

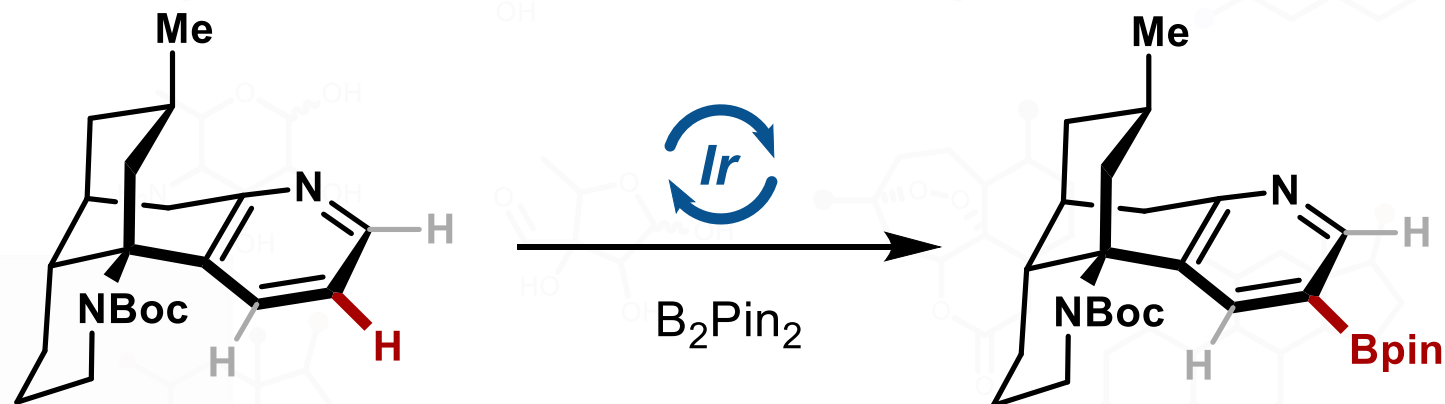
XU GROUP
Department of Chemistry, Peking University

Selected Weekly Literature Presentations

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Ir-Catalyzed Borylation of Aromatic C-H Bonds

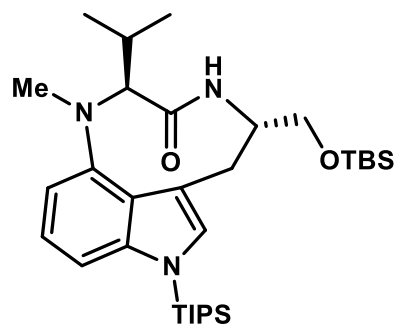


Xizhe Wu

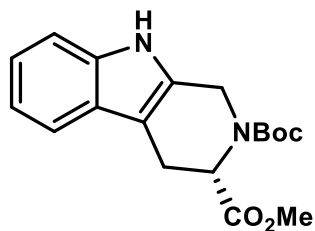
2025.9.20

Problems of the Day

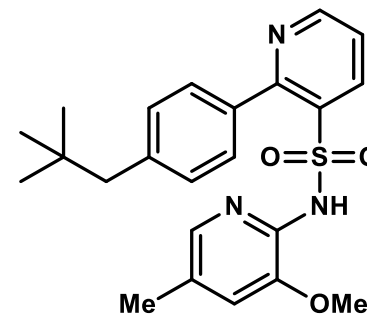
Predict the Major Site of Borylation



[Ir(COD)OMe]₂ (10mol%)
tmphen (20mol%)
HBpin (4eq)
octane/THF, 80°C, 6h



[Ir(COD)OMe]₂ (1mol%)
dtbpy (2mol%)
B₂pin₂ (1.5eq)
THF, 90°C



[Ir(COD)OMe]₂ (1.25mol%)
tmphen (2.5mol%)
B₂pin₂ (2eq)
THF, 80°C

Outline

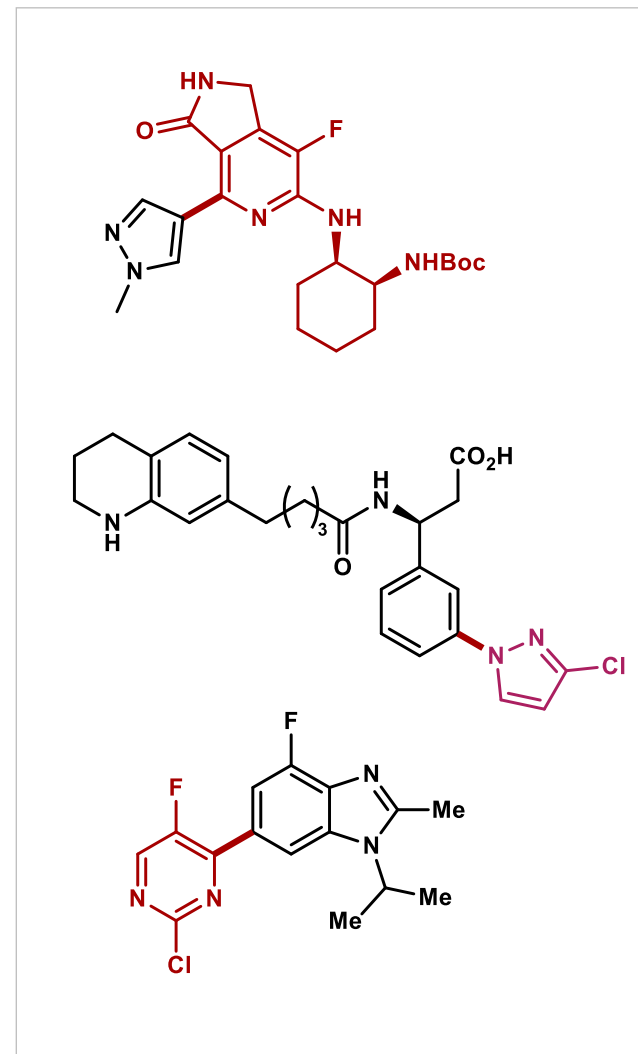
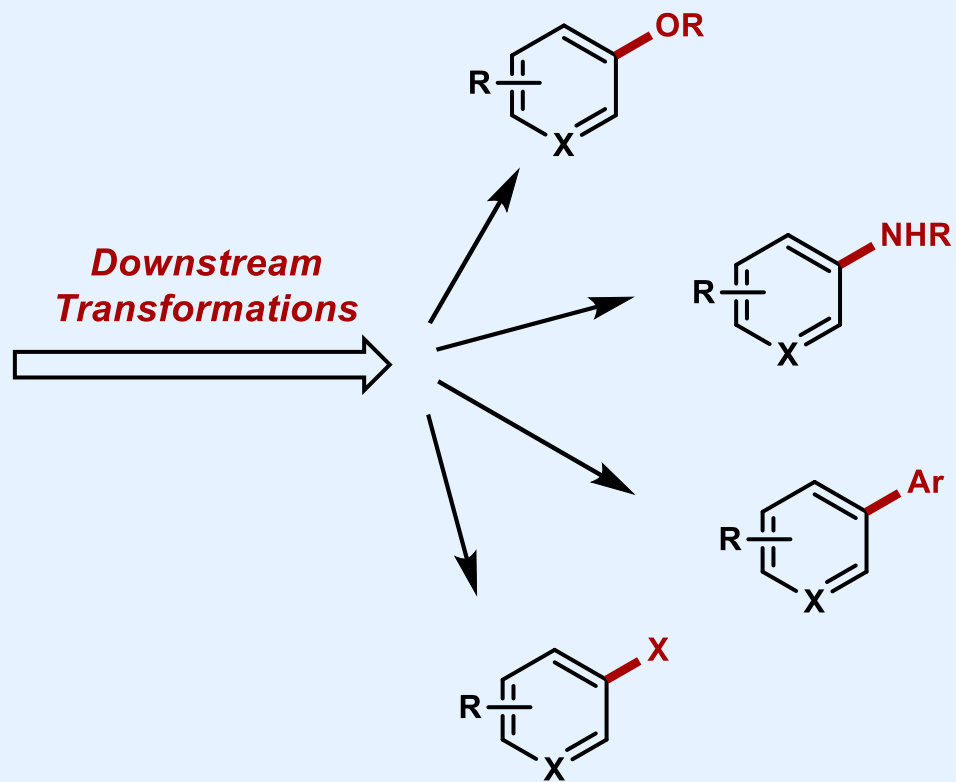
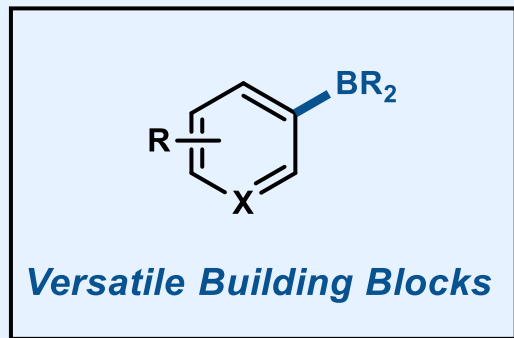
- *Introduction*
- *History of Development*
- *Mechanistic Studies*
- *General Selectivity of Ir-Bipyridine System*
- *Directed Selectivity*

Outline

- ***Introduction***
- ***History of Development***
- ***Mechanistic Studies***
- ***General Selectivity of Ir-Bipyridine System***
- ***Directed Selectivity***

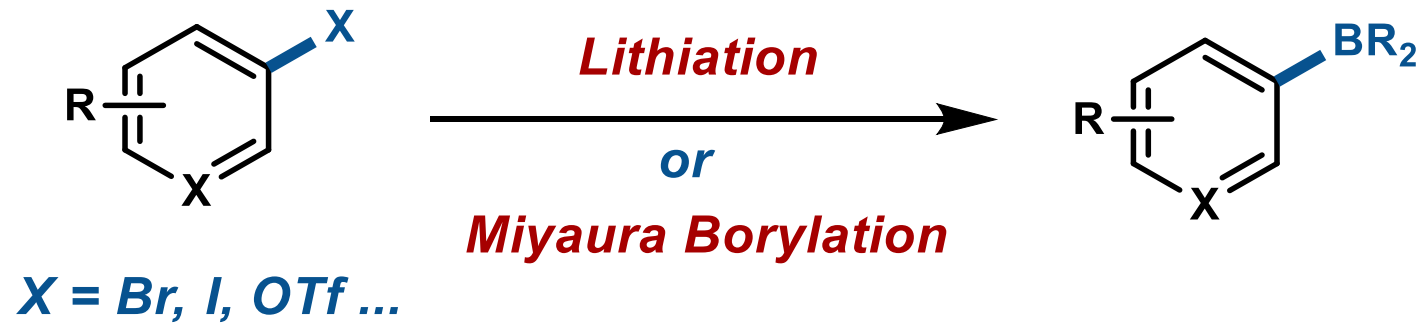
Introduction

Aryl Boronic Compounds in Organic Chemistry



Introduction

Conventional Borylation Methods



- *SM not Readily Available*
- *Harsh Conditions (Lithiation)*

Introduction

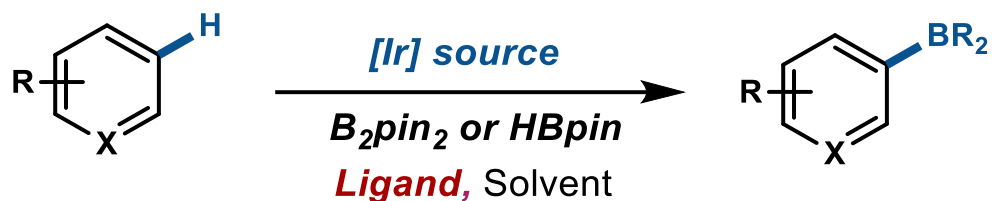
C-H Borylation Methods



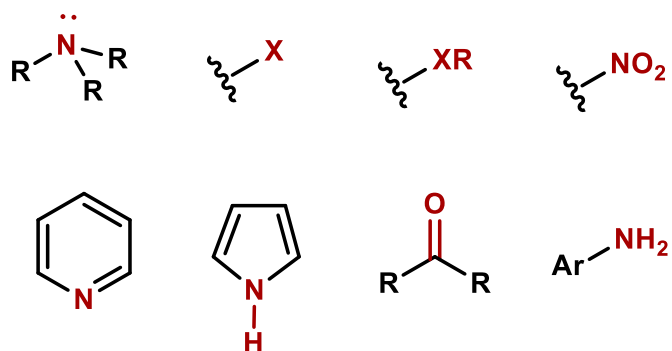
· *Abundant Starting Material*

Introduction

Ir-Catalyzed Borylation



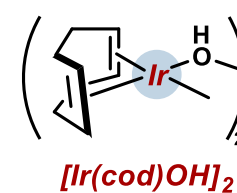
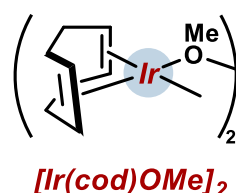
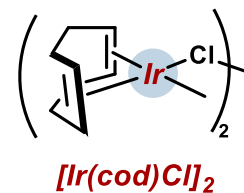
FGs Tolerated



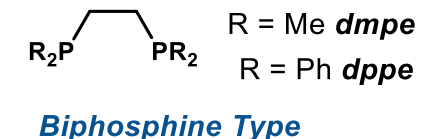
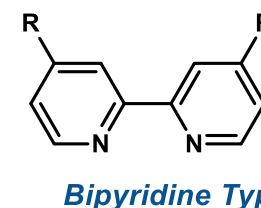
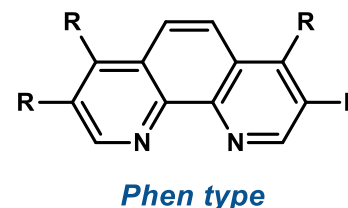
Solvents

THF, 1,4-dioxane,
Alkane, MeCN, DCM
NMP, iPr_2NEt , $iPrOAc$
Cycloalkane, Arene
(as reactant)

Common Precatalysts



Commonly Used Ligand



Outline

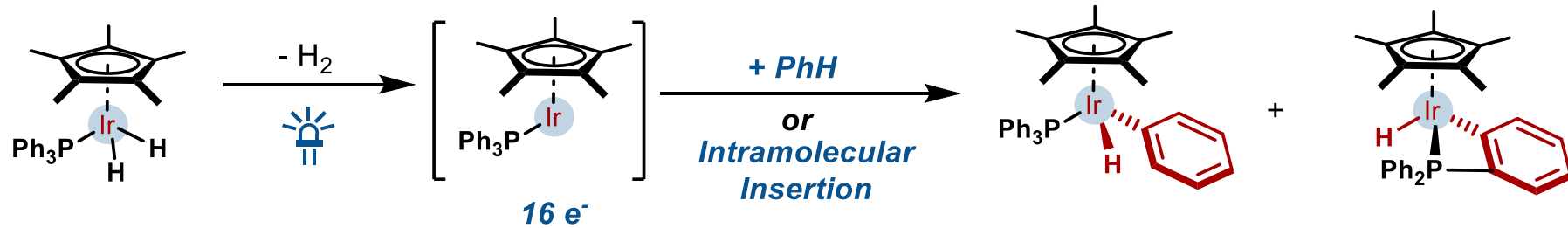
- *Introduction*
- *History of Development*
- *Mechanistic Studies*
- *General Selectivity of Ir-Bipyridine System*
- *Directed Selectivity*

History of Discovery

Heat for C-H Activation

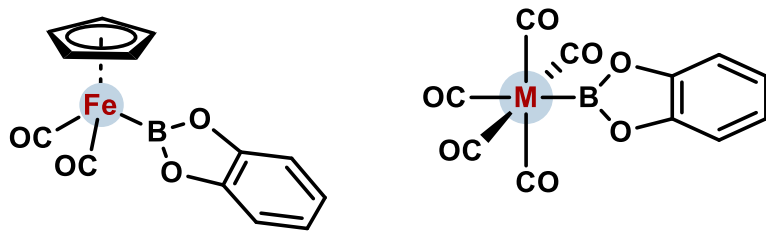
Activation of C-H Bonds with 16e- Organometallic Species

Bergman (1982)



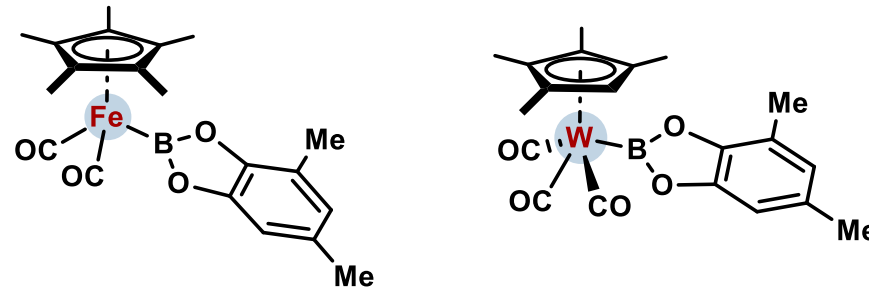
J. Am. Chem. Soc. **1982**, *104*, 352–354

Metal-Boryls-Mediated C-H Borylation



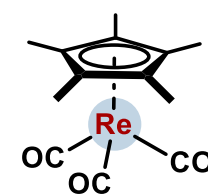
M = Mn, Re

(Stoichiometric sp^2 Borylation)



(Stoichiometric sp^3 Borylation)

Science **1997**, *277*, 211.



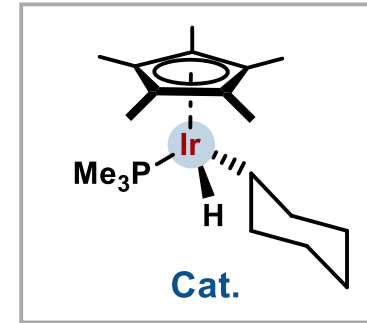
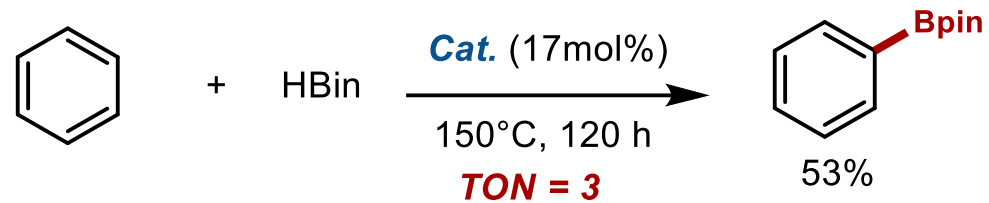
(Catalytic sp^3 Borylation)

Angew. Chem., Int. Ed. **1999**, *38*, 3391.

