

Supporting Information

Merging inline crystallization and pulsed flow operation to enable enantiospecific solid state photodecarbonylation

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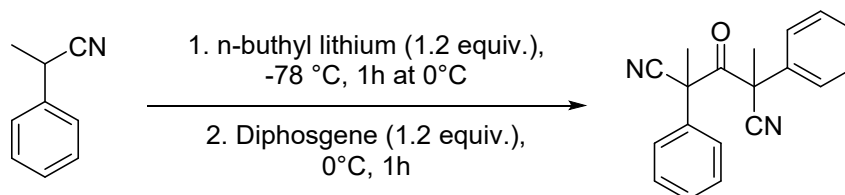
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General information

All reagents (α -methylbenzylcyanide, Butyl lithium, diphosgene etc.) were purchased from Sigma Aldrich and used as such. Absorbance measurements were recorded using the Thermo Scientific Genesys 180 UV-Vis spectrometer UV/VIS spectrometer. NMR spectra were measured with a Bruker Avance Nanobay III NMR spectrometer. The components were dissolved in deuterated chloroform and tetramethylsilane (TMS) as an internal standard. The HANU™ 2X 15 flow photoreactor and quartz glass were purchased from Creaflow. The pulsator was purchased from ProMinent (ProMinent gamma/L pump) with a maximum stroke volume of 0.4 mL (100%) and a maximum frequency of 3 Hz.

Synthesis of 2,4-dimethyl-3-oxo-2,4-diphenylpentanedinitrile (1)



A round bottom flask equipped with a magnetic stirring bar was flame-dried intensively. Directly after that, nitrogen flow is added to the flask to cool it down. After cooling down, a septum is placed on the flask and a nitrogen balloon. The startproduct is added to the flask (2.46 gram, 18.75 mmol) together with 200 mL of dry THF. This is bubbled with nitrogen for several minutes. A bath with ethylacetate and liquid nitrogen ($-78\text{ }^{\circ}\text{C}$) is made. N-BuLi is added (1.2 equiv) dropwise while stirring at $-78\text{ }^{\circ}\text{C}$. Afterwards, the solution is stirred for 1 h min at $0\text{ }^{\circ}\text{C}$ in an ice bath. Diphosgene (1.2 equiv) is added dropwise at $0\text{ }^{\circ}\text{C}$. The reaction was stirred at $0\text{ }^{\circ}\text{C}$ for 1 h. Water is added and this mixture is extracted 3 times with diethyl ether. The combined organic layer is washed with brine, dried over MgSO_4 and the solvent was evaporated under reduced pressure to obtain the crude yellowish solid product. The crude product was recrystallised in ether to obtain the pure white crystals of the enantiomers (yield: 62%).

¹H-NMR *d,l*-2,4-dimethyl-3-oxo-2,4-diphenylpentanedinitrile (CDCl₃, 400 MHz): δ 1.85 (6H, s, 2xCH₃), 7.40–7.54 (10H, m, 2xPh) ppm

¹³C-NMR *d,l*-2,4-dimethyl-3-oxo-2,4-diphenylpentanedinitrile (CDCl₃, 100.6 MHz): δ 27.9, 53.1, 118.4, 126.6, 129.3, 129.5, 134.0, 193.7 ppm

¹H-NMR *meso*-2,4-dimethyl-3-oxo-2,4-diphenylpentanedinitrile (CDCl₃, 400 MHz): δ 1.94 (6H, s, 2xCH₃), 7.22–7.34 (10H, m, 2xPh) ppm (not isolated)

Solution state photodecarbonylation

To assess racemization towards the *meso* compound when the reaction is conducted in the solution state, a test experiment was carried out. 700 mg of *d,l*-1 was dissolved in 20 mL of acetonitrile and irradiated for 1 hour at 254 nm, mirroring the concentration used in the solvent flow during flow experiments. Upon evaporation of the solvent and subsequent high vacuum treatment, an orange solid (instead of white) was obtained. Subsequently, ¹H-NMR analysis was performed, and the yield and product ratio were calculated based on NMR integration, as depicted in Figure 1. The yield was determined to be 53% after 1 hour of irradiation (calculated as $0.38+0.16/(0.38+0.16+0.47)$). The product ratio of *d,l*-2/*meso*-2 was found to be 2.4/1, indicating that the solution-state photodecarbonylation is not enantiospecific compared to performing the reaction in the solid state.

