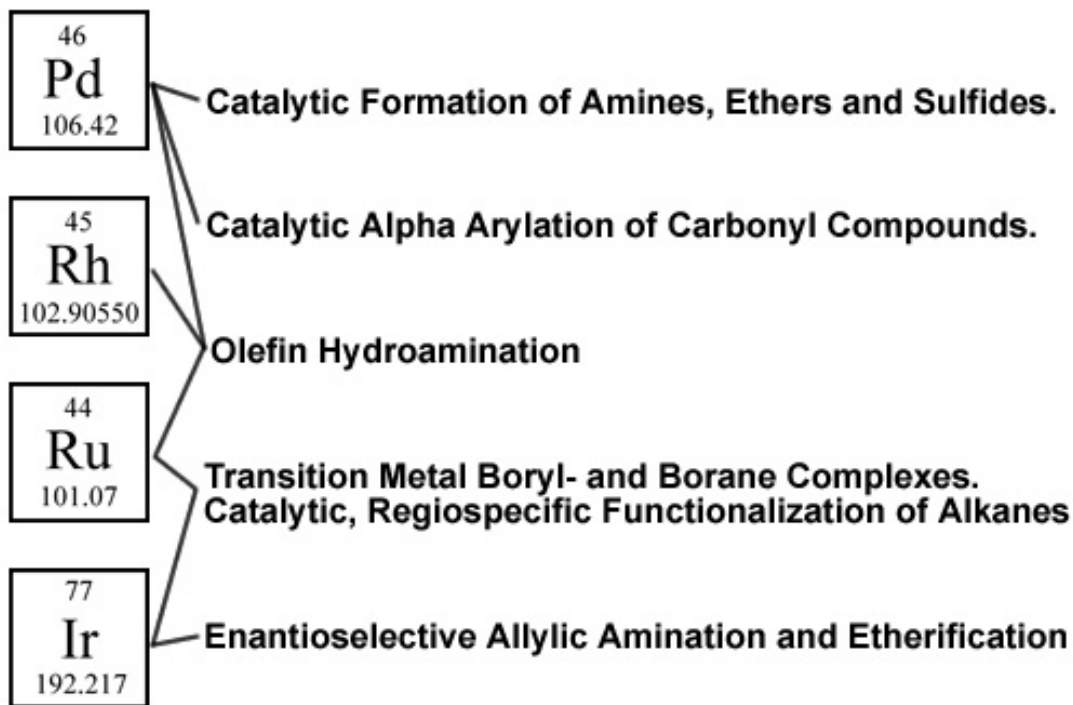


The Hartwig Group



Yubai Zhou

Wulff's Group

Michigan State University

4/4/2014

John F. Hartwig

Educational Experience

A.B. Princeton University, 1986

Undergraduate thesis advisor: Maitland Jones Jr.

Ph.D. University of California, Berkeley, 1990

Ph.D. advisors: Richard A. Anderson and Robert G. Bergman

American Cancer Society Postdoctoral Fellow,
Massachusetts Institute of Technology, 1990-1992

Postdoctoral advisor: Stephen J. Lippard

Professional Experience

1992-1996 Yale University, Assistant Professor of Chemistry

1996-1998 Yale University, Associate Professor of Chemistry

1998-2006 Yale University, Professor of Chemistry

2006-2011 University of Illinois Urbana-Champaign, Professor of
Chemistry

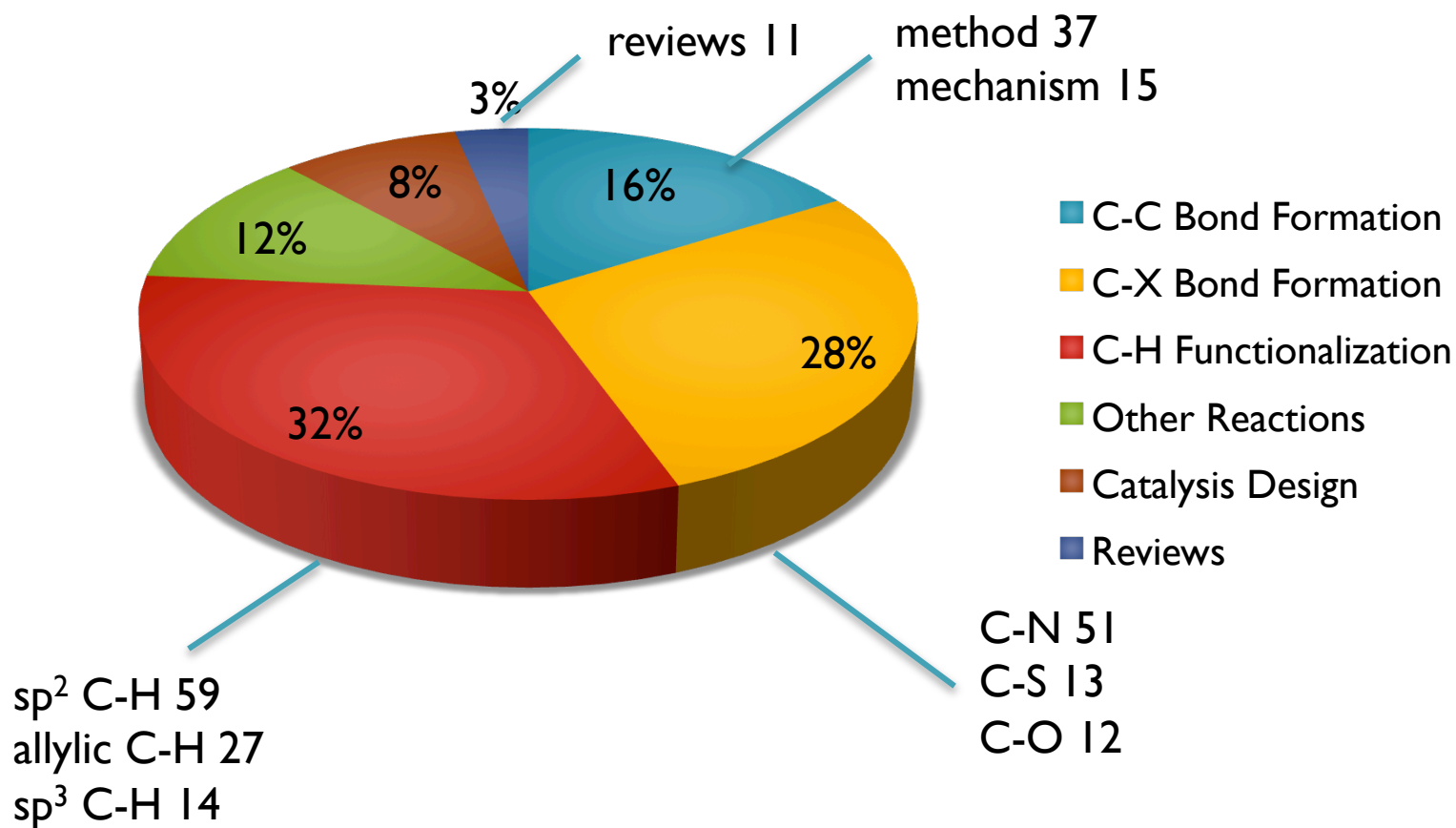
2011-present University of California, Berkeley, Professor of Chemistry



John F. Hartwig

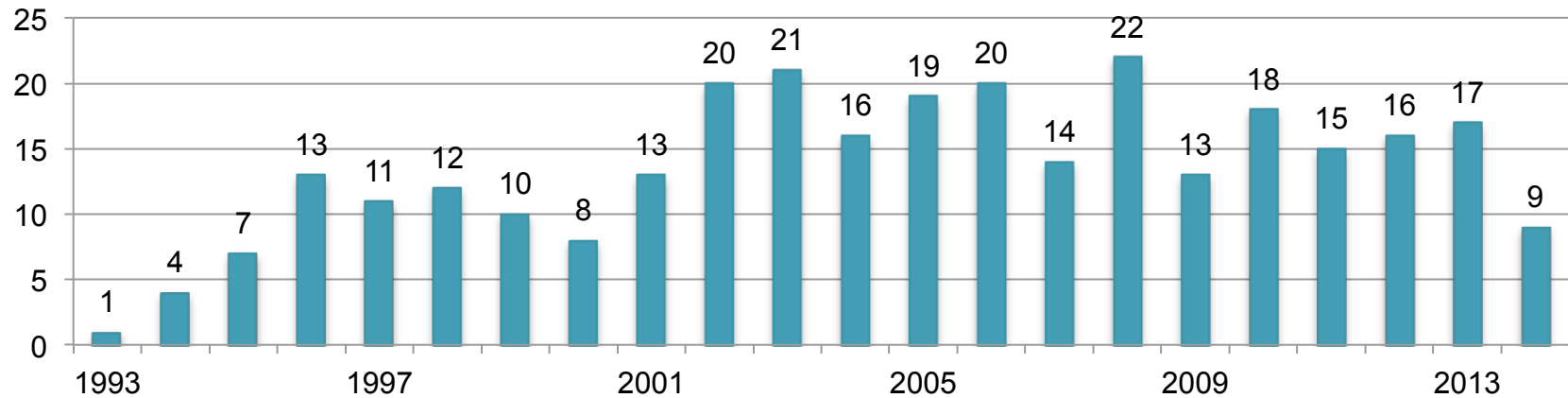
Publication Topics

210 papers

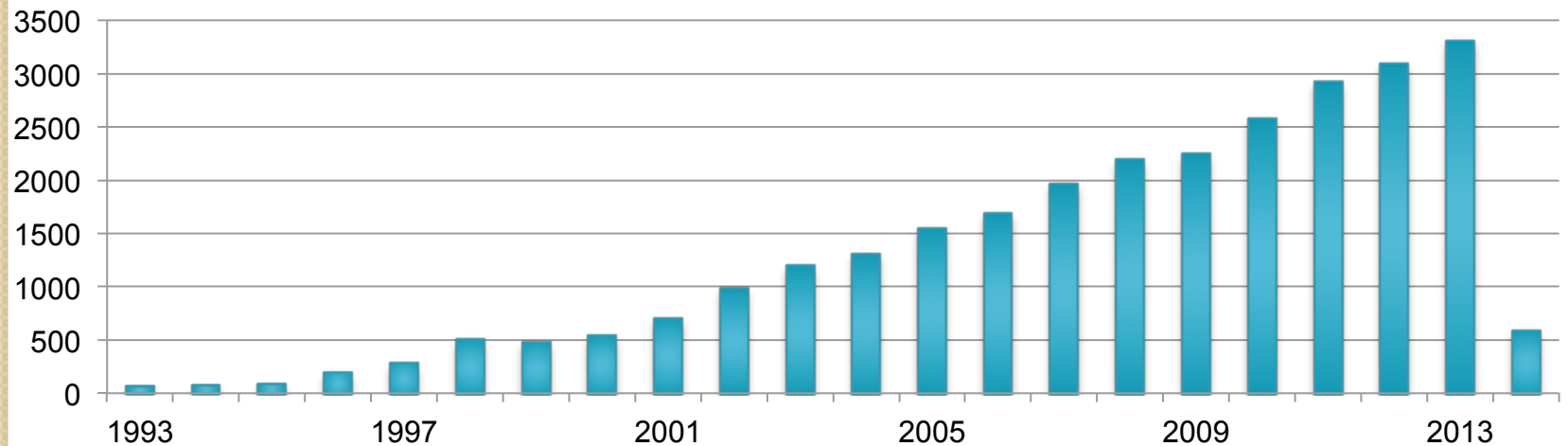


Publication and Citation

Publication



Citation



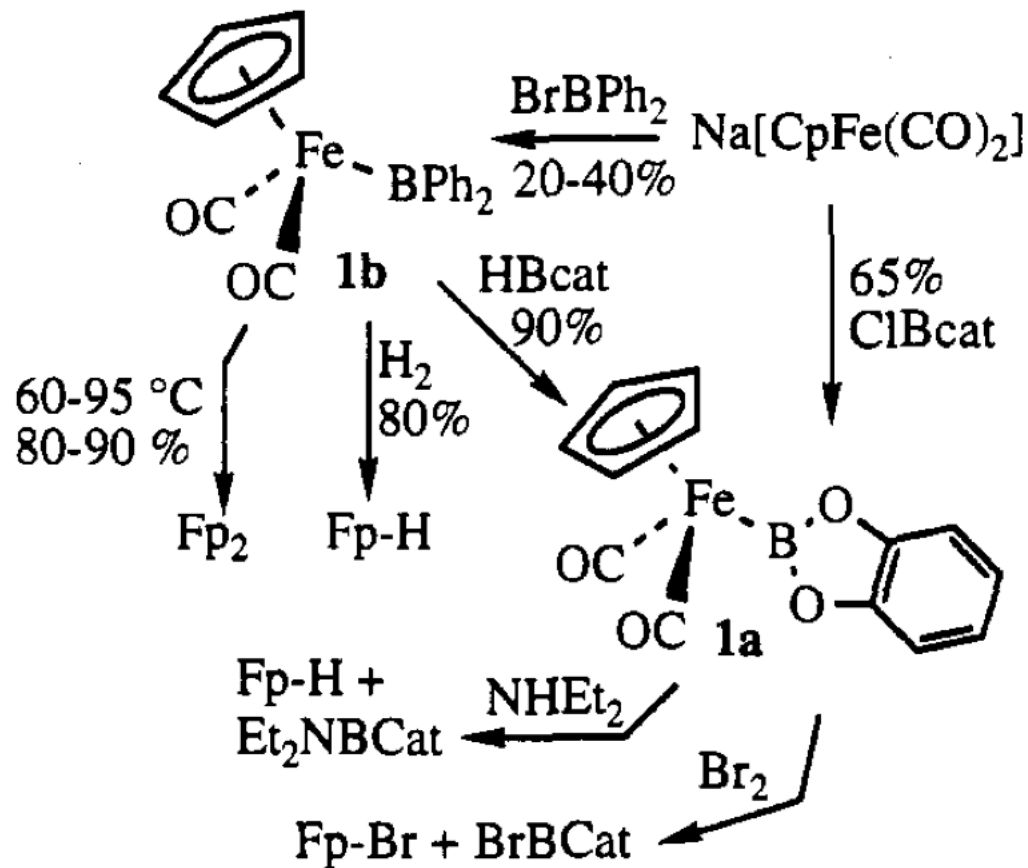
Outline

- C-H Bond Borylation
- C-N Bond Formation
- α -Arylation of Carbonyl Compounds

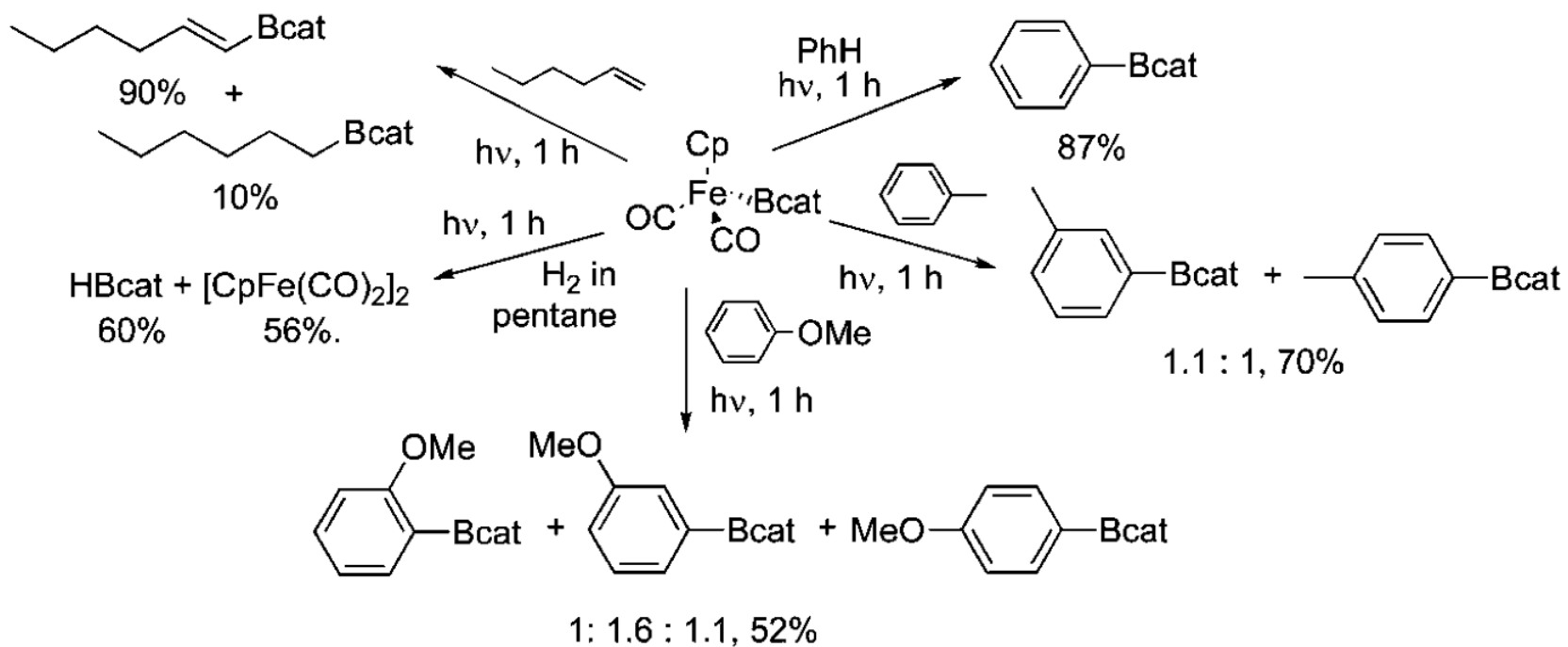
C-H Bond Borylation

- regiospecific borylation of methyl C-H bond
- borylation of arenes and heteroarenes
- secondary C-H bond borylation

