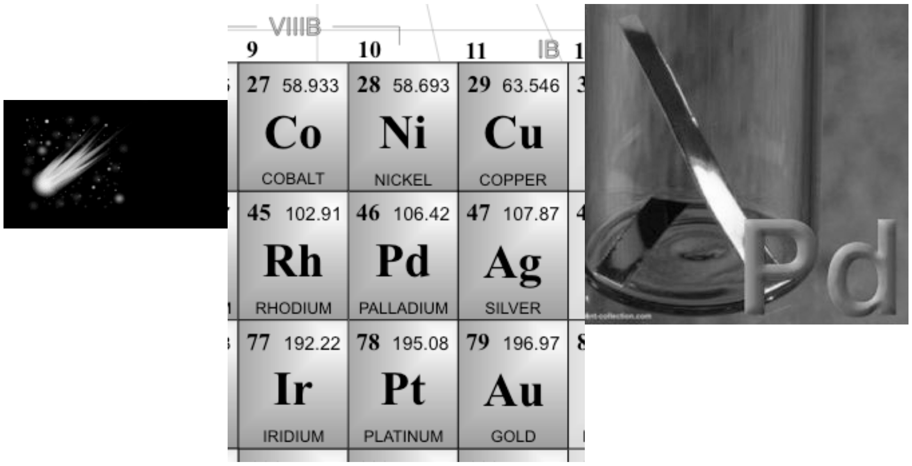
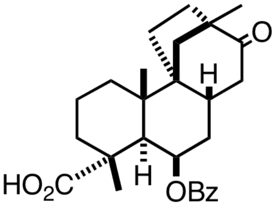
I. Basic Principles

IG. Palladium I



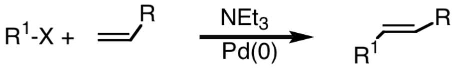
- Heck Reactions
- Stille, Suzuki, Negishi, Sonogashira *etc* Cross Couplings
- π-Allyl Palladium Chemistry
- Heteroatom Couplings
- Applications in Natural Product Synthesis



medical plant
Paraguay, India, Taiwan

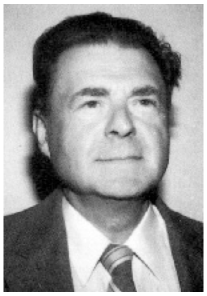
tetracylic diterpene

The Heck Reaction



R. F. Heck
Palladium-reagents in O.S.
Academic Press
N.Y. 1985

1st catalytic paper: JOC **1972**, *37*, 2320
first intramolecular paper: JOC **1983**, *48*, 2792
for stereochemical control by complexation of Pd to alkene: THL **1991**, *32*, 6993



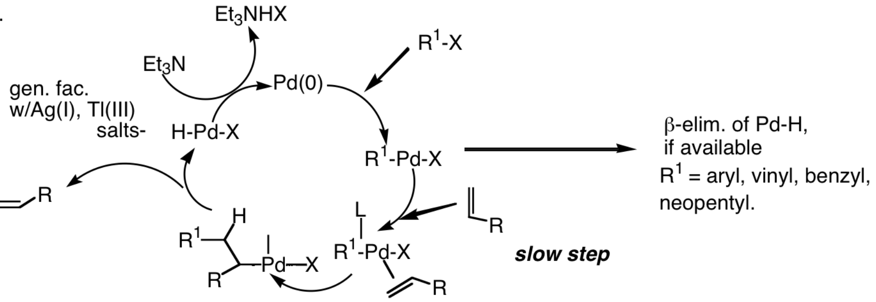
Herbert C. Brown Award for Creative Research in Synthetic Methods
(sponsored in part by Sigma-Aldrich since 1998).

Richard F. Heck (retired) – University of Delaware (USA)

Professor Heck, of “Heck Reaction/Coupling” fame, has had a long and distinguished career in chemistry. Beginning with Co-mediated hydroformylation, Heck was one of the first to apply transition metal catalysis to C-C bond formation. His studies of the mechanisms of transition metal catalyzed reactions led to Pd-mediated couplings that have had a profound impact in many areas of chemistry and materials science.

