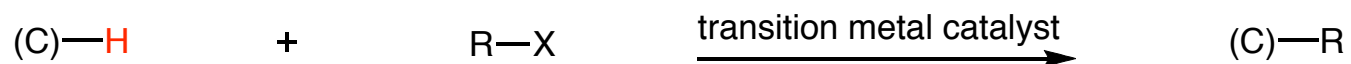


C–H Bond Functionalization

Mark Vander Wal
MacMillan Group Meeting
March 9, 2010

What is C–H Bond Functionalization/Activation?



R = C or heteroatom
X = FG or H

- (C) is sp^2 or sp^3 carbon atom
- (C)—H bond is not a traditionally reactive bond (i.e. $\text{pK}_a > 30\text{-}35$)
- Selectivity is a large issue due to the ubiquitous presence of C–H bonds in all organic molecules

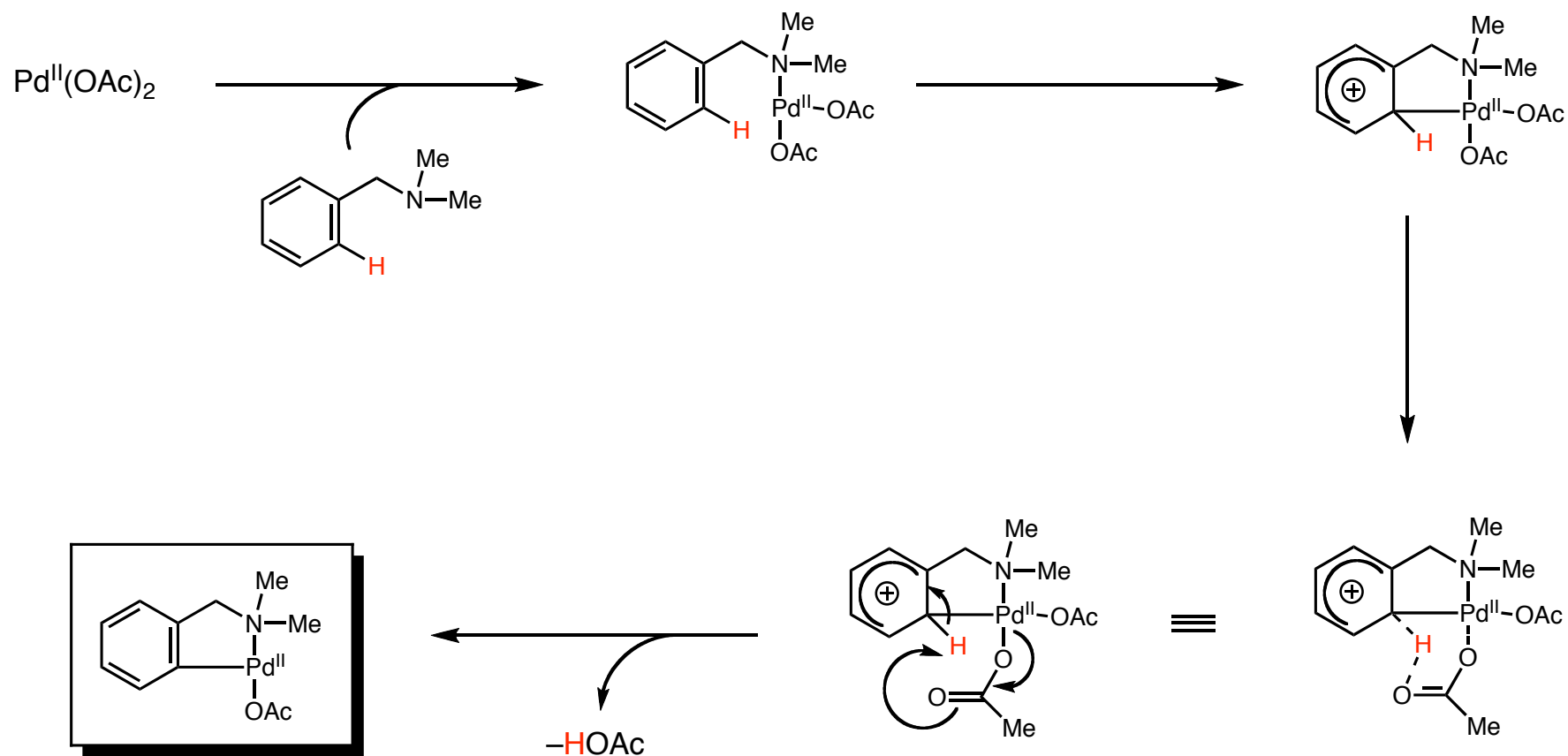
C–H Bond Functionalization/Activation: This Talk

- This talk serves as a very limited survey of the recent literature in C–H bond activation
 - Carbene and nitrene chemistry has been ignored (see Brian Laforteza's talk)
- A great deal of very impressive chemistry has been left out due to the overwhelming amount of recent research in the field of C–H bond activation
 - Selected research presented here is almost exclusively from 2007 and later

A non exhaustive list of recent review articles in the field of C–H bond functionalization

- Thansandote, P.; Lautens, M. *Chem. Eur. J.* **2009**, *15*, 5874.
Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061.
Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.
Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094.
Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242.
Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041.
Godula, K.; Sames, D. *Science* **2006**, *312*, 67.
Joucla, L. Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673.
Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439.
Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.
Hartwig, J. F. *Nature* **2008**, *455*, 314.
West, N. M. Templeton, J. L. *Can. J. Chem.* **2008**, *87*, 288.
Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069.
Garralda, M. A. *Dalton Trans.* **2009**, 3635.
Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949.
Daugulis, O.; Do, J.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074.

Electrophilic Activation Mechanism for C–H Bond Insertion

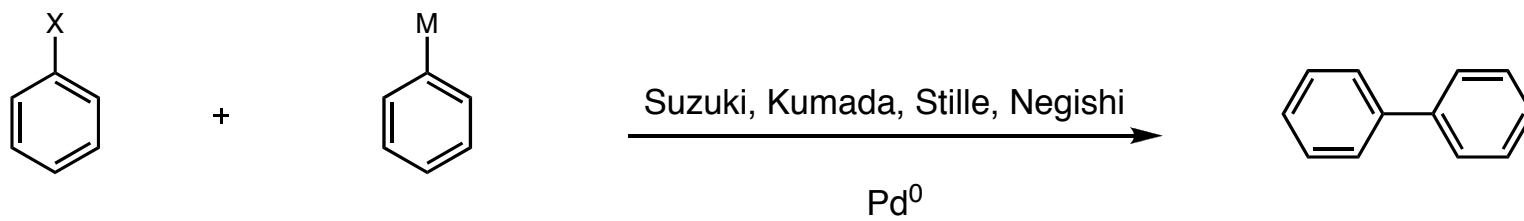


- Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820.
Davies, D. L.; Donald, S. M. A., Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754.
Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403.
Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Chem. Soc., Dalton Trans.* **1985**, 2629.

C–H Bond Arylation

C-H Activation: Arylation of C-H Bonds

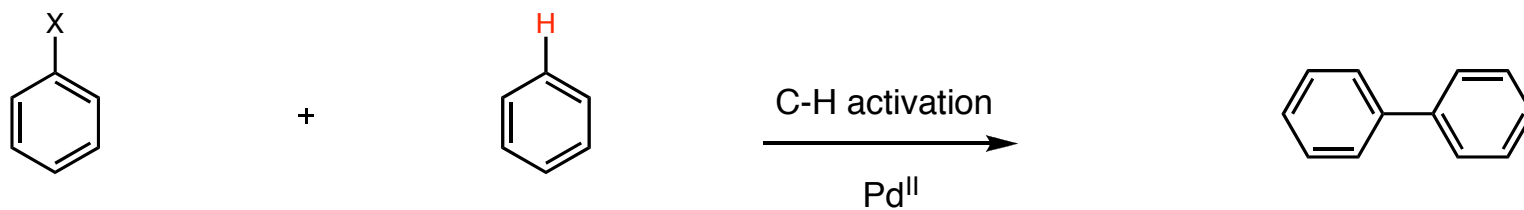
- Reaction methodology mimicking traditional cross coupling reactions



X = Cl, Br, I, OTf

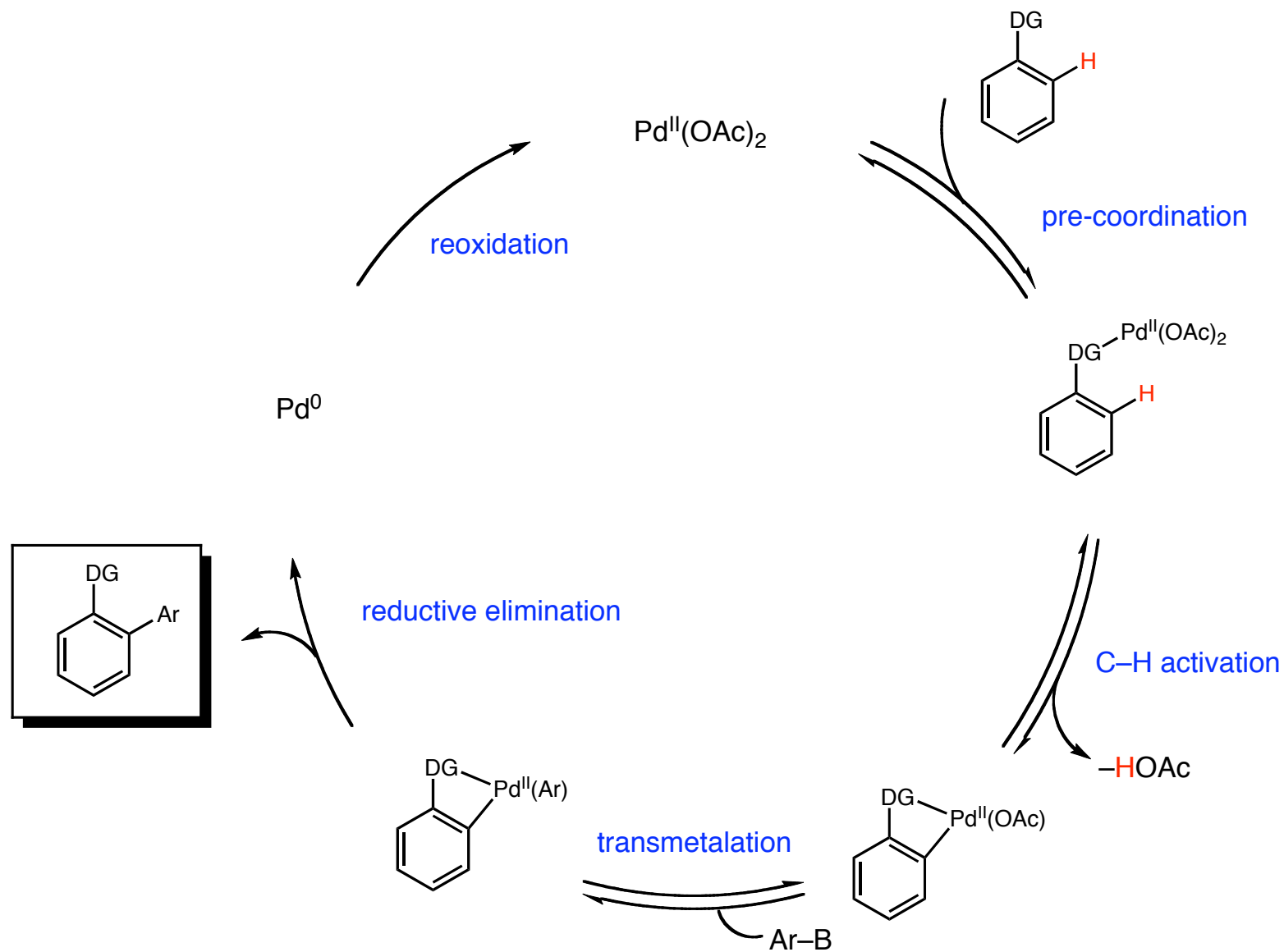
M = Sn, B, Zn, Mg

- C-H bond activation strategy replaces one or two of the preactivation requirements



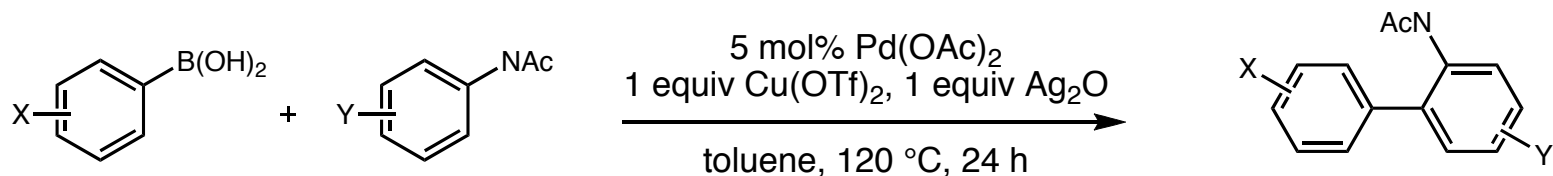
X = Cl, Br, I, OTf, B, Sn, H

Directed Arylations: Pd⁰/Pd^{II} Pathway



Directed Arylations: Pd⁰/Pd^{II} Pathway

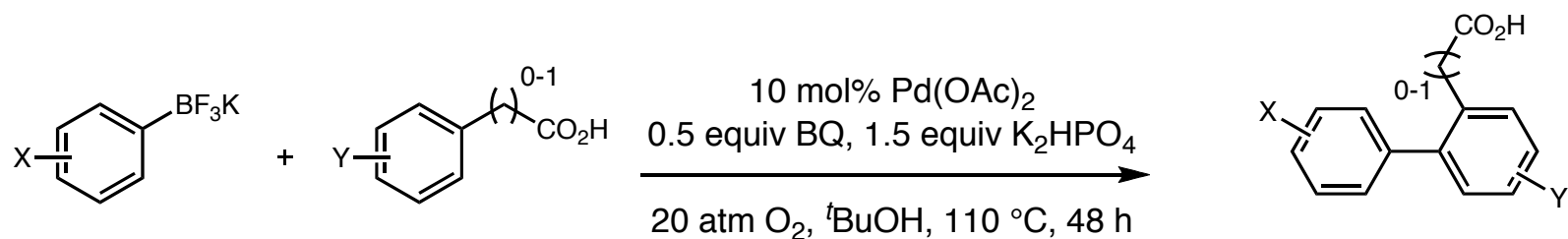
■ Shi's arylation using amides as a directing group



24 examples 31-92% yield

Shi, Z.; Li, B.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 5554.

