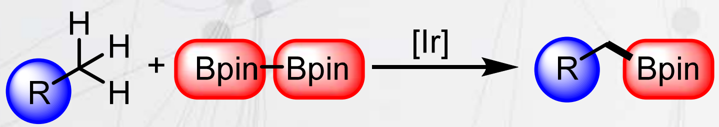
Iridium-Catalyzed Borylation of Primary C(sp^3)-H Bonds



Reporter： Yu Yibo

Supervisor： Prof. Ma Shengming

2020.12.11

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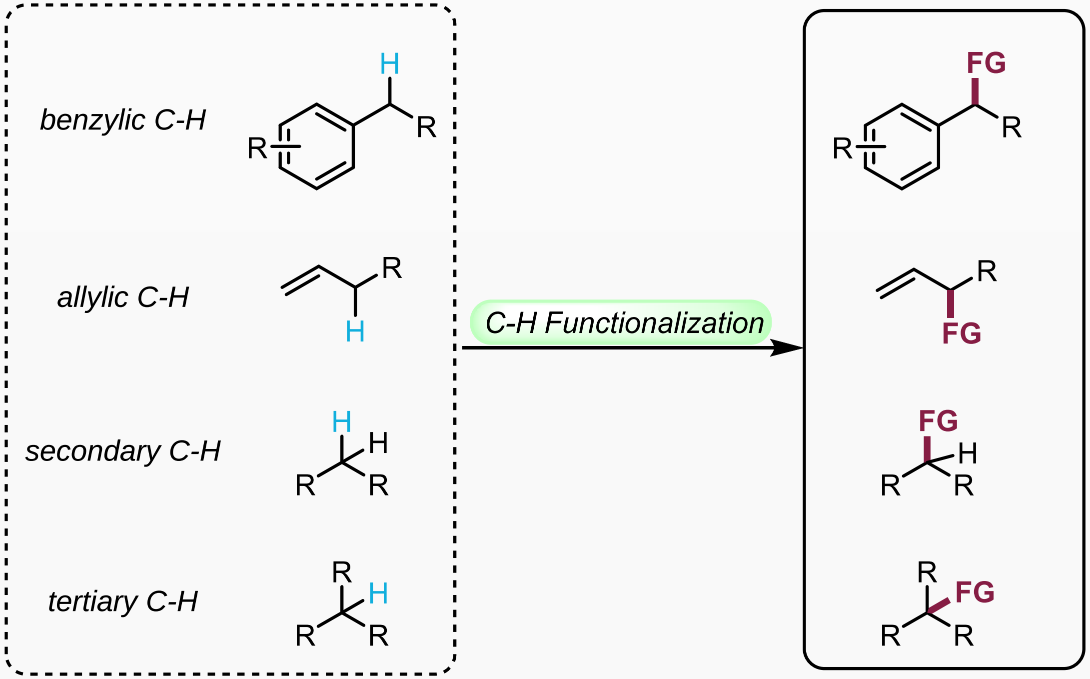
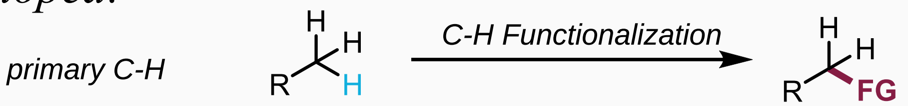
Background

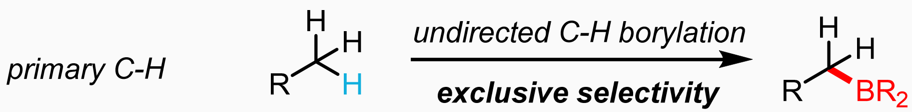
Well developed:



Less developed:



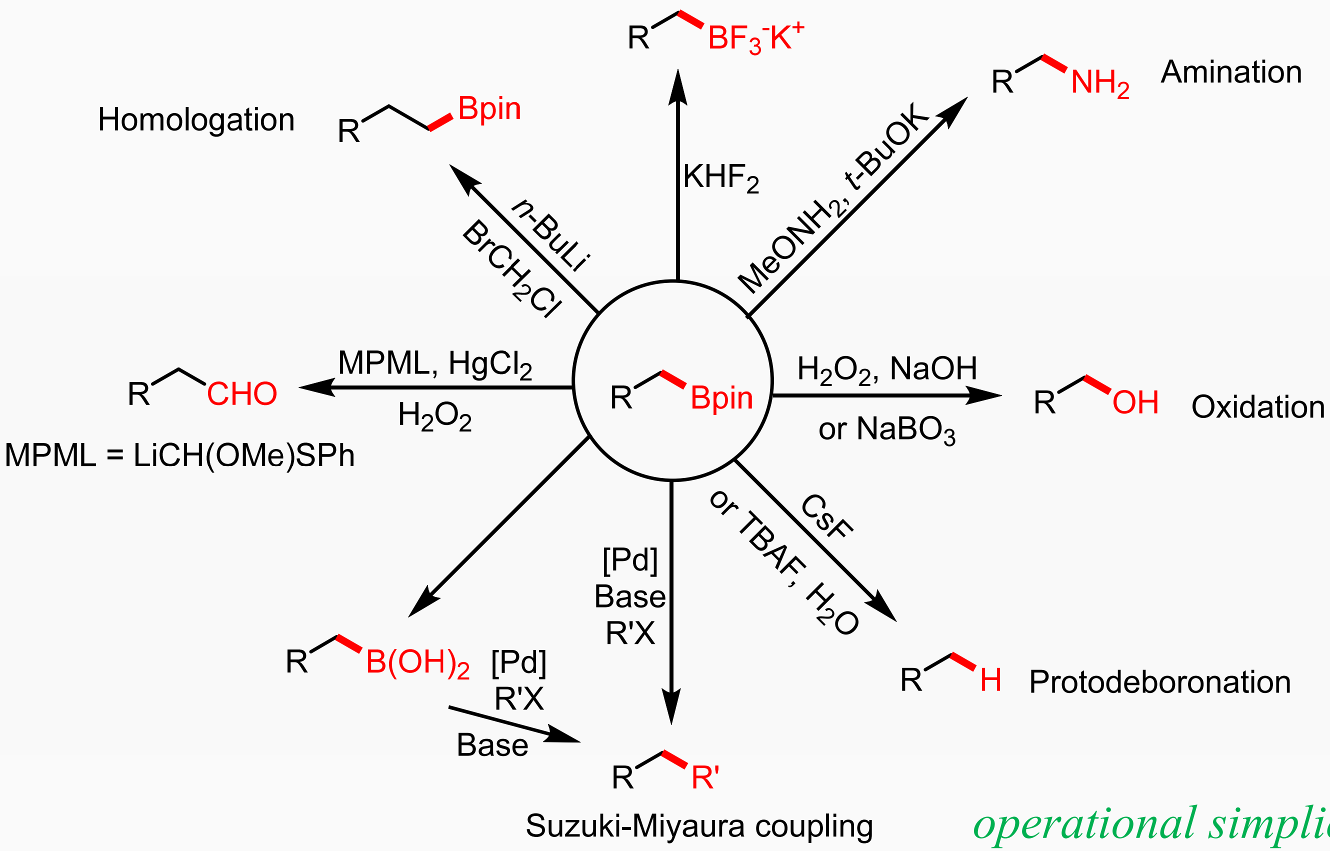
C-H bonds are stronger and less electron rich



Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 2.

Background

Application of Alkylboron Reagents:



operational simplicity

environmentally benign nature

thermal stability of the transmetalation agents

Brown, H. C. *et al.*, *Pure & Appl. Chem.* **1987**, *59*, 879.

Aggarwal, V. K. *et al.*, *Chem. Eur. J.* **2011**, *17*, 13124.

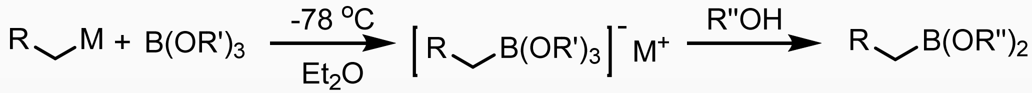
Sigman, M. S. *et al.*, *Chem. Rev.* **2011**, *111*, 1417.

Morken, J. P. *et al.*, *Synlett* **2018**, *29*, 1749.

Background

Tranditional Synthesis of Alkylboron Reagents:

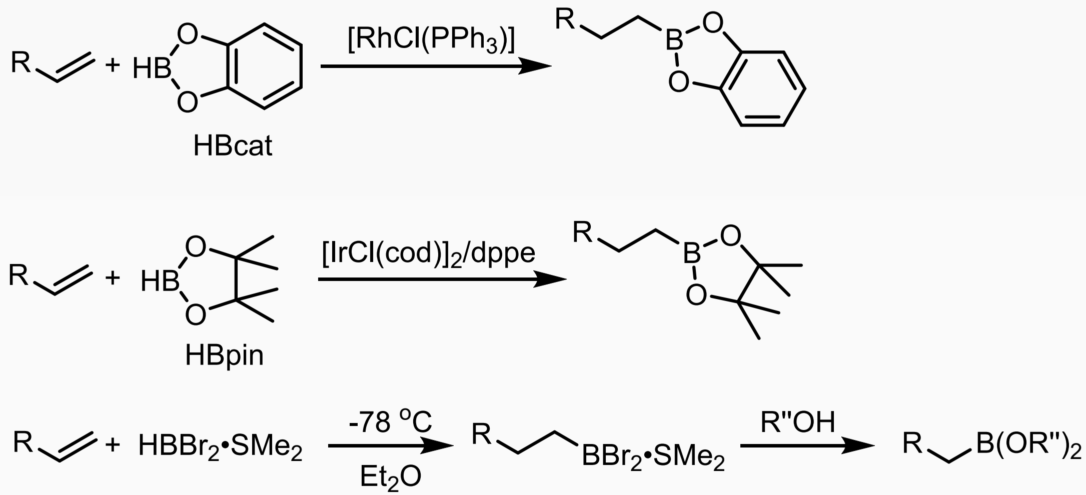
(1) From *Grignard and Lithium Reagents*



M = Li, MgX
R"OH = H_2O, alcohol or diol

Cons: *Multistep synthetic sequences*
Functionalized precursor
Limited functional group compatibility

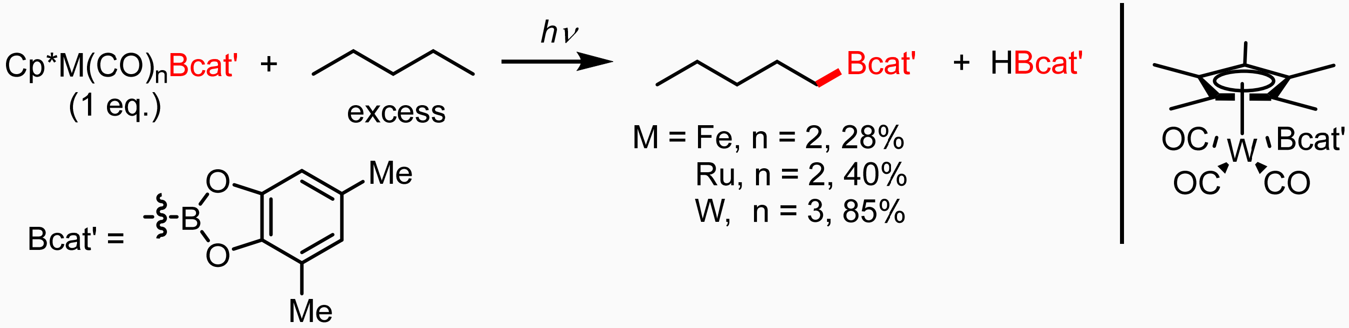
(2) via *Hydroboration*



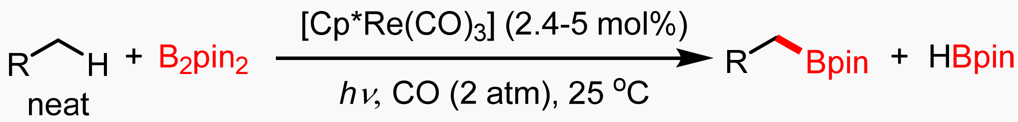
R"OH = H_2O, alcohol or diol

Sigman, M. S. *et al.*, *Chem. Rev.* **2011**, *111*, 1417.

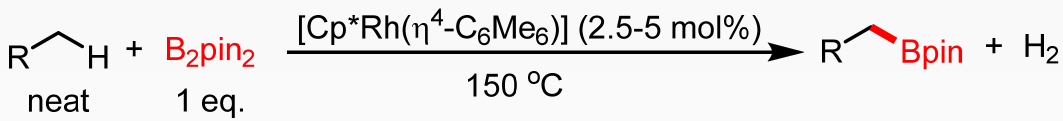
Background



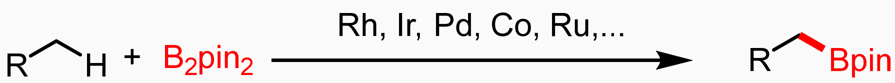
Hartwig, J. F. *et al.*, *Science* **1997**, *277*, 211.



Hartwig, J. F. *et al.*, *Angew. Chem., Int. Ed.* **1999**, *38*, 3391.



Hartwig, J. F. *et al.*, *Science* **2000**, *287*, 1995.



