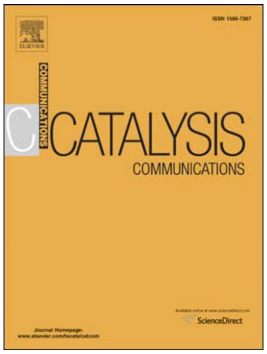

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Palladium nanoparticles catalyzed Suzuki cross coupling reactions in ambient conditions

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Abstract

An efficient pathway to synthesize biaryls and terphenyls through ligand-free palladium nanoparticles (PdNPs) catalyzed Suzuki cross coupling reactions has been developed. Mild reaction conditions, high yields of desired products, absence of inert atmosphere and short reaction times are the worth noting features of this method.

Keywords: Suzuki cross-coupling, Palladium nanoparticles, Ambient conditions, Terphenyl derivatives, Heterocyclic ligands.

1. Introduction

Palladium nanoparticles (PdNPs) supported by a variety of conventional and non-conventional supports have been promising catalysts for Suzuki cross coupling reactions [1-3]. Dendrimers, polymers, anthracene derivatives and metal-organic frameworks stabilized colloidal palladium nanoparticles (PdNPs) are well exploited as catalysts for the Suzuki coupling reactions [4-10]. El-Sayed and co-workers [11] found that palladium nanoparticles stabilized by hydroxyl-terminated poly(amidoamine) (PAMAM) dendrimers (G3-OH, G represents the generation) could efficiently catalyze the Suzuki-Miyaura reactions. Astruc's group [12] have investigated the catalytic activity of palladium dodecanethiolate nanoparticles towards Suzuki coupling reactions which required prolonged reaction time. Recently, Das and co-workers [13] reported Suzuki coupling by using DMF as the solvent at high temperature. Cao and co-workers [14, 15] successfully tested the catalytic activities of cucurbit[*n*]uril (*n*= 6,7,8) protected PdNPs towards Suzuki cross coupling reactions and the same group [16] also tested the SBA-15 stabilized PdNPs, Pd/Au alloy NPs towards Suzuki cross coupling by microwave heating, but C-Br bond was activated at elevated temperatures and synthesis of terphenyls was not discussed. There are some recent methods in the literature for coupling reactions by ligand-free PdNPs as catalyst [17, 18]. However, some of these earlier reports suffer due to the use of bulky, expensive and commercially unavailable ligands, high boiling solvents and prolonged reaction times. There is a high demand for simple, inexpensive and easily accessible catalysts for these coupling reactions. Herein, we report a method for the synthesis of biaryls using ligand-free Suzuki cross coupling reactions catalyzed by palladium nanoparticles at ambient conditions. Terphenyls are also successfully synthesized by the same method. Importantly, the terphenyls was precipitated out from the reaction mixture there by, making this method attractive compared to existing methods.

2. Experimental

2.1. General

All the chemicals were purchased from Sigma-Aldrich chemical company. The PdNPs were characterized by recording powder XRD pattern, TEM, HRTEM and FEG-SEM micrographs and X-ray photoelectron spectroscopy (see SI). The coupling reactions were monitored by TLC (silica gel). ^{1}H and ^{13}C NMR of the products were recorded at room temperature with a Bruker Avance-400 and 500 FT NMR spectrometers. $CDCl_3$ was used as solvent and TMS as the internal standard. HPLC data was obtained by using Waters HPLC instrument fitted with a 515 pump and 2487 dual- wavelength absorbance detector. The TEM sample was prepared by taking drop of metal nanoparticle solution on the carbon coated 200 mesh copper grid and allowed to dry in air at room temperature. Samples for SEM, XRD and XPS were prepared by isolating PdNPs in solid state by evaporating the solution in rotavapor.

2.2. Preparation of palladium nanoparticles (PdNPs)

A 2mM solution of Pd(II) was prepared by dissolving palladium (II) acetate (0.0045 g) in a 1:1 MeCN/MeOH mixture (10 mL). The yellow solution was stirred at room temperature for about 3 h where upon a brownish-black colour was developed due to reduction of Pd(II) to Pd(0) [19].

