

## Pd catalyzed couplings cross couplings

### Cross coupling vs homo coupling (different partners)

Synthetic “toolbox” – these reactions form carbon-carbon bonds

Other ways YOU know to form carbon-carbon bonds:

- Friedel-Crafts alkylation and acylation on aryl substrates (FC alkylation can involve rearrangements)
- Grignard reaction (1, 2 addition to carbonyls, carbon changes hybridization)
- Gilman reagents/Cuprate additions (1, 4 addition to carbonyls, carbon changes hybridization)
- enolate/enol/enamine reactions with alkyl halides or carbonyl groups

1) **Kumada coupling** – Grignard reagent and aryl/alkenyl/alkynyl halide (I, Br, or Cl)

Strengths: Grignard partner easily prepared from aryl, alkenyl, or alkyl halide

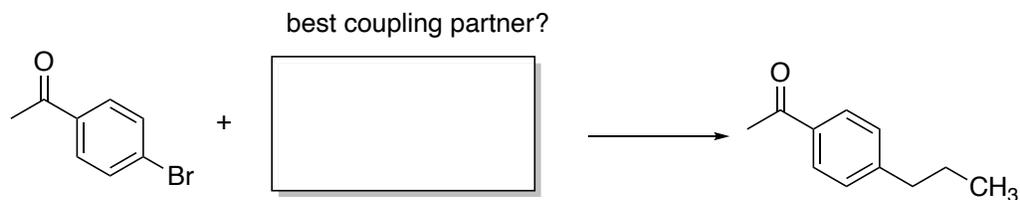
Limitations: coupling reaction cannot be performed if the molecule has acidic hydrogens or carbonyl functional groups present

2) **Negishi coupling** – Organozinc halide reagent and aryl/alkenyl/alkynyl halide

Strengths: Organozinc halide prepared from Grignard reagent  
Reagent is not as basic/nucleophilic so tolerates acidic hydrogens and carbonyl groups.

Limitations: need to prepare organozinc reagent (usually cannot purchase) and the reaction is often not as efficient as other couplings (other products are formed besides desired product)

Kumada vs Negishi



Why can FC alkylation not be used to put propyl group onto ring?

### 3) **Stille coupling** – Aryl or alkenyl tin (stannanes) reagents and aryl/alkenyl/alkynyl halides

Strengths: very versatile reaction; tolerates functional groups including carbonyls and acidic hydrogens

Organotin reagents are stable and can be isolated/stored

Limitations: Tin is very toxic and this transformation requires a stoichiometric amount of tin (not a catalytic amount) because it is part of the reagent

### 4) **Suzuki coupling** – Boronic acid (or ester) reagent and aryl/alkenyl/alkynyl halide

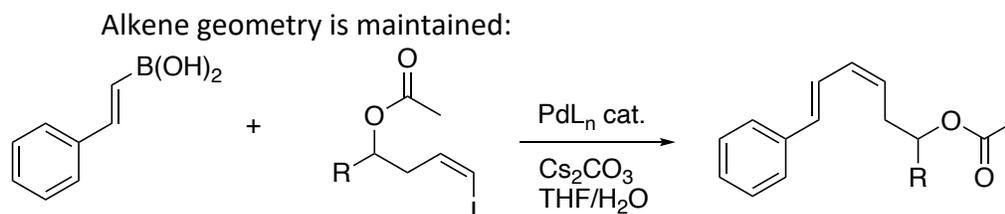
Strengths: the organoboronic acid/ester coupling partner can be  $sp^3$  or  $sp^2$  hybridized (like Negishi and Kumada)

Tolerates carbonyl groups and acidic hydrogens

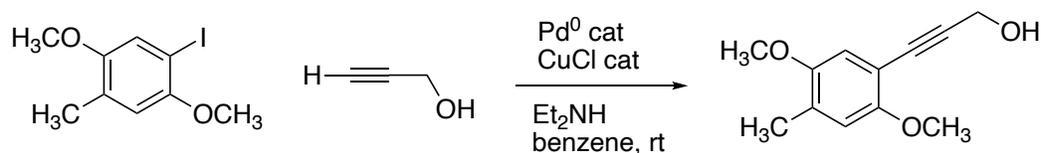
Boronic acids prepared from Grignard reagents; boronic esters prepared from hydroboration reactions of alkenes/alkynes

Many boronic acids can be purchased

Limitations: not many! Boronic acids can be difficult to isolate and the esters (which can be isolated) are sometimes not as reactive; need aqueous base source to activate boronic acid/ester



### 5) **Sonagashira coupling** – Alkyne and aryl halide reaction (Cu catalyst needed in addition to Pd) No activation of alkyne piece (besides Cu catalyst) is needed



quantitative yield reported

K. Shishido, J. Org. Chem. 2001, 66, 309-314

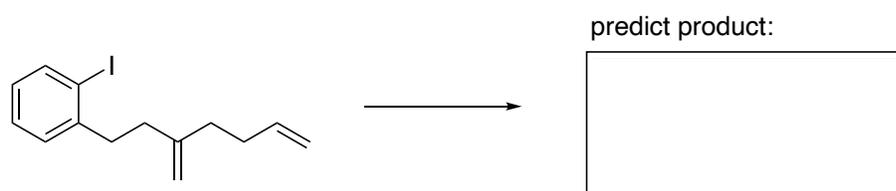
6) **Heck Reaction** – Alkene and aryl halide reaction/coupling; powerful way to create quaternary centers

Note: Syn  $\beta$ -hydride elimination determines placement of alkene product (be sure to understand this part of the mechanism)

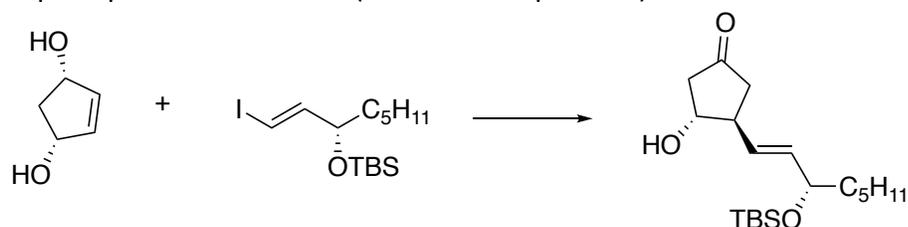
Tandem or cascade reactions (two reactions in one pot) are possible with Heck reactions because an organopalladium (carbon-palladium bond) intermediate is formed

\*\*\*Intramolecular reaction will occur before intermolecular reaction

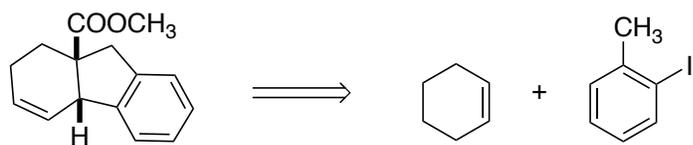
\*\*\*5-membered rings form faster than 6-membered rings



Explain product formation (mechanistic question):



Synthesis Problem:



Retrosynthetic disconnections:

