

7. Palladium-catalyzed cross couplings: C-C couplings, usually at least one sp² C

- general mechanism is the same for different variants; simply differ in the **transmetallation reagent**
- the **Heck** rx and **Buchwald-Hartwig amination** are related (but no transmetallation)

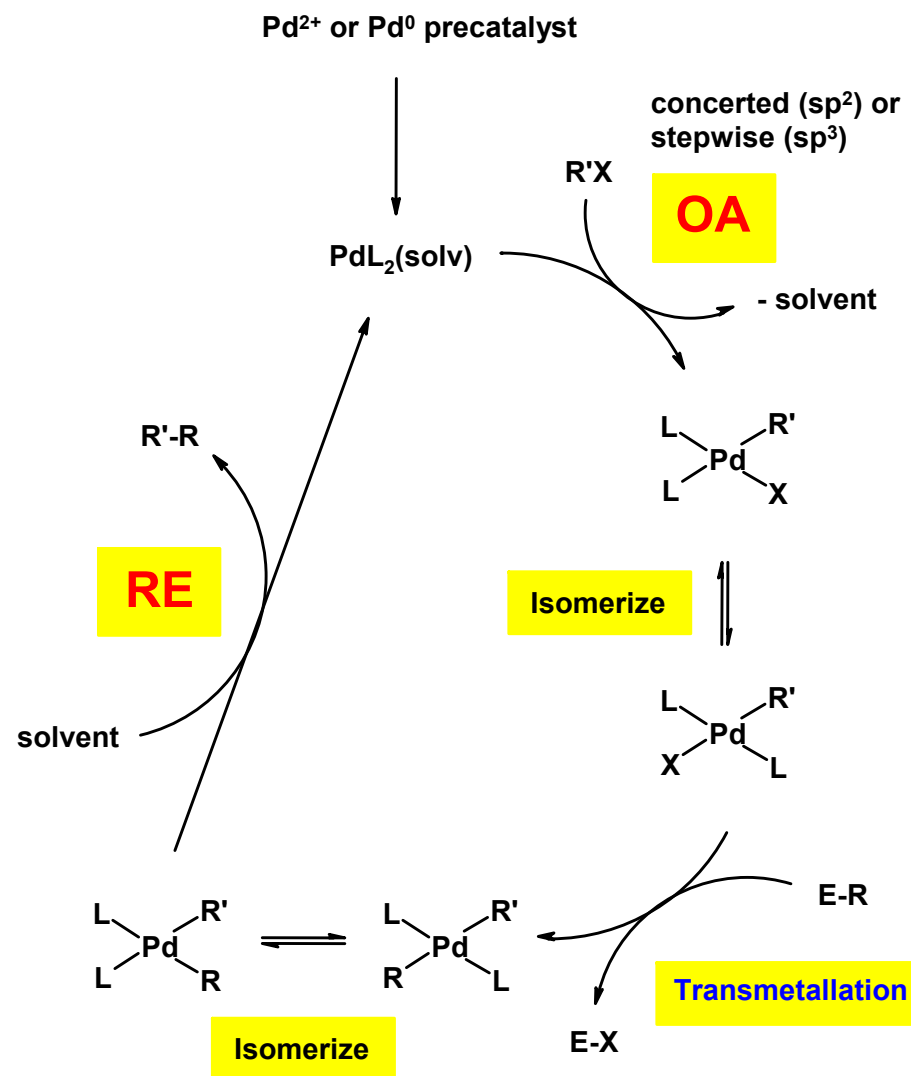
Reaction	E	R' type	R type	Promoter
Stille	SnBu ⁿ ₃	wide range	sp>sp ² >aryl> allylic>sp ³	CuI, LiCl
Hiyama	SiR ⁿ ₃	sp ² , aryl aryl-I best	sp ² , aryl	F ⁻ (required)
Suzuki	B(OH) ₂	sp ² , aryl, alkyl	sp ² , aryl, alkyl (as BR ₃ type)	base (NaOH, Cs ₂ CO ₃)
Kumada Negishi	MgX ZnX	various	various	
Sonogashira*	Cu	sp ² >aryl e ⁻ poor>e ⁻ rich	CCR e ⁻ rich>e ⁻ poor	CuI, base

