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Polyethyleneglycol as scaffold and solvent for reusable C–C coupling homogeneous Pd catalysts

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Abstract

An oxime carbapalladacycle was covalently anchored on a soluble polyethyleneglycol (PEG) (averaged MW 6000 Da) scaffold, and the resulting polymer was used as soluble catalyst for the Suzuki, Sonogashira, and Heck reactions. The reactions were conveniently carried out in PEG as solvent. The catalytic system reported here is among the most active, reusable phosphine-free Pd catalysts. Thus, for low demanding C–C couplings, such as the Suzuki and Sonogashira couplings of aryl bromides, the catalytic system could be reused 10 times with complete substrate conversion and without Pd depletion. However, although the PEG-anchored carbapalladacyle was stable on heating in PEG over extended periods, it decomposes during catalysis to form catalytically less active palladium nanoparticles (averaged particle size 6 nm, $\sigma \pm 2$). For this reason, the initial high catalytic activity of pegylated Pd complex decreases on the first run, completely or partially losing the catalytic activity for highly demanding reactions, such as those of aryl chloride couplings.

Keywords: PEG as solvent; Pegylated carbapalladacycle; Recoverable Pd catalyst; Soluble polymeric catalysts; Reusable Sonogashira catalyst; Reusable Suzuki catalyst

1. Introduction

One current line in catalysis involves developing reusable catalytic systems based on highly active but nonrecoverable catalysts [1–5]. Among the strategies for accomplishing catalyst recovery is to anchor a suitable functionalized derivative of a successful homogeneous catalyst onto a polymeric support [6–10] or an inorganic support [7,11–15]. In this context, using polymers that are soluble in some solvents but insoluble in others is gaining increasing importance as scaffolds on which to attach reagents and catalysts [16–22]. This methodology allows the reaction to be conducted in a homogeneous phase using a solvent that dissolves the polymer as a medium, and after completion of the reaction, the catalytic system can be recovered by precipitation, adding a second solvent in which the polymer becomes insoluble [16,23]. Here we report the use of a PEG-attached Pd organometallic complex as a suitable reusable catalyst for Suzuki [24–31], Sonogashira [32,33], and Heck [5,32,34] C–C cross-coupling reactions. Besides serving as a scaffold to anchor a catalyst, PEG can also be a solvent [35,36], because it becomes liquid at temperatures above 40 °C.

The methodology based on attaching the complex on a soluble polymer somewhat parallels methods developed for fluorous media [37,38] and ionic liquids [39–43]. In these solvents, adequately substituted catalysts can be synthesized in such a way that the affinity and partition coefficient of the catalyst for these nonconventional media increase considerably. This can be achieved simply by introducing in a peripheral position with respect to the catalytic site a tag structurally related to the corresponding solvent, such as a perfluorinated alkyl chain for fluorous media [44] or an imidazolium cation for ionic liquids [12,45]. In our case, selecting PEG as scaffold has considerable advantages, including low toxicity, environmentally tested benignity, and special properties arising from its cation complexation ability. In addition, PEG is readily commercially available at low cost, being formed from ethylene oxide by a simple ring epoxide aperture.

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2. Experimental

The reagents and solvents were obtained from commercial sources and used without purification. The carbapalladacycle was synthesized following the procedure previously described [7,52]. Gas chromatography (GC) analyses were performed on a HP 5890 instrument equipped with a 25-m capillary column of 5% phenylmethylsilicone. GC–mass spectroscopy (MS) analyses were performed on an Agilent 5973N spectrometer equipped with the same column and in the same conditions as for GC. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) were performed with a 300-MHz Bruker Advance instrument using $CDCl_3$, DMSO-d^6, or CD_3OD as a solvent and TMS as an internal standard. UV–vis spectra were recorded on a Shimadzu scanning spectrophotometer using CH_3CN as a solvent. The Pd and Cs content of the organic extracts was determined by removing the solvent under reduced pressure, dissolving the residue in a 1:1 mixture of $HCl:HNO_3$ conc. (ca. 3 mL), diluting the solution in water, and measuring by quantitative atomic absorption spectroscopy (AAS). Transmission electron microscopy (TEM) was performed with a Philips instrument after the sample was dispersed in CH_2Cl_2 and the solvent was allowed to evaporate.

2.1. Synthesis of chlorinated PEG

A solution of PEG (averaged MW 6000 Da, 10 g, 3.33 mmol) in SO_2Cl_2 (40 mL) was placed in a round-bottomed flask capped with a Na_2CO_3 tube to neutralize HCl vapors. The solution was magnetically stirred at 65 °C for 24 h. At this time, the excess SO_2Cl_2 was distilled under reduced pressure, and the residue was placed in the fridge (for ca. 1 h), to achieve almost complete solidification. The solid was washed three times with cold diethyl ether (3 × 200 mL), filtered off, and dried. To remove any trace of SO_2Cl_2 or HCl, the solid was dissolved in neat water and pure K_2CO_3 was added until the solution reached neutral pH. Then the water was removed under reduced pressure, and the chlorinated PEG was isolated as a white solid by dissolving the mixture in CH_2Cl_2, filtering through a Teflon membrane (ALBET, 0.20 μm) under high vacuum, and removing the solvent under reduced pressure (9.9 g, 99%, degree of chlorination by ^{13}C-NMR > 95%, comparing the areas of the peaks at 43 and 68 ppm). IR (neat, cm^{-1}): 3436, 2946, 2888, 2804, 1467, 1455, 1360, 1342, 1281, 1242, 1150, 1110, 1060, 963, 947, 842. ^{1}H NMR δ_H (ppm, 300 MHz, $CDCl_3$): 3.90 (2H, t), 3.80 (2H, t), 3.70 (>200 H, bs), 3.45 (2H, t). ^{13}C NMR δ_C (ppm, 300 MHz, $CDCl_3$): 71.7, 71.0, 68.3, 43.1. Anal. (%) Found: C 50.58; H 9.12.

2.2. Synthesis of PEG-PdL

Chlorinated PEG (5 g, 1.66 mmol) was dissolved in bidistilled water (225 mL), after which a yellow solution of carbapalladacycle (73 mg, 0.25 mmol) dissolved in basic water (pH = 11, 750 mg of K_2CO_3 in 75 mL of water) at 100 °C was added dropwise onto the PEG solution under vigorous stirring, and the resulting mixture was magnetically stirred in a preheated oil bath at 100 °C for 50 h. At this time, the solution was filtered under vacuum and water was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and filtered under vacuum, and the functionalized PEG was precipitated from cold ethanol. The solid was collected, washed with ethanol (2 × 50 mL) and diethyl ether (50 mL), and dried under vacuum pump (10^{-2} atm, 1 h) to obtain a light-brown solid (3.6 g, 72%). IR (neat, cm^{-1}): 3500, 2944, 2884, 2805, 2740, 2694, 1652, 1634, 1467, 1454, 1360, 1342. UV (CH_3CN_3, nm): 380 (b), 320 (b), 280. ^{1}H NMR δ_H (ppm, 300 MHz, $CDCl_3$): 7.60 (d), 7.45 (s), 7.40 (s), 6.90 (d), 6.85 (d), 3.90 (t), 3.75 (t), 3.65 (bs), 3.40 (t), 3.25 (t), 2.1 (s). FAB-MS (m/z): 6572. Anal. (%). Found: C 53.43; H 9.58; N 0.07 (0.059 mmol); Pd 0.6 (0.055 mmol)

2.3. Typical procedure for Suzuki and Heck reactions in water as solvent

2-Chlorobenzonitrile (Suzuki, 27.5 mg, 0.2 mmol) or 4-bromoacetophenone (Heck, 39.8 mg, 0.2 mmol) was placed in a screw-capped vial, and p-tolylboronic acid (Suzuki, 40.8 mg, 0.3 mmol, 1.5 eq.), or styrene (Heck, 34.4 μl, 31.2 mg, 0.3 mmol, 1.5 eq.), potassium carbonate (55.3 mg, 0.4 mmol, 2 eq.), the catalyst PEG-PdL (181 mg, 0.001 mmol, 5 mol%), and bidistilled water (5 mL) were added. The mixture was placed in a preheated oil bath at 100 °C and magnetically stirred. After 24 h, the reaction was cooled and water was removed under reduced pressure. The crude was washed three times with cold diethyl ether (3 × 5 mL), decanting the ethereal supernatant. The extracted ethereal phase was analyzed by GC and GC–MS, using nitrobenzene as an external standard. The solvent was removed under reduced pressure, and the products were analyzed by ^{1}H and ^{13}C NMR. After ether washings, the remaining solid residue was dissolved in CH_2Cl_2 and filtered under vacuum. The extracting solution was concentrated under reduced pressure, and the final brown PEG-PdL solid was weighed and analyzed (Pd: 0.0044 mmol g^{-1}, 8% from the initial). The formation of palladium black aggregates was observed.