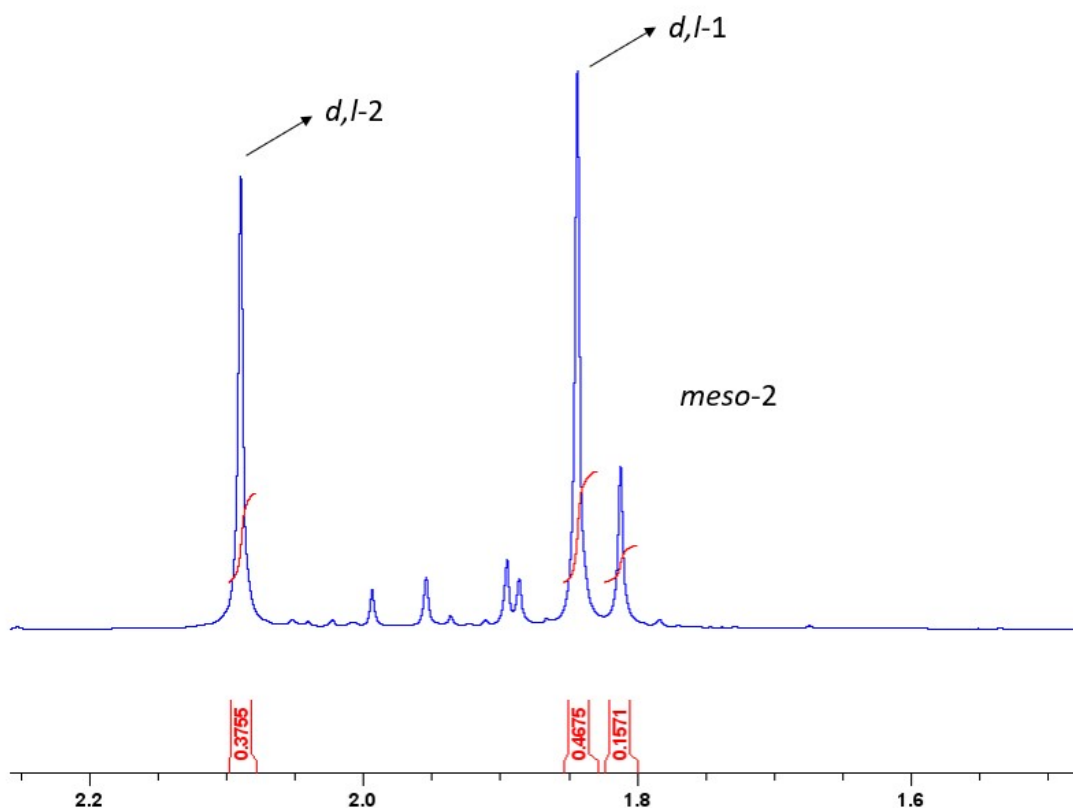


Figure 1. $^1\text{H-NMR}$ of the solution state photodecarbonylation of *d,l*-1.

Inline crystallisation

700 mg of *d,l*-1 was dissolved in 20 mL acetonitrile to obtain a substrate concentration of 35 g/L. Inline crystallisation was performed with a solvent flow rate of 0.135 mL/min using a syringe pump and a water flow rate of 2.37 mL/min using a Vapourtec SF-10 pump module according to the setup below. The PSD was measured with the Blaze 900 (Figure 2/3).

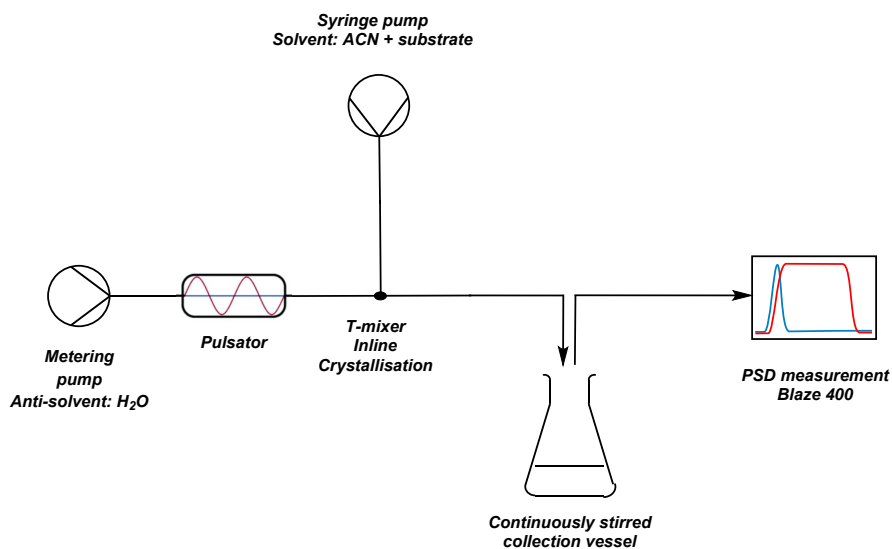


Figure 2. Experimental setup for particle size distribution measurement.

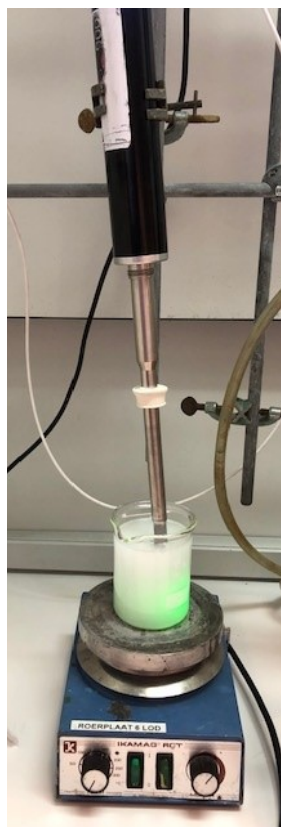


Figure 3. Visualisation of experimental setup for particle size distribution measurement.

Solid state photodecarbonylation in batch

80 mg of *d,l*-1 crystals are crushed between 2 microscopic slides and irradiated with the XX-15 UV device with monochromatic 254 nm lamps. Every 5 minutes, the crystals are recrushed to ensure sufficient refreshing of the top layer that is irradiated. Every 5 minutes, a sample was taken for ^1H -NMR analysis.

^1H -NMR *d,l*-2,3-Dimethyl-2,3-diphenylbutanedinitrile (CDCl_3 , 400 MHz): δ 2.10 (6H, s, 2xCH₃), 7.06–7.10 (4H, m, 2xPh), 7.19–7.33 (6H, m, 2xPh) ppm

^{13}C -NMR *d,l*-2,3-Dimethyl-2,3-diphenylbutanedinitrile (CDCl_3 , 100.6 MHz): δ 23.4, 50.8, 120.8, 127.8, 128.2, 129.1, 134.8 ppm

^1H -NMR *meso*-2,3-Dimethyl-2,3-diphenylbutanedinitrile (CDCl_3 , 400 MHz): δ 1.80 (6H, s, 2xCH₃), 7.06–7.10 (4H, m, 2xPh), 7.19–7.33 (6H, m, 2xPh) ppm

Solid-state photodecarbonylation in continuous flow

700 mg of *d,l*-1 was dissolved in 20 mL acetonitrile to obtain a substrate concentration of 35 g/L. Inline crystallisation was performed with a solvent flow rate of 0.135 mL/min using a

syringue pump and a water flow rate of 2.37 mL/min using a Vapourtec SF-10 pump module. The pulsator amplitude and frequency were set to respectively 100% (stroke volume = 0.4 mL) and 3 Hz. A T-mixer with inner diameter of 1.58 mm (1/8" tubing) was used. From the collection vessel, the slurry was pumped with a Vapourtec SF-10 pump module to the HANU™ 2X 15 reactor. The pulsator was set to 30% amplitude and maximum frequency (3 Hz). The reactor was irradiated with the monochromatic 254 nm XX-15 UV lamp. During all experiments, the reaction temperature can be adjusted/controlled using a thermal oil circuit, via the built-in heat exchanger of the HANU™ 2X 15 reactor and an external Huber thermostat. All experiments were performed at a constant temperature of 25 °C.

