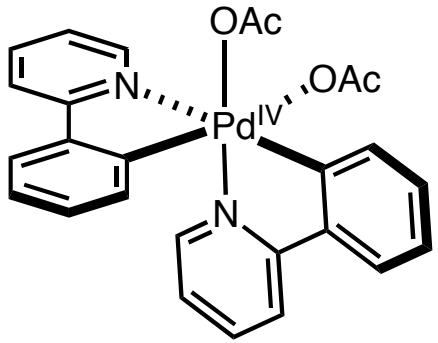
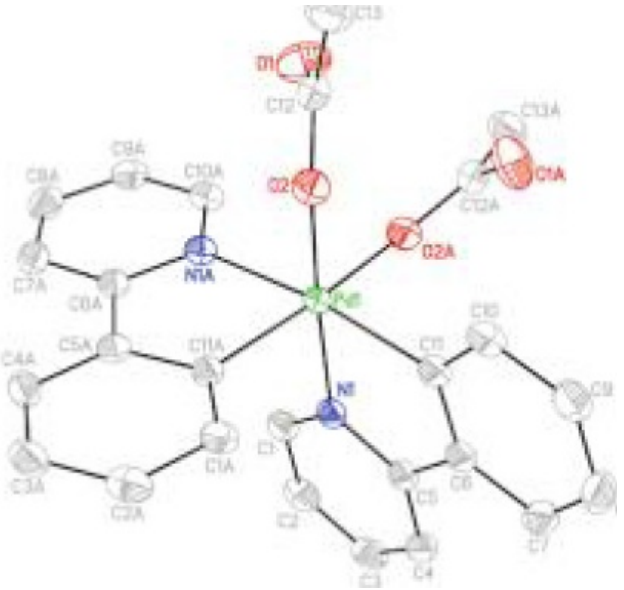
Coupling Chemistry of High Oxidation State Cu and Pd





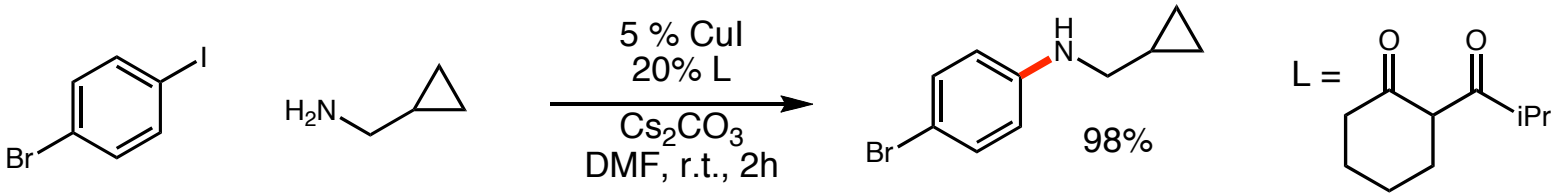
Robert J Comito

MacMillan Group Meeting

May 25, 2011

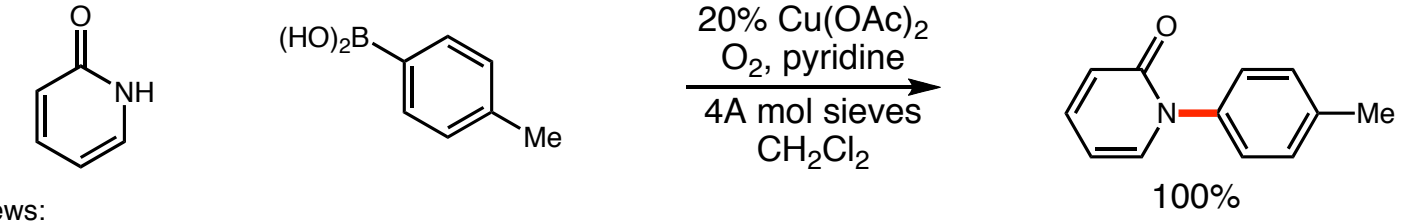
Coupling Reactions

Ullman condensation—Cu(III)



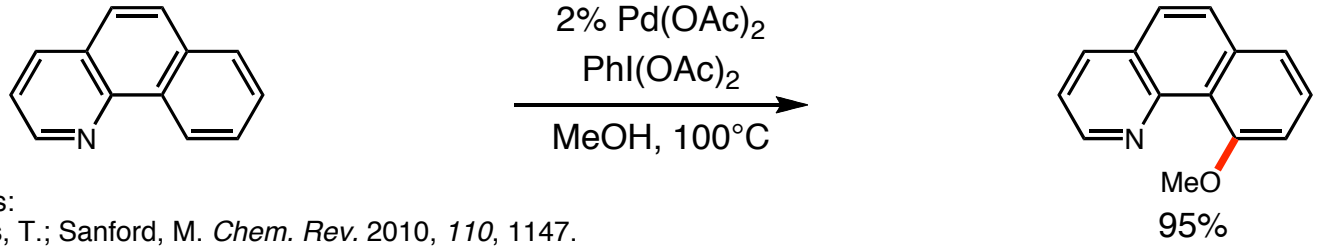
reviews:
Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* 2008, *108*, 3054.
Rao, H.; Fu, H. *Synlett*. 2011, *6*, 745.

Chan-Lam coupling—Cu(III)



reviews:
Ley, S.; Thomas, A. *Angew. Chem. Int. Ed.* 2003, *42*, 5400.
Qiao, J.; Lam, P. *Synthesis*. 2011, *6*, 829.

Ligand-directed CH functionalization—Pd(IV)

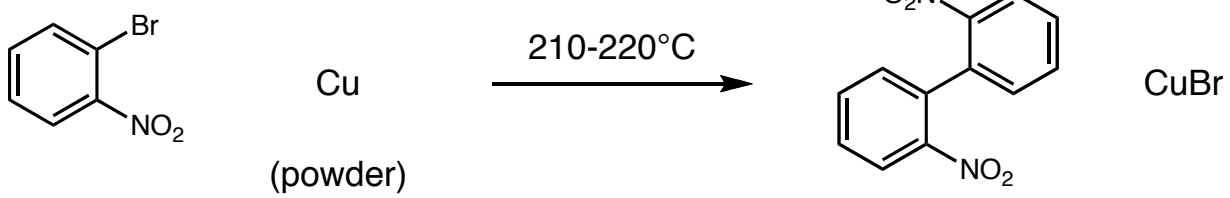


reviews:
Lyons, T.; Sanford, M. *Chem. Rev.* 2010, *110*, 1147.

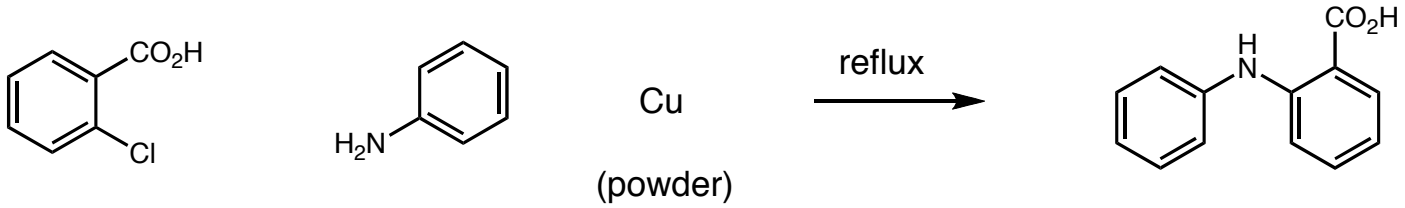
The Ullmann Condensation

Seminal work

- Fritz Ullmann (1901), discovery of the Cu-mediated coupling



- Fritz Ullmann (1903), the Ullmann condensation and the synthesis of diarylamines



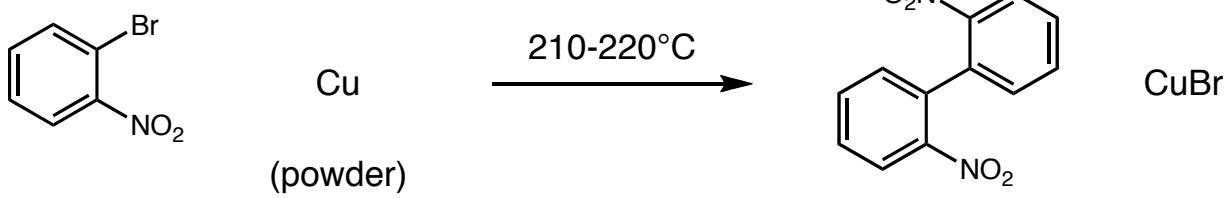
Ullmann, F.; Bielecki, J. *Ber. Dtsch. Chem. Ges.* 1901, *34*, 2174.

Ullmann, F. *Ber. Dtsch. Chem. Ges.* 1903, *36*, 2382.

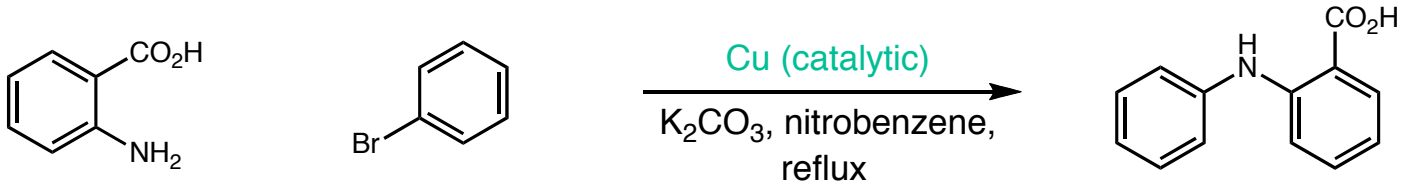
The Ullmann Condensation

Seminal work

- Fritz Ullmann (1901), discovery of the Cu-mediated coupling



- Irma Goldberg (1906), the Ullmann condensation with catalytic Cu



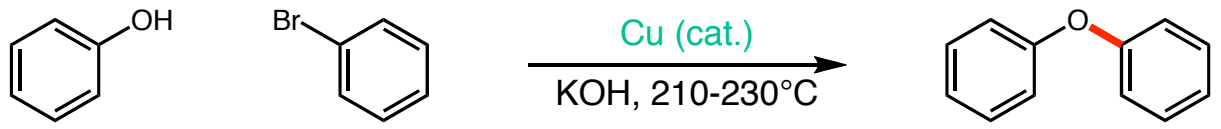
Ullmann, F.; Bielecki, J. *Ber. Dtsch. Chem. Ges.* 1901, *34*, 2174.

Goldberg, I. *Ber. Dtsch. Chem. Ges.* 1906, *39*, 1691.

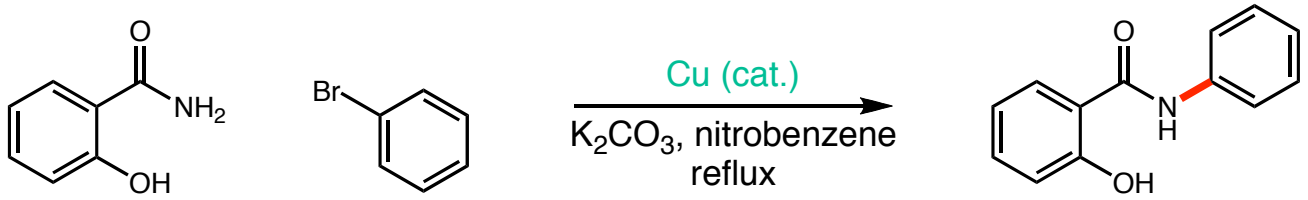
The Ullmann Condensation

Seminal work

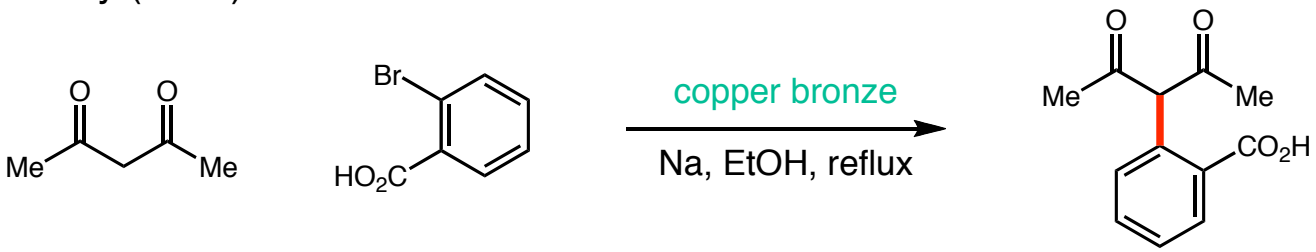
- Ullmann condensation synthesis of diarylethers (1905)



- Goldberg condensation reaction (1906)



- William Hurtley (1929)

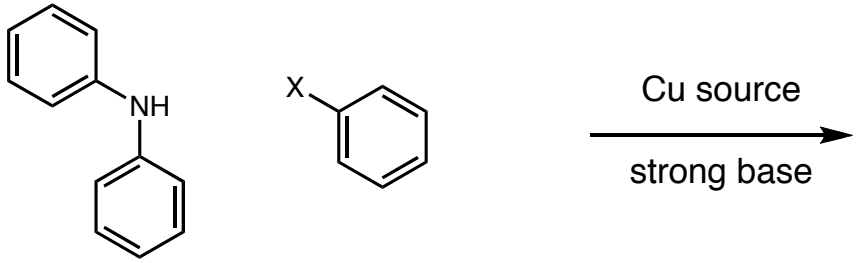


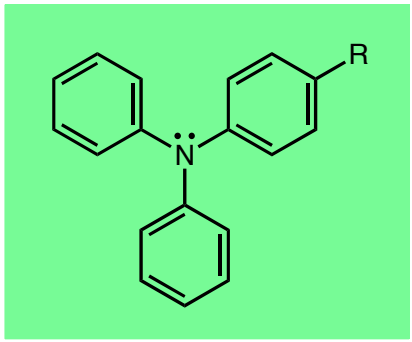
Ullman, F.; Sponagel, P. *Ber. Dtsch. Chem. Ges*. 1905, *38*, 2211.
Goldberg, I. *Ber. Dtsch. Chem. Ges.* 1906, *39*, 1691.
Hurtley, W. *J. Chem. Soc*. 1929, 1870.

The Ullmann Condensation

Identifying the active catalyst

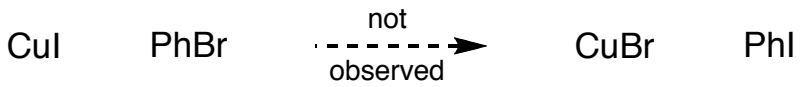
- Paine examined the catalytic condensation of triaryl amines





photoconductors used in Xerox® laser printers and photocopiers

- Initial kinetic observations rule out an S_NAr process
  - $k_I \sim 55\ k_{Br} \sim 480\ k_{Cl} \sim 3300\ k_F \sim 28000\ k_{OMe}$
  - Reaction is zero-order in nucleophile
  - Halogen exchange not observed



Paine, A. *J. Am. Chem. Soc.* 1987, *109*, 1496.

Amthor, S.; Noller, B.; Lambert, C. *Chem. Phys*. 2005, *316*, 141.

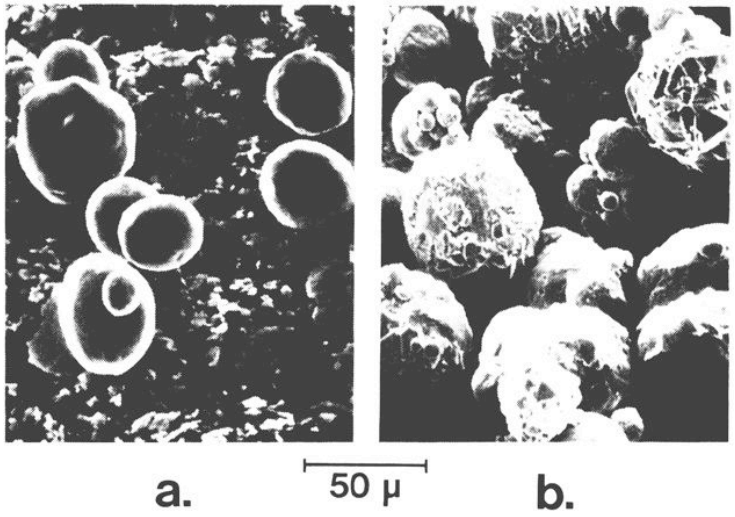
The Ullmann Condensation

Identifying the active catalyst

- Cu(II) sources—reduced to Cu(I) before reaction can proceed

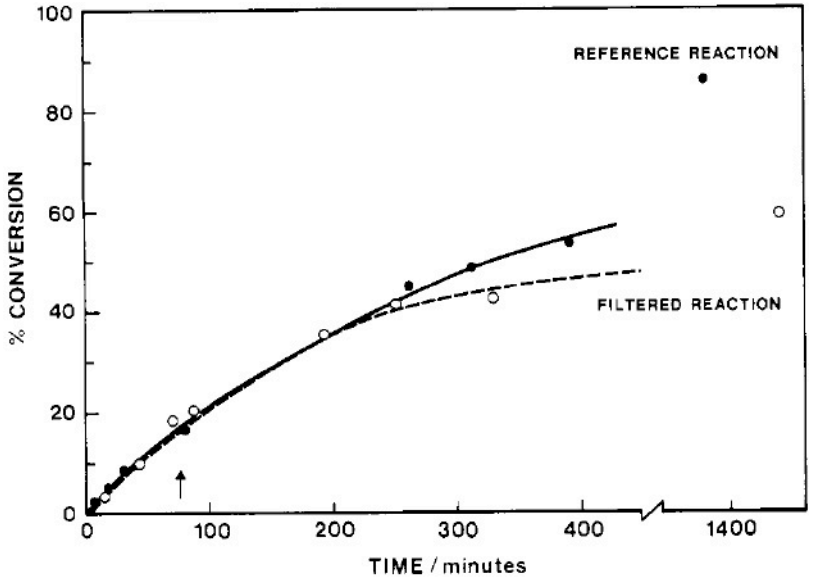
$$2\ Ph_2NLi + 2\ CuX_2 \longrightarrow Ph_2NNPh_2 + 2CuX + 2LiX$$

- Cu(0) sources actually a source of Cu_2O (SEM, TEM, x-ray powder diffraction



- With weaker bases (K_2CO_3) dissolution of Cu(I) source is rate limiting

- Evidence for solution catalysis

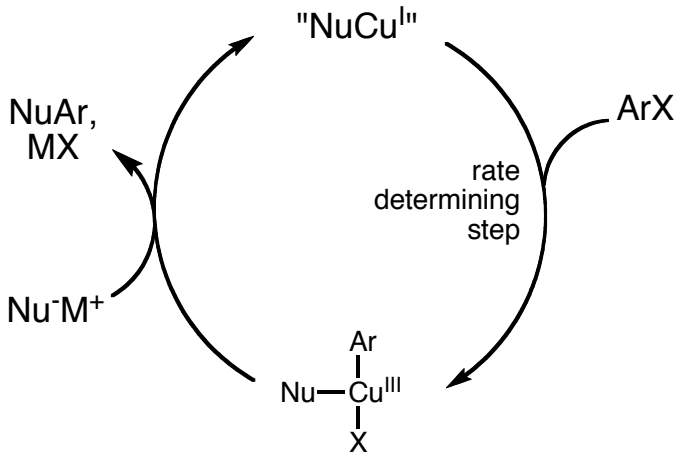


Paine, A. *J. Am. Chem. Soc.* 1987, *109*, 1496.

