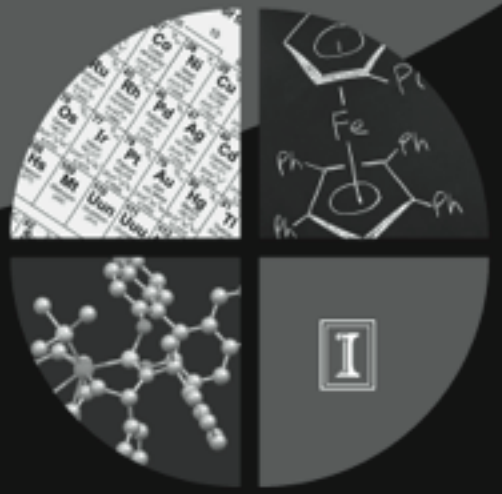
Catalytic Modification of Arenes

John F. Hartwig

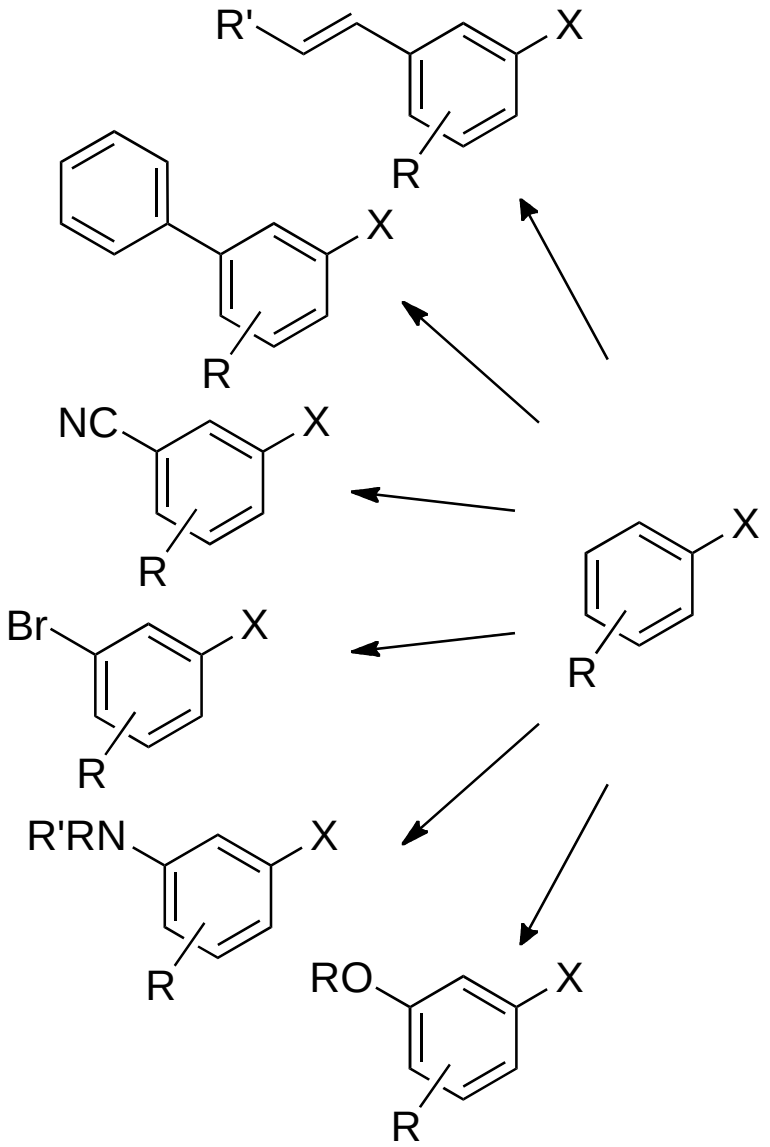
Department of Chemistry

University of California, Berkeley

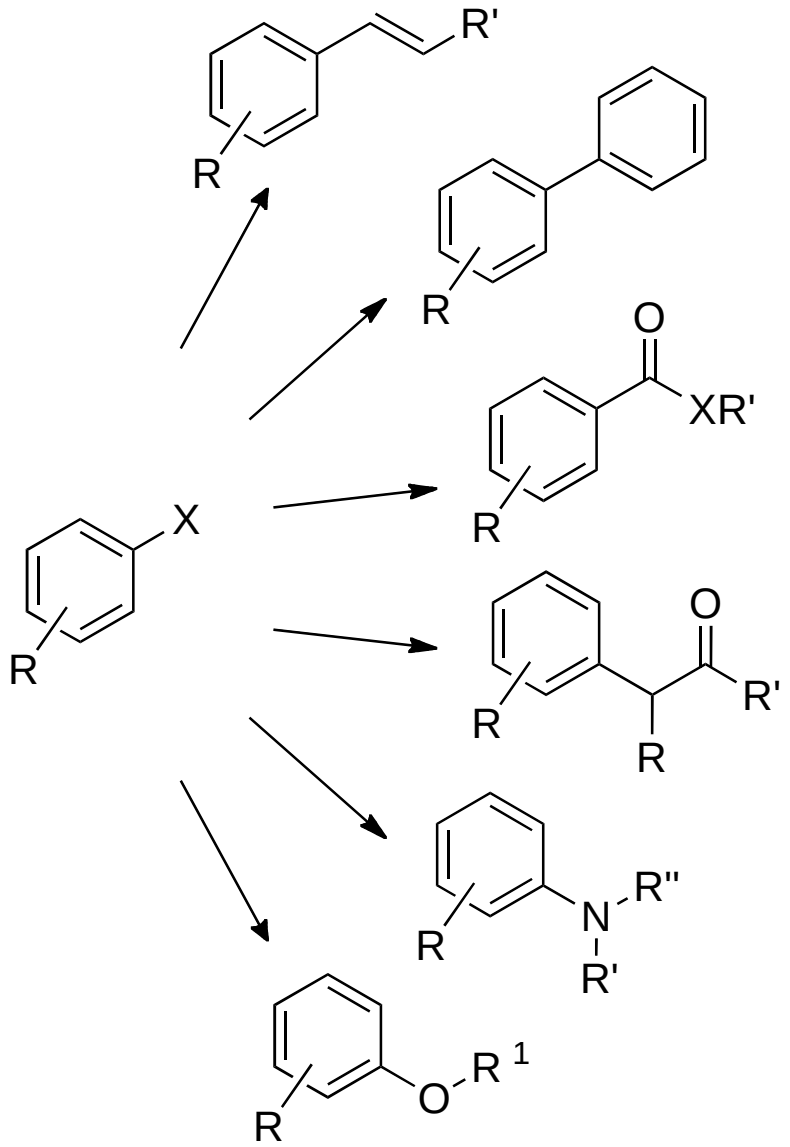


Approaches to Catalytic Modification of Arenes

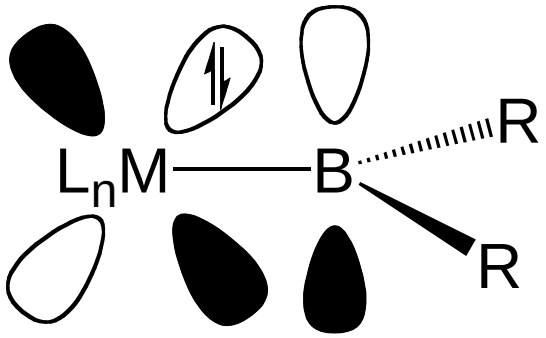
By C-H Bond Functionalization?



By Cross-Coupling Reactions

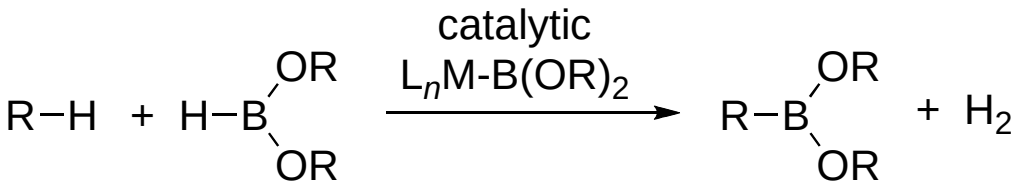


Transition Metal Boryl Complexes

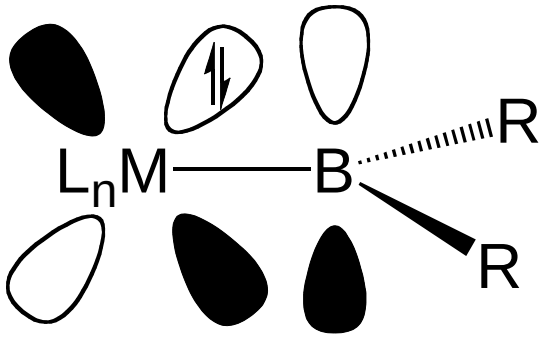


Potential Properties:
- Lewis Acidic at BR_2
- M-B pi-bonding
- Strong σ-Donation from BR_2

These properties lead to selective functionalization of arenes and alkanes:



Transition Metal Boryl Complexes

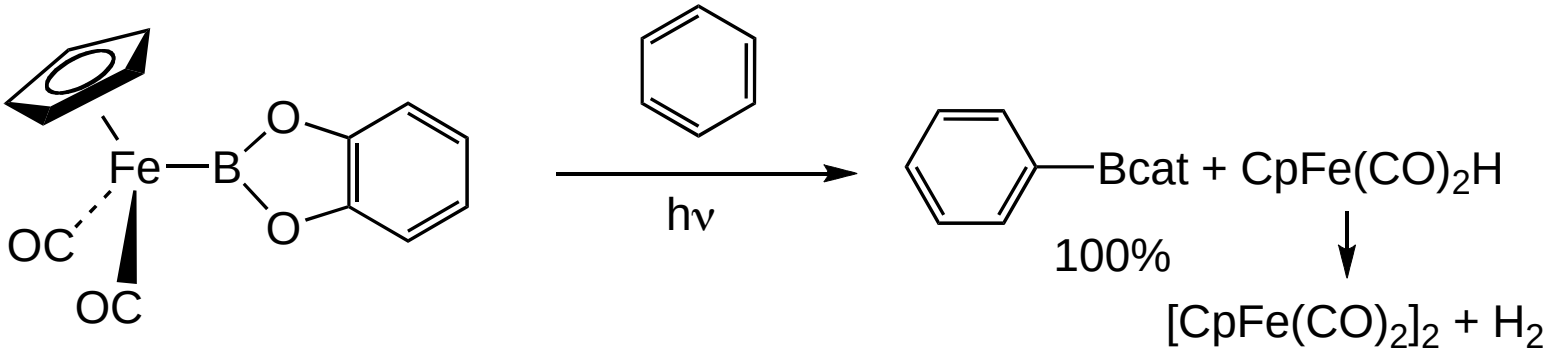


Potential Properties:
- Lewis Acidic at BR_2
- M-B pi-bonding
- Strong σ-Donation from BR_2

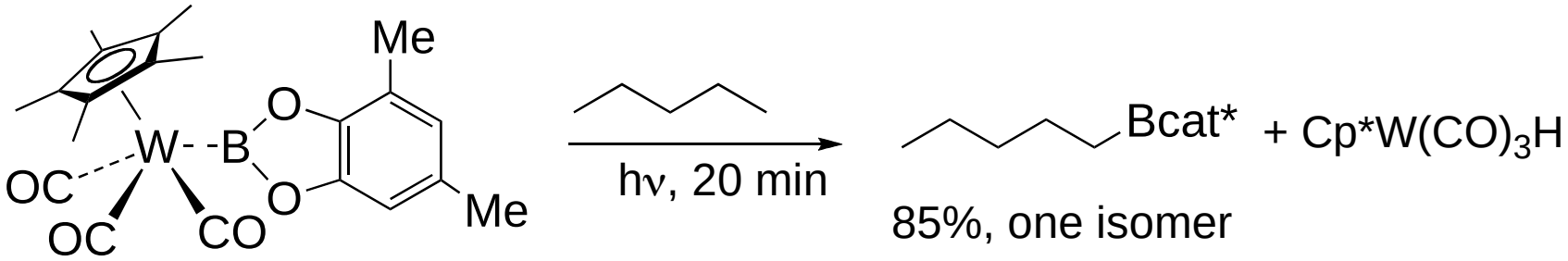
Topics

1. *Discovery of C-H borylation of aliphatic C-H Bonds*
2. *A platform for practical aromatic C-H bond functionalization*
3. *Use of the mechanistic data to develop new functionalizations*
4. *Some new C-C coupling reactions*

Initial Observations of C-H Bond Functionalization with Metal-Boryl Complexes



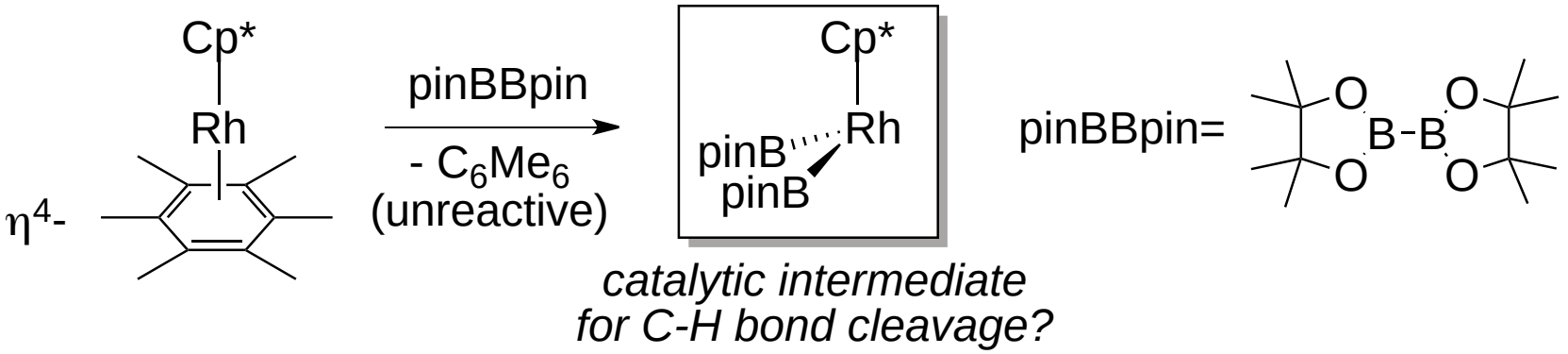
Hartwig, Waltz, He, Muhoro *J. Am. Chem. Soc.* **1995**, *117*, 11357.

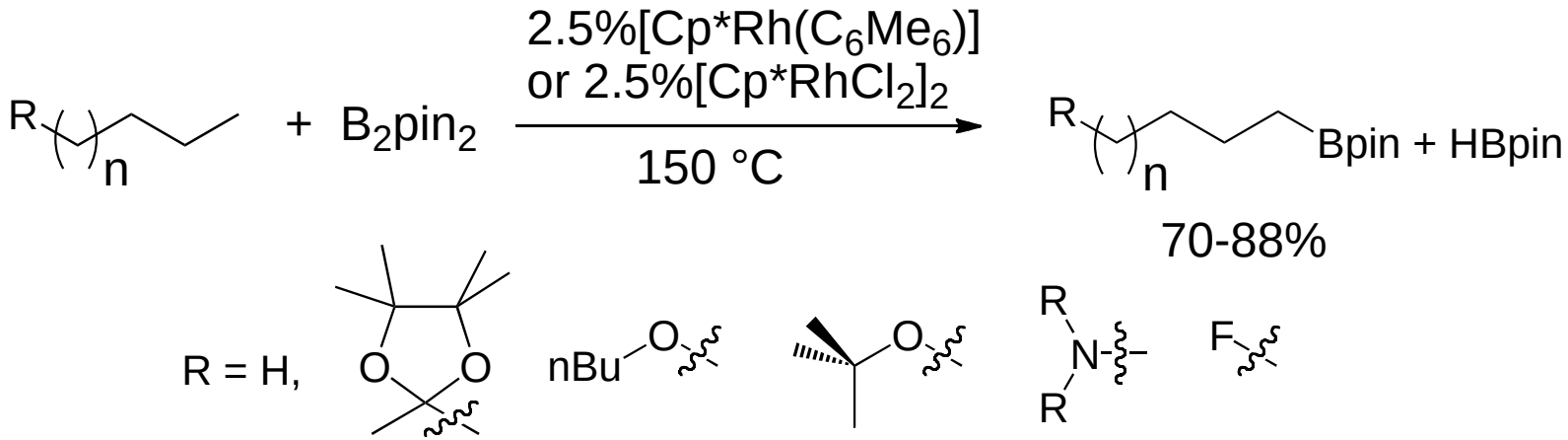


Waltz, K.M.; Hartwig, J.F. *Science*, **1997**, *227*, 211.

For formation of two isomers of tolylboronate ester as trace side product from borylation of toluene solvent when forming [Ir(arene)(Bcat)$_3$], see Nguyen, P.; Blom, H. P.; Westcott, S. A.; Taylor, N. J.; Marder, T. B. *J. Am. Chem. Soc.* **1993**, *115*, 9329.

