A Review on Palladium Catalyzed Coupling Reactions

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ABSTRACT

Palladium compounds are used as catalyst, usually as homogeneous catalyst in many coupling reactions. Unoptimized reactions typically use 10-15 mol% of palladium; whereas optimized, catalyst loadings can be to the order of 0.1 mol %. Palladium readily absorbs hydrogen at room temperature forming palladium hydride - PdH_x, with ‘x’ below 1. While this property is common to many transition metals, palladium is unique by the high absorption capacity, and by that it does not lose its ductility until high x values. This property has been investigated for designing an efficient, yet inexpensive hydrogen storage material (palladium itself is prohibitively expensive for this purpose).

Keywords: Homogeneous Catalyst, Absorption capacity, Unoptimized reaction, Ductility.

INTRODUCTION

Palladium compounds are used as catalyst, usually as homogeneous catalyst in many coupling reactions. Unoptimized reactions typically use 10-15 mol% of palladium; whereas optimized, catalyst loadings can be to the order of 0.1 mol %. Palladium readily absorbs hydrogen at room temperature forming palladium hydride - PdH_x, with ‘x’ below 1. Examples include:

- Heck Reaction
- Suzuki Coupling
- Stille Reaction
- Fukuyama Coupling
- Negishi Coupling
- Buchwald Hartwig
- Hiyama Coupling
- Sonogashira Coupling

Fig. 1: Flow chat of palladium catalysed coupling reaction
**Properties of Palladium**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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<tbody>
<tr>
<td>Atomic number</td>
<td>46</td>
</tr>
<tr>
<td>Atomic mass</td>
<td>106.42 g mol⁻¹</td>
</tr>
<tr>
<td>Density</td>
<td>11.9 g cm⁻³ at 20°C</td>
</tr>
<tr>
<td>Melting point</td>
<td>1560 °C</td>
</tr>
<tr>
<td>Boiling point</td>
<td>2927 °C</td>
</tr>
<tr>
<td>Isotopes</td>
<td>9</td>
</tr>
<tr>
<td>Vander waals radius</td>
<td>0.065 nm (+2)</td>
</tr>
<tr>
<td>Ionic radius</td>
<td>0.137 nm</td>
</tr>
<tr>
<td>Electronic shell</td>
<td>[Kr] 4d¹⁰ 5s⁰</td>
</tr>
<tr>
<td>Energy of first ionization</td>
<td>703 kJ mol⁻¹</td>
</tr>
<tr>
<td>Energy of second ionization</td>
<td>1870 kJ mol⁻¹</td>
</tr>
<tr>
<td>Energy of third ionization</td>
<td>3177 kJ mol⁻¹</td>
</tr>
<tr>
<td>Standard potential</td>
<td>+ 0.85 V (Pd²⁺/Pd)</td>
</tr>
<tr>
<td>Discovered by</td>
<td>William Wollaston</td>
</tr>
</tbody>
</table>

**Palladium is used for coupling because**

- Its electronegativity¹, ², which leads to relatively strong Pd-H and Pd-C bonds, and also develops a polarised Pd-X bond.
- It allows easy access to the Pd (II) and Pd (0) oxidation states, essential for processes such as oxidative addition, transmetalation³,⁴ and reductive elimination.

- Pd (I), Pd (III) and Pd (IV) complexes are also known, though less thoroughly, with Pd (IV) species essential in C-H activation mechanisms.

**Mechanism of Palladium catalysed coupling⁴,¹⁵ reaction**

- Preactivation of catalyst: When a Pd(II) source is used in a reaction, it must be reduced to Pd(0) before entering the catalytic cycle reduction by Phosphines.
- Oxidative addition: Oxidative addition proceeds with retention of stereochemistry with vinyl halides, while giving inversion of stereochemistry with allylic and benzylic halides. The oxidative addition initially forms the cis-palladium complex, which rapidly isomerizes to the trans-complex.
- Reductive elimination: Using deuterium-labelling⁶, the reductive elimination proceeds with retention of stereochemistry and relative reactivity of different metal complexes in the C-C reductive⁷,⁸ elimination was established: Pd(IV), Pd(II) > Pt(IV), Pt(II), Rh(III) > Ir(III), Ru(II), Os(II).