The Ullmann Condensation

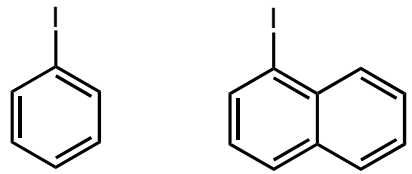
Proposed catalytic cycle

- Kinetics and isolation studies implicate nucleophile Cu(I) species as resting state

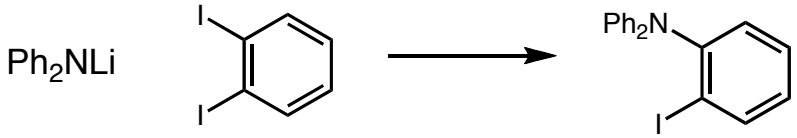


- Evidence against radical activation

no influence by radical traps



$k_{rel} \sim 1$



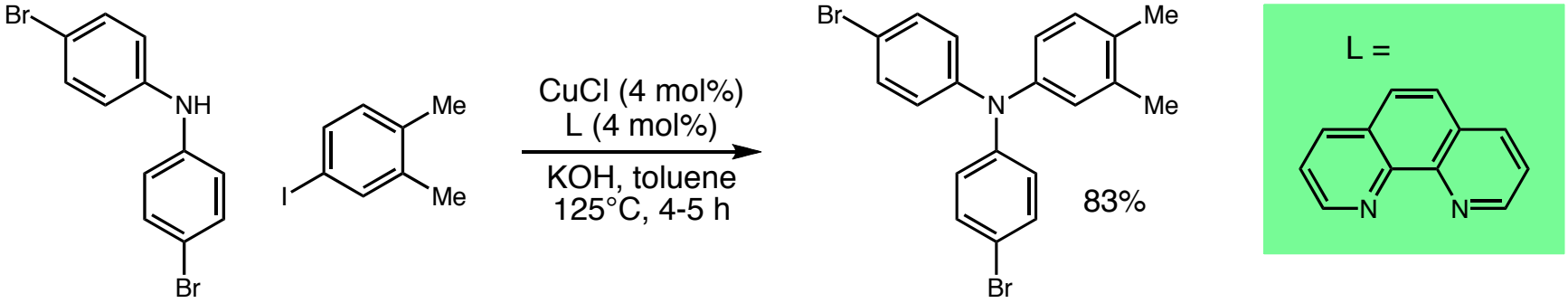
- Aryl halide activation by oxidative addition

Paine, A. *J. Am. Chem. Soc.* 1987, *109*, 1496.

Tye, J.; Weng, Z.; Giri, R.; Hartwig, J. *Angew. Chem.* 2010, 49, 2185-2189.

The Ullmann Condensation

- Ligands accelerate catalysis



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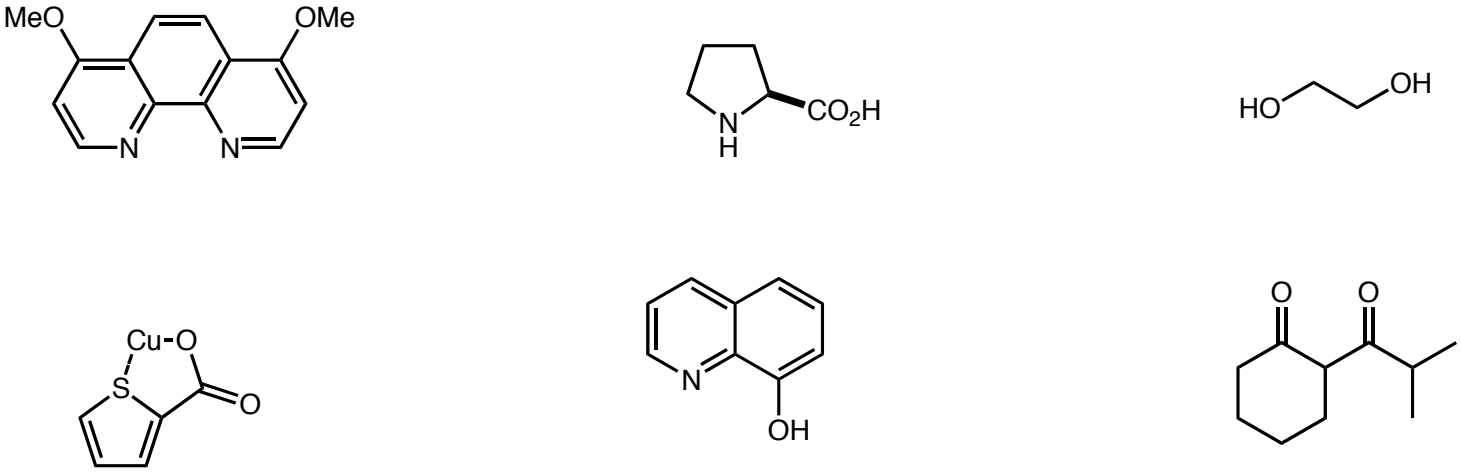
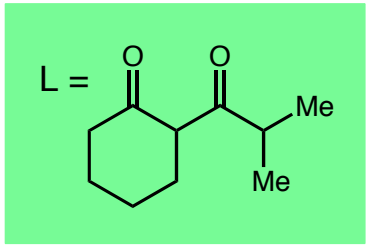
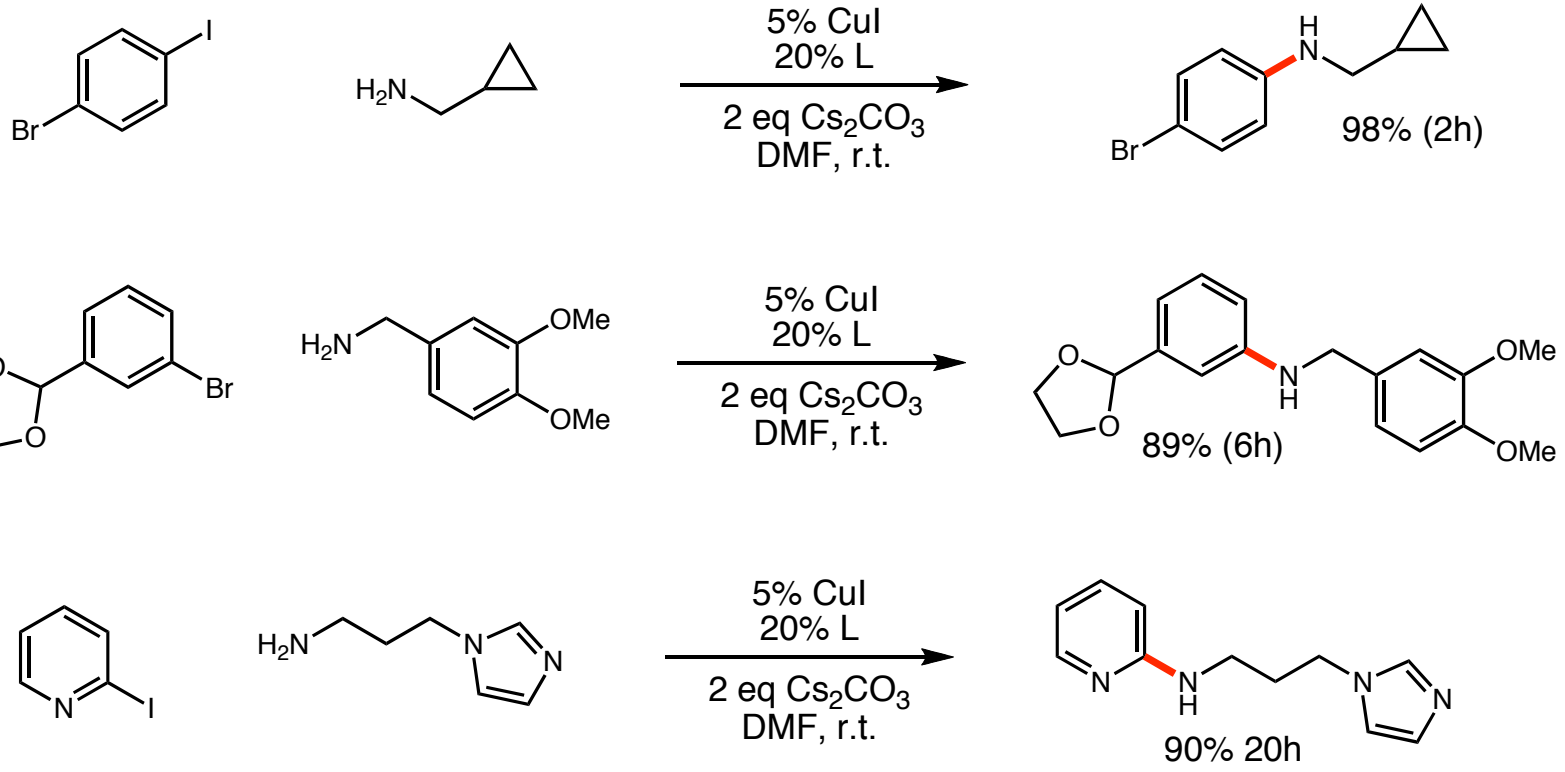


Goodbrand, H.; Hu, N. *J. Org. Chem.* 1999, *64*, 670-674.

The Ullmann Condensation

- Room temperature C(sp^2)—N(alkyl) coupling

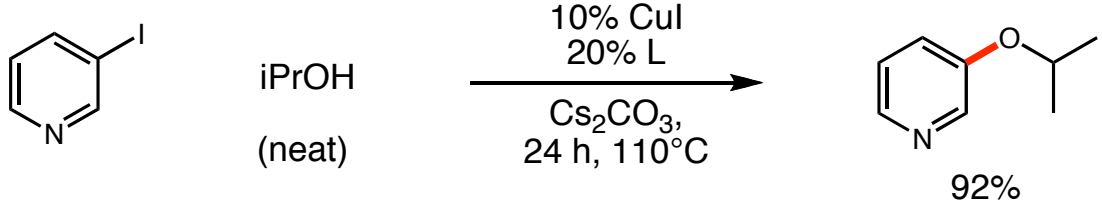


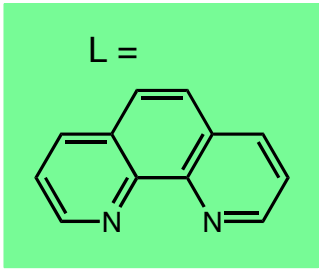


Shafir, A.; Buchwald, S. *J. Am. Chem. Soc.* 2006, *128*, 8742.

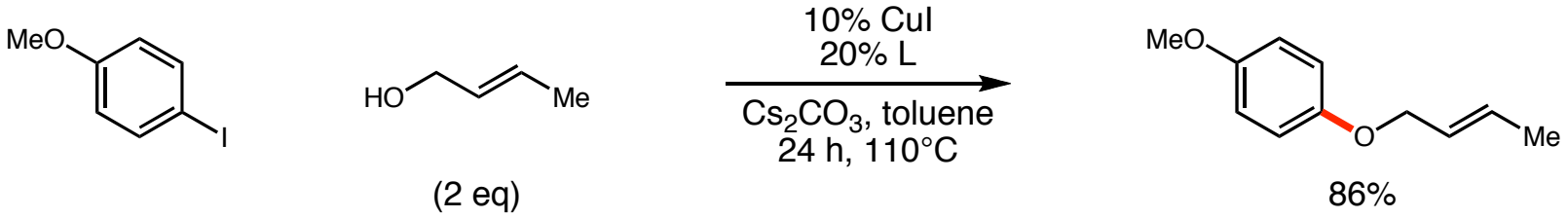
The Ullmann Condensation

- Alkyl aryl ether coupling





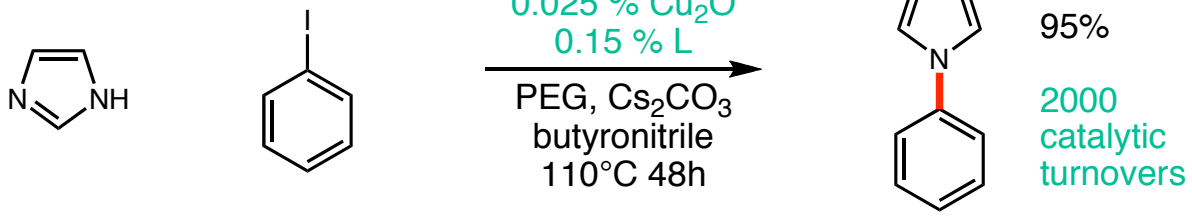
- Stoichiometric coupling of more precious alcohols

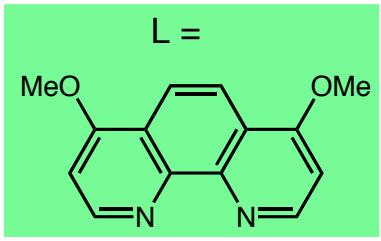


Wolder, M.; Nordman, G.; Job, G.; Buchwald, S. *Org. Lett.* 2002, *4*, 973.

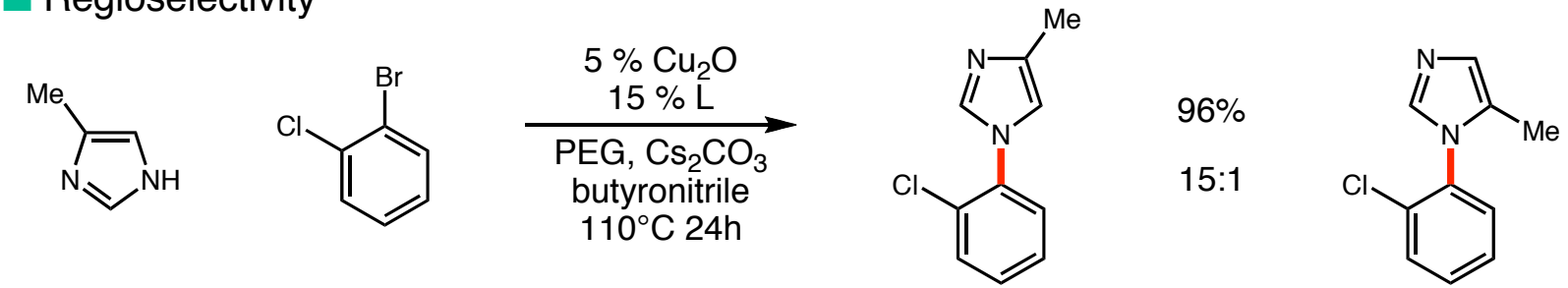
The Ullmann Condensation

N-arylation of imidazoles

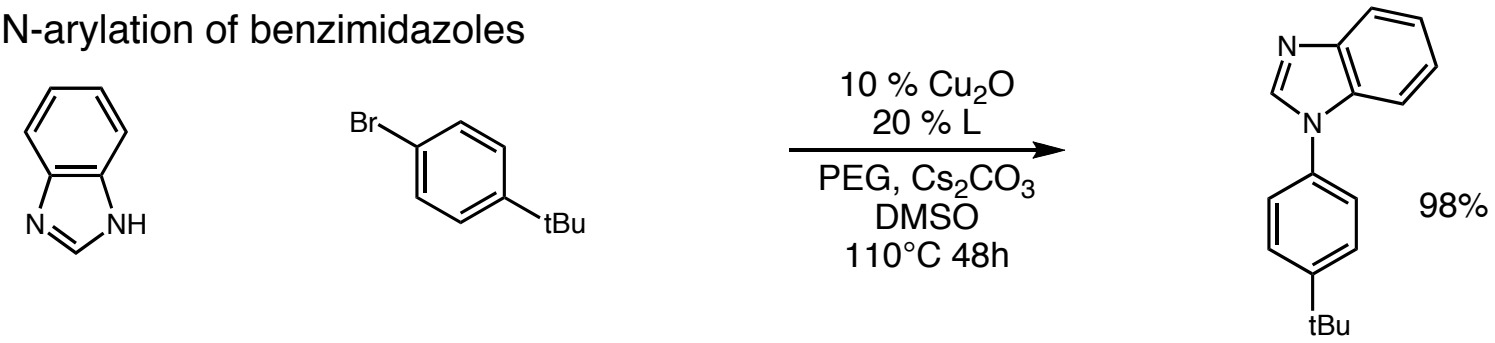




Regioselectivity



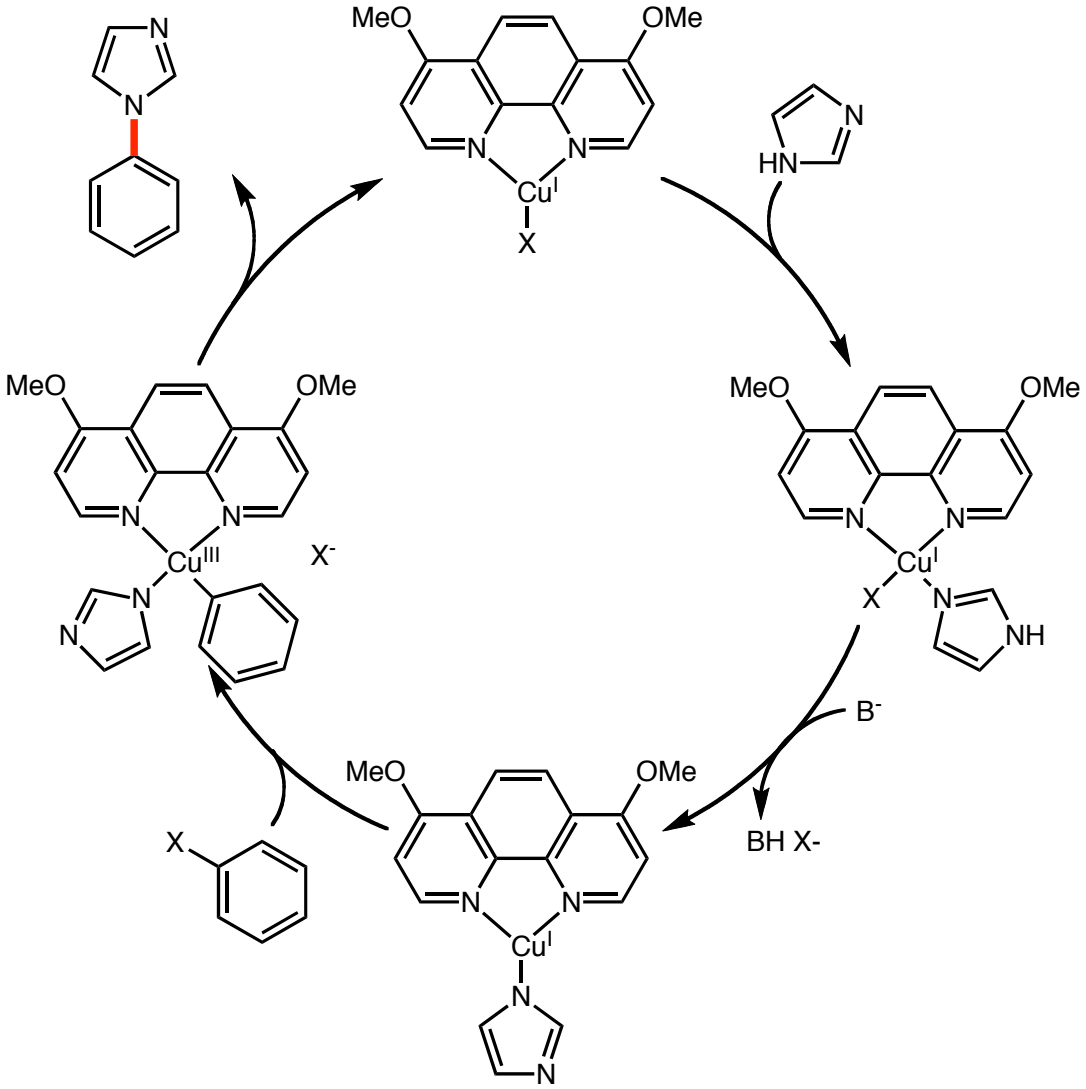
N-arylation of benzimidazoles



Altman, R.; Koval, E.; Buchwald, S. *J. Org. Chem.* 2007, *72*, 6190.

