

# Transition-Metal-Catalyzed C-H Activation on the CMD Pathway

Reporter: Wenjun Miao

2014-3-10

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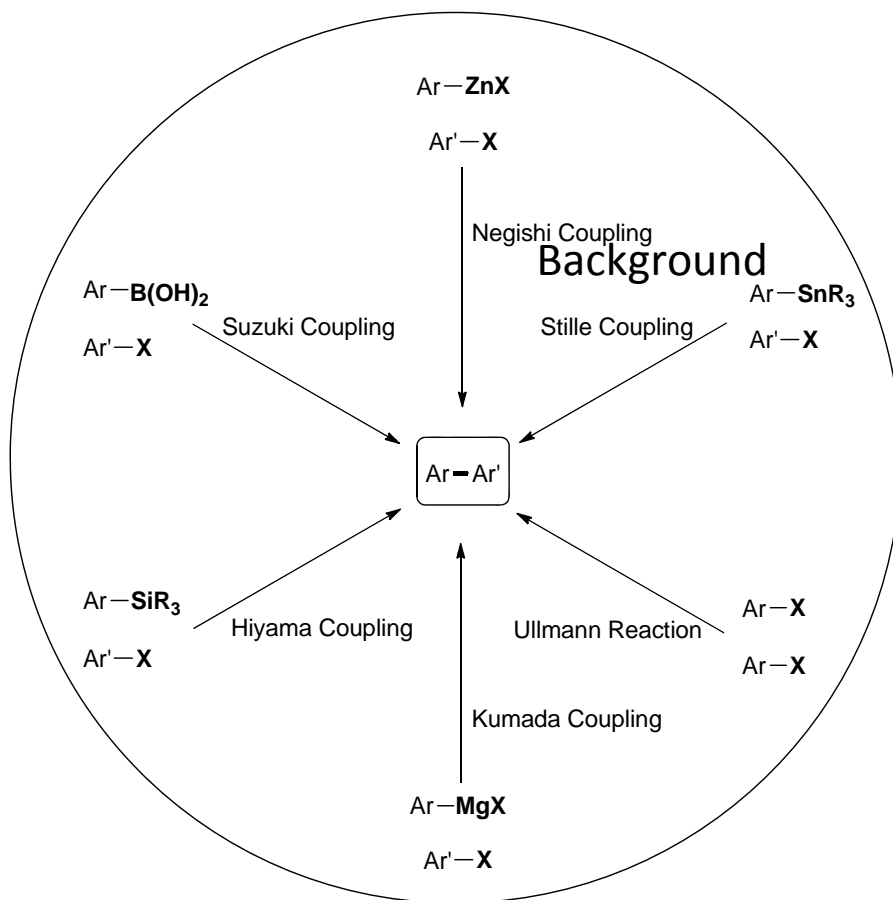
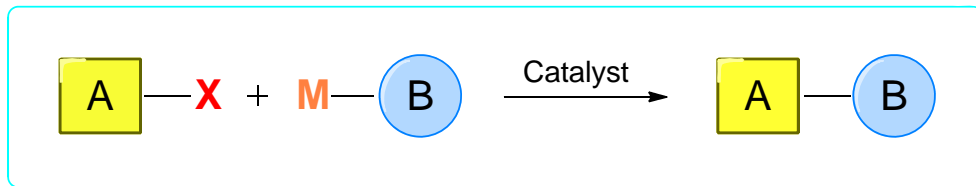
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References

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# Background

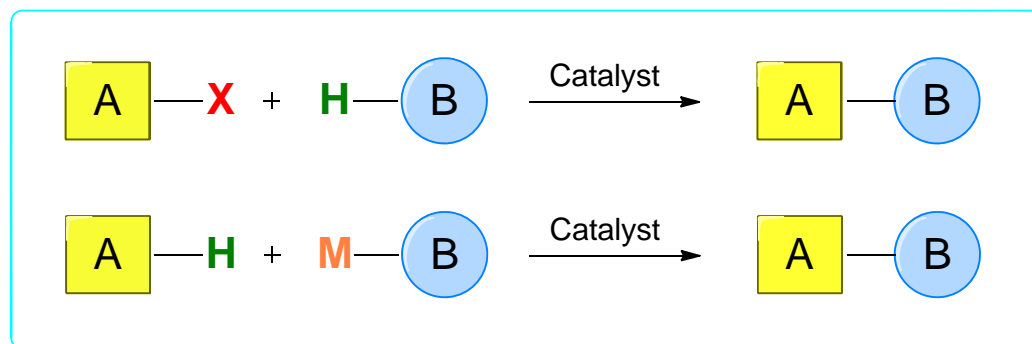
Reaction type 1



Both aromatic compounds must be preactivated

# Background

Reaction type 2



Direct Arylation of  
Unactivated Arenes

## Education

**Ph.D.:** University of Toronto, 2002 (Supervisor: Prof. Mark Lautens)

**M.Sc.:** University of Toronto, 2000

**B.Ed.:** University of Saskatchewan, 1995

## Employment History

**2007-2009** Associate Professor with tenure, University of Ottawa

**2002-2007** Assistant Professor, University of Ottawa

**1998-2002** Graduate Student in Organic Chemistry, University of Toronto

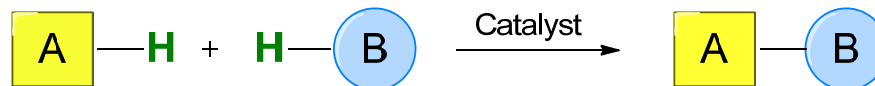
**1995-1996** High School Teacher, Ecole Canadienne Française/St. Joseph HS  
Saskatoon, SK



