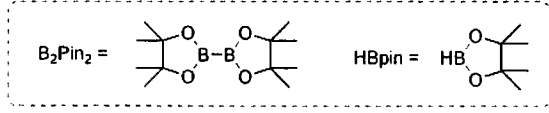
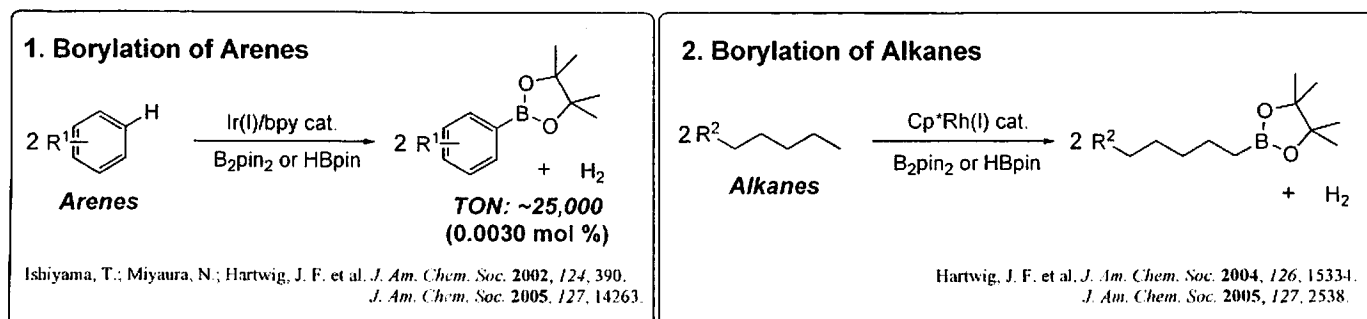


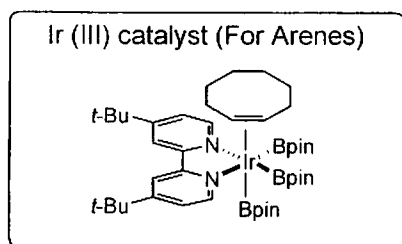
Transition Metal-catalyzed Direct Borylation of Arenes and Alkanes

Introduction

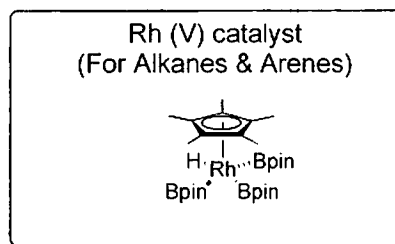
Organoboron compounds have the versatility in organic synthesis (boronates can be directly converted to alcohol, halogen, amine, and C-C bond formation etc.). Recently, direct borylation of unreactive C-H bond have been developed by several groups (as shown in the square). In this seminar, those development would be shown.



The Active (or lead to the active) Catalst



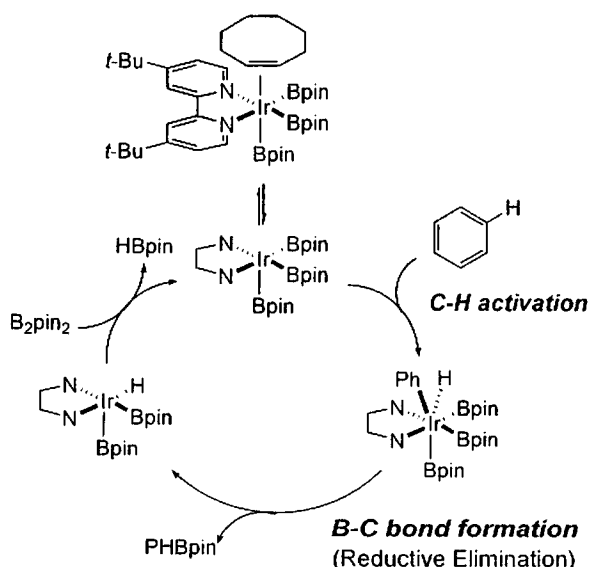
Electrophilic Ligand (Bpin, dtbpy)
 \Rightarrow Stabilize Ir (V) complex
 Sterically Crowded Environment
 \Rightarrow High Chemoselectivity (Only Arenes)
 High Regioselectivity



Electrophilic Ligand (Bpin)
 \Rightarrow Stabilize Rh (V) complex
 Sterically Crowded Environment
 \Rightarrow High Regioselectivity

Both of them...

The driving force of these reactions \Rightarrow



**B-C bond formation
Strong Thermodynamic Driving Force**

Bond Dissociation Energy

C-H: ~100 kcal/mol
 B-C: 110 ~ 120 kcal/mol

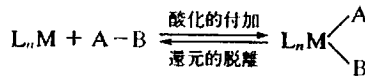
Calculation of borane bond dissociation energies

Rablen, P. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 4121.
J. Am. Chem. Soc. **1996**, *118*, 4648.

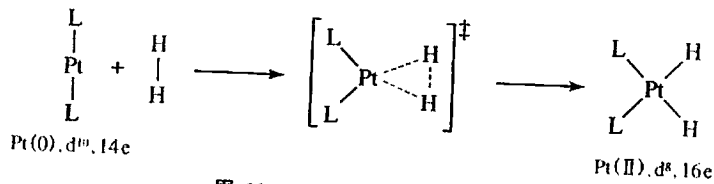
□ C-H Activation (Oxidative Addition Process) □

There are several patterns in the C-H activation (or C-H bond cleavage), such as oxidative addition process, σ -bond metathesis, C-H insertion by metal carbene complex, electrophilic aromatic substitution, and so on. In this time, oxidative addition process would be discussed.

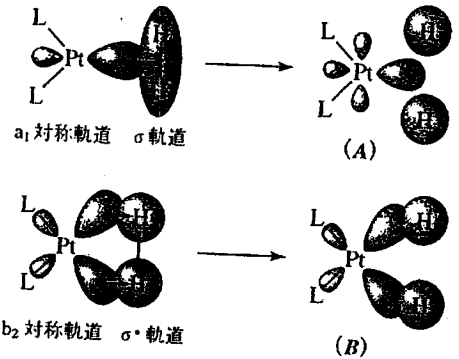
Oxidative Addition Process



ex.) The oxidative addition of saturated H-H to Pt complex ref. 大学院講義 I p. 424.



L = ホスフィンの配位子 図 10・1 PtL₂ 錯体に対する水素分子の酸化的付加反応



The metals required in this process...

- 1) An Accessible ($n + 2$) Oxidation State
- 2) Coordinative Unsaturation (to access to metal vacant orbital)
- 3) Electronic Unsaturation (to accommodate the electrons supplied by the C and H ligands)



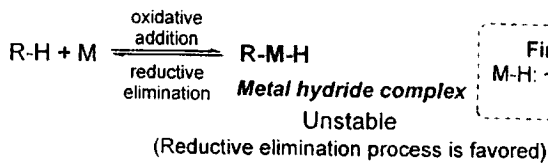
Low-valent & Coordinatively Unsaturated Metal Complexes

(Ni(0), Pd(0), Pt(0), Rh(I), Ir(I), etc. late transition metal)

Mainly utilized metals in C-H activation...

