Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Electronic Supplementary Information (ESI)

Investigation of microflow reactor diameter on condensation reactions in L-proline-immobilized polymer monoliths

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1. Materials

Water with conductivity of 18.2 MΩ cm (Milli-Q, Millipore Co., Bedford, MA) was used in all experiments. *trans*-4-Hydroxy-L-proline (Wako Pure Chemical Industries Ltd., Osaka, Japan), trifluoracetic acid (TFA, Wako Pure Chemical Industries Ltd.), *p*-toluenesulfonicacid (PTSA, Wako Pure Chemical Industries Ltd.) and methacryloyl chroride (Tokyo Chemical Industry Co., Ltd., Tokyo, Japan) were used to synthesis *O*-methacryloyl-*trans*-4-hydroxy-L-proline hydrochloride. Methyl methacrylate (MMA, Wako Pure Chemical Industry Co., Ltd.), ethylene glycol dimethacrylate (EDMA, Tokyo Chemical Industry Co., Ltd.), poly ethylene glycol 6000 (PEG, Tokyo Chemical Industry Co., Ltd), dimethyl sulfoxide (DMSO, Wako Pure Chemical Industry Co., Ltd.) and 2,2'-azobisobutyronitrile (AIBN, Tokyo Chemical Industry Co., Ltd.) were used as gel matrix, crosslinker, porogen, polymerization solvent and radical initiator, respectively. AIBN was purified by recrystallization from methanol and dried in vacuo at room temperature. The polymerization inhibitor in MMA and EDMA was removed using activated alumina column. *p*-Nitrobenzaldehyde and cyclohexanone were used as substrates for asymmetric aldol addition reactions.

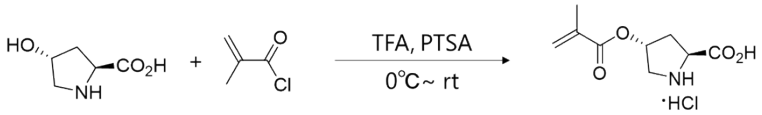
2.Charecterization

The samples for field emission scanning electron microscopy (FE-SEM) analysis were coated with platinum (approx. 4 nm thickness) using an JEOL JFC-1600 auto fine coater (JEOL Ltd., Tokyo, Japan). FE-SEM analysis was performed on a Hitachi SU8000 microscopy (Hitachi High-Technologies Corporation, Tokyo, Japan). Mercury intrusion porosimetry analysis was performed on a Micromeritics AutoPoreIV9520 (Micromeritics Instrument Co., Norcross, GA, USA). Solution nuclear magnetic resonance (NMR) spectra were recorded on a JEOL ECZ400S spectroscopy. High-performance liquid chromatography (HPLC) analyses for product yield were performed on a JASCO LC-2000Plus system equipped with a JASCO DG-4580 degasser, a JASCO PU-4580 pump, a Kanto Chemical Mightysil RP-18 GP 250-4.6 column (Kanto Chemical Co., Tokyo, Japan), a JASCO UV-2077Plus UV detector, and a JASCO CO-2065Plus column oven (JASCO Co., Tokyo, Japan). Acetonitrile/water (60:40 v/v) containing trifluoroacetic acid (0.1 vol%) was employed as a mobile phase in the HPLC measurements. HPLC analyses for enantiomeric excess were performed on a JASCO LC-2000Plus system equipped with a JASCO DG-980-50 degasser, a JASCO PU-986 pump, a CHIRALPAK AD-H 250-4.6 column (Daicel Co., Osaka, Japan), a JASCO MD-4010 photo diode array detector, and a JASCO CO-2060Plus column oven (JASCO Co., Tokyo, Japan). 2-propanol:hexane (10:90 v/v) was employed as a mobile phase in the HPLC measurements.

