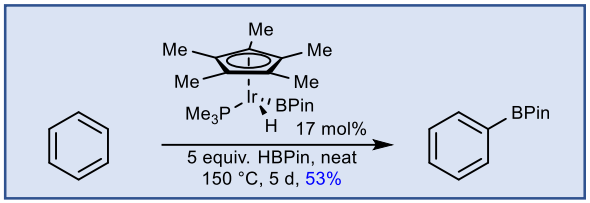
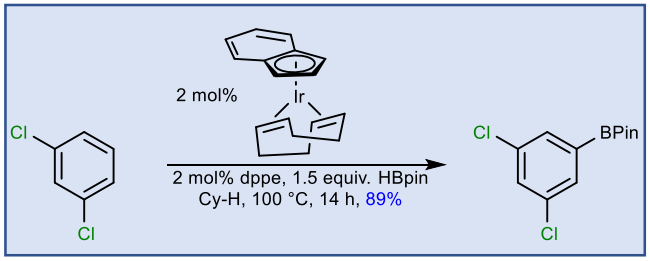
Ir-Catalyzed C-H Borylation of (Hetero)Arenes

Development:

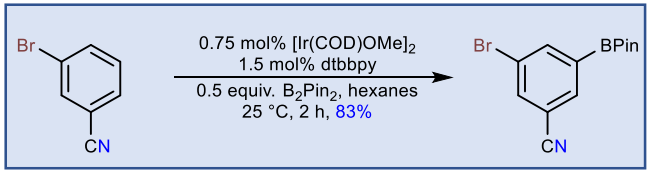
- The first report of Ir-catalyzed C-H borylation of benzene was reported by the Smith lab in 1999.
- In 2002, the Maleczka and Smith have published a general method for the C-H borylation of simple arenes.
- In the same year, Hartwig has developed milder conditions for the transformation by using bpy ligands and expanded the substrate scope.
- Review: Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890 https://doi.org/10.1021/cr900206p



Smith, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 7696 https://doi.org/10.1021/ja991258w

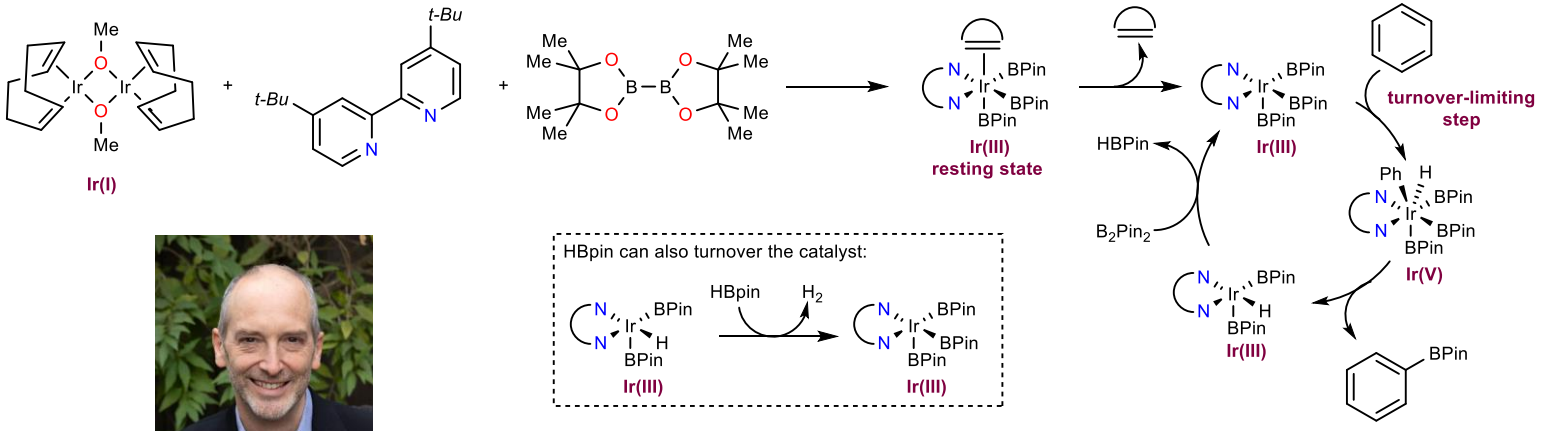


Maleczka, R. E., Smith, M. R. *Science* **2002**, *295*, 305 https://science.sciencemag.org/content/295/5553/305



Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390 https://doi.org/10.1021/ja0173019
Hartwig, J. F. *Angew. Chem. Int. Ed.* **2002**, *41*, 3056 https://doi.org/10.1002/1521-3773(20020816)41:16<3056::AID-ANIE3056>3.0.CO;2-%23

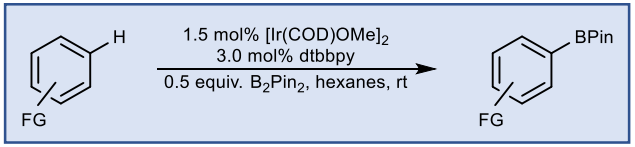
Mechanism:



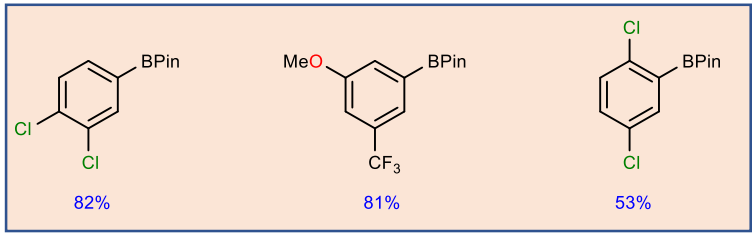
Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263 https://doi.org/10.1021/ja053433g

Ir-Catalyzed C-H Borylation of (Hetero)Arenes

Arene Scope:

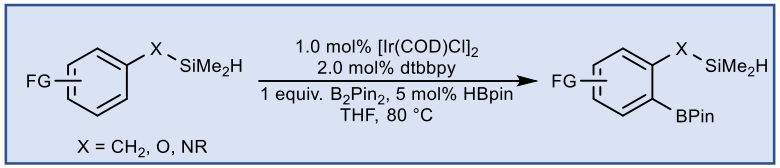


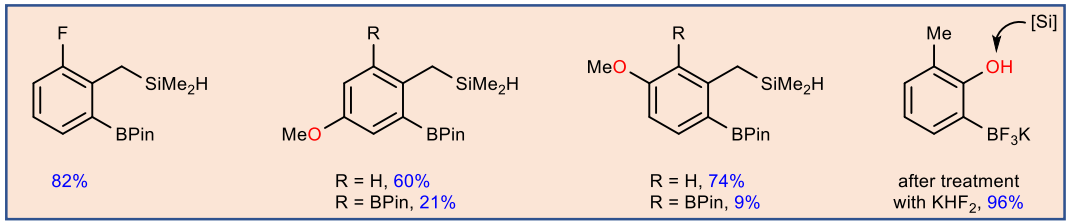
Hartwig, J. F. *Angew. Chem. Int. Ed.* **2002**, *41*, 3056 https://doi.org/10.1002/1521-3773(20020816)41:16<3056::AID-ANIE3056>3.0.CO;2-%23



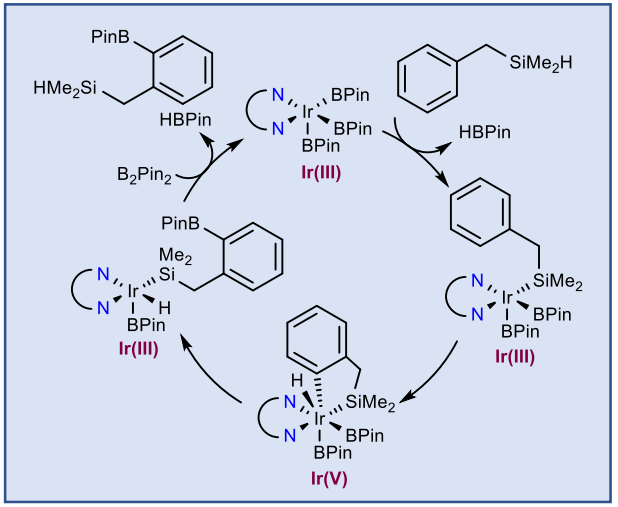
steric effects are predominant

Directed *ortho*-Borylation:

