

# Application of Thiol-Modified Dual-Pore Silica Beads as a Practical Scavenger of Leached Palladium Catalyst in C–C Coupling Reactions

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## S Supporting Information

**ABSTRACT:** A practical and efficient method for scavenging palladium leached into the reaction mixture using thiol-modified dual-pore silica beads has been developed. Reducing the level of metal contamination, especially palladium, in pharmaceutical and bioactive compounds and fine chemicals to below the regulatory value is quite important for the quality assurance of industrial products. We have evaluated the performance of dual-pore silica beads as a palladium scavenger by investigating their ability to eliminate the divalent palladium ions in dilute palladium(II) acetate in methanol (5 and 50 ppm) and ethyl acetate (5 ppm) solutions. The ability of the dual-pore silica beads to eliminate the palladium species leached from a 10% palladium on carbon (Pd/C) catalyst during the ligand- and copper-free 10% Pd/C-catalyzed Sonogashira-type coupling reaction was also investigated. The thiol-modified dual-pore silica beads exhibit a more rapid and effective elimination ability toward leached palladium species in the reaction mixture in comparison with commercially available conventional thiol-modified silica scavengers because of the effects of diffusion and perfusion due to the dual-pore skeleton of the silica beads. When methanol is used as a dilution and eluent solvent for the filtered reaction mixture, the leached palladium species were removed almost entirely (<1 ppm).

**KEYWORDS:** palladium scavenger, thiol-modified silica, dual-pore, perfusion effect, Sonogashira coupling, palladium on carbon

## 1. INTRODUCTION

Palladium-catalyzed cross-coupling reactions are useful and widely applicable tools for the synthesis of active pharmaceutical ingredients (APIs),<sup>1</sup> natural products,<sup>2</sup> and functional materials.<sup>3</sup> However, these catalysts have the potential to become sources of leached palladium in the reaction mixture and/or residual palladium in the desired product. A residual metal impurity in the product frequently results in potential toxicity to human beings and serious degradation in the performance of functional materials.<sup>4</sup> In addition, the maximum permissible amounts of residual metals, including Pd, in medicines are strictly defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q3D guidelines.<sup>5,6</sup> Therefore, the development of practical methods to reduce residual Pd in APIs or the reaction mixtures used in each synthetic step is strongly desired. Palladium on carbon (Pd/C), which is used as a heterogeneous catalyst for various reactions such as hydrogenations,<sup>7</sup> C–H activation reactions,<sup>8,9</sup> and coupling reactions,<sup>10</sup> can be easily removed from the reaction mixture, resulting in reduced Pd contamination in the crude reaction solution in comparison with the homogeneous Pd-catalyzed reaction.<sup>11</sup> However, even a small amount of residual Pd in the product can sometimes exceed the ICH Q3D standard level and become a serious problem even for heterogeneous Pd-catalyzed reactions<sup>10c,12</sup> because of the strong coordination ability of some functional groups for

Pd species, such as aromatic rings and/or  $\pi$ -electron-rich unsaturated bonds within the substrates and/or products. While various methods have been applied to eliminate residual metal species, e.g., distillation, recrystallization, extraction, and absorption, and these combinations have been applied in various industrial fields, the elimination of trace levels of Pd species is quite difficult.<sup>13</sup> Metal scavengers possessing chelating functionalities such as polyamines (eq 1),<sup>14</sup> thiols (eq 2),<sup>15</sup> and thioureas (eq 3)<sup>16a</sup> on supports such as silica<sup>15,16c</sup> and polymers<sup>14,16a,b</sup> have shown good capture capability toward corresponding metal ions and can efficiently eliminate residual metals from the reaction solution.<sup>14–16</sup>

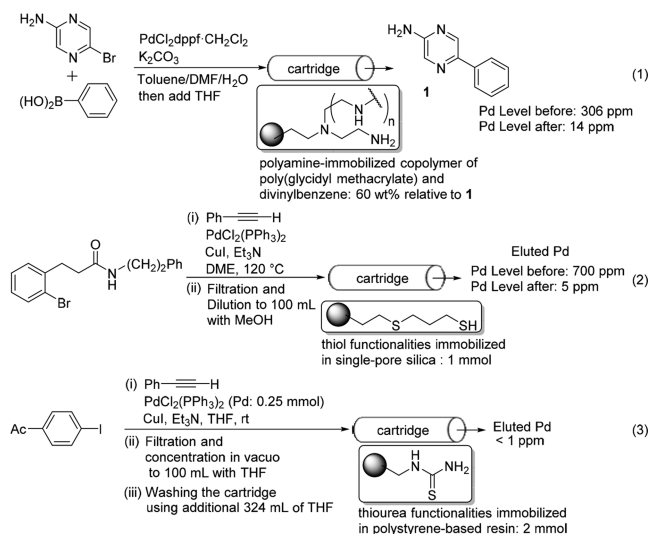
Commercially available dual-pore silica beads,<sup>17–19</sup> which have been utilized as column packing materials for liquid chromatography, consist of fully porous silica particles with high specific surface area due to their bimodal pore structure (Figure 1), consisting of (1) microsized through-pores, which are intricately pierced through the silica particles and allow smooth diffusion of solvents into the particle, and (2) nanosized pores, which accelerate the absorption and separation of molecules as the perfusion theory. Therefore, thiol-modified dual-pore silica beads would more rapidly and