The Ullmann Condensation

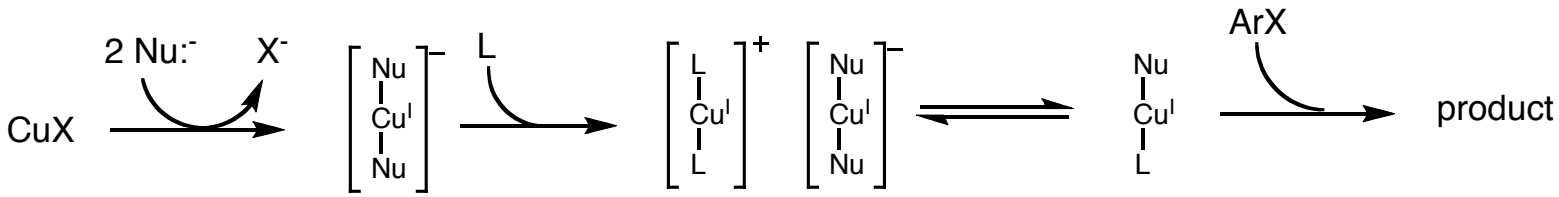
- Strong sigma donation of ligand stabilizes Cu(III) intermediate



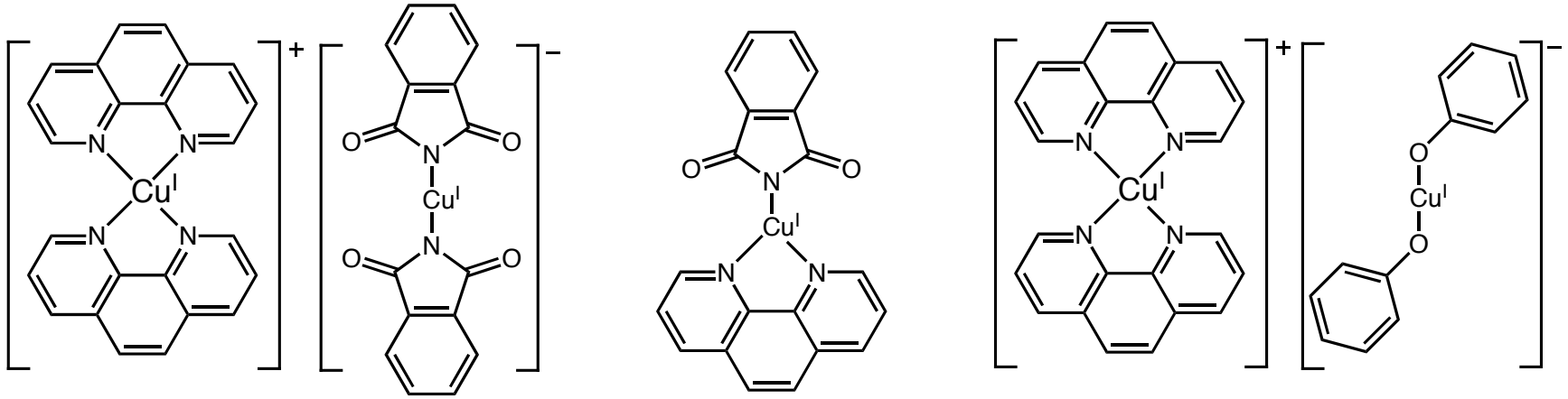
Altman, R.; Koval, E.; Buchwald, S. *J. Org. Chem.* 2007, *72*, 6190.

The Ullmann Condensation

- The formation of a coordination equilibrium



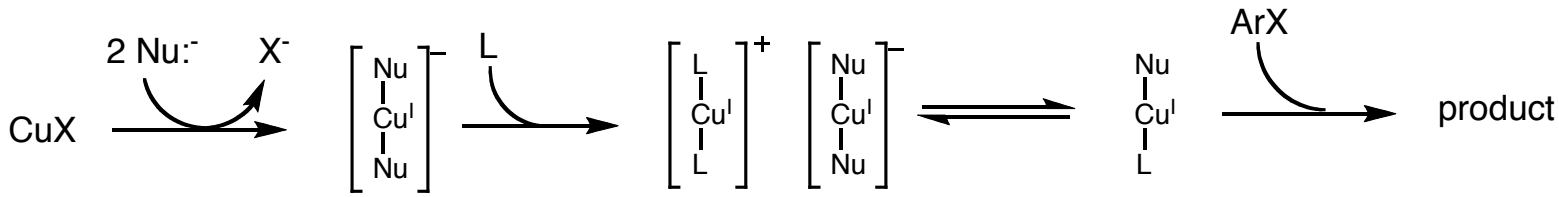
- Isolated and characterized intermediate complexes



Tye, J.; Weng, Z.; Johns, A.; Incarvito, C.; Hartwig, J. *J. Am. Chem. Soc.* 2008, *130*, 9971.
Tye, J.; Weng, Z.; Giri, R.; Hartwig, J. *Angew. Chem. Int. Ed.* 2010, *49*, 2185

The Ullmann Condensation

- The formation of a coordination equilibrium



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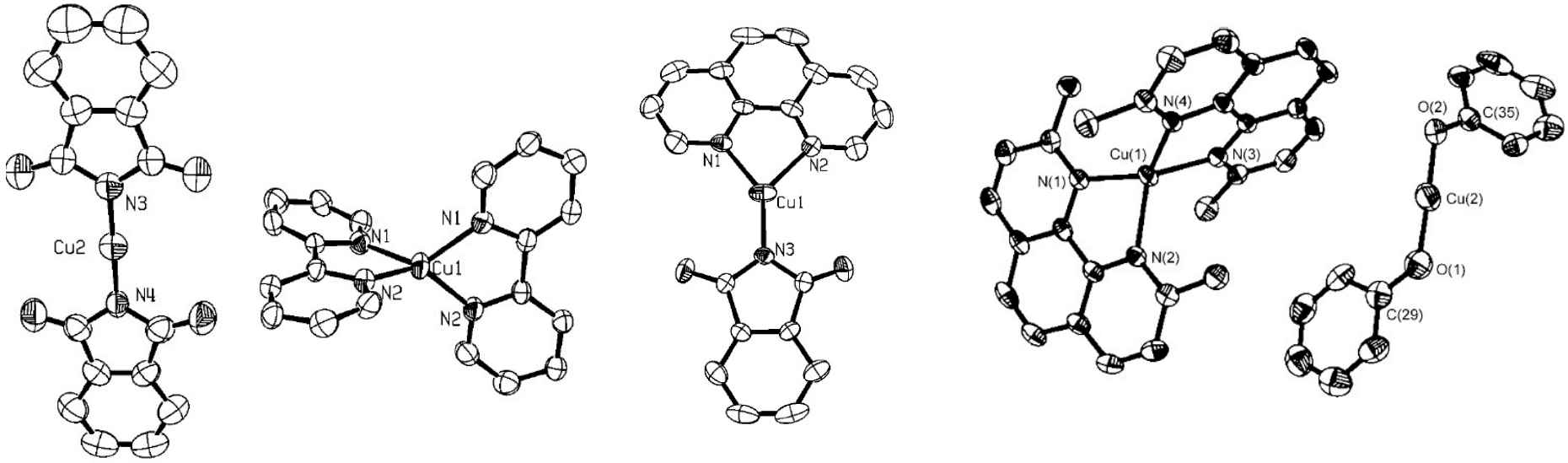
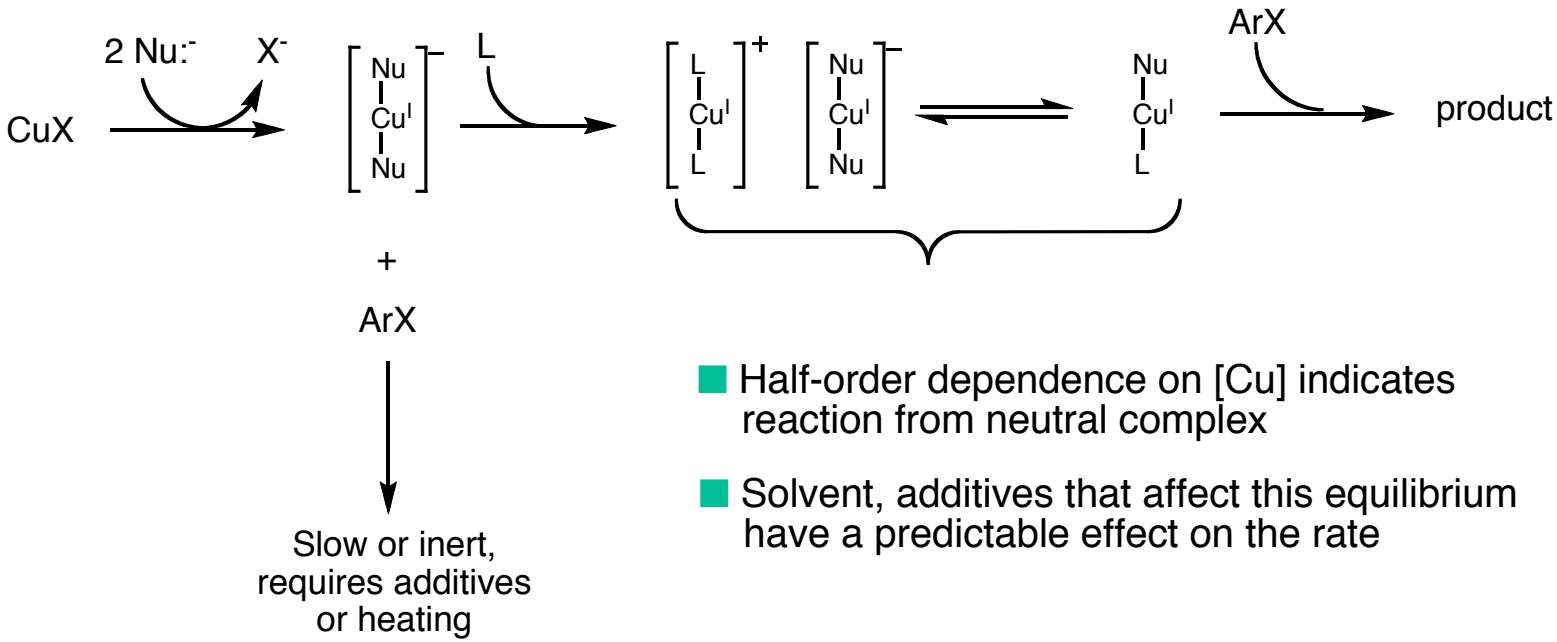


Tye, J.; Weng, Z.; Johns, A.; Incarvito, C.; Hartwig, J. *J. Am. Chem. Soc.* 2008, *130*, 9971.
Tye, J.; Weng, Z.; Giri, R.; Hartwig, J. *Angew. Chem. Int. Ed.* 2010, *49*, 2185

The Ullmann Condensation

- The formation of a coordination equilibrium

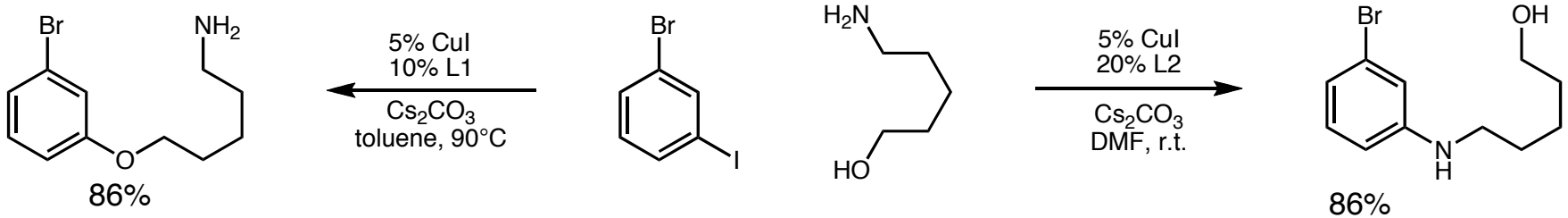


- Half-order dependence on [Cu] indicates reaction from neutral complex
- Solvent, additives that affect this equilibrium have a predictable effect on the rate

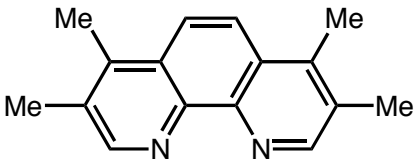
Tye, J.; Weng, Z.; Johns, A.; Incarvito, C.; Hartwig, J. *J. Am. Chem. Soc.* 2008, *130*, 9971.
Tye, J.; Weng, Z.; Giri, R.; Hartwig, J. *Angew. Chem. Int. Ed.* 2010, *49*, 2185

The Ullmann Condensation

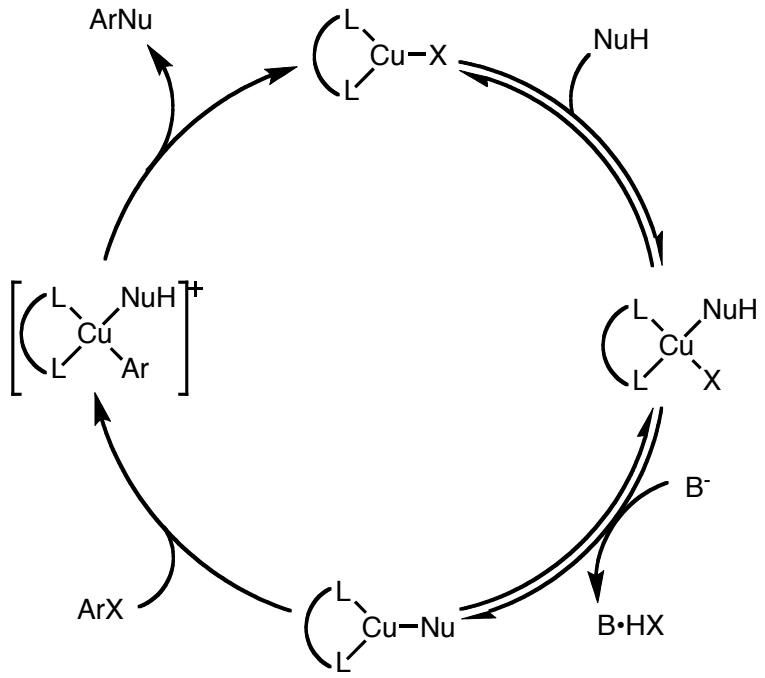
- Selective O/N arylation



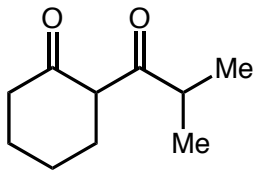
L1 =



- Neutral, sigma-donor ligand promotes oxidative addition
- Favors coordination by deprotonated nucleophile



L2 =

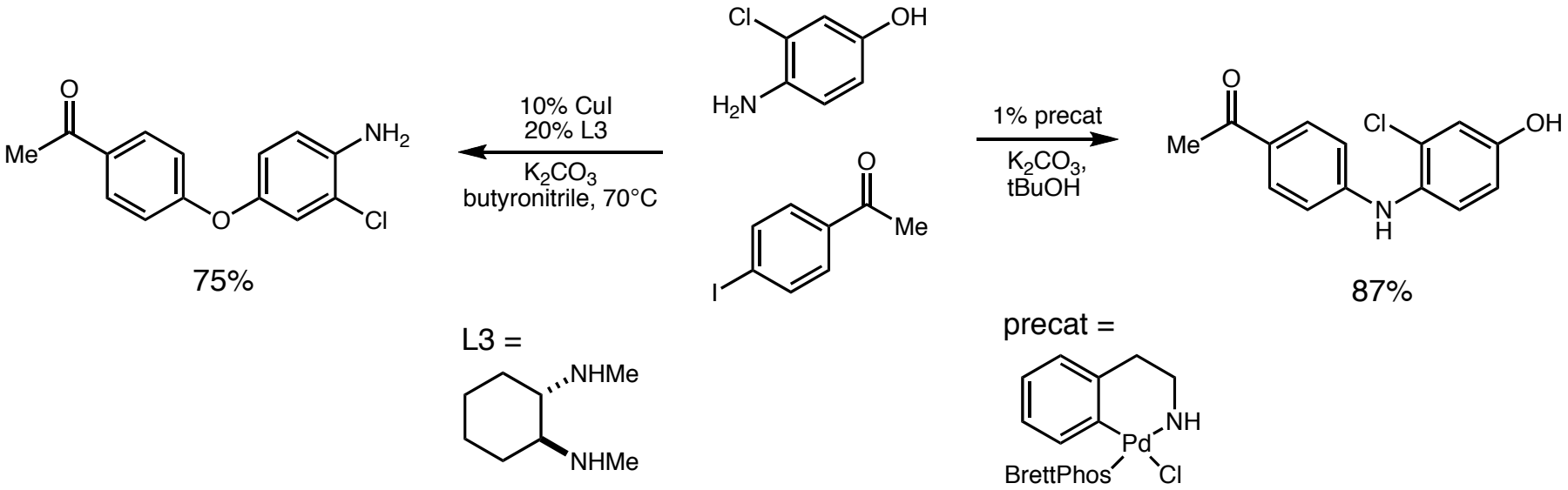


- Anionic ligand favors coordination by softer neutral amine nucleophile
- Slower oxidative addition favors faster amine

Safir, A.; Lichtor, P.; Buchwald. *J. Am. Chem. Soc.* 2007, *129*, 3490.

