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# PEG Modification Effect of Silica on the Suzuki–Miyaura Coupling Reaction Using Silica-immobilized Palladium Catalysts

**Shun-ya Onozawa · Norihisa Fukaya ·
Kaori Saitou · Toshiyasu Sakakura ·
Hiroyuki Yasuda**

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**Abstract** The Pd phosphine complex catalysts immobilized onto polyethylene glycol (PEG)-modified silica were prepared in order to clarify the effect of the PEG modification on the Suzuki–Miyaura coupling reaction in organic solvents. For the reaction of ethyl *p*-bromobenzoate and phenylboronic acid in the presence of potassium carbonate in toluene, the PEG-modified silica-immobilized Pd catalysts exhibited much higher activities than the catalysts without PEG modification.

**Keywords** Immobilized Pd phosphine complex · Polyethylene glycol · Suzuki–Miyaura coupling reaction · Mesoporous silica · Heterogeneous catalysis

## 1 Introduction

Immobilization of molecular catalysts such as transition metal complex catalysts onto organic polymers or inorganic porous materials has attracted much interest in recent organic synthesis because immobilized catalysts are advantageous in terms of their recovery from reaction mixtures by simple filtration and potential for application to flow reaction systems [1–4]. However, heterogenization of molecular catalysts generally sacrifices catalytic performance, including the activity and/or selectivity. One strategy to enhance the activity of immobilized catalysts is modifying the surface of catalyst supports with polymers that have a high affinity for substrates and/or reaction media [5–11].

The palladium-catalyzed Suzuki–Miyaura coupling reaction between organoboranes and organic electrophiles is an important carbon–carbon bond forming reaction in organic synthesis [12–14]. A number of studies about the design and preparation of immobilized catalysts for the Suzuki–Miyaura reaction have been reported [15–21]. Since the reaction takes place in aqueous organic media, modifying supports with amphiphilic polymers such as polyethylene glycol (PEG) effectively promotes the reaction. Uozumi et al. [22, 23] and Lee et al. [24] have demonstrated that polystyrene-immobilized Pd complexes in which PEG is employed as a linker of the complex efficiently catalyze the Suzuki–Miyaura reaction in water. Lee et al. [10] have also developed PEG-modified chitosan-supported Pd nanoparticle catalysts for the reaction in water. Ma et al. [11] have proposed the catalytic system consisting of $Pd(PPh_3)_n$ and PEG-coated mesoporous silica. The excellent performances of these catalysts are owing to the water-compatible nature of the PEG-modified supports. On the other hand, the effect of PEG modification on the catalytic activity for the Suzuki–Miyaura reaction in organic solvents has not yet been clarified. Because the reaction employs both hydrophobic compounds (organic halides) and hydrophilic compounds (inorganic bases) as starting materials, we hypothesized that the amphiphilic PEG modification would efficiently concentrate both substrates near catalytic active sites, and thus lead to an improved catalytic activity even in organic solvents. In this study, we prepared an immobilized catalyst in which Pd phosphine complexes and PEG groups were separately grafted onto the surface of silica supports, and verified the

S. Onozawa (✉) · N. Fukaya · K. Saitou · T. Sakakura ·
H. Yasuda (✉)
National Institute of Advanced Industrial Science and
Technology (AIST), Tsukuba Central 5, 1-1-1 Higashi,
Tsukuba, Ibaraki 305-8565, Japan
e-mail: s-onozawa@aist.go.jp

H. Yasuda
e-mail: h.yasuda@aist.go.jp

effect of the PEG modification on the Suzuki–Miyaura coupling reaction in toluene.

## 2 Experimental

### 2.1 General

All catalyst preparation and reactions were carried out under a nitrogen atmosphere. Chemicals and dry solvents were purchased from Sigma–Aldrich Co., Tokyo Chemical Industry Co., Ltd., and Wako Pure Chemical Industries, Ltd., and used without further purification. Ethyl 4-bromobenzoate and 4-*tert*-butyltoluene were degassed by freeze–pump–thaw (FPT) cycles. Palladium (II) acetate was supplied by N.E. CHEMCAT Co., while amorphous silica CARiACT Q-3 was supplied by Fuji Silysia Chemical Ltd. Ordered mesoporous silica SBA-15 was prepared according to the literature [25, 26]. 3-(Diphenylphosphino)propyltrimethoxysilane (**2**) was synthesized according to the literature [27].

