Supplementary Information

for

Photochemical on-demand production of hydrogen peroxide in a modular flow reactor

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1. Materials and methods

1.1 Reagents and solvents

Commercial reagents and solvents: Unless stated otherwise, all reagents and solvents were obtained from the commercial sources: Sigma–Aldrich, TCI, Boom and Linde-gas and were used as received. For aqueous solutions, Milli-Q water was used.

The following chemicals were purchased from *Sigma Aldrich*:

Iron (0) pentacarbonyl (Sigma Aldrich, 99.99%, SHBN5572, 09-05-22), oleic acid (Sigma Aldrich, 90%, MKCL2492, 21-07-20), trimethylamine N-oxide dihydrate (Sigma Aldrich, 98%, BCCF8795, 08-07-22), hydrochloric acid (Sigma Aldrich, 37%, STBK5583, 20-06-22), starch (Sigma Aldrich, SLCC5527, 21-01-21), sodium thiosulfate (Sigma Aldrich, 99%, BCCC5894, 21-01-21), potassium Iodide (Sigma Aldrich, 99.5%, STBJ7197, 21-01-21), ammonium molybdate tetrahydrate (Sigma Aldrich, 81-83%, SLCH3187, 21-01-21), sodium hydroxide (Sigma Aldrich, 98%, SLCC5278, 07-01-20), 4-Methyl-2-pentanone (Sigma Aldrich, >98.5%, BCCJ6219, 26-09-23), 2-Butanone (Sigma Aldrich, >99.0%, SHBQ0260, 04-10-23), tert-Butyl methyl ether (Sigma Aldrich, >99.0%, SHBQ2623, 26-09-23), furfural (Sigma Aldrich, 1L, 99%, 102410997, MKCP0285).

The following chemicals are purchased from Boom B.V.:

Sulfuric acid (Boom B.V., 95-97%, 26-10-22), ethanol (Boom B.V., 100%, EA99-4422-10SD, 16-12-22), ammonia solution (Boom B.V., 25%, 14-09-21), ethyl acetate (Boom B.V., technical grade, PROD2303098, 26-02-24), Tetrahydrofuran (Boom B.V., 100%, PROD2100983, 16-09-21).

The following chemicals are purchased from *Acros Organics*: Iron (0) pentacarbonyl (Acros Organics, A0425102, 24-12-20), purchased from *TCI*: Dimethyl carbonate (TCI, >98%, DEQYA-LF, 30-06-22), 2-Methyltetrahydrofuran (TCI, >98%, stabilized with BHT, QRCVM-AT, 24-03-22), purchased from *Macron*: Dichloromethane (Macron, UN1593, 13-07-22), purchased from Honeywell: Pentane (Honeywell, >95.0%, Lot No. L1230, 26-02-24), purchased from *Linde-gas*: Oxygen compressed 5,0 (technical grade, SOL SpA, S161280921X01247DI, 01-09-22).

2. Equipment and general analytical information

Photochemical equipment:

- LEDs (OSRAM Oslon SSL 80 royal blue, LDCQ7P-2U3U, 500 mW, λ = 445 nm, 180 mW/cm²) as light source for batch and flow production of hydrogen peroxide, as well as for the photoclick reaction to PQ-PY in flow.
- LEDs (OSRAM Oslon SSL 80 Streetwhite, LT-2753, LED, 500 mW, 152 mW / cm² @ 445 nm) as light source for flow production of hydroxy-butenolide from furfural.

General Analytical Information: Nuclear Magnetic Resonance spectra were measured with an Agilent Technologies 400-MR (400/54 Premium Shielded) spectrometer (400 MHz). All spectra were measured at room temperature (22–24 °C). Chemical shifts for the specific NMR spectra were reported relative to the residual solvent peak [in ppm; CDCl₃: δ H = 7.26; CDCl₃: δ C = 77.16]. The multiplicities of the signals are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad signal), app (apparent). All ¹³C-NMR spectra are ¹H-broadband decoupled.

High-resolution mass spectrometric measurements were performed using a Thermo scientific LTQ OrbitrapXL spectrometer with electrospray ionization. The molecular ion (M+, [M+H]+ and [M-X]+) is given in m/z-units.

UV-vis spectra were recorded with an Agilent 8543 spectrophotometer. The Agilent 8453 UV-Visible spectrometer was equipped with a custom-built (Prizmatix/Mountain Photonics) multi-wavelength fiber coupled LED-system (FC6-LED-WL) including the following LEDs: 365A, 390B, 420Z, 445B, 535R, 630CA. A detailed description of the setup was published earlier by our group (see Figure S1 in reference 1).¹ A Quantum Northwest TC1 temperature controller was used to maintain the temperature at 20 °C during photochemical studies.

Dynamic light scattering (DLS) experiments were performed with a Zetasizer Ultra Red (Malvern Panalytical, ZSU3305).

A Tecnai T20 cryo-electron microscope with 200 keV was used to take the Transmission electron microscopy (TEM) and scanning transmission electron (STEM) images. Energy-dispersive X-ray spectroscopy (EDX) was performed with a silicon drift energy dispersive X-ray (SDD EDX) detector X-max from Oxford Instruments. The elemental ratio was calculated *via* INCA software.

Liquid-chromatography (LC) mass-spectrometry (MS) (LC-MS) measurements were performed on a Agilent InfinityLab LC/MSD (G6125C SG2215N102) with an Agilent 1290 Infinity II. A non-polar column by Waters (BEH-C4, 2.1x150, 1.7 micron) was utilized with 100.0% Water as eluent at a flow rate of 0.300 mL min⁻¹ and 600.00 bar pressure (26 min acquisition time). The injection volume was set to 1.00 μ L. The UV-DAD detector followed products at wavelengths of 200 nm, 210 nm and 250 nm and full spectra were recorded from 190 nm to 350 nm. The SQ Mass Spectrometer was set to follow mass values ranging from 40-600 m/z. Simultaneously SIM scans at masses of 312 m/z, 313 m/z and 281 m/z were conducted.

