




Article

Polyvinylpyridine-Supported Palladium Nanoparticles: An Efficient Catalyst for Suzuki–Miyaura Coupling Reactions

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Abstract: Palladium nanoparticles (Pd NPs) synthesized by the metal vapor synthesis technique were supported on poly(4-vinylpyridine) 2% cross-linked with divinylbenzene (Pd/PVPy). Transmission electron microscopy revealed the presence of small metal nanoparticles ($d_m = 2.9$ nm) highly dispersed on the PVPy. The Pd/PVPy system showed high catalytic efficiency in Suzuki–Miyaura carbon–carbon coupling reactions of both non-activated and deactivated aromatic iodides and bromides with aryl boronic acids, carried out under an air atmosphere. The high turnover of the catalyst and the ability of the PVPy resin to retain active Pd species are highlighted. By comparing the catalytic performances of Pd/PVPy with those observed by using commercially available Pd-based supported catalysts, the reported system showed higher selectivity and lower Pd leaching.

Keywords: Pd catalysts; metal vapor synthesis; polyvinylpyridine; Suzuki–Miyaura reaction

1. Introduction

The palladium-catalyzed coupling of organoboron reagents with aryl halides, known as the Suzuki–Miyaura reaction [1–3] is one of the most convenient and powerful synthetic methods for the preparation of biaryl and alkene derivatives that are essential components of natural products, pharmaceuticals, agrochemicals, and polymers [4–6]. The reaction is mainly unaffected by water, tolerating a huge range of functionality and leading to non-toxic by-products [7]. Traditional reaction conditions for Suzuki–Miyaura couplings involve the use of homogeneous palladium catalysts containing phosphine ligands [1,8–11] or N-heterocyclic carbene ligands [12–14].

This reaction is the most intensively investigated among C–C couplings in the last decade [15–17]. Buchwald and coworkers [18,19] and Fu and coworkers [20] reported the possibility of exploiting this reaction with different compounds such as less-active aryl chlorides, hindered substrates, hetero-aromatic compounds, and alkenyl derivatives as well as at room temperature and in the presence of low-catalyst-loading. However, the main disadvantages are the availability, stability, and cost of the palladium organometallic complexes as well as of the ligands. Furthermore, homogeneous palladium catalysts are typically not reusable and the products are often contaminated by residual palladium and/or ligands, which in turn are difficult to separate from the products [3,21]. These limitations of

homogeneous catalysis boosted the development of new strategies for transition-metal catalysis, which allows for catalyst recovery and reuse. In this framework, supported palladium catalysts can offer several advantages, as they can be easily purified by simple filtration from the reaction mixture and recycled for further reactions, if the active sites have not become deactivated. Moreover, this latter approach can reduce waste derived from reaction workup, favoring the development of green chemical processes [22,23].

For this purpose, palladium salts, organometallic complexes, or Pd nanoparticles (NPs) [24] have been immobilized on a wide range of organic or inorganic supports (e.g., polystyrene [25–27], polyurea [28], polydopamine [29] carbon [30,31], montmorillonite [32], gold [33], zeolites [34], silica gels [35–40]) by covalent, ionic bonding, adsorption, or encapsulation to obtain recoverable supported palladium catalysts [41]. Using a different approach, Schüth and coworkers recently reported the synthesis of Pd NPs confined into a porous polyphenylene network obtained by direct palladium-catalyzed Suzuki–Miyaura coupling. The solid composite was shown to be a very active catalyst for Suzuki coupling reactions [42]. Despite the advantages described above, supported catalysts often suffer from reduced mass transfer and lower catalytic efficiency than homogeneous ones. Moreover, they rapidly lose catalytic activity when reused, mainly due to a re-structuring of the active site leading to Pd NP aggregation as well as Pd leaching [43]. In 2006, McQuade and coworkers reported that the polyurea-encapsulated PdEnCat, a commercially available catalyst used in Mizoroki–Heck and Suzuki–Miyaura coupling reaction, actually acted as a Pd reservoir of soluble catalytic species [44]. As a matter of fact, the TEM analysis of the supernatant from the Heck reaction catalyzed by Pd EnCat[®] 30 clearly revealed metal leaching, leading to the formation of Pd nanoparticles ranging from 5 to 10 nm in size. In the same year, Park and co-workers reported that polystyrene (cross-linked with divinylbenzene) beads doped with palladium quickly loses the original activity in the same reaction, with a yield that in the third cycle was lowered to only 38% from the original 98% [45]. This behavior was addicted to Pd leaching and Pd nanoparticle aggregation occurring during the Suzuki–Miyaura coupling reaction.

