

## Palladium Catalyzed Coupling Reactions

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Palladium complexes catalyze many types of organic reactions. It is particularly useful in forming carbon-carbon bonds. For versatility, no other transition metal can compete with palladium. Palladium is readily available as Pd(II) chloride [PdCl<sub>2</sub>] Na<sub>2</sub>[PdCl<sub>4</sub>] or palladium acetate [Pd(OAc)<sub>2</sub>]; they are relatively cheap compared to rhodium and ruthenium salts.

Aromatic (aryl and heterocyclic) substitution is still one of the most important reactions in the preparation of most of the world's top pharmaceuticals, agrochemicals and color chemicals. We know that aryl halides do not undergo nucleophilic substitution reactions. Thus, Pd-catalyzed carbon-carbon bond forming reactions play an important role in synthesizing more complex and unusual compounds.

### Catalysts

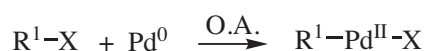
Palladium catalysts/pre-catalysts, which are used for coupling reactions include,

- Pd(OAc)<sub>2</sub> + Phosphine (PR<sub>3</sub>)
- PdCl<sub>2</sub> + Phosphine (PR<sub>3</sub>)
- [PdCl<sub>2</sub>(diphosphine)]
- [Pd(PR<sub>3</sub>)<sub>4</sub>]
- [Pd<sub>2</sub>(dba)<sub>3</sub>] (dba = (PhCH=CH)<sub>2</sub>C=O)
- Cyclometallated Pd(II) complexes  
(dba = dibenzylidene acetone)

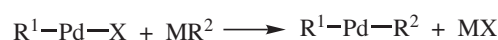
It is believed that phosphines and amines are capable of reducing Pd(II) to Pd(0).

### Mechanism

Palladium catalysts are used to couple two organic groups (R<sup>1</sup> and R<sup>2</sup>). Zerovalent palladium center in L<sub>n</sub>Pd(0) is known to activate the R<sup>1</sup>-X bond, where R<sup>1</sup> = alkyl, aryl and vinyl group; X = I, Br, triflate. It is an **oxidative addition** (O.A.) reaction.



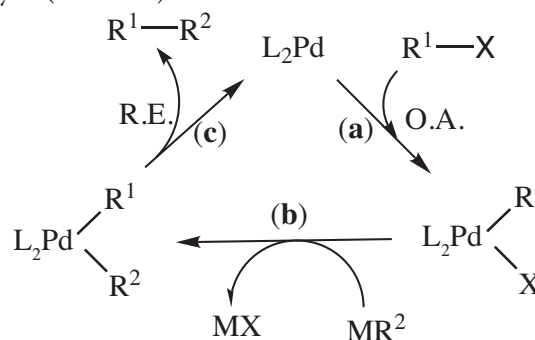
**Transmetalation** of this Pd(II) species with an organometallic reagent (MR<sup>2</sup>) gives the R<sup>1</sup>-Pd-R<sup>2</sup> species.



**Reductive elimination** (R.E.) of R<sup>1</sup>-R<sup>2</sup> generates the active Pd(0) catalyst.



The above three reactions are the key steps in a catalytic cycle (Scheme 1).



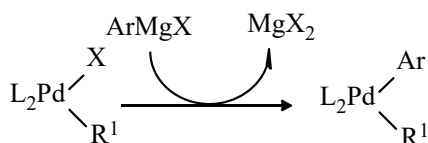
**Scheme 1:** A catalytic cycle for a coupling reaction between R<sup>1</sup> and R<sup>2</sup> groups using the active catalyst [PdL<sub>2</sub>]. L = PR<sub>3</sub>

- Oxidative addition of R<sup>1</sup>-X
- Transmetalation with MR<sup>2</sup> where M = Mg, Sn, Si, B, Hg, Zn, Cu *etc.*
- Reductive elimination of R<sup>1</sup>-R<sup>2</sup> and regeneration of zerovalent palladium complex

Let us consider the named coupling reactions such as Kumada, Negishi, Stille, Suzuki, Heck, Sonogashira and Hiyama, catalyzed by palladium complexes.

