AIChE

Membrane Reactor Immobilized with Palladium-Loaded Polymer Nanogel for Continuous-Flow Suzuki Coupling Reaction

Hirokazu Seto, Tamami Yoneda, Takato Morii, Yu Hoshino, and Yoshiko Miura
Dept. of Chemical Engineering, Graduate School of Engineering, Kyushu University, 744 Motooka, Nishi-ku,
Fukuoka, 819-0395 Japan

Tatsuya Murakami
Center for Nano Materials and Technology, Japan Advanced Institute of Science and Technology,
1-1 Asahidai, Nomi, Ishikawa 923-1292, Japan

DOI 10.1002/aic.14653

A catalytic membrane reactor, which was immobilized with palladium-loaded nanogel particles (NPs), was developed for continuous-flow Suzuki coupling reaction. Palladium-loaded membranes were prepared by immobilization of NPs, adsorption of palladium ions, and reduction into palladium(0). The presence of palladium in the membrane was confirmed by the scanning electron microscopy; palladium aggregation was not observed. The catalytic activity of the membrane reactor in continuous-flow Suzuki coupling reaction was approximately double that of a comparable reactor in which palladium ions were directly adsorbed onto an aminated membrane. This was attributed to the formation of small palladium particles. The reusability in the continuous-flow system was higher than that in a batch system, and the palladium-loaded membrane reactor had high long-term stability. © 2014 American Institute of Chemical Engineers *AIChE J*, 61: 582–589, 2015

Keywords: polymer nanogel particles, membrane reactor, continuous-flow system, catalytic reaction, palladium

Introduction

One of the strategies used for chemical transformations is catalytic reactions using transition metals. Various transition-metal catalysts are useful for chemical transformations, and palladium (Pd) shows catalytic activity for a diverse range of cross-coupling reactions,[1,2] as well as hydrogenation,[3,4] and π-allyl substitution.[5,6] The catalytic activities of nanosized Pd(0) catalysts are high because of the high surface-to-volume ratio.[7,8] Because Pd(0) catalysts are relatively expensive, they are recycled using thiol- and amine-functionalized scavengers for separation and recovery from the product. However, metal recoveries using methods such as adsorption and desorption are complicated, and result in increased industrial wastes. Such catalysts also have the disadvantage of aggregation, which leads to inactivation.

Immobilized catalysts have been used to prevent aggregation.[9] Catalysts immobilized on polymeric and inorganic supports can be easily recovered from reaction solutions by filtration, and the recovered catalysts can be used for a number of times.[10–19] Recently, there have been increasing interests in catalytic reactions in aqueous media, because of the desire to use the green chemistry.[16–21] It has been found that some transition metals show the catalytic activity in aqueous media.[22] Leakage of transition metals leads to decreased catalytic activity and product contamination. To prevent Pd leakage, high-coordinating ligands, such as thiol and amine groups, have been used.[16,20,21]

We have also developed Pd(0) catalysts loaded in polymer nanogel particles (NPs), and used them for hydrogenation and Suzuki coupling reactions.[23] The NPs were synthesized from *N*-isopropylacrylamide (NIPAm), basic monomers, and cross linking monomer. Pd ions were adsorbed on the NPs at a suitable density, and Pd(0) nanoparticles were formed via reduction using $NaBH_4$. The catalytic activities of the Pd(0)-loaded NPs depended on the Pd particle size. The NPs were highly dispersed with small diameter and high flexibility, so contact between the NPs and substances was efficient.[24] The Pd(0)-loaded NPs had high catalytic activities; in particular, the Suzuki coupling reactions using the Pd(0)-loaded NPs were achieved in aqueous media. Pd leakage from the NPs was not detected. In batch systems, aggregation of the support occurs during filtration, so the catalytic activities of used catalysts tend to be lower. Recycling system, which do not change the surface states of the catalyst, are, therefore, required.

Continuous-flow systems have attracted considerable attention as a novel tool for catalytic organic synthesis,[25–27] and enable to improve the reusability of the catalyst. Compared with traditional batch systems, the continuous-flow systems

---

Additional Supporting Information may be found in the online version of this article.

Correspondence concerning this article should be addressed to Y. Miura at miuray@chem-eng.kyushu-u.ac.jp.

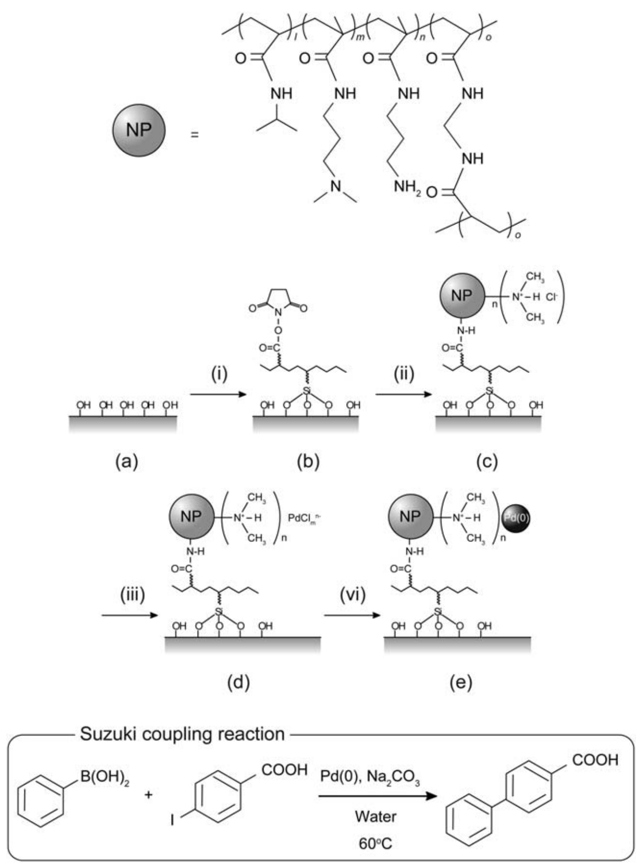

Figure 1. Structure of poly(NIPAm-DMAPM-APM-BIS) NP (*l*:*m*:*n*:*o* = 80:10:5:5), preparation of Pd(0)-loaded membrane: (a) unmodified SiO_2, (b) NAS-activated, (c) NP-immobilized, (d) Pd ion-adsorbed, and (e) Pd(0)-loaded membranes, and Suzuki coupling reaction between phenylboronic acid and 4-iodebenzoic acid.

(1) 10 g L^{-1} poly(TMSMA-*r*-NAS) in DMF, (2) 5 g L^{-1} NPs in water, (3) 1.0 mmol L^{-1} K_2PdCl_4 in 1.0 mmol L^{-1} HCl, and (4) $NaBH_4$ in water (pH 8).

provide some advantages, such as high operability, easy control of the reaction, automation, miniaturization, and scale up. The separation process takes place at the same time as the reaction in the continuous-flow reactor, so recovery and reuse of the catalyst are significantly easy. Particle-packed column reactors are filled with catalysts immobilized on beads, and conventionally applied in the continuous-flow system. Many particles have dead-end pores. Catalytic reaction in the reactor proceeds via film-diffusion and pore-diffusion steps. Reactant mass transport in the pores is limited, which is a disadvantage.[28]

Membranes have consecutive through pores. The solution passes through the membrane pores by convective flow. Mass transport limitations are reduced in a membrane reactor, because the pore-diffusion step is negligible.[28] When a microfilter is used as the matrix, the pressure loss during solution permeation through the membrane pores is lower than that through packed particles. Microchannel reactors, which have small spaces and high permeability, are also a useful process technology for continuous-flow catalytic reactions using Pd.[29–31] Scale-up of a membrane reactor by stacking is simpler than numbering-up of a microchannel reactor. The development of Pd-loaded membrane reactors for continuous-flow catalytic reactions is important for industrial applications.

In this study, a catalytic membrane reactor, which was immobilized with Pd(0)-loaded NPs, was developed for a continuous-flow system. NIPAm, *N*−3-dimethylaminopropyl methacrylamide (DMAPM), *N*-(3-aminopropyl) methacrylamide hydrochloride (APM), and *N*,*N*′-methylenebisacrylamide (BIS) in the NPs acted as the backbone, Pd adsorber, NP immobilizer, and cross-linker sites, respectively (Figure 1). The Pd(0)-loaded membranes were sequentially prepared by immobilization of NPs, adsorption of Pd ions, and reduction into Pd(0). The catalytic activity of the membrane reactor was evaluated using the Suzuki coupling reaction between phenylboronic acid and 4-iodobenzoic acid. This reaction, in which C—C bonds are formed between organoboron and organohalide compounds, has been widely used in the production of many compounds such as medicines and agrochemicals,[32] so the construction of a reactor system for the Suzuki coupling reaction has wide industrial significance. The need to use NPs, flow rate dependence of the reactant solution, storage stability, Pd leakage, and long-term stability were investigated using the Pd(0)-loaded membrane.

Experimental

Reagents

NIPAm (Wako Pure Chemical Industries, Japan) was purified by recrystallization from *n*-hexane, and dried in vacuo at room temperature. DMAPM (Tokyo Chemical Industry Co., Japan) was permeated through alumina column to remove polymerizing inhibitor. APM (Polysciences), BIS (Tokyo Chemical Industry Co., Japan), cetyltrimethylammonium bromide (CTAB; Wako Pure Chemical Industries, Japan), 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPD; Wako Pure Chemical Industries, Japan), iodobenzoic acid (Tokyo Chemical Industry Co., Japan), phenylboronic acid (Tokyo Chemical Industry Co., Japan), potassium tetrachloropalladate (Sigma Aldrich Co.), sodium borohydride (Kanto Chemical Co., Japan), and sodium carbonate (Kanto Chemical Co., Japan) were used without further purification. A copolymer of 3-(trimethoxysilyl)propyl methacrylate and *N*-acryloxysuccinimide (poly(TMSMA-*r*-NAS), Supporting Information Figures. S1 and S2) was synthesized using a previously reported method,[33] and was used to form the NAS-activated surface for the amine coupling reaction.

Synthesis of amine-containing NPs

NIPAm, DMAPM, APM, and BIS were dissolved in water (20 mL). The NIPAm:DMAPM:APM:BIS molar ratios and the total concentration of monomer were adjusted to 80:10:5:5 and 312 mmol L^{-1}, respectively. A surfactant, CTAB (42 μmol), was added to the monomer solution. The solution was degassed under nitrogen for 30 min. The polymeric reaction was initiated by addition of AAPD (52 μmol) at 70°C. After 3 h, the mixture solution was aerated to stop polymerization. The resulting NPs were dialyzed (molecular-weight cut off: 100,000) against water (which was changed more than three times per day) for 3 days. The NP yield was determined from the weight of NPs measured after freeze-drying a portion of the dialyzed solution, and was estimated to be 91%.

Preparation of Pd(0)-loaded membranes

Two types of Pd(0)-loaded membranes were prepared, by adsorption of Pd ions via NPs or by direct adsorption of Pd ions onto the membrane (Figure 1 and Supporting Information Figure S3). A filter paper consisting of SiO_2 (purity > 99%; Toyo Roshi Kaisha, Japan) was used as the membrane matrix (Supporting Information Table S1 and Figure S4). The membranes were conditioned by immersion in methanol and treatment with RCA solution (water:hydrogen peroxide: ammonia = 5:1:1) at 60°C for 20 min. After washing with water, methanol, and dimethylformamide, the membrane surface was activated using poly(TMSMA-*r*-NAS) (see the Supporting Information). The NAS-activated membranes were immersed in NP aqueous solutions (5 g L^{-1}) at 40°C for 14 h. The concentration of NPs in the solution was obtained from the turbidity at 600 nm, determined using ultraviolet-visible (UV-vis) spectroscopy (Agilent 8453, Agilent Technologies). The amount of NPs immobilized on the membrane was calculated using Eq. 1

$$\text{Amount of NPs immobilized}\,(\text{g g}_\text{M}^{-1})=\frac{[\text{NP}]_0-[\text{NP}]}{W_\text{M}}\times v \quad (1)$$

