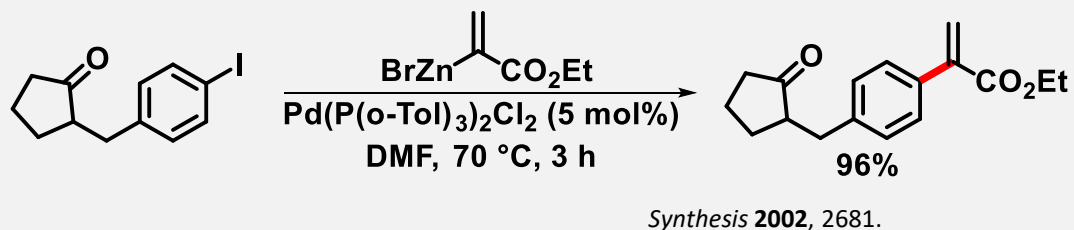


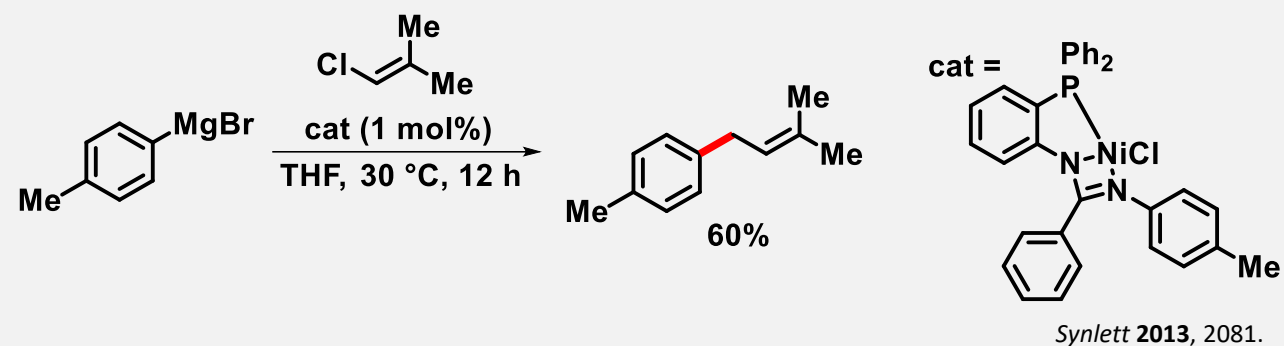
➤ General scheme for transition-metal-catalyzed cross-coupling reactions



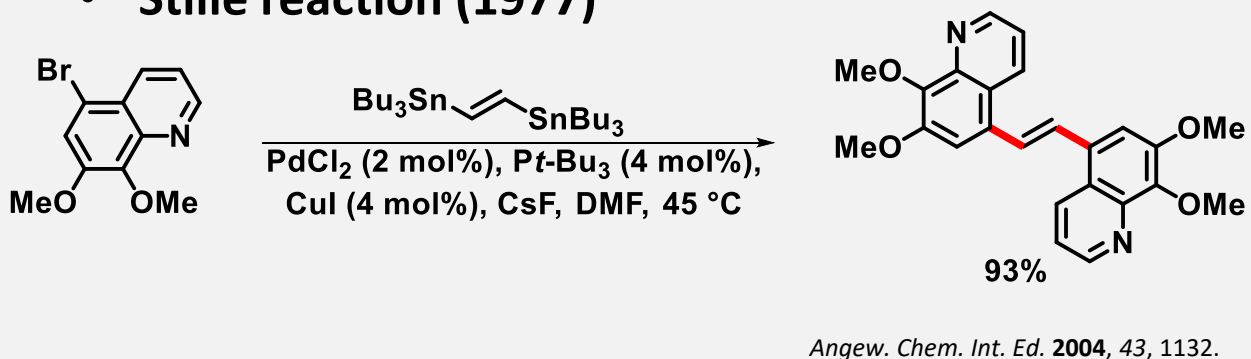
• Negishi reaction



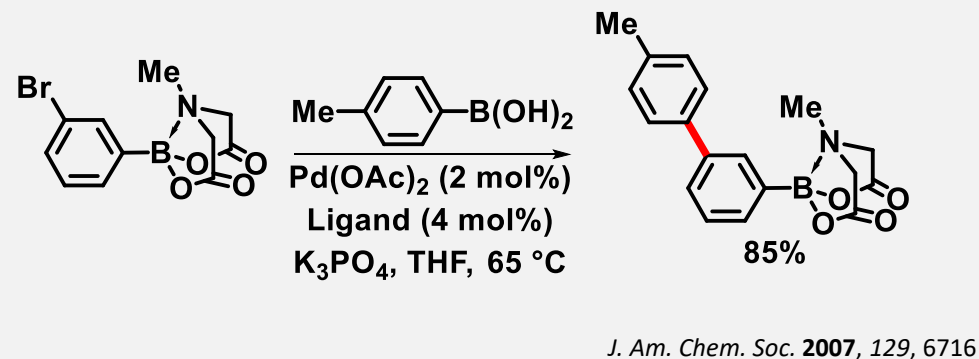
• Kumada reaction (1972)



• Stille reaction (1977)



• Suzuki reaction



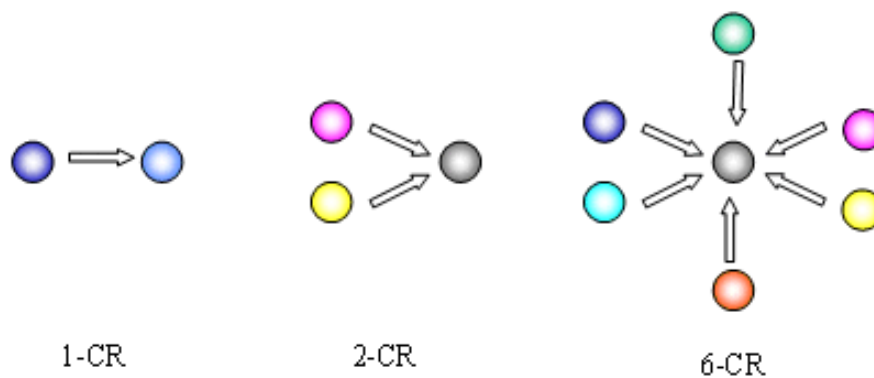
➤ Multicomponent = Domino Reactions

- Definition of Domino Reactions

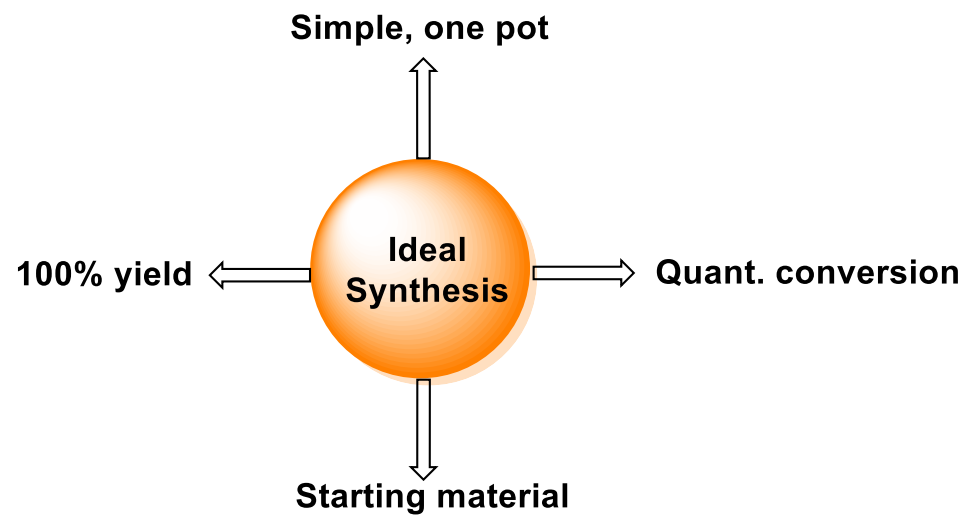
- Reactions that do not require the addition of other reactants, catalysts and two or more bonds are formed.

Chem. Rev. 1996, 96, 115

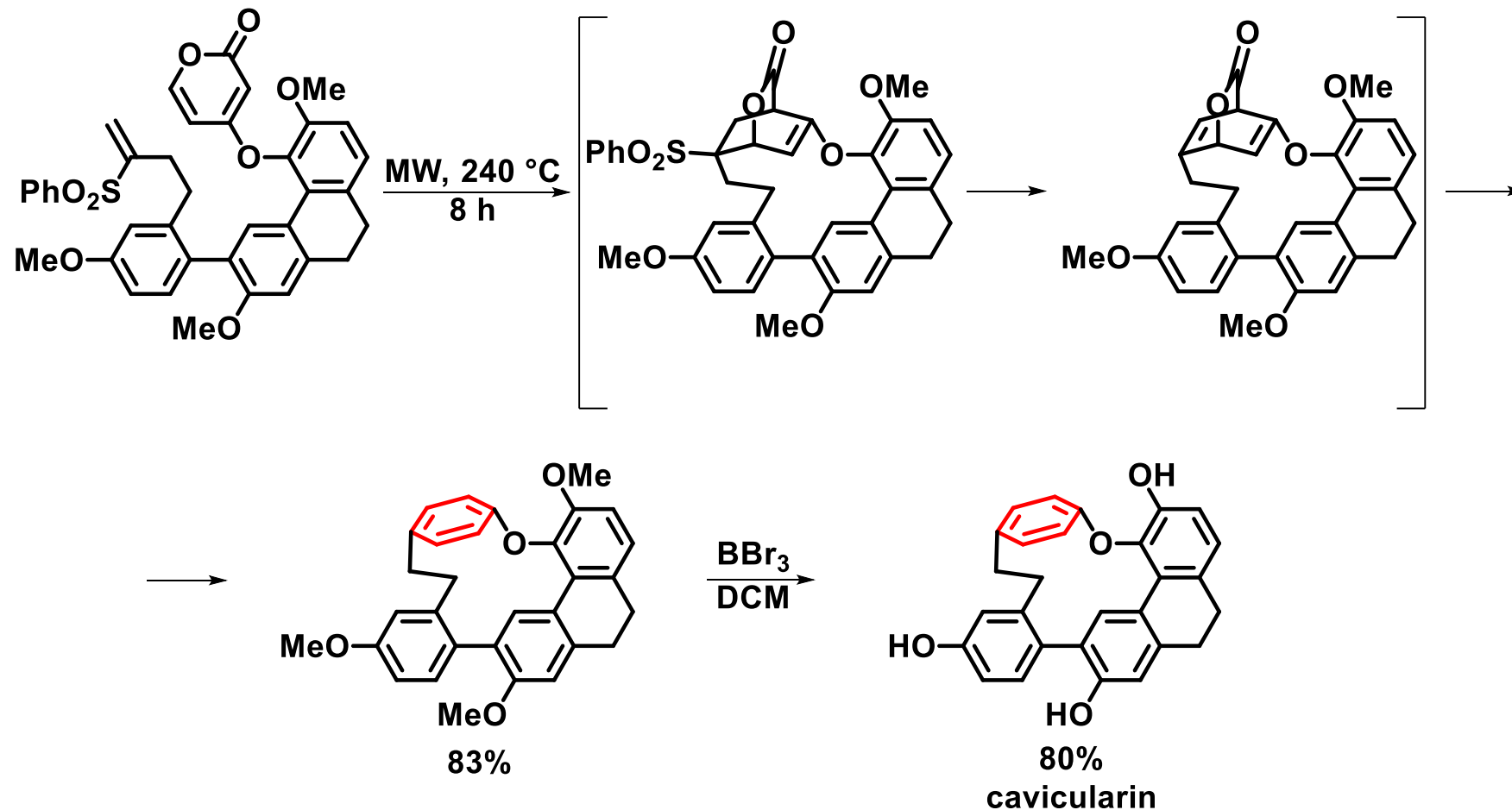
- Definition of multicomponent reactions



➤ Why domino and multicomponent reactions?

