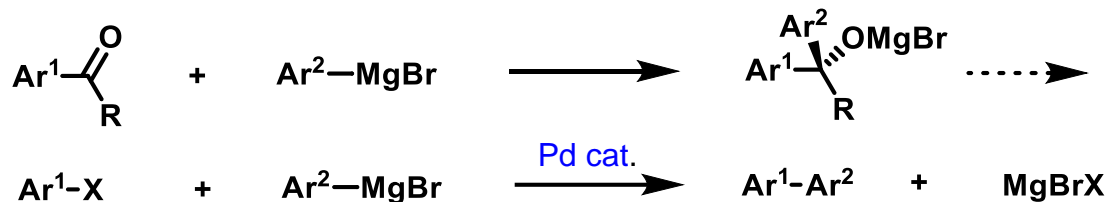


Organic synthesis

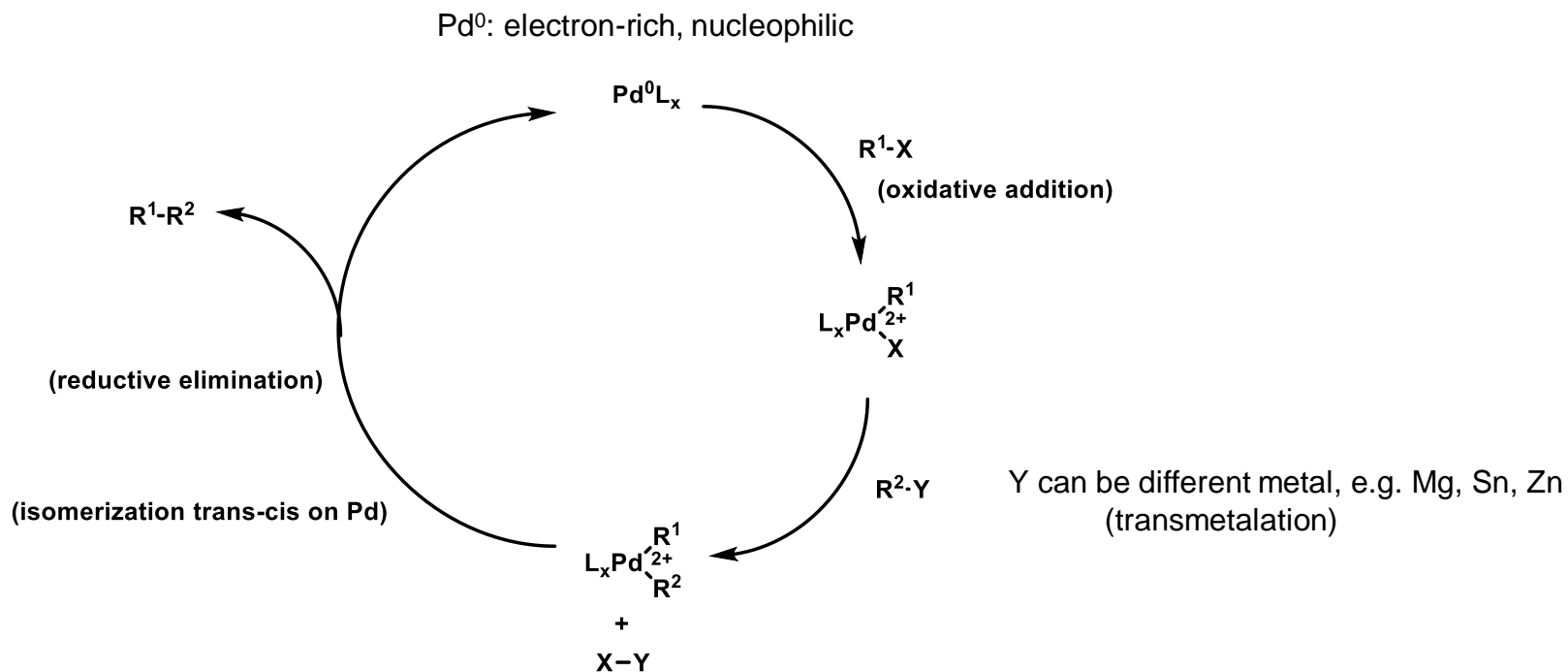
Kamil Paruch

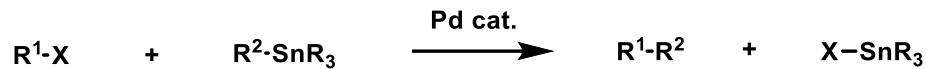
Masaryk University, Brno



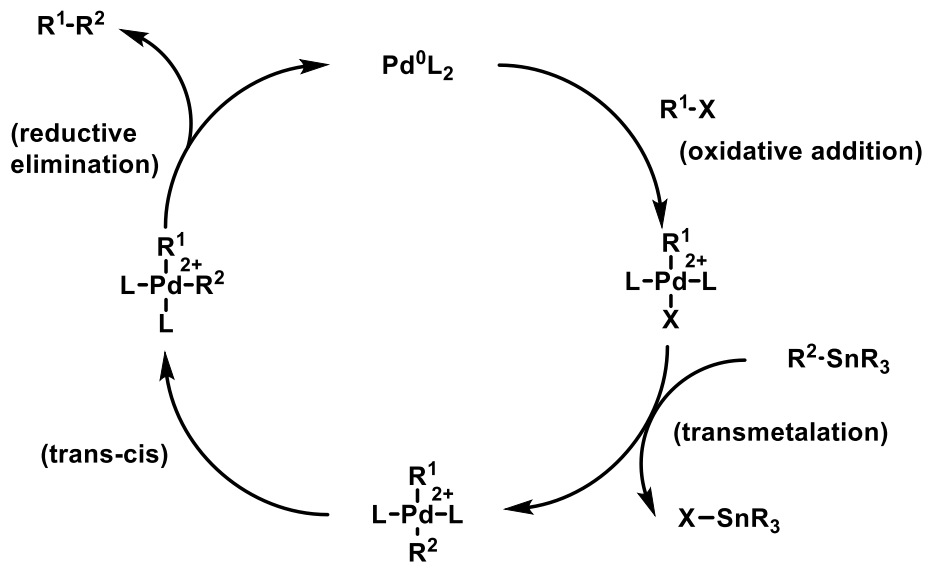
Reactions catalyzed by palladium

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

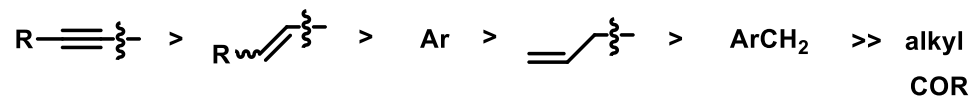




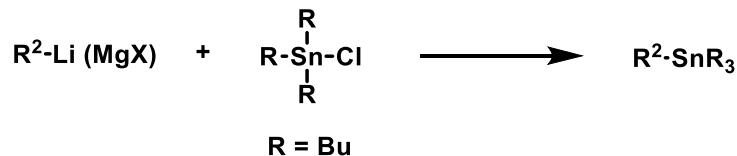
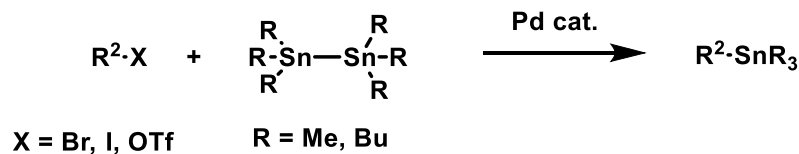
R: typically Bu or Me



