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Efficient hydroxycarbonylation of aryl iodides using recoverable and reusable carbon aerogels doped with palladium nanoparticles as catalyst

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Abstract—Electron-rich and electron-poor aryl iodides are converted, in high to excellent yields, into the corresponding carboxylic acids through a hydroxycarboxylation reaction catalyzed by a recoverable and reusable phosphine free palladium–carbon aerogel catalyst using lithium formate and acetic anhydride as an internal condensed source of carbon monoxide. The catalyst system can be reused several times without any appreciable loss of activity.

1. Introduction

Palladium catalysis is widely used in organic synthesis. In the last decades, its utilization in a variety of transformations has known a continuous impressive growth for achieving an important place in the arsenal of the practicing organic chemist.[1] Palladium catalysts, however, are expensive and this may limit their utilization in some cases. Furthermore, the use of palladium catalysts might result in palladium contamination of the desired isolated product, a significant problem for the pharmaceutical industry, which has to meet strict specifications to limit the presence of heavy metal impurities in active substances.[2] A possible way to overcome these problems, which are of great importance to transfer laboratory-scale methods to large scale cost-effective processes, can be the utilization of immobilized palladium catalysts[3] so as to permit their easy and economical removal from the reaction mixture and their reutilization. Indeed, discovery of new synthetic applications of this precious transition metal has been paralleled by a number of studies devoted to support palladium on inert materials. Activated carbon is the most commonly used insoluble support for palladium. Because of its stability and relatively low cost, palladium on charcoal is widely used in hydrogenation processes and even in carbon–carbon bond forming reactions. Silica has also been used as an inert surface to adsorb palladium. A different approach to support palladium catalysts involves the coordination of palladium to a ligand covalently bound to a polymer backbone. However, in most of these cases, recovery and reuse of the immobilized catalysts have been proven unsatisfactory. More recently, it has been found that microencapsulation of palladium in polymeric coating is an efficient and cost-effective technique to ligate and retain palladium species[4] and, in the same direction, aerogels,[5] a new class of porous solids obtained via sol-gel processes coupled with supercritical drying of wet gels, has also been shown to exhibit a great potential for the preparation of heterogeneous catalysts.[6]

As part of a program devoted to the development of new catalyst systems, some of us found that carbon aerogels doped with palladium nanoparticles are good catalysts for the Mizoroki–Heck reaction.[7] Since the palladium-catalyzed hydroxycarbonylation of organic halides is a key step in many synthetic processes, particularly in the preparation of fine chemicals and complex molecules exhibiting biological activities, we decided to explore the utilization of Pd–carbon

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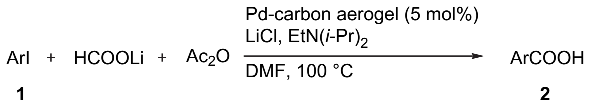
aerogel catalysts in the conversion of aryl iodides into the corresponding carboxylic acids. As the development of techniques where carbon monoxide is gradually generated in situ, omitting the utilization of pressured carbon monoxide, is a target of great current interest,[8] we were particularly attracted by the idea of combining the hydroxycarbonylation protocol based on the in situ generation of carbon monoxide from lithium formate and acetic anhydride[9] with the utilization of nanosized palladium particles embedded in carbon aerogels as catalyst.

Herein, we report that phosphine free Pd–carbon aerogels can effectively catalyze the hydroxycarbonylation of aryl iodides using lithium formate and acetic anhydride as an internal condensed source of carbon monoxide (Scheme 1).



$$\underset{\mathbf{1}}{ArI} + HCOOLi + Ac_2O \xrightarrow[\text{DMF, 100 °C}]{\text{Pd-carbon aerogel (5 mol\%)} \atop \text{LiCl, EtN}(i\text{-Pr})_2} \underset{\mathbf{2}}{ArCOOH}$$

Scheme 1.

