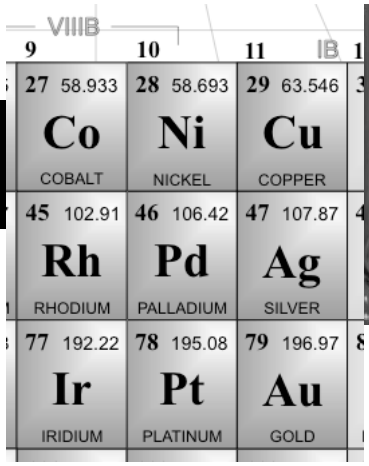
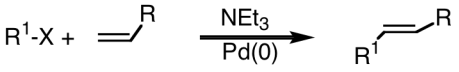
C. The Synthetic & Mechanistic Organic Chemistry of Palladium

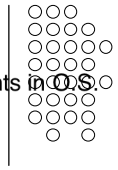


- Heck Reactions
- Stille, Suzuki, Negishi, Sonogashira *etc* Cross Couplings
- π-Allyl Palladium Chemistry
- Heteroatom Couplings
- Applications in Natural Product Synthesis

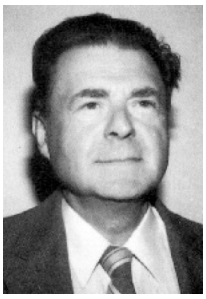
The Heck Reaction



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

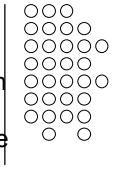


Herbert C. Brown Award for Creative Research in Synthetic Methods
(sponsored in part by Sigma-Aldrich since 1998).

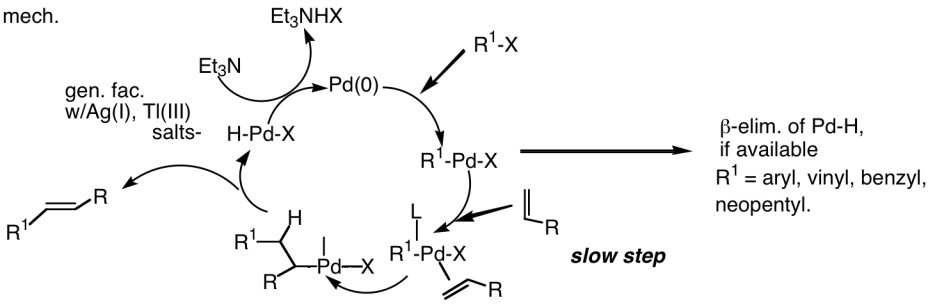
Richard F. Heck (retired) – University of Delaware (USA)

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.



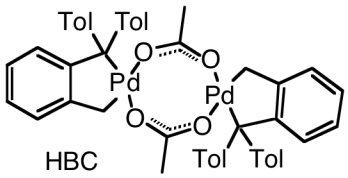
The optimal recipe for the catalyst mixture must be established independently for each reaction:

Pd(II), Pd(0) salts, $P(Aryl)_3$ / $As(Aryl)_3$
amine, solvent, temp. (100-140°C),
(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.

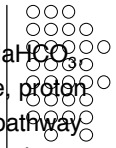
In most cases, 5-20 mol% catalyst is used, even though more stable catalysts such as the Herrmann-Beller palladacycle can be used at much lower loadings.



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.

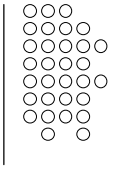
The Ligand. Among the phosphines used for the Heck reaction are PPh_3, P(*o*-tol)$_3$, P(furyl)$_3$, PCy_3, 2-(di-*t*-butylphosphanyl)-biphenyl, dppe, dppp, dppb, and dppf as well as $AsPh_3$. PCy_3 has been found effective for aromatic chlorides. Bidentate phosphines are used when monodentate ligands 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.

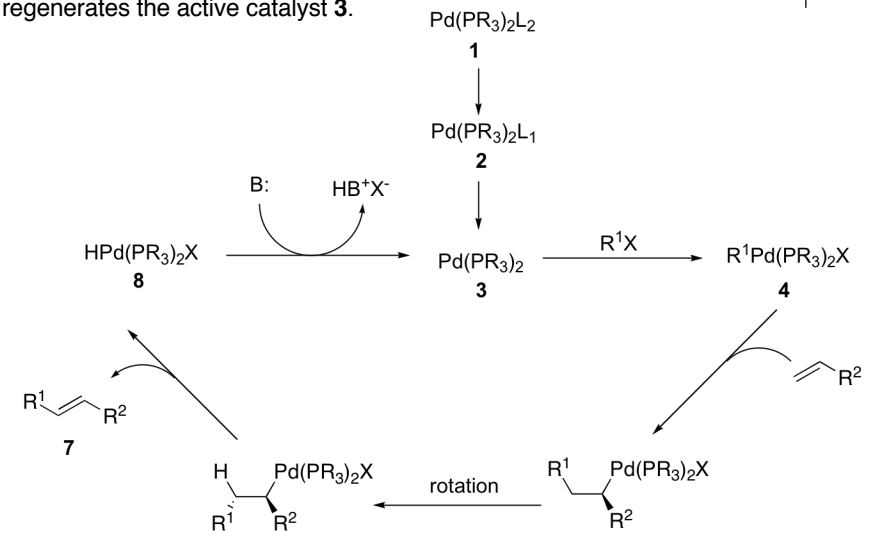
The Solvent. Common solvents for the Heck reaction are THF, DMF, NMP, DMAC, and MeCN. Toluene, benzene, EtOH, and water are also used, as are fluorous reaction conditions. Reaction temperatures vary between room temperature and reflux.