**Fig. 2: Mechanism of palladium catalysed coupling reaction**

**Palladium catalyzed reactions were developed by many scientist¹⁹-²¹**

Heck reaction: The Heck²² reaction (also called the Mizoroki-Heck reaction) is the chemical reaction of an unsaturated halide (or triflate) with an alkene and a base and palladium catalyst or palladium nanomaterial-based catalyst to form a substituted alkene. Together with the other palladium-catalyzed cross-coupling reactions, this reaction is of great importance, as it allows one to do substitution reactions on planar centers. It is named after Tsutomu Mizoroki and Richard F. Heck. Heck²¹, ²² was awarded the 2010 Nobel Prize in Chemistry for the discovery and development of this reaction.
The reaction is performed in the presence of an organo palladium catalyst. The halide (Br, Cl) or triflate is an aryl, benzyl, or vinyl compound and the alkene contains at least one proton and is often electron-deficient such as acrylate ester or an acrylonitrile. The catalyst can be tetrakis(triphenylphosphine) palladium(0), palladium chloride or palladium(II) acetate. The ligand is triphenylphosphine or BINAP. The base is triethylamine, potassium carbonate or sodium acetate.

**Recent application of Heck reaction**

In synthesis of Rhazinal

- Rhazinal is an alkaloid obtained from the stem extract of Kopsia teoi.
- Which is Antimitotic agent.
- It is a promising starting point for anticancer agent.

**Ionic liquid Heck reaction**

In the presence of an ionic liquid a Heck reaction proceeds in absence of a phosphorus ligand. In one modification palladium acetate and the ionic liquid PF$_6$ are immobilized inside the cavities of reversed-phase silica gel. In this way the reaction proceeds in water and the catalyst is re-usable.

**Amino-Heck reaction**

In the amino-Heck reaction a nitrogen to carbon bond is formed. In one example, an oxime with a strongly electron withdrawing group reacts intramolecularly with the terminal end of a diene to a pyridine compound. The catalyst is tetrakis(triphenylphosphine)palladium(0) and the base is triethylamine.

**Suzuki coupling**

Since the discovery of the Ullmann reaction over a century ago, in 1901, the transition-metal-catalyzed cross-coupling reaction has played an important role in the synthesis of C-C bonds. In 1981, Suzuki discovered a novel Pd-catalyzed cross-coupling reaction of aryl boronic acids and aryl halides, which has been applied widely and for which he received the 2010 Nobel prize in chemistry. This reaction has become an extremely powerful process for the synthesis of biaryls, which have a diverse spectrum of applications, ranging from pharmaceuticals to materials science.

The given scheme shows the first published Suzuki Coupling, which is the palladium-catalysed cross coupling between organoboronic acid and halides. Recent catalyst and method developments have broadened the possible applications enormously, so that the scope of the reaction partners is not restricted to aryls, but includes alkyls, alkenyls and alkynyls. Potassium trifluoroborates and organoboranes or boronate esters may be used in place of boronic acids. Some pseudohalides (for example triflates) may also be used as coupling partner.
Recent application of Suzuki coupling\textsuperscript{34, 35} A Highly Efficient Microwave-Assisted Suzuki Coupling Reaction of Aryl Perfluoro-octylsulfonates with Boronic Acids.

Cyclic sulfamide HIV-1 protease inhibitor\textsuperscript{36, 37}, with side chains spanning from P2/P2\textsuperscript{′} to P1/P1: Molecular modeling suggested that this could be achieved with appropriate ortho-substitution of the P2/P2\textsuperscript{′} benzyl groups in our cyclic sulfamide inhibitors.

Suzuki–Miyaura cross coupling The Suzuki–Miyaura cross-coupling\textsuperscript{38, 39} of aryl halides with organoboronic acids is an important tool for synthetic organic chemistry. A range of palladium complexes with different ligands can been used to catalyse this interesting reaction. Their remarkable results indicate there is a correlation between ligand alkyl chain length and catalytic efficiency, however, as their Dalton Transactions, the Pd(II) complexes are precatalysts which generate in situ real catalytic species of approx. 3 nm Pd(0) nanoparticles, protected by organo selenium species.