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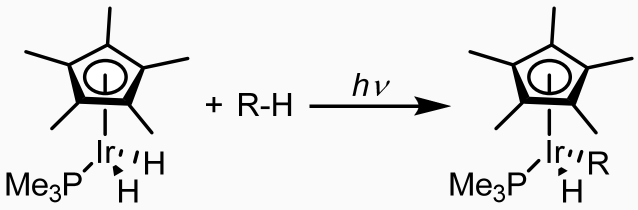
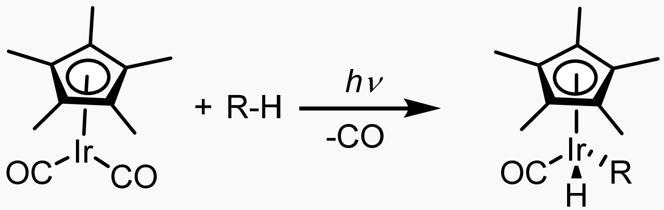
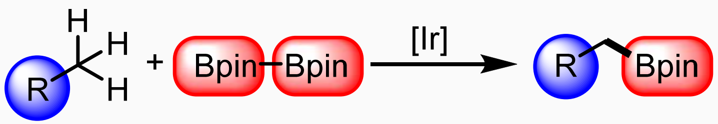


Bergman, R. G. *et al.*, *J. Am. Chem. Soc.* **1982**, *104*, 352.



Graham, W. A. G. *et al.*, *J. Am. Chem. Soc.* **1982**, *104*, 3723.
Graham, W. A. G. *et al.*, *J. Am. Chem. Soc.* **1983**, *105*, 7190.



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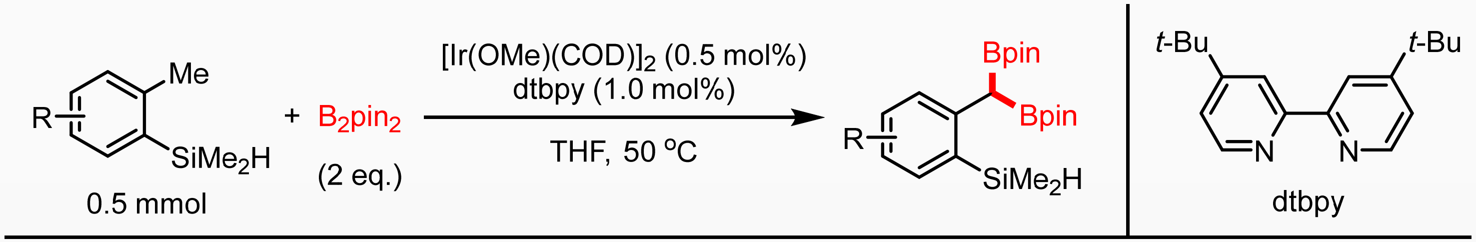
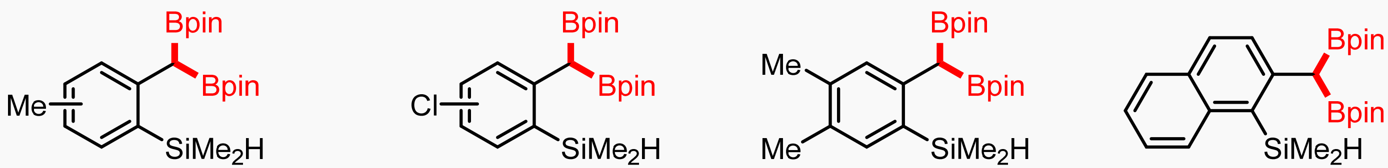
Borylation of activated substrates--Benzylic C-H



selected examples:



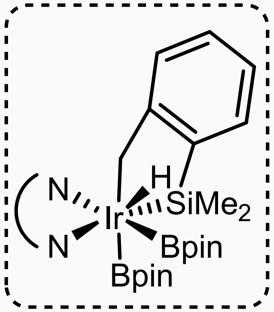
o-Me: 90% (12 h)
m-Me: 84% (6 h)
p-Me: 96% (2 h), 93%[a] (12 h)

o-Me: 85% (12 h)
m-Me: 80% (12 h)
p-Me: 87% (12 h)

84% (12 h)

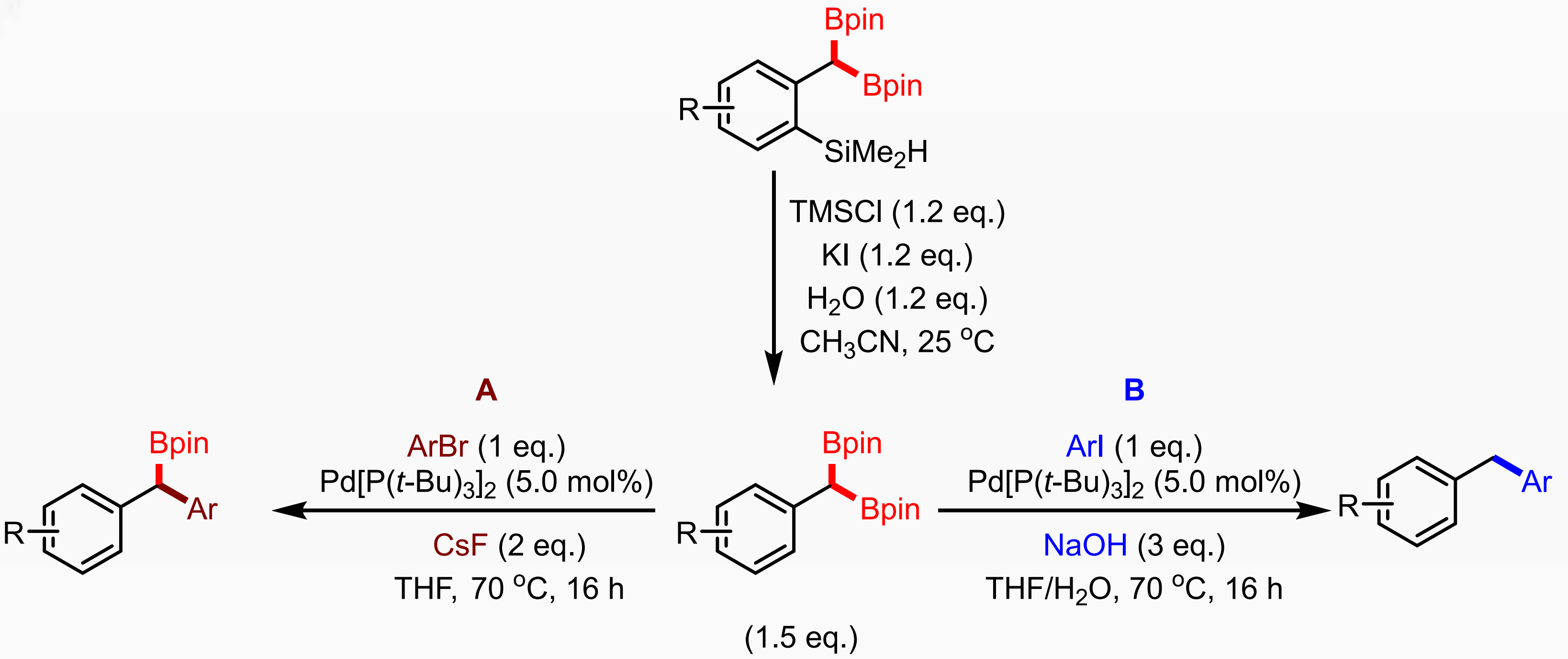
80% (12 h)

[a] 5 mmol scale



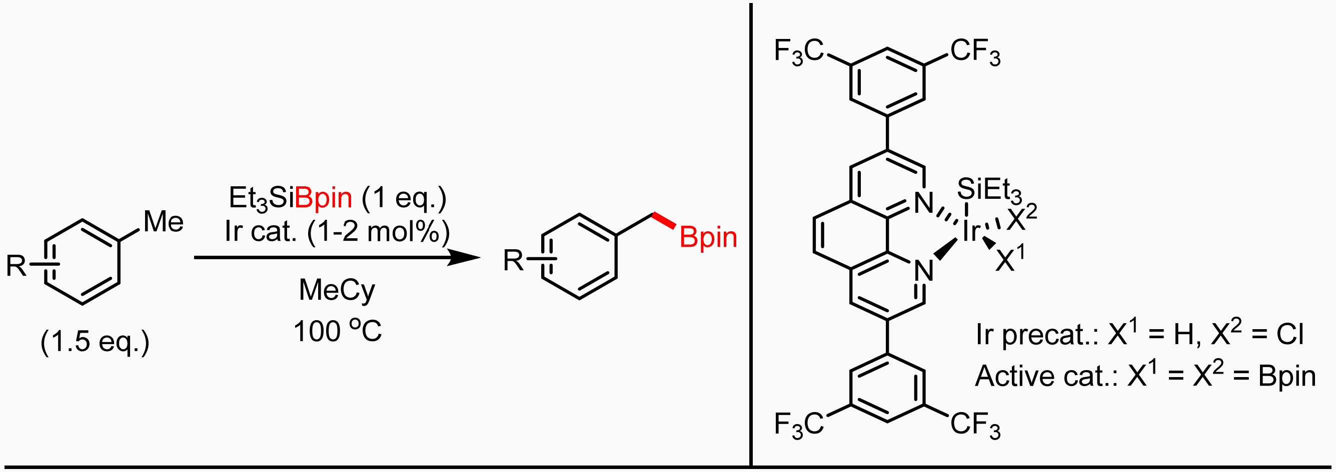
Hartwig, J. F. *et al.*, *Chem. Sci.* **2014**, *5*, 694.

Borylation of activated substrates--Benzylic C-H



Hartwig, J. F. *et al.*, *Chem. Sci.* **2014**, *5*, 694.

Borylation of activated substrates--Benzylic C-H



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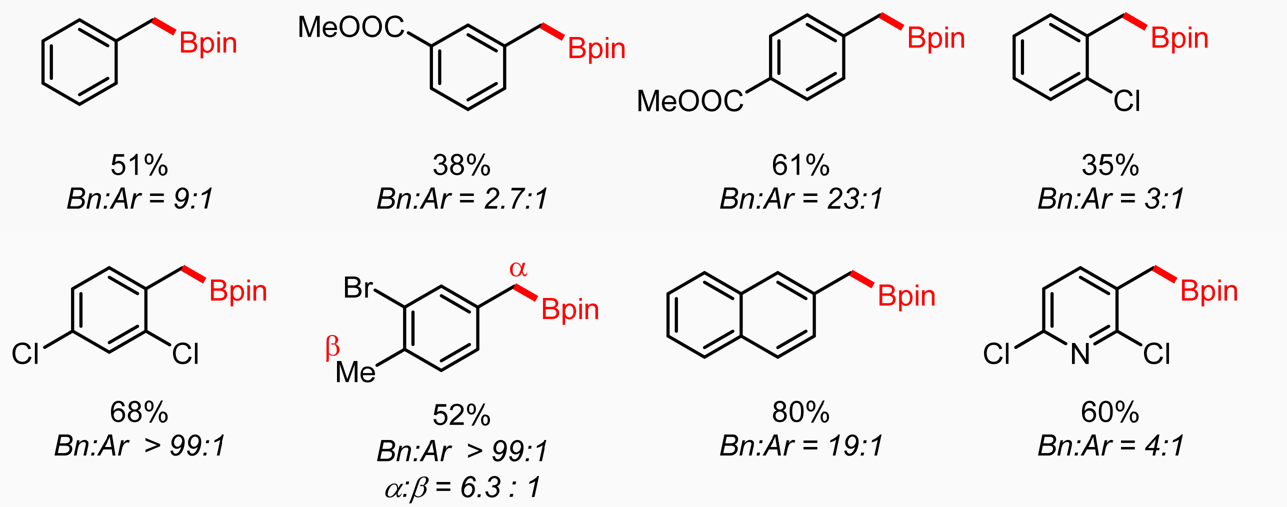
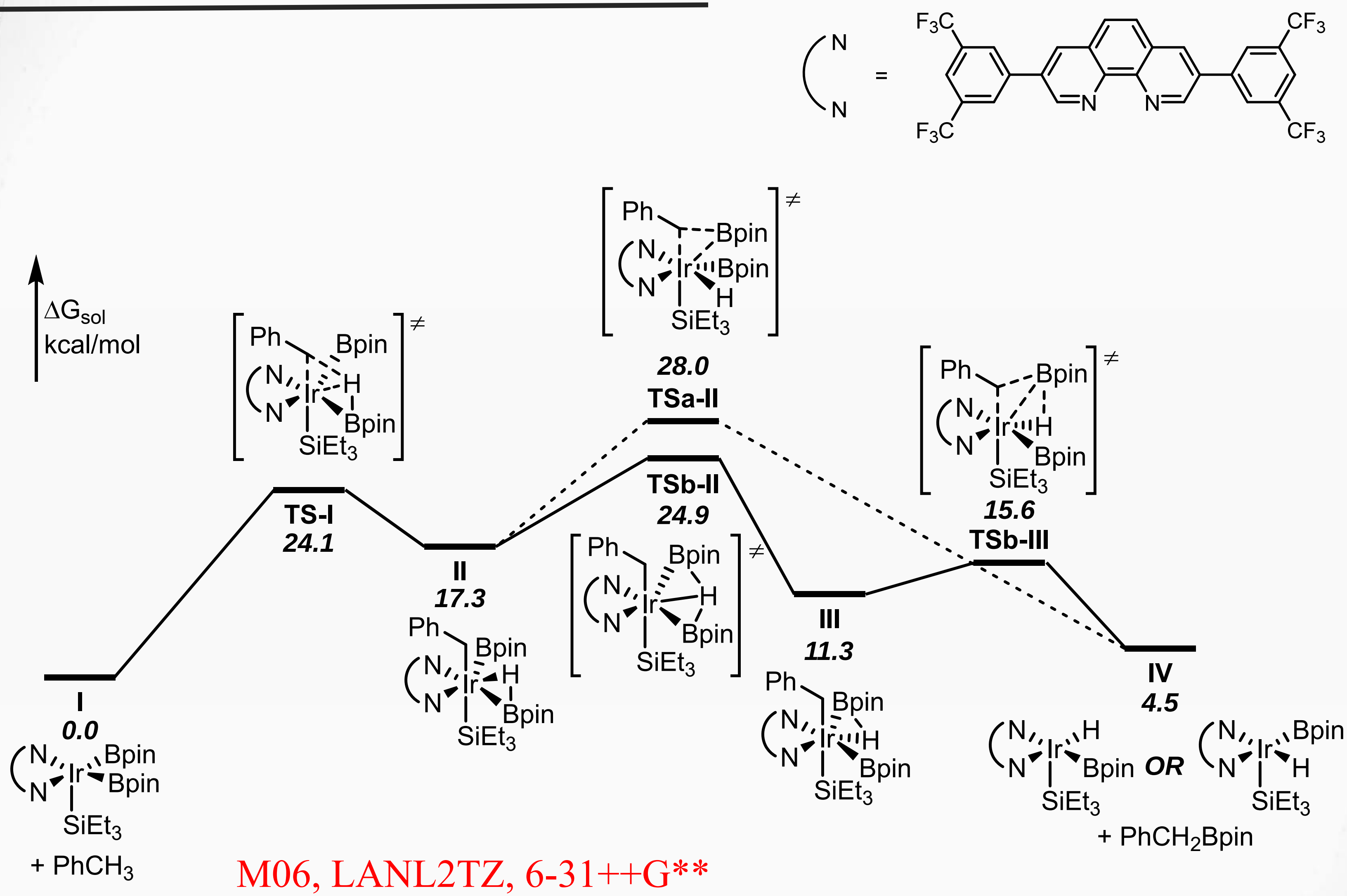


Hartwig, J. F. *et al.*, *J. Am. Chem. Soc.* **2015**, *137*, 8633.

