Electronic Supplementary Material

Continuous flow synthesis of amine oxides by oxidation of tertiary amines

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1. Calculation of the microreactor volume

Microreactor volume for the conducted experiments:

- 5 microchannels (length: 750 mm, internal diameter: 1 mm): 3.02 mL
- PTFE capillary for sampling at the end of the microreactor (length: 300 mm, internal diameter: 1/16”): 0.595 mL
- PTFE capillary to connect the two microreactor plates (length: 68 mm, internal diameter: 1/16”): 0.135 mL

Total volume: **3.75 mL**

Microreactor volume for the scale-up experiments:

- 6 microchannels (length: 750 mm, internal diameter: 1 mm): 3.63 mL
- 2 microchannels (length: 750 mm, internal diameter: 3 mm): 10.60 mL
- PTFE capillary for sampling at the end of the microreactor (length: 300 mm, internal diameter: 1/16”): 0.595 mL
- PTFE capillary to connect the two microreactor plates (length: 68 mm, internal diameter: 1/16”): 0.135 mL

Total volume: **14.96 mL**

2. Calculation of the residence time

The residence time (rt) is calculated as follows:

$$rt\ [min] = \frac{total\ microreactor\ volume\ [mL]}{\left(flow\ rate\ NMM\ (1)\ solution + flow\ rate\ H_2O_2\ solution\right)\ [\frac{ml}{min}]}$$

For example calculation of the residence time for the scale-up experiments:

$$rt\ [min] = \frac{14.96\ [mL]}{(1.2\ + 0.67)\ [\frac{ml}{min}]} = \frac{14.96\ [mL]}{1.87\ [\frac{mL}{min}]} = 8.00\ min$$

3. Experimental procedure for dissolving CO_2 in the NMM (1) stock solution

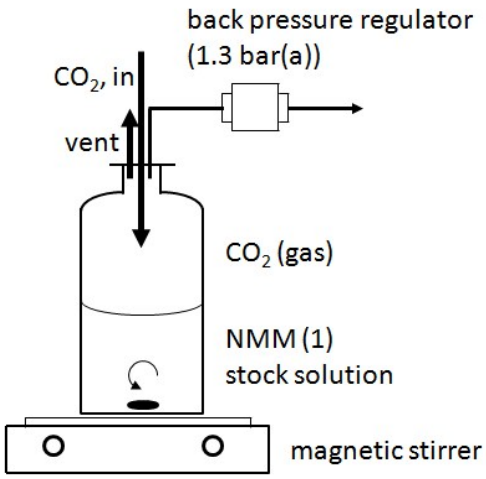

Fig. ESI-1 Experimental procedure for dissolving carbon dioxide (CO_2) in the NMM (1) stock solution.

As described in the main article, carbon dioxide catalyses the oxidation of NMM (1) to NMMO (2). CO_2 is dissolved prior to the reaction in the NMM (1) stock solution according to Figure ESI-1. The CO_2 gas is passed into the laboratory flask and is dissolved under stirring at an excess pressure of 0.3 bar. To achieve the excess pressure a back pressure regulator (0.3 bar, P-790, IDEX, United Sates of America) was attached to the laboratory bottle. The laboratory bottle (DWK Life Sciences GmbH, Germany) was weighed before and after dosing to determine the mass fraction of CO_2 in the NMM (1) stock solution. After dosing of CO_2 the vent valve was opened before the bottle was weighed for the second time.

4. HPLC-Method for quantitative analysis of NMM (1), NMMO (2) and morpholine

Quantitative analyses of the experiments were carried out by HPLC (1100, Agilent Technologies, Inc., United Sates of America) using a VA 150/4.6 Nucleogel RP 100-8 column (150 x 4 mm) (Macherey-Nagel, Germany). Samples to analyze the reaction process were diluted with deionized water in a ratio of 10:1 (v/v) and analyzed immediately after collection.

Chromatographic conditions:

Flow rate: 1 mL/min

Temperature: 10 °C

Injection volume: 100 µL

Wavelength: 200 nm

Mobile phase: Eluent A: methanol

Eluent B: 0.05 M Sodium metaborate tetrahydrate

Gradient:

Time [min]	Eluent A [%]	Eluent B [%]	Type
0 – 8	5	95	isocratic
8 – 18	5 – 65	95 – 35	linear
18 – 22	65 – 100	35 – 0	linear
22 – 27	100	0	isocratic
27 – 29	100 – 5	0 – 95	linear
29 – 33	5	95	isocratic

Different amounts of NMM (1), NMMO (2) and morpholine (by-product) were dissolved in 10 mL of deionized water respectively to obtain standard solutions. The standard solutions were analyzed by HPLC using the described method. The area of the corresponding peaks where plotted against the amounts of substance. The respectively obtained gradient from the straight lines is used for the determination of conversion and yield from the samples of the reaction process. The samples from the lab trials were analyzed according to the described HPLC method like the standard solutions.

Calibration of NMM (1)

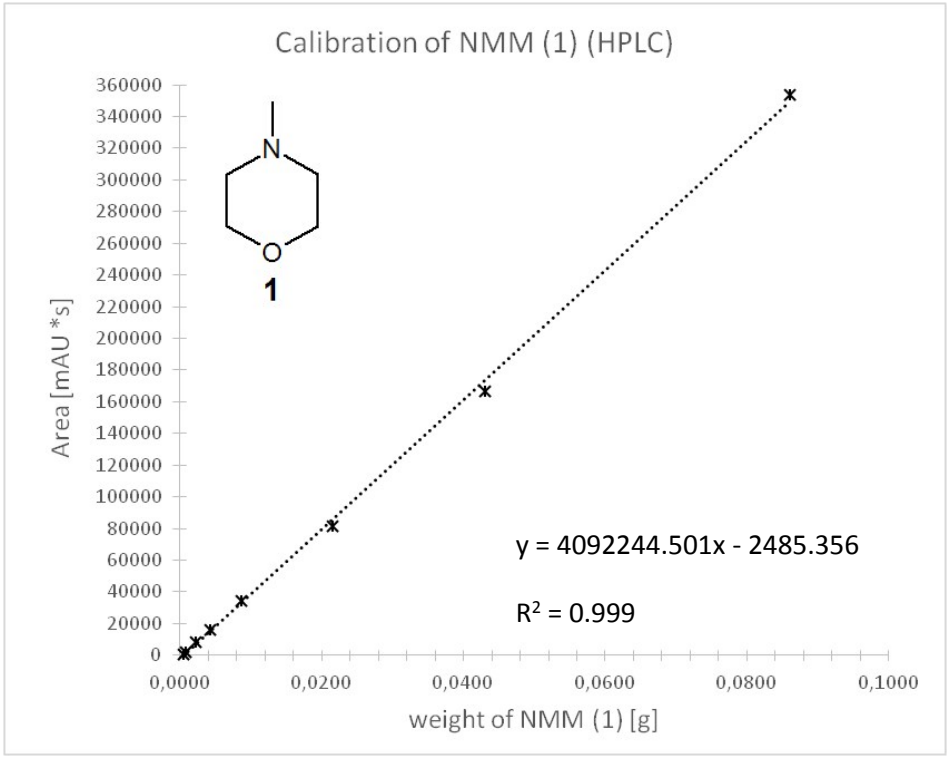

Fig. ESI-2 Calibration of NMM (1) according to the described HPLC method.

Table ESI-1 Sample amount of NMM (1) and the corresponding areas obtained from the HPLC measurement.

sample amount NMM (1) [g]	area integral HPLC [mAu*s]
0.0860	353664
0.0430	166860
0.0215	81144
0.0086	34415
0.0043	16292
0.0022	8225
0.00086	1654
0.00043	772

Calibration of NMMO (2)

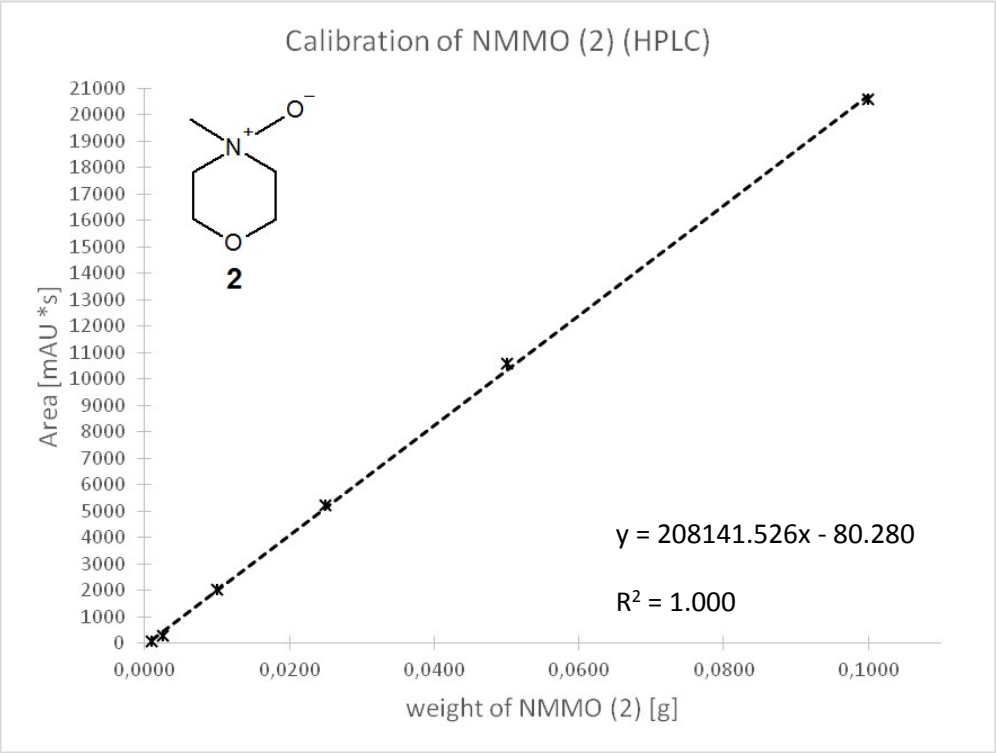

Fig. ESI-3 Calibration of NMMO (2) according to the described HPLC method.