2.3. Typical procedure for the synthesis of biaryls by PdNPs catalyzed Suzuki coupling reactions:

To a freshly prepared solution of PdNPs (10 mL, 0.02 mmol), K_2CO_3 (0.276 g, 2 mmol) was added followed by arylhalide (1 mmol) and arylboronic acid (1.5 mmol). Then, the reaction was allowed to stir at room temperature in open atmosphere. The reaction was monitored by TLC and was stopped after the complete consumption of starting material. Then the mixture was centrifuged and filtered. The filtrate was evaporated to get unclean products and hence purified by column chromatography using hexane as the eluent. Characterization of products was done by ^1H, ^{13}C NMR and ESI-MS (see SI).

2.4. Typical procedure for synthesis of terphenyls:

To a freshly prepared solution of PdNPs (10 mL, 0.02 mmol), required amount of K_2CO_3 (2 mmol) was added followed by aryldihalides/ arylhalide (1mmol) and arylboronic acid (3mmol)/ diboronic acid (0.75mmol). Then, the reaction was allowed to stir at room temperature in open atmosphere. The reaction was monitored by TLC and was stopped after the complete consumption of starting material. The desired product got precipitated out which was separated by filtration and extracted with chloroform. The chloroform layer was evaporated to get the terphenyl in pure state.

2.5. Recyclability of the catalyst:

Recyclability of a catalyst plays an important role in the view of commercial applications. We investigated the recyclability of the catalytic system by choosing the coupling of phenylboronic acid with *p*-bromotoluene as model reactions. After one run, the reaction mixture was filtered off. The residue was washed with hexane and then with methanol for two times to extract the organic products, dried under reduced pressure and was re-dispersed in 10 mL of solvent mixture (CH_3OH: CH_3CN) for the next catalytic cycle. The catalyst system was found to be reusable without any significant loss of the catalytic activity, for at least six cycles that we followed (see Fig 1).

2.6. Hot filtration test:

The presence of colloidal Pd species in the solution was examined by hot filtration test for the coupling reaction of *p*-bromoacetophenone and phenylboronic acid. After ~25% completion of the coupling reaction, the solution was heated to 60 ^{0}C and filtered off with a 0.2 µm pore size filter under hot condition and then the filtrate was allowed to stir at room temperature with further addition of K_2CO_3 (2 mmol). Progress of the reaction was monitored by HPLC, at an interval of successive 20 min, using CH_3CN: H_2O (60:40) as a mobile phase and C18 as a reverse phase column (Fig 2). The HPLC data showed that the 90% completion of coupling reaction even after the catalyst was filtered out. Thus the filtrate presumably contains catalytically active palladium species.

3. Results and discussion

In this communication, we disclose our work on the ligand free PdNPs catalyzed Suzuki coupling reactions at ambient conditions. Initially, a model Suzuki coupling reaction was performed by reacting *p*-bromoacetophenone with phenylboronic acid. The reaction was carried out successfully at room temperature under open air without any special precautions. The results indicated that cross coupling completed within 2 h in the presence of 2 mol% of PdNPs.

The methodology developed was effectively applied to a wide range of aryl iodides and bromides. All these coupling reactions were carried out at room temperature at ambient conditions which resulted in good to excellent isolated yields of the products within short reaction times. The results presented in Table 1, summarize Suzuki cross coupling of phenylboronic acid and aryl halides containing a variety of substituents. The effect of steric hindrance has been studied by coupling *ortho*-methylphenylboronic acid with *ortho* or *para* substituted aryl bromides (Table 1, entries 15- 18). Thus, the steric crowding around the reaction sites is acceptable as it could not hinder the synthesis. However, our attempts to activate C-Cl bond for coupling reactions was found to be unsuccessful. The ICP-AES analysis revealed that there was no palladium content in the isolated biaryl derivatives.

We have also investigated the reactivity of the bromo-substituted heteroaromatics like, pyridine and pyrimide derivatives with phenylboronic acid (Table 2). The reactions proceeded smoothly with nearly quantitative yields.

The substantial catalytic activity of PdNPs was observed up to six cycles without significant loss of activity. Also, the hot filtration test indicated presence of catalytically active colloidal Pd species in the solution.