Nitrogen adsorption/desorption isotherms were measured at −196 °C using a Bel Japan BELSORP-mini II analyzer. Specific surface areas were calculated by the BET method. Pore size distributions were calculated from the adsorption branch of nitrogen isotherms using the BJH method. Solid–state $^{13}C$ and $^{31}P$ CP/MAS NMR spectra were recorded on a Bruker AVANCE 400WB spectrometer equipped with a 4 mm CP/MAS probe head. Liquid NMR spectra were recorded on a JEOL JNM-Lambda 400 spectrometer. Transmission electron microscopy (TEM) measurements were carried out using a JEOL JEM-2010F with an acceleration voltage of 200 kV. Elemental compositions of carbon and phosphorous were determined by a CE Instruments EA 1112 elemental analyzer and a Shimadzu EDX-800HS energy dispersive X-ray spectrometer (EDX), respectively. GC analysis was performed on a Shimadzu GC-14B gas chromatograph with a TCD equipped with an OV-101 column. Palladium concentrations in reaction solutions were measured using a Shimadzu ICPS-8100 inductively coupled plasma-optical emission spectrometer (ICP-OES).

### 2.2 Catalyst Preparation

#### 2.2.1 Preparation of PEG-Functionalized Triethoxysilane (1)

Commercially available poly(ethylene glycol) methyl ether (average Mn of 2,000, 10 g) was dissolved in toluene (50 mL). The solution was added to a suspension of NaH (132 mg) in toluene (30 mL) at room temperature, and the mixture was stirred for 30 min. 3-Bromopropene (0.67 g) was then added and stirred for 15 h under refluxing. After cooling, the precipitate was filtered off and the solvent was removed under a vacuum. Allylated compound was obtained as a white solid (9.3 g). Allylated compound (1.96 g) and $H_2PtCl_6 \cdot 6H_2O$ (1.7 mg) were dissolved in THF (20 mL) and stirred at room temperature. Then, triethoxysilane (0.67 g) was added dropwise and the solution was stirred at 60 °C for 15 h. After cooling, the solvent was removed under a vacuum. The crude PEG-functionalized triethoxysilane **1** was purified by the reprecipitation method using toluene and hexane at 0 °C. The resulting white solid was dried under a vacuum to afford **1** (1.39 g). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.55–0.56 (m, 2H, $SiCH_2$), 1.17 (t, $J = 7.2$ Hz, 9H, $CH_2CH_3$), 1.60–1.69 (m, 2H, $CH_2CH_2CH_2$), 3.33 (s, 3H, $OCH_3$), 3.36–3.68 (brs, 250H, $OCH_2CH_2$), 3.76 (q, $J = 7.2$ Hz, 6H, $OCH_2CH_3$). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 10.6, 18.5, 22.9, 59.1, 70.1, 70.6, 72.0, 72.6, 73.1.

#### 2.2.2 Preparation of Modified Silica Supports

Typically, silica (2 g) was dried under a vacuum at 80 °C for 3 h. After cooling, diglyme (20 mL) and PEG compound **1** (1 g) were added. The resulting mixture was stirred at 110 °C for three days. The suspension was filtered, and the solid residue was washed successively with THF, toluene, chloroform, and methanol. The resulting solid was dried under a vacuum at 80 °C for 3 h. To a suspension of the PEG-modified silica (1 g) in dry toluene (10 mL) was added **2** (0.4 mL). The reaction mixture was refluxed for three days. The suspension was filtered, and the $Ph_2P$-grafted silica was washed successively with toluene, chloroform, and methanol. The resulting solid was dried under a vacuum at 80 °C for 3 h.

#### 2.2.3 Preparation of Palladium Catalysts

Typically, the modified silica PEG-Q-PPh2 (0.5 g) was dried under a vacuum at 80 °C for 3 h prior to use in complexation. After cooling, THF (4 mL) and palladium acetate (8.3 mg) were added. The mixture was stirred at room temperature for 20 h. Then, the solvent was evaporated, and the resulting solid was dried under a vacuum at room temperature for 3 h.

