SCM1 „SYNTHESECHEMIE“
Aktuelle katalytische Synthesemethoden
Teil 1: C-H Aktivierung

Jun.-Prof. Dr. Ivana Fleischer

Fridays 8.15-9.45

WiSe

Modified material by: Jeffrey W. Bode, *OC VI: Advanced Methods and Strategies in Synthesis*, *Catalytic C-H functionalization*, *2019*. (ETH-Zürich), http://www.bode.ethz.ch/lecturenote.

- BLABLABLA

UNTERKAPITEL

ALLES RELEVANT FÜR DIE OC

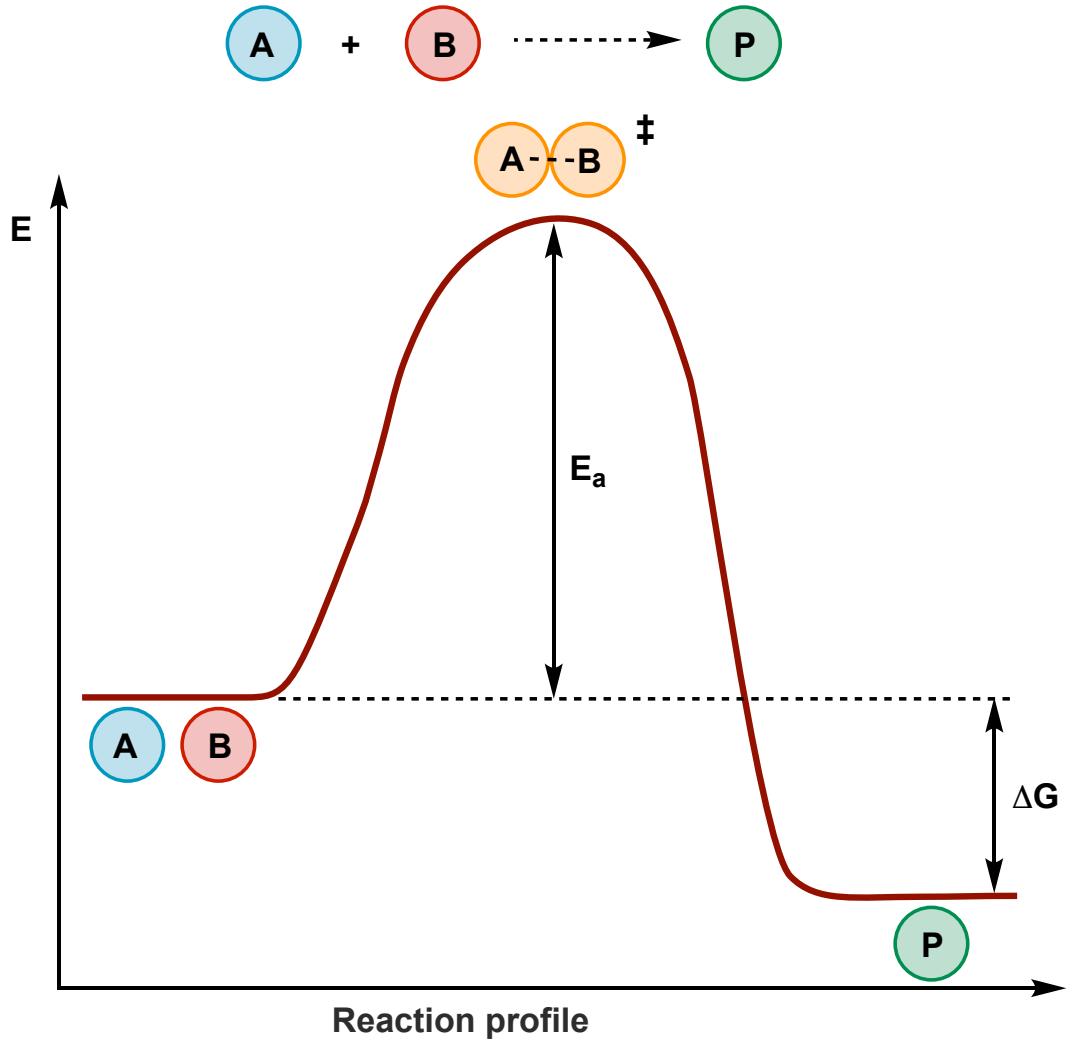
LÜCKE! TAFELANSCHRIFT

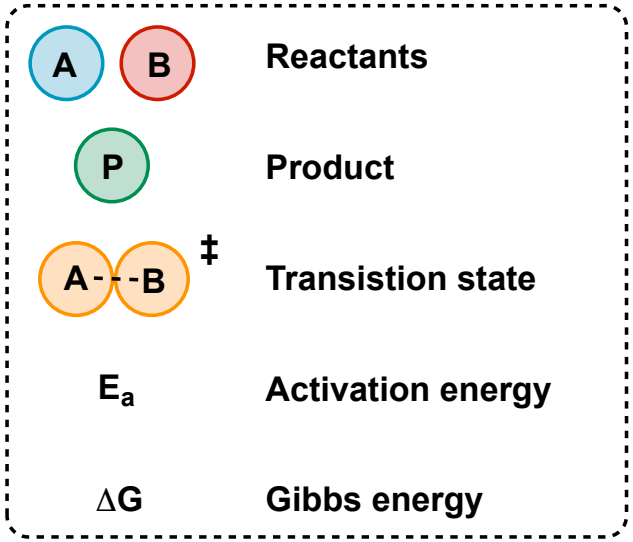
EXTRA INFORMATIONEN: INTERESSANTE FAKTEN, VERTIEFTES WISSEN

„Modern (Homogeneous) Catalysis?“

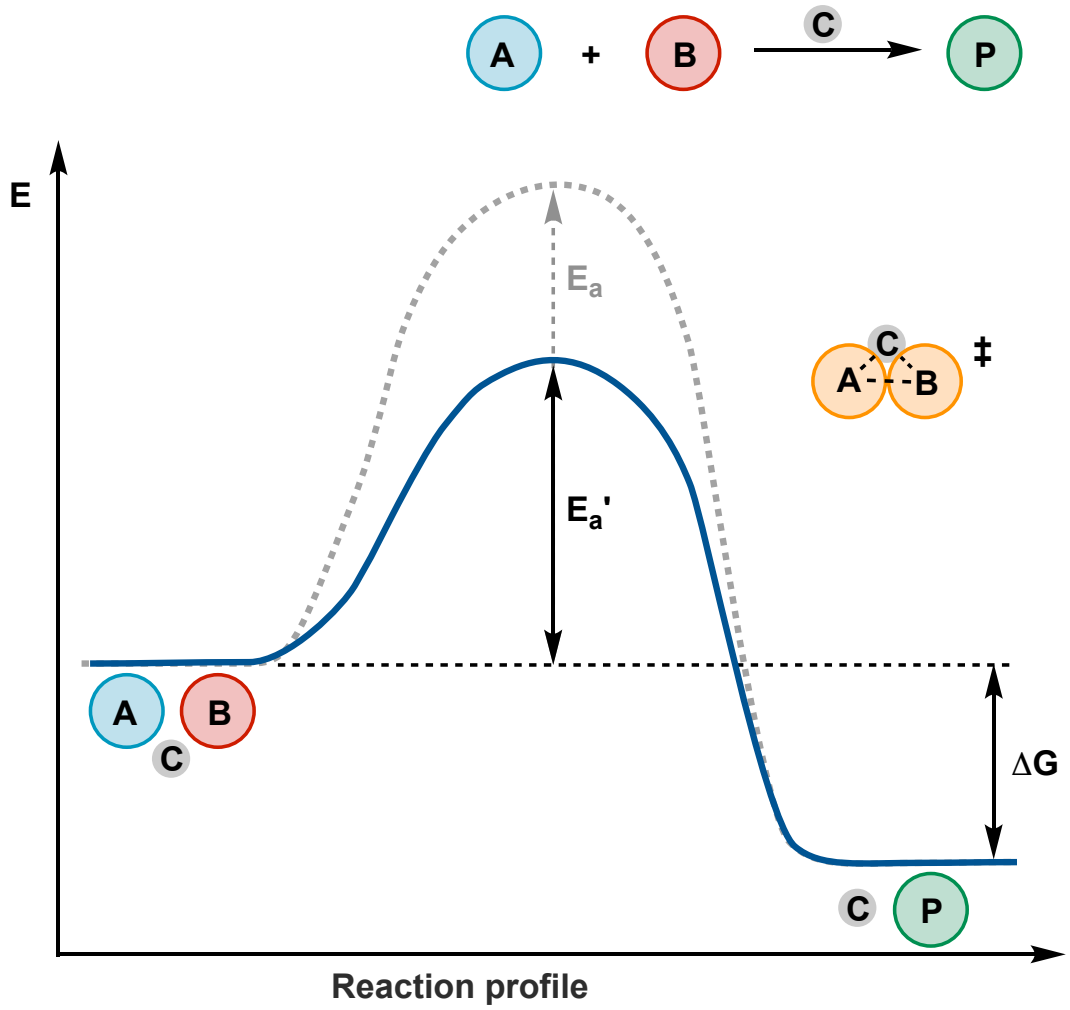
What is catalysis?

What is catalysis?



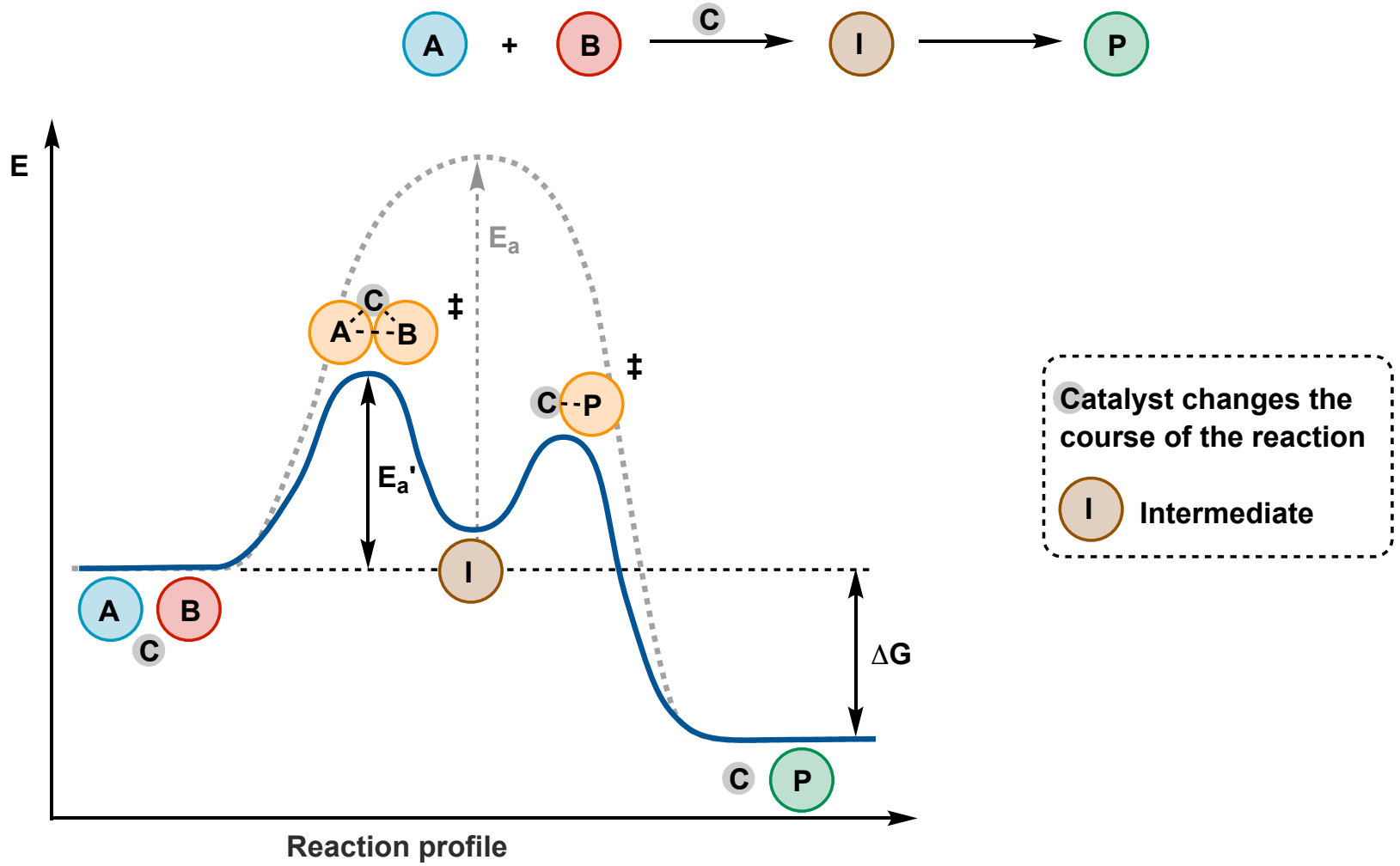


What is catalysis?