ease of transmetalation Sn \rightarrow Pd



stannanes: \$\$\$

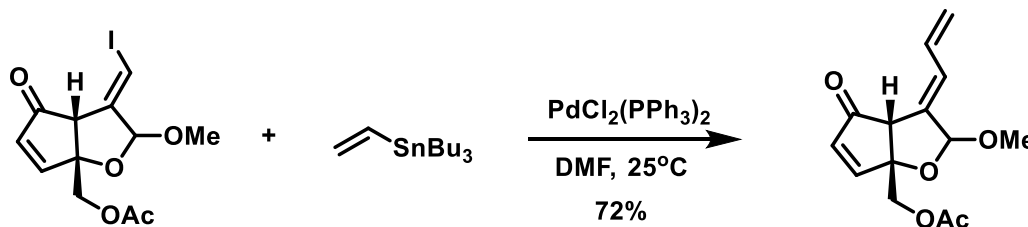


advantages: very mild conditions

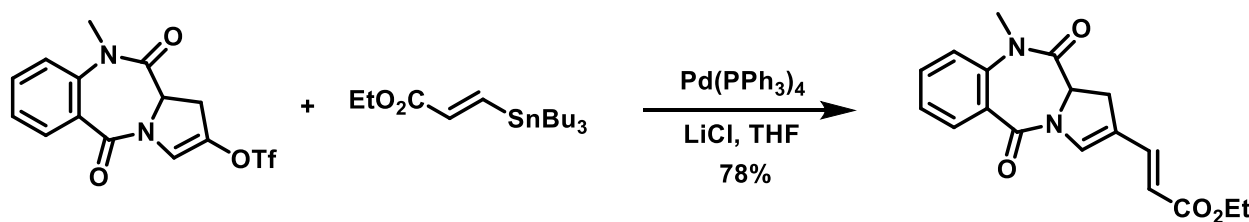
retention of configuration on double bond

triflates: possibility to generate kinetic vs thermodynamic OTf

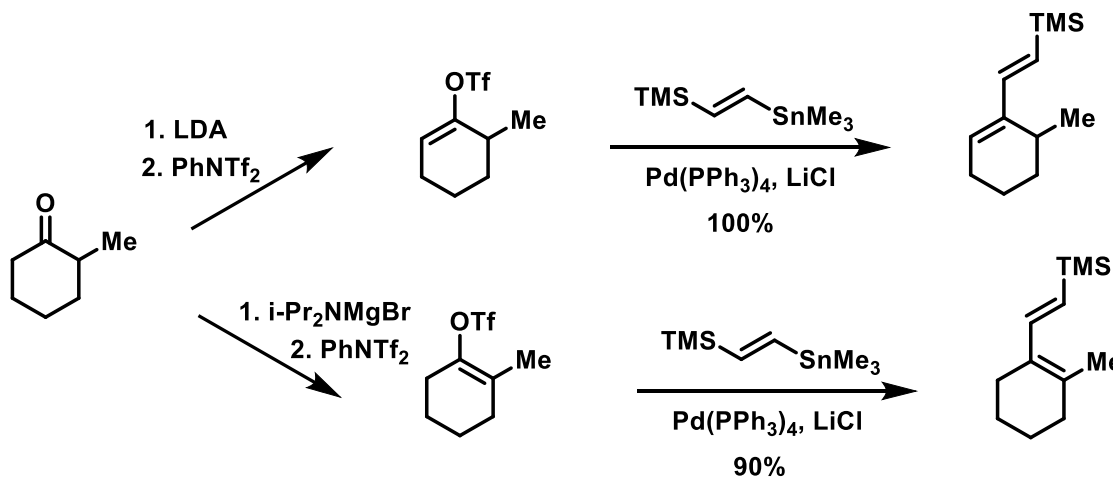
(also: can be made from ArOH)



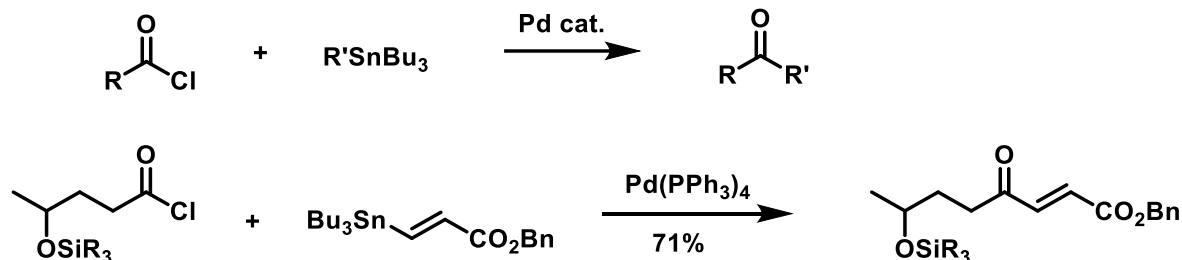
J. Am. Chem. Soc. **1988**, *110*, 5911.



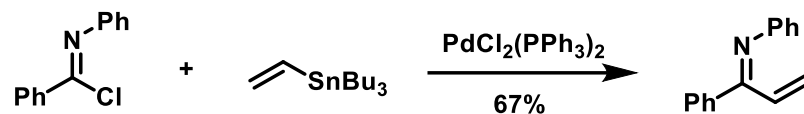
J. Am. Chem. Soc. **1989**, *111*, 5417.



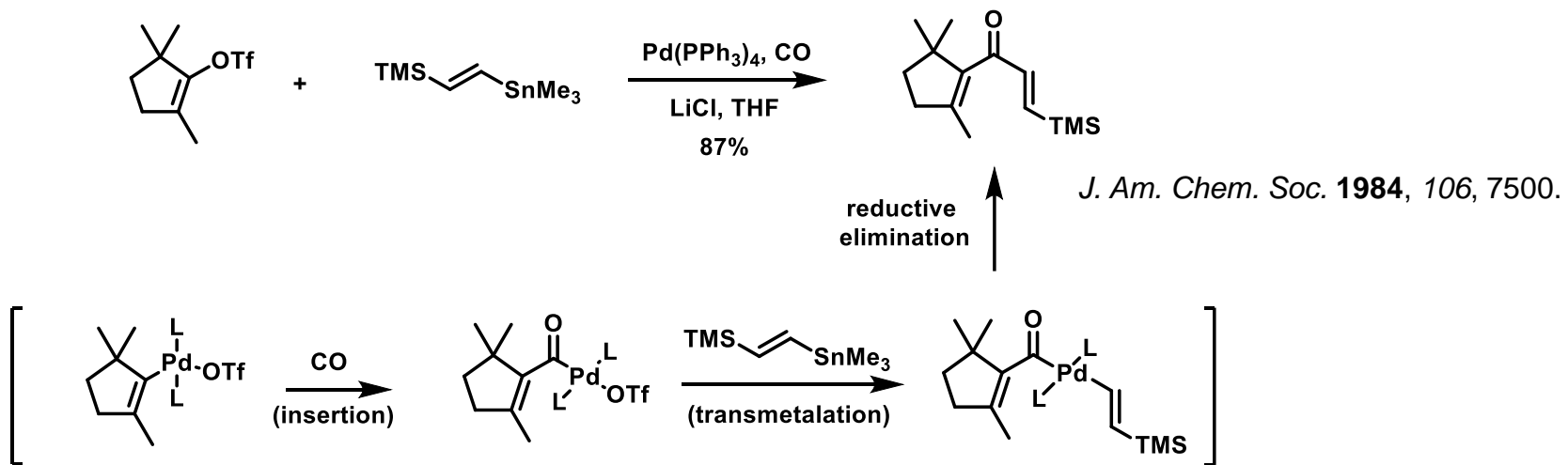
ketones from acid chlorides

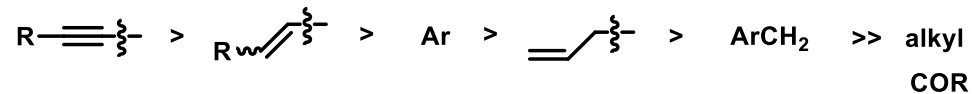
*J. Org. Chem.* **1983**, 58, 4634.