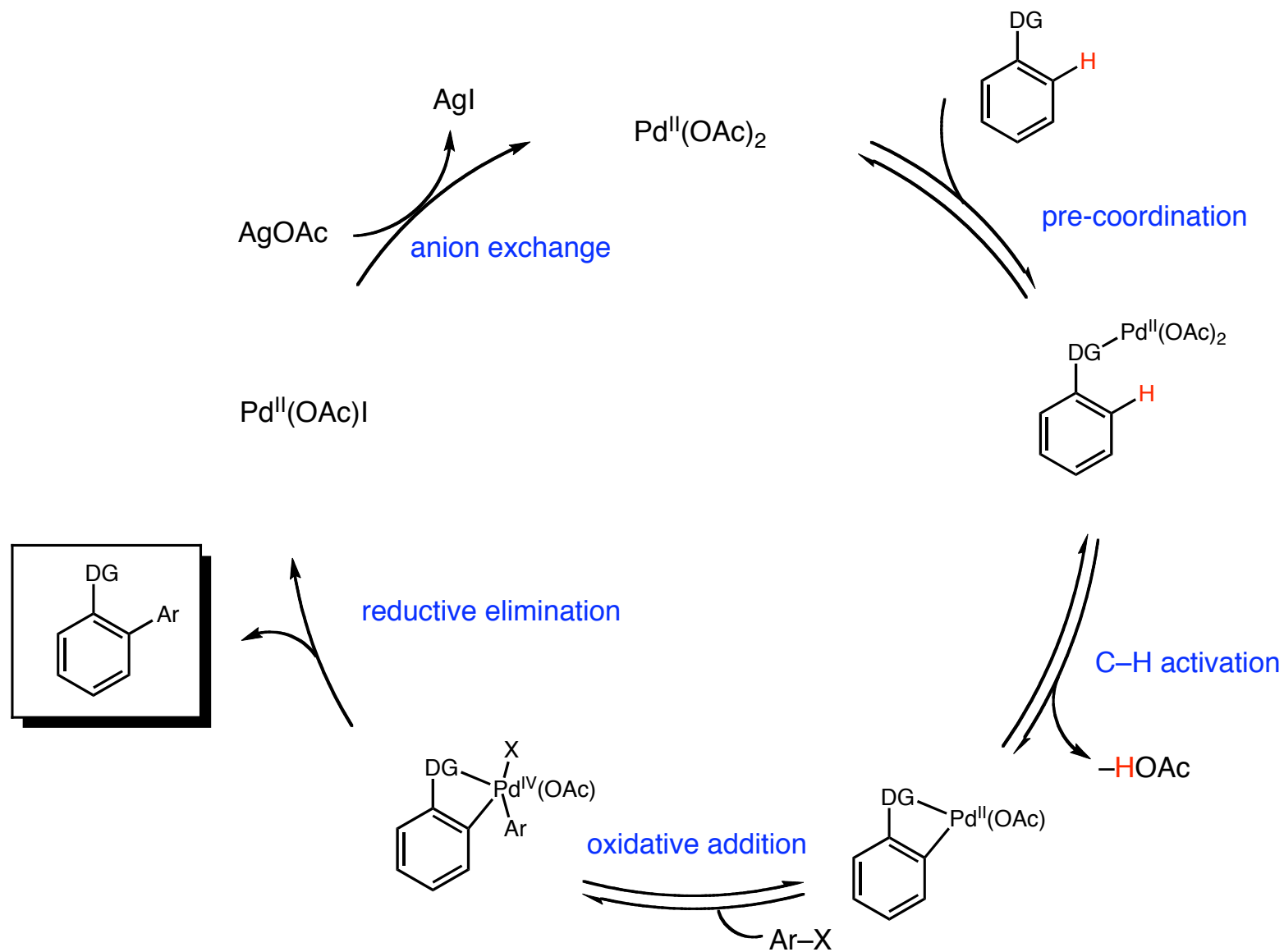
■ Yu's arylation using carboxylic acids as the directing group



24 examples 31-92% yield

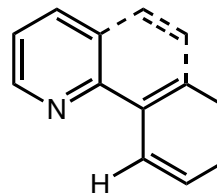
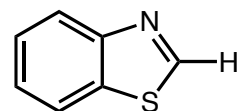
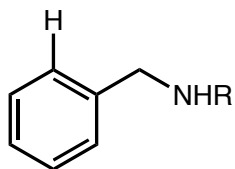
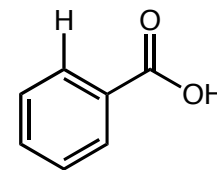
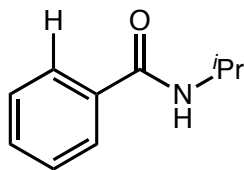
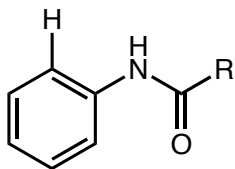
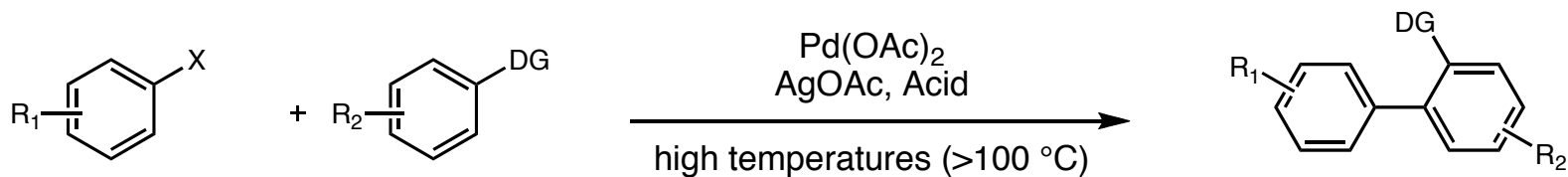
Wang, D.-H.; Mei, T.-S.; Yi, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676.

Directed Arylations: Pd^{II}/Pd^{IV} Pathway



Directed Arylations: Pd^{II}/Pd^{IV} Pathway

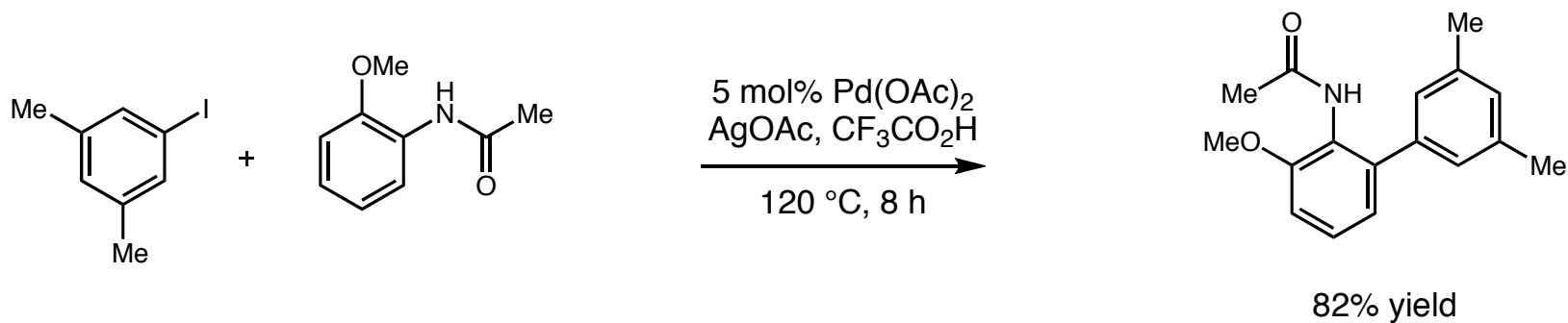
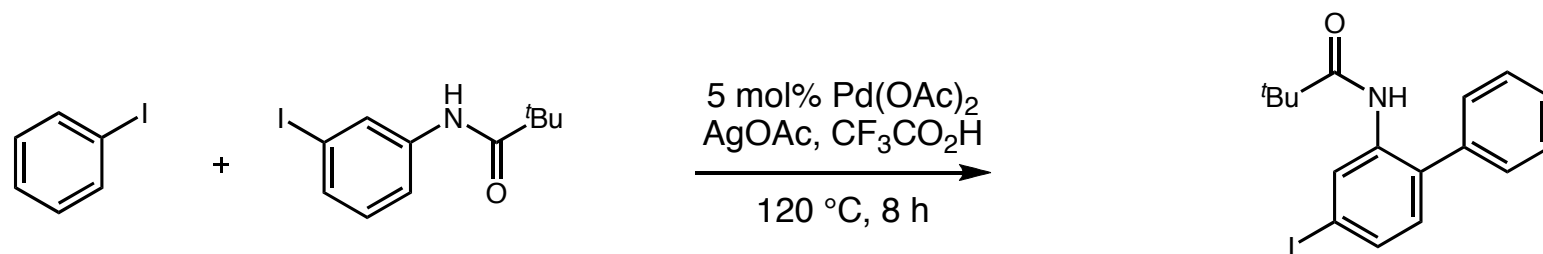
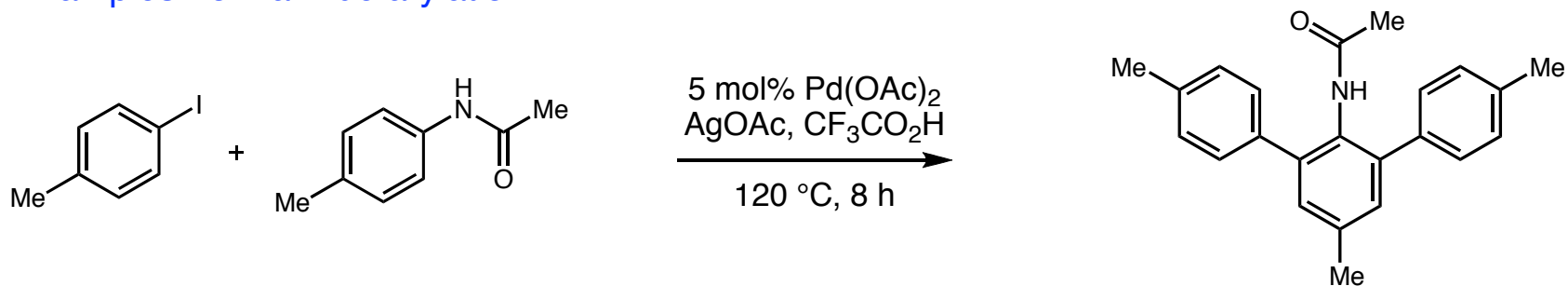
- Daugulis has published similar reactions using a variety of directing groups



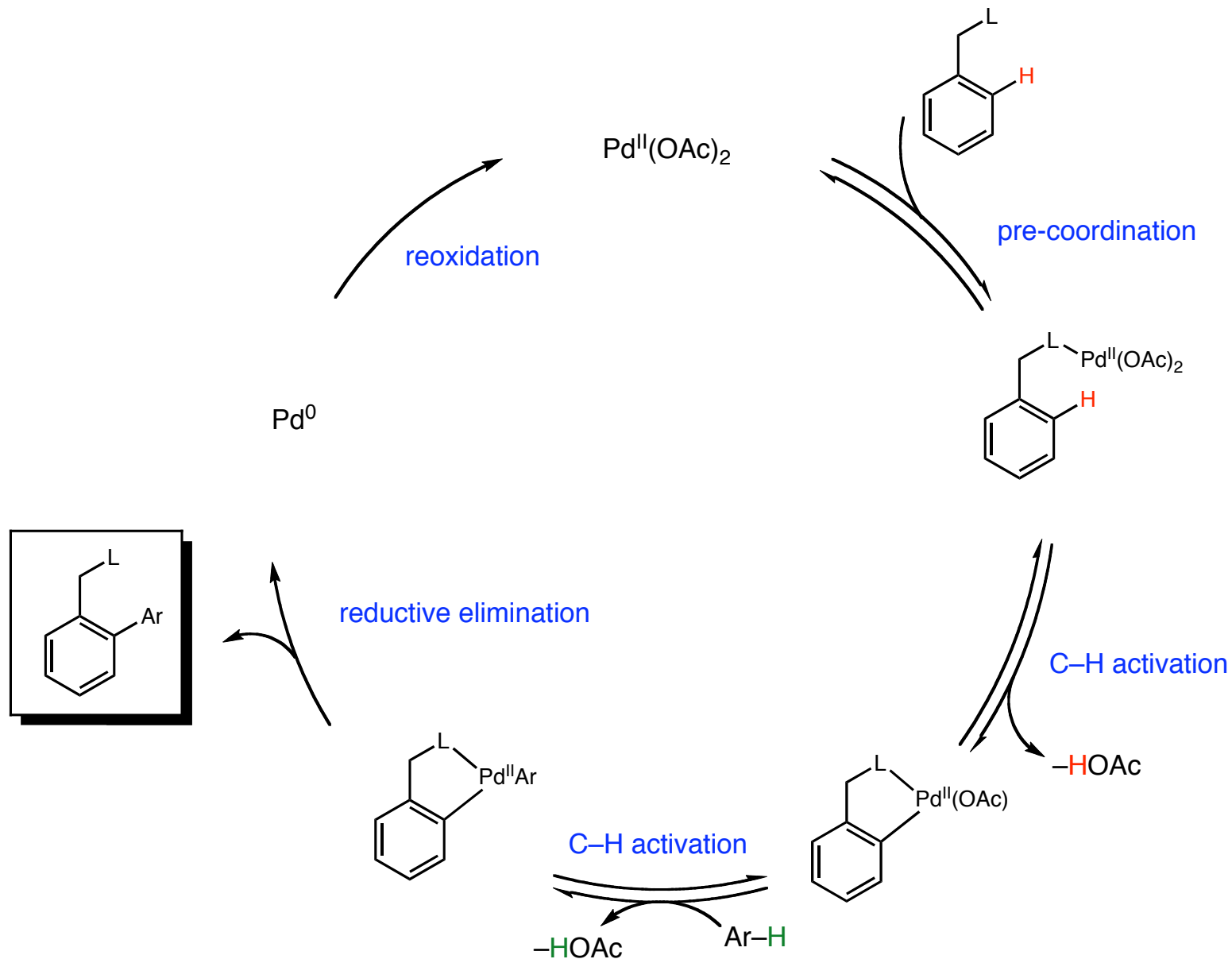
- Generally high yielding (>70% yield)
- Diarylation observed if no *ortho* or *meta* substituent is present