Reviews: Shibasaki, M.; Vogl, E. M.; Ohshima, T. "Asymmetric Heck reaction." *Advanced Synthesis & Catalysis* **2004**, *346*, 1533-1552.
Dounay, A. B.; Overman, L. E. "The asymmetric intramolecular Heck reaction in natural product total synthesis." *Chem. Rev.* **2003**, *103*, 2945-2963.
Beletskaya, I. P.; Cheprakov, A. V. "The Heck reaction as a sharpening stone of palladium catalysis." *Chem. Rev.* **2000**, *100*, 3009-3066.

mech.



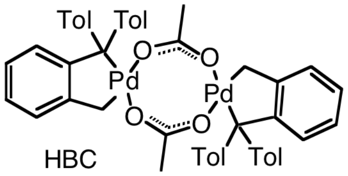
The optimal recipe for the catalyst mixture must be established independently for each reaction:

Pd(II), Pd(0) salts, $P(Aryl)_3$ / $As(Aryl)_3$
amine, solvent, temp. (100-140^oC),
(or carbonate base)

The Complex. Among Pd(0) and Pd(II) complexes commonly used are $Pd(PPh_3)_4$, $Pd_2(dba)_2$, and $Pd_2(dba)_2CHCl_3$. $Pd(PPh_3)_4$ 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 $Pd(OAc)_2$, $PdCl_2(CH_3CN)$, $Pd(PPh_3)_2Cl_2$, and $Pd[(allyl)Cl]_2$. 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.



HBC

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.

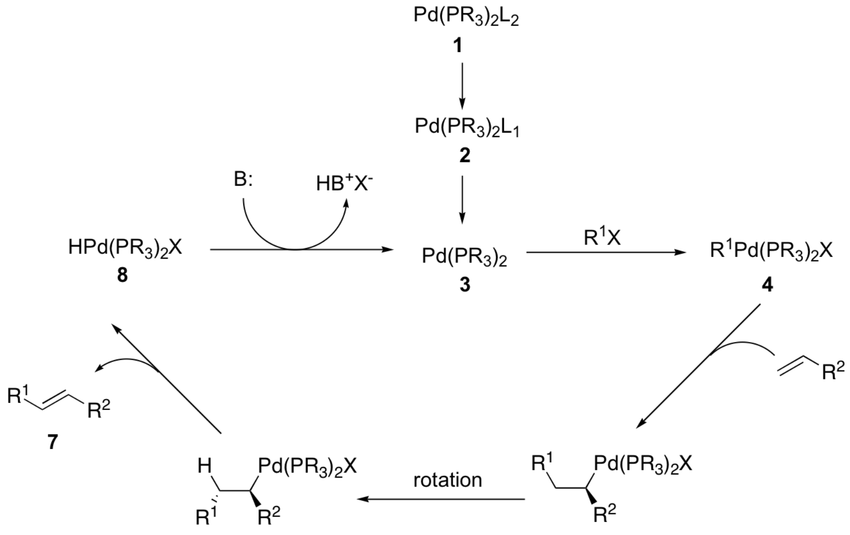
The Ligand. Among the phosphines used for the Heck reaction are PPh_3, P(*o*-tol)$_3$, P(furyl)$_3$, PCy_3, 2-(di-*t*-butylphosphanyl)-biphenyl, dppe, dppp, dppb, and dppf as well as $AsPh_3$. PCy_3 has been found effective for aromatic chlorides. Bidentate phosphines are used when monodentate ligands are ineffective or to influence stereoselectivity in combination with triflates (cationic pathway).
Similarly, 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, $NaHCO_3$, Li_2CO_3, K_2CO_3, $CaCO_3$, Cs_2CO_3 and K_3PO_4 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 increases 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 fluorous reaction conditions. Reaction temperatures vary between room temperature and reflux.

