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Chitosan-supported palladium(0) catalyst for microwave-prompted Suzuki cross-coupling reaction in water

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Abstract—A chitosan-supported palladium (Pd) (0) catalyst was prepared by simple adsorption of palladium(II) ion onto chitosan beads and a subsequent reduction process. To maintain mechanical stability, the chitosan-supported palladium(0) catalyst was cross-linked with either glutaraldehyde or diglycidyl ether polyethylene glycol. The catalysts were utilized for the Suzuki cross-coupling reaction in water. The catalyst, in the presence of a tetrabutylammonium bromide (TBAB) additive, showed excellent catalytic activity in microwave-prompted Suzuki cross-coupling reactions using various aryl halides and boronic acids. In addition, the catalyst was successfully reused up to five times without significant loss of catalytic activity.

Palladium (Pd) is one of the most useful transition metal catalysts for the synthesis of organic compounds, especially carbon–carbon cross-coupling reactions.[1] However, its use is limited in homogeneous reaction systems due to difficulties in separating the palladium catalyst and ligand from the final product and recycling the catalyst. Accordingly, many varieties of solid-supported palladium catalysts have been developed by immobilizing palladium(II) on several supported ligands (phosphine,[2] N-heterocyclic carbene[2,3]) or by immobilizing ligand-free palladium(0) particles[2,4] on various solid supports (Polystyrene (PS),[2] PS-PEG,[2] silica,[2] cellulose,[5a] starch[5b] and so on).

Recently, water and aqueous solvents have received much attention in coupling reactions catalyzed by solid-supported palladium because of their environmental friendliness.[6] Uozumi et al. reported that their amphiphilic resin-supported palladium nanoparticles exhibited catalytic activity in aqueous conditions.[7] A rapid coupling reaction is another important issue for the industrial applications of palladium catalysts. Li et al. recently reported a rapid Suzuki cross-coupling reaction using $Pd(OAc)_2/MeONa$ catalytic system.[8] In the heterogeneous palladium catalyst system, microwave energy can be a useful tool to dramatically enhance organic reactions.[9] Although water has a medium dielectric loss factor[9a] in microwave systems, it may be a useful solvent for microwave-prompted organic synthesis.[10] Indeed, microwave promoted coupling reactions have been reported with palladium catalyst and the use of water as a solvent has been increasingly encouraged.[11]

As a biopolymer, chitosan is considered a suitable water-compatible solid support for the immobilization of metal catalyst because it has a high sorption capacity for metal ions, it can easily be chemically modified and it is highly abundant in nature.[12] Recently, Hardy et al.[13a] reported the use of chitosan as a support to anchor a palladium–pyridyl imine complex to promote the Suzuki and Heck reactions. In addition, Cui et al.[13b] used a chitosan–palladium complex catalyst for the Heck reaction. However, the chitosan–palladium catalysts were used in organic solvent and a relatively long reaction time was required for high product yields with conventional heating in the coupling reaction.

In this Letter, we report the preparation of a bead-type chitosan-supported ligand-free palladium(0) catalyst using a simple reduction process and the application of the prepared catalyst to the Suzuki cross-coupling reaction in water.[14] Also, we applied microwave energy to the heterogeneous system to promote a rapid coupling reaction.

Keywords: Chitosan support; Microwave; Suzuki cross-coupling; Palladium; Water.

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A bead-type chitosan support (M_w 20,000–50,000, 95% deacetylation) was prepared using an air atomization spray nozzle method.[15] The average diameter of prepared wet chitosan beads was 1.3 mm. Chitosan-supported ligand-free palladium catalysts were fabricated by treating the chitosan beads (3 mL) with $Pd(OAc)_2$ (45 mg) in dimethylsulfoxide at 80 °C for 10 min and the resulting mixture was stirred at room temperature for 2 h to obtain the brown chitosan-supported palladium(II) (Fig. 1).[16] After the beads were filtered and washed, palladium(II) in the chitosan beads was converted to palladium(0) by treatment with 10% hydrazine hydrate in methanol.[16] The color of palladium immobilized chitosan beads changed from brown to black (Fig. 2a). The chitosan-supported palladium catalyst **1** was filtered and thoroughly washed with methanol, ethanol, acetone, and water, sequentially.