Ir, Rh, Pt

Still unclear, but

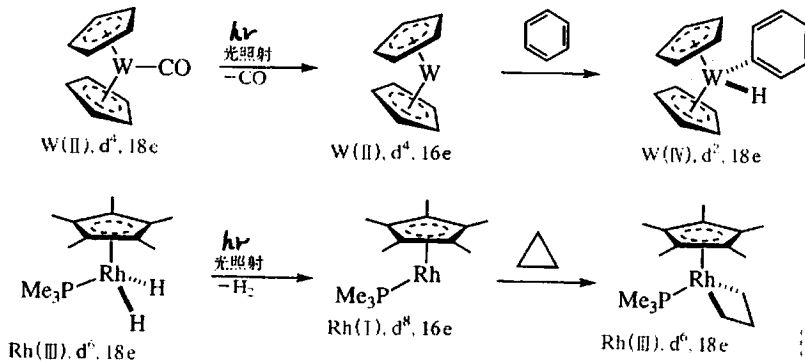


First-row metals (Co, Ni etc.)
M-H: ~60 kcal/mol, M-C: ~30 kcal/mol
(C-H: ~100 kcal/mol)

On the other hand...
Ir-H: 74 kcal/mol, Ir-Cy: 51 kcal/mol
Ir-Ph: 81 kcal/mol

↓
Thermodynamically Favorable
Same tendency was observed in Rh or Pt.

Toward the unsaturated metal complex... (ref. 大学院講義 II p.426.)



<references>
田中正人. 有合化, 1988, 46, 832.
Bergman, R. G. et al. 1995, 28, 154. (Acc. Chem. Res.)
Shilov, A. E.; Shul'pin, G. B. Chem. Rev. 1997, 97, 2879.

□ The First Direct Borylation of Arenes & Alkenes (Stoichiometric) □

J. Am. Chem. Soc. 1995, 117, 11357.
Organometallics 1999, 18, 3383.

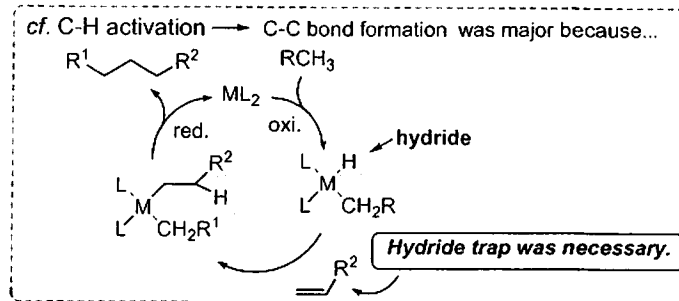
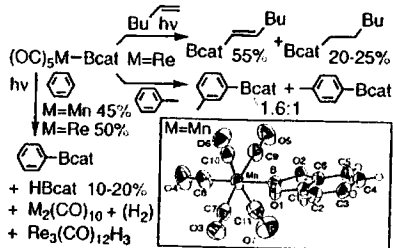
Point

C-H activation → C functionalization

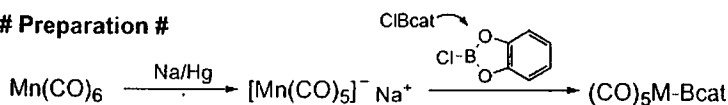
Hydrocarbon Functionalization by Transition Metal Boryls

Karen M. Waltz, Xiaoming He, Clare Muhoro, and John F. Hartwig*

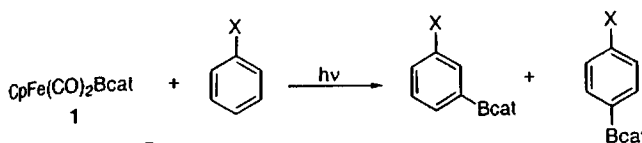
Scheme 1



Preparation



Electronic Effects (Substrate)



X	product isomer ratio		
	<i>o</i>	<i>m</i>	<i>p</i>
Me		1.1	1.0
OMe	1.0	1.6	1.1
Cl		1.5	1.0
CF ₃		1.5	1.0
NMe ₂		1.0	8.0

OMe: Interaction with Boronate ?

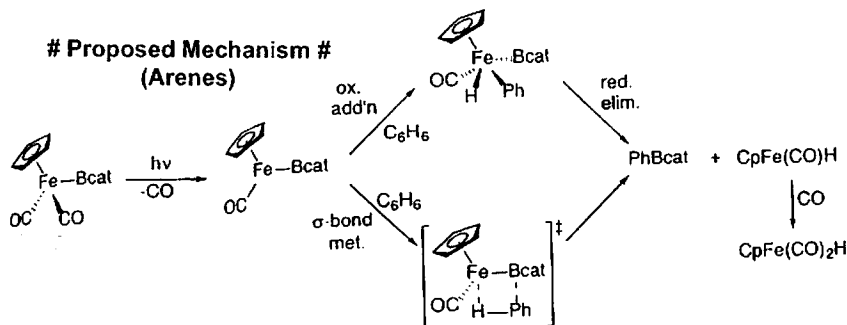
Not so large electronic effect was observed.
(Especially electron withdrawing group)

Alkanes did not react at all.

Table 7. Product Ratios from Competition Reactions of $CpFe(CO)_2Bcat$ (1) with Mixtures of Substituted Arenes

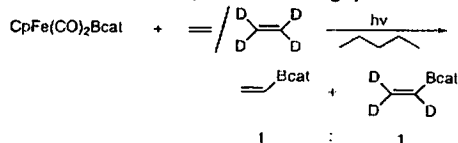
Substrates	Product Ratio
	1 : 1
	1 : 1
	1 : 1
	1 : 3
	1 : 2.4
	1 : 3.4

Proposed Mechanism # (Arenes)

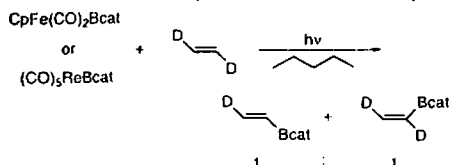


Proposed Mechanism # (Alkenes)

Intermolecular KIE (sp^2 C-H cleavage)

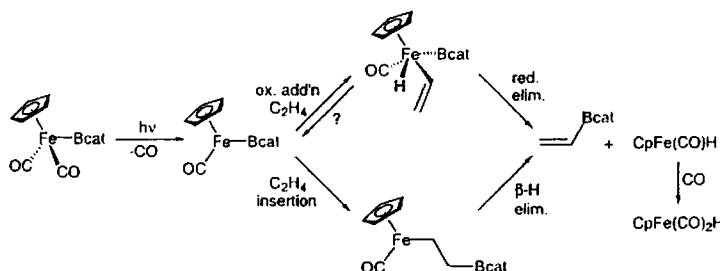


Intramolecular KIE (β -hydride elimination)



Intermolecular & Intramolecular: $k_H/k_D = 1.0$??

Rate-determining step would be insertion step ?

