Polystyrene-Supported Palladium(II) Ethylenediamine Complex: A Highly Active and Recyclable Catalyst for the Synthesis of 2-Benzylimidazo[2,1-*b*]pyridines Through Heteroannulation of Acetylenic Compounds

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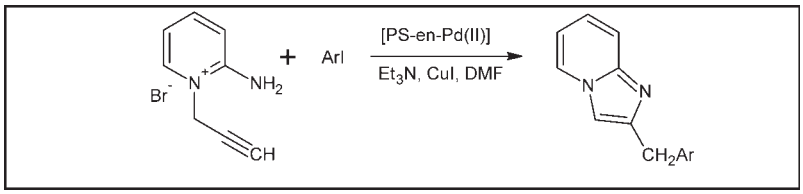

The polymer-supported palladium(II) ethylenediamine [PS-en-Pd(II)] complex is a highly active catalyst for the heterocyclization that takes place during the Sonogashira reaction between an aryl iodide and 2-amino-1-(2-propynyl)pyridinium bromide. This heterogeneous palladium catalyst can readily be recovered from the reaction medium by simple filtration and reused without a significant loss in its activity.

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INTRODUCTION

Sonogashira reaction, the palladium-catalyzed cross-coupling reaction of terminal alkynes with aryl and vinyl halides, is one of the most important, powerful, and versatile tools in organic synthesis, and it has been widely applied to diverse areas such as natural product synthesis and material science [1]. The reaction generally proceeds in the presence of a homogeneous palladium catalyst, which makes the catalyst recovery a tedious operation and might result in unacceptable palladium contamination of the product. From the standpoint of green chemistry, the development of more environmentally benign conditions for the reaction, for example, the use of a heterogeneous palladium catalysts' would be desirable [2].

So far, cross-linked polystyrene or silica-supported palladium catalysts have been used for the Sonogashira reaction [3]. Unfortunately, they often result in lower catalytic activity compared with their soluble counterparts. To overcome this limitation, a novel methodology for creating insoluble and highly active catalysts is needed. Our approach was guided by three imperatives: (1) the support should be easily accessible; (2) starting with readily available and inexpensive reagents; and (3) the ligand anchored on the support should be air stable at room temperature, which should allow its storage in normal bottles with unlimited shelf life. To date, a few palladium complexes on functionalized polystyrene support have been prepared and successfully used in organic reactions [4]. However, to the best of our knowledge, there has been no examples involving arylation of imidazopyridine by [PS-en-Pd(II)] catalyzed (Sonogashira coupling) reactions described to date.

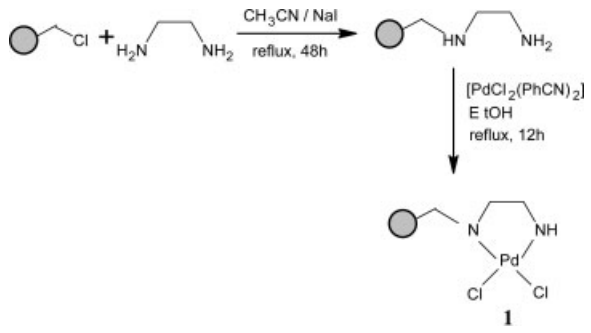
In continuation of our recent studies on the synthesis of fused heterocycles and the Pd-catalyzed reactions of acetylenes leading to heterocyclic compounds of biological significance [5], we became interested in developing a novel synthesis route to 2-substituted imidazo[1,2-*a*]pyridines. In this article, we wish to report the synthesis of the first polystyrene-supported palladium(II) ethylenediamine complex, abbreviated as PS-en-Pd(II), and its catalytic properties in the Sonogashira coupling reaction for the synthesis of imidazo[1,2-*a*]pyridines [6]. The supported catalyst could be reused several times without a significant degradation in its catalytic activity.

RESULTS AND DISCUSSION

We used the well-known chloromethylated polystyrene cross-linked with 2% divinylbenzene as support, because it is flexible enough and allows metallic atoms to be graft on *via* the ligands that are attached to the polymer beads. Reaction of the polystyrene resin with ethylenediamine in acetonitrile under reflux and the subsequent reaction of the aminated polystyrene with a solution of $[PdCl_2(C_6H_5CN)_2]$ in ethanol gave the polymer-supported palladium(II) complex catalyst **1** (Scheme 1).

Successful functionalization of the polymer was confirmed by elemental analysis. The *N* content of the resin was found to be 2.42% (0.82 mmol/g), which indicates

Scheme 1 Polystyrene-supported palladium(II) ethylenediamine complex **1**.



