*CHIMIA* **2025**, *79*, 441-448, https://doi.org/10.2533/chimia.2025.441

# Electronic Supplementary Information:

# Kinetic Investigation of the Asymmetric Hydrogenation of Benzylphenylephrone in Continuous Flow

Maurice Moll[1,3], Björn Wängler[2], Carmen Wängler[3], Thorsten Röder[1]*

[1] Institute of Chemical Process Engineering, Mannheim University of Applied Sciences, 68163 Mannheim, Germany

[2] University Heidelberg, Medical Faculty Mannheim, Clinic of Radiology and Nuclear Medicine, Biomedical Chemistry, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany

[3] University Heidelberg, Medical Faculty Mannheim, Clinic of Radiology and Nuclear Medicine, Molecular Imaging and Radiochemistry, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany

* Corresponding author

## Content

# 1) Microreactor Setup

The setup described in the contribution is shown in Figure S1.

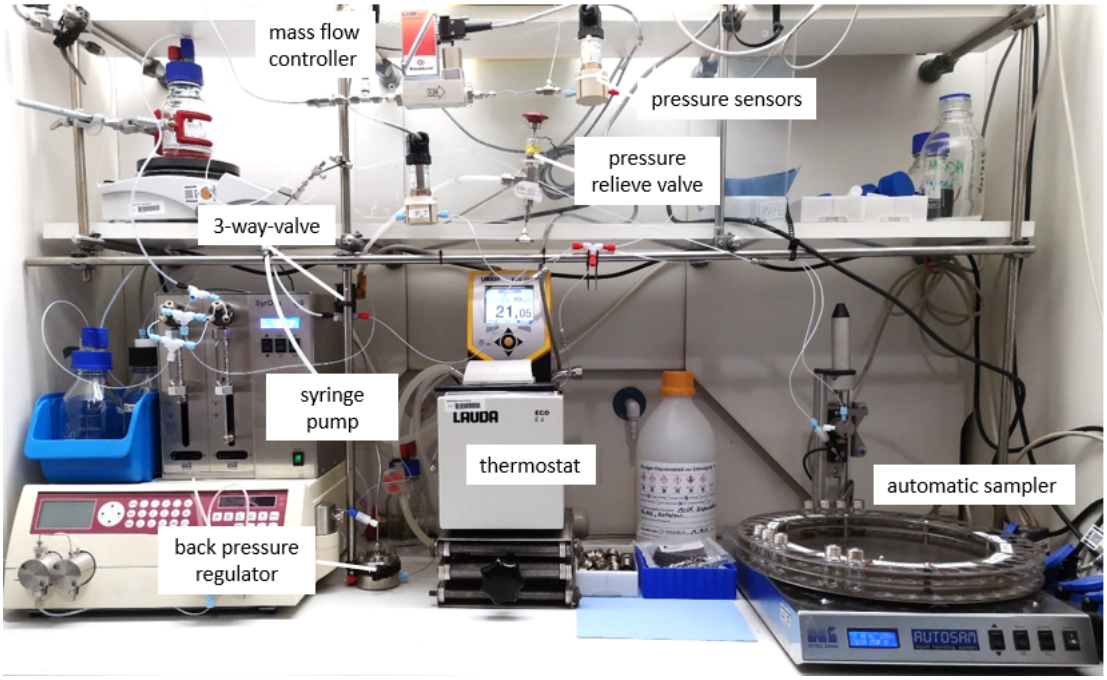


***Figure S1.*** *Microreactor setup for the continuous lab-scale hydrogenation.*

## 2) HPLC Measurements

In order to determine the enantiomeric excess, the product solution was analyzed using a HPLC with a chiral Lux 3 µm i-Cellulose-5 column (150×4.6 mm, Phenomenex, Germany). The mobile phase consists of a mixture of 85% n-hexane (HPLC grade, ≥99%, Carl Roth), 14.9% ethanol (HPLC grade, ≥99.9%, Carl Roth), and 0.1% ethylenediamine (≥99.5%, Carl Roth). 5 µL of the samples are injected and pumped through the column together with the isocratic mobile phase at a flow rate of 1 mL $min^{-1}$ at a pressure of about 90 bar and a run time of 10 minutes. This specific method allows for the separation of the two enantiomers, facilitating the determination of enantiomeric excess (ee) to evaluate the best conditions for high excess of the wanted enantiomer, as can be seen in Figure S2.

