

Article

Immobilized Palladium Nanoparticles on Zirconium Carboxy-Aminophosphonates Nanosheets as an Efficient Recoverable Heterogeneous Catalyst for Suzuki–Miyaura and Heck Coupling

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Abstract: Zirconium phosphate glycine diphosphonate nanosheets (ZPGly) have been used as support for the preparation of solid palladium nanoparticles, namely Pd@ZPGly. Thanks to the presence of carboxy-aminophosphonate groups on the layer surface, ZPGly-based materials were able to stabilize a high amount of palladium (up to 22 wt %) also minimizing the amount of metal leached in the final products of representative important cross-coupling processes selected for proving the catalysts' efficiency. The catalytic systems have been fully characterized and used in low amounts (0.1 mol %) in the Suzuki–Miyaura and Heck cross-couplings. Moreover, the protocols were optimized for the use of recoverable azeotropic mixtures (aq. EtOH 96% or aq. CH₃CN 84%, respectively) and in the flow procedure allowing one to isolate the final pure products, without any purification step, with very low residual palladium content and with a very low waste production.

Keywords: zirconium phosphonates; nanosheets; palladium nanoparticles; heterogeneous catalysis; Heck reaction; Suzuki–Miyaura coupling

1. Introduction

Palladium-catalyzed cross-coupling reactions of aryl halides with organo-boronic acids (Suzuki–Miyaura) and olefins (Heck) are extremely useful carbon–carbon bond formation tools widely investigated and applied in diverse areas such as natural products, agrochemicals, pharmaceutical intermediates and material science [1–4].

A challenging issue for metal-catalyzed transformation is related to the actual recoverability and reusability of the catalytic system while avoiding the possible loss of the metal especially if as precious and exhaustive as palladium. Over the past few years, considerable interest has been focused on supported palladium metallic nanoparticles (PdNPs) as an effective approach to achieve high catalytic activity, easy recovery, along with high stability [5–9]. However, the stability and durable catalytic efficiency of nanoparticles, which are very much related to the avoidance of their aggregation and/or their minimal metal leaching in the reaction products, are still a challenge [10,11]. A large number of supports have been used to stabilize the PdNPs, such as carbon materials [12–14], inorganic materials [15,16], MOFs [17,18], hybrid materials [19–24] and organic polymers [25–27].

Functionalization of the support surface with appropriate functional groups represents a key approach to obtain a better control of the dimensions, dispersion and stability of NPs [20,22–25].

Besides, layered materials with a high surface area and a large amount of exposed active sites have a great potential in the development of new hybrid materials able to efficiently host palladium nanoparticles [19,20,28].

In particular, layered zirconium phosphates and phosphonates can offer a high chemical and thermal robustness together with a facile tunability of their structural features as demonstrated by the large number of applications [15,29–34].

In this study, we used a layered zirconium phosphate glycine diphosphonate [35] because of its peculiarity that revealed it to be suitable for our tasks. This compound possesses a large number of carboxylic, phosphonic and amino groups on the surface of layers that are not coordinated to structural metal atoms and therefore are available for the coordination of Pd. Furthermore, an easy accessibility of these groups can be achieved by complete exfoliation of the material followed by intercalation of propylamine [19]. Propylamine is also a good complexing agent for Pd, and it contributes, together with the surface groups, to efficiently coordinate Pd atoms, aiding its deposition onto the layer surface.

Lately, we have been interested in the development of novel solid metal catalysts to be used in safe reaction media for the design of environmentally-sustainable processes [15,19,34,36–38].

In this paper, we have studied the use of palladium nanoparticles on zirconium phosphate glycine diphosphonate nanosheets in the Suzuki–Miyaura and Heck cross-coupling reactions optimizing the reaction conditions in order to replace classic toxic polar aprotic media by using safer and recoverable azeotropic mixtures of $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ 84% and $\text{EtOH}/\text{H}_2\text{O}$ 96%, respectively [39].

In addition, the reaction conditions have been adapted to perform the synthetic methodologies in flow reactors, which offer several advantages, such as the preservation of the physical integrity of the heterogeneous catalyst by mixing efficiently the reagents while avoiding mechanical stirring, facilitating the recovery and reuse of both the catalyst and products, minimizing the solvents needed to isolate the final product and the waste associated with the process [40].

2. Results and Discussion

2.1. Catalysts Preparation and Characterization

Recently, in our research group, a layered zirconium phosphate-phosphonate with the formula $\text{Zr}_2(\text{PO}_4)[(\text{O}_3\text{PCH}_2)_2\text{NHCH}_2\text{COOH}]_2 \cdot \text{H}_2\text{O}$ (ZPGly) was obtained by the reaction among Zr(IV), phosphoric acid and *N,N*-bis(phosphonomethyl)glycine [35]. For the reader's convenience, a brief description of ZPGly is reported. The surface of the hybrid layers is rich in phosphonate, carboxylic and amino groups differently protonated, non-coordinated to structural metal atoms, so giving polar properties to the material. Owing to these groups, which can act both as ion exchangers and as metal ligands, ZPGly showed very interesting ion exchange and intercalation properties. Previous studies showed that ZPGly undergoes a complete exfoliation by treatment with propylamine, generating a colloidal dispersion of a single layer or packets of a few layers [19]. This phenomenon largely enhances the accessibility of the functional groups located at the surface of layers. Easily reducible ions, such as Pd(II), present in solution and eventually coordinated with propylamine, can be easily immobilized on the surface of layers by ion exchange reactions. A subsequent reduction gives rise to nanometric metallic particles whose dimensions are affected from the layer surface morphology and interactions. Taking into account these properties, the colloidal dispersion in propylamine was successfully used to immobilize a large amount of palladium nanoparticles.

In this work, in order to explore the catalytic activity of the PdNPs supported on ZPGly, different samples were prepared by contacting the white ZPGly dispersion with palladium acetate solutions for 1, 7 and 15 days (named Pd@ZPGly-1, Pd@ZPGly-7, Pd@ZPGly-15) and then recovered by ultracentrifugation as brown solids [19]. The samples were characterized by X-ray powder diffraction (PXRD), inductively-coupled plasma (ICP) and transmission electronic microscopy (TEM), and the

collected data are reported in Table 1. The contacting time influenced the color intensity and the corresponding palladium loading of the three Pd@ZPGly solid samples (Table 1) with the maximum of 2.11 mmol of palladium per gram of solid matrix achieved after 15 days. In Figure 1, a comparison of the PXRD analyses of the Pd@ZPGly samples and that of ZPGly is reported. After a short contacting time (one day), the interlayer distance of ZPGly increased from 14.8–22.7 Å due to the intercalation of palladium ions coordinated with propylamine molecules; the lack of metallic Pd reflections suggests that palladium was mainly present as bivalent Pd(II) cations. In the PXRD of samples Pd@ZPGly-7 and Pd@ZPGly-15, some changes occurred, and the interlayer distance of the palladium phase decreased to 20.3 Å, while the ZPGly phase and the cubic phase of the Pd(0) appeared. It is possible to assert that long contacting times facilitate the reduction of Pd(II) to Pd(0) and that the negative sites of the lamellae recapture the protons regenerating the ZPGly phase. The IR spectrum of Pd@ZPGly-15 shows the presence of typical bands of carboxylate groups instead of carboxylic groups observed for pristine ZPGly, suggesting that palladium ions interact with carboxylates groups (Figure S1). The color change of the samples also reflects the presence of PdNP. Pd@ZPGly-1 and Pd@ZPGly-7, which contain the lower amount of PdNP, were treated with NaBH₄, obtaining Pd@ZPGly-1R and Pd@ZPGly-7R. After reduction, no variation was observed on the amount of palladium, while as expected after NaBH₄ treatment, the color turned from brown to black.

