 129.5, 126.6, 122.7, 122.3, 119.1, 109.6, 83.8, 79.7, 54.2, 52.2, 28.3, 27.9, 25.0. The spectral data were in accordance with literature values.[4]

Deboronation Details for Table 3.2

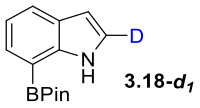
Table 2, entry 1. 7-Bpin-indole (3.18).



3.18

The general Bi-catalyzed deboronation procedure was applied to 2,7-bis(Bpin)-indole **3.10** (36.9 mg, 0.1 mmol, 1 equiv) and $Bi(OAc)_3$ (7.72 mg, 0.02 mmol, 20 mol%) with a solvent mixture of MeOH /THF (0.5 mL /0.4 mL) at 80 °C for 17 h. The crude material was concentrated and purified by column chromatography (5% ethyl acetate/hexanes) on silica gel. Indole **3.18** was isolated as a white solid (20 mg, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.25 (br s, 1 H), 7.79 (d, *J* = 7.9 Hz, 1 H), 7.68 (d, *J* = 7.0 Hz, 1 H), 7.28 (dd, *J* = 2.8, 2.8 Hz, 1 H), 7.15 (dd, *J* = 7.5, 7.5 Hz, 1 H), 6.57 (dd, *J* = 2.8, 2.8 Hz, 1 H), 1.41 (s, 12 H, 4 C*H*$_3$ of Bpin); ^{13}C NMR ($CDCl_3$,125 MHz): δ 141.0 (C), 129.2 (CH), 126.8 (C), 124.2 (CH), 124.0 (CH), 119.3 (CH), 102.0 (CH), 83.8 (2 C), 25.0 (4 CH_3 of Bpin); ^{11}B NMR ($CDCl_3$, 160 MHz): 30.8. The spectral data were in accordance with literature values.[5]

Table 2, entry 2. 7-Bpin-indole-2d (3.18-*d*$_1$).

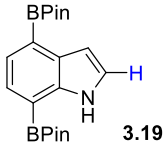


3.18-*d*$_1$

A vial equipped with a magnetic stirring bar was charged with 2,7-bis(Bpin)-indole **3.10** (185 mg, 0.5 mmol, 1 equiv) and $Bi(OAc)_3$ (38.6 mg, 0.1 mmol, 0.2 equiv). A solvent mixture of CD_3OD (810 μL, 20 mmol, 40 equiv) and THF (2 mL) was added to the vial. The vial was sealed and the reaction was carried out at rt. After completion of the reaction as judged by TLC, the crude material was passed through a plug of celite. The celite was washed three times with ethyl acetate. After the volatiles were removed by a rotary evaporation, the crude material was purified by column chromatography (5% ethyl acetate/hexanes) on silica gel. Indole **3.18-*d*$_1$** was isolated

as a white solid (101 mg, 83%, mp 87–88 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.31 (br s, 1 H), 7.84 (d, *J* = 7.8 Hz, 1 H), 7.74 (d, *J* = 6.9 Hz, 1 H), 7.31 (t, *J* = 2.9 Hz, 0.13 H), 7.20 (t, *J* = 7.8 Hz, 1 H), 6.61 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$,125 MHz): δ 140.9, 129.2, 126.7, 124.2, 123.9 (t, *J* = 25.8 Hz), 119.2, 101.9, 101.7, 83.8 (2 C), 25.0 (4 CH_3 of Bpin); ^{11}B NMR ($CDCl_3$, 160 MHz): 31.2; FT-IR (neat) $\tilde{\nu}_{max}$: 3457, 2977, 1592, 1503, 1367, 1314, 1130, 978, 845, 805, 753, 678 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{14}H_{18}DBNO_2$ $[M+H]^+$ 245.15, found 245.1. Percent deuterium incorporation (based on quantitative ^{1}H NMR): 92%

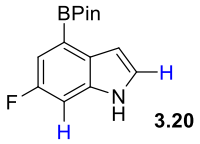
Table 2, entry 3. 4,7-Bis(Bpin)-indole (3.19).



3.19

The general Bi-catalyzed deboronation procedure was applied to 2,4,7-tri(Bpin)-indole **3.11** (100 mg, 0.2 mmol, 1 equiv) and $Bi(OAc)_3$ (15.4 mg, 0.04 mmol, 20 mol%) with a solvent mixture of MeOH /THF (1 mL /0.8 mL) at 80 °C for 17 h. The crude material was concentrated and purified by column chromatography (5% ethyl acetate/hexanes) on silica gel. Indole **3.19** was isolated as a white solid (55.4 mg, 75%, mp 225°C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.24 (br s, 1 H), 7.64 (d, *J* = 7.3 Hz, 1 H), 7.63 (d, *J* = 7.3 Hz, 1 H), 7.31 (dd, *J* = 5.4, 2.9 Hz, 1 H), 7.03 (dd, *J* = 4.9, 2.9 Hz, 1 H), 1.40 (d, *J* = 2.5 Hz, 24 H, 8 C*H*$_3$ of Bpin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.3, 131.5, 128.2, 126.9, 124.4, 103.9, 83.9 (2 C), 83.4 (2 C), 25.0 (8 CH_3 of Bpin); ^{11}B NMR ($CDCl_3$, 160 MHz): δ 31.6; FT-IR (neat) $\tilde{\nu}_{max}$: 3426, 2978, 1400, 1325, 1137, 1067, 968, 856 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{20}H_{30}B_2NO_4$ $[M+H]^+$ 370.23, found 370.3.

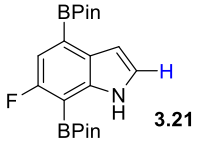
Table 2, entry 4. 4-Bpin-6-fluoro-indole (3.20).



3.20

The general Bi-catalyzed deboronation procedure was applied to 2,4,7-tri(Bpin)-6-fluoroindole **3.12** (513 mg, 1 mmol, 1 equiv) and $Bi(OAc)_3$ (77.2 mg, 0.2 mmol, 20 mol%) with a solvent mixture of MeOH /THF (10 mL /4 mL) at 80 °C for 15 h. The crude material was concentrated and purified by column (10% ethyl acetate/hexanes) on silica gel. Indole **3.20** was isolated as white solid (205 mg, 80%, mp 114°C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.27 (br s, 1 H), 7.46 (dd, *J* = 10.3, 2.5 Hz, 1 H), 7.18 (dd, *J* = 2.9, 2.9 Hz, 1 H), 7.14 (dd, *J* = 9.3, 1.5 Hz, 1 H), 7.07 (dd, *J* = 2.5, 2.5 Hz, 1 H), 1.43 (s, 12 H, 4 C*H*$_3$ of Bpin); ^{13}C NMR ($CDCl_3$,125 MHz): δ 159.3 (d, *J* = 237.0 Hz), 135.3 (d, *J* = 11.5 Hz), 129.1, 125.1 (d, *J* = 3.8 Hz), 115.3 (d, *J* = 22.9 Hz), 104.3, 100.3 (d, *J* = 25.8 Hz), 83.7 (2 C), 24.9 (4 CH_3 of Bpin); ^{11}B NMR ($CDCl_3$, 160 MHz): 31.3; FT-IR (neat) $\tilde{n}_{max}$: 3344, 2979, 1612, 1384, 1264, 1137, 1064, 966, 849, 782, 682 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{14}H_{18}BFNO_2$ $[M+H]^+$ 261.13, found 262.1.

Table 2, entry 5. 4,7-Bis(Bpin)-6-fluoro-indole (3.21).

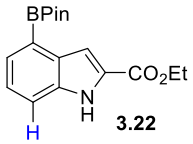


3.21

The general Bi-catalyzed deboronation procedure was applied to 2,4,7-tri(Bpin)-6-fluoroindole **3.12** (513 mg, 1 mmol, 1 equiv) and $Bi(OAc)_3$ (77.2 mg, 0.2 mmol, 20 mol%) with a solvent mixture of MeOH /THF (2.5 mL /4 mL) at 80 °C for 5 h. The crude material was concentrated and purified by column (5% ethyl acetate/hexanes) on silica gel. Indole **3.21** was isolated as white solid (259 mg, 67%, mp 185°C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.34 (br s, 1 H), 7.33 (d, *J* = 10.3 Hz, 1 H), 7.27 (dd, *J* = 2.9, 2.0 Hz, 1 H), 6.98 (dd, *J* = 2.9, 2.0 Hz, 1 H), 1.42 (s, 12 H, 4

C*H*$_3$ of Bpin), 1.39 (s, 12 H, 4 C*H*$_3$ of Bpin); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.3 (d, *J* = 246.0 Hz), 140.4, 128.1, 124.6 (d, *J* = 3.8 Hz), 114.9 (d, *J* = 25.8 Hz), 103.9, 83.9 (2 C), 83.8 (2 C), 25.0 (8 CH_3 of Bpin); ^{11}B NMR ($CDCl_3$, 160 MHz): 30.4; FT-IR (neat) $\tilde{\nu}_{max}$: 3125, 2923, 1559, 1401, 1256, 1139, 1063, 853 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{20}H_{29}B_2FNO_4$ $[M+H]^+$ 387.22, found 388.3.

