Efficient and Recyclable Catalyst of Palladium Nanoparticles Stabilized by Polymer Micelles Soluble in Water for Suzuki–Miyaura Reaction, Ostwald Ripening Process with Palladium Nanoparticles

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Abstract: The Suzuki–Miyaura cross-coupling reaction of ArX (I, Br) with Ar′B(OH)$_2$, catalyzed by Pd-containing water-soluble micelle formed by PS-PEO copolymer and *N*-cetylpyridinium chloride as a surfactant, was studied in water and methanol. The reaction was performed under mild conditions (temperature up to 50 °C) and the catalyst can be recycled (5 runs) by ultrafiltration without any loss of its catalytic activity. The phenomenon was observed, consisting in growing Pd-nanoparticle size because the small nanoparticles dissolve to form larger nanoparticles in the course of reaction as well as in the presence of the only reagent, ArI. In the latter case, additionally, the formation of very small, not completely dissolved Pd nanoparticles, obviously having a high catalyst activity, is observed. This observation, together with the catalyst activity data might have an implication for a leaching mechanism for the studied catalytic system.

Key words: palladium nanoparticles, Suzuki–Miyaura cross-coupling, biaryls, block copolymer micelles, Ostwald ripening process

The great importance of palladium-catalyzed reactions of carbon–carbon bond formation, such as Suzuki–Miyaura (S–M), Sonogashira, Heck, and many other reactions, led to an incessant pursuit of efficient catalysts for these processes. The palladium complexes with phosphine ligands had played a significant role in the development of this field. However, in order to meet the challenges of catalyst separation after the reaction and its possible recycling, fundamentally new catalysts had to be developed – heterogeneous palladium nanoparticles (PdNP) on solid support, for example, on activated carbon,[1] bound to polymer[2] or dendrimer macromolecules.[3] Catalytic systems have been developed based upon PdNP 'homogeneously' dispersed in the solution, stabilized in micelles of block co-polymers of styrene with 4-vinylpyridine[4] and ethylene oxide[5] or sodium acrylate,[3] co-polymers of ethylene oxide with 2-vinylpyridine[6] or propylene oxide,[7] etc. Heterogeneous catalysts of this type meet the demands of Green Chemistry, since they are free from toxic ligands, can be easily separated from the reaction products and are capable of recycling. It emerged recently, that the activity of such catalysts is dependent upon the state of these nanosized particles.[8,9]

The question of the actual active species in the catalytic cycle for the reaction catalyzed by PdNP is still controversial. The reaction is supposed to occur on the surface of PdNP[10] or via leaching of Pd as atoms/ions, especially in the defect sites, into solution.[11] The latter hypothesis has been substantiated experimentally.[12] At the same time, there are research groups, including the authors of the present communication, who are inclined to believe that catalysis in such systems is mainly due to Pd atom leaching from PdNP surface subsequent to the oxidative–addition of organic halide.[3c,11c,13] Palladium(0) is subsequently regenerated in the catalytic cycle and is deposited in the form of nanosized particles.

Previously we used a micelle formed by styrene–ethylene oxide block co-polymer containing PdNP prepared by the reduction of K_2PdCl_4 with $NaBH_4$, as a palladium catalytic system. The micelle was further stabilized by the additive of *N*-cetyl pyridinium chloride, incorporated into the polymer membrane.[14] Such a micelle has a hydrophobic polystyrene core and a hydrophilic polyethylene oxide crown, containing the PdNP. This catalyst showed high activity in Heck reaction with acrylates as well as cascade reactions leading to substituted indoles and isocoumarins.[5]

The elevated temperatures required for these reactions to proceed, unfortunately, led to the micelle destruction. Therefore the recycling of the catalyst with its separation after the end of reaction was impossible, but a 'fresh start', that is, the consecutive addition of a fresh batch of the reagents after the reaction completion, allowed to realize several cycles without losing the catalyst activity. The result clearly indicated that under the set conditions the palladium 'leaching' leads to the formation of catalytically active species.

