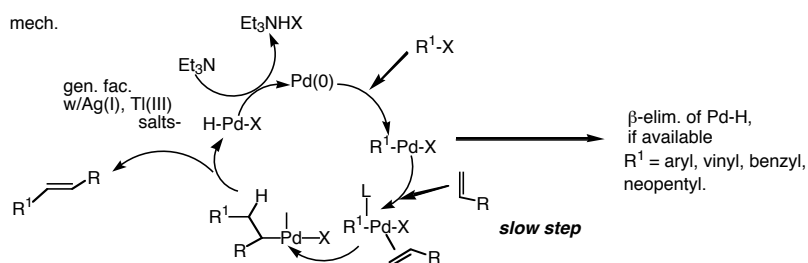


# Organometallics - Pd Feature

VIII B			IB		
9	10	11	12	13	14
27 58.933 <b>Co</b> COBALT	28 58.693 <b>Ni</b> NICKEL	29 63.546 <b>Cu</b> COPPER	30 65.38 <b>Zn</b> ZINC	31 69.723 <b>Ga</b> GALLIUM	32 72.64 <b>Ge</b> GERMANIUM
45 102.91 <b>Rh</b> RHODIUM	46 106.42 <b>Pd</b> PALLADIUM	47 107.87 <b>Ag</b> SILVER	48 112.41 <b>Cd</b> CADMIUM	49 114.818 <b>In</b> INDIUM	50 118.710 <b>Sn</b> TIN
77 192.22 <b>Ir</b> IRIDIUM	78 195.08 <b>Pt</b> PLATINUM	79 196.97 <b>Au</b> GOLD	80 200.59 <b>Hg</b> MERCURY	81 204.39 <b>Tl</b> THALLIUM	82 208.98 <b>Pb</b> LEAD

-Synthetic Applications of Pd include:

## -Heck Reactions



The optimal recipe for the catalyst mixture must be established independently for each reaction:

Pd(II), Pd(0) salts,  $\text{P}(\text{Aryl})_3$  /  $\text{As}(\text{Aryl})_3$   
 amine, solvent, temp. (100-140°C),  
 (or carbonate base)

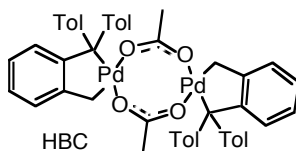
Complex geometry and ligand effects on rate: Amatore, C.; Jutand, A.; Suarez, A., "Intimate mechanism of oxidative addition to zerovalent palladium complexes in the presence of halide ions and its relevance to the mechanism of palladium-catalyzed nucleophilic substitutions." *J. Am. Chem. Soc.* **1993**, *115*, 9531-9541.

**The Complex.** Among Pd(0) and Pd(II) complexes commonly used are Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd<sub>2</sub>(dba)<sub>2</sub>, and Pd<sub>2</sub>(dba)<sub>2</sub>CHCl<sub>3</sub>. Pd(PPh<sub>3</sub>)<sub>4</sub> should be stored cold and under inert gas; the dibenzylideneacetone complexes are more stable catalyst precursors. Both phosphine structure and phosphine/Pd ratio effect catalyst structure and reactivity (the lower the phosphine/Pd ratio, the more reactive the catalyst). A general ratio for high activity system is 2:1.

Pd(II) precatalysts include Pd(OAc)<sub>2</sub>, PdCl<sub>2</sub>(CH<sub>3</sub>CN), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, and Pd[(allyl)Cl]<sub>2</sub>. These complexes are air stable and reduced by phosphines, water, and amines.

In most cases, 5-20 mol% catalyst is used, even though more stable catalysts such as the Herrmann-Beller palladacycle can be used at much lower loadings.

Palladacycles have emerged as promising catalysts for Heck and Suzuki cross-couplings since they exhibit higher air and thermal stability than palladium(0) complexes and can operate through a Pd(II)-Pd(IV) cycle instead of the traditional Pd(0)-Pd(II) mechanism.



**The Ligand.** Among the phosphines used for the Heck reaction are PPh<sub>3</sub>, P(*o*-tol)<sub>3</sub>, P(furyl)<sub>3</sub>, PCy<sub>3</sub>, 2-(di-*t*-butylphosphanyl)-biphenyl, dppe, dppp, dppb, and dppf as well as AsPh<sub>3</sub>. PCy<sub>3</sub> is very effective for aromatic chlorides. Most phosphines favor the trans-complex and thus slow down the catalytic cycle. Bidentate phosphines are used when monodentate ligands are ineffective or to influence stereoselectivity in combination with triflates (cationic pathway).