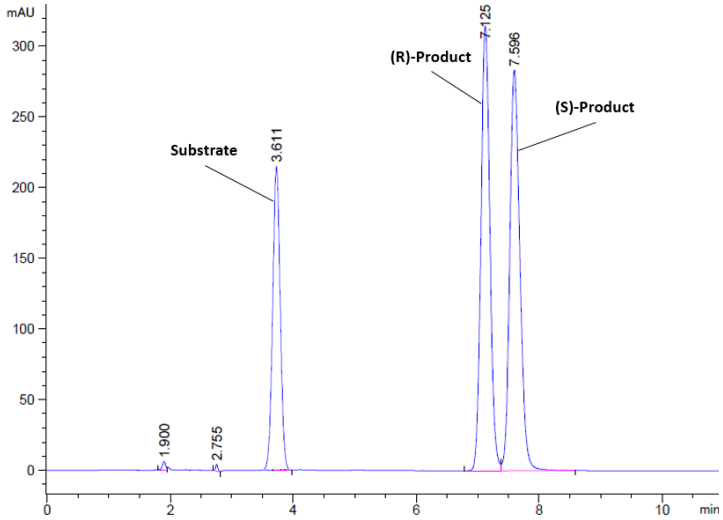


***Figure S2.*** *Chromatogram of a solution consisting of the substrate and the product as racemate.*

The HPLC was calibrated using a five-point calibration, which are shown in Figure S3.

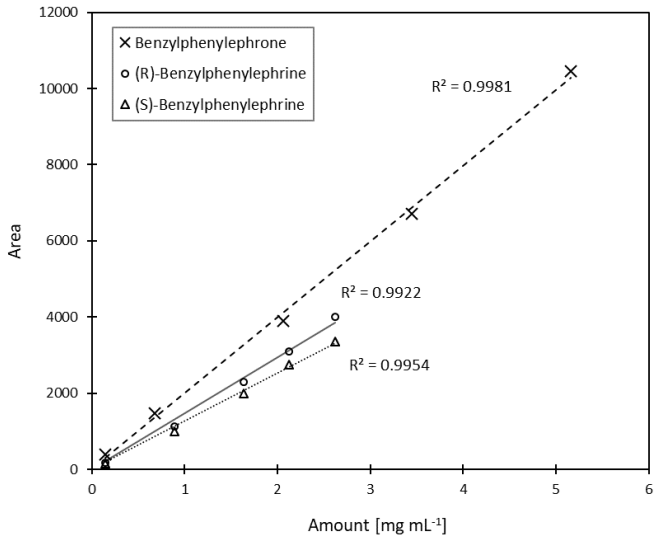


***Figure S3.*** *Calibration curves of the substrate (benzylphenylephrone) and both enantiomers of the product.*

# 3) Reactor Characteristics

## 3.1) Heat Transfer

Before starting an experiment, the temperature in the thermostat bath was set to ensure that the reactor reached the target temperature. To assume isothermality for the kinetic modeling, high heat removal is a key aspect. For this purpose, a rough estimation of the formation of hotspots was used, which is proposed by Westermann et al [1].

$$d_{h,max}(\Delta T) \cong \sqrt{\frac{14.64 \cdot \lambda \cdot \Delta T \cdot t_{0.5}}{c_0 \cdot (-\Delta H_R)}} \tag{1}$$

This correlation can be used to determine the maximum internal diameter of a microreactor for a fixed maximum temperature difference. Rearranging the equation 1 permits to calculate the maximum temperature difference for a given diameter:

$$\Delta T_{max} = \frac{d^2 \cdot c_0 \cdot (-\Delta H_R)}{14.64 \cdot \lambda \cdot t_{0.5}} \tag{2}$$

with

| | |
|---|---|
| $d$ | 1 mm |
| $c_0$ | 0.1 mol $L^{-1}$ |
| $\Delta H_R$ | - 55.7 kJ $mol^{-1}$ |
| $\lambda$ | 0.202 W $m^{-1}$ $K^{-1}$ |
| $t_{0.5}$ | 21.9 s |

The maximum temperature difference in this case is 0.09 *K*, which is why the formation of hotspots can be ruled out and isothermality can be assumed.

