Development of mild and efficient protocol for palladium-catalyzed Suzuki-Miyaura coupling in aqueous media

Abstract: This chapter reviews the development made in the chemistry of Suzuki-Miyaura cross-coupling reactions.
3(a). **Suzuki-Miyaura cross-coupling reaction**

Suzuki-Miyaura cross-coupling reaction involves the cross-coupling of an organoboron compound and a haloarene or pseudo-halide in the presence of palladium catalyst and a base. This method has become an extremely useful in the synthesis of numerous biological and industrially significant organic molecules.\(^1\) In addition, this reaction is used for the development of novel organic materials with unique electrical, optical and mechanical properties.\(^2\) The simple and versatile condition related with this reaction facilitates the construction of large and complex organic molecules which are difficult to prepare using existing methods. In recent years, the application of Suzuki-Miyaura reaction is observed in numerous total synthetic for preparing vital organic molecules (**Figure 3.1**). Suzuki-Miyaura reactions represent an effective alternative over conventional methods which use organometals, because organoboranes are air- and moisture stable with relatively low toxicity.\(^3\)

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**Figure 3.1.** Selected examples of the Suzuki-Miyaura coupling in organic synthesis.
The first method for the preparation of biaryls using palladium catalyzed cross-coupling of arylboronic acid with haloarenes was reported in 1981 by Akira Suzuki. The reaction was performed in benzene under an inert atmosphere catalyzed by Pd(PPh₃)₄ (Scheme 3.1).

![Scheme 3.1. Suzuki-Miyaura coupling of phenylboronic acid with aryl bromides.](image)

This reaction is far superior to the commonly accessible methods for biaryls construction such as Ullmann coupling, Kumada coupling and Negishi Coupling reaction.

The main advantages of Suzuki reaction over the other existing protocols are: (i) mild reaction conditions; (ii) ready availability of organoboron reagents, which also are stable to/in water, organic polar solvents, oxygen and heat; (iii) high regio- and stereo-selectivity; (iv) applicable under open air condition (without dry solvents); (v) low catalyst loading; (vi) less toxic reagents and by-products; (vii) easy separation of inorganic boron byproducts and (viii) environmentally friendly process.

After the discovery of Suzuki-Miyaura reaction a series of major developments in terms of catalyst diversity, efficiency and mild conditions have been done. This also includes expansion of the substrate scope, reaction at room temperatures and reduction in the catalyst loading. The general mechanism proceeds through three important steps including oxidative addition \(i.e.,\) the bond between aryl group \(R^1\) and the halide \(X\) breaks, and two new bonds are formed with palladium to give intermediate organopalladium complex, the palladium is oxidized from Pd(0)
to Pd(II). In the next step, the intermediate undergo transmetallation to generate Pd(II) intermediate having two organic coupling partner fragments. This will undergo reductive elimination to give the final product (Scheme 3.2).

**Scheme 3.2.** General catalytic cycle for Pd-catalyzed Suzuki-Miyaura coupling reactions.

### 3(b). Homogeneous catalytic systems

Homogeneous catalytic systems are the simplest and well-accepted methods in organic synthesis.\(^8\) Since, the reactants are in the same phase homogeneous system provides an effective medium for complete interaction of the reacting components during the reaction. An important part of devising homogeneous protocol is to select ligands or tailoring ligands for palladium complex. Thus, various palladium based catalysts ligated with simple tertiary phosphines, hemilabile type phosphines, sterically crowded biphenyl-type phosphines,\(^9\) imine,\(^10\) NHC,\(^11\) amine,\(^12\) bisamides,\(^13\) triazole,\(^14\) Schiff-base,\(^15\) acetanilide\(^16\) and oxime-ether\(^17\) have been commonly used for Suzuki-Miyaura cross-coupling reaction.

#### 3(b)1. Phosphine-Based Catalytic Systems

It is a well-known fact in Suzuki-Miyaura reaction that, the activity and selectivity of a catalyst depends largely on the steric and electronic properties of the ligand attached
to the metal centre. Thus, right choice of ligand plays a crucial role in such catalysis. In early years of Suzuki coupling, organic phosphines and their derivatives have been the most popular ligands in cross coupling chemistry. Phosphines are known to improve the catalytic activity of palladium by increasing electron density and providing steric shielding to the complexes. Thus, by modifying these properties of phosphines, one can enhance the coordination sphere around the palladium to accelerate the catalytic cycle. Until 1998, triarylphosphine (PAR₃) was the most widely used ligand for palladium-catalyzed Suzuki reaction. Among different phosphine based ligands, hemilabile type phosphines, sterically crowded biphenyl-type phosphines and other electron-rich phosphines have been extensively used as ligands and are able to occupy a significant position in the group of the best ligands in palladium catalyzed Suzuki-Miyaura reaction.¹⁸ The structures of some of the phosphine based ligands are shown in Figure 3.2.

![Figure 3.2](image_url)

**Figure 3.2.** Structures of some phosphine based ligands used in Suzuki reaction

However, these phosphines have significant limitations, such as high toxicity, sensitivity to air and moisture, handling problems, high costs and often generate side-products that obstruct the isolation and purification process due to similar chromatography mobility.¹⁹ Thus, to avoid these side-reactions, alternative phosphine free protocols were developed in subsequent years. Schiff base is another well
recognized excellent alternative to phosphines in Suzuki-Miyaura reactions. Similar to phosphines, the steric and electronic characteristics of Schiff bases can be manipulated by selecting suitable condensing aldehydes and amines.

3(b)2. Schiff-Base ligands

In coordination chemistry and catalysis, Schiff-bases are considered as an important class of N-based ligands, having high sensitivity and selectivity towards metal ions and are well regarded as chelating multitdentate ligands. One of the most important advantages of these Schiff bases is that numerous structurally different ligands are readily available via a simple one-step reaction which can control the well variation of the electronic and steric properties of the ligand attached to the metal. So, this modification can be attained easily with Schiff bases by selecting appropriate condensing aldehydes and/or amines. Schiff bases were first discovered by Schiff in 1864. Different types of Schiff-bases are available in literature including monodentate, bidentate N, N-donor, bidentate N,O-donor, tridentate and tetradentate ligands according to the binding environments to metal ions (Figure 3.3).

![Figure 3.3. Structures of some Schiff base ligands.](image-url)
In Suzuki-Miyaura reaction, there are only a few reports are available where monodentate Schiff-bases are used as a ligand (L1 and L2).\textsuperscript{21} However, in case of bidentate ligand, generally \(N,N\)-donor Schiff bases reported for Suzuki-reactions are symmetrical in nature, although unsymmetrical Schiff bases (L3) are expected to produce greater structural diversity, which might influence their catalytic properties. Wang’s group has developed an air-stable symmetric Schiff base ligands for Suzuki-Miyaura reaction between aryl bromides and arylboronic acids using PdCl\(_2\)(CH\(_3\)CN)\(_2\) as palladium source in toluene at 80 °C under aerobic conditions.\textsuperscript{22} Recently, Das and co-workers developed a highly efficient palladium based Schiff-base complex (C1) for the Suzuki-Miyaura cross-coupling reactions of aryl chloride with arylboronic acid in DMF at 100 °C.\textsuperscript{23} But, the use of water as a solvent for Suzuki reactions has received much attention due to its low cost, easy accessibility, and environmentally benign nature. Several studies have reported the use of Schiff base ligands in aqueous medium for Suzuki reactions including those of Hanhan,\textsuperscript{24} Dewan.\textsuperscript{25} Like \(N,N\)-bidentate ligands, the \(N,O\)- bidentate ligands (L5)\textsuperscript{26} are easy to access, stable and equally effective. Moreover, the process of the complexation of ligand with palladium is straightforward and their palladium complexes are found to be quite suitable for Suzuki cross-coupling reactions.

3(b)3. \textbf{N-Heterocyclic carbene (NHC)-ligands}

Since the early years, phosphines were the prime choice of many chemists working in the field of homogeneous cross-coupling catalysis. NHCs are next significant ligands bearing electron rich nitrogen atom and plays challenging role in replacing toxic phosphines in cross-coupling reaction. This is due to the formation of more stable Pd-
NHC bond, which helps in preventing decomposition of the active catalyst. Since NHCs acts as neutral, strong two electrons σ-donor ligand with very little or no metal to ligand π-back-bonding ability they effectively increases the electron density of over palladium center. This enables to form strong bond with palladium facilitating the oxidative addition step, and simultaneously helps in preventing the decomposition of the active catalyst, which provides longer catalyst lifetime and a constant reactivity throughout the course of the reaction.\textsuperscript{27} NHCs are used in combinations with various palladium sources such as $[\text{Pd(OAc)}_2]$, $[\text{Pd(dba)}_2]$ or $[\text{Pd}_2(\text{dba})_3]$.$^{28}$ Herrmann and co-workers, in 2002 have reported the first method using Pd-NHC($[\text{Pd(IAd)}_2]$) for Suzuki-Miyaura cross-coupling (Figure 3.4).\textsuperscript{29} Since this report numerous well-defined NHC-Pd catalysts were prepared for a number of diverse and effective strategies. Typical examples were presented in Figure 3.4.

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**Figure 3.4.** NHC ligands and Pd-(NHC) complexes used in Suzuki-Miyaura coupling reactions.
3(b)4. Other Commonly Used ligands

In recent years, a variety of other ligands have been utilized in Suzuki-Miyaura reactions. These includes Lin’s chiral complex,\textsuperscript{36} Liu’s palladium complex,\textsuperscript{37} Bora’s acetonilide palladacycles\textsuperscript{38} and Ramesh’s palladacycle etc\textsuperscript{39} (Figure 3.5).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{ligands.png}
\caption{Pd complexes in different ligand systems used in Suzuki-Miyaura reaction}
\end{figure}

Apart from these, various ligand systems were developed and executed in a variety of systems, either in combination with metal salts or as preformed complexes. For example catalyst system based on sucrose,\textsuperscript{40} amino acid,\textsuperscript{41} imidazole,\textsuperscript{42} imine,\textsuperscript{43} glucose\textsuperscript{44} etc.

3(c). Heterogeneous catalytic system

Above discussion illustrates the development made in the field of homogeneous catalysis owing to their high reactivity, mild reaction conditions and high turnover numbers, and particularly the possibility to employ easily accessible and low-cost aryl chloride substrate. However, these homogeneous catalytic systems often suffer the drawback of hard-to-separate and non-reusability. These catalysts also contaminate the final products, especially the pharmaceuticals and medical, and pose a serious issue for large-scale synthesis. Therefore, in order to meet regulatory standards, the
methods for removal of these toxic metals from active pharmaceutical ingredients need to be highly efficient.

