# SUPPORTING INFORMATION

# Efficient Kinetic Data Acquisition and Model Prediction: Continuous Flow Microreactors, Inline FT-IR Spectroscopy, and Self-modeling Curve Resolution

Verena Fath<sup>1,2</sup>, Philipp Lau<sup>3</sup>, Christoph Greve<sup>3</sup>, Norbert Kockmann<sup>1</sup>, Thorsten Röder<sup>2\*</sup>

 <sup>1</sup> Department of Biochemical and Chemical Engineering, Equipment Design, TU Dortmund University, Emil-Figge-Str. 70, 44227 Dortmund/Germany
 <sup>2</sup> Institute of Chemical Process Engineering, Mannheim University of Applied Sciences, Paul-Wittsack-Str. 10, 68163 Mannheim/Germany
 <sup>3</sup> Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt/Germany

\* Email address of corresponding author: t.roeder@hs-mannheim.de (Telephone +49 621 292 6800)

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#### A. Experimental Procedure

#### A.1. Analytical IR spectra and integration method

#### Imine synthesis

Analytical IR spectra of imine synthesis and details on the integration method are exemplarily provided in Figure S1. The evaluation of the characteristic IR band is based on a calculation of absorption height. This is illustrated in Figure S1 for benzaldehyde **1** as starting material (decreasing band at 1680 cm<sup>-1</sup> to 1720 cm<sup>-1</sup>) and n-benzylidenebenzylamine **3** (increasing band at 1620 cm<sup>-1</sup> to 1660 cm<sup>-1</sup>).



Figure S1. Exemplary analytical IR spectra of benzaldehyde 1 and n-benzylidenebenzylamine 3 at different concentrations.

Legend: ..... integration method based on calculation of absorption height.

## Organometallic synthesis

Analytical IR spectra of the organometallic synthesis and details on the integration method are exemplary provided in Figure S2. Evaluation of the characteristic IR band is based on calculation of absorption height. This is illustrated in Figure S2 for the CH-acidic compound **4** (decreasing IR band at 782 cm<sup>-1</sup> to 755 cm<sup>-1</sup>).



**Figure S2.** Exemplary analytical IR spectra of CH-acidic compound at different concentrations. Legend: ..... integration method based on calculation of absorption height.

#### A.2. Reactor characteristics

High mixing efficiency, narrow residence time distribution, and nearly isothermal reaction control are preconditions for determining reliable kinetic data.

#### Mixing efficiency and effects of reactor geometry

In pre-tests, different reactor geometries and micromixers were tested for their influence on the concentration profiles and the related reaction rate. Thus, in order to assess the influence of varying flow velocities, variation of reactor length and inner diameters was conducted with overlapping residence times. Moreover, the following micromixers were compared: glass mixer (HTM-ST-2-1, Little Things Factory, Germany), T mixer (0.5 mm bore, Upchurch, United States), T mixer (1 mm bore, Upchurch, United States), T mixer (1.23 mm bore, Swagelok, United States). In terms of the T mixers' inner bore holes (comparing the 1 mm with the 0.5 mm bore), the cross-sectional area, and therefore also the linear flow velocity, varied by a factor of 4.

The extant literature has already investigated the mixing performances of the micromixers used in this study<sup>1</sup>. It had been demonstrated that, in case of mixing sensitive chemical reactions, the glass mixer (HTM-ST-2-1, Little Things Factory, Germany) has a considerably greater mixing efficiency compared to the T mixers. Thus, in this study, the effect of mixing efficiency on the reaction kinetics could only be neglected in the event that all investigated micromixers yielded the same results, indicating reaction rate's independence of the mixing process.

In Figure S3, it can be demonstrated (exemplarily for the organometallic synthesis) that the influence of varying degrees of mixing efficiency on the resulting conversion profiles (at constant reaction parameters: temperature, concentration of starting materials, and stoichiometric ratio, but with differing microreactor setups as described above), can be assumed to be negligible. Conversion profiles (Figure S3 and Figure S4) were calculated based on previously determined calibration curves.



**Figure S3.** Conversion profiles for different reactor geometries and micromixers. Reaction temperature -35 °C, concentration of CH-acidic compound 0.4 mol L<sup>-1</sup>, stoichiometric ratio n-BuLi:CH-acidic compound 1:1 (steady-state experiments). Legend: GM – glass mixer · TM – T mixer (side-on).

