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Phosphine-Free Perfluoro-Tagged Palladium Nanoparticles Supported on Fluorous Silica Gel: Application to the Heck Reaction[†]

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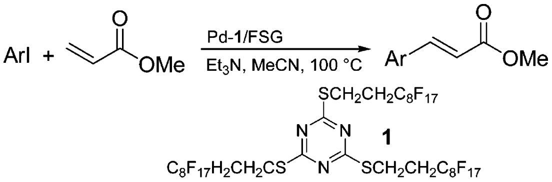
ABSTRACT



The immobilization of phosphine-free perfluoro-tagged palladium nanoparticles Pd-1 on fluorous silica gel (FSG) and their utilization in the Heck reaction have been investigated. High yields of vinylic substitution products have been obtained. Recycling studies have shown that the solid-supported palladium catalyst can be readily recovered and reused several times without significant loss of activity. Reactions and recovery of the solid-supported palladium catalyst system can be carried out in the presence of air, without any particular precaution.

Solid-supported palladium-catalyzed reactions have become a valuable tool for facilitating the separation, recovery, and reuse of expensive palladium catalysts and for reducing palladium contamination of the isolated products. Both of these problems are in fact of primary importance for the pharmaceutical industry which has to transfer laboratory-scale methods to large-scale cost-effective processes and limit the presence of heavy metal impurities in active substances. A large number of materials have been used to support palladium, including activated carbon, silica gel, polymers containing covalently bound ligands, metal oxides, porous aluminosilicates, clays and other inorganic materials, and microporous and mesoporous supports.[1] Palladium has also been microencapsulated in polymeric coating,[2] and aerogels[3] have been used to prepare heterogeneous palladium catalysts.

Recently, some of us found that palladium nanoparticles can be stabilized by entrapment in perfluoro-tagged phosphine-free compounds,[4] although heavily fluorinated compounds are not expected to be the best constituents of protecting shields for nanoparticles (perfluorinated chains are

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[†] Dedicated to the memory of Prof. Marcial Moreno-Mañas, a colleague and a friend.

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(1) For an excellent recent review on the use of heterogeneous palladium catalysts in C−C bond-forming reactions, see: Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133.

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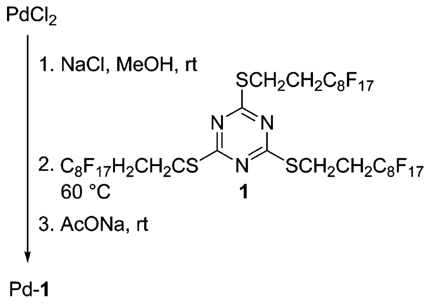
indeed known to exhibit very small attractive interactions toward other materials and among themselves[5]). Thus, we were intrigued by the idea of immobilizing phosphine-free perfluoro-tagged palladium nanoparticles on fluorous[6] silica gel (FSG) and evaluating the utilization of the immobilized catalyst in the Heck reaction.

Herein we report the results of our study.

A previous attractive example of immobilization of palladium on FSG is due to Bannwarth et al.[7] who prepared several catalysts via adsorption of palladium(II) complexes containing perfluoro-tagged phosphine ligands and showed the advantages of their utilization (separation and recovery of perfluoro-tagged catalysts) compared with fluorous biphasic catalysis approaches using expensive and environmentally persistent perfluorinated solvents.[8]

Phosphine-free perfluoro-tagged palladium nanoparticles Pd-**1** (diameter 2.3 ± 0.7 nm; 13.4% palladium) were prepared as described previously for similar systems[4e] by reduction of $PdCl_2$ with methanol at 60 °C in the presence of sodium chloride and compound **1**, a stabilizing agent featuring long perfluorinated chains, followed by the addition of AcONa (Scheme 1 and Figure 1a). The electron diffraction patterns of this sample were obtained, and the diffraction rings can be ascribed to the (111), (200), (220), and (311) crystallographic planes of the fcc-Pd (Figure 1d).