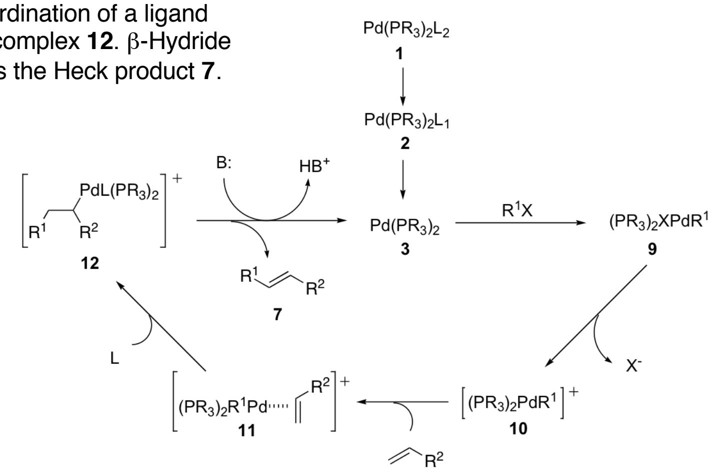
Useful user guidelines: Chapters 3 & 6 by de Meijere and Overman, respectively, in “Metal-catalyzed cross-coupling reactions”, (Diederich & Stang, Eds.), VCH 1997.

Mechanism(s)

Two mechanistic variants, the “neutral” and the “cationic” pathway have been described. In the neutral pathway, the active catalyst is a coordinatively unsaturated 14-electron palladium complex **3**. From the hydridopalladium complex **8**, a stoichiometric amount of base regenerates the active catalyst **3**.

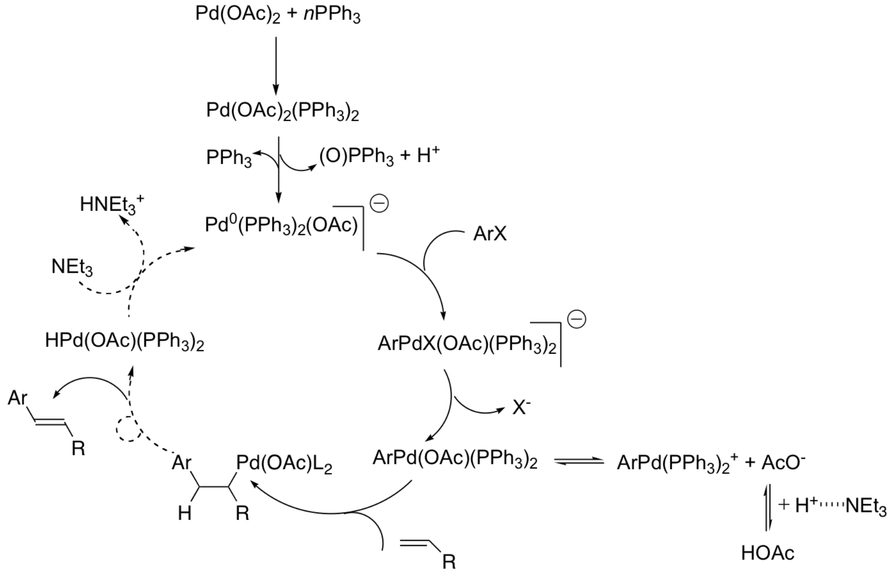


When the substrate is a triflate, or the reaction of halide substrates is carried out in the presence of halide scavengers, a cationic variant is followed. The Pd(II)-intermediate **9** looses a labile X group to give the cationic **10**. Coordination of an alkene delivers **11** which, after migratory insertion and recoordination of a ligand yields the cationic complex **12**. β-Hydride elimination provides the Heck product **7**.

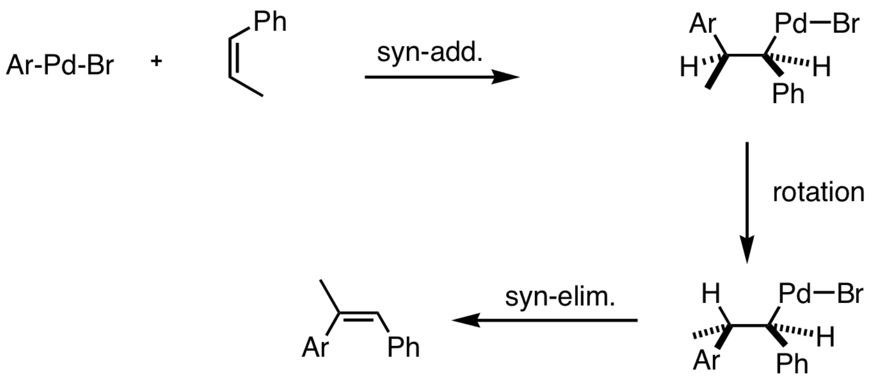


X = OTf or halide with a halide scavenger
L = PR_3 or solvent

A third mechanism was postulated by Amatore and Jutand, "Anionic Pd(0) and Pd(II) intermediates in palladium-catalyzed Heck and cross-coupling reactions." *Acc. Chem. Res.* **2000**, *33*, 314-321).