To enhance the chemical and physical stability in the organic reaction, catalyst **1** was cross-linked using two different cross-linkers, glutaraldehyde and diglycidyl ether polyethylene glycol (M_w 526), to yield catalysts **2** and **3**, respectively.[17] With glutaraldehyde cross-linking, the imine that formed initially was reduced with $NaBH_4$ to prevent hydrolysis of the cross-linker.[17] The final catalysts were washed with water and freeze-dried for 24 h. A TEM image of cross-sectioned catalyst **3** showed that palladium(0) in the chitosan bead formed aggregated nanoparticles (Fig. 2b). Microspot TEM-EDS analysis confirmed the existence of palladium(0) in the chitosan bead (Fig. 2c). Palladium(0) in the chitosan bead was also characterized by X-ray powder diffraction (XRD) spectra (Fig. 3). After a reduction step, specific peaks of palladium(0) ($2\theta = 38°, 46°, 67°, 80°$; Ref. JCPDS 87-0645) appeared as shown in Figure 3b. Both TEM and XRD analyses revealed that the size of palladium particles in the chitosan beads ranged from 3 to 10 nm, which confirmed that palladium existed in an aggregated form. The palladium loading levels of catalysts **1**–**3**, which was measured by inductively coupled plasma-atomic emission spectrometry (ICP-AES), were 1.95, 1.50, and 1.46 mmol/g, respectively. Palladium loading levels were also indirectly analyzed by CHNO elementary analyses, which gave similar values (1.99 mmol/g; Pd 21.19%, 1.67 mmol/g; Pd 17.83% and 1.70 mmol/g; Pd 18.83%, respectively). The palladium loading levels on chitosan beads are rather high compared with previous data for polystyrene beads[3b,c,6d] due to the high metal ion sorption capacity.

The catalytic activity of cross-linked chitosan-supported palladium(0) catalyst **2** was investigated for microwave-prompted Suzuki cross-coupling in water.[18] As a model reaction, the coupling of bromoacetophenone (0.5 mmol) with phenylboronic acid (0.75 mmol) was performed using catalyst **2** (0.5 mol %) in water for 5 min at 150 °C under microwave conditions (100 W). [Caution: Appropriate care should be exercised when water is rapidly heated to 150 °C.] The amount of catalyst and the microwave power were determined considering the effect on deboronation.[11a]

When we first carried out the Suzuki cross-coupling, the reaction did not proceed sufficiently (Table 1, entry 1). We reasoned that the poor solubility of the hydrophobic substrate (aryl halide) in water might cause reduced reaction performance. We therefore added tetrabutylammonium bromide (TBAB), which can assist with Suzuki cross-coupling in water,[11] to the reaction medium in order to increase solubility. As shown in Table 1 (entry 2), the coupling yield improved dramatically from 48% to 95% when TBAB was added. Some reports have indicated that the ammonium salt facilitated solvation of substrates in water and enhanced the rate of coupling by activating boronic acid toward the formation of a boronate complex $[ArB(OH)_3]^-[R_4N]^+$.[11a,b] When we carried out other coupling reactions with TBAB, we obtained high product yields (above 90%), regardless of the base used. To confirm the effectiveness of microwave energy, the same coupling reaction (Table 1, entry 2) was tested in a closed system under conventional heating conditions (150 °C). In the absence of microwave energy, it took 1 h to obtain a similar yield (93%). This reaction time was relatively long compared with that required under microwave conditions (5 min). This indicates that microwave irradiation is a very effective tool in Suzuki coupling using the chitosan-supported palladium catalyst.

