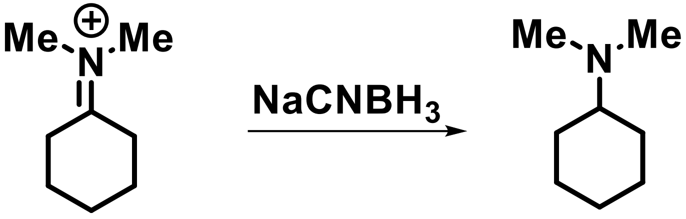
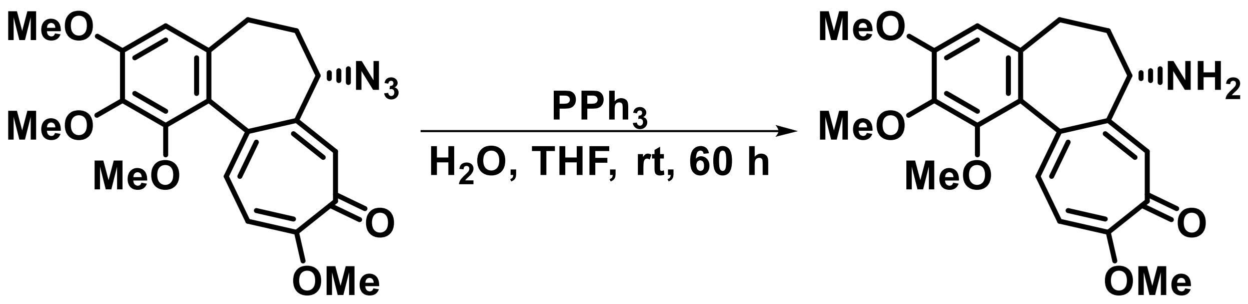
Formation of C–Heteroatom Bonds

