

北京大学 Peking Univ. Ph. D. Dissertation

Aromatic C-H and C-N Bonds Activation and Functionalization

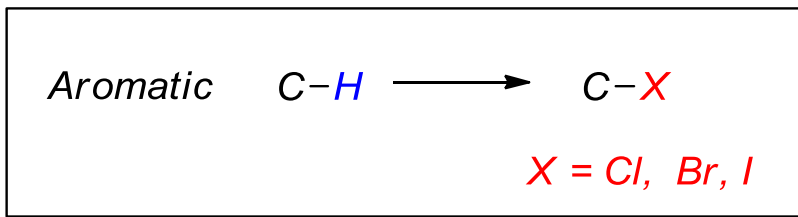


Reporter: Dr. Fanyang Mo
Supervisor: Prof. Jianbo Wang
Peking University
July, 2010

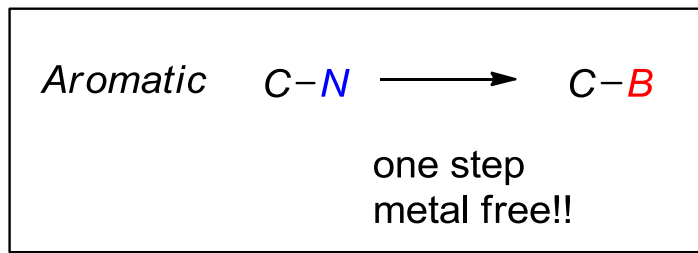
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3. Direct Conversion of Arylamines to Pinacol Boronates

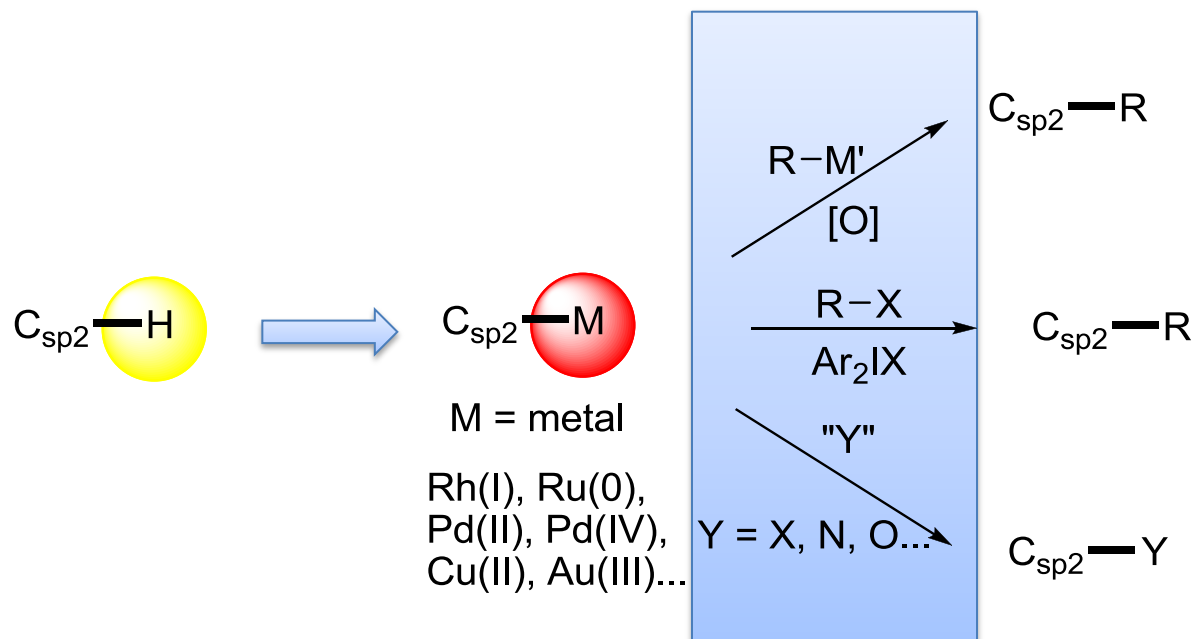


4. Summary

5. Acknowledgement

1. Introduction

Background of aromatic C-H bond activation



Reviews:

Sun, C. -L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, 46, 677.

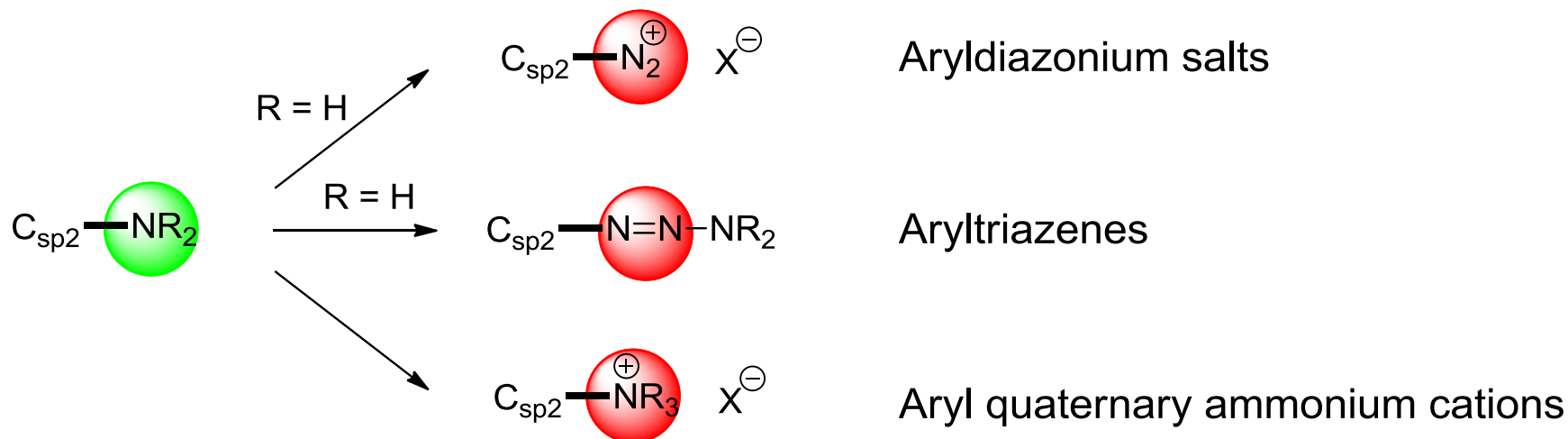
Chen, X.; Engle, K. M.; Wang, D. -H.; Yu, J. -Q. *Angew. Chem. Int. Ed.* **2009**, 48, 5094.

Li, B. -J.; Yang, S.; Shi, Z. -J. *Synlett.* **2008**, 7, 949.

Dyker, G. *Handbook of C-H Transformations. Applications in Organic Synthesis*, Wiley-VCH, Weinheim, **2005**.

3. Direct Conversion of Arylamines to Pinacol Boronates

Background of aromatic C-N bond activation



Examples:

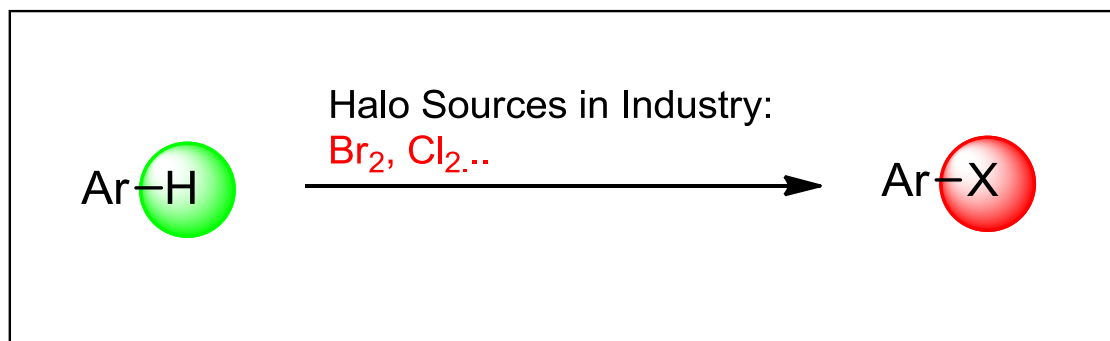
Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046.

Saeki, T.; Son, E. -C.; Tamao, K. *Org. Lett.* **2004**, *6*, 617.

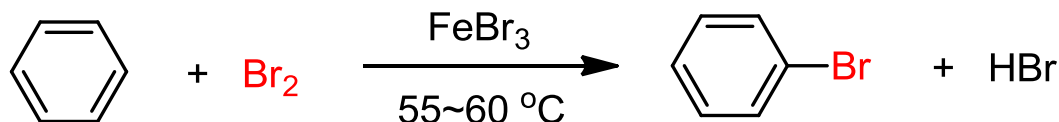
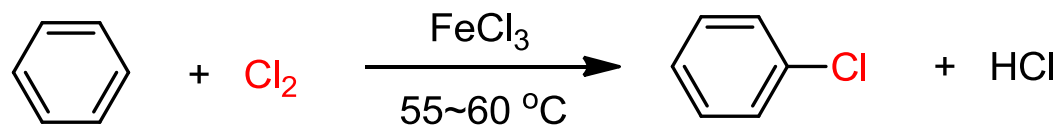
Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 6098.

2. Gold catalyzed Halogenation of Aromatics

Background of halogenating of aromatic compounds



Examples:

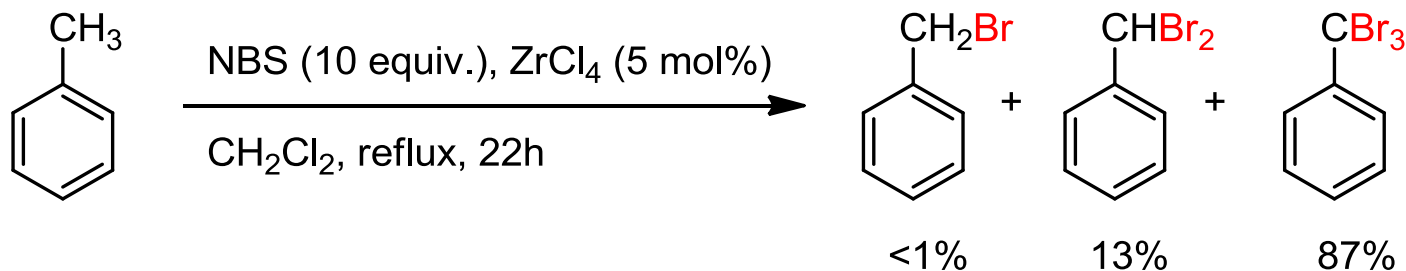
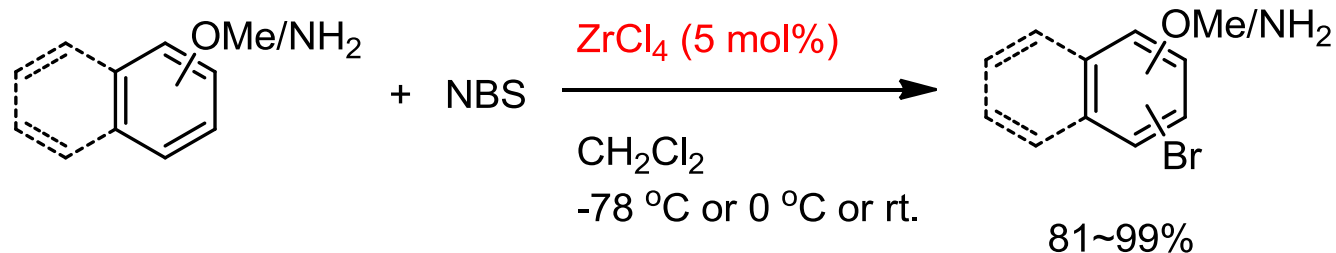


From Textbook...

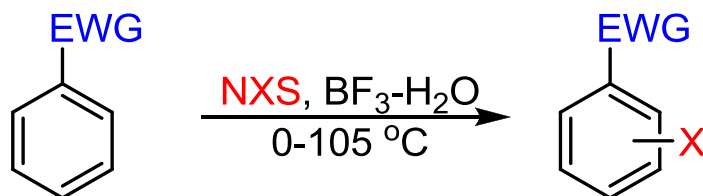
2. Gold catalyzed Halogenation of Aromatics

Background of halogenating of aromatic compounds

More examples:



Zhang, Y.; Shibatomi, K.; Yamamoto, H. *Synlett* **2005**, 2837.