(* without Pd this is the Stephens-Castro)

General mechanism:

- oxidative-addition can be step-wise or concerted depending on R'X so inversion or retention of configuration observed
- L is generally a phosphine although NHC have been used
- Pd²⁺ precatalysts work quite well provided there is a means for *in situ* reduction to Pd⁰ (not usually too difficult)
- bulky alkyl phosphines (eg. PBu^t₃, PCy₃) work best: bulk enforces a lower coordination number and strong donor ability ensures an electron rich metal capable of OA
- many promoters or activators are known that increase rates
- for R'X, order usually parallels leaving group ability:

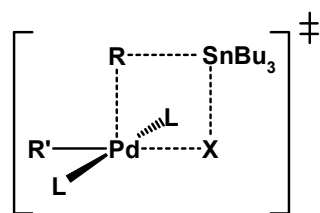
I⁻ > OTf > Br >> Cl⁻



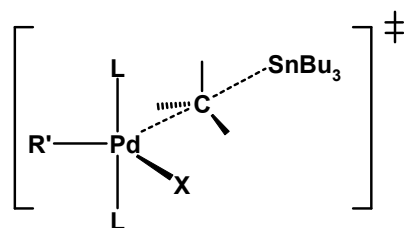
Examples

Stille coupling

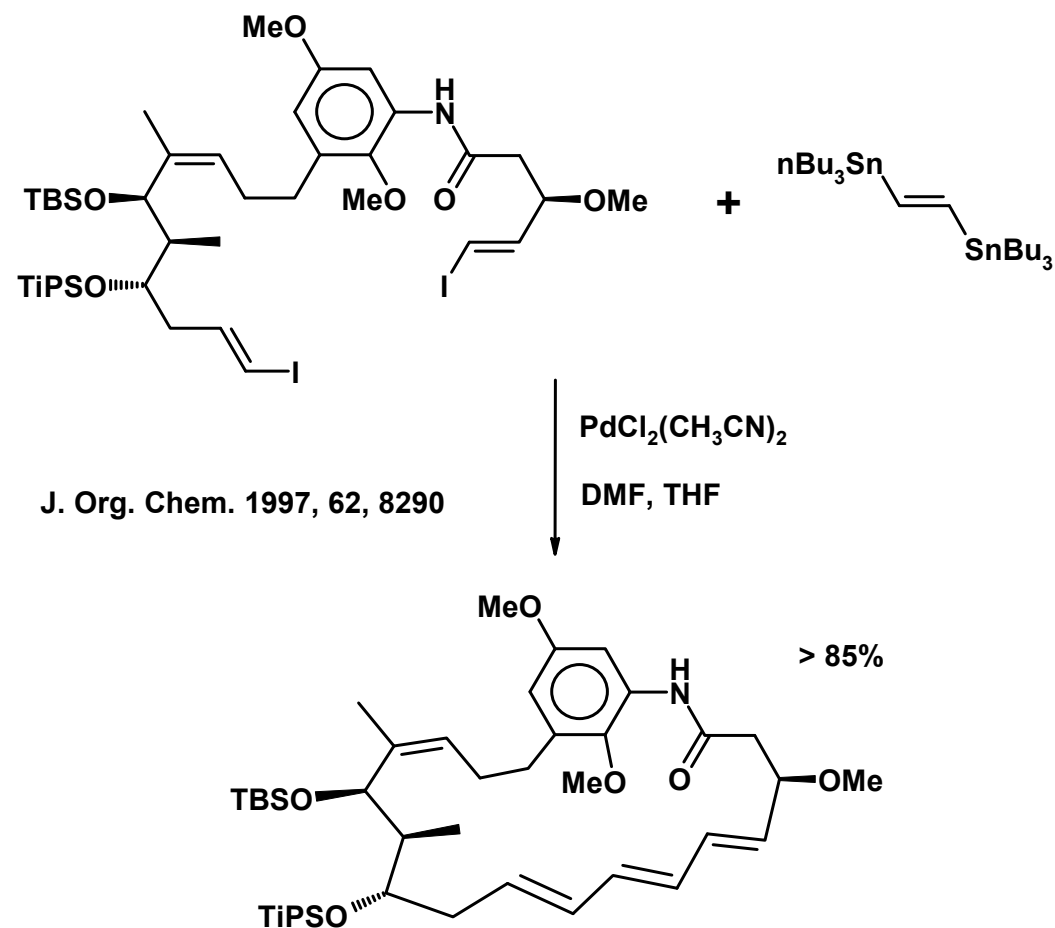
- carried out in polar solvents
- two transition states in the transmetalation step and they lead to different stereochemistry
 - explains the observation of opposite stereochemistry being reported with same partners but different conditions