### Kumada coupling reaction

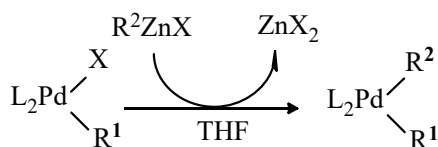
Formation of an Ar-R bond *via* a cross-coupling reaction, involving an Ar group and a R group of a Grignard reagent is called the **Kumada** coupling.



**Scheme 2:** Transmetalation step of a Kumada coupling reaction

### Negishi coupling reaction

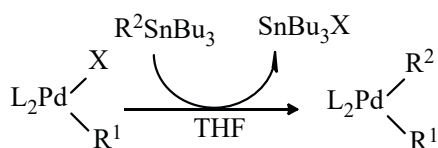
A similar coupling reaction with an R group of an organozinc reagent (RZnX) is known as Negishi coupling;



**Scheme 3:** Transmetalation step of a Negishi coupling reaction

### Stille coupling reaction

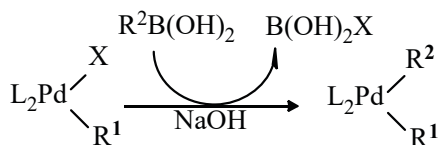
A R group of an organotin reagent (e.g., R<sup>2</sup>SnBu<sub>3</sub>) is involved in a Stille coupling reaction.



**Scheme 4:** Transmetalation step of a Stille coupling reaction

### Suzuki coupling reaction

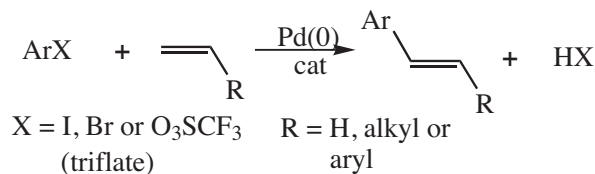
In a Suzuki coupling reaction, a R group of an organoboron reagent (e.g., R<sup>2</sup>B(OH)<sub>2</sub>) is used.



**Scheme 5:** Transmetalation step of a Suzuki coupling reaction

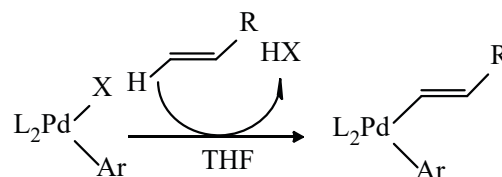
### Heck coupling reaction

Arylation of olefins (or alternatively olefination of aryl groups) is known as the Heck reaction; it is represented as follows.



**Scheme 6:** Heck reaction

We can consider the Heck reaction as a reaction in which an olefinic H is replaced by an Ar group (i.e., arylation of an olefin).

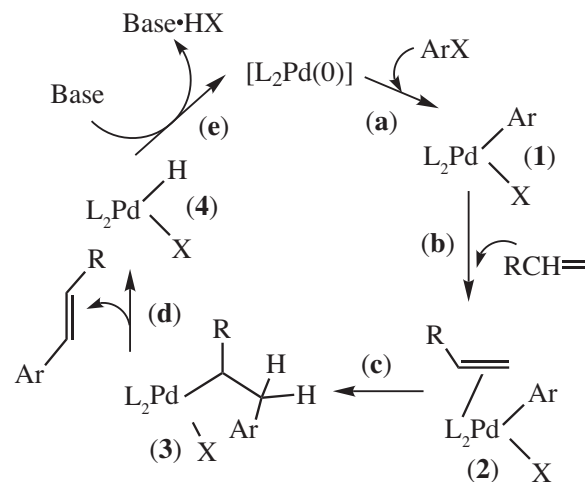


**Scheme 7:** Transmetalation via HX removal

A new C-C bond is formed between an olefinic group and aryl group. Heck reaction is catalyzed by Pd(0) compounds. A base (e.g., Et<sub>3</sub>N, Bu<sub>3</sub>N, NaOAc, K<sub>2</sub>CO<sub>3</sub>) is used to remove HX from the system.

### Catalytic cycle

The catalytic cycle for the Heck reaction is shown in Scheme 8.



**Scheme 8:** Catalytic cycle for the arylation of RCH=CH<sub>2</sub> to give RCH=CHAr using an active catalyst [L<sub>2</sub>Pd].

(a) Oxidative addition of ArX gives the Pd(II) complex (1).