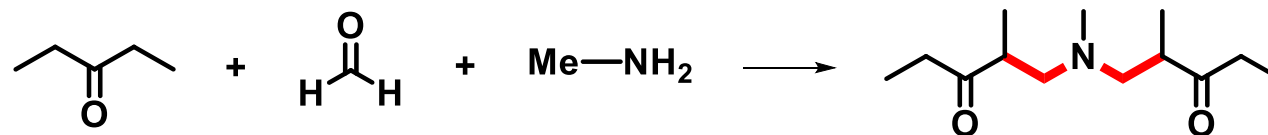


➤ Domino reactions in traditional organic synthesis – synthesis of cavicularin

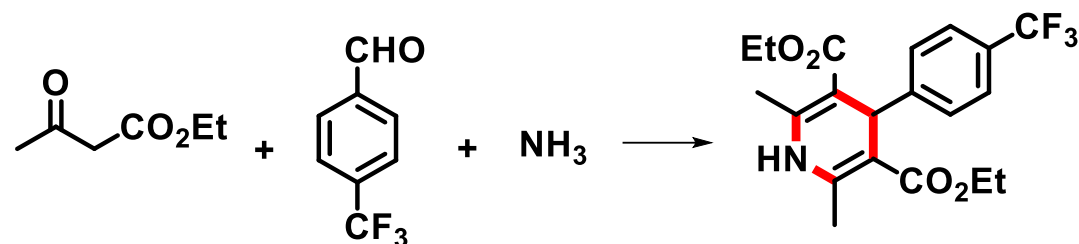


➤ Multicomponent reactions in traditional organic synthesis

✓ Mannich reaction



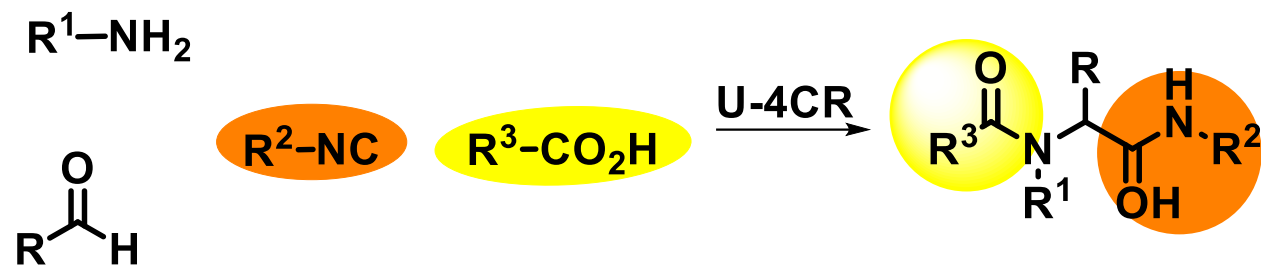
✓ Hantzsch dihydropyridine synthesis



- The most important multicomponent reaction:

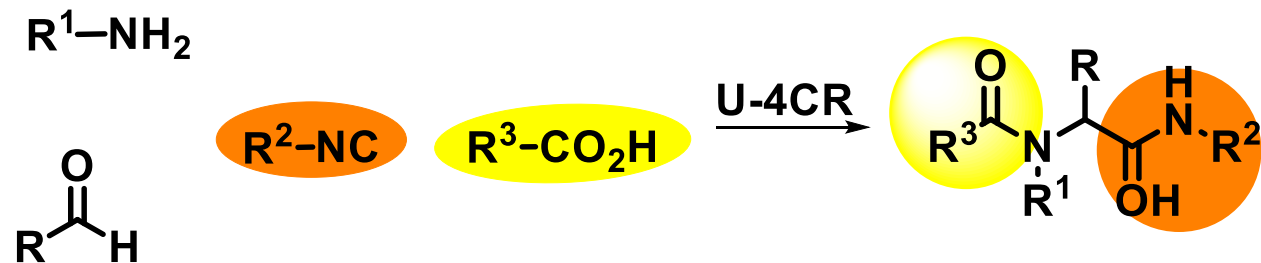
- Isocyanide MCR
- The Biginelli reaction
- Radical MCR
- Transition-metal-catalyzed MCR

- Ugi reaction



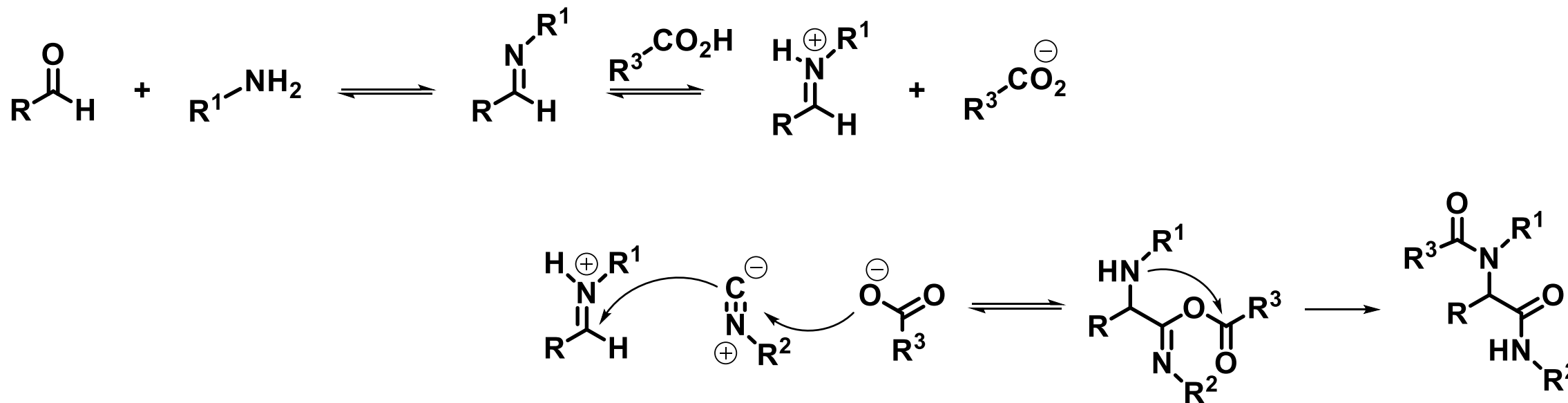
Ivar Karl Ugi

- Ugi reaction

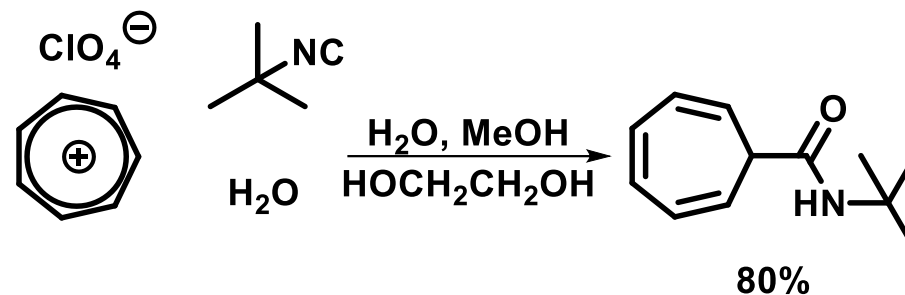


Ivar Karl Ugi

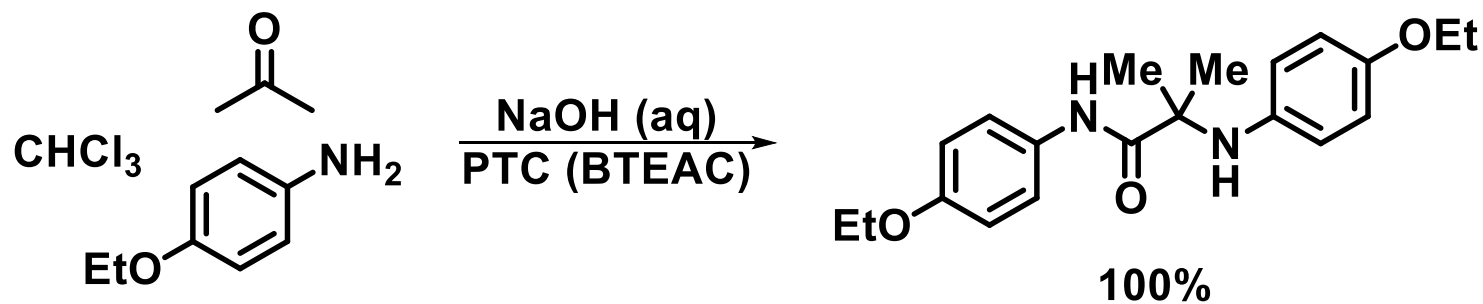
- The mechanism of Ugi reaction:



➤ Other transition-metal-free isocyanide MCR

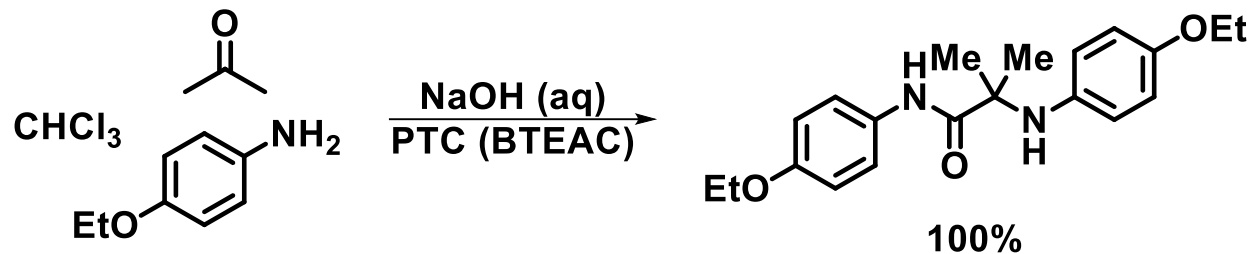


Chem. Ber. **1964**, *97*, 3008

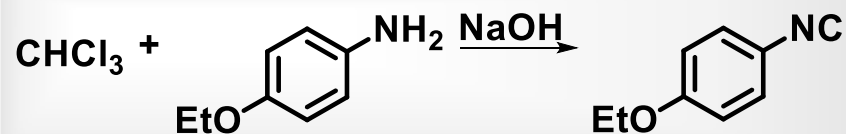


J. Org. Chem. **1980**, *45*, 3671

➤ Other transition-metal-free isocyanide MCR

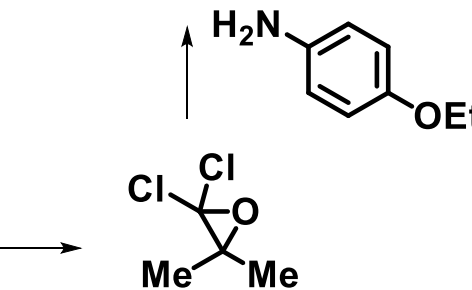
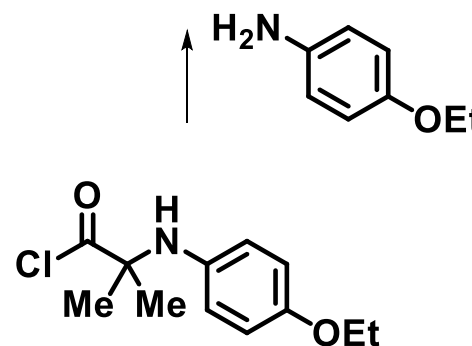