History of Discovery

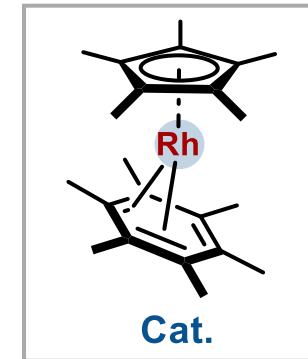
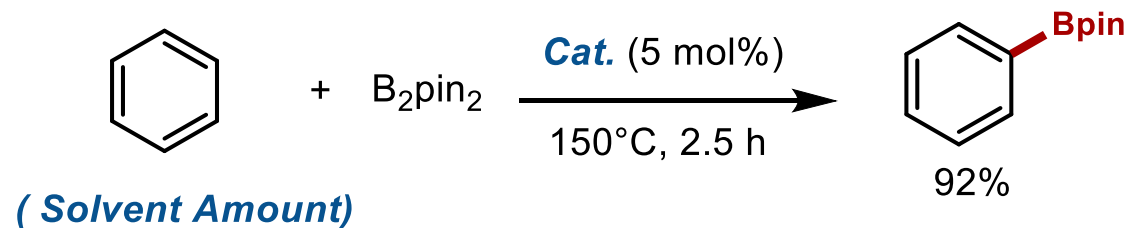
First Ir-Catalyzed Aromatic Borylation

Milton R. Smith (1999)



First Efficient Ru-Catalyzed Aromatic Borylation

Hartwig (1999)



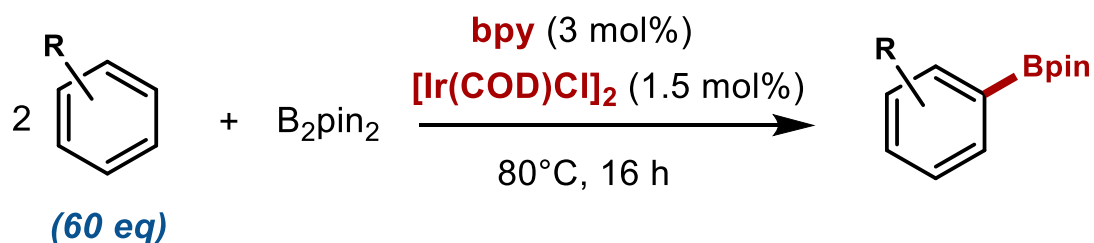
J. Am. Chem. Soc. **1999**, 121, 7696.

Science **2000**, 287, 1995

History of Discovery

Discovery of Bipyridine-Ir System for Catalytic Aromatic Borylation

Hartwig (2001)



- Room Temperature Reaction with $[Ir(COE)_2Cl]_2$ and dtbpy
- TON as high as 8000 with $[Ir(COE)_2Cl]_2 + dtbpy$

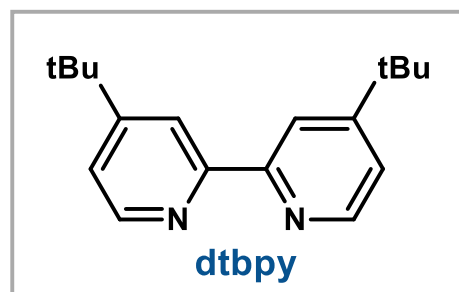
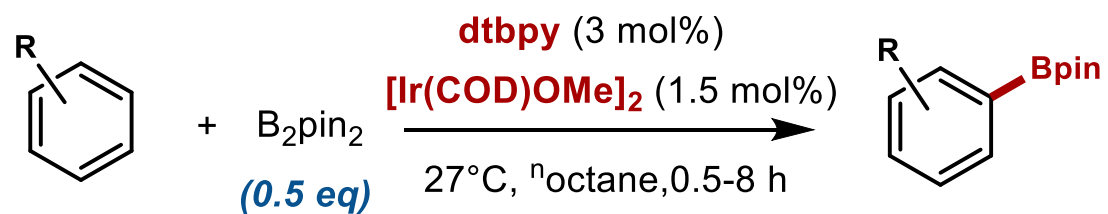
Table 1. Ir-Catalyzed Direct Borylation of Arenes with **1** (eq 1)^a

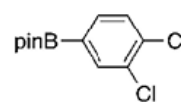
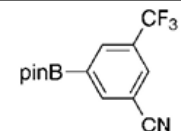
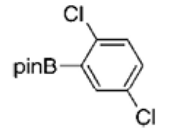
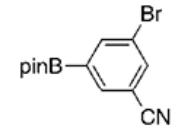
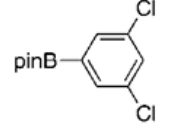
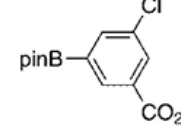
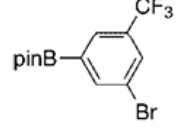
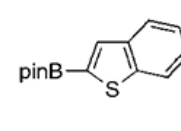
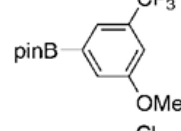
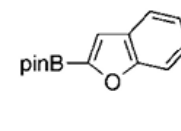
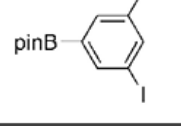
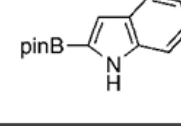
arene	product	yield/% ^b (<i>o</i> : <i>m</i> : <i>p</i>) ^c	arene	product	yield/% ^b (<i>o</i> : <i>m</i> : <i>p</i>) ^c
1	pinB-	95	7	pinB-	83
2	pinB-	95 (1:74:25)	8	pinB-	58
3	pinB-	82 (0:69:31)	9	pinB-	86
4	pinB-	80 (0:70:30)	10	pinB-	72
5	pinB-	83	11	pinB-	73
6	pinB-	86			

History of Discovery

Mild, Catalytic Borylation of Aromatics with Stoichiometric Substrate

Hartwig (2002)



Entry	3	Time [h]	Yield ^[b] [%]	Entry	3	Time [h]	Yield ^[b] [%]
1		8	82	7		2	84
2		24	53	8		2	83
3		2	84	9		8	80
4		4	91	10		2	81
5		8	81	11		4	83
6		4	82	12		0.5	88

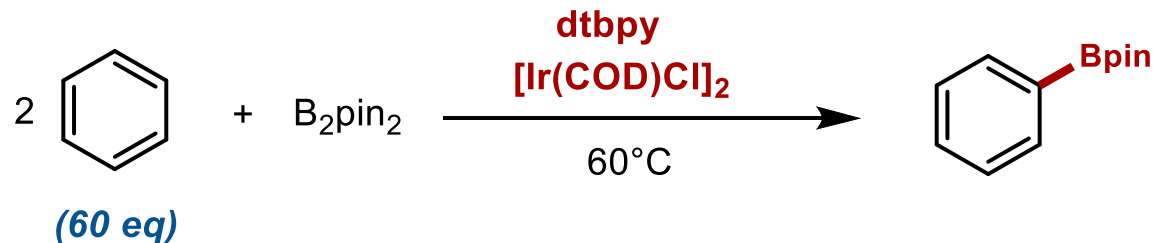
Outline

- *Introduction*
- *History of Development*
- ***Mechanistic Studies***
- *General Selectivity of Ir-Bipyridine System*
- *Ligand-controlled Selectivity*

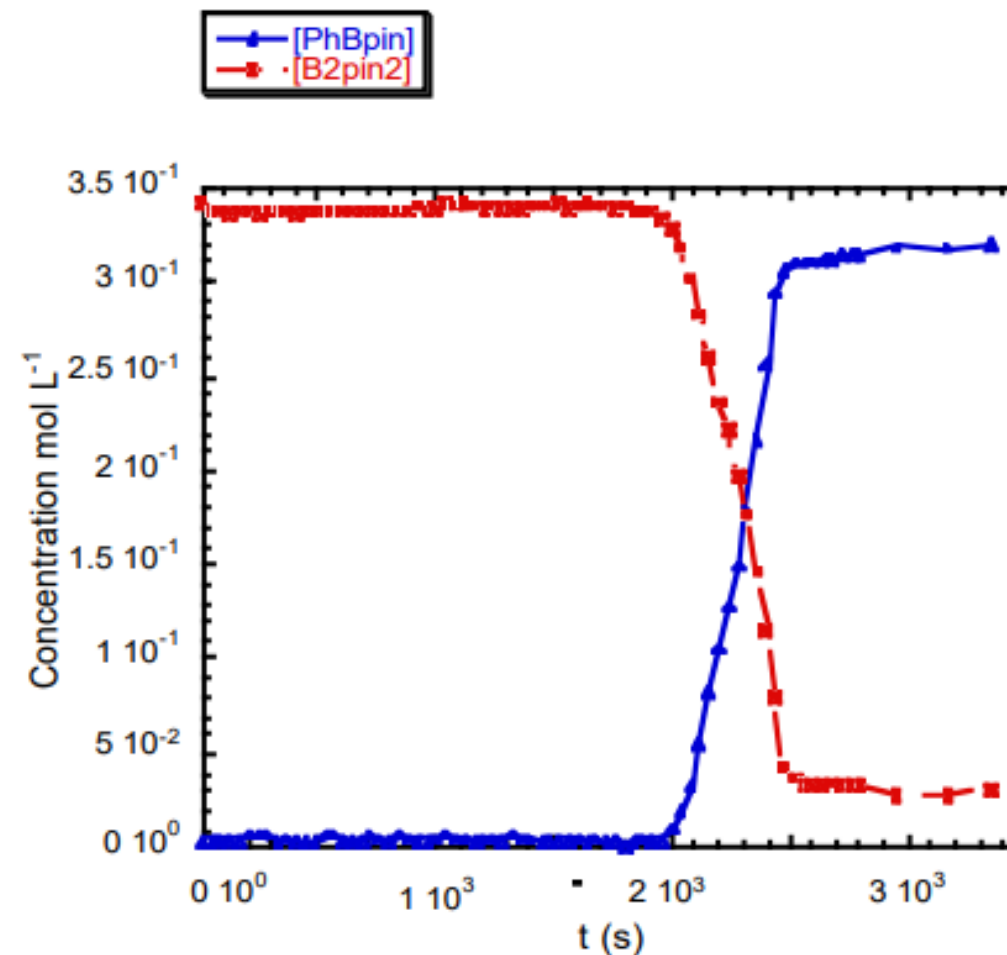
Mechanistic Understanding

Isolation of Potential Intermediate

Hartwig (2001)



- Induction Period Observed
- COD converted to COE during the induction period
- [Ir(COE)₂Cl]₂ reacts faster than [Ir(COD)Cl]₂

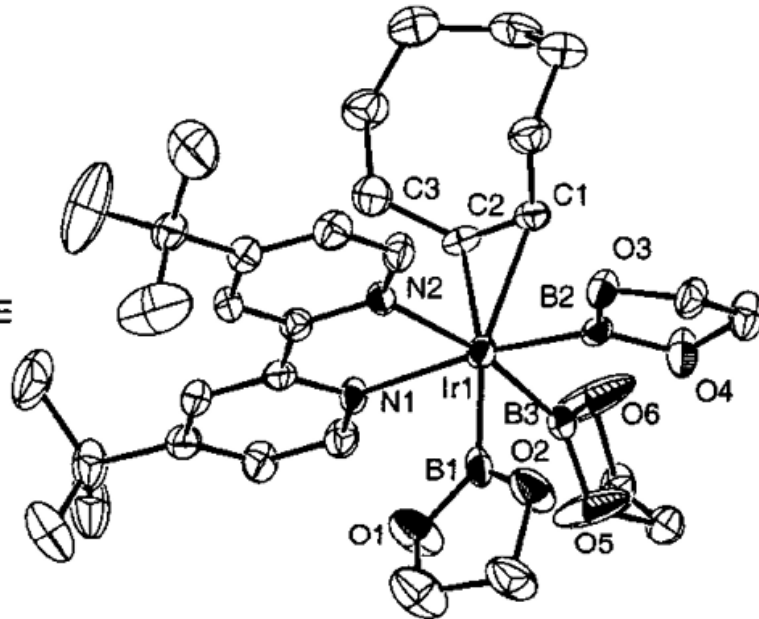
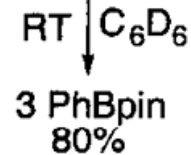
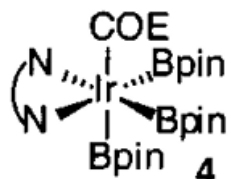
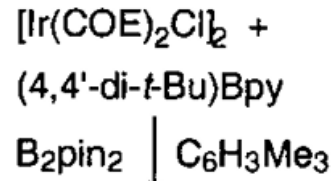


COE-Coordinated-Ir might be an intermediate or resting state

Mechanistic Understanding

Isolation of Potential Intermediate

Scheme 1



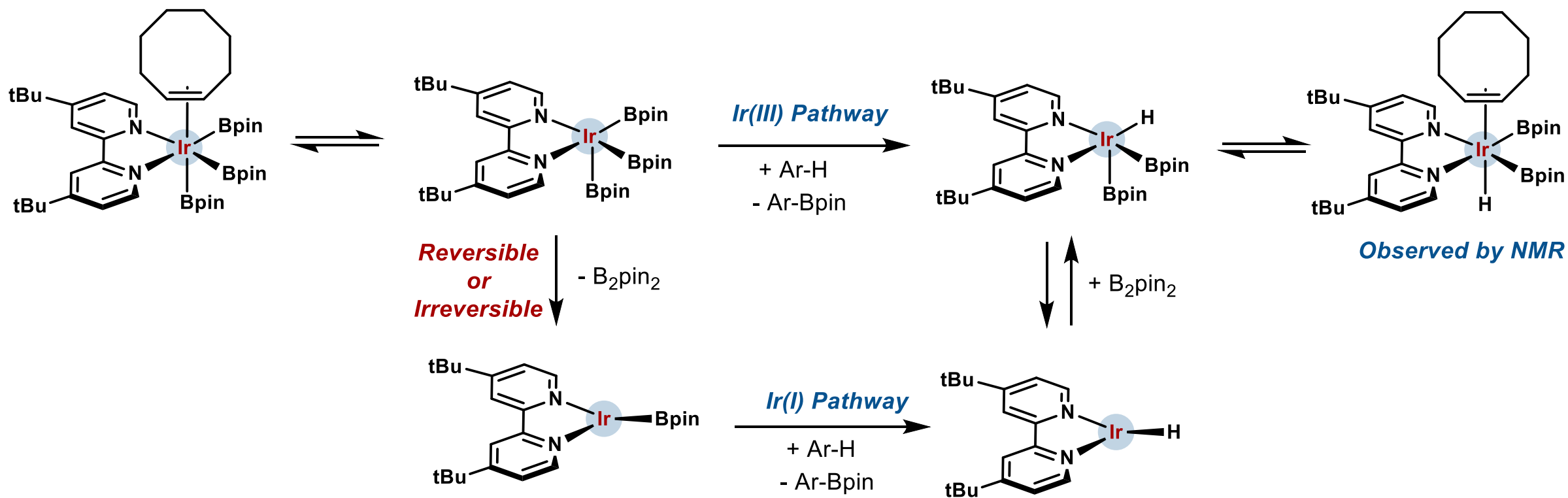
Ir-N1=2.177 Å, Ir-N2=2.221 Å, Ir-B1=2.055 Å Ir-B2=2.057 Å,
Ir-B3=2.027 Å, Ir-C1=2.308 Å Ir-C2=2.318 Å Pinacol methyl
groups and hydrogens have been removed for clarity.

- *Intermediate Observed in reaction identical to synthesized complex*
- *No Induction Period Observed*
- *Identical KIE and Selectivity*

Ir(COE)(dtbpy)Bpin₃ is an intermediate or resting state

Mechanistic Understanding

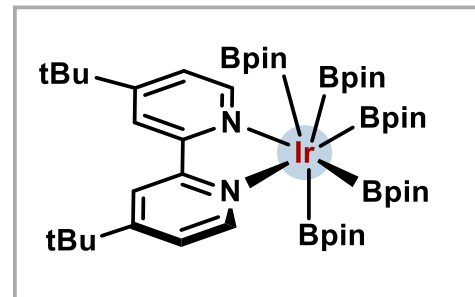
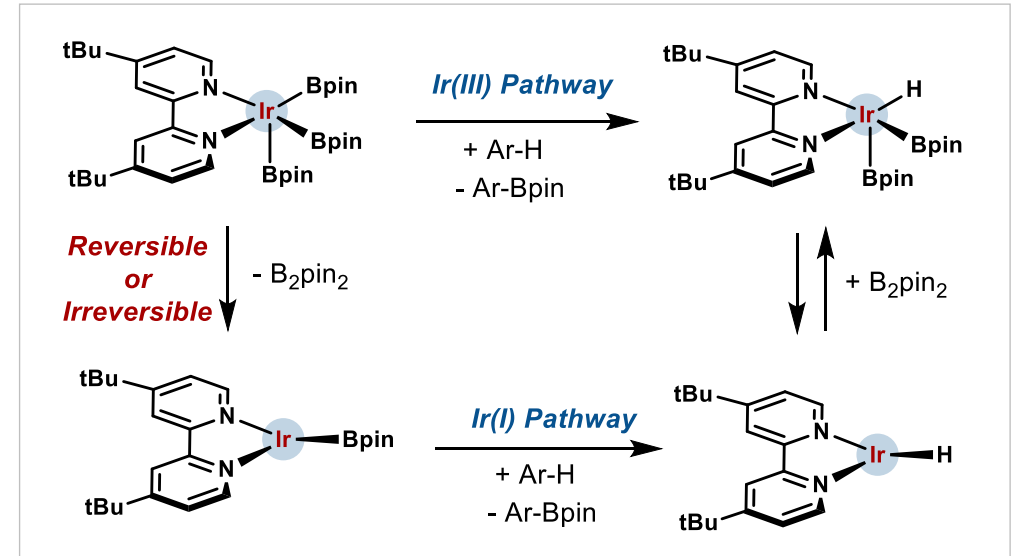
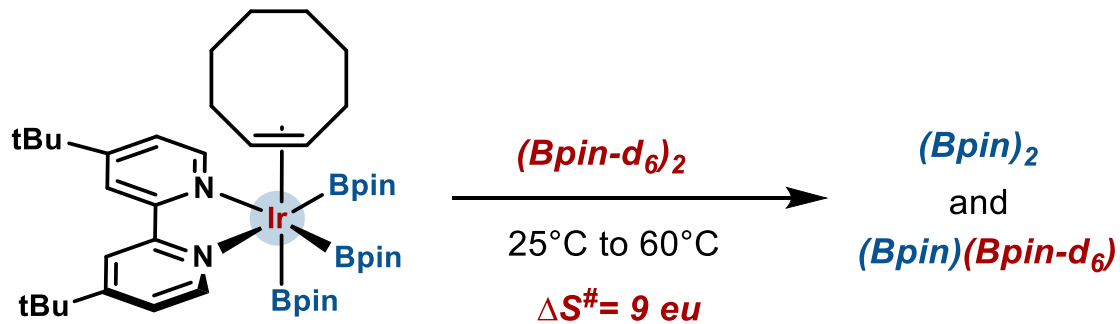
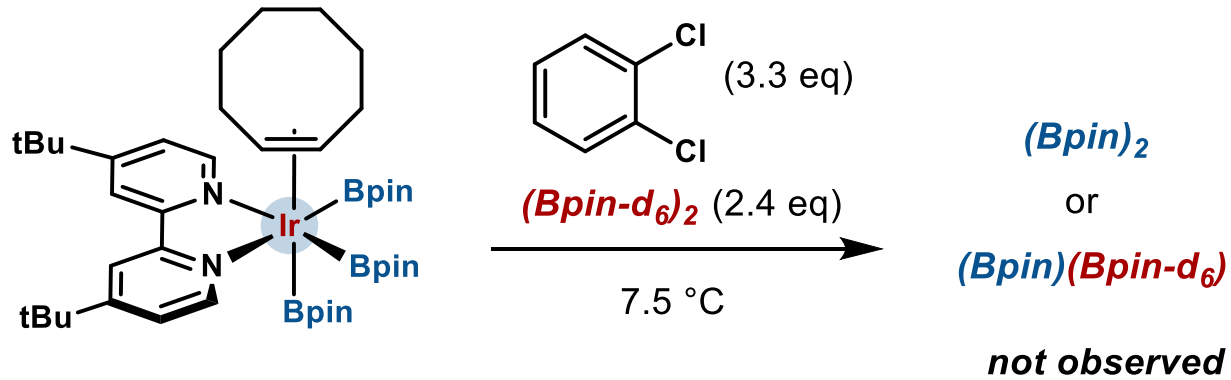
Plausible Reaction Pathway



