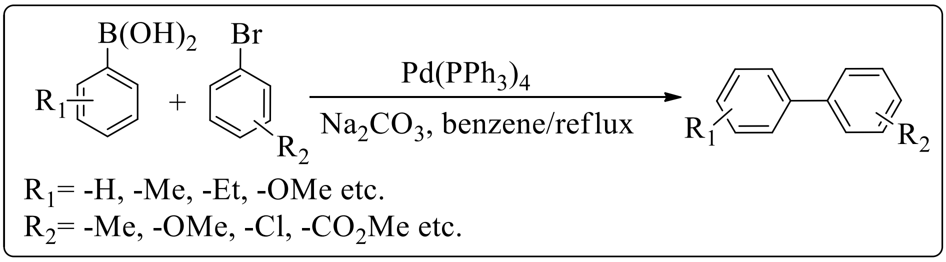
2. Introduction:

The formation of C-C bond signifies a fundamental aspect of synthetic organic chemistry. These bond forming reactions are considered as a sub discipline of chemistry which involves the study of properties, structure and reactions of carbon containing compounds. They are important in every walk of life, as the same are used to form the skeletal backbone of resources to continue life. Synthetic organic chemists have been practicing an incredible development with an explosive acceleration within the sphere of C-C bond formation reaction. The main soul in this boom is the aspiration to improve or discover what has previously been invented. Chemists desire to get better reaction conditions for maximizing resource efficiency, product selectivity, energy efficiency, environmental safety and operational simplicity etc. The improvement in the empire of C-C bond forming reactions will extremely advance overall synthetic competence over the accessible methods. The exercise to produce C-C bonds in a selective manner has revolutionized the agricultural and pharmaceutical industries over and above the area of material science. Historically, some well advanced routes like Aldol, Wittig, Grignard, Diels-Alder type reactions provided chemists with an irresistible numbers of choices to construct complex organic molecules from comparatively simple precursors. But, nowadays, transition metal catalyzed C-C bond formation reactions are extensively used in both academia and industry to synthesize natural products, agrochemicals, pharmaceuticals and biological materials. In general, transition metal mediated C-C bond formation reaction engages the coupling of organic fragments, typically an electrophile and a nucleophile, catalyzed by some transition metals like palladium, nickel, copper, iron, cobalt etc. Some well known C-C bond formation reactions are Heck, Sonogashira, Stille, Negishi, Kumada, Tsuji-Trost, Suzuki-Miyaura etc. Amongst them Suzuki-Miyaura, Sonogashira, Heck reactions are commonly used for these bond formation reactions. Herein, we provide a brief introduction on Suzuki-Miyaura and Sonogashira reaction as this chapter focuses on some novel works on Suzuki-type and Sonogashira cross-coupling reactions.

Suzuki-Miyaura cross-coupling reaction:

Akira Suzuki and his co-workers in 1981 reported [1] a novel method for the synthesis of biaryl compounds employing the cross-coupling of aryl boranes and haloarenes. The reaction was performed in benzene using 3 mol% of [$Pd(PPh_3)_4$] under an inert atmosphere (**Scheme 1**).



Scheme 1: Suzuki-Miyaura cross-coupling reaction

The biaryl derivatives, products of the Suzuki reaction are basic structural scaffolds of numerous drugs, conducting polymers, optical devices, herbicides and advanced functional materials. Additionally, the reaction was found to be applied in the total synthesis of natural products like anti-alkaloid michellamine, vanomycien, palytoxin, lucilactaene etc. In 2010, Akira Suzuki shared the Nobel Prize in Chemistry with Richard Heck and Ei-chi Negishi for the tremendous contribution in chemistry via this reaction. The catalytic cycle of the reaction proceeds through three sequential steps which are, (I) Oxidative addition; (II) Transmetallation; and (III) Reductive elimination (**Fig. 1**). The first step, oxidative addition involves the breaking of bond between R_1 and leaving group X, forming an organopalladium complex along with oxidation of Pd(0) to Pd(II). Apart from Suzuki-Miyaura cross-coupling reaction, this step is the rate determining step in various cross-coupling reactions. It is also observed that the addition of strong sigma-donating ligands accelerates the oxidative addition step and hence enhances the reaction.

The second step is the transmetallation step, which shifts the nucleophillic organic group (R_2) bound to an electropositive boron group to the metal catalyst. This step is highly crucial in the reaction, dependent on the strength of the base used. To know the exact role of base in the transmetalation step, various experimental and theoretical investigations have been carried out and it was found that there are two major roles of base in the concerned step. Either the leaving group X of the organopalladium complex is substituted by the base forming an *oxo*-palladium species or carries out the activation of boronic acid, forming a tetrahedral boronate species which is more nucleophillic in nature.

The final step, reductive elimination regenerates the Pd(0) catalyst and eliminates the desired coupled product. The step is known to be concerted and progresses via the formation of a three coordinated cyclic transition step which regenerates the active Pd(0) catalyst. Based on combined theoretical and experimental study, it is observed that complexes having strong π accepting group, accelerates this step.

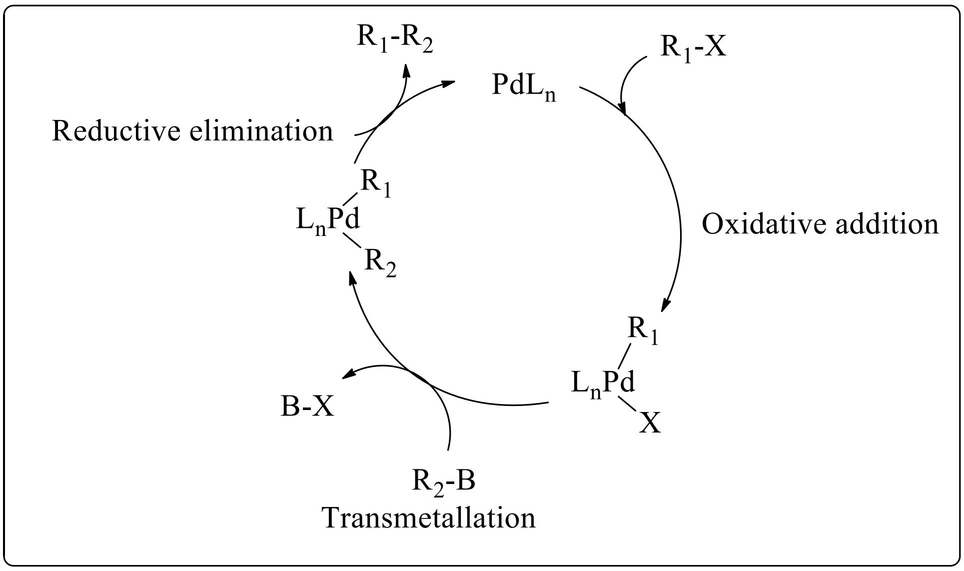


Fig. 1: Mechanism of Suzuki-Miyaura cross-coupling reaction

This reaction was popularized as one of the most important synthetic tools for the construction of C-C bond and dominated the previous methods for the synthesis of biaryl compounds. It is mainly due to the mild nature of the starting material organoboron compound which also has some special useful properties like, heat and air resistance, wide functional group tolerance etc. Again, the reaction is found to be highly regio- and stereoselective and no dry solvent is needed for the required transformation. In addition, the inorganic boron compounds can be easily separated from the reaction mixture and most importantly the byproduct of the reaction is non-toxic.

Although the classical method was efficient towards the synthesis of biaryl compounds, yet the method was associated with some harsh conditions like use of high temperature, carcinogenic solvent benzene, phosphine based catalytic system etc. So, in proceeding years, lots of advancements have been achieved in this reaction including development of mild catalytic system, use of green solvent, room temperature reaction, expansion of substrate scope etc. Here in, we discuss all the recent advances in this field.

Advancement in catalytic system:

From the mechanistic step, it is clear that the presence of a ligand can enhance the efficiency of Pd and thus boost up the reaction. Thereby, developments of phosphine based ligands for the reaction entertained increasing interest. Phosphines are known to improve the activity of palladium by offering stability, steric shielding and electron richness to the compound.

Untill 1998, triarylphosphine ligands were considered as the standard ligand for Suzuki-Miyaura cross-coupling reaction. But, later on, Heck, Osborn, Beller, Buchwald, Hartwig, Fu etc. investigated the effect of the different phosphine based ligands on the activity of Pd complexes. Heck recognized higher catalytic activity of Pd complexes using bulky tri-*o*-tolylphosphine ligand [2]. Again, Osborn [3] observed the higher catalytic activity in phosphanes which was strongly basic and had well defined steric volume. Based on these statements, different phosphine ligands were developed and utilized in Suzuki-Miyaura cross-coupling reaction. Likewise, studies concluded that the bulkiness of the phosphine ligands exert a stronger influence on oxidative addition step. Some of the prominent phosphine ligands (L1-L9) used in Suzuki-Miyaura reaction are shown in **Fig. 2**.

N-based ligands were also used for this reaction as an alternative to phosphine ligands. Hermann *et al*. first reported [13] the use of Pd-NHC (*N*-heterocyclic carbene) for Suzuki-Miyaura cross-coupling reaction. Following this, numerous efficient strategies of Suzuki-Miyaura cross-coupling reaction was observed using Pd-NHC. The examples[L9-L15] are presented in **Fig. 3**.

Apart from NHC, during the last few decades, we have noticed that lots of *N*-based ligands, were employed successfully in Suzuki-Miyaura cross-coupling reaction (**Fig. 4**). Boykin and his co-workers in 2004, reported a new catalyst DAPCy [20] for this cross-coupling reaction. An inexpensive and highly efficient catalytic system $Pd(OAc)_2$/ DABCO [21] was reported by Li and co-workers which was also found to be efficient towards the desired cross-coupling reaction of aryl halide and arylboronic acids.

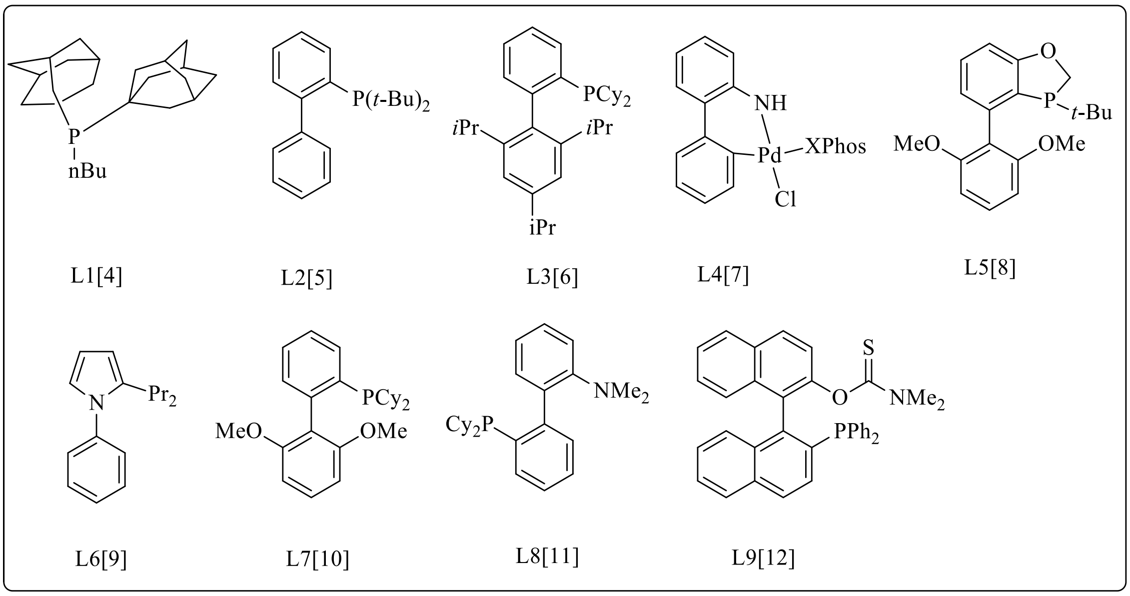


Fig. 2: Phospane-Pd complex and phosphane ligands for Suzuki-Miyaura reaction

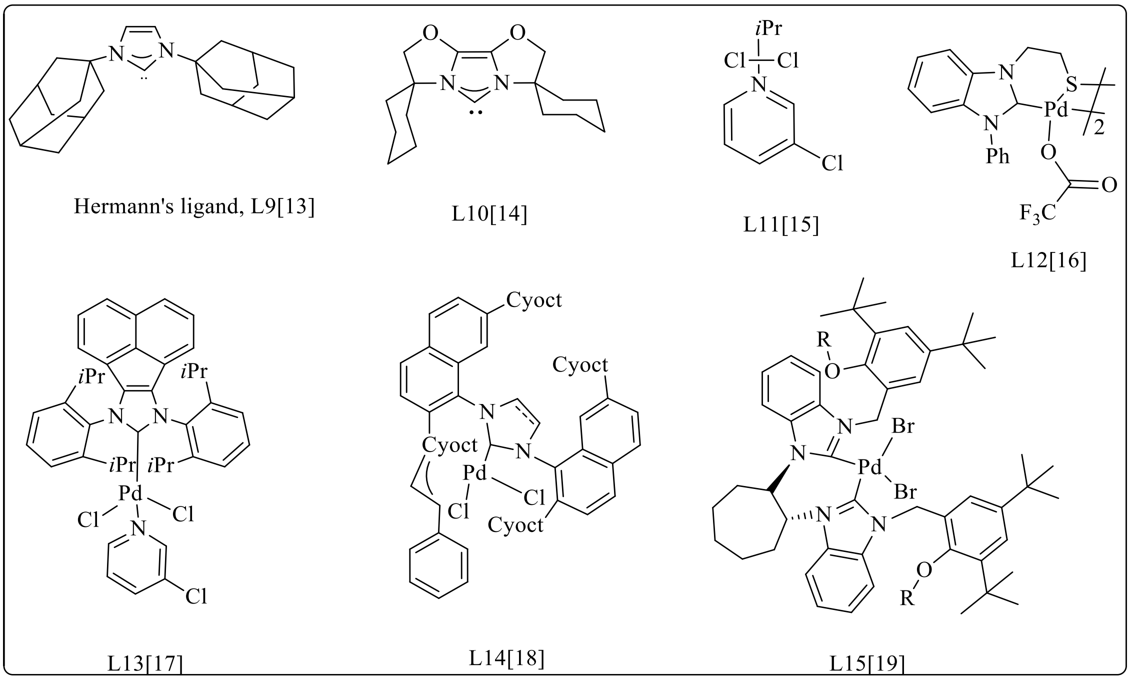


Fig. 3: (NHC)Pd complex and NHC ligands used in Suzuki-Miyaura reaction

Some other catalysts which have shown excellent catalytic activity towards Pd catalyzed Suzuki-Miyaura cross-coupling reaction are Lin's chiral complex [23], bisamide [24], Shing's and Das's Schiff base Pd complex [25], Ramesh's palladacycle [26], Bora's acetanilide palladacycle [27], Liu's Pd complex [28] etc. Apart from these, some easily available *N*-containing ligands like imidazole [29], imine [30], oxime [31], oxazoline [32], triazole [33], aminopyridyl [34], amino acid [35], urea [36], glucose [37] etc. were also utilized for the said reaction.

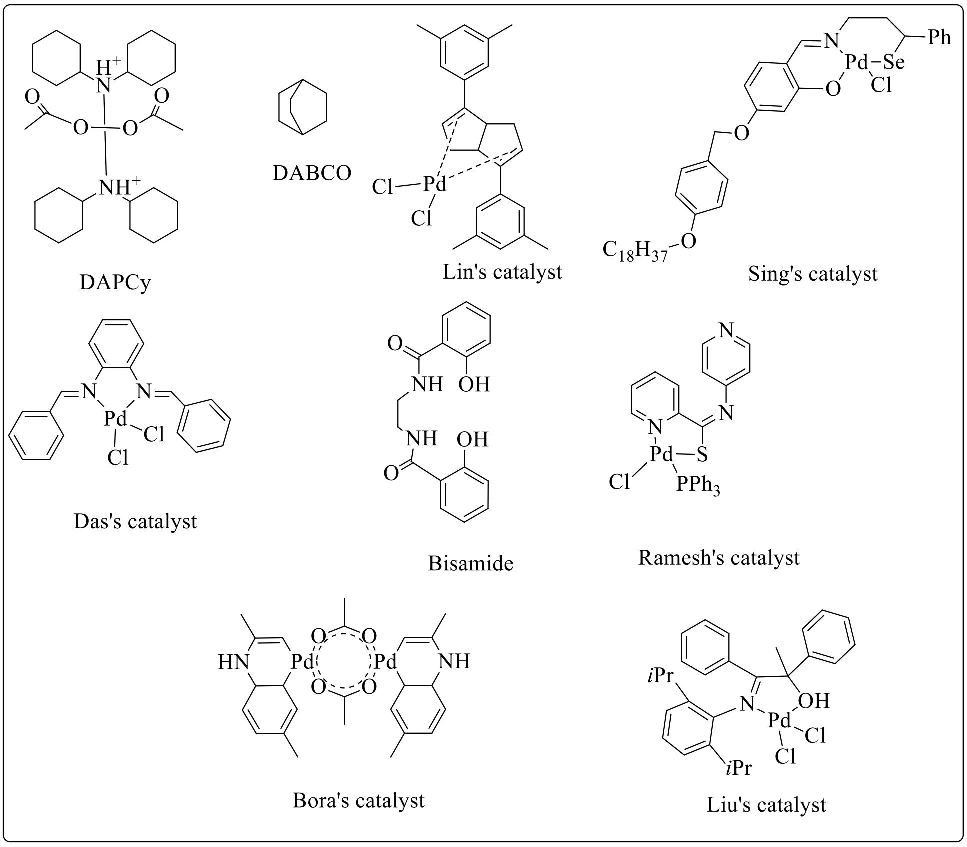


Fig. 4: *N*-containing ligands developed for Suzuki-Miyaura cross-coupling reaction

Although these ligands are evidences for their potentiality towards the stabilization of palladium species, yet they were associated with some major drawbacks related to toxicity, expensiveness, faulty separation, low stability etc. Most importantly, they often produce some side products and so disturb the isolation and purification process. Thus, to overcome these problems some alternative ligand free protocols were developed in the subsequent years.

Pd NPs materialize as a promising alternative for costly Pd complexes. High surface-to-volume ratio and highly active surface atoms compared to the bulk catalyst make them very efficient catalyst for the ligand free Suzuki-Miyaura reaction which reduces the cost, facilitates the easy separation process and simplify the work up procedure. Thereby, numerous [38] Pd NPs catalyzed Suzuki–Miyaura cross-coupling reaction protocols have been developed. Although, Pd NPs exhibit excellent catalytic activity, but, in most of the cases, their synthetic routes require high temperature [39], ultra sonication [40], active reducing agents [41] etc. As a result, there is growing interest for the development of green and eco-friendly routes for the synthesis of Pd NPs in a single step with minimum use of chemicals or by using environmentally acceptable solvents. Biological resources such as plant extracts [42], microorganisms [43] etc. can also be used for the synthesis of NPs as they have the required reduction potential suitable for NPs synthesis. Additionally, considerable efforts have been made to prepare and stabilize Pd NPs by using environmentally benign, robust, cheap and available support/stabilizer [44]. Reports have been found on the synthesis of Pd NPs by using bio-reducing agents like leaf extract of *colocasia esculenta* [45], tea and coffee extract [46], soyabean leaf extract [42], starch [47] etc. But, in most of the cases, temperature is an important parameter for synthesizing metal NPs which is against the prospect of “green chemistry”. So, considering the above factors, synthesis of Pd NPs at room temperature without using any external reducing agent is a very fascinating development in the area of nanocatalysis. Alcoholic solvents have reducing properties itself and can be engaged for the synthesis of metal NPs which is considered as green synthetic process [48]. Again, the synthesis of heterogeneous supported Pd catalyst has broadened enormously on the chemistry of catalyst synthesis. The homogeneous Pd catalysis has been applied for a long term in Suzuki-Miyaura coupling reaction due to their high reactivity, milder reaction condition and high turnover numbers etc. But, the major problems associated with homogeneous catalysis are the tedious separation, contamination of the catalyst with the final product due to which it becomes tough to remove the catalyst from the mixture. To overcome these problems, heterogeneous catalysis has been utilized successfully in Suzuki-Miyaura reaction due to profound advantages of easy recovery and reuse of the catalyst by different methods like by simple filtration, magnetic separation and decantation etc. Furthermore, many of the reused heterogeneous catalysts remain reactive even after consecutive runs without significant loss in efficiency.

Reports have been found about protocols, where Pd NPs are embedded on various metal solid supports such as zeolite [49], micro porous polymer [50], mesoporous silica [51], aluminium hydroxide [52], agarose [53], $BaCO_3$ [54], charcoal [55], clay [56], metal oxides [57] etc. and they show excellent catalytic activity towards Suzuki-Miyaura reaction. Apart from Pd NPs, palladium metal or metal complexes are also supported on different surfaces. Koslick’s MCM-41 supported-palladium [58], Corma's oxime-carbapalladacycles anchored to mercaptopropyl modified silica [59], Ma's pyridine derived catalyst [60], Mallick's palladium-poly(aminoacetanilide) [61] composite catalysts are some of the successful heterogeneous catalysts in Suzuki-Miyaura cross- coupling reaction.

Alternative coupling partners for Suzuki–Miyaura reaction:

At the very beginning, alkenyl boranes and catechol boronic esters were used as boron coupling partners for Suzuki-Miyaura cross-coupling reaction. However, arylboronic acid was used as a potential boron substrate for the reaction in 1990s. Recently, organotrifluroborates [62] and MIDA (*N*-methyliminodiacetic acid) [63] have been used as productive coupling partners for the desired reaction. Similarly, replacements also have been found for aryl halides. Among the aryl halides, aryl chlorides react very sluggishly, so harsh reaction condition is required for the reaction; aryl iodides or bromides are costly. As a result, in many cases some other reagents are successfully utilized for the reaction. Aryl diazonium tetrafluroborate [64], bezene sulphonyl chloride [65], aryl hydrazine [66] etc. are the common substitutes.