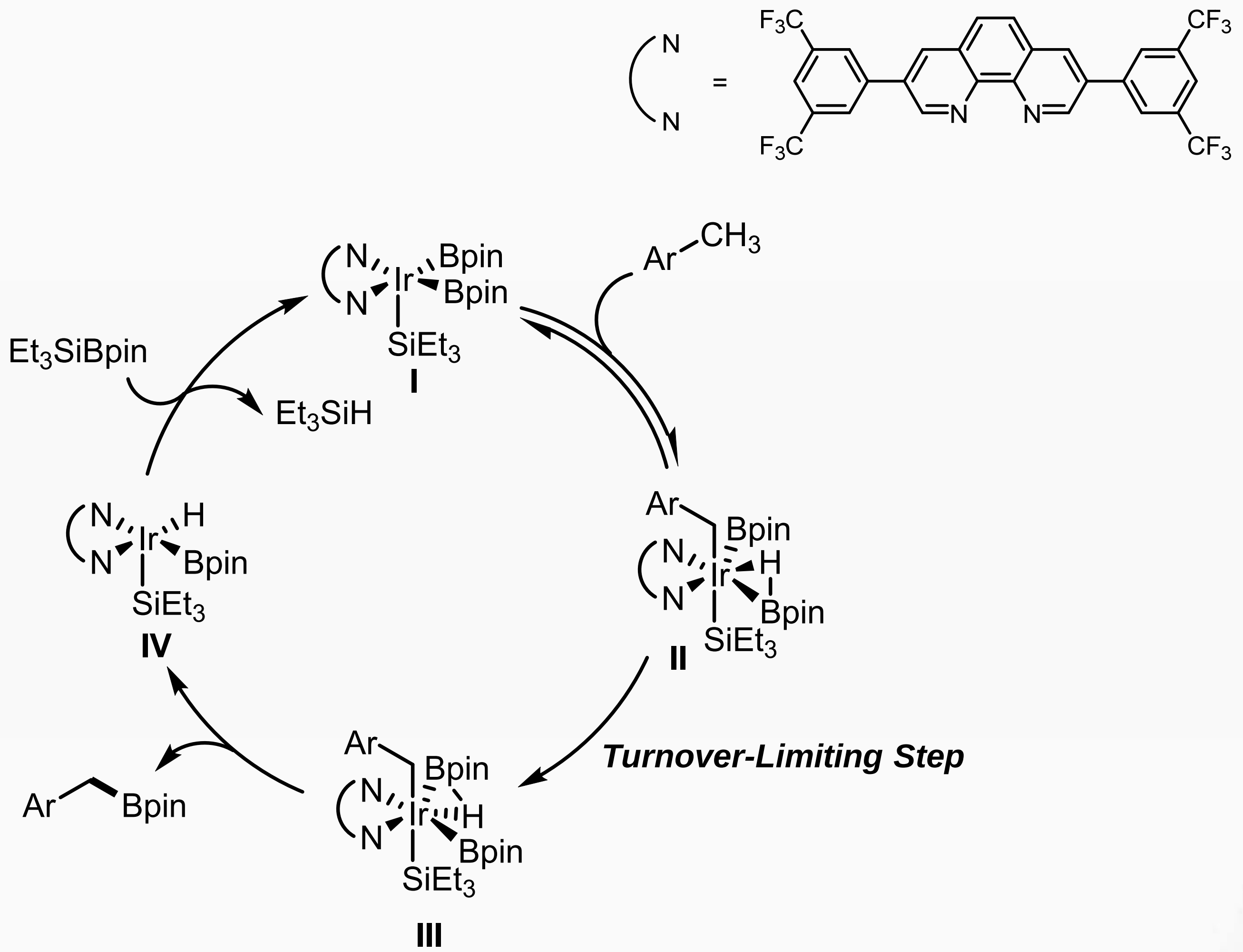
Borylation of activated substrates--Benzylic C-H



M06, LANL2TZ, 6-31++G**

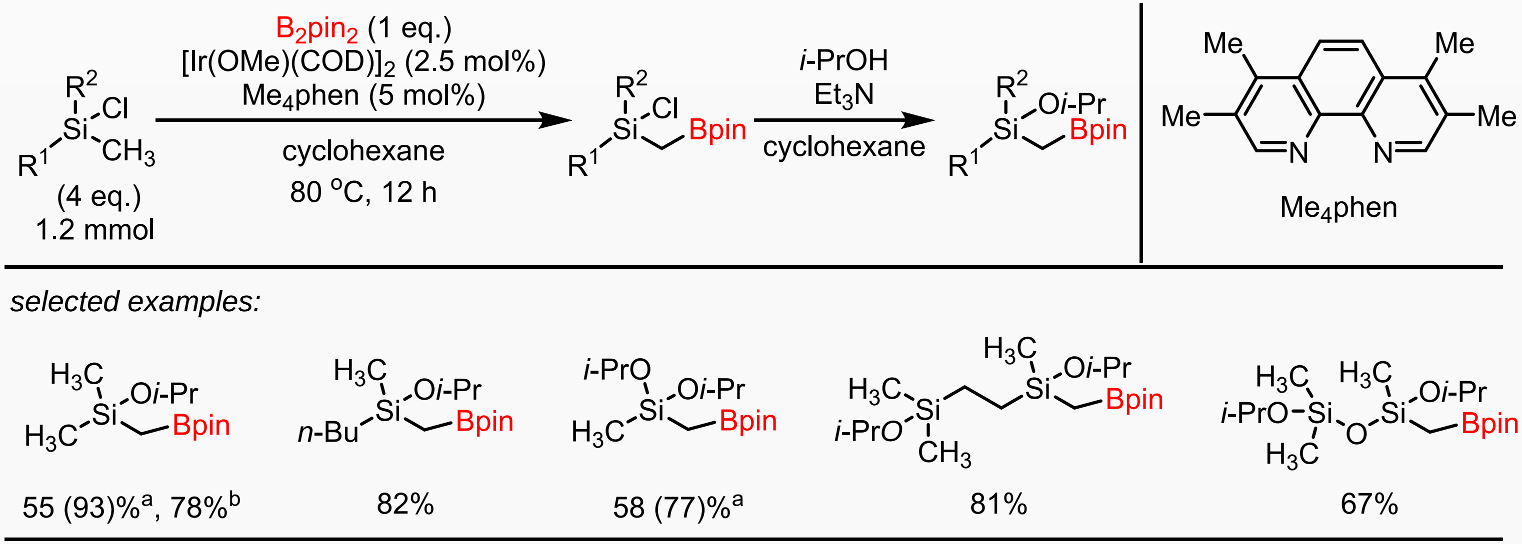
Hartwig, J. F. *et al.*, *J. Am. Chem. Soc.* **2015**, *137*, 8633.

Borylation of activated substrates--Benzylic C-H



Hartwig, J. F. *et al.*, *J. Am. Chem. Soc.* **2015**, *137*, 8633.

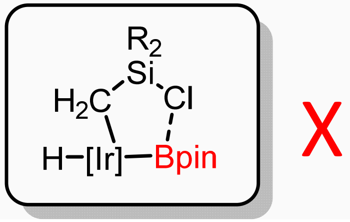
Borylation of activated substrates--Silanes

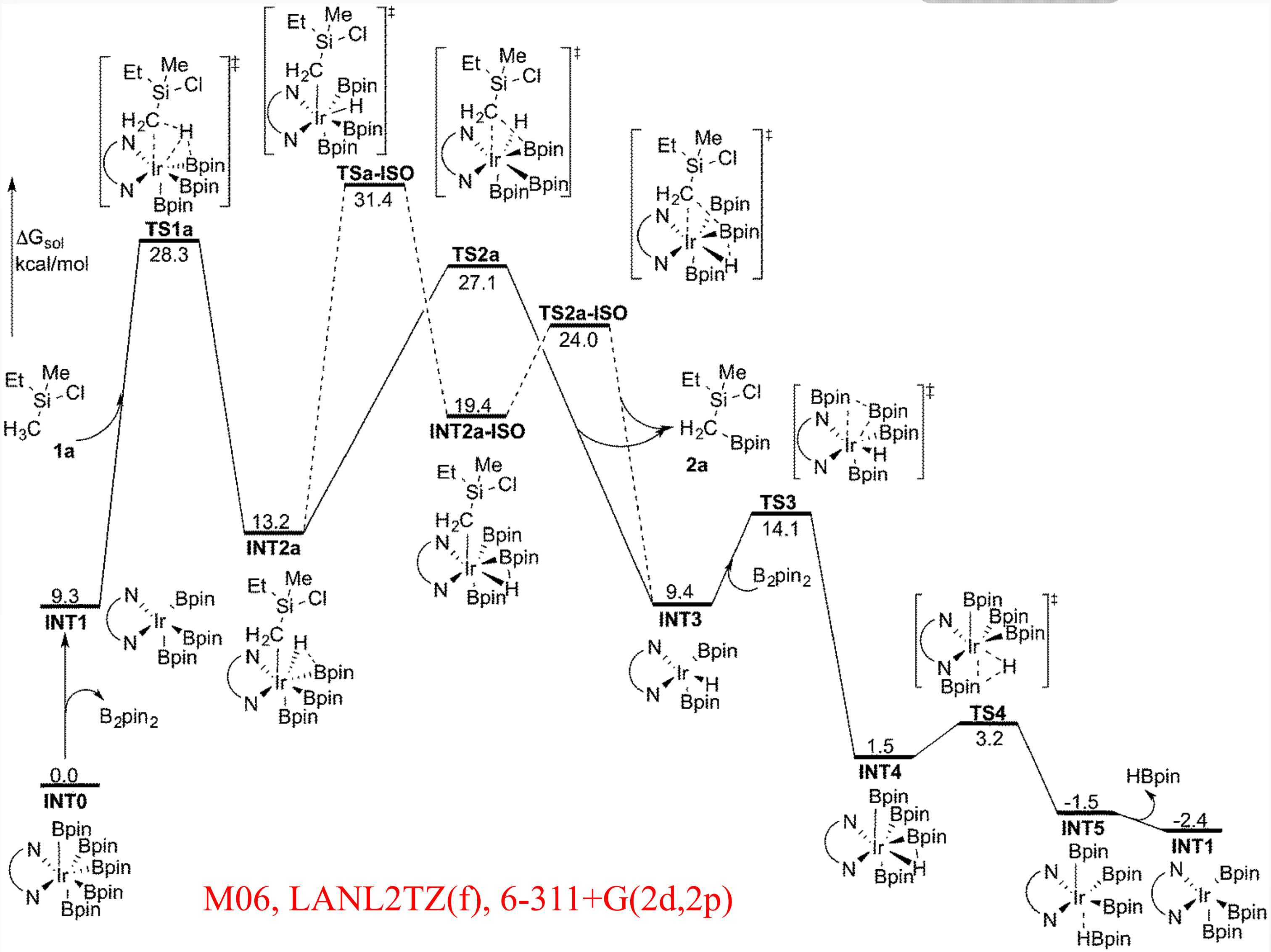


[a] ^{1}H NMR yield before isolated in the parentheses. [b] 120mmol scale.

Suginome, M. *et al.*, *J. Am. Chem. Soc.* **2012**, *134*, 17416.