➢ C–N bond formation

- **Traditional approach to amines**

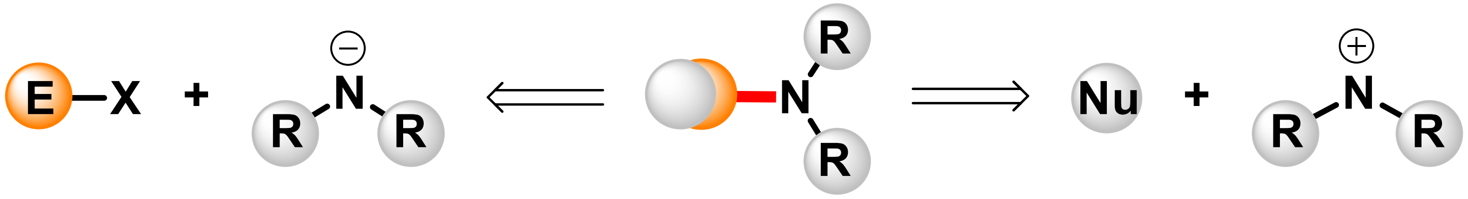


Clayden, J.; Greeves, N.; Waren, S. *Organic Chemistry*

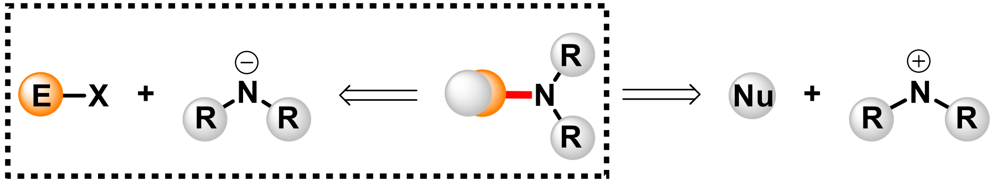


Pure Appl. Chem. **1996**, *68*, 539

- **Transition-metal-catalyzed approach**

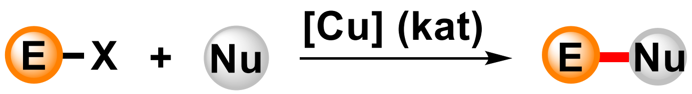


Formation of C–Heteroatom Bonds



➢ C–N bond formation

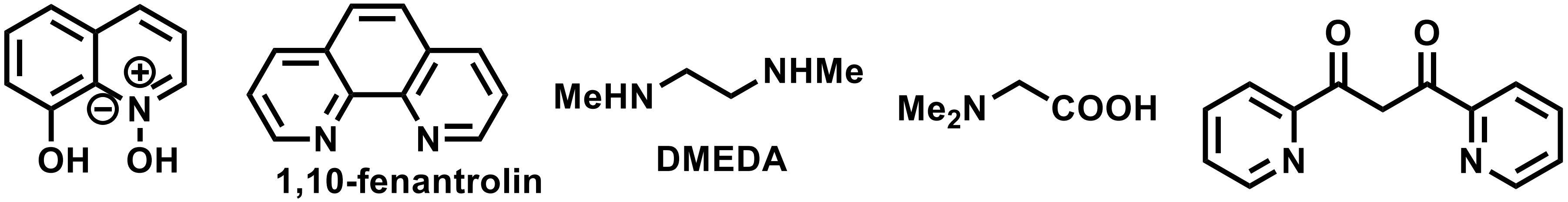
- Ullmann condensation



X = Cl, Br, I

Nu = NH_3, RNH_2, R_2NH, ROH, H_2O, RSH

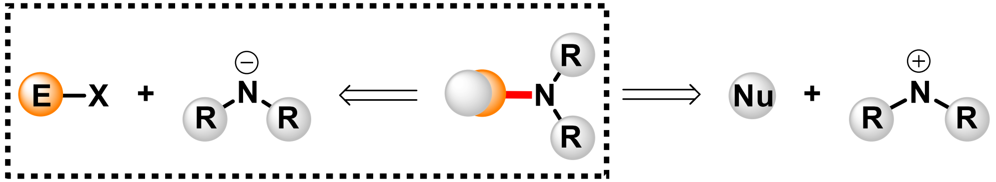
Typical ligands

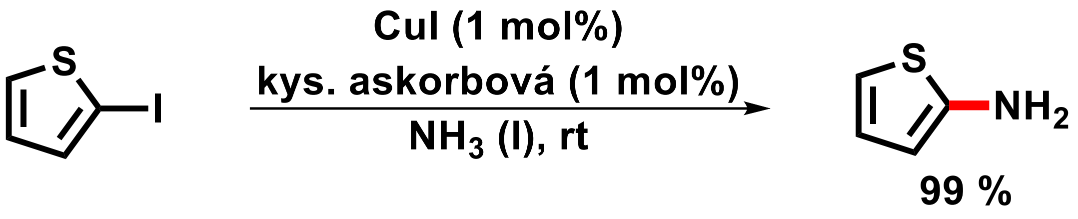


Formation of C–Heteroatom Bonds

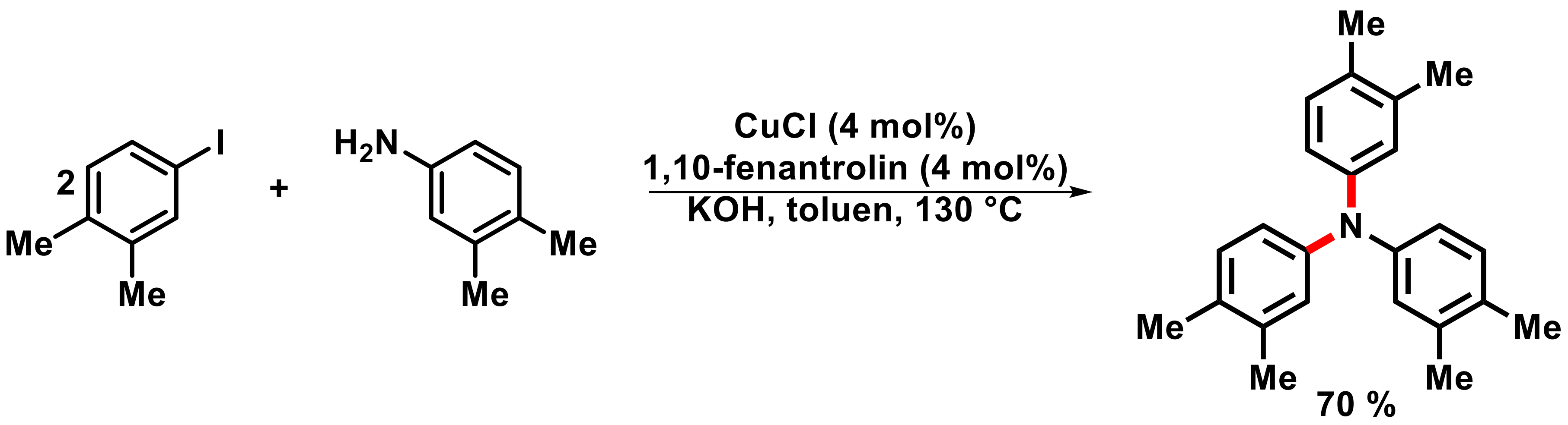
➢ C–N bond formation

- **Ullmann condensation**





J. Org. Chem. **2012**, *77*, 7471

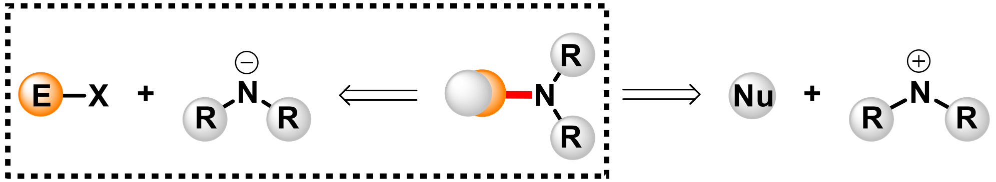


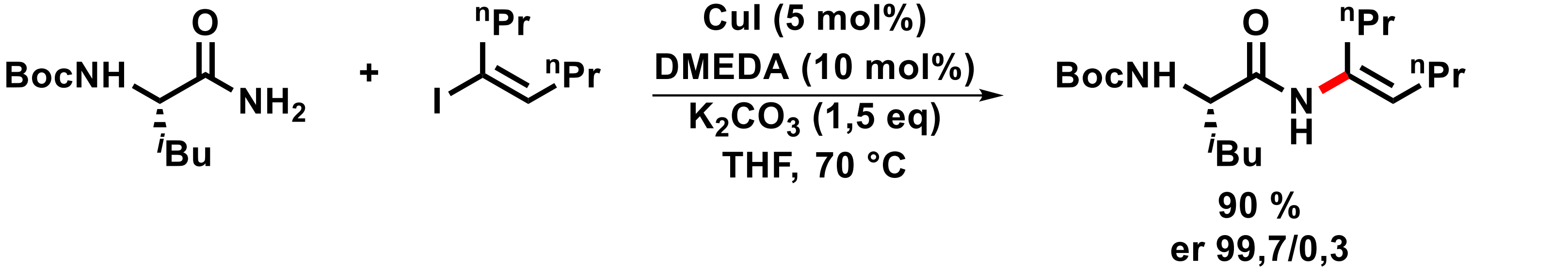
J. Org. Chem. **1999**, *64*, 670

Formation of C–Heteroatom Bonds

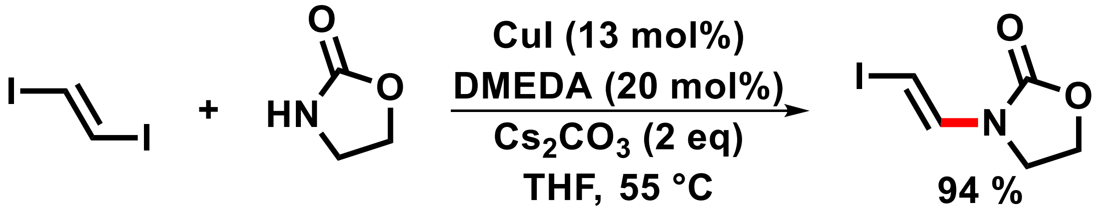
➢ C–N bond formation

- **Ullmann-Goldberg reaction**



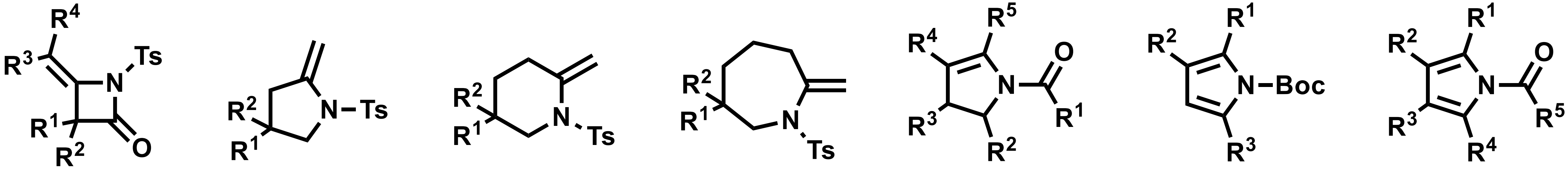


Org. Lett. **2007**, *9*, 5617



Tetrahedron Lett. **2008**, *26*, 4196

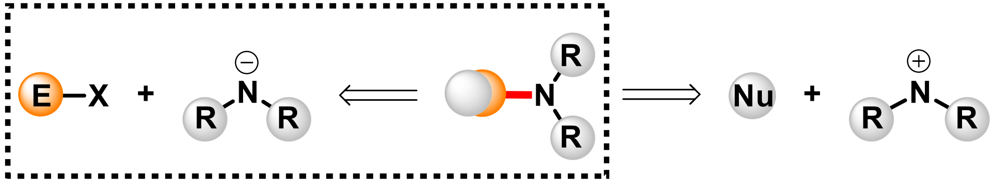
- ○ **Available heterocycles**

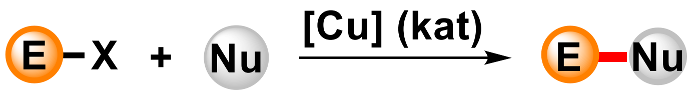


Formation of C–Heteroatom Bonds

➢ C–N bond formation

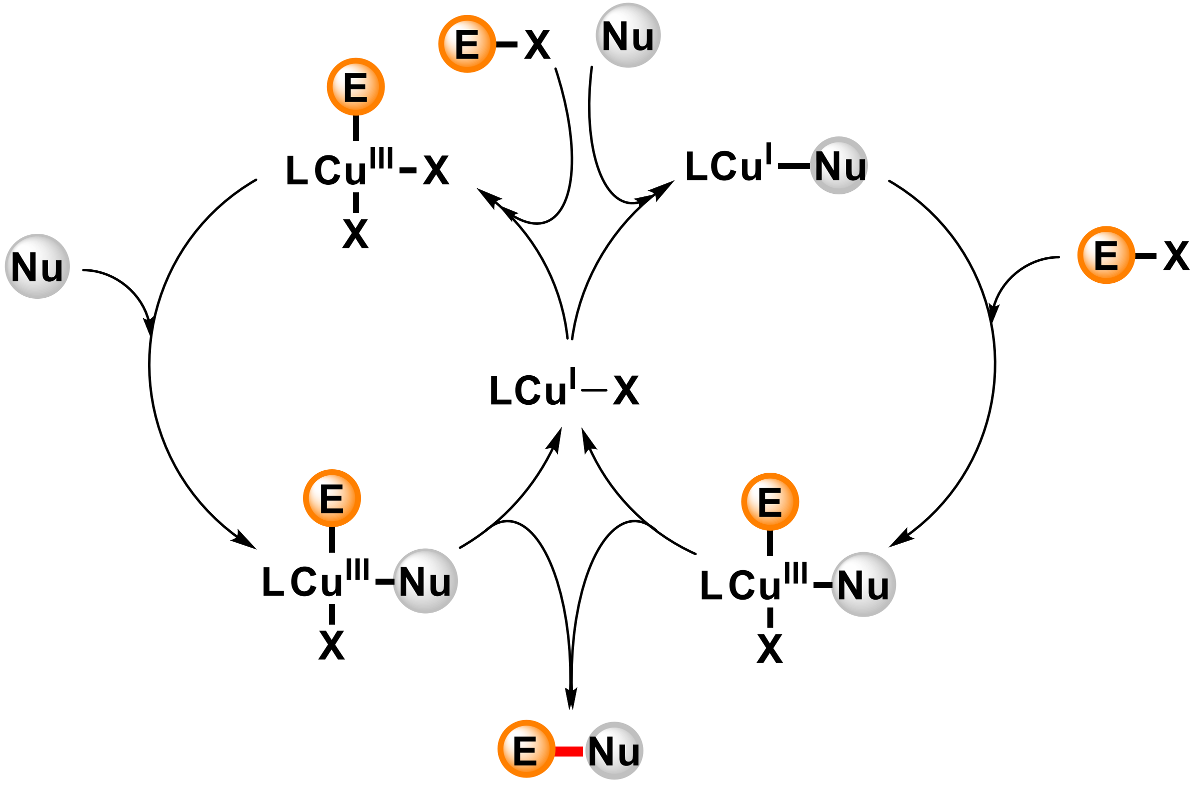
- **Ullmann condensation – Mechanism**



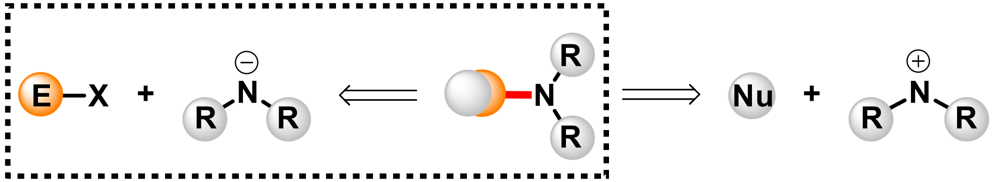


X = Cl, Br, I

Nu = NH_3, RNH_2, R_2NH, ROH, H_2O, RSH



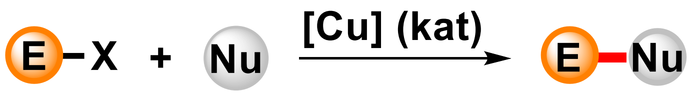
Formation of C–Heteroatom Bonds



➢ C–N bond formation

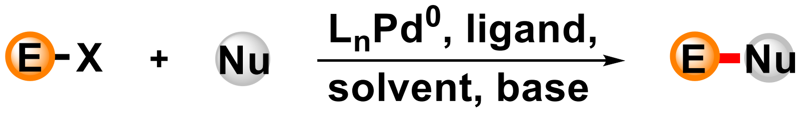
- **Buchwald-Hartwig amination**

○ Ullmann



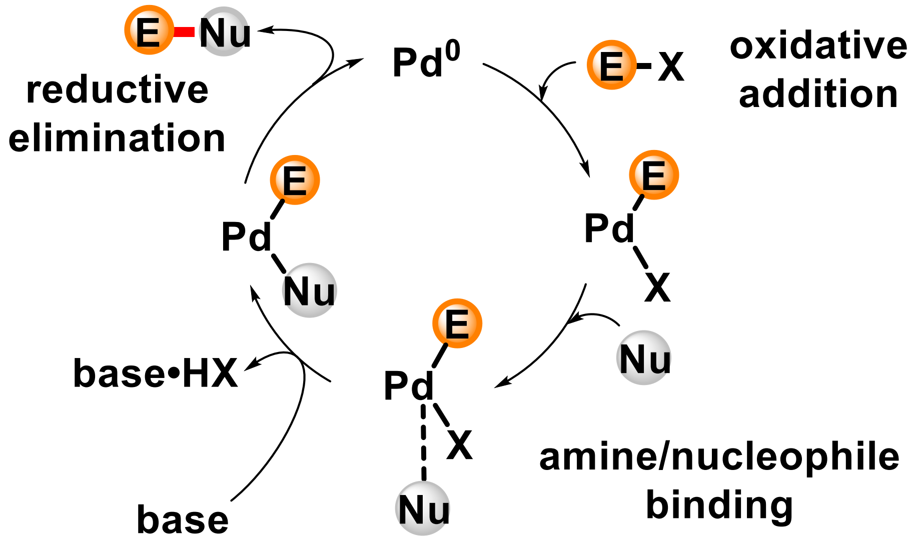
X = Cl, Br, I
Nu = NH_3, RNH_2, R_2NH, ROH, H_2O, RSH

○ Buchwald-Hartwig

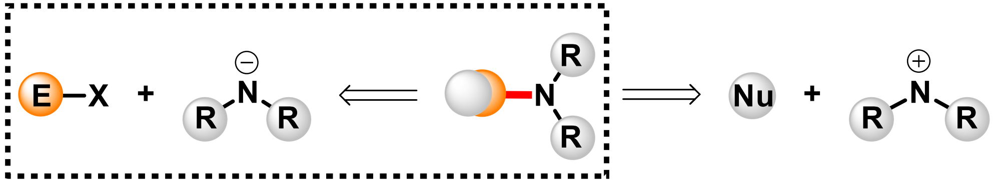


X = Cl, Br, I
Nu = NH_3, RNH_2, R_2NH, ROH, H_2O, RSH

○ Mechanism of the Buchwald-Hartwig reaction

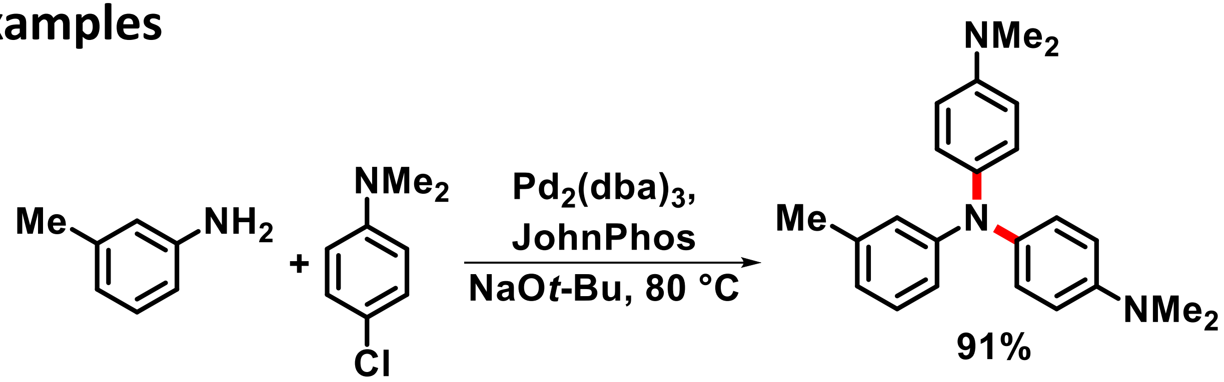


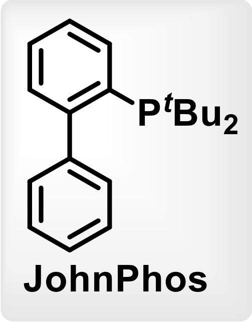
Formation of C–Heteroatom Bonds



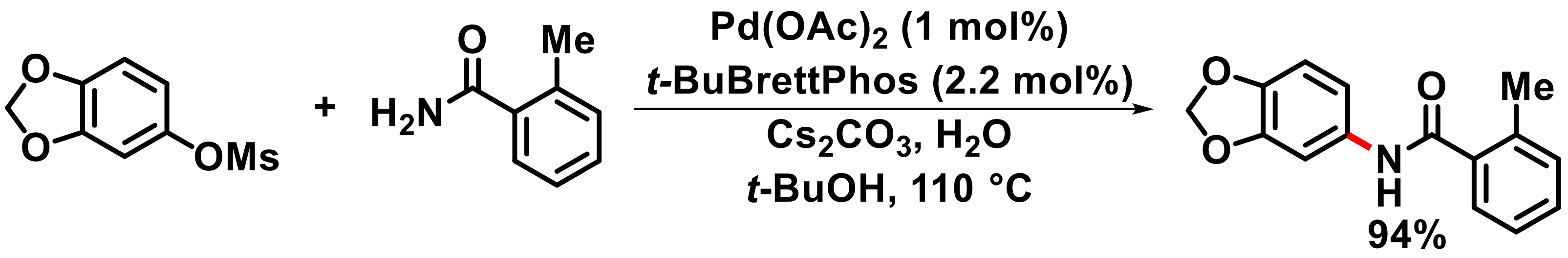
C–N bond formation

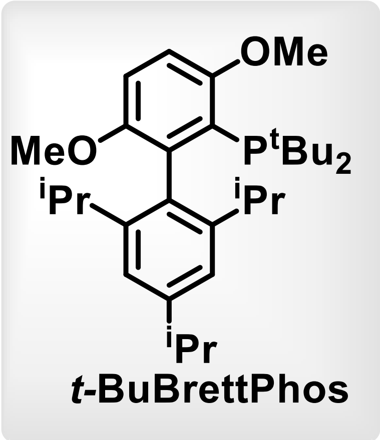
- **Buchwald-Hartwig amination**
  - Selected examples





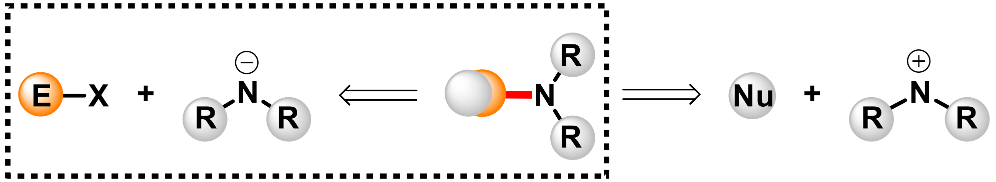
J. Org. Chem. **2000**, *65*, 5327





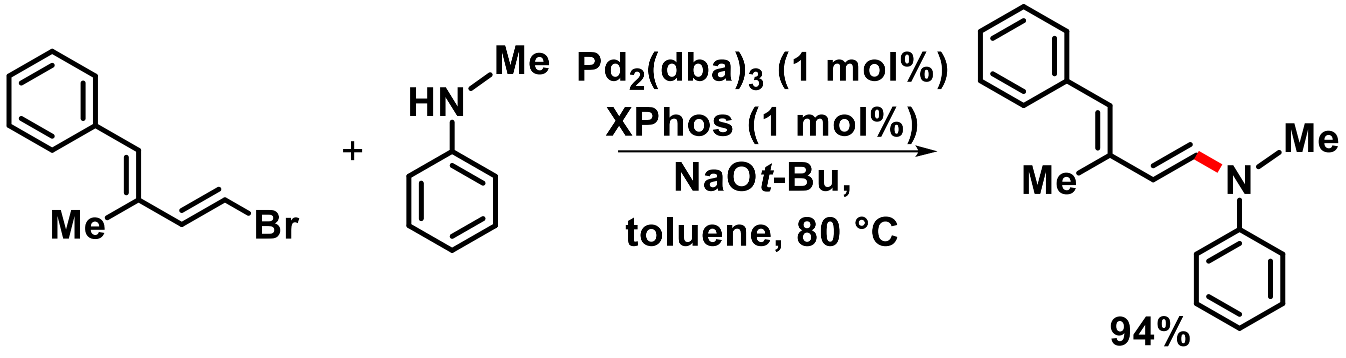
Org. Lett. **2010**, *12*, 2350

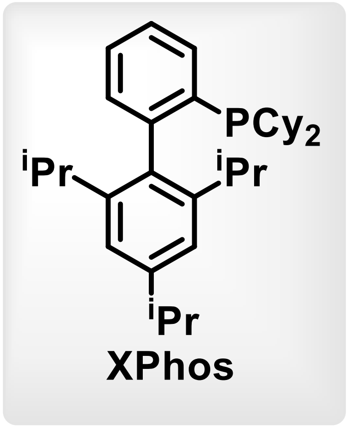
Formation of C–Heteroatom Bonds



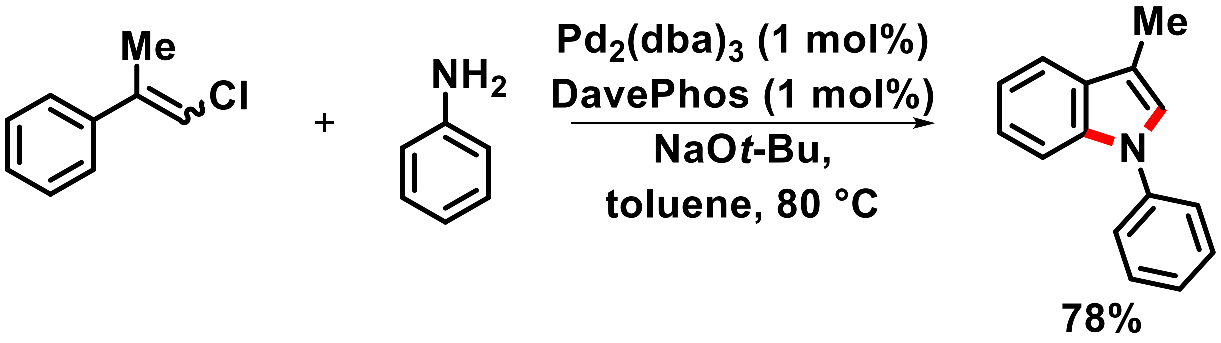
➢ C–N bond formation

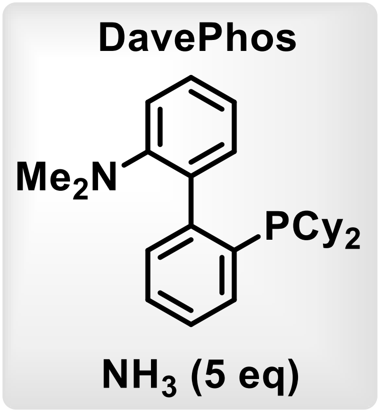
- Buchwald-Hartwig amination
  - Selected examples





