Chapter 3

The Catalytic Chemistry of Palladium (0)

Pd(0) → Pd(II) → Pd(0)
Generation of Pd(0) from Pd(II)

Amines

\[ \text{[Pd(II)]X}_2 \xrightarrow{:\text{NET}_3} \text{[Pd(II)]X} \xrightarrow{\text{dehydropalladation}} \text{H[Pd(II)]X} \xrightarrow{\text{reductive elimination}} \text{[Pd(0)]} \]

Alkenes

\[ \text{[Pd(II)]X}_2 \xrightarrow{\pi\text{-coordination}} \text{H}_2\text{C}=\text{CH}_2 \xrightarrow{\text{halopalladation}} \text{X[Pd]} \xrightarrow{\text{dehydropallad.}} \text{H[Pd(II)]X} \xrightarrow{} \text{[Pd(0)] + XH} \]

Organometallics

\[ \text{[Pd(II)]X}_2 \xrightarrow{2 \text{n-BuLi}} \xrightarrow{2 \text{LiX}} \text{[Pd]—Bu-n} \xrightarrow{\text{Bu-Bu}} \text{[Pd(0)]} \]
Generation of Pd(0) from Pd(II)

Phosphines

\[ \text{Pd(OAc)}_2 + 4 \text{PPh}_3 + \text{H}_2\text{O} \rightarrow (\text{PPh}_3)_3\text{Pd} + \text{O=PPh}_3 + 2\text{AcOH} \]


Amatore, C.; Carre, E. Jutand, A.; M’Barke, M.A. *Organometallics*, **1995**, **14**, *1818*
Palladium (0) Sources

- \( \text{PdCl}_2(\text{PPh}_3)_2 \):
  - Dibal, 2 PPh₃
  - or
  - NH₂NH₂, H₂O, 2 PPh₃

- \( \text{Pd}^{(0)} \):
  - \( \text{PR}_3 / \text{CO} / \text{ROH} \)
  - \( \text{NR}_3 / \text{H}_2\text{C}=\text{CH}_2 / \text{RM} \)

- \( \text{Pd(OAc)}_2 \):
  - \( \text{O}_2 \text{ (air)} \)
  - \( \text{(Ph}_3\text{P)}_2\text{PdO}_2 \)

- \( \text{K}_2\text{PdCl}_4 \):
  - \( \text{K}_2\text{PdCl}_4 \)

- \( \text{Na}_2\text{PdCl}_4 \):

- \( \text{PdCl}_2 \):
  - NaOAc / MeOH reflux

- \( \text{db}a \):
  - \( \text{Ph} \equiv \text{C} \equiv \text{Ph} \)

- \( \text{PPh}_3 \):
  - \( \text{PPh}_3 \text{[H]} \)

- \( \text{Pd}^{(0)} \):
  - \( \text{PPh}_3 \text{K}_2\text{PdCl}_4 \)

- \( \text{Pd}^{(0)} \):
  - \( \text{Pd}^{(0)} \text{(dba)} \)

- \( \text{PPh}_3 \text{K}_2\text{PdCl}_4 \):
  - crystall.
  - CHCl₃
  - \( \text{Pd}^{(0)} \text{CHCl}_3 \)

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Pd$_2$(dba)$_3$ and Pd(dba)$_3$

In Pd(dba)$_3$ each dba has one s-cis and one s-trans configured double bond.
Pd is almost in a planar geometry
Only the s-trans double bonds are involved in complexation to Pd
The Catalytic Chemistry of Palladium: an Overview

Reduction Potential \( Pd(II) + 2e^- \rightarrow Pd(0) : 0.951V \)

- **entering the cycle**: entering the cycle is indicated by green lines.
- **exiting the cycle**: exiting the cycle is indicated by red lines.
- **in the cycle**: reactions occurring within the cycle are indicated by black lines.