The Ullmann Condensation

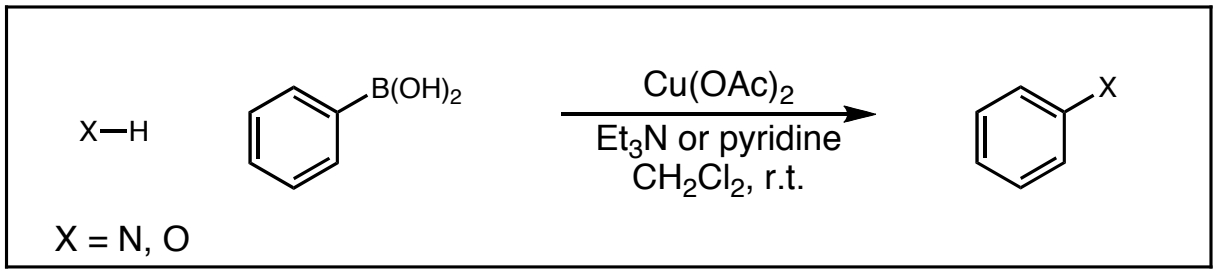
- Selective O/N arylation

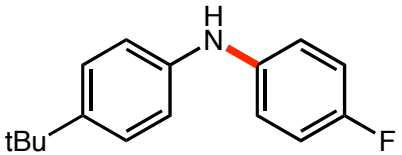


Maiti, D.; Buchwald. *J. Am. Chem. Soc.* 2009, *131*,17423.

The Chan-Lam Reaction

- Chan's original discovery





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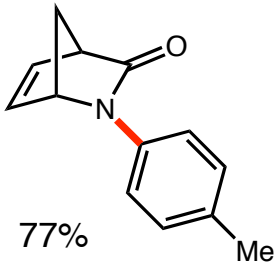
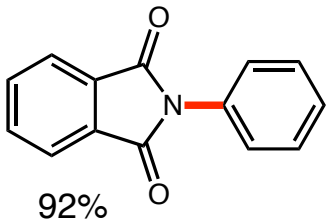


77%



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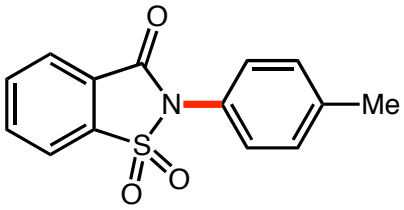

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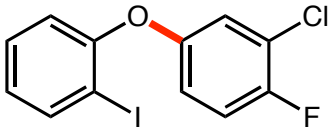
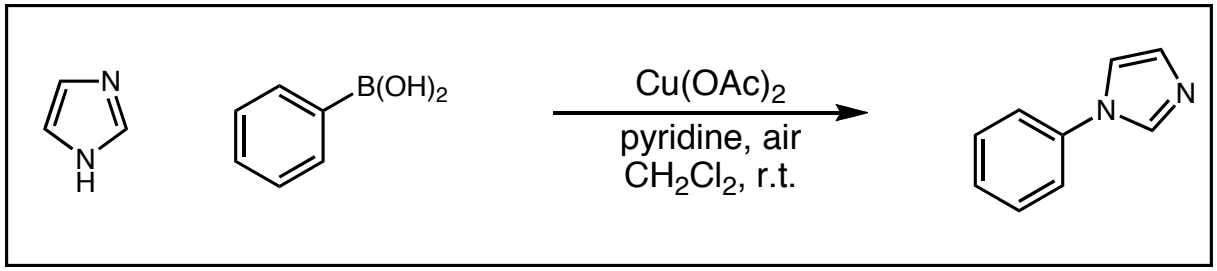


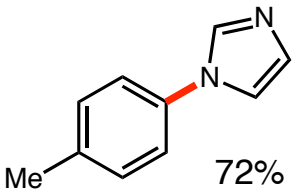
78%

Chan, D.; Monaco, K.; Wang, R.; Winters, M. *Tet. Lett.* 1998, *39*, 2933.

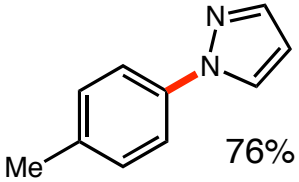
The Chan-Lam Reaction

- Patrick Lam's heteroaryl C—N coupling

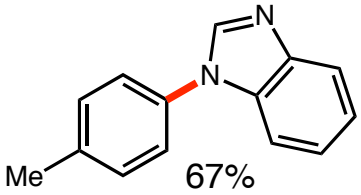




72%



76%

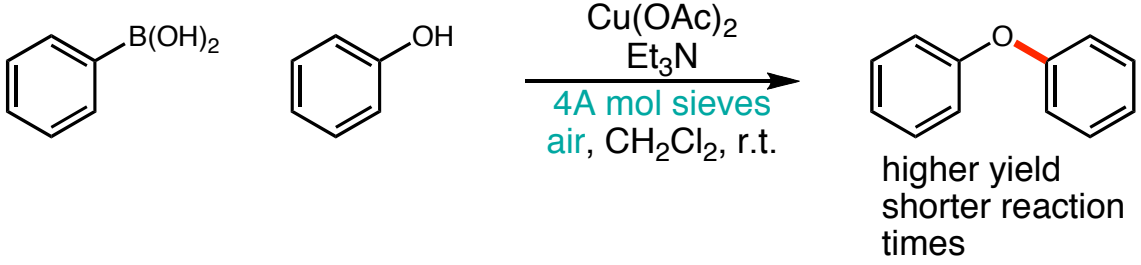


67%

Lam, P.; Clark, C.; Saubern, S.; Adams, J.; Winters, M.; Chan, D.; Combs, A. *Tet. Lett.* 1998, *39*, 2941
.

The Chan-Lam Reaction

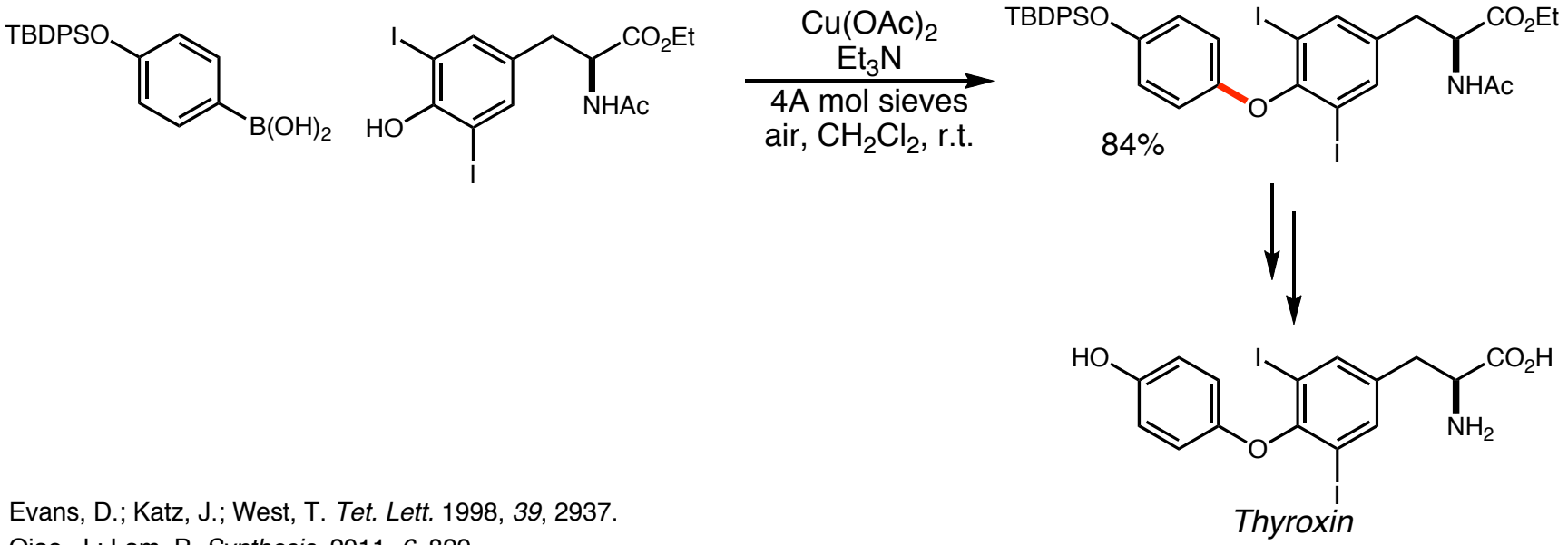
- Evans's application to diaryl ether natural product synthesis



higher yield
shorter reaction
times

"Professor Evan's group found out about the discovery of copper-mediated O-arylation reaction on a National Organic Symposium poster of Dr. Chan's and became interested because of the importance of novel biaryl ether synthesis for the total synthesis of vancomycin."

— Patrick Lam



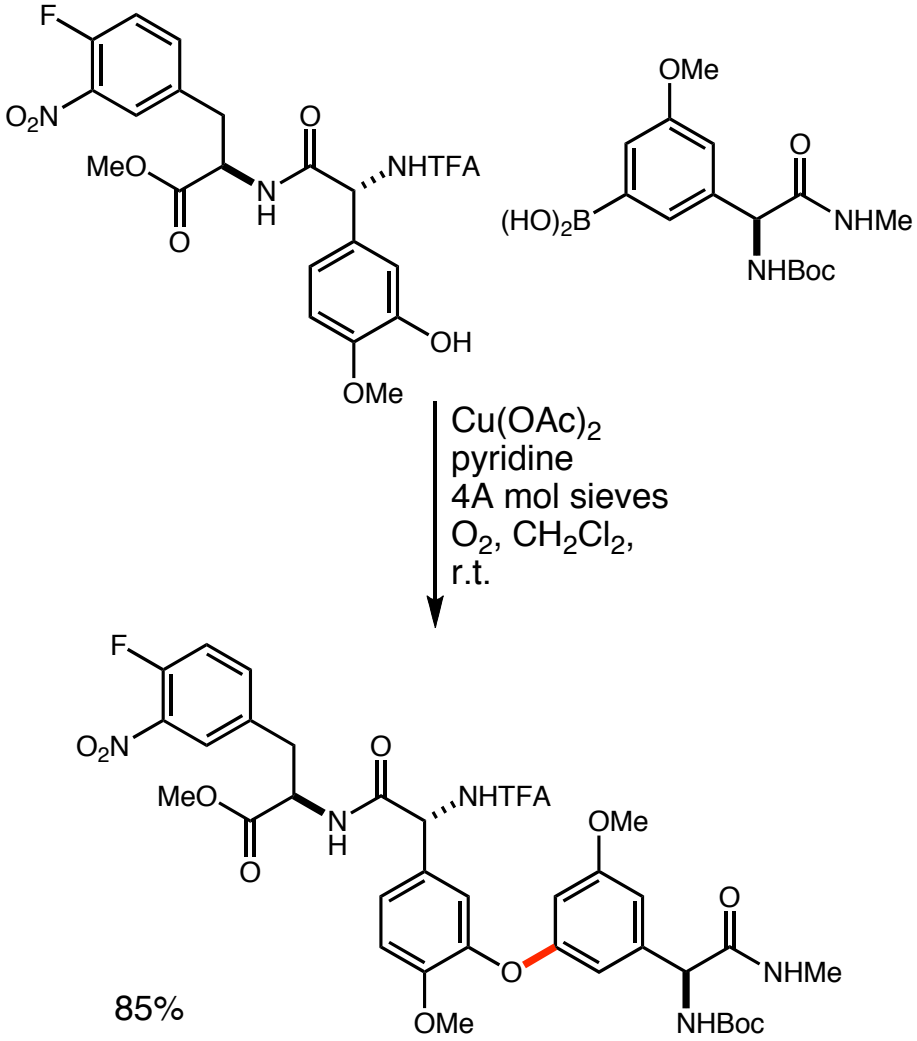
Thyroxin

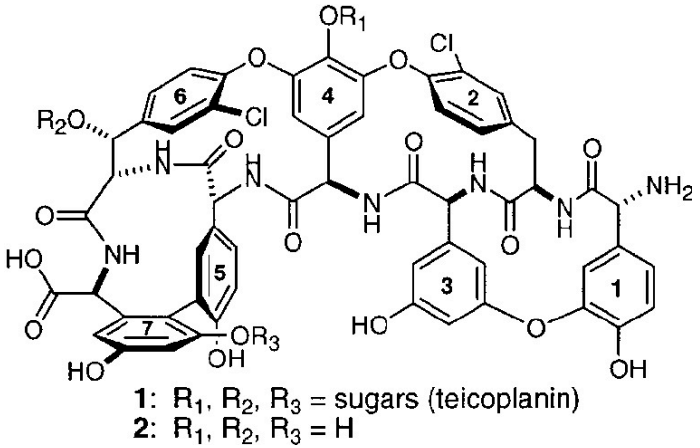
Evans, D.; Katz, J.; West, T. *Tet. Lett.* 1998, *39*, 2937.

Qiao, J.; Lam, P. *Synthesis*. 2011, *6*, 829.

The Chan-Lam Reaction

- Evans's application to diaryl ether natural product synthesis

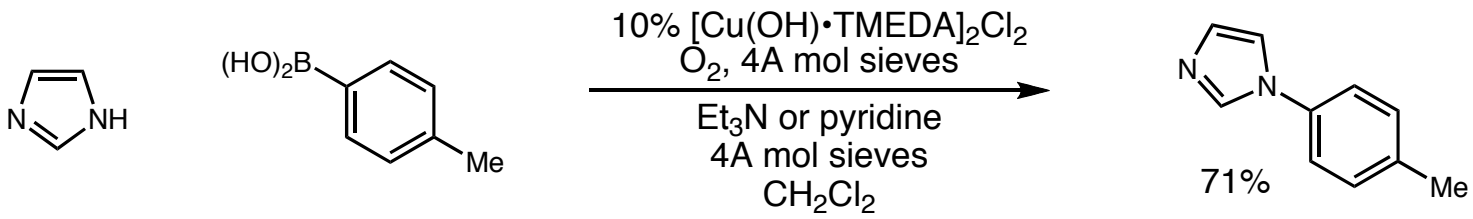




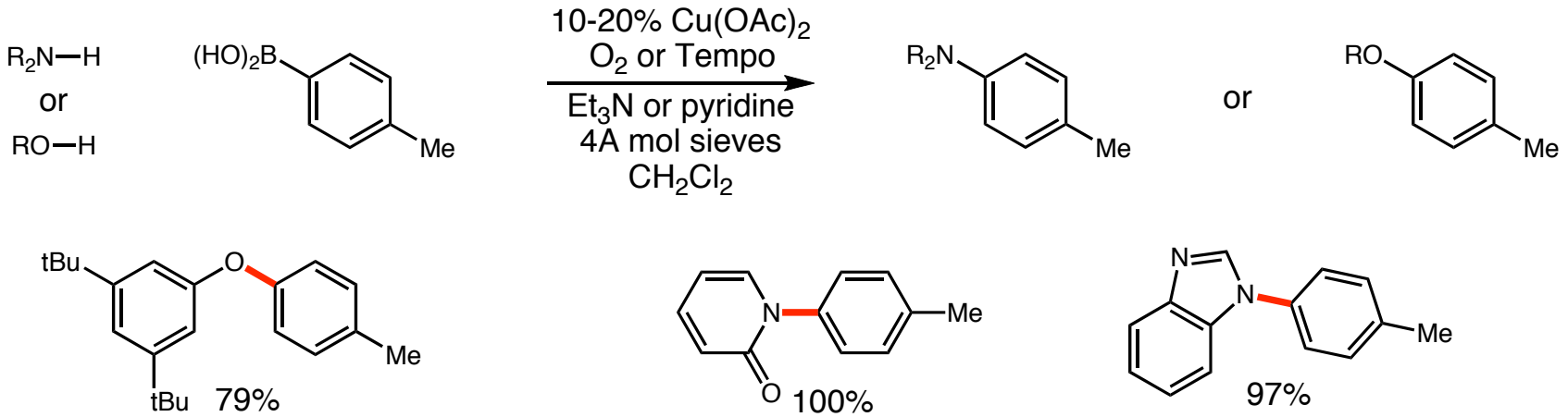
Evans, D.; Katz, J.; Peterson, G.; Hinterman, T. *J. Am. Chem. Soc.* 2001, *123*, 12411.