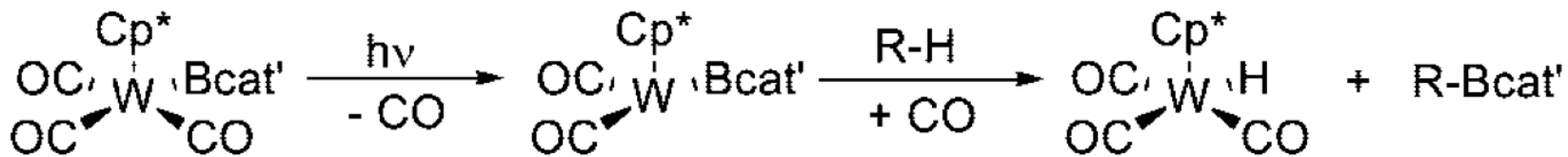
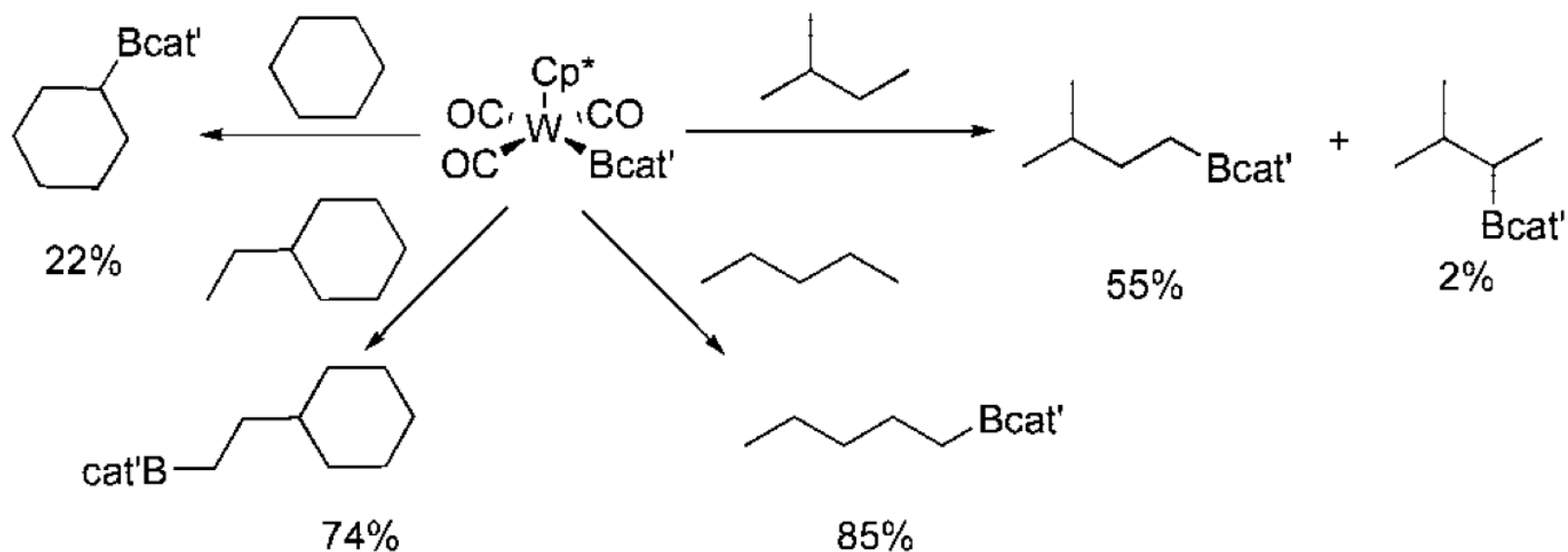
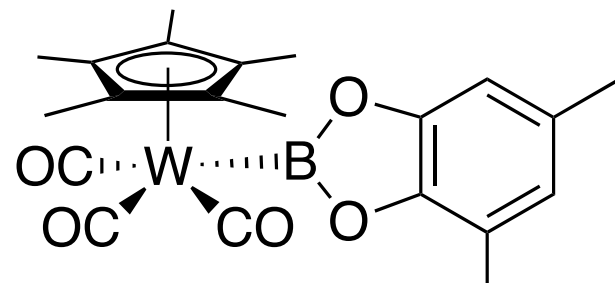
The Beginning of Research Career: The Chemistry of Transition-Metal Boryl Complexes



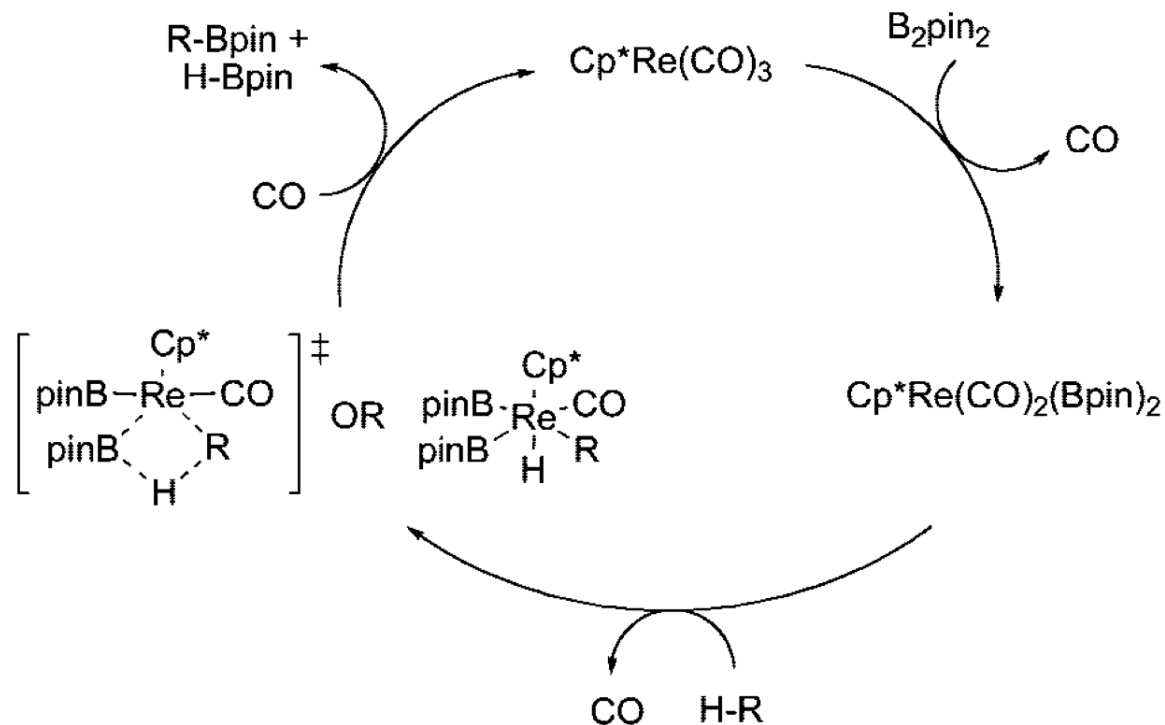
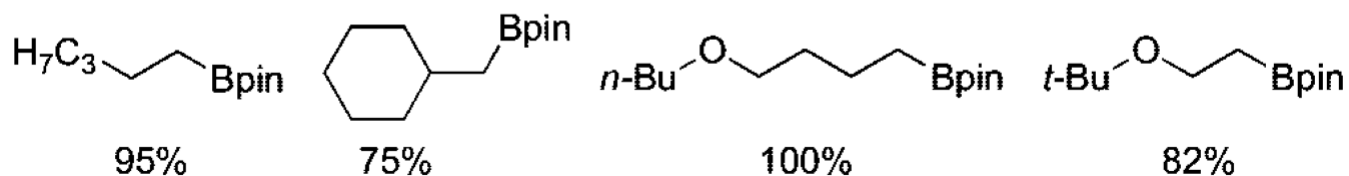
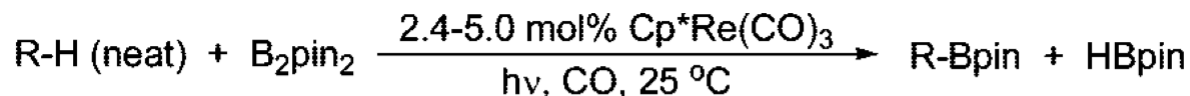
Hydrocarbon Functionalization by Iron Catecholboryl Complexes



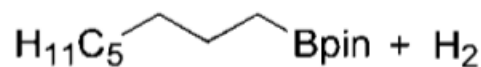
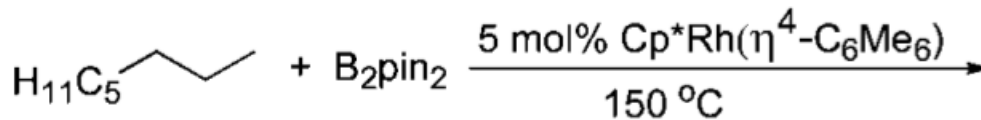
Stoichiometric Alkane Borylation by Tungsten Boryl Complex



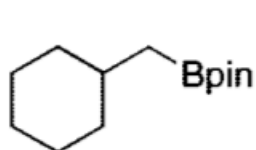
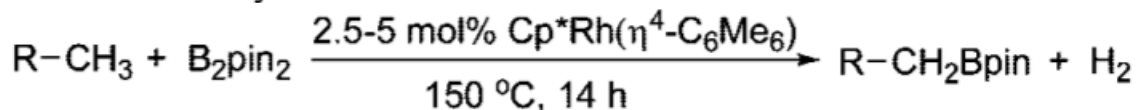
Catalytic Methyl Functionalization under Photochemical Conditions



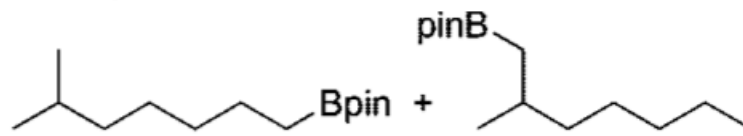
Catalytic Methyl Functionalization under Thermal Conditions



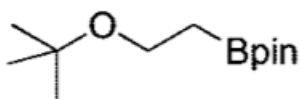
88% yield



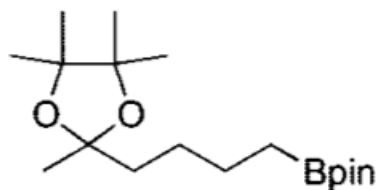
49%



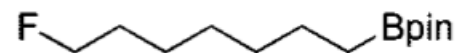
73% (5:1)



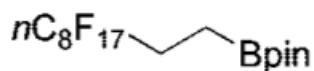
91%



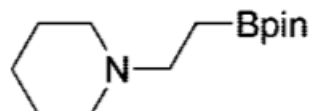
74%



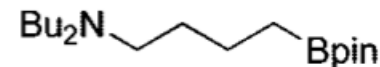
83%



90%



55%

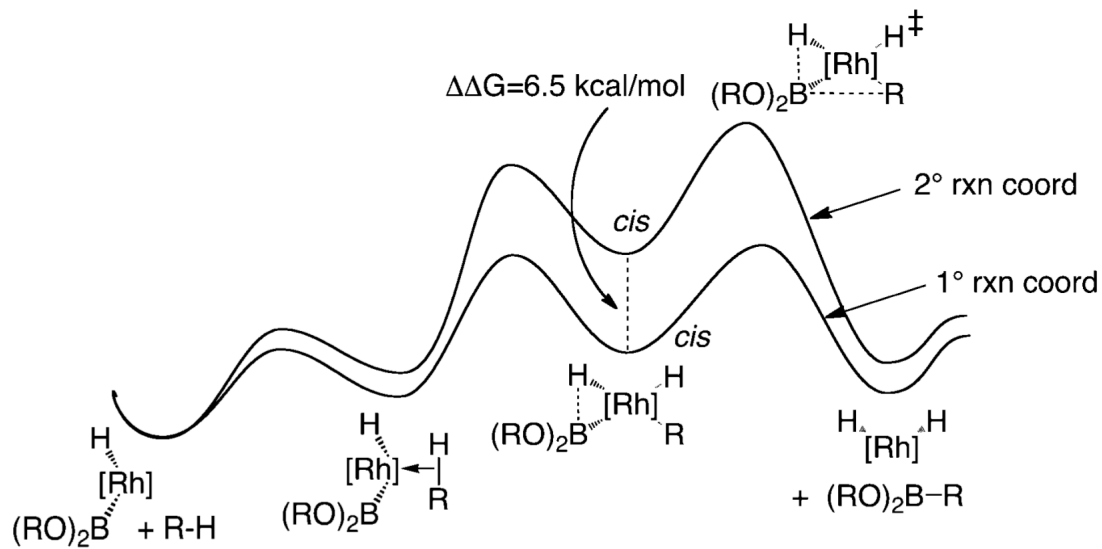
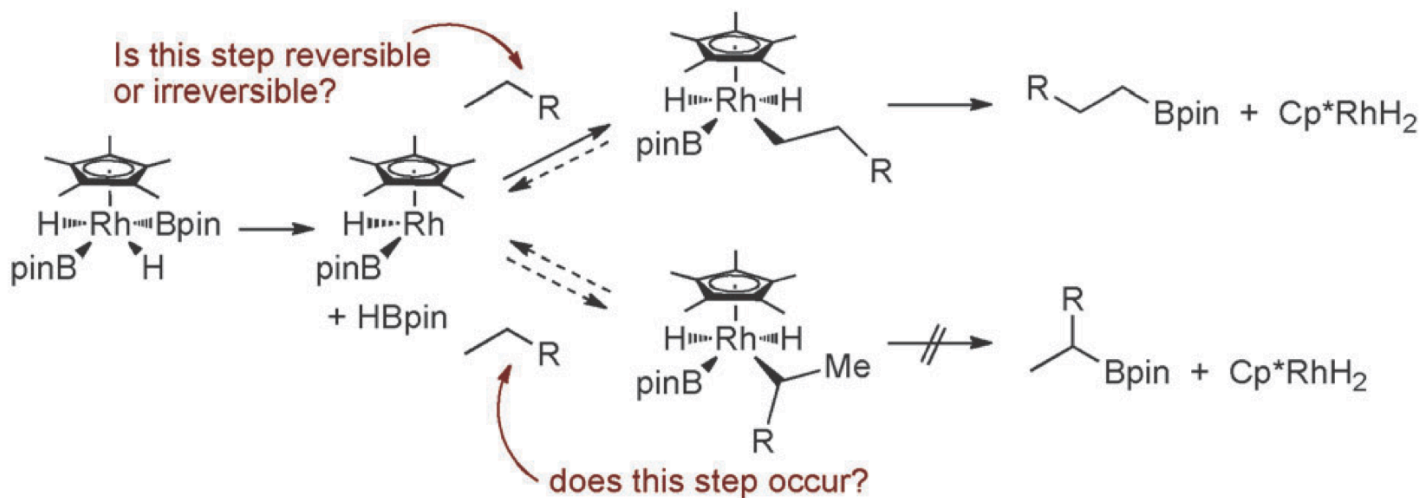


75%

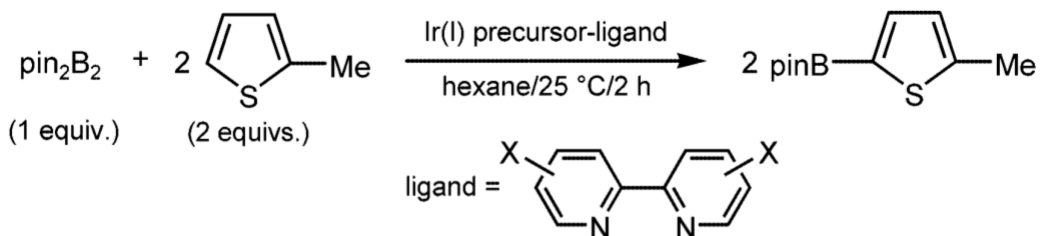
Chen, H.; Hartwig, J. F. *et al. Science*, **2000**, 287, 1995.

Lawrence, J. D.; Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2004**, 126, 15334.

