



Transition Metal Catalysed Borylation of C-H and C-X Bonds

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Challenges in Catalysis for Pharmaceuticals and Fine Chemicals III

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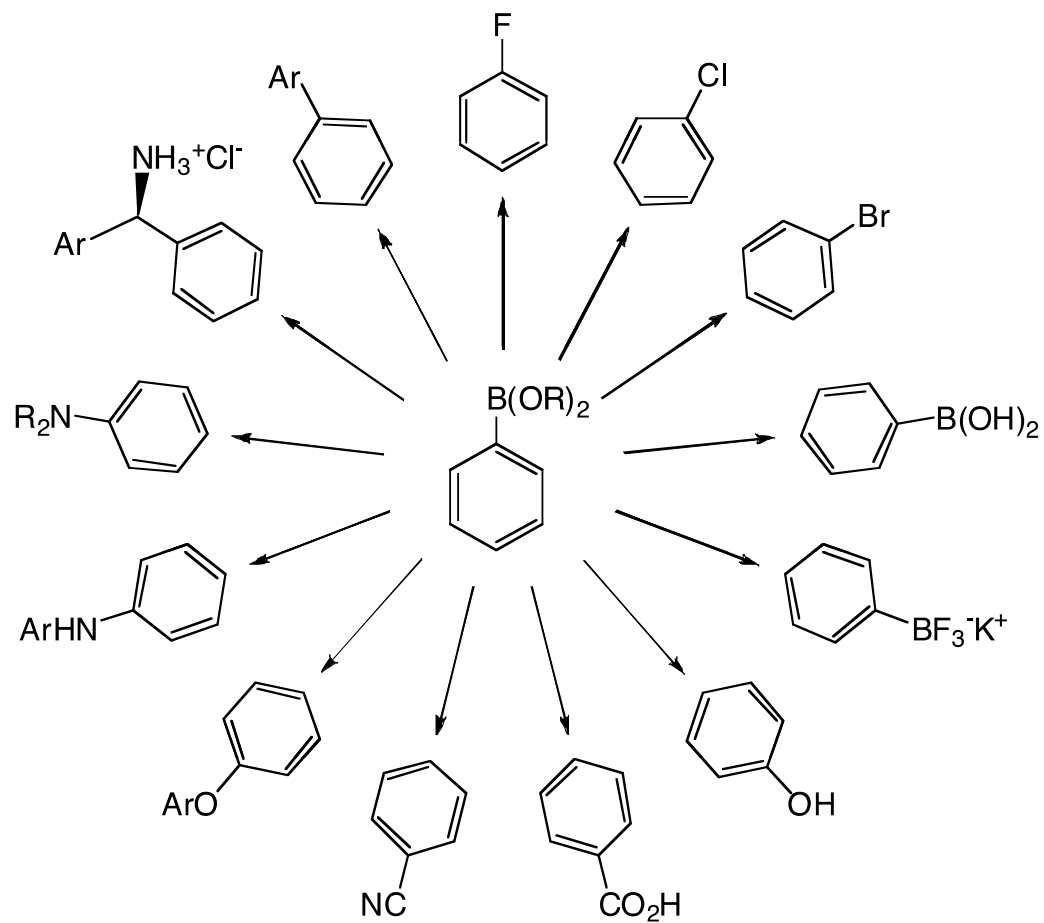
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Dr. Andrei Batsanov (X-ray) **Dr. Lena Shukla (GSK)**

*TBM thanks the Royal Society for a Wolfson Resarch Merit Award
and the Alexander von Humboldt Foundation for a Research Award*



Why Make Aryl Boronates?

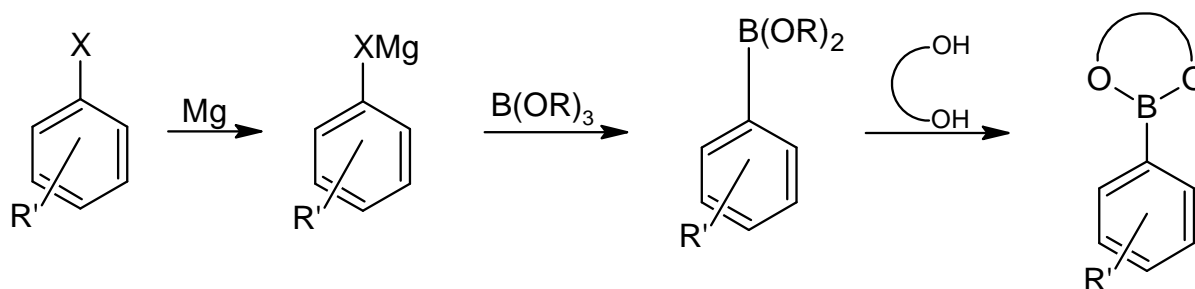


Synthesis and use of aryl boronates

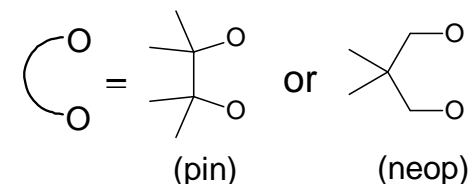
Aryl boronates: Suzuki-Miyaura and other cross-couplings

Often synthesised from aryl halides

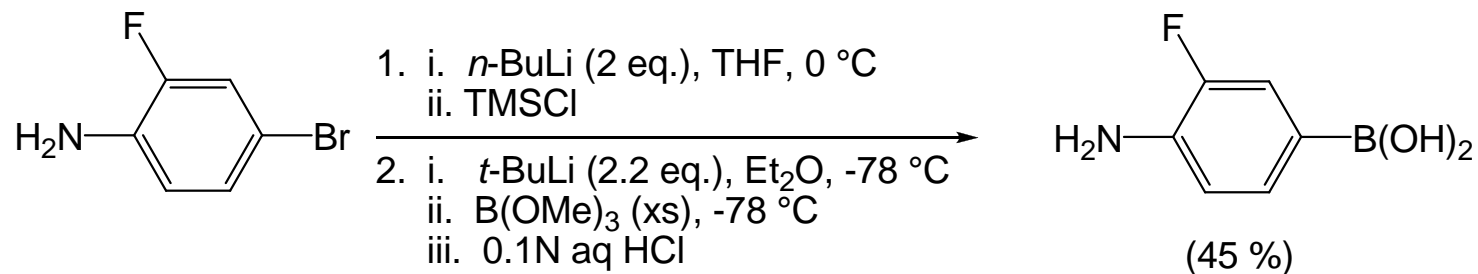
Classical synthesis of aryl boronates via Grignard or ArLi species:



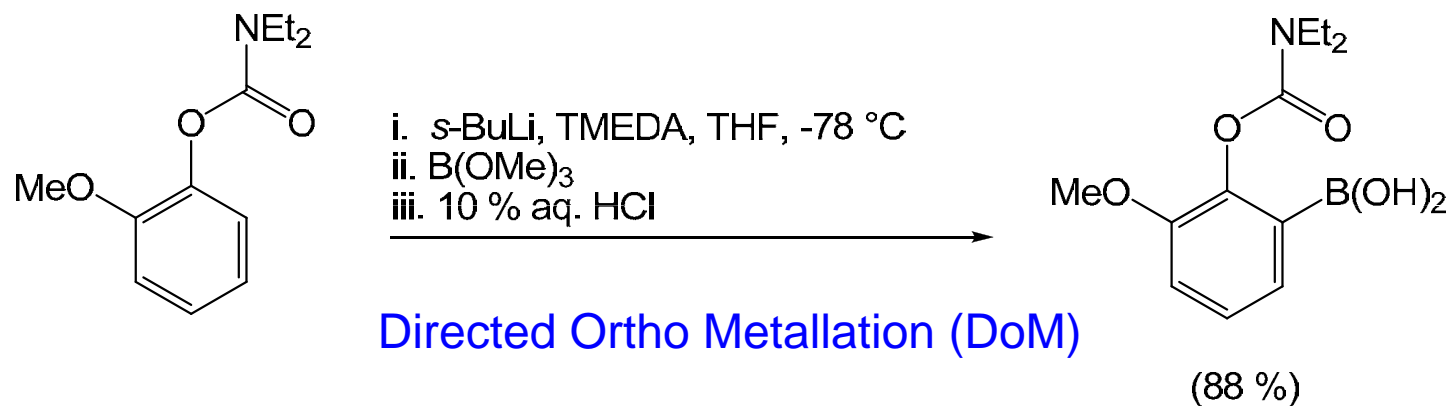
- **Three/two step synthesis**
- **Incompatible with most functional groups (Requires protection/deprotection)**



Classical Arylboronate Synthesis: Low Temperature Lithiation



Asher et al. *Tetrahedron Lett.* **2003**, 44, 7719

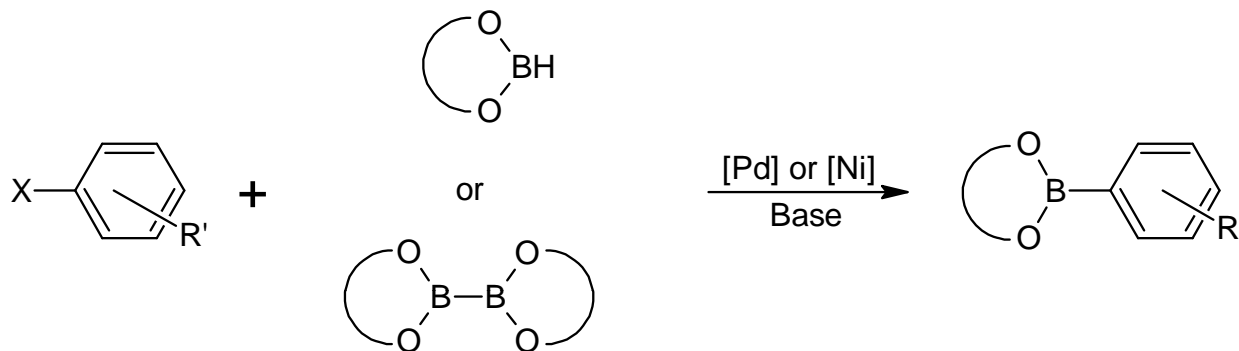


Directed Ortho Metallation (DoM)

Snieckus et al. *J. Org. Chem.* **2009**, 74, 4094

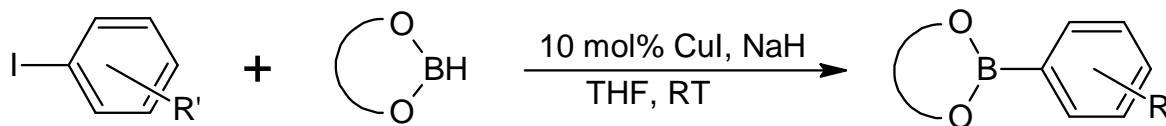
Synthesis of Aryl Boronates: Catalytic Routes

Palladium / Nickel catalysed borylation of aryl halides:



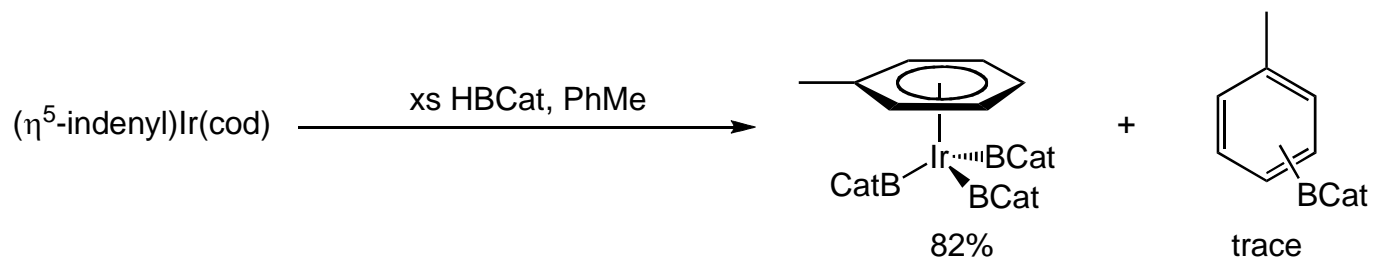
T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508 -7510 • M. Murata, S. Watanabe, Y. Masuda, *J. Org. Chem.* **1997**, *62*, 6458 - 6459 • A. B. Morgan, J. L. Jurs, J. M. Tour, *J. Appl. Polym. Sci.* **2000**, *76*, 1257-1268

Copper catalysed borylation of aryl halides:

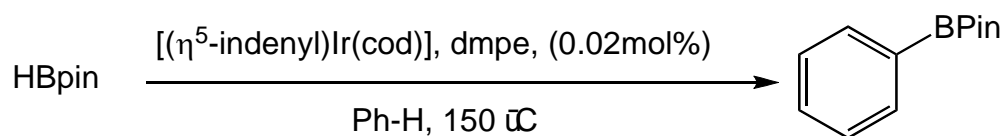


W. Zhu, D. Ma, *Org. Lett.* **2006**, *8*, 261-263

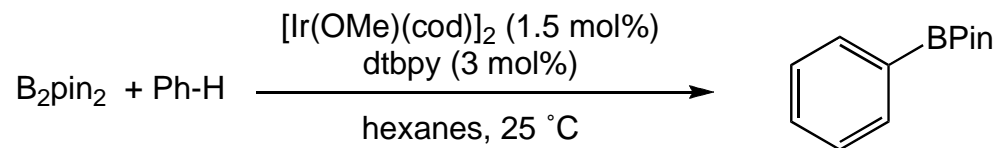
Iridium Catalysed Borylation of C-H Bonds



Marder *et al.*, *J. Am. Chem. Soc.*, 1993, **115**, 9329



Smith *et al.*, *Science*, 2002, **295**, 305

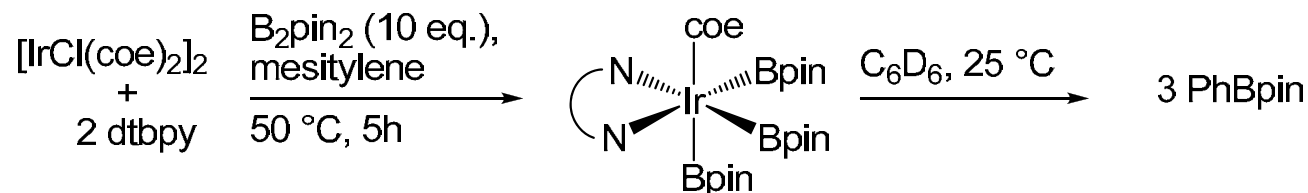


Ishiyama, Hartwig, Miyaura *et al.*, *Angew. Chem. Int. Ed.*, 2002, **41**, 3056

Mkhalid, Barnard, Marder, Murphy, Hartwig, *Chem. Rev.*, **2010**, **110**, 890

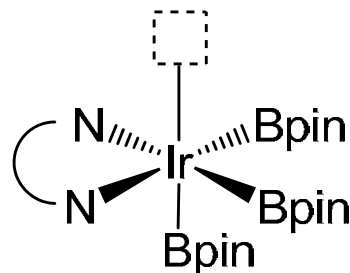
Proposed Active Species

Experimental work by Hartwig *et al.* led to the isolation of $[\text{Ir}(\text{dtbpy})(\text{coe})(\text{Bpin})_3]$ which was viable in the borylation of C_6D_6 .



