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An Amine-, Copper- and Phosphine-Free Sonogashira Coupling Reaction Catalyzed by Immobilization of Palladium in Organic–Inorganic Hybrid Materials

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Abstract: An immobilization of palladium in organic-inorganic hybrid materials-catalyzed Sonogashira coupling reaction has been described. Terminal alkynes reacted with aryl iodides and aryl bromides only in the presence of a 3-(2-aminoethylamino)-propyl-functionalized, silica gel-immobilized palladium catalyst under amine-, copper- and phosphine-free reaction conditions. The reaction generates the corresponding cross-coupling products in excellent yields. Furthermore, the silica-supported palladium can be recovered and recycled by a simple filtration of the reaction solution and used for 30 consecutive trials without any decreases in activity.

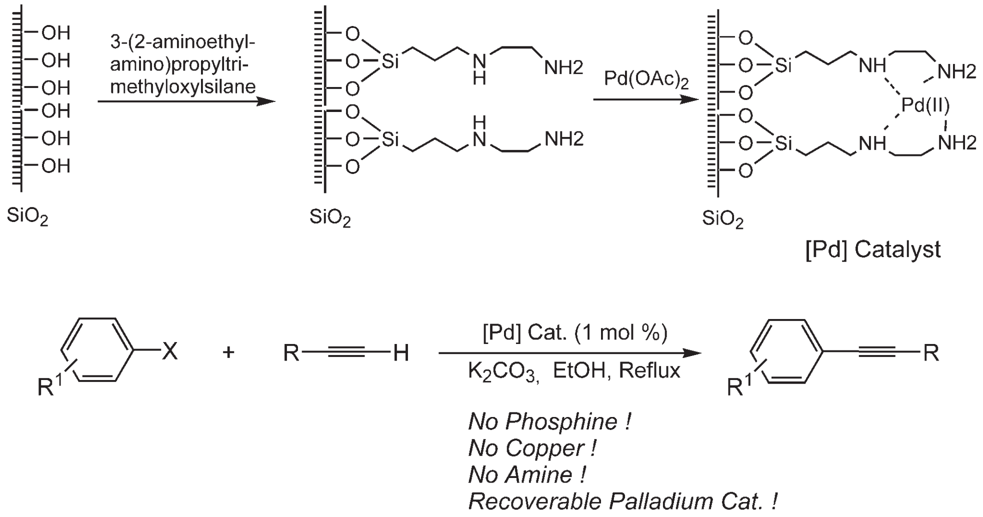
Keywords: amine-, copper- and phosphine-free; heterogeneous catalyst; immobilization of palladium; organic-inorganic hybrid material; Sonogashira coupling reaction

Transition metal catalysts have been widely used in organic synthesis. However, the high costs of transition metal catalysts coupled with the toxic effects associated with many of them has led to an increased interest in immobilizing catalysts onto a support. This class of supported reagent can facilitate both the isolation and recycling of the catalyst by filtration, thus providing environmentally cleaner processes.[1]

The Sonogashira reaction (coupling of terminal alkynes with aryl and alkenyl halides catalyzed by palladium complexes in the presence of an amine and a small amount of CuI) is one of the most powerful and straightforward methods for the construction of sp^2–sp carbon-carbon bonds in organic synthesis.[2] This method has been widely used for the synthesis of natural products,[3] biologically active molecules,[4] non-linear optical materials and molecular electronics,[5] dendrimeric and polymeric materials,[6] macrocycles with acetylene links,[7] and polyalkynylated molecules.[8] However, most of the above reactions were performed in homogeneous media. The major problems associated with the recovery of homogeneous catalysts and their separation from the reaction products and the difficulties associated with the recycling of the catalytic species have in part been addressed by immobilization on a heterogeneous solid support such as polymers or silicas. The grafting of ligands on the surface of organic or inorganic polymers opens the possibility to heterogenize transition metal catalytic species. In addition, problems related to homo-coupling products of terminal alkynes along with the cross-coupling reaction due to the addition of CuI and not eco-friendly reagents PPh_3 and amine may still remain in most of the homogeneous Pd-catalyzed Sonogashira reactions.