Some years ago, we described the preparation of Pd NPs by metal vapor synthesis (MVS) supported on a commercially available poly(4-vinylpyridine) cross-linked with divinylbenzene resin (PVPy), acting as an effective catalyst for Heck-type alkenylations [46]. The catalyst was particularly active and stable, ensuring a very low Pd leaching, and was effectively re-used for further reaction cycles. Herein, we report on the use of a PVPy-supported Pd catalyst for the synthesis of biaryls via the Suzuki–Miyaura couplings of aryl halides with arylboronic acids under air atmosphere.

2. Results and Discussion

2.1. Characterization of Polyvinylpyridine-Supported Palladium (Pd/PVPy) Catalyst

Polyvinylpyridine-supported palladium catalyst, Pd/PVPy, was synthesized according to the previously reported MVS approach [46]. TEM micrographs of the Pd/PVPy (Figure 1) show the PVPy polymer homogeneously populated by Pd nanoparticles in the range 0.5–8.0 nm, with a mean diameter close to 2.9 nm. High resolution TEM analysis (Figure S1) indicates the presence of metal particles well included into the polymeric resin, in agreement with the previously reported data emphasizing the strong affinity of MVS-derived Pd NPs with the pyridine moiety of the support [46–50]. Moreover, lattice fringe analysis, recorded on Pd nanoparticles, showed spots in the FFT pattern at 2.26 Å that can be ascribed to the spacing of (1 1 1) planes of the face centered cubic (fcc) structure of metallic Pd.

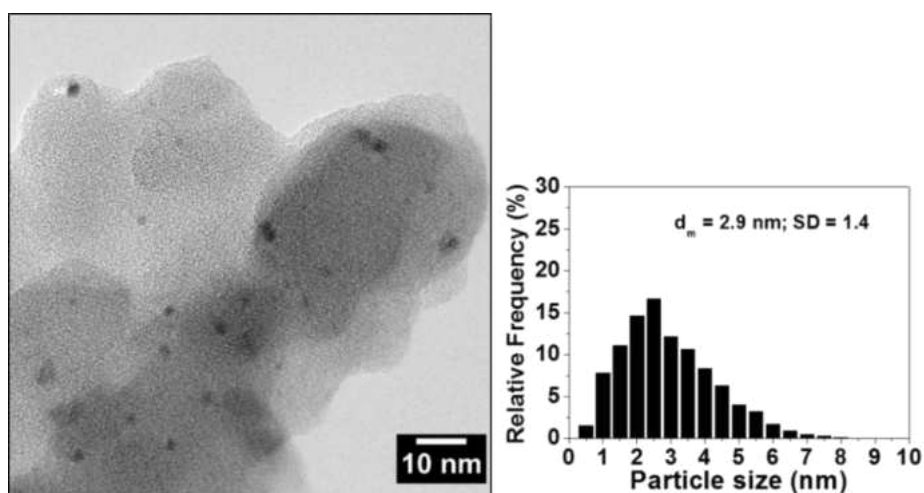
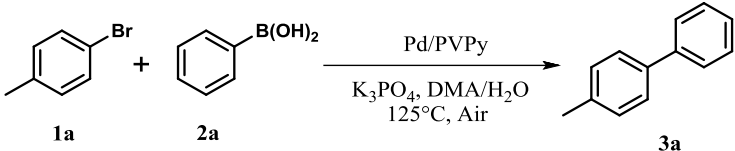


Figure 1. Representative transmission electron microscopy micrograph and histogram of particle size distribution of the polyvinylpyridine-supported palladium catalyst (Pd/PVPy).

