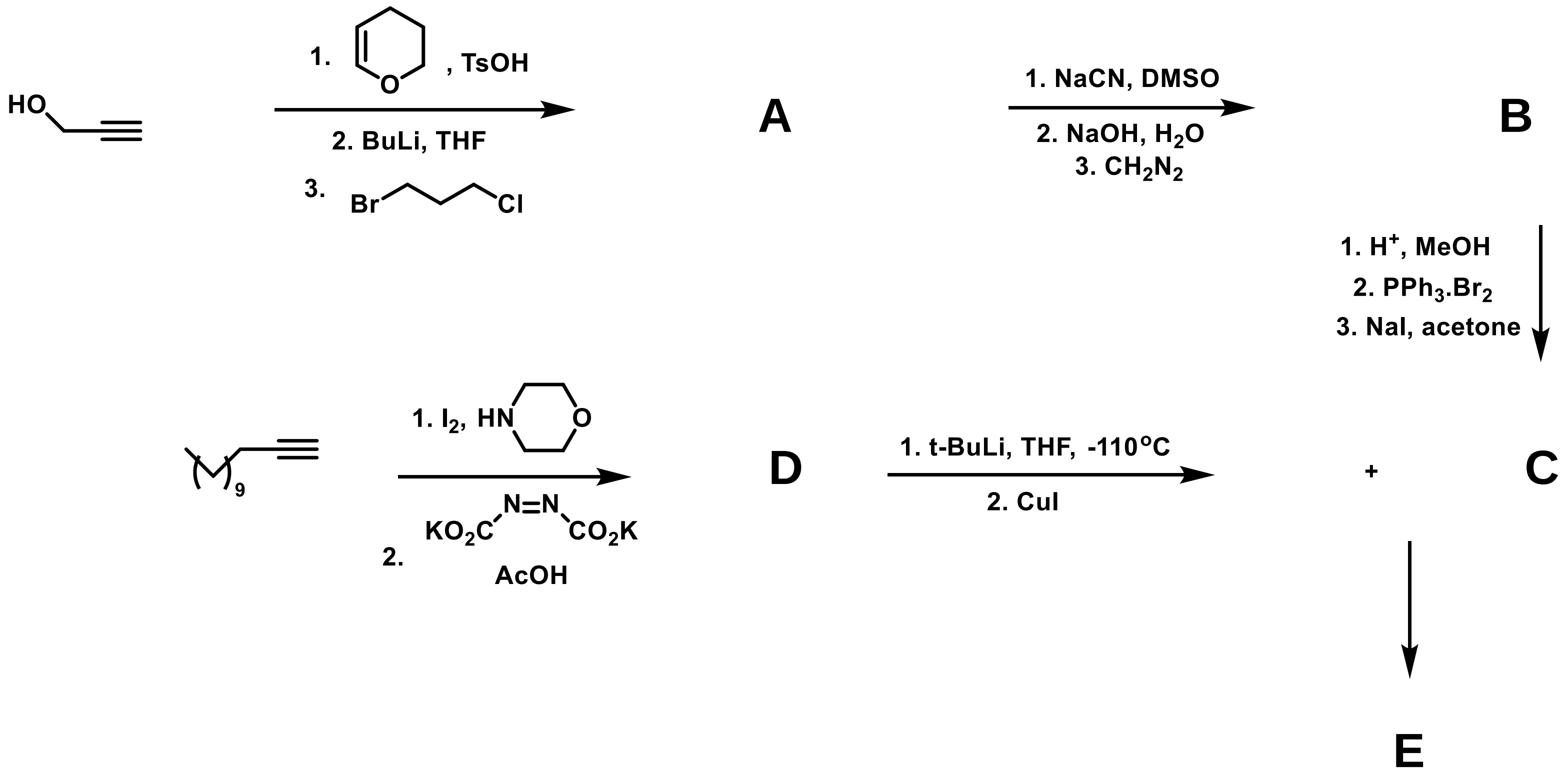
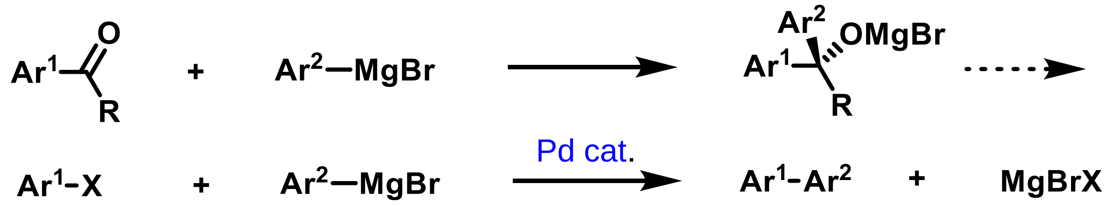
Organic synthesis

Kamil Paruch

Masaryk University, Brno



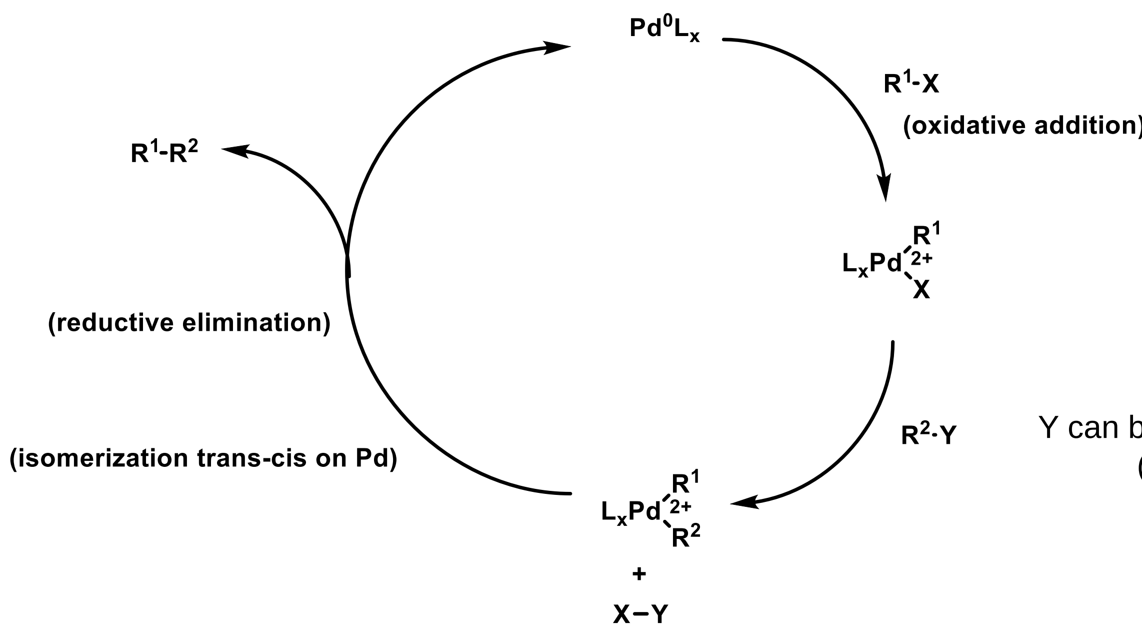
Tetrahedron Lett. **1980**, *21*, 4243.



Reactions catalyzed by palladium

- formation of C-C, C-N, C-O bonds
- catalytic amount of Pd compounds
- mild reaction conditions; compatible with various functional groups

Pd^0: electron-rich, nucleophilic

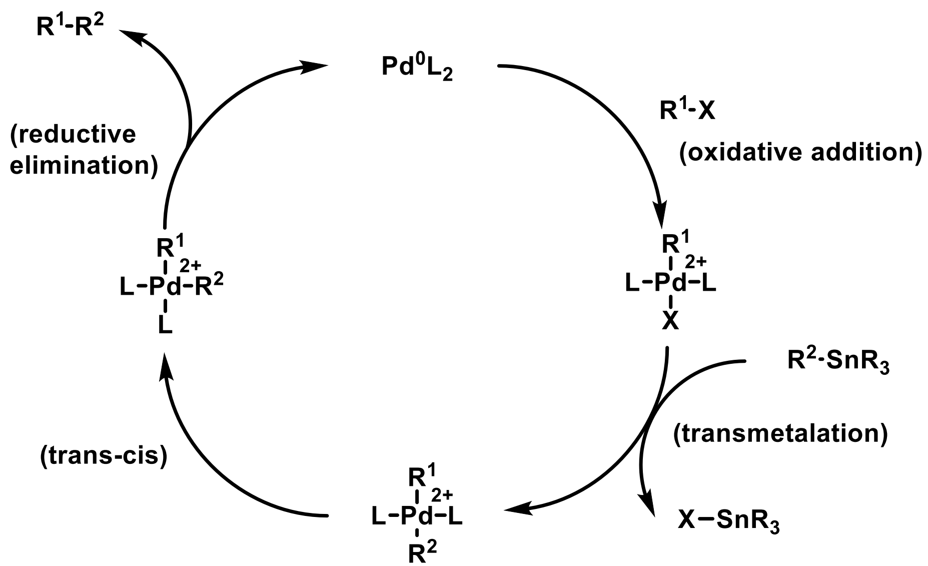


Y can be different metal, e.g. Mg, Sn, Zn
(transmetalation)

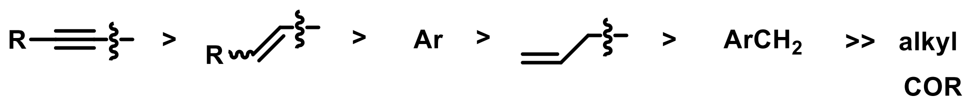
Stille reaction

$$R^1\text{-}X + R^2\text{-}SnR_3 \xrightarrow{\text{Pd cat.}} R^1\text{-}R^2 + X\text{-}SnR_3$$