• Isocyanide from carbenes

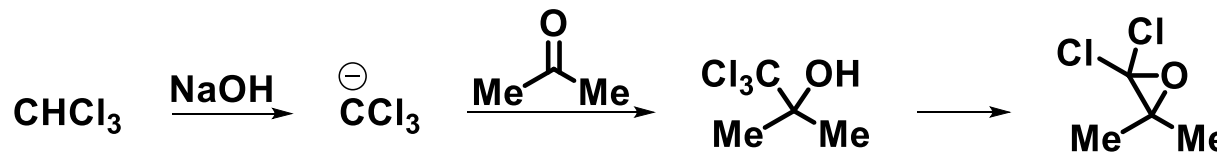


Angew. Chem. Int. Ed. 1972, 11, 530

J. Org. Chem. 1980, 45, 3671

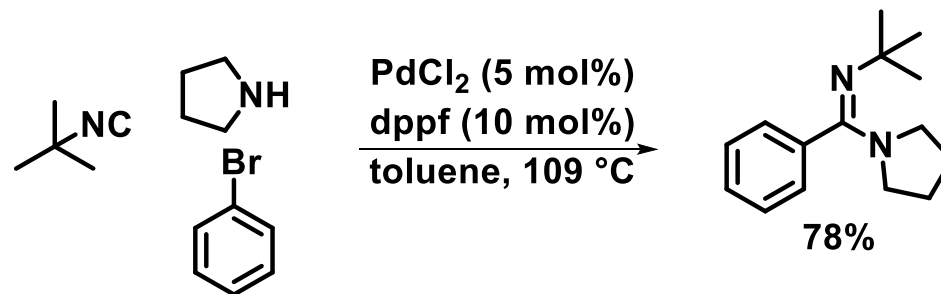


✓ Proposed mechanism

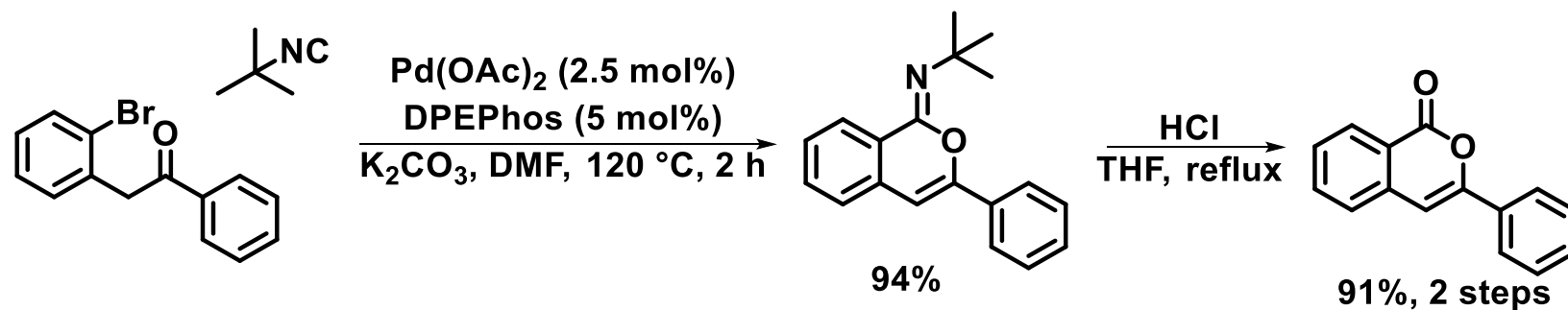


➤ Transition-metal-catalyzed isocyanide MCR

- Synthesis of isocoumarins and amidines by transition-metal-catalyzed MCR of isocyanides:



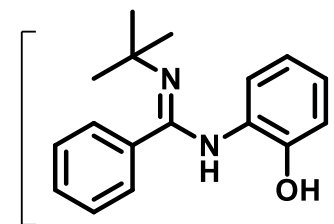
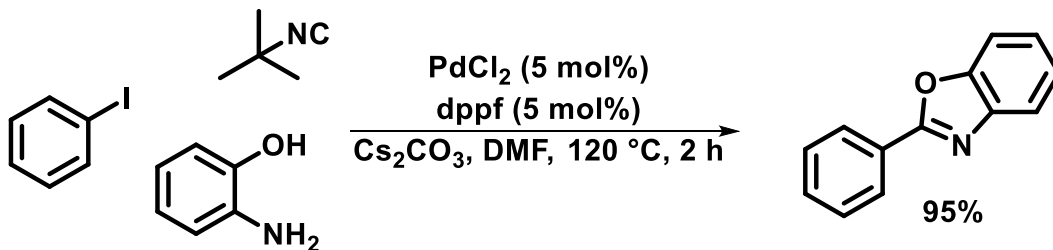
Angew. Chem. Int. Ed. **2000**, 39, 4156



J. Org. Chem. **2012**, 77, 10321

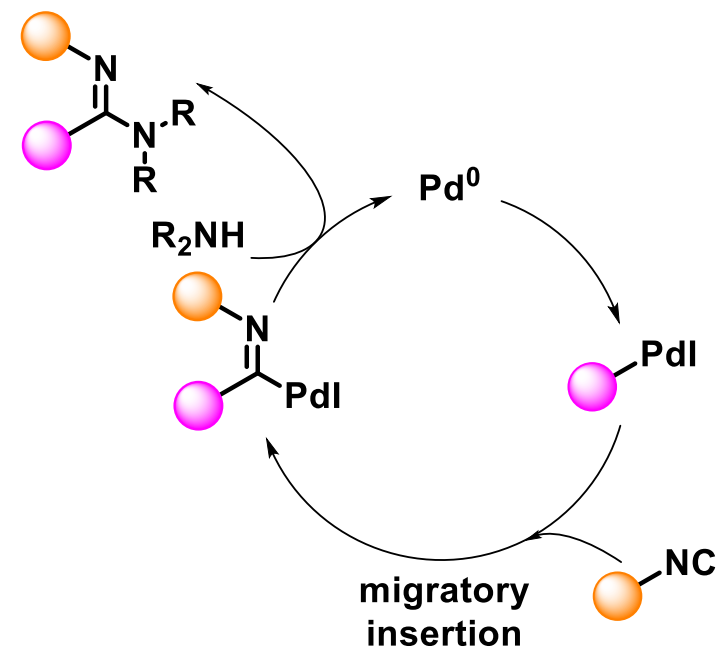
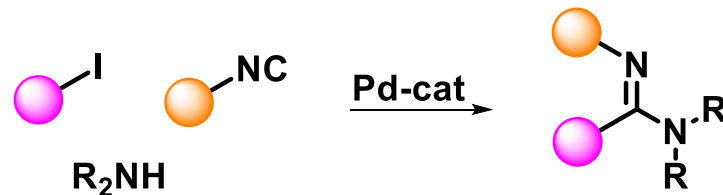
➤ Transition-metal-catalyzed isocyanide MCR

