Electronic Supplementary Information

Process intensification of ozonolysis reactions using dedicated microstructured reactors

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1 Table of Contents

2 General Information

2.1 Materials and Methods

Solvents and chemicals were obtained from commercial suppliers and were used without any further purification unless otherwise noted. Purity is provided in brackets. Thioanisole (≥99%), diphenylsulfide (98%), cyclohexene (≥99.0%), 2-phenylpropene (99%), *p*-chlorostyrene (97%), *p*-methoxystyrene (97%) and sodium metabisulfite (≥99%) were purchased from Sigma-Aldrich. Methanol and water (HPLC grade) were obtained from VWR. Tri-*n*-butylphosphine (95%) was purchased from Acros Organics.

2.2 Ozone Generator

For ozone generation the Ozone Module from ThalesNano Inc. (Budapest, Hungary) was used. The oxygen gas stream (Messer Gas, 5.0 purity) was fed into the ozone generator. The flow rate of gas is precisely controlled through a built-in mass flow controller. The ozone content generated in oxygen was measured within the Ozone Module. The maximum absolute outlet pressure is 2.5 bar absolute. An ozone content between 8.5 – 18.5% O_3 in O_2 was obtained. The ozone concentration is dependent on the flow rate. The correlation of the flow rate and the ozone content is shown below in Fig. S1. The ozone module has a built-in ozone sensor which detects ozone molecules based on absorption of 254 nm UV light (mercury lamp) due to an internal electronic resonance of the O_3 molecule. The ozone concentration calculation is based on the Beer- Lambert equation.

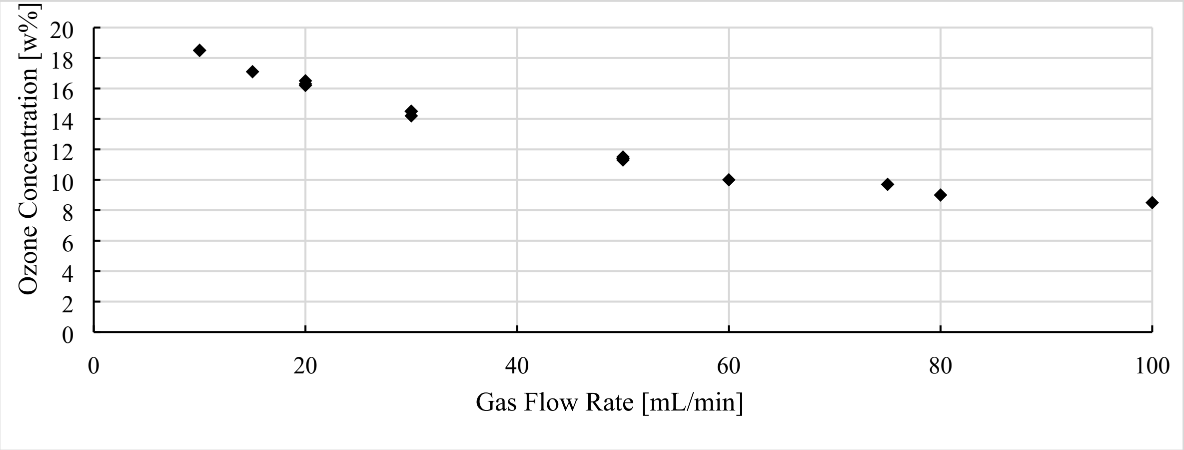

Fig. S1: Dependency of the delivered ozone concentration on the gas flow rate set on the ozone module.

2.3 High Field NMR

NMR spectra were recorded on a Bruker 300 MHz instrument. ^1H and ^{13}C spectra were recorded at 300 MHz and 75 MHz respectively, with a chemical shift relative to TMS expressed in parts per million (ppm). The samples were prepared in $CDCl_3$. The letters s, d, t and m are used to indicate singlet, doublet, triplet and multiplet respectively.

2.4 GC-FID Analysis

GC-FID analysis was performed on a Shimadzu GC FID 230 with a flame ionization detector, using a RTX-5MS column (30 m × 0.25 mm ID × 0.25 µm) and helium as carrier gas (40 cm sec-1 linear velocity). The injector temperature was set to 280 °C. After 1 min at 50 °C, the temperature was increased by 25 °C/min to 300 °C and kept constant at 300 °C for 4 min. The detector gases used for flame ionization were hydrogen and synthetic air (5.0 quality).

2.5 GC-MS Analysis

GC-MS was performed using a Shimadzu GCMS-QP2010 SE, using an Rtx-5MS column (30 m × 0.25 mm × 0.25 µm) and helium as carrier gas with a linear velocity of 40 cm/sec. The injector temperature was set to 280 °C. After 1 min at 50 °C, the oven temperature was increased by 25 °C/min to 300 °C and then kept at 300 °C for 3 min. The mass detector was a quadrupole with pre rods and electron impact ionization. The following settings were used in the detector: ion source temperature 200 °C, interface temperature 310 °C, solvent cut time 2 min 30 sec, acquisition mode scan, mass range m/z = 50 till m/z = 400.

