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# Flow grams-per-hour production enabled by hierarchical bimodal porous silica gel supported palladium column reactor having low pressure drop

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## ARTICLE INFO

### Keywords:

Hierarchical bimodal porous silica gel  
Palladium column  
Suzuki-Miyaura cross coupling  
Flow chemistry

## ABSTRACT

We describe a novel strategy to increase the unit-time-productivity of flow synthesis by using hierarchical bimodal porous silica gel (HBPSG) supported palladium column reactors. Because HBPSG has a significantly large surface area, the column reactors have low pressure drop, enabling high-volume production. We demonstrated flow synthesis of the precursor of adapalene, a pharmaceutical compound, at 5 g/h which is over 10-fold greater productivity than previous approaches.

## 1. Introduction

Flow chemistry has brought great benefits for organic synthetic chemistry [1,2]. Because of its excellent heat- and mass-transfer ability and precise reaction-time control performance, flow synthesis has achieved a lot of synthetic transformations, which are difficult or even impossible for conventional batch processes [3]. Especially, as U.S. Food and Drug Administration (FDA) announced [4], in pharmaceutical manufacturing, continuous flow synthesis has several advantages particularly in terms of productivity, safety, and reproducibility.

Palladium catalyzed cross-coupling reactions are ubiquitous in organic synthesis as well as pharmaceutical manufacturing [5]. Flow chemistry has showcased successful examples of flow-cross-coupling syntheses using transition metal homogeneous and heterogeneous catalysts [6]. From the viewpoint of manufacturing, heterogeneous catalysts, which are typically immobilized in a flow reactor tube, are ideal reactors because of their separation and recycling abilities. Despite these advantages, flow heterogeneous coupling reaction has little potential to scale-up.

Basically, scaling-up for flow synthesis is achieved by increasing the substrate solution flow rate (volume/time). Because the reaction columns are filled with catalysts and supporting materials, the pressure within a column may become much higher than that in a usual flow reactor. Thus slower flow rates (typically mL/h scale) have been

applied in heterogeneous column reactors resulting in lowered productivity of flow coupling reactions (typically hundreds mg/h) [6,7].

We hypothesized that increasing the number of column reactors would overcome the limitation to scale-up, and developed and reported parallel- and linear-column connection flow systems [8]. These systems allowed an increase in the number of catalyst-supported column reactors and simultaneous use of multiple columns, enabling a flow-rate increase corresponding to the number of columns. Although these systems improved productivity of the coupling reactions, the flow rate was insufficient (1 mL/min), prompting the necessity of novel column reactors with lower pressure drops for further improvement.

To solve this problem, we focused on hierarchical bimodal porous silica gel (HBPSG) as a supporting material for column reactors [9]. Three-dimensional silica gel (SiO<sub>2</sub>) with hierarchically macro-mesoporous structures are important porous materials for catalysis support applications. Compared with conventional SiO<sub>2</sub> without hierarchical porosity, microparticles of HBPSG have several inherent advantages, including high surface-area-to-volume ratios, small transverse temperature gradients, and low pressure drop [10]. Thus we envisaged a column reactor with HBPSG as a supporting material for palladium catalyst would be an ideal reactor having low pressure drop, enabling high productivity. Herein we report flow Suzuki–Miyaura cross coupling reaction [11] using HBPSG supported palladium column reactors, which achieved extremely high flow rates such as 8 mL/min and high

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<https://doi.org/10.1016/j.cattod.2020.07.014>

Received 26 March 2020; Received in revised form 2 June 2020; Accepted 13 July 2020

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productivity such as 5 g/h of a precursor of adapalene, a third-generation topical retinoid mainly used in the treatment of mild-moderate acne.