- Synthesis of benzoxazoles



Org. Lett. 2011, 13, 6256

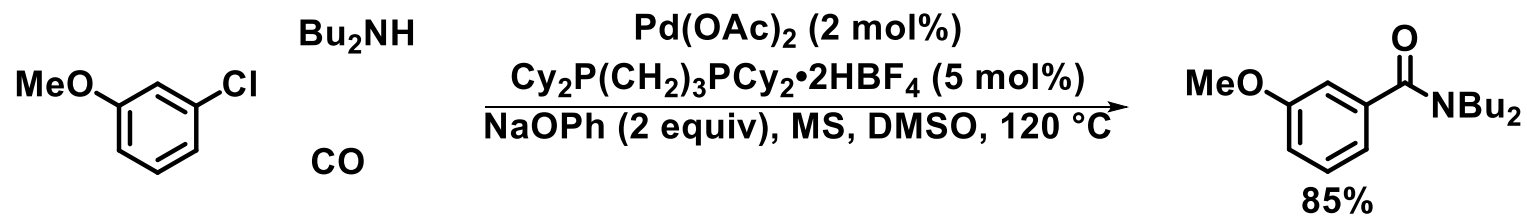
○ General catalytic scheme



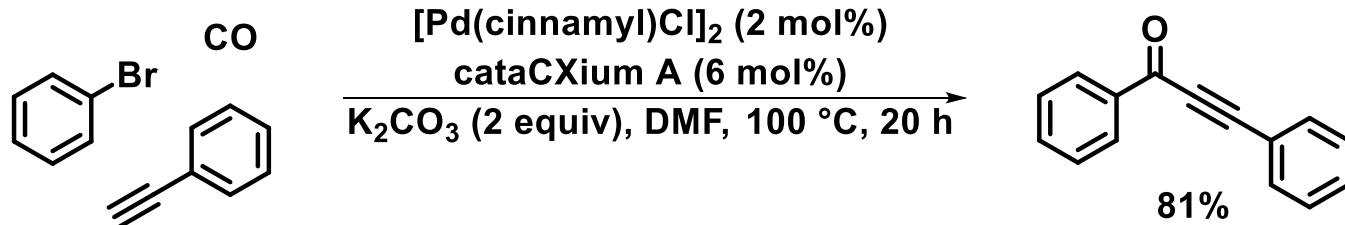
Chem. Soc. Rev. 2013, 42, 4867

➤ Transition-metal-catalyzed carbonylations

• Intermolecular carbonylations

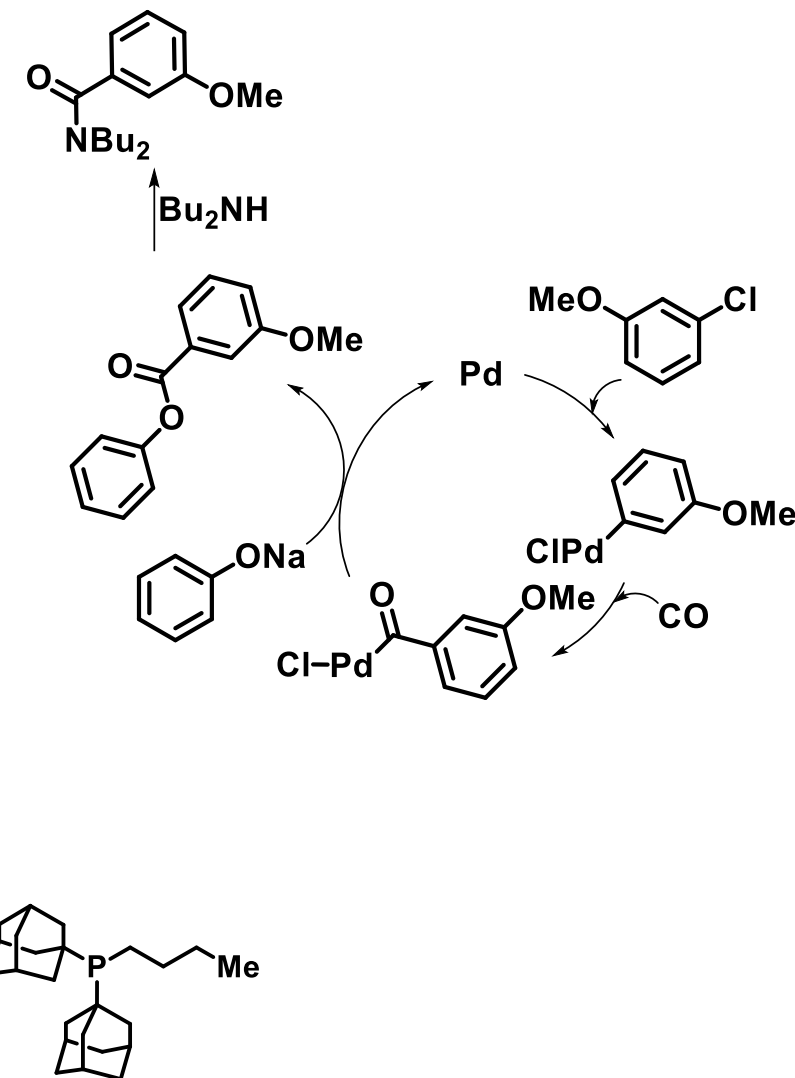


Angew. Chem. Int. Ed. **2007**, *46*, 8460



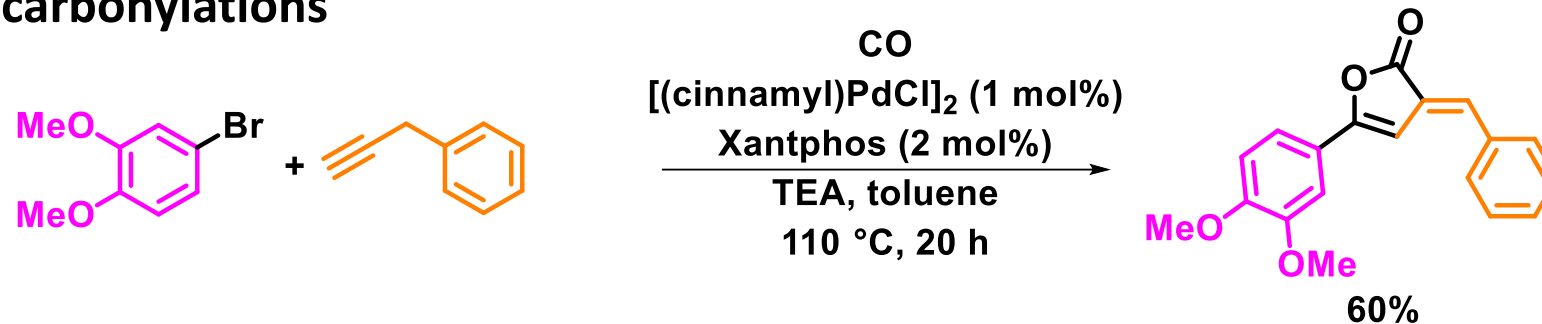
Chem.–Eur. J. **2010**, *16*, 12104

✓ Proposed mechanism

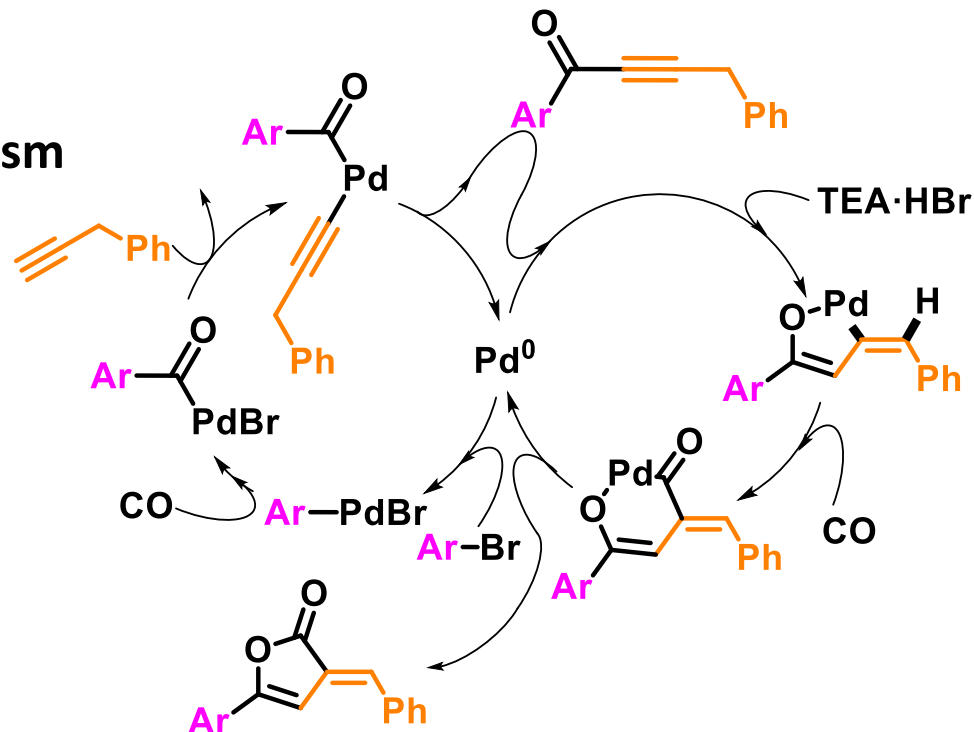


➤ Transition-metal-catalyzed carbonylations

- Intramolecular carbonylations

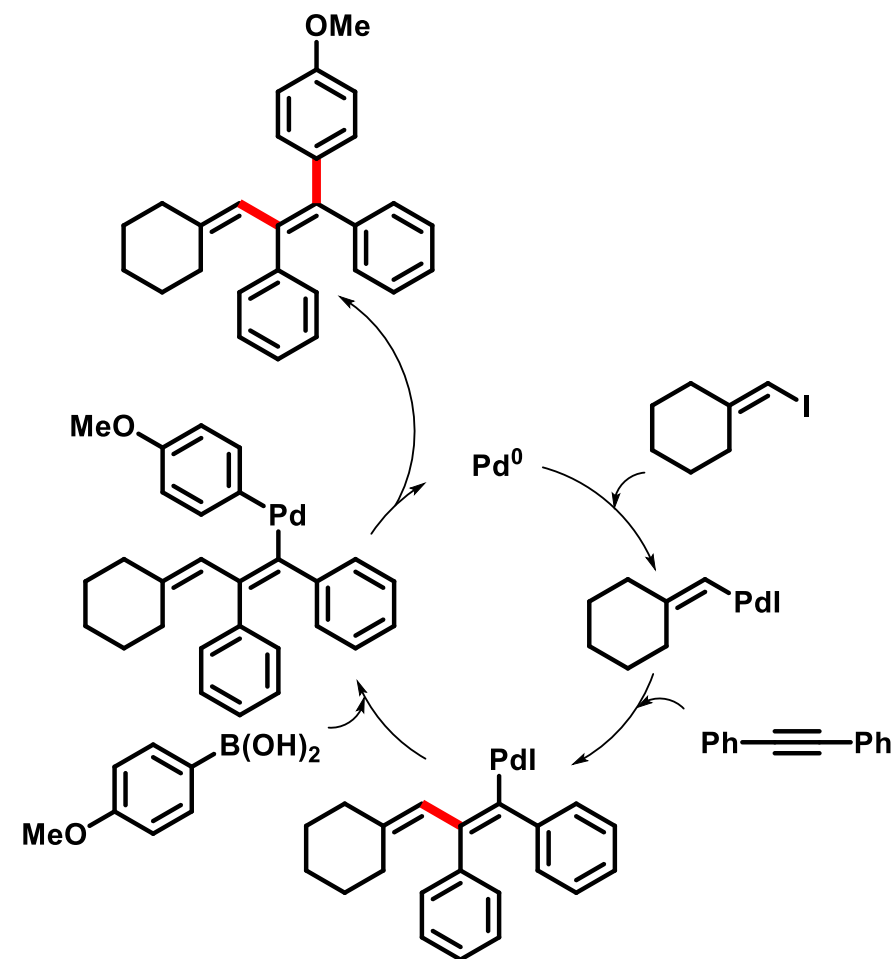
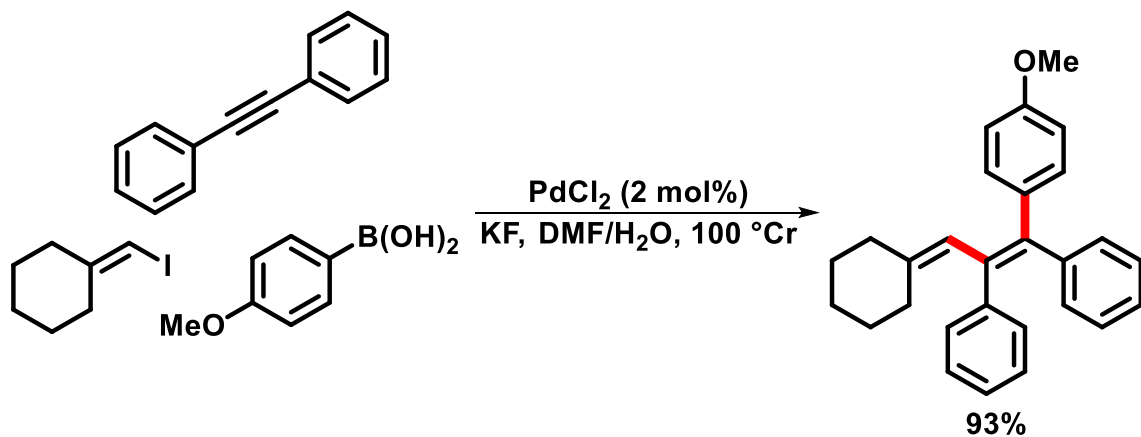


✓ Proposed mechanism



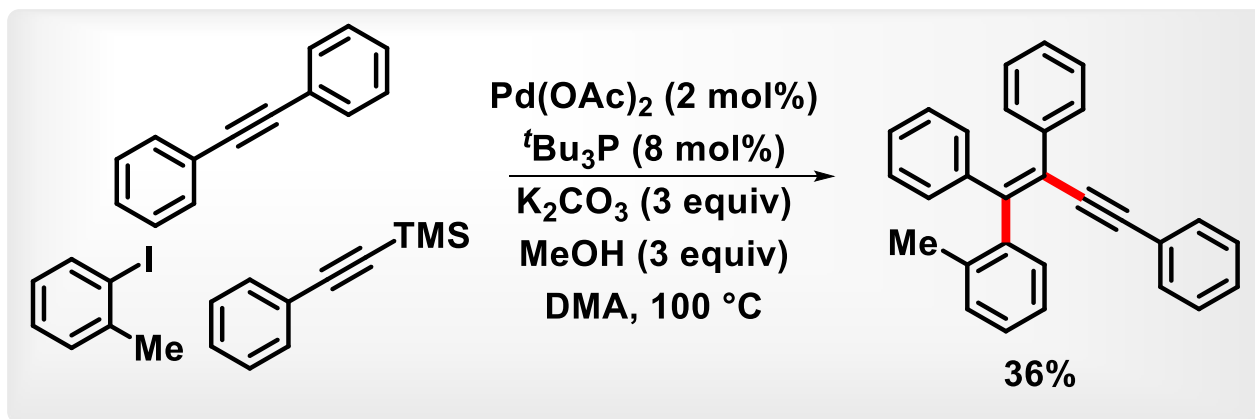
- Transition-metal-catalyzed alkyne carbometallations
 - Carbopalladation

✓ Proposed mechanism

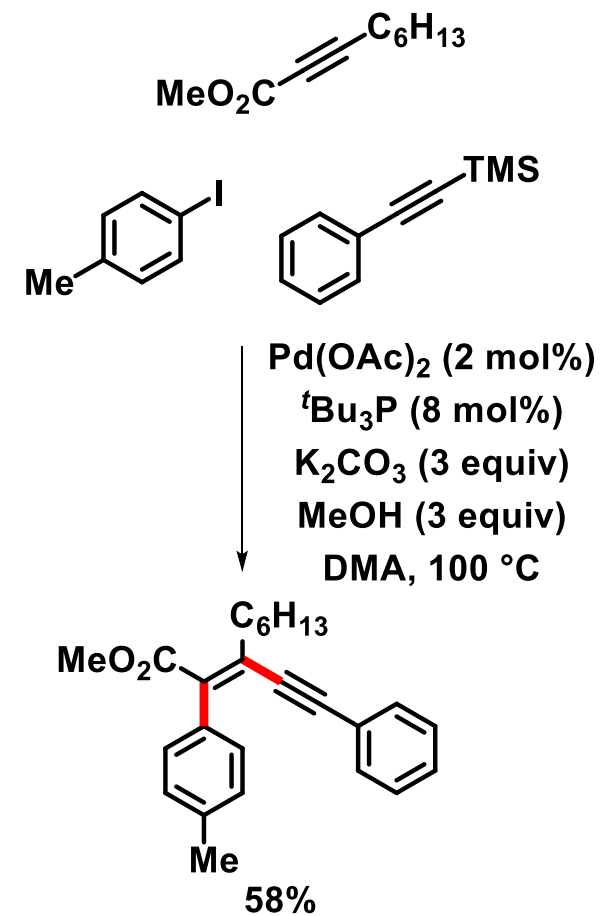
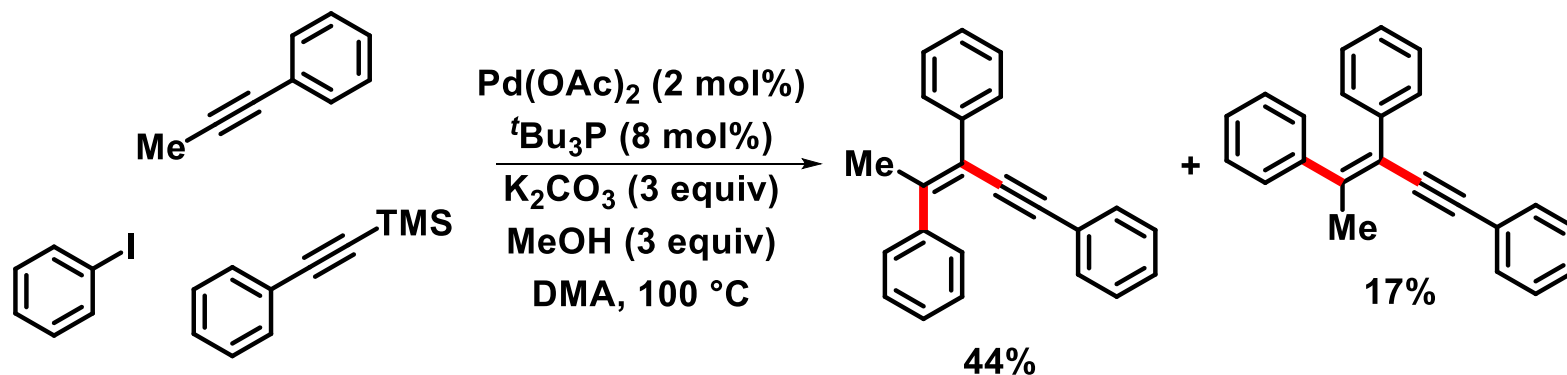