Experiments conducted utilizing a BPR utilize the BPR setting of an SF-10 pump (Vapourtec). In this configuration, the peristaltic rotor executes a reverse motion, generating an adjustable counterpressure against the incoming flow. Since the system operates on the principle of a peristaltic pump, it is capable of handling slurries.

Throughout all experiments, a closed setup was employed to prevent any light from scattering towards the operator. However, internal scattering and subsequent absorption of part of the UV-light by the reactor walls is possible. This effect could not be quantified.

For every experiment, the flow rate was programmed according to the desired residence time. After respecting three residence times to obtain steady state, two samples were collected of both 6 mL for further analysis. The average yield was calculated and reported. The same procedure was performed for different residence times to obtain the data plots of yield in function of time.

Determination of the residence time distribution

Residence time distribution experiments were performed in a slightly modified reactor set-up (Figure 3). Thymol blue was used as a tracer in ethanol ($\pm 10^{-4}$ M concentration). A switch was used to change the tracer flow from waste to the system. The tracer was added to the system via a Y-piece mixer (check valve) between the pulsator and the reactor, in a carrier stream of ethanol. An in-line UV-VIS flow cell was installed between the HANU™ 2X 15 and the pulsation dampener, and connected to an Ocean Optics DH-2000-BAL light source and an Ocean Optics HDX miniature spectrometer. The collection of data (absorbance at 593 nm) was started when the tracer flow was switched from waste to the system. Due to physical

reasons, a step injection was used which was transformed into the typical RTD curves (Figure 4).

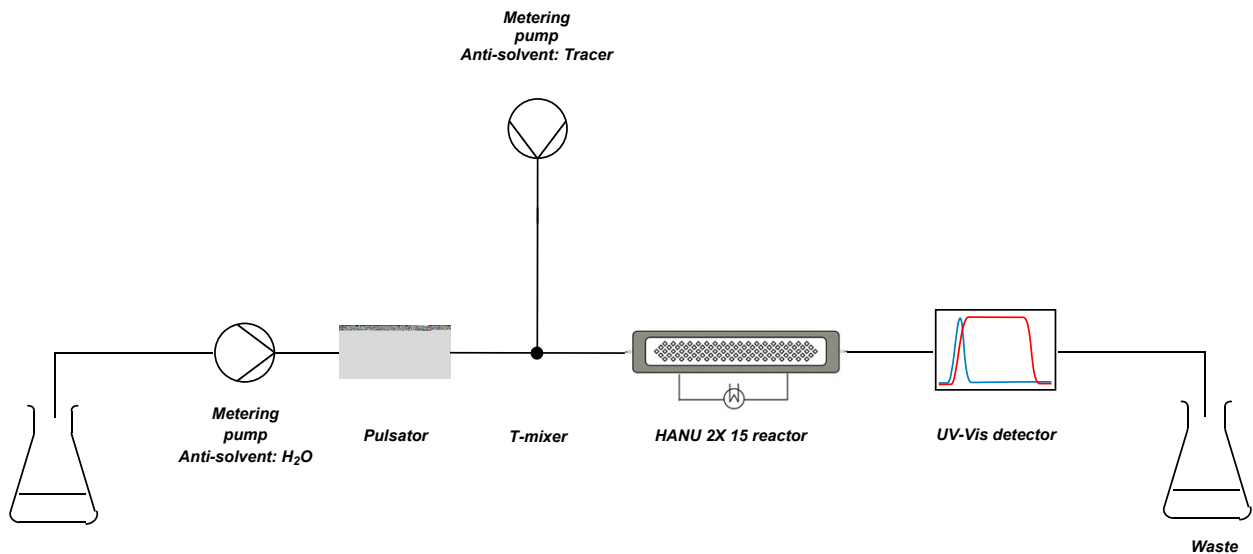


Figure 4. Experimental setup of the tracer experiment for residence time distribution study.

Fluid mechanics

The plug-flow behaviour of the reactor can be quantified using the Bodenstein number (Bo). This dimensionless number is the ratio of the rate of transport by convection to the rate of transport by diffusion and dispersion. A Bodenstein number of 0 corresponds to full back mixing (ideal for a CSTR), while $Bo = \infty$ corresponds to no back mixing and an ideal plug flow, desired in a flow channel. It can be calculated from the average residence time (\bar{t}) and variance (σ^2) obtained from the RTD according to the equation below.

$$\frac{\sigma^2}{\bar{t}^2} = \sigma_{\theta}^2 = \frac{2}{Bo} + \frac{8}{Bo^2} \Rightarrow Bo = \frac{1 + \sqrt{1 + 8 * \sigma_{\theta}^2}}{\sigma_{\theta}^2}$$

Equation 1. Calculation of the Bodenstein number.

