Supporting Information

A continuous flow process for biaryls based on sequential Suzuki–Miyaura coupling and supercritical carbon dioxide extraction

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1. General statements

Solution NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz (^{1}H NMR), 100 MHz (^{13}C NMR). Chemical shifts were given in ppm relative to internal Me$_4$Si (^{1}H NMR: δ 0.00 ppm) and CDCl$_3$ (^{13}C NMR: δ 77.0 ppm). Gas chromatography-flame ionization detector (GC-FID) analysis was performed on a SHIMADZU GC-2025 instrument with a flame ionization detector, using a Restek Rtx®-5 capillary column (30 m, 0.25 mm, 0.25 μm). After 2 min at 60 °C, the temperature was increased in 20 °C min^{-1} rate up to 280 °C and kept at 280 °C for 8 min. High-performance liquid chromatography (HPLC) was performed on SHIMADZU prominence series equipped with UV detector (SPD-20A) using an ODS type column and a guard column (Shim-pack VP ODS (I.D. = 4.6 mm, L = 150 mm) and Shim-pack GVP ODS). Ion chromatography (IC) was performed on Metrohm AG, Eco IC. Inductivity coupled plasma atomic emission spectrometry (ICP-AES) analysis was performed on Seiko Instruments Inc., SPS3100.

4-Bromobenzonitrile (>97%), phenylboronic acid (>95.0%), 4-cyanobiphenyl (>97%), tripotassium phosphate (>95.0%), dipotassium hydrogenphosphate (>99.0%), potassium bromide (>99.0%), ethanol (99.5%), n-dodecane (99.0%) and Celite® 545 were purchased form FUJIFILM Wako Pure Chemical Corporation. Boric acid (99.8%) was purchased from Stream Chemicals Inc. CO$_2$ (>99.95%) was purchased from AIR WATER INC. Formic acid aqueous solution (0.1 wt%) and acetonitrile (>95%) for HPLC analysis were purchased from KANTO CHEMICAL CO., INC. and Thermo Fischer Scientific Inc. Other organic chemicals and solvents were purchased from FUJIFILM Wako Pure Chemical Corporation and Sigma-Aldrich Co., Tokyo Chemical Industry Co., Ltd. These chemicals were used without further purification.

2. Preparation of the Immobilized Pd catalyst

The procedure of the catalyst was carried out according to our previous work.[1]

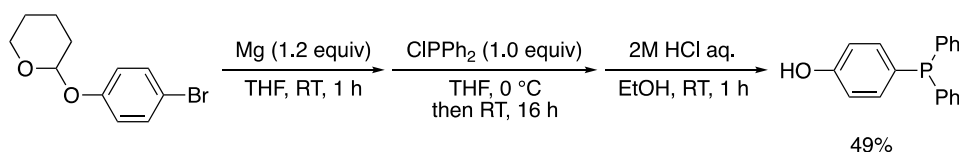### 2.1. 2-(4-Bromophenoxy)tetrahydro-2*H*-pyran
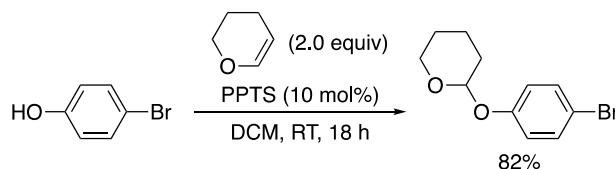
Scheme S1.

To a dichloromethane solution (66 mL) of 4-bromophenol (5.71g, 33.0 mmol) and pyridinium *p*-toluenesulfonate (0.829 g, 3.30 mmol) was added slowly 3,4-dihydro-2*H*-pyran (6.00 mL, 66.0 mmol) over 5 min at room temperature. After stirring at room temperature for 18 h, disappearance of 4-bromophenol was confirmed by TLC analysis. After removing the solvent under reduced pressure, the crude residue (ca. 10 g) was obtained and purified by flash column chromatography (silica gel, hexane:EtOAc = 10:1) to afford 2-(4-bromophenoxy)tetrahydro-2*H*-pyran (6.93 g, 82%) as a white solid.

2-(4-Bromophenoxy)tetrahydro-2*H*-pyran: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.53–1.76 (m, 2H), 1.77–1.91 (m, 2H), 1.92–2.07 (m, 2H), 3.59 (dtd, *J* = 11.4 MHz, 4.0 MHz, 1.4 MHz, 1H), 3.86 (ddd, *J* = 11.2, 9.6, 3.2 Hz, 1H), 5.37 (t, *J* = 3.2 MHz, 1H), 6.90–6.97 (m, 2H), 7.33–7.40 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 18.5, 24.9, 30.0, 61.7, 96.2, 113.6, 118.1, 132.0, 156.0.

Spectral data for this compound showed good agreement with the literature data.[2]

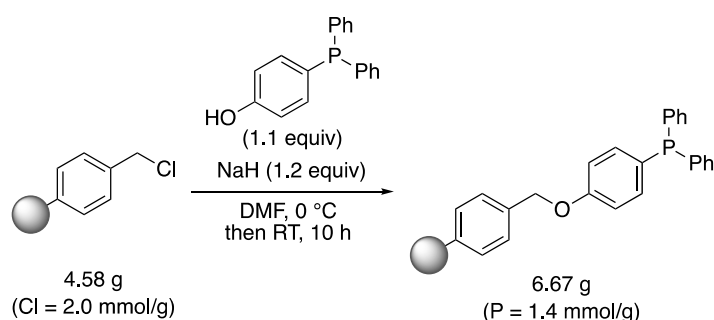### 2.2 4-(Diphenylphosphanyl)phenol

Scheme S2.

To a THF solution (34 mL) of chlorodiphenylphosphine (7.50 g, 34.0 mmol) was added dropwise a THF solution (34 mL) of the Grignard reagent prepared from 2-(4-bromophenoxy)tetrahydro-2*H*-pyran (8.73 g, 34.0 mmol) and magnesium turning (990 mg, 40.7 mmol), at 0 °C over 20 min. After stirring at room temperature for 16 h, the reaction mixture was cooled to 0 °C and aqueous HCl (2 M, 40 mL) and EtOH (20 mL) were added. The resulting solution was stirred for 1 h at room temperature and concentrated under reduced pressure to remove THF and EtOH. The mixture was extracted three times with dichloromethane. The combined extract was washed with brine and dried over anhydrous Na$_2$SO$_4$. After removal of the solvent, the residue was purified

by flash column chromatography (silica gel, hexane–EtOAc) to afford 4-(Diphenylphosphanyl)phenol (4.61 g, 49%) as a white solid.

4-(Diphenylphosphanyl)phenol: ^{1}H NMR (400 MHz, CDCl3): δ 5.52 (s, 1H), 6.82 (d, J = 8.4 Hz, 2H), 7.18–7.24 (m, 2H), 7.25–7.35 (m, 10H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 115.8 (d, J_{CP} = 8 Hz), 127.5, 128.4 (d, J_{CP} = 7 Hz), 128.5, 133.4 (d, J_{CP} = 19 Hz), 135.8 (d, J_{CP} = 21 Hz), 137.6 (d, J_{CP} = 9 Hz), 156.5.

Spectral data for this compound showed good agreement with the literature data.[3]

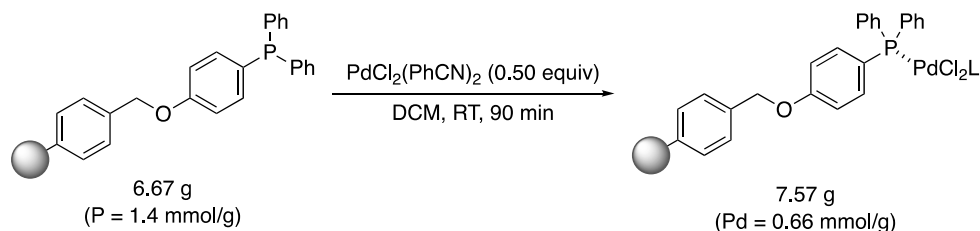## 2.3 Immobilized triarylphosphine resin

Scheme S3.