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## Previously reported Pd scavengers

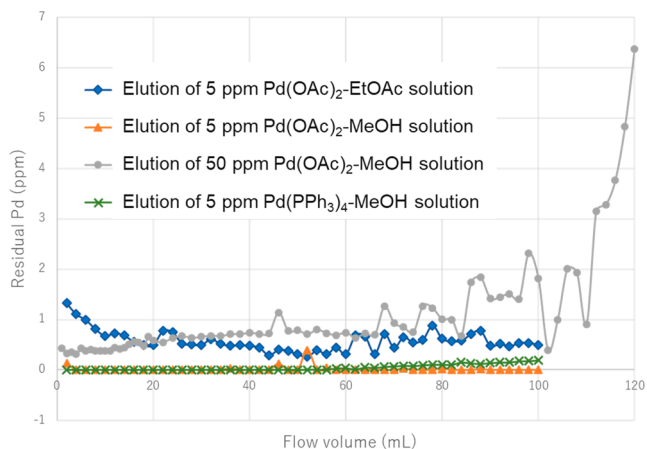


effectively capture residual Pd species in the reaction mixture in comparison with some metal scavengers consisting of single-pore silica particles because of the diffusion and perfusion effect of the dual-pore silica beads.

In this work, we performed a detailed evaluation of the scavenging ability of thiol-modified dual-pore silica beads preppacked in a cartridge toward palladium(II) acetate [Pd(OAc)<sub>2</sub>] solutions and Pd species leached in a reaction mixture after the ligand- and copper-free Pd/C-catalyzed Sonogashira-type reaction<sup>10c</sup> to develop a practical method of eliminating Pd species.

## 2. RESULTS AND DISCUSSION

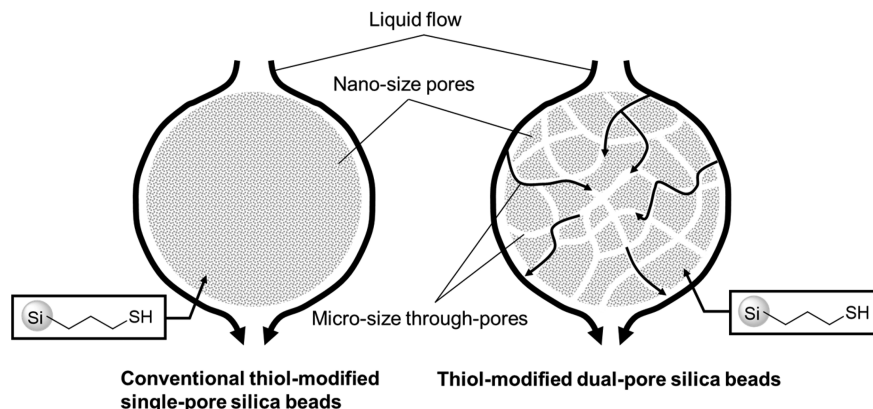
We initially evaluated the scavenging efficiency of a thiol-modified dual-pore silica cartridge (5.5 mm in diameter and 10 mm in length) using solutions of Pd(OAc)<sub>2</sub> in ethyl acetate (EtOAc) and methanol (MeOH) by a single-pass flow method. A 5 ppm Pd(OAc)<sub>2</sub>/EtOAc solution and 5 and 50 ppm Pd(OAc)<sub>2</sub>/MeOH solutions were passed through the cartridge (thiol-modified dual-pore silica, 70 mg; thiol functionalities, 91 μmol) at a flow rate of around 4 mL/min. The divalent Pd(II) contaminant in the eluate was sequentially monitored by atomic absorption spectrometry in 2 mL increments, and the results are shown in Figure 2. When the 5 ppm Pd(OAc)<sub>2</sub>/EtOAc solution was passed through the



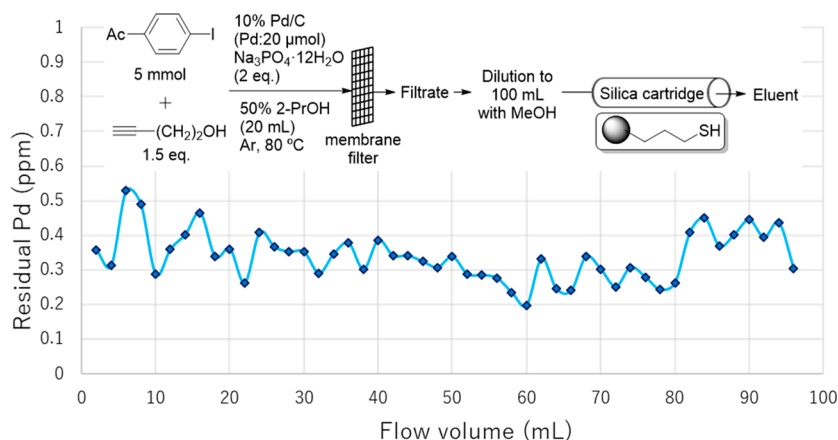
**Figure 2.** Plots of eluted Pd(OAc)<sub>2</sub> in MeOH and EtOAc solutions and Pd(PPh<sub>3</sub>)<sub>4</sub> in MeOH solution after passage through the thiol-modified dual-pore silica cartridge.

