



An efficient and reusable catalyst based on Pd/CeO₂ for the room temperature aerobic Suzuki–Miyaura reaction in water/ethanol

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ABSTRACT

The Pd/CeO₂ system behaves as an efficient precatalyst for the Suzuki–Miyaura cross-coupling under mild conditions (298 K, in air) in ethanol/water. A broad range of aryl bromides, including those deactivated, and arylboronic acids underwent Suzuki–Miyaura coupling with quantitative GC yields of asymmetric biaryls. Isolated yields and purity of the coupling products were good to excellent. A careful investigation through a series of suitable tests unequivocally showed that the C–C cross-coupling is accomplished via homogeneous mechanism by leached palladium(0). Noticeably, the Pd/CeO₂ system can be recycled at least ten times without loss of activity.

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1. Introduction

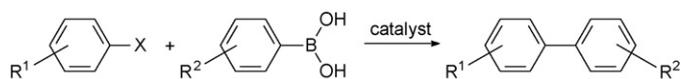
The Suzuki–Miyaura (SM) reaction, based on the use of arylboronic acids or esters, is recognized as one of the most important synthetic methods for the construction of asymmetric biaryls (Scheme 1) [1–11]. It finds application in the production of agrochemical and pharmaceutical drugs and in material science. The recent explosive growth of studies in this area is mainly due to air- and moisture stability of organoboranes as well as to their low toxicity. Furthermore, the reaction tolerates a wide range of functional groups and can be performed under relatively mild experimental conditions. Usually, the SM coupling is homogeneously catalyzed by palladium compounds generally in organic solvents or biphasic systems. Recent investigations have confirmed the formation of soluble colloidal nanoparticles which can act as the catalyst or, more likely, as the precursor of the true catalyst [12–18]. Formation of insoluble non-catalytic palladium black from small aggregates is often observed as an undesired effect. The difficult removal of the catalyst and its decomposition products from the mixture containing the biaryl constitutes the main drawback of the reaction. Furthermore, the ligands used for obtaining catalytically active systems for the less reactive substrates are generally air- and/or water-sensitive, expensive and often commercially not available.

For these practical and economical reasons, as well as for environmental considerations, the use of simple heterogeneous catalysts for the SM coupling is therefore highly desirable. In this context, one of the fundamental aims is the production of fine chemicals (especially pharmaceuticals) which must be free of residual metal (<5 ppm).

While a variety of heterogeneous catalysts such as Pd/C, Pd/zeolites, Pd/sepiolites, Pd/LDH, Pd/hydroxyapatites and Pd(II) complexes anchored on different supports have been the subject of several investigations [8–11], relatively few studies have been focused on the use of palladium supported on metal oxides. To the best of our knowledge, Pd-containing perovskites (in particular LaFe_{0.57}Co_{0.38}Pd_{0.05}O₃) [19,20], Pd/MgLa mixed oxides [21], Pd/MgO [22], Pd/Al₂O₃ [23,24], Pd/TiO₂ [24–26], Pd/SiO₂ [25], and Pd-doped mixed oxides [27] are the only examples in this field reported in the literature. Interestingly, Pd on various MO₂ supports (M=Ti, Si, Zr and Ce) has shown to be catalytically active for the homocoupling of phenylboronic acid [28]. Worth of note is also the catalytic efficiency of supported gold (on Y₂O₃ and CeO₂) for the same reaction [29,30]. The authors have also compared isoelectronic Pd(II) and Au(III) supported on ceria finding that the latter selectively promotes homocoupling, while the former catalyzes the cross-coupling reaction with lower activity and selectivity [30]. In some cases palladium leaching during catalysis was evidenced. Although no noble metal leaching was observed using Pd/MgLa mixed oxides, in the first recycling the activity of the catalytic system slightly decreased (after 1 h the yield dropped

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Scheme 1. The Suzuki–Miyaura reaction (X = halogen).

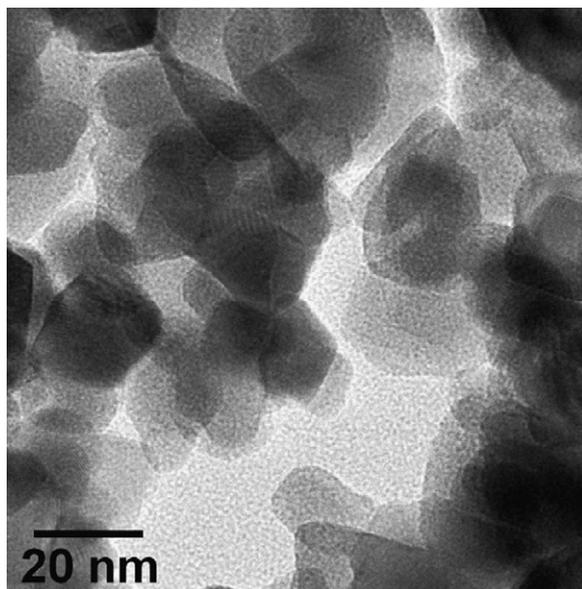


Fig. 1. TEM micrograph of Pd/CeO₂.

from 99 to 95%). No information was given by the authors on further recycling of the catalyst [21]. The Pd-containing perovskite catalyst was recycled four times without apparent loss of activity [19], and a further detailed study revealed that the effective catalytic species was present in solution-phase [20]. It is noteworthy that the catalytic runs have been performed at 60 °C [8], 80 °C [20,21] and 150 °C (under MW irradiation) [26]. Only in the case of the Pd/MgO catalyst the SM reaction was carried out at room temperature starting from aryl bromides and iodides [22]. Significantly, no coupling product was formed at 25 °C using Pd/MgLa mixed oxides [21].