N-heterocyclic carbene ligands (for example with N,N'-bis(2,4,6-trimethylphenyl)imidazolium chloride (IMES·HCl)) provide useful, highly reactive catalytic systems.

**The Base.** A stoichiometric amount of base is needed, and NaOAc, NaHCO<sub>3</sub>, Li<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, CaCO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub> and K<sub>3</sub>PO<sub>4</sub> as well as TEA, Hünig's base, proton sponge, TMEDA, DBU have been used. Silver and thallium salts shift the pathway to the cationic manifold; they often increase the rate of the reaction, lower reaction temperatures, minimize alkene isomerization, modify regioselectivity, and alter enantioselectivity. Halide salts (NaX, KX, LiX, TBAX, etc) can divert reactions of triflate precursors from the cationic to the neutral pathway (or, possibly, the anionic pathway).

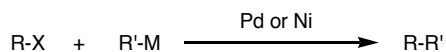
**The Salts.** The heterogeneous conditions reported by Jeffery are routinely employed. TBACl or TBABr are added in stoichiometric amounts and can increase reaction rates and decrease temperatures. It has been proposed that the ammonium halides stabilize the catalytic species by halide coordination, shift the equilibrium from the hydridopalladium species to the catalytically active Pd(0), and promote the anionic pathway.

**The Solvent.** Common solvents for the Heck reaction are THF, DMF, NMP, DMAC, and MeCN. Toluene, benzene, EtOH, and water are also used, as are fluoruous reaction conditions. Reaction temperatures vary between room temperature and reflux.

Useful user guidelines: Chapters 3 & 6 by de Meijere and Overman, respectively, in "Metal-catalyzed cross-coupling reactions"; (Diederich & Stang, Eds.), VCH 1997.

## Stille, Suzuki, Negishi, Hiyama & Related Cross-Coupling Reactions

Cross-Coupling is the reaction of an organometallic reagent R'-M with an organic compound R-X to give a product R-R' and is often catalyzed by a transition metal:

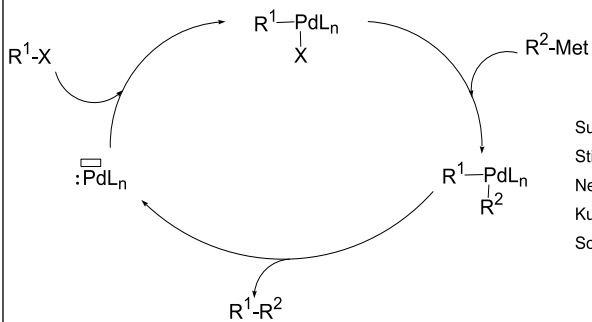
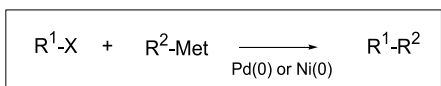


Since C,C-bond formations are among the most important transformations in organic synthesis, this process has received considerable attention.

In 1971, a series of papers by Tamura and Kochi demonstrated that soluble catalysts containing silver, iron, or copper were very effective catalysts for the coupling of Grignard reagents and organic halides. Subsequently, this field developed very rapidly.

**M = Li (Murahashi), Mg (Kumada-Tamao, Corriu, 1972), Zn (Negishi, Normant), B (Suzuki-Miyaura), Al (Nozaki-Oshima, Negishi), Zr (Negishi), Cu (Normant), Sn (Stille, Migita-Kosugi), Si (Hiyama, 1988, Tamao-Ito, 1989, DeShong, 1998, Denmark 1999). Others: Liebeskind, Fukuyama, etc.**

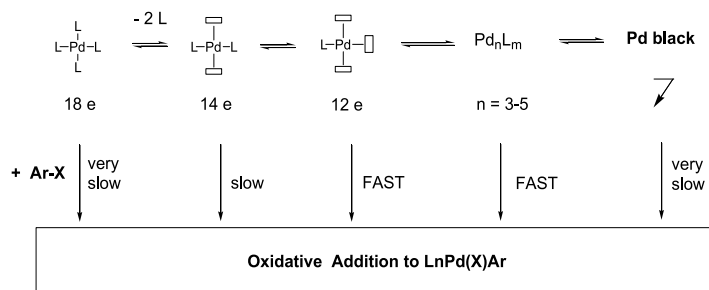
# Metal Catalyzed Cross-Coupling Reactions



