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A novel 1,2,4-triazine-functionalized polystyrene resin-supported Pd(II) complex: A copper- and solvent-free highly efficient catalyst for Sonogashira coupling reactions

Mohammad Bakherad*, Bahram Bahramian, Saeideh Jajarmi

School of Chemistry, Shahrood University of Technology, Shahrood, Iran

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ABSTRACT

A polystyrene-supported triazine palladium complex was prepared and characterized. The catalyst exhibits excellent catalytic activity and stability for the Sonogashira coupling reaction under ambient conditions. Various aryl halides were coupled with a number of terminal alkynes under air in the presence of 0.1 mol% of the catalyst to afford the corresponding coupled products in high yields. Furthermore, the heterogeneous catalyst can be readily recovered by simple filtration and reused for several times without a significant loss in its activity.

1. Introduction

Palladium-catalyzed C–C forming reactions are of great interest in synthetic organic chemistry, and the Sonogashira coupling of aryl halides with terminal alkynes is one of the most important reactions [1,2]. These reactions have been widely employed in the synthesis of natural products, biologically active molecules, and material science [3,4].

In the Sonogashira coupling reaction, copper salts usually play an important role in assisting the oxidative addition of acetylene to palladium metal; this method has drawbacks, though, including waste production and the necessity of separation after the reaction. Recently, some successful examples of copper-free Sonogashira coupling reactions have been reported [5–8].

Moreover, one of the complications with the Sonogashira coupling reactions is that they need degassed solvents, and have to be carried out under an inert atmosphere [9]. This is particularly inconvenient when the reactions are carried out in multiple vessels for library generation. Therefore, the development of a convenient method is an important objective in this effort.

The original Sonogashira reaction generally proceeds in the presence of a homogeneous palladium catalyst, which makes the separation and recovery of the catalysts tedious, if not impossible, and might result in unacceptable palladium contamination of the products. A way to overcome these difficulties would be the use of a heterogeneous palladium catalyst.

Although homogeneous catalysts have many advantages [10–13], catalyst immobilization is a well-known methodology to allow efficient catalyst separation and to obtain metal-free products [14–17]. The successful methods include immobilizing or supporting the active homogeneous catalysts onto various inorganic supports such as zeolites, mesoporous materials, alumina, silica, clays, and high surface carbons [18–20] which assist in controlling reactivity and selectivity besides the advantage of easy workability.

Macquarrie and co-workers have reported the effectiveness of N, P-chelated Pd(II) complexes immobilized on silica gel under solvent-free conditions [21]. Choudary et al. have proposed layered double hydroxide supported nanopalladium works as the Heck-type reactions including the Sonogashira coupling [22]. Vasundhara Singh et al. have described the synthesis and characterization of the recyclable and recoverable MMT-clay exchanged ammonium tagged carbapalladacycle catalyst for the Mizoroki–Heck and Sonogashira reactions in ionic liquid media [6]. Haihong Wu et al. have reported the ionic liquid functionalized phosphine-ligated palladium complex for the copper-free Sonogashira reactions under aerobic conditions [8]. Furthermore, Kenichi Komura et al. have reported the copper-free Sonogashira coupling reaction of terminal

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* Corresponding author. Tel./fax: +98 2733395441.
E-mail address: m.bakherad@yahoo.com (M. Bakherad).

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alkynes with aryl halides catalyzed by a quinoline-2-carboimine palladium complex immobilized on MCM-41 under aerobic conditions [23].

Polystyrene is one of the most popular polymeric supports used in synthetic organic chemistry because of its inexpense, ready availability, mechanical robustness, chemical inertness, and facile functionalization.

Polystyrene-supported palladium catalysts have successfully been used for the Heck [24] and Suzuki [25–27] reactions, and have shown lower levels of palladium leaching during cross-coupling. To date, a few palladium complexes on functionalized polystyrene support have been prepared and successfully used in the Sonogashira reaction.

S.M. Islam and co-workers have described synthesis and characterization of the reusable polystyrene anchored Pd(II) azo complex catalyst for the Suzuki and Sonogashira coupling reaction in water medium [28]. Moreover, Ying He et al. have developed a successful copper-free Sonogashira coupling reaction catalyzed by a reusable polystyrene-supported macrocyclic Schiff base palladium complex in water [29]. Although all the methods provide good yields, some of the reactions are sluggish, requiring high temperature for completion, and the reactions should be performed in the presence of relatively large amounts of palladium.

