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Synthesis and Characterization of the 2-Methylaminopyridine-functionalized Polystyrene Resin-supported Pd(II) Catalyst for the Mizoroki–Heck and Sonogashira Reactions in Water

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A new polystyrene-anchored Pd(II) pyridine complex is synthesized and characterized. This Pd(II) pyridine complex behaves as a very efficient heterogeneous catalyst in the Heck reaction of methyl acrylate with aryl halides and the Sonogashira reaction of terminal alkynes with aryl halides in water. Furthermore, the catalyst shows good thermal stability and recyclability. This polymer-supported Pd(II) catalyst could easily be recovered by simple filtration of the reaction mixture and reused for more than five consecutive trials without a significant loss in its catalytic activity.

Keywords: 2-Methylaminopyridine; Supported catalyst; Heck reaction; Sonogashira reaction; Aryl halides.

INTRODUCTION

The palladium-catalyzed Heck and Sonogashira reactions have been shown as an efficient method for the construction of C-C bonds, and play an important role in the pharmaceutical industry and organic synthesis.[1] These reactions are normally carried out in the homogeneous phase, using soluble palladium composites such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and $Pd(OAc)_2$ as catalysts. Despite its high reaction rate and high turnover numbers (TON), homogeneous catalysis has a number of drawbacks, in particular, the lack of reuse of the catalyst or at least the problem of recycling of the catalyst. From the standpoint of environmentally benign organic synthesis, the development of highly active and easily reusable immobilized catalysts and the use of water instead of organic compounds as solventare of great interest to chemists. Using heterogeneous catalysts has the advantage of allowing easy separation from the reaction mixture, enabling retrieval and reuse of catalyst for consecutive runs, provided that no deactivation and poisoning have occurred. There are several reports addressing the reusability of heterogeneous palladium catalysts.[2]

The immobilization methods used to deposit palladium into heterogeneous solid beds have been studied extensively, and diverse supports such as clay,[3] carbon nanofiber,[4] montmorillonite,[5] magnetic mesoporous silica,[6] zeolite,[7] and metal oxides[8] have been investigated.

In addition, the use of water in palladium-catalyzed coupling reactions has become popular because water-based synthetic processes are inherently safer as well as being inexpensive.[9]

Moreover, products can easily be isolated by extraction. Recently, a variety of aqueous catalytic systems and polymer-supported palladium catalysts for the Heck and Sonogashira cross-coupling reactions have been reported.[10]

Polystyrene is one of the most popular polymeric supports used in synthetic organic chemistry because of its cheap, ready availability, mechanical robustness, chemical inertness, and facile functionalization. S.M. Islam et al. have described synthesis and characterization of the reusable polystyrene anchored Pd(II) azo complex catalyst for the Suzuki and Sonogashira coupling reactions in water medium.[11] Ying He et al. have developed successful copper-free Sonogashira coupling reactions catalyzed by a reusable polystyrene-supported macrocyclic Schiff base palladium complex in water.[12] Moreover, Toshimasa Suzuka et al. have described an amphiphilic polystyrene-poly(ethylene glycol) (PS–PEG) resin-supported palladium–phosphine complex catalyzed Sonogashira coupling reactions of aryl halides with terminal alkynes in water.[13] Very recently, our research team have reported the synthesis and characterization of the polystyrene-supported triazole palladium(II) complex and found that this complex is a highly active and recyclable catalyst for the Suzuki, Heck, and Sonogashira reactions in water.[14] Moreover, we have developed successful Suzuki, Heck, and copper-free Sonogashira reactions catalyzed by dithizone-functionalized polystyrene resin-supported Pd(II) complex under aerobic conditions in water.[15] However, to the best of our