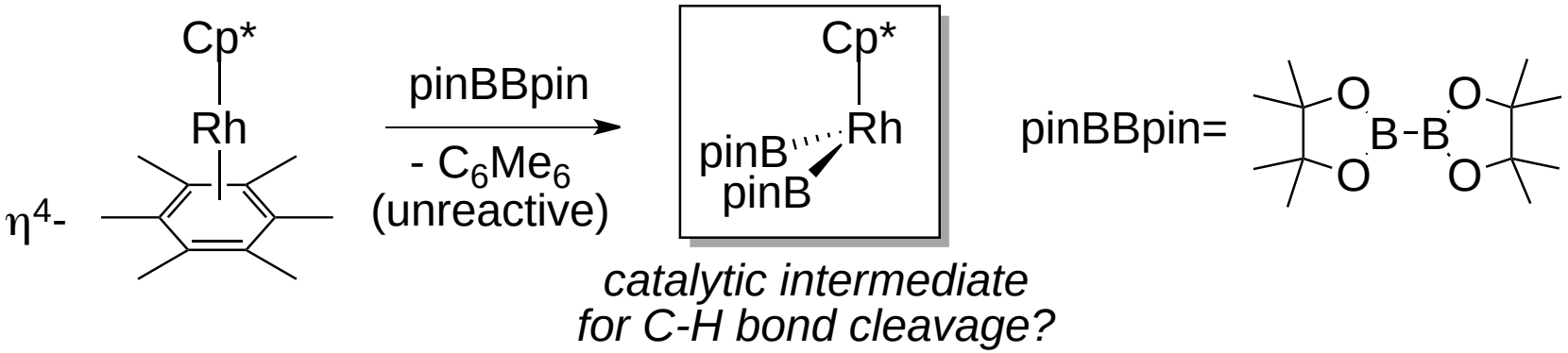
Catalytic Functionalization of Primary C-H Bonds



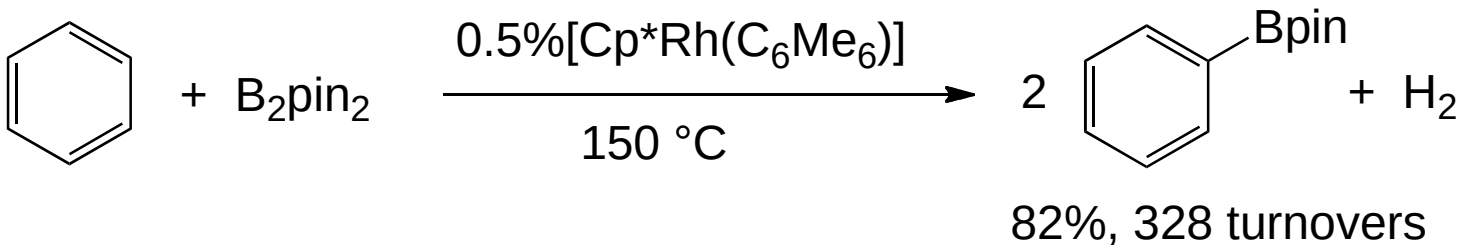


Chen, Schlecht, Semple, Hartwig *Science* **2000**, *287*, 1995-8.
Lawrence, Takahashi, Bae, Hartwig *J. Am. Chem. Soc,* **2004**, *126*, 15334-15335.
For an the borylation of benzene catalyzed by Cp*Ir(PMe_3)(Ph)(H) with three turnovers see, Iverson, C. N.; Smith, M. R., III *J. Am. Chem. Soc.* **1999**, *121*, 7696.

Catalytic Functionalization of Arene C-H Bonds



catalytic intermediate for C-H bond cleavage?



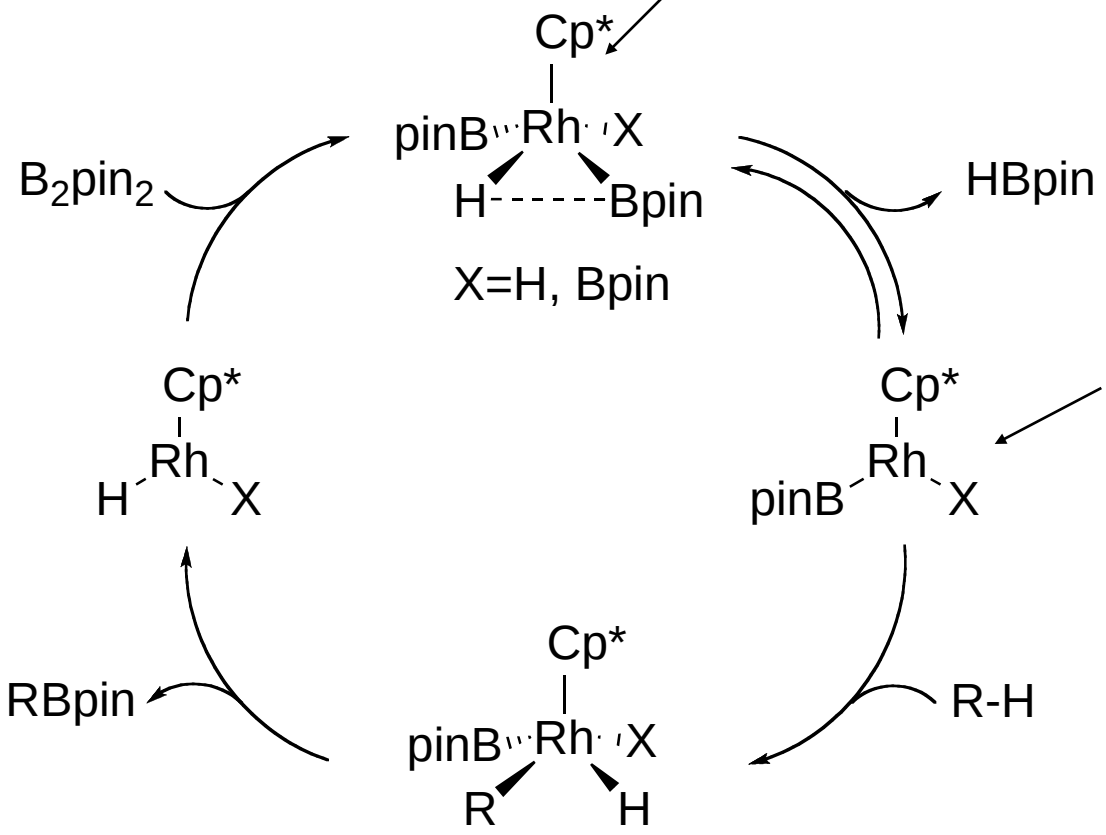
82%, 328 turnovers

Chen, Schlecht, Semple, Hartwig *Science* **2000**, *287*, 1995-8.
Lawrence, Takahashi, Bae, Hartwig *J. Am. Chem. Soc,* **2004**, *126*, 15334-15335.
For an the borylation of benzene catalyzed by Cp*Ir(PMe$_3$)(Ph)(H) with three turnovers see, Iverson, C. N.; Smith, M. R., III *J. Am. Chem. Soc.* **1999**, *121*, 7696.

Mechanism of the Rh-Catalyzed Alkane Functionalization

•Isolated and observed in the catalytic system

•Kinetically and chemically competent

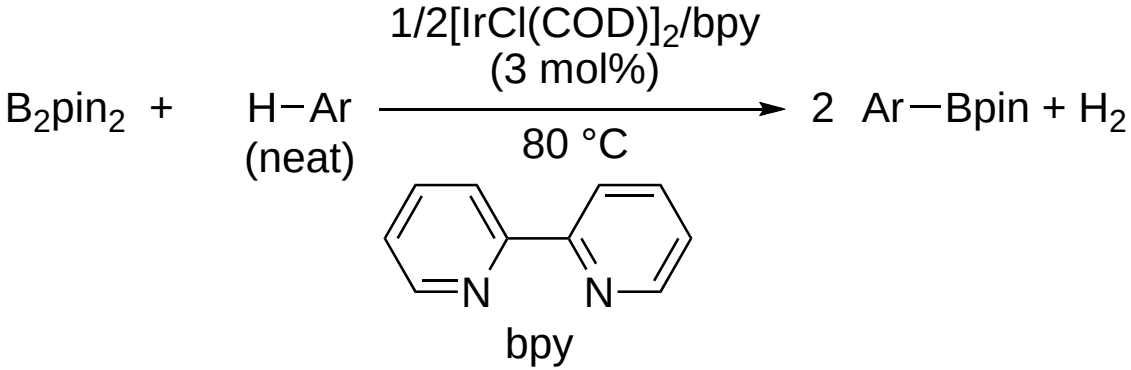


Evidence for this catalytic cycle

Hartwig, Cook, Hanke, Innorvito, Fan, Webster, Hall *J. Am. Chem. Soc.* 2005, *127*, 2538-2552.

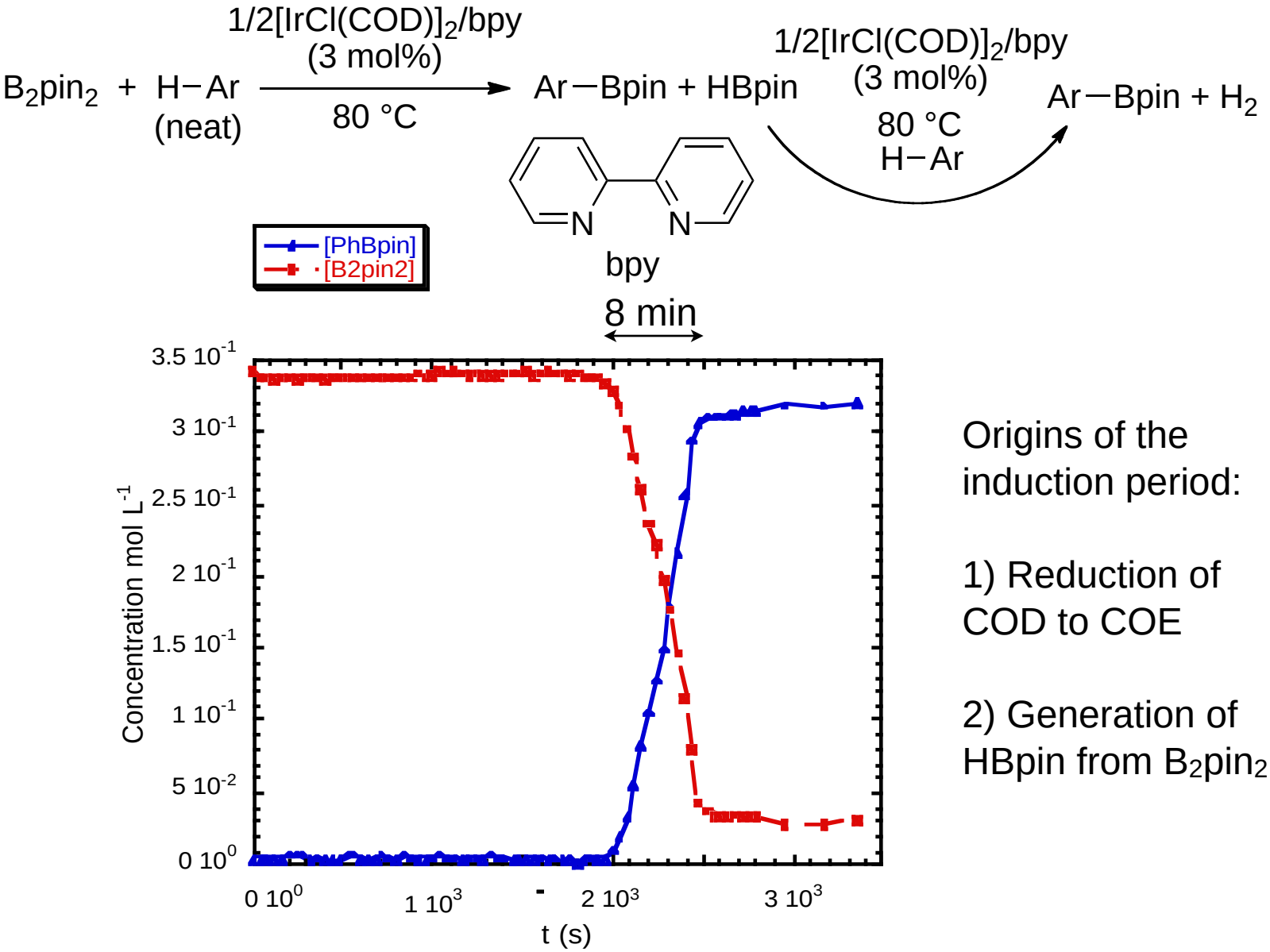
How is the C-H bond cleaved and what is the origin of high terminal regioselectivity?

Practical Arene Borylation Catalysts



Ishiyama, Takagi, Ishida, Miyaura, Anastasi, Hartwig *JACS* **2002**, *124*, 390.

Practical Arene Borylation Catalysts



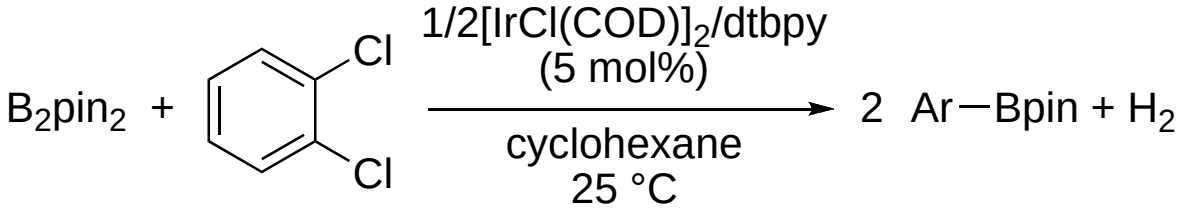
Origins of the induction period:

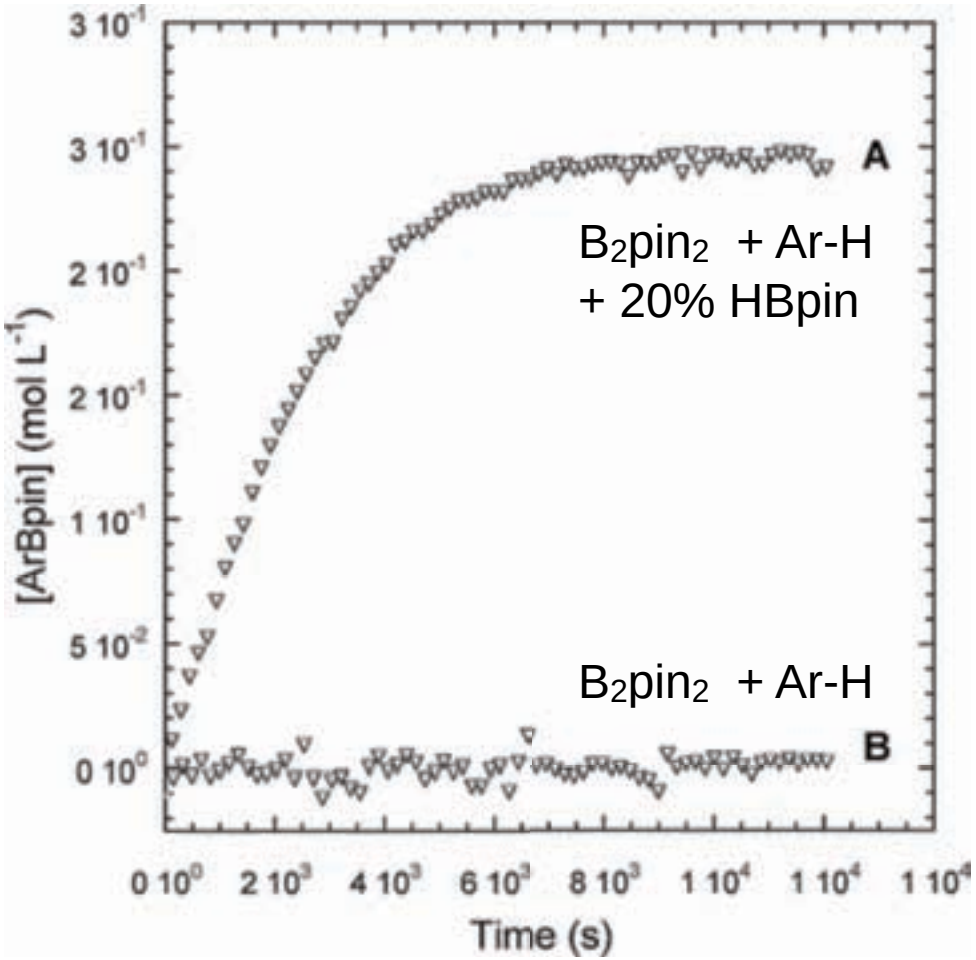
1) Reduction of COD to COE

2) Generation of HBpin from B_2pin_2

Ishiyama, Takagi, Ishida, Miyaura, Anastasi, Hartwig *JACS* **2002**, *124*, 390.