2.6 Reaction Mechanism of the Ozonolysis of Cyclohexene

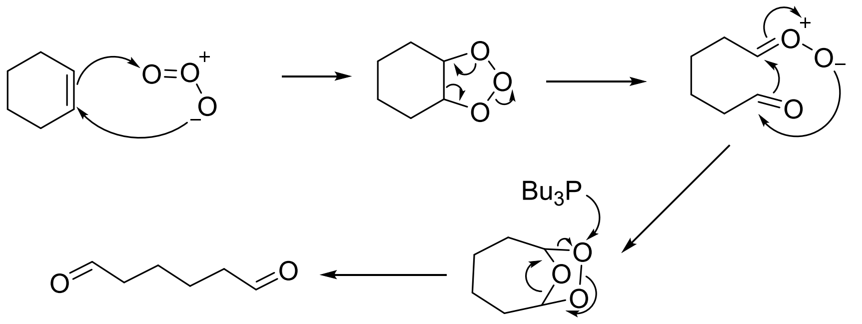

Fig. S2: Reaction mechanism of the ozonolysis of cyclohexene in dichloromethane based on using 1 equivalent of phosphine.

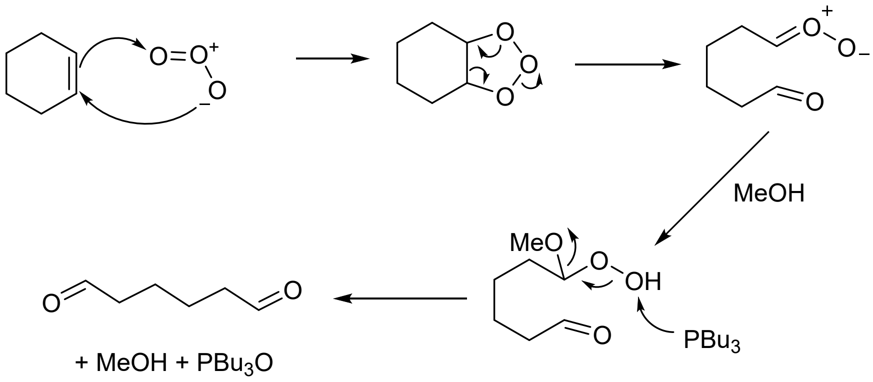

Fig. S3: Reaction mechanism of the ozonolysis of cyclohexene in methanol based on using 1 equivalent of phosphine

3 General Flow Configuration

In the flow setup (Fig. S4), standard PFA tubing (0.8 mm or 1.6 mm i.d.), PTFE or PEEK fittings and T-pieces were used. For pumping reagent solutions, Syrris Asia pumps equipped with 1 and 0.5 mL syringes were used. All the pumps were used with check valves (Upchurch, CV-3321) and internal or external pressure sensors. The pressure limit of the pumps was set to 20 bar. At that point the pumps would turn off automatically for safety reasons. Prior to using the pumping systems, they were calibrated by pumping for a specified time and checking the mass balance. All pumps were found to be accurate within ± 2%.

The ozonolysis reaction was performed in a Modular MicroReaction System (MMRS), manufactured by Ehrfeld Mikrotechnik (Wendelsheim, Germany). For the in- and outlets 1/16” input connectors (0711-2-00224-F) were used. A Lonza FlowPlate Lab (1701-3-0004-F) equipped with a LL design Process Plate (1701-4682-HC, LL mixer, nominal width 0.2 mm, Hastelloy C22) was used, and the temperature controlled by a thermostat (Huber, Ministat 240). The gas stream was introduced at port 1 and the substrate stream entered at port 2. The reaction mixture left the reactor at port 7. The introduction of the quench solution was performed in a T-piece, except for a small number of experiments, when ports 3, 4 or 5 of the process plate were used to achieve shorter residence times. The outlet of the reactor was connected to a sealed Duran bottle, which was flushed with N_2 and connected by a tubing to an exhaust line.