Mechanistic Understanding

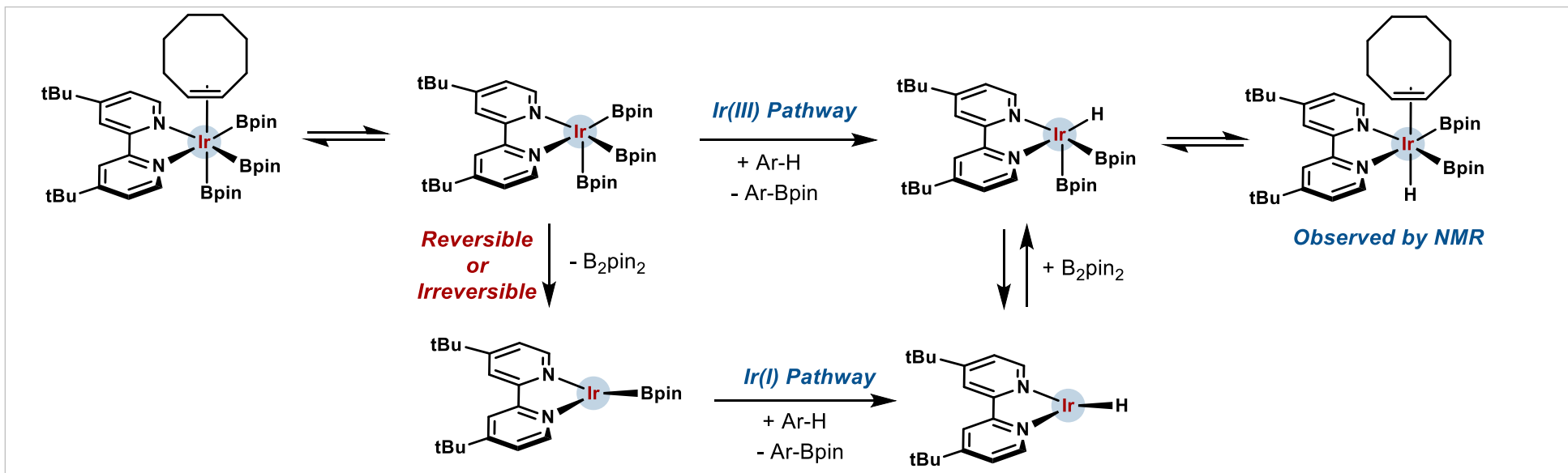
Distinguishing Ir(I) - Ir(III) versus Ir(III) - Ir(V) Pathways

Labeling Studies



Inconsistent with Ir(I) Pathway

Mechanistic Understanding



Kinetic Order Analysis:

First Order in Arene



Rate Limiting Step is or is after C-H Activation

Rate Limiting B₂pin₂ Elimination Excluded

Half Order in Catalysts



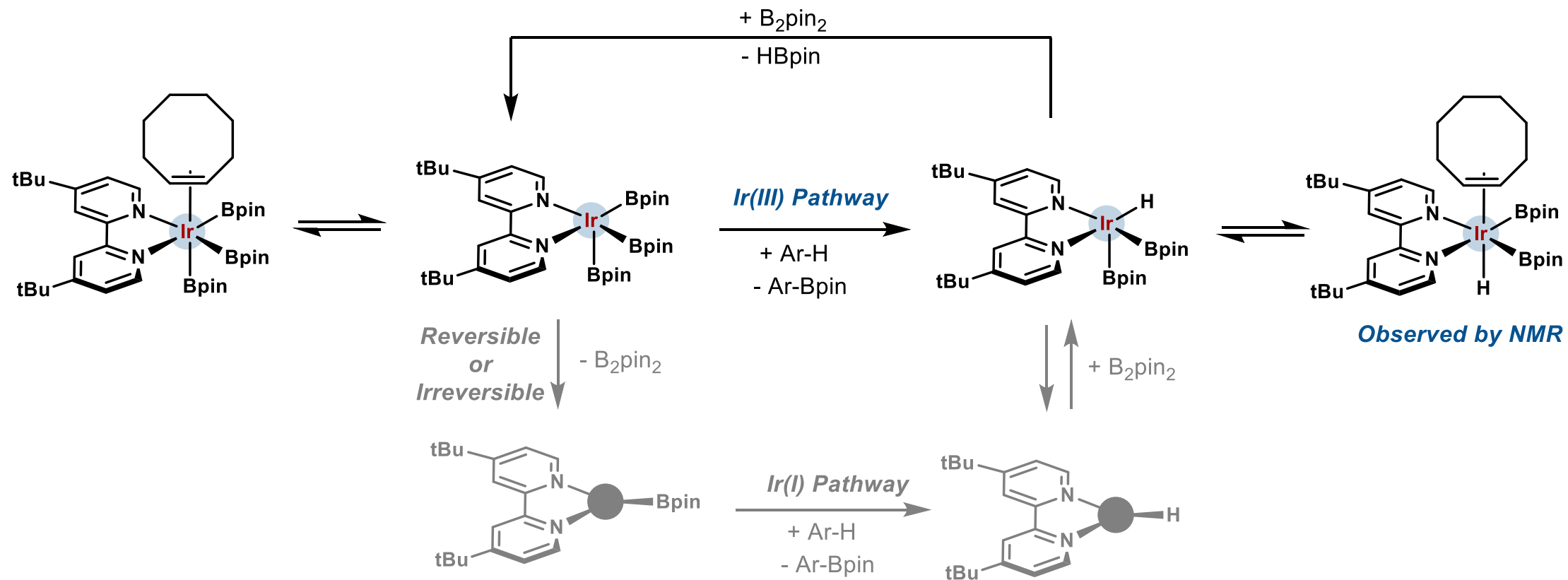
COE Dissociation

Zero Order in Diboron



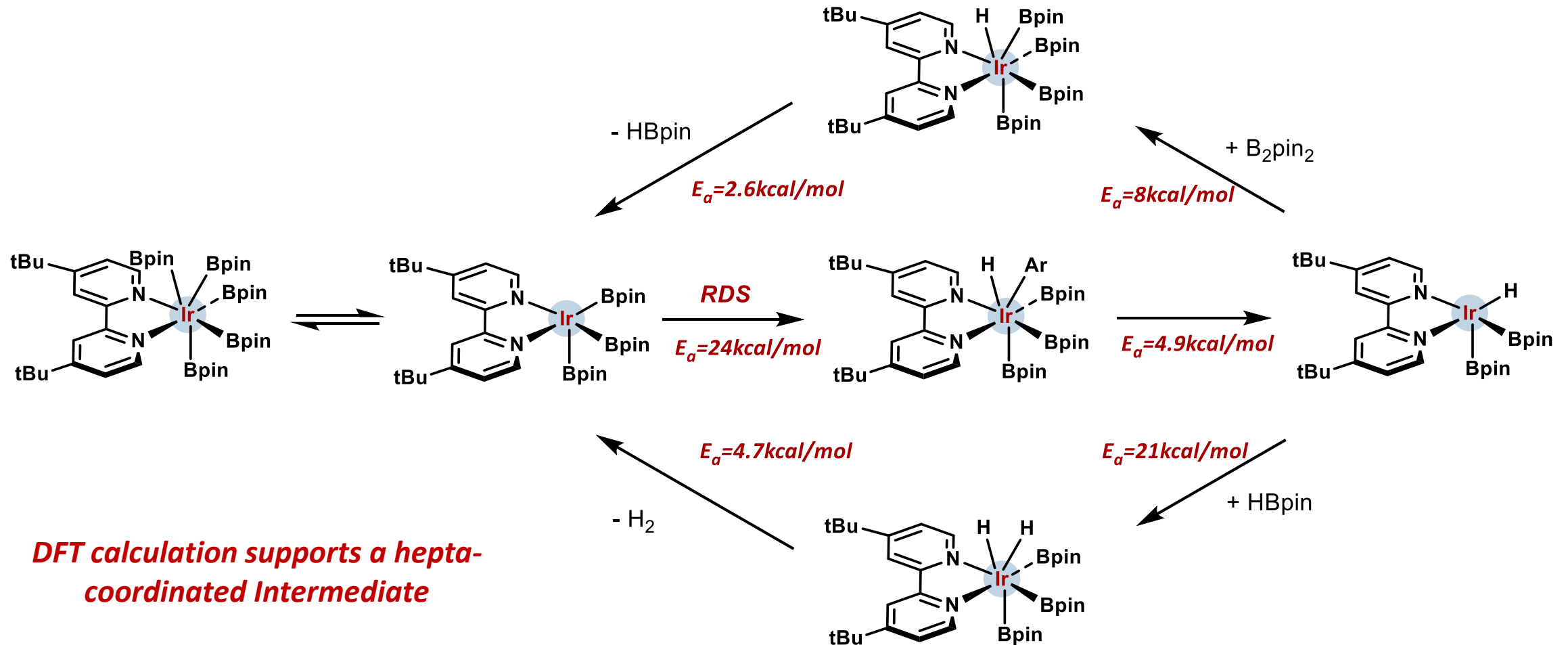
B₂pin₂ Elimination in Equilibrium excluded (Negative Order Expected)

Mechanistic Understanding



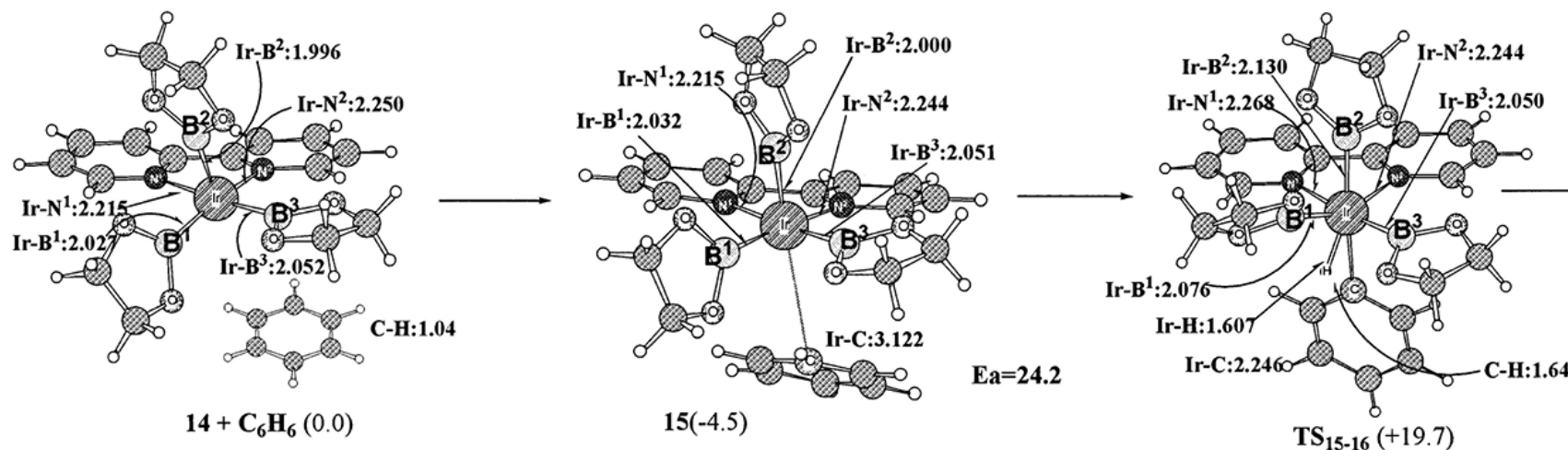
Mechanistic Understanding

Complete Mechanism of C-H Activation



Mechanistic Understanding

Important Features of Oxidative Addition



	$14 + \text{C}_6\text{H}_6$	$\text{Ir}(\text{Beg})_3(\text{bpy})(\text{C}_6\text{H}_6)$ 15	TS_{15-16}	$\text{Ir}(\text{H})(\text{Ph})(\text{Beg})_3(\text{bpy})$ 16
Ir	0 (76.968) ^b	-0.005	-0.011	-0.131
bpy	0 (81.823)	-0.007	-0.075	-0.117
Beg ¹	0 (37.101)	0.025	-0.064	-0.047
Beg ²	0 (36.993)	-0.006	0.101	0.065
Beg ³	0 (37.115)	0.006	-0.065	-0.096
Ph	0 (41.204)	0.035	0.154	0.240
H	0 (0.796)	-0.049	-0.040	0.086

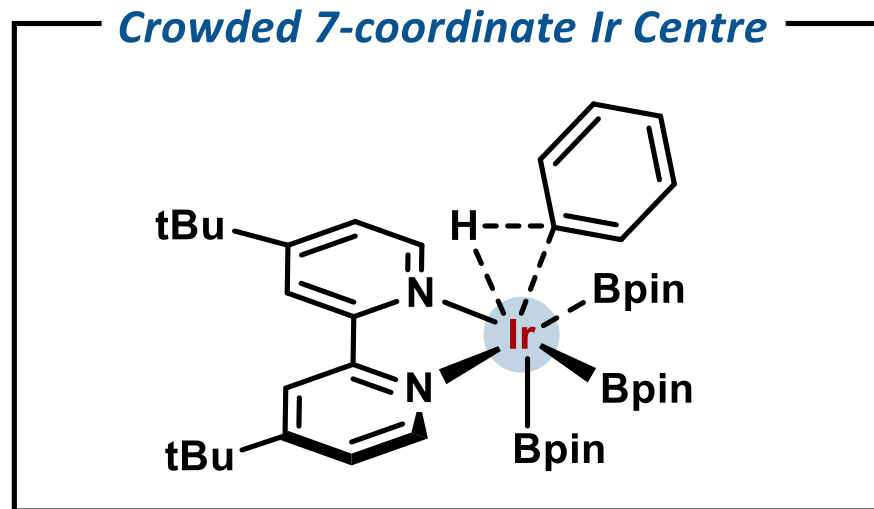
- *Coordination and Addition Both Favors Electron Poor Arene*

- *1,3-di- CF_3 - C_6H_4 reacts > 10 times faster than 1,3-di-Me- C_6H_4*

- *Introduction*
- *History of Development*
- *Mechanistic Studies*
- ***General Selectivity of Ir-Bipyridine System***
- *Directed Selectivity*