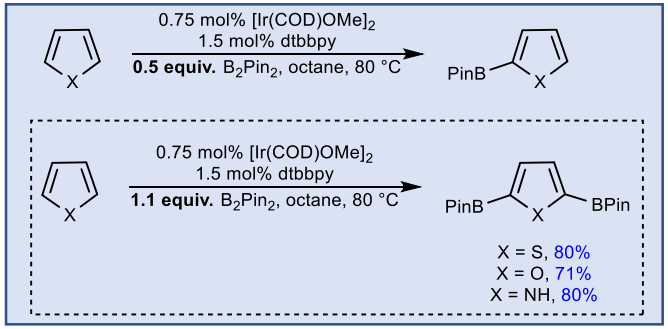


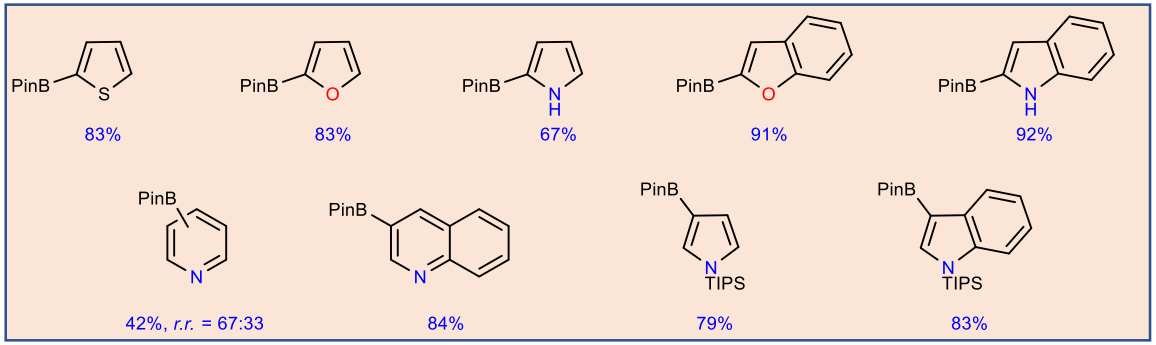


Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534 https://doi.org/10.1021/ja8015878



Heteroarenes:

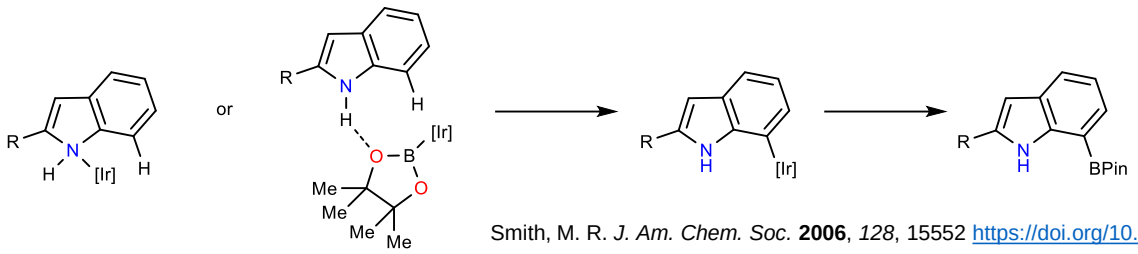




Hartwig, J. F. *Tetrahedron Letters* **2002**, *43*, 5649 https://doi.org/10.1016/S0040-4039(02)01135-8