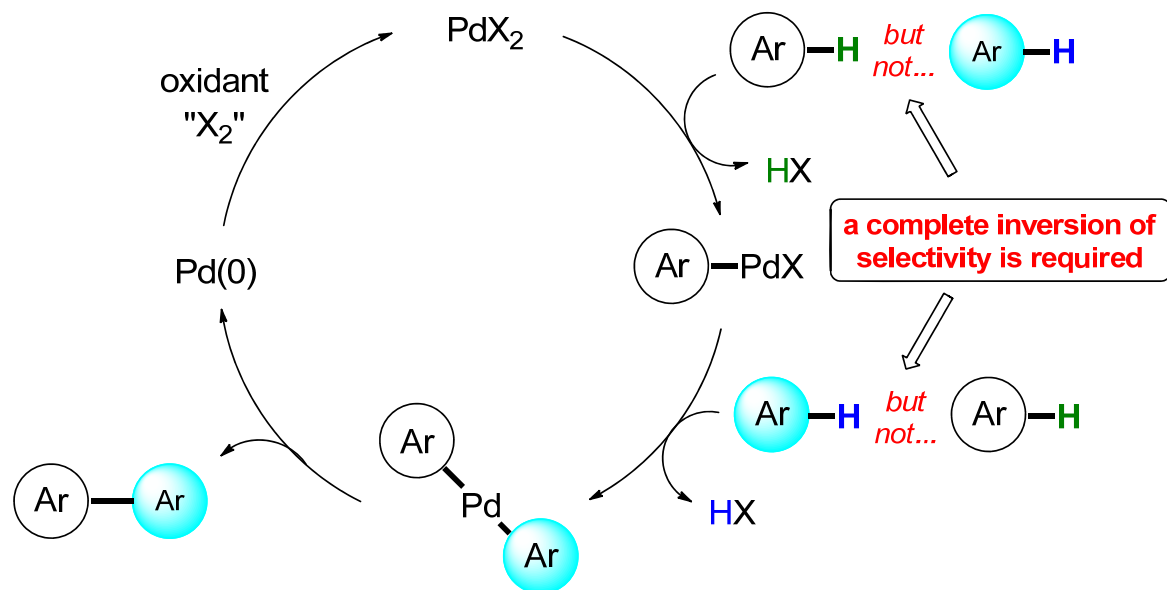
**Keith Fagnou**  
**1971-2009**

# Background

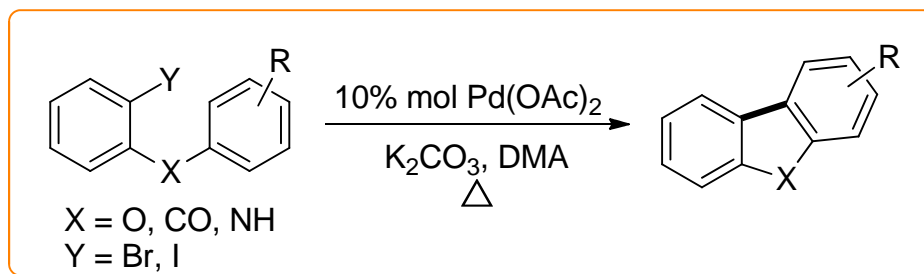
Reaction type 3



Catalytic Oxidative Arene Cross-Coupling

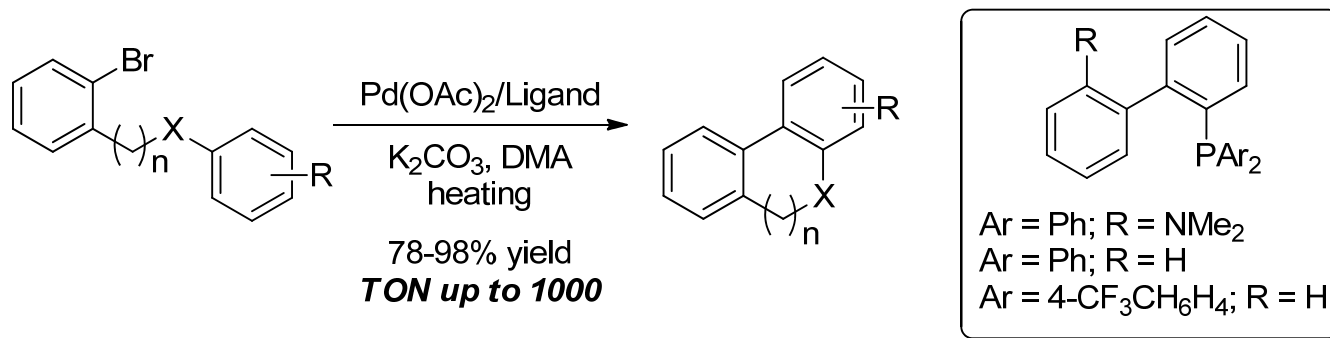


# Direct Catalytic C-H Bond Metallation of Arenes



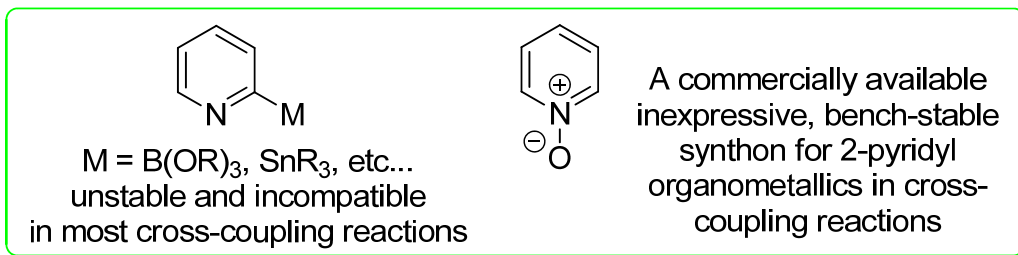
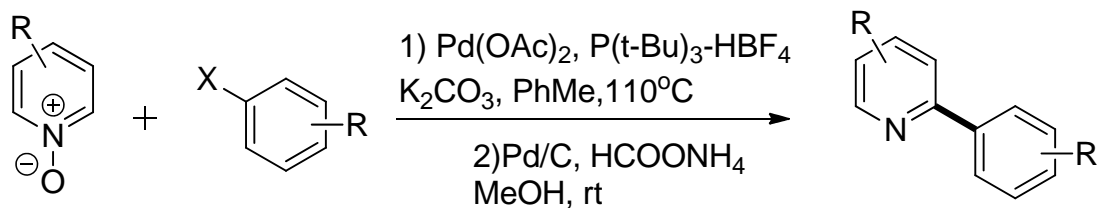
Ames, D. E.; Opalko, A. *Tetrahedron* **1984**, 40, 1919.

Ames, D. E.; Opalko, A. *Synthesis* **1983**, 234.

