**Supporting Information**

# 1 Experimental Description

## 1.1 Reagents

Anhydrous methanol (99.8%) was purchased from KANTO Chemical CO., INC. Trimethylorthoformate (98%) was obtained from NIPPOH CHEMICALS CO., LTD. $[RuCl_2(p\text{-cymene})]_2$ was purchased from N.E CHEMCAT Corporation. (*S*)-XylBINAP ((*S*)-(-)-2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphthyl) was obtained from Takasago International Corporation, 2-Methyl-5-aminotetrazol (**4**) was procured from two vendors, Masuda Chemical Industries Co., Ltd. and Toyobo Co., Ltd. p-toluenesulfonic acid (pTSA) monohydrate was purchased from Junsei Chemical Co., Ltd. Ketone (**1**) was synthesized as reported elsewhere.[1] HPLC grade methanol (99.7%), acetonitrile (99.8%), and ammonium acetate solution (1 M) were purchased from Wako Pure Chemical Industries. Ltd. Ketal (**2**) was synthesized by treatment of (**1**) with trimethylorthoformate in the presence of catalytic amount of pTSA in methanol followed by neutralization using sodium methoxide and crystallization.

## 1.2 Experimental Details

A typical procedure for the preparation of **6** is mentioned herein. Compound **1** (100 g, 404 mmol), *p*-toluenesulfonic acid monohydrate (0.50 g, 2.62 mmol, 0.5wt %), trimethylorthoformate (51.5 g, 485 mmol, 1.2 eq.) and MeOH (100 mL, 1 L/kg) were charged to a 1 L four-neck flask. The flask was purged with $N_2$ three times. The flask was heated at 53~55 °C and agitated until high-performance liquid chromatography (HPLC) showed that the level of **1** was less than 1%. The solution was concentrated under reduced pressure to remove excess trimethylorthoformate (recovery: 150 wt% vs MeOH) and the residue was diluted with MeOH (200 mL, 2 L/kg). Compound **4** (40.1 g, 404.4 mmol, 1.0 eq.) was mixed with MeOH solution of **2** and **3** prepared above and the solution was charge to a 1 L autoclave under $N_2$. In a separate two neck 20 mL flask, under $N_2$ atmosphere was added $[RuCl_2(p\text{-cymene})]_2$ (123.8 mg, 0.202 mmol, S/C = 1000), (*S*)-XylBINAP (297.2 mg, 0.404 mmol, S/C = 1000) and MeOH (4.5 mL). The suspension was heated at 50 °C for 3 h, to obtain [RuCl(p-cymene)((S)-xylbinap)]Cl (**5**). The catalyst solution was charged to the 1 L autoclave. The autoclave was purged with $N_2$ four times and then with $H_2$ four times. The autoclave was charged with $H_2$ to 3.0 MPa and heated to 120 °C. After the temperature reached at 120 °C, $H_2$ was charged to 4.5 MPa. The reaction was complete in 5 h (HPLC area% of **6** became around 96%). The solution was cooled to 40 °C and transferred to a 1 L four-neck flask with MeOH (200 mL, 2 L/kg). The solution was warmed to 60 °C, stirred for 20 minutes then cooled to 30 °C, After 4 hours, the racemic crystals of **6** were separated from the solution and by filtration (4.41 g, chiral purity was 52.0%). The line was rinsed with MeOH (20 mL, 0.2 L/kg) and chiral purity of the **6** in the

filtrate was 99.6%. The reaction samples were withdrawn both manually and via online system from the reaction mixture after regular time intervals and analyzed by HPLC analysis.

For the experiments that prepared **6** from **2**, 118.6 g of compound **2**, *p*-toluenesulfonic acid monohydrate (0.50 g, 2.62 mmol, 0.5wt %), and MeOH (100 mL, 1 L/kg).were charged to a 1 L four-neck flask. The flask was purged with $N_2$ three times. The solution was concentrated under reduced pressure (recovery: 150 wt% vs MeOH) and the residue was diluted again with MeOH (200 mL, 2 L/kg). This procedure ensured similar starting conditions for the DARA reaction when using **2** as the starting material. The remaining procedure was similar to the one mentioned above.