Table ESI-2 Sample amount of NMMO (2) and the corresponding areas obtained from the HPLC measurement.

sample amount NMMO (2) [g]	area integral HPLC [mAu*s]
0.1	20589
0.05	10567
0.025	5230
0.01	2030
0.005	407
0.0025	274
0.001	63

Calibration of morpholine

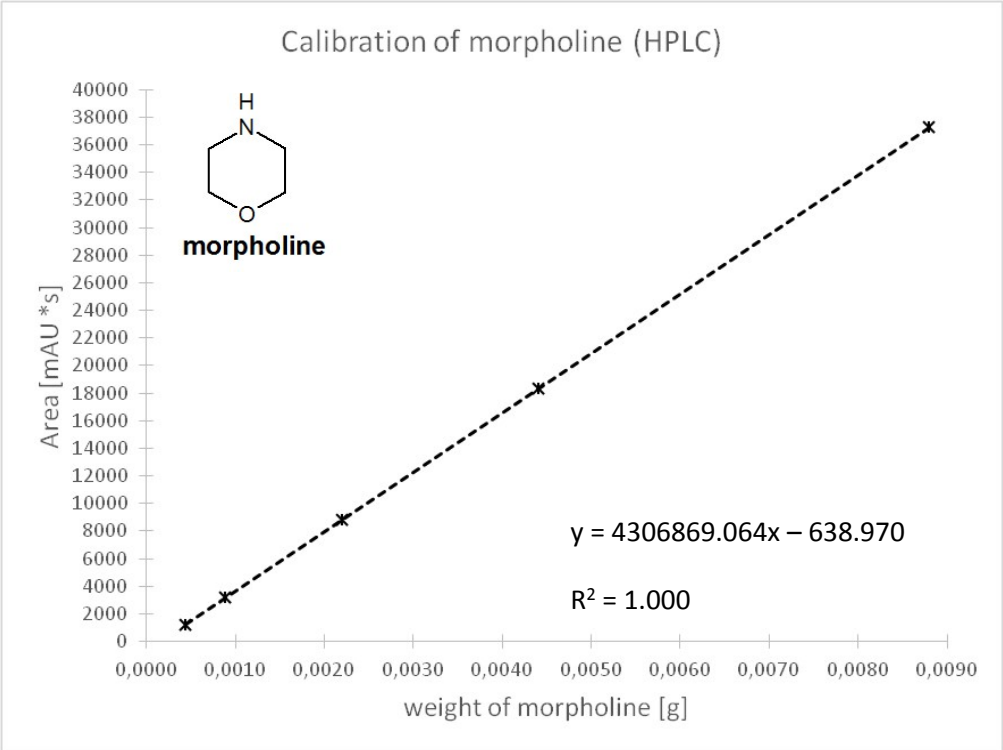

Fig. ESI-4 Calibration of morpholine (by-product) according to the described HPLC method.

Table ESI-3 Sample amount of morpholine (by-product) and the corresponding areas obtained from the HPLC measurement.

sample amount morpholine [g]	area integral HPLC [mAu*s]
0.0088	37255
0.0044	18334
0.022	8807
0.00088	3186
0.00044	1234

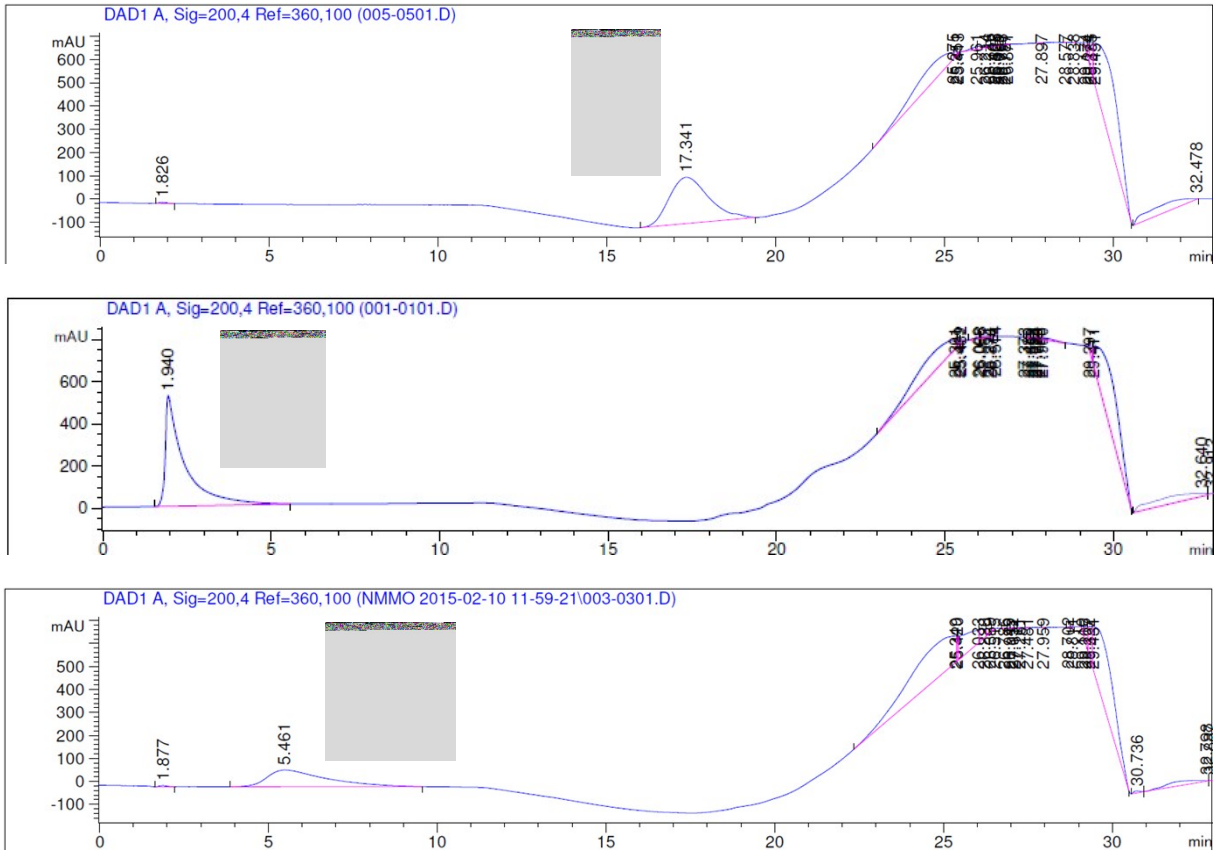

Fig. ESI-5 Chromatogram (standard solutions) of NMM (1) Ret.: 17.341 min (above), NMMO (2) Ret.: 1.940 min (middle) and morpholine (by-product) Ret.: 5.461 min (below).

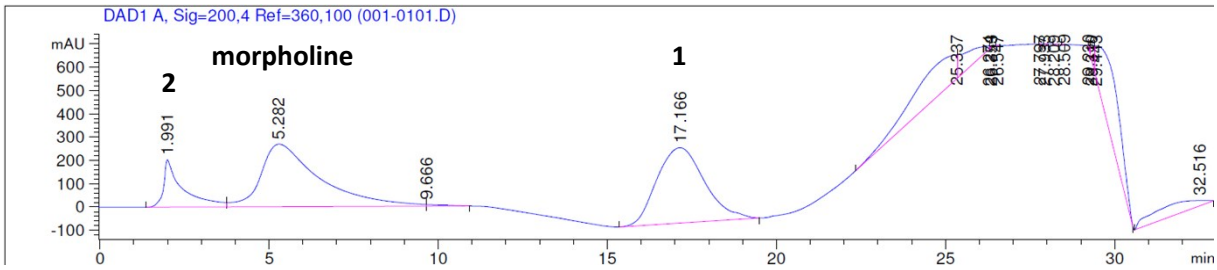

Fig. ESI-6 Chromatogram mixture of NMM (1) Ret.: 17.166 min, NMMO (2) Ret.: 1.991 min and morpholine (by-product) Ret.: 5.282 min.

