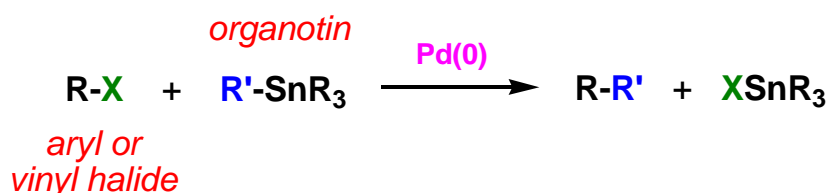


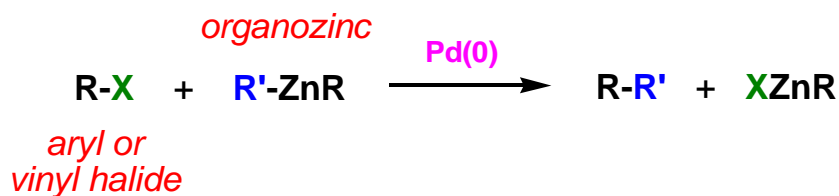
Coupling Reactions

Organometallic chemistry has provided important new methods to carry out carbon-carbon or carbon-heteroatom bond formation. Such processes, termed **coupling reactions**, now have a central place in organic synthesis. The most important ones are summarized below. They often bear the name of their discoverer (organic tradition).

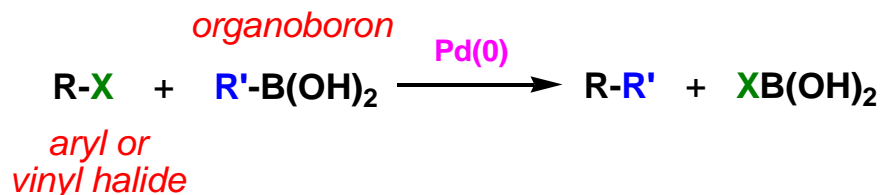
Stille coupling:



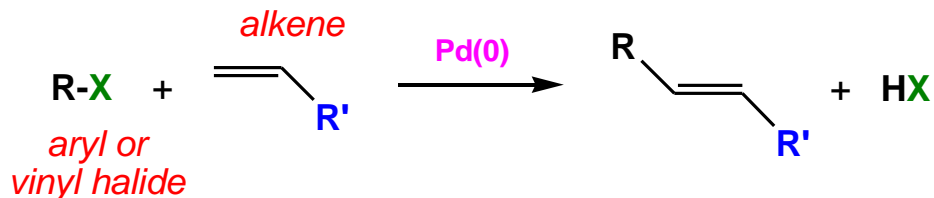
Negishi coupling:



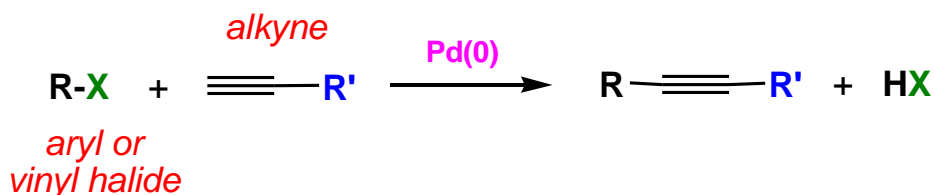
Suzuki coupling:



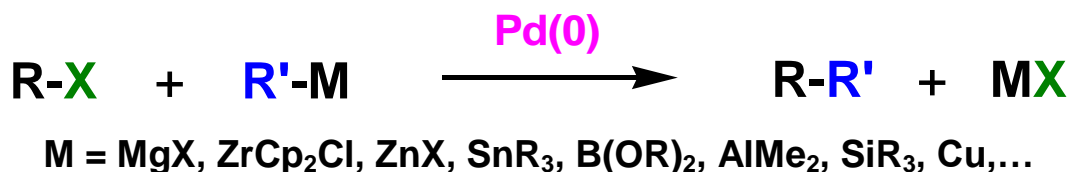
Heck reaction:



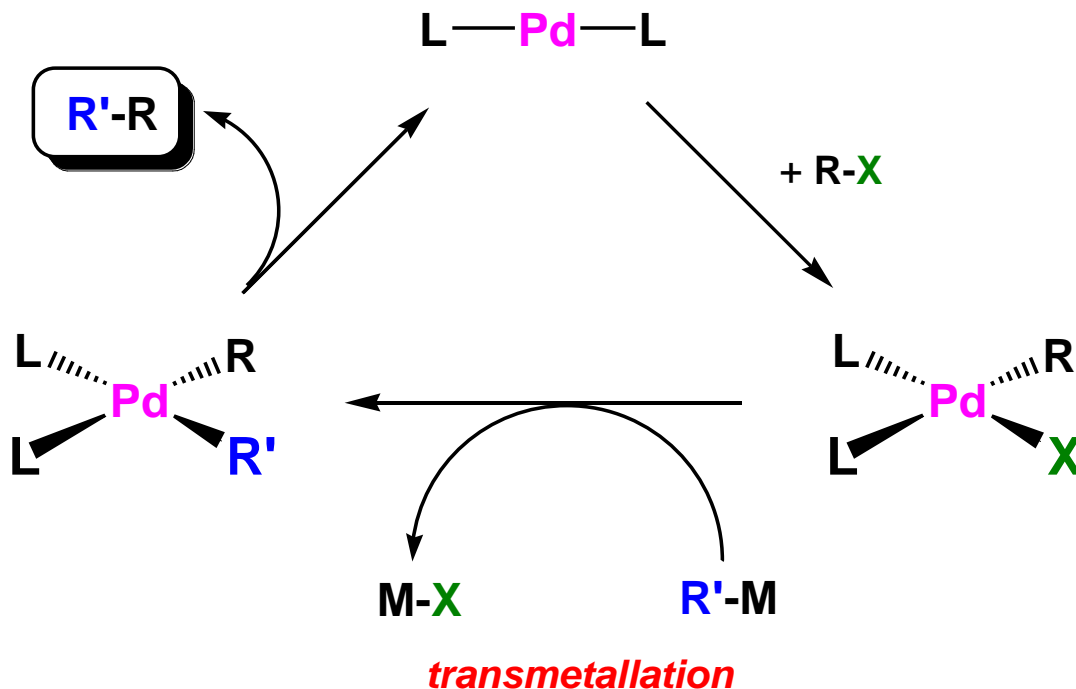
Sonogashira coupling:



Cross-Coupling of Organometallics and Halides



The mechanism involves oxidative addition of the halide or triflate to the initial Pd(0) phosphine complex to form a Pd(II) species. The key slow step is a **transmetallation**, so called because the nucleophile (**R'**) is transferred from the metal in the organometallic reagent to the palladium and the counterion (**X** = halide or triflate) moves in the opposite direction. The new Pd(II) complex with two organic ligands undergoes reductive elimination to give the coupled product and the Pd(0) catalyst ready for another cycle.

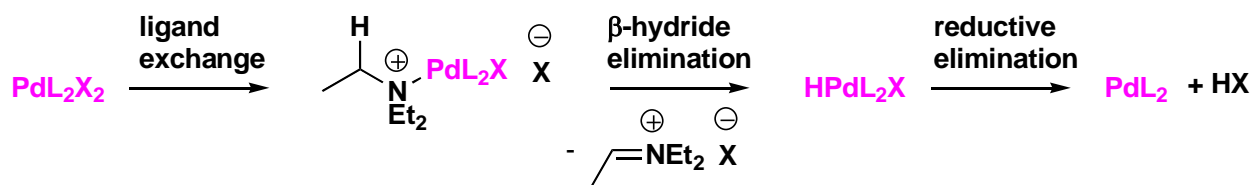


The halide partner (**R-X**) must be chosen with care, as β -hydride elimination would decompose the first intermediate during the slow transmetallation step. The choice for **R** is restricted to substituents without β -hydrogen atoms: vinyl, allyl, benzyl, and polyfluoroalkyl halides, triflates, and phosphates have all been coupled successfully.

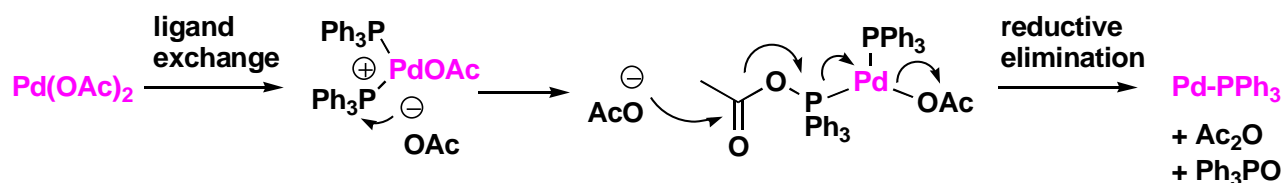
The organometallic reagent ($R'-M$) can be based on Mg, Zn, Cu, Sn, Si, Zr, Al, or B and the organic fragment can have a wide variety of structures as coupling is faster than β -hydride elimination.

