Supporting Information for:

# Management of the Heat of Reaction under Continuous Flow Conditions

# **Using In-Line Monitoring Technologies**

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### HPLC method for analyzing 1–5

Column: Waters Xbridge C18,  $4.6 \times 150$  mm, 5 µm Mobile phase A: 0.1% HCOOH in purified water. Mobile phase B: MeCN. B concentration (Gradient): 0.0-12.0 min 15-90%, 12.0-15.0 min 90%, 15.0-15.1 min 90-15%, 15.1-20.0 min 15%. Flow rate: 1.0 mL/min Injection volume: 10 µL Column temperature: 35°C Wavelength: 254 nm Sample was diluted with MeCN/H<sub>2</sub>O (80/20 (v/v)) containing 0.1 vol% of HCOOH

## The specificity of wave numbers of 1 and 2 in IR spectra



Color	Components	
	THF (blank)	
	<b>1</b> in THF	
	<b>2</b> in THF	
	Reaction mixture	

Figure S1. The overlapped IR spectra

## The limit of quantification and the limit of detection using ReactIR

_	Peak height (AU) of <b>1</b> at 1202 cm <sup>-1</sup> (× $10^{-3}$ )
5.20 × 10 <sup>-3</sup> mmol/mL (0.10 wt%) of <b>1</b> in THF	1.395610
	1.389485
	1.450260
	1.408333
	1.413535
	1.431046
	1.391746
	1.391376
	1.363258
	1.427771
Average	1.406242

Table S1. Measuring IR Spectra of 0.10 wt% of 1 in THF

Standard deviation ( $\sigma$ ): 0.0252685 × 10<sup>-3</sup>

Slope: 0.2478 (from the calibration curve of **1** in Figure 2)

The limit of quantification (LOQ) was calculated from  $10\sigma$ :  $1.02 \times 10^{-3}$  mmol/mL (0.02 wt%)

The limit of detection (LOD) was calculated from  $3\sigma$ :  $0.31 \times 10^{-3}$  mmol/mL (0.006 wt%)

Detailed descriptions of the equipment used for monitoring the reaction rate and the internal temperature



Figure S2. Detailed description of the equipment used for continuous flow synthesis -1



Figure S3. Detailed description of the equipment used for continuous flow synthesis -2



A tube reactor is connected with a flow cell in ReactIR

Figure S4. Detailed description of the equipment used for monitoring the reaction rate



Figure S5. Detailed descriptions of the equipment used for monitoring the internal temperature from the front



Figure S6. Detailed descriptions of the equipment used for monitoring the internal temperature from the side

#### The influence of flow rates at the calculation of U values

Two solutions were fed by a Vapourtec V-3 pump: solution A was 5.0 mmol/mL aqueous solution of NaOH, and solution B was 5.0 mmol/mL aqueous solution of HCl. The flow rate of solution A was set as 5.00 or 10.00 mL/min, and that of solution B as 5.00 or 10.00 mL/min so that the equivalent of HCl would be adjusted to 1.00 equiv. The two solutions were mixed by a T-shaped mixer, and the combined solution was passed through a PFA tube reactor (outer diameter: 2.00 mm, inner diameter: 1.00 mm). The internal temperatures were measured using thermocouples inserted into the tube reactors, and the temperatures were compared to evaluate the influence of flow rates.

 $c_S = 2500 \text{ mol} \cdot \text{m}^{-3}, c_R = 2500 \text{ mol} \cdot \text{m}^{-3}, T_i = 295 \text{ K}, u = 0.21 \text{ m} \cdot \text{s}^{-1} \text{ or } 0.42 \text{ m} \cdot \text{s}^{-1}, \rho = 1062 \text{ kg} \cdot \text{m}^{-3}, c_p = 4580 \text{ J} \cdot \text{kg}^{-1} \cdot \text{K}^{-1}, \Delta H_R = 58 \text{ kJ} \cdot \text{mol}^{-1}, T_j = 291 \text{ K}.$ 

NaOH aq. 5.00 mL/min	Measured internal	NaOH aq. 10.00 mL/min	Measured internal
HCl aq. 5.00 mL/min	temperatures (°C)	HCl aq. 10.00 mL/min	temperatures (°C)
Coordinate in tube length		Coordinate in tube length	
(m) / Residence time (sec)		(m) / Residence time (sec)	
0.25 / 1.2	43	0.50 / 1.2	43
0.50 / 2.4	33	1.00 / 2.4	33
0.75 / 3.6	29	1.50 / 3.6	27

Table S2. Evaluation of the Influence of Flow Rates

Flow rates did not have a great impact on the overall heat transfer coefficient (U value) because almost the same internal temperatures were measured at the same residence time.