### 2.3 Suzuki–Miyaura Coupling Reactions

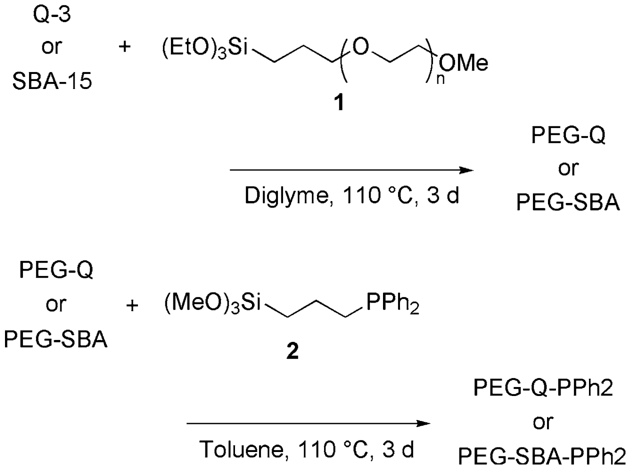
The Suzuki–Miyaura coupling reaction of ethyl 4-bromobenzoate and phenylboronic acid was carried out in a Schlenk flask (30 mL) under a nitrogen atmosphere. Typically, a mixture of ethyl 4-bromobenzoate (3 mmol), phenylboronic acid (3.3 mmol), potassium carbonate (6 mmol), 4-*tert*-butyltoluene (0.5 mL, internal standard), and the catalyst (Pd: 0.05 mol% of aryl bromide) was stirred in a solvent (3 mL) at 100 °C. The reaction was performed for 0.5 or 5 h. Product yield was determined by GC analysis.

## 3 Results and Discussion

Amorphous silica (CARiACT Q-3, abbreviated as Q-3) and ordered mesoporous silica (SBA-15) were used as silica supports. The PEG compound, which contained triethoxysilyl moiety (**1**) to modify the silica surface, was prepared in two steps from poly(ethylene glycol) methyl ether (average Mn of 2,000) [11]. Reactions of Q-3 and SBA-15 with **1** in diglyme at 110 °C for three days gave PEG-modified silicas PEG-Q and PEG-SBA, respectively (Scheme 1). To support the palladium complexes on PEG-modified silicas, a phosphorus ligand was introduced onto PEG-Q and PEG-SBA. The reaction of PEG-Q with 3-(diphenylphosphino)propyltrimethoxysilane (**2**) in toluene while refluxing for three days gave silica support PEG-Q-PPh2 onto which the 3-(diphenylphosphino)propyl group was grafted. The reaction of PEG-SBA with **2** gave silica support PEG-SBA-PPh2. For comparison, silica supports without PEG modification, Q-PPh2 and SBA-PPh2, as well as a silica support modified with tri(ethylene glycol), TEG-Q-PPh2 were also prepared.

Figure 1 shows the $^{13}$C CP/MAS NMR spectrum of PEG-Q-PPh2. The signals at $\delta$ 13–32, 58, and 70 ppm corresponded to trimethylene, terminal methoxy, and dimethylene groups of the grafted PEG group, respectively [28, 29]. The peaks at $\delta$ 13–32 ppm contained the resonance due to trimethylene group in **2**, whereas the peak at $\delta$ 51 ppm was due to the unreacted methoxy group of **2**. The peaks observed at $\delta$ 125–135 ppm were assigned to the phenyl groups of the grafted phosphine ligand. The results clearly show that both the PEG group and the phosphine ligand are successfully loaded onto the Q-3 surface. Table 1 summarizes the loading amounts of the PEG group and the phosphine ligand determined by combining elemental analysis of carbon and EDX measurements of phosphorus. The molar ratios of the phosphine ligand to the PEG group for PEG-Q-PPh2 and PEG-SBA-PPh2 were about seven and four, respectively. Although the phosphine ligand was introduced onto the silica surface after PEG modification, more phosphine ligand was loaded. Compared to the PEG group, about three times as much TEG group was loaded onto Q-3. The loading amounts of the phosphine ligand on the silica supports modified with PEG or TEG were 70–55% of the loading amounts on unmodified silicas. Table 1 includes the textural properties of the silica supports determined by nitrogen adsorption measurements. Modifying the silica surface with PEG, TEG, or phosphine ligands largely decreased the surface area and the pore volume; the surface areas of PEG-Q-PPh2 and PEG-SBA-PPh2 were approximately 15% of Q-3 and 20% of SBA-15, respectively. Modification also narrowed the average pore size of SBA-15 from 7.1 to 4.8 nm.