Formation of the active species may conveniently be carried out *in situ* by reduction of a Pd(II) precursor, for example, PdCl₂, Pd(OAc)₂, or Na₂PdCl₄. The reduction of Pd(II) to Pd(0) can be achieved with amines, phosphines, alkenes, and organometallics such as DIBAL-H, butyl lithium, or trialkylaluminium.

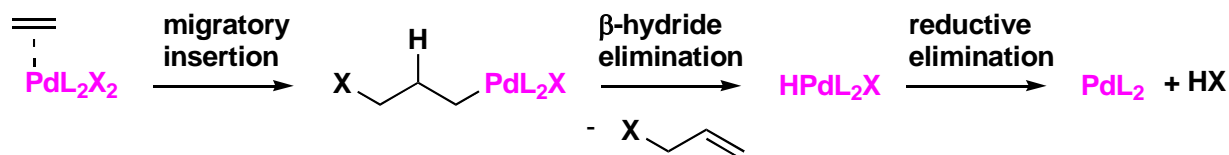
Reduction with Et₃N:



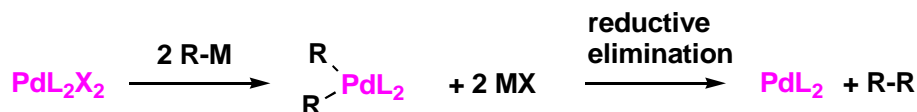
Reduction with PPh₃:



Reduction with ethylene:



Reduction with an organometallic:

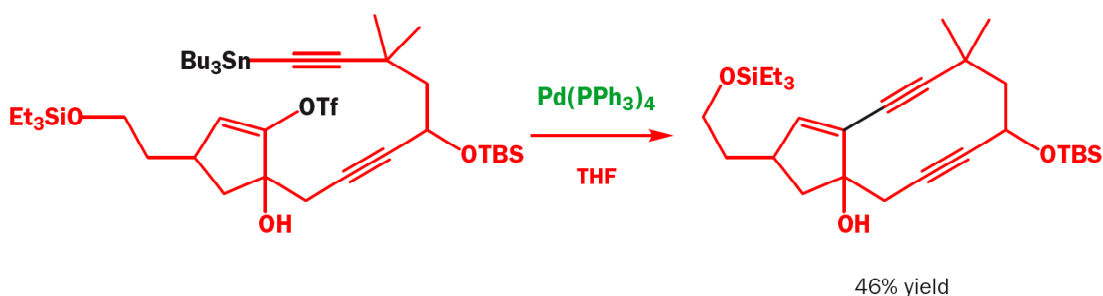


Usually, a stoichiometric excess of an amine such as Et₃N is part of the reaction mixture, serving both as a base to trap the HX formed and as a reducing agent for Pd.

Stille Coupling

The Stille coupling uses organotin compounds (called stannanes) as organometallic components. Since its first reported use in the late 1970's, the reaction has been widely used for the coupling of both aromatic and vinylic systems. The Stille coupling represents over half of all current cross-coupling reactions, however, due to their high toxicity, stannanes tend to be replaced more and more with organozinc and organoboron compounds.

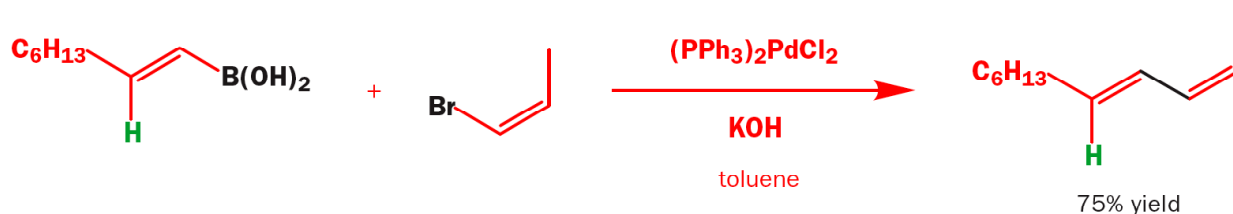
The reaction may be carried out intramolecularly and with alkynyl stannanes instead of the more usual aryl or vinyl stannanes to form medium-sized rings. For example, the reaction below forms a 10-membered ring containing two alkynes.