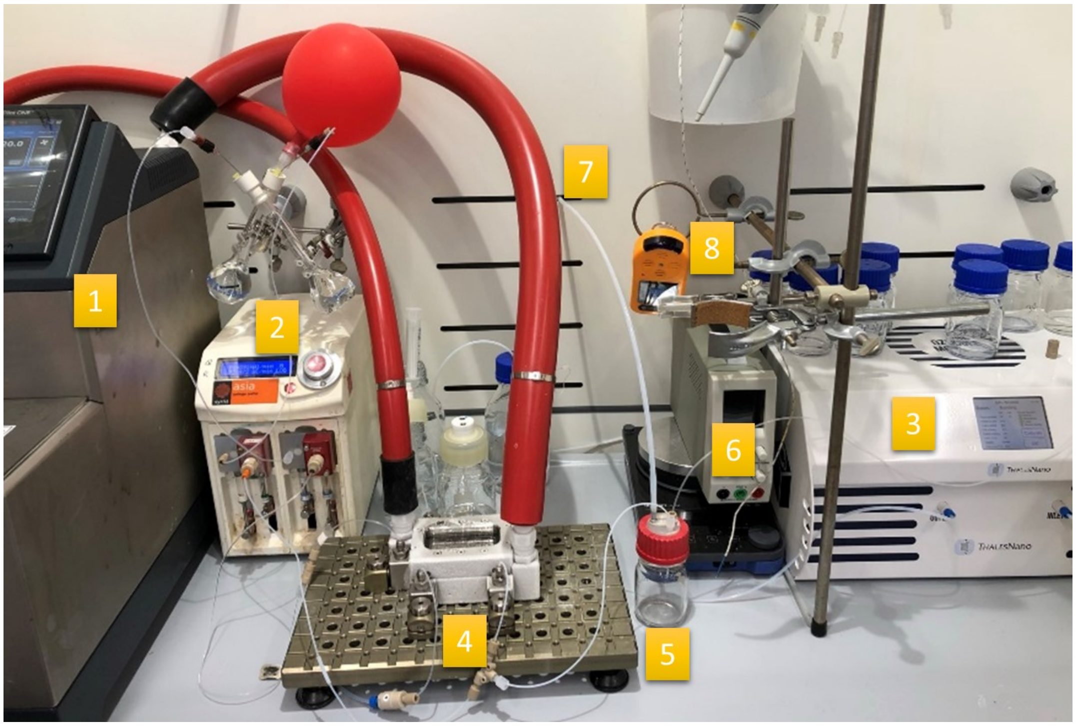

Fig. S4: Setup used for the ozonolysis reactions. 1: Thermostat, 2: SyrrisAsia pump, 3: ThalesNano Ozone Module, 4: Modular MicroReaction System, 5: Collection Flask, 6: N_2 Line, 7: Exhaust Line, 8: Ozone Sensor

4 General Procedures

Caution note: ozone is extremely toxic and can react rapidly with oxidizable substances. Ozone can also react with certain compounds to form explosive and shock-sensitive materials.

All feed solutions were prepared in volumetric flasks. *Example substrate feed preparation:* thioanisole (**14**) (6.25 g, 50.3 mmol) was dissolved in MeOH (250 mL, 0.201 M **14**). *Example quench feed preparation:* $Na_2S_2O_5$ (9.77 g, 51.4 mmol) was dissolved in MeOH (20 mL) and water (215 mL). After mixing, the flasks were sealed and the feed solution was sucked out by a needle through tubing directly into the pump.

The reaction outlet was collected in a Duran bottle, which was also flushed with N_2. The reaction outlet for each set of conditions was collected for 10 minutes (unless otherwise stated).

For GC analysis 50 µL reaction mixture were diluted in 1 mL methanol and injected on the GC. NMR samples were prepared in $CDCl_3$. Compound **15** was identified by GC-FID by comparing against a reference sample. The remaining compounds were identified by GC-MS using their molecular weights.

Some further experiments were performed for the thioanisole oxidation, shown in Table S1. In entry 1 a 10 mL residence coil was used after the reactor plate, which was identified as being unnecessary. A control experiment was performed in entry 2 by using pure oxygen with 0.1% ozone. This reaction gave almost no conversion, which demonstrated that O_2 was not performing the reaction. Entry 3 is showing one more concentration step while process intensification experiments.

Table S1: Additional ozonolysis conditions for the ozonolysis of thioanisole. [a]**Based on GC-FID area%** [b]**at T = 25 °C and P = 1.0 bar**

Entry	Substrate **14** conc. [mol/L]	Temperature [°C]	Gas Flow Rate [mL/min][b]	Equiv. Ozone	Reactor	Residence Time [s]	**14** Conversion [%][a]	**15** Yield [a%][a]
1	0.051	−20	30	3.06	LL + 10 mL coil	41.6	98.5	92.9
2	0.101	−20	30 (99.9% O_2)	0.01	LL	2.7	0.6	0.5
3	0.102	0	20	1.16	LL	3.9	99.5	98.1

The following isolation procedure was used for the long run experiments: the fractions of the long run experiment were combined and the organic phase was evaporated at 140 mbar and 40 °C. Afterwards, brine (6 mL) was added and the aqueous phase was extracted with dichloromethane (3 x 20 mL). The organic phases were combined, washed with water (20 mL) and brine (6 mL) and then dried over Na_2SO_4. The organic solvent was evaporated and dried at 2 mbar at 40 °C to afford methyl phenyl sulfoxide (**15**) (5.57 g) as colorless liquid in 89% isolated yield, with a GC purity of 99.5 a% (see Fig. S10). ^1H and ^{13}C NMR of the purified product can be seen in Fig. S11 & S12.

5 Calorimetric Experiments

Calorimetric experiments were performed in a modular continuous flow 3D printed isothermal heat flow calorimeter. Seebeck elements contacting the reactor plate are used for measuring the direct heat flux based on the thermoelectric Seebeck effect. The calorimeter is controlled by a microcontroller, which adjusted the heat flux of a Peltier element through a PID based control strategy. A detailed description and overview has been reported elsewhere.[S1]

Initially, a calibration with integrated heating foils was performed at a calorimeter set temperature of 25 °C. The thermostat was set to 28 °C. An exothermic reaction was simulated by applying a defined power input at prevailing conditions. The calibration graphs for the preheating and reaction zones can be found below. Ideal heat input of the heating foils was assumed and influences of the heating foils during the measurement were neglected.