The Chan-Lam Reaction

Collman's catalytic system



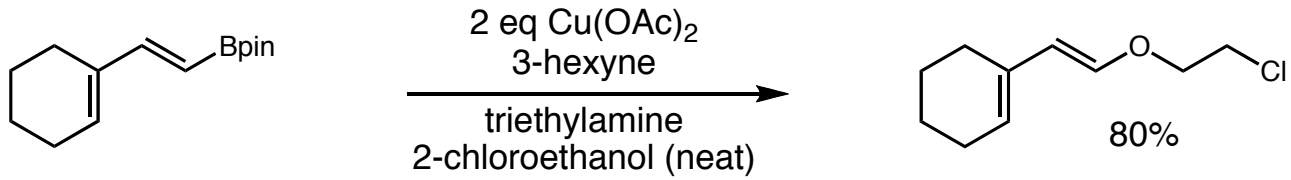
Lam's catalytic system



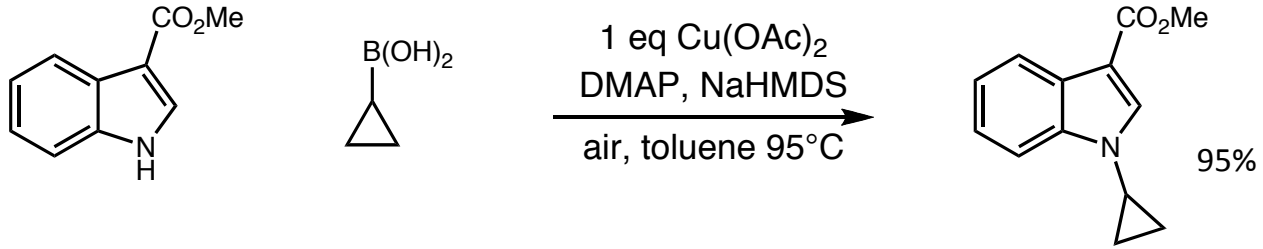
Collman, J.; Zhong, M. *Org. Lett.* 2000, *2*, 1233.
Lam, P.; Vincent, G.; Clark, C.; Deudon, S.; Judhav, P. *Tet. Lett.* 2001, *42*, 3415.

The Chan-Lam Reaction

- Vinylboranes



- Cyclopropanation of heterocycles

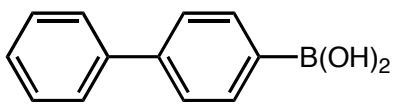


Tsuritani, T.; Strotman, N.; Yamamoto, Y.; Kawasaki, M.; Yasuda, N.; Mase, T. *Org. Lett.* 2008, *10*, 1653.

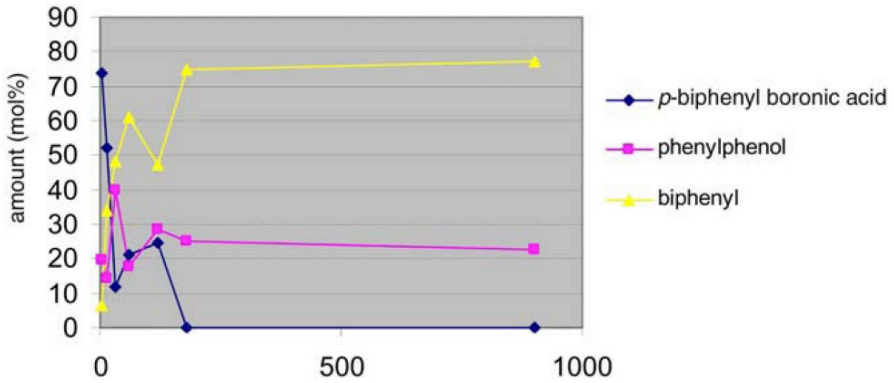
The Chan-Lam Reaction

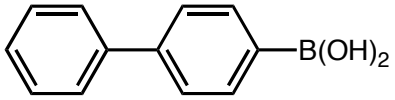
Mechanistic considerations

- Fate of the boronic acid



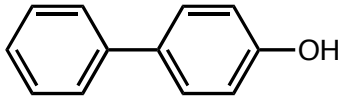
$Cu(OAc)_2$,
O_2, CH_2Cl_2,
no nucleophile



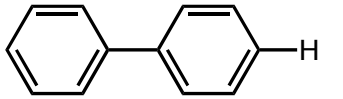


10 eq $H_2{}^{18}O$

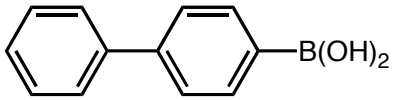
O_2, $Cu(OAc)_2$, TEA
CH_2Cl_2



3:2 ^{16}O:^{18}O
22%

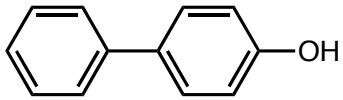


25%

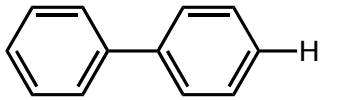


0-10 eq H_2O

$^{18}O_2$, $Cu(OAc)_2$, TEA
CH_2Cl_2



^{16}O only

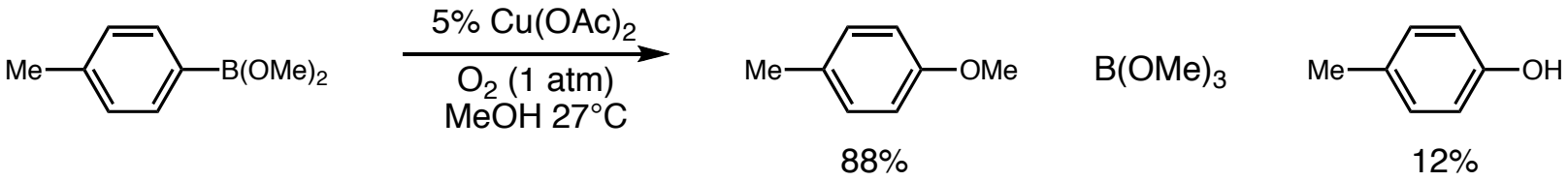


Lam, P.; Bonne, D.; Vincent, G.; Clark, C.; Combs, A. *Tet. Lett.* 2003, *44*, 1691
Qiao, J.; Lam, P. *Synthesis*. 2011, *6*, 829.

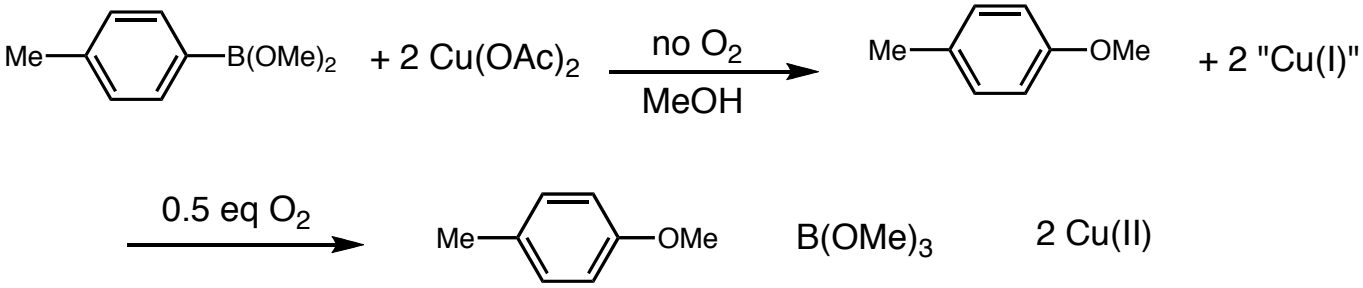
The Chan-Lam Reaction

Mechanistic considerations

- An efficient catalytic reaction



- Non catalytic conditions: 2:1 Cu(II) to product ratio under anaerobic conditions



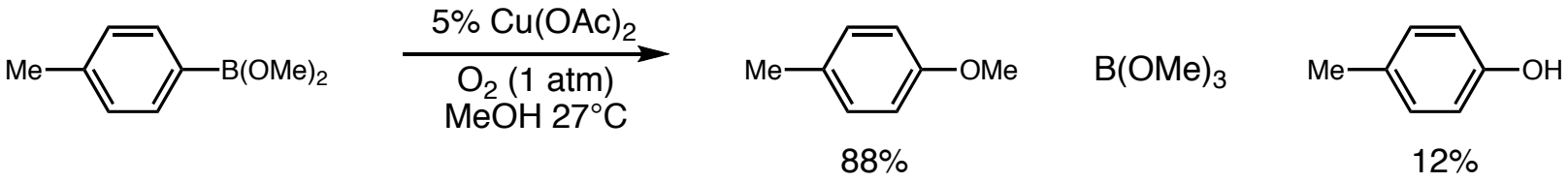
- Oxygen uptake shown to be 0.5 eq from this mixture
- Cu(II) is a 1-electron oxidant and O_2 is a 4-electron oxidant

King, A.; Brunold, T.; Stahl, S. *J. Am. Chem. Soc.* 2009, *131*, 5044.

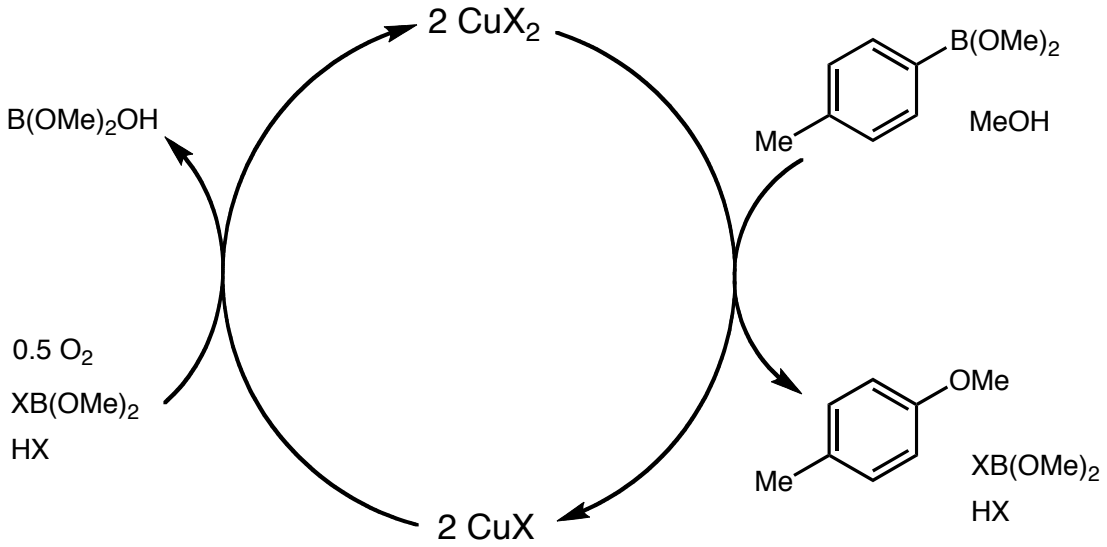
The Chan-Lam Reaction

Mechanistic considerations

- An efficient catalytic reaction



- Catalytic cycle performed stepwise

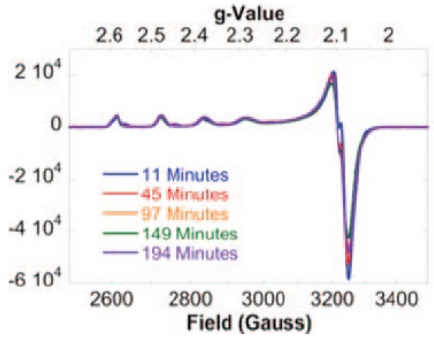


King, A.; Brunold, T.; Stahl, S. *J. Am. Chem. Soc.* 2009, *131*, 5044.

The Chan-Lam Reaction

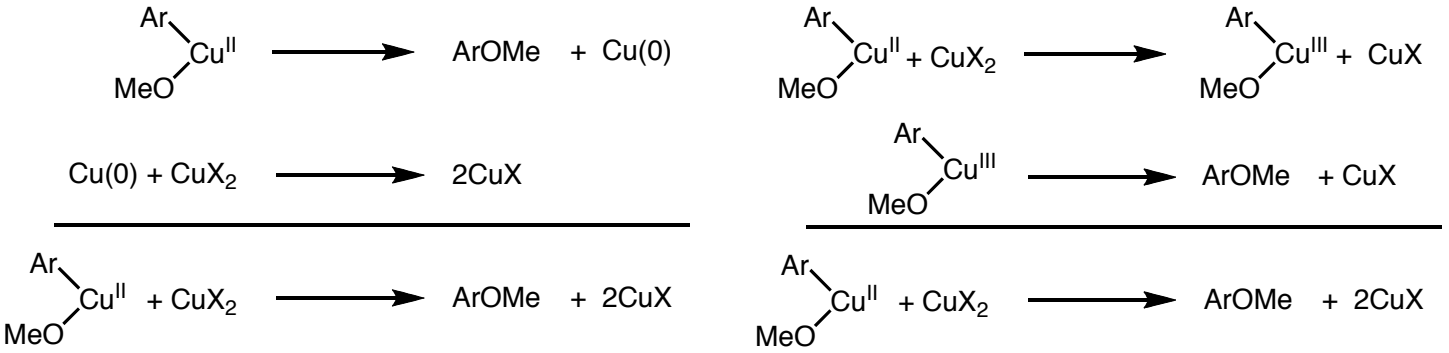
Mechanistic considerations

- EPR studies—strong signal for Cu(II) with weak dative ligands ("CuX_2") as resting state of catalyst



- Kinetics and lack of observed Ar-Cu complex under catalytic conditions suggest that transmetallation to Cu is rate-limiting step

- Reductive elimination—two possibilities

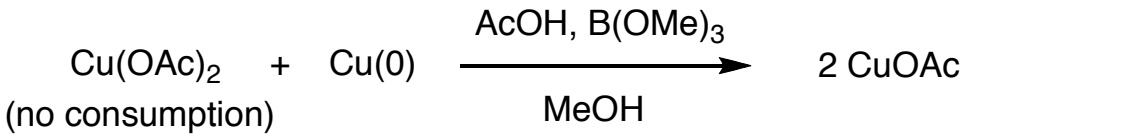


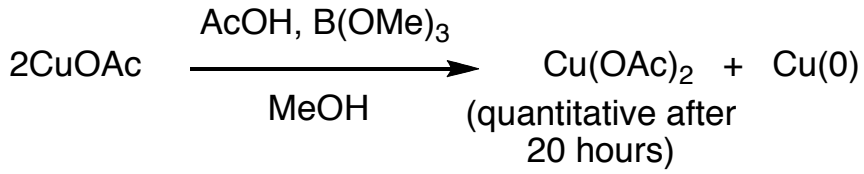
King, A.; Brunold, T.; Stahl, S. *J. Am. Chem. Soc.* 2009, *131*, 5044.

The Chan-Lam Reaction

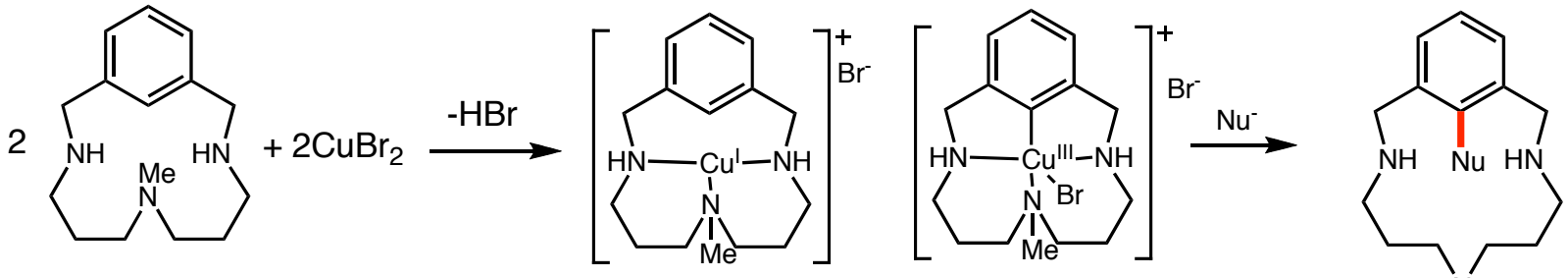
Mechanistic considerations

- Control reactions disfavor conproportionation of Cu(I)



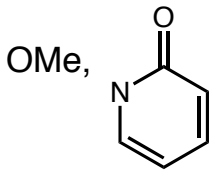


- A Cu(III) complex isolated and demonstrated to be competent



Crystal structures obtained

Nu =



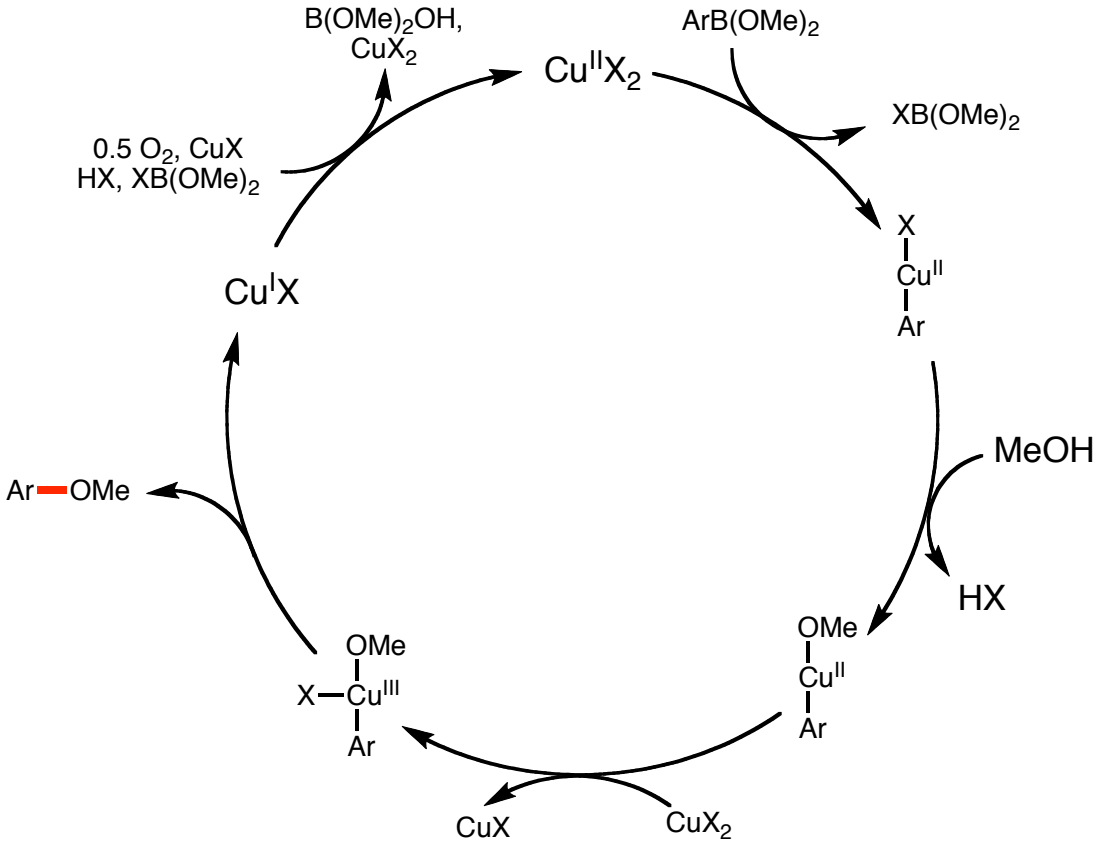
King, A.; Brunold, T.; Stahl, S. *J. Am. Chem. Soc.* 2009, *131*, 5044.