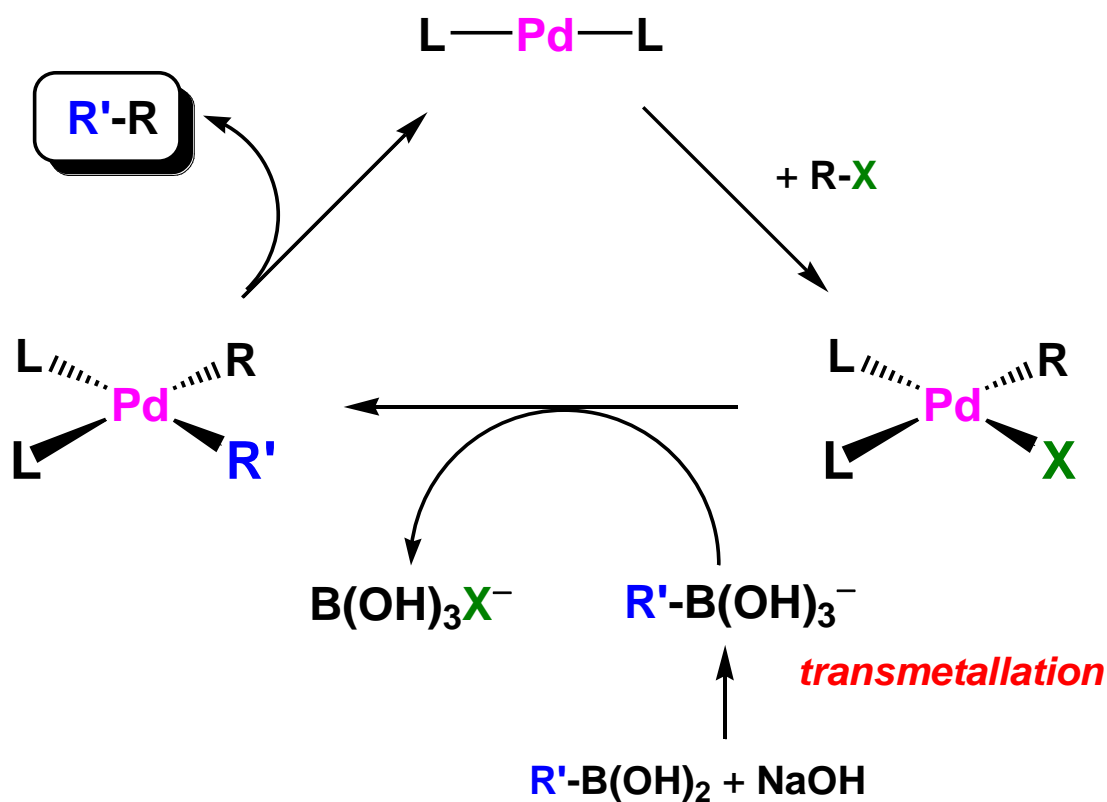
Suzuki Coupling

Since first being published in 1979, the Suzuki coupling of a boronic acid with a halide or triflate has developed into one of the most important cross-coupling reactions, totalling about a quarter of all current palladium-catalysed cross-coupling reactions.

As in the Stille coupling, the geometry of unsaturated components is preserved during the coupling, so this is an excellent method for stereospecific diene synthesis. For example, coupling of an *E*-vinyl boronic acid with a *Z*-vinyl bromide in toluene in the presence of Pd(0) with potassium hydroxide as the base gave the corresponding *E,Z*-diene in good yield.