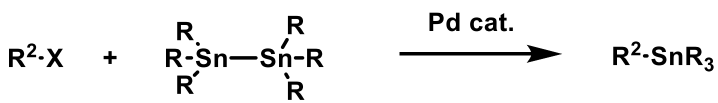
R: typically Bu or Me



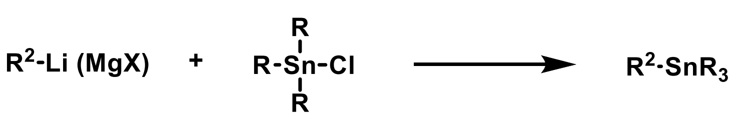
ease of transmetalation Sn -> Pd



stannanes: $$$



X = Br, I, OTf   R = Me, Bu



R = Bu

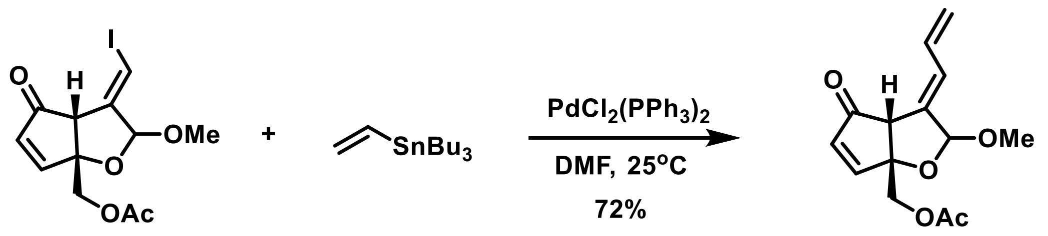
Stille reaction

advantages: very mild conditions

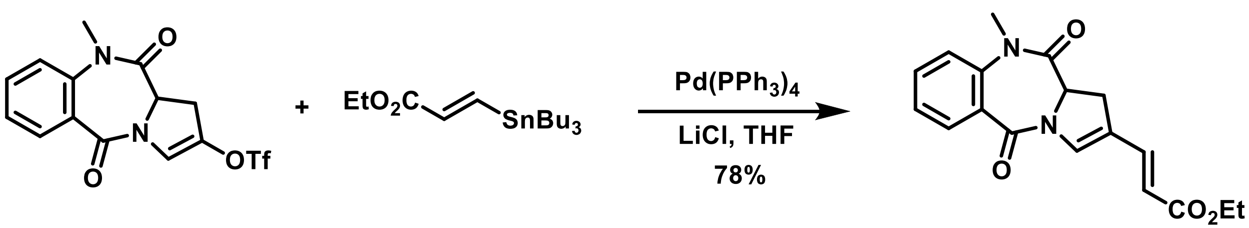
retention of configuration on double bond

triflates: possibility to generate kinetic vs thermodynamic OTf

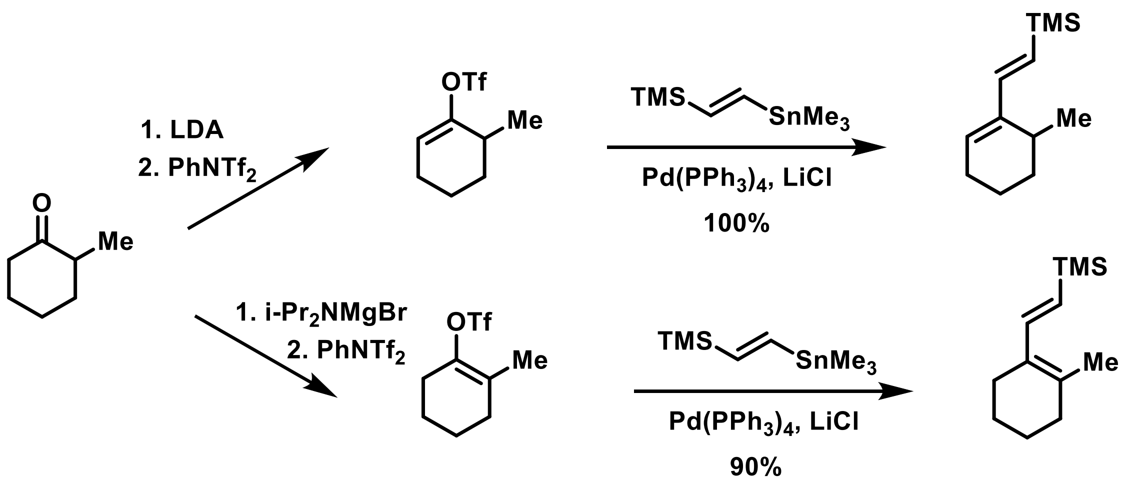
(also: can be made from ArOH)



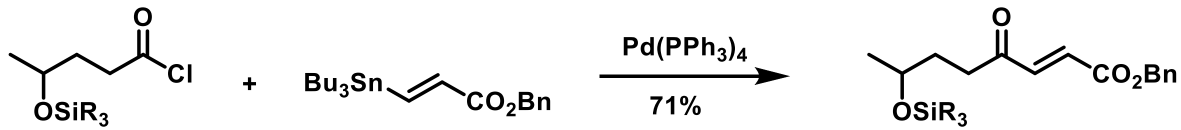
J. Am. Chem. Soc. **1988**, *110*, 5911.



J. Am. Chem. Soc. **1989**, *111*, 5417.

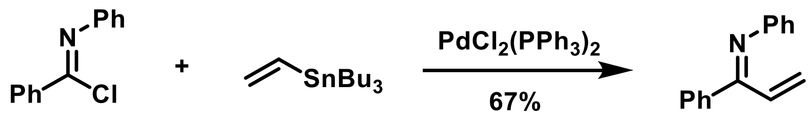


ketones from acid chlorides



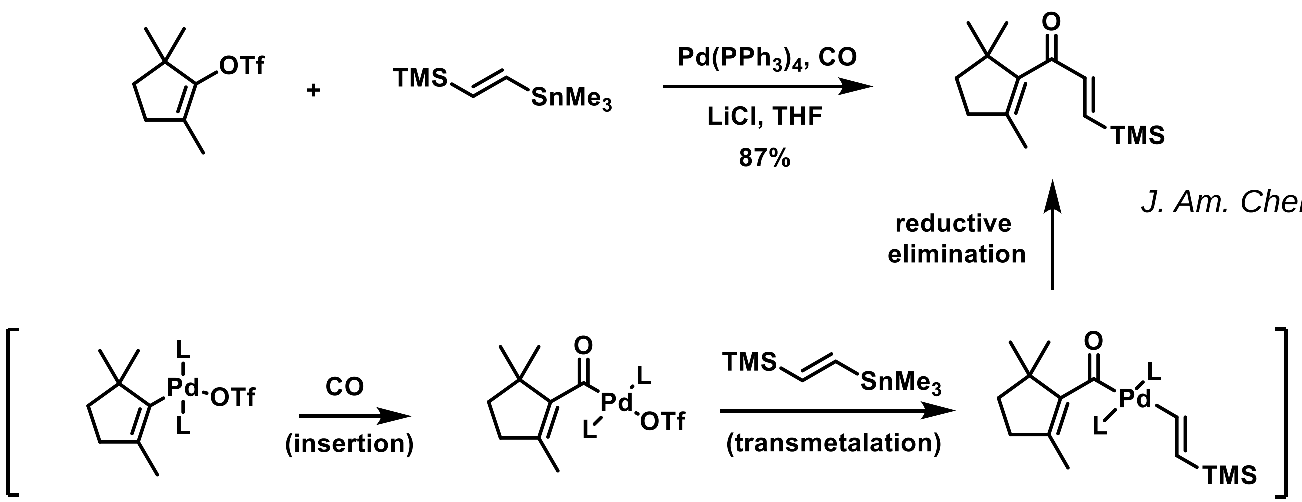
J. Org. Chem. **1983**, *58*, 4634.

imines from imidoyl chlorides



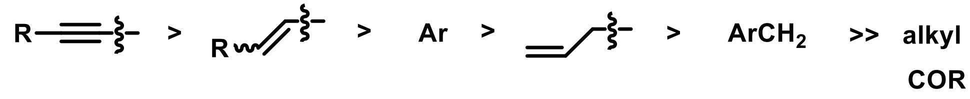
Bull. Chem. Soc. Jpn. **1986**, *59*, 677.

carbonylative Stille: insertion of CO



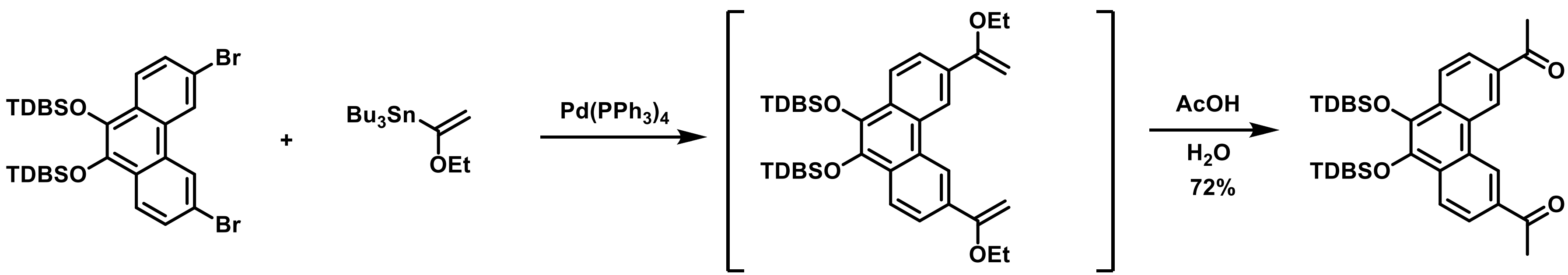
J. Am. Chem. Soc. **1984**, *106*, 7500.

ease of transmetalation Sn → Pd



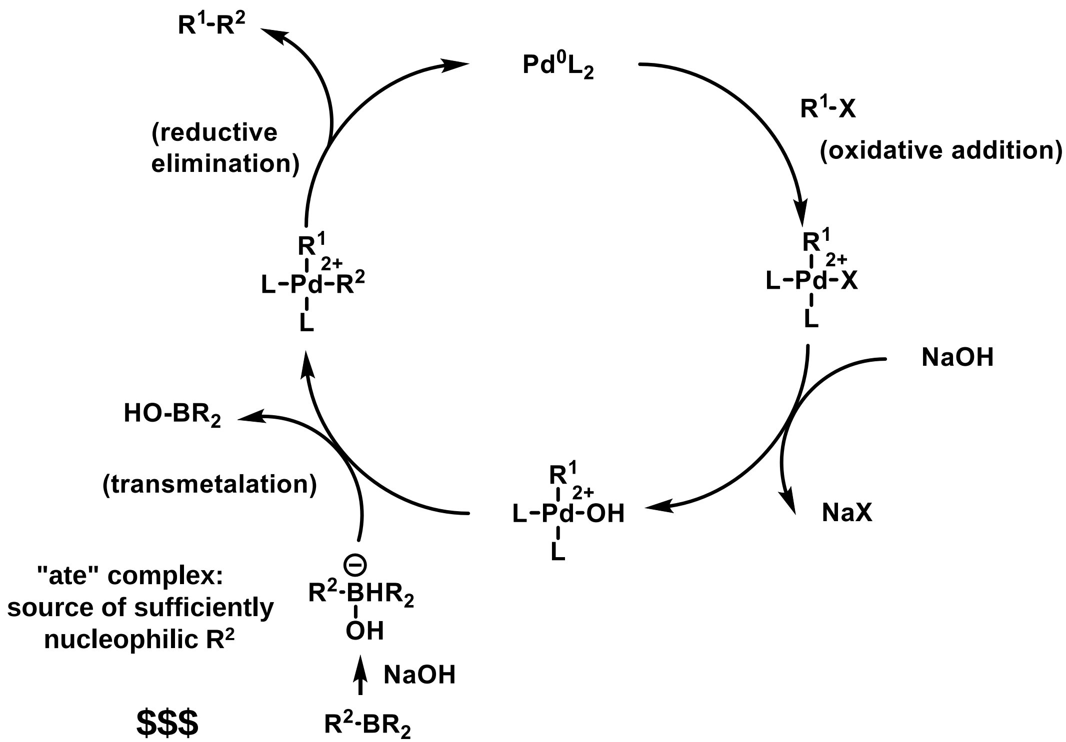
stannyl enol ethers

- acyl equivalents



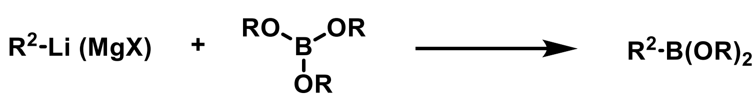
J. Org. Chem. **1998**, *63*, 7456.