Moreover, Figure S4 contrasts the two microreactors (MR1 and MR2) used in this study to investigate the lithiation reaction regarding their resulting conversion profiles at equivalent residence times but differing flow rates (under nonsteady-state conditions). Compared to the results that were obtained under steady-state conditions (Figure S3), slightly sharper differences between MR1 and MR2 become apparent (regarding their respective conversion profiles at overlapping residence times). This may be due to an effect of imperfect mixing, but the experiments under steady-state conditions (Figure 3) have demonstrated that the influence of varying degrees of mixing efficiency on the resulting conversion profiles is nearly negligible. Yet, in case of steady-state experiments, each experimental data point is determined by five repeated measurements, with every measurement consisting of 32 scans, thus, leading to an average value for every data point. By contrast, in case of nonsteady-state experiments, each data point only consists of one single measurement (which consists of 32 scans). Nearly pulsating-free syringe pumps are used within the presented experimental setup. In reality, however, pulsation cannot be completely ruled out. This pulsation effect influences results that are gained under nonsteady-state conditions more strongly (as data points are no averaged values), and particularly occurs when high flow rates are applied (as syringes then have a high turnover rate). To conclude, the slight discrepancies between MR1 and MR2 (in case of nonsteady-state experiments) are considered to rather be induced through a pulsation of syringe pumps (especially at high flow rates) than through an imperfect mixing. Therefore, even in the case of nonsteady-state experiments, the effect of mixing efficiency (due to differing flow rates within the capillaries) is assumed to be (nearly) neglectable.



**Figure S4.** Comparison of microreactor MR1 and MR2 regarding the influence of mixing efficiency on the conversion of the CH-acidic compound (nonsteady-state experiments).

#### Residence time distribution

Table S1 compares the two microreactors regarding the Re, Dn, and Bo numbers (both for straight<sup>2, 3</sup> and for coiled capillary tubes<sup>4</sup>). Those dimensionless parameters depend on the flow rate and are provided for several residence times.

The dimensionless Bodenstein number Bo is utilized to characterize the degree of backmixing:

$$Bo = \frac{u \cdot L}{D_{ax}}$$
(S1)

For straight reactor tubes, the dispersion coefficient  $D_{ax}$  (incorporating molecular diffusion, effects of backmixing due to radial velocity profile in laminar flow, and the development of secondary flows) can be calculated through a correlation according to Taylor<sup>2</sup> and Aris<sup>3</sup>. For coiled reactor tubes,  $D_{ax}$  can be estimated according to Daskopoulos and Lenhoff<sup>4</sup>. According to Daskopoulos and Lenhoff<sup>4</sup>, the Bo number can be increased by including secondary flows. As a rule of thumb, the threshold for assuming nearly plug flow conditions amounts to Bo > 100.<sup>5</sup> As outlined in Table S1, over the whole design space, a narrow residence time distribution due to high Bo numbers (when using coiled capillaries) can be assumed in good approximation (only in case of the lowest residence time of MR2, the threshold Bo > 100 is missed by a narrow margin).

Parameters		MR1		MR2	
Channel diameter [mm]	0.5 + 0	0.75 <sup>a)</sup>	0.5		
Length [m]	5 +	2 <i>a</i> )	2	.5	
Inner volume [mL]	1.8	87	0.	49	
Residence time (lowest – highest) [min]	0.8	5	0.2	1.2	
Flow rate (lowest – highest) [mL min <sup>-1</sup> ]	2.33	0.37	2.45	0.41	
Flow velocity (lowest – highest) [m s <sup>-1</sup> ]	0.061	0.010	0.208	0.035	
Re number	38	6	104	17	
Dn number	8	1	18	3	
Bo number <sup>b)</sup> (straight capillary reactor <sup>2, 3</sup> )	57	353	10	55	
Bo number <sup><i>c</i>)</sup> (coiled capillary reactor <sup>4</sup> )	268	876	65	206	

**Table S1.** Overview of microreactors used during investigation of organometallic synthesis:

 dimensions and calculated dimensionless parameters for selected residence times.

a) MR1: Consisting of two modular reactor pieces that are connected to each other. First capillary: inner diameter 0.5 mm; length 5 m. Second capillary: inner diameter 0.75 mm, length 2 m.

b) Applicable Bo number when reactor is not coiled.

*c)* Actual Bo number present in the experiments given the coiled reactor design.

#### Heat transfer

Especially in the case of highly exothermic reactions (organometallic syntheses), high heat removal is a crucial precondition for determining reliable kinetic data (thus allowing for running the latter at nearly isothermal conditions). Usually, kinetic data is required to estimate the temperature profile in a given reactor, as heat release depends on reaction rate. However, a shortcut approach (as proposed by Westermann<sup>6</sup>) can be used for a rough and rather conservative estimation of hot spot generation at the reactor entrance, depending on the inner capillary diameter (without explicitly requiring kinetic data).