To a DMF solution (50 mL) of 4-(diphenylphosphanyl)phenol (2.81 g, 10.1 mmol) was added slowly NaH (60 wt%, 440 mg, 11.0 mmol) at 0 °C. After stirring at room temperature for 60 min, chloromethyl polystyrene resin crosslinked with 1%-divinylbenzene (ca. 2.0 mmol of Cl /g, 4.58 g, 9.16 mmol) and additional DMF (50 mL) were added to the reaction mixture at room temperature. After the reaction mixture was stirred at room temperature for 20 h, the resulted resin was collected by filtration and washed with H$_2$O and DMF, EtOAc, hexane, respectively and dried under reduced pressure at 40 °C to give the immobilized triarylphosphine resin (6.67 g, ca. 1.35 mmol of P/g) as pale yellow beads. The loading amount of phosphine was estimated by the amount of the consumed 4-(diphenylphosphanyl)phenol.

Immobilized triarylphosphine resin: ^{31}P CP/MS NMR (162.1 MHz): δ –4.3.

2.4 Immobilized Pd catalyst

Scheme S4.

The immobilized triarylphosphine resin (6.67 g, 9.00 mmol of P) and PdCl$_2$(PhCN)$_2$ (1.73 g, 4.50 mmol) were placed in the 300 mL flask (Pd/P = 1:2 molar ratio). Anhydrous dichloromethane (120 mL) was added to the flask, and the mixture was stirred at room temperature for 90 min. The solution color gradually changed from orange to colorless. In contrast, the resin changed from pale yellow beads to orange beads. The resulted resin was collected by filtration and washed with dichloromethane and dried under reduced pressure at room temperature to give the desired catalyst (7.57 g) as orange beads. The loading amount of Pd was determined to be 0.655 mmol/g by ICP-AES analysis.

Immobilized Pd catalyst: ^{31}P CP/MS NMR (162.1 MHz): δ 32.2, 26.9, –4.0.

3. Optimization for the continuous flow synthesis module

3.1. The setup and general procedure
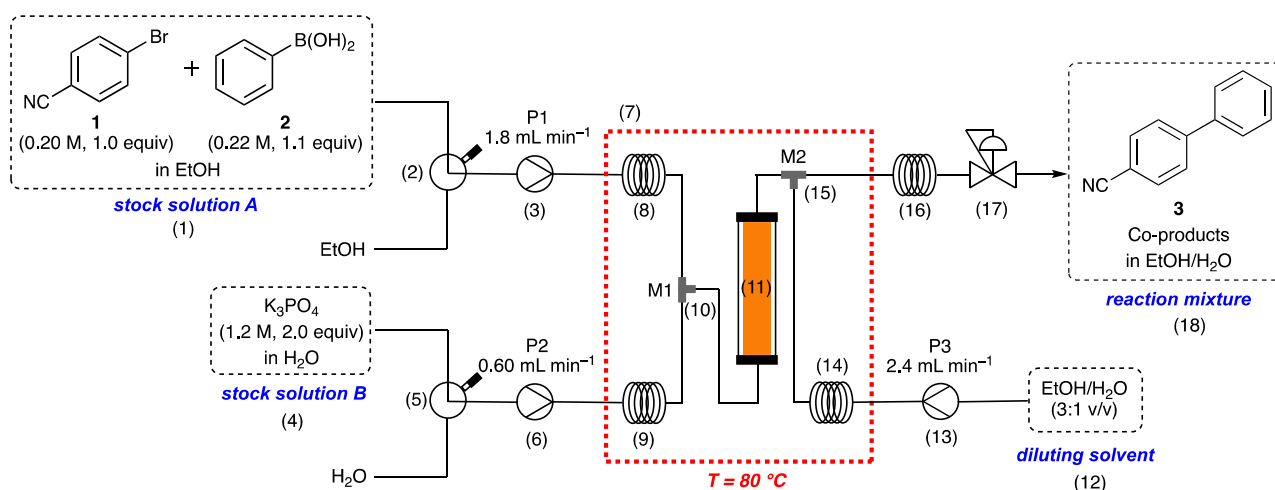
(1) stock solution A, (2) 3-way valve, (3) pump (TACMINA Corporation, Smoothflow Pump Q-10-6T-P-X), (4) stock solution B, (5) 3-way valve, (6) pump (TACMINA Corporation, Smoothflow Pump Q-10-6T-P-X), (7) Oven (ESPEC CORP., Air-forced Oven LC-114), (8) preheating coiled tube (SUS316, I.D. 0.8 mm, 200 cm length), (9) preheating coiled tube (SUS316, I.D. 0.8 mm, 200 cm length), (10) micro T-shaped mixer (I.D. 0.3 mm, Swagelok Co., Low Dead Volume Union Tee, SS-1F0-3GC), (11) column reactor (TOKYO RIKAKIKAI Co., Ltd., Column Flow Reactor LCR-1300 series), (12) aqueous ethanol, (13) pump (TACMINA Corporation, Smoothflow Pump Q-30-6T-P-X), (14) preheating coiled tube (SUS316, I.D. 0.8 mm, 200 cm length), (15) T-shaped mixer (Swagelok Co., Union Tee SS-100-3), (16) cooling coiled tube (I.D. 0.8 mm, 500 cm length), (17) backpressure regulator, (18) outlet for the reaction mixture.

Scheme S5.

An ethanol solution of 4-bromobenzonitrile (**1**, 0.20 M, 1.0 equiv) and phenylboronic acid (**2**, 0.22 M, 1.1 equiv) (*stock solution A*) and an aqueous solution of K$_3$PO$_4$ (1.2 M, 2.0 equiv) (*stock solution B*) were prepared

in the volumetric flask, respectively. An immobilized Pd catalyst (0.655 mmol of Pd/g) was mixed well with Celite®□ (particle size 75–150 μm) at 1:19 weight ratio and packed into the column reactor.

The column reactor was placed in the synthesis module and washed with ethanol (1.80 mL min⁻¹) and water (0.60 mL min⁻¹) flow at room temperature for 30 min to remove gases. Then, the temperature and the internal pressure were controlled at 80 °C and 0.2 MPa while flowing ethanol and water (3:1 v/v, 2.40 mL min⁻¹).

After the temperature and the pressure have become steady, a *stock solution A* (1.80 mL min⁻¹) and a *stock solution B* (0.60 mL min⁻¹) were preheated to 80 °C and then mixed with a micro T-shaped mixer (M1, i.d. 0.3 mm). The mixture was continuously passed through a column reactor filled with the immobilized Pd catalyst and Celite (1:19 w/w). The reaction solution from the column reactor was diluted with aqueous ethanol (EtOH/H$_2$O 3:1 v/v, 2.40 mL min⁻¹) in T-shaped mixer M2 (i.d. 1.3 mm). After cooling to room temperature in a coiled tube (inner diameter = 0.8 mm diameter, length = 500 cm, volume = 2.5 mL, residence time = 31 sec), the reaction mixture was collected from the outlet of BPR with the fraction collector. All crude mixture was immediately quenched with 2M HCl aqueous solution to completely stop the coupling reaction. The resulting mixture was added *n*-dodecane as an internal standard and then extracted with EtOAc. The obtained extracts were analyzed by gas chromatography (GC) to determine the product yield.