Adv. Synth. Catal. **2004**, *346*, 1697



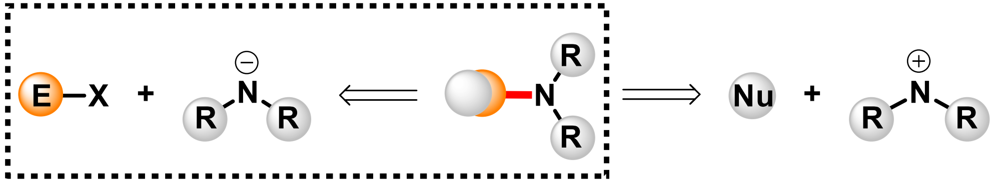


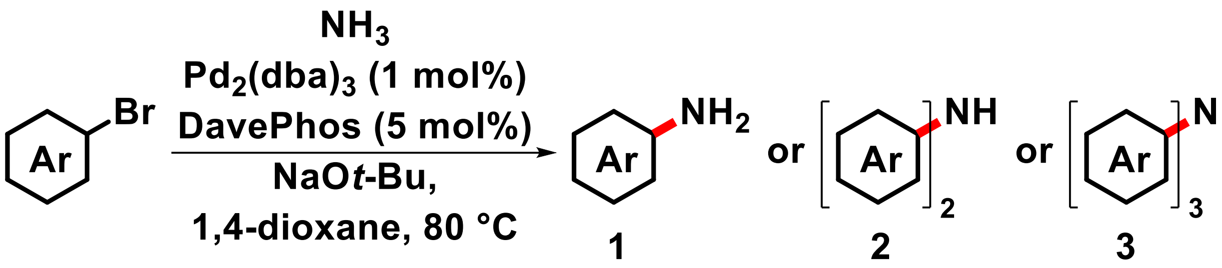
Adv. Synth. Catal. **2006**, *348*, 851

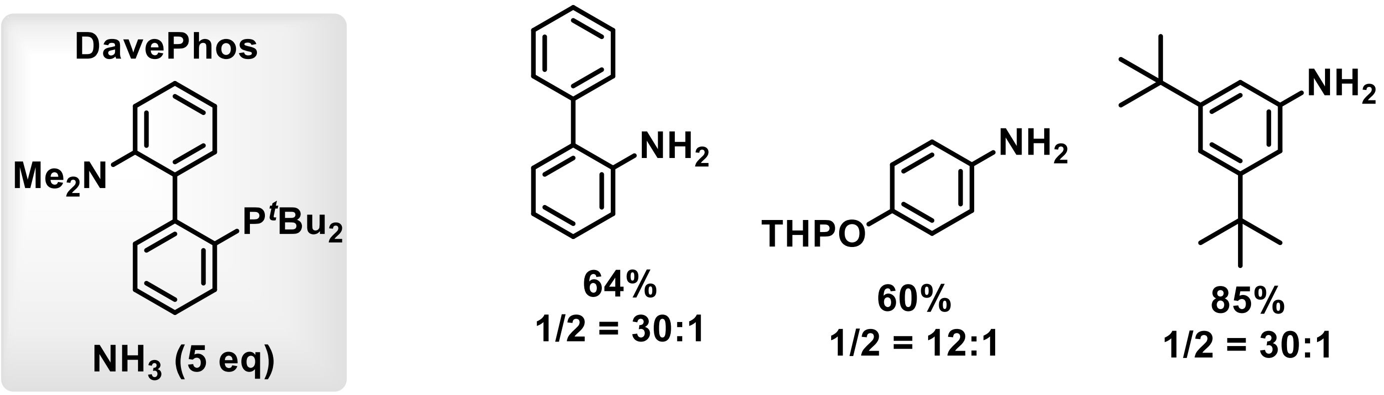
Formation of C–Heteroatom Bonds

➢ C–N bond formation

- **Buchwald-Hartwig amination**
  - **Amination with NH_3**

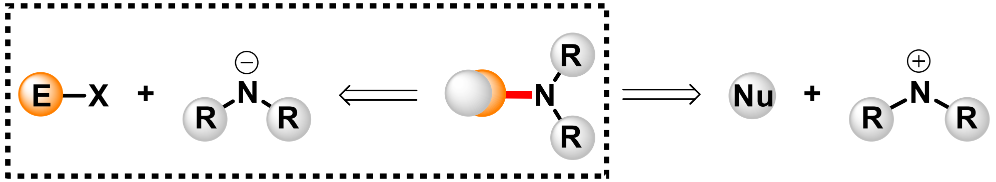






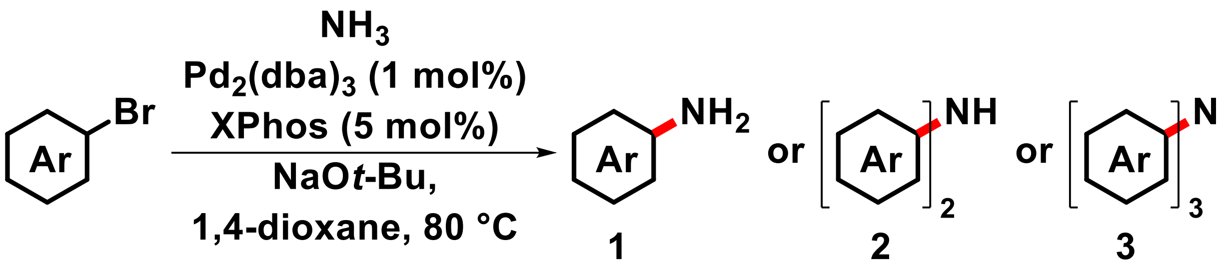
JACS **2007**, *129*, 10354

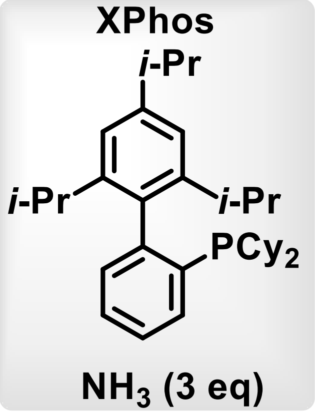
Formation of C–Heteroatom Bonds

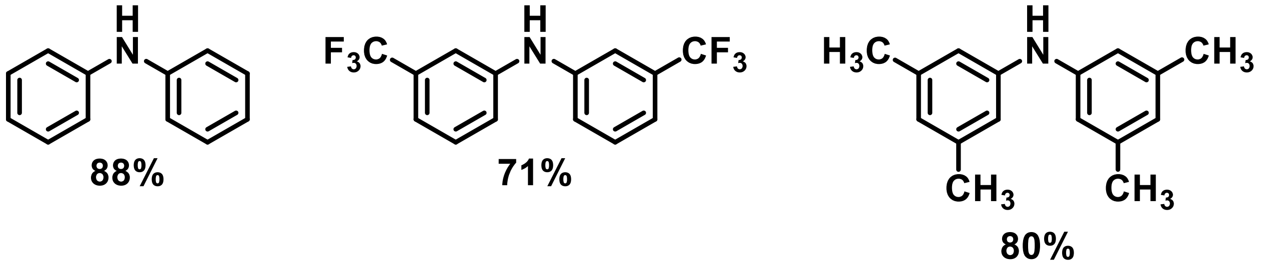


C–N bond formation

- **Buchwald-Hartwig amination**
  - **Amination with NH_3**

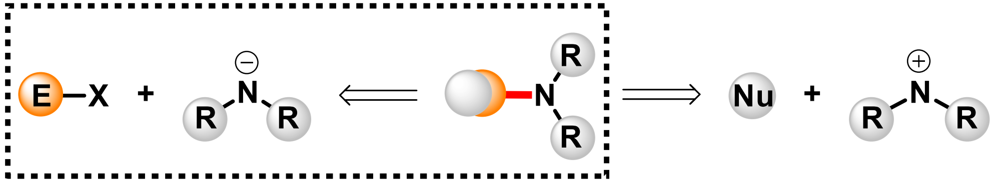






JACS **2007**, *129*, 10354

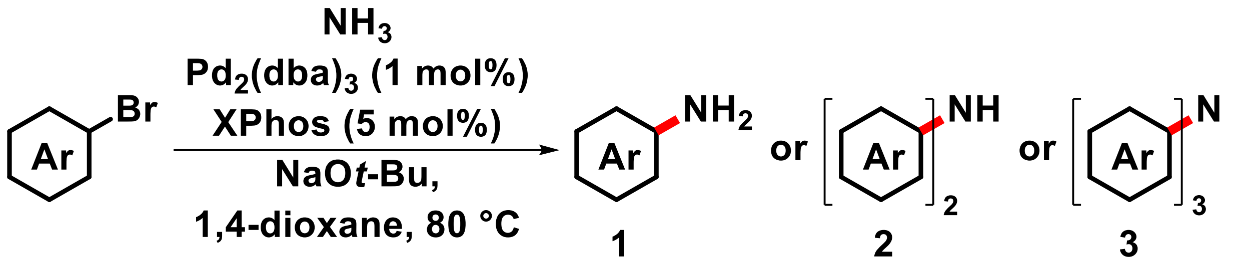
Formation of C–Heteroatom Bonds

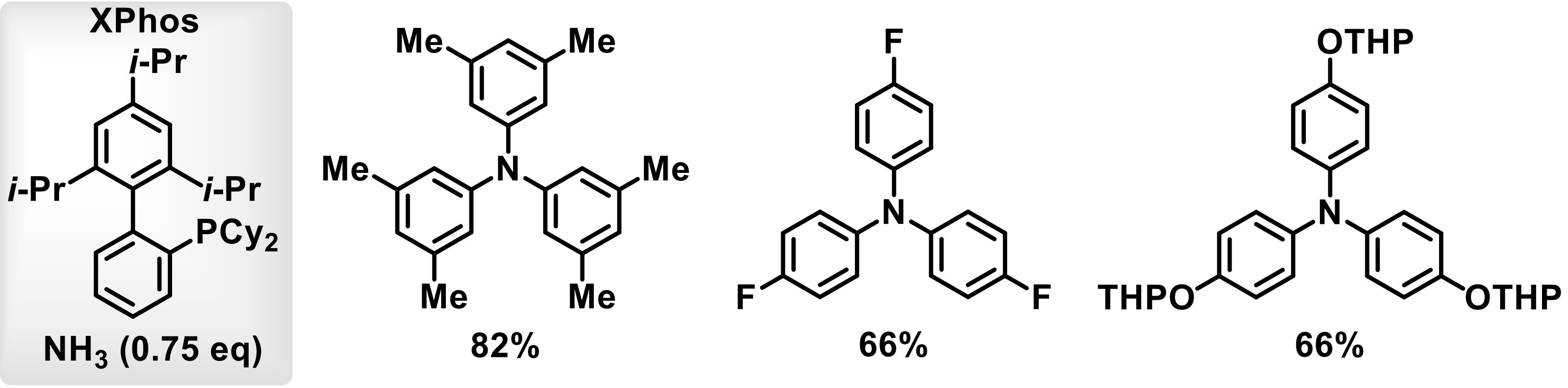


➢ C–N bond formation

- **Buthwald-Hartwig amination**

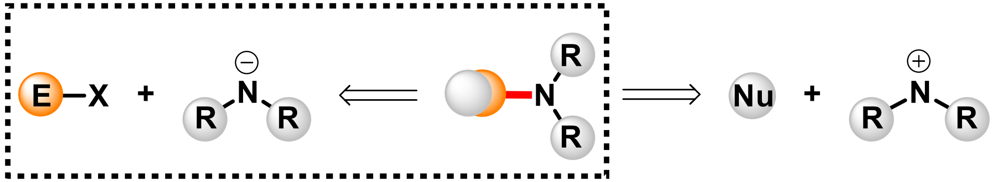
  ○ **Amination with NH_3**





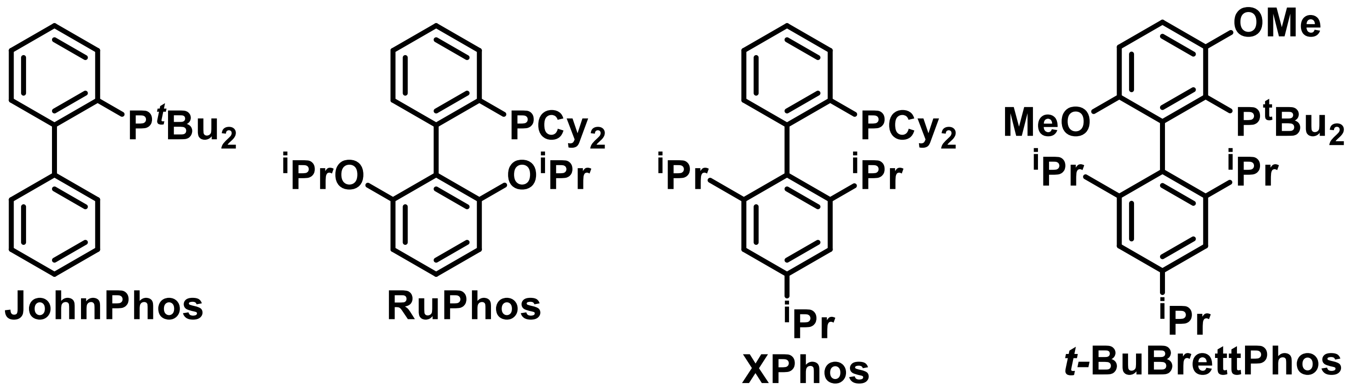
JACS **2007**, *129*, 10354

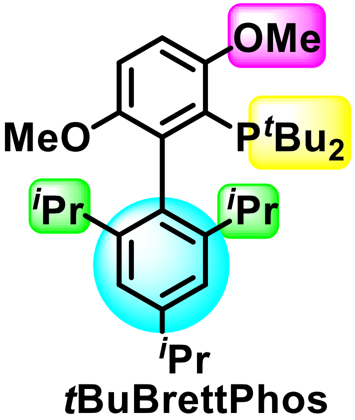
Formation of C–Heteroatom Bonds



➢ C–N bond formation

- **Buchwald-Hartwig amination**
  - **Ligands for the Buchwald-Hartwig reaction**





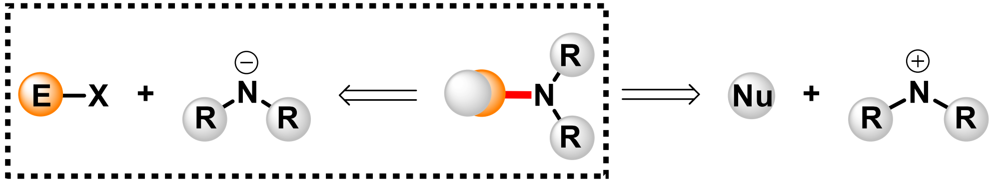
- Large substituents promote reductive elimination
- Electron-rich groups enhance rate of oxidative addition

- Prevent oxidation at P by O_2
- Accelerates reductive elimination

- Substitution accelerates reductive elimination

- Increase catalyst stability by preventing cyclometalation
- Encourage formation of L_1Pd