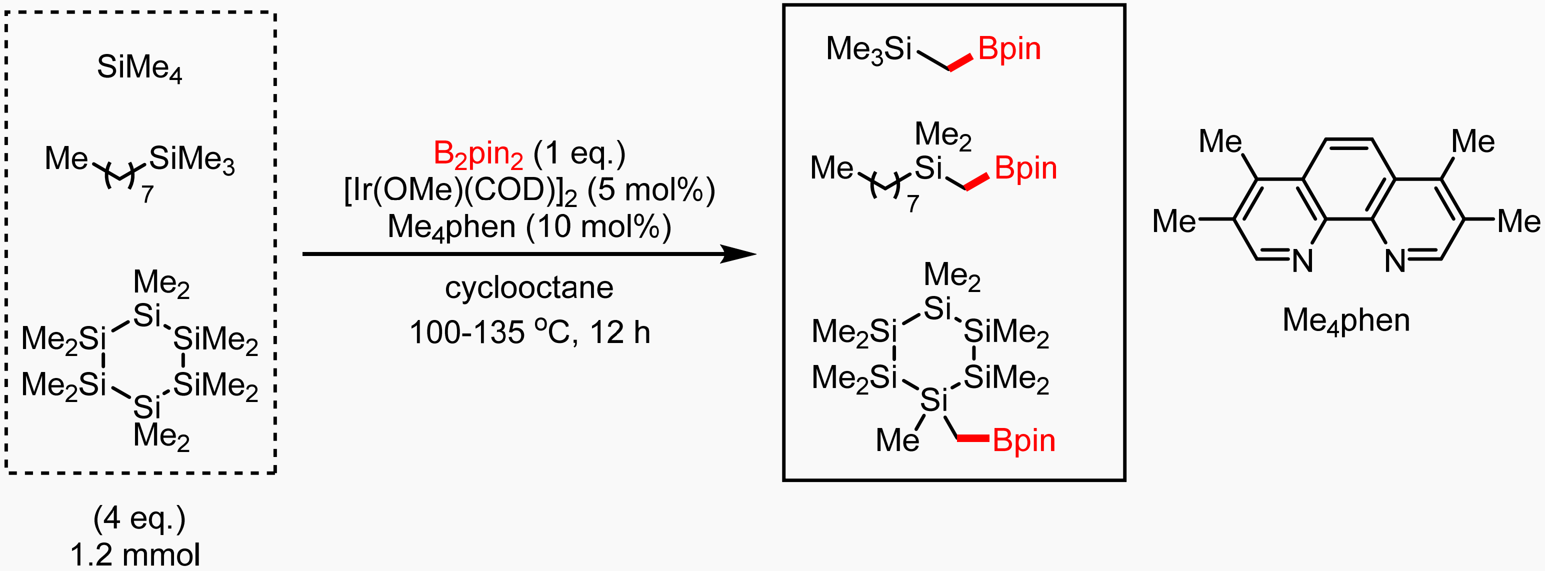
Borylation of activated substrates--Silanes





Himo, F. *et al.*, *Chem. Sci.* **2015**, *6*, 1735.

Borylation of activated substrates--Silanes



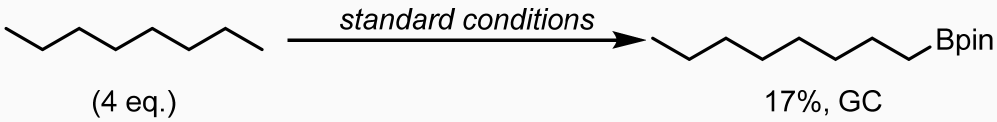
"α-silyl effect"

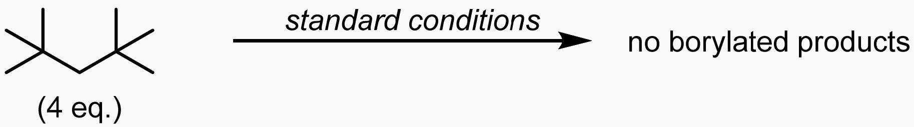
α-carbanion stabilizing effect of silicon

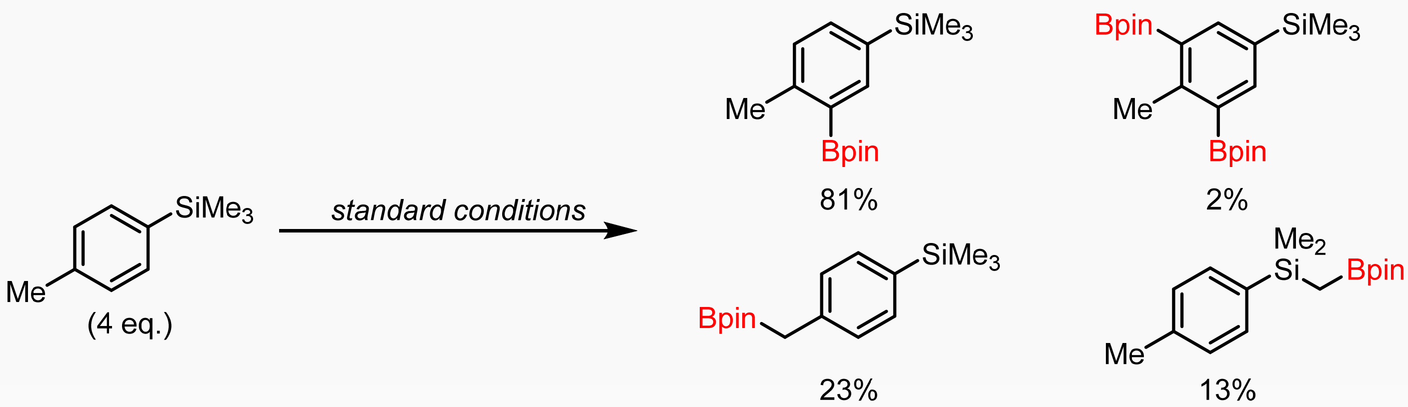
Suginome, M. *et al.*, *Organometallics* **2013**, *32*, 6170

Borylation of activated substrates--Silanes

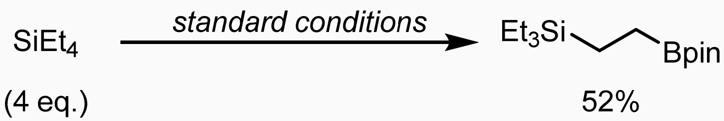
Control experiments:

(1)


(2)


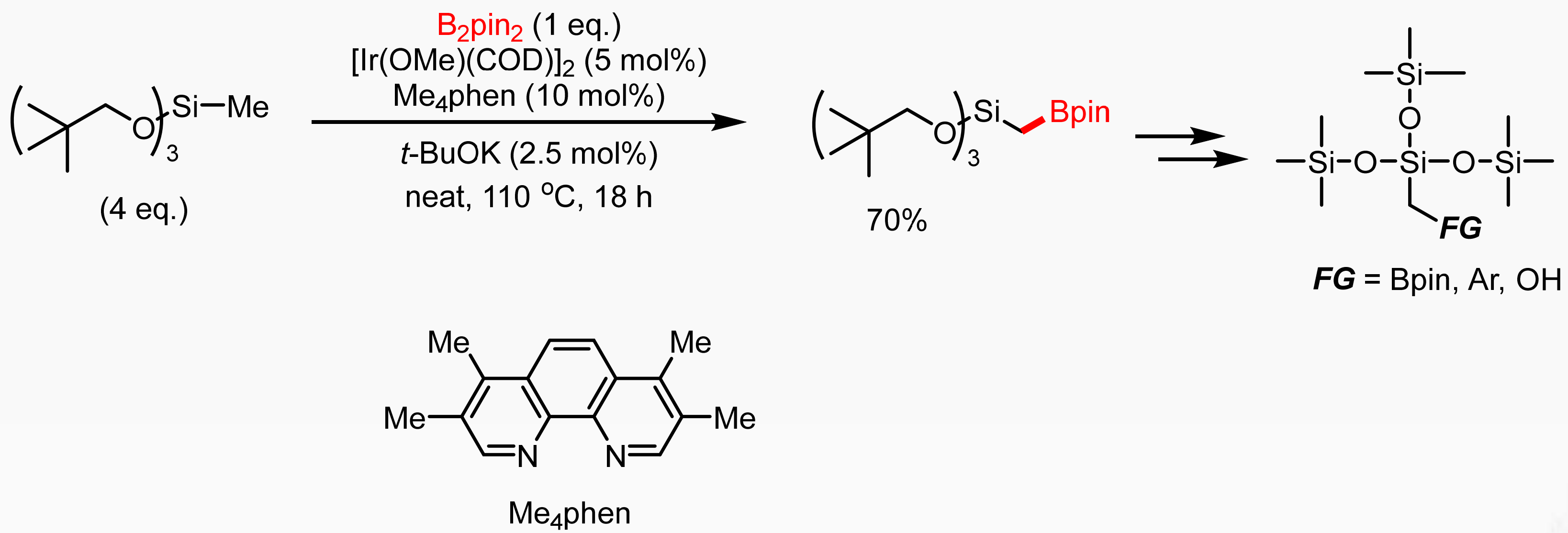
(3)


Reactivity: Ar-H > Ar-CH$_3$ > Si-CH$_3$ > alkyl-CH$_3$

(4)


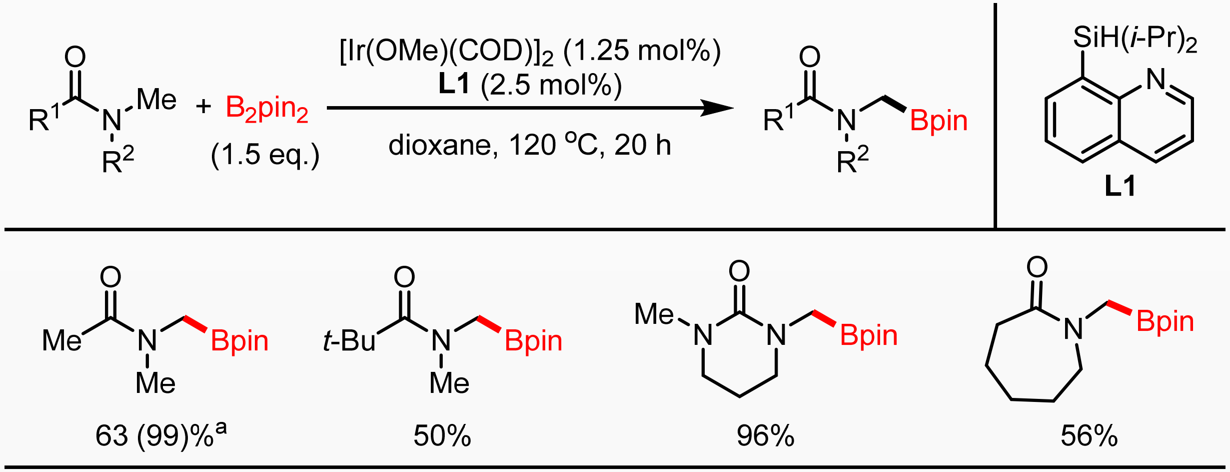
Suginome, M. *et al.*, *Organometallics* **2013**, *32*, 6170

Borylation of activated substrates--Silanes

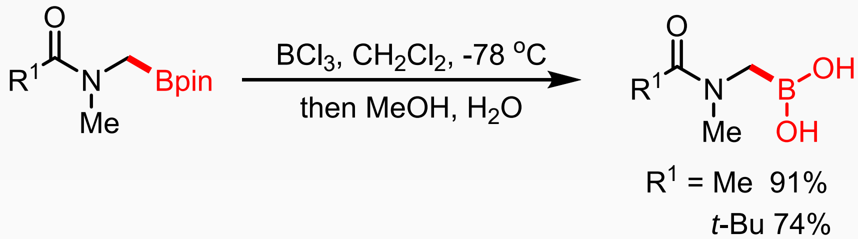


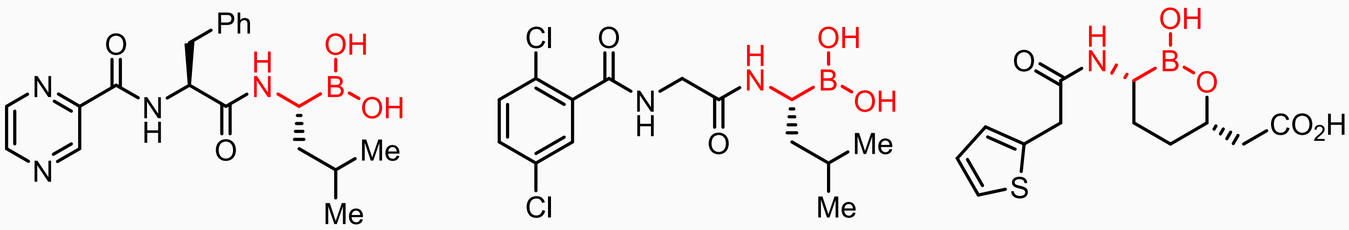
Suginome, M. *et al.*, *Organometallics* **2016**, *35*, 1601

Borylation of activated substrates



[a] ^{1}H NMR yield before isolated in the parentheses.





Bortezomib (Velcade®)

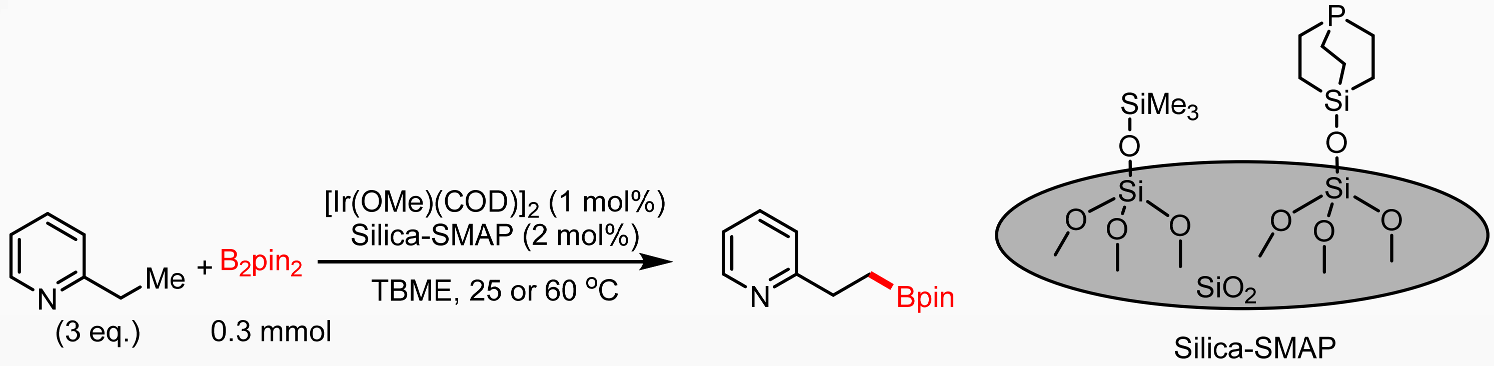
Ixazomib (Ninlaro®)

RPX7009 (Vaborbactam®)