We also examined the feasibility of repetitive use of chitosan-supported palladium catalyst under the same microwave conditions. The catalyst was recovered by

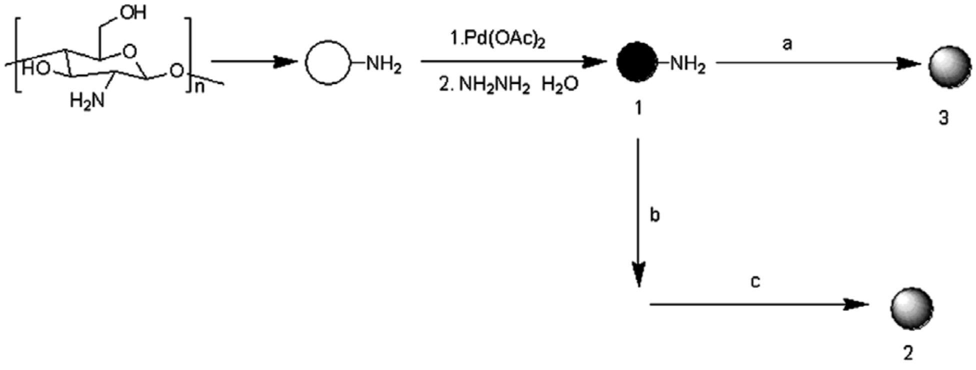


Figure 1. Preparation of chitosan-supported palladium(0) catalyst. Reagents and conditions: (a) Diglycidyl ether polyethylene glycol, NaOH(aq), 50 °C, 12 h; (b) Glutaraldehyde, pH 5.5, 25 °C, 2 h; (c) $NaBH_4$, pH 9, 25 °C, 1 h.