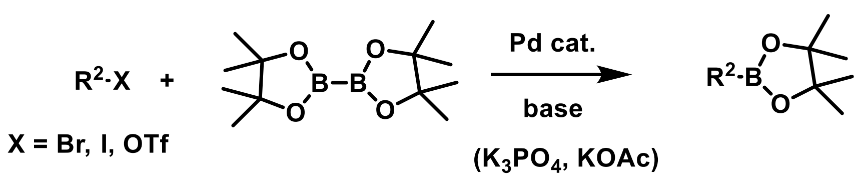
Suzuki reaction



boranes, boronates: **$$$**

addition of R_2BH on alkenes, alkynes

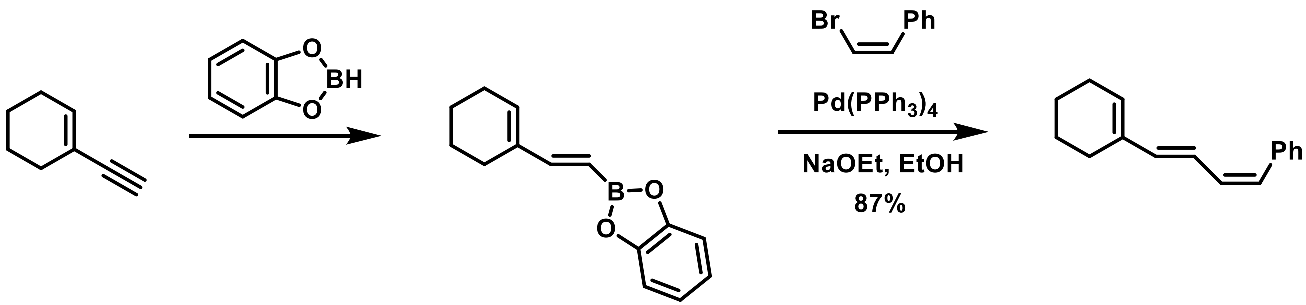


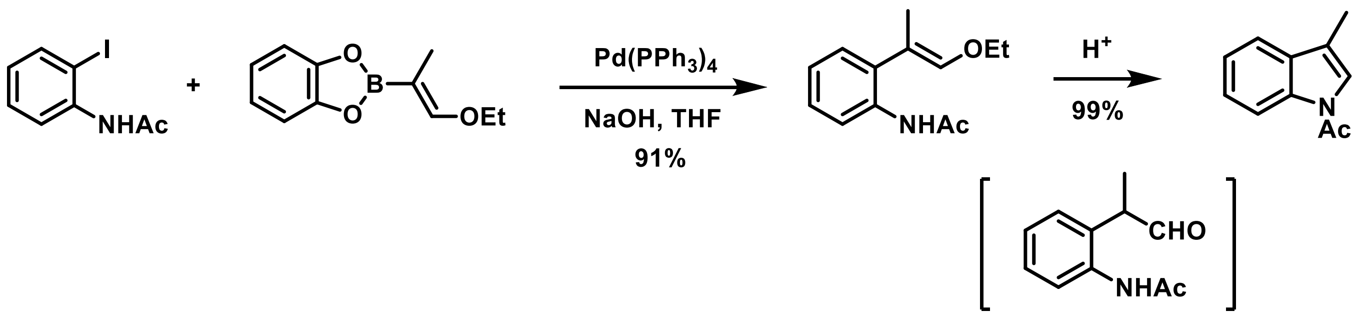


Suzuki reaction

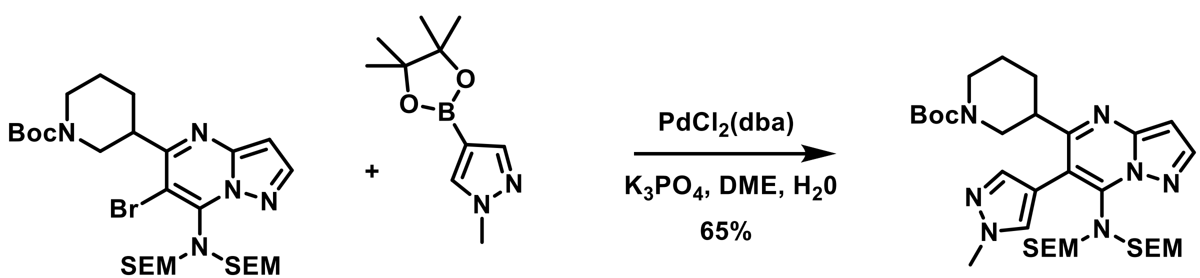
advantages: mild conditions (similar to Stille rxn)

non-toxic side products





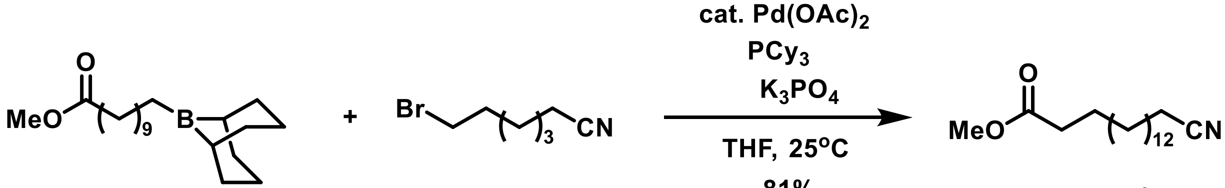
Suzuki coupling is often used for preparation of sterically hindered bis-(hetero)aryls



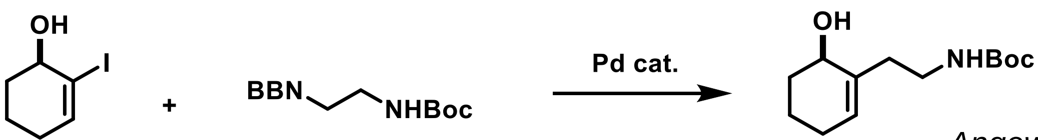
Bioorg. Med. Chem. Lett. **2011**, *21*, 471.

Suzuki coupling with Csp³ boranes

recent review: *Organic Reactions* **100**.



J. Am. Chem. Soc. **2001**, *123*, 10099.

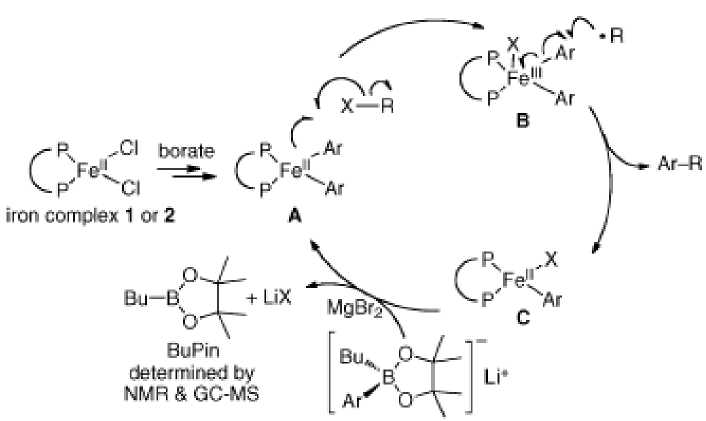


Angew. Chem. Int. Ed. **2022**, *61*, e202203186.

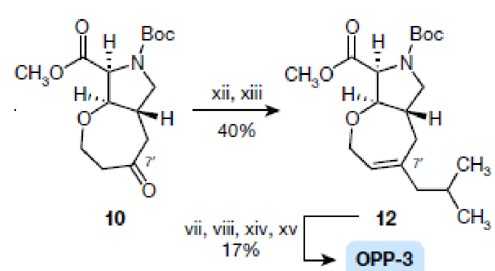
Iron-catalyzed Suzuki-Miyaura coupling of alkyl halides

J. Am. Chem. Soc. **2010**, *132*, 10674.

Scheme 3. Plausible Mechanism



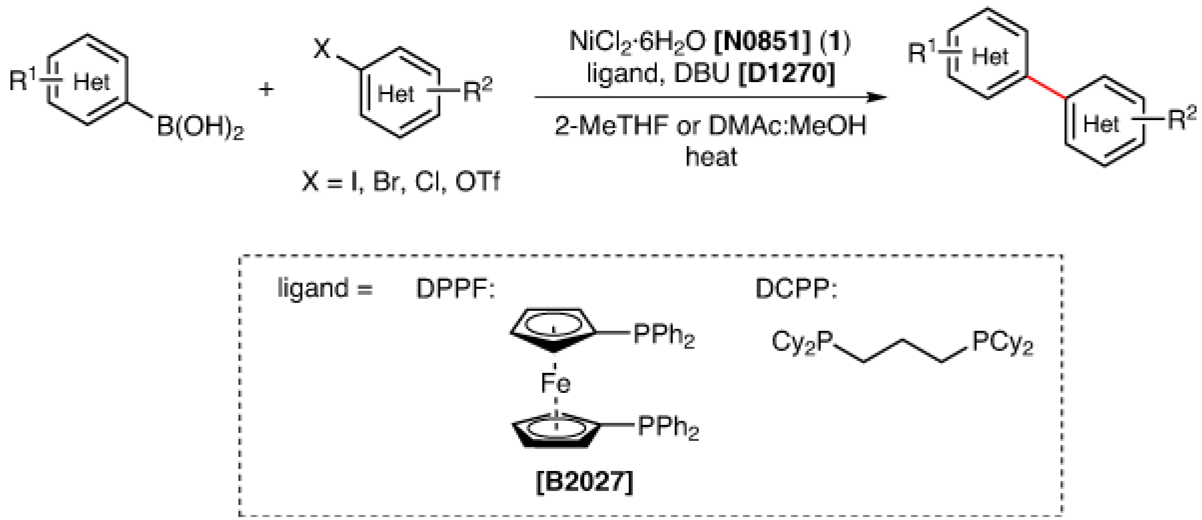
direct Fe-catalyzed coupling: *Nature* **2021**, *559*, 507.



HBF_4 (aq.); (xi) DAST; (xii) LiHMDS, Comins' reagent, 51% (plus, separately, 31% Δ6′ regioisomer); (xiii) ^{i}BuMgCl, $Fe(acac)_3$; (xiv) H_2, $Pd(OH)_2$/C, 1:1 dr; (xv) BSTFA,

Ni-catalyzed Suzuki-Miyaura coupling

- cost-effective variant



Org. Process Res. Dev. **2022**, *26*, 785.

