

Supporting Information

Continuous-Inline Extraction of Polar Co-solvent During Sequential Flow Reactions

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1. General

Gas chromatography was measured on a Shimadzu GC-2014 spectrometer with N₂ gas as a carrier, using Agilent Technologies DB-1 column (Length: 30 m, I.D.: 0.250 mm, Film: 0.25 μm). A dual plunger pump (UI-22 series) was purchased from FLOM, Inc., and flow reactor (XCR-1000, HCR-1000), column (CLM-1010) and fraction collector (DC-1000) were purchased from EYELA. Mixer-setters (MSL-IT-04-00-00, MSL-IT-02-00-00) was purchased from MAK ENGINEERING Co. Ltd. Other chemicals and solvents were purchased from Tokyo Chemical Industry Co., Ltd, FUJIFILM Wako pure chemicals, Kishida chemical Co., Ltd., and Sigma-Aldrich.

2. Procedures for preparation of catalysts

Amberlyst A26 (Sigma-Aldrich)

Amberlyst A26 (10 g) was added into H₂O (20 mL), stirred for 30 min, and filtrated with H₂O (20 mL × 3). Obtained catalysts was added into EtOH (20 mL), stirred for 30 min, and filtrated with EtOH (20 mL × 3). Furthermore, obtained catalysts was added into toluene/EtOH (9/1, 20 mL), stirred for 30 min, and filtrated with toluene/EtOH (9/1, 20 mL × 3).

Amberlyst A21 (Sigma-Aldrich)

Amberlyst A21 (10 g) was added into 5%NaOH aq. (100 mL) and stirred for 16 hours. The supernatant was removed,

and new H₂O (100 mL) was added. After stirring for 10 min, the supernatant was removed, and new H₂O (100 mL) was added. Obtained catalysts was filtrated with H₂O (50 mL) and added in EtOH (100 mL). Obtained catalysts was filtrated with EtOH (50 mL) and added in toluene (100 mL). Obtained catalysts was filtrated with toluene (50 mL).

3. Procedures for the 1,4-conjugate addition under batch conditions (Table 1)

A reaction mixture of chalcone (**3**; 1.0 mmol, 208.3 mg), diethyl malonate (**4**; 1.05 mmol, 168.2 mg), and Amberlyst A21 (100 wt%, 208.3 mg) in toluene (5 mL) was heated at 60 °C and stirred for 24 hours. The reaction mixture was cooled to room temperature and filtered through a filter with ethyl acetate. Obtained filtrates were analyzed by GC to determine yield of **5**.

4. Experimental setup for flow reactions

Reaction apparatus

pump	column reactor	column
		
UI-22 110P, EYELA	XCR-1000, EYELA	CLM-1010, EYELA ID: 10 mm, L: 100 mm
Fraction collector	Mixer-settler	column reactor
		
DC-1000, EYELA	MSL-IT-04-00-00 (setter volume: 11.2 mL), MAK ENGINEERING Co. Ltd.	HCR-1000, EYELA
column	Mixer-settler	

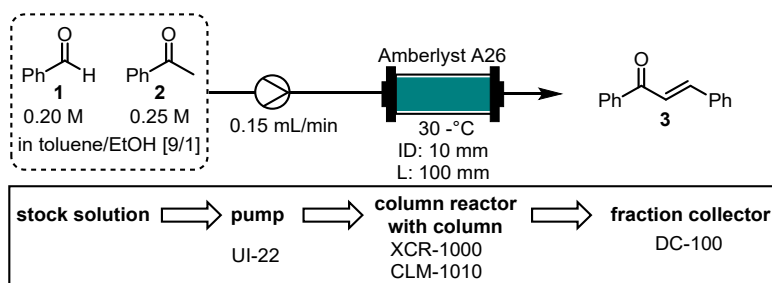


column for HCR-1000, EYELA
ID: 37 mm, L: 300 mm



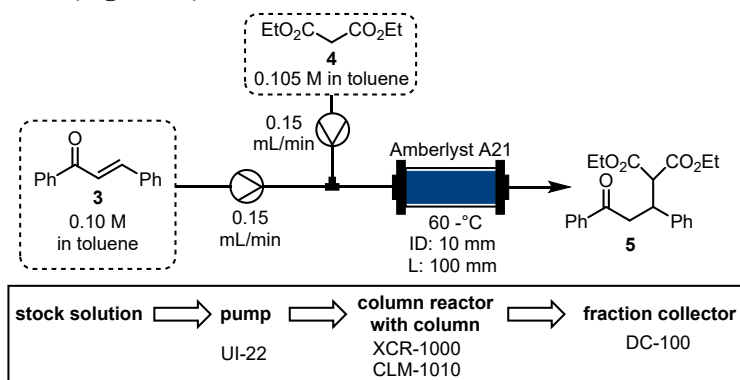
MSL-IT-02-00-00 (setter volume:
28 mL), MAK ENGINEERING Co.
Ltd.

Flow aldol condensation



Amberlyst A26 (5.0 g) was packed into a column (I.D. 10×100 mm, CLM-1010, EYELA). The catalyst column was set onto the reactor, and toluene/EtOH [9/1] was flowed at 0.15 mL/min (pump: UI-22 110P, EYELA) for 30 min to remove residual air inside. The catalyst column was heated at 30 °C (heating controller and column reactor: XCR-1000, EYELA) with solvent flow, after stabilization the reaction was started by changing into stock solution of benzaldehyde (1; 0.20 M) and acetophenone (2, 0.25 M) in toluene/EtOH [9/1]. The resulted solution was fractionated for every 1 hours (9 mL) (Fraction collector: DC-1000, EYELA), and selected fractions were analyzed GC to determine yields.