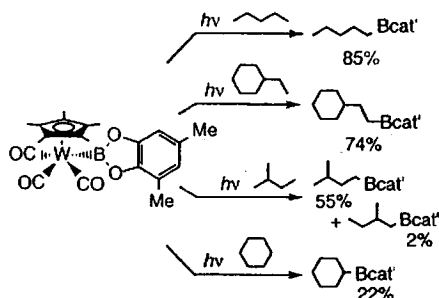
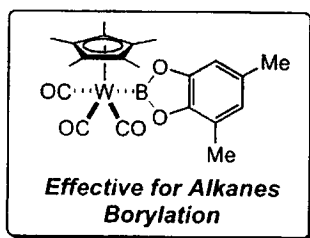


□ The First Direct Borylation of Alkanes (Improvement / Stoichiometric) □

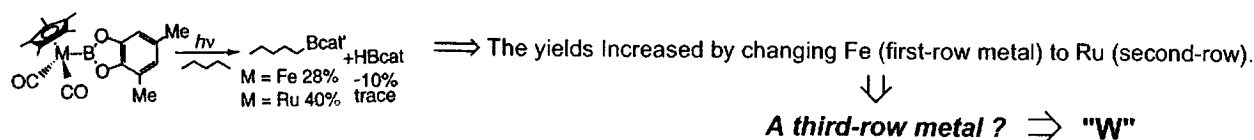
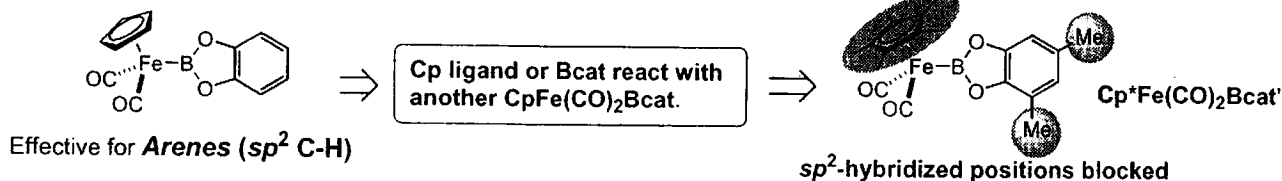
Selective Functionalization of Alkanes by Transition-Metal Boryl Complexes

Science 1997, 277, 211.

Karen M. Waltz and John F. Hartwig*

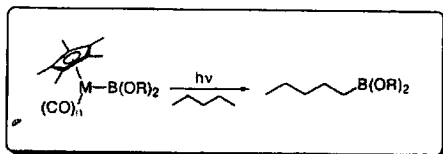


Why alkanes did not react under previous system ?

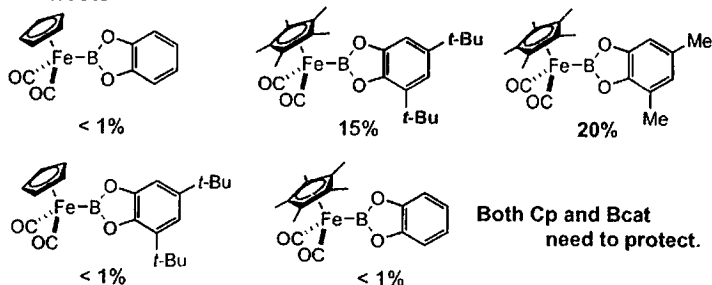


Further Investigations

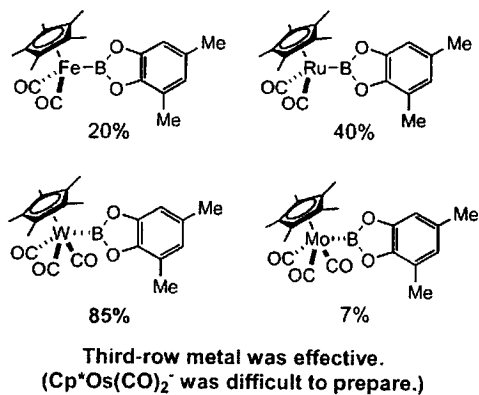
Hartwig, J. F. et al. *J. Am. Chem. Soc.* 2000, 122, 11358.



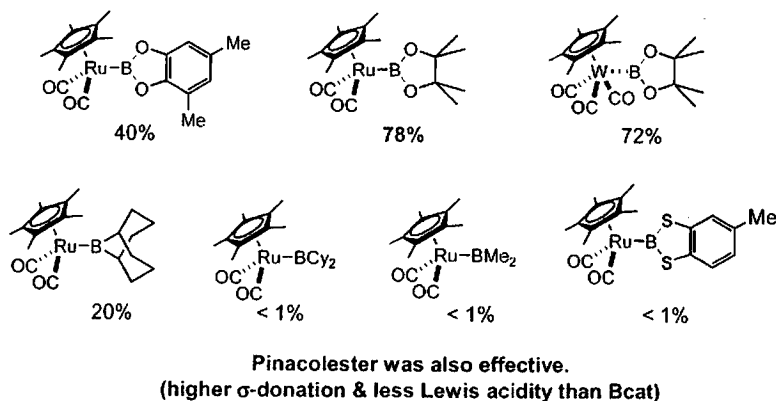
Steric Effects



Metal Effects

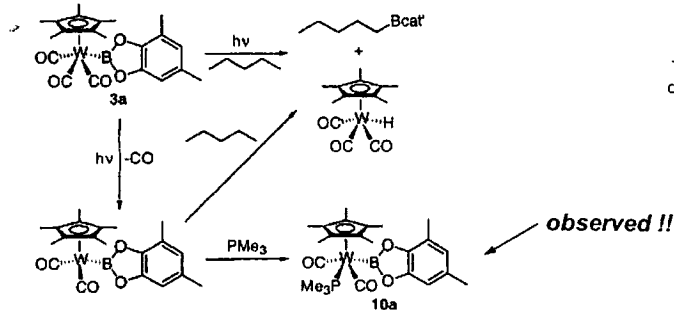


Borone Effects

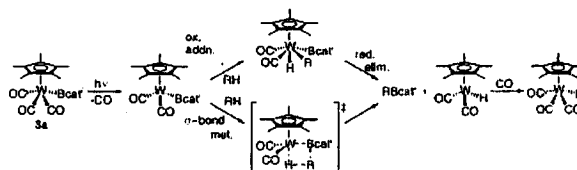


Mechanistic Insights

Scheme 2



Scheme 3



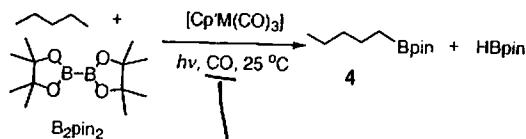
Catalytic Direct Borylation of Arenes & Alkanes

Under Irradiation Conditions

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

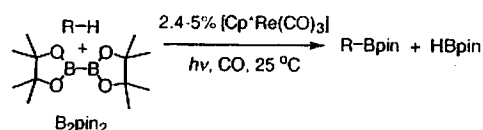
Catalytic, Regiospecific End-Functionalization of Alkanes: Rhenium-Catalyzed Borylation under Photochemical Conditions**

Huiyuan Chen and John F. Hartwig*



Scheme 1. Stoichiometric reaction of B₂pin₂ with [Cp*M(CO)₃] in pentane. Cp' = C₅H₅, C₅H₄Me, C₅Me₅; M = Mn, Re.