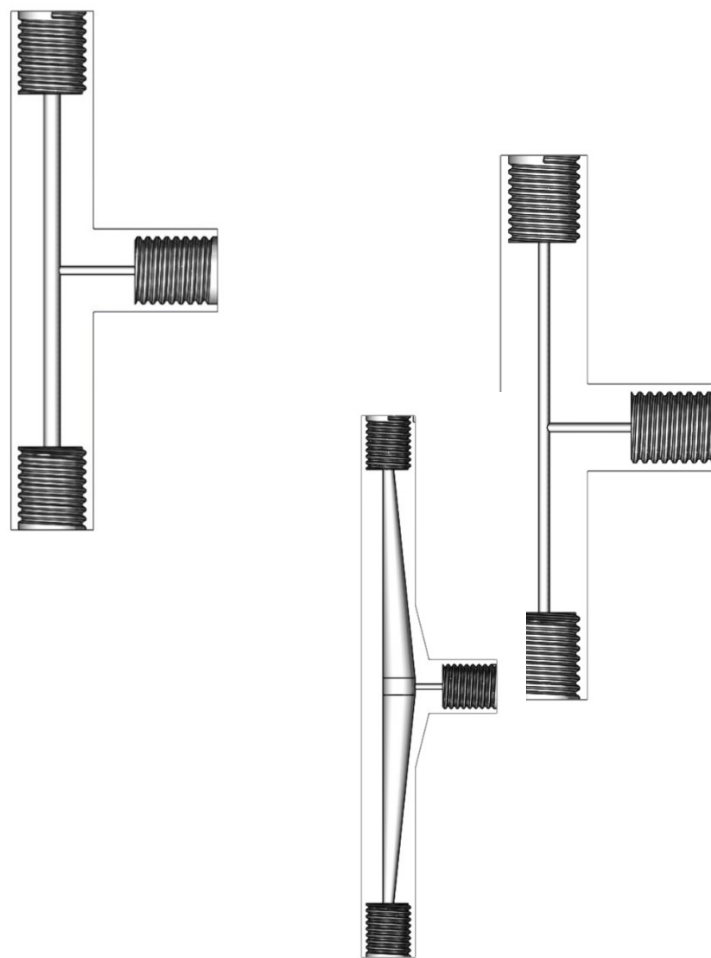
Particle size distribution

A suspension of +/- 200 mL is continuously stirred and measured with the Blaze 900. The Blaze Metrics 900, designed for laboratory and pilot scale reactor use, is an analytical system used for research, development and process optimization. With this system (among other things) the particle size of solids in a mixture can be determined. During the analysis, the Blaze probe is placed in the mixture containing solids. The probe is controlled using the

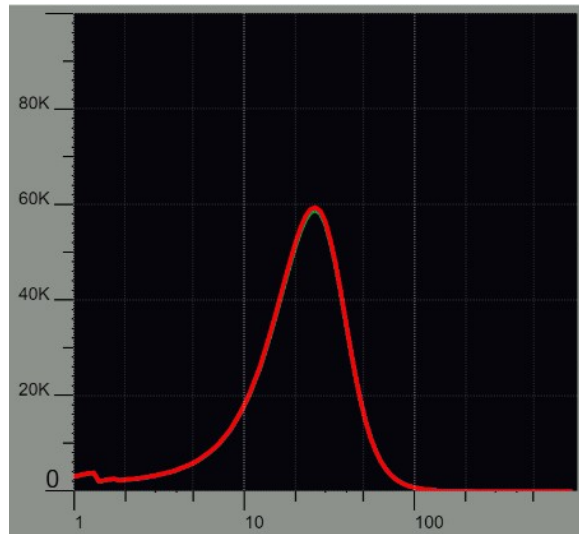
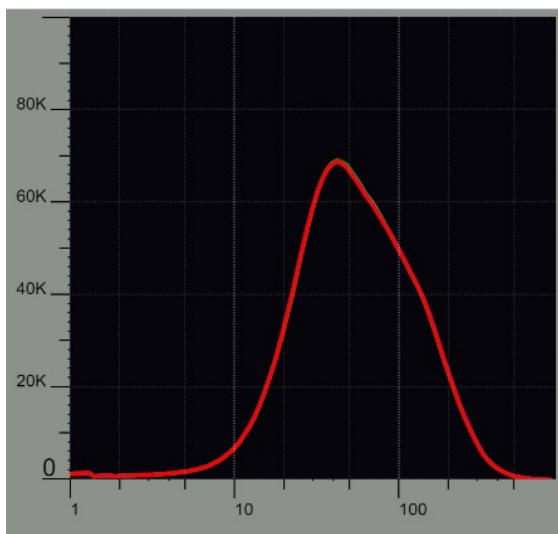
operational computer and associated Blaze Metrics UI program. When activated, the probe will start continuously acquiring microscopic images of the slurry, up to 42 per second. These images are shown live on the operational computer. Of the particle(s) that are shown on the image, the edge to edge chord length can be determined, which is a measure of the size of the particle. By continuously taking images and measuring the edge to edge chord length of the visible particles, the chord length distribution or particle size distribution (PSD) of the slurry can be determined. Correspondingly, a mean and median particle size can be derived from the distribution. Below, some microscopic pictures are added as well. For large amounts of particles, it is suggested to use alternative methods like the Blaze device. However, the microscope remains one of the tools which will give the most accurate result of the size distribution. Therefore, both techniques were used.

Design of different mixers (1.58 mm – 1.00 mm – 4.74 mm)