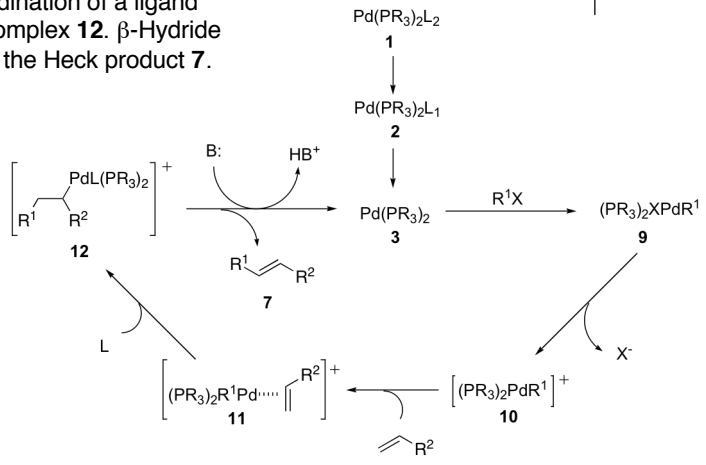
Useful user guidelines: Chapters 3 & 6 by de Meijere and Overman, respectively, in "Metal-catalyzed cross-coupling reactions", (Diederich & Stang, Eds.), VCH 1997.

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**.

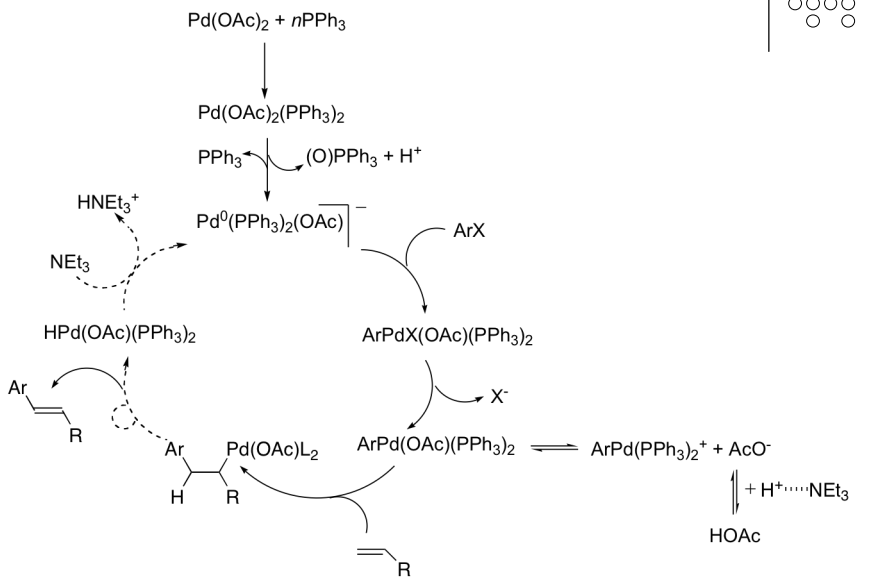


When the substrate is a triflate, or the reaction of halide substrates is carried out in the presence of halide scavengers, a cationic variant is followed. The Pd(II)-intermediate **9** looses a labile X group to give the cationic **10**. Coordination of an alkene delivers **11** which, after migratory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

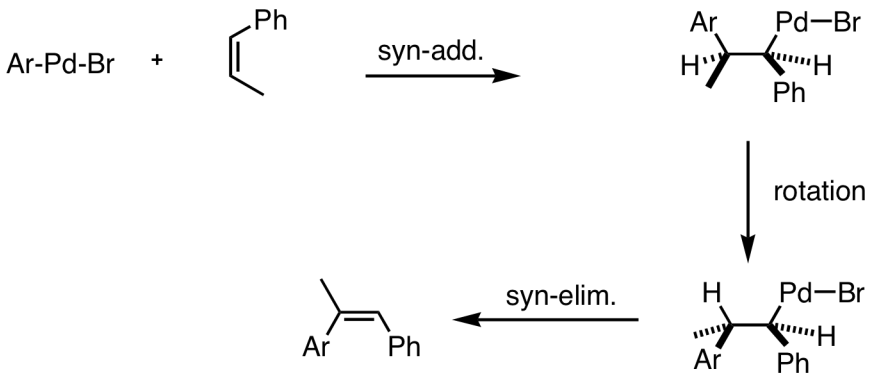


X = OTf or halide with a halide scavenger
L = PR_3 or solvent

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).

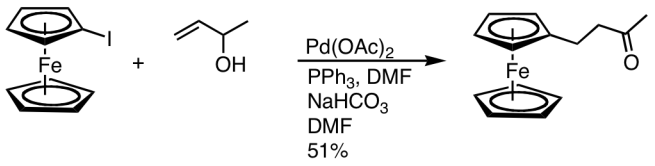


Stereochemistry:

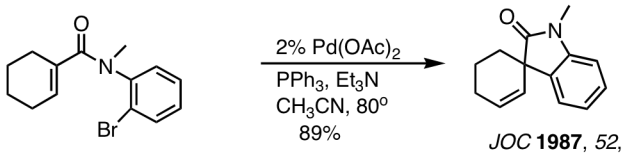


Regiochemistry:

- 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



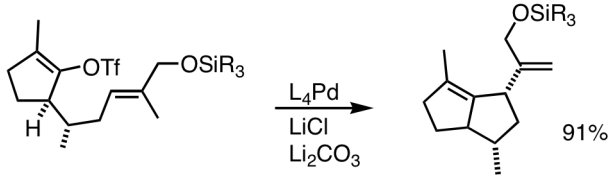
- intramolecular versions:



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:

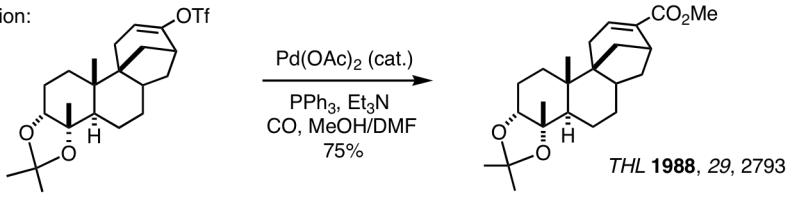


Acta. Chem. Scand. **1992**, *46*, 597

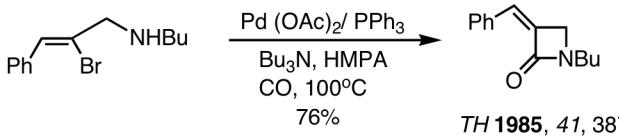
Collini, M. D.; Ellingboe, J. W., "The solid phase synthesis of tri-substituted indoles." *Tetrahedron Lett.* **1997**, *38*, 7963. This is a variant of the synthesis of indoles reported by Arcadi and Cacchi.

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

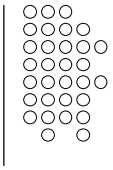
CO insertion:



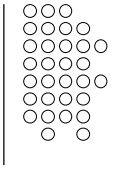
THL **1988**, *29*, 2793



TH **1985**, *41*, 387



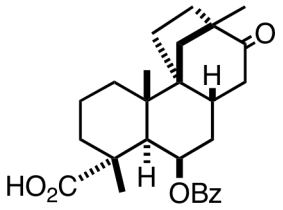
Yang, D.; Ye, X.-Y.; Xu, M., "Enantioselective total synthesis of (-)-triptolide, (-)-triptonide, (+)-triptophenolide, and (+)-triptquinonide." *J. Org. Chem.* **2000**, *65*, 2208-2217. An application of Crisp's method for the synthesis of γ-lactones from β-keto esters.



Overman, L. E.; Paone, D. V.; Stearns, B. A., "Direct stereo- and enantiocontrolled synthesis of vicinal stereogenic quaternary carbon centers. Total synthesis of *meso*- and (-)-chimoanthine and (+)-calycanthine." *J. Am. Chem. Soc.* **1999**, *121*, 7702-7703.

Scopadulcic Acid B

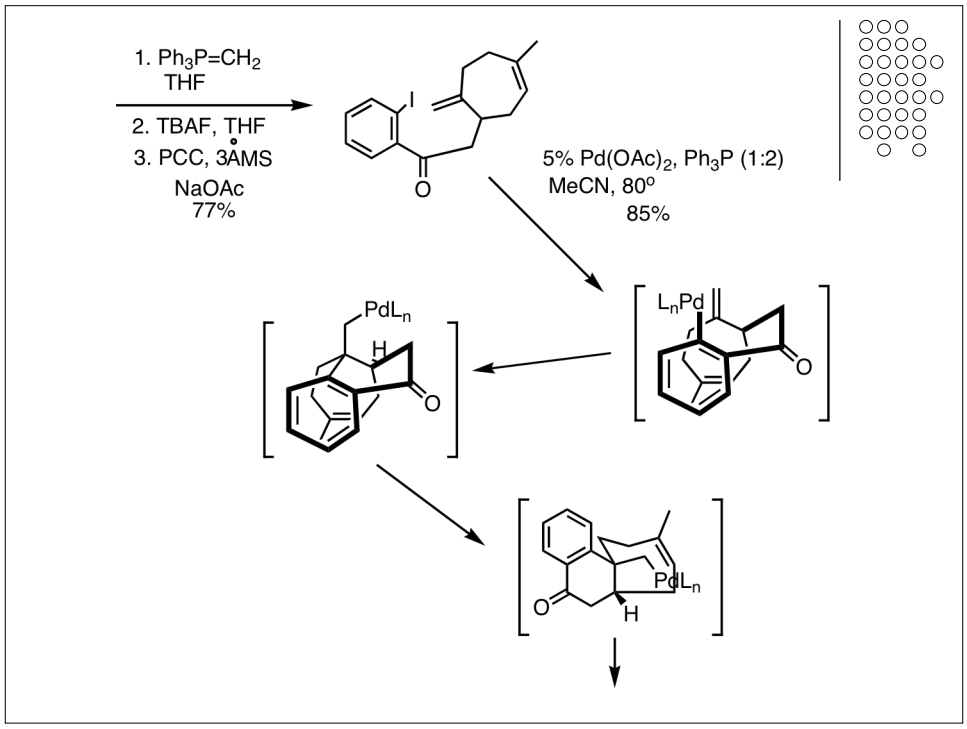
Overman, L. E.; Ricca, D. J.; Tran, V. D. "Total synthesis of (±)-scopadulcic acid B." *J. Am. Chem. Soc.* **1997**, *119*, 12031.

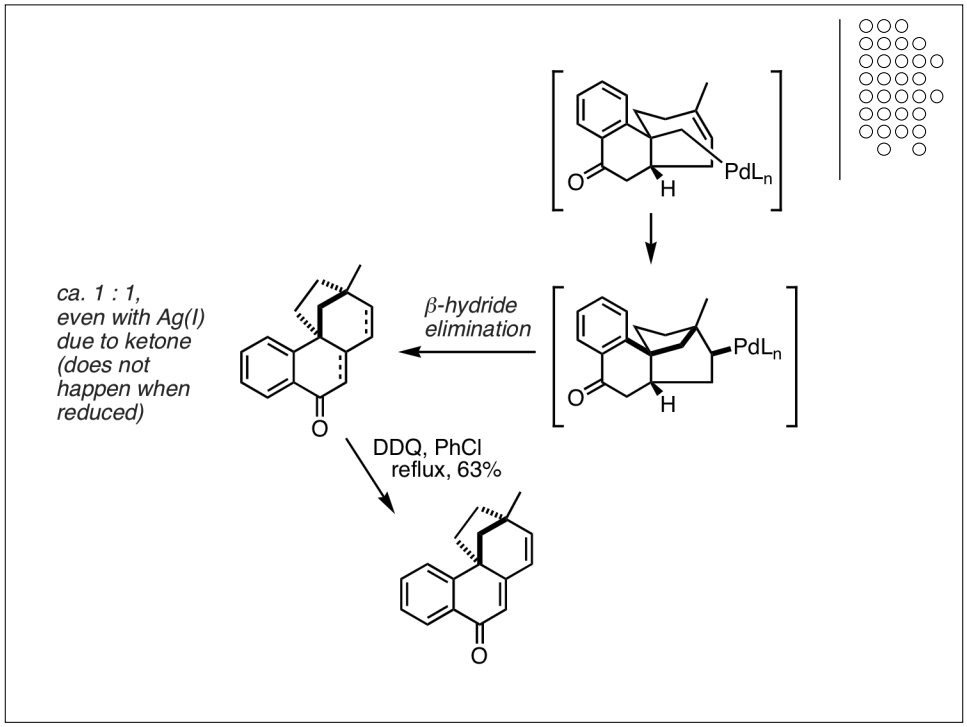


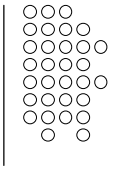
medical plant
Paraguay, India, Taiwan

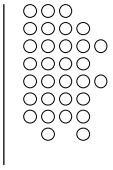
tetracylic diterpene

The widely distributed plant *Scoparia dulcis* L. has long been considered by native populations to posses medicinal properties. It is used to improve digestion and protect the stomach in Paraguay, as a cure for hypertension in Taiwan, and for treating toothaches and stomach disorders in India.