2.2. Catalytic Activity in Suzuki–Miyaura Reaction

The reaction between 4-bromotoluene (1a) and phenylboronic acid (2a) was chosen as a model reaction to evaluate the catalytic behavior of the Pd/PVPy system. In order to optimize the experimental conditions, the factors affecting the conversion and the selectivity of the reaction (i.e., solvent and base) were initially evaluated in the presence of 0.50 mol % of Pd/PVPy, under an argon atmosphere (Table S1). The best results were obtained using DMA/H₂O (4:1) as the solvent and K₃PO₄ as the base (3 equivalent) at 120 °C. In these conditions after 7 h of reaction, the conversion into the 4-methylbiphenyl (3a) cross-coupling product with a yield of 64% occurred along with a complete selectivity. Surprisingly, inorganic bases commonly used for Suzuki–Miyaura reaction (i.e., Na₂CO₃, NaHCO₃, and NaOH) led to poor results. On the other hand, using strong bases such as KF promoted an extensive dehalogenation of the aryl halide as well as the formation of homo-coupling side product. Regarding the solvent employed in the reaction, the mixture DMA/H₂O (4:1) led to the best results without the presence of side reaction products. As a matter of fact, the use of water alone or in combination with alcohols such as *i*-PrOH/H₂O (1:1) and EtOH/H₂O (1:1), and aprotic polar/aqueous solvents (i.e., NMP/H₂O (4:1) and 1,2-dioxane/H₂O (4:1)) resulted in lower yields of the cross-coupling product. Further investigations revealed that the amount of Pd/PVPy can be effectively decreased from 0.5 to 0.15 Pd mol % without significant loss of yield of the 3a product (Table 1, entries 1–3). Nevertheless, a further decrease of the catalyst amount to 0.10 Pd mol % led to a drop in the yield of 3a (entry 4). Finally, the possibility of carrying out the Suzuki–Miyaura coupling under aerobic conditions was investigated. Under these latter conditions, the activity of the Pd/PVPy catalyst was remarkably enhanced, while the selectivity appeared comparable with that obtained under an inert atmosphere (entry 5). As expected, the reaction needed less mild conditions (e.g., higher temperature and longer reaction time) than those reported with Pd organometallic complexes for reactions carried out in the homogeneous phase (see e.g., [13]). However, as discussed above, the use of supported catalysts is a valid alternative in order to (i) facilitate the reaction workup, (ii) limit the Pd contamination of the reaction product, and (iii) favor the reusability of the catalyst.

These results agree with evidence previously reported by other authors on the beneficial effect of the oxygen [43,49–52]. The observed increase in catalytic activity has been ascribed to the formation of oxidized Pd species onto the surface of Pd NPs. As a consequence, the oxidized Pd atoms can be easily released into the solution, leading to “peroxo–palladium complexes” that are stable against aggregation. Moreover, they can directly undergo transmetalation with the arylboronic due to the enhancement of the electron density of palladium.

Table 1. Suzuki–Miyaura reaction catalyzed by the Pd/PVPy catalyst ^a.


Entry	Atmosphere	Pd/PVPy (mol % of Pd)	Conversion ^b (%) ^b	Yield ^c (%) ^c	Pd Leaching (% , ppm) ^d
1	Ar	0.5	64	61	n.d.
2	Ar	1.0	67	62	n.d.
3	Ar	0.15	64	55	1.2, 0.44
4	Ar	0.10	40	35	n.d.
5	Air	0.15	81	76	1.3, 0.48

^a Reaction conditions: 1.00 mmol of **1a**, 1.25 mmol of **2a**, K₃PO₄ (3 mmol), Pd/PVPy, DMA/H₂O (4:1) (4 mL), T = 125 °C, t = 7 h. ^b Evaluated by GC, and determined by the area ratio between product **3a** and total area of **1a** and **3a**. ^c Yield of **3a** evaluated by GLC, determined by internal standard (naphthalene). ^d Evaluated by ICP-OES after microfiltration (0.22 μm).