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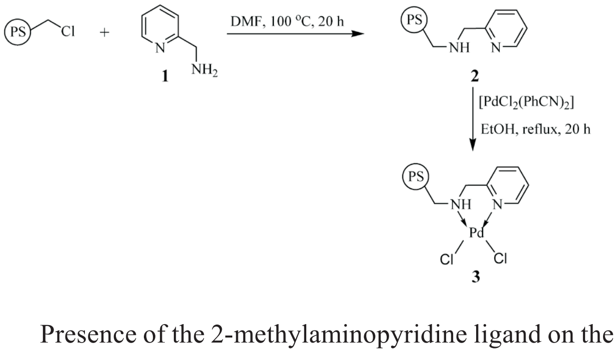
knowledge, no Sonogashira reactions catalyzed by the PS-anchored Pd(II) 2-methylaminopyridine complex have yet been reported.

Herein we report the synthesis and characterization of a new polystyrene anchored Pd(II) pyridine complex catalyst, and illustrate its application for the Heck and Sonogashira reactions in water under aerobic conditions. The catalyst shows a high catalytic activity in the coupling reactions of various aryl halides. Further easy catalyst recovery and excellent recycling efficiency of the catalyst make it an ideal system for coupling reactions in aqueous phase.

RESULTS AND DISCUSSION

We report here anchoring of 2-methylaminopyridine (**1**) on polystyrene polymer (Scheme I). The chelating polymeric matrix is further used for the Heck and Sonogashira reactions. A polystyrene resin (2% DVB) functionalized with 2-methylaminopyridine groups was formed by heating a mixture of chloromethylated polystyrene and 2-methylamino pyridine in DMF at 100 °C for 20 h. Then the 2-methylaminopyridine-functionalized polystyrene resin-supported Pd(II) [PS-mapy-Pd(II)] complex (**3**) was prepared by stirring a suspension of polymer-bound 2-methylamino pyridine (**2**) in a solution of $PdCl_2(PhCN)_2$ in refluxing EtOH for 20 h. The N content of resin was obtained to be 3.2% (0.57 mmol/g), which indicates that only 45% of total chlorines was subsitituted by 2-methylaminopyridine. The amount of palladium incorporated into the polymer was also determined by inductively coupled plasma (ICP), which showed the value of about 2.9%.

Scheme I



Presence of the 2-methylaminopyridine ligand on the polystyrene was confirmed by FT-IR spectra. The sharp C–Cl peak (due to $-CH_2Cl$ groups) at 1265 cm^{-1} in the starting polymer was practically seen as a weak band after introduction of 2-methylaminopyridine ligand on the polymer. Moreover, the spectrum of polystyrene-supported palladium complex shows an absorption band at 3473 cm^{-1}, which is attributed to the N-H bond (Fig. 1). Also, the weak bands observed at 610-650 cm^{-1} may be attributed to Pd-N vibrations.[16]

Scaninig electron micrographs (SEM) were reported for a single bead of pure chloromethylated polystyrene, and polymer-anchored complex to observe the morphological changes. As expected, the pure polystyrene bead had a smooth and flat surface, while the anchored complex showed roughening of the top layer (Fig. 2).

Efficiency of the 2-methylaminopyridine-functionalized polystyrene resin-supported Pd(II) complex (**3**) was tested in the Heck and Sonogashira reactions.

In the initial investigations, we examined the Heck coupling reaction of iodobenzene **4a** with methyl acrylate **5** as a model reaction using the polystyrene-anchored Pd(II) 2-methylaminopyridine complex **3** (1 mol%) as the catalyst