Figure S1. Photographic image of the continuous flow synthesis module

Figure S2. Detail of continuous flow synthesis module

Figure S3. Photographic image of the column reactor
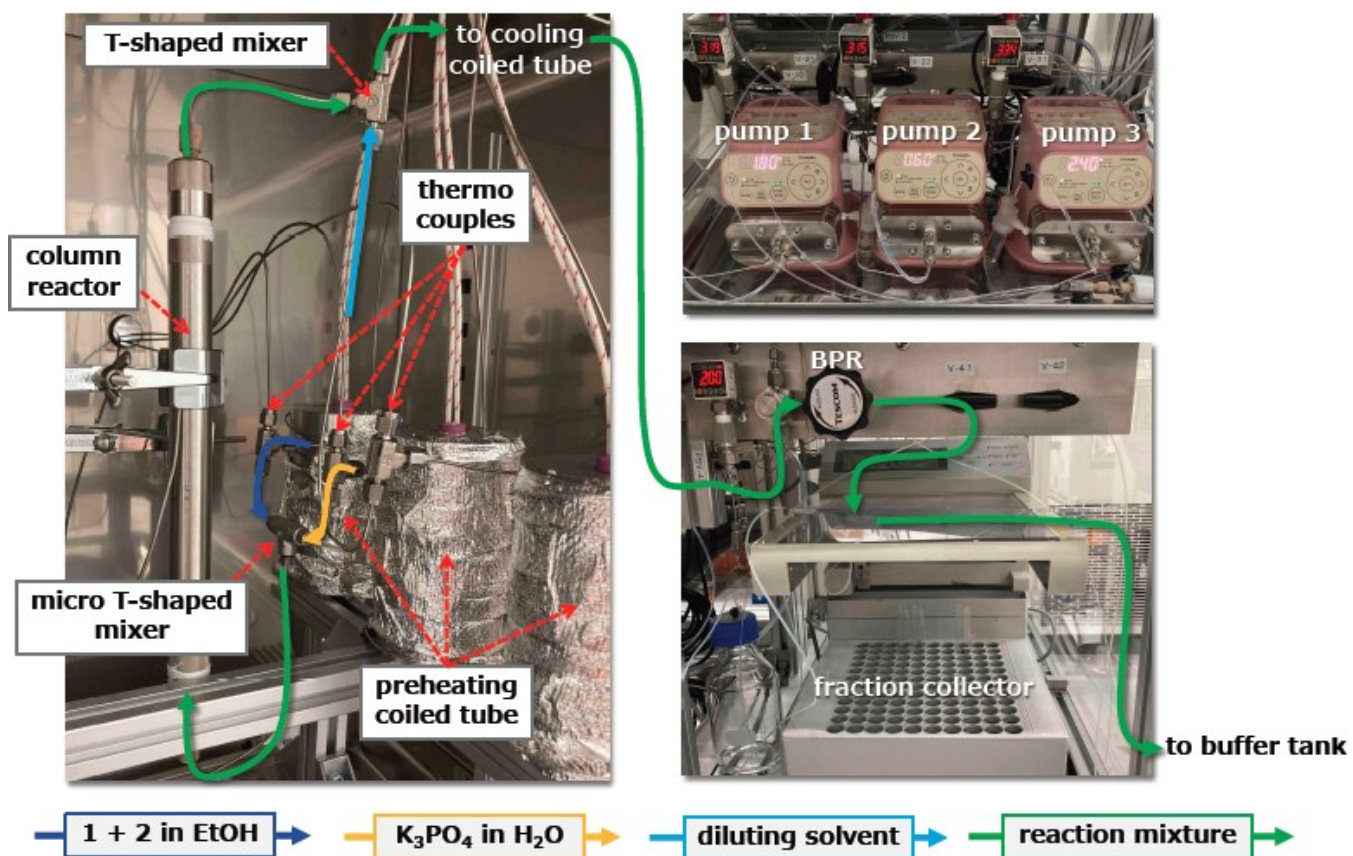
3.2. Kinetic studies for Suzuki-Miyaura coupling under continuous flow conditions

The kinetics of Suzuki–Miyaura coupling over the immobilized Pd catalyst were modeled as a second-order reaction between **1** and **2**. The reaction rate, r can be described an equation as below.

$$r = \frac{d[3]}{dt} = k[1][2] \quad (1)$$

- k = rate constant
- $[1]$: The concentration of **1** in the reaction mixture at time t
- $[2]$: The concentration of **2** in the reaction mixture at time t
- $[3]$: The concentration of **3** in the reaction mixture at time t
- $[1]_0$: The initial concentration of **1**
- $[2]_0$: The initial concentration of **2**

Let x be the concentration of **3** at the time t, then $[1] = [1]_0 - x$; $[2] = [2]_0 - x$.

$$\frac{dx}{dt} = k([1]_0 - x)([2]_0 - x) \quad (2)$$

$$\frac{dx}{([1]_0 - x)([2]_0 - x)} = kdt \quad (3)$$

Integrate between $t = 0$ (when $x = 0$) and $t = t$ (when $x = x$).

$$\int_0^x \frac{dx}{([1]_0 - x)([2]_0 - x)} = \int_0^\tau kdt \quad (4)$$

$$\frac{1}{[2]_0 - [1]_0} \ln \frac{[2][1]_0}{[1][2]_0} = kt \quad (5)$$

$$\ln \frac{[2][1]_0}{[1][2]_0} = k([2]_0 - [1]_0)t \quad (6)$$

In the flow reactions using a packed-bed reactor, the effective contact time (τ), defined as follows, was used as the time t in the above equation. The effective contact time (τ) of the substrate **1** with the Pd catalyst is inversely related to the moles hourly space velocity (MHSV, h^{-1}). MHSV is described using the concentration C (mol L^{-1}) of substrate and the flow rate F (L h^{-1}) of the reaction mixture.

$$MHSV\ (h^{-1}) = \frac{Substrate\ 1\ (mol)}{Pd\ catalyst\ (mol) \times time\ (h)} = \frac{C\ (mol\ L^{-1}) \times F\ (L\ h^{-1})}{Pd\ catalyst\ (mol)} \quad (7)$$

$$\tau\ (h) = \frac{1}{MHSV}(h) = \frac{Pd\ catalyst\ (mol)}{C\ (mol\ L^{-1}) \times F\ (L\ h^{-1})} \quad (8)$$

$$\ln \frac{[2][1]_0}{[1][2]_0} = k([2]_0 - [1]_0)\tau = k([2]_0 - [1]_0)\frac{1}{MHSV} \quad (9)$$

To obtain the experimental data needed for the kinetic analysis, the product yield at each MHSV was investigated by varying the column reactor size while maintaining a constant flow rate (P1: 1.8 mL/min, P2: 0.60 mL/min). All results were summarized in Table S1 and Figure S4.

Table S1.