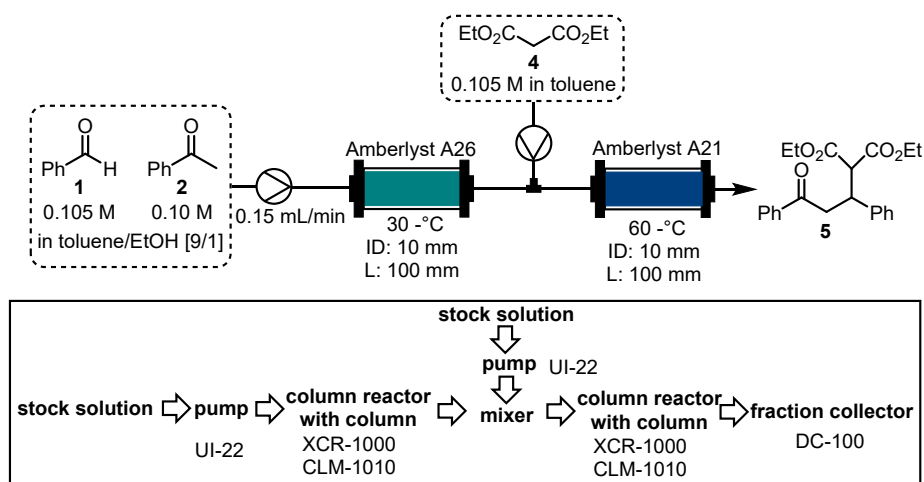
Flow 1,4-conjugate addition (Figure 1a)



Amberlyst A21 (4.6 g) was packed into a column (I.D. 10×100 mm, CLM-1010, EYELA). The catalyst column was set onto the reactor, and toluene was flowed at 0.15 mL/min (pump: UI-22 110P, EYELA) by two pumps for 30 min to remove residual air inside. The catalyst column was heated at 60 °C (heating controller and column reactor: XCR-

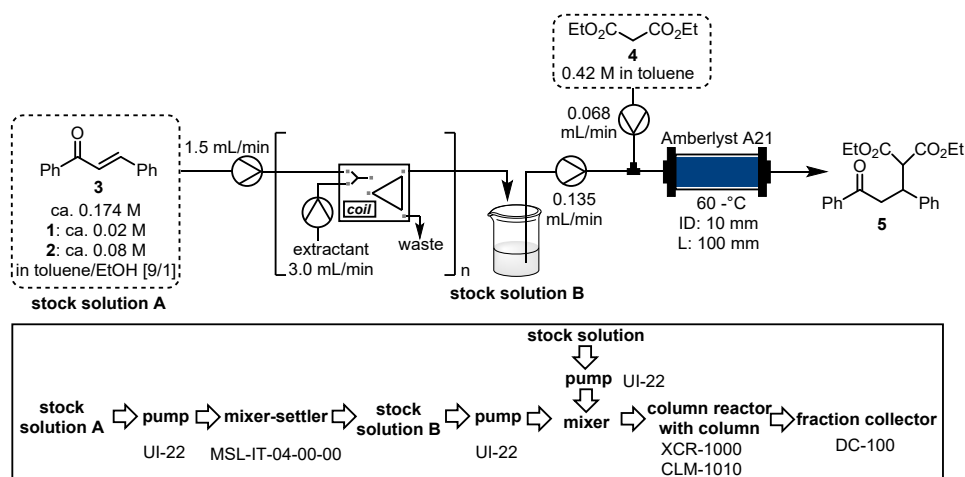
1000, EYELA) with solvent flow, after stabilization the reaction was started by changing into stock solution of chalcone (**3**; 0.10 M) in toluene and stock solution of diethyl malonate (**4**, 0.105 M) in toluene. The resulted solution was fractionated for every 30 min (9 mL) (Fraction collector: DC-1000, EYELA), and selected fractions were analyzed GC to determine yields.

Sequential flow reaction of aldol condensation and 1,4-conjugate addition



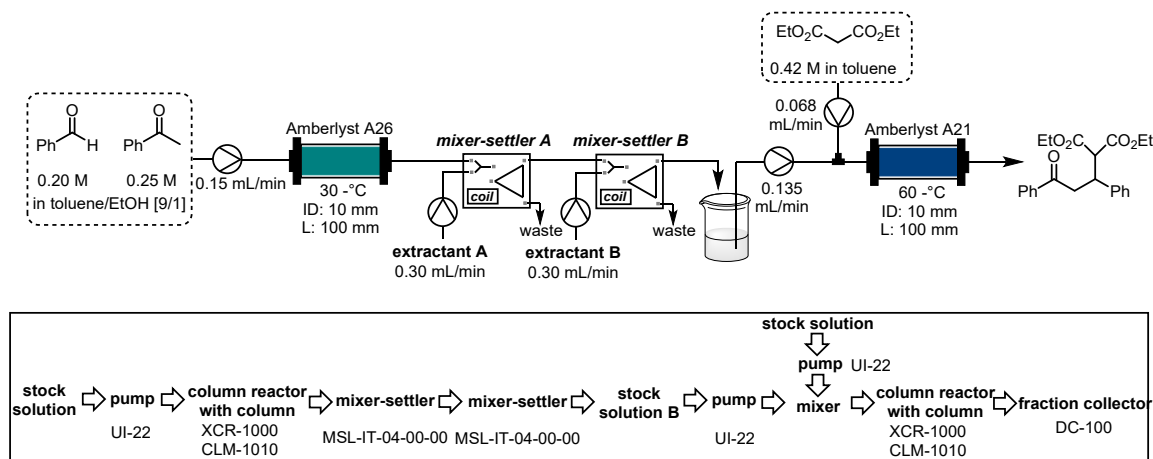
Amberlyst A26 (5.0 g) was packed into a first column (I.D. 10×100 mm, CLM-1010, EYELA). Amberlyst A21 (4.6 g) was packed into a second column (I.D. 10×100 mm, CLM-1010, EYELA). The catalyst columns were set onto the reactors. Toluene/EtOH [9/1] was flowed at 0.15 mL/min (pump: UI-22 110P, EYELA) for the first column, and toluene was flowed at 0.15 mL/min (pump: UI-22 110P, EYELA) for the second column for 30 min to remove residual air inside. The first and second columns were respectively heated at 30 °C and 60 °C (heating controller and column reactor: XCR-1000, EYELA) with solvent flow, and after stabilization the first reaction was started by changing into stock solution of benzaldehyde (**1**; 0.105 M) and acetophenone (**2**, 0.10 M) in toluene/EtOH [9/1]. After 1 hours later, the second reaction was started by changing into stock solution of stock solution of diethyl malonate (**4**, 0.105 M) in toluene. The resulted solution was fractionated for every 30 min (9 mL) (Fraction collector: DC-1000, EYELA), and selected fractions were analyzed GC to determine yields.