1. $Ph_3P=CH_2$
THF
2. TBAF, THF
3. PCC, 3Å MS
NaOAc
77%
I
O
5% $Pd(OAc)_2$, Ph_3P (1:2)
MeCN, 80°
85%
L_nPd
O
PdL_n
H
O
PdL_n
O
H


PdL_n
O
H
ca. 1 : 1,
even with Ag(I)
due to ketone
(does not
happen when
reduced)
β-hydride
elimination
PdL_n
O
H
O
DDQ, PhCl
reflux, 63%
O





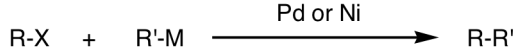
For modified A-ring strategy, see: Fox, M. E.; Marino, J. P.; Overman, L. E., "Enantiodivergent total syntheses of (+)- and (-)-scopadulcic acid A." *J. Am. Chem. Soc.* **1999**, *121*, 5467-5480.

Aminocarbonylation

Ham, W.-H.; Jung, Y. H.; Lee, K.; Oh, C.-Y.; Lee, K.-Y. *Tetrahedron Lett.* **1997**, *38*, 3247.

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

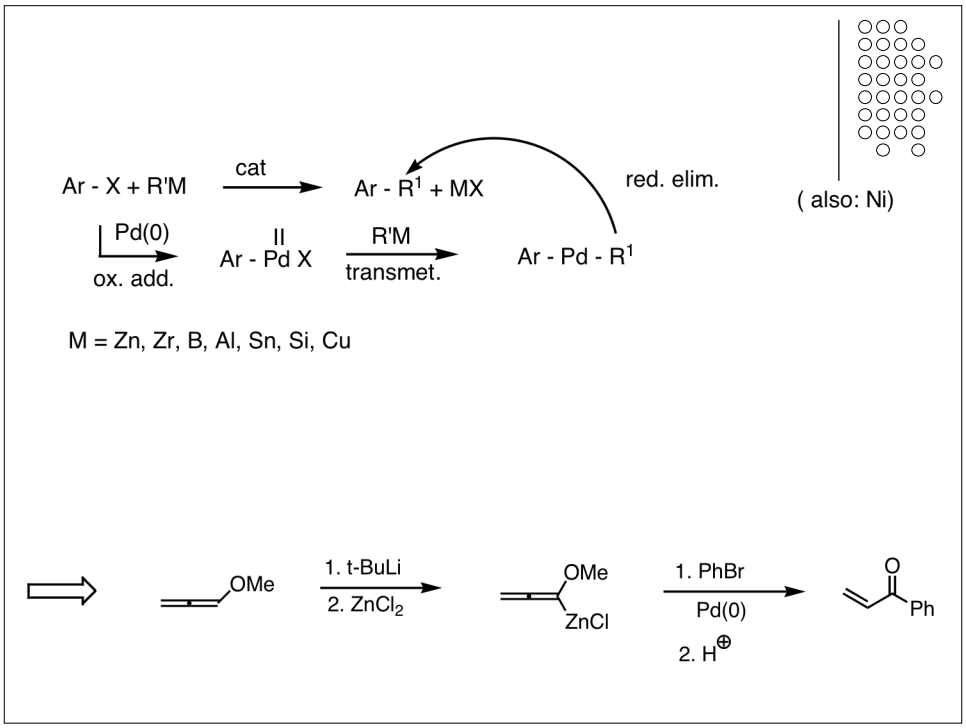
Cross-Coupling is the reaction of an organometallic reagent R'-M with an organic compound R-X to give a product R-R' and is often catalyzed by a transition metal:

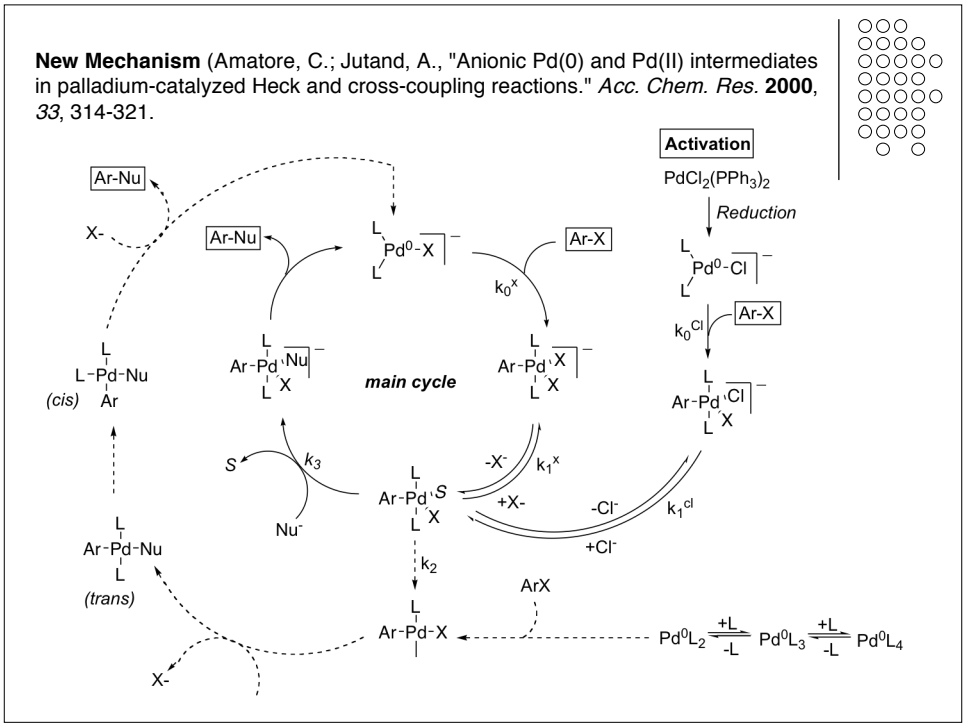


Since C,C-bond formations are among the most important transformations in organic synthesis, this process has received considerable attention.