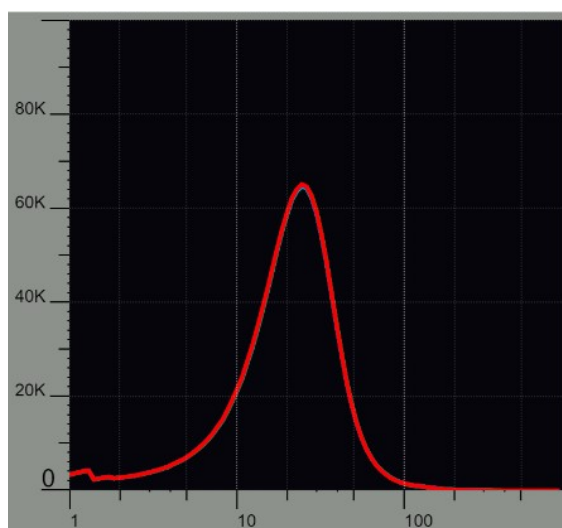
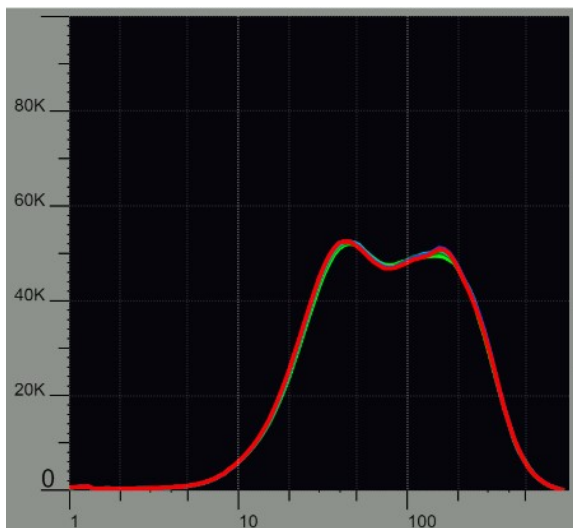
Different prototypes of the mixers were initially 3D printed with the commercially available MARS ELEGOO printer and the standard photopolymer resin (red). The final design was outsourced to Manetco and 3D printed in PEEK and stainless steel to obtain the preferred chemical resistance, temperature and pressure limit and its rigidity in avoiding leakages. The inner diameter of the capillary (solvent flow) was set to 0.45 mm.



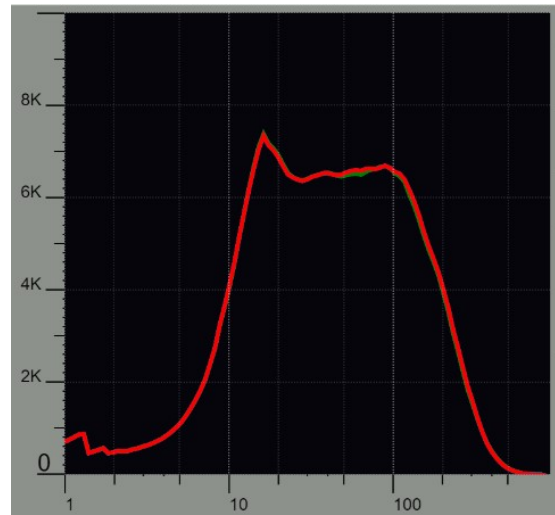
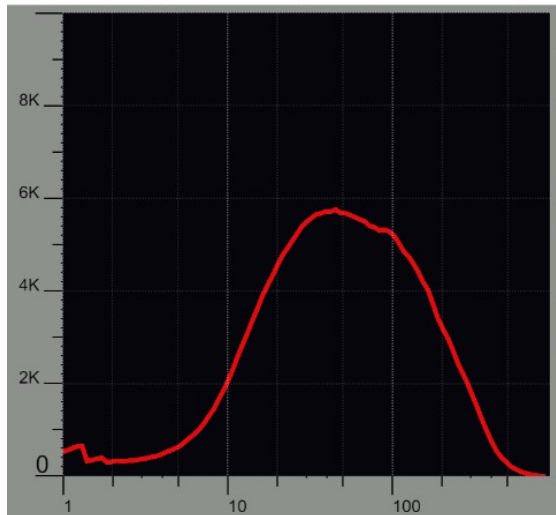
1.58 mm - 100% - 0 and 40 min sonication