### 1.3 Analytical Methods

An innovative approach was implemented for the characterization of preliminary reaction kinetics. Continuous circulation of the high pressure reaction mixture (e.g. 5 MPa) through a minimized external loop allowed for sampling of neat reaction mixture. Subsequent dilution and analysis were performed using online HPLC.[2] An Agilent Technologies © 1290 Infinity series HPLC outfitted with a FlexCube component allowed for acquisition of kinetic data without compromise to the reaction conditions. Initial experiments were conducted utilizing two HPLC instruments sampling in series from the external loop. The first instrument was operated under reversed-phase conditions and allowed for accurate quantitation of starting material, certain intermediates/impurities, and the desired reaction product (see Figure 1). The second HPLC was operated under normal-phase conditions and allowed for the determination of percent enantiomeric excess (% ee) of reaction product. After several reactions under varying conditions were performed showing minimal impact on ee, the normal-phase analysis was excluded from later experiments.

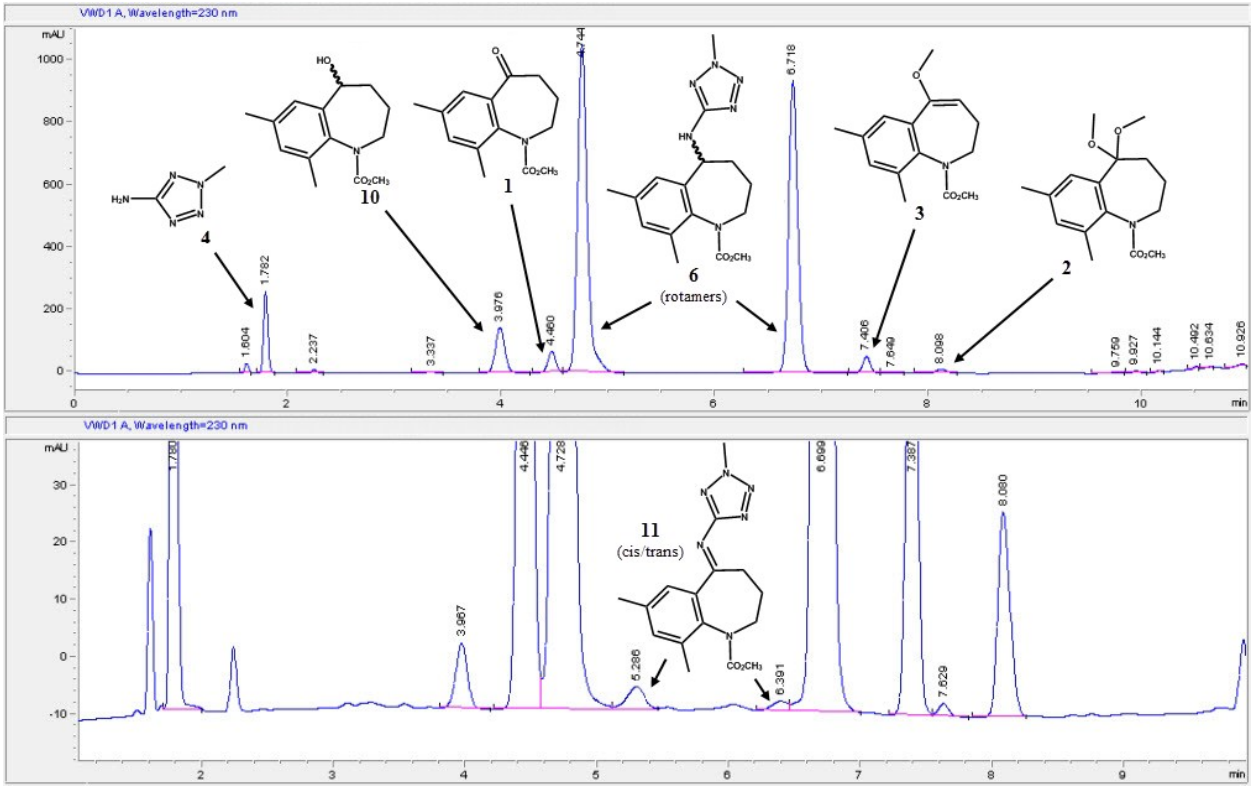


**Figure 1: Chromatographic identification of species via LCMS (mass spectrometry)**

Sampling frequency was limited to the chromatographic run time. Reversed-phase chromatographic separation conditions were developed for the baseline resolution of starting materials (**1**, **2** and **4)**, intermediate **(3, 11, 12),** product **(6),** and impurity **(10)**. The relative response factor (RRF) for each species was established using NMR/HPLC and allowed for the conversion of HPLC area percent values to relative molar concentration of each species in the reaction mixture. UV detection along with nominal mass spectrometer were employed for quantitative and qualitative analysis of the chromatographic separation. Unfortunately, HPLC was incapable of monitoring **11, 12** reproducibly, likely due to on-column hydrolytic degradation giving artificially high levels of **1**. An attempt to quantitate **11, 12** using NMR analysis of the neat reaction mixture was also unsuccessful, however, from a mechanistic perspective it was considered. However, NMR characterization data exhibited evidence of conformers for DARA product (see Figure 2).