Catalysis in green solvent:

The principles of green and sustainable chemistry suggest the execution of naturally available resources in the development of clean and safe synthesis of organic compounds and thus encourage chemists to demonstrate scientific methodologies with high atom economy, efficiency, low E-factor and low mass intensity which can protect environment and can be handled in a safe manner. Green chemistry also deals with no pollution or environmental risk and so the chemicals used in a reaction should be non-toxic in nature.

Again, elimination of organic solvents in a reaction makes the protocol green. In this context, substantial efforts have been devoted towards Suzuki-Miyaura reaction to replace different toxic solvents. Reports have been found on implication of several alcoholic solvents [67], aqueous co-solvents [68] instead of carcinogenic organic solvents. But, a protocol is said to be extremely green if it employs water as a solvent because it is the nature's ultimate solvent and is considered as the most cheap, abundant, non-toxic, non flammable solvent. During the last few decades, a few methods have been developed which utilize water as the solvent medium. In many cases, it has also been noticed that addition of water as a solvent or additive enhances the reaction. It is mainly due to the solvation of the base, which further activates the boronic acid moiety and enhances the reaction rate. Recently, a couple of methods have been reported in which water extract of natural feed stocks like banana peel ash [69] and rice straw ash [70] have been successfully employed for efficient Suzuki-Miyaura reaction. The extracts act as both solvent and base for the reaction.

Sonogashira cross-coupling reaction:

The palladium-catalyzed cross-coupling reaction of terminal alkynes with aryl or alkenyl halides (or triflates), was first described by Sonogashira *et al*. in 1975 [71], is one of the most reliable methods for the synthesis of internal aryl alkynes and conjugated enynes and finds extensive [72] application in the field of pharmaceuticals, natural product and molecular organic materials. Additionally, the arylated alkynes have good demand as intermediates for the synthesis of carbocycles and heterocycles. The coupling reaction is generally performed under mild conditions, using catalytic amount of a palladium complex along with copper iodide and a base (typically an amine), to obtain good yields of coupling products. Several months before this discovery, Cassar [73], Dieck and Heck [74] confectioned that it was possible to execute this coupling only under palladium catalysis using high temperatures. Consequently, Sonogashira-Tohda and Hagihara developed a fascinating protocol for construction of alkynated product which utilized catalytic amount of CuI co-catalyst to enhance the reaction rate at room temperature.

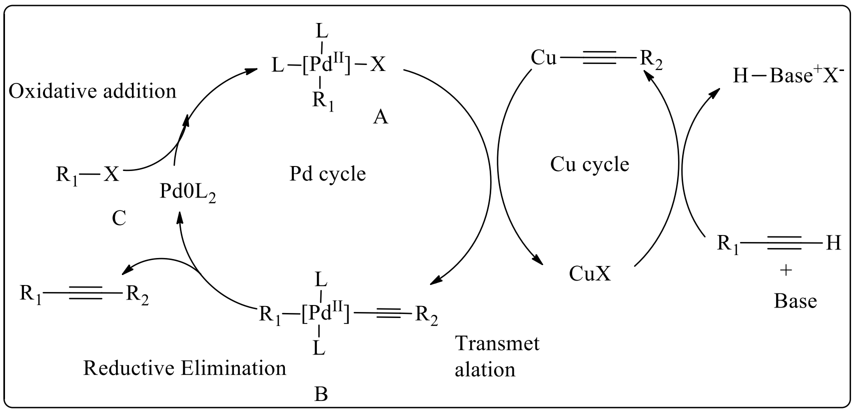


Fig. 5: Mechanism of Sonogashira coupling reaction

Though the exact pathway is not so clear till date, a plausible mechanistic route has been suggested to explain the role of Cu salt in the reaction. The reaction progressed through two independent pathways as shown in the **Fig. 5**. At first, oxidative addition occurs in the Pd cycle, where Pd(0) is transformed to [Pd(II)R^1L_2X] complex. In the next step, it reacts with copper acetylide which is generated from copper cycle yields an adduct B. The adduct B then undergoes reductive elimination to afford the final product and regenerates the original Pd(0) species. So, the main role of CuI is to furnish *in-situ* generated copper acetylide in the presence of a base.

Though, the addition of Copper co-catalyst improved the reactivity of the system, it added some shortcomings too, like promotion of undesired Glaser type homocoupling of terminal alkyne which decreases the yield of the reaction. Therefore, nowadays, researchers are trying to develop Cu free Sonogashira coupling reaction aiming to resist the undesired byproducts by making the use of either some other co-catalysts like Sn [75], Zn [76], Ag [77] etc. or highly active Pd complex [78].

Mechanism of copper free Sonogashira reaction:

Mechanism of Cu free Sonogashira reaction is shown in **Fig. 6.** Deprotonation and carbopalladiation are the two main mechanistic pathways for Cu free Sonogashira coupling reaction. In deprotonation mechanism, deprotonation of alkyne proton and co-ordination of the ligand takes place, yielding a square planar intermediate of Pd complex residing two organic groups in *cis* position. Further, it undergoes reductive elimination to form the desired product.

On the other hand, carbopalladation mechanism (**Fig. 7**) involves the addition of the organic moiety ‘R’ to the alkyne system followed by ligand co-ordination and subsequent reductive elimination. Although these two mechanisms are considered as the usual reaction pathways for the Cu free Sonogashira reaction, still the actual mechanism is unclear.

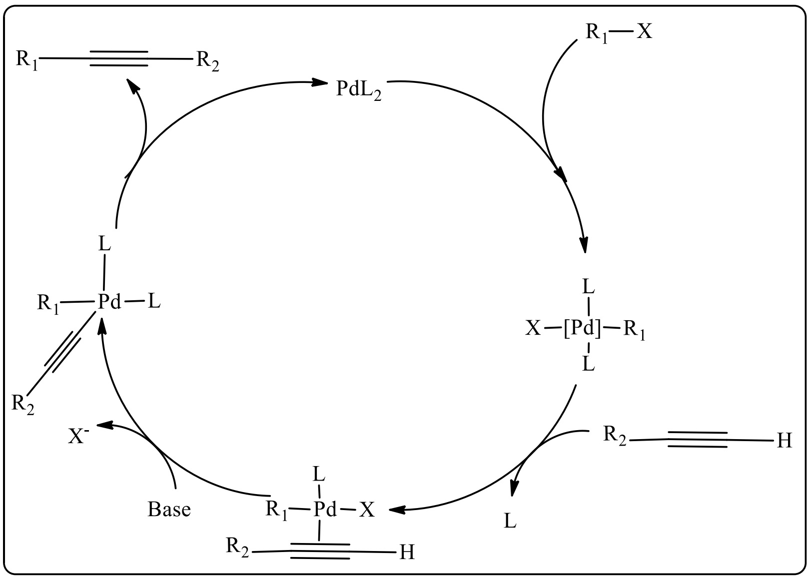


Fig. 6: Deprotonation mechanism for Cu free Sonogarshira reaction

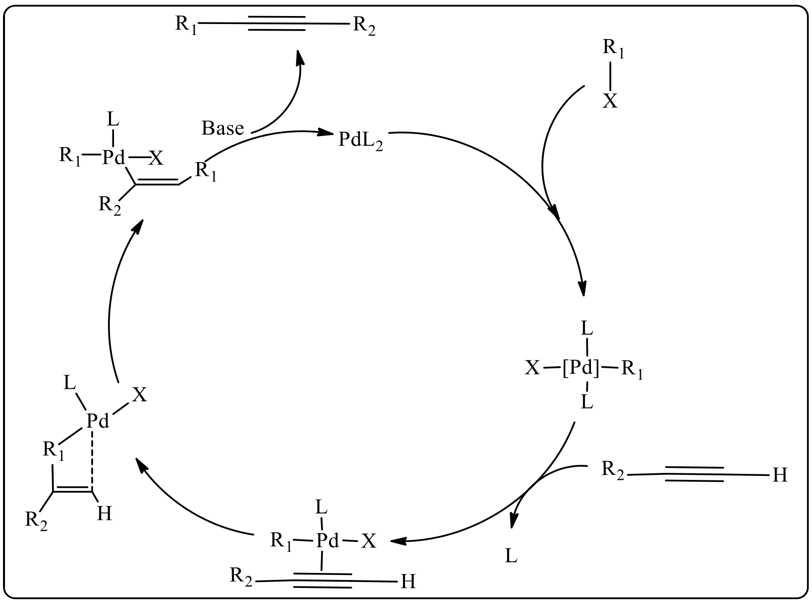


Fig. 7: Carbopalladation mechanism for Cu free Sonogarshira reaction

Since beginning, various ligands have been added in this reaction to improve the catalytic activity. Generally, phosphine based ligands are used mainly in Pd catalyzed cross- coupling reaction. The main purpose concerning this addition is that phosphine based ligands impart beneficial possessions to the Pd metal in terms of electron richness, stability and steric shielding of the complex. Thus makes the catalyst highly active. In addition, electron-rich bulky phosphine ligands enhance the oxidative addition step, where as steric effect makes easy to form the low co-ordinate Pd complex with high activity. Thereby, different phosphine based ligands have been applied for Sonogashira reaction.

Phosphine based ligand for Sonogashira reaction:

In early years, triphenyl phosphine was used as the typical phosphine based ligand for Pd catalyzed cross-coupling reaction. But nowadays, researchers have extended the scope of different phosphine based modified ligands towards the Pd catalyzed reactions. In 1983, Migita [79] and co-workers achieved first major success by introducing bulky phosphanes in Pd catalysis. In 2000, this concept was applied in Sonogashira reaction by Buchwald [80] and co-workers and used $P(tBu)_3$ as an effective ligand system for efficient conversion. Aryl bromides were also coupled easily with alkynes, even at room temperature in the presence of this ligand assisted catalytic system. Kollhofer [81] and Plenio also designed $(1\text{-Ad})_2PBn$ (1-Ad=1-adamantyl) ligand for efficient Sonogashira reaction with sterically demanding aryl bromide as coupling partner. Under this ligand system, reactions with less reactive aryl chlorides were also investigated at high temperature and the positive results were realized. In proceeding years, several phosphanes were designed and utilized in Pd catalyzed Sonogashira reaction. Some common examples are trialkylphosphane [82], fluorenylphosphane [83], indole containing phosphine [84], chiral ferrocenyl containing phosphanine [85], diphosphanes [86], ammonium salt containg phosphanes [87] etc. **Fig. 8** depicts some examples of effective phosphine based ligands for Sonogashira reaction.

From green chemistry perspective, use of water as a solvent in organic chemistry is highly appealing. Sonogashira reaction was also tested in water with different water soluble phosphine based ligands. Here, we have given some examples (**Fig. 9**) of water soluble phosphanes well-suited for Sonogashira reaction in water, *viz.* TXPTS (Tris (2,4-dimethyl-5-sulfophenyl)phosphinetrisodium salt) [88], TPPTS (Triphenylphosphine-3,3',3''-trisulphonic acidtrisodium salt) [89], ^{t}Bu-amphos [90], phosphonious acid [91], ionic guanidine phosphanes [92], 2-aminophenyldiphenylphosphinite [93] and TPPMS (Monosulfonatedtriphenylphosphane) [94] etc.

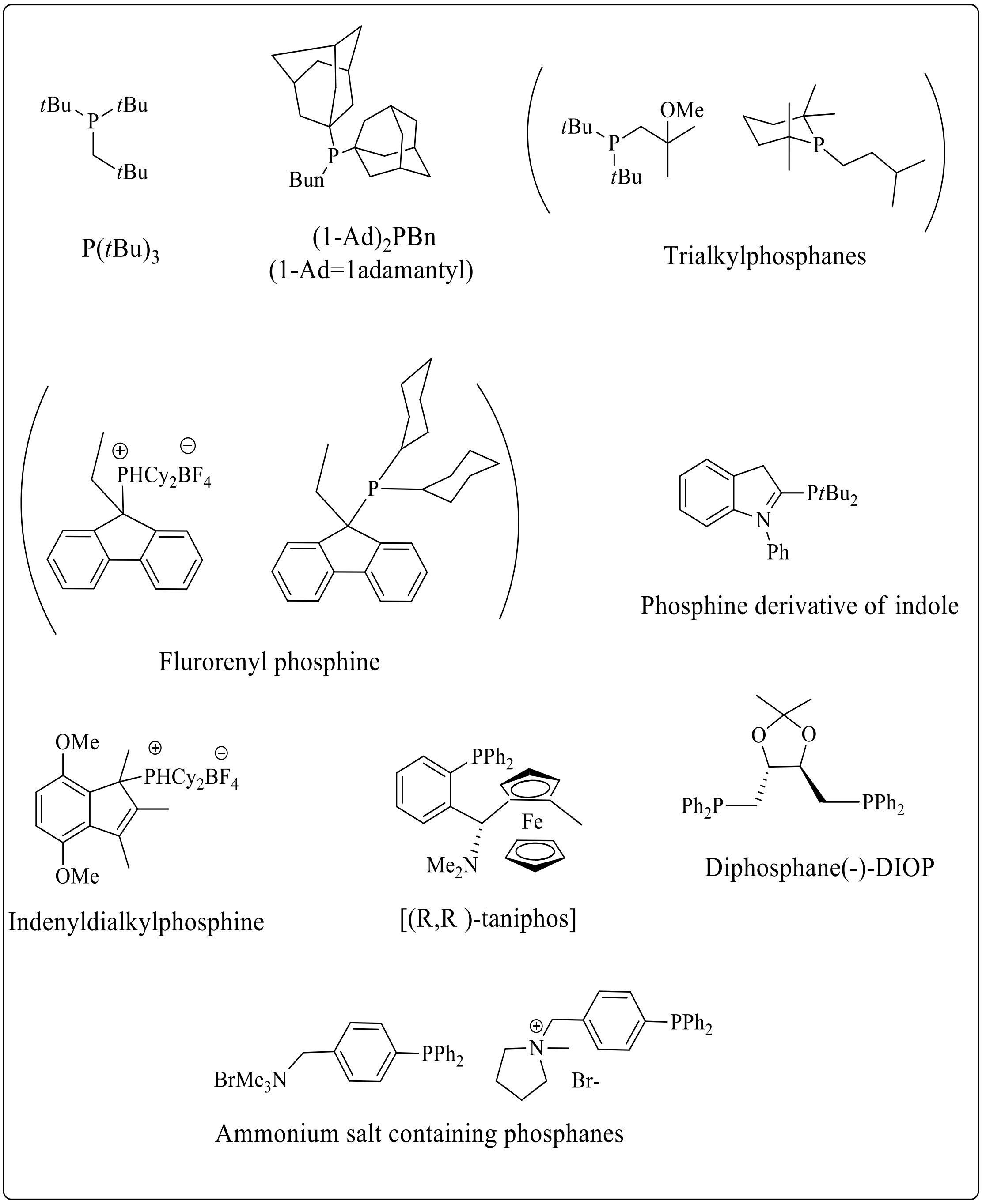


Fig. 8: Phosphine based ligands for Cu co-catalyzed Sonogashira reaction

Besides these, some other highly reactive phosphine based ligands were also designed for Cu free Sonogashira reaction. These are X Phos [95], aminophosphane [96], *N*-substituted bulky heteroaryl phosphanes [97], Xantphos [98] etc. as shown in **Fig. 10**.

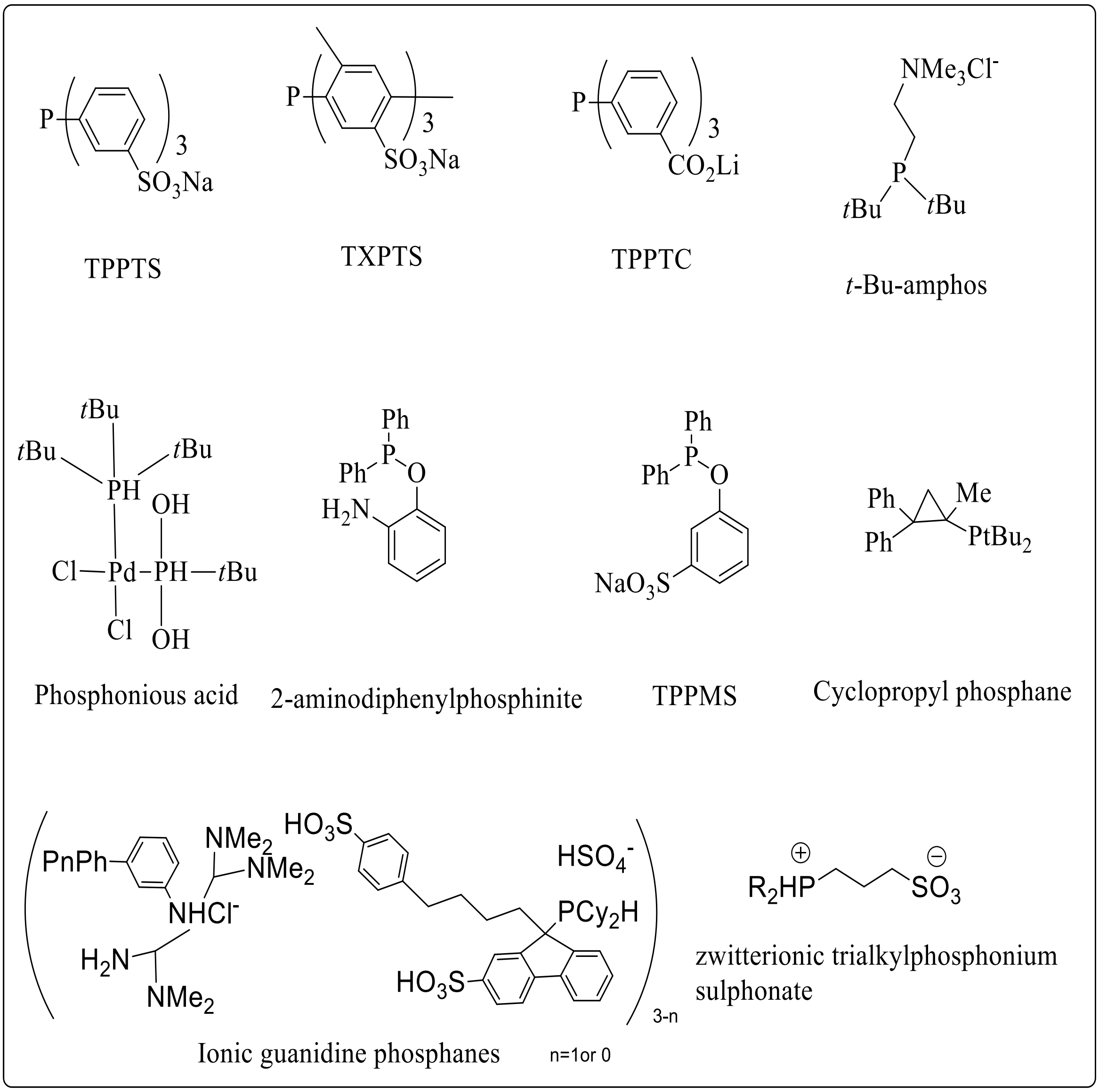


Fig. 9: Phosphine based ligands in Sonogashira reaction

N-based ligands for Sonogashira reaction:

Different *N*-based ligands were also successfully used in Sonogashira reaction. *N*-heterocyclic carbenes are the most prominent example amongst the *N*-based ligands and they have shown excellent activity with good TON. Some common examples of NHCs employed in Sonogashira reaction are is shown in the **Fig. 11**.