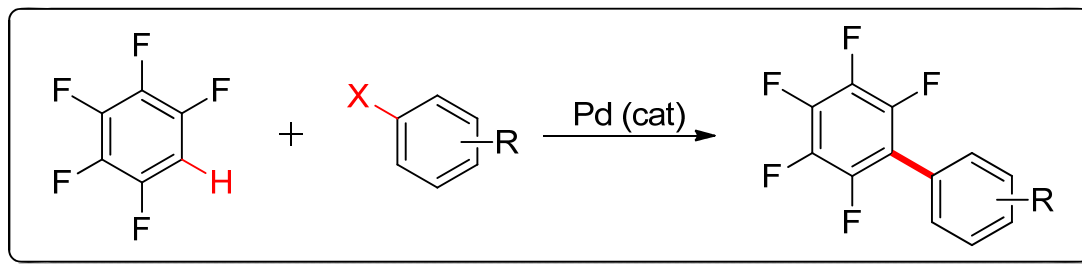


Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, 126, 9186

# Direct Catalytic C-H Bond Metallation of Arenes

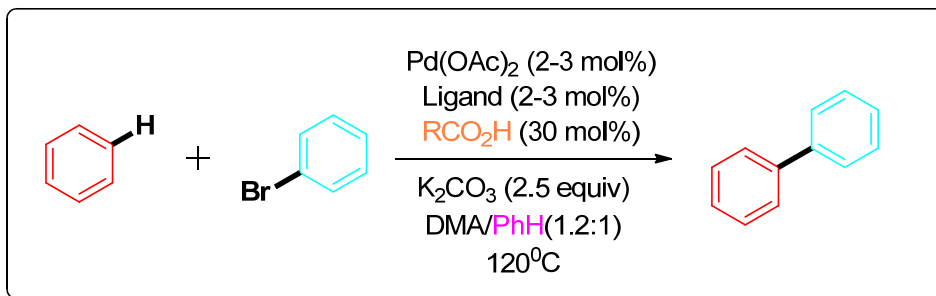


Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020



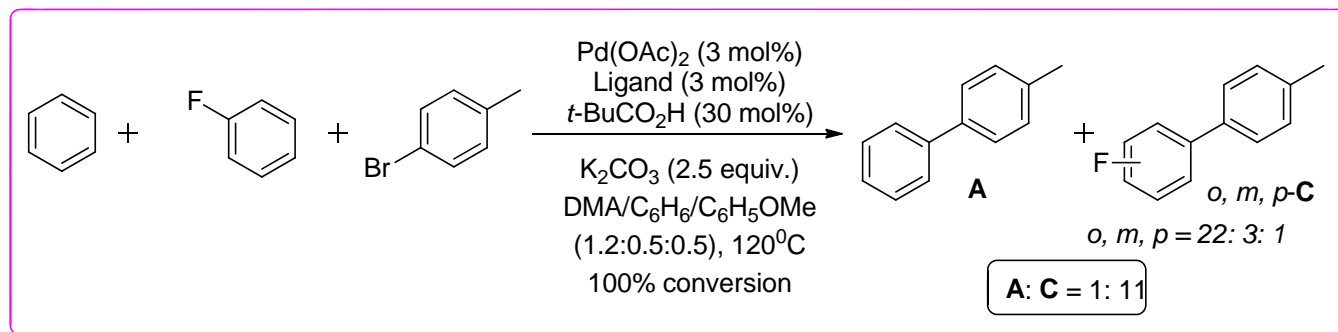
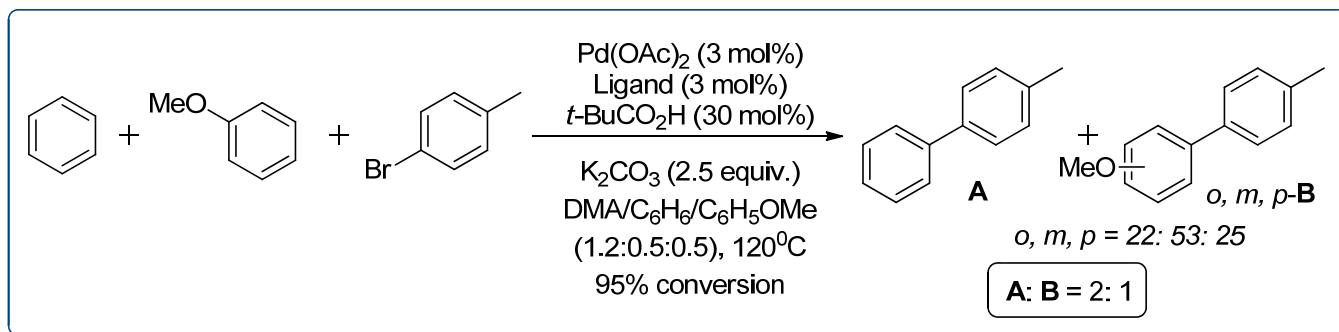
Lafrance, M.; Rowley, C.N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754

# Direct Catalytic C-H Bond Metallation of Arenes



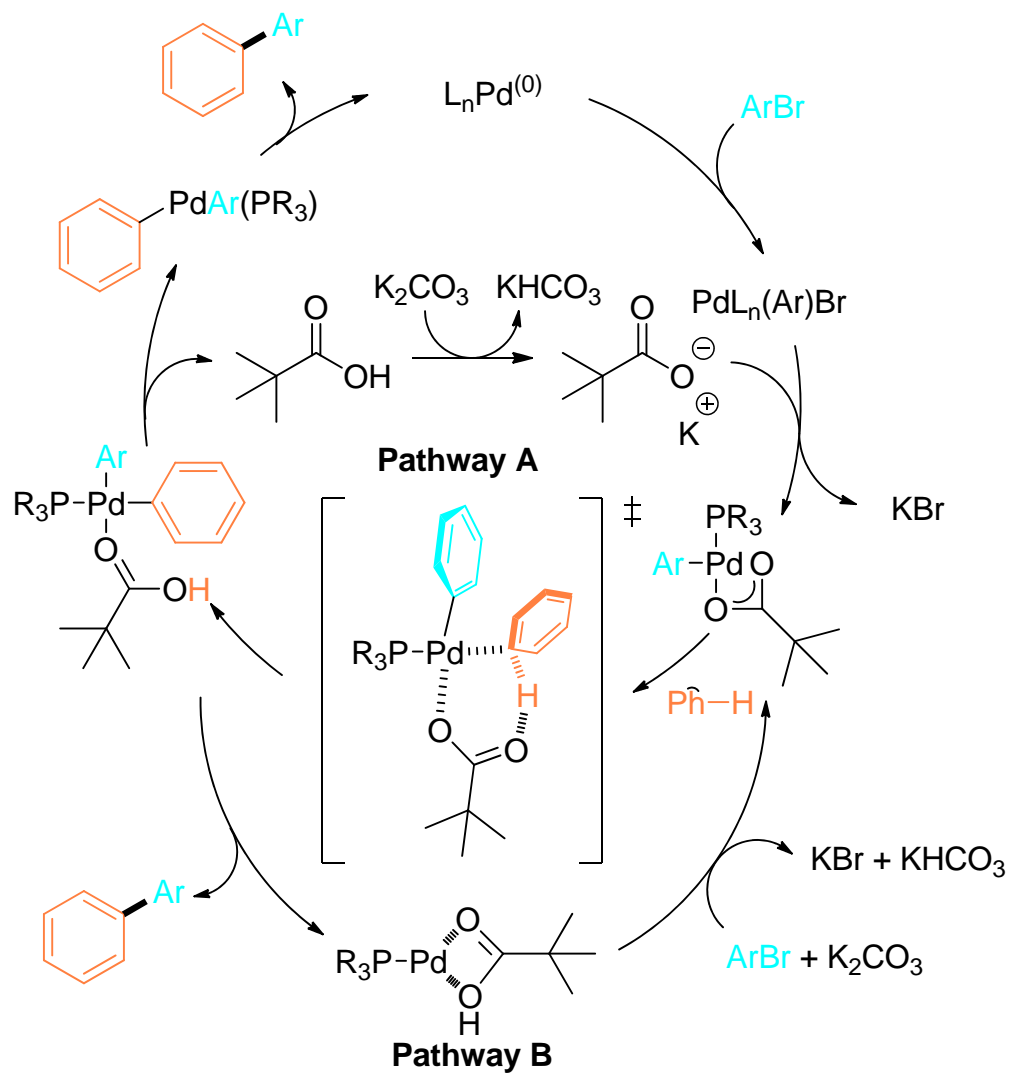
## Direct Arylation of Unactivated Arenes

Unprecedented Reactivity from a Palladium-Pivalic Acid Co-Catalyst System  
Pivalic Acid as a Catalytic Proton Shuttle and a Key Element in Catalyst Design





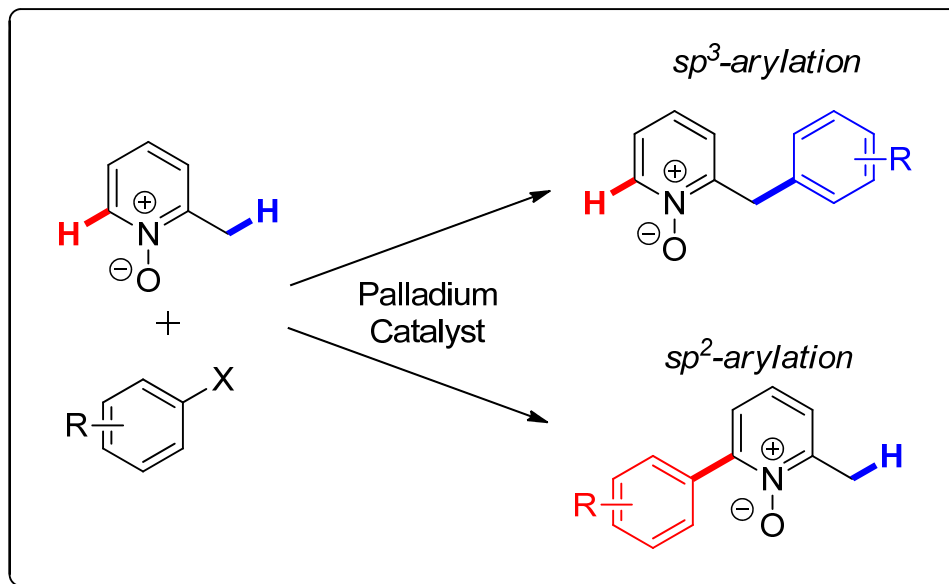
# Direct Catalytic C-H Bond Metallation of Arenes



Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496

# The Catalytic Cross-Coupling of Unactivated Arenes

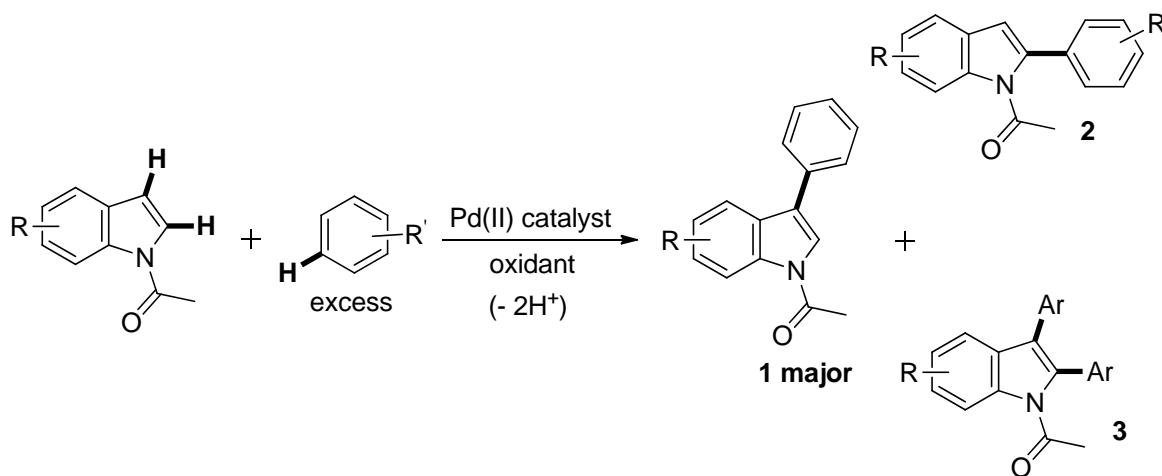
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Campeau, L.-C.; Schipper, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266

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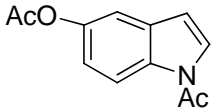

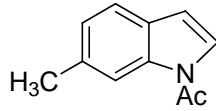

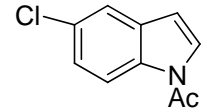

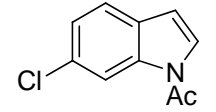

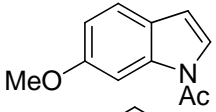

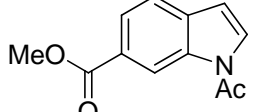

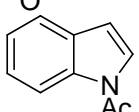
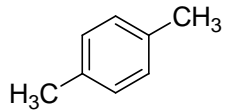
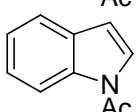
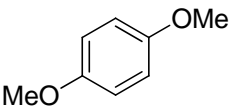
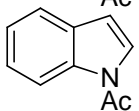
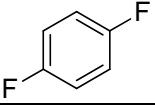
# The Catalytic Cross-Coupling of Unactivated Arenes



Entry	Mol % Pd	Oxidant (equiv.)	Additive (mol %)	Heating method	T (°C)	Time (h)	% Conv.	1:2:3	% Yield 1
1	100	None	None	Oil bath	110	24	75	4.4:1:2.6	55
2	10	Cu(OAc) <sub>2</sub>	CsOPiv (40)	Oil bath	110	24	67	27:1:0.3	64
3	0	Cu(OAc) <sub>2</sub>	3-Nitropyridine (10) CsOPiv (40)	Oil bath	110	24	0	nd	0
4	10	Cu(OAc) <sub>2</sub>	3-Nitropyridine (10) CsOPiv (40)	Microwave	140	5	100	8.9:1:0.3	87*
5	5	Cu(OAc) <sub>2</sub>	3-Nitropyridine (5) CsOPiv (40)	Microwave	140	5	92	13.8:1:0.3	84
6	2	Cu(OAc) <sub>2</sub>	3-Nitropyridine (2) CsOPiv (40)	Microwave	140	5	66	27:1:0	63

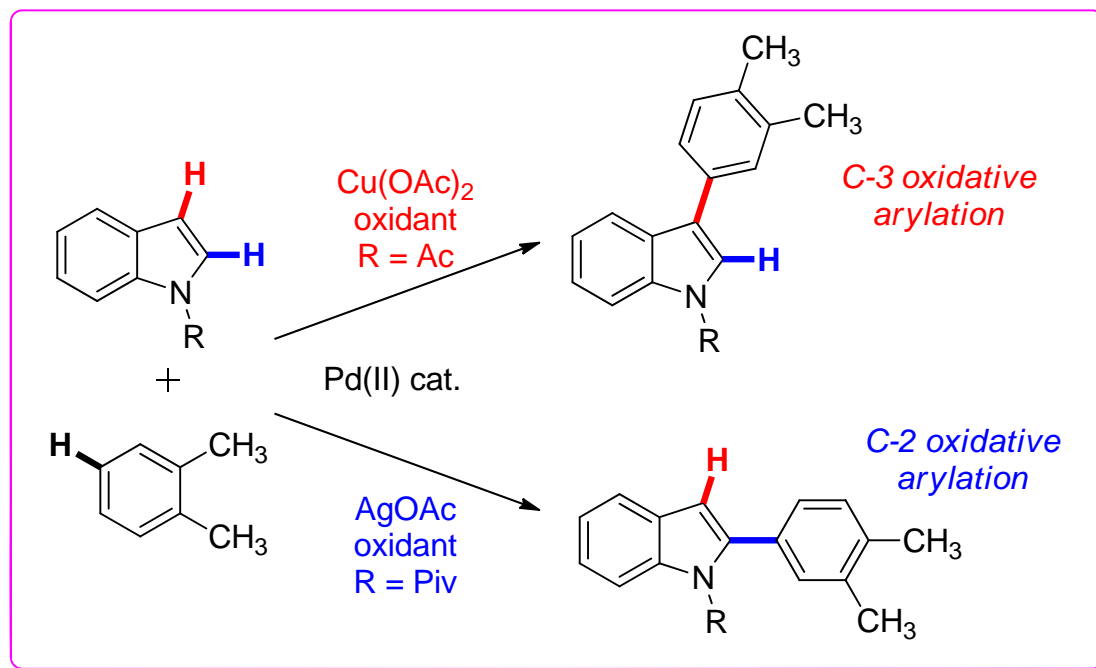
Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172

# The Catalytic Cross-Coupling of Unactivated Arenes

Entry	Indole	Arene	T (°C)	mol % Pd	% Conv.	1:2:3	% Yield 1
1			140	10	100	11.2:1:0.4	84
2			140	10	100	10:1:0.6	81
3			110*	10	83	6.5:1:0	63
4			110*	10	81	5.7:1:0	61
5			140	10	100	10.5:1:0.3	74
6			140	20	80	2.8:1:0	54
7			140	20	nd	10.4:1:0.4	45
8			140	20	72	6.7:1:0	52
9			140	20	nd	9.9:1:0	42

