Supporting Information

Macroporous Gel with Permeable Reaction Platform for Catalytic Flow Synthesis

Hikaru Matsumoto,† Hirokazu Seto,† Takanori Akiyoshi,† Makoto Shibuya,†
Yu Hoshino,† and Yoshiko Miura*,†

† Department of Chemical Engineering, Kyushu University, 744 Motooka, Nishi-ku,
Fukuoka 819-0395, Japan.

‡ Department of Chemical Engineering, Fukuoka University, 8-19-1 Nanakuma,
Joonan-ku, Fukuoka 814-0180, Japan.

*E-mail: miuray@chem-eng.kyushu-u.ac.jp

Tel: +81-92-802-2749

Fax: +81-92-802-2769
Supporting Information

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1. Preparation of MPGs with different gel network sizes

Scheme S1. Synthesis of monolithic porous gel (MPG) with a tertiary-amino group above the lower critical solution temperature of PNIPAm.

Monolithic porous gels (MPGs) were synthesized by the copolymerization of N-isopropylacrylamide (NIPAm) with tertiary-aminated and crosslinking monomers at above the lower critical solution temperature of PNIPAm (Scheme S1). NIPAm (100-10-x mol%), N-(3-dimethylaminopropyl)methacrylamide (DMAPM, 10 mol%), and N,N'-methylenebisacrylamide (BIS, x = 5, 10, and 30 mol%, giving MPG1, MPG2, and MPG3, respectively) were dissolved in water with a total monomer concentration of 1500 mmol L\(^{-1}\) according to the previous report (H. Seto et al. Appl. Polym. Sci. 2017, 134, 44385). The monomer solutions were degassed with nitrogen gas for more than 30 min, followed by the addition of 2,2'-azobis(2-aminopropane) dihydrochloride (AAPD) as a radical initiator (1 mol% of total monomers) to each solution. The mixed solutions (3.14 mL) were poured into glass vials with inner diameters of 20 mm, which were then incubated at 70°C for 3 h. The cylindrical MPGs were removed from the vials, and washed with a sufficient volume of water for more than 1 day. From H\(^+\) adsorption experiments, amine densities in the MPG1, MPG2, and MPG3 were estimated to be 707, 740, and 650 µmol g\(^{-1}\), respectively.

The difference of gel network sizes of the MPG1–3 was confirmed by the evaluation of swelling properties of the MPGs in water. The bulk volumes of the MPGs in water were estimated from their sizes at various temperature and dry weights (Figure S1a). At 30°C, the bulk volumes of the MPG1, MPG2, and MPG3 were 9.8, 7.3, and 5.4 cm\(^3\) g\(^{-1}\), respectively. In particular, the MPG1 showed a drastic change in its bulk volume around 30°C. The thermoresponsiveness was suppressed by increasing the BIS contents.

After loading of Pd(0), the bulk densities of Pd(0)-loaded MPGs (Pd/MPGs) were also determined in the same manner (Figure S1b). At 30°C, the bulk volumes of the Pd/MPG1, Pd/MPG2, and Pd/MPG3 were 10.4, 7.9, and 5.3 cm\(^3\) g\(^{-1}\), respectively. The Pd/MPGs also showed swelling properties similar to those of the original MPGs.
Figure S1. Bulk volumes of MPG1, MPG2, and MPG3 (BIS contents of 5, 10, and 30 mol%) (a) before and (b) after loading of Pd(0), v.s. temperature diagram.
2. Evaluation of internal structure and porous property of Pd/MPG

The internal structures of Pd/MPGs were observed using field emission scanning electron microscopy (FE-SEM, SU8000, Hitachi High-Technologies Corporation, Tokyo, Japan) after lyophilization (Figure S2). Before observation, the Pd/MPGs surfaces were coated with platinum (thickness: approx. 4 nm) using an auto fine coater (JFC-1600, JEOL Ltd., Tokyo, Japan).

The pore size distributions in the Pd/MPGs were determined using a mercury porosimetry (AutoPoreIV9520, Micromeritics Instrument Co., Norcross, GA, USA) after lyophilization (Figure S3 and Table S1). In dry state, the Pd/MPGs had macropores with the median pore sizes of several hundred nanometers to several micrometers. The median pore sizes and surface areas of the Pd/MPGs decreased and increased with increasing their BIS contents, respectively.