Without additional CO (2 atm), the catalyst was decomposed (dimerization).



Scheme 2. Reaction of B₂pin₂ in pentane catalyzed by [Cp*Re(CO)₃]. Cp' = C₅H₅, C₅H₄Me, C₅Me₅; M = Mn, Re; R = *n*-C₅H₁₁, *i*-C₅H₁₁, CH₂C₆H₁₁.

Table 1. Regiospecific, catalytic functionalization of alkanes, alkyl ethers, and benzene.^[a]

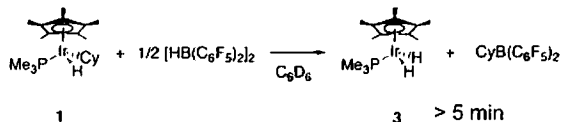
En-try	Substrate	Catalyst (amount [%])	t [h]	Conv. of B ₂ pin ₂ [%]	Yield [%]
					RBpin HBpin
1	<i>n</i> -pentane	3 (2.4)	56	94	95 (4) 32
2	2-methylbutane	3 (3.4)	55	89	83 ^[b] 24
3	methylcyclohexane	3 (5.0)	60	88	75 (6) 27
4	di- <i>n</i> -butyl ether	3 (5.0)	45	100	100 (7) 23
5	<i>tert</i> -butyl ethyl ether	3 (4.9)	46	100	82 (8) 26
6	benzene	1 (10)	36	97	76 (9) 23
7	<i>n</i> -pentane	10a (2.5)	56	92	97 (4) 31

[a] A solution in pentane containing [Cp*Re(CO)₃], dodecahydrotriphenylene (internal standard), B₂pin₂, and CO (2 atm) was irradiated with a Hanovia medium-pressure mercury arc lamp. Yields were determined by GC or ¹H NMR spectroscopy, and yields of isolated products were determined after purification by chromatography on silica gel eluting with pentane or pentane/diethyl ether.
[b] The two terminal regioisomers 5a and 5b were obtained in a 3.6:1 ratio.

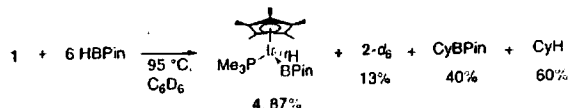
Under Thermal Conditions

Smith III, M. R. et al. *J. Am. Chem. Soc.* 1999, 121, 7696.

From CH activation products (Stoichiometric)

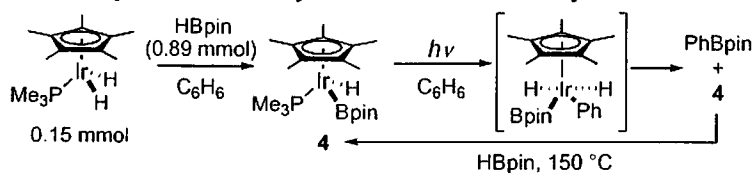


In the case of boronate (Stoichiometric)



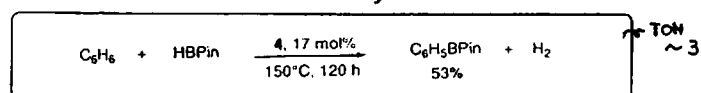
more harsh conditions were needed.

For catalytic reaction they examined irradiation system



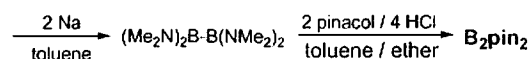
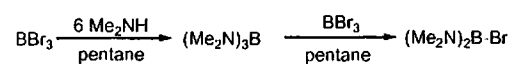
To complete the reaction, five thermal/photolytic cycle would be required. But after third cycle the reaction was completed.

Thermal Catalysis ?



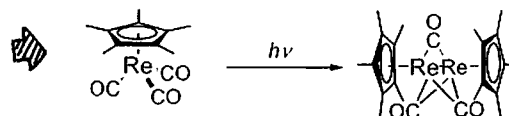
Appendix

○ air-stable, solid
△ expensive
1g: ¥10,200
25g: ¥190,000 (Aldrich)
500g: ¥683,000

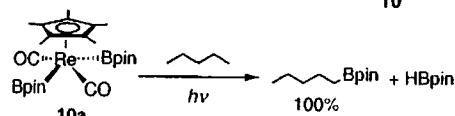
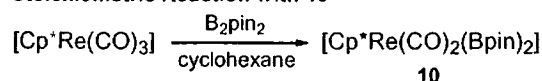


Ishiyama, T.; Miyaura, N. et al. *Org. Synth.* 2000, 77, 176.

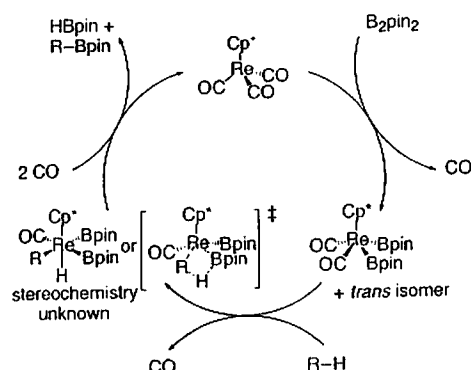
cf. Graham, W. et al. *J. Chem. Soc. Chem. Commun.* 1982, 27.



Stoichiometric Reaction with 10



Oxidative addition of B₂pin₂ → then CH activation

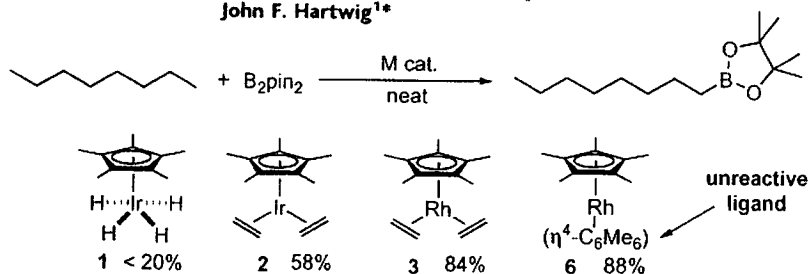


Scheme 3. Proposed mechanism for the photochemical reaction of B₂pin₂ with alkenes catalyzed by [Cp*Re(CO)₃].

Thermal, Catalytic, Regiospecific Functionalization of Alkanes

Science, 2000, 287, 1995.

Huiyuan Chen,¹ Sabine Schlecht,¹ Thomas C. Semple,² John F. Hartwig^{1*}



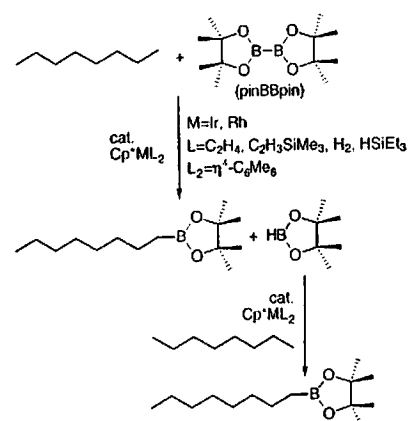
To achieve thermal reaction...