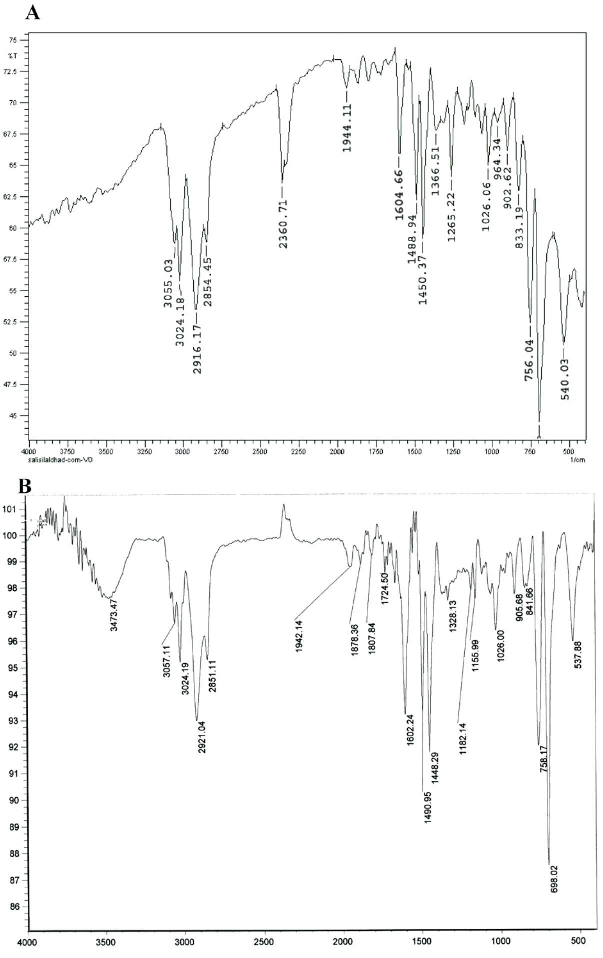


Fig. 1. FT-IR spectra of: A) chloromethylated polystyrene B) [PS-mapy-Pd(II)] complex.

at 70 ºC for 5 h (Table 1).

As it can be seen in Table 1, from the bases screened, KOH showed the best result, and the corresponding coupling product **6a** was obtained in 98% yield (Table 1, entry 6). Effect of temperature on the activity of the PS-mapy-Pd(II) complex was also studied. As the temperature decreased from 70 to 25 °C, the yield of product **6a** decreased from 98% to 50% (entry 8). A low palladium concentration gave a decreased yield (entry 9).

Thus at the optimal reaction conditions, the PS-mapy-Pd(II) complex (1 mol %) as the catalyst and KOH (2.0 equiv) as the base were used at the temperature of 70 ºC in water. As shown in Table 2, a range of aryl iodides were reacted with alkenes to give the desired products. We are pleased to find that all the reactions afford the coupling products **6** in excellent yields. The nature of the substituent, either an electron-donating group such as methoxy (entry 4) or an electron-withdrawing group such as Cl or NO_2 (entries 2, 3 and 6) on the phenyl ring of **4**, had no significant effect on the reaction outcome.

To extend the scope of our work, we next investigated the coupling reaction of aryl bromides with alkenes. As shown in Table 2, activated aryl bromides such as *p*-nitrobromobenzene underwent the Heck reaction with alkenes under similar conditions to afford the corresponding products in 85% and 88% yields respectively (entry 8 and 11), whereas, reaction of *p*-bromoanisol with methyl acrylate gave product **6d** in 60% yield (entry 9).

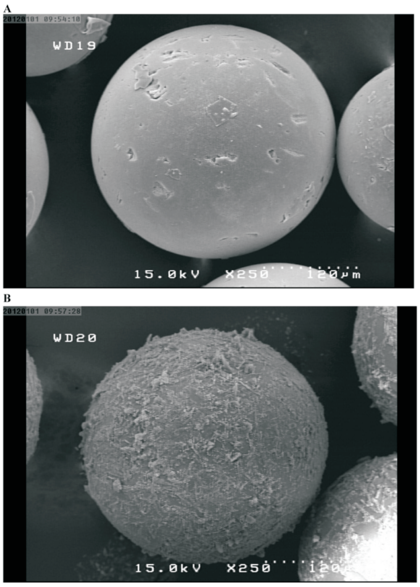
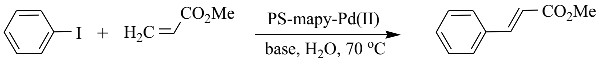


Fig. 2. Scanning electron micrograph of A) chloromethylated polystyrene B) [PS-mapy-Pd(II)] complex.