Gas-chromatography (GC) mass-spectrometry (MS) (GC-MS) measurements were performed on a Shimadzu GC-2010 (Japan) gas chromatograph with a GCMS-QP2010 mass-spectrometer. A non-polar column ((5%-phenyl)-methylpolysiloxane) by Agilent (dimensions 30 m \cdot 0.25 mm \cdot 0.25 μ m) was utilized.



3. Modular photo-flow reactor design and construction manual

Figure S1: Construction manual for several parts utilized in the modular flow reactor. Measures of 3D printable plastic holder for the borosilicate as well as quartz glass plate with holes for screws (A). Depiction and measures of the outer frame of the thin-film flow reactor, which is constructed from stainless steel (B).



Figure S2: Construction of metal cover for the flow reactor, including cooling (A). Measures of 3D printable stand to hold the metal cover at a certain height.

The different layers of the flow reactor (as schematically depicted in **Figure S3**) were made from different types of materials. The outer layers (**1** and **7**) were cut out of stainless steel (**Figure S1 B**). The plastic support layers (**2** and **6**) were 3D printed using polylactic acid (PLA, **Figure S1 A**). The rubber gasket (layer **4**) was cut out of ethylene propylene diene monomer (EPDM, 1 mm thick) rubber. Layer **3** consisted of quartz glass (10 cm x 10 cm x 1 mm) for light irradiation. The inlet and outlet were cut in borosilicate glass (10 cm x 10 cm) and G/L fittings were glued on there. A diaphragm liquid dosing pump (SIMDOS® 02 FEM 1.02 RC-P) was utilized to create flow through the reactor and tubing (Teflon tubing 50FT x 1/8"OD x 0.063" ID (lot: 140321, Supelco, Sigma-Aldrich)).



Figure S3: Schematic representation of the photo-flow reactor.

Table S1: Description of the reactor components depicted in Figure S3.

Layer	Material	Function
1	Stainless steel	-Top part of the reactor
		-Window in the steel construction is necessary for light irradiation
2	Plastic support	-Layer to prevent steel and glass from directly touching, thereby protecting the Quartz glass layer
3	Quartz glass	-Quartz glass opens the possibility for UV-light to be used as a light-source
4	Rubber	-A pattern is cut in this rubber gasket for consistent catalyst deposition from experiment to experiment -Also, the flow pattern is therefore consistent using this gasket
_		
5	Borosilicate glass	-For installing the G/L Fittings, since this is not possible on the thin quartz glass -The catalyst sticks to glass
6	Plastic support	-Layer to prevent steel and glass from directly touching, thereby protecting the glass layer
7	Stainless steel	-Lower part of the reactor



Figure S4: Design of the reactor parts.



Figure S5: Septum for tubing to enter the reactor.



Figure S6: The assembled photo-flow reactor, equipped with a fully open rubber-gasket.



Figure S7: Possible pathways by changing rubber gasket pattern.



Figure S8: Diaphragm liquid dosing pump used for flow experiments: SIMDOS® 02 FEM 1.02 RC-P.





Figure S9: Completely assembled flow reactor in operation with cooler and blue light irradiation (B) to produce H_2O_2 (C).

4. Experimental procedures

4.1 Synthesis of iron oxide nanoparticles with oleic acid

Oleic acid (2.20 g (90%), 7.01 mmol, 2.31 eq.), ethanol (12 mL) and iron pentacarbonyl (0.4 mL, 3.04 mmol, 1 eq.) were added to a 100 mL two-neck round bottom flask and the mixture heated at reflux (150°C Allihn condenser) for 1 h at a stirring speed of 660 rpm (Figure S10). After 1 h the mixture had turned from yellow to orange/brown (Figure S11 (A)). The mixture was initially cooled using an ice bath and then with a 20°C water bath to room temperature (20°C) (B), while filling the decreasing volume of the headspace with nitrogen. To the cooled mixture, trimethyl amine N-oxide dihydrate (1 g (98%), 8.82 mmol, 2.90 eq.) was added while flushing the system with nitrogen, which resulted in bubbling and a dark solution (C). The mixture was then heated to 130°C for 2 h under nitrogen atmosphere resulting in a color change to yellow (E), where overpressure of gas (CO) was allowed to leave the system in the first few minutes (D). After 2 h the temperature was increased to 150°C and kept for 1 h. The reaction was stopped by cooling with an ice bath and subsequently with a water bath until but not further than 20 °C (whole cooling process: 1 min, F), while flushing the headspace with nitrogen. The obtained iron oxide nanoparticles were decanted into a beaker (500 mL, G) and settled from ethanol (200 mL). While rinsing the round bottom flask with the ethanol, the magnetic nanoparticle droplets were already formed inside the flask (H). The magnetic nanoparticles were pulled out of solution (212 mL) by a magnet under the beaker for 1 h (Figure S12 I, J). The ethanol was decanted off and the particles were washed once with ethanol (50 mL) (K, L) and then dried via constant air flow. Next, the particles were suspended in dichloromethane (10 mL) or other, more sustainable solvent alternatives (see sustainable storage alternatives further below) and stored under nitrogen atmosphere and in darkness at 5°C. The particles were stable in DCM, 2-MeTHF, THF or MIBK for at least 6 months without aging, agglomeration or changes in size (Figure S12). The approximate yield was 7-34% corresponding to 100-500 mg varying per batch.



Figure S10: Synthesis equipment used for the FeO_x nanoparticle synthesis. Two-neck round bottom flask equipped with an Allihn condenser and heated *via* metal heating mantle.



Figure S11: Photographs of FeO_x NPs (batch 141) with oleic acid surfactant 2:1. A) t=50 min, B) t=60 min cooled, C) cooled at t=60 min Me₃N added, D) heating up at t=63 min and gas formation E) t=100 min, F) cooled solution after synthesis, G) precipitation on magnet, purely decanted, H) washing and rinsing of round bottom flask for droplet formation.



Figure S12: Precipitation on top of a magnet of FeO_x NPs (batch 141) with oleic acid 2:1 as surfactant. I,J) 1h washing with 200 mL EtOH and droplet formation, K,L) washed FeO_x NPs with ethanol (50 mL). Photograph of FeO_x NPs (batch 153) with oleic acid 2:1 in DCM after 12h - the dispersion is stable, and no precipitates were identified (bottom right).

