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One-pot Synthesis of Dibenzyls and 3-Arylpropionic Acids Catalyzed by Linear Polystyrene-Stabilized Palladium Oxide Nanoparticles in Water

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Reactions that are catalyzed by transition metals have become an important tool in modern organic synthesis because of their high efficiency, selectivity, and wide diversity of possible transformations. The use of heterogeneous catalysts has advantages in separation and recycling, which are important in terms of economic and ecological aspects.^[1] Furthermore, one-pot, multistep reactions are attracting more and more interest because of the emphasis of environmental requirements on waste minimization.^[2] Organic reactions in water are also environmentally benign processes. Indeed, several one-pot, multistep reactions in water have been reported to date.^[3] For example, the synthesis of benzo[*b*]furan derivatives has been achieved by the Sonogashira coupling of *o*-halophenols with terminal alkynes and subsequent hydrogenation.^[4] Recently, Li et al. reported that palladium nanoparticles (PdNPs) confined in the cages of MIL-101 can be used as a catalyst for the domino synthesis of indole derivatives.^[5]

Dibenzyls and 3-arylpropionic acid derivatives form important substructures of several natural and synthetic compounds, such as combretastatin, erianin, and cinacalcet.^[6] Although some groups have reported an efficient method for the synthesis of dibenzyls and 3-arylpropionic acid derivatives by sequential Heck reaction and hydrogenation,^[7] these reactions were performed in organic solvents. Recently, we discovered that linear polystyrene was capable of stabilizing metal nanoparticles, and the resultant polystyrene-stabilized PdO nanoparticles (PS-PdONPs) had high catalytic activities for C–C coupling reactions in water.^[4a,8] Our continuing interest in the scope and applicability of PS-PdONPs led us to investigate their application for the one-

pot syntheses of dibenzyls and 3-arylpropionic acid derivatives in water.

PS-PdONPs were prepared by thermal decomposition of Pd(OAc)₂ in the presence of polystyrene as described previously.^[4a,8] The composition (PdO) and size (2.5 ± 0.3 nm) of the NPs were measured by XRD and TEM, respectively (Figure S1 and S2 in the Supporting Information). A similar loading of Pd (2.5 mmol g⁻¹) was confirmed by ICP-AES analysis.

As little stilbene was obtained from the Heck reaction of iodobenzene with styrene catalyzed by PS-PdONPs in water,^[8a] we examined the sequential Suzuki coupling of β -bromostyrene with various arylboronic acids and subsequent hydrogenation for the one-pot synthesis of dibenzyls. After the Suzuki coupling of β -bromostyrene with phenylboronic acid was carried out at 80 °C for 6 h in the presence of PS-PdONPs (1.5 mol % of Pd), the atmosphere in the reaction vessel was replaced with hydrogen and the reaction was continued at 50 °C for 20 h. After the reaction, a mixture of stilbene and dibenzyl was obtained in 24 % and 60 % yields, respectively (Table 1, entry 1). The addition of tetra-*n*-butylammonium bromide (TBAB) as a phase-transfer agent was beneficial to the progress of the reaction (Table 1, entry 2).^[9]

To test the reusability of PS-PdONPs, the catalyst was recovered by decantation after each cycle. After washing with water and diethyl ether then drying, the recovered catalyst was used for the next run under the same conditions. The yield of the reaction did not markedly decrease, even after five consecutive runs (Table 1, entries 2–6). The reaction solution was analyzed by ICP-AES to determine the amount of palladium leached during the reaction. Palladium was not detectable (< 0.1 ppm) after any of the runs. After five cycles, we also checked the palladium content in the recovered catalyst and the data showed that quantitative recovery of palladium was achieved.