## 2. Material and methods

### 2.1. Experimental instruments and materials

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Varian MERCURY plus-400 spectrometer ( $^1\text{H}$  400 MHz,  $^{13}\text{C}$  100 MHz). Chemical shifts were recorded using TMS (0.0 ppm) or solvent (2.50 ppm for DMSO) signals as an internal standard for  $^1\text{H}$  NMR, and methine signal of  $\text{CHCl}_3$  for  $^{13}\text{C}$  NMR (77.0 ppm) unless otherwise noted. Gas chromatography (GC) analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, CBP1; 0.22 mm x 25 m). High performance liquid chromatography was performed on Shimadzu with YMC TA12S05-2546WT (4.6 x 250 mm, acetone/water = 9/1, v/v, flow rate = 1.0 mL/min, 30 °C, UV = 220 nm) using commercial compounds. Electrospray ionization (ESI) mass spectrum was obtained on Thermo Fisher Scientific EXACTIVE plus. X-ray fluorescence (XRF) analyses were carried out using Shimadzu EDX-8000. For flow coupling reactions, a syringe pump (Harvard Model PHD 2000 or PHD ULTRA) equipped with a gastight syringe (purchased from SGE), or a plunger pump (SHIMADZU LC-20AR) was used for introduction of the reaction solutions into the column reactor. For flow synthesis of lithium arylborate complexes, stainless steel (SUS304) T-shaped micromixers with inner diameter (ID  $\phi$ ) of 250  $\mu\text{m}$  (Sanko Seiki Co., Inc.), stainless steel (SUS316) microtube reactors ID  $\phi$  1000  $\mu\text{m}$  (GL Sciences), and PTFE pre-cooling tube ID  $\phi$  1000  $\mu\text{m}$  (ISIS Co, Ltd.) were used. The solution of *n*-butyllithium was prepared by dilution of the commercial solution with dehydrated *n*-hexane.

### 2.2. Preparation of supercritical fluid-assisted immobilization of palladium nanoparticles in dual-pore silica gel

Palladium (Pd) nanoparticles were immobilized in the pores of dual-pore  $\text{SiO}_2$  using supercritical carbon dioxide ( $\text{scCO}_2$ )-acetone solution. As in our previous report [10d], palladium(II) acetate ( $\text{Pd}(\text{OAc})_2$ ) was used as the precursor of Pd nanoparticles, because of its good solubility to  $\text{scCO}_2$ -acetone solution. To immobilize Pd nanoparticles in the supports, 5 g of dried dual-pore  $\text{SiO}_2$  microparticles [12], 0.3 g of Pd ( $\text{OAc})_2$ , and 180 mL of acetone were placed in a 200 mL high-pressure cell.  $\text{CO}_2$  was pumped into the cell through a preheater at 20 MPa and 343 K. The cell was then placed in an air bath, and the system temperature was maintained at 343 K. The mixture was stirred with a magnetic agitator for 24 h. After which the vessel was slowly depressurized to atmospheric pressure over approx. 30 min and the content removed. Leftover acetone was removed by centrifugation, and the precipitate was successively subjected to reduction in a mixed stream of  $\text{H}_2$  and  $\text{N}_2$  (5 mL/min each) at 573 K for 5 h. During reduction, the formed Pd nanoparticles were dispersed within the pores of dual-pore  $\text{SiO}_2$ . After the reduction, the color of the sample had changed from ochre ( $\text{Pd}(\text{OAc})_2$ ) to gray. XRF analysis indicated that the amount of Pd in dual-pore  $\text{SiO}_2$  was 0.3 wt%. In order to improve hydrophobicity, the surface Pd@dual-pore  $\text{SiO}_2$  was coated with hexamethyldisilazane (HMDS). 2 g of Pd@dual-pore  $\text{SiO}_2$  was added in 100 ml of toluene solution containing 10 wt% HMDS. The mixture was heated under reflux at 373 K for 12 h. Leftover toluene solution was removed by filtration, and Pd@dual-pore  $\text{SiO}_2$  were washed with absolute 2-propanol to remove the free HMDS. The remaining 2-propanol was removed under reduced pressure at 353 K. 0.25 g of Pd@dual-pore  $\text{SiO}_2$  was placed in stainless steel (SUS316) tube reactors ID  $\phi$  4.6 mm and lengths of 100 mm and 250 mm.