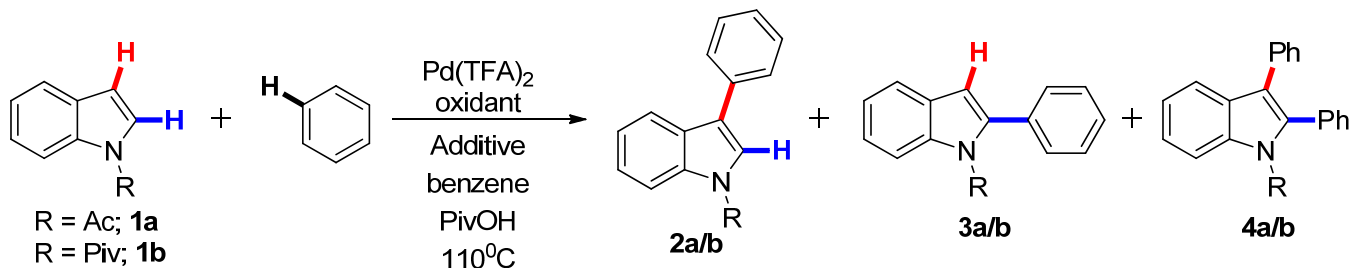
Stuart, D. R.; Fagnou, K. *Science* **2007**, 316, 1172

# The Catalytic Cross-Coupling of Unactivated Arenes



Stuart, D. R.; Villemure, E; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072

# The Catalytic Cross-Coupling of Unactivated Arenes

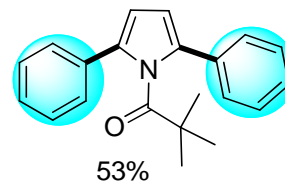
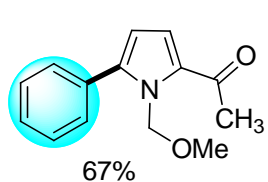
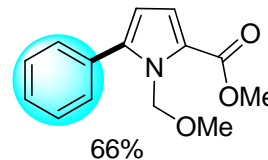
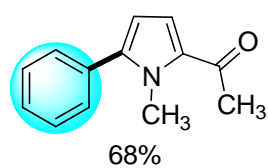
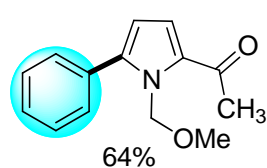
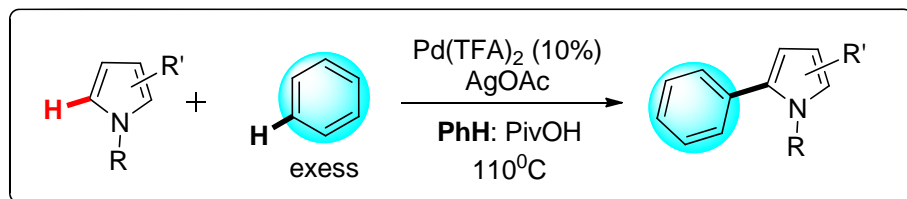


entry	mol % Pd <sup>b</sup>	oxidant (equiv) <sup>b</sup>	additive (mol %) <sup>b</sup>	indole	time	% conv <sup>c</sup>	<b>2:3:4<sup>c</sup></b>
1 <sup>d</sup>	10	Cu(OAc) <sub>2</sub> (3)	3-nitropyridine (10) CsOPiv (40)	<b>1a</b>	5	100	8.9:1:0.26
2	10	AgOAc (2.2)	3-nitropyridine (10) CsOPiv (40)	<b>1a</b>	24	32	1:4:0
3	10	AgOAc (2.2)	3-nitropyridine (10) CsOPiv (40)	<b>1b</b>	24	78	1:8.7:0.3
4	5	AgOAc (3)	none	<b>1b</b>	3	99	1:25:0.7
5	2	AgOAc (3)	none	<b>1b</b>	15	87	1:14:0.4
6	20	none	none	<b>1b</b>	3	18	1.1:1:0
7	50	none	none	<b>1b</b>	3	45	1.3:1:0
8	100	none	none	<b>1b</b>	3	61	3.7:1:0
9	300	none	none	<b>1b</b>	3	100	99:1:0
10	20	none	CsOAc (200)	<b>1b</b>	3	15	1:99:0

<sup>a</sup> Conditions: Pd(TFA)<sub>2</sub>, oxidant, 3-nitropyridine, cesium pivalate, PivOH(6 equiv), and **1a/b** were added to a screw-capped vial followed by the addition of benzene (30-60 equiv; see SI) and heating to 110°C. <sup>b</sup>Relative to **1**. <sup>c</sup>Determined by GC/MS. <sup>d</sup>Microwave heating.

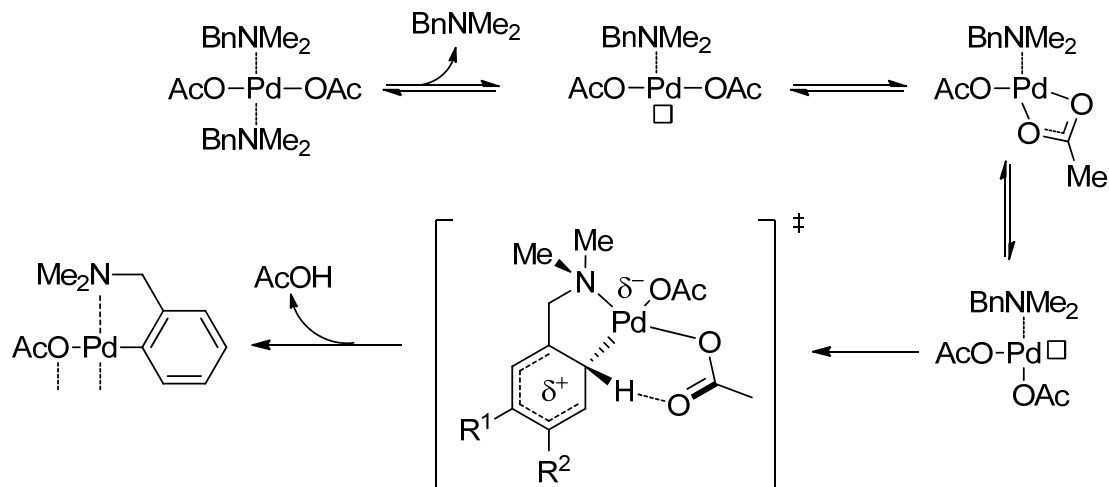
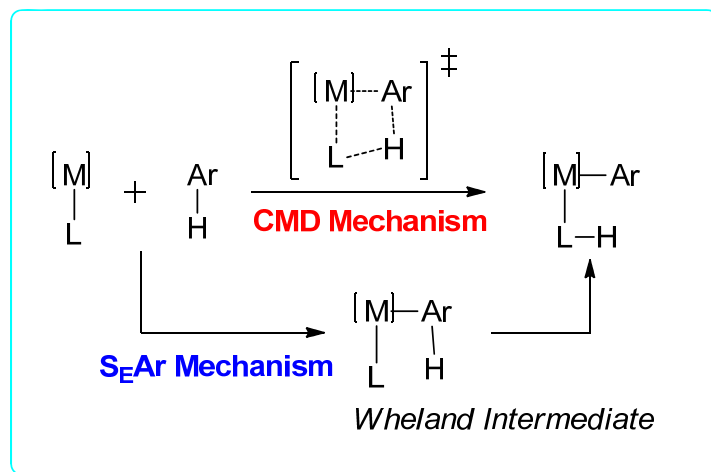
Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172