Additionally, we investigated the Pd leached into the reaction mixture by inductively coupled plasma-optical emission spectroscopy analysis in order to evaluate the amount of Pd released in solution from the Pd/PVPy catalysts under the above mentioned reaction conditions. Furthermore, with the same analysis, we can also obtain information on the capability of the polymeric support to quench the Pd species in solution. For this purpose, after 7 h, the reaction mixture was filtered through a polytetrafluoroethylene syringe filter (0.22 μm diameter) and a portion of the filtrate was dissolved by nitric acid after solvent evaporation. The levels of Pd contamination detected on reactions carried out both in argon and in air atmosphere were exceptionally very low. The obtained values of 0.44 ppm and 0.48 ppm for reaction in argon and air, respectively, corresponded to a Pd leached of 1.2 and 1.3 wt % of the initial available Pd amount in the catalyst. Moreover, the filtrate solution was newly heated at 125 °C and the reaction conversion was monitored to check that the catalytic species was still present in the mixture (Figure 2). The results show that the reaction without the solid catalyst afforded only 1% of conversion after 17 h, indicating that the catalytically active Pd species were effectively removed.

It is worth noting that the leaching test and filtration test alone cannot univocally establish the real nature of the active catalyst (i.e., heterogeneous or homogeneous), as the support can catch the leached Pd so fast that it may not be revealed by the leaching or hot filtration test [43,53]. However, the ability of the PVPy resin to coordinate palladium active species formed in carbon–carbon coupling reactions was previously described [54,55].

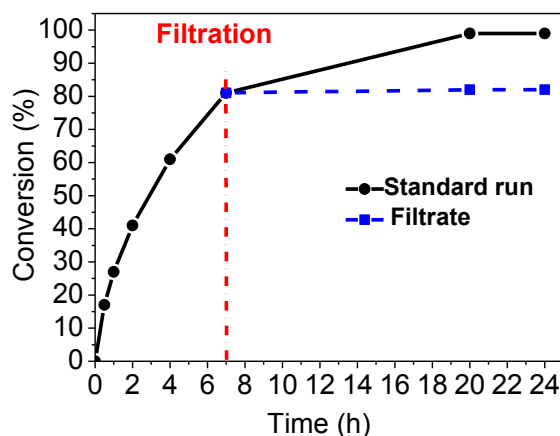


Figure 2. Conversion and hot filtration test during the Suzuki–Miyaura coupling reaction of 4-bromotoluene (**1a**) with phenylboronic acid (**2a**) over Pd/PVPy (see footnotes to Table 1 for experimental conditions).


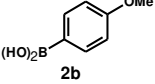
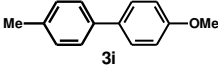

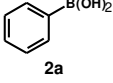
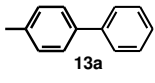

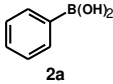
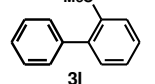

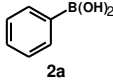
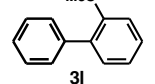

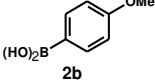
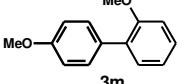

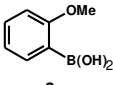
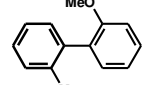

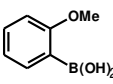
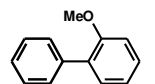
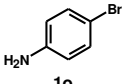
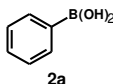
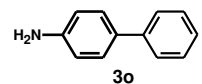
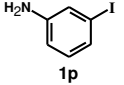
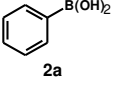
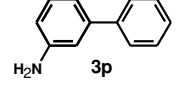

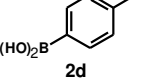
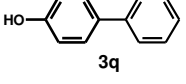
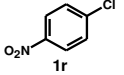
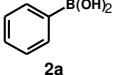
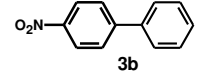
From the data described above, the Pd/PVPy system has the requisites to be transferred into industrial applications. Indeed, from an applicative point of view, the Pd/PVPy catalyst can effectively reduce the issue of the metal contamination in products prepared via the Suzuki–Miyaura cross-coupling reaction (e.g., for the synthesis of active pharmaceutical intermediates), avoiding the time-consuming and expensive cleaning steps needed in order to remove the Pd residue.