5. GC-MS-Method for quantitative analysis of the by-product NNM

Quantitative analyses of the by-product N-nitrosomorpholine (NNM) was carried out by Gas Chromatography/Mass Spectrometry (GC-MS) (HP 6890/HP 5973) equipped with a DB-1701 column (30 m x 0.32 mm x 1 µm) (Agilent Technologies Inc., United States of America). Prior to analyses NNM was extracted from the NMMO (2) product solution by liquid-liquid extraction with a mixture of dichloromethane (DCM) and ethyl formate (EF) in a ratio of 1:1 (v/v).

Chromatographic conditions:

Flow rate:	2.5 mL/min
Temperature:	40 °C for 1.10 min
Gradient I:	8 °C/min to 180 °C
Gradient II:	35 °C/min to 280 °C
End temperature:	280 °C for 15 min
Injection volume:	4 µL
Carrier gas:	Helium

Detection parameters:

Mode:	Selected ion monitoring (SIM)
m/z ratios:	116, 86, 56 (NNM)
	272 (octafluoronaphthalene) internal standard
Dwell time:	20 ms

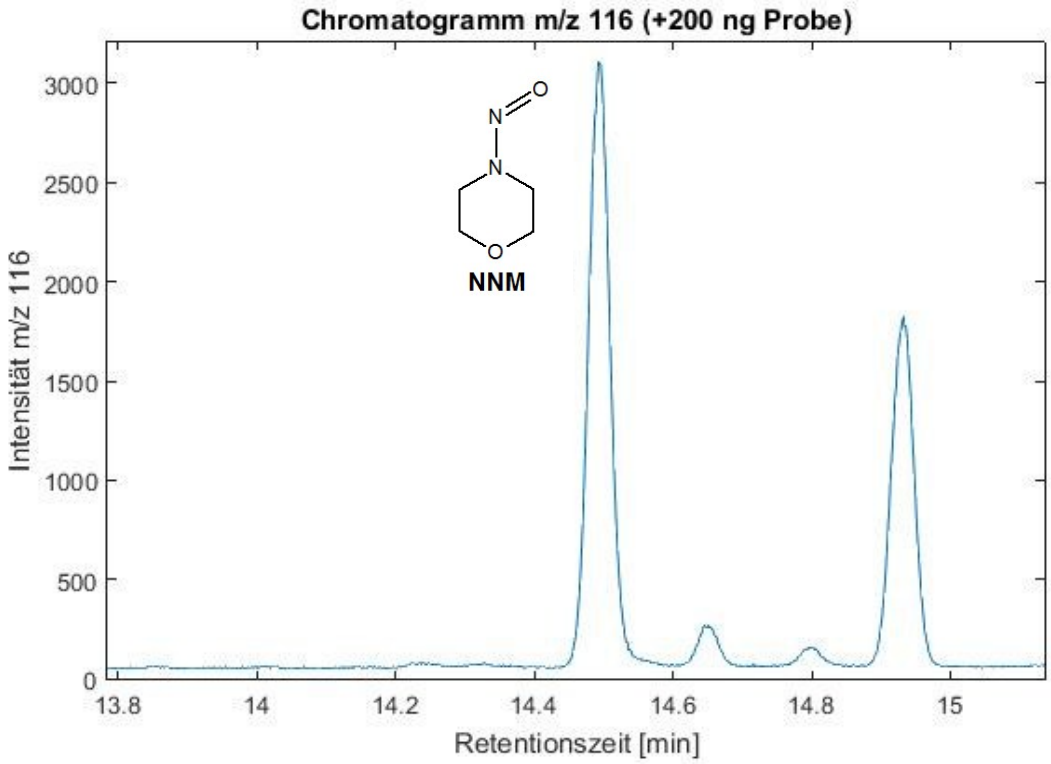

Fig. ESI-7 Chromatogram NNM (m/z: 116).

6. Influence of phosphoric acid on the conversion of NMM (1) and yield of NMMO (2)

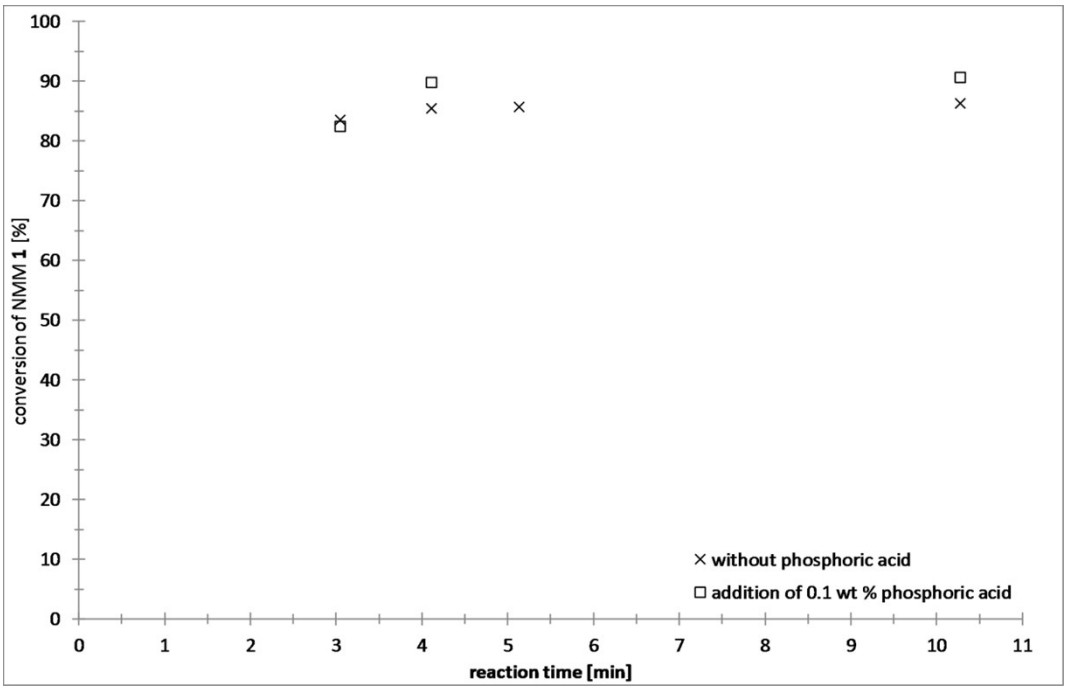

Fig. ESI-8 Influence of phosphoric acid on the conversion of NMM (1), at 60 °C, 17 bar(a), concentration (NMM (1)) 8.5 mol/L, flow rate (NMM (1)) 0.8 – 2.7 mL/min, flow rate (hydrogen peroxide) 0.72 – 2.42 mL/min, concentration (hydrogen peroxide) 32 wt %, concentration of carbon dioxide 1 wt %, ratio of NMM (1)/H_2O_2 1/1.1, residence time 3.04-10.25 min, microreactor volume 15.58 mL.

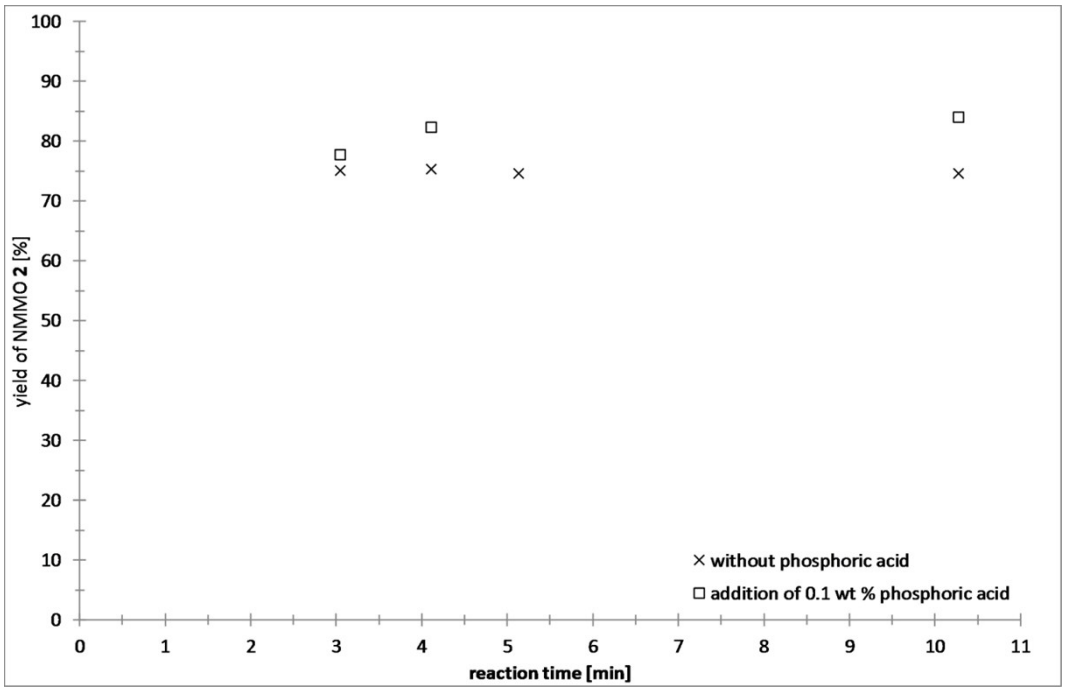

Fig. ESI-9 Influence of phosphoric acid on the yield of NMMO (2) at 60 °C, 17 bar(a), concentration (NMM (1)) 8.5 mol/L, flow rate (NMM (1)) 0.8 – 2.7 mL/min, flow rate (hydrogen peroxide) 0.72 – 2.42 mL/min, concentration (hydrogen peroxide) 32 wt %, concentration of carbon dioxide 1 wt %, ratio of NMM (1)/H_2O_2 1/1.1, residence time 3.04-10.25 min, microreactor volume 15.58 mL.

