Research Article

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Stille, Heck, and Sonogashira coupling and hydrogenation catalyzed by porous-silica-gel-supported palladium in batch and flow

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Abstract: Owing to their recyclability, heterogeneous transition metal catalysts represent a means of conserving depletable resources for the synthesis of pharmaceutical, agricultural, and functional chemicals. We recently developed a novel heterogeneous palladium catalyst and demonstrated its synthetic availability for Suzuki–Miyaura cross-coupling. Herein, we report the further application of the present catalyst to cross-coupling reactions in batch and flow, as well as a hydrogenative reduction reaction in flow. We demonstrate the flow synthesis for useful material, a liquid crystal, and a 1 h sequential operation of the coupling reaction and hydrogenation reaction.

Keywords: heterogeneous catalyst, flow reaction, Stille coupling, hydrogenation

1 Introduction

Reuse of reactants is an important means of achieving green processes in organic synthesis, especially given the Sustainable Development Goal 12 (responsible consumption and production) established by the United Nations. In this context, heterogeneous catalysts have attracted considerable interest in both academic and industrial fields because of their ease of recovery and reuse. A wide range of reactions catalyzed by heterogeneous catalysts have been developed to produce useful organic compounds, including pharmaceutical and functional chemicals [1].

One notable advantage of heterogeneous catalysts is their applicability to flow synthesis, which is usually performed using channel- or tube-type reactors [2–16], as heterogeneous column reactors [17–23]. In addition to the advantages of excellent heat- and mass-transfer ability and precise reaction-time controllability, flow synthesis enables continuous operation; this is beneficial as increasing the operational time increases the synthesis productivity [24,25]. With respect to heterogeneous column reactors, continuous operation can be considered to be a form of catalyst recycling. To recycle a heterogeneous catalyst in batch reactions, the catalyst should be separated (typically by filtration) and used for the next reaction. By contrast, in a flow reaction, multiplying the volume of the reactant solution is equivalent to performing multiple reaction operations (Figure 1). Thus, enhancing the continuous operability of the heterogeneous column reactor can increase the recyclability of the catalyst.

Based on this idea, we recently developed a palladium catalyst supported on a bimodal porous silica gel and reported its synthetic application in Suzuki–Miyaura cross-coupling [26]. The advantage of this catalyst is that the hierarchical macro–mesoporous structure of the silica gel provides a low back pressure [27,28]; this allows a higher flow rate without an exceedance of the pump pressure. Moreover, the low back pressure helps to avoid reactor clogging, which would stop the operation and ruin the recyclability of the catalyst. Using our heterogeneous palladium catalyst, we demonstrated a 1-h operation of flow Suzuki coupling without any decrease in the product

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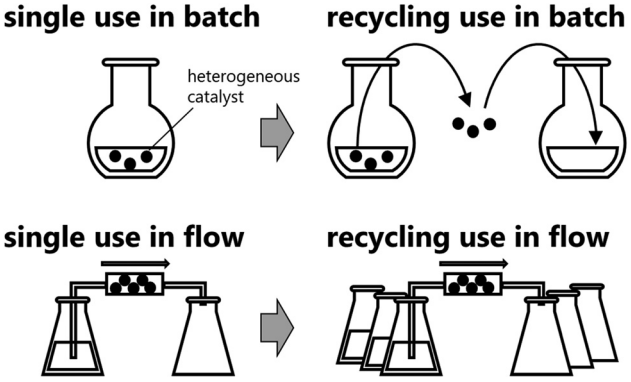


Figure 1: Schematic for recycling a heterogeneous catalyst in batch and flow.

yield. Given the high usability of our immobilized palladium catalyst, we considered its further applications in organic synthesis. In addition to its application to Suzuki coupling, we envisaged that it could be adapted to other palladium-catalyzed cross-coupling reactions. Herein, we report the application of a hierarchical bimodal porous-silica-gel-supported palladium catalyst for cross-coupling reactions in batch and flow, as well as a hydrogenative reduction in flow.