Scheme 1



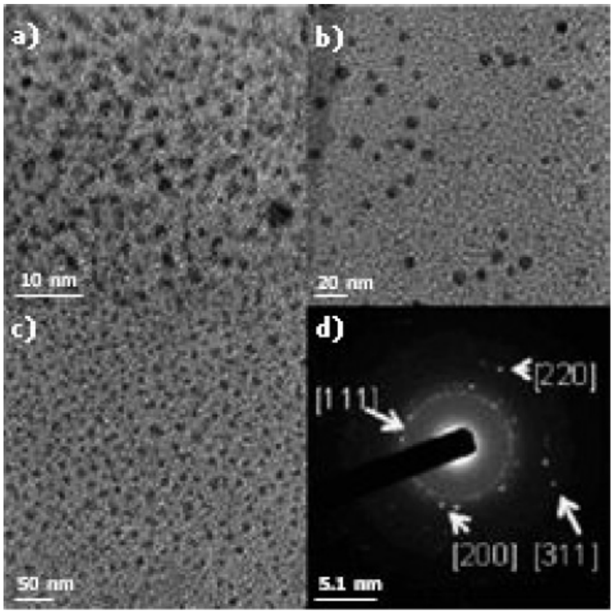


Figure 1. TEM images (Pd-**1** and Pd-**1**/FSG) and electron diffraction (Pd-**1**). (a) TEM image of Pd-**1**. (b) TEM image of Pd-**1**/FSG. (c) TEM image of recovered Pd-**1**/FSG after 15 runs. (d) Electron diffraction of Pd-**1**.

To prepare the immobilized precatalyst, nanoparticles Pd-**1** were dissolved in perfluorooctane, commercially available FSG (C_8; 35−70 μm) was added to the solution, and the solvent was evaporated. The immobilized precatalyst (Pd-**1**/FSG) was obtained as an air-stable powder. Transmission electron microscopy (TEM) of Pd-**1**/FSG was carried out. It showed well-defined spherical particles dispersed in the silica matrix (Figure 1b). The mean diameter of the nanoparticles was about 1.5 ± 0.7 nm.

A silica gel containing 100 mg of Pd-**1** per g of FSG and a 0.6 mol % palladium loading was initially evaluated in the Heck reaction of methyl acrylate with iodobenzene in DMF at 80 °C for 24 h. The reaction could be carried out in the presence of air, and methyl cinnamate was obtained in almost quantitative yield in the first run as well in the second one. However, a loss of activity was observed in the third run (85% yield) which became even more substantial in the

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fourth run (75% yield). Assuming that these results might be due to the leaching of palladium in DMF, we switched to using MeCN. After some experimentation we found that complete conversion could be obtained in MeCN at 100 °C after 24 h using 20 mg of Pd-**1** per g of FSG and a catalyst loading down to 0.1 mol %.

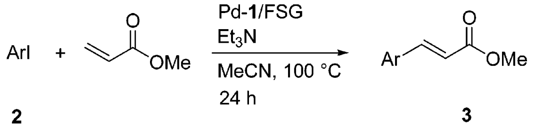
Recycling studies were then performed which showed that the supported catalyst system can be reused several times without significant loss of activity (Table 1). The recovery of the supported palladium involves centrifugation and decanting the solution in the presence of air, without any particular precaution. The resistance of Pd-**1**/FSG to leaching was assessed for the same reaction (iodobenzene and methyl acrylate). Sector field inductively coupled plasma mass spectrometry (SF-ICP-MS) analysis indicated the level of palladium in the crude mixtures to be in the 2−7 ppm range. Agglomeration of nanoparticles was not observed upon recycling. The recovered material after the 15th run was examined by TEM showing nanoparticles of about 1.9 ± 0.3 nm (Figure 1c). Control experiments were also carried out to assess whether leaching of nanoparticle support may take place under reaction conditions. ^{19}F NMR analysis of the crude mixture derived from the reaction of methyl acrylate with *m*-(trifluoromethyl)iodobenzene after filtration revealed the presence of small amounts of **1**, corresponding to an original nanoparticle support loss of about 5%. No evidence of fluorine was attained in the isolated vinylic substitution product. The crucial role of fluorous−fluorous interactions was assessed by immobilizing Pd-**1** on standard reversed-phase silica gel and using the resultant precatalyst in our model reaction (methyl acrylate and iodobenzene). Methyl cinnamate was obtained in 93% yield in the first run. However, a remarkable loss of activity was observed in the second run, the Heck product being isolated only in 59% yield.