Ir-Catalyzed C-H Borylation of (Hetero)Arenes

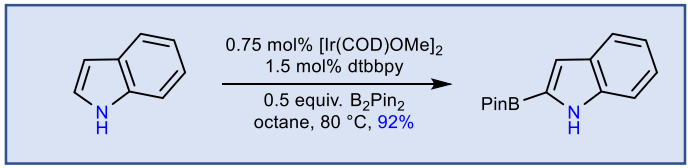
ortho-Borylation of indoles is explained by a directing effect of N-H:

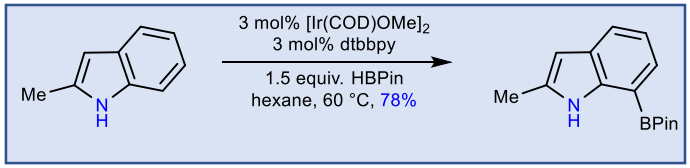


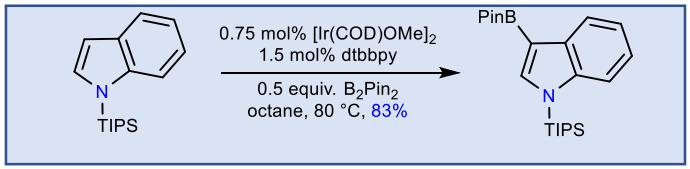
Hartwig: "…*there are not a sufficient number of open coordination sites for both the direct ligation of the indole nitrogen at the metal center and the interaction of the C-H bond with the metal. A possible alternative interaction could involve the indole-nitrogen and a vacant p-orbital on a boryl ligand.*"

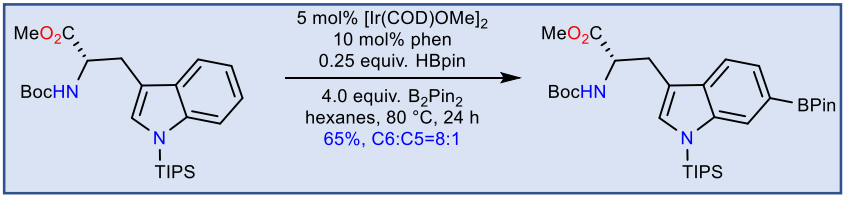
Smith, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 15552 https://doi.org/10.1021/ja0631652

Borylation of Indoles in Different Positions:

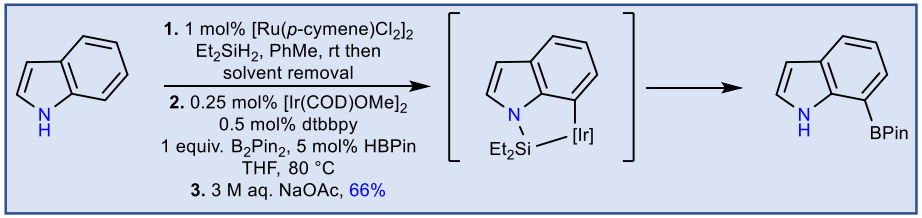




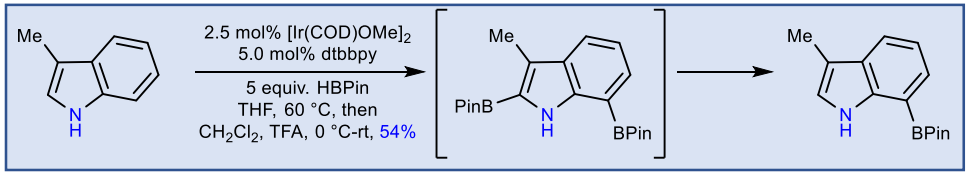




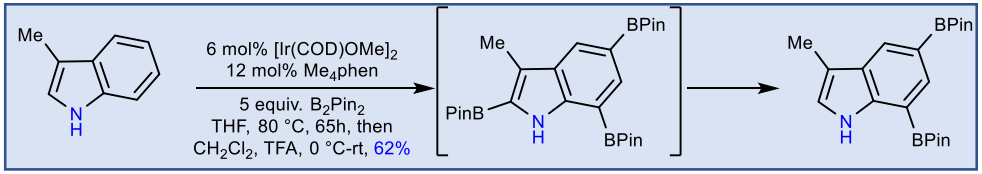
Baran, P. S. *J. Am. Chem. Soc.* **2015**, *137*, 10160 https://doi.org/10.1021/jacs.5b07154