Table 1. Pd content, mean diameter of PdNP in palladium nanoparticle zirconium phosphate glycine diphosphonate nanosheet (Pd@ZPGly) samples. The colors of the collected solids are also reported.

PdNP-Catalyst	Pd (mmol/g Support) ¹	Mean Diameter (nm)	Color
Pd@ZPGly-1	0.92	2–5	light brown
Pd@ZPGly-7	1.49	2–5–20	brown
Pd@ZPGly-15	2.11	2–5–20	dark brown
Pd@ZPGly-1R	0.92	2–10 (aggregates) ²	black
Pd@ZPGly-7R	1.49	2–10 (aggregates) ²	black

¹ Determined by ICP-OES analysis. ² The sample is characterized by PdNP aggregates in which each particle has dimensions ranging from 2–10 nm.

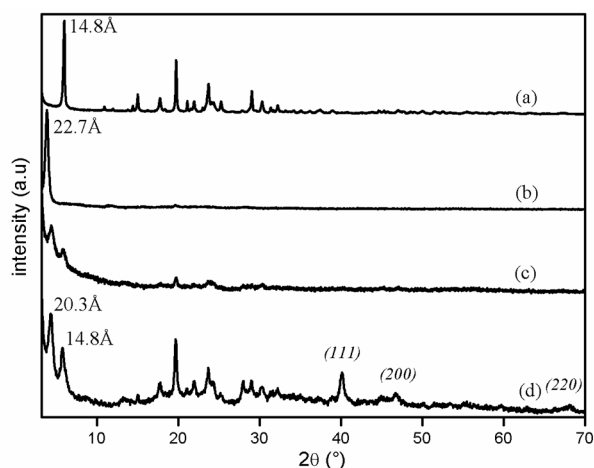


Figure 1. PRXD of ZrPGly (a); Pd@ZPGly-1 (b); Pd@ZPGly-7 (c) and Pd@ZPGly-15 (d). The indexed reflections are assigned to cubic Pd (International Centre for Diffraction Data—PDF2 database code no. 46-1043).

Figure 2 and Figure S2 report TEM images at high and low magnification, respectively, of the samples containing Pd. In all of the samples, the thin sheets of ZPGly are covered by a population of particles of about 2 nm ascribable to metallic Pd. Beside this population, bigger particles, with diameters from about 5 nm–20 nm, are well visible, and their number increases with the reaction time.

To have deeper information about the smaller population, high-resolution TEM (HR-TEM) and STEM images of Pd@ZPGly-15 have been collected (Figure S3). It was observed that the nanosheets were completely covered by PdNPs with a mean diameter of two and with a narrow size distribution. After reduction, the samples (Pd@ZPGly-1R and Pd@ZPGly-7R) show the formation of several aggregates of PdNP having an overage dimension of 10 nm and a detriment of the 2-nm population.

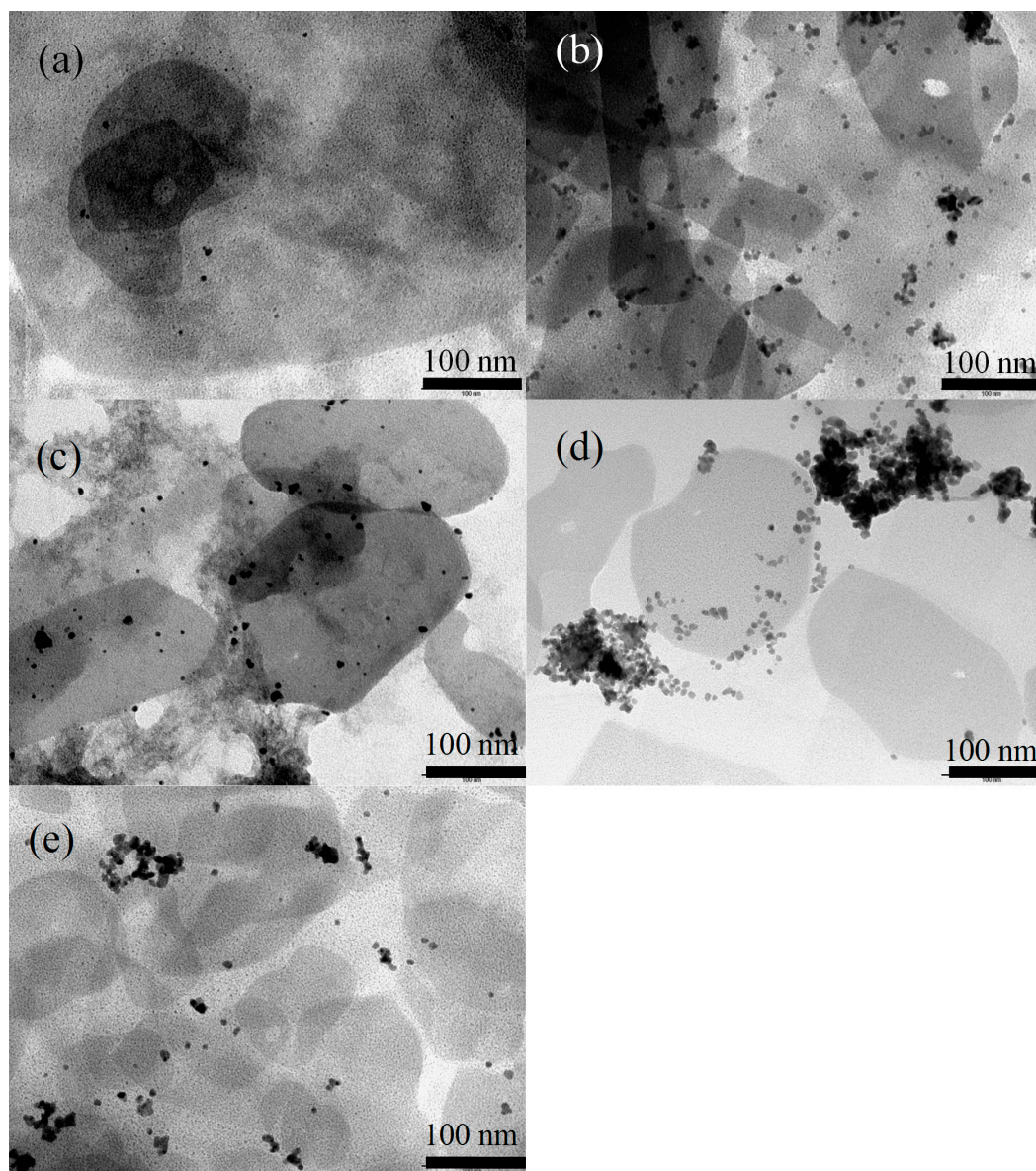


Figure 2. TEM images of Pd@ZPGly-1 (a); Pd@ZPGly-1R (b); Pd@ZPGly-7 (c); Pd@ZPGly-7R (d) and Pd@ZPGly-15 (e).

2.2. Catalytic Activity

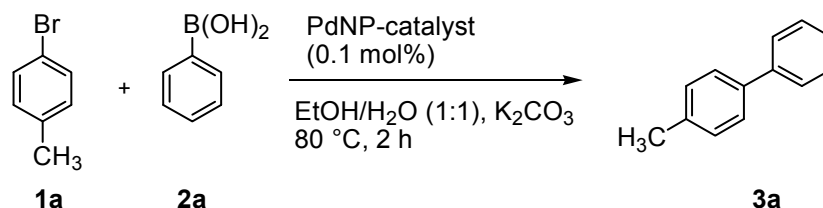
2.2.1. Suzuki–Miyaura Coupling Reaction

We started our study testing the activity of Pd@ZPGly catalysts in the Suzuki–Miyaura reaction of 4-bromotoluene (**1a**) and phenylboronic acid (**2a**) in EtOH/H₂O (1:1) at 80 °C for 2 h.