Thus, the application of heterogeneous catalysis provides profound advantage of simple recovery and reuse of the catalyst system with least contamination on products. Because most of the heterogeneous catalyst are recyclable and it retain reactivity even after successive recycles, without significant loss in efficiency.

Nowadays, many effective solid supports are available that are easily accessible and often provides effective platform for heterogeneous catalysis, such as silica, alumina, poly(vinyl chloride), MCM-41, SBA-15, polymeric ionic liquid etc. Silica, due to its low cost, easy accessibility, high thermal stability, excellent porosity and large surface area received utmost attention compared to other effective supports. Moreover, the highly active surface-silanol groups present in the silica promotes the effective anchoring of organic ligands onto its surface, and subsequently the immobilization of the metal via covalent bond on the support. Among these approaches, the most widely used is the Schiff base condensation approach, where a Schiff-base is either covalently attached to a support for anchorage with Pd, or generated in situ by reacting with an amine that is covalently attached to a support via a reactive carbonyl group linked to a metal complex. A larger number of Schiff base-derived heterogeneous Pd catalysts have been reported for the Suzuki-Miyaura reaction. In 2001, Clark et al. have first reported the silica-supported Schiff base-derived Pd catalysts for the Suzuki reaction. After that several silica-supported Schiff base-derived Pd catalysts were developed for Suzuki-Miyaura reactions with good to excellent yields (Figure 3.6). Das’s silica supported palladium@imine-
SiO$_2$, Ma’s pyridine derived-catalyst, Wang’s phosphine-based palladium complex, Garcia’s silica supported cyclopalladated Schiff-base-Pd catalyst are some of the recently developed heterogeneous palladium catalyst that has been used in Suzuki-Miyaura coupling (Figure 3.6).

![Chemical Structures](image)

**Figure 3.6.** Heterogeneous Schiff base-derived Pd complexes for Suzuki-Miyaura reaction

Apart from these, numerous heterogeneous Pd(II) complexes containing N-heterocyclic carbene (NHC)-Pd complexes have been developed as powerful catalysts for the coupling reactions (Figure 3.7). The use of NHCs as ligands has beneficial effects in Pd-catalyzed reactions due to the strong σ-donating property of NHCs and less decomposition of Pd-NHC bonds. Among all the imidazolium-derived carbene ligands obtained, pincer type compounds appear as a particularly attractive type, due to the stability that they confer to their complexes as a consequence of the combination of a high chelate entropic effect and the strength of the M-C bonds in low valent late transition metals. In particular, chelating bis (NHC) complexes of Pd
have shown extreme stability in the presence of heat and moisture leading to remarkable catalytic properties.\textsuperscript{54}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{silica_complexes.png}
\caption{Examples of some silica based complexes}
\end{figure}

\textbf{3(d). Characterization techniques}

One essential prerequisite for the development, manufacturing and commercialization of solid catalyst is the availability of techniques that allow the characterization of their physical and chemical properties. Due to insolubility of supported Pd-complexes, their structural characterizations were limited only to the physiochemical techniques. Several physiochemical characterization techniques, such as solid-state \textsuperscript{13}C CPMAS, Fourier transform infrared spectroscopy (FT-IR), X-ray diffraction (XRD) analysis, transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM), thermo gravimetric analysis (TGA), X-ray photoelectron spectroscopy (XPS) and EDX mapping are employed to authenticate the synthesis of solid based materials. FT-IR helps in identifying the materials via the analysis of functional groups. The crystalline structure and the phase
purity of solid catalyst are determined using XRD, whereas TEM, SEM and AFM techniques are used to determine the size and morphology of the catalyst. TGA is used to predict the thermal stability, moisture content and possible decomposition of volatile materials. XPS is a surface-sensitive quantitative spectroscopy technique that measures the elemental composition in the parts per thousand ranges and also helps in determining the oxidation state and chemical connectivity of the metal present in the catalyst. EDX mapping provides in addition to the conventional SEM image a meaningful picture of the element distribution of a surface.

3(e). Catalysis in water

According to the Green Chemistry principles, the use of no (toxic) solvent makes a protocol green; therefore reaction under neat or solvent-free condition is the best method in a large number of synthetic processes. Studies of various natural reactions occurring in aqueous medium reveals that water could be an effective medium for almost all organic reactions. Water is the most abundant, non-toxic, non-corrosive and non-flammable solvent, which makes it a very attractive from both economical and environmental viewpoint. In addition, water shows excellent chemical solubility, easy temperature control, thereby enhancing the rate of cross-coupling. In Suzuki-Miyaura coupling reaction base activates the arylboronic acid to convert it into a more reactive electron-rich intermediate for the transmetalation step. The presence of water, either as solvent or additive, assists in the solvation of base during the coupling reaction to enhance the rate of the reaction. In literature, a number of outstanding methods have been reported for the cross-coupling of arylboronic acid with iodo-, bromo- and even chloro-arene substrates in water.
3(f). Heterogeneous catalytic system in water

Heterogeneous catalytic system is well suited for the industrial chemistry as the metal immobilized on solid supports remains insoluble in water and easily removed by simple filtration techniques. Moreover, the catalyst could be reused repeatedly without any significant loss in reactivity. In recent years, various solid supported complexes were developed and used in Suzuki-Miyaura coupling reactions in presence of water.\textsuperscript{55} Typical examples includes Pd-mesoporous silica, Pd-hydrotalcite, Pd-natural phosphate, Pd-polymer-supported phosphine, Pd-C, Pd-PEG-NHC, Pd-silica-organic frameworks, Pd-zeolite etc.\textsuperscript{56}

In heterogeneous catalysis, the characteristics of the support always play a crucial role in the performance of a catalytic system. Most of the novel heterogeneous Pd catalysts reported previously for use in Suzuki reactions are based on silica, mainly because of its low cost, high thermal stability, and its potential to robustly anchor various ligand functionalities into/onto its surface through siloxide chemistry.\textsuperscript{57} Several silica-supported Pd catalysts have been reported for Suzuki-Miyaura reactions, but we focus specifically on Schiff base and NHC-based ligand systems.

3(g). References


Section 3.1

Palladium-imine-silica framework as a highly efficient and recyclable Suzuki-Miyaura catalyst in aqueous media

Abstract: A novel Pd@imine-SiO₂ complex was prepared and characterized. The prepared imine-based complex exhibits excellent catalytic activity in the Suzuki-Miyaura cross-coupling reaction under aqueous media at room temperature, and is reusable up to 8th consecutive cycles.
3.1.1. Introduction

In the last three decades numerous soluble homogeneous palladium catalysts have been synthesized and employed in Suzuki-Miyaura cross-coupling reactions due to their high reactivity and high turnover numbers. However, the use of homogeneous catalyst remains challenging because the expensive metal catalysts hard to separate, non-reusable and often contaminates the final products, especially the pharmaceuticals, and poses a serious issue for large scale synthesis. To overcome this problem heterogeneous catalysis seems promising and advantageous over homogenous catalysts, because simple recovery of the catalyst from the reaction mixture with minimum metal contamination, easy isolation and enduring stability of the solid catalyst. Moreover, many of the heterogeneous systems are recyclcable and retain their reactivity even after several catalytic cycles. A large numbers of materials including organic polymers, clays, oxides, activated carbon, polymeric ionic liquids, zeolites have been used for immobilization of Pd compounds. However, the most common heterogeneous supports are based on silica, because of its easy availability, high stability, and porosity, which allows easy binding of organic groups on the surface. The presence of highly active silanol-sites in the silica-surface promotes effective anchoring of organic ligands,\(^1\) followed by the immobilization of the metal on the support. Till now, several efficient silica-supported heterogeneous palladium catalysts have been synthesized and used in Suzuki-Miyaura cross-coupling reaction. However, many of these methods still suffers from the problem concerning the use of volatile organic solvent system, elevated reaction temperature, high metal loading and poor recyclability.\(^2\) Hence, there is a need to develop recyclable heterogeneous
catalytic systems which can perform efficiently under mild reaction condition with diverse range of substrates.

In this chapter, we report a well-defined palladium-salicylaldehyde imine complex supported on silica gel as heterogeneous catalyst for Suzuki-Miyaura coupling reactions under a mild aqueous condition. The catalyst was highly efficient at low loading and could be recovered, reused effectively up to 8th cycles.

3.1.2. Results and Discussion

3.1.2.1. Synthesis and Characterization

The Pd@imine-SiO₂ complex was synthesized by treating aminopropyl-functionalized silica gel with salicylaldehyde, followed by complexation with palladium(II) acetate as shown in Scheme 3.3.³

![Scheme 3.3 Preparation of the silica supported Pd@imine-SiO₂ complex](image)

The first step involves the refluxing of solid silica (60-120 mesh) with APTES in dry toluene under N₂ atmosphere. The formed APTES@SiO₂ was then condensed with salicylaldehyde to give yellow colored Schiff-base ligand, imine@SiO₂, after final
purification. The imine@SiO₂ was then complex with Pd(OAc)₂ for the synthesis of Pd@imine-SiO₂ complex.

As the Pd@imine-SiO₂ complex is insoluble in almost all organic solvents, we have studied its physicochemical properties only such as FT-IR, SEM-EDX, EDS-mapping, XRD, ICP-AES and N₂ adsorption-desorption spectral data.

