Pd-Catalyzed C−C Cross-Coupling Reactions within a Thermoresponsive and pH-Responsive and Chelating Polymeric Hydrogel

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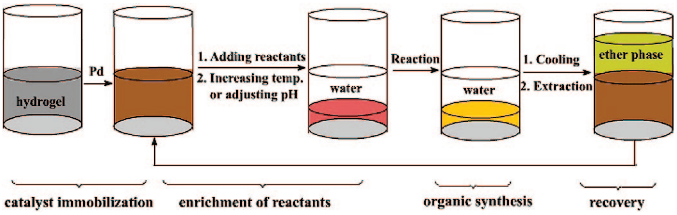

A porous, thermoresponsive and pH-responsive, and chelating hydrogel of poly(*N*-isopropylacrylamide)-*co*-poly[2-methacrylic acid 3-(bis-carboxymethylamino)-2-hydroxypropyl ester] (PNIPAM-*co*-PMACHE) is proposed as both a reaction medium and the Pd catalyst support for organic synthesis. Organic synthesis within the PNIPAM-*co*-PMACHE hydrogel has three merits. First, organic reactions such as Suzuki and Heck reactions within the hydrogel can be accelerated due to the enriched Pd catalyst and reactants within the hydrogel by the reversible deswelling/swelling. Second, organic synthesis within the PNIPAM-*co*-PMACHE hydrogel, which holds about ∼300 times of water and is similar to the environmentally benign reaction medium of water, can be performed efficiently without surfactant or cosolvent being added. Third, the PNIPAM-*co*-PMACHE hydrogel itself and the therein-immobilized Pd catalyst can be easily recycled since the hydrogel/Pd composite can reversibly swell/deswell.

1. Introduction

Organic synthesis in water has drawn much attention because water is an eco-friendly, nontoxic, and economic solvent.[1] Up to date, although a variety of media such as ionic liquids,[2] fluorous solvents,[3] supercritical fluids,[4] and poly(ethylene glycol)[5] have been promoted to replace water, water represents one of the most economically and environmentally viable options. However, a good many of these organic reactions proceed sluggishly in pure water, probably because most organic reagents are not completely dissolved in water.[6] Thus, when organic synthesis is performed in water, surfactants such as tetrabutylammonium bromide (TBAB) or polar cosolvents such as *N*,*N*-dimethylformamide (DMF) are usually used to improve solvation of the organic substrates.[7] Therefore, great effort should be made to perform organic synthesis in a suitable green medium similar to water.

The Suzuki reaction,[8] the Pd-catalyzed cross-coupling of arylboronic acids with aryl halides, is recognized as the most promising and versatile method for construction of biaryls. As to the Heck reaction, it is a well-established method for the

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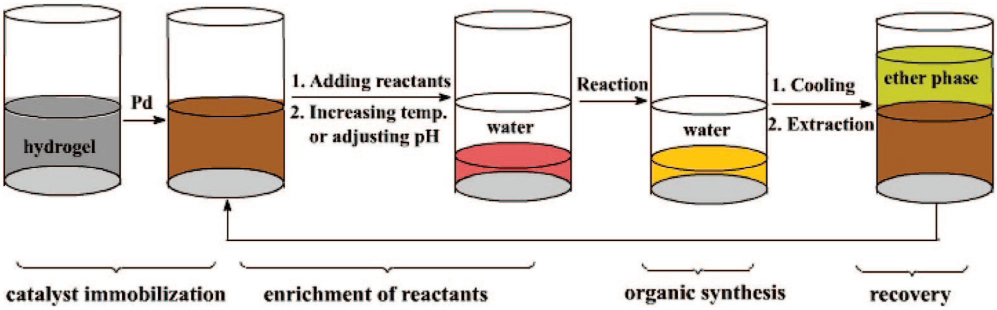
SCHEME 1. Schematic Organic Synthesis within the PNIPAM-*co*-PMACHE Hydrogel



coupling of aryl halides with olefins.[9] Usually, Suzuki and Heck reactions are performed in organic solvent. However, when a hydrophilic ligand is used or the Pd catalyst is immobilized on a hydrophilic or amphiphilic support, they can be performed in water or aqueous solution.[10] For examples, Weberskirch et al. immobilized Pd catalyst in amphiphilic block copolymer micelles and found the Heck reaction using this micelle-Pd catalyst could be performed efficiently in water at 90 °C.[11] Uozumi et al. found the Pd catalyst immobilized on the amphiphilic resin of polystyrene-poly(ethylene glycol) was efficient for the Heck reaction performed in water.[12]

Hydrogels are three-dimensional networks of cross-linked polymers, which can hold up to 1000 times of water.[13] Of all the hydrogels, the poly(*N*-isopropylacrylamide) (PNIPAM) hydrogel is a typical one, which is thermoresponsive and undergoes a large volume change at the volume-phase-transition temperature (VPTT) of ~32 °C.[14] When heated above VPTT, PNIPAM hydrogel exhibits a hydrophilic/hydrophobic transition in aqueous medium; water is expelled from the hydrogel matrix; the PNIPAM hydrogel shrinks or deswells and becomes partly hydrophobic. This shrunk gel can provide a hydrophobic environment for hydrophobic guest molecules. Hydrogels have been utilized in many fields such as controlled drug release, molecular separation, tissue engineering, enzyme immobilization, and chemical valves.[15] Besides, hydrogels have also been used as a scaffold to in situ synthesize inorganic nanoparticles within the three-dimensional hydrogel networks.[16] However, organic synthesis within hydrogel is rarely studied, although a few samples within gel matrix have been reported recently.[17]

Herein, a thermoresponsive and pH-responsive, chelating, and superabsorbent hydrogel of poly(*N*-isopropylacrylamide)-*co*-poly[2-methacrylic acid 3-(bis-carboxymethylamino)-2-hydroxypropyl ester] (PNIPAM-*co*-PMACHE) is synthesized and Suzuki and Heck reactions within the hydrogel are explored. The PNIPAM-*co*-PMACHE hydrogel contains a thermoresponsive segment of PNIPAM and a pH-responsive segment of PMACHE. Besides, the PMACHE segment contains a pendent ligand of iminodiacetic acid (IDA). It is found that the Pd catalyst and either hydrophilic or hydrophobic reactants can be immobilized or encapsulated within the PNIPAM-*co*-PMACHE hydrogel matrix, and Suzuki and Heck coupling reactions can be efficiently performed within the hydrogel without cosolvent or surfactant being added. The results suggest that organic synthesis within the PNIPAM-*co*-PMACHE hydrogel has three advantages. First, the reactants and Pd catalyst can be highly enriched within the PNIPAM-*co*-PMACHE hydrogel by reversible deswelling, which therefore affords efficient organic synthesis at condensed concentration. Second, no additional surfactant or cosolvent is needed, since the reactants are encapsulated within the three-dimensional hydrogel matrix (the present hydrogel seemly can be regarded as a green medium, since it is composed of about 99.7 wt % water and 0.3 wt % polymer). Last, both the immobilized Pd catalyst and the hydrogel itself can be easily recovered and reused, because the PNIPAM-*co*-PMACHE hydrogel can reversibly swell/deswell.