# The Catalytic Cross-Coupling of Unactivated Arenes



Stuart, D. R.; Villemure, E; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072

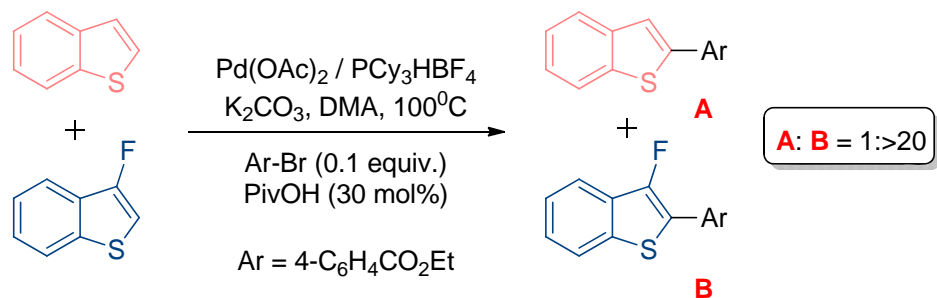
# Mechanistic Work on the CMD Pathway



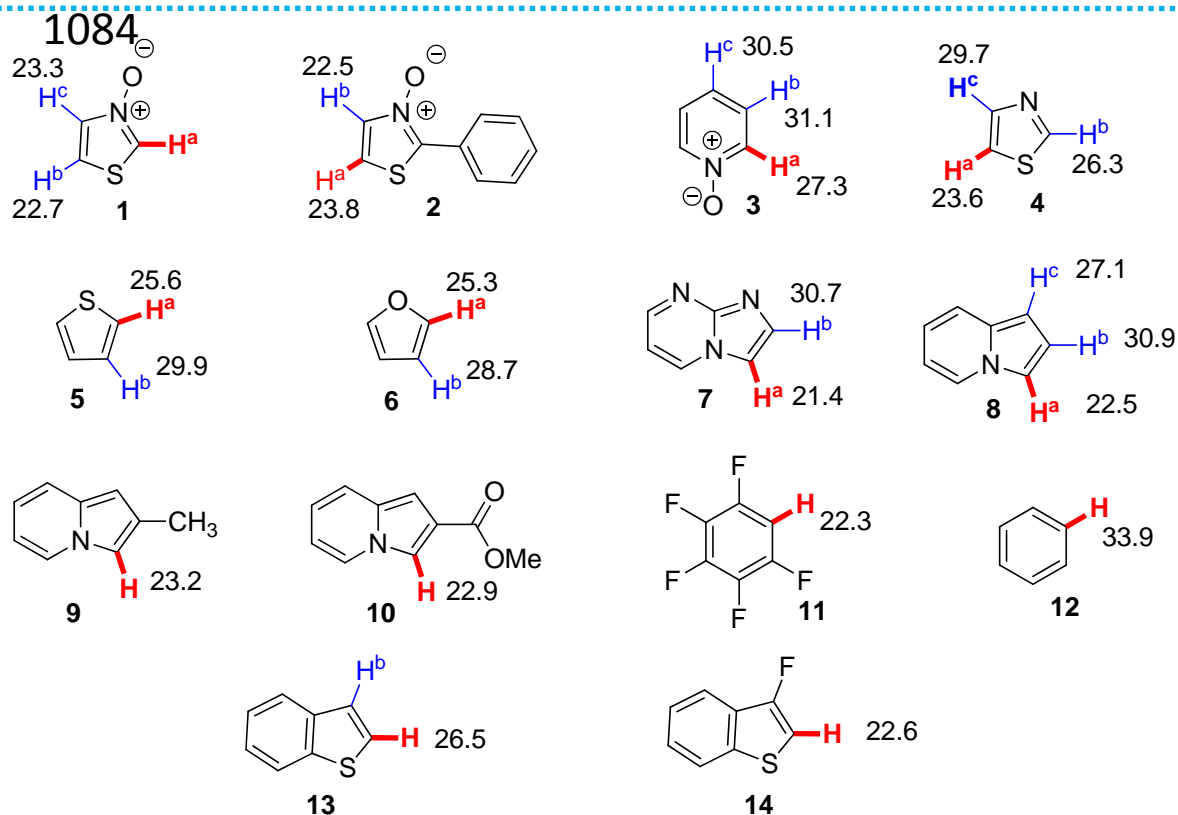
A. D. Ryabov, I. K. Sakodinskaya, A. K. Yatsimirsky. *J. Chem. Soc., Dalton Trans.* **1985**, 2629.



# Mechanistic Work on the CMD Pathway

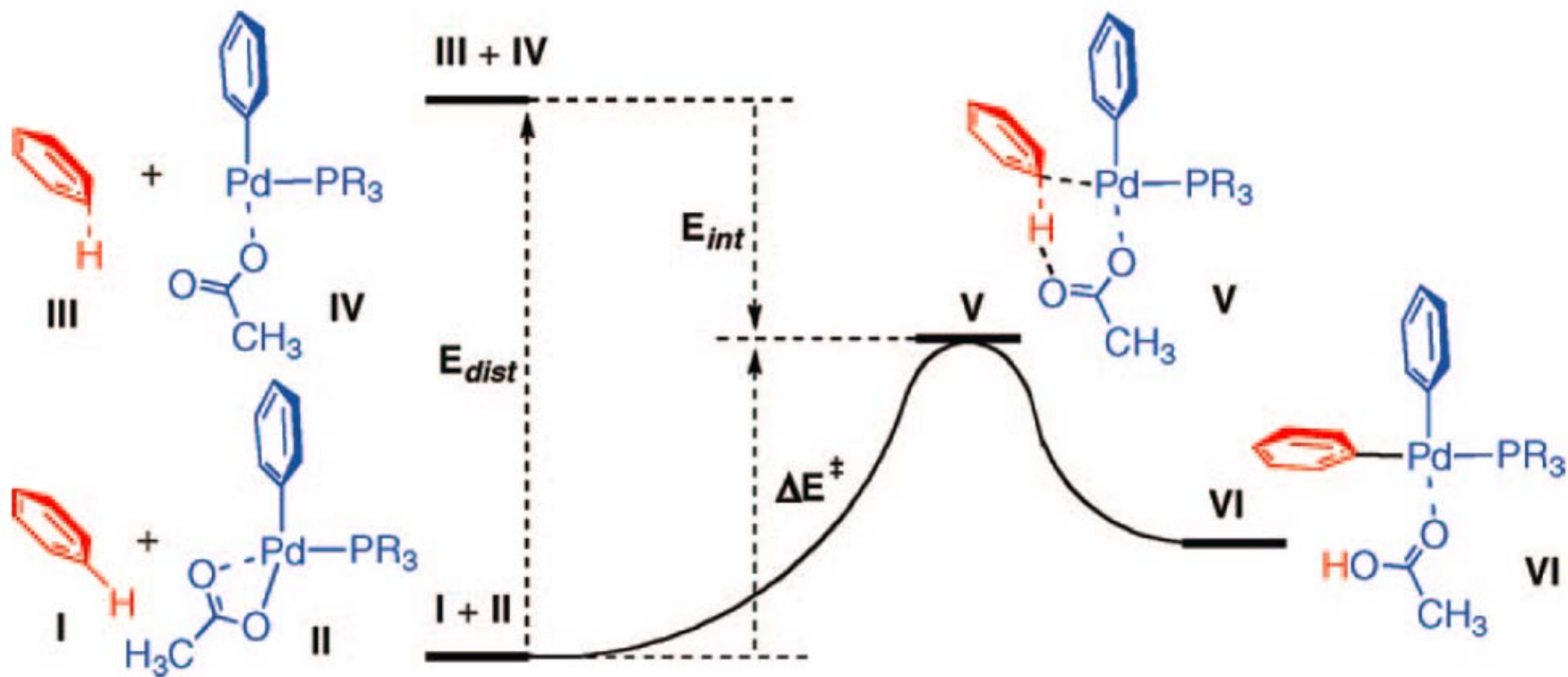


Gorelsky, S.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*,



Calculated activation barrier for the CMD pathway.

