Chapter 1

General Introduction

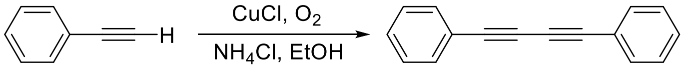
1. General Introduction

With the advent of 21st century numerous synthetically important chemical reactions have been firmly executed by the growing civilization with their innovative ideas. A plethora of organic compounds have been synthesized with their application in medicinal and pharmaceutical agents, fine chemicals, electronics, agrochemicals and related areas. For the construction of nearly every organic molecules, carbon-carbon (C-C) bonds serves as an essential backbone and the formation of C-C bond is regarded as a key transformation in synthetic application. Since the first laboratory construction of C-C bond by Kolbe in 1845 [1], ever-growing number of methods such as nucleophilic additions, substitutions and Friedel-Crafts type reactions are developed for the regio- and stereospecific construction of C-C bonds. However with the contemporary developments in synthetic approach, this bond formation reaction is carried out with pre-functionalized substrates using transition metal catalyst under mild and efficient conditions [2,3]. Transition metal based C-C bond forming strategy have been extensively utilized in industrial processes and are considered as an imperative tool in incorporating essential structural features of bioactive organic molecules.

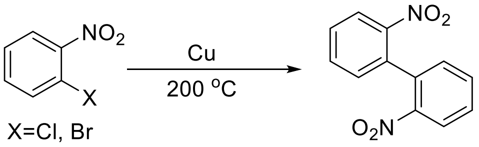
The unique characteristics of transition metal catalyst are the coupling of two organic fragments, a nucleophile and an electrophile in presence of transition metals such as copper, nickel, palladium, iron etc. The first transition metal mediated C-C coupling reaction was reported by Glaser in 1869 [4], using copper(I) salt for the homocoupling of phenylacetylene to give diphenyldiacetylene (Scheme 1.1). In 1901, Ullman homocoupling of aryl halide was reported using stoichiometric amount of copper metal to yield symmetrical biaryl (Scheme 1.2) [5]. Later in 1957, Cadiot-Chodkiewicz presented a selective cross coupling of alkynes with bromoalkynes in presence of catalytic amount of copper salt to give high yield of 1, 3-diyne (Scheme 1.3) [6]. However the emergence of the C-C cross-coupling reaction is increased in 1960s which have revolutionized the field of organic synthesis with the development of palladium and nickel catalytic systems.

1.1. Evolution of Palladium Catalyzed Cross-Coupling Reaction

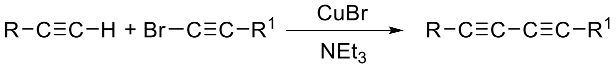
Palladium catalyzed oxidative transformation has been recognized since the production of acetaldehyde by Wacker process. This was the first homogeneous catalysis reaction applied on an industrial scale for the oxidation of ethylene [7,8]. The initial stoichiometric reaction was first reported by Phillips in 1894 [9,10]. Later in 1959, researchers at Wacker Chemie (a German company) reported this similar transformation with acidic solution of catalytic $PdCl_2$ and a stoichiometric amount of $CuCl_2$ in presence of oxygen. It was found that palladium coordinates to the alkene to form a π-complex which after deprotonation and β-hydride elimination generate an enol and a Pd(0) complex. Oxidation of Pd(0) by Cu(II) regenerates the Pd(II) species which is then reoxidized to Cu(II) by molecular oxygen, thereby completing the catalytic cycle. After the successful production plant operation of Wacker Chemie in 1960, Fujiwara in 1967 reported a new synthetic method for substitution of aromatic compounds to an olefin-palladium complex [11]. In the subsequent year, Richard Heck published his article on coupling of organomercuric compound and alkene in presence of catalytic amount of Li_2PdCl_4 [12-18]. Later, this work was extended by Heck and Mizoroki in which they replaced the toxic aryl mercuric halide with an aryl halide in presence of $Pd(OAc)_2$ as the catalytic species (Scheme 1.4) [19].



Scheme 1.1: Copper mediated Glaser coupling.



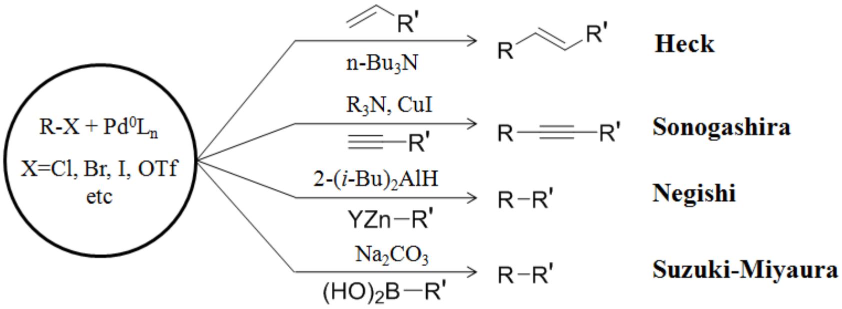
Scheme 1.2: Copper mediated Ulmann coupling.



$$R-C\equiv C-H + Br-C\equiv C-R^1 \xrightarrow[NEt_3]{CuBr} R-C\equiv C-C\equiv C-R^1$$

Scheme 1.3: Copper mediated Cadiot-Chodkiewicz coupling.

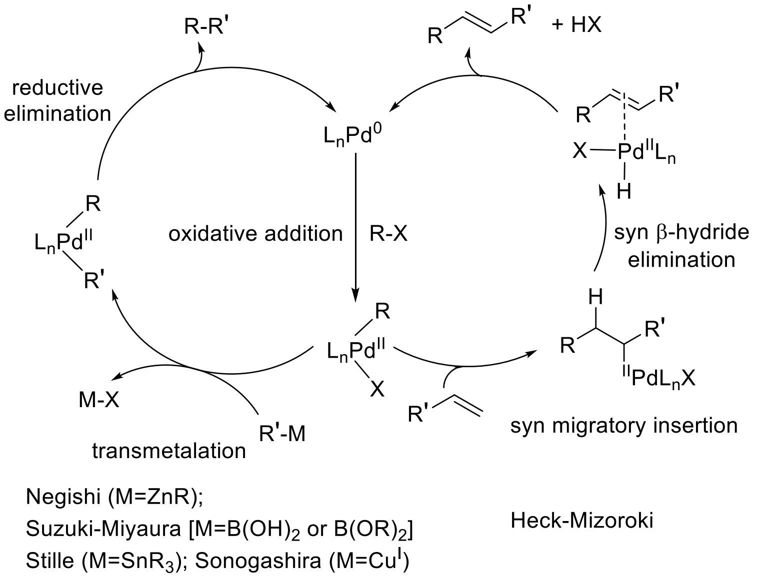
In 1975, Kenkichi Sonogashira, along with Yasuo Tohda, and Nobue Hagihara, reported the palladium catalyzed cross-coupling of C_{sp2}-C_{sp} bonds between a vinyl or an aryl halide and a terminal alkyne, in presence of copper(I) co-catalyst under basic medium (Scheme 1.4) [20]. Another widely employed transition metal catalyzed cross-coupling reaction was developed by Negishi in 1977 using organic halides or triflates and organozinc compounds as coupling partners (Scheme 1.4) [21]. The reaction was performed either in presence of Ni or Pd as the transition metal catalysts, but considering the decay of stereospecifity due to Ni catalyst, the reaction was commonly done in presence of Pd catalyst. Further breakthrough for C-C cross-coupling was made by Akira Suzuki and Norio Miyaura in 1981 with the catalytic transformation of organohalide and organoboron species to biaryl derivatives (Scheme 1.4) [22]. This reaction solely relies on palladium based complexes under basic medium and is readily accepted by the scientific community due to the ease of preparation of organoboron compounds and their resistance towards heat, moisture and air.



Scheme 1.4: Palladium catalyzed common cross-coupling reactions.

The novel contributions made by the Heck, Negishi and Suzuki towards the palladium catalyzed C-C bond forming reaction was recognized by Nobel Committee in 2010, when they were jointly awarded the Nobel Prize in Chemistry. Apart from this flourishing achievements towards C-C bond forming reactions, the emergence of palladium catalysis raises in terms of tolerance towards different functional groups, easily accessible coupling partners, mild reaction conditions and high yield. Some of the relevant oxidative C-C bond formation reactions are Tsuji-Trost [23,24], Stille [25], Hiyama [26], Corriu [27], Kumada [28] etc. These are the nucleophilic substitution-type cross-coupling of organometallic reagents with organic halides. Thereafter the expansion and modification of this organic synthesis continues with the subsequent developments on palladium catalysts and focus has been made towards the simpler and greener reaction conditions.

The ability of palladium to promote both oxidative and reductive processes is the central concept for its consideration for catalytic cross-coupling reaction. It shows high affinity for the soft π- and N-donor ligands and assists in the concerted processes requisite for the catalytic cycle. Since palladium is considered as a metal of choice for myriads of cross-coupling reactions, it consists of same basic mechanistic steps for all the catalytic reactions [29,30]. Initially, Pd(II) precatalyst is *in situ* reduced to Pd(0) species, nevertheless direct Pd(0) sources may also be used. The Pd(0) species then undergo oxidative addition to an aryl halide or pseudohalide to give an arylpalladium(II) complex. From this two alternative catalytic steps may occur, firstly 1, 2-insertion reaction, where a new Pd(II) complex is formed and then undergo β-H elimination to extrude an unsaturated compound (Scheme 1.5). This catalytic cycle occurs in Heck reaction. Secondly, transmetalation, where the halogen is exchanged for another ligand (aryl/heteroaryl fragment) leading to cross-coupling through reductive elimination (Scheme 1.5). This type of catalytic cycle is common for all the cross-coupling reactions. The three mechanistic steps of palladium catalytic cycle for cross-coupling reactions are studied by both experimental and computational method [31].

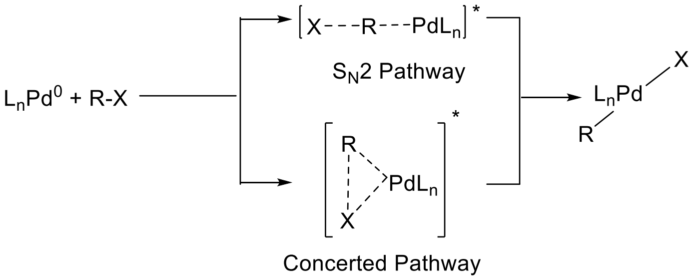


Scheme 1.5: General catalytic cycles for Pd-catalyzed cross-coupling reaction.