Recent examples include immobilized palladium complexes on amphiphilic polystyrene supports for effecting the Suzuki coupling reaction in an aqueous medium as well as a modified aminomethylpolystyrene-supported palladium reagent for use as a catalyst in a range of Sonogashira coupling reaction.[9] The development of organic reagents grafted onto silica gels has attracted increasing attention in recent years because industry seeks more environmentally friendly chemical manufacturing processes.[10] However, applications that involve the Sonogashira reaction have been less widely investigated, and usually employ a polystyrene-based support medium rather than a silica-based support.[11]

Our new approach, described in this communication, was to design and synthesize a new 3-(2-aminoethylamino)propyl-functionalized, silica gel-immobilized palladium catalyst (Scheme 1), which was used as an effective catalyst for the Sonogashira coupling reaction of terminal alkynes with aryl iodides and aryl bromides in the presence of potassium carbonate in ethanol under amine-, copper- and phosphine-free reaction conditions.



Scheme 1.

The reaction generated the corresponding cross-coupling products in excellent yields. It is important to note that the silica-supported palladium can be recovered and recycled by a simple filtration of the reaction solution and used for 30 consecutive trials without significant loss of its reactivity.

The synthesis of the organic-inorganic hybrid materials-immobilized palladium catalyst is illustrated in Scheme 1. It was readily prepared through a two-step procedure. The silica gel (100–200 mesh) was reacted with 3-(2-aminoethylamino)propyltrimethoxysilane in dry toluene at 120 °C for 24 h to afford the 3-(2-aminoethylamino)propyl-functionalized silica gel. The organic-inorganic hybrid materials subsequently reacted with palladium acetate in ethanol at room temperature for 1 h to generate the silica-supported palladium catalyst.

Although P ligands stabilize palladium and influence its reactivity, the simplest and cheapest Pd catalysts are of course ligand-free systems, specifically when used in low loading. In our initial screening experiments, the realization of a Sonogashira reaction catalyzed by the silica-supported palladium catalyst in the absence of copper, ligand and amine was our goal. When we searched for a cross-coupling protocol for use with iodobenzene and phenylacetylene, we observed that iodobenzene could react with phenylacetylene in the presence of 2 mol % of the silica-supported palladium and 2 equivs. of K_3PO_4 in ethanol under ligand-, copper- and amine-free reaction conditions at reflux temperature to afford the desired cross-coupling product in 56% yield. Encouraged by this result, we continued our search to improve the yield of the product by optimization of the reaction conditions.

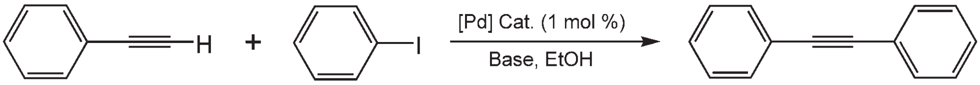
We tested several different bases for the Sonogashira coupling reactions catalyzed by the silica-supported palladium in ethanol. K_2CO_3 was found to be the most effective. Other bases such as Cs_2CO_3, NaOH, Na_2CO_3 and K_3PO_4 were substantially less effective, and triethylamine, diethylamine and piperidine were no longer the effective bases in this catalyst system (Entries 1–8, Table 1).

We then turned our attention to investigate the effect of solvent on the coupling reaction. When the reactions were conducted in EtOH, DMF and DMA, excellent yields (96%, 94% and 92%, respectively) of products were isolated. Use of MeOH, dioxane, THF and CH_3CN as solvents led to slower reactions, and no desired cross-coupling products were observed while reactions run in benzene and toluene (Entries 1–9, Table 2) because of the very poor solubility of K_2CO_3 in unpolar solvents such as benzene and toluene.

During the course of our further optimization of the reaction conditions, when using a 1 mol % loading of the silica-supported palladium, the reactions were generally complete in a matter of hours, but the time, as expected, was inversely proportional to the temperature. A reaction temperature of 80 °C was found to be optimal. Thus, the optimized reaction conditions for this Sonogashira reaction are the silica-supported palladium (1 mol %), K_2CO_3 (2 equivs.) in ethanol under reflux temperature for 6 h.

We have investigated the reactions using a variety of aryl iodides and bromides, and a wide range of terminal alkynes as the substrates under the reaction conditions and the results are outlined in Table 3. As can be seen from Table 3, electron-neutral, electron-rich and electron-poor aryl iodides reacted with phenylacetylene very well to generate the corresponding cross-coupling products in excellent yields under the standard reaction conditions (Entries 1–8, Table 3). This cross-coupling was also tolerant of *ortho*-substitution in aryl iodides and led to the very good yields (Entry 8, Table 3). Regardless of their electronic character, both aromatic terminal alkynes and aliphatic terminal alkynes coupled

Table 1. Effect of base on the Sonogashira coupling reaction.[a]

