**SECTION-I** 

# CHAPTER 1. INTRODUCTION

# **1. INTRODUCTION**

# 1.1. Palladium in synthetic organic chemistry

During the second half of the  $20^{\text{th}}$  century, transition metals have come to play an important role in organic chemistry and this has led to the development of a large number of transition metal-catalyzed reactions for creating new organic molecules. Transition metals have a unique ability to activate various organic compounds and through this activation they can catalyze the formation of new bonds. One metal that was used early on for catalytic organic transformations was palladium (Pd). One event that stimulated research into the use of Pd in organic chemistry was the discovery that ethylene was oxidized to acetaldehyde by air in a Pd-catalyzed reaction, and this became the industrially important Wacker process.<sup>1</sup> Subsequent research on Pdcatalyzed carbonylation led to new reactions for the formation of carbon-carbon (C-C) bonds. In general, transition metals, and in particular palladium, have been of importance for the development of reactions for the formation of C-C bonds. In 2005 the Nobel Prize in chemistry was awarded to metal-catalyzed reactions for the formation of C=C bonds.<sup>2</sup> In year 2010 the Nobel Prize in chemistry was awarded to the formation of C-C single bonds through palladium-catalyzed cross-coupling reactions. The prize was jointly awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki.<sup>3</sup>

Palladium is a group 10 element in periodic table with atomic number 46.<sup>4</sup> Palladium, due to its flexible oxidation states and with the property of getting reduced or oxidized easily, is very useful for the synthetic chemistry point of view. Common oxidation states of palladium are 0, +1, +2 and +4. Although originally +3 was thought of as one of the fundamental oxidation states of palladium, there is no evidence for palladium occurring in the +3 oxidation state; this has been investigated via X-ray diffraction for a number of compounds, indicating a dimer of palladium(II) and palladium(IV) instead. In 2002, palladium(VI) was first identified and reported. Palladium is often used as a catalyst due to its capacity of making covalent as well as co-ordinate bonds. Palladium in its valance shell contains 18 electrons and it follows *18-electron rule* for determining its valency and oxidation state. Counting the number of *d-electrons* and determination of oxidation state is an important aspect of palladium chemistry.<sup>5</sup>

# 1.2. Types of reactions

Almost all of the reactions of Pd can be divided into just a few types. All the reactions promoted by palladium in organic chemistry are a combination of these reactions. These reactions may be classified as follows:

- ligand addition/ligand dissociation/ligand substitution
- oxidative addition/reductive elimination
- insertion/ $\beta$ -elimination
- σ-bond metathesis (transmetallation)

• Ligand addition/dissociation - these are simply Lewis acid-base reactions, either in the forward direction to make a bond (*addition*) or in the reverse direction to break a bond (*dissociation*). Pd undergoes a dissociation or association reaction to form the actual active species, as in  $Pd(PPh_3)_4 \rightarrow Pd(PPh_3)_3 + PPh_3$ . In an addition (or dissociation), the total electron count of Pd increases (or decreases) by 2, but the d electron count and the oxidation state do not change. Pd also easily undergoes *ligand*  *substitution* reactions. These usually proceed in two steps by addition–dissociation or dissociation–addition.

• **Oxidative addition/reductive elimination** - these are the reverse reactions of each other. In oxidative addition, a metal inserts itself into an X–Y bond. The X–Y bond is broken, and Pd–X and Pd–Y bonds are formed. The reaction is an oxidation, because the metal's *oxidation state* increases by 2. Alkyl halides, pseudohalides like triflates (R-OTf) and phosphates (R-OP(O)(OEt<sub>j2</sub>), and other C–X species readily undergo oxidative addition. Oxidative addition is usually fastest for X=I, but not always. Oxidative addition can also occur at  $C(sp^2)$ –X bonds (i.e., at vinyl and aryl halides). It always occurs with retention of configuration about the double bond. In *reductive elimination* as mentioned, the X–Y bond regenerates by eliminating Pd, this time the oxidation number of Pd decreases by 2.

• Insertions/ $\beta$ -eliminations - these are also the microscopic reverse of each other. In an *insertion*, an A=B  $\pi$  bond inserts into an Pd–X bond (Pd–X + A=B  $\rightarrow$  Pd–A–B–X). The Pd–X and A=B bonds are broken, and Pd–A and B–X bonds are formed. Insertion is usually preceded by coordination of the A=B  $\pi$  bond to the metal, so it is sometimes called *migratory insertion*. In an insertion, a Pd–X bond is replaced with a Pd–A bond, so there is no change in oxidation state, d electron count, or total electron count.  $\beta$ -Elimination is the microscopic reverse of insertion. Just as insertion, a  $\beta$ -elimination also causes no change in the oxidation state, d electron count, or total electron count of the metal. By far the most common  $\beta$ -elimination is the  $\beta$ -hydride elimination.