thiol-modified dual-pore silica cartridge, the concentration of the Pd contaminant was maintained below 1 ppm for at least 100 mL of flow (blue diamonds). Furthermore, the divalent Pd(II) contaminant in the 5 ppm Pd(OAc)<sub>2</sub>/MeOH solution was quite efficiently eliminated, and nearly 0 ppm was observed for 100 mL of flow (red triangles). Therefore, MeOH was chosen as an appropriate dilution and elution solvent for the elimination of divalent Pd(II) species of MeOH in comparison with EtOAc. Since divalent Pd(II) species were obviously leaked after elution of around 90 mL of the 50 ppm Pd(OAc)<sub>2</sub>/MeOH solution (ca. 42.1 μmol of Pd) (gray circles), the maximum amount of Pd in the cartridge was nearly 45 μmol, equivalent to roughly half of the thiol functionalities (91.0 μmol) of the thiol-modified dual-pore silica packed in the cartridge. While zero-valent Pd(0) species in the 5 ppm Pd(PPh<sub>3</sub>)<sub>4</sub>/MeOH solution were nearly quantitatively eliminated up to a flow volume of around 50 mL of the 5 ppm Pd(PPh<sub>3</sub>)<sub>4</sub>/MeOH solution, the leakage of small amounts of Pd(0) species was observed with flow volumes of more than 50 mL (green crosses). These results imply the slight difference of the coordination ability of the thiol functionalities on the dual-pore silica to zero- and divalent Pd species.

We next applied the thiol-modified dual-pore silica cartridge to the elimination of the Pd species in a practical Pd/C-

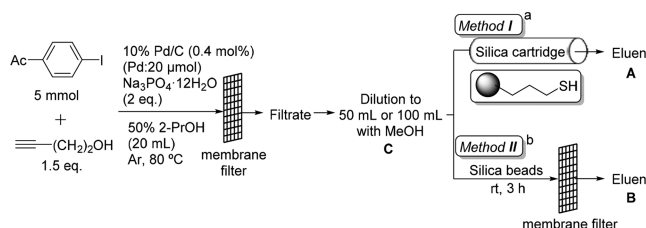


**Figure 1.** Comparison of the structural characters of conventional single-pore silica and dual-pore silica beads.



**Figure 3.** Plot of the contents of Pd species in the eluted fractions of the MeOH-diluted filtrate of the Sonogashira-type reaction after passage through the thiol-modified dual-pore silica cartridge.

**Table 1. Optimization of the Scavenging Conditions from the Diluted Filtrate of the Practical Pd/C-Catalyzed Sonogashira-Type Reaction Using the Thiol-Modified Dual-Pore Silica**



entry	method	volume of dilution (C)	amount of thiol-modified dual-pore silica	Pd conc. in C (Pd quantity) <sup>c</sup>	Pd conc. in A or B (Pd quantity) <sup>c</sup>	scavenging Pd%
1	I <sup>a</sup>	100 mL	70 mg (ca. 0.23 mL)	1.09 ppm (0.99 μmol)	0.34 ppm (0.31 μmol)	70%
2	I <sup>a</sup>	50 mL	70 mg (ca. 0.23 mL)	2.67 ppm (1.10 μmol)	0.20 ppm (0.08 μmol)	92%
3	I <sup>a</sup>	50 mL	210 mg (ca. 0.69 mL)	2.32 ppm (1.09 μmol)	0.47 ppm (0.21 μmol)	81%
4	II <sup>b</sup>	50 mL	70 mg (ca. 0.23 mL)	4.02 ppm (1.89 μmol)	1.89 ppm (0.89 μmol)	53%

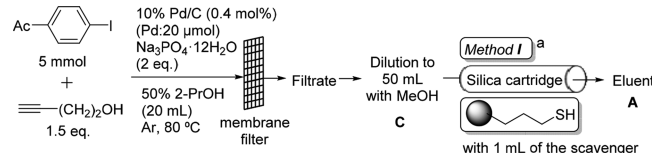
<sup>a</sup>Method I: The filtrate diluted with MeOH was passed through the thiol-modified dual-pore silica cartridge at a flow rate of 4 mL/min. <sup>b</sup>Method II: The filtrate diluted to 50 mL with MeOH was stirred with the bulk thiol-modified dual-pore silica beads at room temperature for 3 h and filtered with a membrane filter (pore size: 0.45 μm) to remove the silica beads. <sup>c</sup>The concentration of Pd species in the eluent was measured by atomic absorption spectrometry (AA-7000, Shimadzu, Kyoto, Japan).

catalyzed reaction mixture. It has been shown that approximately 25% of Pd species were fairly constantly leached from Pd/C during the 4 mol % Pd/C-catalyzed copper- and ligand-free Sonogashira-type coupling reaction developed by us (scheme in Figure 3) because of strong coordination by the alkyne moiety.<sup>10c</sup> Since Pd(0) species like Pd nanoparticles might also be generated during the coupling reaction in conjunction with divalent Pd(II) species, the elimination of the residual Pd species from the reaction mixture would be more difficult in comparison with scavenging of the divalent Pd(II) species of Pd(OAc)<sub>2</sub>. The reaction mixture was diluted with MeOH to 100 mL and passed through the thiol-modified dual-pore silica cartridge at a flow rate of 4 mL/min. Pd species in the eluate were sequentially monitored by atomic absorption spectrometry in 2 mL increments (Figure 3). Quite low levels of residual Pd species (avg 0.35 ppm) were detected in the eluate samples. These results indicate that the thiol-modified dual-pore silica cartridge possesses quite high potential as a Pd scavenger.