Regiospecificity of Primary C-H Bond Functionalization

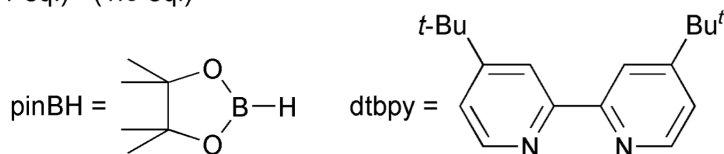
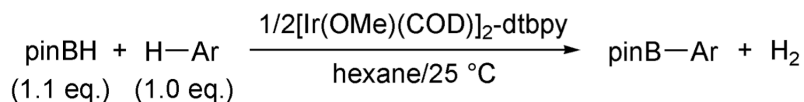


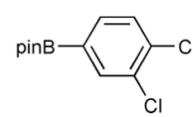
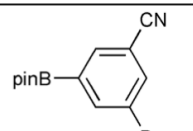
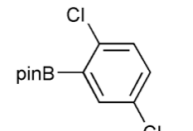
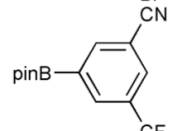
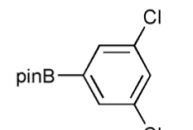
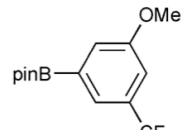
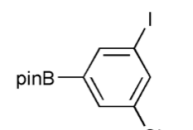
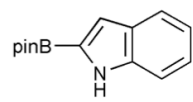
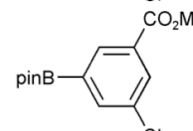
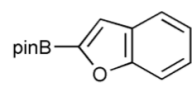
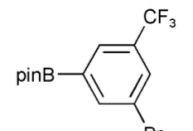
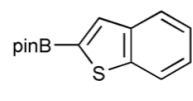
Iridium-Catalyzed C-H Borylation of Arenes and Heteroarenes: Catalyst Screening



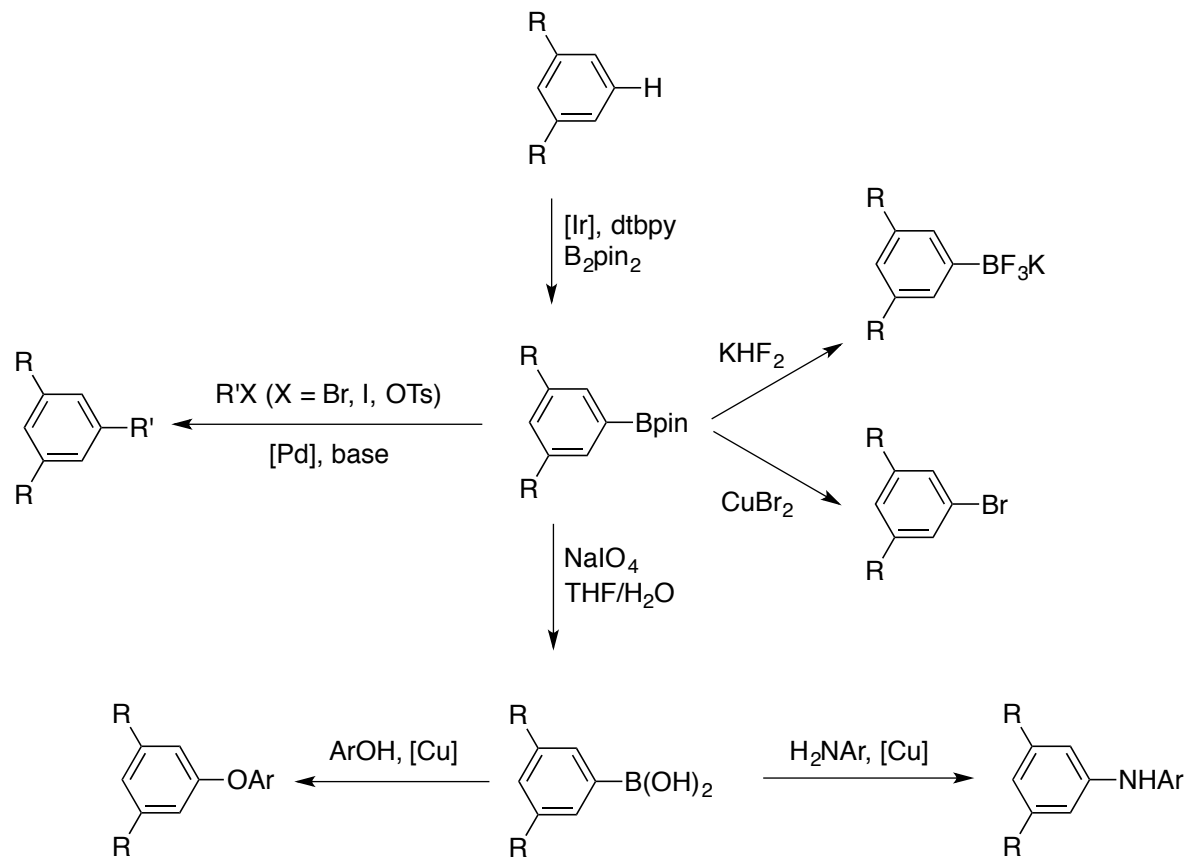
Entry	Ir(I) Precursor	Ligand	Yield [%] ^[b]
1	1/2[Ir(OMe)(COD)] ₂	dtbpy	95
2	1/2[IrCl(COD)] ₂	dtbpy	0
3	[Ir(COD) ₂]BF ₄	dtbpy	0
4	1/2[Ir(OMe)(COD)] ₂	none	0
5	1/2[Ir(OMe)(COD)] ₂	bpy	85
6	1/2[Ir(OMe)(COD)] ₂	3,3'-di-Me-bpy	61
7	1/2[Ir(OMe)(COD)] ₂	4,4'-di-Me-bpy	87
8	1/2[Ir(OMe)(COD)] ₂	5,5'-di-Me-bpy	86
9	1/2[Ir(OMe)(COD)] ₂	6,6'-di-Me-bpy	0
10	1/2[Ir(OMe)(COD)] ₂	4,4'-di-NMe ₂ -bpy	91
11	1/2[Ir(OMe)(COD)] ₂	4,4'-di-OMe-bpy	90
12	1/2[Ir(OMe)(COD)] ₂	4,4'-di-Cl-bpy	35
13	1/2[Ir(OMe)(COD)] ₂	4,4'-di-NO ₂ -bpy	0

Iridium-Catalyzed C-H Borylation of Arenes and Heteroarenes: Substrate Scope



Entry	Product	Yield (%) ^b	Entry	Product	Yield (%) ^b
1		73% (8 h)	7		74% (2 h)
2		22% (24 h)	8		83% (1 h)
3		86% (8 h)	9		73% (24 h)
4		67% (8 h)	10		99% (0.5 h)
5		70% (24 h)	11		90% (1 h)
6		80% (8 h)	12		99% (2 h)

Further Functionalization of Arenes via Iridium-Catalyzed Borylation



Murphy, J. M.; Hartwig, J. F. *et al. Org. Lett.* **2007**, *9*, 757.

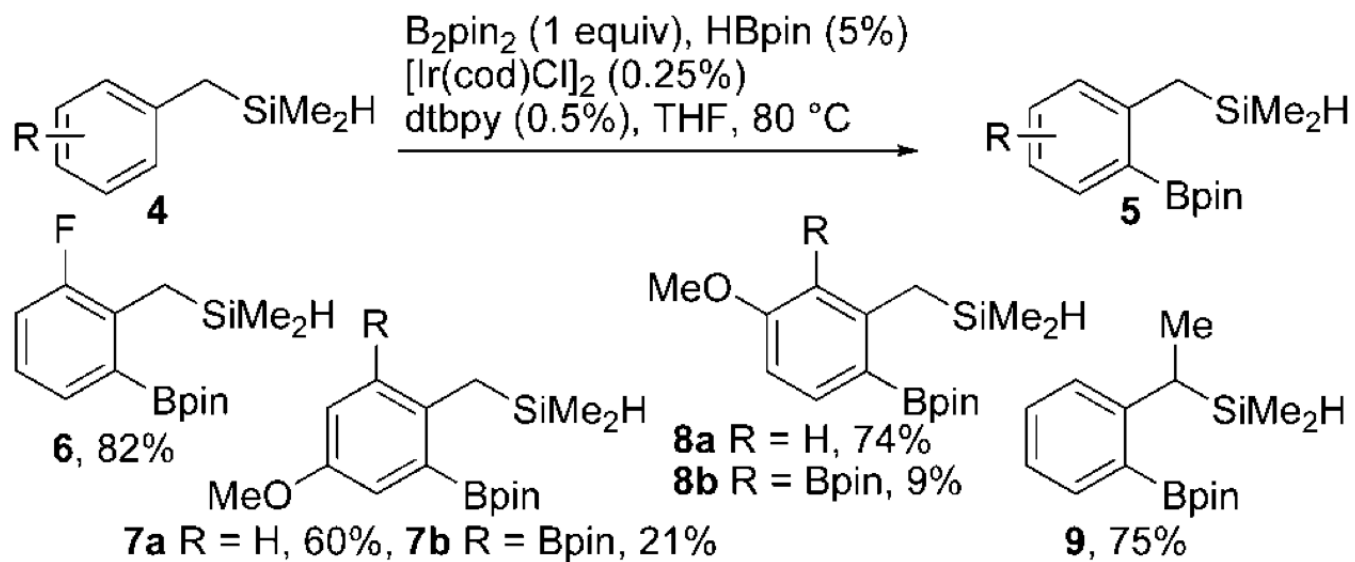
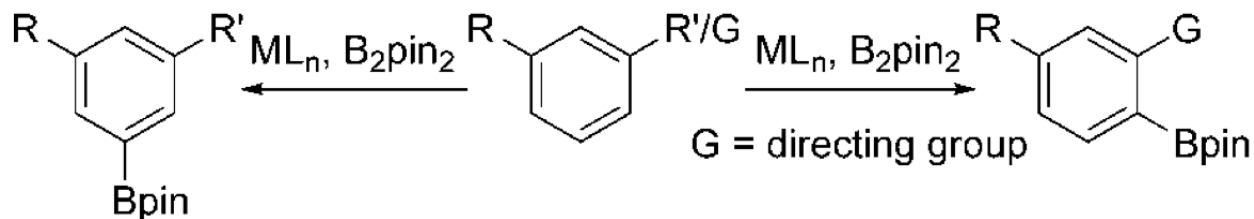
Tzschucke, C. C.; Hartwig, J. F. *et al. Org. Lett.* **2007**, *9*, 761.

Murphy, J. M.; Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2007**, *129*, 15434.

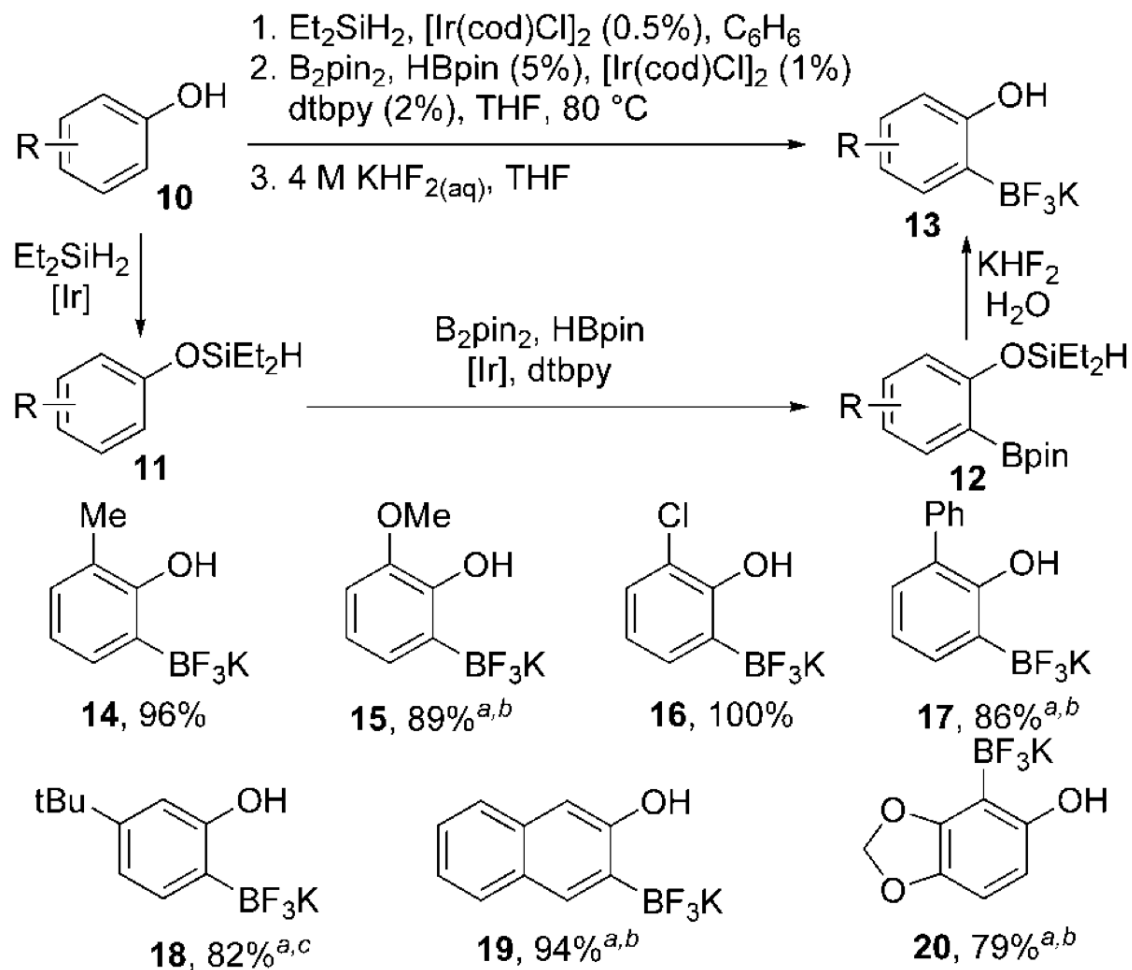
Liskey, C. M.; Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2010**, *132*, 11389.

Robbins, D. W.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2013**, *52*, 933.

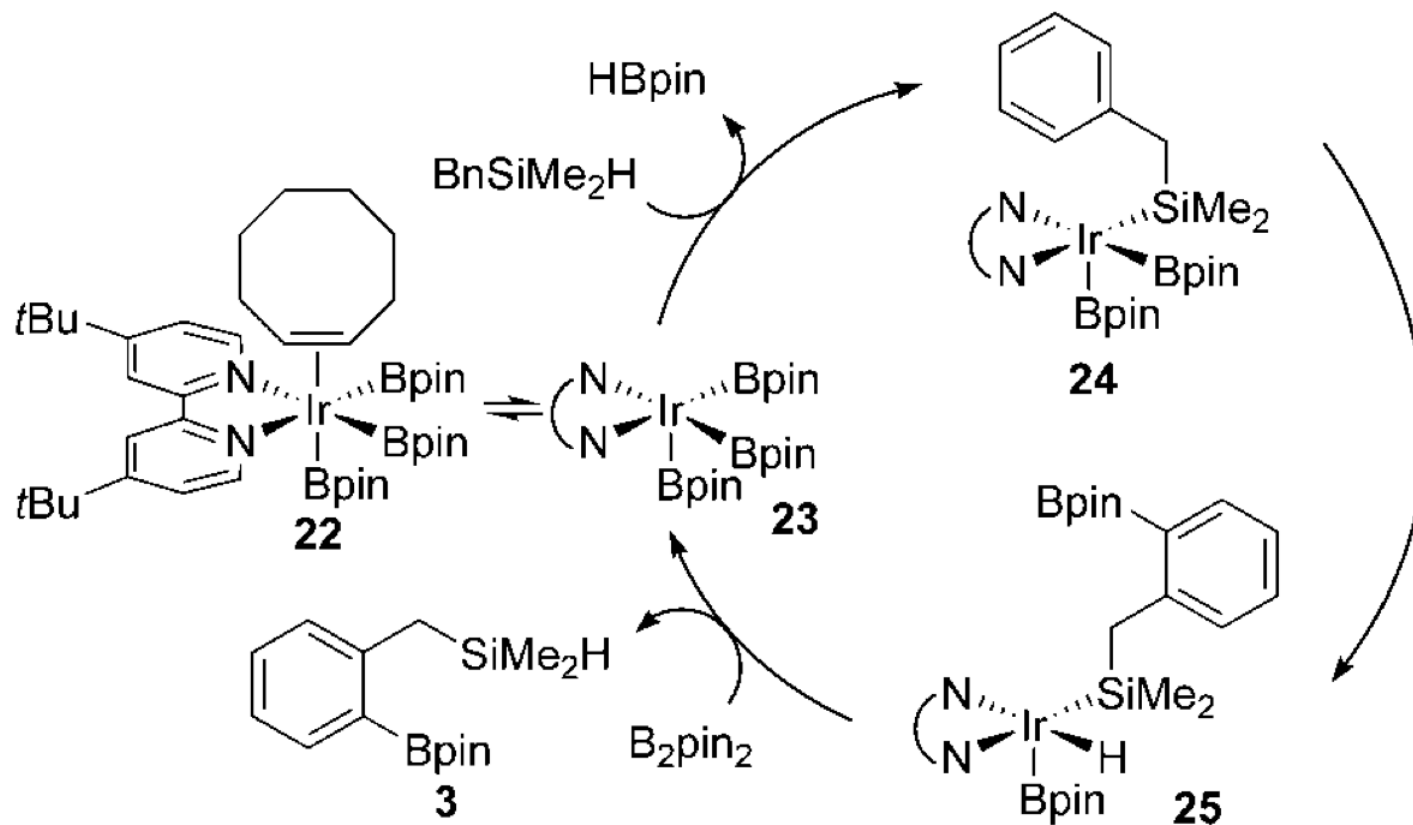
Silyl-Directed Borylation of Arenes



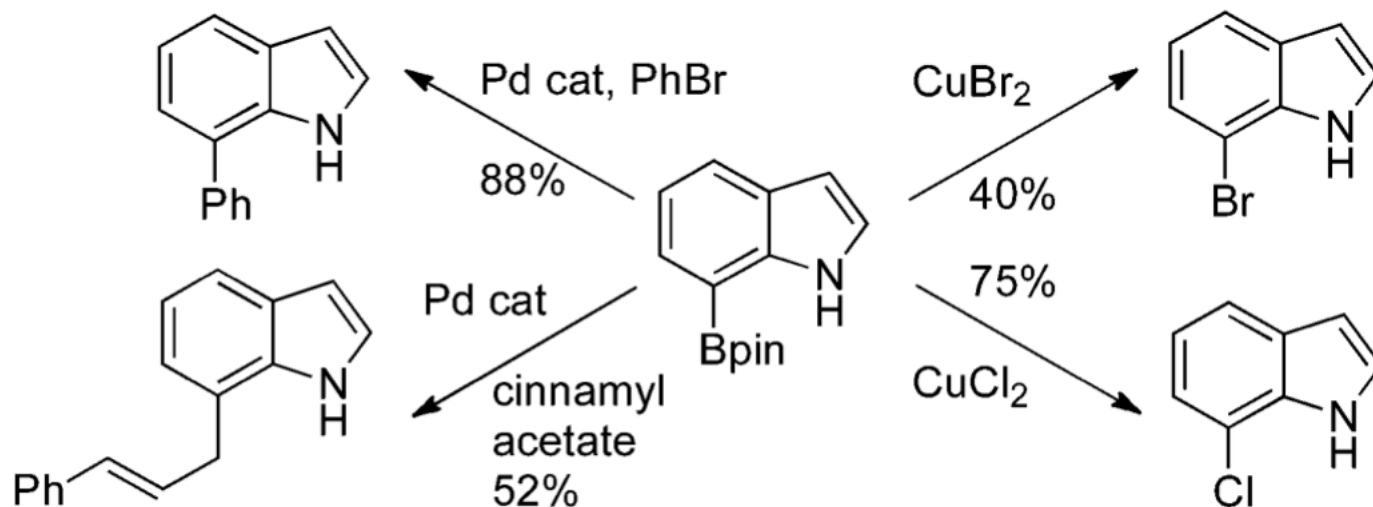
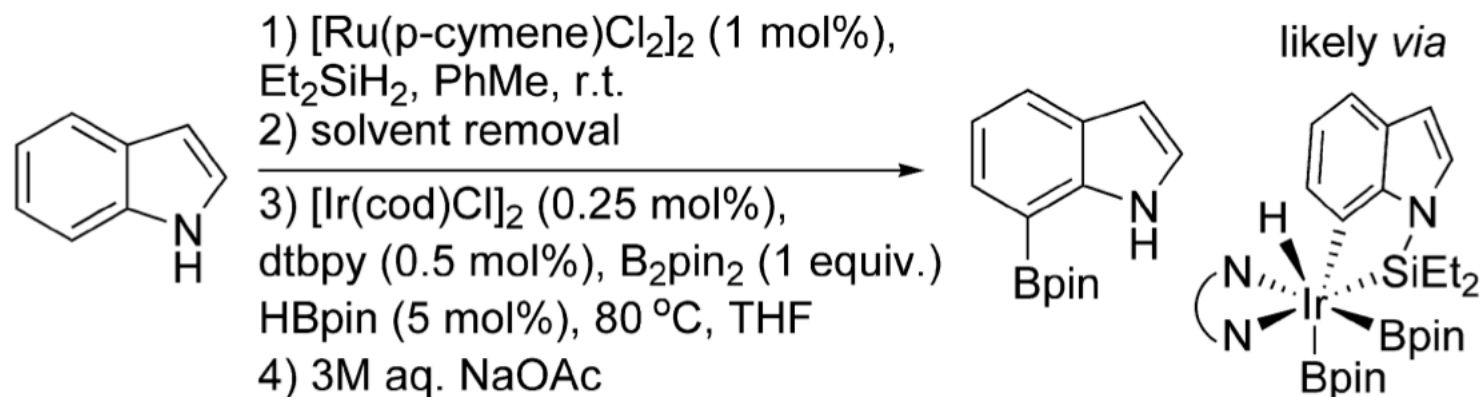
One-Pot *Ortho*-Borylation of Phenols