The silica-supported Pd catalysts were prepared by reacting the modified silicas with palladium acetate in THF at room temperature for 20 h. The amount of palladium acetate was adjusted so that the molar ratio of phosphorous in the supports to Pd was six. In addition to the peaks due to phosphine ($\delta$ −15 ppm) and phosphine oxide ($\delta$ 40 ppm), the $^{31}$P CP/MAS NMR spectrum of the resulting Pd/PEG-Q-PPh2 catalyst exhibited a new peak at $\delta$ 23 ppm, which is indicative of a Pd-P bond [30, 31] (Fig. 2). This observation suggests the formation of palladium phosphine complexes on PEG-Q-PPh2. On the other hand, the TEM images of Pd/PEG-SBA-PPh2 reveal the presence of small amounts of Pd metal aggregates (3–5 nm) in the mesopores and on the external surface of the PEG-SBA-PPh2 support, indicating that Pd partially exists as Pd nanoparticles in the Pd/PEG-SBA-PPh2 catalyst (Fig. 3). The reduction of palladium



**Scheme 1** Preparation of PEG-modified silica supports

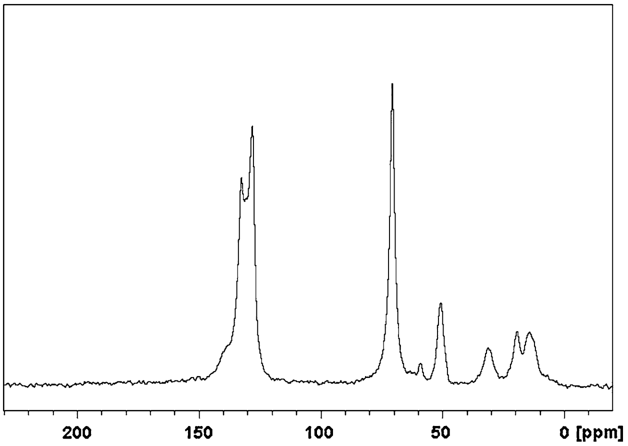


**Fig. 1** $^{13}$C CP/MAS NMR spectrum of PEG-Q-PPh2

**Table 1** Physical properties of silica and modified silica supports

| Support | PEG group (mmol $g^{-1}$) | $Ph_2P$ group (mmol $g^{-1}$) | $S^a$($m^2$ $g^{-1}$) | $V^b$($cm^3$ $g^{-1}$) | $D^c$(nm) |
|---|---|---|---|---|---|
| Q-3 | – | – | 716 | 0.50 | – |
| PEG-Q-PPh2 | 0.059 | 0.43 | 112 | 0.13 | – |
| TEG-Q-PPh2 | $0.18^d$ | 0.54 | 220 | 0.15 | – |
| Q-PPh2 | – | 0.78 | 101 | 0.09 | – |
| SBA-15 | – | – | 926 | 0.89 | 7.1 |
| PEG-SBA-PPh2 | 0.098 | 0.42 | 183 | 0.34 | 4.8 |
| SBA-PPh2 | – | 0.68 | 404 | 0.54 | 6.2 |

[a] Specific surface area (BET)

[b] Pore volume ($P/P_0 = 0.99$)

[c] Average pore size (BJH)

[d] Loading amount of TEG group

acetate by phosphorous ligands to generate unstable Pd(0) species possibly caused the formation of Pd nanoparticles [32, 33].

The Suzuki–Miyaura coupling reaction of ethyl *p*-bromobenzoate and phenylboronic acid using the silica-supported Pd catalysts was carried out in the presence of potassium carbonate in toluene (Scheme 2). The catalyst was adjusted to 0.05 mol% based on Pd. Table 2 summarizes the results. For both Q-3 and SBA-15, modifying the silica surface with PEG remarkably enhanced the catalytic activity (entries 1 vs. 2 and 3 vs. 4). Additionally, SBA-15 was a more effective catalyst support than Q-3 (entries 1 vs. 3 and 2 vs. 4). Modifying the surface of Q-3 with TEG also improved the catalytic activity (entries 2 vs. 5).