### 2.3. Typical procedure for flow Suzuki coupling reaction using commercial boronic acid

To a 200 mL Erlenmeyer flask were placed phenyl boronic acid (1, 1.65 g, 13.5 mmol), 4-iodobenzonitrile (2, 1.03 g, 4.5 mmol), potassium hydroxide (0.50 g, 9.0 mmol), methanol (MeOH, 30 mL), and tetrahydrofuran (THF, 120 mL). After those chemicals had homogeneously dissolved, the solution was introduced into the column reactor (10 cm), which was heated to 60 °C in a water bath, by a syringe pump (flow rate: 1.0 mL/min). After a steady state was reached (typically by 5 min), the product solution was collected for 10 min. To the aliquot, sat.  $\text{NH}_4\text{Cl}$  aq., ethyl acetate (EtOAc), and *n*-tridecane (internal standard) were added, and then the organic phase was analyzed by GC to determine the yield of the desired product, 4-cyanobiphenyl (3), whose retention time on GC was in a good agreement with that of commercial one.

### 2.4. Typical procedure for flow Suzuki coupling reaction using arylborate

The reaction solution containing lithium triisopropoxy phenyl borate (4) with 2 was prepared as follows: To a flame dried round-bottomed flask were added bromobenzene (4.71 g, 30.0 mmol) and THF (200 mL). The solution was stirred at -78 °C, and a solution of *n*-butyllithium (1.6 mol/L, 19.7 mL) was added dropwise. After 15 min, triisopropyl borate (5.92 g, 31.5 mmol) was added to the mixture, and the solution was stirred at the same temperature for 2 h. The reaction was quenched by methanol (54 mL) to obtain 300 mL solution. Finally, to an aliquot (50 mL), 4-iodobenzonitrile (2, 763 mg, 3.33 mmol), THF (10 mL), and methanol (40 mL) were added to prepare the reaction solution (0.033 mol/L for 2).

The reaction solution was introduced into column reactor(s) (10, 20, 25 and 50 cm), whose length was the sum of those of the columns connected by stainless tubes. The column reactor was heated by a water bath. The syringe pump was applied for the reaction with 10 cm column reactor (flow rate: 0.5–5 mL/min), whereas a plunger pump was used for reactions in 20, 25 and 50 cm column reactors (flow rate: 5 mL/min). After a steady state was reached, the product solution was collected. To the aliquot, sat.  $\text{NH}_4\text{Cl}$  aq. and EtOAc were added, and the organic phase was analyzed by GC to determine the yield of the desired product, 4-cyanobiphenyl (3). The yields were determined by area percentage of 3 with 2 using a scaling factor calculated by the commercial compounds.

### 2.5. Flow synthesis of *tert*-butyl 6-(3-(1-adamantyl)-4-anisyl)-2-naphthoate (7) and its transformation to adapalene

The reaction solution containing lithium arylborate complex 5 was prepared using a flow microreactor system comprising two T-shaped micromixers (M1 and M2), two microtube reactors (R1 and R2), and three pre-cooling units dipped into a cooling bath at 0 °C. A solution of 2-(1-adamantyl)-4-bromoanisole (0.10 mol/L in THF, flow rate: 6.0 mL/min) and a solution of *n*-butyllithium (0.42 mol/L in *n*-hexane, flow rate: 1.5 mL/min) were introduced to M1 using syringe pumps, and the mixture was passed through R1 (50 cm, residence time  $t^{\text{R1}} = 3.1$  s). The resulting solution was introduced to M2, where a solution of triisopropyl borate (0.42 mol/L in THF) was introduced (flow rate: 1.5 mL/min). The resulting solution was passed through R2 (100 cm, residence time  $t^{\text{R2}} = 5.2$  s). After a steady state was reached, the product solution was put into a 300 mL round-bottomed flask. To an aliquot (171 mL) of the solution were added *tert*-butyl 6-iodo-2-naphthoate (6, 2.72 g, 7.67 mmol) and methanol (138 mL) to obtain the reaction solution (24.8 mol/L of 6).