Directed Arylations: Pd^{II}/Pd^{IV} Pathway

■ Examples from anilide arylation

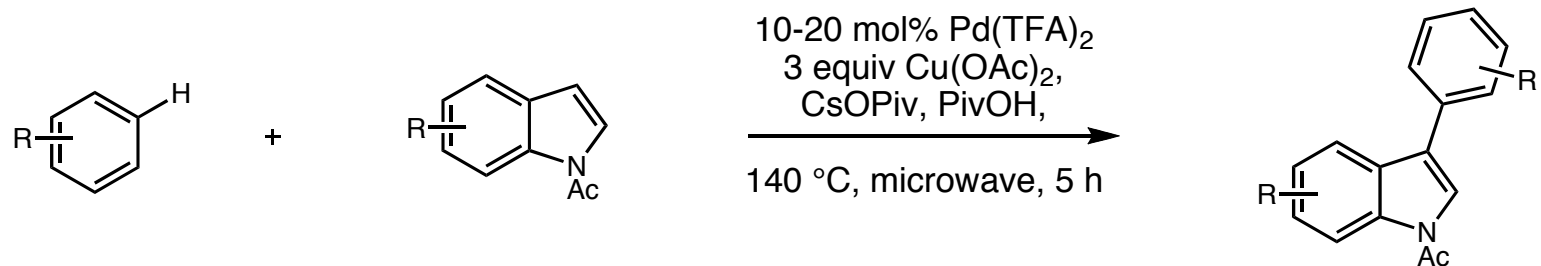


Directed Arylations: Cross-Coupling of C-H Substrates



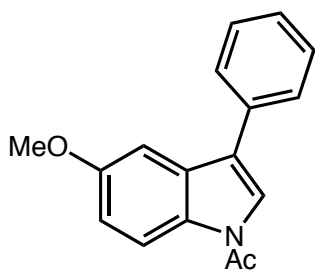
Directed Arylations: Cross-Coupling of C–H Substrates

■ An early example using acetate protected indoles

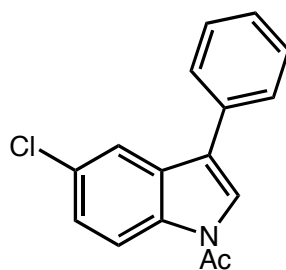


30 equiv

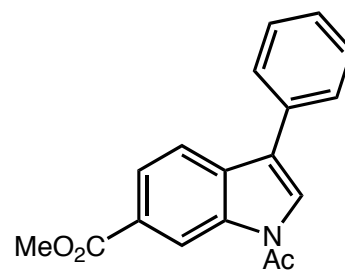
9 examples 42–84% yield



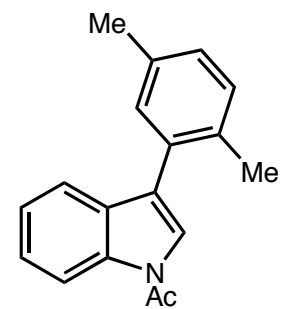
84%



63%



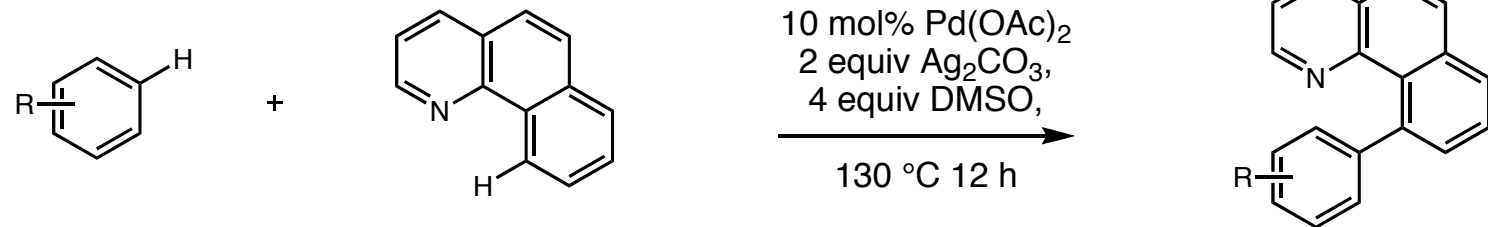
54%



45%

Directed Arylations: Cross-Coupling of C–H Substrates

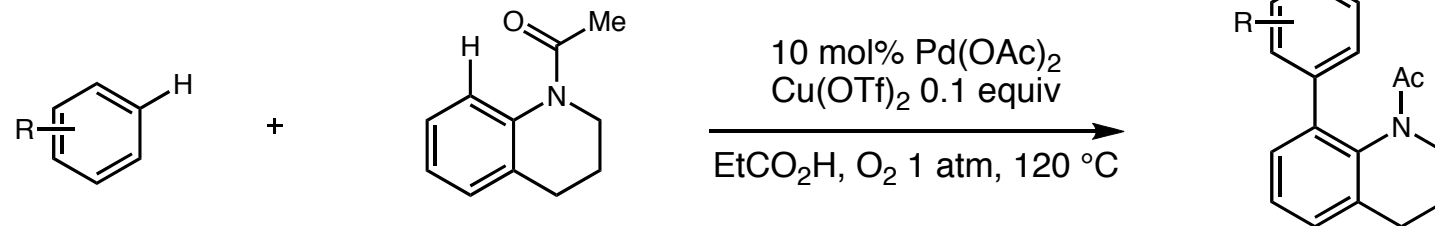
Two recent examples



65-100 equiv

11 examples 49% to 93% yield

Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904.

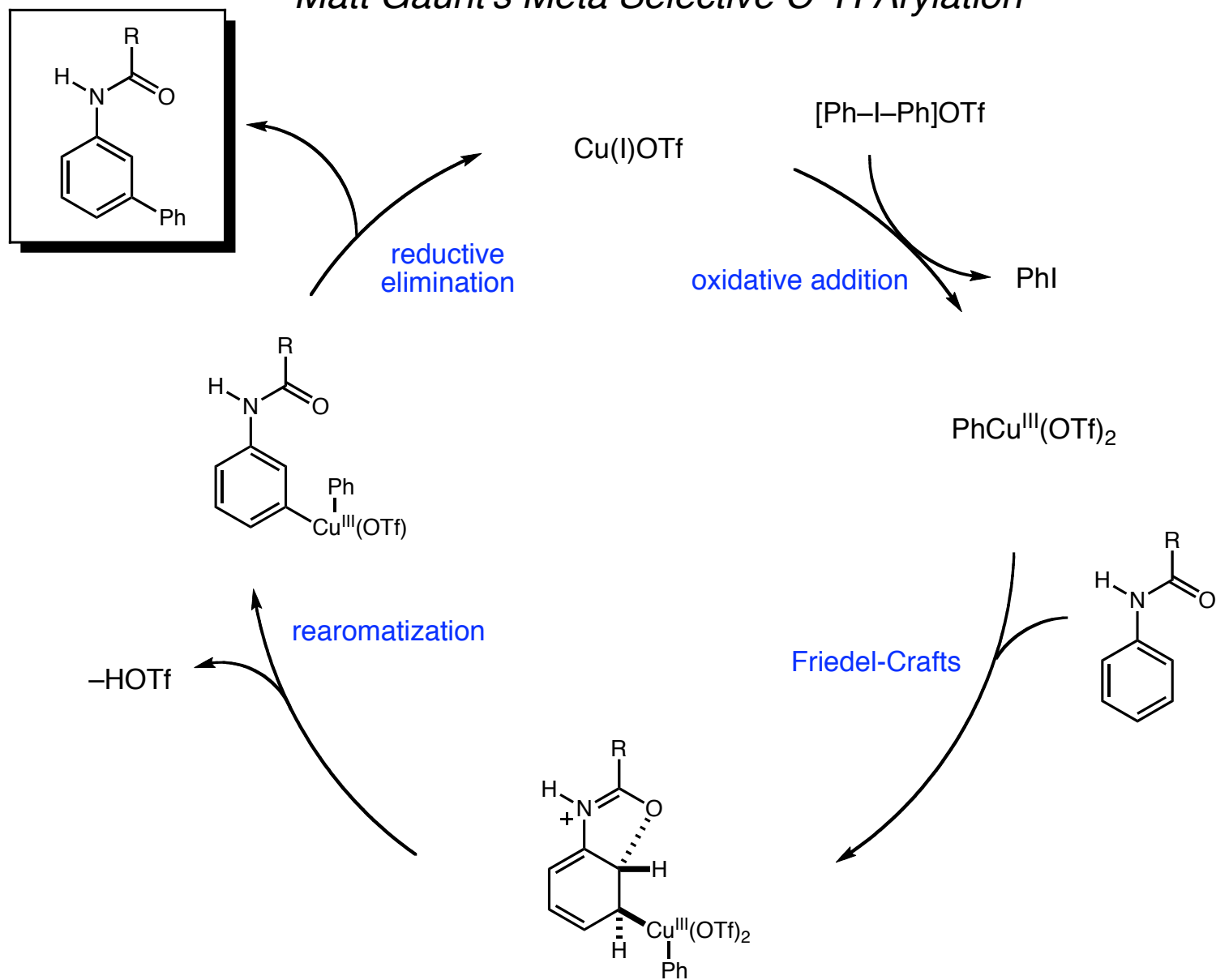


cosolvent

8 examples 43% to 78% yield

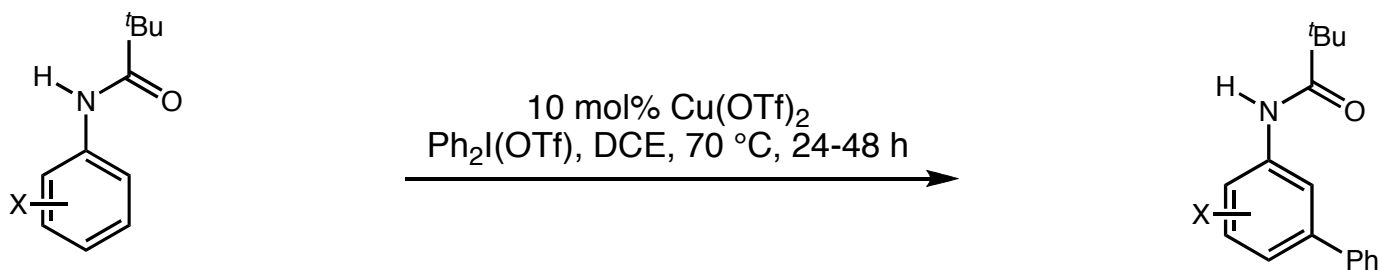
Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2008**, *47*, 1115.

Matt Gaunt's Meta Selective C-H Arylation

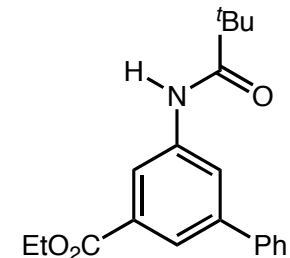
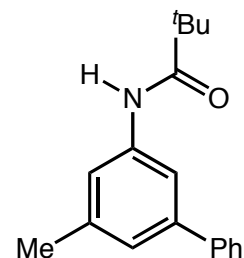
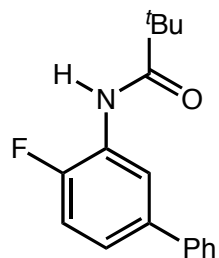
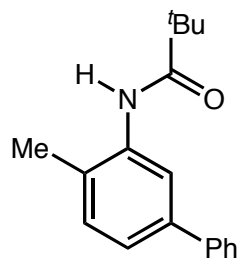


Matt Gaunt's Meta Selective C–H Arylation

■ Reaction and substrate scope

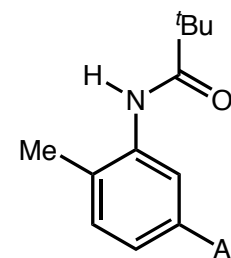
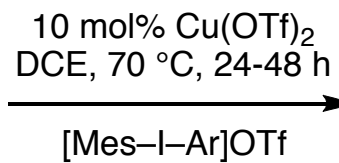
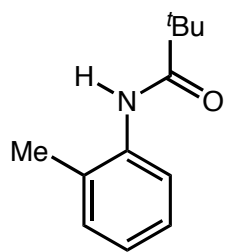