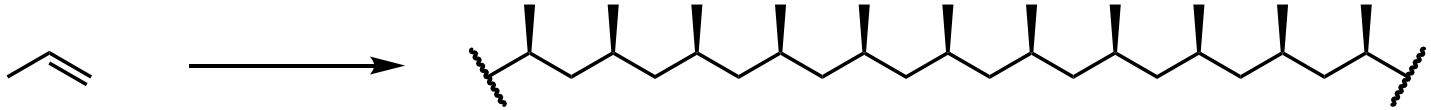


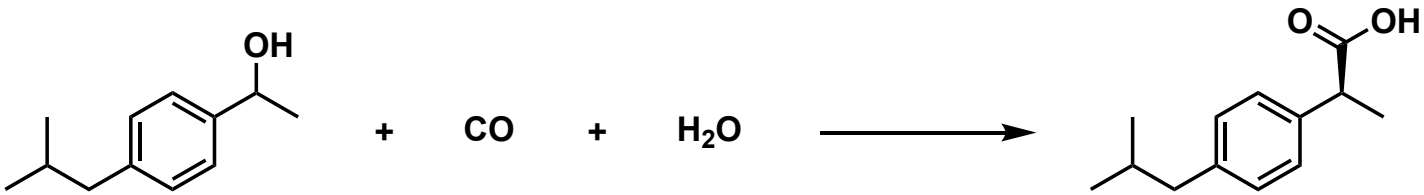
Catalyst enables a reaction

What is catalysis?

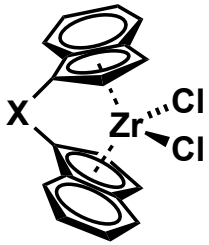


Catalysis = industrial driving force

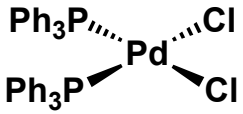




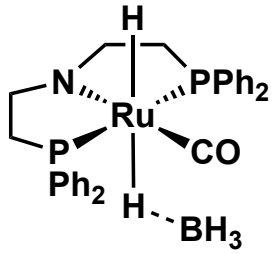
Homogeneous Catalysis



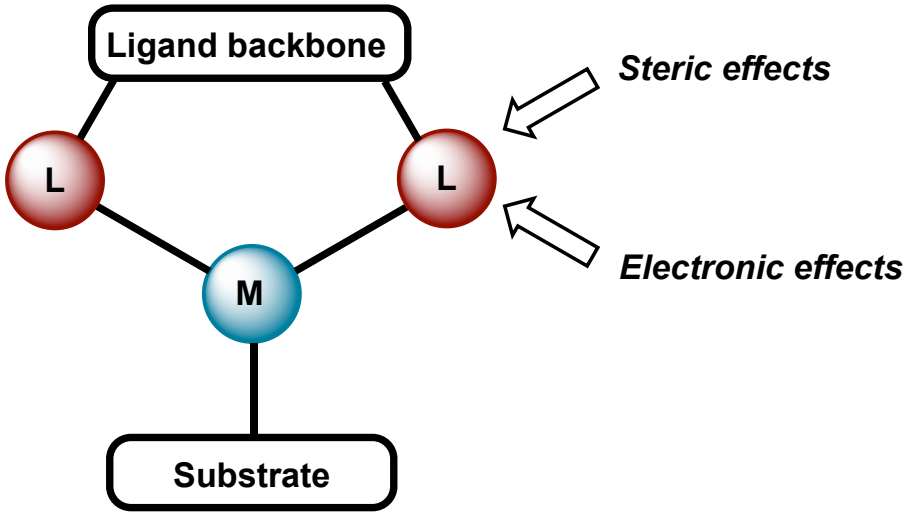
Polymerization



Carbonylation



CO_2 Hydrogenation



HOMOGENEOUS CATALYSIS: ADVANTAGES

- mild reaction conditions
- selectivity
- steric and elektronic properties
- mechanistic investigations

DISADVANTAGES

- recycling
- sensitivity

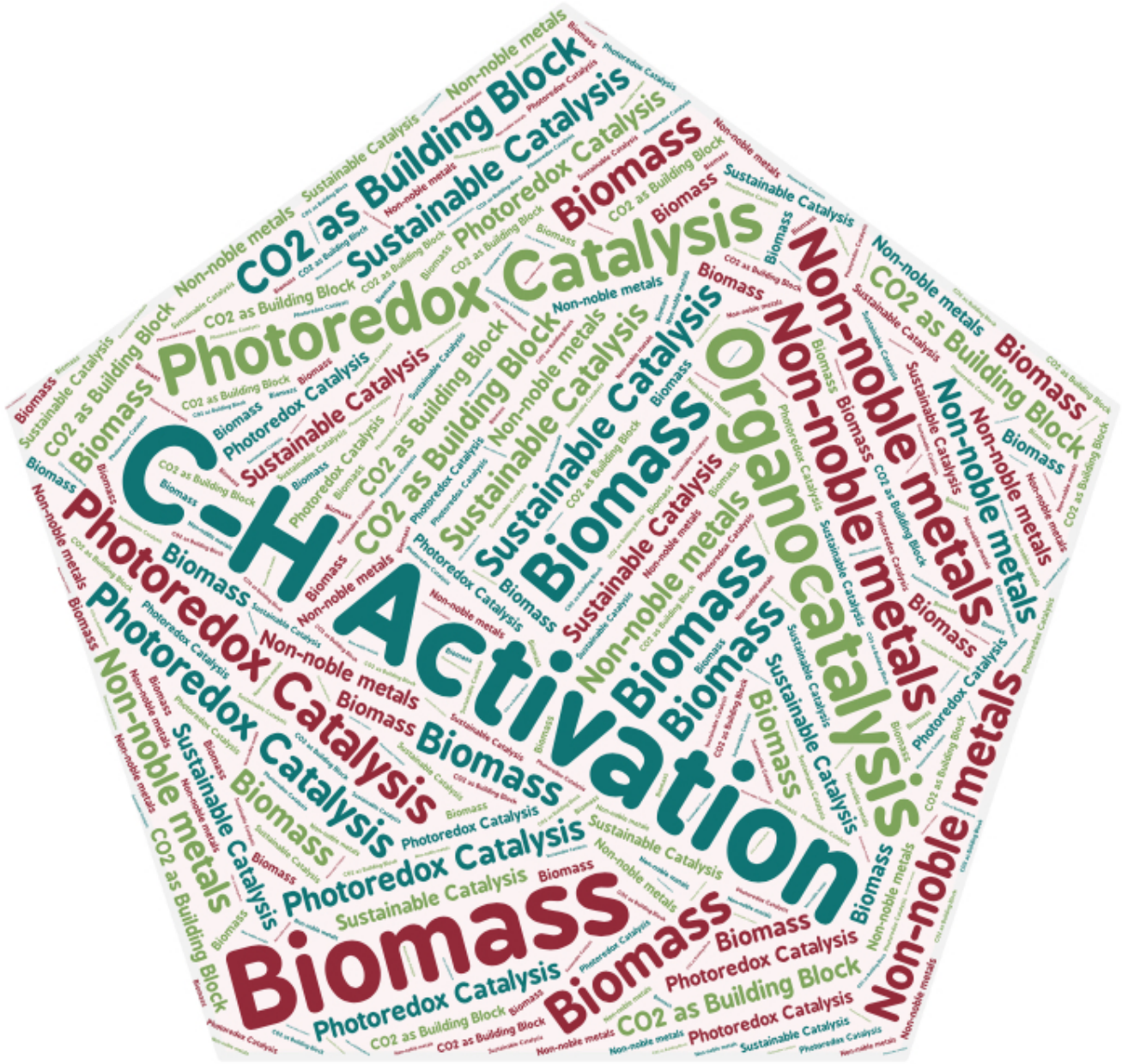
„Modern (Homogeneous) Catalysis?“

- **What is old catalysis? Established catalysis?**
- **Nobel prizes in catalysis?**

„Modern (Homogeneous) Catalysis?“

- **Nobel prizes in catalysis?**

„Modern (Homogeneous) Catalysis?“



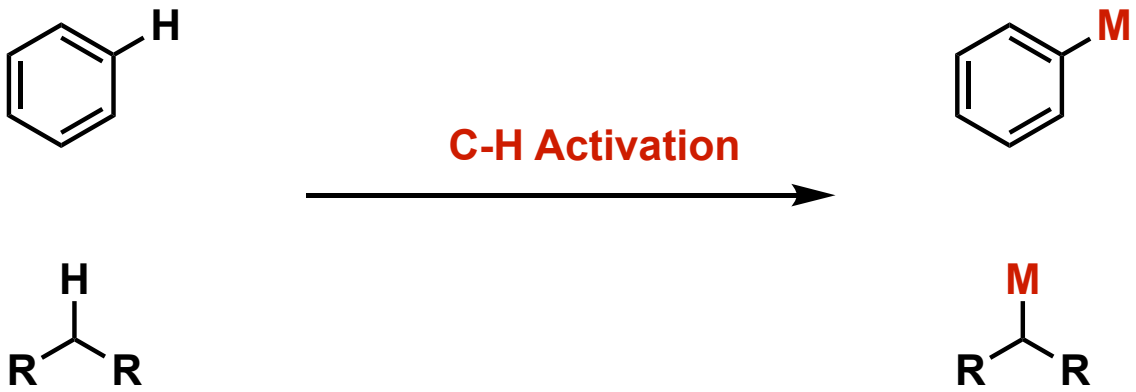
Outline

I. C-H Activation

II. Photoredox Catalysis

- C-H functionalization in general:

- C-H activation: The replacement of a C-H bond by a C-M bond, where M is a transition metal. “Activation” in this sense means the replacement of a relatively unreactive C-H bond with a C-M bond, which can be much more easily functionalized. A C-H activation followed by a reaction from C-M to C-X is therefore a key part of a *C-H functionalization*. Often, the term C-H activation is used to describe the whole process.



Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997,** *97*, 2879-2932.

- Reviews:

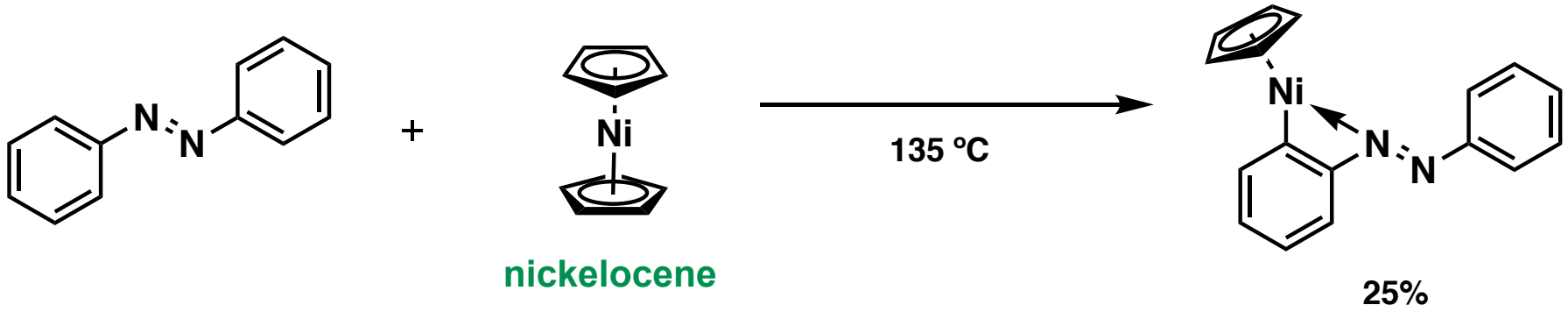
(a) *Chem. Rev.* **2010**, *110*, 1147.
(b) *Chem. Rev.* **2010**, *110*, 890.
(c) *Chem. Rev.* **2010**, *110*, 824.
(d) *Chem. Rev.* **2010**, *110*, 725.
(e) *Chem. Rev.* **2010**, *110*, 681.
(f) *Chem. Rev.* **2011**, *111*, 1315.
(g) *Acc. Chem. Res.* **2009**, *42*, 335.
(h) *Chem. Asian J.* **2009**, *5*, 436.
(i) *Chem Rev.* **2011**, *111*, 1780.
(j) *Chem. Rev.* **2011**, *111*, 1215.
(k) Synlett **2013**, *24*, 6.
(l) Angew. Chem. Int. Ed. **2014**, *53*, 74.

C-H Activation (Topics in Current Chemistry)
Ed. J-Q. Yu, Z. Shi, **2010**, XII.