4.2 Synthesis of iron oxide nanoparticles with oleic acid: troubleshooting

The synthesis was found to be consistent (>240 batches) and could successfully be reproduced by four different researchers in different labs at different locations (a bachelor student at Linnaeusborg (University of Groningen), a master student at Linnaeusborg (University of Groningen), and two PhD candidates at Nijenborgh & Linnaeusborg (University of Groningen) and at University of Amsterdam). Especially for the synthesis of heterogeneous catalyst materials, reproducibility is crucial and often an overlooked aspect.² Successful synthesis was independent of iron(0) pentacarbonyl suppliers (Sigma Aldrich, Acros Organics) with different Lot-numbers, coming from different continents.

Unsuccessful syntheses of a few batches led to extensive troubleshooting. The importance of dry conditions was discovered when once 96% ethanol was used instead of the usual 100% ethanol: big pieces were floating around in the flask after addition of trimethylamine N-oxide dihydrate and heating to reflux, where usually with 100% ethanol a completely dispersed and homogeneous solution is obtained. A similar phenomenon was observed when water was once utilized as 1:1 cosolvent with ethanol, suggesting that water in the synthesis leads to undesired precipitation of nanoparticles out of solution. Wet nitrogen gas from the Schlenk-line also led to unsuccessful nanoparticle synthesis; here the nanoparticles did not magnetically precipitate from the solution during workup. Over time stirring bars became yellow/brown after repeatedly being used for synthesis and cleaning using hydrochloric acid solution (37%), which led to particles not magnetically precipitating during workup. By using new stirring bars, we were able to overcome this problem. Over time iron(0) pentacarbonyl was found to precipitate as a solid in the normally yellow liquid, which led to differently looking pieces magnetically precipitating in the workup. We suspect that precipitation was caused by the septum on the bottle being punctured too often, therefore not sufficiently sealing the nitrogen atmosphere in the bottle anymore. Iron(0) pentacarbonyl is a pyrophoric compound, meaning that it could react with air to oxidize to iron(III) oxide.⁸ By switching to a new bottle of iron(0) pentacarbonyl these problems could be avoided. When the trimethylamine N-oxide dihydrate was too dry (dry powder instead of hygroscopic white solid) inconsistent syntheses were observed. A 'wet' hygroscopic solid is recommended over a dry white powder. During the cooling steps of the reaction mixture nitrogen has to be flushed into the decreasing volume of the headspace. Furthermore, the cooling should be performed rapidly with an ice bath for up to 1 min, but not longer and the temperature should not drop below 20°C; this can be monitored by replacing the initial ice cooling with an additional water bath. Letting the solution drop below 16°C leads to precipitation of frozen oleic acid. These crystals will trap the 2 nm FeO_x onto 400-600 nm crystals of oleic acid, which is not desired. Extensive cooling also leads to gel/droplet/oil formation at the bottom of the round bottom flask, resulting in tedious workup and transfer to the beaker.

Below a list of requirements is given as a guide, which should be consulted if there are difficulties in synthesis.

List of requirements for successful nanoparticle synthesis

- 100% ethanol as solvent
- clean and dry glassware (100 mL 2-neck flask, Allihn condenser, adapter to Schlenk-line)
- clean stirring bar (egg shaped, 2 cm)
- clean Schlenk-line tubing
- dry nitrogen (make sure phosphorus pentoxide is still dry by moisture indicator)
- clean oil in Schlenk-line
- 660 rpm stirring speed
- sufficient reflux
- 500 mL beaker during workup on magnet
- cooling with the ice bath not below 20 °C to avoid precipitation of oleic acid (16 °C)
- hygroscopic trimethylamine N-oxide dihydrate

4.3 Sustainable storage of iron oxide nanoparticles with oleic acid, U.S. Environmental Protection Agency (EPA) ban on methylene chloride (dichloromethane, DCM).

Usually, the particles were suspended in dichloromethane (10 mL) and stored in nitrogen atmosphere and darkness at 5°C, where they were stable for >6 months. Recently though (30th April 2024), the United States Environmental Protection Agency (EPA) finalized a ban on most uses of methylene chloride (dichloromethane, DCM). Hence, for our catalyst system to stay relevant and especially align with its goal for sustainable production of H_2O_2 we investigated greener solvent alternatives.

Experimental procedure:

Several stable and active batches of FeO_x NPs stored in DCM were taken and combined. From the solution obtained, the NPs were taken out *via* syringe and put into 8 different vials (4 mL of DCM and NPs per vial). The DCM was evaporated completely. Afterwards 4 mL of the respective greener alternative solvent was added to each vial, thereby maintaining the same concentration which was obtained through NP synthesis and storage in DCM. The NPs were redispersed through sonication and vortex shaking. The obtained NPs dispersions were stored in nitrogen atmosphere and darkness at 5°C, where they were checked for stability and precipitation on a regular basis (daily for a duration of 8d).

Highly hazardous	Hazardous		Problematic		Recommended
Diethyl ether Benzene Pyridine Sulfolane Chloroform CCl ₄ Dichloroethane Dichloromethane Nitromethane	Diisopropyl ether 1,4-dioxane Dimethoxyethane Pentane Hexane DMF DMAc NMP Methoxy-ethanol Et ₃ N	MTBE THF Formic acid Cyclohexane Pyridine	Acetone 2-MeTHF Heptane Me-cyclohexane <i>tert</i> -butyl acetate Toluene Xylenes Chlorobenzene Acetonitrile DMPU DMSO Cyrene	MeOH t-BuOH Methyl ethyl ketone (MEK) MeOAc AcOH Ac ₂ O Dimethyl carbonate (DMC) Cyclopentyl methyl ether (CPME) y-Valerolactone (GVL) Hydroxymethylfurfural (HMF)	Water (H ₂ O) EtOH <i>i</i> -PrOH <i>n</i> -BuOH EtOAc <i>i</i> -PrOAc <i>n</i> -BuOAc Anisole Methyl isobutyl ketone (MIBK) Cyclohexanone Ethylene glycol Benzyl alcohol

Figure S13: Ranking of solvents with respect to their sustainability.^{1–3}

Table S2: Stability test of nanoparticle dispersions in greener solvent alternatives following the ban on DCM. Stability was investigated daily for a duration of two months (56 d, 4 mL solution). Size differences among solvents can be correlated to the solvation shell and measurement *via* dynamic light scattering and are not having an impact on photochemical activity. A Zetasizer Ultra Red (ZSU3305) from Malvern Panalytical was used for dynamic light scattering experiments. All samples (1 mL with a concentration of 1 mg mL⁻¹) were measured at 298.15 K. The particle size was measured *via* DLS (**Table S3**).