1.1.1. Oxidative Addition

The catalytic cycle starts with the Pd zerovalent species, where oxidative addition occurs with the insertion of Pd into the C-X σ-bond, thereby increasing its coordination number by two. Reactivity of cross-coupling of organo-halogen species is of the order I > Br > Cl >> F. The formation of R-Pd-X intermediate *i.e* the oxidative addition step is believed to be the rate determining step [32,33]. As such attention has been paid towards increasing the electron density over palladium in order to accelerate the rate of reaction. The use of strong σ-donating ligand stabilizes the metal oxidation state and accelerates the coordination of substrates to the palladium center. The organo-halide substrates have been known to react through two different mechanisms (Scheme 1.6).

Firstly, the oxidative addition of Pd(0) takes place through S_N2-type process, where the Pd attacks the carbon and halide is displaced to give a cationic species. This is followed by rapid coordination of both the charged species to give the oxidative product. Secondly, a concerted pathway involving a 3-center transition state, followed by intramolecular ligand bond cleavage leading to the formation of a *cis*-[PdL_2RX] complex. Subsequently, the *cis*-complex undergoes rapid isomerization to the more stable *trans*-[PdL_2RX] complex.



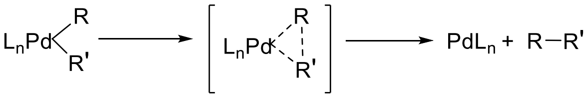
Scheme 1.6: Mechanistic pathways for oxidative addition step.

1.1.2. Transmetalation

The transmetalation step is specific to cross-coupling reaction. This is an organometallic reaction stage which involves the migration of nucleophilic organic group to generate a Pd(II) intermediate bearing the two organic coupling fragments. Several studies have been done on this mechanistic pathway. But the exact mechanism is variable and dependent on the identity of the incoming nucleophile.

1.1.3. Reductive Elimination

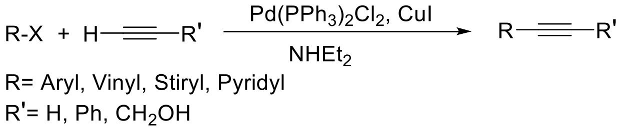
This is the reverse of oxidative addition regenerating the Pd(0) species and eliminates the final coupled product. The mechanism of reductive elimination is analogous to oxidative addition and proceeds via a concerted pathway forming a 3-centered transition state (Scheme 1.7). Prior to elimination, this step is preceded by a *trans/cis* isomerization leading to retention of stereochemistry.



Scheme 1.7: Mechanistic pathways for reductive elimination step.

1.2. Sonogashira Cross-Coupling Reaction

In the arena of alkyne chemistry, one of the most significant developments since 1975 is the palladium catalyzed Sonogashira cross coupling reaction between vinyl/aryl halides and terminal acetylenes in the presence of CuI and amine as reaction medium (Scheme 1.8). This discovery came after Stephens and Castro synthesis of diarylacetylenes by coupling of aryl halides with alkynylcopper(I) species in 1963 [34]. Typically, this reaction is carried out in polar solvents in presence of organic bases depending upon the substrate compatibility. Literature studies refer to the influence of amines on the palladium catalyst in order to enhance the rate of reaction. Other than amine, phosphine and various N-based ligands such as NHC, oxime, salen etc. are used as beneficial possessions to the Pd metal in terms of electron richness, stability and steric shielding of the complex.

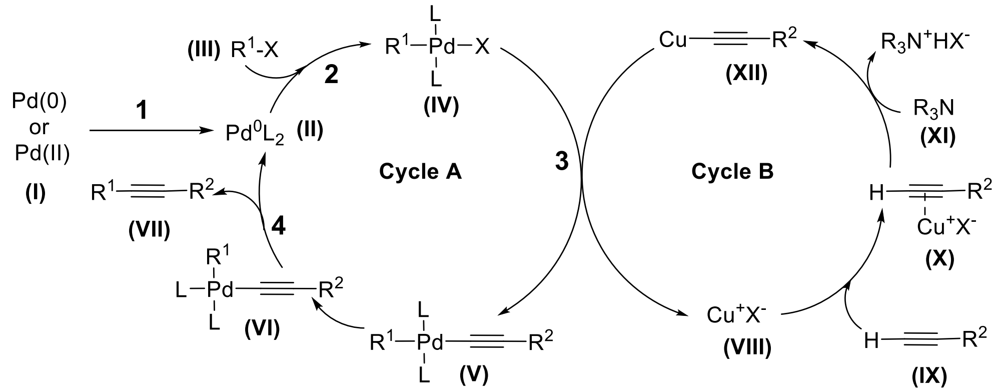


Scheme 1.8: Sonogashira cross-coupling reaction.

1.2.1. Mechanistic Aspects

Though the exact mechanistic pathway is not known, the combined action of palladium and copper catalyst involves two independent catalytic cycles according to the following four successive steps (Scheme 1.9):

1. *Formation of the catalytically active species* Pd^0L_2 *(**II**).*
2. *Oxidative addition of the substrate R-X (**III**) to the catalytically active* Pd^0L_2 *(**II**) species.*
3. *Transmetallation of the copper acetylide units to form organopalladic species (**V**) which further undergoes trans/cis isomerization to form (**VI**).*
4. *Reductive elimination to produce the reaction product (**VII**) followed by regeneration of the catalytically active species (**II**) for a new catalytic cycle.*



Scheme 1.9: Palladium/copper co-catalyzed catalytic cycle for Sonogashira reaction.

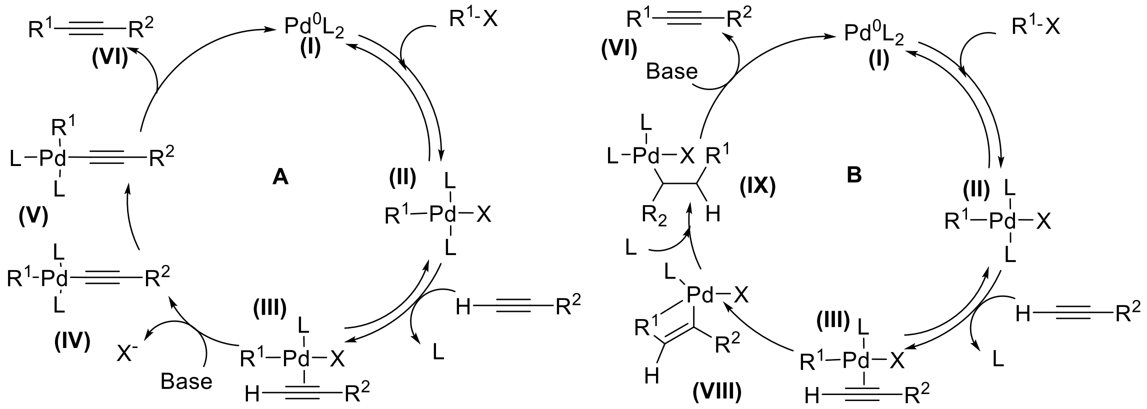
At first oxidative addition occurs with the transformation of Pd(0) to $R^1Pd(II)XL_2$ complex (**IV**). In the next step, i.e. the transmetallation step occurs with the attack of copper acetylide (**XII**) to palladium complex which is generated from copper cycle to form an adduct (**V**). The π-alkyne copper complex (**X**) generated in the copper cycle induces the acidity of acetylenic proton and subsequently captured by the organic or inorganic base (**XI**) from the reaction medium to form the copper acetylide moiety (**XII**). As a result, transmetallation step is facilitated by the *in situ* generated copper acetylide in presence of a base. The adduct (**VI**) undergoes reductive elimination preceded by *trans/cis* isomerization leading to the coupling product (**VII**) with the regeneration of catalytically active species Pd^0L_2.

Although copper co-catalyst increases the reactivity of the reaction, but it possesses significant shortcomings such as decreases the atom economy and additionally required anaerobic condition since presence of oxygen along with copper catalyst leads to the formation of Glaser type homocoupling byproduct [35]. As a result, researchers are nowadays trying to develop Cu free procedures to avoid the undesired homocoupling product of terminal alkynes by making use of either some other co-catalysts like Sn [36], Zn [37], Ag [38], Au [39] etc. or by developing highly active Pd catalytic systems [40].

1.2.2. Copper-Free Sonogashira Coupling Reaction

The copper-free mechanism for Sonogashira coupling involves two mechanistic pathways: (A) Deprotonation and (B) Carbopalladation [41] (Scheme 1.10).

Initially, the proposed catalytic cycle is as usual with the oxidative addition of aryl or vinyl halide with the active Pd^0L_2 species. In the next step, complexation to the Pd(0) catalyst occurs with the displacement of one ligand to create a new intermediate complex. This occurs with a reversible-coordination of the alkyne, producing an alkyne-Pd(II) complex. As a result, the acetylenic proton becomes more acidic and facilitates the ligand exchange in presence of base. In the deprotonation mechanism, a *cis*-square planar intermediate of Pd complex is formed which further undergoes reductive elimination to form the desired product. On the other hand, in the carbopalladation mechanism, the organic fragment is added to the alkyne system followed by ligand coordination and subsequent reductive elimination to yield the coupling product. Although, recent studies have depicted the mechanism of the simple copper free Sonogashira reaction, this reaction is still far off being clearly understood since different catalytic cycles can operate depending on substrates or bases.

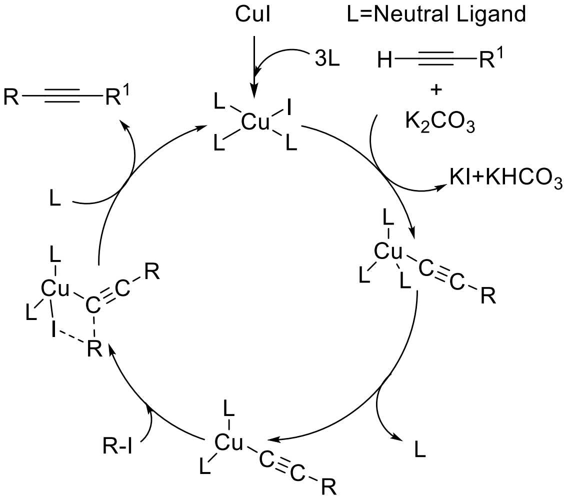


Scheme 1.10: Copper free catalytic cycles for Sonogashira reaction.