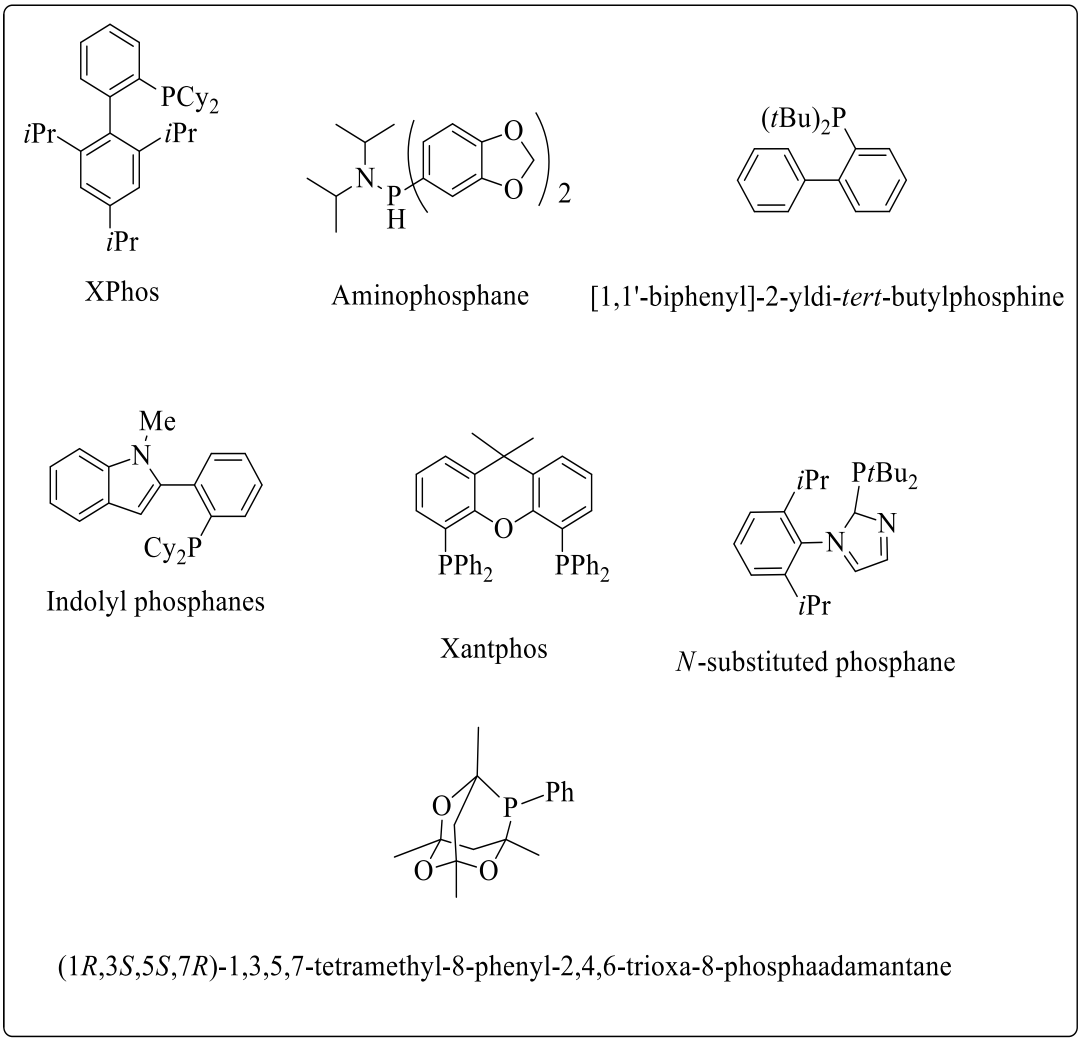


Fig. 10: Phosphine based ligands used in Copper free Sonogashira reaction

On the other hand, some amine based compounds were also used to play the dual role of solvent and ligand, for example, pyrimidine, bispyrimidine, hydrazone etc. Additionally, some bidentate ligands were also examined in Sonogashira reaction like diphosphanes [106], ferrocene based phosphinimine-phosphane [107] etc. Tridentate ligands were also exploited in the mentioned reaction, for example, C,N,C-dicarbene pincer [108], ferrocylphosphane [109] etc.

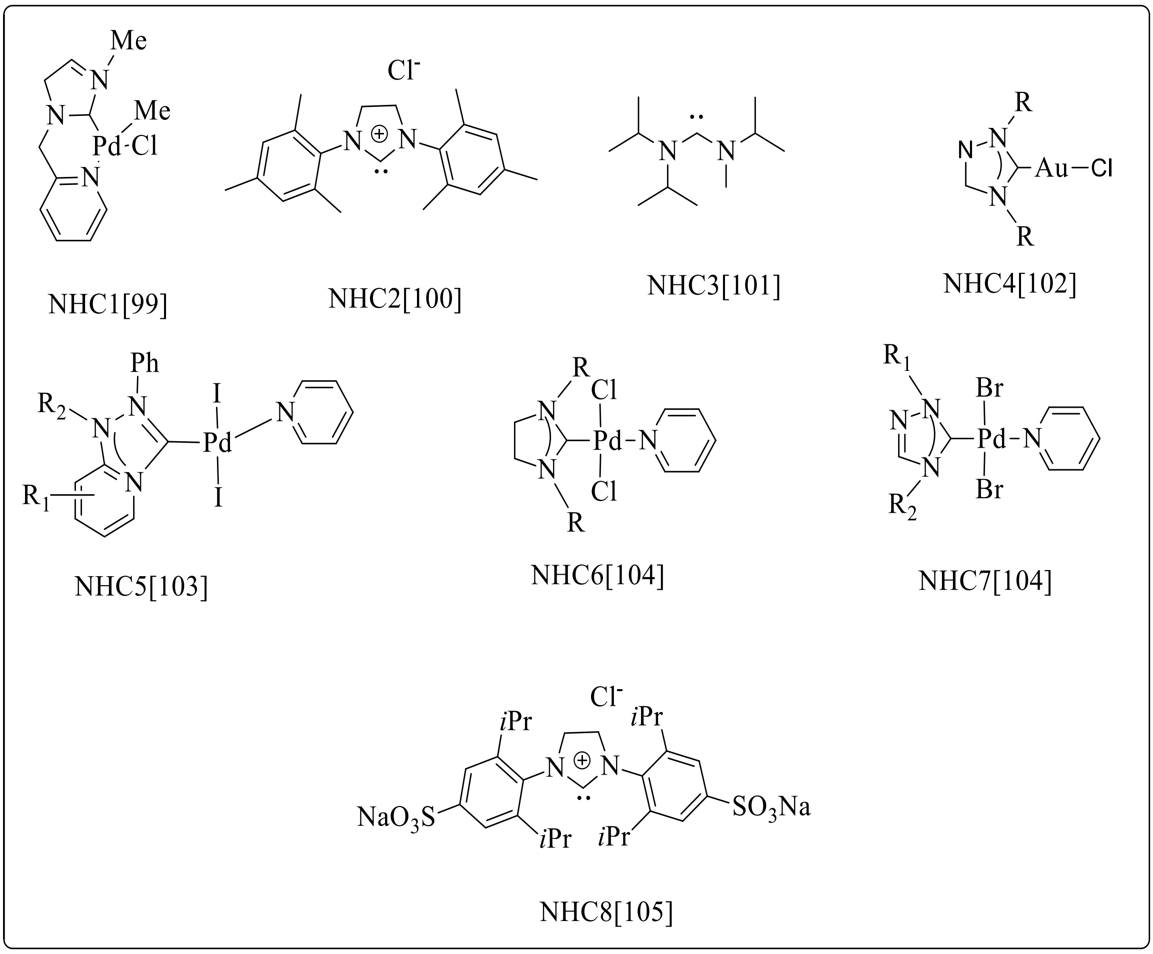


Fig. 11: NHCs used in Sonogashira reaction

Palladacycles in Sonogashira reaction:

Palladacycles are highly reactive palladium complexes and different types of these complexes were employed in Sonogashira reaction. Some of the common examples are oxime palladacycles [110], sulfilimine palladacycles [111], tridented pincer ligand based palladacycle [112], P,C,P-pincer palladacycle [113] etc. (**Fig. 12)**.

Ligand free Sonogashira reaction:

As discussed in the above section, ligands hamper during the isolation of product and most of them are highly expensive. Moreover, additional reaction steps are required to synthesize some of the ligands. Therefore, ligand free catalytic protocol for Sonogashira reaction is of high demand. There are few reports on ligand free Sonogashira reaction.

The first ligand free Sonogashira reaction was developed by Urgaonkar [114] and Verkade using tetrabutylammonium acetate in presence of $Pd(OAc)_2$ (**Scheme 2**).

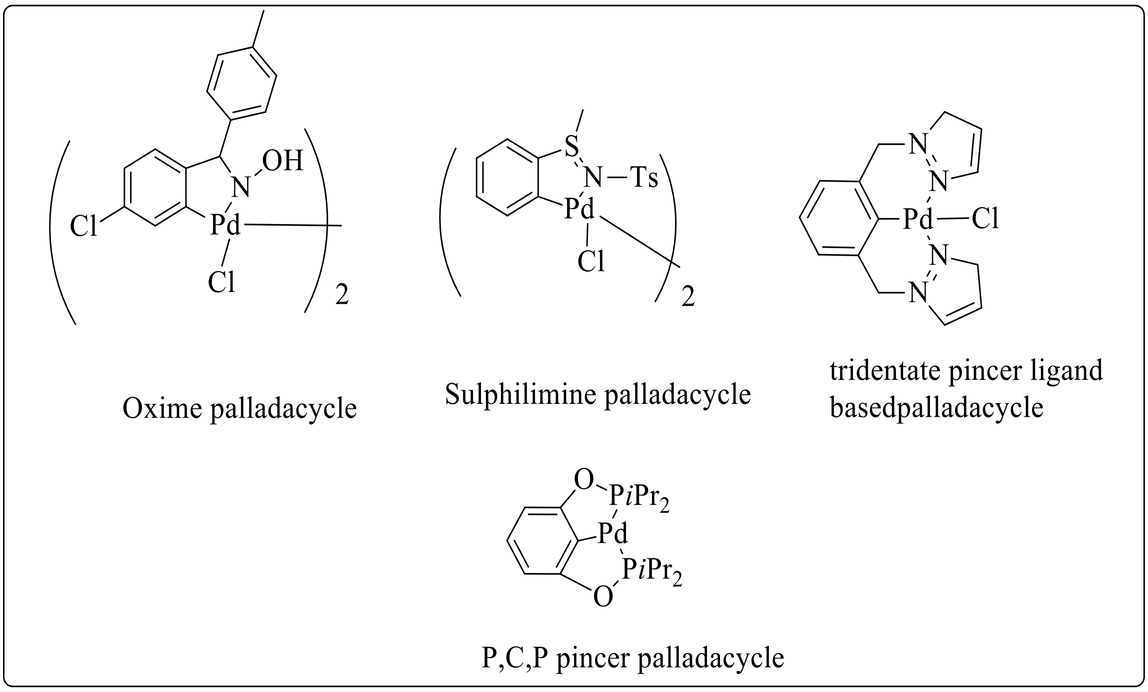
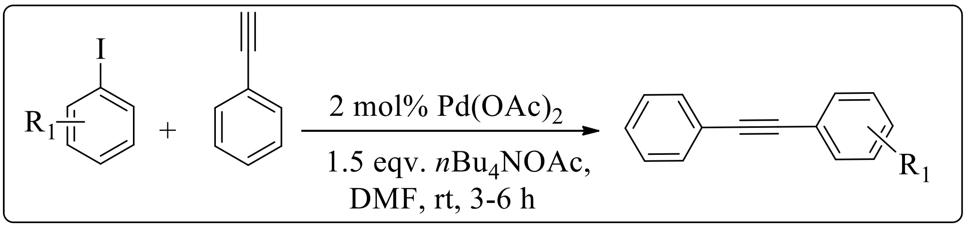
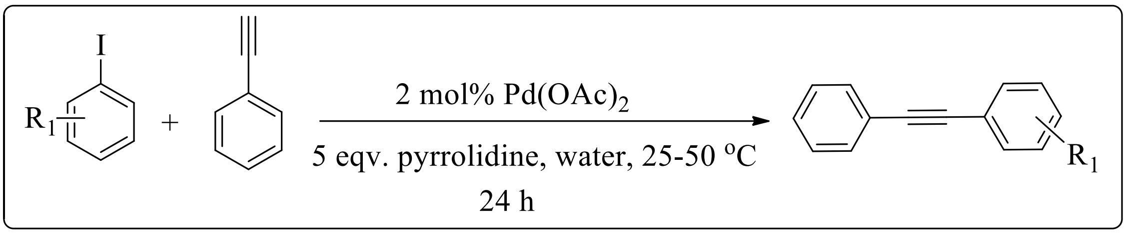


Fig. 12: Palladacycles used in Sonogashira reaction



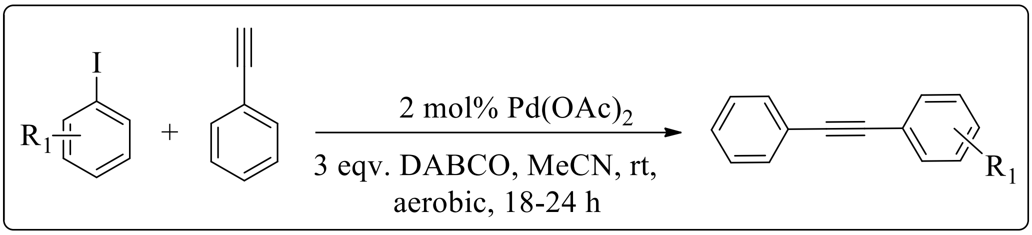
Scheme 2: Urgaonkar's and Verkade's ligand free Sonogashira reaction

Another ligand free reaction protocol for Sonogashira reaction was illustrated by Yang [115] and co-workers using $PdCl_2$ and pyrrolidine under aerobic condition (**Scheme 3**).



Scheme 3: Pyrrolidine promoted ligand free sonogashira reaction in water

In contemporary times, Li [116] *et al.* developed a DABCO/ Pd(OAc)$_2$ mediated ligand free Sonogashira reaction (**Scheme 4**).



Scheme 4: Ligand free Sonogashira reaction using DABCO

Nowadays, highly reactive Pd NPs are widely used for effective ligand free Sonogashira reaction. These catalysts are highly active and have high surface to volume ratio having highly active surface atoms. The shape, size, compositions are the main factors on which the selectivity, catalytic activity and stability of these catalysts depend. Their reactivity increase when the contact between the reactants and the catalysts enlarges by the addition of the small nano-sized particles to the bare surface area of the active component of the catalyst [117]. There are lots of reports regarding Pd NPs catalyzed ligand free Sonogashira reaction. In most of the reports, Pd NPs are immobilized on a porous support material to make the catalyst a heterogeneous one such that it can be recovered easily and reused many times. Pd NPs supported on polysaccharide derived mesoporous material [118], Pd NPs supported on MOF-5 [119], β-cyclodextrin capped Pd NPs [120] are some common examples of heterogeneous Pd NPs utilized in Sonogashira reaction. On the other hand, reports on homogeneous Pd NPs for Sonogashira reaction are also available. Bimetallic nanoparticles are also found to be very effective for this cross-coupling reaction. Pd/Cu [121], Pd/Ni [122], Pd/Co [123] are extensively used bimetallic catalysts for the said reaction. So, it can be concluded that Pd NPs are economical and sustainable alternative for bulky phosphine or *N*-containing ligand assisted Sonogashira reaction.

Base and solvent diversity in Sonogashira reaction:

Base is considered as the key component in Pd catalyzed Sonogashira reaction. It becomes impossible to perform the reaction in absence of a base because; it drives a major step called transmetalation in the catalytic cycle. In the earlier stages, organic bases were used exclusively for the Sonogashira reaction. But, nowadays some inorganic bases like carbonate salts, metal hydroxides also replace the organic bases with good yield of product. Like bases, many polar and nonpolar solvents are also used in the Sonogashira reaction. Various solvents like DMF, toluene, xylene, DMSO, MeCN are also used successfully in the reaction providing high yield. Few reports are also available regarding the use of green solvents like alcohols and water in the Sonogashira reaction. Ionic liquids like [bimim]PF_6 [124], [bimim]PF_4 [125] are also used for both Copper co-catalyzed and Cu free Sonogashira cross-coupling reaction. Recently, an agro waste mediated Sonogashira cross-coupling reaction is reported where water extract of papaya bark ash [126] is used both as solvent and base for the desired cross-coupling reaction.

Palladium free Sonogashira reaction:

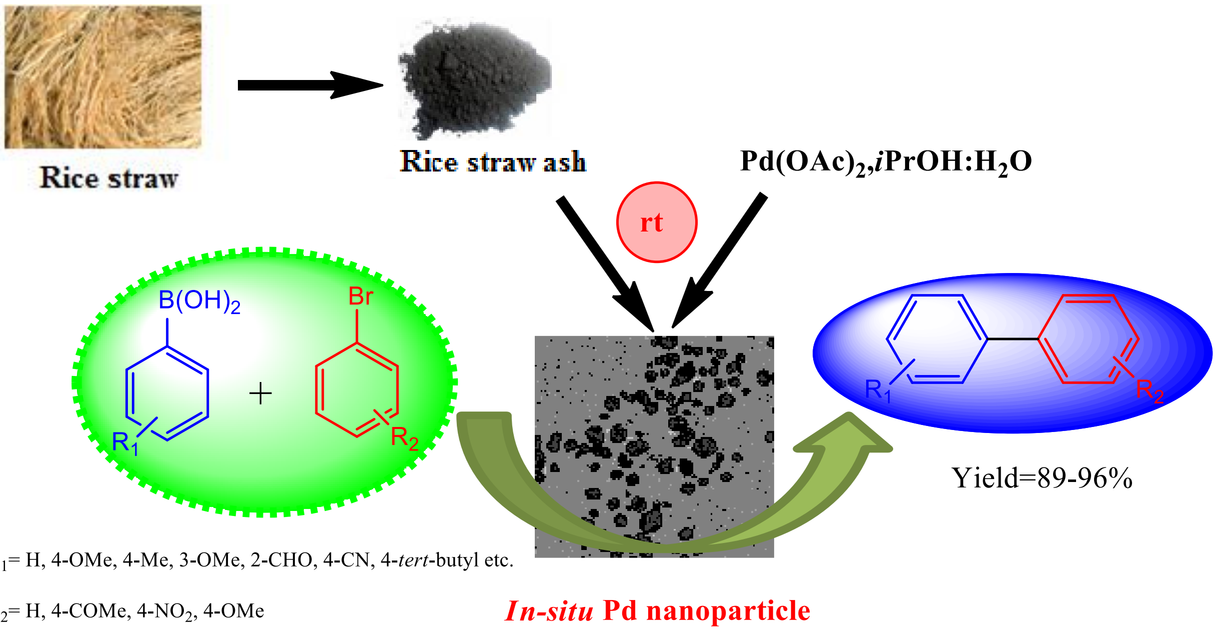
Palladium catalysis free Sonogashira reaction protocols are also developed using different ligands. Some catalyst systems effective for Pd free protocols are CuI/PPh_3 [126], CuI/DABCO [127], CuI/*N,N'*-dimethylglyoxime [128], $[Cu(DMEDA)_2Cl_2]\cdot H_2O$ [129], CuI-*N,N'*-dibenzyl BINAP [130] etc. Moreover, ligands and Pd free catalyst systems were also employed for the reaction which includes CuI/K_2CO_3/PEG/ microwave [131], CuI/K_2CO_3/DMF/55 ˚C [132] and $CuI/Ag_2O/Cs_2CO_3$ [133].

Some other transition metal catalysts like Fe [134], Au [135], Ni [136], and Co [137] are also used in palladium free Sonogashira reaction.

CHAPTER 2

Section 2.1

Improved Suzuki-Miyaura cross-coupling reaction in Rice Straw Ash: Evidence for enhancing effect of water: *i*-propanol with *in-situ* generated Pd NPs.



The work described in this section has been published in *Tetrahedron Letters*, 2016, *57*, 3091-3095.

2.1. A. Introduction:

As we have discussed in the introduction part of chapter 2, in recent years, the palladium catalyzed Suzuki-Miyaura cross-coupling reaction has received utmost applications in several imperative fields like pharmaceutical, natural products etc. due to its mild reaction condition and wide substrate scope [139-140]. The oxidative addition is considered as the most crucial step in the catalytic cycle of Suzuki-Miyaura cross-coupling reaction. Therefore, researchers are paying attention towards the development of palladium complexes enclosing electron-rich phosphorous and nitrogen based ligands which speed up the oxidative addition step by increasing the electron density over palladium [141-143]. Although, these ligands have done a great job in stabilizing palladium species, they are generally toxic, costly, inseparable, and often create problems in easy isolation and purification. To conquer this, ligandless catalysis with highly active Pd catalyst seems particularly well suited, mainly due to the profound advantage of easy recovery and proficient cost/reactivity relationship [144]. On the other hand, the Suzuki-Miyaura coupling reaction is greatly dependent on the presence of external base and solvent system [145-148]. A base activates the organoborons species during the transmetalation step and helps in the transfer of nucleophilic organic group linked with boron species to the organopalladium species. As a result, a proper selection of base is very important for such coupling reaction which can lower the side-reactions due to compatible functional groups, homo-coupling [149-150] and protodeboronation [151] reactions. Again, for a reaction, solvent is often necessary during various steps, such as, reactant mixing, proper isolation and energy supply etc. Thus, to develop an environmentally benign and economically sustainable Suzuki-Miyaura cross-coupling reaction, a catalytic system involving ligandless metal catalyst and a mild base with wide compatibility is one of the significant topics in green chemistry.

Recently, Sarma *et al.* have developed a novel catalytic system for Suzuki–Miyaura cross-coupling reaction using $Pd(OAc)_2$ and Water Extract of Rice Straw Ash (WERSA) where ‘WERSA’ is used as source of base and solvent. Although, water has a great ability to solvate polar and ionic substances, the reaction delivers moderately lower efficiency in WERSA, perhaps due to the non-polar reactants and products which are not miscible with water [70].

So, as a part of our continuing efforts to develop sustainable protocols for Suzuki-Miyaura cross-coupling reaction, we determined to revisit the coupling chemistry in WERSA with the aim to increase the atom economy and to evaluate the exact role of extract during the reaction. The agro-waste rice straw-derived ash was characterized by Energy-dispersive X-ray spectroscopy (EDX), Ion chromatography (IC) and Flame photometry analysis. Moreover, an effort was also made for better efficiency of the reaction by employing isopropanol co-solvent. Throughout our investigation, we have also noticed that the *i*PrOH-WERSA facilitates the reduction of Pd(II) to Pd(0) and generate Pd NPs even in the absence of the normally accepted reducing agents. The isolated coupling products were characterized using ^{1}H and ^{13}C NMR spectroscopy.

2.1. B. Experimental:

General information:

^{1}H and ^{13}C NMR spectra of the products were recorded in a JNM ECS 400 MHz NMR spectrophotometer (JEOL) using tetramethylsilane (TMS) as the internal standard. Chemical shift values are expressed in ppm. Coupling constants are expressed in Hertz. Reactions were monitored by thin-layer chromatography using aluminium sheets with silica gel 60F$_{254}$ (Merck). UV light and Iodine vapour were used as visualizer. Chemicals are obtained from commercial source. The Transmission electron microscopy (TEM) analysis of the *in-situ* generated catalyst was carried on a JEM-2010 (JEOL) instrument which was equipped with a slow-scan CCD camera. The accelerating voltage was 200 kV. EDX analysis of the RSA was carried out on a Scanning Electron Microscope (JEOL, JSM, Model 6390 LV).The ion analysis of “WERSA”was carried out in an Ion Chromatograph (Metrohm, 882). Flame photometry experiments were conducted in a Flame Photometer (Systronics, 128). The powder XRD pattern analysis was done on a Rigaku Multiflex instrument. It uses Cu K (0.15418 nm) radiation source and has a scintillation counter detector. The intensity data were recorded over a 2 range of 5–90˚.