• Sigma-bond metathesis - these reactions involve the swapping of Pd–X and  $Y-Z \sigma$  bonds to give Pd–Z and X–Y (or Pd–Y and X–Z). The reaction is a concerted one, involving a four-centre transition state. No change in oxidation state or total electron count occurs. *Transmetallations*, in which Pd–X and M'–Y swap partners to give Pd–Y and M'–X, are a special kind of  $\sigma$ -bond metathesis reaction.<sup>6</sup>

Organometallic and inorganic catalysts are often classified as *homogeneous* or *heterogeneous*. In the next part, an account of homogeneous catalysis of Pd metal is reported. As reported earlier that the Pd catalysis involves multistep mechanism to complete a reaction cycle, a number of most widely explored Pd catalyzed cross-coupling reactions are described.

#### 1.2.1. Heck reaction

The *Heck reaction* is the coupling of an aryl or alkenyl halide with an alkene in the same molecule.<sup>7</sup> The reaction may be used to produce carbocyclic or heterocyclic organic compounds with a variety of ring sizes. Chiral Pd-complexes can be used to synthesize chiral intramolecular Heck reaction products in non-racemic form. In the Heck reaction, an aryl or vinyl halide (R'–X) and an alkene (H<sub>2</sub>C=CHR) are converted to a more highly substituted alkene (R'–CH=CHR) under Pd catalysis (**Scheme 1**). Base is used to neutralize the by-product (HX). The Heck reaction can be carried out in intra- or inter-molecular fashion. In inter-molecular reactions, the reaction proceeds best when the alkene is electrophilic. In intra-molecular reactions, more highly substituted alkenes can be used. Together with other Pd-catalyzed cross-coupling reactions, this reaction is of great importance, as it allows one to do substitution reactions on planar centres. It is named after Tsutomu Mizoroki and Richard F. Heck.

Heck was awarded the 2010 Nobel Prize in Chemistry for the discovery and development of this reaction.

#### **General transformation**



# Scheme 1

The C–X bond is broken, and a new C–C bond is formed. The first step, as always, is oxidative addition of Pd(0) to the C–X bond to give a Pd(II)–C complex. Insertion of the alkene into the Pd(II)–C bond now takes place to give the new C–C bond. A  $\beta$ -hydride elimination gives the product and H–Pd(II)–X, which is deprotonated by base to regenerate Pd(0). There are two types of mechanisms involved in Heck reactions:

- The neutral pathway
- The cationic pathway

• *The neutral pathway:* As shown in **Scheme 2**, the neutral pathway of the Heck reaction begins with the oxidative addition of the aryl or alkenyl halide into a co-ordinatively unsaturated Pd(0) complex (typically bound to two phosphine ligands) to give Pd-X complex. Dissociation of a phosphine ligand followed by association of the alkene yields Pd(II) complex, and migratory insertion of the alkene into the carbon-palladium bond establishes the key carbon-carbon bond. Insertion takes place in a

suprafacial fashion, but the dihedral angle between the alkene and palladium-carbon bond during insertion can vary from 0° to ~90°. After insertion,  $\beta$ -hydride elimination affords the product and a Pd(II)-hydrido complex, which is reduced by base back to Pd(0).



Scheme 2 Mechanism of the Heck Reaction: neutral Pd

• *The cationic pathway:* Most asymmetric Heck reactions employing chiral phosphines proceed by the cationic pathway, which does not require the dissociation of a phosphine ligand. Oxidative addition of an aryl halide followed by insertion in presence of a silver salt generates a cationic Pd complex. The mechanism then proceeds as in the neutral case, with the difference that an extra site of coordinative unsaturation exists on Pd throughout the process. Thus, coordination of the alkene does not require ligand dissociation. Stoichiometric amounts of base are still required to reduce the Pd(II)-hydrido complex back to Pd(0).