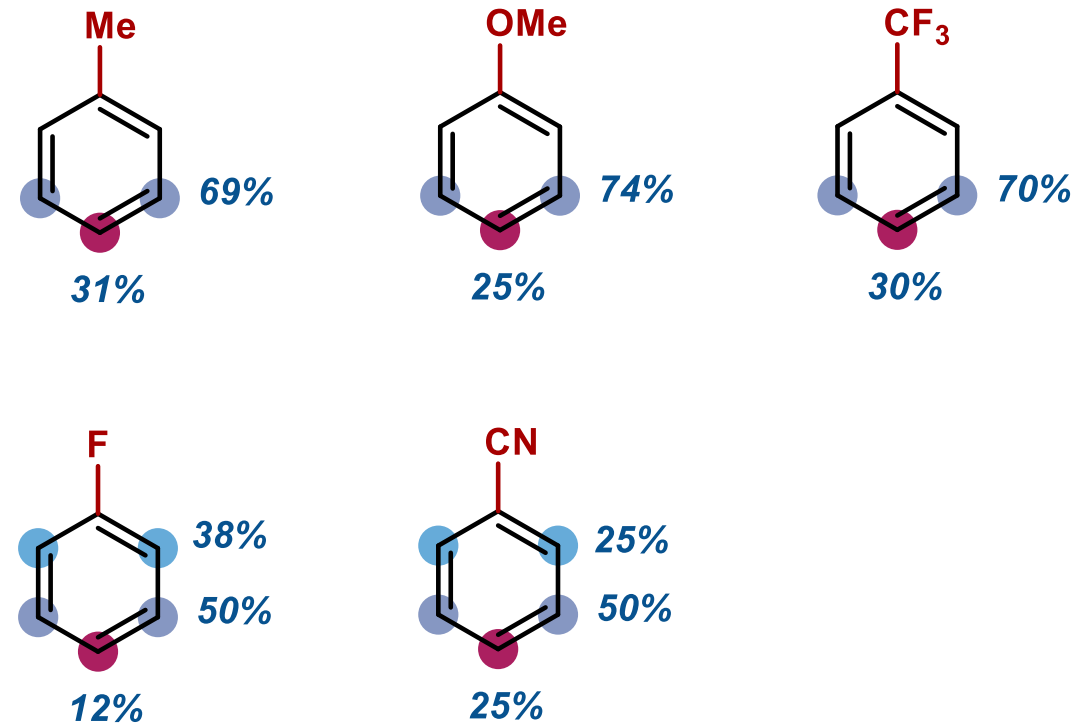
General Selectivity

Simple Benzene Derivatives



Steric Effects Predominates
Electronic Effects Also Plays a Role

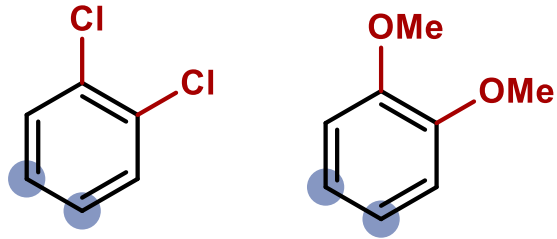
Selectivity under Ir-biyridine system



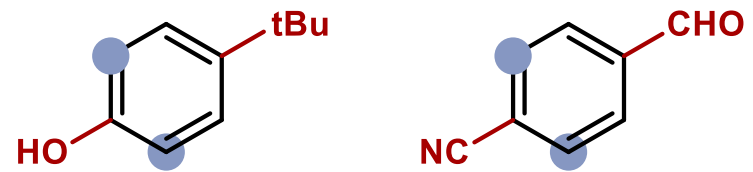
General Selectivity

Selectivity under Ir-bipyridine system

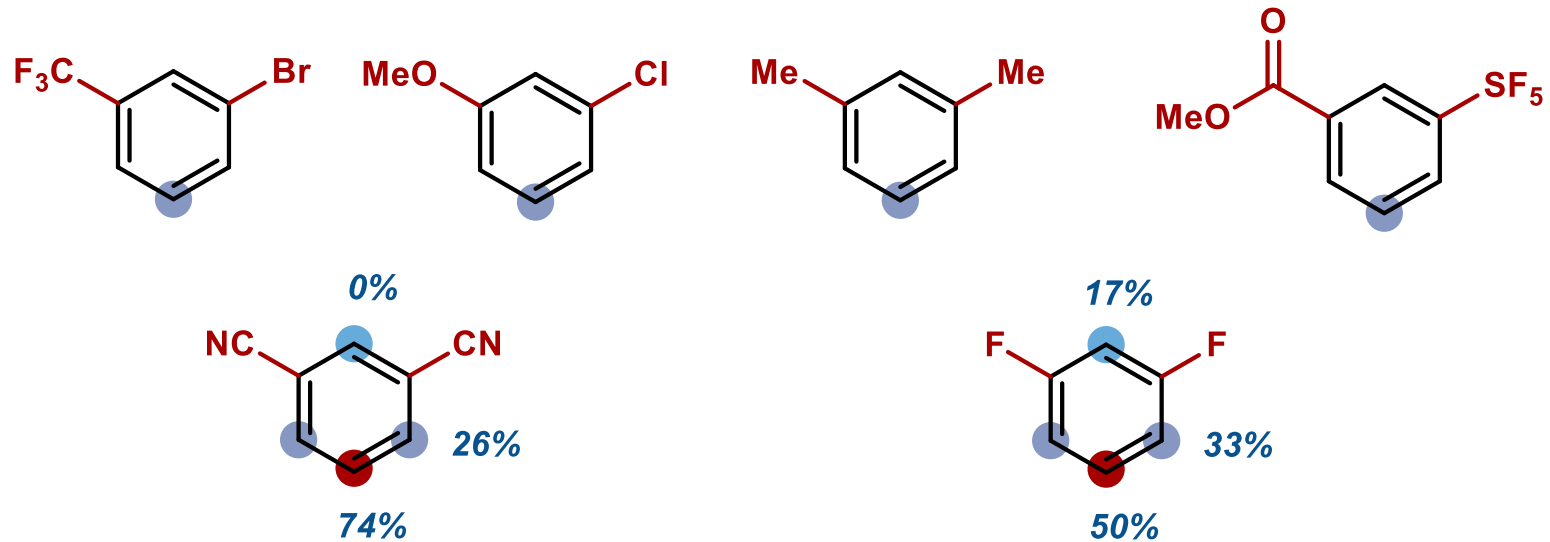
1,2- Di-substituted



1,4- Di-substituted



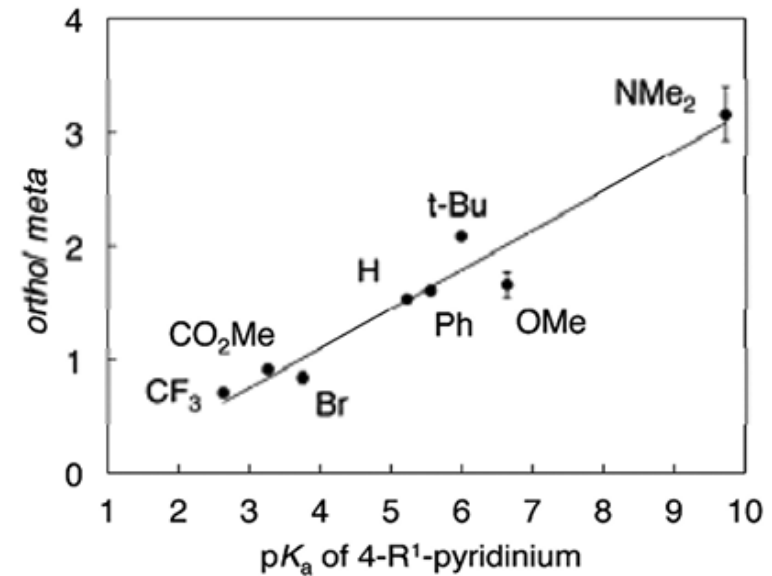
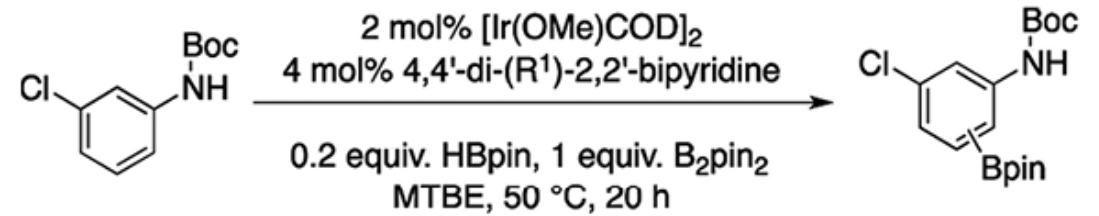
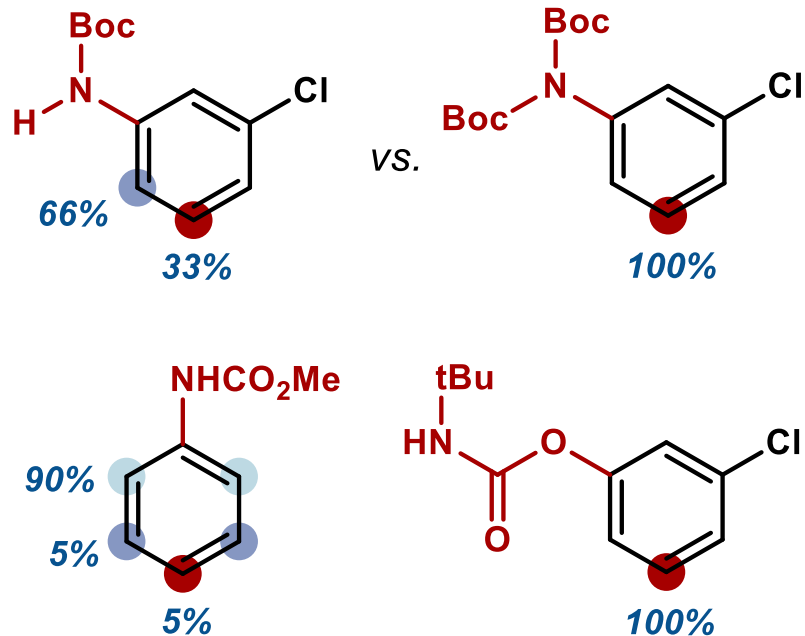
1,3- Di-substituted



General Selectivity

N-H is Different

Selectivity under Ir-bipyridine system

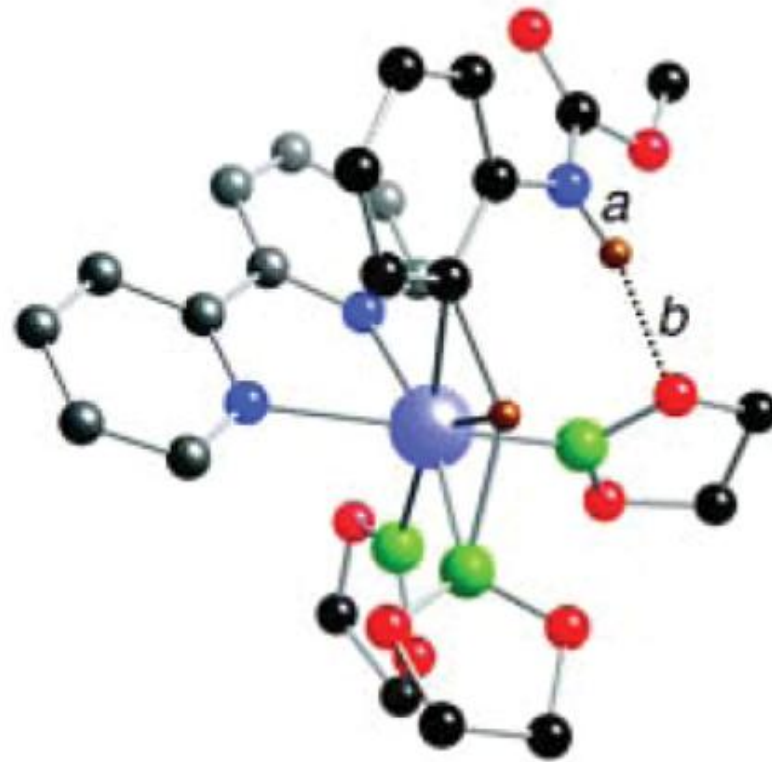


N-Coordination and N-H Metalation Excluded

General Selectivity

N-H is Different

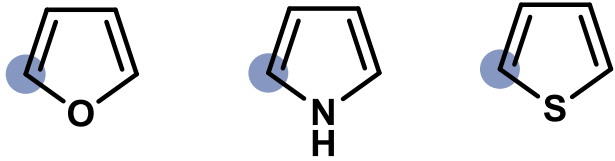
Selectivity under Ir-bipyridine system



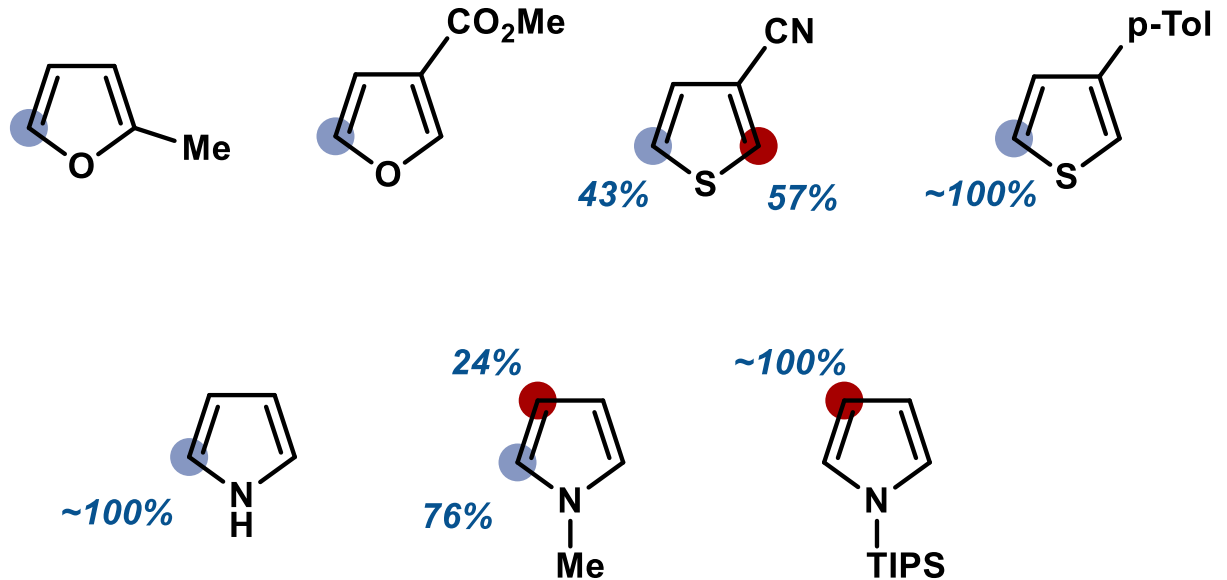
N-H Hydrogen Bonding with the Ligand Bpin

General Selectivity

Five-membered Heterocycles

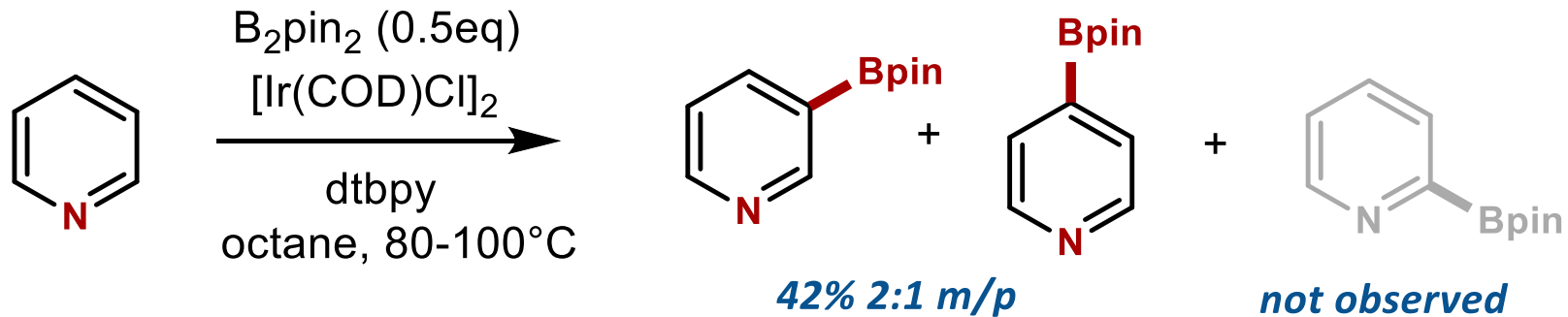


More Acidic α -Proton



General Selectivity

Six-membered Heterocycles

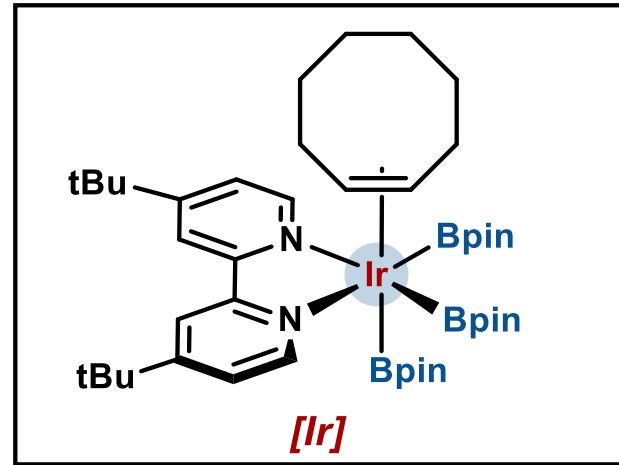
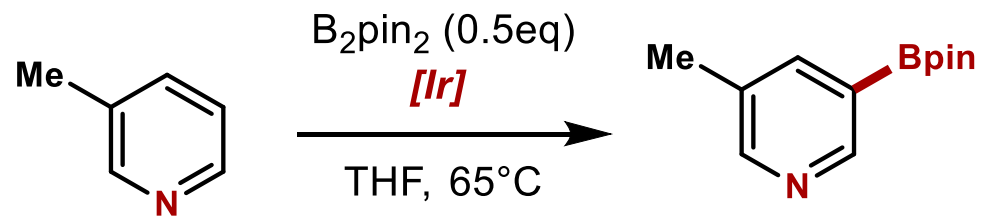


- *Nearly statistical m/p ratio*
- *α -Bpin often not observed*
- *Reacts Slowly with Coordinating N*

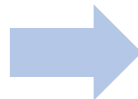
General Selectivity

Six-membered Heterocycles

Kinetic Studies



- **First Order in Catalyst**
- **Zero Order in Arene**
- **Zero Order in Diboron**