Procedure for preparation rice straw ash and ‘WERSA’:

After harvesting rice, the straw is generally left behind in the fields. The straw was cut and oven dried. It was then burnt in a mud oven until full transformation into ashes. Thereafter, 10 g of the ash was suspended in distilled water (100 mL) and stirred for half an hour at room temperature. The mixture was then filtered. The filtrate is known as 'WERSA' (**Fig. 1**).

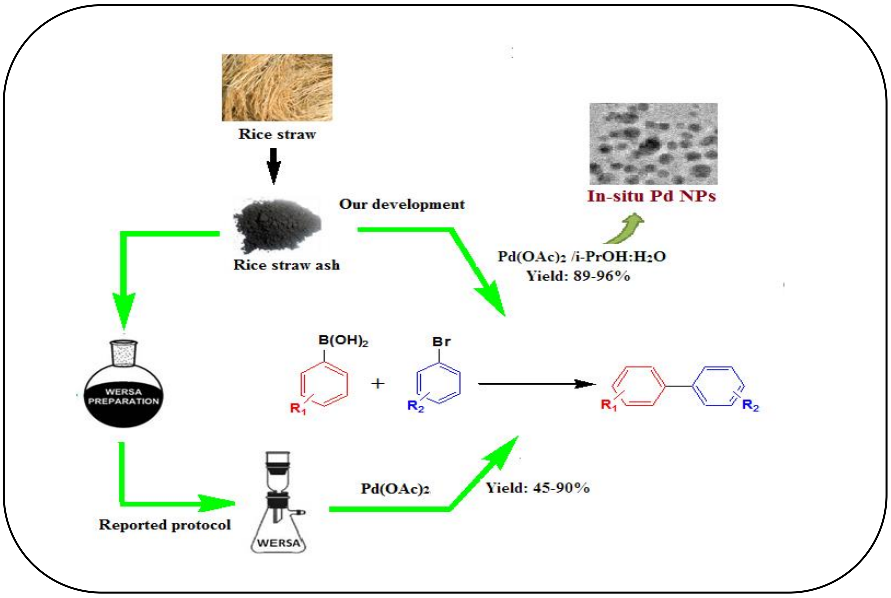
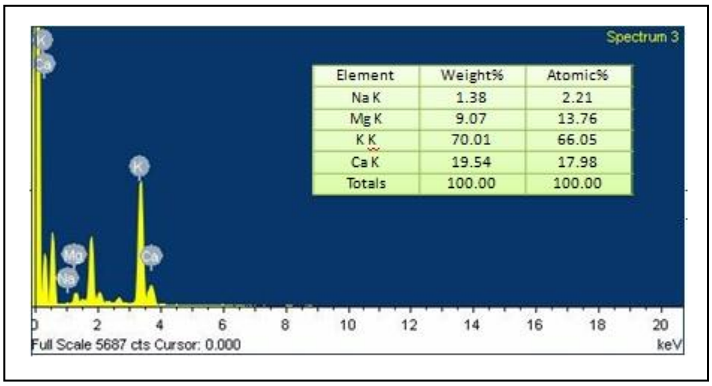


Fig. 1: Preparation of ' WERSA' and our development

Analysis of Rice straw ash:

The alkaline nature of the extract was determined by litmus test, and its pH was found to be around 12. The distribution of elements as based on the EDX analysis of the rice straw ash is shown in **Fig. 2**. The report reveals a very high concentration of oxides of potassium followed by calcium and magnesium.



Element	Weight%	Atomic%
Na K	1.38	2.21
Mg K	9.07	13.76
K K	70.01	66.05
Ca K	19.54	17.98
Totals	100.00	100.00

Fig. 2: EDX spectrum of rice straw ash

Thereafter, we have performed the Ion-Exchange Chromatography and Flame photometry, to analyse the metal and ion concentration of the water-extract. The results are summarized **Fig. 3** and **Table 1**.

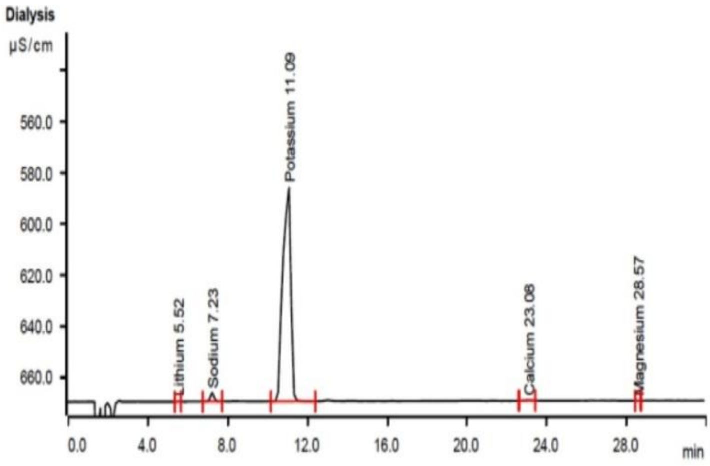


Fig. 3: IC analysis of rice straw ash

Table 1. Comparisons of metals contents (in ppm) in 'WERSA' using Ion-Exchange chromatography and Flame photometry analysis.

Entry	Metal	Metal concentration by IC [ppm]	Metal concentration by flame photometry [ppm]
1	Li	Trace	Trace
2	Na	28.31	25.36
3	K	3215.5	3025.25
4	Ca	3.43	4.05
5	Mg	Trace	Trace

General procedure for Suzuki-Miyura cross-coupling reaction:

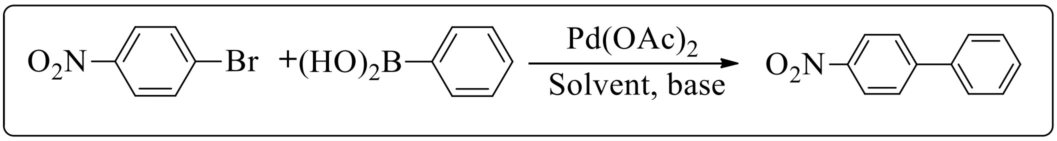
A 50 mL round-bottomed flask was charged with a mixture of arylboronic acid (1.2 mmol), aryl halide (1 mmol), 2 mL distilled water and 2 mL of iso-propanol. To this mixture, 1 mol% of $Pd(OAc)_2$ was added followed by the addition of the 0.3g of rice straw ash. The whole reaction mixture was stirred for the required time resulting a black coloured solution. The reaction was monitored by TLC and after completion of the reaction the solution was extracted three times with ethylacetate (3x10 mL). The products were purified by column chromatography and confirmed by ^{1}H, and ^{13}C NMR spectroscopy.

2.1. C. Results and discussion:

Sarma *et al.* have presented a general method for the room temperature external base-free Suzuki-Miyaura coupling of aryl (or hetero aryl) bromides and arylboronic acids in ‘WERSA’. While a wide range of functional groups on the reacting substrate are tolerated in the reaction, only the coupling with electron rich bromoarene worked well with high efficiency. Our first objective in reassessing the methodology was to determine the role played by ‘WERSA’ during the reaction. Since, metal ions or oxides can react with water to produce metal hydroxides; the above distribution data substantiates the basic nature of ‘WERSA’. Our next investigation was to improve the efficiency of the cross-coupling reaction. We revisited the reaction prototype; phenylboronic acid (1.2 mmol), 4-bromonitrobenzene (1.0 mmol), $Pd(OAc)_2$ (1 mol%) and ‘WERSA’ (3 mL) at room temperature and found 45% of the isolated yield (Table 2, Entry 1). In the next step, we intended to observe the reaction protocol by organic “co-solvent” effect. In literature, several reports mentioned the use of organic-water co-solvents, *viz.* water-DMF [152], water-THF [153], water-alcohol [48(a), 154-155] etc. which assist in the complete dissolution of the organic substrates, and enhance the rate of reaction. To our delight, the reaction proceeded with 87% isolated yield within 3.5 h in ethanol-WERSA (1:1) (Table 2, Entry 3). On further optimizing with different co-solvents, we found that the use of isopropanol-WERSA (1:1) efforded highest efficiency (Table 2, Entry 4). However, lower ratio of WERSA decreases the yield of the desired product (Table 2, Entry 5).

Given the remarkable improvement demonstrated by the WERSA-*i*PrOH, we became interested in investigating the role of the co-solvent during the reaction. TEM images of the reaction mixture after the completion indicated the formation of homogeneous palladium nanoparticles (Pd NPs) with spherical aggregate structures having smaller and average particle size of 5-10 nm (**Fig. 4**). The production of Pd NPs, in the absence of the normally adopted reducing agents, is most likely due to the iso-propanol which enables the reduction of Pd(II) to Pd(0), while its hydroxyl groups are oxidized to carbonyl groups. The TEM image showed the aggregates of Pd NPs dispersed over the thin layer of WERSA-isopropanol. This observation suggested that the biphasic system coated the Pd NPs and kept them strongly attached to each other.

Table 2. Optimization of reaction condition for catalyst and solvent[a]



Entry	Pd(OAc)$_2$ (mol%)	Solvent (4 mL)	Rice straw ash (g)	Time (h)	Yield (%)[b]
[c]1	1	WERSA	-	12	45
2	1.5	WERSA	-	12	45
3	1	WERSA-EtOH(1:1)	-	3.5	87
4	1	WERSA-*i*PrOH(1:1)	-	3.5	89
5	1	WERSA-*i*PrOH(1:3)	-	6	80
6	1	WERSA-DMF(1:1)	-	3	87
7	0.5	WERSA-*i*PrOH(1:1)	-	4	75
8	1	Do	0.5	3.5	89
9	1	Do	0.7	3.5	89
10	1	Do	0.3	3.5	89
11	1	Do	0.2	6	82

[a]Reaction condition: 4-bromonitrobenzene (1 mmol), Phenylboronic acid (1.2 mmol), Solvent (4 mL) *ca*. 27 °C in air, unless otherwise noted. [b]Isolated yield. [c]2 mL of 'WERSA' was used.

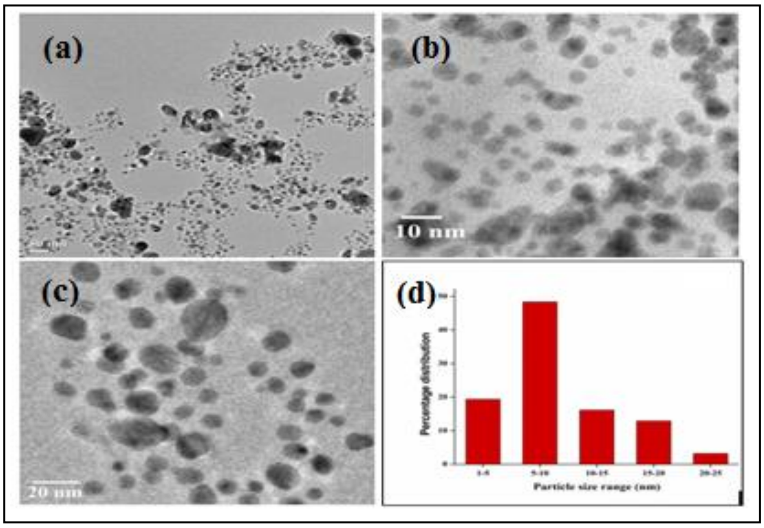


Fig. 4: TEM images of Pd NPs (a-c) and Pd NPs distributions (d)

XRD analysis was performed to investigate the size and structure of recovered Pd NPs (**Fig. 5**). Three peaks were observed at 2θ=39.55˚, 45.94˚ and 67.64˚ corresponding to the reflections of (111), (200), and (220) planes of Pd NPs (JCPDS no. 88-2335). The broadening of the peak indicated that the palladium particles were of nano-size.

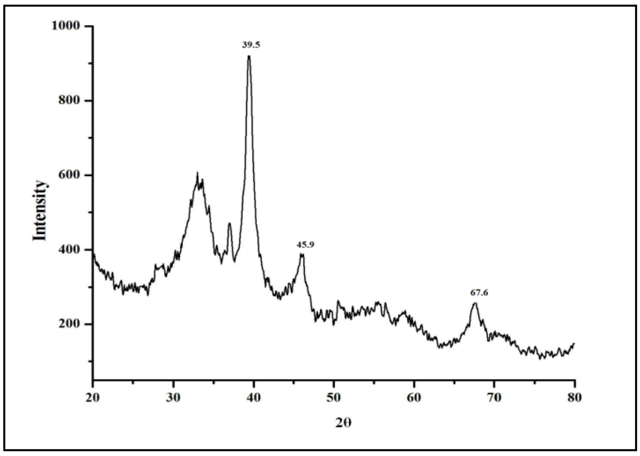
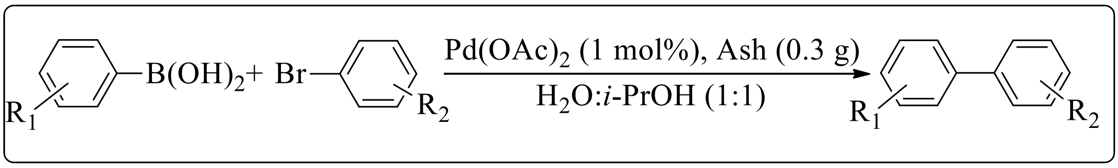


Fig. 5: X-ray diffraction pattern of Pd NPs

Previously, we have reported that the *in-situ* generated catalytic system based on palladium salt with sodium sulphate, sodium acetate or sodium chloride exhibits excellent catalytic activity in the Suzuki-Miyaura cross-coupling reactions at room temperature in water and iso-propanol [156]. Later on, these catalytic systems have received a wide range of applications in various organic syntheses [153, 157-159]. Moreover, the XPS and FT-IR data provided strong evidence for the existence of interactions between the salt particles with palladium catalyst and aryl bromide [160]. It is believed that such synergic interactions are perhaps possible under present reaction condition with 'WERSA'. Being succeed in our first aim to improve the yield of the desired cross-coupled product, in the next assessment we tried to generate an *in-situ* alkaline system in the reaction medium. From analysis, it was clear that the rice straw ash contained metals like K, Na, Li, Ca, Mg etc. So, we believed that the containing metal would have the capability to form metal hydroxide with water in the reaction from their corresponding metals and these would be suitable bases for the concerned reaction. Based upon this point of view, the reaction of phenylboronic acid (1.2 mmol) and 4-bromonitrobenzene (1 mmol) was performed under isopropanol: water (1:1) with 0.5 g of rice straw ash keeping the amount of catalyst same with the earlier reaction of isopropanol: WERSA (1:1) (Table 2, Entry 8) and more interestingly 89% of isolated yield of desired cross-coupled product was found. To look more thoroughly at the scope of the amount of ash in the efficiency of cross-coupling, on increasing the ash loading from 0.5 g to 0.7 g no considerable effect on the reaction efficiency was noticed (Table 2, Entry 9). Thus, varying the amount of ash keeping other conditions constant we found that 0.3 g of the ash was enough for the suitable conversion to the desired product (Table 2, Entry 10).

With the optimum reaction conditions being defined, we next investigated the substrate scope and limitations of the reaction by using diverse range of aryl bromides and arylboronic acids (Table 3). Aryl bromides having both electron withdrawing and electron donating groups underwent effective coupling reactions with arylboronic acid to afford the desired biaryls in excellent yields (89-96%) in water-isoproponol. Moreover, the catalytic system is equally effective for differently substituted arylboronic acids (Table 3). These results are quite significant as the desired biaryls could be achieved at room temperature using water-isoproponol co-solvent and with natural base and low catalyst loading without using any ligand.

Table 3. Rice straw ash promoted Suzuki-Miyaura cross-coupling reaction of aryl bromides and arylboronic acids[a]



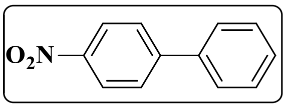
Entry	R_1	R_2	Time (h)	Yield (%)[b]
1	-H	4-NO_2	3.5	89
2	4-Me	4-OMe	1	93
3	4-CHO	-H	1	96
4	-H	4-COMe	2.5	93
5	4-OMe	-H	1.5	95
6	4-OMe	4-OMe	1	94
7	4-*tert*-butyl	4-NO_2	1	96
8	4-CN	-H	1.5	95
9	4-F	-H	4	94
10	2-Me	4-OMe	1	92
11	4-Cl	4-NO_2	1.5	89
12	4-F	4-OMe	1	92
13	-H	-H	1	95
14	3-OMe	-H	3	90
15	2-CHO	-H	2	94
16	3-NH_2	-H	2	91

[a]Reaction condition: Arylboronic acid (1.2 mmol), aryl bromide (1 mmol), $Pd(OAc)_2$ (1 mol%), *i*-PrOH (2 mL), water (2 mL), *ca*. 27 °C in air, unless otherwise noted. [b]Isolated yield.

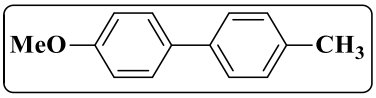
2.1. D. Conclusions:

In conclusion, we have shown that when the Suzuki-Miyaura reaction is performed with rice straw ash in water-isopropanol, metal oxide concentration to a level of above 3,000 ppm is present in ash are responsible for the basicity of the reaction medium. Moreover, the use of isopropanol as co-solvent generates Pd NPs responsible for the enhanced yield of the coupling reaction. We have presented here a revised methodology for Suzuki-Miyaura couplings using 'WERSA'. The chief attraction of the present reaction system is a highly abundant agro waste, which presents a remarkable outcome towards the development of sustainable chemistry.

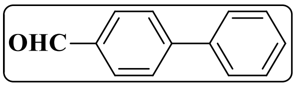
Characterisation data for the products:



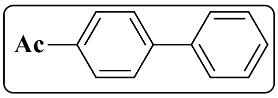
4-nitrobiphenyl (**Entry 1, Table 3**): Black solid (Yield=89%), mp= 114-117 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30(d, *J*=8Hz, 2H), 7.74(d, *J*=8Hz, 2H), 7.61(d, *J*=8Hz, 2H), 7.50-7.40(m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 138.8, 129.2, 129.0, 128.1, 127.8, 127.4, 124.1 ppm.



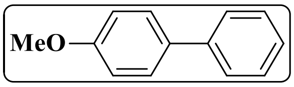
4-methyl-4'-methoxybiphenyl (**Entry 2, Table 3**): White solid (Yield=93%), mp= 175-180 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51(d, *J*=8Hz, 2H), 7.45(d, *J*=8Hz, 2H), 7.24(d, *J*= 8Hz, 2H), 6.95(d, *J*=8Hz, 2H), 3.83(s, 3H), 2.36(s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 158.9, 136.4, 129.5, 128.0, 126.6, 114.2, 55.4, 21.1 ppm.



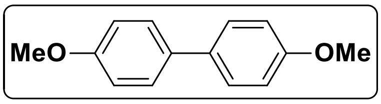
4-formylbiphenyl (**Entry 3, Table 3**): Brown solid (Yield=96%), mp= 80-82˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 10.05(s, 1H), 7.95(d, *J*=8Hz, 2H), 7.75(d, *J*=8Hz, 2H), 7.63(d, *J*=8Hz, 2H), 7.47(d, *J*=8Hz, 2H), 7.42-7.40(m, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 192.08, 147.3, 139.7, 135.2, 130.3, 129.1, 128.5, 127.7, 127.4 ppm.



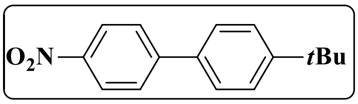
4-acetobiphenyl (**Entry 4, Table 3**): White solid (Yield=93%), mp= 152-155˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.02(d, *J*=8Hz, 2H), 7.69(d, *J*=8Hz, 2H), 7.63(d, *J*=8Hz, 2H), 7.47(d, *J*=8Hz, 2H), 7.42-7.40(m, 1H), 2.64(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 197.0, 145.9, 140.8, 135.2, 129.3, 129.2, 127.8, 127.4, 127.0, 26.4. ppm.



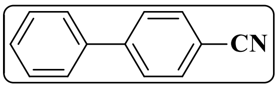
4-methoxybiphenyl (**Entry 5, Table 3**): White solid (Yield=95%), mp= 90-92 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.56-7.51(m, 4H), 7.44-7.41(m, 2H), 7.34-7.28(m, 1H), 6.97(d, *J*=8Hz, 2H), 3.85(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.2, 140.9, 133.8, 128.2, 126.8, 126.7, 114.2, 55.4 ppm.



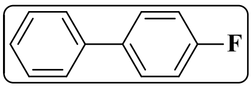
4,4'-dimethoxybiphenyl (**Entry 6, Table 3**): White solid (Yield=93%), mp= 176-180 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.48-7.46(m, 4H), 6.96-6.94(m, 4H), 6.97(d, *J*=8Hz, 2H), 3.84(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.7, 133.5, 127.8, 114.2, 55.4 ppm.



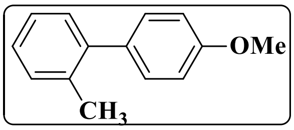
4-nitro-4-*tert*-butylbiphenyl (**Entry 7, Table 3**): Yellow solid (Yield=96%), mp= 110-112 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.28(d, *J*=8Hz, 2H), 7.73(d, *J*=8Hz, 2H), 7.58(d, *J*=8Hz, 2H), 7.52(d, *J*=8Hz, 2H), 1.37(s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 152.3, 147.5, 146.9, 135.8, 127.6, 127.1, 126.2, 124.1, 31.3 ppm.