King, A.; Brunold, T.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. *J. Am. Chem. Soc.* 2010, *132*, 12068.

The Chan-Lam Reaction

Mechanistic considerations

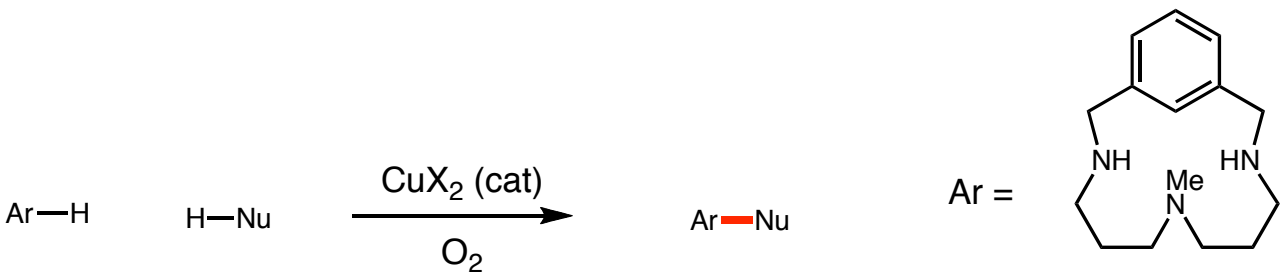
Proposed mechanism



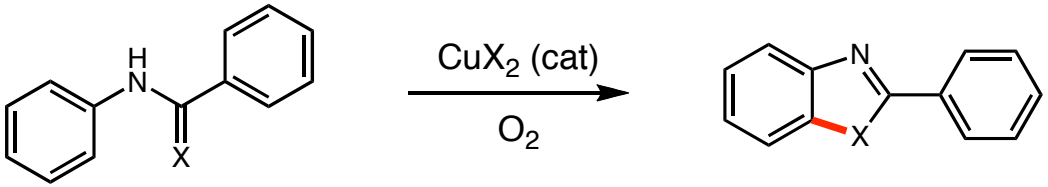
King, A.; Brunold, T.; Stahl, S. *J. Am. Chem. Soc.* 2009, *131*, 5044.
King, A.; Brunold, T.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. *J. Am. Chem. Soc.* 2010, *132*, 12068.

C-H Functionalization

- A C–H activation

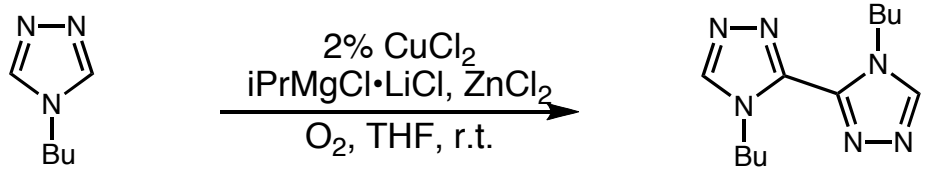


- Benzimidazole/Benzodioxole oxidation



X = O Nagasawa
NH Buchwald

- "Aromatic Glazer-Hay"



King, A.; Brunold, T.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. *J. Am. Chem. Soc.* 2010, *132*, 12068.

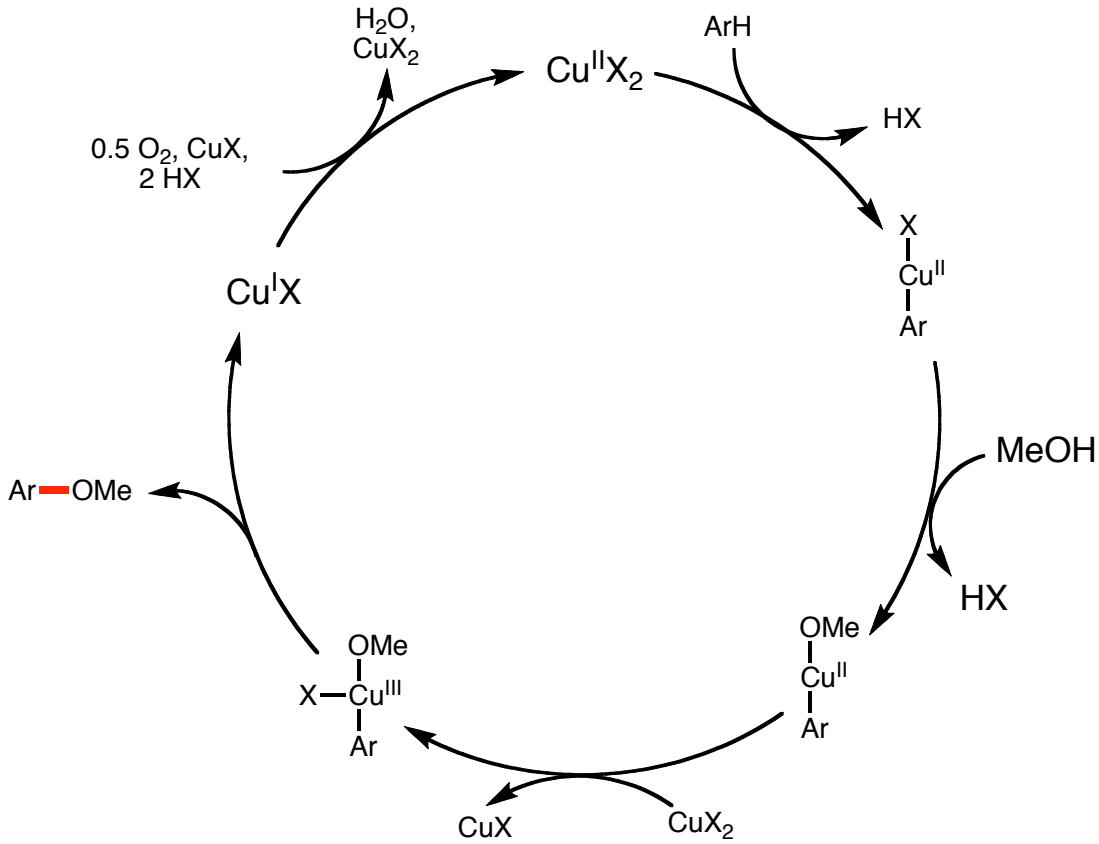
Brasche, G.; Buchwald, S. *Angew. Chem. Int. Ed.* 2008, *47*, 1932.

Ueda, S.; Nagasawa, H. *Angew. Chem. Int. Ed.* 2008, *47*, 6411.

Do, H.; Daguilis, O. *J. Am. Chem. Soc.* 2009, *131*, 17052.

C-H Functionalization

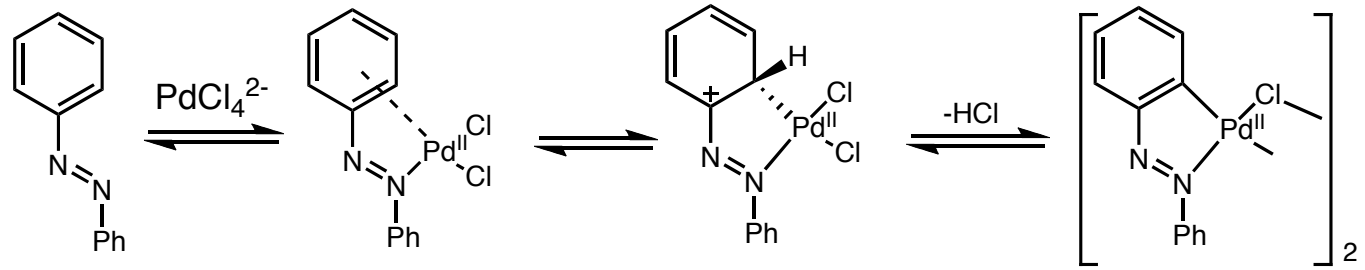
- Proposed mechanism



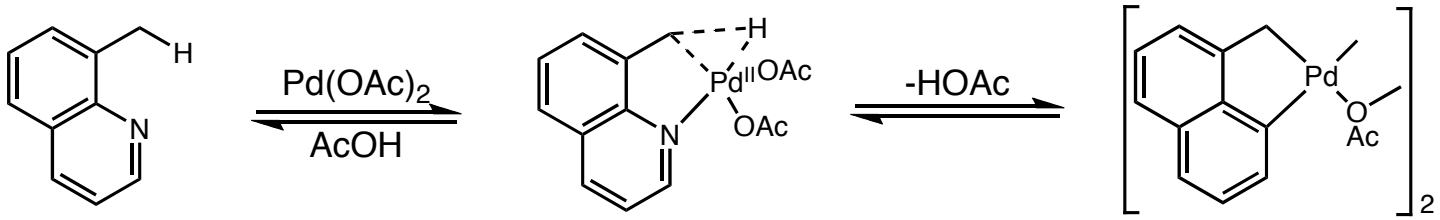
King, A.; Brunold, T.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. *J. Am. Chem. Soc.* 2010, *132*, 12068.

C-H Functionalization

- Arene addition—analogous to electrophilic aromatic addition based on substituent effects



- sp^3 C–H are believed to be activated through agostic complexes

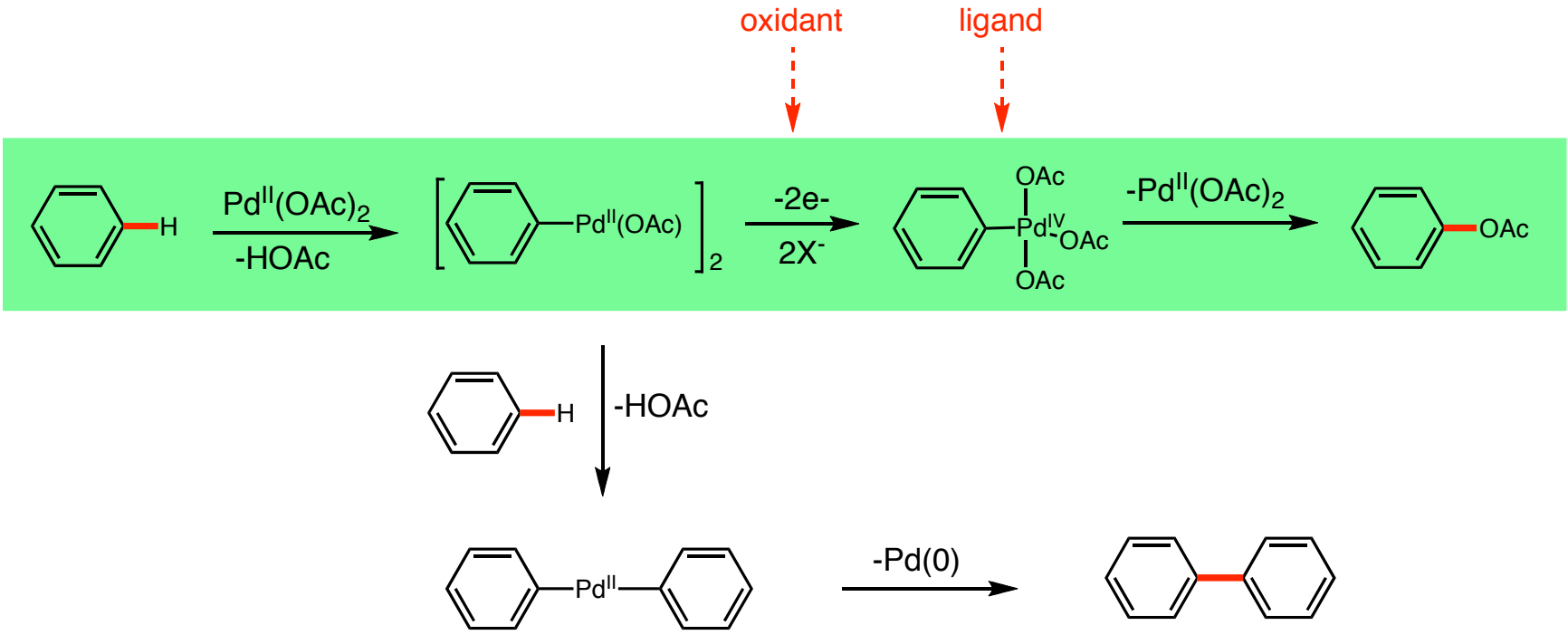


Parshall, G. *Acc. Chem. Res.* 1970, *3*, 139.

Dupont, J. Consorti, C.; Spencer, J. *Chem. Rev.* 2005, *105*, 2527.

C-H Functionalization

- Oxidation, reductive elimination mechanism

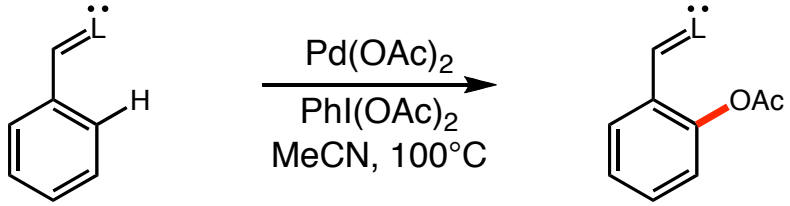


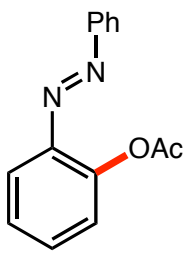
- Choice of oxidant ($PhI(OAc)_2$, $Na_2Cr_2O_7$) improves selectivity
- Ligand (picolinic acid) stabilizes Pd(IV) intermediate
- Lewis acids and Ag^+ favor biphenyl coupling

Yoneyama, T.; Crabtree, R. *J. Mol. Catal. A.* 1996, *108*, 35.

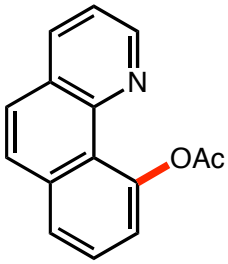
C-H Functionalization

- Ligand-directed sp^2 C—H bond oxygenation

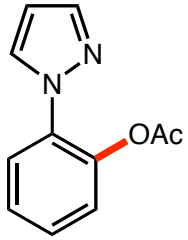




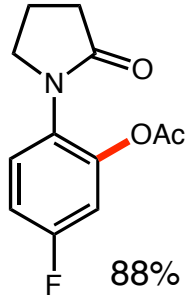
62%



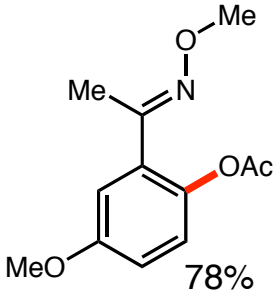
86%



54%



88%

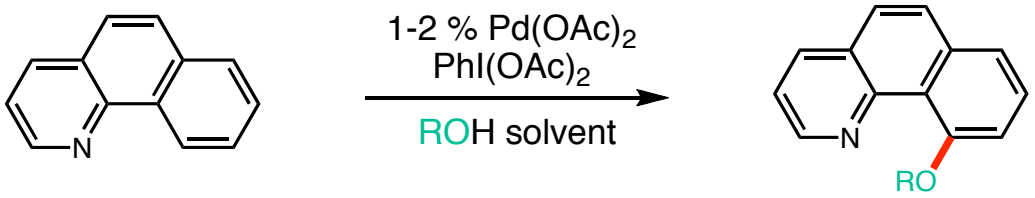


78%

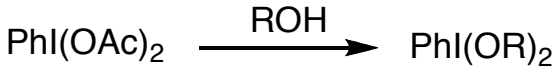
Lyons, T.; Sanford, M. *Chem. Rev.* 2010, *110*, 1147-1169.

C-H Functionalization

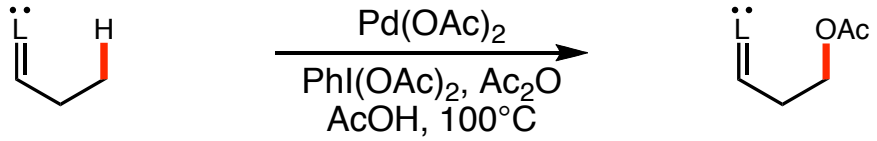
- Solvent alcohol as oxygen source

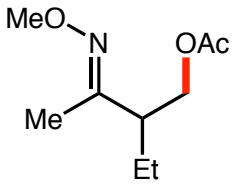


ROH	
MeOH	95%
EtOH	80%
iPrOH	72%
CF_3CH_2OH	71%



- sp^3 CH oxygenation





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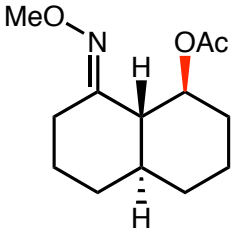
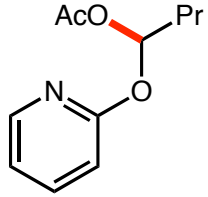
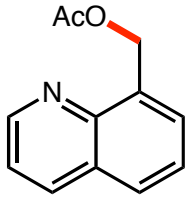


81%



44%

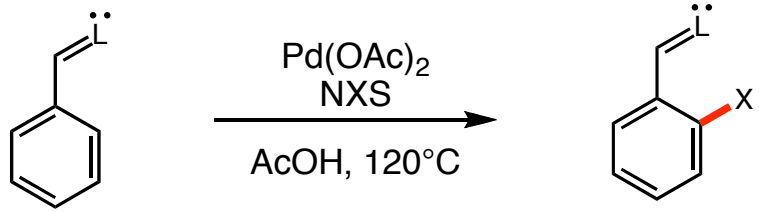


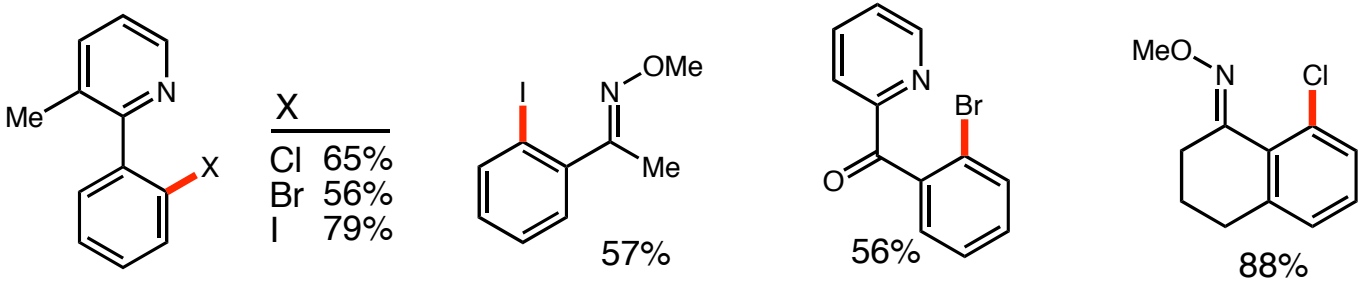
88%

Lyons, T.; Sanford, M. *Chem. Rev.* 2010, *110*, 1147-1169.