2. Results and discussion

Carbon aerogels doped with metallic palladium nanoparticles were synthesized as described previously.[7] Summarizing, high content Pd–carbon aerogels have been prepared by sol-gel polymerization of formaldehyde with potassium salt of 2,4-dihydroxybenzoic acid, followed by the K^+-exchange with Pd^{2+} ions from 0.1 M $Pd(OAc)_2$ acetone solution and subsequent supercritical drying with CO_2. Carbonization at 1050 °C, under an inert atmosphere, transformed the metal ion doped organic aerogels into metal nanoparticles-doped carbon aerogels. Before its utilization in hydroxycarbonylation reactions, the catalyst was washed with DMF, the solvent, which gave the best results with homogeneous catalysis. A sample of Pd–carbon aerogel containing 46% of palladium in 8 mL of DMF was heated for three days at 100 °C and then recovered by decanting the solvent. The procedure was repeated three times. Sector field inductively coupled plasma mass spectrometry (SF-ICP-MS) analysis indicated the level of palladium in DMF, after decanting, to decrease from 16 to 8 ppm approximately (Table 1, entry 1), corresponding to an original metal loss of 0.9% and 0.4%. The resistance of Pd–carbon aerogel to leaching in other solvents was also briefly investigated (Table 1).

Initial attempts to prepare carboxylic acids from aryl iodides were carried out with *p*-iodotoluene as the model system and 0.05 equiv of Pd–carbon aerogel (a sample of Pd–carbon aerogel containing 35.3% of palladium was used in this case) under the conditions that gave the best results with homogeneous conditions [2 equiv of acetic anhydride, 3 equiv of HCOOLi, 2 equiv of $EtN(i\text{-}Pr)_2$, 3 equiv of LiCl in 1.5 mL of DMF at 80 °C].[9] The TEM image of Pd–carbon aerogel (Fig. 1) showed nanoparticles with a mean particle size of 19±4 nm and the corresponding X-ray diffraction pattern was characteristic of fcc-Pd. Other features of this particular sample were a BET surface area of 422 $m^2\,g^{-1}$, a total pore volume of 0.9 $m^3\,g^{-1}$, and a bulk density of 0.85 $g\,cm^{-3}$. *p*-Toluic acid was obtained in very low yield showing that, in comparison with palladium on charcoal, Pd–carbon aerogel is less reactive. Indeed, under the same conditions, *p*-toluic acid was isolated in 89% yield after 22 h in the presence of 0.05 equiv of 5% palladium on charcoal. Pleasingly, increasing the reaction temperature to 100 °C led to the isolation of *p*-toluic acid in 88% yield (24 h) in the presence of Pd–carbon aerogel. The reaction most probably involves the formation of acetic formic anhydride (generated in situ by the reaction of formate anion with acetic anhydride), which, as a result of its thermal instability,[10] acts as an internal condensed source of carbon monoxide. The general applicability of these conditions was investigated with a series of electron-rich and electron-poor aryl iodides. Our results are summarized in Table 2. Benzoic acids were usually isolated in high to excellent yields. Minor amounts of aldehydes, very likely formed via reduction of σ-acylpalladium intermediates by formate anions,[11] were isolated in some cases.

Table 1. Leaching of palladium from Pd–carbon aerogel (ppm)[a]

Entry	Solvent	First washing	Second washing	Third washing
1	DMF	16	8	8
2	MeCN	2	2	
3	Dioxane	<1	<1	
4	THF	<1	<1	
5	Toluene	—[a]	—[a]	

[a] Below the detectability limit (2 ng/mL).

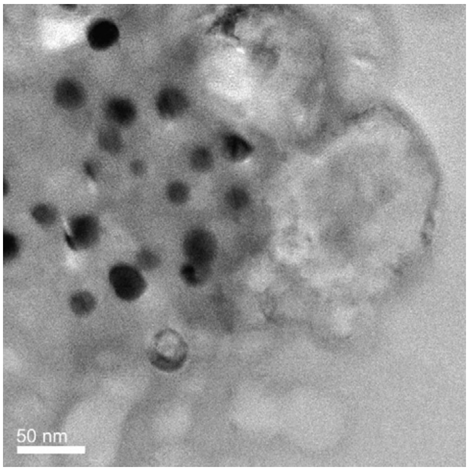


Figure 1. TEM image of Pd–carbon aerogel (35.3% of palladium).