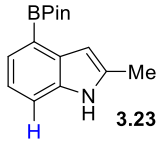
Table 2, entry 6 (Ir). 4-Bpin-2-carboethoxy-indole (3.22).



3.22

The deboronation step was carried out neat with 4,7-bis(Bpin)-2-ethyl ester-indole **3.14** (220.5 mg, 0.5 mmol), $[Ir(OMe)(COD)]_2$ (10 mg, 0.015 mmol, 6 mol % Ir) in MeOH (800 μL, 20 mmol, 40 equiv) and THF (5 mL) at rt for 12 h and worked up as described in the general Ir-catalyzed deboronation procedure. The crude material consisting of a 3:1 mixture of **3.22** and 2-ethylesterindole was concentrated by rotary evaporation and purified by column chromatography (5% ethylacetate/hexanes) on silica gel. Indole **3.22** was isolated as a white solid (85 mg, 54%, mp 139 °C) along with 2-ethylesterindole (12 mg, 13%). For **3.22**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.14 (br s, 1 H), 7.70 (m, 1 H), 7.68 (dd, *J* = 6.9, 1.0 Hz, 1 H), 7.54 (d, *J* = 8.3 Hz, 1 H), 7.34 (dd, *J* = 8.3, 7.3 Hz, 1 H), 4.45 (q, *J* = 6.9 Hz, 2 H, *C*H_2CH$_3$), 1.45 (t, *J* = 7.3 Hz, 3 H, CH$_2$*C*H_3), 1.41 (s, 12 H, 4 C*H*$_3$ of Bpin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.3 (C=O), 136.2, 131.7, 129.0, 127.6, 124.6 (C), 114.8, 110.5, 83.6 (2 C), 61.0 (CH_2), 24.9 (4 CH_3 of Bpin), 14.4 (CH_3); ^{11}B NMR ($CDCl_3$, 160 MHz): δ 30.8; FT-IR (neat) $\tilde{\nu}_{max}$: 3331, 2979, 1686, 1521, 1250, 1146, 1022, 980, 852, 769, 681 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{17}H_{23}BNO_4$ $[M+H]^+$ 316.16, found 316.2.

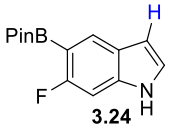
Table 2, entry 7 (Ir). 4-Bpin-2-methyl-indole (3.23).



3.23

The deborylation step was carried out neat with 4,7-Bpin-2-methylindole **3.15** (38 mg, 0.1 mmol, 1 equiv), $[Ir(OMe)(COD)]_2$ (1 mg, 0.0015 mmol, 3 mol % Ir) in MeOH and DCM (2:1, 0.5 mL) at 60 °C for 2 h and worked up as described in the general Ir-catalyzed deboronation procedure. The crude material was purified by silica gel chromatography (5% ethyl acetate/hexanes) on silica gel to afford **3.23** as a white solid (20 mg, 74%, mp 157–160 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.88 (br s, 1 H), 7.58 (d, *J* = 6.9 Hz, 1 H), 7.38 (d, *J* = 7.8 Hz, 1 H), 7.11 (t, *J* = 7.8 Hz, 1 H), 6.71 (s, 1 H), 2.47 (s, 3 H), 1.39 (s, 12 H, 4 C*H*$_3$ of Bpin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.7, 135.4, 133.9, 127.6, 120.3, 113.0, 102.4, 83.3 (C), 25.0 (4 CH_3 of Bpin), 13.8 (CH_3); ^{11}B NMR ($CDCl_3$, 160 MHz): δ 30.9; FT-IR (neat) $\tilde{\nu}_{max}$: 3436, 2976, 1549, 1371, 1269, 1130, 1064, 973, 858, 637 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{15}H_{21}BNO_2$ $[M+H]^+$ 258.16, found 258.2.

Table 2, entry 8 (Bi). 5-Bpin-6-fluoro-indole (3.24).



3.24

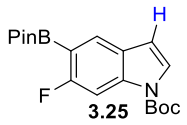
The general Bi-catalyzed deboronation procedure was applied to 3,5-bis(Bpin)-6-fluoro-indole **3.16** (77 mg, 0.2 mmol, 1 equiv) and $Bi(OAc)_3$ (15.4 mg, 0.04 mmol, 20 mol%) with a solvent mixture of MeOH /THF (0.8 mL /0.4 mL) at 80 °C for 3 h. The crude material was concentrated and purified by column (5% ethyl acetate/hexanes) on silica gel. Indole **3.24** was isolated as a white solid (46 mg, 88%, mp 159-162°C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.18 (br s, 1 H), 8.05 (d, *J* = 5.4 Hz, 1 H), 7.17 (dd, *J* = 3.4, 2.5 Hz, 1 H), 7.04 (d, *J* = 10.3 Hz, 1 H), 6.53 (dd, *J* = 2.5 Hz, 1.0 H), 1.38 (s, 12 H, 4 C*H*$_3$ of Bpin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.1 (d, *J* = 242 Hz),

138.2 (d, J = 13.4 Hz), 129.6 (d, J = 10.5 Hz), 128.3, 124.7 (d, J = 3.8 Hz), 103.1, 97.1 (d, J = 29.6 Hz), 83.5 (2 C), 24.8 (4 CH_3 of Bpin); ^{11}B NMR ($CDCl_3$, 160 MHz): 30.7; FT-IR (neat) $\tilde{\nu}_{max}$: cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{14}H_{18}BFNO_2$ $[M+H]^+$ 261.13, found 262.1.

Table 2, entry 8 (Ir). 5-Bpin-6-fluoro-indole (3.24).

The deboronation step was carried out neat with 3,5-bis(Bpin)-6-fluoro-indole **3.16** (193 mg, 0.5 mmol, 1 equiv), $[Ir(OMe)(COD)]_2$ (5 mg, 0.0075 mmol, 3 mol % Ir) in MeOH and DCM (2:1, 2.5 mL) at 60 °C for 2 h and worked up as described in the general Ir-catalyzed deboronation procedure. The crude material was purified by silica gel chromatography (30% ethyl acetate/hexanes) on silica gel to afford **3.24** as white solid (86 mg, 66%).

Table 2, entry 9 (Ir). 5-Bpin-N-Boc-indole (3.25).

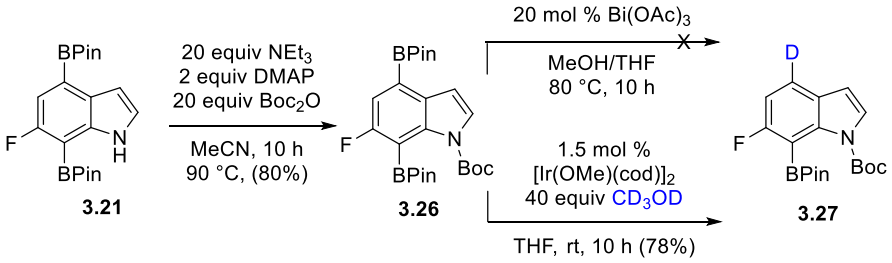


3.25

The deborylation step was carried out neat with 3,5-bis(Bpin)-N-Boc-indole **3.17** (195 mg, 0.4 mmol), $[Ir(OMe)(COD)]_2$ (8 mg, 0.012 mmol, 6 mol % Ir) in MeOH (800 μL, 20 mmol, 50 equiv) and THF (4 mL) at rt for 10 h and worked up as described in the general Ir-catalyzed deboronation procedure. The crude material was concentrated by by rotary evaporation and purified by column chromatography (5% ethyl acetate/hexanes) on silica gel. Indole **3.25** was isolated as a colorless oil (67 mg, 47%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 (d, J = 5.9 Hz, 1 H), 7.82 (br d, J = 8.3 Hz, 1 H), 7.53 (d, J = 2.9 Hz, 1 H), 6.53 (d, J = 3.9 Hz, 1 H), 1.66 (s, 9 H, 3 CH_3 of Boc), 1.38 (s, 12 H, 4 CH_3 of Bpin); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.1 (d, J = 244 Hz), 149.4, 129.1 (d, J = 9.5 Hz), 126.6, 126.2 (d, J = 3.8 Hz), 107.2, 102.2 (d, J = 31.5 Hz), 84.1 (C), 83.7 (2 C), 28.1 (3 CH_3 of Boc), 24.8 (4 CH_3 of Bpin); ^{11}B NMR ($CDCl_3$, 160 MHz):

30.1; FT-IR (neat) $\tilde{\nu}_{max}$: 3443, 2979, 1737, 1622, 1446, 1359, 1257, 1143, 1085, 959, 860, 732 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{19}H_{26}BFNO_4$ $[M+H]^+$ 362.19, found 362.3.