All of the catalysts showed high activity, but only with Pd@ZPGly-1 and Pd@ZPGly-15 catalysts a complete conversion was observed after 2 h and for three consecutive run (Table 2, Entries 1 and 3). For each reuse, the catalysts were recovered by centrifugation, washed with EtOH/H₂O (1:1) and

reused in the next cycle. Pd@ZPGly-7, Pd@ZPGly-1R and 7R showed a lower activity that also decreased after recovery and reuse (Table 2, Entries 2, 5 and 6). This could be ascribable to the distribution of the Pd nanoparticle sizes on the surface of the supports. Indeed, in these samples, the particles having mean dimensions of 10–20 nm are highly represented, and after reduction, also a relevant aggregation phenomenon occurred. The ICP-OES analysis of crude products, obtained by usual work-up procedure (filtration, extraction with ethyl acetate, distillation of solvent under reduced pressure), showed a high content of palladium (20–31 ppm, Table 2).

Table 2. Comparison of efficiency of different PdNP-catalytic system in the Suzuki reaction of 4-bromotoluene (**1a**) and phenylboronic acid (**2**) in EtOH/H₂O (1:1) at 80 °C for 2 h.



Entry ¹	PdNP-Catalyst	Run	Conv % ²	Pd (ppm) ³
1	Pd@ZPGly-1	1°	>99	26
		2°	>99	
		3°	>99	
2	Pd@ZPGly-7	1°	97	29
		2°	98	
		3°	96	
3	Pd@ZPGly-15	1°	>99	21
		2°	99	
		3°	99	
5	Pd@ZPGly-1R	1°	99	20
		2°	98	
		3°	97	
6	Pd@ZPGly-7R	1°	97	31
		2°	95	
		3°	95	
7	Pd/α-ZrPK ⁴	1°	78 ⁵	n.d.
8	Pd/C 10 wt %	1°	>99	192

¹ Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), K₂CO₃ (1.2 mmol), catalyst (0.1 mol %), EtOH/H₂O 1:1 (2.4 mL).

² Conversion of **1a** to **3a** is measured by Gas–Liquid Chromatography (GLC) analyses; the remaining material is unreacted **1a**. ³ Determined by ICP-OES analysis of crude reaction product. ⁴ [15]. ⁵ [19].

It is known that both semicrystalline and microcrystalline zirconium phosphate (α-ZrP) undergo hydrolysis to some extent in basic media, especially at high temperatures [41]. The pH of aqueous K₂CO₃ reaction medium is about 12, and therefore, the hydrolysis process of the support could be also responsible for the high palladium leaching that exceeded the allowed upper limit value [42].

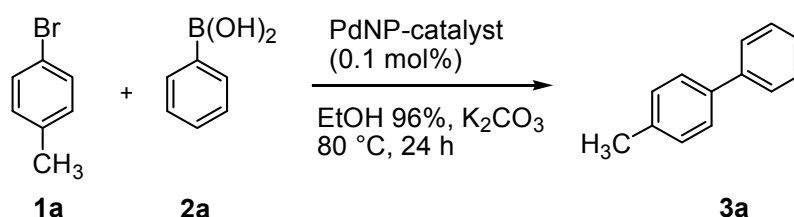
The efficiency of these novel Pd@ZPGly catalysts has been compared to Pd/α-ZrPK catalyst (palladium nanoparticles on layered potassium zirconium phosphate), a similar catalytic system recently reported by our group [15] and with Pd/C 10 wt %. By using the same reaction conditions, Pd/α-ZrPK showed a significantly lower efficiency (Table 2, Entry 6), while when the reaction was performed in the presence of Pd/C, the catalytic activity was comparable with that of Pd@ZPGly catalysts, but the amount of Pd in the product is extremely high (192 ppm, Table 2, Entry 8).

In order to simplify the procedure of the work-up and also reduce the leaching of the metal into the product, we investigated the use of the heterogeneous K₂CO₃/aq. EtOH azeotrope (EtOH 96%) system [43]. K₂CO₃ is in fact insoluble in aqueous ethanol azeotrope, and therefore, it can be removed

together with the catalyst by simple filtration making possible the separation of the pure product, after the distillation and recovery of the reaction medium, therefore reducing the waste of the process. In addition, the heterogeneous conditions can significantly protect the support avoiding its hydrolysis under basic aqueous conditions.

Pd@ZPGly catalysts were tested in the Suzuki–Miyaura reaction of 4-bromotoluene (**1a**) and phenylboronic acid (**2a**) in aq. EtOH azeotrope at 80 °C (Table 3). The reaction time was longer (24 vs. 2 h), and high conversion was obtained by using Pd@ZPGly-1, -7, -15 (97–98%, Table 3, Entries 1 and 3), while lower conversions were observed with Pd@ZPGly-1R and -7R (78% and 85%, respectively, Table 3, Entries 4 and 5), again presumably due to the aggregation extent of Pd nanoparticles. The comparable Pd/ α -ZrPK catalyst [15] and Pd/C 10 wt % showed a much lower efficiency (Table 3, Entries 6 and 7).

Table 3. Comparison of the efficiency of different PdNP-catalytic systems in the Suzuki reaction of 4-bromotoluene (**1a**) and phenylboronic acid (**2a**) in aq. EtOH azeotrope at 80 °C.



Entry ¹	PdNP-Catalyst	Conv % ²	Pd (ppm) ³
1	Pd@ZPGly-1	98	13
2	Pd@ZPGly-7	97	15
3	Pd@ZPGly-15	98	11
4	Pd@ZPGly-1R	78	9
5	Pd@ZPGly-7R	85	17
6	Pd/ α -ZrPK ⁴	38 ⁵	n.d.
7	Pd/C 10 wt %	82	184

¹ Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), K₂CO₃ (1.2 mmol), catalyst (0.1 mol %), EtOH 96% (2.4 mL).

² Conversion of **1a** to **3a** is measured by GLC analyses; the remaining material is unreacted **1a**. ³ Determined by ICP-OES analysis of crude reaction product. ⁴ [15]. ⁵ [19].

The ICP-OES analysis of crude products revealed that by using the ethanol azeotrope, a much lower content of palladium was obtained than when EtOH/H₂O (1:1) was used as the reaction medium (9–17 ppm vs. 20–31 ppm). This is consistent with the milder pH conditions achieved when the heterogeneous K₂CO₃/aq. EtOH azeotrope system is used, resulting in higher stability of the support. When Pd/C 10 wt % was used, a very high level of Pd content in the product was observed again (184 ppm, Table 3, Entry 7). Pd@ZPGly-15 proved to be the best catalyst in terms of activity and leaching of palladium (Table 3, Entry 3).

The kinetics of the Suzuki–Miyaura reaction of 4-bromotoluene (**1a**) and phenylboronic acid (**2a**) in aq. EtOH azeotrope in the presence of Pd@ZPGly-1, -7, -15 was further studied (Figure 3). After 1 h at 80 °C, the difference in reactivity was significant. Pd@ZPGly-1, which mainly contains Pd(II) species, provided a lower conversion (63%) as compared to Pd@ZPGly-7 and -15 (78% and 85%, respectively) that also contained Pd(0) species. During the reaction, the reduction of Pd(II) occurs at the expense of EtOH [15,44,45], and after 9 h, the conversion was comparable (93–96%). At the end of the reactions, all of the recovered catalysts were black, supporting the more complete presence of Pd(0) species. Pd@ZPGly-15 showed the highest activity and also the best stability. The Pd content (2.11 mmol/g) was very high, and also, these features can be useful in view of a large-scale flow protocol, allowing the use of the minimal quantity of catalytic material to be packed into a flow reactor.