18 examples
11-93% yield

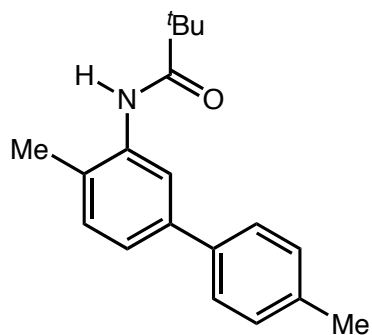


Matt Gaunt's Meta Selective C–H Arylation

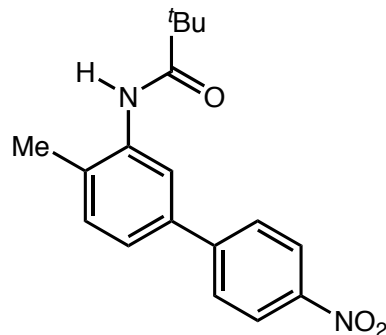
■ Reaction and substrate scope



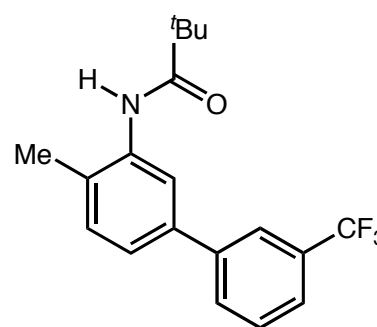
8 examples
44-82% yield



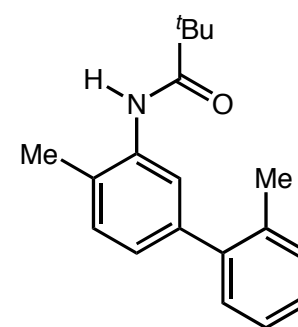
82% yield



60% yield



70% yield

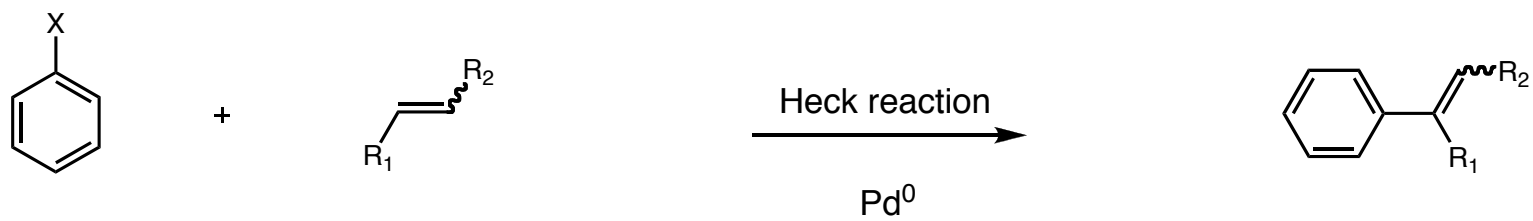


44% yield

C–H Bond Olefination

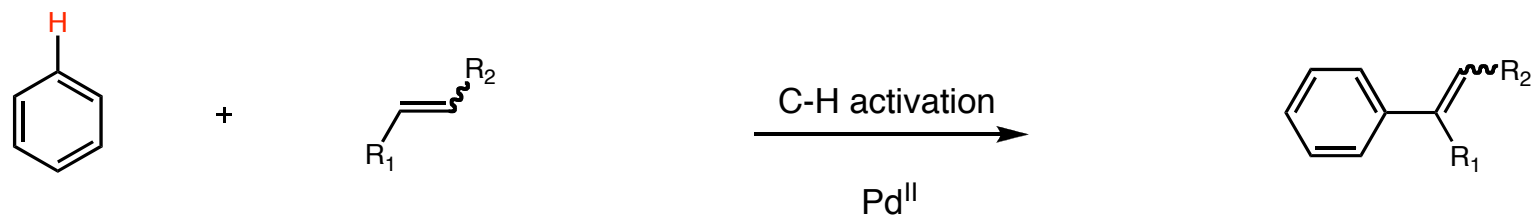
C–H Activation: Olefination of C–H Bonds

■ Reaction methodology mimicking traditional Heck reaction

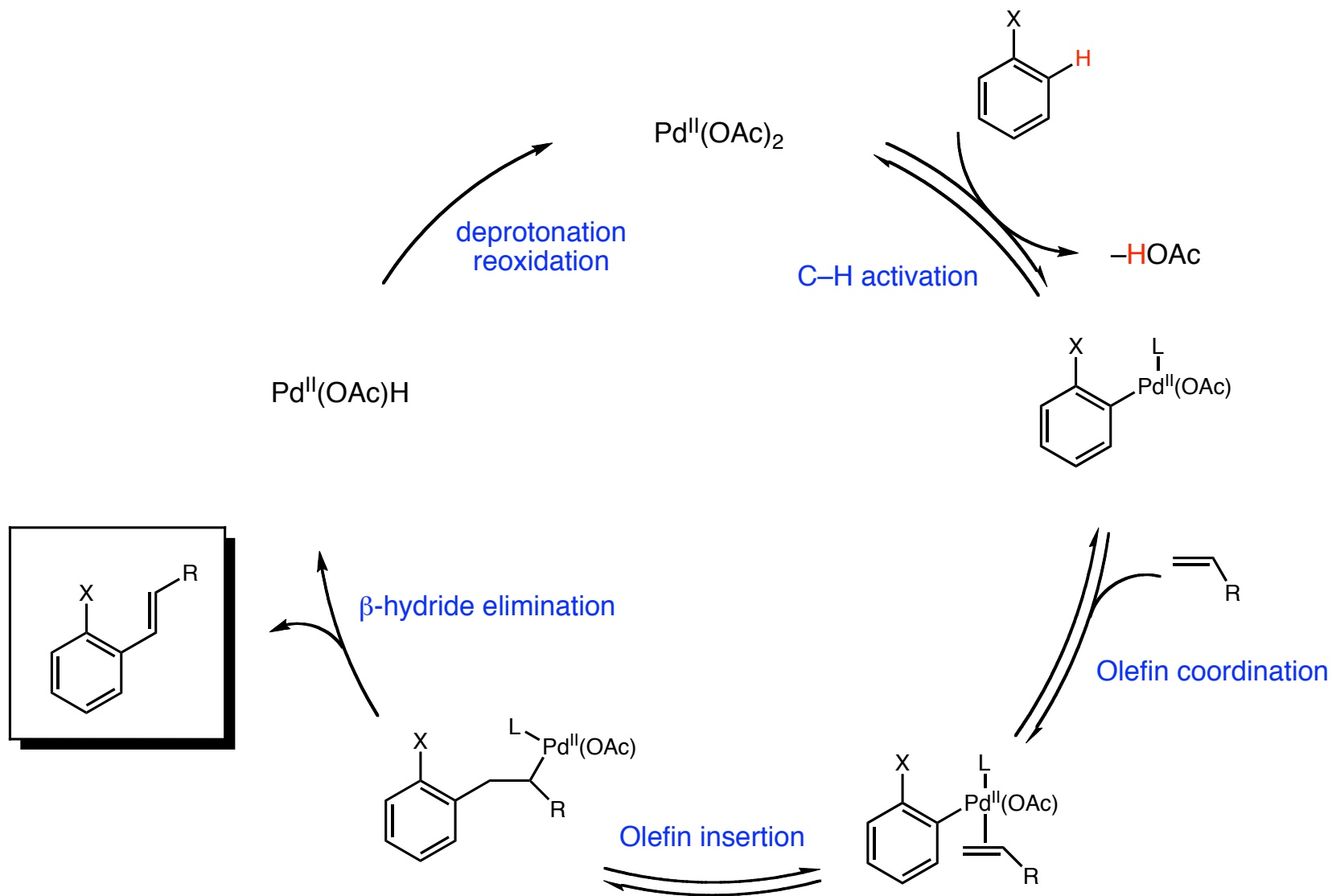


X = Cl, Br, I, OTf

■ C–H bond activation strategy replaces halogen functional group

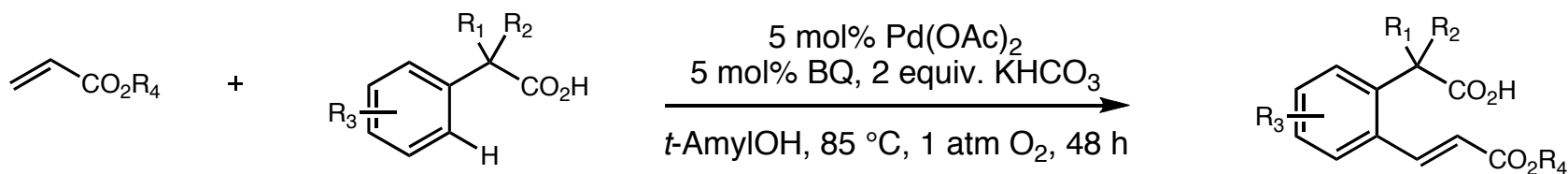


Olefination Reactions via Aryl C-H Activation



Olefinations Reactions via Aryl C–H Activation

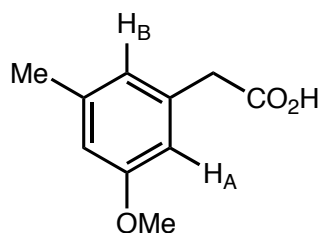
■ Olefination via carboxylic acid directing group



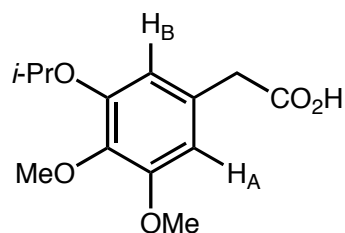
2 equiv

20 examples 73% to 98% yield

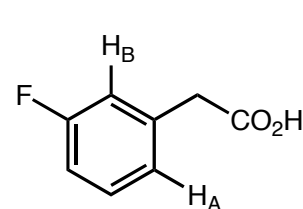
■ Amino acid ligands enable selectivity for unsymmetrical aryl substrates



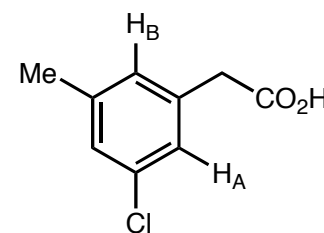
Formyl-Ile ligand
75% yield 20:1 A:B



Boc-Ile ligand
86% yield 23:1 A:B



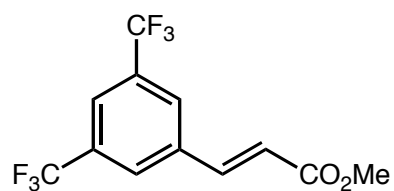
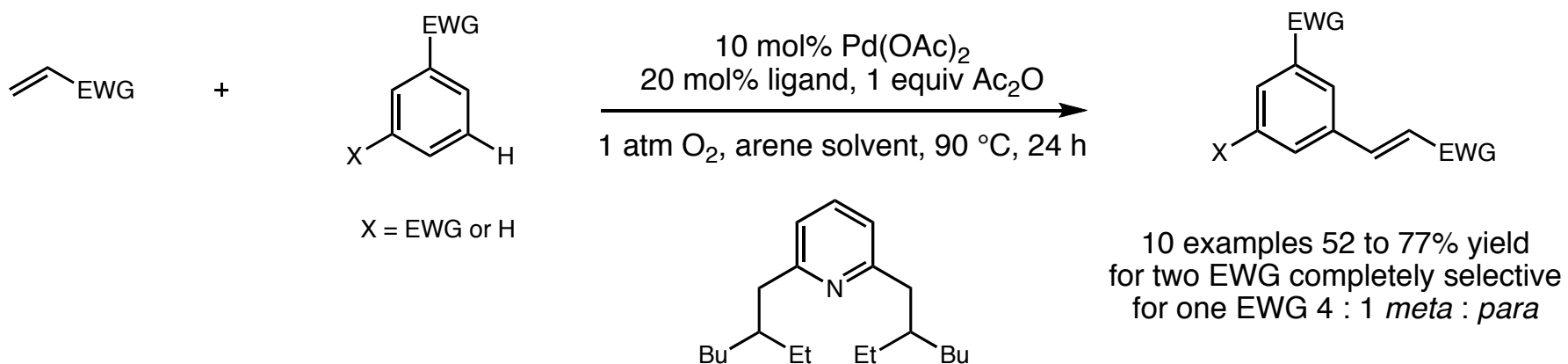
Formyl-Ile ligand
77% yield 3.5:1 A:B



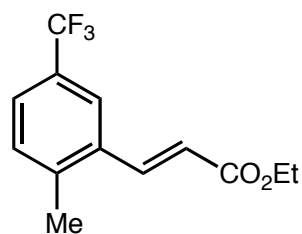
Formyl-Ile ligand
50% yield 4.7:1 A:B

Olefination Reactions via Aryl C–H Activation

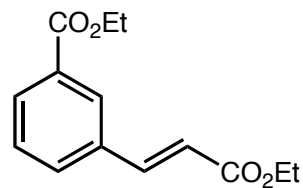
- Olefination without a directing group shows selectivity for *meta* functionalization relative to EWG's



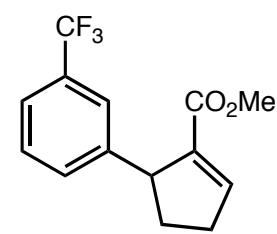
62% yield



68% yield



70% yield
4:1 *m* : *p*

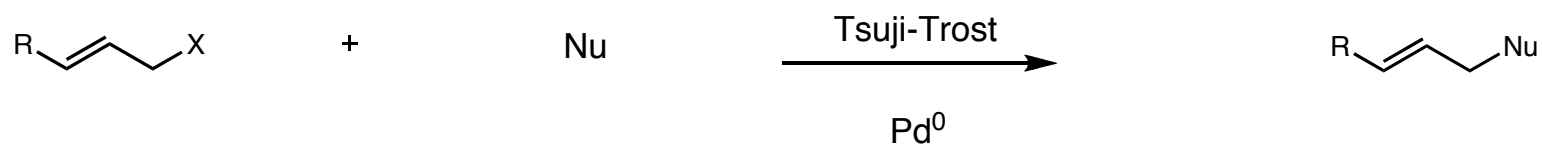


71% yield
4:1 *m* : *p*

Allylic C–H Bond Functionalization

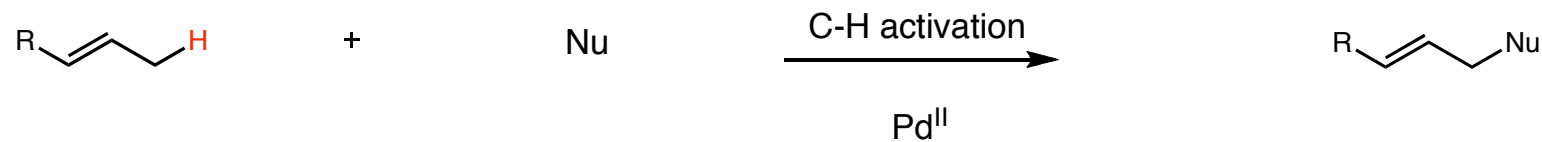
C-H Activation: Π -Allyl Type Functionalization