Preparation of 4,7-bis(Bpin)-6-fluoro-N-Boc-indole (3.26) via Scheme 3.6.



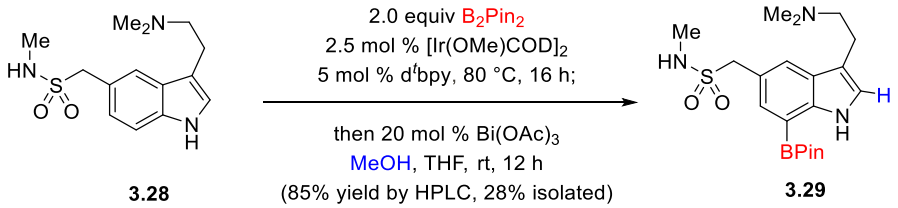
A round bottom flask equipped with a magnetic stirring bar, a condenser, and an additional funnel was charged with 4,7-bis(Bpin)-6-fluoro-indole **3.21** (217 mg, 0.56 mmol, 1 equiv). MeCN (1 mL) and NEt_3 (1.6 mL, 11.2 mmol, 20 equiv) were injected into the flask. The resulting mixture was heated at 80 °C for 30 min. DMAP (137 mg, 1.12 mmol, 2 equiv) and Boc_2O (2.4 g, 11.2 mmol, 20 equiv) were weighted together in a vial and diluted with MeCN (1 mL). The resulting mixture was stirred at rt until it became a yellow homogenous solution. This solution was then introduced into an addition funnel and allowed flow at the rate of 1 drop per 2 min to the round bottom flask. Upon complete addition the reaction mixture was refluxed at 80 °C for 10 h. At that time the reaction was judged to be complete by TLC. After being concentrated by rotary evaporation the crude material was purified by column chromatography (5% acetone/heptane) on silica gel. Boc-Indole **3.26** was isolated as white solid (250 mg, 80%, mp 158 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (d, *J* = 3.4 Hz, 1 H), 7.37 (d, *J* = 9.8 Hz, 1 H), 7.01 (d, *J* = 3.9 Hz, 1 H), 1.62 (s, 9 H, 3 C*H*$_3$ of Bpin), 1.45 (s, 12 H, 4 C*H*$_3$ of Bpin), 1.37 (s, 12 H, 4 C*H*$_3$ of Bpin); ^{13}C NMR ($CDCl_3$,125 MHz): δ 163.6 (d, *J* = 237 Hz), 150.1, 136.7, 131.0, 125.0 (d, *J* = 3.8 Hz), 117.2 (d, *J* = 25.8 Hz), 109.6, 84.0 (2 C), 83.9 (C), 83.8 (2 C), 28.2 (3 CH_3 of Boc), 25.6 (4 CH_3 of Bpin), 25.0 (4 CH_3 of Bpin); ^{11}B NMR ($CDCl_3$, 160 MHz): 29.1; FT-IR

(neat) $\tilde{\nu}_{max}$: 3422, 2979, 1723, 1540, 1458, 1039, 1233, 1145, 935, 852, 769, 668 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{25}H_{37}B_2FNO_6$ $[M+H]^+$ 488.27, found 488.2.

Preparation of 7-Bpin-6-fluoro-N-Boc-indole-4-d (3.27) via Scheme 3.6.

The deborylation step was carried out neat with 4,7-bis(Bpin)-6-fluoro-N-Boc-indole **3.26** (76 mg, 0.156 mmol, 1 equiv) and $[Ir(OMe)(COD)]_2$ (0.78 mg, 0.0012 mmol, 1.5 mol % Ir) in CD_3OD (253 μL, 6.24 mmol, 40 equiv) and THF (253 μL) at rt for 10 h and worked up as described in the general Ir-catalyzed deboronation procedure. The crude material was concentrated by rotary evaporation and purified by column chromatography (10% ethyl acetate/hexanes) on silica gel. Deuterated indole **3.27** was isolated as a colorless oil (44 mg, 78%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 (dd, *J* = 8.8, 5.9 Hz, 0.16 H), 7.40 (d, *J* = 3.4 Hz, 1 H), 6.94 (d, *J* = 9.3 Hz, 1 H), 6.49 (d, *J* = 3.4 Hz, 1 H), 1.63 (s, 9 H, 3 C*H*$_3$ of Boc), 1.46 (s, 12 H, 4 C*H*$_3$ of Bpin); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.1 (d, *J* = 237 Hz), 150.0, 125.8, 125.0 (d, *J* = 3.8 Hz), 110.7 (d, *J* = 27.7 Hz), 107.7, 84.0 (3 C), 28.2 (3 CH_3 of Boc), 25.6 (4 CH_3 of Bpin); ^{11}B NMR ($CDCl_3$, 160 MHz): 28.4; FT-IR (neat) $\tilde{\nu}_{max}$: 3439, 2978, 1724, 1601, 1541, 1353, 1257, 1151, 1093, 984, 854, 736, 613 cm^{-1}; LRMS (ESI): *m/z* calculated for $C_{19}H_{25}DBFNO_4$ $[M+H]^+$ 363.19, found 363.2. Percent deuterium incorporation (based on quantitative ^{1}H NMR): 84%.

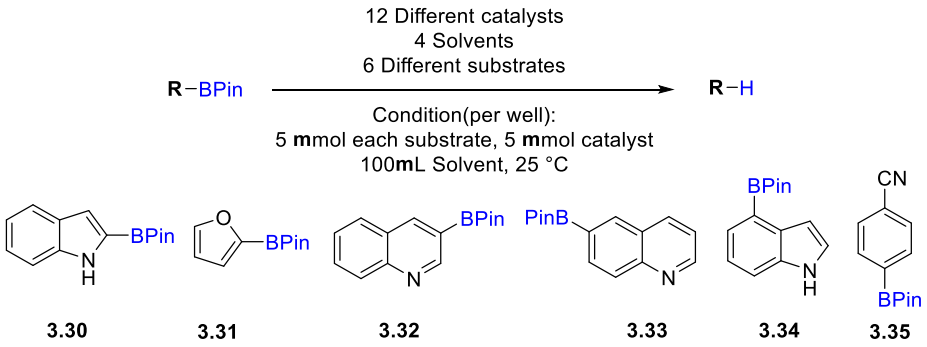
Preparation of 1-(3-(2-(dimethylamino)ethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-5-yl)-N-methylmethanesulfonamide (3.29) via Scheme 3.7.



In a glove box a 20 mL vial equipped with a magnetic stirring bar was charged with sumatriptan **3.28** (200 mg, 0.677 mmol, 1 equiv) and B_2pin_2 (344 mg, 1.354 mmol, 2 equiv). A separate vial was charged with $[Ir(OMe)(COD)]_2$ (11.2 mg, 0.017 mmol, 5.0 mol % Ir) and dtbpy (9.1 mg, 0.034 mmol, 5.0 mol %). THF (1 mL) was added to the vial containing dtbpy, and after mixing for 1 min the resulting solution was transferred to the vial containing the sumatriptan substrate. Additional THF (5 mL) was used to wash, and the washings were transferred to the sumatriptan substrate vial which was then sealed and stirred at 80°C. After 16 h, the reaction mixture was cooled to room temperature and removed from the glove box. Poly(styrene)-bound bipyridine (70 mg, Sigma-Aldrich; 100-200 mesh, 1.0-2.0 mmol/g loading) was added to the reaction mixture, and the solution was stirred for 30 minutes. The mixture was filtered and concentrated under reduced pressure to give the crude 2,7-bis(Bpin)-sumatriptan. To the above crude 2,7-bis(Bpin)-sumatriptan, $Bi(OAc)_3$ (53.2 mg, 0.135 mmol, 0.2 equiv) and a solvent mixture of CH_3OH (1.64 mL, 40.6 mmol, 60 equiv) and THF (5.2 mL) were added. The vial was sealed and heated to 50 ^oC for 12 hours. The reaction mixture was cooled to room temperature, filtered, and the volatile materials were removed by rotary evaporation. The solution yield was determined by quantitative HPLC to be 85% compared to a pure reference standard. The crude material was purified by supercritical fluid chromatography (SFC) under isocratic conditions (Chiral ID, 21x250cm, 25% IPA + 0.2% Diethylamine/CO_2, 70mL/min, 35 °C, 100 Bar, 220nm, ~15mg/mL