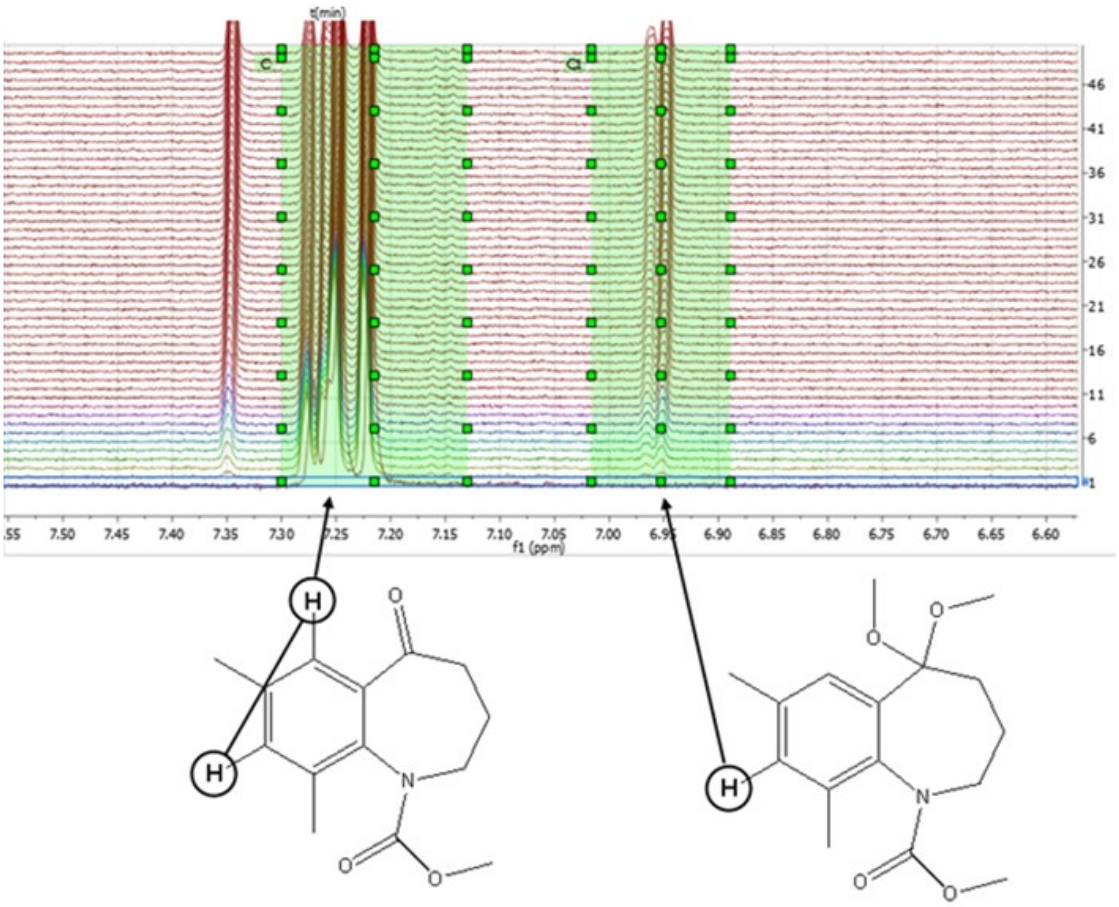


**Figure 2: NMR data exhibiting existing of conformers of DARA product**

Additional kinetic data under varying reaction conditions were obtained via offline HPLC analysis. The offline HPLC system consisted of HITACHI Chromaster, 5110 delivery pumps, 5410 UV-vis detector, 5210 auto sampler, 5310 column oven and Agilent EZChrom Elite software. The mobile phase was prepared using 0.01 M Ammonium acetate solution (mobile phase A) and methanol /acetonitrile = 90/10 (mobile phase B). A gradient method was used with the program as: 0 min 60% A, 40% B; 23 min 25% A, 75% B; 23.1-28 min 5% A, 95% B; and 33 min 60%, A 40% B, The diluent flow rate on column was 1.2 mL/min. Separation was achieved using Agilent Zorbax SB-C8 (4.6 × 150 mm, 3.5 µm) column. The detection wavelength was set at 230 nm. The column oven temperature was set at 30 °C.

**Table 1: DARA reaction trends, enantio-selectivity, and mass balance data as a function of temperature and reaction time**

| Temperature (°C) | Time (hr) | Mole% | | | | | Enantiomeric excess | Mass Balance (%) |
|---|---|---|---|---|---|---|---|---|
| | | [6] | [10] | [1] | [3] | [2] | | |
| 110 | 0 | 0.00 | - | 0.36 | 5.36 | 94.28 | - | 100.00 |
| | 1 | 42.59 | - | 1.70 | 8.37 | 18.89 | - | 71.55 |
| | 2 | 48.22 | - | 2.23 | 7.32 | 19.45 | - | 77.22 |
| | 3 | 59.60 | 0.02 | 2.52 | 5.97 | 16.22 | - | 84.32 |
| | 4 | 66.56 | - | 2.76 | 4.26 | 14.37 | - | 87.95 |
| | 5 | 73.71 | 0.04 | 2.48 | 3.73 | 11.30 | 96.8 | 91.26 |