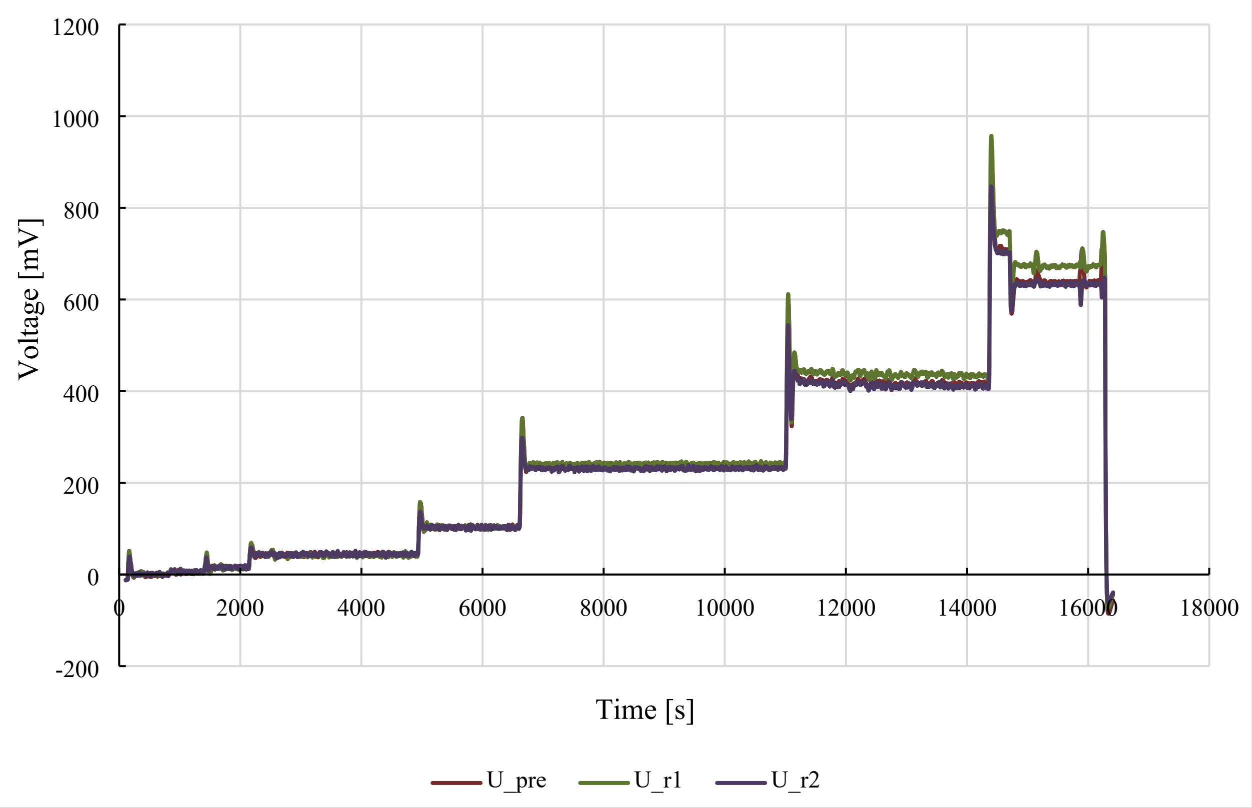

Fig. S5: Diagram of the measured voltage versus the time during the calibration of the calorimeter. brown: voltage measured in the pre-heating/cooling zone; green: voltage measured in the first reactor segment; purple: voltage measured in the second reactor segment.