where v and W_M are the solution volume and membrane weight, respectively. The subscript 0 denotes the initial condition. Pd solutions were prepared by dissolving potassium tetrachloropalladate in 1.0 mmol L^{-1} HCl. The unmodified and NP-immobilized membranes were immersed in the Pd solution at 40°C for 24 h. The concentration of Pd ions in the solution was determined by UV absorption at 420 nm. The amount of Pd ions adsorbed on the membrane was calculated using Eq. 2

$$\text{Amount of Pd ions adsorbed (mol g}_\text{M}^{-1})=\frac{[\text{Pd ion}]_0-[\text{Pd ion}]_\text{e}}{W_\text{M}}\times v \quad (2)$$

where the subscript e denotes the equilibrium state. The Pd ion-adsorbed membranes were washed with 1.0 mmol L^{-1} HCl and immersed in the $NaBH_4$ solution (pH: 8, water) for reduction into Pd(0). After washing with excess water, the Pd(0)-loaded membrane was obtained. The success of each process was confirmed using X-ray photoelectron spectroscopy (XPS; AXIS-ultra, Shimadzu/Kratos, Japan) using a silicon wafer. The XPS spectra were calibrated using the peak at 285.0 eV corresponding to C—C. The XPS spectra were peak-divided using commercially available software, Peak Fit (v4.12, Systat Software). For comparison, a Pd(0)-loaded membrane was prepared by direct adsorption of Pd ions onto an aminated membrane (Supporting Information Figure S3). SiO_2 membranes were modified by *N*-(3-dimethylaminopropyl) trimethoxysilane. Details for amination of the SiO_2 membrane surface are given in the Supporting Information. The surfaces of the unmodified, NAS-activated, NP-immobilized, and Pd(0)-loaded membranes were observed using field-emission scanning electron microscopy (FE-SEM; Ultra55, Carl Zeiss NTS GmbH, Germany). SEM images were obtained using secondary electron (SE2) and energy selective backscattered (EsB) detectors.

Suzuki coupling reaction using Pd(0)-loaded membrane reactor

Four membrane sheets were joined using a connector, and the membrane reactor was placed in an incubator at 60°C (Supporting Information Figure S5). The reactant solution was prepared by dissolving phenylboronic acid (50 mmol L^{-1}), 4-iodebenzoic acid (55 mmol L^{-1}, 1.1 equivalent), and Na_2CO_3 (55 mmol L^{-1}, 1.1 equivalent) in water. The reactant solution was passed through the membrane reactor at various flow rates using a syringe pump (Harvard Pump 11 Plus Single Syringe, Harvard Apparatus). The effluent was continuously collected, and the concentrations of phenylboronic acid and 4-phenylbenzoic acid in the effluent were determined using a high performance liquid chromatography system (LC-2000Plus, JASCO Co., Japan) with a reverse phase column (Mightysil RP-18 GP 250-4.6, Kanto Chemical Co., Japan) and a UV detector. The mobile phase was a mixture solution of acetonitrile and water (50:50) with 0.1 v/v% trifluoroacetic acid. The amount of 4-phenylbenzoic acid produced by the membrane reactor and the turnover number (TON) were calculated using Eqs. 3 and 4, respectively

$$\text{Amount of 4-phenylbenzoic acid produced (mol g}_\text{M}^{-1}) = \int_0^v \frac{[\text{4-Phenylbenzoic acid}]}{W_\text{M}}\,dv \quad (3)$$

$$\text{TON}(-)=\frac{\text{Amount of 4-phenylbenzoic acid produced}}{\text{Amount of Pd adsorbed}} \quad (4)$$

Assuming that there are no spaces between the stacked membranes, the residence time (τ) was defined by Eq. 5

$$\tau(\text{h})=\frac{n\pi r^2 \varepsilon L}{V} \quad (5)$$

where n, r, ε, L, and V are the membrane sheet number, membrane radius, membrane porosity, membrane thickness, and flow rate, respectively. The kinetics of the reaction were analyzed based on the following pseudo-first-order reaction

$$ln(1-x)=-k_\text{obs}\tau \quad (6)$$

where x and k_{obs} are the conversion rate and the observed rate constant, respectively. The k_{obs} of the Pd(0)-loaded membrane reactor in the continuous-flow system was compared with that of Pd(0)-loaded NPs in the batch system. Details for the preparation of Pd(0)-loaded NPs and the Suzuki coupling reaction using the Pd(0)-loaded NPs are given in the Supporting Information.

Cycling usage of Pd(0)-loaded membrane reactor for Suzuki coupling reaction

Four membrane sheets were joined using a connector, and the membrane reactor was placed in an incubator at 60°C. The reactant solution was passed through the membrane reactor at 1.0 mL h^{-1} (τ; 2.2 h) until the conversion percentage into 4-phenylbenzoic acid reached a steady state. The used membranes were washed by alternate permeation with water and methanol at 5.0 and 1.0 mL h^{-1}, respectively, for a total of more than 10 h. The Pd(0)-loaded membrane reactor was reused for the Suzuki coupling reaction. The relative activity of the Pd(0) catalyst was estimated from the concentration of 4-phenylbenzoic acid in the steady-state effluent. The Suzuki coupling reaction and washing were repeated six times. The storage stability of the Pd(0)-loaded membrane reactor in a continuous-flow system was compared with that of Pd(0)-loaded NPs in a batch system. Details for the storage stability of the Pd(0)-loaded NPs are given in the Supporting Information. The leakage of the Pd(0) catalyst from the membrane reactor was confirmed from the concentration of Pd in the effluent and washing solutions. The concentration of Pd was determined using atomic absorption spectroscopy (AA-7000, Shimadzu Co., Japan). To evaluate the

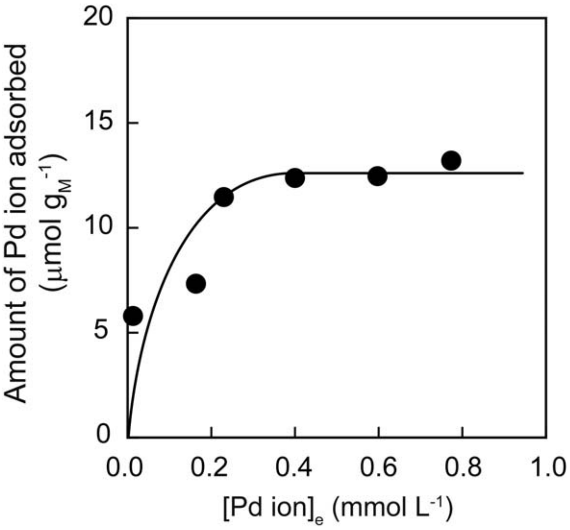

Figure 2. Adsorption isotherm for Pd ions on NPs immobilized on the membrane.

long-term stability of the Pd(0)-loaded membrane reactor, the reactant solution was incessantly passed through the membrane reactor at 1.0 mL h^{-1} for 6 days. The concentration of 4-phenylbenzoic acid in the effluent was monitored at 24 h intervals.