2.4. Recovery and reuse of the catalyst

The dry solid was weighed and reused in another run, with proportional amounts of reactants and water added to keep the substrate-to-catalyst and the solvent-to-catalyst ratios constant.

2.5. Typical procedure for Suzuki reactions in PEG as solvent

PEG-PdL (181 mg, 0.001 mmol, 5 mol%) was placed in a screw-capped vial or in a capped round-bottomed flask, and 4-chloroacetophenone (26 μL, 30.8 mg, 0.2 mmol), o-tolylboronic acid (40.8 mg, 0.3 mmol, 1.5 eq.), cesium acetate (154 mg, 0.8 mmol, 4 eq.), and PEG (1.8 g) were added. The mixture was placed in a preheated oil bath at 150 °C (or the required temperature) and magnetically stirred. After 24 h, the reaction was cooled for 1 min, and diethyl ether was added to precipitate the PEG. The solid was washed with diethyl ether

(7 × 20 mL at room temperature or 5 × 20 mL at 40 °C), and the ethereal supernatant was decanted. The combined extracts from the ethereal phase were filtered and analyzed by GC and GC–MS using nitrobenzene as an external standard. After the solvent was removed under reduced pressure, the products were analyzed by ^{1}H and ^{13}C NMR.

2.6. *Recovery and reuse of the catalyst*

For a consecutive run, the PEG mixture was dried under a vacuum pump (10^{-2} atm, 20 min) to remove the remaining diethyl ether, and similar amounts of fresh reagents were added, with the reaction performed under the same conditions. An aliquot of the PEG phase was obtained for analysis by TEM. The dry solid was weighed and reused in a next run, with the proportional amounts of reactants added to keep the substrate-to-catalyst and the solvent-to-catalyst ratios constant.

2.7. *Typical procedure for Sonogashira reactions in PEG as solvent*

PEG-PdL (181 mg, 0.001 mmol, 5 mol%) was placed in a screw-capped vial or in a capped round-bottomed flask, and 4-bromoacetophenone (39.8 mg, 0.2 mmol), phenylacetylene (26.4 µL, 24.8 mg, 0.24 mmol, 1.2 eq.), cesium acetate (76.8 mg, 0.4 mmol, 2 eq.), and PEG (3.6 g) were added. The resulting mixture was placed in a preheated oil bath at 150 °C under magnetic stirring. The experimental procedure, product analysis, and catalyst reuse were performed as described previously for the Suzuki reaction in PEG.

2.8. *Typical procedure for Heck reactions in PEG as solvent*

PEG-PdL (181 mg, 0.001 mmol, 5 mol%) was placed in a screw-capped vial or in a capped round-bottomed flask, and 4-bromoacetophenone (39.8 mg, 0.2 mmol), styrene (34.4 µL, 31.2 mg, 0.3 mmol, 1.5 eq.), cesium carbonate (130 mg, 0.4 mmol, 2 eq.), and PEG (3.6 g) were added. The mixture was placed in a preheated oil bath at 150 °C and magnetically stirred. The experimental procedure, product analysis, and catalyst reuse were performed as described earlier for the Suzuki reaction in PEG.

2.9. *Chemical analysis of the Pd and Cs content in the solid PEG phase*

The final dry PEG phase after several uses (250 mg) was dissolved in bi-distilled water (1 mL) and concentrated HCl/HNO_3 solution (1 mL, 1:1 v/v) was added. The solution was magnetically stirred for 1 h at room temperature. After this time, the solution was diluted with 3 mL of bi-distilled water and extracted with CH_2Cl_2 (3 × 25 mL). Pd and Cs in the aqueous phase were analyzed by quantitative AAS. After this, Pd and Cs in the organic phase were also analyzed by quantitative AAS; no Pd and only minor quantities of Cs were present in the organic phase after the extraction. When the solid PEG phase was treated with only concentrated HCl, Pd was not extracted quantitatively to the aqueous phase, probably due to the beneficial oxidative properties of the nitric acid, that promote the complete oxidation of the Pd nanoparticles.

3. Results and discussion

3.1. *Catalyst synthesis*

As a scaffold on which to anchor a Pd organometallic complex, we chose a commercial PEG of average molecular weight of 6000 Daltons. This polymer is completely soluble in water, CH_3CN, and CH_2Cl_2 but highly insoluble in diethyl ether (even at its boiling point temperature) and methanol. We used this PEG to anchor a carbapalladacycle complex that has been reported by Nájera and coworkers as being one of the most active palladium catalysts for the Suzuki [46,47] and other [33,48–51] cross-coupling reactions. The advantages of this organometallic complex include easy preparation [7,52] and accessibility of the ligand. Furthermore, the presence of a phenolic group makes the complex easily anchorable by nucleophilic substitution onto appropriate supports containing leaving groups [7,12, 14]. We synthesized our catalytic polymer in two steps, as indicated in Scheme 1.

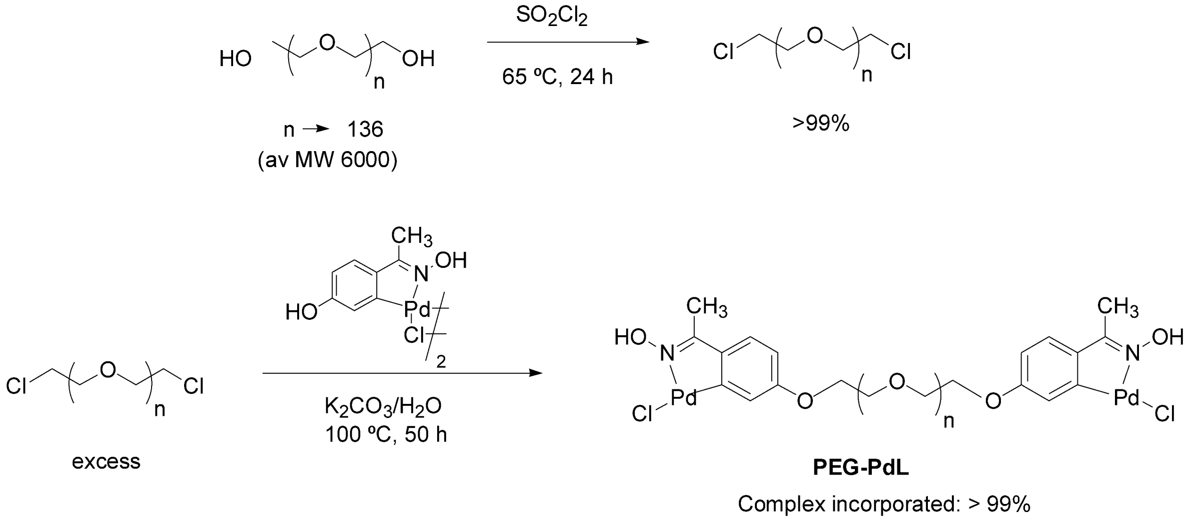
The first step involves formation of the chlorinated PEG from PEG-OH by reaction with thionyl chloride. The percentage of PEG chlorination (>90%) was estimated from the relative intensity in ^{13}C NMR of the peaks corresponding to the terminal methylene groups attached to chlorine (43 ppm) or hydroxy groups (68 ppm). In a subsequent step, an excess of chlorinated PEG was reacted, in basic aqueous medium, with the oxime complex previously prepared by reaction of Li_2PdCl_4 and acetophenone oxime [7,52].