Table 2. The Hydroxycarbonylation of aryl iodides catalyzed by Pd–carbon aerogel[a]

Entry	Aryl iodide **1**	Reaction time (h)	Yield (%)[b] of **2**	
1	*p*-Me–C_6H_4–I	24	88	**2a**
2	*p*-EtOOC–C_6H_4–I	8	90	**2b**
3	1-Iodonaphthalene	10	89	**2c**
4	*p*-MeOC–C_6H_4–I	10	77[c]	**2d**
5	*p*-Cl–C_6H_4–I	24	85[d]	**2e**
6	*p*-NO_2–C_6H_4–I	4	89	**2f**
7	*m*-MeO–C_6H_4–I	24	94	**2g**

[a] All reactions were carried out on a 0.463 mmol scale in 1.5 mL of DMF at 100 °C using 1 equiv of aryl iodide, 3 equiv of HCOOLi, 2 equiv of Ac_2O, 2 equiv of $EtN(i\text{-}Pr)_2$, 3 equiv of LiCl, and 0.05 equiv of Pd–carbon aerogel.

[b] Yields are given for isolated products.

[c] The corresponding aldehyde was isolated in 10% yield.

[d] The corresponding aldehyde was isolated in 8% yield.

We next explored the reutilization of the catalyst, one of the main aims of this research effort. Using *p*-iodotoluene and ethyl *p*-iodobenzoate as models of electron-rich and electron-poor aryl iodides, we investigated the number of times that we could reuse the catalyst system. With *p*-iodotoluene the Pd–carbon aerogel was reused 12 times without any obvious loss in activity (Table 3). Its limit of recyclability remains to be tested. The recovery of the catalyst is particularly convenient since it involves only decanting the solution and separating mechanically the Pd–carbon aerogel from the salts in the presence of air, without any particular precaution. SF-ICP-MS analysis of the solutions in the 12 runs showed the level of palladium to range from 3 to 6 ppm approximately, corresponding to an original palladium loss of 0.1% and 0.2%. A comparison between the BET parameters of the fresh aerogel catalyst and the used one reveals that both the surface area and total pore volume have decreased, from 422 to 171 $m^2\,g^{-1}$ and from 0.9 to 0.6 $cm^3\,g^{-1}$. We attribute the decrease of the total pore volume and, consequently the decrease of surface area, to the collapse of the micropores during the many ambient dryings undergone by the material after each use as catalyst, which is on the other hand supported by the results of the BET analysis. This indicates that the porous aerogel microstructure went through a slow deterioration although it maintained a large accessibility of the reactants to the palladium nanoparticles. Neither a loss of activity (Table 3) nor an appreciable leaching of palladium after 12 cycles was observed. The total amount of palladium remained essentially the same (within the experimental error; 35.3% in the initial sample and 36% in the sample recovered after 12 cycles) and still in the form of Pd(0) species, as shown by an X-ray diffraction (XRD) analysis (Fig. 2).

Similar results were obtained with ethyl *p*-iodobenzoate, which was successfully reused 10 times (Table 3).

To sum up, we have shown that phosphine free Pd–carbon aerogel is an effective catalyst for the hydroxycarbonylation of aryl iodides in the presence of lithium formate and acetic anhydride as an internal condensed source of carbon monoxide. Apparently it is air-stable under typical storage conditions, its recovery is straightforward and it can be reused several times without any appreciable loss of activity.

Table 3. Recycling studies for the hydroxycarbonylation of *p*-iodotoluene and ethyl *p*-iodobenzoate in the presence of Pd–carbon aerogel as catalyst[a]

Number of cycles	Yield (%)[b] (with *p*-iodotoluene)	Yield (%)[b] (with ethyl *p*-iodobenzoate)
1	88	90
2	93	93
3	93	93
4	95	93
5	95	94
6	95	91
7	91	94
8	93	97
9	96	97
10	95	93
11	96	
12	95	

[a] All reactions were carried out on a 0.463 mmol scale in 1.5 mL of DMF at 100 °C (*p*-iodotoluene, 24 h; ethyl *p*-iodobenzoate, 8 h) using 1 equiv of aryl iodide, 3 equiv of HCOOLi, 2 equiv of Ac_2O, 2 equiv of $EtN(i\text{-}Pr)_2$, 3 equiv of LiCl, and 0.05 equiv of Pd–carbon aerogel.