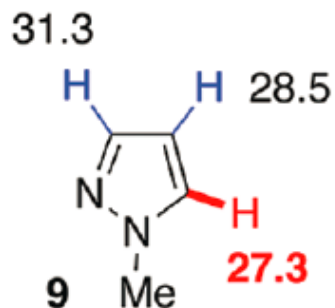
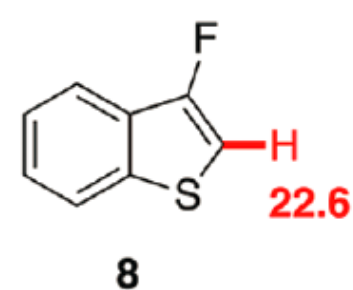
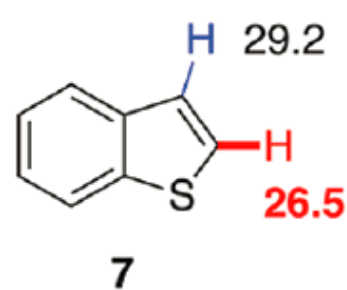
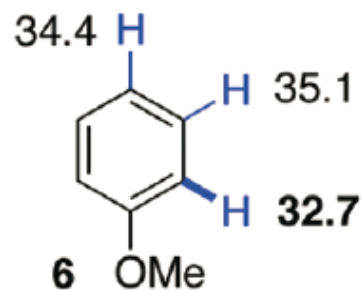
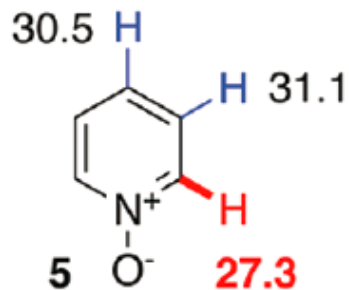
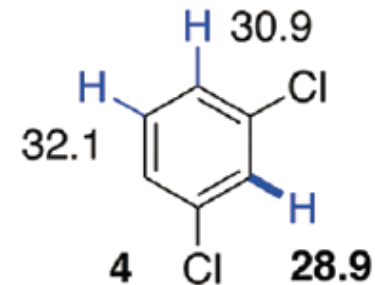
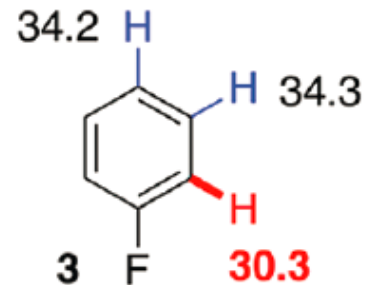
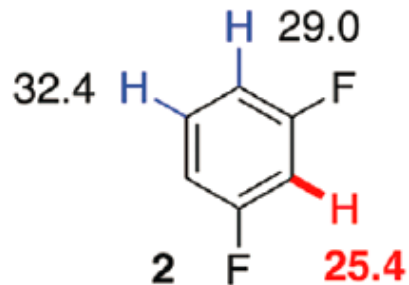
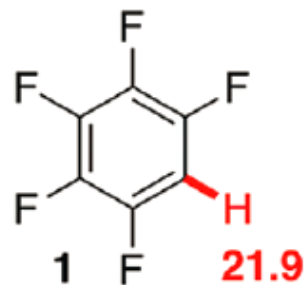
# Mechanistic Work on the CMD Pathway



Gorelsky, S.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 1084

# Mechanistic Work on the CMD Pathway

## Class I

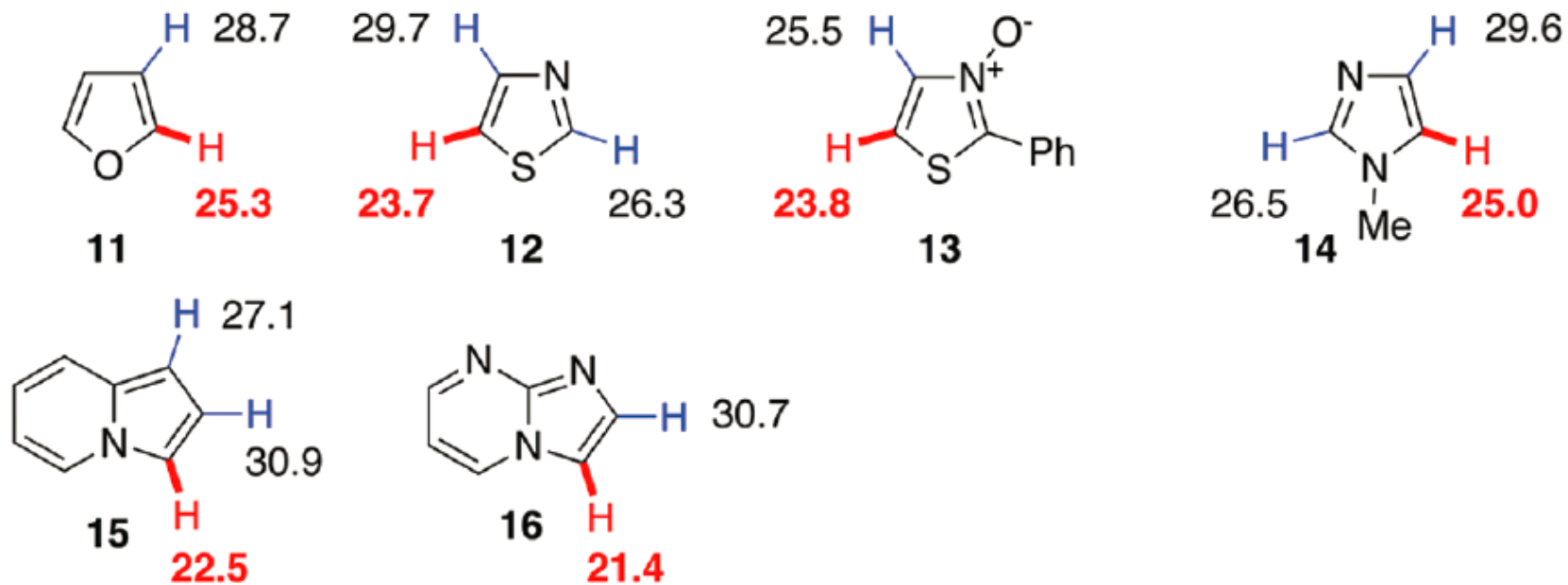


Gorelsky, S. I. *Coordination Chemistry Reviews* **2013**, 257, 153.