Hartwig, Miyaura *et al.* *J. Am. Chem. Soc.* **2002**, 124, 390

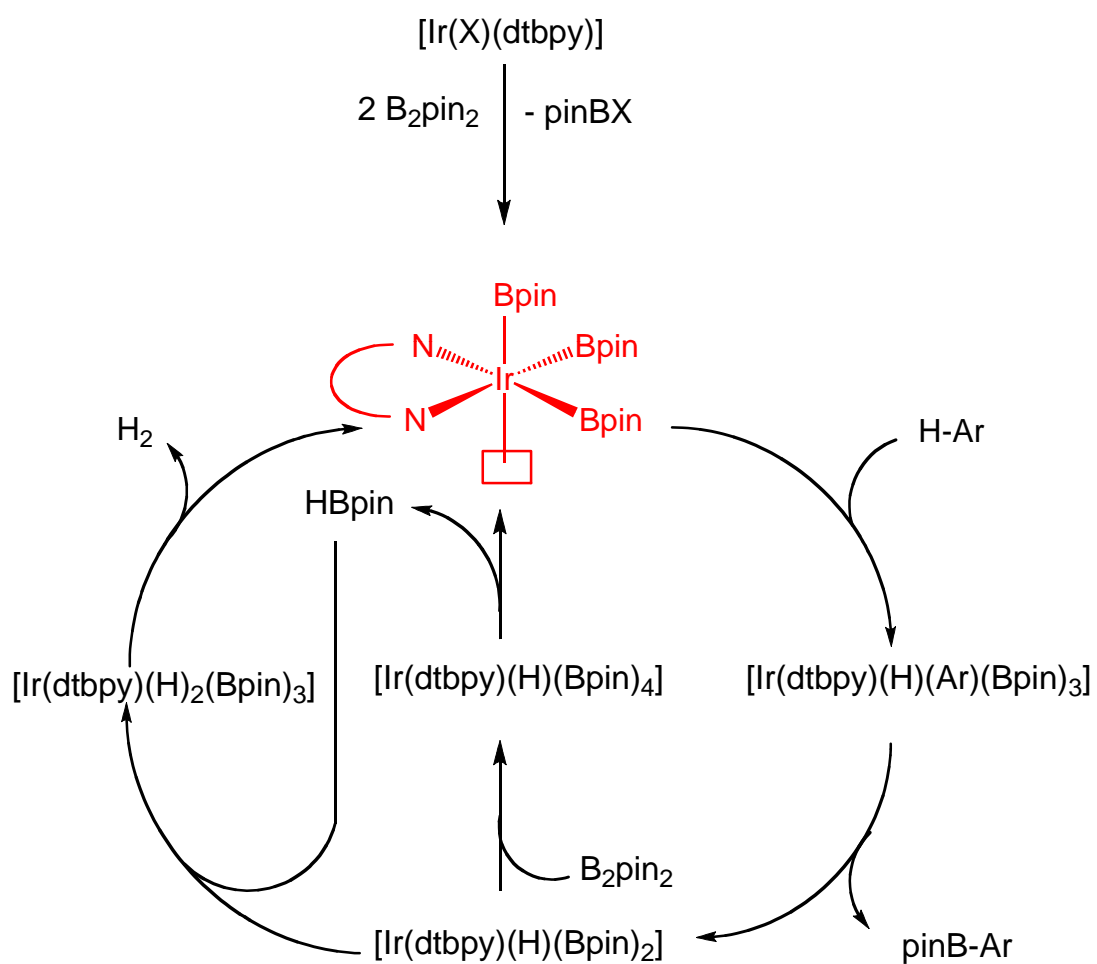
Theoretical work by Sakaki *et al.* also suggests a 5-coordinate $\text{L}_2\text{Ir}(\text{Bpin})_3$ *fac-tris*-(boryl) complex as the active species, with a vacant site available for C-H activation.



Sakaki *et al.* *J. Am. Chem. Soc.* **2003**, 125, 16114

Marder *et al.* *J. Am. Chem. Soc.* **1993**, 115, 9329

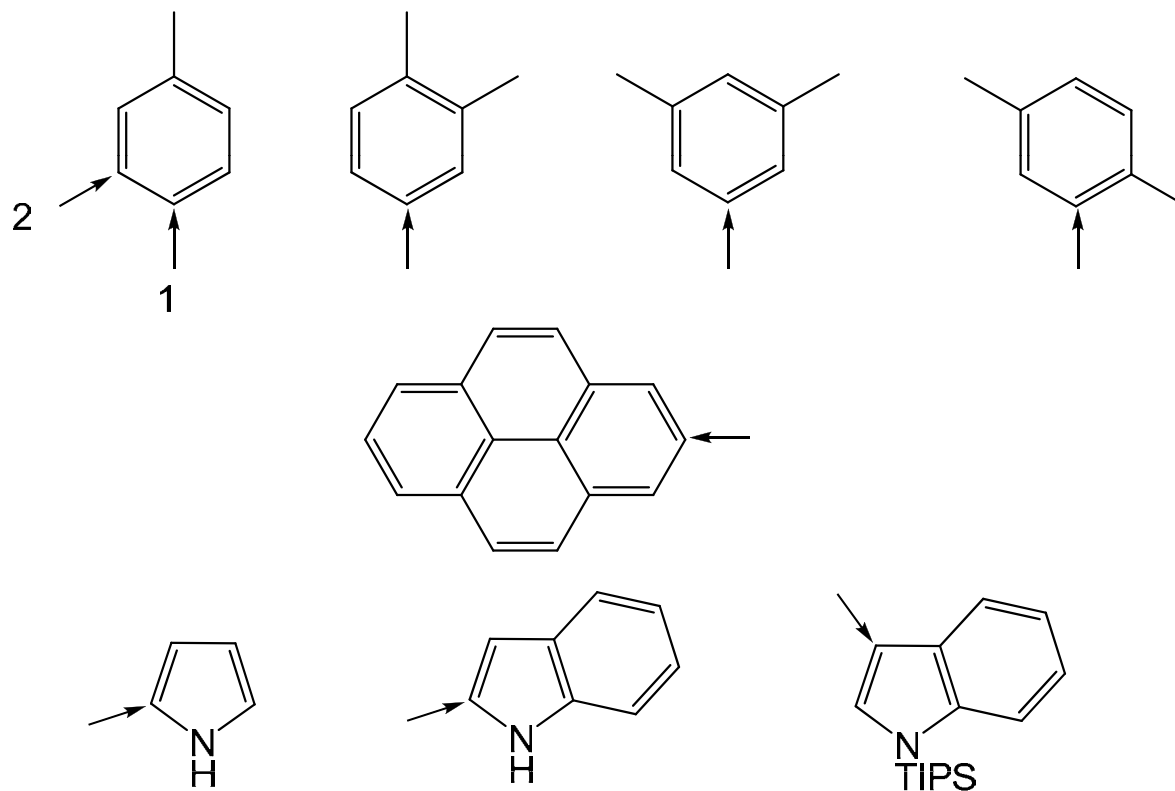
Ir Catalysed Arene Borylation



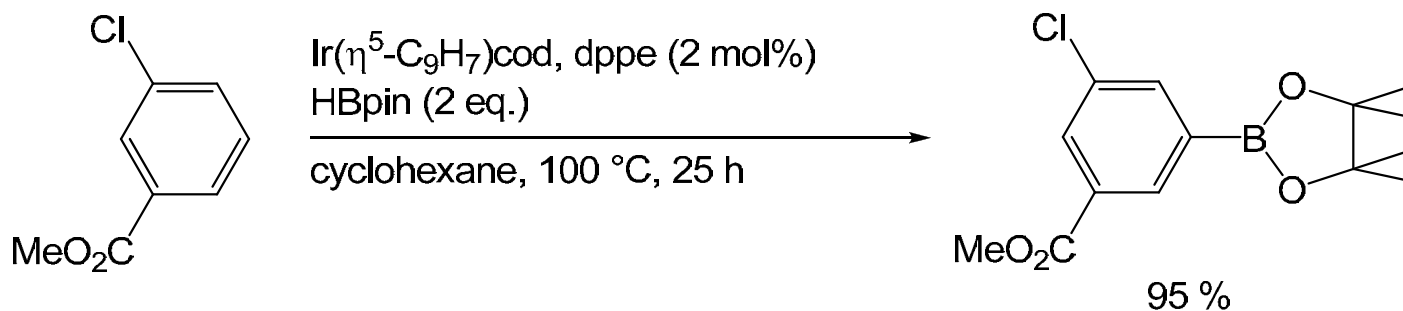
Selectivity of Iridium-Catalysed Aromatic C-H Borylation

Selectivity driven by steric factors due to the hindered nature of the active species

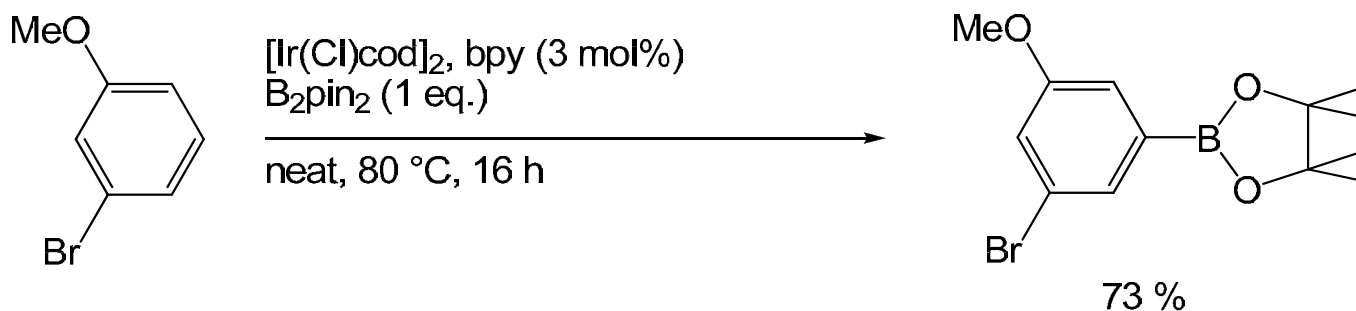
Borylation avoids positions *ortho* to substituents or ring junctions



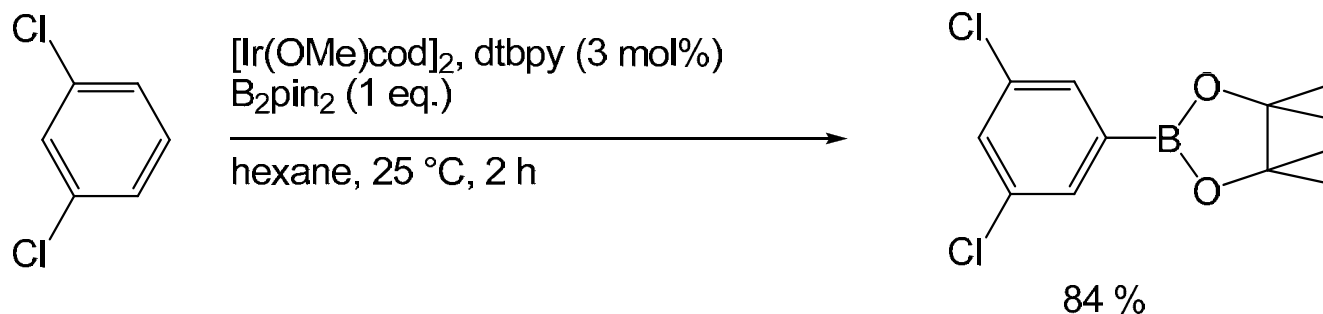
Iridium-Catalysed Aromatic C-H Borylation