[b] Yields are given for isolated products.

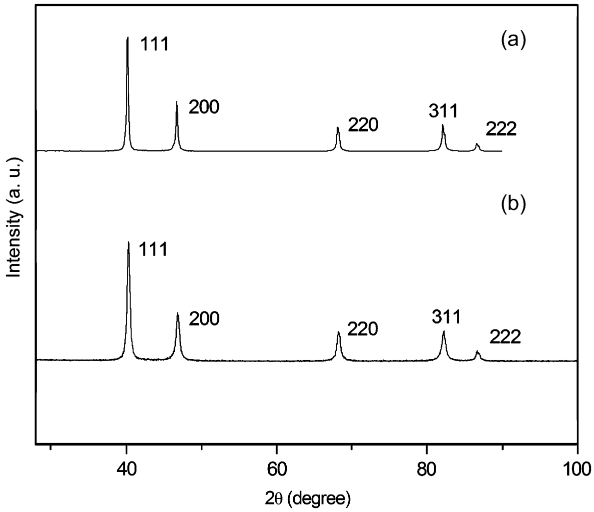


Figure 2. XRD patterns of: (a) original Pd–carbon aerogel and (b) recovered Pd–carbon aerogel after 12 reaction cycles.

3. Experimental

3.1. General

Melting points were determined with a Büchi B-545 apparatus and are uncorrected. $HCOOLi\cdot H_2O$ was dried in an oven at 70 °C for at least 24 h before use. Pd–carbon aerogels were prepared as described previously.[7] All other reagents and solvents are commercially available and were used as purchased without further purification. Reaction products were purified by flash chromatography eluting with *n*-hexane/AcOEt/AcOH mixture. ^1H NMR (200 MHz) and ^{13}C NMR spectra (50.3 MHz) were recorded with a Bruker Avance 200 spectrometer using DMSO-d_6 as solvent and TMS as a shift reference. IR spectra were recorded with a Jasco FT/IR 430 spectrometer.

3.2. Sample treatment

The content of Pd in five different organic solvents, namely acetonitrile, dimethylformamide (DMF), dioxane, tetrahydrofuran (THF), and toluene, has been quantified. Three samples for each solvent were analyzed for a total of 15 samples.

Samples in acetonitrile, dioxane, DMF, and THF were simply diluted with high-purity deionized water (EASY pure UV, BarnsteadyThermolyne, Dubuque, USA) and directly analyzed. In particular, samples in DMF were diluted in the 1:400 ratio and the others in the 1:20 ratio.

As regards toluene, in consideration of its immiscibility with water, samples were evaporated to dryness and subsequently a 0.6 M HCl solution was added to obtain a final 1:20 dilution.

3.3. Instrumentation, reagents, and analysis

Determination of Pd at mass 105 was performed by means of a sector field inductively coupled plasma mass spectrometry technique (SF-ICP-MS) in medium resolution ($m/\Delta m$=3000). The necessity of the medium resolution was mandatory to avoid those signals coming from molecular or isobaric species, such as $^{40}Ar^{65}Cu$, could overlap the signal of Pd at the chosen mass and overestimate the actual Pd values. Quantification of Pd was carried out through the standard addition calibration method in the case of dioxane, DMF, and THF, whereas the external calibration curve was adopted in the case of acetonitrile and toluene. Rhodium (Rh), selected at mass 103, was used as an internal standard to keep under control the instrumental drift. Single-element calibrant and internal standard were prepared from 1000 mg/mL stock solutions of Pd in 10% HNO_3 and Rh in 10% HCl by dilution with high-purity deionized water.

The Pd-doped aerogels were characterized by X-ray diffraction (XRD) with a D5000 Siemens X-ray powder diffractometer using Cu Kα incident radiation. Transmission electron microscopy (TEM) observations were performed using a JEOL-JEM-2010 microscope operating at 200 keV. Surface area determinations were carried out following the BET (Brunauer–Emmett–Teller) method with a ASAP-2000 surface area analyzer (Micromeritics Instruments Corp).