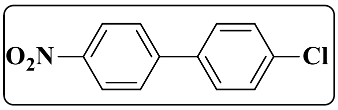
4-cyanobiphenyl (**Entry 8, Table 3**): White solid (Yield=95%), mp= 85-90˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.50-7.48(m, 2H), 7.44-7.41(m, 2H), 7.39-7.36(m, 2H), 6.96-6.89(m, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 135.0, 131.6, 131.5, 129.0, 128.6, 127.8, 111.7, 111.7, 111.5, 111.5, 104.7, 104.4 ppm.



4-fluorobiphenyl (**Entry 9, Table 3**): Brown solid (Yield=94%), mp= 110-112 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.55-7.52(m, 4H), 7.46-7.43(m, 2H), 7.37-7.32(m, 1H), 7.13(d, *J*=8Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 163.7, 161.3, 140.3, 137.4, 128.9, 128.8, 128.7, 127.3, 127.1, 115.8, 115.6 ppm.

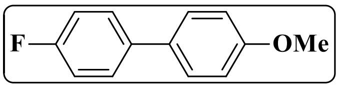


2-methyl-4'-methoxybiphenyl (**Entry 10, Table 3**): White solid (Yield=92%), mp= 80-85 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.53-7.50(m, 2H), 7.36-7.30(m, 3H), 7.15-7.12(m, 1H), 6.98-6.95(m, 2H), 3.84(s, 3H), 2.40(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.1, 140.8, 138.3, 133.9, 128.7, 128.2, 127.6, 127.4, 123.9, 114.2, 55.4, 21.6 ppm.

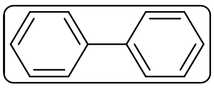


4-nitro-4'-chlorobiphenyl (**Entry 11, Table 3**): Brown solid (Yield=89%), mp= 114-118 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.30-8.27(m, 2H), 7.69(d, *J*=8Hz, 2H), 7.54(d, *J*=

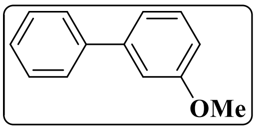
8Hz, 2H), 7.45(d, *J*=8Hz, 2H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.4, 137.2, 135.3, 129.4, 128.7, 127.7, 124.3 ppm.



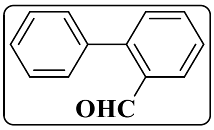
4-methoxy-4'-fluorobiphenyl (**Entry 12, Table 3**): White solid (Yield=92%), mp= 110-115 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45(d, *J*=8Hz, 4H), 7.08(d, *J*=8Hz, 2H), 6.95(d, *J*=8Hz, 2H), 3.83(s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 137.0, 132.9, 128.3, 128.2, 128.1, 115.7, 115.5, 114.3, 55.4 ppm.



Biphenyl (**Entry 13, Table 3**): Brown solid (Yield=95%), mp= 70-72˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.58(m, 4H), 7.47-7.44(m, 4H), 7.39-7.30(m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3, 128.8, 127.3, 127.2 ppm.

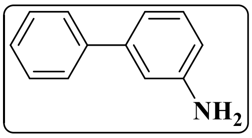


3-methoxybiphenyl (**Entry 14, Table 3**): White solid (Yield=90%), mp= 88-90 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68(d, *J*=8Hz, 2H), 7.55(d, *J*=8Hz, 2H), 7.45-7.44(m, 3H), 7.20-7.16(m, 2H), 7.09(d, *J*=8Hz, 2H), 3.85(s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 138.7, 131.1, 130.9, 129.7, 128.8, 128.2, 127.5, 126.9, 121.0, 111.4, 55.7 ppm.



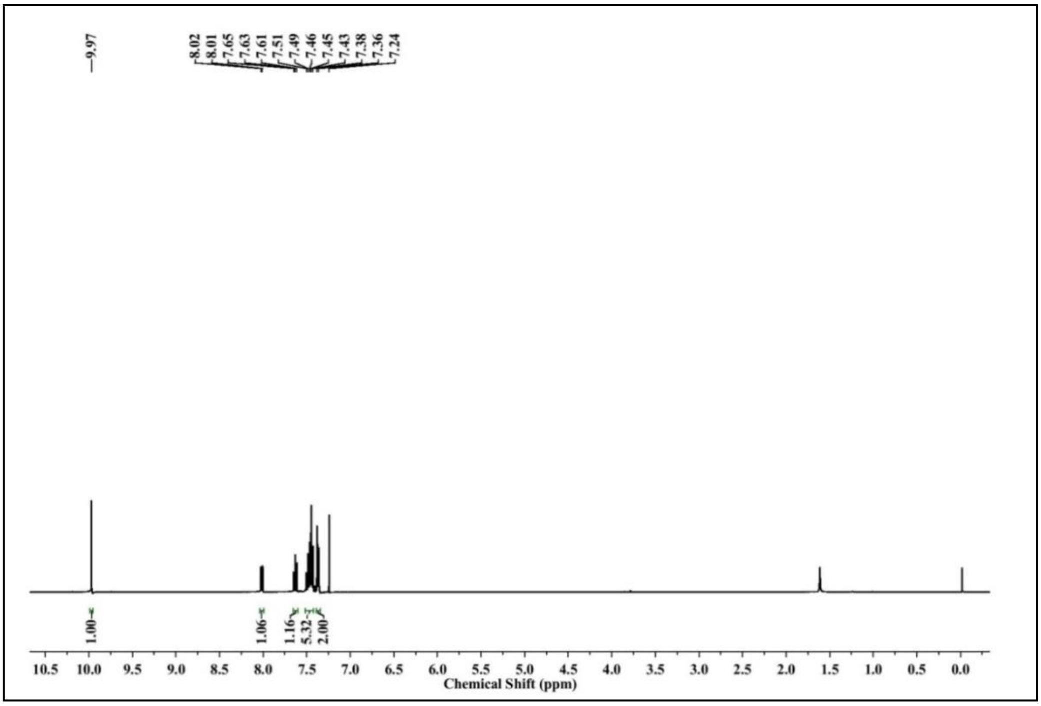
2-formylbiphenyl (**Entry 15, Table 3**): Brown solid (Yield=94%), mp= 90-92 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97(s, 1H), 8.02-8.01(m, 1H), 7.65-7.61(m, 1H), 7.51-

7.45(m, 5H), 7.43-7.36(m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.6, 146.0, 137.8, 133.7, 133.6, 130.8, 130.2, 128.5, 128.2, 127.8, 127.6 ppm.

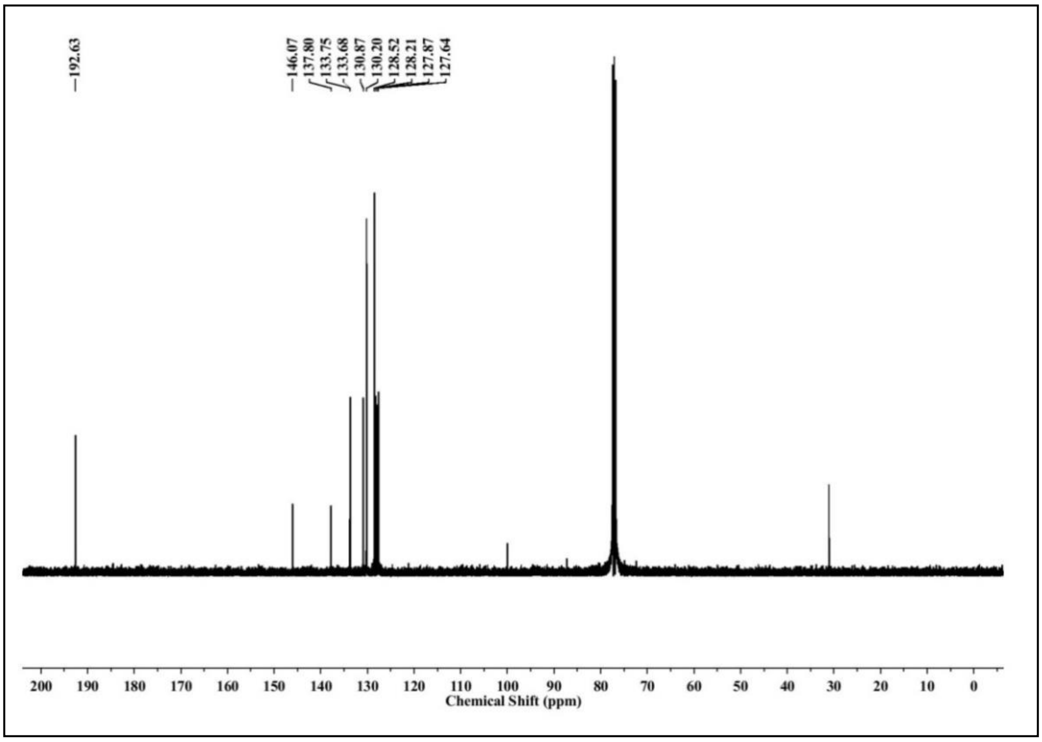


3-aminobiphenyl (**Entry 16, Table 3**): White solid (Yield=91%), mp= 140-145 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55(d, *J*=8Hz, 2H), 7.42-7.38(m, 2H), 7.35-7.30(m, 1H), 7.24-7.21(m, 1H), 7.02-6.97(m, 1H), 6.90-6.89(m, 1H), 6.70-6.65(m, 1H), 3.7(s, br, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) :δ 146.7, 142.5, 141.4, 129.7, 128.7, 127.3, 127.2, 117.7, 114.1, 113.9 ppm.

^{1}H NMR spectrum of 2-formylbiphenyl



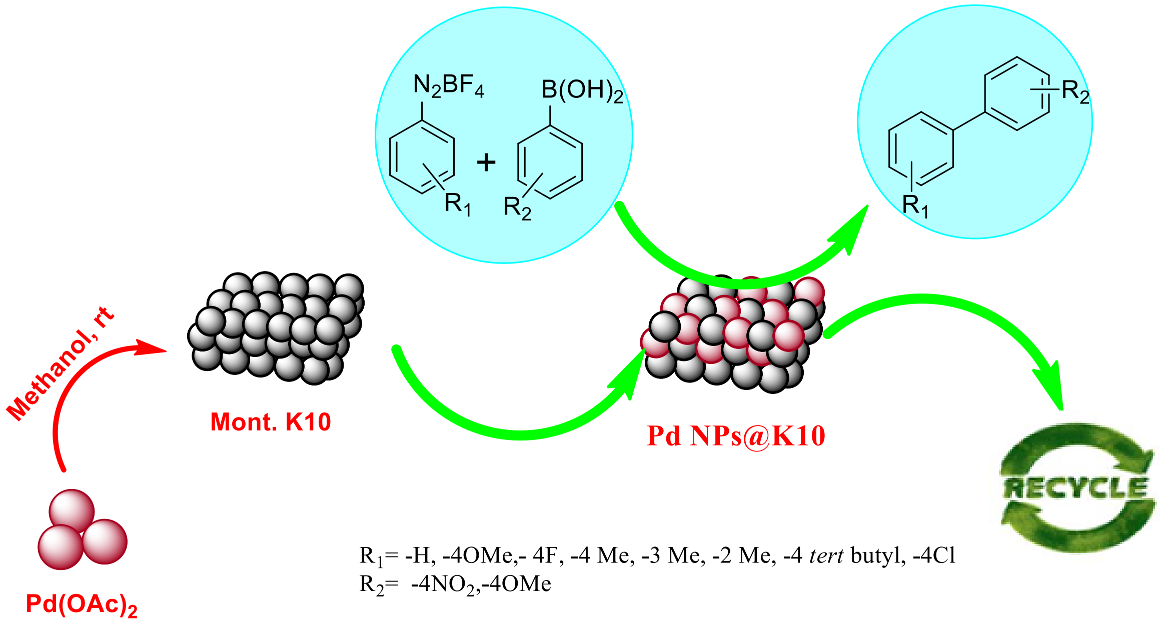
^{13}C NMR spectrum of 2-formylbiphenyl



CHAPTER 2

Section 2.2

External reducing agent free facile synthesis of Pd NPs decorated on Montmorillonite K10 and its implication in Suzuki type cross-coupling reaction under base free condition.



R_1= -H, -4OMe,- 4F, -4 Me, -3 Me, -2 Me, -4 *tert* butyl, -4Cl
R_2= -4NO_2,-4OMe

The work described in this section has been just accepted in *Applied Organometallic Chemistry*, Nov, 2017.

2. 2. A. Introduction:

For centuries, the pursuit of designing eco-friendly protocol for the synthesis of efficient nano catalyst has become an utmost goal among research community as the chemistry of nano materials has gained much interest because of their higher efficiency compared to bulk materials. Besides they have vast applications in electronics, biochemical sensor [119] etc. They also find their importance in C-C and C-heteroatom bond formation reaction. Reports also found on the utilization of highly active Pd NPs in ligand free Suzuki type cross-coupling reaction. But, the main problem is concerned with the preparation of the Pd NPs in a greener pathway. As discussed in the introduction section, most of the synthetic procedures for Pd NPs synthesis involve strong reducing agent, refluxing condition, ultrasonication etc. As a result, there is increasing interest for the development of greener and eco-friendly route for the synthesis of Pd NPs in a single step with minimum use of chemicals or by using environmentally acceptable solvents. Nowadays, though biological resources such as plant extract, microorganisms etc. have been used for the synthesis of Pd NPs, these routes also require high temperature. Additionally, considerable efforts have been made to prepare and stabilize Pd NPs by using environmentally benign, robust, cheap and available support/stabilizer.

Here, we wish to report a mild methodology for synthesizing Pd NPs decorated on Montmorillonite (K10) by simple stirring at room temperature using methanol as solvent without using any external reducing agent. Montmorillonite (K10) is a hydrophilic clay with high cation exchange capacity and thus it can be easily pillared with various metals and metal complexes of choice [161] and this heterogeneous catalytic system is able to overcome the drawbacks of homogeneous catalysts in case of recoverability issue and due to the lack of recovery facility of such expensive homogeneous catalysts their uses become less feasible in industry [162].

Again, aryl bromide and aryl iodides are the common coupling partners in Suzuki-Miyaura reaction. However, it is a challenging task to perform Suzuki-Miyaura reaction using aryl chlorides as coupling partner under mild condition as they react sluggishly and are considered as pollutants. Furthermore, aryl bromides and iodides are found to be costly, so it is distinctively an endeavor to find readily available, non-toxic and inexpensive alternatives for aryl halides as a coupling partner for concerned coupling reaction. In last few decades, aryl diazonium salts come out to be an extremely productive coupling partner for Suzuki-Miyaura cross-coupling reaction as they can be easily prepared from anilines which are more economical than aryl halides. The other advantages of diazonium salts are that they are more reactive than corresponding halides; so, reaction takes place within short reaction time and is feasible under mild and aqueous condition as diazonium salts are better electrophile [163] than the aryl halides. So, as a part of our ongoing programme to develop simplistic protocol for Suzuki type C-C bond forming reaction herein, we wish to report Pd NPs@K10 as an efficient heterogeneous catalyst for base free Suzuki type cross-coupling reaction in aqueous medium at room temperature.

2.2. B. Experimental:

General information:

^{1}H and ^{13}C NMR spectra of the products were recorded in a JNM ECS 400 MHz NMR spectrophotometer (JEOL) using tetramethylsilane (TMS) as the internal standard. Reactions were monitored by thin-layer chromatography using aluminium sheets with silica gel 60F$_{254}$ (Merck). UV light and Iodine vapour were used as visualizer. Chemicals are obtained from commercial source. The transmission electron microscopy (TEM) analyses were carried on a JEM-2010 (JEOL) instrument equipped with a slow-scan CCD camera and the accelerating voltage was 200 kV. EDX and SEM analysis of the catalyst was carried out on a Scanning Electron Microscope (JEOL, JSM, Model 6390 LV operating at an accelerating voltage of 15 kV). The powder XRD patterns analyses were done on a Rigaku Multiflex instrument. It uses Cu K (0.15418 nm) radiation source and has a scintillation counter detector. The intensity data were recorded over a 2 range of 5–90˚. The BET surface area analyses were determined by N$_2$ adsorption by means of a Quantachrome Instruments (Model: NOVA 1000e).

Preparation of the catalyst:

In a round bottom flask containing methanol as solvent, 0.075 g of Palladium acetate and 0.750 g of Montmorillonite K10 were taken and the solution was stirred for two days at room temperature. The colour of the reaction mixture turned to black from brown colour. It was filtered by suction funnel and washed with MeOH for several times, the residue was collected and dried. The collecting residue was kept under a flow of air overnight and under vacuum for 24 h which gave a black powder of heterogeneous K10 supported palladium catalyst.

General experimental procedure for Suzuki type reaction:

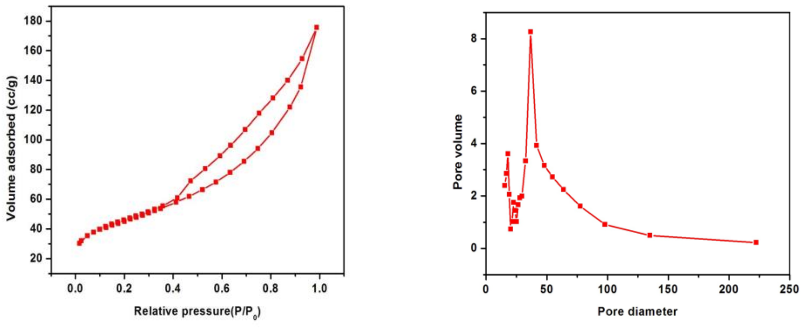
A 50 mL round-bottom flask was charged with a mixture of 10 wt% Pd NPs @K10 catalyst, 1.2 mmol of arylboronic acid and 1 mmol of aryldiazonium salt and stirred at room temperature in 3 mL distilled water for the required time. The reaction was monitored by TLC and after completion of the reaction the solution was extracted three times with ethyl acetate (3x10 mL). The products were purified by column chromatography and confirmed by ^{1}H, ^{13}C NMR spectroscopy and mass spectrometry.

Characterizations of the catalyst:

The catalyst was characterised by BET surface area measurement, Energy Dispersive X-Ray analysis (EDX), Powder XRD, Scanning electron microscopy (SEM), Transmission Electron Microscopy (TEM) and high resolution transmission electron microscopy (HRTEM).

BET surface area analysis:

Fig. 1 depicts the N_2 adsorption–desorption isotherm and pore size distribution of the prepared catalyst under study. It can be predicted from the **Fig. 1** that the compounds are mesoporous material with highly uniform pore size distribution (Type IV isotherm). The BET surface area of the clay and the catalyst was found to be 209 and 154 m^2g^{-1} respectively. The decrease in the value for the catalyst indicates the incorporation of the metal to the clay. Furthermore, from ICP-OES analysis it was found that 0.056 g of Pd was loaded on montmorillonite, i.e. 0.33 mg/g.



(a) (b)

Fig. 1: (a) N_2 adsorption–desorption isotherm and (b) pore size distribution curve of the catalyst

SEM and EDX analysis:

EDX analysis of the catalyst clearly depicts the presence of Pd in the catalyst (**Fig. 2a**). EDX spectrum also shows the presence of elements Si, Fe, K, Mg, Cl, O etc. which are the basic constituents of the clay Montmorillonite. The SEM image for catalyst shows the surface morphology of the catalyst (**Fig. 2b**). The SEM analysis represents the irregularities in shapes of the prepared NPs. The analysis also tells that NPs have different sizes which might be possibly due to agglomeration.

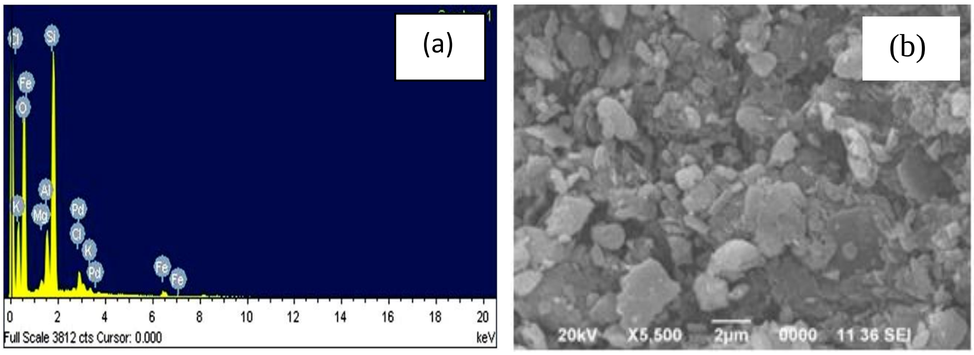


Fig. 2: (a) EDX spectrum and (b) SEM image of the catalyst

TEM analysis:

The particle size and surface morphology of the synthesized catalyst was studied by TEM and HRTEM. The TEM image (**Fig. 3**) of the NPs clearly shows uniformly dispersed Pd(0)NPs on the surface of montmorillonite and most of the particles are spherical in nature. The crystal lattice of Pd NPs is clearly resolved in the HRTEM image (**Fig. 3f**) and it is found to be 0.20 nm. The average size of the NPs is found to be around 10 nm which is determined from the particle size distribution graph. The bright spots in the SAED pattern (**Fig. 3a**) signify the crystalline state of the NPs.