Next, the scavenging conditions of the Pd species leached during the Pd/C-catalyzed Sonogashira-type reaction were optimized (Table 1). We initially investigated the effect of diluting the filtrate of the Pd/C-catalyzed Sonogashira-type

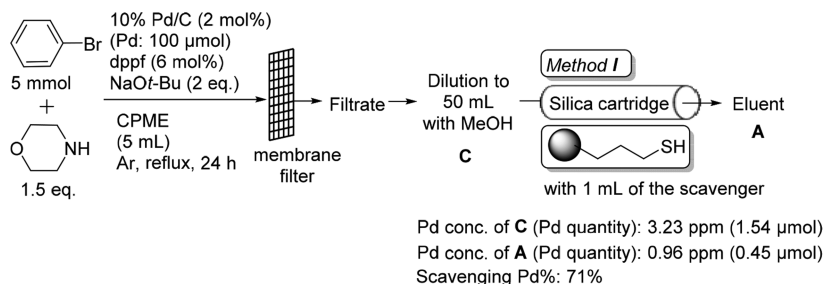
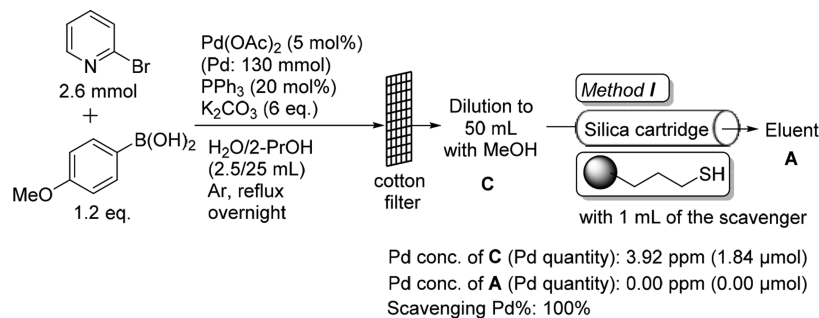
reaction. Samples of the filtrate diluted to 50 and 100 mL with MeOH were passed through the thiol-modified dual-pore silica cartridge (thiol-modified dual-pore silica: 70.0 mg, ca. 0.23 mL) at a flow rate of 4 mL/min (method I; Table 1, entries 1 and 2). It was observed that the use of Pd eluent diluted to 50 mL with MeOH resulted in higher scavenging efficiency (92% Pd removal) in comparison with the Pd eluent diluted to 100 mL with MeOH (70% Pd removal). Increasing the amount of thiol-modified dual-pore silica beads<sup>19</sup> (from 70 mg, ca. 0.23 mL to 210 mg, ca. 0.69 mL) was ineffective for increasing the Pd scavenging efficiency, as the amount of Pd species in the Pd eluent diluted to 50 mL with MeOH was reduced by only 81% (method I; Table 1, entry 3). This result might be caused simply by the difference in the probability of contact with the thiol functions with Pd species. The results in entries 1 and 3 indicate that 70 mg (ca. 0.23 mL) of the thiol-modified dual-pore silica was sufficient to remove most of the Pd species leached during the Pd/C-catalyzed Sonogashira-type reaction (5 mmol scale), while a small amount of Pd species, probably possessing a low affinity for the thiol-modified dual-pore silica, still remained regardless of the usage of silica beads.

A batch scavenging method (method II) was also examined using 70 mg of the bulk thiol-modified dual-pore silica beads

**Table 2. Comparison of the Pd Scavenging Abilities of the Present Thiol-Modified Dual-Pore Silica Cartridge and Other Commercially Available Thiol-Modified Silica Cartridges**


entry	scavenger (skeleton of thiol-modified silica)	amount of thiol functionalities in the cartridge	Pd conc. of C (Pd quantity) <sup>b</sup>	Pd conc. of A (Pd quantity) <sup>b</sup>	scavenging Pd%
1	thiol-modified dual-pore silica (dual-pore) <sup>17</sup>	91 $\mu\text{mol}^c$	2.67 ppm (1.10 $\mu\text{mol}$ )	0.20 ppm (0.08 $\mu\text{mol}$ )	92%
2	3-mercaptopropyl-functionalized silica gel (single-pore) <sup>20</sup>	220 $\mu\text{mol}^d$	2.27 ppm (0.94 $\mu\text{mol}$ )	0.37 ppm (0.15 $\mu\text{mol}$ )	84%
3	thiol-modified single-pore silica gel <sup>21</sup>	193 $\mu\text{mol}^e$	2.14 ppm (1.01 $\mu\text{mol}$ )	0.97 ppm (0.46 $\mu\text{mol}$ )	55%