Exemplarily for the investigated (highly exothermic) lithiation reaction, hot spot generation was assessed according to Westermann's shortcut approach<sup>6</sup>:

For an inner capillary diameter of 0.5 mm (educt concentration  $c_0 = 0.4 \text{ mol } \text{L}^{-1}$ , half life time  $t_{0.5} = 5 \text{ s}$ , reaction enthalpy  $\Delta h_R = -178 \text{ kJ mol}^{-1}$ ) the maximum temperature release (at reactor entrance) was assessed to not exceed 1.8 K, indicating a nearly isothermal behavior<sup>6</sup>.

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

$$\Delta T_{\max} (d = 0.5 \text{ mm}) \approx 1.8 \text{ K}$$
(S2)

Otherwise, if kinetic data is available, the temperature profile can be calculated using the energy and mass balance (Figure S5):

$$\frac{\mathrm{d}T}{\mathrm{d}t} = -\frac{R_4 \cdot \Delta h_R + \dot{q}_W \cdot \frac{2}{r}}{\rho \cdot c_n} \tag{S3}$$

$$\frac{\mathrm{d}c_4}{\mathrm{d}t} = R_4 = -k \cdot c_4^n \cdot c_5^m \tag{S4}$$

$$\dot{q}_W = \alpha_i \cdot (T - T_0) \tag{S5}$$

$$\alpha_i = \frac{\mathrm{Nu} \cdot \lambda}{d} \tag{S6}$$

In this case,  $\alpha_i$  was defined by assuming fully developed laminar flow heat transfer with Nu = 3.66 (constant wall temperature). It was considered that heat transfer in the oil bath and heat conduction in the wall of the stainless steel capillary is much higher than the inner heat transfer.



**Figure S5.** Temperature profile of lithiation reaction (concentration of CH-acidic compound amounting to 0.4 mol L<sup>-1</sup>, inner capillary diameter 0.5 mm, cooling temperature –15 °C).

#### A.3. Nonsteady-state experiments

In case of the nonsteady-state experiments, a decay function of the total volumetric flow rate was applied, while IR spectra were continuously measured. The constant gradient  $\alpha$  (that was applied to the volumetric flow rate) was calculated as function of overall measurement time  $t_{end}$  (eq. 1)<sup>7</sup>.

$$\alpha = \frac{V_r}{t_{\text{end}}} \left( \frac{1}{Q_{\text{end}}} - \frac{1}{Q_0} \right)$$
(S7)

The measurement interval (every measurement consisted of 24 scans) amounted to 30 s. Thus, a suitable value for the overall measurement time  $t_{end}$  had to be chosen. A suitable value had to guarantee that the volumetric flow rate was not varied too fast. Otherwise, high deviations of the respective investigated residence times (during the measurement time of 30 s) would have occurred.

Values for the constant gradient  $\alpha$  (applied in this work) are exemplarily provided in Table S2 and Table S3 in case of investigating the deprotonation reaction (utilizing MR1 and MR2). Moreover, deviations of residence times (during the measurement interval) are illustrated whilst investigating the lowest respectively the highest residence time.

 Table S2. Reactor specifications conducting nonsteady-state experiments. Investigation of organometallic synthesis utilizing microreactor MR1.

Starting point		End point		
$ au_0$	$Q_0$	$ au_{ m end}$	$Q_{ m end}$	t <sub>end</sub>
[min]	[mL/min]	[min]	[mL/min]	[min]
0.8	2.33	5	0.37	20
	Star           τ <sub>0</sub> [min]           0.8	Starting point $\tau_0$ $Q_0$ [min][mL/min]0.82.33	Starting pointE $\tau_0$ $Q_0$ $\tau_{end}$ [min][mL/min][min]0.82.335	Starting pointEnd point $\tau_0$ $Q_0$ $\tau_{end}$ $Q_{end}$ [min][mL/min][min][mL/min]0.82.3350.37

α	$\Delta t$ (during measurement)	deviation (lowest $\tau$ )	deviation (highest $\tau$ )
[-]	[s]	[%]	[%]
0.212	6.36	13.25	2.12

 Table S3. Reactor specifications conducting nonsteady-state experiments. Investigation of organometallic synthesis utilizing microreactor MR2.

	Starting point		End point		
$V_r$	$ au_0$	$Q_0$	$ au_{ m end}$	$Q_{ m end}$	<i>t</i> <sub>end</sub>
[mL]	[min]	[mL/min]	[min]	[mL/min]	[min]
0.49	0.2	2.45	1.2	0.38	20

α	$\Delta t$ (during measurement)	deviation (lowest $\tau$ )	deviation (highest $\tau$ )
[-]	[s]	[%]	[%]
0.055	1.64	13.64	2.27

#### A.4. Data fitting

Figure S6 schematically contrasts the two data evaluation procedures (evaluation based on previously determined calibration curves and SMCR soft-modeling) to determine concentration profiles based on the experimental results that were gained through inline FT-IR measurements.



