Research Article

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

Supplementary material

S1 General

S1.1 Materials

4-Iodobenzonitrile, 4-cyanobiphenyl, lithium chloride, a THF solution of tri-*n*-butylammonium fluoride, diisopropylethylamine, copper iodide(I), and dimethyl sulfoxide (DMSO) were purchased from FUJIFILM Wako Pure Chemical Corporation. *n*-Butyl acrylate, methanol, 1-bromo-4-*n*-pentylbenzene, tri-*n*-butyltin chloride, 4-cyano-4′-pentylbiphenyl (5CB), 4-ethylnitrobenzene, and 4-ethylaniline were purchased from Tokyo Chemical Industry Co., Ltd. A solution of *n*-butyl lithium was purchased from Kanto Chemical Co., Inc. Tri-*n*-butylphenylstannane and palladium(II) acetate were purchased from Aldrich. The dual-pore silica gel (DualPore^{TM}) was supplied by DPS Inc. All chemicals were used without further purification.

S1.2 Methods

^{1}H and ^{13}C NMR spectra were recorded on a Varian MERCURY plus400 spectrometer (^{1}H 400, ^{13}C 100 MHz). Chemical shifts were recorded using a TMS (0.0 ppm) signal as an internal standard. 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 × 25 m). Prior to the GC analysis, the standard solution was analyzed five times to determine the standard deviation of the measurements. Electron ionization (EI) mass spectrum was obtained on JEOL JMS-SX102A. X-ray fluorescence (XRF) analyses were carried out using Shimadzu EDX-8000. Transmission electron microscopy (TEM) was measured by JEOL JEM-2010. 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. For an introduction of gases, a mass flow controller (BROOKS INSTRUMENT SLA5850S) was used.

S2 Immobilization of palladium on silica gel

Palladium nanoparticles were immobilized in the pores of DualPore using supercritical carbon dioxide-acetone solution. To a 200 mL high-pressure cell were added 5 g of dried DualPore microparticles, 0.3 g of $Pd(OAc)_2$, and 180 mL of acetone. Then CO_2 was pumped into the cell through a preheater at 20 MPa and 70°C. The cell was then placed in an air bath, and the system temperature

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was maintained at 70°C. The mixture was stirred with a magnetic agitator for 24 h, and then the vessel was slowly depressurized to atmospheric pressure over 30 min and the content was removed. The leftover acetone was removed by centrifugation, and the precipitate was successively subjected to reduction in a mixed stream of H_2 and N_2 (5 mL·min^{-1} each) at 300°C for 5 h. XRF analysis indicated that 0.3 wt% of the Pd was immobilized on the DualPore. The TEM image of the Pd@DualPore is shown in Figure S1a. The image indicates that the palladiums are widely dispersed on the silica gels, whereas palladiums immobilized by acetonitrile under ambient conditions [1] seems to agglutinate (Figure S1b). To stainless steel (SUS316) tubes having 4.6 mm of inner diameter and 100 or 150 mm of length, were placed Pd@DualPore to afford the column reactor. The weight of Pd@DualPore in the tubes is typically 400 mg in 100 mm tube, or 600 mg in 150 mm tube.

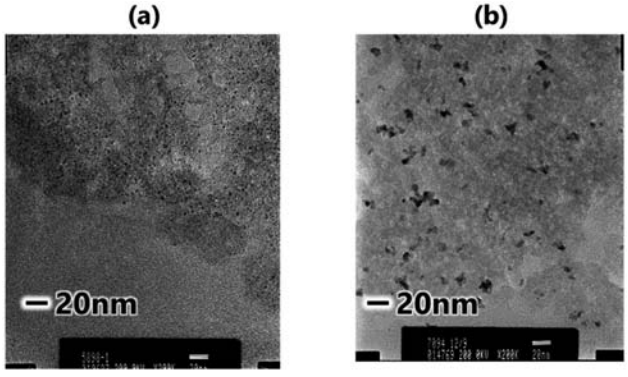

Figure S1: TEM image of Pd@DualPore (a) Pd@DualPore (sCO_2), (b) Pd@DualPore (CH_3CN).