In continuous-flow setup, SGE glass gas-tight syringe (SGE Analytical Science Pty. Ltd., Melbourne, Australia), which was mounted on YMC YSP-101 syringe pump (YMC Co. Ltd., Kyoto, Japan), and FLOM VI-11 injection valve (FLOM Co., Tokyo, Japan) were connected to column in a

thermo-controlled incubator with PTFE or PFA tubing (0.75 mm inner diameter). For residence time distribution (RTD) studies, a FLOM VI-11 injection valve (FLOM Co., Tokyo, Japan) with a 10 μL loop, an Ocean Optics USB2000+ ultraviolet-visible (UV-Vis) spectrometer, an Ocean Optics tungsten halogen light source HL-2000, and an Ocean Optics FIA-Z-SMA-ML-TE Z-type flow cell (Ocean Optics Inc., Dunedin, FL, USA) were included in continuous-flow setup.

3. Synthesis of *o*-methacryloyl-*trans*-4-hydroxy-L-proline hydrochloride



TFA (29.3 mL, 382 mmol) was poured into a 300 mL two-necked eggplant flask and placed in an ice/water bath. Powdered *trans*-4-hydroxy-L-proline (10.0 g, 76 mmol, dried at 70 °C for 16 h) was added in small portions under vigorous stirring to give a viscous solution. The reaction mixture was stirred for 5 min, then removed from the ice/water bath and PTSA (2.62 g, 15.2 mmol) was added. After 5 min of stirring, methacryloyl chloride (14.71 mL, 152 mmol) was added. The reaction mixture was stirred at room temperature for 4 h, giving a clear and colorless solution. The reaction flask was then cooled in an ice/water bath, and Et_2O (100 mL) was added under vigorous stirring over a period of 10 min, slowly at first. The resulting white suspension was stirred at 0-5 °C for 15 min after completed addition, and then filtered by vacuum. The resulting solid was dried in vacuum to obtain a white solid. The white solid can be recrystallized by suspending in boiling acetone, containing a small amount of inhibitor, and adding water dropwise until complete dissolution. An analytical sample of small, transparent and sugar-like crystals (see picture to the right) was prepared by recrystallization from boiling acetone/water in the same manner. The clear colorless solution was cooled at -20°C for 24 h. The solution containing the precipitated crystals was filtered by vacuum and washed with cold Acetone, and the crystals were dried in vacuum to give *o*-methacryloyl-*trans*-4-hydroxy-L-proline hydrochlorid (Pro monomer, yield = 32.9%).[1]

^{1}H NMR (400 MHz, METHANOL-D4) δ 6.20 (d, *J* = 1.4 Hz, 1H), 5.76-5.71 (m, 1H), 5.50 (t, *J* = 4.8 Hz, 1H), 4.62 (dd, *J* = 10.5, 7.8 Hz, 1H), 3.72 (dd, *J* = 13.3, 4.6 Hz, 1H), 3.54 (dt, *J* = 13.3, 1.6 Hz, 1H), 2.65 (ddt, *J* = 14.6, 7.9, 1.7 Hz, 1H), 2.52-2.41 (m, 1H), 1.96 (t, *J* = 1.1 Hz, 3H)

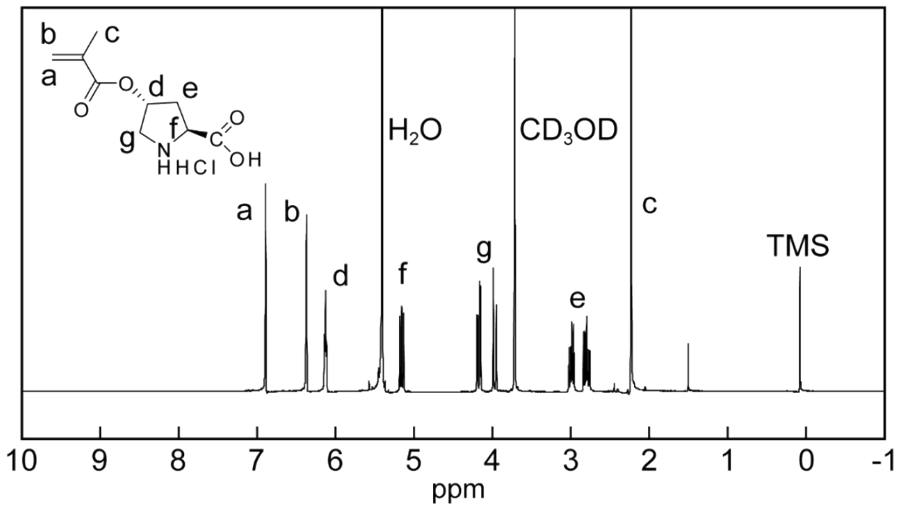
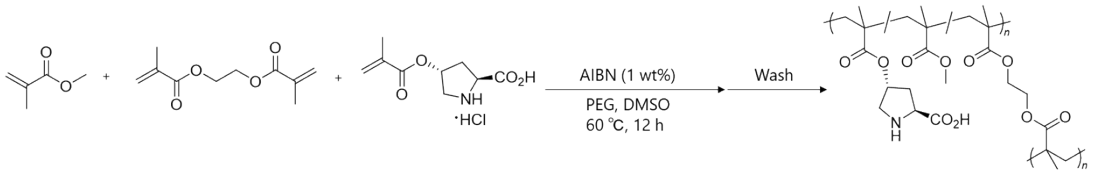