7. Influence of the molar excess of hydrogen peroxide on the conversion of NMM (1) and yield of NMMO (2)

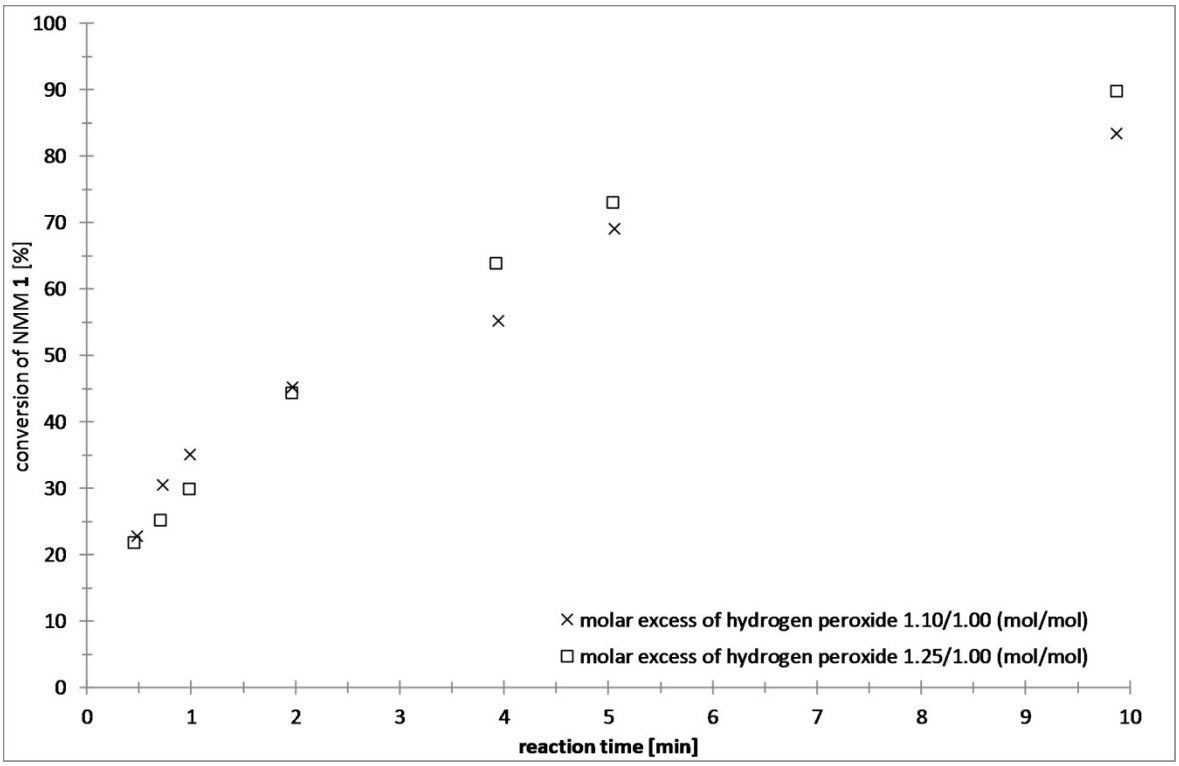

Fig. ESI-10 Influence of the molar excess of hydrogen peroxide on the conversion of NMM (1), at 50 °C, 17 bar(a), concentration (NMM (1)) 8.5 mol/L, flow rate (NMM (1)) 0.2 – 4.1 mL/min (**X**), flow rate (NMM (1)) 0.18 – 3.9 mL/min (□), flow rate (hydrogen peroxide) 0.18 – 3.68 mL/min (**X**), flow rate (hydrogen peroxide) 0.20 – 4.38 mL/min (□), concentration (hydrogen peroxide) 29 wt %, concentration of carbon dioxide 0.5 wt %, ratio of NMM (1)/H_2O_2 1/1.1 (**X**), ratio of NMM (1)/H_2O_2 1/1.25 (□), residence time 0.48 - 9.87 min (**X**), residence time 0.45 - 9.87 min (□), microreactor volume 3.75 mL.

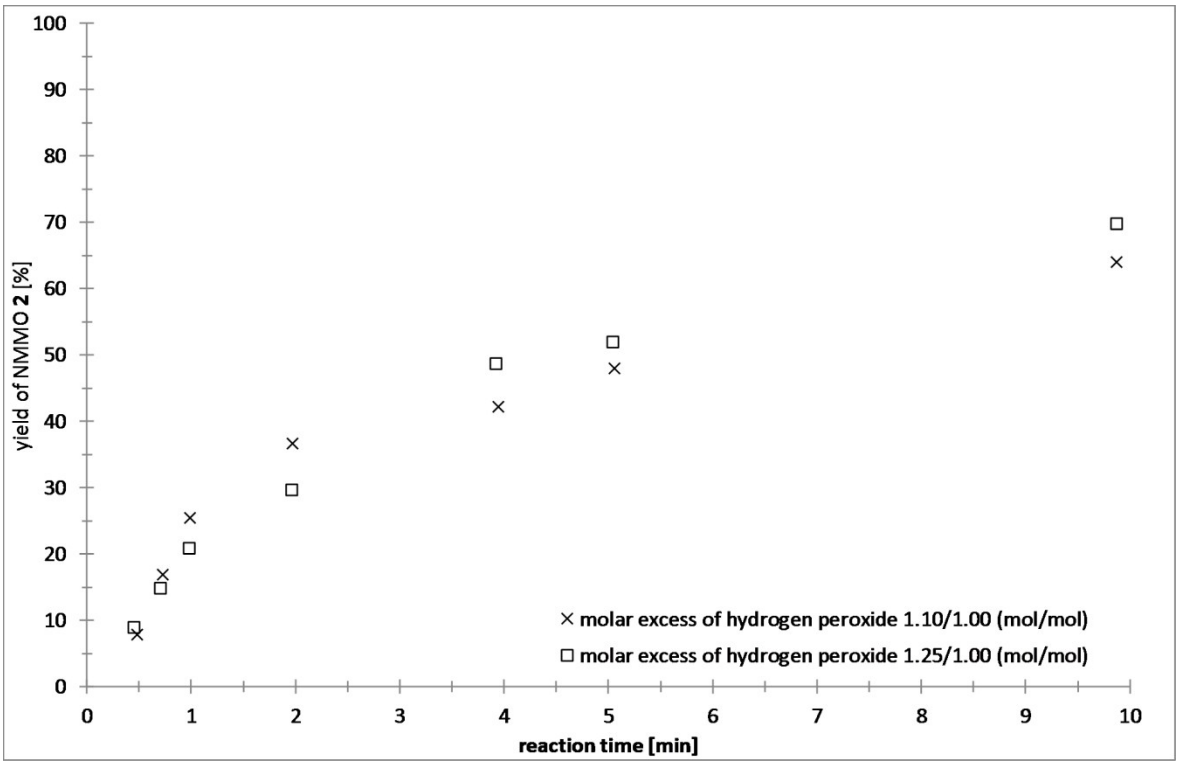

Fig. ESI-11 Influence of the molar excess of hydrogen peroxide on the yield of NMMO (2), at 50 °C, 17 bar(a), concentration (NMM (1)) 8.5 mol/L, flow rate (NMM (1)) 0.2 – 4.1 mL/min (**X**), flow rate (NMM (1)) 0.18 – 3.9 mL/min (□), flow rate (hydrogen peroxide) 0.18 – 3.68 mL/min (**X**), flow rate (hydrogen peroxide) 0.20 – 4.38 mL/min (□), concentration (hydrogen peroxide) 29 wt %, concentration of carbon dioxide 0.5 wt %, ratio of NMM (1)/H_2O_2 1/1.1 (**X**), ratio of NMM (1)/H_2O_2 1/1.25 (□), residence time 0.48 - 9.87 min (**X**), residence time 0.45 - 9.87 min (□), microreactor volume 3.75 mL.