Fig. 3: Palladium catalyst used in Suzuki coupling
Negishi coupling\textsuperscript{40, 41}

Negishi coupling an exceedingly useful alternative to other cross-coupling procedures, as well as carbon–carbon bond formation.

Recent application of Negishi coupling\textsuperscript{42}

1) Synthesis of beta-carotene

\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{AllMe}(Cp)\text{ZrCl}_2 \\
\text{Zirconium promoted carboalumination} \\
\text{ZnCl}_2 \quad \text{DMF} \quad 23^\circ\text{C} \\
\text{Negishi coupling} \\
\text{AllMe}(Cp)\text{ZrCl}_2 \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Beta-carotene}
\end{align*}

2) A Highly Efficient Microwave-Assisted Suzuki Coupling Reaction of Aryl Perfluoro- octylsulfonates with Boronic Acids\textsuperscript{43, 44}.

\begin{align*}
\text{C}_9\text{H}_7\text{SO}_{\text{O}} & \quad \text{C}_6\text{H}_{9}\text{R}_1 \\
\text{Suzuki microwave} \\
\text{F-SPE separation} \\
\text{R}_2 \quad \text{R}_1
\end{align*}

3) Suzuki coupling sequence to the stereoselective synthesis of E-trisubstituted olefins\textsuperscript{45, 46}

\begin{align*}
\text{N}^+ & \quad \text{Me} \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{TMS} \\
\text{Two step}\overset{\text{Pd cat.}}{\rightarrow} \\
\text{TMS}
\end{align*}

Hiyama-coupling\textsuperscript{47-49}

It is a palladium-catalyzed cross-coupling reaction of organosilanes with organic halides used in organic chemistry to form carbon-carbon bonds (C-C bonds). This reaction was discovered in 1988 by Tamejiro Hiyama and Yasuo Hatanaka as a method to form carbon-carbon bonds synthetically with chemo- and regioselectivity. This reaction has been applied to the synthesis of natural products such as Papulacadin D, an anti-fungal agent.

Recent application of Hiyama Coupling

1) Many modifications to the Hiyama-coupling\textsuperscript{50-52} have been developed that avoid the use of a fluoride activator base. Using organo chlorosilanes, Hiyama found a coupling scheme utilizing NaOH as the basic activator. Modifications using alkoxy silanes have been reported with the use of milder bases like NaOH.
and even water. Study of these mechanisms have led to the development of the Hiyama-Denmark coupling which utilize organosilanols as coupling partners.

2) **Hiyama-Denmark coupling**\(^{53, 54}\): The Hiyama-Denmark coupling is the modification of the Hiyama-coupling that does not require a fluoride additive to utilize organosilanols and organic halides as coupling partners. The general reaction scheme is shown below, showcasing the utilization of a Brønsted base\(^{55}\) as the activating agent as opposed to fluoride, phosphine ligands are also used on the metal center.

\[
\begin{array}{c}
\text{R-Si-CH} \rightarrow \text{R-X} \xrightarrow{\text{Base, Rf cat.}} \text{R} - \text{R'}
\end{array}
\]

**Stille coupling**\(^{56-58}\)

The Stille reaction (also known as Stille Coupling) is a chemical reaction coupling an organotin compound with an sp\(^2\)-hybridized organic halide catalyzed by palladium. The Stille reaction was discovered in 1977 by John Kenneth Stille and David Milstein, a post-doctorate in his laboratory. Stille reactions were used in 50% of all cross-coupling reactions published in 1992. The reaction continues to be exploited industrially, especially for pharmaceuticals. The reaction is widely used in organic synthesis. X is typically a halide, such as Cl, Br, I. Additionally, X can be a pseudohalide such as a triflate, CF\(_3\)SO\(_3\)\(^{-}\).