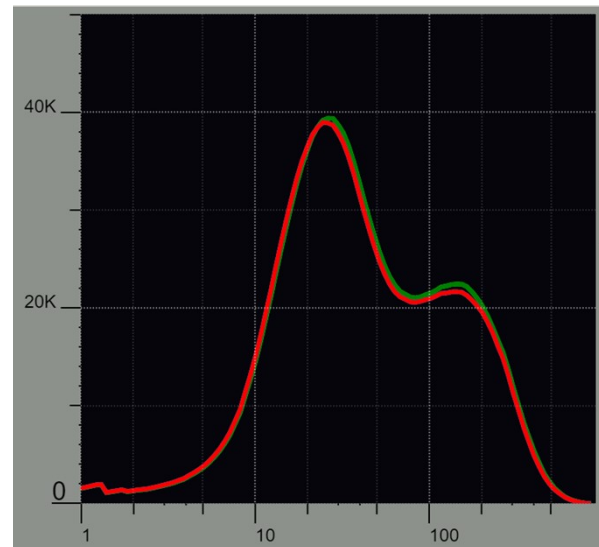
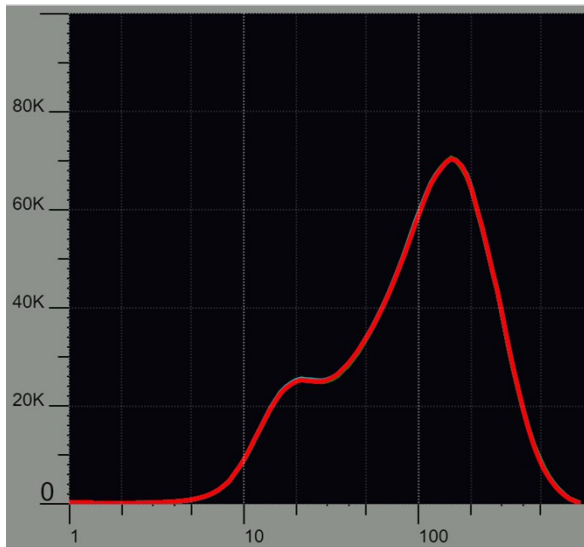
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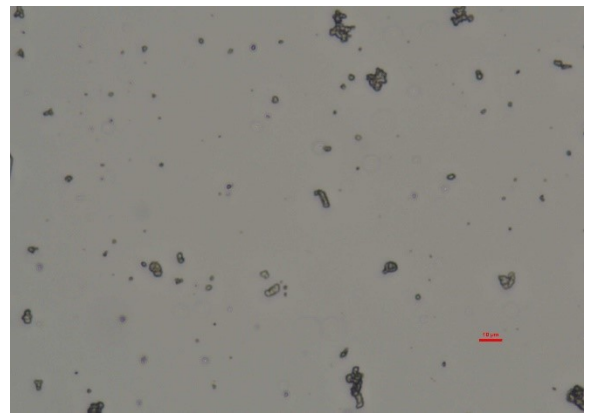
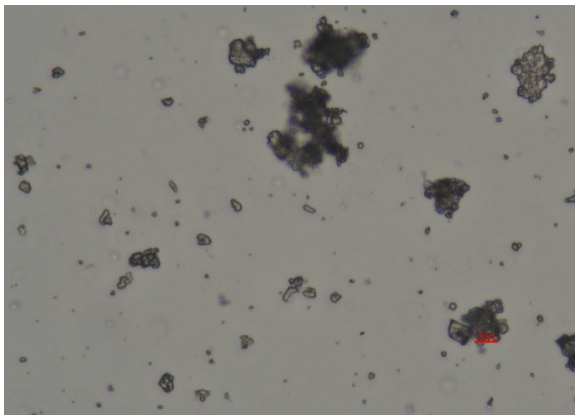
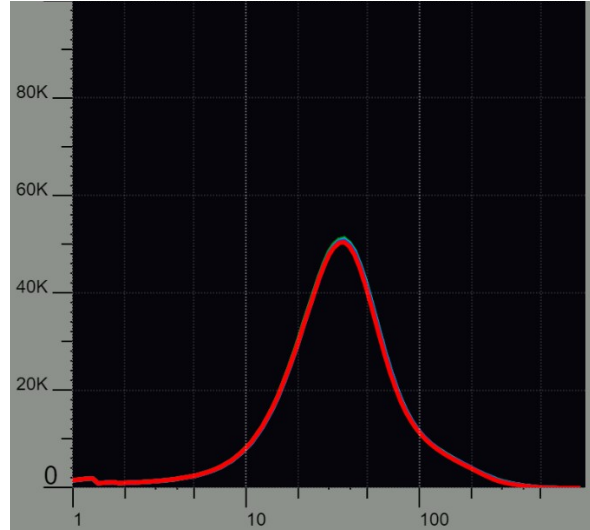
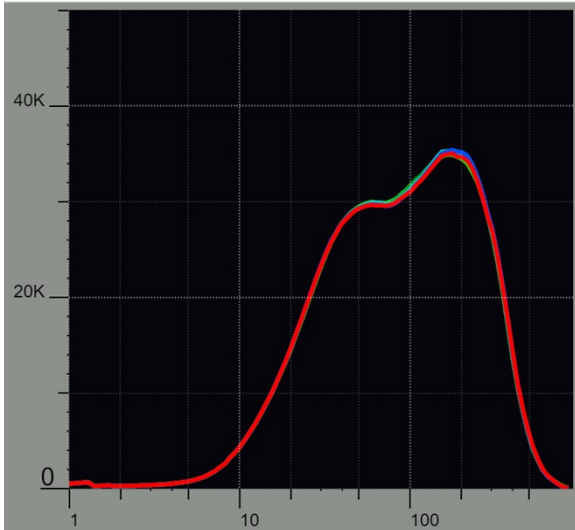
4.74 mm - 100% - 20 and 40 min sonication



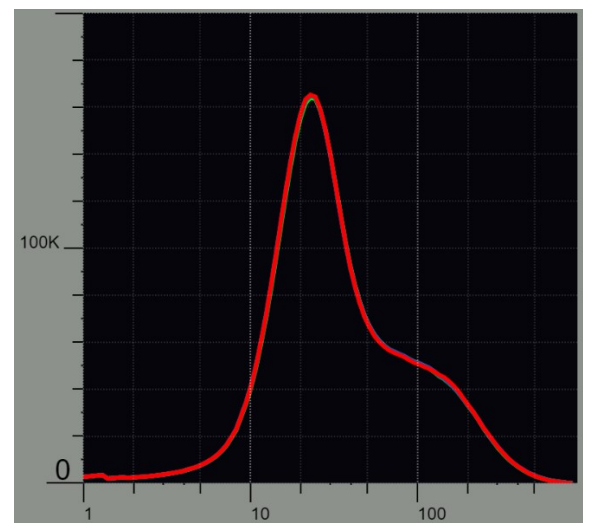
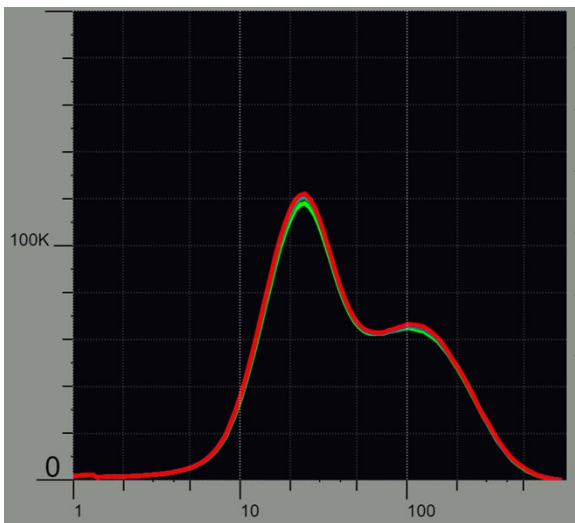
1.58 mm - 70% - 0 and 40 min sonication