in MeCN). After evaporation of solvents from the pure fractions, **3.29** was isolated as a solid (80 mg, 28%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.00 (s, 1 H), 7.65 (s, 1 H), 7.44 (s, 1 H), 7.16 (s, 1 H), 6.80 (q, J = 5.3 Hz, 1 H), 4.37 (s, 2 H), 2.81 (t, J = 7.8 Hz, 2 H), 2.54 (d, J = 4.8 Hz, 3 H), 2.49 (m, 2 H), 2.21 (s, 6 H), 1.35 (s, 12 H). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 140.4, 131.7, 127.3, 124.9, 124.3, 120.0, 113.1, 84.1, 60.5, 56.8, 45.6, 29.4, 25.2, 23.5. ^{11}B NMR (DMSO-d_6, 160 MHz): δ 20.0. HRMS (ESI-TOF): *m/z* calculated for $C_{20}H_{33}BN_3O_4S$ $[M+H]^+$ 422.2289, found 422.2296.

HTE Experiment 4. Study of relative rate of Deborylation of substituted Heteroarenes and conditions that effect.



Preparation of Additive plates with new screening additives.

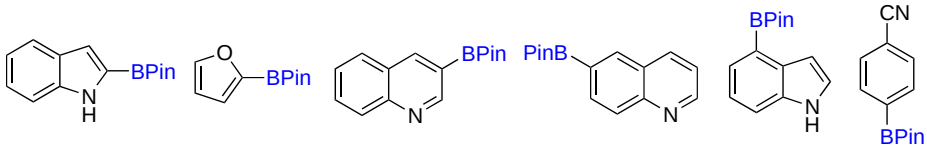
As given in the general procedure A, the additives (5 μmol of additives per well) were dosed into the 96-well reactor vial as solutions or well-stirred slurries (30 μL of 0.166 M) in MeOH. Slurries were dosed using a single-tip pipettor with the sampling tip cut to allow free flow of the slurry. Plates of these additives were dosed in advance of the reaction, the solvent was removed by evacuation on the GeneVac and the plates were stored in the glovebox. In this way 4 additives plates were produced.

Additive plate screening.

A parylene stir-bar was added to each vial of the additive plates. Then the 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline 12, 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline 13, 2-(furan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 14, 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole 15, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole 16, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile 11 (5 μmol/reaction) and 1,3,5-tri-tertbutylbenzene (0.5 μmol/reaction) (used as an internal standard to quantify the reaction) were dosed together into the reaction vials in THF (100 μL) and the solvent was removed by evacuation on the GeneVac. Then THF (100 μL), NMP (100 μL), DMF (100 μL) and MeCN (100 μL) was added for wells from A1 – A12, B1 – B12, C1- C12 and to D1 –D2 respectively. . Finally 40 equiv of MeOH was added to all the reactions. The reactions were then sealed and stirred at 30 ^{o}C for 2h. Then 10 μL of the reactions was measured into 96-well plate LC block and were diluted with 600 μL of acetonitrile. The 96-well plate LC block was then sealed with a silicon-rubber storage mat, and the reactions were analyzed using standard reverse-phase Agilent HPLC (see methods above).

	Catalyst	Control	Bi(OAc)3	$[Ir(OMe)COD]_2$	Ag2O	Bi(OTf)3	Ga(ClO4)3	Hf(OTf)4	Cu(OTf)2	CuCl	Cu(MeCN)4 PF6	Cd(OAc)2	[Ir(COD)(PCy3(py)]
Solvent	Row/Col	1	2	3	4	5	6	7	8	9	10	11	12
THF	A												
NMP	B												
DMF	C												
Acetonitrile	D												

Protodeboronations of selected heterocyclic boronic esters.



3.30 **3.31** **3.32** **3.33** **3.34** **3.35**

Entry		Catalyst	Solvent	% Deborylation of substrates[a] **3.30**	**3.32**	**3.33**	**3.34**	**3.35**
1	A:2	$Bi(OAc)_3$	THF	63				
2	B:2		NMP	28				
3	C:2		DMF	35				
4	D:2		ACN	84				
5	A:3	$[Ir(OMe)COD]_2$	THF	80	20	11		
6	B:3		NMP	73	32			
7	C:3		DMF	74	29			
8	D:3		ACN	89	41	20	20	
9	A:4	Ag_2O	THF	100	100	52	19	100
10	B:4		NMP	81	69			24
11	C:4		DMF	89	90			17
12	D:4		ACN	96	100	48	14	75

Rate constant calculations : At 25 C, 3.5 hrs

			PhCNBpin		In-2-Bpin		In-4-Bpin	Qu-3-Bpin		Qu-6-Bpin	
		Solvent	% conversion	kobs / 10-4 S-1	% conversion	kobs / 10-5 S-1		% conversion	kobs / 10-5 S-1	% conversion	kobs / 10-5 S-1
A:2	Bi(OAc)3	THF			62.59	7.80					
B:2		NMP			28.04	2.61					
C:2		DMF			34.58	3.37					
D:2		Acetonitrile			83.74	10.44					
A:3	$[Ir(OMe)COD]_2$	THF			79.73	12.70		20.24	1.79		
B:3		NMP			72.92	10.40		32.00	3.06		
C:3		DMF			73.81	10.60		28.63	2.68		
D:3		Acetonitrile			100.00	NA		40.80	4.16		
A:4	Ag2O	THF	100.00	NA	100.00	NA		100.00	NA	52.3050417	3.18
B:4		NMP	23.88	1.10	80.60	13.00		68.61	9.20	4.88408963	0.54
C:4		DMF	16.76	1.56	89.07	17.60		90.44	18.60		
D:4		Acetonitrile	74.59	2.28	95.61	24.80		100.00	NA	48.1237691	2.86
A:5	Bi(OTf)3	THF			5.08	0.41					
B:5		NMP			36.39	3.59					
C:5		DMF			52.88	5.97					
D:5		Acetonitrile			88.73	1.73					

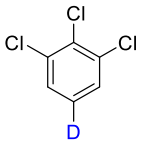
In-2-Bpin	Including the area of In-B(OH)2
Qu-6-Bpin	Including the area of Qu-B(OH)2

In - Indole
Qu - Quinoline
NA -No Starting Material
kobs -Rate Constant at 25 C
Represent no or less than 10% conversions

General Procedure for Preparation of Deuterated Aromatics[6]

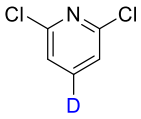
To 1 mmol borylated arene were added 20 mol% Ag_2O, 0.1 mL D_2O and 0.5 mL dry THF. Then flask was sealed and heated in an oil bath to 80 °C until the reaction was judged complete by TLC thin plate. Upon completion, the mixture was filtered through 1 mL silica gel, dried over $MgSO_4$ and evaporated. Column chromatography (5% ethyl acetate/hexane) afforded the product.

1,2,3-Trichlorobenzene-5-d.



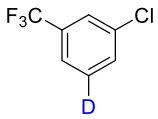
The deuteration step was then carried out at 80 °C for 1 h as described in the general procedure, after which the crude material was purified with a silica gel chromatography to afford 100 mg of the deuterated compound (55%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (t, ^{J}H-D = 1.1 Hz). The spectral data were in accordance with literature.[4]

2,6-Dichloropyridene-4-d.



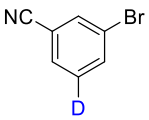
The deuteration step was then carried out at 80 °C for 1 h as described in the general procedure, after which the crude material was purified with a silica gel chromatography to afford 58 mg of the deuterated compound (40%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (t, ^{J}H-D = 1.1 Hz). The spectral data were in accordance with literature. [4]

3-Chlorobenzotrifluoride-5-d.



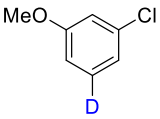
The deuteration step was then carried out at 80 °C for 2.5 h as described in the general procedure, after which the crude material was purified with a silica gel chromatography to afford 111 mg of the deuterated compound (78%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (br, 1 H), 7.54–7.48 (m, 2 H). The spectral data were in accordance with literature.[4]

3-Bromobenzonitrile-5-d.