➤ Transition-metal-catalyzed alkyne carbometallations

• Carbopalladation

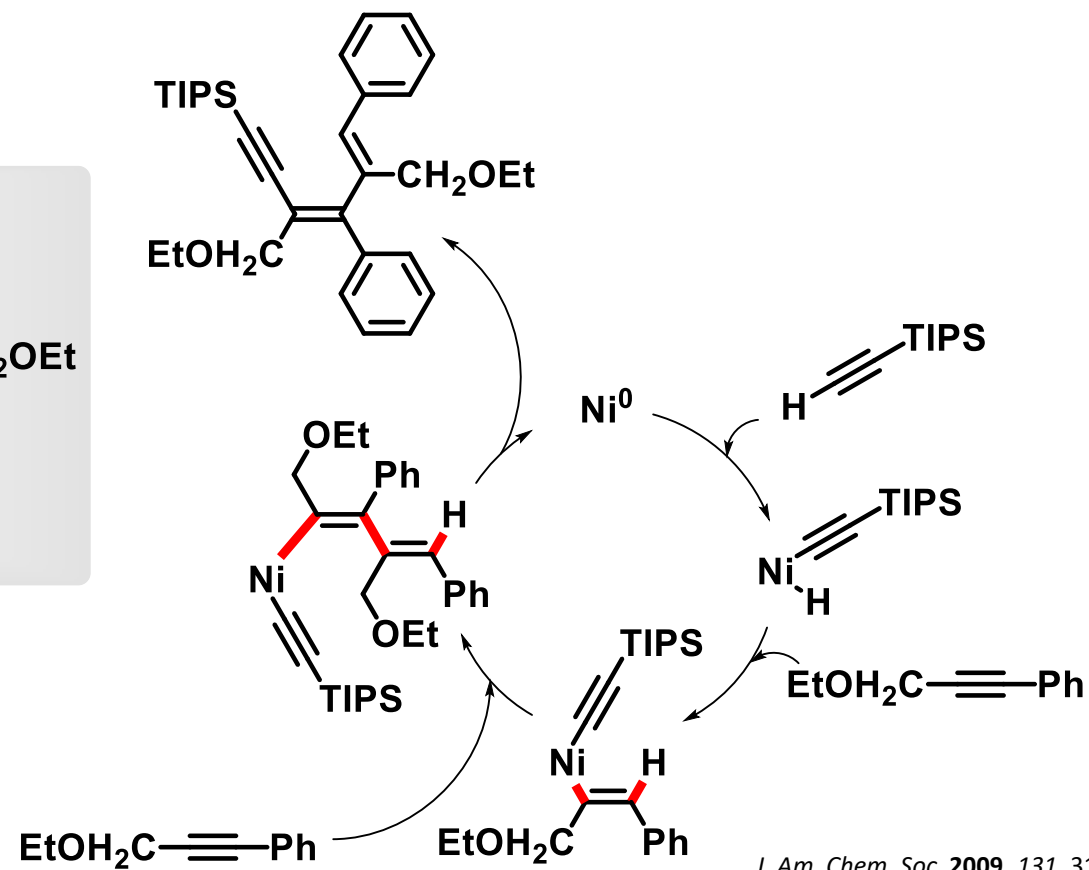
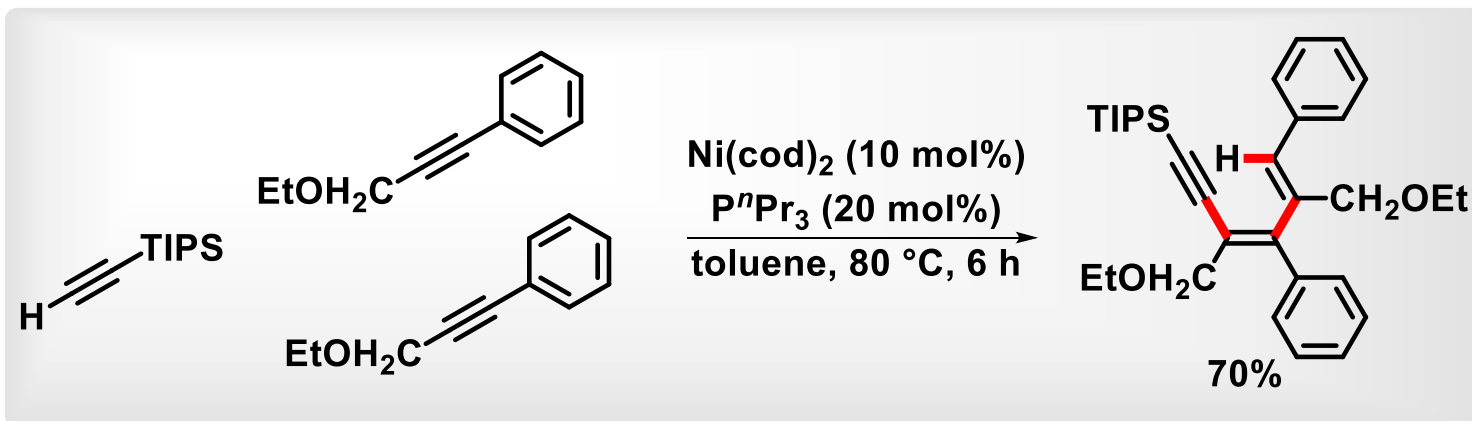


○ Sensitive to the structure of the starting substrate



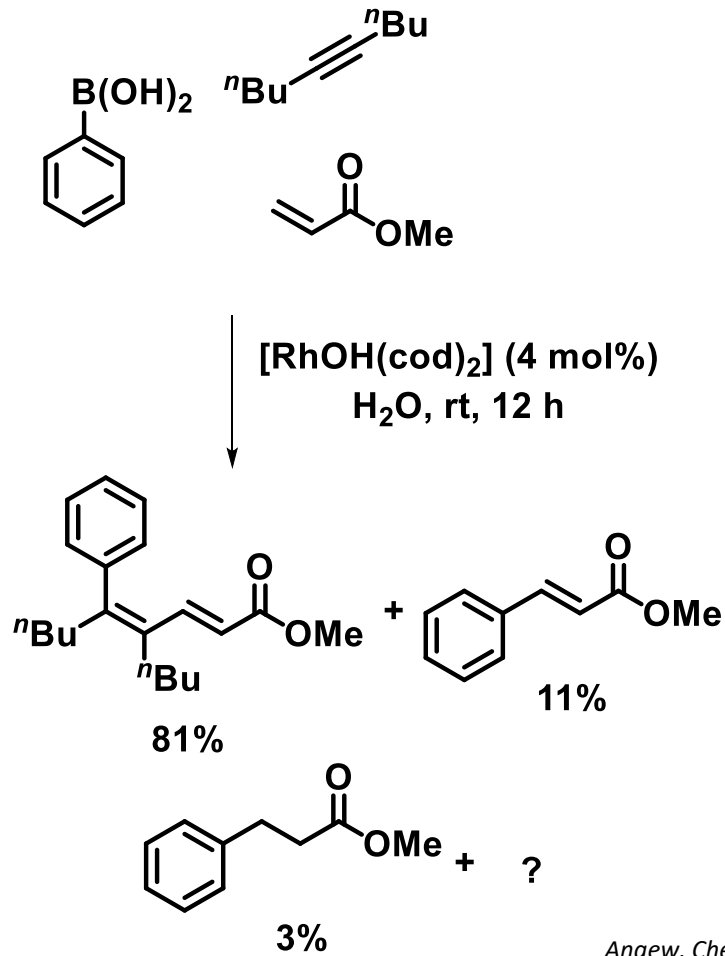
- Transition-metal-catalyzed alkyne carbometallations
 - Carbonickelation

✓ Proposed mechanism



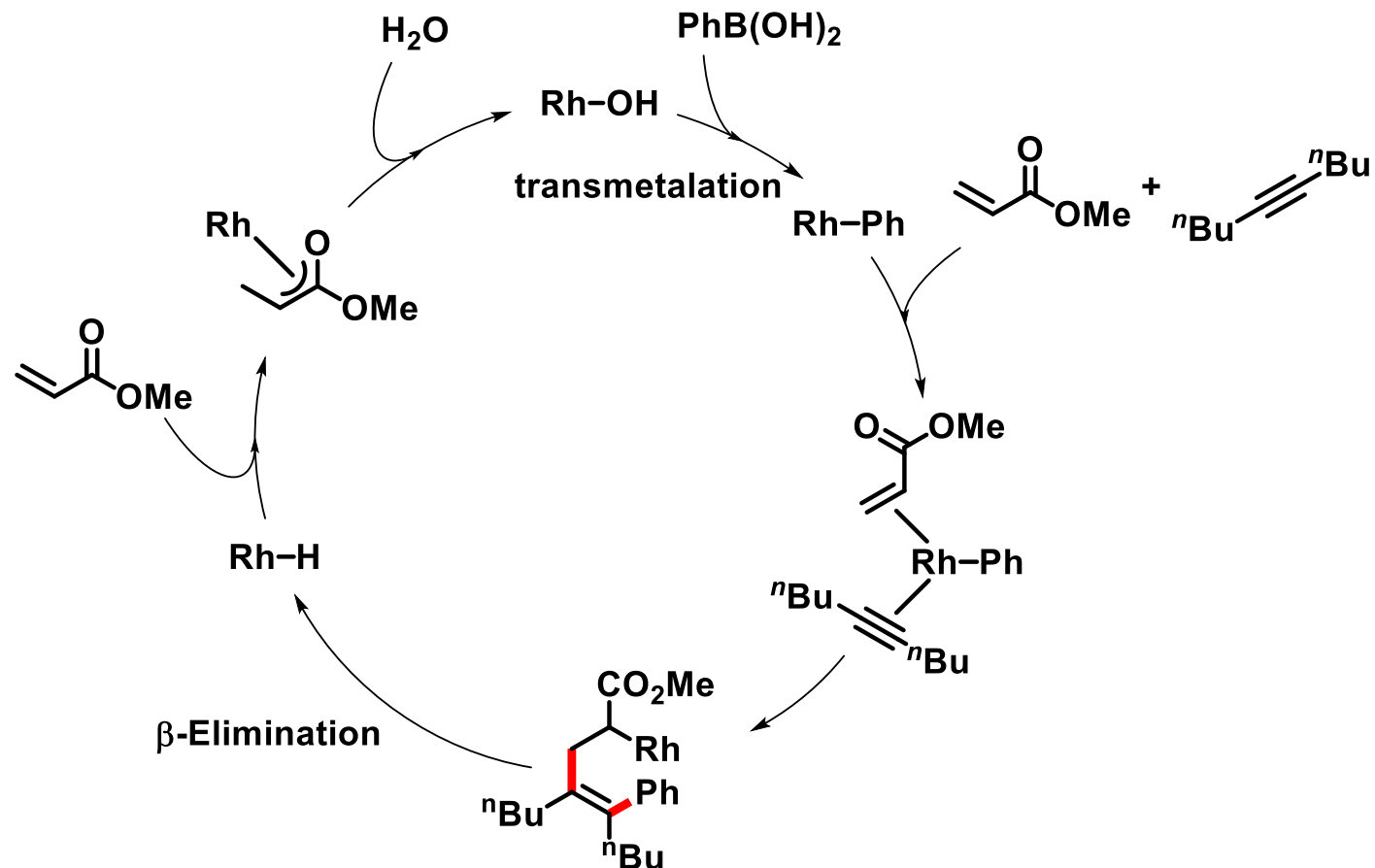
J. Am. Chem. Soc. 2009, 131, 3176

- Transition-metal-catalyzed alkyne carbometallations
 - Carborhodation

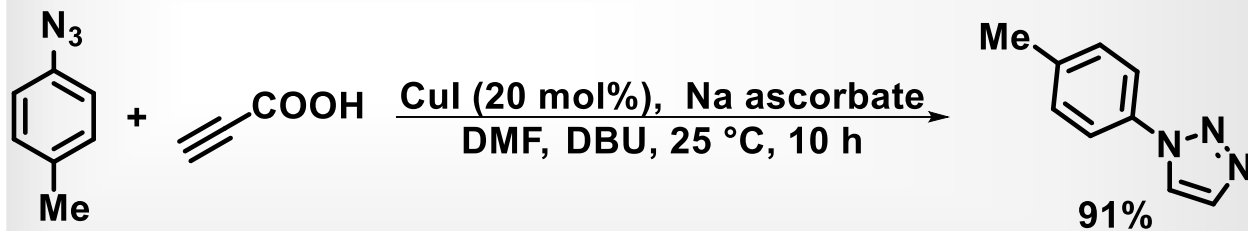


Angew. Chem. Int. Ed. 2006, 45, 6336

✓ Proposed mechanism



➤ CAAC (Copper-catalyzed azide-alkyne cycloaddition)