The Pd content of the resulting PEG-PdL was determined by chemical analysis to be 0.055 mmol g^{-1}. This analysis is in good agreement with the N content of PEG-PdL determined by combustion chemical analysis. The loading of PdL-PEG is about 20% of the maximum theoretical loading estimated according to the average molecular formula. This indicates that we have a mixture of polymers having two, one, and zero Pd complexes attached, with the unsubstituted PEG being the predominant component. Nevertheless, we notice that the presence of uncompletely functionalized PEG is not detrimental for the catalytic activity of the attached complex. In fact, as we show later, PEG can be used as the solvent of choice for this catalytic system, and an excess of PEG could play a positive role in stabilizing Pd nanoparticles as they are formed from complex decomposition.

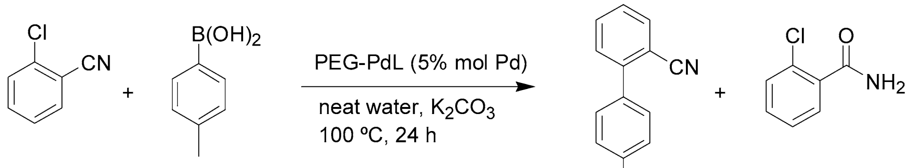
3.2. *Catalytic tests*

3.2.1. *Reactions using water as solvent*

Using the mixture PEG-PdL as a catalyst, we screened a series of general Pd-catalyzed C–C bond-forming reactions with the aim of studying the reusability of the system. Preliminary reactions were carried out in water as a solvent, but the results were not fully satisfactory. Thus, we started with



Scheme 1. Synthesis of the polymeric PEG-PdL catalyst.



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1st use	42%	-
2nd use	10%	84%

Scheme 2. Results obtained for the Suzuki reaction of chlorobenzonitrile (27.5 mg, 0.2 mmol) and *p*-tolylboronic acid (40.8 mg, 0.3 mmol, 1.5 eq.), using potassium carbonate (55.3 mg, 0.4 mmol, 2 eq.) as base and PEG-PdL as catalyst (181 mg, 0.001 mmol, 5 mol%) in water (5 mL).

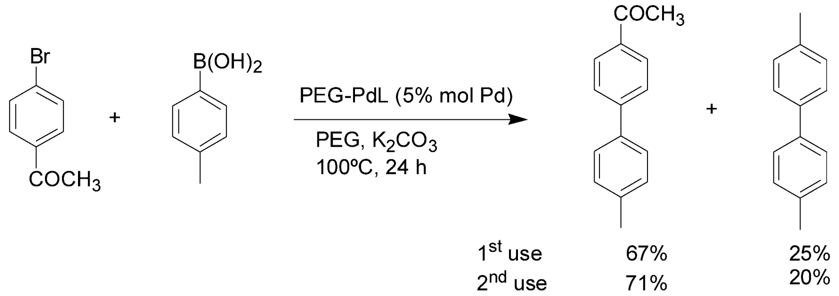
the Suzuki coupling of aryl chlorides, a process previously reported by Nájera in water using dissolved PdL carbapalladacycle as a catalyst [46]. As could be anticipated, chloro-substituted aryl halides reacted more slowly and required higher amounts of catalyst than the corresponding bromides. For 4-chloroacetophenone, low product yields were obtained using a substrate-to-Pd molar ratio <2 (30.8 mg × 72 mg of PEG-PdL). In contrast to this, the reaction between phenylboronic and 4-bromobenzoic acids using a substrate-to-Pd molar ratio of 0.02 resulted in a complete conversion of the limiting reagent with almost total selectivity to 4-phenylbenzoic acid. Water as solvent was also tested for the Heck reaction between 4-bromoacetophenone and styrene, whereby 4-acetylstilbene was formed in 87% product yields.

Concerning the reusability of the PEG-PdL catalyst in water, we studied the cross-coupling of *p*-tolylboronic acid and 2-chlorobenzonitrile. This reaction leads to a cyanobiphenyl compound that is one of the compounds produced industrially by Suzuki coupling in largest quantities [2]. Catalyst recovery was possible by concentrating the aqueous solution after the reaction and extracting the products with ethyl ether before using the catalyst in a second run, under the same conditions. The catalyst underwent a considerable decrease in activity using this experimental procedure, and extensive 2-chlorobenzamine was formed due to nitrile hydrolysis by the base needed for the Suzuki coupling. The results are shown in Scheme 2.

These findings indicate that PdL-PEG cannot be easily reused under these conditions. An additional problem is that at temperatures close to the boiling point of water, PEG polymer starts to aggregate, becoming notoriously insoluble. On the other hand, at insufficiently high temperatures, most of the reactants do not become soluble, and the coupling reaction fails. In an attempt to increase the solubility of the substrates in water, we used $NaBPh_4$ as a reactant instead of phenylboronic acid, but found that this replacement also led to a remarkable decrease in the reaction rate and final product yield compared with reactions performed at the same temperature with phenylboronic acid as a reagent. Furthermore, boiling a PEG-PdL solution for a prolonged period leads to significant decomposition of the organometallic complex and formation of black Pd metal particles, as indicated by the color change from yellow to black. For this reason, and considering that PEG-PdL is also highly soluble in PEG, which is commercially available in large quantities and is environmentally friendly, we performed a series of reactions using PEG as solvent.

3.2.2. *Reactions using PEG as solvent*

3.2.2.1. Suzuki coupling The Suzuki reaction of *p*-tolylboronic acid and 4-bromoacetophenone was performed in PEG (average MW 6000 Da) using K_2CO_3 as a base. The corresponding 4-acetyl-4′-methylbiphenyl product was formed in good yield, accompanied by 4,4′-dimethylbiphenyl arising from homocou-



Scheme 3. Results obtained for the Suzuki reaction of 4-bromoacetophenone (39.8 mg, 0.2 mmol) and *p*-tolylboronic acid (40.8 mg, 0.3 mmol, 1.5 eq.), using potassium carbonate (55.3 mg, 0.4 mmol, 2 eq.) as base and PEG-PdL as catalyst (181 mg, 0.001 mmol, 5 mol%) in PEG (450 mg).

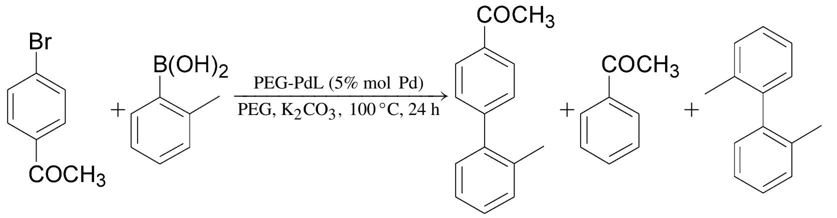
pling of the *p*-tolylboronic acid present in excess. For experimental convenience, the reaction products were recovered by extraction with diethyl ether, which also causes precipitation and solidification of PEG-PdL and PEG. At an industrial scale, extraction of reaction products for PEG can be done using $scCO_2$ [53]. This solid catalytic system (PEG-PdL + PEG) was used in a second run, with no decrease in catalytic activity (Scheme 3). This represents a clear improvement with respect to the use of water as a solvent.