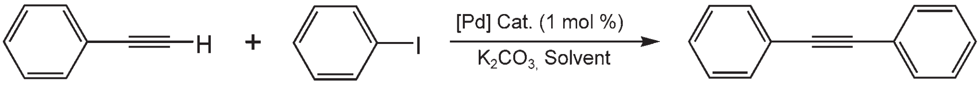


Entry	Base	Yield[b] [%]
1	Na_2CO_3	87
2	K_2CO_3	96
3	Cs_2CO_3	91
4	K_3PO_4	56
5	NaOH	90
6	Triethylamine	43
7	Piperidine	36
8	Diethylamine	40

[a] Phenylacetylene (1.00 mmol), iodobenzene (1.00 mmol), silica-supported Pd catalyst (25.4 mg, contains 0.01 mmol of Pd), base (2.00 mmol) in EtOH (4 mL) at 80 °C stirring for 6 h.

[b] Isolated yields.

Table 2. Effect of solvent on the Sonogashira coupling reaction.[a]



Entry	Solvent	Yield[b] [%]
1	CH_3OH	89
2	C_2H_5OH	96
3	THF	69
4	Dioxane	76
5	CH_3CN	56
6	DMF	94
7	DMA	92
8	Benzene	0
9	Toluene	0

[a] Phenylacetylene (1.00 mmol), iodobenzene (1.00 mmol), silica-supported Pd catalyst (25.4 mg, contains 0.01 mmol of Pd), K_2CO_3 (2.00 mmol) in solvent (4 mL) at 80 °C stirring for 6 h.

[b] Isolated yields.

smoothly with iodobenzene to produce the desired products in excellent yields (Entries 9–13, Table 3). Activated aryl bromides reacted with phenylacetylene to provide the products in good yields in C_2H_5OH at 80 °C for 6 h. When the reactions of activated aryl bromides with phenylacetylene were carried out in DMF at 110 °C for 8 h, excellent yields of desired cross-coupling products were observed (Entries 14–19, Table 3). For an electron-rich aryl bromide, a good yield (85%) of product was obtained when the reaction was performed in DMF at 110 °C for 8 h (Entry 20, Table 3).

The recyclability of the silica-supported palladium was also surveyed. After carrying out the reaction, the reaction solution was vacuum filtered using a sintered glass funnel and he residue washed with CH_2Cl_2 (5 mL), Et_2O (5 mL), C_2H_5OH (5 mL), and hexane (5 mL), respectively. After being dried in an oven, the catalyst can be reused directly without further purification. The silica-supported palladium can be recovered, recycled and used for 30 consecutive trials without loss of activity.

In conclusion, we have developed a novel, efficient, practical and economic catalyst system for the Sonogashira reaction by using the organic-inorganic (silica) hybrid materials-supported palladium as catalyst in ethanol under amine-, copper- and phosphine-free reaction conditions. The cross-coupling reaction of terminal alkynes with aryl iodides and aryl bromides generates the corresponding coupling products in excellent yields under the present reaction conditions. Furthermore, the silica-supported palladium can be recovered and recycled by a simple filtration of the reaction solution and used for 30 consecutive trials without any decreases in activity.

Table 3. Silica-supported palladium-catalyzed Sonogashira coupling reaction.[a]

Entry	Terminal alkyne	Organic halide	Yield[b] [%]
1	C$_6$H$_5$C$\equiv$CH	p-CH$_3$OC$_6$H$_4$I	96
2	C$_6$H$_5$C$\equiv$CH	p-CH$_3$C$_6$H$_4$I	98
3	C$_6$H$_5$C$\equiv$CH	C$_6$H$_5$I	94
4	C$_6$H$_5$C$\equiv$CH	p-N$_2$OC$_6$H$_4$I	98
5	C$_6$H$_5$C$\equiv$CH	p-CH$_3$COC$_6$H$_4$I	97
6	C$_6$H$_5$C$\equiv$CH	m-CF$_3$C$_6$H$_4$I	95
7	C$_6$H$_5$C$\equiv$CH	p-CF$_3$C$_6$H$_4$I	98
8	C$_6$H$_5$C$\equiv$CH	o-CF$_3$C$_6$H$_4$I	93
9	p-C$_6$H$_5$C$_6$H$_4$C$\equiv$CH	C$_6$H$_5$I	96
10	p-CH$_3$C$_6$H$_4$C$\equiv$CH	C$_6$H$_5$I	96
11	p-ClC$_6$H$_4$C$\equiv$CH	C$_6$H$_5$I	97
12	n-C$_8$H$_{17}$C$\equiv$CH	C$_6$H$_5$I	92
13	HOCH$_2$C$\equiv$CH	C$_6$H$_5$I	90
14	C$_6$H$_5$C$\equiv$CH	2-Bromopyridine	78; 94[c]
15	C$_6$H$_5$C$\equiv$CH	3-Bromopyridine	80; 92[c]
16	C$_6$H$_5$C$\equiv$CH	p-NO$_2$C$_6$H$_4$Br	96[c]
17	C$_6$H$_5$C$\equiv$CH	m-NO$_2$C$_6$H$_4$Br	96[c]
18	C$_6$H$_5$C$\equiv$CH	p-NO$_2$C$_6$H$_4$Br	92[c]
19	C$_6$H$_5$C$\equiv$CH	p-CNC$_6$H$_4$Br	98[c]
20	C$_6$H$_5$C$\equiv$CH	p-CH$_3$C$_6$H$_4$Br	85[c]