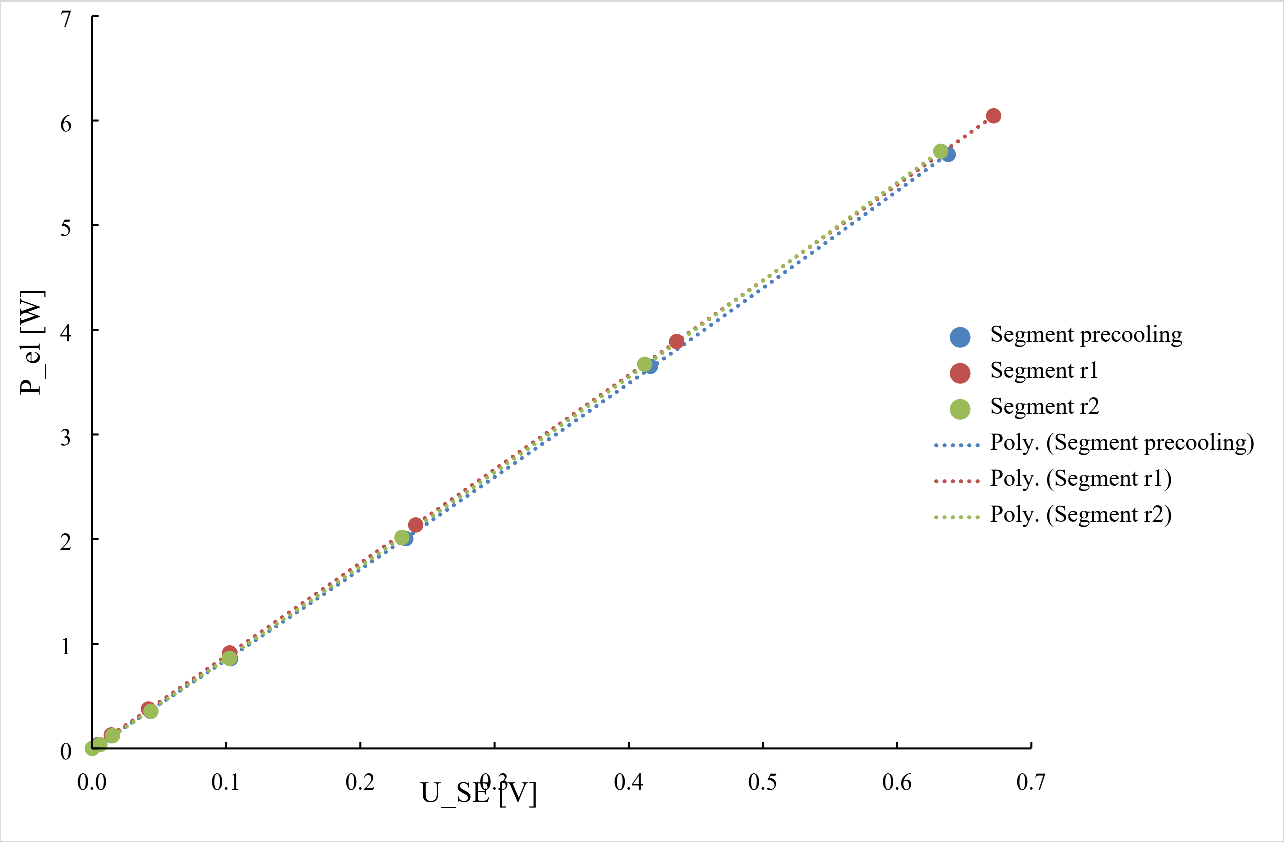

Fig. S6: Correlation of the measure voltage versus the applied power output at different calibration points.

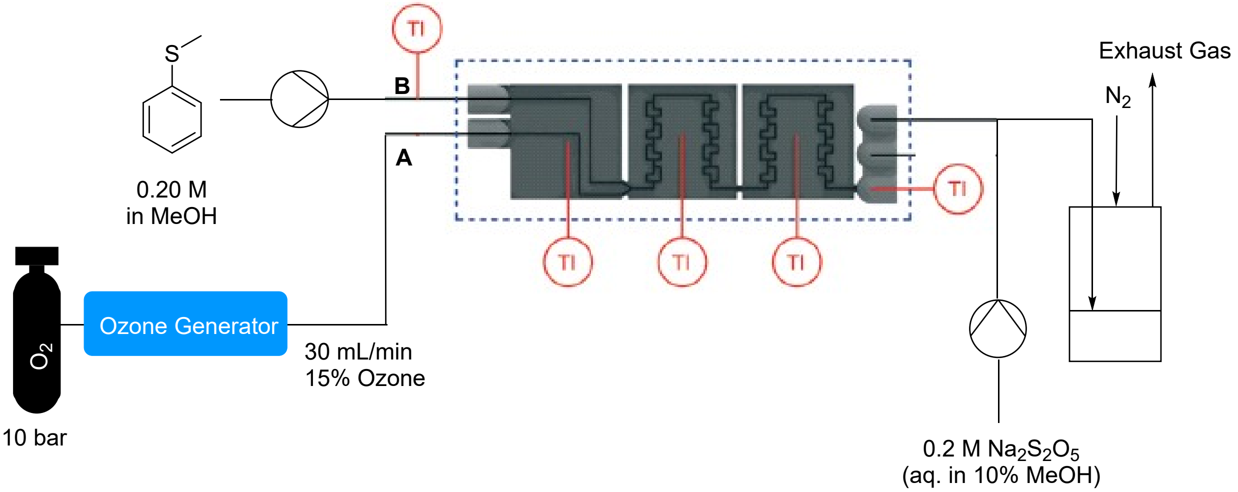

Fig. S7: Experimental setup of the flow calorimeter. TI stands for temperature indicator.

For the calorimetry experiments, the same pump units and ozone generation system were used as described above. The ozone feed was attached to inlet A and 0.202 M thioanisole (**14**) in methanol feed was introduced at inlet B. The temperature was controlled to 28 °C by a thermostat (Huber, Ministat 240). The set temperature in the PID control was 25 °C. For the addition of the quench solution after the calorimeter, a T-piece with a coil (0.1 mL, PFA tubing, 0.8 mm i.d.) was used. The quenching solution was an aqueous 0.200 M $Na_2S_2O_5$ solution, and the quench was performed at room temperature. In table S2 the respective flow rates and conditions can be found. One set of conditions was run until a stable status was reached. The measured temperatures and voltages are shown in Fig. S8 & S9.

Table S2: Conditions for the flow calorimetric experiments in the ozonolysis of thioanisole. [a]Reactor plate + connection tubing to the quench inlet.

Run	$V_{thioanisole}$ [mL/min]	V_{ozone} [mL/min]	Conc. O_3 [%]	Equiv. O_3	$T_{calorimeter}$ [°C]	P_{abs} [bar]	t_{res} [sec]	V_{quench} [mL/min]	Conversion [a%]
1	0.59	30	15.3	1.060	25	2.2	1.6[a]	0.58	97.0
2	0.44	30	15.3	1.393	25	2.1	1.6[a]	0.45	99.3