2. Results and Discussion

The main content of the present study is shown in Scheme 1. First, PNIPAM-*co*-PMACHE hydrogel is synthesized. This hydrogel is designed to be porous, thus the hydrogel has the ability to encapsulate reactants. Second, the Pd catalyst is immobilized and the reactants are encapsulated within the hydrogel matrix. Third, the hydrogel holding the Pd catalyst and reactants deswells to enrich the reactants and Pd catalyst within the gel by increasing the temperature or adjusting pH, and then organic synthesis occurs with concentrated reactants and Pd catalyst. Last, when organic synthesis is completed, temperature decreases and pH is adjusted; ether is added to extract the synthesized product; and the hydrogel containing Pd catalyst reversibly swells and is reused in the next run. In the subsequent study, the synthesis and characterization of the PNIPAM-*co*-PMACHE hydrogel, the immobilization of Pd(II) or Pd(0) catalyst, the encapsulation and enrichment of the

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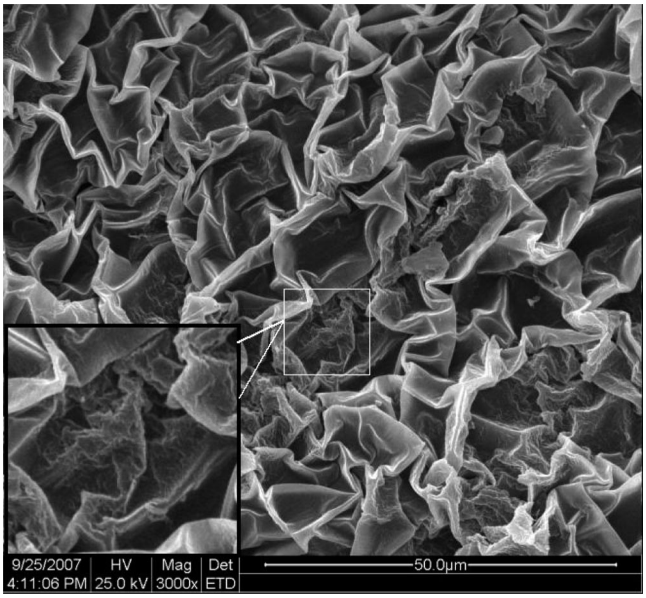

FIGURE 1. The SEM image of the PNIPAM-*co*-PMACHE hydrogel.

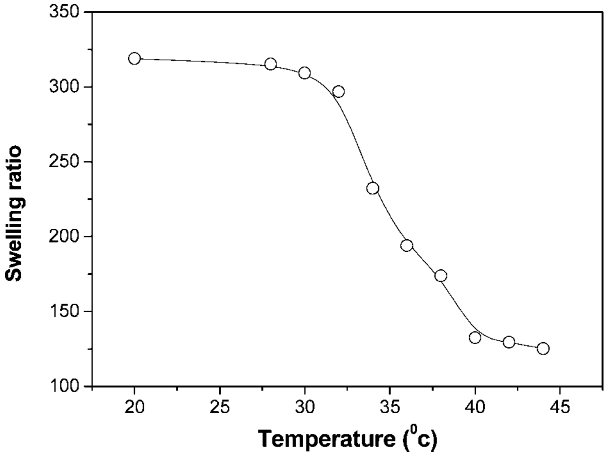

FIGURE 2. Temperature dependence of the swelling ratio of the PNIPAM-*co*-PMACHE hydrogel in neutral water, where the swelling time at a given temperature is 24 h.

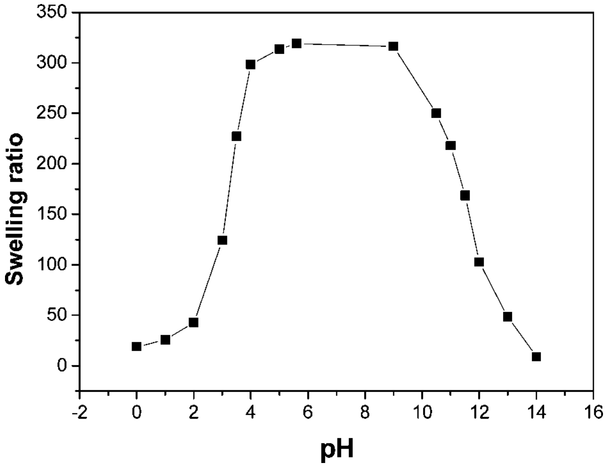

FIGURE 3. pH-dependence of the swelling ratio of the PNIPAM-*co*-PMACHE hydrogel at room temperature, where the swelling time is 1 h.

reactants, and the Suzuki and Heck reactions within the hydrogel are discussed.

2.1. Synthesis and Characterization of the PNIPAM-*co*-PMACHE Hydrogel. Usually, PNIPAM-based hydrogel is synthesized by free-radical polymerization in organic solvents or water.[14] In the present study, the polymerization of the two hydrophilic monomers of *N*-isopropylacrylamide (NIPAM) and 2-methacrylic acid 3-(bis-carboxymethylamino)-2-hydroxypropyl ester (MACHE) was performed in the solvent mixture of water and THF with the existence of the cross-linker of *N*,*N*′-methylenebisacrylamide (BIS), the redox initiator of $K_2S_2O_8$, and the accelerator of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED). As discussed elsewhere,[18] synthesis of PNIPAM-based hydrogel in the mixture of a polar organic solvent and water favors formation of a porous structure in the hydrogel matrix. Herein, it is found that porous hydrogel as shown in Figure 1 is synthesized. This porous structure in hydrogel provides the potential of encapsulation of reactants within the hydrogel matrix, which will be discussed subsequently.