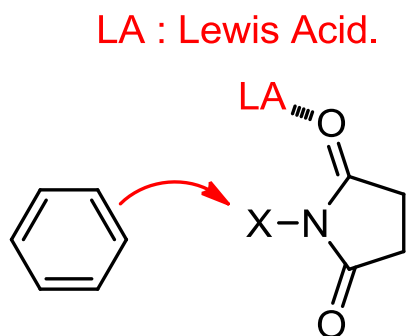


EWG = Electron withdrawing group
X = Cl, Br or I

2. Gold catalyzed Halogenation of Aromatics

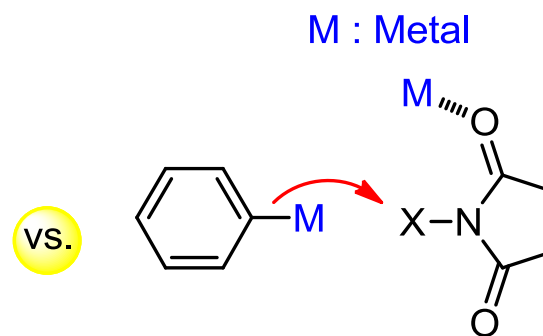
Strategies

Previous Strategy

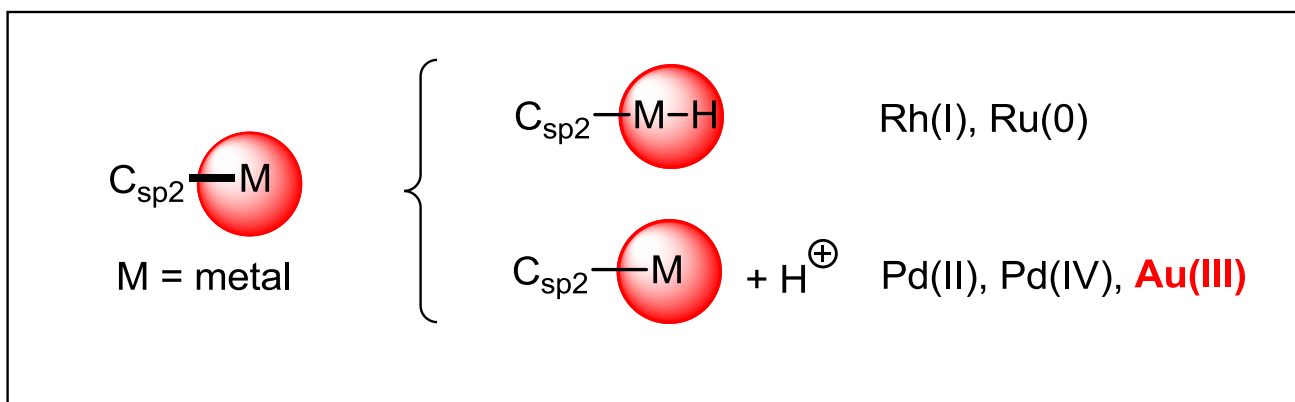


Activation of NXS

Our Design

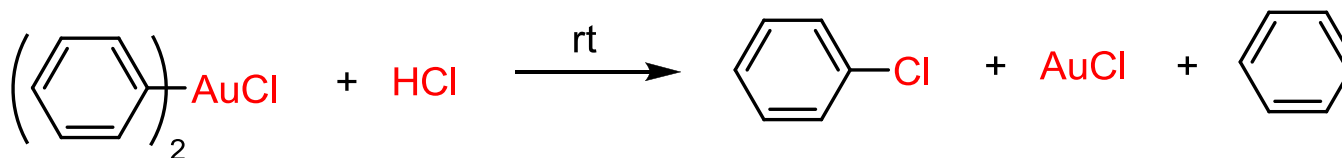
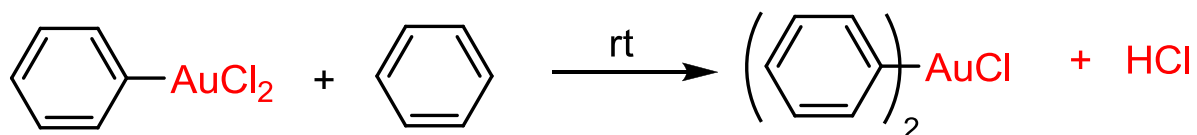
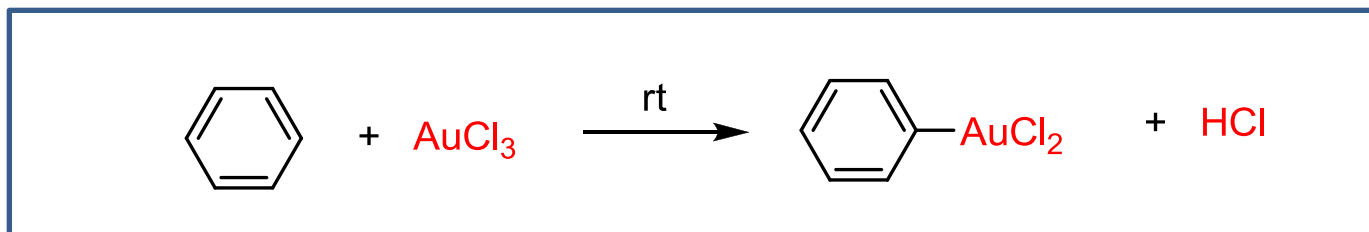


Dual Activation



2. Gold catalyzed Halogenation of Aromatics

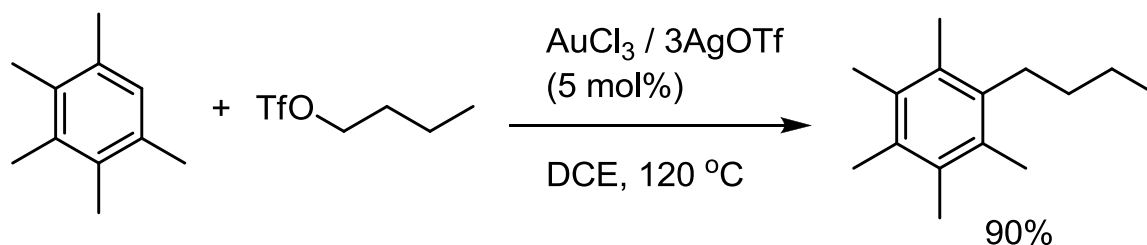
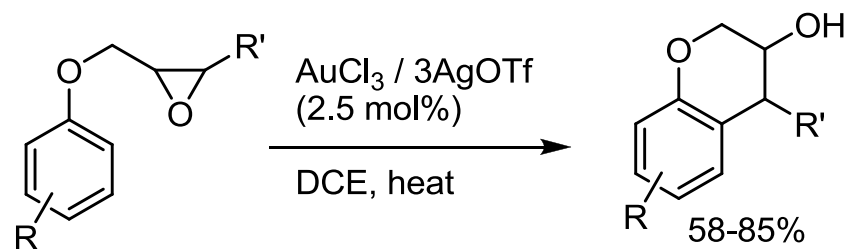
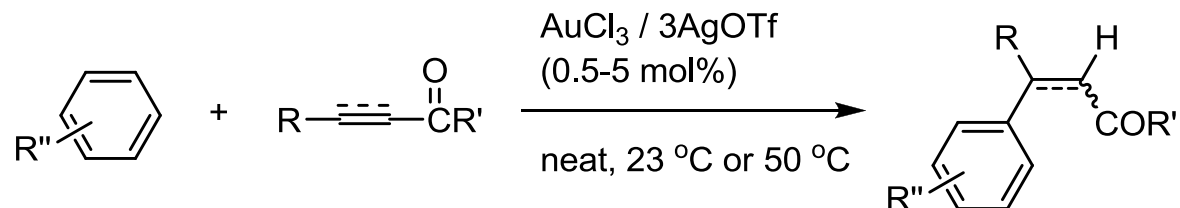
Reaction between benzene and AuCl_3



Kharasch, M. S.; Isbell, H. S. *J. Am. Chem. Soc.* **1931**, 53, 3053.

2. Gold catalyzed Halogenation of Aromatics

AuCl₃-catalyzed arenes transformations



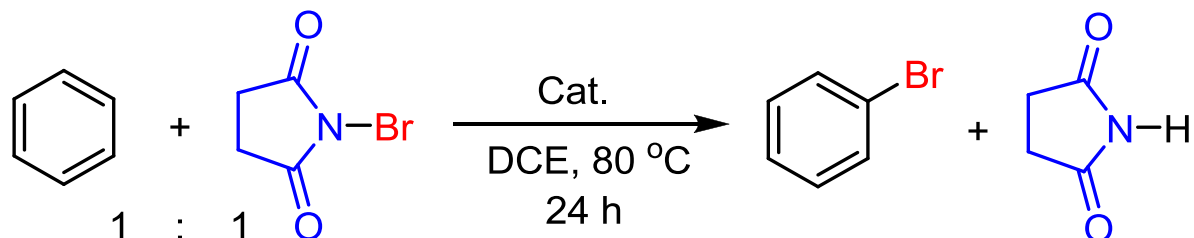
Shi, Z.; He, C. *J. Org. Chem.* **2004**, 69, 3669.

Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, 126, 5964.

Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, 126, 13596.

2. Gold catalyzed Halogenation of Aromatics

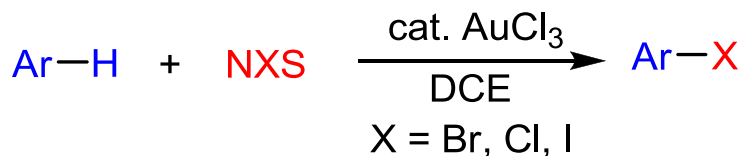
Bromination of benzene with NBS using various catalysts


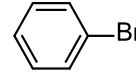

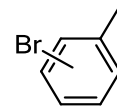
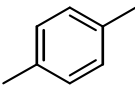
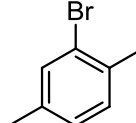
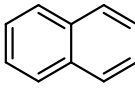
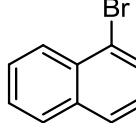
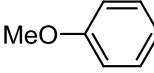
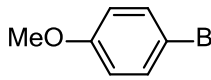
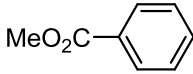
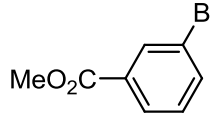
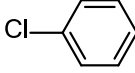
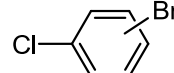
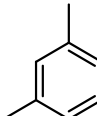
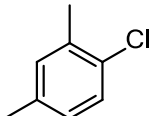


Entry	Catalyst (mol%)	Yield
1	AuCl₃ (1)	99%
2	FeCl ₃ (20)	27%
3	FeBr ₃ (20)	25%
4	BF ₃ OEt ₂ (20)	7%
5	NH ₄ NO ₃ (20)	<1%
6	ZrCl ₄ (20)	5%
7	AlCl ₃ (20)	<1%
8	Pd(OAc) ₂ (20)	0%
9	HCl (20)	0%
10	H ₂ SO ₄ (20)	25%

2. Gold catalyzed Halogenation of Aromatics

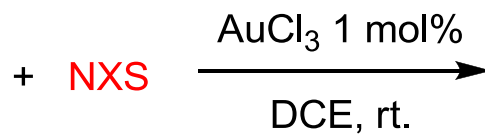
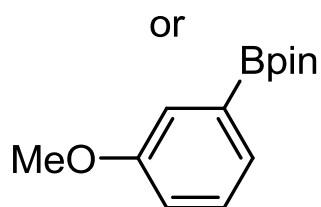
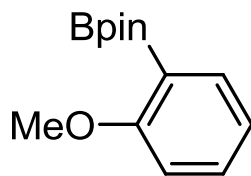
Scope exploration



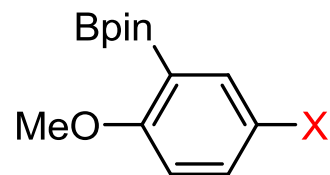
Entry	ArH	AuCl ₃ (mol%)	T (°C)	T (h)	ArX	Yield
1		1	80	11		>99%
2		1	rt	40		>99%, o:p = 1:2
3		0.5	rt	30		>99%
4		0.1	80	15		>99% (95%)
5		0.1	rt	1		>99% (96%)
6		5	80	48		80%
7		1	80	12		>99% o:m:p = 7:1:2
8		1	80	15		>99%