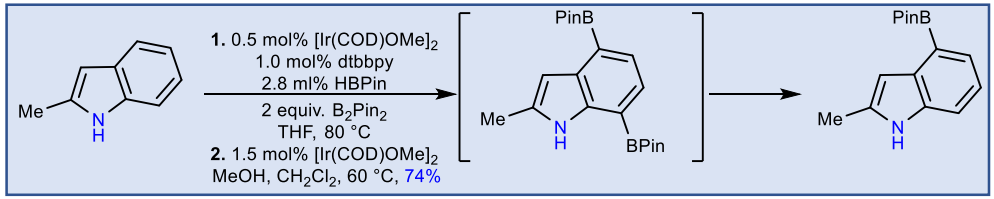
Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068 https://doi.org/10.1021/ja1006405



Movassaghi, M. *J. Org. Chem. Soc.* **2014** *79*, 11254 https://doi.org/10.1021/jo502062z



Sperry, J. *Synthesis* **2017** *49*, 4731 DOI: 10.1055/s-0036-1589018

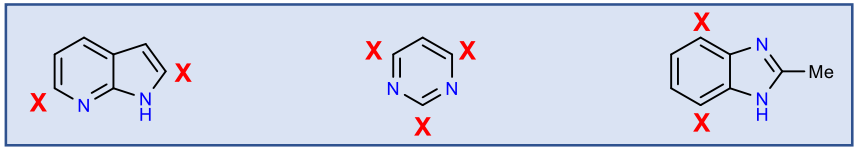


Many more examples: Smith, M. R. *J. Org. Chem.* **2015**, *80, 8341*, https://doi.org/10.1021/acs.joc.5b01588 and Smith, M. R. *Org. Lett.* **2016**, *18, 1554*, https://doi.org/10.1021/acs.orglett.6b00356

Ir-Catalyzed C-H Borylation of (Hetero)Arenes

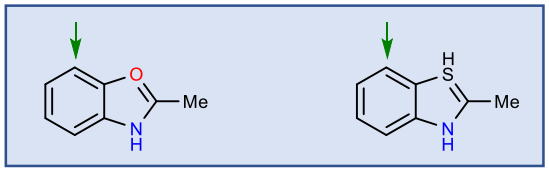
Borylation of Heteroarenes with Multiple Heteroatoms:

Rule 1: No borylation *ortho* or alpha to free N-H or basic nitrogen

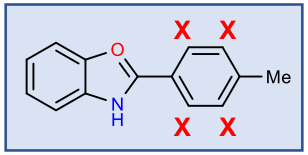


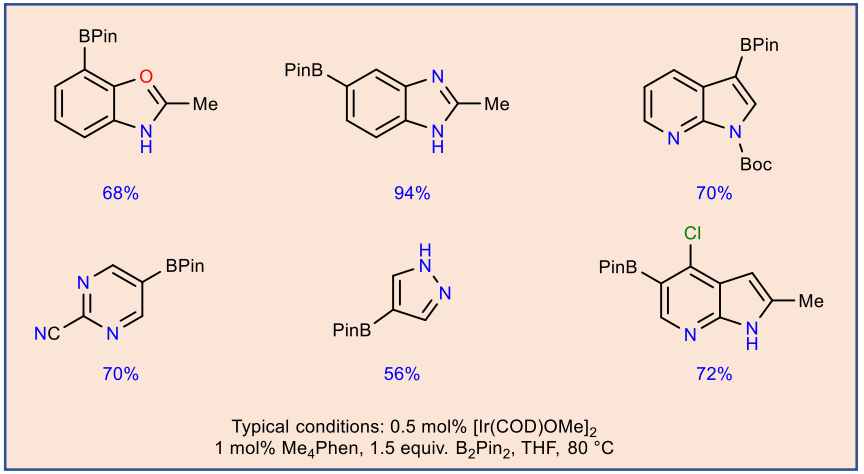
Note that this is in contrast with the selectivity observed with indoles. N-borylation likely occurs, blocking the alpha/ortho position.