Ranking	Solvent alternative	Stability	Comments	Photo
1	2-MeTHF	Dispersion is stable and no precipitates were identified	Recommended	
2	THF	Dispersion is stable and no precipitates were identified	-	
3	МІВК	Dispersion is stable and no precipitates were identified	Slightly less solubility than #1 and #2	
4	MTBE	Not stable	-	
5	MEK	Not stable	-	
6	EtOAc	Not stable	-	
7	Pentane	Not stable	-	
8	DMC	Not stable	-	

5. Catalyst properties

5.1 DLS results and size in different solvents

A Zetasizer Ultra Red (ZSU3305) from Malvern Panalytical was used for dynamic light scattering experiments. All samples (1 mL with a concentration of 1 mg mL⁻¹) were measured at 298.15 K.

Table S3: Particle size and diffusion coefficient of FeO_x NP scope with concentration 1 mg mL⁻¹, obtained *via* DLS measurements.

Surfactant (Batch #)	Measured in solvent	Particle size (nm) by number %	Diffusion coefficient (µm ² s ⁻¹)
Oleic acid (173), Acros organics	DCM	1.88±0.37	8.13±1.49
Oleic acid (174), Sigma aldrich	DCM	1.97±0.31	7.27±1.29
Oleic acid (131)	THF	3.82±0.42	1.20±0.67
Oleic acid (B9, Dec. 2023)	DCM	2.52±0.15	-
Oleic acid (B9, Jun. 2024)	DCM	2.56±0.78	-
Oleic acid (B4-B6, Dec. 2023)	DCM	2.46±0.65	-
Oleic acid (B4-B6, Jun. 2024)	2-MeTHF	9.24±4.89	11.67±0.02
Oleic acid (B4-B6, Jun. 2024)	THF	11.51±6.81	10.96±0.54
Oleic acid (B4-B6, Jun. 2024)	MIBK	10.49±5.06	9.22±0.09

5.2 Transmission electron microscopy (TEM), scanning transmission electron microscopy (STEM) and energy-dispersive X-ray spectroscopy (EDX) of FeO_x NPs

TEM characterization:

A PHILIPS CM 120 Cryo electron microscope with 120 keV was used to take the TEM images. The sample grid was prepared by dropping 5 μ L of the solution (1 mg/mL in THF or DCM) onto an ultrathin carbon film coated copper grid (or graphene grid in the case of oleic acid and linoleic acid). After 30 seconds of drying the grid was washed with 5 μ L ethanol (EtOH) and any surplus solvent was dried on a filter paper. In the case of oleic acid and linoleic acid (1 mg/mL THF), the graphene grids were placed in a desiccator at full vacuum over-night.

STEM characterization:

A Tecnai T20 cryo-electron microscope with 200 keV was used to take the Transmission electron microscopy (TEM) and scanning transmission electron (STEM) images. EDX analysis was performed with a SDD EDX detector from Oxford xmax instruments, and the elemental ratio was calculated *via* INCA software.

5.2.1 FeO_x NP with oleic acid (cis)



Figure S14: A) Transmission electron microscopy of FeO_x (batch 131, oleic acid 2:1, Acros Organics, 1 mg mL⁻¹ in THF), at a magnification of 100000x (inlet: zoomed); particle size by DLS 1.94±0.34 nm. B) Scanning transmission electron microscopy of FeO_x (batch 131, oleic acid 2:1, 1 mg mL⁻¹ in THF), inlet: zoom towards A. C) EDX of FeO_x (batch 131, oleic acid 2:1, 1 mg mL⁻¹ in THF), inlet: acid 2:1, 1 mg mL⁻¹ in THF), drying spots of solvents contain more FeO_x NP and concentration decreases towards the edges of the droplets; oxygen is depicted in red – iron in green.⁴



Figure S15: Full spectrum of the elemental analysis (EDX) of FeO_x (batch 131, oleic acid 2:1, Acros Organics, 1 mg mL⁻¹ in THF).



Figure S16: Transmission electron microscopy of FeO_x (batch 131, oleic acid 2:1, Acros Organics, 1 mg mL⁻¹ in THF), at a magnification of 100000x; particle size by DLS 1.94±0.34 nm, higher contrast for better visibility (right).⁴



Figure S17: Transmission electron microscopy of FeO_x (batch 131, oleic acid 2:1, Acros Organics, 1 mg mL⁻¹ in THF), at a magnification of 240000x; particle size by DLS 1.94±0.34 nm, higher contrast for better visibility (right).⁴



Figure S18: left) Transmission electron microscopy of FeO_x (batch 174, oleic acid 2:1, Sigma Aldrich, 1 mg mL⁻¹ in THF), at a magnification of 100000x; particle size by DLS 1.94 \pm 0.34 nm, higher contrast for better visibility. right) Transmission electron microscopy of FeO_x (batch 174, oleic acid 2:1, Sigma Aldrich, 1 mg mL⁻¹ in THF), at a magnification of 125000x; particle size by DLS 1.94 \pm 0.34 nm, higher contrast for better visibility.⁴

5.3 UV-Vis



Figure S19: UV-Vis spectrum of FeO_x NPs with oleic acid (2:1, Acros Organics, batch 188) in DCM, dilutions from 1 mg mL⁻¹ onwards (left). UV-Vis spectrum of FeO_x NPs with oleic acid (2:1, Sigma Aldrich, batch 189) in DCM, dilutions from 1 mg mL⁻¹ onwards (right).⁴

6. Irradiation studies

6.1 Batch photocatalytic oxygen reduction

Photocatalytic oxygen reduction to hydrogen peroxide (H_2O_2) via FeO_x NPs was carried out in 10 mL vials, in a block of 6 slots, with irradiation of 500 mW LED from the bottom (**Figure S20**). To allow for an oxygen atmosphere and saturation of the solution, oxygen was bubbled (30 min solvent + 5 min headspace) using a needle. The temperature of the LEDs was controlled at 20°C by a liquid circulator. The photooxygenation was carried out according to the **Experimental procedure**.