S_E2 (cyclic)

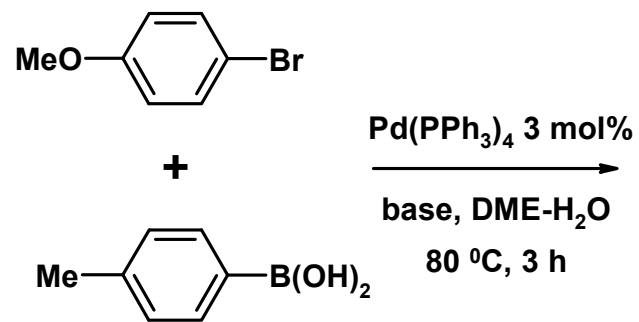
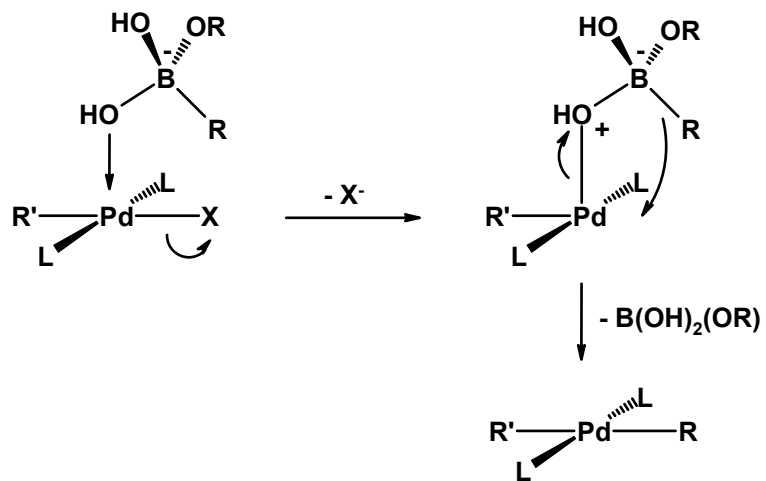
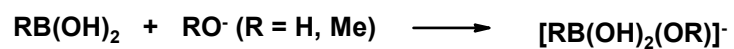


S_E2 (open)