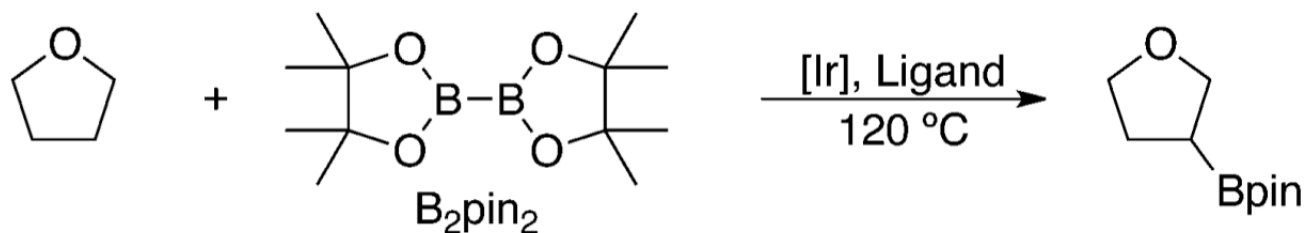
Silyl-Directed Borylation Catalytic Cycle



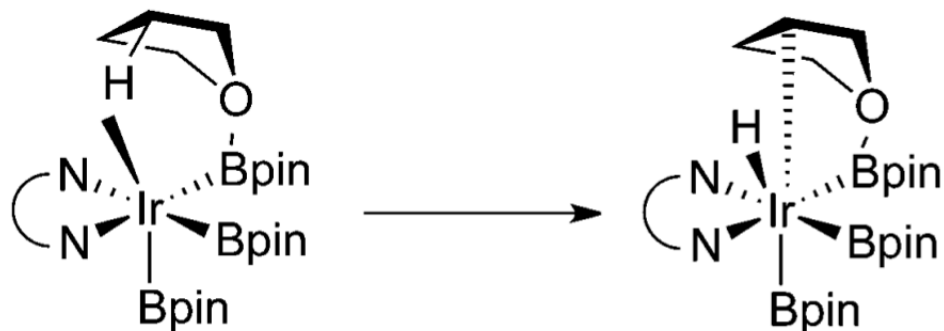
Silyl-Directed Borylation of Indole Derivatives



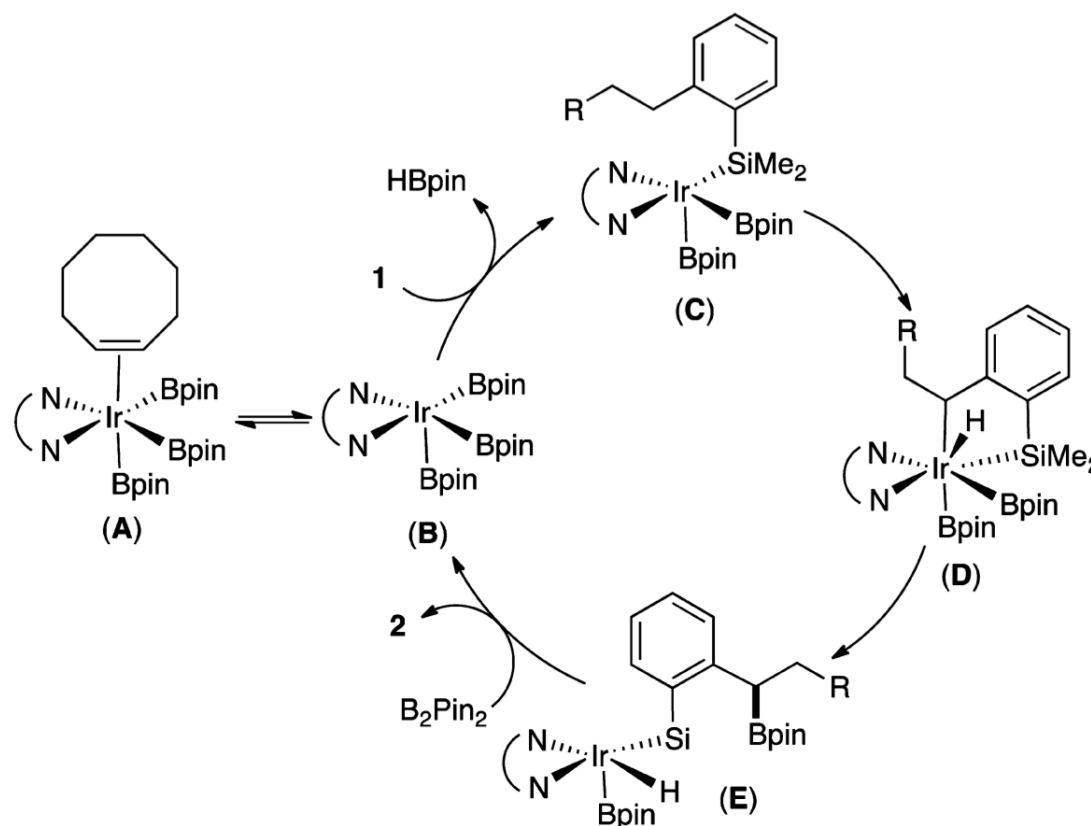
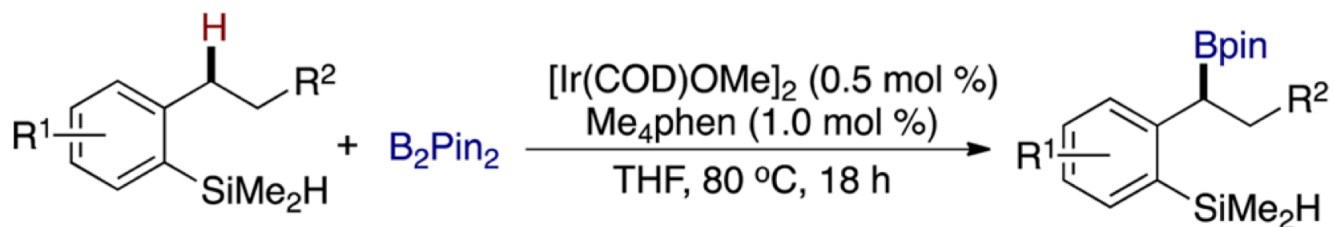
Borylation of Secondary C-H Bond



entry	source of Ir	ligand	catalyst	yield (%) ^a
1	$[\text{Ir}(\text{COD})\text{OMe}]_2$	Me_4phen	10 mol %	70
2	$[\text{Ir}(\text{COD})\text{OMe}]_2$	phen	10 mol %	48
3	$(\eta^6\text{-mes})\text{IrBpin}_3$	Me_4phen	4 mol %	104
4	$(\eta^6\text{-mes})\text{IrBpin}_3$	Me_4phen	4 mol %	72 ^b



Hydrosilane-Directed Borylation of Secondary Benzylic C-H Bond



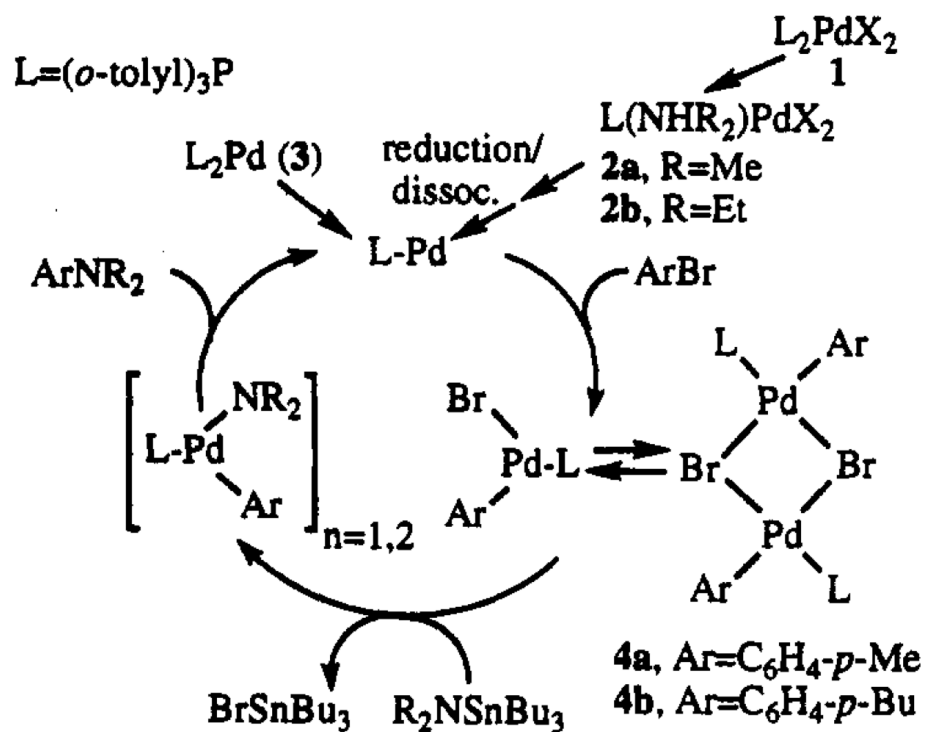
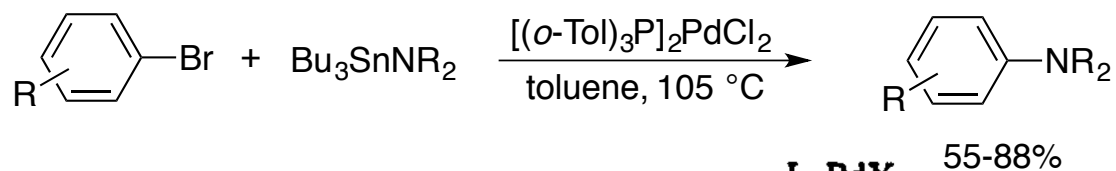
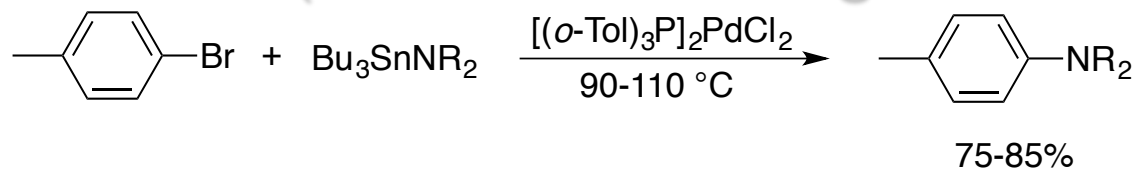
Summary

- Cp* Rh -Catalyzed Regiospecific Borylation of Primary Alkane C-H Bond
- *meta*-Borylation of Substituted Arenes
- Silyl-Directed *ortho*-Borylation
- Ir-Catalyzed Secondary C-H Bond Borylation

C-N Bond Formation

- direct amination of arenes and heteroarenes
- hydroamination of olefins

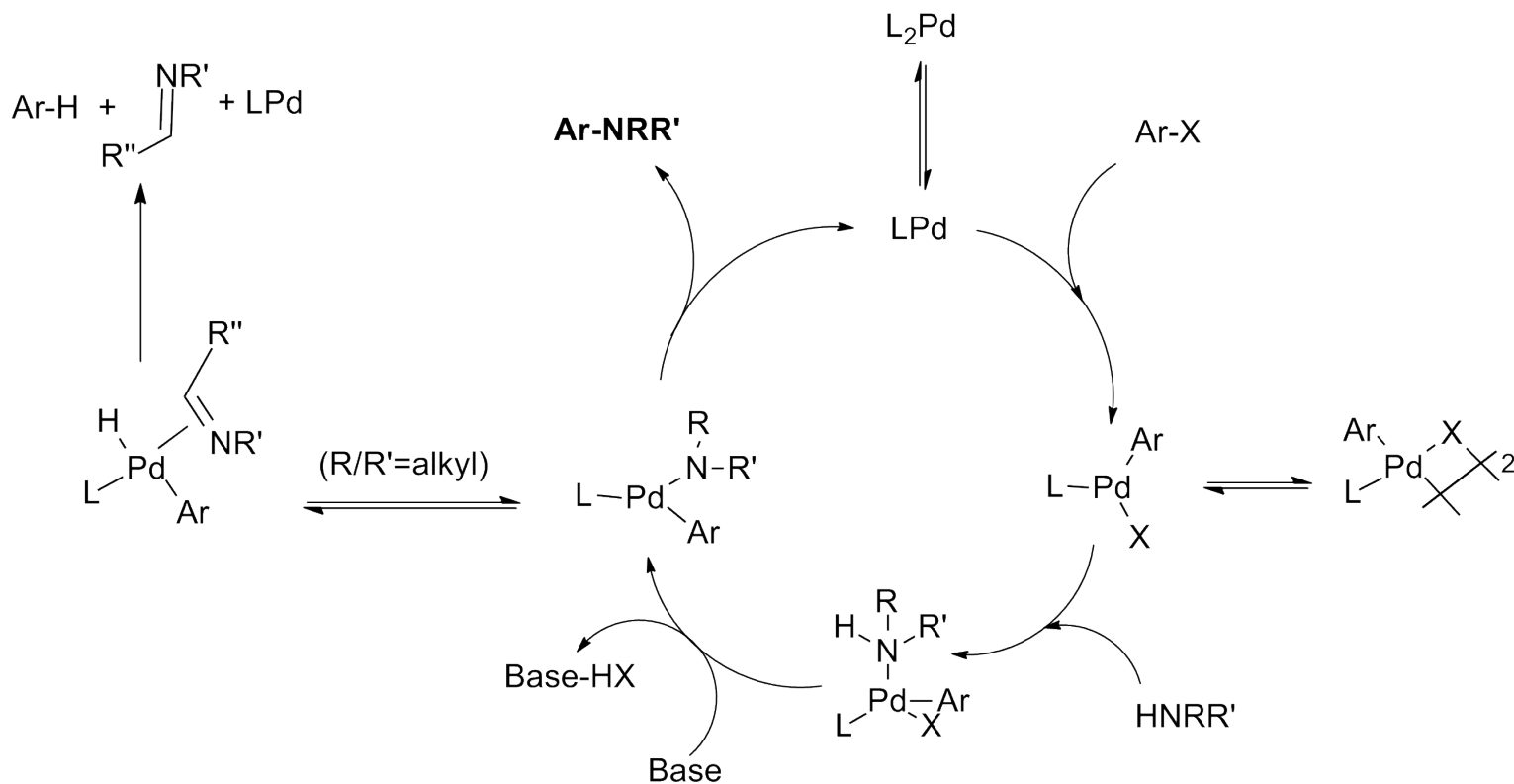
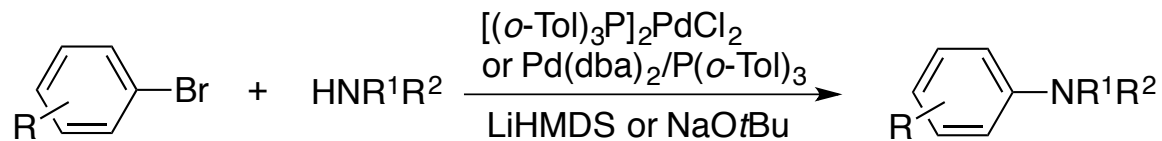
Early Work On Cross Coupling of Aryl Halides and Tin Amides (Buchwald-Hartwig Amination)



Paul, F.; Hartwig, J. F. *et al.* *J. Am. Chem. Soc.* **1994**, *116*, 5969.

Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901.