| 120 | 0 | 0.00 | 0.00 | 0.41 | 5.18 | 94.41 | - | 100.00 |
| | 1 | 59.57 | - | 2.02 | 7.58 | 13.26 | - | 82.44 |
| | 2 | 77.32 | - | 2.49 | 4.03 | 6.75 | - | 90.58 |
| | 3 | 83.58 | - | 2.86 | 2.10 | 7.13 | - | 95.68 |
| | 4 | 90.51 | - | 2.48 | 1.33 | 3.61 | - | 97.94 |
| | 5 | 93.77 | - | 2.26 | 0.84 | 1.77 | 97.1 | 98.64 |
| | 6 | 95.32 | 0.07 | 2.11 | 0.54 | 0.97 | - | 98.99 |
| 130 | 0 | 0.00 | 0.00 | 0.38 | 3.63 | 95.99 | - | 100.00 |
| | 1 | 79.40 | - | 1.72 | 4.79 | 6.30 | - | 92.21 |
| | 2 | 91.50 | 0.05 | 1.57 | 1.85 | 2.37 | - | 97.34 |
| | 3 | 93.74 | 0.10 | 1.47 | 1.26 | 1.65 | - | 98.22 |
| | 4 | 95.22 | 0.21 | 1.26 | 0.89 | 1.13 | - | 98.72 |
| | 5 | 95.77 | 0.45 | 1.01 | 0.71 | 0.87 | 96.8 | 98.81 |
| 140 | 0 | 0.00 | 0.00 | 0.41 | 3.86 | 95.74 | - | 100.00 |
| | 1 | 93.77 | 0.08 | 1.93 | 1.30 | 1.26 | - | 98.33 |
| | 2 | 94.05 | 0.33 | 1.62 | 1.28 | 1.11 | - | 98.40 |
| | 3 | 94.65 | 0.72 | 1.10 | 1.21 | 1.06 | - | 98.75 |
| | 4 | 94.65 | 1.07 | 0.59 | 1.18 | 1.05 | - | 98.54 |
| | 5 | 94.85 | 1.31 | 0.29 | 1.15 | 1.01 | 96.5 | 98.61 |
| | 6 | 94.96 | 1.50 | 0.06 | 1.12 | 1.01 | - | 98.65 |
| 150 | 0 | 0.00 | 0.00 | 0.41 | 3.63 | 95.97 | - | 100.00 |
| | 1 | 93.60 | 0.19 | 1.52 | 1.54 | 1.36 | - | 98.21 |
| | 2 | 94.43 | 0.51 | 1.01 | 1.41 | 1.09 | - | 98.45 |
| | 3 | 94.68 | 0.97 | 0.49 | 1.35 | 0.94 | - | 98.44 |
| | 4 | 94.83 | 1.19 | 0.20 | 1.29 | 0.86 | - | 98.37 |
| | 5 | 94.95 | 1.20 | 0.08 | 1.26 | 0.83 | 96.3 | 98.31 |

