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Water-Soluble Palladium Nanoparticles: Click Synthesis and Applications as a Recyclable Catalyst in Suzuki Cross-Couplings in Aqueous Media

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Dedicated to the memory of Professor José Manuel Concellón Gracia

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A new PEG-tagged material, which was prepared by a three-fold copper-catalyzed [3+2] cycloaddition (click chemistry), was found to act as an efficient stabilizer for palladium nanoparticles. The newly formed material proved to be active as a recyclable catalyst in Suzuki coupling; the presence of polyether chains allowed for the catalytic runs to be conducted in aqueous media.

Introduction

The development of chemical processes with minimal environmental impact has become an important challenge for the chemistry community. One of the promising directions in this field has been the development of industrial processes that use water as a cheap, safe, and non-toxic reaction medium. In particular, the development of water-based catalytic processes has spurred the development of an entire field of water-soluble catalytic systems. The majority of these are discrete metal complexes supported by the ligands that are suitably modified to impart greater hydrophilicity. Commonly, such ligands are based on traditional phosphorus-, sulfur- and nitrogen-containing derivatives.[1] Most often, efforts have been directed towards adapting traditional palladium-based catalytic processes, such as hydrogenation, oxidation, as well as C–C, and C–heteroatom bond-forming reactions to the aqueous medium.[2] Frequently, the palladium-catalyzed Suzuki–Miyaura cross-coupling[3] reaction, which is a powerful synthetic tool in its own right, has served as a "sharpening stone"[4] for the honing of other cross-coupling processes. In this context, a relatively small but steadily growing number of publications have been devoted to the catalytic applications of water-soluble metal nanoparticles (NPs).[5] These developments, in addition to their potential in sustainable green chemistry, may help simplify separation, recovery and recycling of the catalyst, which is a scientific challenge of economic and environmental relevance.[1]

In catalytic processes, metal NPs tend to be more reactive than their particulate metal counterparts as a result of increasing surface area with decreasing particle size. However, a protective agent is necessary to prevent aggregation of transition-metal NPs in solution towards the thermodynamically favored bulk metal.[6] Such stabilization has been provided by polymers, dendrimers, β-cyclodextrines, and ionic and non-ionic surfactants, in addition to nitrogen-, phosphorus-, and sulfur-based ligands, and several ionic compounds. The nature of the protecting shield determines to a great extent the solubility of the resulting metal colloid. Thus, a judicious choice of stabilizer may render the material soluble in organic, aqueous or even fluorous medium, and may facilitate recycling. In 2001, some of us described the use of fluorous-phase soluble palladium nanoparticles as recoverable catalysts for C–C coupling reactions.[7] More recently, we also reported that the use of 15-membered triolefinic azamacrocycles bearing polyoxyethylenated chains (Figure 1, product **1**) led to the formation of water-soluble metal NPs (Pd, Pt, Ru, Rh, and Au).[8] Of these, the Pd NPs appeared to be promising catalysts in the Heck[8a] and the Suzuki[8b] reactions in organic or aqueous media. Furthermore, the material proved to be recoverable and was reused in several catalytic runs. In addition to this work, several other examples of metal NPs supported by PEG-based moieties have been reported. Thus, poly(ethylene oxide) units are present in some block copolymers and in some surfactants that have been used as protecting agents (Au, Pd and Pt NPs).[9] PEG-modified dendrimers[10] and

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PEG derivatives immobilized on silica[11] have also been described (Au and Pd NPs, respectively). A few reports[12] are available on the use of PEG-tagged compounds (such as bisphenol A derivatives, phosphane oxides, bipyridines, Fischer carbenes, and oxime carbapalladacycles) as capping agents or direct metal sources for Pd and Au nanoclusters. Although there are examples of metal NPs dispersed in unfunctionalized poly(ethylene glycols),[13] in most instances the incorporation of amino[14] or thiol[15] functional groups in the PEG matrix was found to improve the stabilizing capacity for Au NP formation.

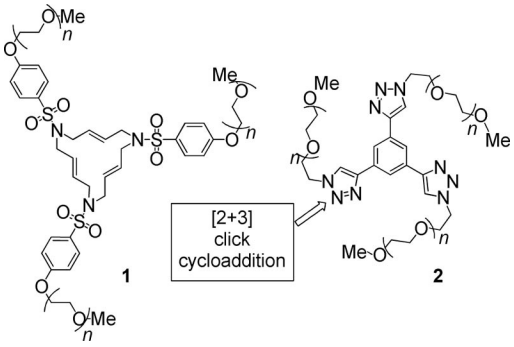


Figure 1. PEG-tagged compounds **1** and **2**.

Encouraged by the promise shown by PEG-tagged macrocycles of type **1** in the formation of metal NPs,[8] we sought to improve the structure by creating a stabilizer that would be easier to prepare and that would lead to NPs with a better performance in the catalytic C–C coupling reactions in aqueous media. Given that system **1** featured a coordinating macrocycle flanked by three long polyoxyethylenated chains, a related PEG-tagged compound (Figure 1, product **2**) was devised. Its synthesis would be accomplished through a copper-catalyzed Huisgen 1,3-dipolar cycloaddition between an azide and an alkyne ("click chemistry").[16]

The "click" [2+3] cycloaddition reaction has recently been applied to the synthesis of a number of materials in polymer chemistry and material science, mainly as a result of their virtually quantitative yields, displaying high selectivity and functional-group tolerance in a wide range of substrates.[17] In the case of the proposed stabilizer **2**, the reaction would also provide potentially coordinating triazole moieties, which would presumably enhance the ability of the material to stabilize metal NPs.[10c,18]

We report herein the synthesis of **2** and its use in the formation of palladium NPs. We also report the application of the newly prepared materials as recoverable catalysts for Suzuki–Miyaura coupling reactions of aryl iodides and bromides in aqueous media.