Entry	column reactor I.D. x length (volume)	loaded Pd catalyst (mmol)	MHSV (h^{-1})	1/MHSV (10^{-3} h)	yield of **3** (%)[b]	TOF (h^{-1})
1	5.0 x 50 mm (0.98 mL)	0.0145	1317	0.759	30	391
2	5.0 x 100 mm (1.96 mL)	0.0293	653	1.53	41	268
3	5.0 x 150 mm (2.94 mL)	0.0438	436	2.29	55	241
4	10 x 50 mm (3.93 mL)	0.0624	307	3.26	65	200
5	10 x 100 mm (7.85 mL)	0.122	157	6.37	82	129

[a] Yield was determined by GC analysis using *n*-dodecane as an internal standard.
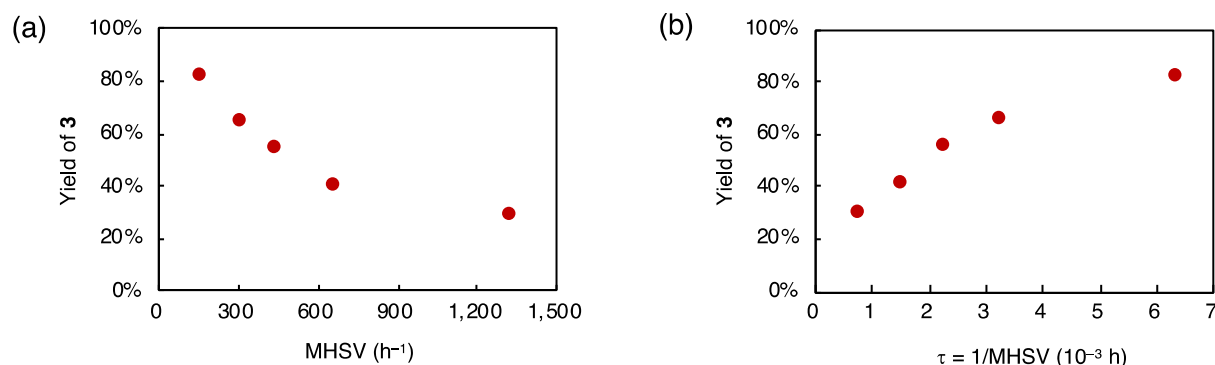

Figure S4.

The rate constant, k, was calculated graphically by plotting $\ln\dfrac{[2][1]_0}{[1][2]_0}$ versus τ, based on eqn (9). As shown in Figure S5, a linear relationship was obtained up to a product yield of 82%, indicating second-order kinetics with $k = 3.78 \times 10^3$ [L mol^{-1} h^{-1}].
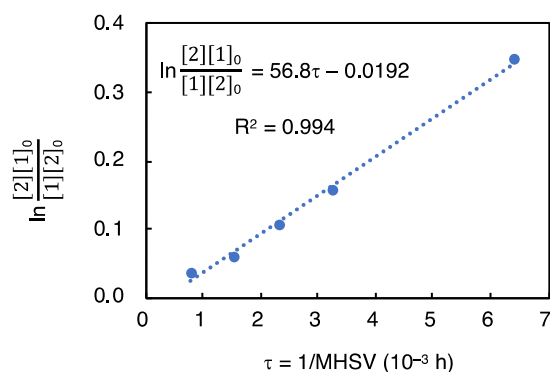

$$\ln\frac{[2][1]_0}{[1][2]_0} = 56.8\tau - 0.0192$$

$$R^2 = 0.994$$

Figure S5.

$$\frac{\ln\dfrac{[2][1]_0}{[1][2]_0}}{\tau\,(h)} = Slope\,(h^{-1}) = k([2]_0 - [1]_0) \quad (10)$$

$$k = \frac{Slope\,(h^{-1})}{([2]_0 - [1]_0)\,(mol\,L^{-1})} = \frac{56.8\,(h^{-1})}{0.165\text{–}0.150\,(mol\,L^{-1})} = 3.78 \times 10^3\,(L\,mol^{-1}\,h^{-1}) \quad (11)$$

The kinetic model according to eqn (9) and the obtained value of k = 3.78 x 10^3 [L mol^{-1} h^{-1}] indicate the prediction value as shown in Figure S6 (green line). Based on this result, it is estimated that quantitative yield (more than 99% yield) could be achieved at an MHSV of 25 h^{-1}.
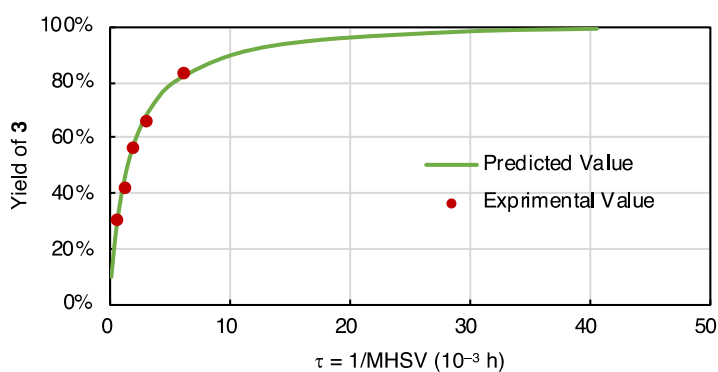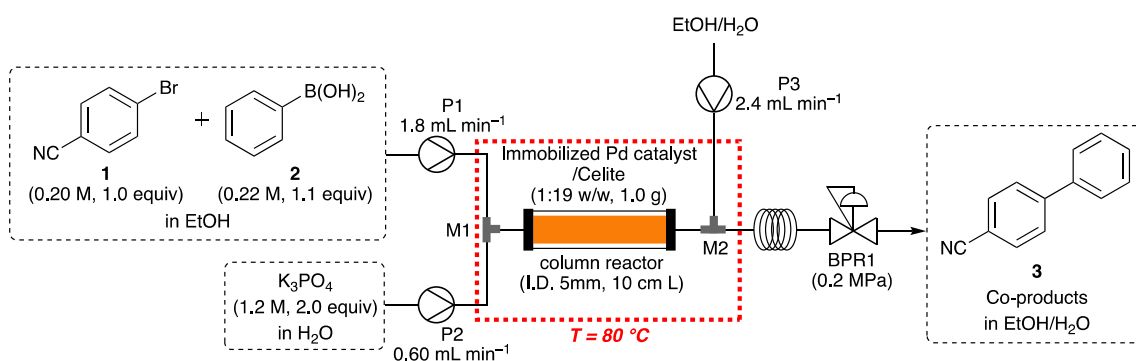

Figure S6.

3.3. The accelerated life testing of the Pd catalyst under continuous flow conditions

Scheme S6.

To investigate the catalyst deactivation, the accelerated life testing was performed at a high MHSV of 6.53×10^2 h^{-1}. According to the *General Procedure* (page S5), Suzuki-Miyaura coupling was performed at a total flow rate of 2.40 mL min^{-1} (P1 = 1.80 mL min^{-1}, P2 = 0.60 mL min^{-1}) by using with the continuous-flow synthesis module equipped with the column reactor (Pd = 33 µmol). The changes in product yield and turnover frequency (TOF) were monitored by GC analysis every 5 to 10 min for 4 h. The plot of the turnover frequency of the catalyst (TOF) against the total turnover number (TON) was shown in Figure S7.
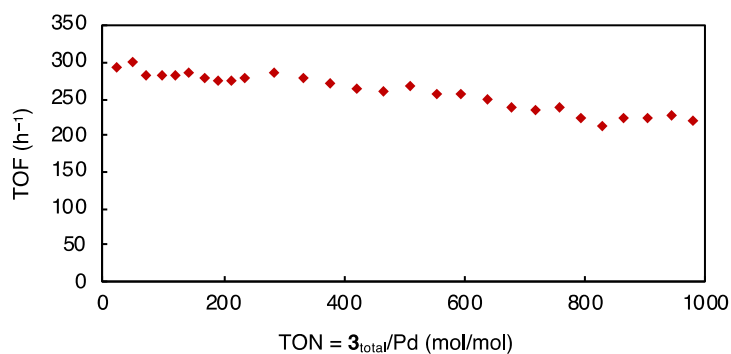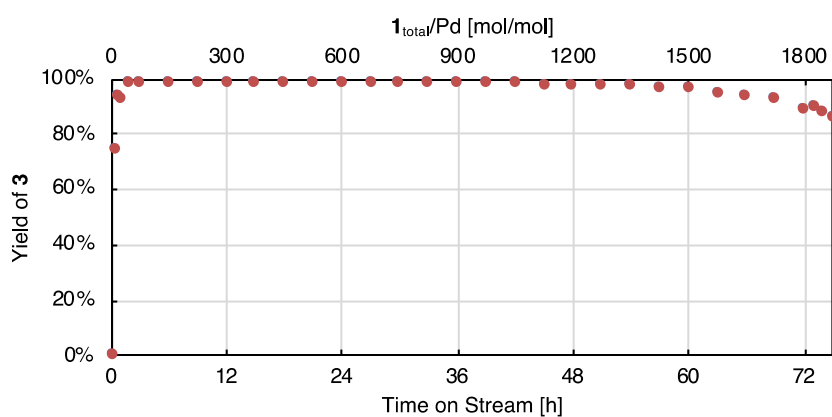

Figure S7.