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.

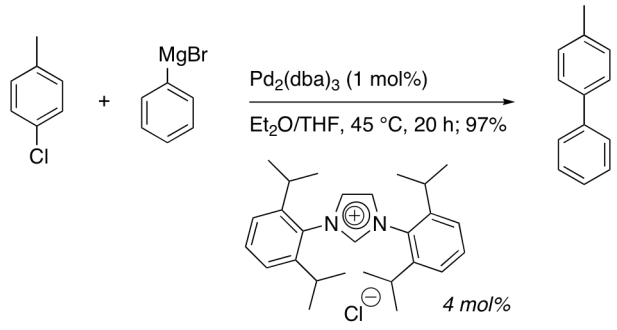
M = Li (Murahashi), Mg (Kumada-Tamao, Corriu, 1972), Zn (Negishi, Normant), B (Suzuki-Miyaura), Al (Nozaki-Oshima, Negishi), Zr (Negishi), Cu (Normant), Sn (Stille, Migita-Kosugi), Si (Hiyama, 1988, Tamao-Ito, 1989, DeShong, 1998, Denmark 1999). Others: Liebeskind, Fukuyama, etc.


Ar - X + R'M
cat
Ar - R1 + MX
red. elim.
(also: Ni)
Pd(0)
ox. add.
II
Ar - Pd X
R'M
transmet.
Ar - Pd - R1
M = Zn, Zr, B, Al, Sn, Si, Cu
OMe
1. t-BuLi
2. ZnCl2
OMe
ZnCl
1. PhBr
Pd(0)
2. H⊕
O
Ph

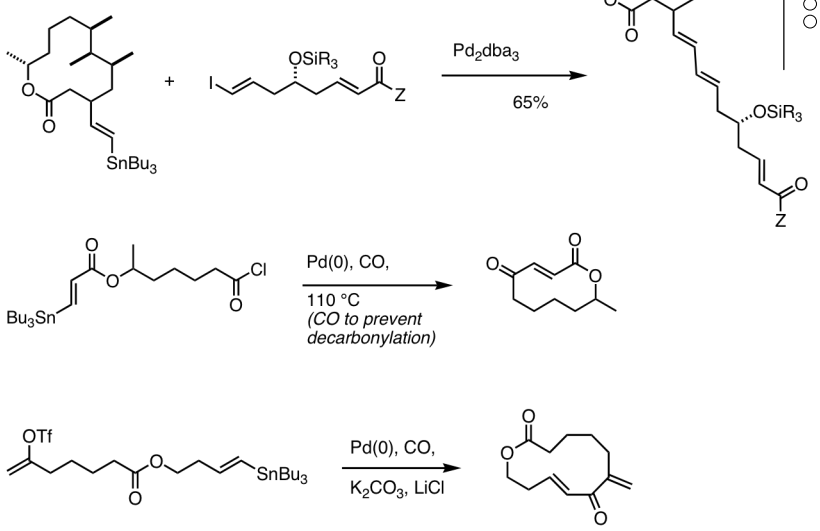

New Mechanism (Amatore, C.; Jutand, A., "Anionic Pd(0) and Pd(II) intermediates in palladium-catalyzed Heck and cross-coupling reactions." Acc. Chem. Res. 2000, 33, 314-321.
Activation
PdCl2(PPh3)2
Reduction
Ar-Nu
X-
Ar-Nu
Ar-X
k0x
Ar-X
k0Cl
main cycle
(cis)
(trans)
S
k3
Nu-
-X-
k1x
+X-
-Cl-
k1cl
+Cl-
k2
ArX
X-
Pd0L2
Pd0L3
Pd0L4
+L
-L

Kumada Coupling [Mg]

Huang, J.; Nolan, S. P., "Efficient cross-coupling or aryl chlorides with aryl Grignard reagents (Kumada reaction) mediated by a palladium/imidazolium chloride system." *J. Am. Chem. Soc.* **1999**, *121*, 9889-9890.

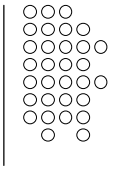


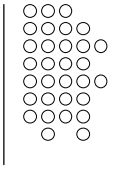
Stille Coupling [Sn]



JOC **1991**, *56*, 2883. *TH* **1992**, *48*, 2957. *Organometallics* **1991**, *10*, 1993.