imines from imidoyl chlorides

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

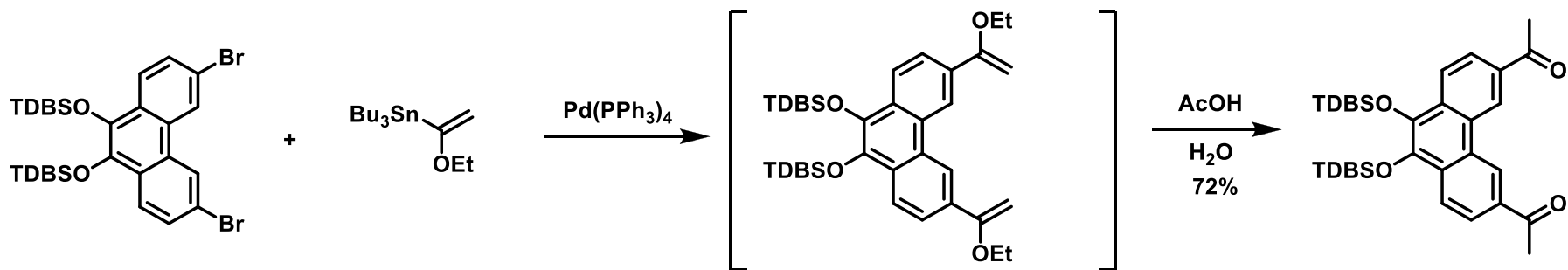
carbonylative Stille: insertion of CO

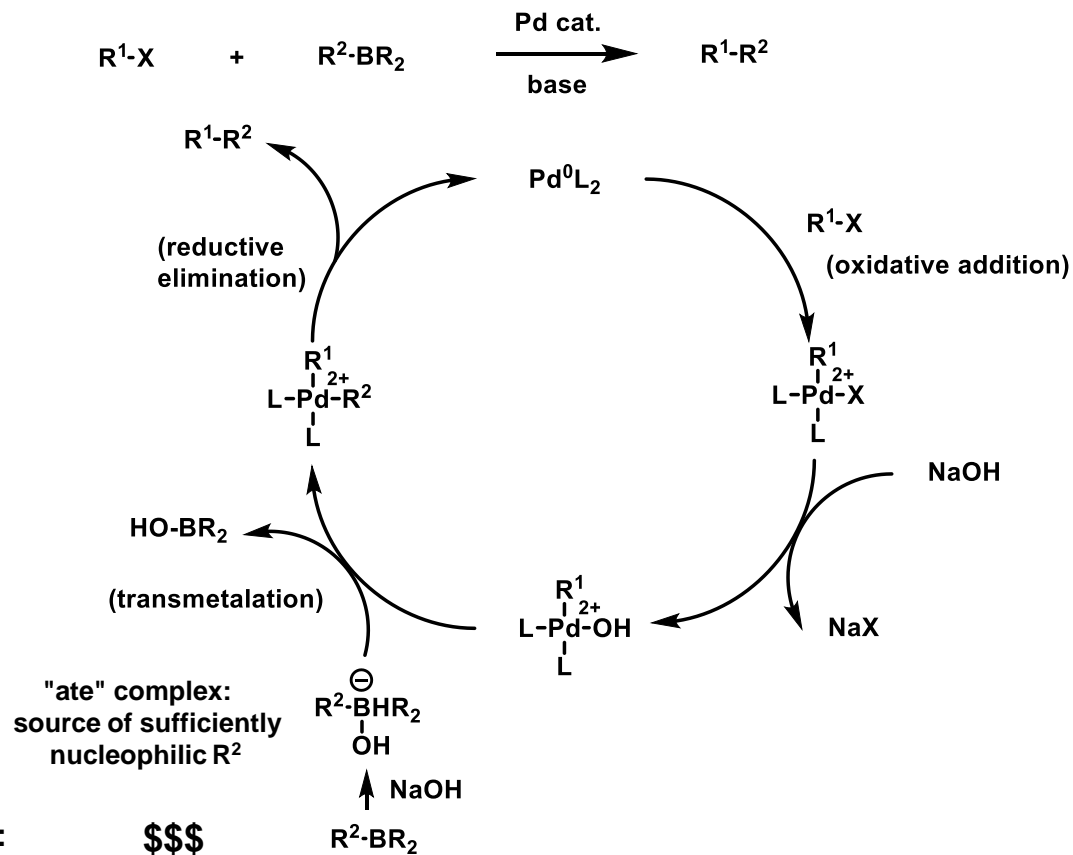


ease of transmetalation Sn \longrightarrow Pd

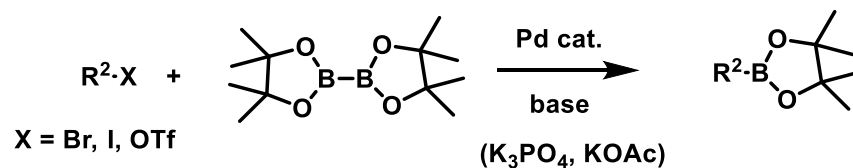
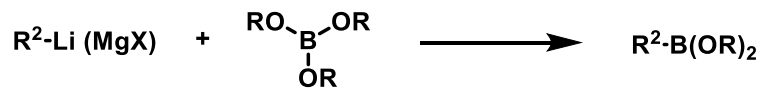
stannyl enol ethers

- acyl equivalents

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

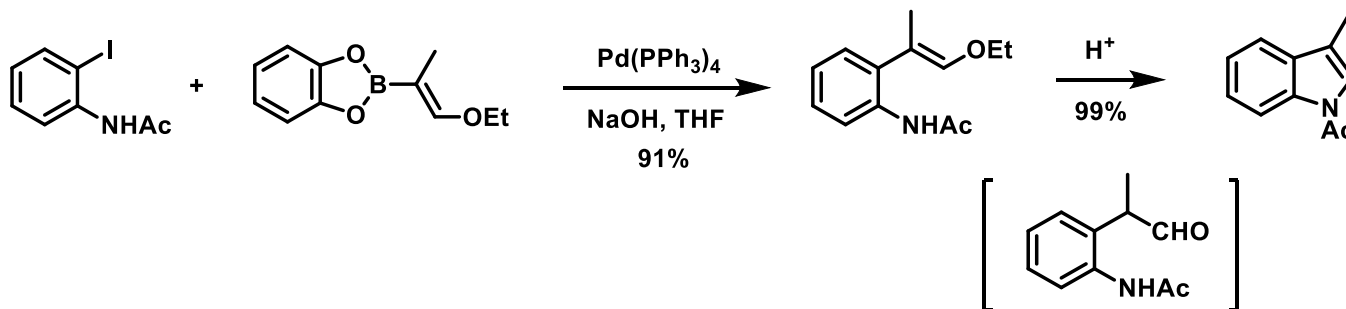
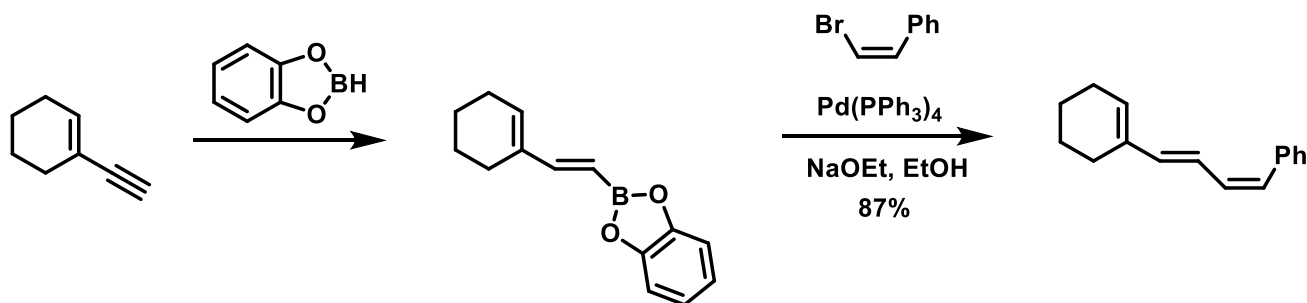


addition of R₂BH on alkenes, alkynes

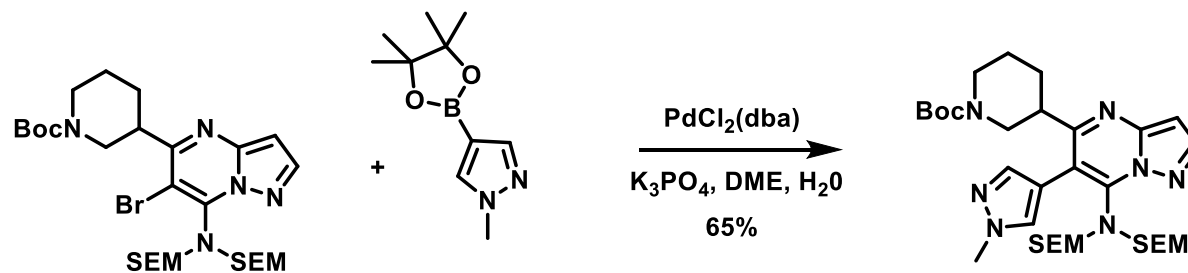


advantages: mild conditions (similar to Stille rxn)