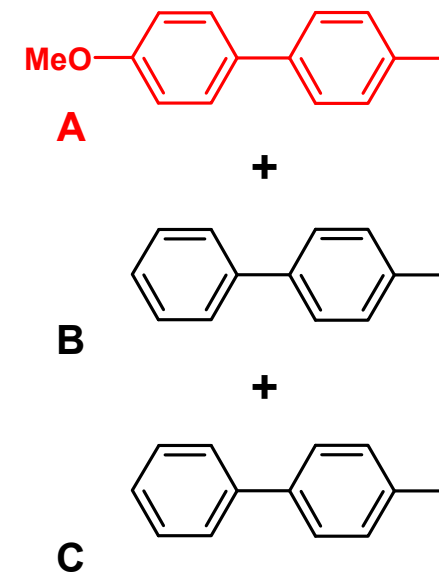


Suzuki

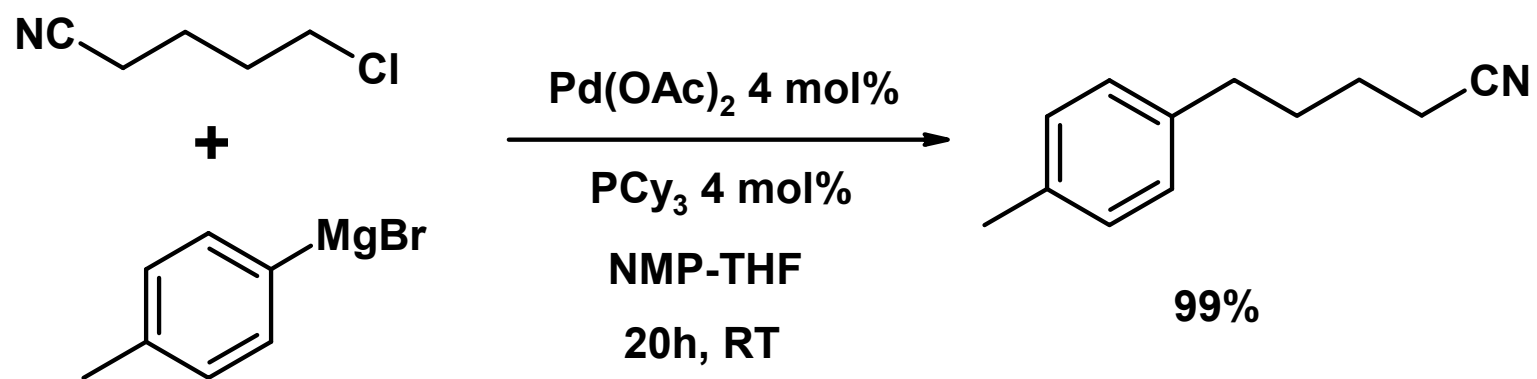
- aryl exchange with PPh_3 is observed where transmetallation is slow
- stronger bases favour faster transmetallation



base	conversion	A	B	C
Na_2CO_3	100%	66	33	1
K_3PO_4	88	94	4	2
NaOH	82	92	1	7



Kumada (M= Mg) and Negishi (M = Zn)