Figure S20: Batch irradiation setup for high-throughput screening.⁴



Figure S21: Normalized emission spectrum LED OSRAM Oslon SSL 80 royal blue (500 mW, λ = 445 nm, 180 mW/cm²) as light source for batch and flow photo-reactions.⁴

6.2 Screening and batch irradiation of NPs synthesized in ethanol

Iron oxide nanoparticles suspended in DCM were added to a 10 mL vial to obtain 4 mg after evaporation of DCM. Pre-oxygenated (30 minutes) Milli-Q water (4 mL) was added to the dried nanoparticles to obtain a catalyst loading of 1 mg mL⁻¹. A Teflon stirring bar was added after which the vial was closed by capping. The sample was then extensively vortexed and sonicated for 5 min for better dispersion of the nanoparticles. Finally, 5 min of oxygen bubbling through the solution was conducted to ensure an oxygen atmosphere in the vial. Irradiation studies were conducted for 5 h at 20°C by 445 nm irradiation in triplicate. The photoreactions were carried out in a block of 6 slots, with irradiation of 500 mW LED (180 mW/cm²) from the bottom. Blanks in darkness were also performed as triplicate measurements for comparison.

Catalyst recycling was performed by drying the catalyst after each irradiation reaction. The dried catalyst (~4mg) was then redispered in DCM (0.5 mL), and stored in nitrogen atmosphere and darkness at 5°C. The method as described above could then be followed after evaporation of DCM. These catalyst recycling reactions were conducted until catalyst activity was depleted.



Figure S22: Left) Schematic representation of a prepared sample for irradiation studies. Right) FeO_x NPs with oleic acid (2:1) surfactant sticking to glass (batch 126).

6.3 Production of H_2O_2 in flow.

First, a specified amount of iron oxide nanoparticles (FeO_x NPs) suspended in organic solvent (e.g. DCM) was drop-cast onto the quartz glass component of the flow reactor. The organic solvent was evaporated using air flow, leaving the catalyst immobilized on the glass, as shown in Figure S23. A rubber gasket was used for immobilizing the catalyst on the glass in a desired pattern (Figure S7). Following catalyst immobilization, the layers of the flow reactor were assembled and secured in the order illustrated in Figure S3. Milli-Q water was pre-oxygenated for 30 min. to ensure oxygen saturation. The perfluoroalkoxy alkane (PFA) tubing was connected sequentially from the reactant flask to the pump, then to the flow reactor, and finally to the product flask. After priming the lines and the flow reactor with solvent, ensuring the removal of all air, the collection of the blank in darkness was initiated. Following one hour of blank collection, the light was turned on to commence photochemical hydrogen peroxide (H_2O_2) production via the oxygen reduction reaction (ORR). Aliquots were collected hourly for the first four hours, with a final aliquot taken after 20 h. From each aliquot, 4 mL of the solution was taken and the produced H_2O_2 was quantified using iodometric titration. In the absence of iron in the product flask, decantation was not required, allowing the 4 mL sample to be directly analyzed with the iodometric assay. The determined H₂O₂ concentration for the 4 mL aliquot was then extrapolated to the entire collected solution to obtain the total amount of H₂O₂ produced per reaction.

The kinetic graphs and production table illustrate the cumulative amounts of hydrogen peroxide produced in flow over time. The data point at 20 h was excluded from these figures. In some experiments, stable flow was not consistently maintained, as the flow rate of the oxygenated Milli-Q water solution through the reactor decreased slightly overnight. Therefore, for a fair comparison, only the data from the first four hours are presented in the maintext **Figure 4**. Residence times were calculated using **Equation S8**.

Equation S1: Calculation of residence times at different flowrates.

residence time =
$$\frac{\text{reactor volume}}{\text{flowrate}}$$

Cleaning of the flow-reactor was conducted by first uncoupling the tubing from the flow-reactor. Acetone was flushed through the reactor to dry the inside of the reactor. Subsequently, the reactor could be screwed open for removal of the immobilized nanoparticles by wiping it off using DCM and a paper towel.



Figure S23: Iron oxide nanoparticles immobilized in the flow reactor.

6.4 Distillation of produced hydrogen peroxide

Hydrogen peroxide solutions produced in flow could be concentrated *via* rotary evaporation. The hydrogen peroxide solution was added to an appropriate size round bottom flask and attached to a rotary evaporator. The water bath was heated to 32°C and the pressure slowly decreased to full vacuum. The reaction was stopped when a desired amount of water was distilled off by increasing pressure to ambient pressure.

6.5 Safety note on distillation and handling of hydrogen peroxide

Mixtures of organics and hydrogen peroxide must be handled with extreme caution. The complex chemistry involved in these reactions necessitates a thorough examination of potential safety hazards. Distillation is the preferred approach for concentration in academia and industry, which always should be conducted with necessary experience and safety precautions.⁵

7. Quantification of hydrogen peroxide

7.1 Peroxide test strips

Peroxide test strips contain an organic redox indicator. Upon contact with peroxides the peroxide test strips produce a blue oxidation product. The peroxide concentration is measured **semiquantitatively** by visual comparison of the reaction zone of the test strip with the fields of a color scale. For accurate measuring the pH of the samples should be within the range 2-12.

Measurements were performed by immersing the test strips for one second in the samples. Excess liquid was allowed to run off and after approximately 10-15 sec a **semiquantitative** comparison was made using the color scale.

In case organic solvents were utilized, a slightly different procedure was necessary. The peroxide test strips were first immersed in the organic sample. Subsequently a few water drops were utilized to humidify the reaction zone. A **semiquantitative** comparison could then be made 10-15 sec after the water drops were added to the reaction zone.

Peroxide test strips are depicted in **Figure S24** indicating produced hydrogen peroxide in Milli-Q water without additives after 5 h irradiation (445 nm) and their comparison in darkness.