**Figure S6.** Generalized procedures for determining concentration profiles. Schematic flow chart with individual working steps, contrasting data evaluation based on previously determined calibration curves with soft-modeling (SMCR).

The resulting concentration profiles (concentrations over time at defined reaction temperatures and stoichiometric ratios; independent of the respective data evaluation procedure – calibration curves or soft-modeling –) were transferred to the scale-up and kinetic modeling tool *DynoChem* (Scale-up Systems Ltd., Ireland).

Kinetic parameters were estimated by fitting the resulting concentration profiles to a kinetic model that was defined with the software *DynoChem* (Figure S7). This kinetic model was based on the differential equations describing the reaction rate as a function of the concentration of all involved reactants. In order to perform a data fit and to calculate kinetic parameters that best represent the experimental data, the least squares method was applied. During least squares fitting, the minimization of *SSQ* (sum of squares; weighted *SSQ* which scaled with the number of data points within the model and the profile maximum value) was used as objective function (while Levenberg-Marquardt constituted the fitting algorithm). The data fitting resulted in a calculation of rate coefficient  $k_{ref}$  at a defined reference temperature  $T_{ref}$  and activation energy  $E_A$ . In case of the organometallic synthesis, reaction orders *n* and *m* were calculated as well. Moreover, quality parameters of the model fit were provided, including confidence intervals and correlation matrices.



Figure S7. Generalized procedure for estimating kinetic parameters through software DynoChem (Scale-up Systems Ltd., Ireland).

## **B.** Imine Synthesis

#### B.1. Bilinear model decomposition applying SMCR

The decomposition of the experimental data matrices (eq. 2)<sup>8</sup> into concentration profiles, pure component spectra (first derivative), and residuals (error matrix), is exemplarily discussed in Figure S8.

$$D = C \cdot S^T + E \tag{S8}$$

Applying SMCR, concentration profiles were obtained directly from the measured IR spectra (experimental data matrix). A spectra processing (baseline-correction, calculation of first derivative) was followed by an estimation of the number of involved components (Singular Value Decomposition<sup>9, 10</sup>). In case of imine synthesis, two components were identified: the starting material benzaldehyde **1** and the product n-benzylidenebenzylamine **3**.



residuals (error matrix)

**Figure S8.** Investigation of imine synthesis. Data evaluation utilizing SMCR technique. Decomposition of experimental data matrix into concentration profiles, pure component spectra (first derivative), and residuals (error matrix).

Quality parameters of the model fit (explained variance, lack of fit)<sup>11, 12</sup> are provided in Table S4 (comparing the evaluation of steady-state and nonsteady-state experiments).

The equations defining the explained data variance (eq. 3) and the lack of data fit (eq. 4)  $are^{11, 13}$ :

$$R^{2} = 100 \sqrt{\frac{\sum_{i,j} d_{ij}^{2} - \sum_{i,j} e_{ij}^{2}}{\sum_{i,j} d_{ij}^{2}}}$$
(S9)

lack of fit (%) = 
$$100 \sqrt{\frac{\sum_{i,j} e_{ij}^2}{\sum_{i,j} d_{ij}^2}}$$
 (S10)

where  $d_{ij}$  is an element of the experimental data matrix and  $e_{ij}$  is the related residual value obtained from the difference between the experimental data matrix (D) and the reproduced data ( $C \cdot S^T$ ).

Quality parameters	Steady-state experiments	Nonsteady-state experiments		
Soft-m	odeling			
Lack of fit (LOF) [%]	8.6	3.1		
Percent of variance explained [%]	99.3	99.9		
Hard-modeling				
Lack of fit (LOF) [%]	9.5	3.6		
Percent of variance explained [%]	97.8	99.4		

Table S4. Quality parameters of SMCR model fit. Investigation of imine synthesis.

Error limits of model decomposition (applying SMCR) calculated under nonsteady-state conditions are slightly more narrow compared to their steady-state counterparts as a drastically higher number of data points is evaluated in case of nonsteady-state experiments.

#### B.2. Constraints set up for SMCR technique

Whilst utilizing the SMCR technique as data evaluation method, the following constraints, relating to the row mode (matrix C, concentration profiles), were applied: non-negativity, horizontal unimodality (single concentration maximum), and a mass balance closure. In case of hard-modeling, a hard constraint was implemented in order to make the concentration profiles fit to a kinetic model.

If no constraints were applied, a nearly infinite number of possible solutions would arise. This is especially crucial when there are two or more linearly independent components within the experimental data matrix: model decomposition may then lead to spectra and concentration profiles that constitute an unknown linear combination of the true component spectra and the true concentration profiles respectively, also referred to as rotational ambiguity<sup>14</sup>.