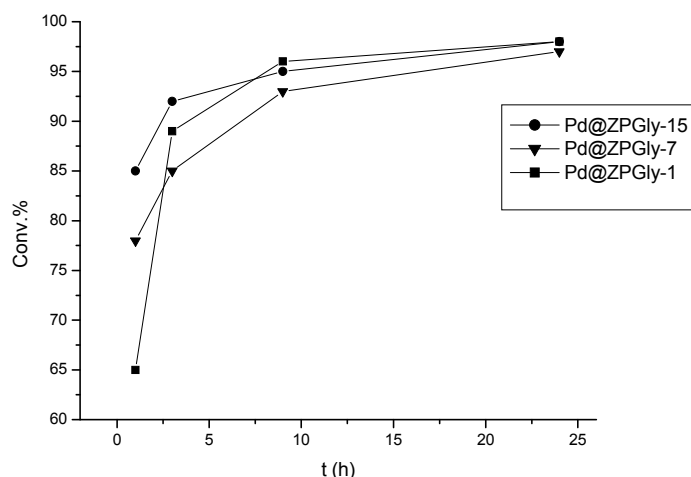
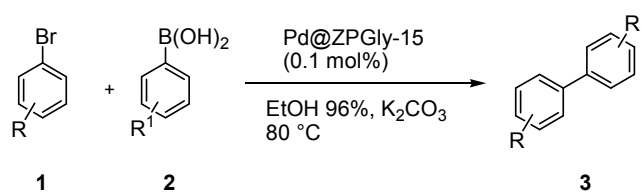


Figure 3. Comparative Suzuki reaction of 4-bromotoluene (**1a**) and phenylboronic acid (**2a**) in aq. EtOH azeotrope at 80 °C catalyzed by Pd@ZPGly-1, Pd@ZPGly-7, Pd@ZPGly-15 under batch conditions at 1, 3, 9, 24 h.

To confirm the efficiency of Pd@ZPGly-15 in combination with the K_2CO_3 /aq. EtOH azeotrope system, the protocol has been extended to the reactions of a series of aryl bromides **1a–n** with phenyl boronic acids **2a,b** (Table 4). The reactions were carried at 80 °C, in the presence of 0.1 mol % of Pd@ZPGly-15, obtaining from high to quantitative conversion of **1** and excellent yields of isolated products **3a–n**. Bromobenzene and aryl bromide with electron-donating groups (**1a,b,d**) showed as expected a lower reactivity (reaction time 24 h) with respect to 4-substituted aryl bromide with electron-withdrawing groups (**1c,e,f,g,l**) (reaction time of 3–9 h), while 2- and 3-CHO aryl bromide (**1h,i**) reacted in a longer reaction time (24 h) maybe due to steric hindrance (2-CHO) or non-conjugative meta substitution (3-CHO). 2-CN aryl bromide reacted with 4-formyl phenyl boronic acids (**2b**) to furnish in very high isolated yield the biphenyl **3n**, a useful intermediate for the synthesis of valsartan [46].

Table 4. Suzuki reaction between aryl bromides **1a–n** and phenyl boronic acids **2a,b** catalyzed by Pd@ZPGly-15 in aq. EtOH azeotrope at 80 °C.



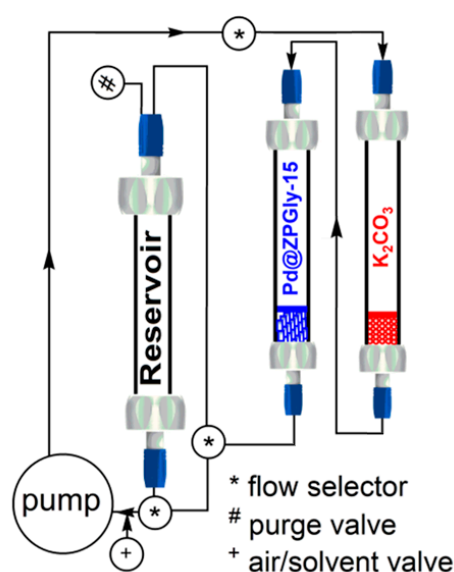
Entry ¹	R	R ¹	t (h)	Product	Conv (%) ²	Yield (%) ³
1	4-CH ₃	H	24	3a	>99	97
2	H	H	24	3b	97	95
3	4-NO ₂	H	3	3c	>99	98
4	4-OCH ₃	H	24	3d	94	92
5	4-CN	H	3	3e	>99	99
6	4-COOH	H	9	3f	>99	97
7	4-CHO	H	3	3g	>99	98
8	2-CHO	H	24	3h	>99	96
9	3-CHO	H	24	3i	95	93
10	4-COCH ₃	H	3	3l	>99	99
11	2-CH=CH-CH=CH-3	H	9	3m	99	97
12	2-CN	4-CHO	6	3n	>99	98

¹ Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), K_2CO_3 (1.2 mmol), Pd@ZPGly-15 (0.1 mol %), EtOH 96% (2.4 mL).

² Conversion of **1** to **3** is measured by GLC analyses; the remaining material is unreacted **1**. ³ Yield of isolated products **3**.

Continuing with our project and taking into account the optimized batch protocol, we have investigated the catalytic performance of Pd@ZPGly-15 in the Suzuki–Miyaura coupling of phenyl boronic acid (**2a**) with 4-bromo benzaldehyde (**1g**) in a flow protocol to assess the ability of ZPGly nanosheets to stabilize PdNPs and evaluate the catalytic activity of the recovered catalyst over time. The flow approach is also strategic to preserve the physical features of solid catalyst throughout the process and allows its simple, efficient and reproducible recovery and reuse.

To this aim, the reactor system was set up as depicted in Scheme 1, where the base K_2CO_3 (48 mmol) and the catalyst Pd@ZPGly-15 (0.1 mmol %) were both dispersed in solid glass beads (1 mm diameter) and respectively charged into two separate glass column. Reactants (40 mmol of 4-bromo benzaldehyde (**1g**) and 44 mmol of phenyl boronic acid (**2a**)) dissolved in aq. EtOH azeotrope (0.33 M) were charged into a third glass column, used as the reservoir. The columns were connected to a pump by using the appropriate valves and installed into a thermostated box at 70 °C (not shown in Scheme 1 for clarity).



Scheme 1. Schematic flow reactor for the preparation of **3g**.

The reaction mixture was pushed at a 1.5-mL/min flow rate through the base and the catalyst columns for 10 h until complete conversion was obtained (monitored by Gas–Liquid Chromatography (GLC) analyses). After this time and only the removal of the solvent by distillation (90% of solvent recovered), the product **3g** was obtained as a white solid (98% yield, Table 5).

Table 5. Suzuki reaction between 4-bromo benzaldehyde (**1g**) and phenylboronic acid (**2a**) catalyzed by Pd@ZPGly-15 nanosheets under flow conditions.

Entry	Yield (%)	Pd Leaching (ppm)
run 1	98	5
run 2	98	3
run 3	98	3

The reusability of the catalyst was investigated, and this process was repeated for three consecutive runs with the same catalyst to obtain always the corresponding product **3g** in a 98% yield.

Hot filtration test has been performed on the Suzuki reaction in aq. EtOH azeotrope with Pd@ZPGly-15. The reaction mixture was stirred at 80 °C for 20 min (conversion 71%), and the hot filtration was performed. K₂CO₃ was added again and the reaction mixture stirred at 80 °C. After a total reaction time of 1 h, the conversion was 74%, and the same conversion was observed after 24 h. This suggests that the homogeneous palladium released in solution (see Table 3, Entry 3) does not effectively promote the process. In agreement, the reaction performed with homogeneous Pd catalyst (Pd(OAc)₂) did not give a satisfactory result as for Pd@ZPGly-15 (see the Supplementary Materials).

When the reactions were performed under flow conditions, although the catalyst and the base were loaded into two separate columns, an excellent catalytic activity was observed. A “release and catch” mechanism has been hypothesized in which soluble active palladium species are released from the solid catalyst during the oxidative addition of the halide and then redeposited on the support as a consequence of the reductive elimination step when the new carbon–carbon bond is formed [43,47].