For Suzuki coupling, the 80 cm column reactor system comprising three 10 cm reactors with two 25 cm reactors connected by stainless tubes, heated to 97 °C by a water bath, was applied. The reaction solution was introduced into the column reactor by plunger pump (flow rate: 8 mL/min). After a steady state was reached, the product solution

was collected for 20 min. To the solution, water was added, and the mixture was extracted by dichloromethane. The combined organic phase was concentrated under reduced pressure, and the obtained solid was washed by methanol to afford *tert*-butyl 6-(3-(1-adamantyl)-4-anisyl)-2-naphthoate (**7**) in 91 % yield (1.70 g, 3.62 mmol) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.66 (s, 9 H), 1.80 (s, 6 H), 2.10 (s, 3 H), 2.18 (s, 6 H), 3.90 (s, 3 H), 6.99 (d,  $J = 8.4$  Hz, 1 H), 7.54 (dd,  $J = 2.4, 8.4$  Hz, 1 H), 7.60 (d,  $J = 2.4$  Hz, 1 H), 7.78 (dd,  $J = 2.0, 8.4$  Hz, 1 H), 7.88 (d,  $J = 8.8$  Hz, 1 H), 7.97 (d,  $J = 8.4$  Hz, 1 H), 8.00 (br, 1 H), 8.03 (dd,  $J = 1.6, 8.4$  Hz, 1 H), 8.54 (br, 1 H),  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  28.3, 29.1, 37.1, 37.2, 40.6, 55.1, 81.1, 112.0, 124.7, 125.6, 125.7, 125.9, 126.3, 127.9, 128.8, 129.6, 130.4, 131.2, 132.6, 135.7, 138.9, 141.0, 158.8, 166.0, HRMS (ESI) calculated for  $\text{C}_{32}\text{H}_{36}\text{O}_3\text{Na}$  [ $\text{M} + \text{Na}^+$ ]: 491.2557, found 491.2541.

To a 200 mL round-bottomed flask were added **7** (1.68 g, 3.59 mmol, the whole amount of the product of the former synthesis), trifluoroacetic acid (38 mL), and dichloromethane (115 mL). The mixture was stirred at room temperature for 22 h then added to distilled water (450 mL). After extraction ( $\text{CH}_2\text{Cl}_2$ , 50 mL), the combined organic phase was concentrated under reduced pressure to afford 6-(3-(1-adamantyl)-4-anisyl)-2-naphthoic acid (adapalene) in 100 % yield (1.48 g, 3.59 mmol) as a pale yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.76 (s, 6 H) 2.07 (s, 3 H), 2.14 (s, 6 H), 3.87 (s, 3 H), 7.12 (d,  $J = 8.8$  Hz, 1 H), 7.58 (d,  $J = 2.4$  Hz, 1 H), 7.66 (dd,  $J = 2.4, 8.4$  Hz, 1 H), 7.89 (dd,  $J = 2.0, 8.4$  Hz, 1 H), 7.98 (dd,  $J = 1.6, 8.4$  Hz, 1 H), 8.08 (d,  $J = 8.8$  Hz, 1 H), 8.16 (d,  $J = 8.8$  Hz, 1 H), 8.22 (s, 1 H), 8.58 (s, 1 H), 13.05, br, 1 H). The spectrum was in good agreement with a previous one [8b].

### 3. Results and discussion

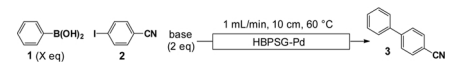
#### 3.1. Flow Suzuki–Miyaura coupling reaction of phenylboronic acid with 4-iodobenzonitrile using HBPSG-Pd column reactor