2. Gold catalyzed Halogenation of Aromatics

Bromination of aryl boronates

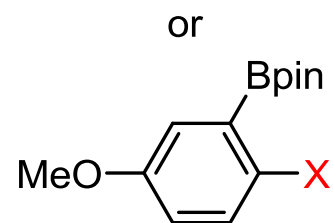


Bpin = Boronic pinacol ester



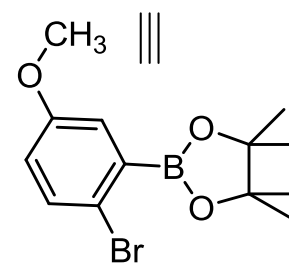
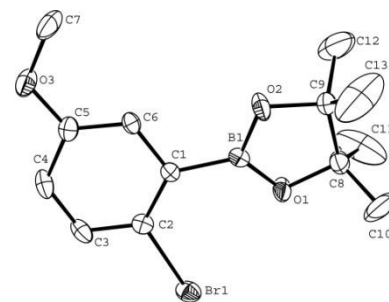
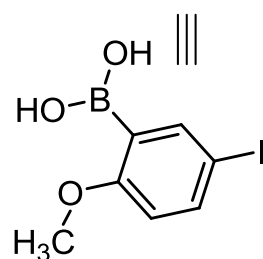
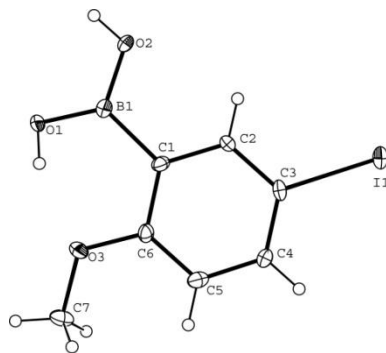
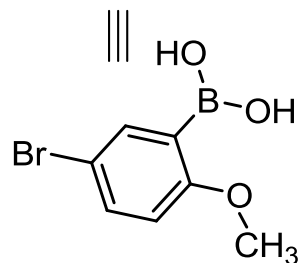
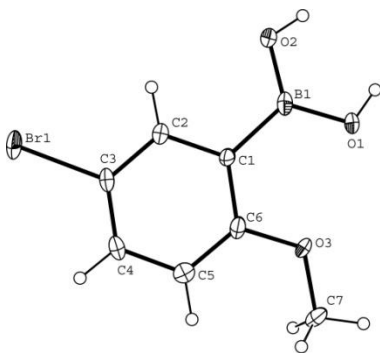
X = Br, 91%

X = I, 80%



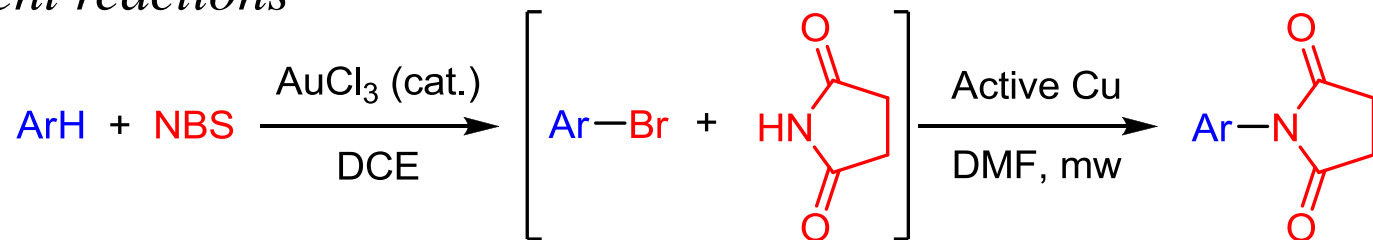
X = Br, 93%


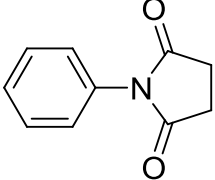
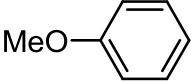
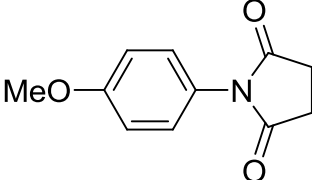
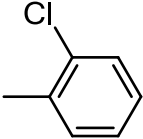
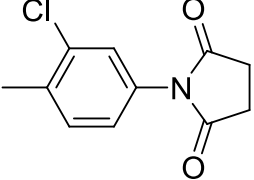
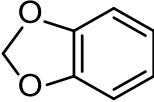
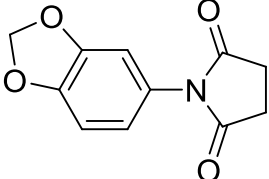
X = I, 92%



2. Gold catalyzed Halogenation of Aromatics

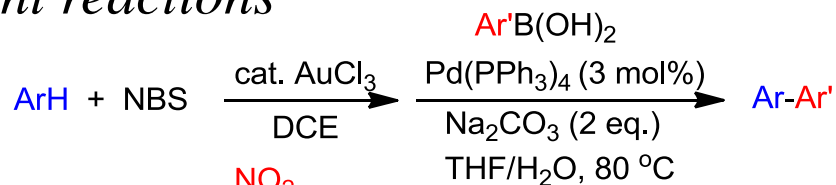
Subsequent reactions



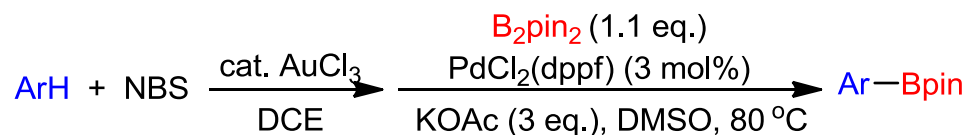
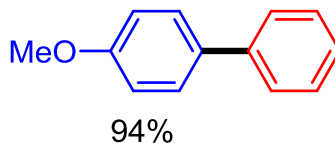
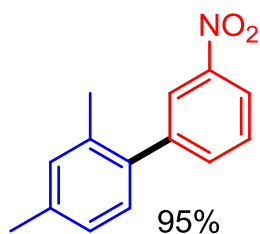
Entry	ArH	Products	Yield (%)
1			83
2			78
3			57
4			65

2. Gold catalyzed Halogenation of Aromatics

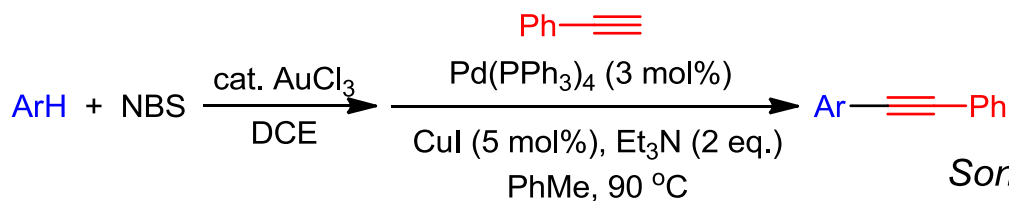
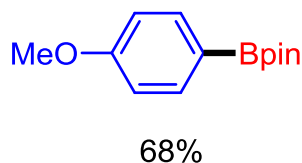
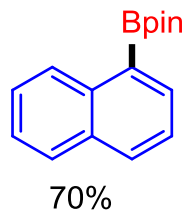
Subsequent reactions



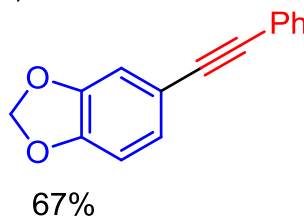
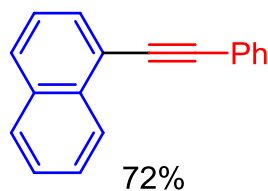
Suzuki-Miyaura coupling



Miyaura Borylation



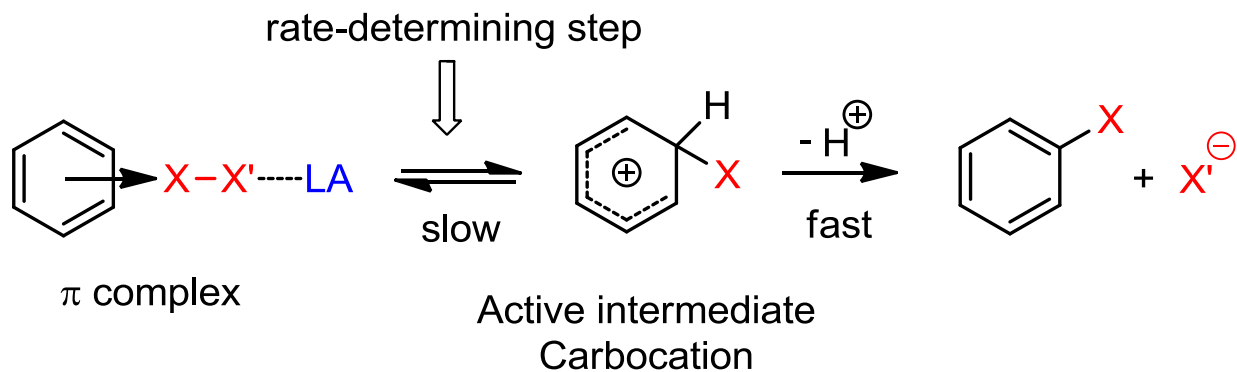
Sonogashira coupling



2. Gold catalyzed Halogenation of Aromatics

The Mechanism

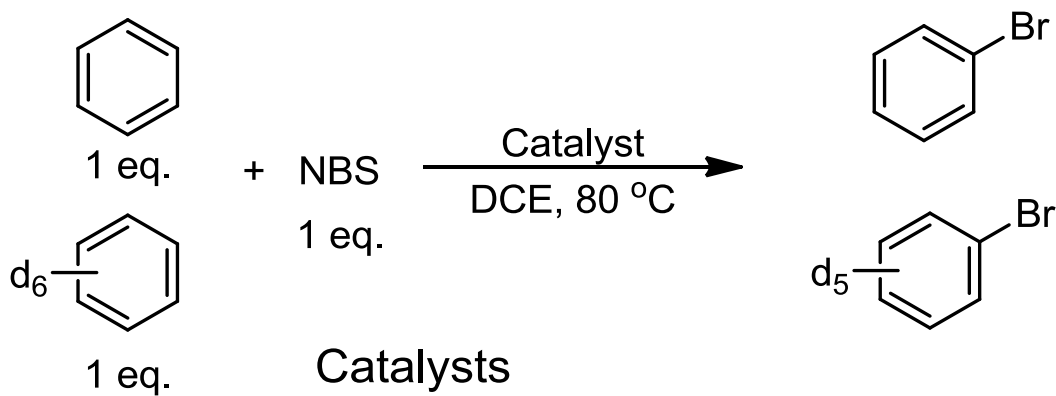
Classic electrophilic process



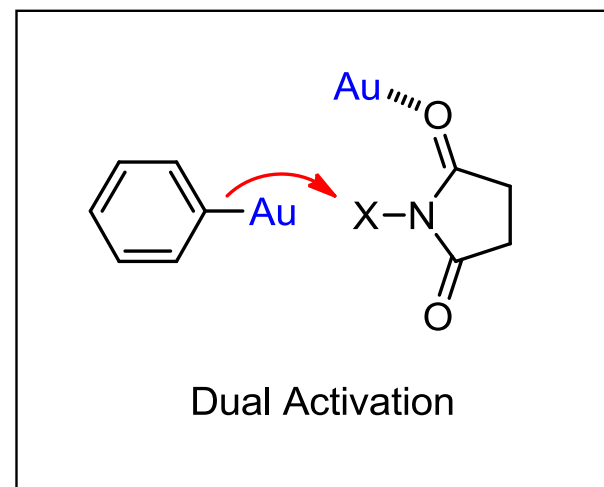
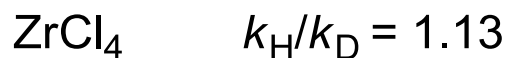
2. Gold catalyzed Halogenation of Aromatics