Scanning electron microscopy (SEM) used to study the surface of the catalyst. The SEM image concluded that the diameters of PdNPs are in the range of nanometers (see SI). TEM measurements revealed that size of the palladium nanoparticles ranges from ~ 4- 6nm and HRTEM picture of PdNPs shows the highly crystalline nature of the sample (see SI). Powder XRD pattern of the catalyst before the catalysis and after six catalytic cycles (see SI) are found to be identical and displayed the usual fcc lattice as expected for palladium. The XPS spectrum of PdNPs shows two well resolved peaks at 335.6 and 340.8 eV corresponding to $Pd3d_{5/2}$ and $Pd3d_{3/2}$ respectively, refer to C_{1s} = 285 eV, indicating the zerovalent Pd (see SI). The peaks at 337.4 and 342.7 eV correspond to PdO [20]. It was confirmed that 68.6% of the total Pd present in zero oxidation state and rest as a PdO by taking their relative peak areas. Thus the formation of some PdO could not be avoided, also found by other workers [21].

Terphenyls and its derivatives play promising roles in the fields of high performance engineering and optical materials, liquid crystals, as well as spacers particularly in catenanes and porphyrins chemistry [22, 23]. Moreover, terphenyls are found useful in a wide range of biological applications including neuroprotective, antithrombotic, anticoagulant and cytotoxic activities [24]. The reported methods for the preparation of terphenyls recommend the reaction of aryl zinc reagents with functionalized biphenyl nonaflates, Grignard reagents with dihalobenzenes and triazene-substituted arylboronic esters [25-27]. As of late, Suzuki cross coupling reactions are also employed for the synthesis of biaryls, terphenyls and polyaryls by using a variety of palladium sources [28-30]. Although, there are some recent reports which narrate the synthesis of biaryls using palladium nanoparticles (PdNPs), the synthesis of terphenyls is not well exploited by using these palladium nanoparticles [31-33]. In fact, most of the above quoted methods employ commercially unavailable materials and harsh reaction conditions. In this work, we report a simple and most convenient reaction pathway, in terms of synthesis as well as easy isolation of the products.

We focused our attention to synthesize terphenyls by two different ways as shown in schemes 1 and 2. The best of this methodology is the easy separation of the products. The products were precipitated out during the reaction which enabled us to separate them easily by filtration and purify by extracting with chloroform. A variety of terphenyls were synthesized, by coupling aryl di-halides with phenyl mono-boronic acids (Scheme 1, Tables 3 and 4) and aryl mono-halides with phenyl di-boronic acids (Scheme 2, Tables 5 and 6). The dibromo, diiodo and iodo-bromo derivatives (Table 3, entries 1-3), provided comparable reactivity when coupled with phenylboronic acid. Sterically hindered substrates (Table 3, entries 4-6) also afforded their corresponding terphenyls with high yields. Synthesis of *ortho* and *meta*-terphenyls is summarized in Table 4. Here also the products were isolated in good yields irrespective of position and nature of the halides (iodo or bromo) substitution.

Suzuki cross-coupling reactions between aryl bromides and aryl diboronic acids to synthesize terphenyls was first reported by Abell et al. [34] by using $Pd(PPh_3)_4$ as a catalyst under inert atmosphere. Later, Chaumeil and co-workers [35] reported synthesis of symmetric terphenyls under reflux conditions and inert atmosphere by employing $Pd(PPh_3)_4$ as a catalyst. Afterward, the use of aryl diboronic acids for the synthesis of terphenyls was not well explored. We have prepared a variety of *p*-terphenyls by coupling aryl mono-halides with phenyl di-boronic acids (Scheme 2, Tables 5 and 6). In our work, we have screened a wide range of functionalized aryl halides which contain functional groups such as NO_2, $COCH_3$, OCH_3, CHO and CN for the preparation of terphenyls in good yields. Among these reactants, 4-chloro-1-iodobenzene is more interesting (Table 5, entry 8) because the resultant product contains untouched chlorides thus offering chances for further derivatization. The ICP-AES analysis revealed that there was no palladium content in the isolated terphenyl derivatives.

Pyridine appended bidentate non-chelating ligands are useful in supramolecular coordination chemistry. We offer a simple method for the synthesis of such compounds as discussed below. The reaction of bromo susbstituted pyridine, pyrimidine and quinoline derivatives with diboronic acids were carried out to prepare corresponding ligands in reasonable yields. The data is summarized in Table 6. For entries 3 and 4, products were precipitated during the reaction whereas products of entries 1 and 2 were purified by column chromatography.