Continuous-extraction and 1,4-conjugate addition (Table 2)



Stock solution A was prepared by the procedure of **Flow aldol condensation**. Stock solution A was flowed at 1.5 mL/min (pump: UI-22 110P, EYELA) to a mixer-settler (MSL-IT-04-00-00, MAK ENGINEERING Co. Ltd.) with extractant at 3.0 mL/min to store a stock solution B. Stock solution B was analyzed GC to determine extraction rate of EtOH, extraction rate of **1**, and survival rate of **3**. Amberlyst A21 (4.6 g) was packed into a column (I.D. 10×100 mm, CLM-1010, EYELA). The catalyst column was set onto the reactor, and toluene was flowed at 0.135 mL/min and 0.068 mL/min (pump: UI-22 110P, EYELA) by two pumps for 30 min to remove residual air inside. The catalyst column was heated at 60 °C (heating controller and column reactor: XCR-1000, EYELA) with solvent flow, after stabilization the reaction was started by changing into the stock solution B and a stock solution of diethyl malonate (**4**, 0.105 M) in toluene. The resulted solution was fractionated for every 1 hours (12 mL) (Fraction collector: DC-1000, EYELA), and selected fractions were analyzed GC to determine yields.

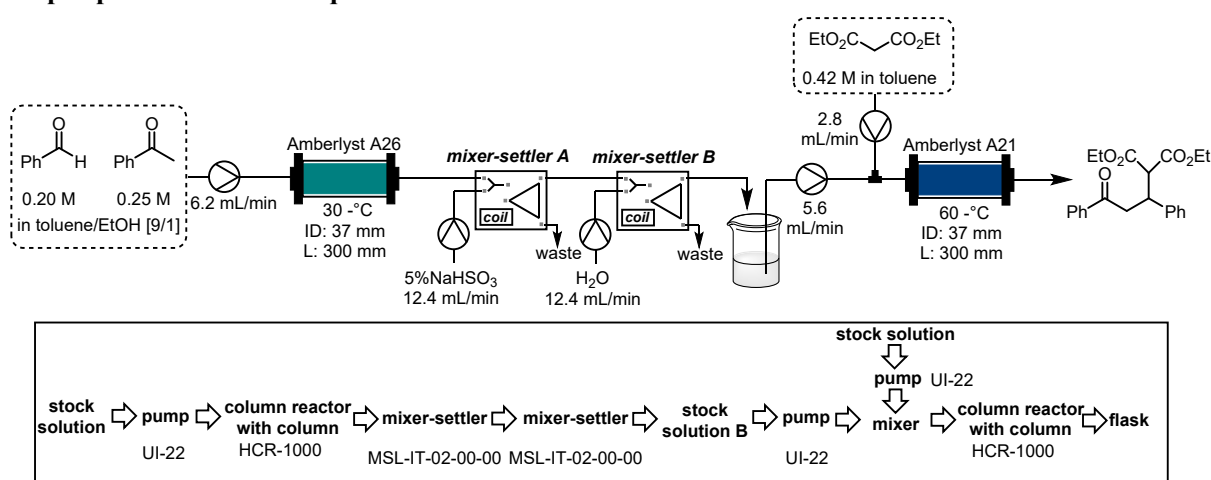
Flow aldol condensation, continuous-extraction, and 1,4-conjugate addition (Table 3)



Amberlyst A26 (5.0 g) was packed into a column (I.D. 10×100 mm, CLM-1010, EYELA). The catalyst column was set onto the reactor, and toluene/EtOH [9/1] was flowed at 0.15 mL/min (pump: UI-22 110P, EYELA) for 30 min to remove residual air inside. The catalyst column was heated at 30 °C (heating controller and column reactor: XCR-1000, EYELA) with solvent flow, after stabilization the reaction was started by changing into stock solution of benzaldehyde (**1**; 0.20 M) and acetophenone (**2**, 0.25 M) in toluene/EtOH [9/1]. A solution of aldol condensation was flowed at 0.15 mL/min (pump: UI-22 110P, EYELA) to a mixer-settler A (MSL-IT-04-00-00, MAK ENGINEERING

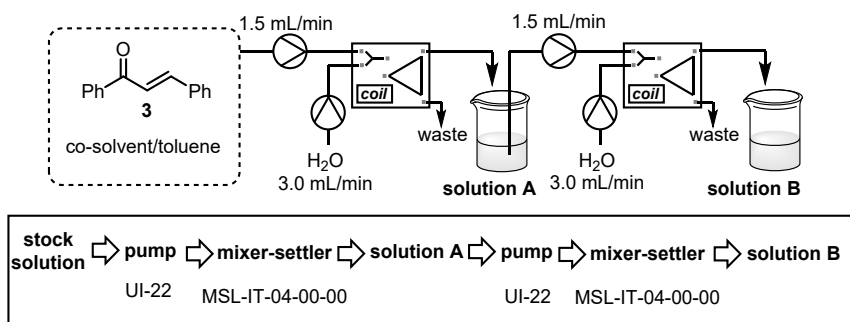
Co. Ltd.) with extractant at 0.3 mL/min. Organic phase was sent to a mixer-setter B with extractant at 0.3 mL/min to store a stock solution B. Stock solution B was analyzed GC to determine extraction rate of EtOH, extraction rate of **1**, and survival rate of **3**. Amberlyst A21 (4.6 g) was packed into a column (I.D. 10×100 mm, CLM-1010, EYELA). The catalyst column was set onto the reactor, and toluene was flowed at 0.135 mL/min and 0.068 mL/min (pump: UI-22 110P, EYELA) by two pumps for 30 min to remove residual air inside. The catalyst column was heated at 60 °C (heating controller and column reactor: XCR-1000, EYELA) with solvent flow, after stabilization the reaction was started by changing into the stock solution B and a stock solution of diethyl malonate (**4**, 0.105 M) in toluene. The resulted solution was fractionated for every 1 hours (12 mL) (Fraction collector: DC-1000, EYELA), and selected fractions were analyzed GC to determine yields.