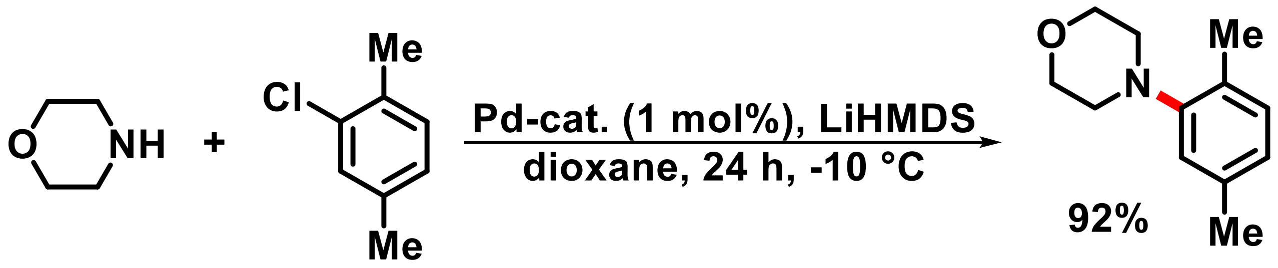
Formation of C–Heteroatom Bonds

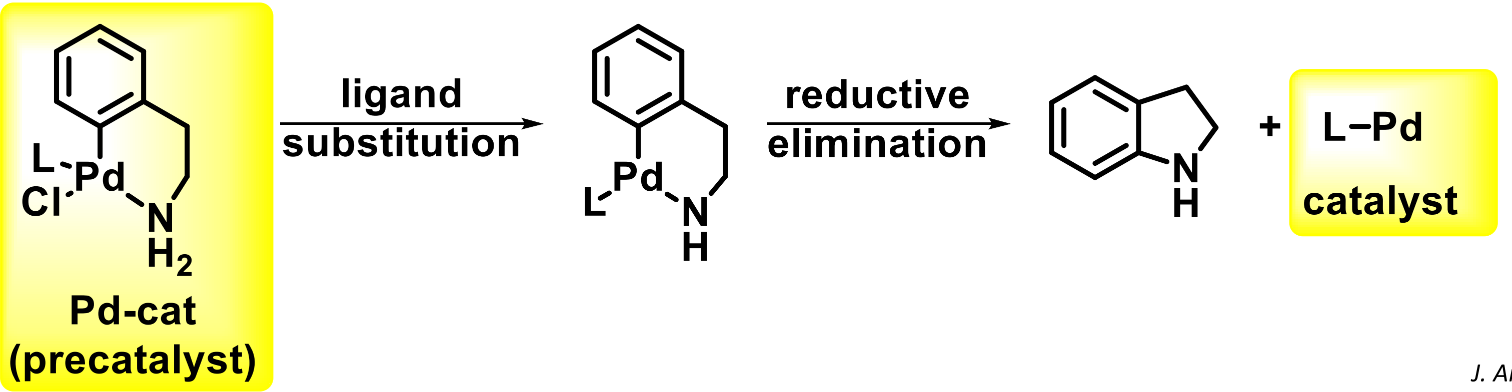


➢ C–N bond formation

- Buchwald-Hartwig amination

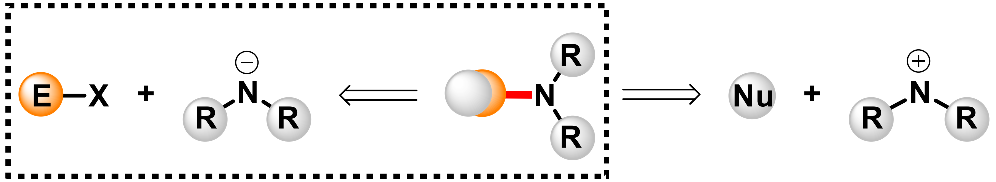
  ○ Highly active catalyst for Buchwald-Hartwig reaction