Practical Arene Borylation Catalysts





With 0.003 mol % Ir
24,800 turnovers

Origins of the induction period:

1) Reduction of COD to COE

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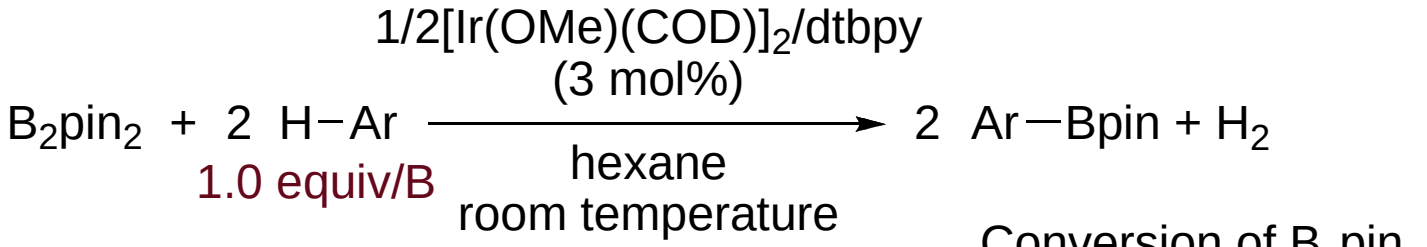
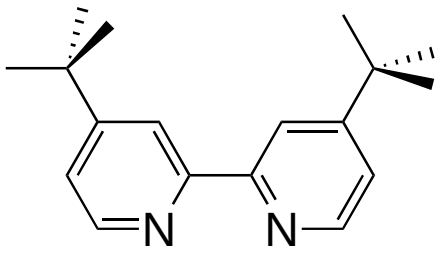
Ishiyama, Takagi, Ishida, Miyaura, Anastasi, Hartwig *JACS* **2002**, *124*, 390.

Highly Active Arene Borylation Catalysts



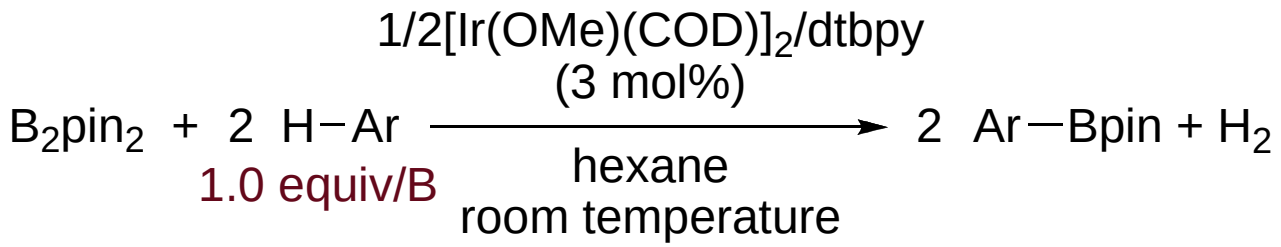
Conversion of B_2pin_2 and HBpin

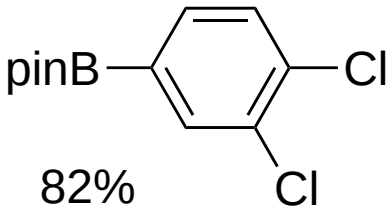


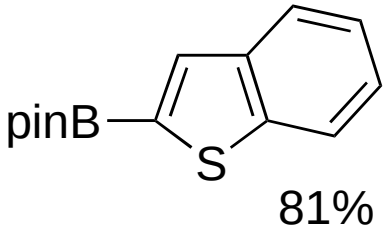
dtbpy

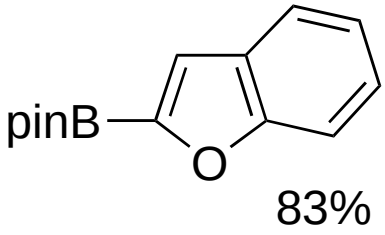
Ishiyama, Takagi, Ishida, Miyaura, Anastasi, Hartwig *JACS* **2002***, 124*, 390.
Ishiyama, Takagi, Hartwig, Miyaura *Angew. Chem. Int. Ed.* **2002**, 41 , 3056.
Boller, Murphy, Hapke, Ishiyama, Miyaura, Hartwig, *JACS* **2005**, *127,* 14263.
see also with Ir-bisphosphine complexes as catalyst: Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. *Science* **2002**, *295*, 305-308.

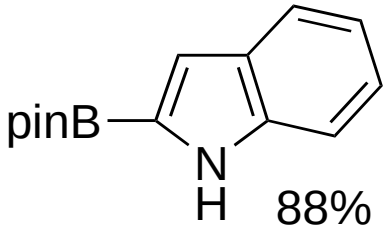
Highly Active Arene Borylation Catalysts

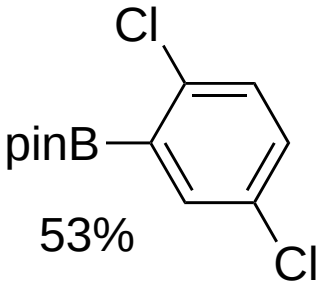


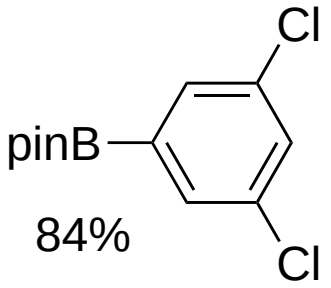


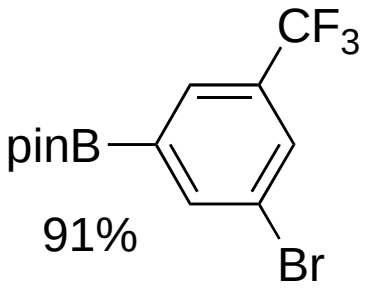


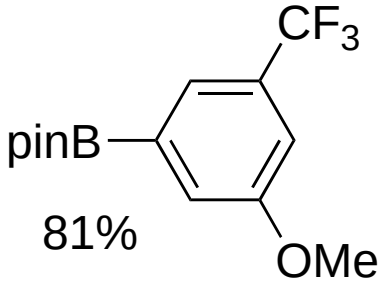


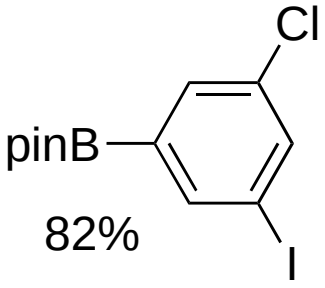


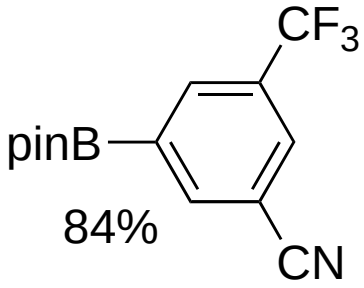


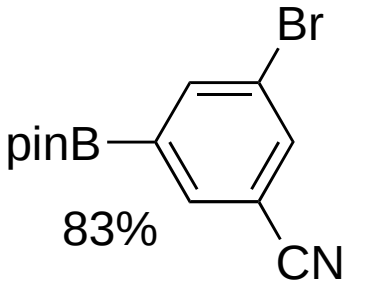


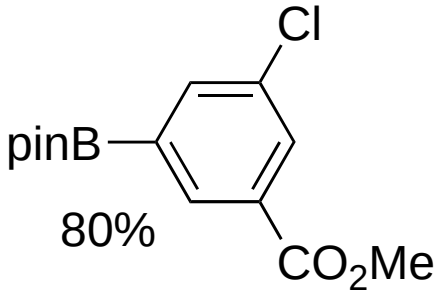






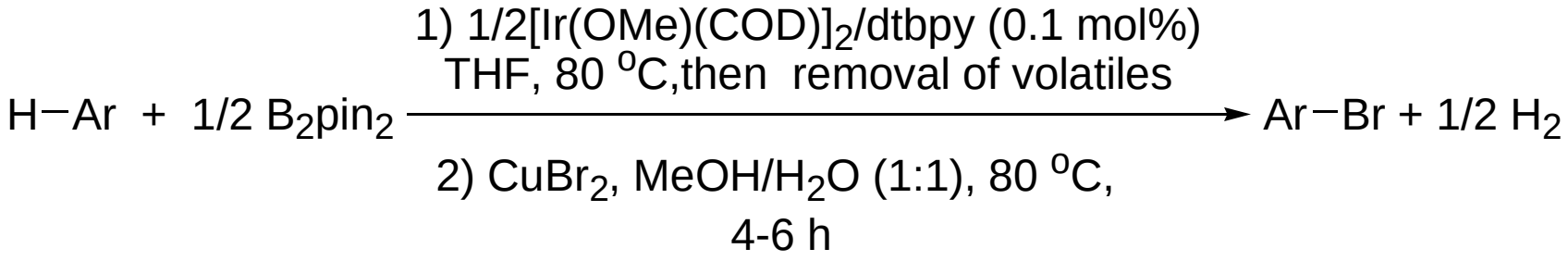


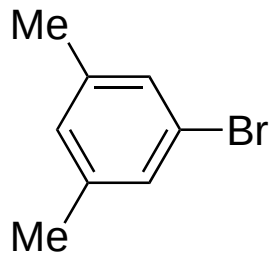




Ishiyama, Takagi, Hartwig, Miyaura *Angew. Chem. Int. Ed.* **2002**, 41 , 3056.

Meta-Halogenation of Arenes





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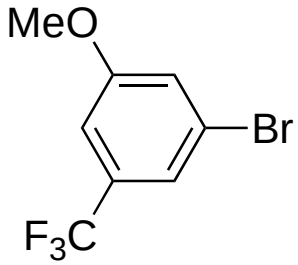

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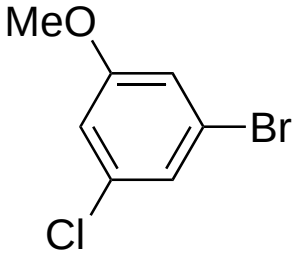

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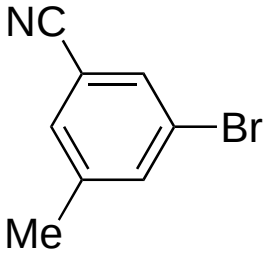

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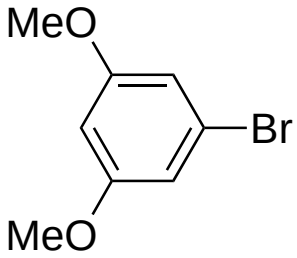

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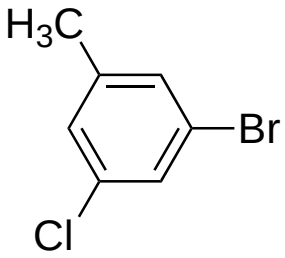

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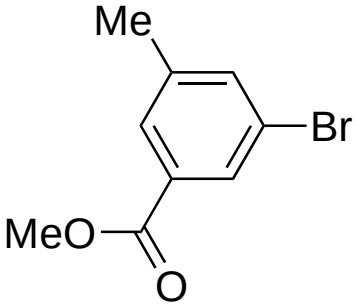

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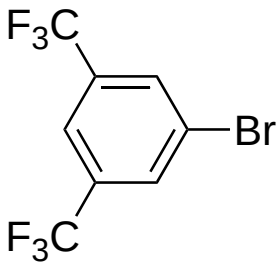

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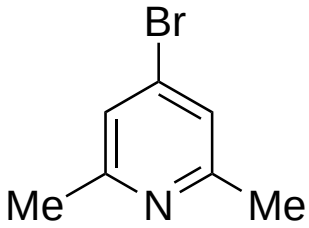

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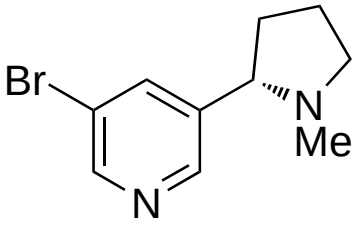
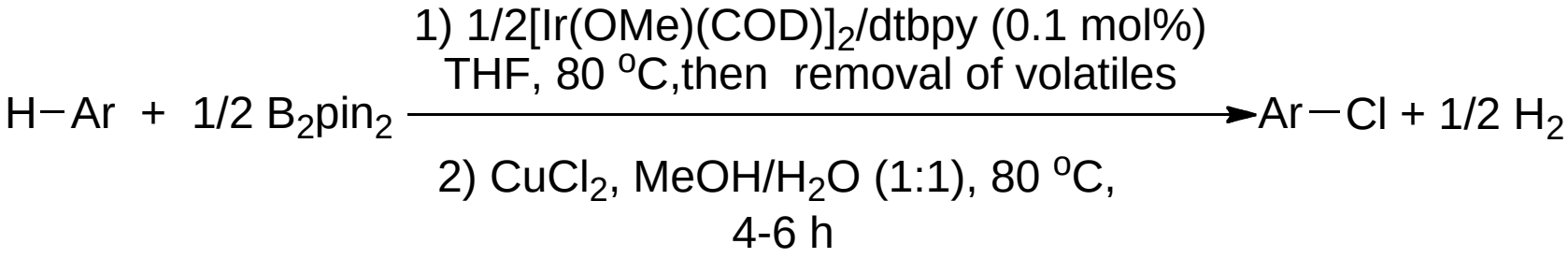
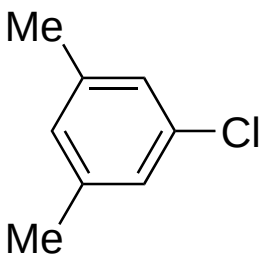


6 mol% Ir
61%

Murphy, J.M.; Liao, X, Hartwig, J.F. *J. Am. Chem. Soc.* **2007**, *129*, 15434-15435.

Meta-Halogenation of Arenes





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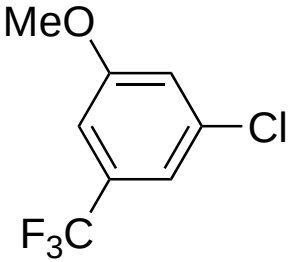

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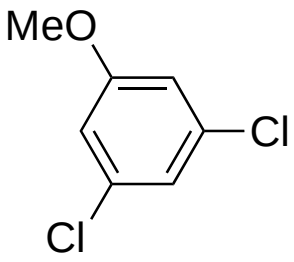

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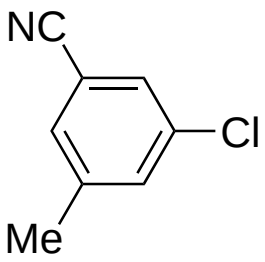

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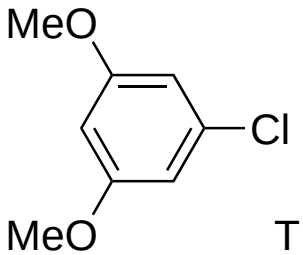

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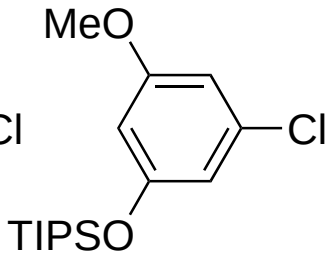

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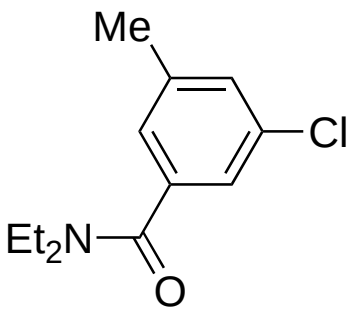

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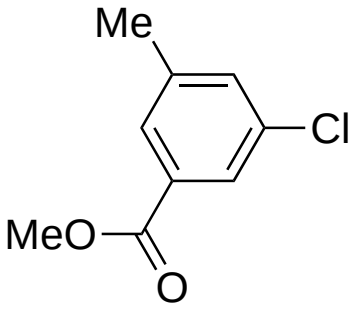

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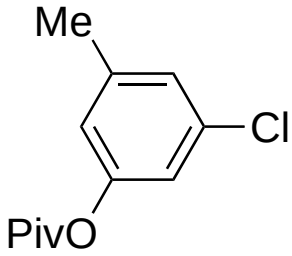
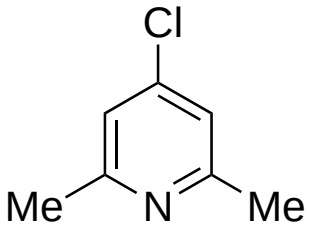


81%



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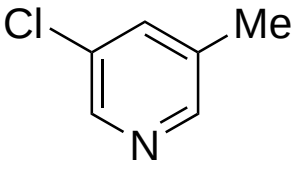
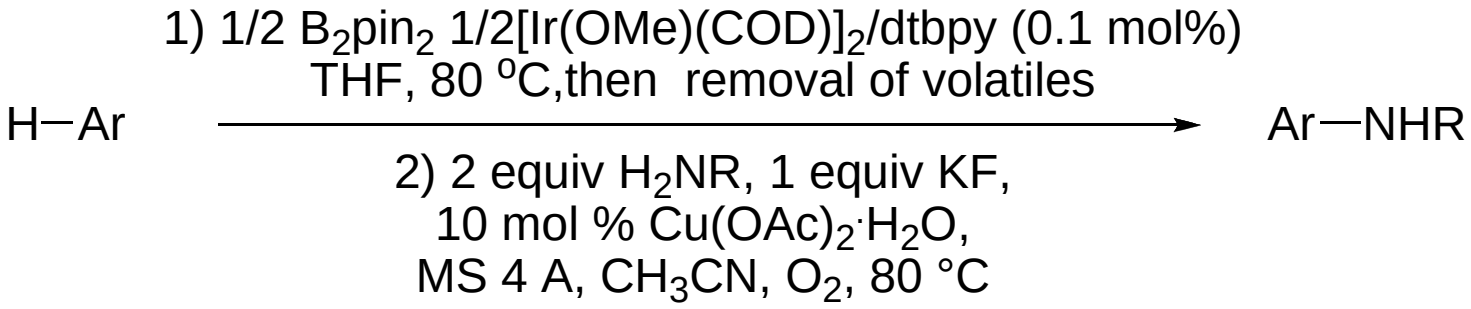
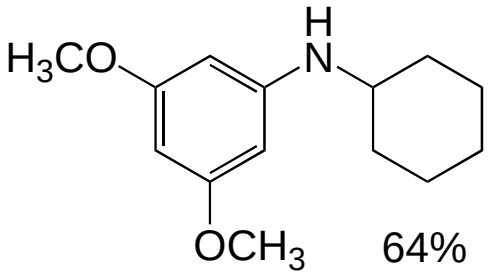


6 mol% Ir
46%

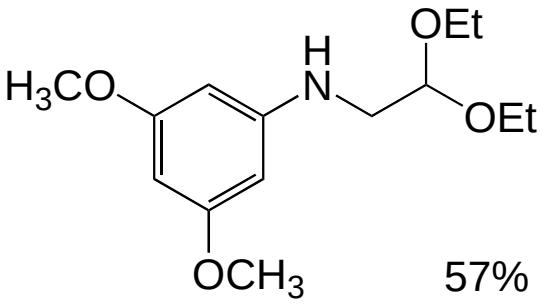
Murphy, J.M.; Liao, X, Hartwig, J.F. *J. Am. Chem. Soc.* **2007**, *129*, 15434-15435.