The solubility of this micellar catalyst in water allowed us to perform the usually facile S–M reaction with water-soluble reagents in neat water, the 'greenest' of all solvents.[15] For water-insoluble reagents we also used methanol to extent the scope of reagents for the reaction with this catalyst. The reaction temperature did not exceed 50 °C, which allowed performing the recycling of the catalysts[16] since low temperatures favor the micelle stability.

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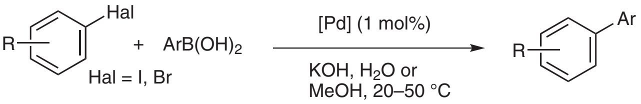
The S–M reaction was performed in water and methanol with KOH as a base (Equation 1). The use of other bases (K_2CO_3, $NaHCO_3$, Bu_4NOH solution saturated with CO_2) at required concentrations leads to the coagulation of the catalyst or the precipitation of salts of arylboronic acid. The reactions were usually carried out under aerobic conditions, since – as it has been shown for the model reaction of *m*-iodobenzoic acid with phenylboronic acid – the product yield is not dependant on the used type of atmosphere (air, argon) or high vacuum.



Equation 1

The analysis of estimated data has shown that the period of ten hours is enough to complete the reaction, for example, of *m*-iodobenzoic acid with phenylboronic acid at room temperature and the set conditions (0.3 mmol of aryl halide in the presence of 1.2 equiv of arylboronic acid, 5 equiv of KOH and, usually, not more than 1 mol% of Pd catalyst). To complete the reaction and, especially, to get high isolated product yield, reaction time varied from 4–20 hours. However, it was not possible to raise the product yield for the reaction with *p*-iodophenol over 75% because of the byproduct formation (biphenyl). The corresponding data on the conversion of the aryl halide and the product yield for the reaction in water are summarized in Table 1.

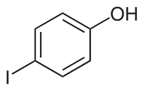
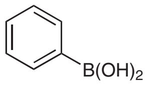
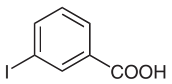
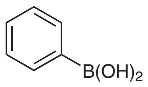
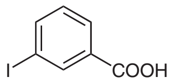
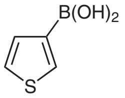
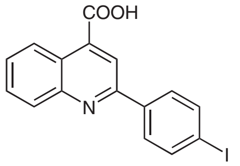
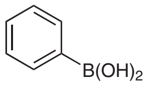
The example of the reaction of *m*-iodobenzoic acid with phenylboronic acid shows that under used conditions the reaction proceeds at almost the same rate as the reaction catalyzed by $Pd(OAc)_2$ at 20 °C (Table 1, entries 5, 7), though slower than the latter reaction at 75 °C.[17]

The formation of biphenyl as byproduct can be observed for some reactions with phenylboronic acid, which results in decreasing the cross-coupling product yield. The yield of biphenyl is minimal in case of the reaction with *m*-iodobenzoic acid (4%) and is maximal for the reaction with *p*-iodophenol (more than 8%). This byproduct can be separated from the alkaline solution of reaction mixture by filtration or centrifugation. As biphenyl is formed in the absent of aryl iodide in trace quantity, its formation can be supposed to be catalyzed by the active Pd(0) species formed in the main S–M reaction.

In case of the reactions with aryl iodide and bromide insoluble in water,[18] methanol was used as a solvent, and to accelerate some reactions the temperature was increased from 20 °C up to 50 °C (Table 2).

As in the case of the reaction in water, the reaction in methanol proceeded without Pd-black formation, which is evidence of the catalyst stability under these reaction conditions. The example of the reaction of *m*-iodobenzoic acid with phenylboronic acid at 20 °C shows that the reaction in methanol proceeds slower than in water – a 52% yield in methanol in seven hours (Table 2, entry 2) compared to a 85% yield in water in four hours (Table 1, entry 5).

Table 1 Suzuki–Miyaura Cross-Coupling Reaction with Pd Nanoparticles as Catalyst in Water[a]

Entry	Aryl iodide	Arylboronic acid	Time (h)	Yield (%)[b]	Conversion (%)[b]
1			4	68	91
2[c]			4	75	95
3			10	74	95
4[d]			4	58	67
5			4	85	89
6			10	93	100
7[e]			4	92	100
8[f]			20	97	100
9[f]			20	98	100

[a] Reaction conditions: ArI (0.075 mmol), $Ar'B(OH)_2$ (0.09 mmol), KOH (0.38 mmol), Pd (1 mol%), H_2O (0.25 mL), 20 °C.