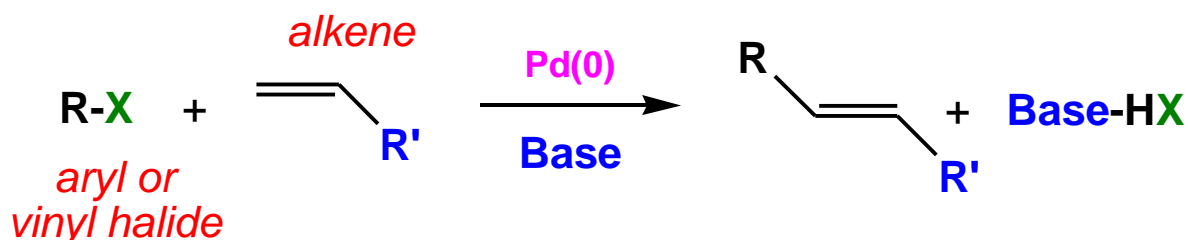


The mechanism of the Suzuki reaction proceeds by oxidative addition of the vinylic or aromatic halide to the Pd(0) complex and generates a Pd(II) intermediate. This intermediate undergoes a transmetalation with the alkenyl boronate, from which the product is expelled by reductive elimination, regenerating the Pd(0) catalyst. One difference between the Suzuki and Stille couplings is that the boronic acid must be activated, usually with a base such as sodium or potassium ethoxide or hydroxide. The base converts the borane (BR_3) into more a reactive boronate ($\text{BR}_3(\text{OH})^-$). Activation of the boron atom enhances the polarization of the organic ligand and facilitates the transmetalation step.



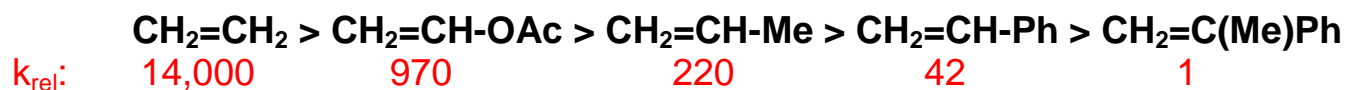
Heck Reaction

The Heck reaction is a powerful and efficient method for C–C bond formation in which haloarenes and haloalkenes (or triflates) couple with alkenes in the presence of a Pd(0) catalyst to form a new alkene. The process is often stereo- and regioselective.



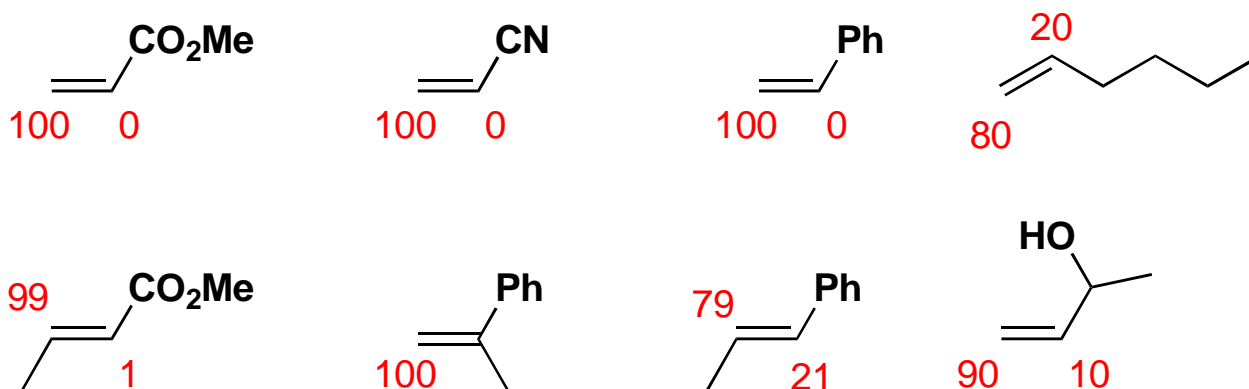
- **R** can be an aryl, vinyl, benzyl or allyl group (in other words, any group without β -hydrogens on a sp^3 carbon atom).
- **X** can be a halide (Cl, Br, or I) or triflate (OSO_2CF_3).
- The **alkene** can be mono- or disubstituted and can be electron-rich, -poor, or neutral.
- The **base** does not have to be strong. Et_3N , NaOAc , or aqueous Na_2CO_3 are often used. The **base** is, however, stoichiometric and one equivalent of base is generated for each equivalent of product.
- The catalyst is a **Pd(0)** complex either preformed or generated *in situ* from stable Pd(II) precursors.