Smith *et al.* *Science* **2002**, 295, 305

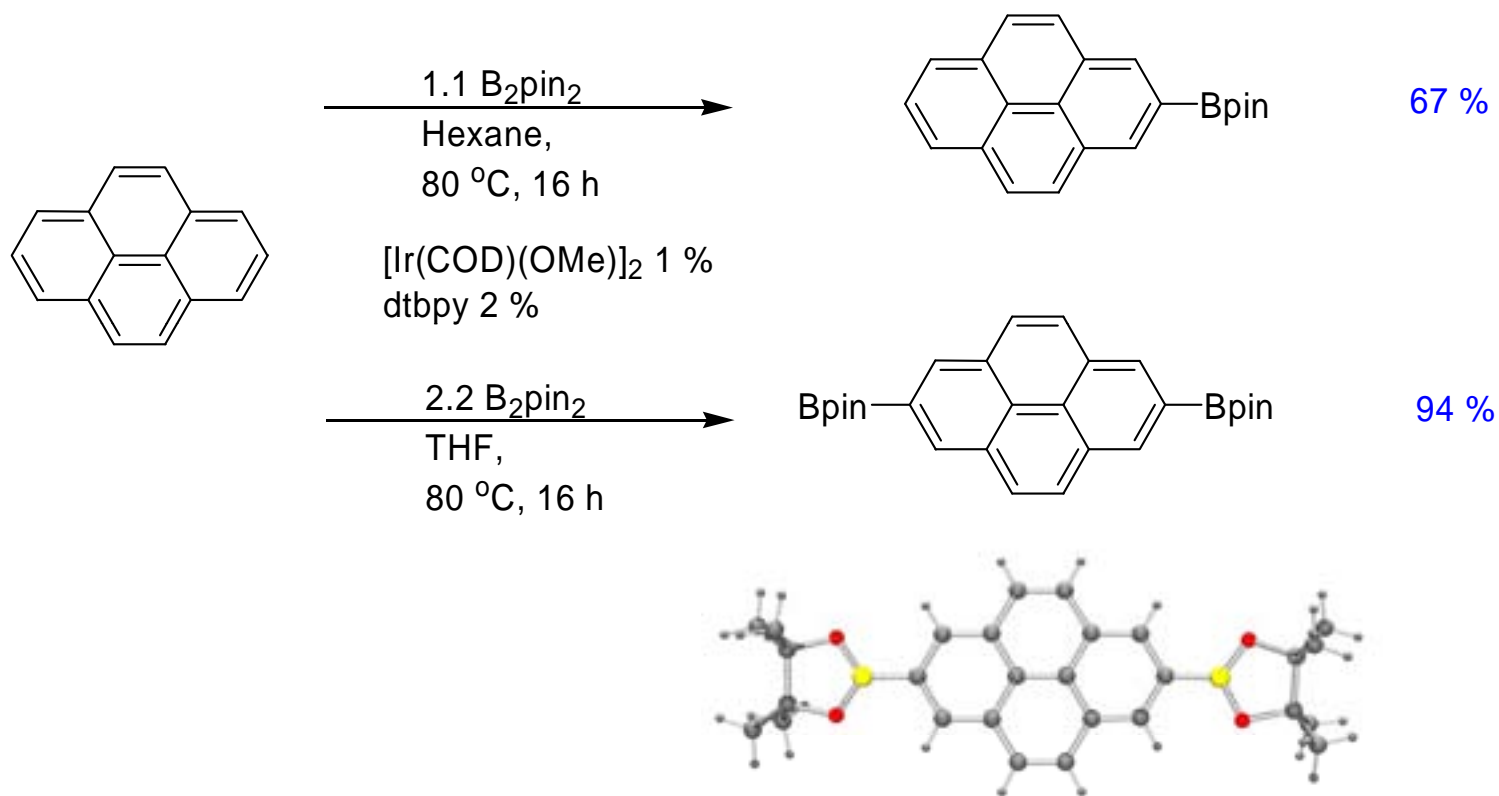


Ishiyama, Hartwig, Miyaura *et al.* *J. Am. Chem. Soc.* **2002**, 124, 390



Ishiyama, Hartwig, Miyaura *et al.* *Angew. Chem. Int. Ed.* **2002**, 41, 3056

Borylation of Pyrene Exclusively at the 2- and 2,7- Positions (used to prepare ca. 30 derivatives for photophysical studies)

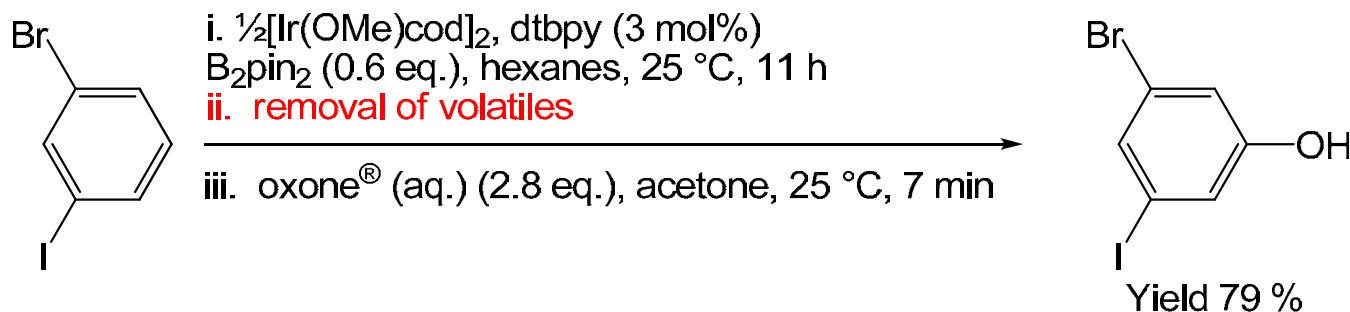


Three polymorphs, two 1:1 toluene solvates and a 1:2 co-crystal (with hexafluorobenzene) of 2,7-bis(Bpin)pyrene were analyzed

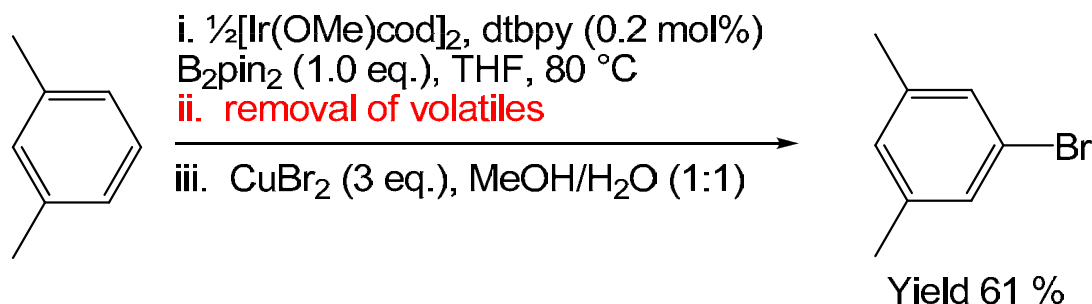
Coventry, Batsanov, Goeta, Howard, Marder, Perutz, *Chem. Commun.* **2005**, 2172

Crawford, Dwyer, Liu, Steffen, Beeby, Palsson, Tozer, Marder, *J. Am. Chem. Soc.* **2011**, 133, 13349

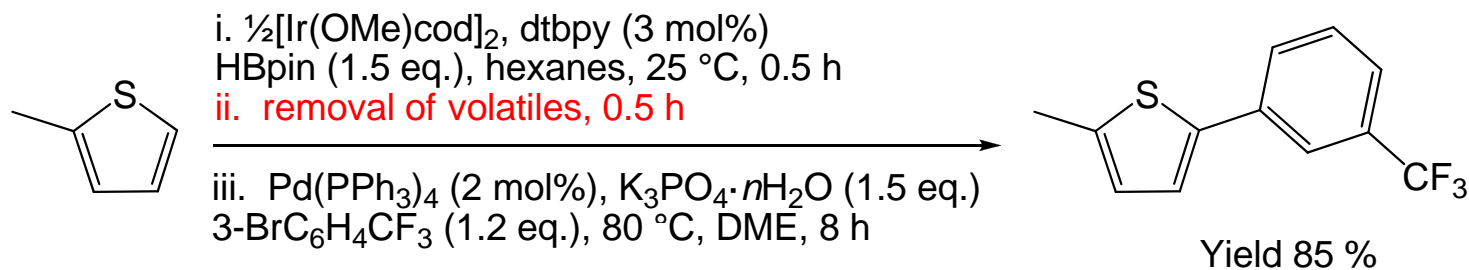
Some 'One-pot' Transformations from Aromatic Substrates



Smith et al. *J. Am. Chem. Soc.* **2003**, 125, 7792



Hartwig et al. *J. Am. Chem. Soc.* **2007**, 129, 15434



Smith et al. *Tetrahedron* **2008**, 64, 6103

One-pot C-H Borylation/Suzuki-Miyaura Cross-Coupling

The Problem:

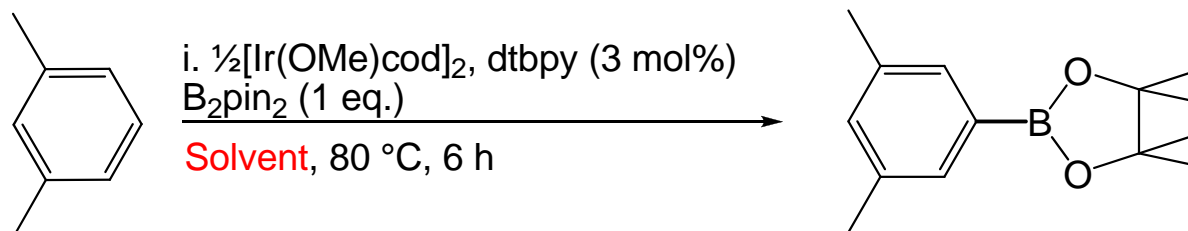
Borylation reactions work well in **non-coordinating solvents** such as hexanes, cyclohexane, octane

Suzuki-Miyaura reactions are most effective when carried out in **polar solvents** such as DME, DMF, EtOH, 1,4-dioxane, MeCN

One-pot C-H Borylation/Suzuki-Miyaura Cross-Coupling

The solution (part 1):

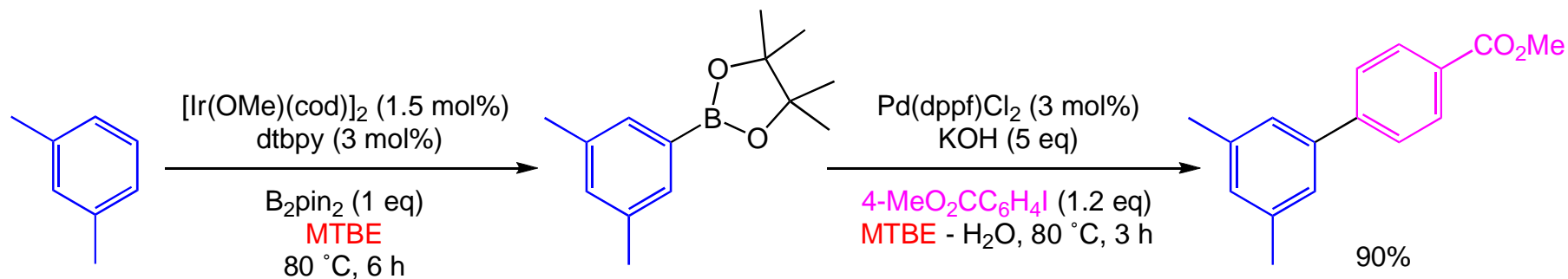
MTBE (Methyl *tert*-butyl ether) is a suitable borylation solvent.



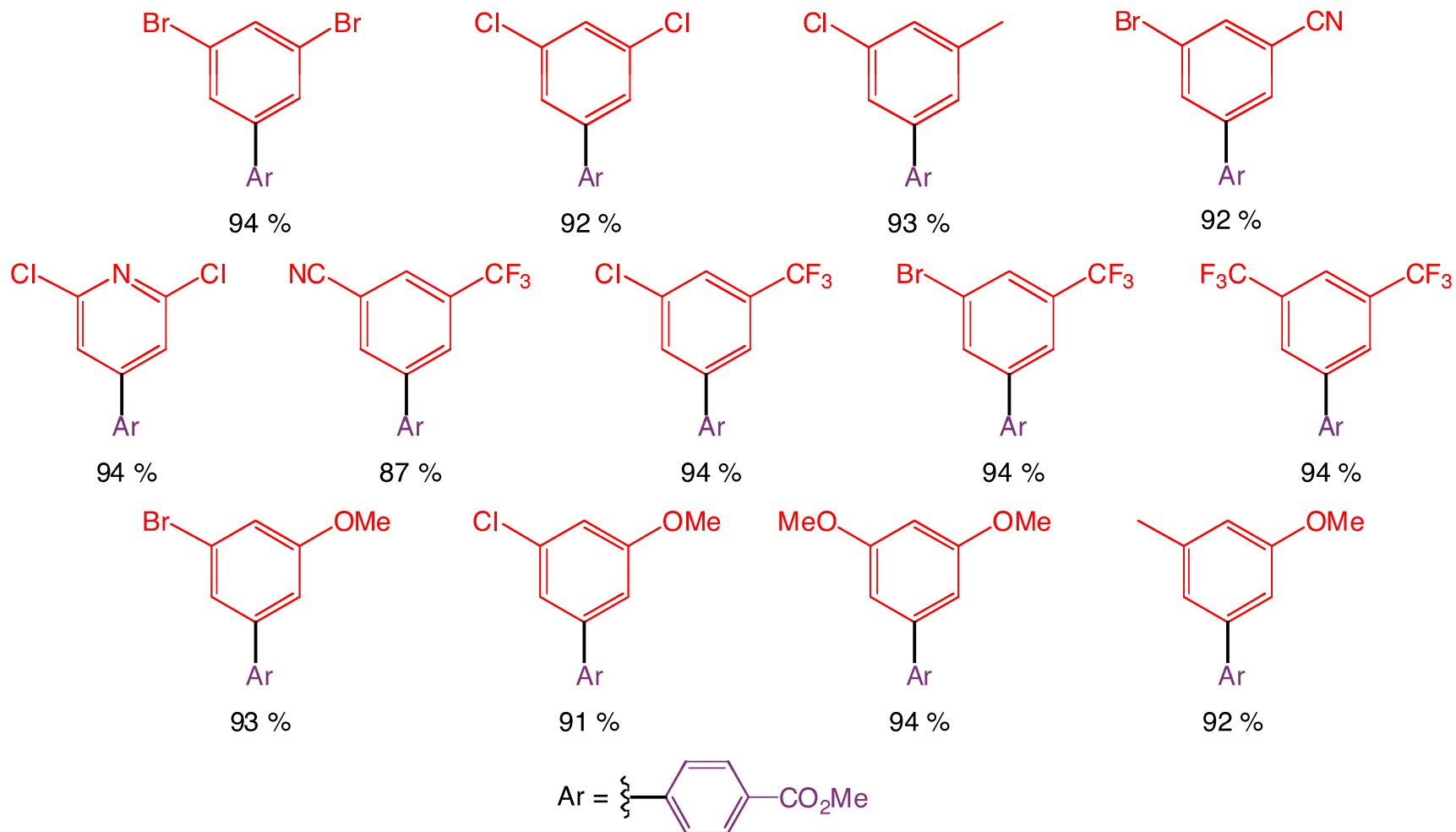
GC-MS conversion

DMF	0 %
1,4-dioxane	25 %
MeCN	37 %
2-MeTHF	87 %
MTBE	100 %

The solution: (Part 2): Is **MTBE** a suitable solvent for Suzuki-Miyaura reactions?