- Reaction methodology mimicking traditional π -allyl reaction



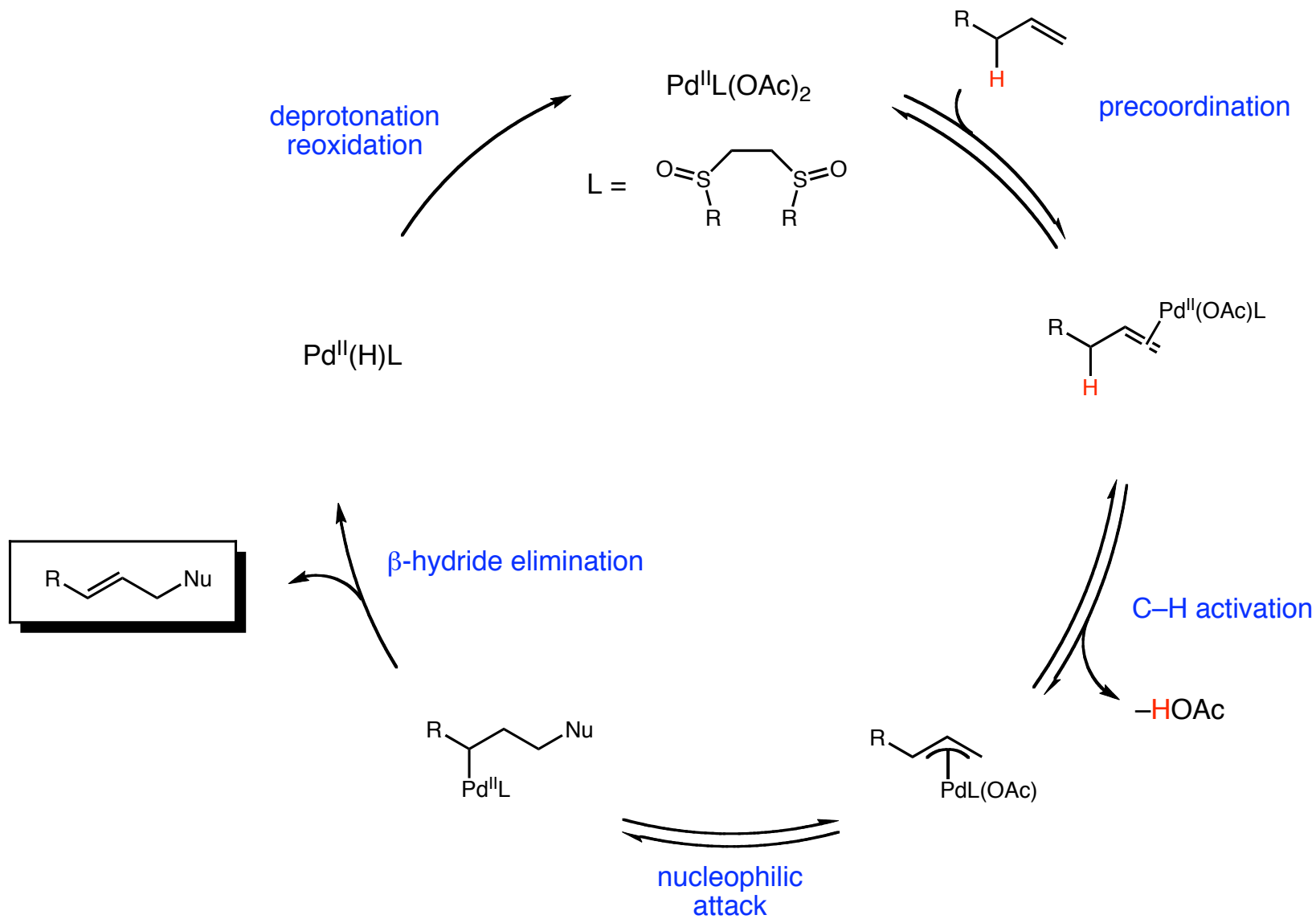
X = OH, OCOR, OCO₂R etc.

- C-H bond activation strategy replaces functional group



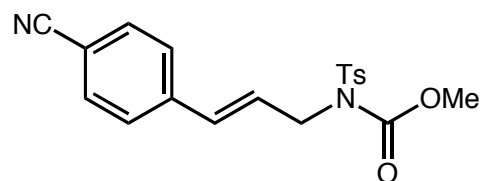
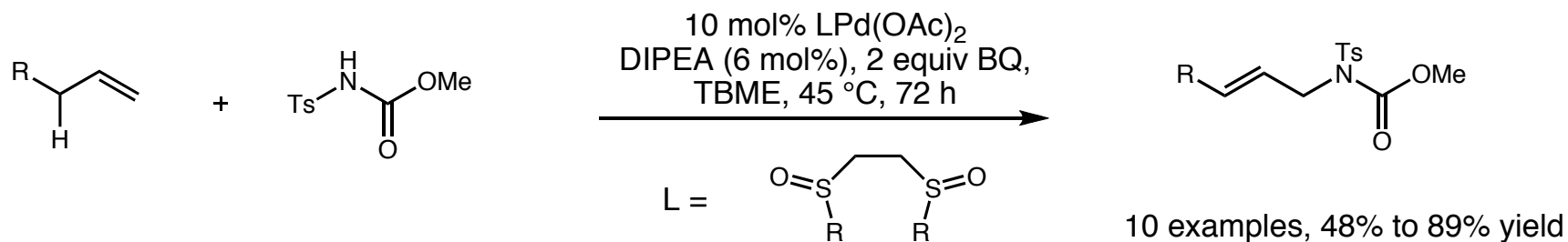
Christina White's Allylic Functionalizations

■ Intermolecular amination and alkylation

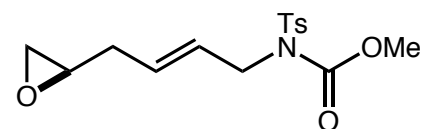


Christina White's Allylic Functionalizations

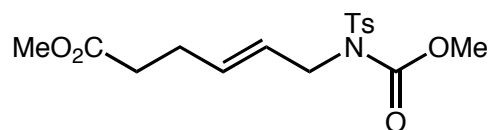
■ Intermolecular amination reaction and scope



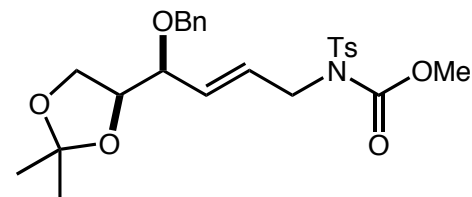
79% yield



48% yield



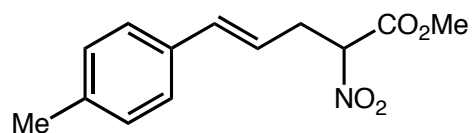
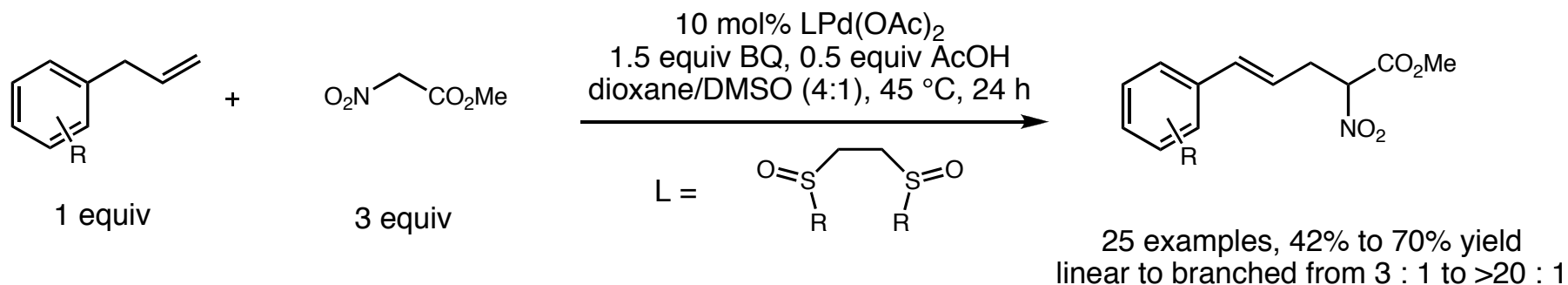
61% yield



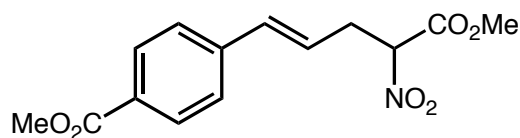
76% yield

Christina White's Allylic Functionalizations

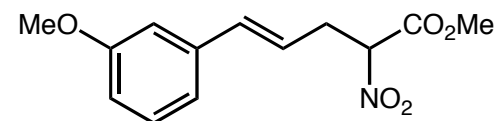
■ Intermolecular alkylation reaction and scope



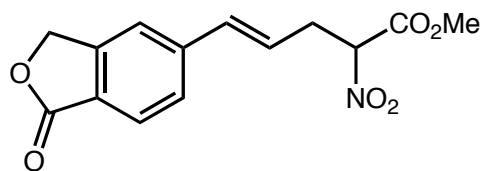
61% yield, 3 : 1 L : B



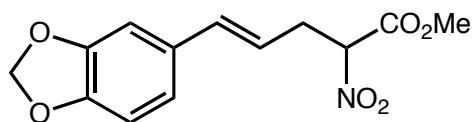
61% yield, 10 : 1 L : B



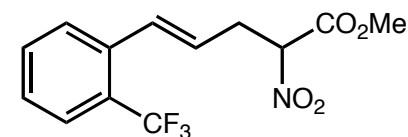
58% yield, 5 : 1 L : B



70% yield, 15 : 1 L : B



56% yield, 3 : 1 L : B

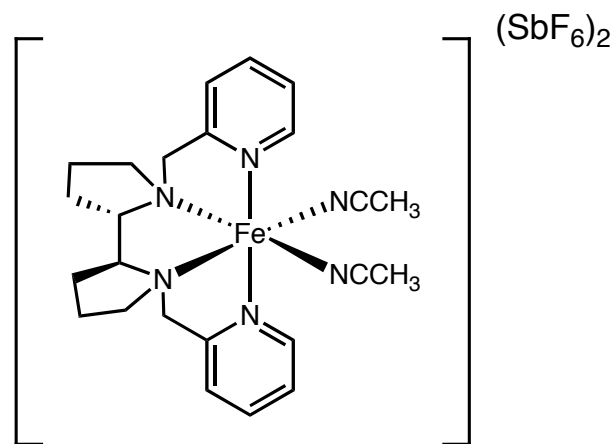
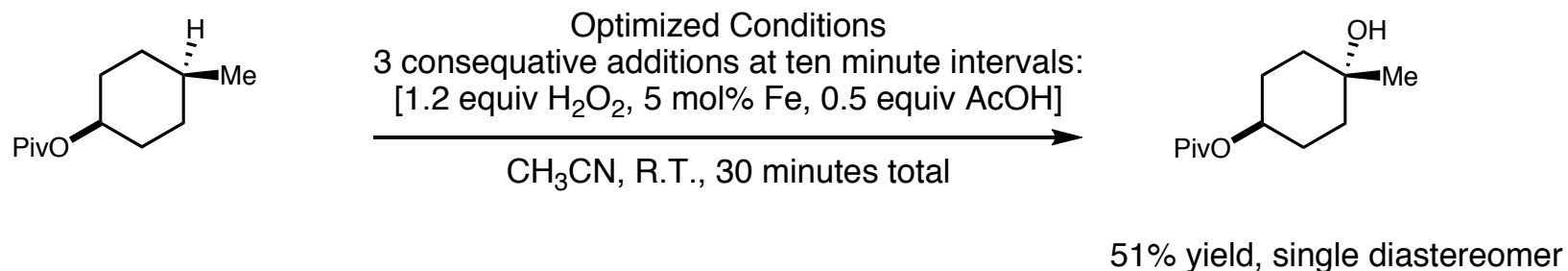


59% yield, >20 : 1 L : B

Unactivated C–H Bond Oxidation

Christina White's Iron Catalyzed Oxidations of Unactivated sp^3 C-H Bonds

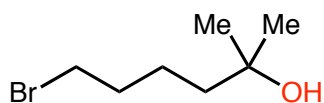
- Tertiary methyne protons are preferentially oxidized to the corresponding alcohols



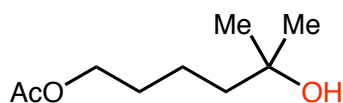
Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783.
Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566.

Christina White's Iron Catalyzed Oxidations of Unactivated sp^3 C-H Bonds

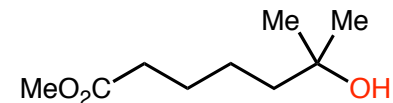
■ Remote functionality tolerated but has effect on reaction efficiency



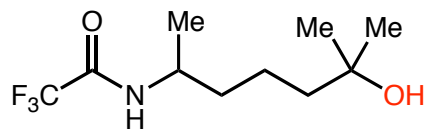
46% (26% rsm)



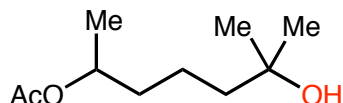
53% (43% rsm)



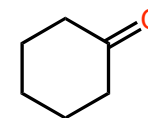
60% (18% rsm)



43% (33% rsm)

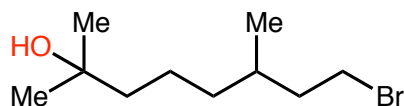


52% (21% rsm)

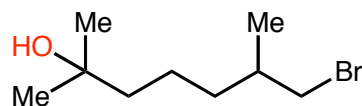


92% (GC yield)

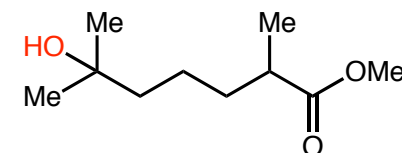
■ EWG promote selectivity for the more remote tertiary C-H bond