ISBN 978-3-642-12355-9

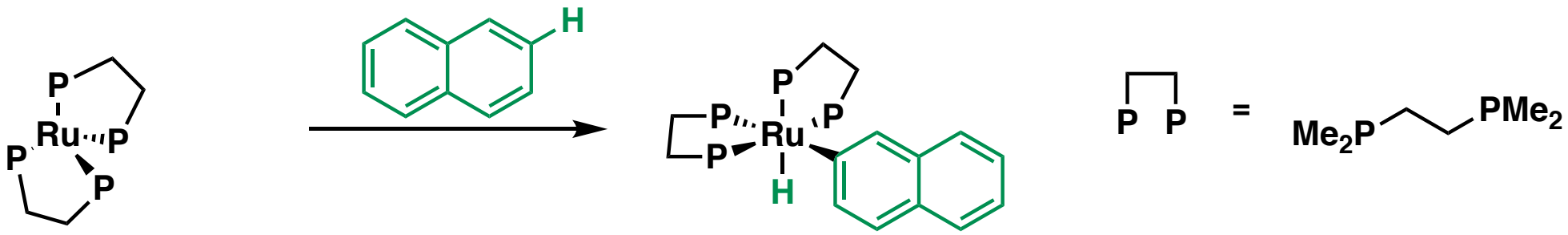
a) Stoichiometric C-H activation: sp^2

Seminal work on azobenzene:



Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544-1545.

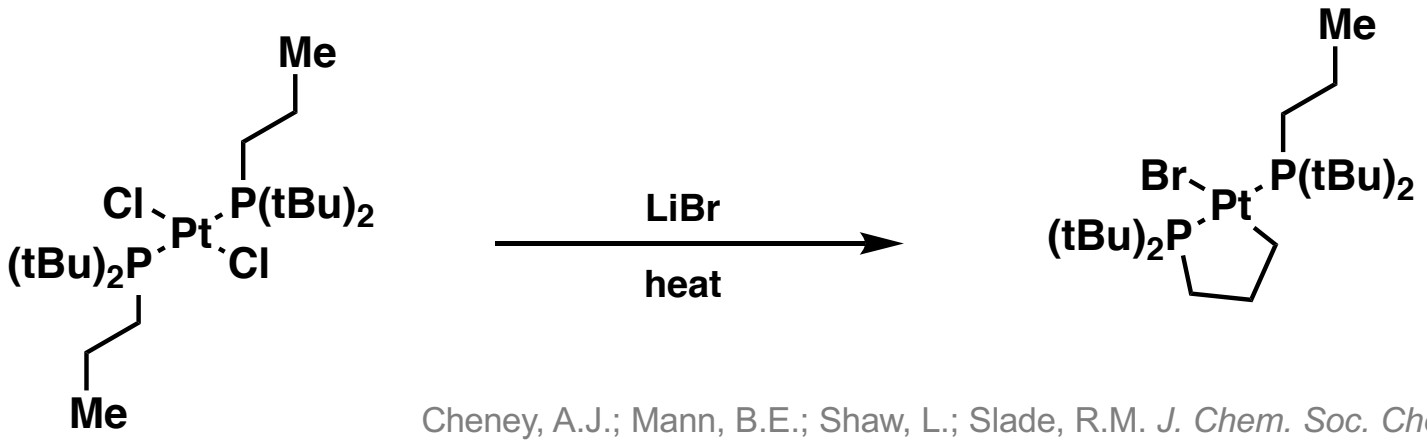
Activation of naphtalene by Ru:



Chatt, J.; Davidson, J. M. *J. Chem. Soc.* **1965**, 843-855.

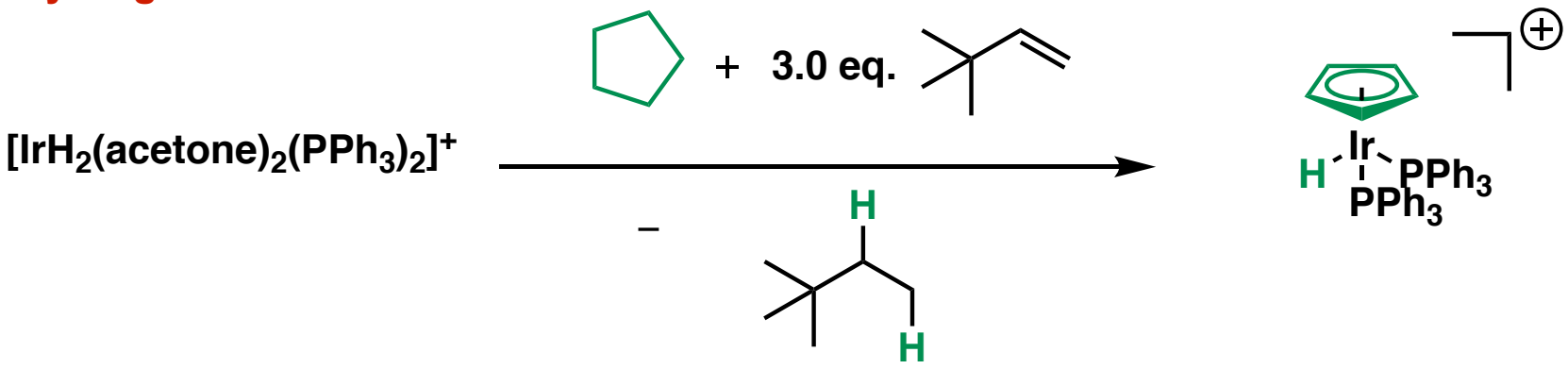
a) Stoichiometric C-H activation: sp^3

Intramolecular activation by Pt:



Cheney, A.J.; Mann, B.E.; Shaw, L.; Slade, R.M. *J. Chem. Soc. Chem. Commun.* **1970**, 1175-1176.

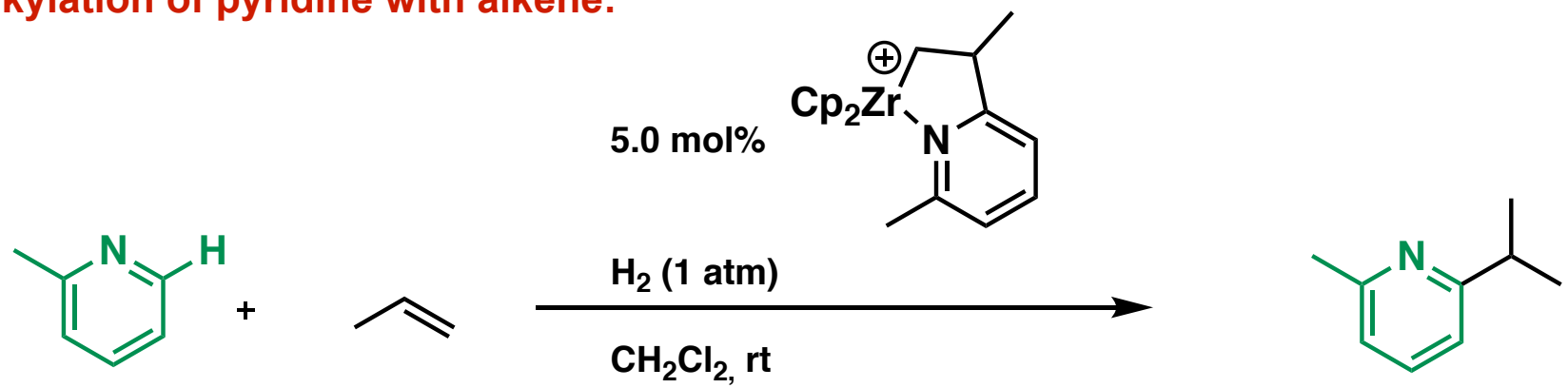
Dehydrogenation:



Crabtree, R. H.; Mihelcic, J. M.; Quirk, J. M. *J. Am. Chem. Soc.* **1979,** *101*, 7738-7740.

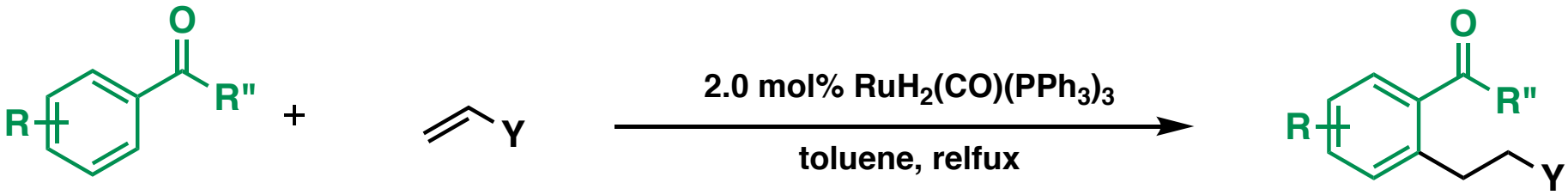
b) Catalytic C-H activation:

Alkylation of pyridine with alkene:



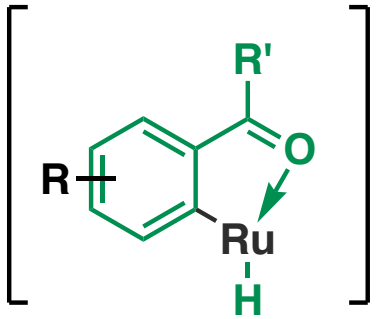
Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989,** *111*, 778-779.

Murai reaction:



Y = $Si(OEt)_3$, Ph, tBu, CH_2SiMe_3

proposed intermediate:

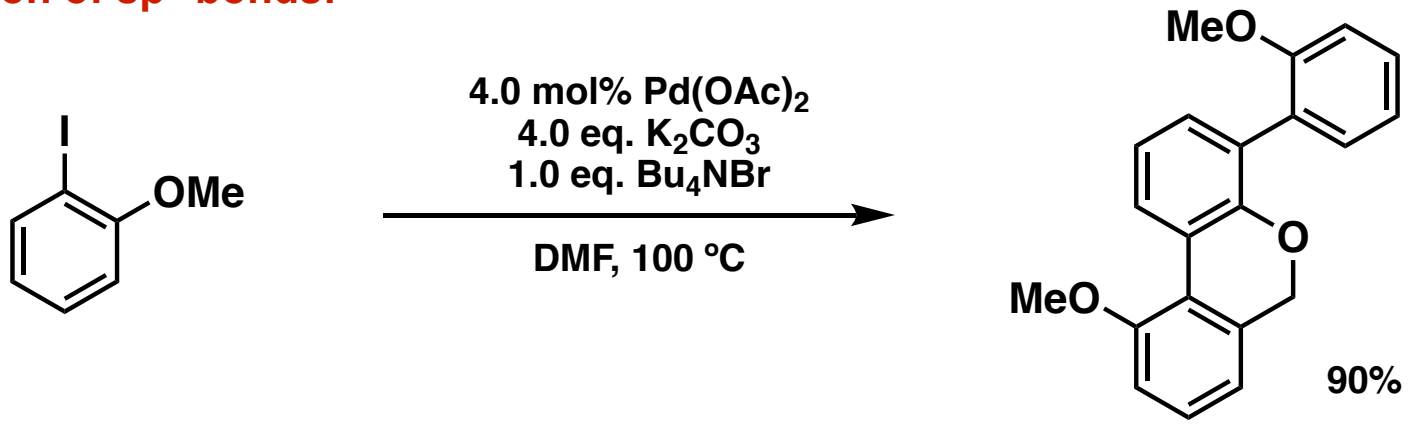


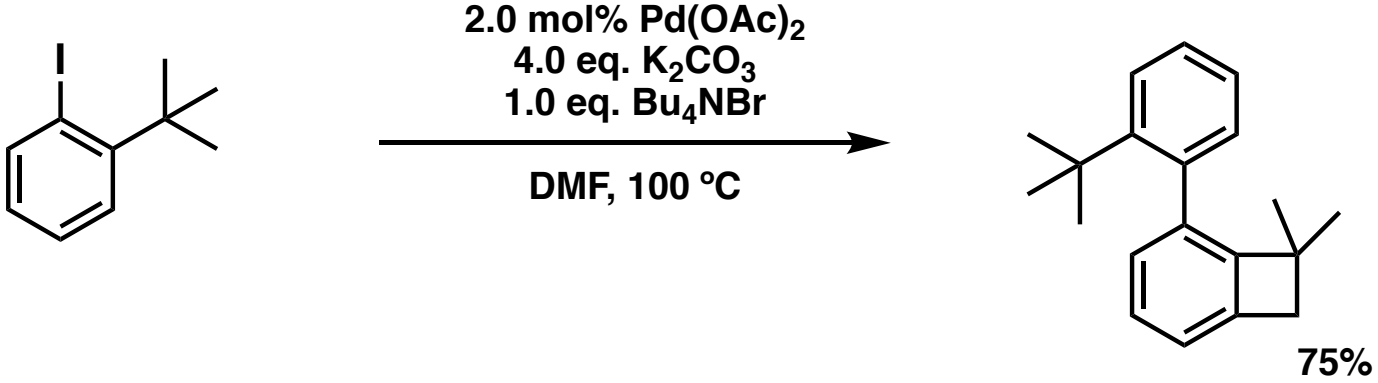
Directing group!

Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993,** *366*, 529-531.

b) Catalytic C-H activation:

Functionalization of sp^3 bonds:





Dyker, G. *Angew. Chem. Int. Ed.* **1992,** *31* (8), 1023-1025.
Dyker, G. *Angew. Chem. Int. Ed.* **1994,** *33* (1), 103-105.

- The starting materials are cheap and easily accessible
- Reactions are atom economical
- no further functional group transformations are required (compare to cross coupling reactions, where functionalities of both coupling partners have to be installed)
- Reactions are cost effective

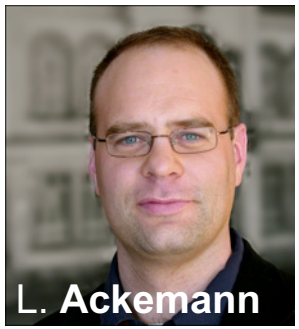

M. **Sanford**


K. **Fagnou**†


J. Q. **Yu**


M. **Gaunt**

From Germany…


L. **Ackemann**


F. **Glorius**


T. **Ritter**


A. **Charrete**


N. **Chatani**


J.F. **Hartwig**


O. **Baudoin**

and many more ……

a) Reactivity: Most of the C-H bonds are stronger than the corresponding C-X bonds, therefore a C-H functionalization is thermodynamically unfavoured.

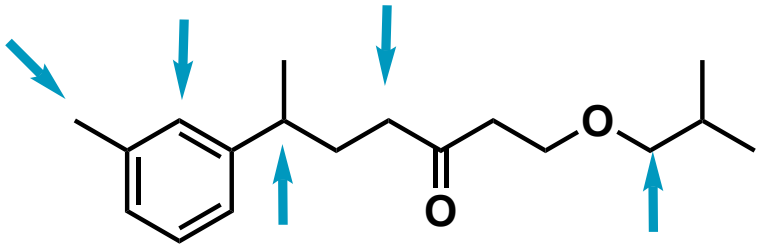
Bond	Bond Strenth (in kcal/mol)	Bond	Bond Strenth (in kcal/mol)
C_{Methyl}-H	105	C-C (in ethane)	90
$C_{Isopropyl}$-H	99	C-O (in MeOH)	92
$C_{tertbutyl}$-H	97	C-N (in $MeNH_2$)	85
C_{allyl}-H	89	C-F (MeF)	115
C_{phenyl}-H	113	C-Cl (MeCl)	84
HCC-H (ethyne)	133	C-Br (MeBr)	72
		C-I (MeI)	58

- Possible solution(s): Use of transition metal catalysts to lower the activation barrier

b) Chemoselectivity: Once the desired C-X bond is formed, this bond itself has a lower bond strength than the C-H bond before, and over-reactions such as catalyst inhibition can occur. Secondly, the introduction of a C-X bond might change the reactivity of a whole molecule (for example by changing the electron density of an aromatic system), it is important to suppress overreaction.

- Possible solutions: Running the reaction to low conversion, employ excess of substrate over oxidant, carry out intra- vs intermolecular reactions, use deactivating functional groups, catalyst design.

c) Regioselectivity: In most molecules, more than one C-H bond of a certain type, and more than one type of C-H bond exist. Therefore, a catalyst should exert high selectivity towards one particular type of C-H bond.



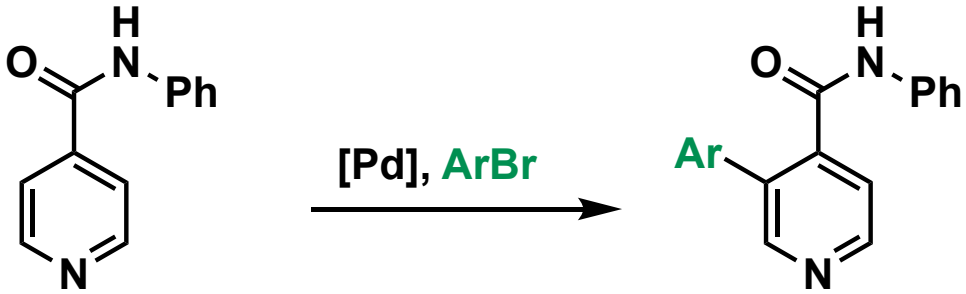
and many more possibilities…

- Possible solutions: Use weak or activated C-H bonds (allylic, benzlic), use coordinating (directing) groups, try to achieve intramolecular reactions via 5- or 6-membered transition states, catalyst design.

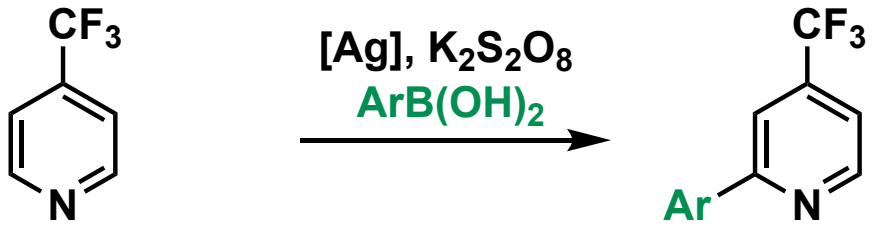
b) Regioselectivity: guided or innate

i. Innate selectivity: natural reactivity of the molecule based on steric and electronic effects

ii. Guided selectivity: functional groups change the nature of C-H bonds, coordination

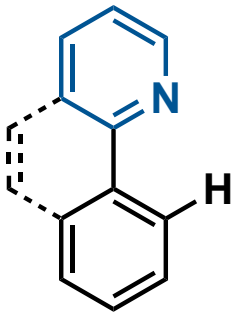


Guided C-H Arylation

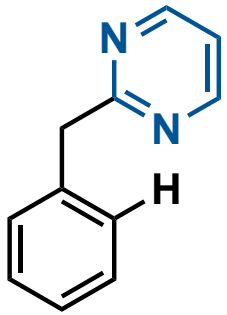


Innate C-H Arylation

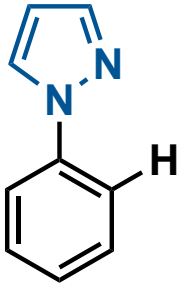
b) Regioselectivity: directing groups



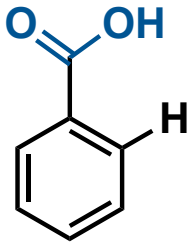
Pyridine



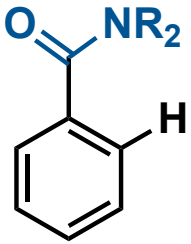
Pyrimidine



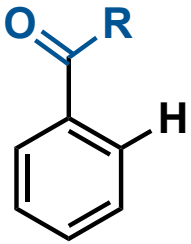
Pyrazine



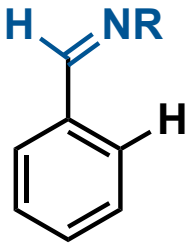
Carboxylic acid



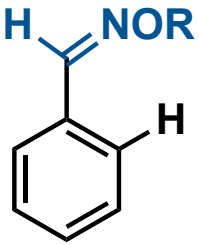
Amide



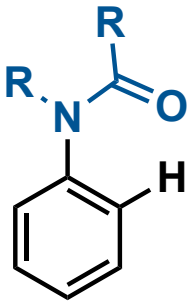
Acyl group



Imine



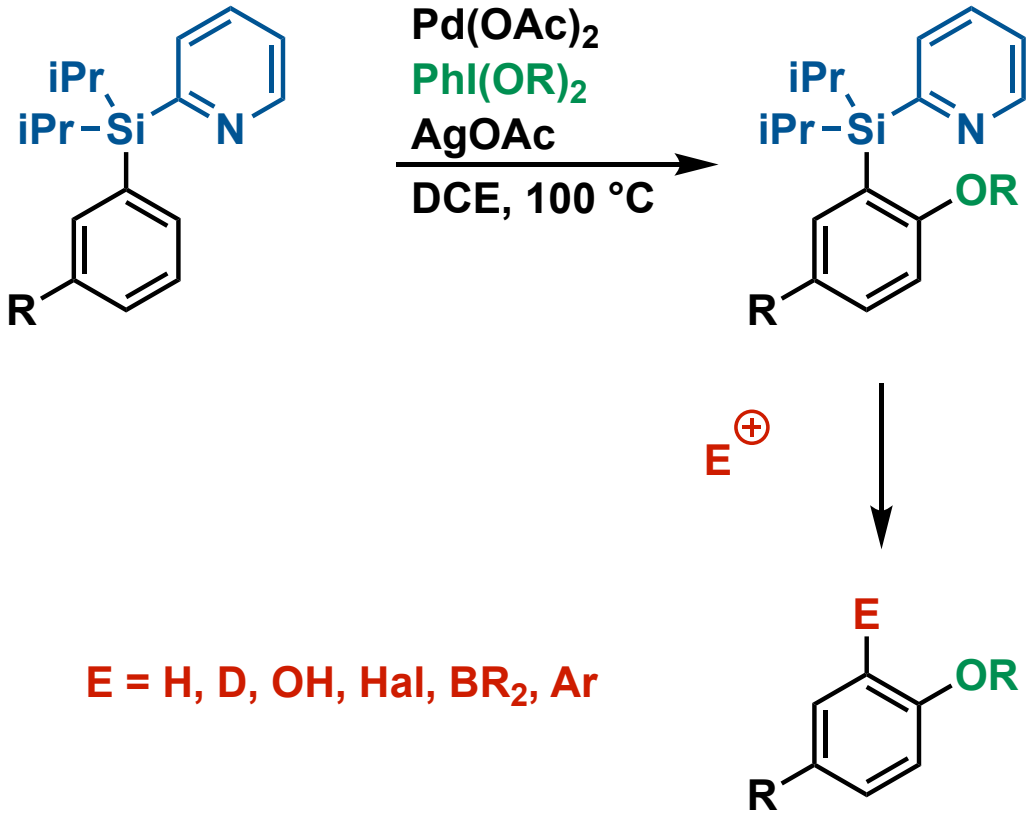
Oxime ether



Amide

b) Regioselectivity: directing groups

Removable/exchangeable directing groups: example

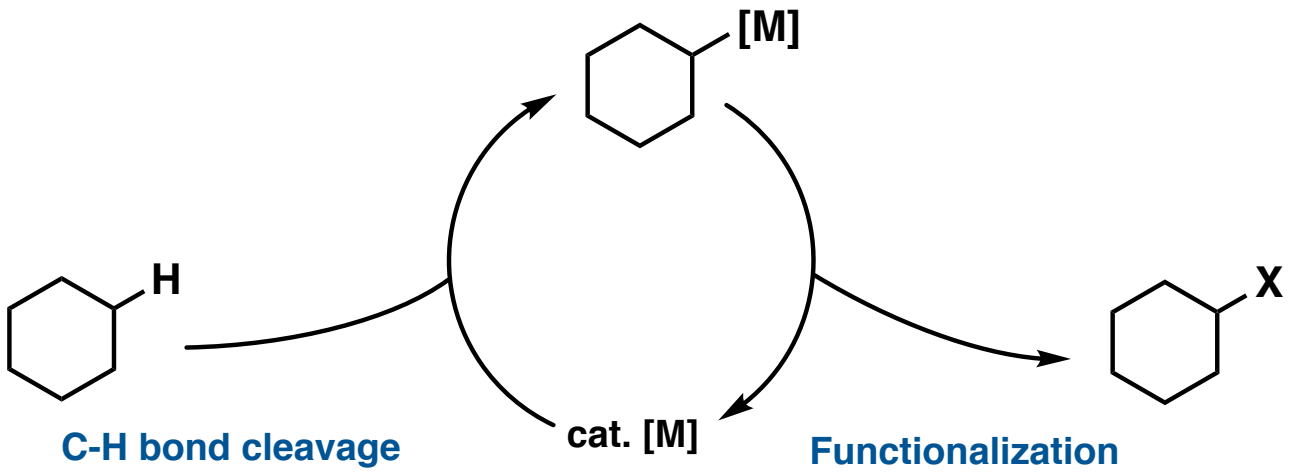


N. Chernyak, A. S. Dudnik, C. Huang, V. Gevorgyan, *J. Am. Chem. Soc*. **2010**, *132*, 8270.

For the C-H activation step:

a) Inner sphere mechanism

- C-M species is the defining factor of this mechanism. It governs all follow-up reaction with respect to regio- and stereoselectivity.
- Generally, inner sphere mechanism has a tendency to prefer less hindered C-H bonds, since they avoid radical or electrophilic steps.
- Since organometallic species are generally oxidation-labile, reactions via inner sphere mechanisms normally employ no or very weak oxidants.