Results and Discussion

Preparation of Pd(0) catalysts

Polymeric NPs were synthesized by free-radical polymerization. The ratios of the NIPAm, amines (DMAPM and APM), and BIS units in the NPs were estimated to be 77:14:9, in agreement with the feed ratio (Supporting Information Figure S6). The theoretical amine density was 1190 μmol (tertiary amine: 790 μmol, primary amine: 400 μmol) per gram of the NPs. Dynamic light scattering (DLS) measurements showed that the NP hydrodynamic diameter was 383 nm (Supporting Information Figure S7). The size distribution in the DLS profile was relatively uniform (polydispersity index: 0.097), and NP aggregation was not observed. The NPs, therefore, had high dispersion stability. The maximum adsorption capacity of the NPs for Pd ions was 495 μmol per gram of NPs (Supporting Information Figure S8). Pd ions form anionic complexes with chlorides in HCl. It was, therefore, suggested that the Pd ions were adsorbed on the NPs via electrostatic and coordination interactions. When the Pd ions on the NPs in a solution medium were reduced by $NaBH_4$, the presence of Pd(0) particles with several nanometer was observed (Supporting Information Figure S9). The resulting Pd(0)-loaded NPs were used in a batch system for the Suzuki coupling reaction.

A Pd(0)-loaded membrane was also prepared by immobilization of NPs, adsorption of Pd ions, and reduction into Pd(0). The amount of NPs immobilized on the NAS-activated membrane was 40.3 mg g_M^{-1}, which corresponded to 48.0 μmol g_M^{-1} of the amine density. The Pd ions were then adsorbed onto the NP-immobilized membrane (Figure 2). The maximum adsorption capacity of the NP-immobilized membrane for Pd ions was 12.8 μmol g_M^{-1}. This adsorption capacity corresponded to 318 μmol per gram of NPs. The adsorption capacity of the NPs immobilized on the membrane was less than that of the NPs in solution media, because primary amine groups in the NPs were used for immobilization and the mass-transfer resistance of Pd ions to the NPs in the membrane pores was enhanced. When Pd(0)-loaded NPs were immobilized on the NAS-activated membrane, the amount of Pd(0)-loaded NPs was 10 times smaller than the amount of normal NPs. Pd ions were not adsorbed on the unmodified SiO_2 membrane. The amount of Pd ions adsorbed on the aminated membrane was 7.9 μmol g_M^{-1} (see the Supporting Information). When the Pd ions adsorbed on the membranes were reduced by $NaBH_4$, the membranes became brown.

Confirmation of presence of Pd(0) on membrane surface

The XPS spectra of the unmodified, NAS-activated, NP-immobilized, and Pd(0)-loaded surfaces were obtained (Figure 3). In the C(1s) spectrum of the NAS-activated surface, the peak corresponding to C—N and C—O was observed at around 286 eV, and the peak corresponding to C═O was observed at 288.1 eV. However, the expected characteristic peaks were not detected in the N(1s) spectrum of the NAS-activated surface, as a result of the low elemental percentage of nitrogen in poly(TMSMA-*r*-NAS). When the NPs were immobilized, the peak intensities in the C(1s) spectrum increased significantly. Moreover, a peak corresponding to multiple amide and amine groups was clearly observed at 400 eV in the N(1s) spectrum. In the Pd(3d) spectrum of the Pd(0)-loaded surface, two peaks appeared in the range from 335 to 345 eV, confirming the presence of Pd.

The Pd(0) catalysts loaded on the membranes were observed using FE-SEM (Figure 4). FE-SEM images of the unmodified, NAS-activated, NP-immobilized, and Pd(0)-loaded (via an aminated membrane) membranes were also obtained (Supporting Information Figure S10). The FE-SEM images obtained using an SE2 detector showed that the fiber structures were retained in all the membranes, suggesting that the NAS-activated, NP-immobilized, and Pd(0)-loaded membranes had high porosities. In general, the FE-SEM image using an EsB detector is vibrantly observed with increasing the number of atoms. The parts, that were brighter than the SiO_2 fiber matrix, indicated Pd atoms. The brighter parts, that is, the Pd(0) catalysts, were finely observed on the Pd(0)-loaded membranes in the FE-SEM image obtained using the EsB detector. The Pd(0) catalysts were also distributed at the membrane cross-section. The sizes of Pd(0) in the NP-immobilized and aminated membranes were different; those in the NP-immobilized membrane were small, whereas those in the aminated membrane formed the aggregates of size ca. 1 μm. The incorporation of small Pd(0) particles in the NP-immobilized membrane was visually confirmed.