8. Experimental data for the conversion of NMM (1) and yield of NMMO (2) without CO_2

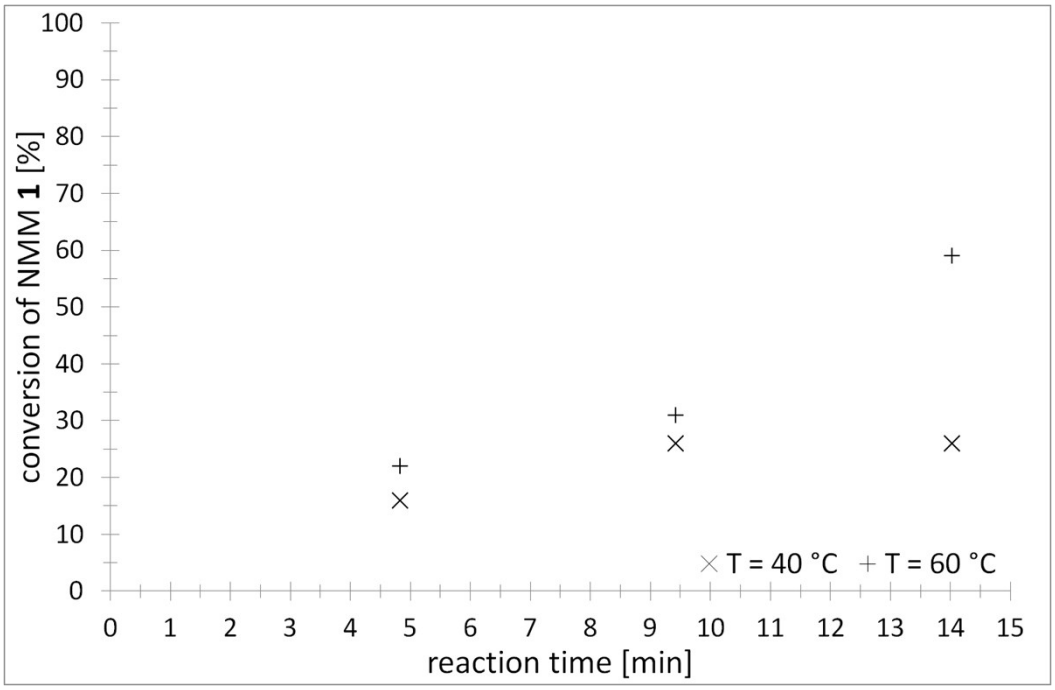

Fig. ESI-12 Conversion of NMM (1) without CO_2 at 40 and 60 °C, concentration (NMM (1)) 8.5 mol/L, flow rate (NMM (1)) 0.23 – 0.67 mL/min, flow rate (hydrogen peroxide) 0.20 – 0.58 mL/min, concentration (hydrogen peroxide) 30 wt %, ratio of NMM (1)/H_2O_2 1.0/1.0, residence time 5.08 - 14.80 min, microreactor volume 6.36 mL.

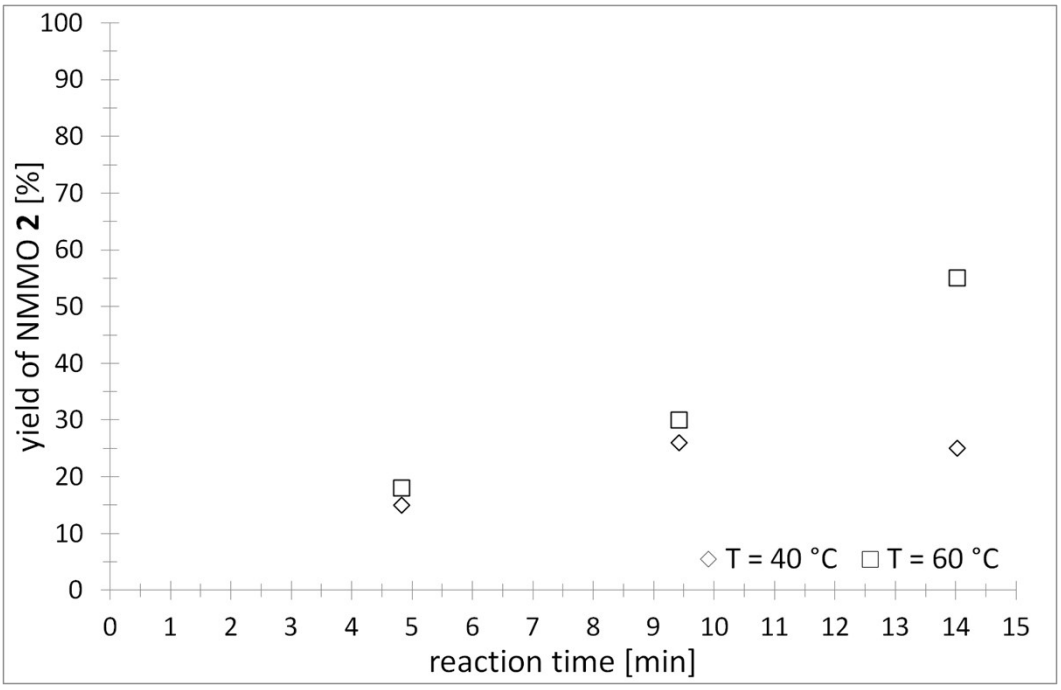

Fig. ESI-13 Yield of NMMO (2) without CO_2 at 40 and 60 °C, concentration (NMM (1)) 8.5 mol/L, flow rate (NMM (1)) 0.23 – 0.67 mL/min, flow rate (hydrogen peroxide) 0.20 – 0.58 mL/min, concentration (hydrogen peroxide) 30 wt %, ratio of NMM (1)/H_2O_2 1.0/1.0, residence time 5.08 - 14.80 min, microreactor volume 6.36 mL.

9. Corresponding selectivity of the experiments at 40 °C - 60 °C from Fig. 4

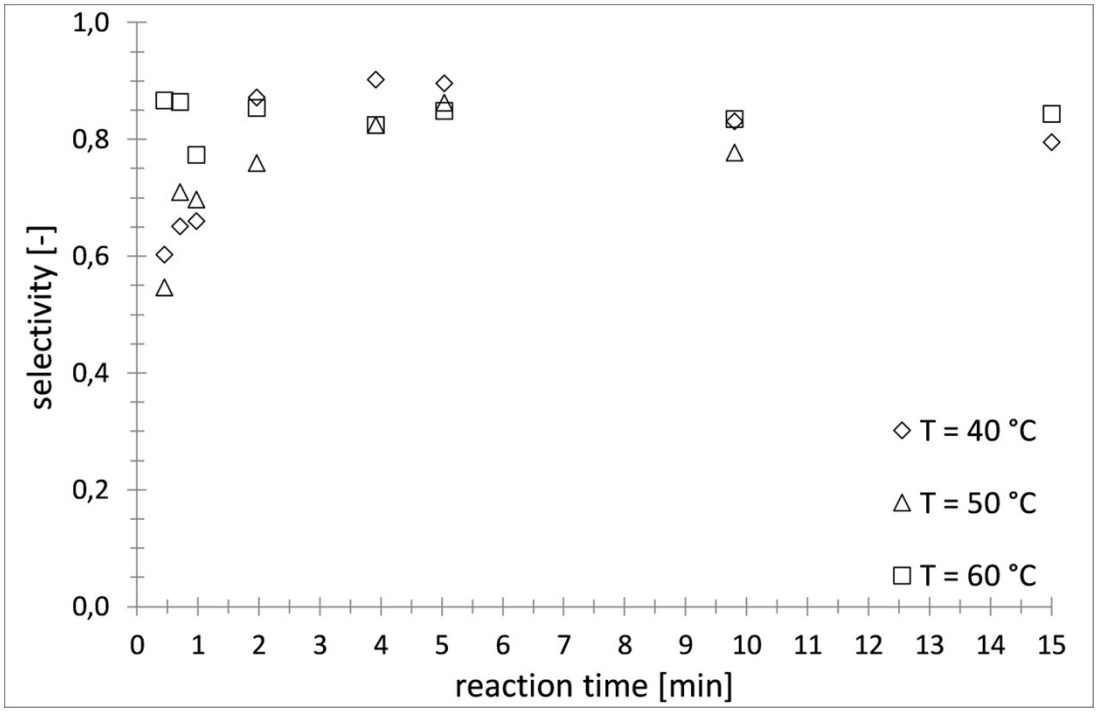

Fig. ESI-14 Selectivity at different reaction temperatures 40, 50 and 60 °C, concentration of hydrogen peroxide 29 wt %, 1 wt % of carbon dioxide, 17 bar(a), concentration (NMM (1)) 8.5 mol/L, flow rate (NMM (1)) 0.12 – 3.9 mL/min, flow rate (hydrogen peroxide) 0.13 – 4.38 mL/min, ratio of NMM (1)/H_2O_2 1/1.25, residence time 0.45 – 15.00 min, microreactor volume 3.75 mL.