With this scenario in mind, we initiated a study to evaluate the catalytic efficacy of Pd/CeO₂ in the SM reaction. To the best

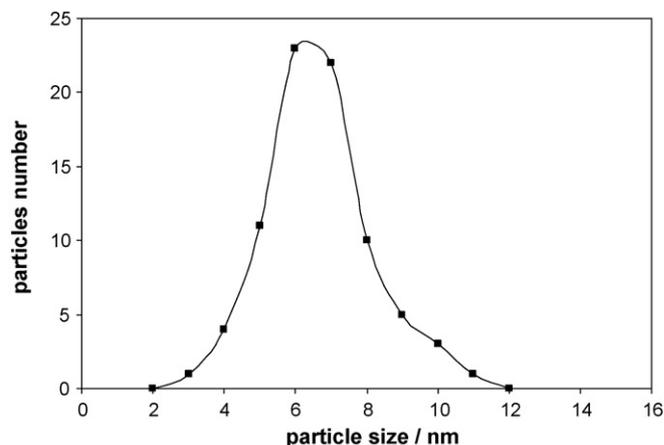
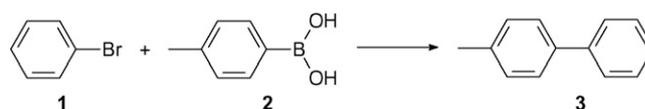


Fig. 3. Particle size distribution relative to a fresh sample of Pd/CeO₂.



Scheme 2. The model SM reaction between bromobenzene (1) and 4-tolylboronic acid (2) leading to 4-methyl-1,1'-biphenyl (3).

of our knowledge, such a catalytic system has been previously employed in two single experiments of Suzuki cross-coupling reaction [24,30]. As a matter of fact, Pd/CeO₂ showed less efficiency with respect to Pd/Al₂O₃ and Pd/TiO₂ systems [24]. On the contrary, the Pd/CeO₂ system has found application in other catalytic processes, for example CO, CO₂, and hydrocarbons hydrogenations

Table 1

Suzuki–Miyaura reaction of bromobenzene (1) with 4-tolylboronic acid (2) to yield 4-methyl-1,1'-biphenyl (3)^a.

Entry	Catalyst	Solvent (v/v ratio)	Base	Yield (%) ^b	Time (h)
1	Pd/CeO ₂ (2 wt% Pd)	EGME/H ₂ O 3:1	K ₂ CO ₃	>99%	11
2	Pd/CeO ₂ (2 wt% Pd)	Ethanol/H ₂ O 3:1	K ₂ CO ₃	>99%	8
3	CeO ₂	Ethanol/H ₂ O 3:1	K ₂ CO ₃	0%	12
4	Pd/CeO ₂ (2 wt% Pd)	Ethanol/H ₂ O 1:3	K ₂ CO ₃	>99%	40
5	Pd/CeO ₂ (2 wt% Pd)	H ₂ O	K ₂ CO ₃	95%	72
6	Pd/CeO ₂ (2 wt% Pd)	Methanol/H ₂ O 3:1	K ₂ CO ₃	>99%	8
7	Pd/CeO ₂ (2 wt% Pd)	2-Propanol/H ₂ O 3:1	K ₂ CO ₃	>99%	30
8	Pd/CeO ₂ (2 wt% Pd)	Ethanol/H ₂ O 3:1	KF	87%	8
9	Pd/CeO ₂ (2 wt% Pd)	Ethanol/H ₂ O 3:1	KO ^t Bu	92%	8
10	Pd/CeO ₂ (2 wt% Pd) ^c	Ethanol/H ₂ O 3:1	K ₂ CO ₃	>99%	16
11	Pd/CeO ₂ ^d (2 wt% Pd)	Ethanol/H ₂ O 3:1	K ₂ CO ₃	>99%	10 min

^a Reagents and conditions: 1 (0.5 mmol), 2 (0.6 mmol), base (0.6 mmol), catalyst (mol 1/mol Pd = 100), 2 mL solvent, and T = 298 K.

^b Determined by GC using diethylene glycol diⁿbutyl ether as internal standard.

^c 1/Pd molar ratio = 1000.

^d At 353 K.

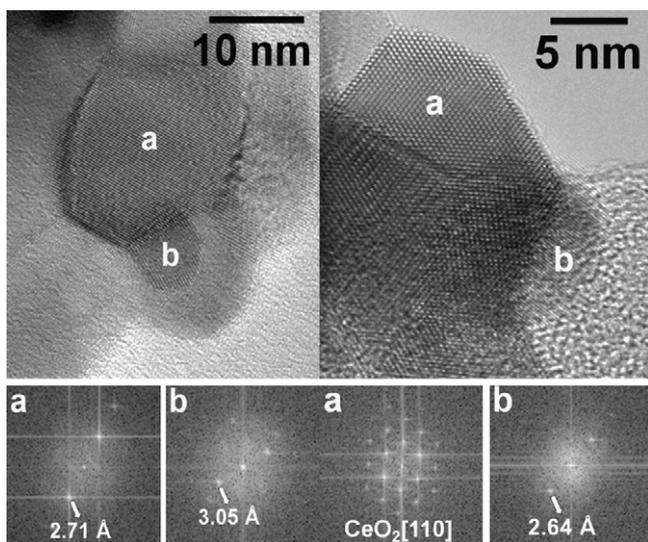
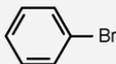
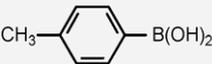
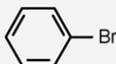
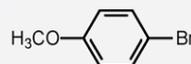
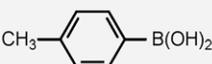
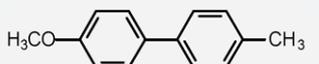
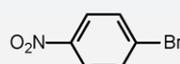
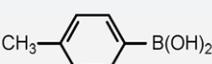
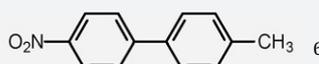
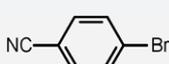
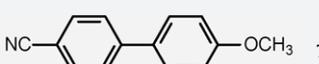
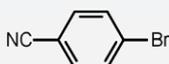
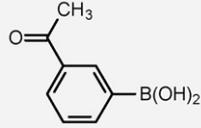
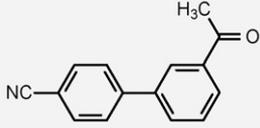
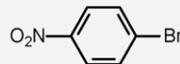
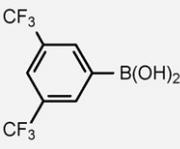
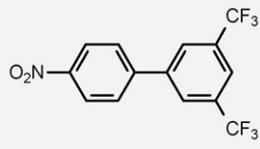
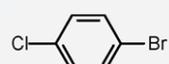
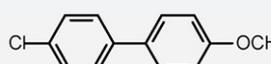
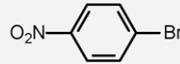
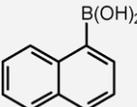
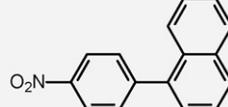
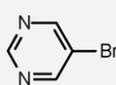
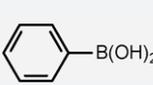
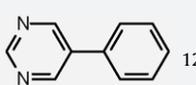