**Table 2: DARA reaction trends, enantio-selectivity, and mass balance data as a function of concentration**

| Reaction Concentration (L/kg) | Time (hr) | Mole% | | | | | Enantiomeric excess | Mass Balance (%) |
|---|---|---|---|---|---|---|---|---|
| | | [6] | [10] | [1] | [3] | [2] | | |
| 5 | 0 | 0.00 | - | 0.41 | 4.66 | 94.93 | - | 100.00 |
| | 1 | 80.13 | 0.22 | 2.57 | 2.61 | 5.15 | - | 90.69 |
| | 2 | 90.30 | 0.11 | 1.98 | 1.41 | 3.05 | - | 96.86 |
| | 3 | 93.94 | 0.18 | 1.54 | 0.81 | 1.30 | - | 97.78 |
| | 4 | 94.96 | 0.44 | 1.11 | 0.62 | 0.80 | - | 97.93 |
| | 5 | 95.29 | 0.71 | 0.74 | 0.58 | 0.72 | 96.7 | 98.04 |
| | 6 | 95.50 | 0.93 | 0.45 | 0.56 | 0.67 | - | 98.11 |
| | 7 | 95.64 | 1.08 | 0.24 | 0.55 | 0.66 | - | 98.16 |
| | 8 | 95.68 | 1.26 | 0.10 | 0.52 | 0.61 | - | 98.17 |
| 3 | 0 | 0.00 | - | 0.36 | 2.85 | 96.79 | - | 100.00 |
| | 1 | 84.49 | - | 1.62 | 3.73 | 4.90 | - | 94.74 |
| | 2 | 90.96 | 0.08 | 1.59 | 1.80 | 2.73 | - | 97.16 |
| | 3 | 94.23 | 0.14 | 1.44 | 0.94 | 1.29 | - | 98.04 |
| | 4 | 95.34 | 0.36 | 1.10 | 0.69 | 0.86 | - | 98.36 |
| | 5 | 95.46 | 0.61 | 0.78 | 0.64 | 0.77 | 96.6 | 98.26 |
| | 6 | 95.74 | 0.87 | 0.40 | 0.59 | 0.71 | - | 98.32 |
| 2 | 0 | 0.00 | - | 0.38 | 3.63 | 95.99 | - | 100.00 |
| | 1 | 79.40 | - | 1.72 | 4.79 | 6.30 | - | 92.21 |
| | 2 | 91.50 | 0.05 | 1.57 | 1.85 | 2.37 | - | 97.34 |
| | 3 | 93.74 | 0.10 | 1.47 | 1.26 | 1.65 | - | 98.22 |
| | 4 | 95.22 | 0.21 | 1.26 | 0.89 | 1.13 | - | 98.72 |
| | 5 | 95.77 | 0.45 | 1.01 | 0.71 | 0.87 | 96.8 | 98.81 |
| 1.5 | 0 | 0.00 | - | 0.45 | 3.58 | 95.97 | - | 100.00 |
| | 1 | 82.57 | 0.00 | 1.50 | 4.15 | 5.27 | - | 93.49 |
| | 2 | 91.38 | 0.00 | 1.49 | 1.70 | 2.15 | - | 96.72 |
| | 3 | 93.73 | 0.00 | 1.47 | 1.11 | 1.82 | - | 98.12 |
| | 4 | 95.41 | 0.11 | 1.29 | 0.84 | 1.12 | - | 98.77 |
| | 5 | 95.89 | 0.29 | 1.07 | 0.75 | 0.89 | 96.8 | 98.89 |