Results and Discussion

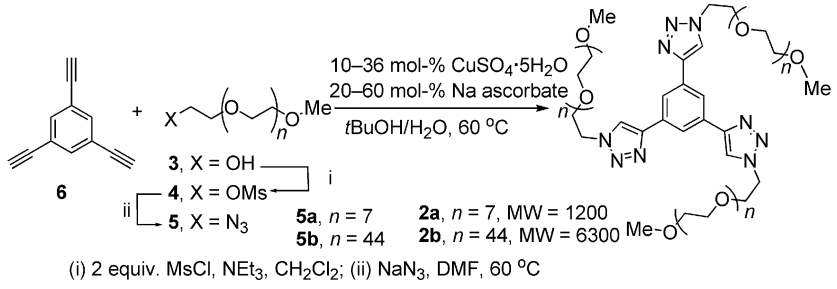
Preparation of Materials 2a and 2b

Two different chain lengths for the MeO-PEG-X component were used in this investigation, one with $n = 7$ and the second with $n = 44$. The preparation of compounds **2** (**2a**, $n = 7$; **2b**, $n = 44$) is summarized in Scheme 1.

Treatment of commercially available MeO-PEG-OH **3a** and **3b** ($n = 7$ and $n = 44$, respectively) with methanesulfonyl chloride in the presence of triethylamine furnished the corresponding mesylates **4a** and **4b**. Although initially a procedure involving toluene as solvent and a large excess of mesylating agent was applied,[19] we later found that on larger scales (5 g for **3a** and 10 g for **3b**), the use of dichloromethane and only 2 equiv. of methanesulfonyl chloride[20] was more convenient to give the corresponding mesylates in 95 and 61% yield, respectively. These were then allowed to react with sodium azide in dimethylformamide at 60 °C for 1 d to afford the corresponding azides **5a** and **5b** in good yields. The second coupling partner, 1,3,5-triethynylbenzene (**6**), was obtained in two steps from 1,3,5-tribromobenzene through 1,3,5-tris(trimethylsilylethynyl)benzene as described previously.[21]

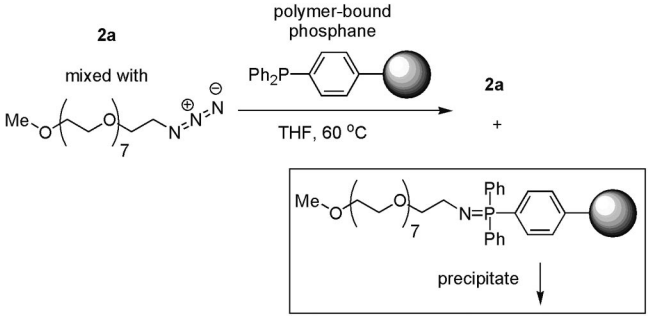
Finally, threefold copper-catalyzed 1,3-dipolar cycloaddition between trialkyne **6** and either azide **5a** or **5b** (1:3.3 molar ratio) under the standard click conditions[22] provided the desired compounds **2a** and **2b** in nearly quantitative yields. However, our initial attempts to remove the residual azide **5** (used in slight excess) using standard procedures encountered some difficulties due to the predominance of the polyether chain in both the starting material and the product, which led to poor separation. We, therefore, sought to develop alternative procedures for obtaining **2a** and **2b** free of impurities.

In the case of compound **2a** ($n = 7$), purification was based on the reactivity of organic azides with phosphanes (the Staudinger reaction). Thus, the crude reaction mixture was treated with a commercial polymeric triphenylphosphane in tetrahydrofuran (THF) at 50 °C (Scheme 2) until



Scheme 1. Synthesis of stabilizers **2a** and **2b**.

the IR spectrum showed complete disappearance of the RN_3 band at 2099 cm^{-1}. At this point, the polymer-bound phosphinimine byproduct and the unreacted phosphane were removed by filtration, leaving behind pure **2a**.

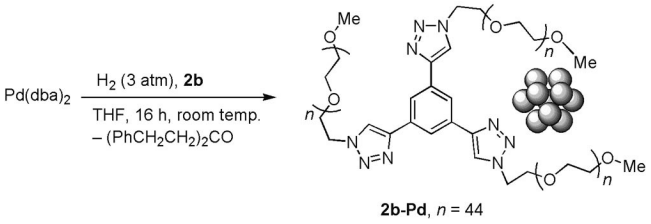


Scheme 2. Removal of azide **5a** by Staudinger trapping.

Although the same procedure could, in principle, be employed for the purification of compound **2b** (MW ≈ 6300), we opted for the removal of excess azide **5b** (n = 44, MW ≈ 2000) by dialysis in water using a membrane with a molecular weight cut-off (MWCO) of 3500 Da.[19]

Preparation of Palladium Nanoparticles

With compounds **2a** and **2b** in hand, we tested their suitability as stabilizers of palladium NPs. Although chemical reduction of Pd^{II} salts remains the most widely used method for the synthesis of Pd^0 nanoparticles,[5] a careful and laborious search for optimal reaction conditions is often necessary. On the other hand, the organometallic approach (reduction and subsequent displacement of a ligand from an M^0 organometallic precursor) developed by Chaudret and collaborators,[23] offers a more straightforward and reliable alternative for the controlled synthesis of metal NPs with a narrow size distribution. The preparation of palladium NPs stabilized by phosphorus- or nitrogen-based ligands following the organometallic synthesis has been reported.[24] Very recently, this methodology has also been used for the synthesis of water-soluble ruthenium and platinum NPs by using 1,3,5-triaza-7-phosphaadamantane as stabilizer.[25] In a collaboration with Chaudret and Philippot, we have previously succeeded in the preparation of ruthenium[26] and platinum[27] NPs in the presence of heavily fluorinated protecting agents. Taking advantage of these precedents, we opted to use this strategy for the preparation of palladium NPs with the newly obtained PEG-based stabilizers **2** (Scheme 3, Table 1).



Scheme 3. Synthesis of palladium(0) NPs **2b**-Pd.

As summarized in Table 1, a variety of conditions were tested by using both **2a** and **2b**; in all cases, hydrogenation with $[Pd(dba)_2]$[28] was performed in a stirred THF solution under H_2 (3 bar) at room temperature overnight.