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that only 58% of the total chlorines were substituted by amine. The metal loading of the polymer-supported palladium complex, which was determined by neutron activation analysis (NAA), was found to be 4.35% (0.41 mmol/g). In the IR spectrum of the polymer-bound ethylenediamine, the sharp C—Cl peak (due to the —CH_2Cl groups) at 1264 cm^{-1} in the starting polymer was practically omitted or was seen as a weak band after introduction of ethylenediamine and palladium on the polymer. The various IR frequencies for the catalyst were assigned as (Pd—N) ≈ 506 cm^{-1}, (C—N) ≈ 1100 cm^{-1}, and (N—H) ≈ 3400 cm^{-1}.

To evaluate the catalytic activity of the first polymer-supported PS-en-Pd(II) complex, the heterocyclization during Sonogashira coupling of 2-amino-1-(2-propynyl)-pyridinium bromide **3** with the aryl iodides **4a–i** was studied (Scheme 2). The reactions were performed under conditions similar to those used in the corresponding homogenous reactions. The influences of the bases, solvents, amounts of copper(I) iodide, and the catalyst on the catalytic property of the [PS-en-Pd(II)] complex were investigated using the coupling reaction of compound **3** with *o*-iodonitrobenzene. The results are tabulated in Table 1.

Among the bases tested, triethylamine proved to be the most efficient, and among the solvents used, dimethylformamide was the best choice. Increasing the amount of the palladium catalyst could shorten the reaction time, but does not increase the yield (entry 11). Low palladium concentration often prolonged the reaction time and decreased the yield (entries 12 and 13). We also found that with increase in the amount of copper(I) iodide, the reaction yield did not increase (entry 14). No product was obtained under copper-free conditions (entry 15). Copper(I) iodide was found to be an essential cocatalyst.

The reactions had to be carried out under an argon atmosphere, and we had to degas the mixture of DMF and triethylamine prior to use. The experimental results are summarized in Table 2. As it can be seen in this table, reaction of the aryl iodides with compound **3** proceeded smoothly under very mild conditions, giving the corresponding products in excellent yields.

The stability of [PS-en-Pd(II)] was studied in repeated Sonogashira coupling reactions. The coupling reaction of *o*-iodonitrobenzene with compound **3** was chosen as a model substrate to study the catalyst reuse and stability. The catalyst was separated from the reaction mixture after each experiment by filtration, washed with water and acetonitrile, and dried carefully before using it in the subsequent run. The reaction promoted by the fifth recycled catalyst gave **5a** in 75% yield (Table 3, entry 5).

The low yield could be due to the formation of by-products. For instance, formation of a coupled intermediate without ring formation or ring closure without participation of the aryl group could be responsible for the low yield.

This reusability demonstrates the stability of the heterogeneous catalyst. Although no significant change in the activity of the catalyst was observed, we performed analysis of the catalyst after the fifth run in order to determine any change in the catalyst structure. The nature of the recovered catalyst was traced by IR spectroscopy. The results indicated that the catalyst showed no change in its IR spectrum after reuse for several times.

To determine the absolute amount of the palladium species leached into the solution, the crude reaction mixtures were evaporated to dryness and analyzed by NAA. It was shown that less than 0.5% of the total amount of the original palladium species was lost into the solution during the course of the reaction.

In conclusion, we developed a reusable heterogeneous catalyst [PS-en-Pd(II)] by first reacting the commercially available cross-linked chloromethylated polystyrene with ethylenediamine and the subsequent reaction of the product thus formed with dibenzonitrile palladium chloride. It efficiently catalyzed the heterogeneous Sonogashira coupling followed by cyclization reaction for the syntheses of various 2-substituted imidazopyridines. The

Scheme 2

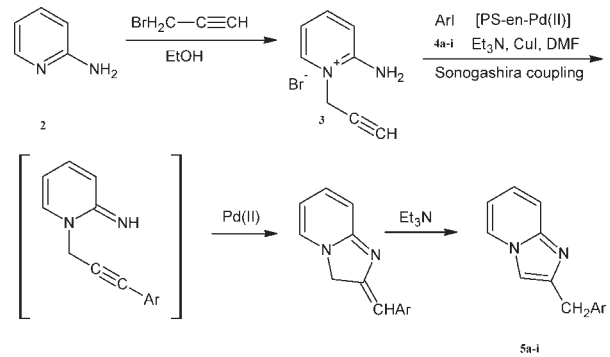


Table 1

Heterocyclization during the Sonogashira coupling of *o*-iodonitrobenzene with compound **3** in the presence of several bases, solvents, and amounts of catalyst.[a]