3.1.2.2. FT-IR, XRD, ICP-AES, SEM-EDX and EDS mapping analysis

The FT-IR spectra of the samples are presented in Figure 3.8. All sample shows absorption bands around 1638 and 3400 cm⁻¹, corresponding to stretching and bending vibrations of adsorbed water molecules. The silica framework and Si-O-Si group shows characteristic band at 1050-1150 cm⁻¹ owing to their stretching vibrations. Medium intensity vibration around 2830-2930 cm⁻¹ is due to the νC-H stretching of methylene groups. The attachment of APTES to silica is visible in all three samples (II, III and IV) in the region 1500-1600 cm⁻¹ (νN-H vibration). The bands at 1670 cm⁻¹ and 1460 cm⁻¹ in III are due to the νC=O and νC=O stretching frequency. Immobilization of Pd was further supported by the observation of band at 540 cm⁻¹ in IV, assigned to νPd-N stretching frequency.⁴

The formation of palladium complex onto the silica surface was confirmed by the powder X-ray diffraction analysis as shown in Figure 3.9. The peak at 2θ value of 21.10 is for free SiO₂. Characteristic peaks at 2θ= 38.12 and 47.23 corresponds to the (111) and (200) lattice planes of the fcc phase of palladium are consistent with literature.³⁵
Figure 3.8. FT-IR spectra; (I) Silica, (II) APTES@SiO$_2$, (III) Schiff base (imine@SiO$_2$), and (IV) Pd@imine-SiO$_2$

Figure 3.9. XRD pattern of (a) SiO$_2$, and (b) Pd@imine-SiO$_2$

Figure 3.10. SEM-EDX spectra of (a) SiO$_2$, (b) Pd@imine-SiO$_2$

The palladium content in Pd@imine-SiO$_2$ was analyzed by ICP-AES analysis, reveals the presence of 0.023 mmol or 0.023 mol% Pd in 1 mg of solid catalyst. The SEM-
EDX spectrum of the complex shows the presence of palladium along with O- and Si-proportions, confirming the anchoring of palladium on silica.

On comparing the SEM images of free silica and Pd@imine-SiO₂, we observed morphological change on the silica surface after palladium loading (Figure 3.11). When silica was functionalized with APTES and salicyldehye its surface probably got modified and finally when Pd(II)acetate reacts its morphology further gets modified with varying particle sizes. The presence of palladium particle significantly decreases the size of the formed particles.

![SEM Image](image-url)

**Figure 3.11.** SEM image of (a) SiO₂, (b) Pd@imine-SiO₂

The elemental mapping of Pd@imine-SiO₂ using energy dispersive X-ray absorption spectroscopy (EDS) (Figure 3.12) shows the uniform distribution of active palladium species and silica.

3.1.2.3. **N₂ Adsorption-Desorption isotherm**

N₂ adsorption- desorption isotherm analysis of the silica matrixes before and after the encapsulation of the palladium provides complete detail on the specific surface area and porosity (Figure 3.13). Isotherms of all samples are similar to the type IV isotherm of IUPAC classification having typical hysteresis loop. This shows the presence of mesoporous material with uniform pore size. The structural parameters
are summarized in Table 3.1. A decrease of the specific surface area and the specific pore volume are observed after successive treatment of all the materials.

![Figure 3.12](image)

**Figure 3.12** (a) SEM-EDS mapping of: (b) Oxygen, (c) Si, (d) Pd and (e) Si+O+Pd.

![Figure 3.13](image)

**Figure 3.13.** $N_2$ adsorption-desorption isotherm of the prepared samples

The surface area and pore volume of free SiO$_2$ was 421.9 m$^2$g$^{-1}$ and 0.449 cm$^3$ g$^{-1}$ which upon functionalized with APTES and salicylaldehyde changes to 293.5 m$^2$g$^{-1}$ and 0.374 cm$^3$ g$^{-1}$ respectively. However, these values are further decreased to 210.1
m² g⁻¹ and 0.274 cm³ g⁻¹ after immobilization of palladium. However, we observed an increase in pore radius on successive immobilizations, this may be due to the cracking of some smaller pores of SiO₂ by the Pd particles to generate bigger one during the formation of the complex.⁶ The BET surface area and pore volume of the complex gets decreased to a considerable value, which proves the successfully anchoring of organic moieties on the surface of SiO₂.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Surface area (m² g⁻¹)</th>
<th>Pore volume (cm³ g⁻¹)</th>
<th>Pore radius (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SiO₂</td>
<td>421.9</td>
<td>0.449</td>
<td>2.05</td>
</tr>
<tr>
<td>2</td>
<td>APTES@SiO₂</td>
<td>333.2</td>
<td>0.415</td>
<td>2.20</td>
</tr>
<tr>
<td>3</td>
<td>Imine@SiO₂</td>
<td>293.5</td>
<td>0.374</td>
<td>2.29</td>
</tr>
<tr>
<td>4</td>
<td>Pd@imine-SiO₂</td>
<td>210.1</td>
<td>0.274</td>
<td>3.26</td>
</tr>
</tbody>
</table>

3.1.3. Pd@imine-SiO₂ catalyzed Suzuki-Miyaura cross-coupling reaction

3.1.3.1. Catalyst, base and solvent optimization

The reaction conditions were optimized by using 4-bromonitrobenzene and phenylboronic acid as a model substrate to evaluate the effect of different solvents, types of bases and the amount of catalyst for the reaction (Table 3.2). The reaction was carried out in various aqueous/organic media at room temperature in open air without any special precautions. The reaction proceeded in both protic and aprotic solvents in presence of K₂CO₃, although significant variation in yields was noticed. When iPrOH, EtOH, PEG (PEG₄₀₀), and THF are used as solvent, lower yield upto 63% of the desired cross-coupling products are produced (Table 3.2, entries 1-4). When pure water was used as a solvent the product yield was very low (Table 3.2, entry 5), however water as a co-solvent in the reaction medium, increases the yield.
upto 99% (Table 3.2, entries 6, 7). Among the solvent examined iPrOH/H₂O (1:1) is found to be the best reaction medium (Table 3.2, entries 7).

**Table 3.2.**
Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>iPrOH</td>
<td>K₂CO₃</td>
<td>7</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>K₂CO₃</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>PEG₄₀₀</td>
<td>K₂CO₃</td>
<td>5</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>K₂CO₃</td>
<td>9</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>H₂O</td>
<td>K₂CO₃</td>
<td>5</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>PEG₄₀₀/H₂O (1:1)</td>
<td>K₂CO₃</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>iPrOH/H₂O (1:1)</td>
<td>K₂CO₃</td>
<td>8</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>iPrOH/H₂O (1:1)</td>
<td>Na₂CO₃</td>
<td>3</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>iPrOH/H₂O (1:1)</td>
<td>Na₃PO₄·12 H₂O</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>iPrOH/H₂O (1:1)</td>
<td>NaOH</td>
<td>6</td>
<td>52</td>
</tr>
<tr>
<td>11</td>
<td>iPrOH/H₂O (1:1)</td>
<td>KOH</td>
<td>6.5</td>
<td>56</td>
</tr>
<tr>
<td>12</td>
<td>iPrOH/H₂O (1:1)</td>
<td>Et₃N</td>
<td>8</td>
<td>48</td>
</tr>
<tr>
<td>13</td>
<td>iPrOH/H₂O (1:1)</td>
<td>—</td>
<td>24</td>
<td>No reaction</td>
</tr>
<tr>
<td>14</td>
<td>iPrOH/H₂O (1:1)</td>
<td>Na₂CO₃</td>
<td>9</td>
<td>82⁴</td>
</tr>
</tbody>
</table>

⁴Reaction conditions: 4-bromonitrobenzene (0.5 mmol), phenylboronic acid (0.6 mmol), base (1.5 mmol), solvent (4 mL), Pd@imine-SiO₂ (20 mg, 0.463 mol% Pd), base (1.5 mmol) ca. 27 °C in air unless otherwise noted.

⁵Isolated yield.

Further investigation was carried out to study the influence of different bases on the same reaction condition, and found that metal carbonate bases provides higher yields with excellent reactivity in comparison to other bases (Table 3.2, entries 6-8). Among various bases screened in iPrOH/H₂O (1:1), Na₂CO₃ provided the highest cross-coupling yield of 99% in 3 h (Table 3.2, entry 8). The organic base like Et₃N is not efficient and provides a very low isolated yield of 48% in 8 h. (Table 3.2, entry 12).
No coupling product was observed in absence of base, which confirmed the essentiality of base during the cross-coupling (Table 3.2, entry 13).

3.1.3.2. Substrate Scope

Encouraged by the efficiency of our Pd@imine-SiO₂ catalyst describes above, we explored the scope and limitation of different substrates for the Suzuki-Miyaura cross-coupling reaction (Table 3.3).

<table>
<thead>
<tr>
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*Reaction conditions: aryl bromide (0.5 mmol), arylboronic acid (0.6 mmol), Pd@imine-SiO₂ (20 mg, 0.463 mol% Pd), Na₂CO₃ (1.5 mmol), iPrOH/H₂O (4 mL), ca. 27 °C in air unless otherwise noted. *Isolated yield.*
Aryl bromides bearing electron donating and electron withdrawing substituents are well tolerated providing desired coupling products in high yields (Table 3.3, entries 1-19). The present catalytic system is equally effective for arylboronic acids bearing either electron-donating or electron-withdrawing groups. These results are quite significant and show that the stronger the electron donating group in arylboronic acid, higher the catalytic activity at short reaction time. With chloroarene substrates coupling reaction was observed under present conditions (Table 3.3, entry 20).

3.1.3.3. Large scale synthesis

To expand the scope of present catalytic system to industrial level, we have scale-up the synthesis to grams instead of milligrams. The reaction of five time excess of reactant; 4-bromonitrobenzene (5 mmol), phenylboronic acid (6 mmol), Pd@imine-SiO₂ (100 mg), Na₂CO₃ (7.5 mmol) and iPrOH/H₂O (20 mL) was carried out. After purification, we have obtain 0.9885 grams (99.3%) of 4-nitro-1,1'-biphenyl.

3.1.3.4. Distinguishing homogeneous or heterogeneous pathway

Solid catalysts generally follows the heterogeneous route in the reaction medium, however, in certain cases they are found to be act as precatalyst for more active soluble palladium species or nanoparticles. To evaluate the actually catalytic species of our Pd@imine-SiO₂ complex, various control experiments have been carried out. First, we pretreated Pd@imine-SiO₂ (20 mg) with Na₂CO₃ in iPrOH/H₂O for 3 h at room temperature and then the solution was filtered, and the filtrate was subjected to another run of coupling using fresh amount of reactants. Only 2 % (vide GC-MS) of coupling product was observed after stirring the filtrate for another 3 h. The amount of leached palladium in the filtrate was determined by ICP-AES analysis and was
found to be 0.18 ppm. While these results establish the presence of strong coordination and stability of palladium within the complex, it is not always the prime criteria for considering the heterogeneity of a supported catalyst.

Thus, to further confirm heterogeneity of Pd@imine-SiO₂, we performed recycling experiments by using phenylboronic acid with 4-bromonitrobenzene. The result shows that the catalyst could be reused successively for eight consecutive cycles (Figure 3.14). After the first reaction catalytic run, the reaction mixture was centrifuged and washed thoroughly with iPrOH/H₂O and EtOAc, and the recovered catalyst was dried overnight. With the recovered catalyst fresh coupling reactions were performed. It is observed that the reactions with recovered catalyst proceed well but requires more reaction time. The filtrate after 8th run was subjected to ICP-AES analysis and found to content 0.24 ppm. Although, no significant leaching of palladium occurs during the reaction, the reason for decrease in catalytic activity after successive cycle is may be due to deactivation of catalyst.