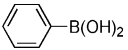
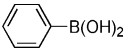
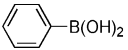
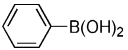
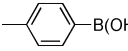
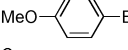
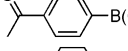
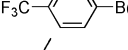
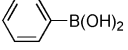
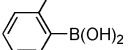
When the reaction was interrupted at 10 % conversion and continued after removal of the catalyst (hot filtration test), the residual activity of the reaction mixture was significant (67 % after 6 h). However, similar sizes of the NPs were observed by TEM after the recycling experiments (3.3 ± 0.6 nm, Figure 1), probably because the NPs were stabilized by phenylboronic acid.^[10] Furthermore, the formation of Pd⁽⁰⁾NPs was confirmed by XRD analysis of the recovered catalyst after the reaction (Figure 2). Electron-rich

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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ajoc.201300042>.

Table 1. One-pot synthesis of dibenzyls in water.

$\text{Ph-CH=CH-Br} + \text{Ar-B(OH)}_2 \xrightarrow[\text{KOH, H}_2\text{O, 80}^\circ\text{C, 6 h}]{\text{PS-PdONPs (1.5 mol\% of Pd), H}_2 \text{ (1 atm.)}} \text{Ph-CH}_2\text{-CH}_2\text{-Ar}$			
Entry	Arylboronic acid	TBAB [equiv.]	Yield [%] ^[a]
1		—	60 ^[b]
2		1	90
3 ^[c]		1	89
4 ^[d]		1	88
5 ^[e]		1	86
6 ^[f]		1	86
7		1	88
8		1	99
9		1	96
10		1	85
11		1	97
12		1	91

[a] Determined by ¹H NMR spectroscopy. [b] Stilbene was obtained in 24 % yield. [c] 2nd use. [d] 3rd use. [e] 4th use. [f] 5th use.

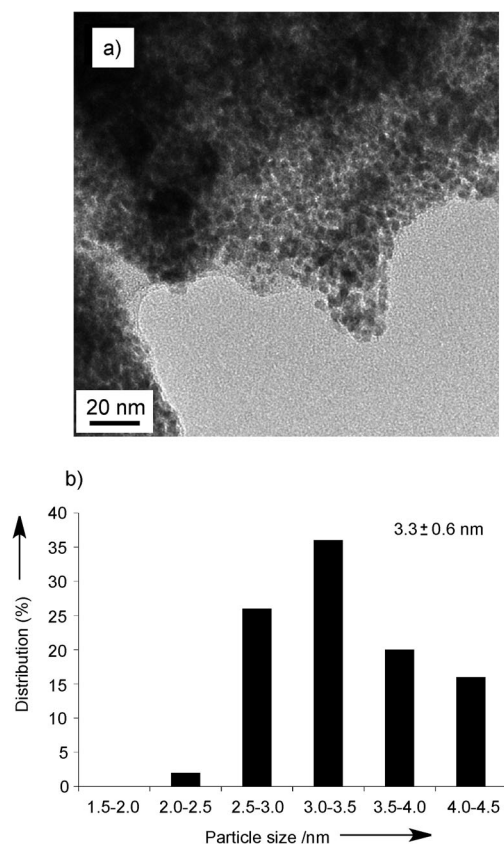


Figure 1. a) TEM micrograph of recovered catalyst (scale bar = 20 nm); b) Size distribution of recovered catalyst.

and electron-deficient arylboronic acids were reactive, and the reactions afforded the corresponding products in high yields (Table 1, entries 7–10). Sterically hindered 2-methylphenylboronic acid and 2,6-dimethylphenylboronic acid also underwent the sequential Suzuki coupling and hydrogenation under the same reaction conditions to give the desired products in near quantitative yields (Table 1, entries 11 and 12).