[b] Conversion – ArI conversion value – and product yield determined by GLC, using n-$C_{16}H_{34}$ as an internal standard, biphenyl is formed as a byproduct in a 4–8% yield.

[c] Pd (2 mol%).

[d] Pd (0.2 mol%).

[e] Catalyst $Pd(OAc)_2$ (1 mol%).

[f] Isolated yield upon threefold increase of the reagents and water quantity, after acidation in EtOH, the purity of the products was confirmed by ^{1}H NMR.

Table 2 Suzuki–Miyaura Cross-Coupling Reaction of Functionalized Halobenzenes with Phenylboronic Acid in Methanol with Pd Nanoparticles as Catalyst[a]

Entry	R in RC_6H_4X	X in RC_6H_4X	Temp (°C)	Time (h)	Conversion of RC_6H_4X (%)	Yield (%)[b]
1[c]	3-COOH	I	20	7	69	67
2			20	7	54	52
3			40	7	79	77
4			50	7	98	94
5	3-CHO	I	50	20	83	18
6	4-MeO	I	20	20	78	75
7			50	4	88	86
8	$2-NO_2$	I	20	4	15	10
9			50	4.5	99	87
10	$4-NO_2$	I	20	4	99	92
11		Br	20	4	19	12
12			50	4.5	72	65
13		Cl	20	4	0	0
14[d]			50	4.5	65	0
15	4-Ac	Br	50	24	55	23
16				48	98	8

[a] Reaction conditions: ArI (0.075 mmol), $Ar'B(OH)_2$ (0.09 mmol), KOH (0.38 mmol), Pd (1 mol%), MeOH (0.25 mL), 20 °C.

[b] Yield determined by GLC, using $n-C_{16}H_{34}$ as an internal standard.

[c] Pd (2 mol%).

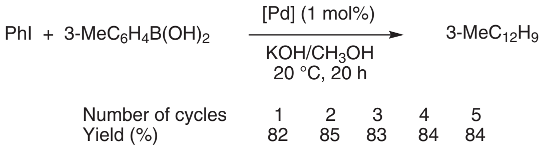
[d] Yield 63% of $4-O_2NC_6H_4OMe$.

It is evident from Table 2 that the cross-coupling product yield is high in many of the studied reactions not only with aryl iodide but also with electron-deficient aryl bromides. The reactions of phenylboronic acid with *m*-iodobenzaldehyde and with *p*-bromoacetophenone are exceptions, as their product yield is low at the full conversion of reactants. This is evidently determined by a side reaction, for example, Cannizzaro reaction with the previously formed cross-coupling product, since the product yield decreases at a long reaction time (Table 2, entry 16).

The reaction of activated *p*-nitrochlorbenzene in methanol proceeds with formation of *p*-nitroanisole (as product of S_NAr process) instead of the cross-coupling product. The attempt to carry out the reactions of phenylboronic acid with the electron-rich aryl bromide of *p*-bromophenol and even with activated *m*-bromobenzoic acid has failed although these reactions are catalyzed by $Pd(OAc)_2$ as efficiently as the reactions of corresponding iodides.[17]

The reuse of the catalyst was studied in water and methanol. The example of the reaction of *m*-iodobenzoic acid with phenylboronic acid in water at 20 °C shows that the catalyst can be separated from the reaction mixture by ultrafiltration and reused (no less than five runs) without loss of its activity (Table 3).[19] The membrane used for ultrafiltration efficiently captures polymer micelles with the Pd nanoparticles. The filtrate contains an insignificant quantity of the catalyst, since it exhibits a very low catalytic activity – 48% conversion of *m*-iodobenzoic acid in the reaction with phenylboronic acid in six days, compared to 45 minutes under normal reaction conditions with the usual amount of the catalyst (1 mol%).