- Suzuki-coupling : Met = B(OH)<sub>2</sub>
- Stille-coupling : Met = SnR<sub>3</sub>
- Negishi-coupling : Met = ZnX
- Kumada-coupling : Met = MgX
- Sonogashira-coupling : Csp-Csp<sup>2</sup>

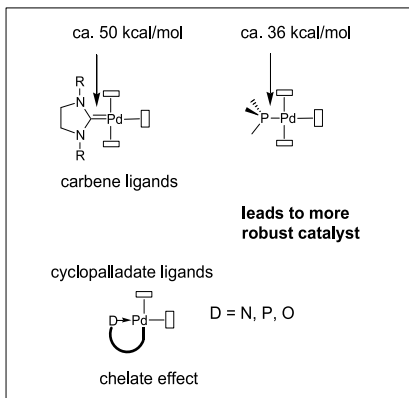
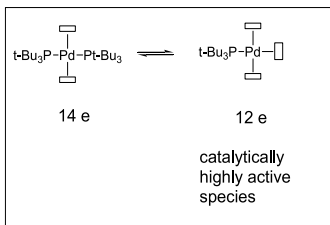
Miyaura, N. Cross-Coupling. A Practical Guide Springer, 2002  
 Diederich, F.; Stang, P.J. Metal-catalyzed Cross-Coupling Reactions, Wiley-VCH, 1998; new edition 2004

## Cross Coupling reactions principles

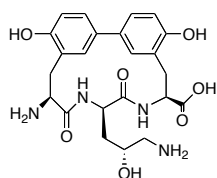


- low coordination at palladium is favored by bulky ligands
- low coordination at palladium is favored by high reaction temperature

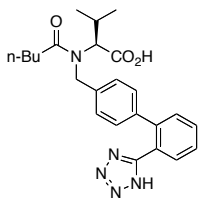
## • Optimum Ligand Search



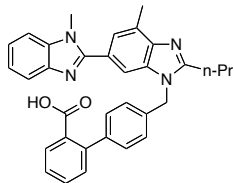
The significance of biaryl systems is high:



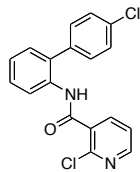
Biphenomycin B (antibiotic)



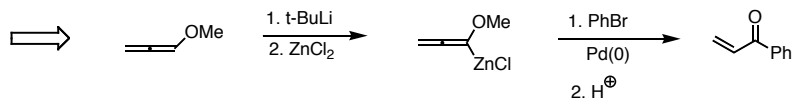
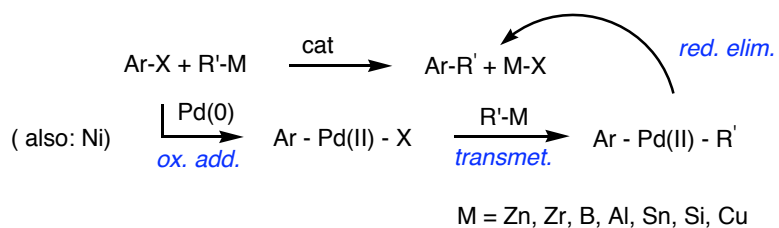
Diovan (Valsartan, Novartis)



Micardis (Telmisartan, Boehringer)

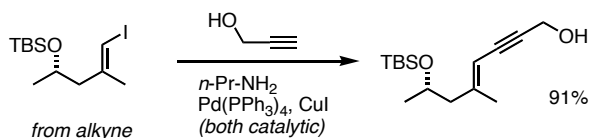


Boscalid (BASF)