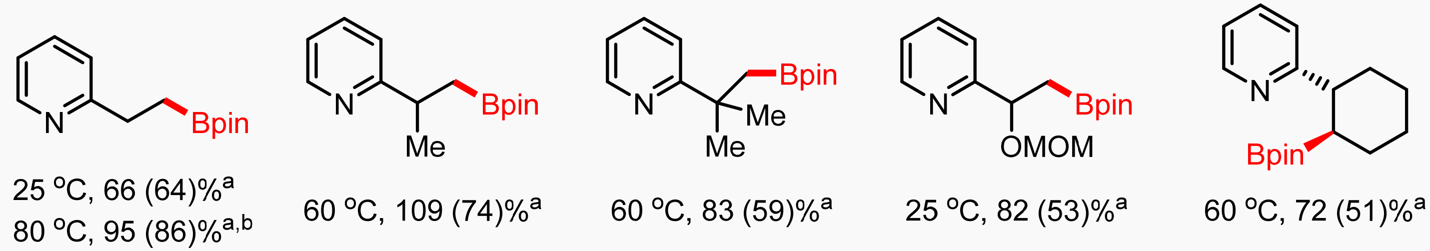
Hyland, S.N. *et al.*, *Tetrahedron Letters* **2019**, *60*, 1096

CONTENT >>

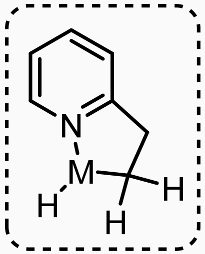
Borylation of unactivated substrates



Selected examples:

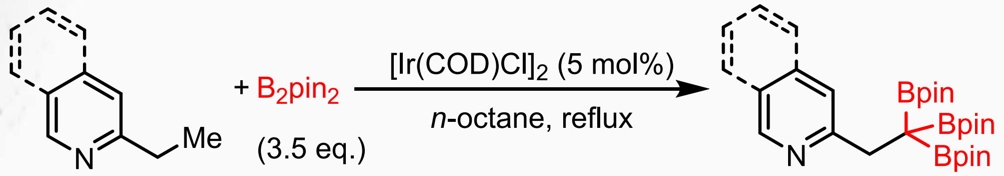


[a] isolated yield in the parentheses. [b] 5 mmol scale

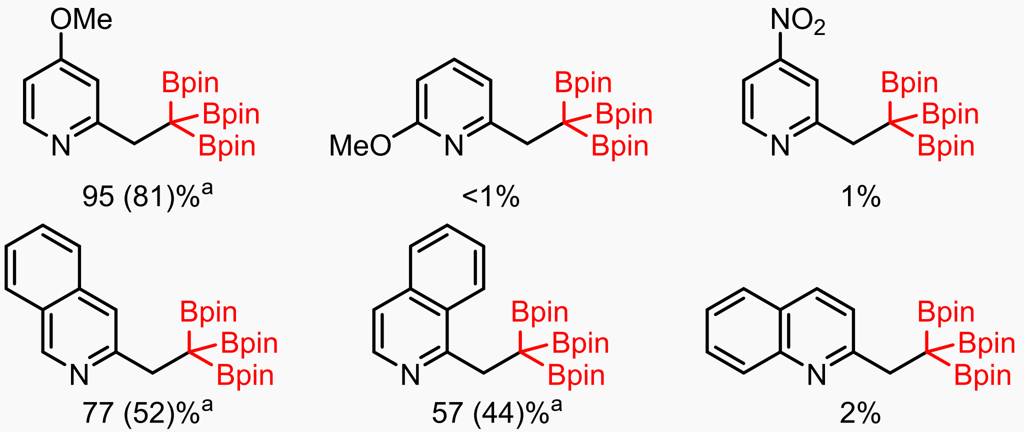


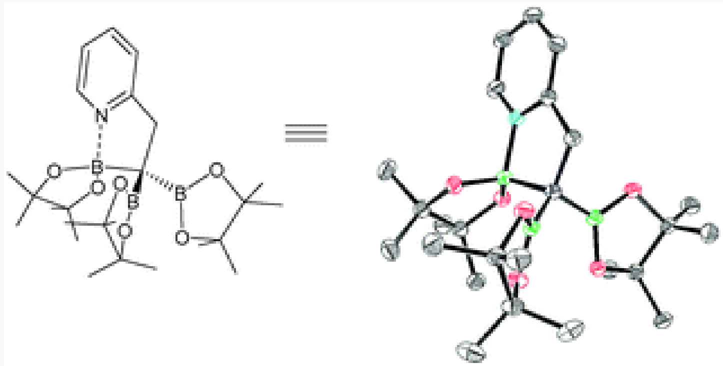
Sawamura, M. *et al.*, *J. Am. Chem. Soc.* **2013**, *135*, 2947

Borylation of unactivated substrates

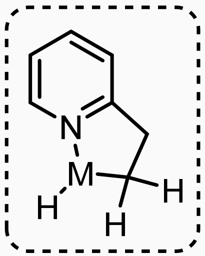


selected examples:



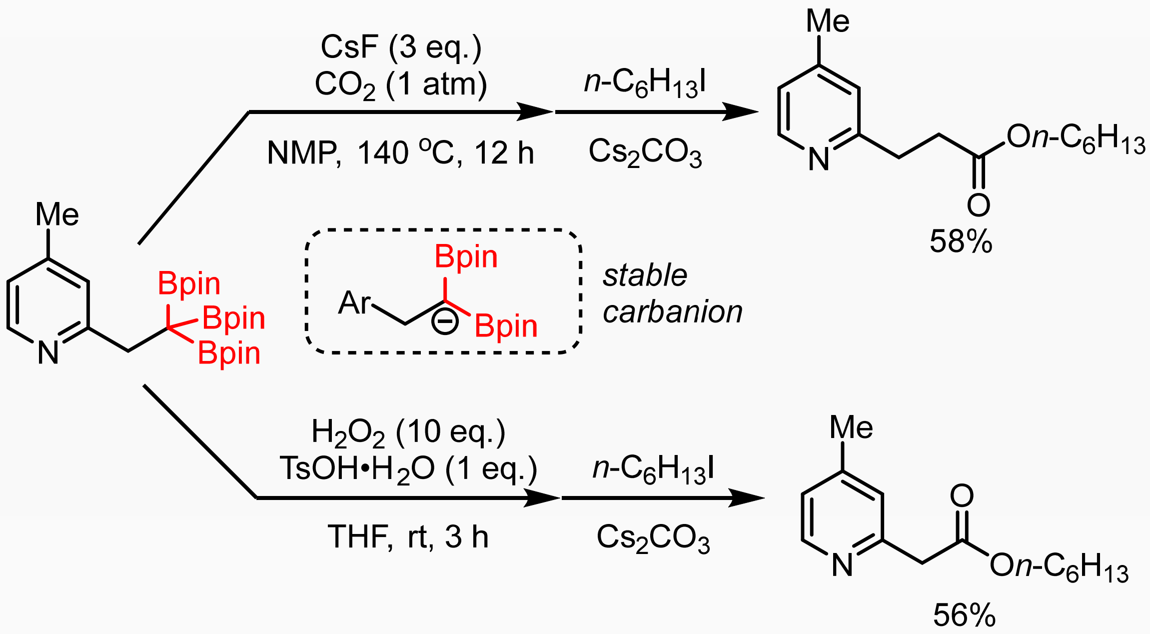


[a] isolated yield in the parentheses.



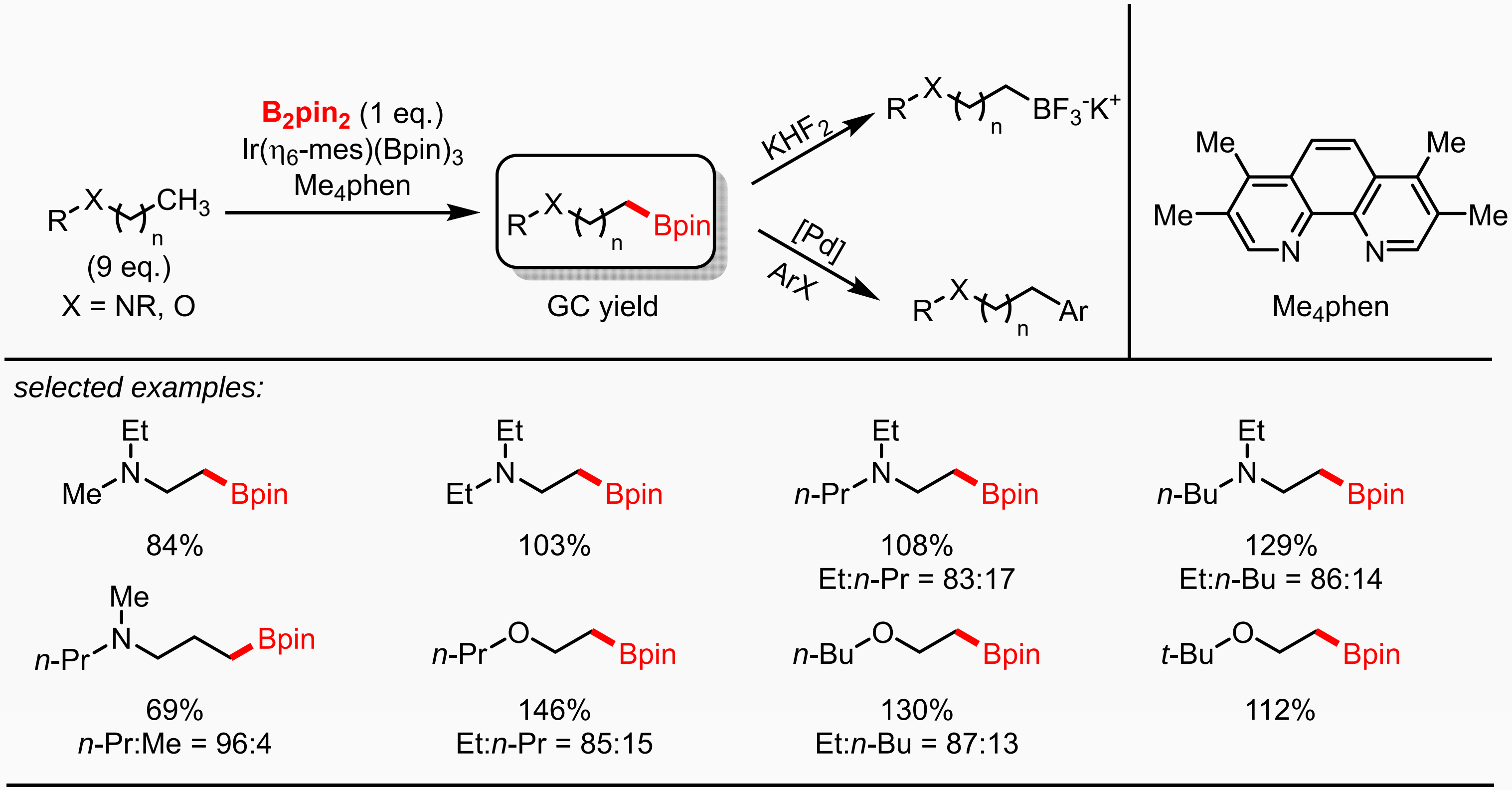
Sato, Y. *et al.*, *Chem. Commun.* **2013**, *49*, 5601

Borylation of unactivated substrates



Sato, Y. *et al.*, *Chem. Commun.* **2013**, *49*, 5601

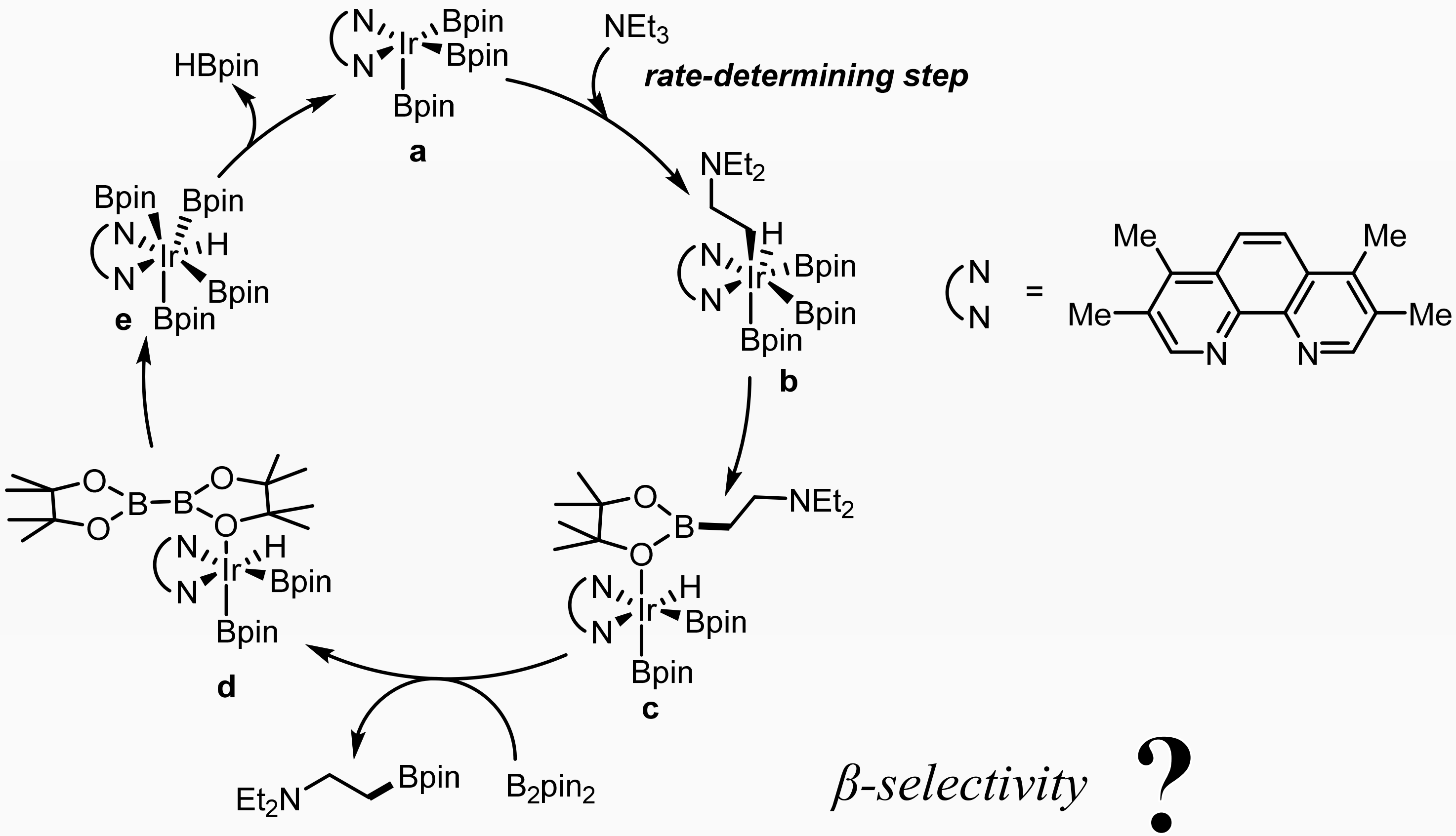
Borylation of unactivated substrates



β-selectivity

Hartwig, J. F. *et al.*, *J. Am. Chem. Soc.* **2014**, *136*, 8755.