Figure S24: Semiquantitative analysis by peroxide test strips of sample irradiated (445 nm) for 5h (right), and their respective blanks in darkness (left).

7.2 Iodometric titration

Reaction S1: Iodide oxidation by hydrogen peroxide.

$$H_2O_2 + H_2SO_4 + 2 KI \rightarrow I_2 + K_2SO_4 + 2 H_2O$$

Reaction S2: Iodometric titration.

$$I_2 + 2 Na_2S_2O_3 \rightarrow Na_2S_4O_6 + 2 NaI$$

It was opted for iodometric titration, because titration by potassium permanganate ($KMnO_4$) led to interference with organic matter such as the surfactants of the FeO_x photocatalyst.

7.2.1 Stock solution preparation

Potassium iodide solution (2 wt%)

Potassium iodide (2 g, 12.04 mmol) was dissolved in demineralized water (100 mL). The solution was stored in a brown bottle to protect it from light irradiation. Properly stored, the solution is stable for six months, provided no change occurs in the color of the solution.⁴

Ammonium molybdate solution

Ammonium molybdate tetrahydrate (9 g, 7.7 mmol) was dissolved in ammonium hydroxide (10 mL aqueous NH_3 (25%, 13.5M), of which 42% is converted to ammonium hydroxide 5.6M NH_4OH). Subsequently, ammonium nitrate (24 g, 0.3 mol) was added, and the reaction mixture was diluted to 100 mL using Milli-Q water.

Sulfuric acid solution (3.5M)

One part of sulfuric acid (98%) was added carefully to four parts of demineralized water. This resulted in a solution that is stable indefinitely. Acid was always added to water, not water to acid, to avoid excess heat formation and spitting of acid. The solution was stirred while adding acid.⁴

Starch indicator solution

Reagent-grade NaCl was dissolved in double-distilled water (100 mL) while stirring, until no more dissolved. The beaker was subsequently heated until everything dissolved. NaCl crystals were observed on the sides of the beaker while cooling. This resulted in a solution that is stable for up to 12 months. Chemical starch (1 g) was dissolved in double-distilled water (10 mL) in a separate piece of glassware. The reaction mixture was heated until the contents were dissolved. The saturated NaCl solution was added to make 100 mL starch solution.⁴

Sodium thiosulphate solution (0.0001M)

Sodium thiosulphate (0.0316 g, 0.2 mmol) was dissolved in Milli-Q water (2 L). The resulting solution was stable for at least one month, if stored in the dark.

Standardization of sodium thiosulfate with a volumetric solution of potassium iodate is recommended. The concentration of the sodium thiosulfate could be adjusted to accommodate the analysis of larger sample weights.⁴

Normalization of sodium thiosulphate solution (0.0001M)

Every two weeks the sodium thiosulphate solution was standardized with a volumetric solution of potassium dichromate. Potassium dichromate (0.2 mg, 0.68 μ mol) was dissolved in Milli-Q water (10 mL) in an Erlenmeyer flask. Subsequently, potassium iodide solution (5 mL, 2 wt%, 602 μ mol),

sulfuric acid (2 mL, 3.5 M), ammonium molybdate solution (1 mL) and starch indicator (2 mL) were added to the potassium dichromate solution, resulting in a blue solution (**Reaction S3**). The blue color was titrated away by dropwise addition of sodium thiosulphate solution (0.0001M) (**Reaction S4**).

Reaction S3: Oxidation of potassium iodide by potassium dichromate.

 $K_2Cr_2O_7 + 6 KI + 7 H_2SO_4 \rightarrow Cr_2(SO_4)_3 + 4 K_2SO_4 + 7 H_2O + 3 I_2$

Reaction S4: Reaction between sodium thiosulphate and iodine.

$$2 Na_2 S_2 O_3 + I_2 \rightarrow 2 NaI + Na_2 S_4 O_6$$

7.2.2 Quantification procedure

Iodometric titration was utilized to accurately quantify the hydrogen peroxide amounts produced *via* the ORR. After uncapping the vials, they were first **semiquantitatively** analyzed *via* peroxide test strips. Subsequently, the Milli-Q water was decanted in a 20 mL vial while a magnet was held to the bottom of the initial 10 mL vial to ensure catalyst to stay in the vial. The inside of the 10 mL vial was washed once with Milli-Q water (1 mL), which was also decanted in the 20 mL vial for analysis.

Syringe filters (0.2 μ m, Sartorius) were used in case solids were dispersed in the sample (*e.g.* iron oxides as additive) or when a suspension was obtained after reaction. The samples were then decanted into a syringe (5 mL) with a filter (0.2 μ m) instead of decantation directly into the 20 mL vial.

For analysis potassium iodide solution (2 mL), sulfuric acid solution (1 mL) and ammonium molybdate solution (5 drops) were added to the sample. The vial was then immediately capped and stored in darkness for (exactly) 5 min. After these 5 min in darkness the solution had turned from colorless to slightly yellow. Upon addition of starch indicator, a blue/purple color was obtained, which was titrated away with 0.0001 M sodium thiosulfate solution.

The amount of potassium iodide added to each sample should be in excess. 2 mL KI (2wt%) = 236 μ mol, of which 118 μ mol are available for reaction with H₂O₂ (**Reaction S1**). This amount is a few orders of magnitude higher (81–844 times) than typical produced amounts of hydrogen peroxide (0.14 - 1.45±0.07 μ mol).

7.2.3 Troubleshooting iodometry

As mentioned in **ESI 6.2.2**, samples were capped and stored in darkness for exactly 5 minutes. It was found to be crucial that every sample stood in darkness for 5 min, as otherwise comparison was not possible anymore. Over time potassium iodide is oxidized by oxygen and carbon dioxide to form iodine and potassium carbonate, which interferes with the measurements.

Also, having iron ions in solution interfered with iodometric test results *via* **Reaction S5**. This effect was observed when iron oxides were added to the reaction mixtures, but also in the blank reactions (**ESI 5.6**) when surfactants dissolved the iron oxide nanoparticles. In standard screening reactions with iron oxide nanoparticles this effect was not observed, as successful heterogeneous immobilization of the nanoparticles on glass surfaces was achieved without considerable amounts of leaching.