The PNIPAM-*co*-PMACHE hydrogel has a high swelling ratio of ∼300 in double-distilled water (pH ∼6) at room temperature. This means that the hydrogel is composed of 99.7 wt % water and 0.3 wt % polymer at room temperature. The super absorbability suggests that the PNIPAM-*co*-PMACHE hydrogel has a potential of being used as an environmentally benign reaction medium similar to water. Besides, the PNIPAM-*co*-PMACHE hydrogel is thermoresponsive and pH-responsive since it contains a thermoresponsive segment of PNIPAM and a zwitterionic, pH-responsive segment of PMACHE. When temperature increases above 32 °C, it is optically observed that the hydrogel deswells and becomes opaque, and the swelling ratio decreases from ∼300 at 32 °C to a constant of ∼125 at 40 °C as shown in Figure 2. These results suggest that phase transition occurs and the PNIPAM-*co*-PMACHE hydrogel has a VPTT at 32 °C similar to that of the homopolymer of PNIPAM.[19] The PNIPAM-*co*-PMACHE hydrogel is also pH-responsive as shown in Figure 3. The swelling ratio almost remains constant at ∼300 in the pH range of 4−10, suggesting that the PNIPAM-*co*-PMACHE hydrogel is highly swollen at this pH range. When the pH value is below 4 or above 10, water is expulsed off the hydrogel, the hydrogel collapses, and the swelling ratio gradually decreases until it reaches a minimum of ∼10. It is known that addition of inorganic compounds such as inorganic salt, acid, or base can decrease the VPTT of PNIPAM.[20] Thus, the deswelling of the hydrogel at pH below 4 or above 10 is partly ascribed to the pH-responsive segment of PMACHE, partly ascribed to the phase transition of the PNIPAM segment induced by the inorganic compound of NaOH and HCl.

2.2. Immobilization of Pd(II) or Pd(0) Catalyst within the PNIPAM-*co*-PMACHE Hydrogel. To achieve organic synthesis within hydrogel, two factors including immobilization of the Pd catalyst and encapsulation of organic reactants within the three-dimensional hydrogel networks should be concerned and they are discussed in the subsequent sections.

Because the ligand of IDA can coordinate with various transition metal ions such as Cu(II), Ni(II), Pd(II), etc.,[21] Pd(II)

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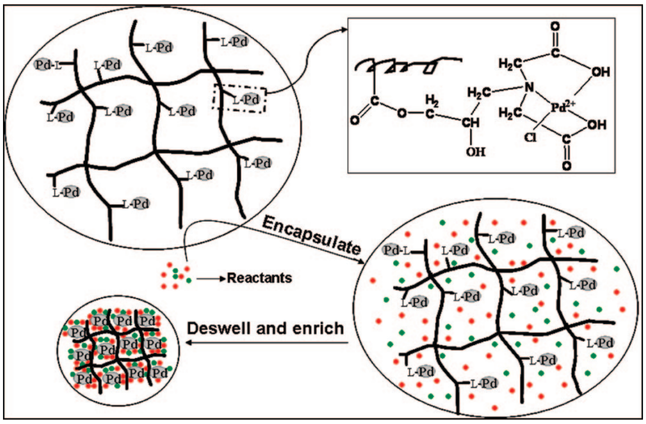
SCHEME 2. Schematic Structure of the PNIPAM-*co*-PMACHE Hydrogel/Pd(II) Composite and Encapsulation and Enrichment of the Pd Catalyst and Reactants within the Hydrogel



can be easily immobilized in the PNIPAM-*co*-PMACHE hydrogel to form hydrogel/Pd(II) composite as shown in Scheme 2. In fact, when a suitable amount of the PNIPAM-*co*-PMACHE hydrogel is placed in $PdCl_2$ aqueous solution for about 5 min, the hydrogel becomes yellow, indicating immobilization of Pd(II) catalyst in the hydrogel matrix (Figure S2, Supporting Information).

Synthesis of inorganic nanoparticles with hydrogel as the scaffold has been extensively reported recently.[16] The introduction of the Pd(0) catalyst into the PNIPAM-*co*-PMACHE hydrogel is easily achieved by reducing the hydrogel/Pd(II) composite, which was just discussed above, with $NaBH_4$ aqueous solution. The average size of the Pd nanoparticles in situ synthesized within the hydrogel matrix observed by TEM is ~3 nm (Figure S3, Supporting Information).

2.3. Encapsulation and Enrichment of Reactants within the PNIPAM-*co*-PMACHE Hydrogel. To fulfill organic synthesis within the PNIPAM-*co*-PMACHE hydrogel, the substrates should be first encapsulated. For hydrophilic molecules such as phenol, benzoic acid, and their derivatives, the PNIPAM-based hydrogel has the ability to entrap them due to strong hydrogen bonding between the PNIPAM segment and the hydrophilic molecules.[22] In fact, when the hydrophilic substrates such as phenylboronic acid, 4-bromophenol, and 4-bromobenzoic acid are mixed with the hydrogel at room temperature, the transparent hydrogel becomes opaque in several minutes, indicating that these substrates are encapsulated within the hydrogel (Figure S4, Supporting Information). Besides the strong hydrogen bonding between the PNIPAM segment and the hydrophilic substrates, the porous structure of the hydrogel also provides fast encapsulation of these hydrophilic substrates within the hydrogel matrix. Furthermore, the PNIPAM-*co*-PMACHE hydrogel is thermoresponsive and pH-responsive, and therefore the hydrophilic substrates encapsulated within the hydrogel can be enriched due to the hydrogel deswelling either by increasing temperature above VPTT (Figure S4, Supporting Information) or adding a suitable base such as K_2CO_3 or Et_3N as shown in Scheme 2.

It is known that amphiphilic hydrogels can swell both in organic solvents and in water. When swelling in water, amphiphilic hydrogels can adsorb a significant amount of hydrophobic substances.[23] The present PNIPAM-*co*-PMACHE hydrogel contains a thermoresponsive segment of PNIPAM and a hydrophilic segment of PMACHE and it becomes amphiphilic above VPTT of the PNIPAM segment. Therefore, the PNIPAM-*co*-PMACHE hydrogel has the potential of adsorption or encapsulation of hydrophobic substrates. In fact, when temperature increases above VPTT and a base such as K_2CO_3 or Et_3N is added, the PNIPAM-*co*-PMACHE hydrogel undergoes a transition from a hydrophilic structure to a partly hydrophobic one; water is expelled from the gel matrix and the hydrophobic substrates are encapsulated and enriched within the gel by deswelling. For example, the hydrophobic reactant of bromobenzene (4.0 mmol, 0.63 g) is almost absolutely encapsulated within the hydrogel (10 g) (Figure S5, Supporting Information). At 90 °C, the hydrogel containing the encapsulated bromobenzene deswells, and the deswelled gel phase (~1 g) contains 60 wt % organic reactants (~0.6 g), 40 wt % water (~0.4 g), and 0.3 wt % polymer. At 40 °C, the gel phase contains about 30 wt % organic substrates, 70 wt % water, and 0.3 wt % polymer. Clearly, the water content in the deswelled gel phase at lower temperature is a litter higher than those at high temperature. Different from the hydrogen bonding between the PNIPAM segment and the hydrophilic substrates, the driven force for encapsulation of hydrophobic substrates within the hydrogel is mainly ascribed to the hydrophobic−hydrophobic interaction between the substrates and the hydrogel.