Scheme 3 Mechanism of the Heck Reaction: cationic Pd

# 1.2.2. Regioselectivity in the Heck Reaction

The type of mechanism in action is incredibly important, as it can manifest itself in a variety of ways, especially the regioselectivity. In the neutral catalytic cycle, the



regioselectivity is governed by steric factors – generally addition occurs to the terminal end of the alkene. However, in the cationic cycle, regiochemistry is affected by electronic factors. The cationic Pd-complex increases the polarization of the alkene favouring transfer of the vinyl or aryl group to the site of least electron density. The

type of mechanism in effect is generally controlled by choice of halide/pseudohalide acting as a leaving group in the cationic cycle; triflate promotes, whereas bromide detracts.<sup>8,9</sup> Several reviews have been published on this aspect.<sup>10-12</sup>

# 1.3. Coupling reactions between nucleophiles and C(sp<sup>2</sup>)–X: Negishi, Suzuki, Sonogashira and Buchwald–Hartwig reactions

Aryl and vinyl halides can undergo substitution with nucleophiles by one of three mechanisms: addition–elimination, SRN<sub>1</sub> or elimination–addition. The addition–elimination mechanism requires strongly electron withdrawing groups such as NO<sub>2</sub> group on the ring to make the ring carbon more electrophilic. The SRN<sub>1</sub> reaction involves light or radiation catalyzed radical stabilization and the leaving group essentially must be bromide or iodide. Lastly the elimination–addition involves strongly basic conditions. Many of the normally used aromatic halides do not fulfil these conditions therefore the aromatic nucleophilic substitution is believed to be a difficult transformation.

In the mid-1970<sub>s</sub>, it was discovered that Ni complexes catalyzed the substitution of aryl halides with Grignard reagents at room temperature. The Ni catalysts were mostly phosphine complexes of NiCl<sub>2</sub> [e.g., (Ph<sub>3</sub>P)<sub>2</sub>NiCl<sub>2</sub>], although other phosphine complexes sometimes gave better results. The reaction was named *Kumada reaction*.<sup>13</sup> After the discovery of the Kumada reaction, intensive efforts were made to discover other group ten metal-catalyzed reactions. These efforts paid off tremendously with the development of some of the most widely used C–C bond forming reactions in organic synthetic methodology, including the *Stille coupling*, the *Suzuki coupling*, the *Negishi coupling*, and related reactions.

#### 1.3.1. Negishi Coupling

The use of organozinc reagents as the nucleophilic component in Pd-catalyzed cross-coupling reactions is known as the Negishi coupling.<sup>14</sup> The Negishi coupling, published in 1977, was the first reaction that allowed the preparation of unsymmetrical biaryls in good yields. Organozinc reagents exhibit a very high intrinsic reactivity in Pd-catalyzed cross-coupling reactions, which combined with the availability of a number of procedures for their preparation and their relatively low toxicity, makes the Negishi coupling an exceedingly useful alternative to other cross-coupling procedures, as well as constituting an important method for carbon–carbon bond formation in its own right (**Scheme 4**).

#### **General transformation**

 $\begin{array}{rcl} \hline R_{1}-ZnX & + & \hline R_{2}-X & \underline{cat. \ [Pd^{0}Ln]} & \hline R_{1}-R_{2} \\ \hline R_{1} & = alkyl, alkynyl, aryl, vinyl \\ \hline R_{2} & = acyl, aryl, benzyl, vinyl \\ X & = Br, I, OTf, OTs \end{array}$ 

#### Scheme 4

The active catalyst in this reaction is zero valent  $(Pd^0)$  and the reaction in general proceeds through an oxidative addition step of the organic halide followed by transmetallation with the zinc compound and then reductive elimination (**Scheme 5**). The versatile Ni- or Pd-catalyzed coupling of organozinc compounds with various halides (aryl, vinyl, benzyl, or allyl) has broad scope, and is not restricted to the formation of biaryls.



Scheme 5 Mechanism of the Negishi coupling

# 1.3.2. Suzuki coupling

The Suzuki reaction was formally developed by Suzuki Group<sup>15</sup> in 1979; although the inspiration for this work can be traced back to publications by Heck and Negishi, and their earlier presentation of these papers at conferences. The popularity of this reaction can be partially attributed to the ease of preparation of the required organoboron reagents, their general stability and the lack of toxic by-products. Progress in the last quarter-century has shown that the Suzuki reaction is incredibly powerful, with examples of  $C(sp^2)-C(sp^3)$  and even  $C(sp^3)-C(sp^3)$  now well documented. It is the cross-coupling reaction of an aryl- or vinyl-boronic acid with an aryl- or vinyl-halide catalyzed by a Pd(0) complex (**Scheme 6**). The reaction also works with pseudohalides, such as triflates (OTf), instead of halides. Boronic esters and organotrifluoroborate salts may be used instead of boronic acids.