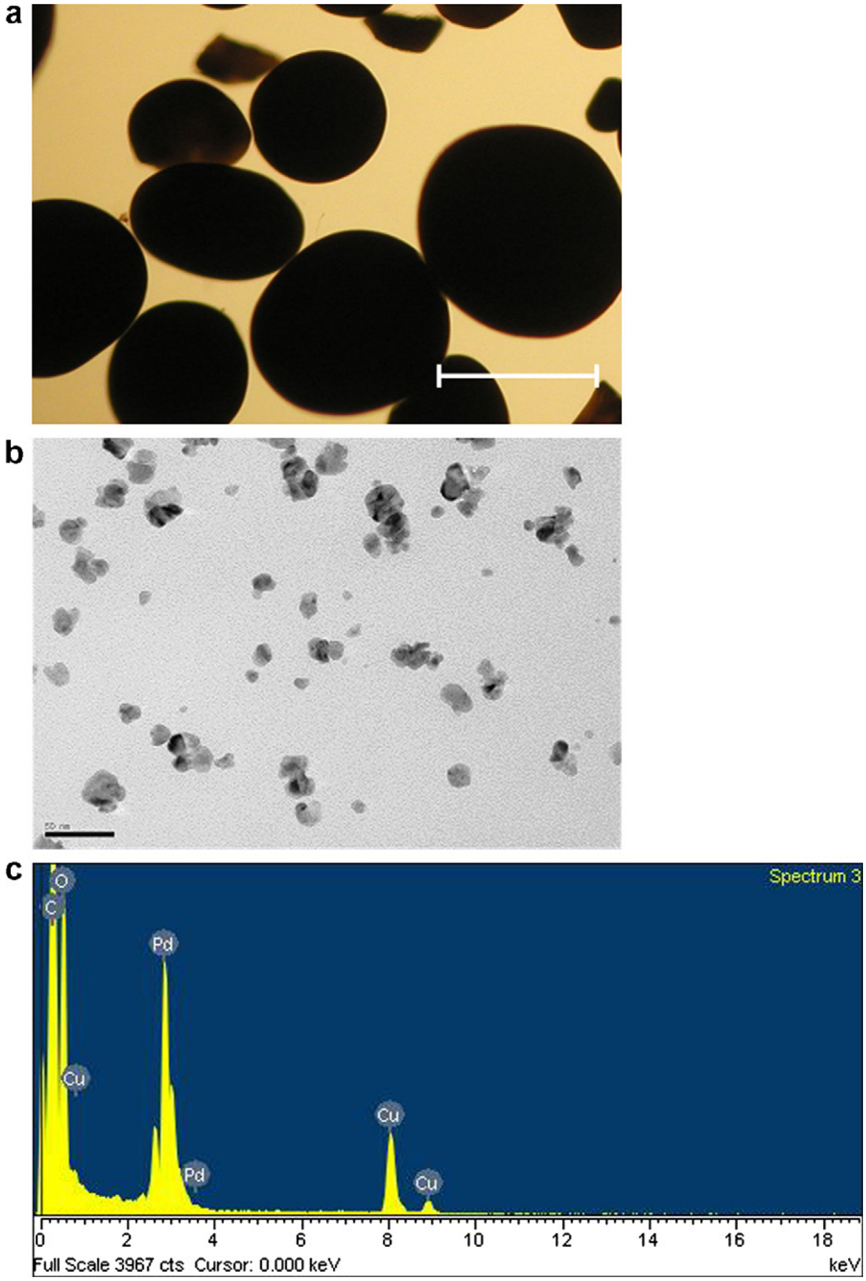


Figure 2. (a) Optical microscope image of catalyst **3** in water (scale bar 1 mm); (b) TEM image of cross-sectional catalyst **3** (scale bar 50 nm); (c) TEM-EDS of cross-sectional catalyst **3**.

filtration and washed with H_2O and ethanol. Catalysts **2** and **3** (0.5 mol % Pd) were reused five times in the reaction of 4-iodoacetophenone and phenylboronic acid. However, catalyst **2** was subsequently excluded because it exhibited unstable mechanical properties during the reuse test. Catalyst **3** continued to exhibit consistent catalytic activity without significant loss in product yield (Table 2). This is probably due to negligible palladium loss during reuse. The total amount of palladium leaching after the fifth cycle was 3.3% after ICP-AES analysis of the left over solution.

After optimizing the reaction conditions, we performed the Suzuki cross-coupling of various aryl halides with aryl boronic acid in water under microwave conditions. Eleven different substrates were applied to Suzuki cross-coupling in the presence of catalyst **3** (0.5 mol %) and potassium phosphate as a base.[18] Reaction times varied from 5 min to 30 min, according to the reactivities of the aryl halides.

As shown in Table 3, we obtained satisfactory yields of biaryl products with most substituted aryl halides and boronic acids. The aryl iodides produced good yields irrespective of their substituents with the exception of 4-iodotoluene (Table 3, entries 1–6). Some aryl bromides with different substituents also gave good yields in the coupling reaction (Table 3, entries 7–9). In the case of aryl bromides, product yields were improved compared with our previous studies in water despite the short

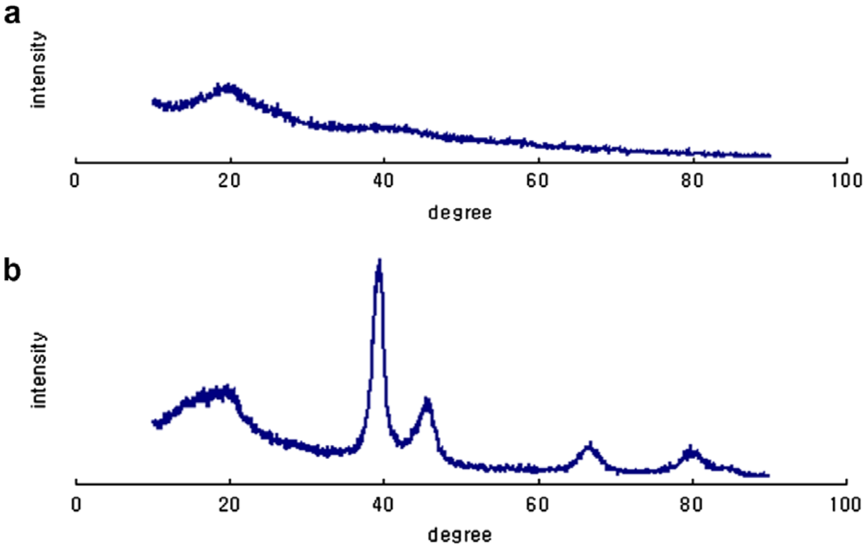
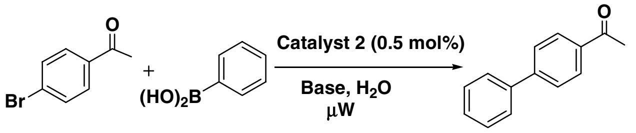