2 Materials and methods

All chemicals were purchased from Fujifilm Wako Pure Chemical Corporation, Tokyo Chemical Industry Co., Ltd., Kanto Chemical Co., Inc., or Aldrich, and used without any further purification. Gas chromatography (GC) analysis was performed on a Shimadzu GC-2014 instrument equipped with a flame ionization detector using a fused silica capillary column (column, CBP1; 0.22 mm × 25 m). X-ray fluorescence (XRF) analyses were performed using a Shimadzu EDX-8000 system. For flow reactions, a syringe pump (Harvard PHD 2000 or PHD ULTRA) equipped with a gastight syringe (purchased from SGE) or a plunger pump (Shimadzu LC-20AR) was used to introduce solutions into the column reactor. To introduce gases, a mass flow controller (Brooks Instrument SLA5850S) was used.

2.1 Immobilization of palladium on silica gel

Palladium nanoparticles were immobilized in the pores of a dual-pore silica gel (DualPore^{TM}) [29] using a supercritical carbon dioxide/acetone solution at 20 MPa and 70°C for 24 h. The vessel was depressurized to atmospheric pressure and the contents were removed. After the removal of acetone, the precipitate was reduced by H_2 and N_2 at 300°C for 5 h. TEM analyses indicated that palladium was widely dispersed on the DualPore (see Supporting Information). Pd@DualPore was placed in stainless steel (SUS316) tubes.

2.2 Coupling reactions in batch

2.2.1 Stille coupling

The following were added to a Schlenk tube capped by a septum: 4-iodobenzonitrile (**1**, 0.1 mmol), tri-*n*-butylphenylstannane (**2**, 1.5 eq), lithium chloride (3 eq), Pd@DualPore (2 mol%), and dimethylformamide (3 mL). The mixture was stirred at 120°C in an argon atmosphere for 18 h. The solution was mixed with aqueous ammonium chloride, *n*-hexane, ethyl acetate, and *n*-tridecane as internal standards. The organic phase was analyzed by GC to determine the yield of the desired product **3**.

2.2.2 Heck and Sonogashira coupling

The starting materials, Pd@DualPore (2 mol%), and dimethylformamide (3 mL) were added to a Schlenk tube capped by a septum. The mixture was stirred at 120°C in an argon atmosphere for 18 h. After extraction, the crude mixture was analyzed by NMR.

2.3 Typical procedure for Stille coupling in flow

A methanol/dimethyl sulfoxide solution (MeOH/DMSO) **1** (0.033 M), arylstannane (1.5 eq), and lithium chloride (3 eq) were introduced into a column reactor filled with Pd@DualPore using a syringe pump or a plunger pump. The column reactor was heated at 97°C in a water bath; after it had reached a steady state, the solution was collected for 10 min. The solution was extracted and analyzed by GC to determine the yield of the product.

2.4 Typical procedure for hydrogenation in flow

A methanol solution containing 1-ethyl-4-nitrobenzene (**11**, 1.25 M) was introduced into the column reactor using

a plunger pump. In addition, hydrogen gas was introduced using a mass flow controller. The column reactor was dipped in a water bath to maintain its temperature at 25°C. After it had reached a steady state, the solution was collected for 10 min. The solution was analyzed by GC to determine the yield of the desired product **12**.

3 Results and discussion

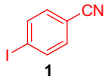
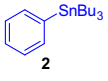
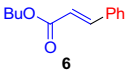
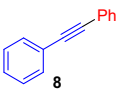
First, we tested the feasibility of the immobilized catalyst for cross-coupling reactions in a batch process. As shown in Table 1, we investigated three types of coupling reactions, in which aryl iodides (**1** and **4**) were reacted with arylstannane **2** (Stille coupling [30]), alkene **5** (Heck coupling [31]), or alkyne **7** (Sonogashira coupling [32,33]) in the presence of a 2-mol% immobilized palladium catalyst. From the Stille coupling (Table 1, entry 1), the corresponding biphenyl **3** was obtained in a high yield. The Heck and Sonogashira couplings (entries 2 and 3) resulted in full conversions of **4**. In particular, after the Heck and Sonogashira couplings, filtration, and extraction, pure products **6** and **8** were obtained, respectively.