Meta-Amination of Arenes

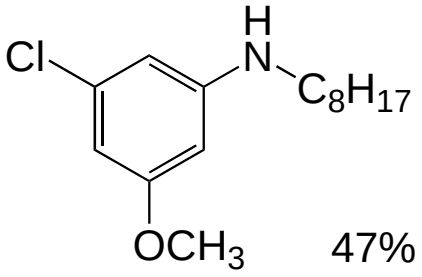




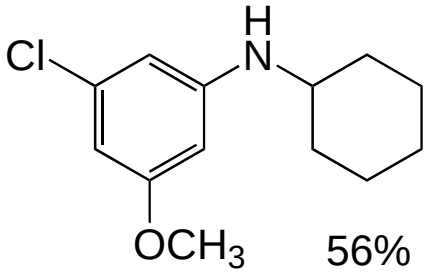
64%



57%



47%



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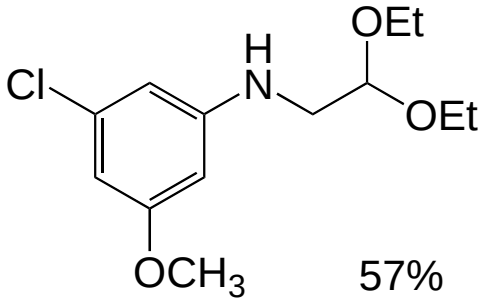

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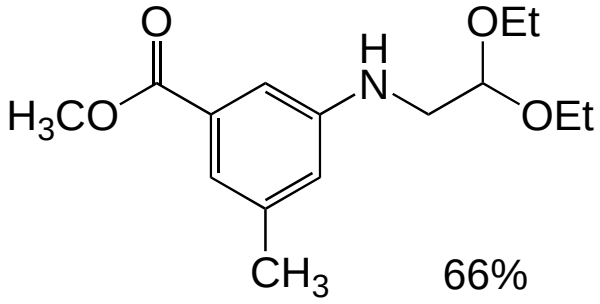
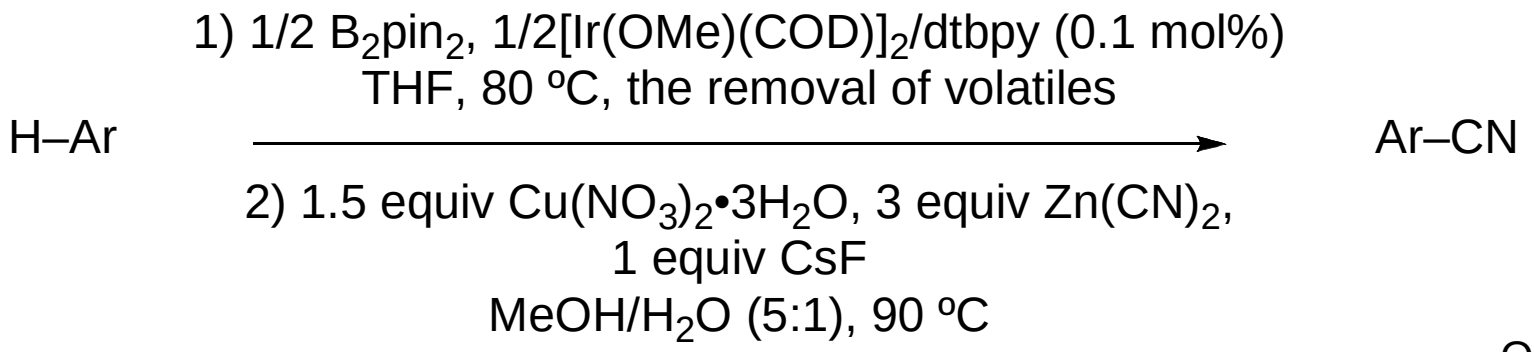
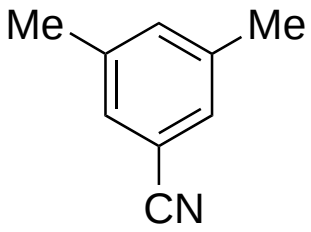


66%

Tzschucke, C. C.; Murphy, J. M.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 761-764

Meta-Cyanation of Arenes





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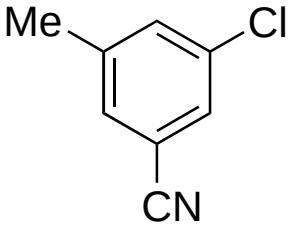

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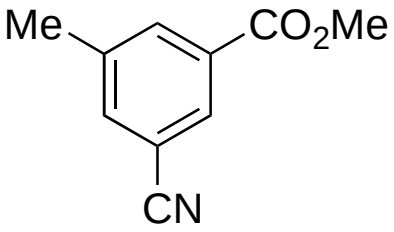

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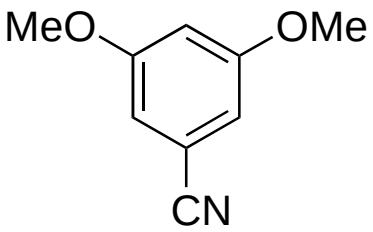

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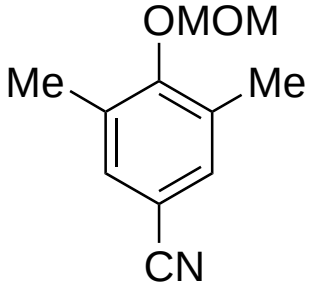

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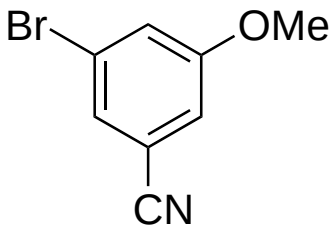
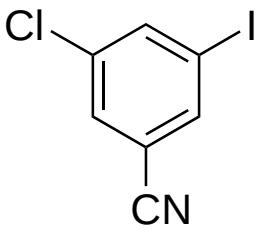
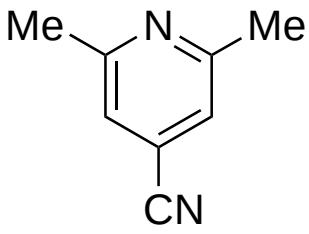


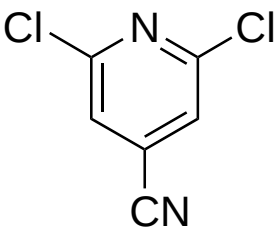
58%



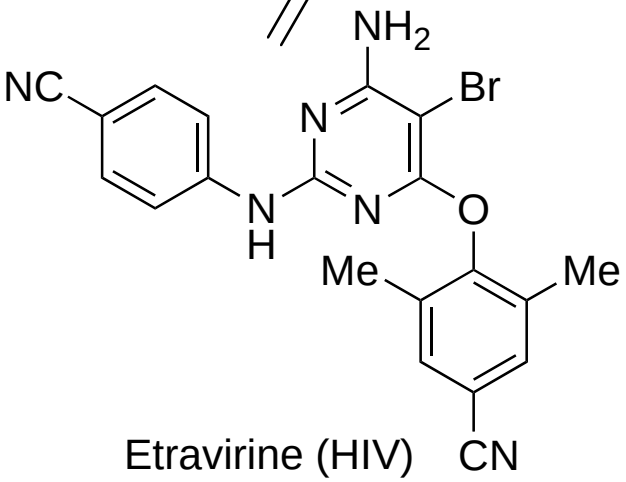
57%



46%



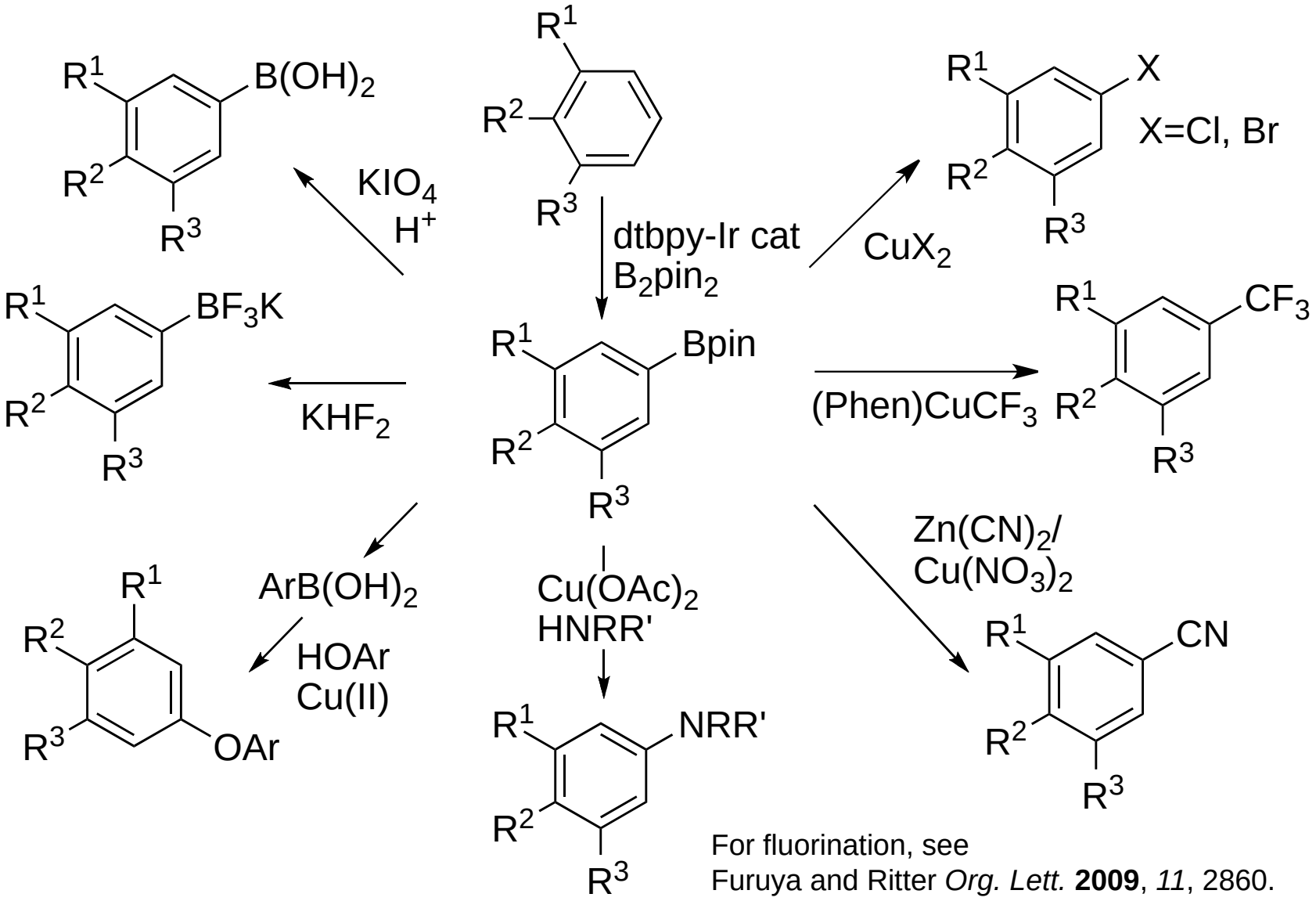
58%



Etravirine (HIV)

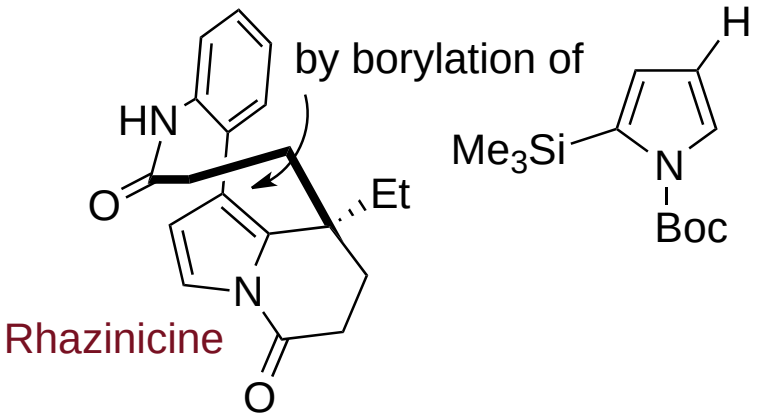
Liskey, C.W.; Liao, X.; Hartwig, J.F.
J. Am. Chem. Soc. **2010**, *132*, 11389-11391

A General meta-Functionalization of 1,3, and 1,2,3-Substituted Arenes



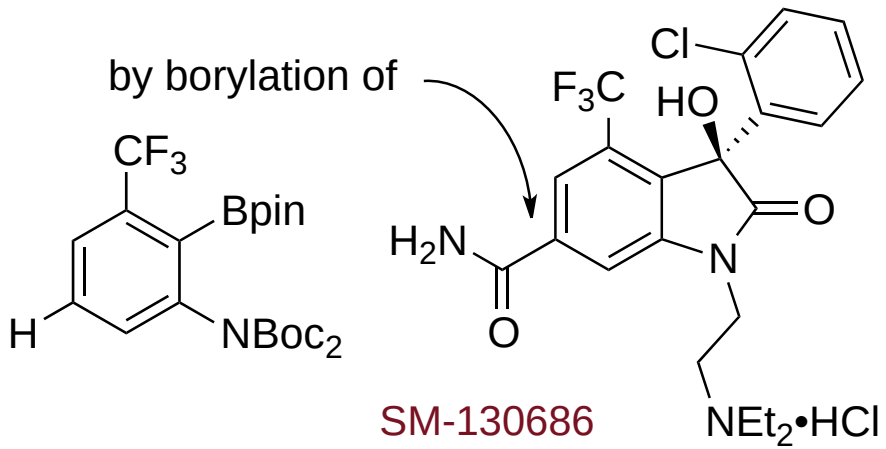
For fluorination, see
Furuya and Ritter *Org. Lett.* **2009**, *11*, 2860.

[Ir(COD)X]/dtbpy Catalyst in Total Synthesis



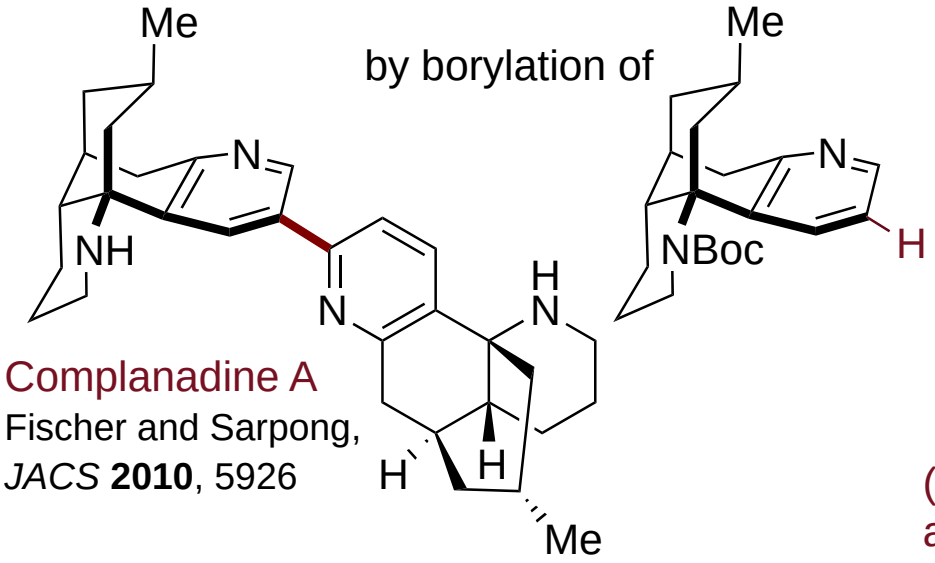
Rhazinicine

Beck, E. M.; Hatley, R.; Gaunt, M. J.
Angew. Chem. Int. Ed. **2008**, *47*, 3004-3007.



