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A diphenylphosphinoethane-functionalized polystyrene resin-supported Pd(0) complex as an effective catalyst for copper-free Sonogashira coupling reactions under aerobic conditions

Mohammad Bakherad *, Ali Keivanloo, Bahram Bahramian, Samira Mihanparast

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

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ABSTRACT

A polymer-supported palladium(0) diphenylphosphinoethane complex was found to be a highly active catalyst for the copper-free Sonogashira coupling reaction of aryl iodides with terminal alkynes, giving excellent yields of products (85–98%) under aerobic conditions.

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The Sonogashira coupling reaction of terminal alkynes with aryl or vinyl halides is a powerful tool for carbon–carbon bond formation and has been widely applied in areas such as natural product synthesis, pharmaceuticals, and materials science.[1] This reaction usually proceeds in the presence of a homogeneous palladium catalyst and a copper salt. The presence of the copper co-catalyst facilitates the coupling reaction by the in situ generation of copper acetylide. However, it can also induce a Glaser-type oxidative homocoupling[2] of the terminal acetylene to yield a diyne. Focusing on suppression of the formation of this undesired side product, several copper-free versions of the palladium-catalyzed Sonogashira coupling have been developed.[3]

Numerous modifications have been reported for the Sonogashira coupling procedure, such as reaction in ionic liquids,[4] various copper-free conditions,[3l,5] a zeolite-supported reaction system,[6] fluorous biphasic systems (FBS) using fluorous palladium catalysts,[7] phase-transfer catalytic reaction conditions,[8] use of promoters[9] such as Zn, Mg, and Sn, and by employing microwave irradiation.[10]

The use of heterogeneous catalysts for Sonogashira coupling reactions leads to a reduction in waste. Polymer-supported transition metal complexes having high activity have attracted significant interest because they can be easily recovered and reused.[11] Despite numerous reports on the use of the Sonogashira reaction in organic synthesis, polymer-supported palladium catalysts have not been widely applied for this reaction yet.[12] Thus, the study of new types of polymer-supported palladium catalysts which might be suitable for the Sonogashira reaction has practical significance.

Polymer-supported palladium complex catalysts derived from chloromethyl polystyrene resin have been employed in both the Heck[13] and Suzuki[14] reactions, and have shown lower leaching of palladium during cross-coupling. This encouraged us to investigate the diphenylphosphinoethane-functionalized polystyrene resin-supported Pd(0) complex, PS–dpp–Pd(0) for the Sonogashira reaction. We have already reported the use of an ethylenediamine-functionalized polystyrene resin-supported Pd(II) complex[15] as an air-stable, active, and reusable catalyst in Sonogashira reactions.

We used known chloromethylated polystyrene cross-linked with 2% divinylbenzene as the support as it allows grafting of metallic atoms via ligands which are attached to the polymer beads. Reaction of polystyrene resin with diphenylphosphinoethane in DMF at 100 °C, and then treatment of the phosphinated polystyrene with a solution of $[PdCl_2(PhCN)_2]$ in ethanol, and finally reduction with hydrazine monohydrate resulted in covalent attachment of the palladium complex to give the polymer-supported palladium(0) complex catalyst **1** (Scheme 1). Successful functionalization of the polymer was confirmed by elemental analysis. The P content of the resin was found to be 4.25% by ICP, which indicates that the resin had reacted with diphenylphosphinoethane. The metal loading of the polymer-supported palladium complex, determined by neutron activation analysis (NAA), was 5.42% (0.51 mmol/g). In the IR spectrum of the polymer-bound diphenylphosphinoethane, the sharp C–Cl peak at 670 cm^{-1} (due to –CH_2Cl

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* Corresponding author. Fax: +98 2733335441.
E-mail address: mbakherad@shahroodut.ac.ir (M. Bakherad).