3.4. The experimental validation of the prediction model based on kinetic studies

To validate the prediction model, flow synthesis of biaryl **3** with different flow rates at a constant MHSV of 25 h^{-1} was performed. All experiments were carried out according to the *General Procedure* (page S5). The total flow rate (P1 and P2) of the reaction solution from 0.60, 1.2, and 2.4 mL/min were examined. All results were summarized in Table S2 and Figure S8–S10.

Table S2.

entry	flow rate (P1 + P2) (mL min^{-1})	column reactor I.D. x length	Pd catalyst (mmol)	yield of **3** (%)[b]	productivity of **3** (g/h)
1	0.60	10 x 150 mm	0.218	99	0.96
2	1.20	10 x 300 mm	0.432	99	1.91
3	2.40	10 x 600 mm	0.864	98	3.79

[a] Yield was determined by GC analysis using *n*-dodecane as an internal standard.

Flow rate = 0.60 mL min^{-1} (Table S2, Entry 1)
Figure S8.
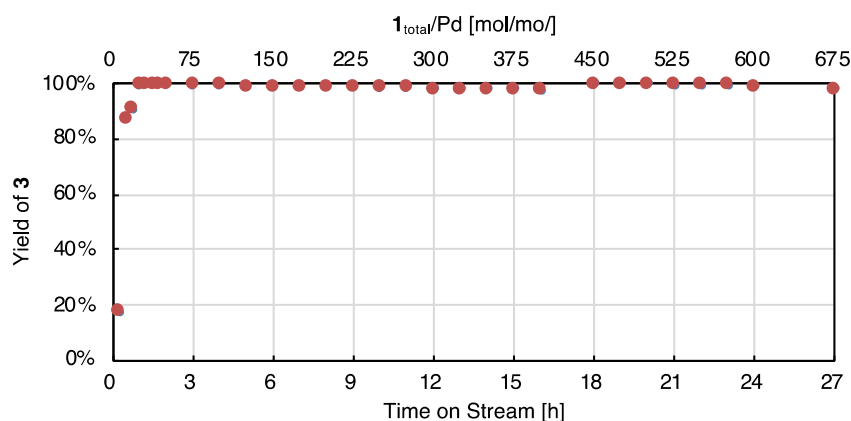
Flow rate = 1.20 mL min^{-1} (Table S2, Entry 2)
Figure S9.

Flow rate = 2.40 mL min^{-1} (Table S2, Entry 2)

Figure S10.

ICP-AES analysis

The Pd catalyst leaching during the continuous flow synthesis for 3 days was investigated by the inductively coupled plas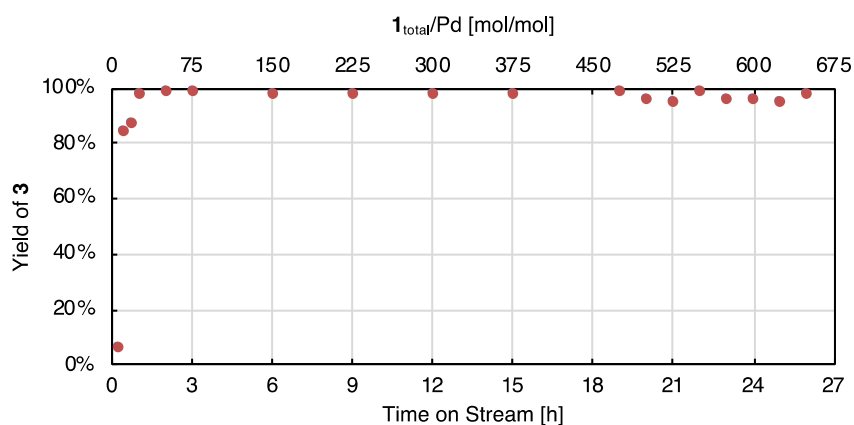ma atomic emission spectroscopy analysis (ICP-AES). A part of crude mixture (0.351 g) was weighted into the test tube and treated with concentrated H_2SO_4 (3.0 mL) and fuming HNO_3 at 120~200 °C until a homogeneous solution was obtained. The resulting homogeneous solution diluted with distilled water to 50 mL. The ICP-AES analysis of the obtained solution was performed to quantitatively determine the leached Pd. As the result, the ICP-AES analysis clarified that after 3 days operation, only 0.80 ppm of Pd (0.24 mg, 1.0 % of loaded Pd) was present in crude mixture of **3** before purification.

Table S3.

Sample	Pd concentration in the crude mixture (ppm)	Pd amount in the crude mixture (mg)	Leaching ratio of Pd (%)
1 (1~24 h)	0.81	0.080	0.34%
2 (25~49 h)	0.46	0.045	0.19%
3 (49~73 h)	1.15	0.113	0.49%
Total (1~73 h)	0.80	0.238	1.03%

4. Optimization for the continuous flow extraction module

4.1. The setup and general procedure
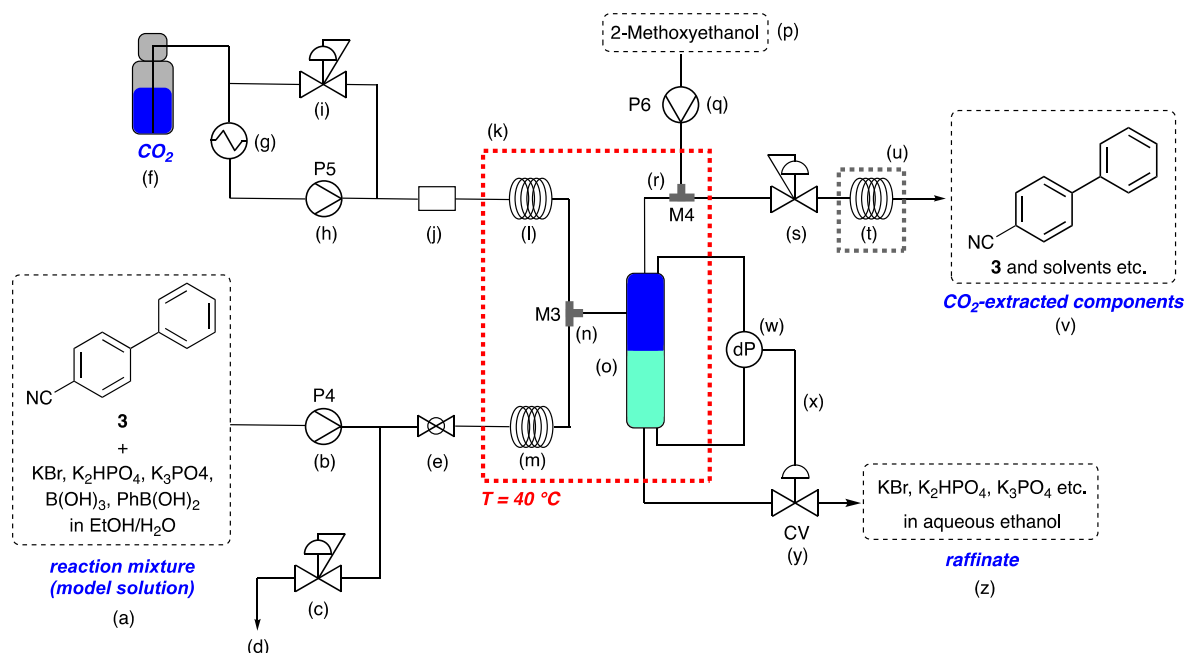
(a) reaction mixture (model solution) (b) high pressure pump P4 for the reaction mixture, (c) backpressure regulator, (d) outlet for the flow rate measurement, (e) stop valve, (f) CO_2 tank, (g) heat exchanger, (h) high pressure pump P5 for CO_2, (i) backpressure regulator, (j) flowmeter, (k) isothermal water bath (40 °C), (l) preheating coiled tube, (m) preheating coiled tube, (n) micro T-shaped mixer (I.D. = 0.3 mm), (o) separator, (p) 2-methoxyethanol, (q) high pressure pump P6 for 2-methoxyethanol, (r) T-shaped mixer, (s) backpressure regulator, (t) cooling coiled tube, (u) cold water bath, (v) outlet for CO_2-extracted component, (w) differential pressure meter, (x) PID control, (y) control valve, (z) outlet for raffinate

Scheme S8.