1.2.3. Palladium-Free Sonogashira Coupling Reaction

Recently, researchers are searching for a more simplified and cost effective strategies for cross-coupling reaction. Considering the high price of palladium catalyst, nowadays approach has been made towards various palladium-free catalytic systems. Some examples of copper catalyzed palladium-free Sonogashira coupling are CuI/PEG in microwave [42], CuI/Ag_2O [43], CuBr/phen/TBAB [44], CuI/DABCO [45] and Cu NPs [46] in different reaction conditions. Although the exact mechanism for copper catalyzed palladium-free Sonogasihra coupling is not known, according to the Ullmann arylation studies, a proposed Cu(I) based catalytic cycle has been depicted in the literature [47] (Scheme 1.11).

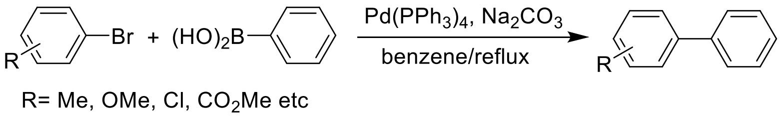
Unlike palladium catalytic cycle, in the first step the coordination/deprotonation of alkyne occurs in presence of base to yield a copper(I) acetylide intermediate. Then oxidative addition takes place with the aryl halide to give a four coordinated copper(III) complex from which the cross-coupling product is expelled and the catalytically active species is reformed by reductive elimination. Apart from copper catalyst, other transition metal catalysts like Fe [48], Au [49], Ni [50], and Co [51] are also used to catalyze palladium free Sonogashira cross-coupling reaction.



Scheme 1.11: Palladium-free copper catalytic cycles for Sonogashira reaction.

1.3. Suzuki-Miyaura Cross-Coupling Reaction

The formation of carbon-carbon bonds by transition metal catalyzed cross-coupling of carbon nucleophiles with carbon electrophiles has emerged to be a key synthetic approach for the construction of complex organic molecules. One of the novel method for C-C cross-coupling was recognized since 2010, when Akira Suzuki received Noble prize for his work on palladium catalyzed cross-coupling of aryl boranes and haloarenes (Scheme 1.12). The biaryl units formed as a result of Suzuki-Miyaura cross-coupling is an important structural scaffold present in natural products, pharmaceuticals, herbicides, conducting polymers, molecular wires and advance functional materials [30].



Scheme 1.12: Suzuki-Miyaura cross-coupling reaction.

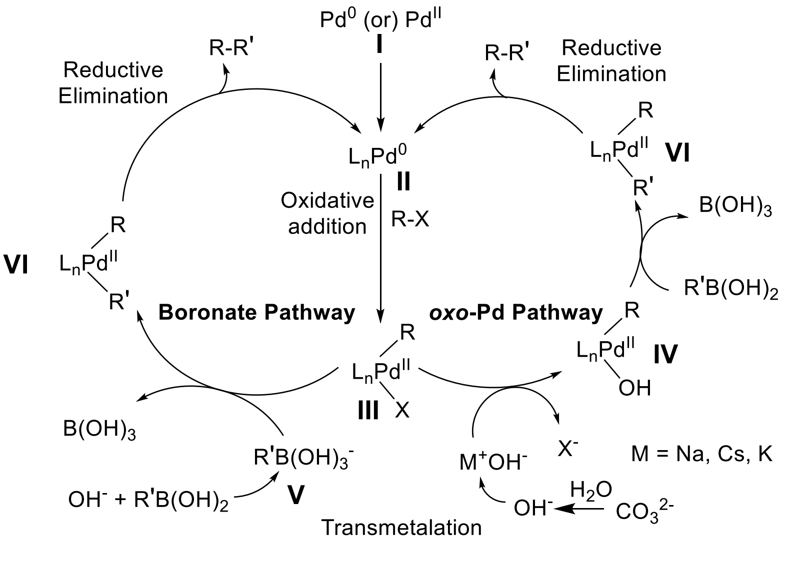
The Suzuki-Miyaura coupling provides a facile and selective way to synthesize wide range of stereoisomeric products. The coupling involves mild reaction condition and the organoboron partners are readily available and stable to/in water, organic solvents, heat and air. Moreover, the inorganic boron by-product of the reaction is non-toxic and easily removable from the reaction mixture thereby making the Suzuki-Miyaura coupling suitable not only for laboratories but also for industrial processes.

1.3.1. Mechanistic Aspects

The mechanism of the Suzuki-Miyaura coupling reaction involves a palladium catalytic cycle which proceeds through the following stages (Scheme 1.13) [52]:

1. *Formation of the catalytically active species Pd^0L_n (**II**).*
2. *Oxidative addition of the organo halogen substrate R-X to the catalytically active Pd^0L_n (**II**) species.*
3. *Transmetallation to generate a new Pd(II) intermediate with two organic coupling fragments*
4. *Reductive elimination to produce the reaction product followed by regeneration of the catalytically active species (**II**) for a new catalytic cycle.*

The oxidative addition of the halide to active palladium species form an R-Pd(L)$_n$-X organopalladium species (**III**). Then it undergoes transmetallation to form the new Pd(II) intermediate. The transmetalation in Suzuki-Miyaura coupling is highly dependent on the base. The exact transmetalation pathway depends in the two main role of external base. Firstly, it may follow an oxo-palladium pathway by substituting the first leaving group, X of (**III**) to form a more reactive *alkoxo*- or *oxo*-palladium species (**IV**). Secondly, a boronate pathway in which base initially activates the organoboron species to form a more nucleophilic tetrahedral boronate species (**V**). Finally, reductive elimination of (**VI**) occurs to give the desired cross-coupling product.



Scheme 1.13: Palladium catalytic cycle for Suzuki-Miyaura cross-coupling reaction.

1.4. The ligands Influence on the Palladium Catalyst

The catalytically active species, Pd(0) in the Suzuki-Miyaura and Sonogashira coupling is coordinated with various ligands in order to improve the reaction efficiency. The effect of ligands on the metal center is both of electronic and steric type. The electron rich bulky ligands enhance the oxidative addition step by increasing the electron density over palladium center and steric effect favours the formation of low coordinate and highly active Pd-complex. The ligands used in combination with palladium are in general: monodentate and bidentate phosphines, *N*-heterocyclic carbenes, palladacycles or salen.

Phosphine based ligands

The effect of increasing steric crowd of the phosphine in C-C cross-coupling reactions was recognized in 1983 when Migita and co-workers introduce P(*o*-tolyl)$_3$ as a ligand in a palladium complex [53]. In early years, most commonly used monodentate phosphine is triphenylphosphine, usually as $Pd^{II}(PPh_3)_2Cl_2$ or $Pd^0(PPh_3)_4$.

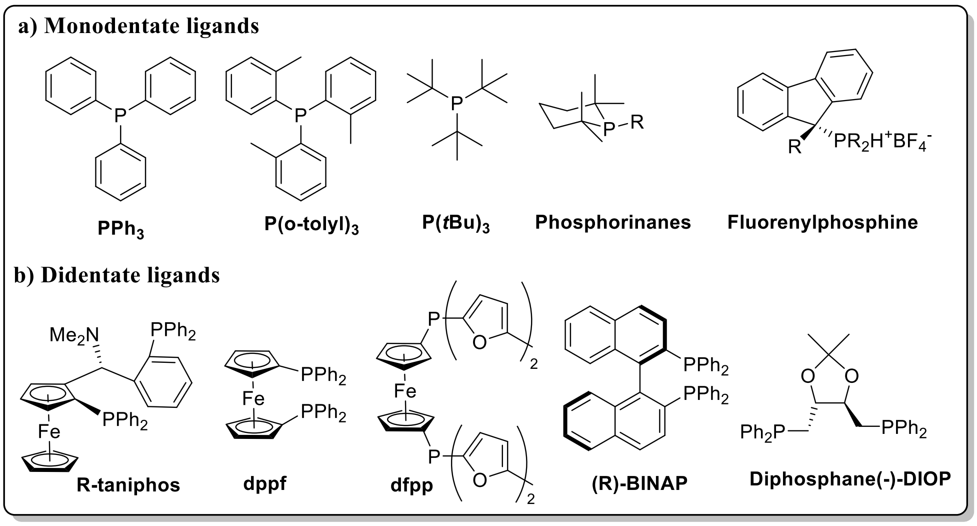


Figure 1.1: Phosphine based ligands for Suzuki-Miyaura and Sonogashira coupling.

But, since 2000, use of bulky phosphines such as P(*t*Bu)$_3$ or P(Cy)$_3$ has been used as a ligand in palladium catalyze C-C cross coupling reaction [,55]. Again bidentate phosphine ligands are more stable than the monodendate ones and apart from enhanced oxidative addition, they accelerates the reductive elimination step, by forcing a *cis* geometry of the moieties to be easily removed and thus increases the overall rate of the reaction [56]. Examples of such ligands in Suzuki-Miyaura and Sonogashira coupling of aryl halides are BINAP and ferrocen derivatives as dppf and dfpp [30,57-59]. In the preceding years several phosphines were designed for palladium catalyzed Suzuki-Miyaura and Sonogashira cross-coupling reaction. Some examples of phosphine based ligands for the cross-coupling reactions are shown in Figure. 1.1 [30,60-63].

Besides these bulky phosphine ligands, various water soluble phosphine based ligands have been developed considering the Green Chemistry perspectives [64]. Figure 1.2 depicts some water soluble phosphanes well-suited for Suzuki-Miyaura and Sonogashira cross-coupling in water. Again some highly reactive phosphine based palladium complexes such as XPhos [65,66], aminophosphane [67,68], *N*-substituted bulky heteroaryl phosphanes [69,70], Xantphos [63,71], SPhos [30,71] etc. were designed for Sonogashira and Suzuki-Miyaura coupling reaction. As already discussed, presence of copper draws significant limitation in Sonogashira coupling. As such these ligands are used in generation of highly effective palladium complexes for copper free Sonogashira coupling reaction.