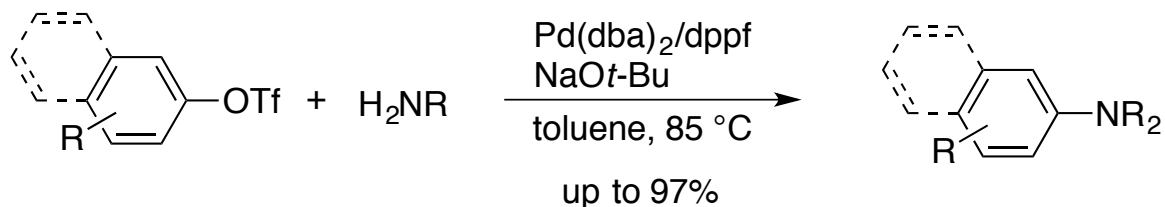
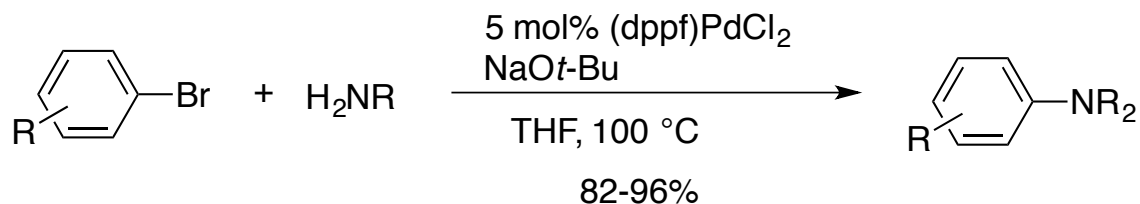
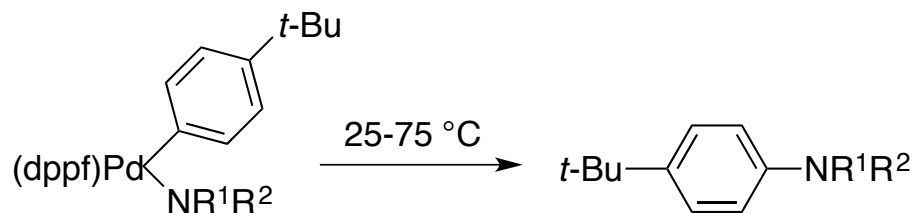
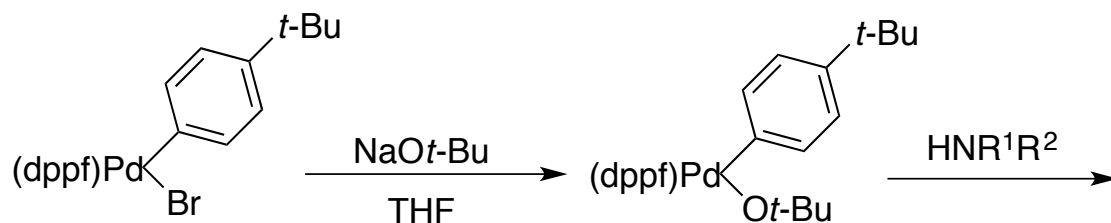
Direct Aryl Halide Amination by Amines with Bulky Bases



Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, 36, 3609.

Guram, A. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995**, 34, 1348.

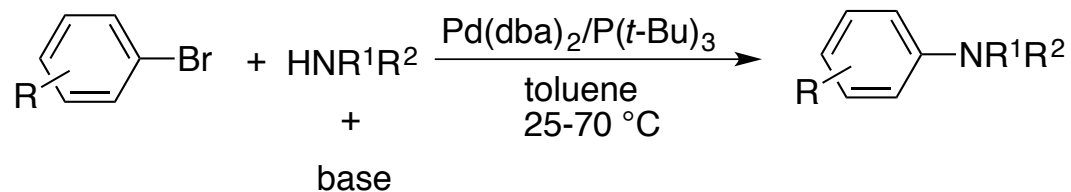
A Second-Generation Catalyst in Aryl Amination



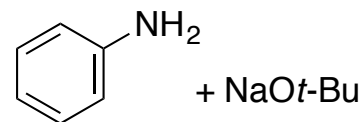
Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

Louie, J.; Hartwig, J. F. *et al. J. Org. Chem.* **1997**, *62*, 1268.

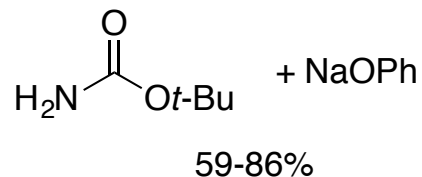
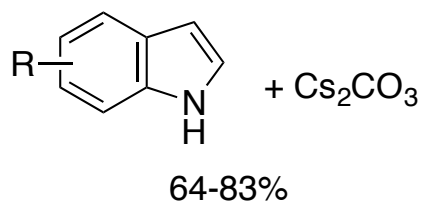
Substrate Scope with Amines



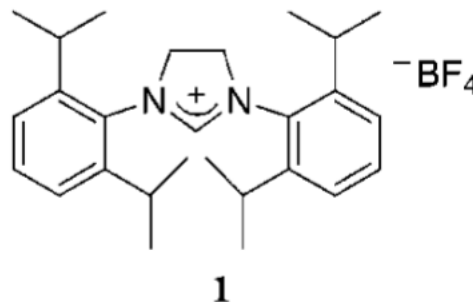
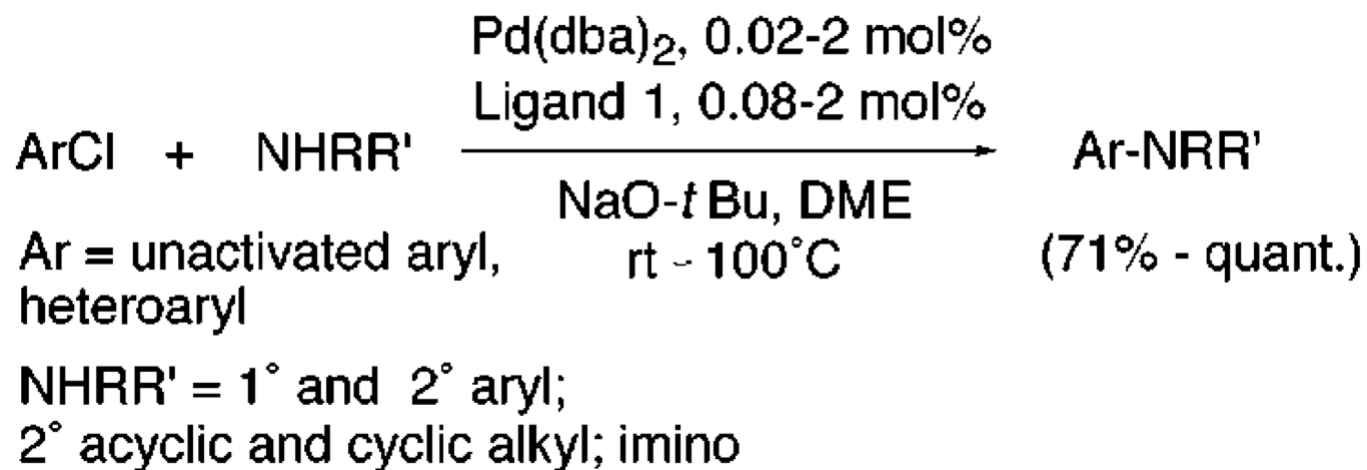
Ar_2NH + NaOt-Bu
85-97%



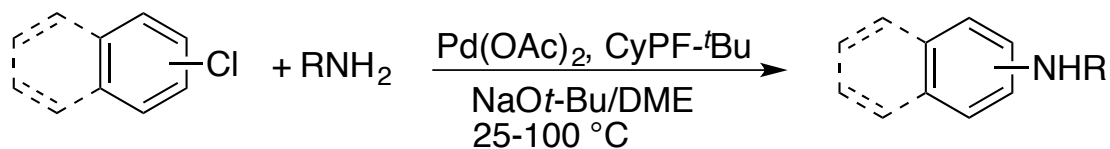
87%



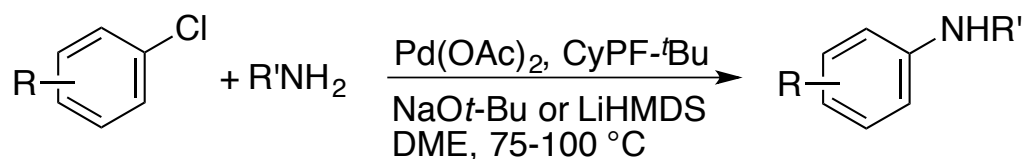
High Efficient Chloroarene Amination Catalyzed by A Third-Generation Catalyst



A Fourth-Generation Catalyst Applied to Wide-Ranged Amines and Mild Reaction Conditions

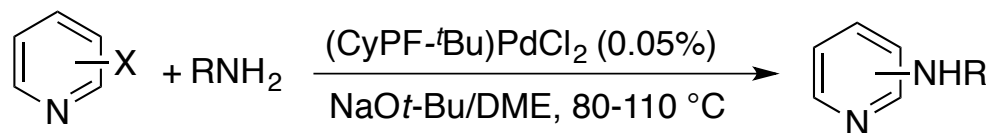
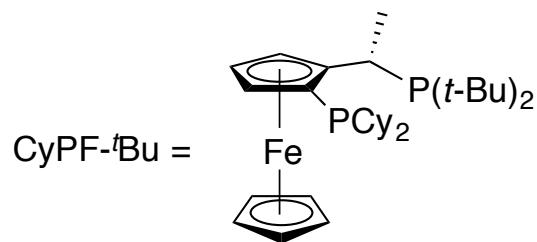


60-99%



61-99%

R = alkyl, OH, OMe, CN, $(\text{CH}_2)_n\text{OH}$, CH_3CO , HOOC, H_2NCO



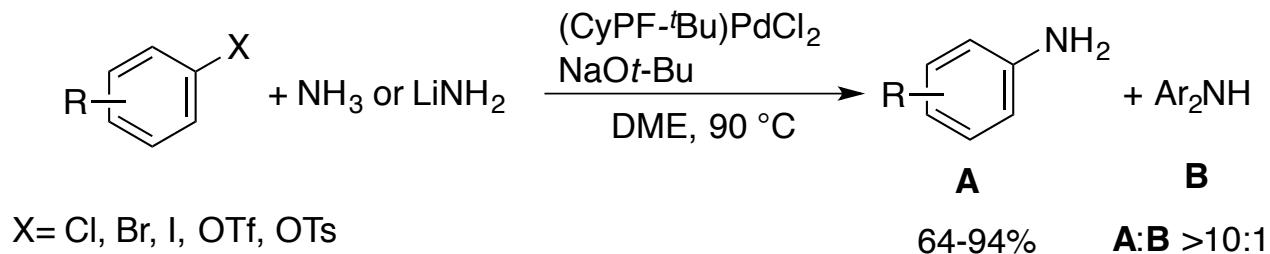
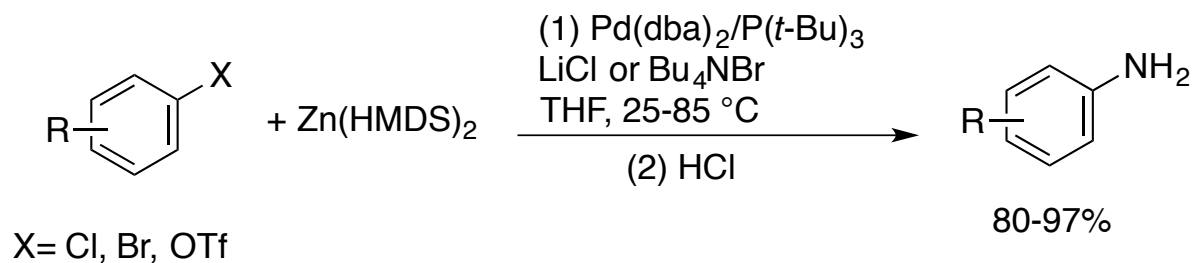
X = Cl, Br, I

70-96%

Shen, Q.; Hartwig, J. F. *et al. Angew. Chem. Int. Ed.* **2005**, *44*, 1371.

Shen, Q.; Hartwig, J. F. *Org. Lett.* **2008**, *18*, 4109.

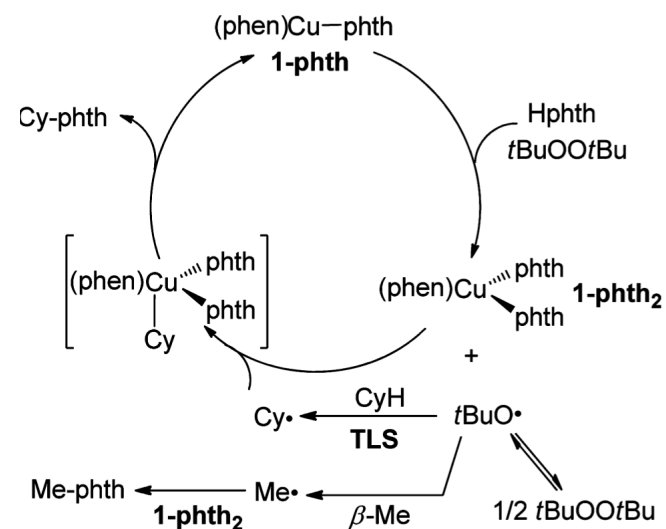
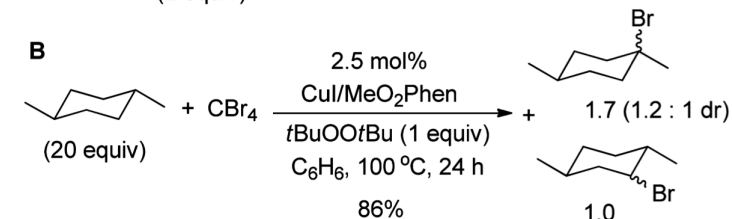
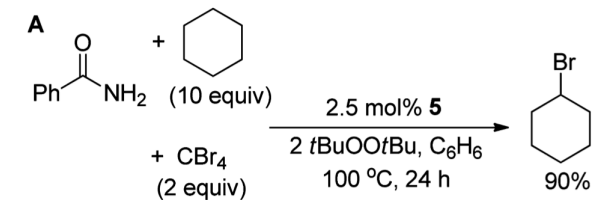
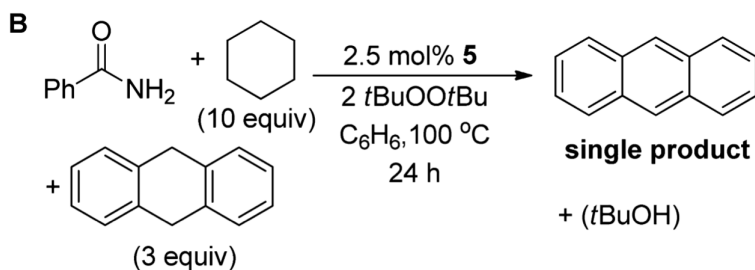
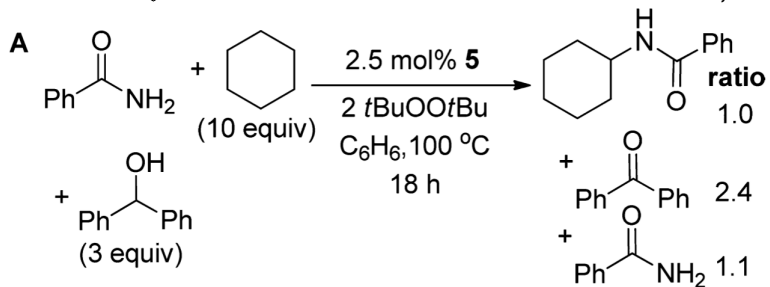
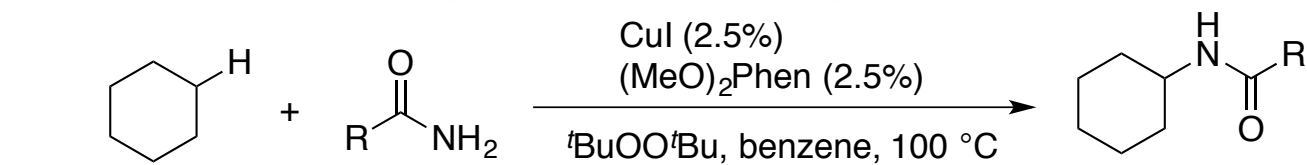
Aniline Derivatives from Direct Amination



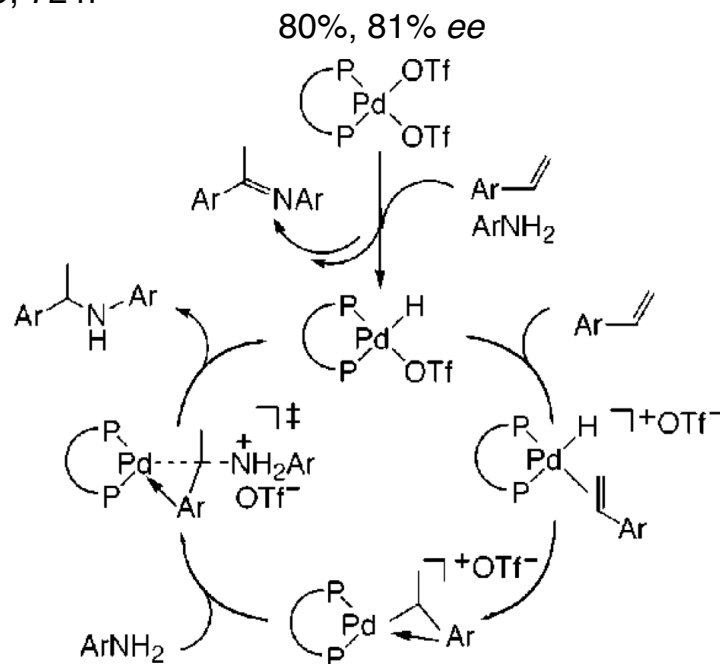
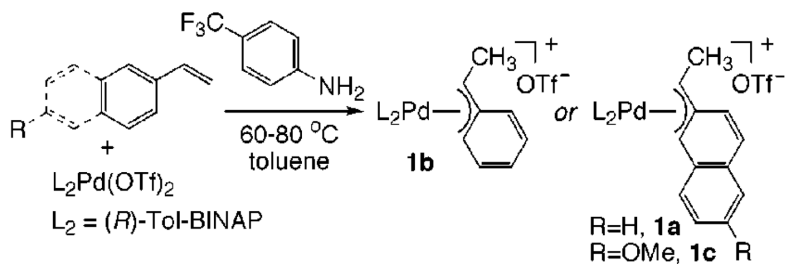
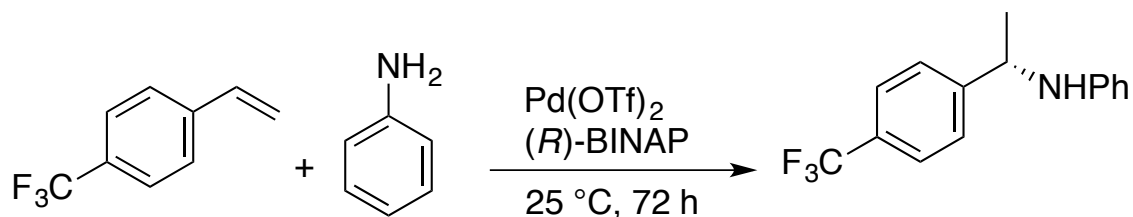
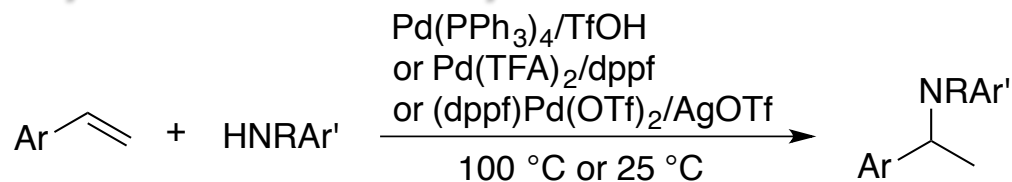
Lee, D. -Y.; Hartwig, J. F. *Org. Lett.* **2005**, 7, 1169.

Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, 128, 10028.

Recent Published Work on Cu-Catalyzed Amidation of Unactivated C-H Bond



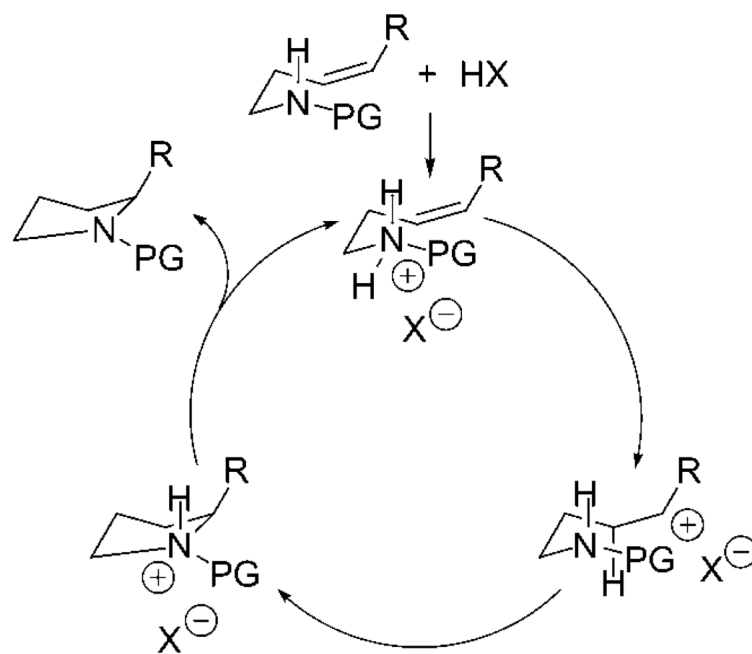
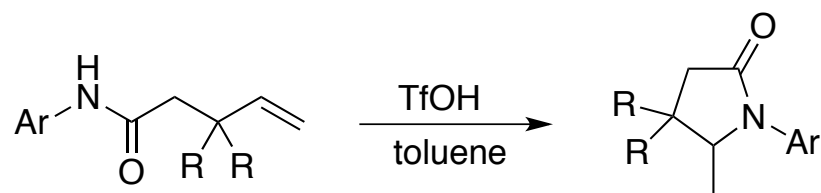
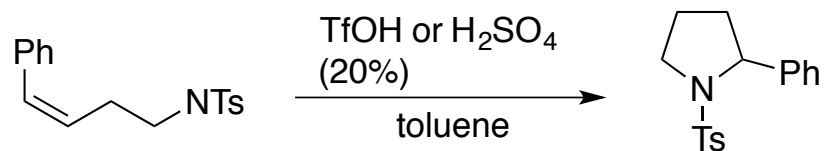
Pd-Catalyzed Olefin Hydroamination



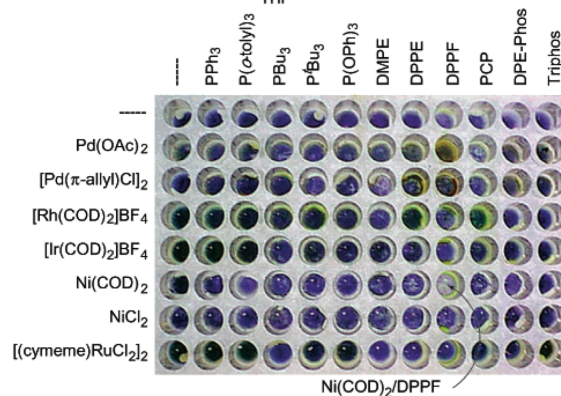
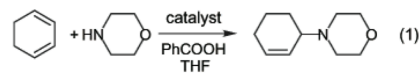
Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 8546.

Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1166.

Brønsted Acid-Catalyzed Intramolecular Hydroamination

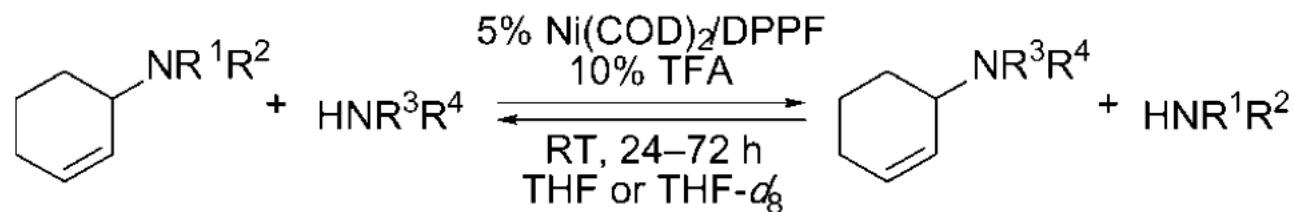


Hydroamination of 1,3-diene

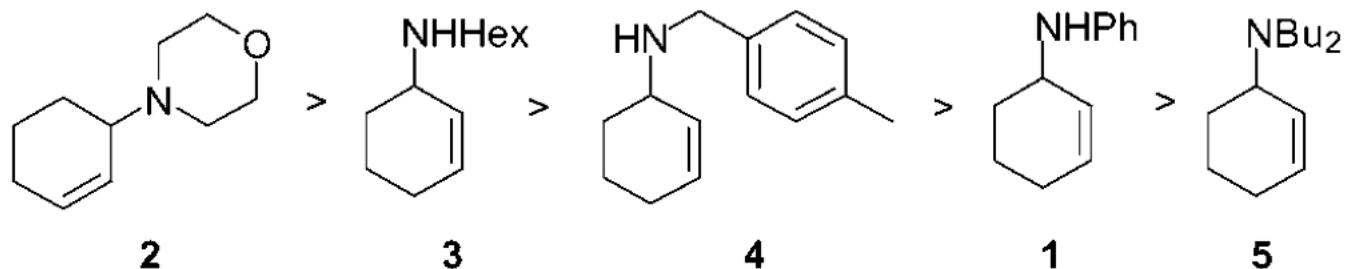


Entry	Product	Time (h)	Yield (%)	Entry	Product	Time (h)	Yield (%)
1		20	78	9		60	85
2		20	82	10		113	56
3		20	80	11		72 ^b	71
4		20	89	12		43	91
5		7	89	13		60	94
6		6	93	14		60	83
7		37	82	15		84 ^b	38 ^c
8		30	87	16		0.5	83 ^d

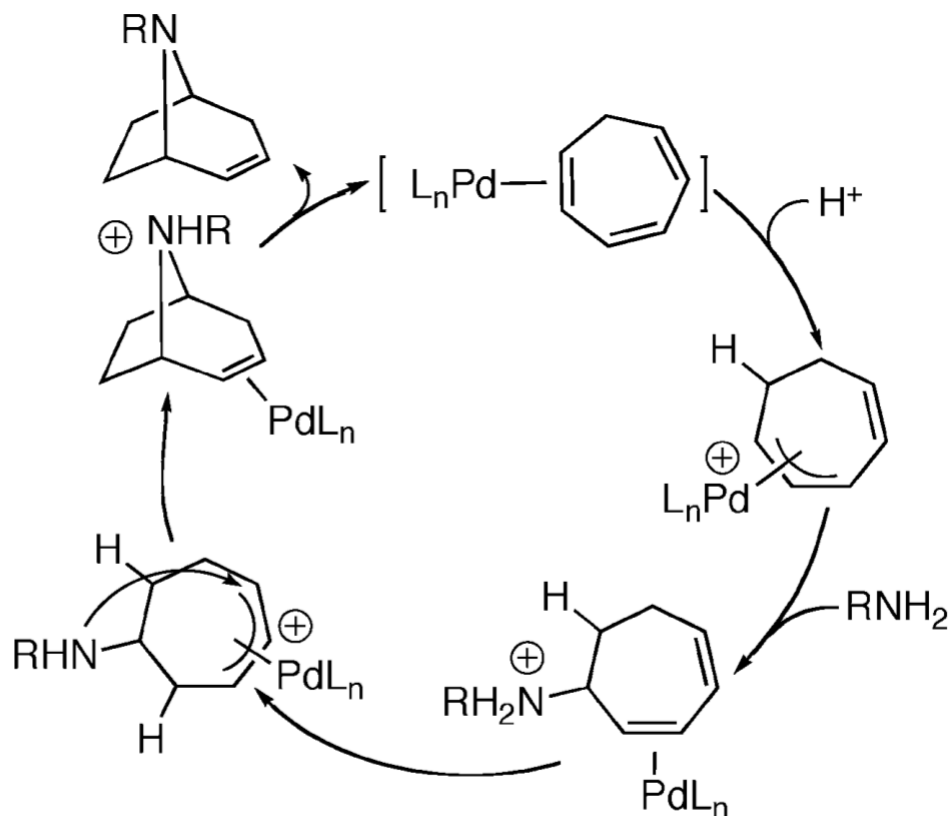
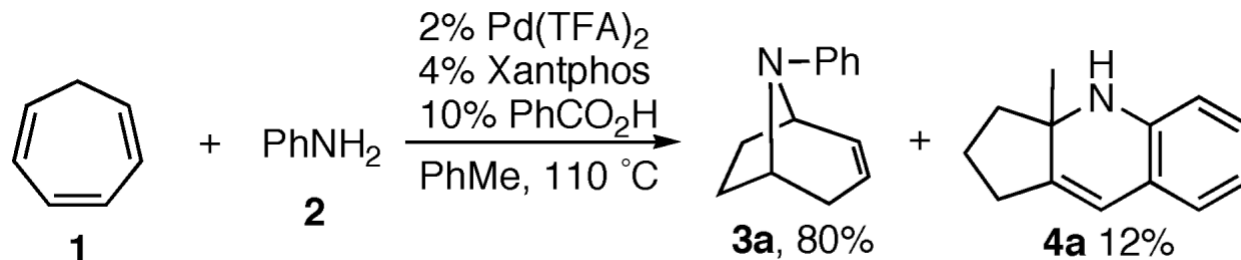
Exchange Amines with Allylic Amines



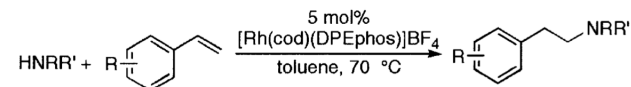
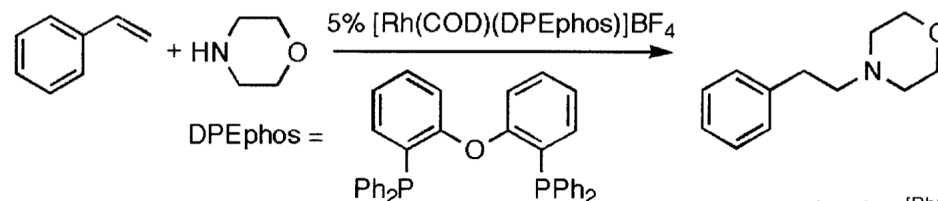
2 : 3 = 67 : 33 (GC) **3 : 4 = 56 : 44 (¹H NMR)** **4 : 1 = 60 : 40 (¹H NMR)**
2 : 4 = 70 : 30 (GC) **3 : 1 = 63 : 37 (¹H NMR)** **4 : 5 = 88 : 12 (GC)**
2 : 1 = 77 : 27 (GC) **3 : 5 = 85 : 15 (¹H NMR)** **1 : 5 = 85 : 15 (GC)**
2 : 5 = 93 : 7 (GC)



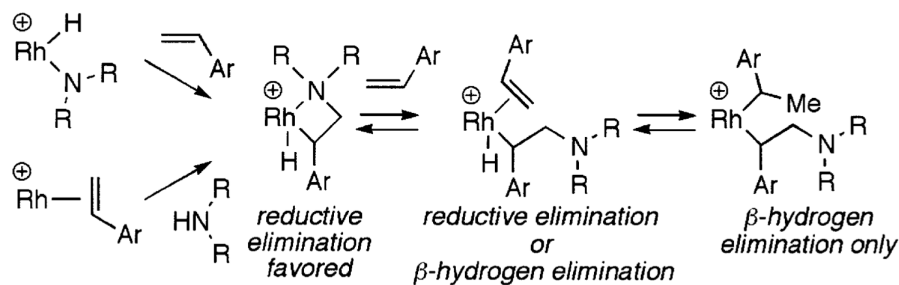
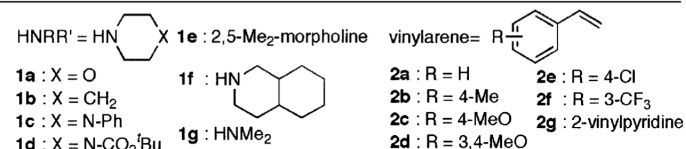
Tropene Derivatives from Hydroamination of Cycloheptatriene



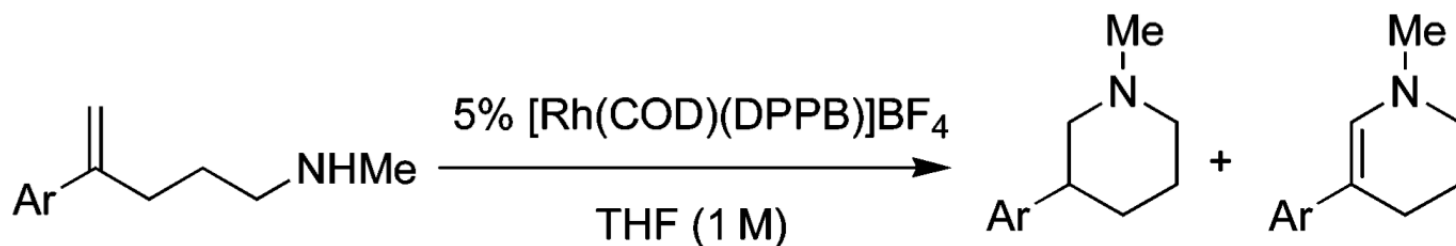
Rh-Catalyzed Anti-Markovnikov Hydroamination



entry	amine	vinylarene	time (h)	yield ^b (%)	amine/enamine ^c
1	1a	2a	48	71	75:25
2	1a	2b	48	72	79:21
3	1a	2c	48	71	85:15
4	1a	2d	48	70	78:22
5 ^e	1a	2e	72	48	60:40
6 ^{e,f}	1a	2f	72	41	57:43
7 ^g	1b	2a	72	57	63:37
8	1b	2d	48	66	77:23
9 ^g	1c	2a	72	58	86:14
10	1d	2a	72	53	96:4
11 ^{g,h}	1e	2a	72	51 ^k	76:24
12	1f	2c	48	62 ^l	72:28
13 ⁱ	1g	2b	72	50 ^d	54:46
14 ^{i,j}	1g	2d	72	74	82:19
15 ⁱ	1g	2g	48	79 ^d	90:10



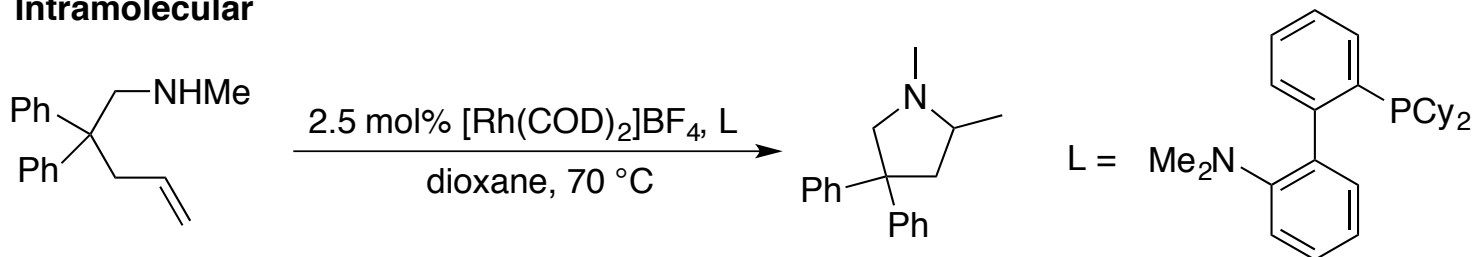
Intramolecular Anti-Markovnikov Hydroamination



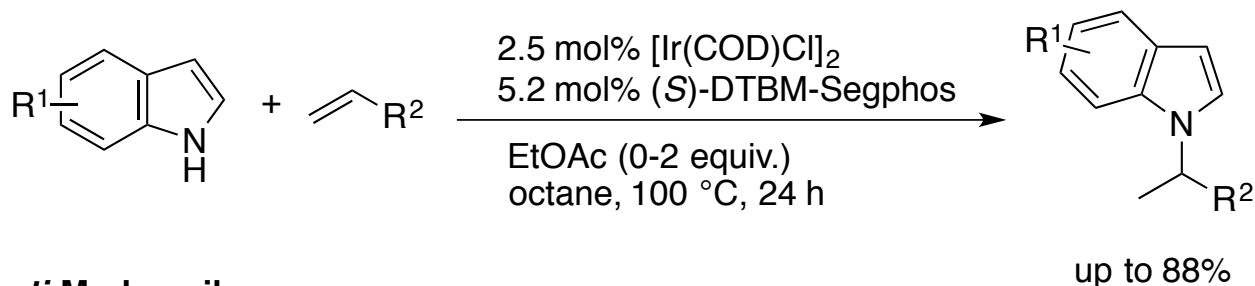
entry	Ar	temp (°C)/ time (h)	yields: amine ^a (%)	enamine ^b (%)
1	Ph	80/24	76	4
2	4-OMeC ₆ H ₄	80/24	78	1
3	4-OMeC ₆ H ₄	70/48	83	1
4	4-FC ₆ H ₄	80/24	78	3
5	3,4-OMeC ₆ H ₃	80/24	82	3
6	3,4-FC ₆ H ₃	80/72	71	trace