![Figure S2. SEM images of Pd/MPG1, Pd/MPG2, and Pd/MPG3 (BIS contents of 5, 10, and 30 mol%).](image)
Figure S3. Pore size distributions of Pd/MPG1, Pd/MPG2, and Pd/MPG3 (BIS contents of 5, 10, and 30 mol%).

Table S1. Median pore sizes and surface areas of Pd/MPGs.

| Entry   | BIS content (mol%) | Median pore size (nm) | Surface area (m² g⁻¹) |
|---------|--------------------|-----------------------|-----------------------|
| Pd/MPG1 | 5                  | 8497                  | 6.0                   |
| Pd/MPG2 | 10                 | 3312                  | 7.6                   |
| Pd/MPG3 | 30                 | 805                   | 12.7                  |
3. Preparation of Pd/MPGs

Pd/MPGs were prepared by the adsorption of Pd(II) ions and subsequent reduction. The MPGs were cut into 3 mm-thick section after washing in water without lyophilization. The MPGs were immersed in K$_2$PdCl$_4$ (0.1 mmol L$^{-1}$) solutions dissolved in 10 mmol L$^{-1}$ aqueous HCl solutions, then incubated at 30°C for 72 h. After washing the Pd(II)-adsorbed MPGs in water, the Pd(II) ions were reduced into Pd(0) by immersion in aqueous NaBH$_4$ solutions (pH 8) at 30°C for 72 h. The solid/liquid ratio was set to 180 mg of the dry MPG for 90 mL of the solution.

The Pd(0) loaded in the MPGs were observed using transmission electron microscopy (TEM, TECNAI 20, Philips FEI, Netherlands, Figure S4a). It was revealed that the average sizes of the Pd(0) loaded in the MPG1, MPG2, and MPG3 (BIS contents of 5, 10, and 30 mol%) were 2.4 ± 0.7, 2.2 ± 0.7, and 2.1 ± 0.7 nm, respectively. The Pd(0) loaded in the MPGs did not aggregate after long-term use in Suzuki coupling reaction (Figure S4b).

![Figure S4. TEM images of Pd/MPG1, Pd/MPG2, and Pd/MPG3 (BIS contents of 5, 10, and 30 mol%) (a) before and (b) after 30-days uses in Suzuki coupling reaction.](image-url)
4. Preparation of Pd/nonporous gel

Nonporous gels were prepared by the copolymerization of NIPAm with tertiary-aminated and crosslinking monomers at below the lower critical solution temperature of PNIPAm (Figure S5). NIPAm (100-10-x mol%), DMAPM (10 mol%), and BIS (x = 5, 10, and 30 mol%) were dissolved in water with a total monomer concentration of 1500 mmol L\(^{-1}\). The monomer solutions were degassed with nitrogen gas for more than 30 min, followed by the addition of ammonium persulfate (APS, Sigma-Aldrich Co., St. Louis, MO, USA) and \(N,N,N',N'\)-tetramethylethylenediamine (TEMED, Sigma-Aldrich Co.) as a radical initiator and an accelerator (1 and 11 mol% of total monomers), respectively. The mixed solutions (3.14 mL) were poured into glass vials with inner diameters of 20 mm, which were then incubated at 0°C for 3 h. The cylindrical gels were removed from the vials, and washed with sufficient volume of water for more than 1 day.

Pd(0)-loaded nonporous gel (Pd/nonporous gel) was prepared by the adsorption of Pd(II) ions and subsequent reduction. The nonporous gel with BIS content of 5 mol% was cut into 3 mm-thick section after washing in water without lyophilization. The gel was immersed in \(\text{K}_2\text{PdCl}_4\) (0.1 mmol L\(^{-1}\)) solution dissolved in 10 mmol L\(^{-1}\) aqueous HCl solution, then incubated at 30°C for 72 h. After washing the Pd(II)-adsorbed gel in water, the Pd(II) ions were reduced into Pd(0) by immersing them in aqueous NaBH\(_4\) (pH 8) solution at 30°C for 72 h. The solid/liquid ratio was set to 180 mg of the dry gel for 90 mL of the solution.
Figure S5. Synthesis of nonporous gels using redox polymerization below the lower critical solution temperature of PNIPAm. The appearance of the gel is shown inset (BIS content of 5 mol%).