For the reaction using the Pd/PEG-Q-PPh2 and Pd/Q-PPh2 catalysts, potassium carbonate was replaced with an organic base like triethylamine. However, the effect of the PEG modification was not observed (entries 6 vs. 7). Additionally, when diglyme having the similar structure as PEG was used as a solvent, the effect of the PEG modification was negligible (entries 8 vs. 9). Therefore, the PEG groups in the presence of an ionic compound like potassium carbonate in a non-polar solvent such as toluene may attract ionic compounds and assist in its dissociation near the active Pd sites, which accelerates the Pd-catalyzed reaction. In the case of the reaction in diglyme, inorganic bases that have a high solubility in diglyme may be easily accessible to the hydrophilic surface of silica surface, which reduces the PEG modification effect. The reaction using the Pd/Q-PPh2 catalyst was conducted while adding the same amount of poly(ethylene glycol) methyl ether (average Mn of 2,000) (1 mg) as the amount of PEG in the Pd/PEG-Q-PPh2 catalyst. However, an additive effect was not observed; the yields after 30 min and 5 h were almost the same as those for Pd/Q-PPh2 (entries 2 vs. 10). Moreover, the addition of 10 mg of poly(ethylene glycol) methyl ether greatly decreased the yields (entries 2 vs. 11). Therefore, it is likely that the role of the immobilized PEG groups in the neighborhood of the Pd species is important for promoting the reaction.

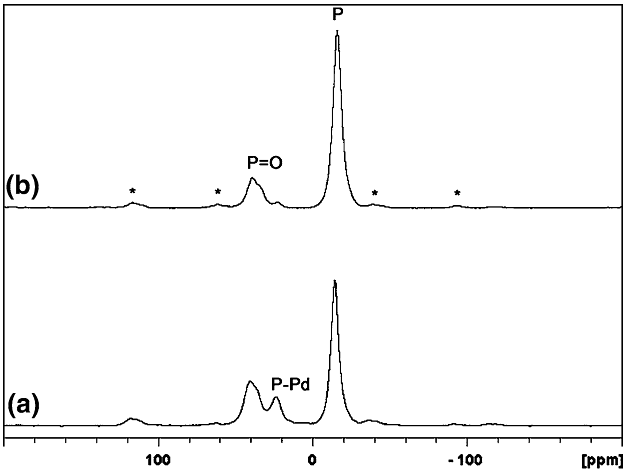


**Fig. 2** $^{31}P$ CP/MAS NMR spectra of (**a**) Pd/PEG-Q-PPh2 and (**b**) PEG-Q-PPh2

After the reaction using the Pd/PEG-Q-PPh2 catalyst in toluene was carried out for 5 h, the catalyst was separated by filtration. Then Pd leaching into the reaction solution was measured by ICP-AES. The Pd content in each filtrate was below the detectable limit (<0.5 ppm), indicating the supported Pd species is relatively stable on the PEG-Q-PPh2 support. The recyclability of the Pd/PEG-Q-PPh2 catalyst was also examined. After the reaction in toluene was done for 5 h, the catalyst was separated by vacuum filtration, rinsed successively with by toluene, water, and ethanol under a nitrogen atmosphere. Then it was dried in a vacuum at room temperature, and reused in a second reaction. However, the catalytic activity of the recovered Pd/PEG-Q-PPh2 notably decreased (the first reaction: 52% yield, the second reaction: 18% yield). Because the potassium salt of boronic acid and/or potassium bromide

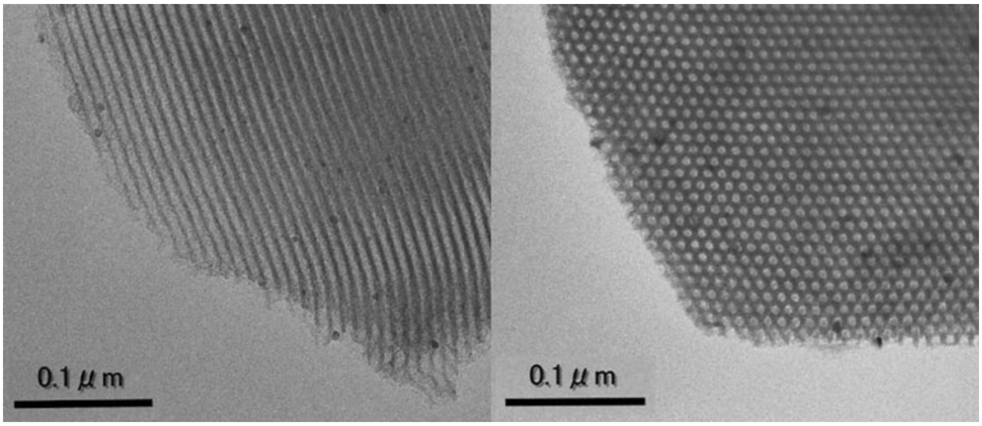
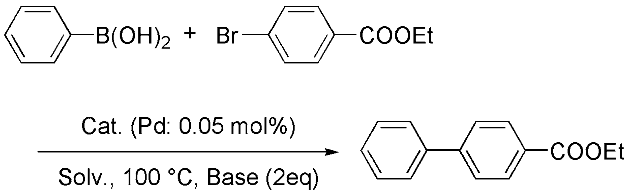