The deuteration step was then carried out at 80 °C for 3 h as described in the general procedure, after which the crude material was purified with a silica gel chromatography to afford 109 mg of the deuterated compound (60%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (t, J = 1.6 Hz, 1 H), 7.73 (br, 1 H), 7.59 (br, 1 H). The spectral data were in accordance with literature.[4]

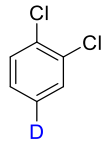
3-Chloroanisole-5-d.



The deuteration step was then carried out at 80 °C for 2 h and worked up as described in the general procedure, after which the crude material was purified with a silica gel chromatography to afford 89 mg of the deuterated compound (62%) as a colorless oil. ^{1}H NMR (300 MHz,

CDCl3): δ 6.91 (br, 1 H), 6.88 (t, J = 2.3 Hz, 1 H), 6.77 (br, 1 H), 3.78 (s, 3 H). The spectral data were in accordance with literature.[4]

1,2-Dichlorobenzene-4-d.



The deuteration step was then carried out at 80 °C for 3 h and worked up as described in the general procedure, after which the crude material was afford 135 mg of the deuterated compound (91%) as a colorless oil. 1H NMR (300 MHz, CDCl3): δ 7.41-7.44 (m, 2 H), 7.16-7.20 (m, 1 H). The spectral data were in accordance with literature.[4]

5.3. Experimental details for Chapter 4: Reversibility in Ir-Catalyzed C–H Polyborylation: A Boronic Ester Dance.

General Materials and Methods

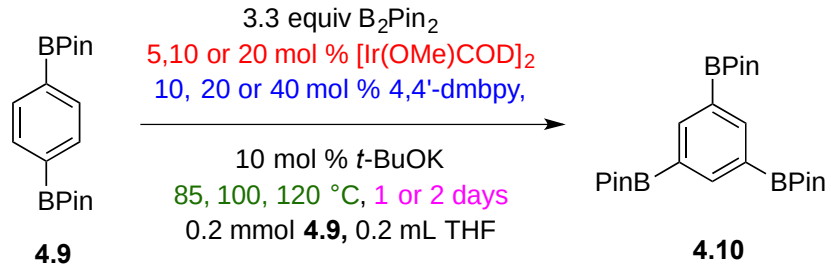
Unless otherwise stated, the reported yields refer to chromatograph-ically and spectroscopically pure compounds. All reactions were conducted in a nitrogen filled glove-box. All the solvents were used as received from Sigma-Aldrich (Sure/SealTM) and were stored in the glove-box. All other commercially available materials were used as received. Bis(η^4-1,5-cyclooctadiene)-di-μ-methoxy-diiridium(I) ([Ir(OMe)(cod)]$_2$), Pinacolborane (HBpin), B_2pin_2 and 4,4′-Di-*t*-butyl-2,2′-bipyridine (dtbpy) were purchased from Aldrich. All borylated starting substrates were purified by column chromatography prior to use. Reactions were monitored by thin layer chromatography on precoated silica gel plates (Merck), using UV light or phosphomolybdic acid stain for visualization. Column chromatography was performed on 60 Å silica gel (230–400 mesh). NMR spectra were recorded on Varian VXR-500, Varian Unity-500-Plus (499.74 MHz for ^{1}H and 125.67 MHz for ^{13}C) and Bruker 500 (500.13 MHz for ^{1}H and 125.77 MHz for ^{13}C) spectrometer. ^{1}H and ^{13}C chemical shifts (in ppm) were referenced to the residual protonated or natural abundance solvent signals.[3] ^{11}B spectra were recorded at 160.32 MHz. All coupling constants are apparent *J* values measured at the indicated field strengths. Melting points are uncorrected. High-resolution mass spectrum was acquired at the MSU Mass Spectrometry facility using a Waters GCT Premier GC/TOF instrument (in ESI mode) (Waters Milford, MA) and at Merck (Rahway, NJ) using a Waters Xevo G2 QTof instrument (in ESI mode). Low-resolution mass spectra were performed at the Molecular Metabolism and Disease Collaborative Mass Spectrometry Core facility at MSU on a Thermo Scientific LTQ-Orbitap Velos using the Ion Trap analyzer in positive ionization mode by nano-ESI. HPLC assays were carried out using

a C-18 reversed-phase column eluted with 0.1% H_3PO_4 (aq) and acetonitrile (ACN) monitoring the compounds at 210 nm and 320 nm.

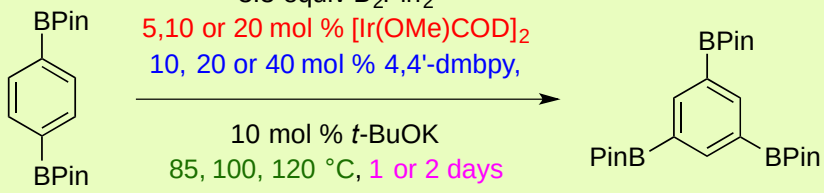
General Procedures for Screening Ir-catalyzed C–H polyborylation Conditions.

All reactions were conducted in a nitrogen filled glove-box. All other commercially available materials were used as received. Reactions for high through-put screening were conducted in either 8 × 30 mm borosilicate glass shell vials arranged in 96 well metal blocks (Symyx) with magnetic stirring or in Biotage microwave reaction vials (2-5 mL). Materials were dispensed to the vials whenever possible as solutions in the reaction solvent, otherwise in suitable solvents (in which the material was soluble in) via micro pippetters followed by evaporation of the solvent in vacuuo in a GenevacTM centrifugal evaporator in the glove box. The reactions that were set up in borosilicate glass shell vials were heated via the metal 96 well blocks after sealing with a perfluoroelastomeric backed metal top plate screwed to the metal block. The reactions that were setup in biotage vials were heated in a metal block. Analysis was accomplished by reversed phase HPLC (Zorbax Eclipse Plus C18, 1.8 micron, 4.6 × 50 mm column eluted with 0.1% aq H_3PO_4 and acetonitrile) using an internal standard such as dodecahydrotriphenylene to facilitate quantitative HPLC solution assay yield determination.

Effect of catalysts/ ligand load, reaction time and temperature on the Ir-catalyzed C–H polyborylation of 1,4-bis(Bpin)benzene



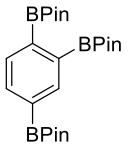
		Loading		
		5% $[Ir(OMe)COD]_2$	10% $[Ir(OMe)COD]_2$	20% $[Ir(OMe)COD]_2$
		10% 4-4'-dmbpy	20% 4-4'-dmbpy	40% 4-4'-dmbpy
Time		1	2	3
Day 1	A			
Day 2	B			



A reactor heating block consist of Biotage microwave reaction vials equipped with a magnetic stir bar arrayed in a 4x4 reaction plate, 3 columns labeled 1-3 and 2 rows labeled A-B. In a nitrogen filled glovebox, 125 µL of a solution containing 10 µmol $[Ir(OMe)COD]_2$ (0.08 M stock solution) in THF was added to each well across column 1 (wells A1 and B1) via micro pipette. Smilarly, 250 µL of a solution containing 20 µmol $[Ir(OMe)COD]_2$ (0.08 M stock solution) in THF were added to each well across column 2 (wells A2 and B2) and 500 µL of a solution

containing 40 μmol of $[Ir(OMe)COD]_2$ to each well across column 3 (wells A3 and B3). To the reaction wells A1 and B1, 125 μL of stock solution containing 10 μmol 4-4'-dmbpy ligand (0.16 M stock solution) in THF were added. Similarly, 250 μL of stock solution containing 20 μmol 4-4'-dmbpy ligand (0.16 M stock solution) for A2-B2 and 500 μL of stock solution containing 40 μmol 4-4'-dmbpy ligand (0.16 M stock solution) to A3-B3 were added. In to a vial 1,4-bis(Bpin)benzene (2.97 g, 9 mmol), *t*-BuOK (100.1 mg, 0.9 mmol), B_2Pin_2 (7.54 g, 27.7 mmol) and 1,3,5-trimethoxybenzene (4.5 mmol, 756.8 mg) were measured and the content was diluted upto 60 mL with THF to make a stock soultion of 0.15 M 1,4-bis(Bpin)benzene, 0.015 M *t*-BuOK, 0.495 M B_2Pin_2 and 0.075 M 1,3,5-trimethoxybenzene (4.5 mmol, 756.8 mg). Then 1.33 mL of this sloution mixture was introduced to all the vials across column 1-3 and rows A-B to add 0.2 mmol 1,4-bis(Bpin)benzene, 0.02 mmol *t*-BuOK, 0.66 mmol B_2Pin_2 and 1 mmol 1,3,5-trimethoxybenzene. Then solvent was removed using a GeneVac system located inside the glovebox and 0.2 mL of THF was added across the plate. The vials were sealed and then heated at 85 °C for 1-2days. Two tother plates exactly similar to one decribed was made according to the above mention method and was heated at 100 °C and 120 °C for 1-2 days. After desired reaction time the content was analyzed by reversed phase HPLC (Zorbax Eclipse Plus C18, 1.8 micron, 4.6 × 50 mm column eluted with 0.1% aq H_3PO_4 and acetonitrile).