Our strategy for developing a versatile heterogeneous catalyst is based upon the concept of immobilizing an organometallic complex onto polystyrene. This is because the usage of polystyrene often offers enhanced catalytic activity due to its high surface area, and can be expected to have negligible leaching of precious metal species and high catalytic activity.

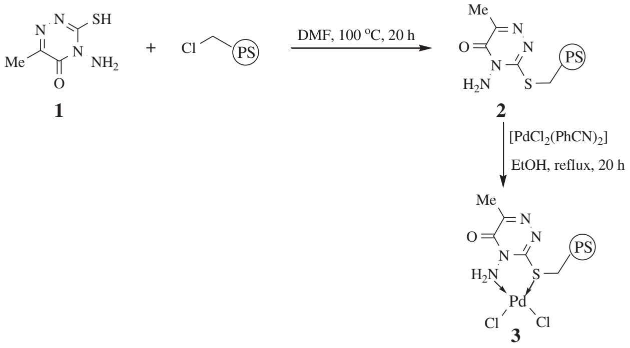
We have recently reported the synthesis and characterization of the polystyrene-supported bidentate phosphine palladium(0) complex and the polystyrene-supported palladium(II) 1-phenyl-1,2-propanedione-2-oxime thiosemi-carbazone complex, and found that these complexes are highly active and recyclable catalysts for the Sonogashira reaction of aryl halides with terminal alkynes under aerobic conditions [30,31]. Moreover, we have developed successful Suzuki, Heck, and copper-free Sonogashira reactions catalyzed by 4-amino-5-methyl-3-thio-1,2,4-triazole-functionalized polystyrene resin-supported Pd(II) under aerobic conditions in water [32]. However, to the best of our knowledge, no Sonogashira reactions catalyzed by PS-anchored Pd(II) triazine complex have yet been reported.

Thus we were encouraged to develop a further application toward the sophisticated chemical transformations, especially the carbon–carbon bond forming reactions.

Here, we report the heterogeneous copper-free Sonogashira coupling reaction of terminal alkynes with aryl halides catalyzed by the triazine-functionalized polystyrene resin-supported Pd(II) complex.

2. Results and discussion

We report here anchoring of 4-amino-5-methyl-1,2,4-triazine [33–35] on the cross linked polystyrene polymer (Scheme 1). The chelating polymeric matrix was further used for the Sonogashira reactions. A polystyrene resin (cross-linked with 2% divinylbenzene, 4–5% Cl content, 1.14–1.40 mmol/g Cl) functionalized with triazine groups was formed by heating a mixture of chloromethylated polystyrene and triazine in DMF at 100 °C for 24 h. PS-triazine prepared was characterized by elemental analysis. The nitrogen content of this resin was 3.67%. According to this value, the degree of triazine introduced to the polymer was 0.65 mmol/g of the support. This shows that only 46–57% of the total chlorine content was substituted by triazine. The reaction of polymer-bound triazine with a solution of $PdCl_2(C_6H_5CN)_2$ in ethanol under reflux conditions resulted in the covalent attachment of palladium onto the functionalized polymer. The catalyst prepared, PS-triazine-Pd(II), was characterized by FT-IR and SEM. The amount of palladium incorporated into the polymer was also determined by inductively coupled plasma (ICP), which showed a value of 0.12 mmol/g of the heterogenized catalyst.



Scheme 1. Preparation of the supported Pd-triazine complex.

In order to ascertain the functionalized polymer and its corresponding Pd complex, IR spectra were recorded separately at different stages of preparation. As it can be seen in Fig. 1, the spectrum of chloromethylated polystyrene resin shows an absorption band at 1265 cm^{-1}, attributed to the C–Cl bond, and weakened after the introduction of 4-amino-5-methyl-1,2,4-triazine. Also the stretching vibrations of the C=O band appeared at 1697 cm^{-1} for the PS-triazine-Pd(II). Moreover, the spectrum of polystyrene-supported palladium complex shows an absorption band at 3425 cm^{-1}, which is attributed to the N–H bond. Scanning electron micrographs (SEM) were reported for a single bead of pure chloromethylated polystyrene, and polymer-anchored complex to observe the morphological changes. It can easily be seen in Fig. 2 that the resin beads have different size and roughness. The presence of Pd has caused changes, demonstrated by change in the polymer particle size and roughness of the surface.