**Fig. 3** TEM images of Pd/PEG-SBA-PPh2



**Scheme 2** Suzuki–Miyaura coupling reaction using silica-immobilized Pd catalysts

**Table 2** Suzuki-Miyaura coupling reaction using silica-immobilized Pd catalysts

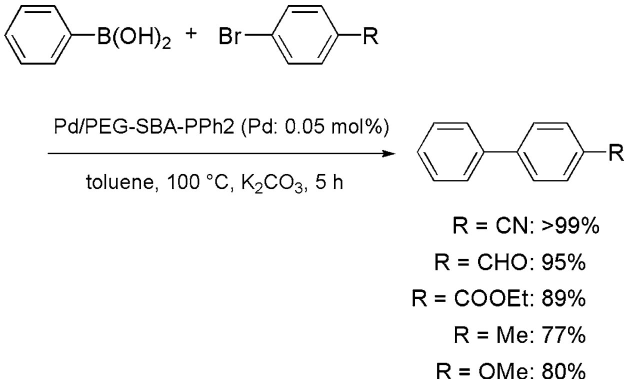
| Entry | Catalyst | Solvent | Base | Yield (%)[a] | |
|---|---|---|---|---|---|
| | | | | 0.5 h | 5 h |
| 1 | Pd/PEG-Q-PPh2 | Toluene | $K_2CO_3$ | 20 | 52 |
| 2 | Pd/Q-PPh2 | Toluene | $K_2CO_3$ | 4 | 24 |
| 3 | Pd/PEG-SBA-PPh2 | Toluene | $K_2CO_3$ | 53 | 89 |
| 4 | Pd/SBA-PPh2 | Toluene | $K_2CO_3$ | 30 | 48 |
| 5 | Pd/TEG-Q-PPh2 | Toluene | $K_2CO_3$ | 34 | 68 |
| 6 | Pd/PEG-Q-PPh2 | Toluene | $NEt_3$ | 5 | 8 |
| 7 | Pd/Q-PPh2 | Toluene | $NEt_3$ | 7 | 8 |
| 8 | Pd/PEG-Q-PPh2 | Diglyme | $K_2CO_3$ | 53 | 75[b] |
| 9 | Pd/Q-PPh2 | Diglyme | $K_2CO_3$ | 55 | 81[b] |
| 10[c] | Pd/Q-PPh2 | Toluene | $K_2CO_3$ | 3 | 25 |
| 11[d] | Pd/Q-PPh2 | Toluene | $K_2CO_3$ | 2 | 3 |

[a] Each yield was determined by GC using 4-*tert*-butyltoluene as an internal standard

[b] Yield at a time of 3 h

[c] 1 mg of poly(ethylene glycol) methyl ether (average Mn: 2,000) was added

[d] 10 mg of poly(ethylene glycol) methyl ether was added



**Scheme 3** Suzuki–Miyaura coupling reaction of various aryl bromides

co-produced during the reaction have a low solubility in toluene, they possibly remain on the recovered catalyst, resulting in the reduced catalytic activity. Actually, when the reaction was performed in water, the recovered Pd/PEG-Q-PPh2 catalyst could be recycled twice without a significant loss in the catalytic activity (the first reaction: 82% yield, the second reaction: 81% yield, the third reaction: 75% yield).

The Suzuki–Miyaura coupling reaction in toluene using the Pd/PEG-SBA-PPh2 catalyst was applicable to various aryl bromides bearing electron-donating and electron-withdrawing substituents at their para-positions, giving the corresponding biaryl compounds in good yields (Scheme 3).

## 4 Conclusions

We prepared Pd phosphine complex catalysts immobilized onto amorphous and mesoporous silica supports in which the surface was modified with PEG. For the Suzuki–Miyaura coupling reaction in toluene, the PEG-modified silica-immobilized Pd catalysts exhibited much higher activities than the catalysts without PEG modification. The immobilization of PEG groups in the neighborhood of the Pd species seems important for promoting the reaction. These results show that modifying the surface of catalyst supports with appropriate polymers can enhance the activity of immobilized metal complex catalysts.

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