The affect of the PEG:PEG-PdL weight ratio and the presence or absence of oxygen and moisture were addressed for Suzuki coupling between 4-bromoacetophenone and *o*-tolylboronic acid in 1.5 eq. excess. The results are summarized in Table 1. Besides the expected acetylbiphenyl arising from Suzuki cross-coupling, debrominated acetophenone and tolylboronic homocoupling products were also formed. Clearly, oxygen and moisture play significant roles in the catalytic reaction; product yields are significantly decreased using dried PEG under nitrogen. Although various factors may explain the beneficial affect of oxygen and moisture (an area certainly meriting further study), we suggest that oxygen may decrease Pd agglomeration that would be favored in anaerobic conditions, whereas moisture may improve base solubility that otherwise would remain mostly undissolved in dry PEG. Concerning the PEG:PEG-PdL wt% ratio, a 10:1 ratio was considered to represent a good compromise among solvent economy, selectivity, and product yield.

As anticipated, PEG-PdL is considerably less active for the coupling of chlorinated aromatic compounds than for the brominated ones, despite the fact that chloroaromatics are the most interesting for commercial applications [2,5]. Thus, we attempted to optimize the conditions for improving the activity of Suzuki coupling with aryl chlorides. To study this, the coupling of 4-chloroacetophenone and *o*-tolylboronic acid [46] was selected as a model reaction. The first parameter studied was the reaction temperature. The remarkable thermal stability of PEG allowed the use of high reaction temperatures at atmospheric pressure, because no noticeable PEG decomposition occurred up to around 200 °C, after which an increase in reaction temperature of 70–180 °C (Table 2) increased the yield of the cross-coupling product from 4-chloroacetophenone while reducing the percentage of undesirable homocoupling products. Note that although some soluble palladium catalysts promote cross-coupling at much lower temperatures, they use phosphines as ligands, and recovery of the catalytic system is not possible.

Further work was carried out to study the influence of the base, Pd loading, and reaction temperature using the reaction between aryl chlorides and *o*-tolylboronic acid, considered to be a benchmark reaction for assessing catalyst perfor-

Table 1
Results for the Suzuki reaction of 4-bromoacetophenone (39.8 mg, 0.2 mmol) and *o*-tolylboronic acid (40.8 mg, 0.3 mmol, 1.5 eq.) at 100 °C for 24 h reaction time, using potassium carbonate (110.6 mg, 0.8 mmol, 4 eq.) as base, PEG-PdL (181 mg, 0.001 mmol, 5 mol%) as catalyst and PEG as solvent

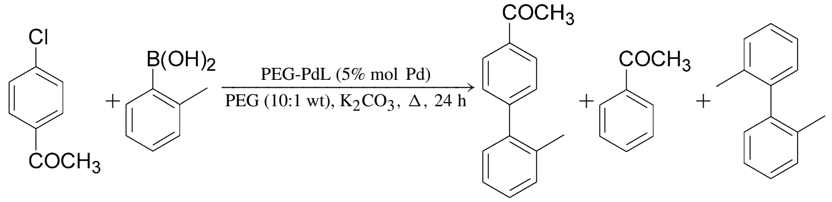


Conditions	PEG/PEG-PdL (wt:wt)	Product (%)	Debromination (%)	Deboronation + homocoupling[a] (%)
Open air	3:1	74	1	70
Open air	10:1	77	2	20
Under nitrogen dehydrated PEG	10:1	21	2	<10
Open air	20:1	81	10	30

[a] Respect from the initial amount of *o*-tolylboronic acid.

Table 2

Results for the Suzuki reaction of 4-chloroacetophenone (26 µl, 30.8 mg, 0.2 mmol) and *o*-tolylboronic acid (40.8 mg, 0.3 mmol, 1.5 eq.) at different temperatures for 24 h reaction time, using potassium carbonate (110.6 mg, 0.8 mmol, 4 eq.) as base, PEG-PdL (181 mg, 0.001 mmol, 5 mol%) as catalyst, and PEG (1.8 g) as solvent



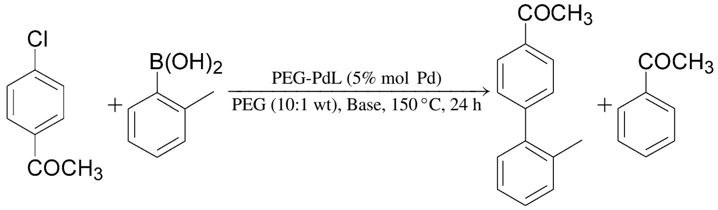
Temperature (°C)	Product (%)	Dechlorination (%)	Deboronation + homocoupling[a] (%)
70	5	3	80
100	6	3	60
150	12	10	50
180[b]	27	2	50

[a] Respect from the initial amount of *o*-tolylboronic acid.

[b] No decomposition of PEG was observed.

Table 3

Results for the Suzuki reaction of 4-chloroacetophenone (26 µl, 30.8 mg, 0.2 mmol) and *o*-tolylboronic acid (40.8 mg, 0.3 mmol, 1.5 eq.) at 150 °C for 24 h reaction time, using PEG-PdL (181 mg, 0.001 mmol, 5 mol%) as catalyst, PEG (1.8 g) as solvent, and different bases (0.8 mmol, 4 eq.)



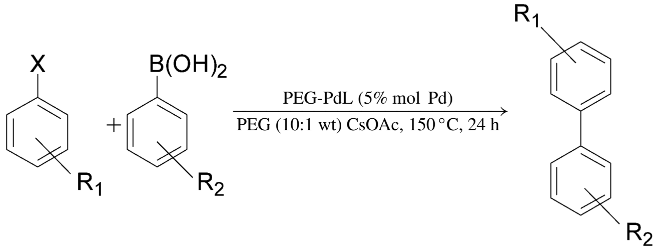
Base	Product (%)	Dechlorination (%)	Other by-products (%)
K_2CO_3	12	10	
KOAc	12	4	
KF	8	40	
Bu_4NBr	1	19	Bromoacetophenone (7)
Bu_4NF	50	17	1-(4-chlorophenyl)-ethanol (reduced reactive) (15)
Bu_4NOAc	2	27	1-(4-chlorophenyl)-ethanol (reduced reactive) (6)
Cs_2CO_3	28	10	
CsF	16	4	
CsOAc	75	2	
CsOAc[a]	10	8	
CsOAc + Bu_4NBr	9	34	Bromoacetophenone (4) 1-(4-chlorophenyl)-ethanol (reduced reactive) (6)

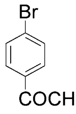
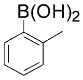
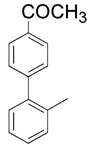
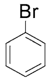
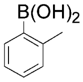
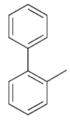
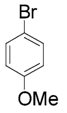
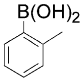
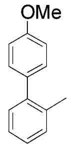
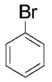
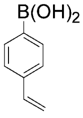
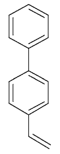
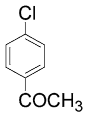
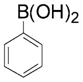
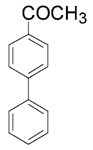
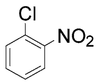
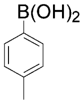
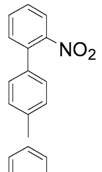
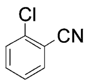
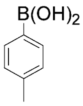
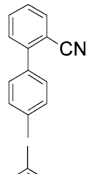
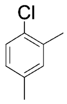
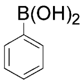
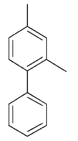
[a] 0.5 mol% of PEG-PdL.

mance. The results are given in Table 3, in which the bases are grouped according the counter cation. The table shows that for $Bu_4N^+F^-$, selectivity was low due to dechlorination and hydrogenation to 1-(4-chlorophenyl)ethanol. We believe that this product is formed by catalytic reductive hydrogenation, with hydrogen arising due to the thermal instability of the quaternary ammonium ion.