<sup>a</sup>Method I: The filtrate was diluted to 50 mL with MeOH and passed through the dual- or single-pore thiol-modified silica cartridge at a flow rate of 4 mL/min. <sup>b</sup>The concentration of Pd species in the eluent was measured by atomic absorption spectrometry (AA-7000, Shimadzu, Kyoto, Japan). <sup>c</sup>The cartridge was packed with 0.23 mL of the thiol-modified dual-pore silica beads (bulk density, 0.30 g/mL; thiol functionalities per unit mass, 1.3 mmol/g).<sup>17</sup> <sup>d</sup>The cartridge was packed with 0.23 mL of 3-mercaptopropyl-functionalized silica gel (bulk density, 0.80 g/mL; thiol functionalities per unit mass, 1.2 mmol/g).<sup>20</sup> <sup>e</sup>The cartridge was packed with 0.23 mL of thiol-modified single-pore silica gel (bulk density, 0.70 g/mL; thiol functionalities per unit mass, 1.2 mmol/g).<sup>21</sup>

**Scheme 1. Elimination of Pd from the Filtrate of the Pd/C-Catalyzed Buchwald–Hartwig Amination****Scheme 2. Elimination of Pd from the Reaction Mixture of the Suzuki–Miyaura Coupling Reaction Using Pd(OAc)<sub>2</sub> as a Homogeneous Catalyst**

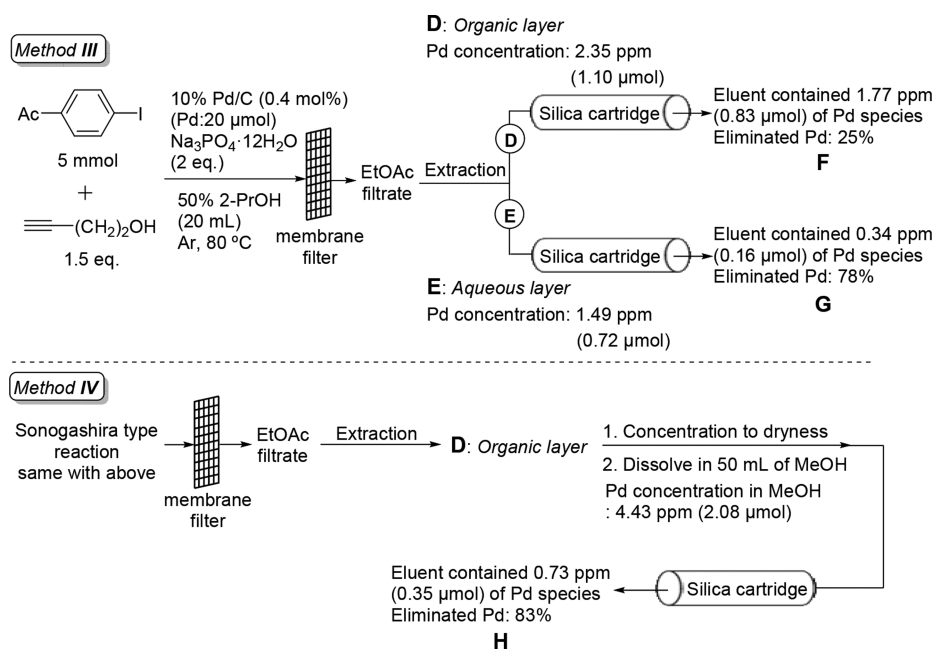
and the filtrate diluted to 50 mL with MeOH after the Sonogashira-type reaction, resulting in the elimination of 53% of the Pd species (Table 1, entry 4). This result apparently indicates that the diffusion and perfusion effects derived from the dual-pore skeleton of the thiol-modified dual-pore silica beads played an absolutely vital role and Pd species were effectively captured under the flow conditions. Therefore, the use of the cartridge packed with thiol-modified dual-pore silica beads as a flow method contributed to saving cost and time in comparison with batch operation.

The Pd scavenging performance of the thiol-modified dual-pore silica cartridge was directly compared with the performance of cartridges packed with bulk particles of other commercially available thiol-modified silicas using the filtrate of the Sonogashira-type reaction diluted to 50 mL with MeOH (Table 2). Three cartridges were packed with 0.23 mL each of

the three different thiol-modified silica scavengers. Since each silica scavenger possesses a different bulk density and amount of thiol functionalities per unit mass (thiol-modified dual-pore silica: bulk density of 0.30 g/mL and 1.3 mmol/g thiol functionalities; 3-mercaptopropyl-functionalized silica gel: bulk density of 0.80 g/mL and 1.2 mmol/g thiol functionalities; thiol-modified single-pore silica gel: bulk density of 0.70 g/mL and 1.2 mmol/g thiol functionalities), the total amounts of thiol functionalities in each cartridge were 91, 220, and 193  $\mu\text{mol}$ , respectively. The highest Pd scavenging efficiency (92%) was achieved with the 0.23 mL thiol-modified dual-pore silica cartridge (entry 1), even though the total amount of thiol functional groups (91  $\mu\text{mol}$ ) was quite low (fewer than half). On the other hand, 84% and 55% of the leached Pd species could be eliminated using the commercially available 0.23 mL single-pore thiol-modified silica cartridges with 220  $\mu\text{mol}$ <sup>20</sup>



Scheme 3. Effect of the Extraction Process on the Scavenging of Pd Species Leached from the Practical Pd/C-Catalyzed Sonogashira-Type Reaction



and 193 μmol<sup>21</sup> of thiol functionalities (entries 2 and 3, respectively). These results indicate that the thiol-modified silica beads possessing the dual-pore skeleton effectively scavenged leached Pd species from the filtrate by the diffusion and perfusion phenomena.