First we tried flow Suzuki–Miyaura cross coupling reaction of commercially available reagents using HBPSG-Pd column. The combination of phenylboronic acid (**1**) with 4-iodobenzonitrile (**2**) was selected as reagents to compare catalyst activity to our previous report [8b]. Since the support was silica gel, we avoided highly polar solvent such as water. Thus, we chose to use THF, toluene, and co-solvent of methanol with THF as reaction solvent. In those solvent conditions, inorganic base, which is typically used for conventional Suzuki–Miyaura coupling reaction, was not applicable because they are not soluble to such less polar solvents. Thus, we used organic base such as triethylamine ( $\text{Et}_3\text{N}$ ) and tri-*n*-butylammonium fluoride (TBAF) instead of the inorganic base. The investigation was carried out using 10 cm column reactor in a 60 °C water bath. The solution of **2**, **1** ( $X$  equiv to **2**), and base (2 equiv to **1**) in the respective solvent was introduced into the column reactor by syringe pumps at the flow rate of 1 mL/min. The results are summarized in Table 1.

Entries 1–5 of Table 1 indicate the combination of less polar solvents with organic base was not applicable for flow Suzuki–Miyaura cross coupling reaction. Only entry 6 (10 % MeOH/THF with TBAF) yielded an amount of product **3** but the yield rapidly decreased during continuous collection of the reacted solution (62 % to 44 %), suggesting this condition may seriously damage the column reactor. Although those reactions resulted in dismal yields, the trial of TBAF suggested adequate reaction conditions would achieve a high yield of **3**, so we continued to optimize reaction conditions. We found that potassium hydroxide, an inorganic base, was soluble to 10 % MeOH/THF solvent, and using this condition, 45 % of product was obtained (entry 7). The yield was increased when the amount of **1** was increased (entry 8). Finally, 83 % yield was achieved with 3 equivalent of phenylboronic acid in 20 % methanol/THF solution (entry 9). While our previous column reactor required temperatures above 80 °C for over 80 % yield of this particular transformation [8b], in the present study 83 % yield

**Table 1**

Flow Suzuki–Miyaura coupling reaction of phenylboronic acid (**1**) with 4-iodobenzonitrile (**2**) using HBPSG-Pd column reactor.



Entry	solvent	X eq.	base	Yield (%)
1	THF	1.1	$\text{Et}_3\text{N}$	1
2			TBAF	1
3	Toluene	1.1	$\text{Et}_3\text{N}$	1
4			TBAF	7
5	10 % MeOH/THF	1.1	$\text{Et}_3\text{N}$	12
6			TBAF	44
7			KOH	45
8		3	KOH	61
9	20 % MeOH/THF	3	KOH	83

was accomplished at 60 °C, which indicated the novel column reactor filled with HBPSG-Pd has higher reactivity than the previous one.

Since the optimized condition (Table 1 entry 9) was in hand, we demonstrated continuous production using this column reactor. The solution containing **1**, **2** (3 eq), and KOH in 20 % methanol/THF was passed through 10 cm of HBPSG-Pd column reactor dipped in 60 °C water bath with a 1 mL/min flow rate. The 100 mL solution was continuously introduced and an aliquot was collected every 10 min. The results are shown in Fig. 1. During 80 min the reaction yield remained around 80 %, strongly suggesting high productivity and high reusability of this column reactor. It should be mentioned that after a long-time flow synthesis, all palladium might be finally removed from the support [6b] although the reaction efficiency was not diminished after 80 min operation in our reactor. Therefore, the preferred long operation for larger scale experiments would be considered as a combination with an appropriate catalyst recycling technology in near future.

#### 3.2. Flow Suzuki–Miyaura coupling reaction of phenylborate with 4-iodobenzonitrile using HBPSG-Pd column reactor

We next investigated the integration of lithiation, borylation, and coupling reaction to enhance the process. We previously reported Suzuki–Miyaura cross coupling reaction using lithium arylborate complex, which is synthesized from halogen–lithium exchange reaction of aryl halide with butyllithiums followed by reaction with boronic esters. Because the products are lithium arylborate complexes, Suzuki reaction can proceed without a base [13]. We envisaged that if our new column reactor was applicable for the coupling reaction of such aryl borates, a high productive integrated coupling process would be achieved.