Reaction S5: Interference by iron ions to form iodine from iodide.⁴

 $2 Fe^{3+} + 2 I^- \rightarrow 2 Fe^{2+} + I_2$

8. List of photochemical H₂O₂ production values

Entry	Condition	Peroxide Teststrip [mg L ⁻¹]	Produced H ₂ O ₂ [μmol L ⁻¹]	Produced H ₂ O ₂ [mmol g ⁻¹ L ⁻¹]	Productivity H ₂ O ₂ [mmol g ⁻¹ L ⁻¹ h ⁻¹]	Normalized production H ₂ O ₂ [mmol g ⁻¹ L ⁻¹]
1	FeO _x NP Standard (4 mg, darkness)	0	0	0	0	0
2	FeO _x NP Standard (4 mg)	0.5 to 2	34±2	9.4±1.3	1.7±0.3	9.4±1.3
Kinetic	s FeO _x NPs with ole	ic acid surfacta	nt			
25	1 h	0.5	10±2	2.6±1.4	2.6±1.4	2.6±1.4
26	2.5 h	0.5	13±2	3.9±1.0	1.6±0.4	3.9±1.0
27	5 h	0.5 to 2	29±2	9.0±0.4	1.8±0.1	9.0±0.4
28	20 h	2	36±1	14.2±1.1	0.7±0.1	14.2±1.1
29	67 h	2 to 5	63±13	12.8±2.5	0.2±0.1	12.8±2.5

Table S4: List of production values for the photochemical production of H_2O_2 via FeO_x NPs in batch.

Entry	Flowrate mL/min	Catalyst (mg)	Wavelength light (nm) Solvent		Reaction Time (h)	Production (µmol)	Productivity (μmol h ⁻¹)
Batch	-	4	445 nm	4 mL Milli-Q water	5	0.136±0.020	0.027
6			50:50		4	0.731	0.183
(28°C)	0.1	30	445	Milli-Q water/EtOH	20	2.254	0.113
Q	0.1	60	115	Milli-Q	4	0.230	0.058
o	0.1	00	445	water	20	0.761	0.038
9 (28°C)	0.1	30	445	EtOH	No conve	rsion, NPs disso	lved in EtOH
10	0.3	20	445	Milli-Q	4	0.492	0.123
		30	445	water	20	2.402	0.120
11	0.1	30	365	Milli-Q water	2	0.104	0.052
4, 12, 17	0.1 30	20	44E	Milli-Q	4	0.379±0.017	0.095±0.004
(28°C)		445	water	20	1.938±0.306	0.097±0.015	
13	0.3	30	365	Milli-Q water	2	0.238	0.119
14	0.1	20	44E	Milli-Q	4	0.125	0.031
14	0.1	20	445	water	20	0	0
15	0.1	20	265	Milli-Q	2	0.070	0.0352
(32°C)	0.1	50	202	water	20	0	0
16	0.1	30	265	Milli-Q	4	0	0
(26°C)	0.1	30	202	water	20	0	0
18	0 1	30	445	Milli-Q	4	0.262	0.065
(23°C)	0.1	50		water	20	1.214	0.061

Table S5: List of production values for the photochemical production of H_2O_2 via FeO_x NPs in flow.

Table S6: Comparison of selected recent articles on the heterogeneous photocatalytic production of hydrogen peroxide using water as electron donor if not depicted otherwise. The blue cell depicts a homogeneous reference system. The selection criteria for the articles were variety of different catalyst materials, original introduction, citations and year of publication. †: Oxo[5,10,15,20-tetra(4-pyridyl) porphyrinato] titanium(IV); [TiO(tpypH4)]⁴⁺ complex (Ti-TPyP reagent). a: EtOH (4%); b: BA (17%); c: TEOA (17%); d: IPA (10%); e: 353K f: BA (10%); g: BA (90%).

	.	Cond	itions			H ₂ O ₂	H ₂ O ₂
Photocatalyst	Reaction Pathway	atmosp here	λ [nm]	SCC	AQY	productivity [mmol g ⁻¹ L ⁻¹ h ⁻ ¹]	concentration [mmol L ⁻¹] (time)
[Ru ^{ll} (Meanhen)a ^{]2+6}	indirect	0.	> 420	0.25%	37% at	22	0.3 (17h)
	1e⁻ ORR	02	2 420	0.2378	450 nm	25	0.4 (1h)
AuAg/TiO ₂ ⁷	direct 2e⁻ ORR	O ₂	280	N/A	N/A	0.15 ª	3.6 (24h) ª
						0.01	0.2 (20h)
Ni/MIL_125_NH ₃ 8	indirect	01	> 420	N/A	N/A	0.6	1.5 (3h)
	1e⁻ ORR	02	2 420	11/ 7	11/7	1.2 ^b	8.0 (8h) ^b
						0.2 ^c	0.5 (3h) ^c
		Air			10.2% at	0.04	0.4 (10h)
oxygen-enriched	direct 2e⁻ ORR	O ₂		N/A	420 nm,	0.10	1.0 (10h)
g-C ₃ N ₄ (O-C ₃ N ₄) ⁹		Air	≥ 420			1.2 ^d	6.0 (5h) ^d
		O ₂			28.5% at 365nm	2.9 ^d	14.6 (5h) ^d
Posorsipol	direct 2e⁻ ORR		≥ 420			0.08	3.3 (24h)
formaldehyde resins ¹⁰		O ₂	sim. solar light	0.5%	7.5% at 420 nm	0.22	5.4 (5h)
Linear Conjugated	indirect	Air	sim.		8.7% at	1.2	3.0 (1.5h)
Polymer DE7 ¹¹	1e ⁻ ORR	O ₂	solar light	0.23%	420 nm	2.1	5.3 (1.5h)
Lignin supported BiOBr (LBOB) ¹²	indirect 1e⁻ ORR	O ₂	≥ 427	N/A	N/A	0.5	4.1 (6 h)
Self-assembled porphyrin (SA- TCPP) ¹³	indirect 1e ⁻ ORR	O ₂	≥ 420	1.2%	14.9% at 420 nm	1.2 ^e	6.9 (6h) ^e
CoO _x /Mo:BiVO ₄ /Pd ¹⁴	direct 2e⁻ ORR	O ₂	≥ 420	0.29%	5.8% at 420 nm	0.9	1.4 (1h)
		Air				1.2	1.1 (1.5 h)
	indirect				4 8% at	1.9	1.7 (1.5 h)
Imine sonoCOF-F2 ¹⁵	1e ⁻ ORR	02	≥ 420	N/A	420 nm	2.4 ^f	2.2 (1.5 h) ^f
		02				0.2 ^f	26.7 (166 h) ^f
						0.4 ^g	116 (168 h) ^g