# Mechanistic Work on the CMD Pathway

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## Class II

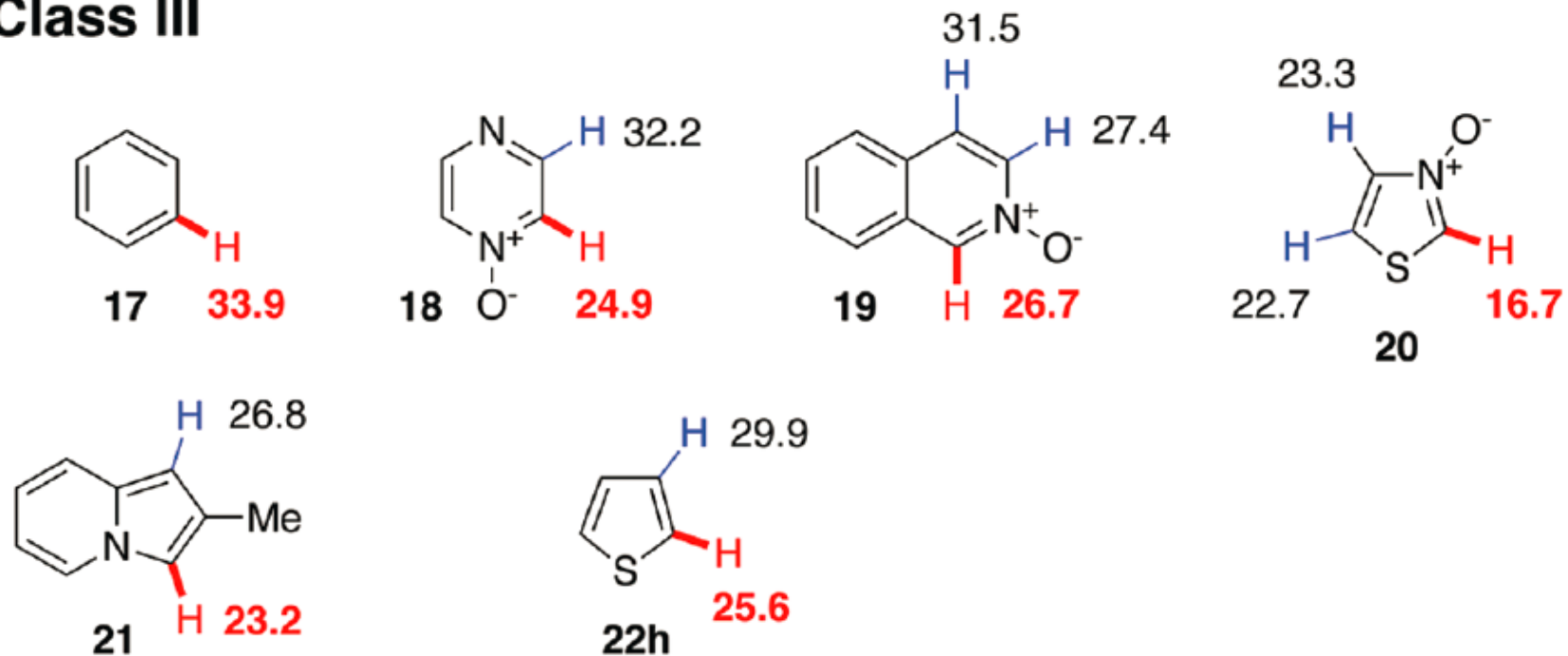


Gorelsky, S. I. *Coordination Chemistry Reviews* **2013**, 257, 153.

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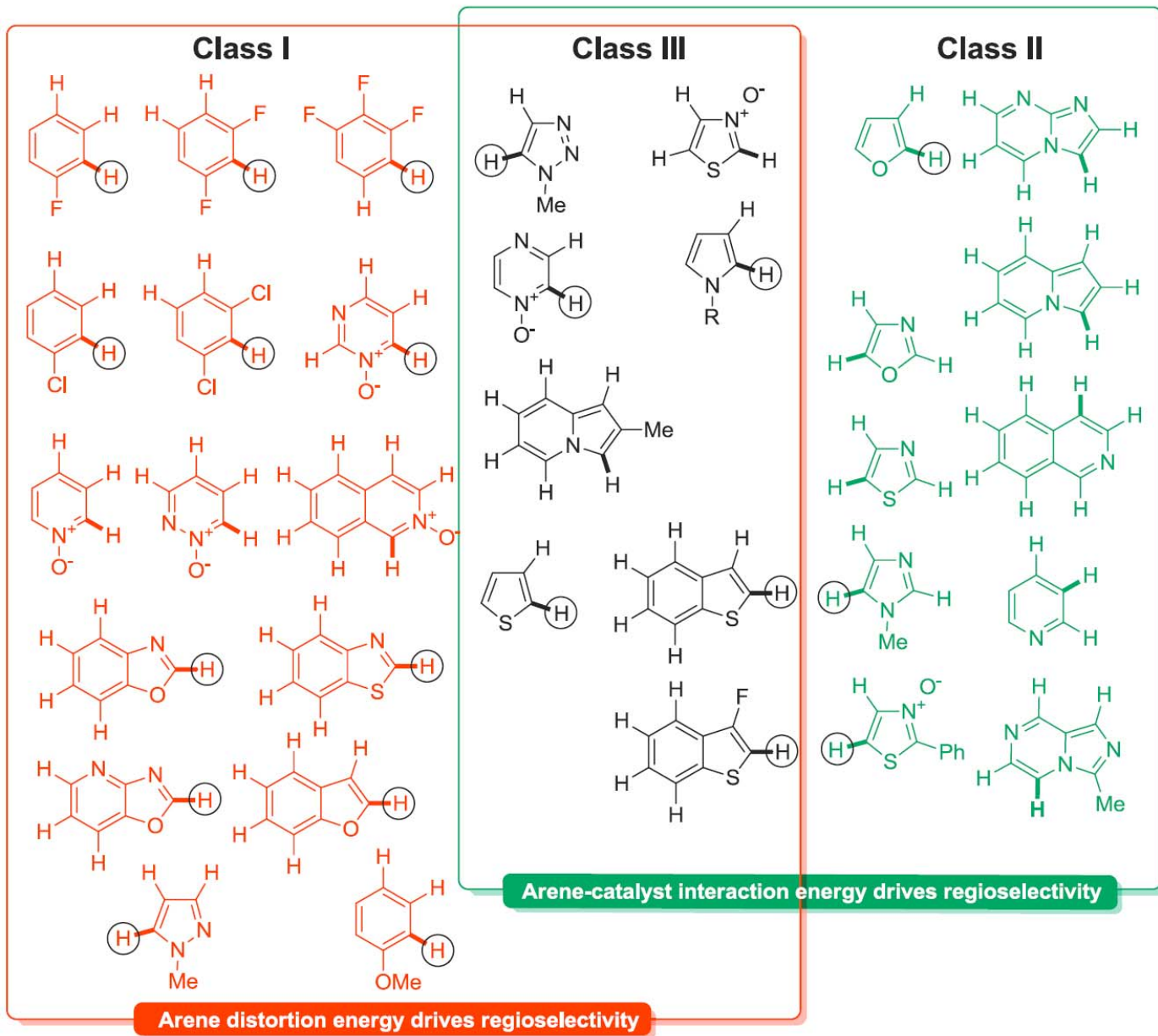
# Mechanistic Work on the CMD Pathway

## Class III



Gorelsky, S. I. *Coordination Chemistry Reviews* **2013**, 257, 153.

# Mechanistic Work on the CMD Pathway



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Thank you for your attention !