Figure S1. ^{1}H NMR spectrum of Pro monomer (CD_3OD, 400 MHz).

4. Synthesis of the monolithic column containing Pro monomer



A 6 mL vial was charged with DMSO (559.5 μL). PEG (Mw = 2000, 4000, 6000 and 10000, 205.2 mg) and Pro monomer (13.9 mg, 0.059 mmol) were added and mixed by using heat at 70℃. After the solution was brought to room temperature, MMA (16.2 μL, 0.15 mmol), EDMA (167.6 μL, 0.89 mmol) and AIBN (1 wt% respect to the total monomers) were added and stirred for a few minutes. The monomer solution was degassed with a nitrogen gas for 30 min. The mixed solution was poured into a stainless column (4.0 mm i.d., 50 mm *L*) or capillary (0.53 mm i.d., 50-125 mm *L*), which was then incubated at 60℃ for 12 h. After incubation, the monolith was then flushed with a residence time of 30 min for 5 h with MeOH.

5. Measurement of permeabilities of the monolithic columns.

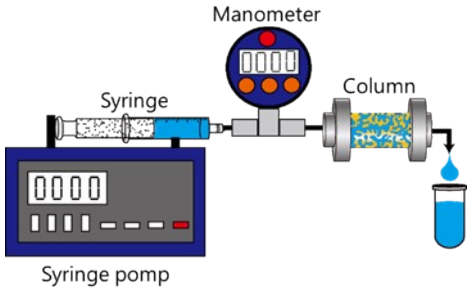


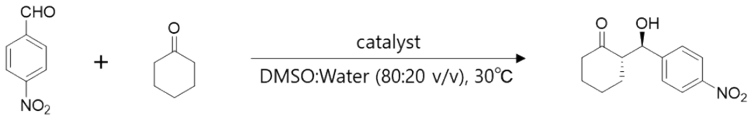
Figure S2. Experimental setup of permeability performance evaluation using a monolithic column.

To evaluate the permeation performance, the washed monolithic column was connected to a syringe pump and a pressure gauge. DMSO: water solution (80:20 v/v), which was used for asymmetric aldol addition reaction, was permeated through the monolithic column at various flow rates. Pressure losses at steady state were determined. The permeability was evaluated from the Darcy's law, as follows:

$$\frac{\Delta P}{L} = \frac{\mu Q}{kA}$$

where ΔP, μ, L, A, and Q are the pressure loss, viscosity, thickness, base area, and flow rate, respectively.

6. The asymmetric aldol addition reaction between cyclohexanone and *p*-nitrobenzaldehyde in continuous-flow system.



The substrate solution was prepared by mixing the substrates *p*-nitrobenzaldehyde (0.18 mmol, 1 eq.) and cyclohexanone (0.90 mmol, 5 eq.) in DMSO:water (80:20 v/v, 1mL). The washed monolithic column, manual injector and syringe filled with DMSO:water (80:20 v/v) were connected using a fitting. DMSO:water (80:20 v/v) was pumped through the monolithic column by syringe pump, and the reaction was started by injecting the substrate solution after the flow reached a steady state. All the continuous-flow operation was carried out in an incubator at 30°C. The eluent was collected and the reaction progress was followed by HPLC equipped with a reversed-phase column at 310 nm (acetonitrile:water = 60:40 v/v, 1 mL/min). The enantiometric excess (ee) of the product was determined by HPLC equipped with a chiral column (2-propanol:hexane = 10:90 v/v, 1 mL/min).