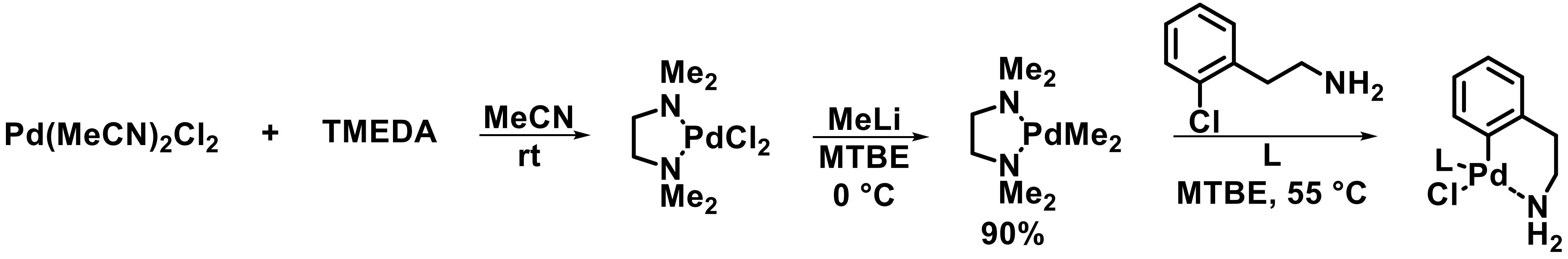
J. Am. Chem. Soc. **2008**, *130*, 6686

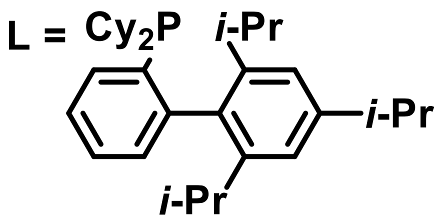
Formation of C–Heteroatom Bonds



➢ C–N bond formation

- **Buchwald-Hartwig amination**
  - **Highly active precatalyst preparation**

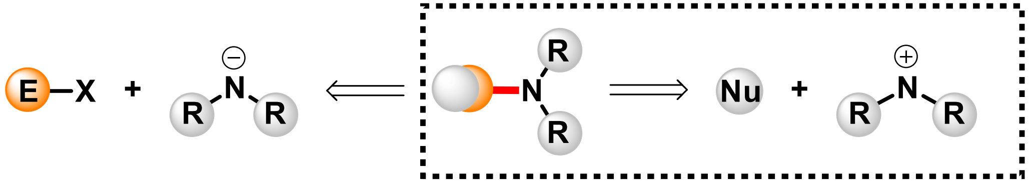




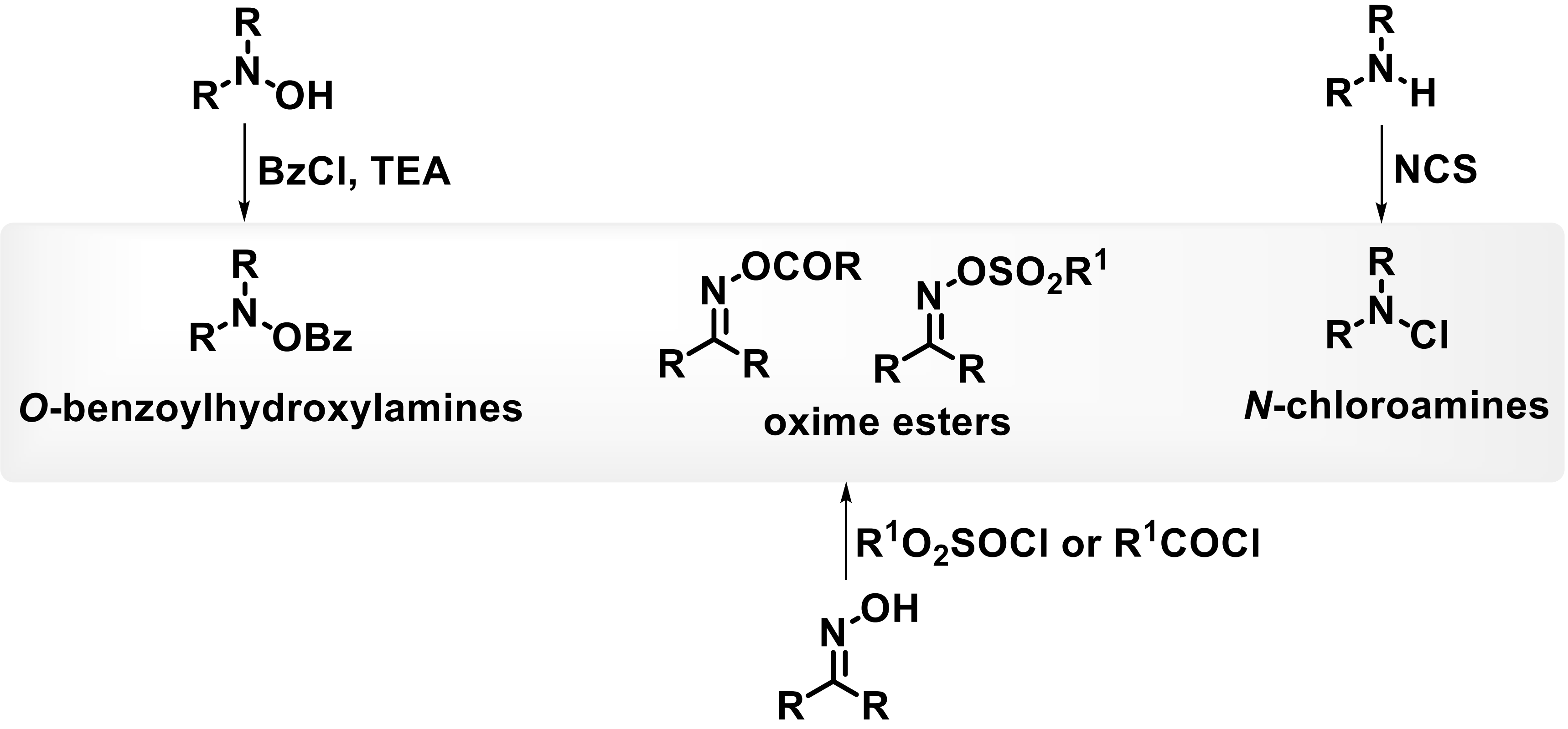
J. Am. Chem. Soc. **2008**, *130*, 6686

Formation of C–Heteroatom Bonds

➢ C–N bond formation

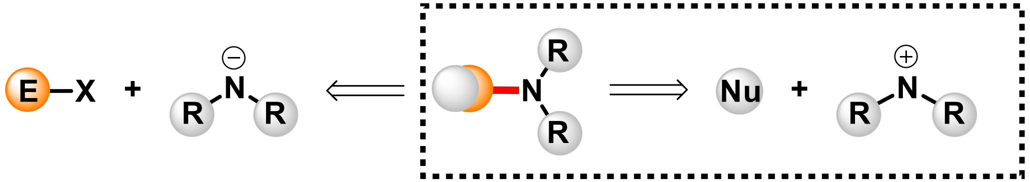


- Electrophilic amination – available *N*-electrophiles

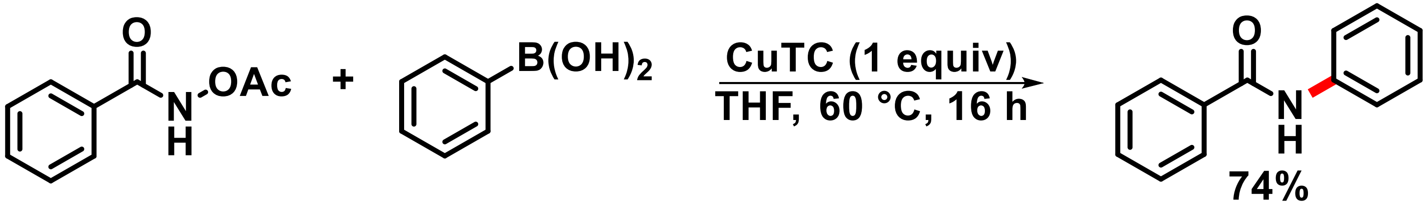


Formation of C–Heteroatom Bonds

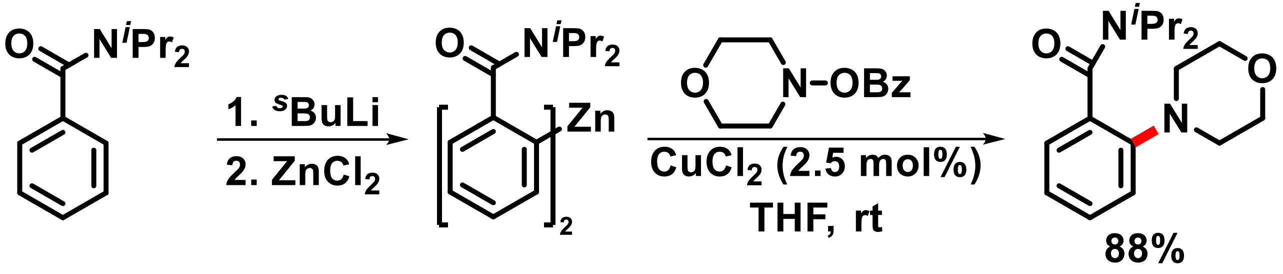
➢ C–N bond formation



- Electrophilic amination – copper-catalyzed reactions



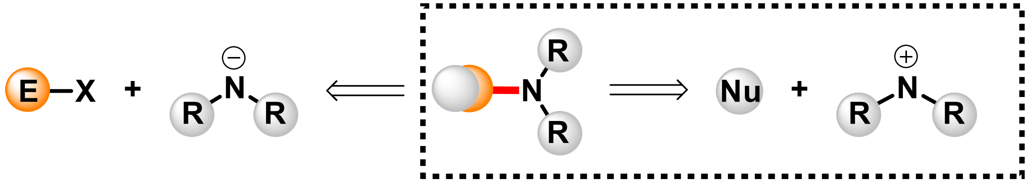
Org. Lett. **2008**, *10*, 3005



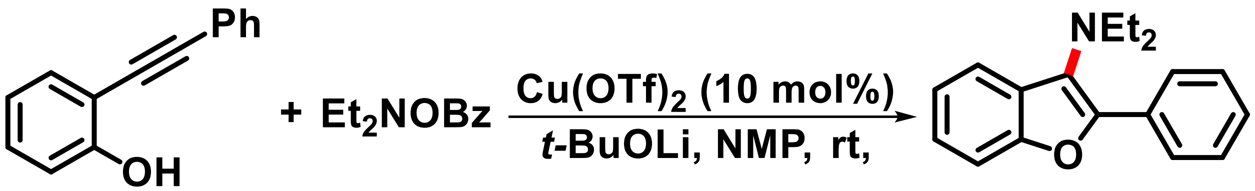
J. Org. Chem. **2006**, *71*, 219

Formation of C–Heteroatom Bonds

➢ C–N bond formation

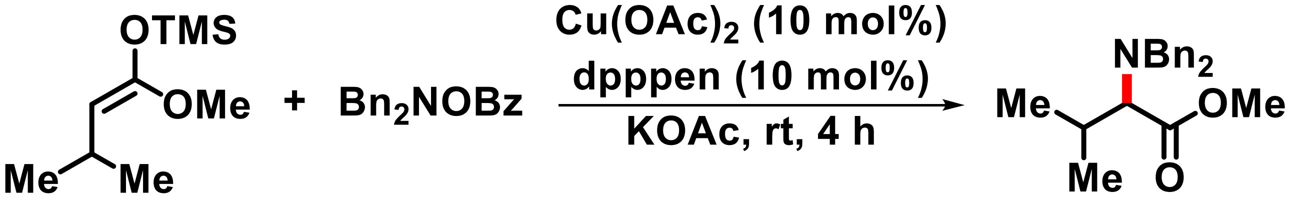


- **Electrophilic amination – copper-catalyzed reactions**



61%

J. Org. Chem. **2012**, *77*, 617



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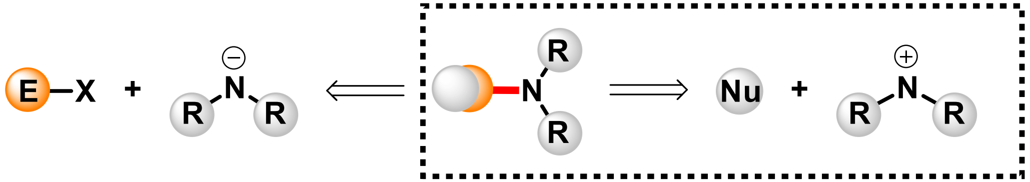
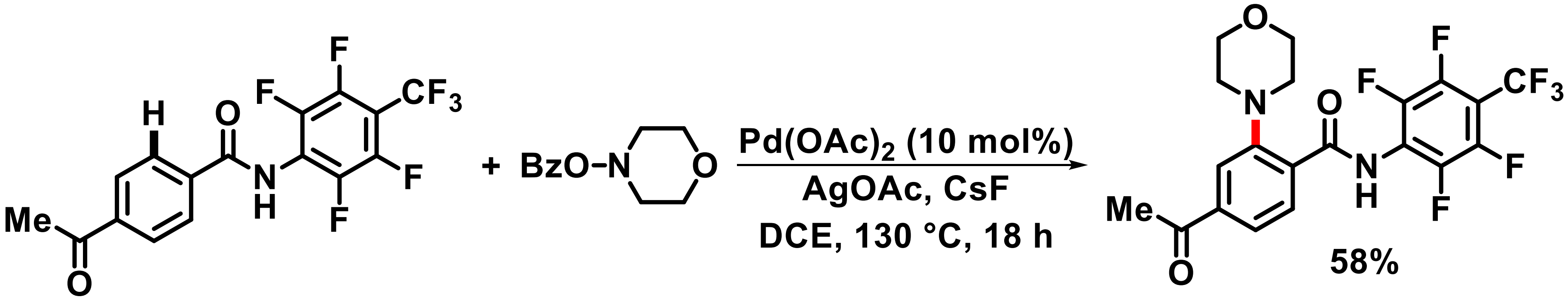
Angew. Chem. Int. Ed. **2012**, *51*, 11827

Formation of C–Heteroatom Bonds

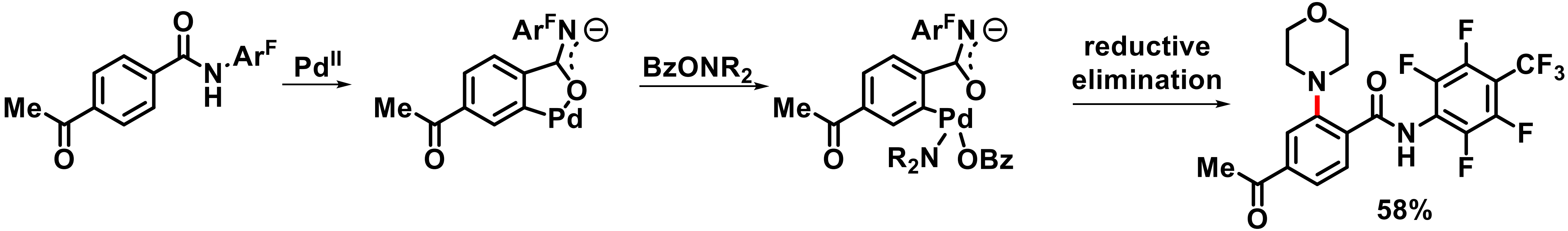
➢ C–N bond formation



- Electrophilic amination – palladium-catalyzed electrophilic amination



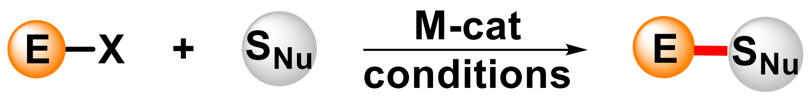
- Proposed mechanism – Pd^{II}/Pd^{IV} catalytic cycle