The rate of reaction and regioselectivity are sensitive to steric hindrance about the C=C bond of the vinylic partner. For simple aryl halides reacting with alkenes, the rate of reaction as a function of alkene substitution varies according to the following sequence:

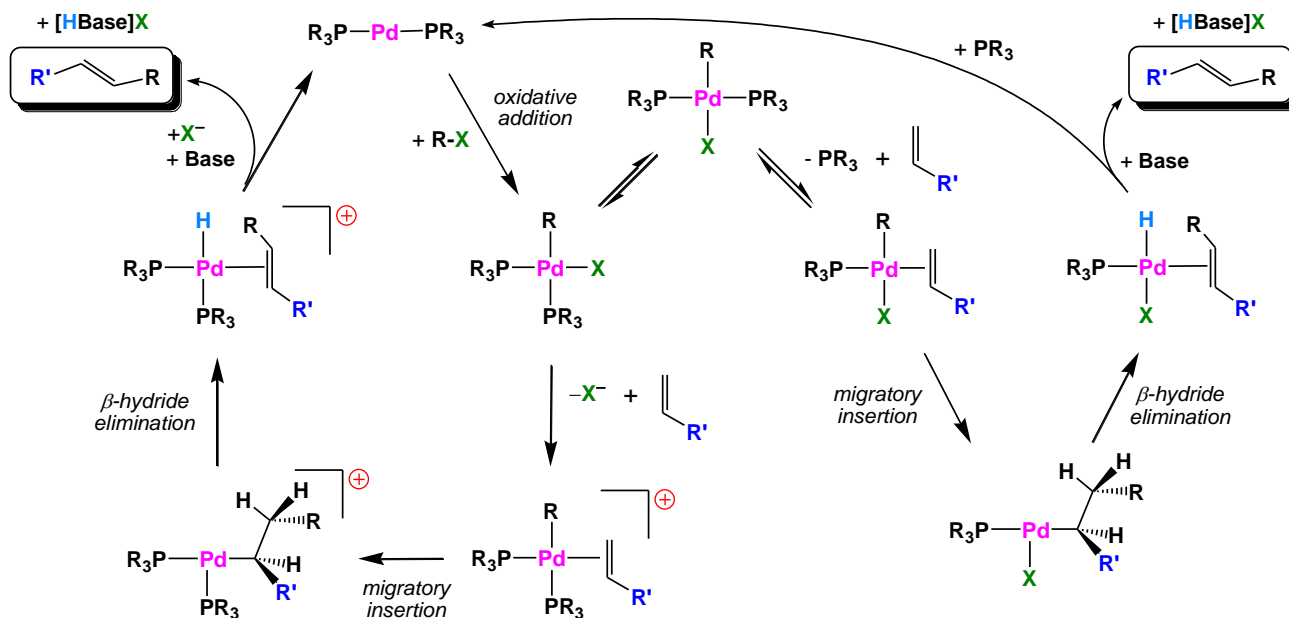


The regioselectivity of addition is given below for a number of alkenes. Although electronic effects may play a small role in directing attack by the

metal in the insertion step, steric effects seem to be the dominant factor by far.



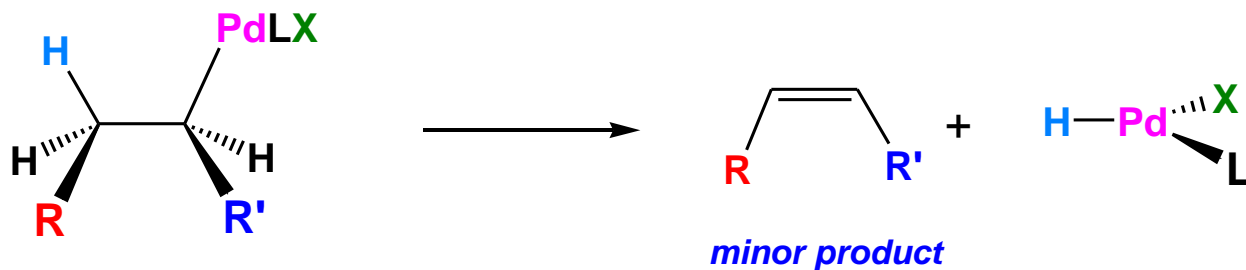
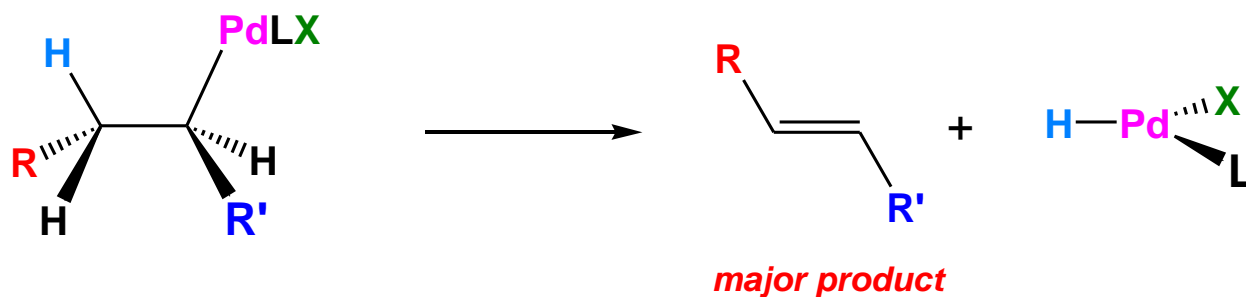
The mechanism involves the oxidative addition of the halide, insertion of the olefin, and release of the product through a β -hydride elimination. A base then regenerates the Pd(0) catalyst via reductive elimination and closes the catalytic cycle. Two alternate mechanisms (one cationic) are shown below with the same general sequence of steps.