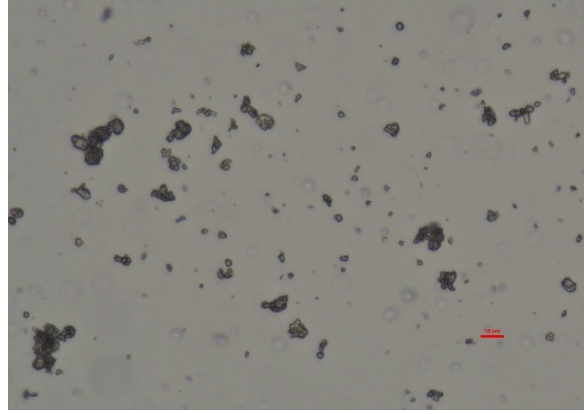
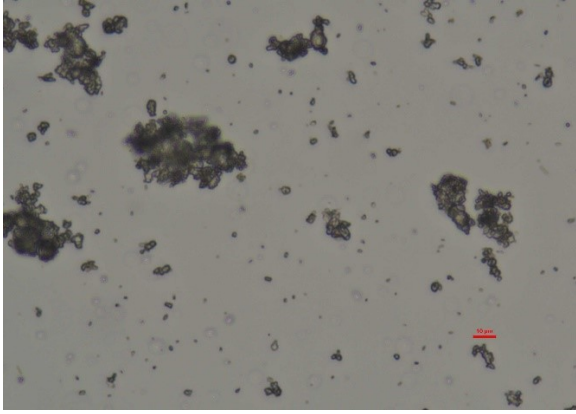


1.58 mm - 50% - 0 and 40 min sonication – microscopic view x40

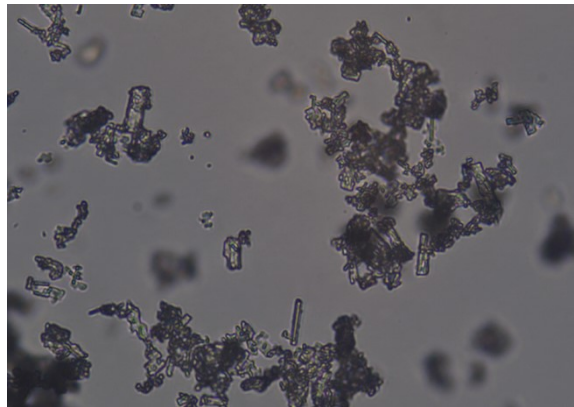
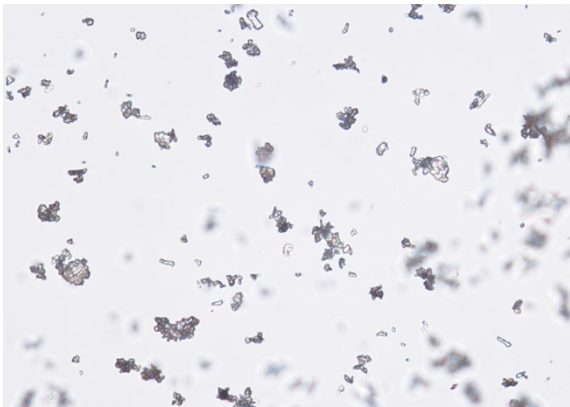
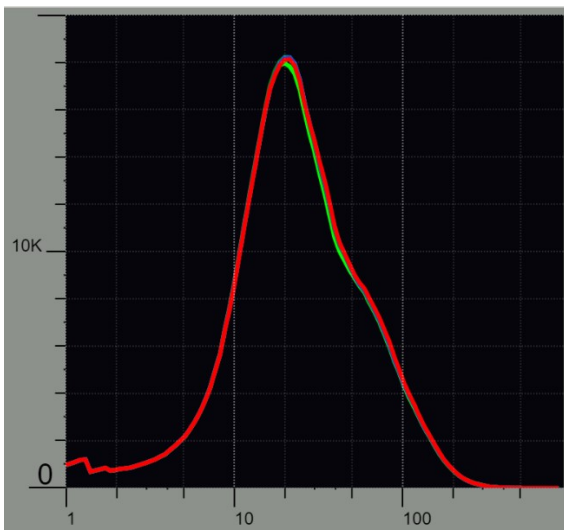


1.58 mm - 30% - 0 and 40 min sonication – microscopic view x40

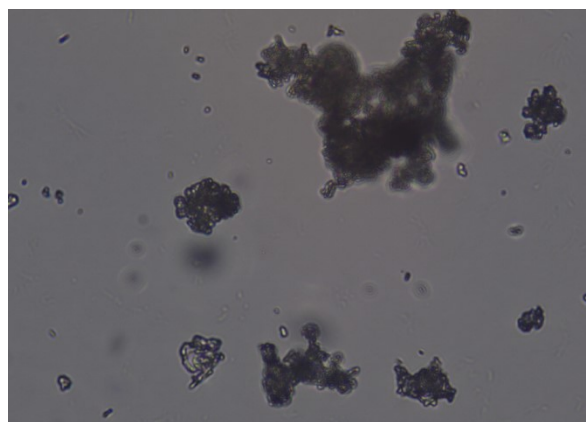
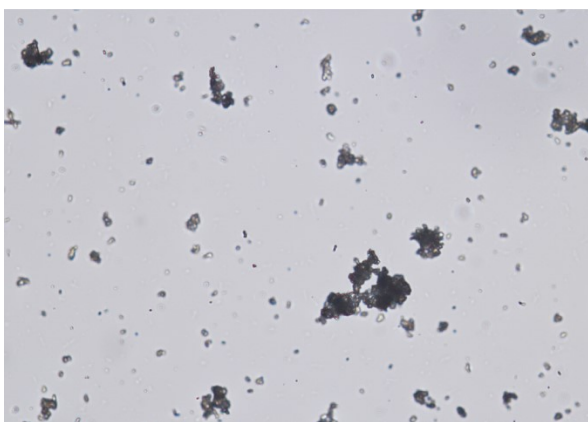
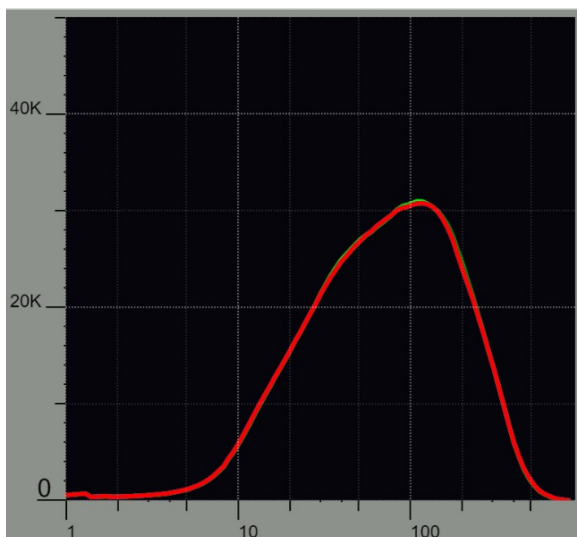