J. Am. Chem. Soc. **2011**, *133*, 7652

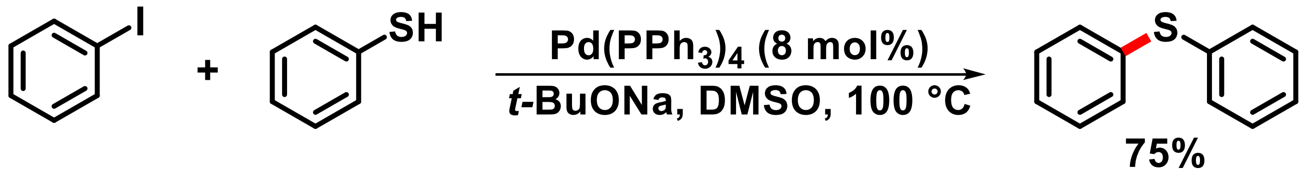
Formation of C–Heteroatom Bonds

➢ C–S bond formation



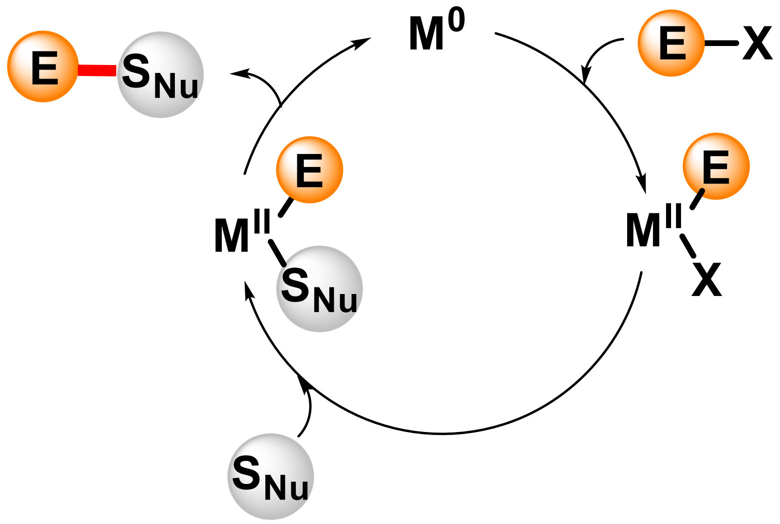
X = Cl, Br, I

- **Early example of palladium catalyzed sulfenylation:**



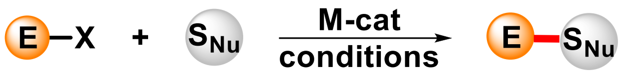
Chem. Lett. **1978**, *13*

- **General mechanism for the formation of C–S bond**



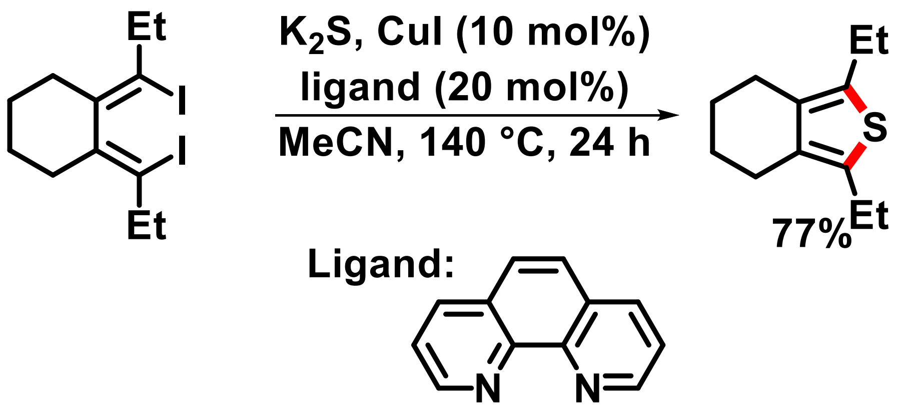
Formation of C–Heteroatom Bonds

➢ C–S bond formation



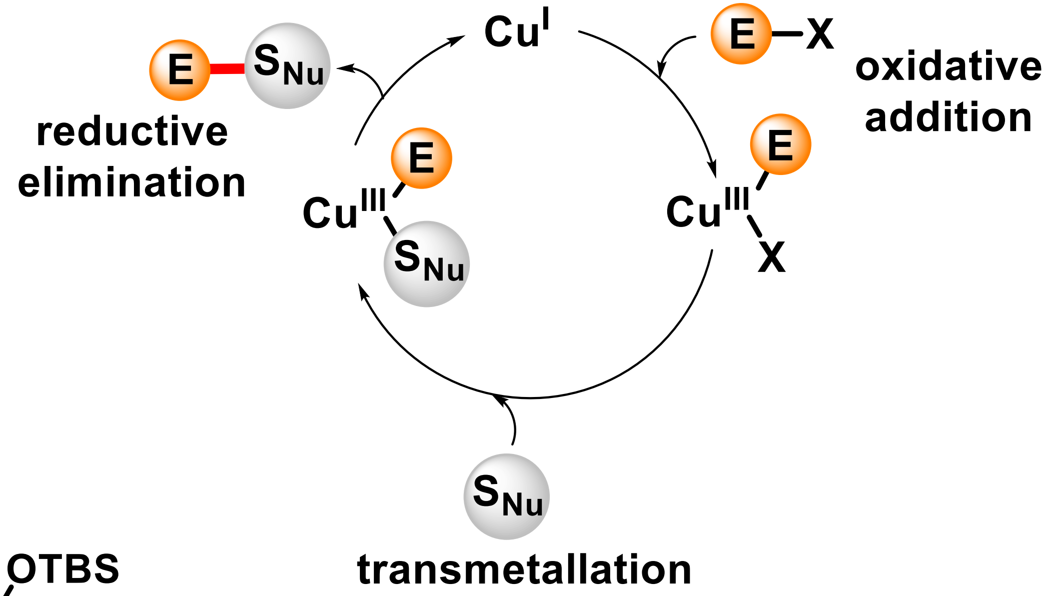
X = Cl, Br, I

- Selected examples

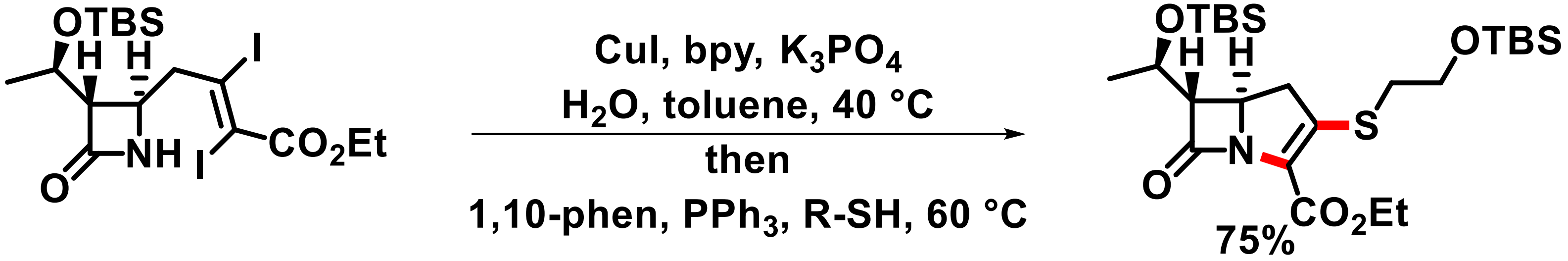


Org. Lett. **2010**, *12*, 3930

- Mechanism for the copper-catalyzed formation of C–S bond



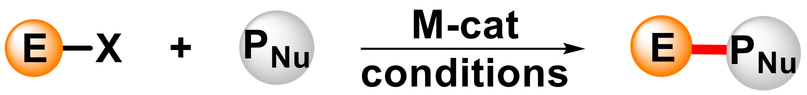
- Synthesis of carbapenems



Org. Lett. **2008**, *10*, 2737

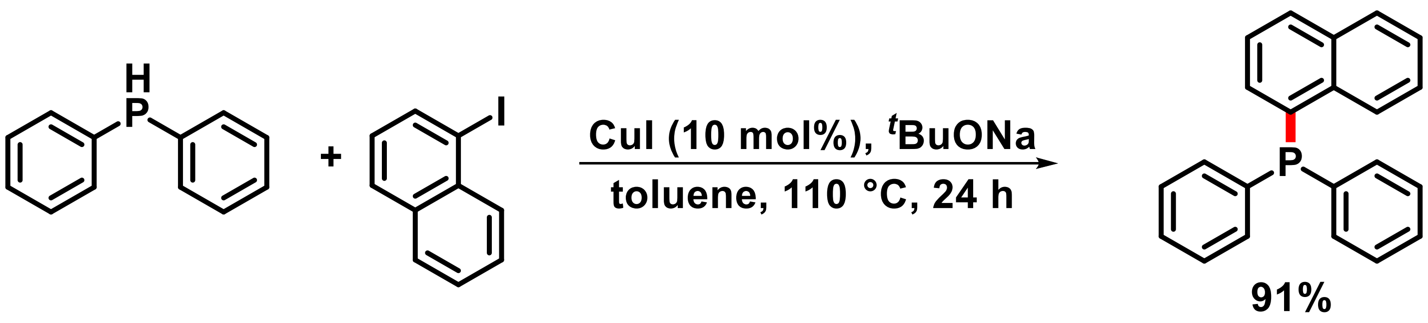
Formation of C–Heteroatom Bonds

➢ C–P bond formation

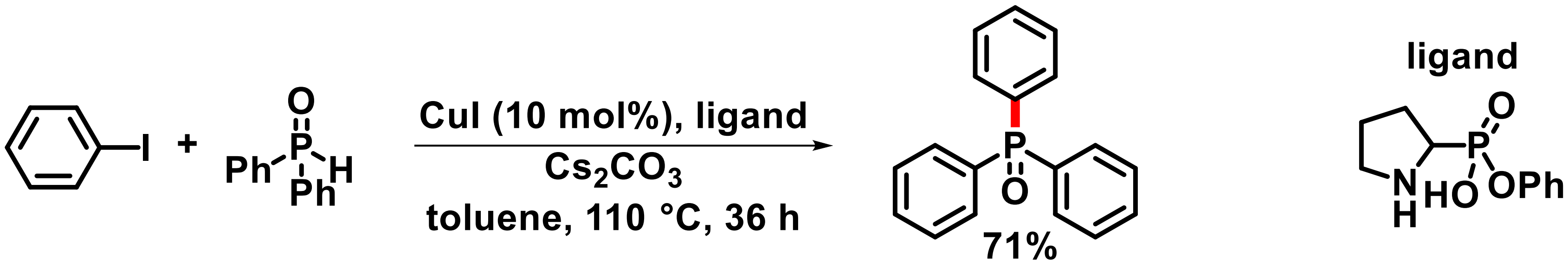


X = Cl, Br, I

- Palladium-catalyzed reactions



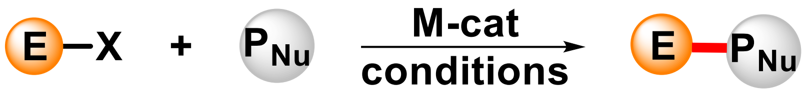
J. Org. Chem. **2003**, *68*, 4590



Chem. Eur. J. **2006**, *12*, 3636

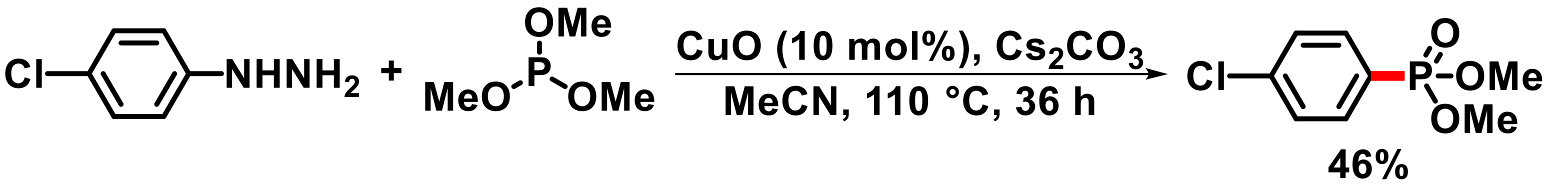
Formation of C–Heteroatom Bonds

➢ C–P bond formation

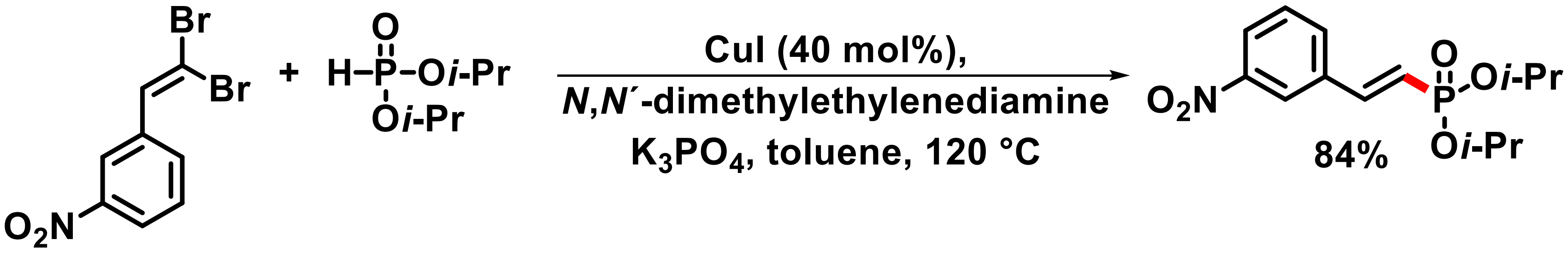


X = Cl, Br, I

- Copper-catalyzed reactions

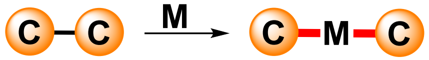


J. Org. Chem. **2014**, *79*, 1449



Chem. Commun. **2011**, *47*, 179

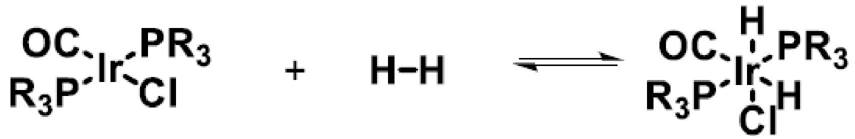
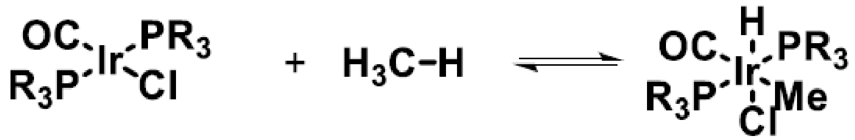
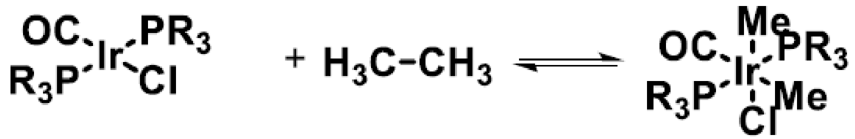
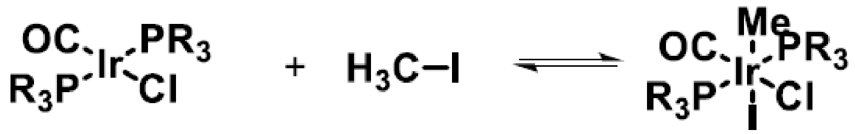
Formation of C–Heteroatom Bonds



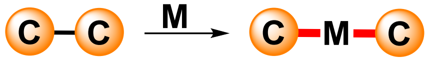
➢ Activation of C–C, C–N, C–S, C–P bonds

- **Activation of C–C bond**

  - **Thermodynamics of oxidative addition for Vaska´s complex**

Reaction	Estimated ΔH (kcal/mol)	Estimated ΔG (kcal/mol)
	-15	-6
	-2	+3
	-4	+6
	-35	-25

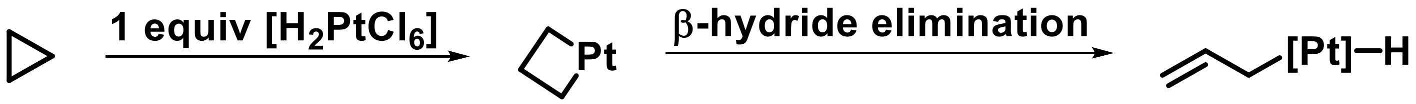
Formation of C–Heteroatom Bonds



➢ Activation of C–C, C–N, C–S, C–P bonds

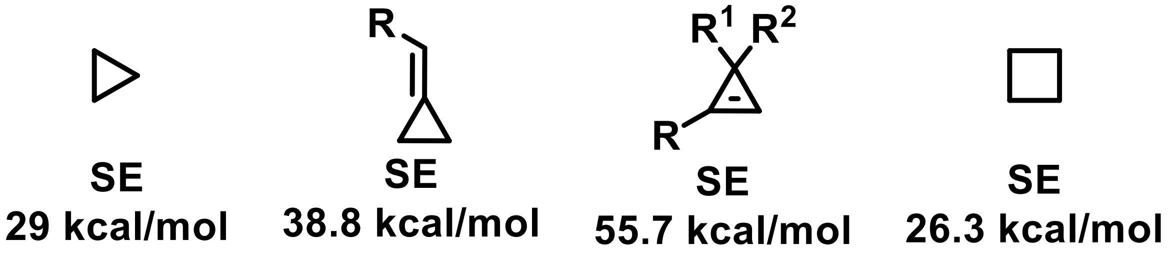
- **Activation of C–C bond**

  - **The first report on cyklopropane C–C bond cleavage**

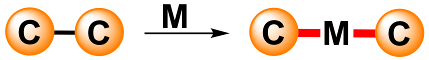


J. Chem. Soc. **1955**, *2043*

  - **Strain energy-driven (SE) process**

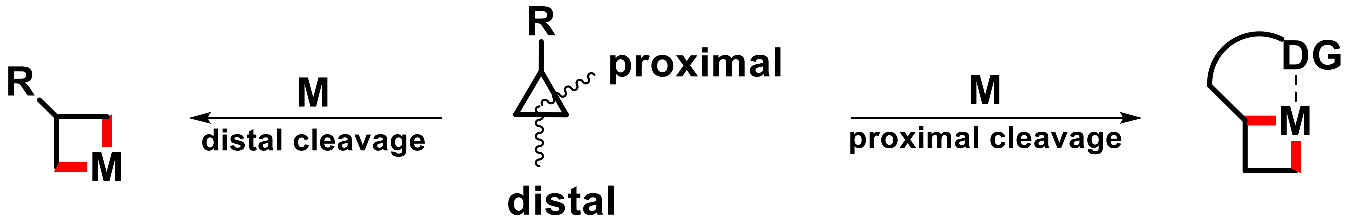


Formation of C–Heteroatom Bonds

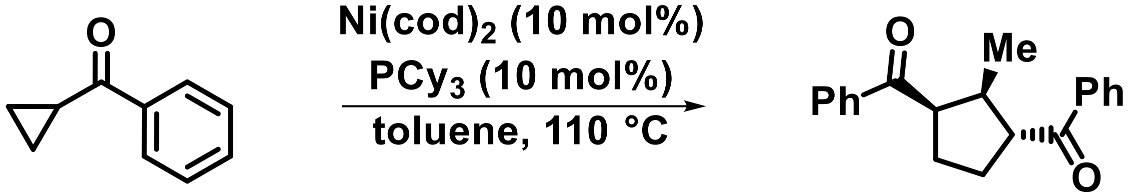


➢ Activation of C–C, C–N, C–S, C–P bonds

- Activation of C–C bond



- Selected example



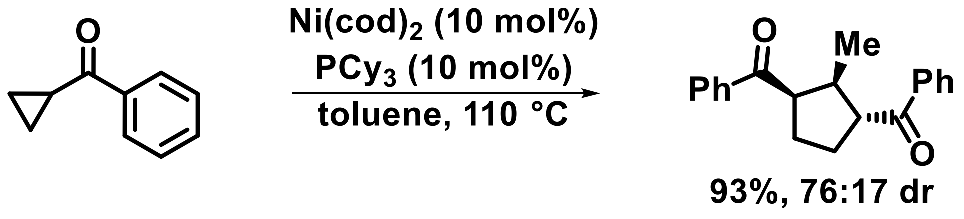
93%, 76:17 dr

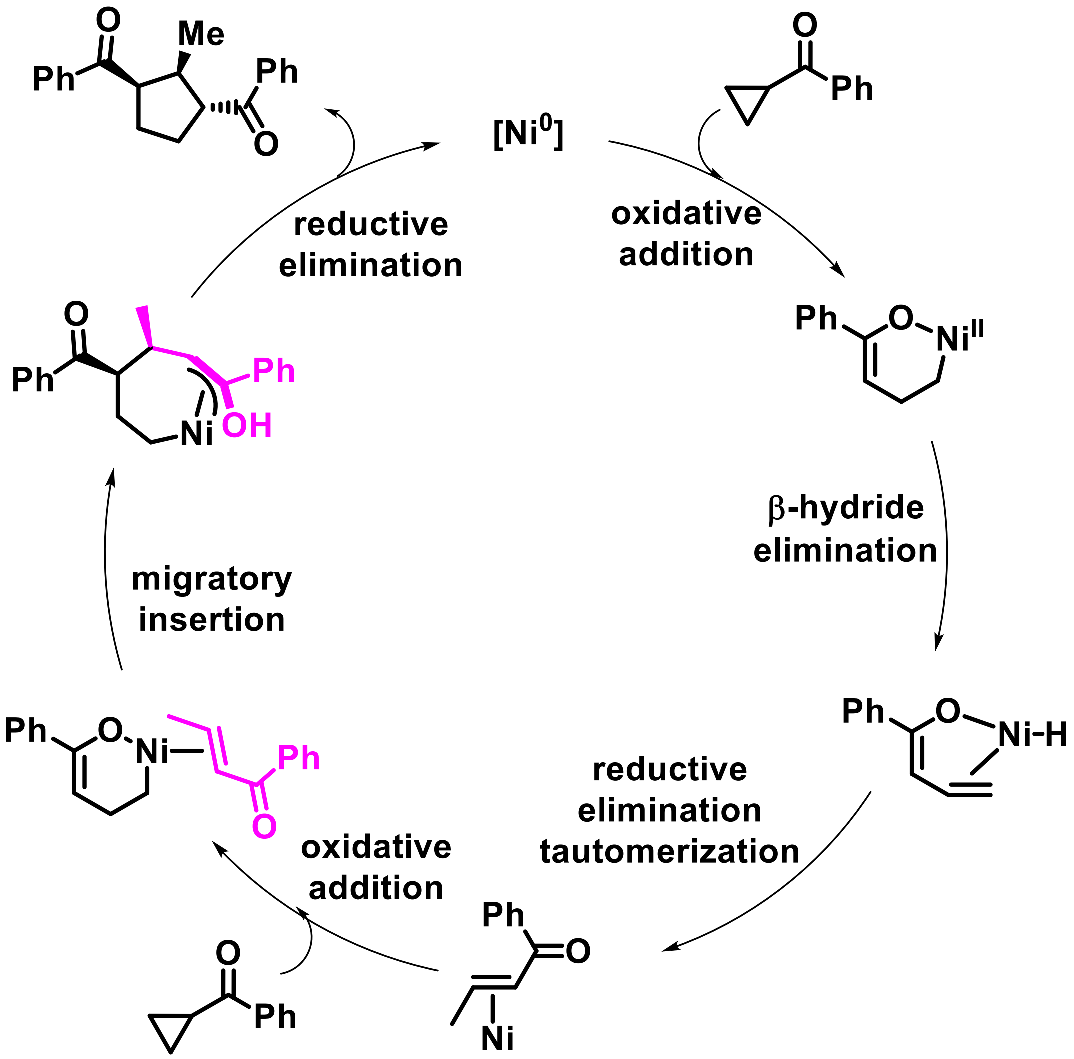
J. Am. Chem. Soc. **2006**, *128*, 5348

Formation of C–Heteroatom Bonds

➢ Activation of C–C, C–N, C–S, C–P bonds

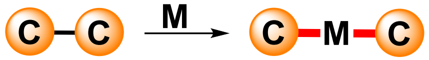
- Activation of C–C bond





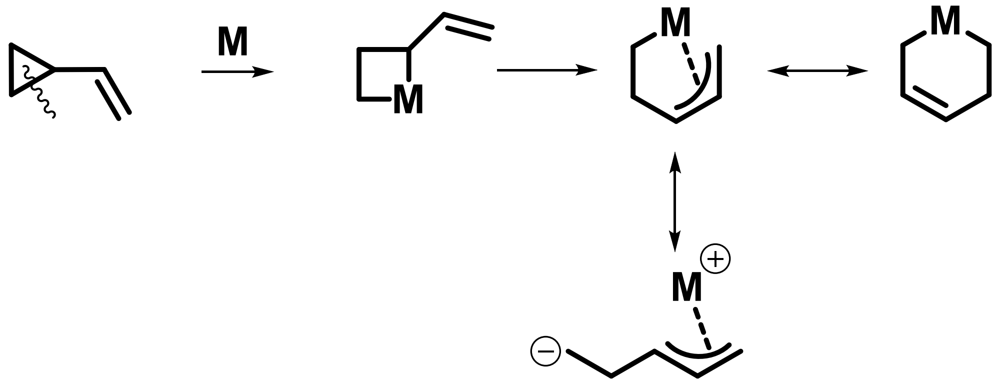
J. Am. Chem. Soc. **2006**, *128*, 5348

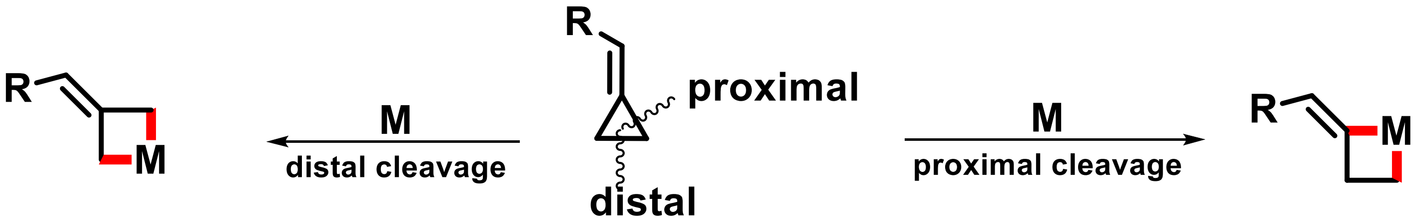
Formation of C–Heteroatom Bonds



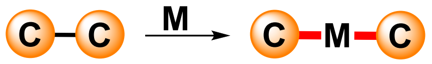
➢ Activation of C–C, C–N, C–S, C–P bonds