\[
\text{R} \text{Si} \text{R}_3 \xrightarrow{\text{R-X}} \text{RR} \xrightarrow{\text{X} \text{Si} \text{R}_3}
\]

**Recent application of Stille coupling**\(^{59, 60}\)

1) Use of the Stille Coupling Reaction on Heteroaromatic Cations

Synthesis of Substituted Quinolizinium Salts. We describe the first efficient application of the Stille coupling reaction on heteroaromatic cations. In the presence of Pd(0)/Cul, the reaction of bromoquinolizinium salts and various tributy lstannyl\(^{61}\) compounds proceeds in satisfactory yield under mild reaction conditions, affording different substituted quinolizinium salts.

\[
\begin{array}{c}
\text{N} \text{Br} \xrightarrow{\text{stannane, Pd(PP}_3)_4 (5\% \text{ mol})} \text{Cul (10% mol), DMF, Ar, RT}}
\end{array}
\]

2) In the realm of green chemistry a Stille reaction\(^{64-66}\) is reported taking place in a low melting and highly polar mixture of a sugar such as mannitol, a urea such as dimethylurea and a salt such as ammonium chloride\(^ {67, 68}\). The catalyst system is tris (dibenzylideneacetone) dipalladium(0) with triphenylarsine\(^ {69-72}\).
Fukuyama coupling\textsuperscript{73-75}

It is a coupling reaction taking place between a thioester and an organozinc halide in the presence of a palladium catalyst. The reaction product is a ketone. This reaction was discovered by Tohru Fukuyama et al. in 1998. Advantages are high chemoselectivity, mild reaction conditions and the use of less-toxic reagents.

\[
\text{R}_1\text{S}^- + \text{Zn-R}_2 \xrightarrow{\text{Pd}} \text{R}_1\text{R}_2
\]

Recent application of Fukuyama coupling

1) Synthesis of multi-functionalized ketones\textsuperscript{76-78}

Fukuyama and co-workers have recently developed a highly efficient synthetic method for the generation of ketones. Treatment of thiol esters with zinc reagents in the presence of dichlorobis(triphenylphosphine) palladium(II) \([\text{PdCl}_2(\text{PPh}_3)_2]\) provides highly functionalized ketones in excellent yields. The reaction is featured by unusually high chemoselectivity, mild reaction conditions and the use of less-toxic reagents\textsuperscript{83-85}.

\[
\begin{align*}
A, \quad &\text{RCH} = \text{CHO} \xrightarrow{\text{EDCI, DCC, DMF}} \text{RCH} = \text{C} = \text{SEt} \quad 1 \\
B, \quad &\text{RCH} = \text{C} = \text{SEt} \xrightarrow{\text{Zn, BrCH-CHBr, TMS-OH, THF}} \text{RCH} = \text{C} = \text{SEt} \quad 2 \\
C, \quad &\text{RCH} = \text{C} = \text{SEt} \xrightarrow{\text{PdCl}_2(\text{H}_2}\text{C}}, \text{DMF, THF, toluene} \quad \text{RCH} = \text{C} = \text{SEt} \quad 3
\end{align*}
\]

2) The reaction has been used in the synthesis of biotin\textsuperscript{86, 87}.

\[
\begin{align*}
\text{Bn} = \text{N} = \text{N} = \text{Bn} \xrightarrow{0.1 \text{ eq PdCl}_2(\text{PPh}_3)_2, \text{THF, toluene, DMF}} \left[\begin{array}{c}
\text{Bn} = \text{N} = \text{Bn} \\
\text{CO}_2\text{Et}
\end{array}\right] \\
\text{H}_2\text{PdC} \xrightarrow{\text{p-TsOH, toluene}} \text{Bn} = \text{N} = \text{Bn} \quad \text{CO}_2\text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{H-N} - \text{N} - \text{H} \xrightarrow{\text{EDCI, HCl}} \text{Bn} = \text{N} = \text{Bn} \quad \text{CO}_2\text{Et}
\end{align*}
\]
**Buchwald–Hartwig amination**\(^{88-90}\)

It is a chemical reaction used in organic chemistry for the synthesis of carbon–nitrogen bonds via the palladium-catalyzed cross-coupling of amines with aryl halides. Though publications with similar focus were published as early as 1983, credit for its development is typically assigned to Stephen L. Buchwald and John F. Hartwig, whose publications between 1994 and the late 2000s established the scope of the transformation. The reaction’s synthetic utility stems primarily from the shortcomings of typical methods (nucleophilic substitution, reductive amination).