Ultra Turrax – 40 minutes mixing (16000 rpm) – microscopic view x20 and x40



Wet-milling – IKA module Dispax Reactor (6F, 18000 rpm) – microscopic view x20 and x40



Photon flux determination: Actinometry

Calculate the needed flow rates to achieve the residence times of 36, 60, 90 and 120 seconds using the internal irradiated volume of the reactor. For every residence time, the following procedure is followed. When the reaction mixture enters the irradiated volume, the timer is started and three residence times are respected to obtain steady state. Afterwards, two samples are taken. Finally, the lamp is shut of first, before shutting of the pump (or changing the flow rate) and the procedure can be repeated for the next residence time. For further calculations, the average absorbance of both samples is used. Two blanco samples (no irradiation) are collected as well. During all the experiments, the HANU™ 2X 15 is set to a constant temperature of 25 °C to ensure reproducibility. Further details see reference 15. The ferrioxalate conversion is shown in Figure 5 . The photon flux was determined to be 0.65 $\mu\text{Einstein}/\text{sec}$.

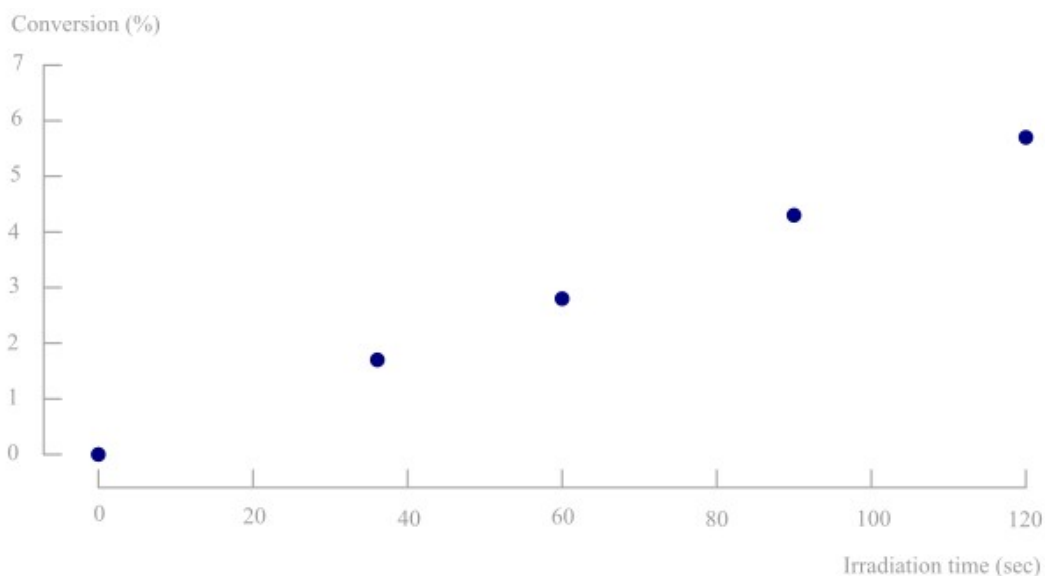


Figure 5. Ferrioxalate conversion for the determination of the photon flux.

Quantum yield determination (photon efficiency)

For a given reaction setup, the incident photon flux (mol of photons/s or Einstein/s) that reaches the reaction mixture depends on many different factors, e.g. reactor type (batch vs. flow), reactor design, reactor material, glass thickness, tubing, path length, reaction setup, wavelength, lamp type, lamp power... Therefore, it is of high importance to quantify the amount of photons provided to the reaction mixture in the reactor. Only then, the efficiency of the performed process in a particular reactor set-up can be evaluated, reactor set-ups can be compared, the process becomes reproducible for other labs and scaling-up can be performed. According to a previously reported protocol, the photon flux was determined by actinometry: 0.65 μ Einstein/sec. The quantum yield describing the number of molecules undergoing a photochemical event per absorbed photon, can now be calculated. It quantifies how efficient excitation is converted into a chemical reaction instead of deactivating processes (phosphorescence, internal conversion etc.). Yield data of the shortest residence time (5 min) is used to avoid that physical phenomena are taken into account in the quantum yield parameter (see supporting information). A quantum yield within the 0.1 – 0.2 range is accepted as a high efficiency.

$$\Phi = \frac{\text{number of molecules undergoing the reaction of interest} \left(\frac{\text{mol of product formed}}{\text{sec}} \right)}{\text{photon flux} \left(\frac{\text{mol of photons}}{\text{sec}} \right)}$$

$$= 0.197 \text{ (19.7\%)}$$

Equation 2. Calculation of the quantum yield.

Space-time yield calculation

By using a 2 g/L slurry density of *d,l*-1, 0.03 grams or 0.104 mmol of ketone is present in 1 reactor volume (15 mL). When full conversion is obtained, 0.027 grams of product (0.104 mmol * 260.13 g/mol) is obtained from 1 reactor volume. Since the reaction time necessary to obtain full conversion is 30 min, 0.054 gram of product is collected in 1h.

$$STY = \frac{0.027 \text{ gram}}{0.5h * 15 * 10^{-6} m^3} = 3600 g h^{-1} m^{-3} = 3.6 kg h^{-1} m^{-3}$$

Equation 3. Calculation of the Space-time yield.