Having confirmed the good tolerance of our immobilized palladium catalyst, we attempted to utilize it under flow conditions. We chose Stille coupling for demonstration purposes (Table 2). First, we applied the previous Suzuki coupling condition [26] to the flow Stille coupling using a co-solvent of methanol and tetrahydrofuran (THF) at 97°C. When tetra-*n*-butylammonium fluoride (TBAF) was used as an additive (Table 2, entry 1), the reaction yield was low. The reaction without the additive did not significantly change the result (entry 2), indicating that TBAF is not suitable for this reaction. Thus, we decided to use lithium chloride as an additive. As LiCl is not soluble in THF, we changed the co-solvent to methanol with DMSO. The use of LiCl increased the product yield (entry 3). By contrast, the reaction in MeOH/DMSO without the additive resulted in a dismal yield (entry 4), indicating that the addition of LiCl was crucial for this Stille coupling, presumably because the acceleration of the transmetallation step varies according to the strength of the Stannane–halogen bond

To increase the yield, we decreased the flow rate of the substrate solution to prolong the reaction time. When a flow rate of 0.3 mL·min^{-1} was applied (the previous flow rate was 1.0 mL·min^{-1}), the yield increased (entry 5), and a further decrease in the flow rate to 0.1 mL·min^{-1} led to a high yield of 72% (entry 6). After investigating the effects of the solvent ratio (entries 7–9), we found that 30% methanol with DMSO gave the best yield (79%, entry 7). However, although the yield was satisfactory, the lower flow rate resulted in lower productivity, calculated as the weight of the generated product (**3**) per time unit. Thus, we increased the flow rate to 1.0 mL and increased the length of the column reactor from 10 to 25 cm to achieve a sufficient reaction time. As anticipated, the longer column helped to maintain the product yield with a higher flow rate (entry 10), increasing the productivity tenfold.

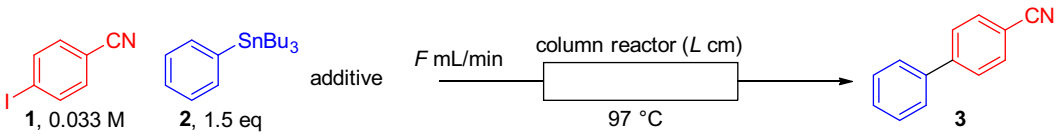
Having confirmed the usability of the palladium catalyst immobilized on DualPore, we decided to demonstrate the synthetic utility of this heterogeneous Stille coupling by producing a functional molecule. As a target, we selected 4-cyano-4′-*n*-pentylbiphenyl (**10**), named 5CB, which is a commonly used liquid crystal [34], because cross-coupling reactions have made important contributions in this field [35]. Using optimized conditions (Table 2, entry 10), we reacted tri-*n*-butyl-4-*n*-pentylphenylstannane (**9**) with **1**. As shown in Scheme 1, from a 60-min operation, **10** was

Table 1: Immobilized Pd-catalyzed coupling reactions in batch[a]

Entry	Aryl iodide	Coupling partner	Additive	Product	Conversion (%)
1	 1	 2	LiCl	 3	80[b]
2	 4	 5	iPr_2NEt	 6	quant
3	 4	 7	iPr_2Net CuI	 8	quant

[a] The reactions were carried out at 97°C for 18 h. [b] The product yield was determined by GC. See the supporting information for details. Bu: *n*-butyl group, iPr: isopropyl group, Ph: phenyl group.