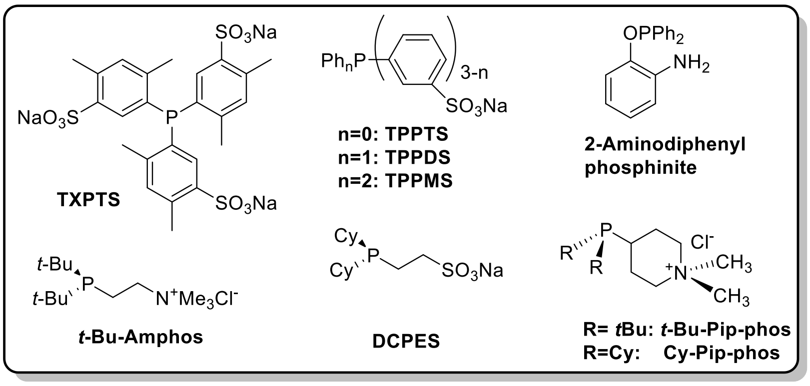


Figure 1.2: Water soluble phosphine based ligands for Suzuki-Miyaura and Sonogashira coupling.

Nitrogen based ligands and palladacycles

Among the N-based ligands, N-heterocyclic carbenes (NHC) serves to be the most prominent for Sonogashira and Suzuki-Miyaura coupling reaction. Some common examples of NHC-palladium complex used in the later two coupling reactions are shown in Figure 1.3a (1-7) [63,72]. Palladacycles as well, proved to be a highly reactive and efficient palladium complex for these cross-coupling reactions. Some common examples of palladacycles are P,C,N-pincer and P,C,P-pincer palladacycle, tridentate pincer ligand based palladacycle, oxime palladacycles and sulfilimine palladacycles. Few examples of palladacycle complexes are depicted in Figure 1.3b (8-14) [63,72].

Other than phosphine and NHC-based ligands, some amines were also used as a ligand source for Sonogashira and Suzuki-Miyaura coupling reaction. Some examples of amines that play dual role as solvent and *in situ* ligand in palladium catalyzed Sonogashira coupling are pyrimidine [73], bispyrimidine [74], hydrazone [75] etc. Simple amines such as DAPCy [76] and DABCO [77] were also used in these coupling reactions in presence of palladium catalyst. Some easily available *N*-containing ligands like imidazole [78], imine [79], oxime [80,81], oxazoline [82], triazole [83], and amino acid [84,85] were also utilized for the said reaction. Other than these, various Schiff base palladium complexes were designed which shows excellent catalytic activity in Suzuki-Miyaura and Sonogashira coupling reaction [86,87].

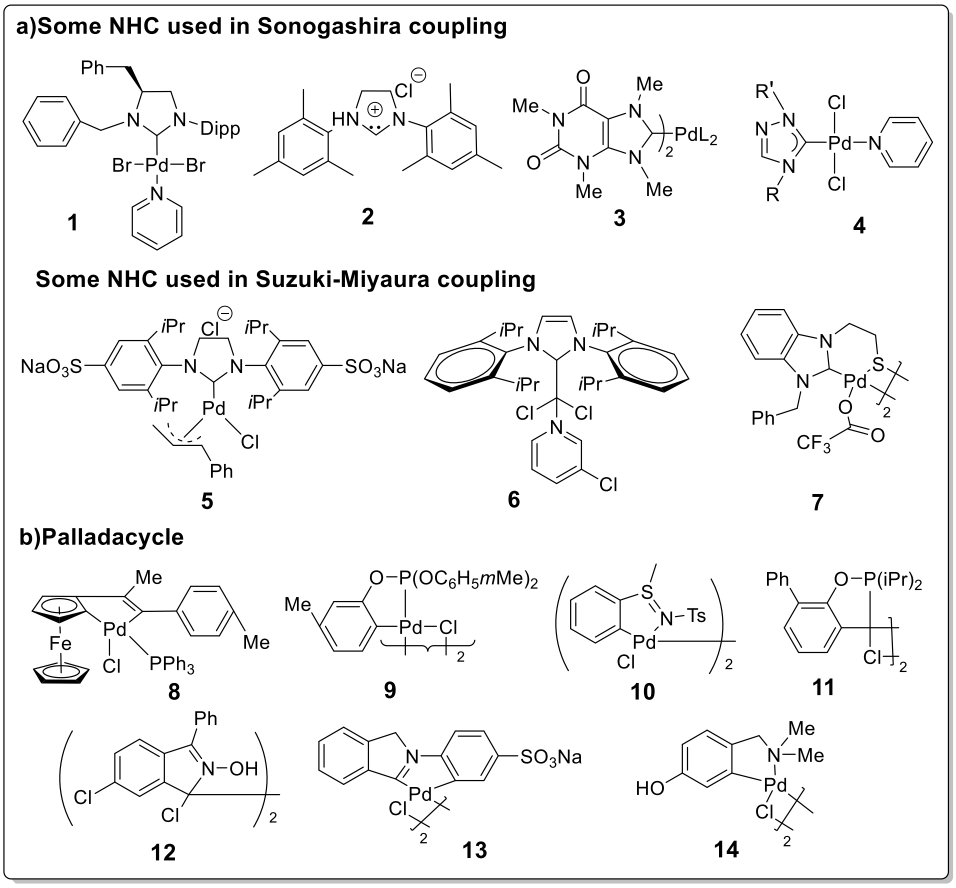
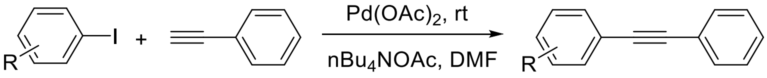


Figure 1.3: **(a)** NHC Palladium complexes **(b)** Palladacycles used in Sonogashira and Suzuki-Miyaura cross-coupling reactions.

1.5. Ligand-free Sonogashira Cross-Coupling Reaction

As we have discussed above, various ligand assisting system for Sonogashira coupling have been developed. However, ligand based system cause difficulty in isolation of product and requires additional synthesizing approach. Moreover, industrial wastes, containing them would lead to environmental deposition and as such requires additional treatment which increases the overall cost of the procedure. Considering the industrial and economic standpoint, a ligandless and copper-free process would serve as better catalytic systems for Sonogashira couplings. Further, such a process would be advantageous for synthetic chemists who prefer inexpensive and simple reaction protocols. As such various ligand-free protocols have been developed for the Sonogashira coupling reaction. The first ligand-free approach for this coupling reaction was developed by Urgaonkar and Verkade using tetrabutylammonium acetate in presence of $Pd(OAc)_2$ (Scheme 1.14) [88]. Later various ligand-free catalytic systems have been developed using various salt additives along with palladium salt for the coupling reaction [89,90].



Scheme 1.14: Urgaonkar’s and Verkade’s ligand-free Sonogashira reaction.

Nowadays, another suitable alternative i.e. metal nanoparticle (NP) with high catalytic potential have been developed which connects both the homogeneous and heterogeneous catalyst. They possess high surface active sites thereby enhancing the contact between reactants and the catalyst [91]. However, their insolubility in the reaction medium facilitates easy separation from the reaction mixture like heterogeneous catalysts, which in turn make the isolation of product easier. The selectivity, catalytic activity and stability of these catalysts depend upon its shape, size, compositions and the method of its preparation. The activity and selectivity of the nanocatalyst can be manipulated by tuning its chemical and physical properties. Various methods for generation of metal NPs both by *in situ* and *ex situ* approach (such as chemical, physical and biological) are reported in the literature [92,93]. They are widely used as effective catalytic system for ligand-free Sonogashira coupling reaction. Literature reveals lots of work regarding Pd NPs catalyzed ligand-free Sonogashira reaction [63]. Various bimetallic NPs such as Pd/Cu [94], Pd/Ni [95], Pd/Au [96] and Pd/Co [97] are effective for this cross-coupling reaction. Apart from these nano catalytic systems, various supported Pd NPs are used to catalyzed Sonogashira cross-coupling reaction. Some common examples are Pd NPs supported on rGO [98], Pd NPs supported on MOF-5 [99], Pd NPs supported on Chitosan [100] and Pd NPs supported on polysaccharide derived mesoporous material [101,102]. The heterogeneous catalytic system facilitates easy separation by simple filtration and provides greater reusability of the catalyst. Few reported works on ligand-free Sonogashira coupling are listed in Table 1.1.

Table 1.1: Ligand-free Sonogashira coupling reaction

$$R{-}X + \equiv{-}R' \xrightarrow{\text{Reaction condition}} R{-}\equiv{-}R'$$

Entry	Reaction condition	Ref	Entry	Reaction condition	Ref
1	$PdCl_2$/AgI, Et_3N, MeCN	[103]	6	$Pd(OAc)_2$, MeOH/MeCN(1:1), K_2CO_3	[104]
2	$PdCl_2$/Na_2SO_4, K_2CO_3, EtOH	[89]	7	Pd/Fe_3O_4 NPs, DMF, Piperidine	[105]
3	$Pd(OAc)_2$/DABCO, Ball mill(800 rpm)	[106]	8	Au/Ag/Pd Trimetallic NP, K_2CO_3, DMF-H_2O	[107]
4	$PdCl_2$, Acetone or [bbim]BF_4, TEA, ultrasound	[108]	9	rGO@Cu/Pd, KOH, DMF,	[109]
5	Pd/C, $Na_3PO_4.12H_2O$, *i*PrOH	[110]	10	Silica@Pd(0), microwave (200W)	[111]

1.6. Ligand-free Suzuki-Miyaura Cross-Coupling Reaction

The first ligand-free approach for Suzuki-Miyaura cross-coupling was reported by Beletskaya by cross-coupling of organic halides with organic derivatives of tin, mercury and copper in presence of palladium [112]. Later in 1997, Badone and co-workers reported an alternative strategy using aryl halides and triflates in presence of $Pd(OAc)_2$, TBAB and water [113]. Since then various ligand-free approaches for Suzuki-Miyaura cross-coupling has been developed. However, Pd NPs serves to be a promising alternative amongst all the palladium based catalytic system regarding reactivity, stability, cost and toxicity. Due to their high surface-to-volume ratio and greater surface active sites as compared to bulk catalyst, makes them very effective for Suzuki-Miyaura coupling reaction. Moreover, they avoid laborious preparative methods and additionally do not hamper the product isolation procedure. Although, Pd NPs show excellent catalytic potential in the reaction system, in some cases their synthetic routes require high temperature, ultra sonication, and active chemical reducing agents. Again use of chemical reducing agent for reduction of palladium(II) species leads to toxic environmental deposition. As such synthesis of Pd NPs at room temperature in absence of external reducing agent is a very fascinating approach in the field of nanocatalysis. In this respect biogenic reducing agent such as plant extracts and microorganisms were adopted for the generation of metal NPs [114].

Again various heterogeneous catalytic systems such as Pd NPs embedded on heterogeneous solid support have been used for the Suzuki-Miyaura coupling reaction.