The catalytic system ultimately operates as an efficient heterogeneous system, and Pd content in the final product, determined by ICP analyses, is very low (3–5 ppm, Table 5), proving that the ZPGly system is able to efficiently re-capture palladium. Moreover, the recovered catalytic system showed the same activity.

The flow system, with a separate column for the base K₂CO₃ and the catalyst Pd@ZPGly-15, allows optimizing the recovery and reuse of the solid catalyst and keeps its physical and chemical integrity over its use. In fact, the palladium leaching was much lower than that observed in batch conditions (3–5 vs. 11 ppm).

The TEM images of recovered Pd@ZPGly-15 after three catalytic cycles show that the ZPGly nanosheets' structure and the distribution of PdNPs on the layers are maintained (Figure 4).

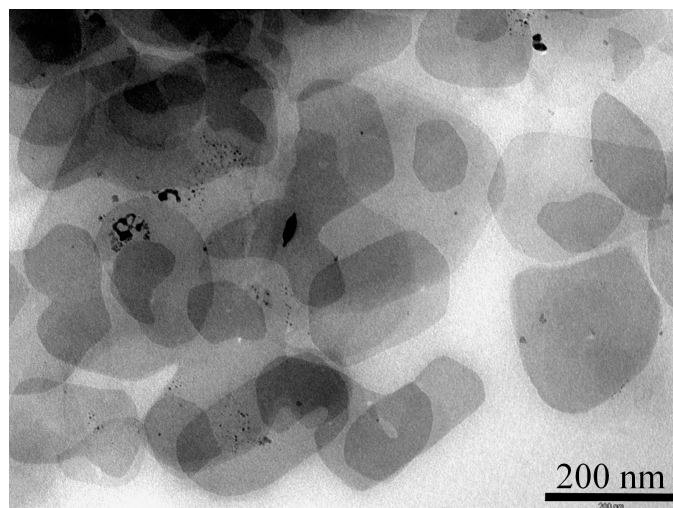


Figure 4. TEM images of Pd@ZPGly-15 after three catalytic runs.

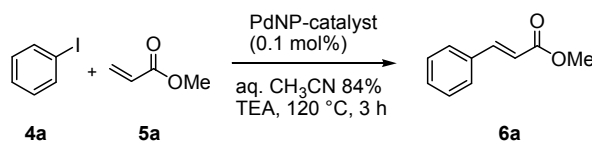
Furthermore, to assess the waste minimization for both batch and flow protocols, we calculate the E-factor values. When the reaction was performed in homogeneous K₂CO₃/EtOH–H₂O (1:1), the use of the not easily recoverable mixture of solvents and the need for extraction work-up lead to an E-factor value of 76. Using the heterogeneous K₂CO₃/aq. EtOH azeotrope system, the sustainability of the batch protocol has been greatly improved since no purification step is needed (E-factor 27.7), and this value is noticeably reduced in a large-scale flow protocol process by the recovery of azeotrope reaction medium by distillation (E-factor 3.2).

2.2.2. Heck Reaction

The catalytic activity of Pd@ZPGly catalysts has been investigated in the representative Heck reaction between iodobenzene (**4a**) and methyl acrylate (**5a**) in aqueous CH₃CN azeotrope (aq. CH₃CN 84%), an alternative to conventional polar aprotic media, as a safer and easily recoverable reaction medium [15,48].

In the presence of a soluble base, such as triethylamine (TEA), at 120 °C for 3 h, all of the Pd@ZPGly catalysts promoted the complete conversion (Table 6, Entries 1–5), but after a 1-h reaction time, lower conversions were observed in the case of Pd@ZPGly-1R and -7R (Table 6, Entries 4 and 5), again due to the presence of larger PdNPs aggregates. Pd/ α -ZrPK catalyst, already reported by our group [15], and Pd/C 10 wt% showed a comparable catalytic efficiency (Table 6, Entry 6).

Table 6. Comparison of the efficiency of different PdNP-catalytic systems in the Heck reaction between iodobenzene (**4a**) and methyl acrylate (**5a**) in aq. CH₃CN azeotrope at 120 °C for 3 h.



Entry ¹	PdNP-Catalyst	Conv % (1 h) ²	Conv % (3 h) ²	Pd (ppm) ³
1	Pd@ZPGly-1	88	>99	21
2	Pd@ZPGly-7	78	>99	16
3	Pd@ZPGly-15	80	>99	13
4	Pd@ZPGly-1R	76	99	20
5	Pd@ZPGly-7R	62	99	21
6	Pd/ α -ZrPK ⁵	-	>99	34 ⁵
7	Pd/C 10 wt %	-	98	187
8 ⁴	Pd@ZPGly-15	-	>99	2
9 ⁴	Pd/ α -ZrPK ⁵	-	>99	6 ⁵

¹ Reaction conditions: **4a** (1.0 mmol), **5a** (1.2 mmol), base (1.2 mmol), catalyst (0.1 mol %), aq. CH₃CN 84% (1 M, 1 mL). ² Conversion of **4a** to **6a** is measured by GLC analyses; the remaining material is unreacted **4a**. ³ Determined by ICP-OES analysis of crude reaction product. ⁴ In the presence of polystyrene (PS)-TEA as the base. ⁵ [15].

A remarkable difference was, however, observed in the Pd content determined by ICP-OES analyses of the crude products obtained by filtration and the usual extraction work-up procedure. In fact, the Pd@ZrPGly catalysts showed a Pd leaching in the products of 13–21 ppm, while in the case of Pd/ α -ZrPK, the leaching was higher (34 ppm). Extremely high was the content of Pd in the product obtained by Pd/C catalysis (187 ppm, Table 6, Entry 7). This result is very notable and proves that the presence of glycine groups on the surface of ZPGly nanosheets allows better efficiency in re-capturing palladium. As well as for the Suzuki–Miyaura reaction, the best result in terms of activity and release of Pd was obtained with Pd@ZrPGly15.

It is known that a “release and catch” mechanism is operative for a PdNP-catalyzed Heck reaction [15,36,48] and that the required organic base strongly binds the soluble palladium species, facilitating their dissolution from the solid catalyst and consequently the leaching into the products. Besides, the base has the fundamental role of regenerating the active Pd(0) species [49], with the formation of the corresponding ammonium salt.

In order to reduce the leaching of Pd and the amount of waste but also simplify the work-up procedure, we investigated the use of diethylaminomethyl-polystyrene (PS-TEA) as the heterogeneous base, which can be removed by simple filtration from the reaction mixture, and therefore, the isolation of the final product can be obtained simply by distillation of the azeotropic reaction medium. Since the polystyrene-bonded amino groups may act as capping agents for the Pd nanoparticles, a significantly reduced Pd leaching is expected [50–53].

As shown in Table 6, when the reaction was performed in the presence of PS-TEA as the base, the catalytic activity of Pd@ZrPGly-15 was unchanged, while the Pd content in the final product was only 2 ppm (Table 6, Entry 8 vs. Entry 3), much below the allowed limit value [42]. The comparable

Pd/ α -ZrPK catalyst [15] showed a lower efficiency to recapture Pd (6 ppm, Table 6, Entry 9), proving that ZrPGly can act as an excellent scavenger for palladium nanoparticles.

Recycle test was performed in batch, by using homogeneous TEA as the base, to evaluate the robustness of Pd@ZPGly-15. For each cycle, the solid catalyst was separated by centrifugation, washed with aq. CH₃CN azeotrope and used again in the next cycle (Table 7). Pd@ZPGly-15 was used six times always maintaining the same activity and achieving a TON (turnover number) of ca. 6000 and a TOF (turnover frequency) of ca. 333 h^{−1}. The ICP-OES analyses of crude products showed a stable palladium leaching at each cycle (10–12 ppm).

Table 7. Recycling test of Pd@ZPGly-15 in the Heck reaction between iodobenzene (**4a**) and methyl acrylate (**5a**) in aq. CH₃CN azeotrope at 120 °C for 3 h.