\[ \text{NIPAm (100-10-}x \text{ mol\%)} + \text{DMAPM (10 mol\%)} + \text{BIS (}x \text{ mol\%)} \]

\[ \text{APS (1 mol\%) / TEMED (11 mol\%)} \]

\[ \text{Water, 0°C} \]

* \( x = 5, 10, \text{ or 30 mol\%} \)

Nonporous gel
5. Preparation and characterization of Pd-loaded inorganic supports

Tertiary-aminated porous glass membrane and silica particles were synthesized using silane-coupling reaction similar to that of the previous report (K. Shimizu et al. *Tetrahedron Lett.* 2002, 43, 9073–9075). Porous glass membrane (mean pore size: 2000 nm, 20 mmφ, 90 g L⁻¹, SPG Technology Co. Ltd., Miyazaki, Japan) or silica particles (particle size: 40-63 µm, 200 g L⁻¹, Merck Co., Darmstadt, Germany), and N,N-(dimethylaminopropyl)tri-methoxysilane (DMAPTMS, 9 or 100 mmol L⁻¹, Sigma-Aldrich Co.) were added to toluene, and stirred at 110°C for 3 h. After washing with toluene and acetone, the resulting supports were dried in vacuo at room temperature. From H⁺ adsorption experiments, amine densities on the porous glass membrane and silica particles were determined to be 57.6 and 780 μmol g⁻¹, respectively.

Pd(0)-loaded porous glass membrane (Pd/porous glass membrane) and silica particles (Pd/silica particles) were prepared by the adsorption of Pd(II) ions and subsequent reduction. The tertiary-aminated porous glass membrane and silica particles were immersed in K₂PdCl₄ (0.1 mmol L⁻¹) solution dissolved in 10 mmol L⁻¹ aqueous HCl solution, then incubated at 30°C for 72 h. After washing the Pd(II)-adsorbed supports in water, the Pd(II) ions were reduced into Pd(0) by immersion in aqueous NaBH₄ solution (pH 8) at 30°C for 72 h. The solid/liquid ratio was 180 mg of the dry inorganic support for 90 mL of the solution. After washing the Pd/porous glass membrane and Pd/silica particles in water, they were lyophilized before or after catalytic reactions. Pd loaded on the supports and Pd/C were observed using TEM (Figure S6a). It was revealed that the average sizes of the Pd loaded on the porous glass membrane, silica particles, and carbon were 2.1 ± 0.6, 2.0 ± 0.4, and 2.5 ± 0.5 nm, respectively. The Pd(0) loaded on the supports did not aggregate after long-term use in Suzuki coupling reaction (Figure S6b).

Pd/porous glass membrane, Pd/silica particles, and Pd/C were immersed in aqua regia for 24 h. The eluent was analyzed using inductively coupled plasma-atomic emission spectroscopy (ICP-AES, ICPS-8100, Shimadzu Corporation, Kyoto, Japan). The amounts of the Pd loaded on the porous glass membrane, silica particles, and carbon were estimated to be 1.6, 6.3, and 131 μmol cm⁻³, respectively.
Figure S6. TEM images of Pd/porous glass membrane and Pd/silica particles (a) before and (b) after 30-days uses in Suzuki coupling reaction.
6. Permeability of continuous-flow reactor

The water permeabilities of support materials were evaluated for application in a continuous-flow process. Pressure loss changes during water permeating through a MPG1 and a nonporous gel at 30°C were measured (Figure S7a). When water permeated through the MPG1 at a flow rate of 100 mL h⁻¹, moderate pressure loss was achieved at steady state. However, using the nonporous gel, pressure loss was much high under the same condition and drastically increased with increasing the permeation volume.