Ligand: CO \rightarrow polyhydride (1) or alkene (2 ~ 6)
(These ligands would dissociate under thermal condition.)

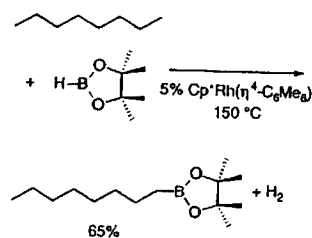
Table 1. Regiospecific, catalytic functionalization of alkanes, alkyl ethers, and benzene. A solution of catalyst and diboron compound was heated at 150°C. A known amount of dodecahydrotriphenylene (internal standard) was added to the reaction after complete consumption of both pinBBpin and HBpin. Yields were determined by GC for the overall reaction $\text{pinBBpin} + \text{R-H} \rightarrow \text{RBpin} + \text{H}_2$.

Entry	Substrate	Catalyst	Time (hours)	Yield of RBpin (%)
1	<i>n</i> -Octane	3, 5.0 mol%	5	84
2	<i>n</i> -Octane	3, 1.0 mol%	110	64
3	<i>n</i> -Octane	6, 5.0 mol%	25	88
4	<i>n</i> -Octane	6, 1.0 mol%	80	72
5	2-Methylheptane	3, 2.5 mol%	30	73
6	2-Methylheptane	6, 1.0 mol%	60	61
7	Methylcyclohexane	6, 6.0 mol%	80	49
8	<i>n</i> -Butyl ether	6, 4.0 mol%	80	64
9	Benzene	6, 5.0 mol%	2.5	92
10	Benzene	6, 0.5 mol%	45	82

Complete Conversion



Reaction with Pinacolborane



HBpin was also reactive in this system.

J. Am. Chem. Soc. 2004, 126, 15334.

Regiospecific Functionalization of Methyl C-H Bonds of Alkyl Groups in Reagents with Heteroatom Functionality

Joshua D. Lawrence, Makoto Takahashi, Chulsung Bae, and John F. Hartwig*

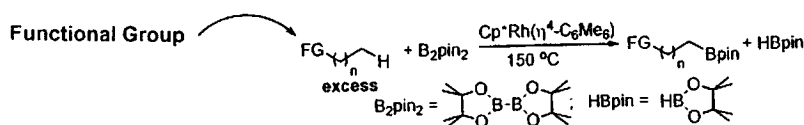


Table 1. Rhodium-Catalyzed Terminal Borylation of Alkyl Groups^a

Reactant	Product	reactant: B ₂ pin ₂	mol% 1	Yield(%) ^b
		10:1	5	91
		1:1	10	48 ^c
		10:1	5	74
		1:2	17	70
		10:1	5	83 ^d
		1:2	10	46
		10:1	5	90
		1:2	10	84
		10:1	5	75 ^e
		1:1	10	33
		10:1	5	55 ^e
		1:2	10	67

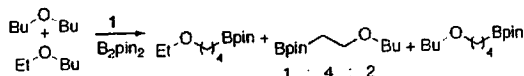
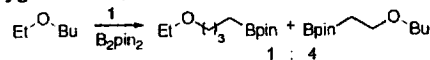
^a Conditions: B₂pin₂, 1, neat, 150 °C, 24 h. ^b Yields calculated by GC areas. ^c In cyclohexane solvent (3 equiv). ^d 140 °C, 12 h. ^e Yield based on conversion to H₂.

Another functionalized compounds were **not** observed.
(Only terminal CH was borylated.)

cf. C-H (alkyl): 105 kcal/mol, C-H (arene): 113 kcal/mol
C-F (alkyl): 128 kcal/mol

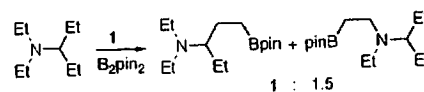
Electronic Effects of Heteroatoms

1) Oxygen Effects



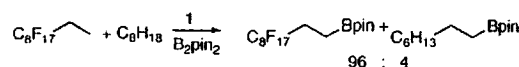
Acidic Me was functionalized.

2) Nitrogen Effects



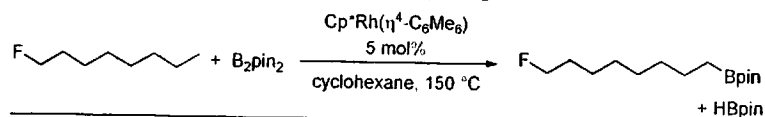
Not so different (compared to O)

3) Fluorine Effects



Less electron-rich methyl group was favored in this reaction.

Limiting Reagent (alkane) # ~ from supporting information ~



F-octane : B ₂ pin ₂ : cyclohexane	yield (%)
1 : 10 : 10	55
2 : 1 : 3	39
3 : 1 : 2 : 3	40
4 : 10 : 1 : 0	83
5 : 1 : 2 : 0	46

Neat conditions were favored.
(entry 4, 5)

Excess B₂pin₂
⇒ not so effective
(entry 3, 5)

What is the factor for low conversion?
... Mechanistic Insights

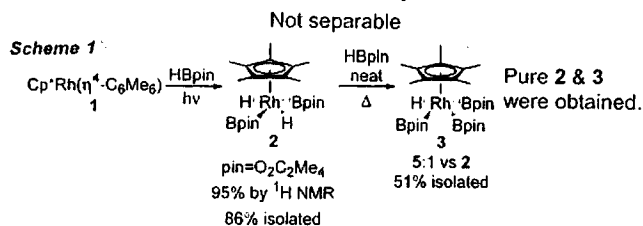
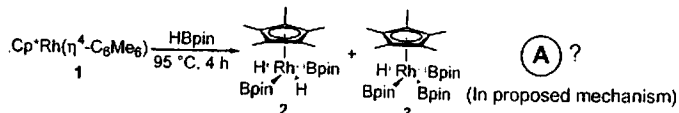
J. Am. Chem. Soc. 2005, 127, 2538.

Rhodium Boryl Complexes in the Catalytic, Terminal Functionalization of Alkanes

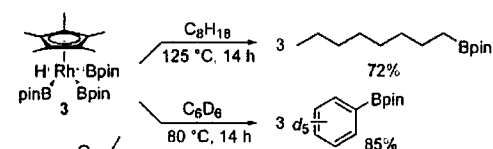
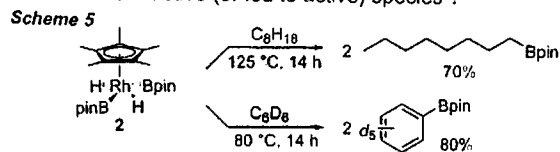
John F. Hartwig,^{*,†} Kevin S. Cook,[†] Marko Hapke,[†] Christopher D. Incarvito,[†] Yubo Fan,[‡] Charles Edwin Webster,[‡] and Michael B. Hall^{*,‡}

Contribution from the Departments of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520-8107, and Texas A&M University, College Station, Texas 77843-3255

What species are involved in this catalytic reaction?