The Mechanism

Kinetic Isotopic Effect Experiment

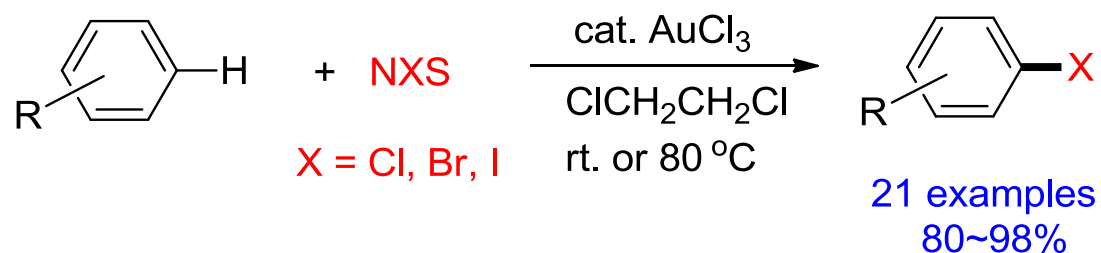


Catalysts



2. Gold catalyzed Halogenation of Aromatics

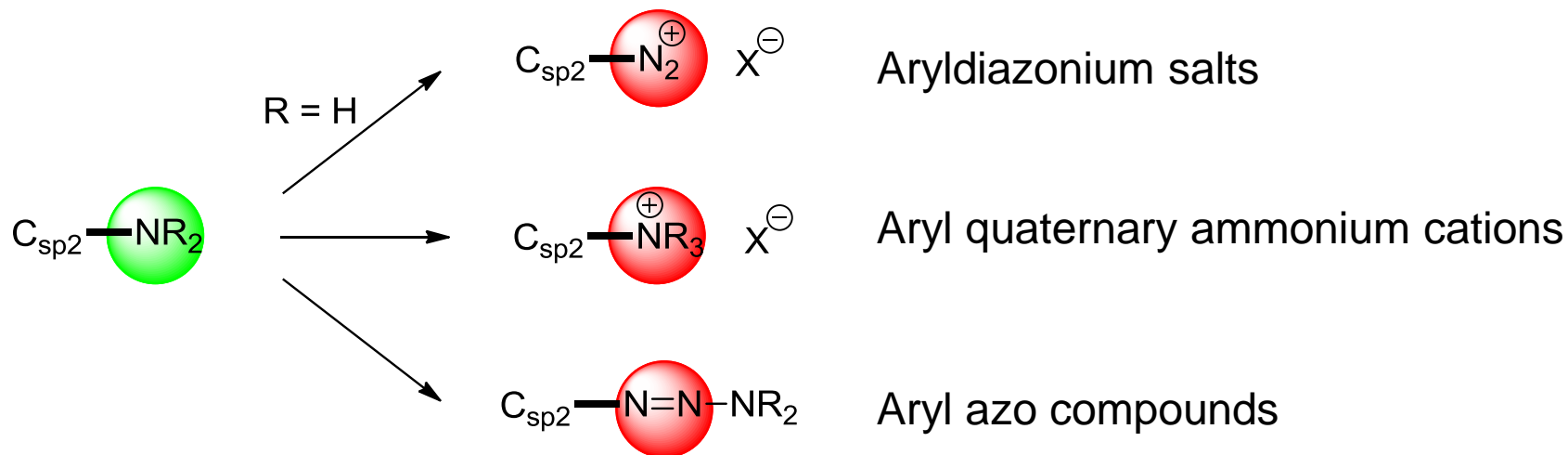
Summary



- ✓ Low catalyst loading (0.01~1%)
- ✓ Mild reaction conditions
- ✓ Clean transformations
- ✓ High yields
- ✓ Subsequent reaction

3. Direct Conversion of Arylamines to Pinacol Boronates

Background of aromatic C-N bond activation



Examples:

Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046.

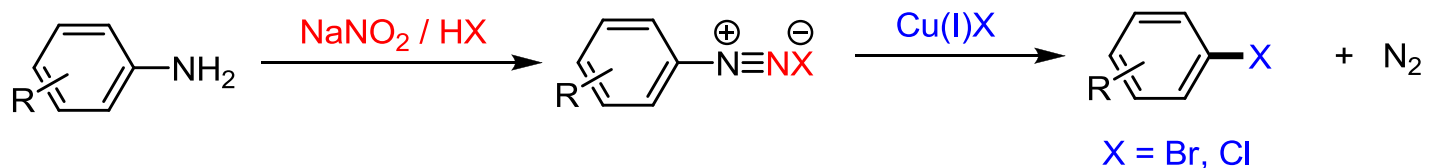
Saeki, T.; Son, E. -C.; Tamao, K. *Org. Lett.* **2004**, *6*, 617.

Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 6098.

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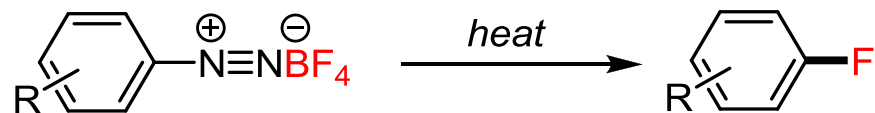
Long road of Sandmeyer reaction development

I. Seminal reaction



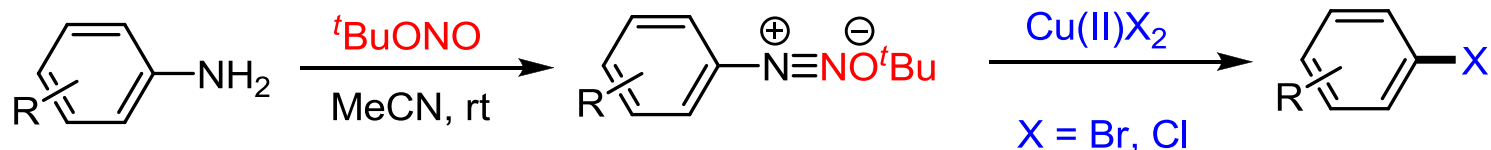
Sandmeyer, T. *Ber. Dtsch. Chem. Ges.* **1884**, 17, 1633.

II. Balz-Schiemann reaction



Balz, G.; Schiemann, G. *Ber.* **1927**, 60B, 1186.

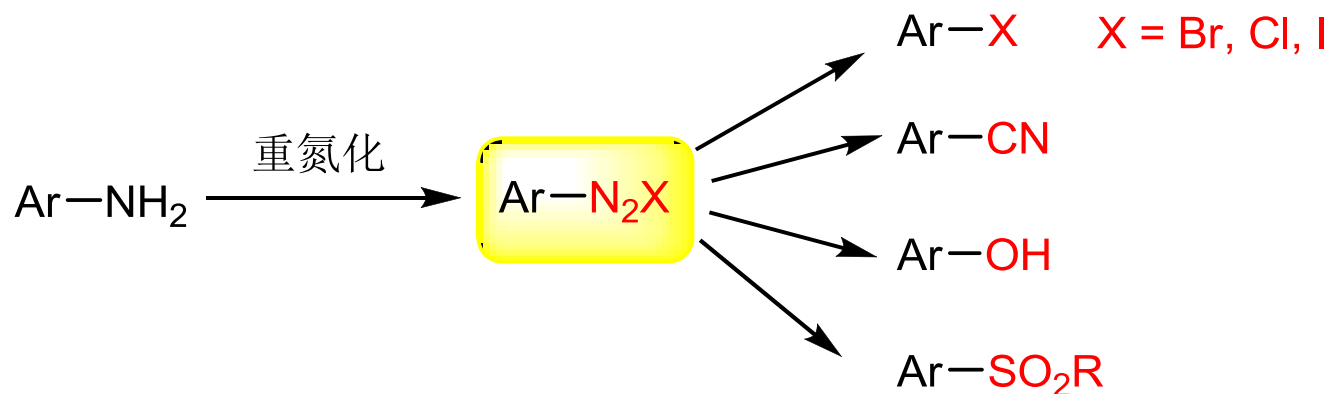
III. Sandmeyer reaction in organic solvent



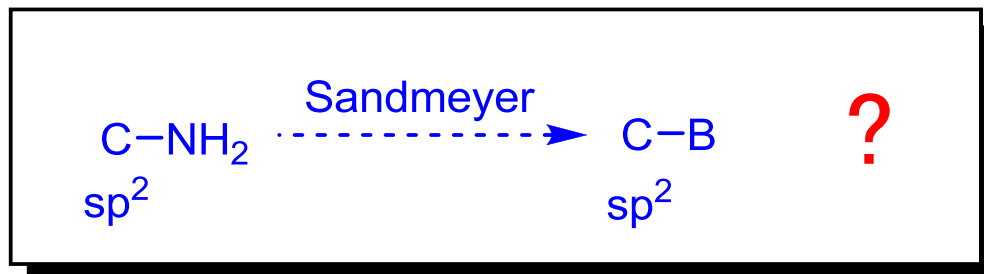
Doyle, M. P.; Siegfried, B.; Dellaria, J. F., Jr. *J. Org. Chem.* **1977**, 42, 2426;

3. Direct Conversion of Arylamines to Pinacol Boronates

What Sandmeyer reaction can do?

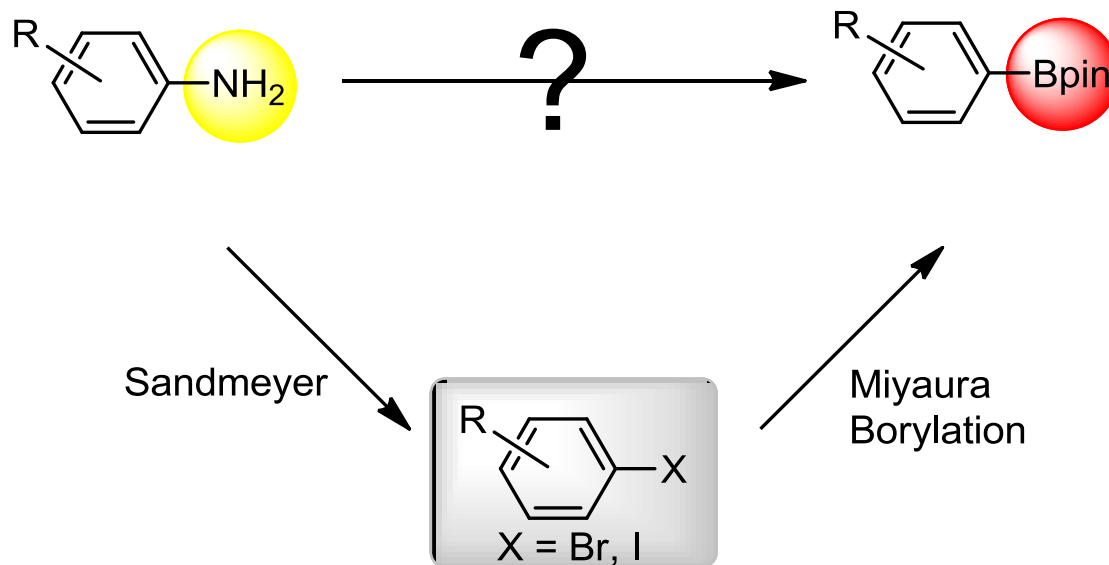


Galli, C. *Chem. Rev.* **1988**, 88, 765.



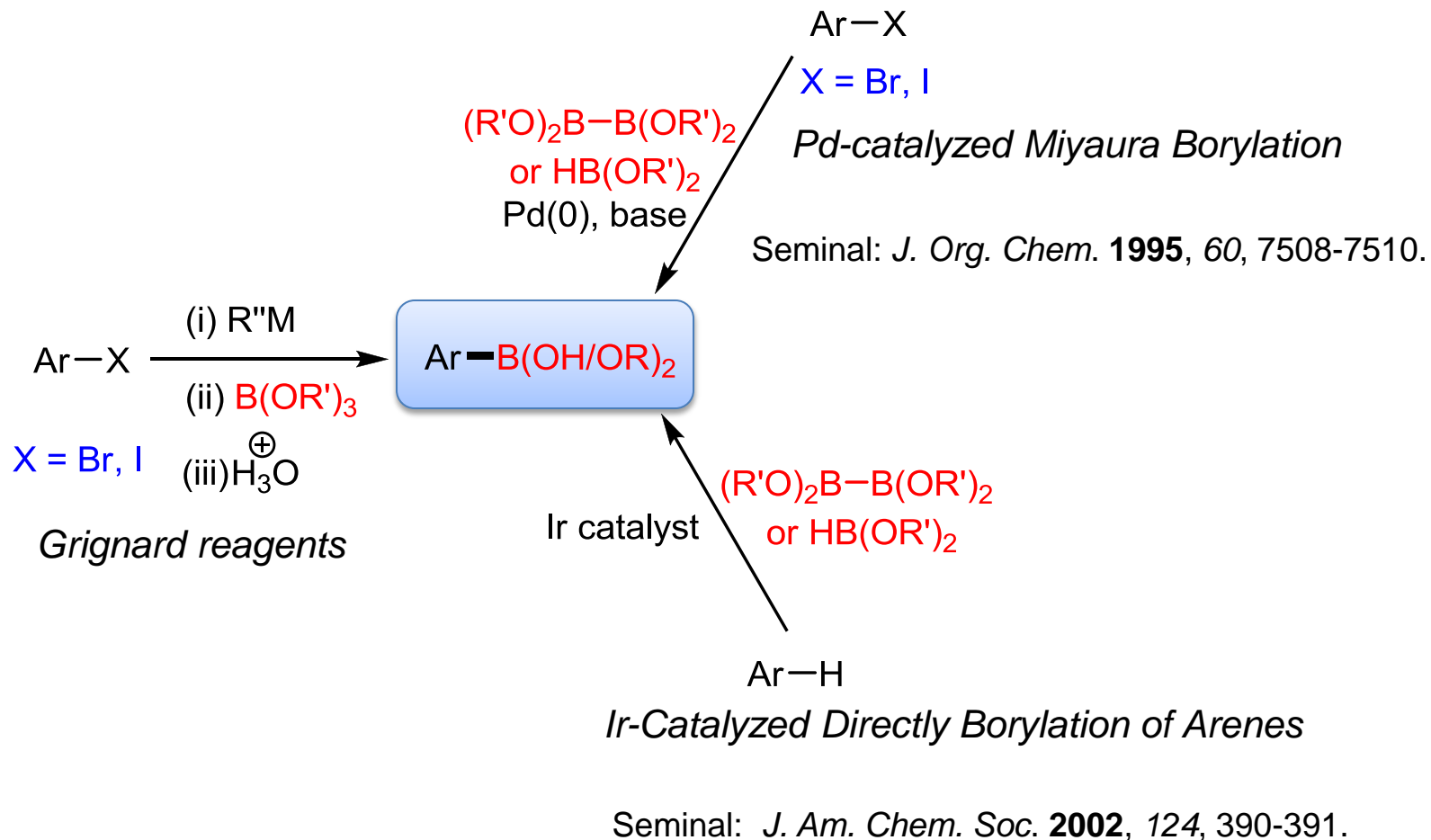
3. Direct Conversion of Arylamines to Pinacol Boronates