# **General transformation**

$$\begin{array}{rcl} \hline \textbf{R}_1 - \textbf{B}\textbf{Y}_2 & + & \hline \textbf{R}_2 - \textbf{X} & \underbrace{ \text{cat. } [\textbf{Pd}^0 \textbf{Ln}] }_{\text{base}} & \hline \textbf{R}_1 - \hline \textbf{R}_2 \\ \hline \textbf{R}_1 = alkyl, alkynyl, aryl, vinyl \\ \textbf{R}_2 = alkyl, alkynyl, aryl, benzyl, vinyl \\ \textbf{X} = \textbf{Br, Cl, I, OAc, OP(=O)(OR)2, OTf} \\ \textbf{Y} = OH, F \end{array}$$

#### Scheme 6

The mechanism of the Suzuki reaction is common as previously discussed. The first step is the oxidative addition of Pd to the halide to form the organopalladium species. This via transmetallation with the boronate complex forms the organopalladium complex. Reductive elimination in the last step restores the original Pd-catalyst with desired product (**Scheme 7**).



Scheme 7 Mechanism of the Suzuki coupling

# 1.3.3. Sonogashira coupling

The coupling of terminal alkynes with vinyl or aryl halides via palladium catalysis was first reported independently and simultaneously by the groups of Cassar and Heck. A few months later, Sonogashira and co-workers<sup>16</sup> demonstrated that, in many cases, this cross-coupling reaction could be accelerated by the addition of cocatalytic CuI salts to the reaction mixture. This protocol was later known as the *Sonogashira reaction* (**Scheme 8**).

# **General transformation**



# Scheme 8

The reaction mechanism is not clearly understood but the reported mechanism revolves around two cycles:

- palladium cycle
- copper cycle

• **The palladium cycle:** The active Pd-catalyst is the 14 electron compound  $Pd^{0}L_{2}$ , complex, which reacts with the aryl or vinyl halide in an oxidative addition to produce a Pd(II) intermediate. This step is believed to be the rate-limiting step of the reaction. This intermediate reacts in a transmetallation step with the copper acetylide, which is produced in the copper cycle. Both organic ligands are transoriented and

convert to cis form in a trans-cis isomerisation. In the final step, reductive elimination takes place to produce the alkyne, with regeneration of the Pd(0)-catalyst.

• *The copper cycle:* It is suggested that the presence of base results in the formation of a  $\pi$ -alkyne complex, which makes the terminal proton on the alkyne more acidic, leading to the formation of the copper acetylide. This copper acetylide continues to react with the Pd intermediate with regeneration of the copper halide.



Scheme 9 Mechanism of the Sonogashira coupling

#### 1.3.4. Buchwald-Hartwig Coupling: The C-N and C-O coupling

The transition metal catalyzed cross-coupling between aryl-halides and triflates and primary or secondary amines to anilines is called the *Buchwald-Hartwig reaction*. Though published as early as 1983 with similar focus, credit for its development is typically assigned to Stephen L. Buchwald and John F. Hartwig, whose publications<sup>17-</sup><sup>23</sup> between 1994 and late 2000<sup>s</sup> established the scope of the transformation. The reaction's synthetic utility stems primarily from the shortcomings of typical methods (nucleophilic substitution, reductive amination, etc.) for the synthesis of aromatic C–N bonds, with most of the methods suffering from limited substrate scope and functional group tolerance. By replacing the amines with alcoholes or phenoles the reaction leads to arylethers, although the rate determining "reductive elimination" step is somewhat more difficult. The yields in the Buchwald-Hartwig reaction can be improved by using sterically and strongly hindered phosphine-ligands or the very potent N-heterocyclic carbenes, which can be made from imidazolium salts.

#### **General transformation**





The first example of a palladium catalyzed C–N cross-coupling reaction was published in 1983 by Migita and co-workers<sup>24</sup>. In 1984, Dale L. Boger and James S. Panek<sup>25</sup> reported an example of Pd(0)-mediated C–N bond formation. These reports remained virtually uncited for a decade, until the reports from the laboratories of Steve Buchwald and John Hartwig. In February 1994, the Hartwig group published a systematic study of the palladium compounds involved in the original Migita paper; their findings indicated that the d<sup>10</sup> complex Pd[P(o-Tolyl)<sub>3</sub>]<sub>2</sub> was the active catalyst

and supported a catalytic cycle involving oxidative addition of the aryl bromide. In May of the same year, Buchwald group published an extension of the Migita paper offering two major improvements over the original paper. First, trans-amination of Bu<sub>3</sub>SnNEt<sub>2</sub> followed by argon purge to remove the volatile diethylamine allowed extension of the methodology to a variety of secondary amines and primary anilines (Scheme 11).