**Reactions:**

1. **Oxidative Addition**
2. **Transmetallation**
3. **Reductive Elimination**
4. **Dehydropalladation** (β-H elimination)
5. **Insertion**
6. **CO Insertion**
7. **Nu Addition**

**Color Code:**
- Green: entering the cycle
- Red: exiting the cycle
- Black: in the cycle

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Syn Carbopalladations:
The Mizoroki-Heck Reaction
Arylation of Olefin with Aryl Iodide Catalyzed by Palladium

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(Received October 20, 1970)

The arylation of olefin with aromatic hydrocarbon\(^1\) or arylmercuric compound\(^2\) by the reaction with palladium(II) compound has been reported, where the reaction consumes almost stoichiometric amount of the palladium(II) compound, forming metallic palladium. In this communication we wish to report that the arylation of olefin with iodobenzene in the presence of a catalytic amount of palladium(II) dichloride takes place smoothly when potassium acetate is added as an acceptor of hydrogen iodide formed. A characteristic feature of this reaction is that the arylation of olefin is effectively catalyzed by palladium or palladium(II) compounds without accompanying polymerization of the corresponding styrene derivatives formed, as long as the amount of potassium acetate added is greater than that of iodobenzene used. The reaction can be represented as follows:

\[
\begin{align*}
C_6H_5I + CH_2=CHX + CH_3COOK & \rightarrow C_6H_5CH=CHX + CH_3COOH + KI \\
& (X = H, C_6H_5, CH_3, and COOCH_3)
\end{align*}
\]

As shown in Table 1, metallic palladium has also high catalytic activity for the arylation of olefin (No. 5). This differs considerably from the stoichiometric arylation of olefin with palladium(II) compounds. Pyridine, triethylamine, or potassium benzoate was also used as the acceptor of hydrogen iodide formed, potassium acetate being the most effective. Ethylene, propylene, styrene, and methyl acrylate were used as olefin. The corresponding styrene derivatives (styrene, \(\alpha\)-or \(\beta\)-methylstyrreine, trans-stilbene and methyl cinnamate, respectively) were produced in high yields. The results are summarized in Table 1.

The experimental procedure is illustrated by the arylation of ethylene with iodobenzene. Iodobenzene (50 mmol), potassium acetate (60 mmol), palladium dichloride (0.5 mmol), and methanol (1.0 mol) were placed in a titanium-alloy autoclave (100 ml) equipped with a magnetic stirrer. The gas phase in the autoclave was displaced by nitrogen stream, and ethylene from commercial sources was then introduced up to
Palladium-Catalyzed Vinylic Hydrogen Substitution Reactions with Aryl, Benzyl, and Styryl Halides

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Received January 13, 1972

Aryl, benzyl, and styryl halides react with olefinic compounds in the presence of a hindered amine and a catalytic amount of palladium metal to form vinylic derivatives in which the aryl, benzyl, or styryl group has replaced a vinylic hydrogen of the original olefin. The reactions occur readily at 100° and yields are generally good.

Mizoroki and coworkers have recently reported a palladium-catalyzed arylation reaction of olefinic compounds with aryl iodides and potassium acetate in methanol at 120°. We have independently discovered this reaction and find that it can be carried out under much more convenient laboratory conditions than were used by Mizoroki and that the reaction provides an extremely convenient method for preparing a variety of olefinic compounds.

very useful, they suffer from two major difficulties. There is often a problem of obtaining the necessary organomercury, -lead, or -tin compounds and there is the problem of working with thick slurries of salts, particularly if the reaction is carried out catalytically in palladium. This new method eliminates both difficulties.

Results and Discussion
The Mizoroki-Heck Reaction

\[
\begin{align*}
\text{aryl, vinyl, benzyl (no } \beta\text{- sp}^3 \text{ H, otherwise: dehydropalladation !)} \\
X: & \quad \text{N}_2\text{BF}_4, \text{COCl, I, OTf, Br, Cl} \\
R: & \quad \text{an alkene (neutral, rich, or poor)} \\
Pd \text{ cat:} & \quad \text{a Pd(0) cat. or a Pd(II) cat. which is reduced in situ to Pd(0)} \\
\text{base:} & \quad \text{usually: NEt}_3, \text{AcOK, Na}_2\text{CO}_3...
\end{align*}
\]

In difficult cases electron-rich and bulky phosphines perform better. Electron richness is expected to favor oxidative addition (with these phosphines the very difficult oxidative addition to aryl chlorides is possible). Bulkiness is expected to favor the reductive elimination (in the cross-coupling reactions). Very reactive iodides, diazonium salts and acyl chlorides can be used without ligands. N-heterocyclic carbenes are known to mimic phosphines. They are very good σ-donors.
Reviews dealing with ligands in cross-couplings and Heck reactions:
The Ligandless Conditions

Very reactive iodides, diazonium salts and acyl chlorides can be used without ligands.