4. Conclusion

In conclusion, we have successfully screened the catalytic activity of our PdNPs towards C-C bond formation *via* Suzuki cross coupling reactions at ambient conditions. A wide variety of aryl iodides and bromides were coupled with different boronic acids within short reaction times. Synthesis of *ortho-*, *meta-* and *para*-terphenyls is demonstrated with a convenient isolation process due to precipitation of the products. A family of ligands required for supramolecular coordination chemistry can be prepared by this method. Since the reactions can be carried out in a very simple manner at room temperature without inert atmosphere this method is likely to find applications in synthesis.

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The Sequence of Schemes and Tables:

Table 1. Suzuki cross coupling reactions of aryl halides and aryl boronic acids.

Table 2. Suzuki cross coupling reactions of hetero-arenes and phenyl boronic acid.

Scheme 1. Suzuki cross coupling reactions between aryl dihalides and aryl monoboronic acids.

Scheme 2. Suzuki cross coupling reactions between aryl monohalides and aryl diboronic acids.

Table 3. Synthesis of *p*-terphenyls using phenyl boronic acid

Table 4. Synthesis of *o*-terphenyls and *m*-terphenyls

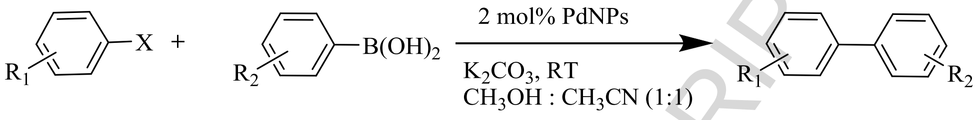
Table 5. Suzuki cross coupling reactions between aryl monohalides and phenyl diboronic acid.

Table 6. Suzuki cross coupling reactions of hetero-arenes and phenyl diboronic acids.

Figure 1. Data showing recyclability of catalyst

Figure 2. A plot showing percentage of product versus time during Suzuki coupling reaction of 4-bromoacetophenone and phenylboronic acid: (a) Standard run and (b) Run during hot filtration

Table 1
Suzuki cross-coupling reaction of aryl halides with arylboronic acid[a]

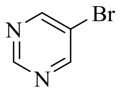
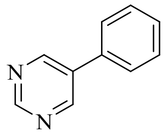
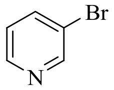
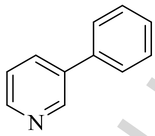
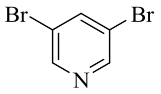
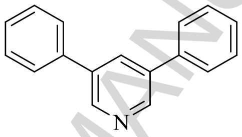
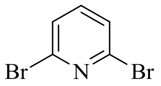
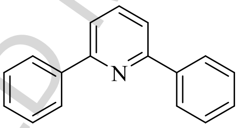


Entry	X	R_1	R_2	Time (hr)	Yield[b] (%)
1	I	H	H	2	99
2	I	4-$COCH_3$	H	2	93
3	I	4-NO_2	H	2	98
4	Br	H	H	2.5	99
5	Br	4-CH_3	H	2.5	94
6	Br	4-OCH_3	H	3.5	90
7	Br	4-CHO	H	3	95
8	Br	4-$COCH_3$	H	2	93
9	Br	4-NO_2	H	2	98
10	Br	3-NO_2	H	2.5	92
11	Br	4-CH_3	4-CH_3	2	92
12	Br	4-CH_3	4-CHO	2	90
13	Br	4-CH_3	4-$COCH_3$	2	90
14	Br	2-OCH_3	H	2.5	91
15	Br	4-$COCH_3$	2-CH_3	2.5	85
16	Br	4-CH_3	2-CH_3	2	91
17	Br	2-CH_3	2-CH_3	2.5	90
18	Br	2-OCH_3	2-CH_3	6	81

[a] Reaction conditions: ArX (1 mmol), $ArB(OH)_2$ (1.5 mmol), K_2CO_3 (2 mmol), CH_3OH: CH_3CN = 5:5 mL, RT.
[b] Isolated yields.