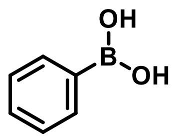
other Ni-catalyzed couplings

e.g.

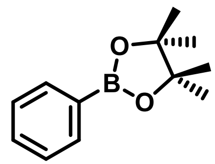
J. Am. Chem. Soc. **2023**, *145*, 7736.

Suzuki reaction

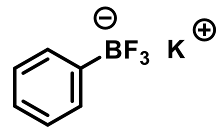
relative stability/reactivity of boron coupling partners



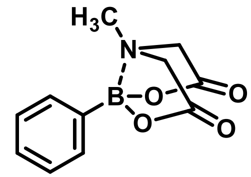
boronic acid



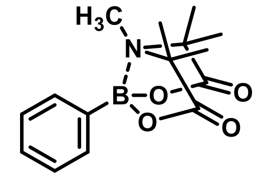
(pinacol) boronate



(potassium) trifluoroborate



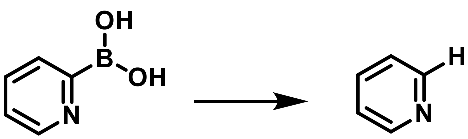
MIDA ester



TIDA ester

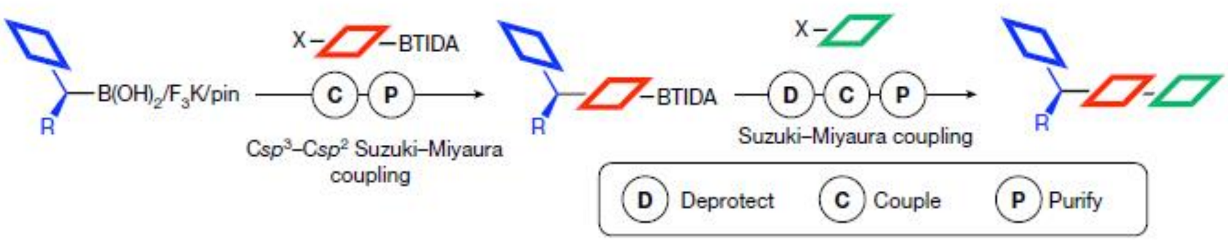
http://organicreactions.org/index.php/Cross-coupling_reactions_of_organotrifluoroborates

- some boronic acids are unstable (e.g. vinylboronic acid) and/or can undergo rapid protodeborylation
  - ➢ boronates/trifluoroborates are used instead



- „the 2-pyridyl problem“ and its general solution through MIDA ester *Angew. Chem. Int. Ed.* **2012**, *51*, 2667.

- TIDA esters are very stable towards hydrolytic cleavage
  - ➢ they can be used orthogonally in the presence of other boron coupling partners

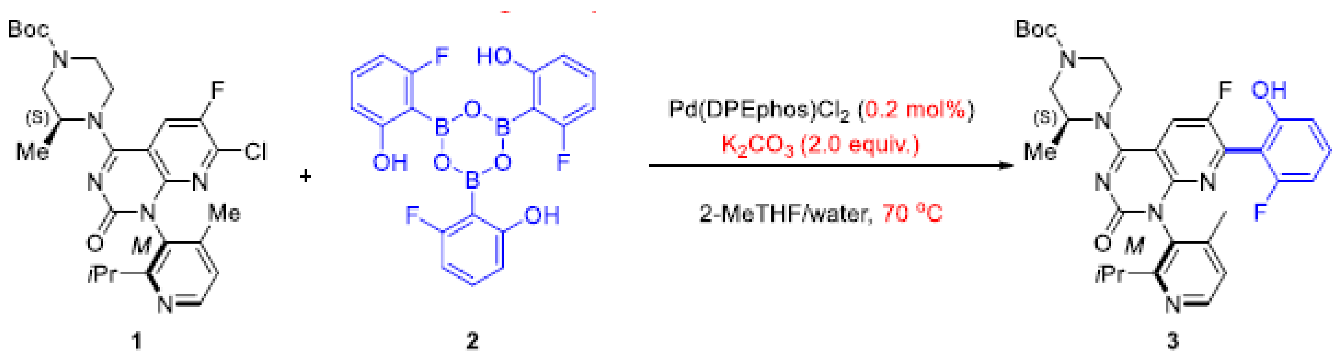


Nature **2022**, *604*, 92.

Rate-determining step can depend on the base

KOAc: rds: reductive elimination

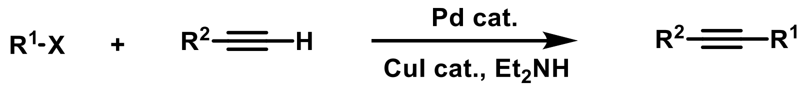
K_2CO_3: rds: transmetalation (significantly better yield in the „bulk charge“ format)

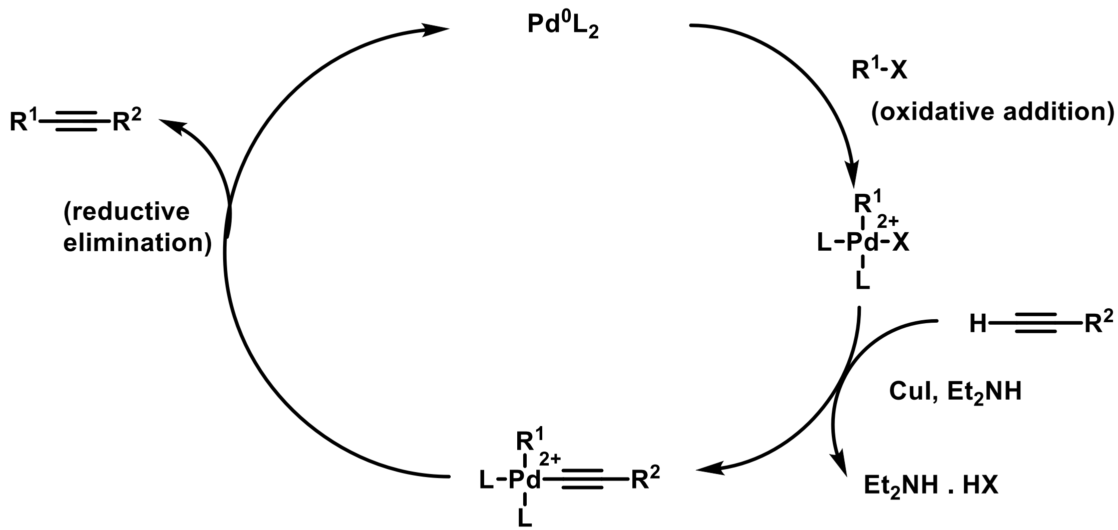


sotorasib

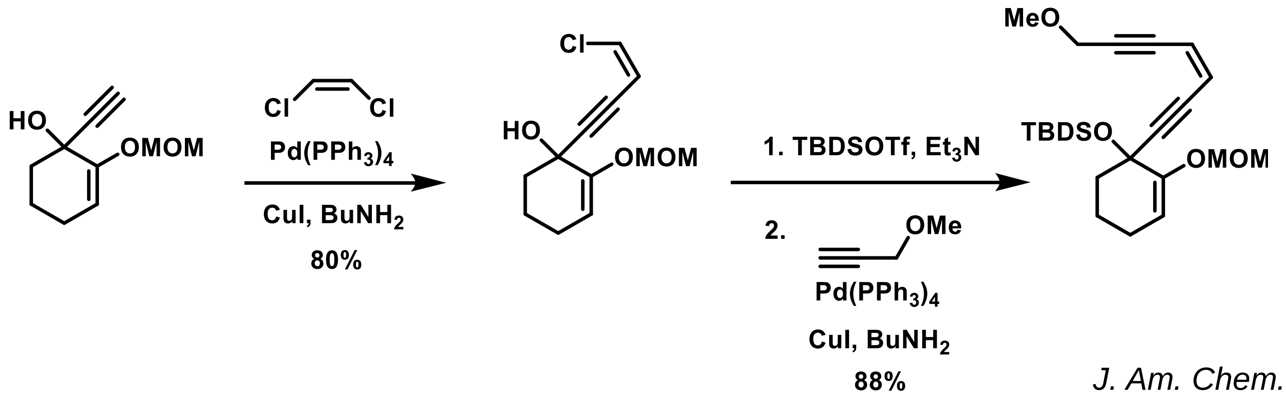
Org. Process Res. Dev. **2023**, *27*, 198.

Sonogashira reaction

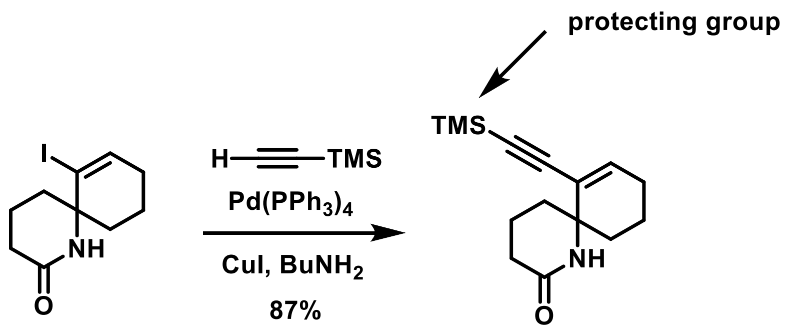




Sonogashira reaction



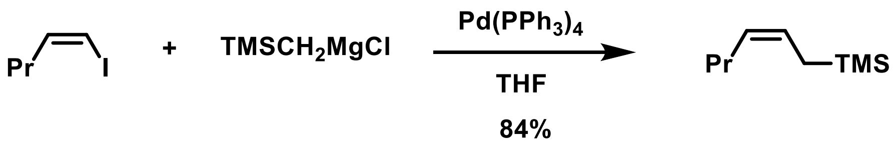
J. Am. Chem. Soc. **1988**, *110*, 6921.



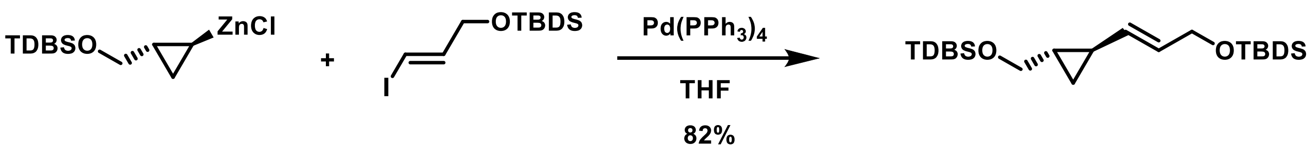
Tetrahedron Lett. **1988**, *29*, 2989.