Synthesis 2011, 223

The Nobel Prize in Chemistry 2022



III. Niklas Elmehed © Nobel Prize Outreach
 Carolyn R. Bertozzi
 Prize share: 1/3



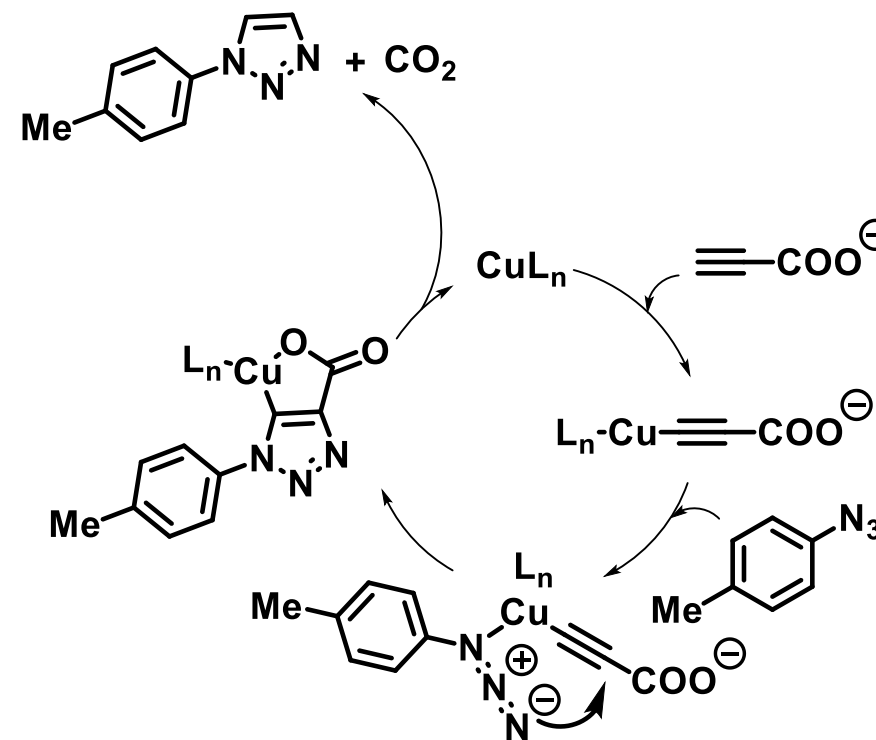
III. Niklas Elmehed © Nobel Prize Outreach
 Morten Meldal
 Prize share: 1/3



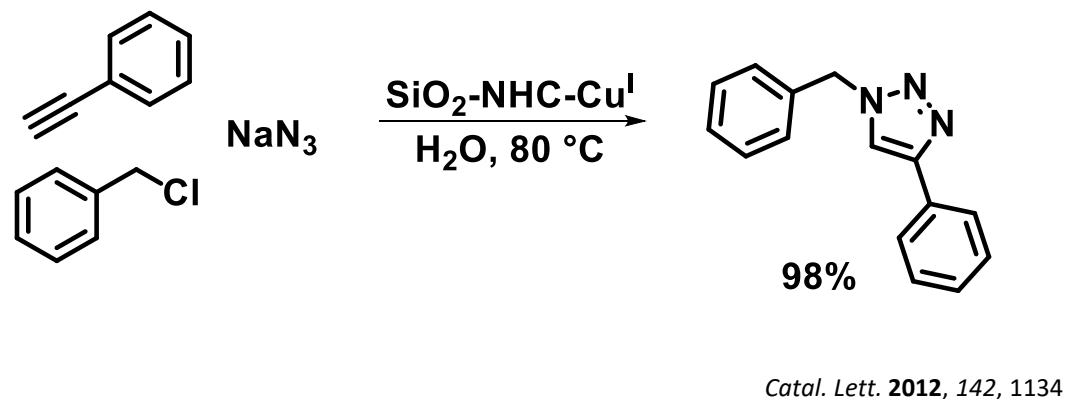
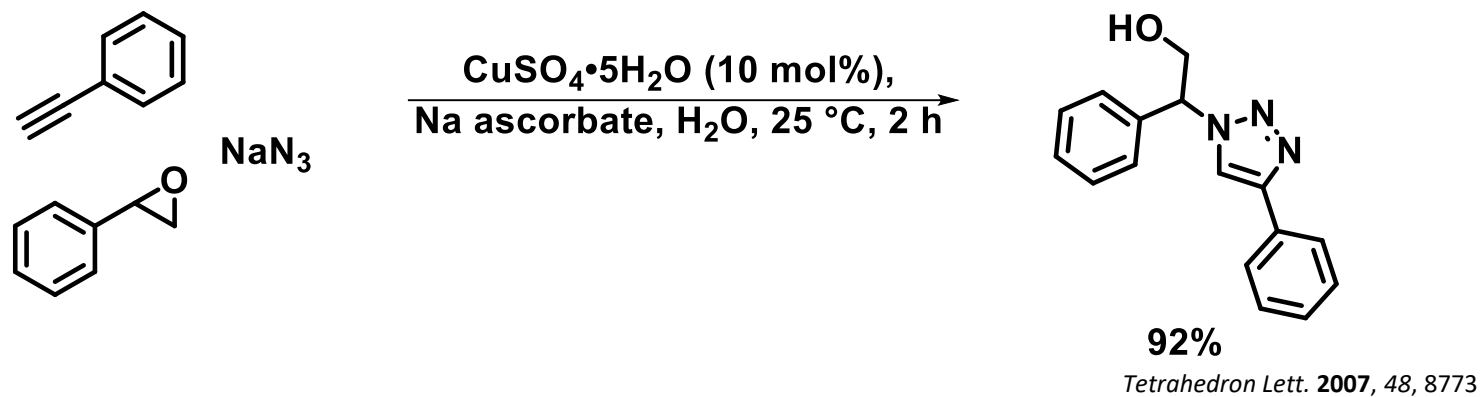
III. Niklas Elmehed © Nobel Prize Outreach
 K. Barry Sharpless
 Prize share: 1/3

<https://www.nobelprize.org/prizes/chemistry/2022/prize-announcement/>

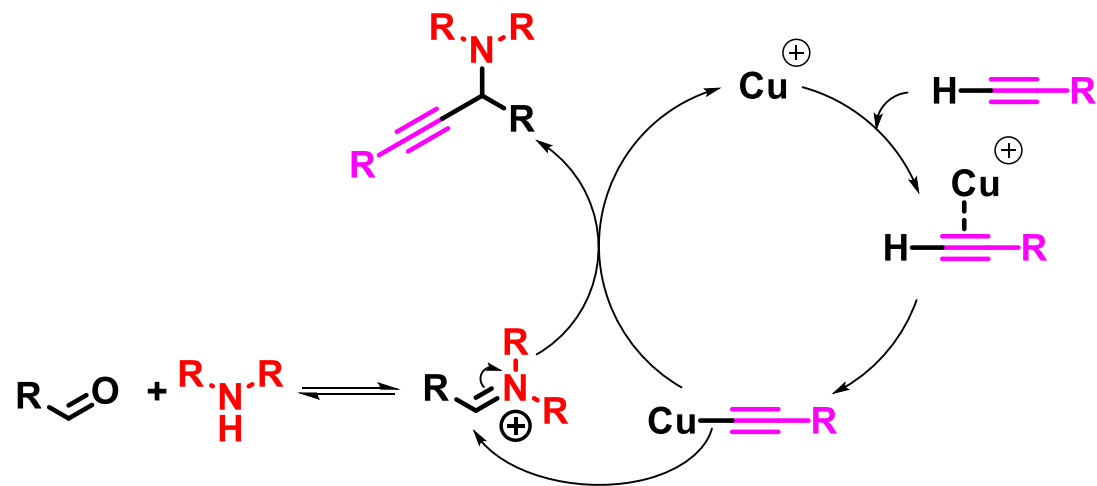
✓ Proposed mechanism



➤ CAAC (Copper-catalyzed azide-alkyne cycloaddition)

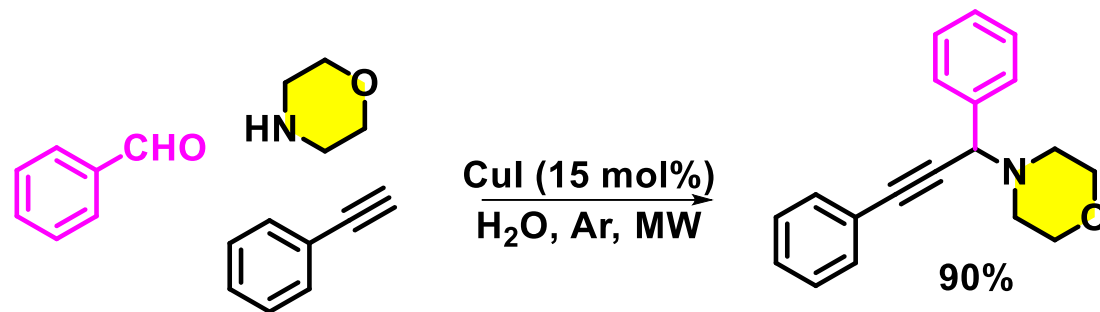


➤ **A³-Coupling** (A³ means alkyne-aldehyde-amine)



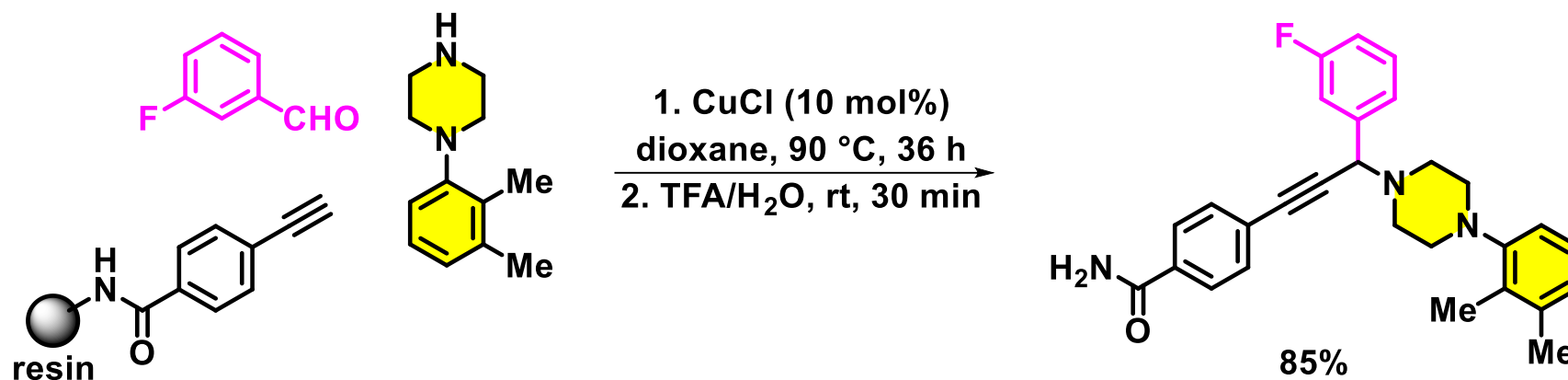
▪ For review see: *Chem. Soc. Rev.* **2012**, *41*, 3790