S3 Coupling reactions in batch

S3.1 Stille coupling

To a Schlenk tube capped by a septum, were added 4-iodobenzonitrile (**1**, 22.9 mg, 0.100 mmol), tri-*n*-butylphenylstannane (**2**, 49.0 µL, 0.15 mmol), lithium chloride (13 mg, 0.3 mmol), Pd@DualPore (7 mg, 0.002 mmol), and dimethylformamide (3.0 mL). The mixture was stirred at 120°C under an argon atmosphere. After 18 h, the mixture was allowed to be cooled at room temperature. After an addition of NH_4Claq to the mixture followed by an addition of *n*-hexane, ethyl acetate, and *n*-tetradecane (an internal standard), the organic phase analyzed by GC using a calibration line derived from the commercial compound. The yield was indicated as 80%.

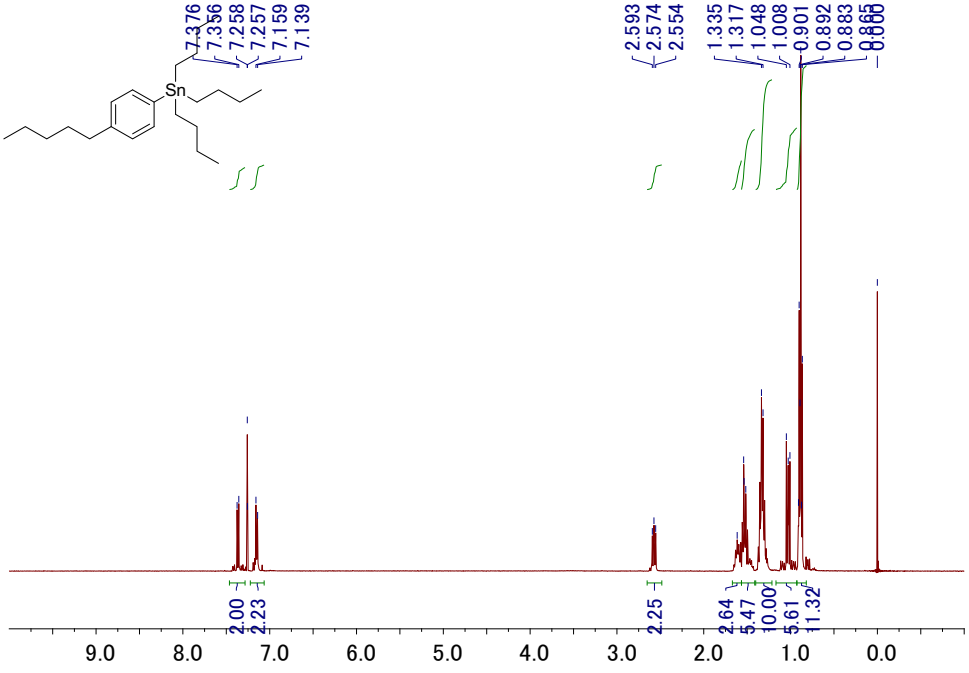

Figure S2: ^{1}H NMR spectrum of tri-*n*-butyl-4-*n*-pentylphenylstannane (400 MHz, $CDCl_3$).