Rule 2: Borylation occurs preferentially *ortho* to oxygen or sulfur



Rule 3: Steric factors still have a large effect



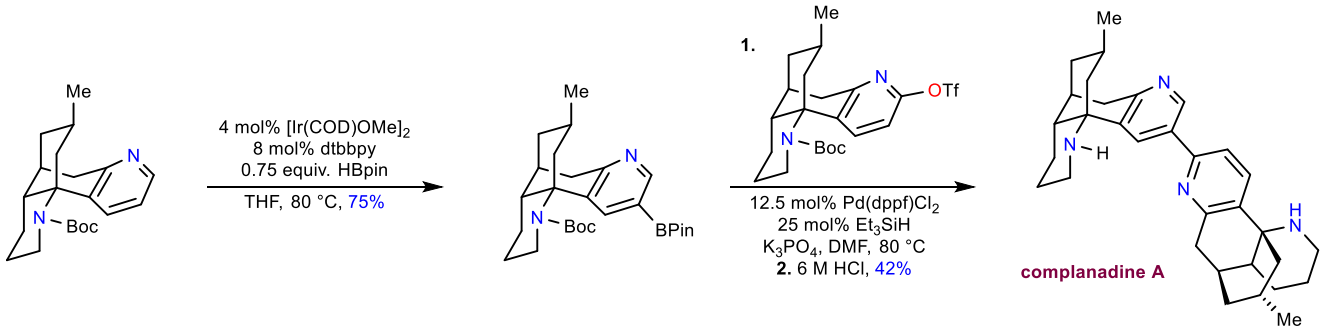


Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4287 https://doi.org/10.1021/ja412563e

NMR can be used in some cases to predict the outcome of C-H borylation. The aryl hydrogen with the furthest downfield chemical shift is typically the reactive site.

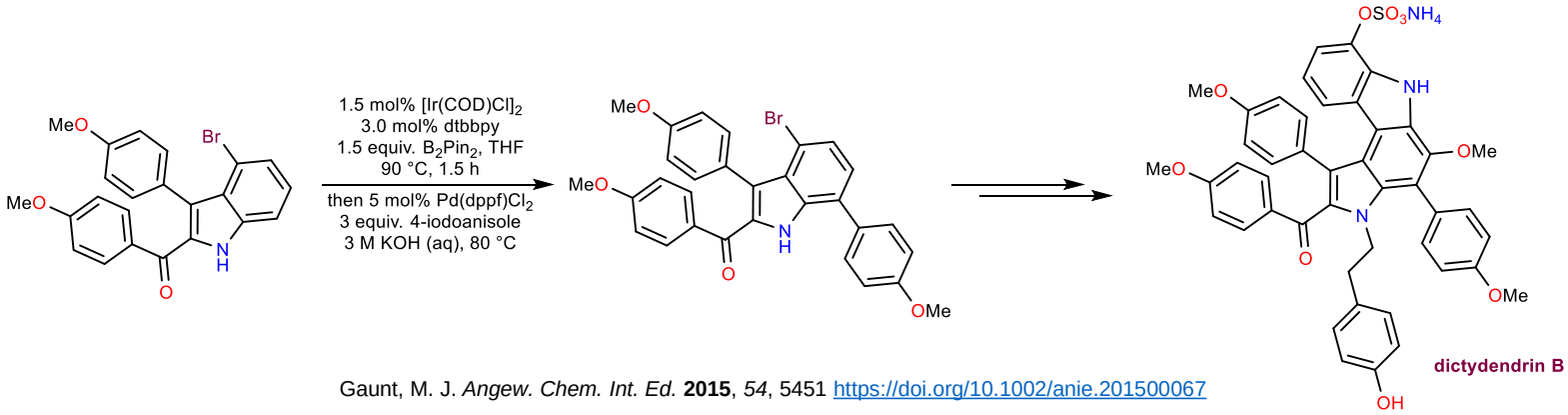
Steel, P. G. *Chem. Sci.* **2012**, *3*, 3505 https://doi.org/10.1039/C2SC20776A