Fig. 2. Representative HRTEM image of Pd/CeO₂ along with Fourier transform (FT) images.

Table 2
Suzuki–Miyaura reaction between different aryl halides and arylboronic acids catalyzed by Pd/CeO₂^a.

Entry	Aryl halide	Arylboronic acid	Product	Yield (%) ^b	Time (h) ^c
1			 3	89	8
2			 4	86	14
3			 5	87	10
4			 6	85	1
5			 7	95	1
6			 8	83	3
7			 9	88	4
8			 10	88	7
9			 11	91	1.5
10			 12	85	96

^a Reaction conditions: aryl bromide (0.5 mmol), arylboronic acid (0.6 mmol), K₂CO₃ (0.6 mmol), Pd 1 mol%, ethanol 1.5 mL, H₂O 0.5 mL, and T = 298 K.

^b Isolated yield. GC yields of all compounds **3–12**, determined using diethylene glycol diⁿbutyl ether as internal standard, were >99%.

^c Necessary for quantitative formation of the product. Using Pd 0.1 mol%, compounds **3**, **5** and **6** were obtained in >99% GC yield after 16, 48 and 3 h, respectively.

and C₂–C₆ hydrogenolysis [31]. Herein we report the results of our investigation which showed that Pd/CeO₂ behaves as a very efficient promoter of the SM reaction in a safety and benign solvent (ethanol/water). Furthermore, this catalyst can be reused several times (at least ten) without apparent loss of activity and such an issue is crucial for scaling up this environmentally friendly catalytic process.

2. Results and discussion

2.1. Preparation and characterization of Pd/CeO₂

The catalyst was prepared by the incipient wetness impregnation method, followed by calcination at 1073 K, as previously described for analogous compounds [32]. With respect to the nominal 2 wt% Pd content, the elemental analysis of two distinct

samples gave 1.85 ± 0.04 wt%; however, for the sake of simplicity, the nominal palladium percentage is reported throughout this paper. The B.E.T. surface area was 28 m² g⁻¹ after calcination. The X-ray diffraction analysis showed the presence of peaks belonging to fluorite lattice of ceria but did not show distinct peaks attributable to either PdO and Pd. To spread light into this feature, high-resolution transmission electron microscopy (HRTEM) analysis of a freshly prepared sample was undertaken, and a general view is shown in Fig. 1. The sample is dominated by particles of CeO₂ of ca. 20 nm in size. Fig. 2 (left) shows a representative HRTEM image of the sample along with Fourier transform (FT) images of particles labeled **a** and **b**. Particle **a** exhibits lattice fringes at 2.71 Å, which corresponds to (200) crystallographic planes of CeO₂. Particle **b** shows spots in the FT image at 3.05 Å, which are ascribed to the (100) crystallographic planes of PdO. PdO crystallites are well distributed over the CeO₂ support, with a particle size distribution centered at 6.7 nm (the particle size dis-

tribution is shown in Fig. 3). In the sample prepared by Willis and Guzman using a nanocrystalline ceria support, a larger range for the particle size was observed (2–35 nm), which was centered at about 15 nm [28]. Another representative image of this sample is shown in Fig. 2 (right). Again, a PdO particle (labeled **b**) is supported over a CeO₂ crystallite (particle **a**). The image shows an atomically resolved CeO₂ crystal oriented along the [1 1 0] crystallographic direction, as deduced from the corresponding FT image. In particle **b**, lattice fringes at 2.64 Å correspond to (1 0 1) crystallographic planes of PdO. The HRTEM analysis of the sample did not evidenced the presence of metallic palladium particles on the ceria surface. On the other hand a portion of ca. 25% of total Pd present in the sample did not cycle if exposed to O₂ under temperature programmed oxidation (TPO) conditions, which could indicate the presence of Pd metal. Undetection of metallic Pd by HRTEM could originate either from their dimensions which fall outside the range of 2–100 nm and from the presence of Pd–PdO core-shell particles when PdO particles are covered by thin Pd metal shells.