An aqueous ethanol (EtOH/H_2O = 1:1 w/w) solution of 4-cycnobiphenyl (**3**, 15 mmol/kg), phenylboronic acid (**2**, 1.5 mmol/kg), B(OH)$_3$ (15 mmol/kg), KBr (15 mmol/kg), K_2HPO_4 (15 mmol/kg), and K_3PO_4 (15 mmol/kg) was prepared as a model solution of the reaction mixture.

The model solution (6.0 g min^{-1}) and CO_2 (12 g min^{-1}) were separately pumped and preheated to 40 °C. At the micro T-shaped mixer (M3, I.D. 0.3 mm), two fluids were mixed by counter flow (the model solution and CO2 entered from opposite sides of the tee). The flow rate of the solution was determined by weighting the solution obtained from the outlet (d). The flow rate of CO_2 was also determined by using a mass flow meter (j). The mixed fluid entered into a separator (o) where it separates into a CO_2-rich phase (upper phase) and a water-rich phase (lower phase). The separator is cylindrical in shape with an inner diameter of 10–40 mmm a height of 450 mm, and the mixed fluid flows in from the top of separator (For details of the separator, please refer to our previous literature.[4]). The liquid level, that is, the interface between the CO_2- and water-rich phases, was measured using a differential pressure meter as the pressure difference between the lines from the bottom and

top of the separator. The aperture of the control valve (y) was regulated so that the differential pressure was automatically maintained constant (by PID control). The extraction pressure was regulated by a backpressure regulator (s) downstream of the CO_2-rich phase. The outlet flow rate of each phase was determined by dividing the weight of the sampled solution by the sampling time. Sampling of extracted solutions and raffinates were conducted 3 times, respectively (sampling time = 10 min).

The amount of each chemicals (4-cyanobiphenyl, phenylboronic acid, $B(OH)_3$ and K^+ salts) emitted from the upper (CO_2-extracts) and the bottom (raffinate) lines was calculated by using the flow rate and the concentration of these chemicals in each outlet solution.

4-Cyanobiphenyl and Phenylboronic acid

- Analysis: high-performance liquid chromatography (HPLC)
- Apparatus: SHIMADZU Corp., Prominence series
- Column: ODS type column (Shim-pack VP ODS (I.D. = 4.6 mm, L = 150 mm) and Shim-pack GVP ODS)
- Detector: UV detector (SPD-20A), wavelength = 280 nm
- Eluent: acetonitrile/0.1%-formic acid aqueous solution = 50/50 v/v%

K^+ ion, Br^- ion and Boric acid

- Analysis: ion chromatography (IC)
- Apparatus: Metrohm AG, Eco IC
- Method for cation analysis (K^+)
  - ➢ Column: SHOWA DENKO K. K., Shodex IC SI-90 and SI-90-G
  - ➢ Eluent: 1.8 mM Na_2CO_3/1.7 mM $NaHCO_3$
- Method for anion analysis (Br^-)
  - ➢ Column: SHOWA DENKO K. K., Shodex IC YS-50 and YS-G
  - ➢ Eluent: 4 mM HNO_3
- Method for organic acid analysis (*boric acid*)
  - ➢ Column: SHOWA DENKO K. K., Shodex IC KC-811 and KC-G
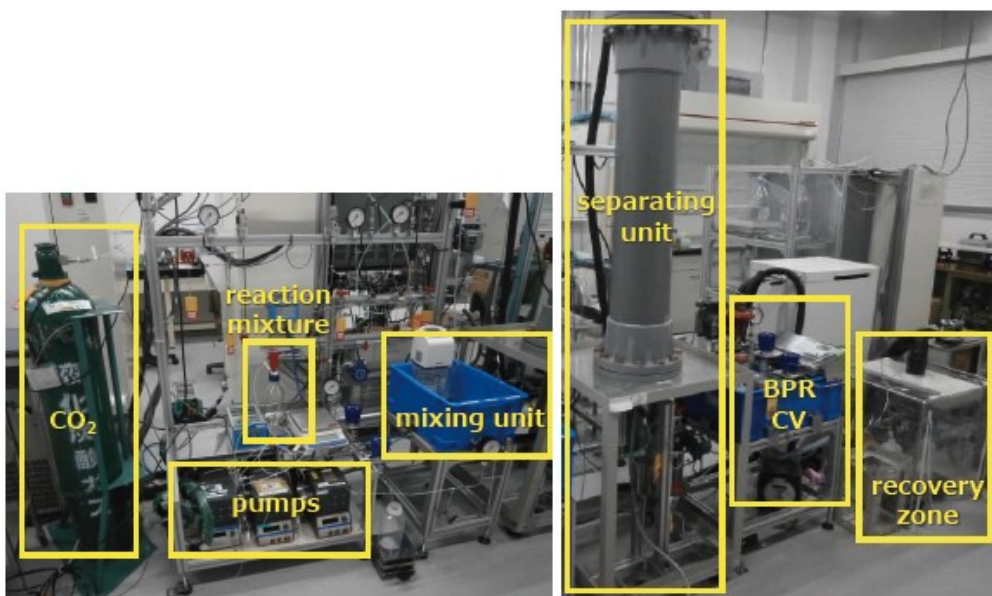 - ➢ Eluent: 1 mM $HClO_4$/100 mM mannitol