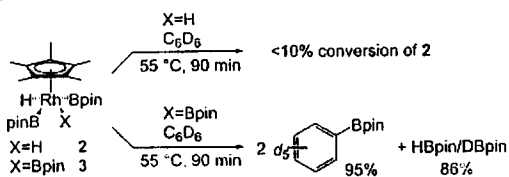


Are 2 and 3 active (or led to active) species?



Reactivity of substrate: arene > alkane

Scheme 6



Reactivity of Catalyst: 3 > 2

Proposed Mechanism

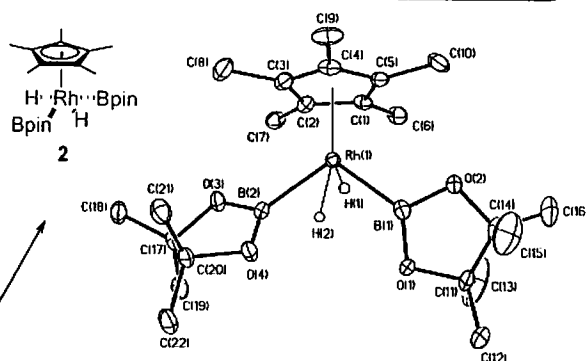
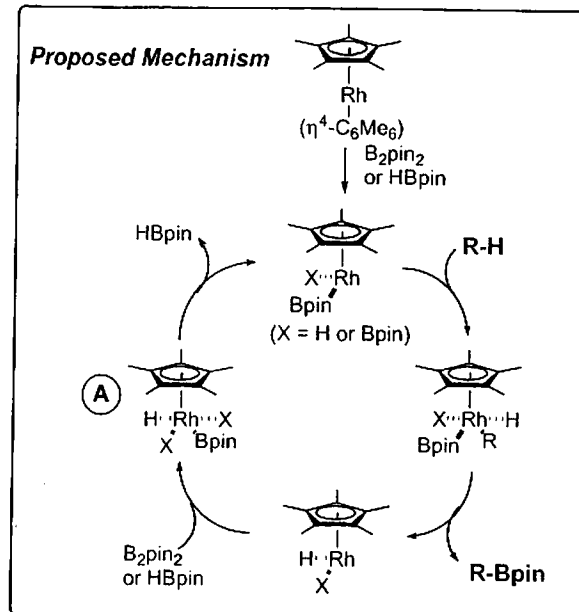


Figure 2. ORTEP drawing of one of two independent molecules of Cp*Rh(H)(Bpin); (2) in the asymmetric unit with 30% thermal ellipsoids.

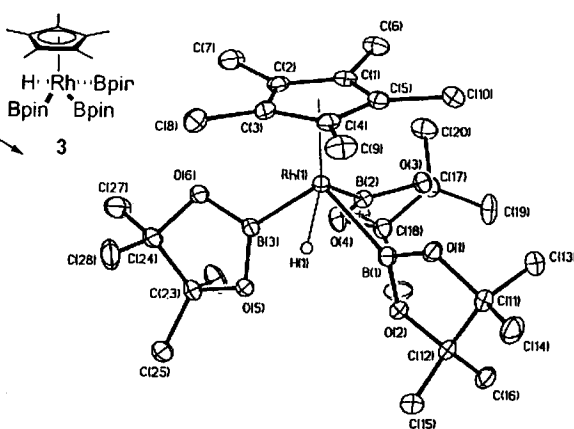
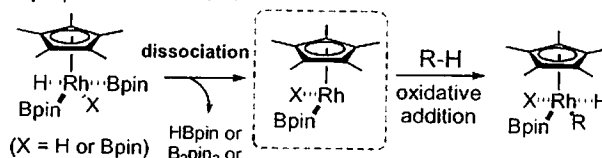


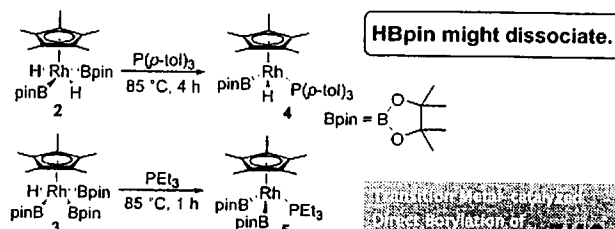
Figure 4. ORTEP drawing of one of two independent molecules of Cp*Rh(H)(Bpin); (3) in the asymmetric unit with 30% thermal ellipsoids.

What is the factor for low conversion (Alkane)?

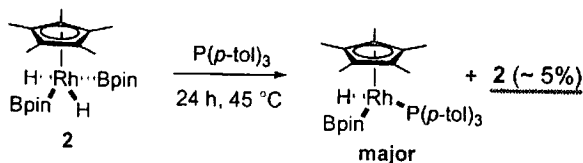
In proposed mechanism...



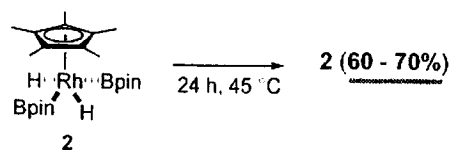
Scheme 4



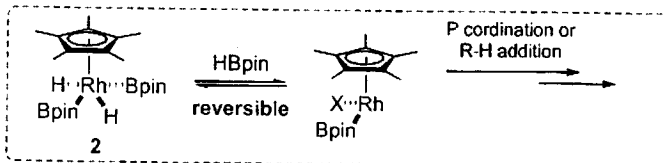
In the reaction of **2** with P(*p*-tol)₃...



In the absence of P(*p*-tol)₃

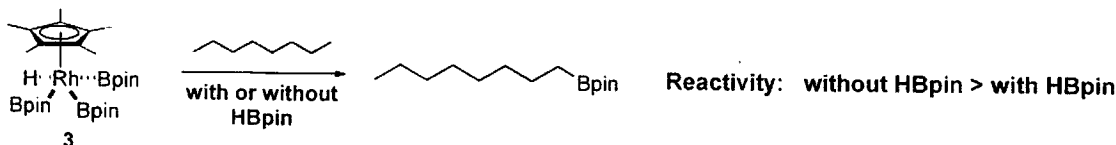


⇒ This dissociation pathway is reversible.



Does the generation of HBpin inhibit the reaction pathway (especially alkane's case)?

Indeed...



As reaction proceeds, HBpin generates and prevents the reagent from binding to the catalyst.