For the catalyst recycling in methanol one can use not only an ultrafiltration but a centrifugation. The latter procedure allows appreciable time reduction at catalyst separation. The example of the reaction of *m*-tolylboronic acid with iodobenzene in methanol at 20 °C shows that the catalyst can be reused in this way in no less than five runs (Scheme 1).

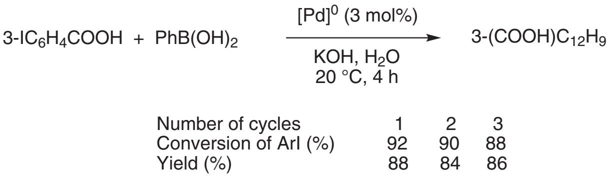


$$PhI + 3-MeC_6H_4B(OH)_2 \xrightarrow[\text{KOH/CH}_3\text{OH, 20 °C, 20 h}]{\text{[Pd] (1 mol\%)}} 3-MeC_{12}H_9$$

Number of cycles	1	2	3	4	5
Yield (%)	82	85	83	84	84

Scheme 1 Recycling of catalyst by centrifugation for Suzuki–Miyaura reaction of iodobenzene with *m*-tolylboronic acid in methanol

Another situation arises if a centrifugation is used to separate the catalyst from the reaction mixture after, for example, the reaction of *m*-iodobenzoic acid with phenylboronic acid in water is completed. In this case, the catalyst is not separated quantitatively – a part of it remains in the solution. For this reason, a centrifugation cannot be used for catalyst recycling. In addition, the activity of the precipitated catalyst decreases sharply as the run number increases [especially at Pd (1 mol%), Table 4]. Using a centrifugation, however, we succeeded in finding a certain important phenomenon. In the study of the catalyst activity after the first run it was found that 75% of the loaded Pd amount (3 mol%) affords 35% yield of the product in four hours. The smaller part of Pd (25%, contained in the solution taken from the first run after centrifugation of the reaction mixture) provides 86% yield in the same conditions. In the following successive runs the activity of the precipitated catalyst continues to decrease, but the activity of the catalyst fraction in the solution, remains practically unchanged (Scheme 2). It means that only a quarter of the loaded Pd amount becomes catalytically active in the studied reaction.



$$3-IC_6H_4COOH + PhB(OH)_2 \xrightarrow[\text{KOH, H}_2\text{O, 20 °C, 4 h}]{[Pd]^0 \text{ (3 mol\%)}} 3-(COOH)C_{12}H_9$$

Number of cycles	1	2	3
Conversion of ArI (%)	92	90	88
Yield (%)	88	84	86

Scheme 2 Recycling of the catalyst for Suzuki–Miyaura reaction of *m*-iodobenzoic acid with phenylboronic acid under fresh starting conditions in aqueous solution taken from the first run after centrifugation

The change of the catalyst morphology caused by different perturbations was assessed using transmission electron microscopy (TEM). It was found out that after the first run of the reaction of *m*-iodobenzoic acid with phenylboronic acid the precipitated catalyst contains the ag-

Table 3 Recycling of Catalyst by Ultrafiltration for Suzuki–Miyaura Reaction of *m*-Iodobenzoic Acid and Phenylboronic Acid[a]

	Number of cycles				
	1	2	3	4	5
Conversion of ArI (%) in H_2O[b]	95	91	93	90	95
Yield of product (%) in H_2O[b]	93	89	91	87	94
Conversion of ArI (%) in MeOH[c]	53	49	51	54	52
Yield of product (%) in MeOH[c]	52	47	50	53	51

[a] Reaction conditions: ArI (0.31 mmol), $PhB(OH)_2$ (0.36 mmol), KOH (1.53 mmol), Pd (1 mol%), H_2O or MeOH (1 mL), 20 °C.
[b] In 10 h.
[c] In 7 h.