To check the potency of 1,2,4-triazine-functionalized polystyrene resin-supported Pd(II) complex, it was used in the Sonogashira coupling reaction. The coupling between phenyl acetylene and iodobenzene was chosen as the model reaction. Initially, we examined the effects of bases on the copper- and solvent-free Sonogashira reaction at room temperature. The organic bases Et_3N, DIEA, pyridine, piperidine, and pyrrolidine were investigated (Table 1, entries 1–5). As shown in Table 1, Et_3N was the best base for the reaction with high TON 990. Also the inorganic bases KOH, K_2CO_3, and Na_2CO_3 were studied but unsatisfactory yields were obtained (Table 1, entries 6–8). Then different catalyst loadings were tested for the reaction. As illustrated in Table 1, 0.05 mol% of the catalyst gave rise to extremely high TON 1800 (Table 1, entry 9) but a lower yield was obtained. Thus we selected Et_3N as the base and 0.1 mol% of the catalyst as the optimal conditions for the reaction. Since bromoarenes are cheaper and more readily available than iodoarenes and hence are synthetically more useful as educts, we examined the reaction of bromobenzene with phenyl acetylene under the above conditions and found that it was not efficient since it afforded only a 50% yield of diphenyl acetylene **6a** (entry 10). However, by changing the base to piperidine, bromobenzene could be smoothly coupled with phenyl acetylene resulting in a high yield (98%) of diphenyl acetylene (entry 13).

After the optimized conditions were found, we explored the general applicability of the PS-triazine-Pd(II) complex **3** as a catalyst for copper-free coupling of different alkynes with aryl halides containing electron withdrawing or donating substituents.