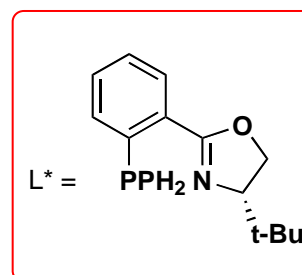
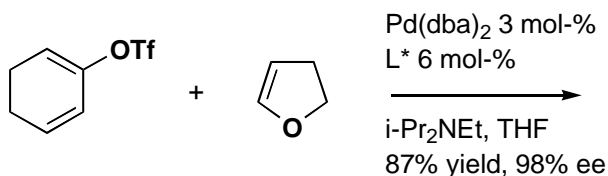
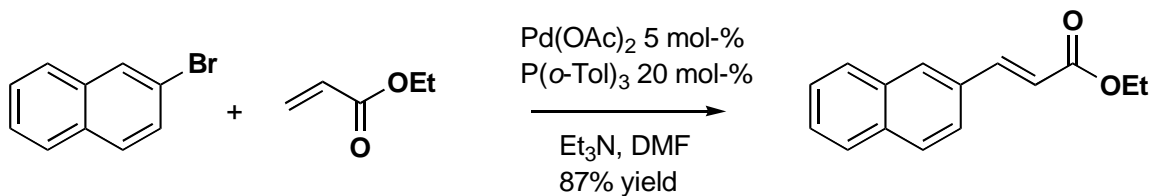
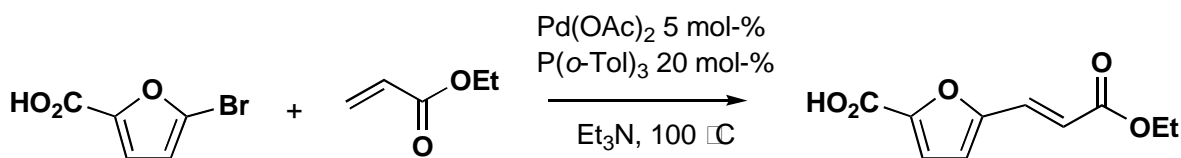
The Heck reaction differs significantly from the earlier Pd(0)-catalyzed cross-coupling reactions because:

- 1) it involves an insertion after the oxidative addition step
- 2) the catalytic cycle is closed with a β -hydride elimination, whereas the other couplings end with a reductive elimination.

In the β -hydride elimination step, the palladium and hydride must be coplanar for the reaction to take place, as this is a *syn* elimination process. For steric reasons, the **R** group will tend to eclipse the smallest group on the adjacent carbon as elimination occurs, leading predominantly to a *trans* double bond in the product.