**Reaction:** 







#### Scheme 11

Secondly, the yield for electron rich and electron poor arenes was improved via minor modifications to the reaction procedure, although no *ortho*-substituted aryl groups were included in that publication. The following year, back to back studies from each lab showed that the couplings could be conducted with free amines in the presence of a bulky base, allowing for organotin-free coupling (**Scheme 12**).

**Reaction:** 

ArBr + HNRR' 
$$\xrightarrow{L_2Pd \text{ or } L_2PdCl_2}$$
 ArNRR'  
LiN(SiMe\_3)<sub>2</sub> ArNRR'  
L=P(o-tol)<sub>3</sub>

Catalytic cycle:



#### Scheme 12

Though these improved conditions proceeded at a faster rate, the substrate scope was limited almost entirely to secondary amines due to competitive hydrodehalogenation of the bromoarenes.

After a reasonable discussion for the Pd catalyzed cross-coupling reactions and the mechanisms involved, the next part of this review emphasizes on a particular set of Pd-catalyzed cross-coupling reactions that are  $\alpha$ -arylation of amide functionality.

# 1.4. Palladium catalyzed α-arylation of amides

Palladium-catalyzed couplings of aryl and vinyl halides or pseudohalides with organometallic reagents are widely used in modern synthetic organic chemistry. Despite a wide variety of organometallic reagents mediating these types of cross coupling reactions, examples of enolate additions to aryl and vinyl halides have been limited in scope. This catalytic process has been sufficiently explored and reported by many research groups.  $\alpha$ -Arylation of carbonyl compounds was considered as a

difficult transformation trditionally but with palladium catalysis it has been achieved with simpler and mild methods. Even after that, the  $\alpha$ -arylation of amides is still considered to be one of the most difficult transformations because amides require a strong base to generate the enolate, which (i. e. strong base) has significant drawbacks. Very few groups internationally have worked for the improvement of the methodology to achieve  $\alpha$ -arylation of amides. Among them Hartwig, Honda and Cossy have played a considerable role.

Hartwig group has published several reports for the synthesis of inter- and intramolecular  $\alpha$ -arylation of amides. They have reported an inter-molecular arylation of *N*,*N*-dialkylamide and an intra-molecular arylation of amides for the synthesis of oxindoles in a single paper.<sup>26</sup> For the intermolecular arylation of *N*,*N*-dimethylamides and lactams an aryl halide, silylamide base and a palladium catalyst were utilized and



#### Scheme 14

for intra-molecular arylation of *N*-(2-halophenyl)amides an alkoxide base and a palladium catalyst were used. In these reactions the active palladium catalyst was generated *in situ* from a Pd catlyst Pd(dba)2 (dba=*trans*,*trans*-dibenzylideneacetone)

and a ligand BINAP [2,2-bis(diphenylphosphino)-1,1-binaphthalene] (Schemes 13-14).

To overcome the drawbacks associated with the use of strong base, Hartwig group has reported the intermolecular  $\alpha$ -arylation and vinylation of amides by palladium-catalyzed coupling of aryl bromides and vinyl bromides with zinc enolates of amides.<sup>27</sup> Reactions of three different types of zinc enolates were developed. The reactions of aryl halides occurred in high yields with isolated Reformatsky reagents, generated from  $\alpha$ -bromoamides, and with zinc enolates generated by quenching lithium enolates of amides with zinc chloride. The use of zinc enolates, instead of alkali metal enolates has expanded the scope of amide arylation (**Scheme 15**).

$$R \xrightarrow{O} R \xrightarrow{I} R = \frac{2 \text{mol}\% \text{ Pd}(\text{dba})_2 / 2 \text{mol}\% \text{ Q-Phos}}{\text{ArBr}} \xrightarrow{O} R \xrightarrow{O} R \xrightarrow{I} R \xrightarrow{I}$$

#### Scheme 15

To an extension of the work Hartwig, Cossy and group<sup>28</sup> have reported a general method for the direct  $\alpha$ -arylation of *N*-tosyl and *N*-benzylpiperidinones. They generated zinc enolate *in situ* instead of generating it through Reformatsy reagent which facilitated the yield and fate of the reaction and demonstrated its superiority over alkali metal enolates (**Scheme 16**).



Scheme 16

Honda and group<sup>29</sup> have reported an intra-molecular coupling of aryl halides and amide enolates for the formation of arylisoquinoline derivatives which were further converted into isoquinoline alkaloids cherylline and latifine (**Scheme 17**).



Scheme 17

In summary, the details and applications of palladium chemistry have been reported. A systematic mechanistic approach has been compiled with the emphasis on most widely used palladium catalyzed cross-coupling reactions. An account of a limited type of reactions i. e.  $\alpha$ -arylation of amides has also been explained with suitable examples.