The best results were obtained with bases having Cs^+ as a counter cation depending on their solubility in PEG. Thus, the most active base was CsOAc, for which the highest cross-coupling yield was achieved. These results can be rationalized considering that PEG can form a loose complex with large alkali metal ions such as Cs^+, leaving the basic anion as a free ion in the medium and increasing the base solubility and strength. To support this hypothesis, we added tetrabutylammonium bromide to cesium acetate dissolved in PEG. Under these conditions, dissociated AcO^- should form an ion pair with Bu_4N^+, after which the overall catalyst efficiency should diminish. As expected, the results in Table 3 indicate that adding tetrabutylammonium had a detrimental effect and clearly inhibited formation of the Suzuki coupling product. Although most of the experiments were performed using 5 mol% of Pd complex as a catalyst, to determine the activity of the PEG-PdL we also carried out an experiment using 0.5 mol% of Pd complex. The results, given in Table 3, suggest that our catalytic system works better with Pd loadings >1% for the Suzuki reaction of

Table 4
Results obtained for the Suzuki reaction of different aryl bromides and chlorides (0.2 mmol) and arylboronic acids (0.3 mmol, 1.5 eq.) at 150 °C for 24 h reaction time, using cesium acetate (192 mg, 1 mmol, 5 eq.) as base, PEG-PdL (181 mg, 0.001 mmol, 5 mol%) as catalyst, and PEG (1.8 g) as solvent

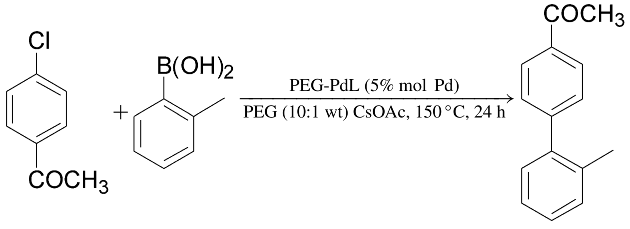


Run	Aryl halide	Boronic acid	Suzuki product	Yield (%)
1				95
2				80
3				53
4				9 (35)[a]
5				43
6				59
7				25
8				0

[a] The number in brackets corresponds to the yield of stilbene arising from the Heck reaction with styrene.

aryl chlorides. Although other soluble palladium systems can effect this reaction with a lower Pd-to-substrate molar ratio, all of them use phosphines as ligands; our PEG-PdL compares favorably with homogeneous phosphine-free Pd catalysts.

Table 5
Results obtained for the Suzuki reaction of 4-chloroacetophenone (26 µl, 30.8 mg, 0.2 mmol) and *o*-tolylboronic acid (40.8 mg, 0.3 mmol, 1.5 eq.) at 150 °C for 24 h reaction time, using cesium acetate (154 mg, 0.8 mmol, 4 eq.) as base, PEG-PdL (181 mg, 0.001 mmol, 5 mol%) as catalyst, and PEG (1.8 g) as solvent



Run	Yield (%)
1 use	>99
2 use	61
3 use	1
4 use[a]	5

[a] Solid washed with diluted HCl:ether.

To determine the scope of Suzuki cross-coupling in PEG, we performed the reaction with other substrates, including aryl bromides and chlorides with electron-withdrawing and electron-donating substituents. The results, given in Table 4, indicate that PEG-PdL in PEG in the absence of annoying phosphine ligands is among the most efficient cross-coupling systems ever reported. As expected, aryl bromides give comparatively higher yields than chlorides, and there is a beneficial influence of the presence of electron-withdrawing substituents on the reaction product yield. These features are in agreement with the general behavior of Pd catalysts [24,25,28,46].

As noted in the Introduction, a main objective of using PEG as a support/solvent is to study the reusability of the system. With this objective in mind, we studied the reusability of the catalyst by performing product extraction after a first reaction cycle. Subsequently, the resulting PEG phase containing palladium together with fresh reagents was allowed to react for a second run, and so on. Using 4-bromoacetophenone as a reactant, essentially complete conversion with the same selectivity as for the fresh catalyst was obtained in four consecutive reuses (conversion, >99%; selectivity, >90%). At that point, we felt that a more demanding test for reusability would be to perform consecutive reactions using a chloride reactant. In this case, as shown in Table 5, the catalytic activity of the PEG system decreased significantly, becoming deactivated on the third use.

To determine the causes of deactivation, we performed TEM of the PEG solid. This technique provides very useful information for understand the mechanism behind catalyst deactivation. As shown in Fig. 1, the presence of Pd nanoparticles is evident in these images. Therefore, the most reasonable proposal for catalyst deactivation is to admit that the carbapalladacycle complex undergoes extensive decomposition under the reaction conditions with the concomitant formation of Pd nanoparticles [10,39,54–59]. These Pd nanoparticles, although still active for some low-demanding Suzuki couplings, are apparently less active than the initial carbapalladacycle complex and will gradually lose activity as reaction and reuse progresses, due to

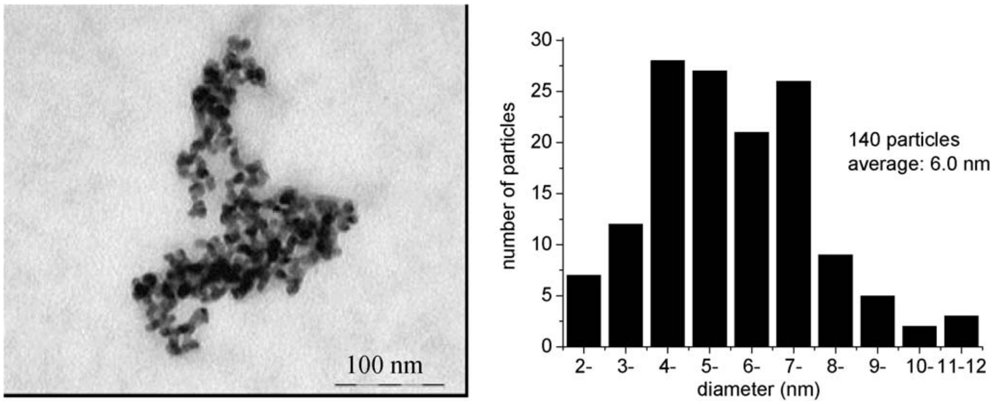
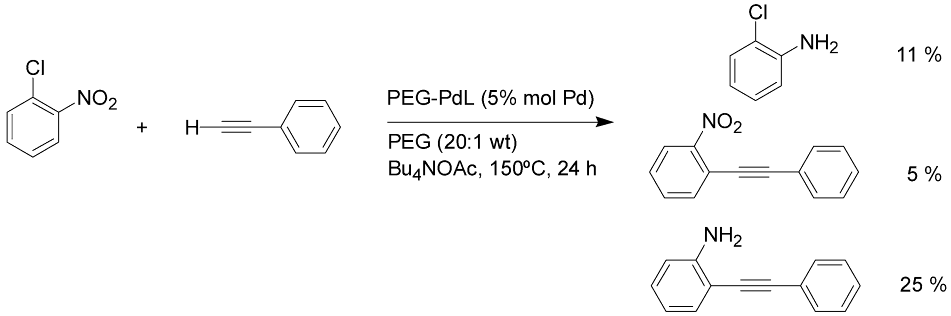


Fig. 1. Transmission electron microscopy image for PEG-PdL after three consecutive Suzuki reactions between 4-chloroacetophenone and *o*-tolylboronic acid (see conditions in experimental section and Table 5 caption) together with its diameter size distribution analysis (averaging five different TEM images of 500 × 500 nm^2).