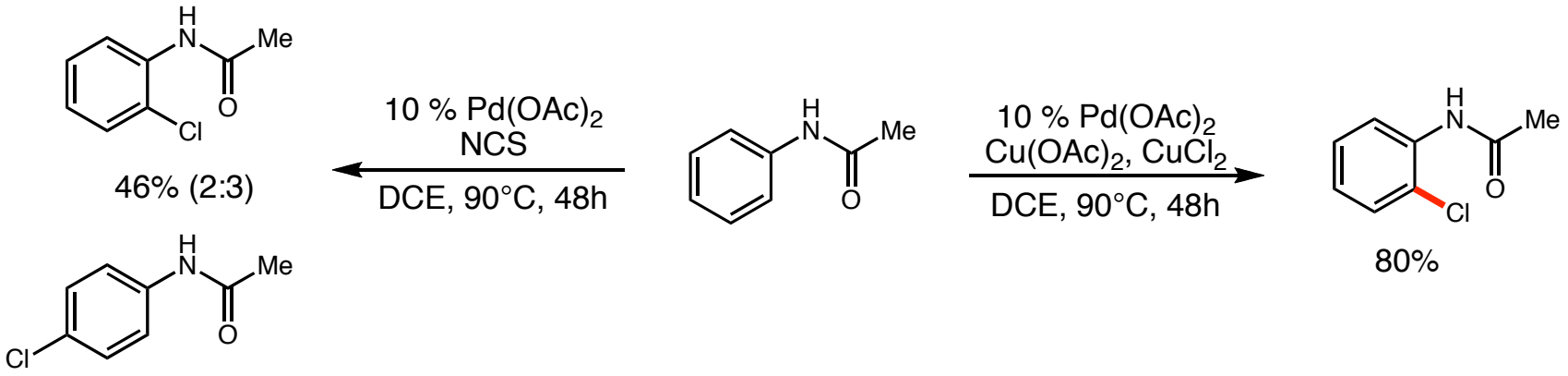
C-H Functionalization

- Halogenation with succinimide reagents





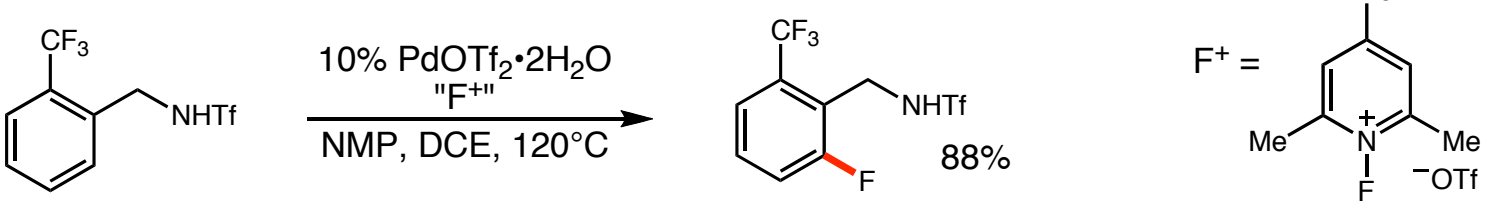
- Less reactive halogen sources give more controlled reactivity



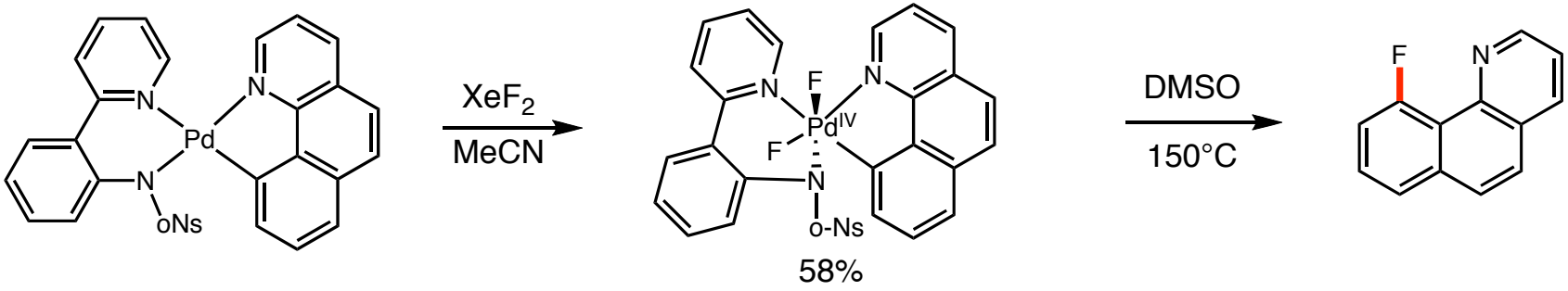
Lyons, T.; Sanford, M. *Chem. Rev.* 2010, *110*, 1147-1169.

C-H Functionalization

- Fluorination with 2,4,6-trimethylpyridinium triflate



- Pd(IV) intermediate isolated and characterized



Wang, X.; Mei, T.; Yu, J. *J. Am. Chem. Soc.* 2009, *131*, 7520.
Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* 2008, *130*, 10060.

C-H Functionalization

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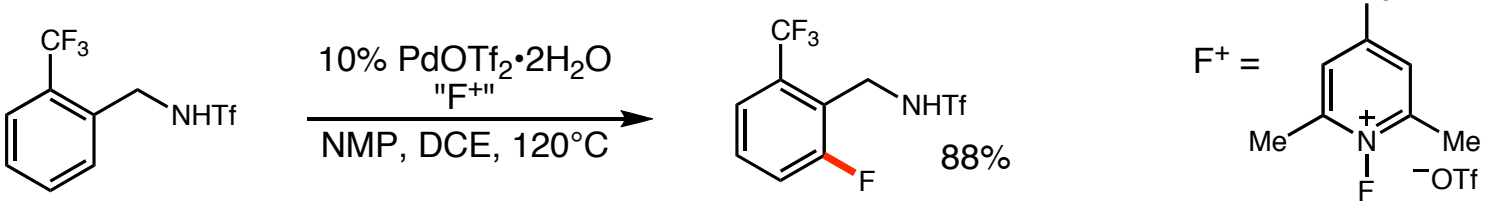

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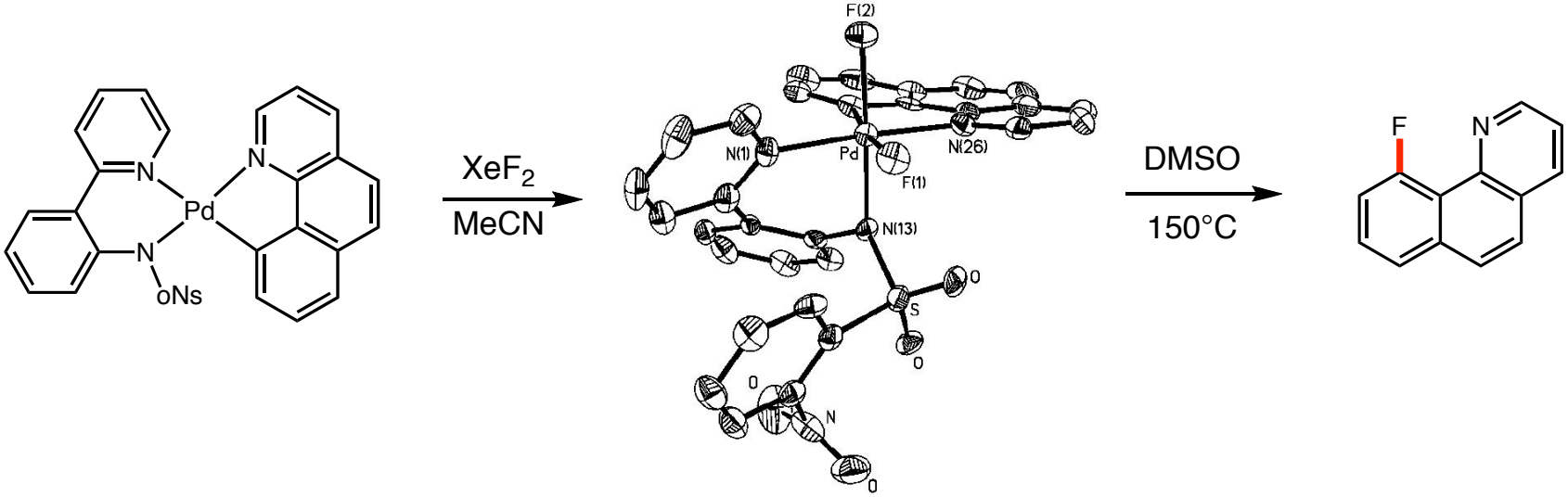
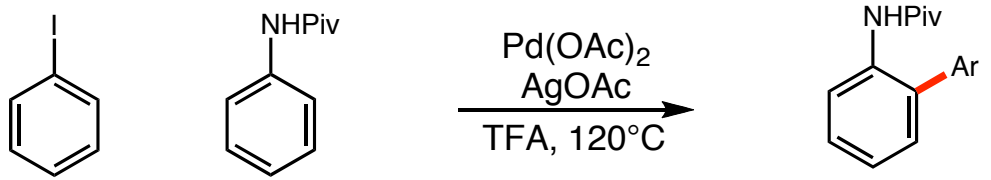
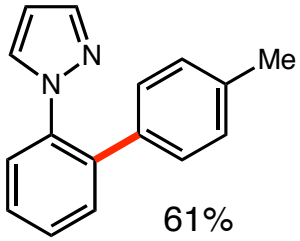


Wang, X.; Mei, T.; Yu, J. *J. Am. Chem. Soc.* 2009, *131*, 7520.
Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* 2008, *130*, 10060.

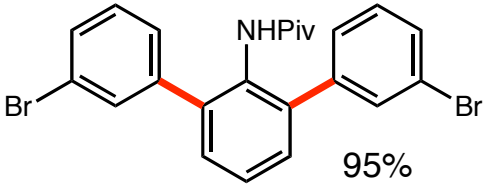
C-H Functionalization

- Arylation with aryl iodides

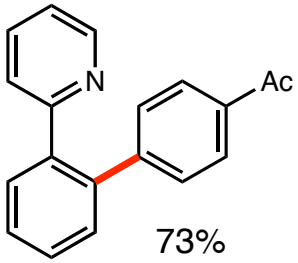




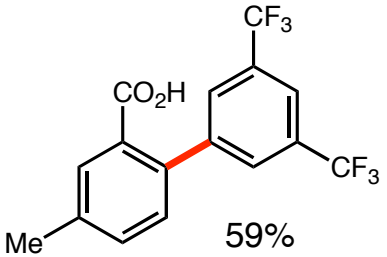
61%



95%

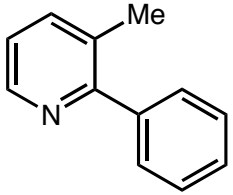


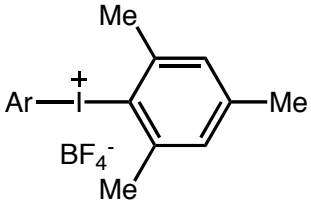
73%

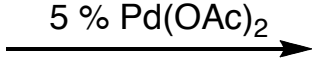


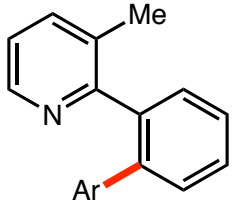
59%

- Faster reactions and higher yield with unsymmetrical mesityl/aryl iodonium salts









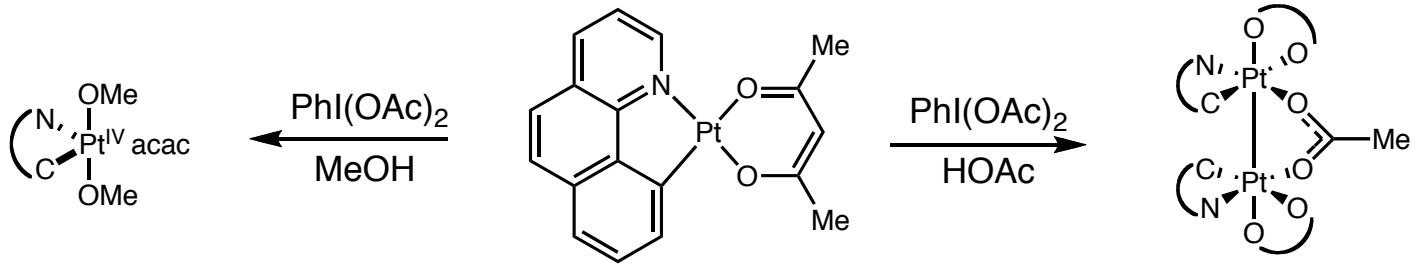
Ar = p-CF_3 87%

Ar = p-OMe 81%

Lyons, T.; Sanford, M. *Chem. Rev.* 2010, *110*, 1147-1169.

Intermediate Pd complexes

- Evidence for a Pd(III) dimer?



Pt(IV)

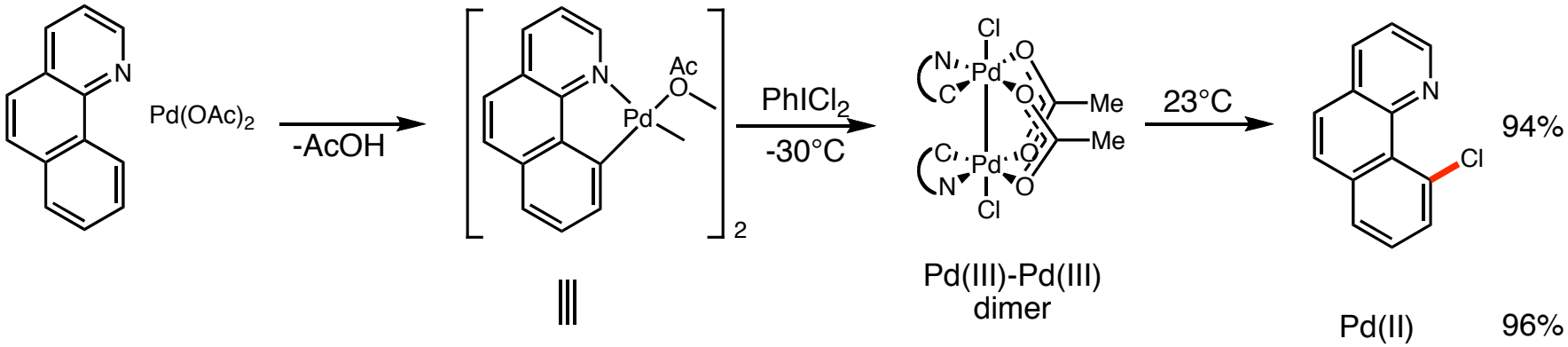
Pt(III)-Pt(III) dimer

- EPR studies show no evidence of Pd(III) under catalytic conditions

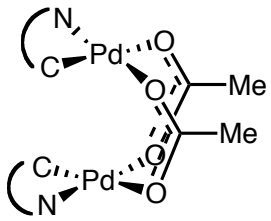
Dick, A.; Kanf, J.; Sanford, M. *Organometallics*. 2005, *24*, 482

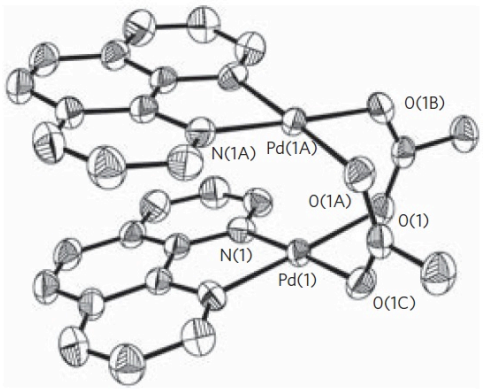
Intermediate Pd complexes

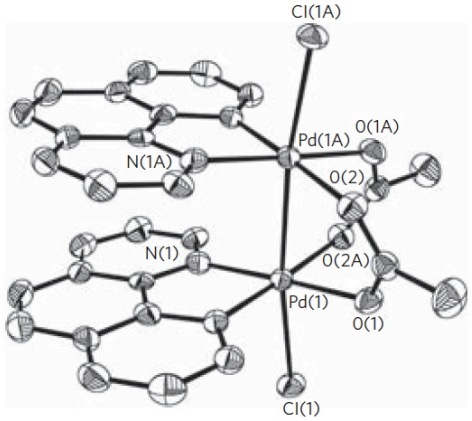
- Pd(III) dimer during chlorination with $PhICl_2$



III







Powers, D.; Ritter, T. *Nat. Chem.* 2009, *1*, 302.