The idea



3. Direct Conversion of Arylamines to Pinacol Boronates

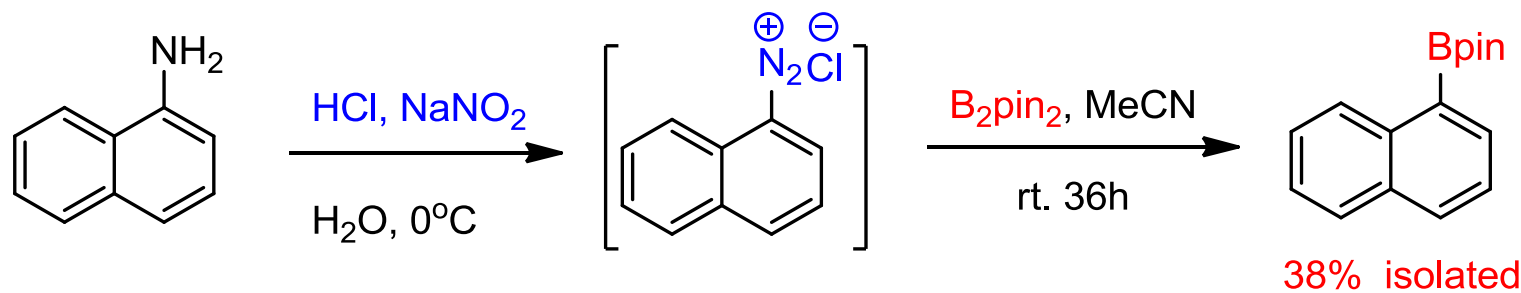
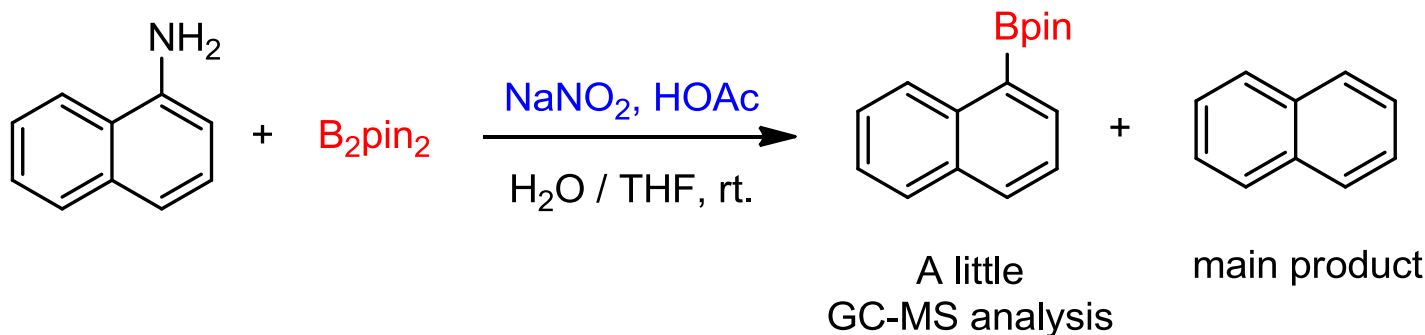
Traditional approaches to Boronates



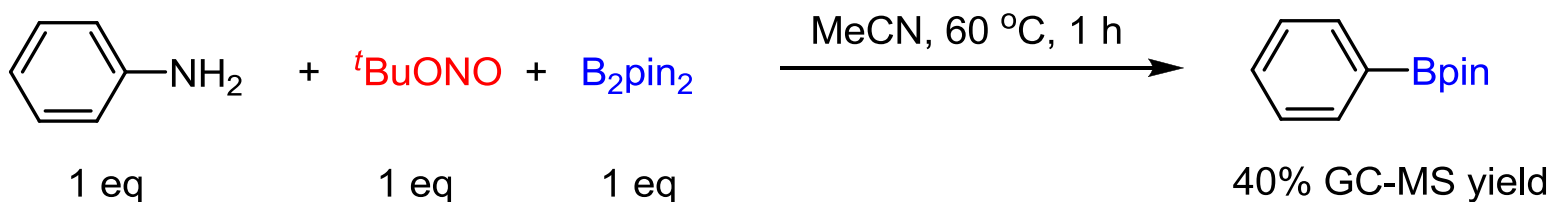
3. Direct Conversion of Arylamines to Pinacol Boronates

Initial attempts

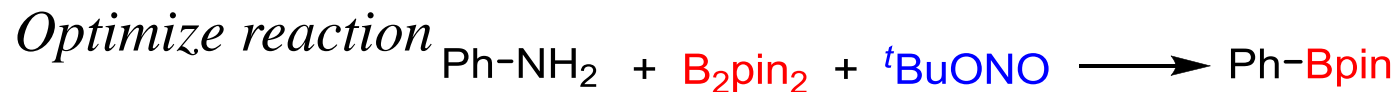
In aqueous media



In organic media



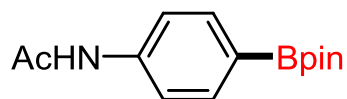
3. Direct Conversion of Arylamines to Pinacol Boronates



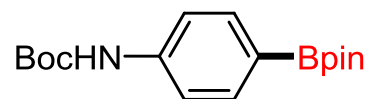
Entry	ratio	Solvent	Additive (mol%)	T (°C)	Yield (%)
1	1:1:1	MeCN	none	60	40
2	1:1:1	MeCN	KOAc (100)	60	30
3	1:1:1	MeCN	CuPF ₆ (MeCN) ₄ (100)	60	8
4	1:1:1.5	MeCN	Cu(OAc) ₂ (100)	60	7
5	1:1.2:1.5	MeCN	SnCl ₂ (100)	60	29
6	1:1.2:1.5	MeCN	Fe(OAc) ₂ (100)	60	62
7	1:1:1	MeCN	BPO (10)	60	49
8	1:1:1	MeCN	AIBN (10)	60	47
9	1:1.2:1.5	MeCN	BPO (10)	60	57
10	1:1.2:1.5	MeCN	BPO (10)	rt	66
11	1:0.5:1.5	MeCN	BPO (10)	rt	11
12	1:1.1:1.5	MeCN	BPO (5)	rt	70
13	1:1.1:1.5	MeCN	BPO (2)	rt	77
14	1:1.1:1.5	DCM	BPO (2)	rt	49
15	1:1.1:1.5	DCE	BPO (2)	rt	65
16	1:1.1:1.5	Toluene	BPO (2)	rt	65
17	1:1.1:1.5	EtOAc	BPO (2)	rt	66

3. Direct Conversion of Arylamines to Pinacol Boronates

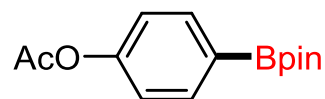
Scope of the reaction



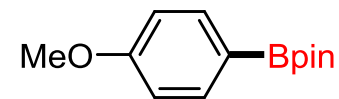
2 h, 93%



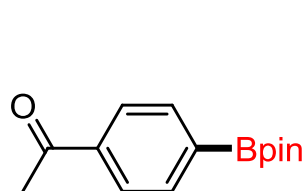
2 h, 70%



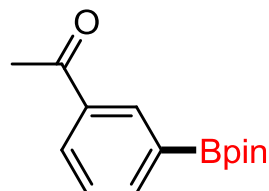
2 h, 73%



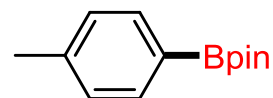
2 h, 72%



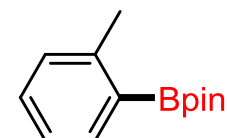
1 h, 67%



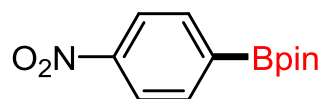
2 h, 65%



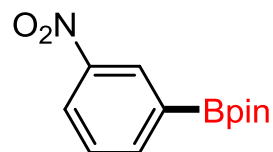
1 h, 66%



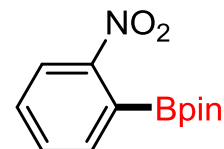
2 h, 53%



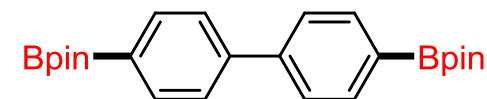
1 h, 91%



1 h, 62%



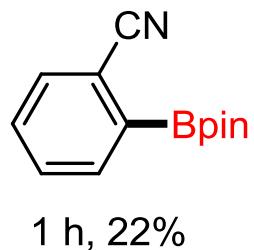
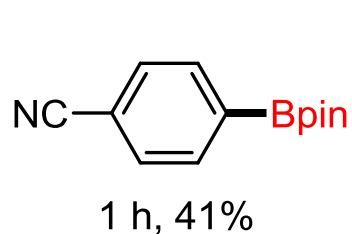
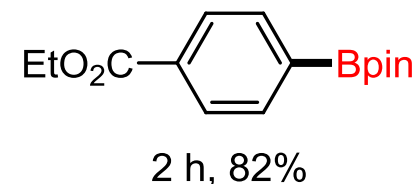
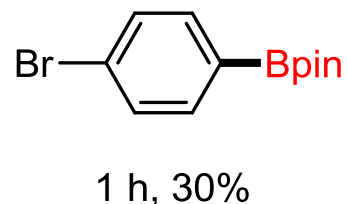
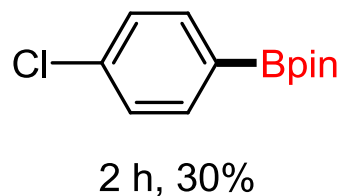
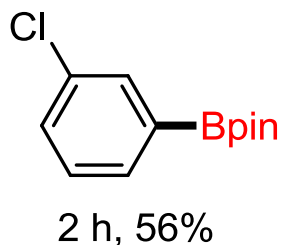
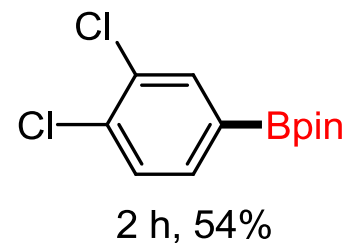
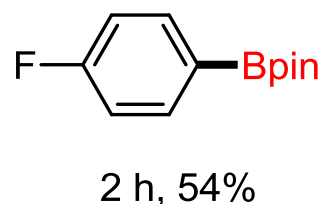
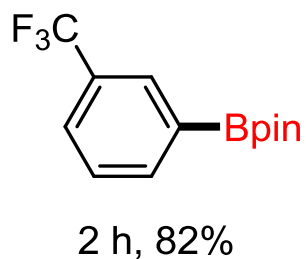
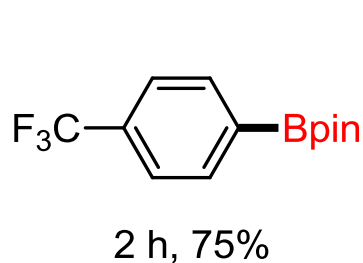
trace