Thus, constraints are set up in order to reduce this number of possible solutions and to refine the result (and to decrease the range of rotational ambiguity). They are usually derived from physical nature (non-negativity of concentrations) and previous knowledge of the system (mass balance closure)<sup>14–16</sup>. Table S5 provides an overview of the constraints set up for the SMCR technique in this study and their respective effects on the results. Note that, in general, a non-negativity constraint may also be applied to the column mode (spectroscopic component spectra, matrix  $S^T$ ). However, this study worked with the first derivative of all IR spectra (yielding the advantage that the impact of a general offset trend throughout the entire spectral range could be eliminated). As the first derivative represents the gradient throughout the respective spectrum, it may also include negative values.

<b>Table S5.</b> Overview of constraints	(related to the concentrations	s profiles) set up	for the SMCR
	technique.		

Constraints	Soft- modeling	Hard- modeling	Effect on the result	Justification
Non-negativity	х	х	No negative concentration values allowed	Physical nature of concentration profiles
Horizontal unimodality	х	х	One single concentration maximum within the profile	Physical nature of concentration profiles
Mass balance closure	X	X	Relative concentration values are translated into absolute ones	Previous knowledge of the system (initial concentrations); however, only expedient if all involved species could be identified
Kinetic model	-	X	Concentration profiles are made to fit to a kinetic model <i>(rotational</i> <i>ambiguity is</i> <i>minimized)</i>	Previous knowledge of the kinetic mechanism, hard constraint (strongly effects the result)

#### B.3. Evaluation of steady-state experiments applying SMCR

The resulting concentration profiles of imine synthesis, when evaluating steady-state experiments using the SMCR technique, are displayed in Figure S9. Herein, the results of soft- and hard-modeling are compared.



**Figure S9.** Kinetic modeling of experimental data. Data evaluation using SMCR technique. Imine Synthesis. Steady-state experiments. a) Soft-modeling. b) Hard-modeling.

#### C. Organometallic Synthesis

#### C.1. Kinetic model prediction based on previously determined calibration curves

The fitted conversion-residence time curves (whilst evaluating nonsteady-state experiments based on previously determined calibration curves) for different temperatures and stoichiometric ratios are displayed in Figure S10.



Figure S10. Kinetic modeling of experimental data. Data evaluation based on previously determined calibration curves. Organometallic Synthesis.a) Temperature dependence. b) Influence of varying stoichiometric ratios.

The relative errors of fitted reaction orders n (CH-acidic compound 4) and m (n-butyllithium 5) are illustrated in Table S6. Note that, within the final kinetic model, their values were rounded to one decimal place and therefore set to constant.

 Table S6. Calculated reaction orders of CH-acidic compound and n-butyllithium

 (organometallic synthesis) and their respective confidence intervals (data evaluation based on previously determined calibration curves).

Kinetic parameters	Steady-state experiments <sup>17</sup>	Nonsteady-state experiments
Reaction order <i>n</i> (CH-acidic compound <b>4</b> ) (confidence level 95 %)	1.125 (± 11.5 %)	1.113 (± 8.6 %)
Reaction order <i>m</i> (n-butyllithium <b>5</b> ) (confidence level 95 %)	0.306 (± 16.4 %)	0.301 (± 10.1 %)

#### C.2. Comparison Data evaluation applying SMCR

IR spectra that had been gained in a prior work under steady-state conditions as well as IR spectra gathered in this study's experimental data sets under nonsteady-state conditions (investigating the deprotonation reaction) were evaluated using a modified version of the SMCR technique (becoming capable of handling complex reaction mechanisms with broken reaction orders).

In case of the deprotonation reaction, a spectrum range between 1800 and 600 cm<sup>-1</sup> was chosen to construct the experimental data matrix (IR spectra over time). All IR spectra were baseline-corrected, and the respective first derivative was subsequently calculated. Such a spectra processing is exemplarily demonstrated in Figure S11, displaying a spectrum range between 782 and 755 cm<sup>-1</sup> (corresponding to the characteristic IR band of the CH-acidic compound **4** which was identified in case of data evaluation based on previously determined calibration curves).

This spectra processing was followed by an estimation of the number of involved components (applying a Singular Value Decomposition algorithm<sup>9, 10</sup>), resulting in identification of one component (CH-acidic compound **4**). In a next step, initial estimates were generated through the Evolving Factor Analysis method<sup>18–20</sup>. Finally, constraints relating to the row mode (matrix C, concentration profiles) were defined: non-negativity, horizontal unimodality, and a mass balance closure (closure 0.34 mol L<sup>-1</sup> lower or equal than).