We also applied the present Pd elimination method using the thiol-modified dual-pore silica cartridge to the Pd/C-catalyzed Buchwald–Hartwig amination<sup>12b</sup> and homogeneous Pd-catalyzed Suzuki–Miyaura coupling<sup>16a</sup> (Schemes 1 and 2).

It has been reported that a small amount of leakage of Pd species was observed during the Pd/C-catalyzed Buchwald–Hartwig amination.<sup>12b</sup> By the treatment using the thiol-modified dual-pore silica cartridge (method I; Scheme 1), 71% of the leached Pd species could be eliminated from the filtrate of the Buchwald–Hartwig amination diluted to 50 mL with MeOH (Pd concentration: 3.23 ppm).

On the other hand, the Pd(OAc)<sub>2</sub>-catalyzed Suzuki–Miyaura coupling reaction proceeded smoothly in association with the gradual precipitation of Pd black, and the pale-yellow filtrate obtained by filtration through a simple cotton plug was diluted to 50 mL with MeOH and passed through the thiol-modified dual-pore silica cartridge in the same manner (method I; Scheme 2). The Pd species in the filtrate were quantitatively eliminated after passage through the thiol-modified dual-pore silica cartridge because the residual Pd species in the filtrate were provably divalent.

From these results, it is obvious that the present Pd elimination method is widely applicable to eliminate Pd species from reaction mixtures.

We next investigated the combination of the usual extraction process and the present Pd scavenging method (method III; Scheme 3). An organic layer (D, 30 mL) containing 2.35 ppm (1.10 μmol) of Pd species and an aqueous layer (E, 30 mL) containing 1.49 ppm (0.72 μmol) of Pd species were obtained by the extraction of the filtrate of the Sonogashira-type reaction with additional EtOAc (20 mL) and H<sub>2</sub>O (20 mL). Only 25% of the Pd species of the organic layer (D) could be eliminated

by the subsequent treatment using the thiol-modified dual-pore silica cartridge (method III in Scheme 3; the eluent (F) contained 1.77 ppm (0.83 μmol) of Pd species). Since MeOH was an effective solvent for eliminating Pd(OAc)<sub>2</sub> in comparison with EtOAc (Figure 2), the organic layer was concentrated under reduced pressure, and the residue was dissolved in 50 mL of MeOH (method IV; Scheme 3). As a result, 83% of the Pd species in the resulting MeOH solution could be eliminated by the thiol-modified dual-pore silica cartridge (the eluent (H) contained 0.73 ppm (0.35 μmol) of Pd species).

On the other hand, the amount of residual Pd species in the aqueous layer (E, 1.49 ppm, 0.72 μmol) was moderately (78%) eliminated by passage through the thiol-modified dual-pore silica cartridge (method III, G; Scheme 3). It is noteworthy that the thiol-modified dual-pore silica cartridge could be applied to the elimination of Pd species from both the methanolic and aqueous solutions.

### 3. CONCLUSION

We have developed a practical and rapid method to remove Pd species from a 5 ppm MeOH solution of Pd(OAc)<sub>2</sub> and the filtrate of the ligand- and copper-free Pd/C-catalyzed Sonogashira-type reaction using a thiol-modified dual-pore silica-cartridge based on the diffusion and perfusion effect of the dual-pore silica beads. Since the Pd species leached during the practical C–C coupling reaction were quite difficult to eliminate in comparison with the divalent Pd species derived from Pd(OAc)<sub>2</sub>, detailed tests of Pd scavengers using the actual filtrates of the C–C coupling reactions containing leached Pd species were extremely important to clearly demonstrate their practical scavenging ability. Using the thiol-modified dual-pore silica cartridge, 92% elimination of Pd species leached during the practical Pd/C-catalyzed Sonogashira-type reaction could be achieved. Furthermore, the selective elimination of the leached Pd species from the complex reaction mixture containing reagents, inorganic bases,

and products was possible. Therefore, these protocols are expected to be widely applicable in both laboratory and industrial processes to eliminate Pd contaminants from reaction mixtures including APIs and functional materials.

#### 4. EXPERIMENTAL SECTION

**Materials.** 4'-Iodoacetophenone, 3-butyne-1-ol,  $\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$ , and 2-propanol were purchased from commercial sources and used without further purification.  $\text{Pd}(\text{OAc})_2$  and 10% Pd/C were obtained from N.E. Chemcat Corporation (Tokyo, Japan). Thiol-modified dual-pore silica beads and prepacked thiol-modified dual-pore silica cartridges were obtained from DPS Inc. (Kyoto, Japan). Other thiol-modified single-pore scavengers were purchased from Aldrich and Biotage. The amount of Pd in the eluent was measured by atomic absorption spectrometry (AA-7000, Shimadzu, Kyoto, Japan).