Details for Ir-catalyzed C–H polyborylation of 1,4-bis(Bpin)benzene (Scheme 4.5):

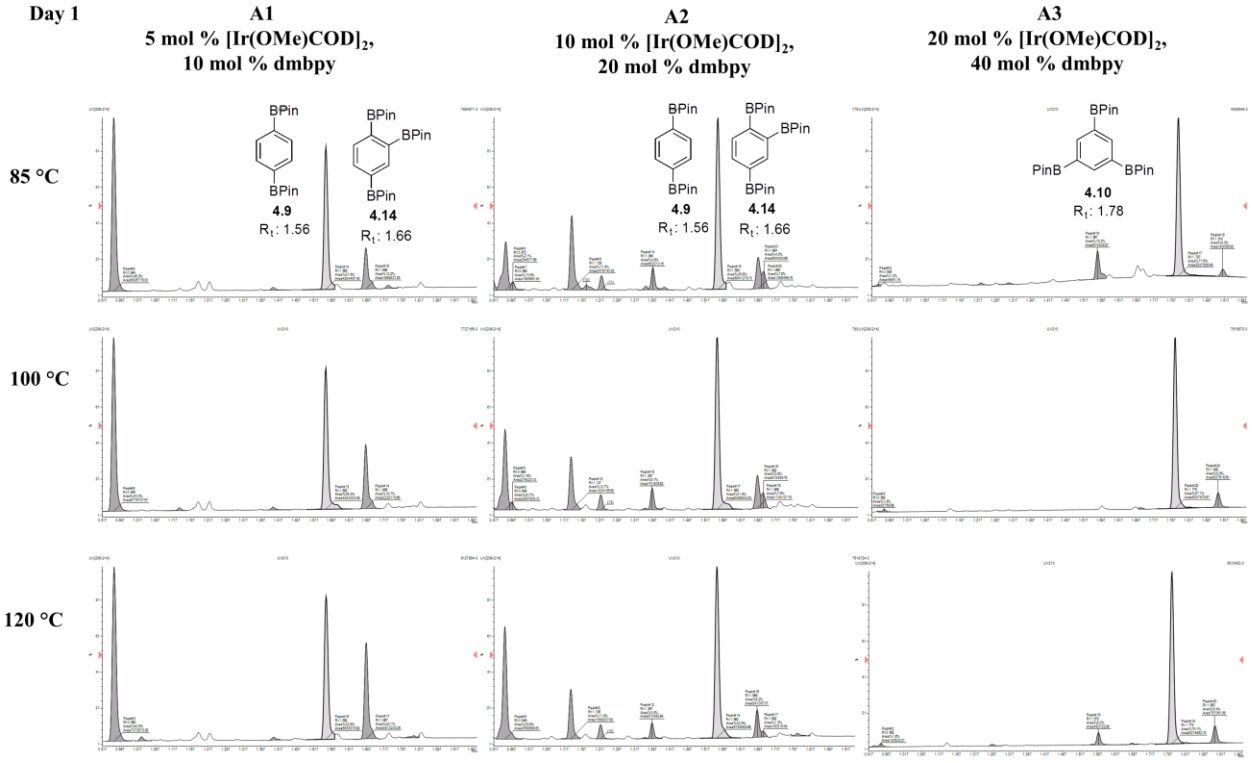


4.14

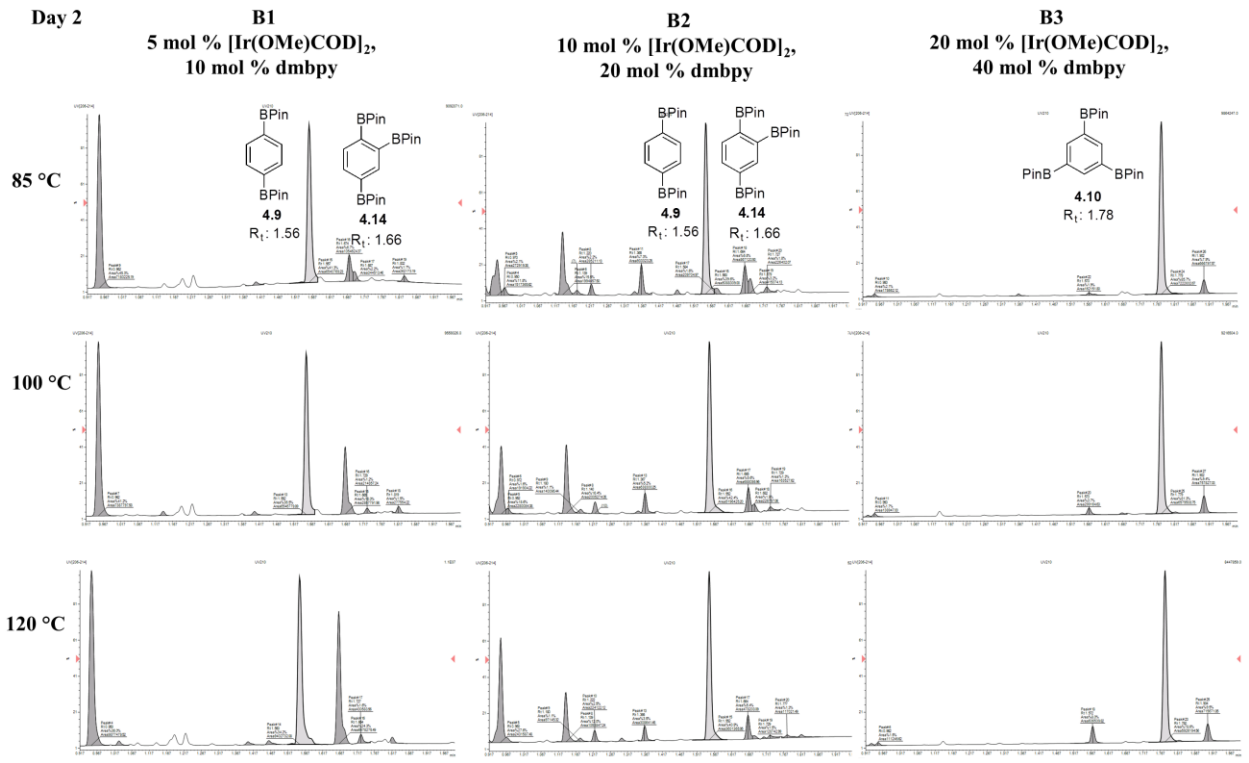
The reaction well A1 from the reaction time 120 °C was passed through a silica plug. After further elution with DCM, the volatile materials were removed by rotary evaporation. The crude

material was purified by column chromatography (gradient from 100% Hexane to 40% ethyl acetate/hexanes) on silica gel. The 1,2,4-*tris*(Bpin)benzene (**4.14**) was isolated in 18 % isolated yield (16 mg, white solid). The isolated product of 1,2,4-*tris*(Bpin)benzene contained 10% impurity of 1,4 *bis*(Bpin)benzene. The spectral data were in accordance with literature values.[7]

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 12H), 1.36 (d, J = 1.5 Hz, 24H), 7.62 (dd, J = 7.4, 0.2 Hz, 1H), 7.80 (dd, J = 7.4, 1.2 Hz, 1H), 8.08 (s, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 25.18, 83.65, 83.85, 83.98, 84.05, 132.63, 135.55, 139.70.