2.4. Suzuki Reaction within the PNIPAM-*co*-PMACHE Hydrogel with Pd(II) Catalyst. As discussed above, the immobilization of Pd catalyst and encapsulation of the reactants afford the potential for organic synthesis within the hydrogel. In preliminary organic synthesis, the Suzuki reaction of 4-bromoacetophenone with phenylboronic acid within the PNIPAM-*co*-PMACHE hydrogel is studied. To explore the hydrogel effect, the Suzuki reaction of 4-bromoacetophenone within different amounts of hydrogel is studied. As shown in Figure 4, the hydrogel plays an important role in the Suzuki reaction of 4-bromoacetophenone. Without the hydrogel, the Suzuki reaction employing 0.050 mol % of IDA-Pd(II) catalyst just affords 47% yield of 4-acetylbiphenyl in 2.5 h at 40 °C. In the presence of the PNIPAM-*co*-PMACHE hydrogel, the yields dramatically increase. For example, when the ratio of hydrogel to 4-bromoacetophenone equals 0.50 g/mmol, 92% yield is achieved. When the ratio further increases above 1.0 g/mmol, more than 98% yield is achieved. In the following study, the ratio of the hydrogel to aryl halide is set at 2.5 g/mmol if not specifically pointed out.

To further evaluate the hydrogel effect, the Suzuki reaction of 4-bromoacetophenone within the PNIPAM-*co*-PMACHE hydrogel is further compared with that in water. As shown in Figure 5, when the Suzuki reaction employing the IDA-Pd(II) catalyst is performed in water at 40 °C, the yield of 4-acetylbiphenyl increases to 40% in 1 h and further slowly increases to 48% in 3 h. Compared with the Suzuki reaction performed in water, the Suzuki reaction performed within the hydrogel runs more efficiently, wherein the yield of 4-acetylbiphenyl increases almost linearly with time until it reaches 98% in 2.5 h. We think the encapsulation and enrichment of the hydrophobic

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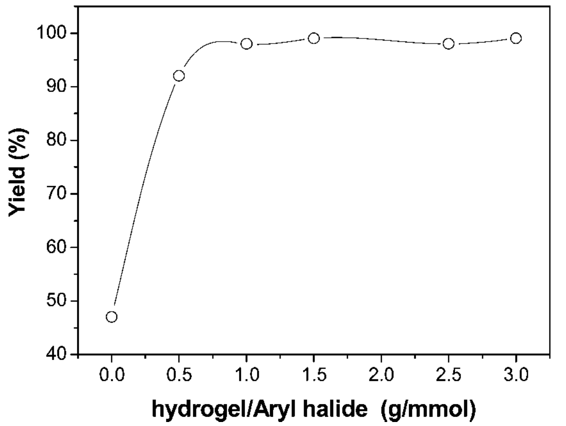

FIGURE 4. The hydrogel effect on the Suzuki reaction of 4-bromoacetophenone with phenylboronic acid. Reaction conditions: 4-bromoacetophenone (1.0 mmol) and phenylboronic acid (1.5 mmol, 1.5 equiv), K_2CO_3 (3.0 mmol, 3 equiv), Pd catalyst (0.50 μmol, 0.050 mol % of Pd(II) catalyst within the PNIPAM-*co*-PMACHE hydrogel or 0.050 mol % of IDA-Pd(II) catalyst in water), total weight of the hydrogel and water being 3.0 g, 2.5 h, and 40 °C.

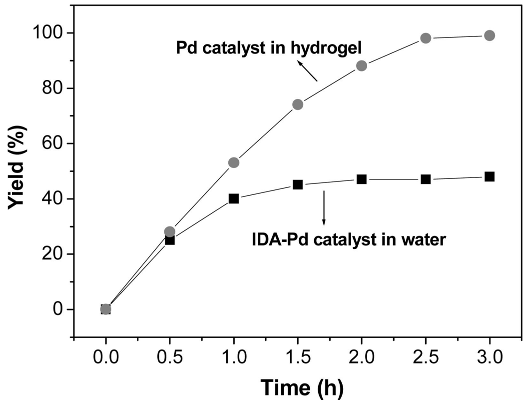

FIGURE 5. The kinetics of Suzuki reaction of 4-bromoacetophenone with benzenboronic acid within the PNIPAM-*co*-PMACHE hydrogel (●) and in water (□). Reaction conditions: 1.0 mmol of 4-bromoacetophenone, 1.5 mmol of benzenboronic acid, 3.0 mmol of K_2CO_3, 2.5 g of hydrogel containing 0.050 mol % of Pd(II) catalyst or 2.5 mL of water containing 0.050 mol % of IDA-Pd(II) catalyst, 40 °C. The molar ratio of the IDA ligand to Pd in the IDA-Pd(II) catalyst is the same as those in the hydrogel/Pd(II) composite.

reactants and the Pd catalyst within the hydrogel increases the accessibility of the active catalytic site and therefore accelerates the reaction within the hydrogel. When the Suzuki reaction is performed in water at a higher temperature of 90 °C, it is found that the IDA-Pd(II) catalyst is not stable and formation of black Pd can be optically observed just after the Suzuki reaction begins in 1 h,[24] whereas the Pd catalyst immobilized in the hydrogel is stable and the Suzuki reaction runs smoothly at 90 °C as discussed below. These results suggest that the hydrolgel not only increases the stability of the immobilized Pd catalyst at high temperature but also accelerates the reaction.