Figure S11. Spectra processing of experimental data matrix (IR spectra over time): baseline-correction and calculation of first derivative. Exemplarily provided for a wave number range between 782 and 755 cm<sup>-1</sup> (characteristic IR band of the CH-acidic compound 4 identified in case of data evaluation based on previously determined calibration curves).
 a) Raw spectra. b) First derivative.

#### C.3. Comparison of soft- and hard-modeling

#### Soft-modeling

The resulting concentration profiles of the organometallic synthesis, when evaluating steady-state experiments through a soft-modeling, are displayed in Figure S12 (for different temperatures and stoichiometric ratios).





Table S7 illustrates the confidence intervals of fitted reaction orders n (CH-acidic compound 4) and m (n-butyllithium 5), resulting from soft-modeling. Again, within the final kinetic model, their values were rounded to one decimal place and set to constant.

Kinetic parameters	Soft-modeling steady-state experiments	Soft-modeling nonsteady-state experiments
Reaction order <i>n</i> (CH-acidic compound <b>4</b> ) (confidence level 95 %)	1.481 (± 18.9 %)	1.455 (± 16.4 %)
Reaction order <i>m</i> (n-butyllithium <b>5</b> ) (confidence level 95 %)	0.312 (± 20.4 %)	0.310 (± 16.7 %)

**Table S7.** Calculated reaction orders of CH-acidic compound and n-butyllithium (organometallic synthesis) and their respective confidence intervals (soft-modeling).

## Hard-modeling

In Figure S13, the resulting concentration profiles of the organometallic synthesis, when evaluating steady-state experiments through a hard-modeling are illustrated (for different temperatures and stoichiometric ratios).





Quality parameters of the model fit whilst conducting a soft-modeling (explained variance, lack of fit)<sup>8, 11, 12</sup> are provided in Table S8 (comparing the evaluation of steady-state and nonsteady-state experiments).

 Table S8. Quality parameters of SMCR model fit, conducting soft-modeling. Investigation of organometallic synthesis.

Quality parameters	Steady-state experiments	Nonsteady-state experiments
Lack of fit (LOF) [%]	12.2	10.3
Percent of variance explained [%]	97.8	98.7

Again, error limits of model decomposition (applying SMCR as soft-modeling) calculated under nonsteady-state conditions are slightly more narrow compared to their steady-state counterparts as a drastically higher number of data points is evaluated in case of nonsteady-state experiments.

Using SMCR as hard-modeling, a case study was performed to evaluate the sensitivity of different reaction orders on the quality of model decomposition (percent of variance explained, lack of fit). The resulting quality parameters of model fit are summarized in Table S9.

Quality parameters	Steady-state experiments	Nonsteady-state experiments		
$\frac{\mathrm{d}c_4}{\mathrm{d}t} = R_4 = -k \cdot c_4^1 \cdot c_5^1$				
Lack of fit (LOF) [%]	15.5	14.6		
Percent of variance explained [%]	95.1	95.5		
$\frac{\mathrm{d}c_4}{\mathrm{d}t} = R_4 = -k \cdot c_4^1 \cdot c_5^{0.5}$				
Lack of fit (LOF) [%]	14.6	13.1		
Percent of variance explained [%]	95.8	96.2		
$\frac{\mathrm{d}c_4}{\mathrm{d}t} = R_4 = -k \cdot c_4^1 \cdot c_5^{0.3}$				
Lack of fit (LOF) [%]	12.9	11.1		
Percent of variance explained [%]	96.9	97.9		
$\frac{\mathrm{d}c_4}{\mathrm{d}t} = R_4 = -k \cdot c_4^{1.1} \cdot c_5^{0.3}$				
Lack of fit (LOF) [%]	12.4	10.6		
Percent of variance explained [%]	97.3	98.5		
$\frac{\mathrm{d}c_4}{\mathrm{d}t} = R_4 = -k \cdot c_4^{1.3} \cdot c_5^{0.3}$				
Lack of fit (LOF) [%]	12.6	10.8		
Percent of variance explained [%]	97.0	98.1		
$\frac{\mathrm{d}c_4}{\mathrm{d}t} = R_4 = -k \cdot c_4^{1.5} \cdot c_5^{0.3}$				
Lack of fit (LOF) [%]	13.0	11.3		
Percent of variance explained [%]	96.8	97.8		

# **Table S9.** Quality parameters of SMCR model fit, investigating the organometallic synthesis.Evaluation of sensitivity of different reaction orders (describing the complex reaction<br/>mechanism) on the quality of model decomposition.