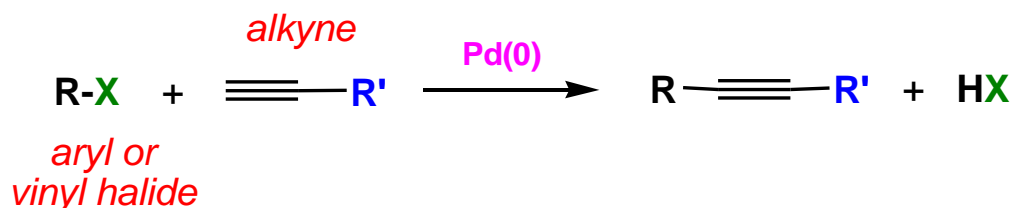


Applications of the Heck reaction in organic synthesis

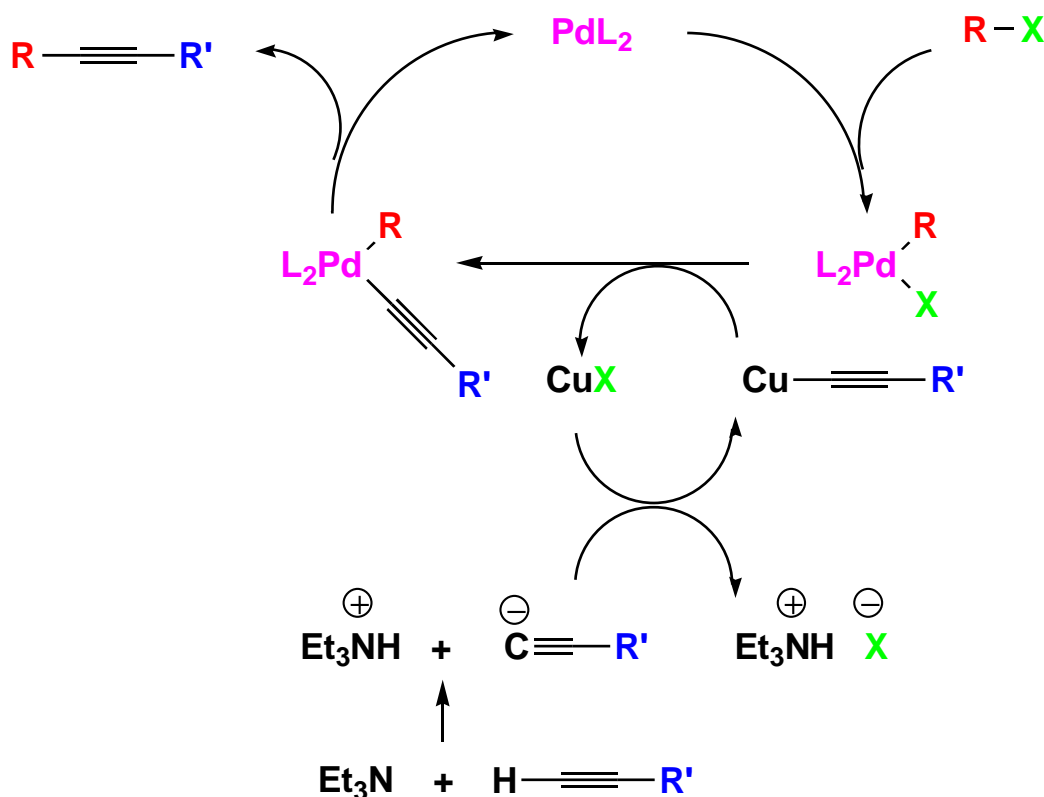


Sonogashira Coupling

The coupling of terminal alkynes with aryl or vinyl halides under palladium catalysis is known as the Sonogashira reaction. This catalytic process requires the use of a palladium(0) complex, is performed in the presence of base, and generally uses copper iodide as a co-catalyst.



The mild conditions usually employed (frequently room temperature) mean that the Sonogashira coupling can be applied to thermally sensitive substrates. The mechanism of the reaction is similar to that of the Stille and Suzuki couplings. Oxidative addition of the organic halide gives a Pd(II) intermediate that undergoes transmetalation with the alkynyl copper (generated from the terminal alkyne, base, and copper iodide). Reductive elimination with coupling of the two organic ligands gives the product and regenerates the Pd(0) catalyst.



As in the Heck reaction, It is often more convenient to use a stable and soluble Pd(II) source such as $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ instead of Pd(0). This precursor is rapidly reduced *in situ* to give a coordinatively unsaturated, catalytically active, Pd(0) species. The geometry of the alkene is generally preserved so that *cis* (*Z*) and *trans* (*E*) dichloroethylene give the two different geometrical isomers of the enyne below in >99% stereochemical purity as well as excellent yield.