Scale-up experiment for the sequential flow reaction



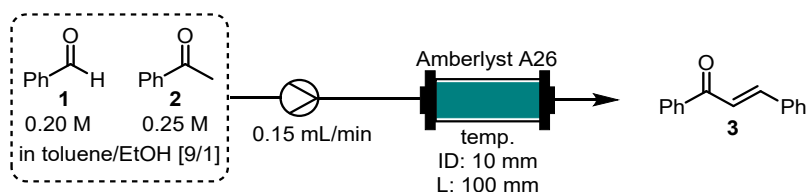
Amberlyst A26 (186.5 g) was packed into a column (I.D. 37×300 mm, HCR-1000, EYELA). The catalyst column was set onto the reactor, and toluene/EtOH [9/1] was flowed at 6.2 mL/min (pump: UI-22 110P, EYELA) for 30 min to remove residual air inside. The catalyst column was heated at 30 °C (heating controller and column reactor: HCR-1000, EYELA) with solvent flow, after stabilization the reaction was started by changing into stock solution of benzaldehyde (**1**; 0.20 M) and acetophenone (**2**, 0.25 M) in toluene/EtOH [9/1]. A solution of aldol condensation was flowed at 6.2 mL/min (pump: UI-22 110P, EYELA) to a mixer-setter A (MSL-IT-02-00-00, MAK ENGINEERING Co. Ltd.) with extractant at 12.4 mL/min. Organic phase was sent to a mixer-setter B with extractant at 12.4 mL/min to store a stock solution B. Stock solution B was analyzed GC to determine extraction rate of EtOH, extraction rate of **1**, and survival rate of **3**. Amberlyst A21 (185.0 g) was packed into a column (I.D. 37×300 mm, HCR-1000, EYELA). The catalyst column was set onto the reactor, and toluene was flowed at 5.6 mL/min and 2.8 mL/min (pump: UI-22 110P, EYELA) by two pumps for 30 min to remove residual air inside. The catalyst column was heated at 60 °C (heating controller and column reactor: HCR-1000, EYELA) with solvent flow, after stabilization the reaction was started by changing into the stock solution B and a stock solution of diethyl malonate (**4**, 0.105 M) in toluene. The resulted solution was stored to the plastic container and taken samples to to determine yields by GC.

Continuous-extraction for various co-solvent with toluene



Solution of **3** (0.2 M) in co-solvent/toluene was flowed at 1.5 mL/min (pump: UI-22 110P, EYELA) to a mixer-settler (MSL-IT-04-00-00, MAK ENGINEERING Co. Ltd.) with H₂O at 3.0 mL/min to store a solution A. Solution A was analyzed GC to determine extraction rate of EtOH and survival rate of **3**. Solution A was flowed at 1.5 mL/min (pump: UI-22 110P, EYELA) to a mixer-settler (MSL-IT-04-00-00, MAK ENGINEERING Co. Ltd.) with H₂O at 3.0 mL/min to store a solution B. Solution B was analyzed GC to determine extraction rate of EtOH and survival rate of **3**.

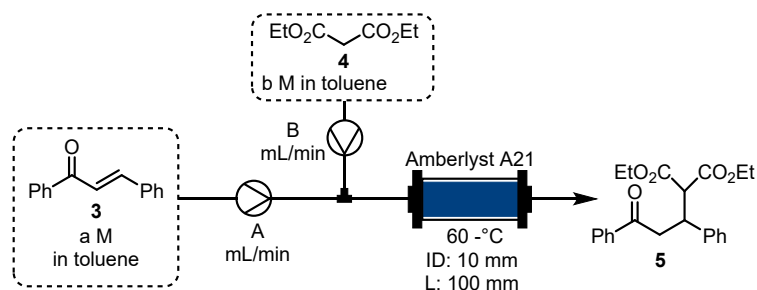
5. Optimization for the flow aldol condensation



According to procedure of **Flow aldol condensation**.

entry	temp. (°C)	yield (%)
1	30	86
2	40	79
3	50	68
4	60	52

6. Optimization for the flow 1,4-conjugate addition



According to procedure of **Flow 1,4-conjugate addition**.

entry	a (M)	b (M)	A (mL/min)	B (mL/min)	yield (%)
1	0.20	0.21	0.27	0.27	59
2	0.20	0.21	0.135	0.135	65

3	0.20	0.21	0.068	0.068	78
4	0.20	0.42	0.135	0.068	74

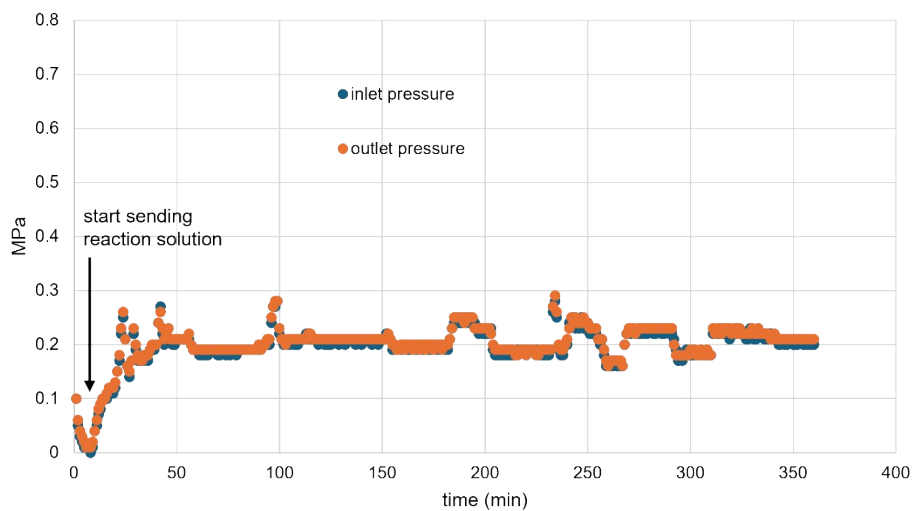
7. Procedure and calculation for the void volume of the catalyst column

A catalyst was packed into a column. The catalyst column was sealed with plugs and weighted. Sealed plugs were removed, and the catalyst column was set onto a flow reactor. The catalyst column was filled with toluene by a pump. After solvent filling, the catalyst column was sealed with plugs and weighted. The void volume of catalyst column was calculated as follows with the density of toluene (0.867 g/mL).