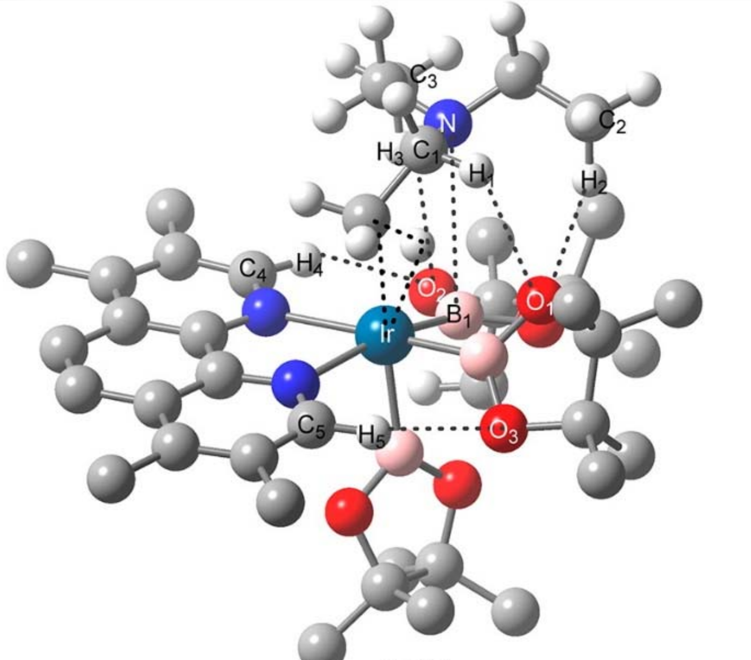
Borylation of unactivated substrates



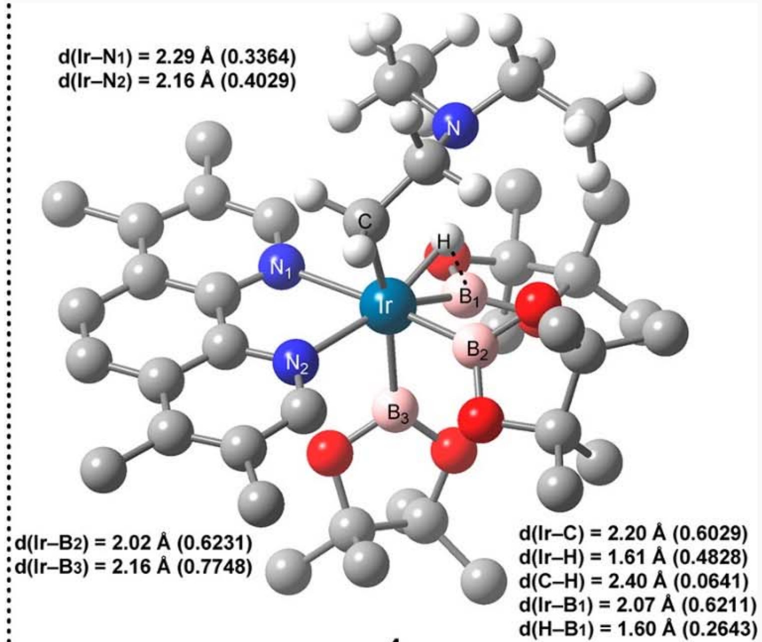
β-selectivity ?

Hartwig, J. F. *et al.*, *J. Am. Chem. Soc.* **2014**, *136*, 8755.

Borylation of unactivated substrates



3-TS



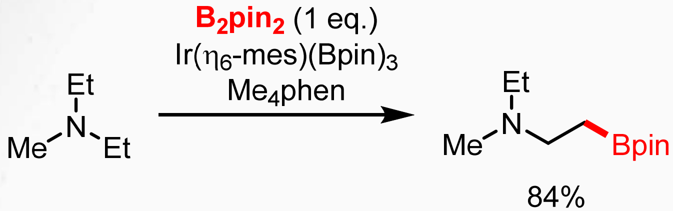
4

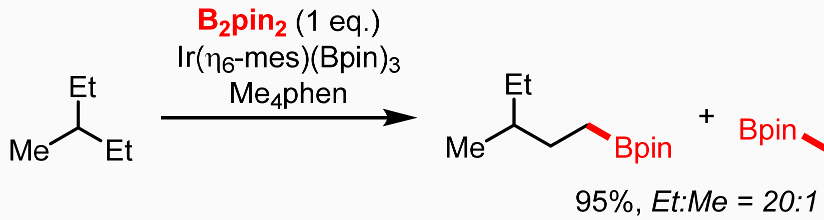
C–H···O interaction	E_{NBO}(C-H activation TS) (in kcal/mol)	d(C–O) (in Å)	d(O–H) (in Å)	∠(C–H–O)
C1–H1···O1	0.7	3.25	2.49	125.0°
C2–H2···O1	1.0	3.31	2.51	128.9°
C3–H3···O2	1.2	3.57	2.50	163.9°
C4–H4···O2	2.8	3.18	2.26	140.0°
C5–H5···O3	0.7	3.39	2.46	142.1°

1. Weak Lewis acid-base interaction
2. C-H···O interaction

Hartwig, J. F. *et al.*, *J. Am. Chem. Soc.* **2014**, *136*, 8755.

Borylation of unactivated substrates



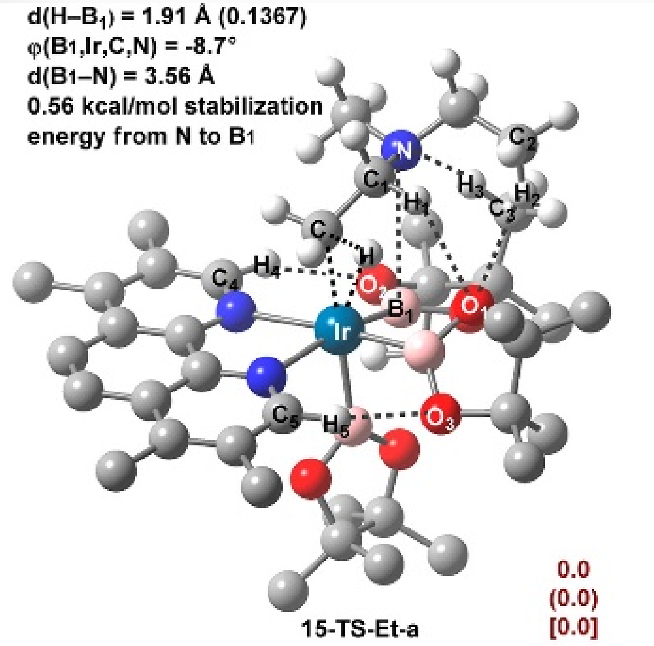


1. Repulsive steric interactions

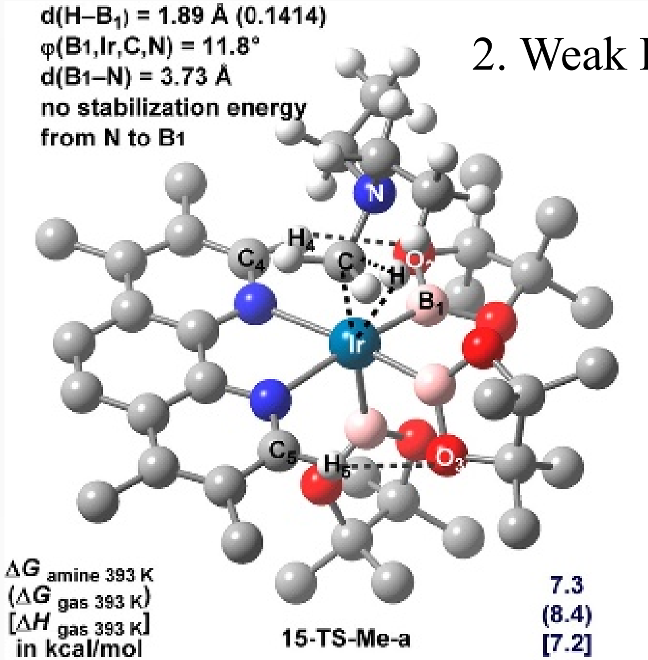
2. Weak Lewis acid-base interactions

3. C-H···O interactions

β-selectivity



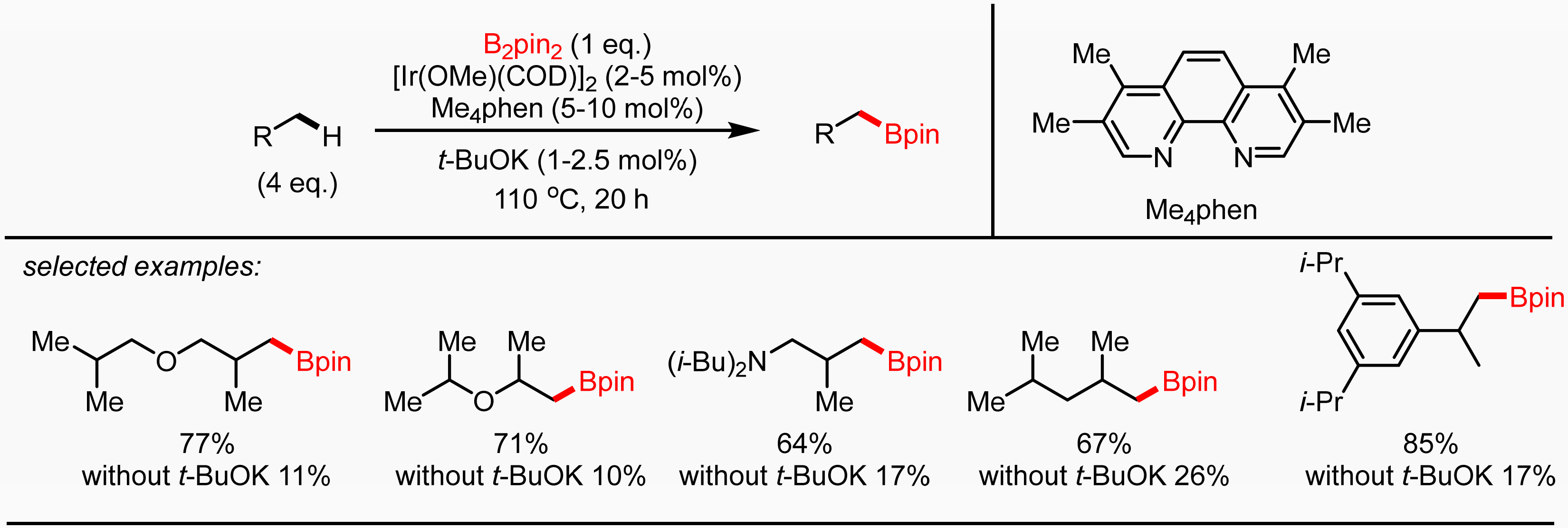
C–H···O interaction	E_{NBO}(C-H activation TS) (in kcal/mol)	d(C–O(N)) (in Å)	d(O(N)–H) (in Å)	∠(C–H–O(N))
C1–H1···O1	0.7	3.25	2.47	127.1°
C6–H2···O1	0.7	3.36	2.59	126.3°
C3–H3···N	0.7	3.65	2.68	147.8°
C4–H4···O2	2.7	3.19	2.28	139.6°
C5–H5···O3	1.6	3.32	2.39	141.3°



C–H···O interaction	E_{NBO}(C-H activation TS) (in kcal/mol)	d(C–O) (in Å)	d(O–H) (in Å)	∠(C–H–O)
C4–H4···O2	2.4	3.25	2.32	141.8°
C5–H5···O3	0.9	3.35	2.43	142.1°