Pd-catalyzed reactions with RMgX a RZnX

• transmetalation from Mg (Kumada coupling) or Zn (Negishi coupling)

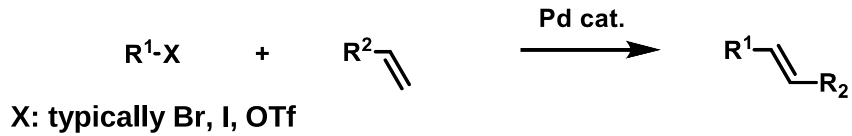


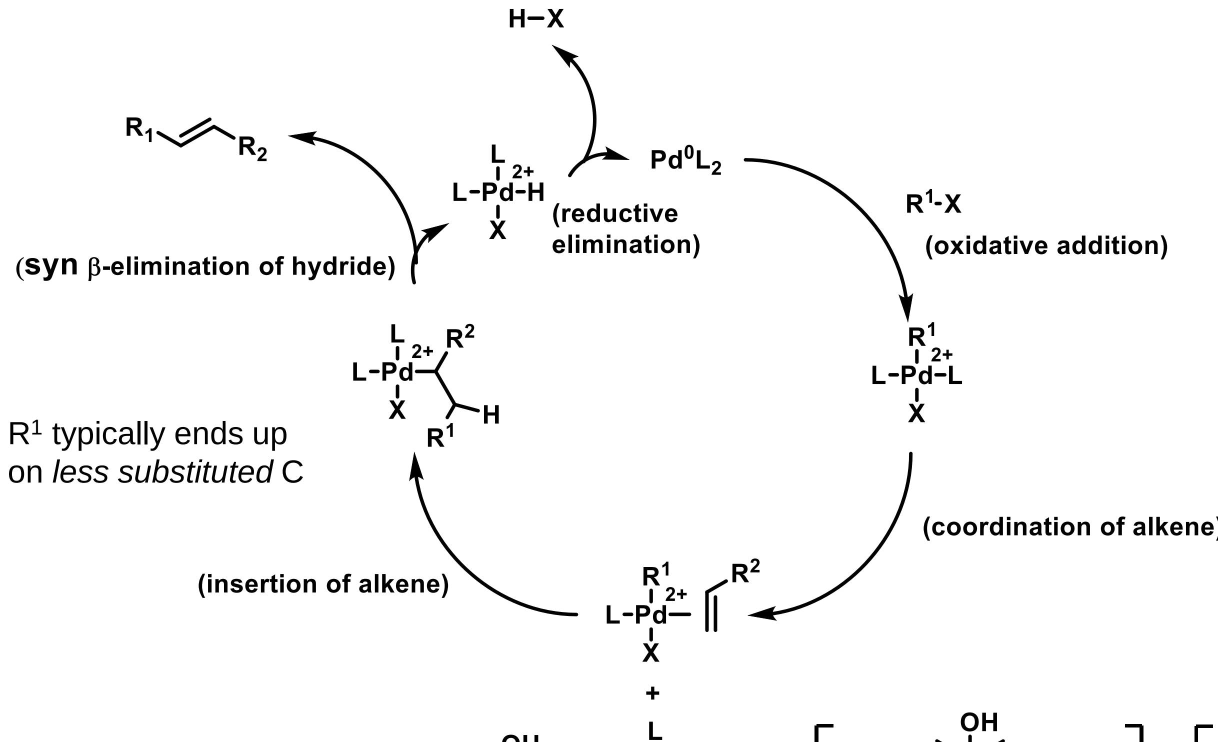
Tetrahedron Lett. **1982**, *23*, 27.

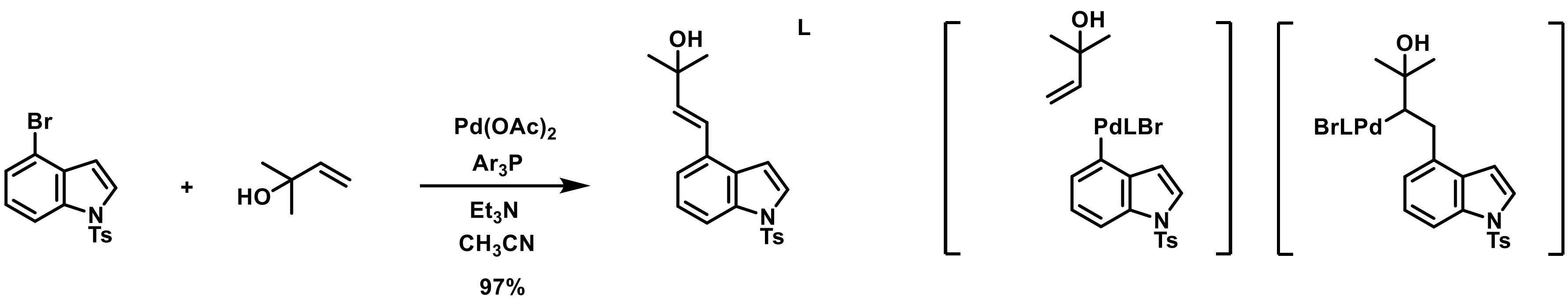


Tetrahedron Lett. **1987**, *28*, 5075.

Heck reaction

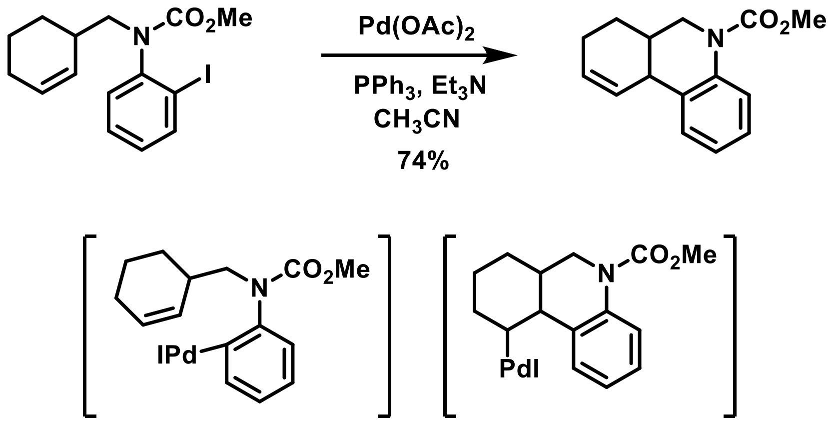




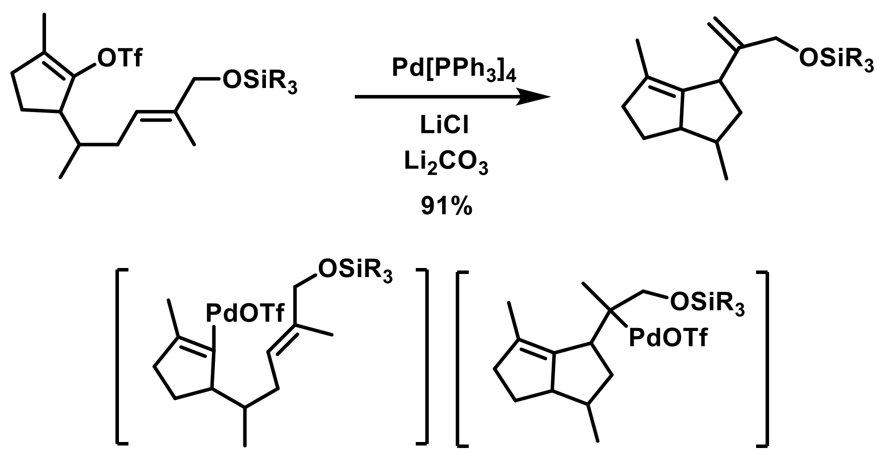


J. Org. Chem. **1984**, *49*, 2657.

Heck reaction

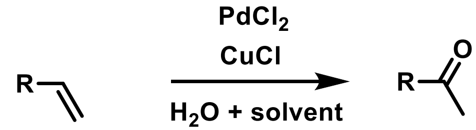


J. Org. Chem. **1987**, *52*, 4130.

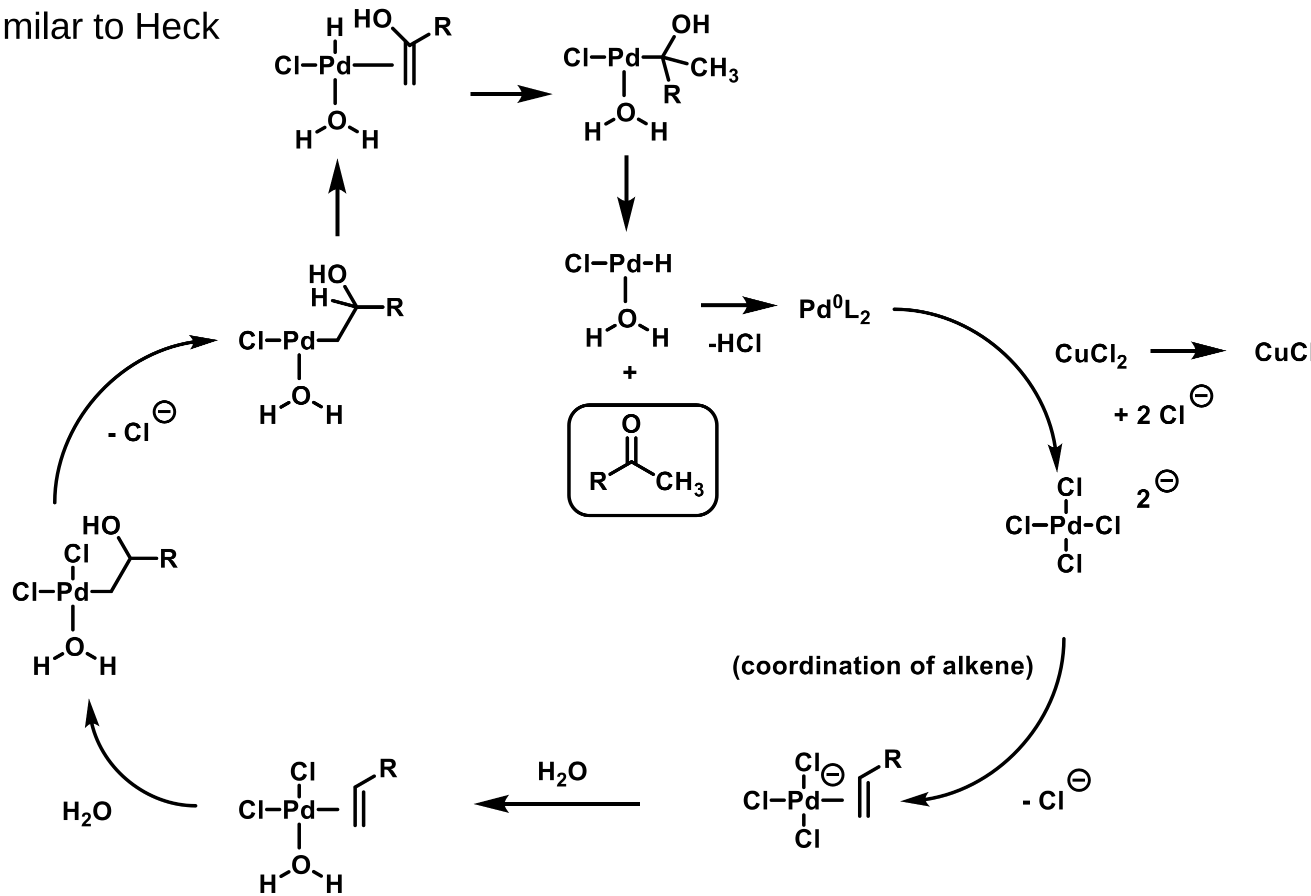


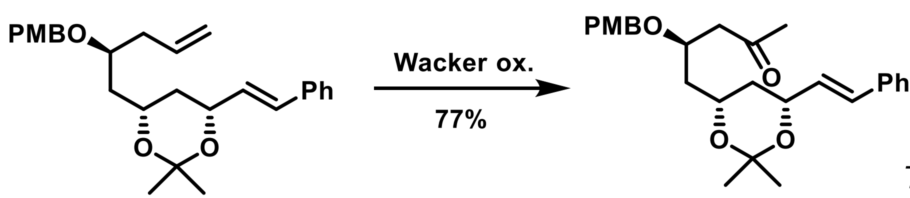
Acta Chem. Scand. **1992**, *46*, 597.