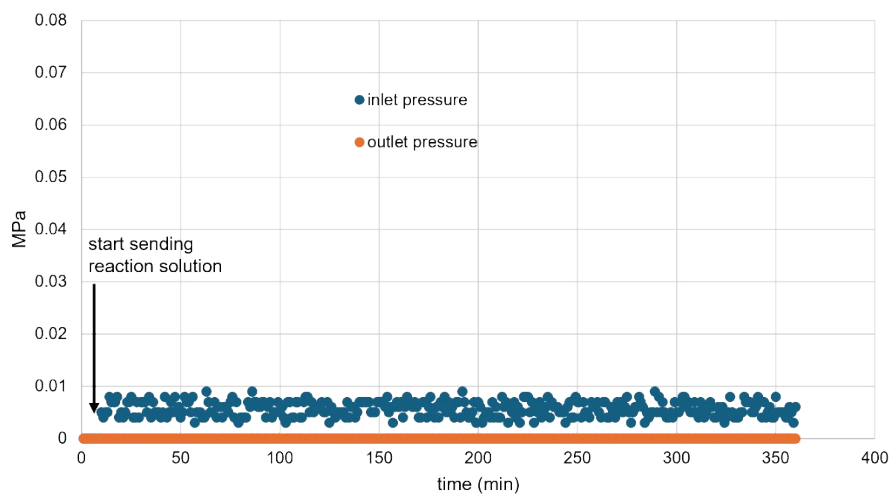
catalyst	column size	void volume (mL)	total flow rate (mL/min)	residence time (min)
Amberlyst A26	ID: 10 mm, L: 100 mm	2.13	0.15	14.2
Amberlyst A26	ID: 37 mm, L: 300 mm	85.2	6.2	13.7
Amberlyst A21	ID: 10 mm, L: 100 mm	2.78	0.30	9.3
Amberlyst A21	ID: 10 mm, L: 100 mm	2.78	0.203	13.7
Amberlyst A21	ID: 37 mm, L: 300 mm	111.2	8.4	13.2

8. Reaction pressure profiles for the scale-up experiments (Figure 2)

Flow aldol condensation

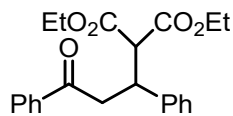


Flow 1,4-conjugate addition



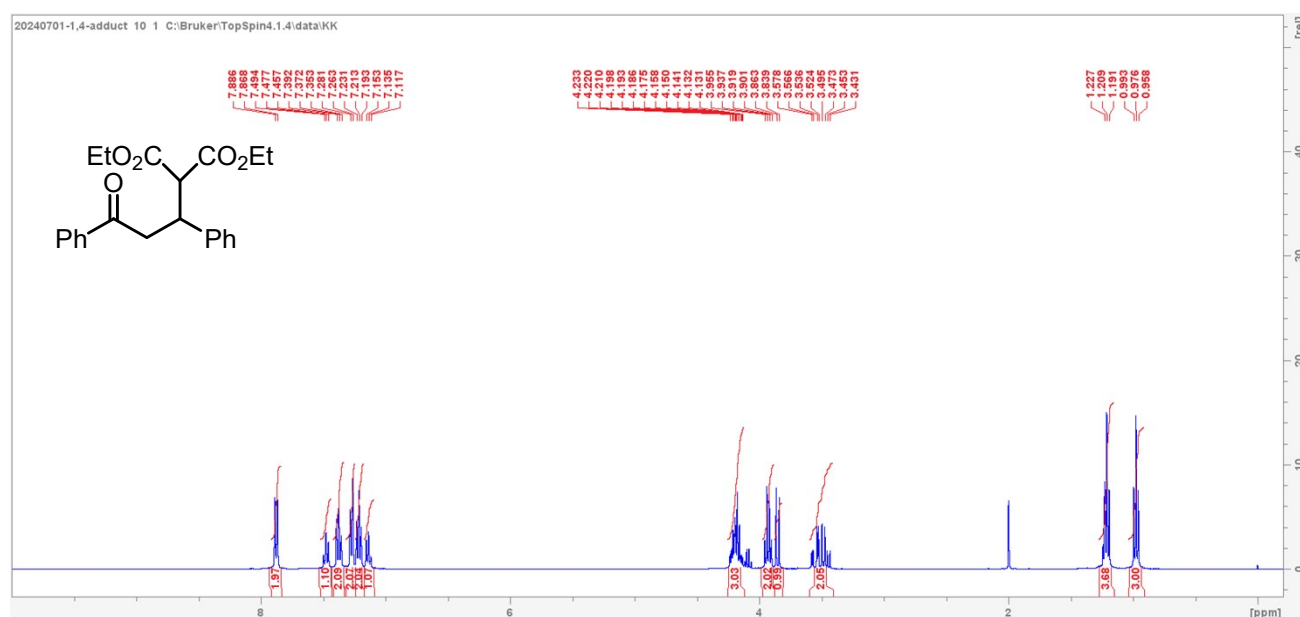
9. ¹H and ¹³C NMR spectra

Diethyl 2-(3-oxo-1, 3-diphenylpropyl)malonate (5)