Lithium triisopropoxy phenylborate (**4**) was synthesized from the reaction of phenyl lithium, which was generated by halogen–lithium exchange of bromobenzene with *n*-butyllithium, with triisopropyl borate, shown in Scheme 1. To the solution, 4-iodobenzonitrile (**2**) and methanol were added to make the concentration of **2** to 0.033 M. The resultant solution was introduced into the HBPSG-Pd column reactor (10 cm) by syringe pump at the respective flow rates. The results are summarized in Table 2.

The initial condition (flow rate: 0.5 mL/min, reaction temperature: 60 °C, entry 1) gave an excellent result where **2** was perfectly converted to the desired product **3**. Encouraged by this result, we increased the flow rate to 1.0 mL/min in order to increase the volume per unit time. However, disappointingly, the product yield was dramatically decreased, leading to decreased productivity (entry 2). Then we raised the reaction temperature (entries 3 and 4). When applying higher temperature, product yields were increased, and finally 99 % yield was achieved at 97 °C (entry 4), doubling productivity. As expected, this temperature produced higher flow rate with high productivity and increased flow rates (entries 5–9). As anticipated, productivity increased

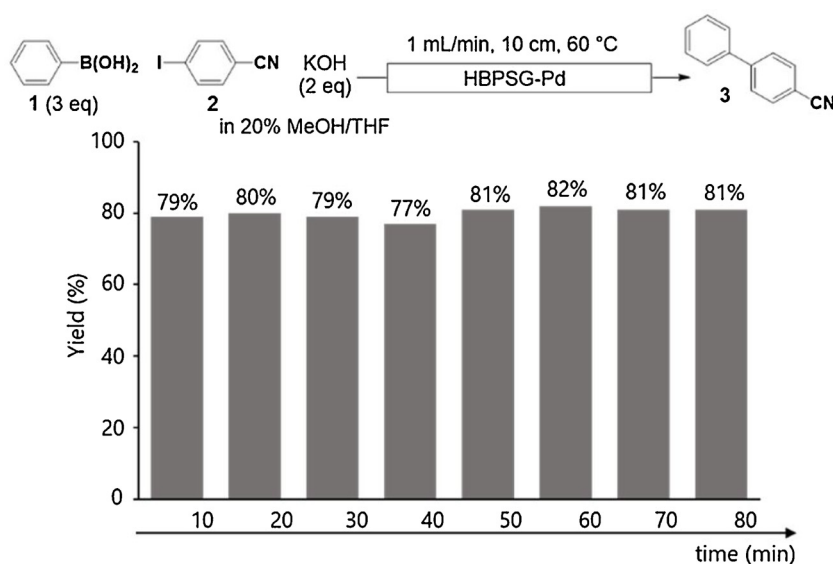
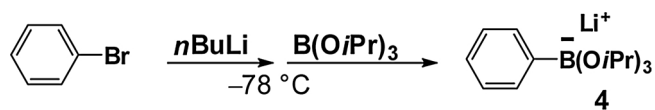


Fig. 1. 80 min continuous production of 3 using HBPSG-Pd column. Yields of 3 in the solution collected every 10 min determined by gas chromatography are shown.



Scheme 1. Synthesis of lithium triisopropoxy phenylborate (4).

Table 2

Flow Suzuki–Miyaura coupling reaction of triisopropoxy phenylborate (4) with 4-iodobenzonitrile (2) using HBPSG-Pd column reactor.

Entry	T (°C)	F (mL/min)	L (cm)	Yield (%)	Productivity (g/h)
1	60	0.5	10	100	0.18
2	60	1.0		37	0.13
3	80	1.0		79	0.28
4	97	1.0		99	0.32
5	97	1.5	10	89	0.47
6		2.0		80	0.57
7		3.0		65	0.70
8		4.0		56	0.79
9		5.0		51	0.90
10	97	5.0	20	87	1.5
11		5.0	25	89	1.6
12		5.0	50	96	1.7