They have profound advantages over homogeneous catalytic systems such as easy recovery with least contamination by simple filtration, magnetic separation, decantation etc. and reuse of the catalyst without significant loss in efficiency. Some effective solid supports which provides an easy platform for synthetic applications are silica, alumina, PVC, MCM-41, SBA-15, polymeric materials, clay, charcoal etc. Some typical examples for heterogeneous supported Pd NPs used in Suzuki-Miyaura coupling are Pd-mesoporous silica, Pd-PEG-NHC, Pd-zeolite, Pd-rGO etc. [115-117]. Few examples of ligand-free Suzuki-Miyura cross-coupling reaction are shown in Table 1.2.

Table 1.2: Ligand-free Suzuki-Miyaura coupling reaction

$$R{-}X + (HO)_2B{-}R' \xrightarrow{\text{Reaction condition}} R{-}R'$$

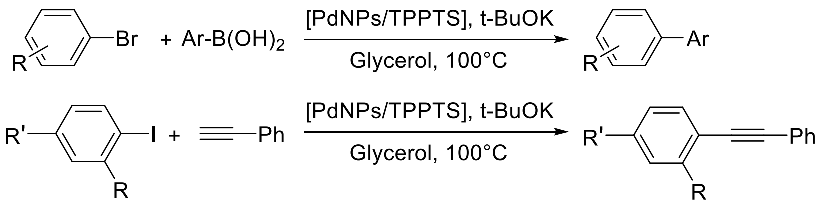
Entry	Reaction condition	Ref	Entry	Reaction condition	Ref
1	$Pd(OAc)_2$, Na_2CO_3, PEG-H_2O	[118]	6	$PdCl_2$, Na_2SO_4, *i*PrOH/ H_2O	[119]
2	$Pd(OAc)_2$, K_2CO_3, EtOH/DMA	[120]	7	$Pd/BaSO_4$, K_2CO_3, PEG-H_2O	[121]
3	$PdCl_2$, K_2CO_3, DMF/ H_2O	[122]	8	Pd(II)-SBA-16, K_2CO_3, EtOH/ H_2O	[123]
4	Pd/C, K_2CO_3, DMA/ H_2O	[124]	9	$Pd(OAc)_2$, Glucose, K_2CO_3,*i*PrOH	[125]
5	$Pd(OAc)_2$, K_2CO_3, PEG-400	[126]	10	Chitosan-Ulva@Pd,K_2CO_3,	[127]

1.7. Cross-coupling Reaction in Green Solvent

It has been estimated that about 80% of the chemical waste from a synthetic processes corresponds to the use of solvents. Solvents are the key source which gives rise to toxicity, pollution and waste treatment issues. The main role of solvent in the reaction system other than substrate mixing is that, they control the reaction rates, selectivity and the position of equilibrium. So, the appropriate choice of a solvent for an effective catalytic transformation is of prime necessity.

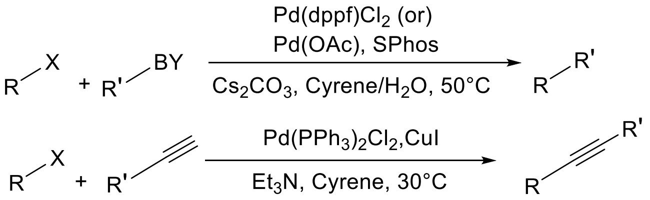
In order to meet the Green Chemistry principle, the best solution is to substitute the classical VOCs based methodologies with green and cleaner non-conventional alternatives. During the past decades various promising green solvents such as ionic liquids [128], polyethylene glycol [129], supercritical fluids [130,131] (particularly supercritical carbon dioxide, $scCO_2$) and perfluorinated solvents [132] were introduced for chemical transformations. However apart from their positive effect such as low volatility, structural tenability and high heat capacity, they bear certain drawbacks, like high cost, toxicity and long-tedious synthetic methods.

Nowadays biomass derived solvents has grown to be an emerging interest for the researchers due to their attractive advantages such as biodegradability, low vapor pressure, and high boiling point. Various bio-based solvents, such as glycerol, 2-methyltetrahydrofuran, ethyl lactate, and cyrene have been used for synthetic application. These solvents assist the reaction to achieve better efficiency in terms of catalyst activity, selectivity, stability and reusability, and also help in the product isolation processes [133]. Recently reports have been found where these green solvent systems were applied to Suzuki-Miyaura and Sonogashira coupling. Glycerol performs well at relatively high temperature conditions due to its high boiling and good thermal stability. Gómez and co-workers reported a Pd NPs catalyzed Suzuki-Miyaura and Sonogashira coupling in glycerol where excellent cross-coupling was observed (Scheme.1.15) [134].



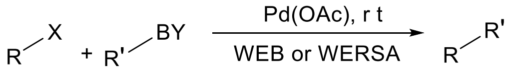
Scheme 1.15: Glycerol as solvent in Suzuki-Miyaura and Sonogashira coupling.

Another bio-based solvent cyrene (dihydrolevoglucosenone) have been commercialized in recent years which serve as an alternative to DMF and NMP with identical physical properties. Watson and his group reported a highly efficient Suzuki-Miyaura and Sonogashira reaction using cyrene as a bio-alternative to DMF (Scheme 1.16) [135,136].



Scheme 1.16: Cyrene as solvent in Suzuki-Miyaura and Sonogashira coupling.

In spite of the unique characteristics of these bio-based solvents, they still possess issues similar to petroleum based solvents. As a result, a novel type of solvent particularly derived from agro-waste extracts (AWEs) has been developed in the recent years. Sarma et al. for the first time reported a Suzuki-Miyaura cross-coupling reaction using ash water extract of banana peel (WEB) (Scheme.1.17) [137]. The banana peels contain high distribution of potassium, sodium, carbonate and chloride with a host of other trace elements. These elemental compositions in WEB act as promoters for Suzuki-Miyaura coupling reaction and additionally provide an *in situ* basic medium to the reaction system. Later another alternative source has been developed using water extract of rice straw ash (WERSA) (Scheme.1.17) [138] and showed similar efficiency in Suzuki-Miyaura cross-coupling reaction. As such development of AWEs proves to be an excellent alternative medium in the field of organic transformation.



Scheme 1.17: Suzuki-Miyaura coupling reaction using WEB and WERSA

1.8. Conclusions

Since palladium catalyzed cross-coupling reaction is one of most the powerful method for development of C-C bonds, this introductory review presents the advancements made in the field of Sonogashira and Suzuki-Miyaura cross-coupling reaction. We have included the developments of different ligands and other palladium based catalytic system for these respective cross-coupling reactions. Recent developments of green solvent system utilized in Suzuki-Miyaura and Sonogashira cross-coupling reaction have also been presented in this section.

1.9. Thesis Outline

Through this thesis, we wish to report some newer catalytic protocol for Suzuki-Miyaura and Sonogashira cross-coupling reaction. The works are primarily based on green methodologies such as development of alternative medium for ligands assisting catalytic system, design of safer and environmentally benign solvent system, design of reusable, low cost and bio-based catalyst for the Suzuki-Miyaura and Sonogashira cross-coupling reaction. Detailed experimental procedures and systematic investigation of the reaction parameters and substrate compatibility along with results and discussion for each methodology will be presented in the following chapters. Spectroscopic and analytical data of the synthesized organic moiety and catalyst will be provided in each section.

1.10. References

[1] Kolbe, H. "Beiträge zur Kenntniß der gepaarten Verbindungen"[Contributions to [our] knowledge of paired compounds]. *Annalen der Chemie und Pharmacie (in German),* 54(2):145-188, 1845.

[2] Evano, G., Blanchard, N., and Toumi, M. Copper-mediated coupling reactions and their applications in natural products and designed biomolecules synthesis. *Chemical Reviews*, 108(8):3054-3131, 2008.

[3] Cahiez, G. and Moyeux, A. Cobalt-catalyzed cross-coupling reactions. *Chemical Reviews*, 110(3):1435-1462, 2010.

[4] Glaser, C. Preparation of diethynylbenzenes. *Ber Dtsch Chem Ges*, 2(1):422-424, 1869.

[5] Ullmann, F. and Bielecki, J. Ueber synthesen in der biphenylreihe. *Berichte der deutschen chemischen Gesellschaft*, 34(2):2174-2185, 1901.

[6] Chodkiewicz, W. Synthesis of acetylenic compounds. *Ann de Chimie (Paris),* 2:819-869, 1957.

[7] Smidt, J., Hafner, W., Jira, R., Sedlmeier, J., Sieber, R., Rüttinger, R., and Kojer, H. Katalytische umsetzungen von olefinen an platinmetall-verbindungen das consortium-verfahren zur herstellung von acetaldehyd. *Angewandte Chemie*, 71(5):176-182, 1959.

[8] Smidt, J., Hafner, W., Jira, R., Sieber, R., Sedlmeier, J., and Sabel, A. The oxidation of olefins with palladium chloride catalysts. *Angewandte Chemie International Edition in English*, 1(2):80-88, 1962.

[9] Phillips, F. C. Researches upon the phenomena of oxidation and chemical properties of gases. *American Chemical Journal*, 16:255-277,1894.

[10] Phillips, F. C. Untersuchungen über die chemischen Eigenschaften von Gasen. I. Mitteilung. Erscheinungen bei der Oxydation von Wasserstoff und Kohlenwasserstoffen. *Zeitschrift für Anorganische Chemie*, 6(1):213-228, 1894.

[11] Moritanl, I. and Fujiwara, Y. Aromatic substitution of styrene-palladium chloride complex. *Tetrahedron Letters*, 8(12):1119-1122, 1967.

[12] Heck, R. F. Acylation, methylation, and carboxyalkylation of olefins by group viii metal derivatives. *Journal of the American Chemical Society*, 90(20):5518-5526, 1968.

[13] Heck, R. F. The arylation of allylic alcohols with organopalladium compounds. A new synthesis of 3-aryl aldehydes and ketones. *Journal of the American Chemical Society*, 90(20):5526-5531, 1968.

[14] Heck, R. F. Allylation of aromatic compounds with organopalladium salts. *Journal of the American Chemical Society*, 90(20):5531-5534, 1968.

[15] Heck, R. F. The palladium-catalyzed arylation of enol esters, ethers, and halides. a new synthesis of 2-aryl aldehydes and ketones. *Journal of the American Chemical Society*, 90(20):5535-5538, 1968.

[16] Heck, R. F. Aromatic haloethylation with palladium and copper halides. *Journal of the American Chemical Society*, 90(20):5538-5542, 1968.