39% (32% rsm) 9:1 regioselectivity



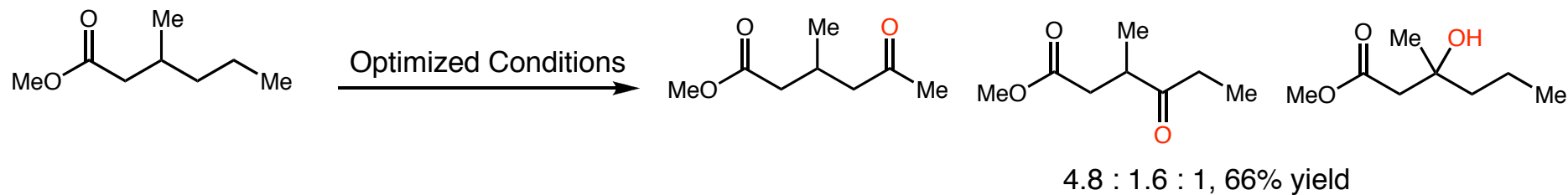
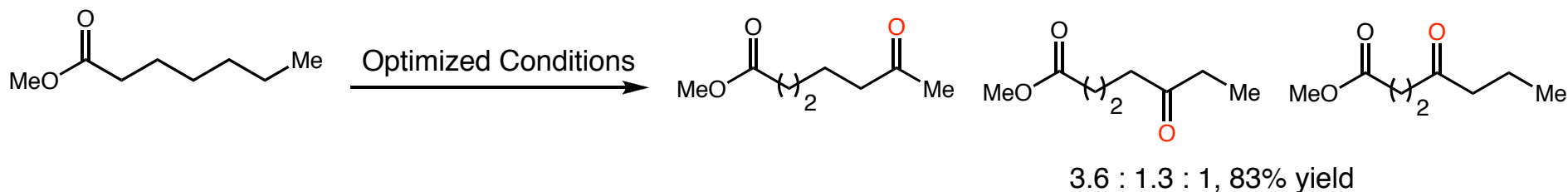
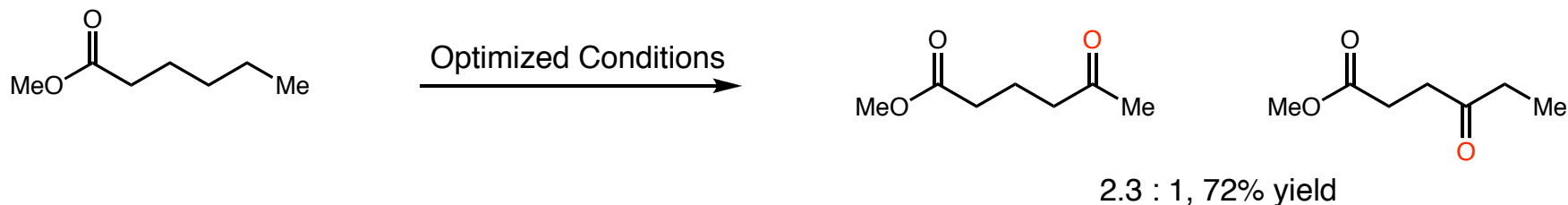
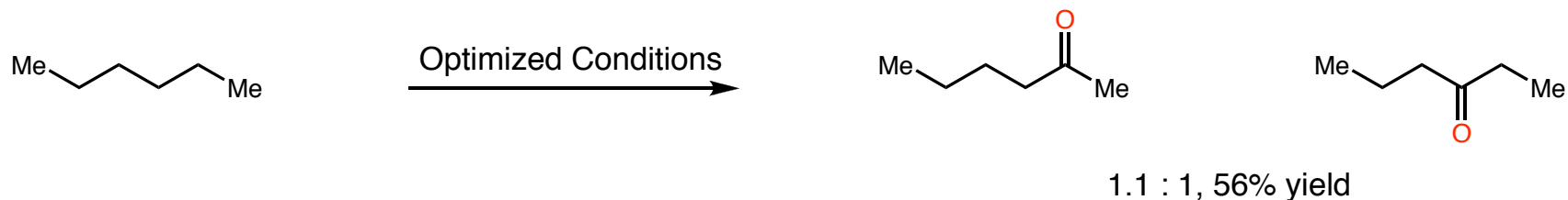
48% (17% rsm) 20:1 regioselectivity



56% (32% rsm) >99:1 regioselectivity

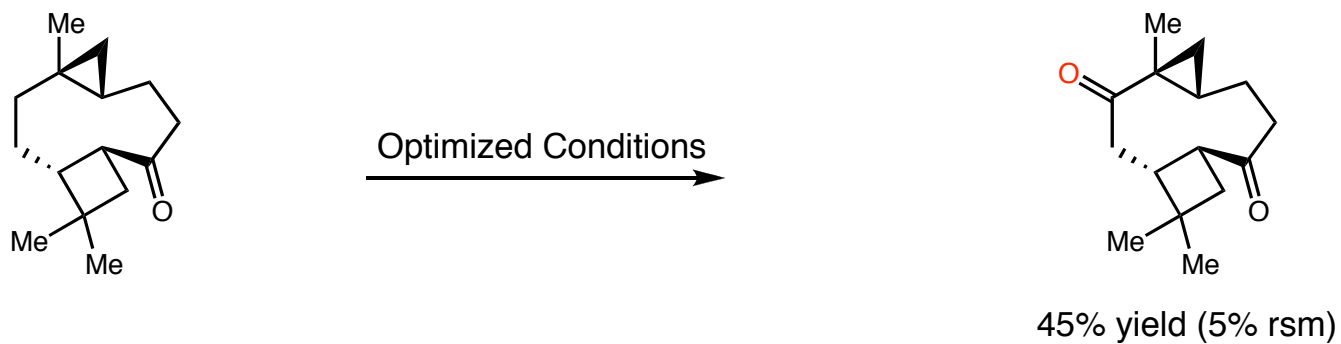
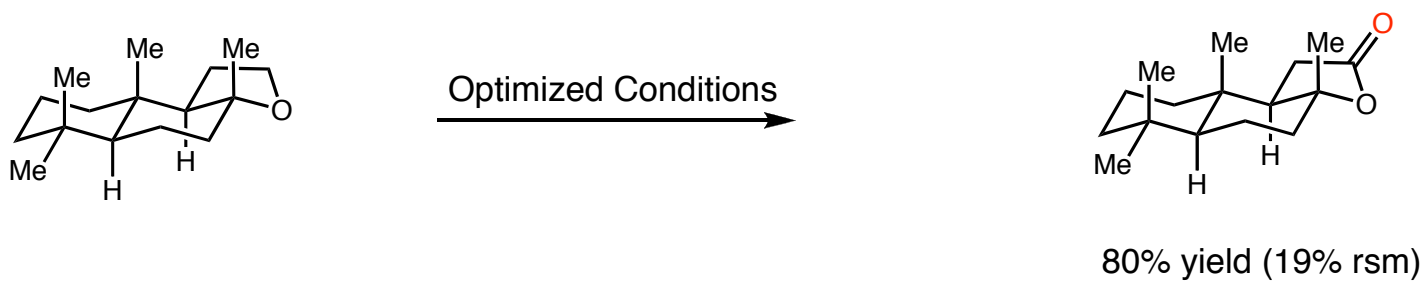
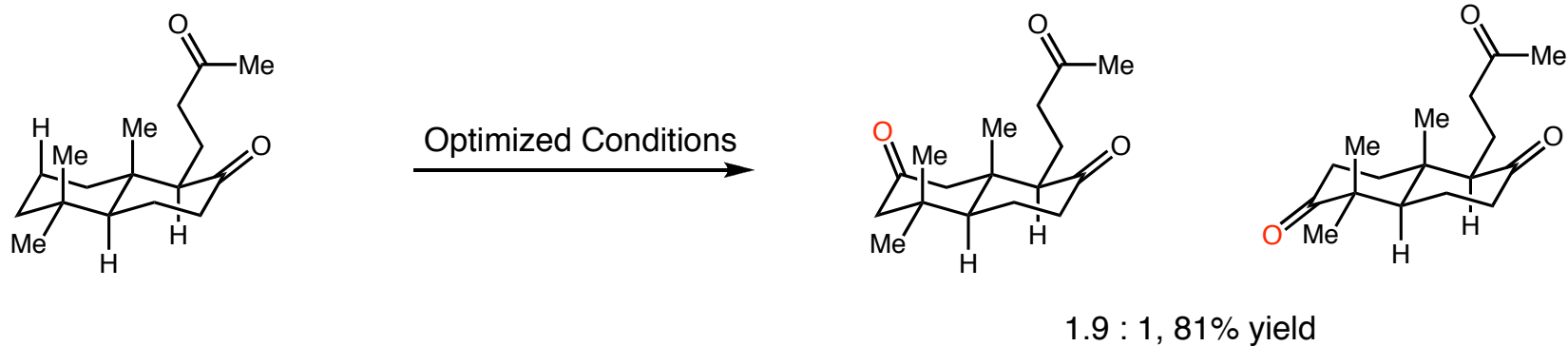
Christina White's Iron Catalyzed Oxidations of Unactivated sp^3 C-H Bonds

- Methylene oxidation occurs when methyne C-H bond activation is disfavored or not present



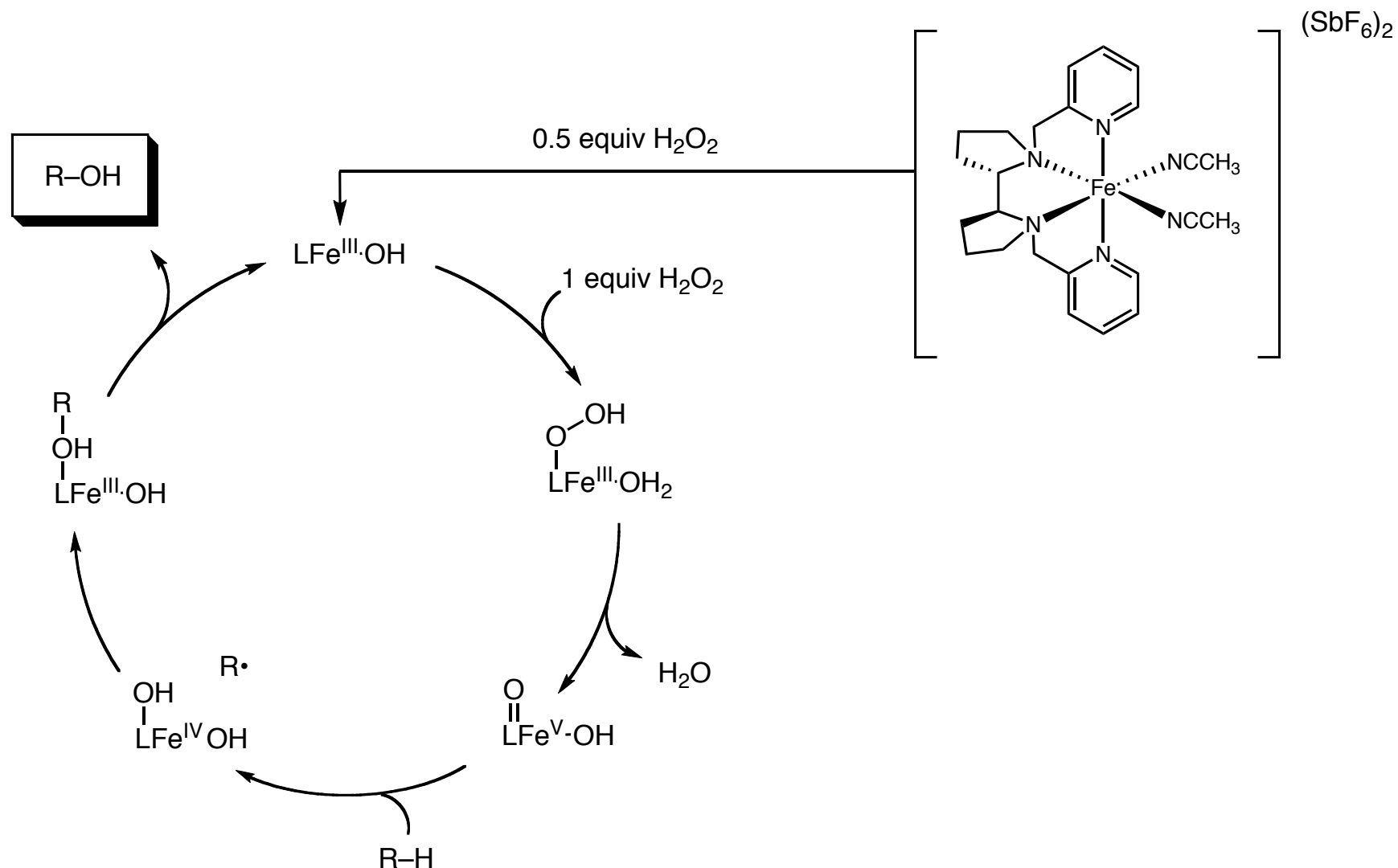
Christina White's Iron Catalyzed Oxidations of Unactivated sp^3 C-H Bonds

■ Complex substrates do show some selectivity



Christina White's Iron Catalyzed Oxidations of Unactivated sp^3 C-H Bonds

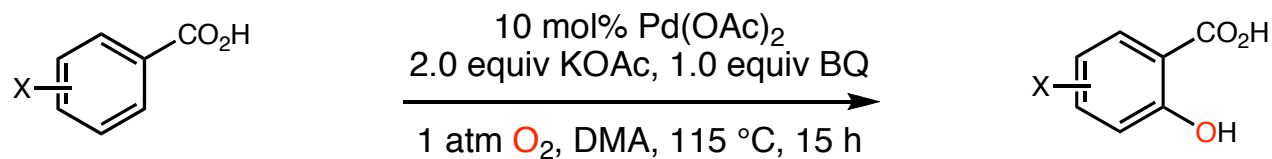
- Literature evidence supports iron(V) mechanism similar to iron heme complexes



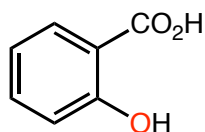
Chen, K.; Costas, M.; Que, L. *J. Chem. Soc., Dalton Trans.* **2002**, 672.
England, J.; Britovsek, J. P.; Rabadia, N.; White, A. J. P. *Inorg. Chem.* **2007**, 46, 3752.
Bassan, A.; Blomberg, M. R. A.; Siegbahn, P. E. M.; Que, L. *Chem. Eur. J.*, **2005**, 11, 692.