In order to further investigate the applicability of the Pd/PVPy catalyst, we extended the substrate scope by creating a library of suitable aryl halide and boronic acid investigated under the optimized reaction conditions (Table 2). Deactivated aryl iodides as well as activated and deactivated aryl bromides were completely converted with a yield of the corresponding isolated products ranging from 58 to 99%. The reaction exhibited good diversity with both electron withdrawing and donating groups. For the deactivated aryl halides sterically hindered, both bromides and iodides, a satisfactory yield could be obtained increasing the reaction time (entries 11–14). Interestingly, both protic free groups (i.e., NH₂ and OH) were well-tolerated in the reaction (entries 16–18). Furthermore, aryl chlorides (entry 19) were converted with low yield into the product even after a longer reaction time because of their low reactivity, as a consequence of their reluctance to oxidatively add to Pd(0). Regarding aryl boronic acids, the coupling reaction of electron-rich aryl boronic acid (e.g., 4-methoxyphenylboronic acid, (**2b**)) proceeded more efficiently when compared with non-substituted phenylboronic acid (**2a**). Noteworthy, the reaction with aryl boronic acid sterically hindered such as 2-methoxyphenylboronic acid (**2c**) led to the corresponding product in moderate yield (48%) in conjunction with the product of homocoupling (entry 15).

Table 2. Suzuki–Miyaura coupling reactions catalyzed by Pd/PVPy ^a.

Entry	(Het)Ar-X 1	Ar'-B(OH) ₂ 2	Time (h)	Product 3	Yield ^b (%)
1			22		91
2			1.5		98
3			15		99
4			24		92
5			3.5		82
6			2.5		87
7			2.5		98
8			21		83

Table 2. Cont.

Entry	(Het)Ar-X 1	Ar'-B(OH) ₂ 2	Time (h)	Product 3	Yield ^b (%)
9			12		92
10			1.0		94
11			24		72
12			3.5		84
13			24		67
14			18		80
15			24		48
16			24		58
17			20		86
18			24		64
19			48		16

^a Reaction conditions: 2.00 mmol of **1**, 2.50 mmol of **2**, K₃PO₄ (6 mmol), Pd/PVPy (0.15 mol % of Pd), 4.0 mL DMA/H₂O (4:1), T = 125 °C. ^b Isolated yield evaluated by medium pressure liquid chromatography purification on silica gel.

2.3. Catalyst Reusability

We investigated the lifetime of the Pd/PVPy catalyst and its level of reusability in consecutive Suzuki–Miyaura reactions using both an electron-poor aryl bromide (e.g., 4-bromonitrobenzene, **1a**) and an electron-rich aryl bromide (e.g., 4-bromotoluene, **1b**) in combination with the phenylboronic acid (**2a**) (Figure 3). After each cycle, the catalyst was recovered by filtration and afterward washed with water and acetone and then dried under vacuum. The solid catalyst was then reused without further activation. As a result, the catalyst showed a comparable performance for five consecutive

runs, showing a slight decrease of the efficiency only during the fifth catalytic cycle. TEM analysis of a Pd/PVPy sample recovered after the first catalytic run (Figure 4, right side) confirmed only a slight increase in the particle size ($d_m = 3.5$ nm) with respect to the freshly prepared sample.

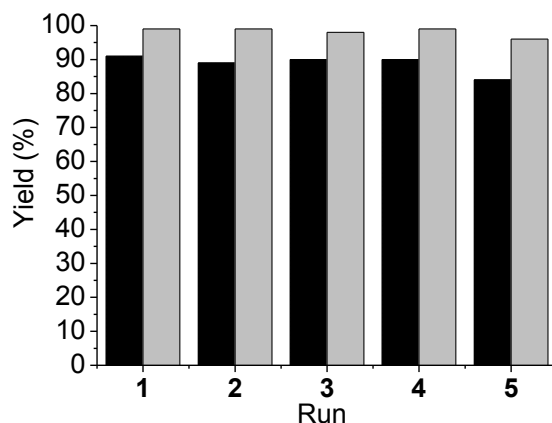


Figure 3. Recycling tests on Pd/PVPy catalysts for the Suzuki–Miyaura coupling reaction of 4-bromotoluene (**1a**, black bars) and 4-bromonitrobenzene (**1b**, grey bars) with phenylboronic acid (**2a**) (see Table 2 for experimental conditions).