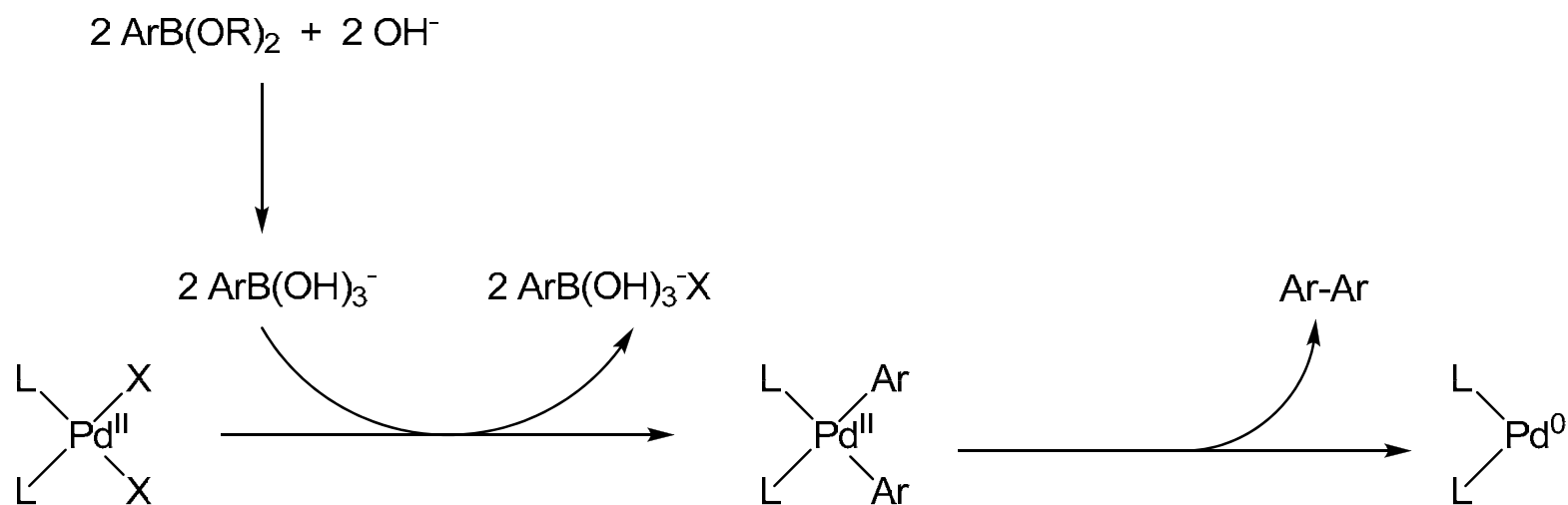


One-pot C-H Borylation/Suzuki-Miyaura Cross-Coupling

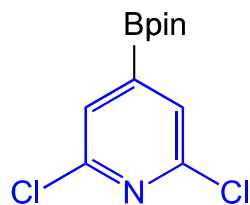


Reduction of Pd^(II) to Pd⁽⁰⁾

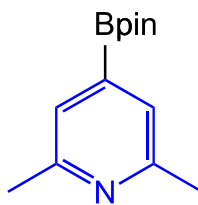
6 % homocoupled biaryl isolated, consistent with reduction of 3 mol% Pd^(II) to Pd⁽⁰⁾
Thus, overall yields of 2-step process = 94% max. based on initial arene



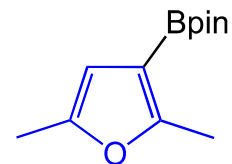
Microwave Accelerated Ir-Catalysed C-H Borylation



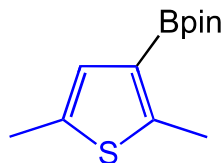
Δ 96%, 20 min
 μW 98%, 3 min



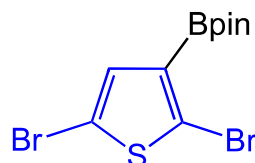
Δ 95%, 30 min
 μW 98%, 5 min



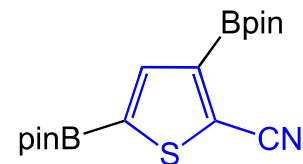
Δ 98%, 5 min
 μW 99%, 2 min



Δ 99%, 120 min
 μW 99%, 15 min

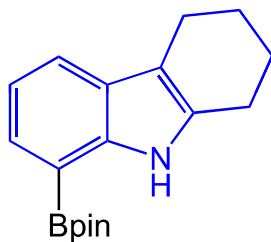


Δ 84%, 1080 min
 μW 82%, 60 min

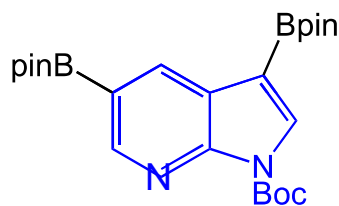


Δ 98%, 120 min
 μW 99%, 15 min

(1.5 eq B₂pin₂)

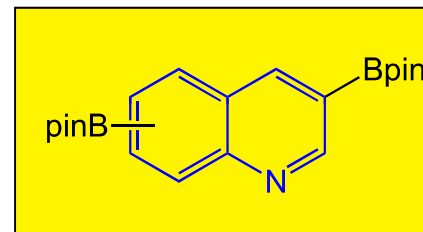


Δ 89%, 120 min
 μW 90%, 15 min



Δ 90%, 360 min
 μW 92%, 20 min

(2.0 eq B₂pin₂)

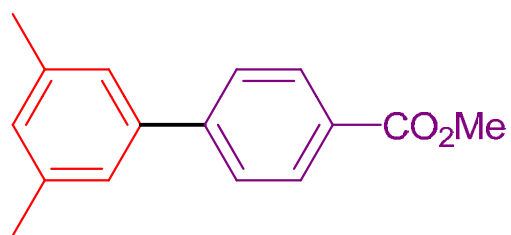
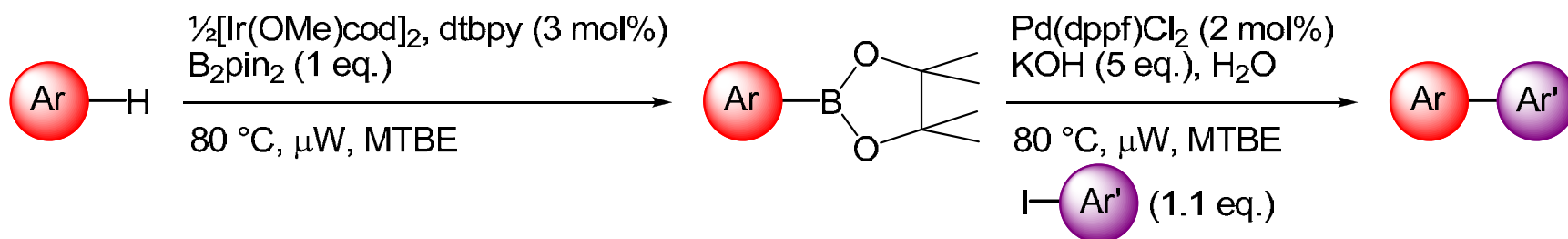


Δ 92%, 120 min
 μW 89%, 15 min

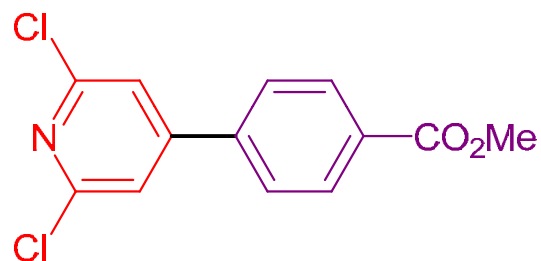
(2.0 eq B₂pin₂)

Harrison, Morris, Marder, Steel, *Org. Lett.* 2009, 11, 3586

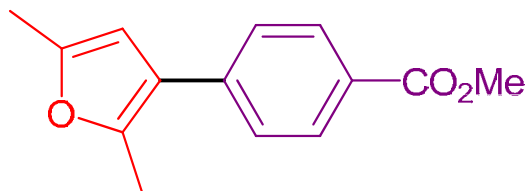
Microwave Accelerated C-H Borylation/Suzuki-Miyaura Sequence



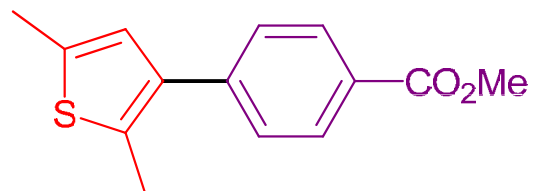
Borylation 60 min
Cross-coupling 5 min
Yield - 95 %



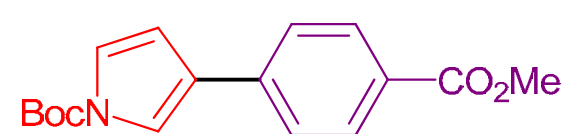
Borylation 5 min
Cross-coupling 5 min
Yield - 96 %



Borylation 5 min
Cross-coupling 5 min
Yield - 96 %

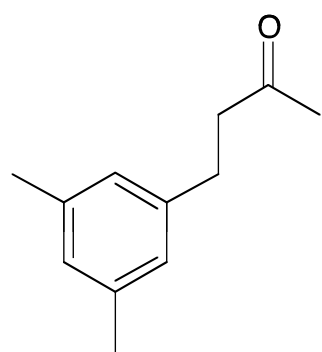
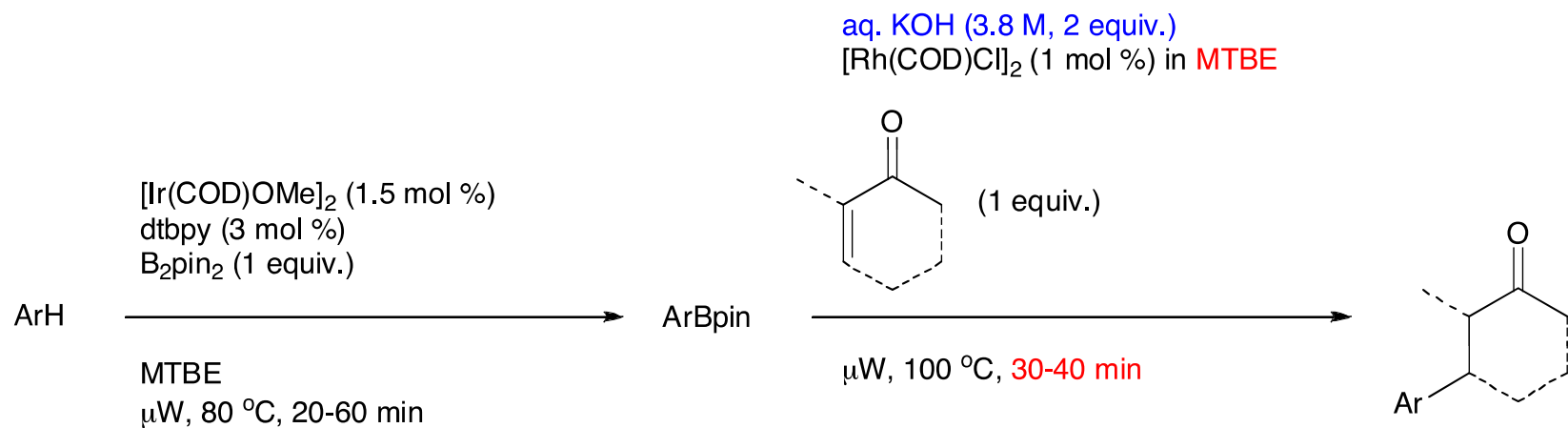


Borylation 15 min
Cross-coupling 5 min
Yield - 96 %

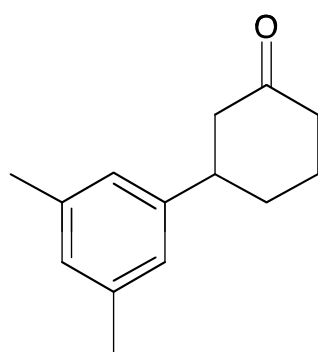


Borylation 5 min
Cross-coupling 5 min
Yield - 95 %

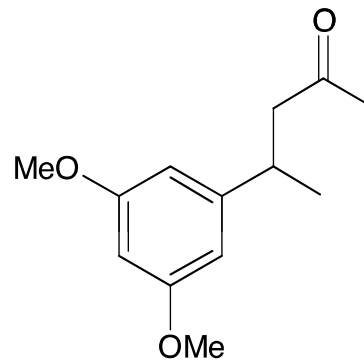
One-Pot Borylation / 1,4-Conjugate Addition



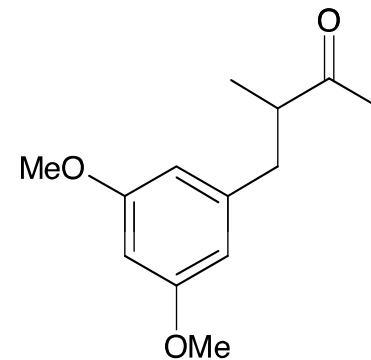
68 %



65 %

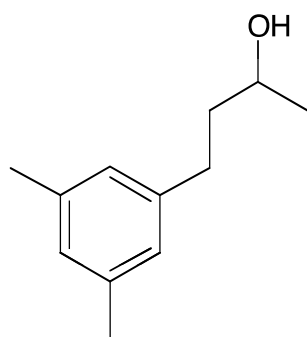
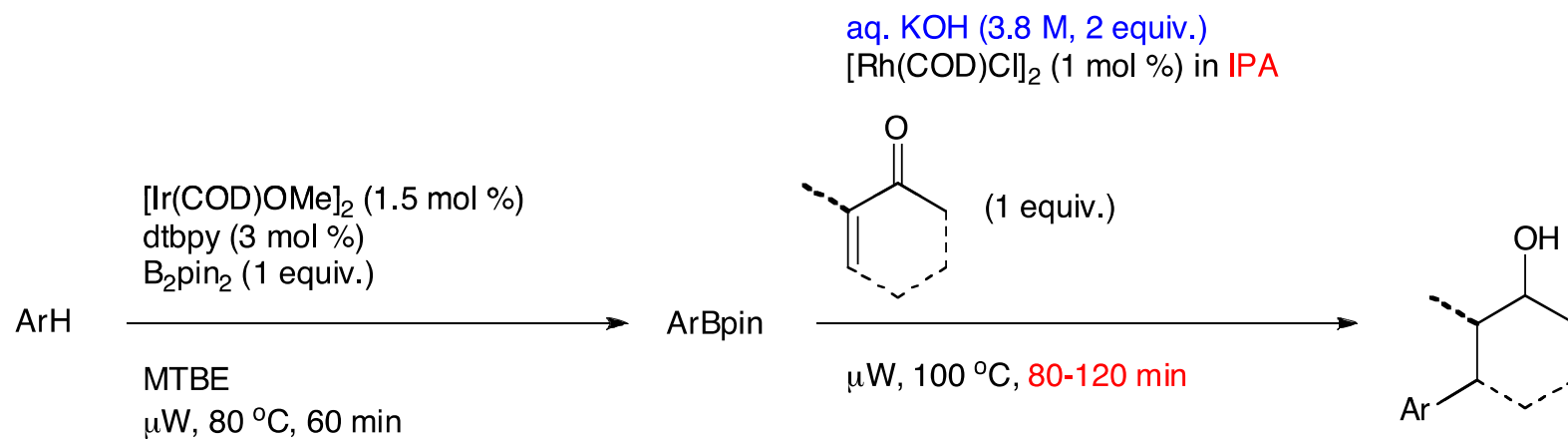