2.2. Catalytic activity of Pd/CeO₂ in the Suzuki–Miyaura reaction

Initially, the catalytic trials were run in EGME/H₂O (3:1, v/v) (EGME—ethylene glycol monomethyl ether), according to our previous studies that demonstrated the beneficial effect of this type of solvent on the rate of Pd-catalyzed Heck [33,34] and Suzuki [35] reactions. At 25 °C, a complete conversion of bromobenzene (**1**) and 4-tolylboronic acid (**2**) into 4-methyl-1,1'-biphenyl (**3**) (model reaction, Scheme 2) was achieved in 11 h by using K₂CO₃ as the base and 1 mol% amount of Pd with respect to **1** (Table 1, entry 1). However, the reaction run in ethanol/H₂O (3:1, v/v) was faster, as complete formation of **3** was obtained in 8 h (Table 1, entry 2). The beneficial role played by ethanol in the SM reaction has been already reported [36]. It is important to stress that, in the same experimental conditions, no product was formed within 12 h by employing palladium-free CeO₂ (Table 1, entry 3). The use of ethanol/H₂O in 1:3 (v/v) ratio or water alone, resulted in a neat increase of the reaction time (Table 1, entries 4 and 5). Finally, the reaction rate did not substantially change when ethanol was replaced by methanol (Table 1, entry 6), while a very slow formation of **3** was observed by using 2-propanol/H₂O (3:1, v/v) (Table 1, entry 7). On the light of these preliminary results, further catalytic tests were run exclusively in ethanol/H₂O 3:1 (v/v). Other inorganic bases have been screened, thus also KF and KO^tBu have shown to be effective. Though the reaction went to completion with both bases, less than 92% of **3** was obtained after 8 h (Table 1, entries 8 and 9). A neat decrease of catalyst amount apparently did not markedly affect the reaction rate. For example, in the presence of 0.1 mol% of Pd the yield of **3** after 8 h was 92%, while the complete conversion of **1** into **3** was achieved in 16 h (Table 1, entry 1). Finally, completion of the model reaction was achieved within 10 min at 353 K (Table 1, entry 11).

The results of a screening of different electron rich and electron poor aryl halides and arylboronic acids to give products **4–12**, which are collected in Table 2, successfully confirmed the efficiency of Pd/CeO₂ as promoter of the SM reaction and scope of the protocol. Compounds **4–11** were formed quantitatively after 1–14 h, while the heterocycle **12** required about 4 days. All products were isolated in the solid state in good to excellent yield and high purity (≥97% checked by ¹H NMR). Purity was lower (93%) only in the case of 4-methyl-1,1'-biphenyl (**3**), as it was contaminated by 7% 4,4'-dimethyl-1,1'-biphenyl (the byproduct arising from homocoupling of **2**), which could not be separated by chromatography or fractionated crystallization.

As reported above, the biaryl **3** can be quantitatively formed even by lowering the catalyst amount to 0.1 mol% Pd. In order to

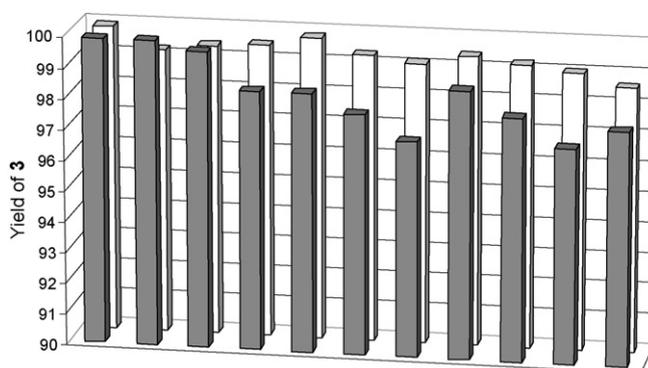


Fig. 4. Pd/CeO₂ recycling tests for the standard reaction between **1** and **2** to afford **3**. Reagents and conditions: **1** (0.5 mmol), **2** (0.6 mmol), K₂CO₃ (0.6 mmol), catalyst (mol **1**/mol Pd = 100), ethanol 1.5 mL, H₂O 0.5 mL, 298 K. Yield of **3** (based on **1**) was determined by GC after 9 h (298 K). The GC yields of **3** relative to the first use and ten consecutive (grey columns) and parallel reuses (white columns) of the catalyst are reported.

test the limits of the catalytic system, also the formation of compounds **5** and **6** starting from an electron rich and an electron poor aryl bromide, respectively, was evaluated by using 0.1 mol% Pd. Successfully, both biaryls were obtained again quantitatively.

2.3. Catalyst reuse

The reusability of the catalyst was examined in the case of the model reaction (Scheme 2). Measurements were carried out using a 1 mol% palladium amount for both consecutive and parallel recycling (explicative details are given in Section 4). The results have been summarized in Fig. 4, where yields of **3** relative to the first use and ten successive reuses of the catalyst are reported. As clearly evidenced by the histogram, the catalytic performance of Pd/CeO₂ did not appreciably fade after ten reuses. In particular, the GC yield values found for the consecutive recycling were never below 97%. Both sets of experiments were stopped after the tenth reuse, but the lack of a neat decreasing trend may suggest that Pd/CeO₂ effectively behaves as an outstanding long-living catalyst, and such a finding is of particular interest for its possible application in large-scale syntheses of biaryls. As reported above, when the reaction was performed at 353 K, complete formation of **3** was achieved in about 12 min. At this temperature, the yield after the

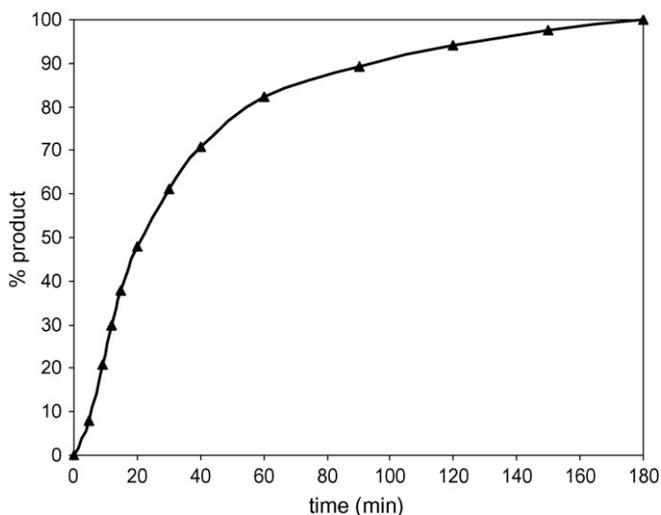
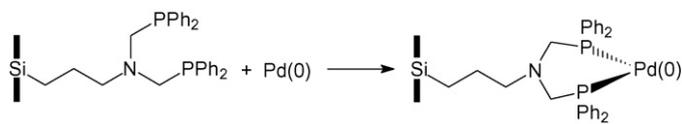


Fig. 5. Formation of product **3** as a function of time. Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), K₂CO₃ (0.6 mmol), Pd 1 mol%, ethanol 1.5 mL, H₂O 0.5 mL, T = 298 K.