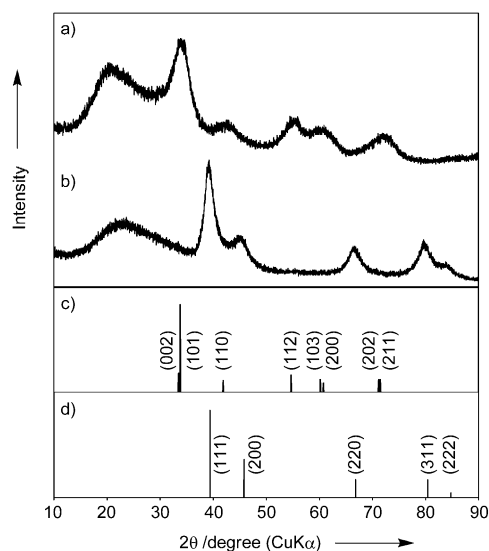


Figure 2. a) XRD patterns of PS-PdONPs; b) XRD patterns of the recovered catalyst; c) Joint Committee on Powder Diffraction Standards (JCPDS) data (#41-1107) for PdO; d) JCPDS data (#46-1043) for Pd.

As PS-PdONPs were shown to function efficiently for the Heck reaction of aryl iodides with acrylic acid in water,^[8a] the one-pot synthesis of 3-arylpropionic acids by a Heck reaction and subsequent hydrogenation was also investigated. As shown in Table 2, electron-rich and electron-deficient aryl iodides were reactive, and the reactions afforded the desired 3-arylpropionic acids in excellent yields. It is noteworthy that a synthetic intermediate for the production of cinacalcet, which acts on the calcium-sensing receptor of the parathyroid, was prepared quantitatively by this method (Table 2, entry 8).^[7c] In contrast to the synthesis of dibenzyls, a significantly lower yield of product was obtained from the hydrogenation in the recycling experiments.^[11] ICP-AES analysis of the aqueous phase revealed barely detectable levels of palladium residue after the Heck-hydrogenation. However, aggregation of the NPs was observed in the TEM image (Figure 3) of the recovered catalyst, probable because of Ostwald ripening.^[12] Indeed, leaching of palladium into the reaction medium occurred in the Heck reaction.^[8a]

The one-pot syntheses of dibenzyls and 3-arylpropionic acid derivatives catalyzed by PS-PdONPs in water was demonstrated. Dibenzyls were prepared by sequential Suzuki coupling of β -bromostyrene with arylboronic acid and subsequent hydrogenation of the alkenyl double bond.

Table 2. One-pot synthesis of 3-arylpropionic acids in water.

$\text{Ar-I} + \text{CH}_2=\text{CHCOOH} \xrightarrow[\text{KOH, H}_2\text{O, 90}^\circ\text{C, 5 h}]{\text{PS-PdONPs (1.5 mol\% of Pd), H}_2 \text{ (1 atm.)}} \text{Ar-CH}_2\text{CH}_2\text{COOH}$			
	0.5 mmol	0.75 mmol	
Entry	Aryl iodide	Product	Yield [%] ^[a]
1			99
2 ^[b]			99
3 ^[c]			58 ^[d]
4 ^[e]			27 ^[f]
5			99
6			99
7			99
8			99
9			99
10			99

[a] Determined by ¹H NMR spectroscopy. [b] 2nd use. [c] 3rd use. [d] Cinnamic acid was obtained in 31 % yield. [e] 4th use. [f] Cinnamic acid was obtained in 56 % yield.

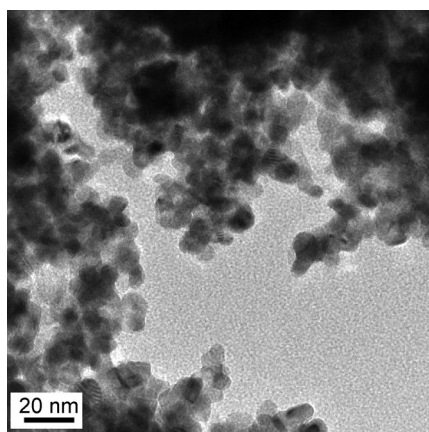


Figure 3. TEM micrograph of recovered catalyst after the 3rd run (scale bar = 20 nm).