TableS1. Amount of immobilization catalyst in each column

Column	Amount of immobilization catalyst (μmol)[a]
0.53 mm i.d. × 50 mm *L*	0.88
0.53 mm i.d. × 75 mm *L*	1.31
0.53 mm i.d. × 100 mm *L*	1.75
0.53 mm i.d. × 125 mm *L*	2.19
4.0 mm i.d. × 50 mm *L*	49.8

[a]Calculated based on the composition ratio of catalyst, MMA and EDMA.

HPLC analysis of the aldol products for identification of enantiomers.

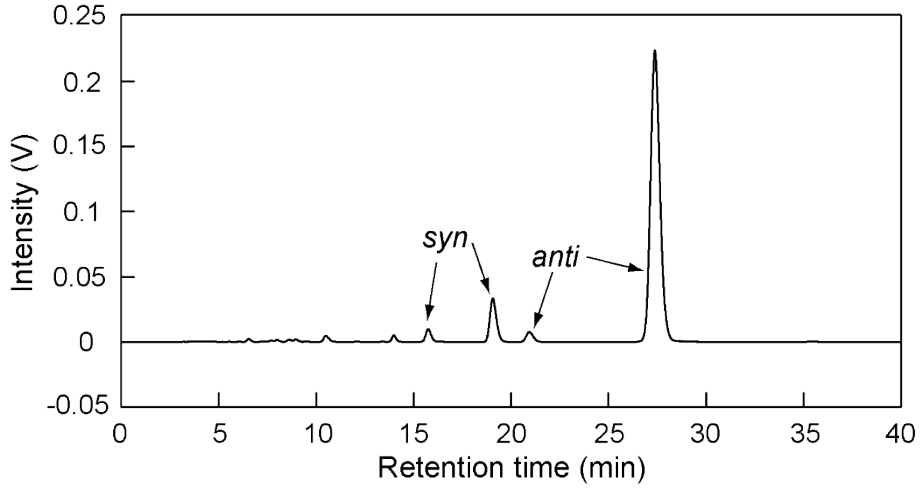


Figure S3. HPLC chromatogram of the aldol products.

RT	Area	% Area	Height	% Height
15.748	188392	2.161	9697	3.545
19.060	785152	9.005	33364	12.198
20.938	197605	2.266	7753	2.835
27.375	7547830	86.568	222696	81.421

^{1}H NMR (400 MHz, CHLOROFORM-D) δ 8.21 (dd, J = 8.7, 2.3 Hz, 2H), 7.50 (t, J = 8.2 Hz, 2H), 7.26 (s, 1H), 5.51-5.47 (m, 0H), 4.90 (dd, *J* = 8.5, 3.0 Hz, 1H), 4.07 (d, *J* = 3.2 Hz, 1H), 3.17 (d, *J* = 3.2 Hz, 0H), 2.70-2.28 (m, 3H), 2.12 (tt, *J* = 9.5, 3.0 Hz, 1H)

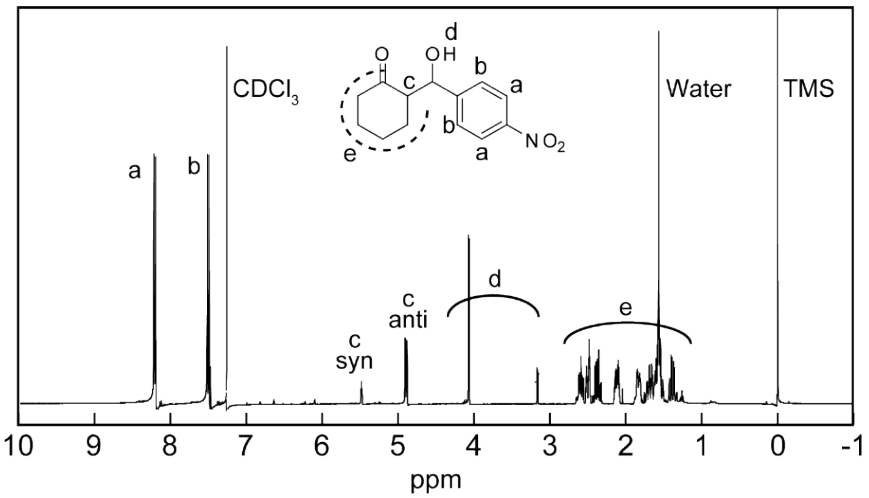


Figure S4. ^{1}H NMR spectra of aldol product ($CDCl_3$, 400 MHz).