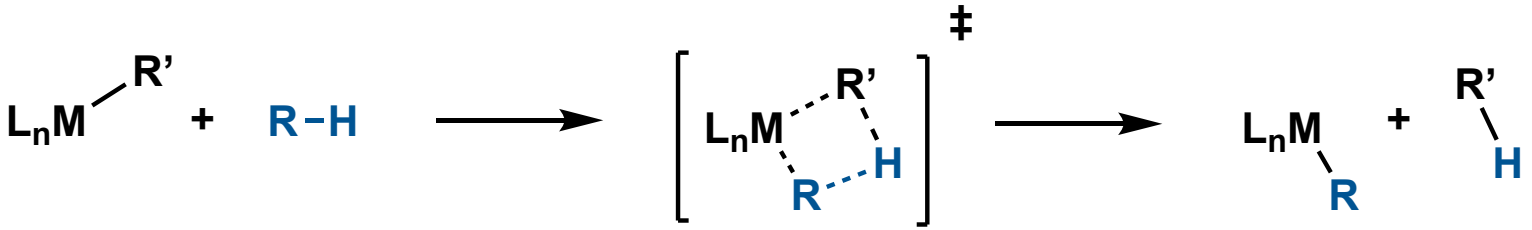
Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006,** *62*, 2439-2463.

For the C-H activation step:

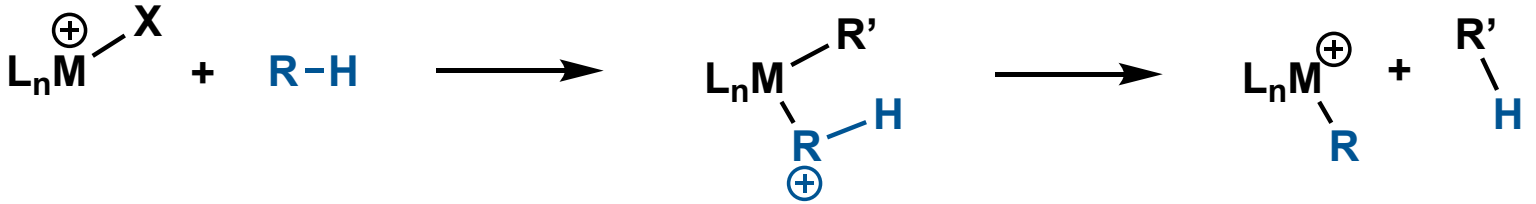
a) Inner sphere mechanism: C-H cleavage

Oxidative addition

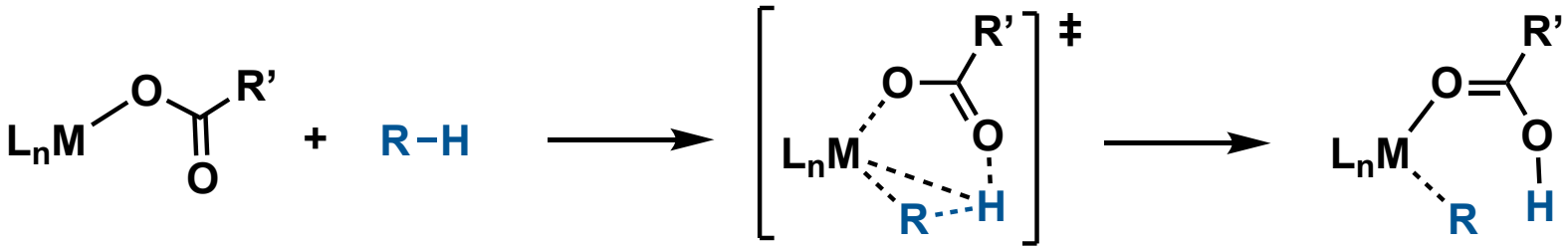
σ-Bond metathesis



Electrophilic substitution



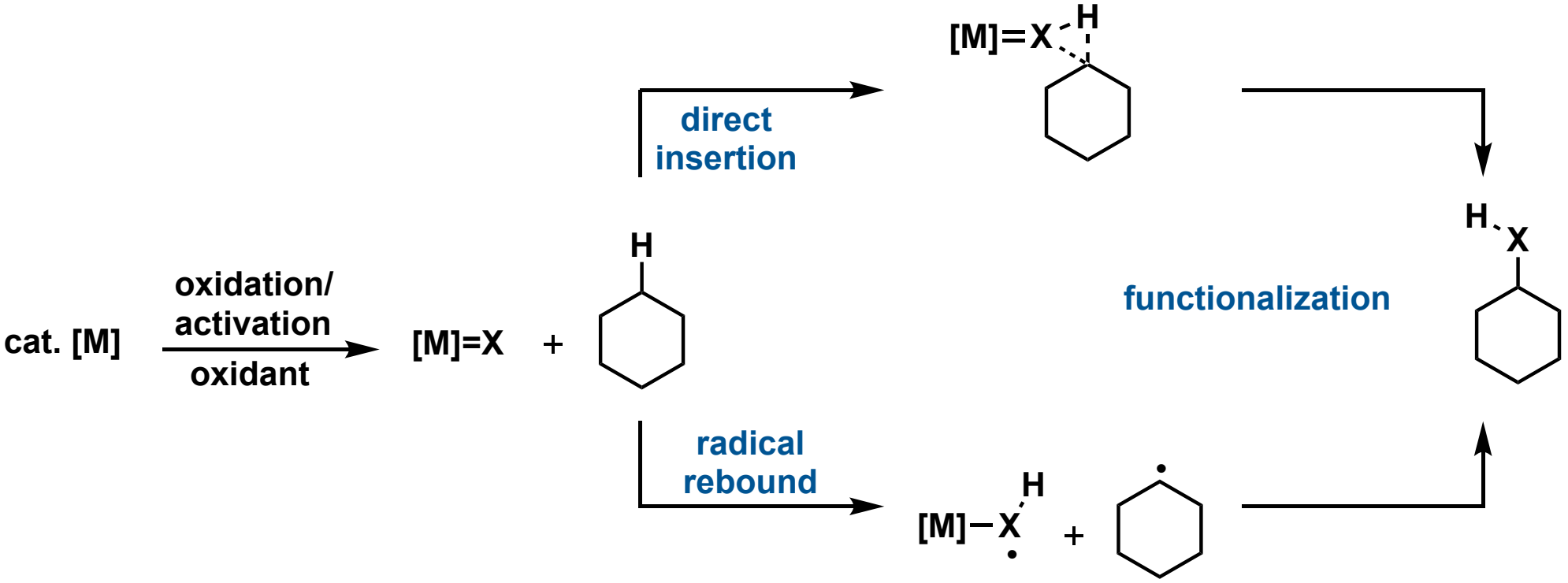
Base assisted metalation



For the C-H activation step:

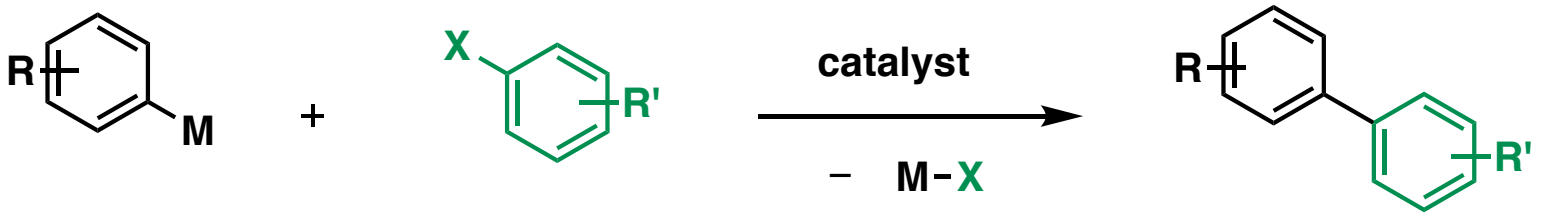
b) Outer sphere mechanism

- Formation of a high oxidation state metal complex with and activated ligand X (generally oxo-, nitrene or carbene species)
- No distinct organometallic species has to be present and that the substrate does not directly interact with the metal catalyst (instead, it reacts with the activated ligand).
- Note: In practice, direct insertion and radical rebound steps are hard to distinguish.
- higher selectivity towards weaker C-H bonds (tertiary, allylic, benzylic or alpha to heteroatoms) due to radical or cationic character



3.1.1. Direct Arylation

"Classical" cross-coupling

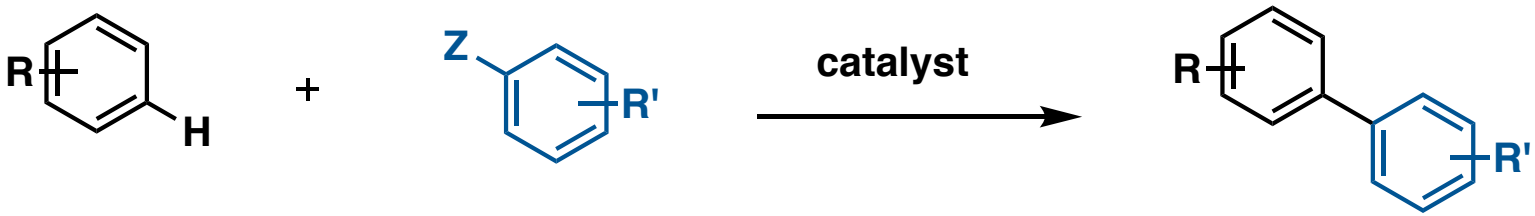


M= SnR_3, $B(OR)_2$, MgX...

X= Cl, Br, I, OSO_2R...