Table 2

Suzuki cross coupling reactions of hetero-arenes and phenyl boronic acid[a]

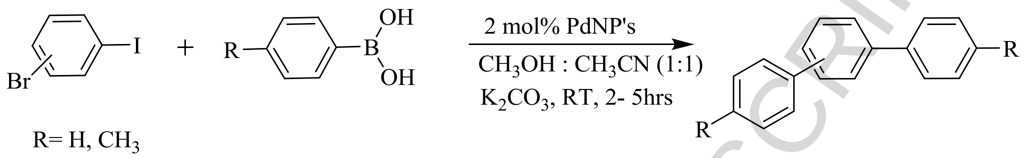
Entry	Substrate	Product	Time (h)	Yield (%)[b]
1			5	86
2			4	85
3			3.5	82
4			4.5	83

[a] Reaction conditions: ArX (1 mmol), $ArB(OH)_2$ (1.5 mmol), K_2CO_3 (2 mmol), CH_3OH: CH_3CN = 5:5 mL, RT.

[b] Isolated yields.

Scheme 1

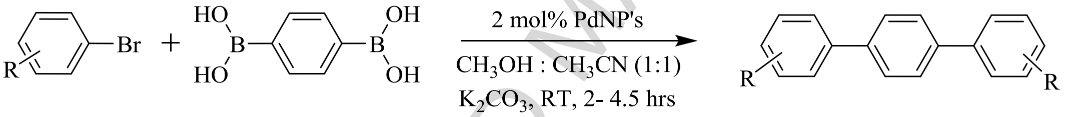
Suzuki coupling reaction between aryl dihalides and aryl monoboronic acids.



R= H, CH_3

Scheme 2

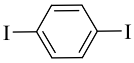
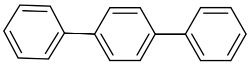
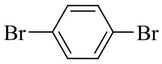
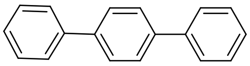
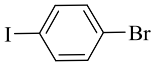
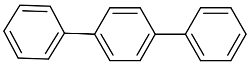
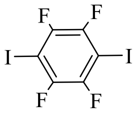
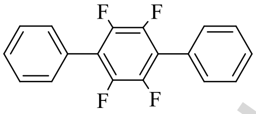
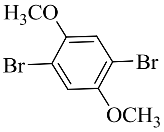
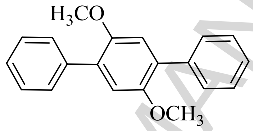
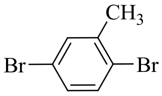
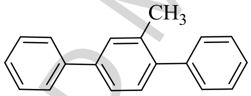
Suzuki coupling reaction between aryl monohalides and aryl diboronic acids.



R = 4-NO_2, 4-$COCH_3$, 4-CHO, 4-CH_3, 4-OCH_3, 3-OCH_3, 4-CN, 4-Cl

Table 3

Synthesis of p-terphenyls using phenyl boronic acid[a]

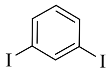
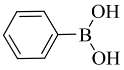
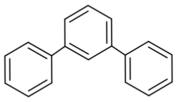
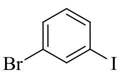
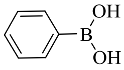
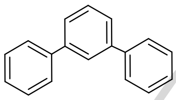
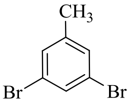
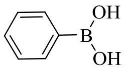
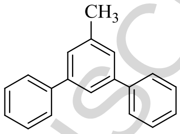
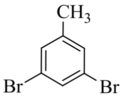
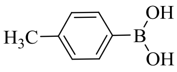
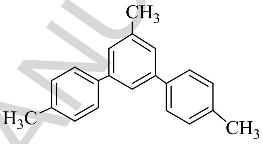
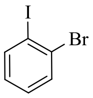
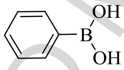
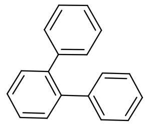
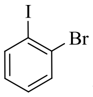
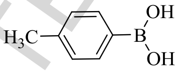
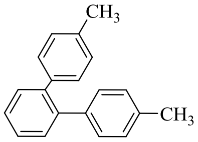
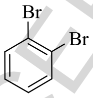
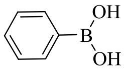
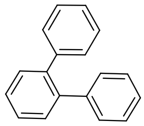
Entry	Arylhalide	Product	Time (hr)	Yield (%)[b]
1			2	88
2			2.5	84
3			2	85
4			5	78
5			3	80
6			2	83

[a] Reaction conditions: ArX (1 mmol), $ArB(OH)_2$ (3 mmol), K_2CO_3 (2 mmol), CH_3OH: CH_3CN = 5:5 mL, RT.