Wacker oxidation



- mechanistically similar to Heck

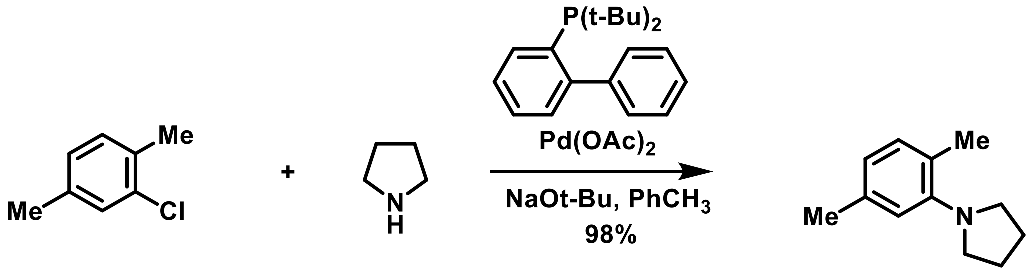




Tetrahedron **2001**, *57*, 6311.

Buchwald-Hartwig amination

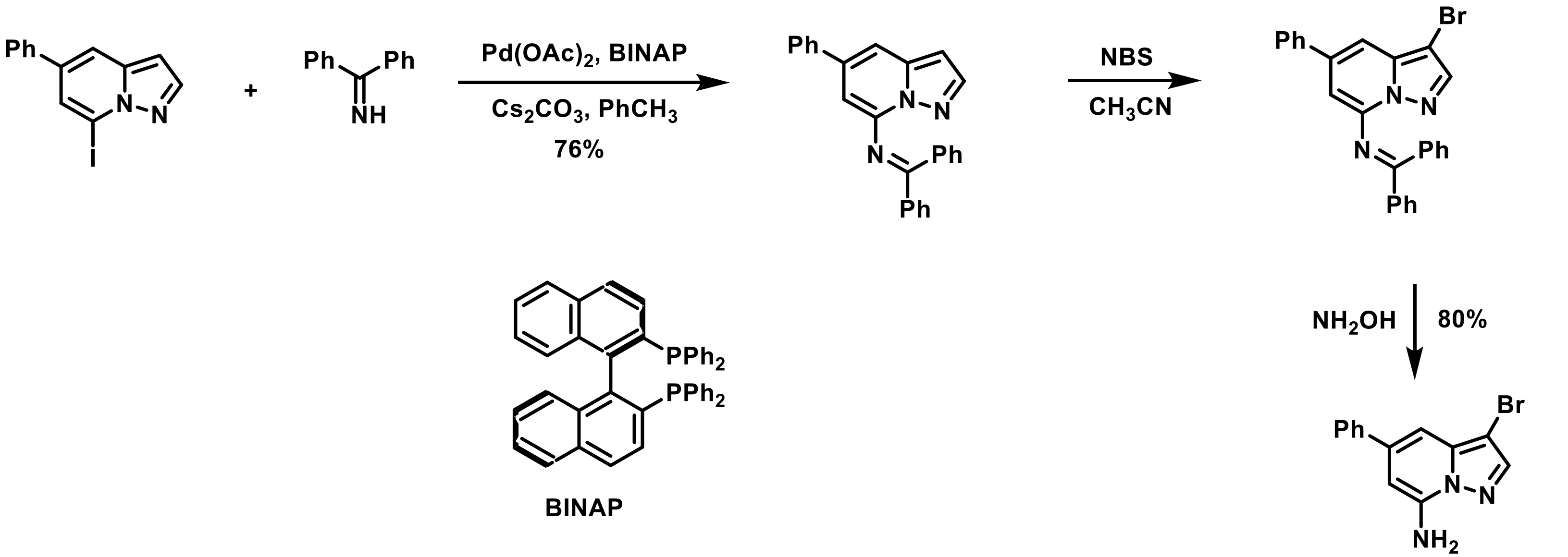
• typically: preparation of arylamines



J. Org. Chem. **2000**, *65*, 1158.

recent review „Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions“*: Chem. Rev.* **2016**, *116*, 12564.

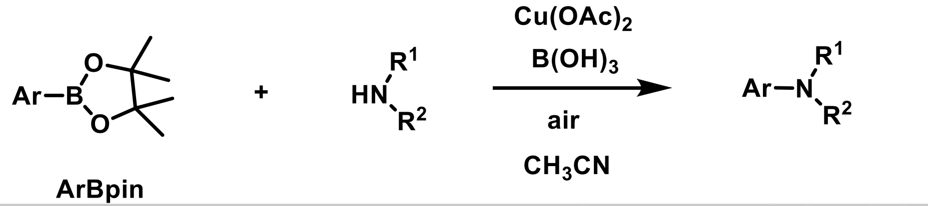
• ammonia equivalents: benzophenone imine; $BocNH_2$

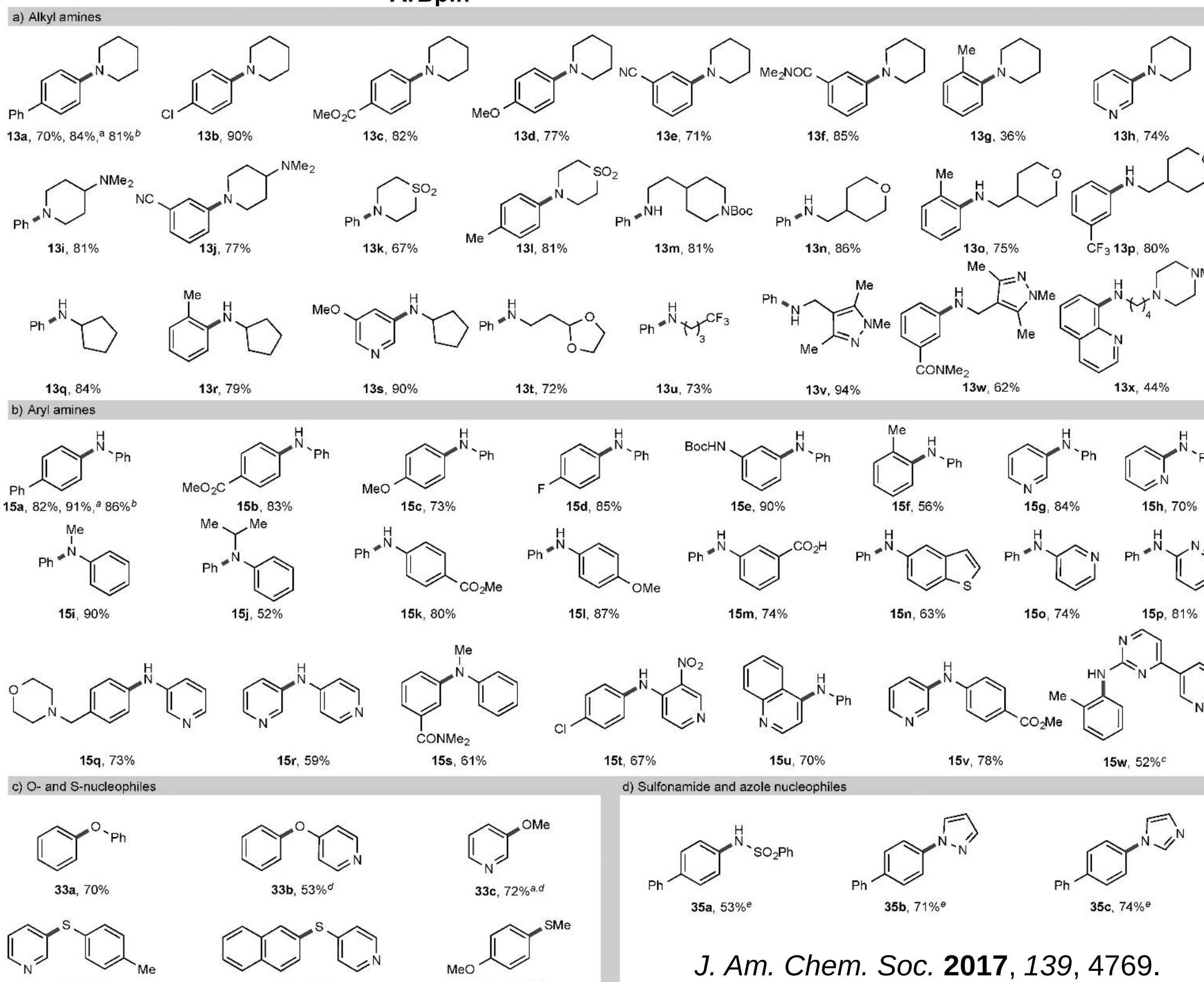


Bioorg. Med. Chem. Lett. **2007**, *17*, 6216.