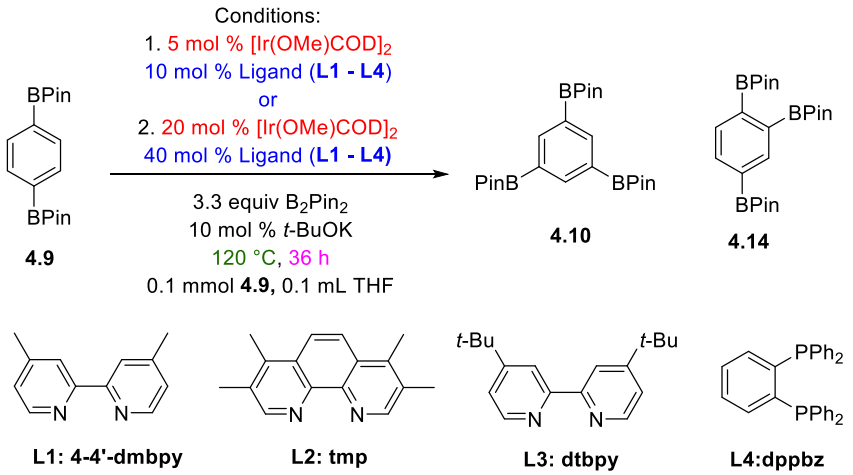


HPLC chromatograms of the reactions (A1-A3 at 80, 100 and 120 °C)



HPLC chromatograms of the reactions (B1-B3 at 80, 100 and 120 °C)

Effect of ligand and base on the Ir-catalyzed C–H polyborylation of 1,4-bis(Bpin)benzene:



First, 1 mL glass vials equipped with a micro-magnetic stir bar, arrayed in a 4x4 reaction plate, 2 columns labeled 1-2 and 4 rows labeled A-D. In a nitrogen filled glovebox, 100 µL of a solution containing 10 µmol 1,4-bis(Bpin)benzene (0.01 M stock solution) in THF, 50 µL of a solution containing 33 µmol B_2Pin_2 (0.66 M stock solution) in THF and 50 µL of a solution containing 1 µmol *t*-BuOK (0.02 M stock solution) in THF were added to all the wells via micro pipette. Then solvent was removed using a GeneVac system located inside the glovebox. Next, 25 µL of a solution containing 0.5 µmol $[Ir(OMe)COD]_2$ (0.02 M stock solution) in THF was added to each well across column 1 (wells A1-D1) and 100 µL of a solution containing 2 µmol of $[Ir(OMe)COD]_2$ to each well across column 2 (wells A2-D2). To the reaction wells A1-D1 across the column, 25 µL of solution containing 1 µmol ligand and to wells A2-D2 across the column 100 µL of solution containing 4 µmol ligand (0.04 M stock solution, wells A1, A2: 4'-dmbpy ligand, wells B1, B2: TMP ligand, wells C1, C2: dtbpy ligand and wells D1, D2: dppbz ligand) in THF were added. Then solvent was removed using a GeneVac system located inside the glovebox and 100 µL of THF was added across the plate. The vials were sealed and then heated at 120 °C for 36 hours. After desired reaction time the content was analyzed by reversed

phase HPLC (Zorbax Eclipse Plus C18, 1.8 micron, 4.6 × 50 mm column eluted with 0.1% aq H_3PO_4 and acetonitrile).

Effect of ligand for Ir-catalyzed C–H polyborylation of 1,4-*bis*(Bpin)benzene

		Yield of **4.10** and **4.14** at each condition [a] (yields determined by HPLC)			
		Condition 1 5 mol % $[Ir(OMe)COD]_2$ 10 mol % Ligand (**L1 - L4**)		**Condition 2** 20 mol % $[Ir(OMe)COD]_2$ 40 mol % Ligand (**L1 - L4**)	
Entry	**Ligand**	**4.10**	**4.14**	**4.10**	**4.14**
1	**L1**: dmbpy	0	18	25	9
2	**L2**: tmp	65	3	67	0
3	**L3**: dtbpy	0	0	0	5
4	**L4**: dppbz	0	0	0	0

General procedures for Ir-catalyzed C–H polyborylation

General Ir-catalyzed C–H polyborylation procedure: Condition A, 20 mol% [Ir(OMe)(COD)]$_2$ and 40 mol% TMP ligand.

In a glove box, Biotage microwave reaction vial, equipped with a magnetic stirring bar, was charged with [Ir(OMe)(COD)]$_2$ (20 mol%) and TMP (40 mol%). Then, THF (200 µL) was added to the vial and was stirred for few minutes. Next, B_2Pin_2 (3.3 mmol) was added to the vial along with another 200 µL of THF. The the reaction mixture was then charged with starting material (1 mmol). Additional THF (600 µL) was added to the reaction vial. Then the vial was sealed, brought out of the glove box and the reaction was carried out at desired temperature for 16 h. After completion of the reaction, the mixture was passed through a silica plug. After further elution with DCM, the volatile materials were removed by rotary evaporation. The crude material was purified by column chromatography (gradient from 100% Hexane to 40% ethyl acetate/hexanes) on silica gel.

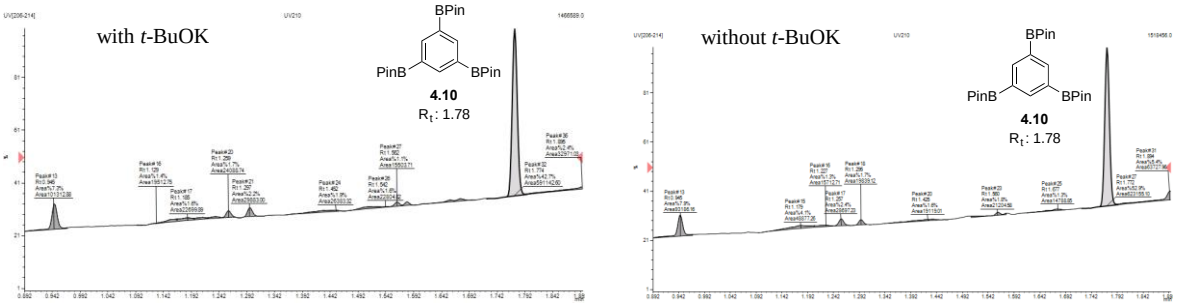
General Ir-catalyzed C–H polyborylation procedure: Condition B, 5 mol% [Ir(OMe)(COD)]$_2$ and 10 mol% TMP ligand.

In a glove box, Biotage microwave reaction vial, equipped with a magnetic stirring bar, was charged with [Ir(OMe)(COD)]$_2$ (5 mol%) and TMP (10 mol%). Then, THF (200 µL) was added to the vial and was stirred for few minutes. Next, B_2Pin_2 (3.3 mmol) was added to the vial along with another 200 µL of THF. The the reaction mixture was then charged with starting material (1 mmol). Additional THF (600 µL) was added to the reaction vial. Then the vial was sealed, brought out of the glove box and the reaction was carried out at desired temperature for 16 h. After completion of the reaction, the mixture was passed through a silica plug. After further elution with DCM, the volatile materials were removed by rotary evaporation. The crude

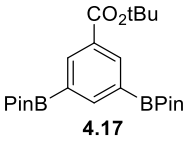
material was purified by column chromatography (gradient from 100% Hexane to 40% ethyl acetate/hexanes) on silica gel.

Effect of base for Ir-catalyzed C–H polyborylation of 1,4-bis(Bpin)benzene.

Inside the glove box two reactions were set up following general procedure with condition A. First reaction was set up with $[Ir(OMe)(COD)]_2$ (26.5 mg, 0.04 mmol, 20 mol%), TMP (18.9 mg, 0.08 mmol, 40 mol%), B_2Pin_2 (167 mg, 0.66 mmol) and *t*-BuOK (2.2 mg, 0.02 mmol). Then, THF (200 µL) was added to the vial and was heated for 16 h. For the second reaction similar procedure was carried out without adding the base *t*-BuOK. The reactions were monitored after 16 h by HPLC and the chromatograms are shown below and quantitative conversions to **4.10** were observed.