with increased flow rate, and 0.9 g/h productivity was achieved (entry 9). To our amazement, quite high flow rates, such as 5 mL/min, were achieved by use of the syringe pump, which is usually considered unsuitable equipment for introducing reaction solution into column reactors with high flow rates. This strongly signified that our HBPSG-Pd column reactor has extraordinarily low pressure drop. Although this flow rate strategy increased productivity near to g/h scale, conversion worsened (51 %), reducing the benefits of this process in terms of green economy. To overcome the low conversion, we decided to take advantage of the series connection of the reactors (entries 10–12) [8b]. With increasing reactor length, the conversion of 2 increased, and finally 96 % yield was achieved with a 50 cm column reactor (entry 12). Compared to entry 4, this result seemed reasonable; a five times longer reactor with 5-fold faster flow rate achieved a corresponding product yield, quintupling productivity.

Since a benchmark condition (entry 12) was established, our interest moved toward further improvement of productivity. First, in

order to take full advantage of the low pressure drop column reactor, we investigated reactions with higher flow rates. With a 50 cm column reactor, the flow rate was gradually increased to 10 mL/min, which was double the benchmark giving an acceptable product yield (90 %) as shown in Fig. 2(a). Another possibility for productivity improvement is increase of the concentration. We carried out the flow coupling reaction with increased concentration of 2 (and 4). The results summarized in Fig. 2(b) were beyond expectation; the product yield was not diminished, but, if anything, increased. Although the detailed reason was unclear, the coupling reaction in HBPSG reactors seemed to be accelerated by higher concentration. Finally, a 4-fold higher concentration enabled over quadruple higher productivity, 7.1 g/h.

During these series of experiments, the general idea for improvement of productivity was established. Increasing reaction temperature and length helped to increase the product yield, and increasing flow rate and concentration directly contributed to improvement of the mass of production in this process.

### 3.3. Flow synthesis of adapalene precursor using HBPSG-Pd column reactor and its transformation to adapalene

Finally, we demonstrated flow synthesis of *tert*-butyl 6-(3-(1-adamantyl)-4-anisyl)-2-naphthoate (7), the precursor of adapalene, which is a third-generation topical retinoid mainly used in the treatment of mild-moderate acne. In accordance with the above mentioned benchmark, we adopted 80 cm length HBPSG-Pd column reactor with 8 mL/min flow rate, depicted in Fig. 3.

In accordance with our previous method [14], lithium arylborate 5 was synthesized from the corresponding arylbromide in a flow micro-reactor. To the solution of 5, the coupling partner 6, which has *tert*-butyl group instead of methyl group to increase solubility and accessibility to adapalene, was added, and the obtained solution was passed through the column reactors at 97 °C. After 20 min operation, we isolated 1.7 g of the coupling product 7 (91 % yield), which was quantitatively converted to adapalene. It is noteworthy that our previous report using another column reactor [8b], although the ester moiety was methyl group instead of *tert*-butyl group, showcased 370 mg/h production of this coupling process. This means over 10-fold higher productivity was achieved by our new HBPSG-Pd reactor. Because our reactor has quite lower pressure drop than the previous one, dramatically high flow rate of the reaction solution was applicable, leading such a high productivity.



