Insertion Reactions

The Pd(II) species formed via oxidative addition can be engaged into other reactions not involving transmetallation. Migratory insertion reactions are very common. These can involve olefins, alkynes, and CO. Cascade reactions in which multiple insertion reactions take place are also possible. Depending on how the sequence is devised, the reaction can be terminated by either reductive elimination or β-hydride elimination.
**Carbonylation Reactions Of Carbon Electrophiles**

In contrast to acylrhodium intermediates, acylpalladium (and nickel) intermediates are reasonably stable at low pressures of CO (1 atm). They can also be formed directly from acid chlorides.

By running the carbonylation in the presence of an alcohol or amine, esters or amides can be formed.

\[
R^1 - X \xrightarrow{PdL_n} R^1-Pd-L_n + CO \rightarrow R^1-Pd-L_n \rightarrow R^1-Pd-L_n - Pd(0) \rightarrow R^1-OR + HX
\]

\[R = \text{alkene, arene, allyl} \]
\[X = \text{Br, I, OTf, etc.} \]

Alkenyl triflates are some of the more common substrates as they can be easily made from ketones.

Final trapping can also be intramolecular

Acyl metal intermediate can undergo insertions by alkenes/alkynes

Carbonylation Reactions

1. MeLi, THF
   then PhN(SO$_2$CF$_3$)$_2$
   94%

2. 5% Pd(OAc)$_2$, 6% dppf
   Bu$_3$N, CO (1 atm)
   DMF, MeOH, 90ºC
   99%

from Robinson annulation
and Li/NH$_3$ reduction


2% PdCl$_2$(PPh$_3$)$_2$
K$_2$CO$_3$, CO (4 atm)
DMF, 50 ºC
78%

Performing the carbonylation at higher pressures (3+ atm) in the presence of Bu$_3$SnH or slow addition of the tin hydride will form the aldehyde.

\[
\text{Me}_{\text{OTf}} \xrightarrow{\text{Pd(PPh$_3$)$_4$ CO, Bu$_3$SnH}} \text{MeCHO} \quad 53\% \ (89\% \ GC)
\]

\[
\text{Br} \quad \text{I} \quad \text{Br} \quad \text{I} \quad \text{OH} \quad \text{OH} \quad \text{CHO} \quad \text{CHO}
\]

\[
\text{Br} \quad \text{I} \quad \text{OH} \quad \text{OH} \quad \text{CHO} \quad \text{CHO}
\]

\[1.2\% \text{PdCl}_2(\text{PPh}_3)_2 \]
\[3.2\% \text{PPh}_3, \text{Bu}_3\text{N} \]
\[\text{CO (200 psi)} \]
\[10:1 \text{DMF/H}_2\text{O}, 100 \degree \text{C} \]
\[70–75\% \text{ after recryst.} \]
Heck Reactions


In general terms, the Heck (or Mizoroki-Heck) reaction involves an oxidative addition followed by insertion into an alkene. The reaction is terminated by a $\beta$-hydride elimination to "regenerate" the olefin.

In principle any halide or pseudohalide electrophile can be used, except those with $\beta$-hydrides.

$$R^1 - X + \text{Z} \xrightarrow{\text{PdL}_n \text{base}} R^1\text{=Z}$$

$R^1 = $ alkene, arene, allyl

$X = $ Br, I, OTf, etc.

Phosphines required with aryl bromides, but hinder reactions with iodides. Typically amines bases are used. Originally, high reaction temps were required. The insertion step is thought to be the difficult step.

So-called "Jeffery conditions" have become quite popular as they allow lower reaction temperatures to be used. These conditions involve ligandless Pd(OAc)$_2$ with polar solvents (e.g., DMF, NMP) and tetraalkylammonium salts (usually Bu$_4$NCl or Bu$_4$NBr), often with carbonate bases. There is evidence that Pd nanoparticles are formed and are stabilized by the anions (*Angew. Chem. Int. Ed.* **2000**, *39*, 165.). Chloride anions also help promote oxidative addition processes (*J. Am. Chem. Soc.* **1991**, *113*, 8375.).


Wide range of olefins can be employed: cyclic and acyclic, electron-deficient (esters, amides, ketones, nitriles, aldehydes), unactivated, electron-rich (enol ethers).

The insertion proceeds with *syn*-addition of R group and metal. BHE is a cis process as well.
**Heck Reactions**

Electron-poor and unactivated are sterically controlled and place R-group on less-substituted position.


![J. Am. Chem. Soc. 1998, 120, 7133.](image)


![J. Org. Chem. 2000, 65, 7990.](image)

Heck Reactions


![Chemical structures and reactions](image-url)
**Heck Reactions**

Use of allylic alcohols gives aldehyde or ketone via $\beta$-hydride elimination toward alcohol.