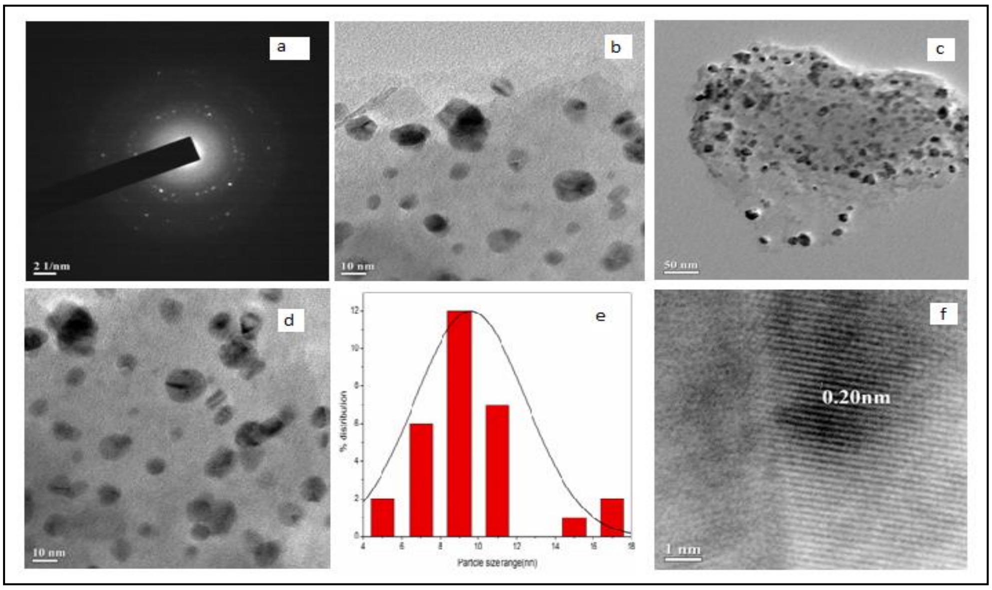


Fig. 3: (a) SAED pattern of Pd NPs, (b-e) TEM images along with particle size distribution, and (f) HRTEM image along with fringe spacing**.**

Powder XRD analysis:

In the Powder XRD pattern, three peaks are observed for the catalyst at 2θ=39.57°, 46.17° and 67.90° corresponding to the reflections of (111), (200), and (220) planes of Pd NPs (JCPDS no. 88-2335) respectively. The broadening of the peak reveals the formation of Pd NPs.

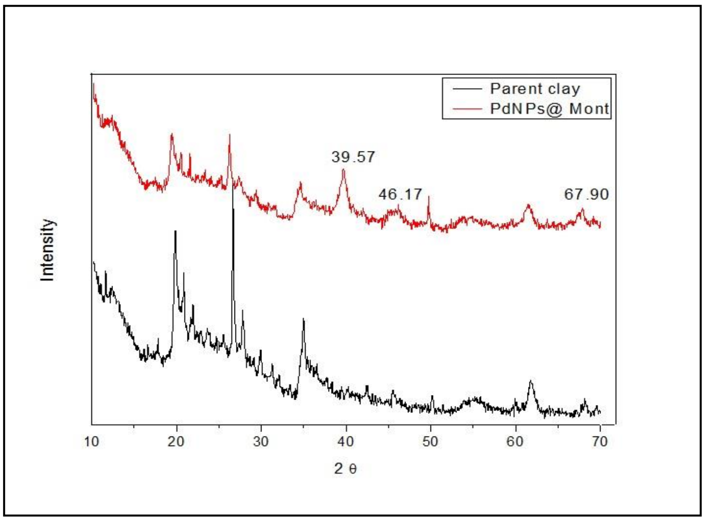


Fig. 4: Powder XRD pattern of the catalyst and the parent clay

2. 2. C. Results and discussion:

Optimization of reaction condition:

To explore the catalytic activity of the newly synthesized catalyst in Suzuki type cross-coupling reaction, a model reaction between phenyl boronic acid (1.2 mmol) and 4-nitrobenzenediazonium tetrafluroborate (1 mmol) was investigated in presence of 10 wt% of the catalyst under open air condition using methanol at room temperature (Table 1, Entry 1). It was observed that no base was required when aryl diazonium tetraflouroborate salt was used as a substrate for Suzuki type cross-coupling reaction. It may be due to the *in-situ* generation of conjugate base BF_4^- ion in the system which can activate the boronic acid moiety. We first checked the reaction in methanol as it was reported to be most apposite solvent for this coupling reaction [163]. Encouraging us, the reaction was found to be completed with excellent yield of desired product within 45 min. Though various reports are found on base free Suzuki type reaction with benzene diazonium tetraflouroborate, but still literature reveals only a few methodologies for the concerned reaction which have been performed at room temperature.

Again, a reaction in aqueous solvent and at room temperature is highly appreciable because it refers to an exciting area of research from green chemistry point of view and has good application in both academia and industries due to availability, low cost and environmental acceptability of water. To advance the progress of the aforementioned reaction, we optimized the effect of different solvents like ethanol, iso-propanol, iso-propanol: water (1:1) and water keeping fixed the amount of catalyst (Table 1, Entries 2-5). Interestingly, the reaction showed excellent progress in water with 93% isolated yield. Though benzene diazomium tetraflouroborate salt is sparingly soluble in water, but here, in this case we believe that the heterogeneous catalyst provides a better surface for smooth advancement of the reaction and it seems to progress through "on water" reaction route. The reaction under aqueous system completed within the comparable time as the alcoholic reaction system. For the next assessment, an attempt was made with both 5 wt% and 15 wt% of catalyst loading keeping other reaction conditions same using water as reaction medium. Interestingly, we found no significant variation in yield and time for 15 wt% of the catalyst, but found slightly less yield with 5 wt% of the catalyst (Table 1, Entries 6 and 7). Therefore, we fixed the reaction condition with 10 wt% of the catalyst (Table 1, Entry 5). We also investigated the activity of homogeneous Pd(OAc)$_2$ and heterogeneous Pd(0)/C catalysts towards the coupling reaction (Table 1, Entries 8 and 9). Both of the catalysts failed to show better result than Pd NPs@K10. The reactions catalysed by homogeneous Pd(OAc)$_2$ and heterogeneous Pd(0)/C were not fully converted towards the desired product till 2 hours.

The higher reactivity of Pd NPs@ K10 may be due to the presence of hydroxyl groups of aluminium, silica etc. on montmorillonite surface which might activate the arylboronic acid moiety as shown in **Fig. 5**.

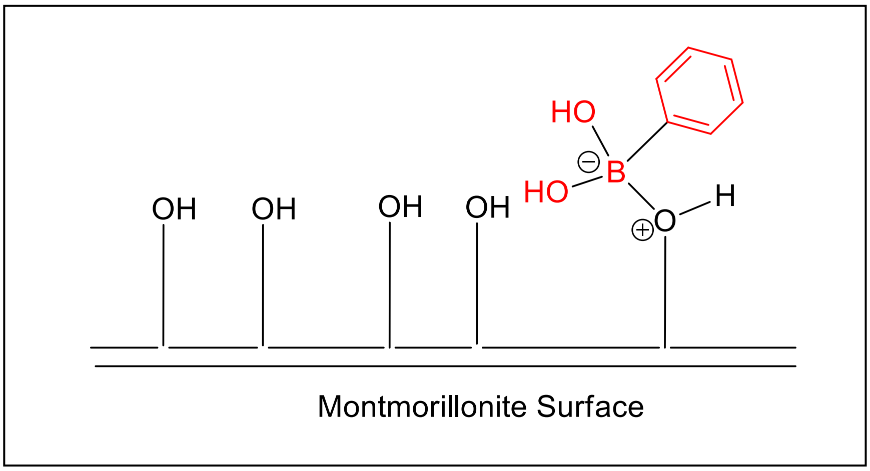
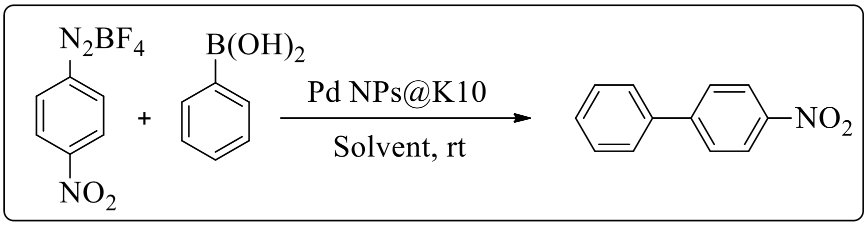


Fig. 5: Activation of the boronic acid moiety by the hydroxyl groups of montmorillonite

Table 1. Optimization of reaction condition for catalyst, base, and solvent[a]



Entry	Catalyst	Solvent (3 mL)	Time (min)	Yield (%)[b]
1	10 wt%	Methanol	45	93
2	10 wt%	Ethanol	45	92
3	10 wt%	Iso-propanol	45	92
4	10 wt%	Iso-propanol:water	45	92
5	10 wt%	Water	45	93
6	15 wt%	Water	45	93
7	5 wt%	Water	90	86
8[c]	1 mol%	Water	120	Not completed
9[d]	10 wt%	Water	120	Not completed

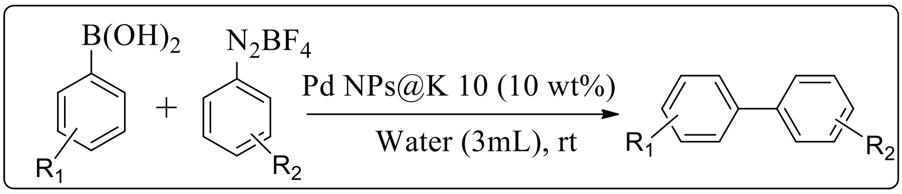
[a]Reaction condition: Phenylboronic acid (1.2 mmol), 4 nitrobenzediazonium tetraflurobor ate (1 mmol). [b]Isolated yield. [c]homogeneous $Pd(OAc)_2$ was used. [d]heterogeneous Pd(0)/C was used.

Moreover, such an enhancement and increase in activity of the Pd NPs@ K10 catalyst may be due to the formation of Pd-O interaction at the particle/support interface between Pd NPs and metal oxides present in the montmorillonite [164].

Generalization of the reaction:

Being inspired by the above studies, next, we focused on the substrate scope of the reaction with arylboronic acids having different electron donating and withdrawing groups and aryl diazonium salts and found satisfactory result with excellent yield in most of the cases within 3 hours. No observable effect of electron donating and withdrawing groups on the rate of the reaction was noticed (**Table 2)**.

Table 2. Cross-coupling of aryl diazonium salt and arylboronic acid[a]



Entry	(R_1)	(R_2)	Time	Yield (%)[b]
1	-H	4-OMe	1.5 h	92
2	4-OMe	4-OMe	55 min	98
3	4-F	4-NO_2	1 h	89
4	4-Cl	4-NO_2	1.5 h	95
5	4-CHO	4-OMe	50 min	95
6	-H	4-NO_2	45 min	93
7	4-F	4-OMe	75 min	87
8	4-CH_3	4-OMe	1.5 h	88
9	3-Me	4-OMe	2.5 h	92
10	4-OMe	4-NO_2	45 min	96
11	2-Me	4-OMe	1 h	89
12	4-*tert*-butyl	4-NO_2	2 h	95
13	4-*tert*-butyl	4-OMe	2 h	92

[a]Reaction condition: Phenylboronic acid (1.2 mmol), 4-bromonitrobenzene (1 mmol), Pd NPs@K10 (10 wt%), water (3 mL) at room temperature. [b]Isolated yield

Mechanism study:

A plausible mechanism is designed and schematic mechanistic pathway (**Fig. 6**) is discussed based on the literature report [165].In the mechanism, the palladium catalyst first inserts into the C-N_2 bond to form an intermediate II. In the next step, a fluoride from tetraflouroborate counter ion displaces the diazonium and an intermediate III is formed then the Palladium-flouride complex III undergoes transmetallation with arylboronic acid through the formation of a strong fluorine boron bond. Finally, step IV undergoes reductive elimination to form the biaryls.

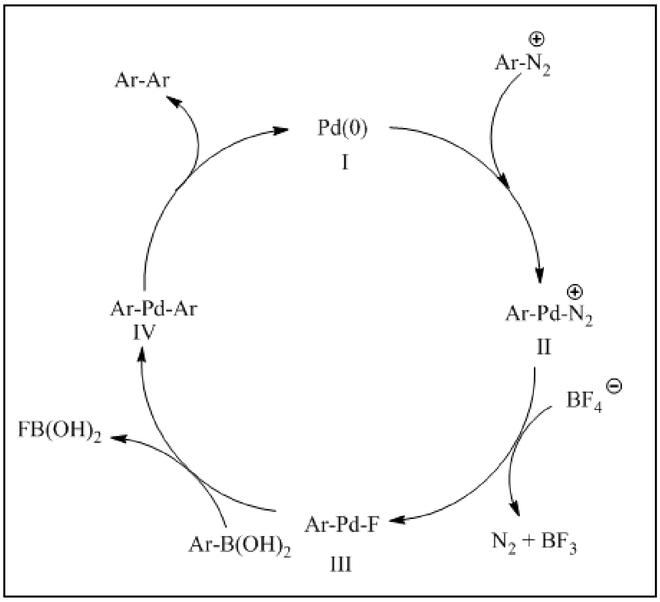


Fig. 6: Mechanistic route for the reaction over the heterogeneous catalyst

Reusability study:

From the green chemistry perspective, the reusability of catalysts makes them more attractive. For the investigation of the reusability of our catalyst, a reaction taking 2.4 mmol of phenylboronic acid and 2 mmol of 4-nitrodiazonium salt as model substrates, 20 wt% of Pd NPs@K10 catalyst and 6 mL of water at room temperature was carried out. For easy recovery issue, scale of the model reaction was increased by two times.

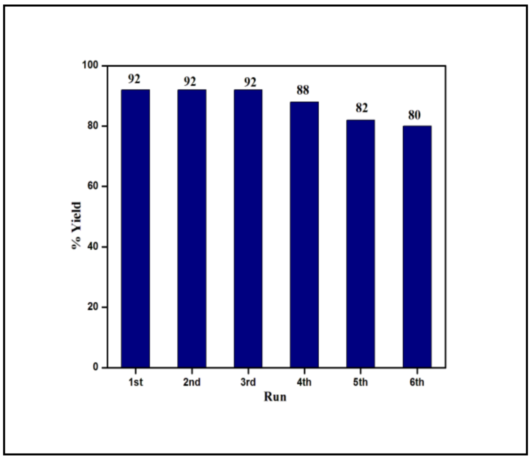


Fig. 7: Reusability plot of the catalyst

As indicated in the **Fig. 7**, the catalyst is reusable upto 3rd run without any loss of catalytic activity but after the 3rd run, small decrease in catalytic activity was observed which might be due to the agglomeration of the catalyst that was also indicated from SEM image (Fig. 2b).

TEM and XRD pattern after the reaction:

To investigate the surface morphology and size of the reused Pd NPs, we have characterized the catalyst by XRD, and TEM after performing the reaction. For that, we have chosen the recovered catalyst after 4thcycle of the reaction. The XRD and TEM images of the Pd NPs on montmorillonite after the reaction are shown in **Figs**. **9** and **8** respectively. The XRD pattern shows the prominent peaks at 2θ values of 39.94˚, 45.96˚, and 67.43˚ which are assigned to the (111), (200), and (220) crystallographic planes of Pd NPs (**Fig**. **9**) that clearly confirms that Pd NPs remain in zero oxidation state as before performing the reaction. Again, TEM images show the immobilized Pd NPs on montmorillonite also have particle size in the range of approx. 10 nm [**Fig. 8** (i-iv)] which is also found from the TEM image of the catalyst before the reaction. Therefore, from the above results, it is evident that the catalyst does not undergo any change in size as well as morphology, which in turn does not show any major decrease in the catalytic activity of Pd NPs.

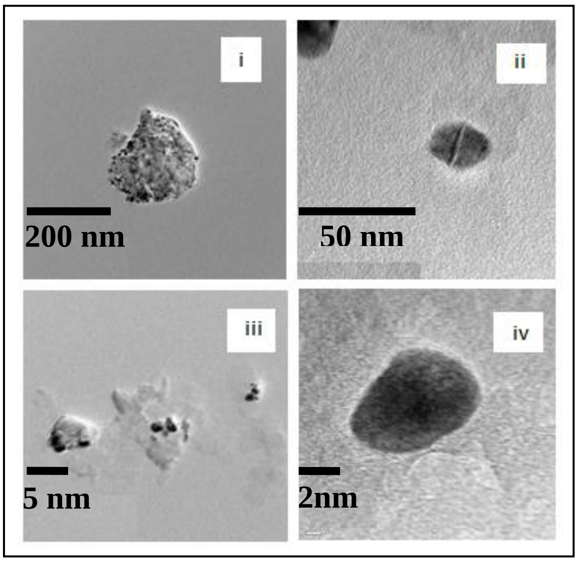


Fig. 8: TEM images (i-iv) of the recovered catalyst after 4th cycle

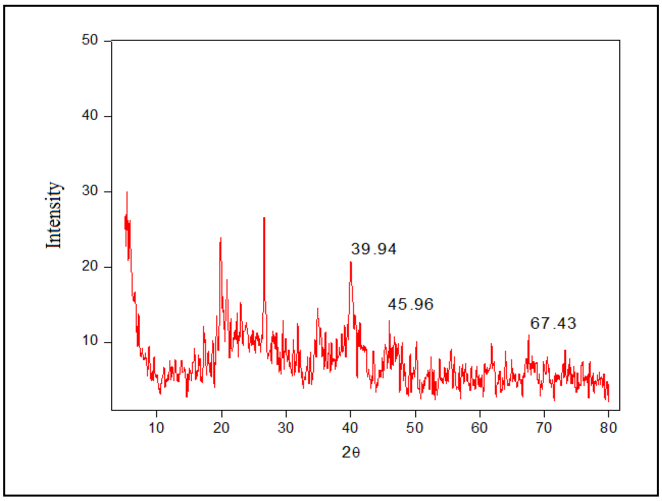


Fig. 9: PXRD pattern of the recovered catalyst after 4th cycle

Hot filtration test:

To check the heterogeneous nature of the catalyst, hot filtration test was done. To do this, the reaction was carried out at different time intervals taking the model reaction condition and after half completion of the reaction, i.e. after 15 minutes the catalyst Pd NPs@K10 was filtered off from the reaction mixture. After removal of the catalyst, the reaction was monitored for an additional 6 h and found no further product formation (**Fig. 10**). This proves the heterogeneous nature of the catalyst

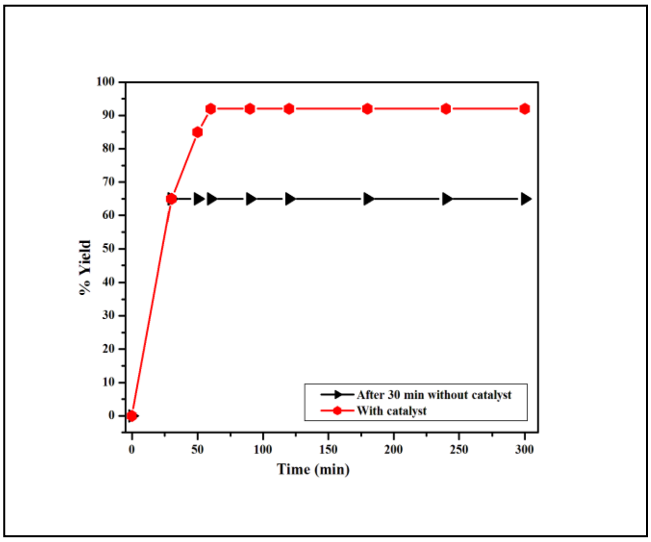
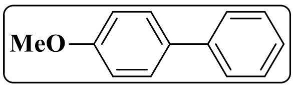


Fig.10: Hot filtration test

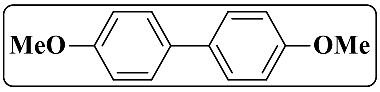
2. 2. D. Conclusions:

In conclusion, a highly efficient heterogeneous catalyst Pd NPs@K10 has been developed for the cross-coupling reaction between aryl diazonium salt and arylboronic acids with a wide range of both of the reactants under base free condition. The reaction proceeds in easily available green solvent water and at room temperature. The catalyst we have synthesized showed excellent catalytic activity and could be reused upto six times with slight decrease of the yield of the product.

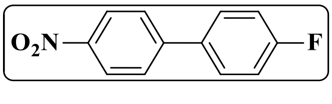
Characterisation data of the products:



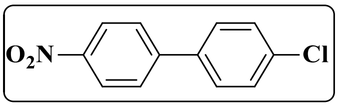
4-methoxybiphenyl (Entry 1, Table 2): White crystal (Yield=92%), mp= 90-92 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.54-7.52(m, 4H), 7.43-7.41(m, 2H), 7.29-7.27(m, 1H), 6.98 (d, *J*=8Hz, 2H), 3.85(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.2, 140.9, 133.8, 128.8, 128.2, 126.8, 126.7, 114.2, 55.4 ppm.



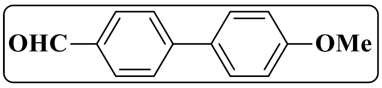
4,4′-dimethoxybiphenyl (Entry 2, Table 2): White Crystalline solid (Yield=92%), mp=175-180 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.47(d, *J*=8Hz, 4H), 6.95(d, *J*=8Hz, 4H), 3.84(s, 6H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.7, 133.5,127.8, 114.2, 55.4 ppm.



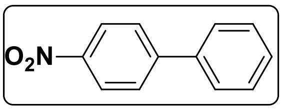
4-nitro-4′-flourobiphenyl (Entry 3, Table 2): White crystal (Yield=89%), mp= 110-112 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.30(d, *J*=8Hz, 2H), 7.69(d, *J*=8Hz, 2H), 7.59(d, *J*=8Hz, 2H), 7.19(d, *J*=8Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.2, 129.1, 127.7, 124.2, 116.1, 87.2 ppm.