- Stille, Suzuki, Kumada, …
- aryl halide reacts with organometallic nucleophile

Direct arylation

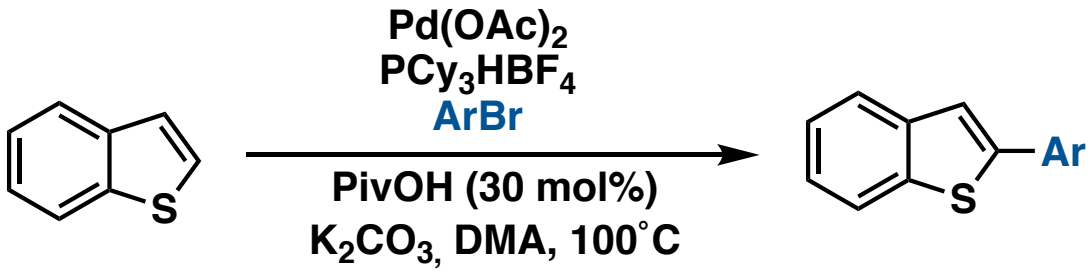


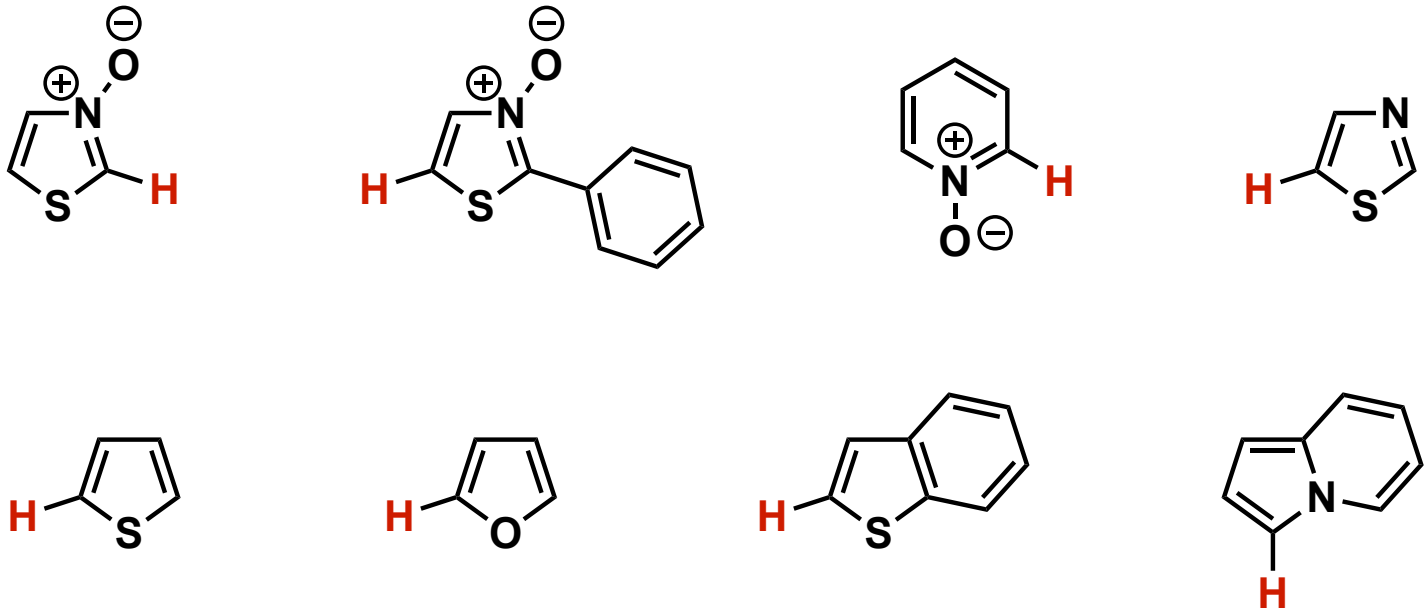
Z = pseudohalide or organometallic

- C-H activation
- replacement of one or both reaction partners

3.1.1. Direct Arylation

Example 1: With aryl halides

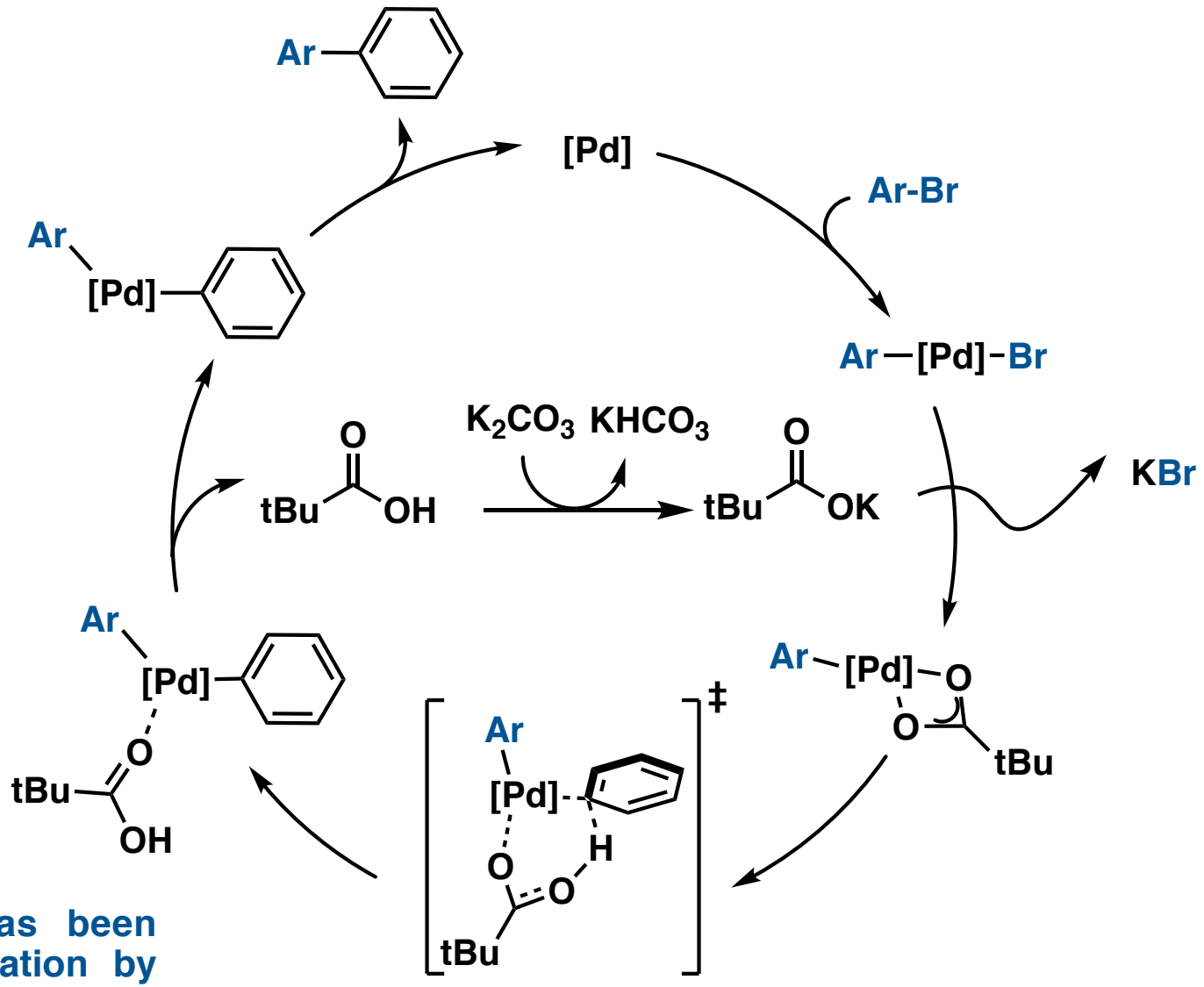




S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.*, **2008**, *130*, 10848–10849.

3.1.1. Direct Arylation

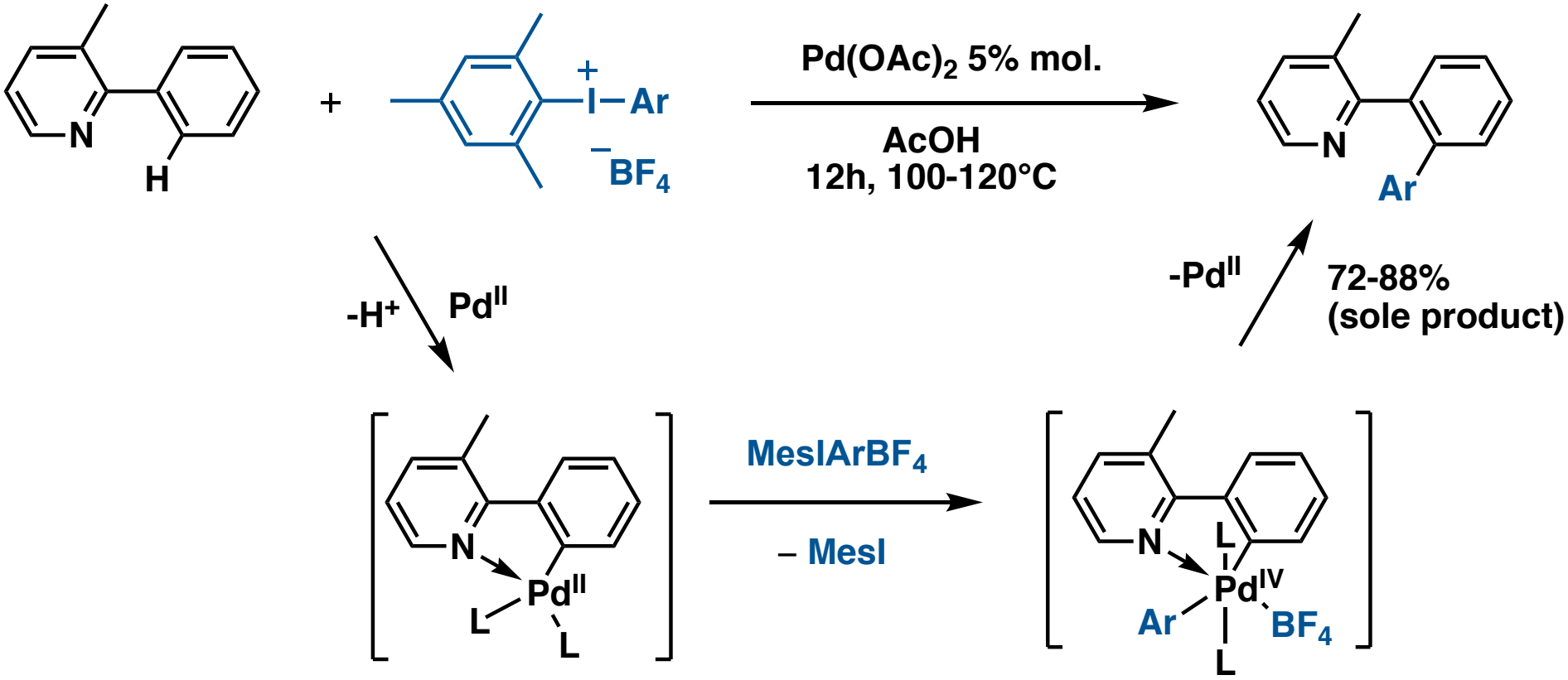
Example 1: With aryl halides



In-situ generated pivalate has been shown to help the C-H activation by stabilizing the Pd and abstracting hydrogen (CMD = Concerted Metalation Deprotonation).

3.1.1. Direct Arylation

Example 2: With aryl iodonium salts



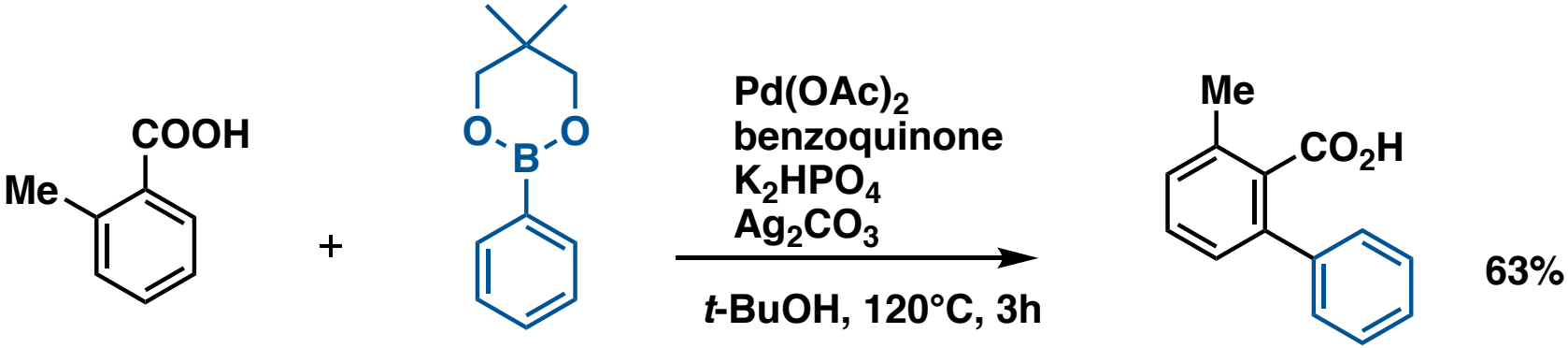
Oxidation of the stable Pd(II) intermediate to unstable Pd(IV) enables reductive elimination.

Review: N. R. Deprez, M. S. Sanford, *Inorg. Chem.*, **2007**, *46*, 1924–1935.

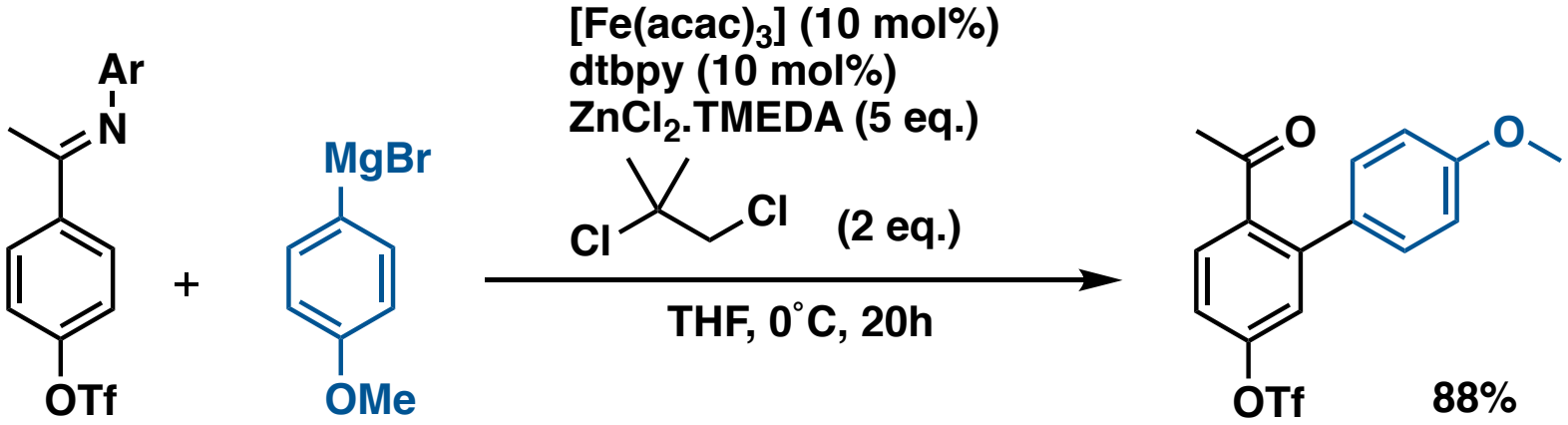
3.1.1. Direct Arylation

Example 3: With organometallic reaction partner

- less studied: requirement of terminal oxidant
  organometallics often more expensive or difficult to prepare



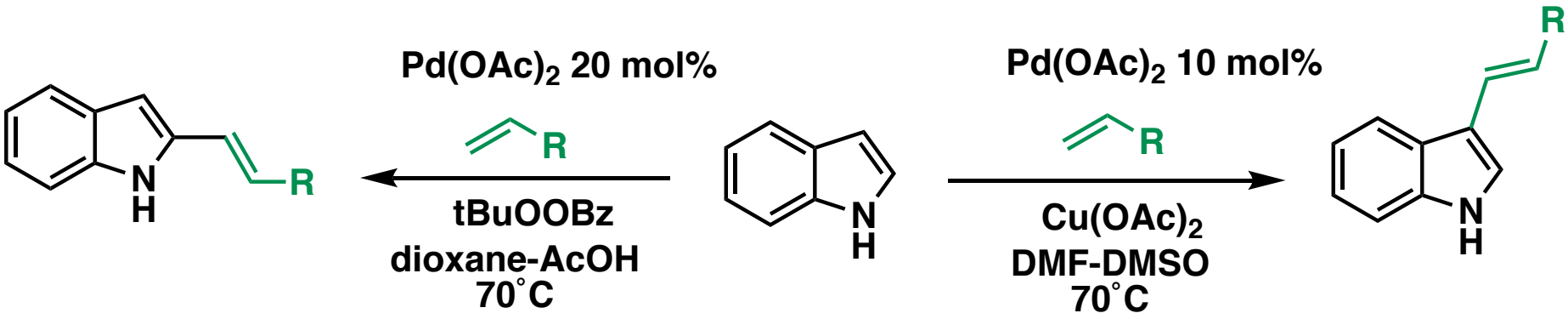
D.-H. Wang, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.*, **2008**, *130*, 17676–17677.