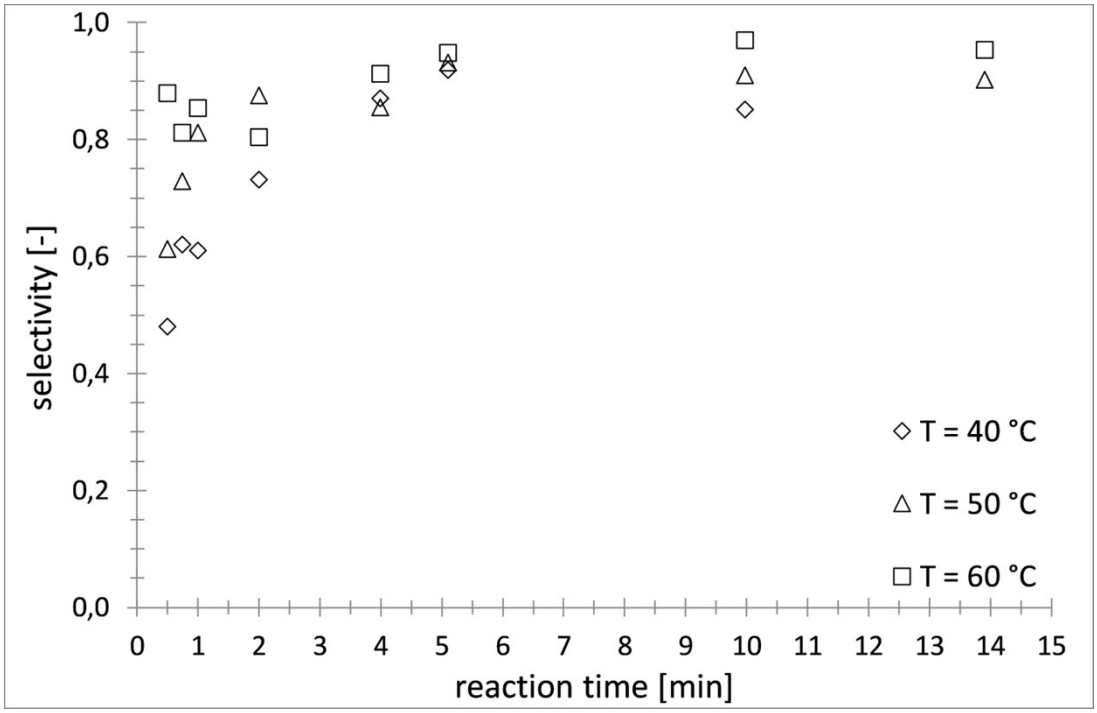

Fig. ESI-15 Selectivity at different reaction temperatures 40, 50 and 60 °C, concentration of hydrogen peroxide 50,75 wt %, 1 wt % of carbon dioxide, 17 bar(a), concentration (NMM (1)) 8.5 mol/L, flow rate (NMM (1)) 0.17 – 4.8 mL/min, flow rate (hydrogen peroxide) 0.10 – 2.71 mL/min, ratio of NMM (1)/H_2O_2 1/1.1, residence time 0.50 – 13.90 min, microreactor volume 3.75 mL.

10. Experimental Data for the conversion of NMM (1) at 70 °C

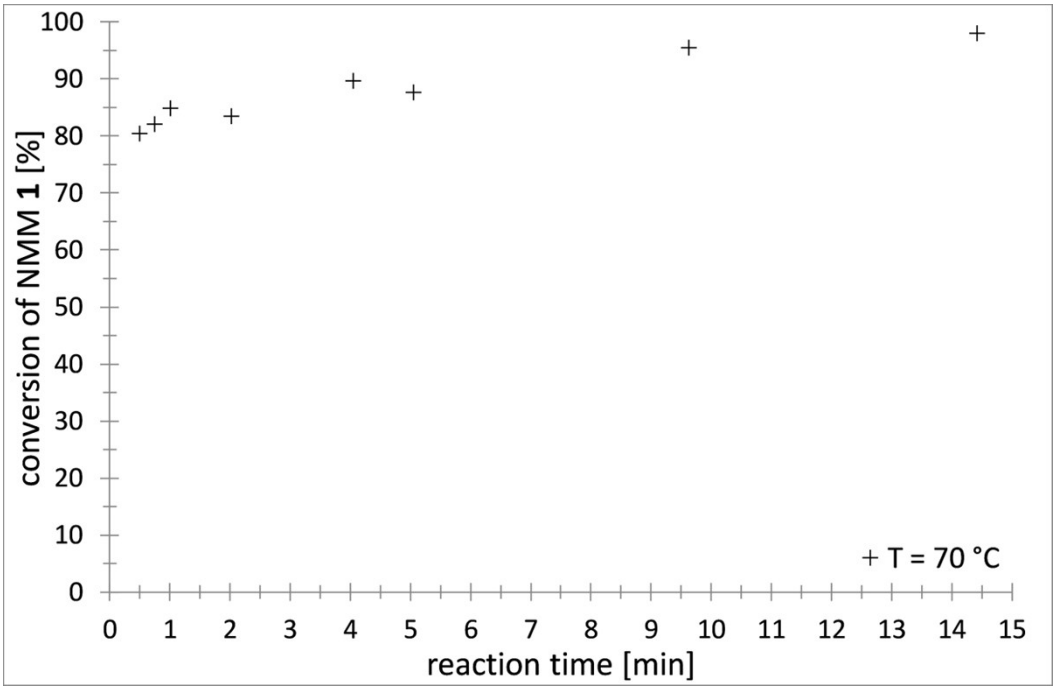

Fig. ESI-16 Conversion of NMM (1) at 70 °C, 17 bar(a), concentration (NMM (1)) 8.5 mol/L, flow rate (NMM (1)) 0.14 – 4.1 mL/min, flow rate (hydrogen peroxide) 0.12 – 3.50 mL/min, concentration (hydrogen peroxide) 33.6 wt %, ratio of NMM (1)/H_2O_2 1/1.1, residence time 0.49 - 14.42 min, microreactor volume 3.75 mL.

11. Experimental Data of the scale-up experiments

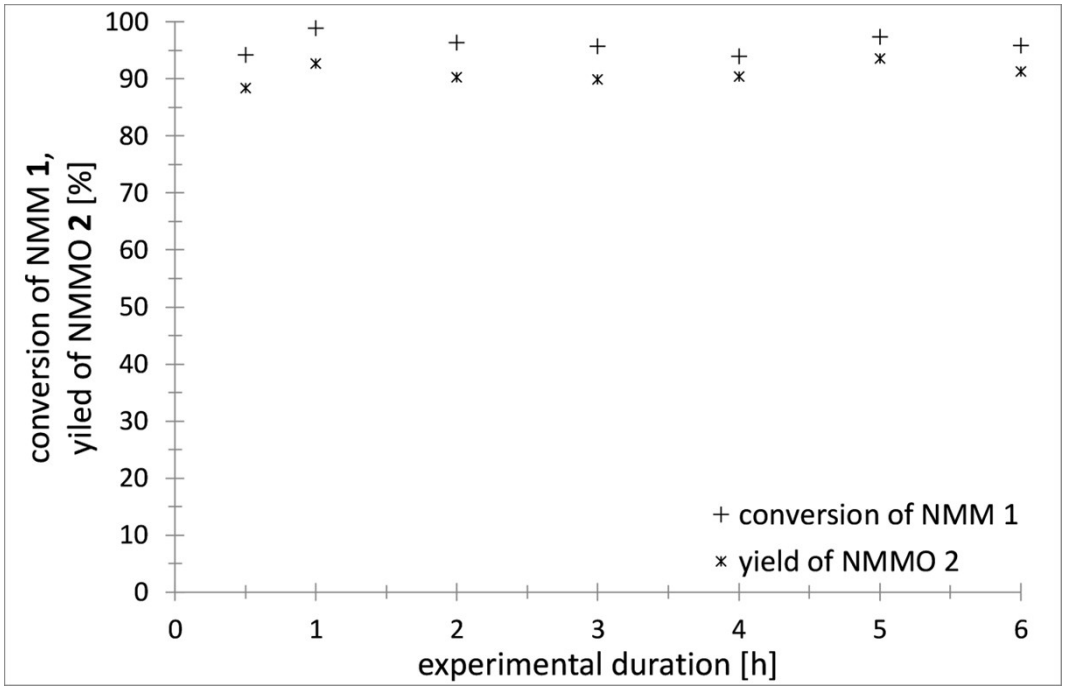

Fig. ESI-17 Conversion of NMM (1) and yield of NMMO (2) at 60 °C, 17 bar(a), concentration (NMM (1)) 8.5 mol/L, flow rate (NMM (1)) 1.20 mL/min, flow rate (hydrogen peroxide) 0.67 mL/min, concentration (hydrogen peroxide) 51 wt %, ratio of NMM (1)/H_2O_2 1/1.1, residence time 8.00 min, microreactor volume 14.96 mL. This leads to a scale-up factor of 4 for flow rate (NMM (1)), flow rate (hydrogen peroxide) and microreactor volume.