Continuous-flow Suzuki coupling reaction using Pd(0)-loaded membranes

The catalytic activities of Pd(0)-loaded membranes for the continuous-flow Suzuki coupling reaction between phenylboronic acid and 4-iodebenzoic acid were evaluated. The TONs for 4-phenylbenzoic acid production using Pd(0) loaded on NP-immobilized and aminated membrane reactors are shown in Figure 5. After the catalytic reactions reached a steady state, the amounts of 4-phenylbenzoic acid produced increased linearly with reactant solution permeation. The TON using Pd(0) loaded on the NP-immobilized membrane reactor was more than double that using Pd(0) loaded on the

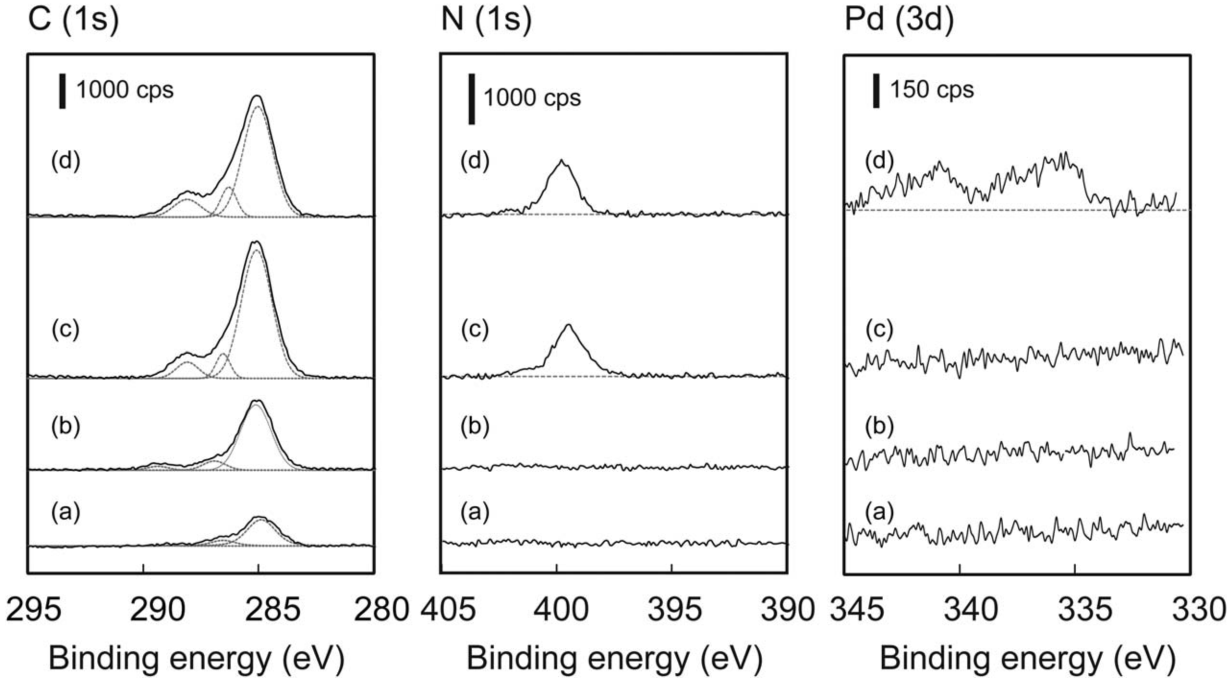

Figure 3. XPS spectra of (a) unmodified, (b) NAS-activated, (c) NP-immobilized, and (d) Pd(0)-loaded surfaces.

aminated membrane reactor. The turnover frequencies (TOFs) for Pd(0) loaded on NP-immobilized and aminated membrane reactors were 9.3 and 4.7 h^{-1}, respectively. In general, the TOFs of transition-metal catalysts are inversely proportional to the particle size,[34] that is, the surface area. Catalysts with small particles have high catalytic reactivities because of their high surface-to-volume ratios. Figure 4 showed that Pd(0) catalysts loaded on the aminated membrane were aggregated. Aggregation led to a decrease in the effective surface area, so the catalytic activity in the Suzuki

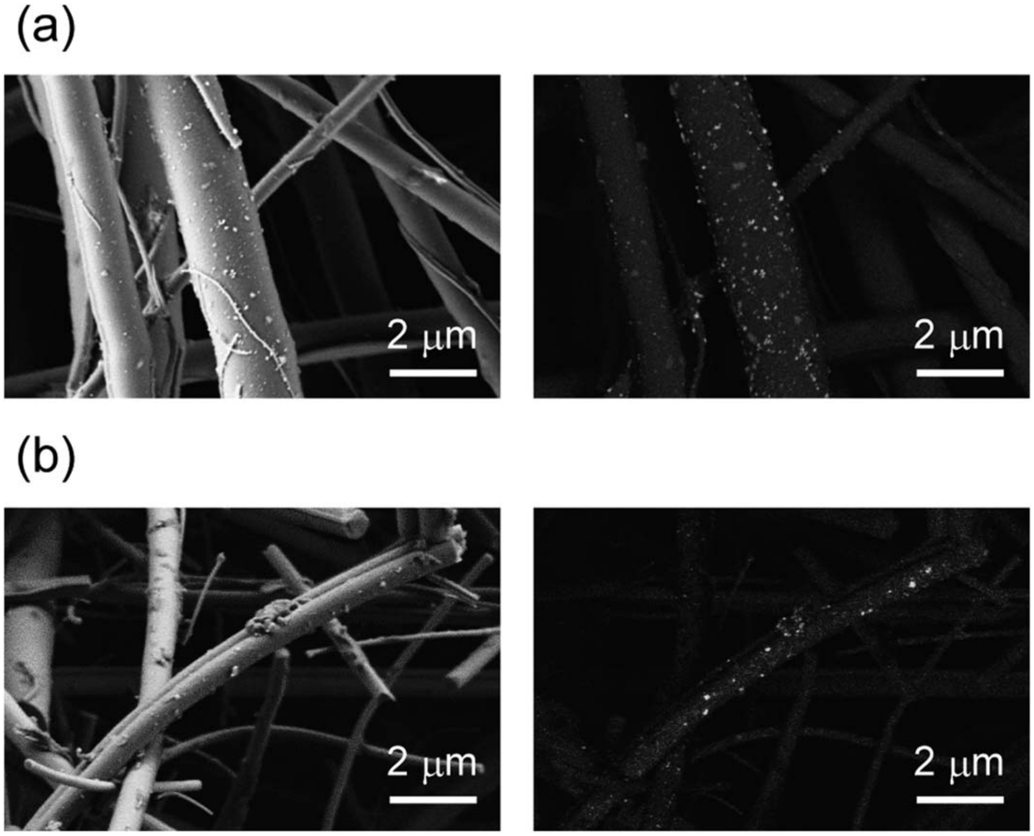

Figure 4. SEM images of Pd(0) loaded on NP-immobilized membrane at (a) plane and (b) cross-sectional surfaces.