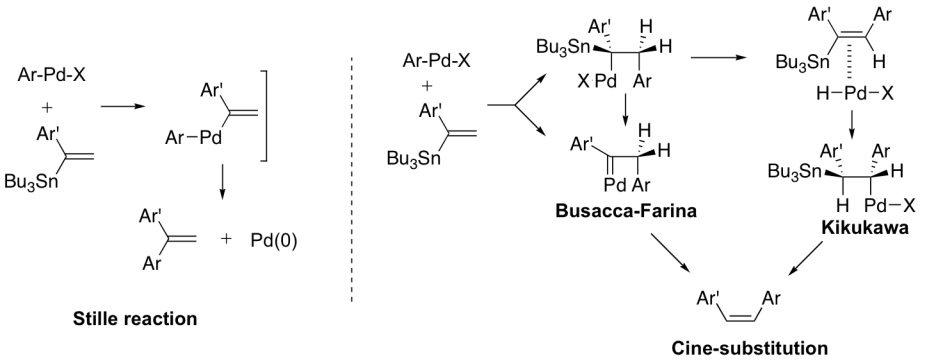
JACS **1984**, *106*, 7500: capnellene

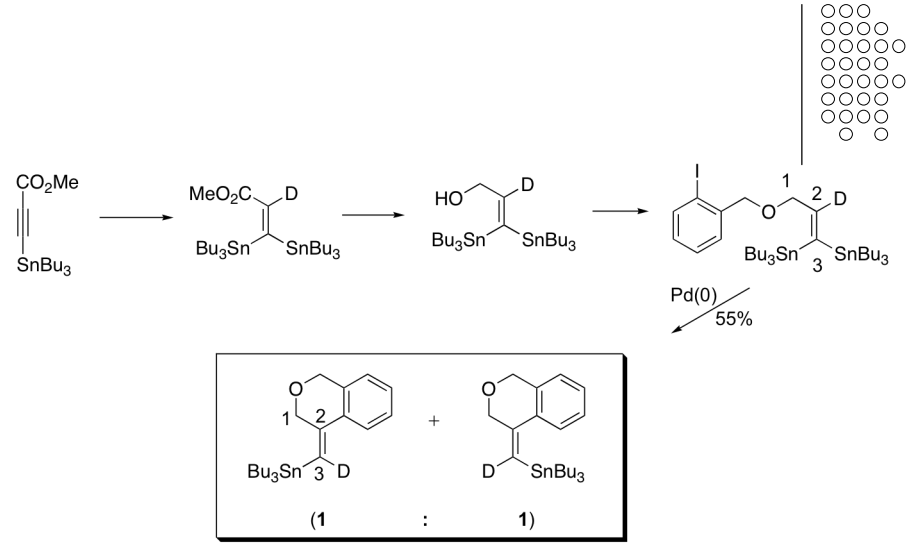




Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J., "The total synthesis of eleutherobin." *J. Am. Chem. Soc.* **1999**, *121*, 6563-6579.

Quayle, P.; Wang, J.; Xu, J.; Urch, C. J. *Tetrahedron Lett.* **1998**, *39*, 489.
Occasionally, as in the intramolecular coupling reactions of α-styryl tin derivatives, products of *cine* substitution are observed. The mechanism of this reaction has been the subject of some debate, although the intermediacy of palladium carbene complexes (Busacca-Farina pathway) now appears likely. Steric and electronic factors have been held responsible for this switch in mechanism.





The fact that cyclization proceeded without double bond isomerization or deuterium label scrambling is inconsistent with the hydridopalladium re-addition proposed by Kikukawa.

A major limitation of Stille coupling reactions arises from steric screening, especially in the vinyl stannane component. For example, with 1-substituted vinylstannanes and aryl perfluoroalkanesulfonates or halides, low yields are observed due to very slow reaction times and competing *cine* substitution. After initial observations by Piers et al., Liebeskind suggested the use of CuI or Cu(I)thiophene-2-carboxylate to alleviate this problem. Corey suggested that CuCl/LiCl is a more effective reaction condition:

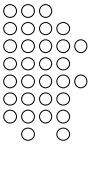
- Piers, E.; McEachern, E. J.; Burns, P. A., "Intramolecular Michael additions: Copper(I) chloride-mediated conjugate addition of vinyltrimethylstannane functions to α,β-unsaturated ketones." *J. Org. Chem.* **1995**, *60*, 2322.

- Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S., "On the nature of the "copper effect" in the Stille cross-coupling." *J. Org. Chem.* **1994**, *59*, 5905.

- Allred, G. D.; Liebeskind, L. S., "Copper-mediated cross-coupling of organostannanes with organic iodides at or below room temperature." *J. Am. Chem. Soc.* **1996**, *118*, 2748.

- Han, X.; Stoltz, B. M.; Corey, E. J., "Cuprous chloride accelerated Stille reactions. A general and effective coupling systems for sterically congested substrates and for enantioselective synthesis." *J. Am. Chem. Soc.* **1999**, *121*, 7600-7605. See also: Piers, E.; Gladstone, P. L.; Yee, J. G. K.; McEachern, E. J., "Intermolecular homocoupling of alkenyltrimethylstannane functions mediated by CuCl: Preparation of functionalized conjugated diene and tetraene systems." *Tetrahedron* **1998**, *54*, 10609.

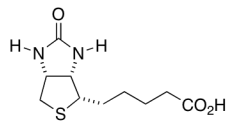
Negishi Coupling [Zn]



Tius, M. A.; Gomez-Galeno, J.; Gu, X.; Zaidi, J. H., "C-glycosylanthraquinone synthesis: Total synthesis of vineomycinone B2 methyl ester." *J. Am. Chem. Soc.* **1991**, *113*, 5775-5783.

Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558; Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157.

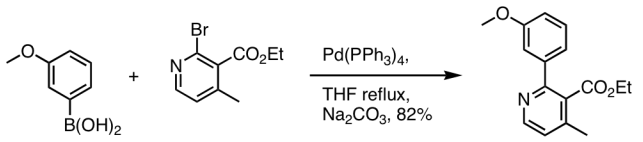
Mori, Y.; Seki, M., "Highly efficient phosphine-free $Pd(OAc)_2$-catalyzed Fukuyama coupling reaction: Synthesis of a key intermediate for (+)-biotin under low catalyst loading." *Synlett* **2005**, 2233-2235.

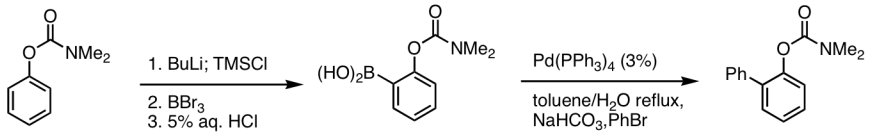


Biotin

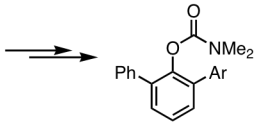
Suzuki Coupling [B]

esp. for biaryl couplings:

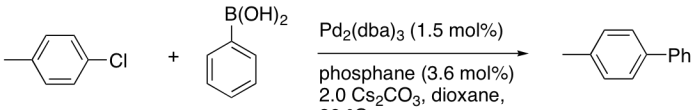




Snieckus, THL **1987**, 5093



Ligand selection: It is often crucial to optimize ligand selection by empirical screening of ligands and catalyst/ligand ratios:

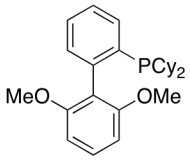


phosphane	yield (GC)
-	0%
PPh_3	0%
BINAP	0%
dppf	0%
P(*o*Tol)$_3$	10%
$Ph_2(CH_2)_3PPh_2$	0%
$Cy_2P(CH_2)_3PCy_2$	0%
PCy_3	75%
P*t*-Bu$_3$	86%

Angew. Chem. Int. Ed. ***1998****, 37, 3387*

For difficult substrates in the Suzuki coupling, it is useful to apply the following conditions:

K_3PO_4, n-BuOH as solvent for heterocycles, and



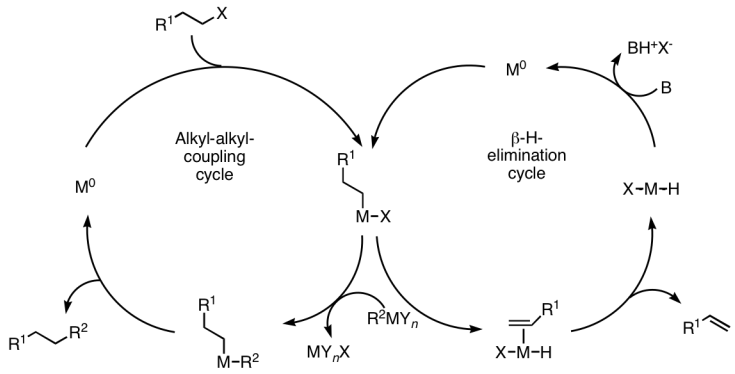
as ligand for sterically hindered substrates

Patil, P. A.; Snieckus, V. *THL* **1998**, *39*, 1325.

Review: Frisch, A. C.; Beller, M., "Catalysts for cross-coupling reactions with non-activated alkyl halides." *Angew. Chem., Int. Ed.* **2005**, *44*, 674-688.

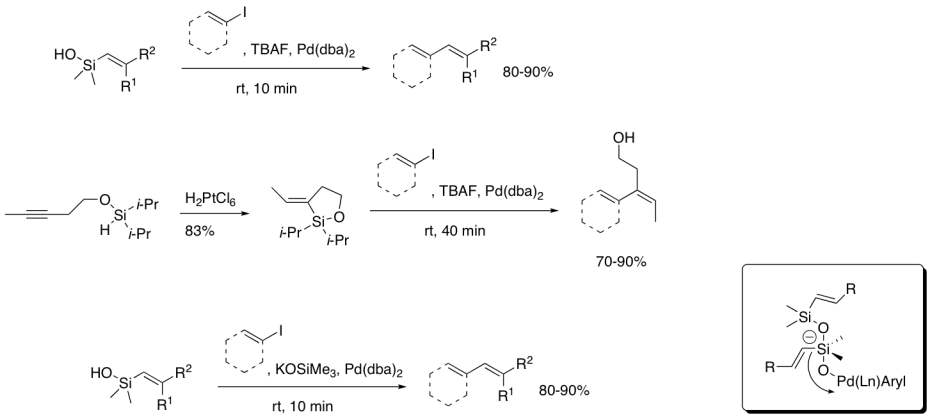
As the C(sp3)-X bond in alkyl halides is more electron rich than the C(sp2)-X bond in aryl and vinyl halides, the propensity of alkyl halides to undergo oxidative addition to a low-valent transition-metal complex (i.e. formal reduction of C(sp3)-X) is much lower than that of aryl and vinyl halides. The resulting alkyl–metal complex is highly reactive owing to the absence of stabilizing electronic interactions with the metal d-orbitals. The fast and thermodynamically favored β-hydride elimination leads to the predominant formation of olefinic by-products with most catalyst systems. The relatively slow reductive elimination of the cross-coupling product from the catalyst (aryl–aryl>aryl–alkyl>alkyl–alkyl) makes side reactions even more likely. Therefore, the design of new, more active catalyst systems and the development of suitable reaction conditions for cross coupling reactions of alkyl halides have generally been aimed at facilitating the oxidative-addition and reductive-elimination steps and preventing the competing β-hydride elimination.

Postulated mechanism of the alkyl–alkyl cross-coupling and the β-H elimination as a side reaction:



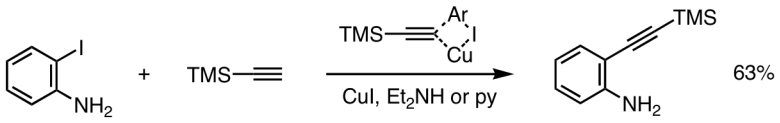
Organohalosilanes (Hiyama, Hatanaka) & Siloxanes (DeShong, Tamao, Shibata, Denmark):

Denmark, S. E.; Sweis, R. F., "Design and implementation of new, silicon-based, cross-coupling reactions: Importance of silicon-oxygen bonds." *Acc. Chem. Res.* **2002**, *35*, 835-846.

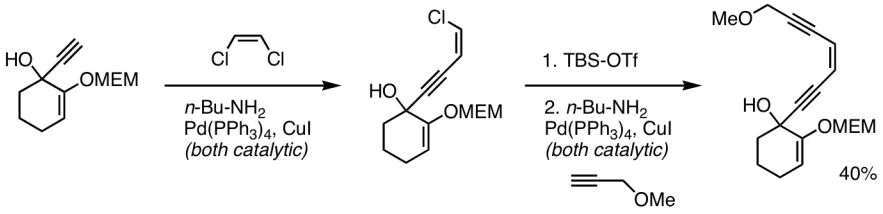


Related: sp^2 - sp Couplings:

Castro-Stevens, 1963

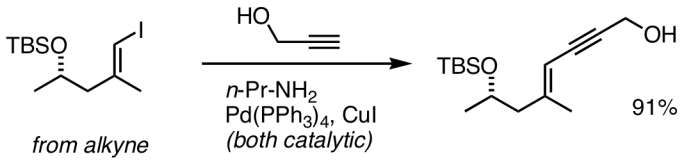


Calicheamicin/esperamicin studies:



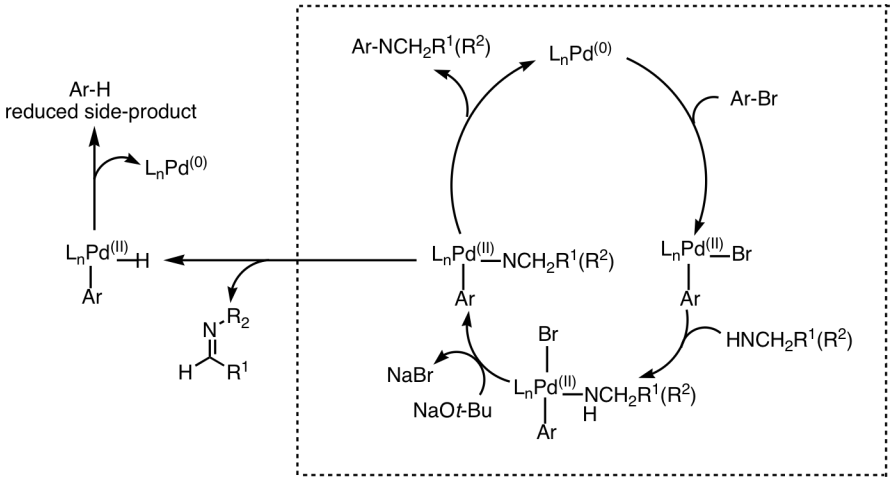
Sonogashira Coupling [Cu]

Over the past few decades, the Pd-catalyzed alkynylation 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 alkynylation. *Chem. Rev.* **2003***, 103*, 1979-2017.