To compare the effectiveness of the present catalyst we have examined the Suzuki-Miyaura coupling reaction using Pd/C. When the coupling reaction of 4-bromonitrobenzene and phenylboronic acid was performed in the presence of Pd/C (0.46 mol%), Na₂CO₃ and isopropanol-water, trace amount of couple product was detected (compared to 99% yield with Pd@imine-SiO₂ under identical condition).

To reveal the actual catalytic nature of Pd@imine-SiO₂ catalyst we have performed catalyst poisoning test using Hg(0). Mercury is known for the capability of metal poisoning to forming an amalgam with metals like Pt, Pd or Ni. For this test, excess Hg(0) and required amount of catalyst was stirred before the addition of other
reactants. Complete suppression of the reaction infers the presence of Pd(0) species, whereas, retention of catalytic activity will confirm the presence of Pd(II) species. Herein, we observed that the catalyst retains its high reactivity even in the presence of Hg(0), to provide the corresponding coupling products in high yield (99%). This suggests that the catalyst remains in higher oxidation state within the complex and throughout the course of the reaction.

![Graph showing yield vs. number of cycles](image)

**Fig. 3.14.** Reusability of the catalyst for the Suzuki-Miyaura reaction.

### 3.1.4. Conclusions

In conclusion, we have developed a palladium-based solid complex by immobilizing Pd(OAc)$_2$ into imine-functionalized silica and characterized. The synthesized complex exhibited excellent catalytic activity in the cross-coupling of aryl bromides with arylboronic acids at low catalyst loading (20 mg, 0.463 mol% Pd). Moreover, the reaction proceeds efficiently in aqueous condition and the catalyst is easy to isolate and recycle, offering an effective alternative to the existing protocols.

### 3.1.5. Experimental Section

#### 3.1.5.1. Instrumentation and Chemicals
All chemicals are commercially available and used as received without further purification or drying. Silica gel (60-120 mesh) was purchased from SRL Chemicals, India. APTES was purchased from Sigma Aldrich. Pd(OAc)$_2$ was purchased from Spectrochem Pvt. Ltd., India. The reaction was monitored using TLC on silica gel plates (Merck, silica gel 60F$_{254}$). Isolated products were confirmed by comparing their $^1$H NMR spectra with the literature. FT-IR spectra (4000-250 cm$^{-1}$) were recorded in CHCl$_3$ or KBr on a Shimadzu Prestige-21 FT-IR spectrophotometer. For the N$_2$ adsorption-desorption experiments, the samples were first degassed for 2 h at 150 °C. Then, the isotherms were determined using liquid N$_2$ at -78 °C. The surface areas of the silica samples were calculated using the BET equation. Pore size distribution was calculated using BJH algorithm. $^1$H NMR spectra were recorded in CDCl$_3$ using TMS as internal standard on a JEOL, JNM ECS NMR spectrometer operating at 400 MHz or on a Advance DPX 300 MHz FT-NMR spectrometer operating at 300 MHz. Gas chromatographic analysis coupled with mass spectrometry (GC-MS) was performed on an Agilent Technologies GC system 7820A coupled with a mass detector 5975 and SHRXI-5MS column (15 m length, 0.25 mm inner diameter, 0.25 micron film thickness). Inductively coupled plasma-atomic emission spectrometry (ICP-AES) was done on a Thermo Electron IRIS Intrepid II XSP DUO. The SEM-EDX data were obtained from “JEOL, JSM Model 6390 LV”.

3.1.5.2. Catalyst preparation

Modification of Silica Surface: APTES@SiO$_2$

The silica gel was dehydrated at 100 °C for 2 h before the use. 5 g of silica was refluxed for 7 h with 442.7 mg (2 mmol) of APTES in 50 mL of dry toluene under N$_2$
atmosphere. After completion, the mixture was cooled, filtered and washed repeatedly using Soxhlet extraction with dry toluene. The product was dried overnight in oven at 100 °C and the resulting solid material was denoted as APTES@SiO₂.

**Synthesis of Schiff-base functionalized Silica gel**

1.25 g of APTES@SiO₂ and 1.06 mmol (129.4 mg) of salicylaldehyde was refluxed in the ethanol for 6 h. The resulting yellow solid was filtered and washed using Soxhlet extraction in ethanol followed by acetone and dried overnight in oven at 100 °C and resultant Schiff base was denoted as imine@SiO₂.

**Immobilization of Pd(OAc)₂ onto imine@SiO₂**

For the preparation of Pd@imine-SiO₂ catalyst, 1 g of imine@SiO₂ was treated with Pd(OAc)₂ (50 mg) in 20 mL of acetone at room temperature for 24 h. The yellow solid gradually changes to charcoal-grey. The resulting solid was then washed using Soxhlet in acetone, and then dried.

**General Information about Catalytic Experiments**

Suzuki-Miyaura cross-coupling reactions were performed in air at room temperature (ca. 28 °C). The coupling products were isolated using column chromatographic using silica gel (60-120 mesh). The isolated products were confirmed by comparing their ¹H NMR, mass spectral data and melting point with the authentic samples.

**Typical Procedure for Suzuki-Miyaura Reactions**

To a 50 ml round-bottom flask a mixture of aryl halide (0.5 mmol), aryl boronic acid (0.6 mmol), Na₂CO₃ (1.5 mmol), Pd@imine-SiO₂ (20 mg) and solvent (4 mL) was added. The mixture was then stirred at room temperature for the required time. After completion, the reaction mixture was centrifuged and the residual solid was washed
with the same solvent (3×4 mL). The filtrate added with water (10 mL) and extracted with diethyl ether (3×10 mL). The resultant organic extract was washed with brine (2×10 mL) and dried over anhydrous Na₂SO₄, filtered and evaporated under vacuum. The residue was subjected to silica gel column chromatography (ethyl acetate-hexane, 1:9) to obtain the desired products.

For recycling experiments, residue catalyst was washed with water (3×5 mL) and diethyl ether (3×5 mL) in sequence. The recovered catalyst was at dried overnight in an oven at 100 °C. The residual catalyst was subjected to further catalytic cycle by charging with the substrates (aryl halide, arylboronic acid), Na₂CO₃ and isopropanol-water.

**Representative example of Suzuki-Miyaura coupling on high Scale**

A 100 ml round-bottom flask was charged with 4-bromonitrobenzene (5 mmol), phenylboronic acid (6 mmol), Na₂CO₃ (7.5 mmol), Pd@imine-SiO₂ (100 mg) and iPrOH/H₂O (20 mL). The reaction mixture was stirred at room temperature for 3 h. After completion, the mixture was subjected to centrifugation and the filtrate was diluted with water (25 mL) and extracted with diethyl ether (3×25 mL). The resultant organic extract was washed with brine (3×25 mL) and dried over anhydrous Na₂SO₄, filtered and reduced under vacuum. The residue was subjected to silica gel column chromatography (ethyl acetate-hexane, 1:9) to isolate the desired products. The analytically pure coupling product 4-nitro-1,1'-biphenyl was obtained in 0.9885 grams (99.3%).
3.1.5.3. Analytical data of the prepared biaryl derivatives

4-Methoxybiphenyl: (Table 3.3, entry 1).\(^9\) White solid, \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm) δ: 7.54-7.52 (m, 4H), 7.42-7.41 (m, 2H), 7.28-7.25 (m, 1H), 7.06-6.97 (m, 2H), 3.89 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz, ppm) δ: 159.2, 140.9, 133.8, 128.8, 128.2, 126.8, 126.7, 114.2, 55.4; GC-MS m/z: 184.1 (M\(^+\), 100).

4-Flouro-4'-methoxybiphenyl: (Table 3.3, entry 2).\(^9\) White solid, \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm) δ: 7.46-7.44 (m, 4H), 7.90-7.07 (m, 2H), 6.98-6.96 (m, 2H), 3.83 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz, ppm) δ: 162.4, 160.8, 159.2, 137.1, 132.7, 127.3 (d, J=7.5 Hz, 1C), 114.7 (d, J=20.8 Hz, 1C), 114.2, 55.2; GC-MS m/z: 202.4 (M\(^+\), 100).

4, 4'-Dimethoxybiphenyl: (Table 3.3, entry 3).\(^9\) Colourless solid, \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm) δ: 7.47-7.45 (m, 4H), 6.97-6.95 (m, 4H), 3.85 (s, 6H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz, ppm) δ: 158.6, 132.5, 126.8, 114.5, 55.3; GC-MS m/z: 214.10 (M\(^+\), 100).

4-Nitrobiphenyl (Table 3.3, entry 4).\(^9\) Yellow solid, \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm) δ: 8.30-8.28 (m, 2H), 7.76-7.73 (m, 2H), 7.64-7.61 (m, 2H), 7.53-7.49 (m, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz, ppm) δ: 146.6, 145.3, 138.9, 128.2, 129.3, 127.6, 125.4, 122.1; GC-MS m/z: 199.1 (M\(^+\), 100).
4-Chloro-4'-nitro-biphenyl (Table 3.3, entry 5): White solid, $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ: 8.30-8.27 (m, 2H), 7.72-7.69 (m, 2H), 7.61-7.58 (m, 2H), 7.21-7.18 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ: 146.1, 144.2, 135.2, 133.0, 127.2, 125.1, 124.7, 122.2; GC-MS m/z: 233.10 (M$^+$, 100).

[1,1'-Biphenyl]-4-carbaldehyde (Table 3.3, entry 6): White solid, $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ: 10.03 (s, 1H), 7.94 (d, J= 8.26 Hz, 2H), 7.74 (d, J= 8.27 Hz, 2H), 7.64 (d, J= 7.37 Hz, 2H) 7.48 (d, J= 7.37 Hz, 2H), 7.44-7.42 (m, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ: 190.0, 146.3, 138.7, 134.2, 131.3, 128.1, 127.4, 126.7, 125.6; GC-MS m/z: 182.1 (M$^+$, 100).