Oxidation of Arenes Using Molecular Oxygen

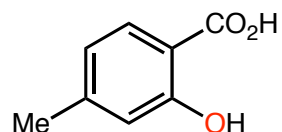
Jin-Quan Yu's carboxylic acid directed hydroxylation of arenes



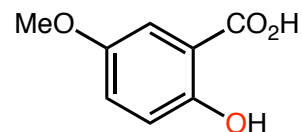
20 examples 35-82% yield



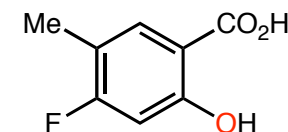
74% yield



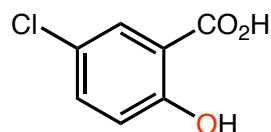
82% yield



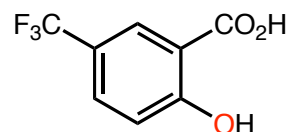
73% yield



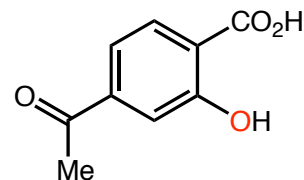
72% yield



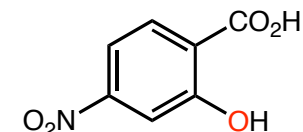
52% yield
95% (5 atm O₂)



48% yield
93% (5 atm O₂)



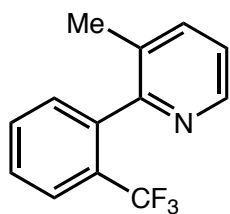
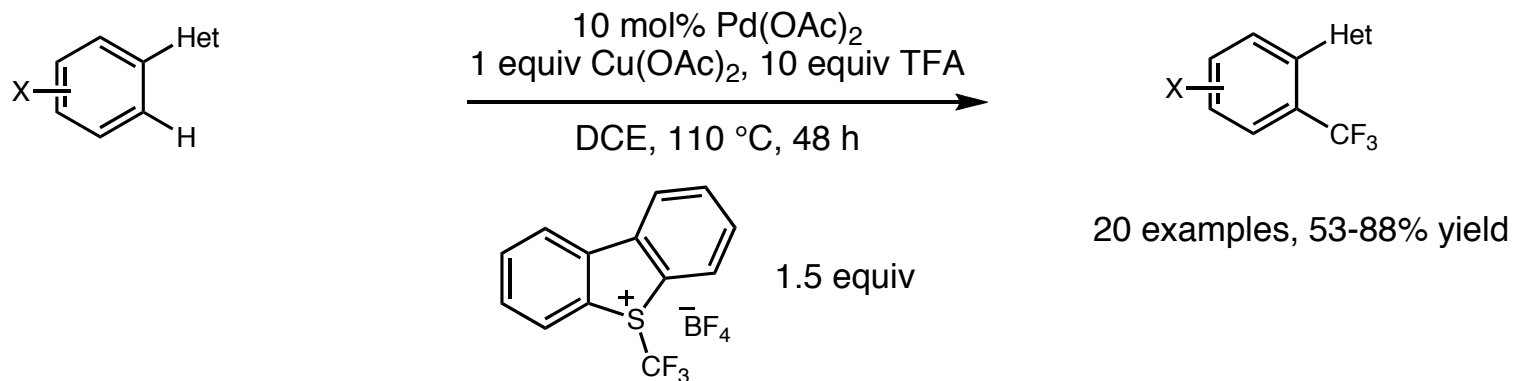
51% yield
63% (5 atm O₂)



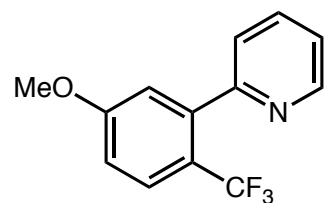
54% yield
91% (5 atm O₂)

Directed Functionalization of Arenes with CF_3 Groups

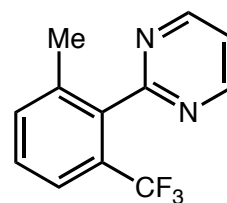
■ Nitrogen heterocycles act as directing groups



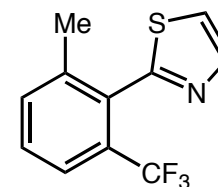
82% yield



54% yield



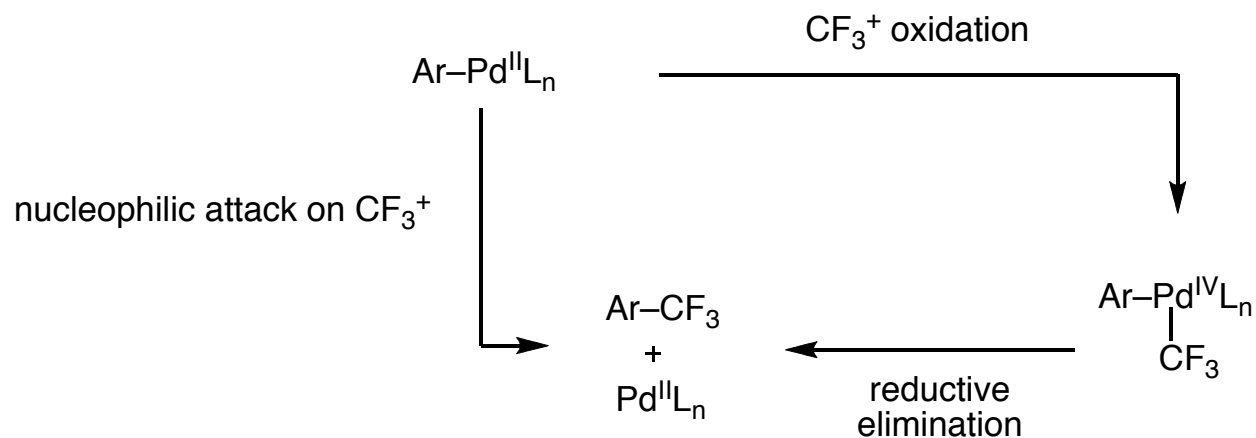
88% yield



74% yield

Directed Functionalization of Arenes with CF_3 Groups

■ Possible mechanisms

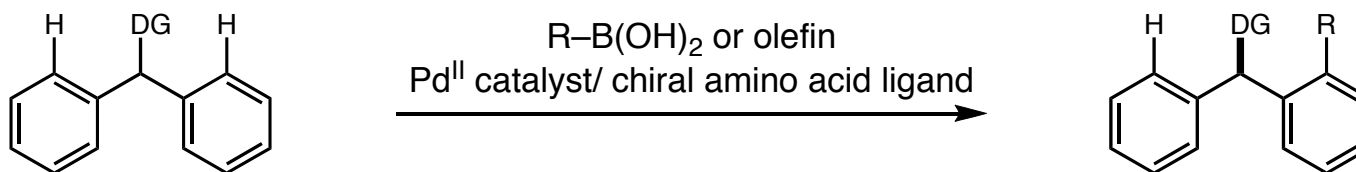


- TFA is necessary for reactivity
- $Cu(OAc)_2$ is not necessary for reactivity, however it provides a 30% bump in yield
- $Cu(OAc)_2$ could be a scavenger for the dibenzothiophene byproduct as a Lewis Acid
- Dibenzothiophene byproduct could also reduce Pd^{II} to Pd^0 and $Cu(OAc)_2$ could act as a reoxidant

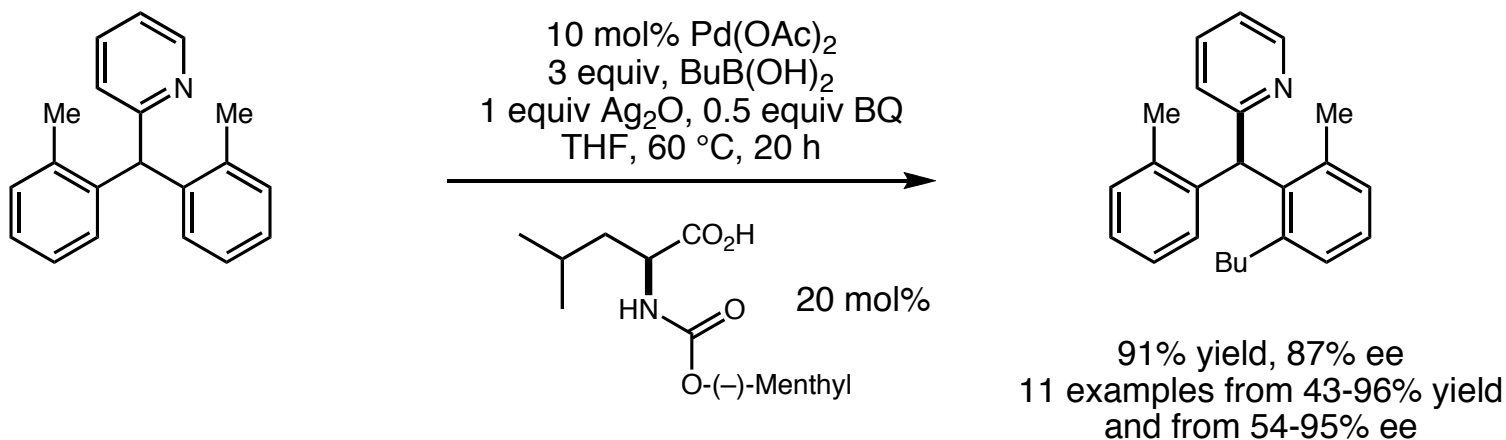
Enantioselective C–H Bond Activation

Enantioselective C-H Activation: Recent Developments

- Jin-Quan Yu has published two recent examples of desymmetrizing aryl functionalization

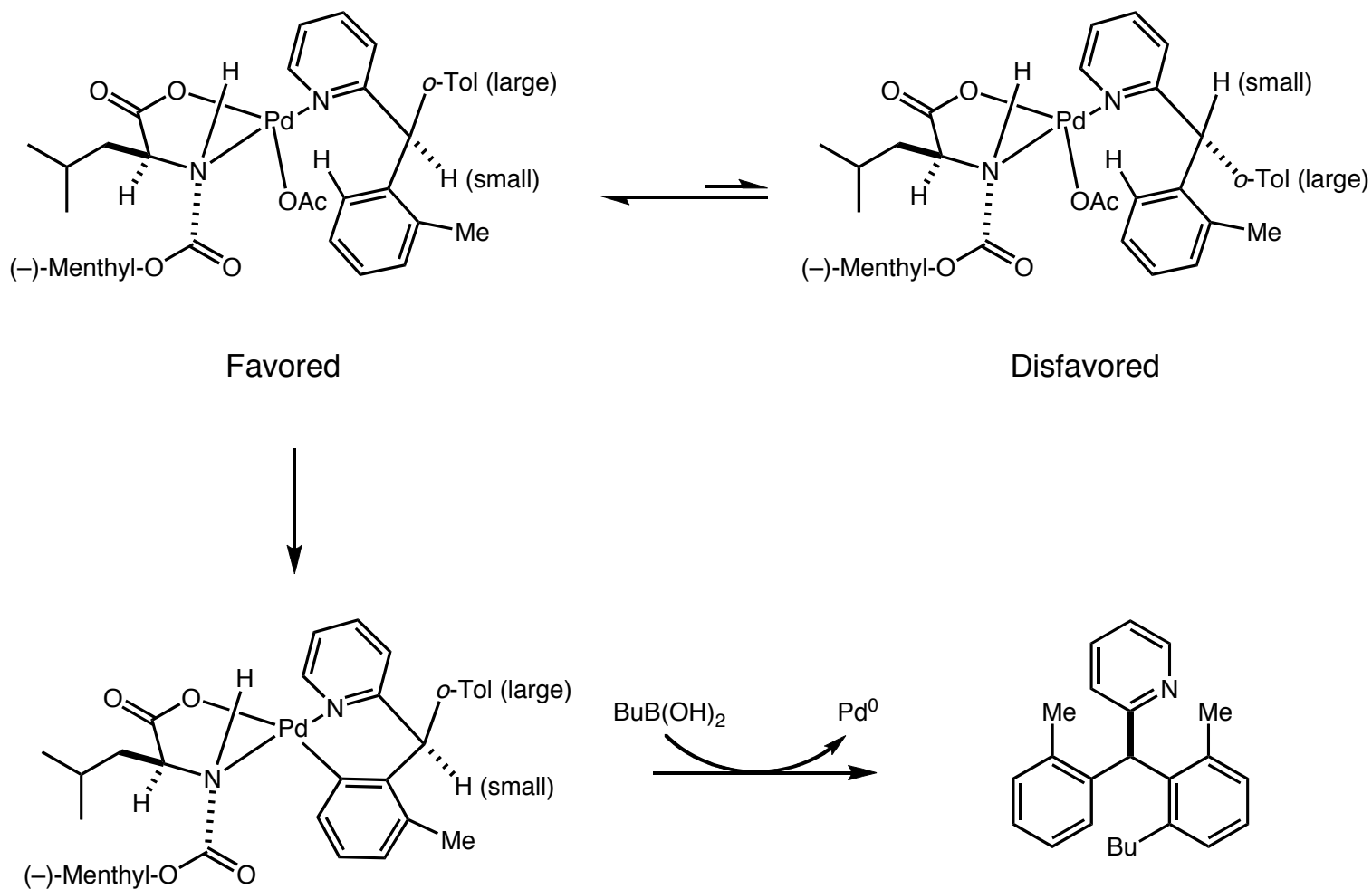


- First example involved alkylation using boronic acids



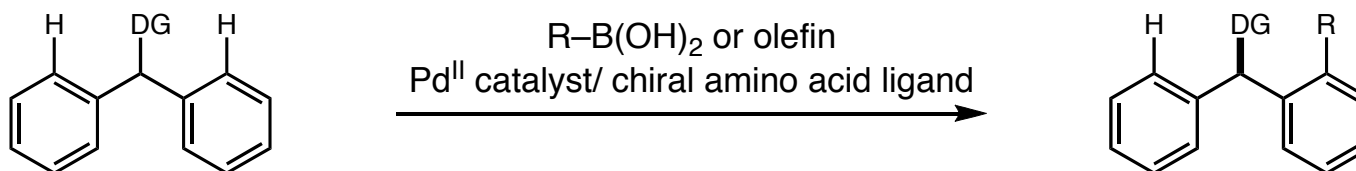
Enantioselective C-H Activation: Recent Developments