Using MPG1–3, porous glass membrane, and silica particles, pressure losses at steady state were determined at various flow rate. Water permeabilities ($k_D$) were evaluated using the Darcy’s law, as follows;

$$\frac{\Delta P A}{\mu L} = \frac{1}{k_D} Q$$

where $\Delta P$, $\mu$, $L$, $A$, and $Q$ are the pressure loss, water viscosity, thickness, base area, and flow rate, respectively. The pressure losses were proportional to the flow rates up to at least 400 mL h⁻¹, in which the reciprocal of the slope corresponded to the permeation coefficient in the Darcy’s law (Figure S7b). The $k_D$ of the support materials were estimated to be around $10^{-14}$ and $10^{-13}$ m², which were comparable to those of hydrophilic polytetrafluoroethylene membrane filters (Omnipore, Millipore Co., Billerica, MA, USA) with the pore size range of 1000–10000 nm (H. Seto et al. J. Mater. Chem. B 2017, 5, 1148–1154).

The permeabilities of Pd(0)-loaded supports were also determined in the same condition (Figure S7c). All the $k_D$ did not significantly changed after loading of Pd(0).
Figure S7. Water permeation properties of MPGs at 30°C. (a) Pressure loss changes along with water permeating through MPG and nonporous gel (BIS content: 5 mol%). (b) Pressure loss v.s. flow rate of water diagram using support materials before loading of Pd(0). (c) Pressure loss v.s. flow rate of water diagram using Pd-loaded support materials.
7. Suzuki coupling reactions in the batch system

Scheme S2. Suzuki coupling reaction between phenylboronic acid (1) and aryl halide (2) to give biphenyl (3) in batch system.

Suzuki coupling reactions of phenylboronic acid (1) and 4-bromobenzoic acid (2, X = Br, R = COOH) to give 4-phenylbenzoic acid (3, R = COOH) in aqueous Na$_2$CO$_3$ solution were conducted using Pd/MPG1, Pd/nonporous gel (BIS content: 5 mol%), Pd/porous glass membrane, Pd/silica particles, and Pd/C in batch system (Scheme S2). The reactions were initiated by addition of the catalysts to solutions of 1 (10 mmol L$^{-1}$) and 2 (11 mmol L$^{-1}$, 1.1 eq.) in aqueous Na$_2$CO$_3$ (11 mmol L$^{-1}$, 1.1 eq.). The solutions were shaken at 30 °C for 36 h. The solid/liquid ratio was set to 5 mg of dry gel for every 5 mL of solution. Small aliquots from the reaction mixture were analyzed using a high-performance liquid chromatography (HPLC, LC-2000Plus, JASCO CO., Tokyo, Japan) system with a reverse phase column (Mightysil RP18 GP 250-4.6, Kanto Chemical Co., Tokyo, Japan) and an ultraviolet detector. Acetonitrile and water (50:50) containing 0.1 vol% trifluoroacetic acid was employed as a mobile phase. After reactions, the catalysts were immersed in aqua regia for 24 h. Using ICP-AES, the eluent was analyzed to estimate the amount of Pd added to the system. The initial molar ratio of 1 to Pd in the reaction mixture was around 500–1000. Percentage conversions into 3 and turnover numbers (TONs) of the Pd(0)-loaded supports were estimated (Table S2).

Suzuki coupling reaction between 1 and other types of aryl halides (2) under batch condition was also conducted using Pd/MPG1 (Table S3). The percentage conversions were estimated using similar method as mentioned above. When aryl iodides or bromides were used, almost all the substrates were converted into 3 successfully. However, the conversions of aryl chlorides into 3 were not observed using Pd/MPG1.
**Table S2.** Catalytic activities of Pd(0)-loaded supports in Suzuki coupling reaction

| Pd(0)-loaded support       | Percentage conversion into 3 (%) | TON  |
|----------------------------|----------------------------------|------|
| Pd/MPG1                    | 99                               | 987  |
| Pd/nonporous gel           | 74                               | 520  |
| Pd/porous glass membrane   | 41                               | 248  |
| Pd/silica particles        | 99                               | 1004 |
| Pd/C                       | 68                               | 720  |

*a* Conditions: 1 (10 mmol L⁻¹), 2 (11 mmol L⁻¹), Na₂CO₃ (11 mmol L⁻¹), Pd(0)-loaded support (0.09–0.16 mol%), water, 30°C, 36 h.  

*b* Determined from concentration of 3 after reaction using HPLC.