4'-Methoxy-[1,1'-biphenyl]-4-carbaldehyde (Table 3.3, entry 7): White solid, $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ: 10.05 (s, 1H), 7.95-7.92 (m, 2H), 7.69-7.71 (m, 2H), 7.63-7.59 (m, 2H), 7.04-7.01 (m, 2H), 3.85 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ: 192.5, 161.1, 145.7, 134.7, 132.4, 130.7, 127.5, 126.1, 116.5, 54.4; GC-MS m/z: 212.1 (M$^+$, 100).

4-Formyl-4'-chloro biphenyl (Table 3.3, entry 8): White solid, $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ: 10.4 (s, 1H), 7.96 (d, J= 8.14 Hz, 2H), 7.70 (d, J= 8.17 Hz, 2H),
7.61-7.59 (m, 2H), 7.22-7.17 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ: 192.8, 147.9, 137.2, 134.4, 133.8, 131.4, 127.3, 126.6, 125.6; GC-MS $m/z$ 216.10 (M$^+$, 100).

4-Acetyl biphenyl (Table 3.3, entry 9):$^9$ White solid, $^1$H NMR (CDCl$_3$, 400 MHz, ppm, TMS) δ: 8.07-8.05 (m, 2H), 7.72-7.69 (m, 2H), 7.65-7.63 (m, 2H), 7.52-7.50 (m, 2H), 7.47-7.44 (m, 1H), 2.65 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ: 198.8, 147.8, 138.9, 137.9, 128.7, 128.0, 127.9, 127.3, 127.3, 26.7; GC-MS $m/z$: 196.10 (M$^+$, 100).

4-Acetyl-4'-methoxy biphenyl (Table 3.3, entry 10):$^9$ White solid, $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ: 8.04-7.97 (m, 2H), 7.63-7.61 (m, 2H), 7.56-7.53 (m, 2H), 7.05-7.02 (m, 2H), 3.88 (s, 3H), 2.61 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ: 199.7, 157.9, 146.4, 136.3, 134.3, 130.0, 129.4, 127.7, 116.4, 54.4, 25.7; GC-MS $m/z$: 226.10 (M$^+$, 100).

1-(4'-Chloro-[1,1'-biphenyl]-4-yl)ethanone (Table 3.3, entry 11):$^9$ White solid, $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ: 8.06-8.04 (m, 2H), 7.68-7.65 (m, 2H), 7.58-7.55 (m, 2H), 7.45-7.43 (m, 2H), 2.61 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ: 195.7, 141.5, 136.3, 134.1, 133.5, 130.2, 129.0, 128.7, 127.4, 26.2; GC-MS $m/z$: 230.10 (M$^+$, 100).
1,1'-Biphenyl (Table 3.3, entry 12): White solid, $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ: 7.66-7.63 (m, 4H), 7.48-7.45 (m, 4H), 7.38-7.35 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ: 143.1, 129.9, 128.3, 125.9; GC-MS m/z: 154.10 (M$^+$, 100).

4-methyl-1,1'-biphenyl: (Table 3.3, entry 13): White solid, $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ: 7.58-7.55 (m, 2H), 7.49-7.35 (m, 2H), 7.43-7.41 (m, 3H), 7.35-7.32 (m, 2H), 2.38 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ: 141.2, 139.9, 136.8, 130.8, 129.2, 126.8, 124.7, 123.2, 21.4; GC-MS m/z: 168.23 (M$^+$, 100).

4-Flouro biphenyl (Table 3.3, entry 14): White solid, $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ: 7.57-7.54 (m, 4H), 7.46-7.43 (m, 2H), 7.37-7.35 (m, 1H), 7.15-7.14 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ: 162.3, 161.7, 141.1, 137.5, 129.7, 127.7, 126.5, 115.6; GC-MS m/z: 173.10 (M$^+$, 100).

5-Phenylpyrimidine (Table 3.3, entry 15): White solid, $^1$H NMR (CDCl$_3$, 400 MHz, ppm) δ: 9.24 (s, 1H), 8.95 (m, 2H), 7.58-7.55 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) δ: 156.3, 154.7, 134.3, 132.2, 128.5, 127.6, 126.0; GC-MS m/z: 156.1 (M$^+$, 100).
5-(4'-Methoxyphenyl)pyrimidine (Table 3.3, entry 16): Yellow solid, $^1$H NMR (CDCl$_3$, 400 MHz, ppm) $\delta$: 9.13 (s, 1H), 8.93 (s, 2H), 7.54-7.41 (m, 2H), 7.06-7.03 (m, 2H), 3.16 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) $\delta$: 161.3, 156.6, 154.3, 133.8, 128.4, 126.4, 116.8, 54.5; GC-MS m/z: 186.1 (M$^+$, 100).

5-(4-Fluorophenyl)pyrimidine (Table 3.3, entry 17): White solid, $^1$H NMR (CDCl$_3$, 400 MHz, ppm) $\delta$: 9.23 (s, 1H), 8.92 (s, 2H), 7.54-7.52 (m, 2H), 7.25-7.22 (m, 2H), $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) $\delta$: 162.1, 156.5, 154.8, 128.6, 126.8, 116.3, 116.5; GC-MS m/z: 174.1 (M$^+$, 100).

4'-Methoxy-2-methyl-1,1'-biphenyl (Table 3.3, entry 18): White solid, $^1$H NMR (CDCl$_3$, 400 MHz, ppm) $\delta$: 7.31-7.25 (m, 6H), 6.92-6.89 (m, 2H), 3.91 (s, 3H), 2.42 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) $\delta$: 158.3, 142.6, 137.4, 134.1, 131.6, 130.1, 129.1, 126.4, 125.2, 115.6, 54.8, 21.5; GC-MS m/z: 198.10 (M$^+$, 100).

4'-Methoxy-[1,1'-biphenyl]-3-carbonitrile (Table 3.3, entry 19): White solid, $^1$H NMR (CDCl$_3$, 400 MHz, ppm) $\delta$: 7.82 (m, 1H), 7.73 (m, 1H), 7.53 (m, 1H), 7.51-7.49 (m, 3H), 7.03-6.96 (m, 2H), 3.83 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) $\delta$: 158.7, 141.3, 133.1, 132.4, 131.2, 130.6, 126.1, 119.6, 114.7, 113.2, 54.7; GC-MS m/z: 209.1 (M$^+$, 100).
$^1$H and $^{13}$C NMR of 4-Methoxybiphenyl: (Table 3.3, entry 1)
Section 3.2

Silica-supported bis-(NHC)-palladium(II) complex: an efficient and reusable catalyst for Suzuki-Miyaura cross-coupling reaction in aqueous media

Abstract: Unique bis-(NHC) palladium-SiO₂ complex was prepared and characterized. This solid complex exhibits high efficiency and recyclable (up to 6th cycle) catalytic activity in Suzuki-Miyaura cross-coupling reactions under mild aqueous medium. The catalytic activity of the NHC-Pd-complex was investigated theoretically.
3.2.1. Background

Considering the extensive applicability of Suzuki-Miyaura cross coupling reactions for the synthesis of biaryls, many significant developments have been achieved. Among them the use of heterogeneous catalytic system in organic synthesis is an important one, which provides strong advantages of easy recovery of catalyst by simple decantation and filtration and reused of the catalyst in consecutive cycles. Easy workup procedures and handling of catalysts is an important characteristic for industrial appliance of a catalyst.

As part of our continuing efforts to develop functionalized silica-based palladium catalyst, we decided to study the silica supported complex bearing bis-(NHC) at their surface to form palladium complex and to evaluate this new catalyst for the Suzuki-Miyaura cross-coupling reaction under aqueous media. NHCs are neutral two electrons σ-donor ligand having little or no metal to ligand π-back-bonding ability. When coordinated with palladium they effectively increases the electron density at palladium center and enhances the oxidative addition step. Although, the reaction mechanism involving the homogeneous palladium catalyst is well known, the theoretical of the heterogeneous catalysis is less frequent. We herein present our experimental and theoretical results.

3.2.2. Results and Discussion

3.2.2.1. Synthesis and Characterisation of the Complex

The “anchoring-coordination to silica” methodology was applied for the synthesis of metal catalyst. Numerous silane molecules are available for the efficient anchoring and functionalization over silica surface and among them triethoxysilane
functionalized molecules are most popular. Therefore, we condensed chloropropyltriethoxysilane (CPTES) and silica followed by the condensation of imidazole in a three-step process to obtain anchored molecule contain two N-heterocyclic carbene binding sites (imidazole-CPTES@SiO₂) (Scheme 3.14).

Scheme 3.14. Synthesis of silica-supported Pd-NHC-CPTES@SiO₂ complex

The solid imidazole-CPTES@SiO₂ was then coordinated to the salt of palladium through both carbene derivatives to obtain the bis-(NHC) palladium complex. In the first step, silica surface was functionalized by refluxing silica (60-120 mesh) and CPTES in toluene under N₂-atmosphere to obtaining the CPTES@SiO₂. The incorporation of CPTES molecules on the surface of silica was confirmed by the Fourier transform infrared (FT-IR) spectroscopy which shows a major vibration bands characteristics of SiO₂ (Figure 3.15). Soxhlet extraction was used to remove all the unreactive CPTES ligand through repeatedly washing with toluene.

In the second step, refluxing of CPTES@SiO₂ with imidazole in toluene followed by 1,3-dibromopropan-2-ol in DMF at 120 °C gave the bis-(NHC)-silica
derivative. Finally, Pd-NHC-CPTES@SiO₂ complex was prepared by applying the procedure described previously by Kühn and co-workers.²¹ The immobilization of palladium onto the bis-(NHC)-silica surface was performed in DMSO by simply heating the NHC@SiO₂ and Pd(OAc)₂ at 60 °C (2 h), 40 °C (2 h), 80 °C (3 h) and from 100 °C (2 h) to 130 °C. The excess of palladium was removed by filtration and washed repeatedly with acetone followed by toluene and then dried. The successive treatment of CPTES on silica followed by imidazole and palladium, a considerable decrease in the BET surface area and pore volume compared to the free silica was observed, indicating the surface modification on the silica matrix (Table 3.4).