Scheme 4. Sonogashira coupling of *o*-chloronitrobenzene (15.8 mg, 0.1 mmol) and phenylacetylene (13.2 µl, 12.4 mg, 0.12 mmol, 1.2 eq.), using $Bu_4N^+OAc^-$ (60.4 mg, 0.2 mmol, 2 eq.) as base and PEG-PdL as catalyst (90.5 mg, 0.0005 mmol, 5 mol%) in PEG (1.8 g).

poisoning by inorganic byproducts (Br^- or Cl^-, BO_3^{3-}, Cs^+). Chemical analysis of the ethereal extracts indicated the almost complete absence of Pd, Cs, and B (Pd, 0.9; Cs, 0.00; B, 0.7% of the total amount), indicating that these elements were retained in the PEG phase. Based on this finding, we suggest that coupling of chlorides is catalyzed mainly by the presence of cyclopalladated oxime before being decomposed, with Pd nanoparticles being much less active for this process.

Concerning the size distribution of the Pd nanoparticles formed during the course of the catalytic reaction by complex decomposition, statistical analysis (also presented in Fig. 1) shows an average diameter of ca. 6 nm with a fairly narrow distribution ($\sigma = 2$ nm). We propose that PEG acts as ligand stabilizing small Pd nanoparticles, minimizing the tendency of palladium to undergo agglomeration and particle size growth. This assumption was supported by the finding that prolonged heating had no effect on particle size in the colloidal Pd suspension in PEG.

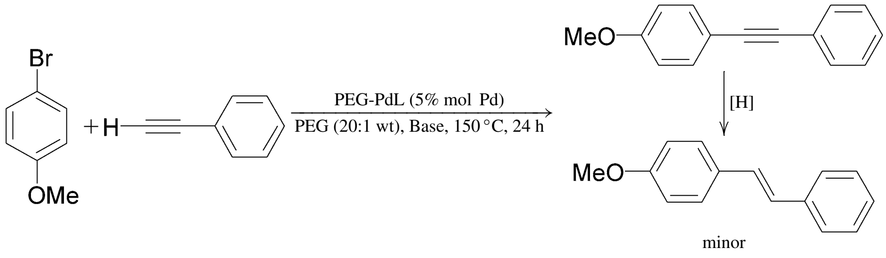
3.2.2.2. Sonogashira coupling We expanded our initial study of the activity of PEG-bonded carbapalladacycle to the Sonogashira coupling of *o*-chloronitrobenzene and phenylacetylene, using $Bu_4N^+OAc^-$ as a base [33]. The results, presented in Scheme 4, indicate that Pd-catalyzed nitro reduction is occurring in a substantial proportion, leading to complex mixtures of nitro and aminoaromatics. Nonetheless, the high activity of the pegylated carbapalladacycle is revealed by the fact that, in the absence of any copper cocatalyst and using a chloro derivative as a reagent, significant yields of diarylacetylenes were formed. Although the source of hydrogen for the nitro reduction is not clear, we speculate that the tetrabutylammonium cation can act as a reducing agent under these conditions, as proposed earlier for $Bu_4N^+F^-$ and 4-chloroacetophenone forming 1-(4-chlorophenyl)-ethanol.

We selected the coupling between 4-bromoanisole and phenylacetylene as a model reaction and studied the behavior of other bases. The selection of 4-bromoanisole instead of *o*-chloronitrobenzene avoids the problems arising from the instability of the nitro group while still using a benchmark reactant (i.e., an electron-rich bromoaromatic). The product yield should give an idea of the activity of PEG-anchored carbapalladacycle. Table 6 summarizes the results obtained as a function of the base used. Note the significant influence of the base on product yield and selectivity. CsOAc gave the best results, with moderate to high product yields, and allowed C–C triple bond reduction in only very minor amounts.

Although substrate conversion was not complete, we attempted to reuse PEG-PdL for this highly demanding Sonogashira coupling. However, the catalyst became significantly deactivated in the second use. In view of the results given in Table 6, in which PEG-PdL was not a sufficiently active catalyst to enable the Sonogashira coupling of aryl chlorides, we felt that the reusability of PEG-PdL should be tested for other, less demanding Sonogashira couplings, including the reaction of aryl bromides with electron-withdrawing substituents.

Table 6

Results for the Sonogashira reaction of 4-bromoanisole (12.4 µl, 18.7 mg, 0.1 mmol) and phenylacetylene (13.2 µl, 12.4 mg, 0.12 mmol, 1.2 eq.) at 150 °C for 24 h reaction time, using cesium acetate (38.5 mg, 0.2 mmol, 2 eq.) as base, PEG-PdL (90.5 mg, 0.0005 mmol, 5 mol%) as catalyst, and PEG (1.8 g) as solvent



Base	Product (%)	Stilbene (%)
Bu_4NOAc	12	5
Bu_4NF	36	1
CsOAc	61	1
CsF	16	<1[a]

[a] 44% of (4,4′-dimetoxi)biphenyl from self-coupling of the aryl halide was observed.

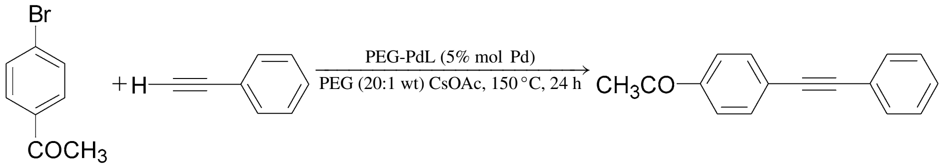
In this regard, it has been reported [60] that Sonogashira coupling between 4-bromoacetophenone and phenylacetylene is a benchmark test, particularly for the use of phosphine and copper-free systems. Generally, this coupling requires the use of phosphine ligands and copper salts for total conversions; only highly active homogeneous systems are exceptions to this general behavior [60]. To the best of our knowledge, the recoverable and reusable palladium catalysts reported in the literature for the Sonogashira coupling of aryl bromides or chlorides are based on phosphine Pd complexes [37,41,43,61–63] except in the case of double-layered hydroxide-supported Pd nanoparticles [64]. First, as in the Suzuki reaction, we studied the intrinsic activity of the PEG-PdL catalyst performing experiments using 0.5 or 5 mol% of catalyst. Similar activity at the final reaction time (conversion, >99%) was observed.

This result demonstrates that for this probe reaction, our catalytic system is comparable in activity with some of the most active Pd-phosphine complexes reported previously [24,25,65]. Results for reusability are summarized in Table 7. In view of the aforementioned precedents, the results obtained for reuse of the PEG-based catalytic system in the benchmark reaction of 4-bromoacetophenone and phenylacetylene are remarkable and without equivalent in the literature.

We found that the PEG-bonded carbapalladacycle, in which a turnover number of about 180 mol of product per mol of Pd was reached, still showed very high activity after 10 uses, demonstrating the reusability of the PEG-bonded carbapalladacycle. Concerning the reaction mass balance, note that product extractions in the reuse experiments were performed simply with cold ethyl ether. Working under these experimentally convenient conditions, we found that the mass balances in the first runs were not satisfactory, and some products must have been retained in the PEG phase due to insufficient ethyl ether extraction (see Table 7). However, on consecutive reuses, saturation of PEG as a solvent was reached and, as the number of reuses increased, considerably better mass balances up to complete product recovery were obtained. Obviously, an alternative, less convenient extraction procedure using hot ethyl ether can lead

Table 7

Results obtained for catalyst reuse in the Sonogashira reaction of 4-bromoacetophenone (39.8 mg, 0.2 mmol) and phenylacetylene (26.4 µl, 24.8 mg, 0.24 mmol, 1.2 eq.) at 150 °C for 24 h reaction time, using cesium acetate (76.8 mg, 0.4 mmol, 2 eq.) as base, PEG-PdL (181 mg, 0.001 mmol, 5 mol%) as catalyst, and PEG (3.6 g) as solvent



Use	1	2	3	4	5	6	7	8	9	10
Yield[a] (%)	>99	>99	>99	>99	>99	>99	>99	88	83	75
Mass balance (%)[b]	66	50	68	60	86	86	90	94	97	116

[a] The selectivity is >99%.