- **Activation of C–C bond**
  - **Alkylidenecyclopropanes and vinyl cyclopropanes**



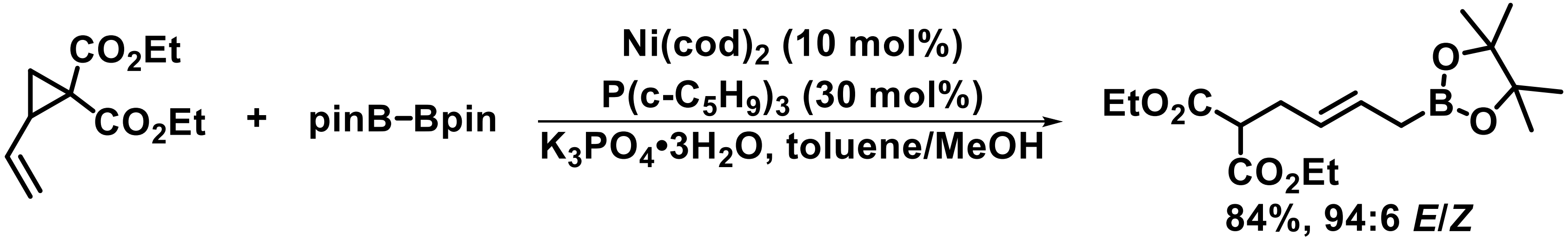


Formation of C–Heteroatom Bonds

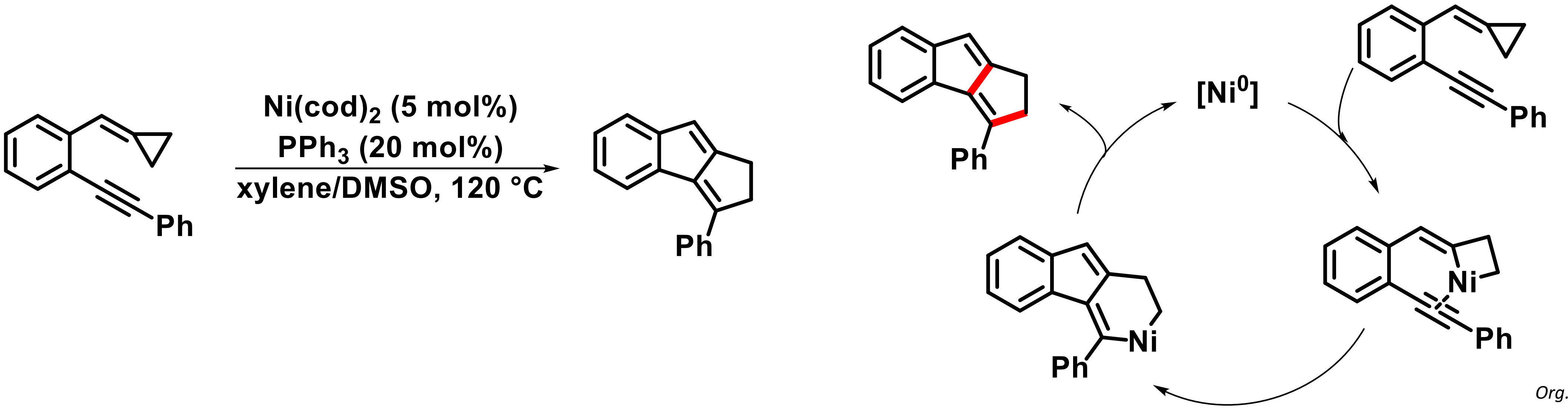


➢ Activation of C–C, C–N, C–S, C–P bonds

- Activation of C–C bond
  - Selected examples

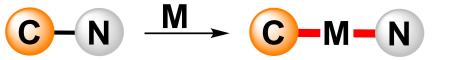


Org. Lett. **2008**, *10*, 4677



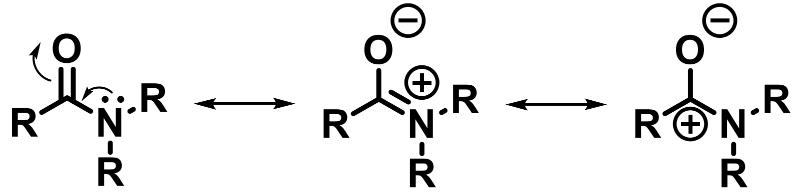
Org. Lett. **2011**, *13*, 640

Formation of C–Heteroatom Bonds

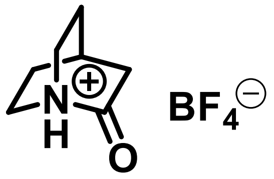


➢ Activation of C–C, C–N, C–S, C–P bonds

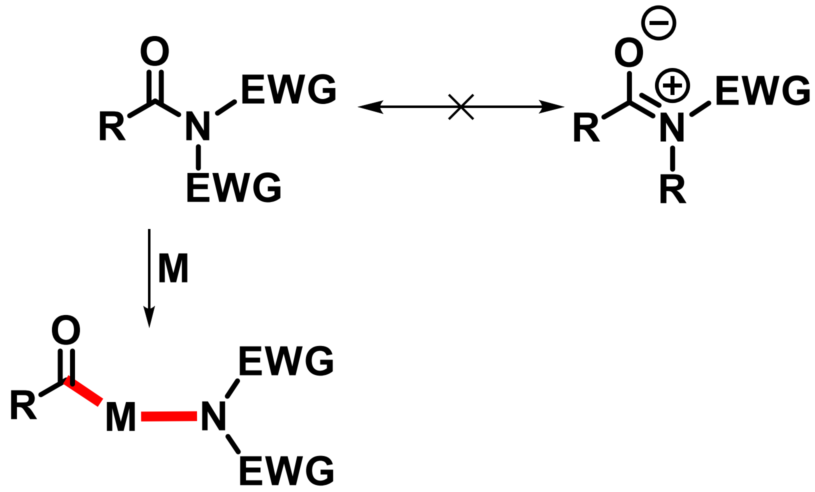
- **Activation of C–N bond**
  - **The most difficult is C–N bond activation for amides – amide stabilization**



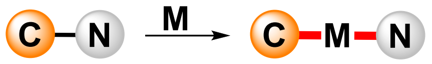
- **Sterically or electronically blocked amides stabilization**



Nature **2006**, *441*, 731

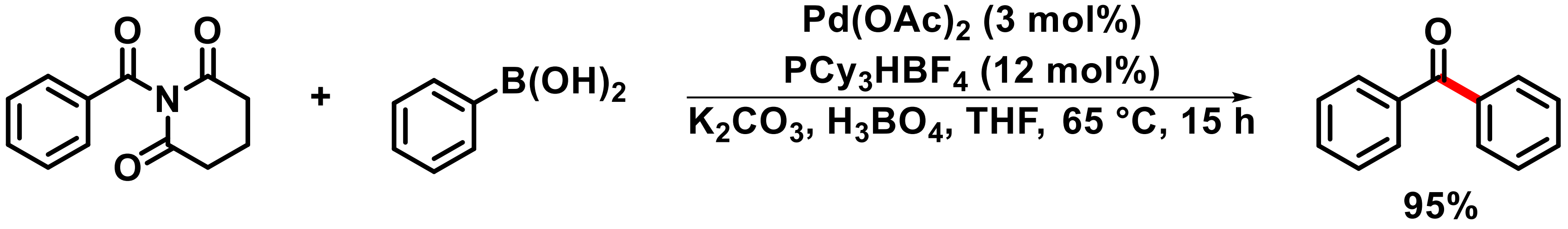


Formation of C–Heteroatom Bonds

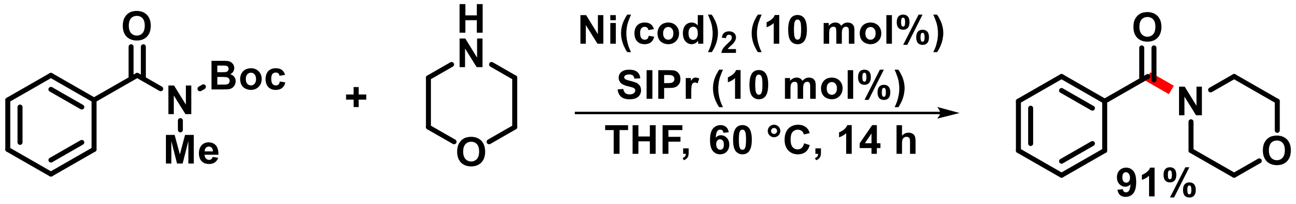


➢ Activation of C–C, C–N, C–S, C–P bonds

- Activation of C–N bond
  - Selected examples

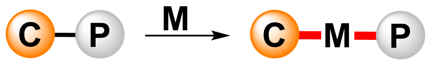


Org. Lett. **2015**, *17*, 4364, *Org. Biomol. Chem.* **2016**, *14*, 5690



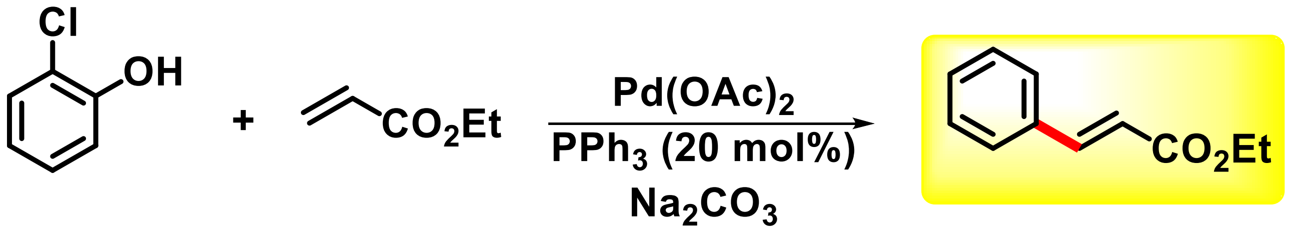
Nature Commun. **2016**, *7*, 11554

Formation of C–Heteroatom Bonds



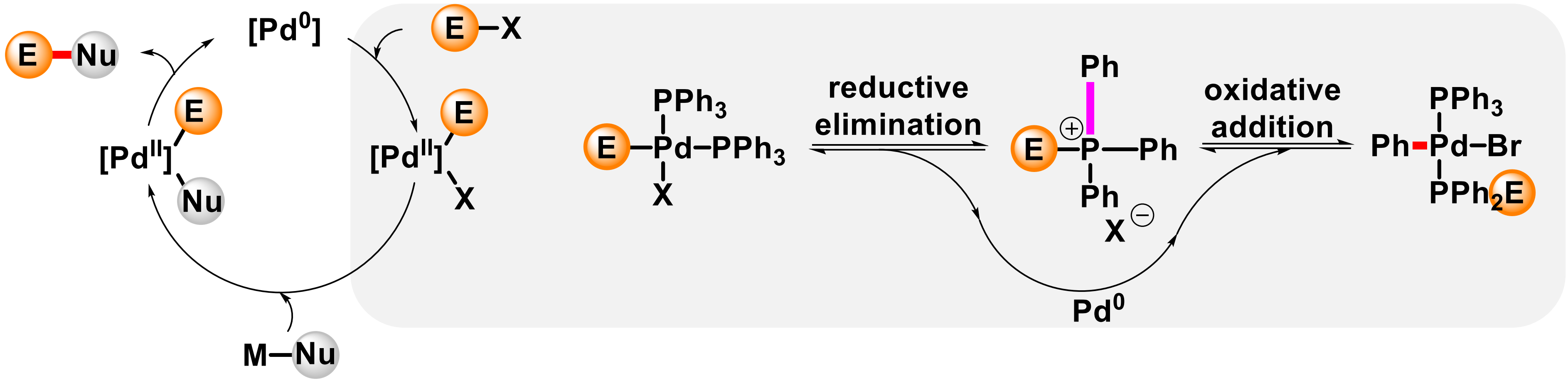
➢ Activation of C–C, C–N, C–S, C–P bonds