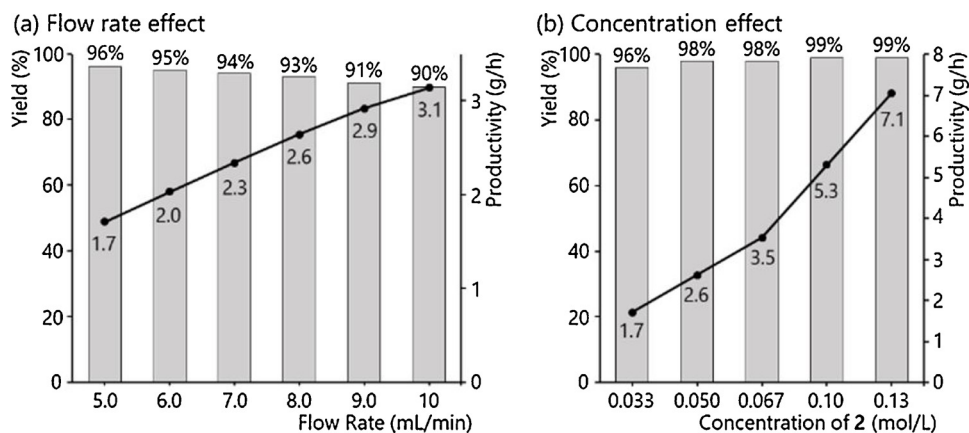


Fig. 2. Effects of flow rate and concentration for Suzuki–Miyaura coupling reaction of trisopropoxy phenylborate with 4-iodobenzonitrile (2). Bar: yield (%). Dot: productivity (g/h).

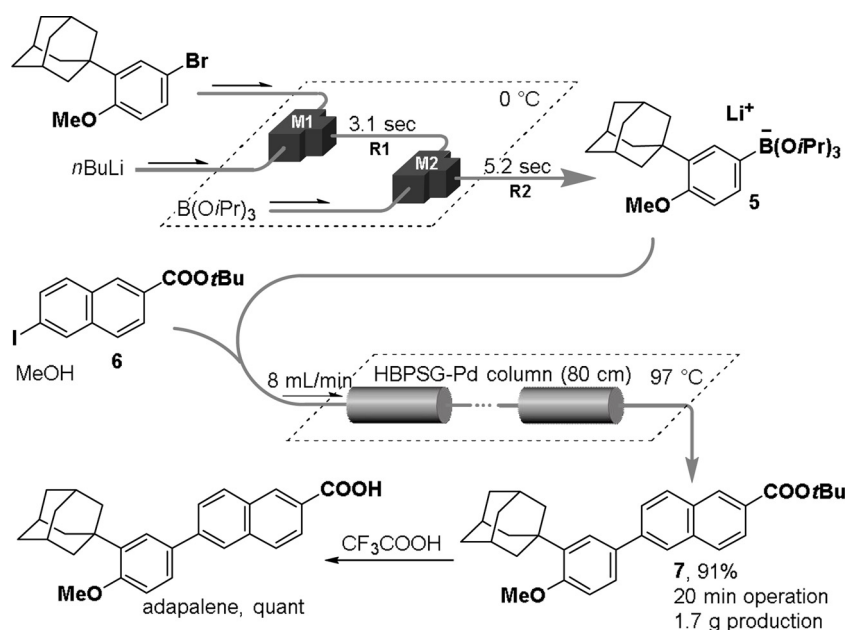


Fig. 3. Flow synthesis of *tert*-butyl 6-(3-(1-adamantyl)-4-anisyl)-2-naphthoate (7) and its transformation to adapalene.

#### 4. Conclusion

Gram-per-hour productive flow Suzuki coupling was developed by means of a hierarchical bimodal porous silica gel supported palladium catalyst reactor. Because HBPSG has a significantly big surface area, this present column reactor has low pressure drop. This remarkable characteristic enabled extremely high productivity improved by increasing reaction temperature, flow rate, reactor length, and concentration of reagents. Just 20 min operation produced 1.7 g of the precursor to adapalene, a pharmaceutical compound, demonstrating the practicality of this process and column reactor. We are confident that this study represents a major step in the field of flow manufacturing.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Acknowledgments

This work was partially supported by JSPS KAKENHI Grant Numbers JP15H05849 (Grant-in-Aid for Scientific Research on Innovative Areas 2707 Middle molecular strategy), JP26288049 (Grant-in-Aid for Scientific Research (B)), JP26220804 (Grant-in-Aid for Scientific Research (S)), JP25220913 (Grant-in-Aid for Scientific Research (S)), and JP17865428 (Grant-in-Aid for Scientific Research (C)). This work was also partially supported by AMED (JP19ak0101090), the Japan Science and Technology Agency's (JST) A-step program (18067420), CREST, and the Ogasawara Foundation for the Promotion of Science & Engineering.

#### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.cattod.2020.07.014>.

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