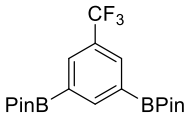


Ir-catalyzed C–H polyborylation details for Table 4.8:



In a glove box, Biotage microwave reaction vial, equipped with a magnetic stirring bar, was charged with $[Ir(OMe)(COD)]_2$ (132.6 mg, 0.2 mmol, 20 mol%) and TMP (94.5 mg, 0.4 mmol, 40 mol%). Then, THF (200 µL) was added to the vial and was stirred for few minutes. Next,

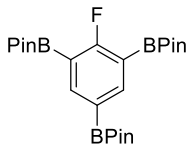
B_2Pin_2 (838.2 mg, 3.3 mmol) was added to the vial along with another 200 µL of THF. The the reaction mixture was then charged with 4-Bpin-*tert*-butylbenzoate (304.18 mg, 1 mmol). Additional THF (600 µL) was added to the reaction vial. Then the vial was sealed, brought out of the glove box and the reaction was carried out at 80 °C for 16 h. After completion of the reaction, the mixture was passed through a silica plug. After further elution with DCM, the volatile materials were removed by rotary evaporation. The crude material was purified by column chromatography (gradient from 100% Hexane to 40% ethyl acetate/hexanes) on silica gel. The 3,5-di(Bpin)*tert*-butylbenzoate (**4.17**) was isolated in 60 % isolated yield (261 mg). Smilar procedure was carried out with the starting material *tert*-butylbenzoate (178.23 mg, 1 mmol) to obtain 3,5-di(Bpin)*tert*-butylbenzoate (**4.17**) in 79 % isolated yield (amorphous solid, 340 mg). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 24H), 1.59 (s, 9H), 8.38 (t, J = 1.2 Hz, 1H), 8.47 (d, J = 1.3 Hz, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 25.00, 28.35, 81.08, 84.09, 130.93, 138.48, 145.06, 166.12; LCMS (ESI): *m/z* calculated for $C_{22}H_{34}B_2O_6$ $[M\text{-}CH_3]^+$ 416.25, found 416.20.



4.20

In a glove box, Biotage microwave reaction vial, equipped with a magnetic stirring bar, was charged with $[Ir(OMe)(COD)]_2$ (132.6 mg, 0.2 mmol, 20 mol%) and TMP (94.5 mg, 0.4 mmol, 40 mol%). Then, THF (200 µL) was added to the vial and was stirred for few minutes. Next, B_2Pin_2 (838.2 mg, 3.3 mmol) was added to the vial along with another 200 µL of THF. The the reaction mixture was then charged with 4-Bpin-trifluoromethylbenzene (272.1 mg, 1 mmol). Additional THF (600 µL) was added to the reaction vial. Then the vial was sealed, brought out of the glove box and the reaction was carried out at 120 °C for 16 h. After completion of the

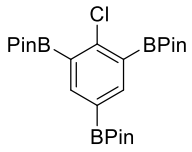
reaction, the mixture was passed through a silica plug. After further elution with DCM, the volatile materials were removed by rotary evaporation. The crude material was purified by column chromatography (gradient from 100% Hexane to 40% ethyl acetate/hexanes) on silica gel. The 3,5-di(Bpin)-trifluoromethylbenzene (**4.20**) was isolated in 61 % isolated yield (230 mg) Smilar procedure was carried out with the starting material α,α,α-trifluorotoluene (146.1 mg, 122 µL, 1 mmol) to obtain 3,5-di(Bpin)-trifluoromethylbenzene (**4.20**) in 58 % isolated yield (white solid, 243 mg). The spectral data were in accordance with literature values.[4] ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 24H), 8.13 (s, 2H), 8.41 (s, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$): 144.5, 134.1 (q, $^{3}J_{C-F}$ = 3.5 Hz), 129.6 (q, $^{2}J_{C-F}$ = 32 Hz), 124.5 (q, $^{1}J_{C-F}$ = 271 Hz), 84.3, 24.9 ppm.



4.23

In a glove box, Biotage microwave reaction vial, equipped with a magnetic stirring bar, was charged with $[Ir(OMe)(COD)]_2$ (33.1 mg, 0.05 mmol, 5 mol%) and TMP (23.6 mg, 0.1 mmol, 10 mol%). Then, THF (200 µL) was added to the vial and was stirred for few minutes. Next, B_2Pin_2 (838.2 mg, 3.3 mmol) was added to the vial along with another 200 µL of THF. The the reaction mixture was then charged with 4-Bpin-fluorobenzene (222.1 mg, 1 mmol). Additional THF (600 µL) was added to the reaction vial. Then the vial was sealed, brought out of the glove box and the reaction was carried out at 80 °C for 16 h. After completion of the reaction, the mixture was passed through a silica plug. After further elution with DCM, the volatile materials were removed by rotary evaporation. The crude material was purified by column

chromatography (gradient from 100% Hexane to 40% ethyl acetate/hexanes) on silica gel. The 2,4,6-tris(Bpin)fluorobenzene (**4.23**) was isolated in 56 % isolated yield (264 mg). Smilar procedure was carried out with the starting material 3-Bpin-fluorobenzene (222.1 mg, 1 mmol) to obtain 2,4,6-tris(Bpin)fluorobenzene (**4.23**) in 45 % isolated yield (white solid, mp 282-284 °C, 214 mg). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 12H), 1.33 (s, 24H), 8.28 (d, J = 6.4 Hz, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 24.99, 25.01, 83.93, 83.98, 147.25 (d, *J* = 9.1 Hz), 173.95 (d, *J* = 259.5 Hz); ^{11}B-NMR (160 MHz, $CDCl_3$): δ 31.02; HRMS (ESI): *m/z* calculated for $C_{24}H_{38}B_3FO_6$ $[M+H]^+$ 475.3009, found 475.3026.



4.25

In a glove box, Biotage microwave reaction vial, equipped with a magnetic stirring bar, was charged with $[Ir(OMe)(COD)]_2$ (33.1 mg, 0.05 mmol, 5 mol%) and TMP (23.6 mg, 0.1 mmol, 10 mol%). Then, THF (200 µL) was added to the vial and was stirred for few minutes. Next, B_2Pin_2 (838.2 mg, 3.3 mmol) was added to the vial along with another 200 µL of THF. The the reaction mixture was then charged with 4-Bpin-chlorobenzene (238.52 mg, 1 mmol). Additional THF (600 µL) was added to the reaction vial. Then the vial was sealed, brought out of the glove box and the reaction was carried out at 120 °C for 16 h. After completion of the reaction, the mixture was passed through a silica plug. After further elution with DCM, the volatile materials were removed by rotary evaporation. The crude material was purified by column chromatography (gradient from 100% Hexane to 40% ethyl acetate/hexanes) on silica gel. The 2,4,6-tris(Bpin)chlorobenze (**4.25**) was isolated in 60 % isolated yield (white solid, mp 270-272 °C,

261 mg). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.32 (s, 12H), 1.35 (s, 24H), 8.06 (s, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 24.95, 24.98, 84.04, 84.21, 144.17, 147.37; ^{11}B-NMR (160 MHz, $CDCl_3$): δ 31.32; HRMS (ESI): *m/z* calculated for $C_{14}H_{18}DBNO_2$ $[M+H]^+$ 491.2714, found 491.2740.

REFERENCES

REFERENCES

1. (a) Crabtree, R. H.; Quirk, J. M.; Felkin, H.; Fillebeenkhan, T. *Synth. React. Inorg. Met.-Org. Chem.* **1982**, *12*, 407–413. (b) Uson, R.; Oro, L. A.; Cabeza, J. A. *Inorg.Synth.* **1985**, *23*, 126–130.

2. (a)Song, C.; Ma, Y.; Chai, Q.; Ma, C.; Jiang, W.; Andrus, M. B. *Tetrahedron* **2005**, *61*, 7438–7446. (b) Baker, Aaron. Organometallic Chemistry Pertaining to Main Group Elements Silicon, Germanium, Tin, and Boron. Ph. D. Dissertation, Michigan State University. East Lansing, Michigan, 2016.

3. (a) Luo, B.; Liu, H.; Lin, Z.; Jiang, J.; Shen, S.; Liu, R.; Ke, Z.; Liu, F. *Organometallics*. **2015**, *34*, 4881-4894

4. Kallepalli, V. A.; Gore, K. A.; Shi, F.; Sanchez, L.; Chotana, G. A.; Miller, S. L.; Maleczka, R. E., Jr.; Smith, M. R., III *J. Org. Chem.* **2015**, *80*, 8341–8353.

5. The experimental data are reported: (a) Shen, F.; Tyagarajan, S.; Perera, D.; Krska, S. W.; Maligres, P. E.; Smith, M. R., III; Maleczka, R. E., Jr.; *Org. Lett*. **2016**, *18*, 1554–1557. (b) Shen, F. carried out the experiments and also reported as Shen, F. Discovery and the Development of Bismuth Salt Mediated Catalytic Deborylation and Allied Studies. MSc. Thesis, Michigan State University, East Lansing, 2015.

6. Our manuscript on this is in preparation and also see; Shen, F. Discovery and the Development of Bismuth Salt Mediated Catalytic Deborylation and Allied Studies. MSc. Thesis, Michigan State University, East Lansing, 2015.

7. Mfuh, A. M.; Nguyen, V. T.; Chhetri, B.; Burch, J. E.; Doyle, J. D.; Nesterov, V. N.; Arman, H. D.; Larionov, O. V. *J. Am. Chem. Soc.*, **2016**, *138* , 8408–8411.