The system KHCO$_3$ / Bu$_4$NCl in DMF without ligands is very effective. Under these conditions,\textsuperscript{1} known as the Jeffery’s ligandless conditions, R$_4$N$^+$X$^-$-stabilized Pd colloids are formed and function as active catalysts.\textsuperscript{2}

\textsuperscript{1} Jeffery, T. \textit{Tetrahedron}, 1996, 52, 10113.

The Mechanism of the Mizoroki-Heck Reaction

\[
Pd(OAc)_2 + 2 \text{PPh}_3 \rightarrow Pd(OAc)_2(\text{PPh}_3)_2
\]

\[
PPh_3 + H_2O + \text{NEt}_3 \rightarrow Ph_3P=O + \text{AcOH}
\]

\[
[Pd^{(0)}(\text{PPh}_3)_2(OAc)] + \text{NEt}_3 \rightarrow [Pd(\text{PPh}_3)_2](\text{OAc}) + \text{HNEt}_3
\]

\[
[ArPd(OAc)(\text{PPh}_3)_2] + 16 \text{e}^- \rightarrow [ArPd(\text{PPh}_3)_2]^{+}\text{AcO}^-
\]

\[
[ArPd(\text{PPh}_3)_2] + 14 \text{e}^- \rightarrow [ArPd(\text{PPh}_3)_2]^{+}\text{AcO}^-
\]

Halides and Pseudohalides

The diazonium salts are very conveniently obtained from the corresponding anilines (via diazotation), which in turn may derive from the nitro derivatives. The diazonium salts are the most reactive reaction partners.


Order of reactivity in the oxidative addition: \(N_2 >> I >> OTf > Br >> Cl\)

Halides and Pseudohalides

Iodides react smoothly even in the absence of a ligand, and bromides in the presence or the absence of a phosphine ligand. Chlorides react only in the presence of bulky electron-rich phosphines.


These reactions condition do not racemize aminoacid derivatives.

Triflates are conveniently obtained from the corresponding ketones or phenols.

Crisp, G. T. Tetrahedron, 1992, 48, 3541
Regioselectivity of the Mizoroki-Heck

\[ \text{more reactive alkenes} \quad \rightarrow \quad \text{less reactive alkenes} \]


Allylic Alcohols as Alkenes

When allylic alcohols are used as alkenes dehydropalladation occurs from an oxygen-bearing carbon. As a result, carbonyl compounds are generated rather than β-arylated allylic alcohols.

\[
\text{[Pd(0)]} + \text{MeCHO} \rightarrow \text{MeCHO}
\]


Thus, a dihydrocinnamaldehyde target can be retrosynthetically disconnected via a Mizoroki-Heck reaction.
Intramolecular Mizoroki-Heck Reactions
Formation of 6-Membered Rings


No problem for C-C formation at quaternary center

Halo-1,6-Dienes

Type I substrates: 1-halo-1,6-dienes

Type II substrates: 2-halo-1,6-dienes

Apparent 6-exo cyclization

Owing to its mechanism the cyclopropylcarbinyl-to-homoallyl rearrangement can take place only if the two red bonds (C-C and C-Pd) can become syncoplanar. It can be understood as an unusually facile retro-carbopalladation. Notice that the double bond configuration of the final product is reversed with respect to that of the starting material.