Hydroamination of Unactivated Olefins

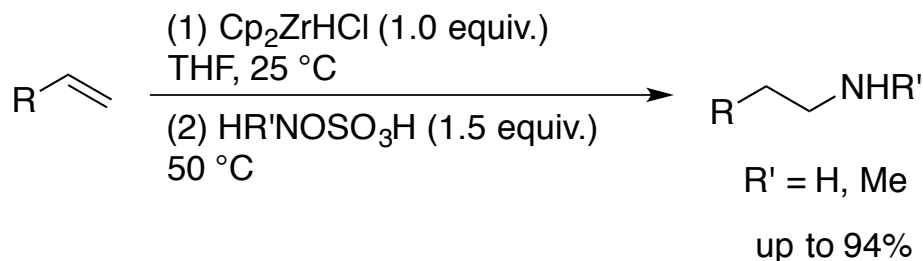
Intramolecular



Intermolecular



anti-Markovnikov

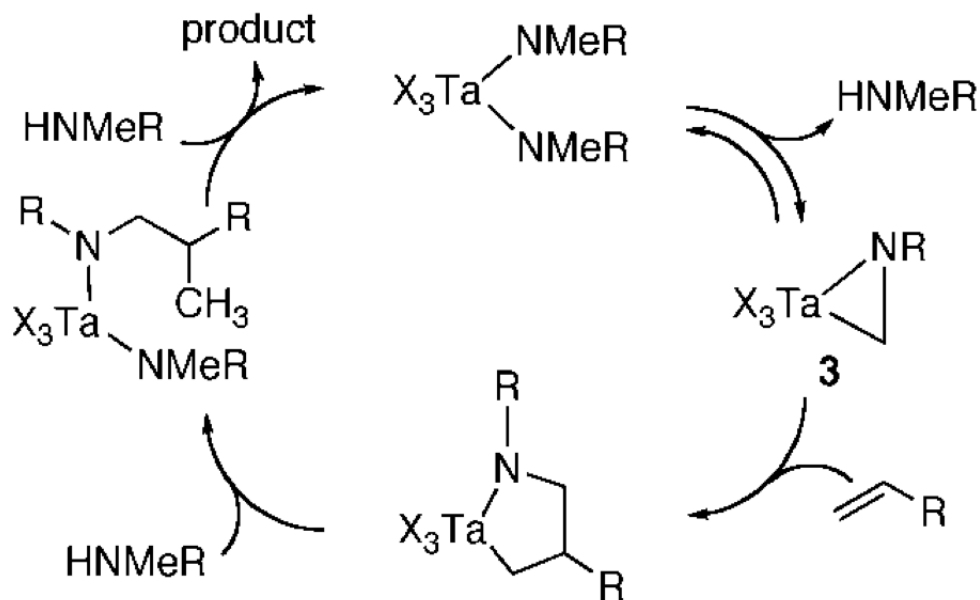
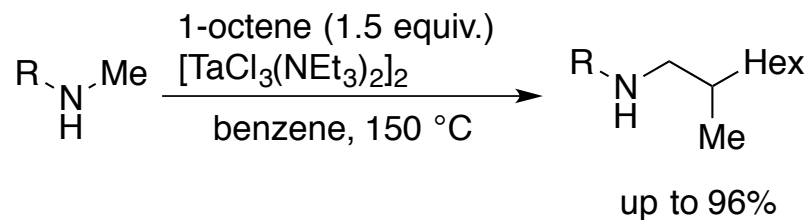


Liu, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570.

Sevov, C. S.; Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2014**, *136*, 3200.

Strom, A. E.; Hartwig, J. F. *J. Org. Chem.* **2013**, *78*, 8909.

Hydroaminomethylation of Unactivated Olefins



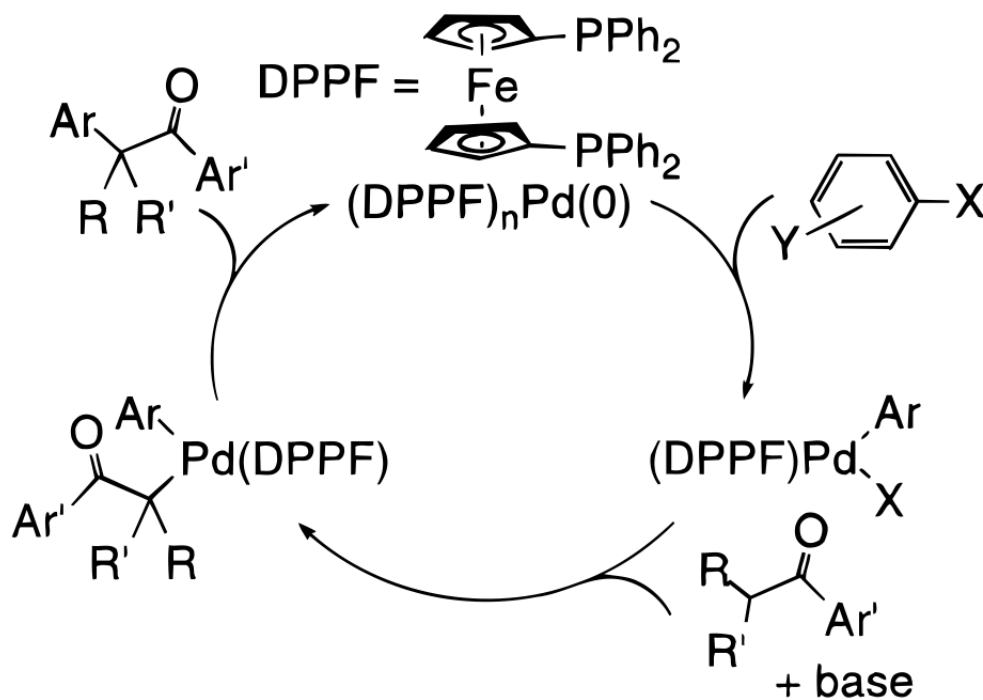
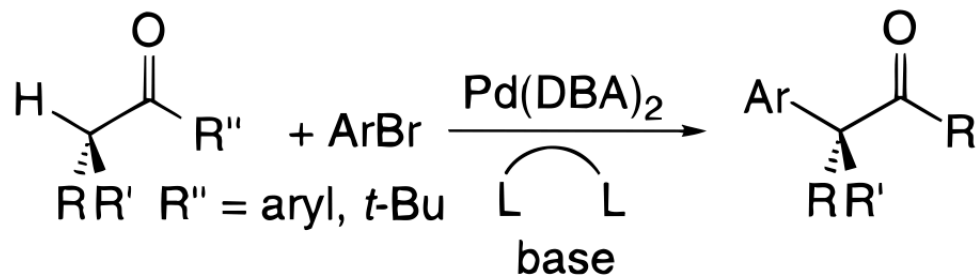
Summary

- Amination of Arenes and Heteroarenes by Four Generations Palladium Catalysts
- (phen)Cu(I)-Catalyzed Amination on Alkyl C-H Bond
- Controlled Regioselectivity of Hydroamination of Styrene Derivatives and Unactivated Olefins

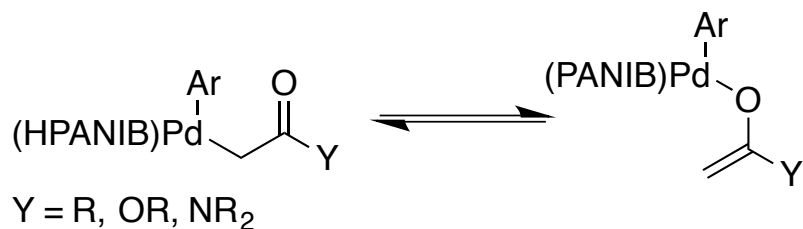
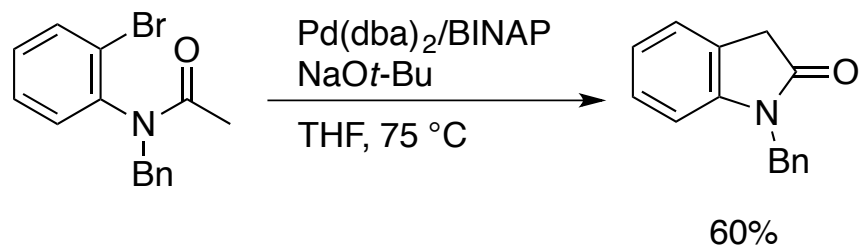
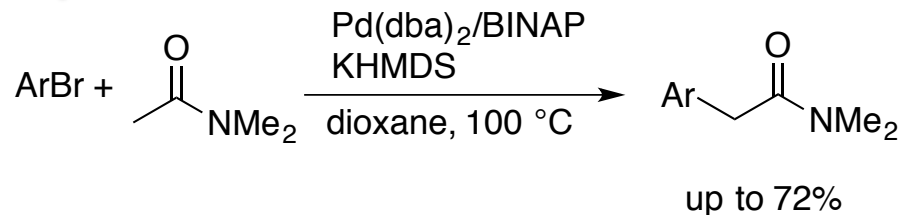
α -Arylation of Carbonyl Compounds

- α -arylation and heteroarylation of ketones, aldehydes and carboxylic derivatives
- α -arylation of activated enolates

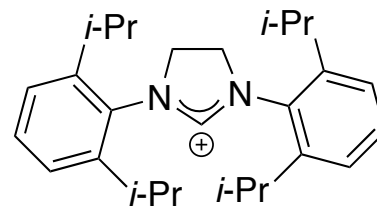
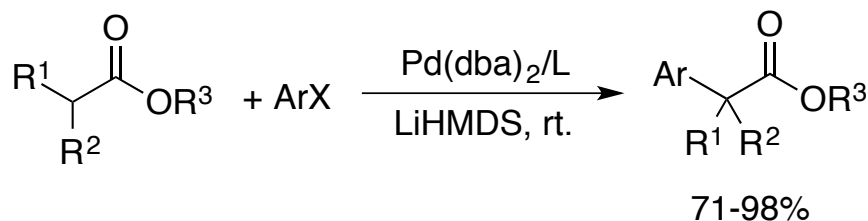
Palladium-Catalyzed α -Arylation of Ketones



α -Arylation of Amides and Esters



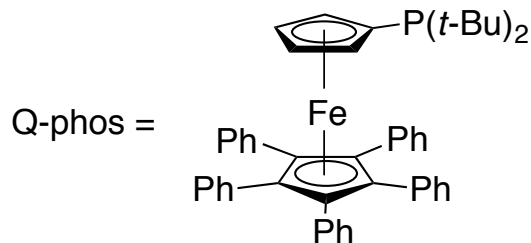
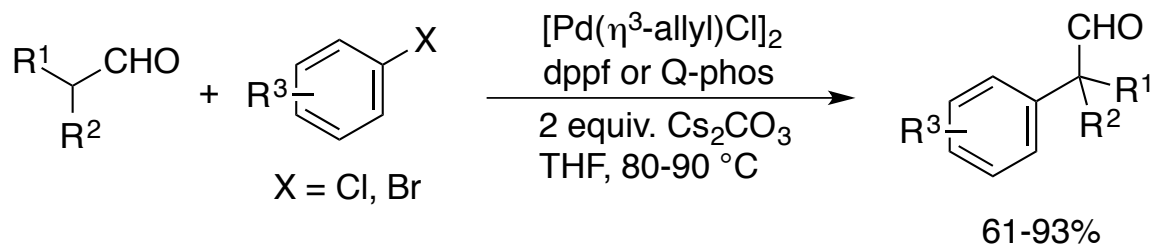
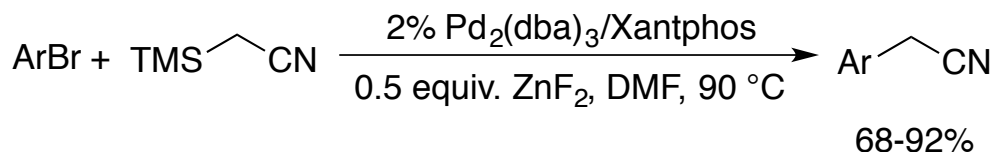
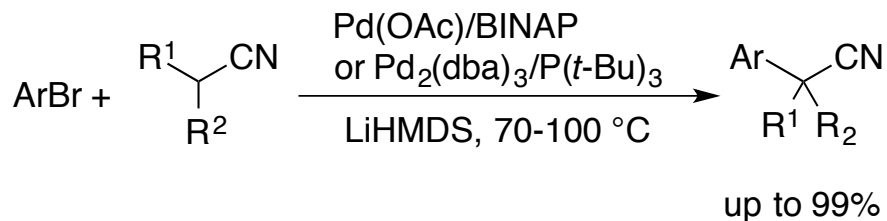
L = P(*t*-Bu)₃ or



Shanghnessy, K. H.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546.

Lee, S.; Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2001**, *123*, 8410.

α -Arylation of Nitriles and Aldehydes

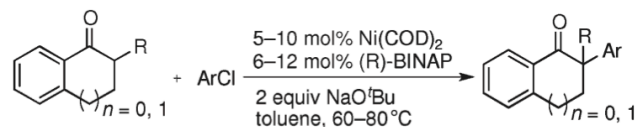
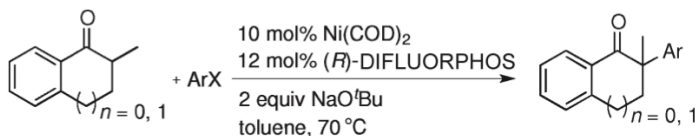


Culkin, D.A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330.

Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824.

Vo, G. D.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 2127.

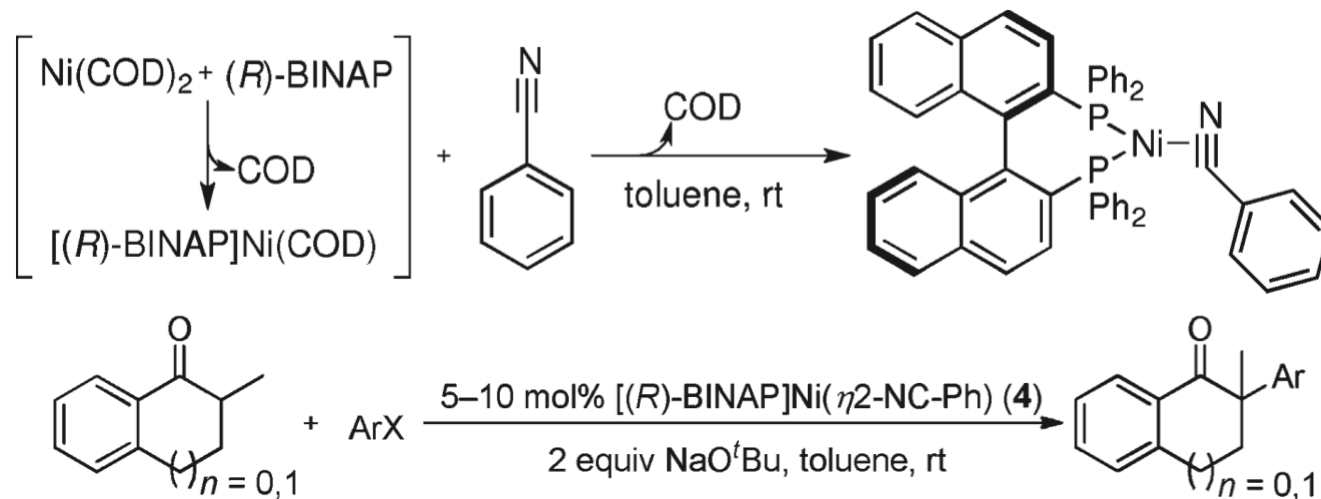
Asymmetric α -Arylation and Heteroarylation of Ketones



entry	ArX	yield (%)	ee (%)	entry	ArX	yield (%)	ee (%)		
<i>n</i> = 0				<i>n</i> = 1					
1		X = Br	69	57	13		X = Br	73	55
2		X = Cl	93	97	14		X = Cl	89	99
3			54	91	15			68	94
4		R = OMe	75	41	16		R = OMe	72	35
5		R = Me	87	94	17		R = Me	86	98
6		R' = CF ₃	85	81	18		R' = CF ₃	85	96
7		R' = F	86	98	19		R' = F	89	99
8		R' = CN	87	21	20		R' = CF ₃	84	93
9			76	96	21			54	96
10			54	95	22			45	97
11			90	99	23			87	99
12			85	90	24			79	92