Figure 3. X-ray powder diffraction spectra (a) chitosan-supported $Pd(OAc)_2$, (b) catalyst **2**.

Table 1. Suzuki cross-coupling of 4-bromoacetophenone and phenylboronic acid with catatyst **2**[a]



Entry	Base	TBAB (equiv)	Time (min)	Temperature (°C)	Yield[b] (%)
1	K_3PO_4	No	5	150	48
2	K_3PO_4	1	5	150	95
3	Na_2CO_3	1	5	150	90
4	K_2CO_3	1	5	150	95
5	Cs_2CO_3	1	5	150	93
6	NaOH	1	5	150	95

[a] All of the reactions were carried out with the mole ratio 4-bromoacetophenone/phenylboronic acid/base/Pd(0) = 0.5:0.75:1.5:0.0025. Microwave condition; 100 W, 150 °C, 5 min, 4 mL of H_2O.

[b] Isolation yields were determined from the mass of biaryl products after flash column chromatography.

Table 2. Reusability test of catalyst **3** for Suzuki cross-coupling of 4-iodoaceotophenone with $Ph–B(OH)_2$[a]

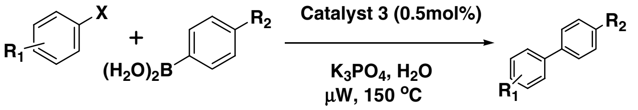
The number of recycle	1st	2nd	3rd	4th	5th
Isolation yield[b] (%)	93	94	93	94	94

[a] All of the reactions were carried out with the mole ratio 4-iodoacetophenone/TBAB/phenylboronic acid/K_3PO_4/Pd(0) = 0.5:0.5:0.75:1.5:0.0025. Microwave condition; 100 W, 150 °C, 5 min, 4 mL of H_2O.

[b] Isolation yields were determined from the mass of biaryl products after flash column chromatograph.

reaction time.[6d] However, catalyst **3** gave a poor yield with aryl chloride under the same reaction conditions (Table 3, entry 10). The problem was somewhat improved by increasing the reaction time from 15 min to 30 min (14% → 40%, Table 3, entries 10 and 11).

Table 3. Suzuki cross-coupling of various aryl halide and aryl boronic acid with the catalyst **3** in water[a]



Entry	R_1	X	R_2	Time (min)	Yield[b] (%)
1	H	I	H	15	87
2	*p*-CH_3	I	H	15	70
3	*p*-OCH_3	I	H	10	98
4	*o*-OCH_3	I	H	15	95
5	*p*-$COCH_3$	I	H	5	95
6	*p*-NO_2	I	H	10	94
7	*p*-$COCH_3$	Br	H	5	98
8	*p*-OCH_3	Br	H	15	87
9	*p*-CHO	Br	H	15	95
10	*p*-$COCH_3$	Cl	H	15	14
11	*p*-$COCH_3$	Cl	H	30	40
12	*p*-OCH_3	I	*p*-$COCH_3$	10	98

[a] All of the reactions were carried out with the mole ratio aryl halide/TBAB/phenylboronic acid/K_3PO_4/Pd(0) = 0.5:0.5:0.75:1.5:0.0025. Microwave condition; 100 W, 150 °C, 4 mL of H_2O.

[b] Isolation yields were determined from the mass of biaryl products after flash column chromatograph.