N. Yoshikai, A. Matsumoto, J. Norinder, E. Nakamura, *Angew. Chem., Int. Ed.* **2009**, *48*, 2925-2928.

3.1.2. Other C-C Bond Forming Reactions

Alkene-arene coupling (Heck reaction alternative)



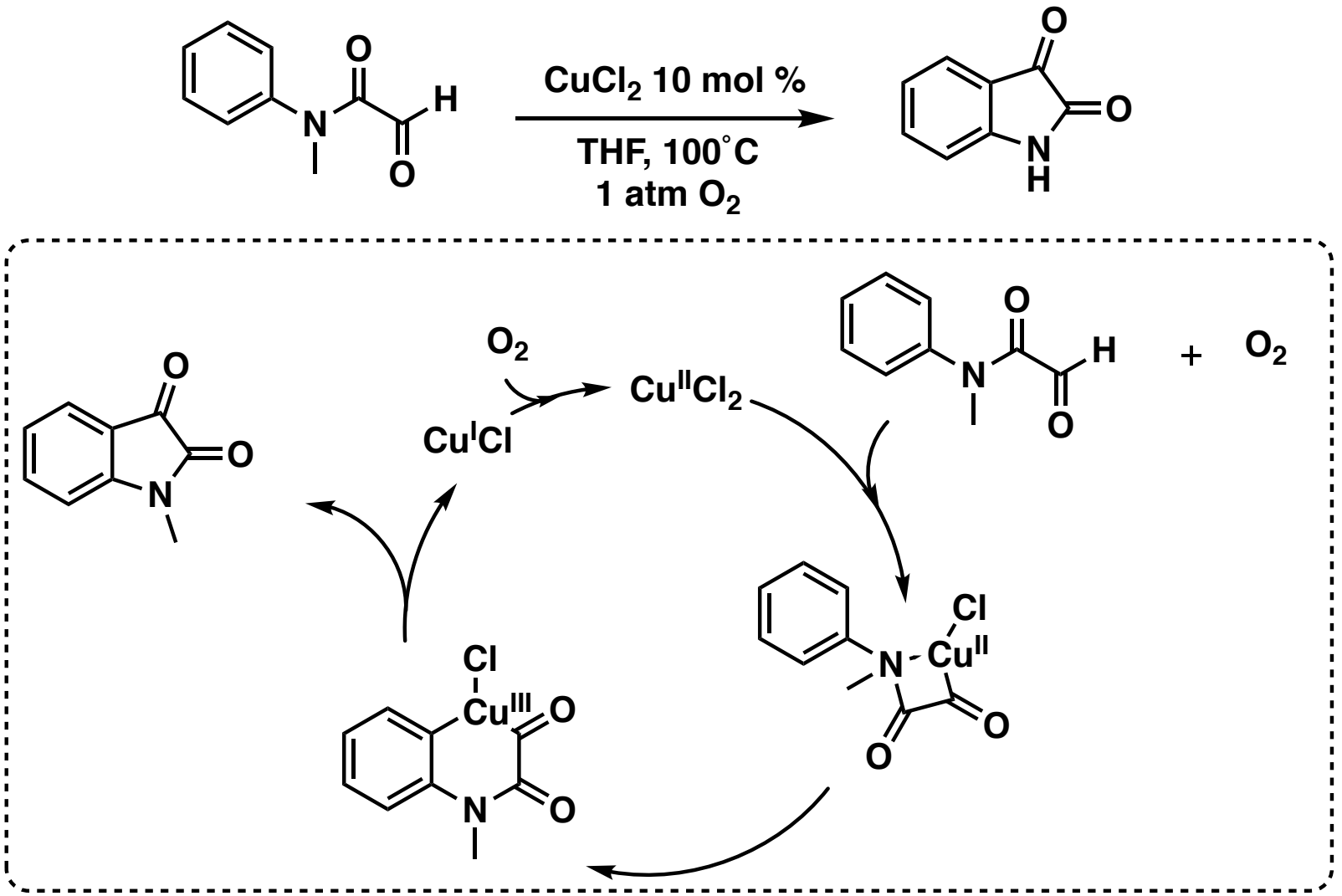
In the presence of acid, Pd at C2 thermodynamically more stable

Innate reactivity

N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem., Int. Ed.* **2005**, *44*, 3125-3129.

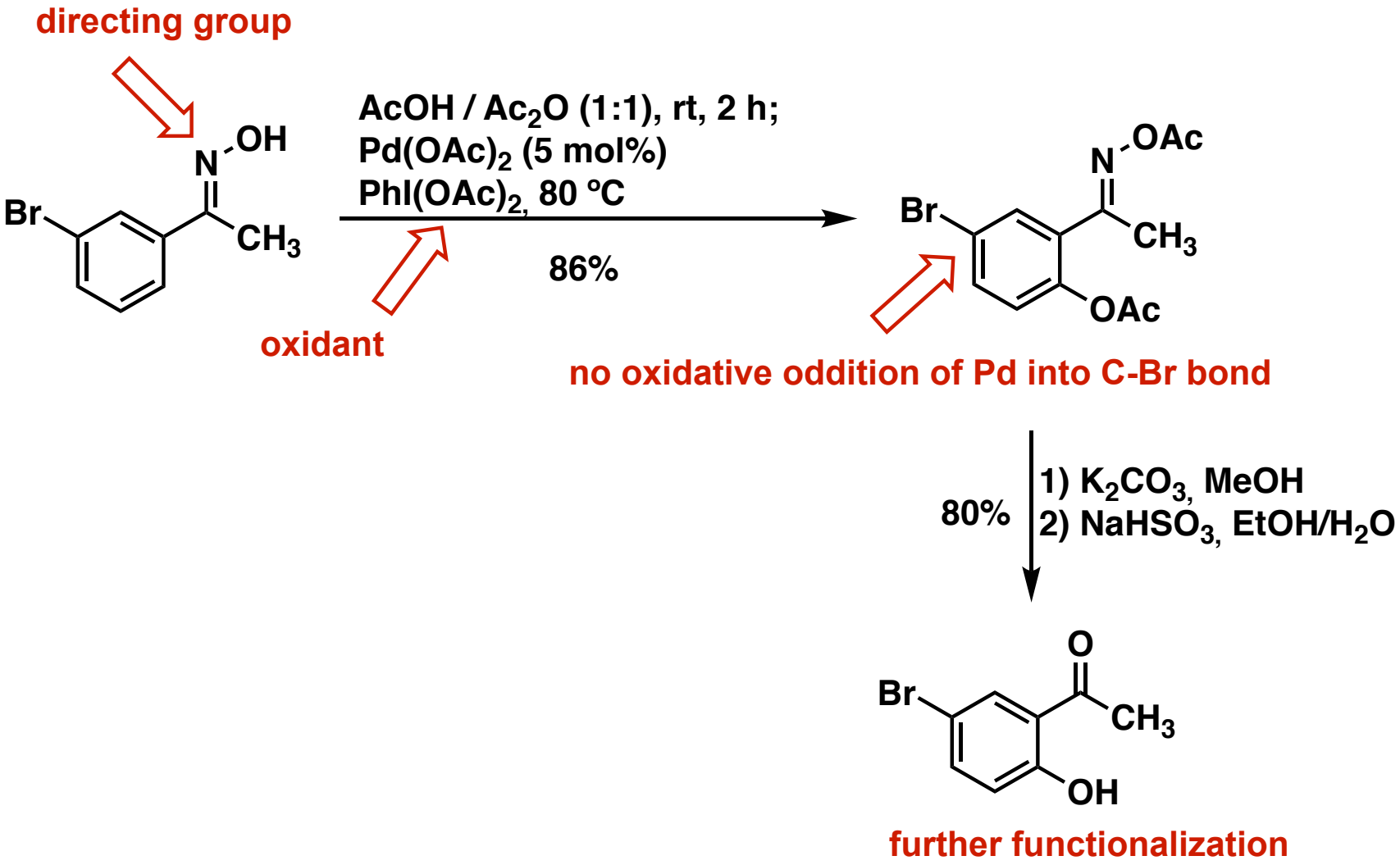
3.1.2. Other C-C Bond Forming Reactions

Aldehyde-arene coupling (Heck reaction alternative)



B.-X. Tang, R.-J. Song, C.-Y. Wu, Y. Liu, M.-B. Zhou, W.-T. Wei, G.-B. Deng, D.-L. Yin, J.-H. Li, *J. Am. Chem. Soc.* **2010**, *132*, 8900-8902.

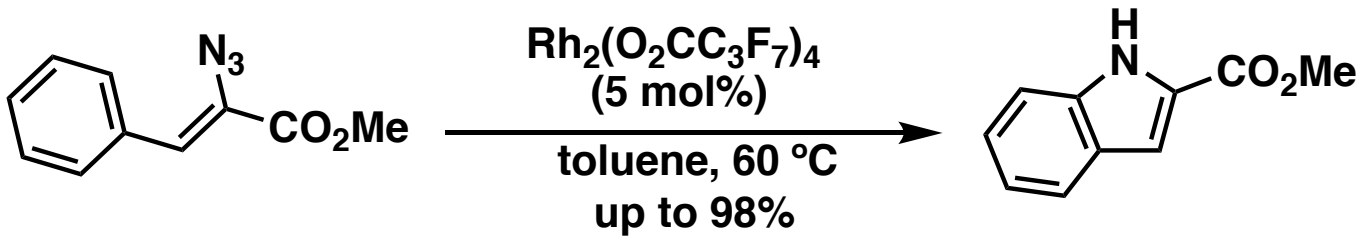
3.2.1. C-O Bond Formation



S. R. Neufeldt, M. S. Sanford, *Org. Lett.* **2010**, *12*, 532-535.

3.2.2. C-N Bond Formation

Intramolecular C-N bond formation via nitrenes

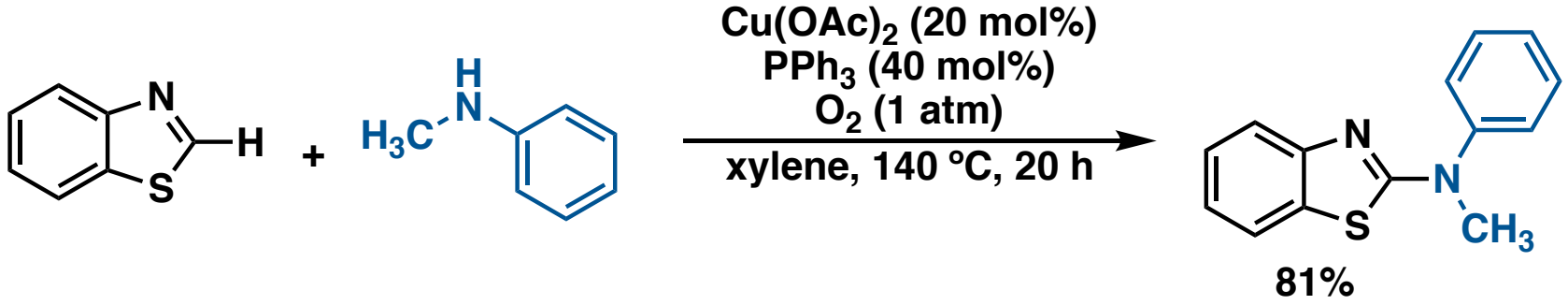


Vinyl azide

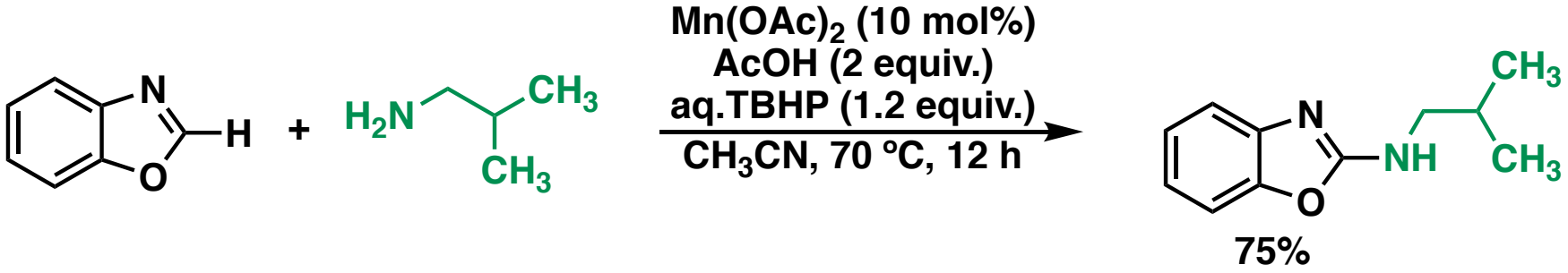
B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey, T. G. Driver, *J. Am. Chem. Soc.* **2007**, *129*, 7500-7501.