□ Ir-Catalyzed Borylation of Arenes □

J. Am. Chem. Soc. 2002, 124, 390.

Mild Iridium-Catalyzed Borylation of Arenes. High Turnover Numbers, Room Temperature Reactions, and Isolation of a Potential Intermediate

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Natia R. Anastasi and John F. Hartwig*

Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520-8107

catalyst: 1/2[IrCl(COD)]₂/bpy
(3 mol %)

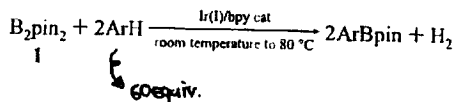
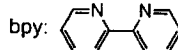
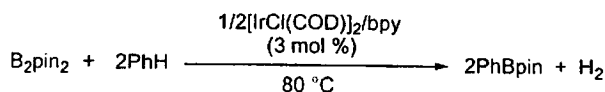


Table 1. Ir-Catalyzed Direct Borylation of Arenes with **1** (eq 1)^a

arene	product	yield% ^b (<i>α:m:p</i>)	arene	product	yield% ^b (<i>α:m:p</i>)
1	pinB-Ph	95	7	pinB-1,3-Cl ₂ -Ph	83
2	pinB-4-Me-Ph	95 (1:74:25)	8	pinB-3-Me-Ph	58
3	pinB-Ph	82 (0:69:31)	9	pinB-4-Me-Ph	86
4	pinB-4-CF ₃ -Ph	80 (0:70:30)	10	pinB-4-Me-2-OMe-Ph	72
5	pinB-4-Me-2-OMe-Ph	83	11	pinB-4-Me-3-OMe-Ph	73
6	pinB-4-Me-2,6-OMe-Ph	86			

^a All reactions conducted at 80 °C for 16 h with **1** (1.0 equiv), an arene (60 equiv), and 1/2[IrCl(COD)]₂/bpy (3 mol %) without solvent. ^b GLC yields based on boron atom in **1**. ^c Isomer ratios determined by ¹H NMR.

Cyclooctene ligand is effective.



There was an induction period.

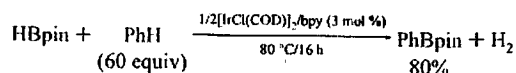
Further analyzing...

The reaction proceeded after COD () reduction to COE ().

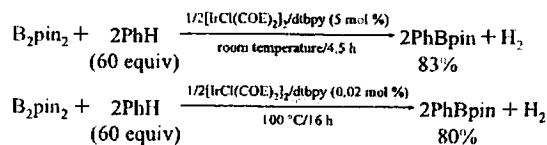
1/2[IrCl(COE)]₂/bpy showed no induction period.

Alternative way: 1/2[IrCl(COD)]₂/bpy + HBpin

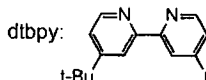
Full conversion (HBpin)



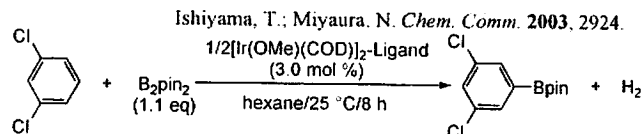
High Catalyst Loading



COE: cyclooctene ← Why?



The Effect of dpy Ligand



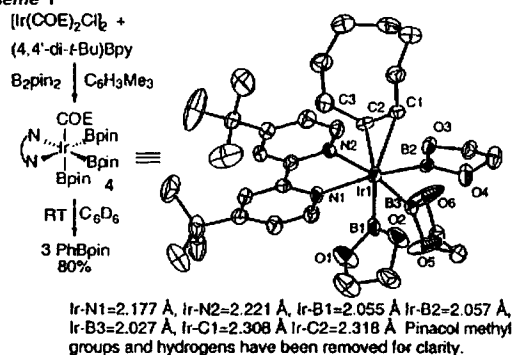
Entry	Ligand	Yield (%)
1	dtbbpy	86
2	4,4'-di-Me-bpy	75
3	4,4'-di-NMe ₂ -bpy	88
4	4,4'-di-NO ₂ -bpy	0
5	4,4'-di-Cl-bpy	7
6	3,3'-di-Me-bpy	8
7	5,5'-di-Me-bpy	46
8	6,6'-di-Me-bpy	1

Electron donating
Planar Conformation
favored

Electron donating
Planar Conformation
favored

Active (or led to active) Species

Scheme 1



4 was also observed in reaction mixture (1H NMR).

Turnover Number

Table 1. Maximum Turnover Numbers for Borylation Reactions after 24 h at 100 °C

catalyst	catalyst loading (%)	yield (%)	turnover numbers
(dtbpy)(COE)Ir(Bpin) ₃ (1)	0.0027	39	14 300
[Ir(COE) ₂ Cl] ₂ /dtbpy	0.0023	18	7 900
[Ir(COD)Cl] ₂ /dtbpy	0.0091	94	10 300
[Ir(COD)Cl] ₂ /dtbpy	0.0030	75	24 800
[Ir(COD)Cl] ₂ /dtbpy	0.0030	72	23 800 ^a
[Ir(COD)(OMe)] ₂ /dtbpy	0.0091	100	10 900
[Ir(COD)(OMe)] ₂ /dtbpy	0.0030	49	16 000

^a Sample contained 25 μL of pinacolborane to assist in catalyst initiation.

Regioselectivity & Substrate Scope

Smith III, M. R. et al. *J. Am. Chem. Soc.* 2005, 127, 10539.

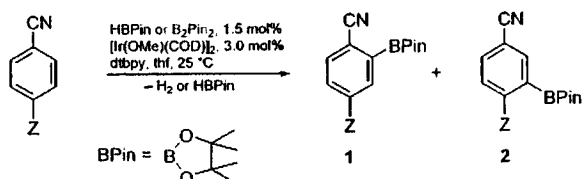


Table 1. Regioselectivities of 4-substituted Benzonitrile Borylations^a

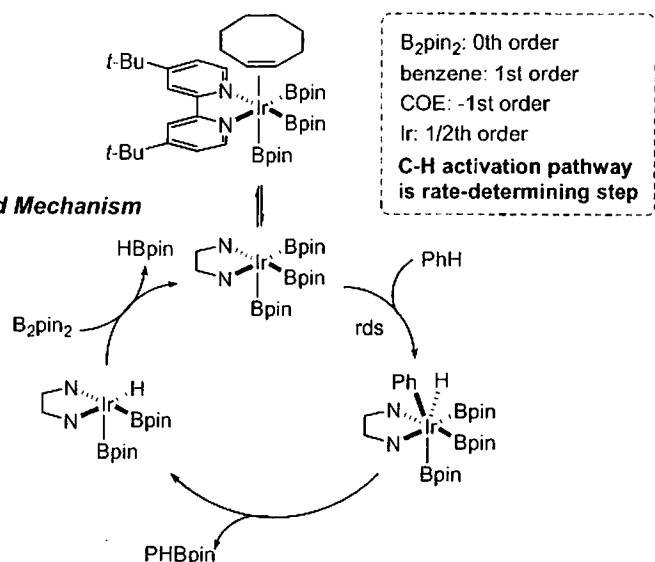
entry	Z	borane (equiv)	time (h)	% yield ^b	%1:2 ^c
1	F	HBPin (0.25)	8	71	11:89 (8:92)
2	Cl	HBPin (0.25)	36	76	80:20 (81:19)
3	Br	HBPin (0.25)	48	73	95:5 (97:3)
4	I	B ₂ Pin ₂ (1.0)	40	70	>99:1 (>99:1)
5 ^d	CH ₃	HBPin (0.25)	72	64	94:6 (92:8)
6	OMe	HBPin (0.25)	24	65	67:33 (67:33) ^e
7 ^f	SMe	B ₂ Pin ₂ (0.25)	18	55	90:10 (87:13) ^e
8 ^d	NMe ₂	B ₂ Pin ₂ (1.0)	72	58	>99:1 (>99:1)
9	CO ₂ Me	B ₂ Pin ₂ (0.8)	48	65	>99:1 (>99:1)
10 ^g	NHAc	B ₂ Pin ₂ (1.6)	18	62	>99:1 (>99:1)
11 ^h	CF ₃	HBPin (1.1)	24	68	>99:1 (>99:1)