2 h, 55%

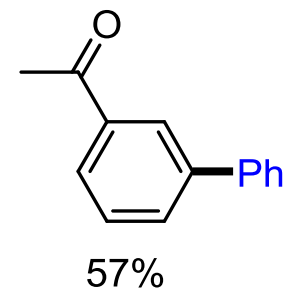
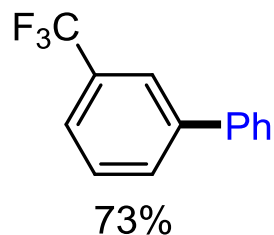
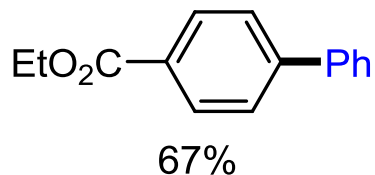
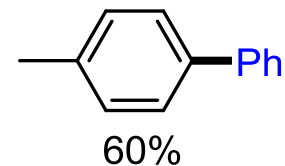
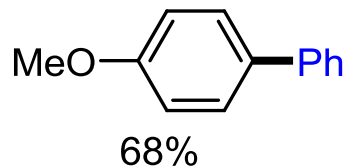
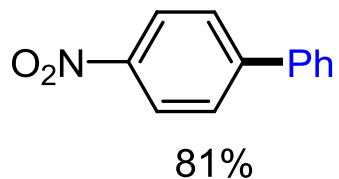
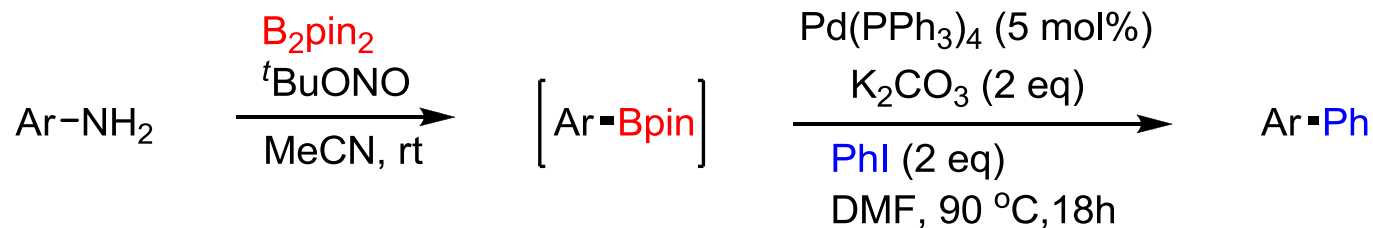
3. Direct Conversion of Arylamines to Pinacol Boronates

Scope of the reaction



3. Direct Conversion of Arylamines to Pinacol Boronates

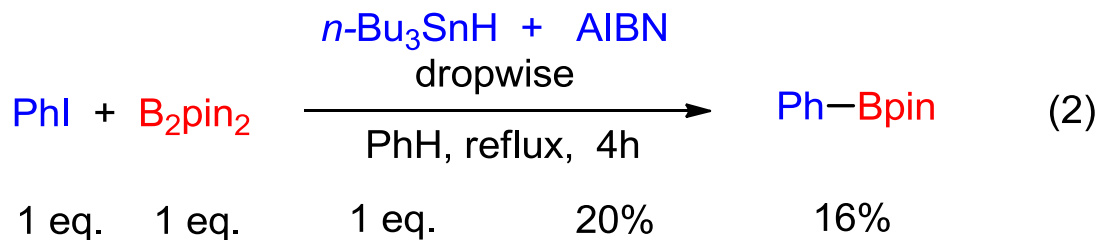
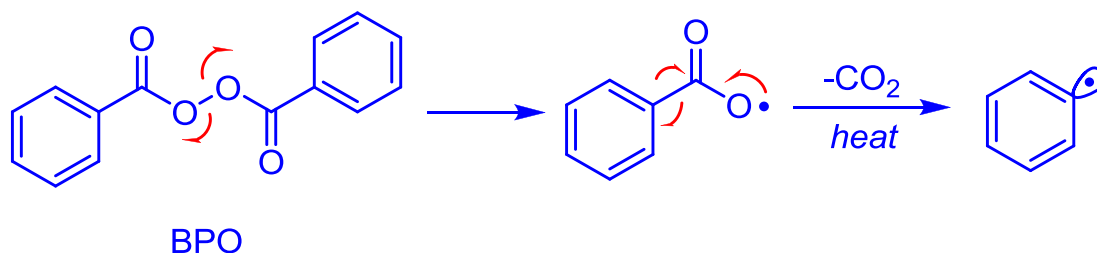
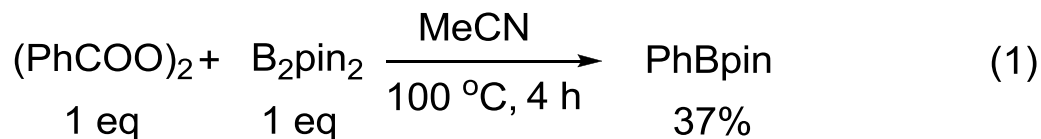
Subsequent reaction



3. Direct Conversion of Arylamines to Pinacol Boronates

The Mechanism

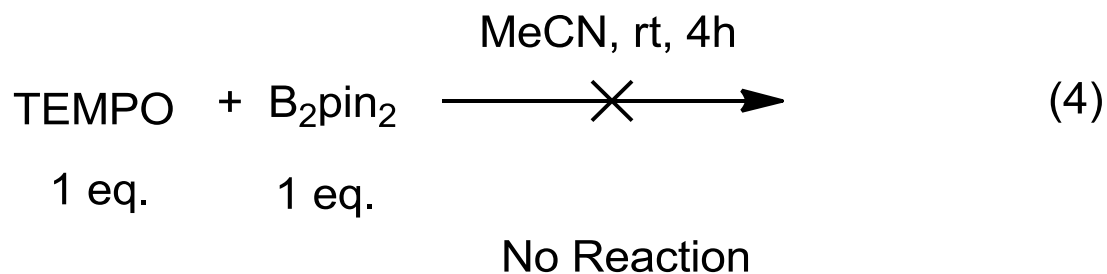
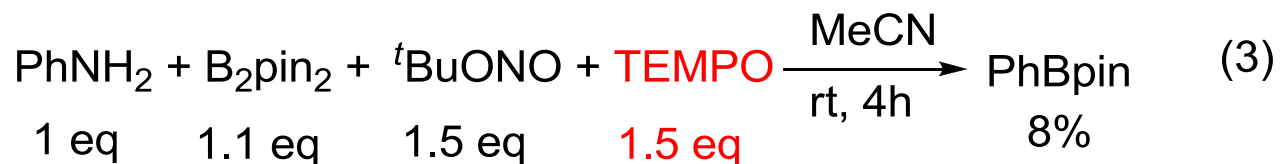
The reaction of phenyl radical and B_2pin_2



Conclusion: phenyl radical can react with B_2pin_2 to afford phenyl boronate!

3. Direct Conversion of Arylamines to Pinacol Boronates

The Mechanism



Conclusion: radical scavenger TEMPO effectively block this reaction.

3. Direct Conversion of Arylamines to Pinacol Boronates

The Mechanism



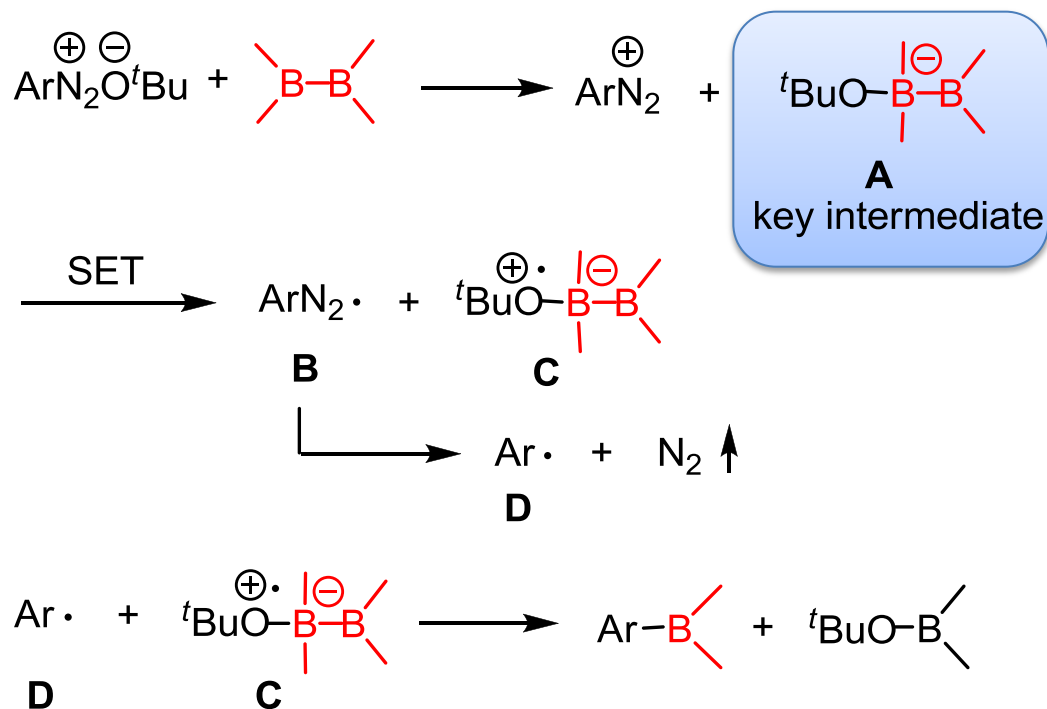
Entry	Additive (mol%)	T (°C)	Time	Yield (%)
1	none	rt	10 h	0
2	none	70	10 h	3
3	BPO (10)	rt	10 h	0
4	BPO (10)	70	10 h	5
5	K ^t OBu (100)	rt	10 min	40
6	Na ^t OBu (100)	rt	10 min	7
7	NaOMe (100)	rt	10 min	15
8	NaOEt (100)	rt	10 min	33
9	KOAc (100)	rt	10 min	38

Conclusion: the kind of anions of diazonium salts have a great impact on the reaction.