A wide range of Suzuki reactions of iodinated and brominated aromatic compounds within the PNIPAM-*co*-PMACHE hydrogel are further studied and the results are summarized in Table 1. At a high temperature of 90 °C, the reactants and Pd catalyst are encapsulated and highly enriched within the gel; the Suzuki reactions of the hydrophobic aryl bromides and aryl iodides are performed efficiently and 95−99% yields of biaryls are achieved employing a low content of 0.050 mol % of Pd catalyst (Table 1, entries 1−5). At a much lower temperature of 40 °C, the reactants are also relatively enriched within the gel and the Suzuki reactions within the hydrogel afford reasonable yields (Table 1, entries 1−5). For the hydrophilic substrates such as 4-bromophenol, 4-bromobenzoic acid, 4-iodophenol, and 4-iodobenzoic acid, they can be encapsulated and enriched within the gel by hydrogen bonding whether at room temperature below VPTT or above VPTT of the hydrogel. Therefore, the Suzuki reactions of these hydrophilic aryl halides within the hydrogel run efficiently and 93−99% yields are achieved even at room temperature employing a low content of 0.050 mol % of Pd catalyst (Table 1, entries 6−9). Furthermore, for the electron-deficient and therefore active aryl halide of 4-iodobenzoic acid, 0.0010 mol % of Pd catalyst affords a turnover frequency (TOF) of 4.3×10^4 h^{-1} and 99% yield in 4 h (Table 1, entry 6). Considering that the hydrogel is composed of 99.7 wt % water and 0.3 wt % polymer, it can be regarded as a green medium similar to water. Therefore, we think, the present TOF value for the Suzuki reaction within the hydrogel compares favorably with those performed in the sole solvent of water.[25]

2.5. Heck Reaction within the PNIPAM-*co*-PMACHE Hydrogel with Pd(II) Catalyst. Heck reactions of aryl halides with acrylic acid within the PNIPAM-*co*-PMACHE hydrogel are also studied. As discussed elsewhere, teh Heck reaction is generally performed in organic solvent or aqueous solution at a relatively high temperature employing a high content of Pd catalyst.[26] Herein, all Heck reactions within the PNIPAM-*co*-PMACHE hydrogel are performed at 100 °C employing 0.20 mol % of Pd catalyst. As shown in Table 2, Heck reactions of aryl iodides are efficiently performed within the gel and 91−99% yields are achieved in 12 h (Table 2, entries 1−3). For aryl bromides, Heck reactions also run efficiently and high yields are achieved when reaction time increases to 24 h (Table 2, entries 4 and 5).

2.6. Suzuki Reaction within the PNIPAM-*co*-PMACHE Hydrogel with Pd(0) Catalyst. Besides the Pd(II) catalyst, Pd nanoparticles are also immobilized within the PNIPAM-*co*-PMACHE hydrogel (Figure S3, Supporting Information). To further explore organic synthesis within the hydrogel, a typical Suzuki reaction of 4-bromoacetophenone with phenylboronic acid at 40 °C employing 0.050 mol % of Pd catalyst of 3-nm Pd nanoparticles is studied. At these conditions, the reactants are encapsulated and relatively enriched within the hydrogel. As shown in Figure 6, the Suzuki reaction within the hydrogel employing the catalyst of 3-nm Pd nanoparticles runs efficiently, similar to those employing the Pd(II) catalyst. That is, the yield of 4-acetylbiphenyl increases almost linearly with time until it reaches 95% in 2 h.

Up to now, various catalysts of Pd nanoparticles used in the C−C cross-coupling reaction in different reaction media are reported.[27] To evaluate the efficiency of the Suzuki reaction

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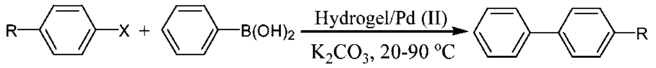
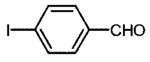
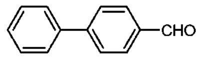
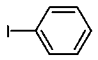
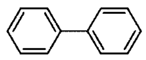
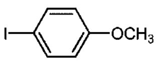
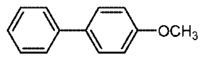
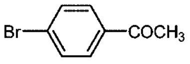
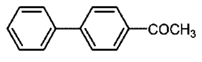
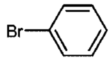
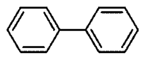
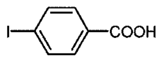
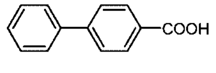
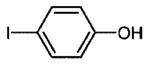
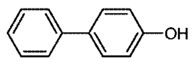
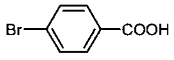
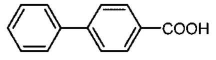
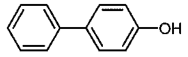
TABLE 1. Suzuki Reaction within the PNIPAM-*co*-PMACHE Hydrogel with Pd(II) Catalyst[a]

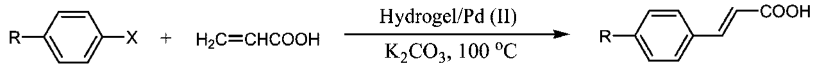


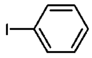
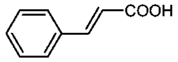
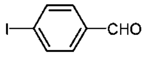
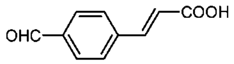
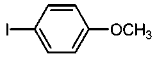
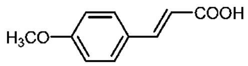
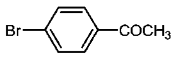
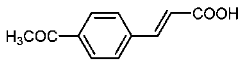
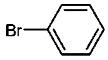
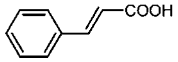
Entry	Substrate	Cat (mol%)	Temp (°C)	Time (h)	Product	Yield[b] (%)	TOF[d] (h^{-1})
1.1		0.050	90	1/4		99	1.1×10^4
1.2		0.050	40	2		99	1.0×10^3
2.1		0.050	90	1		99	5.6×10^3
2.2		0.050	40	24		75	1.0×10^2
3.1		0.050	90	1.5		95	1.2×10^3
3.2		0.050	40	24		56	65
4.1		0.050	90	1		99 (99[c])	3.1×10^3
4.2		0.050	40	3		99	1.1×10^3
5.1		0.050	90	1		99	2.4×10^3
5.2		0.050	40	24		44	60
6.1		0.050	90	1/12		99	2.4×10^4
6.2		0.0010	90	4		99	4.3×10^4
6.3		0.050	40	2		99	2.6×10^3
6.4		0.050	25	6		99	1.0×10^3
7.1		0.050	90	1/4		99	8.0×10^3
7.2		0.0010	90	24		95	1.0×10^4
7.3		0.050	40	3		98	1.6×10^3
7.4		0.050	25	6		97	7.5×10^2
8.1		0.050	90	1/6		99	1.2×10^4
8.2		0.050	40	3		99	1.8×10^3
8.3		0.050	25	6		98	7.8×10^2
9.1		0.050	90	1/4		99	8.0×10^3
9.2		0.050	40	10		96	6.5×10^2
9.3		0.050	25	10		93	4.1×10^2