**Table S3.** Catalytic activities of Pd/MPG1 in Suzuki coupling reaction using various aryl halides

| Entry | Aryl halide (2) | Product (3) | Percentage conversion into 3 (%) |
|-------|-----------------|-------------|----------------------------------|
| 1     | ![I-phenyl](image) | ![Phenyl](image) | 98                               |
| 2     | ![I phenol](image) | ![Phenol](image) | 92                               |
| 3     | ![I phenol O](image) | ![Phenol O](image) | 96                               |
| 4     | ![I benzaldehyde](image) | ![Benzaldehyde](image) | >99                             |
| 5     | ![I benzoic acid](image) | ![Benzoic acid](image) | >99                             |
6
\[ \text{Br} \quad \text{O} \quad \text{H} \]
\[ \text{95} \]

7
\[ \text{Br} \quad \text{O} \quad \text{H} \]
\[ \text{97} \]

8
\[ \text{Cl} \quad \text{H} \]
\[ \text{0} \]

9
\[ \text{Cl} \quad \text{SO}_3\text{H} \]
\[ \text{0} \]

10
\[ \text{Cl} \quad \text{OH} \]
\[ \text{0} \]

- Conditions: 1 (10 mmol L\(^{-1}\)), 2 (11 mmol L\(^{-1}\)), \(\text{Na}_2\text{CO}_3\) (11 mmol L\(^{-1}\)), Pd/MPG1 (0.1 mol%), water, 30°C, 36 h.
- Determined from concentration of 3 after reaction using HPLC.
8. Diffusion experiment of substrates and product in gel network

The diffusion coefficients (D) of substrates and product in Suzuki coupling reaction in a gel network were evaluated. Nonporous gels with different BIS contents were prepared by polymerization in a cylindrical mold with a diameter of 1.5 mm. The resulting gels were cut into 25 mm-long cylinders. The each gel was added to the solutions of 1 (10 mmol L\(^{-1}\)), 2 (11 mmol L\(^{-1}\)), or 3 (10 mmol L\(^{-1}\)) in aqueous Na\(_2\)CO\(_3\) solution (11 mmol L\(^{-1}\), 10 mL) at 30°C for over 5 days. The equilibrium concentration of 1, 2, and 3 in the outer solution were determined using ultraviolet and visible spectroscopy (Agilent 8453, Agilent technologies Inc., Santa Clara, CA, USA) at wavelength of 270, 285, and 309 nm, respectively. After imbibing the diffusing species, the dimensions of the gels were measured with calipers. The each gel was suspended in a glass cuvette employing a wire basket and containing aqueous Na\(_2\)CO\(_3\) solution (11 mmol L\(^{-1}\), 3.5 mL) and stirrer (350 rpm). The concentration changes of 1, 2, or 3 in the solution were measured periodically at sampling intervals of 1 min (Figure S8). The diffusion of a solute from an infinite circular cylinder to a well stirred solution of limited volume was dealt by Carman and Haul (P. C. Carman, R. A. W. Haul, *Proc. R. Soc. A* 1954, 222, 109–118) as follows:

\[
\frac{C(t)}{C_\infty} = 1 - \sum_{n=1}^{\infty} \frac{4\alpha(1+\alpha)}{4+4\alpha+\alpha^2q_n^2} \exp\left(-\frac{Dtq_n^2}{a^2}\right)
\]

where \(t\), \(a\), \(C(t)\), and \(C_\infty\) are the time, radius of cylindrical gel, solute concentration at \(t = t\), and solute concentration at \(t = \infty\) (equilibrium state), respectively. \(\alpha\) and \(q_n\) satisfy following equations.

\[
\alpha = \frac{\text{Solution volume}}{\text{gel volume}} \times K
\]

\[
2J_1(q_n)+\alpha q J_0(q_n) = 0
\]

where \(K\) and \(J_m(q_n)\) are the equilibrium partition coefficient and Bessel's function of the \(m\)-th order. The diffusivities of solutes in gel networks were estimated by iteration with those to minimize the root-mean-square errors between experimental data and simulated data.
Figure S8. Diffusion curves for substrates and product in Suzuki coupling reaction from a cylindrical gel.