Scheme 3. Palladium “trapping” by a diphosphane arm anchored to silica.

first two consecutive reuses was 98.9 and 99.1, thus apparently the catalyst seems to maintain its stability even at high temperature.

2.4. Evidences for homogeneous catalysis

To possibly ascertain whether Pd/CeO₂ operates by heterogeneous or homogeneous mechanism at room temperature, the filtration test [37,38] and the CS₂ test [38] were run on the model reaction. The catalyst was filtered off from the reaction mixture after 15 min and the solution was then stirred at 25 °C. The GC measurement run immediately after filtration showed 19.8% yield of **3**, which increased to only 23.9% after 8 h, the time necessary for completion of the reaction in the presence of Pd/CeO₂. Thus, a drastic slowing down of the reaction rate was effectively achieved upon elimination of the catalyst, but such a result did not provide a decisive answer about the nature of the true active species. The CS₂ test was accomplished by using three different CS₂/Pd molar ratios, namely, 1:1, 1:10, and 1:50. In the first two cases product **3** was not detected in solution by GC within 24 h. Differently, the C–C coupling occurred when the CS₂/Pd molar ratio was 1:50 at roughly the same rate as that observed in the absence of carbon sulfide. Such a result is generally considered as proof of occurrence of heterogeneous mechanism, although it should not be viewed as conclusive [7,20,38]. On the contrary, enlightening was the result of a third test, which was performed by introducing in the reaction mixture a Davisil silica with a 150 Å mean pore size functionalized with a bis(diphenylphosphane) bidentate ligand [39], (Scheme 3). Such a kind of poisoning test was first adopted in the Heck C–C coupling by Jones and co-workers [40] and then applied by Richardson and Jones to both Heck [41,42] and SM [42] reactions. Thus, in the presence of a twice molar amount of the –N(CH₂PPh₂)₂ functionality with respect to total palladium present in the reaction vessel, the catalytic activity was nearly suppressed, as only 2.8% of **3** was formed after 8 h. The amount of added silica was based on the loading of organic functionality (0.39 mmol g⁻¹) obtained by combination between elemental analysis (N, P) and TGA measurements [39]. Therefore, the diphosphane arm is able to extinguish catalysis by chelating a soluble form of palladium, which acts as the effective catalyst. Some authors have suggested that the true catalyst should be a mononuclear Pd(0) species generated by soluble colloidal nanoparticles, which in turn arise from the precatalyst [12–18,43]. As only traces of noble metal are effectively present in solution at a ppb level (see below), there is indeed a large excess of supported poisoning bidentate ligand. Notably, Richardson and Jones have found that 35 equiv. of PVPy poison are ineffective, while catalysis was almost stopped in the presence of 350 equiv. of the same polymer [42]. In line with the hypothesis of formation of an active soluble species from supported palladium, the kinetic plot (Fig. 5) shows the typical sigmoidal shape associated with an induction period of the reaction due to formation of the true catalyst in C–C coupling reactions starting from aryl halides [40–47]. It is quite evident, however, that its generation takes place very rapidly. To check the presence of any nanometric palladium species in solution, after the third reuse of the catalyst, the mother liquor was carefully analyzed by HRTEM, but no evidence for the presence of metal nanoparticles was found. The detection limit of Pd entities under the conditions employed is about

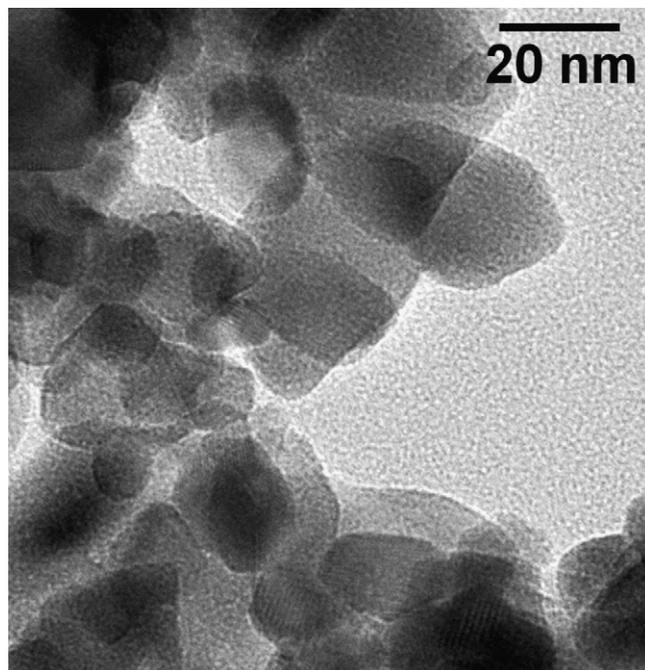


Fig. 6. TEM micrograph of a sample of Pd/CeO₂ after four uses in catalysis.

0.8 nm. When directly observed, the size of catalytically active colloidal nanoparticles were 1.7 nm (mean value) [14] or in the range 1.1–2.6 nm [12]. On the other hand, the ICP-MS analysis showed that 1.4 ppb (instrumental detection limit: 0.5 ppb) of palladium was present, at the end of the reaction, in the filtered solution after the first use of the catalyst. Thus, though in very low concentration, palladium is effectively present in solution as result of metal leaching from the solid precatalyst. These results seem to suggest that Pd/CeO₂ acts as a reservoir of “homeopathic” amounts [48–50] of catalytically active palladium. Furthermore, the maintenance of catalytic activity upon several reuses could be reasonably explained by a release/re-deposition mechanism [46,51–54], the latter being favoured by the low temperature at which the catalytic process is carried out [54]. Our finding is in line with the results reported by Köhler et al. who nicely demonstrated the presence of higher concentration of noble metal during SM catalysis with respect to that measured when the reagents are almost consumed [24]. In our