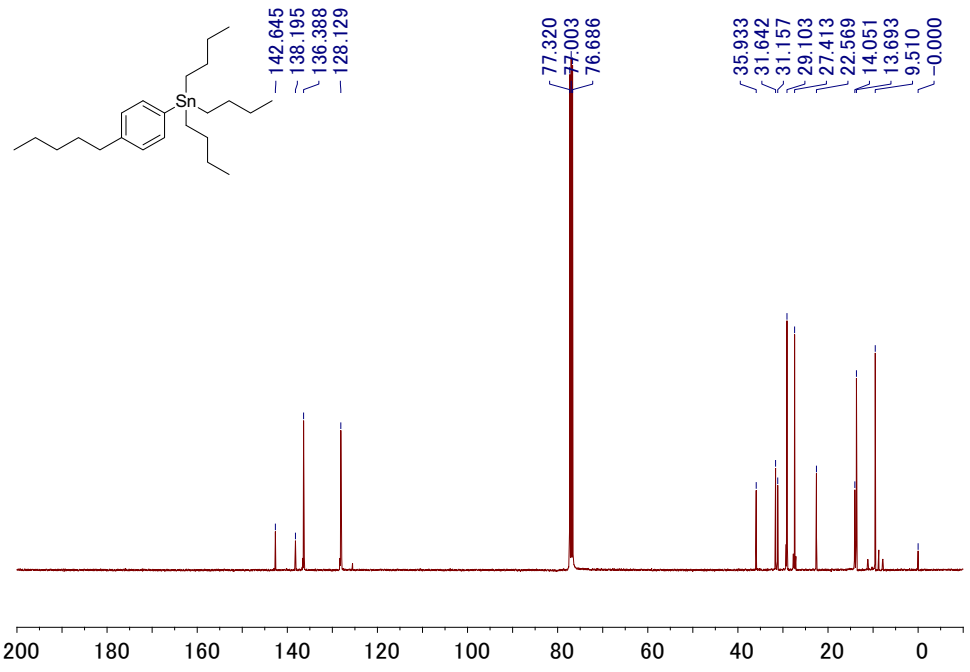

Figure S3: ^{13}C NMR spectrum of tri-*n*-butyl-4-*n*-pentylphenylstannane (100 MHz, $CDCl_3$).

S3.2 Heck coupling

To a Schlenk tube capped by a septum, were added iodobenzene (**4**, 11.0 µL, 0.0987 mmol), *n*-butyl acrylate (**5**, 29.0 µL, 0.204 mmol), diisopropylethylamine (26.0 µL, 0.153 mmol), Pd@DualPore (7 mg, 0.002 mmol), and dimethylformamide (3.0 mL). The mixture was stirred at 120°C under an argon atmosphere. After 18 h, the mixture was allowed to be cooled at room temperature. After an addition of water to the mixture followed by an extraction with *n*-hexane and ethyl acetate (1/1 volume ratio, 5 mL × 3), the organic phase was dried over sodium sulfate. After a filtration, the solvent was removed under a reduced pressure. An NMR analysis of the crude compound indicated a full conversion of **4** and a generation of the desired product **6** (*n*-butyl cinnamate), whose spectrum was in a good agreement with the previous reported [2].

S3.3 Sonogashira coupling

To a Schlenk tube capped by a septum, were added iodobenzene (**4**, 11.0 µL, 0.0987 mmol), phenylacethylene (**7**, 17.0 µL, 0.155 mmol), diisopropylethylamine (51 µL, 0.30 mmol), copper iodide(I) (10 mg, 0.053 mmol), Pd@DualPore (7 mg, 0.002 mmol), and dimethylformamide (3.0 mL). The mixture was stirred at 120°C under an argon atmosphere. After 18 h, the mixture was allowed to be cooled at room temperature. After an addition of water to the mixture followed by an extraction with *n*-hexane and ethyl acetate (1/1 volume ratio, 5 mL × 3), the organic phase was dried over sodium sulfate. After a filtration, the solvent was removed under a reduced pressure. An NMR analysis of the crude compound indicated a full conversion of **4** and a generation of the desired product **8** (diphenylacethylene), whose spectrum was in a good agreement with that of the commercial one.

S4 Stille coupling in flow

S4.1 Typical procedure

To a column reactor filled with Pd@DualPore, a methanol-DMSO solution (MeOH/DMSO 3/7) containing 4-iodobenzonitrile (**1**, 0.033 M), tri-*n*-butylphenylstannane (**2**, 0.050 M), lithium chloride (0.10 M) was introduced by a syringe pump or a plunger pump. Typically, the substrate-solution was prepared in an Erlenmeyer flask with 1.14 g of **1** (4.98 mmol), 2.4 mL of **2** (7.4 mmol), 0.64 g of lithium chloride (15.1 mmol), 45 mL of methanol and 105 mL of DMSO, and the pumping pressure was less than 1 MPa. The column reactor (10 cm or 10 cm + 15 cm) was dipped in a water bath to be heated at 97°C. After reaching a steady state, the passed solution was collected for 10 min. The solution was mixed with aqueous ammonium