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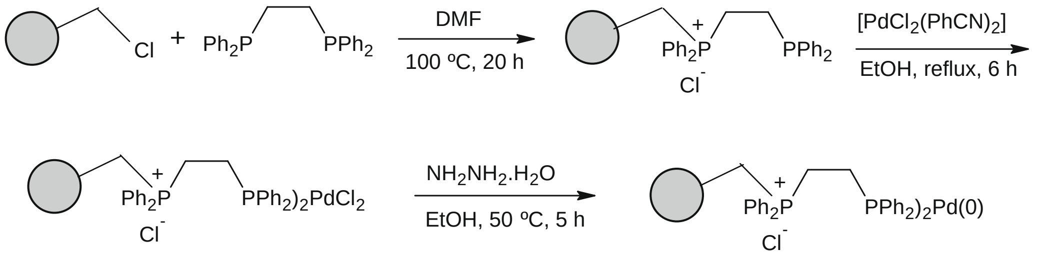


1

Scheme 1.

Table 1

Copper-free Sonogashira reaction of iodobenzene with phenylacetylene in the presence of several bases and solvents[a]

Entry	Solvent	Base	PS–dpp–Pd(0) (mol %)	Time (h)	Yield[b] (%)
1	DMF	Et_3N	1.0	7	70
2	DMF	DIEA[c]	1.0	6	62
3	DMF	Piperidine	1.0	2	93
4	DMF	Pyrrolidine	1.0	3	90
5	CH_3CN	Et_3N	1.0	9	73
6	CH_3CN	DIEA	1.0	10	70
7	CH_3CN	Piperidine	1.0	4	78
8	CH_3CN	Pyrrolidine	1.0	5	75
9	Piperidine	Piperidine	1.0	2	97
10	Pyrrolidine	Pyrrolidine	1.0	3	92
11	Et_3N	Et_3N	1.0	6	60
12	DIEA	DIEA	1.0	6	58
13	Dioxane	Et_3N	1.0	4	82
14	Dioxane	DIEA	1.0	5	70
15	Dioxane	Piperidine	1.0	3	84
16	Dioxane	Pyrrolidine	1.0	4	75
17	Piperidine	Piperidine	2.0	1.5	95
18	Piperidine	Piperidine	0.5	5	87

[a] Reaction conditions: iodobenzene (1.0 mmol), phenylacetylene (1.5 mmol), base (2.0 mmol), solvent (5 mL), room temperature, aerobic conditions.

[b] GC yield.

[c] Diisopropylethylamine.

Table 2

Copper-free Sonogashira reactions of terminal alkynes with aryl iodides[a]

Entry	R^1	R^2	Time (h)	Product	Yield[b] (%)
1	Ph	H	2	**4a**	97
2	Ph	4-NO_2	2	**4b**	98
3	Ph	3-NO_2	3	**4c**	94
4	Ph	2-NO_2	3	**4d**	95
5	Ph	4-$COCH_3$	3	**4e**	88
6	Ph	4-OCH_3	5	**4f**	85
7	n-C_4H_9	H	2	**4g**	90
8	n-C_4H_9	4-NO_2	2	**4h**	97
9	n-C_4H_9	4-$COCH_3$	3	**4i**	93
10	n-C_4H_9	4-OCH_3	5	**4j**	86
11	Me_3Si	H	4	**4k**	90
12	Me_3Si	4-NO_2	3	**4l**	96
13	Me_3Si	3-NO_2	4	**4m**	92
14	Me_3Si	2-NO_2	3	**4n**	90
15	Me_3Si	4-OCH_3	6	**4o**	85
16	CH_2OH	H	6	**4p**	87
17	CH_2OH	3-NO_2	5	**4q**	90
18	CH_2OH	4-OCH_3	7	**4r**	85

[a] Reaction conditions: **2** (1.5 mmol), **3** (1.0 mmol), PS–dpp–Pd(0) (0.01 mmol), piperidine (5 mL), room temperature, aerobic conditions.

[b] GC yield.

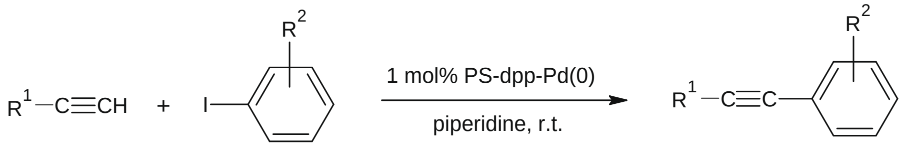
groups) and the strong peak at 1260 cm^{-1} corresponding to the H–C–Cl wagging modes in the starting polymer were virtually absent after introduction of diphenylphosphinoethane and palladium to the polymer. This confirms binding of the metal complex on the surface of the polymer.