![FT-IR spectra](image)

**Figure 3.15.** FT-IR spectra: (I) SiO₂, (II) NHC@SiO₂ and (III) Pd-NHC-CPTES@SiO₂

The synthesis of the Pd-NHC-CPTES@SiO₂ complex was confirmed by the appearance of significant characteristics vibration bands in the FT-IR spectrum of the Pd-catalyst. The bands observed at 3180 cm⁻¹ (sp² C-H stretching vibration of the imidazole moiety), 2820 cm⁻¹ (N-CH₂ stretching vibration) and 1574 cm⁻¹ (C-N and
C=C vibrations of the imidazole ring) indicates the attachment of the all materials (Figure 3.15). On complexation with Pd, the band observed at low frequency region around 470 cm⁻¹ (ν_Pd-C) is also apparent in the spectrum of the complex.²² The specific surface area and pore size distribution of the free silica, supported ligands and metal complex were determined by N₂ adsorption-desorption study. All the samples exhibited the type IV isotherm according to the IUPAC classification with a sharp hysteresis loop, which are characteristics of mesoporous materials (Figure 3.16) with highly uniform pore size distribution.

![N₂ adsorption-desorption isotherm of the prepared samples](image)

**Figure 3.16.** N₂ adsorption-desorption isotherm of the prepared samples

According to the BET measurements, the specific surface area and pore volume for the catalyst was 197.5 m²g⁻¹ and 0.187 cm³g⁻¹ respectively compared to parent silica. The structural parameters are summarized in the Table 3.4 which indicates the immobilization of palladium on the silica matrix.

The powder XRD of silica and silica supported Pd(II) complex were recorded in the range of 2θ=15-60° (Figure 3.17). Both silica and Pd(II) complex shows an
intense reflection at $2\theta=21.9^\circ$ for (100), corresponding to the hexagonal mesoporous structure of silica.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sample</th>
<th>Surface area (m² g⁻¹)</th>
<th>Pore volume (cm³ g⁻¹)</th>
<th>Pore radius (nm)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.339</td>
<td>3.15</td>
</tr>
<tr>
<td>2</td>
<td>CPTES@SiO₂</td>
<td>353.2</td>
<td>0.251</td>
<td>3.02</td>
</tr>
<tr>
<td>3</td>
<td>Imidazole-CPTES@SiO₂</td>
<td>249.7</td>
<td>0.228</td>
<td>2.84</td>
</tr>
<tr>
<td>4</td>
<td>NHC@SiO₂</td>
<td>204.3</td>
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<td>2.47</td>
</tr>
<tr>
<td>5</td>
<td>Pd-NHC-CPTES@SiO₂</td>
<td>197.5</td>
<td>0.187</td>
<td>2.12</td>
</tr>
</tbody>
</table>

This indicates that during the course of preparation of the catalyst, silica remained more or less roughly intact in the whole matrix.

Figure 3.17. XRD pattern of (a) SiO₂ and (b) Pd-NHC-CPTES@SiO₂

On immobilization of palladium salt, there is no shift in the main peak position ($2\theta = 21.9^\circ$), while the intensity of the peak reduced to some extent. Conversely, the Pd-NHC-CPTES@SiO₂ complex shows two weak peaks at angles $2\theta = 34.9^\circ$ and $47.6^\circ$, corresponds to (111) and (200) planes of the fcc phase of palladium crystal.²³
The SEM (scanning electron microscopy) micrograph (Figure 3.18) shows that contrast to the free silica matrix, the average particle size of the Pd-NHC-CPTES@SiO₂ complex is considerably smaller because of the reaction of silica with silane, NHC and Pd(OAc)₂.²⁴ It is also observed that compared to unfunctionalized silica, the Pd-immobilized silica surface (Figure 3.18b) shows more roughness (Figure 3.18a) and the grey color of the silica gel indicates the binding of palladium to the silica gel.

![SEM images](image)

Figure 3.18. SEM image of (a) SiO₂, (b) Pd-NHC-CPTES@SiO₂

Next, we have taken the elemental mapping by energy dispersive X-ray absorption spectroscopy (EDS) to further confirm the structure of the complex. The distributions of silica and palladium sites are very uniform and saturated throughout the whole matrix (Figure 3.19). The TEM images (Figure 3.20) shows the well dispersed distribution of spherical Pd-NHC-CPTES@SiO₂ nanoparticles with average diameter of 3 ± 0.5 nm on the surface of the silica. Electron dispersive X-ray (EDX) analysis of the palladium complex shows the metal content along with the O and Si and suggests the formation of the metal with the anchored ligand at the various sites of the silica support (Figure 3.21). According to ICP-AES analysis, the content of palladium in
the supported catalyst was confirmed and it suggested that 1 mg solid catalyst contains 0.00012 mmol palladium.

**Figure 3.19.** SEM image; EDS mapping of elements C, O, Si and Pd

**Figure 3.20.** TEM images of Pd-NHC-CPTES@SiO$_2$

**Figure 3.21.** SEM-EDX spectra of (a) silica gel (SiO$_2$), (b) Pd-NHC-CPTES@SiO$_2$
The electronic property of the Pd-NHC-CPTES@SiO₂ complex was investigated by X-ray photoelectron spectroscopy (XPS) analysis (Figure 3.22). The XPS spectrum of the Pd 3d core displays main peaks at 340.9 and 346.2 eV, which suggest the binding energy of Pd 3d₅/₂ and Pd 3d₃/₂, respectively.²⁵ These values correspond to the Pd(II) binding energies of the Pd-NHC-CPTES@SiO₂ complex. The presence of Pd(II) in the Pd–NHC-CPTES@SiO₂ complex was also confirmed by the solid UV-Vis spectroscopy owing to the presence of a characteristic peak at 401 nm (Figure 3.24).²⁶

![XPS spectra of the catalyst](image.png)

**Figure 3.22.** XPS spectra of the catalyst

3.2.3. Pd-NHC-CPTES@SiO₂ catalyzed Suzuki-Miyaura reaction

3.2.3.1. Catalyst Screening and Base-Solvent Optimization

To evaluate the catalytic activity of Pd-NHC-CPTES@SiO₂ complex a typical Suzuki-Miyaura reaction was performed by using 4-bromonitrobenzene with phenylboronic acid as a model substrate. Reactions were performed in different solvent like iPrOH, CH₃CN, toluene, THF, CH₂Cl₂, ethanol, PEG-400 and H₂O under aerobic conditions (Table 3.5). Water was used as a solvent in the coupling reaction
because water facilitates the solubility of bases which further enhances the transmetalation step.

Water helps to reconver any phenylboroxine,\textsuperscript{27} formed by during the dehydration of phenylboronic acid,\textsuperscript{28} to phenylboronic acid and improves overall yield. Although, arylboronic acid is highly soluble in water, the efficiency of Suzuki-Miyaura coupling often gets lowered with low-polar halides.\textsuperscript{29} In addition, the solid supported catalyst doesn’t easily interact with the organic reactants and forms cluster during the reaction. To eliminate this drawback, a mixture of water and a organic solvent could provide an effective medium for the present silica supported palladium-catalyzed Suzuki-Miyaura reaction. It is believed that the present silica-based catalyst bearing hydroxyl group on its surface provides an effective interaction between the hydrophobic aryl halides and arylboronic acids to improve the overall efficiency.

After optimization of various solvents, time and temperature (Table 3.5) the best result upto 98% isolated yield was obtained in the mixture of iPrOH and H\textsubscript{2}O (1:1) at 50 °C with 0.03 mol% Pd loading (Table 3.5, entry 7). It is known that besides catalyst, a well chosen base is essential for the success of the coupling reaction. Different types of inorganic and organic bases such as Na\textsubscript{2}CO\textsubscript{3}, Na\textsubscript{3}PO\textsubscript{4}.12H\textsubscript{2}O, NaOH, KOH, NEt\textsubscript{3} were investigated under optimized reaction condition for better coupling efficiency (Table 3.5). Under the above optimized reaction conditions, best catalytic performance was obtained using K\textsubscript{2}CO\textsubscript{3} at 50 °C in water-isopropanol (Table 3.5, entry 7). When the reaction was performed without the base or catalyst (Table 3.5, entries 13, 14) no traces of coupling product was observed suggesting the significance of added base and catalyst. By lowering the catalyst
loading to 0.012 mol% Pd the yield declined significantly even after increasing the
reaction time up to 24 h. (Table 3.5, entry 15).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Time (h)</th>
<th>Yield(%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>iPrOH</td>
<td>K$_2$CO$_3$</td>
<td>4</td>
<td>65$^c$</td>
</tr>
<tr>
<td>2</td>
<td>iPrOH</td>
<td>K$_2$CO$_3$</td>
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<td>80</td>
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<tr>
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<td>PEG$_{400}$</td>
<td>K$_2$CO$_3$</td>
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<td>60</td>
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<td>Ethanol</td>
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<td>H$_2$O</td>
<td>K$_2$CO$_3$</td>
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<td>35</td>
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<tr>
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<td>PEG$_{400}$-H$_2$O (1:1)</td>
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<tr>
<td>7</td>
<td>iPrOH-H$_2$O (1:1)</td>
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<td>iPrOH-H$_2$O (1:1)</td>
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<td>—$^d$</td>
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<tr>
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<td>iPrOH-H$_2$O (1:1)</td>
<td>—</td>
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<td>—</td>
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<tr>
<td>15</td>
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<td>K$_2$CO$_3$</td>
<td>24</td>
<td>80$^e$</td>
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</tbody>
</table>

$^a$Reaction conditions: 4-bromonitrobenzene (0.5 mmol), phenylboronic acid (0.6 mmol), base (1.0 mmol), solvent (4 mL), Pd-NHC-CPTES@SiO$_2$ (2.5 mg, 0.03 mol% Pd), base (1 mmol) ca. 50 °C in air unless otherwise noted. $^b$Isolated yield. $^c$at room temperature, $^d$without catalyst, $^e$Pd-NHC-CPTES@SiO$_2$ (1 mg, 0.012 mol%)

### 3.2.3.2. Substrate Scope

Encouraged by the excellent efficiency of reaction protocol described above, we believed that the solid Pd-NHC-CPTES@SiO$_2$ catalyst could be applicable to a variety of electronically diverse substrates. As shown in Table 3.6, a wide range of both electron-rich and -deficient aryl bromides has also been studied in the reaction. The coupling reaction between aryl halide and arylboronic acid proceeded readily to afford the corresponding products with excellent yields upto 98% with high TOF.
It is observed that, compared to the electron deficient aryl halides, the reactivity of electron rich aryl halides is low. However, no such variation was noticed as both varieties of substrates were effectively coupled with excellent isolated yield under present reaction conditions (Table 3.6).