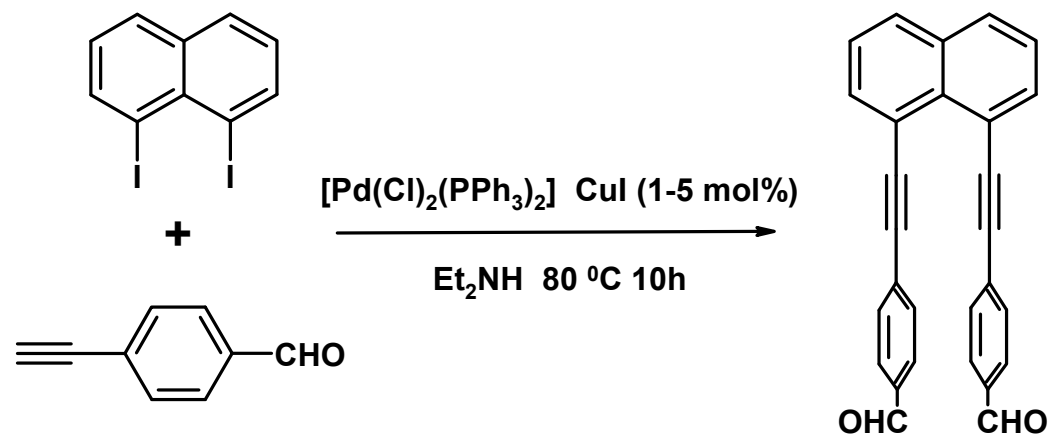
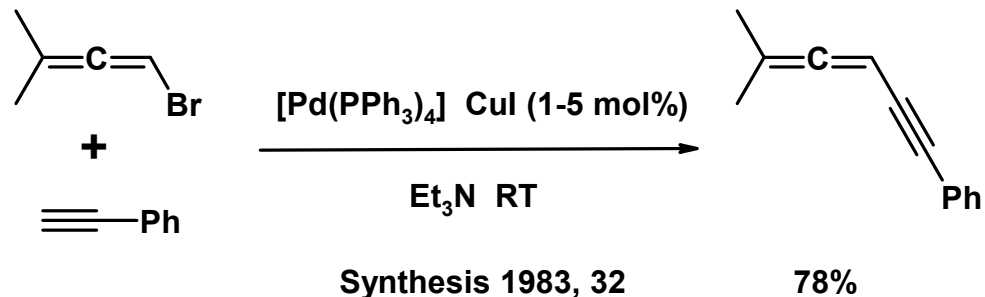


Angew. Chem. Int. Ed. Engl. 2002, 41, 4056

Sonogashira

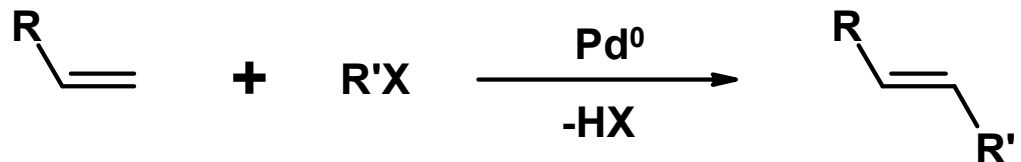
- **Cu(I) alkynide** is the transmetalation species increasing base strength of the amine speeds up the reaction, presumably because it is better able to deprotonate the alkyne and form a Cu-CCAr species
- CuI may act as a phosphine scavenger helping to mitigate phosphine inhibition effects
- amine inhibition is observed

not too bad as amines are poor ligands Pd⁰ but reactions do proceed faster in mixed amine/THF than in pure amine