**Table 3: DARA reaction trends and mass balance data as a function of pressure**

| Reaction Pressure (MPa) | Time (hr) | Mole% | | | | | Mass Balance (%) |
|---|---|---|---|---|---|---|---|
| | | [6] | [10] | [1] | [3] | [2] | |
| 5 | 0 | 0.00 | - | 1.21 | 1.22 | 98.00 | 100.43 |
| | 1 | 70.55 | 0.06 | 3.17 | 5.35 | 13.21 | 92.33 |
| | 2 | 91.34 | 0.06 | 2.81 | 1.33 | 2.95 | 98.49 |
| | 3 | 94.86 | 0.04 | 2.41 | 0.65 | 1.26 | 99.23 |
| | 4 | 96.05 | 0.04 | 2.09 | 0.42 | 0.77 | 99.38 |
| | 5 | 96.55 | 0.06 | 1.91 | 0.33 | 0.59 | 99.43 |
| 4.5 | 0 | 0.00 | - | 0.35 | 5.68 | 93.97 | 100.00 |
| | 1 | 80.60 | - | 3.21 | 4.18 | 7.49 | 95.48 |
| | 3 | 90.64 | - | 3.17 | 1.53 | 2.93 | 98.27 |
| | 5 | 94.28 | - | 2.64 | 0.74 | 1.53 | 99.20 |
| | 6 | 96.07 | - | 2.11 | 0.43 | 0.81 | 99.42 |
| 3 | 0 | 0.00 | - | 0.40 | 5.00 | 94.60 | 100.00 |
| | 1 | 70.81 | - | 4.46 | 6.05 | 11.06 | 92.37 |
| | 3 | 86.48 | - | 3.89 | 2.35 | 4.25 | 96.98 |
| | 5 | 92.24 | - | 3.17 | 1.22 | 2.38 | 99.01 |
| | 7 | 94.29 | - | 2.66 | 0.75 | 1.55 | 99.25 |
| | 9 | 95.27 | 0.69 | 1.95 | 0.51 | 0.94 | 99.36 |
| 1 | 0 | 0.00 | - | 0.18 | 1.76 | 98.07 | 100.00 |
| | 3 | 54.87 | - | 4.07 | 9.28 | 16.38 | 84.60 |
| | 7 | 76.77 | - | 4.38 | 4.27 | 7.10 | 92.52 |
| | 12 | 85.95 | 0.29 | 3.95 | 2.51 | 3.85 | 96.56 |
| | 20 | 89.04 | 1.29 | 2.61 | 2.06 | 3.38 | 98.38 |
| | 24 | 90.72 | 2.13 | 1.36 | 1.73 | 2.91 | 98.85 |