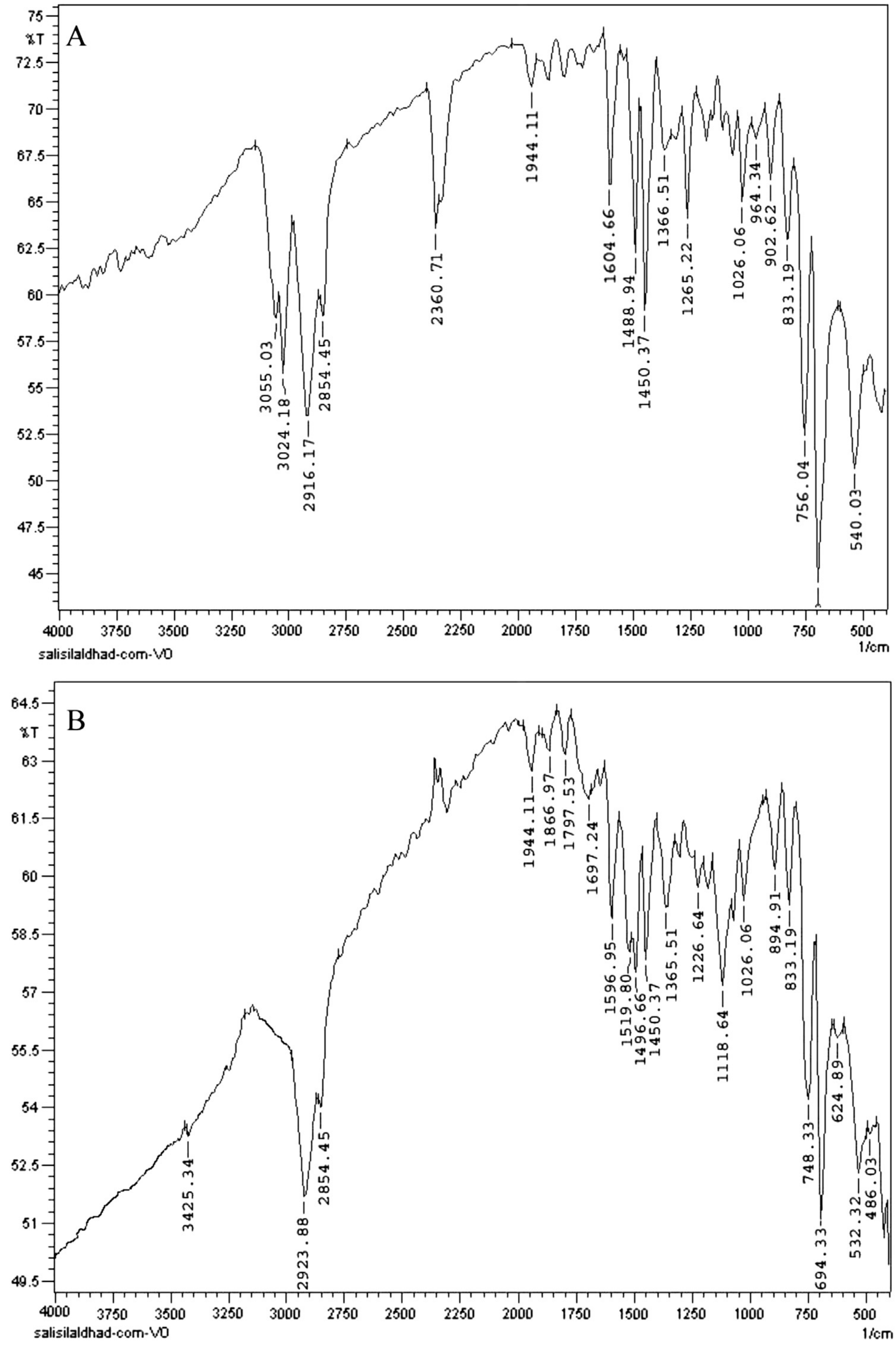


Fig. 1. FT-IR spectra of: A) chloromethylated polystyrene B) supported Pd-triazine complex.

The electron-neutral, electron-rich or electron-poor aryl iodides were reacted with phenyl acetylene to generate the corresponding cross-coupling products in high yields under the standard reaction conditions (Table 2, entries 1–6). The Sonogashira coupling of the less reactive acetylene, 1-hexyne, and propargyl alcohol with aryl iodides bearing electron-donating or electron-withdrawing groups all gave the corresponding products in high yields (entries 7–13).

To extend the scope of our work, we next investigated the coupling of various aryl bromides with terminal alkynes. As expected, aryl iodides were more reactive than aryl bromides, and the substituent effects in aryl iodides appeared to be less significant than in aryl bromides. However, as shown in Table 2, high catalytic activity was observed in the coupling of activated aryl bromides such as *p*-nitrobromobenzene (entries 15, 20, and 24) and unactivated aryl bromides such as *p*-bromoanisole (entries 18 and 22) as well as *p*-nitroiodobenzene and *p*-iodoanisol. It should be noted that the coupling reactions of the aryl chlorides (entries 26–28), also took place under similar copper-free conditions, though the reactivity was much lower than their iodo and bromo counterparts.

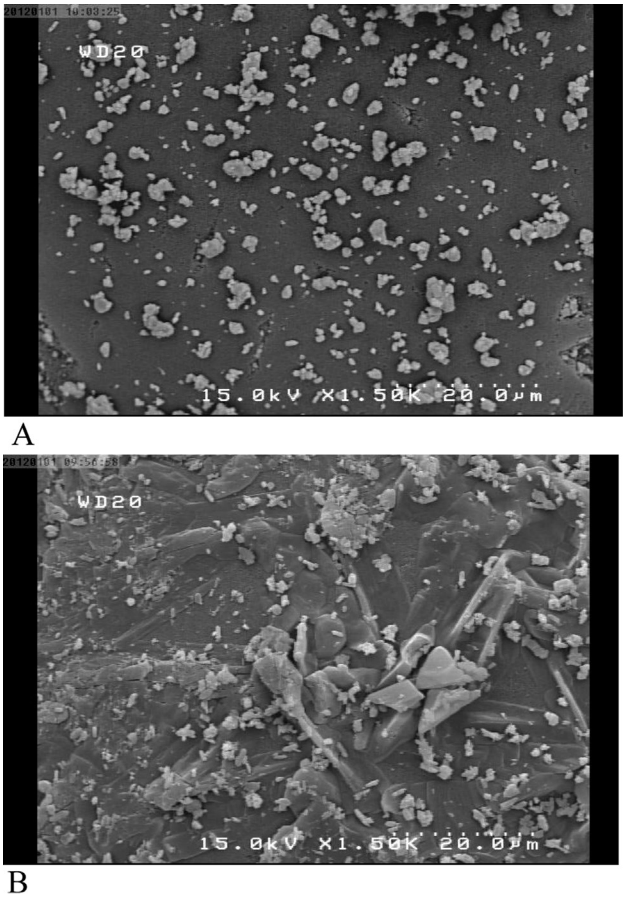
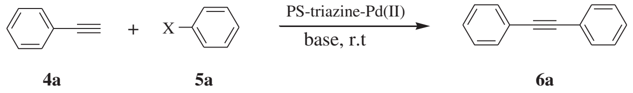


Fig. 2. Scanning electron micrograph of A) chloromethylated polystyrene B) supported Pd-triazine complex.