Chan-Lam coupling

RYH: anilines, phenols, amides, carbamates, ureas, sulfonamides

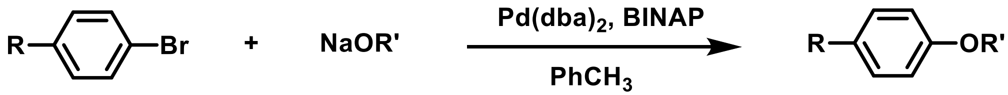




J. Am. Chem. Soc. **2017**, *139*, 4769.

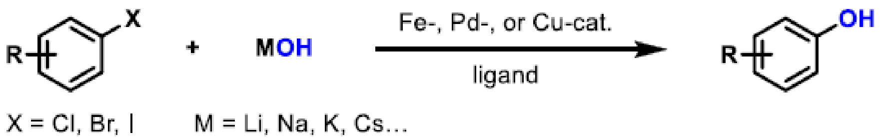
Pd-catalyzed formation of C-O bond

- historically somewhat less developed than amination

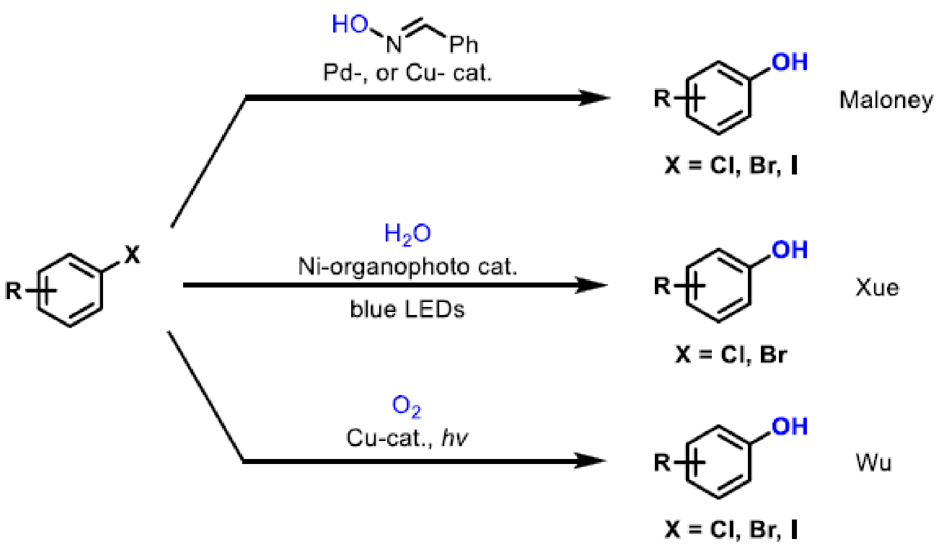


J. Am. Chem. Soc. **1996**, *118*, 13109.

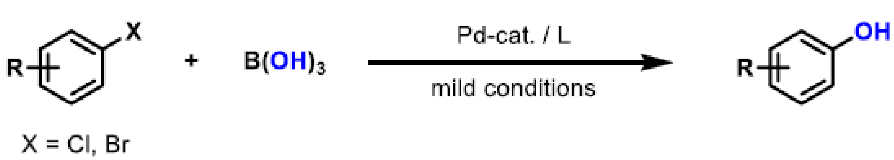
a, Transition-metal-catalyzed coupling of hydroxide with (hetero)aryl halides



b, Transition-metal-catalyzed coupling of hydroxide surrogate with (hetero)aryl halides



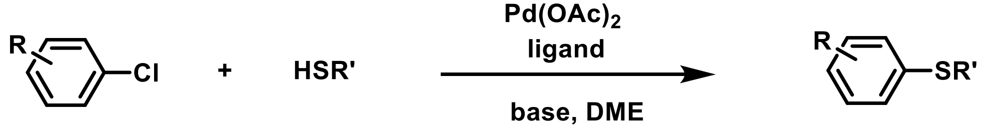
c, Boric acid in the coupling reaction with (hetero)aryl halides (*this work*)



Org. Lett. **2020**, *22*, 8470.

Pd-catalyzed formation of C-S bond

- relatively recent technology

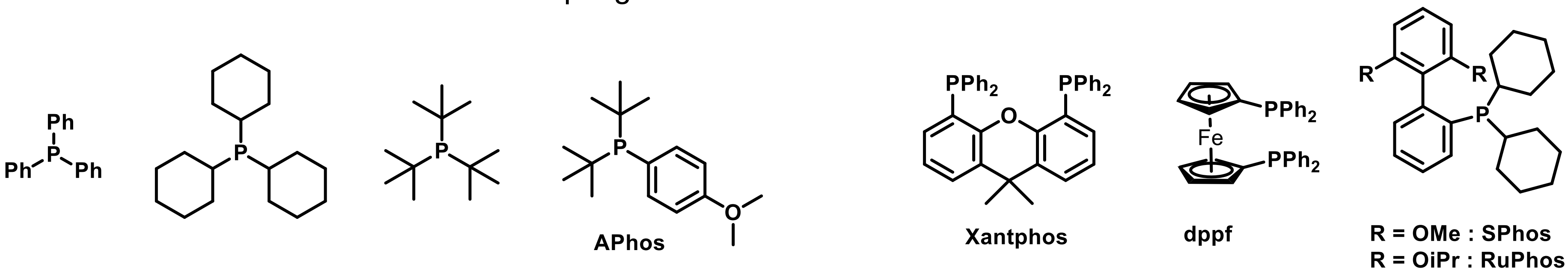


J. Am. Chem. Soc. **2006**, *128*, 2180.

Pd catalysts: ligands

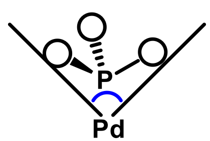
- the ligand(s) can have profound impact on the catalyst's activity

➢ can be used in chemoselective couplings



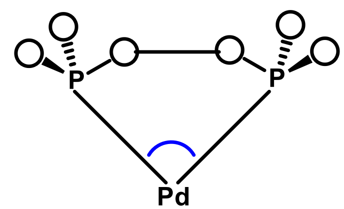
https://www.acros.com/mybrochure/aowhpapdbrochuslow.pdf

cone angle: defined by outer edge of the substituents on P and the metal center



PH_3: 87 °
PMe_3: 118 °
PPh_3: 145 °
PCy_3: 170 °
P(*t*-Bu)$_3$: 182 °
P(*o*-tol)$_3$: 194 °

bite angle: defined as L-Pd-L angle



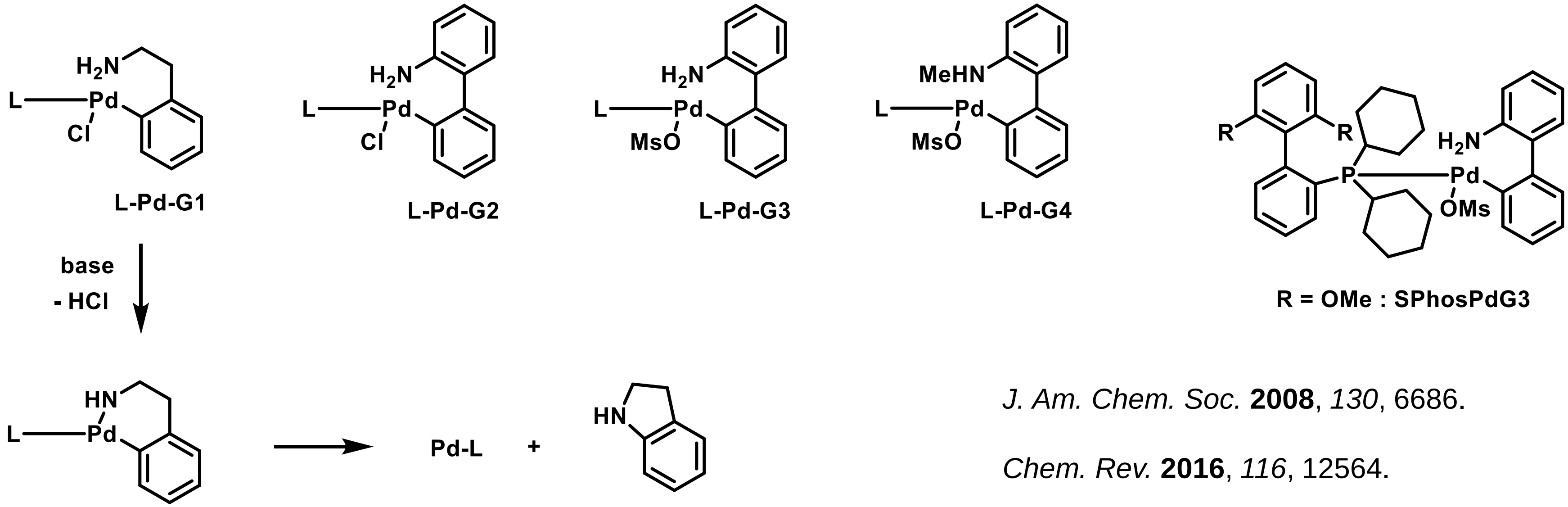
dppf: 99 °
Xantphos: 107 °
BINAP: 92 °

J. Chem. Soc. Dalton Trans. **1999**, 1519.

large bite angle -> faster reductive elimination
(the preferred geometry of the Pd(0) product is linear)

Pd catalysts: ligands

- base-activated palladacycles (precatalysts): air stable, form active catalysts in the presence of base



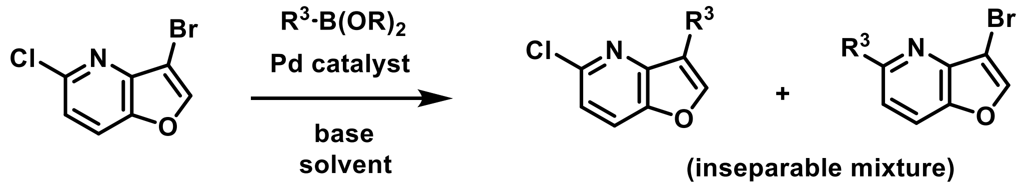
J. Am. Chem. Soc. **2008**, *130*, 6686.

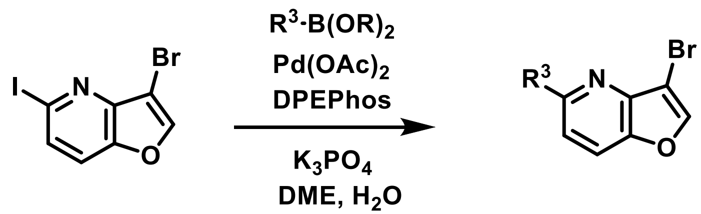
Chem. Rev. **2016**, *116*, 12564.

Chemoselectivity

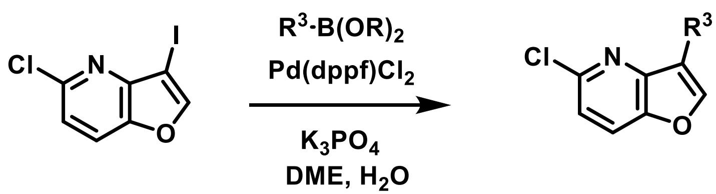
- the ligand(s) can have profound impact on the catalyst's activity

➢ can be used in chemoselective couplings

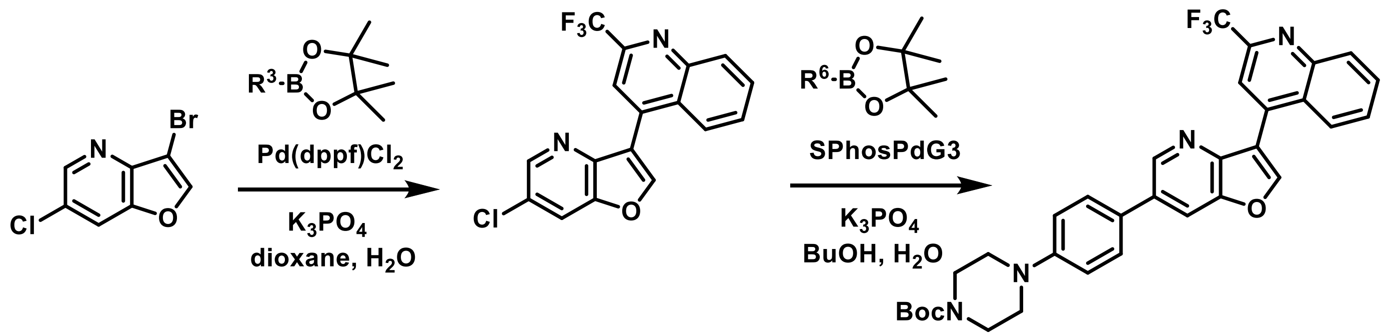




Angew. Chem. Int. Ed. **2019**, *58*, 1062.