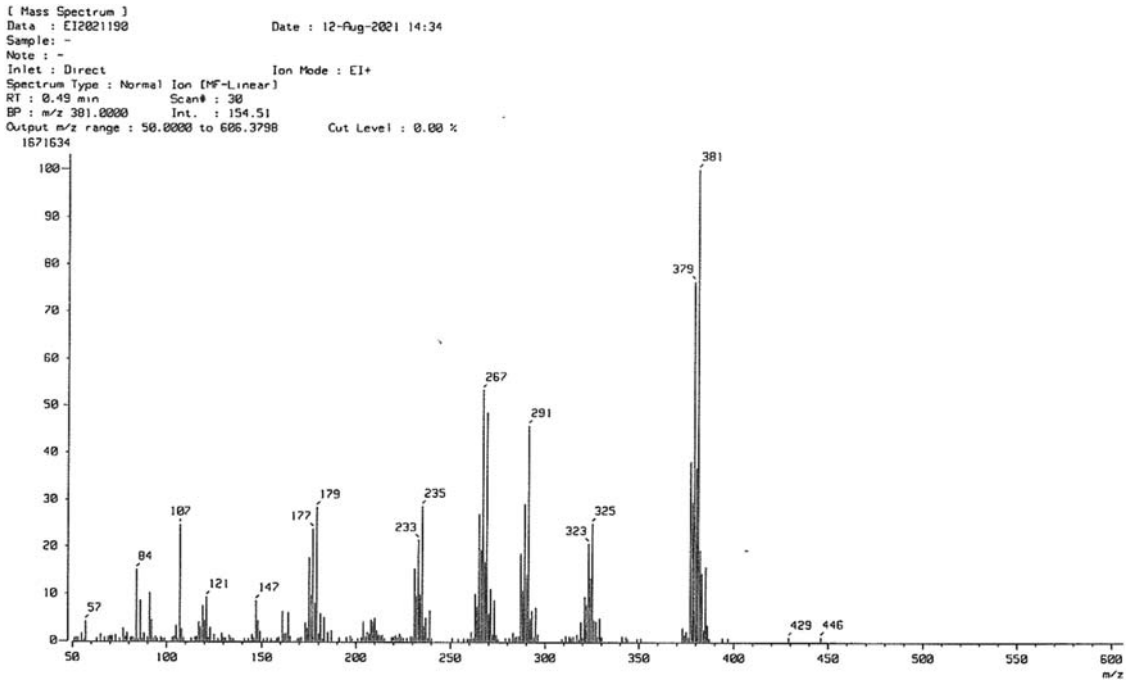

Figure S4: Low resolution MS spectrum of tri-*n*-butyl-4-*n*-pentylphenylstannane (EI).

chloride, *n*-hexane, ethyl acetate, and *n*-tridecane (an internal standard). The organic phase was analyzed by the GC to determine the yield of the desired product **3** (4-cyanobiphenyl) using a calibration line made by the commercial compound.

S4.2 Synthesis for liquid crystal 5CB

To a 100 mL round-bottomed flask were added 1-bromo-4-*n*-pentylbenzene (2.0 mL. 10.7 mmol) and THF (dehydrated, 80 mL), and the mixture was cooled at −78°C. A solution of *n*-butyllithium (1.57 mol/L, 7.1 mL. 11.1 mmol) was added dropwise, and the resulting mixture was stirred at the same temperature for 30 min. Then, tri-*n*-butyltinchloride (3.2 mL, 11.8 mmol) was added, and the mixture was stirred at the same temperature for further 30 min, followed by being warmed at room temperature. After an addition of aqueous ammonium chloride, the mixture was extracted by ethyl acetate (50 mL × 3), and the organic phase was washed by aqueous ammonium chloride. The organic phase was dried over sodium sulfate, which was then removed by a filtration. After the solvent was removed under reduced pressure, the crude mixture was purified by a flash chromatography to afford tri-*n*-butyl-4-*n*-pentylphenylstannane (**9**, 4.49 g, 10.3 mmol) in 96% yield as a colorless oil. The NMR spectra are shown in Figures S2 and S3, and MS data is shown in Figures S4 and S5." Also please place those figures (S2-5) after section S4.2, because these figures are all corresponding to the compound synthesized in this section. ^{1}H NMR (400 MHz,