- Activation of C–P bond
  - Unwanted side reaction during cross-couplings



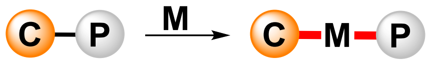
J. Am. Chem. Soc. **1976**, *98*, 4499

  - Proposed mechanism for C–P bond activation in cross-coupling reactions



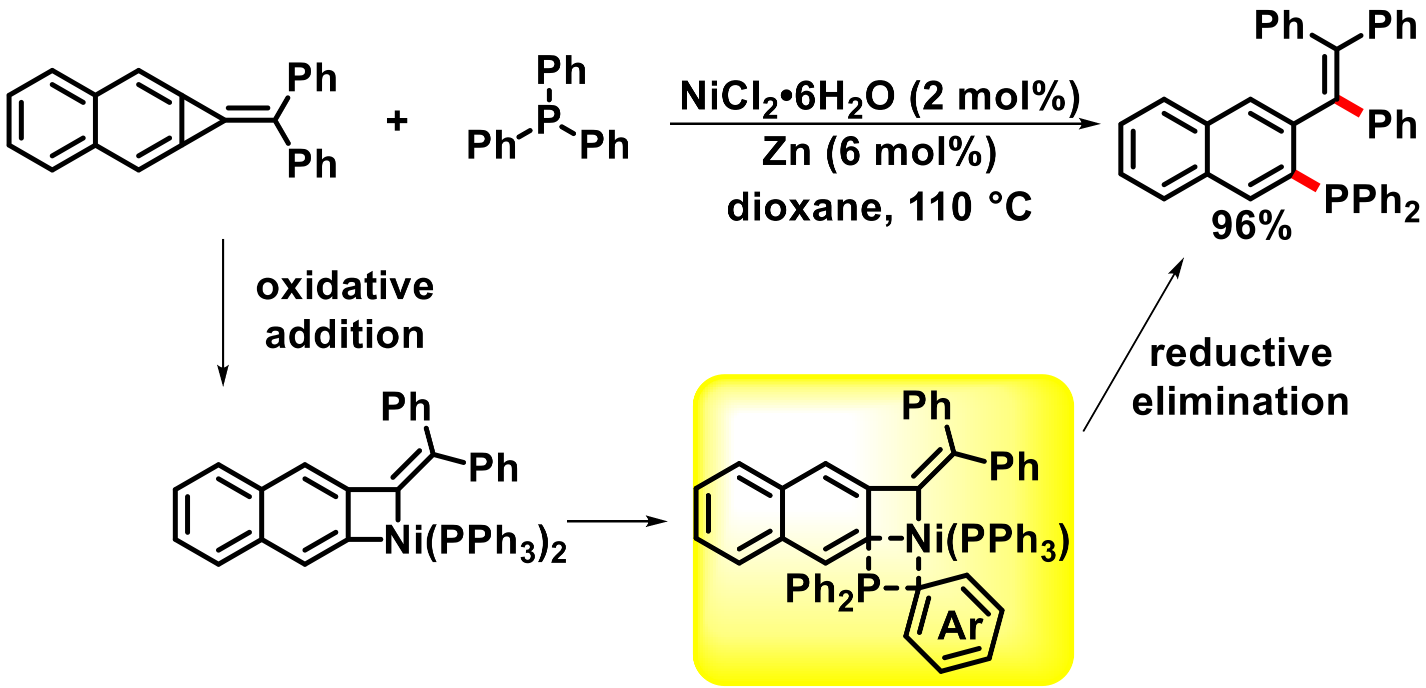
J. Org. Chem. **1995**, *60*, 12

Formation of C–Heteroatom Bonds



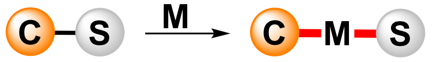
➢ Activation of C–C, C–N, C–S, C–P bonds

- Activation of C–P bond
  - Selected example



Chem. Commun. **2013**, *49*, 7747

Formation of C–Heteroatom Bonds



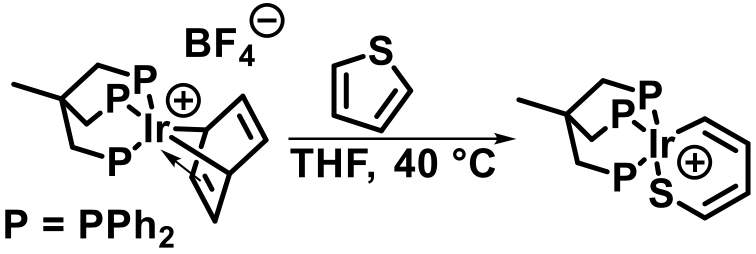
➢ Activation of C–C, C–N, C–S, C–P bonds

- Activation of C–S bond

  ○ BDE for carbon-heteroatom bonds

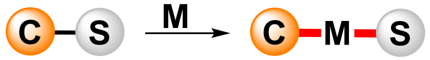
H_3C–H	H_3C–F	H_3C–Cl	H_3C–Br
438.6 kcal/mol	459.7 kcal/mol	350.7 kcal/mol	350.7 kcal/mol
H_3C–C_{sp3}	H_3C–N	H_3C–O	H_3C–S
307.8 kcal/mol	356.0 kcal/mol	385.7 kcal/mol	307.8 kcal/mol

- Stoichiometric C–S bond activation



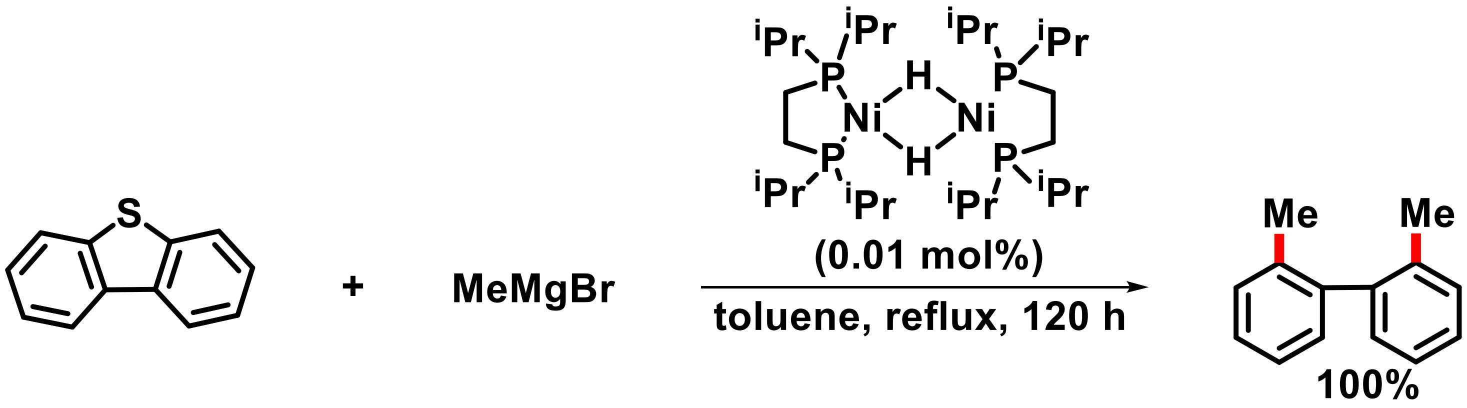
J. Am. Chem. Soc. **1993**, *115*, 2731

Formation of C–Heteroatom Bonds

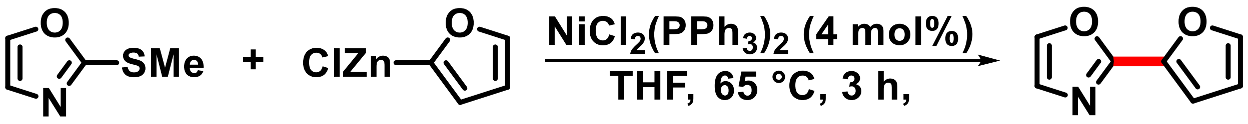


➢ Activation of C–C, C–N, C–S, C–P bonds

- Activation of C–S bond
  - Selected examples

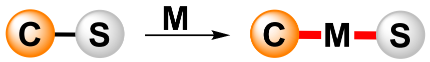


Organometallics **2004**, *23*, 4534



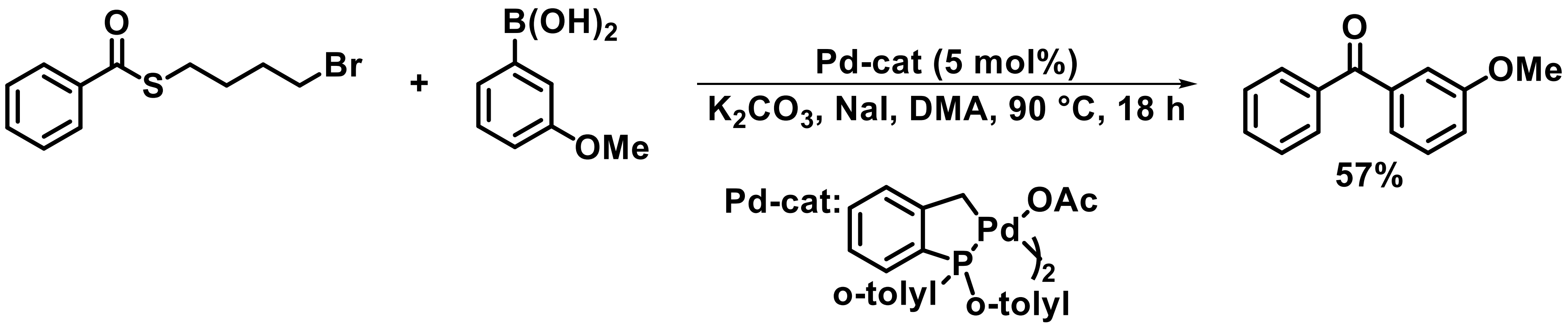
Org. Lett. **2009**, *11*, 1457

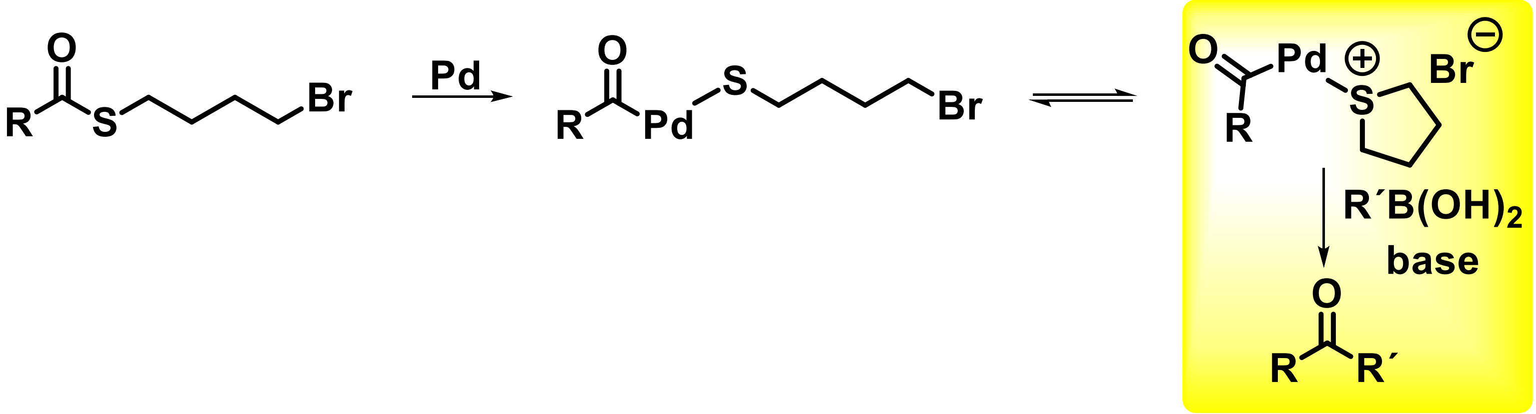
Formation of C–Heteroatom Bonds



➢ Activation of C–C, C–N, C–S, C–P bonds

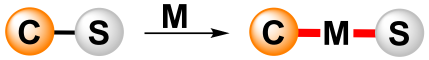
- Activation of C–S bond
  - Alkylative activation





Org. Lett. **2000**, *2*, 3229

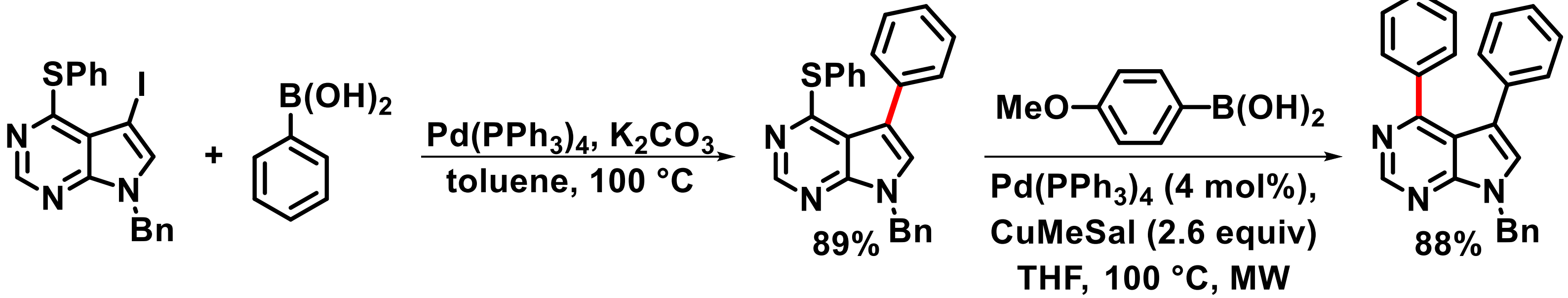
Formation of C–Heteroatom Bonds



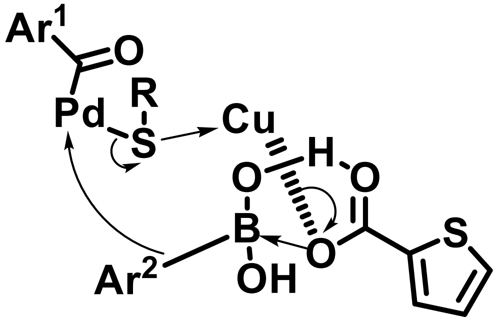
➢ Activation of C–C, C–N, C–S, C–P bonds

- Activation of C–S bond
  - Liebeskind-Šrogl cross-coupling reaction

- Stochiometric Liebeskind-Srogl cross-coupling

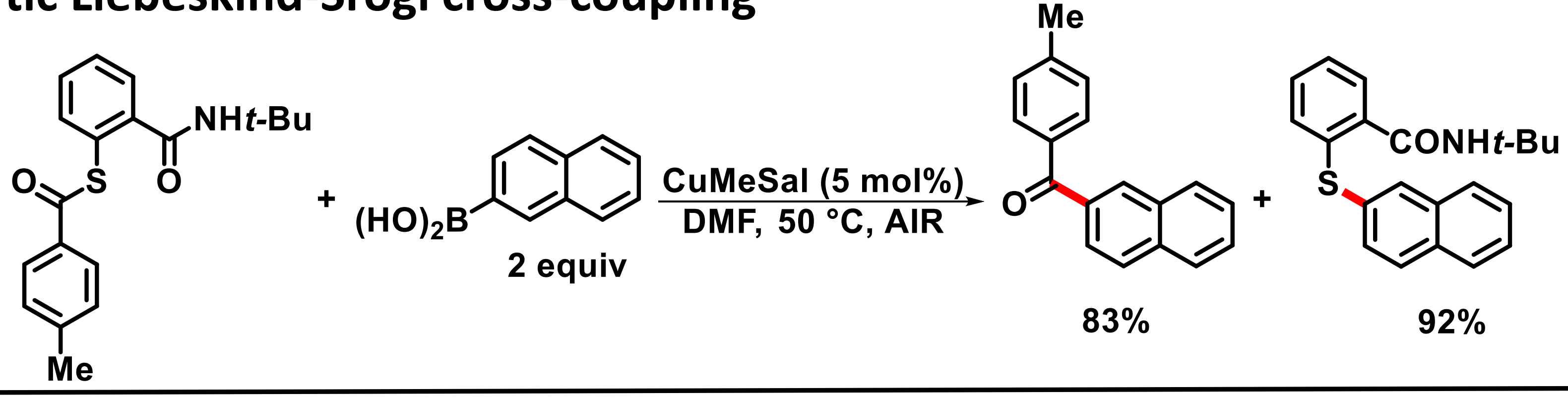


- Transmetallation step



Eur. J. Org. Chem. **2014**, 7203

- Catalytic Liebeskind-Srogl cross-coupling



J. Am. Chem. Soc. **2007**, *129*, 15734