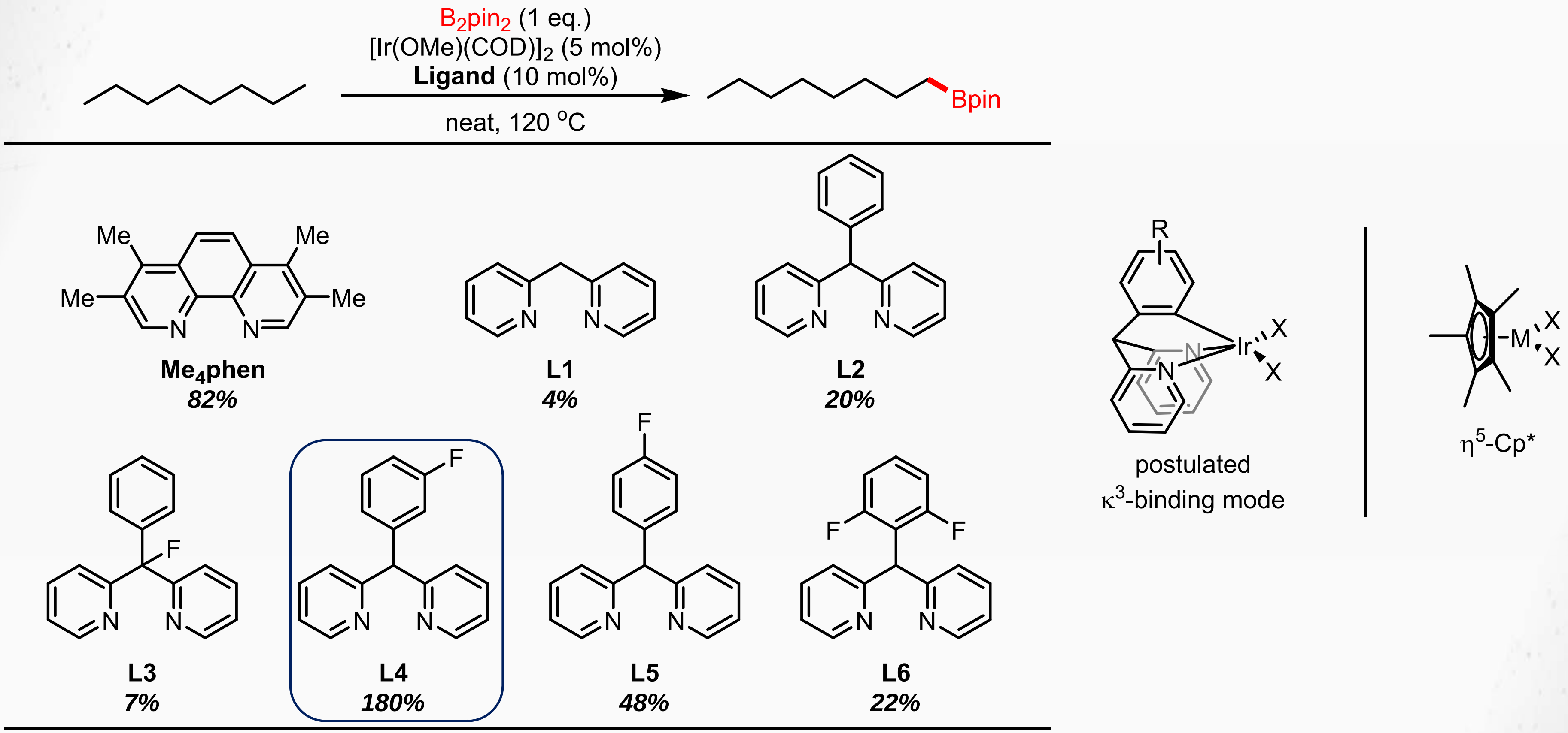
Hartwig, J. F. *et al.*, *J. Am. Chem. Soc.* **2014**, *136*, 8755.

Borylation of unactivated substrates



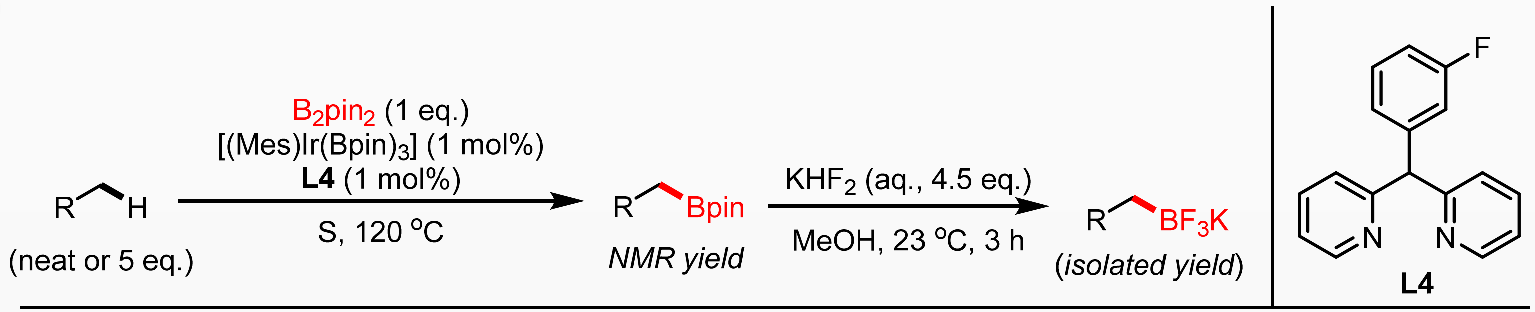
Suginome, M. *et al.*, *Chem. Commun.* **2014**, *50*, 6333

Borylation of unactivated substrates

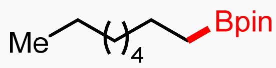


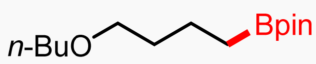
Schley, N. D. *et al.*, *J. Am. Chem. Soc.* **2020**, *142*, 6488

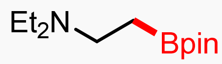
Borylation of unactivated substrates



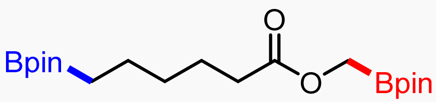
selected examples:

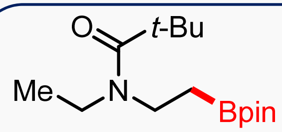


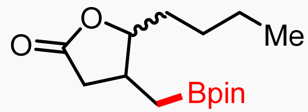




neat, 24 h	>199 (156)%[a]	183 (167)%[a]	159 (126)%[a]
cyclohexane, 48 h	103 (76)%[a]	89 (79)%[a]	99 (74)%[a]





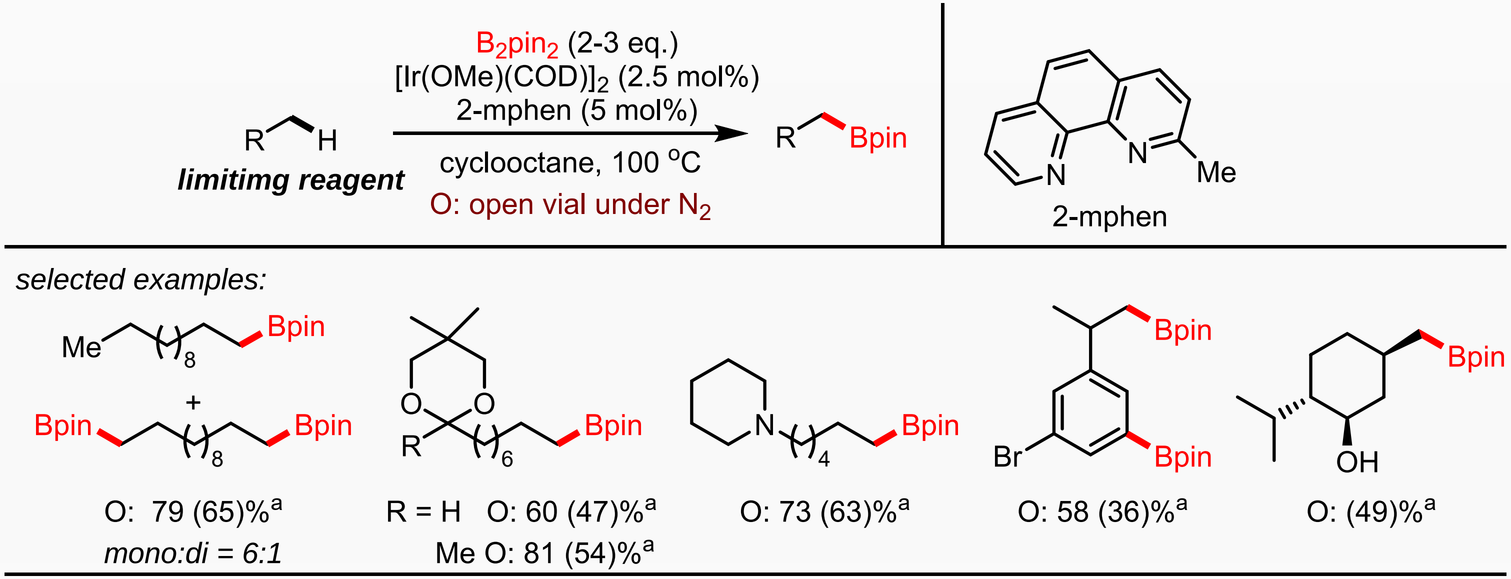


neat, 24 h	125 (89)%[a]; 4:96	2%	0%
cyclohexane, 48 h	82 (64)%[a]	96 (64)%[a]	68 (48)%[a]

[a] isolated yield in the parentheses.

Schley, N. D. *et al.*, *J. Am. Chem. Soc.* **2020**, *142*, 6488

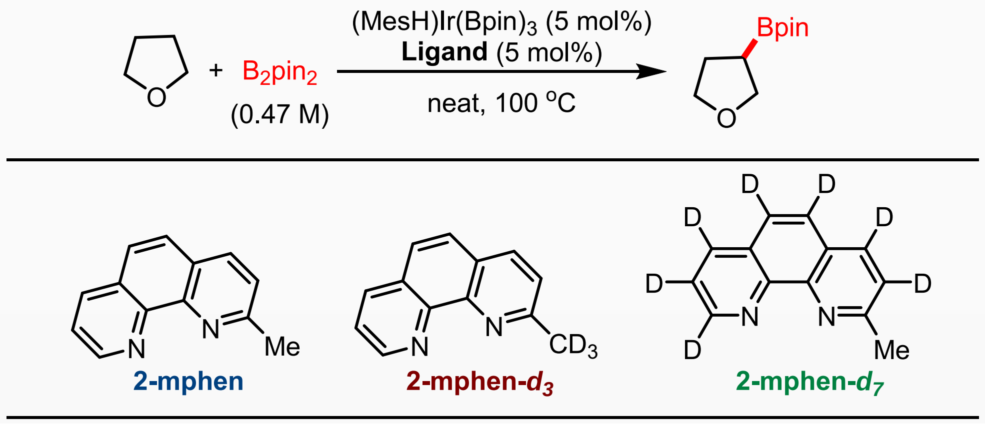
Borylation of unactivated substrates

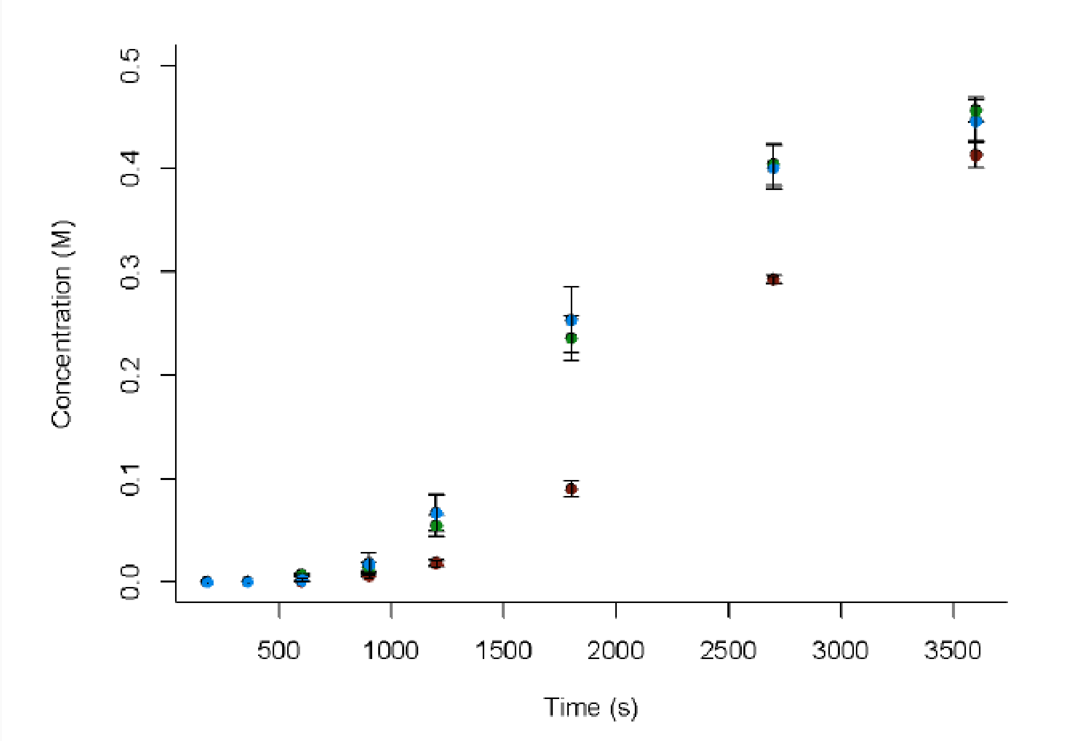


a isolated yield in the parentheses.

Hartwig, J. F. *et al.*, *Science* **2020**, *368*, 736.

Borylation of unactivated substrates





Hartwig, J. F. *et al.*, *Science* **2020**, *368*, 736.