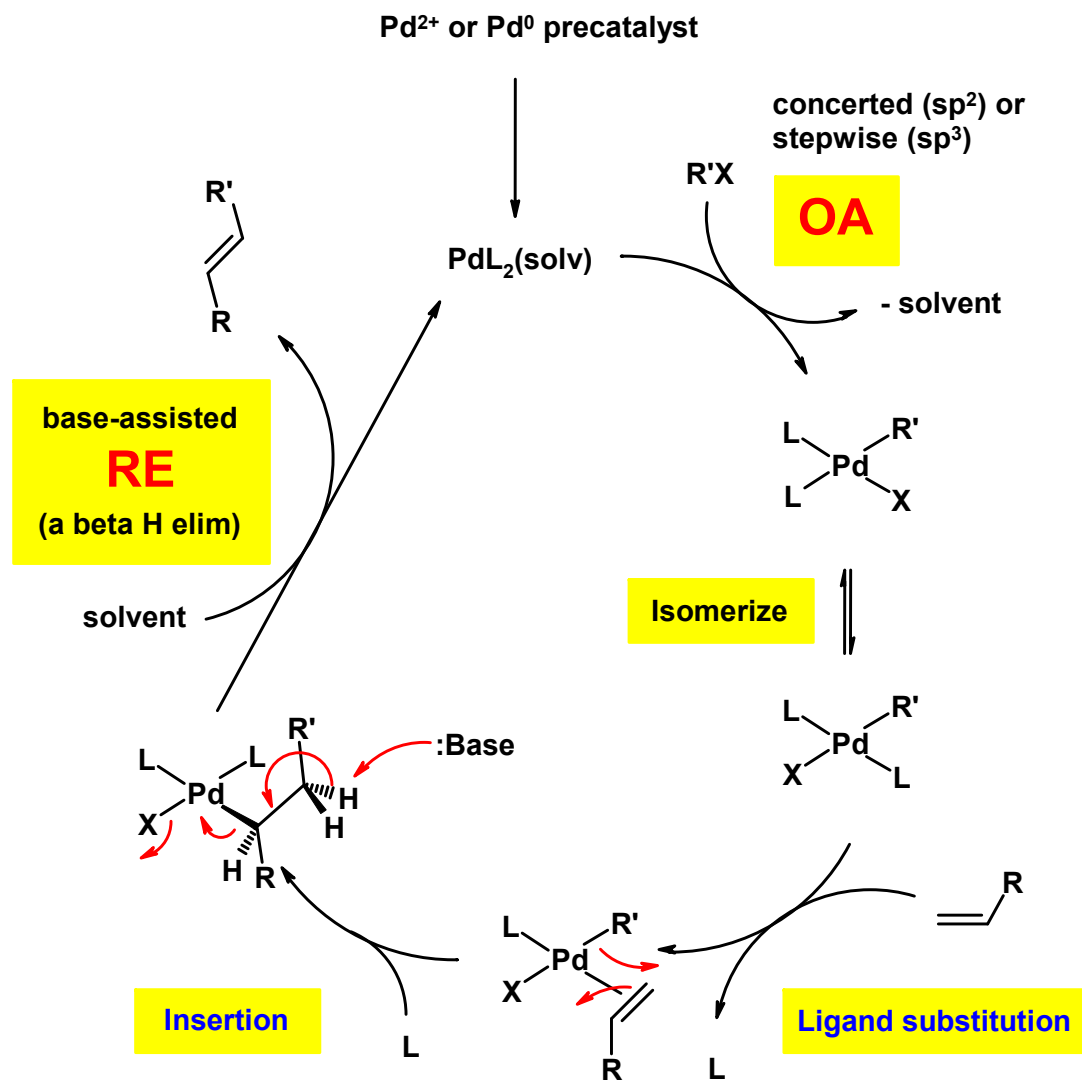


Bull. Chem. Soc. Jpn. 1982, 55, 2434 35%

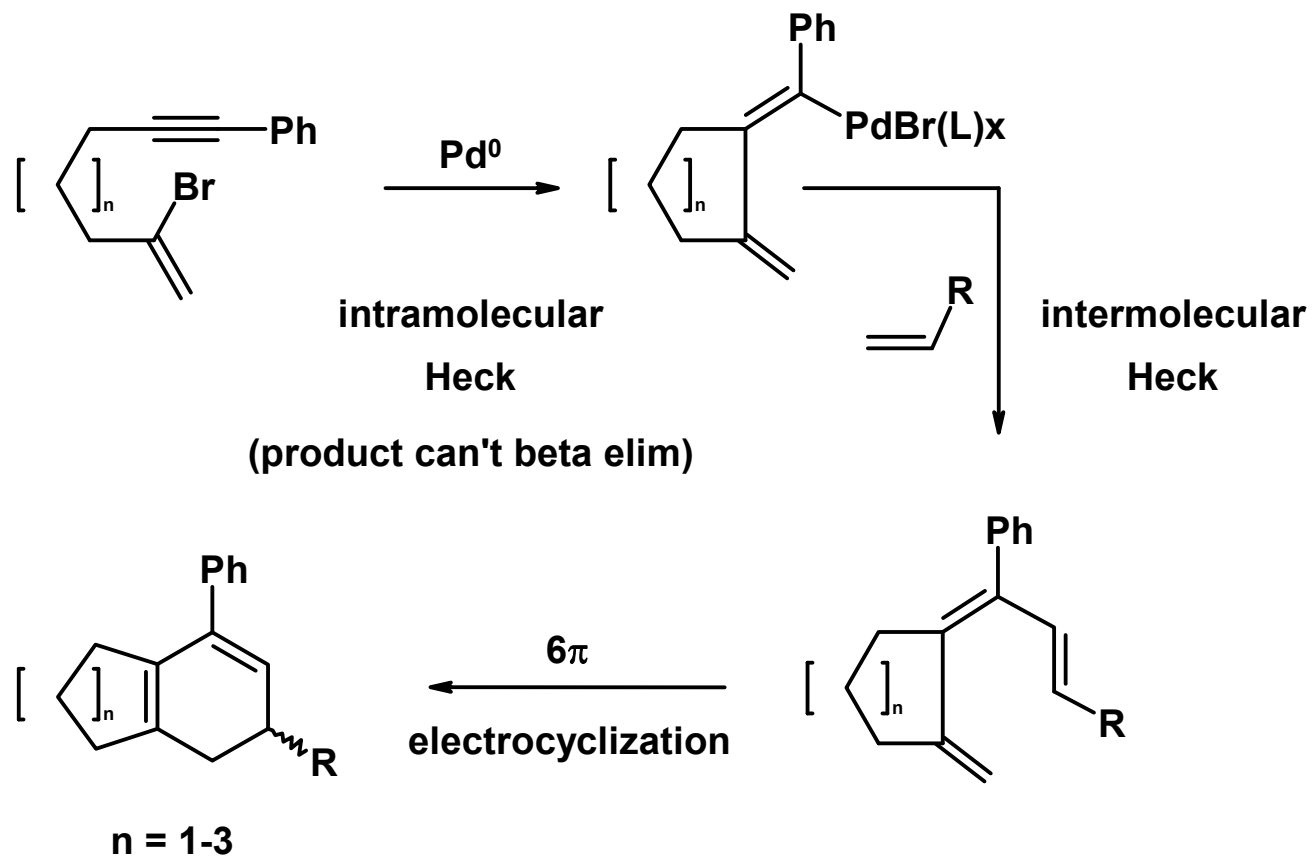
Heck reaction (via carbopalladation of an alkene)



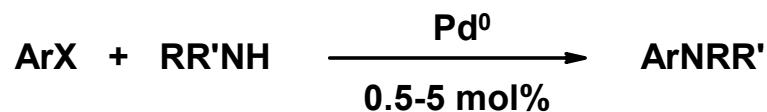
- first reaction of this family developed (c. 1970) but fundamentally different from others in that it involves alkene (or alkyne) insertion
- works best on monosubstituted or 1,1-disubstituted alkenes to form β -coupled product
- same reactivity order for R'X as in other reactions: X = I > OTf > Br >> Cl
- electron rich and bulky phosphines work best



Heck cascades useful in synthesis:



Buchwald-Hartwig Amination

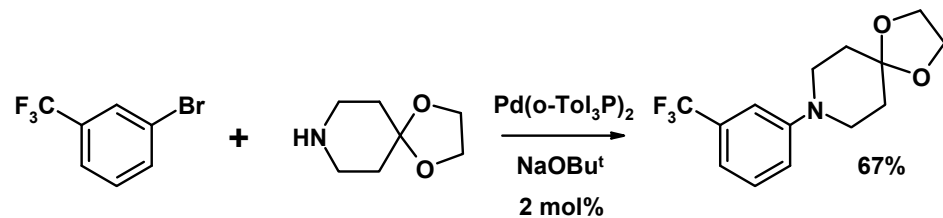


R = aryl, alkyl

base, -HX

R' = alkyl, H

- some catalysts require a strong base like KOBut but others can utilize excess amine as base
- yields typically > 90%



Tet. Lett. 1996, 37, 6993