➤ **A³-Coupling** (A³ means alkyne-aldehyde-amine)



Org. Lett. 2004, 6, 1001

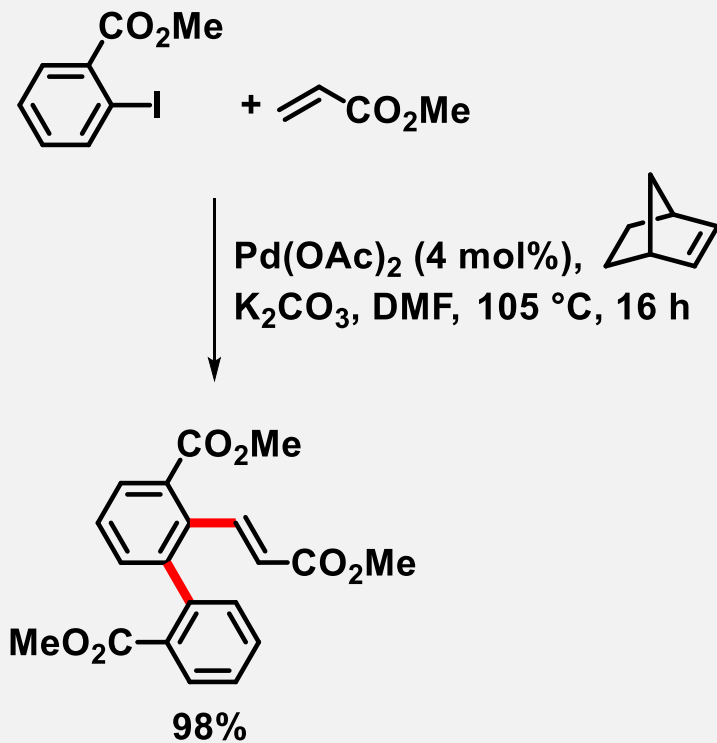
- **A³-Coupling in solid-phase synthesis:**



Tetrahedron Lett. 1998, 39, 3647

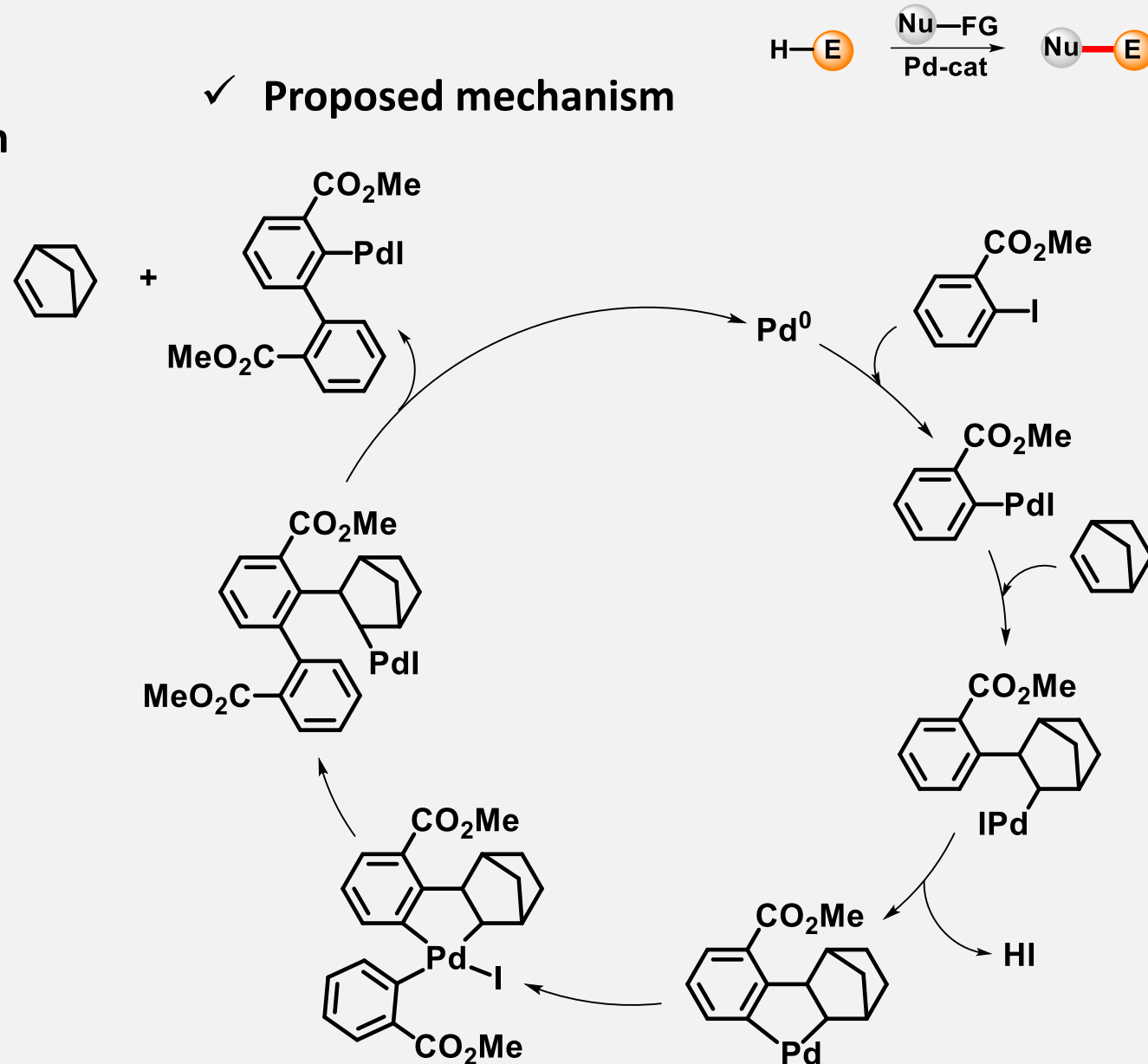
➤ Transition-metal-catalyzed C–H activation