[17] Heck, R. F. The addition of alkyl and arylpalladium chlorides to conjugated dienes. *Journal of the American Chemical Society*, 90(20):5542-5546, 1968.

[18] Heck, R. F. A synthesis of diaryl ketones from arylmercuric salts. *Journal of the American Chemical Society*, 90(20):5546-5548, 1968.

[19] Mizoroki, T., Mori, K., and Ozaki, A. Arylation of olefin with aryl iodide catalyzed by palladium. *Bulletin of the Chemical Society of Japan*, 44(2):581-581, 1971.

[20] Sonogashira, K., Tohda, Y., and Hagihara, N. A convenient synthesis of acetylenes: Catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines. *Tetrahedron Letters*, 16(50):4467-4470, 1975.

[21] Negishi, E., King, A. O., and Okukado, N. Selective carbon-carbon bond formation via transition metal catalysis: a highly selective synthesis of unsymmetrical biaryls and diarylmethanes by the nickel or palladium-catalyzed reaction of aryl and benzylzinc derivatives with aryl halides. *The Journal of Organic Chemistry*, 42(10):1821-1823, 1977.

[22] Miyaura, N., Yanagi, T., and Suzuki, A. The palladium-catalyzed cross-coupling reaction of phenylboronic acid with haloarenes in the presence of bases. *Synthetic Communications*, 11(7):513-519, 1981.

[23] Tsuji, J., Takahashi, H., and Morikawa, M. Organic syntheses by means of noble metal compounds xvii. reaction of π-allylpalladium chloride with nucleophiles. *Tetrahedron Letters*, 6(49):4387-4388, 1965.

[24] Trost, B. M. and Fullerton, T. J. New Synthetic reactions. allylic alkylation. *Journal of the American Chemical Society*, 95(1):292-294, 1973.

[25] Milstein, D. and Stille, J. K. A general, selective, and facile method for ketone synthesis from acid chlorides and organotin compounds catalyzed by palladium. *Journal of the American Chemical Society*, 100(11):3636-3638, 1978.

[26] Hatanaka, Y. and Hiyama, T. Cross-coupling of organosilanes with organic halides mediated by a palladium catalyst and tris (diethylamino) sulfonium difluorotrimethylsilicate. *The Journal of Organic Chemistry*, 53(4):918-920, 1988.

[27] Corriu, R. J. P. and Masse, J. P. Activation of grignard reagents by transition-metal complexes. a new and simple synthesis of trans-stilbenes and polyphenyls. *Journal of the Chemical Society, Chemical Communications*, 0(3):144a-144a, 1972.

[28] Tamao, K., Sumitani, K., and Kumada, M. Selective carbon-carbon bond formation by cross-coupling of grignard reagents with organic halides. catalysis by nickel-phosphine complexes. *Journal of the American Chemical Society*, 94(12):4374-4376, 1972.

[29] Denmark, S. E. and Sweis, R. F. *Metal-Catalyzed Cross-Coupling Reactions*. Wiley-VCH, Weinheim, Germany, 2004.

[30] Biajoli, A. F., Schwalm, C. S., Limberger, J., Claudino, T. S., and Monteiro, A. L. Recent progress in the use of pd-catalyzed C-C cross-coupling reactions in the synthesis of pharmaceutical compounds. *Journal of the Brazilian Chemical Society*, 25(12):2186-2214, 2014.

[31] García-Melchor, M., Braga, A. A., Lledos, A., Ujaque, G., and Maseras, F. Computational perspective on pd-catalyzed C-C cross-coupling reaction mechanisms. *Accounts of Chemical Research*, 46(11):2626-2634, 2013.

[32] Christmann, U. and Vilar, R. Monoligated palladium species as catalysts in cross-coupling reactions. *Angewandte Chemie International Edition*, 44(3):366-374, 2005.

[33] Smith, G. B., Dezeny, G. C., Hughes, D. L., King, A. O., and Verhoeven, T. R. Mechanistic studies of the Suzuki cross-coupling reaction. *The Journal of Organic Chemistry*, 59(26):8151-8156, 1994.

[34] Stephens, R. D. and Castro, C. E. The substitution of aryl iodides with cuprous acetylides. A synthesis of tolanes and heterocyclics. *The Journal of Organic Chemistry*, 28(12):3313-3315, 1963.

[35] Evano, G., Blanchard, N., and Toumi, M. Copper-mediated coupling reactions and their applications in natural products and designed biomolecules synthesis. *Chemical Reviews*, 108(8):3054-3131, 2008.

[36] Negishi, E. I. and Anastasia, L. Palladium-catalyzed alkynylation. *Chemical Reviews*, 103(5):1979-2018, 2003.

[37] Finke, A. D., Elleby, E. C., Boyd, M. J., Weissman, H., and Moore, J. S. Zinc chloride-promoted aryl bromide−alkyne cross-coupling reactions at room temperature. *The Journal of Organic Chemistry*, 74(22):8897-8900, 2009.

[38] Mori, A., Kawashima, J., Shimada, T., Suguro, M., Hirabayashi, K., and Nishihara, Y. Non-Sonogashira-type palladium-catalyzed coupling reactions of terminal alkynes assisted by silver (I) oxide or tetrabutylammonium fluoride. *Organic Letters*, 2(19):2935-2937, 2010.

[39] Lauterbach, T., Livendahl, M., Rosellón, A., Espinet, P., and Echavarren, A. M. Unlikeliness of Pd-free gold (I)-catalyzed Sonogashira coupling reactions. *Organic Letters*, 12(13):3006-3009, 2010.

[40] Nájera, C., Gil-Moltó, J., Karlström, S., and Falvello, L. R. Di-2-pyridylmethylamine-based palladium complexes as new catalysts for Heck, Suzuki, and Sonogashira reactions in organic and aqueous solvents. *Organic Letters*, 5(9):1451-1454, 2003.

[41] Ljungdahl, T., Bennur, T., Dallas, A., Emtenäs, H., and Mårtensson, J. Two competing mechanisms for the copper-free Sonogashira cross-coupling reaction. *Organometallics*, 27(11):2490-2498, 2008.

[42] Chen, G., Xie, J., Weng, J., Zhu, X., Zheng, Z., Cai, J., and Wan, Y. CuI/PPh3/PEG–Water: An efficient catalytic system for cross-coupling reaction of aryl iodides and alkynes. *Synthetic Communications*, 41(21):3123-3133, 2011.

[43] Pan, C., Luo, F., Wang, W., Ye, Z., and Cheng, J. Ligand-free copper (I)-catalyzed Sonogashira-type coupling of arylboronic acids with terminal alkynes. *Tetrahedron Letters*, 50(35):5044-5046, 2009.

[44] Yang, D., Li, B., Yang, H., Fu, H., and Hu, L. Efficient copper-catalyzed Sonogashira couplings of aryl halides with terminal alkynes in water. *Synlett*, 2011(05):702-706, 2011.

[45] Li, J. H., Li, J. L., Wang, D. P., Pi, S. F., Xie, Y. X., Zhang, M. B., and Hu, X. C. Cu(I)-catalyzed Suzuki-Miyaura and Sonogashira cross-coupling reactions using DABCO as ligand. *The Journal of Organic Chemistry*, 72(6):2053-2057, 2007.

[46] Thathagar, M. B., Beckers, J., and Rothenberg, G. Palladium-free and ligand-free Sonogashira cross-coupling. *Green Chemistry*, 6(4):215-218, 2004.

[47] Monnier, F., Turtaut, F., Duroure, L., and Taillefer, M. Copper-catalyzed Sonogashira-type reactions under mild palladium-free conditions. *Organic Letters*, 10(15):3203-3206, 2008.

[48] Carril, M., Correa, A., and Bolm, C. Iron-catalyzed Sonogashira reactions. *Angewandte Chemie International Edition*, 47(26):4862-4865, 2008.

[49] Li, P., Wang, L., Wang, M., and You, F. Gold (I) iodide catalyzed Sonogashira reactions. *European Journal of Organic Chemistry*, 2008(35):5946-5951, 2008.

[50] Bakherad, M., Keivanloo, A., and Mihanparast, S. Nickel-catalyzed alkynylation of aryl iodides (Sonogashira Reaction) in water. *Synthetic Communications*, 40(2):179-185, 2009.

[51] Hajipour, A. R., Rezaei, F., and Khorsandi, Z. Pd/Cu-free Heck and Sonogashira cross-coupling reaction by co nanoparticles immobilized on magnetic chitosan as reusable catalyst. *Green Chemistry*, 19(5):1353-1361, 2017.

[52] Mathew, J. S., Klussmann, M., Iwamura, H., Valera, F., Futran, A., Emanuelsson, E. A., and Blackmond, D. G. Investigations of Pd-catalyzed ArX coupling reactions informed by reaction progress kinetic analysis. *The Journal of organic chemistry*, 71(13):4711-4722, 2006.

[53] Kosugi, M., Kameyama, M., and Migita, T. Palladium-catalyzed aromatic amination of aryl bromides with N, N-diethylamino-tributyltin. *Chemistry Letters*, 12(6):927-928, 1983.

[54] Hundertmark, T., Littke, A. F., Buchwald, S. L., and Fu, G. C. Pd(PhCN) $2Cl_2$/P (t-Bu)$_3$: A versatile catalyst for Sonogashira reactions of aryl bromides at room temperature. *Organic Letters*, 2(12):1729-1731, 2000.

[55] Yi, C. and Hua, R. Efficient copper-free $PdCl_2(PCy_3)_2$-catalyzed Sonogashira coupling of aryl chlorides with terminal alkynes. *The Journal of Organic Chemistry*, 71(6):2535-2537, 2006.

[56] Birkholz, M. N., Freixa, Z., and van Leeuwen, P. W. Bite angle effects of diphosphines in C–C and C–X bond forming cross coupling reactions. *Chemical Society Reviews*, 38(4):1099-1118, 2009.

[57] Luo, Y., Gao, H., Li, Y., Huang, W., Lu, W., and Zhang, Z. Copper-free Sonogashira reaction using 7-chloro camptothecins. *Tetrahedron*, 62(11):2465-2470, 2006.

[58] Hopkins, C. R. and Collar, N. 6-Substituted-5H-pyrrolo [2, 3-b] Pyrazines via palladium-catalyzed heteroannulation from n-(3-chloropyrazin-2-yl)-methanesulfonamide and alkynes. *Tetrahedron Letters*, 45(43):8087-8090, 2004.