47 %

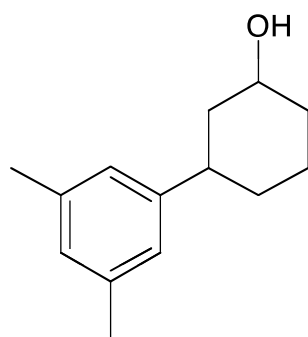


45 %

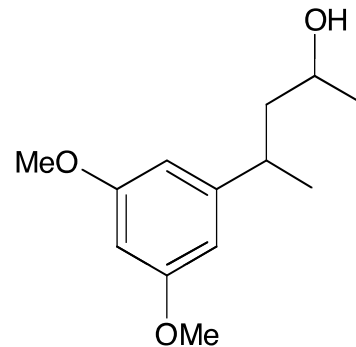
One-Pot Borylation / 1,4-Conjugate Addition / Reduction



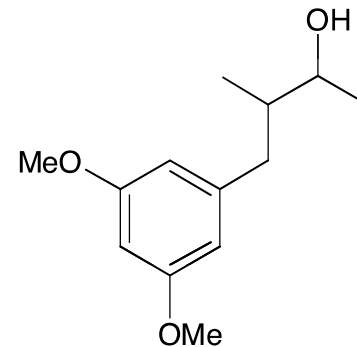
61 %



58 %
dr = 1:1



51 %
dr = 1:1.2



52 %
dr = 1:1.3

One-Pot Borylation / 1,4-Conjugate Addition / Reduction: Applications in Array Chemistry

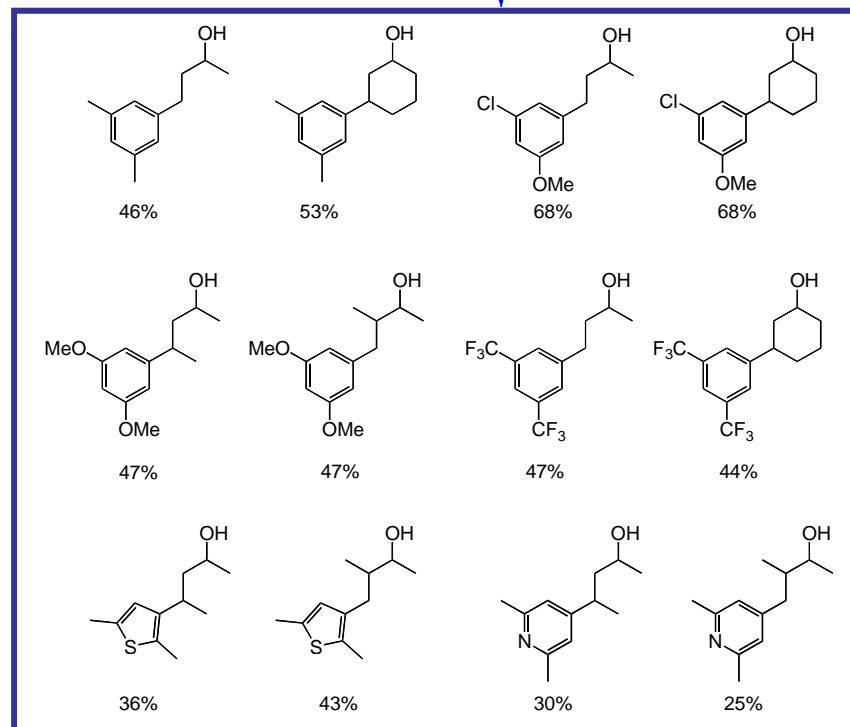
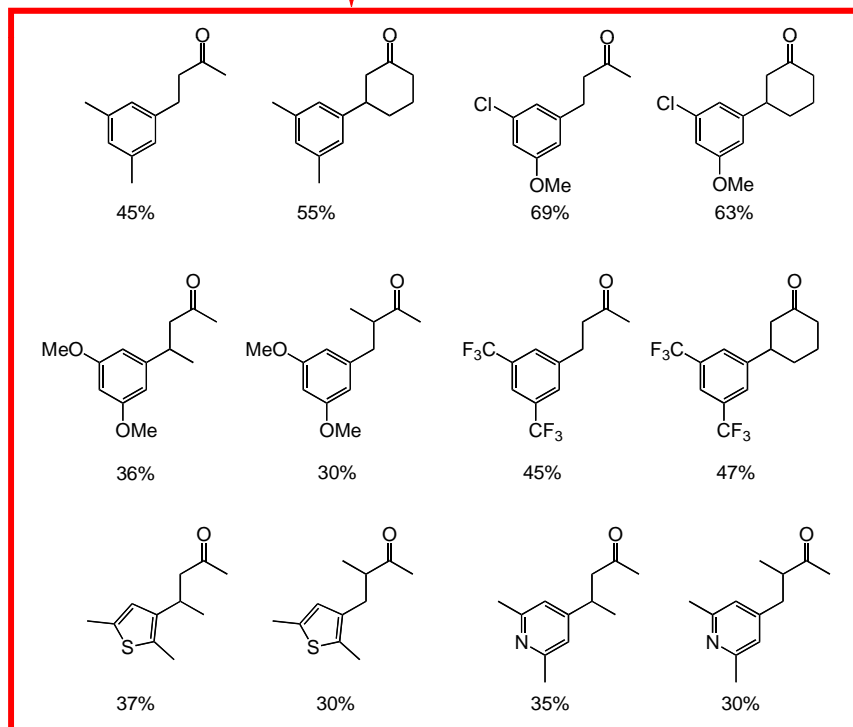
Ar-H

i. $[\text{Ir}(\text{OMe})(\text{cod})]_2$ (1.5 mol%), dtbpy (3 mol%)
 B_2pin_2 (1 eq), MTBE, μW , 80 °C, 60 min

ii. aq. K_3PO_4 ; enone, $\text{Rh}(\text{COD})\text{Cl}]_2$ (1 mol%)
solvent, μW , 100 °C, 30 min

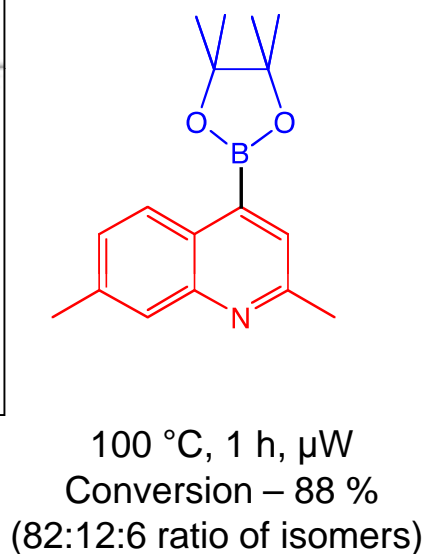
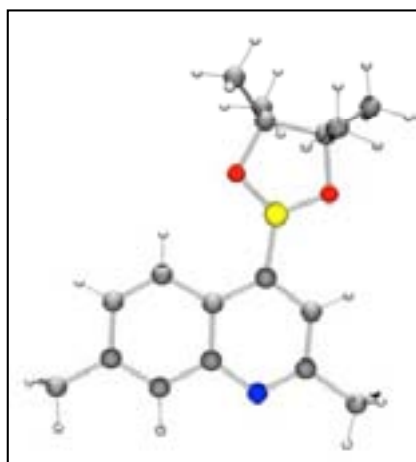
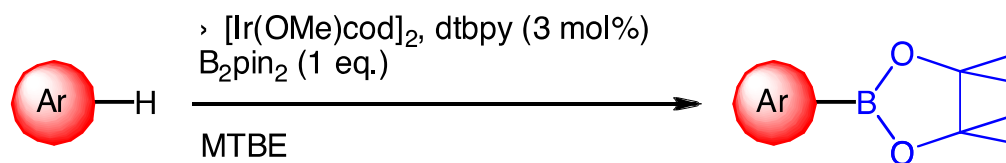
MTBE

IPA

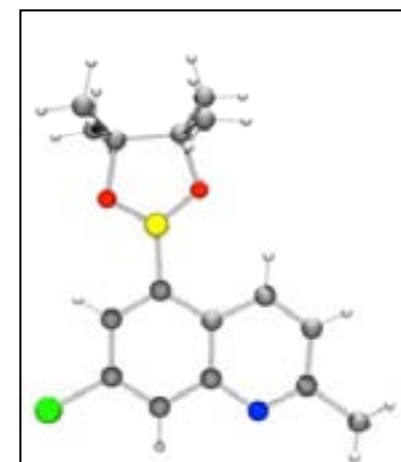
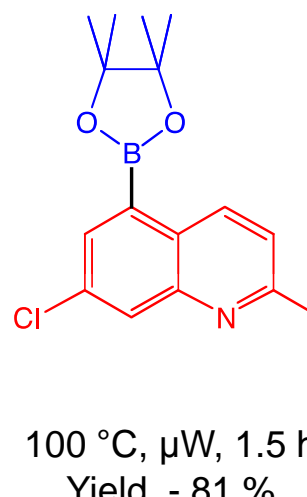


Tajuddin, Shukla, Maxwell, Marder, Steel, *Org. Lett.* 2010, 12, 5700

Quinoline Borylation: Regioselectivity



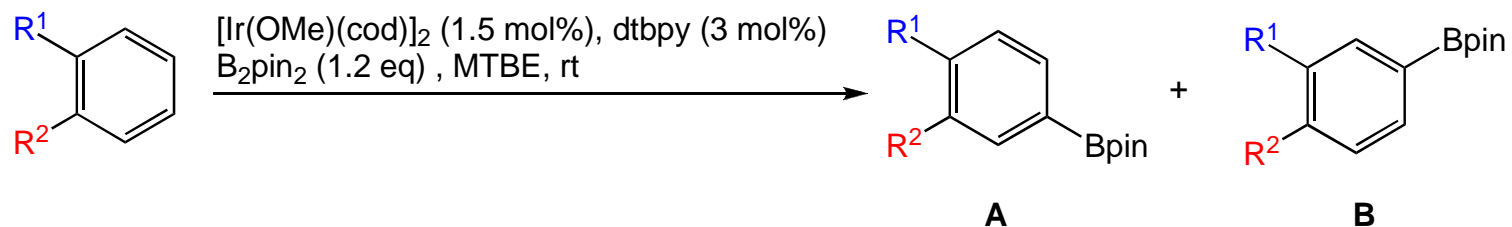
RT, 72 h
Yield - 80 %
(>95 % major isomer)



Lower temperature increases selectivity

Peter Harrison

Regioselectivity in 1,2-Disubstituted Benzene Borylation

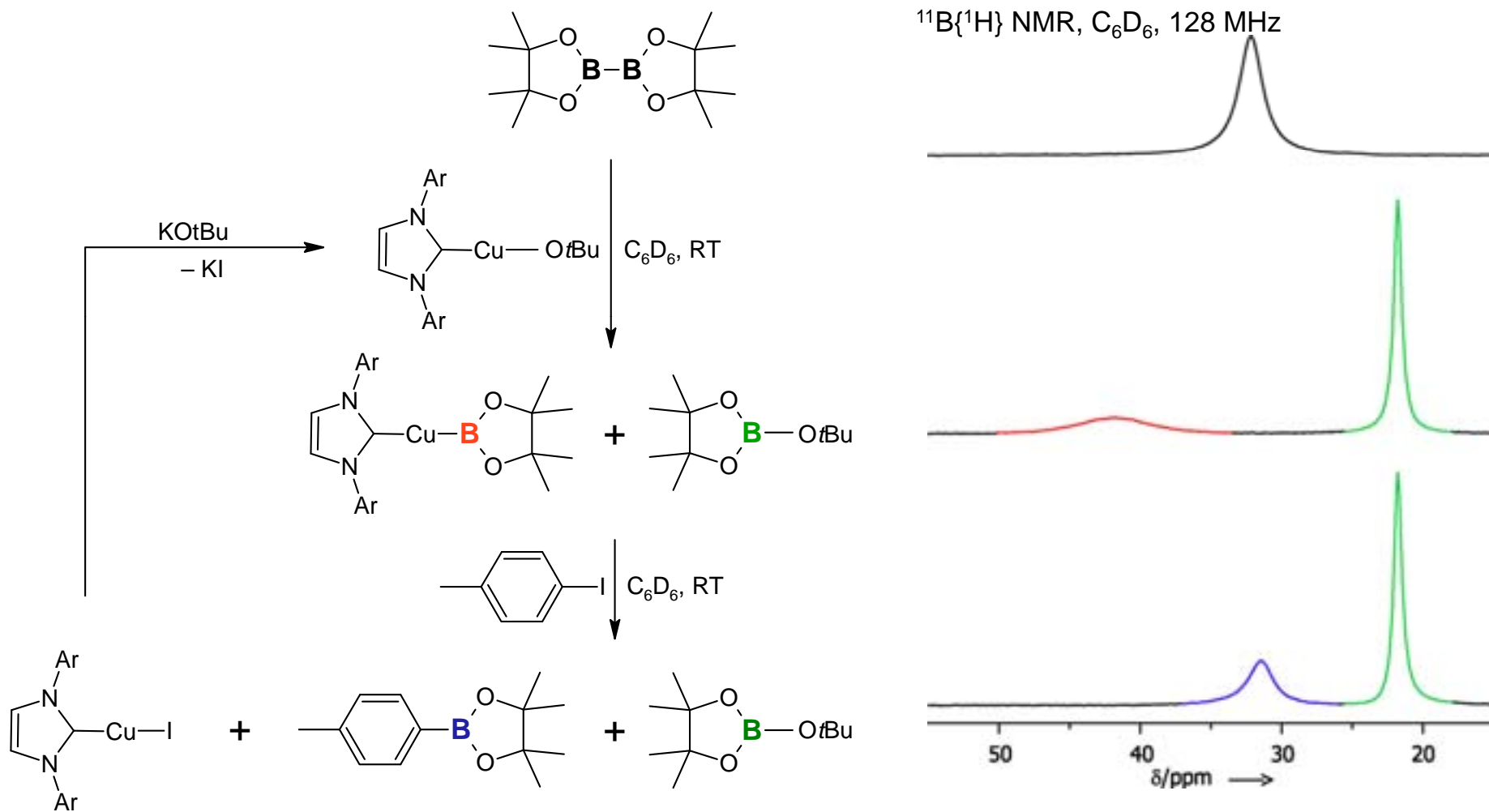


R ¹	R ²	Time (h)	GC Conversion [%]	NMR ratio A:B
OMe	COMe	18	> 99	13:87
Me	COMe	18	87	38:62
OMe	Me	18	75	26:74
OMe	Cl	18	94	37:63
Cl	COMe	18	> 99	34:66
OMe	COOMe	18	> 99	16:84
Me	CN	18	> 99	40:52:(8)