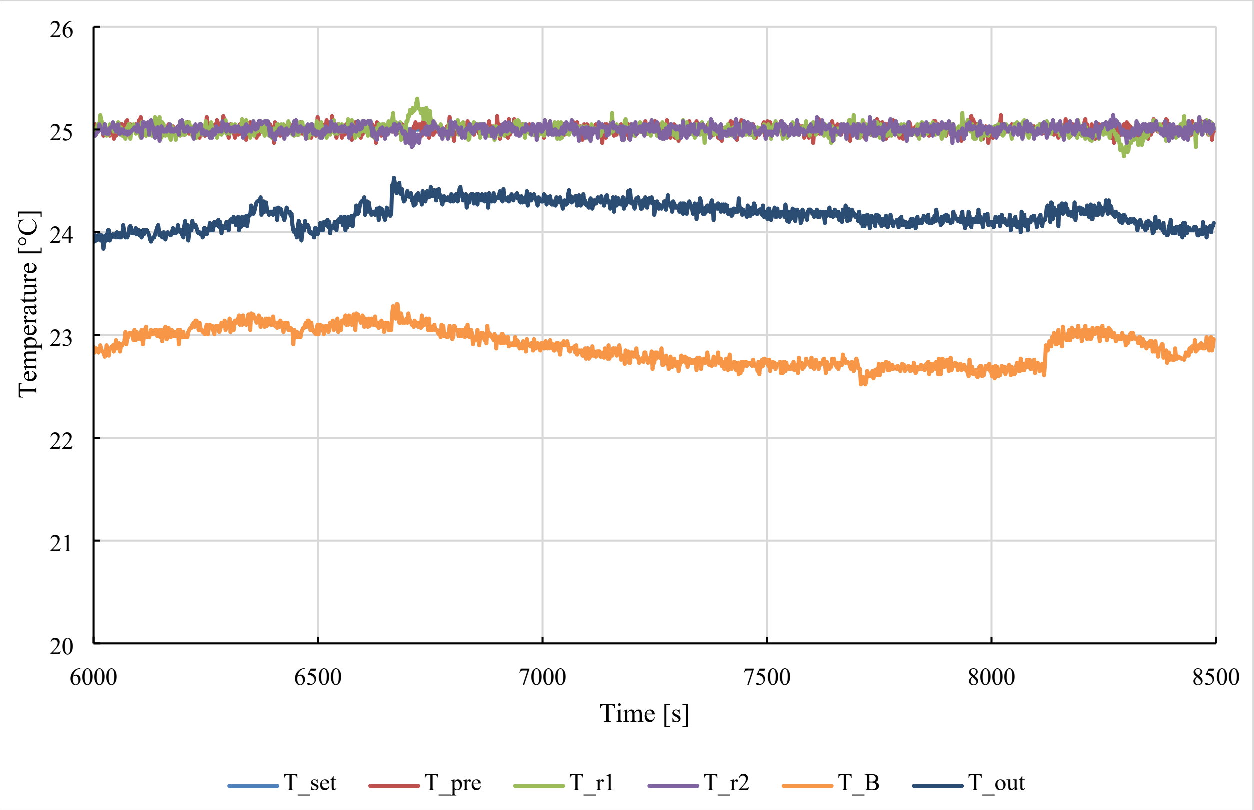

Fig. S8: Measured temperatures during the calorimetric flow experiments. T_{set} set temperature of the calorimeter, T_{pre} temperature in the preheating zone, T_{r1} temperature in the first reactor segment, T_{r2} temperature in the second reactor segment, T_B inlet temperature of the substrate feed, T_{out} outlet temperature.