For the synthesis of aromatic C–N bonds, with most methods suffering from limited substrate scope and functional group tolerance. The development of the Buchwald–Hartwig reaction\(^{91-93}\) allowed for the facile synthesis of aryl amines, replacing to an extent harsher methods (the Goldberg reaction, nucleophilic aromatic substitution, etc.) while significantly expanding the repertoire of possible C–N bond formation.

![Chemical Reaction Diagram](image)

**Application of Buchwald–Hartwig amination**

1) A palladium catalyzed C–N cross-coupling reaction was published in 1983 by Migita and coworkers and described a reaction between several aryl bromides and N,N-diethylamino-tributyltin using 1 mol% PdCl\(_2\)(P(o-tolyl))\(_3\). Though several aryl bromides were tested, only electronically neutral, sterically unencumbered substrates\(^{94,96}\) gave good yields.

![Chemical Reaction](image)

2) In 1984, Dale L. Boger and James S. Panek reported an example of Pd(0)-mediated C–N bond formation in the context of their work on the synthesis of lavendamycin\(^{97,99}\) which utilized stoichiometric Pd(PPh\(_3\))\(_4\).

![Chemical Reaction](image)

3) **Sonogashira reaction**\(^{100}\):

It is a cross-coupling reaction used in organic synthesis to form carbon–carbon bonds. It makes use of a palladium catalyst to form a carbon–carbon bond between a terminal alkyne and an aryl or vinyl halide.

![Chemical Reaction](image)

**Recent application of Sonogashira coupling**

A Copper-Free Sonogashira Coupling Reaction in Ionic Liquids\(^{100}\) and Its application to a Microflow System for Efficient Catalyst Recycling. The PdCl\(_2\)(PPh\(_3\))\(_2\)-catalyzed Sonogashira coupling reaction, in
good to high yields, was performed in an ionic liquid ([BMIm][PF₆]) in the absence of a copper salt. The use of an ionic liquid allows for the facile separation and recycling of the catalyst.

\[
\begin{align*}
\text{Ar}-\text{I} + \text{H} & \xrightarrow{\text{PdCl}_2(\text{PPh}_3)_2} \text{Ar} \equiv \equiv \text{R} \\
\text{R} & = \text{alkyl, aryl} \\
& \text{[BMIm][PF}_6] \\
& \text{Pr}_2\text{NH or piperidine}
\end{align*}
\]

REFERENCES

31. Gyanshwumar Kumar, Rao; Arun Kumar; Bharat Kumar; Dinesh Kumar and Ajai Kumar Singh; Dalton Trans (2012).
38. K., Uttam; T., Stoltz; Group Literature Series (2003).
40. K., Antony; N., Okukado and E., Negishi; "Highly general stereo, regio-, and chemo- selective synthesis of terminal and internal conjugated enynes by the Pd-catalysed reaction of alkynylzinc reagents with alkynyl halides", Journal of the Chemical Society Chemical Communications (1977).


75. Y., Mori; M., Seki; “Synthesis of multifunctionalized ketones through the Fukuyama Coupling reaction catalysed by pearlmans catalyst: Preparation of ethyl 6-oxtridecanoate (Tridecanoic acid, 6-oxo-, ethyl ester)”, Org. Synth., vol 84, pp 285–294.

76. Y., Mori; M., Seki; “Synthesis of multifunctionalized ketones through the Fukuyama Coupling reaction catalysed by pearlmans catalyst: Preparation of ethyl 6-oxtridecanoate (Tridecanoic acid, 6-


81. H., Tokuyama; T., Miyazaki; S., Yokoshiba; T., Fukuyama; T., Synlett; (2003) vol 37, pp 1512.