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In this case the cyclopropylcarbinyl-to-homoallyl rearrangement cannot take place since the two red bonds (C-C and C-Pd) cannot become syncoplanar.
Asymmetric Mizoroki-Heck Reactions
The non-coordinating triflate anion is crucial.


\[
\text{Ph}^\text{OTf} + \text{C} = \text{O} \xrightarrow{\text{Pd}_{2}\text{dba}_3 \text{cat L^*}, i-\text{Pr}_2\text{NEt, PhH 70}^\circ\text{C (100\% conv)}} \text{C} = \text{O} \quad 96\% \text{ ee}
\]


\[
\text{Ph}^\text{OTf} + \text{C} = \text{O} \xrightarrow{\text{Pd(OAc)}_2 \text{cat L^*, 40}^\circ\text{C (65\% conv)}} \text{C} = \text{O} \quad 98\% \text{ ee}
\]
Intermolecular Asymmetric Reactions

The selectivity of this reaction is highly dependent on the nature of the (pseudo)halide and of the ligand.


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Intramolecular Asymmetric Reactions

The importance of non-coordinating anions

\[ \text{cationalic} \quad i \quad \text{neutral} \quad ii \]

\[ \begin{align*}
(S) & \quad 71\% \text{ ee} \\
(R) & \quad 66\% \text{ ee}
\end{align*} \]

i: \( \text{Pd}_2(\text{dba})_3 \) 5\%; (R)-BINAP 11\%; DMA; \( \text{Ag}_3\text{PO}_4 \), 80\(^\circ\text{C} \), (81\%)

ii: \( \text{Pd}_2(\text{dba})_3 \) 5\%, (R)-BINAP 11\%, DMA; PMP, 110\(^\circ\text{C} \) (71\%)

Intramolecular Asymmetric Reactions

The presence of the silicon atom in the precursor directs the dehydropalladation thereby avoiding $\beta$-H elimination from the undesired side.

Palladium-ene Cyclizations

Palladium-ene Cyclizations

Pd Catalyzed C-C Cleavage

β- Carbon Elimination

Pd β- Carbon elimination is the microscopic reverse reaction of carbopalladation. Although carbopalladation is usually the thermodynamically favored step, some particular cases (i.e. strain release and the impossibility of dehydropalladation) may drive the equilibrium in favor of Pd β- Carbon elimination.
Cleavage of CPC-Pd and CP-Pd

The different modes

CPC-Pd : cyclopropylcarbinylpalladium
CP-Pd : cyclopropylpalladium
From Methylene-cyclopropane


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Exercices

Propose a plausible mechanism for the following reactions


Propose a plausible mechanism for the following reaction:

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{Me} \\
\text{CN} & \quad \text{Pd(PPh}_3\text{)}_4 \quad 10\% \\
\text{THF, heat} & \\
\rightarrow & \\
\text{EtO}_2\text{C} & \quad \text{Me} \\
\text{CN} & \\
\end{align*}
\]

From Tertiary Cyclopropanols [Pd(II)]

From Tertiary Cyclopropanols [Pd(II)]

\[
\begin{align*}
\text{HO} & \quad \text{OTIPS} \\
\downarrow & \quad \downarrow \\
\text{AcOH} & \quad \text{O}_2, \text{DMSO} \\
\text{Pd(OAc)}_2 & \quad \text{[Pd(0)]} \\
\text{AcOH} & \quad \text{H[Pd]OAc} \\
\text{OTIPS} & \quad \text{AcO[Pd]} \\
\end{align*}
\]

\[
\begin{align*}
\text{cyclopropyl} & \quad \text{bond is preferentially cleaved} \\
\text{less substituted} & \quad \beta-\gamma \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

Pd(OAc)$_2$ 10%
DMSO
Tol MS 4A, O$_2$, 80°C

major regioisomer
75% (+ 18% other regioisomer)

Park, S.-B.; Cha, J. K.; Org. Lett. 2000, 2, 147
To obtain decarbopalladation, competitive dehydropalladation must be forbidden in the substrate (tertiary substituent) and strain release must operate. Indeed, dehydropalladation of oxypalladium intermediates is a key step in Pd-mediated oxidations.
From Tertiary Cyclopropanols [Pd(0)]

Arylative Fragmentation $\alpha,\alpha$-Disubstituted Arylmethanols

No strain release in this case

Bulky phosphines are necessary


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Arylative Fragmentation of 2,2-Disubstituted 3-Allen-1-ols