Table 1. Recycling studies for the reaction of iodobenzene with methyl acrylate catalyzed by Pd-**1**/FSG (0.1 mol %)[a]

run	yield % of **3a**	run	yield % of **3a**
1	90 (91)	9	95 (94)
2	96 (90)	10	98 (95)
3	96 (90)	11	97
4	93 (86)	12	90
5	87 (88)	13	90
6	89 (95)	14	84
7	97 (100)	15	80
8	96 (99)		

[a] Reactions were carried out using 1 mmol of iodobenzene, 2 mmol of methyl acrylate, 3 mmol of Et_3N at 100 °C for 24 h in the presence of 0.1 mol % of Pd-**1**/FSG in 2 mL of MeCN. [b] Yields in parentheses refer to a second set of experiments.

Scheme 2



We then evaluated the efficiency of Pd-**1**/FSG with other aryl iodides (Scheme 2). Our preparative results are summarized in Table 2.

Table 2. Reaction of aryl iodides with methyl acrylate catalyzed by Pd-**1**/FSG (0.1 mol %)[a]

entry	aryl iodide **2**		time (h)	yield % of **3**[b,c]
1	*p*-MeCO-C_6H_4-I	**b**	5	89 (90)
2	*p*-MeO-C_6H_4-I	**c**	23	90 (70)
3	*p*-Me-C_6H_4-I	**d**	23	90
4	*p*-NO_2-C_6H_4-I	**e**	48	74 (65)
5	*m*-CF_3-C_6H_4-I	**f**	6	93 (90)
6	*p*-EtOCO-C_6H_4-I	**g**	5	98
7	*m*-Me, *p*-NO_2-C_6H_3-I	**h**	23	96
8	*o*-NH_2-C_6H_4-I	**i**	48	84
9	*o*-MeOCO-C_6H_4-I	**j**	7	89

[a] Reactions were carried out using 1 mmol of aryl iodide, 2 mmol of methyl acrylate, 3 mmol of Et_3N at 100 °C in the presence of 0.1 mol % of Pd-**1**/FSG in 2 mL of MeCN. [b] Yields are given for isolated products. [c] Yields in parentheses are for the second run carried out with the recovered catalyst.

Recycling studies were also performed using 10 mg of Pd-**1** per 3 g of FSG and a palladium loading down to 0.001 mol % (Table 3). The cumulated turn-over number (TON) over three runs is 265000.

Table 3. Recycling studies with 0.001 mol % of Pd-**1**/FSG[a]

run	yield % of **3a**
1	100
2	82
3	83

[a] Reactions were carried out using 1 mmol of iodobenzene, 2 mmol of methyl acrylate, 3 mmol of Et_3N at 140 °C for 24 h in the presence of 0.001 mol % of catalyst in 2 mL of MeCN.

We have not investigated in detail whether the nanoparticles on the solid surface are the actual catalyst or just a source that leaches active catalyst species.[9] Nevertheless, when methyl acrylate, *p*-iodoanisole, and Et_3N were added to the crude mixture derived from the reaction of methyl acrylate with iodobenzene (after separation of the solid material), the corresponding vinylic substitution derivative was isolated in 40% yield after 23 h at 100 °C, showing that palladium species leached from the solid surface are, at least in part, responsible for the catalytic activity.

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In conclusion, we have demonstrated that phosphine-free perfluoro-tagged palladium nanoparticles can be immobilized on fluorous silica gel to give a precatalyst which can be successfully used in the Heck reaction. The utilization of Pd-**1**/FRG does not require an inert atmosphere. Reactions and recovery of the catalyst system can be carried out in the presence of air without any particular precaution. The catalyst system can be easily recovered and reused several times without any appreciable loss of activity in many cases. It is also conceivable that the characteristics of this type of precatalyst can be adjusted by using different heavily fluorinated compounds. In general, the immobilized palladium nanoparticles described herein holds promise as the first example of a new class of solid-supported precatalysts. Further studies on this immobilization strategy are currently underway.

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Supporting Information Available: Complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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