[b] Mass balance as defined by mol of product and 4-bromoacetophenone recovered by ether extraction from the PEG solution divided by initial 4-bromoacetophenone mol, in percentage.

Table 8
Chemical analysis of Pd and Cs, measured by quantitative atomic absorption spectroscopy after acidic HCl/HNO_3 treatment of the combined ethereal extracts of several reuses

Extracts corresponding to uses	Pd		Cs	
	mol ($\times 10^6$)[a] in the extracts	Leaching from PEG[b] (%)	mol ($\times 10^6$)[a] in the extracts	Leaching from PEG[c] (%)
1–3	0	0	0.063	0.006
4–6	0	0	0.5	0.02
7–10	0.092	1.0	2.3	0.07

[a] Amount found in the combined extracts.
[b] Respect to the initial Pd amount.
[c] Respect to the accumulative amount of Cs.

to almost full mass balances in even the first run, but the experimental procedure using hot ether is unnecessary when the system will be reused.

The amounts of Pd and Cs remaining in the PEG phase on consecutive reuses of the catalytic system were inferred from chemical analyses of the combined ethereal extracts after the catalytic reactions. To minimize the error of the analytical method, we concentrated the combined extracts of several successive reactions and determined the global Pd and Cs content by quantitative AAS. The results, given in Table 8, indicate that almost all of the initial Pd present in the PEG phase remained unextracted after recovery of the reaction products during reuse. The Pd content of the products extracted in the 10 uses was 25 ppm, well within the industrial specification limits for products of Pd-catalyzed reactions. The same is valid for the Cs^+ ions. Thus, although initially 5 eq. of CsOAc were used, the fact that it remained in PEG is advantageous, because subsequent reuses may require lesser amounts. The results, based on the indirect measurement of Pd and Cs in the extracts, were also roughly confirmed by direct chemical analyses of Pd and Cs in the PEG phase. Note, however, that exact determination of the percentage of Pd and Cs in the PEG phase is complicated by the fact that reuses require the addition of the corresponding stoichiometric amounts of base, and that some reaction byproducts (e.g., bromide salts) remain in the PEG phase after the reaction, making determination of the exact Pd and Cs percentage in the PEG phase somewhat uncertain due to the PEG phase weight increase.

We also analyzed the Pd and Cs content of the solid PEG phase by dissolving these phases in HCl/HNO_3 solution, extracting the resulting acid aqueous solution with dichloromethane to remove PEG and some organic compounds and analyzing Pd and Cs content in the acid aqueous phase. This analytical procedure gives an estimation of Pd and Cs content corresponding to about 85 and 95%, respectively, of the initial amount, consistent with Pd and Cs metals remaining in the PEG phase after 10 reuses.

Concerning reusability, one area of interest was to determine the formation and size evolution of the Pd nanoparticles from the initial carbopalladacycle complex. As determined in an independent blank control, the Pd complex anchored to PEG was stable on prolonged heating (100 °C) in PEG in the absence of reagents; however, most of the carbapalladacycle complex decomposes during the first catalytic cycle, forming Pd nanoparticles. Statistical analysis of the average particle size distribution after the first use for the Sonogashira coupling of 4-bromoacetophenone and phenylacetylene shows formation of Pd nanoparticles with an average of 14 nm and a broad size distribution of 4–40 nm. Importantly, this particle size distribution varied sluggishly toward larger particle sizes, broadening the dispersion in size on 10 reuses, and thus similar TEM images of the PEG-containing Pd catalyst are observed after extensive reuse (Fig. 2). This result is again consistent with the proposal that PEG as a macroligand is surrounding and interacting with the dispersed Pd nanoparticles, stabilizing them and minimizing their tendency to undergo agglomeration and particle size growth. Moreover, a small Pd particle size allows more favorable oxidative addition of the aryl halide to the Pd(0) atoms at the rim of the nanoparticles [66,67].

3.2.2.3. Heck coupling To test the activity of PEG-PdL as a reusable catalyst for the Heck reaction, we selected the coupling of 4-bromoanisole with styrene [48,50]. The reaction was carried out in the presence of 5 mol% of Pd in PEG as solvent at 150 °C. The activities of three different Cs bases were screened; the results are presented in Table 9.

Although Cs_2CO_3 was the most active base, the selectivity of Heck coupling was not fully satisfactory, and formation of differing proportions of two byproducts arising from styrene oxidation to acetophenone and homocoupling of aryl bromide was observed. When the expected stilbene was present in the reaction mixture in sufficiently high concentration, the presence of small amounts of its corresponding *cis*-isomer was also seen. When 4-bromoacetophenone was reacted instead of electron-rich aryl bromides, higher yields of the corresponding stilbene were obtained, accompanied by variable amounts of aryl bromide homocoupling and styrene oxidation.

Reusability of the PEG-PdL was also studied; the results are given in Table 9. There was a significant decrease in activity between the first and the second uses, indicating a change in the Pd catalytic species having distinctive activity. Note that for the Heck coupling of 4-bromoacetophenone and styrene, formation of acetophenone increased for the reused PEG-PdL catalyst, but in this case acetophenone could arise either from the debromination of 4-bromoacetophenone or from the partial oxidation of styrene. No differences in activity between the second and the third reuse were observed. As in the previous C–C cross-coupling reactions, chemical analyses indicate the almost complete absence of Pd ($<1.3\%$ of the initial amount) and Cs ($<0.01\%$) in the combined extracts. This suggests that catalyst

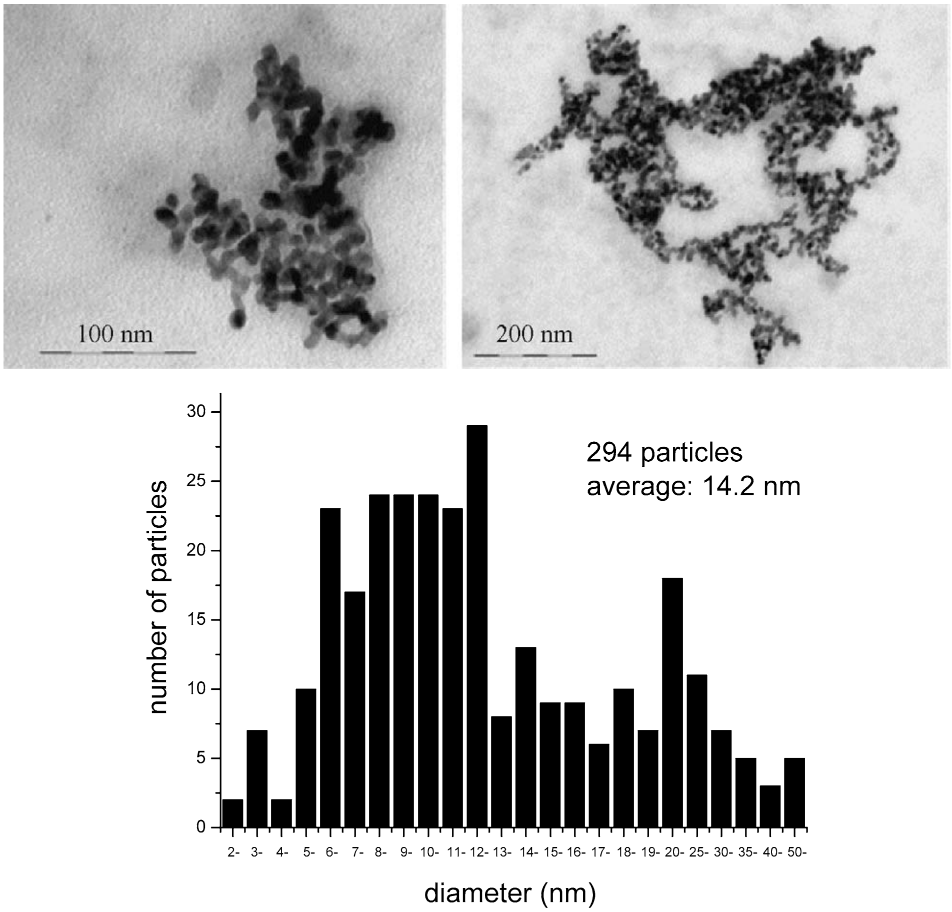
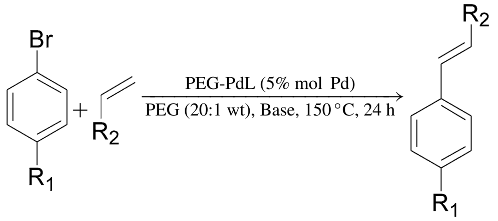