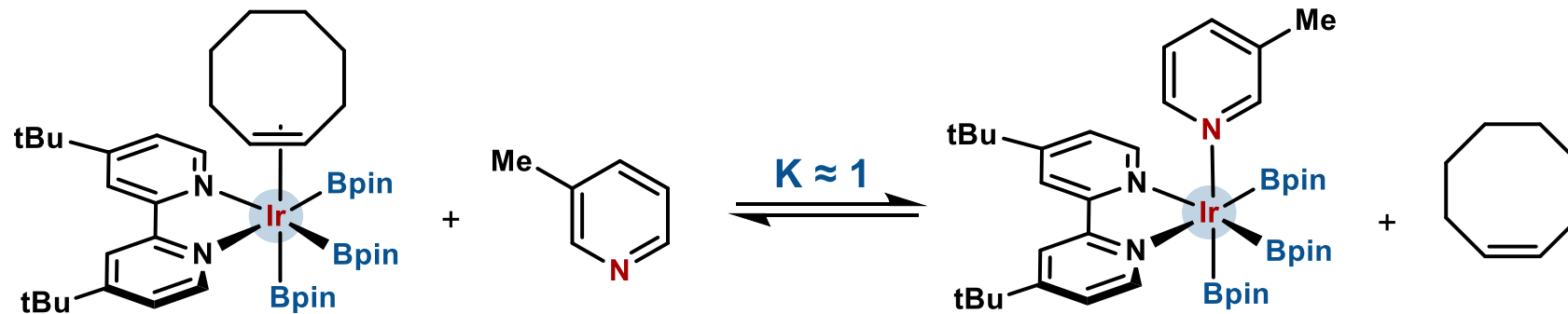


A Change in Mechanism

General Selectivity

Six-membered Heterocycles

Mechanistic Studies

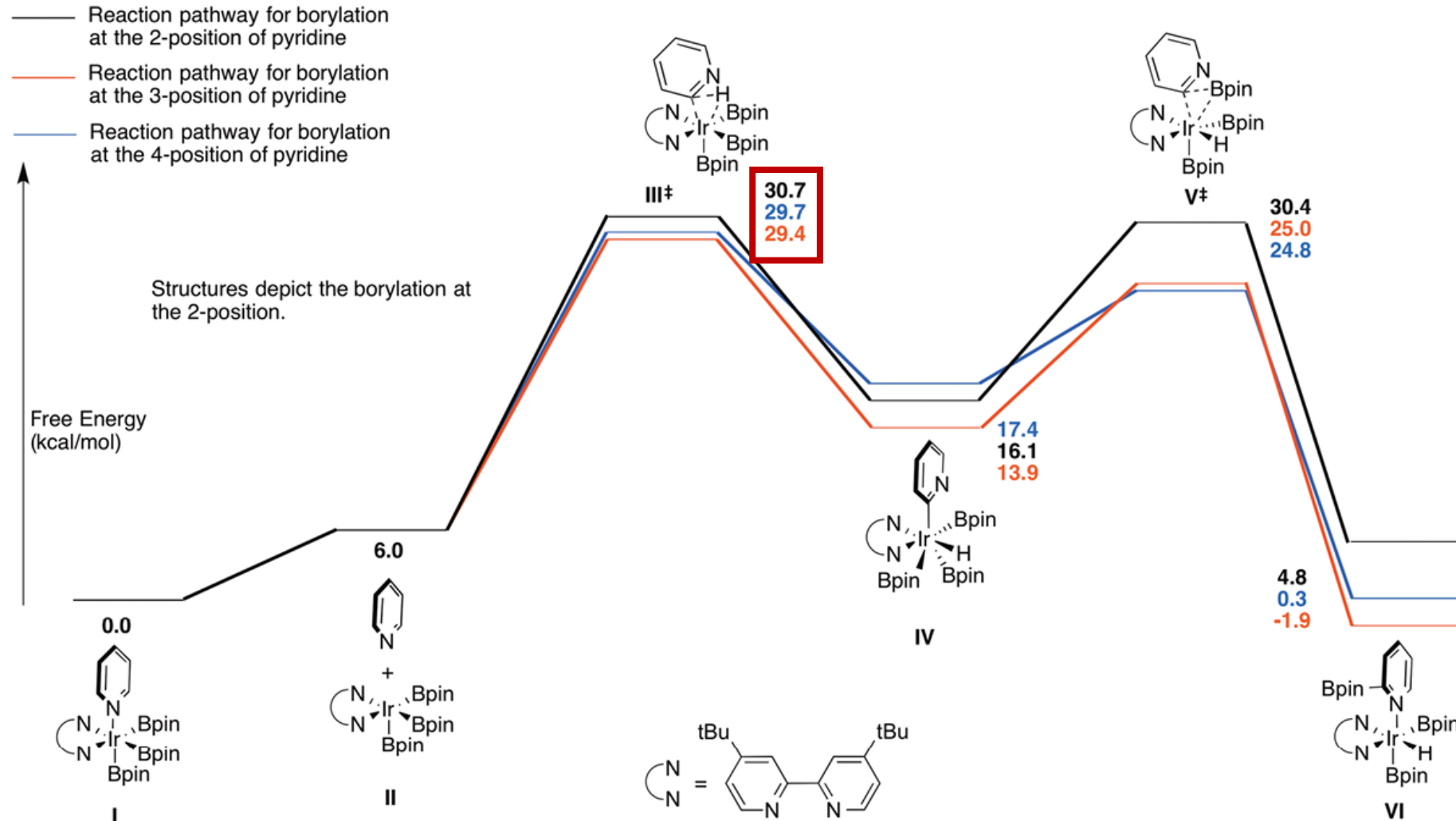


- **Substrate-Ligated Ir is the Dominant Species During Catalysis**

J. Am. Chem. Soc. **2014**, *136*, 4287–4299

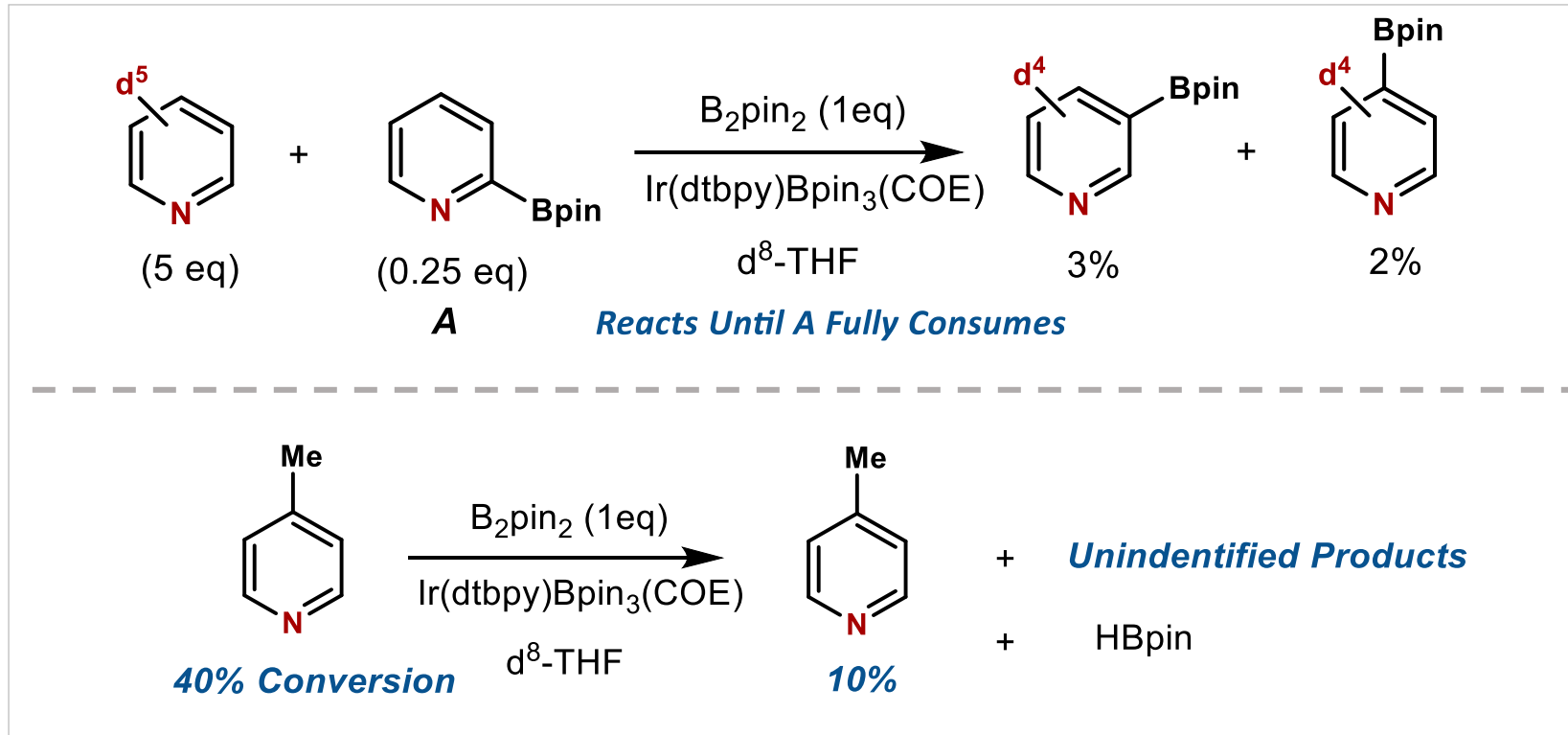
General Selectivity

Six-membered Heterocycles



General Selectivity

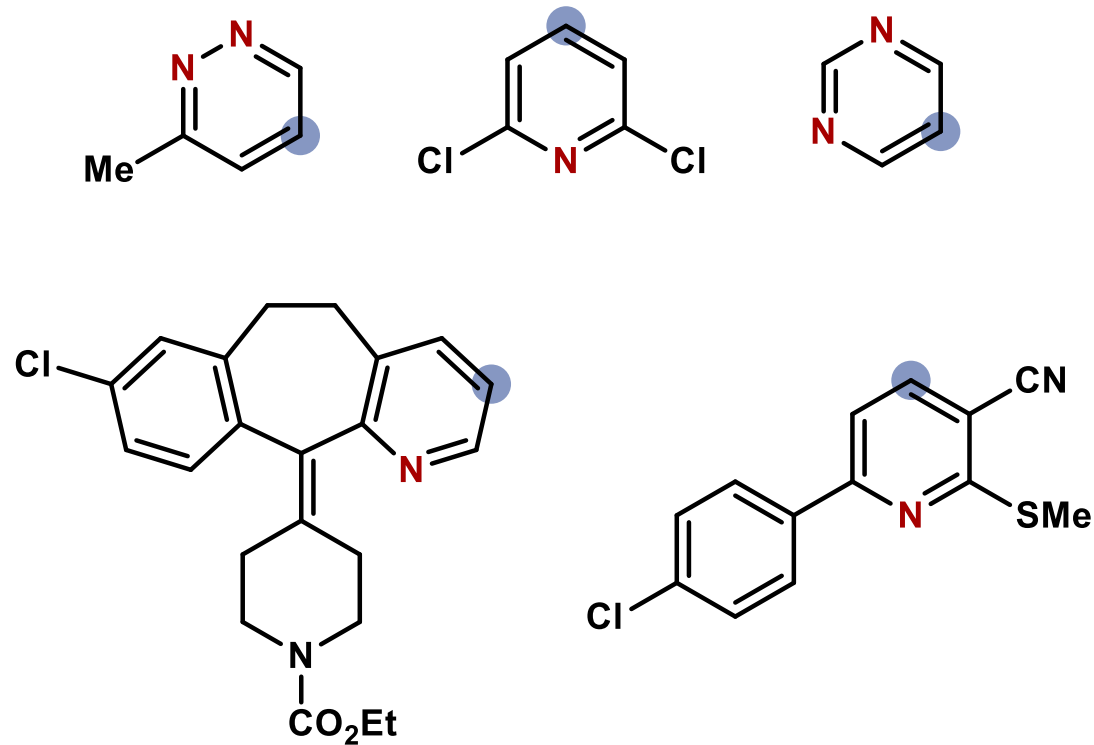
Origin for Lack of α -Borylation



Lack of α -Borylation is due to Fast Product Decomposition

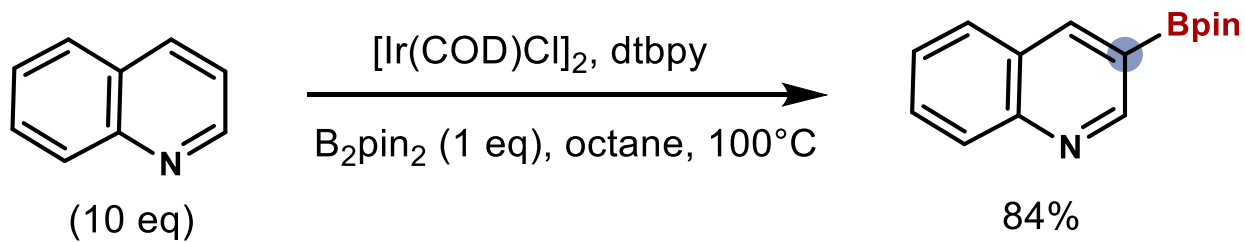
General Selectivity

Examples on Selectivity of Borylation of Pyridine Derivatives

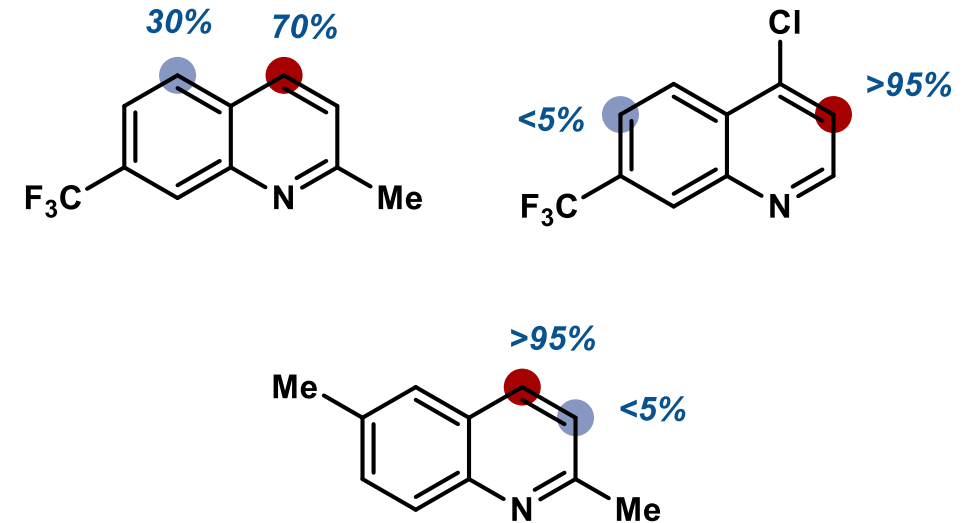


General Selectivity

Bicyclic Heterocycle: Benzo-fused-azines



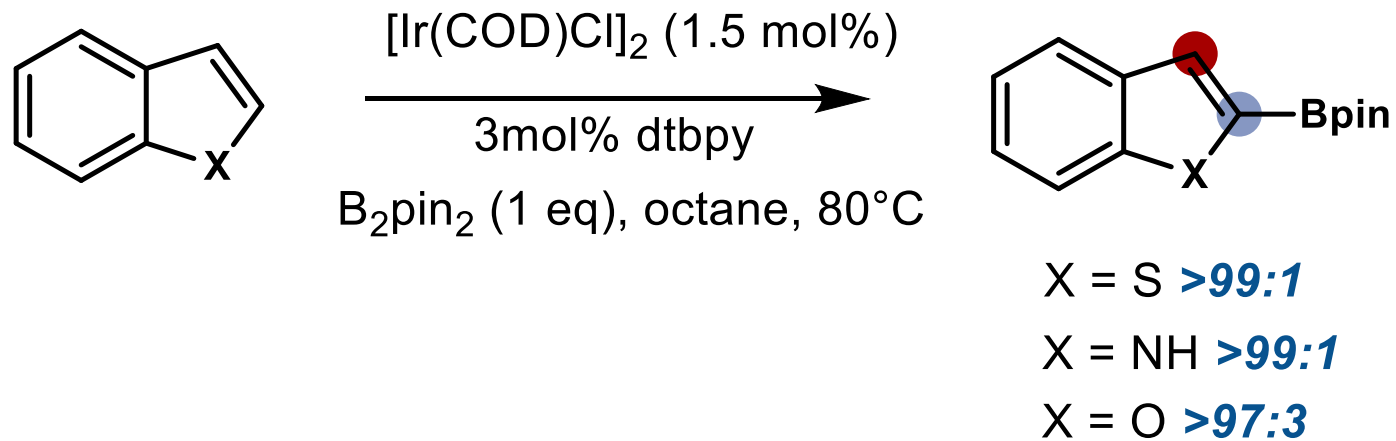
Reaction at More Electron-Deficient Heterocycle



Chem. Sci., 2012, 3, 3505

General Selectivity

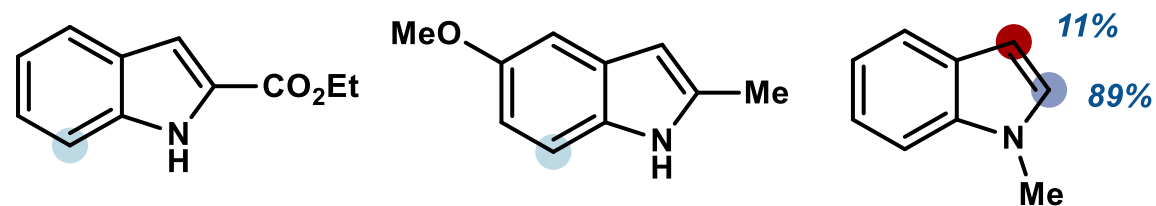
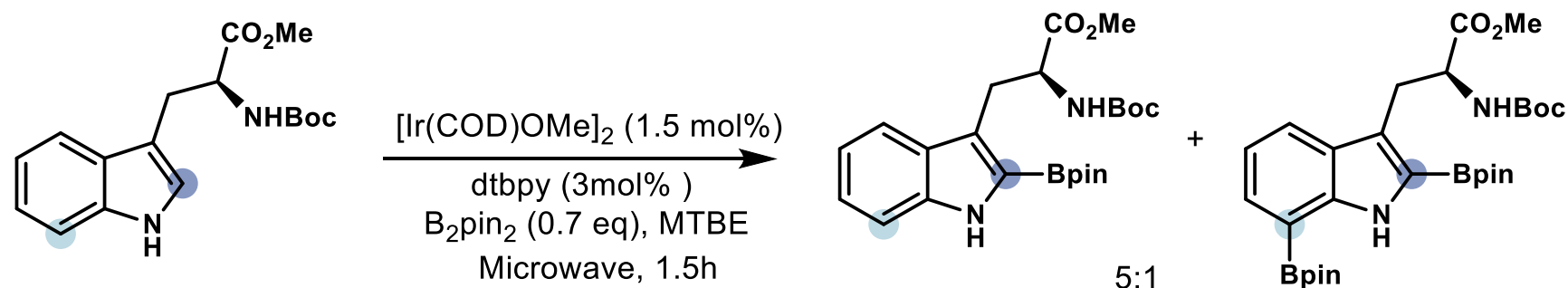
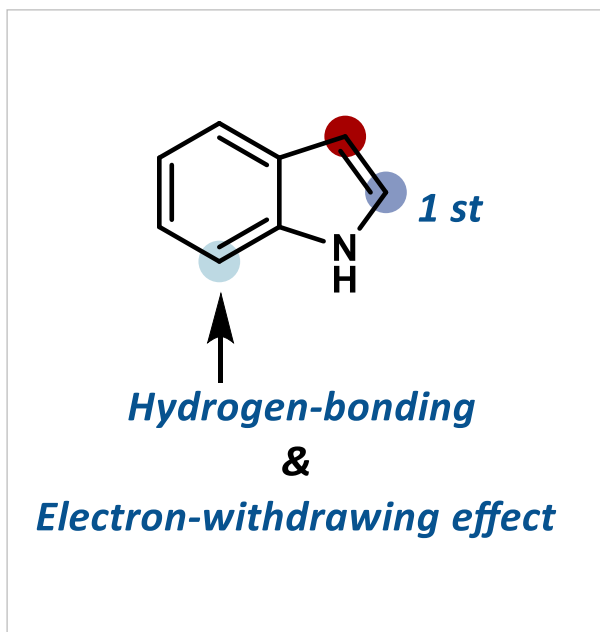
Benzo-fused-five-membered Heterocycle