Table 2: Investigation for flow Stille coupling[a]



Entry	Solvent	Additive[b]	F (mL·min^{-1})	L (cm)	Yield (%)	Productivity (mg·h^{-1})
1	MeOH/THF (2/8)	TBAF	1.0	10	17	60
2		None			10	35
3	MeOH/DMSO (2/8)	LiCl			29	103
4		None			10	35
5	MeOH/DMSO (2/8)	LiCl	0.3	10	44	47
6			0.1		72	26
7	MeOH/DMSO (3/7)	LiCl	0.1	10	79	28
8	MeOH/DMSO (5/5)				43	15
9	MeOH				Trace	<0.1
10	MeOH/DMSO (3/7)	LiCl	1.0	25	84	298

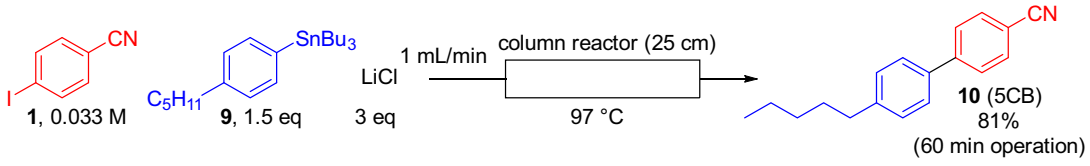
[a] The reaction solutions were collected for 10 min and analyzed by GC. [b] TBAF: 1.8 eq, LiCl: 3.0 eq.

successfully obtained in a high yield. It is noteworthy that after the 1-hour experiment, the weight difference of the palladium on the DualPore was only 7% even though the reaction was performed with the highly polar solvents. This strongly supports that this flow process can tolerate a long-time operation to increase productivity.

Having demonstrated the flow cross-coupling of the palladium catalyst immobilized on DualPore, we next focused on reactions using gases. Owing to the ubiquity of the nitro reduction process in organic synthesis [36], we decided to investigate the hydrogenation of nitro compounds to amines. We had previously shown that this transformation could be catalyzed by Pd@DualPore but only under batch conditions [37]. Thus, we attempted the flow hydrogenation of nitro compounds to demonstrate the utility and recyclability of the catalyst.

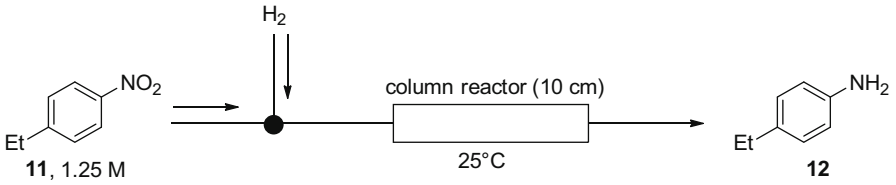
We chose to study the reduction of 1-ethyl-4-nitrobenzene (**11**); the results are summarized in Table 3. First, the substrate solution was mixed with hydrogen gas at a flow rate of 10 mL·min^{-1} and passed through the column reactor at 25°C. Under these conditions, we obtained the desired amine product **12**, albeit in low yield (Table 3, entry 1). Having confirmed the feasibility of the flow hydrogenation of nitro groups, we optimized the flow rate of the hydrogen gas (entries 1–5) and found that using 50 mL·min^{-1} of hydrogen gas afforded 80% yield (entry 5). To increase the product yield, we optimized the flow rate of the solution of **11** (entries 5–8). When the flow rate was decreased, the product yield increased (entries 6 and 7); however, the productivity was diminished. As a higher flow rate (entry 8) resulted in lower productivity, we concluded that the condition given in entry 5 was the best one.

Finally, once the flow Stille coupling and hydrogenation catalyzed by the palladium catalyst immobilized on DualPore had been achieved, we attempted to demonstrate a long-timescale operation. When the flow Stille cross-coupling was continued for 60 min, we found that the yield did not diminish (Figure 2a). Similarly, a 60-min operation for the nitro group reduction was also successfully carried out without any decrease in the yield (Figure 2b). These results strongly indicate the high recyclability of the immobilized catalyst under a wide range of reaction conditions.



Scheme 1: Flow synthesis for liquid crystal 5CB.