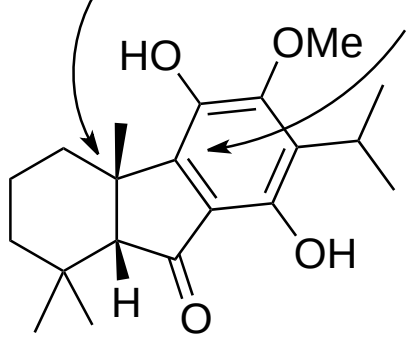
SM-130686

Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M.
J. Am. Chem. Soc. **2009**, *131*, 6946-7.



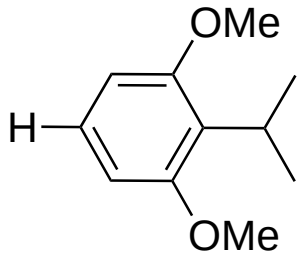
Complanadine A
Fischer and Sarpong,
JACS **2010**, 5926

Benzylic stereocenter set by asymmetric α-arylation



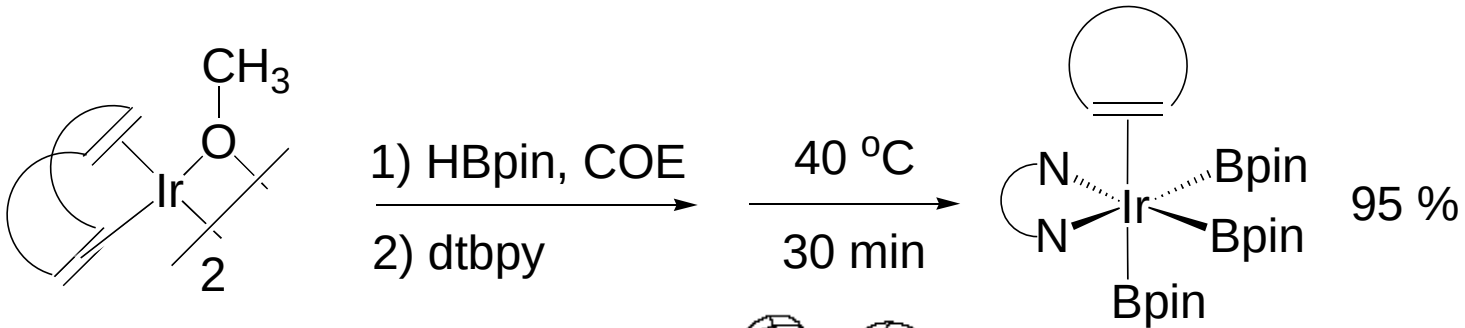
(-)-Taiwaniaquinol B
and Taiwaniaquinone D

by borylation/
halogenation of



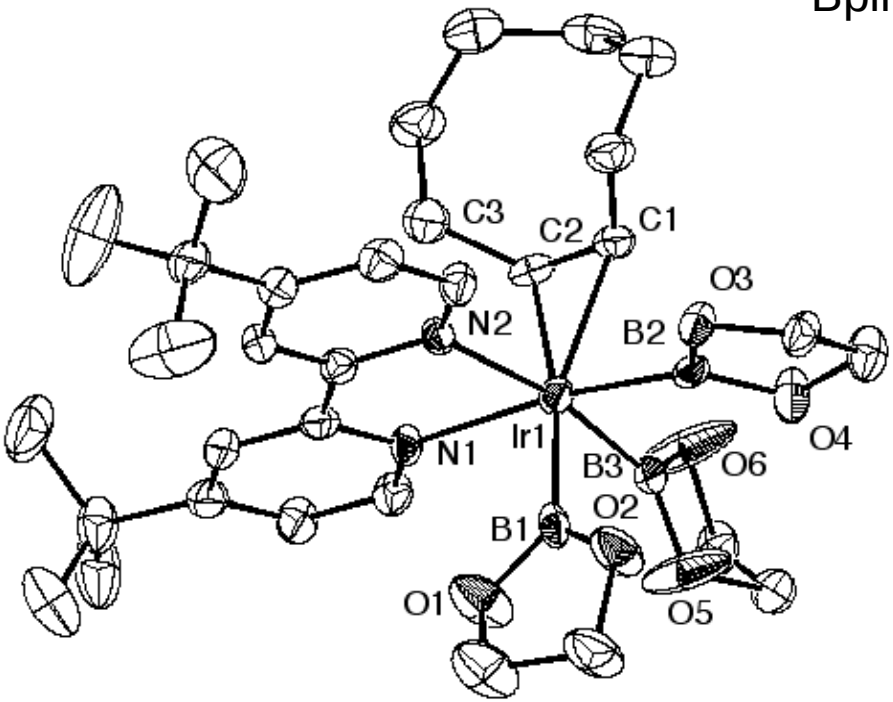
Liao, X.; Stanley, L. M.;
Hartwig, J. F. *JACS*
2011, *133*, 2088.

Intermediate in the Functionalization of Arenes by Bpy-Ir



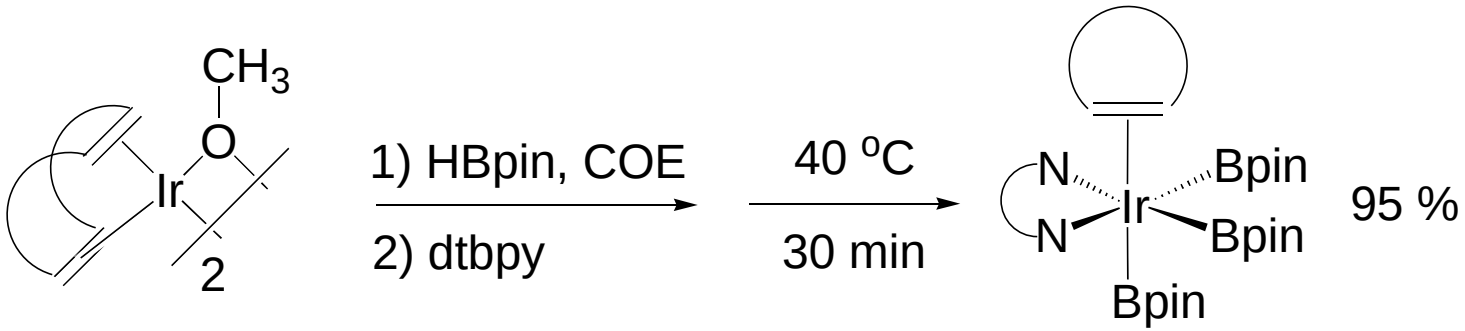
Ishiyama, Takagi, Ishida, Miyaura, Anastasi, Hartwig, *JACS* **2002**, *124*, 390.

Boller, Murphy, Hapke, Ishiyama, Miyaura, Hartwig *JACS* **2005**, *127,* 14263



Ir-N1=2.177 Å, Ir-N2=2.221 Å, Ir-B1=2.055 Å Ir-B2=2.057 Å, Ir-B3=2.027 Å, Ir-C1=2.308 Å Ir-C2=2.318 Å

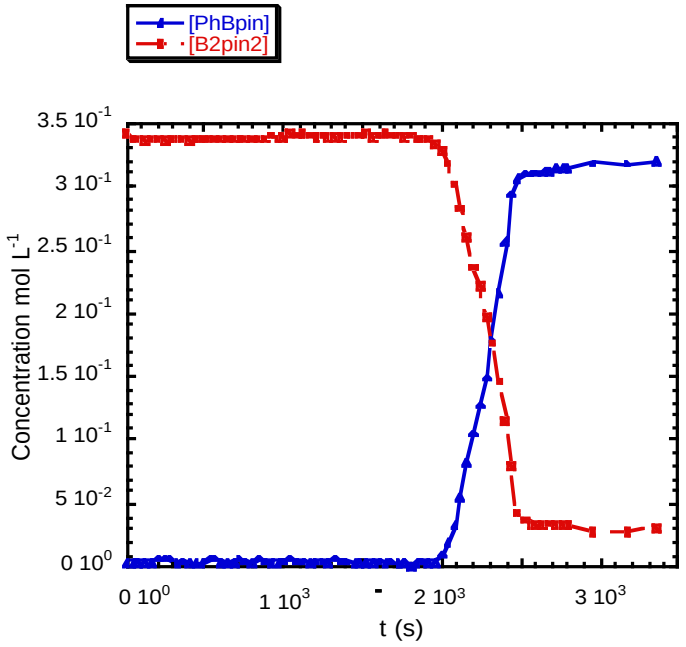
Intermediate in the Functionalization of Arenes by Bpy-Ir



Ishiyama, Takagi, Ishida, Miyaura, Anastasi, Hartwig, *JACS* **2002**, *124*, 390.

Boller, Murphy, Hapke, Ishiyama, Miyaura, Hartwig *JACS* **2005**, *127,* 14263

Recall that HBpin eliminated this induction period:

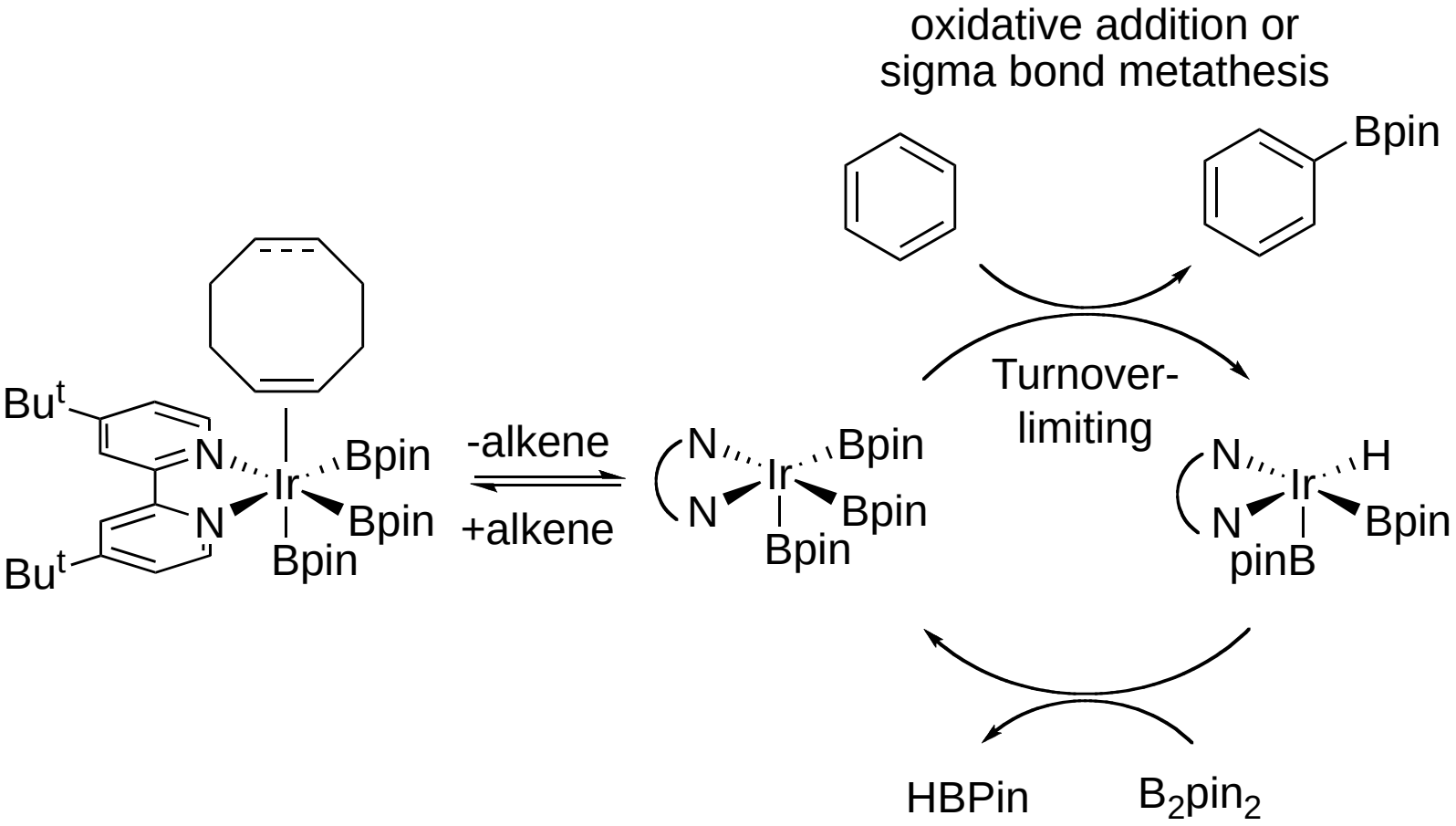


Origins of the induction period:

1) Reduction of COD to COE

2) Generation of HBpin from B_2pin_2

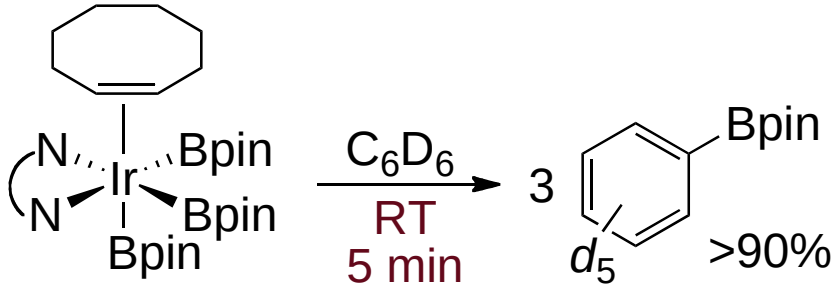
Mechanism for Arene Borylation by Ir(III) Complexes

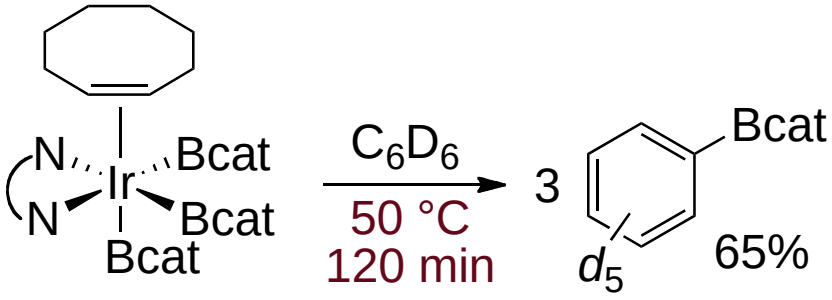


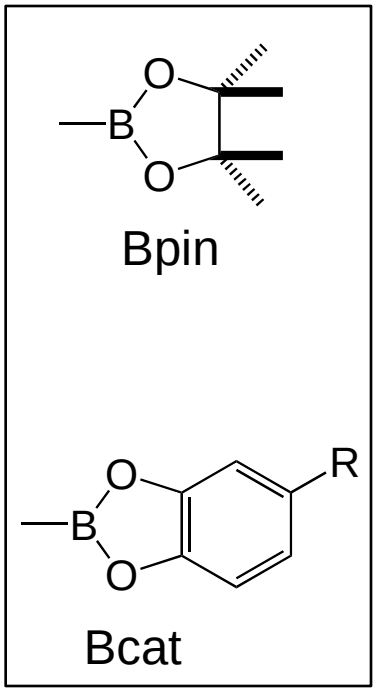
Ishiyama, Takagi, Ishida, Miyaura, Anastasi, Hartwig, *JACS* **2002**, *124*, 390
Boller, Murphy, Hapke, Ishiyama, Miyaura, Hartwig *JACS* **2005**, *127,* 14263.

Electronic Effects on C-H Borylation

Effect of pinacolate or catecholate on the electron density at Ir







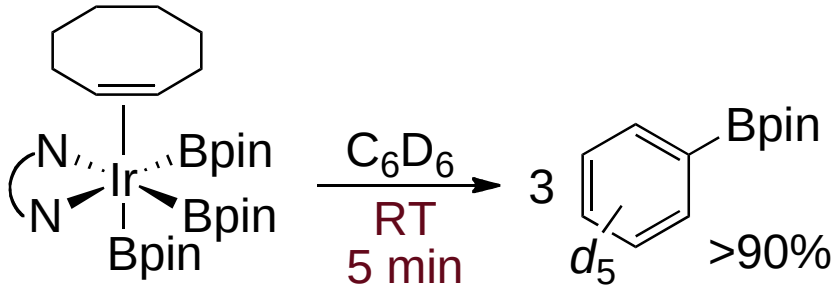
Ishiyama, Takagi, Ishida, Miyaura, Anastasi, Hartwig, *JACS* **2002**, *124*, 390.