Factors such as the length of the PEG side chains, the Pd/**2** ratio, and the concentration were all found to have an effect on the outcome (Table 1). Initial experiments were performed by using **2b**. Thus, an experiment involving 0.016 mmol of **2b** and a Pd/**2b** molar ratio of 1:1 led to the generation of NPs with a mean diameter of 2.3 nm, as determined by TEM (Table 1, Entry 1). A Pd/**2b** ratio of 2:1 did not improve the yield based on palladium, and the mean size of the nanoparticles was 4.8 nm (Table 1, Entry 2). When the conditions described in Table 1, Entry 1 were reproduced on a larger scale (0.064 mmol of **2b**), a material with similar mean particle size and with a similar percentage of Pd was obtained with an improved yield (Table 1, Entry 3). In all cases, the resulting homogeneous black suspension was filtered through a Milli-Pore filter to eliminate residual bulk palladium. The solvent was then evaporated, and the black residue was washed thoroughly with diethyl ether to remove the hydrogenated dibenzylideneacetone; the remaining insoluble material was then examined by high-resolution transmission electron microscopy (HRTEM) (Figure 2). In all cases, the presence of **2b** as stabilizer was confirmed by IR and ^1H NMR analysis, and the metal content in the samples was determined by inductively coupled plasma (ICP) analysis. Electron diffraction (ED) confirmed the presence of palladium(0) with a face-centered cubic (fcc) structure (Figure 2). The newly obtained nanoparticulated materials were soluble in water, THF, dichloromethane and ethyl acetate, and insoluble in diethyl ether.

Table 1. Preparation of Pd NPs stabilized by polyoxyethylenated compounds **2** by decomposition of $[Pd(dba)_2]$ under H_2 (3 bar) (Scheme 3).[a]

Entry	Pd [mmol][b]	**2** ([mmol])	Pd/**2**	[Pd][c]	Pd [%][d]	Yield [%][e]	Ø [nm][f]
1	0.016	**2b** (0.016)	1:1	0.0016	1.57	59.5	2.3 ± 0.4
2	0.032	**2b** (0.016)	2:1	0.0016	2.13	45.6	4.8 ± 1.2
3	0.064	**2b** (0.064)	1:1	0.0016	1.58	70.4	2.7 ± 0.7
4	0.015	**2a** (0.015)	1:1	0.0015	–	–[g]	–
5	0.145	**2a** (0.145)	1:1	0.0072	–	–[g]	–

[a] Performed in THF at room temperature overnight. [b] Based on %Pd in $[Pd(dba)_2]$ determined by ICP. [c] In mol/L. [d] Determined by ICP analysis. [e] Defined as (total Pd in nanoparticles)/(initial Pd) × 100. [f] Mean diameter determined by TEM. [g] Bulk Pd.

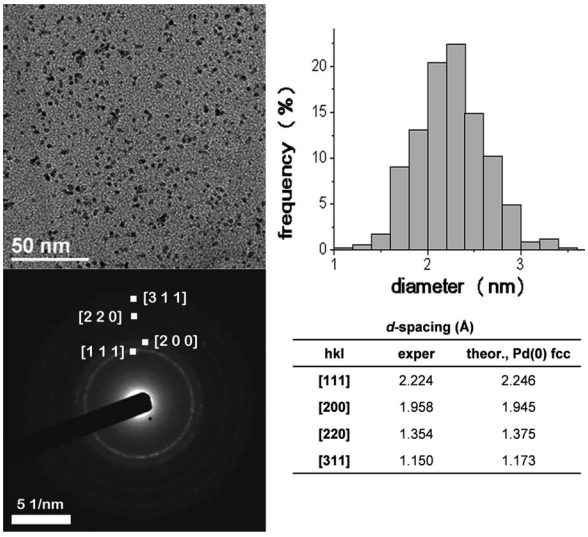


Figure 2. HRTEM image and particle-size distribution diagram for **2b**-Pd (top); electron-diffraction pattern for **2b**-Pd (bottom).

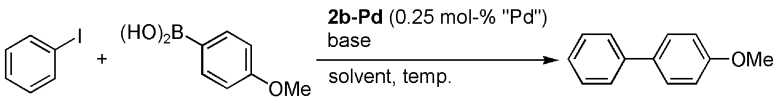
Despite the good stabilizing ability of **2b**, the procedure failed with **2a** (n = 7), leading to the precipitation of bulk metal (Table 1, Entries 4 and 5).

Assay of Palladium Nanoparticles as Recoverable Catalysts in Suzuki–Miyaura Cross-Coupling

The activity and recyclability of palladium nanoparticles **2b**-Pd was first tested in the Suzuki cross-coupling between iodobenzene (**7a**) and *p*-methoxyphenylboronic acid (**8a**) to give *p*-methoxybiphenyl (**9aa**; Table 2). Several bases, solvent systems, reagent ratios, and temperatures were assayed by using a 0.25% loading of palladium. Triethylamine in water as solvent afforded good yields in the first cycle (Table 2, Entries 1 and 2), but the recyclability was poor (Table 2, Entries 3 and 4). After testing other bases and solvent mixtures (Table 2, Entries 5–10), it was found that good performances were achieved by using K_2CO_3 in water at 100 °C (Table 2, Entry 5), K_2CO_3 in acetone/water (3:2) at 60 °C (Table 2, Entry 8), and KOH in water at 60 °C (Table 2, Entry 9). The catalyst was recycled (Table 2, Entries 5 and 8) by a simple procedure: the coupling product was extracted with diethyl ether (in Entry 8, acetone was previously removed), and the aqueous phase containing the catalyst was used in the next run (1 equiv. of the base was added and the corresponding amount of acetone when required). HRTEM analysis after the first cycle showed no appreciable change in the nanoparticle size, although ICP analysis of the organic fraction did show ppm levels of leached Pd. The latter observation may explain the increase in the reaction time upon recycling (see the Supporting Information).