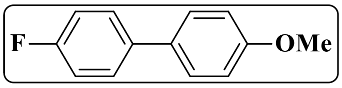
4-chloro-4′-nitrobiphenyl (Entry 4, Table 2): White crystal (Yield=92%), mp= 140-145 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.30(d, *J*=8Hz, 2H), 7.70(d, *J*=8Hz, 2H), 7.56(d, *J*=8Hz, 2H), 7.47(d, *J*=8Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 146.4, 137.2, 135.3, 129.4, 128.7, 127.7, 124.3 ppm.



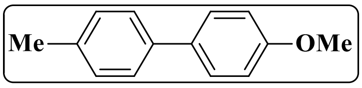
4-formyl-4′-methoxy biphenyl (Entry 5, Table 2): White crystal (Yield=95%), mp= 98-100 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.03(s, 1H), 7.92(d, *J*=8Hz, 2H), 7.71(d, *J*=8Hz, 2H), 7.59(d, *J*=8Hz, 2H), 7.01(d, *J*=8Hz, 2H), 3.87(s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 130.3, 128.5, 127.0, 114.4, 55.4 ppm.



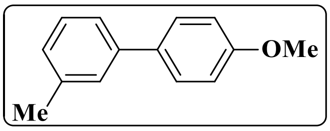
4-nitrobiphenyl (Entry 6, Table 2): Yellow solid (Yield=93%), mp= 113-115 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29(d, *J*=8Hz, 2H), 7.73(d, *J*=8Hz, 2H), 7.61-7.60(m, 2H), 7.49-7.44(m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 138.6, 129.2, 127.9, 127.4, 124.1 ppm.



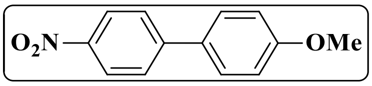
4-fluro-4′-methoxy biphenyl (Entry 7, Table 2): White crystal (Yield=87%), mp= 112-115 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.45(m, 4H), 7.10-7.09(m, 2H), 6.98-6.95(m, 2H), 3.85(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.1, 132.8, 128.2, 128.1, 128.0, 115.6, 115.4, 114.2, 55.3 ppm.



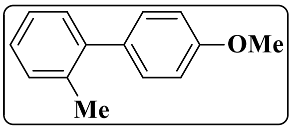
4-methyl-4′-methoxybiphenyl (Entry 8, Table 2): White crystal (Yield=88%), mp= 110-115 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51(d, *J*=8Hz, 2H), 7.44(d, *J*=8Hz, 2H), 7.22(d, *J*=8Hz, 2H), 6.96(d, *J*=8Hz, 2H), 3.84(s, 3H), 2.38(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.9, 138.0, 136.4, 133.8, 129.5, 128.0, 126.6, 114.2, 55.4, 21.1 ppm.



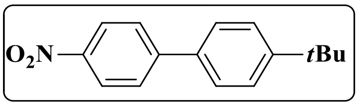
3-methyl-4′-methoxy biphenyl (Entry 9, Table 2): White solid (Yield=92%), mp = 94-98 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.51(d, *J*=8Hz, 2H), 7.36-7.26(m, 3H), 7.15-7.00 (m, 1H), 6.97(d, *J*=8Hz, 2H), 3.85(s, 3H), 2.41(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.1, 140.8, 138.3, 133.9, 128.2, 127.4, 123.9, 114.2, 55.4, 21.6 ppm.



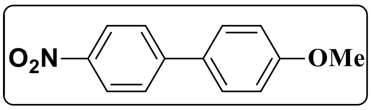
4-nitro-4′-methoxy biphenyl (Entry 10, Table 2): White crystal (Yield=96%), mp= 90-95 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.28-8.25(m, 4H), 7.69(d, *J*=8Hz, 2H), 7.58(d, *J*=8Hz, 2H), 7.48-7.46(m, 1H), 7.02(d, *J*=12Hz, 2H), 6.95-6.92(m, 1H), 3.87(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.2, 140.9, 133.8, 128.8, 128.2, 126.8, 126.7, 114.2, 55.4 ppm.



2-methyl-4′-methoxybiphenyl (Entry 11, Table 2): White crystal (Yield=89%), mp= 69-72 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.52(d, *J*=12Hz, 2H), 7.36-7.24(m, 3H), 7.10-7.03(m, 1H), 6.97(d, *J*=12Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.1, 140.8, 138.3,133.9, 128.2, 127.4, 123.9, 114.2, .55.4, 21.6 ppm.

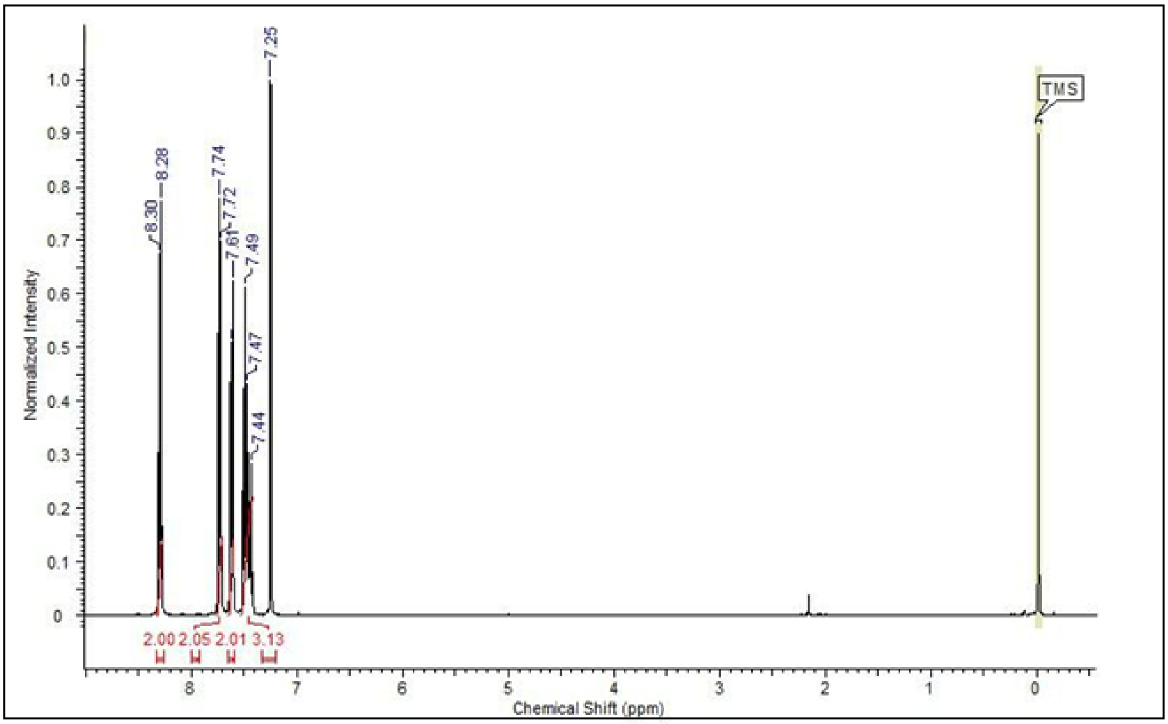


4-nitro-4′-*tert*butylbiphenyl (Entry 12, Table 2): White crystal (Yield=95%), mp =110-112 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.28(d, *J*=8 Hz, 2H), 7.73(d, *J*=8Hz, 2H), 7.57(d, *J*=8Hz, 2H), 7.51(d, *J*=8Hz, 2H), 1.37(s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 152.3, 147.5, 146.9, 135.8, 127.5, 127.1, 126.2, 124.1, 31.3 ppm.

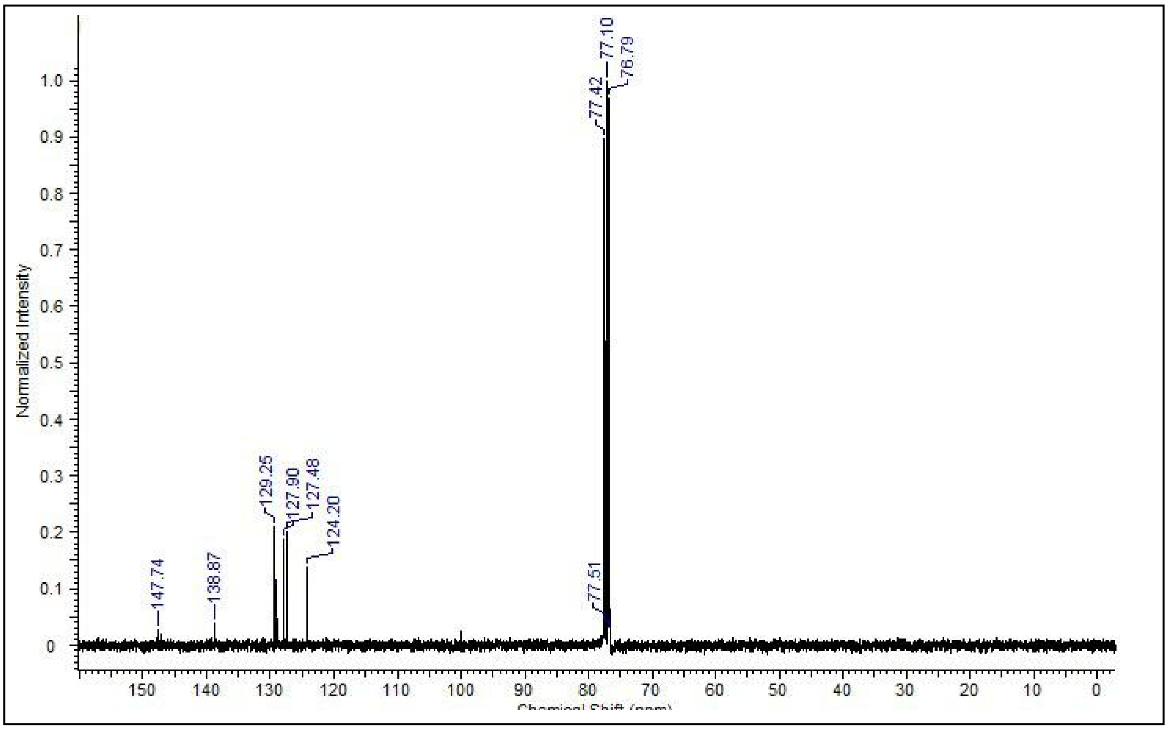


4-methoxy-4′-*tert*butylbiphenyl (Entry 13, Table 2): White crystal (Yield=92%), mp=110-114 ˚C, ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.52-7.44(m, 6H), 3.84(s, 3H), 1.35(s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.0, 149.6, 138.0, 133.0, 128.0, 126.4, 125.7, 123.5, 114.2, 55.4, 31.4 ppm.

^{1}H NMR spectrum of 4-nitrobiphenyl



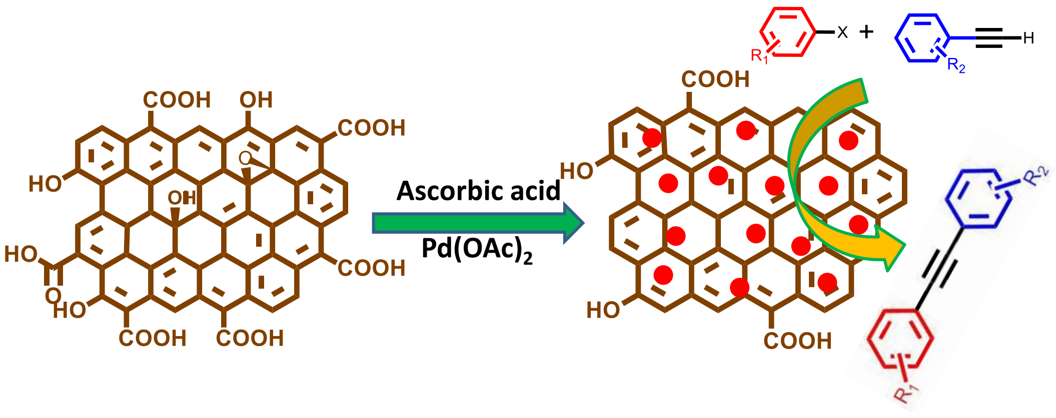
^{13}C NMR spectrum of 4-nitrobiphenyl



CHAPTER 2.

Section 2.3

A room temperature ligand and copper free Sonogashira cross-coupling reaction catalyzed by Pd NPs decorated on reduced graphene oxide.



The work described in this section has been published in *Applied Organometallic Chemistry*, 2017, 31, 85-89

2. 3. A. Introduction:

Palladium catalyzed Sonogashira reaction of terminal alkyne with aryl or vinyl halide has continuously received attention over the last few decades which provide an influential tool for the construction of C-C bond. Since copper co-catalyzed reactions generate Glaser type homocoupling byproduct, therefore, nowadays researchers are searching for some highly active Pd catalyst needed for Copper free Sonogashira reaction. Though N and P containing Pd complexes are very effective for the said reaction, but those complexes contain the shortcomings like high cost, formation of side products and tedious separation procedure etc. Thus, palladium nanoparticles (Pd NPs) have emerged as one of the most exciting alternative catalysts for Sonogashira cross-coupling reaction and their additional characteristic features are low preparation cost, excellent activity, excellent recovery, high surface area [117] etc. They are generally stabilized by ionic liquids [166], dendrimers [167], polyvinylpyridine [168] etc. The heterogeneous nature of the catalyst is one of the most attractive contributions to the field of catalysis as it overcomes the drawback of homogeneous catalyst of non-recoverability from the reaction medium. So, substantial efforts have been devoted to immobilize and stabilize the Pd NPs in various heterogeneous supports such as organic matrix, organic–inorganic fluorinated hybrid materials, polymers, glass–polymer composites, and ionic liquids. In addition to this, Pd NPs are also synthesized in different inorganic supports such as carbon [169], carbon nanotubes [170], alumina [171], silica [172], zeolite [173], clays [174] and zinc ferrite [175]. Among these, especially owing to the chemical stability in various aggressive media, profusion, light weight, inertness to supported metals, graphene based supports draw special attention in the field of catalysis, they also avoid the surface poisoning problem and possesses the easy recovery of the precious metal by burning the support and its diverse structural allotropes. Graphene is predominantly an amazing candidate as a host material with a two-dimensional (2D) sp^2-hybridized carbon structure and densely packed with a honey comb structure [176]. Because of the oxygen functionalized surface and its typical conductivity, it is considered as the most utilized carbon based supports for the synthesis of Pd NPs. It has also additional advantages of availability, high absorption coefficient, high thermal stability, low cost, high corrosion resistance and excellent dispersive nature [177, 178]. Such properties of graphene and graphene-based composite materials make them excellent candidates in the field of catalysis, particularly in photocatalysis, electrocatalysis [179] and organic reaction catalysis.

Herein, we wish to report an eco-friendly and highly active Pd supported on reduced graphene oxide catalysed Sonogashira coupling reaction at room temperature in alcoholic solvent.

2. 3. B. Experimental:

General information:

^{1}H and ^{13}C NMR spectra of the products were recorded in a JNM ECS 400 MHz NMR spectrophotometer (JEOL) using tetramethylsilane (TMS) as the internal standard. Reactions were monitored by thin-layer chromatography using aluminium sheets with silica gel 60F$_{254}$ (Merck). UV light and Iodine vapour were used as visualizer. Chemicals are obtained from commercial source. The transmission electron microscopy (TEM) analyses were carried on a JEM-2010 (JEOL) instrument equipped with a slow-scan CCD camera and the accelerating voltage was 200 kV. The powder XRD patterns analyses were done on a Rigaku Multiflex instrument. It uses Cu K (0.15418 nm) radiation source and has a scintillation counter detector. The intensity data were recorded over a 2 range of 5–90˚. The palladium content in the supported catalyst was determined by using MWD (Microwave Digestion System using 1200 MW, model no: ETH0S, EASY, Part no: 49030) method followed by inductively coupled plasma analysis (ICP-OES, Perkin Elmer, Optima 2100 V). Multilevel calibration of Pd was performed using a metal standard of ICP (sigma).

Materials:

Graphite powder (<20μm, Sigma-Aldrich, Germany), sulfuric acid (AR grade, Qualigens, India), hydrochloric acid (AR grade, Qualigens, India), H_2O_2 (30%, Qualigens, India), potassium permanganate (>99 %, E-Merck, India).

Preparation of the catalyst and its characterization:

Pd NPs were synthesized onto the reduced graphene oxide sheets by using hydrogen gas as reducing agent. The detailed synthesis method and its characterizations were reported in our published paper [180].

General procedure for Sonogashira cross-coupling reaction:

A 50 mL round-bottomed flask was charged with a mixture of phenylacetylene (0.75 mmol), aryl halide (0.5 mmol) and 3 mL of ethanol. To this mixture, 5 wt% of Pd@ reduced graphene catalyst was added followed by the addition of 1.5 mmol of K_2CO_3. The whole reaction mixture was stirred for the required time. Thereaction was monitored by TLC and after completion of the reaction the solution was extracted three times with ethylacetate (3x10 mL). The products were purified by column chromatography and confirmed by ^{1}H and ^{13}C NMR spectroscopy.

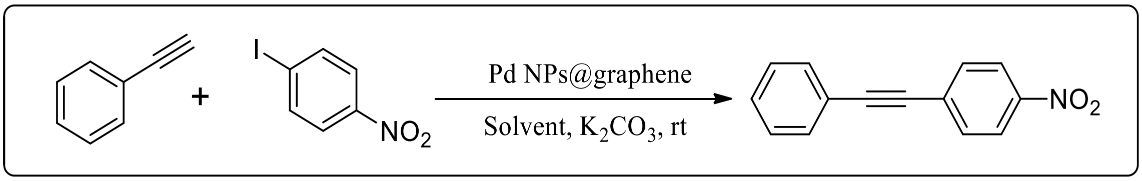
2.3. C. Results and discussion:

Optimization of the reaction condition:

To check the catalytic efficiency of the catalyst, we initiated our reaction protocol with 0.75 mmol of phenylacetylene and 0.5 mmol of 4-iodonitrobenzene as model substrates. Iso-propanol was chosen as solvent for this test reaction with 10 wt% of the catalyst and 1.5 mmol of the base K_2CO_3. The reaction was performed at room temperature and the progress of the reaction was monitored by TLC. After 7 h, 92% isolated product was found (Table 1, Entry 1). So, being encouraged by our first observation, the effect of different solvents [water, ethanol, methanol, iso-propanol:water (1:1), water: ethanol (1:1) etc.] (Table 1, Entries 2-5) on the reaction was investigated, keeping other conditions same. Perceptibly, it was found that the coupling in ethanol provided highest isolated % yield (Table 1, Entry 3). In our next observation, the reaction condition was optimized for various amounts of catalyst: 10 wt%, 15 wt% and 5 wt% in ethanol as solvent (Table 1, Entries 3, 6 and 7) and significantly found no remarkable change because the reaction completed within same time with same yield of the product. So, 5 wt% of the catalyst was found suitable for the best conversion. Noticeably, base plays an important role in Sonogashira cross-coupling reaction, hence studies were also done with different amount of bases with 1 mmol and 0.5 mmol (Table 1, Entries 8-9) and interestingly observed less yield in case of both the above mentioned amounts. All the results are summarized in the table 1. From the above discussion it is found that 1.5 mmol of the base and 5wt% of the catalyst were enough to get the highest yield of the reaction (Table 1, Entries 8 and 9).

With the optimized reaction conditions in hand (Table 1, Entry 6), we tried to evaluate the generality of the reaction protocol. A wide variety of electron withdrawing and electronically diverse halogen-ides with substituted terminal acetylenes were investigated. The whole results are summarized in table 2.

Table 1. Screening of the reaction condition for solvent, catalyst and base[a]

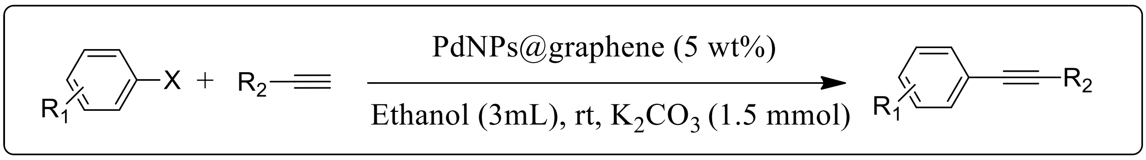


Entry	Catalyst (wt %)	K_2CO_3 (mmol)	Solvent (3 mL)	Time (h)	Yield (%)[b]
1	10	1.5	iso-propanol	7	92
2	10	1.5	Water	7	85
3	10	1.5	Ethanol	7	94
4	10	1.5	Methanol	7	94
5	10	1.5	Water: ethanol	7	88
6	5	1.5	Ethanol	7	94
7	15	1.5	Ethanol	7	94
8	5	1	Ethanol	10	86
9	5	0.5	Ethanol	10	80

[a] Reaction condition: Phenylacetylene (0.75 mmol), 4-iodonitrobenzene (0.5 mmol), K_2CO_3 (1.5 mmol). [b] Isolated yield.

We are very glad to observe that the reaction progressed smoothly with excellent to good yield of product formation in case of both electron withdrawing and donating substituents. We also investigated the protocol with substituted phenyl acetylenes and showed positive results in case of both donating and withdrawing groups. Literature reveals that Sonogashira reaction is not easily feasible with aliphatic alkynes, so to check the effectiveness of our catalyst towards this type of system we tried the reaction with cyclohexyl alkynes for different iodides (Table 2, Entries 8 and 9) but appreciably found good yield of the cross coupled products for diverse aryl iododides. Moreover, the reaction showed positive result in case of aryl bromide also but, failed to give satisfactory yield as it gave only 47% and 53% (Table 2, Entries 11 and 12).