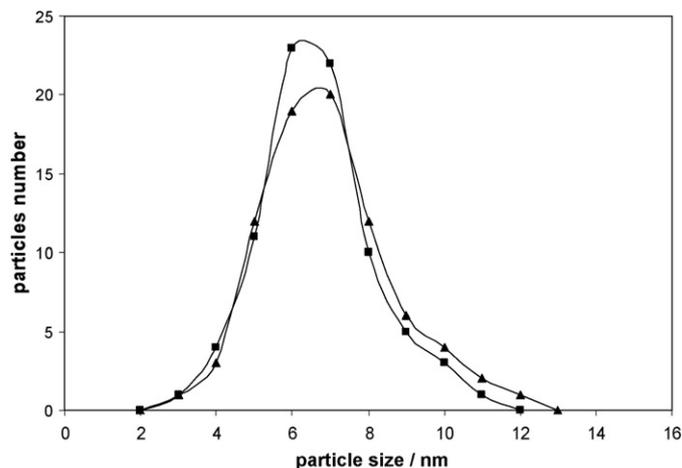


Fig. 7. Comparison of particle size distribution between a fresh sample of Pd/CeO₂ (squares) and a sample used four times as catalyst of the standard reaction (triangles).

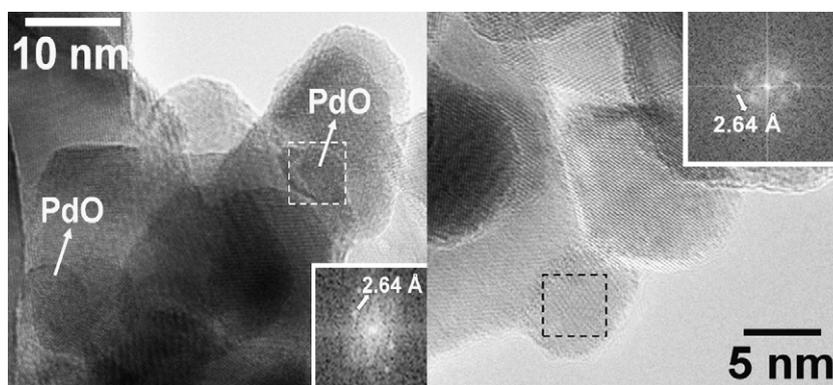


Fig. 8. Representative HRTEM image of a sample of Pd/CeO₂ after four uses in catalysis along with Fourier transform (FT) images.

case, the results of the HRTEM analysis of a catalyst sample used four times show that it is virtually indistinguishable from the fresh material. Fig. 6 corresponds to a low magnification image of the recycled sample, where the distribution and appearance of CeO₂ support particles are similar to those of the freshly prepared catalyst (Fig. 1). The HRTEM study of the used sample also denotes the presence of PdO crystallites, and the particle size distribution is only slightly biased towards larger particles (Fig. 7). The mean particle size has increased only from 6.7 to 6.9 nm. Fig. 8 shows a representative HRTEM picture of the used sample, where two PdO particles have been identified. The FT image recorded over the selected area shows spots at 2.64 Å, which are ascribed to the (101) crystallographic planes of PdO. A second representative HRTEM image is depicted in the same figure. Again, spots at 2.64 Å are recognized in the FT image of the area selected, in accordance to PdO (101) crystallographic planes.

3. Conclusions

We have shown that Pd/CeO₂ behaves as an efficient catalyst in the SM coupling reaction starting from aryl bromides with different electronic substituents. The most remarkable results of the present investigation are the following: (i) the catalyst is active at room temperature, in air, in an environmentally friendly solvent such as 3:1 ethanol/water mixture; (ii) Pd/CeO₂ can be easily prepared, is relatively cheap and is active also in low amount (Pd 0.1 mol%); (iii) all couples of substrates employed were quantitatively transformed into the coupling product; (iv) the catalyst can be recycled at least ten times without appreciable decrease of activity. For all these reasons, the Pd/CeO₂ system seems to be a good candidate for large-scale applications of the SM reaction. We have also demonstrated that a homogeneous mechanism takes place most probably through a release/re-deposition process. At the end of the reaction the amount of palladium in solution was at the ppb level. Thus, if the coupling product showed comparable metal content, it is clear that our procedure meets the requirements of the pharmaceutical industry (<5 ppm residual metal in the commercial product).

4. Experimental

4.1. General

All reagents were purchased from Aldrich and used without further purification. Commercial solvents were dried according to standard methods and freshly distilled before use. The ¹H and ¹³C{¹H} NMR spectra (at 200.13 and 50.32 MHz, respectively) have been recorded on a Bruker AC 200 F QNP spectrometer. For both nuclei the chemical shifts were referenced to the signal of the sol-

vent (residual CHCl₃ at 7.26 ppm for ¹H and CDCl₃ at 77.0 ppm for ¹³C). The high-resolution transmission electron microscopy (HRTEM) was carried out at 200 kV with a JEOL 2010F instrument equipped with a field emission gun. The point-to-point resolution of the microscope was 0.19 nm and the resolution between lines was 0.14 nm. The powder samples were directly deposited on holey-carbon coated Cu grids, whereas a drop of the mother liquor was deposited and evaporated on a grid covered by a thin polymer. The Pd loading of the catalyst was measured in the Micro-analytical Laboratory of the Department of Chemical Sciences and Technologies (Udine) on a Spectro Analytical Instruments Spectromass 2000 Type MSDIA10B Inductively Coupled Plasma Mass spectrometer. Samples (20 mg) were digested on a microwave apparatus MILESTONE Mega 1200 by use of 1 mL of 65% HNO₃, 0.4 mL of 30% H₂O₂ and 0.1 mL of 40% HF with a mineralization program at 650 W for 20 min in Teflon vessels. The mean value for two different samples was 1.85 ± 0.04%. For the Pd determination in solution, four different samples were prepared by filtration and centrifugation (1 min at 4000 rpm) of the reaction mixture obtained after a catalytic complete conversion of **1** into **3**. Each sample was digested as described above on a microwave apparatus MILESTONE Mega 1200. The mean concentration value of Pd was 1.4 ppb (instrumental detection limit: 0.5 ppb). Calibration curves were obtained by using a Palladium ICP/DCP standard solution purchased from Aldrich (10,000 mg/mL Pd in 6% HCl solution). The GC–MS analyses, run to control the identity of the compounds obtained in the catalytic trials, were carried out with a Fisons TRIO 2000 gaschromatograph–mass spectrometer working in the positive ion 70 eV electron impact mode. Injector temperature was kept at 250 °C and the column (Supelco® SE-54, 30 m long, 0.25 mm i.d., coated with a 0.5 μm phenyl methyl silicone film) temperature was programmed from 60 to 300 °C with a gradient of 10 °C/min. The GC analyses were run on a Fisons GC 8000 Series gaschromatograph equipped with a Supelco® PTA-5 column (30 m long, 0.53 mm i.d., coated with a 3.0 μm poly(5% diphenyl–95% dimethylsiloxane) film) Injector and column temperatures as indicated above.