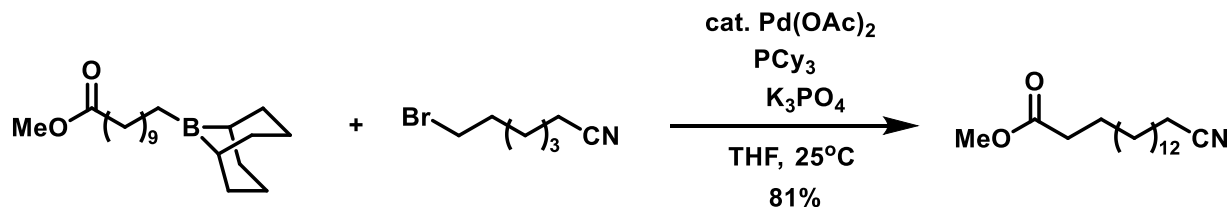
non-toxic side products



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



alkyl-alkyl Suzuki coupling



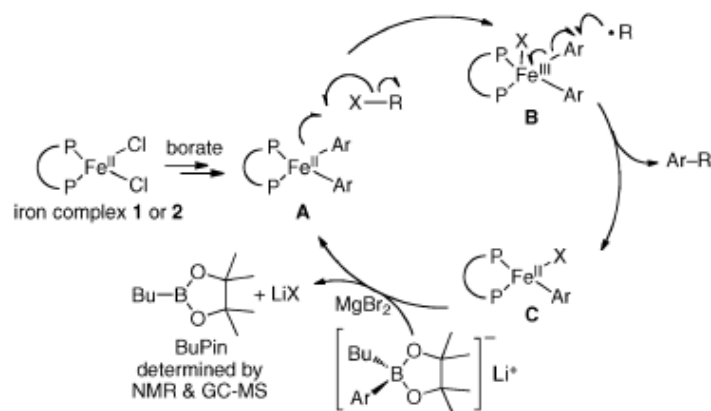
J. Am. Chem. Soc. **2001**, 123, 10099.

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

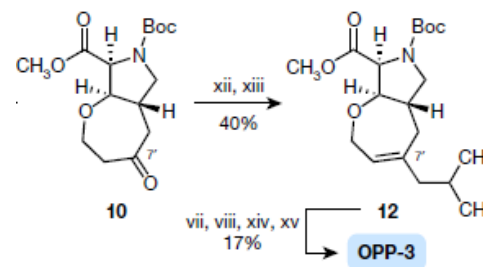
Iron-catalyzed Suzuki-Miyaura coupling of alkyl halides

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

Scheme 3. Plausible Mechanism



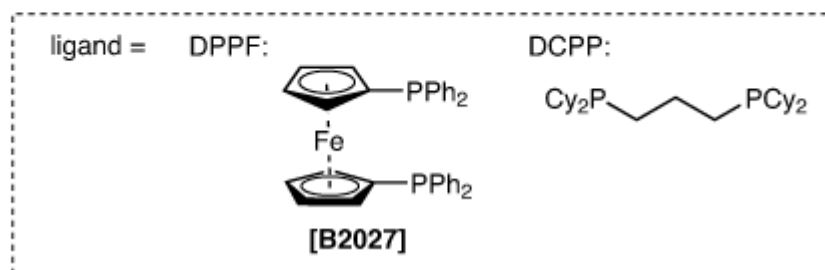
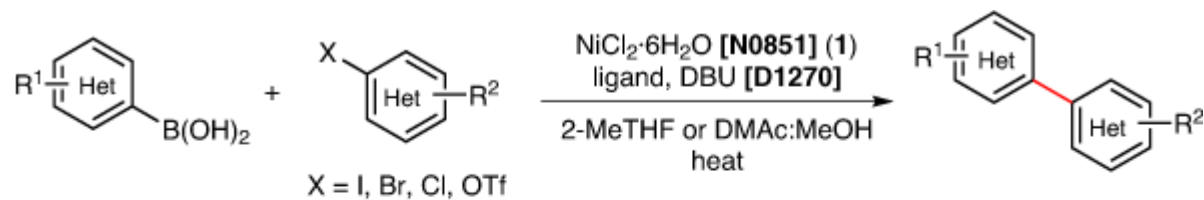
direct Fe-catalyzed coupling: *Nature* **2021**, 559, 507.



HBF₄ (aq.); (xi) DAST; (xii) LiHMDS, Comins' reagent, 51% (plus, separately, 31% Δ6' regioisomer); (xiii) ^tBuMgCl, Fe(acac)₃; (xiv) H₂, Pd(OH)₂/C, 1:1 dr; (xv) BSTFA,

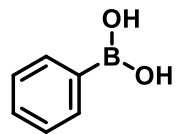
Ni-catalyzed Suzuki-Miyaura coupling

- cost-effective variant

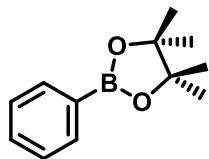


Org. Process Res. Dev. **2022**, 26, 785.

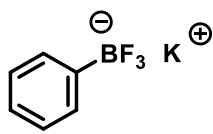
relative stability/reactivity of boron coupling partners



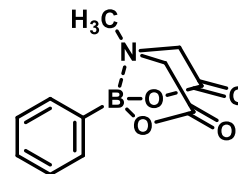
boronic acid



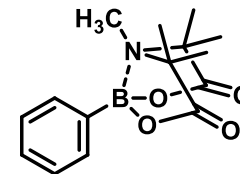
(pinacol) boronate



(potassium) trifluoroborate



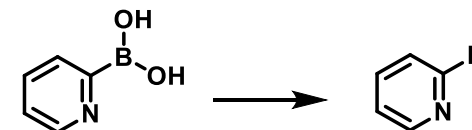
MIDA ester



TIDA ester

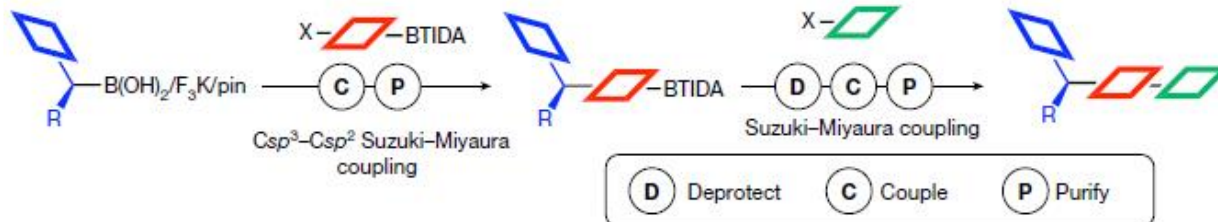
http://organicreactions.org/index.php/Cross-coupling_reactions_of_organotrifluoroborates

- 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.

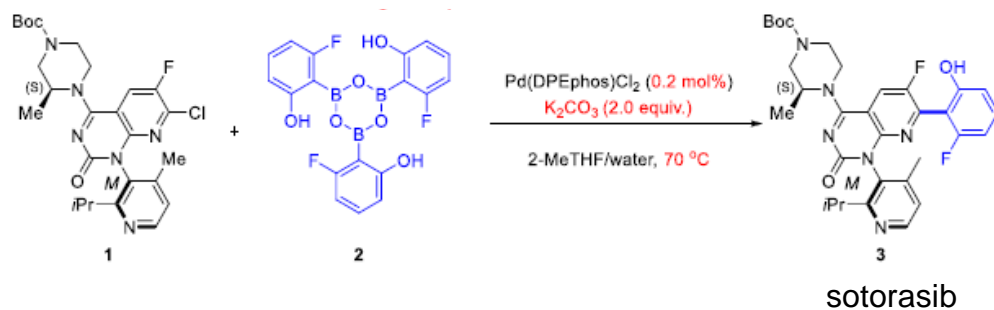
- TIDA esters are very stable towards hydrolytic cleavage
 - they can be used orthogonally in the presence of other boron coupling partners