Tett. Lett. **2002**, 43, 5649–5651

General Selectivity

Benzo-fused-five-membered Heterocycle

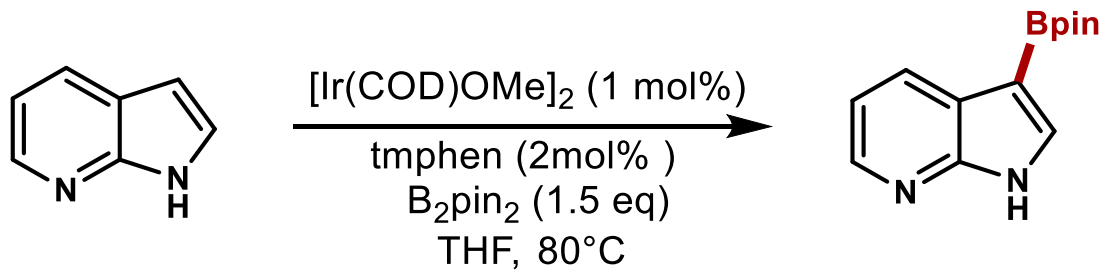


J. Org. Chem. **2014**, *79*, 11254–11263
J. Am. Chem. Soc. **2006**, *128*, 15552–15553

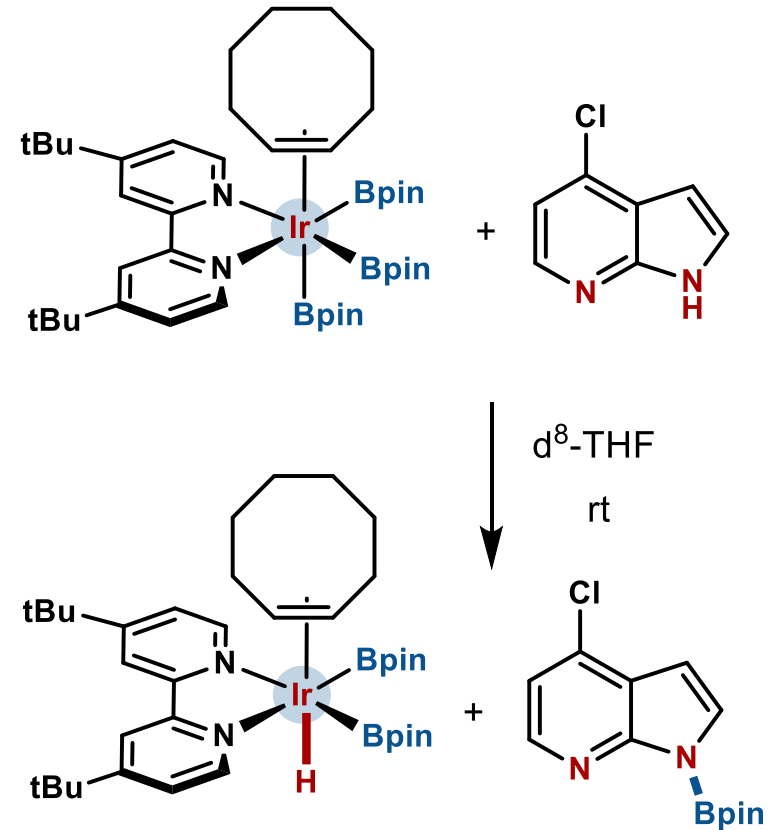
General Selectivity

X-H Bond Matters: Aniline, Acidic Azoles

'Abnormal' Selectivity

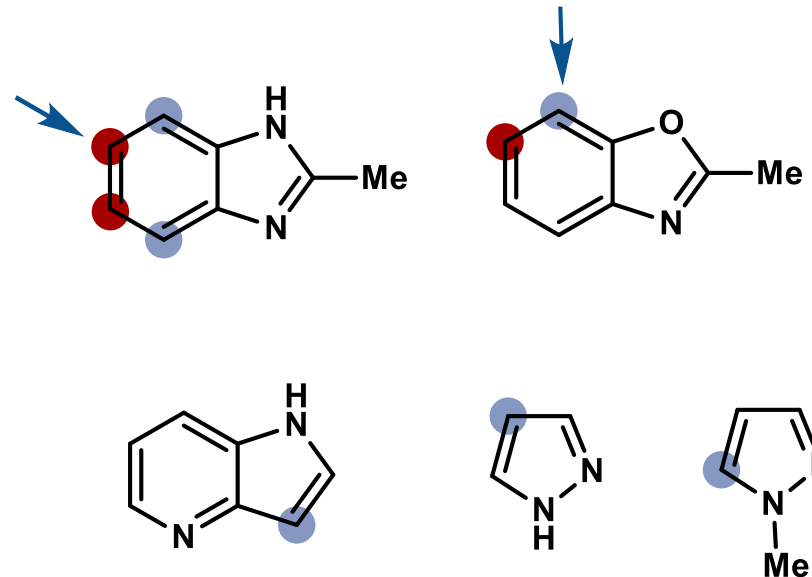
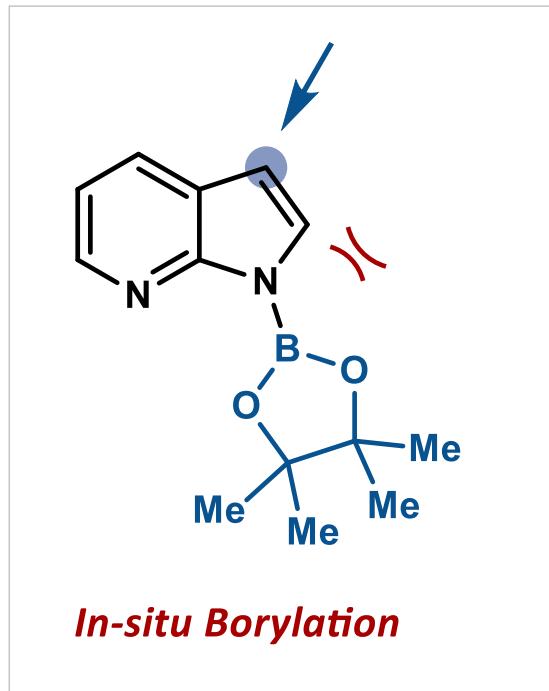


- *More Diboron Needed for High Conversion*
- *Gas Evolution Observed on Mixing*



General Selectivity

X-H Bond Matters : Aniline, Acidic Azoles

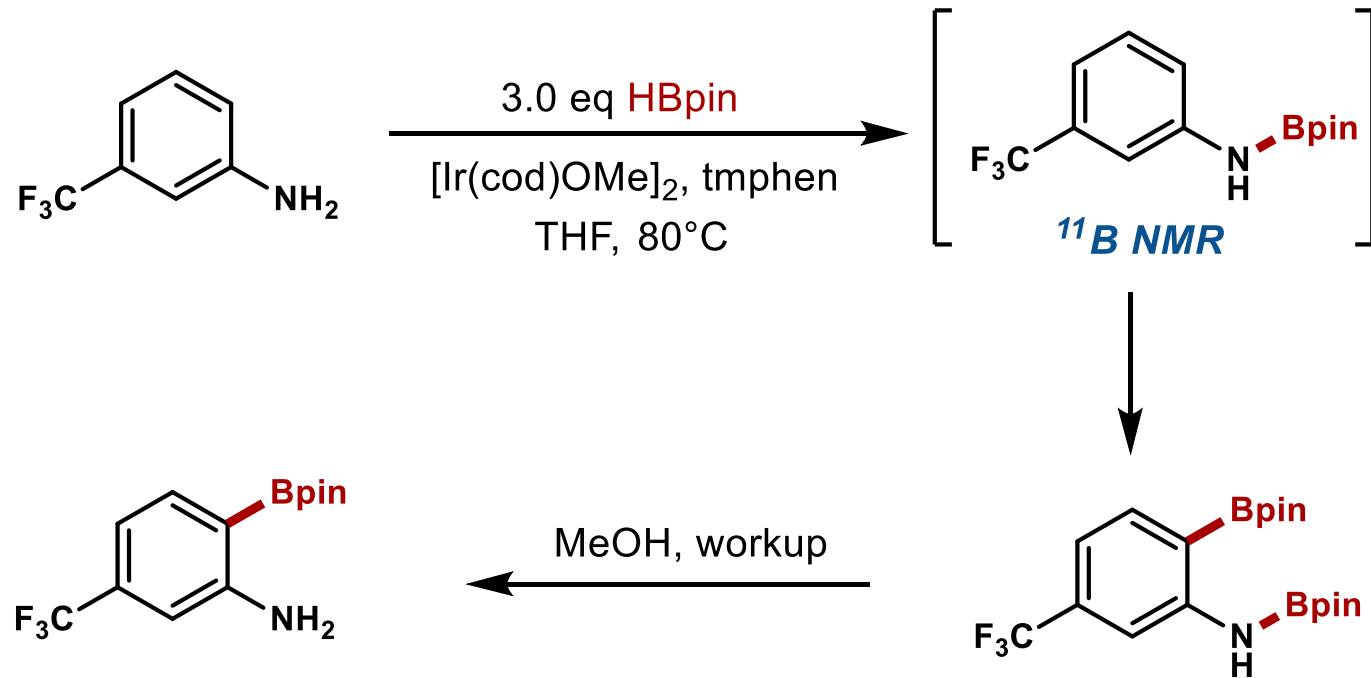


J. Am. Chem. Soc. **2014**, *136*, 4287–4299

General Selectivity

X-H Bond Matters: Aniline, Acidic Azoles

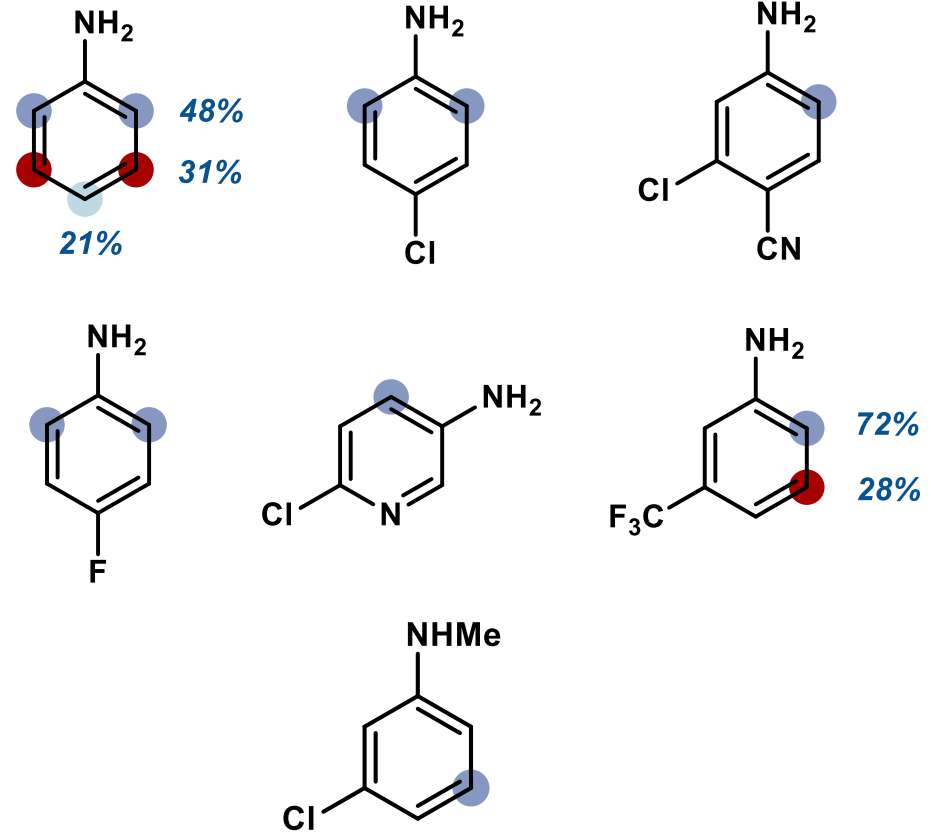
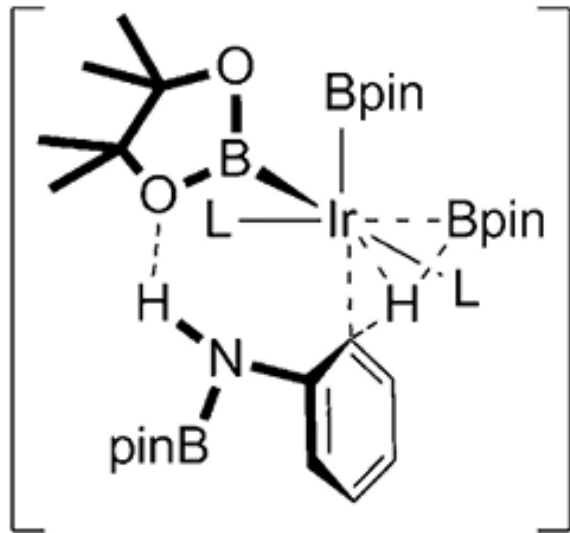
Ortho-selective Borylation



General Selectivity

X-H Bond Matters: Aniline, Acidic Azoles

Ortho-selective Borylation

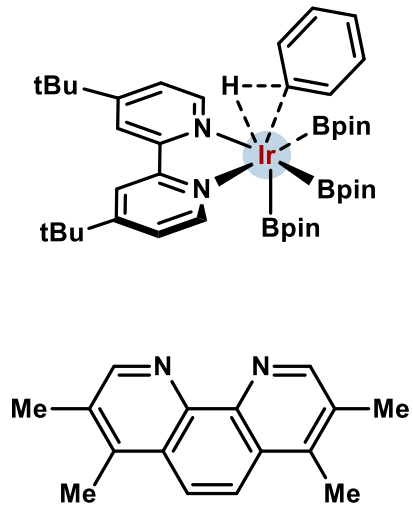


- *Introduction*
- *History of Development*
- *Mechanistic Studies*
- *General Selectivity of Ir-Bipyridine System*
- *Directed Selectivity*

Directed Selectivity

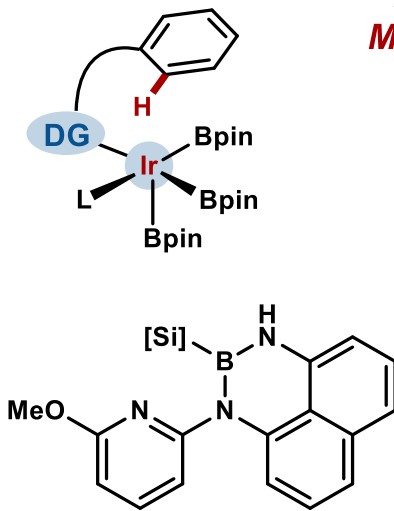
Ir Catalyzed C-H Borylation

*Sterically or
Electronically Directed*

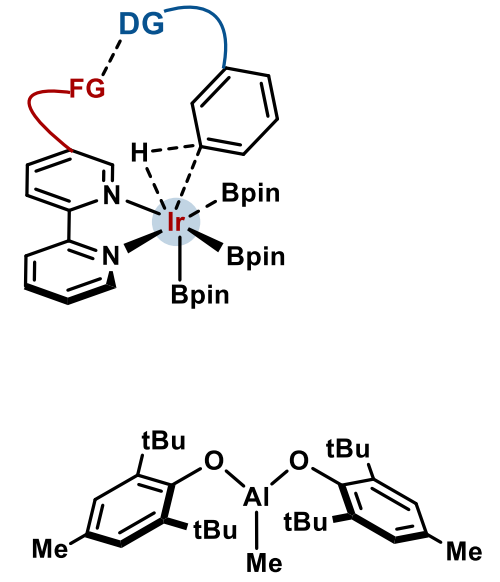
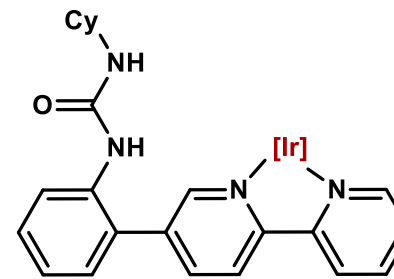


*FG-Directed
Borylation*

*Inner Sphere
Metal-Substrate
cholate formation*

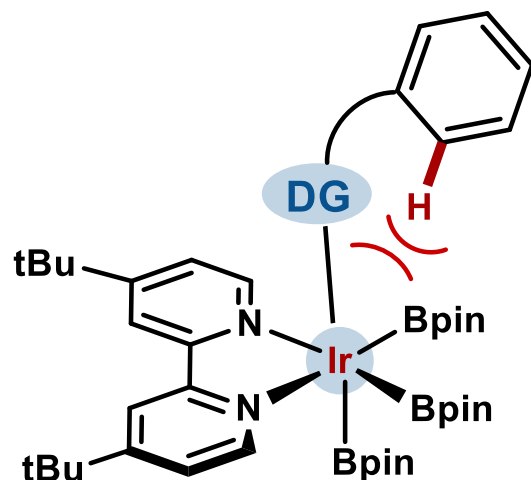


*Outer Sphere
Ligand-Substrate
supramolecular interactions*

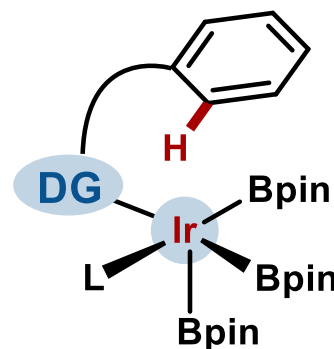


Directed Selectivity: Inner Sphere

Methods to achieve Substrate-Directed Borylation



Non-directed Borylation

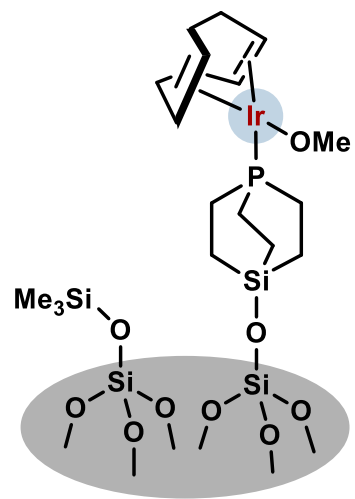
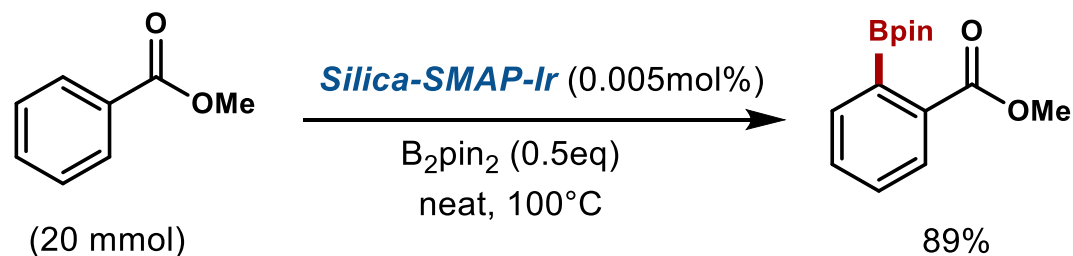