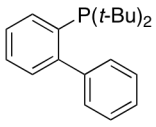


Amination [N]

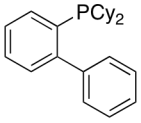
Recent advances in the palladium-catalyzed amination of aryl halides offer considerable advantages for aniline formation over the classical methods, which require either activated substrates or severe reaction conditions.



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

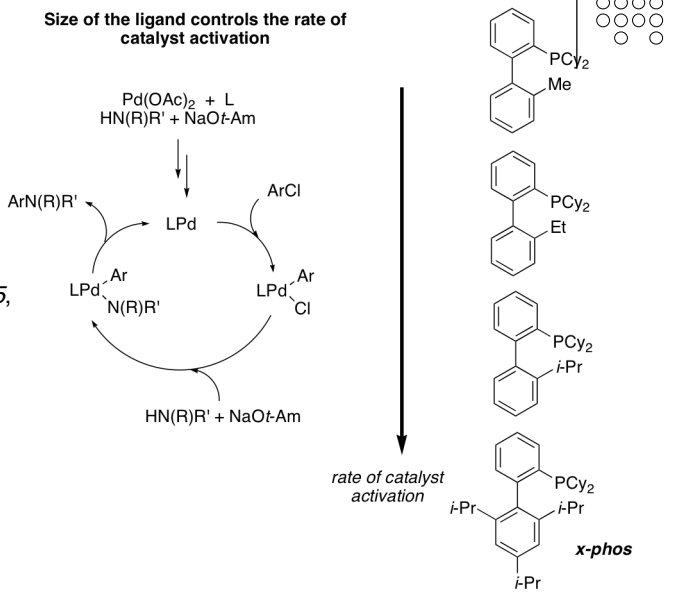


often the optimal ligand for amination of aryl bromides and aryl chlorides



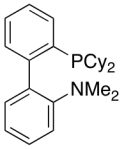
often the optimal ligand for amination of aryl iodides

Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. Insights into the origin of high activity and stability of catalysts derived from bulky, electron-rich monophosphinobiaryl ligands in the Pd-catalyzed C-N bond formation. *J. Am. Chem. Soc.* **2003**, *125*, 13978-13980.



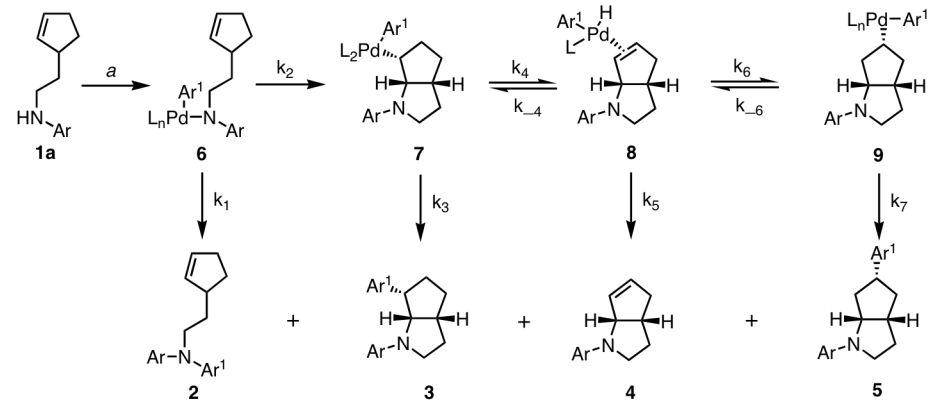
X-Phos prevents the formation of palladcycle resting states, and so turns out to be overall the more active catalyst. In addition, its large size and cone angle of 250-280° leads to a L_1Pd (1:1) complex, a more active species than L_2Pd complexes. Finally, this ligands binds to Pd in a four-membered complex through the phosphine atom and an *ipso*-interaction.

Another complex that works well for amination is the bidentate aniline complex:



Ney, J. E.; Wolfe, J. P., "Selective synthesis of 5- or 6-aryl octahydrocyclopenta[*b*]pyrroles from a common precursor through control of competing pathways in a Pd-catalyzed reaction." *J. Am. Chem. Soc.* **2005**, *127*, 8644-8651.

A significant challenge in the development of metal-catalyzed reactions is the suppression of competing mechanistic pathways without inhibiting desired steps in a catalytic cycle. In recent years, several remarkable transformations have been effected through the use of palladium catalysts that minimize side reactions (e.g., -hydride elimination) while still allowing reductive elimination or transmetalation processes to occur. Despite these achievements, the factors that affect the relative rates of competing mechanistic pathways in catalytic reactions (e.g., reductive elimination versus olefin insertion, or C-C versus C-N bond-forming reductive elimination) are not well understood. If these fundamental processes could be controlled, the selective construction of a diverse array of products from common starting materials could be achieved under similar reaction conditions by varying catalyst structure.



[a]Conditions: 1.0 equiv of **1a**, 1.2 equiv of 4-Ph(C_6H_4)Br, 1.4 equiv of NaO*t*Bu, 1 mol % $Pd_2(dba)_3$, 4 mol % P(*o*-tol)$_3$, toluene, 110 °C. Isolated yield: **2** (19%), **3** (32%), **4** (5%), **5** (12%) for Ar = 4-methoxyphenyl, Ar^1 = 4-(phenyl)phenyl.