Entry	Base	Solvent	[PS-en-Pd(II)] (mmol)	CuI (mmol)	Time (hours)	Yield (%)
1	Et_3N	Dioxan	0.03	0.2	14	30
2	Et_3N	CH_3CN	0.03	0.2	16	45
3	Et_3N	DMF	0.03	0.2	12	92
4	Et_3N	Et_3N	0.03	0.2	15	25
5	DIEA	DMF	0.03	0.2	17	60
6	DIEA	DIEA	0.03	0.2	16	50
7	Piperidine	DMF	0.03	0.2	14	35
8	Piperidine	Piperidine	0.03	0.2	16	32
9	Pyrrolidine	DMF	0.03	0.2	14	23
10	Pyrrolidine	Pyrrolidine	0.03	0.2	19	20
11	Et_3N	DMF	0.06	0.4	10	88
12	Et_3N	DMF	0.02	0.12	20	75
13	Et_3N	DMF	0.005	0.03	24	62
14	Et_3N	DMF	0.03	0.3	14	87
15	Et3N	DMF	0.03	0	24	0

[a] All reactions were performed using 1.5 mmol of **3**, 1.0 mmol of *o*-iodonitrobenzene, 0.06 mmol of PPh_3, 3.0 mmol of base, and 5 mL of solvent at room temperature.

catalyst could be reused five times with reasonable catalytic activity on the fifth cycle. The advantages of our heterogeneous catalytic system over others are as follows: (1) the catalyst could be conveniently prepared from commercially available reagents; and (2) excellent performance and reusability of the catalyst.

EXPERIMENTAL

All the reagents used were of commercial reagent grade. Chloromethylated polystyrene (4–5% Cl and 2% cross-linked with divinylbenzene) was a Merck product. Scanning electron micrographs of the catalyst and polymer were taken on a SEM Philips XL 30. The IR spectra were obtained as potassium bromide pellets in the range 400–4000 cm^{-1} on a Shimadzo Model 460. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker BRX 500 AVANCE spectrometer. The elemental analyses were obtained on a Thermo Finnigan Flash EA microanalyzer.

Preparation of polymer-bound ethylenediamine. To functionalize the polymer support with ethylenediamine, it was prepared by the following procedure: to a 250-mL round bottom flask equipped with a magnetic stir bar containing 120 mL acetonitrile, chloromethylated polystyrene (2 g, 2.5 mmol/Cl), and ethylenediamine (25 mmol), NaI (0.13 mmol) was added. The reaction mixture was refluxed for 48 h at which time the solid material and was collected by filtration and washed with 5 × 40 mL of CH_3CN, 5 × 40 mL of CH_3OH:K_2CO_3 (1 *M*) (1:1, v/v), 5×40 mL of CH_3OH:H_2O (1:1 v/v), and 3 × 40 mL of diethyl ether, and was subsequently dried in an oven.

Preparation of polystyrene-supported PS-en-Pd(II) complex (1). The functionalized polymer was kept in contact with 100 mL of ethanol for 30 min. An ethanolic solution of 0.25 g of $[PdCl_2(C_6H_5CN)_2]$ was added to it and heated to 50° for 6 h. The bright yellow colored polymer, impregnated with the metal complex, was collected by filtration, washed thoroughly with ethanol, and finally dried in vacuum at 70° for 24 h.

Synthesis of 2-amino-1-(2-propynyl) pyridinium bromide (3). A mixture of 2-amino pyridine (1.9 g, 20 mmol) and propargyl bromide (2 mL, 24 mmol) in ethanol (10 mL) was heated under reflux for 1 h. The precipitate formed was filtered off and recrystallized from ethanol to afford the title compound.

80% yield; m.p. 168–169°; ^1H NMR (DMSO-d_6): δ 3.85 (s, 1H, CH), 5.12 (s, 2H, CH_2), 6.85–8.23 (m, 4H, PyH), 8.72(s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 43.86, 76.04, 80.46, 114.00, 115.84, 139.83, 143.57, 154.52; ir (potassium bromide): 3300, 3200, 2100 cm^{-1}; Anal. Calcd. for $C_8H_9BrN_2$ (213.06): C, 45.09; H, 4.26; N, 13.15. Found: C, 45.50; H, 4.08; N, 13.51.