Highest quality of model decomposition (lowest lack of fit, highest percent of variance explained) is reached in case of modeling with broken reaction orders (reaction order of CH-acidic compound **4** amounting to 1.1, reaction order of n-butyllithium **5** amounting to 0.3). This indicates that a complex reaction mechanism is involved and is in line with the results of a previous publication<sup>17</sup>.

#### **D.** Discussion

#### D.1. Comparison of steady-state and nonsteady-state experiments

Figure S14 demonstrates both methods' speed in generating data points, comparing experiments under steady-state and under nonsteady-state conditions. In terms of efficiency, when conducting steady-state experiments, data points need to be separated by three hydrodynamic residence times each (the higher the respective residence time, the longer the waiting time between two measurements). Thus, the overall experiment time increases exponentially. Conversely, in nonsteady-state-conditions, the constant volumetric flow rate gradient eliminates the waiting times between measured data points (linear increase of overall experiment time). Hence, a nonsteady-state approach generates 100 data points in 20 min, whereas a steady-state approach requires three times as long (60 min) to generate the same number of data points.



Figure S14. Methods' speed in generating data points: comparison of steady-state and nonsteady-state experiments.

# Nomenclature

1	[-]	benzaldehyde
2	[-]	benzylamine
3	[-]	n-benzylidenebenzylamine
4	[-]	CH-acidic compound
5	[-]	n-butyllithium
Bo	[-]	Bodenstein number
$C_j$	$[mol L^{-1}]$	concentration of compound <i>j</i>
$c_p$	$[J kg^{-1} K^{-1}]$	specific heat capacity
С	[-]	pure concentration profiles
D	[-]	experimental data matrix
$D_{ax}$	$[m^2 s^{-1}]$	axial dispersion coefficient
d	[m]	Inner capillary diameter
$d_{ m ij}$	[-]	element of the experimental data matrix
Ε	[-]	error matrix (residuals)
e <sub>ij</sub>	[-]	related residual value
$\Delta h_R$	$[kJ mol^{-1}]$	reaction enthalpy
$\Delta h_R$ $k_i$	$ [kJ mol^{-1}]  [(m3 mol^{-1})n+m-1 s-1] $	reaction enthalpy reaction rate coefficient of reaction <i>i</i>
$\Delta h_R$ $k_i$ L	$[kJ mol^{-1}]$ $[(m3 mol^{-1})n+m-1 s-1]$ [m]	reaction enthalpy reaction rate coefficient of reaction <i>i</i> length
$\Delta h_R$ $k_i$ L MR1	[kJ mol <sup>-1</sup> ] [(m <sup>3</sup> mol <sup>-1</sup> ) <sup>n + m - 1</sup> s <sup>-1</sup> ] [m] [-]	reaction enthalpy reaction rate coefficient of reaction <i>i</i> length microreactor no. 1
$\Delta h_R$ $k_i$ L MR1 MR2	[kJ mol <sup>-1</sup> ] [(m <sup>3</sup> mol <sup>-1</sup> ) <sup>n + m - 1</sup> s <sup>-1</sup> ] [m] [-] [-]	reaction enthalpy reaction rate coefficient of reaction <i>i</i> length microreactor no. 1 microreactor no. 2
$\Delta h_R$ $k_i$ $L$ MR1 MR2 $m$	[kJ mol <sup>-1</sup> ] [(m <sup>3</sup> mol <sup>-1</sup> ) <sup>n + m - 1</sup> s <sup>-1</sup> ] [m] [-] [-]	reaction enthalpy reaction rate coefficient of reaction <i>i</i> length microreactor no. 1 microreactor no. 2 reaction order of <b>4</b>
$\Delta h_R$ $k_i$ $L$ MR1 MR2 $m$ $n$	[kJ mol <sup>-1</sup> ] [(m <sup>3</sup> mol <sup>-1</sup> ) <sup>n + m - 1</sup> s <sup>-1</sup> ] [m] [-] [-] [-]	reaction enthalpy reaction rate coefficient of reaction <i>i</i> length microreactor no. 1 microreactor no. 2 reaction order of <b>4</b> reaction order of <b>5</b>