Next, we turned our attention to the coupling of aryl bromides. Before testing the more challenging substrates, we investigated the model Suzuki reaction between *p*-bromoacetophenone (**7b**) and phenylboronic acid (**8b**), to afford 4-acetylbiphenyl (**9bb**) (Table 3). Several reaction conditions (base, solvent, molar ratios of reagents) were tested by using a multireactor with closed vessels at 100 °C, monitoring the GC yield of **9bb** after 16 h (Table 3, Entries 1–16). In most cases, the formation of **9bb** was accompanied by small amounts of biphenyl as a result of the homocoupling of **8b**. This side-reaction was minimized by the use of potassium and cesium carbonates in acetone/water (3:2) with 1.5 equiv. of **8b** (Table 3, Entries 14 and 15). When the reaction progress was monitored over time (see the Supporting Information), it was found that the use of either of these two bases in an acetone/water mixture (3:2) at 100 °C

Table 2. Suzuki cross-coupling between iodobenzene (**7a**) and *p*-methoxyphenylboronic acid (**8a**) catalyzed by **2b**-Pd.[a]

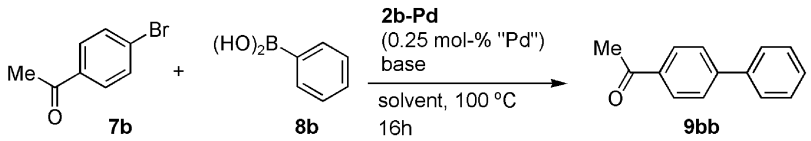


7a **8a** **9aa**

Entry	Base	Solvent	**7a**/**8a**/base	T [°C]	t [h]	**9aa** [%][b]
1	NEt_3	H_2O	1:2:3	90	1	94
2	NEt_3	H_2O	1:2:3	60	3	60
3	NEt_3	H_2O	1:1.25:2.5	60	4/21/144	99/53/–[c]
4	NEt_3	H_2O	1:1.25:2.5	90	1.5/7	83/–[c]
5	K_2CO_3	H_2O	1:1.25:2.5	100	2.2/2.5	97/50[c,d]
6	K_2CO_3	H_2O	1:1.5:2.5	60	1	70
7	K_2CO_3	MeOH/H_2O (3:1)	1:1.25:2.5	60	3	70
8[e]	K_2CO_3	acetone/H_2O (3:2)	1:1.5:2.5	60	0.5/3.5/5.5	95/91/91[b,c]
9	KOH	H_2O	1:1.25:2.5	60	1	93
10	KOH	THF/H_2O (3:1)	1:1.25:2.5	50	168	67

[a] Using **7a** (0.3 mmol) and Pd (0.25 mol-%) in solvent (4.5 mL); for details see Exp. Sect. and the Supporting Information. [b] Yields of isolated product. [c] Yields for consecutive cycles. [d] Calculated based on NMR integration. [e] At triple the normal scale (i.e., based on 0.9 mmol **7a**).

Table 3. Suzuki cross-coupling between *p*-bromoacetophenone (**7b**) and phenylboronic acid (**8b**) catalyzed by **2b**-Pd.[a]



Entry	Base	Solvent	**8b** [equiv.]	**9bb** [%][b]	Ph–Ph [%]
1	KOH	H_2O	1.25	64	5.4
2	NaOAc	H_2O	1.25	37	0.9
3	CsOAc	H_2O	1.25	35	0.9
4	K_2CO_3	H_2O	1.25	83	2.9
5	Na_2CO_3	H_2O	1.25	80	4.7
6	K_2CO_3	H_2O	1.5	>99	6.9
7	K_3PO_4	H_2O	1.5	85	4.1
8[c]	K_2CO_3	H_2O	1.5	>99	6.6
9[c]	Cs_2CO_3	H_2O	1.5	82	1.4
10[c]	K_2CO_3	THF/H_2O (4:1)	1.5	57	0.6
11[c]	Cs_2CO_3	THF/H_2O (4:1)	1.5	59	0.6
12[c]	K_2CO_3	DMF/H_2O (4:1)	1.5	>99	7.8
13[c]	Cs_2CO_3	DMF/H_2O (4:1)	1.5	>99	traces
14[c]	K_2CO_3	acetone/H_2O (3:2)	1.5	>99	–
15[c]	Cs_2CO_3	acetone/H_2O (3:2)	1.5	>99	–
16[c]	Cs_2CO_3	EtOH/H_2O (1:1)	1.5	66	26.5
17[d]	K_2CO_3	acetone/H_2O (3:2)	1.5	99 (3 h) 98 (5.5 h) 99 (10 h) 98 (24 h) 95 (20 h)[e]	–

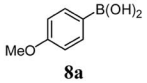
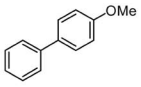
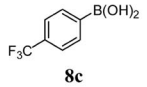
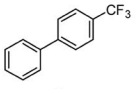
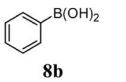
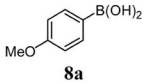
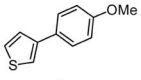
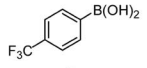
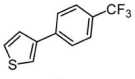
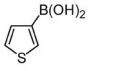
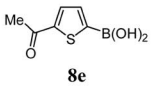
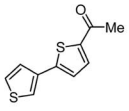
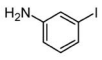
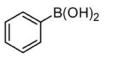
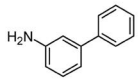
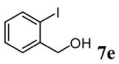
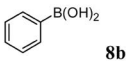
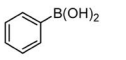
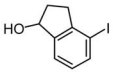
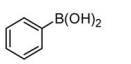
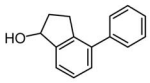
[a] Performed in closed vessels (60 mL) in a multireactor with orbital stirring, with **7b** (0.3 mmol), base (2.5 equiv.) and Pd (0.25 mol-%) in solvent (4.5 mL). Unless stated otherwise, all reactions were run at 100 °C for 16 h. [b] GC yields corrected to internal undecane. [c] Argon and degassed solvent. [d] Reaction performed at 60 °C. [e] Isolated yields in consecutive cycles. Quantitative GC yields at the indicated times.