**Elimination Study of Divalent Pd(II) and Pd(0) Species (Figure 2).** The 50 and 5 ppm  $\text{Pd}(\text{OAc})_2/\text{MeOH}$ , 5 ppm  $\text{Pd}(\text{OAc})_2/\text{EtOAc}$ , and 5 ppm  $\text{Pd}(\text{PPh}_3)_4/\text{MeOH}$  solutions (100 mL each) were prepared using 10.5 and 1.05 mg of  $\text{Pd}(\text{OAc})_2$  and 5.4 mg of  $\text{Pd}(\text{PPh}_3)_4$ , respectively. The solutions were passed through the thiol-modified dual-pore silica cartridge at a flow rate of 4 mL/min by the use of a pumping system for the mobile phase. The amount of Pd species in the eluent was sequentially monitored by atomic absorption spectrometry in 2 mL increments. The detailed results related to Figure 2 are shown in the Supporting Information.

**Plotting Study of the Concentration of the Pd Species in the Eluted Fractions of the MeOH-Diluted Filtrate of the Pd/C-Catalyzed Sonogashira-Type Coupling Reaction (Figure 3).** To a solution of 4'-iodoacetophenone (1.23 g, 5.0 mmol), 10% Pd/C (21.3 mg, 20.0  $\mu\text{mol}$ ), and  $\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$  (3.80 g, 10.0 mmol) in 2-PrOH (10 mL) and  $\text{H}_2\text{O}$  (10 mL) was added 3-butyne-1-ol (567  $\mu\text{L}$ , 7.5 mmol) at room temperature under an argon atmosphere. The reaction mixture was stirred at 80 °C (external oil bath temperature), and the reaction progress was monitored by thin-layer chromatography. After completion of the reaction, the reaction mixture was cooled to room temperature and filtered using a membrane filter (pore size: 0.45  $\mu\text{m}$ ) to remove Pd/C and insoluble salts. The filtrate was diluted to 100 mL with MeOH and passed through the thiol-modified dual-pore silica cartridge (70 mg, 91  $\mu\text{mol}$  of thiol functionalities) at a flow rate of 4 mL/min by the use of a pumping system for the mobile phase. The amount of Pd species in the eluent was sequentially monitored by atomic absorption spectrometry in 2 mL increments. The detailed results related to Figure 3 are shown in the Supporting Information.

**Elimination Study of the Pd Species Partially Leached during the Pd/C-Catalyzed Sonogashira-Type Coupling Reaction Using the Thiol-Modified Dual-Pore Silica Cartridge (Method I; Table 1, Entry 2).** To a solution of 4'-iodoacetophenone (1.23 g, 5.0 mmol), 10% Pd/C (21.3 mg, 20.0  $\mu\text{mol}$ ), and  $\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$  (3.80 g, 10.0 mmol) in 2-PrOH (10 mL) and  $\text{H}_2\text{O}$  (10 mL) was added 3-butyne-1-ol (567  $\mu\text{L}$ , 7.5 mmol) at room temperature under an argon atmosphere. The reaction mixture was stirred at 80 °C (external oil bath temperature), and the reaction progress was monitored by thin-layer chromatography. After completion of the reaction, the reaction mixture was cooled to room

temperature and filtered using a membrane filter (pore size: 0.45  $\mu\text{m}$ ) to remove Pd/C and insoluble salts. The filtrate was diluted to 50 mL with MeOH and passed through the thiol-modified dual-pore silica cartridge (70 mg, 91  $\mu\text{mol}$  of thiol functionalities) at a flow rate of 4 mL/min by the use of a pumping system for the mobile phase. The amount of Pd species in the eluent was measured by atomic absorption spectrometry, and 92% elimination of Pd species was achieved.

**Elimination Study of the Pd Species Partially Leached during the Pd/C-Catalyzed Sonogashira-Type Coupling Reaction Using the Bulk Thiol-Modified Dual-Pore Silica Beads (Method II; Table 1, Entry 4).** To a solution of 4'-iodoacetophenone (1.23 g, 5.0 mmol), 10% Pd/C (21.3 mg, 20.0  $\mu\text{mol}$ ), and  $\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$  (3.80 g, 10.0 mmol) in 2-PrOH (10 mL) and  $\text{H}_2\text{O}$  (10 mL) was added 3-butyne-1-ol (567  $\mu\text{L}$ , 7.5 mmol) at room temperature under an argon atmosphere. The reaction mixture was stirred at 80 °C (external oil bath temperature), and the reaction progress was monitored by thin-layer chromatography. After completion of the reaction, the reaction mixture was cooled to room temperature and filtered using a membrane filter (pore size: 0.45  $\mu\text{m}$ ) to remove Pd/C and insoluble salts. The thiol-modified dual-pore silica beads (70 mg, 91  $\mu\text{mol}$  of thiol functionalities) were added to the filtrate, and the mixture was stirred for 3 h at room temperature and then filtered to remove the silica beads. The amount of Pd species in the filtrate was measured by atomic absorption spectrometry, and 53% elimination of Pd species was achieved.