Directed Borylation

Directed Selectivity: Inner Sphere

Monobidentate Ligand

(Sawamura)



Silica-SMAP-Ir

• Reaction also proceeds with:

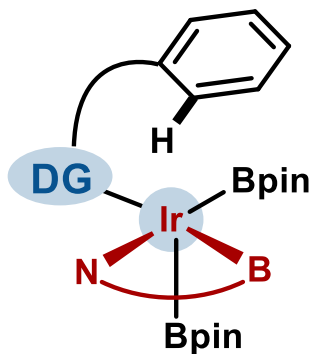
***PCy₃ (P/Ir = 1:1 or 2:1),
PPh₃ (P/Ir = 1:1) and PMe₃ (1:1)***

J. Am. Chem. Soc. **2009**, *131*, 5058–5059

entry	arene	product	temp (°C)	time (h)	yield ^b (%)	ratio of <i>o</i> /(<i>m</i> + <i>p</i>) ^c
1	<chem>COC(=O)c1ccccc1</chem> (1k)	<chem>COC(=O)c1ccccc1B(C1OC(C)OC1)C(C)C</chem> (3k)	50	1	87 (101)	>99:1
2	<chem>CN(C)C(=O)c1ccccc1</chem> (1l)	<chem>CN(C)C(=O)c1ccccc1B(C1OC(C)OC1)C(C)C</chem> (3l)	50	3	79 (97)	>99:1
3	<chem>COS(=O)(=O)c1ccccc1</chem> (1m)	<chem>COS(=O)(=O)c1ccccc1B(C1OC(C)OC1)C(C)C</chem> (3m)	50	2	89 (103)	>99:1
4	<chem>C1CCOCC1c1ccccc1</chem> (1n)	<chem>C1CCOCC1c1ccccc1B(C1OC(C)OC1)C(C)C</chem> (3n)	70	2	105 (116)	>99:1
5	<chem>COC(=O)C1=CC=CC=C1</chem> (1o)	<chem>COC(=O)C1=CC=CC=C1B(C1OC(C)OC1)C(C)C</chem> (3o)	100	6	72 (95)	>99:1
6	<chem>Clc1ccccc1</chem> (1p)	<chem>Clc1ccccc1B(C1OC(C)OC1)C(C)C</chem> (3p)	50	24	50 (71)	92:8
7	<chem>Clc1ccc(cc1)C(F)(F)F</chem> (1q)	<chem>Clc1ccc(cc1)C(F)(F)FB(C1OC(C)OC1)C(C)C</chem> (3q)	50	4	75 (83)	>99:1 ^d
8	<chem>CCOC(=O)c1ccc(Cl)cc1</chem> (1r)	<chem>CCOC(=O)c1ccc(Cl)cc1B(C1OC(C)OC1)C(C)C</chem> (3r)	70	20	87 (105)	>99:1 ^d

Directed Selectivity: Inner-Sphere

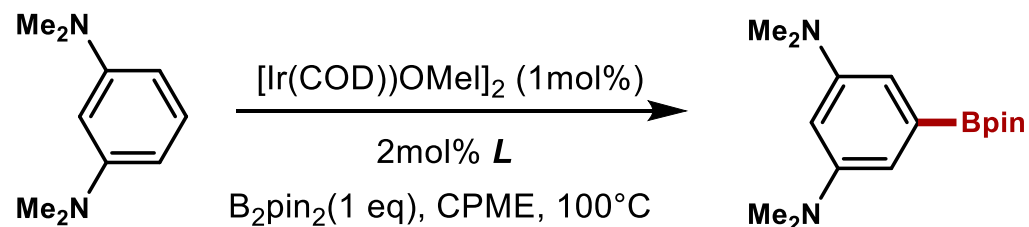
Anionic Ligand



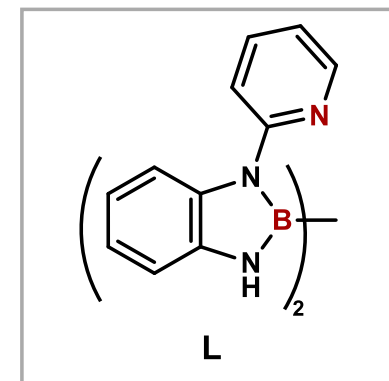
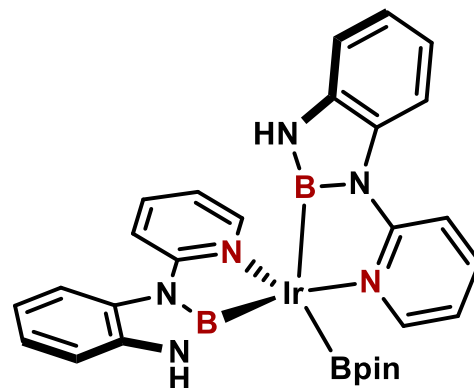
Maintained Stability via
Bidentate B-N Ligand

Previous Work

(Pengfei Li)



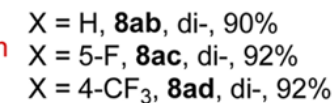
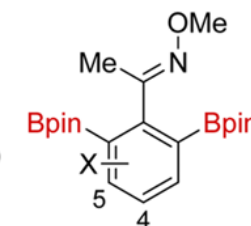
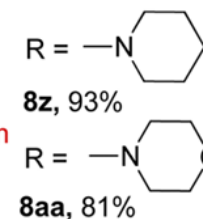
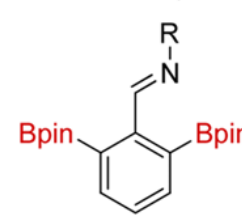
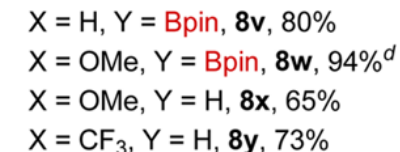
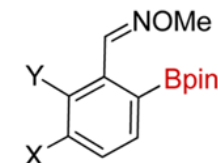
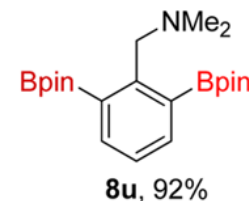
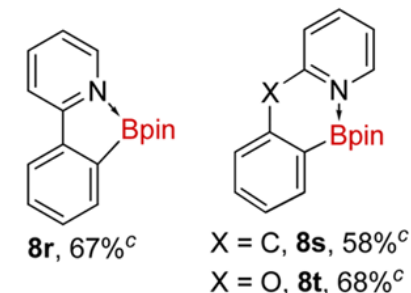
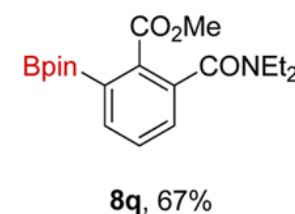
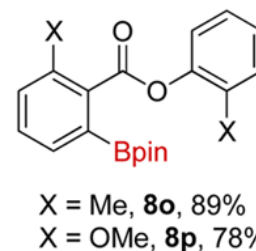
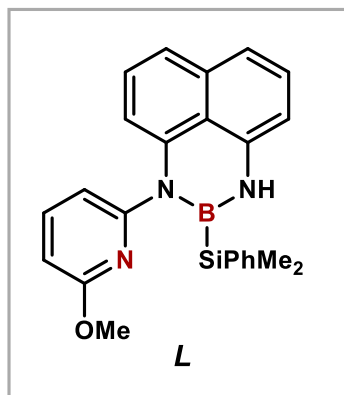
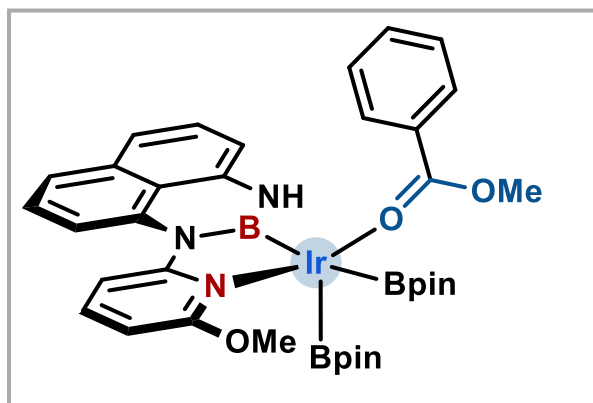
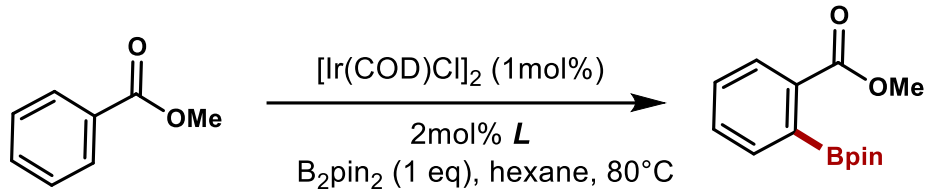
Proposed Active Species



Directed Selectivity: Inner Sphere

Anionic Ligand

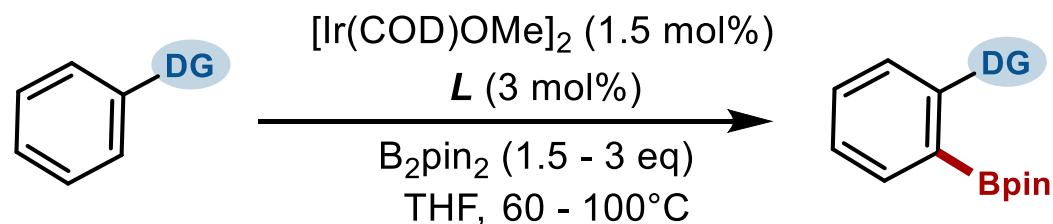
Pengfei Li (2016)



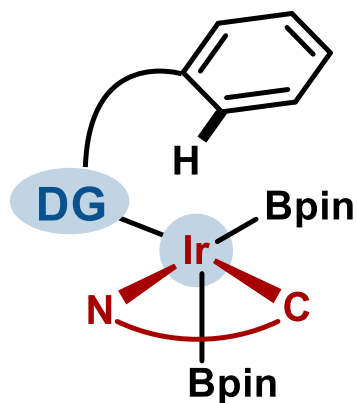
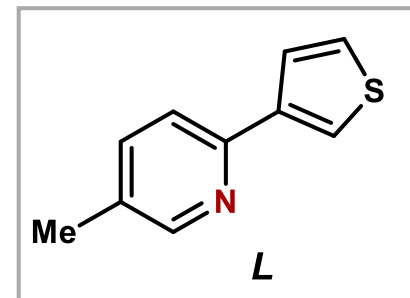
Directed Selectivity: Inner Sphere

Cyclometallated Catalysts

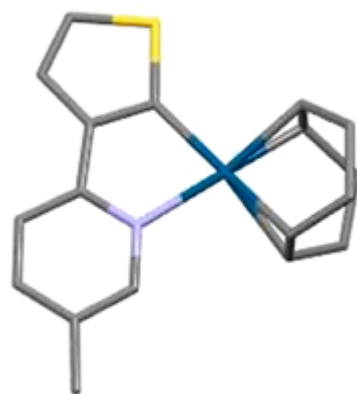
Chattopadhyay (2021)



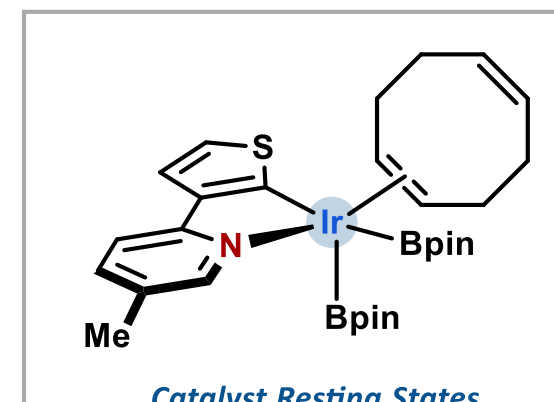
DG = Diverse O, N, S, Based Functional Group



Bidentate C-N Ligand



Synthesized Precatalysts



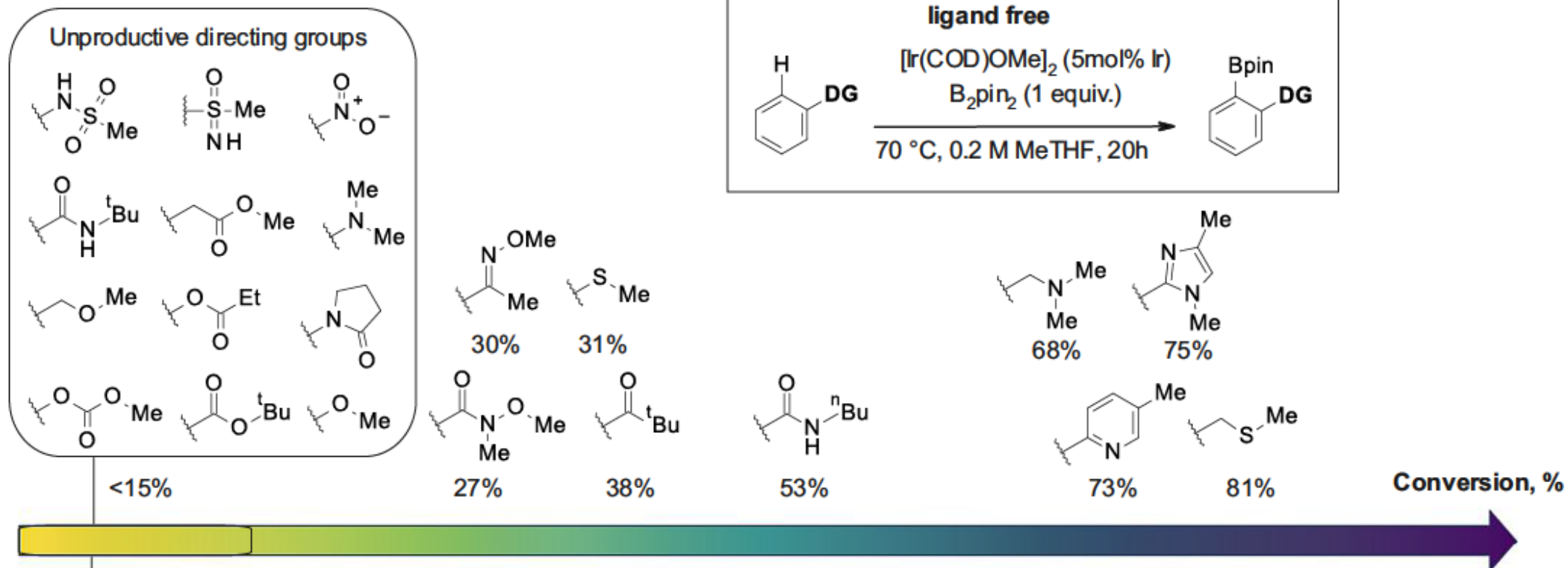
Catalyst Resting States

1D and 2D NMR characterized

Directed Selectivity: Inner Sphere

Ligand-Free Cyclometallation

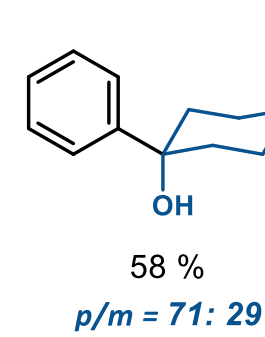
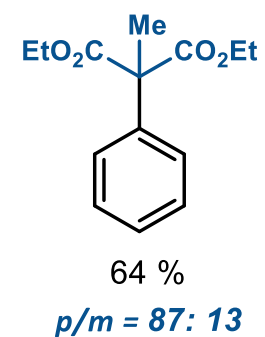
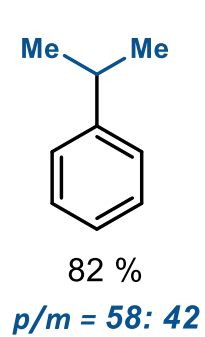
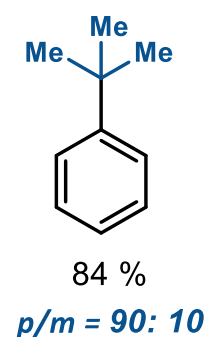
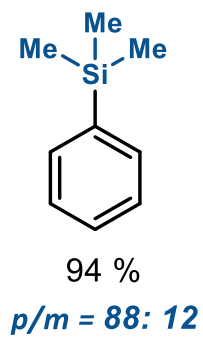
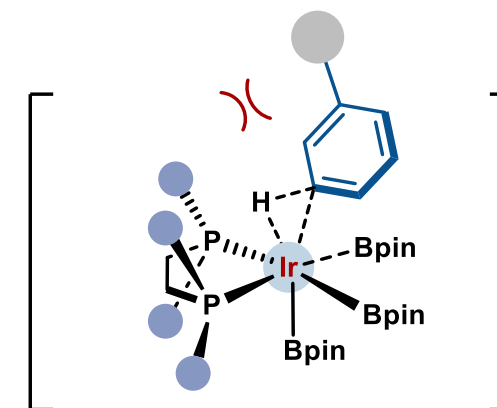
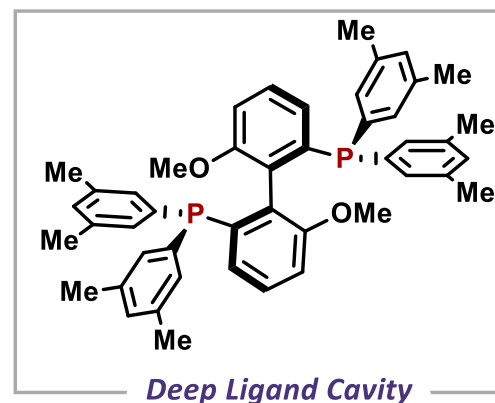
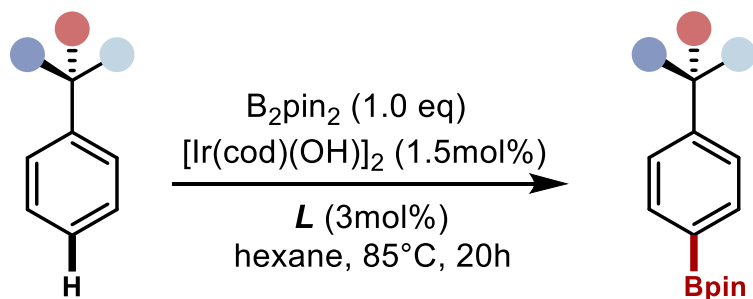
a)