Table 1. Optimization of the conditions for Heck reaction of iodobenzene with methyl acrylate[a]

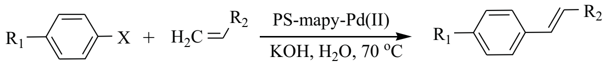


4a **5** **6a**

Entry	Base	Cat (mol %)	Yield(%)[b]
1	DIEA	1.0	95
2	Et_3N	1.0	86
3	Pyrrolidine	1.0	38
4	Piperidine	1.0	88
5	Pyridine	1.0	71
6	KOH	1.0	98
7	K_2CO_3	1.0	84
8[c]	KOH	1.0	50
9	KOH	0.5	70

[a] Conditions: iodobenzene (1.0 mmol), methyl acrylate (1.5 mmol), base (2.0 mmol), H_2O (5 mL), 70 °C, 5 h.
[b] GC yield.
[c] Reaction at 25 °C.

Table 2. Heck reactions of aryl halides with alkenes using PS-mapy-Pd(II) complex **3**[a]



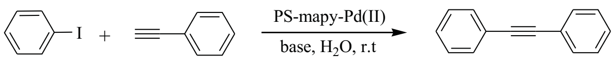
4 **5** **6**

Entry	R_1	R_2	X	Product	Yield (%)[b]
1	H	CO_2Me	I	**6a**	97
2	Cl	CO_2Me	I	**6b**	98
3	NO_2	CO_2Me	I	**6c**	98
4	MeO	CO_2Me	I	**6d**	95
5	H	Ph	I	**6e**	95
6	NO_2	Ph	I	**6f**	96
7	H	CO_2Me	Br	**6a**	72
8	NO_2	CO_2Me	Br	**6c**	85
9	MeO	CO_2Me	Br	**6d**	60
10	H	Ph	Br	**6e**	75
11	NO_2	Ph	Br	**6f**	88

[a] Conditions: aryl halide (1.0 mmol), alkene (1.5 mmol), PS-mapy-Pd(II) (0.01 mmol), KOH (2.0 mmo), H_2O (5 mL), 70 °C, 5 h.
[b] GC yield.

Another important Pd-catalyzed coupling reaction is the alkynylation of aryl halides, i.e. the Sonogashira reaction. The application of this reaction is to be found in the synthesis of numerous natural products including enediyne antibiotics.[17] Thus we next investigated the polystyrene-anchored Pd(II) 2-methylaminopyridine complex catalytic

Table 3. Optimization of the conditions for the Sonogashira reaction of phenyl acetylene with iodobenzene[a]

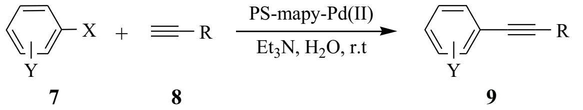


Entry	Base	Cat (mol%)	Yield (%)[b]
1	Et_3N	1.0	98
2	DIPEA	1.0	80
3	pyridine	1.0	82
4	piperidine	1.0	93
5	pyrrolidine	1.0	91
6	KOH	1.0	95
7	K_2CO_3	1.0	80
8	Na_2CO_3	1.0	30
9	Et_3N	0.5	82

[a] Conditions: phenylacetylene (1.0 mmol), iodobenzene (1.0 mmol), base (2.0 mmol), H_2O (3 mL), room temperature, 3 h.

[b] GC yield.