As the liquid feed is only preheated to around 30 °C and not to the process temperature, the time required for the fluid passing through the reactor to reach the desired temperature must be considered as well. This is important in order to be able to assume that the temperature in the entire reactor is constant. The table below (Table S1) lists the different reactors (R1 – R4) along with the maximum flow rate and the absolute and relative times required to heat the fluid from 30 °C to 80 °C, based on the total residence time for each reactor. It can be observed that a maximum of approximately 3.64% of the total residence time is required to reach the desired temperature. Therefore, the time required for heating can be considered negligible.

***Table S1*** *Reactor overview and necessary heat up times for each reactor.*

| Parameter | | R1 | R2 | R3 | R4 |
|---|---|---|---|---|---|
| Inner diameter | [mm] | 1.0 | 1.0 | 1.0 | 0.5 |
| Outer diameter | [mm] | 1.6 | 1.6 | 1.6 | 1.6 |
| Length | [m] | 5 | 10 | 14 | 20 |
| Volume | [mL] | 3.93 | 7.85 | 11.00 | 3.93 |
| Highest flow rate | [mL $min^{-1}$] | 2.5 | | | |
| Heating time | [s] | | 2.17 | | 0.62 |
| Heating time fraction | [s] | 3.64% | 1.82% | 1.30% | 0.99% |

## 3.2) Gas-liquid Mass Transfer

Depending on the nature of the case at hand, there are various approaches to determine the $k_La$ value. In the case of gas-liquid Taylor-flows, there are numerous studies on determining the $k_La$ value using empirical correlations. Examples include the work of Bercic and Pinter [2], who found that the cell velocity and the liquid slug length have the greatest influence on mass transfer and thus on $k_La$. In addition to the work by Bercic and Pinter, investigations in this area have been carried out by other groups [3–5]. Within this study, the model proposed by Yue, Lup et al. to determine the $k_La$ values was used. In this model, the mass transfer of air in water was studied and the following approach was proposed with the focus of the described main parameters [6]:

$$k_{\mathrm{L}}a = \frac{2}{d}\left(\frac{D\,u_{\mathrm{b}}}{L_{\mathrm{U}}}\right)^{0.5}\left(\frac{L_{\mathrm{b}}}{L_{\mathrm{U}}}\right)^{0.3} \tag{3}$$

Necessary for this correlation is the inner diameter of the reactor $d$ = 1 mm and the diffusion coefficient for hydrogen in methanol at room temperature, which is $D = 1.65\times10^{-7}$ $m^2$ $s^{-1}$ according to [7]. For the Taylor unit bubble and the gas bubble length, $L_U$ = 6 mm and $L_b$ = 2 mm was assumed, respectively. The gas bubble velocity $u_b$ was calculated through the set volumetric gas flow. In Table S2, the determined values for $k_La$ along with corresponding volumetric flows and bubble velocities are presented while $D$ is assumed to be constant throughout all experiments.

***Table S2*** *Calculated values for the volumetric gas-liquid mass transfer coefficient ($k_La$) at different volumetric liquid and gas flowrates with corresponding gas bubble velocities $u_b$.*

| $Q_l$ [mL min$^{-1}$] | $Q_g$ [mL min$^{-1}$] | $u_b$ [m s$^{-1}$] | $k_La$ [s$^{-1}$] |
|---|---|---|---|
| 0.4 | 0.4 | 0.008 | 0.69 |
| 0.8 | 0.9 | 0.016 | 0.96 |
| 1.0 | 1.0 | 0.020 | 1.07 |
| 1.3 | 1.2 | 0.028 | 1.27 |
| 1.7 | 1.7 | 0.036 | 1.44 |
| 2.2 | 2.2 | 0.047 | 1.63 |
| 2.5 | 2.5 | 0.053 | 1.74 |

As can be seen from the table, the values for the gas-liquid mass transfer coefficient are lying in a range between 0.69 and 1.74 $s^{-1}$ for the investigated parameters. The magnitude is in line with other studies where $k_La$ values for slug flow in microchannel reactors were determined [8]. It is worth mentioning that these values are noticeably higher compared to conventional coefficients in batch autoclaves or bubble columns, where the maximum $k_La$ value is typically around 1 and 0.24 $s^{-1}$, respectively, whereas the values for batch autoclaves generally range from $10^{-3}$ to $10^{-2}$ $s^{-1}$ [9,10]. This leads to the conclusion that limitations due to mass transport can be excluded.