**Table 4 : DARA reaction trends and mass balance as a function of [4]**

| Temperature (°C) | Pressure (MPa) | Reaction Concentration (L/kg) | [4] (Eq.) | Time (hr) | Mole% | | | | | Mass Balance (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | [6] | [10] | [1] | [3] | [2] | |
| 135 | 5.2 | 2 | 0.9 | 0 | 0.00 | - | 0.61 | 4.92 | 94.47 | 100.00 |
| | | | | 5 | 89.31 | 0.57 | 0.92 | 3.19 | 3.70 | 97.69 |
| | | | 0.98 | 0 | 0.00 | - | 0.76 | 5.92 | 93.32 | 100.00 |
| | | | | 5 | 96.23 | 0.57 | 1.27 | 0.78 | 0.61 | 99.44 |
| 120 | 4.5 | 5 | 1.1 | 0 | 0.00 | - | 0.53 | 5.91 | 93.55 | 100.00 |
| | | | | 5 | 96.82 | 0.00 | 1.50 | 0.19 | 1.02 | 99.52 |

**Table 5: DARA reaction trend and mass balance starting with [2] at 140 °C, 5L/kg, S/C = 1000:1, 5 MPa**

| Time (mins) | Mol % | | | | | Mass Balance |
|---|---|---|---|---|---|---|
| | [6] | [10] | [1] | [3] | [2] | |
| 0 | | | 0.73 | 1.46 | 97.50 | 99.69 |
| 40 | 0.00 | 0.00 | 8.17 | 6.24 | 91.71 | 106.13 |
| 50 | 0.80 | 0.00 | 14.16 | 10.64 | 65.09 | 90.68 |
| 60 | 1.08 | 0.00 | 23.08 | 10.33 | 48.09 | 82.58 |
| 70 | 13.51 | 0.00 | 16.96 | 12.60 | 38.07 | 81.14 |
| 80 | 50.70 | 0.03 | 5.92 | 9.52 | 20.45 | 86.62 |
| 90 | 79.81 | 0.03 | 3.62 | 4.04 | 7.19 | 94.69 |
| 100 | 90.56 | 0.03 | 2.78 | 1.76 | 2.55 | 97.68 |
| 110 | 94.14 | 0.04 | 2.51 | 0.99 | 1.20 | 98.89 |
| 120 | 95.37 | 0.04 | 2.17 | 0.72 | 0.81 | 99.12 |
| 130 | 95.76 | 0.04 | 1.98 | 0.66 | 0.71 | 99.15 |
| 140 | 95.95 | 0.06 | 1.91 | 0.63 | 0.66 | 99.20 |
| 150 | 96.03 | 0.07 | 1.87 | 0.63 | 0.64 | 99.25 |
| 160 | 96.06 | 0.10 | 1.83 | 0.63 | 0.63 | 99.25 |
| 190 | 96.15 | 0.18 | 1.72 | 0.62 | 0.63 | 99.29 |
| 220 | 96.24 | 0.29 | 1.57 | 0.61 | 0.63 | 99.34 |
| 250 | 96.35 | 0.37 | 1.41 | 0.61 | 0.62 | 99.36 |
| 280 | 96.44 | 0.55 | 1.21 | 0.59 | 0.61 | 99.40 |
| 310 | 96.55 | 0.69 | 1.04 | 0.59 | 0.61 | 99.47 |
| 340 | 96.65 | 0.82 | 0.84 | 0.58 | 0.61 | 99.50 |
| 370 | 96.76 | 0.97 | 0.66 | 0.58 | 0.59 | 99.57 |
| 400 | 96.83 | 1.08 | 0.51 | 0.58 | 0.59 | 99.60 |