3.3.1. Typical procedure for the preparation of carboxylic acids from aryl iodides. A solution of $HCOOLi\cdot H_2O$ (97.2 mg, 1.389 mmol), $EtN(i\text{-}Pr)_2$ (161 μL, 0.926 mmol), and acetic anhydride (127 μL, 0.926 mmol) in anhydrous DMF (0.5 mL) was stirred at room temperature for 1 h. Then, *p*-iodotoluene (101.0 mg, 0.463 mmol), 35.3% Pd–carbon aerogel (7.0 mg, 0.023 mmol), and LiCl (54.4 mg, 1.389 mmol) in anhydrous DMF (1 mL) were added. The reaction mixture was stirred at 100 °C for 24 h. After cooling, the Pd–carbon aerogel was recovered by decanting the solution and separating the catalyst system mechanically (it was simply picked up with a spatula and immersed in DMF to maintain it wet till the subsequent utilization) from the salts in the presence of air. Then, the reaction mixture was diluted with ethyl acetate, washed with 2 N HCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 30 g; *n*-hexane/ethyl acetate/acetic acid 85/14/1 v/v) to give 55.5 mg (88% yield) of **2a**: mp: 179–180 °C; lit.[8] mp 179–180 °C; ^1H NMR δ 12.78 (br s, 1H), 7.83 (d, J=8.1 Hz, 2H), 7.28 (d, J=8.1 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR δ 167.9, 143.6, 129.9, 129.7, 128.6, 21.7.

3.3.1.1. Compound 2b. Mp: 168–170 °C; lit.[8] mp 168–170 °C; ^1H NMR δ 13.37 (br s, 1H), 8.07 (s, 4H), 4.35 (q, J=7.1 Hz, 2H), 1.35 (t, J=7.1 Hz, 3H); ^{13}C NMR δ 167.1, 165.6, 135.3, 134.0, 130.1, 129.8, 61.7, 14.6.

3.3.1.2. Compound 2c. Mp: 161–162 °C; lit.[8] mp 161–162 °C; ^1H NMR δ 13.18 (br s, 1H), 8.90 (d, J=8.5 Hz, 1H), 8.19–8.12 (m, 2H), 8.10–7.98 (m, 1H), 7.7–7.4 (m, 3H); ^{13}C NMR δ 169.0, 133.8, 133.3, 131.0, 130.2, 129.0, 128.1, 127.9, 126.5, 125.9, 125.2.

3.3.1.3. Compound 2d. Mp: 208–209 °C; lit.[8] mp 208–209 °C; ^1H NMR δ 13.32 (br s, 1H), 8.04 (s, 4H), 2.62 (s, 3H); ^{13}C NMR δ 198.2, 167.1, 140.3, 135.0, 130.0, 128.8, 27.4.

3.3.1.4. Compound 2e. Mp: 239–240 °C; lit.[8] mp 239–240 °C; ^1H NMR δ 13.16 (br s, 1H), 7.93 (d, J=8.4 Hz, 2H), 7.54 (d, J=8.5 Hz, 2H); ^{13}C NMR δ 166.9, 138.2, 131.6, 130.1, 129.1.

3.3.1.5. Compound 2f. Mp: 237–238 °C; lit.[8] mp 237–238 °C; ^1H NMR δ 13.6 (br s, 1H), 8.29 (dd, J_1=8.0 Hz, J_2=1.9 Hz, 2H), 8.13 (dd, J_1=8.0 Hz, J_2=1.9 Hz, 2H); ^{13}C NMR δ 165.9, 150.0, 136.4, 130.7, 123.7.

3.3.1.6. Compound 2g. Mp: 105–107 °C; lit.[8] mp 105–107 °C; ^1H NMR δ 13.0 (br s, 1H), 7.57–7.38 (m, 3H), 7.20–7.16 (m, 1H), 3.79 (s, 3H); ^{13}C NMR δ 167.7, 159.8, 132.7, 130.2, 122.1, 119.4, 114.4, 55.8.

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