Boller, Murphy, Hapke, Ishiyama, Miyaura, Hartwig *JACS* **2005**, *127,* 14263

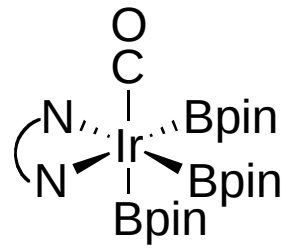
Liskey, C.W.; Wei, C.S.; Pahls, D.R.; Hartwig, J.F. *Chem. Commun.,* **2009**, 5603 web theme issue: 'Selective Catalysis for Organic Synthesis'

Electronic Effects on C-H Borylation

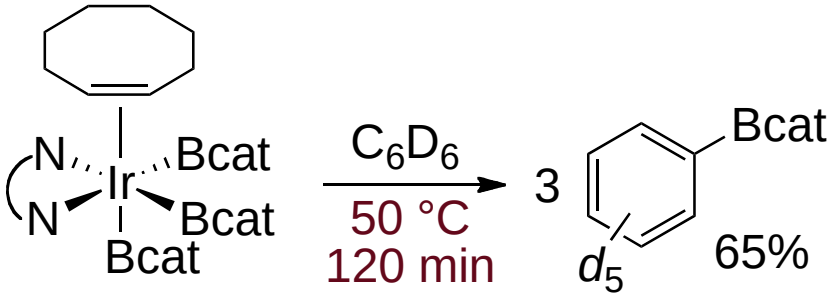
Effect of pinacolate or catecholate on the electron density at Ir



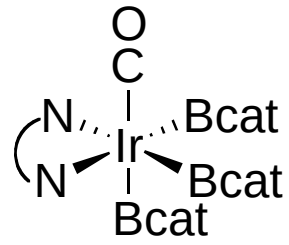
∂_{COE} = 3.92



μ_{CO}=1987 cm^{-1}



∂_{COE} = 4.77



μ_{CO}=2017 cm^{-1}

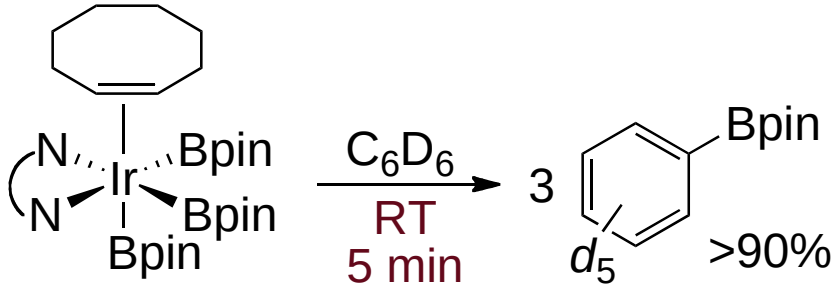
Ishiyama, Takagi, Ishida, Miyaura, Anastasi, Hartwig, *JACS* **2002**, *124*, 390.

Boller, Murphy, Hapke, Ishiyama, Miyaura, Hartwig *JACS* **2005**, *127,* 14263

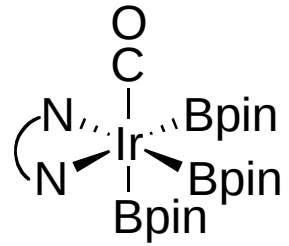
Liskey, C.W.; Wei, C.S.; Pahls, D.R.; Hartwig, J.F. *Chem. Commun.,* **2009**, 5603 web theme issue: 'Selective Catalysis for Organic Synthesis'

Electronic Effects on C-H Borylation

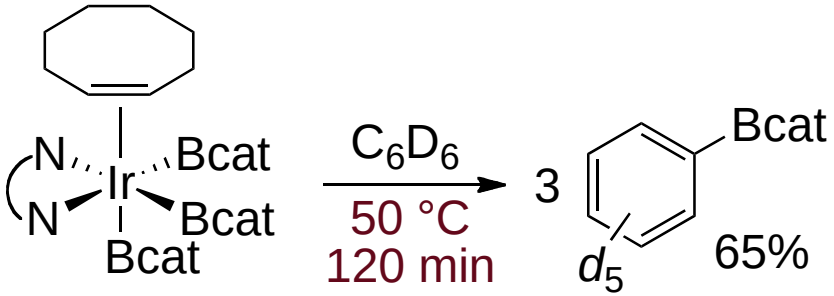
Effect of pinacolate or catecholate on the electron density at Ir



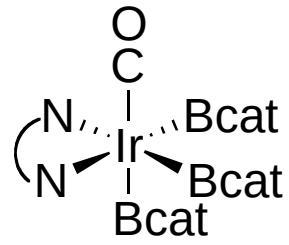
∂_{COE} = 3.92



μ_{CO}=1987 cm^{-1}



∂_{COE} = 4.77



μ_{CO}=2017 cm^{-1}

Therefore, although the C-H cleavage can occur by σ-bond metathesis...

- *This C-H bond cleavage is favored for more electron-rich Ir centers.*
- *Strong σ-donation by the boryl group is important for C-H bond cleavage.*

Developing More Active Catalysts

Electronic properties of ligands used for Ir-catalyzed arene boryation:

ν(CO) Values for $L_2M(CO)_m$ complexes:

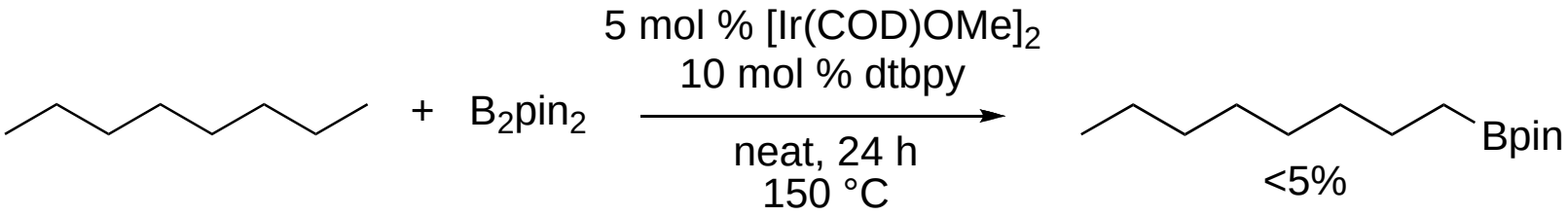
L_2	ν(CO) for $L_2Ni(CO)_2$		reference	for $L_2Mo(CO)_4$
2 PPh_3	2000	1940	*a,b,c*	highest ν = 2023
2 PMe_3	1990	1926	*c*	2019
bpy	1978	1904	*a,c*	2017
phen	1977-1980	1897-1915	*a,c*	-
4,4'-Me_2py	1973	1893	*d*	2014
3,4,7,8-Me_4-phen	1967-1970	1875-1993	*predicted*	-

[a] Plankey, B. J.; Rund, J. V. *Inorg. Chem.* **1979,** *18*, 957. *b*. Meriwether, L. S.; Fiene, M. L. *J. Am. Chem. Soc.* **1959,** *81*, 4200. [b] Tolman, C. A. *J. Am. Chem. Soc.* **1970,** *92*, 2956. [c] Christensen, P. A.; Hamnett, A.; Higgins, S. J.; Timney, J. A. *J. Electroanal. Chem.* **1995,** *395*, 195. [d] Sieler, J.; Than, N.-N.; Benedix, R.; Dinjus, E.; Walther, D. *Z. Anorg. Allg. Chem.* **1985,** *522*, 131.

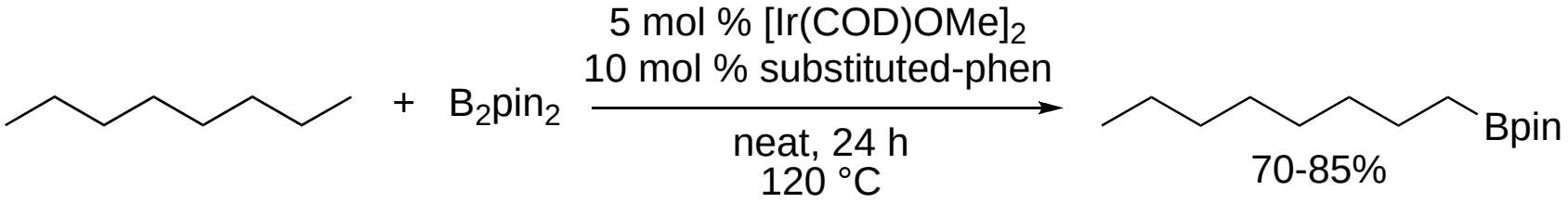
Among this series, tetramethylphenanthroline is the most donating... and the one to generate a catalyst for alkane borylation.

Developing More Active Catalysts

The arene borylation catalyst does not functionalize aliphatic C-H bonds

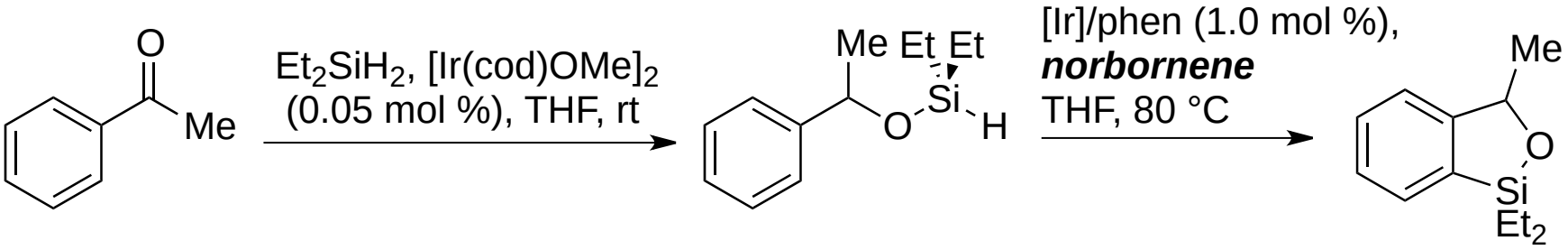


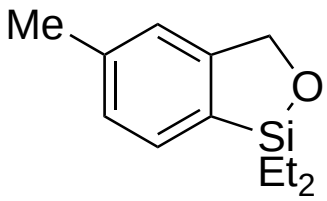
But the catalysts containing substituted phenanthrolines do...



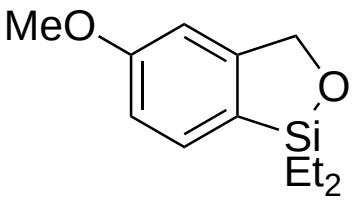
Carl Liskey, unpublished

Intramolecular Silylation of Aromatic C-H Bonds

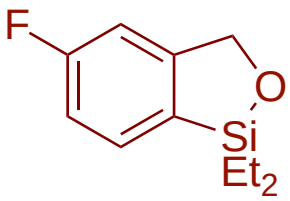




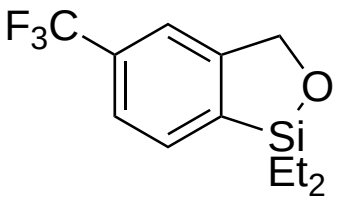
58%
>20:1 selectivity



88%
>20:1 selectivity



73%
1:1 selectivity

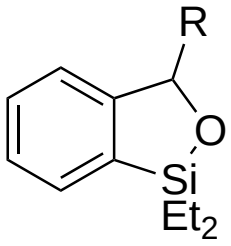


55%
>20:1 selectivity

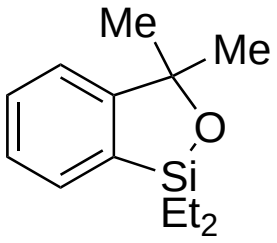
Regioselectivity appears to be controlled by steric effects.

Simmons, E. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 17092.

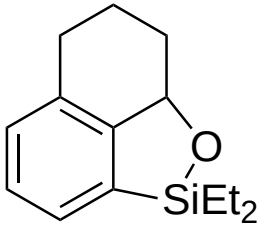
Intramolecular Silylation of Aromatic C-H Bonds



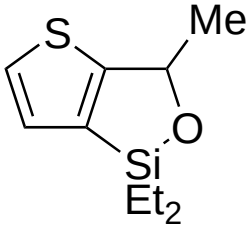
R=Et, 63%
R=Pr, 65%



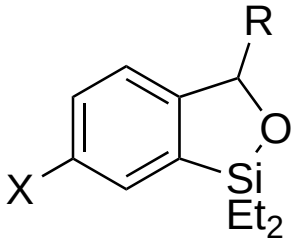
70%



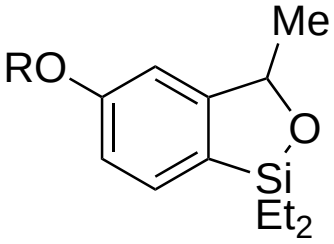
71%



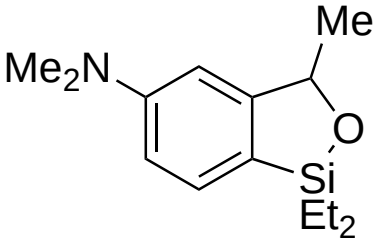
61%



R=H, X=I, 86%
R=Me, X=Br, 75%



R=TBS, 86%
R=Piv, 83%



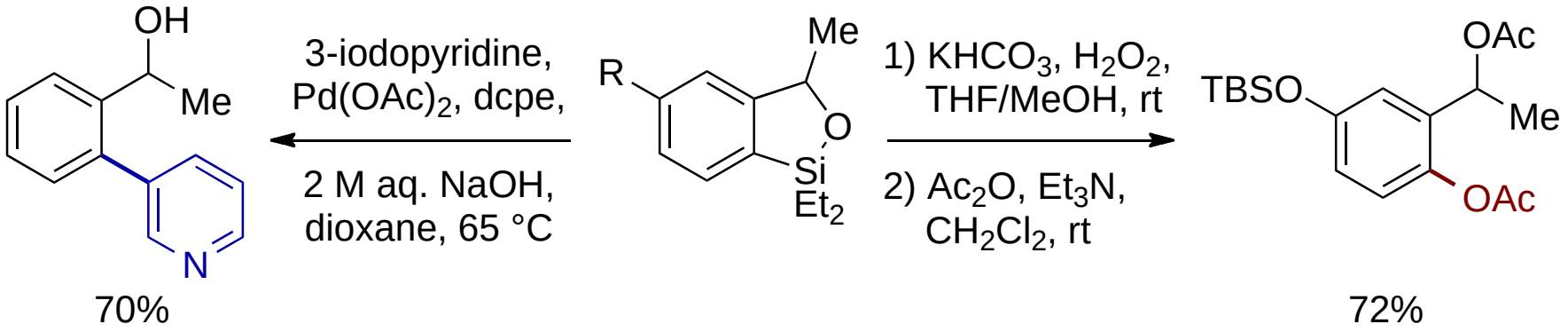
82%

Regioselectivity appears to be controlled by steric effects.
...and functional group tolerance looks high.

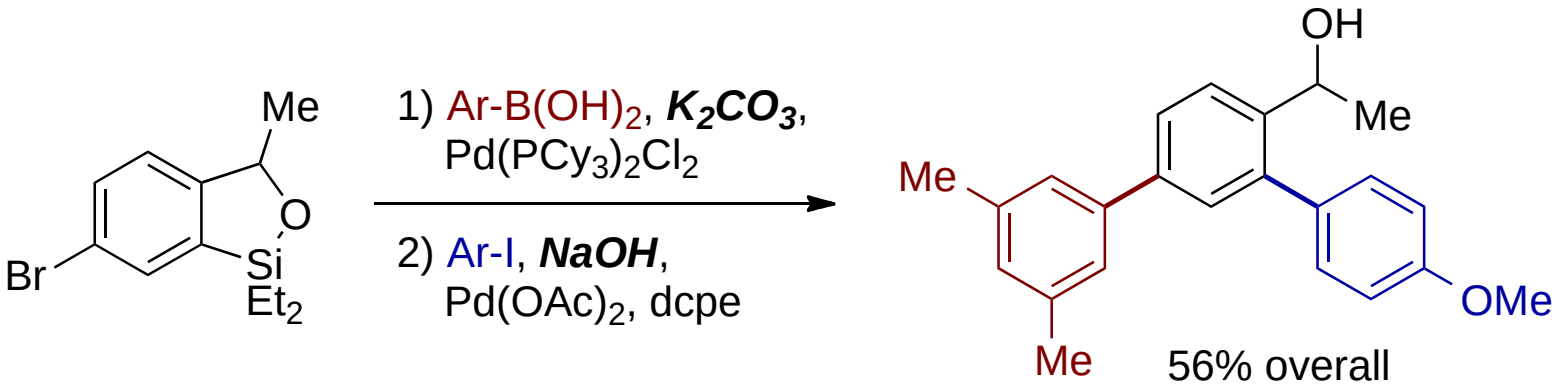
Simmons, E. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 17092.

Transformations of the Siloles from Directed Silylation

Cross coupling and oxidation can be conducted on the oxasiloles



Orthogonal Coupling of Halogen-Containing Oxasiloles



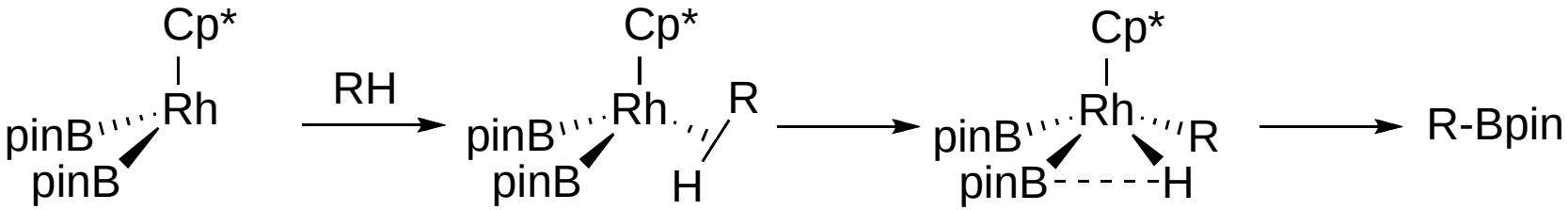
Simmons, E. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 17092.