Reaction with another arylboronic acid (4-acetylphenylboronic acid) also proceeded with high yield within 5 min (Table 3, entry 12). Therefore, chitosan-supported palladium catalyst **3** coupled with microwave technology was very effective for the Suzuki cross-coupling reaction in water.

In summary, chitosan-supported palladium(0) catalyst was prepared by the adsorption of $Pd(OAc)_2$ on chitosan beads followed by simple reduction and cross-linking. The use of chitosan beads allowed high loading of palladium because of the high metal ion sorption capacity of chitosan. In Suzuki reactions using chitosan-supported palladium catalysts in water, the addition of TBAB significantly enhanced the product yields. The chitosan-supported palladium(0) catalyst, used in combination with microwave technology, exhibited a rapid reaction rate, excellent catalytic activity and reusability for Suzuki cross-coupling reactions in water.

Acknowledgements

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Supplementary data

The supplementary data include analytical data for the chitosan-supported palladium catalyst and biphenyl compound for Suzuki cross-coupling. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.093.

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15. Chitosan beads were prepared by an air atomization spray nozzle method (Model MS 8A, Fuso Seiki Co., Ltd, Japan). The chitosan solution (4 wt % in 2% (v/v) acetic acid, M_w 20,000–50,000) was sprayed into 2 L of 1 N sodium hydroxide aqueous solution containing ethanol (500 mL). The beads that resulted were cured in the NaOH solution for 12 h and then washed up to ten times with distilled water.
16. In a 20 mL vial, 3 mL of the chitosan beads (5.5 mmol of NH_2/g, dried weight 110 mg) was put and then 45 mg of palladium acetate and 12 mL of dimethylsufoxide (DMSO) were added. The mixture was heated to 80 °C for 10 min and gently stirred at room temperature for 2 h. The beads were filtered and washed with DMSO (5 × 10 mL), ethanol (5 × 10 mL), acetone (5 × 10 mL), water (5 × 10 mL) and methanol (5 × 10 mL). The beads were then treated with 10% hydrazine hydrate in methanol (10 mL) for 2 h yielding the chitosan-supported palladium catalyst **1** (1.95 mmol of Pd/g).
17. In the case of glutaraldehyde cross-linking, catalyst **1** was reacted with 264 μL of 25% glutaraldehyde aqueous solution (0.7 mmol) in 12 mL of citric acid buffer (100 mM, pH 5.5). After shaking for 2 h at 25 °C, the catalyst was washed with water. Catalyst **2** (1.50 mmol of Pd/g) was prepared by treatment with 12 mL of 0.5% $NaBH_4$ (60 mg) in boric acid buffer (100 mM, pH 9.0) for 1 h at 25 °C. Catalyst **1** was also cross-linked with 926 μL of diglycidyl ether PEG (2.1 mmol) in 12 mL of 0.1% NaOH solution. After shaking for 12 h at 50 °C, catalyst **3** (1.46 mmol of Pd/g) was obtained. Finally, catalysts **2** and **3** were washed with excess water and freeze-dried over 24 h.
18. The chitosan-supported palladium catalyst (0.5 mol %), phenylboronic acid (91 mg, 0.75 mmol), K_3PO_4 (318 mg, 1.5 mmol), tetrabutylammonium bromide (TBAB, 161 mg, 0.5 mmol) and aryl halides (0.5 mmol) were added to a screw-capped reactor (10 mL) containing 4 mL of water. The reaction mixture was pre-stirred for 30 s and then microwave-irradiated (2.0 microwave synthesizer, Biotage Co.) for 5–30 min at 100 W (150 °C). After allowing to cool to room temperature, the catalyst was filtered and washed with chloroform and water. The product was extracted with chloroform and purified by flash column chromatography (*n*-hexane:chloroform = 1:1). Isolation yields were determined from the mass of the biaryl products. All isolated products were confirmed by ^{1}H NMR and GC–Mass and were demonstrated to be more than 99% pure by GC.