**Table 6: Summary of model parameter estimates**

| Reaction # | Parameter | Value | Units | Parameter | Value | Units | Parameter | Value | Units |
|---|---|---|---|---|---|---|---|---|---|
| **1** | $k_{1f}$ | 1.30E+04 | L/mol/min | $E_{a1}$ | 13.7 | kJ/mol | | | |
| **2** | $k_{2f}$ | 1.10E+04 | L/mol/min | $E_{a2}$ | 8.5 | kJ/mol | $K_2$ | 1.70E-04 | mol/L |
| **3** | $k_{3f}$ | 5.00E+02 | L/mol/min | $E_{a3}$ | 60.5 | kJ/mol | | | |
| **4** | $k_{4f}$ | 1.00E+03 | 1/min | $E_{a4}$ | 99 | kJ/mol | $K_4$ | 2.50E-02 | mol/L |
| **5** | | | | $E_{a5}$ | 147 | kJ/mol | $K_5$ | 3.60E-05 | - |
| **6** | | | | $E_{a6}$ | 208.3 | kJ/mol | | | |
| **7** | | | | $E_{a7}$ | 261.7 | kJ/mol | | | |
| **5 & 6** | $A_{5-6}$ | 11.8 | L/mol | $m_{5-6}$ | 0.85 | - | $n_{5-6}$ | 5 | - |
| **5 & 7** | $A_{5-7}$ | 1.70E+07 | L/mol | $m_{5-7}$ | 0.9 | - | $n_{5-6}$ | 6.75 | - |
| **6 & 7** | $A_{6-7}$ | 1.50E+06 | - | $m_{6-7}$ | 0.05 | - | $n_{6-7}$ | 1.75 | - |

**PFR Governing Equations**

The governing equation for PFR with dispersion is shown by eqn (I)[3].

$$\tau\frac{\partial c_j}{\partial t} = -\frac{\partial c_j}{\partial z} + \left(\frac{D}{uL}\right)\frac{\partial^2 c_j}{\partial z^2} + \tau r_j \qquad (I)$$

where, t is time (in mins)

z is dimensionless length along reactor (fraction of reactor length L)

$c_j$ is the concentration of species j at length z along the reactor (in mol/$m^3$)

D/uL is the dispersion number

$r_j$ is the rate of reaction of species j, given by eqn (1) – (7) & eqn (11) of the main paper, in all there being 8 species of interest

Initial condition is based on starting the PFR with no reactants [eqn (II)], while boundary conditions [eqn (III), eqn (IV)] impose a Neumann's boundary condition at the inlet and outlet of the reactor ($c_j^{in}$ (t) is the concentration in inlet to PFR and has the fluctuations for the catalyst). MATLAB R2015a software was used to solve the partial differential equation.

$$c_j(t = 0,z) = 0 \qquad (II)$$

$$c_j^{in}(t) = c_j(t,z = 0) - \left(\frac{D}{uL}\right)\frac{\partial c_j}{\partial z}(t,z = 0) \qquad (III)$$

$$\frac{\partial c_j}{\partial z}(t,z = 1) = 0 \qquad (IV)$$

[1] R.K. Vaid, S.K. Boini, C.A. Alt, J.T. Spitler, C.E. Hadden, S.A. Frank, and E.D. Moher. "Synthesis of Methyl 7,9-Dimethyl-5-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepine-1-carboxylate and its analogues," *Synthesis* **2014**, 46, 2463-2470

[2] N.A. Magnus, B.A. Astleford, D.L. Laird, T.D. Maloney, A.D. McFarland, J.R. Rizzo, J.C. Ruble, G.A. Stephenson, and J.P. Wpsiec. " Additives promote Noyori-type reductions of a β-Keto-γ-lactum asymmetric syntheses of Serotonin Norepinephrine Reuptake inhibitors,"*J. Org. Chem.* **2013**, 78, 5768-5774

[3] O. Levenspiel. *Chemical Reaction Engineering*, 3rd Ed., John Wiley & Sons, Chapter 13