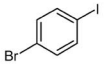
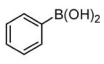
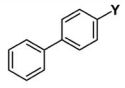
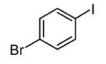
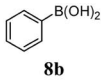
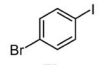
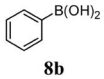
led to a complete reaction after 3 h, with the use of K_2CO_3 leading to a slightly faster process. With this base, lowering the temperature to 60 °C still kept the reaction time under 3 h (see the Supporting Information). Finally, under the optimized reaction conditions, the catalyst **2b**-Pd could be recycled five times (Table 3, Entry 17), leading to good isolated yields in all runs, albeit at the cost of an increase in the reaction time for later runs.

Once the activity and recyclability of **2b**-Pd NPs in aqueous media had been established, the method was extended to the Suzuki coupling of a range of other aryl and heteroaryl halides **7** with several aryl (heteroaryl) boronic acids **8**. The results are summarized in Table 4.

Thus, under the optimized conditions (Table 2, Entry 7), excellent yields were achieved in the coupling of iodobenzene with arylboronic acids **8a** and **8c** (Table 4, Entries 1 and 2). A heteroaryl iodide (3-iodothiophene, **7c**) was also successfully coupled with substituted aryl and heteroaryl boronic acids (Table 4, Entries 3–6). Only in the case of 2-acetylthiophene-5-boronic acid (**8e**) was the reaction sluggish, giving a low yield and resulting in the formation of the protodeboronation product and unreacted **7c** (Table 4, Entry 7). Other aryl iodides, with both the electron-donating and -withdrawing substituents, were allowed to react with arylboronic acid **8b** (Table 4, Entries 8–11) to afford the desired product in isolated yields ranging from 67 to 87%. The system performed well for *ortho*-substituted substrates and was compatible with the presence of amino, hydroxy and carbonyl groups. However, in the case of 2-iodobenzaldehyde (**7f**; Table 4, Entry 10), acetone had to be excluded from the reaction medium, and neat water was used as a solvent to avoid the formation of aldol side-products. Surprisingly, little or no selectivity was achieved for the monoarylation of 4-bromoiodobenzene (**7h**). Thus, use of 1.5 equiv. of **8b** at 60 °C led to a mixture of monosubstituted and disubstituted compounds, **9hb** and **10bhb** (Table 4, Entry 12). Lowering of the reaction temperature and the amount of boronic acid did not improve the selectivity (Table 4, Entry 13). On the other hand, a nearly quantitative yield of the disubstituted compound **10bhb** was obtained under the standard conditions by using a slight excess (2.5 equiv.) of phenylboronic acid (**8b**; Table 4, Entry 14). Similarly, the coupling of substrates **7h** and **7i** led to high yields of the doubly arylated products **10aha**, **10chc**, and **10bib** (Table 4, Entries 15–17). As was the case for **7f**, the presence of an aldehyde moiety in bromide **7j** required just water as solvent to avoid aldol condensation (Table 4, Entry 18). The use of water at 100 °C also proved to be optimal for the coupling of the deactivated anisole derivatives **7k** and **7l** (Table 4, Entries 19 and 20). The more challenging aryl chloride **7m** gave a 17% yield of the coupling product with the phenylboronic acid under the reaction conditions given in Table 4, Entry 21, with the mass balance being the recovered starting material.

Table 4. Suzuki cross-coupling between aryl or heteroaryl halides **7** and boronic acids **8** catalyzed by **2b**-Pd.[a]

Entry	ArX, **7**	Ar'B(OH)$_2$, **8**	Ar-Ar', **9**	Yield (%)[b]
1	 **7a**	 **8a**	 **9aa**	96
2	 **7a**	 **8c**	 **9ac**	84
3	 **7c**	 **8b**	 **9cb**	96
4	 **7c**	 **8a**	 **9ca**	70
5	 **7c**	 **8c**	 **9cc**	92
6	 **7c**	 **8d**	 **9cd**	93
7	 **7c**	 **8e**	 **9ce**	16[c]
8	 **7d**	 **8b**	 **9db**	87
9	 **7e**	 **8b**	 **9eb**	82
10[d]	 **7f**	 **8b**	 **9fb**	67
11	 **7g**	 **8b**	 **9gb**	86

Entry	ArX, **7**	Ar'B(OH)$_2$, **8**	Ar-Ar', **9**	Yield (%)[b]
12	 **7h**	 **8b**	 Y = Br, **9hb** Y = Ph, **10bhb**	17 79
13[e,f]	 **7h**	 **8b**	**9hb** **10bhb**	20 34
14[g]	 **7h**	 **8b**	**10bhb**	97
15[g]	**7h**	**8a**	Y = *p*-MeOC$_6$H$_4$, **10aha**	89
16[g]	**7h**	**8c**	Y = *p*-CF$_3$C$_6$H$_4$, **10chc**	91
17[g]	**7i**	**8b**	**10bib**	98
18[d]	**7j**	**8b**	**9jb**	90
19[h]	**7k**	**8b**	**9kb**	81
20[h]	**7l**	**8b**	**9lb**	77
21[i]	**7m**	**8b**	**9mb**	17[j]

[a] Unless otherwise stated, the reactions were performed in closed vessels (10 mL) by using ArX (0.3 mmol), Ar′B(OH)$_2$ (1.5 equiv.), K_2CO_3 (2.5 equiv.), Pd (0.25 mol-%), acetone/H_2O (3:2, 4.5 mL), 60 °C. [b] Isolated yield. [c] Protodeboronation gave 2-acetylthiophene as the main side-product. [d] Reaction performed in H_2O (4.5 mL) at 60 °C. [e] By using ArB(OH)$_2$ (1.0 equiv.). [f] Performed at room temperature. [g] By using ArB(OH)$_2$ (2.5 equiv.). [h] Reaction performed in H_2O (4.5 mL) at 100 °C. [i] Performed with KOH (2.5 equiv.) in H_2O (4.5 mL) at 130 °C. [j] Yield based on ^{1}H NMR integration.