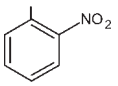
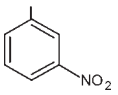
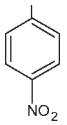
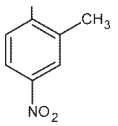
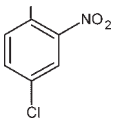
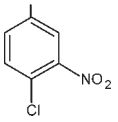
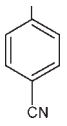
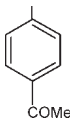
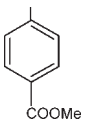
Synthesis of 2-substituted imidazo[2,1-b]pyridines (5a–i). A mixture of the aryl iodides (1.0 mmol), [(PS-en-Pd(II)] (60 mg, 0.03 mmol Pd), CuI (0.2 mmol), and triethylamine (3 mmol) was stirred in DMF (5 mL) at room temperature under an argon atmosphere. 2-Amino-1-(2-propynyl)pyridinium bromide (3) (1.50 mmol) was then added, and the mixture was stirred at room temperature for 12–16 h. After completion of the reaction, the resulting solution was concentrated *in vacuo*, and the crude product was subjected to column chromatography using $CHCl_3$:CH_3OH (95:5, v/v) as eluent to afford the pure product (Table 1).

2-(2-Nitrobenzyl)imidazo[1,2-a]pyridine (5a). This compound was obtained as a white solid. ^1H NMR (DMSO-d_6): δ 4.46(s, 2H, CH_2), 6.98–8.00 (m, 8H, PyH, ArH), 8.66 (s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 34.25, 114.60, 116.24, 122.85, 123.15, 129.10, 130.22, 130.95, 132.15, 134.27, 136.23, 139.12, 146.25, 148.33; ir (potassium bromide): 1510, 1340 cm^{-1}; Anal. Calcd. for $C_{14}H_{11}N_3O_2$ (253.25): C, 66.4; H, 4.38; N, 16.59. Found: C, 66.12; H, 4.11; N, 16.65.

2-(3-Nitrobenzyl)imidazo[1,2-a]pyridine (5b). This compound was obtained as a white solid. ^1H NMR (DMSO-d_6): δ

Table 2

Melting points and yields of 2-benzylimidazo [1,2-*a*]pyridines **5a–i**.[a]

Product	Ar	Time (hours)	Mp (°C)	Yield (%)
5a		12	250–251	92
5b		14	294–295	71
5c		14	256–257	87
5d		16	263–264	72
5e		16	231–232	60
5f		14	246–247	83
5g		13	210–211	85
5h		15	236–237	77
5i		16	260–261	89

[a] All reactions were performed using 1.5 mmol of **3**, 1.0 mmol of aryliodides, 0.2 mmol of CuI, 0.03 mmol of [PS-en-Pd(II)], 0.06 mmol of PPh_3, 3.0 mmol of Et_3N, and 5 mL of DMF at room temperature.

4.29 (s, 2H, CH_2), 6.97–8.32 (m, 8H, PyH, ArH), 8.58(s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 33.92, 114.35, 116.55, 122.30, 127.95, 128.26, 130.15, 130.90, 133.17, 133.86, 135.86, 138.60, 146.20, 147.31; ir (potassium bromide): 1500, 1335 cm^{-1}; Anal. Calcd. for $C_{14}H_{11}N_3O_2$ (253.25): C, 66.4; H, 4.38; N, 16.59. Found: C, 66.51; H, 4.42; N, 16.37.

2-(4-Nitrobenzyl)imidazo[1,2-a]pyridine (5c). This compound was obtained as a white solid. ^{1}H NMR (DMSO-d_6): δ 4.31(s, 2H, CH_2), 6.96–8.31 (m, 8H, PyH, ArH), 8.65(s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 34.21, 114.60, 116.76, 123.25, 128.30, 131.10, 131.87, 132.90, 135.82, 138.86, 145.27, 147.32; ir (potassium bromide): 1510, 1340 cm^{-1}; Anal. Calcd. for $C_{14}H_{11}N_3O_2$ (253.25): C, 66.4; H, 4.38; N, 16.59. Found: C, 66.22; H, 4.26; N, 16.41.

2-(2-Methyl-4-nitrobenzyl)imidazo[1,2-a]pyridine (5d). This compound was obtained as a white solid. ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 3H, CH_3), 4.28 (s, 2H, CH_2), 7.00–8.02 (m, 7H, PyH, ArH), 8.58(s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 20.03, 33.95, 114.86, 116.46, 121.65, 121.97, 125.30, 128.06, 130.83, 131.38, 133.05, 136.21, 139.13, 146.35, 147.86; ir (potassium bromide): 1520, 1340 cm^{-1}; Anal.