4.2. Catalyst preparation and characterization

The catalyst was prepared by incipient wetness on a commercial CeO₂ support (B.E.T. surface area after calcination at 1073 K = 31 m² g⁻¹). The Pd precursor was a 10% Pd(NO₃)₂ solution (99.999%), which was added to the support drop by drop to obtain a catalyst with a nominal Pd loading of 2 wt%. After impregnation the powder was dried overnight at 393 K and then calcined at 1073 K for 2 h. B.E.T. surface area was 28 m² g⁻¹ after calcination. The X-ray spectra were recorded on a Philips X'Pert

diffractometer equipped with Cu K-alpha radiation source. Step size was 0.01° with a time-per-step of 80 s. The temperature programmed oxidation (TPO) experiment was carried out on 150 mg of Pd/CeO₂. The catalyst was exposed to a flow of 2% of oxygen in nitrogen, while the temperature was increased from room temperature up to 1273 K and then decreased to 373 K for two subsequent heating/cooling cycles at 10 °C/min. Oxygen release during heating (due to PdO decomposition) and oxygen uptake during cooling (due to Pd reoxidation) were measured. Quantitative analysis of the oxygen release/uptake allowed to evaluate the amount of Pd in oxide form (75%) present on the catalyst surface.

4.3. Synthesis and NMR characterization of biaryls 3–12

In a thermostatted bath at 25 °C, a 25 mL Schlenk flask was charged in air with a magnetic stir bar, Pd/CeO₂ (Pd 2 wt%) (53.2 mg), the appropriate arylboronic acid (1.2 mmol) and aryl bromide (1.0 mmol), K₂CO₃ (1.2 mmol), ethanol (3.0 mL) and H₂O (1.0 mL). The reaction mixture was kept under vigorous stirring until the GC control showed no residual aryl bromide in solution. Water (10 mL) was added to the suspension and the organics were extracted with dichloromethane (3 × 10 mL). The organic phase was dried over Na₂SO₄ and then passed through a column filled with silica gel (**3–11**) or Celite® (**12**). Elimination of the solvent under vacuum gave the desired biaryl as white microcrystalline solid. Purity was checked by ¹H NMR.

¹H and ¹³C{¹H} NMR data (spin multiplicity is given by s: singlet, q: quartet, st: septet, m: multiplet, dt: doublet of triplets, and ddt: doublet of doublets of triplets):

4-Methyl-1,1'-biphenyl **3**. Yield, 89%; purity, 93% (7% 4,4'-dimethylbiphenyl); ¹H NMR (CDCl₃) δ 7.73–7.26 (9H, m), 2.47 (3H, s); ¹³C NMR (CDCl₃) δ 141.1, 138.3, 137.0, 135.7, 129.5, 128.7, 127.0, 126.9, 21.1 (CH₃).

4-Methoxy-1,1'-biphenyl **4**. Yield, 86%; purity, 98%; ¹H NMR (CDCl₃) δ 7.63–7.28 (7H, m), 7.06–6.96 (2H, m), 3.88 (3H, s); ¹³C NMR (CDCl₃) δ 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3 (OCH₃).

4-Methoxy-4'-methyl-1,1'-biphenyl **5**. Yield, 87%; purity, 98%; ¹H NMR (CDCl₃) δ 7.64–7.48 (4H, m), 7.36–7.25 (2H, m), 7.09–7.00 (2H, m) 3.90 (3H, s), 2.47 (3H, s); ¹³C NMR (CDCl₃) δ 158.9, 137.9, 136.3, 133.7, 129.4, 127.9, 126.5, 114.1, 55.2 (OCH₃), 21.0 (CH₃).

4-Methyl-4'-nitro-1,1'-biphenyl **6**. Yield, 85%; purity, 98%; ¹H NMR (CDCl₃) δ 8.32–8.23 (2H, m), 7.76–7.67 (2H, m), 7.58–7.49 (2H, m), 7.36–7.27 (2H, m), 2.44 (3H, s); ¹³C NMR (CDCl₃) δ 147.5, 146.7, 139.0, 135.7, 129.8, 127.4, 127.1, 124.0, 21.1 (CH₃).

4-Cyano-4'-methoxy-1,1'-biphenyl **7**. Yield, 95%; purity, 99%; ¹H NMR (CDCl₃) δ 7.73–7.48 (6H, m), 7.04–6.95 (2H, m), 3.86 (3H, s); ¹³C NMR (CDCl₃) δ 160.1, 145.1, 137.0, 132.5, 132.4, 131.4, 128.3, 127.0, 110.0 (CN), 55.3 (OCH₃).