Table 4. Copper-free Sonogashira reactions of terminal alkynes with aryl halides[a]



Entry	R	X	Y	Product	Yield (%)[b]
1	Ph	I	H	**9a**	98
2	Ph	I	4-NO_2	**9b**	99
3	Ph	I	4-Cl	**9c**	97
4	Ph	I	4-Br	**9d**	96
5	Ph	I	4-OCH_3	**9e**	95
6	n-C_4H_9	I	H	**9f**	97
7	n-C_4H_9	I	4-Cl	**9g**	98
8	n-C_4H_9	I	4-Br	**9h**	97
9	n-C_4H_9	I	4-NO_2	**9i**	98
10	n-C_4H_9	I	4-OCH_3	**9j**	95
11	Ph	Br	H	**9a**	96
12	Ph	Br	4-NO_2	**9b**	98
13	Ph	Br	3-NO_2	**9k**	97
14	Ph	Br	4-CN	**9l**	98
15	Ph	Br	4-F	**9m**	94
16	Ph	Br	4-OCH_3	**9e**	94
17	n-C_4H_9	Br	H	**9f**	93
18	n-C_4H_9	Br	4-NO_2	**9i**	95
19	n-C_4H_9	Br	4-OCH_3	**9j**	91
20	Ph	Cl	H	**9a**	40
21	Ph	Cl	4-NO_2	**9b**	50
22	Ph	Cl	4-Cl	**9c**	46

[a] Reaction conditions: aryl halide (1.0 mmol), terminal alkyne (1.0 mmol), PS-mapy-Pd(II) (0.01 mmol), Et_3N (2.0 mmol), H_2O (3 mL), room temperature, 3 h.

[b] GC yield.

system for the copper-free Sonogashira coupling reaction in water. Since no copper salt was used, the undesired formation of the oxidative homocoupling product, a diyne, was avoided. We employed the copper-free coupling reaction of iodobenzene (1.0 mmol) with phenylacetylene (1.0 mmol) as a model reaction using complex **3** (1 mol%) as the catalyst at room temperature to study the effect of the base on the reaction (Table 3). Among various bases, Et_3N was found to be the best (entry 1). A low palladium concentration gave a decreased yield (entry 9).

After the optimized conditions were found, we explored the general applicability of the PS-mapy-Pd(II) complex **3** as a catalyst for the copper-free coupling of different alkynes **8** with aryl halides **7** containing electron-withdrawing or donating substituents. The results obtained are shown in Table 4.

The coupling of phenylacetylene with iodobenzene took place smoothly at room temperature in the presence of Et_3N (2 mmol) and palladium (1 mol%) of the PS-mapy-Pd(II) complex **3** to give a quantitative yield of diphenylacetylene (entry 1). The Sonogashira coupling of phenylacetylene with *p*-iodoanisol bearing electron-donating groups at their para-positions gave the corresponding biarylacetylene **9e** in 95% yield (entry 5). *p*-Nitroiodobenzene, *p*-chloroidobenzene, and *p*-bromoiodobenzene, having electron-deficient aromatic rings, also underwent the Sonogashira coupling with phenylacetylene under similar conditions to afford the corresponding biarylacetylenes **9b**, **9c**, and **9d** in excellent yields (entries 2, 3, and 4).

The Sonogashira coupling of the less reactive acetylene, 1-hexyne with aryl iodides bearing electron-donating or electron-withdrawing groups all gave the corresponding products in high yields (entries 6-10).

To further 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 the aryl iodides appeared to be less significant than in the aryl bromides. However, as shown in Table 4, high catalytic activity was observed in the coupling of aryl bromides such as *p*-nitrobromobenzene (entries 12, and 18) and *p*-bromoanisole (entries 16 and 19) as well as *p*-nitroiodobenzene (entries 2 and 9) and *p*-iodoanisol (entries 5 and 10). Moreover, *m*-nitrobromobenzene, *p*-bromobenzonitrile, and *p*-fluorobromobenzene, having electron-deficient aromatic rings, also underwent the Sonogashira coupling reaction with terminal alkynes under similar conditions to afford the corresponding products in excellent yields. The electron-neutral, or electron-poor aryl chlorides were reacted with phenylacetylene to generate the corresponding cross-coupling products in low yields under the standard reaction conditions (entries 20-22).