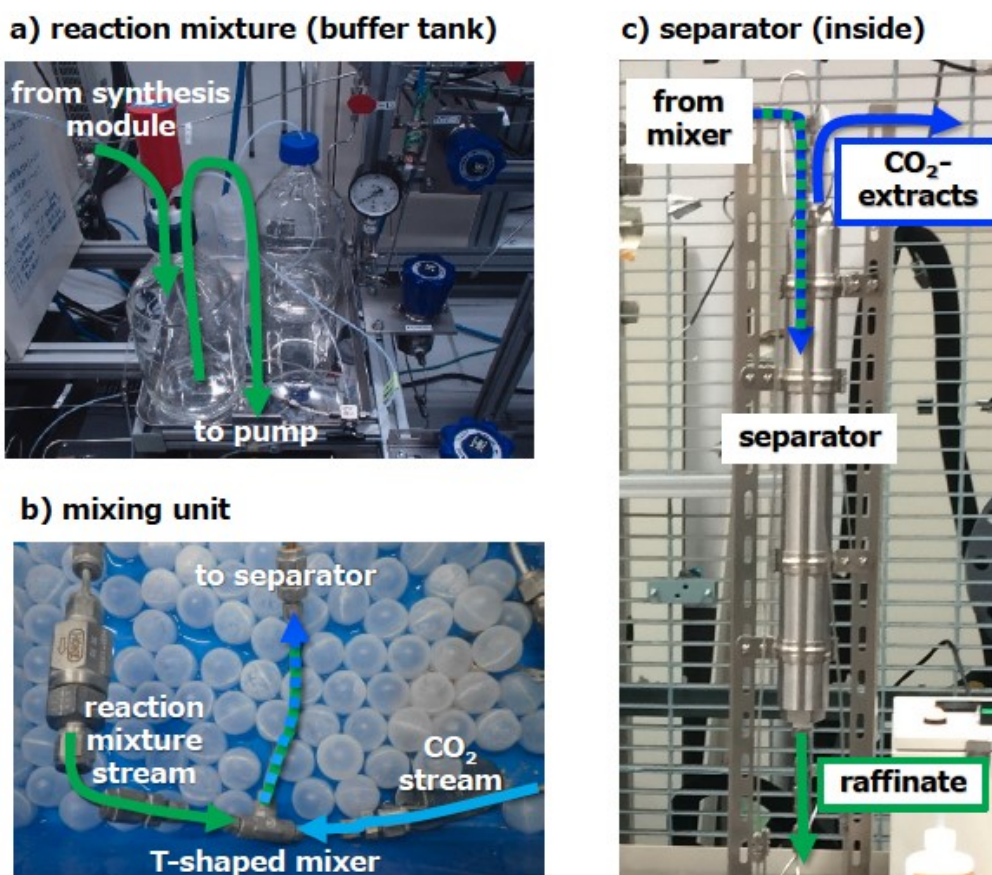**Figure S11.** Photographic image of the extraction module

Figure S12. Detail of the extraction module

4.2 Extraction of the model solution

Experiments were carried out according to General Procedure as shown in page S11. All results were summarized in Tables S4 and S5.

Table S4.

| entry | model solution | | | CO_2 | extracted yield of **3** (%)[b] | productivity of **3** (g/h) |
	Conc. of **3** (mmol/kg)[a]	EtOH:H_2O (w/w)	flow rate (g/min)	flow rate (g/min)		
1	15	0.5:0.5	6.0	12	87	0.84
2	15	0.5:0.5	6.0	24	96	0.93
3	30	0.6:0.4	6.0	24	93	1.77

[a] Concentration was determined by HPLC analysis. [b] Extraction yield was determined by HPLC analysis based on eqn (12). [c] Production rate of **3** at the upper stream outlet.

$$Extracted\ yiled\ of\ 3(\%) = \frac{n^E(g/min)}{n^F(g/min)} \times 100 = \frac{F^E(g/min) \times C^E(g/g)}{F^F(g/min) \times C^F(g/g)} \times 100 \quad (12)$$

$$Productivity\ of\ 3\ (g/h) = F^E(g/h) \times C^E(g/g) \quad (13)$$

- n^E: weight flow rate of **3** in the extracts (g/min)
- n^F: weight flow rate of **3** in the feed solution (g/min)
- F^E: flow rate of the extracts emitted from the upper line (g/min, g/h)
- F^F: flow rate of the feed solution (g/min, g/h)
- C^E: concentration of **3** in the extracts (g/g)
- C^F: concentration of **3** in the feed solution (g/g)

Table S5.

| entry | extraction Conditions | | | extracted yield in CO2-rich phase (%)[b] | | | | | | Purity of **3** (wt%) |
	conc. of **3** (mmol/kg)	EtOH:H_2O (w/w)	CO_2 flow rate (g/min)	**3**	**2**	K^+	Br^-	PO_4^{3-}	$B(OH)_3$	
1	15	0.5:0.5	12	87	32	0.3	n.d.	n.d.	5.7	94
2	15	0.5:0.5	24	96	58	0.7	n.d.	n.d.	9.5	91
3	30	0.6:0.4	24	93	52	0.5	n.d.	0.7	n.a.	–

[a] Concentration was determined by HPLC analysis. [b] Extraction yield was determined by HPLC and IC analysis based on equation (12).

5. A continuous flow process based on a sequential synthesis and extraction
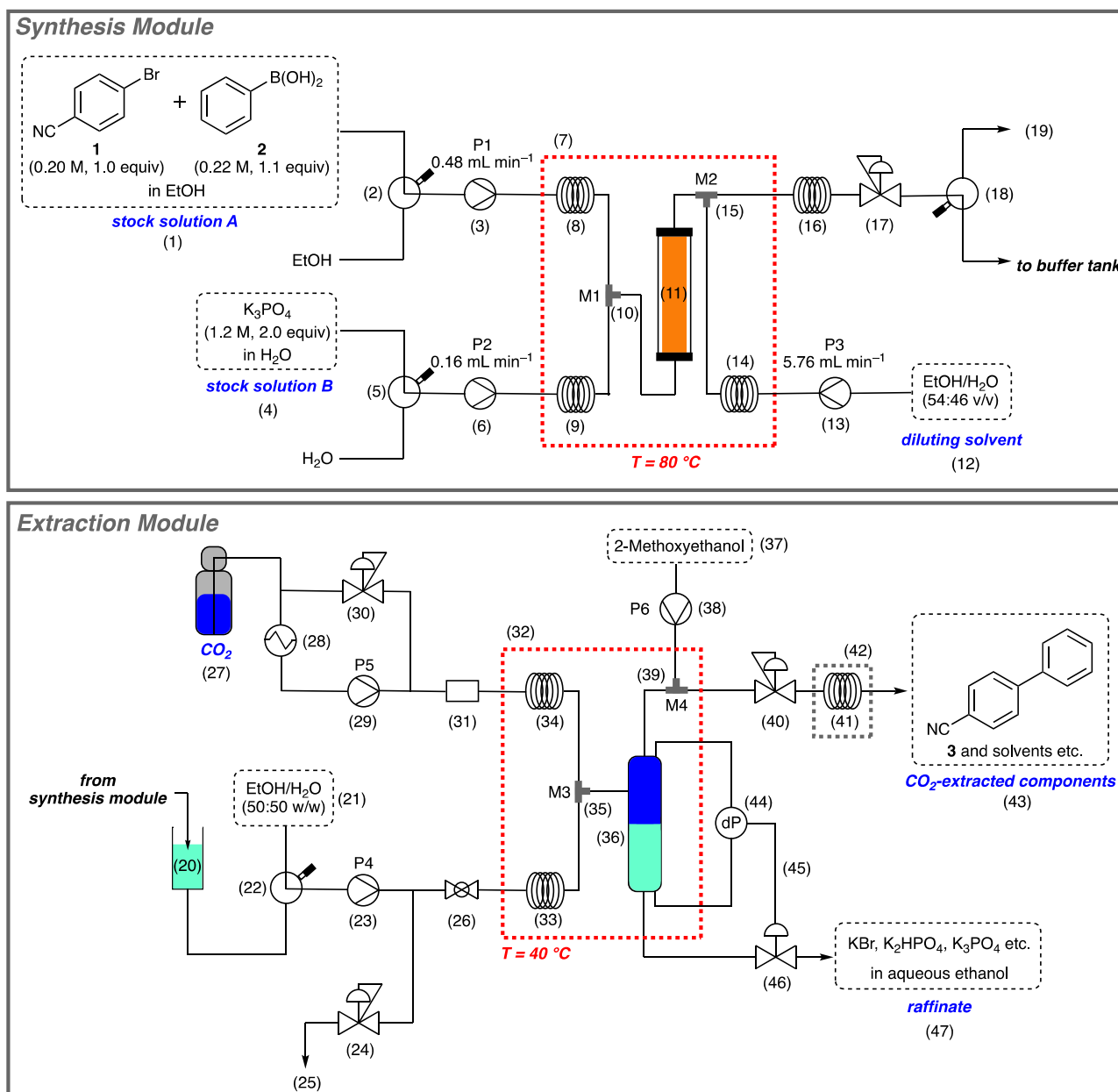
(1) stock solution A, (2) 3-way valve, (3) pump, (4) stock solution B, (5) 3-way valve, (6) pump, (7) Oven, (8) preheating coiled tube (I.D. 0.8 mm, 200 cm length), (9) preheating coiled tube (I.D. 0.8 mm, 200 cm length), (10) micro T-shaped mixer (I.D. = 0.3 mm), (11) column reactor (I.D. 10 mm, 20 cm length), (12) aqueous ethanol, (13) pump, (14) preheating coiled tube (I.D. 0.8 mm, 200 cm length), (15) T-shaped mixer, (16) cooling coiled tube (I.D. 0.8 mm, 500 cm length), (17) backpressure regulator, (18) 3-way valve, (19) outlet for sampling the reaction mixture, (20) buffer tank, (21) aqueous ethanol, (22) 3-way valve, (23) high pressure pump P4 for the reaction mixture, (24) backpressure regulator, (25) outlet for the flow rate measurement, (26) stop valve, (27) CO_2 tank, (28) heat exchanger, (29) high pressure pump P5 for CO_2, (30) backpressure regulator, (31) flowmeter, (32) isothermal water bath (40 °C), (33) preheating coiled tube, (34) preheating coiled tube, (35) micro T-shaped mixer (I.D. = 0.3 mm), (36) separator, (37) 2-methoxyethanol, (38) high pressure pump P6 for 2-methoxyethanol, (39) T-shaped mixer, (40) backpressure regulator, (41) cooling coiled tube, (42) cold water bath, (43) outlet for CO_2-extracted component, (44) differential pressure meter, (45) PID control, (46) control valve, (47) outlet for raffinate