## 3.3) Residence Time Calculation

To accurately determine the residence time in the reactor, both the volumetric liquid and gas flow rates must be considered. The gas flow, initially given in standard milliliters per minute, was adjusted to the process conditions and added to the liquid flow. The portion of gas dissolving in the solvent was neglected. Consequently, the total volumetric flow rate can be calculated as follows:

$$Q_{\mathrm{total}} = Q_l + Q_{\mathrm{H2,N}} * \left(\frac{T}{273.15\ K}\right) * \left(\frac{1.01315\ bar}{p}\right) \quad (4)$$

The following table (Table S3) exemplifies the residence times in reactor R1 at a temperature of 60 °C and a pressure of 50 bar:

***Table S3*** *Residence times in reactor R1 at 50 bar und 60 °C.*

| $\dot{Q}_l$ [mL min$^{-1}$] | $\dot{Q}_{H2,N}$ [mL$_N$ min$^{-1}$] | $\dot{Q}_{H2}$ [mL min$^{-1}$] | $\tau_l$ [min] | $\tau_g$ [min] | $\tau$ [min] |
|---|---|---|---|---|---|
| 2.20 | 90 | 2.22 | 1.78 | 1.77 | 0.89 |
| 1.10 | 70 | 1.73 | 3.57 | 2.27 | 1.39 |
| 0.70 | 50 | 1.24 | 5.61 | 3.18 | 2.03 |
| 0.50 | 40 | 0.99 | 7.85 | 3.97 | 2.64 |
| 0.35 | 35 | 0.86 | 11.22 | 4.54 | 3.23 |
| 0.25 | 30 | 0.74 | 15.71 | 5.30 | 3.96 |

# Abbreviations

| | |
|---|---|
| D | Diffusion coefficient |
| $c_0$ | Starting concentration |
| d | Channel diameter |
| ee | Enantiomeric excess |
| HPLC | High pressure liquid chromatography |
| $k_La$ | Volumetric gas liquid coefficient |
| $L_b$ | Length of gas bubble |
| $L_U$ | Length of taylor unit bubble |
| p | Pressure |
| $Q_g$ | Volumetric gas flow |
| $Q_l$ | Volumetric liquid flow |
| T | Temperature |
| $t_{0.5}$ | Reaction halftime |
| $u_b$ | Gas bubble velocity |
| $\Delta H_R$ | Reaction enthalpie |
| λ | Thermal conductivity |

# References


[1] T. Westermann, L. Mleczko, *Org. Process Res. Dev.* **2016**, *20 (2)*, 487–494. DOI: 10.1021/acs.oprd.5b00205.

[2] G. Bercic, A. Pintar, *Chemical Engineering Science* **1997**, *52 (21-22)*, 3709–3719. DOI: 10.1016/S0009-2509(97)00217-0.

[3] *Tenth International Symposium on Chemical Reaction Engineering*, Elsevier **1988**.

[4] S. Irandoust, B. Andersson, in *Tenth International Symposium on Chemical Reaction Engineering*, Elsevier **1988**.

[5] M. T. Kreutzer, *Hydrodynamics of Taylor flow in capillaries and monolith reactors*.

[6] J. Yue, L. Luo, Y. Gonthier, G. Chen, Q. Yuan, *Chemical Engineering Science* **2009**, *64 (16)*, 3697–3708. DOI: 10.1016/j.ces.2009.05.026.

[7] K. Sporka, J. Hanika, V. Růžička, *Collect. Czech. Chem. Commun.* **1969**, *34 (10)*, 3145–3148. DOI: 10.1135/cccc19693145.

[8] P. Sobieszuk, P. Cygański, R. Pohorecki, *Volumetric liquid side mass transfer coefficient in a gas–liquid microreactor* **2008**.

[9] J. Hagen, *Chemiereaktoren: Grundlagen, Auslegung und Simulation,* 2nd ed., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim **2017**.

[10] H. Hichri, A. Accary, J. P. Puaux, J. Andrieu.