Why C-H Activation with Boron Reagents?

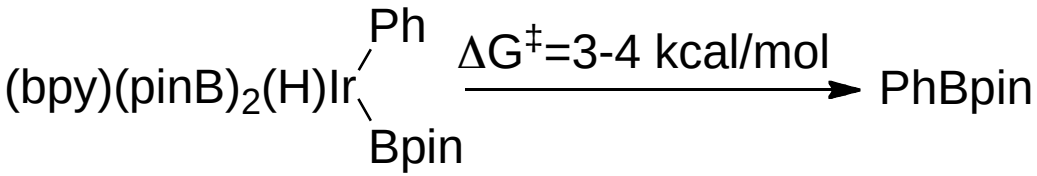
•Strong B-C bond makes the C-H bond functionalization favored thermodynamically

21 kcal/mol exothermic for B_2pin_2
2-4 kcal/mol exothermic for HBpin

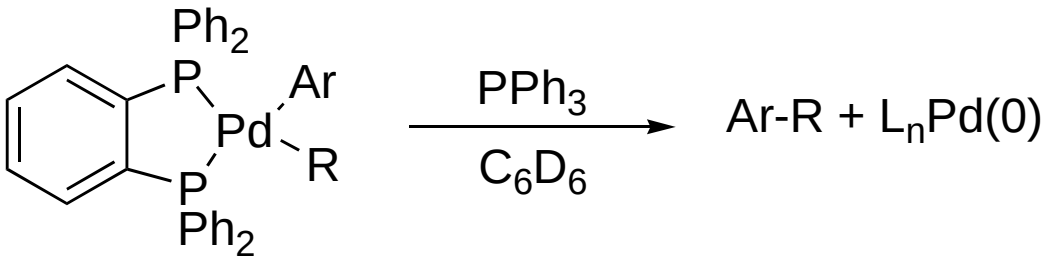
•Participation of the p-orbital and the strong σ-donation by an "anionic" boryl ligand leads to a low barrier for C-H bond cleavage



•Reversal of bond polarity leads to rapid formation of B-C bonds by metathesis or reductive elimination



Electronic Effect on C-C Reductive Elimination



Taft parameter

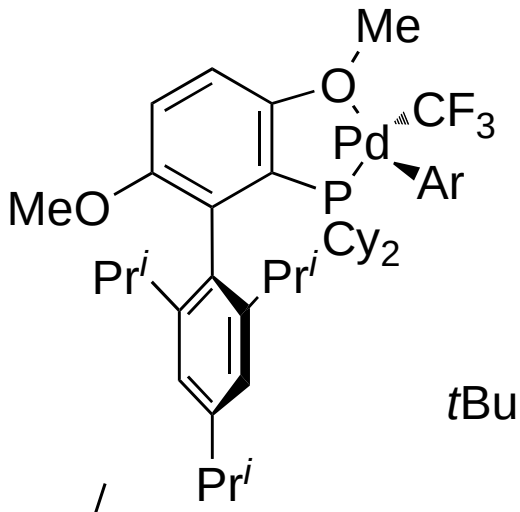
R=	σ*	k_{rel}(110 °C)
Me	0.00	>600
CH_2Ph	0.22	>250
$CH_2C(O)Ar$	0.60	31
CH_2CF_3	0.92	1.7
CH_2CN	1.30	1
CF_3	2.60	no rxn
$CH(CO_2Me)_2$		no rxn

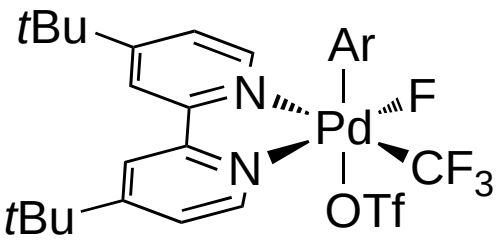
Culkin, D.A.; Hartwig, J.F. *J. Am. Chem. Soc.* **2001**, 123, 5816-5817.

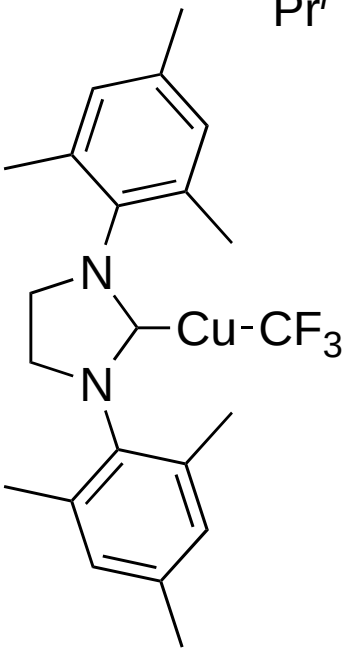
Culkin, D.A.; Hartwig, J.F. *J. Am. Chem. Soc.* **2002**, *124*; 9330-9331.

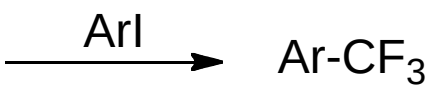
Culkin, D.A., Hartwig, J.F. *Organometallics*, **2004**, *23*, 3398-3416.

Reductive Elimination of Trifluoroarenes









Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679.

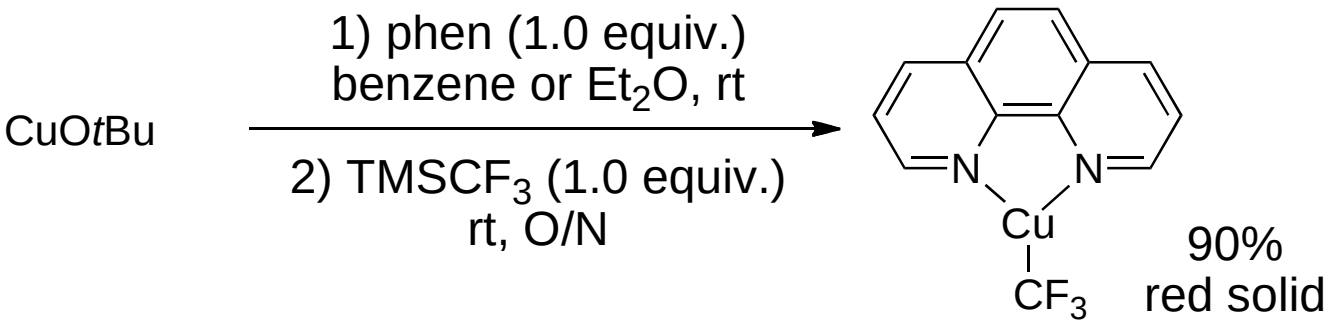
For Xantphos-Pd see:
Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, *128*, 12644.

Ball, N. D.; Kampf, J. W.; Sanford, M. S.
J. Am. Chem. Soc. **2010**, *132*, 2878.

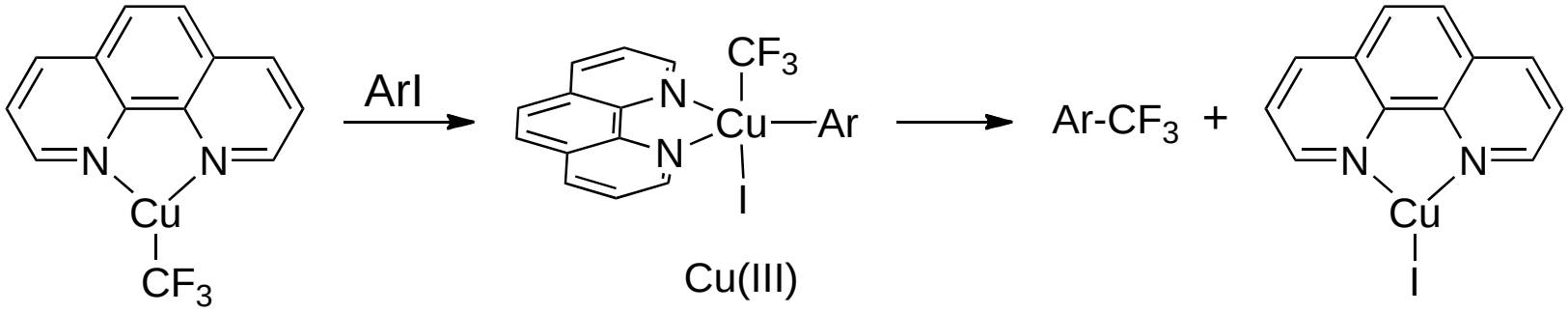
Dubinina, G. G.; Furutachi, H.; Vicic, D. A.
J. Am. Chem. Soc. **2008**, *130*, 8600.

Can reductive elimination of trifluoroarenes occur with an inexpensive metal, ligand and reagent?

Synthesis and Reactivity of (phen)CuCF$_3$



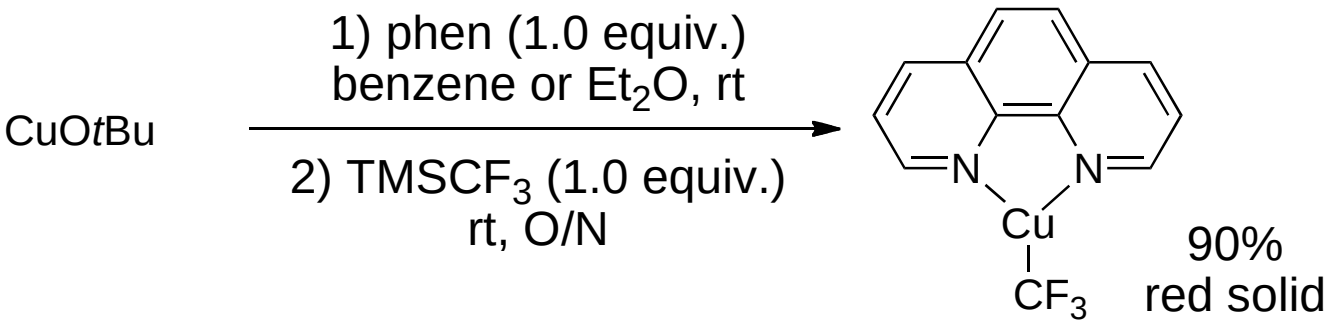
If an aryl-Cu(III) intermediate is generated, reductive elimination should be faster than from palladium(II).



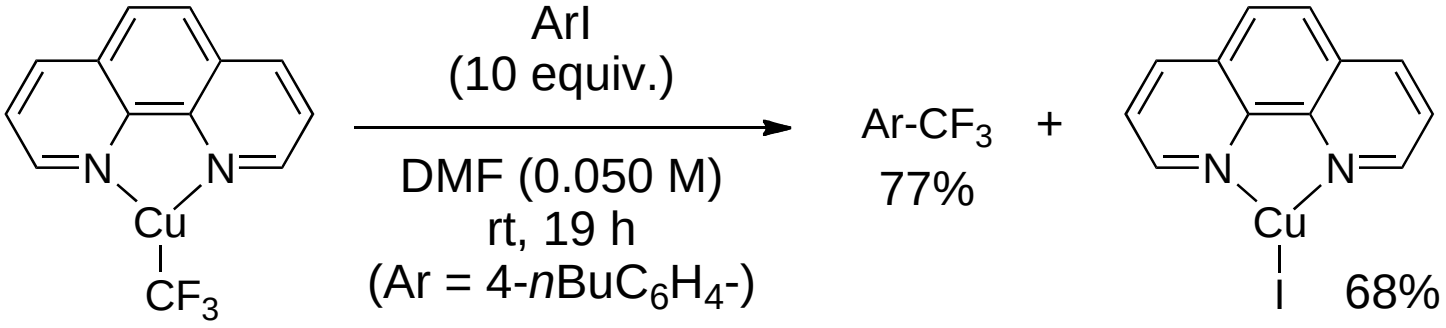
Reductive elimination from Cu(III) occurs with a low barrier:

Tye, J. W.; Weng, Z.; Johns, A. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 9971.
Zhang, S.-L.; Liu, L.; Fu, Y.; Guo, Q.-X. *Organometallics* **2007**, *26*, 4546.
Tye, Jesse W.; Weng, Z.; Giri, R.; Hartwig, John F. *Angew. Chem. Int. Ed.* **2010**, *49*, 2185.

Synthesis and Reactivity of (phen)CuCF$_3$



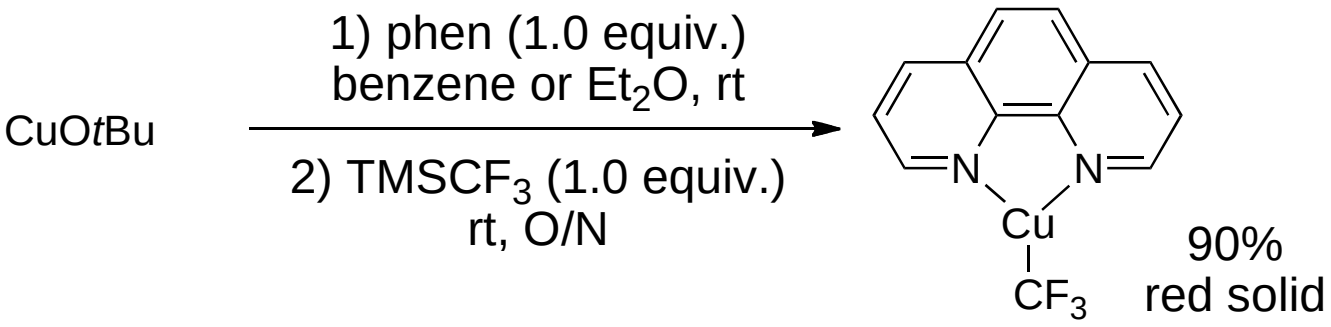
In the lab...



What is the stability of (phen)Cu-CF$_3$ and what is the scope of its reactions with ArX?

Hiroyuki Morimoto

Stability of (phen)CuCF$_3$



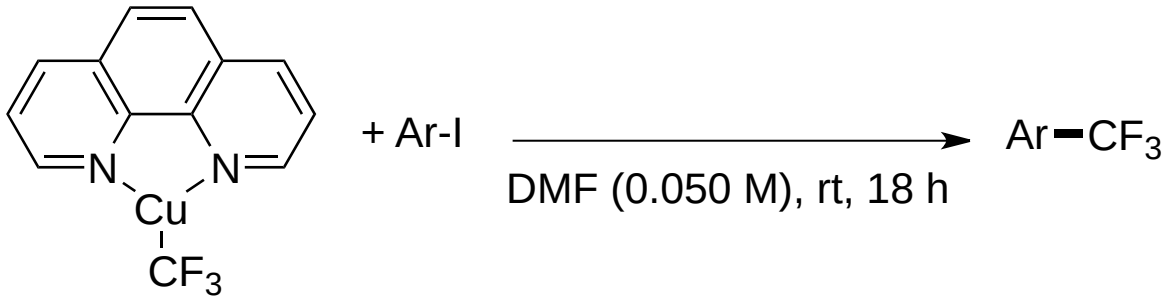
Available from Aldrich
(agreement with Catylix)

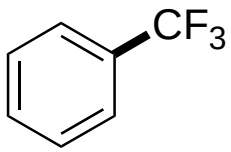
Stability:

conditions	solid state	in solution (0.05 M in DMF)
under N_2	stable at rt > 1 month	stable at rt for 1 day decomposed at 50 °C
in air	decomposed < 1 day	not examined

Hiroyuki Morimoto

Trifluoromethylation with (phen)CuCF$_3$





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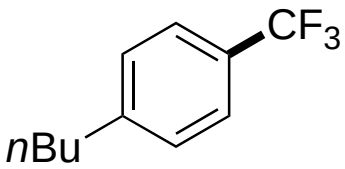

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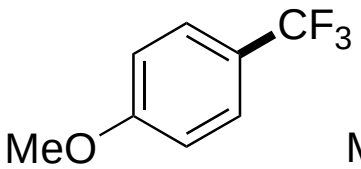

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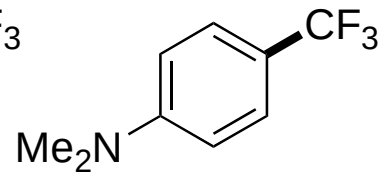

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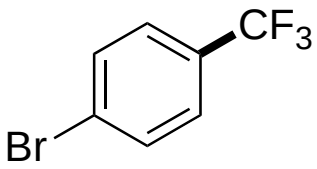

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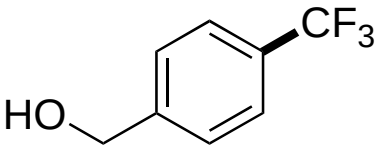

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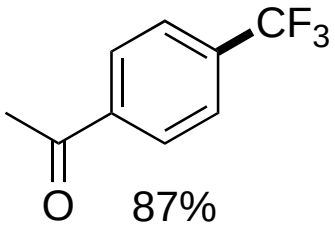