Bianca Bitterlich

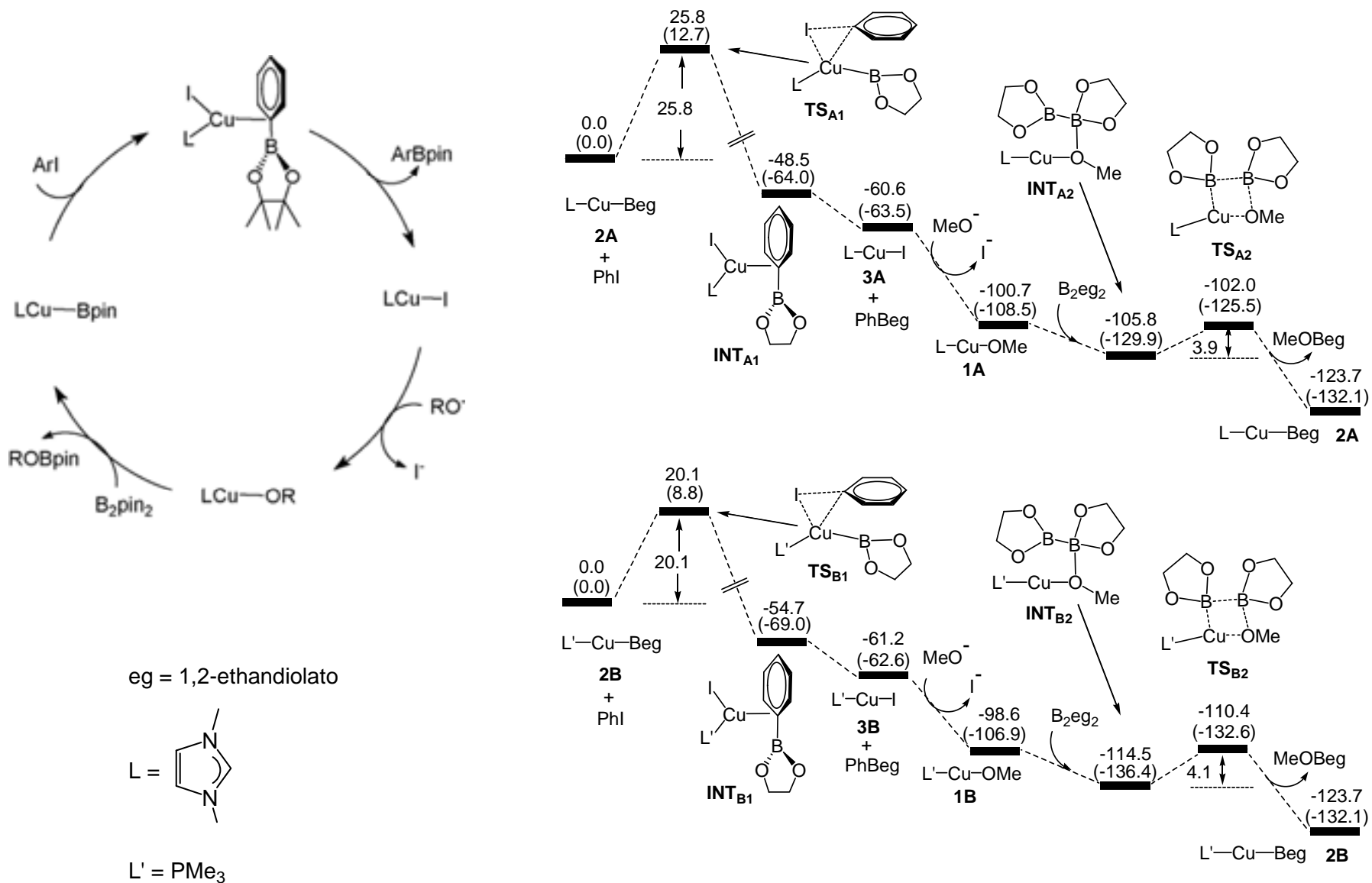
Copper-catalysed Borylation of Aryl and Alkyl Halides

Synthesis and Reactivity of a Cu-Boryl Complex

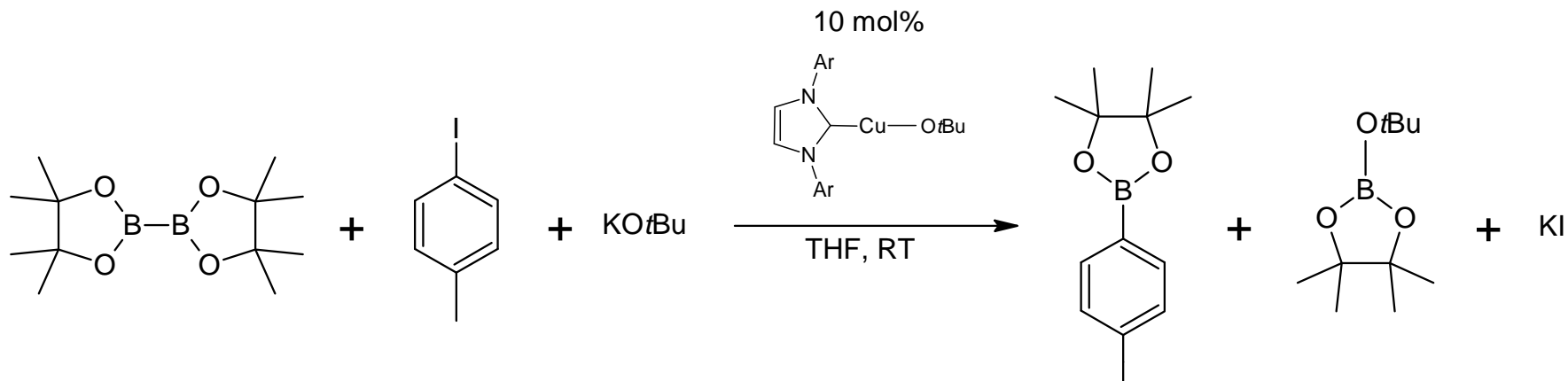


C. Kleeberg, L. Dang, Z. Lin and T. B. Marder, *Angew. Chem. Int. Ed.* **2009**, *48*, 5350
For step 1, see: D. S. Laitar, P. Müller, J. P. Sadighi, *J. Am. Chem. Soc.* **2005**, *127*, 17196

Copper Catalysed Borylation – Computed Catalytic Cycle

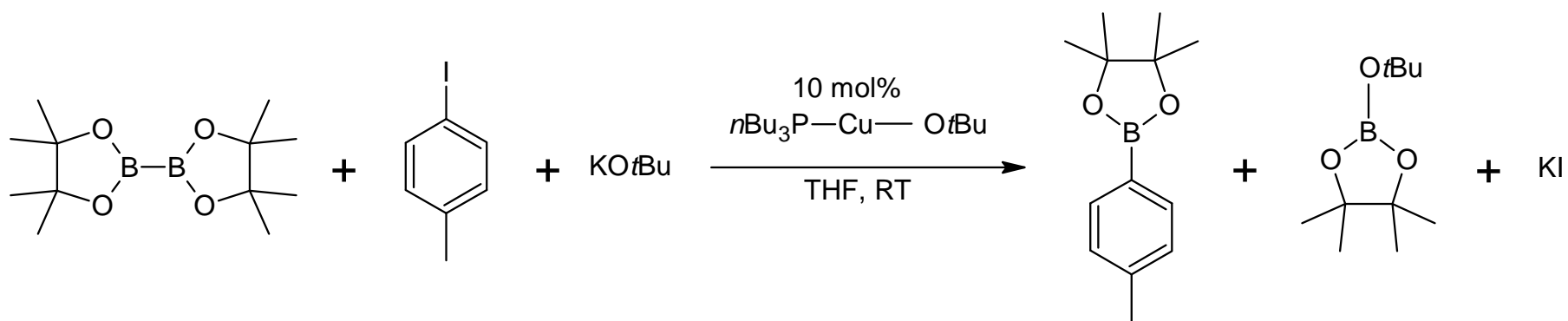


Copper Catalysed Borylation of Aryl Halides Using L-Cu-O^tBu



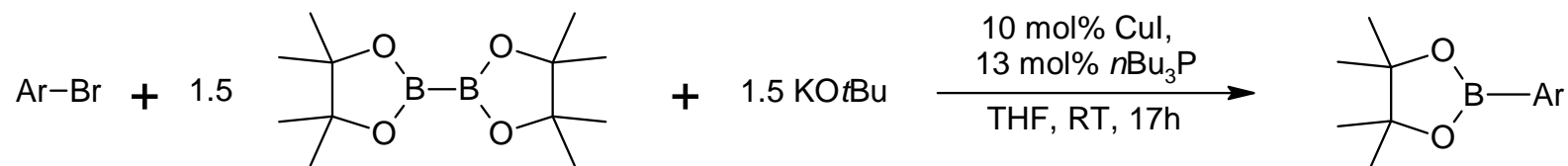
5 h – 18% conversion

17 h – 55% conversion



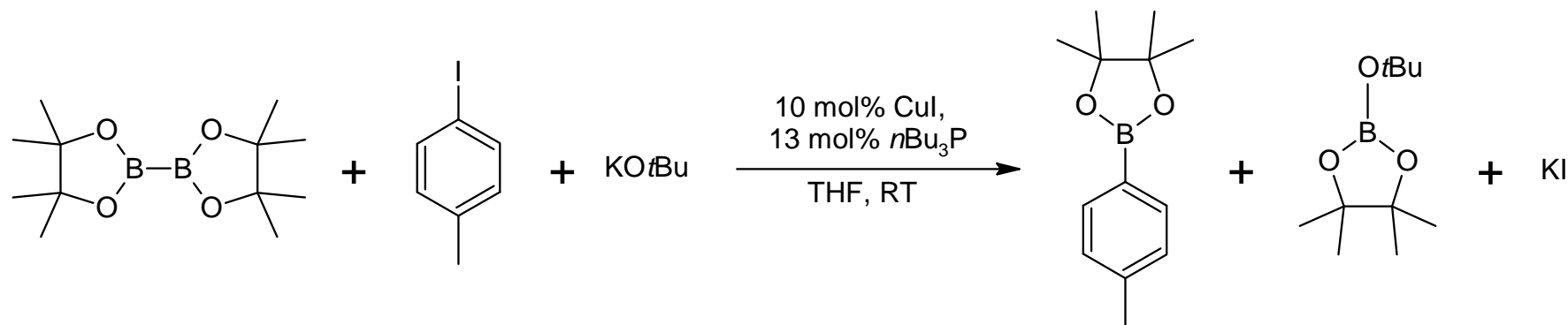
5 h – 100% conversion

Copper Catalysed Borylation: Scope with ArBr



Ar	Conv. Ar-Bpin	Conv. Ar-H	isolated yield Ar-Bpin
4-MeC ₆ H ₄	100%	—	83%
2-MeC ₆ H ₄	100%	—	91%
2,4,6-Me ₃ C ₆ H ₂	90%	10%	69%
4-CF ₃ C ₆ H ₄	100%	—	65%
4-Me ₂ NC ₆ H ₄	88%	12%	69%
2-thiophenyl	100%	—	83%

Copper Catalysed Borylation of Aryl Halides



Unchanged performance upon recharging:

- 82% yield after recharging 5 times

At a reduced catalyst loading of 3 mol% CuI and 3 mol% nBu₃P

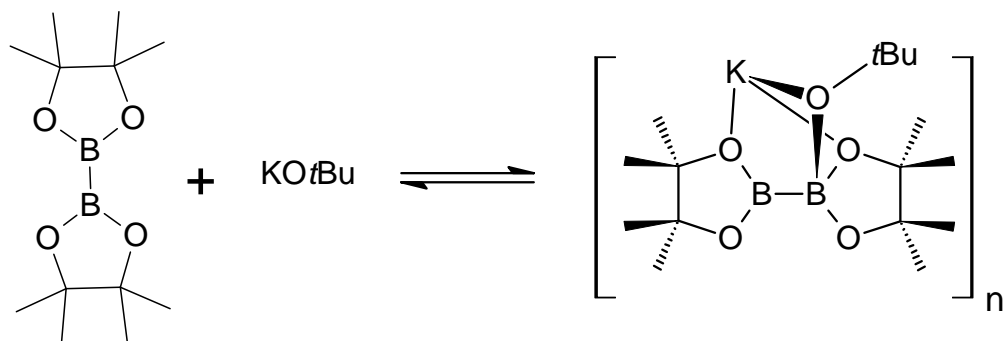
- RT, 24 h – 75% conversion
- 48 h – 100% conversion
- 60 °C, 2.5 h – 100% conversion