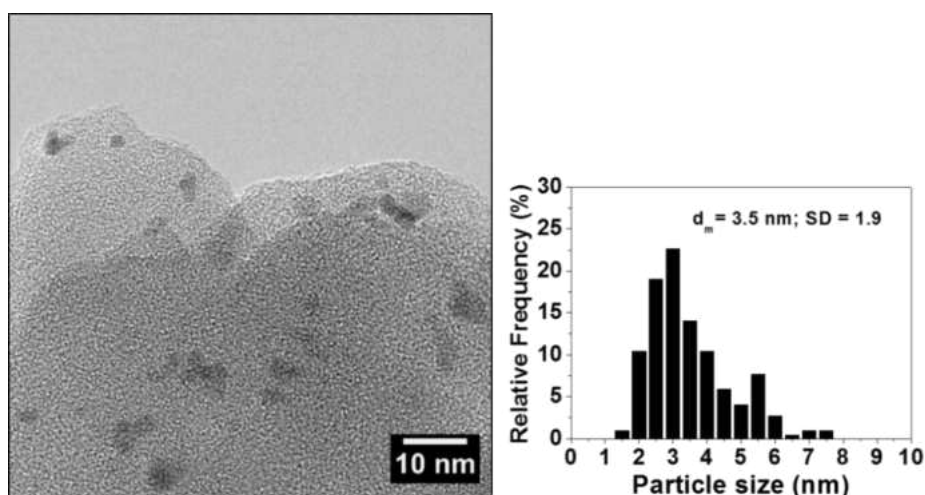


Figure 4. Representative transmission electron microscopy micrograph and histogram of particle size distribution of Pd/PVPy system after the first catalytic cycle.

2.4. Comparison with Commercially Available Pd-Based Catalysts

The catalytic performances of the Pd/PVPy system used in the reaction of 4-bromonitrobenzene (**1a**) with phenylboronic acid (**2a**) was compared with other commercially available heterogeneous catalysts such as Pd/C and palladium acetate microencapsulated in polyurea matrix (Pd EnCat[®] 40) (Table 3). The results showed that Pd/PVPy led to the best results in terms of selectivity (99.9%), without the formation of the homocoupling side-product. Moreover, the presented system provides a lower Pd leaching (1.3 Pd wt % of the initial Pd content) than the other commercially available systems examined (2.2–2.6 Pd wt % of the initial Pd content).

Table 3. Comparison of the performances of Pd/PVPy in the Suzuki–Miyaura reaction ^a.

Entry	Catalyst	Conversion ^b (%)	Selectivity ^b 3a/3b	Yield ^c (%)	Pd Leaching ^d (%, ppm)
1	Pd/PVPy	81	99.9/0.1	76	1.3, 0.48
2	Pd/C	99	90/10	75	7.2, 2.67
3	Pd EnCat [®] 40	97	98/2	62	2.4, 0.89

^a Reaction conditions: 2.00 mmol of **1a**, 2.50 mmol of **2a**, 6.00 mmol of K₃PO₄, 0.15 mol % of Pd (0.0030 mmol Pd), 4 mL DMA/H₂O (4:1), T = 125 °C, t = 7 h. ^b Evaluated by GC; ^c Yield of 3a evaluated by GLC, determined by internal standard (naphthalene). ^d Evaluated by inductively coupled plasma-optical emission spectroscopy after microfiltration (0.22 μm).

3. Materials and Methods

All operations involving the MVS products were carried out under an argon atmosphere. The co-condensation of palladium and the solvent was carried out in a previously described static reactor [46]. Solvents were purified by conventional methods, distilled, and stored under argon. Poly(4-vinylpyridine) 2 % cross-linked with divinylbenzene (PVPy), Pd/C, and Pd EnCat[®] 40 were from Merck (Darmstadt, Germany). K₃PO₄, aryl iodides, aryl bromides, and boronic acids were from Merck and used as received.

Gas-liquid chromatography (GLC) analyses were performed on a Dani GC1000 gas chromatograph (Milano, Italy), equipped with a flame ionization detector (FID) using a SiO₂ capillary column FSOT Alltech (AT-5, 30 m × 0,25 mm i.d.) and nitrogen as the carrier gas. Gas-liquid chromatography–mass spectrometry (GLC-MS) analyses were performed on an Agilent 6890 Network GC System (Santa Clara, CA, USA), equipped with an electron impact mass detector (Agilent 5973 Network Mass Selective Detector) using a SiO₂ capillary column FSOT Agilent (HP-5MS, 30 m × 0,25 mm i.d.) with helium as the carrier gas. Inductively coupled plasma-optical emission (ICP-OES) analysis was carried out by inductively coupled plasma-optical emission spectroscopy (ICP-OES) (Perkin Elmer Optima 8000, Waltham, MA, USA) and an external calibration methodology. The limit of detection (LOD) calculated for palladium was 2 ppb.