- Pd^{II}/Pd^{IV} catalytic cycle – Catellani reaction



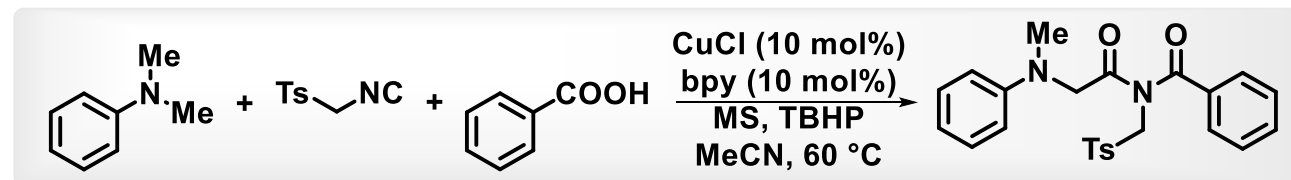
Synthesis 2003, 2671

✓ Proposed mechanism

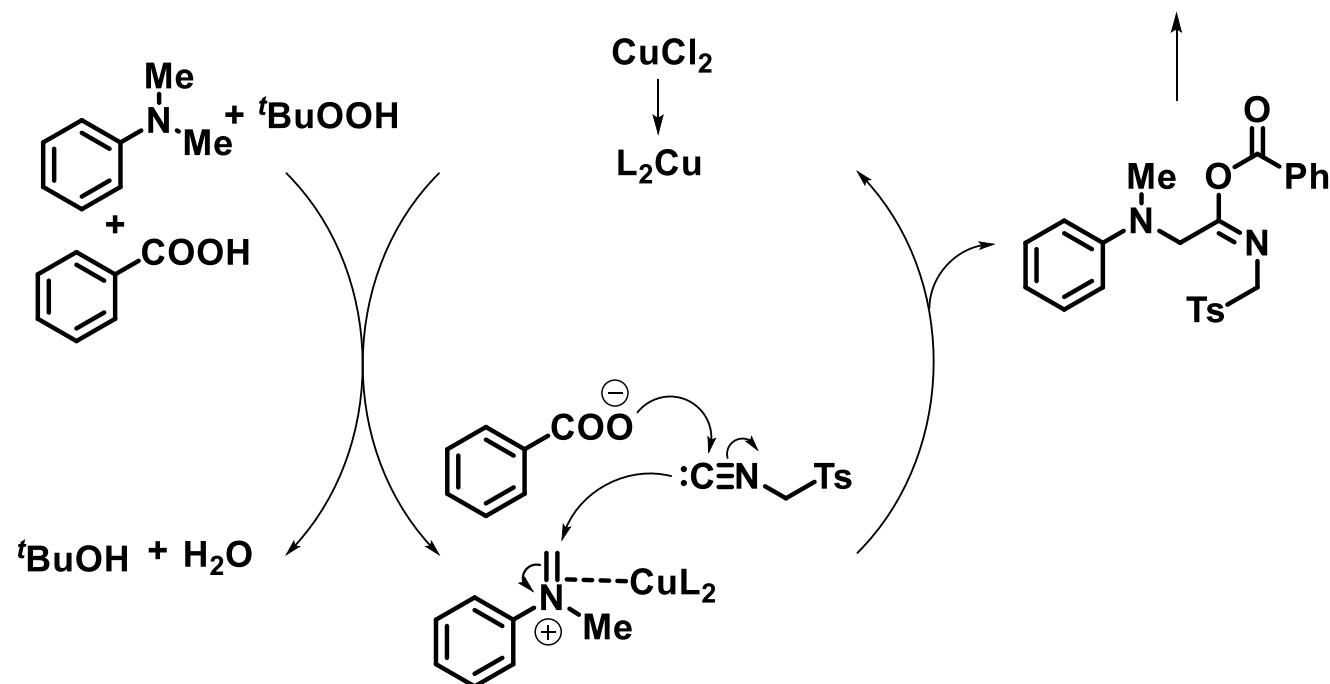


➤ Transition-metal-catalyzed C–H activation

- C(sp³)–H bond functionalization

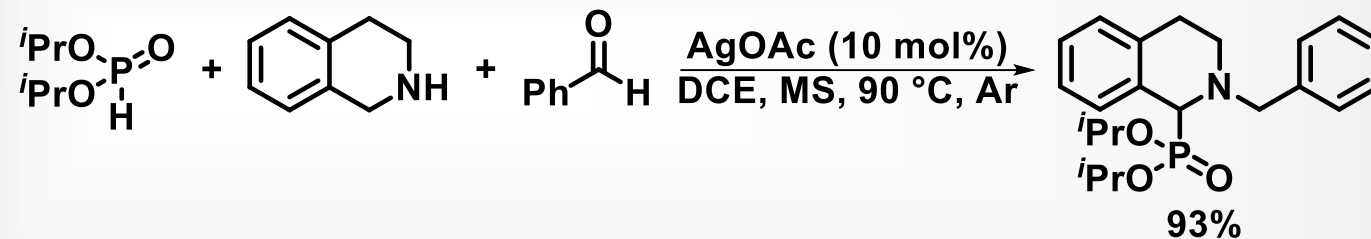


✓ Proposed mechanism

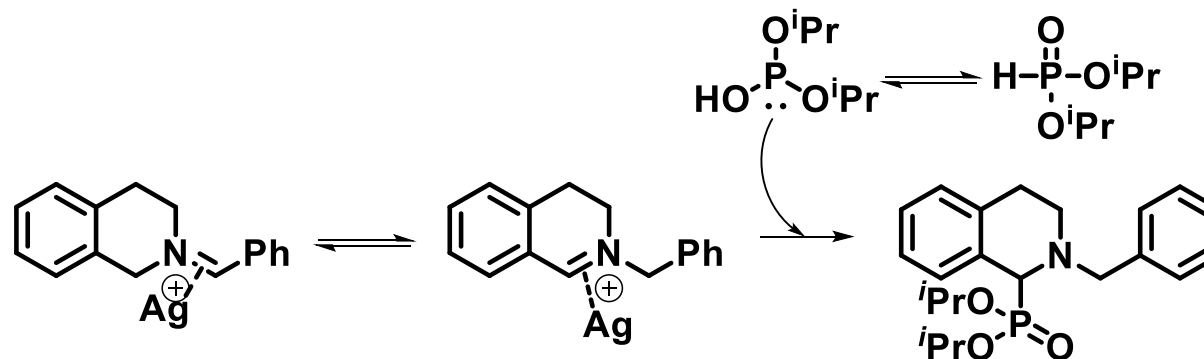


➤ Transition-metal-catalyzed C–H activation

- C(sp³)–H bond functionalization



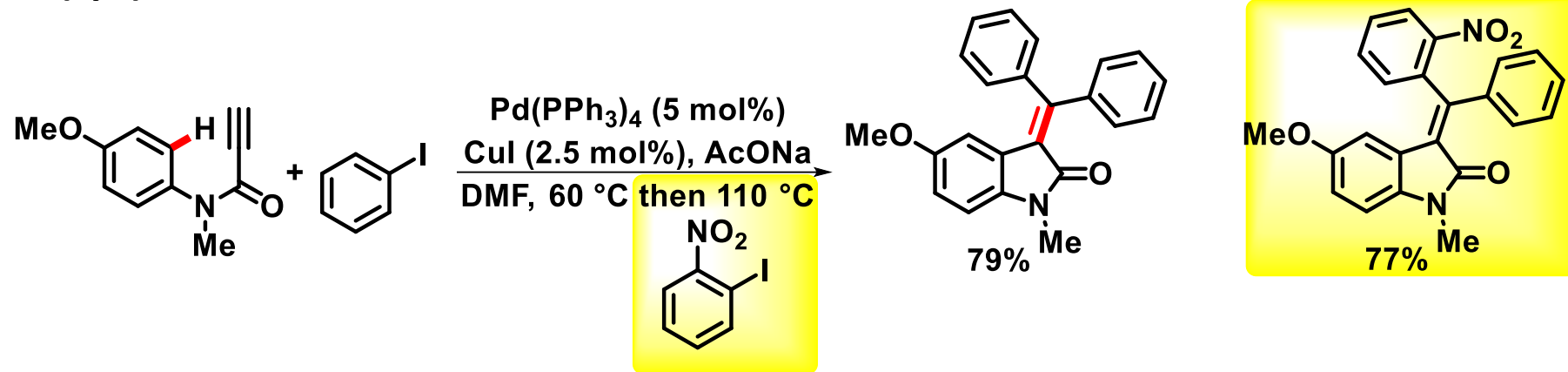
✓ Proposed mechanism



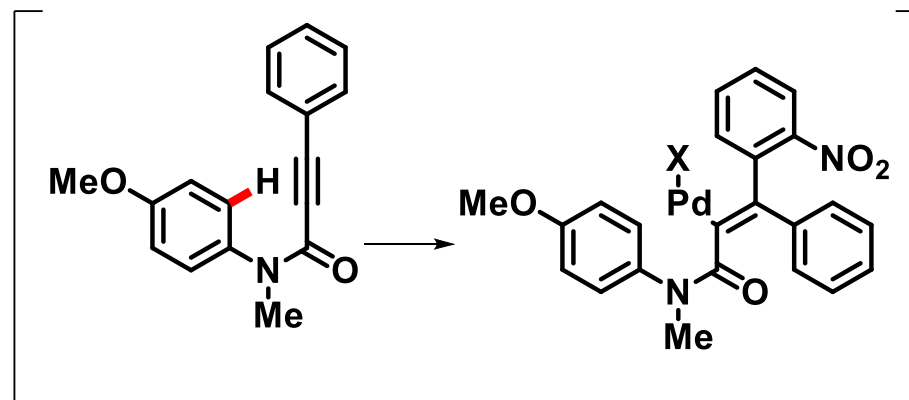
J. Org. Chem. 2016, 81, 1704

➤ Transition-metal-catalyzed C–H activation

- C(sp²)–H bond functionalization

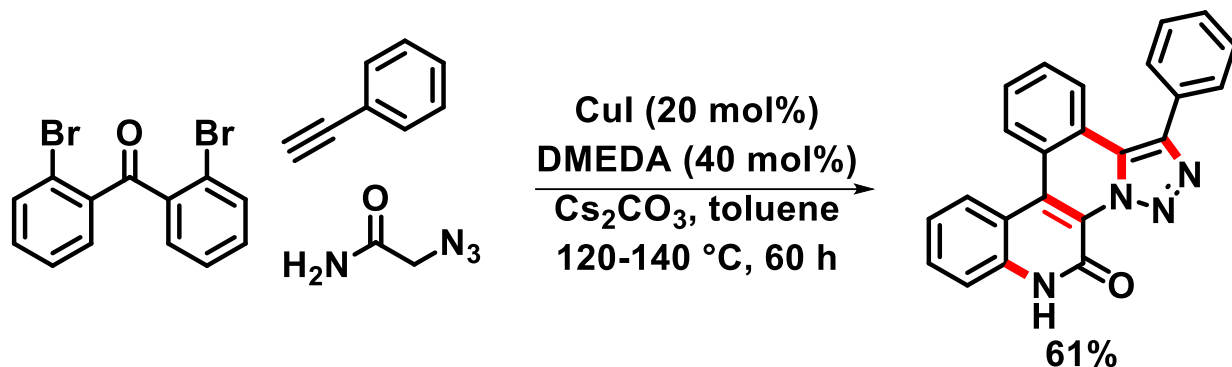


✓ Important intermediate

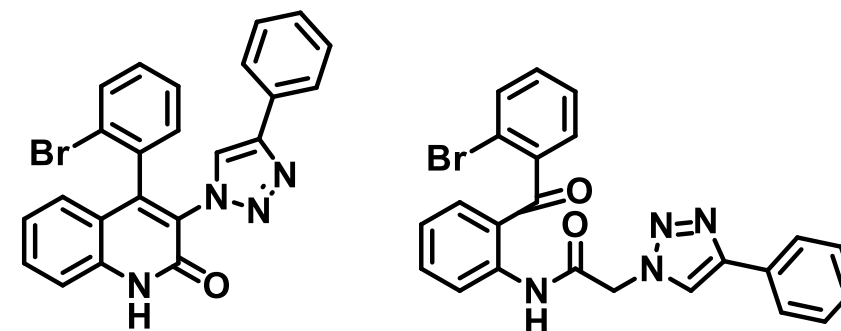


➤ Transition-metal-catalyzed C–H activation

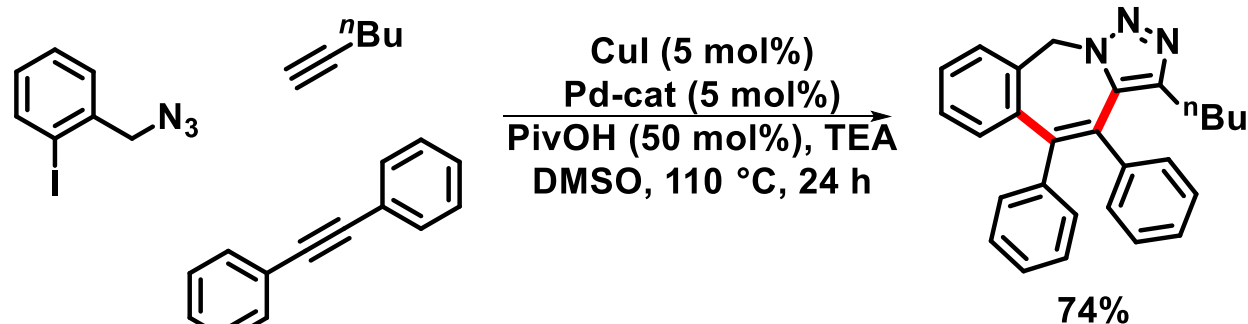
- C(sp²)–H bond functionalization



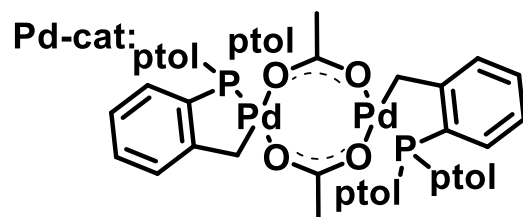
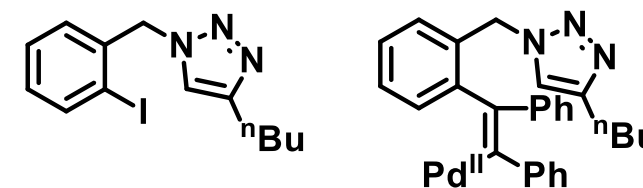
✓ Proposed intermediates



Angew. Chem. Int. Ed. **2013**, 52, 10992



✓ Proposed intermediates

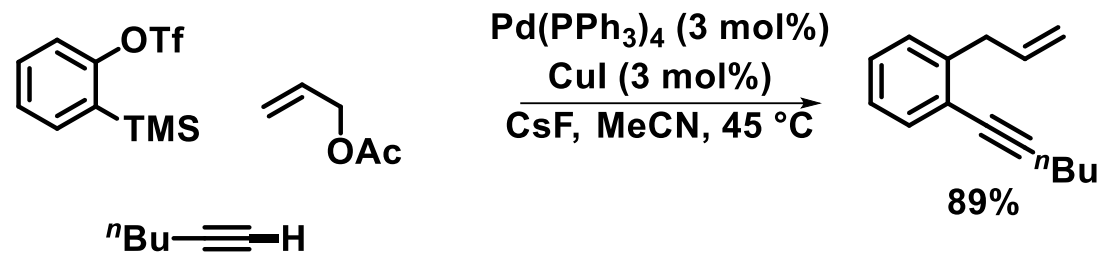


Herrmann-Beller palladacycle

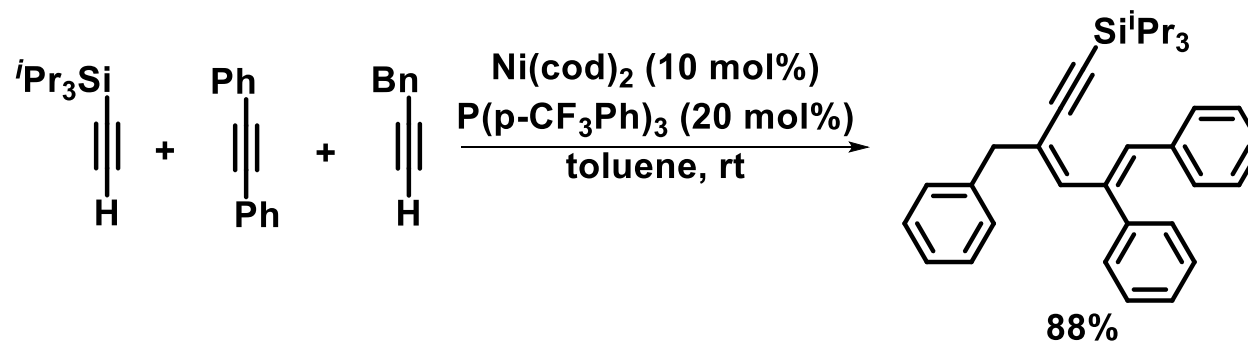
ACS Catal. **2016**, 6, 4946

➤ Transition-metal-catalyzed C–H activation

- C(sp)–H bond functionalization:



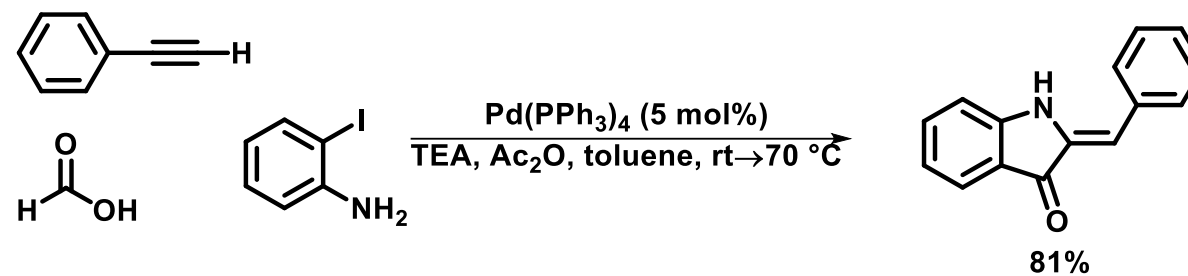
Chem. Commun. **2008**, 2158



Org. Lett. **2011**, 13, 122

➤ Transition-metal-catalyzed C–H activation

- C(sp)–H bond functionalization:



Org. Biomol. Chem. **2017**, *15*, 6905