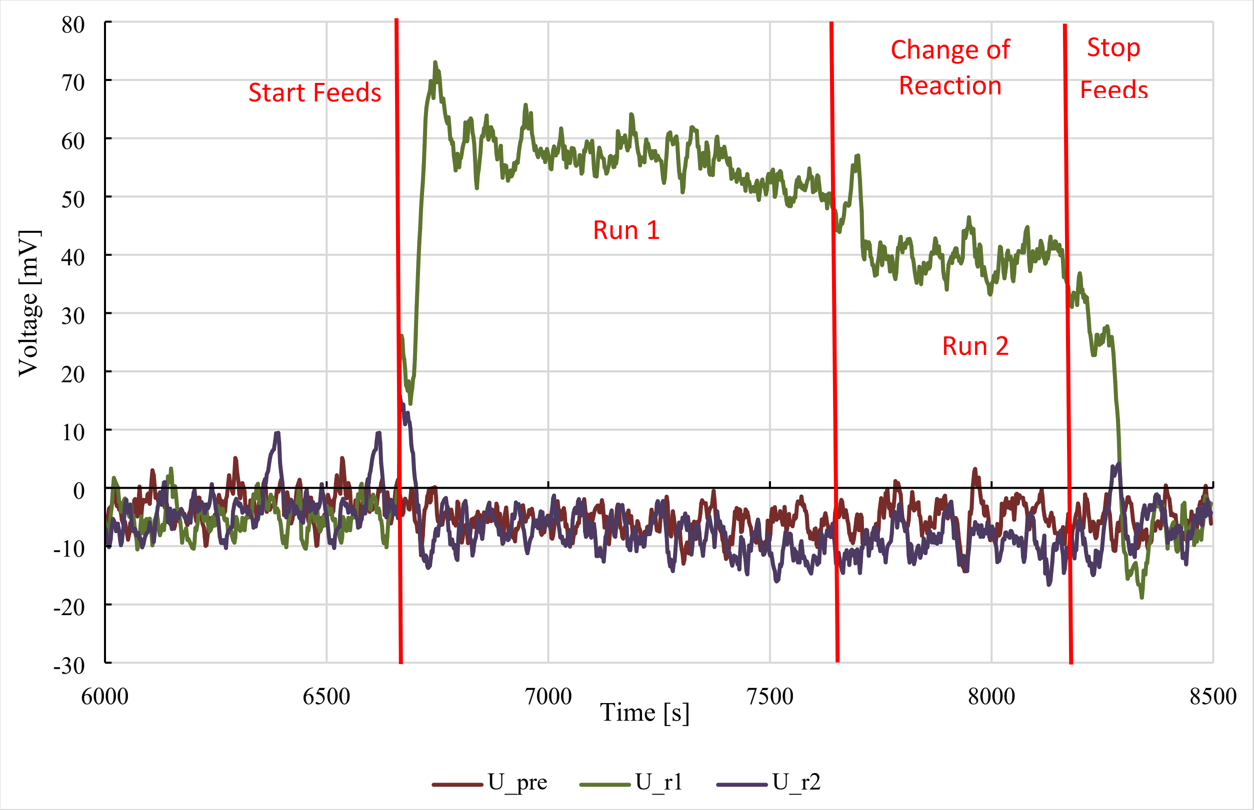

Fig. S9: Measured voltage during the calorimetric flow experiment. U_{pre} voltage in the preheating section, U_{r1} voltage in the first reactor segment, U_{r2} voltage in the second reactor segment. Start of the feeds at 6657 sec, change of the reaction conditions to run 2 at 7647 sec, stop of the feeds at 8213 sec.

6 GC-FID & NMR Spectra

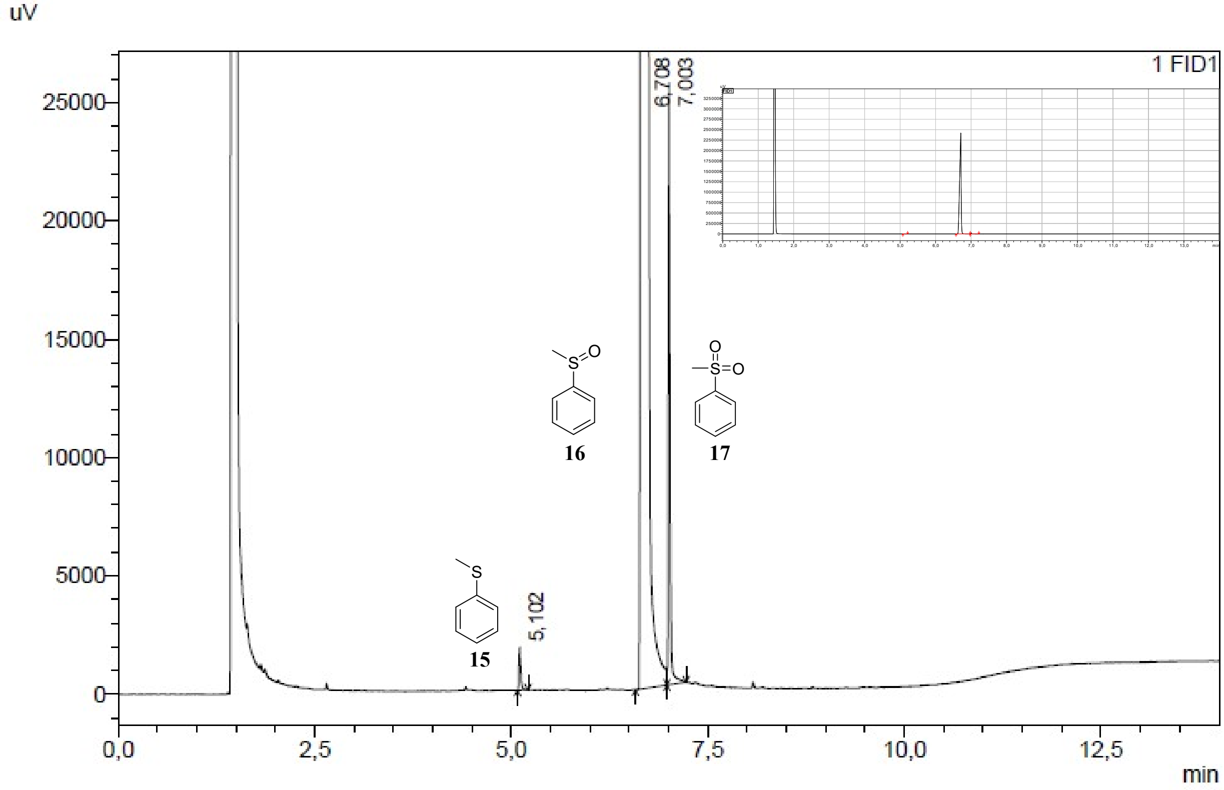

Fig. S10: GC-FID spectrum of the isolated product from the long run experiment for the ozonolysis of thioanisole in methanol.