Table 2. PdNPs@graphene catalysed Sonogashira reaction[a]



Entry	$-R_1$	$-R_2$	X	Time (h)	Yield (%)[b,c]
1	4-NO_2	C_6H_5	I	7	94
2	3-Me	C_6H_5	I	7	96
3	4-Me	C_6H_5	I	8	95
4	3-NO_2	C_6H_5	I	8	95
5	4-OMe	C_6H_5	I	8	92
6	H	C_6H_5	I	7	96
7	4-Me	4-MeC_6H_5	I	7	98
8	4-Me	C_6H_{11}	I	10	85
9	H	C_6H_{11}	I	10	80
10	4-OMe	4-MeC_6H_5	I	7.5	98
11	4-NO_2	C_6H_5	Br	12	47
12	4-OMe	C_6H_5	Br	12	53

[a] Reaction condition: Acetylene (0.75 mmol), aryl halide (0.5 mmol). [b] Isolated yield. [c] Purified by column chromatography.

Reusability study of the catalyst:

The reusability of a catalyst is one of most important parameters of green chemistry. Reusability of a catalyst makes the reaction protocol more attractive. To check the reusability of the catalyst, we took 1.2 mmol of phenylacetylene and 0.75 mmol of 4-bromonitrobenzene in 5 mL ethanol. To this mixture, we added 10 wt% of the catalyst and 3 mmol of the base K_2CO_3. To our delight, the catalyst was reusable up to 4th run with almost constant yield but after 5th run there was slight decrease in the yield product formation as shown in the **Fig. 1**.

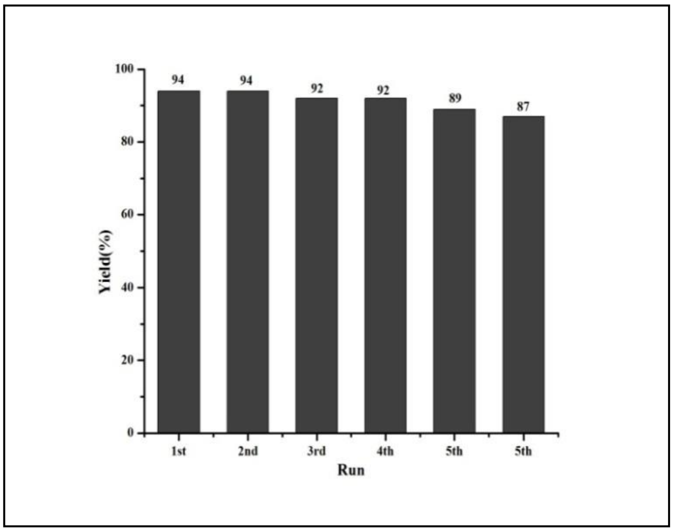


Fig. 1: Reusability of the catalyst

Also to investigate the surface morphology and size of the Pd NPs in the nanocomposite catalyst, we have characterized the catalyst by XRD, TEM and HRTEM after performing the reaction. For that, we have chosen the recovered catalyst after 2nd cycle and 5th cycle of the reaction. The XRD and TEM images of the Pd NPs-graphene composite after reaction are shown in **Figs. 2** and **3**, respectively. The XRD pattern shows the prominent peaks at 2θ values of about 40.10, 46.6, 68.18, and 82.30 are assigned to the (111), (200), (220) and (311) crystallographic planes of Pd NPs which clearly confirms that Pd NPs remains in zero oxidation state as before performing the reaction. Also, the crystallite size of the Pd NPs is calculated by Sherrer equation using PDXL software and found to be ~2 nm which is very close to the particle size analyzed by TEM. The TEM images (**Fig**. **3**) clearly demonstrated the uniform distribution of Pd NPs onto the surface of rGO nanosheets and most of the particles are spherical in nature as fresh catalyst. The TEM images of the fresh catalyst are already reported in published paper [180]. Also, the crystallinity of Pd NPs@graphene composite material after performing the reaction is confirmed by the HRTEM images as shown in **Figs**. **3(c)** and **3(g)**, which showed clear lattice fringes with an interplanar spacing of 0.19 nm corresponding to (200) plane of Pd NPs. Therefore, from the above results, it is evident that the catalyst does not undergo any change in size as well as morphology, which in turn does not show any significant decrease in the catalytic activity as shown in the **Fig**. **2**.

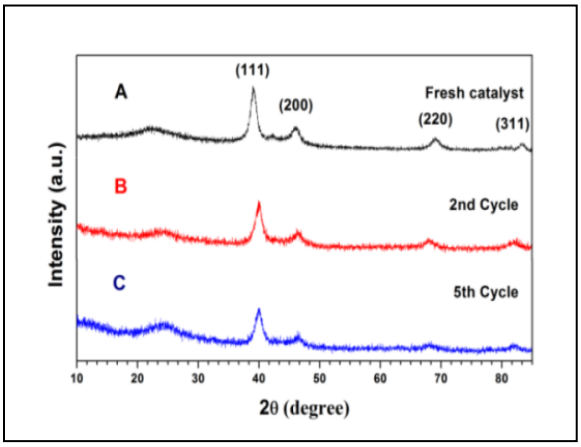


Fig. 2: PXRD pattern of (A) fresh catalyst, (B) after 2nd cycle and (C) after 5th cycle

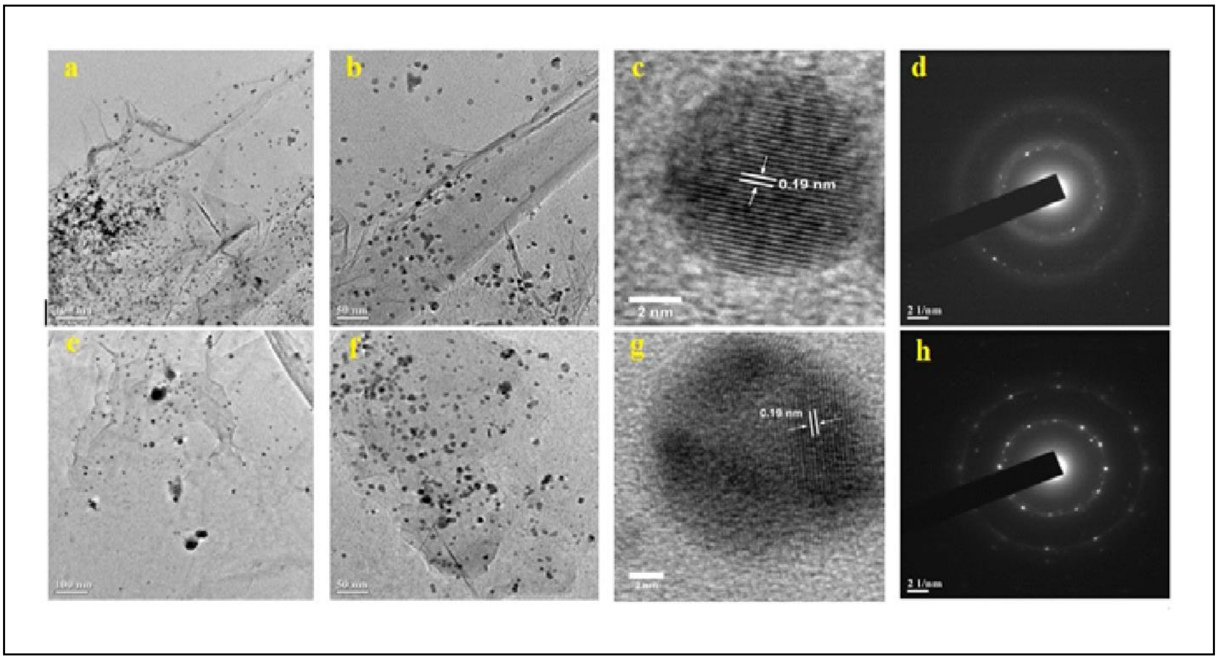


Fig. 3: TEM images of the catalyst after (a-d) 2nd cycle and (e-f) after 5th cycle

Hot filtration test:

To test the heterogeneity of the catalyst, the model reaction was again performed under the optimized reaction condition (**Fig. 4**). After 3.5 h, 65% of the isolated yield was found and the reaction mixture was filtered, after filtration, the filtrate was allowed to proceed for additional 15 h and found no increase in the yield of the cross-coupled product which proves the heterogeneity of the catalyst.

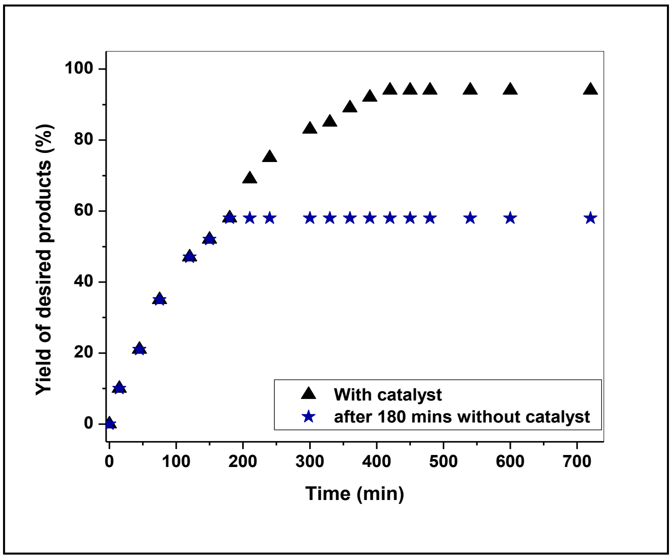
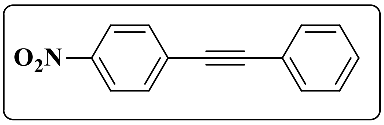


Fig. 4: Hot filtration test for the catalyst

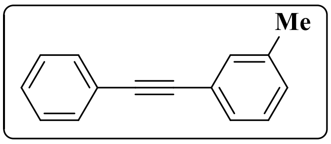
2.3. D. Conclusions:

In conclusion, we have developed a simple and convenient method for Sonogashira cross-coupling reaction at room temperature catalyzed by homogeneously deposited Pd NPs on reduced graphene oxide sheets. The reaction was successfully completed in short reaction with high yield and the catalyst was found to be recycled up to 5th run with almost constant yield.

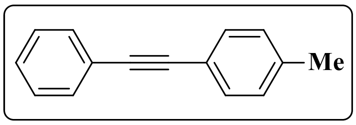
Characterisation data for the products:



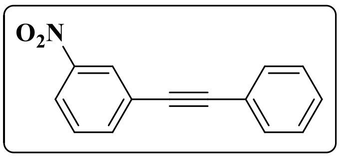
1-nitro-4-(2-phenylethynyl)benzene (Entry 1, Table 2): Yellow gum (Yield=94%), ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21(d, 2H, *J*=8.7Hz), 7.65(d, 2H, *J*=8.7Hz), 7.56-7.54(m, 2H), 7.39-7.37(m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.0, 132.3, 131.9, 130.3, 129.4, 128.6, 123.7, 122.1, 94.8, 87.6 ppm.



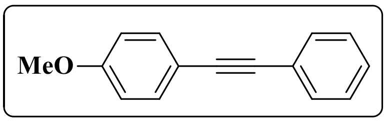
1-methyl-3-(phenylethynyl)benzene (Entry 2, Table 2): Brown liquid (Yield=96%), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.50(m, 3H), 7.33-7.31(m, 3H), 7.26-7.23(m, 1H), 7.15-7.13(m, 1H), 6.99-6.97(m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.0, 133.3, 132.3, 129.3, 128.7, 128.4, 128.3, 128.2, 127.4, 122.6, 93.3, 87.9, 20.7 ppm.



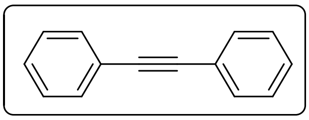
1-methyl-4-(2-phenylethynyl)benzene (Entry 3, Table 2): Brown liquid (Yield=95%), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.52(m, 4H), 7.42(d, 2H, *J*=7.7Hz), 7.35-7.33(m, 3H), 7.16(d, 2H, *J*=7.7Hz), 2.37(s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 132.5, 131.6, 129.2, 128.4, 128.1, 123.5, 120.2, 89.6, 88.8, 21.6 ppm.



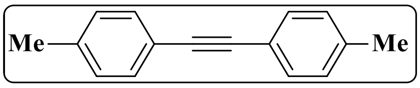
1-nitro-3-(2-phenylethynyl)benzene (Entry 4, Table 2): Yellow gum (Yield=95%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.36(s, 1H), 8.19-8.17(m, 1H), 7.62(d, 1H, *J*=7.7Hz), 7.57-7.51(m, 3H), 7.40-7.38(m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 137.3, 131.8, 129.4, 129.1, 128.6, 126.4, 125.2, 122.9, 122.2, 92.0, 86.9 ppm.



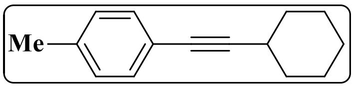
1-methoxy-4-(2-phenylethynyl)benzene (Entry 5, Table 2): White solid (Yield=92%), mp= 145-150 ˚C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.46(m, 4H), 7.33-7.31(m, 3H), 6.87(d, 2H, *J*=8.2Hz), 3.82(s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.7, 133.1, 131.5, 128.4, 128.0, 123.6, 115.4, 114.0, 89.4, 88.1, 55.4 ppm.



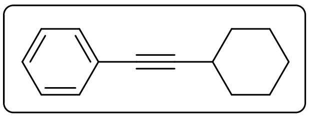
Diphenylacetylene (Entry 6, Table 2): White liquid (Yield=96%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: δ 7.56-7.54(m, 4H), 7.38-7.34(m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$)**:** δ 131.7, 128.4, 128.3, 123.3, 89.4 ppm.



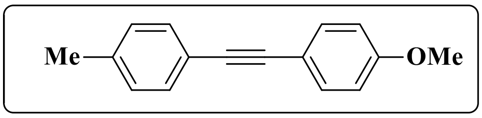
1,2-di-*p*-tolylethyne (Entry 7, Table 2): White liquid (Yield=98%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41(d, *J*=8Hz, 4H), 7.15-713(d, *J*=8Hz, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$**:** δ 138.2, 132.4, 129.2, 120.4, 88.9, 21.5 ppm.



1-(2-cyclohexylethynyl)-4-methylbenzene (Entry 8, Table 2): White liquid (Yield=85%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27(d, *J*=8Hz, 2H), 7.07(d, *J*=8Hz, 2H), 2.39-2.37(m, 1H), 2.31(s, 3H), 1.59-1.46(m, 6 H), 0.95-0.92(m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$**:** δ 137.4, 131.4, 129.0, 121.1, 89.6, 80.6, 31.0, 22.1, 21.4, 19.1, 13.7 ppm.

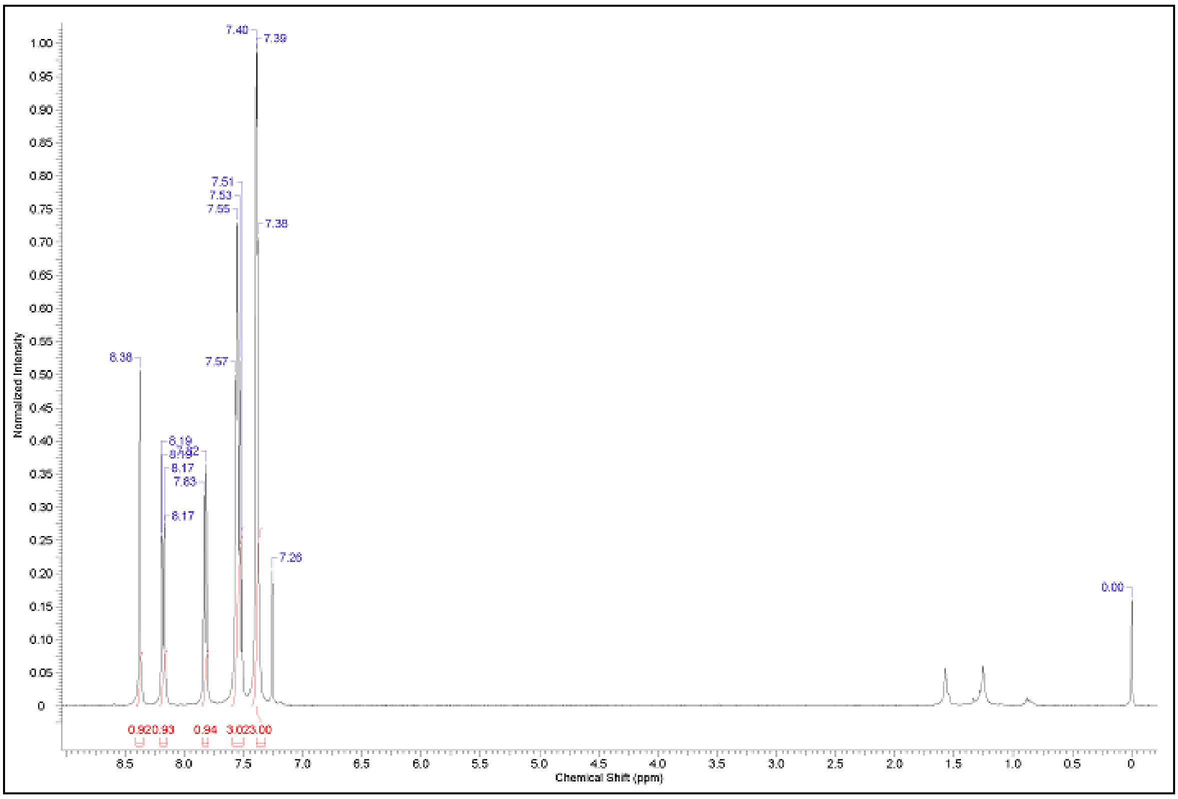


(Cyclohexylethynyl)benzene (Entry 9, Table 2): White liquid (Yield=80%), ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.38-7.35(m, 2H), 7.25-7.24(m, 3H), 2.43-2.38(m, 1H), 1.60-1.57(m, 7 H), 0.96-0.92(m, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$**:** δ 131.6, 128.2, 127.5, 124.1, 90.4, 80.6, 30.9, 29.8, 21.1, 19.1, 13.7 ppm.

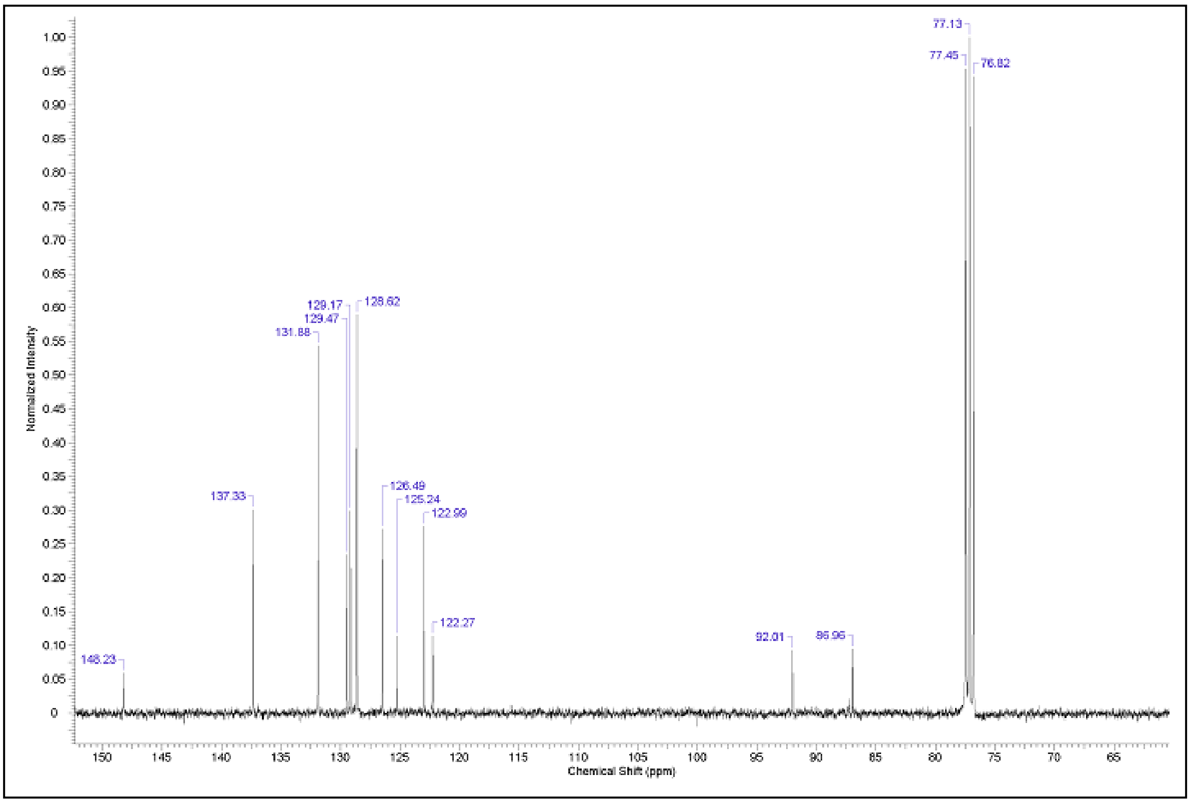


1-methoxy-4-(*p*-tolylethynyl)benzene (Entry 10, Table 2): White solid (Yield=90%), mp= 124-128˚C, ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.46(d, *J*=8Hz, 2H), 7.40(d, *J*=8Hz 2H), 7.14(d, *J*=8Hz, 2H), 6.87(d, *J*=8Hz, 2H), 3.82(s, 3H), 2.36(s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ: 160.3 138.1, 133.3, 132.2, 128.6, 119.7, 115.0, 113.9, 89.7, 55.8, 21.3 ppm.

^{1}H NMR spectrum of 1-Nitro-3-(2-phenylethynyl)benzene



^{13}C NMR spectrum of 1-Nitro-3-(2-phenylethynyl)benzene



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