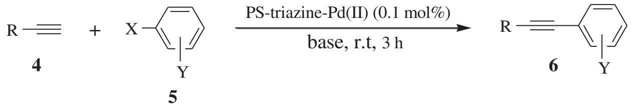
Table 1
Copper- and solvent-free coupling reaction of phenyl acetylene with aryl halides in the presence of different bases.[a]



Entry	X	Base	Cat (mol%)	Yield[b](%)	TON
1	I	Et_3N	0.1	99	990
2	I	DIEA	0.1	90	900
3	I	Pyridine	0.1	62	620
4	I	Piperidine	0.1	95	950
5	I	Pyrrolidine	0.1	60	600
6	I	KOH	0.1	52	520
7	I	K_2CO_3	0.1	57	570
8	I	Na_2CO_3	0.1	70	700
9	I	Et_3N	0.05	90	1800
10	Br	Et_3N	0.1	50	500
11	Br	DIEA	0.1	71	710
12	Br	Pyridine	0.1	70	700
13	Br	Piperidine	0.1	98	980
14	Br	Pyrrolidine	0.1	75	750
15	Br	KOH	0.1	45	450
16	Br	K_2CO_3	0.1	56	520
17	Br	Na_2CO_3	0.1	60	600

[a] Reaction conditions: phenyl acetylene (1.0 mmol), aryl halides (1.0 mmol), base (1.0 mmol), room temperature, 3 h, aerobic conditions.
[b] GC yield.

Table 2
Copper- and solvent-free Sonogashira reactions of terminal alkynes with aryl halides.[a]



Entry	R	X	Y	Base	Product	Yield[b] (%)	TON
1	Ph	I	H	Et_3N	**6a**	99	990
2	Ph	I	4-NO_2	Et_3N	**6b**	99	990
3	Ph	I	3-NO_2	Et_3N	**6c**	98	980
4	Ph	I	4-Br	Et_3N	**6d**	95	950
5	Ph	I	4-Cl	Et_3N	**6e**	94	940
6	Ph	I	4-OCH_3	Et_3N	**6f**	99	990
7	n-C_4H_9	I	H	Et_3N	**6g**	98	980
8	n-C_4H_9	I	4-NO_2	Et_3N	**6h**	99	990
9	n-C_4H_9	I	4-Cl	Et_3N	**6i**	98	980
10	n-C_4H_9	I	4-OCH_3	Et_3N	**6j**	97	970
11	CH_2OH	I	H	Et_3N	**6k**	95	950
12	CH_2OH	I	4-NO_2	Et_3N	**6l**	98	980
13	CH_2OH	I	4-$COCH_3$	Et_3N	**6m**	94	940
14	Ph	Br	H	Piperidine	**6a**	98	980
15	Ph	Br	4-NO_2	Piperidine	**6b**	99	990
16	Ph	Br	3-NO_2	Piperidine	**6c**	98	980
17	Ph	Br	4-CN	Piperidine	**6n**	98	980
18	Ph	Br	4-OCH_3	Piperidine	**6f**	97	970
19	n-C_4H_9	Br	H	Piperidine	**6g**	98	980
20	n-C_4H_9	Br	4-NO_2	Piperidine	**6h**	99	990
21	n-C_4H_9	Br	4- Cl	Piperidine	**6i**	96	960
22	n-C_4H_9	Br	4-OCH_3	Piperidine	**6j**	95	950
23	CH_2OH	Br	H	Piperidine	**6k**	97	970
24	CH_2OH	Br	4-NO_2	Piperidine	**6l**	98	980
25	CH_2OH	Br	4-$COCH_3$	Piperidine	**6m**	94	940
26	Ph	Cl	H	Piperidine	**6a**	65	650
27	Ph	Cl	4-NO_2	Piperidine	**6b**	78	780
28	Ph	Cl	4-OCH_3	Piperidine	**6f**	50	500

[a] Reaction conditions: **4** (1.0 mmol), **5** (1.0 mmol), PS-triazine-Pd(II) (0.001 mmol), base (1.0 mmol), 3 h, room temperature, aerobic conditions.
[b] GC yield.