**Partially Leached Pd Elimination Study Using the Filtrate of the Pd/C-Catalyzed Buchwald–Hartwig Amination and the Thiol-Modified Dual-Pore Silica Cartridge (Method I; Scheme 1).** A mixture of bromobenzene (0.79 g, 5.0 mmol), morpholine (567  $\mu\text{L}$ , 7.5 mmol), 10% Pd/C (106.4 mg, 0.1 mmol), 1,1'-bis-(diphenylphosphino)ferrocene (166.3 mg, 0.3 mmol), and  $\text{NaOtBu}$  (0.96 g, 10.0 mmol) in cyclopentyl methyl ether (5 mL) was stirred at reflux (external oil bath temperature: 120 °C) under argon. After 24 h, the reaction mixture was cooled to room temperature and filtered using a membrane filter (pore size: 0.45  $\mu\text{m}$ ) to remove Pd/C and insoluble salts. The filtrate was diluted to 50 mL with MeOH and passed through the thiol-modified dual-pore silica cartridge (70 mg, 91  $\mu\text{mol}$  of thiol functionalities) at a flow rate of 4 mL/min by the use of a pumping system for the mobile phase. The amount of Pd species in the eluent was measured by atomic absorption spectrometry, and 71% elimination of Pd species was achieved.

**Partially Leached Pd Elimination Study Using the Filtrate of the Pd(OAc)<sub>2</sub>-Catalyzed Suzuki–Miyaura Coupling Reaction and the Thiol-Modified Dual-Pore Silica Cartridge (Method I; Scheme 2).** A mixture of 2-bromopyridine (252  $\mu\text{L}$ , 2.6 mmol), 4-methoxyphenylboronic acid (474.1 mg, 3.12 mmol), palladium(II) acetate (29.2 mg, 0.13 mmol), triphenylphosphine (136.4 mg, 0.52 mmol), and  $\text{K}_2\text{CO}_3$  (2.16 g, 15.6 mmol) in 2-PrOH (25 mL) and  $\text{H}_2\text{O}$  (2.5 mL) was stirred at reflux (external oil bath temperature: 100 °C) under argon. The reaction progress was monitored by thin-layer chromatography, and the pale-yellow solution gradually altered to yellow-tinged dark gray. After the completion of the reaction, the reaction mixture was cooled to room temperature and filtered using a simple cotton plug to remove the insoluble salts and the Pd black precipitated during the reaction. The pale-yellow filtrate was diluted to 50 mL with MeOH and passed through the thiol-modified dual-pore silica

cartridge (70 mg, 91  $\mu\text{mol}$  of thiol functionalities) at a flow rate of 4 mL/min by the use of a pumping system for the mobile phase. The amount of Pd species in the eluent was measured by atomic absorption spectrometry, and 100% elimination of Pd species was achieved.

#### Elimination Study Using the Combination Method of the Extraction Process and the Pd Elimination Method Using the Thiol-Modified Dual-Pore Silica Cartridge.

**Method III (Scheme 3).** To a solution of 4'-iodoacetophenone (1.23 g, 5.0 mmol), 10% Pd/C (21.3 mg, 20.0  $\mu\text{mol}$ ), and  $\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$  (3.80 g, 10.0 mmol) in 2-PrOH (10 mL) and  $\text{H}_2\text{O}$  (10 mL) was added 3-butyn-1-ol (567  $\mu\text{L}$ , 7.5 mmol) at room temperature under an argon atmosphere. The reaction mixture was stirred at 80  $^\circ\text{C}$  (external oil bath temperature), and the reaction progress was monitored by thin-layer chromatography. After completion of the reaction, the reaction mixture was cooled to room temperature and filtered using a membrane filter (pore size: 0.45  $\mu\text{m}$ ) to remove Pd/C and insoluble salts. The filtrate was extracted with additional EtOAc (20 mL) and  $\text{H}_2\text{O}$  (20 mL), and the organic and aqueous layers were passed through thiol-modified dual-pore silica cartridges (70 mg, 91  $\mu\text{mol}$  of thiol functionalities) at a flow rate of 4 mL/min by the use of a pumping system for the mobile phase. The amounts of Pd species in the organic and aqueous layers were measured by atomic absorption spectrometry, and 25% and 78% elimination of Pd species were achieved, respectively.

**Method IV (Scheme 3).** To a solution of 4'-iodoacetophenone (1.23 g, 5.0 mmol), 10% Pd/C (21.3 mg, 20.0  $\mu\text{mol}$ ), and  $\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$  (3.80 g, 10.0 mmol) in 2-PrOH (10 mL) and  $\text{H}_2\text{O}$  (10 mL) was added 3-butyn-1-ol (567  $\mu\text{L}$ , 7.5 mmol) at room temperature under an argon atmosphere. The reaction mixture was stirred at 80  $^\circ\text{C}$  (external oil bath temperature), and the reaction progress was monitored by thin-layer chromatography. After completion of the reaction, the reaction mixture was cooled to room temperature and filtered using a membrane filter (pore size: 0.45  $\mu\text{m}$ ) to remove Pd/C and insoluble salts. The filtrate was extracted with additional EtOAc (20 mL) and  $\text{H}_2\text{O}$  (20 mL). The organic layer was concentrated in vacuo to remove EtOAc, and the residue was dissolved in MeOH (50 mL) and passed through the thiol-modified dual-pore silica cartridge (70 mg, 91  $\mu\text{mol}$  of thiol functionalities) at a flow rate of 4 mL/min by the use of a pumping system for the mobile phase. The amount of Pd species in the eluent was measured by atomic absorption spectrometry, and 83% elimination of Pd species was achieved.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00291.

Detailed data for the eluted Pd species in Figures 2 and 3 (PDF)

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## Notes

The authors declare no competing financial interest.

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