Directed Selectivity: Outer Sphere

Van der Waals Repulsion Driven Selectivity

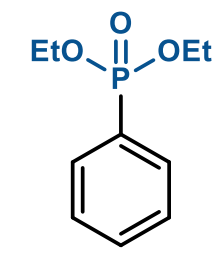
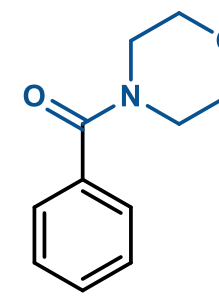
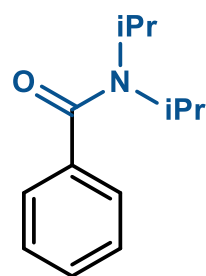
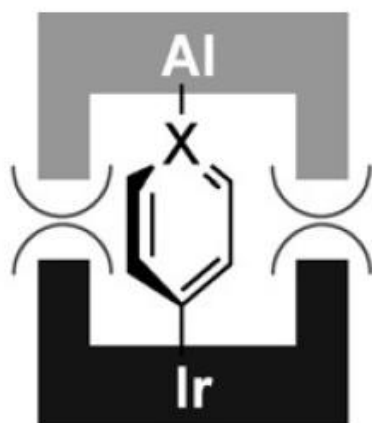
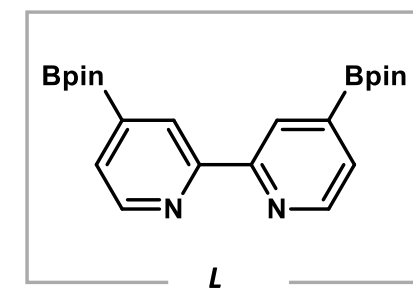
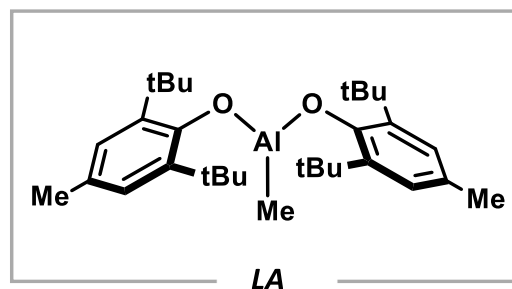
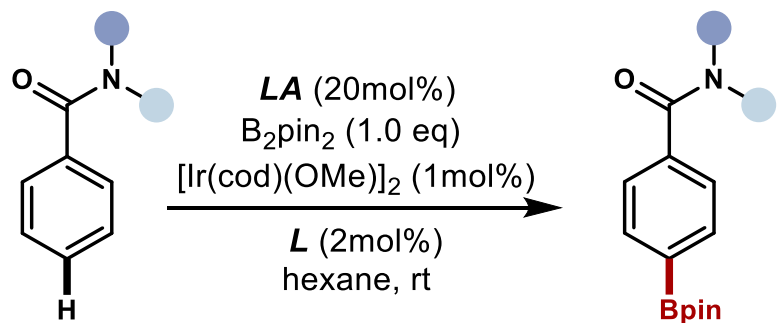
Itami (2015)



Directed Selectivity: Outer Sphere

Van der Waals Repulsion Driven Selectivity

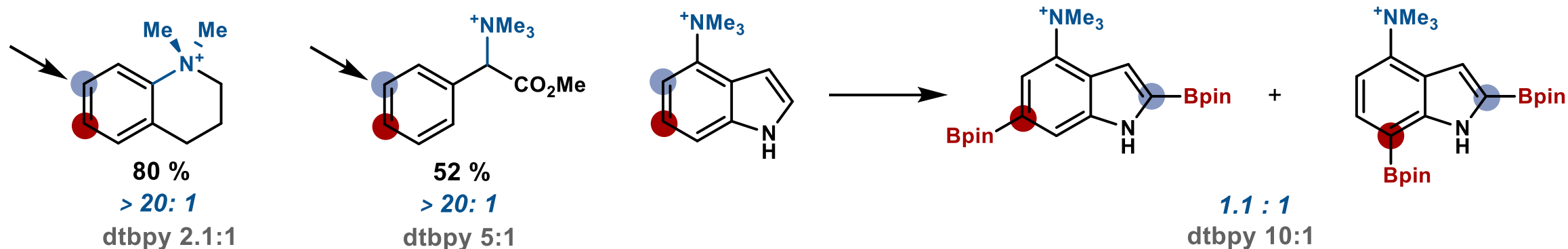
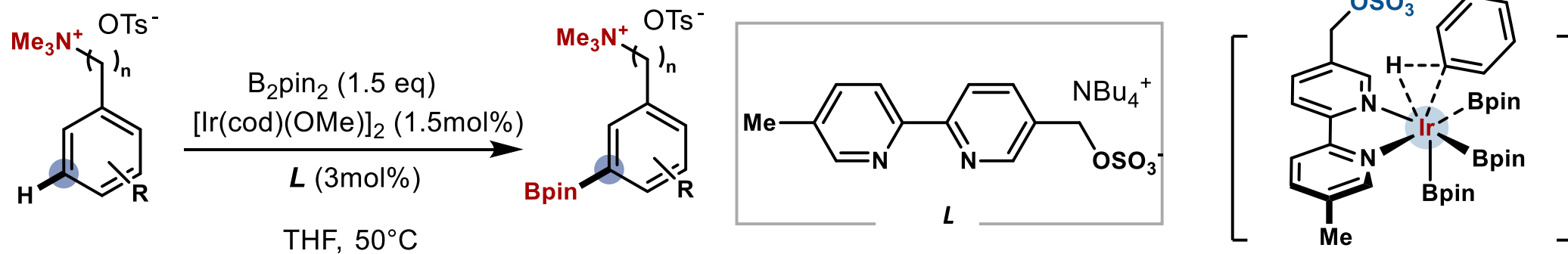
Nakao (2017)



Directed Selectivity: Outer Sphere

Electrostatic Driven Selectivity

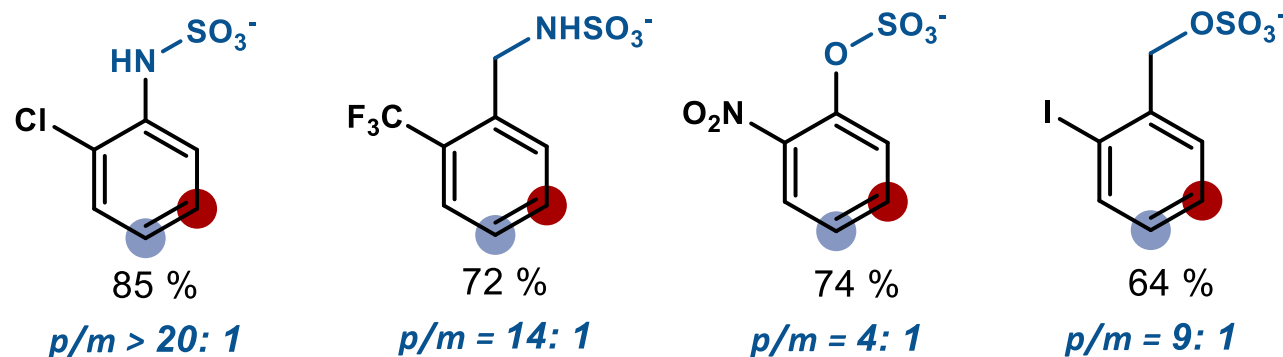
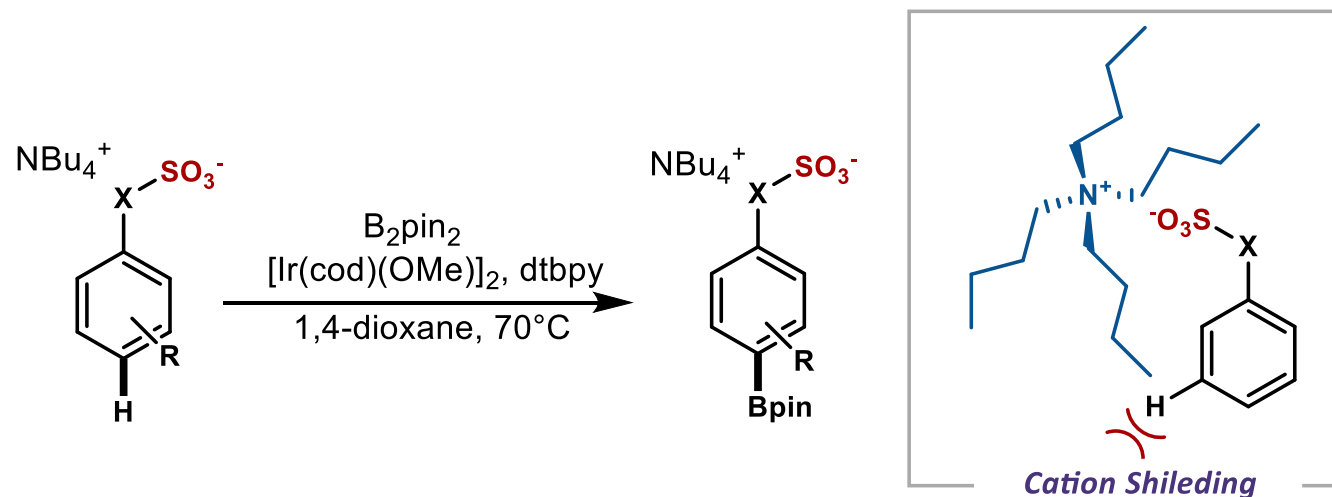
(Phillips, 2017)



Directed Selectivity: Outer Sphere

Electrostatic Driven Selectivity

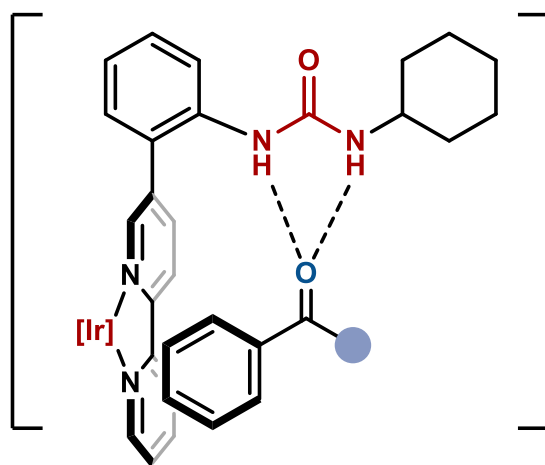
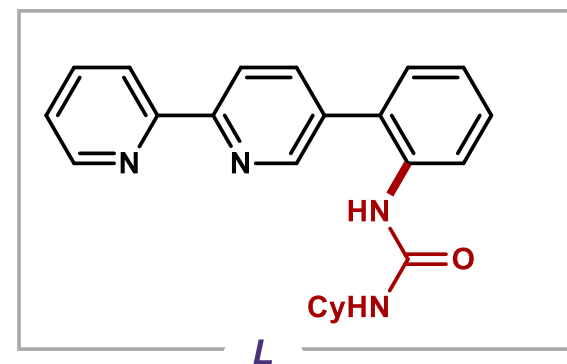
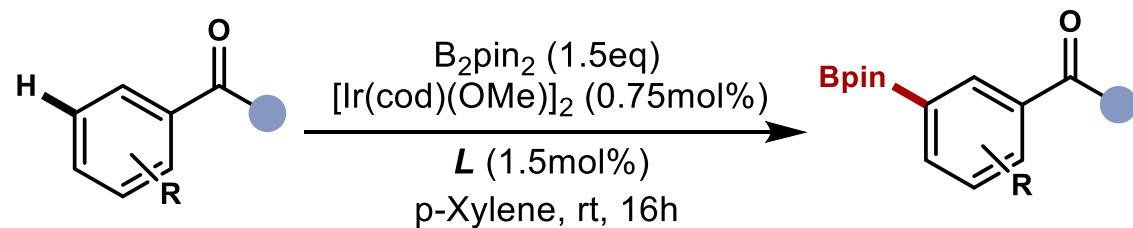
(Phillps, 2019)



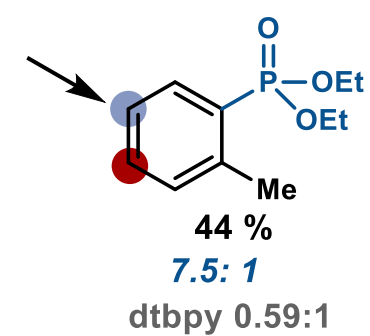
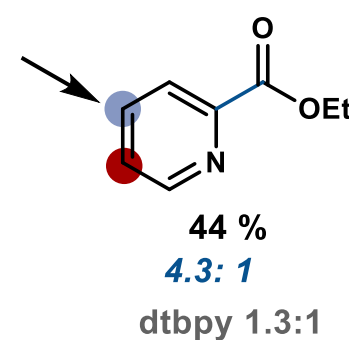
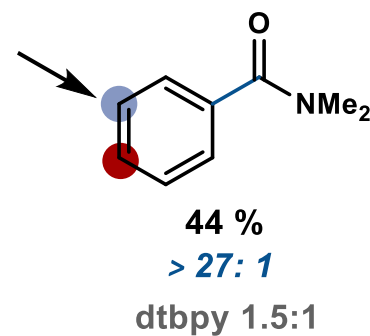
Directed Selectivity: Inner Sphere

Coordinating Side-Chain Driven Selectivity

(Kanai, 2015)

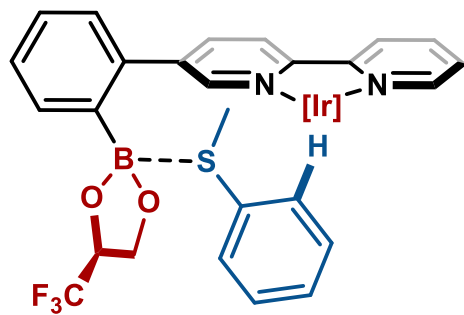


Selected Scope

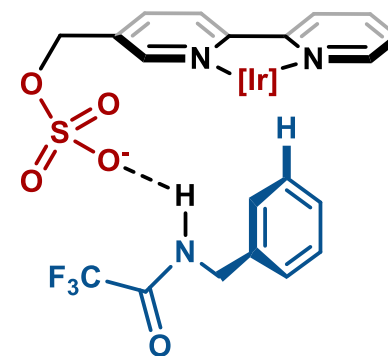


Directed Selectivity: Outer Sphere

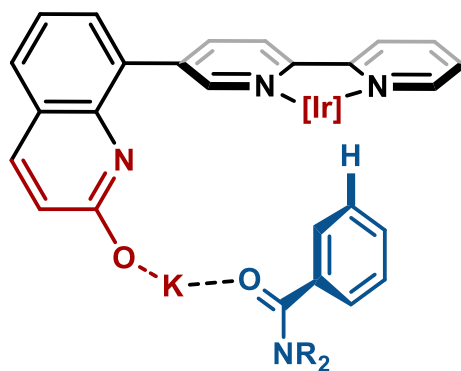
Coordinating Side-Chain Driven Selectivity



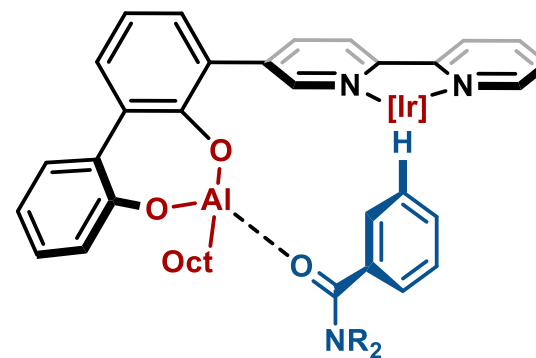
(2017, Kanai)



(2017, Phillips)



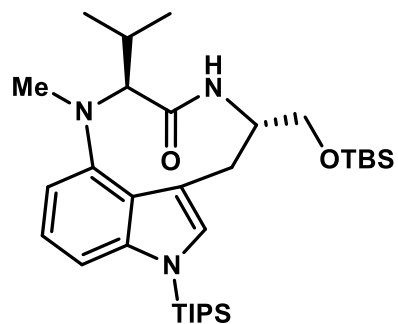
(2018, Chattopadhyay)



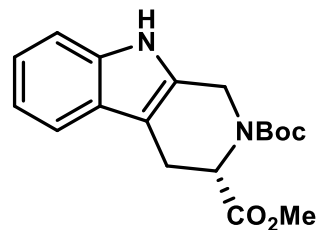
(2019, Nakao)

Problems

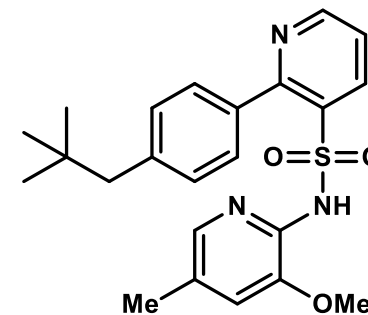
Predict the Major Site of Borylation



[Ir(COD)OMe]₂ (10mol%)
tmphen (20mol%)
HBpin (4eq)
octane/THF, 80°C, 6h



[Ir(COD)OMe]₂ (1mol%)
dtbpy (2mol%)
B₂pin₂ (1.5eq)
THF, 90°C



[Ir(COD)OMe]₂ (1.25mol%)
tmphen (2.5mol%)
B₂pin₂ (2eq)
THF, 80°C

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