Selected Examples in Synthesis:

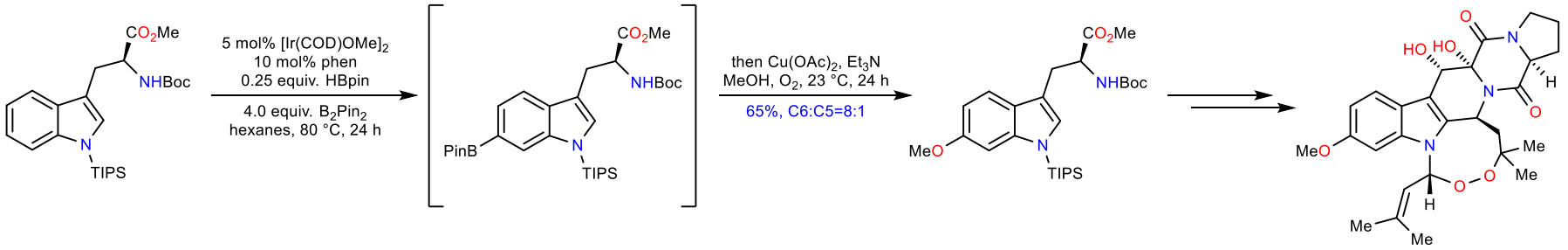


Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 5926 https://doi.org/10.1021/ja101893b

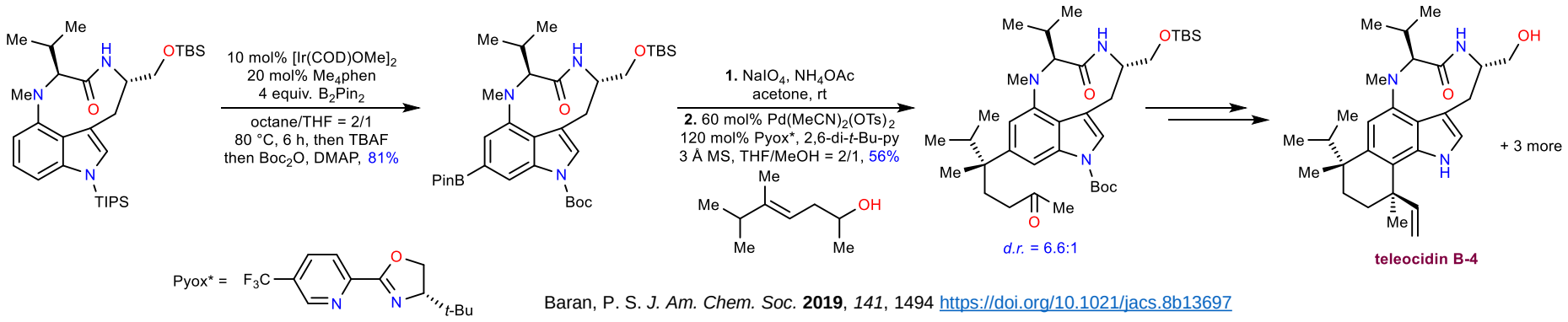
Ir-Catalyzed C-H Borylation of (Hetero)Arenes



Gaunt, M. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 5451 https://doi.org/10.1002/anie.201500067