12. Kinetic model for the oxidation of NMM (1)

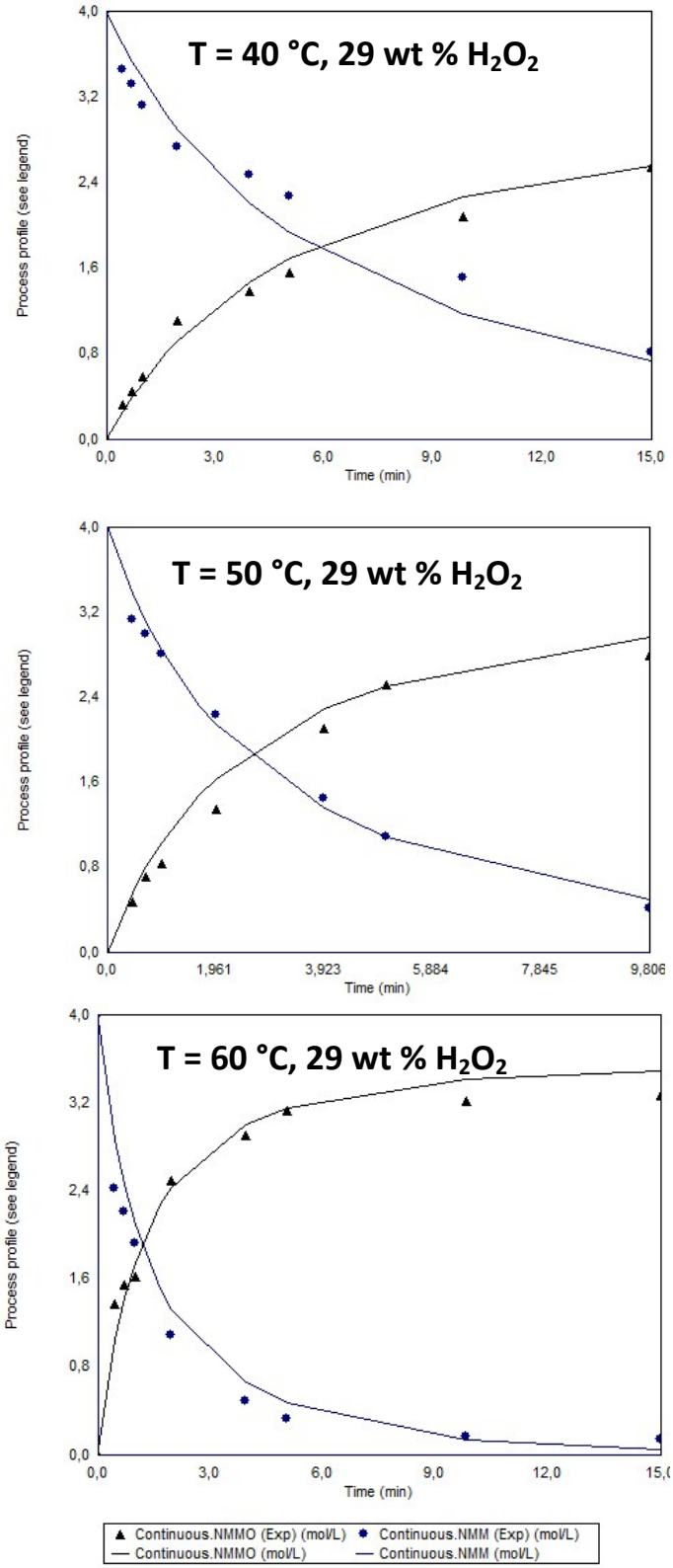

Fig. ESI-18 Kinetic model and experimental data for the conversion of NMM (1) and yield of NMMO (2) at different reaction temperatures 40, 50 and 60 °C ,concentration of hydrogen peroxide 29 wt %, 1 wt % of carbon dioxide, 17 bar(a), concentration (NMM (1)) 8.5 mol/L, flow rate (NMM (1)) 0.12 – 3.9 mL/min, flow rate (hydrogen peroxide) 0.13 – 4.38 mL/min, ratio of NMM (1)/H_2O_2 1/1.25, residence time 0.45 – 15.00 min, microreactor volume 3.75 mL.

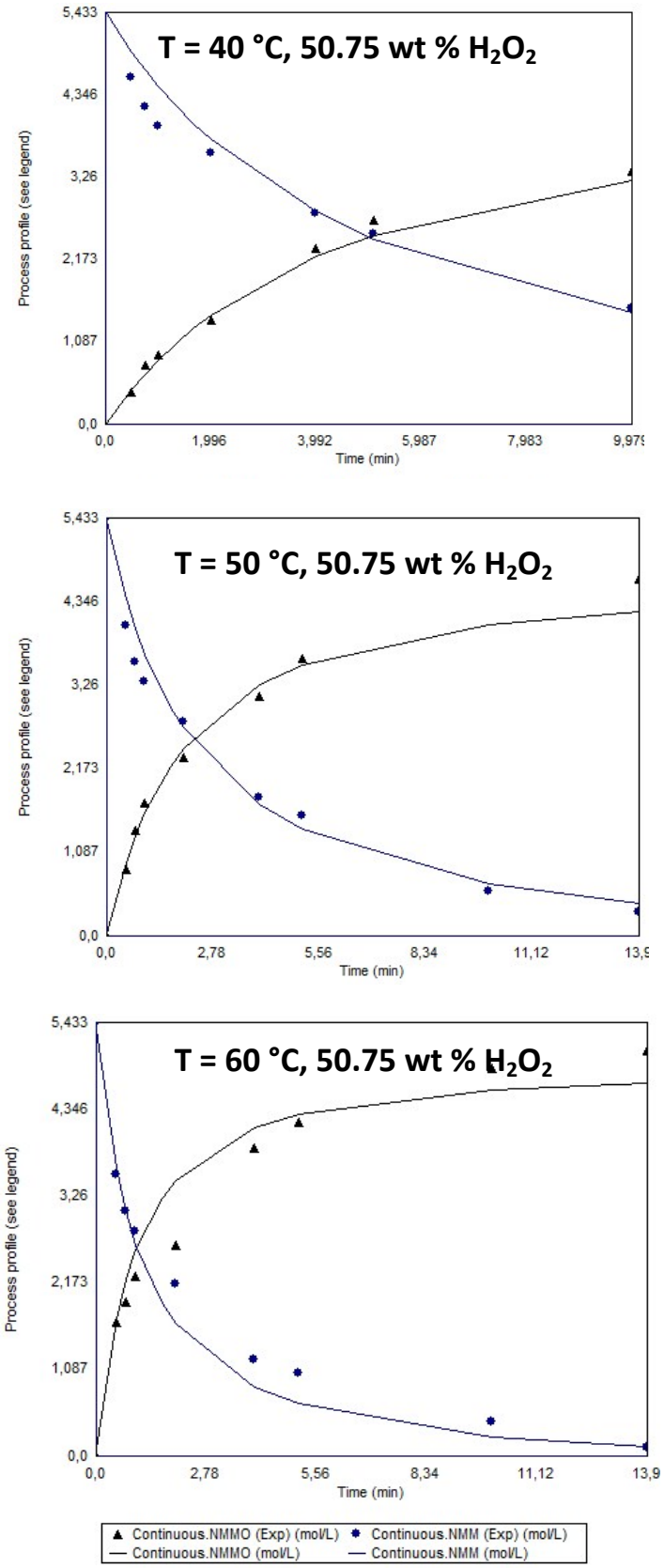

Fig. ESI-19 Kinetic model and experimental data for the conversion of NMM (1) and yield of NMMO (2) at different reaction temperatures 40, 50 and 60 °C, concentration of hydrogen peroxide 50.75 wt %, 1 wt % of carbon dioxide, 17 bar(a), concentration (NMM (1)) 8.5 mol/L, flow rate (NMM (1)) 0.17 – 4.8 mL/min, flow rate (hydrogen peroxide) 0.10 – 2.71 mL/min, ratio of NMM (1)/H_2O_2 1/1.1, residence time 0.50 – 13.90 min, microreactor volume 3.75 mL.