One of the purposes for designing this heterogeneous catalyst is to enable recycling of the catalyst for use in subsequent reactions. The reusability of the catalyst was tested upon the reaction of iodobenzene with methyl acrylate (Heck reaction) and iodobenzene with phenylacetylene (Sonogashira reaction) as the representative reactants and in the presence of 1 mol% of PS-mapy-Pd(II) in order to study the recyclability of this heterogeneous catalyst. Similarly, the reactions for the repeated runs were conducted after separation of the organic compounds from the reaction mixture by extraction, and the recovered solid catalyst was recycled for another run. The recycling process was repeated for five cycles without any significant loss of efficiency (Table 5). To determine the degree of leaching of the metal from the heterogeneous catalyst, the catalyst was removed by filtration after the 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.

Table 5. The Heck and Sonogashira reactions catalyzed by the recycled catalyst[a]

Entry	Cycle	Heck yield (%)[b]	Sonogashira yield (%)[b]
1	1	98	98
2	2	98	98
3	3	97	96
4	4	95	95
5	5	93	93

[a] Reaction conditions: iodobenzene (1.0 mmol), methyl acrylate (Heck reaction) (1.5 mmol), iodobenzene (1.0 mmol), phenyl acetylene (Sonogashira reaction) (1.0 mmol), PS-mapy-Pd(II) complex (0.01 mmol), base (2.0 mmol), 70 °C (for Heck reactions), room temperature (for Sonogashira reactions).

[b] GC yield.

CONCLUSION

The first example of the Heck and Sonogashira reactions catalyzed by the cheap and air stable 2-methylamino-pyridine-functionalized polystyrene resin-supported Pd(II) complex as catalyst was described. The ease of preparation of the complex, indefinite shelf life, and stability toward air make it an ideal complex for the above transformations. Moreover, the catalyst could be reused for five consecutive cycles without a significant loss in its catalytic activity. These advantages make the process highly valuable from the synthetic and environmental points of view.

EXPERIMENTAL

Preparation of polymer-anchored PS-mapy-Pd(II) 3: To a 250-mL round bottom flask equipped with a magnetic stirrer bar and containing DMF (15 mL) were added chloromethylated polystyrene (2 g, 1.25 mmol/g of Cl) and 2-methylaminopyridine (7.0 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 2-methylaminopyridine functionalized polymer **2** (2.0 g) was treated with ethanol (30 mL) for 30 min. An ethanolic solution of $PdCl_2(PhCN)_2$ (1.0 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-mapy-Pd(II) **3** (Scheme I).

General procedure for the Heck reaction: A mixture of an aryl halide (1.0 mmol), an alkene (1.5 mmol), PS-mapy-Pd(II) (0.01 mmol), and KOH (2.0 mmol) in water (5 mL) was stirred at 70 ºC for 5 h. After completion of the reaction, the mixture was filtered to recover the catalyst. The polymer was washed with water and acetonitrile, vacuum-dried, and stored for a new run. After GC 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.

General procedure for the Sonogashira coupling reaction: An aryl halide (1.0 mmol) and a terminal alkyne (1.0 mmol) were added to a mixture of PS-mapy-Pd(II) (0.01 mmol), Et_3N (2.0 mmol), and water (3 mL) in a glass flask under vigorous stirring. The mixture was stirred at room temperature for 3 h under aerobic conditions. After completion of the reaction, the mixture was filtered to recover the catalyst. The polymer was washed with water and acetonitrile, vacuum-dried, and stored for a new run. After GC analysis, the solvent was removed under vacuum, and the crude product was subjected to silica gel column chromatography using $CHCl_3$–CH_3OH (95:35) as eluent to afford the pure product.

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