The left-hand and right-hand images were obtained using SE2 and EsB detectors, respectively.

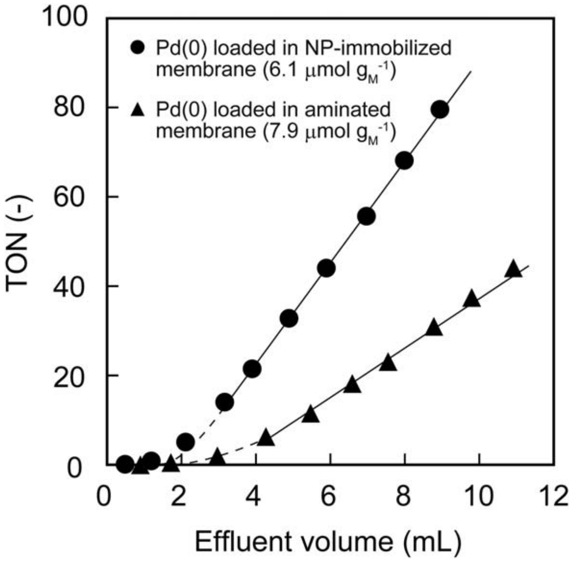

Figure 5. Turnover numbers of continuous-flow Suzuki coupling reaction for 4-phenylbenzoic acid production using Pd(0) loaded on NP-immobilized and aminated membranes, at 2.2 h residence time.

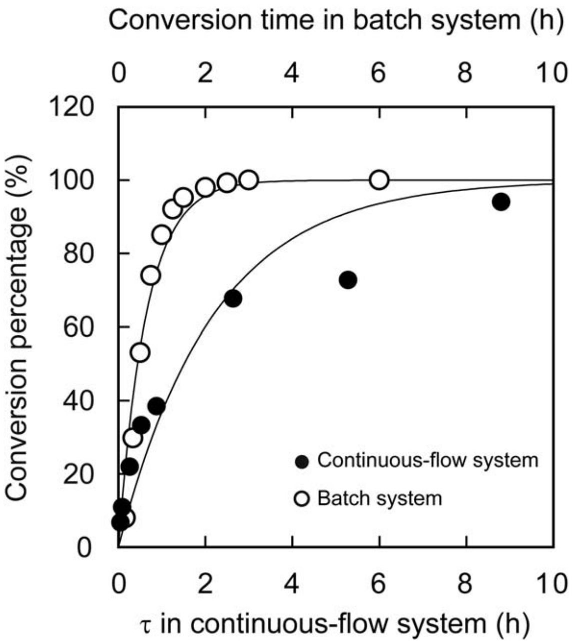

Figure 6. Effect of residence time on conversion percentages in Suzuki coupling reaction using Pd(0)-loaded membrane in continuous-flow system, and comparison with time conversion curve using Pd(0)-loaded NPs in batch system.

The solid lines represent the curve fitted using Eq. 6. R^2: 0.8909 (continuous-flow system) and 0.9531 (batch system).

coupling reaction was low. In contrast, the use of NPs effectively dispersed the Pd(0) catalyst, and led to high catalytic activity.

The kinetics of the Suzuki coupling reaction using the Pd(0)-loaded membrane reactor in a continuous-flow system and the Pd(0)-loaded NPs in a batch system were compared. The effect of residence time on the conversion into 4-phenylbenzoic acid using the Pd(0)-loaded membrane in a continuous-flow system is shown in Figure 6, along with the time conversion curve using Pd(0)-loaded NPs in a batch system. The reactants were completely converted into 4-phenylbenzoic acid within 2 h in the batch system. When the Pd(0)-loaded membrane reactor was used, the conversion percentage increased with increasing residence time. In the continuous-flow system, 4-phenylbenzoic acid is produced via three steps: (1) mass transfer of phenylboronic acid and 4-iodebenzoic acid to the NPs immobilized in the membrane pores; (2) NP-internal diffusion of phenylboronic acid and 4-iodebenzoic acid to the Pd(0) catalyst; and (3) catalytic conversion into 4-phenylbenzoic acid by Suzuki coupling reaction. The results demonstrate that the rate-determining step for the continuous-flow Suzuki coupling reaction is the first step. The k_{obs} values in the batch and continuous-flow systems using Pd(0)-loaded NPs were 1.6 and 0.46 h^{-1}, respectively. The TOF for Pd(0)-loaded NPs in batch system was 145 h^{-1}. The NPs had high dispersibility in water, whereas the mobility of Pd(0) loaded on the membrane was lost.

Storage and long-term stabilities of Pd(0)-loaded membrane reactor

The storage stability of Pd(0) loaded on the NP-immobilized membrane was investigated by alternating the Suzuki coupling reaction and washing. The relative activity of the Pd(0) catalyst in the continuous-flow system was compared with that in the batch system (Figure 7). When the Pd(0)-loaded membrane reactor was reused for the Suzuki coupling reaction, its activity was maintained (more than 80%). Repeated use of the Pd(0) catalyst was possible. The slight decrease in the activity could be attributed to an increase in the size of the Pd(0) particles in the NPs (Supporting Information Figure S11).The relative activity of Pd(0) reused six times in the batch system was one-quarter (Supporting Information Figure S12). Although all the reactants were converted into 4-phenylbenzoic acid in the batch system, the conversion rate became slow as a result of the

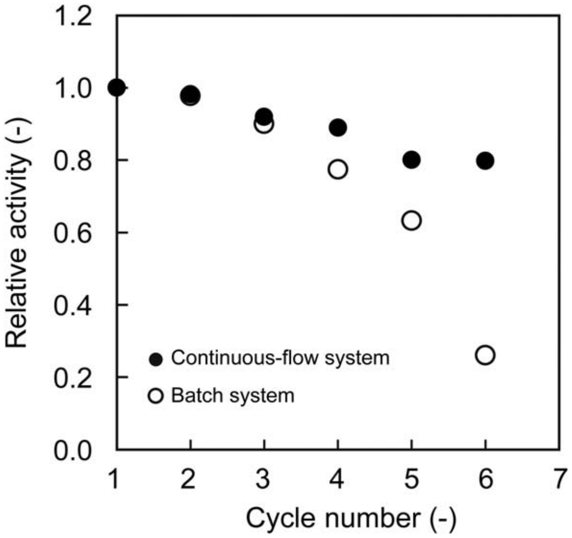

Figure 7. Storage stabilities of Pd(0)-loaded membrane in continuous-flow system and Pd(0)-loaded NPs in batch system for Suzuki coupling reaction.