Conclusions

Using an efficient protocol based on a threefold [2+3] click coupling, new PEG-tagged compounds **2a** and **2b** were prepared. The latter material bearing longer polyether chains was successfully used as a stabilizer for the synthesis of water-soluble palladium NPs by the organometallic approach. The newly prepared nanomaterial **2b**-Pd displayed good activity as a catalyst in the Suzuki coupling of aryl iodides, and the more challenging bromides, in aqueous media, providing good to excellent yields in the coupling of a range of aryl and heteroaryl substrates. The recyclability of the nanocatalyst for aryl iodides and bromides has also been established (up to five cycles) giving rise to good isolated yields in successive runs.

Experimental Section

General Remarks: PEG derivatives **3a** and **3b** were purchased from Fluka and dried as described; substrate **7f** was prepared according to a published procedure,[29] and substrate **7g** was synthesized by using a copper-catalyzed halide-exchange reaction[30] as described in the Supporting Information. Other substrates were purchased from commercial sources and used as received. The preparation of

Pd NPs was carried out in Fischer–Porter glassware. Water Milli-Q was used for the preparation and purification of compounds; the organic solvents were purchased from Scharlau. Dialysis membrane was obtained from Spectrum Laboratories [Spectra Por 3 Regenerated Cellulose (RC)] with a formal molecular weight cut-off (MWCO) of 3500. When required, experiments were carried out with standard high-vacuum and Schlenk techniques. The solvents were dried and distilled just before use. Catalytic runs with orbital stirring were carried out in a Heidolph synthesis system equipped with 12 sealed 60 mL glass vessels. All NMR measurements were carried out at the Servei de Ressonància Magnètica Nuclear at the Universitat Autònoma de Barcelona. Spectra were recorded with Bruker AC250 (250 MHz for ^{1}H), Avance360 (360 MHz for ^{1}H), and AvanceII 400 MHz (400 MHz for ^{1}H) spectrometers. MALDI-TOF-MS analyses were performed at the Institute of Material Science of Aragon (Unidad de Nuevos Materiales Orgánicos, Facultad de Ciencias, CSIC-Universidad de Zaragoza) and at the Proteomics and Bioinformatics facility at the Universitat Autònoma de Barcelona (a member of ProteoRed network) with a Bruker mass spectrometer, model Ultraflex with Modus Reflection. The ionization was performed with a laser source operating at 337 nm and at 25 kV. In the MALDI experiments, ditranol was used as a matrix for products **4b**, **5b**, and **2b**; DHB or matrix-free conditions were used for the analysis of other compounds. Infrared spectra were recorded with a Bruker Tensor 27 instrument equipped with an ATR Golden Gate cell and a diamond window. ICP measurements of palladium content were carried out at the Serveis Cientificotècnics of the Universitat de Barcelona with a multichannel Perkin–Elmer instrument, model Optima 3200 RL. TEM analyses were performed at the Servei de Microscòpia of the Universitat Autònoma de Barcelona, with a JEOL JEM-2010 model instrument operating at 200 kV. The TEM measurements were carried out by sonication of the nanoparticulate material in THF for several minutes; then a specially produced structureless carbon support film, which has a thickness of 4–6 nm, was placed in the solution for a few seconds and dried before observation. The size distributions were determined by manual analysis of enlarged micrographs by measuring a high number of particles on a given grid to obtain a statistical size distribution and a mean diameter (Gatan Digital Micrograph Program). Gas chromatographic analysis was accomplished with an Agilent Technologies 7890A GC system equipped with an Agilent HP-5 column (30 m × 0.320 mm × 0.25 μm). The integrated areas and peak positions in the chromatograms were referenced internally to undecane in Table 3, Entries 1–16. Mass spectral analysis of the Suzuki products were carried out with an Agilent 6850 GC system equipped with a 5975C Triple Axis EI Mass Detector. Melting points were determined with a Reichert brand melting-point apparatus. Alugram SIL G/UV$_{254}$ sheets (Macherey–Nagel) were used for TLC. Column chromatography was carried out by using SDS brand silica gel with a grain size of 35–70 μm and a pore size of 60 Å.

Synthesis of Mesylate 4a: Commercial MeO-PEG-OH **3a** (average n = 7; 5.0 g, 14.2 mmol) was dried by heating at 80 °C under vacuum overnight. The material was then dissolved in anhydrous CH_2Cl_2 (100 mL), and triethylamine (6 mL, 4.37 g, 43.2 mmol) was added. The mixture was cooled to 0 °C, and methanesulfonyl chloride (2.2 mL, 1.49 g, 28.42 mmol) was added dropwise with stirring for 15 min. When all of the reagent was added, the mixture was stirred at 0 °C for an additional 15 min, and then stirred at room temp. for 4 h. The reaction mixture was then filtered through a plug of silica gel with CH_2Cl_2 as eluent and the solvent was evaporated to afford an orange oil. This residue was partitioned between CH_2Cl_2 and water, the organic phase was dried with anhydrous sodium sulfate, and the solvent was evaporated to give **4a** as a pale-yellow oil (5.8 g, 95% yield). IR (ATR, neat): $\tilde{\nu}$ = 2869, 1454, 1348, 1095, 917, 800 cm^{-1}. ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 3.05 (s, 3 H, SO_2Me), 3.34 (s, 3 H, OMe), 3.51–3.52 (m, 2 H, CH_2), 3.61–3.62 (m, 26 H, CH_2), 3.72–3.76 (m, 2 H, CH_2CH$_2$OMes), 4.33–4.36 (m, 2 H, CH_2OMes) ppm. MALDI-TOF MS: m/z range for [M + Na] from 353 (5 × CH_2CH_2O units) to 705 (13 CH_2CH_2O units) separated by 44 Da (CH_2CH_2O); the most intense peak was at 485 (8 CH_2CH_2O units).