### Sonogashira Coupling [Cu]

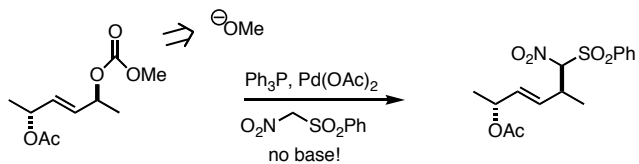
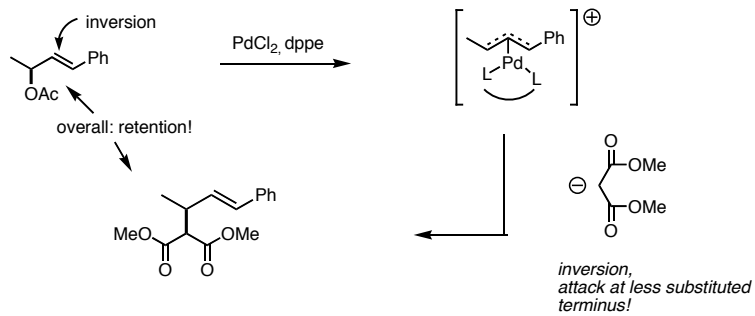
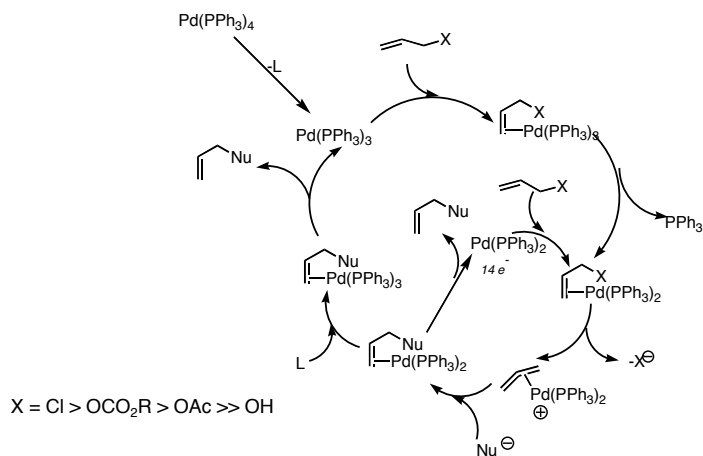
Over the past few decades, the Pd-catalyzed alkylation has emerged as one of the most general and reliable methods for the synthesis of alkynes. Currently, the most widely used by far is a hybrid of the Cu-promoted Castro-Stephens reaction and the alkyne version of the Heck reaction, which is known as the Sonogashira reaction originally reported in 1975. This reaction is considered generally superior to either the Castro-Stephens reaction or the Heck protocol without the use of a Cu salt, and it is normally used without checking the comparative merits among them, even though the Heck protocol, which is inherently simpler than the Sonogashira reaction, has been shown to be highly satisfactory in a number of cases. For a review, see: Negishi, E.-I.; Anastasia, L. Palladium-catalyzed alkylation. *Chem. Rev.* **2003**, *103*, 1979-2017.



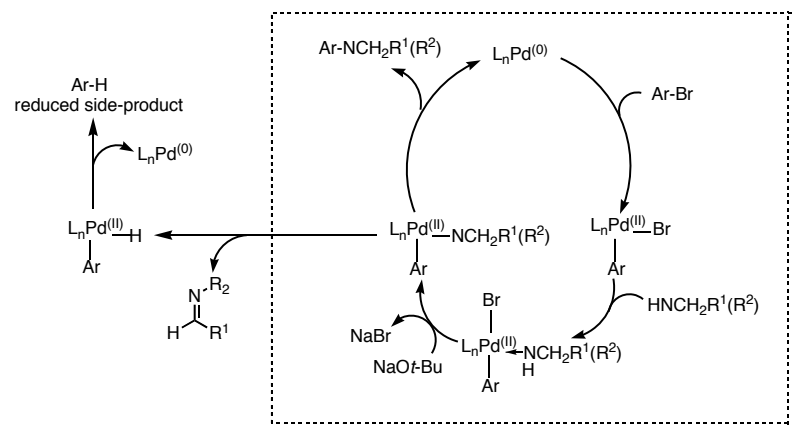
Magnus, P.; Lewis, R. T.; Huffman, J. C., "Synthesis of a remarkably stable bicyclo[7.3.1]dienes esperamicin  $\alpha$ /calicheamicin  $\gamma$  system. Structural requirements for facile formation of a 1,4-diyli." *J. Am. Chem. Soc.* **1988**, *110*, 6921-6923.

## $\pi$ -Allyl Palladium Chemistry

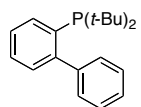
Trost, Tsuji; catalytic cycle:



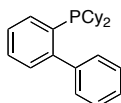
Recent advances in the palladium-catalyzed amination of aryl halides offer considerable advantages for aniline formation over the classical methods, which require either activated substrates or severe reaction conditions.



Ali, M. H.; Buchwald, S. L., "An improved method for the palladium-catalyzed amination of aryl iodides." *J. Org. Chem.* **2001**, *66*, 2560-2565.



often the optimal ligand for amination of aryl bromides and aryl chlorides



often the optimal ligand for amination of aryl iodides