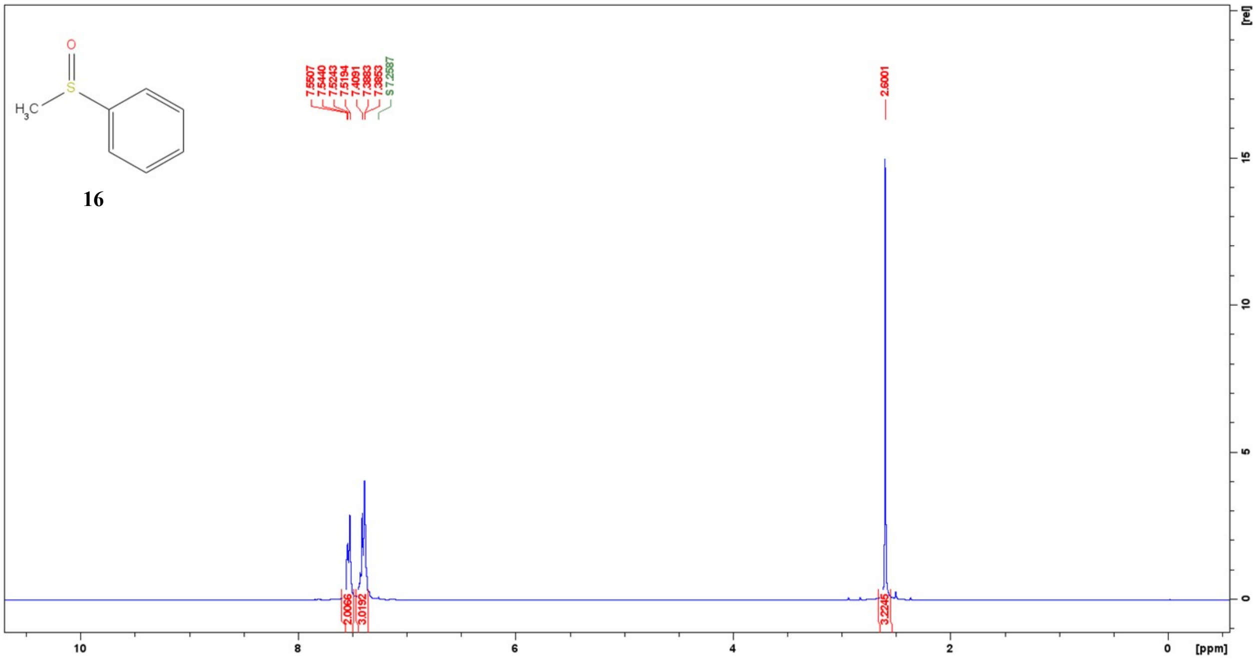

Fig. S11: ^{1}H-NMR spectrum of the isolated product from the long run experiment for the ozonolysis of thioanisole in $CDCl_3$.

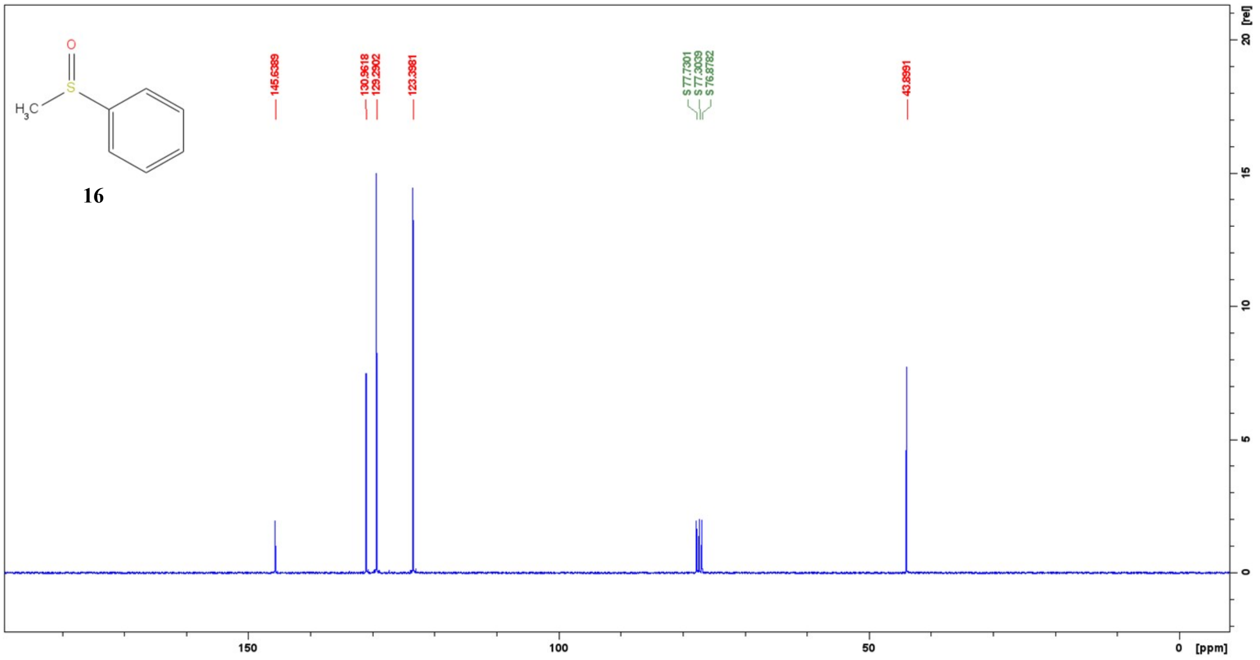

Fig. S12: ^{13}C-NMR spectrum of the isolated product from the long run experiment for the ozonolysis of thioanisole in $CDCl_3$.

7 References

S1 M. C. Maier, M. Leitner, C. O. Kappe, and H. Gruber-Woelfler, *React. Chem. Eng.*, 2020, **5**, 1410–1420.