Fig. 2. Transmission electron microscopy images for PEG-PdL after one (upper left) or ten (upper right) consecutive Sonogashira reactions between 4-bromoacetophenone and phenylacetylene (see conditions in experimental section and Table 7 caption) together with particle size distribution analysis of palladium nanoparticles after ten reuses, obtained averaging five different TEM images of 500 × 500 nm^2.

Table 9

Results for the Heck reaction of different aryl bromides (0.2 mmol) and alkenes (0.3 mmol, 1.5 eq.) at 150 °C for 24 h reaction time, using different bases (0.4 mmol, 2 eq.), PEG-PdL (181 mg, 0.001 mmol, 5 mol%) as catalyst, and PEG (3.6 g) as solvent



Entry	R_1	R_2	Base	Product[a] (%)	By-products[b] (%)
1	$-OCH_3$	–Ph	CsOAc	4 (–)	8
2	$-OCH_3$	–Ph	Cs_2CO_3	52 (1)	10
3	$-OCH_3$	–Ph	CsF	15 (1)	14
4	$-COCH_3$	–Ph	Cs_2CO_3	76 (3)	15
5[c]	$-COCH_3$	–Ph	Cs_2CO_3	11 (2)	15
6[d]	$-COCH_3$	–Ph	Cs_2CO_3	11 (2)	11
7[e]	–H	–O–*n*Bu	Cs_2CO_3	6 (1)	–

[a] In brackets (*cis* + 1,1) isomers.

[b] (4,4′-Dimethoxy)biphenyl + acetophenone.

[c] Reused from entry 4.

[d] Reused from entry 5.

[e] At 80 °C for 44 h.

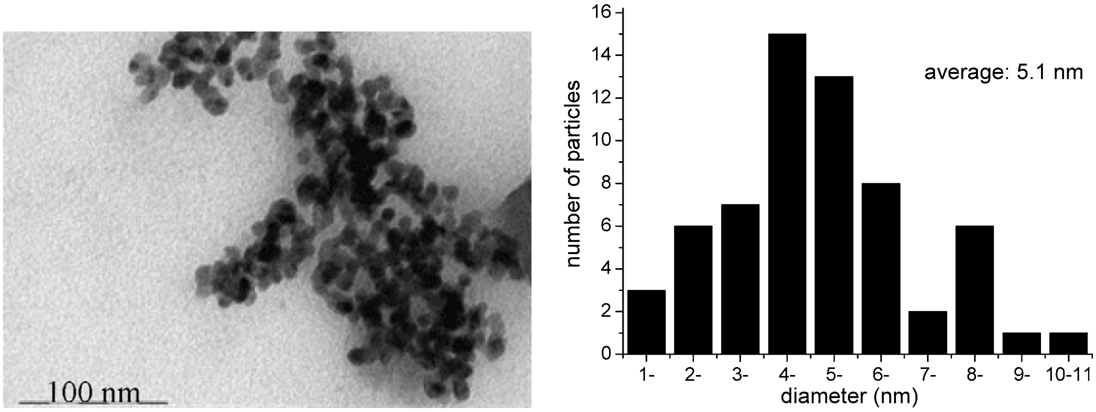


Fig. 3. Transmission electron microscopy image for PEG-PdL after three consecutive Heck reactions between 4-bromoacetophenone and styrene (see conditions in experimental section) together with size distribution analysis of palladium nanoparticles obtained averaging three different TEM images of 500 × 500 nm^2.

deactivation is not related to the loss of Pd from the PEG phase. Electron microscopy of the PEG-PdL after three consecutive uses of the catalyst for the Heck reaction (Fig. 3) revealed, as expected, the presence of Pd metal nanoparticles with an average particle size of ca. 5 nm. In this case, a relatively narrow particle size distribution (1–10 nm) was observed. According to this, we suggest that the initial carbapalladacycle exhibited higher activity as a catalyst for the Heck reaction, after which the catalytic activity of the cyclopalladated complex decreased significantly when the complex was progressively decomposed and Pd nanoparticles started to form in PEG. These Pd nanoparticles still exhibited a high catalytic activity for the Heck reaction of iodobenzene as a substrate [10], which is directly related to the easy oxidative addition of aryl iodide to the Pd(0) atoms on the surface of the nanoparticles [66,67]. Following a similar rationalization, we suggest here that these nanoparticles present in PEG-Pd on reuse still retain a residual catalytic activity for the coupling of aryl bromides (Table 9, entries 5 and 6).

Finally, we also studied the activity of PEG-PdL as a catalyst for the Heck reaction of an aliphatic enol ether, namely *N*-butyl vinyl ether [68]. In this case, the low boiling point of this reagent makes it advisable to limit the reaction temperature to 80 °C; this is most likely the reason for the lower yield observed for the corresponding C–C coupling with this reagent (Table 9, entry 7).

4. Conclusion

PEG is suitable both as a scaffold to anchor active Pd catalysts and as a novel solvent to conduct C–C coupling reactions. Thus, PEG (averaged MW 6000 Da), being solid at room temperature, is a suitable liquid medium for developing a recoverable and reusable Pd catalyst. Starting from PEG-PdL, although the Pd complex is stable on prolonged heating in the absence of reagents, the decomposition and formation of Pd metal nanoparticles occur during reaction/reuse of the system. For some highly demanding reactions, reusability is low due to the lower activity of Pd particles developed in PEG compared with the initial carbapalladacycle. In other, less demanding Pd-catalyzed reactions, such as the Sonogashira coupling of aryl bromides, the catalytic system can be reused for many cycles with no significant decrease in catalytic activity. This is because PEG acts as a ligand stabilizing the Pd nanoparticles around 6 nm, although a relatively broad particle size distribution may occur, depending on the reactants. However, the lack of large Pd particles causes the systems to retain some catalytic activity, because small particles are more prone to oxidative addition in the presence of aryl halide with formation of the aryl Pd(II) intermediate. PEG has the advantage of retaining Pd and other inorganic salts formed as by-products during the C–C coupling reaction. Therefore, no detectable depletion of Pd from the PEG phase occurs, and product recovery becomes very simple experimentally. The foregoing findings, along with low cost and nontoxicity, make PEG a preferred solvent for many Pd-catalyzed reactions, with significant advantages over perfluorinated solvents and ionic liquids.

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