[a] Reaction conditions: aryl halide (1.0 mmol) and phenylboronic acid (1.5 mmol, 1.5 equiv), K_2CO_3 (3.0 mmol, 3 equiv), 2.5 g of PNIPAM-*co*-PMACHE hydrogel. [b] Isolated yield and the purity of isolated product being confirmed by ^1H NMR. [c] Et_3N instead of K_2CO_3 being used as base. [d] TOF was measured as moles of product per mole of Pd catalyst per hour at the initial reaction time.

within the hydrogel, the present hydrogel/Pd(0) system is compared with five other catalysts of Pd nanoparticles by using the Suzuki reaction of 4-bromoacetophenone with phenylboronic acid as a typical example under other similar conditions. The first TBAA-Pd catalyst is the Pd nanoparticles stabilized by a surfactant of tetrabutylammonium acetate (TBAA) by Nacci et al.[28] The second microgel-Pd catalyst is the Pd nanoparticles stabilized with polymeric microgel by Biffis et al.[29] The third Pd/cyclodextrin is the Pd nanoparticles stabilized with surface-attached perthiolated cyclodextrin by Kaifer et al.[30] The fourth PS-*co*-P4VP-Pd catalyst is the Pd nanoparticles stabilized with poly(styrene-*co*-4-vinylpyridine) core−shell micospheres pro-

TABLE 2. Heck Reaction within the PNIPAM-*co*-PMACHE Hydrogel with Pd(II) Catalyst[a]



Entry	Substrate	Time[b] (h)	Product	Yield[c] (%)
1		12		99
2		12		91
3		12		95
4		24		98[d]
5		24		73[d]

[a] Reaction conditions: aryl halide (1.0 mmol) and acrylic acid (1.5 mmol, 1.5 equiv), K_2CO_3 (3.0 mmol, 3 equiv), 5.0 g of hydrogel, 0.20 mol % of Pd(II) catalyst. [b] Time is not optimized. [c] Isolated yield and the purity of isolated product being confirmed by ^{1}H NMR. [d] Et_3N instead of K_2CO_3 being used as base.

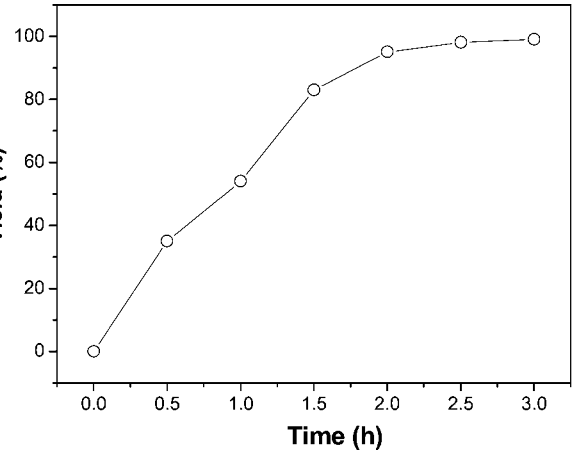


FIGURE 6. The kinetics plot of Suzuki reaction of 4-bromoacetophenone with phenylboronic acid within the PNIPAM-*co*-PMACHE hydrogel with the catalyst of 3-nm Pd nanoparticles. Reaction conditions: 1.0 mmol of 4-bromoacetophenone, 1.5 mmol of phenylboronic acid, 3.0 mmol of K_2CO_3, 2.5 g of hydrogel, 0.050 mol % of Pd(0) catalyst, 40 °C.

posed by us recently.[31] The last GnDenP-Pd catalyst is the Pd nanoparticles stabilized with phosphine dendrimer by Fan et al.[32] As shown in Table 3, the present Suzuki reaction within the PNIPAM-*co*-PMACHE hydrogel is the most efficient and affords the highest apparent turnover frequencies (TOF) of 780 h^{-1} (Table 3, entries 1−6) even at the lowest temperature of 40 °C in all six examples. For example, the apparent TOF value of the present hydrogel/Pd(0) system is about 14 times of the moderately efficient catalyst of microgel-Pd (Table 3, entry 3) and even the later Suzuki reaction is performed in a solvent mixture of DMF/H_2O at a high temperature of 80 °C. Compared with the Suzuki reaction in water employing the PS-*co*-P4VP-Pd catalyst, the present Suzuki reaction within the hydrogel affords an 8-times-higher TOF value even at a much lower temperature. Considering the easy synthesis, high efficiency, and easy reuse of the hydrogel/Pd system discussed subsequently, organic synthesis within the present hydrogel is believed to be a promising alternative.

2.7. Reuse of the PNIPAM-*co*-PMACHE Hydrogel/Pd Composite. The Suzuki reaction of 4-bromoacetophenone with phenylboronic acid is chosen as a typical example to investigate the reuse of the PNIPAM-*co*-PMACHE hydrogel/Pd(II) composite. To minimize the base/salt effect during the reuse of the hydrogel/Pd(II) composite, a volatile base of Et_3N instead of K_2CO_3 is used. After the extraction of the organics with diethyl ether, the pH value of the hydrogel phase is adjusted to 7, and the deswelled hydrogel/Pd(II) composite reversibly swells in water until the aqueous phase disappears. The swelled hydrogel/Pd(II) composite, which is just like a "soft" solid phase as shown in Scheme 1, is reused in the next run of organic synthesis. The reversible swelling of the deswelled hydrogel/Pd(II) composite affords two great advantages for the catalyst recycling. First, no Pd catalyst leaching occurs since the potential Pd leaching into water and the water itself are readsorbed into the swelled hydrogel phase during the reversible swelling of the deswelled gel. Second, no separation of Pd catalyst is need. To further explore the possible catalyst leaching into the organic phase during the extraction with ether, the analysis of the organic phase is made by atomic absorption spectrum (AAS). No Pd catalyst leached into the ether phase is detected whether the hydrophobic substrate of 4-bromoacetophenone or the hydrophilic 4-bromobenzoic acid is employed in the Suzuki reation (detection limit is 0.03 ppm). The results shown in Table 4 further demonstrate that the product yield does not decrease and the Pd catalyst is not deactivated at the fourth cycle (Figure

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(27) Astruc, D. *Inorg. Chem.* **2007**, *46*, 1884.