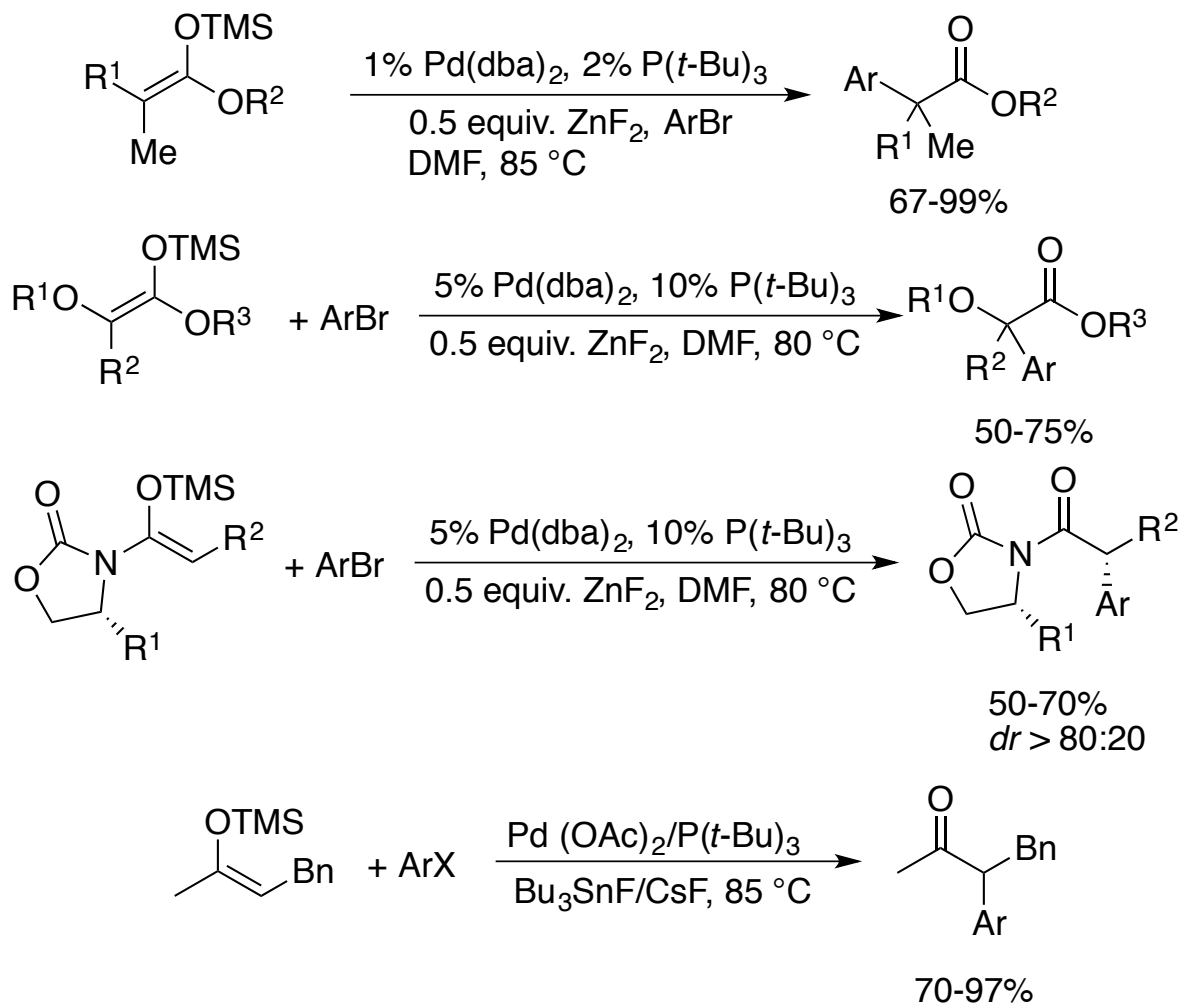
entry	ArX	yield (%)	ee (%)	entry	ArX	yield (%)	ee (%)	
<i>n</i> = 0, R = CH ₃				<i>n</i> = 0, R = CH ₂ Ph				
1 ^b		3-CF ₃	75	96	14		89	99
2 ^b		4-CF ₃	81	95	15		77	98
3 ^b			58	92	16		83	98
4		3-F	72	94	<i>n</i> = 1, R = CH ₃			
5		4-F	75	95	17		74	96
6 ^b			41	99	18		80	94
7 ^b			82	96	19		73	90
8			73	98	20		61	96
9 ^b		3-OMe	79	96	21		69	92
10 ^b		4-OMe	81	96	22		72	97
<i>n</i> = 0, R = CH ₂ CH ₃				<i>n</i> = 1, R = CH ₂ Ph				
11			66	92	23		76	94
12			77	98	24		72	98
13			72	94	25		53	99

Asymmetric α -Arylation and Heteroarylation of Ketones



entry	ArX	X	yield (%)	ee (%)	entry	ArX	X	yield (%)	ee (%)
$n = 0$, (entries 1-10)					7 ^c		Cl	92	>99
1 ^b		Cl	91	>99	8 ^c		Br	96	>99
2 ^c		Br	95	>99	9 ^b		Cl	72	>99
3 ^b		Cl	64	98	10 ^c		Br	50	98
4 ^c		Br	74	99	-----				
5 ^b		Cl	93	99	$n = 1$, (entries 11-12)				
6 ^c		Br	61	98	11 ^b		Cl	59	95
					12 ^b		Br	74	83

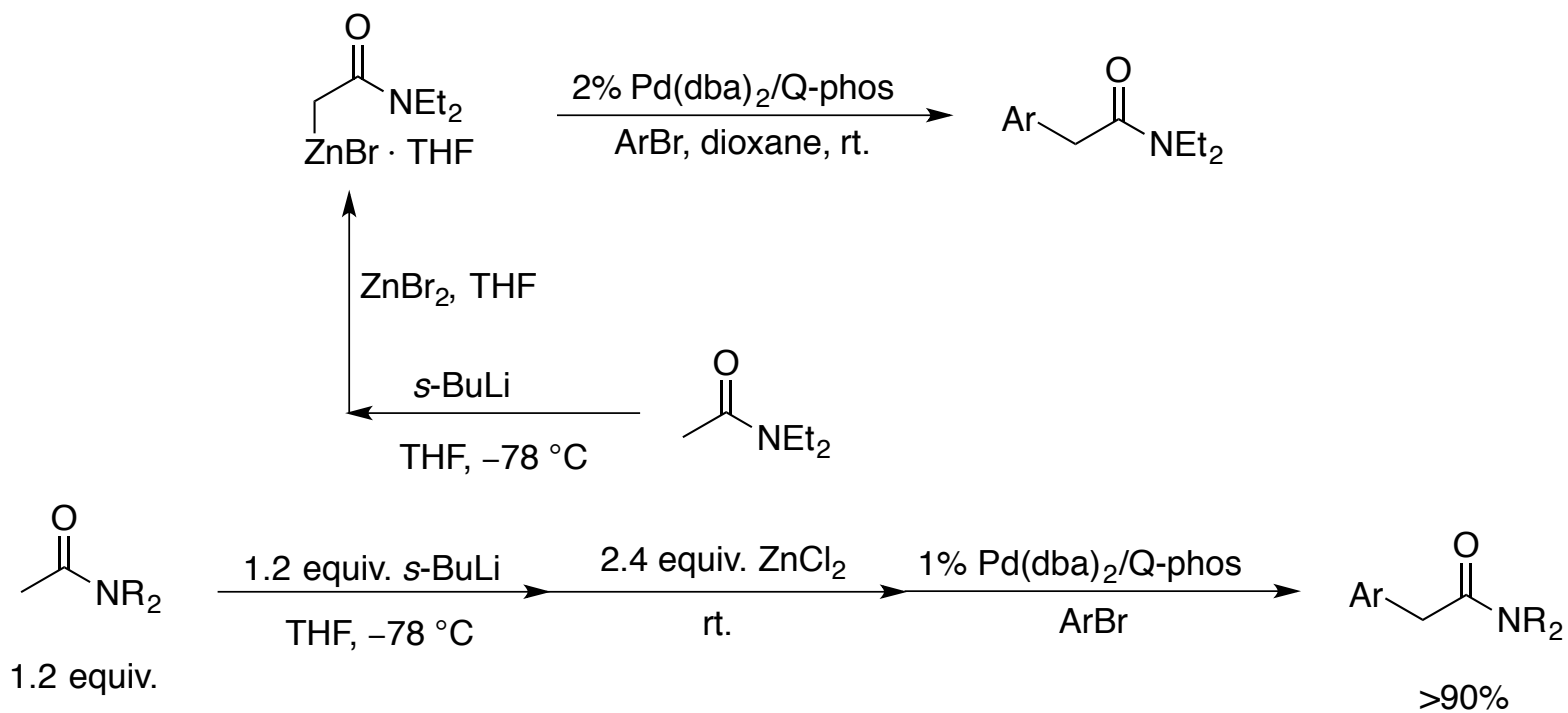
α -Arylation of Silyl Enolates



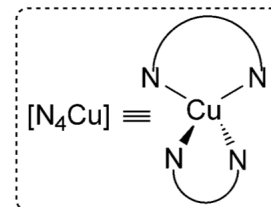
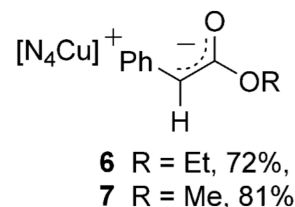
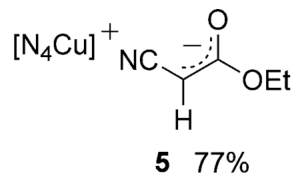
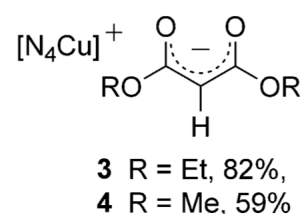
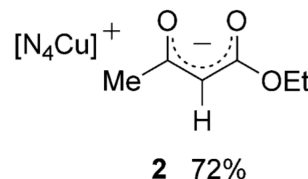
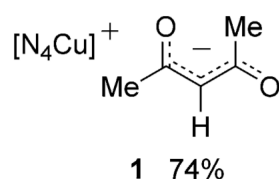
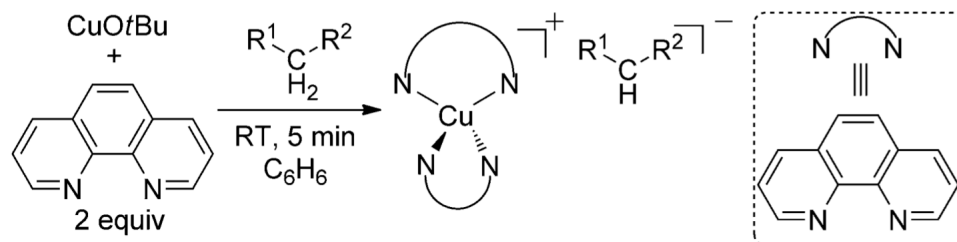
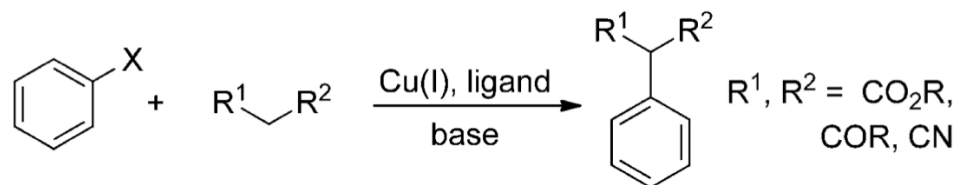
Liu, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182.

Su, W.; Hartwig, J. F. *et al. Angew. Chem. Int. Ed.* **2006**, *45*, 5852.

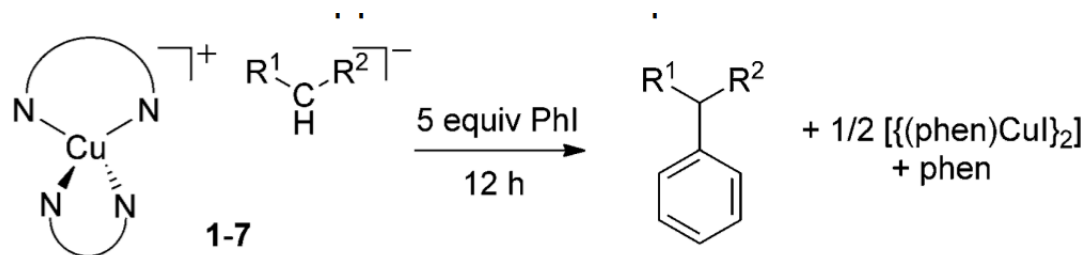
α -Arylation via *in-situ* Zinc Enolates



Copper(I) Enolate-Mediated α -Arylation: Synthesis of Cu(I) Enolated Complexes

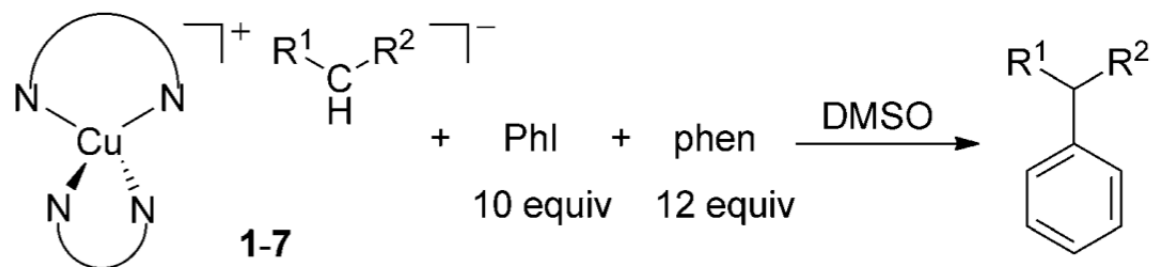


Copper(I) Enolate-Mediated α -Arylation: Reactions with PhI



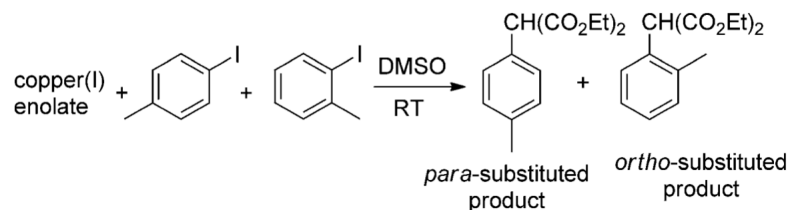
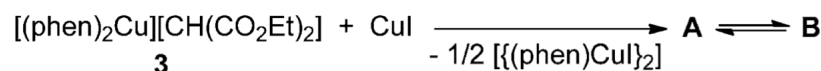
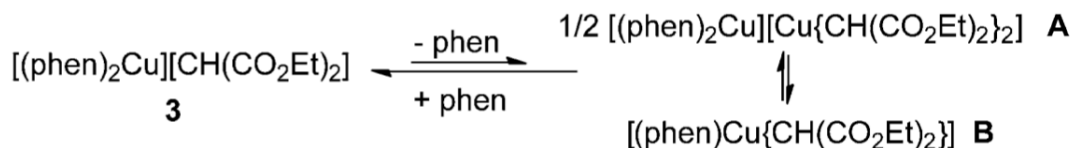
Complex	R ¹	R ²	T [°C]	Yield [%] ^[b]
1	MeCO	MeCO	60	0
2	MeCO	EtCO ₂	60	63 ^[c]
3	EtCO ₂	EtCO ₂	25	79
4	MeCO ₂	MeCO ₂	25	80
5	CN	EtCO ₂	25	86
6	Ph	EtCO ₂	25	68
7	Ph	MeCO ₂	25	70

Copper(I) Enolate-Mediated α -Arylation: Kinetic Studies



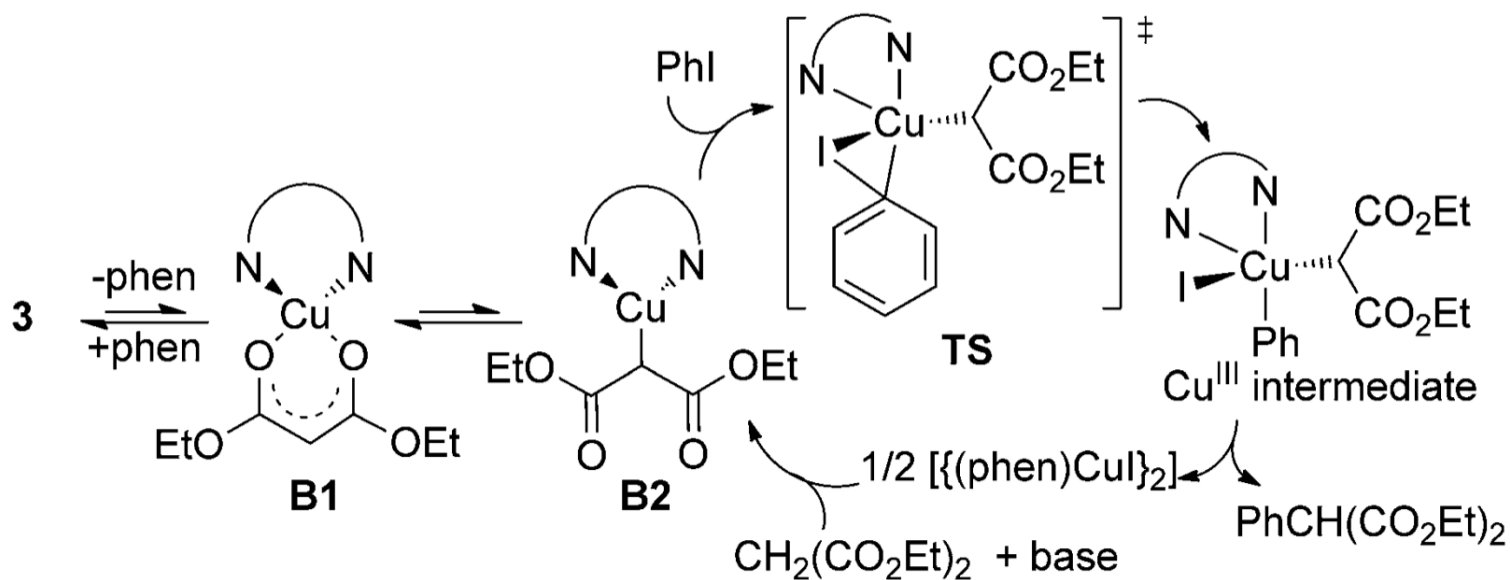
complex	T [$^{\circ}\text{C}$]	k_{obs} [s^{-1}]
1	60	inactive ^[a]
2	60	inactive ^[a]
3	60	2.6×10^{-5}
4	60	5.4×10^{-5}
5	60	7.2×10^{-5}
6	25	3.3×10^{-4}
7	25	4.1×10^{-4}

Copper(I) Enolate-Mediated α -Arylation: Selectivity with *o*- and *p*-Substituted Iodobenzene



Entry	Cu ^I enolate	<i>t</i>	Yield [%]		Ratio
			<i>para</i> -substituted product	<i>ortho</i> -substituted product	
1	3	1 h	45	2	95:5
		3 h	73	3	95:5
2	A or B	< 5 min	62	2	97:3
3	K[CH(CO ₂ Et) ₂] + CuI	1 h	6.2	2.4	72:28
		21 h	13	6	69:31
4	2 K[CH(CO ₂ Et) ₂] + CuI	2 h	23	10	70:30
		23 h	37	16	69:31

Copper(I) Enolate-Mediated α -Arylation: Proposed Catalytic Cycle





Thank You!