Intermediate Pd complexes

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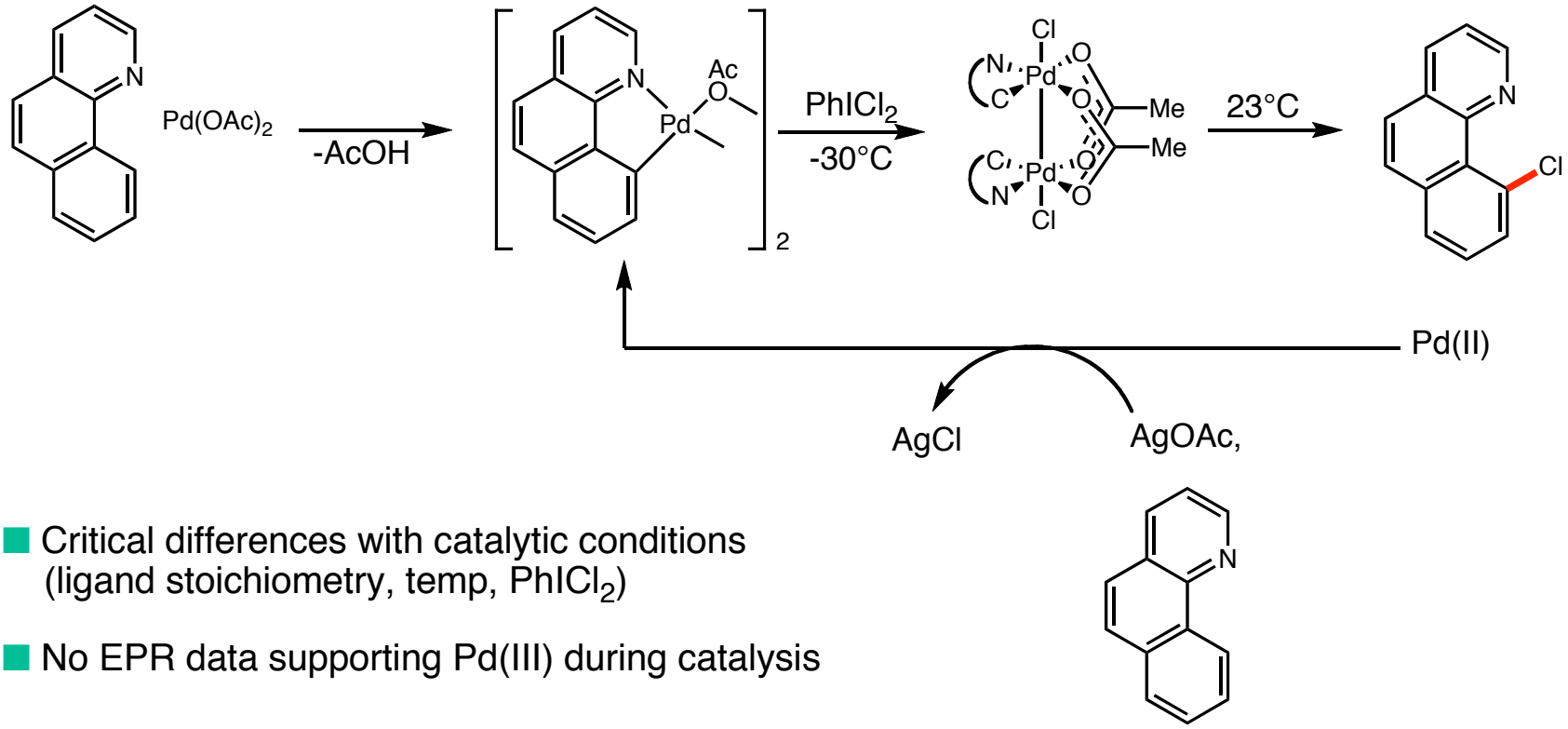
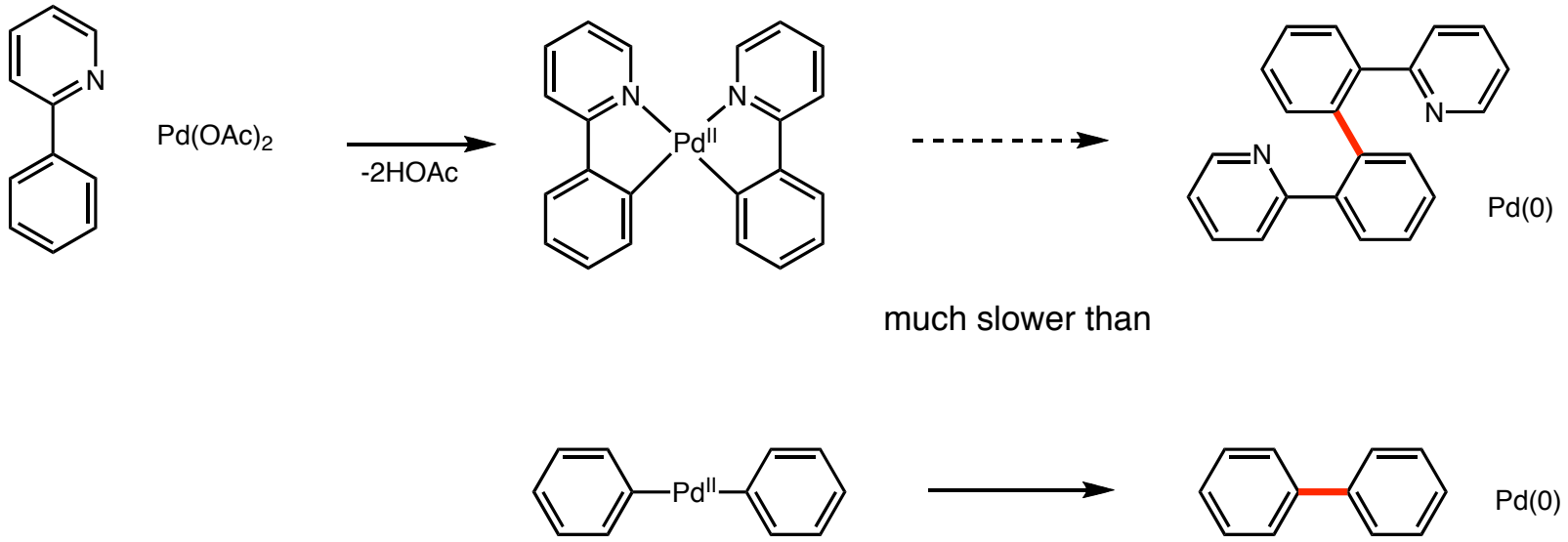


- Critical differences with catalytic conditions (ligand stoichiometry, temp, $PhICl_2$)
- No EPR data supporting Pd(III) during catalysis

Powers, D.; Ritter, T. *Nat. Chem.* 2009, *1*, 302.

Intermediate Pd complexes

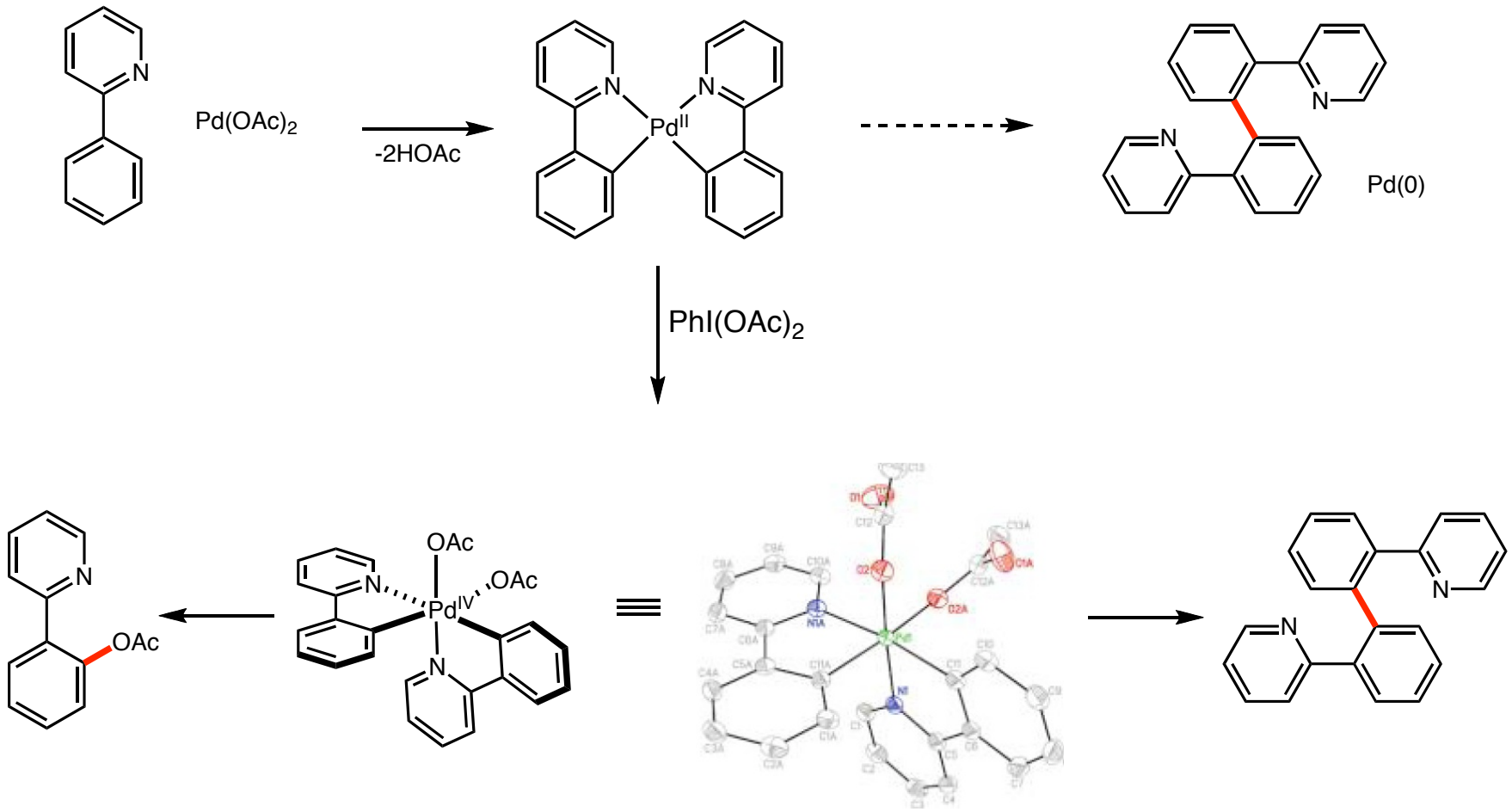
- Invoking Pd(IV)



Racowski, J.; Dick, A.; Sanford, M. *J. Am. Chem. Soc.* 2009, *131*, 10974

Intermediate Pd complexes

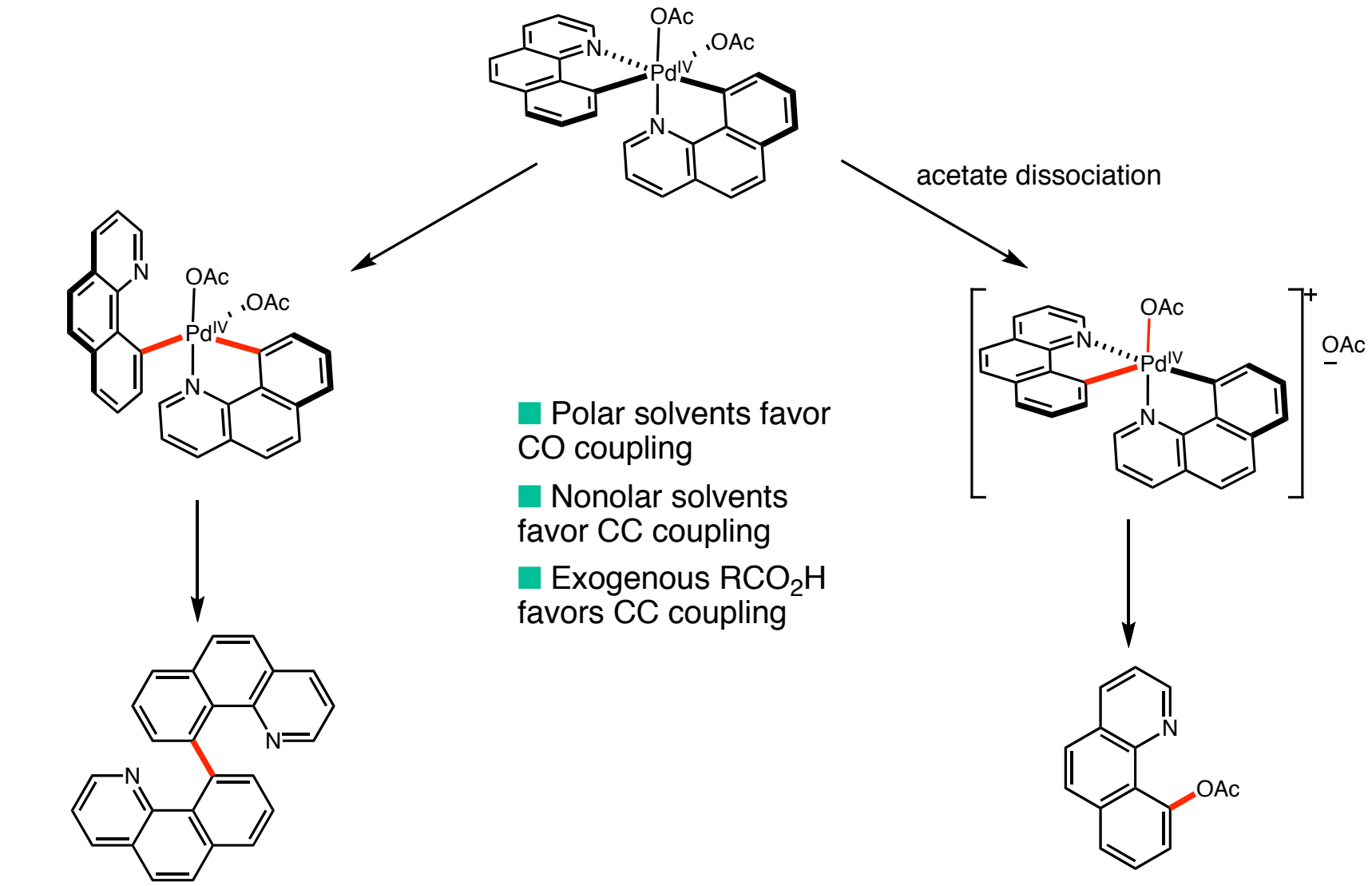
- Invoking Pd(IV)



Racowski, J.; Dick, A.; Sanford, M. *J. Am. Chem. Soc.* 2009, *131*, 10974

Intermediate Pd complexes

- Controlling reductive elimination

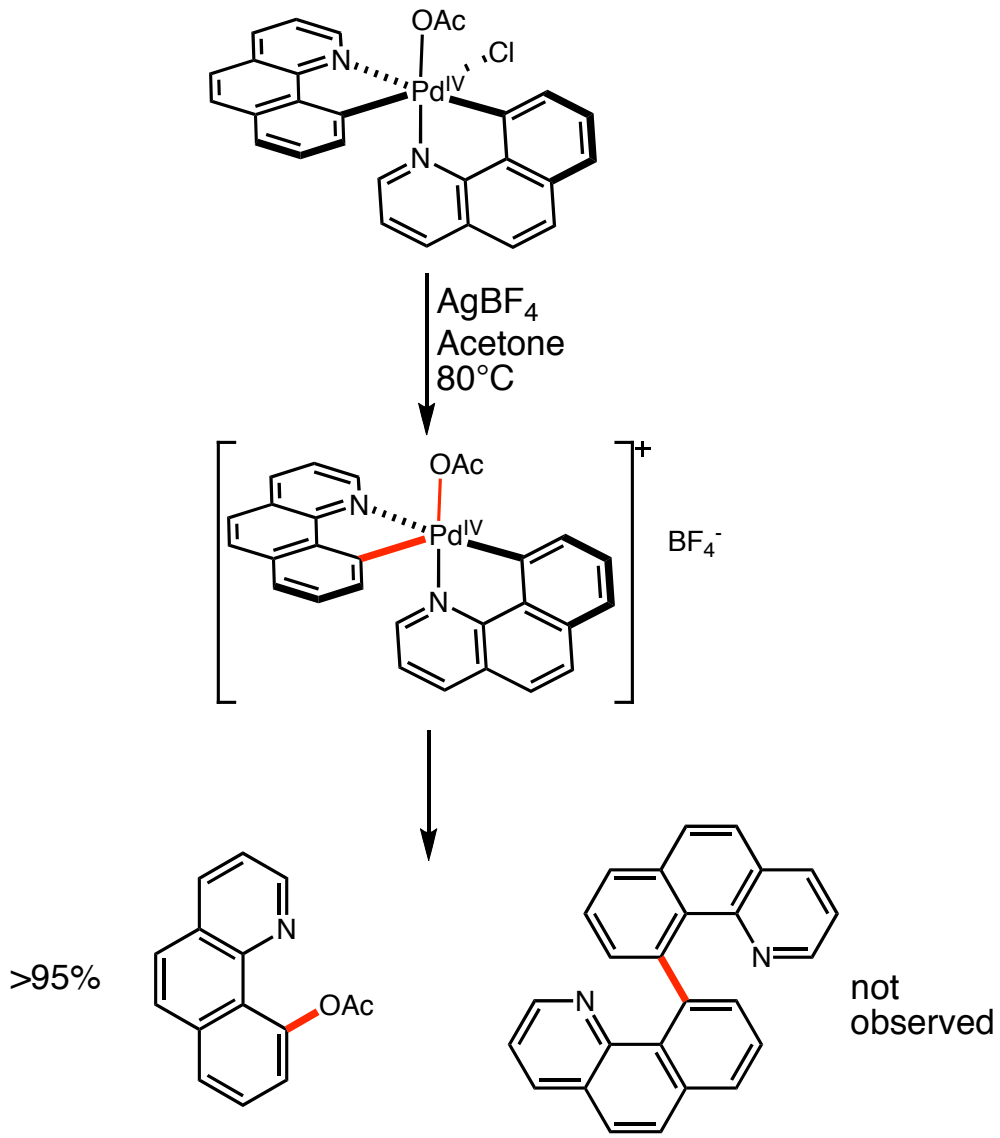


- Polar solvents favor CO coupling
- Nonolar solvents favor CC coupling
- Exogenous RCO_2H favors CC coupling

Racowski, J.; Dick, A.; Sanford, M. *J. Am. Chem. Soc.* 2009, *131*, 10974

Intermediate Pd complexes

- Chloride abstraction experiment

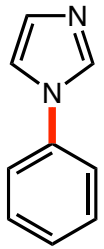


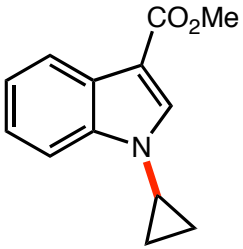
Racowski, J.; Dick, A.; Sanford, M. *J. Am. Chem. Soc.* 2009, *131*, 10974

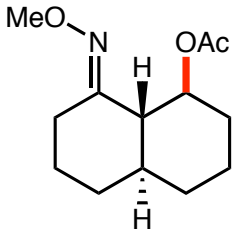
Summary

Value of Cu(III) and Pd(IV) coupling

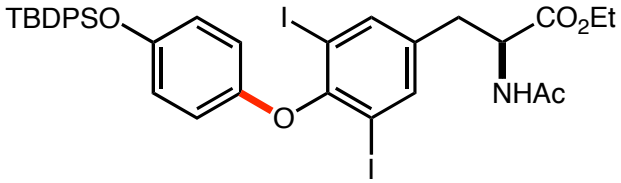
- Substrate scope







- Tolerance of reducible functional groups



- Stability to O_2, H_2O

- Advanced understanding of organometallic chemistry