The catalyst was recovered by simple decantation and reused for several cycles without significant loss of activity. PS-PdONPs also have high catalytic activity for the synthesis of 3-arylpropionic acids by a Heck reaction and subsequent hydrogenation.

Experimental Section

Typical Procedure for the One-pot Synthesis of Dibenzyls

β -Bromostyrene (91.5 mg, 0.5 mmol), 4-methylphenylboronic acid (102 mg, 0.75 mmol), PS-PdONPs (2.9 mg, 1.5 mol % of Pd), TBAB (161 mg, 0.5 mmol), and aqueous KOH solution (1.5 M, 1 mL) were added to a screw-capped vial with a stirring bar. After stirring at 80 °C for 6 h, the reaction mixture was cooled to room temperature by immediately immersing the vial in water (ca. 20 °C) for about 10 min. Then water (2 mL) degassed under a stream of H₂ was added, and the reaction mixture stirred at 50 °C for a further 20 h under H₂ (1 atm.). After separating the catalyst and the aqueous phase by centrifugation, the aqueous phase was decanted. The recovered catalyst was washed with water (5 \times 3.0 mL) and diethyl ether (5 \times 3.0 mL), then the aqueous and the organic washes were added to the previously separated aqueous phase. The aqueous phase was extracted eight times with diethyl ether. The combined organic extracts were dried with MgSO₄ and concentrated under reduced pressure. The product was analyzed by ¹H NMR spectroscopy. The recovered catalyst was dried in vacuo and reused. The amount of palladium in the aqueous phase determined by ICP-AES analysis was < 0.1 ppm.

Typical Procedure for the One-pot Synthesis of 3-Arylpropionic Acids

Iodobenzene (102 mg, 0.5 mmol), acrylic acid (54.1 mg, 0.75 mmol), PS-PdONPs (2.9 mg, 1.5 mol % of Pd), and aqueous KOH solution (1.5 M, 1 mL) were added to a screw-capped vial with a stirring bar. After stirring at 90 °C for 5 h, the reaction mixture was cooled to room temperature by immediately immersing the vial in water (ca. 20 °C) for about 10 min. Then water (2 mL) degassed under a stream of H₂ was added, and the reaction mixture was stirred at 50 °C for a further 20 h under H₂ (1 atm.). After separating the catalyst and the aqueous phase by centrifugation, the aqueous phase was decanted. Recovered catalyst was washed with H₂O (5 \times 3.0 mL) and diethyl ether (5 \times 3.0 mL), then the aqueous and the organic washes were added to the previously separated aqueous phase. The aqueous phase was extracted eight times with diethyl ether. The combined organic extracts were dried with MgSO₄ and concentrated under reduced pressure. The product was analyzed by ¹H NMR spectroscopy. The recovered catalyst was dried in vacuo and reused. The amount of palladium in the aqueous phase determined by ICP-AES analysis was < 0.1 ppm.

Acknowledgements

We are grateful to the Nanomaterials and Microdevices Research Center (NMRC) of OIT for financial support and instrumentation. This work was supported by the Joint Studies Program (2012) of the Institute of Molecular Science and the Science Research Promotion Fund. We wish to thank Prof. Uozumi, Dr. G. Hamasaka, Dr. T. Shinagawa, and Dr. Y. Kashiwagi for assistance with TEM, ICP-AES, and XRD measurements.

Keywords: Heck reaction • hydrogenation • nanoparticles • palladium • Suzuki reaction

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- [11] The catalytic activity for hydrogenation decreased with an increase in the size of PdNPs. Indeed, when hydrogenation of cinnamic acid was performed with PS-PdNPs (2.5 nm, 4.1 nm, and > 5 nm), 3-phenylpropionic acid was obtained in 91 %, 59 %, and 25 % yields, respectively.
- [12] The NPs aggregated even in the presence of TBAB (Figure S3 in the Supporting Information), which indicates that TBAB is not a stabilizer for the NPs.

Received: March 5, 2013
Published online: April 24, 2013