(28) Calo, V.; Nacci, A.; Monopoli, A.; Montingelli, F. *J. Org. Chem.* **2005**, *70*, 6040.

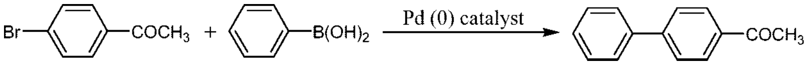
(29) Biffis, A.; Sperotto, E. *Langmuir* **2003**, *19*, 9548.

(30) Strimbu, L.; Liu, J.; Kaifer, A. E. *Langmuir* **2003**, *19*, 483.

(31) Wen, F.; Zhang, W.; Wei, G.; Wang, Y.; Zhang, J.; Zhang, M.; Shi, L. *Chem. Mater.* **2008**, *20*, 2144.

(32) Wu, L.; Li, B.-L.; Huang, Y.-Y.; Zhou, H.-F.; He, Y.-M.; Fan, Q.-H. *Org. Lett.* **2006**, *8*, 3605.

TABLE 3. Suzuki Reactions of 4-Bromoacetophenone with Phenylboronic Acid Employing Pd(0) Catalyst in Different Reaction Medium



entry	ref	Pd catalyst (mol %)	temp/time	medium	yield (%)/ TOF[a] (h^{-1})
1		hydrogel/Pd (0.050)	40 °C/2.5 h	hydrogel	98/780[b]
2	28	TBAA-Pd (2.5)	60 °C/16 h	ionic liquid	100/2.5
3	29	microgel-Pd (1)	80 °C/2 h	DMF/H_2O	100/55
4	30	Pd/cyclodextrin (1)	88 °C/7 h	H_2O/CH_3CN	88/13
5	31	PS-*co*-P4VP-Pd (0.25)	90 °C/4 h	H_2O	99/99
6	32	GnDenP-Pd (0.06)	101 °C/20 h	dioxane	99/82

[a] The apparent TOF value, which is calculated from the yield at the time just when the reaction is completed. [b] The real TOF value is 1.1×10^3 h^{-1}, which is also shown in Table 1.

TABLE 4. Reuse of the PNIPAM-*co*-PMACHE Hydrogel/Pd(II) Composite[a]

	fresh use	1st reuse	2nd reuse	3rd reuse
yield[b] (%)	99	99	99	99

[a] Reaction conditions: 4-bromoacetophenone (1.0 mmol), phenylboronic acid (1.5 mmol, 1.5 equiv), Et_3N (3.0 mmol, 3 equiv), 2.5 g of hydrogel, 0.050 mol % of Pd(II) catalyst, 1 h, 90 °C. [b] Isolated yield and the purity of isolated product being confirmed by ^1H NMR.

S6, Supporting Information). These results suggest the good reusability of the hydrogel/Pd(II) composite.

2.8. Comparison. Cross-linked functional polymers (CFPs) and some soluble polymers have been implemented in a wide range of synthetic methodologies.[33] Primarily, the synthetic use of these polymers has fallen into one of two scenarios: (1) the use of the polymer as support for reactants and/or (2) the use of the polymer to support catalyst[34] or encapsulate catalyst (EnCat).[35] As discussed above, the present hydrogel plays three roles in the organic synthesis: (1) the support for the Pd catalyst, (2) the encapsulant for reactants, and (3) the reaction medium. Besides, the encapsulated reactants and the immobilized Pd catalyst can even be highly enriched within the hydrogel matrix by reversible deswelling of the hydrogel, which is beyond the EnCat catalyst.

Usually, synthesis of an amphiphilic block copolymer is not an easy thing and an amphiphilic block copolymer is much more expensive than a random one. The Pd catalyst encapsulated in amphiphilic block copolymer micelles has been demonstrated to be very efficient in water and aqueous solution,[11] possibly since these micelles have the ability to encapsulate organic reactants and can be used as a nanoreactor,[36] whereas the separation of the micelles system from the reaction mixture is not easy since the amphiphilic block copolymer micelles are highly dispersed in the reaction medium and their size is usually smaller than 100 nm. Compared with the Pd catalyst immobilized in amphiphilic block copolymer micelles, the present hydrogel system has the advantages of easy synthesis of the polymeric materials and the convenient reuse of the Pd catalyst. Besides, the present hydrogel system has the other advantage to encapsulate and enrich the reactants and catalyst, and therefore to accelerate the reaction as discussed above.

Bergbreiter et al. proposed a PNIPAM-based thermomorphic system for organic synthesis.[37] This thermomorphic system employs the phase-selective solubility of PNIPAM in binary or ternary organic solvent mixture to facilitate the catalyst recovery and the product separation. Similar to the thermomorphic system, the recovery of the present hydrogel/palladium composite and the separation of the synthesized products are also convenient. However, the present hydrogel is much different from those of the PNIPAM-based thermomorphic system. First, the present PNIPAM-*co*-PMACHE hydrogel is used not only as the Pd catalyst support, but also as the reaction medium. In the former PNIPAM-based thermomorphic system, the soluble PNIPAM-based polymer just acts as a catalyst support and the reaction is performed in the binary or ternary organic solvent mixture. Second, the substrates are encapsulated and highly enriched within the hydrogel, and therefore organic synthesis within the PNIPAM-*co*-PMACHE gel is, at least in principle, more active than those in general solvents such as water, organic solvent, or the above-mentioned binary/ternary solvent mixture. Third, the cross-linked PNIPAM-*co*-PMACHE hydrogel instead of the soluble PNIPAM-based thermomorphic polymer is used, and this cross-linked hydrogel is insoluble and therefore easily separable.

3. Conclusion

A porous hydrogel of PNIPAM-*co*-PMACHE is synthesized. The hydrogel is superabsorbent and it can hold ~300 times of water within the hydrogel matrix; it is thermoresponsive and can reversibly swell and deswell at the phase-transition temperature of about 32 °C; it is pH-responsive and the swelling ratio almost remains constant at ~300 in the pH range of 4−10, and further gradually decreases until a minimum of ~10 when the pH value is below 4 or above 10; the PNIPAM-*co*-PMACHE hydrogel contains a ligand of IDA, and therefore Pd(II) or 3-nm Pd nanoparticles can be easily immobilized in the hydrogel matrix. The PNIPAM-*co*-PMACHE hydrogel can encapsulate

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hydrophilic reactants by hydrogen bonding between the PNIPAM segment and the hydrophilic reactants. Hydrophobic reactants can also be encapsulated within the hydrogel during the reversible hydrophilic/hydrophobic phase transition of the hydrogel. The encapsulated reactants and the immobilized Pd catalyst can be highly enriched within the hydrogel by increasing temperature above VPTT of the hydrogel or by adjusting pH, and therefore organic synthesis can be efficiently performed at concentrated reactants and Pd catalyst. Suzuki and Heck reactions performed within the PNIPAM-*co*-PMACHE hydrogel demonstrate that the hydrogel is a suitable reaction medium within which organic synthesis can be accelerated, since the reactants and Pd catalyst are highly enriched. The PNIPAM-*co*-PMACHE hydrogel/Pd composite is easily recovered and reused since the hydrogel/Pd composite can reversibly swell/deswell.