Transmission electron microscopy (TEM) analysis was performed by a ZEISS LIBRA200FE microscope (Oberkochen, Germany) equipped with a 200 kV field-emission gun source. The sample was finely smashed in an agate mortar, suspended in toluene and sonicated, then the suspension was dropped onto a holey carbon coated copper grid (300 mesh) followed by the evaporation of the solvent.

3.1. Preparation of Pd/PVPy System

In a typical experiment, Pd vapor, generated at 10^{−4} mbar by resistive heating of the metal (500 mg) in an alumina-coated tungsten crucible, was co-condensed at liquid nitrogen temperature with a 1:1 mixture of mesitylene (30 mL) and 1-hexene (30 mL). The reactor chamber was then heated to the melting point of the solid matrix, and the resulting red-brown solution was siphoned and handled at low temperature (−30/−40 °C).

For ICP-OES analysis, the metal-containing mesitylene/1-hexene solution (1 mL) was heated in a porcelain crucible over a heating plate and the solvent was evaporated. The solid residue was dissolved in aqua regia (2 mL), heated until complete evaporation and the solid residue was dissolved in 0.5 M aqueous HCl. The palladium content of the solvated metal solution was 2.8 mg/mL. The mesitylene/1-hexene Pd atoms solution (36 mL, 100.8 mg Pd) was added to a suspension of PVPy (10 g) in mesitylene (30 mL). The mixture was stirred at room temperature for 24 h. The colorless solution was removed and the light-brown solid was washed with *n*-pentane (3 × 40 mL) and dried under reduced pressure. The metal content of Pd on the PVPy catalyst (1.0 wt % Pd) was determined by ICP-OES analysis.

3.2. General Procedure for the Suzuki–Miyaura Reactions

3.2.1. Suzuki–Miyaura Reactions

Aryl halides (2.0 mmol), aryl boronic acid (2.5 mmol), $K_3PO_4 \cdot 12H_2O$ (6.0 mmol), Pd/PVPy (32 mg, 3.0×10^{-3} mmol Pd), and DMA:H₂O 4:1 (4 mL) were introduced into a 25 mL round-bottomed, two-necked flask equipped with a stirring magnetic bar, a condenser, and a silicon stopper. The reaction mixture was stirred at 125 °C. For GLC analysis, the samples were treated with 0.5 M aqueous HCl. The organic products were then extracted with diethyl ether, and dried over anhydrous sodium sulfate. The coupling products were purified by column medium-pressure chromatography (silica, solvent mixture). The reaction was stopped at the time reported in Table 2. All the products were characterized by using mass spectrometry (see Supplementary Materials).

3.2.2. Recycling Tests

The coupling reaction of aryl bromide (**1a** and **1b**) with phenylboronic acid (**2a**) was carried out as described in the general procedure of Suzuki–Miyaura cross-coupling reactions (4.2.1.). After filtering off the product, the catalyst was washed with H₂O (3 × 10 mL), acetone (3 × 5 mL), and Et₂O (3 × 5 mL), respectively, and dried under vacuum for 12 h. Then, the recovered catalyst was used in a further coupling experiment.

4. Conclusions

In conclusion, the Pd/PVPy catalytic system synthesized by the MVS approach is an effective catalyst for the Suzuki–Miyaura coupling reaction under aerobic conditions. This catalyst remarkably expands the scope of palladium supported catalysts by enabling the possibility of using various arylboronic acids for the coupling of aryl bromides. The catalytic system exhibits high recyclability, with coupling yields preserved over five catalytic cycles, and a very low Pd leaching (i.e., product contamination). Further applications of the reported system can be foreseen due to the high versatility of this catalyst.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2073-4344/10/3/330/s1>, Figure S1: High resolution TEM micrograph (800000X) of Pd/PVPy and FFT pattern taken from the yellow squared area, Table S1: Optimization reaction conditions: Isolation and characterization of Suzuki–Miyaura products.

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