Run ¹	Conv % ²	Yield (%) ³	Pd (ppm) ⁴
1	>99	97	11
2	>99	98	10
3	>99	97	11
4	>99	96	12
5	>99	97	10
6	>99	97	11

¹ First cycle: **4a** (6.0 mmol), **5a** (7.2 mmol), TEA (7.2 mmol), catalyst (0.1 mol %), aq. CH₃CN 84% (1 M, 6 mL), 120 °C, 3 h. Successive cycles: the reagents and medium quantities were calculated on the basis of the amount of recovered catalyst. ² Conversion of **4a** to **6a** is measured by GLC analyses; the remaining material is unreacted **4a**.

³ Yield of isolated product. ⁴ Determined by ICP-OES analysis of crude reaction product.

In Figure 5, the TEM images of Pd@ZPGly-15 after six cycles are shown. The sample is almost unchanged, and the result is constituted by thin lamellae that support PdNPs with dimensions comparable to those of the fresh prepared catalyst.

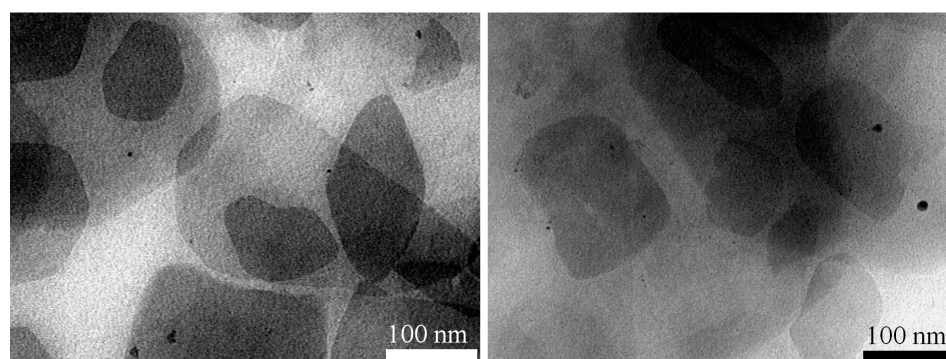


Figure 5. TEM micrographs of Pd@ZPGly-15 after six catalytic cycles.

To confirm the efficiency of Pd@ZPGly-15 in the Heck coupling reaction, we extended the study to several aryl iodides **4a–h** with methyl acrylate (**5a**) or with styrene (**5b**) (Table 8). The reactions of the aryl iodides (**4a–h**) with methyl acrylate (**5a**) were carried at 120 °C for 3 h, in the presence of 0.1 mol % of Pd@ZPGly-15 and TEA as the base, obtaining from high to quantitative conversions of **4** and excellent yields of isolated products **6a–h** (Table 8, Entries 1–8). For 4-nitro-iodobenzene (**4b**), 2'-iodoacetophenone (**4f**) and 2-iodothiophene (**4h**), we observed the formation of the corresponding homocoupling products, the biphenyls **8b**, **8f** and **8h**, and therefore, the products **6b**, **6f** and **6h** were purified by column chromatography (Table 8, Entries 2, 6 and 8).

The columns were connected to a pump and installed into a thermostated box at 120 °C (not shown in Scheme 2 for clarity). The reaction mixture was pumped at a 2.0-mL/min flow rate through the columns for 1.5 h to obtain quantitative conversion of **4a** to **6a** (monitored by GLC, Table 9, Entry 1).

Table 9. Catalytic activity and reusability of Pd@ZPGly-15 in the flow reactor for the Heck reaction of iodobenzene **4a** with methyl acrylate (**5a**) and styrene (**5b**).

Entry	R ¹	Cycle	Product	t (h)	Yield (%)	Pd Leaching (ppm)
1	CO ₂ Me	run 1	6a	1.5	87	4
2	CO ₂ Me	run 2	6a	1.5	87	4
3	CO ₂ Me	run 3	6a	1.5	85	2
4	C ₆ H ₅	run 4	6i ¹	2	86 ²	2

¹ A 5% of product **7i** was observed. ² Yield of isolated products **6i** + **7i**.

The column that contained both the PS-TEA and catalyst was then washed with aq. CH₃CN azeotrope to clean the apparatus and completely recover the product. Finally, the product **6a** was obtained in pure form, after distillation of the reaction medium and without any further purification step, in 87% yield (Table 9, Entry 1).

The aqueous CH₃CN azeotrope, recovered by distillation, was pure (GLC analysis), comparable to the starting azeotropic mixture and, therefore, fully reusable.

The reusability of the catalyst, in flow conditions, was evaluated for the reaction of iodobenzene (**4a**) with methyl acrylate (**5a**). The column that contained both the PS-TEA and catalyst was washed with a solution of TEA in aq. CH₃CN azeotrope to regenerate the supported ammine by removal of hydriodic acid (HI) formed during the Heck reaction and then washed with azeotrope to remove the residual TEA. After this treatment, a second batch of reactants was charged in the reservoir, and quantitative conversion was achieved again in 1.5 h (Table 9, Entry 2). An unchanged catalytic activity was also obtained in the third run (Table 9, Entry 3).

After three runs, iodobenzene (**4a**) and styrene (**5b**) were charged in the reservoir, and the reaction mixture was pumped through the column, containing the recovered PS-TEA and catalyst, to obtain after 2 h a quantitative conversion of **4a** to **6i** (86% yield, Table 9, Entry 4).

To evaluate the sustainability of the processes, we calculated the E-factor value for both the batch and the flow protocols. When TEA was used as the base in the batch condition, an E-factor value of 70.4 was obtained, mainly due to the need of extraction work-up. Under flow conditions by using PS-TEA as the base, we were able to easily run the process on a larger scale (50 mmol) and to reduce this value to 4.7, since the reaction products can be recovered simply by distillation of the reaction medium that was totally recovered.

The ICP analyses of the final products revealed the presence of a very low Pd content of ca. 2–4 ppm, below the allowed limit value [42] (Table 9). The low residual of Pd in the products and the high activity over more runs is in agreement with the aforementioned “release and catch” mechanism [36,48].

3. Experimental Section

3.1. General Remarks

All chemicals were purchased and used without any further purification. ^1H -NMR and ^{13}C -NMR spectra were recorded at 400 MHz and 100.6 MHz, respectively, on a Bruker DRX-ADVANCE 400 MHz in CDCl_3 using TMS as the internal standard.

Zr, P and Pd analyses were performed on an ICP Varian Liberty inductively-coupled plasma-optical emission spectrometry (ICP-OES) with axial injection. C, H, N elemental analyses (EA) were performed on a Fisons EA1108CHN.

Powder X-ray diffraction patterns (PXRD) of powders were collected with a Philips X'Pert PRO MPD diffractometer operating at 40 kV and 40 mA, with a step size of 0.03341° 2θ and a step scan of 40 s, using $\text{Cu K}\alpha$ radiation and an X'Celerator detector.

Transmission electron microscopy (TEM) analysis was carried out by a Philips 208 transmission electron microscope, operating at an accelerating voltage of 100 kV. Powders were rapidly diluted in water, then supported on copper grids (200 mesh) precoated with Formvar carbon films and quickly dried.

GLC analyses were performed by using the Hewlett-Packard HP 5890A equipped with a capillary column DB-35MS (30 m, 0.53 mm), an FID detector and hydrogen as the gas carrier. Gas Chromatography with Electron Impact Mass Spectrometry (GC-EIMS) analyses were carried out by using a Hewlett-Packard HP 6890N Network GC system/5975 Mass Selective Detector equipped with an electron impact ionizer at 70 eV. Thin layer chromatography analyses were performed with silica gel on aluminum plates (silica gel 60 F254, Fluka). Column chromatography purification was performed with silica gel (230–400 mesh) eluting with hexane or mixture hexane/ethyl acetate (98:2–70:30). Melting points were measured on a Büchi 510.