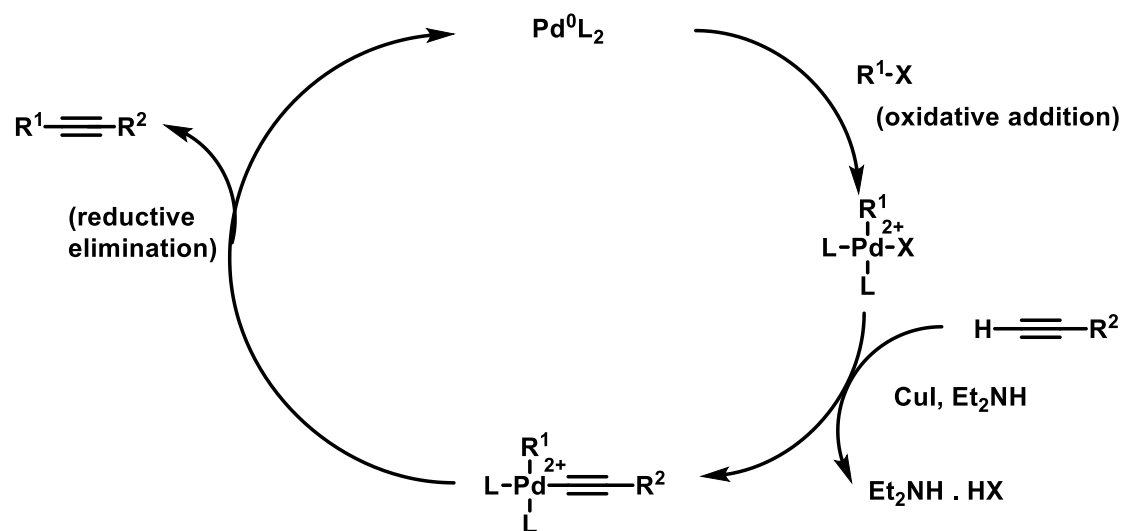
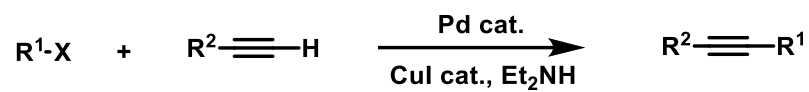
Rate-determining step can depend on the base

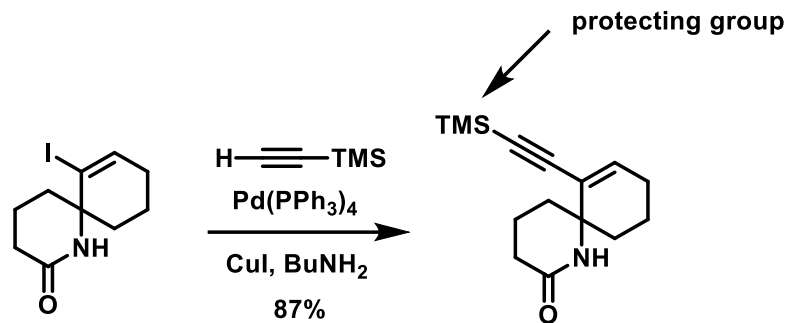
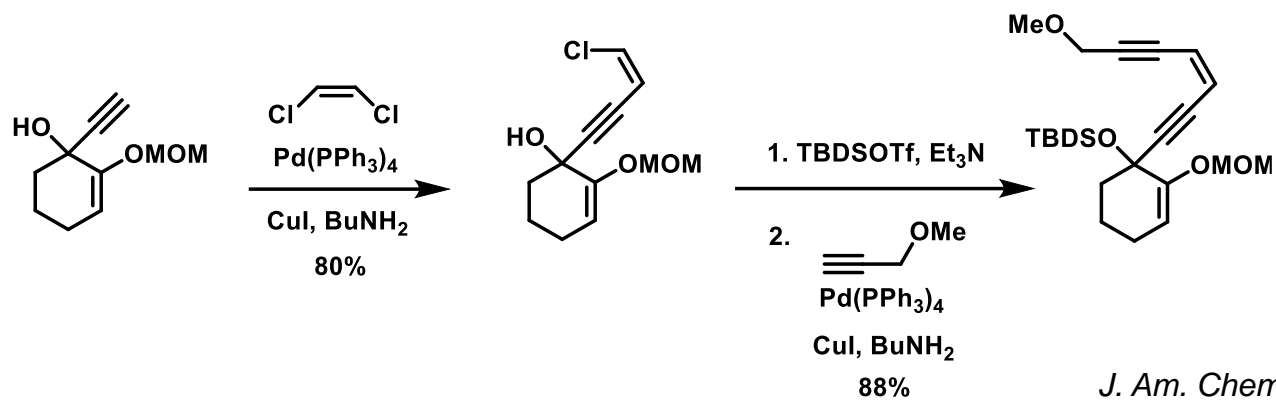
KOAc: rds: reductive elimination

K₂CO₃: rds: transmetalation (significantly better yield in the „bulk charge“ format)

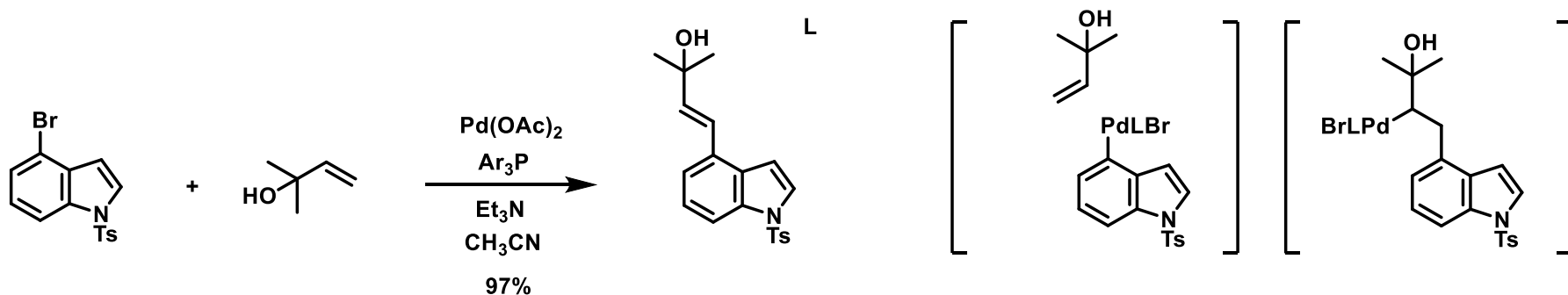
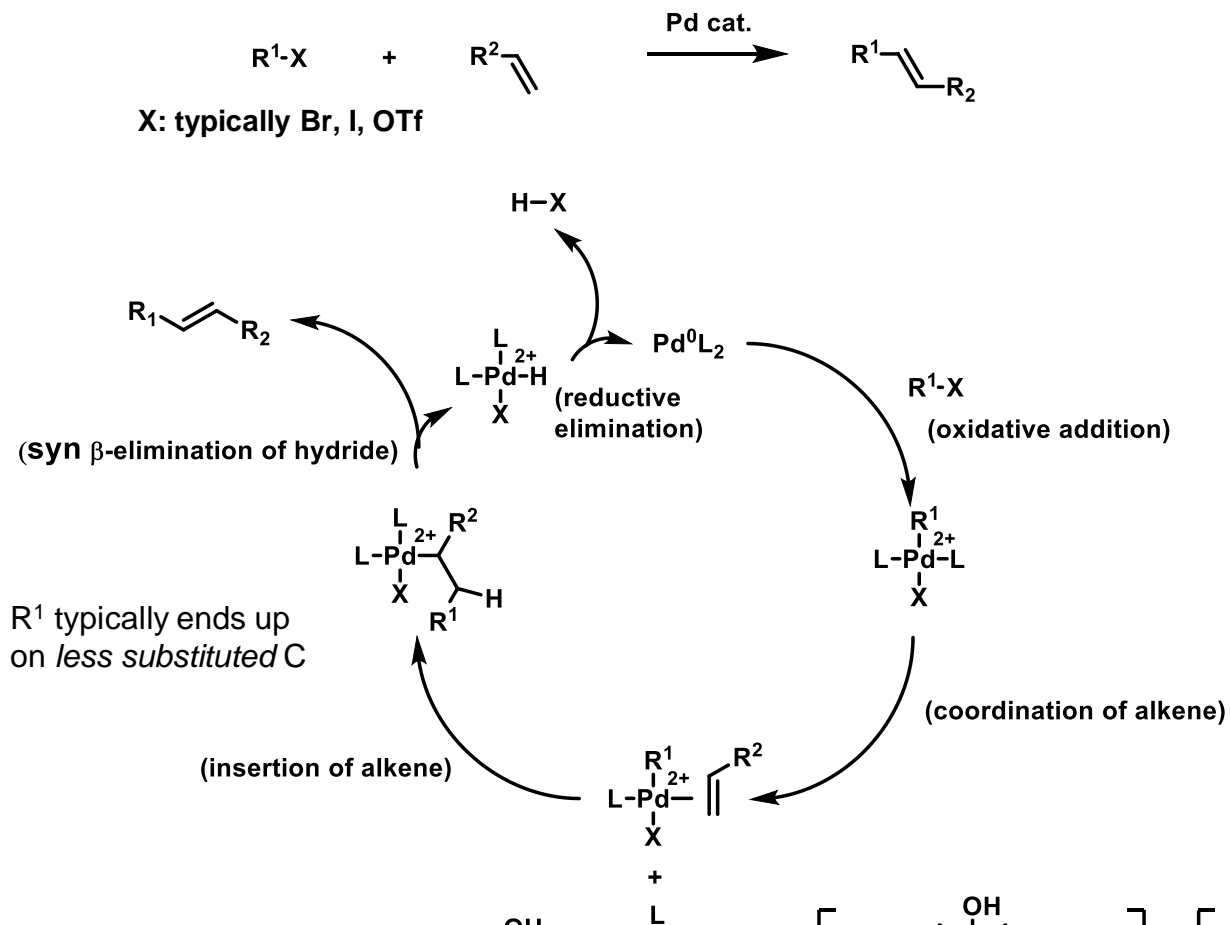