[59] Hierso, J. C., Fihri, A., Amardeil, R., Meunier, P., Doucet, H., and Santelli, M. Use of a bulky phosphine of weak σ-donicity with palladium as a versatile and highly-active catalytic system: allylation and arylation coupling reactions at 10-1-10-4 mol% catalyst loadings of ferrocenyl bis (difurylphosphine)/Pd. *Tetrahedron*, 61(41):9759-9766, 2005.

[60] Brenstrum, T., Clattenburg, J., Britten, J., Zavorine, S., Dyck, J., Robertson, A. J., and Capretta, A. Phosphorinanes as Ligands for palladium-catalyzed cross-coupling chemistry. *Organic Letters*, 8(1):103-105, 2006.

[61] Fleckenstein, C. A. and Plenio, H. 9-Fluorenylphosphines for the Pd-catalyzed Sonogashira, Suzuki, and Buchwald–Hartwig coupling reactions in organic solvents and water. *Chemistry-A European Journal*, 13(9):2701-2716, 2007.

[62] Fu, X. L., Wu, L. L., Fu, H. Y., Chen, H., and Li, R. X. Efficient diphosphane-based catalyst for the palladium-catalyzed Suzuki cross-coupling reaction of 3-pyridylboronic Acids. *European Journal of Organic Chemistry*, 2009(13):2051-2054, 2009.

[63] Chinchilla, R. and Nájera, C. Recent advances in Sonogashira reactions. *Chemical Society Reviews*, 40(10):5084-5121, 2011.

[64] DeVasher, R. B., Moore, L. R., and Shaughnessy, K. H. Aqueous-phase, palladium-catalyzed cross-coupling of aryl bromides under mild conditions, using water-soluble, sterically demanding alkylphosphines. *The Journal of Organic Chemistry*, 69(23):7919-7927, 2004.

[65] Gelman, D. and Buchwald, S. L. Efficient palladium-catalyzed coupling of aryl chlorides and tosylates with terminal alkynes: Use of a copper co-catalyst inhibits the reaction. *Angewandte Chemie International Edition*, 115(48):6175-6178, 2003.

[66] Surry, D. S. and Buchwald, S. L. Biaryl phosphane ligands in palladium-catalyzed amination. *Angewandte Chemie International Edition*, 47(34):6338-6361, 2008.

[67] Cheng, J., Sun, Y., Wang, F., Guo, M., Xu, J. H., Pan, Y., and Zhang, Z. A copper and amine-free Sonogashira reaction employing aminophosphines as ligands. *The Journal of Organic Chemistry*, 69(16):5428-5432, 2004.

[68] Cheng, J., Wang, F., Xu, J. H., Pan, Y., and Zhang, Z. Palladium-catalyzed Suzuki–Miyaura reaction using aminophosphine as ligand. *Tetrahedron Letters*, 44(37):7095-7098, 2003.

[69] Torborg, C., Huang, J., Schulz, T., Schaeffner, B., Zapf, A., Spannenberg, A., and Beller, M. Improved Palladium-catalyzed Sonogashira coupling reactions of aryl chlorides. *Chemistry-A European Journal*, 15(6):1329-1336, 2009.

[70] Maluenda, I. and Navarro, O. Recent developments in the Suzuki-Miyaura reaction: 2010–2014. *Molecules*, 20(5):7528-7557, 2015.

[71] Blakemore, D. C. Suzuki–Miyaura coupling. In Blakemore, D. C., Doyle, P. M., and Fobian, Y. M., editors, *Synthetic Methods in Drug Discovery*, volume 1. pages 1-69, 978-1-78262-208-6. Royal Society of Chemistry, London, UK, 1 august 2016.

[72] Gürbüz, N., Karaca, E. Ö., Özdemir, İ., and Cetinkaya, B. Cross coupling reactions catalyzed by (NHC)Pd(II) complexes. *Turkish Journal of Chemistry*, 39(6):1115-1157, 2015.

[73] Li, J. H., Zhang, X. D., and Xie, Y. X. Efficient and copper-free Sonogashira cross-coupling reaction catalyzed by Pd $(OAc)_2$/pyrimidines catalytic system. *European Journal of Organic Chemistry*, 2005(20):4256-4259, 2005.

[74] Buchmeiser, M. R., Schareina, T., Kempe, R., and Wurst, K. Bis (pyrimidine)-based palladium catalysts: synthesis, x-ray structure and applications in Heck–, Suzuki–, Sonogashira–Hagihara couplings and amination reactions. *Journal of Organometallic Chemistry*, 634(1):39-46, 2001.

[75] Mino, T., Shirae, Y., Saito, T., Sakamoto, M., and Fujita, T. Palladium-catalyzed Sonogashira and Hiyama reactions using phosphine-free hydrazone ligands. *The Journal of Organic Chemistry*, 71(25):9499-9502, 2006.

[76] Tao, B. and Boykin, D. W. Simple amine/$Pd(OAc)_2$-catalyzed Suzuki coupling reactions of aryl bromides under mild aerobic conditions. *The Journal of Organic Chemistry*, 69(13):4330-4335, 2004.

[77] Li, J. H., Hu, X. C., Liang, Y., and Xie, Y. X. PEG-400 promoted Pd (OAc) 2/DABCO-catalyzed cross-coupling reactions in aqueous media. *Tetrahedron*, 62(1):31-38, 2006.

[78] Zhang, L. M., Li, H. Y., Li, H. X., Young, D. J., Wang, Y., and Lang, J. P. Palladium (II) chloride complexes of n, n′-disubstituted imidazole-2-thiones: syntheses, structures, and catalytic performances in Suzuki–Miyaura and Sonogashira coupling reactions. *Inorganic Chemistry*, 56(18):11230-11243, 2017.

[79] Jin, M. J. and Lee, D. H. A practical heterogeneous catalyst for the Suzuki, Sonogashira, and Stille coupling reactions of unreactive aryl chlorides. *Angewandte Chemie International Edition*, 49(6):1119-1122, 2010.

[80] Mondal, M. and Bora, U. O-aryloxime ether analogues as novel and efficient ligands for palladium-catalyzed Suzuki–Miyaura coupling in water. *Tetrahedron Letters*, 55(19):3038-3040, 2014.

[81] Alonso, D. A., Nájera, C., and Pacheco, M. C. Oxime palladacycles: stable and efficient catalysts for carbon-carbon coupling reactions. *Organic Letters*, 2(13):1823-1826, 2000.

[82] Hussain, S. S., Ibrahim, M. B., Fazal, A., Suleiman, R., Fettouhi, M., and El Ali, B. Palladium–bis (oxazoline) complexes with inherent chirality: synthesis, crystal structures and applications in Suzuki, Heck and Sonogashira coupling reactions. *Polyhedron*, 70:39-46, 2014.

[83] Wang, D., Denux, D., Ruiz, J., and Astruc, D. The clicked pyridyl-triazole ligand: from homogeneous to robust, recyclable heterogeneous mono-and polymetallic palladium catalysts for efficient Suzuki–Miyaura, Sonogashira, and Heck reactions. *Advanced Synthesis & Catalysis*, 355(1):129-142, 2013.

[84] Sarmah, G. and Bora, U. simple aminobenzoic acid promoted palladium catalyzed room temperature Suzuki–Miyaura cross-coupling reaction in aqueous media. *Tetrahedron Letters*, 56(22):2906-2909, 2015.

[85] Das, S. K., Sarmah, M., and Bora, U. An ambient temperature Sonogashira cross-coupling protocol using 4-aminobenzoic acid as promoter under copper and amine free conditions. *Tetrahedron Letters*, 58(22):2094-2097, 2017.

[86] Gogoi, A., Dewan, A., Borah, G., and Bora, U. A palladium salen complex: an efficient catalyst for the Sonogashira reaction at room temperature. *New Journal of Chemistry*, 39(5):3341-3344, 2015.

[87] Das, P. and Linert, W. Schiff base-derived homogeneous and heterogeneous palladium catalysts for the Suzuki–Miyaura reaction. *Coordination Chemistry Reviews*, 311:1-23, 2016.

[88] Urgaonkar, S. and Verkade, J. G. Ligand-, copper-, and amine-free Sonogashira reaction of aryl iodides and bromides with terminal alkynes. *The Journal of Organic Chemistry*, 69(17):5752-5755, 2004.

[89] Gogoi, A., Dewan, A., and Bora, U. A highly efficient copper and ligand free protocol for the room temperature Sonogashira reaction. *RSC Advances*, 5(1):16-19, 2015.

[90] Negishi, E. I. and Anastasia, L. Palladium-catalyzed alkynylation. *Chemical Reviews*, 103(5):1979-2018, 2003.

[91] Lu, J., Elam, J. W., and Stair, P. C. Synthesis and stabilization of supported metal catalysts by atomic layer deposition. *Accounts of Chemical Research*, 46(8):1806-1815, 2013.

[92] Chen, A. and Ostrom, C. Palladium-based nanomaterials: synthesis and electrochemical applications. *Chemical Reviews*, 115(21):11999-12044, 2015.

[93] Duan, H., Wang, D., and Li, Y. Green chemistry for nanoparticle synthesis. *Chemical Society Reviews*, 44(16):5778-5792, 2015.

[94] Sengupta, D., Saha, J., De, G., and Basu, B. Pd/Cu bimetallic nanoparticles embedded in macroporous ion-exchange resins: an excellent heterogeneous catalyst for the Sonogashira reaction. *Journal of Materials Chemistry A*, 2(11):3986-3992, 2014.

[95] Son, S. U., Jang, Y., Park, J., Na, H. B., Park, H. M., Yun, H. J., and Hyeon, T. Designed synthesis of atom-economical Pd/Ni bimetallic nanoparticle-based catalysts for Sonogashira coupling reactions. *Journal of American Chemical Society*, 126(16):5026-5027, 2004.

[96] Li, G., and Jin, R. Catalysis by gold nanoparticles: Carbon-Carbon coupling reactions. *Nanotechnology Reviews*, 2(5):529-545, 2013.

[97] Feng, Y. S., Lin, X. Y., Hao, J., and Xu, H. J. Pd–Co bimetallic nanoparticles supported on graphene as a highly active catalyst for Suzuki–Miyaura and Sonogashira cross-coupling reactions. *Tetrahedron*, 70(34):5249-5253, 2014.

[98] Mahanta, A., Hussain, N., Das, M. R., Thakur, A. J., and Bora, U. Palladium nanoparticles decorated on reduced graphene oxide: An efficient catalyst for ligand

and copper-free Sonogashira reaction at room temperature. *Applied Organometallic Chemistry*, 31(8):e3679, 2017.