Synthesis of Mesylate 4b: Commercial MeO-PEG-OH **3b** (average n = 44; 10.0 g, 5 mmol) was dried by heating at 80 °C overnight under vacuum. The material was then dissolved in anhydrous CH_2Cl_2 (140 mL), and triethylamine (2.1 mL, 1.53 g, 15.1 mmol) was added. The mixture was cooled to 0 °C, and methanesulfonyl chloride (0.8 mL, 1.184 g, 10.2 mmol) was added dropwise whilst stirring for 15 min. Upon addition of all of the reagent, the mixture was stirred at the same temperature for an additional 15 min, then at room temp. for 3.5 h. At this point, the reaction mixture was filtered through a plug of silica gel, and the plug was washed with additional portions of CH_2Cl_2. The solvent was evaporated, and the oily residue was triturated with diethyl ether to yield compound **4b** as a white solid, which was isolated by filtration, washed and dried under vacuum (6.29 g, 61%). IR (ATR, neat): $\tilde{\nu}$ = 2884, 1468, 1342, 1102, 959, 843 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.06 (s, 3 H, SO_2CH_3), 3.36 (s, 3 H, OCH_3), 3.51–3.53 (m, 2 H, CH_2), 3.62 (m, 174 H, CH_2), 3.73–3.76 (m, 2 H, CH_2CH$_2$OMes), 4.35–4.37 (m, 2 H, CH_2OMes) ppm. MALDI-TOF MS: m/z range for [M + Na] from 1806 (38 CH_2CH_2O units) to 2511 (54 CH_2CH_2O units) separated by 44 Da (CH_2CH_2O); the most intense peak was at 2114 (45 CH_2CH_2O units).

Synthesis of Azide 5a: Sodium azide (2.781 g, 42.34 mmol) was added to a solution of **4a** (1.806 g, 4.22 mmol) in dimethylformamide (400 mL), and the stirred mixture was heated at 60 °C for 24 h. The solvent was evaporated under reduced pressure, and the white solid residue was partitioned between CH_2Cl_2 and water. The organic phase was dried with anhydrous sodium sulfate, and the solvent was evaporated to afford **5a** as a pale-yellow oil (1.574 g, 100% yield). IR (ATR, neat): $\tilde{\nu}$ = 2865, 2099, 1452, 1286, 1098, 942, 850 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.38–3.40 (m, 5 H, OCH_3 and CH_2), 3.53–3.56 (m, 2 H, CH_2), 3.64–3.69 (m, 28 H, CH_2) ppm. MALDI-TOF MS: m/z range for [M + Na] from 215 (2 CH_2CH_2O units, $CH_2CH_2N_3$, OMe) to 655 (12 CH_2CH_2O units, $CH_2CH_2N_3$, OMe) separated by 44 Da (CH_2CH_2O), the most intense peak was at 346 (5 CH_2CH_2O units, $CH_2CH_2N_3$, OMe).

Synthesis of Azide 5b: Sodium azide (1.034 g, 15.75 mmol) was added to a solution of **4b** (3.275 g, 1.57 mmol) in dimethylformamide (200 mL), and the stirred mixture was heated at 60 °C for 24 h. The solvent was evaporated at reduced pressure, and the residue was partitioned between CH_2Cl_2 and water. The organic phase was dried with anhydrous sodium sulfate, and the solvent was evaporated. Upon addition of diethyl ether to the residue, azide **5b** precipitated as a white solid, which was filtered, washed with diethyl ether, and dried (2.78 g, 87% yield). IR (ATR, neat): $\tilde{\nu}$ = 2881, 2103, 1963, 1466, 1454, 1341, 1103, 958, 842 cm^{-1}. ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 3.36–3.39 (m, 5H, OCH_3 and CH_2), 3.81–3.41 (m, 178 H, CH_2) ppm. MALDI-TOF MS: m/z range for [M + Na] from 1534 (32 CH_2CH_2O units, $CH_2CH_2N_3$, OMe) to 2440 (48 CH_2CH_2O units, $CH_2CH_2N_3$, OMe) separated by 44 Da (CH_2CH_2O), the most intense peak was at 1666 (35 CH_2CH_2O units, $CH_2CH_2N_3$, OMe).

Synthesis of PEG-Tagged Stabilizer 2a: To a stirred solution of azide **5a** (0.576 g, 1.41 mmol) and **6** (0.065 g, 0.43 mmol) in a mix-

ture of *tert*-butayl alcohol (5.4 mL) and water (1 mL) maintained under argon and protected from light, a solution of $CuSO_4 \cdot 5H_2O$ (38.2 mg, 0.15 mmol, 12%) in water (2 mL) was added followed by a solution of sodium ascorbate (57 mg, 0.29 mmol, 22%) in water (3 mL). The stirred mixture was left at room temp. in the dark for 24 h; then the organic solvent was evaporated, and the remaining aqueous solution was extracted with CH_2Cl_2. The organic phase was dried with anhydrous sodium sulfate, and the solvent was evaporated to give a pale-yellow oil. Purification of the crude mixture was undertaken as follows. Anhydrous THF (3.5 mL) was added to polymeric triphenylphosphane (125 mg) in a Schlenk flask. The stirred mixture was heated at 50 °C for 1 h, then the solvent was removed with a cannula. The operation was repeated two more times. The solution of the crude mixture containing **2a** and excess **5a** in anhydrous THF (4 mL) was added to the Schlenk flask containing the previously washed polymeric triphenylphosphane, and the mixture was stirred at 50 °C until no azide signal was observed by IR spectroscopy. The mixture was centrifuged to remove the polymer, and the solvent from the supernatant solution was evaporated to give pure **2a** as a pale-yellow oil (0.589 g, 99.7%). IR (ATR, neat): $\tilde{\nu}$ = 2867, 1457, 1258, 1096, 798 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.33–3.35 (m, 15 H, OCH_3 and CH_2OMe), 3.53–3.65 (m, CH_2 of PEG), 3.92–3.94 (m, 6 H, CH_2 CH_2-triazole), 4.60–4.64 (m, 6 H, CH_2-triazole), 8.18 (s, 3 H, triazole-H), 8.32 (s, 3 H. ArH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 50.5, 59.06, 61.7, 69.6, 70.3, 70.6 (br.), 71.9, 72.6, 121.7, 122.3, 132.0, 147.1 ppm. MALDI-TOF MS: *m*/*z* range for [M + H] from 850 (9 CH_2CH_2O units, 3 CH_2CH_2, 3 OMe, benzenetriazole core) to 1554 (25 CH_2CH_2O units, 3 CH_2CH_2, 3 OMe, benzenetriazole core) separated by 44 Da (CH_2CH_2O); the most intense peak was at 1202 (17 CH_2CH_2O units, 3 CH_2CH_2, 3 OMe, benzenetriazole core).