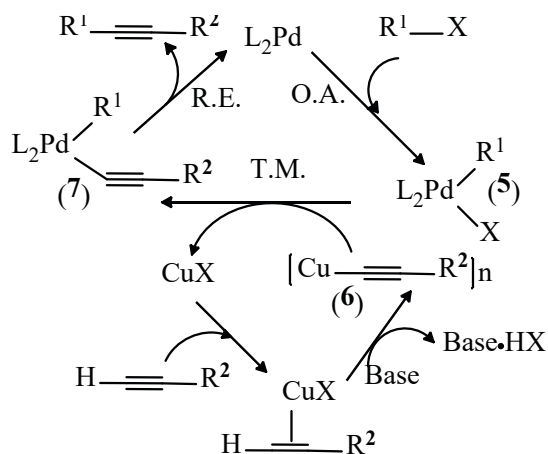
(b) Coordination of RCH=CH<sub>2</sub> gives (2).

- (c) Migration of the Ar group on to the olefin giving the intermediate (3). (This step is regioselective where Ar ends up in the terminal carbon)
- (d)  $\beta$ -Hydride abstraction gives the complex (4), and eliminates the coupled product ( $RCH=CHAr$ ).
- (e) Removal of HX by a base, regenerates the active catalyst  $[L_2Pd(0)]$ .

### Sonogashira coupling reaction

The Sonogashira reaction is a cross coupling reaction between aryl or vinyl halides and terminal alkynes to generate conjugated enynes and arylalkynes (Scheme 9). The reaction proceeds in the presence of a Pd(0) catalyst, a Cu(I) cocatalyst, and an imine base.

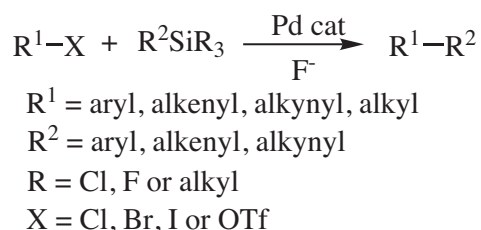
The catalytic cycle of the Sonogashira reaction is consisting of oxidative addition, transmetallation and reductive elimination as in scheme 1. Transmetallation of (5) with (6) produces (7). The cuprate(I) (6) was generated *in situ* using catalytic amount of CuX.



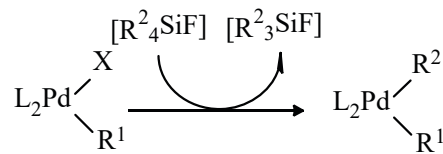
Scheme 9: The two catalytic cycles of the Sonogashira reaction

### Hiyama coupling reaction

In Hiyama coupling reactions, **organosilanes** and organic halides are employed in the presence of fluoride ions as shown below.



The transmetallation step is as follows.



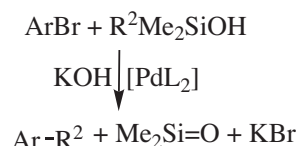
Scheme 10: Transmetallation of  $R^1PdL_2X$

The organosilane is activated with a fluoride/base to form a pentavalent silicon center, which makes the C-Si bond more labile.



Scheme 11: Activation of silanes

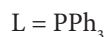
The Hiyama–Denmark coupling reaction uses **organosilanol**s and organic halides as coupling partners, where base is utilized as the activating agent instead of fluoride.



Scheme 12: Hiyama-Denmark reaction

### Problems

1. Predict the product(s) of the following reactions.



- (a)  $PhMgBr \xrightarrow{[Pd]_{cat}}$
- (b)  $PhBr + CH_2=CHSnBu_3 \xrightarrow{[Pd]_{cat}}$
- (c)  $MeO-C_6H_4-CH=CH-Br + Ph-B(OAc)_2 \xrightarrow{NaOH, PdL_4}$
- (d)  $PhZnBr + 2\text{-bromothiophene} \xrightarrow{Pd(OAc)_2, PdL_4}$
- (e)  $PhI + \text{styrene} \xrightarrow{NEt_3}$
- (f)  $Ph-I + \text{alkyne} \xrightarrow{CuI/R_3N, PdL_4}$
- (g)  $PhCH_2Br + ArSi(OMe)_3 \xrightarrow{Bu_4NF, PdBr_2}$