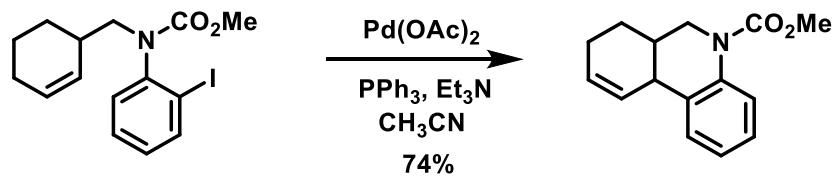
Org. Process Res. Dev. **2023**, 27, 198.



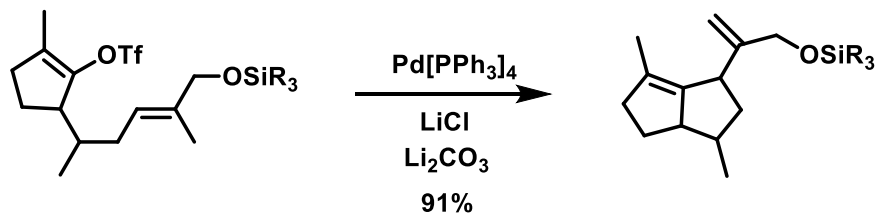
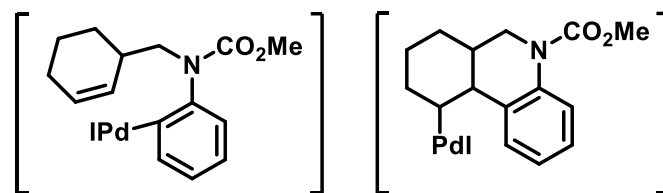


Tetrahedron Lett. **1988**, 29, 2989.

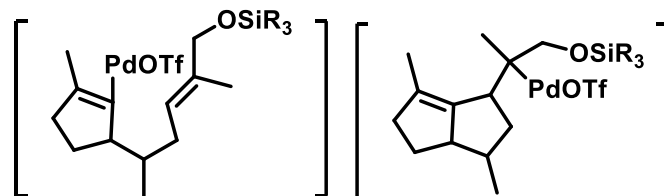


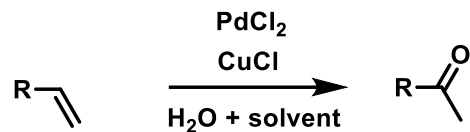


J. Org. Chem. **1987**, 52, 4130.

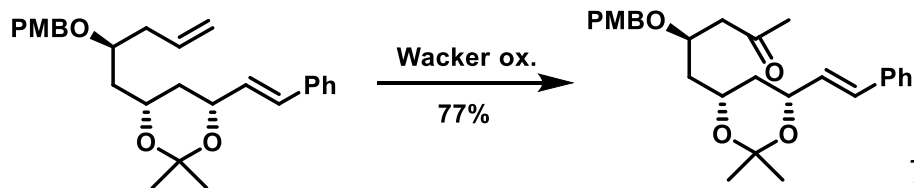
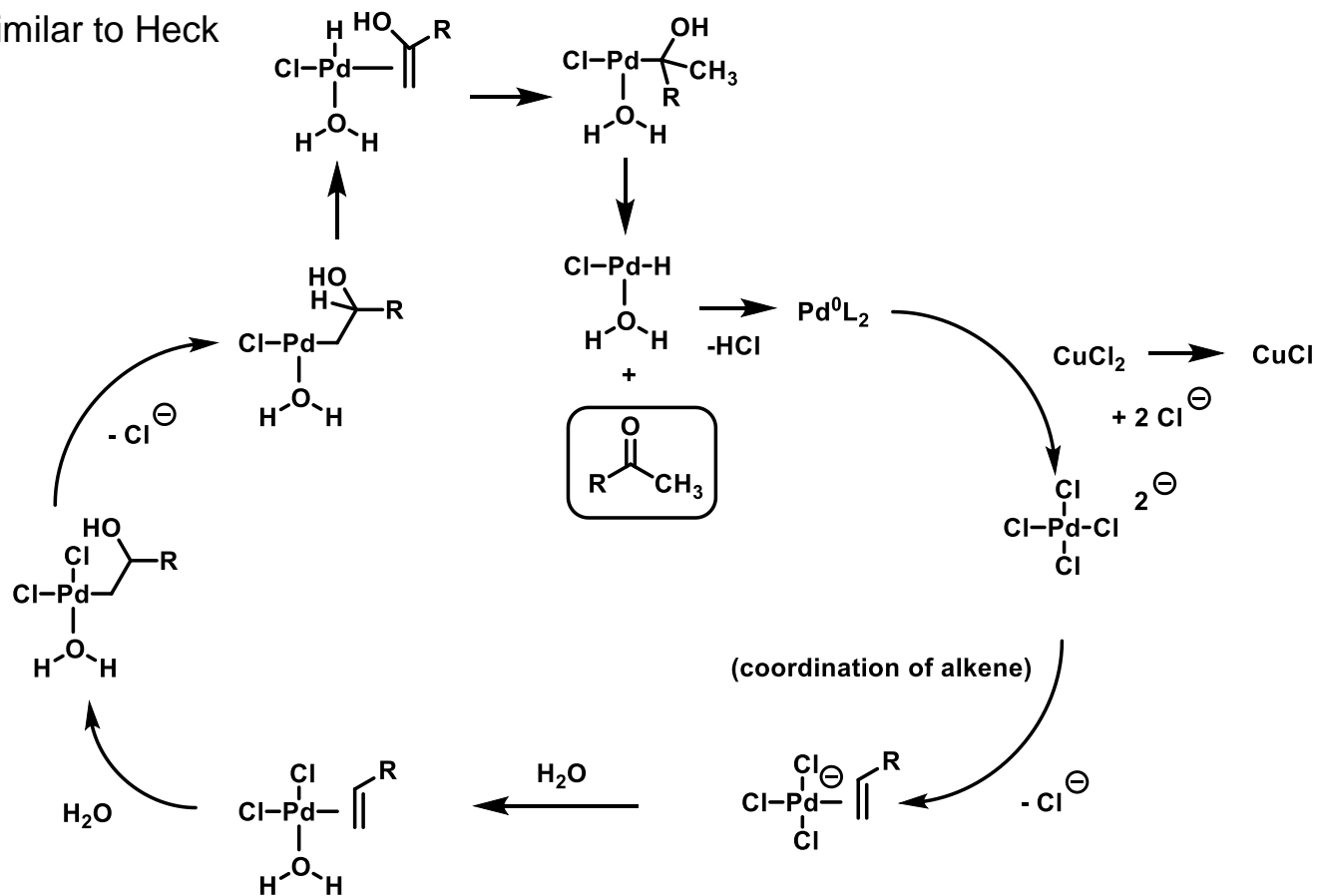


Acta Chem. Scand. **1992**, 46, 597.