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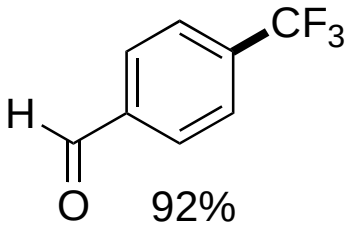

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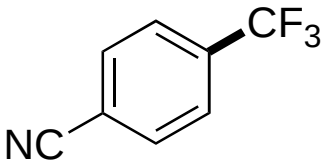

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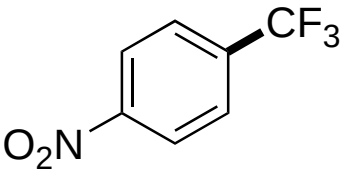

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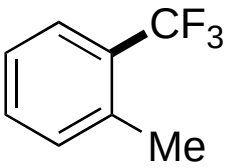

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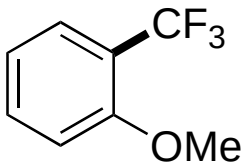

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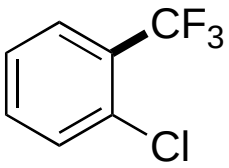

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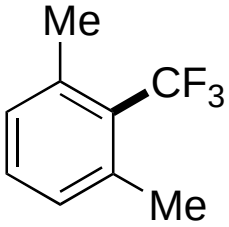

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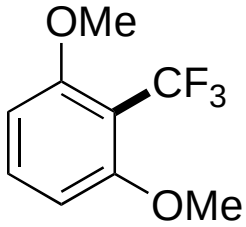

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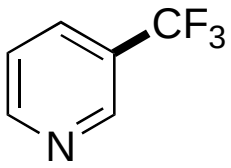

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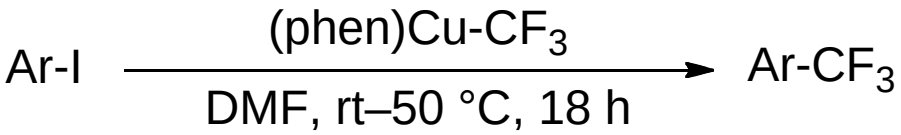
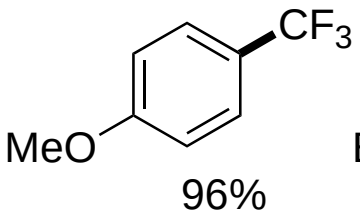
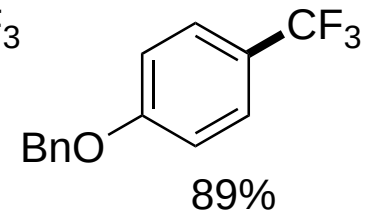
Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 3793.

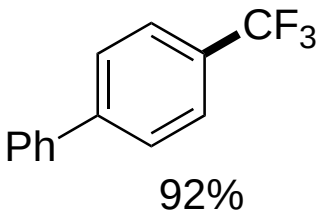
Scope of the Reactions of (phen)$CuCF_3$

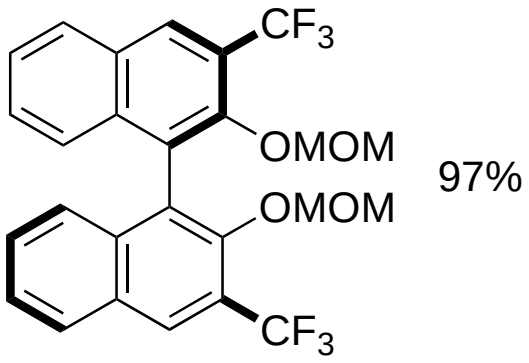
Reactions with 1:1 ArI to copper

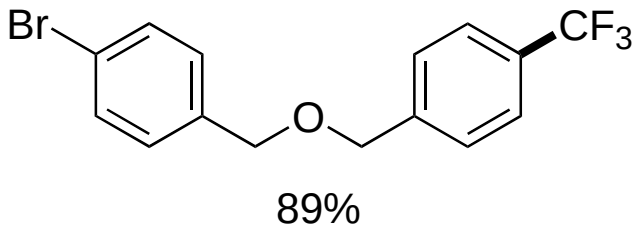








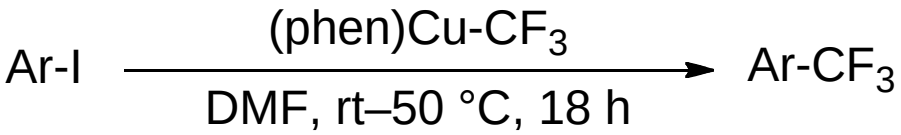


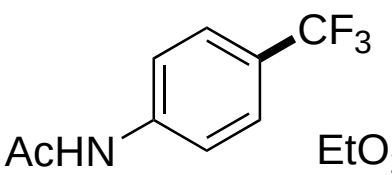


Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 3793.

Scope of the Reactions of (phen)$CuCF_3$

Reactions with 1:1 ArI to copper





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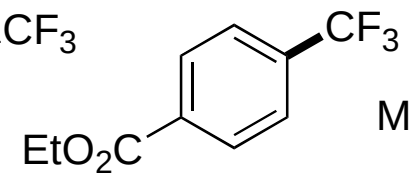

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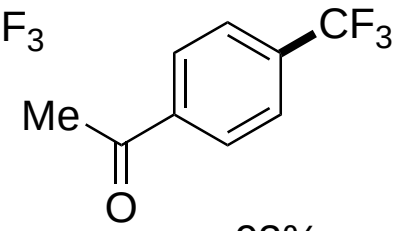
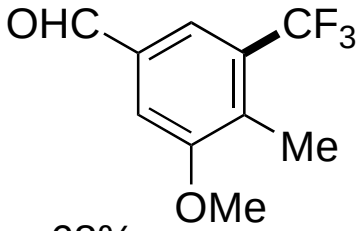


93%



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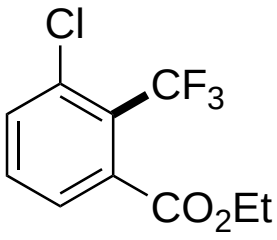

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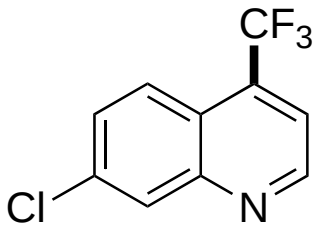

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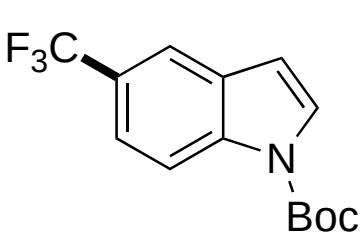

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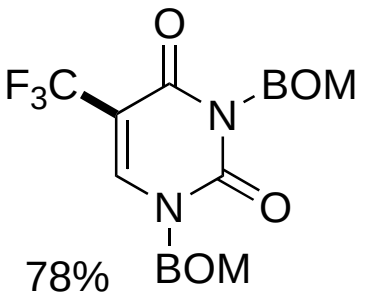


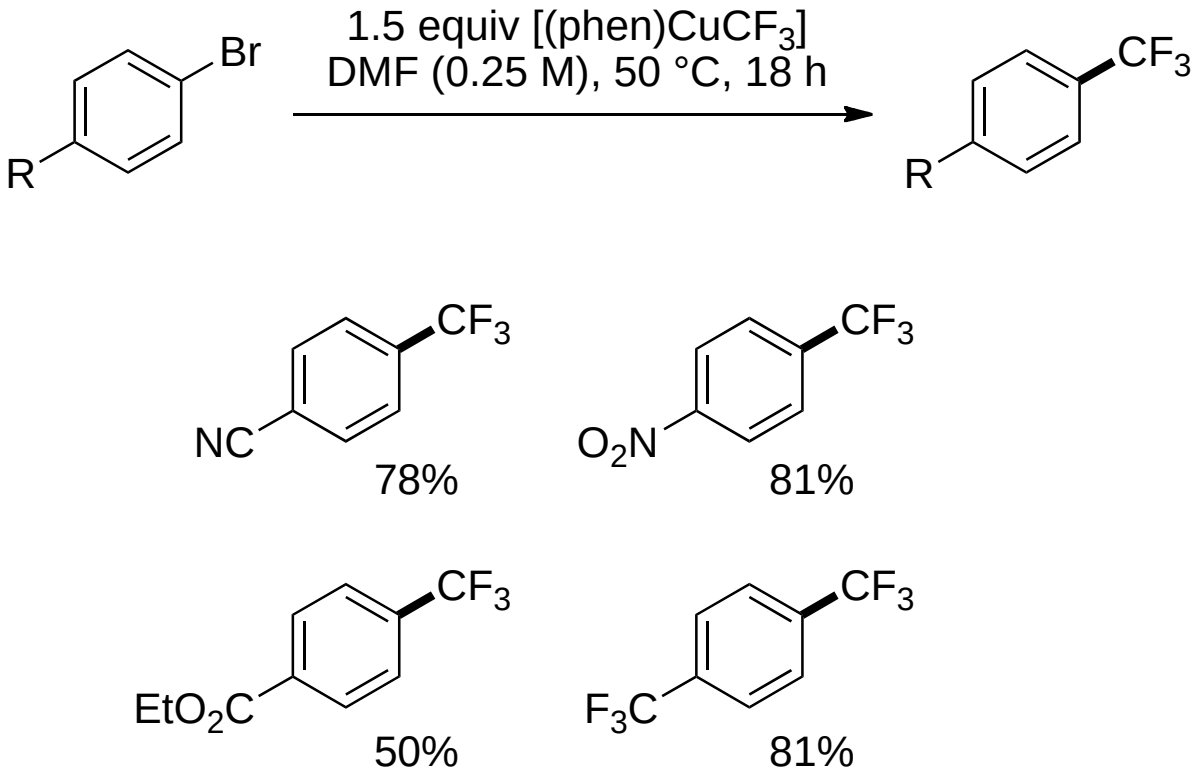
78%

Trifluoromethylthymidine

Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 3793.

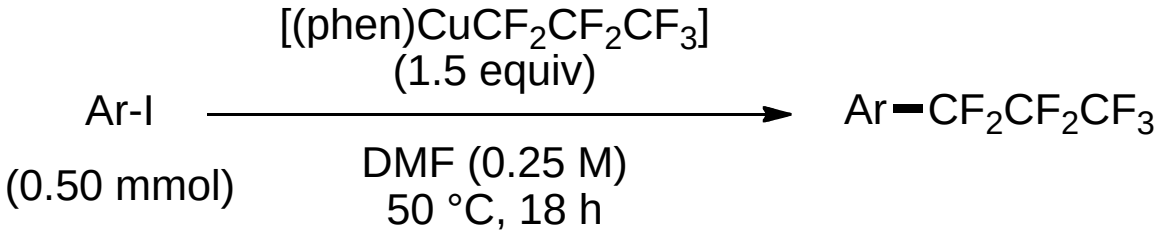
Scope of the Reactions of (phen)$CuCF_3$

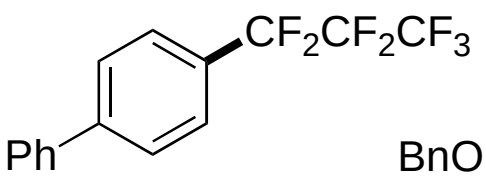
Reactions of aryl bromides



Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 3793.

Trifluoroalkylation by (phen)CuR$_f$





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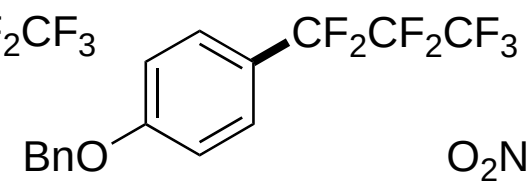

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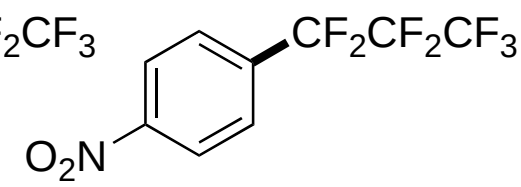

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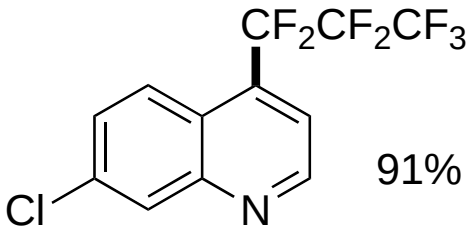

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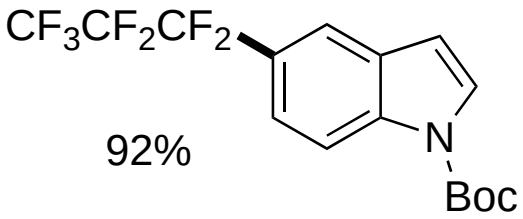

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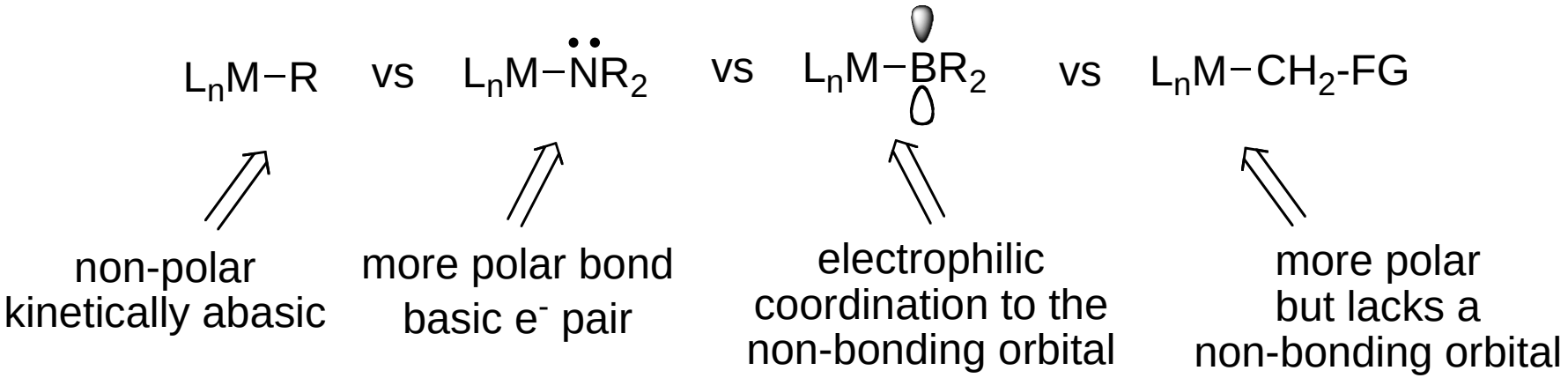
Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 3793.

Organometallic Chemistry of Metal-Heteroatom vs Metal-Carbon Bonds

Underlying Principles

comparison of the properties of "anionic" ligands



Pauling Electronegativities: Pd: 2.20
C: 2.55
N: 3.04
B: 2.04

Acknowledgments

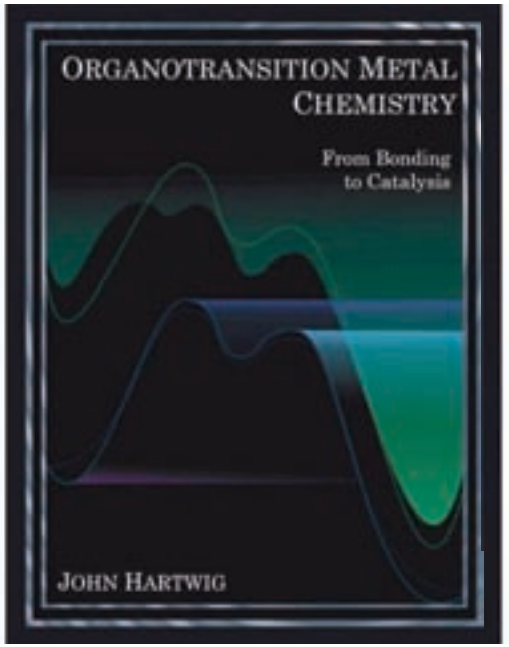
C-H Bond Functionalization

Karen Waltz
Huiyuan Chen
Sabine Schlecht
Kazumori Kawamura
Kevin Cook
Natia Anstasi
Makato Takahashi
Domingo Garcia
Yuichiro Kondo
Chulsung Bae
Doris Kunz
Joshua Lawrence
Timothy Boller
Naofumi Tsukada (Si)
Jaclyn Murphy
Christoph Tzschucke
Carolyn Wei
Tim Boebel
Dan Robbins
Carl Liskey
Eric Simmons

Shell:
Tom Semple (Shell)
Minnesota:
Marc Hillmyer
Nicole Wagner, Nicole Boaen
Hokkaido:
Tatsuo Ishiyama
Norio Miyaura
Jun Takagi, Yusuke Nobuta
Texas A&M:
Mike Hall
C. Edwin Webster, Yubo Fan
Charles Harris
Karma Sawyer et al.

NSF, NIH, Shell
Johnson-Matthey
Frontier Science
Allychem, BASF

Now available:



Cu-Mediated Trifluoromethylation

Hiroyuki Morimoto
Tetsu Tsubogo
Nichole Litvinas

NIH NIGMS