Synthesis of PEG-Tagged Stabilizer 2b: To a stirred solution of azide **5b** (4.037 g, 1.98 mmol) and **6** (0.0905 g, 0.63 mmol) in a mixture of *tert*-butyl alcohol (7.2 mL) and water (1.1 mL) maintained under argon and protected from light, a solution of $CuSO_4 \cdot 5H_2O$ (167.7 mg, 0.672 mmol, 36%) in water (3 mL) was added followed by a solution of sodium ascorbate (261.5 mg, 1.13 mmol, 60%) in water (7.2 mL). The stirred mixture was left at room temp. in the dark for 2 h, the organic solvent was evaporated, and the remaining aqueous solution was extracted with CH_2Cl_2. The organic phase was dried with anhydrous sodium sulfate, and the solvent was evaporated to afford a pale-yellow solid. Purification of the crude mixture was undertaken as follows. The mixture was suspended in water, and the insoluble part was removed by centrifugation. The aqueous solution was placed in a dialysis bag (MWCO 3500 membrane) and introduced into pure water in a beaker provided with magnetic stirring. Every hour, the aqueous solution from the beaker was removed and replaced by fresh pure water. After 5 h, the azide **5b** was no longer observed in this aqueous solution (IR monitoring). The solvent from the aqueous solution of the dialysis bag was evaporated under reduced pressure to afford pure **2b** as a pale-yellow solid (3.609 g, 96% yield). IR (ATR, neat): $\tilde{\nu}$ = 2882, 1466, 1341, 1101, 959, 842 cm^{-1}. ^1H NMR ($CDCl_3$, 360 MHz): δ = 3.37–3.40 (m, 15 H, OCH_3 and CH_2OMe), 3.42–3.45 (m, 6 H, CH_2), 3.53–3.63 (m, CH_2 of PEG), 3.81–3.84 (m, 6 H, CH_2), 3.92–3.96 (m, 6 H, CH_2CH_2-triazole), 4.61–4.63 (m, 6 H, CH_2-triazole), 8.19 (s, 3 H, triazole-H), 8.32 (s, 3 H, ArH) ppm. MALDI-TOF MS: *m*/*z* range for [M + Na] from 5413 (112 CH_2CH_2O units, 3 CH_2CH_2, 3 OMe, benzenetriazole core) to 6865 (145 CH_2CH_2O units, 3 CH_2CH_2, 3 OMe, benzenetriazole core) separated by 44 Da (CH_2CH_2O); the most intense peak was at 6116 (128 CH_2CH_2O units, 3 CH_2CH_2, 3 OMe, benzenetriazole core).

Synthesis of Palladium(0) Nanoparticles Stabilized by 2b (2b-Pd): Table 1, Entry 1. A Fischer–Porter apparatus equipped with a magnetic stir bar was charged with **2b** (100 mg, 0.016 mmol) and [$Pd(dba)_2$] (9.8 mg, 0.016 mmol). The apparatus was closed, and the contents were subjected to three evacuate–refill cycles with argon. Anhydrous THF (10 mL) was added and the system was purged with H_2 three times (bringing the pressure of H_2 to 3 atm), and then the mixture was stirred at room temp. for 18 h. The hydrogen was evacuated, and the solution was filtered through a Milli-Pore filter. The solvent from the filtrate was evaporated and the black solid residue was washed with diethyl ether and dried to afford the nanoparticulate material (65 mg, 59.5% yield with respect to initial palladium). The IR and ^1H NMR spectra are identical to those of **2b**. Pd: 1.57% (ICP); size of the nanoparticles: (2.3 ± 0.4) nm (TEM).

Suzuki Cross-Coupling Between *p*-Bromoacetophenone (7b) and Phenylboronic Acid (8b) To Give *p*-Acetylbiphenyl (9bb) Catalyzed by 2b-Pd Nanoparticles: Table 3, Entry 17. Given that **2b**-Pd is air-stable and for reasons of convenience, the cross-coupling reactions were conducted in screw-top disposable tubes to prevent the loss of solvent during heating.

A screw-top sealable tube was charged with a magnetic stir bar, *p*-bromoacetophenone (**7b**; 58.5 mg, 0.3 mmol), phenylboronic acid (**8b**; 55.9 mg, 0.45 mmol), K_2CO_3 (103.7 mg, 0.75 mmol) and **2b**-Pd NP (0.25 mol-% Pd). Acetone/water (3:2, 4.5 mL) was added, and the tube was sealed and heated to 60 °C. The reaction was monitored by gas chromatography until it was complete. The tube was then allowed to cool to room temp., and the product was extracted with Et_2O, reserving the catalyst-containing aqueous fraction for subsequent runs. The organic fraction was concentrated, and the residue was partitioned between water and CH_2Cl_2. The resulting organic fraction was separated and washed with additional water, dried with anhydrous Na_2SO_4, and the solvents were evaporated. Compound **9bb** was obtained in pure form as a white solid (for yields see Table 3, Entry 17). The aqueous fraction was reused for four more cycles, by each time adding *p*-bromoacetophenone (58.5 mg, 0.3 mmol), phenylboronic acid (55.9 mg, 0.45 mmol), acetone (2.7 mL), and K_2CO_3 (41.8 mg, 0.3 mmol). After each cycle, the reaction was treated in a manner analogous to the first run.

Supporting Information (see footnote on the first page of this article): Spectral data for **2**, **4**, and **5**. HRTEM and particle size distribution histograms for **2b**-Pd (Table 1, Entries 1–3); reaction progress plots, general procedure for Suzuki cross-couplings (Table 4) and characterization data for the corresponding cross-coupling products **9**.

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