4. Experimental Section

4.1. Materials. The monomer of NIPAM (>99%) was purified by recrystallization from a benzene/*n*-hexane mixture and dried carefully under vacuum. Iminodiacetic acid (IDA, >99%) was used as received. The IDA-functioned monomer of MACHE was synthesized as described elsewhere.[38] The reagents such as BIS (>98%), TEMED (>99%), phenylboronic acid (>99%), 4-bromophenol (>99%), 4-bromoacetophenone (>99%), iodobenzene (>98%), 4-iodophenol (>99%), 4-iodobenzoic acid (>99%), 4-iodobenzaldehyde (>99%), 4-iodoanisole (>99%), bromobenzene (>99%), and 4-bromobenzoic acid (>99%) were commercial reagents and used as received. Double-distilled water was used in the present experiments.

4.2. Synthesis of the PNIPAM-*co*-PMACHE Hydrogel. In a 500 mL beaker, NIPAM (10.85 g, 95.9 mmol), MACHE (4.47 g, 17.3 mmol), and BIS (0.66 g, 6.5 mmol) were dissolved in 200 mL of H_2O/THF solvent mixture (4:1 by volume). Gelation was initiated by $K_2S_2O_8$ (0.32 g, 1.2 mmol) and accelerated by TEMED (0.28 mL, 1.8 mmol) at ∼28 °C for 4 h. After the reaction, the resulting hydrogel was immersed in deionized water at room temperature for 72 h. During this period, water was replaced every 3 h to leach out the potential chemical residues.

4.3. Typical Procedures for Suzuki Reaction within the PNIPAM-*co*-PMACHE Hydrogel with Pd(II) Catalyst. To a screw-capped vial with a side tube were added 2.5 g of hydrogel and 0.50 mL of 0.020−1.0 mmol/L of $PdCl_2$ aqueous solution. The mixture was kept at room temperature for 30 min with stirring. Then, 1.0 mmol of aryl halide, 3.0 mmol of base such as K_2CO_3 or triethylamine (Et_3N), and 1.5 mmol of phenylboronic acid (50% excess to the aryl halide) were added. The mixture was degassed under nitrogen purge for 10 min. Subsequently, the vial content was heated at a given temperature and magnetically stirred under nitrogen for a given time. After the reaction was stopped, the product was extracted with diethyl ether (3 × 20 mL) and then washed with water. For the substrates of 4-halogenated phenols and 4-halogenated benzoic acids, the reaction mixture was first acidified with 1 mol/L of HCl aqueous solution and then the product was extracted with diethyl ether. Last, the organic phase was washed with water and concentrated, and then the resulting product was dried under vacuum at 40 °C, weighed, and analyzed by ^{1}H NMR.

4.4. Typical Procedures for Suzuki Reaction within the PNIPAM-*co*-PMACHE Hydrogel with Pd(0) Catalyst. The hydrogel/Pd(0) composite was first prepared by reducing hydrogel/Pd(II) with $NaBH_4$ aqueous solution. To a screw-capped vial with a side tube were added 2.5 g of hydrogel and 0.50 mL of 1.0 mmol/L of $PdCl_2$ aqueous solution. The mixture was kept at room temperature for 30 min with stirring. Subsequently, 0.10 mL of 0.10 mol/L of $NaBH_4$ aqueous solution was added. The mixture was kept overnight at room temperature with stirring. Then, 1.0 mmol of aryl halide, 1.5 mmol of phenylboronic acid, and 3.0 mmol of K_2CO_3 were added and the mixture was degassed at room temperature. The Suzuki reaction was performed at 40 °C for a given time and the synthesized biaryls were extracted and analyzed similar to what was described above.

4.5. Typical Procedures for the Heck Reaction within the PNIPAM-*co*-PMACHE Hydrogel with Pd(II) Catalyst. To a screw-capped vial with a side tube were added 5.0 g of hydrogel and 0.50 mL of 4.0 mmol/L of $PdCl_2$ aqueous solution. The mixture was kept at room temperature for 30 min with stirring. Then, 1.0 mmol of aryl halide, 1.5 mmol of acrylic acid, and 3.0 mmol of base such as K_2CO_3 were added. The mixture was degassed under nitrogen purge for 10 min and then the vial content was heated in an oil bath at 100 °C and magnetically stirred under nitrogen. After the reaction was completed, the mixture was cooled to room temperature instantly and then acidified with 1 mol/L of HCl aqueous solution. The synthesized product was extracted from the reaction mixture with diethyl ether (3 × 20 mL), washed with cold water, and concentrated. Last, the resulting product was dried under vacuum at 40 °C, weighed, and analyzed by ^{1}H NMR.

4.6. Reuse of the Hydrogel/Pd Composite. The reuse of the hydrogel/Pd composite was evaluated by using the Suzuki reaction of 4-bromoacetophenone with phenylboronic acid as an example. After the reaction was completed, the mixture was cooled to room temperature and degassed under vacuum for 10 min to remove the volatile base of Et_3N. Then the reaction mixture was extracted with diethyl ether; the organic phase was washed with water and then concentrated; and the resulting product was dried, weighed, and analyzed by ^{1}H NMR. The pH of the hydrogel phase was adjusted to 7 with 1 mol/L of HCl aqueous solution and then the composite was reused in another run of the Suzuki reaction with the same amounts of reactants being added as those in the fresh run.

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Supporting Information Available: Text showing the synthesis of PNIPAM-*co*-PMACHE hydrogel, optical photos on the immobilization of Pd catalyst and the encapsulation and enrichment of the typical reactants within the PNIPAM-*co*-PMACHE hydrogel, the kinetics plot of the Suzuki reaction of 4-bromoacetophenone with phenylboronic acid within the hydrogel employing Pd(II) catalyst at 90 °C, and the ^{1}H NMR spectra of the synthesized products. This material is available free of charge via the Internet at http://pubs.acs.org.

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