Table 4 Recycling of Catalyst by Centrifugation for Suzuki–Miyaura Reaction of *m*-Iodobenzoic Acid and Phenylboronic Acid in Water[a]

	Number of cycles			
	1	2	3	4
Conversion of ArI (%) at Pd (1 mol%)[b]	90	22	15	10
Yield of product (%) at Pd (1 mol%)[b]	89	19	10	8
Conversion of ArI (%) at Pd (3 mol%)[c]	92	40	35	32
Yield of product (%) at Pd (3 mol%)[c]	88	35	25	20

[a] Reaction conditions: ArI (0.075 mmol), $PhB(OH)_2$ (0.09 mmol), KOH (0.38 mmol), H_2O (0.25 mL), 20 °C.
[b] In 8 h.
[c] In 4 h.

glomerates of micelles (up to 50 nm in size) with the PdNP (2.4–3.1 nm in size, Figure 1, C). These PdNP are larger than the ones contained in the original catalyst (1.7 nm in size, Figure1, A) and in the solution after centrifugation (1.9 nm in size, Figure 1, B).

Thus, it becomes clear why the activity of the above-mentioned precipitated catalyst is substantially lower than the activity of the catalyst remaining in the solution after a centrifugation. It is due to significant growing the PdNP size in the precipitated catalyst (from 1.7 nm to 2.4–3.1) as well as to the formation of micelle agglomerates already after the first run of the reaction.[20] As a rule, the growing in size of metal nanoparticles results in the reduction of its catalytic activity which is usually attributed to the increase of their surface area.[8]

As regards the catalyst present in the solution of the first run after centrifugation (with PdNP size being 1.9 nm), it is a new catalyst but not the original catalyst remaining after the first run, otherwise its activity would be changeable in the reaction under fresh start conditions (contrary to the data of Scheme 2) because of the formation of the catalyst precipitate.

These results, which could not be obtained using ultrafiltration, are in agreement with the fact that it is during the first run when both a new poor active catalyst fraction and a soluble active catalyst fraction appear. The original catalyst transformation in the first run of S–M reaction is also supported by the fact that the centrifugation of the reaction mixture results in partial precipitation of the catalyst, while in the absence of the organic iodide the catalyst remains in the solution, unchanged.

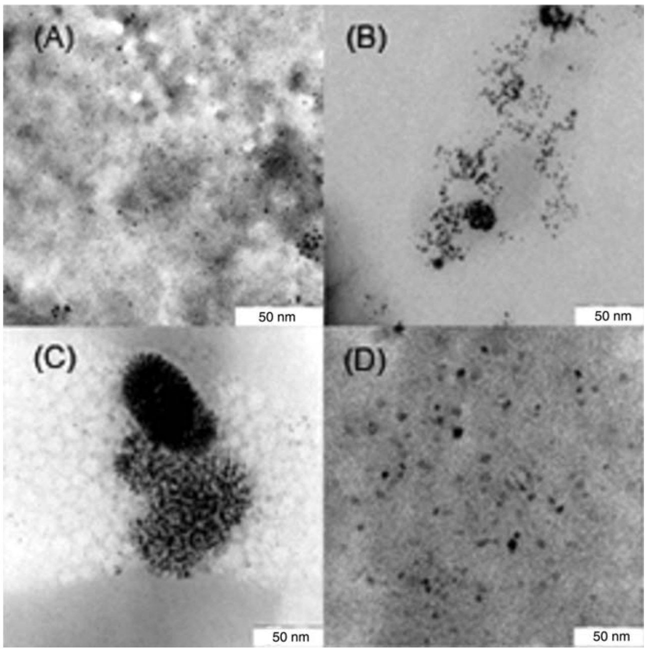
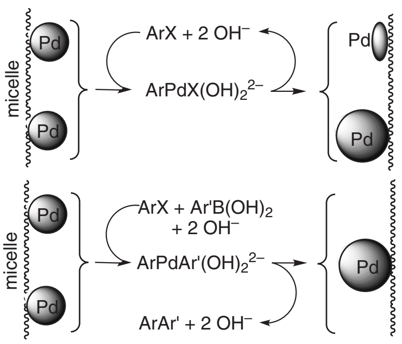


Figure 1 TEM images of the PdNP before (A) and after Suzuki–Miyaura reaction (B for liquid phase, C for deposited phase) and after interaction of the catalyst with *m*-iodobenzoic acid in the presence of KOH (D)