CONTENT > >

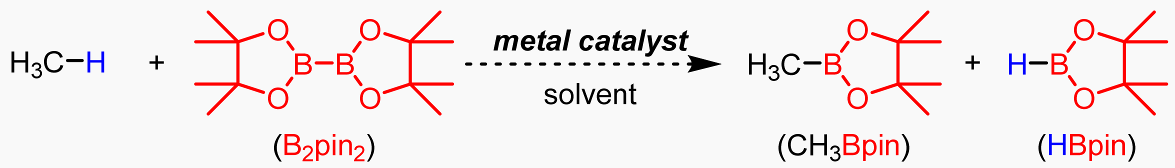
Borylation of methane

A ***Thermodynamics of methane borylation with $B_2(OR)_4$ or $HB(OR)_2$:***

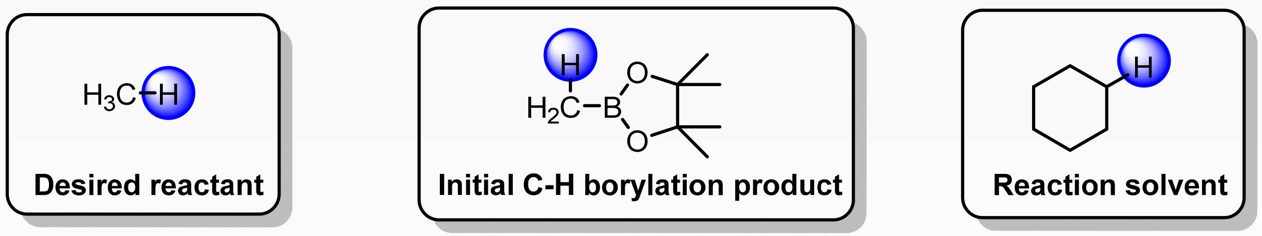
$$H_3C{-}H + H{-}B(OR)_2 \longrightarrow H_3C{-}B(OR)_2 + H_2 \qquad \Delta H_o = -1 \text{ to } +1 \text{ kcal/mol}$$

$$H_3C{-}H + (RO)_2B{-}B(OR)_2 \longrightarrow H_3C{-}B(OR)_2 + H{-}B(OR)_2 \qquad \Delta H_o = -13 \text{ kcal/mol}$$

B ***Proposed selective mono-C-H borylation of methane:***



C ***Selectivity challenges:***



sterically activated
(most sterically accessible C-H bond)

electronically activated
(most acidic C-H bond)

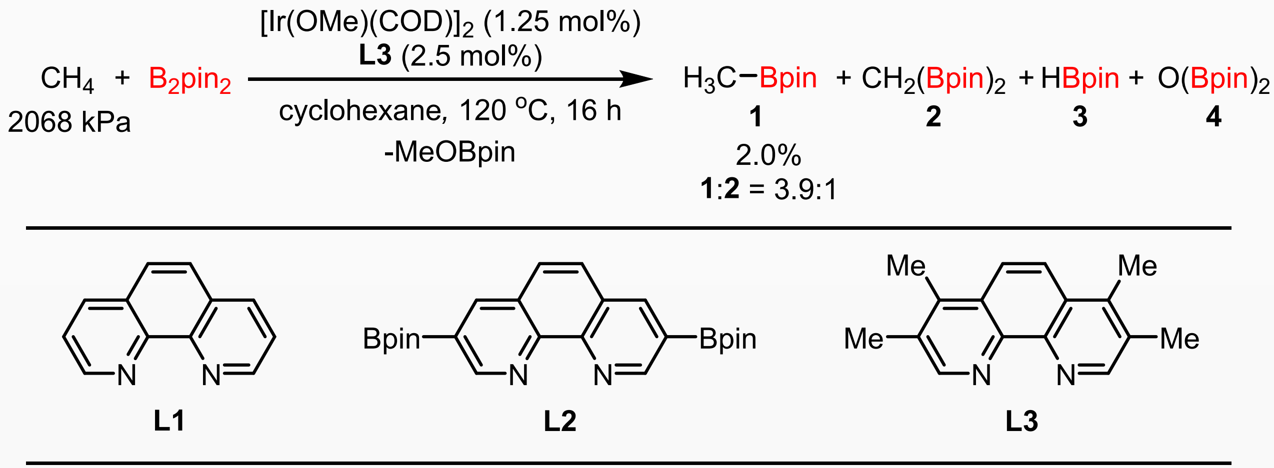
statistically favored
(highest concentration C-H bond)

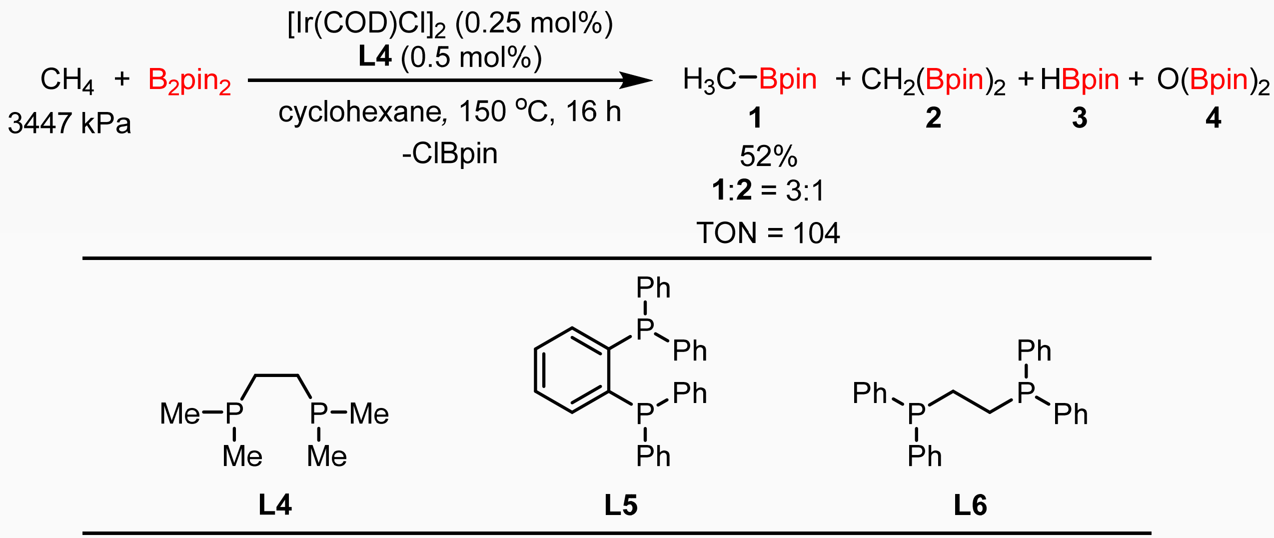
Poor selectivity
Overfunctionalization

Challenge !

Mindiola, D. J. *et al.*, *Science* **2016**, *351*, 1424.
Sanford, M. S. *et al.*, *Science* **2016**, *351*, 1421.

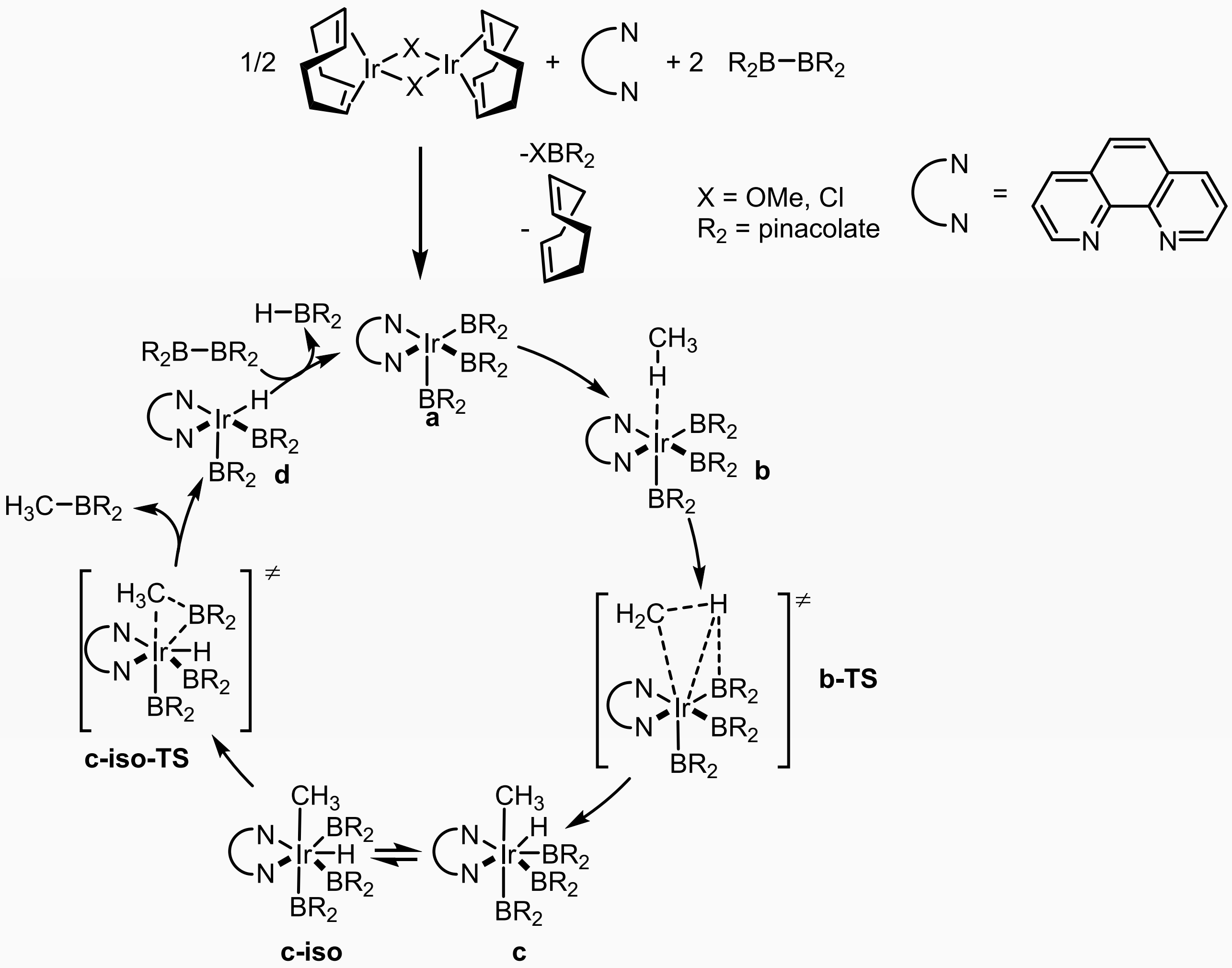
Borylation of methane





Mindiola, D. J. *et al.*, *Science* **2016**, *351*, 1424.

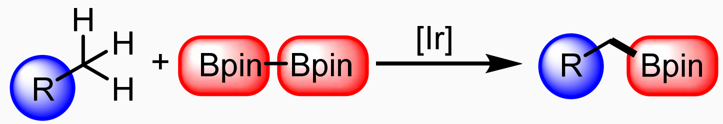
Borylation of methane



Mindiola, D. J. *et al.*, *Science* **2016**, *351*, 1424.

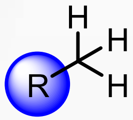
CONTENT > >

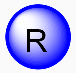
Summary and outlook



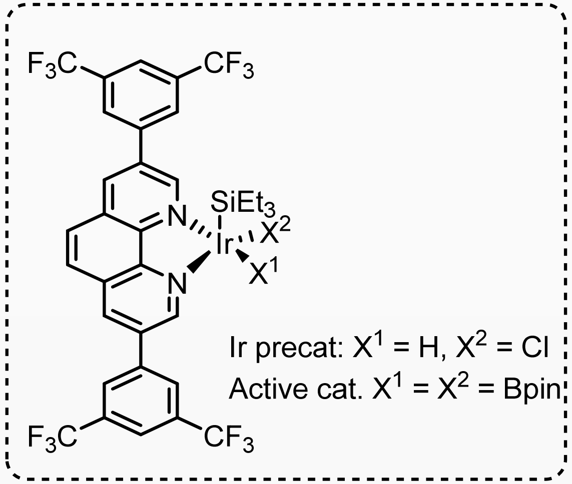
Summary

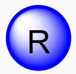
Activated substrates:





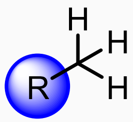
= Ar **Hartwig, J. F.** An electron-deficient phenanthroline as ligand; $Et_2SiBpin$ as reagent





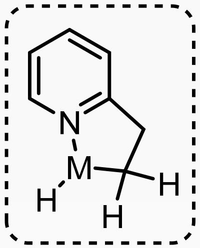
= Siliyl **Suginome, M.** *α-silyl effect*

Unactivated substrates：



Directed by N or O

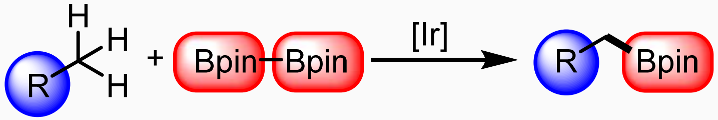
Sawamura, M.
Sato, Y.



Hartwig, J. F. *β-selectivity*

1. Repulsive steric interactions
2. Weak Lewis acid-base interactions
3. C-H•••O interactions

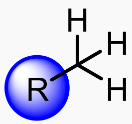
Summary and outlook



Summary

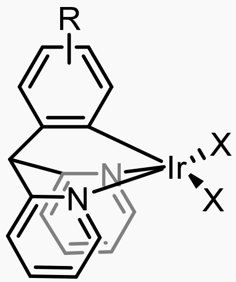
Unactivated substrates：

Suginome, M. cat. *t*-BuOK



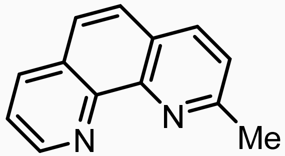
Undirected

Schley, N. D.



postulated
κ^3-binding mode

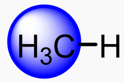
Hartwig, J. F.

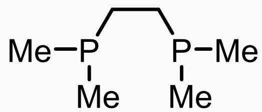


2-mphen

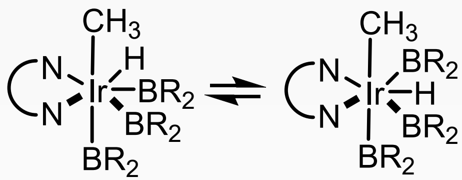
Methane：

Mindiola, D. J.





dmpe



c **c-iso**

Summary and outlook

Outlook

1. The utilization of HBpin
2. The utilization of phosphine ligands
3. The borylation of tertiary C-H bonds
4. Metal-free

Thanks for your attention