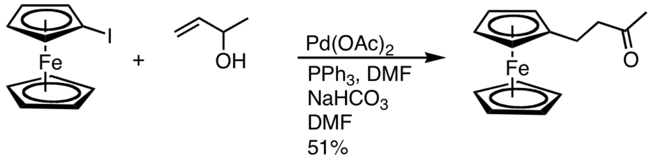


Stereochemistry:

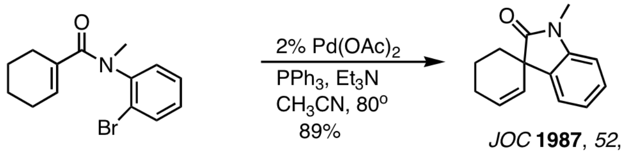


Regiochemistry:

- governed primarily by steric effects, with C-C- coupling occurring at the less-subst. C of the olefin.
- allylic alcohols prefer to undergo β-elim. in the direction of the hydroxy function → enol → ketone



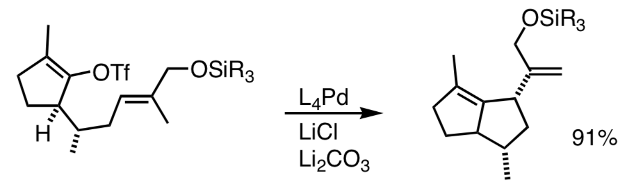
- intramolecular versions:



JOC **1987**, *52*, 4130

Chen, C.; Liebermann, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676. A bicyclic amine is necessary to resist oxidation to the imine.

triflates:



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

Huang, Q.; Larock, R. C., "Synthesis of isoquinolines by palladium-catalyzed cyclization, followed by a Heck reaction." *Tetrahedron Lett.* **2002**, *43*, 3557-3560.

CO Insertion

Yang, D.; Ye, X.-Y.; Xu, M., "Enantioselective total synthesis of (-)-triptolide, (-)-triptonide, (+)-triptophenolide, and (+)-triptquinonide." *J. Org. Chem.* **2000**, *65*, 2208-2217. An application of Crisp's method for the synthesis of γ-lactones from β-keto esters.

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:

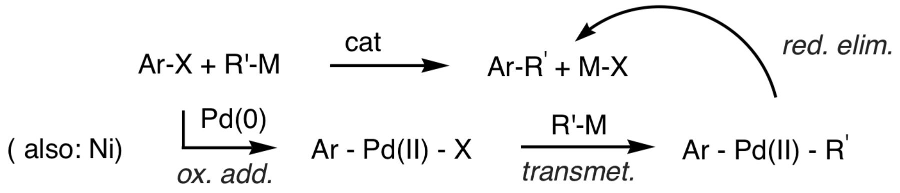
$$\text{R-X} + \text{R'-M} \xrightarrow{\text{Pd or Ni}} \text{R-R'}$$

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.

The significance of biaryl systems is high:

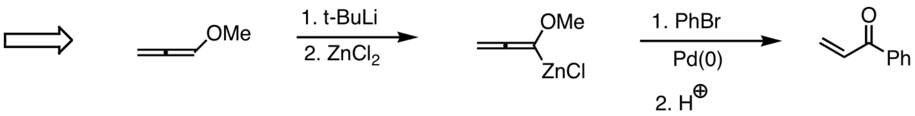


$$\mathrm{Ar\text{-}X + R'\text{-}M \xrightarrow{cat} Ar\text{-}R' + M\text{-}X}$$

(also: Ni) $\xrightarrow[\textit{ox. add.}]{\mathrm{Pd(0)}}$ Ar - Pd(II) - X $\xrightarrow[\textit{transmet.}]{\mathrm{R'\text{-}M}}$ Ar - Pd(II) - R'

red. elim.

M = Zn, Zr, B, Al, Sn, Si, Cu



New Mechanism (Amatore, C.; Jutand, A., "Anionic Pd(0) and Pd(II) intermediates in palladium-catalyzed Heck and cross-coupling reactions." *Acc. Chem. Res.* **2000**, *33*, 314-321.