Scheme S9.

Synthesis Module

An ethanol solution of 4-bromobenzonitrile (**1**, 0.20 M, 1.0 equiv) and phenylboronic acid (**2**, 0.22 M, 1.1 equiv) (*stock solution A*) and an aqueous solution of K_3PO_4 (1.2 M, 2.0 equiv) (*stock solution B*) were prepared in the volumetric flask, respectively. An immobilized Pd catalyst (0.655 mmol of Pd/g, 440 mg, Pd = 0.288 mmol) was mixed well with Celite®□ (8.36g, particle size 75–150 μm) at 1:19 weight ratio and packed into the column reactor (SUS316, I.D. 10 mm, 20 cm length).

The column reactor was placed in the synthesis module and washed with ethanol (0.48 mL min⁻¹) and water (0.16 mL min⁻¹) flow at room temperature for 30 min to remove gases. Then, the temperature and the internal pressure were controlled at 80 °C and 0.2 MPa while flowing ethanol and water (3:1 v/v, 0.64 mL min⁻¹).

After the temperature and the pressure have become steady, a *stock solution A* (0.48 mL min⁻¹) and a *stock solution B* (0.16 mL min⁻¹) were preheated to 80 °C and then mixed with a micro T-shaped mixer (M1, I.D. 0.3 mm). The mixture was continuously passed through a column reactor. The reaction solution from the column reactor was diluted with aqueous ethanol (EtOH/H_2O = 54:46 v/v, 5.76 mL min⁻¹) in mixer M2 (I.D. 1.3 mm). After cooling to room temperature in a coiled tube (inner diameter = 0.8 mm diameter, length = 500 cm, volume = 2.5 mL, residence time = 23 sec), the reaction mixture was collected from the outlet of BPR and analyzed by gas chromatography (GC). After confirming that the reaction has stabilized and the yield of **3** has reached more than 99% (after 60 min), the reaction mixture emitted from the outlet of BPR was fed to the buffer tank by switching the 3-way valve.

Extraction Module

In advance, the extraction module was stabilized under the desired conditions with flowing CO_2 and aqueous ethanol. After confirming each module has stabilized, the reaction mixture (6.0 g min⁻¹) and CO_2 (12 g min⁻¹) were separately pumped and preheated to 40 °C. At the micro T-shaped mixer (M3, I.D. 0.3 mm), two fluids were mixed by counter flow (the model solution and CO_2 entered from opposite sides of the tee). The mixed fluid entered into a separator where it separates into a CO_2-rich phase (upper phase) and a water-rich phase (lower phase). The liquid level, that is, the interface between the CO_2- and water-rich phases, was measured using a differential pressure meter as the pressure difference between the lines from the bottom and top of the separator. The aperture of the control valve was regulated so that the differential pressure was automatically maintained constant (by PID control). The extraction pressure was regulated by a backpressure regulator downstream of the CO_2-rich phase. The outlet flow rate of each phase was determined by dividing the weight of the sampled solution by the sampling time. After the extraction process reached steady state, sampling of extracts and raffinates were conducted 3 times, respectively (sampling time = 10 min).

Table S6.

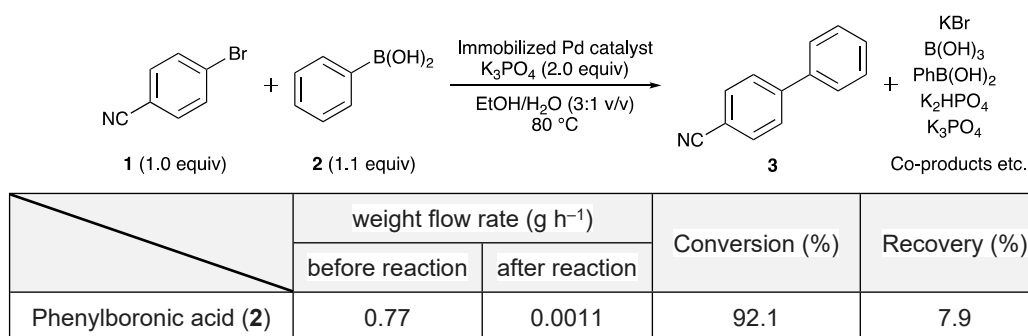| Component	Feed (the reaction mixture)		Extracts (CO₂-rich phase)			Raffinate (H₂O-rich phase)		
	weight flow rate (g h⁻¹)	purity (wt%)	weight flow rate (g h⁻¹)	purity (wt%)	yield (%)	weight flow rate (g h⁻¹)	purity (wt%)	yield (%)
4-Cyanobiphenyl	1.12	28	0.93	94	83	0.18	5.9	16
Phenyboronic acid	0.066	1.7	0.035	3.6	54	0.056	1.8	84
$B(OH)_3$	0.36	9.0	0.019	1.9	5.3	0.28	9.3	79
K^+	1.14	28	0.001	0.1	0.1	1.18	39	103
Br^-	0.47	12	0.000	0.0	0.0	0.48	16	100
PO_4^{3-}	0.84	21	0.000	0.0	0.0	0.88	29	105

[a] The weight flow rate was calculated by using the flow rate of each solution and the concentration of each component.
[b] The purity of each component except for solvents (H_2O, ethanol) was calculated based on the weight flow rate.
[c] Yield of each component was determined based on equation (12).

Conversion of Phenylboronic Acid

The concentration of $PhB(OH)_2$ in the solution before and after the flow reaction was confirmed by HPLC analysis. This allowed us to determine the amount of $PhB(OH)_2$ consumed by the reaction and the amount of $PhB(OH)_2$ contained in the aqueous solution of the reaction mixture, respectively. It was confirmed that 92.1% (1.0 equiv out of 1.1 equiv) of the $PhB(OH)_2$ supplied as substrate was used in the reaction, and the remaining 7.9% (0.1 equiv out of 1.1 equiv) remained unreacted in the aqueous solution.

	weight flow rate (g h⁻¹)		Conversion (%)	Recovery (%)
	before reaction	after reaction		
Phenylboronic acid (**2**)	0.77	0.0011	92.1	7.9

Scheme S10.

6. References

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