^a Unless otherwise noted, all reactions were run in thf solution at 25 °C with [Ir] = 3 mol %. ^b Yields are for isolated products based on the limiting reagent. ^c The major isomer was assigned by NMR, and ratios were determined from crude reaction mixtures by GC integration. Isomer ratios for isolated products are in parentheses. ^d [Ir] = 6 mol %. ^e Isomer ratio was determined from NMR integration. ^f Reaction run at 80 °C. ^g [Ir] = 8 mol %. ^h Reaction run in *n*-hexane.

Steric order



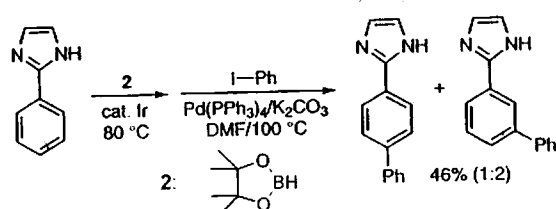
Proposed Mechanism



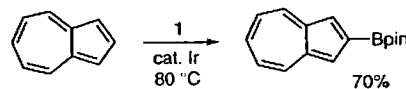
Hartwig, J. F. et al. *J. Am. Chem. Soc.* 2005, 127, 14263.

Theoretical Study: Sakaki, S. et al. *J. Am. Chem. Soc.* 2003, 125, 16114.

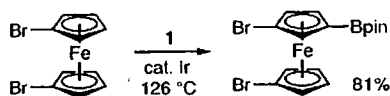
Sames, D. et al. *J. Am. Chem. Soc.* 2003, 125, 10580.



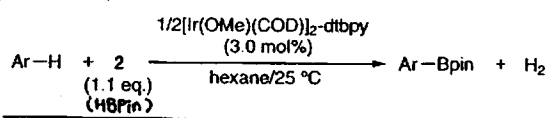
Sugihara, Y. et al. *Eur. J. Org. Chem.* 2003, 3663.



Datta, A. et al. *Chem. Commun.* 2004, 1508.



Ishiyama, T.; Miyaura, N. *Chem. Comm.* 2003, 2924.



product	yield (%)
	73 (24 h)
	67 (8 h)
	70 (24 h)
	74 (2 h)
	73 (8 h)
	22 (24 h)
	95 (0.5 h)
	99 (2 h)
	75 (2 h)

Transformaion of Boronates

Hatwig, J. F. et al. *J. Am. Chem. Soc.* 2004, 126, 15334.

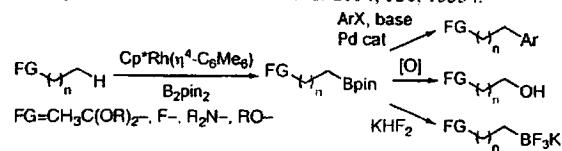
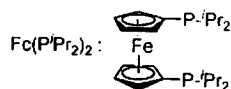


Table 2. Tandem Functionalization of Methyl Groups

Entry	Reactant	Product	Cond. ^a	Yield(%)
1			A,B	87 ^b
2			A,C	29 ^b
3			A,B	64 ^b
4			A,D	68 ^c
5			A,E	86 ^c
6			A,E	69 ^{c,d}

^a Conditions: (A) B₂pin₂, 5 mol % 1, neat, 150 °C; (B) 1-bromo-4-*tert*-butylbenzene (2 equiv), CsOH (4 equiv), Pd(dba)₂ (10 mol %), and Fc(P^{*i*}Pr)₂ (10 mol %) in toluene, 100 °C; (C) Same as B, but CsF and DMF used in place of CsOH and toluene; (D) H₂O₂ and KOH in THF and H₂O; (E) KHF₂ in MeOH. ^b Yields calculated by GC. ^c Yields calculated by ¹H NMR. ^d Yield based on the reaction of B₂pin₂ with R-H to form R-Bpin and H₂.

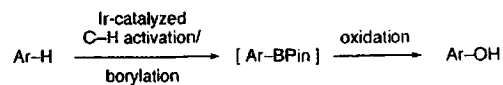


J. Am. Chem. Soc. 2003, 125, 7792.

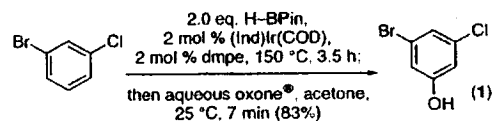
C-H Activation/Borylation/Oxidation: A One-Pot Unified Route To Meta-Substituted Phenols Bearing Ortho-/Para-Directing Groups

Robert E. Maleczka, Jr.,* Feng Shi, Daniel Holmes, and Milton R. Smith, III*

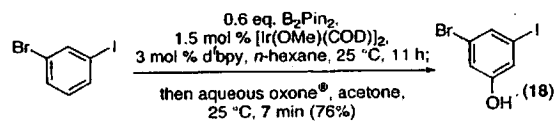
Scheme 1



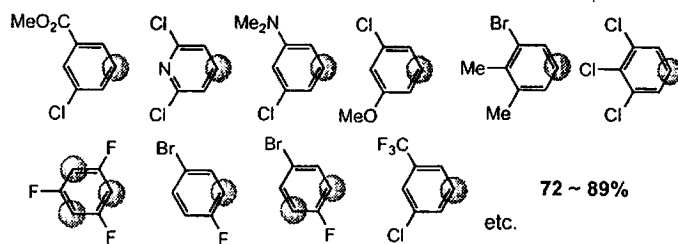
Scheme 2



Scheme 3



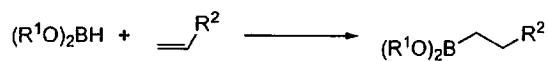
Ind: Indene



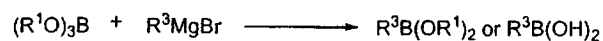
HBPin (1.5 ~ 2.5 eq, tri-oxi: 5.0 eq)

General Method for Boronate Synthesis

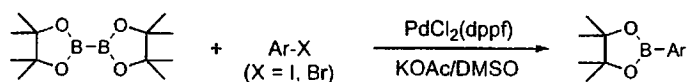
Hydroboration



Organolithium or Grignard Reagent



Cross-Coupling (Miyaura et al. *J. Org. Chem.* 1995, 60, 7508. etc.)



などなど