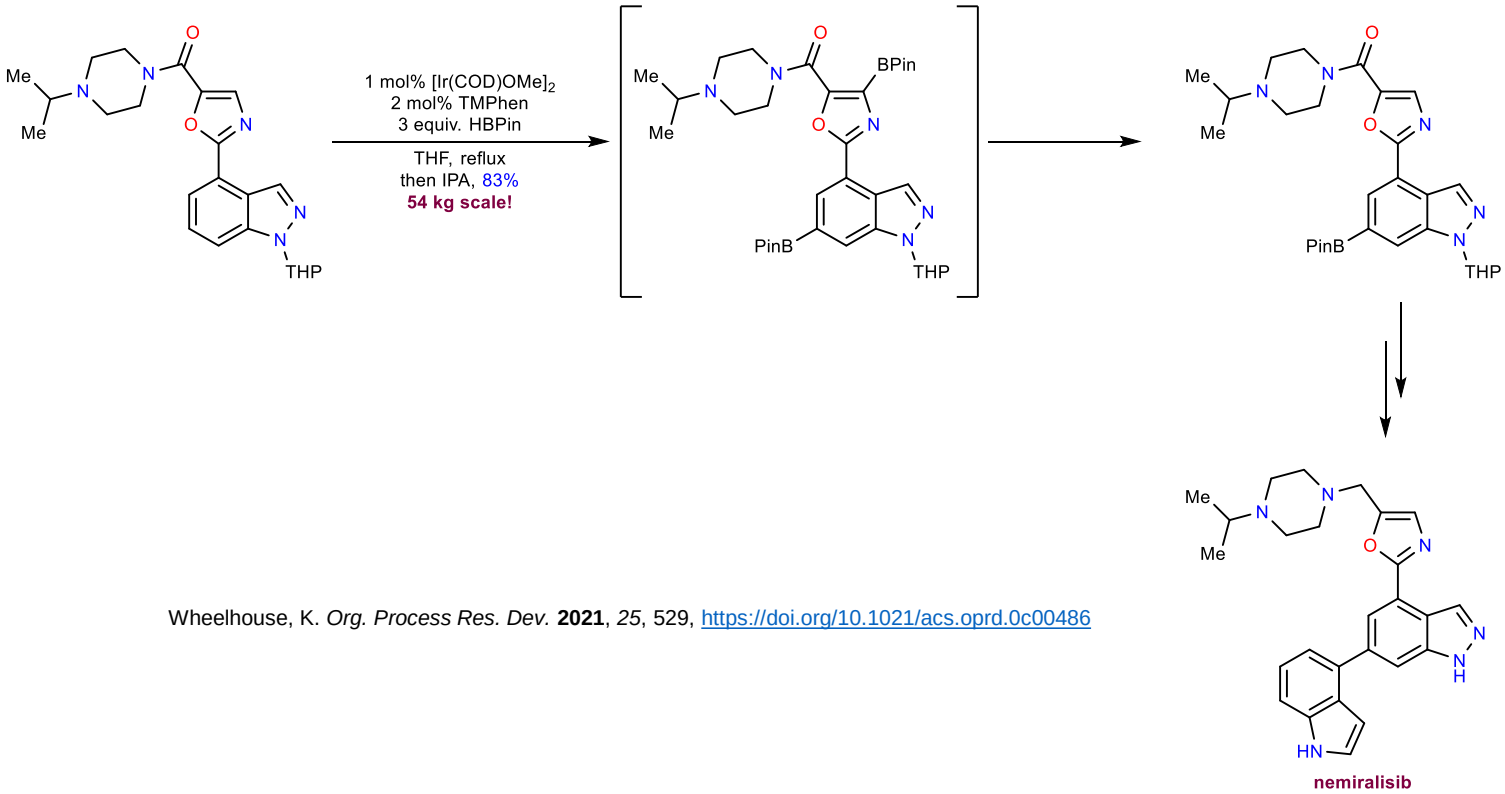


Baran, P. S. *J. Am. Chem. Soc.* **2015**, *137*, 10160 https://doi.org/10.1021/jacs.5b07154



Baran, P. S. *J. Am. Chem. Soc.* **2019**, *141*, 1494 https://doi.org/10.1021/jacs.8b13697

Ir-Catalyzed C-H Borylation of (Hetero)Arenes



Wheelhouse, K. *Org. Process Res. Dev.* **2021**, *25*, 529, https://doi.org/10.1021/acs.oprd.0c00486