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[ Elemental Composition ]
Data  : EI2021191                    Date : 12-Aug-2021 14:36
Sample: -
Note : -
Inlet : Direct                       Ion Mode : EI+
RT : 2.40 min                        Scan#: 287
Elements : C 50/0, 1H'100/0, Sn 1/1
Mass Tolerance      : 5mmu
Unsaturation (U.S.) : -1.0 - 40.0

Observed m/z Int%   Err[ppm / mmu]    U.S.  Composition
  381.1605   100.0     +0.2 /  +0.1     3.5  C 19 1H 33 Sn
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Figure S5: High resolution MS spectrum of tri-*n*-butyl-4-*n*-pentylphenylstannane (EI).

$CDCl_3$): δ 0.88 (t, J = 7.2 Hz, 9 H), 0.89 (t, J = 7.2 Hz, 3 H), 1.03 (dd, J = 8.0, 8.0 Hz, 6 H), 1.27–1.37 (m, 10 H), 1.43–1.56 (m, 6 H), 1.57–1.63 (m, 2 H), 2.57 (dd, J = 8.0, 8.0 Hz, 2 H), 7.15 (d, J = 8.0 Hz, 2 H), 7.37 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.5, 13.7, 14.1, 22.6, 27.4, 29.1, 31.2, 31.6, 35.9, 128.1, 136.4, 138.2, 142.6; HRMS (EI) calcd for $C_{19}H_{33}Sn^+$ [$(M–Bu)^+$]: 381.1599, found 381.1605.

To the column reactor, a MeOH/DMSO (3/7) solution containing 4-iodobenzonitrile (**1**, 0.033 M), tri-*n*-butyl-4-*n*-pentylphenylstannane (**9**, 0.050 M), lithium chloride (0.10 M) was introduced by a plunger pump (1 mL/min, pump pressure was less than 0.3 MPa). The column reactor (10 cm + 15 cm) was dipped in a water bath to be heated at 97°C. After reaching a steady state, the passed solution was collected for 60 min. The solution was mixed with aqueous ammonium chloride, *n*-hexane, ethyl acetate, and *n*-tridecane (an internal standard). The organic phase was analyzed by a GC to determine the yield of the desired product **10** (4-cyano-4′-*n*-pentylbiphenyl, 5CB) using a calibration line made by the commercial compound (81%).

S4.3 XRF analyses before and after Stille coupling

After the experiment described in section 4.2 (the flow Stille coupling for 5CB, 60 min), the column tube was washed by 50% of THF/MeOH (1 mL·min^{-1}, 20 min). Then the Pd@DualPore inside was ejected and analyzed by XRF to show 0.314 wt% of palladium was immobilized. Since the initial result of XRF was 0.339 wt%, the difference of the weight of palladium was calculated as 7.4%.

S5 Typical procedure for hydrogenation in flow

To the column reactor, a methanol solution containing 4-ethylnitrobenzene (**11**, 1.25 M) and *n*-tridecane (an internal standard, 0.03 M) was introduced by a plunger pump. Additionally, hydrogen gas was also introduced by a mass flow controller. The column reactor was dipped in a water bath to maintain the temperature (25°C). After reaching a steady state, the passed solution was collected for 10 min. The solution was analyzed by a GC to determine the yield of the desired product (**12**, 4-ethylaniline) using *n*-tridecane as an internal standard.

References

[1] Yamada T, Ogawa A, Masuda H, Teranishi W, Fujii A, Park K, et al. Pd catalysts supported on dual-pore monolithic silica beads for chemoselective hydrogenation under batch and flow reaction conditions. Catal Sci Technol. 2020;10(18):6359–67. doi: 10.1039/D0CY01442G.

[2] Iwasaki T, Maegawa Y, Hayashi Y, Ohoshima T, Mashima K. Transesterification of various methyl esters under mild conditions catalyzed by tetranuclear zinc cluster. J Org Chem. 2008;73(13):5147–50. doi: 10.1021/jo800625v.