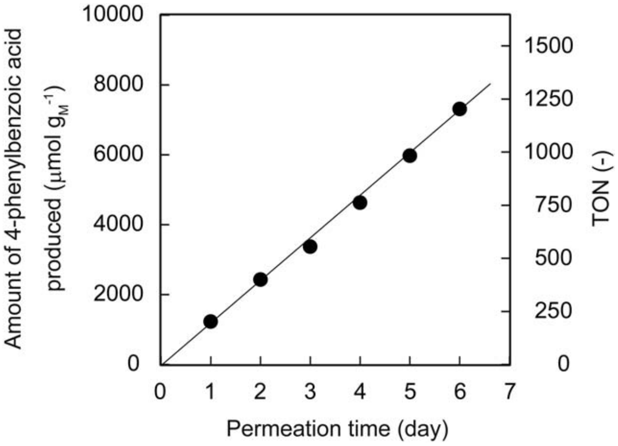

Figure 8. Long-term production of 4-phenylbenzoic acid using Pd(0)-loaded membrane in continuous-flow system for Suzuki coupling reaction.

reduction in the Pd(0) surface area. During use of the recycled Pd(0)-loaded membrane reactor for the Suzuki coupling reaction, leakage of Pd(0) catalyst into the effluent and washing solutions was not detected. Even when the Pd(0)-loaded membrane reactor was reused six times, the leakage percentage of the Pd(0) catalyst from the membrane was less than 1%. The XPS spectrum and FE-SEM images indicate that the Pd remained on the membrane that had been reused six times (Supporting Information Figures S13 and S14). Because recovery of the Pd(0) catalyst from the product solution and washing of the Pd(0) catalyst are easy, immobilization on the membrane improved the storage stability of the Pd(0) catalyst.

The long-term stability of the Pd(0)-loaded membrane reactor was also investigated by a continuous Suzuki coupling reaction for 6 days. The amount of 4-phenylbenzoic acid produced using the Pd(0)-loaded membrane in the continuous-flow system is shown in Figure 8. When the Pd(0)-loaded membrane reactor was used for the Suzuki coupling reaction over a long time, it retained the catalytic activity. The Pd(0)-loaded membrane reactor produced 1200 μmol g_M^{-1} of 4-phenylbenzoic acid per one day. The TON using the Pd(0)-loaded membrane reactor reached 1200 in 6 days. This corresponds to 2.7×10^4 molecules nm^{-2}, which is the activity normalized by the surface area of a Pd(0) particle. After operation of the Pd(0)-loaded membrane for 6 days, the presence of Pd on the membrane was confirmed (Supporting Information Figures S13 and S14). In addition, the fibrous structures of the used membrane were maintained. No limitation on the catalyst lifetime was observed. Because the Pd(0)-loaded membrane reactor has long-term stability, larger amounts of biphenyl can be produced using a continuous Suzuki coupling reaction over the long term.

Conclusions

In summary, a Pd(0)-loaded membrane reactor was developed for the Suzuki coupling reaction between aryl halide and phenyl boronic acid. In the continuous-flow Suzuki coupling reaction, the catalytic activity of Pd(0) loaded on the NP-immobilized membrane reactor was higher than that on the aminated membrane reactor, because the Pd(0) aggregates were not formed on the NP-immobilized membrane. Although the observed rate constant in the continuous-flow system was less than that in the batch system, the storage stability of the Pd(0) catalyst was improved by immobilization on the membrane. It was not necessary to recover the catalyst from the products and remaining reactants, because there was no leakage of Pd, and the Pd(0)-loaded membrane reactor was reusable. In addition, the Pd(0)-loaded membrane reactor had high long-term stability. Chemical transformation in fully aqueous media, which is a goal in green chemistry, was achieved using a Pd(0)-loaded membrane reactor. The rate constant in the continuous-flow Suzuki coupling reaction using the Pd(0)-loaded membrane reactor emphasizes the need for improvement. The small rate constant is attributed to the low density of Pd catalyst in the membrane reactor. Densification of the Pd catalyst in the membrane leads to construction of a superior continuous-flow system. There is still a paucity of reaction-engineering investigations of the continuous-flow Suzuki coupling reaction. This reactor is expected to be applicable to a wide range of catalytic reactions such as allylic arylation, Heck, Sonogashira, and Buchwald–Hartwig reactions. The development of continuous-flow systems for chemical transformations has industrial significance and is a step toward sustainable manufacturing.

Acknowledgments

This work was supported by a Grant-in-Aid for JSPS Fellows (25.5206), a Grant-in-Aid for Challenging Exploratory Research (24655157), and a Grant-in-Aid for Young Scientists (A) (23685027).