### Table 3.6.
Suzuki cross-coupling reaction of aryl halides with arylboronic acids

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<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
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<th>R²</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>TON</th>
<th>TOF</th>
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<th>Atom Efficiency (%)</th>
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<tr>
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<td>3133</td>
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<td>49.85</td>
</tr>
</tbody>
</table>

*aReaction conditions: aryl halide (0.5 mmol), arylboronic acid (0.6 mmol), Pd-NHC-CPTES@SiO₂ (2.5 mg, 0.03 mol% Pd), K₂CO₃ (1 mmol), iPrOH-H₂O (4 mL), ca. 50 °C in air unless otherwise noted. bIsolated yield, creaction was performed at 80 °C.*
On the basis of the yield of the final isolated product and time (in min), the turnover number (TON) and turnover frequency (TOF) values were determined and the results are comparably better than the previously reported in literature for the immobilized palladium catalyst.\textsuperscript{30} It was also observed that, the reactivity of aryl chloride in Suzuki-Miyaura coupling reaction is low compared to the aryl bromides at given conditions due to the higher bond energy of C-Cl than C-Br. However, by increasing the reaction temperature from 50 to 80 °C the reactivity of aryl chloride with arylboronic acid could be improved (Table 3.6, entry 12-19).

To demonstrate that Pd(II) was covalently bonded to the functionalized silica surface, a hot filtration test was performed before the catalyst was used in reaction. The Pd catalyst was heated in iPrOH-H\textsubscript{2}O at 80 °C for 30 min and then filtered under hot condition. To the filtrate, 4-bromonitrobenzene, phenylboronic acid and K\textsubscript{2}CO\textsubscript{3} were added and the resulting mixture was stirred at 50 °C. After 2 h, negligible progress in reaction was observed, establishing the heterogeneous nature of our catalyst. No palladium species were detected on ICP-AES analysis of the filtrate so obtained. Further, to identify the catalytic nature of palladium, we performed the Hg(0)-poisoning test.\textsuperscript{31} Hg(0) can amalgamate with most metals, thereby disrupting the catalytic cycle and resulting in reaction bring to a close.\textsuperscript{32} However, molecular homogeneous complexes in higher oxidation states are unaffected by mercury. For Hg poisoning test, a Suzuki-Miyaura reaction is performed in the presence of excess Hg(0) (molar ratio to [Pd]~450) and Pd-NHC-CPTES@SiO\textsubscript{2} catalyst but no coupling product is observed even after 3 h. This suggested that the Pd(II)-silica complex
decomposes under present reaction conditions to form soluble Pd(0) species which interacts with Hg(0) to completely stop the reaction.

![Figure 3.23. XPS spectra of the catalyst recovered from half done catalytic mixture](image)

This indicates that the Pd-complex is acting here as active heterogeneous species. To further confirm the reduction of the Pd(II) to Pd(0) species, XPS analysis of the recovered catalyst (after 10 minutes of the reaction) was performed. The Pd 3d core level high resolution XPS spectrum of the recovered catalyst shows the binding energy at 343.0, 337.3 eV and 341.3, 335.9 eV, which confirms that both Pd(II) and Pd(0) species are present during the first catalytic cycle, respectively (Figure 3.23). These results support the reduction of Pd(II) to Pd(0) (catalyst pre-activation) under the experimental conditions. This was additionally confirmed by comparing the solid UV-Vis spectrum of the complex before and after the reaction (Figure 3.24). The solid UV-Vis spectrum of Pd-NHC-CPTES@SiO₂ shows the presence of Pd(II) species. However, after completion of the reaction reduction of Pd(II) to Pd(0) was
observed due to the absence of the peak at 401 nm, which belongs to Pd(II) species. This indicates that the Pd complex is acting here as active heterogeneous species.

**Figure 3.24.** Solid UV-Vis spectra of Pd-NHC-CPTES@SiO₂ catalyst, (a) fresh and (b) after 1st catalytic cycle

### 3.2.3.3. Reusability Test

The reusability of a catalyst is a very important for commercial applications and it determines its sustainability. The reusability of our catalyst was investigated using 4-bromonitrobenzene with phenylboronic acid as model substrates. After completion of the reaction, the catalyst was separated from the reaction mixture by centrifugation and subsequent decantation, washed thoroughly with water and acetone, dried and reused for subsequent runs. The efficiency of the catalyst was not much decreased even after six cycles (**Table 3.8**). In the meantime, it was found that after sixth run of the catalyst the size of the Pd particles had increased from 3-4 nm to 6-8 nm (**Figure 3.25**). This could be due to agglomeration. Furthermore, the ICP-AES analysis of the recovered catalyst showed no change in palladium content after consecutive recycling, indicating that no significant leaching of palladium to the solution occurs during the catalytic process.
Figure 3.25. TEM images of used catalyst

The gradual decrease in yield (98% to 85%) could be due to the physical loss of the catalyst during the separation, filtration and washings steps as very low amount of catalyst was used (2.5 mg of catalyst). Moreover, excellent efficiency, stability and reusability of the catalyst confirmed the presence of strong bonding between NHC and palladium in the functionalized silica surface, which prevents palladium leaching from the surface.

Table 3.8.
Recycling of the Pd-NHC-CPTES@SiO<sub>2</sub> catalyst the Suzuki-Miyaura coupling reaction<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Run</th>
<th>Time (min)</th>
<th>Yield [%]&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>40</td>
<td>98</td>
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</tr>
<tr>
<td>3</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>55</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>4&lt;sup&gt;th&lt;/sup&gt;</td>
<td>60</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>5&lt;sup&gt;th&lt;/sup&gt;</td>
<td>60</td>
<td>90</td>
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<tr>
<td>6</td>
<td>6&lt;sup&gt;th&lt;/sup&gt;</td>
<td>75</td>
<td>85</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: aryl halide (1 mmol), arylboronic acid (1.2 mmol), Pd-NHC-CPTES@SiO<sub>2</sub> (5 mg, 0.03 mol% Pd), K<sub>2</sub>CO<sub>3</sub> (2 mmol), iPrOH-H<sub>2</sub>O (6 mL), ca. 50 °C in air unless otherwise noted. <sup>b</sup>Isolated yield.

To test the potential for practical industrial applications, we carried out a larger scale synthesis of Suzuki-Miyaura coupling reaction, and the 5 mmol scale reaction preceded efficiently giving 99% yield of the desired product.
Scheme 3.5. Probable mechanism of the Pd-NHC catalyzed Suzuki-Miyaura reaction.

3.2.3.4. Theoretical Calculation

To understand the mechanism involved in the coupling reaction, a theoretical calculation was performed at B3LYP functional with 6-31G** basis set for main group element (including Br) and SDD for palladium atom. The energetics (ΔH) of the reactions (Table 3.9) in gas phase at 25 °C was calculated (Scheme 3.5). The zero-point energy corrected values of ΔH are reported here. It has been found that the oxidative addition step is highly endothermic (ΔH = 167.57 kcal/mol), whereas the transmetalation step is highly exothermic (ΔH = -169.09 kcal/mol).

Table 3.9.
Energetics (ΔH at 25 °C) of the proposed mechanism (kcal/mol)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Steps</th>
<th>ΔH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oxidative Addition</td>
<td>167.57</td>
</tr>
<tr>
<td>2</td>
<td>Transmetalation</td>
<td>-169.09</td>
</tr>
<tr>
<td>3</td>
<td>Reductive Elimination</td>
<td>-35.25</td>
</tr>
</tbody>
</table>

Notably, the experimental reaction is conducted in solvent and at 50 °C, therefore, it is quite possible that the solvation energies and thermal energies mutually lowers the calculated high ΔH values under experimental conditions. We have also compared the catalytic activity of our catalyst with Pd(OAc)_2 and PdCl_2. For this, we calculate
energy at a larger 6-31++G** basis set for main group element on the above optimized geometries.

![Isosurface of HOMO and HOMO-1](image)

**Figure 3.26.** Isosurfaces of HOMO and HOMO-1.

Natural population analysis and Hirshfeld population analysis indicated that the electron density over palladium in the present complex is more than Pd(OAc)$_2$ and PdCl$_2$, which signifies superior activity during the oxidative addition (**Table 3.10**).

<table>
<thead>
<tr>
<th>Species</th>
<th>Natural Charge</th>
<th>Hirshfeld Charge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd-NHC-CPTES@SiO$_2$</td>
<td>-0.3548</td>
<td>-0.1147</td>
</tr>
<tr>
<td>Pd(OAc)$_2$</td>
<td>0.6510</td>
<td>0.4070</td>
</tr>
<tr>
<td>PdCl$_2$</td>
<td>0.5324</td>
<td>0.4357</td>
</tr>
</tbody>
</table>

**Table 3.10.** Natural charge and Hirshfeld charge of catalyst, Pd(OAc)$_2$ and PdCl$_2$

It is also observed that the HOMO is largely localised on palladium atom, whereas HOMO-1 is localised on the NHC-Pd-NHC complex moiety. This observation suggest that oxidative addition occur mainly through the HOMO orbital (**Figure 3.26**). All these calculations are performed using GAUSSIAN09 software.$^{34}$

3.2.4. Conclusion

In conclusion, we have successfully synthesized a immobilized recyclable palladium catalyst with NHC ligand anchored on silica. The Pd-NHC-CPTES@SiO$_2$ complex
showed good catalytic activities in Suzuki-Miyaura coupling reactions in aqueous media, with small loading (0.03 mol% Pd). Overall, good to excellent coupling yield were achieved with various electronically diverse substrates. Moreover, the catalyst can be easily isolated and recyclable up to many times with negligible palladium leaching. Moreover, theoretical calculation of the probable reaction mechanism was done, which correlates well with the experimental results.

3.2.5. Experimental section

3.2.5.1. Instrumentation and Chemicals

Instruments and chemicals used are identical with Chapter 3, Section 3.1, unless otherwise mention. 3-chloropropyltriethoxysilane (CPTES) was purchased from Sigma Aldrich.