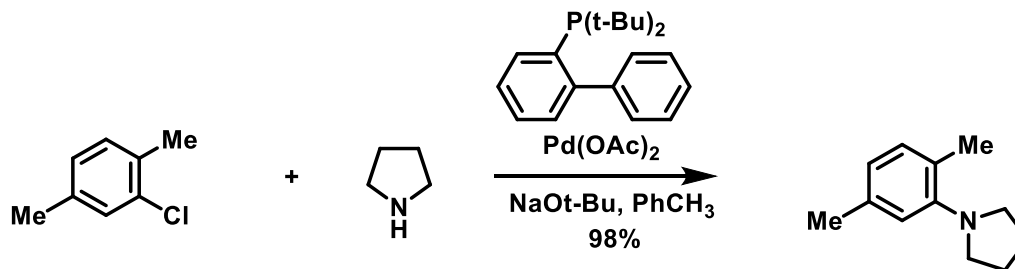


- mechanistically similar to Heck



Buchwald-Hartwig amination

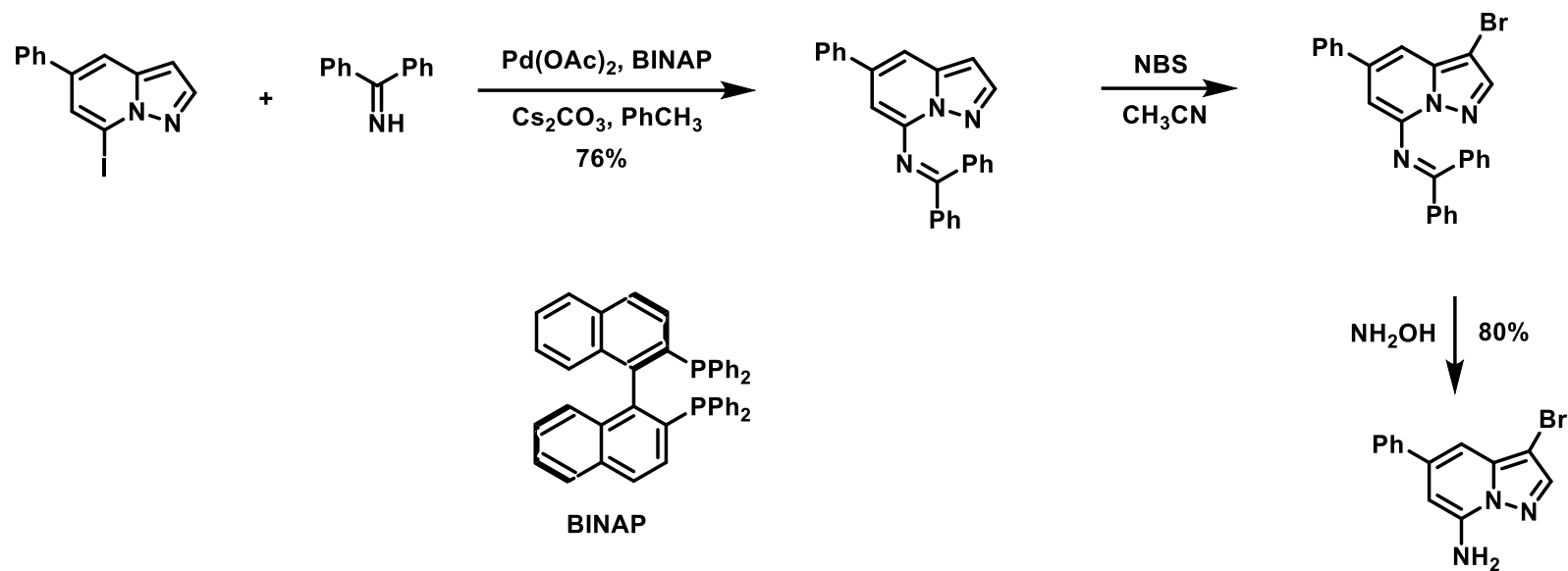
- typically: preparation of arylamines



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

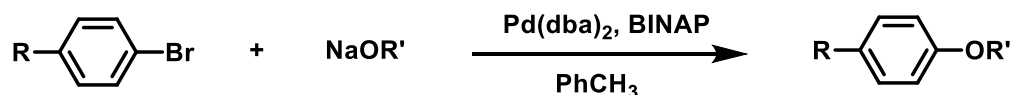
recent review „Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions“: *Chem. Rev.* **2016**, 116, 12564.

- ammonia equivalents: benzophenone imine; BocNH_2

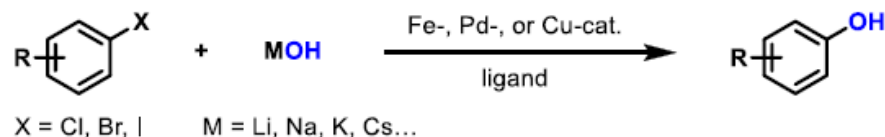


Bioorg. Med. Chem. Lett. **2007**, 17, 6216.

- historically somewhat less developed than amination

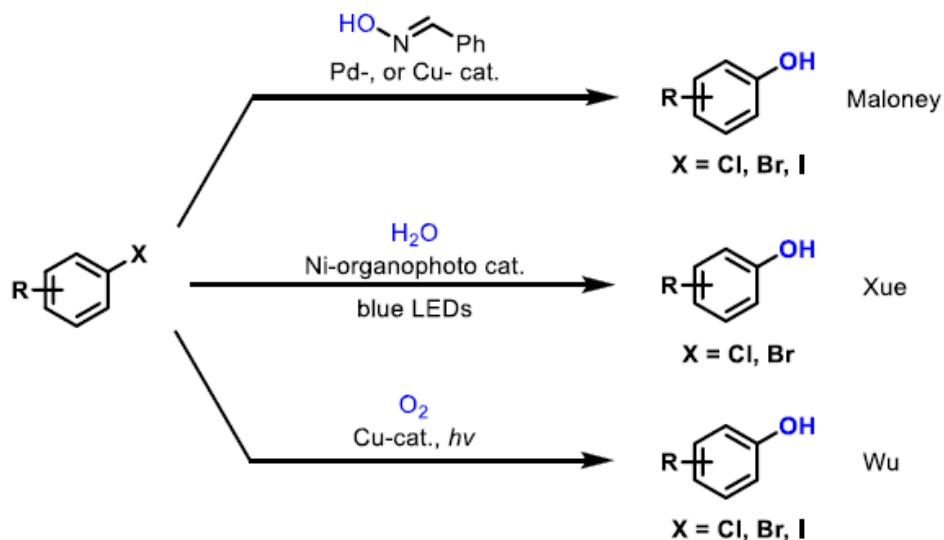


a, Transition-metal-catalyzed coupling of hydroxide with (hetero)aryl halides



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

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

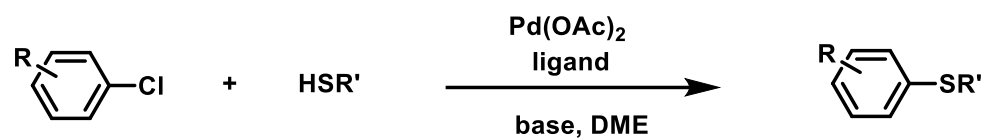


c, Boric acid in the coupling reaction with (hetero)aryl halides (*this work*)



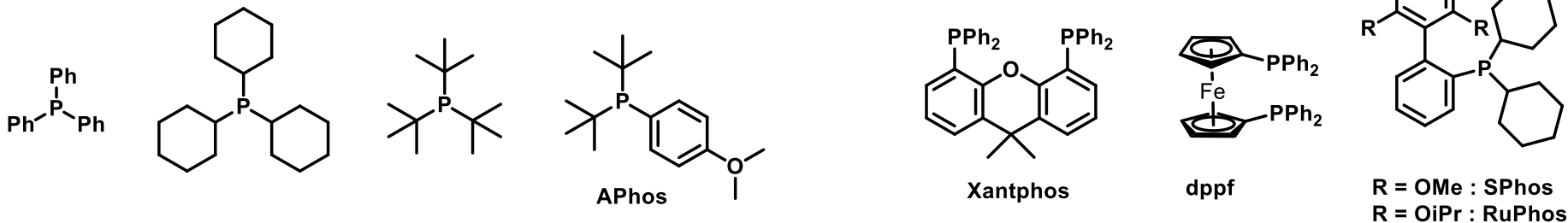
Org. Lett. **2020**, *22*, 8470.

- relatively recent technology



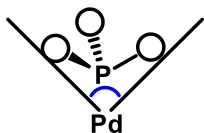
J. Am. Chem. Soc. **2006**, 128, 2180.