[99] Gao, S., Zhao, N., Shu, M., and Che, S. Palladium N supported on MOF-5: A highly active catalyst for a ligand and copper-free Sonogashira coupling reaction. *Applied Catalysis A: General*, 388(1):196-201, 2010.

[100] Cui, Q., Zhao, H., Luo, G. and Xu, J. An efficient chitosan/silica composite core–shell microspheres-supported pd catalyst for aryl iodides Sonogashira coupling reactions. *Industrial & Engineering Chemistry Research*, 56(1):143-152, 2017.

[101] Tukhani, M., Panahi, F., and Khalafi-Nezhad, A. Supported palladium on magnetic nanoparticles–starch substrate (Pd-MNPSS): Highly efficient magnetic reusable catalyst for C–C coupling reactions in water. *ACS Sustainable Chemistry & Engineering*, 6(1):1456-1467, 2018.

[102] Reddy, K. R., Kumar, N. S., Reddy, P. S., Sreedhar, B., and Kantam, M. L. Cellulose supported palladium (0) catalyst for Heck and Sonogashira coupling reactions. *Journal of Molecular Catalysis A: Chemical*, 252(1-2):12-16, 2006.

[103] Zhu, M., Zhou, Z., and Chen, R. A novel Pd/Ag-catalyzed Sonogashira coupling reaction of terminal alkynes with hypervalent iodonium salts. *Synthesis*, 2008(17):2680-2682, 2008.

[104] Mandali, P. K. and Chand, D. K. Palladium nanoparticles catalyzed Sonogashira reactions for the one-pot synthesis of symmetrical and unsymmetrical diarylacetylenes. *Catalysis Communications*, 47:40-44, 2014.

[105] Nasrollahzadeh, M., Sajadi, S. M., Rostami-Vartooni, A., and Khalaj, M. Green synthesis of Pd/Fe_3O_4 nanoparticles using euphorbia condylocarpa m. bieb root extract and their catalytic applications as magnetically recoverable and stable recyclable catalysts for the phosphine-free Sonogashira and Suzuki coupling reactions. *Journal of Molecular Catalysis A: Chemical*, 396:31-39, 2015.

[106] Thorwirth, R., Stolle, A., and Ondruschka, B. Fast copper-, ligand-and solvent-free Sonogashira coupling in a ball mill. *Green Chemistry*, 12(6):985-991, 2010.

[107] Venkatesan, P. and Santhanalakshmi, J. Designed synthesis of Au/Ag/Pd trimetallic nanoparticle-based catalysts for Sonogashira coupling reactions. *Langmuir*, 26(14):12225-12229, 2010.

[108] Gholap, A. R., Venkatesan, K., Pasricha, R., Daniel, T., Lahoti, R. J., and Srinivasan, K. V. Copper-and ligand-free Sonogashira reaction catalyzed by pd (0)

nanoparticles at ambient conditions under ultrasound irradiation. *The Journal of Organic Chemistry*, 70(12):4869-4872, 2005.

[109] Diyarbakir, S., Can, H., and Metin, O. Reduced graphene oxide-supported CuPd alloy nanoparticles as efficient catalysts for the Sonogashira cross-coupling reactions. *ACS Applied Materials & Interfaces*, 7(5):3199-3206, 2015.

[110] Mori, S., Yanase, T., Aoyagi, S., Monguchi, Y., Maegawa, T., and Sajiki, H. Ligand-free Sonogashira coupling reactions with heterogeneous Pd/C as the catalyst. *Chemistry–A European Journal*, 14(23):6994-6999, 2008.

[111] Ciriminna, R., Pandarus, V., Gingras, G., Béland, F., Demma Carà, P., and Pagliaro, M. Heterogeneous Sonogashira coupling over nanostructured silia cat Pd (0). *ACS Sustainable Chemistry & Engineering*, 1(1):57-61, 2013.

[112] Beletskaya, I. P. The cross-coupling reactions of organic halides with organic derivatives of tin, mercury and copper catalyzed by palladium. *Journal of Organometallic Chemistry*, 250(1):551-564, 1983.

[113] Badone, D., Baroni, M., Cardamone, R., Ielmini, A., and Guzzi, U. Highly efficient palladium-catalyzed boronic acid coupling reactions in water: Scope and limitations. *The Journal of Organic Chemistry*, 62(21):7170-7173, 1997.

[114] Shankar, S. S., Rai, A., Ahmad, A., and Sastry, M. Rapid synthesis of Au, Ag, and bimetallic Au core-Ag shell nanoparticles using neem (*Azadirachta indica*) leaf broth. *Journal of Colloid Interface Science*, 275:496-502, 2004.

[115] Paul, S., Islam, M. M., and Islam, S. M. Suzuki–Miyaura reaction by heterogeneously supported pd in water: recent studies. *RSC Advances*, 5(53):42193-42221, 2015.

[116] Polshettiwar, V., Len, C., and Fihri, A. Silica-supported palladium: sustainable catalysts for cross-coupling reactions. *Coordination Chemistry Reviews*, 253(21-22):2599-2626, 2009.

[117] Scheuermann, G. M., Rumi, L., Steurer, P., Bannwarth, W., and Mülhaupt, R. Palladium nanoparticles on graphite oxide and its functionalized graphene derivatives as highly active catalysts for the Suzuki−Miyaura coupling reaction. *Journal of the American Chemical Society*, 131(23):8262-8270, 2009.

[118] Liu, L., Zhang, Y., and Wang, Y. Phosphine-free palladium acetate catalyzed Suzuki reaction in water. *The Journal of Organic Chemistry*, 70(15):6122-6125, 2005.

[119] Mondal, M. and Bora, U. An efficient protocol for palladium-catalyzed ligand-free Suzuki–Miyaura coupling in water. *Green Chemistry*, 14(7):1873-1876, 2012.

[120] Yang, W., Liu, C., and Qiu, J. In situ formation of N, O-bidentate ligand via the hydrogen bond for highly efficient Suzuki reaction of aryl chlorides. *Chemical Communications*, 46(15):2659-2661, 2010.

[121] de Souza, A. L. F., Silva, A. D. C., and Antunes, O. A. C. Suzuki–Miyaura reactions in PEG–water solutions using Pd/$BaSO_4$ as catalytic source. *Applied Organometallic Chemistry*, 23(1):5-8, 2009.

[122] Liu, C., Ni, Q., Bao, F., and Qiu, J. A simple and efficient protocol for a palladium-catalyzed ligand-free Suzuki reaction at room temperature in aqueous DMF. *Green Chemistry*, 13(5):1260-1266, 2011.

[123] Wei, S., Ma, Z., Wang, P., Dong, Z., and Ma, J. Anchoring of palladium (II) in functionalized SBA-16: An efficient heterogeneous catalyst for Suzuki Coupling reaction. *Journal of Molecular Catalysis A: Chemical*, 370:175-181, 2013.

[124] LeBlond, C. R., Andrews, A. T., Sun, Y., and Sowa, J. R. Activation of aryl chlorides for Suzuki cross-coupling by ligandless, heterogeneous palladium. *Organic Letters*, 3(10):1555-1557, 2001.

[125] Camp, J. E., Dunsford, J. J., Cannons, E. P., Restorick, W. J., Gadzhieva, A., Fay, M. W., and Smith, R. J. Glucose-derived palladium (0) nanoparticles as in situ-formed catalysts for Suzuki–Miyaura cross-coupling reactions in isopropanol. *ACS Sustainable Chemistry & Engineering*, 2(3):500-505, 2014.

[126] Han, W., Liu, C., and Jin, Z. L. In situ Generation of Palladium Nanoparticles: A simple and highly active protocol for oxygen-promoted ligand-free Suzuki Coupling reaction of aryl chlorides. *Organic Letters*, 9(20):4005-4007, 2007.

[127] Baran, T., Sargin, I., Kaya, M., and Menteş, A. An environmental catalyst derived from biological waste materials for green synthesis of biaryls via Suzuki coupling reactions. *Journal of Molecular Catalysis A: Chemical*, 420:216-221, 2016.

[128] Plechkova, N. V. and Seddon, K. R. Applications of ionic liquids in the chemical industry. *Chemical Society Reviews*, 37(1):123-150, 2008.

[129] Chen, J., Spear, S. K., Huddleston, J. G., and Rogers, R. D. Polyethylene glycol and solutions of polyethylene glycol as green reaction media. *Green Chemistry*, 7(2):64-82, 2005.

[130] Brennecke, J. F. New applications of supercritical fluids. *Chemistry and Industry*, 1996(21):831-834, 1996.

[131] Eckert, C. A., Knutson, B. L., and Debenedetti, P. G. Supercritical fluids as solvents for chemical and materials processing. *Nature*, 383(6598):313, 1996.

[132] Horváth, I. T. Fluorous biphase chemistry. *Accounts of Chemical Research*, 31(10):641-650, 1998.

[133] Hernaiz, M. J., Alcántara, A. R., Garcia, J. I., and Sinisterra, J. V. Applied biotransformations in green solvents. *Chemistry–A European Journal*, 16(31):9422-9437, 2010.

[134]Chahdoura, F., Pradel, C., and Gomez, M. Palladium nanoparticles in glycerol: A versatile catalytic system for C-X bond formation and hydrogenation processes. *Advanced Synthesis & Catalysis*, 355(18):3648-3660, 2013.

[135] Wilson, K. L., Murray, J., Jamieson, C., and Watson, A. J. Cyrene as a bio-based solvent for the Suzuki–Miyaura cross-coupling. *Synlett*, 29(05):650-654, 2018.

[136] Wilson, K. L., Kennedy, A. R., Murray, J., Greatrex, B., Jamieson, C., and Watson, A. J. Scope and limitations of a DMF bio-alternative within Sonogashira cross-coupling and Cacchi-type annulation. *Beilstein Journal of Organic Chemistry*, 12:2005-2011, 2016.

[137] Boruah, P. R., Ali, A. A., Saikia, B., and Sarma, D. A novel green protocol for ligand free Suzuki–Miyaura cross-coupling reactions in WEB at room temperature. *Green Chemistry*, 17(3):1442-1445, 2015.

[138] Boruah, P. R., Ali, A. A., Saikia, B., and Sarma, D. Pd $(OAc)_2$ in WERSA: A novel green catalytic system for Suzuki–Miyaura Cross-coupling reactions at room temperature. *Chemical Communications*, 51(57):11489-11492, 2015.