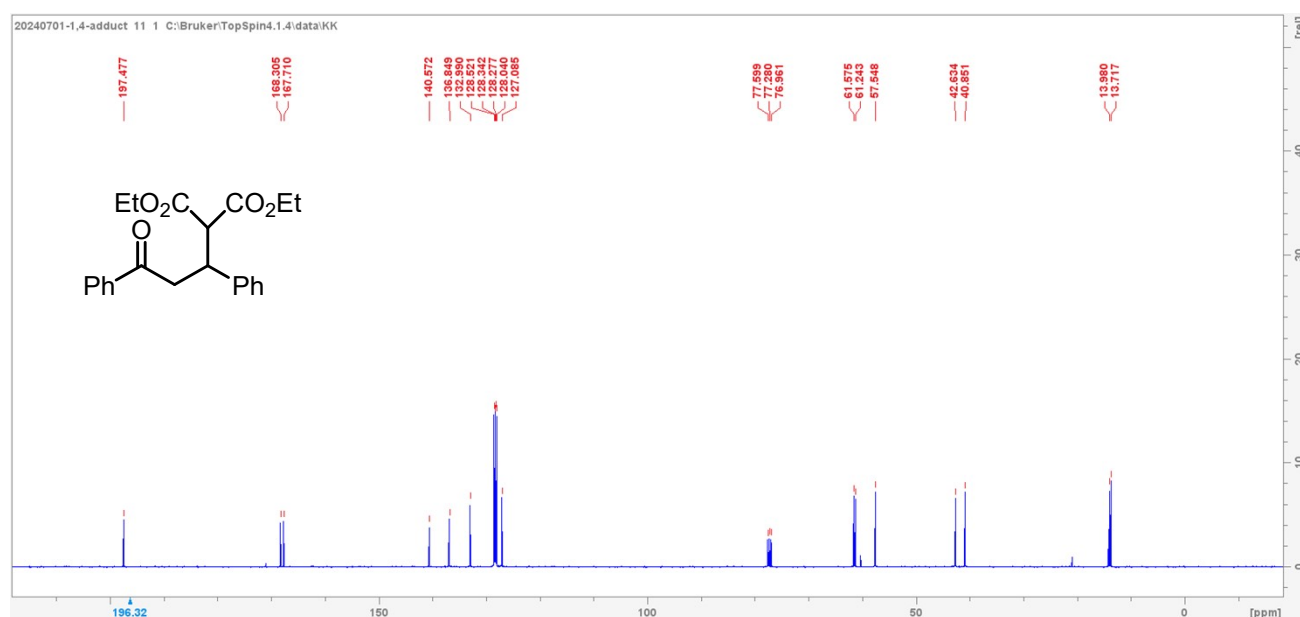


¹H NMR (400 MHz, CDCl₃): δ 7.88 (d, *J* = 7.2 Hz, 2H), 7.48 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.37 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.27 (d, *J* = 7.2 Hz, 2H), 7.21 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.14 (dd, *J* = 7.2 Hz, 1H), 4.23–4.13 (m, 3H), 3.93 (q, *J* = 7.2 Hz, 2H), 3.85 (d, *J* = 9.6 Hz, 1H), 3.58–3.43 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.98 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 197.5, 168.3, 167.7, 140.6, 136.8, 133.0, 128.5, 128.3, 128.0, 127.1, 61.6, 61.2, 57.5, 42.6, 40.9, 14.0, 13.7. Spectroscopic data of ¹H and ¹³C NMR were identical to *Org. Biomol. Chem.* **2014**, *12*, 3166.

¹H NMR of **5** (CDCl₃, 400 Hz)

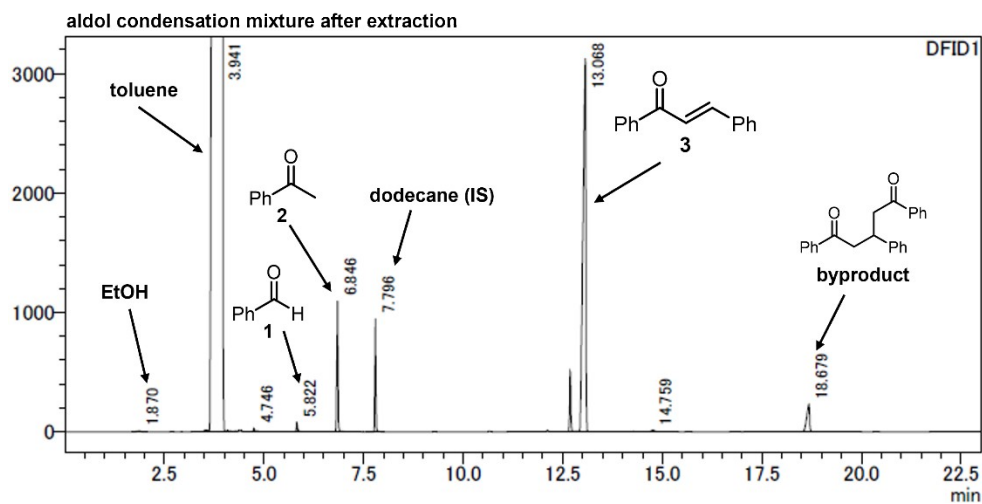


¹³C NMR of **5** (CDCl₃, 100 Hz)

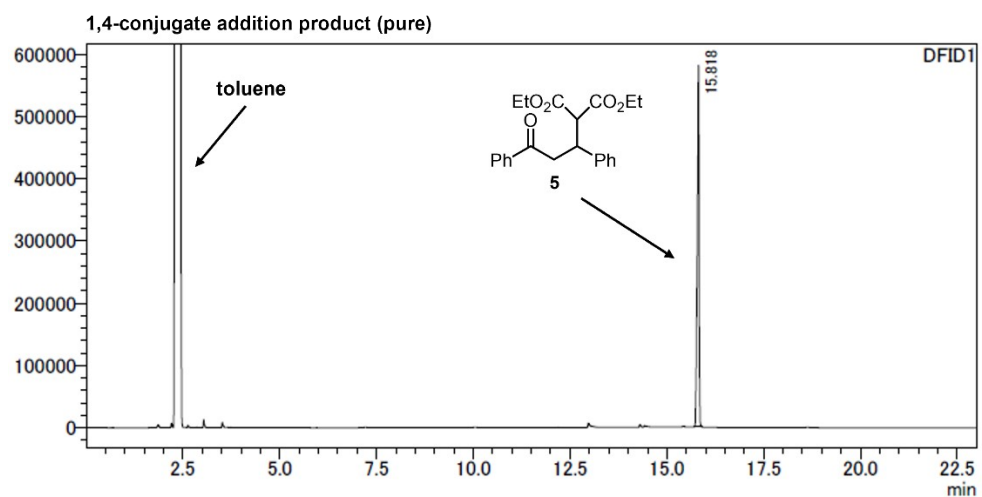


10. GC charts for continuous extraction (Table 4)

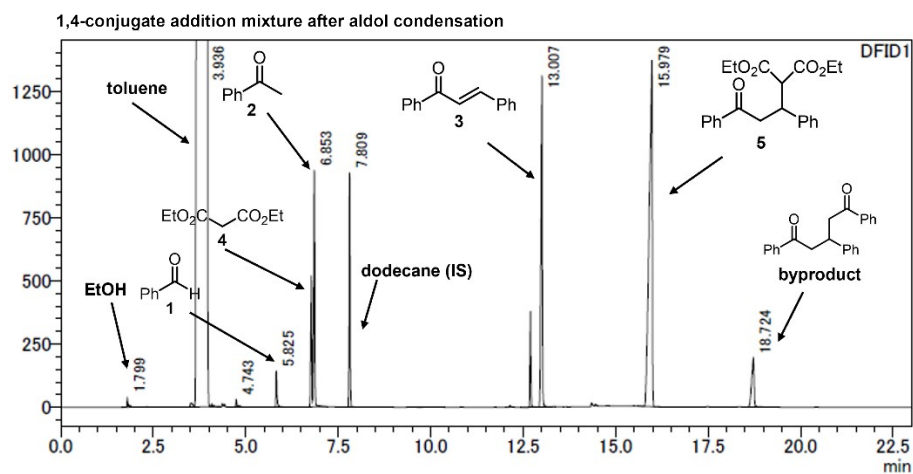
Aldol condensation (Table 3)