Reaction mixture is heterogeneous, as a grey precipitate is formed

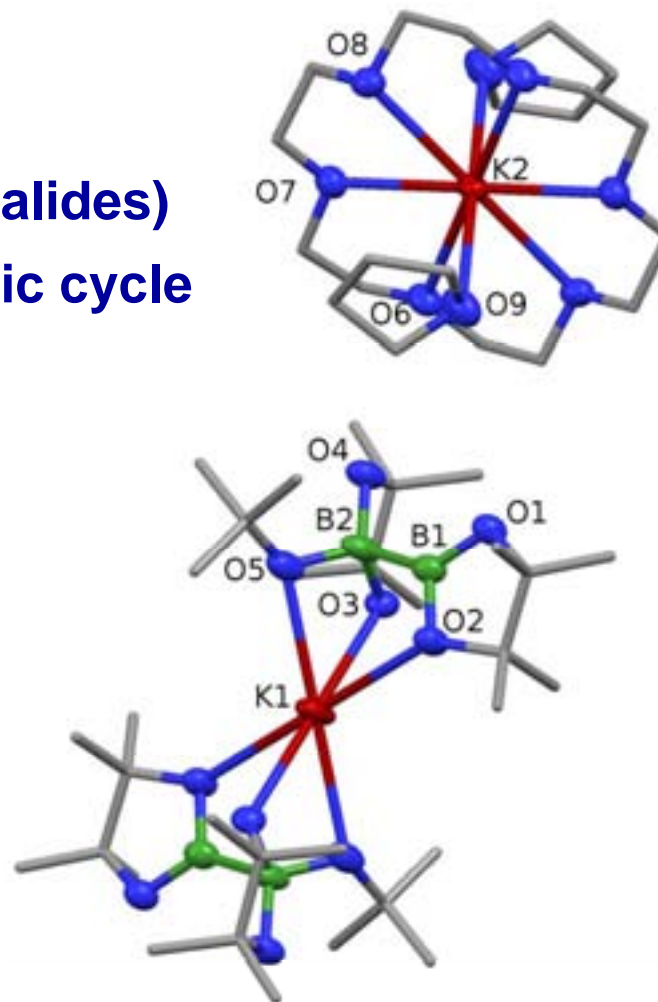
Copper Catalysed Borylation – The Mechanism?

B₂pin₂ and KO^tBu form a relatively insoluble adduct

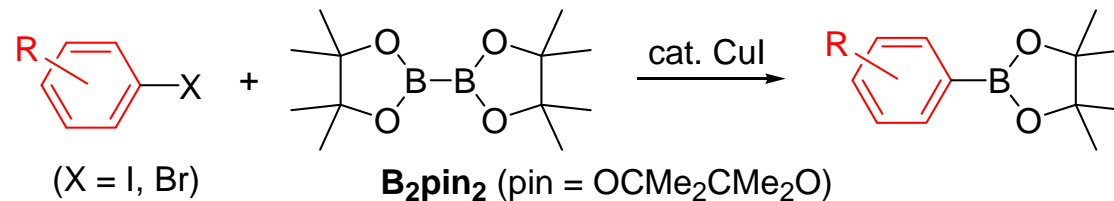
- **Renders the reaction heterogeneous**
- **Adduct gives rise to an uncatalysed background reaction (slow with aryl halides)**
- **Adduct may be involved in the catalytic cycle**



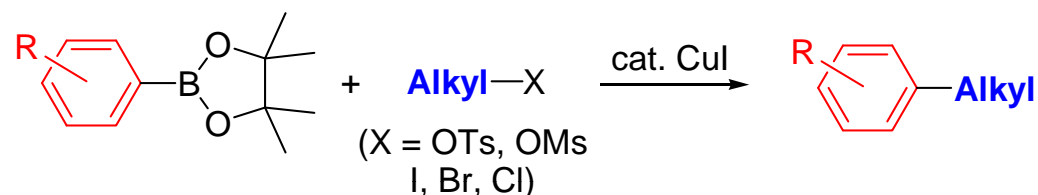
B1-B2	1.730(4) Å
B1-O1	1.383(3) Å
B1-O2	1.395(3) Å
B2-O3	1.591(6) Å
B2-O4	1.481(4) Å
B2-O5	1.492(3) Å



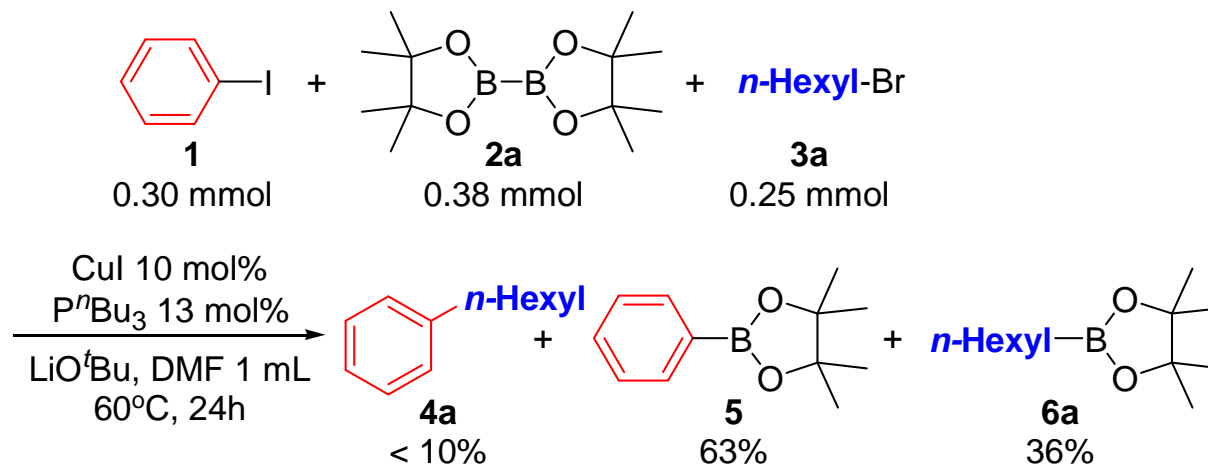
a) Our aryl borylation reaction¹



b) Lei Liu's aryl-alkyl coupling reaction²

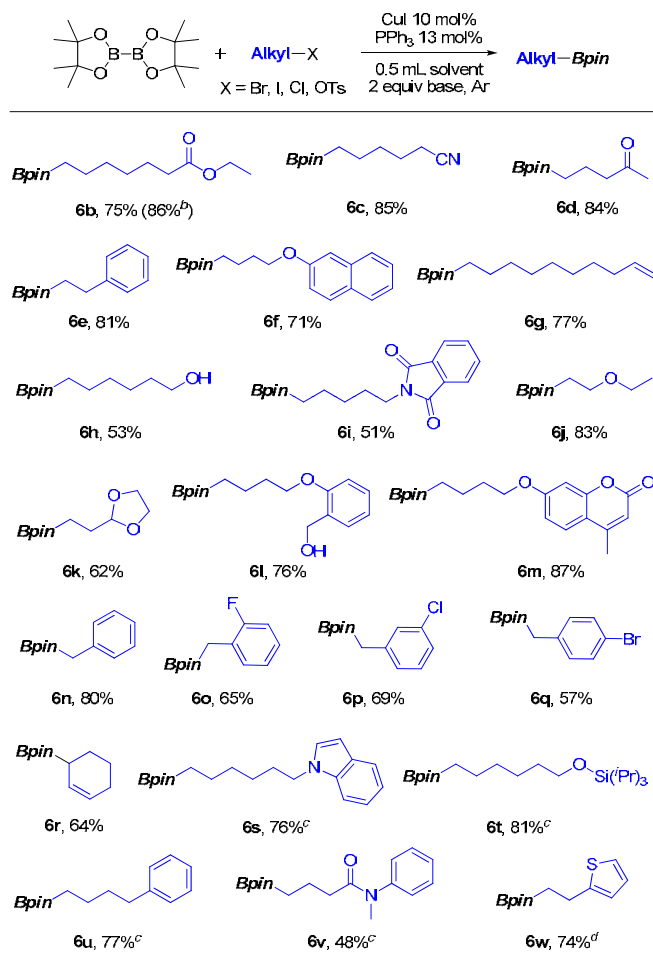


c) One-pot borylation & cross-coupling?



1. C. Kleeberg, L. Dang, Z. Lin and T. B. Marder, *Angew. Chem. Int. Ed.* **2009**, 48, 5350
2. C.-T. Yang, Z.-Q. Zhang, Y.-C. Liu, L. Liu, *Angew. Chem. Int. Ed.* **2011**, 50, 3904

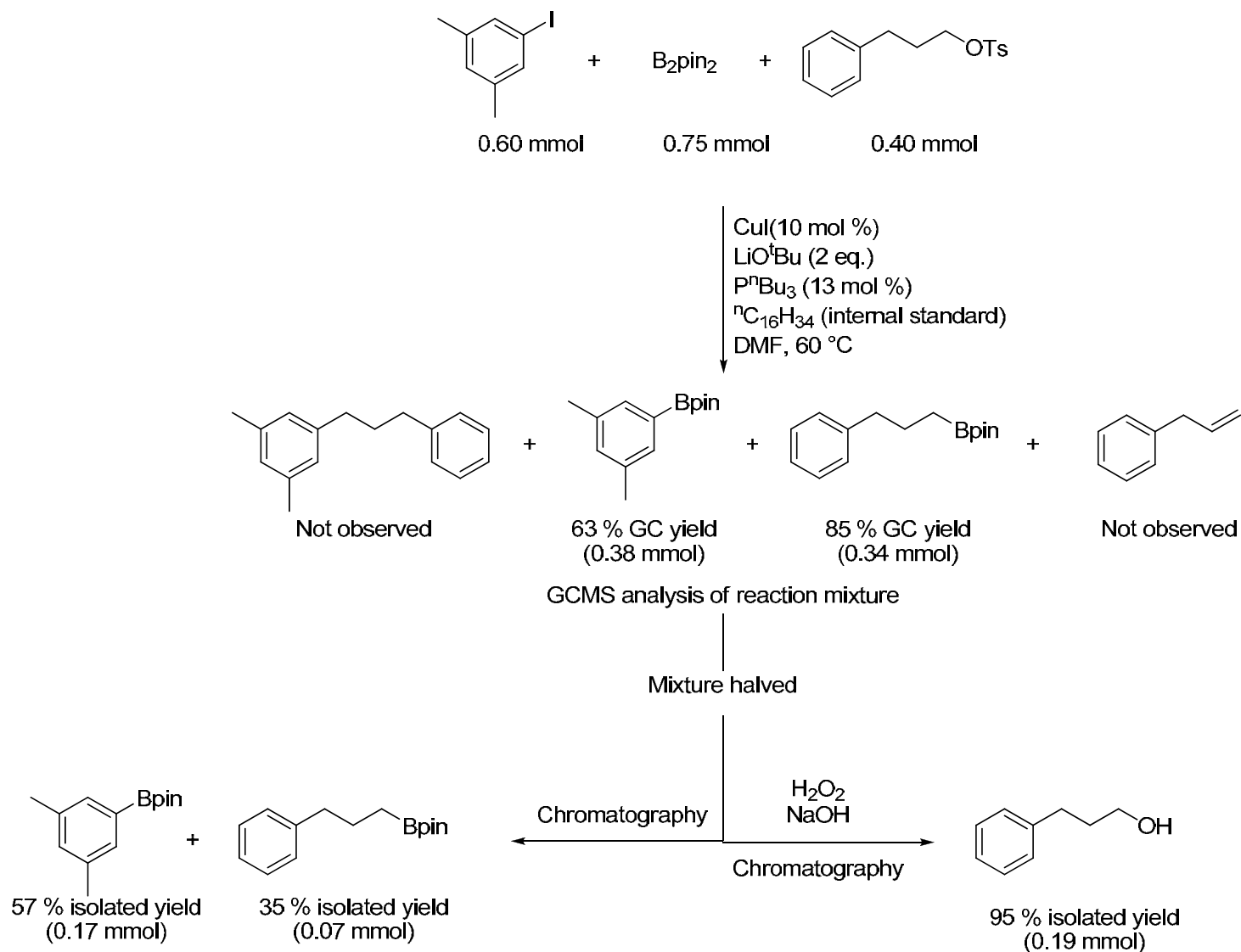
Alkylboronic Esters from Copper-Catalysed Borylation of Primary Alkyl Halides and Pseudo-Halides



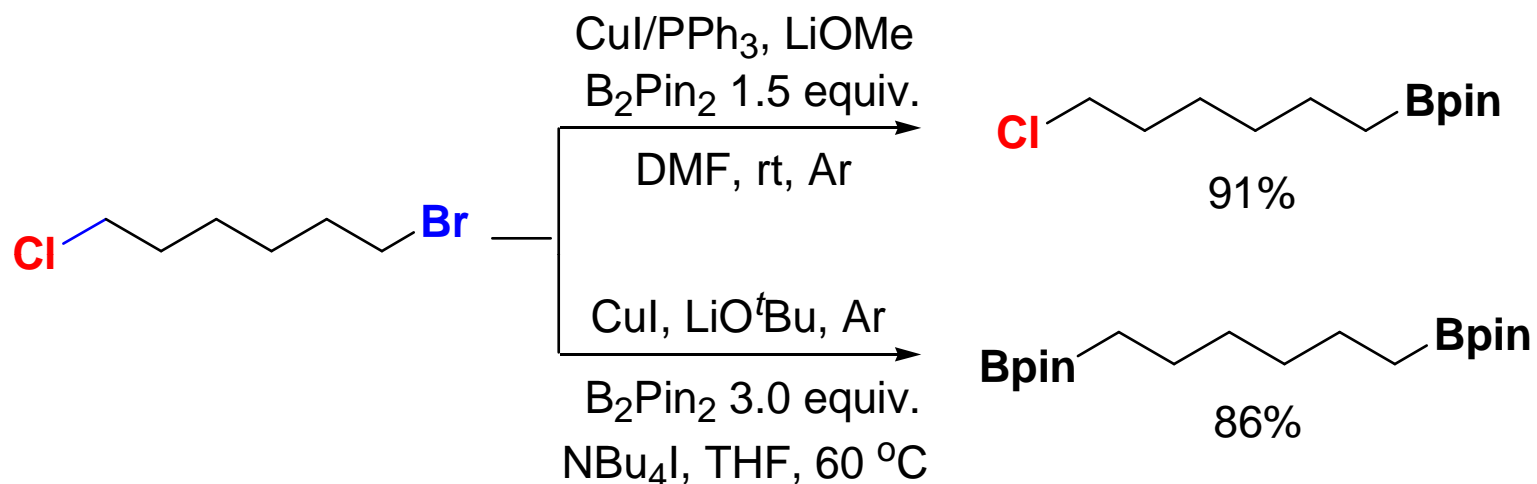
^a Reactions were carried out at 25 °C for 18 h using 10 mol% CuI, 0.38 mmol B₂pin₂, 0.5 mmol base, 0.25 mmol alkyl bromide, unless otherwise stated. Yields quoted are for purified, isolated products. pin = OCMe₂CMe₂O.