- the ligand(s) can have profound impact on the catalyst's activity
- can be used in chemoselective couplings



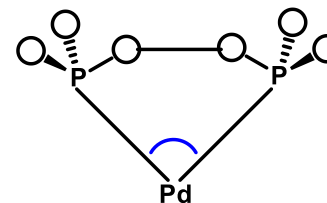
<https://www.acros.com/mybrochure/aowhpadbrochuslow.pdf>

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 °
 $\text{P}(t\text{-Bu})_3$: 182 °
 $\text{P}(o\text{-tol})_3$: 194 °

bite angle: defined as L-Pd-L angle

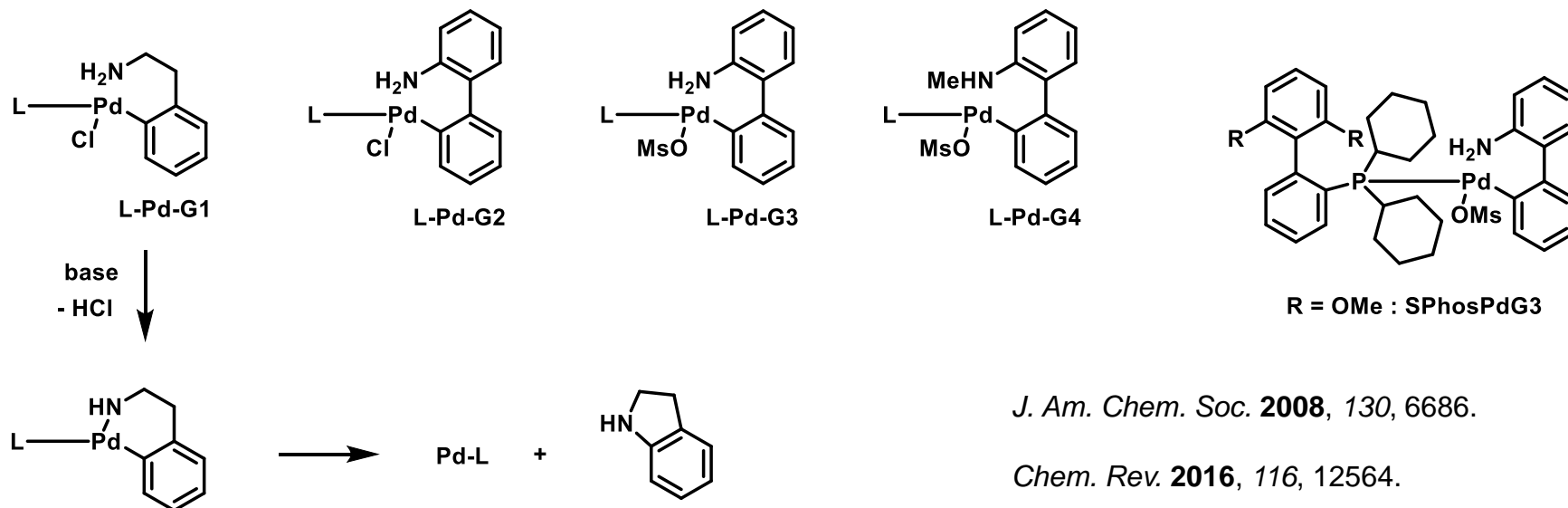


dppf: 99 °
 Xantphos: 107 °
 BINAP: 92 °

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

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

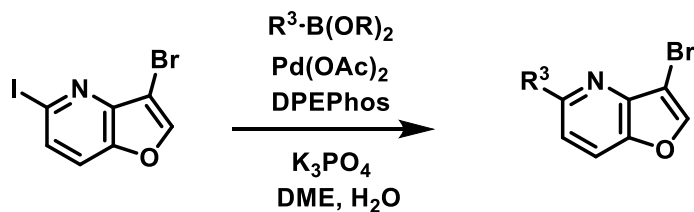
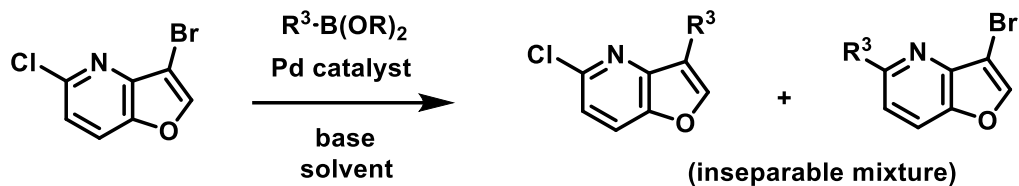
- base-activated palladacycles (precatalysts): air stable, form active catalysts in the presence of base



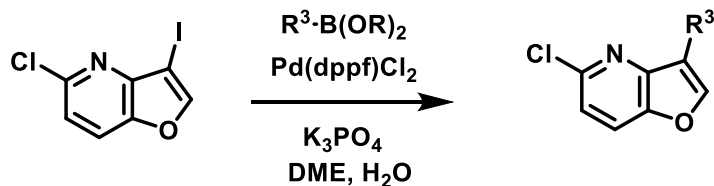
J. Am. Chem. Soc. **2008**, *130*, 6686.

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

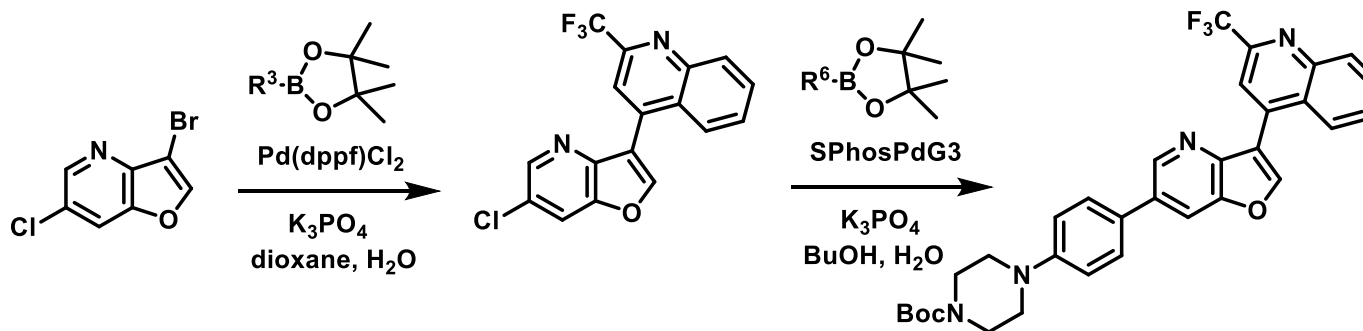
- the ligand(s) can have profound impact on the catalyst's activity
- can be used in chemoselective couplings



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



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



- chemoselectivity?

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 Pd⁰ 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

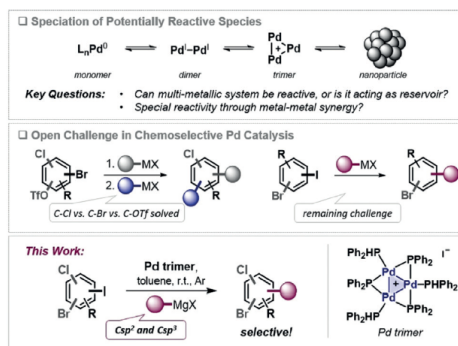


Figure 1. Challenges encountered in multi-metal catalysis (top) and in chemoselective palladium-catalyzed cross-coupling reactions (middle). This work (bottom)

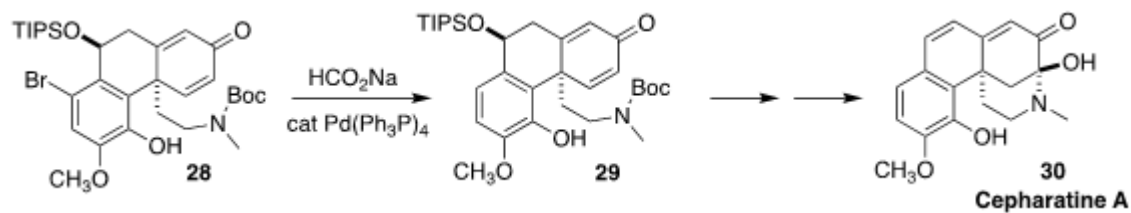
- removal of residual palladium

QuadraPure

<https://www.sigmaaldrich.com/catalog/product/aldrich/655422?lang=en®ion=CZ>

- Pd-catalyzed chemoselective dehalogenation

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



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