![Chemical structure 1]


![Chemical structure 2]


$\beta$-alkoxide (or hydroxide) eliminations can occur if BHE cannot.

![Chemical structure 3]

Heck Reactions

Intramolecular Heck reactions work especially well and many examples exist. Regioselectivity is usually high, but mode of addition (exo vs endo) is less predictable. In general, 5-exo and 6-eso are favored.

![Chemical structures and reaction conditions]


Asymmetric Heck Reactions

Many olefins are prochiral. By including chiral ligands, Heck reactions can, in principle, be used to generate new stereocenters. In order for this to occur, the β-hydride elimination must occur away from the newly formed stereocenter. This restricts substrates to cyclic olefins or the formation of quaternary stereocenters.

**cyclic substrates**

$$\begin{align*}
\text{Ar} \quad \text{Pd} \quad X \\
H_A & \quad H_B & \quad H_C \\
\text{syn-palladation} \\
\end{align*}$$

**acyclic substrates** – mixtures likely

$$\begin{align*}
\text{Ar} \quad \text{Pd} \quad X \\
H_A & \quad H_B & \quad H_C \\
\text{syn-palladation} \\
\end{align*}$$
Asymmetric Heck Reactions

1. 10% Pd$_2$(dba)$_3$
   23% (S)-BINAP
   PMP, DMAC, 100 ºC

2. 3N HCl
   84% yield, 95% ee


O

O

TfO

O

O

TfO

+ TfO

3% Pd$_2$(dba)$_3$
6% t-BuPHOX

DIPEA, THF

70 ºC

70% yield, 92% ee


BocNH

OTf

CO$_2$Me

BocNH

CO$_2$Me

10% Pd(OAc)$_2$, t-BuPHOX

PMP, toluene, 170 ºC, µw

75-87% yield, 99% ee

"Aromatic" Heck Reactions

"Insertions" can also occur with electron-rich (or neutral) aromatic groups. Two mechanisms are possible, likely due to electronics of aromatic partner. Calculations have supported both.

"metathesis" mechanism – neutral aromatics

\[ \text{I} \quad \text{Pd(OAc)}_2, \text{PCy}_3\cdot\text{HBF}_4 \quad \text{K}_2\text{CO}_3, \text{AgCO}_3 \quad 81\% \]

\[ \text{J. Am. Chem. Soc. 2006, 128, 581.} \]

electrophilic addition – electron-rich aromatics

\[ \text{MeO} \quad \text{MeO} \quad \text{OTf} \quad \text{O} \quad \text{Me} \quad \text{O} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \]

\[ \text{Pd(PPh}_3\text{)}_4 \quad \text{DMA, DIPEA} \quad 70\% \]

\[ \text{Angew. Chem. Int. Ed. 2002, 41, 1569.} \]
Reductive Heck Reactions

If the insertion is set up such that $\beta$-hydride elimination is not possible, the $\sigma$-alkyl palladium intermediate can be intercepted by other processes. If carried out in the presence of formic acid or ammonium formate, a "reductive Heck" reaction will take place. This is most common with bicyclic olefins.

\[
\text{I} + \text{Br} \quad \text{1 mol$\%$ PdCl$_2$(PPh$_3$)$_2$} \\
\text{Et$_3$N, HCO$_2$H, DMF, 50$\degree$C} \\
\rightarrow \quad \text{Br} \\
\text{91\% (5.5 g)}
\]


\[
\text{Me,} \quad \text{I} \\
\text{Pd(OAc)$_2$, KO$_2$CH} \\
\text{Bu$_4$NBr} \\
\text{DMF, rt} \\
\rightarrow \quad \text{Me} \\
\text{79\%}
\]

Cascade reactions are also possible. In these cases, several alkene/alkyne insertions take place with a polyunsaturated substrate. Excellent strategy for constructing polycyclic products. Incorporating CO is also possible, but high pressures required to suppress β-hydride elimination.

**Chemical Reaction:***

\[ \text{MeO} \quad \text{Me} \quad \text{MeO} \quad \text{OTf} \quad \text{Me} \quad \text{Me} \quad \text{MeO} \]

\[ \text{Pd}_2(\text{dba})_3, (S)-\text{BINAP} \quad \text{toluene, base, 110 °C} \]

\[ 82\% \text{ yield, 68\% ee} \]

\[ \text{MeO} \quad \text{Me} \quad \text{Me} \quad \text{Me} \]

\[ \text{J. Am. Chem. Soc. 1996, 118, 10766.} \]
Cascade Reactions

**Tetrahedron Lett. 1996, 37, 59.**

**Angew. Chem. Int. Ed. 1996, 35, 2125.**

**J. Am. Chem. Soc. 1990, 112, 8590.**

4 rings, 4 C–C bonds
1 new stereocenter