[b] Isolated yields.

Table 4

Synthesis of *o*-terphenyls and *m*-terphenyls [a]

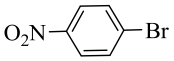
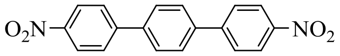
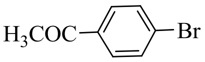
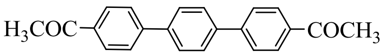
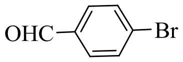
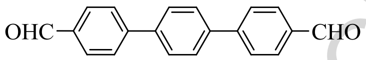
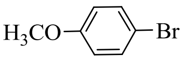
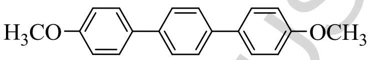
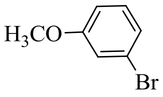
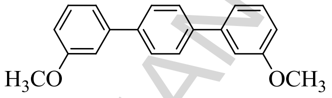
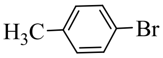
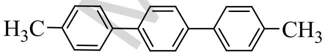
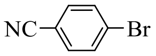
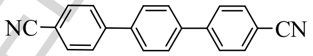
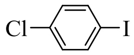
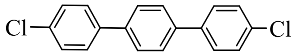
Entry	Arylhalide	Arylboronic acid	Product	Time (h)	Yield (%)[b]
1				3.5	80
2				3.5	81
3				3	85
4				3	85
5				3	85
6				2.5	86
7				3	82

[a] Reaction conditions: ArX (1 mmol), ArB(OH)$_2$ (3 mmol), K$_2$CO$_3$ (2 mmol), CH$_3$OH: CH$_3$CN = 5:5 mL, RT.

[b] Isolated yields.

Table 5

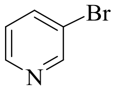
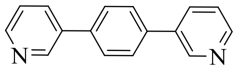
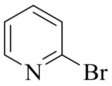
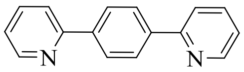
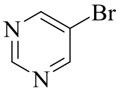
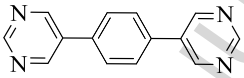
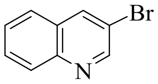
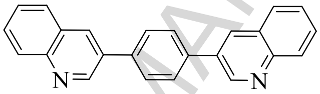
Suzuki coupling reaction between aryl monohalides and phenyl diboronic acids [a]

Entry	Arylhalide	Product	Time (h)	Yield (%)[b]
1			2	88
2			2	87
3			2	82
4			3	80
5			4.5	80
6			2.5	84
7			2	86
8			3	75

[a] Reaction conditions: ArX (1 mmol), $ArB(OH)_2$ (0.75 mmol), K_2CO_3 (2 mmol), CH_3OH: CH_3CN = 5:5 mL, RT.

[b] Isolated yields.

Table 6
Suzuki coupling reactions between hetero-arenes and phenyl diboronic acid [a]

Entry	Arylhalide	Prodcut	Time (h)	Yield (%)[b]
1			2	72
2			2.5	62
3			3.5	89
4			4	52

[a] Reaction conditions: ArX (1 mmol), $ArB(OH)_2$ (0.75 mmol), K_2CO_3 (2 mmol), CH_3OH: CH_3CN = 5:5 mL, RT.
[b] Isolated yields.