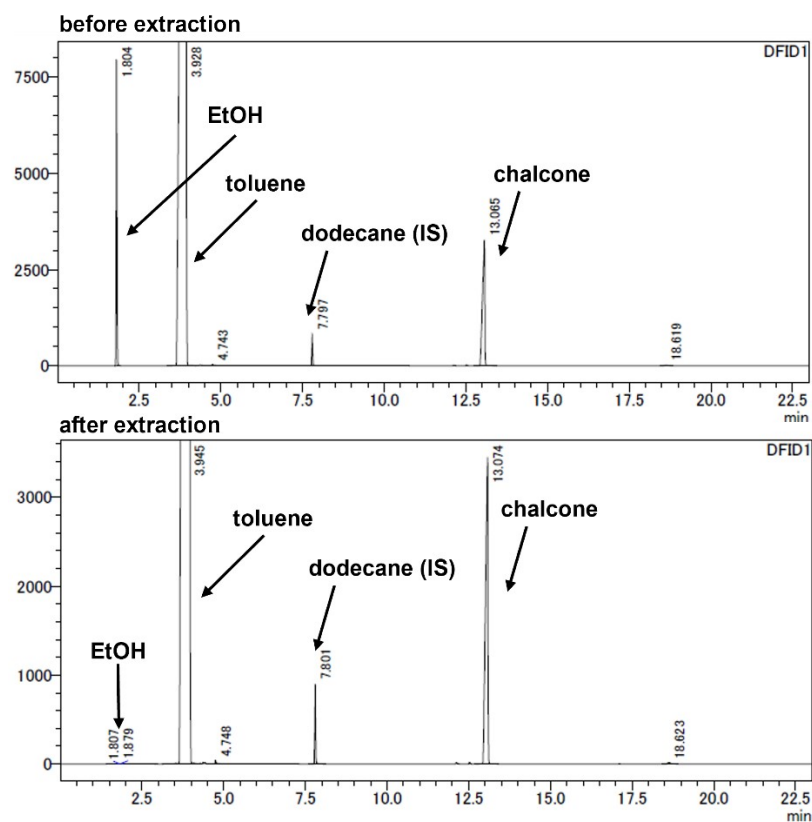
Diethyl 2-(3-oxo-1,3-diphenylpropyl)malonate (5)



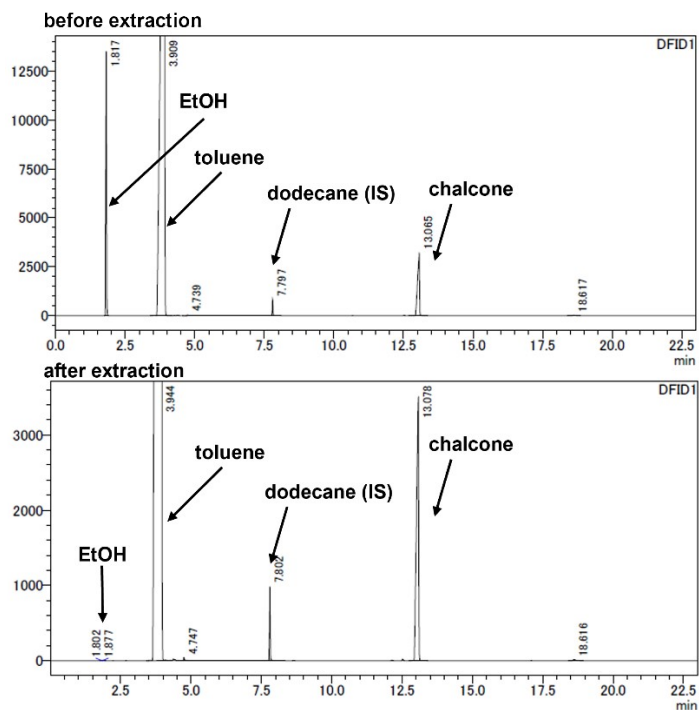
1,4-Conjugate addition (Table 3, entry 4)



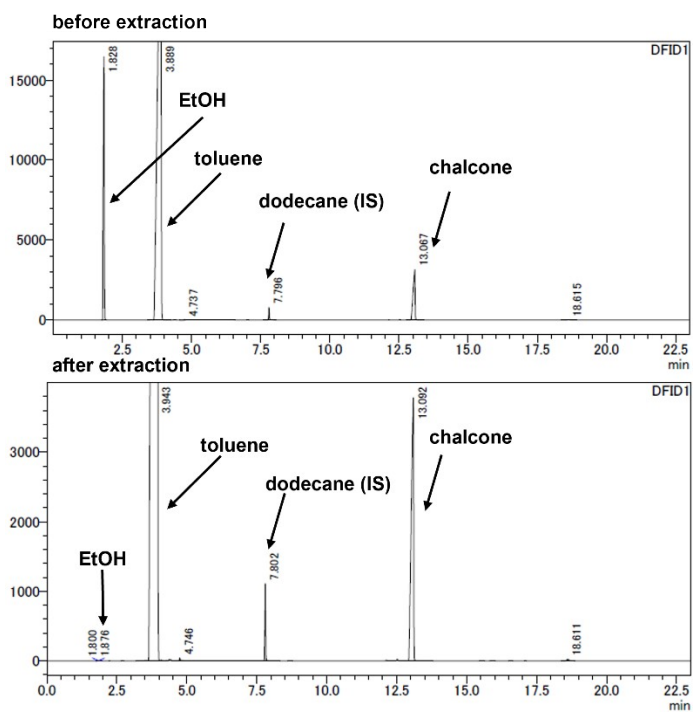
10% EtOH (Table 4, entry 1)



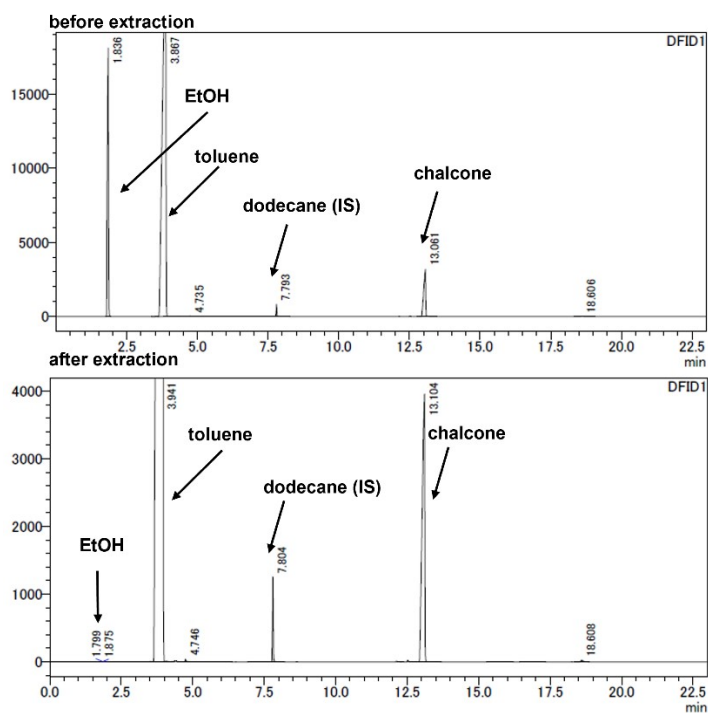
20%EtOH (Table 4, entry 2)