Literature Cited

1. Diederich F, Stang PJ. *Metal-Catalyzed Cross-Coupling Reactions*. New York: Wiley-VCH, 1998.
2. Nicolaou KC, Bulger PG, Sarlah D. Palladium-catalyzed cross-coupling reactions in total synthesis. *Angew Chem Int Ed*. 2005;44: 4442–4489.
3. Kidambi S, Dai J, Li J, Bruening ML. Selective hydrogenation by Pd nanoparticles embedded in polyelectrolyte multilayers. *J Am Chem Soc*. 2004;126:2658–2659.
4. Bhandari R, Knecht MR. Isolation of template effects that control the structure and function of nonspherical, biotemplated Pd nanomaterials. *Langmuir*. 2012;28:8110–8119.
5. Uozumi Y, Danjo H, Hayashi T. Palladium-catalyzed asymmetric allylic substitution in aqueous media using amphiphilic resin-supported MOP ligands. *Tetrahedron Lett*. 1998;39:8303–8306.
6. Danjo H, Tanaka D, Hayashi T, Uozumi Y. Allylic substitution in water catalyzed by amphiphilic resin-supported palladium-phosphine complexes. *Tetrahedron*. 1999;55:14341–14352.
7. Roucoux A, Schultz J, Patin H. Reduced transition metal colloids: a novel family of reusable catalysts? *Chem Rev*. 2002;102:3757–3778.
8. Balanta A, Godard C, Claver C. Pd nanoparticles for C-C coupling reactions. *Chem Soc Rev*. 2011;40:4973–4985.
9. Uozumi Y. Recent progress in polymeric palladium catalysts for organic synthesis. *Top Curr Chem*. 2004;242:77–112.
10. Akiyama R, Kobayashi S. The polymer incarcerated method for the preparation of highly active heterogeneous palladium catalysts. *J Am Chem Soc*. 2003;125:3412–3413.
11. Okamoto K, Akiyama R, Kobayashi S. Recoverable, reusable, highly active, and sulfur-tolerant polymer incarcerated palladium for hydrogenation. *J Org Chem*. 2004;69:2871–2873.
12. Okamoto K, Akiyama R, Kobayashi S. Suzuki-Miyaura coupling catalyzed by polymer-incarcerated palladium, a highly active, recoverable, and reusable Pd catalyst. *Org Lett*. 2004;6:1987–1990.
13. Hagiwara H, Sugawara Y, Isobe K, Hoshi T, Suzuki T. Immobilization of Pd(OAc)$_2$ in ionic liquid on silica: application to sustainable Mizoroki-Heck reaction. *Org Lett*. 2004;6:2325–2328.
14. Nishio R, Sugiura M, Kobayashi S. Novel polymer incarcerated palladium with phosphinated polymers: active catalyst for Suzuki-

Miyaura coupling without external phosphines. *Org Lett*. 2005;7: 4831–4834.

15. Hagio H, Sugiura M, Kobayashi S. Practical preparation method of polymer-incarcerated (PI) palladium catalysts using Pd(II) salts. *Org Lett*. 2006;8:375–378.
16. Wei G, Zhang W, Wen F, Wang Y, Zhang M. Suzuki reaction within the core-corona nanoreactor of poly(*N*-isopropylacrylamide)-grafted Pd nanoparticle in water. *J Phys Chem C*. 2008;112:10827–10832.
17. Fujii S, Matsuzawa S, Nakamura Y, Ohtaka A, Teratani T. Synthesis and characterization of polypyrrole-palladium nanocomposite-coated latex particles and their use as a catalyst for Suzuki coupling reaction in aqueous media. *Langmuir*. 2010 26 6230–6239.
18. Ohtaka A, Kono Y, Teratani T, Fujii S, Matsuzawa S, Nakamura Y, Nomura R. Polypyrrole-palladium nanocomposite-coated latex particles as a heterogeneous catalyst in water. *Catal Lett*. 2011;141: 1097–1103.
19. Yamada YMA, Sarkar SM, Uozumi Y. Self-assembled poly(imidazole-palladium): highly active, reusable catalyst at parts per million to parts per billion levels. *J Am Chem Soc*. 2012;134:3190–3198.
20. Crudden CM, Sateesh M, Lewis R. Mercaptopropyl-modified mesoporous silica: a remarkable support for the preparation of a reusable, heterogeneous palladium catalyst for coupling reactions. *J Am Chem Soc*. 2005;127:10045–10050.
21. Hagiwara H, Sugawara Y, Hoshi T, Suzuki T. Sustainable Mizoroki-Heck reaction in water: remarkably high activity of $Pd(OAc)_2$ immobilized on reversed phase silica gel with the aid of an ionic liquid. *Chem Commun*. 2005;2942–2944.
22. Kobayashi S. The new world of organic reactions in water. *Pure Appl Chem*. 2013;85:1089–1101.
23. Seto H, Morii T, Yoneda T, Murakami T, Hoshino Y, Miura, Y. Preparation of palladium-loaded polymer nanoparticles with catalytic activity for hydrogenation and Suzuki coupling reactions. *Chem Lett*. 2013;42:301–303.
24. Hoshino Y, Nakamoto M, Miura Y. Control of protein-binding kinetics on synthetic polymer nanoparticles by tuning flexibility and inducing conformation changes of polymer chains. *J Am Chem Soc*. 2012;134:15209–15212.
25. Jas G, Kirschning A. Continuous flow techniques in organic synthesis. *Chem Eur J*. 2003;9:5708–5723.
26. Wiles C, Watts P. Continuous flow reactors, a tool for the modern synthetic chemist. *Eur J Org Chem*. 2008;2008:1655–1671.
27. Noël T, Buchwald SL. Cross-coupling in flow. *Chem Soc Rev*. 2011; 40:5010–5029.
28. Thömmes J, Kula MR. Membrane chromatography-An integrative concept in the downstream processing of proteins. *Biotechnol Prog*. 1995;11:357–367.
29. Uozumi Y, Yamada YMA, Beppu T, Fukuyama N, Ueno M, Kitamori T. Instantaneous carbon-carbon bond formation using a microchannel reactor with a catalytic membrane. *J Am Chem Soc*. 2006;128:15994–15995.
30. Yamada YMA, Watanabe T, Beppu T, Fukuyama N, Trii K, Uozumi Y. Palladium membrane-installed microchannel devices for instantaneous Suzuki-Miyaura cross-coupling. *Chem Eur J*. 2010;16: 11311–11319.
31. Li H, Gao X, Ding H, Yang M, Pu Q. Highly efficient Suzuki cross-coupling reaction within an open channel plastic microreactor immobilized with palladium complexes. *Microfluid Nanofluid*. 2012;12: 981–989.
32. Suzuki A. Cross-coupling reactions of organoboranes: an easy way to construct C-C bonds (Nobel lecture). *Angew Chem Int Ed*. 2011; 50:6722–6737.
33. Park S, Lee KB, Choi IS, Langer R, Jon S. Dual functional, polymeric self-assembled monolayers as a facile platform for construction of patterns of biomolecules. *Langmuir*. 2007;23:10902–10905.
34. Jia C-J, Schüth F. Colloidal metal nanoparticles as a component of designed catalyst. *Phys Chem Chem Phys*. 2011;13:2457–2487.

Manuscript received June 6, 2014, and revision received Sep. 11, 2014.