The catalytic activity of complex **1** (1 mol %) was studied at room temperature under aerobic conditions in a copper-free Sonogashira reaction using phenylacetylene and iodobenzene. Our optimization data are shown in Table 1.

The reaction is influenced significantly by the nature of the base employed. Among the bases tested, piperidine proved to be the most efficient. Among the solvents used, piperidine was also the best choice (entry 9). Increasing the amount of palladium catalyst shortened the reaction time but did not increase the yield of diphenylacetylene (entry 17). A low palladium concentration led to a long reaction time (entry 18). The optimum conditions for the coupling reaction were 1 mol % of PS–dpp–Pd(0) in piperidine at room temperature (entry 9).

To examine the scope of this coupling reaction, a variety of terminal alkynes **2** were coupled with various aryl iodides **3** containing electron-withdrawing or electron-donating groups (Scheme 2). As shown in Table 2, the Sonogashira coupling reactions proceeded smoothly under very mild conditions giving the corresponding products in excellent yields.

The stability of PS–dpp–Pd(0) was studied in repeated Sonogashira coupling reactions of phenylacetylene with iodobenzene. The catalyst was separated from the reaction mixture after each experiment by filtration, washed with water and acetonitrile, and dried carefully before use in subsequent runs. A yield of **4a** of 93% was obtained from the 5th catalyst cycle (Table 3, entry 5).

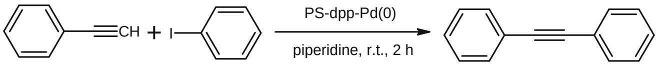


2 **3** **4**

Scheme 2.

Table 3

Copper-free Sonogashira reaction of iodobenzene with phenylacetylene catalyzed by the recycled catalyst[a]



4a

Entry	Cycle	Yield[b] (%)
1	1	97
2	2	96
3	3	96
4	4	94
5	5	93

[a] Reaction conditions: phenylacetylene (1.5 mmol), iodobenzene (1.0 mmol), PS–dpp–Pd(0) (0.01 mmol), piperidine (5 mL), room temperature, aerobic conditions.

[b] GC yield.

In conclusion, we have developed PS–dpp–Pd(0) as a reusable catalyst for the heterogeneous copper-free Sonogashira coupling reaction of terminal alkynes with aryl iodides under aerobic conditions.

Diphenylphosphinoethane-functionalized polymer-supported Pd(0) complex 1: To a 250 mL round-bottomed flask equipped with a magnetic stirrer bar, and containing DMF (100 mL), were added chloromethylated polystyrene (2 g, 1.25 mmol/g of Cl) and diphenylphosphinoethane (25 mmol), and the reaction mixture was stirred for 20 h at 100 °C. The reaction mixture was filtered and washed thoroughly with benzene or methanol and dried in vacuo for 20 h. The diphenylphosphinoethane-functionalized polymer (1.5 g) was treated with ethanol (50 mL) for 30 min. An ethanolic solution of 0.12 g of [$PdCl_2(PhCN)_2$] was added and the mixture heated to 80 °C for 6 h. The resulting bright-yellow colored polymer, impregnated with the metal complex, was filtered, washed with ethanol, and then stirred with hydrazine monohydrate (1 g) in ethanol (20 mL) at 50 °C under Ar for 5 h. The resulting product was filtered, washed with ethanol, and dried at 50 °C to give PS–dpp–Pd(0) (Scheme 1).

Sonogashira coupling reaction; General procedure: A round-bottomed flask was charged with aryl iodide (1.0 mmol), terminal acetylene (1.5 mmol), PS–dpp–Pd(0) (0.01 mmol), and piperidine (5 mL). The mixture was stirred at room temperature for 2–7 h under aerobic conditions. Upon completion of the reaction, the solution was concentrated in vacuo, and the crude product was subjected to silica gel column chromatography using $CHCl_3$–CH_3OH (98:2) as eluent to afford the pure product (Table 2).

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