Catalyst preparation

The silica gel (60-120 mesh) was dehydrated by heating at 120 °C for 5 h prior to use. 5 g of silica gel was added to 3-chloropropyltriethoxysilane (6mmol) in dry toluene (10 mL) under N₂ atmosphere at reflux temperature for 8 h. After cooling, the 3-chloropropyl-functionalized silica solid was filtered and washed repeatedly through Soxhlet extraction with toluene and dried in an oven for 12 h at 100 °C to obtained the product of CPTES@SiO₂ (Scheme 3.4, step I). In the next step, a mixture of CPTES@SiO₂ (2 g) and imidazole (5 mmol) in dry toluene was refluxed for 6h. After reaction, the solids was filtered, washed through Soxhlet extraction with toluene and dried overnight in oven at 100 °C and the resulting material is denoted as imidazole-CPTES@SiO₂ (Scheme 3.4, step II). In a suspension of 1.5 g of imidazole-CPTES@SiO₂ in 10 mL DMF 200 mg 1,3-dibromopropan-2-ol was added and the
resulting mixture was heated at 120 °C for 6h. The resulting mixture was cooled, filtered and then dried in an oven at 100 °C for 6h to obtain a bisimidazolium compound with a hydroxyl-functionalized propyl-bridge ligand NHC@SiO₂ (Scheme 3.4, step III). And finally, for the synthesis of bis-carbene Pd(II) complex, Pd(OAc)₂ (50 mg) was added to a stirred solution of NHC@SiO₂ (1 g) in 10 mL DMSO and heated for 2 h to 60 °C, 2 h to 40 °C, 3 h to 80 °C and 2 h from 100 °C to 130 °C. Then a fine powder was collected by filtration and was successively washed by acetone followed by toluene and dried to obtain Pd-NHC-CPTES@SiO₂ complex (Scheme 3.4, step IV).

**General Information about Catalytic Experiments**

Cross-coupling reactions were performed in open air at temperature (50-80 °C). Progress of the reaction was monitored using thin layer chromatography. The reaction products were isolated by column chromatographic using silica gel (60-120 mesh). The isolated products were confirmed by comparing the ¹H and ¹³C NMR spectral data with literature data.

**Typical procedure for Suzuki-Miyaura coupling reaction**

A 50 ml round-bottom flask was charged with aryl halide (0.5 mmol), arylboronic acid (0.6 mmol), K₂CO₃ (1 mmol), catalyst (5 mg) and iPrOH/H₂O (4 mL). The resultant mixture was stirred at given temperature for the indicated time. After completion, the reaction mixture was filtered and the residual was washed with the same solvent (3×5 mL). The resultant filtrate was diluted with brine (2×10 mL) and extracted with diethyl ether (3×10 mL), dried over anhydrous Na₂SO₄, and evaporated.
using rotavapor. The crude residue was subjected to column chromatography (ethyl acetate-hexane, 0.5:9.5) to obtain the desired pure products.

In the recycling experiments, the residue catalyst was washed thoroughly with H₂O followed by acetone. After drying overnight at 100 °C in oven, the catalyst was subjected to next catalytic run by charging with the required amount of substrates (aryl halide, arylboronic acid), K₂CO₃ and iPrOH/H₂O, without further addition of the catalyst.

3.2.5.2. Characterization data of the product

4'-Methoxy-[1,1'-biphenyl]-4-carbaldehyde (Table 3.6, entry 1):³ ¹H NMR (CDCl₃, 400 MHz, ppm) δ: 10.03 (s, 1 H), 7.93-7.91 (m, 2H), 7.72-7.70 (m, 2H), 7.60-7.58 (m, 2H), 7.02-7.00 (m, 2H), 3.87 (s, 3H).¹³C NMR (CDCl₃, 100 MHz, ppm) δ: 192.0, 160.1, 146.8, 134.7, 132.1, 130.4, 128.5, 127.1, 114.5, 55.4; GC-MS m/z: 212.1 (M⁺, 100).

4-Formyl-4'-Flouro biphenyl (Table 3.6, entry 2):³ ¹H NMR (CDCl₃, 400 MHz, ppm) δ: 10.05 (s, 1H), 7.98-7.96 (m, 2H), 7.92-7.90 (m, 2H), 7.61-7.56 (m, 2H), 7.21-7.16 (m, 2H).¹³C NMR (CDCl₃, 100 MHz, ppm) δ: 191.3, 145.9, 138.2, 135.4, 134.8, 130.4, 129.3, 128.6, 116.6; GC-MS m/z: 200.10 (M⁺, 100).
4-Nitro biphenyl (Table 3.6, entry 3 and 12): $^9$ $^1$H NMR (CDCl$_3$, 400 MHz, ppm) $\delta$: 8.31-8.29 (m, 2H), 7.75-7.73 (m, 2H), 7.64-7.61 (m, 2H), 7.52-7.48 (m, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) $\delta$: 146.7, 145.1, 137.8, 128.2, 127.5, 125.8, 124.4, 123.1; GC-MS m/z: 199.2 (M$^+$, 100).

4-Flouro-4'-nitro-biphenyl (Table 3.6, entry 4): $^9$ $^1$H NMR (CDCl$_3$, 400 MHz, ppm) $\delta$: 8.31-8.29 (m, 2H), 7.71-7.69 (m, 2H), 7.59-7.55 (m, 2H), 7.48-7.46(m, 2H). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) $\delta$: 148.1, 145.6, 136.2, 135.6, 129.3, 128.1, 126.7, 122.6; GC-MS m/z: 217.10 (M$^+$, 100).

4-Flouro-4'-methoxybiphenyl (Table 3.6, entry 5 and 15): $^9$ $^1$H NMR (CDCl$_3$, 400 MHz, ppm) $\delta$: 7.54-7.49 (m, 4H), 7.12-7.09 (m, 2H), 6.99-6.96 (m, 2H), 3.84 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) $\delta$: 164.4, 161.7, 160.1, 138.5, 133.9, 129.2 (d, $J=$7.5 Hz, 1C), 115.7 (d, $J=$22.4 Hz, 1C), 113.3, 56.4; GC-MS m/z: 202.3 (M$^+$, 100).

4, 4'-Dimethoxybiphenyl (Table 3.6, entries 6 and 13): $^9$ $^1$H NMR (CDCl$_3$, 400 MHz, ppm) $\delta$: 7.48-7.43 (m, 4H), 6.96-6.92 (m, 4H), 3.83 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz, ppm) $\delta$: 159.7, 134.3, 128.8, 115.1, 56.43; GC-MS m/z: 214.3 (M$^+$, 100).
4-Methoxybiphenyl (Table 3.6, entry 7): \(^9\) \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm) \(\delta\): 7.59-7.54 (m, 2H), 7.45-7.41 (m, 2H), 7.37-7.32 (m, 1H), 7.06-7.00 (m, 2H), 3.85 (s, 3H). \(^1^3\)C NMR (CDCl\(_3\), 100 MHz, ppm) \(\delta\): 158.2, 139.3, 135.8, 129.8, 126.2, 124.8, 121.7, 113.2, 54.4; GC-MS m/z: 183.1 (M\(^+\), 100).

4-Acetyl biphenyl (Table 3.6, entry 8): \(^9\) \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm) \(\delta\): 8.05-8.02 (m, 2H), 7.70-7.68 (m, 2H), 7.65-7.62 (m, 2H), 7.50-7.47 (m, 2H), 7.46-7.45 (m, 1H), 2.64 (s, 3H). \(^1^3\)C NMR (CDCl\(_3\), 100 MHz, ppm) \(\delta\): 196.4, 144.1, 138.6, 134.9, 128.1, 127.0, 126.3, 125.8, 125.1, 28.7; GC-MS m/z: 196.3 (M\(^+\), 100).

4-Acetyl-4'-methoxy biphenyl (Table 3.6, entry 9): \(^9\) \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm) \(\delta\): 8.05-7.96 (m, 2H), 7.69-7.53 (m, 3H), 7.30-7.22 (m, 1H), 7.05-6.95 (m, 2H), 3.86 (s, 3H), 2.63 (s, 3H). \(^1^3\)C NMR (CDCl\(_3\), 100 MHz, ppm) \(\delta\): 196.7, 156.9, 144.4, 135.3, 132.9, 129.4, 127.4, 126.1, 116.4, 54.4, 25.7; GC-MS m/z: 226.5 (M\(^+\), 100).

1-(4'-Flouro-[1,1'-biphenyl]-4-yl)ethanone (Table 3.6, entry 10): \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm) \(\delta\): 8.04-8.02 (m, 2H), 7.66-7.64 (m, 2H), 7.57-7.55 (m, 2H), 7.47-7.45 (m, 2H), 2.64 (s, 3H). \(^1^3\)C NMR (CDCl\(_3\), 100 MHz, ppm) \(\delta\): 196.7, 145.5, 139.3, 136.1, 135.5, 128.2, 127.0, 125.5, 117.1, 27.7; GC-MS m/z: 230.2 (M\(^+\), 100).
4’-methoxy-2-methyl-1,1’-biphenyl (Table 3.6, entry 11):\(^\text{1}\) \(^1\)H NMR (CDCl\(_3\), 500 MHz, ppm) \(\delta\): 7.25-7.14 (m, 6H), 7.94-7.91 (m, 2H), 3.80 (s, 3H), 2.26 (s, 3H). \(^13\)C NMR (CDCl\(_3\), 100 MHz, ppm) \(\delta\): 159.6, 142.9, 135.8, 134.2, 131.9, 129.2, 128.7, 125.7, 125.3, 113.7, 55.5, 20.5; GC-MS m/z: 198.5 (M\(^+\), 100).

5-(4’-Methoxyphenyl)pyrimidine (Table 3.6, entry 20):\(^\text{1}\) \(^1\)H NMR (CDCl\(_3\), 500 MHz, ppm) \(\delta\): 9.14 (s, 1H), 8.91 (s, 2H), 7.53-7.49 (m, 2H), 7.04-7.01 (m, 2H), 3.86 (s, 3H). \(^13\)C NMR (CDCl\(_3\), 100 MHz, ppm) \(\delta\): 161.3, 157.4, 155.3, 134.8, 128.0, 125.4, 114.8, 55.3; GC-MS m/z: 186.2 (M\(^+\), 100).

5-(4-Fluorophenyl)pyrimidine (Table 3.6, entry 21):\(^\text{1}\) \(^1\)H NMR (CDCl\(_3\), 500 MHz, ppm) \(\delta\): 9.18 (s, 1H), 8.89 (s, 2H), 7.55-7.51 (m, 2H), 7.21-7.17 (m, 2H). \(^13\)C NMR (CDCl\(_3\), 100 MHz, ppm) \(\delta\): 161.2, 156.5, 153.8, 127.9, 126.1, 116.7, 114.5; GC-MS m/z: 174.2 (M\(^+\), 100).
$^1$H and $^{13}$C NMR spectra of 4'-Methoxy-[1,1'-biphenyl]-4-carbaldehyde (Table 3.6, entry 1)
3.2.6. References


Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox,

*Gaussian 09, Revision D. 01*, Gaussian, Inc., Wallingford CT, 2013.