^b X = I. ^c X = Cl. ^d X = OTs.

Alkyl Halides are Generally More Reactive than Aryl Halides

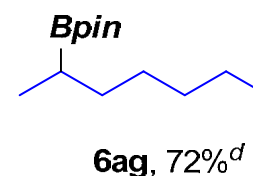
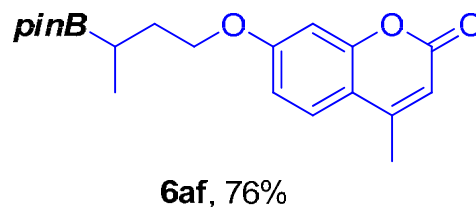
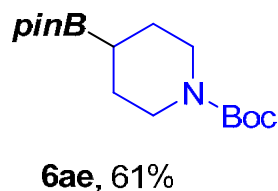
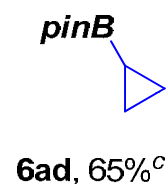
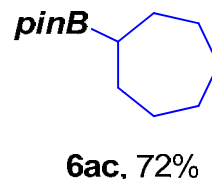
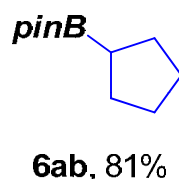
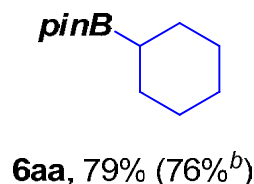
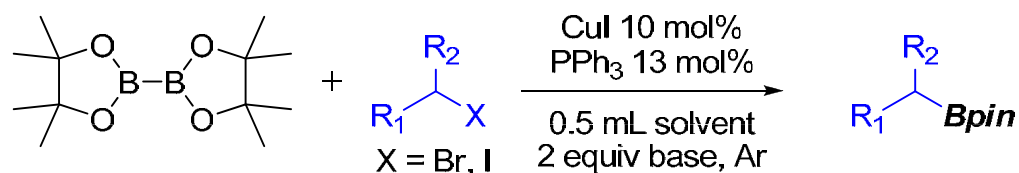


Alkylboronic Esters from Copper-Catalysed Borylation: Site-selective Borylation



Reactivity order: iodide > bromide > chloride ~ tosylate
Generally, chloride and tosylate require addition of ⁿBu₄NI
Primary alkyl iodides do not require addition of phosphine ligand
Aryl halides are generally less reactive than alkyl halides

Alkylboronic Esters from Copper-Catalysed Borylation of Secondary Alkyl Halides and Pseudo-Halides

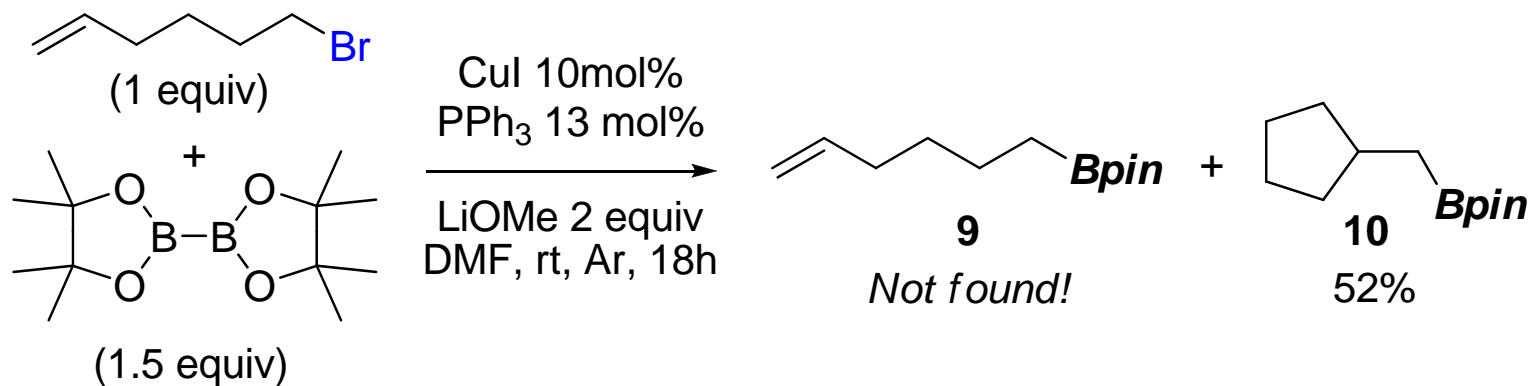


^a Reactions were carried out at 37 °C for 24 h using 10 mol% CuI, 0.38 mmol B₂pin₂, 0.5 mmol base and 0.25 mmol alkyl bromide. Yields quoted are those for purified, isolated products. pin = OCMe₂CMe₂O. ^b X = I, solvent = THF, base = LiOtBu, T = 25 °C. PPh₃ was not added. ^c 2 equiv of B₂pin₂ was used. ^d Polymer supported PPh₃ was used.

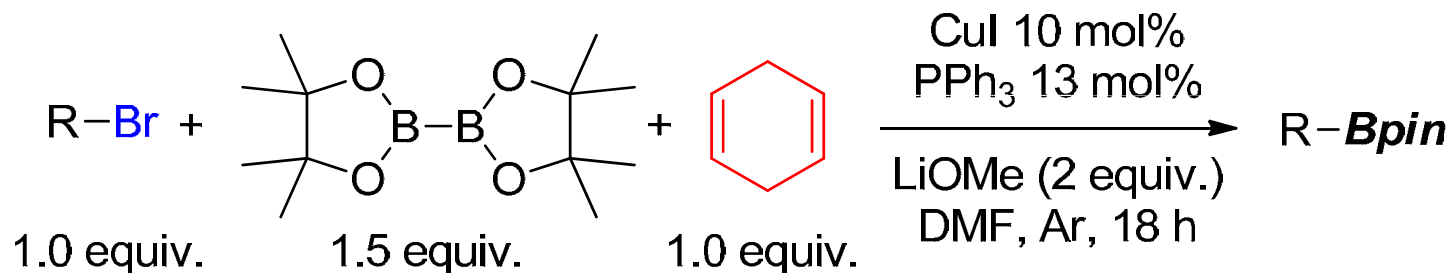
Yang, Zhang, Tajuddin, Wu, Liang, Liu, Fu, Czyzewska, Steel, Marder, Liu, *Angew. Chem.* Accepted.

Preliminary Mechanistic Studies

Borylation of 6-bromohex-1-ene



Radical scavenger experiments

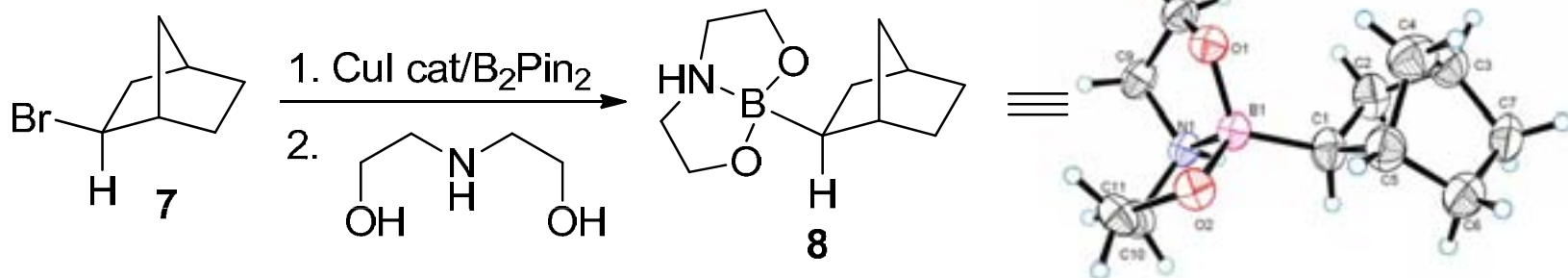


R = *n*-Hexyl, 81% GC yield (rt)

R = Cyclohexyl, 68% GC yield (40 °C)

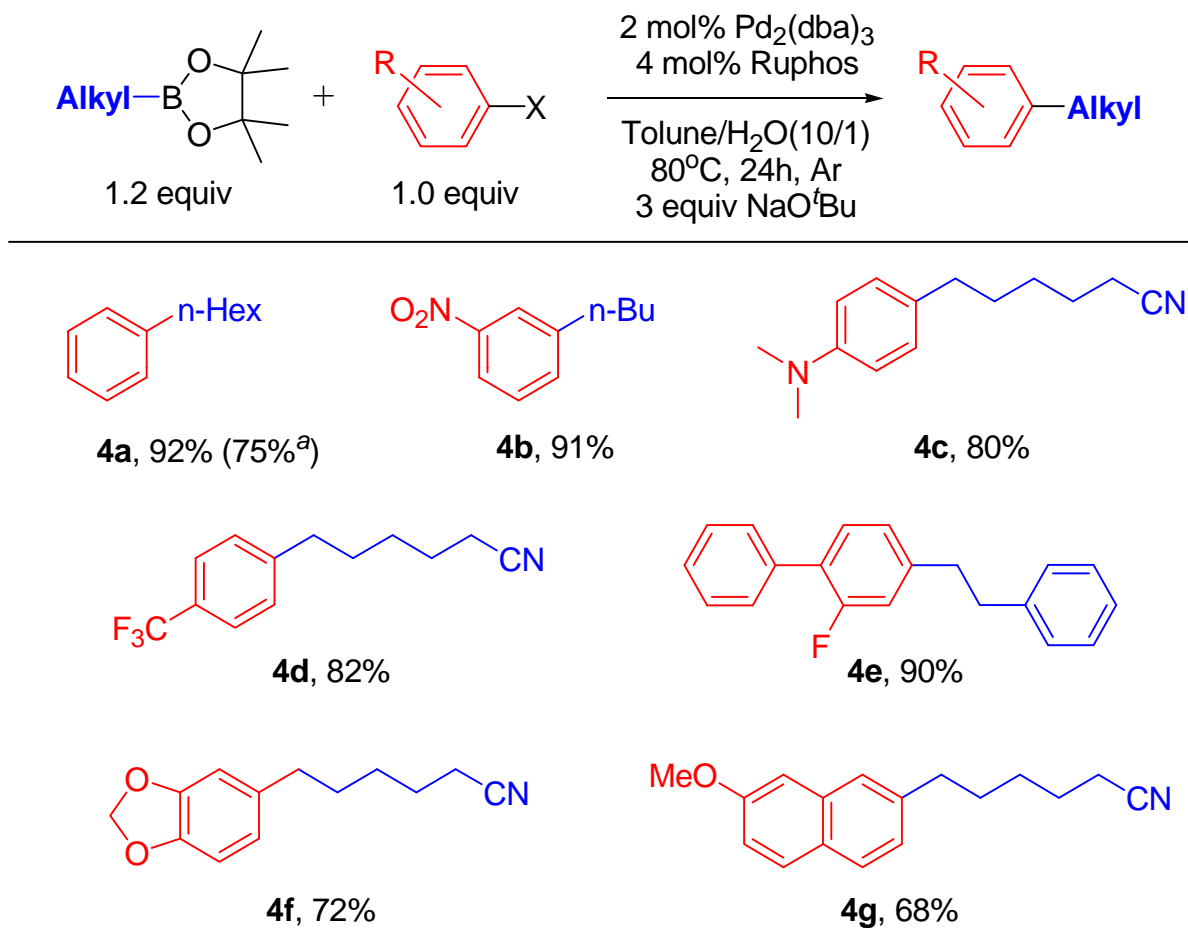
Preliminary Mechanistic Studies

Borylation of *exo*-2-bromonorbornane^a



^a PPh_3 as ligand and LiOMe as base

Suzuki-Miyaura coupling of alkylboronic esters



X = Br. Reactions were carried out at 80 °C for 24 h on a 0.25 mmol scale. Yields quoted are those for purified, isolated products. ^a X = Cl, 110 °C for 24 h.

Ruphos = $\text{Cy}_2\text{P}-2-(\text{C}_6\text{H}_4-2,6-\{\text{iPrO}\}_2\text{C}_6\text{H}_3)$

Conclusions

Ir-catalysed C-H borylation is a powerful strategy for arene functionalisation.

MTBE is a 'good solvent' for arene borylation and enables efficient one-pot single-solvent C-H borylation Suzuki-Miyaura and C-H borylation 1,4-conjugate addition sequences.

C-H borylation reactions are significantly accelerated under microwave conditions.

Whilst the regiochemistry of Ir-catalysed C-H borylation is dominated by steric effects, there is an underlying electronic selectivity. This effect may be qualitatively estimated using hydrocarbon C-H acidities. Selectivities are improved at lower temperatures.

Cu-catalysed aryl C-X borylation represents an inexpensive alternative to Pd-catalysed Miyaura borylation and proceeds at room temperature. Even electron rich and hindered aryl bromides can be employed.

Pd costs 3000 times as much as Cu.

Cu-catalysed C-X borylation can now be extended to primary and secondary alkyl halides and pseudo-halides, and the resulting alkyl boronates can be coupled with aryl halides.