■ Stereochemical model for desymmetrizing alkylation reaction

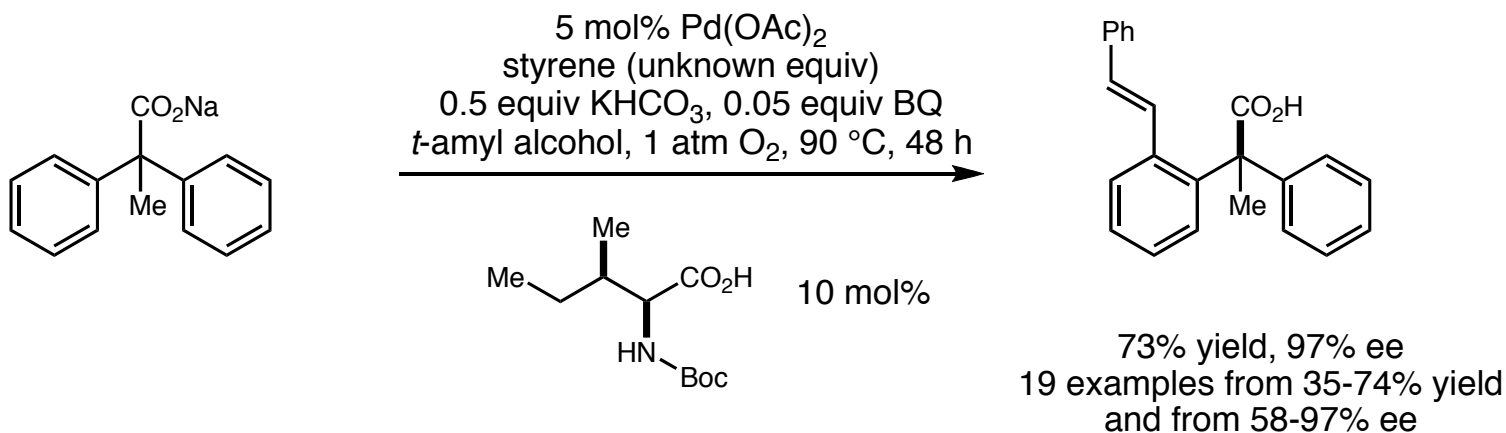


Enantioselective C-H Activation: Recent Developments

- Jin-Quan Yu has published two recent examples of desymmetrizing aryl functionalization

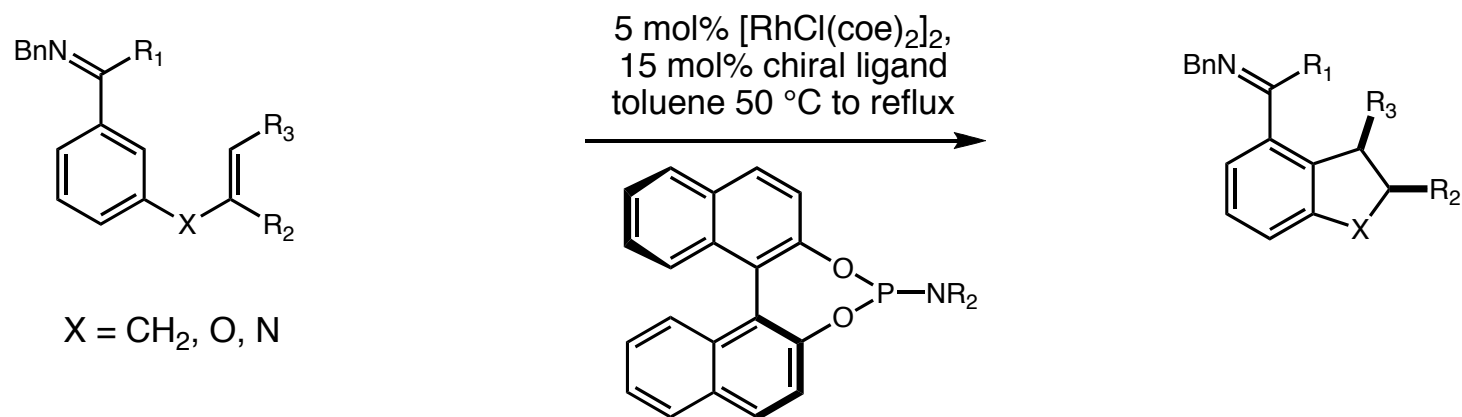


- Second example involved olefination



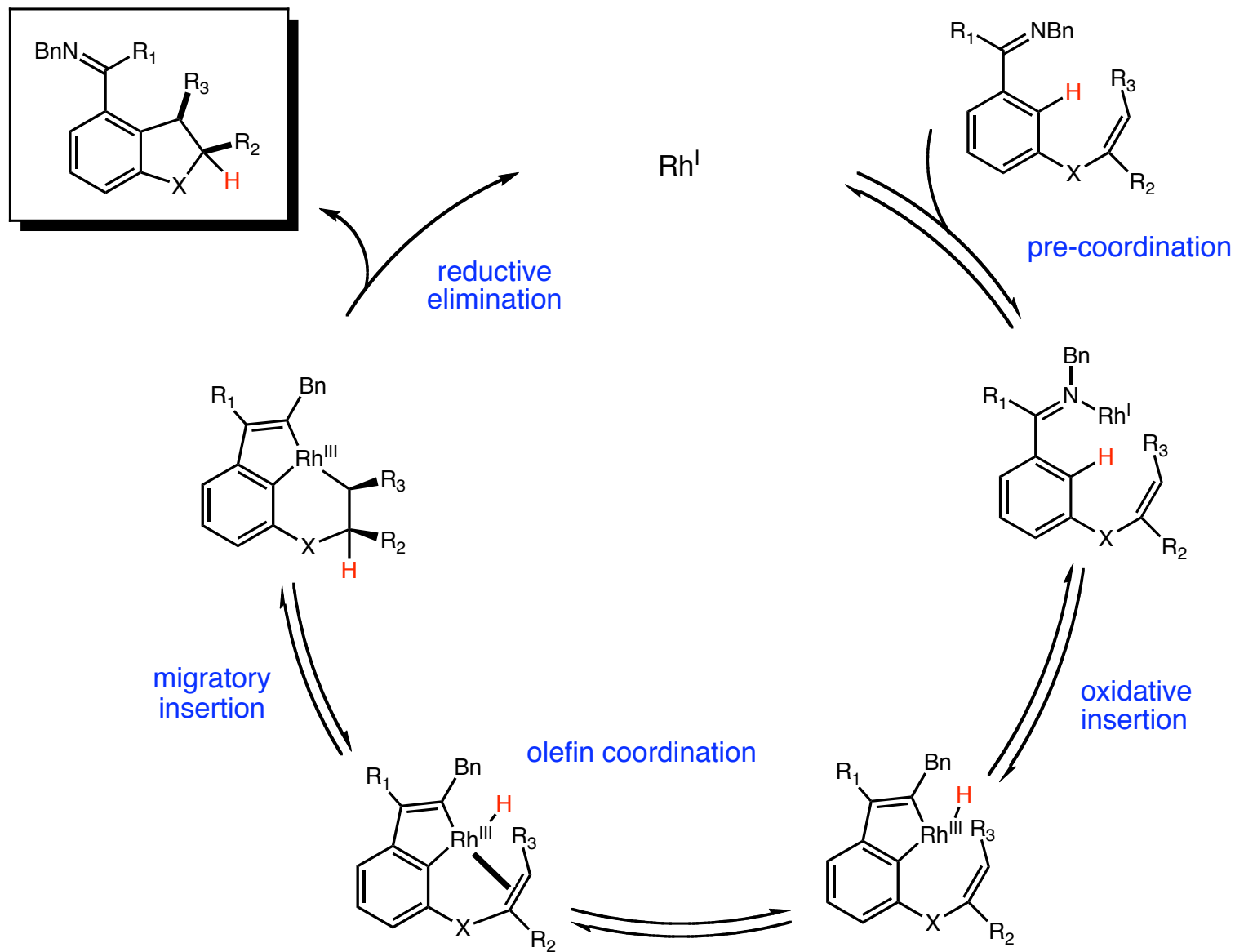
Enantioselective C-H Activation: Recent Developments

- Bergman and Ellman have published a few examples of enantioselective intramolecular cyclizations



Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192.
Harada, J.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2008**, *73*, 6772.

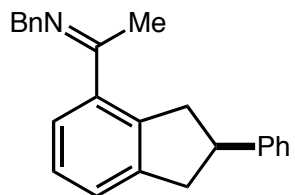
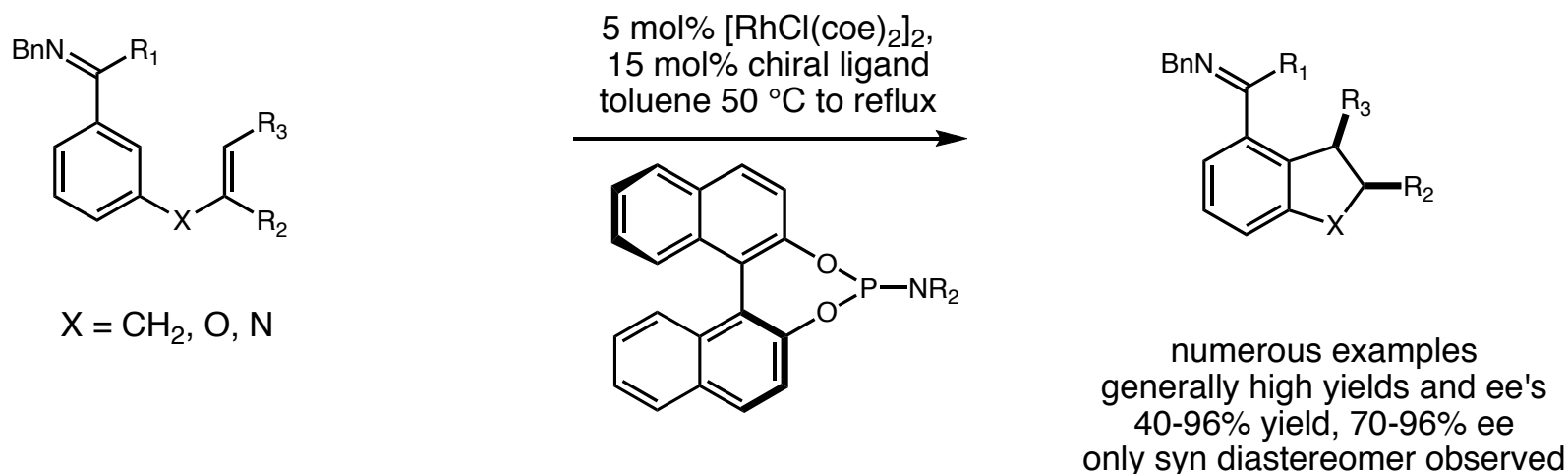
Enantioselective C-H Activation: Recent Developments



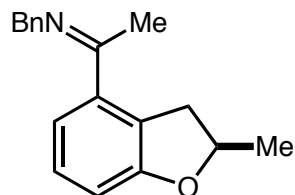
Harada, J.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2008**, *73*, 6772.

Enantioselective C-H Activation: Recent Developments

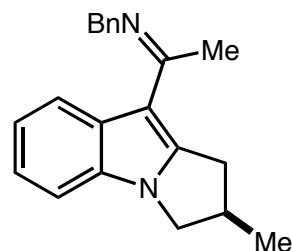
- Bergman and Ellman have published a few examples of enantioselective intramolecular cyclizations



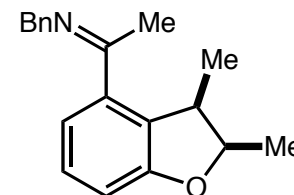
98% yield, 90% ee



99% yield, 96% ee



90% yield, 70% ee

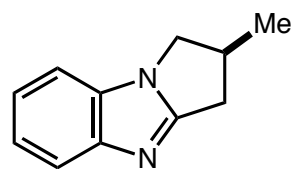
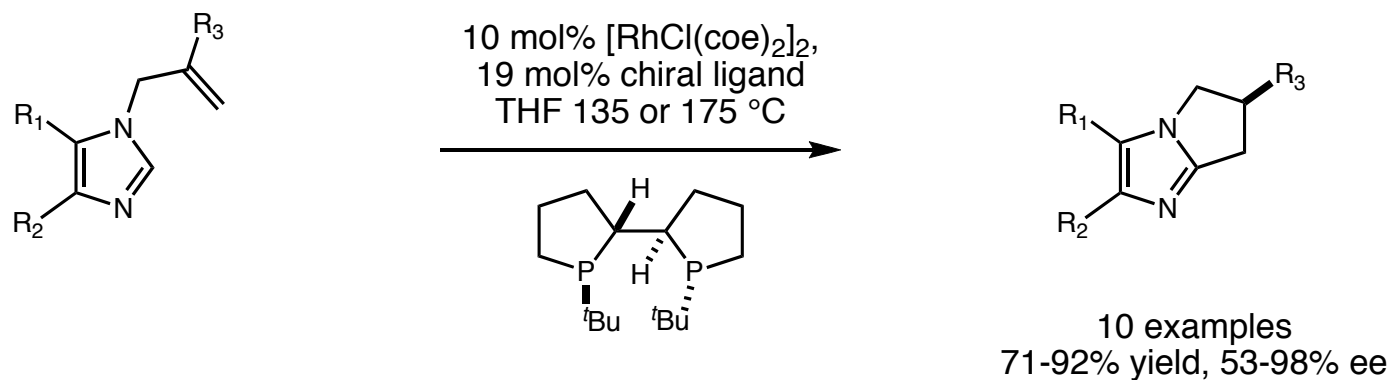


80% yield, 91% ee

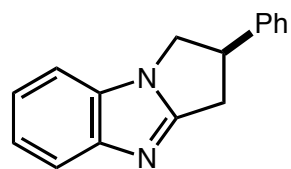
Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192.
Harada, J.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2008**, *73*, 6772.

Enantioselective C-H Activation: Recent Developments

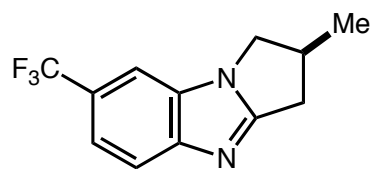
■ A similar example using benzimidazoles



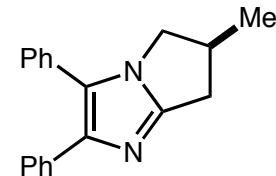
89% yield, 98% ee



91% yield, 97% ee



83% yield, 53% ee



80% yield, 91% ee