4'-Cyano-3-ethanoyl-1,1'-biphenyl **8**. Yield, 83%; purity, 99%; ¹H NMR (CDCl₃) δ 8.18 (1H, dt), 7.99 (1H, ddt), 7.82–7.66 (5H, m), 7.59 (1H, dt), 2.66 (3H, s); ¹³C NMR (CDCl₃) δ 197.6 (C=O), 144.5, 139.6, 137.8, 132.6, 131.6, 129.4, 128.5, 127.8, 126.8, 118.6, 111.4 (CN), 26.8 (CH₃).

3,5-Di(trifluoromethyl)-4'-nitro-1,1'-biphenyl **9**. Yield, 88%; purity, 98%; ¹H NMR (CDCl₃) δ 8.43–8.21 (2H, m), 8.11–7.91 (3H, m), 7.87–7.74 (2H, m); ¹³C NMR (CDCl₃) δ 148.1, 144.3, 141.0, 132.7 (q, J_{CF} = 33.6 Hz), 128.3, 127.5 (q, J_{CF} = 4.7 Hz), 124.5, 123.1 (q, J_{CF} = 272.2 Hz, CF₃), 122.5 (st, J_{CF} = 4.3 Hz).

4-Chloro-4'-methoxy-1,1'-biphenyl **10**. Yield, 88%; purity, 99%; ¹H NMR (CDCl₃) δ 7.55–7.45 (4H, m), 7.43–7.34 (2H, m), 7.04–6.94 (2H, m), 3.86 (3H, s); ¹³C NMR (CDCl₃) δ 159.3, 139.2, 132.6, 132.4, 128.8, 127.9, 114.3, 55.3 (CH₃).

1-(4-Nitrophenyl)naphthalene **11**. Yield, 91%; purity, 98%; ¹H NMR (CDCl₃) δ 8.40–8.31 (2H, m) 8.01–7.91 (2H, m), 7.84–7.77 (1H,

m), 7.73–7.41 (6H, m); ¹³C NMR (CDCl₃) δ 147.4, 147.1, 137.7, 133.7, 130.8, 128.9, 128.5, 127.0, 126.7, 126.2, 125.3, 125.1.

5-Phenylpyrimidine **12**. Yield, 85%; purity, 97%; ¹H NMR (CDCl₃) δ 9.19 (1H, s), 8.93 (2H, s), 7.61–7.43 (5H, m); ¹³C NMR (CDCl₃) δ 157.4, 154.8, 134.3, 134.2, 129.3, 128.9, 126.8.

4.4. Catalytic runs

The following procedure was adopted for the standard reaction catalyzed by Pd/CeO₂ (1 mol% Pd). In a thermostatted bath at 25 °C, a 10 mL Schlenk flask was charged in air with a magnetic stir bar, Pd/CeO₂ (Pd 2 wt%) (26.6 mg), 4-tolylboronic acid (**2**) (0.6 mmol), diethylene glycol diⁿbutyl ether (GC internal standard, 0.5 mmol), K₂CO₃ (0.6 mmol), ethanol (1.5 mL) and H₂O (0.5 mL). Then the reaction was started by addition of bromobenzene (**1**) (0.5 mmol). The mixture was extracted from the flask by means of a syringe (the volume of the sample was ca. 0.1 mL). To the sample was added 0.5 mL of water, followed by immediate extraction with dichloromethane (2 × 1 mL). The solution was dried over Na₂SO₄ and analyzed by GC after purification on a micro-column filled with silica gel. All other catalytic trials were carried out similarly, using Celite® instead of silica gel in the case of product **12**.

4.5. Catalyst recycling

Two different methods for catalyst recycling were employed: (a) consecutive reuse, (b) parallel reuse. Method (a): in a thermostatted bath at 25 °C, a 8 mL conical centrifuge test tube was charged in air with a magnetic stir bar, Pd/CeO₂ (2 wt% Pd) (26.6 mg), 4-tolylboronic acid (**2**) (0.6 mmol), diethylene glycol diⁿbutyl ether (GC internal standard, 0.5 mmol), K₂CO₃ (0.6 mmol), ethanol (1.5 mL) and H₂O (0.5 mL), and the reaction was started upon addition of bromobenzene (**1**) (0.5 mmol). After 9 h, the suspension was centrifuged for 3 min at 3500 rpm and the supernatant was removed and analyzed by GC. The solid was washed with water and ethanol, dried on air and reused for the second test, which was performed upon addition in sequence of solvents, **2**, GC internal standard, base and **1**, as indicated above. Again, the reaction was stopped after 9 h by centrifugation and the successive workup was analogous to that previously described. Iteration of this procedure was continued for other nine reuses of the catalyst. The yields of **3** from the GC measurements were the following: 99.9 (first use), 99.9, 99.6, 98.4, 98.4, 97.8, 97.0, 98.7, 97.9, 97.0, 97.6. Method (b): a 50 mL Schlenk flask was charged with a magnetic stir bar, Pd/CeO₂ (2 wt% Pd) (400 mg), 4-tolylboronic acid (**2**) (9 mmol), K₂CO₃ (9 mmol), ethanol (22.5 mL) and H₂O (7.5 mL), and the reaction was started upon addition of bromobenzene (**1**) (7.5 mmol). The reaction was stopped when **1** was quantitatively converted into product **3**, as judged by GC. The solid was then recovered by filtration, washed with water and ethanol and dried under vacuum. A sample of 26.6 mg was used for the first recycling test (amounts of organic substrates, GC internal standard, base and solvents were as indicated above for method (a)), the reaction was stopped after 9 h and the solution was analyzed by GC. The remaining amount of catalyst, after weighting, was used to convert completely **1** into **3** by employing appropriate amounts of organic substrates, base, GC internal standard and solvents. Again, a sample of 26.6 mg was used for the second recycling test which was stopped after 9 h, while all the remaining catalyst was used for the catalytic transformation of **1** and **2** into **3**. This procedure was then iterated for a total of ten reuses of the catalyst. The yields of **3** from the GC measurements were the following: 99.9 (first use), 99.2, 99.4, 99.5, 99.8, 99.3, 99.1, 99.4, 99.2, 99.0, 98.6.

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