3. Direct Conversion of Arylamines to Pinacol Boronates

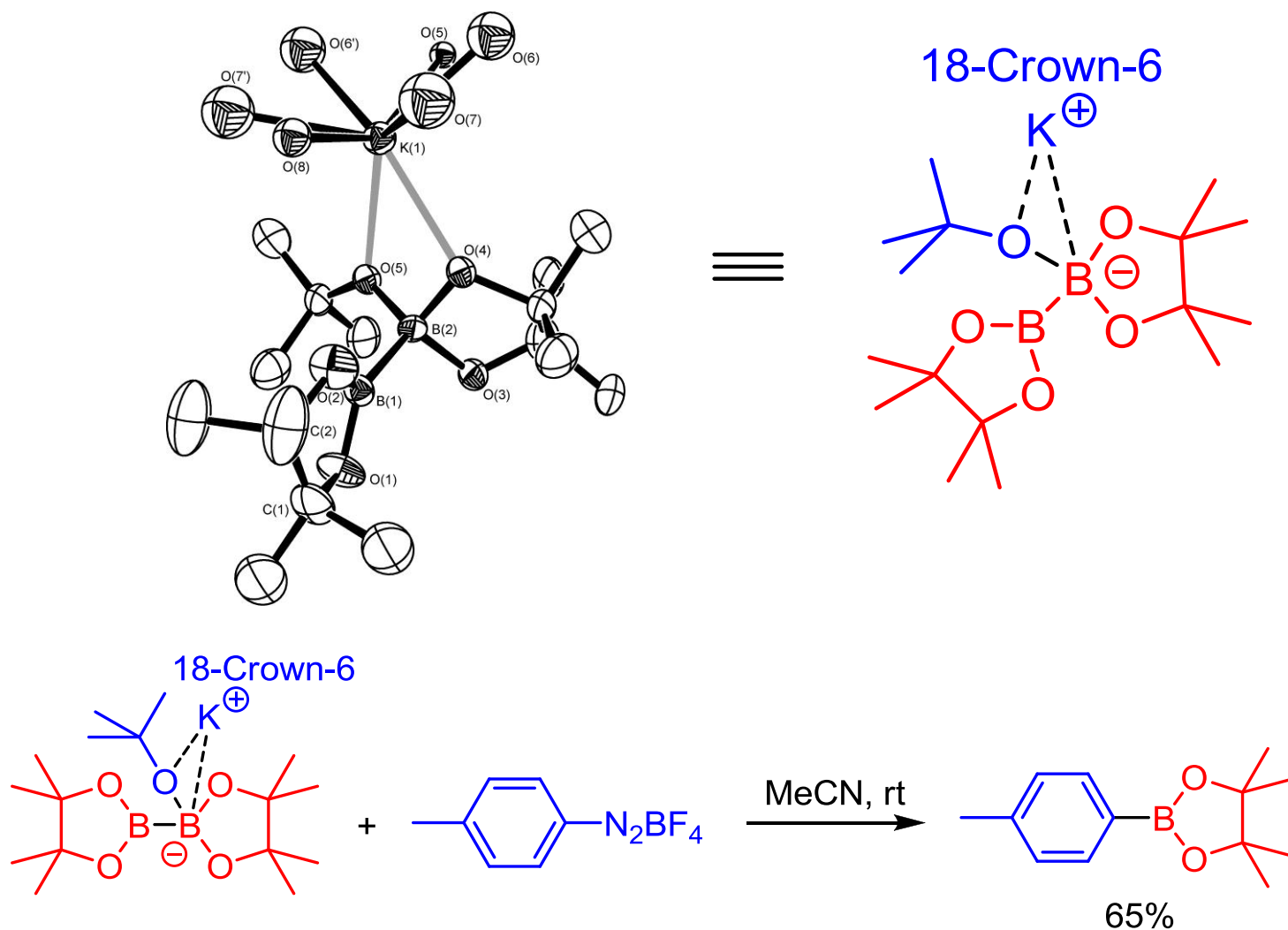
The Mechanism

A proposed mechanism



3. Direct Conversion of Arylamines to Pinacol Boronates

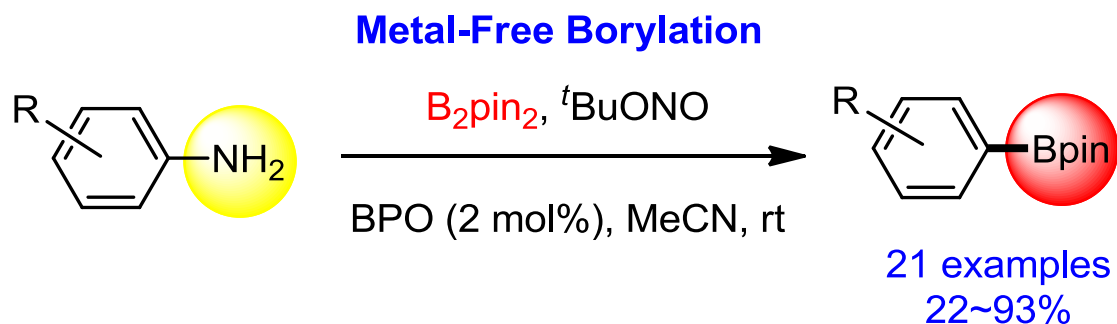
The Mechanism



Kleeberg, C.; Mo, F.; Qiu, D.; Sing, A.; Dang, L.; Wang, J.; Linc, Z.; Marder, T. B. *to be submitted*.

3. Direct Conversion of Arylamines to Pinacol Boronates

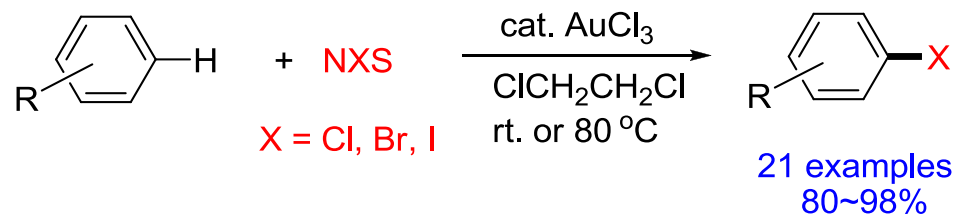
Summary



- ✓ Cheap starting materials and Valuable products
- ✓ Mild reaction conditions
- ✓ Metal-free!!
- ✓ Subsequent reaction

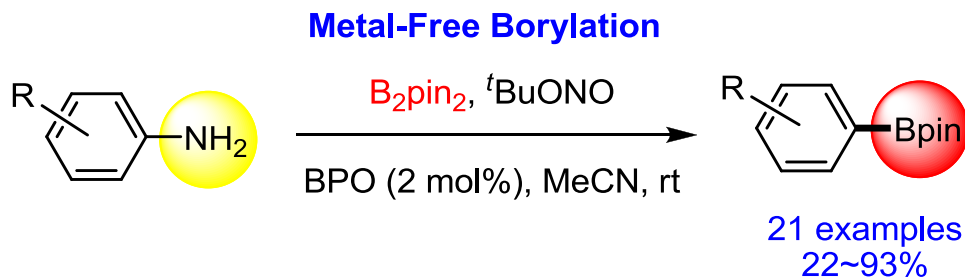
4. Summary

1. Gold-Catalyzed Halogenation of Aromatics by *N*-Halosuccinimides



Mo, F.; Yan, J. M.; Qiu, D. Li, F.; Zhang, Y.; Wang, J.*
Angew. Chem. Int. Ed. **2010**, *49*, 2028-2032.

2. Direct Conversion of Arylamines to the Pinacol Boronates: A Metal-Free Borylation Process



Mo, F.; Jiang, Y.; Qiu, D.; Zhang, Y.; Wang, J.*
Angew. Chem. Int. Ed. **2010**, *49*, 1846-1849.
Selected by Editor as A Hot Paper
Selected by Synfacts and Synform
WO2011035532

5. Acknowledgment

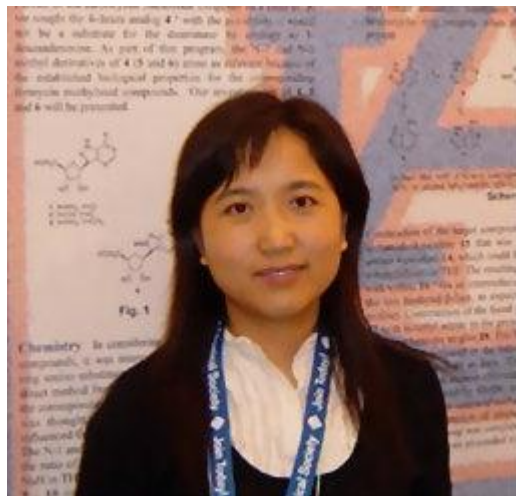
Prof. Jianbo Wang



Graduates:

Changqing Dong
Di Qiu, Fei Li, Jerry Yan
Changkun Li
Cheng Peng
Zhenhua Zhang
Xia Zhao
Xiao Qing
Xi Wang
Huan Li

Prof. Yan Zhang



Undergraduates:

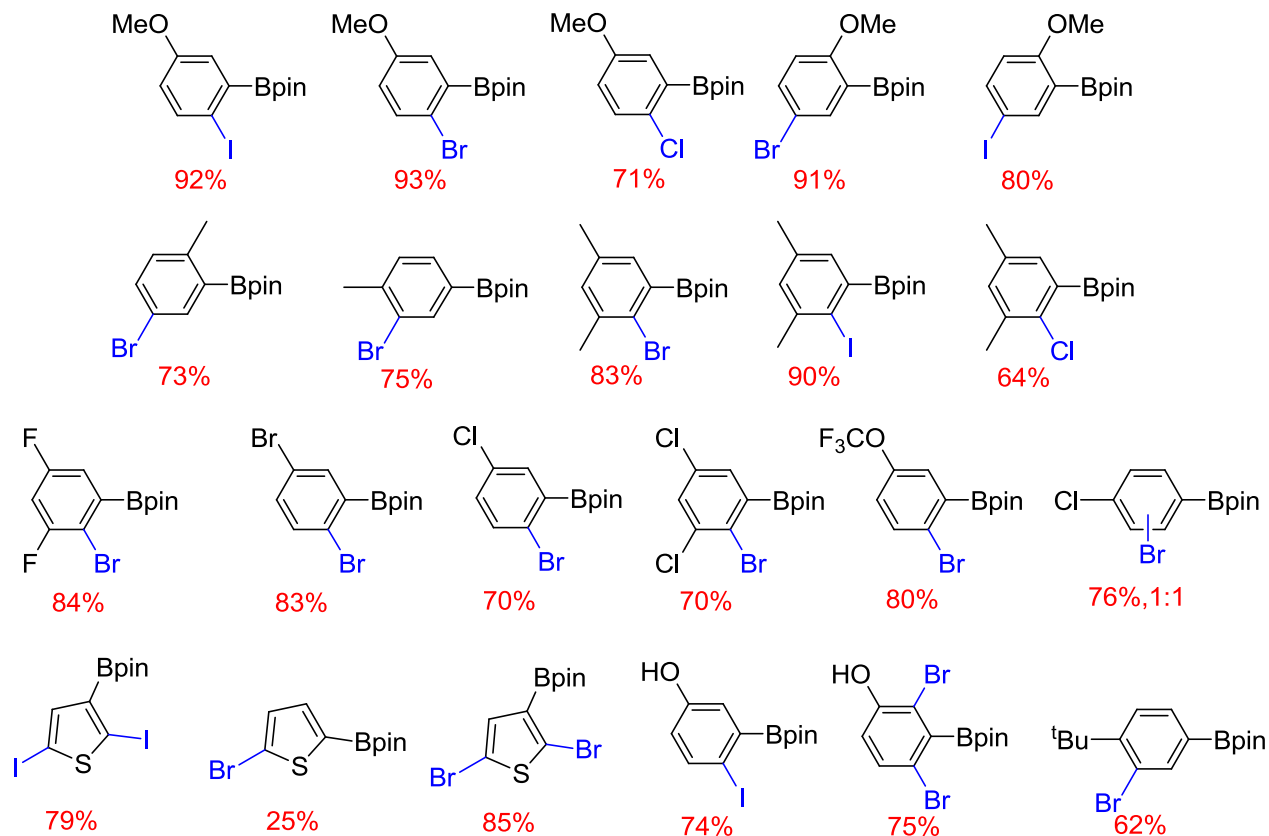
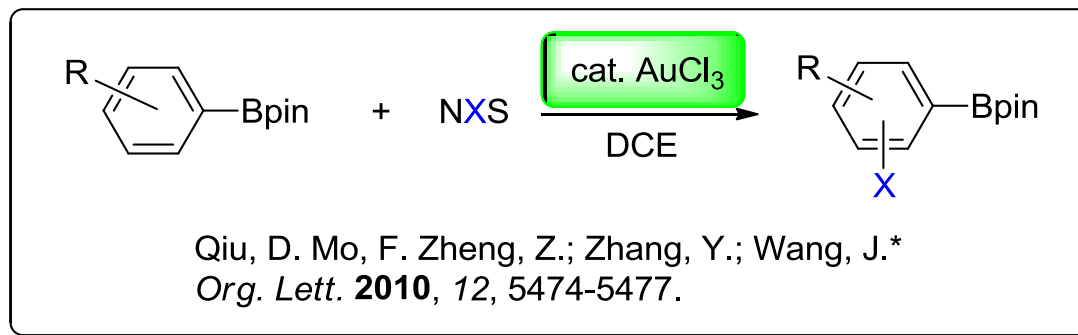
Yang Yang
Yiyang Liu
Jian Ma



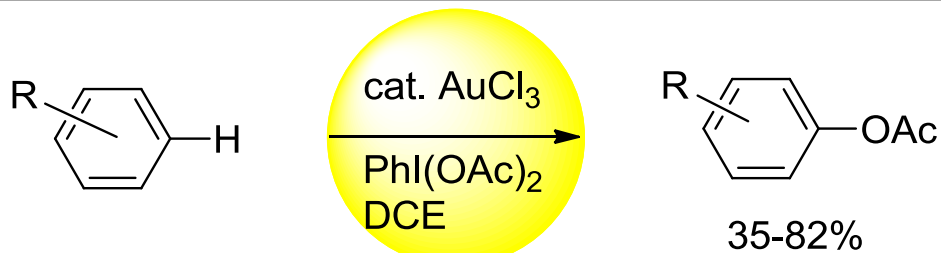
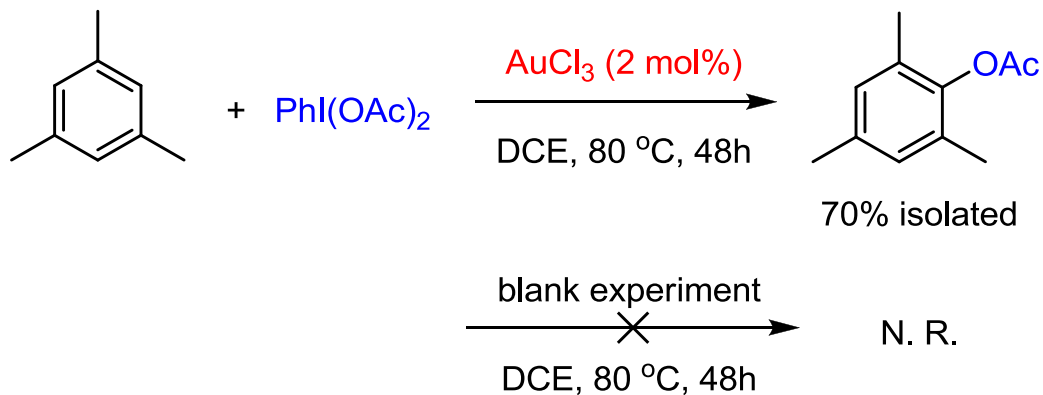
Thank you for your attention!