Table 3

Heterocyclization during Sonogashira coupling of *o*-iodonitrobenzene with compound **3** catalyzed by recycled catalyst.[a]

Entry	Catalyst cycle	Isolated yield (%)
1	1st	92
2	2nd	90
3	3rd	87
4	4th	82
5	5th	75

[a] All reactions were performed using 1.5 mmol of **3**, 1.0 mmol of *o*-iodonitrobenzene, 0.2 mmol of CuI, 0.03 mmol of [PS-en-Pd(II)], 0.06 mmol of PPh_3, 3.0 mmol of Et_3N, and 5 mL of DMF at room temperature.

Calcd. for $C_{15}H_{13}N_3O_2$ (267.28): C, 67.40; H, 4.90; N, 15.72. Found: C, 66.91; H, 4.24; N, 15.91.

2-(4-Chloro-2-nitrobenzyl)imidazo[1,2-a]pyridine (5e). This compound was obtained as a white solid. ^{1}H NMR (DMSO-d_6): δ 4.41 (s, 2H, CH_2), 6.94–8.32 (m, 7H, PyH, ArH), 8.56 (s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 33.81, 114.16, 116.32, 123.30, 128.36, 130.04, 130.64, 131.24, 132.43, 134.27, 137.46, 138.87, 144.30, 148.68; ir (potassium bromide): 1510, 1350 cm^{-1}; Anal. Calcd. for $C_{14}H_{10}ClN_3O_2$ (287.70): C, 58.45; H, 3.50; N, 14.61. Found: C, 58.30; H, 3.41; N, 14.50.

2-(4-Chloro-3-nitrobenzyl)imidazo[1,2-a]pyridine (5f). This compound was obtained as a white solid. ^{1}H NMR (DMSO-d_6): δ 4.25 (s, 2H, CH_2), 6.95–8.03 (m, 7H, PyH, ArH), 8.59 (s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 33.75, 114.37, 116.86, 123.80, 126.58, 127.72, 128.23, 130.85, 131.47, 132.36, 135.30, 137.65, 141.11, 148.15; ir (potassium bromide): 1510, 1345 cm^{-1}; Anal. Calcd. for $C_{14}H_{10}ClN_3O_2$ (287.70): C, 58.45; H, 3.50; N, 14.61. Found: C, 58.34; H, 3.38; N, 13.95.

2-(4-Cyanobenzyl)imidazo[1,2-a]pyridine (5g). This compound was obtained as a white solid. ^{1}H NMR (DMSO-d_6): δ 4.31 (s, 2H, CH_2), 6.99–8.32 (m, 8H, PyH, ArH), 8.59 (s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 34.26, 113.15, 114.86, 116.34, 120.06, 129.10, 130.55, 131.08, 131.67, 137.35, 140.22, 141.37, 148.24; ir (potassium bromide): 2200 cm^{-1}; Anal. Calcd. for $C_{15}H_{11}N_3$ (233.26): C, 77.23; H, 4.75; N, 18.01. Found: C, 77.52; H, 4.63; N, 18.08.

2-(4-Acetylbenzyl)imidazo[1,2-a]pyridine (5h). This compound was obtained as a white solid. ^{1}H NMR (DMSO-d_6): δ 2.51(s, 3H, CH_3), 4.22 (s, 2H, CH_2), 6.96–7.87 (m, 8H, PyH, ArH), 8.60(s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 27.49, 34.20, 114.33, 116.12, 127.51, 129.26, 130.09, 130.77, 133.27, 135.98, 137.35, 138.49, 145.30, 198.26; ir (potassium bromide): 1690 cm^{-1}; Anal. Calcd. for $C_{16}H_{14}N_2O$ (250.29): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.60; H, 5.46; N, 11.25.

2-[4-(Methoxycarbonyl)benzyl]imidazo[1,2-a]pyridine (5i). This compound was obtained as a white solid. ^{1}H NMR (DMSO-d_6): δ 3.81 (s, 3H, CH_3), 4.24 (s, 2H, CH_2), 7.01–8.32(m, 8H, PyH, ArH), 8.64(s, 1H, imidazole proton); ^{13}C NMR (DMSO-d_6): δ 33.89, 51.76, 114.54, 116.28, 128.36, 129.15, 130.05, 130.68, 132.84, 136.98, 138.08, 139.31, 148.93, 167.35; ir (potassium bromide): 1710 cm^{-1}; Anal. Calcd. for $C_{16}H_{14}N_2O_2$ (266.29): C, 72.16; H, 5.30; N, 10.52. Found: C, 71.74; H, 5.45; N, 10.30.

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