Flow procedures were performed using a Jasco PU-2080 HPLC pump, an Omnifit glass column as the reservoir and a Supelco HPLC column blank as the base/catalyst column. All of the equipment was connected using 1/16" OD PTFE tubing and stainless steel 1/16 OD \times 0.02 ID capillary tubing and Hamilton HPV Plug Valves. The system was placed in a ventilated Plexiglas box equipped with electrical resistance heating.

Diethylaminomethyl-polystyrene (PS-TEA) was prepared by reacting Merrifield resin (200–400 mesh, 4.4 mmol/g Cl loading, 2% cross-linked with divinylbenzene) with diethylamine (2.5 equiv) in toluene at 100°C for 24 h. The resin was then washed with a 0.5 M solution of diethylamine in toluene, then toluene, dichloromethane, water and acetone to remove the excess amine, then dried under vacuum. The loading of amine is calculated by C, H, N elemental analysis (EA) on the element nitrogen, which is not contained in the purified and fully-dried polymeric support. Solid NMR analyses also confirm the absence of free amine. Compounds **3a–n** [22,43,46,54] and **6a–l** [15] are known.

3.2. Synthesis of $\text{Zr}_2(\text{PO}_4)[(\text{O}_3\text{PCH}_2)_2\text{NHCH}_2\text{COOH}]_2\cdot\text{H}_2\text{O}$

The synthesis of ZPGly was achieved as reported in [14]. In particular, 2.37 g (9 mmol) of *N,N*-bis(phosphonomethyl)glycine (L) were dissolved in 93 mL of deionized water (0.097 M), and then, 6 mL of phosphoric acid 1 M were added to this solution. Then, 1.93 g (6 mmol) of $\text{ZrOCl}_2\cdot 8\text{H}_2\text{O}$ were dissolved in 20.4 mL of HF 2.9 M (59 mmol), molar ratio $\text{HF}/\text{Zr}^{\text{IV}} = 10$. These two solutions were mixed in a 500-mL Teflon bottle and placed in an oven at 90°C . After three days, the solid was filtered under vacuum, washed three times with deionized water and dried at 60°C for 24 h. The empirical formula was $\text{Zr}_2\text{P}_5\text{O}_{21}\text{C}_8\text{N}_2\text{H}_{19}$ (Formula weight = 816, ionic exchange capacity = 3.67 mmol/g).

3.3. Preparation of ZPGly Dispersion

One gram of ZPGly (1.23 mmol) was suspended in 108 mL of deionized water, and then 22 mL of *n*-propylamine 0.1 M (2.2 mmol corresponding to 60% of IEC) were added under vigorous magnetic stirring. A stable dispersion was obtained.

3.4. Preparation of Pd@ZPGly Composites

Fourteen milliliters of Pd(CH₃COO)₂ 0.05 M in acetone (0.7 mmol of Pd^{II}) were added drop by drop to 32.5 mL of the ZPGly dispersion (containing 250 mg of ZPGly) under vigorous stirring. The dispersion was left under magnetic stirring for 1 day (Pd@ZPGly-1). Additional composites were obtained by increasing the reaction time to 7 days (Pd@ZPGly-7) and to 15 days (Pd@ZPGly-15). The solids were recovered by ultracentrifugation (15,000 rpm for 10 min) and washed once with acetone and twice with deionized water. The solids were dried over P₂O₅.

3.5. Preparation of Pd@ZPGly-1R and Pd@ZPGly-7R

To a suspension of Pd@ZPGly-1 and Pd@ZPGly-7 (100 mg) in deionized water (10 mL), a solution of NaBH₄ (10 equiv) in deionized water (10 mL) was added drop by drop, under magnetic stirring. At the end of the addition, the reaction mixture was left under stirring for one hour. The solids were recovered by ultracentrifugation (hereafter Pd@ZPGly-1R, Pd@ZPGly-7R) washed with deionized water and dried over P₂O₅.

3.6. Determination of Pd Content

A weighed amount of the catalyst was first treated with concentrated HF in order to dissolve ZPGly, then with aqua regia to digest the Pd species, and the obtained solution was diluted with deionized water and analyzed by ICP-OES.

3.7. Typical Procedure for the Suzuki Reaction in EtOH/H₂O (1:1) under Batch Conditions

In a vial, Pd@ZPGly-15 catalyst (0.47 mg, 2.11 mmol of Pd per g, 0.1 mol %), phenylboronic acid (**2a**, 134 mg, 1.2 mmol), K₂CO₃ (167 mg, 1.10 mmol), 4-bromotoluene (**1a**, 171 mg, 1 mmol), ethanol (1.2 mL) and water (1.2 mL) were placed. The reaction mixture was stirred at 80 °C; the conversion of the aryl bromide was monitored by GLC analyses. After 2 h, water was added (2 mL) and the mixture extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried with sodium sulfate and evaporated under reduced pressure.

E-factor calculation: E-factor = [0.171 g (4-bromotoluene, **1a**) + 0.134 g (phenylboronic acid, **2a**) + 0.167 g (K₂CO₃) + 0.00047 g (Pd@ZPGly-15) + 0.947 g (EtOH) + 3.2 g (water) + 8.1 g (ethyl acetate) – 0.165 g (4-methyl-1,1'-biphenyl (**3a**), 98% yield)]/0.165 g (4-methyl-1,1'-biphenyl (**3a**), 98% yield) = 76.

3.8. Typical Procedure for the Suzuki Reaction in aq. EtOH Azeotrope under Batch Conditions

In a vial, Pd@ZPGly-15 catalyst (0.47 mg, 2.11 mmol of Pd per g, 0.1 mol %), phenylboronic acid (**2a**, 134 mg, 1.1 mmol), K₂CO₃ (167 mg, 1.10 mmol), 4-bromotoluene (**1a**, 171 mg, 1 mmol) and ethanol 96% (2.4 mL) were placed. The reaction mixture was stirred at 80 °C; the conversion of the aryl bromide was monitored by GLC analyses. After 24 h, the reaction mixture was filtered and the solid residue washed with ethanol (3 mL). The organic layer was evaporated under reduced pressure.

E-factor calculation: E-factor = [0.171 g (4-bromotoluene, **1a**) + 0.134 g (phenylboronic acid, **2a**) + 0.167 g (K₂CO₃) + 0.00047 g (Pd@ZPGly-15) + 4.26 g (EtOH) – 0.165 g (4-methyl-1,1'-biphenyl (**3a**), 98% yield)]/0.165 g (4-methyl-1,1'-biphenyl (**3a**), 98% yield) = 27.7.

3.9. Typical Procedure for the Suzuki Reaction in aq. EtOH Azeotrope under Flow Conditions

A pre-mixed mixture of 4-bromobenzaldehyde (**1g**, 40 mmol, 7.4 g), phenylboronic acid (**2a**, 44 mmol, 5.36 g) and ethanol 96% (0.33 M, 121.2 mL) was charged into a glass column functioning

as a reservoir. Potassium carbonate (48 mmol, 6.7 g), dispersed in 1 mm diameter solid glass beads, was charged in a glass column; the catalyst Pd@ZPGly-15 (18.9 mg, 2.11 mmol of Pd/g, 0.1 mmol %) was also charged in another glass column and dispersed in 1 mm diameter solid glass beads; the equipment was installed into a thermostated box and connected, by using the appropriate valves, to a pump. The reaction mixture was continuously pumped (flow rate $1.5 \text{ mL} \cdot \text{min}^{-1}$) through the base and catalyst columns at 70°C for 10 h to reach the complete conversion of reactant to 1,1'-biphenyl-4-carbaldehyde (**3g**). At this stage, the pump was left to run in order to recover the reaction mixture into the reservoir. To completely recover the product and clean the reactor, ethanol ($2 \times 8 \text{ mL}$ at a $1.5 \text{ mL} \cdot \text{min}^{-1}$) was cyclically pumped through the base and the catalyst columns for 10 min (each fraction) and then collected into the reservoir to isolate the product in a 98% yield (>99% purity) after removal and recovery of the solvent (90% of solvent recovered) via distillation.