3.2.2. C-N Bond Formation

Intermolecular oxidative amination of heterocycles



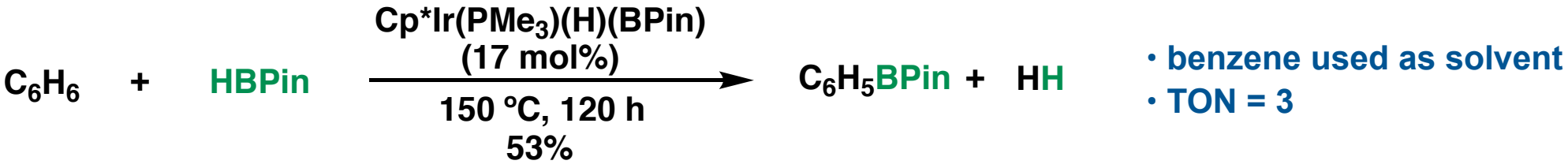
D. Monguchi, T. Fujiwara, H. Furukawa, A. Mori, *Org. Lett.* **2009**, *11*, 1607-1610.



J. Y. Kim, S. H. Cho, J. Joseph, S. Chang, *Angew. Chem., Int. Ed.* **2010**, *49*, 9899-9903.

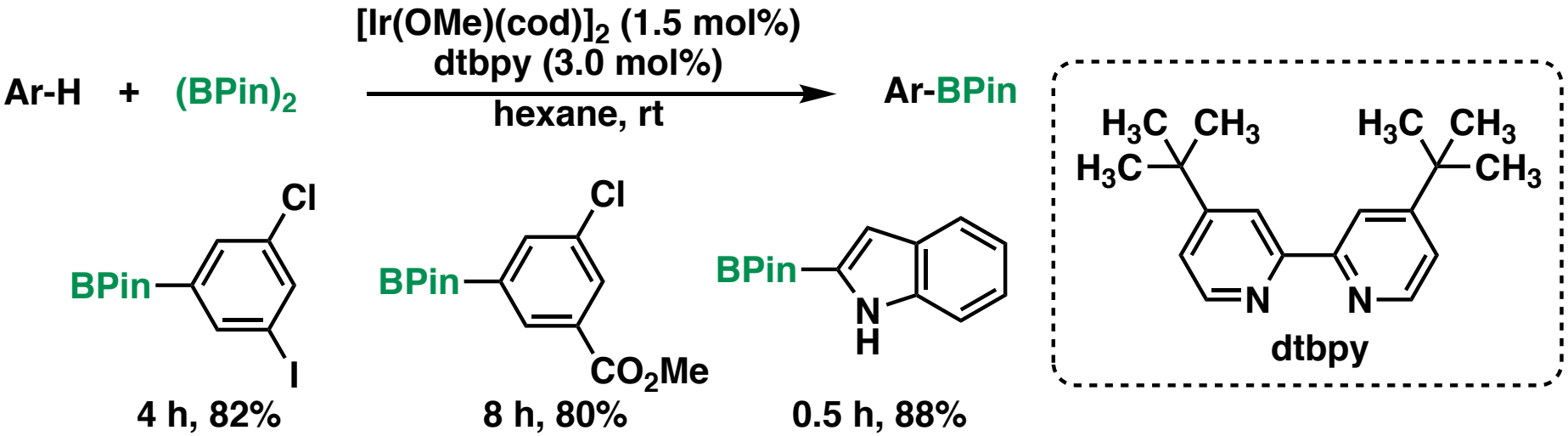
3.2.3. C-B Bond Formation

Seminal work



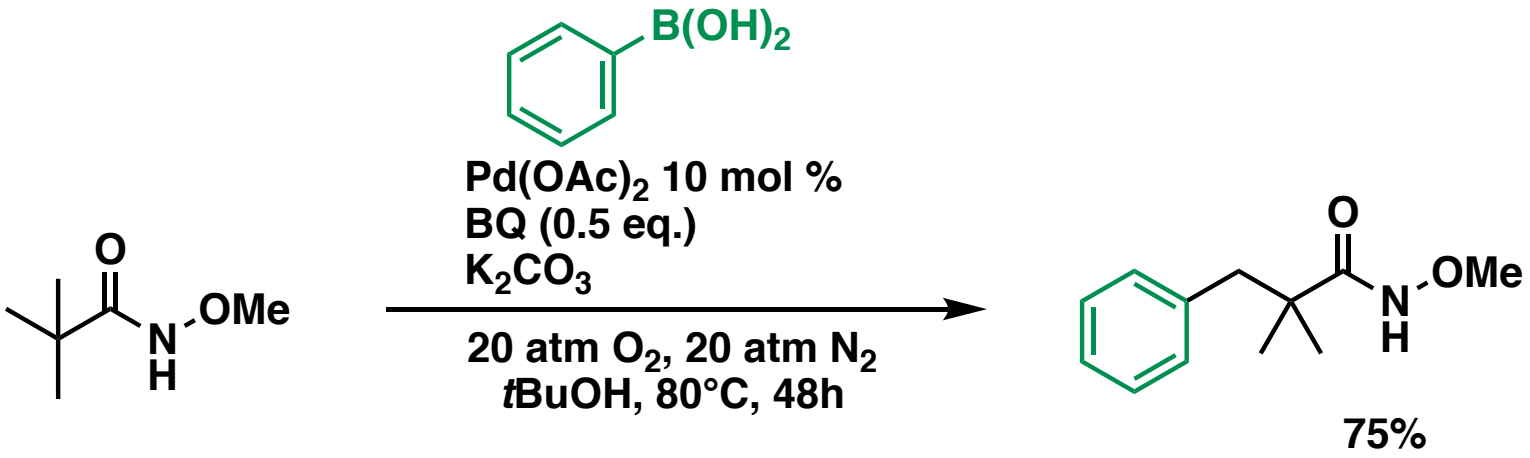
C. N. Iverson, M. R. Smith, *J. Am. Chem. Soc.* **1999**, *121*, 7696-7697.

Increased activity with ligands



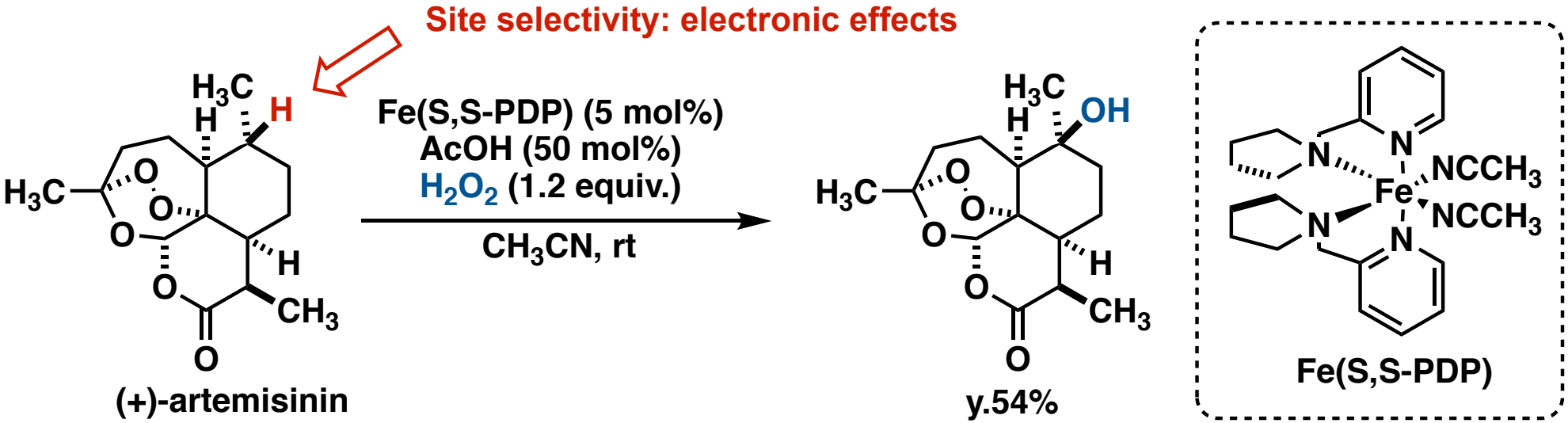
T. Ishiyama, J. Takagi, J. F. Hartwig, N. Miyaura, *Angew. Chem. Int. Ed.* **2002**, *41*, 3056-3058.

4.1.1. Direct Arylation



D.-H. Wang, M. Wasa, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 7190-7191.

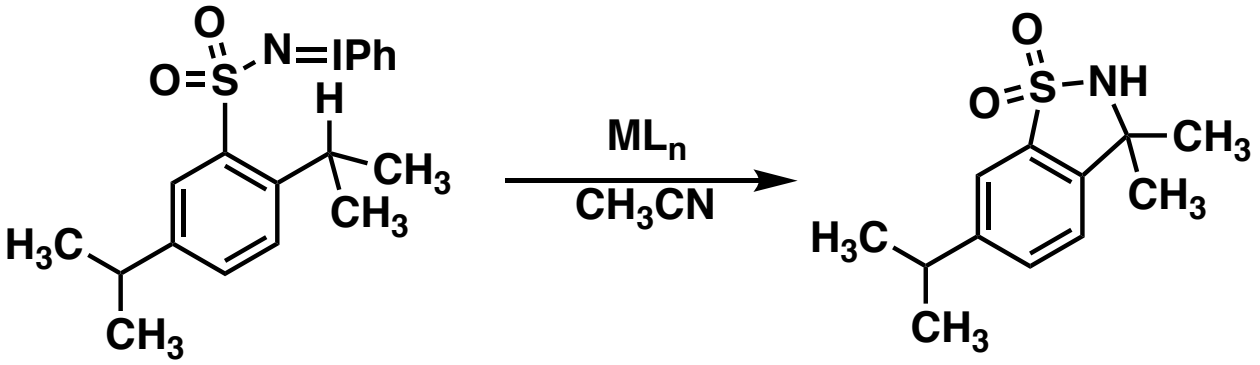
4.2.1. C-O Bond Formation



M. S. Chen, M. C. White, *Science* **2007**, *318*, 783-787.

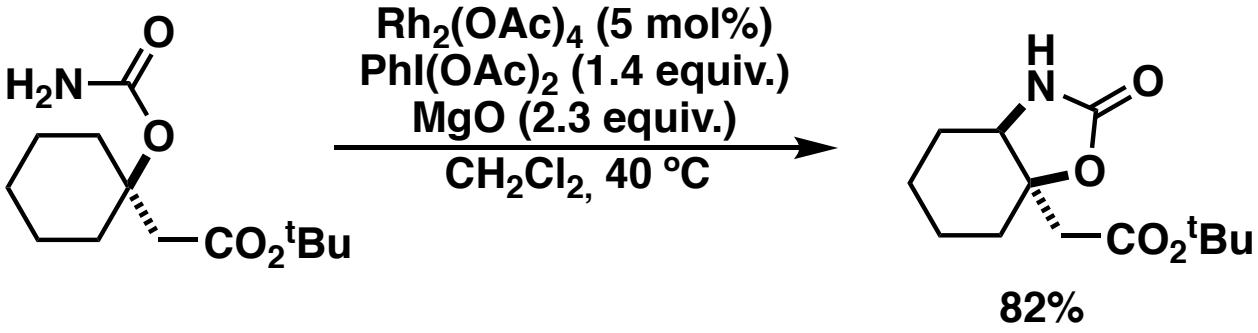
4.2.2. C-N Bond Formation

Via nitrenes:



ML_n	yield (%)
Mn(TPP)Cl	16
Fe(TPP)Cl	77
$[Fe(cyclam)Cl_2]Cl$	42
$FeCl_3$	16
$Rh_2(OAc)_4$	86

R. Breslow, S. H. Gellman, *J. Am. Chem. Soc.* **1983**, *105*, 6728-6729.



82%

C. G. Espino, J. Du Bois, *Angew. Chem., Int. Ed.* **2001**, *40*, 598-600.

4. Total Syntheses