4. Summary and Outlook

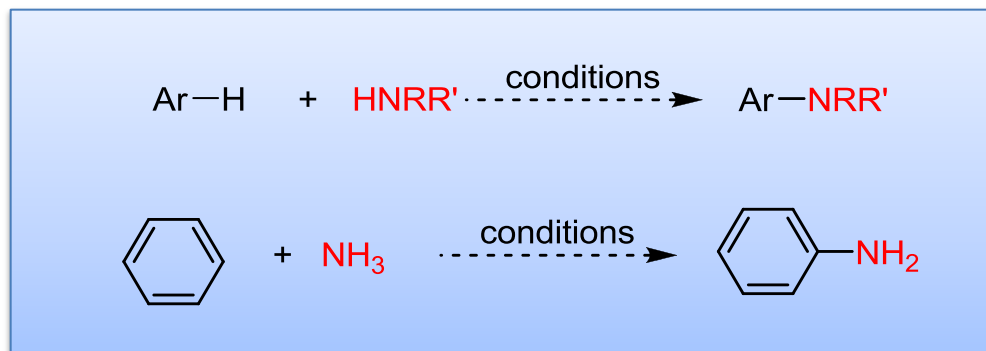
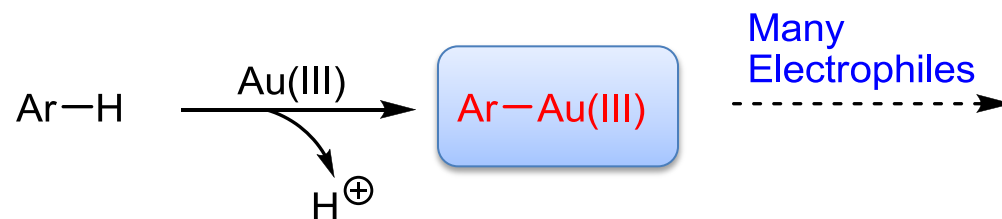


4. Summary and Outlook

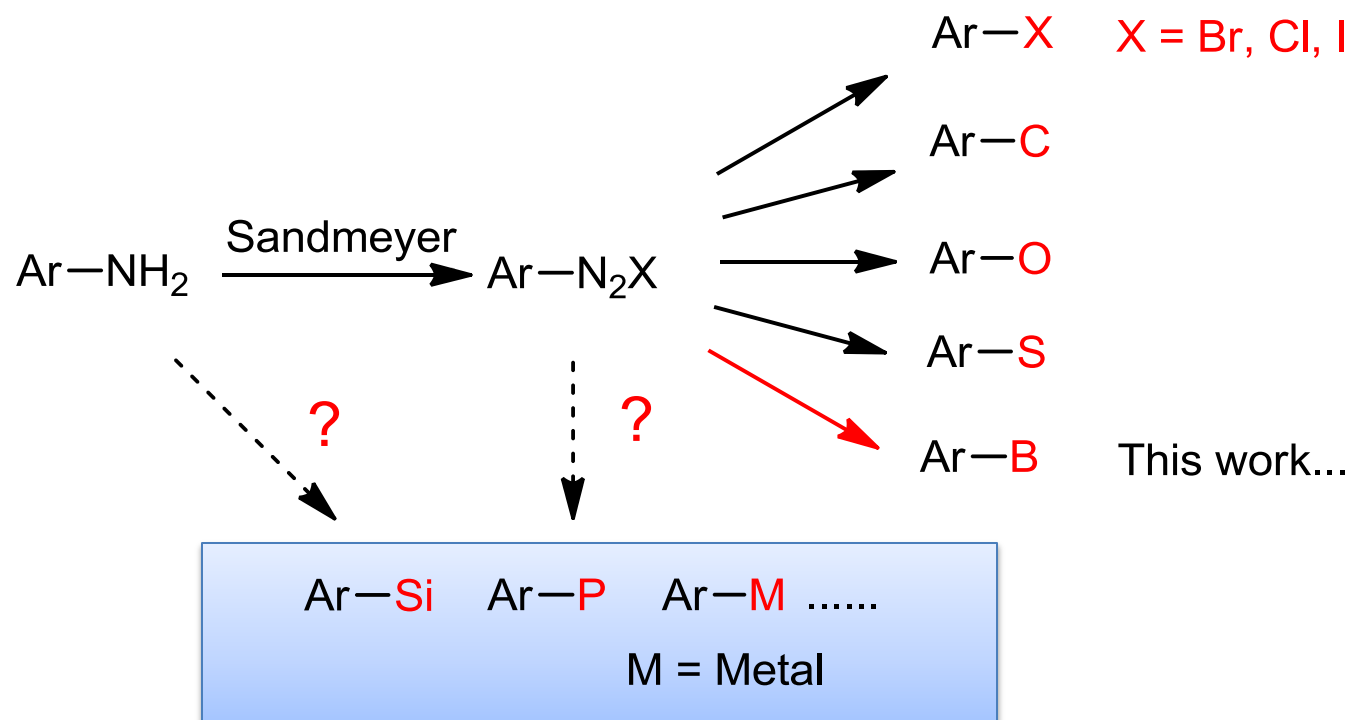


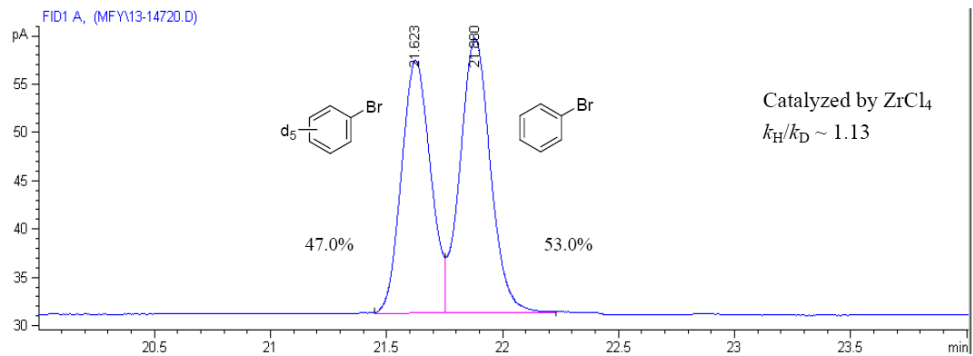
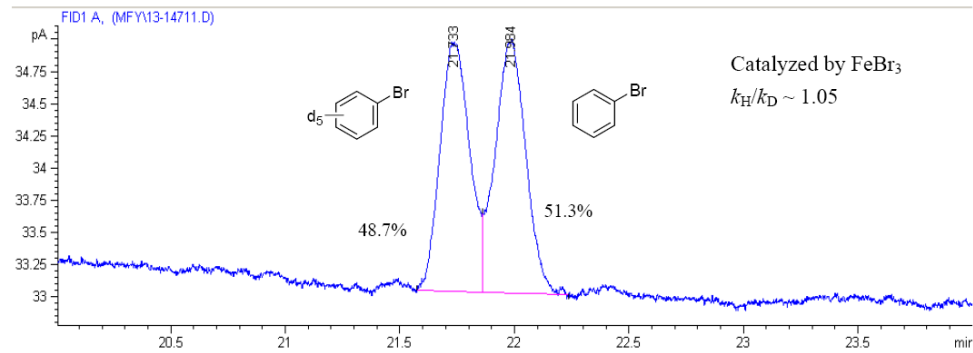
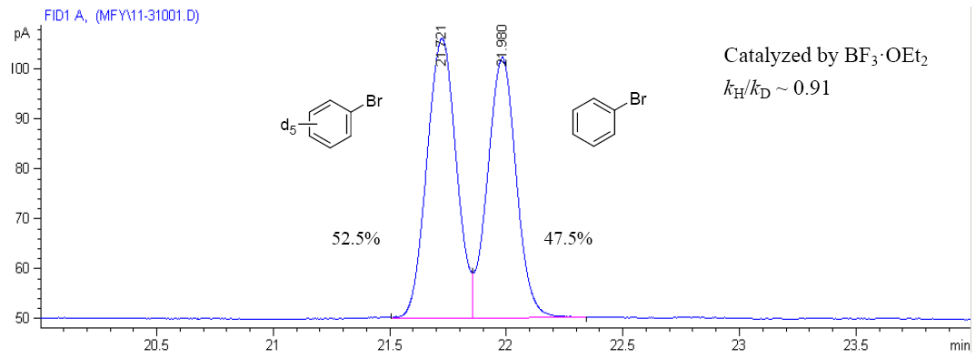
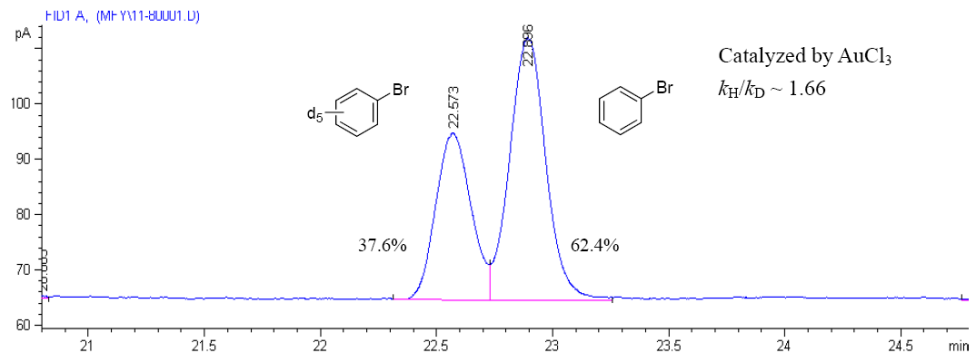
Qiu, D.; Zheng, Z.; Mo, F.; Wang, J.* *et. al.*
Org. Lett. **2011**, 13, 4988-4991.

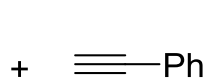
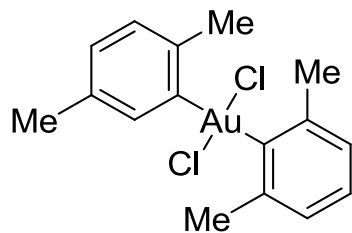
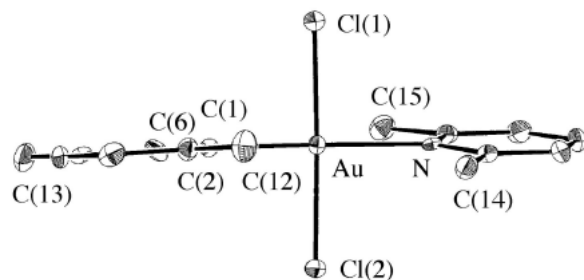
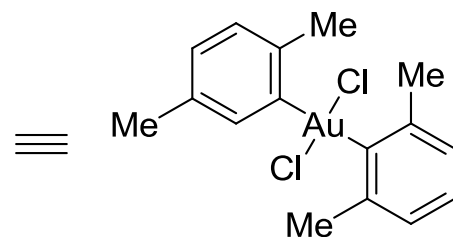
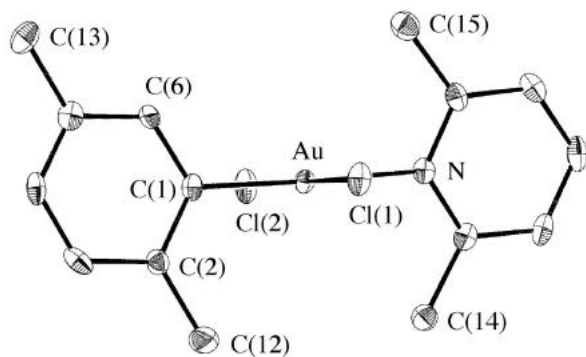
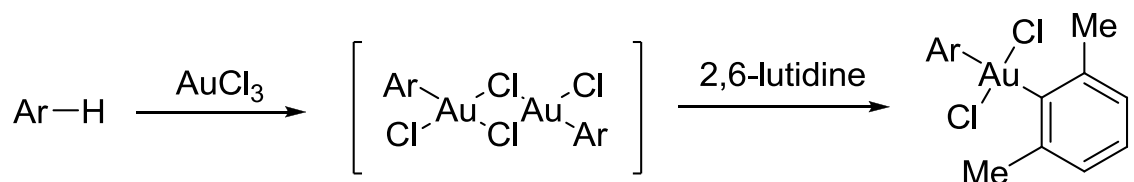
4. Summary and Outlook



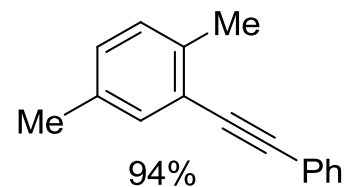
4. Summary and Outlook







$\xrightarrow{\text{THF, } 50^\circ\text{C, } 5\text{ h}}$



Fuchita, Y.; Utsunomiya, Y.; Yasutake, M. *J. Chem. Soc. Dalton Trans.* **2001**, 2330.