Reusability of the catalyst is a very important theme, especially for commercial applications. Therefore, the recovery and reusability of the catalyst were investigated using the reaction of iodobenzene with phenyl acetylene as the model system. After completion of the reaction, $CHCl_3$ was added. The mixture from the first-run reaction was filtered, and the solid substance obtained was washed alternately with water, methanol, and acetonitrile. After drying under vacuum for 10 h, the recovered catalyst was reused in the same reaction under identical conditions. As a result, the recovered catalyst was used successfully for the next five subsequent reactions and exhibited consistent catalytic activity which indicated the excellent reusability of this heterogeneous catalyst (Table 3). To determine the degree of leaching of the metal from the heterogeneous catalyst, the catalyst was removed by filtration after the

Table 3
The Sonogashira reactions catalyzed by the recycled catalyst.[a]

Entry	Cycle	Yield[b]
1	1	99
2	2	99
3	3	98
4	4	97
5	5	97

[a] Reaction conditions: iodobenzene (1.0 mmol), phenyl acetylene,(1.0 mmol), PS-triazine-Pd(II) **3** (0.001 mmol), Et_3N (1.0 mmol), room temperature.
[b] GC yield.

reaction was completed, and the palladium content of the filtrate was determined by ICP. It was shown that less than 0.2% of the total amount of the original palladium species was lost into the solution during the course of the reaction. This leaching level was negligible, confirmed by the excellent recoverability and reusability of the heterogeneous catalyst.

3. Conclusion

We successfully prepared the polystyrene supported triazine palladium complex, which was used as a heterogeneous catalyst for the room temperature Sonogashira reaction. The catalyst shows high activity for the reaction affording a diverse range of aryl acetylenes in excellent yields within 3 h, and could be easily recovered by simple filtration and reused for 5 times without a significant loss in its activity. The excellent catalytic efficiency as well as the recyclability make it an attractive alternative to the large number of heterogeneous palladium catalysts reported to date.

4. Experimental

All the materials used were commercial reagent grade. Chloromethylated polystyrene (4–5% Cl and 2% cross-linked with divinylbenzene) was a product of Merck. The alkyne and aryl halide compounds were obtained from Merck or Fluka.

4.1. Preparation of polymer-anchored PS-triazine-Pd(II) ***3***

To a 250-ml round bottomed flask equipped with a magnetic stirrer bar and containing DMF (50 mL), were added chloromethylated polystyrene (2 g, 1.25 mmol/g of Cl) and 4-amino-6-methyl-3-thio-1,2,4-triazine (5.0 mmol). The reaction mixture was stirred for 20 h at 100 °C, and was subsequently filtered and washed thoroughly with DMF, and dried in vacuo for 12 h. The triazine-functionalized polymer **2** (2.0 g) was treated with ethanol (50 mL) for 30 min. An ethanolic solution of $PdCl_2(PhCN)_2$ (2.0 g) was added, and the resulting mixture was heated to 80 °C for 20 h. The resulting bright yellow colored polymer, impregnated with the metal complex, was filtered and washed with ethanol to obtain PS-triazine-Pd(II) **3** (Scheme 1).

4.2. General procedure for the Sonogashira coupling reaction

An aryl halide (1.0 mmol) and a terminal alkyne (1.0 mmol) was added to a mixture of PS-triazine-Pd(II) (0.001 mmol) and base (1 mmol) in a glass flask under vigorous stirring. The mixture was stirred at room temperature for 3 h under aerobic conditions. Upon completion of the reaction, the reaction mixture was dissolved in chloroform (2 mL). The palladium catalyst was separated from the mixture by filtration, washed with acetonitrile (10 mL), and reused in the next run. Then to the chloroform solution was added toluene (1.0 mmol) as the internal standard for GC analysis. After the analysis, the solvent was removed under vacuum, and the crude product was subjected to silica gel column chromatography using $CHCl_3$–CH_3OH (95:5) as eluent to afford the pure product.

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