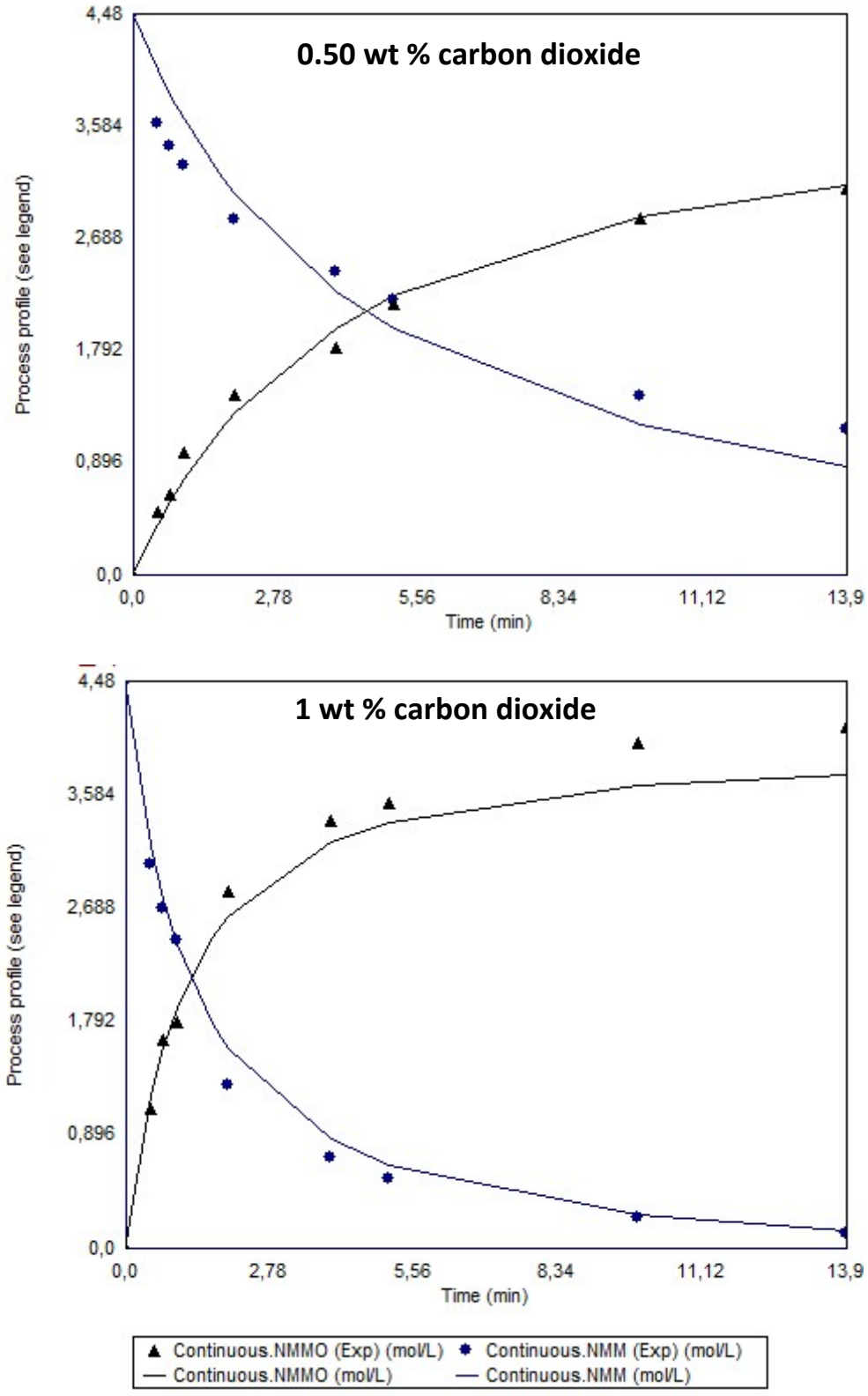

Fig. ESI-20 Kinetic model and experimental data for the conversion of NMM (1) and yield of NMMO (2) at 0.5 and 1 wt % of carbon dioxide, 50 °C, 17 bar(a), concentration (NMM (1)) 8.5 mol/L, flow rate (NMM (1)) 0.14 – 4.1 mL/min, flow rate (hydrogen peroxide) 0.13 – 3.68 mL/min, concentration (hydrogen peroxide) 29 wt %, ratio of NMM (1)/H_2O_2 1/1.1, residence time 0.48 – 13.90 min, microreactor volume 3.75 mL.

13. Calculation of the temperature profile for the oxidation of NMM (1)

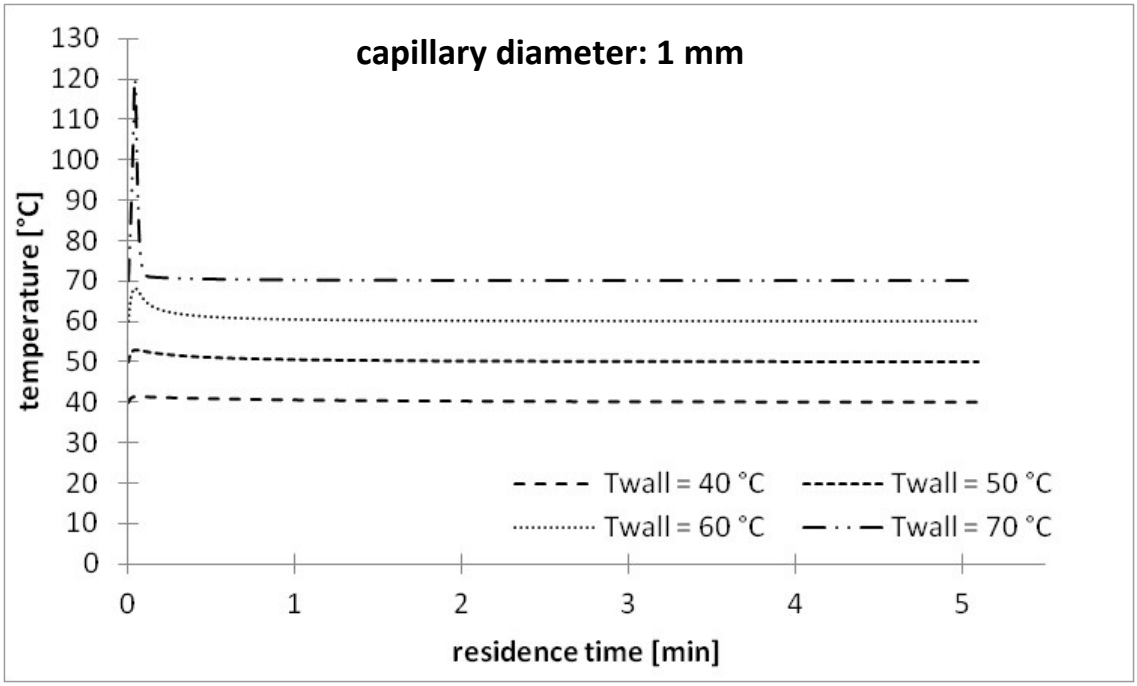

Fig. ESI-21 Simulation of the temperature in the microreactor channel (internal diameter: 1 mm) for a wall temperature of 40, 50, 60 and 70 °C.

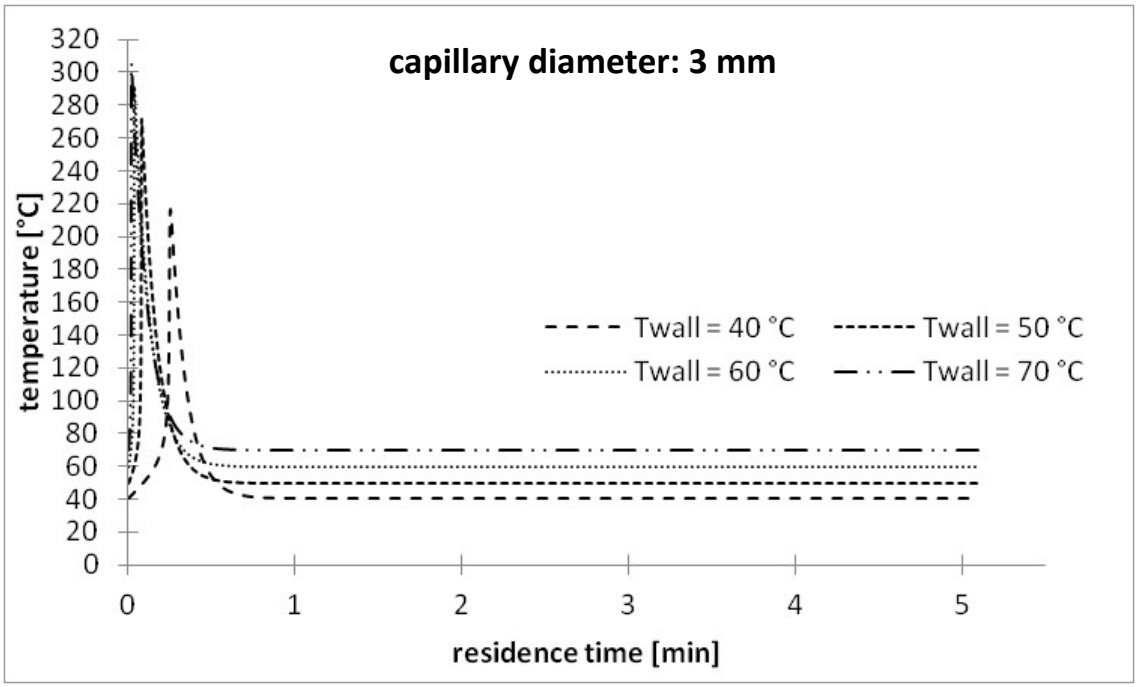

Fig. ESI-22 Simulation of the temperature in the microreactor channel (internal diameter: 3 mm) for a wall temperature of 40, 50, 60 and 70 °C.