Table 3: Optimization of flow hydroxylation of nitro compounds[a]



Entry	H_2 flow rate (mL·min^{-1})	11 flow rate (mL·min^{-1})	Yield (%)	Productivity (g·h^{-1})
1	10	0.8	22	1.6
2	20		41	3.0
3	30		54	3.9
4	40		70	5.1
5	50		80	5.8
6	50	0.5	99	4.5
7		0.7	90	5.7
8		1.0	61	5.5

[a] The reaction solutions were collected for 10 min and analyzed by GC.

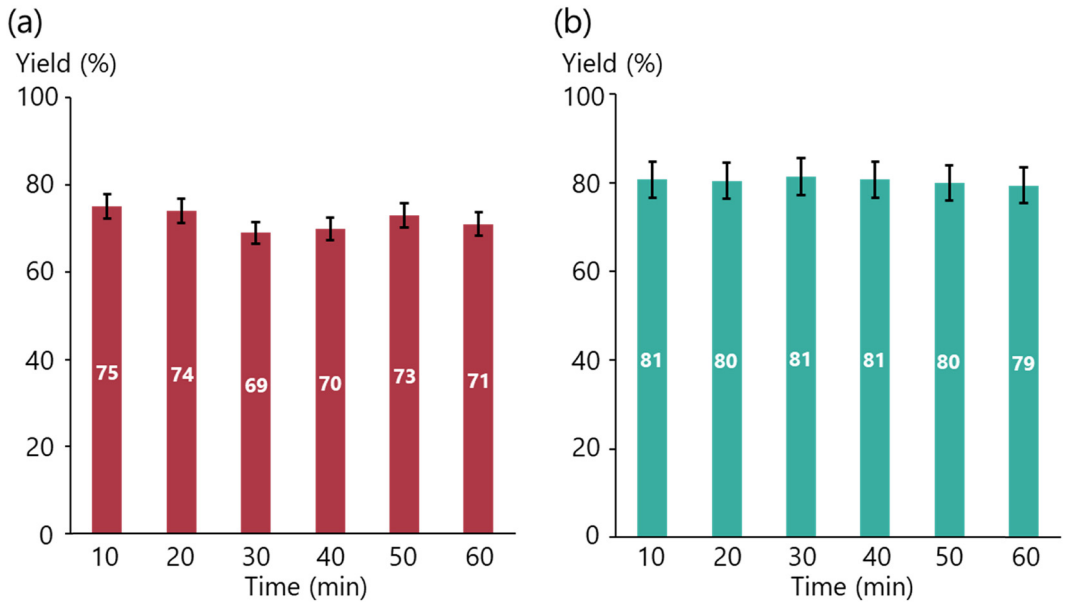


Figure 2: Long time operation for the flow reactions: (a) Stille cross-coupling and (b) hydrogenation. Error bars indicate the standard deviation of the measurements.

4 Conclusion

We demonstrated the utility of our palladium catalyst immobilized on dual-pore silica gel for coupling reactions under both batch and flow conditions, as well as for flow hydrogenation of the nitro compound. Although homogeneous flow cross-couplings have been widely developed and utilized [38,39], heterogeneous coupling reactions have great benefits, including the high recyclability of the catalyst. In particular, heterogeneous catalytic reactions promote the recyclability of the catalyst during long-timescale reactions, as proven by the 60-min operation demonstrated here. Further investigations are underway; these include optimizing the structure of

DualPore to increase immobilized palladium, synthesizing important molecules, and integrating [40] the coupling reactions with hydrogenation reactions using the same column reactor.

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Author contributions: Yosuke Ashikari: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, validation, visualization, writing – original draft, writing – review and editing; Kei Maekawa: investigation, resources; Chiemi Fujita: investigation; Kiyonari Shiosaki: investigation; Hongzhi Bai: resources; Kiyoshi Matsuyama: conceptualization, formal analysis, investigation, methodology, resources, writing – review and editing; Aiichiro Nagaki: conceptualization, funding acquisition, project administration, supervision, writing – review and editing.

Conflict of interest: Hongzhi Bai is working at DPS. Inc., and provided DualPore™.

Data availability statement: All data generated or analyzed during this study are included in this published article and the supporting material.

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