[a] Terminal alkyne (1.00 mmol), organic halide (1.00 mmol), silica-supported Pd catalyst (25.4 mg, contains 0.01 mmol of Pd), K$_2$CO$_3$ (2.00 mmol) in EtOH (4 mL) at 80 °C stirring for 6 h.

[b] Isolated yields.

[c] In DMF (4 mL) at 110 °C for 8 h.

Experimental Section

Preparation and Characterization of the Immobilized Palladium Catalyst in Organic-Inorganic Hybrid Materials

This catalyst was prepared in the following steps from commercial silica.

Activation of silica: 10 g of silica (100–200 mesh, Aldrich) were introduced in a round-bottom flask equipped with a reflux condenser, 80 mL of concentrated H$_2$SO$_4$ and 15 mL of HNO$_3$ were added and the mixture was heated in an oil-bath at 140 °C for 24 h. The solution was filtered and the white powder was washed with distilled water until neutral pH was attained. The solid was again washed with acetone, methanol and dichloromethane, respectively, and dried under vacuum at 150 °C for 48 h.

In a 50-mL round-bottom flask were introduced successively 20 mL of anhydrous toluene, 3 g of activated silica and 10 mL of 3-(2-aminoethylamino)propyltrimethoxylsilane (AAPTS). The solution was refluxed for 24 h. The solution was filtered and the solid was washed with acetone and dichloromethane, respectively, and dried under reduced pressure at 60 °C. 3.38 g of the material were obtained. FT-IR (KBr): $\nu_{\text{Si-O}} = 1088$; $\nu_{\text{C-H}} = 2941\ \text{cm}^{-1}$; anal. found: C 6.56, H 1.55, N 2.56, corresponding to 0.914 mmol/g of 2-aminoethylaminopropyl groups based on the N percentage.

In a small Schlenk tube, 1 g (0.914 meq NHCH$_2$CH$_2$NH$_2$/g) of the above-functionalized silica was mixed with 0.112 g (0.5 mmol) of Pd(CH$_3$CO$_2$)$_2$ in 5 mL of dry ethanol. The mixture was stirred for 1 h under a nitrogen atmosphere at room temperature. The solution was filtered and the solid was washed with acetone and methanol, respectively, and the solid was dried under reduced pressure at room temperature for 16 h, leading to a yellow powder; yield: 1.05 g. FT-IR (KBr): $\nu_{\text{Si-O}} = 1035$; $\nu_{\text{C-H}} = 2928\ \text{cm}^{-1}$; anal. by ICP (atomic %): Pd 4.18.

Typical Procedure for the Sonogashira Reaction

Under a nitrogen atmosphere, an oven-dried, round-bottomed flask was charged with the silica-supported palladium (25.4 mg, containing 0.01 mmol of Pd), K$_2$CO$_3$ (276 mg, 2.0 mmol), aryl halide (1.0 mmol), terminal alkyne (1.0 mmol) and ethanol (4 mL). The reaction mixture was refluxed at 80 °C for 6 h. After cooling to the room temperature, the reaction mixture was vacuum filtered using a sintered glass funnel and washed with CH$_2$Cl$_2$ (2 × 5 mL). The combined organic phases were dried over Na$_2$SO$_4$, filtered, concentrated, and the residue was purified by flash chromatography on silica gel to give the desired cross-coupling product.

The Recyclability of the Silica-Supported Palladium

After carrying out the reaction, the mixture was vacuum filtered using a sintered glass funnel and the residue washed with CH$_2$Cl$_2$ (5 mL), Et$_2$O (5 mL), C$_2$H$_5$OH (5 mL), and hexane (5 mL), respectively. After being dried in an oven, the catalyst can be reused directly without further purification.

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