E-factor calculation: E-factor = $[7.4 \text{ g (4-bromobenzaldehyde, 1g)} + 5.36 \text{ g (phenylboronic acid, 2a)} + 6.7 \text{ g (K}_2\text{CO}_3\text{)} + 108.2 \text{ g (EtOH)} - 7.1 \text{ g (1,1'-biphenyl-4-carbaldehyde (3g), 98\% \text{ yield)} - 97.8 \text{ g (recovered EtOH)}] / 7.1 \text{ g (1,1'-biphenyl-4-carbaldehyde (3g), 98\% \text{ yield)} = 3.2.$

3.10. Typical Procedure for the Heck Reaction under Batch Conditions

In a steel reactor, to a solution of the aryl iodide **4a–h** (1 mmol) and the alkene **5a–b** (1.2 mmol) in aq. CH_3CN 84% (1 M, 1 mL), triethylamine (0.167 mL, 1.2 mmol) and catalyst Pd@ZPGly-15 (0.47 mg, 2.11 mmol of Pd per g, 0.1 mol %) were added. The reaction mixture was stirred at 120°C for 3 h with methyl acrylate (**5a**) and for 4 h with styrene (**5b**); the conversion of the aryl iodide **1a–h** was monitored by GLC analyses. The reaction mixture was diluted with water (2 mL) and extracted with ethyl acetate ($3 \times 3 \text{ mL}$). The combined organic layers were dried with sodium sulfate and evaporated under reduced pressure.

Representative E-factor calculations: E-factor for Heck reaction of iodobenzene (**4a**) (1 mmol) and methyl acrylate (**5a**) (1.2 mmol) (98% isolated yield): E-factor = $[0.204 \text{ g (iodobenzene (1a))} + 0.103 \text{ g (methyl acrylate (2))} + 0.121 \text{ g (TEA)} + 0.818 \text{ g (1 mL CH}_3\text{CN/H}_2\text{O 84:16)} + 2 \text{ g (water)} + 8.1 \text{ g (ethyl acetate)} - 0.159 \text{ g (methyl cinnamate (6a))}] / 0.159 \text{ g (methyl cinnamate (6a))} = 70.4$ (catalyst was not considered due to its recovery and recycle).

3.11. Typical Procedure for Recovery and Reuse of Pd@ZPGly-15 in the Heck Reaction under Batch Conditions

In a steel reactor, to a solution of iodobenzene (**4a**, 1.22 g, 6 mmol) and methyl acrylate (**5a**, 0.62 g, 7.2 mmol) in aq. CH_3CN 84% (1 M, 6 mL), triethylamine (1 mL, 7.2 mmol) and catalyst Pd@ZPGly-15 (2.8 mg, 2.11 mmol of Pd per g, 0.1 mol %) were added. The reaction mixture was stirred at 120°C for 3 h; the conversion of the iodobenzene (**4a**) was monitored by GLC analyses. The solid catalyst was separated by centrifugation and then washed with aq. CH_3CN azeotrope ($2 \times 1 \text{ mL}$), dried at 50°C for 3 h and reused in a successive cycle. The product was isolated after extraction with ethyl acetate.

3.12. Typical Procedure for the Heck Reaction in the Presence of PS-TEA under Batch Conditions

In a steel reactor, to a solution of iodobenzene (**4a**, 0.204 g, 1 mmol) and methyl acrylate (**5a**, 0.103 g, 1.2 mmol) in aq. CH_3CN 84% (1 M, 1 mL), diethylaminomethyl-polystyrene (PS-TEA, 0.312 g, 3.84 mmol/g, 1.2 equiv) and catalyst Pd@ZPGly-15 (0.47 mg, 2.11 mmol of Pd per g, 0.1 mol %) were added. The reaction mixture was stirred at 120°C for 3 h; the conversion of the iodobenzene (**4a**) was monitored by GLC analyses. The heterogeneous base and catalyst were separated by filtration, washed with aq. CH_3CN azeotrope (1 mL) and the product **6a** isolated by distillation of the azeotrope.

E-factor calculations: (96% isolated yield): E-factor = $[0.204 \text{ g (iodobenzene (4a))} + 0.103 \text{ g (methyl acrylate (5a))} + 0.312 \text{ g (PS-TEA)} + 0.00047 \text{ g (Pd@ZPGly-15)} + 1.64 \text{ g (2 mL CH}_3\text{CN/H}_2\text{O 84:16)} - 0.155 \text{ g (methyl cinnamate (6a))}] / 0.155 \text{ g (methyl cinnamate (6a))} = 13.6.$

3.13. Heck Reaction of Iodobenzene (4a) and Methyl Acrylate (5a) under Flow Conditions

A pre-mixed mixture of iodobenzene (4a, 5.60 mL, 50 mmol) and methyl acrylate (5a, 5.40 mL, 60 mmol) in aq. CH₃CN 84% (50 mL) was charged into a glass column functioning as a reservoir. The supported base PS-TEA (19.5 g, 3.84 mmol/g, 75 mmol) and the catalyst Pd@ZPGly-15 (23.7 mg, 2.11 mmol of Pd per g, 0.1 mol %) were mixed and dispersed in 1 mm diameter solid glass beads and charged in a stainless steel HPLC column; the equipment was connected, by using the appropriate valves, to a pump and installed into a thermostated box. The reaction mixture was continuously pumped (flow rate 2.0 mL/min) through the base-catalyst column at 120 °C until complete conversion of reactants to methyl cinnamate (6a) was achieved (the reaction was monitored by GLC). At this stage, the pump was left to run in order to recover the reaction mixture in the reservoir. To completely recover the product and clean the reactor, aq. CH₃CN azeotrope (3 × 25 mL at a 2 mL/min) was cyclically pumped through the base-catalyst column for 15 min (each fraction) and then collected in the reservoir to isolate the product in 87% yield, after removal and recovery of the azeotrope (95% of which was recovered) via distillation. A solution of TEA (15 mL in 30 mL of aq. CH₃CN azeotrope) was cyclically pumped through the base/catalyst column (2 mL/min, 30 min) to regenerate the diethylaminomethyl-polystyrene. Finally, azeotrope (40 mL) was cyclically pumped through the base/catalyst column in two portions to remove residual TEA.

Representative E-factor calculations: (87% isolated yield): E-factor = [10.2 g (iodobenzene (4a)) + 5.16 g (methyl acrylate (5a)) + 102.25 g (CH₃CN/H₂O 84:16) + 19.5 g (PS-TEA) + 0.0275 g (catalyst) – 7.05 g (methyl cinnamate (6a)) – 97.15 g (95% recovered medium)]/7.05 g (methyl cinnamate (6a)) = 4.7.

4. Conclusions

The immobilization of palladium nanoparticles on zirconium phosphate glycine diphosphonate nanosheets provided stable catalysts with high Pd content (up to 22 wt %). The prepared materials were used as catalysts in a low amount (0.1 mol %) in the Suzuki–Miyaura and Heck reactions by using the aqueous azeotropic mixture (EtOH 95%, CH₃CN 84%) as a safe and easily recoverable reaction media. Pd@ZPGly-15 was found to be the best catalyst, in terms of activity and release of Pd, both in the Suzuki and Heck reaction. The robustness of the catalyst was tested, and a high reactivity was obtained over more runs. Finally, the waste production (E-factor) and the residual palladium content in the reaction products have been considerably reduced by using the flow technology.

Supplementary Materials: The following are available online at www.mdpi.com/2073-4344/7/6/186/s1.

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