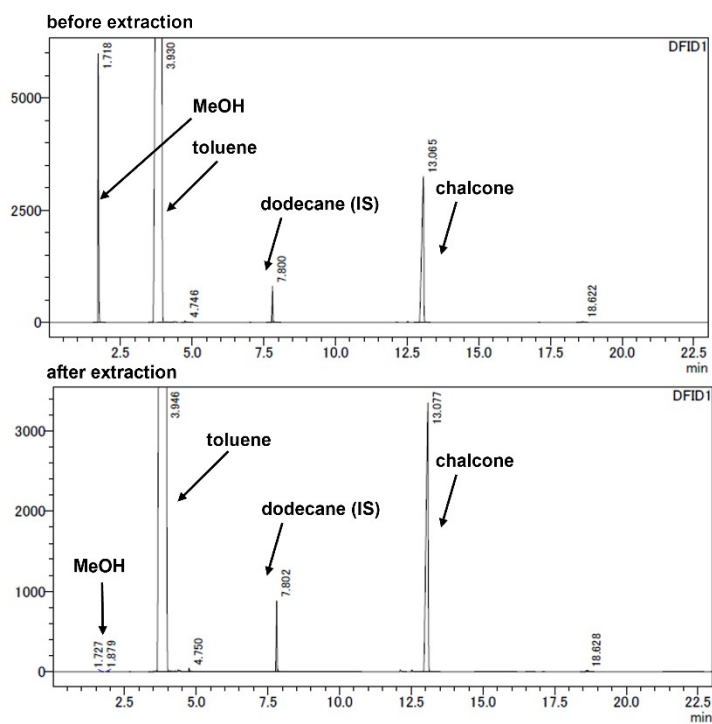
30%EtOH (Table 4, entry 3)



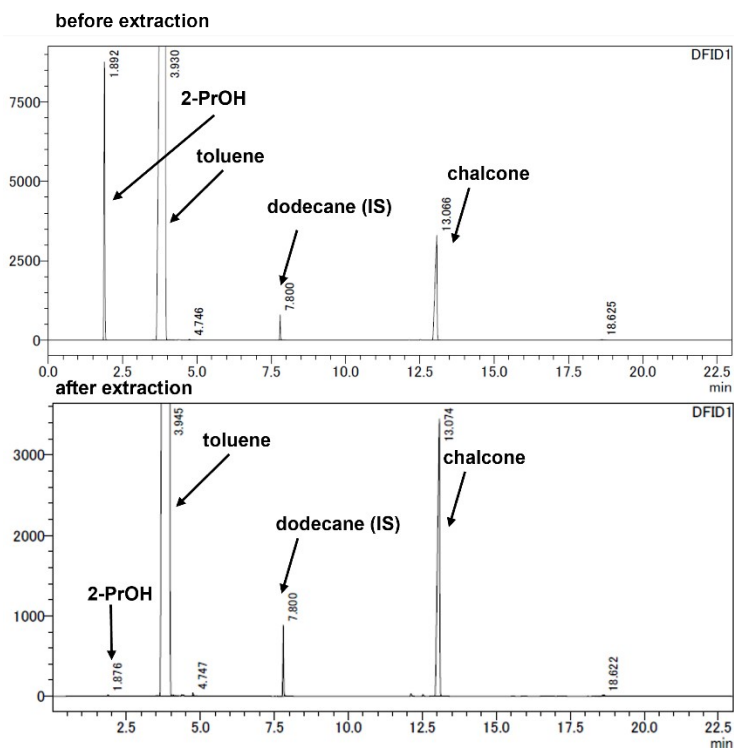
40%EtOH (Table 4, entry 4)



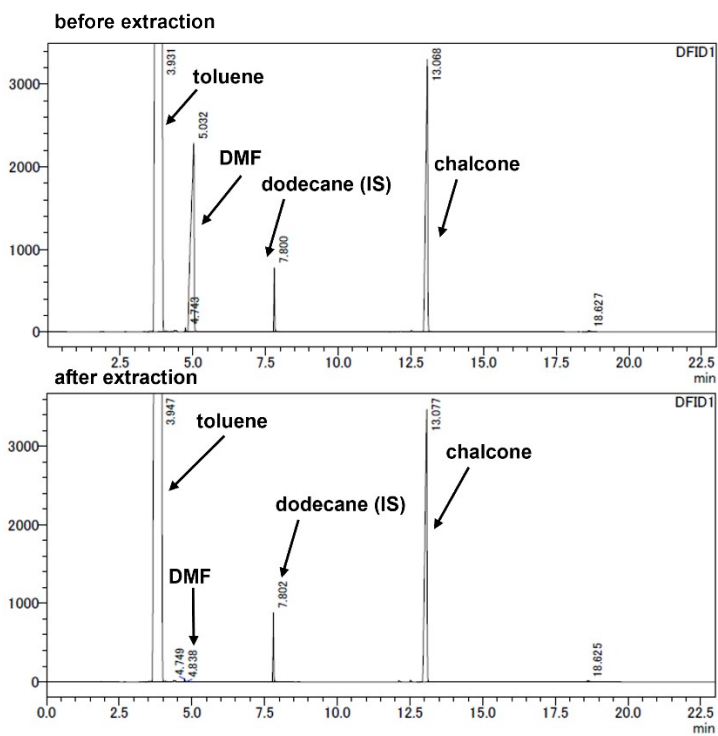
10%MeOH (Table 4, entry 5)



10%2-PrOH (Table 4, entry 6)



10%DMF (Table 4, entry 7)



10%DMSO (Table 4, entry 8)