$\Delta h_R$ $k_i$ $L$ MR1 MR2 $m$ $n$ Nu	[kJ mol <sup>-1</sup> ] [(m <sup>3</sup> mol <sup>-1</sup> ) <sup>n + m - 1</sup> s <sup>-1</sup> ] [m] [-] [-] [-] [-] [-]	reaction enthalpy reaction rate coefficient of reaction <i>i</i> length microreactor no. 1 microreactor no. 2 reaction order of <b>4</b> reaction order of <b>5</b> Nusselt number
$\Delta h_R$ $k_i$ $L$ MR1 MR2 $m$ $n$ Nu $Q$	[kJ mol <sup>-1</sup> ] [(m <sup>3</sup> mol <sup>-1</sup> ) <sup>n + m - 1</sup> s <sup>-1</sup> ] [m] [-] [-] [-] [-] [-] [-] [mL min <sup>-1</sup> ]	reaction enthalpy reaction rate coefficient of reaction <i>i</i> length microreactor no. 1 microreactor no. 2 reaction order of <b>4</b> reaction order of <b>5</b> Nusselt number volumetric flow rate
$\Delta h_R$ $k_i$ $L$ MR1 MR2 $m$ $n$ Nu $Q$ $\dot{q}_W$	[kJ mol <sup>-1</sup> ] [(m <sup>3</sup> mol <sup>-1</sup> ) <sup>n + m - 1</sup> s <sup>-1</sup> ] [m] [-] [-] [-] [-] [-] [mL min <sup>-1</sup> ] [W m <sup>-2</sup> ]	reaction enthalpy reaction rate coefficient of reaction <i>i</i> length microreactor no. 1 microreactor no. 2 reaction order of <b>4</b> reaction order of <b>5</b> Nusselt number volumetric flow rate wall heat flux density
$\Delta h_R$ $k_i$ $L$ MR1 MR2 $m$ $n$ Nu $Q$ $\dot{q}_W$ $Rj$	$[kJ mol^{-1}]$ $[(m3 mol^{-1})n + m - 1 s-1]$ [m] [-] [-] [-] [-] [-] [mL min <sup>-1</sup> ] [W m <sup>-2</sup> ] [mol L <sup>-1</sup> s <sup>-1</sup> ]	reaction enthalpy reaction rate coefficient of reaction <i>i</i> length microreactor no. 1 microreactor no. 2 reaction order of <b>4</b> reaction order of <b>5</b> Nusselt number volumetric flow rate wall heat flux density reaction rate of compound <i>j</i>
$\Delta h_R$ $k_i$ $L$ MR1 MR2 $m$ $n$ Nu $Q$ $\dot{q}_W$ $Rj$ $r$	$[kJ mol^{-1}]$ $[(m^{3} mol^{-1})^{n+m-1} s^{-1}]$ $[m]$ $[-]$ $[-]$ $[-]$ $[mL min^{-1}]$ $[W m^{-2}]$ $[mol L^{-1} s^{-1}]$ $[m]$	reaction enthalpy reaction rate coefficient of reaction <i>i</i> length microreactor no. 1 microreactor no. 2 reaction order of <b>4</b> reaction order of <b>5</b> Nusselt number volumetric flow rate wall heat flux density reaction rate of compound <i>j</i> tube radius
$\Delta h_R$ $k_i$ $L$ MR1 MR2 $m$ $n$ Nu $Q$ $\dot{q}_W$ $Rj$ $r$ $S^T$	$[kJ mol^{-1}]$ $[(m^{3} mol^{-1})^{n+m-1} s^{-1}]$ $[m]$ $[-]$ $[-]$ $[-]$ $[-]$ $[mL min^{-1}]$ $[W m^{-2}]$ $[mol L^{-1} s^{-1}]$ $[m]$ $[-]$	reaction enthalpy reaction rate coefficient of reaction <i>i</i> length microreactor no. 1 microreactor no. 2 reaction order of <b>4</b> reaction order of <b>5</b> Nusselt number volumetric flow rate wall heat flux density reaction rate of compound <i>j</i> tube radius pure component spectra
$\Delta h_R$ $k_i$ $L$ MR1 MR2 $m$ $n$ Nu $Q$ $\dot{q}W$ $Rj$ $r$ $S^T$ $t_{end}$	$[kJ mol^{-1}]$ $[(m^{3} mol^{-1})^{n+m-1} s^{-1}]$ $[m]$ $[-]$ $[-]$ $[-]$ $[-]$ $[mL min^{-1}]$ $[W m^{-2}]$ $[mol L^{-1} s^{-1}]$ $[m]$ $[-]$ $[s]$	reaction enthalpy reaction rate coefficient of reaction <i>i</i> length microreactor no. 1 microreactor no. 2 reaction order of <b>4</b> reaction order of <b>5</b> Nusselt number volumetric flow rate wall heat flux density reaction rate of compound <i>j</i> tube radius pure component spectra overall measurement time

u	$[m s^{-1}]$	flow velocity
V <sub>r</sub>	[m <sup>3</sup> ]	reactor volume
α	[-]	constant gradient
$\alpha_i$	$[W m^{-2} K^{-1}]$	heat transfer coefficient
ρ	[kg m <sup>-3</sup> ]	density
λ	$[W m^{-1} K^{-1}]$	thermal conductivity
τ	[s]	residence time

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