Eur. J. Med. Chem. **2021**, *215*, 113299.



Chemoselectivity

- chemoselectivity?

VIP **Palladium Trimer Catalysis** *Very Important Paper*

International Edition: DOI: 10.1002/anie.201811380
German Edition: DOI: 10.1002/ange.201811380

C–I-Selective Cross-Coupling Enabled by a Cationic Palladium Trimer

*Claudia J. Diehl, Thomas Scattolin, Ulli Englert, and Franziska Schoenebeck**

Abstract: *While there is a growing interest in harnessing synergistic effects of more than one metal in catalysis, relatively little is known beyond bimetallic systems. This report describes the straightforward access to an air-stable Pd trimer and presents unambiguous reactivity data of its privileged capability to differentiate C–I over C–Br bonds in C–C bond formations (arylation and alkylation) of polyhalogenated arenes, which typical Pd^0 and Pd^I-Pd^I catalysts fail to deliver. Experimental and computational reactivity data, including the first location of a transition state for bond activation by the trimer, are presented, supporting direct trimer reactivity to be feasible.*

While mononuclear catalysts have dominated the field of homogeneous catalysis in the past decades, there is a growing interest in harnessing the synergistic interplay of multi-metal catalysts to access novel reactivities and selectivities.[1] However, with more than one metal in a catalyst, there is also an

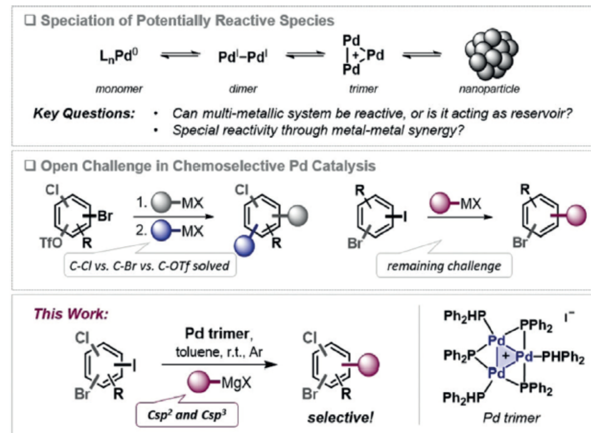


Figure 1. Challenges encountered in multi-metal catalysis (top) and in chemoselective palladium-catalyzed cross-coupling reactions (middle). This work (bottom)

Angew. Chem. Int. Ed. **2019**, *58*, 211.

- removal of residual palladium

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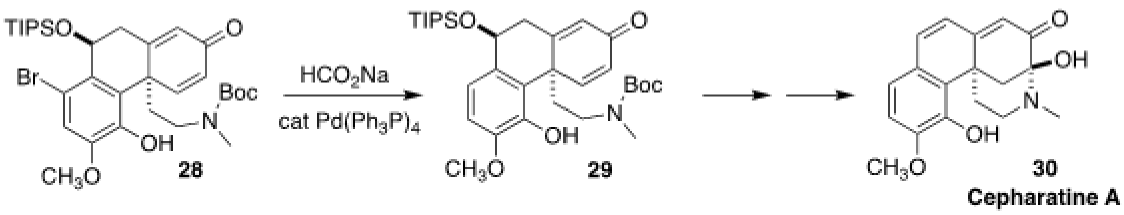
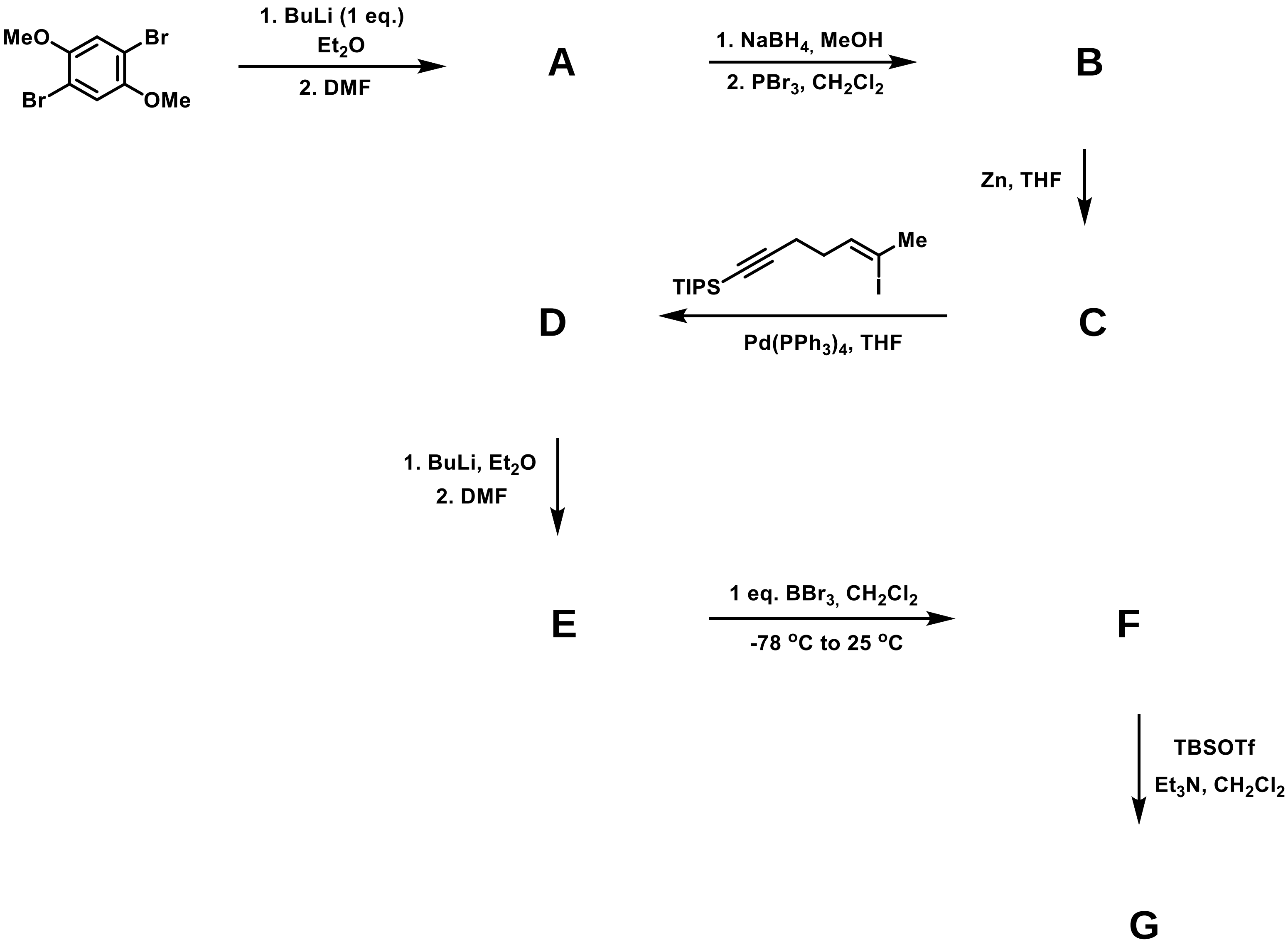
• Pd-catalyzed chemoselective dehalogenation

debromination of **28** to **29**, without interference by the two readily-reduced alkenes



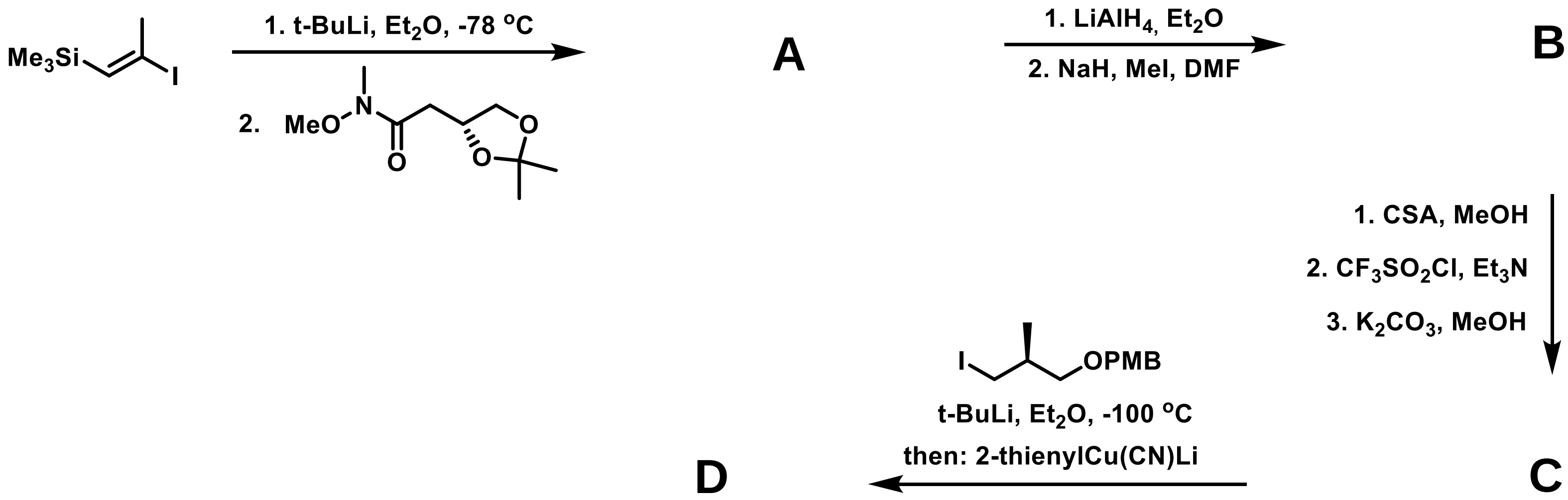
J. Org. Chem. **2022**, *87*, 1065.

Reactions catalyzed by palladium



J. Am. Chem. Soc. **2002**, *124*, 773.

Reactions catalyzed by palladium



PMB: p-methoxybenzyl