To ascertain what factors influence the change of PdNP size in a micelle and, accordingly, their activity in the course of S–M reaction we have studied the individual action of each reagent on the original catalyst. Using the reaction of phenylboronic acid with *m*-iodobenzoic acid as an example, we have shown that it is the organic iodide and not phenylboronic acid that effects the changes in the catalyst structure. The benzoic acid added instead of *m*-iodobenzoic acid does not influence the catalyst structure either. The catalyst transformation in the presence of aryl iodide is also supported by the fact mentioned above, that the centrifugation of the alkaline solution of the catalyst and ArI results in its partial precipitation, while in the absence of the organic iodide the catalyst remains in the solution unchanged.

As in the S–M reaction, in the presence of *m*-iodobenzoic acid the formation of new PdNP takes place. According to TEM data, relatively small blackberry-like agglomerates (2.6–7.2 nm) containing the very small Pd particles (0.6–0.8 nm) are present in the solution after centrifugation (Figure 1, D). The precipitate, in turn, consists of larger loose agglomerates (about 20 nm in size), containing small nanoparticles 1–3 nm in size, and solitary large Pd particles having the size of about 3 nm and a pronounced spherical form.

It can be supposed that leaching of the small PdNP takes place by the action of *m*-iodobenzoic acid, further facilitated by the coordination of hydroxyl ion to palladium[21] as well as by the stabilization of the $[ArPdX(OH)_2]^{2-}$ intermediate formed in this process by the hydroxyl ions as ligands. Since the oxidative addition process is reversible, the breakup of the intermediate should lead to the deposition of Pd(0) on the surface of larger PdNP, increasing their size. Such disproportionation in size of the PdNP (the increase in size from 1.7 nm to 3 nm of some particles and the decrease in size from 1.7 nm to 0.6–0.8 nm of others) is much related to the Ostwald ripening process in which small nanoparticles dissolve to form the large ones.[20,22] The disproportionation in size of the PdNP in the S–M reaction is related to the fast reductive elimination for ArPdR′ intermediate giving Pd(0). The latter is deposited on the larger PdNP further increasing their size.[22b]



Scheme 3 Suggested mechanism for the Ostwald ripening process with the PdNP in the presence of ArX (top) and in Suzuki–Miyaura reaction (bottom)

Thus, the size of PdNP will be determined by the actual ratio between the rates of all steps of S–M reaction, and, in general, may differ from that observed in the presence of the only reagent, *m*-iodobenzoic acid (Scheme 3, top). The measurement of the size of Pd particles after the reaction showed that if in the presence of *m*-iodobenzoic acid the disproportionation in size of the PdNP leads to nanoparticles from 0.6–0.8 nm to 3 nm in size, in the S–M reaction larger PdNP are formed, from 1.9 nm to 3.1 nm in size. The fact, that 0.6–0.8 nm sized particles are not found after the S–M reaction (Scheme 3, bottom) is in agreement with the view on the participation of exactly these obviously more active PdNP in the catalysis of the reaction, resulting in the growth of other particles.

To the best of our knowledge, the formation of PdNP – with the size smaller than the size of PdNP in the original catalyst – in S–M and related reactions has not been observed. The discovered process of the PdNP ‘grinding’ with the formation of very small PdNP, obviously having a high catalyst activity, points to a new role of the organic halides in the activation of the Pd precatalyst in S–M and related reactions.

In summary, the studied catalyst is efficient in S–M reactions carried out in water or methanol at relatively low temperatures. The catalyst can be recycled using ultrafiltration, when all the micelles containing the PdNP are efficiently captured. However, the analysis of the data obtained from the centrifugation and TEM experiments reveals that in the first run of the reaction the original catalyst converts to a new well recyclable catalyst along with the formation of low active clusters of PdNP. This process is accompanied by the change in size of the PdNP, which is related to the Ostwald ripening process, when the small PdNP dissolve to form the large ones. In addition, the very small, not completely dissolved PdNP, obviously having a high catalyst activity, are formed from the original catalyst under the action of the organic iodide. It seems that the significant size growing of the PdNP in the reaction limits the run number in which the catalyst can be efficiently recycled.

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