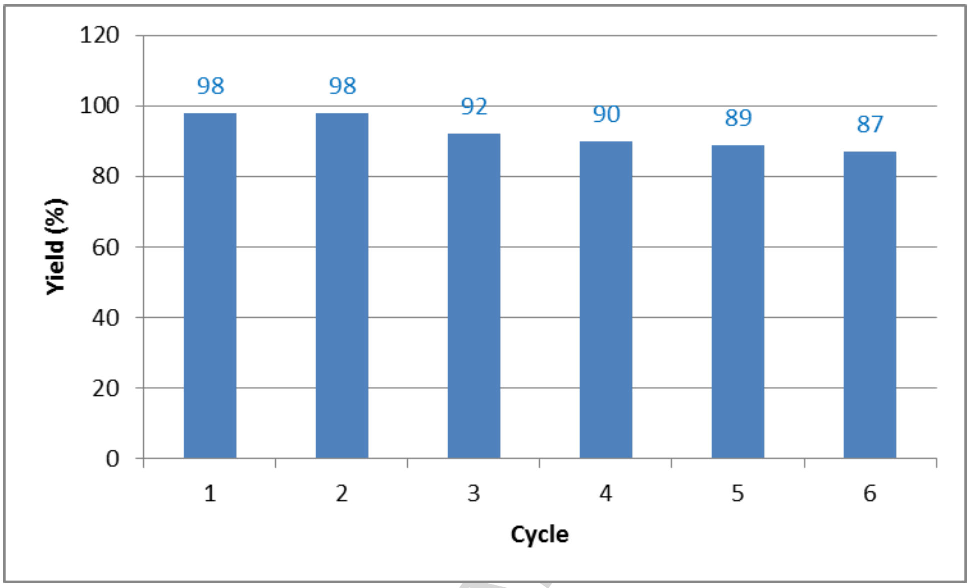


Figure 1. Data showing recyclability of catalyst

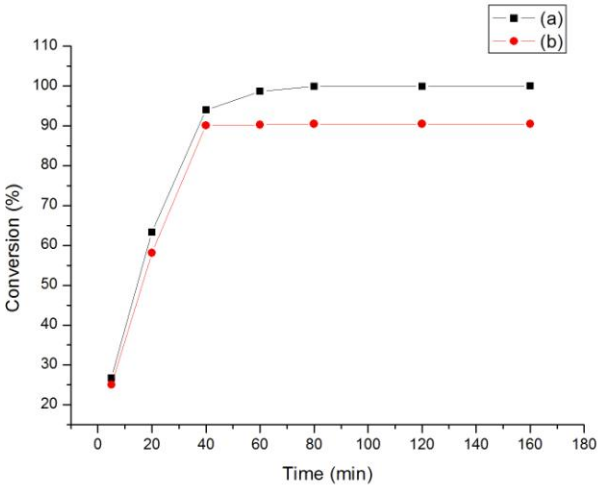
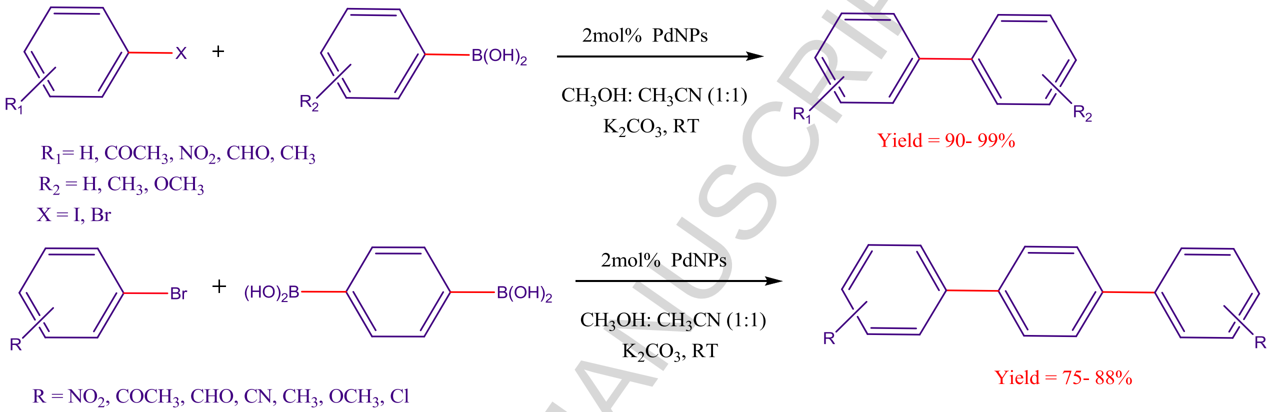


Figure 2. A plot showing percentage of product versus time during Suzuki coupling reaction of 4-bromoacetophenone and phenylboronic acid: (a) Standard run and (b) Run during hot filtration

Graphical abstract



Highlights

- A variety of biaryls and terphenyls are syntheized efficiently by ligand-free palladium nanoparticles (PdNPs) catalysed Suzuki coupling reactions in ambient conditions.
- Terphenyls are isolated from the reaction mixture as precipitates which can be simply washed to get the pure products.
- Simple method to synthesize hetero-atom bearing terphenyls through Suzuki cross coupling.