Asymmetric aldol addition reaction at residence time 30 min for a long time.

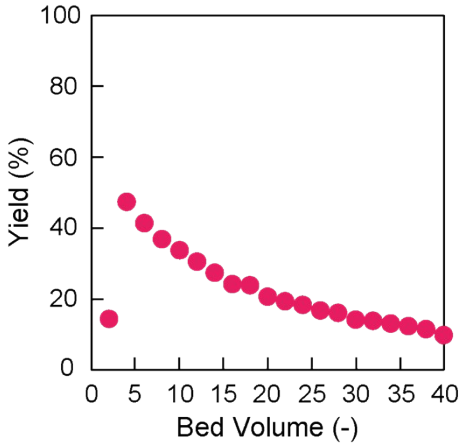


Figure S5. Plots of the yields of the asymmetric aldol addition reaction between cyclohexanone (0.90 mmol/L) and *p*-nitrobenzaldehyde (0.18 mmol/L) at residence time 30 min (flow rate: 44.12 μL/h) using PEG-6000-based monolithic microflow reactor (0.53 mm i.d. × 100 mm *L*) for 20 h.

Asymmetric aldol addition reaction at residence time 60 min.

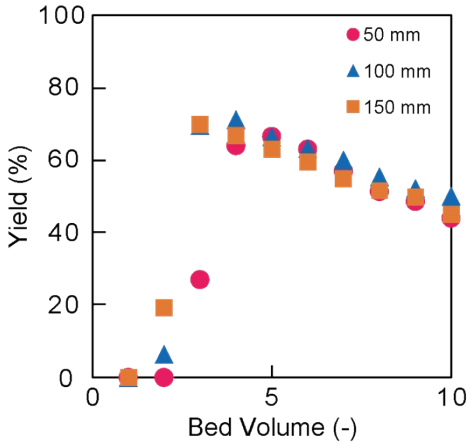


Figure S6. Plots of the yields of the asymmetric aldol addition reaction between cyclohexanone and *p*-nitrobenzaldehyde at 60 min residence time using PEG-6000-based monolithic microflow reactors of different length (red circle: 50 mm *L*, blue triangle: 100 mm *L*, orange square: 150 mm *L*).

7. Pulse tracer experiments for RTD study.

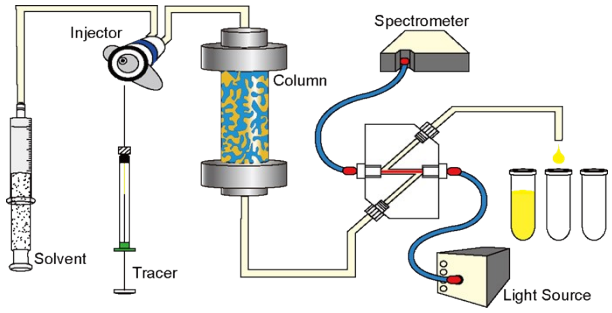


Figure S7. Schematic illustration of pulse tracer experimental set-up for the RTD study.

The tracer solution was prepared by mixing the tracer methylene blue (0.2 mg) in DMSO: water (80:20 v/v, 1mL). The monolithic column was attached just before the flow cell, and the flow pattern of the solution was observed by measuring the absorbance of the tracer molecules. DMSO:water (80:20 v/v) was pumped through the monolithic column by syringe pump, and the RTD study was started by pulsed injecting the tracer solution after the flow reached a steady state.

References

[1] Lu, A., Cotanda, P., Patterson, J. P., Longbottom, D. A., & O'Reilly, R. K. *Chemical communications*, 2012, 48.78, 9699-9701.