9. Additional blank reactions

As validation of our previously discussed proposed mechanism we repeated some blank reactions and expanded on those. Irradiation reactions of oleic acid (50 mg) in Milli-Q water (4 mL) were conducted to confirm catalysis by the iron oxide nanoparticles. The chemicals were added (as described in **Table S7**) to a 10 mL vial with Milli-Q water (4 mL, 30 min pre-oxygenated). Pure oleic acid was also pre-oxygenated for 5 minutes prior to addition and irradiation. A Teflon stirring bar was added after which the vial was closed by capping. The sample was then extensively vortexed and sonicated for 5 min for better dispersion of the nanoparticles. Finally, 5 min of oxygen bubbling through the solution was conducted to ensure an oxygen atmosphere in the vial. Irradiation studies were conducted for 5h at 20°C by 445 nm irradiation. Blanks in darkness were also performed for comparison. Additionally, we conducted the same procedure with pure oleic acid (50 mg) without further addition of water. No oxidation of 1,3,5-Trimethoxybenzene (10 mg)), whereas peroxide test strips turned blue and were thus indicating peroxides.

Table S7: List of production values for the photochemical production of H_2O_2 via FeO_x NPs in batch. Blank reactions in darkness and light of oleic acid.

Entry	Condition	Peroxide Teststrip [mg L ⁻¹]	Produced H ₂ O ₂ [µmol L ⁻¹]	Produced H ₂ O ₂ [mmol g ⁻¹ L ⁻¹]	Productivity H ₂ O ₂ [mmol g ⁻¹ L ⁻¹ h ⁻¹]	Normalized production H ₂ O ₂ [mmol g ⁻¹ L ⁻¹]
1	FeO _x NP Standard (4 mg, darkness)	0	0	0	0	0
2	FeO _x NP Standard (4 mg)	0.5 to 2	34±2	9.4±1.3	1.7±0.3	9.4±1.3

Entry	Chemical 1 [mg]	Peroxide teststrip [mg L ⁻¹]	Produced H ₂ O ₂ [µmol L ⁻¹]	Produced H ₂ O ₂ [mmol g ⁻¹ L ⁻¹]	Comment
3	Oleic acid pure, after storage	0.5	-	-	Autooxidation through storage
4	Oleic acid pure, after 5 min O ₂	0.5	-	-	No difference through oxygenation
3	Oleic acid (<i>cis;</i> 50 mg), darkness, H₂O	0	-	-	No production
4	Oleic acid (<i>cis;</i> 50 mg), irradiation, H₂O	0.5	-	-	Autooxidation or storage
5	Oleic acid (cis; 50 mg), darkness, pure	0.5	0	0	No production, Autooxidation through storage
6	Oleic acid (cis; 50 mg), irradiation, pure	2	-	-	Autooxidation



Figure S25: ¹H-NMR spectra of oleic acid after 5h of irradiation to evaluate autoxidation and sacrificial agent behavior, measured in CDCl₃. No oxidation could be observed (also not in the zoomed in spectrum, bottom) as the detection limit of 1H-NMR was not reached or no autooxidation took place.

10. Applications of modular flow reactor in other reactions

In reactions without gases, such as the photoclick reaction, a notable enhancement in productivity and yield is observed. These enhancements are correlated to the elimination of the necessity for mass transfer of gas, which is necessary in processes like hydrogen peroxide (H_2O_2) synthesis via oxygen reduction reaction and the conversion of furfural to hydroxy butanolide through 1O_2 .¹⁶



10.1 Photoclick reaction of PQ and PY to PQ-PY in flow

Figure S26: Photoclick reaction of 9,10-phenanthrenequinone with N Boc-2,3-dihydro-1H-pyrrole within 180s.

MeCN (100 mL) was deoxygenated and enriched with N₂ for 30 min. 9,10-phenanthrenequinone (**PQ**) (1 eq., 10.42 μ mol, 2.17 mg) and N-Boc-2,3-dihydro-1H-pyrrole (PY, electron-rich alkene (**ERA**) (5 eq., 65.59 μ mol, 11.10 mg) were dissolved in 20 mL MeCN (N₂ enriched). The PFA tubing was connected between reactant flask, pump #1, flow-reactor, product flask. After priming (*i.e.* filling) the lines and flow-reactor with the reaction mixture to replace remaining air bubbles, N₂ atmosphere was ensured through a balloon. The flow reaction was then started (N₂ atmosphere, flowrate 2.13 mL min⁻¹, residence time t_R = 3 min.) at room temperature (20 °C) and irradiated with blue light (445 nm, 4 x 500 mW, 180 mW / cm²). The reaction was completed after 180 s and was monitored through UV-Vis spectroscopy and HPLC (0 s, 60 s, 120 s, 180 s, 300 s). For the HPLC analysis, the reaction mixture was diluted with 0.5 mL of H₂O before injection. Full conversion of PQ to the desired product PQ-PY (68% yield) was achieved.

Entry	Time [s]	PQ-PY yield [%]
1	0	0
2	60	17
3	120	60
4	180	66
5	300	68

As previously described^{17–19} the product can be purified as follows: For purification the volatiles were evaporated and the resulting residue was purified by column chromatography on silica gel (dichloromethane/ethyl acetate = 1:4, v/v) to afford PQ-PY as a colorless powder (54 mg, 0.14 mmol, 75 % yield). 1 H NMR (400 MHz, DMSO-d₆) δ 8.73 (d, J = 8.2 Hz, 2H), 8.05 (t, J = 6.6 Hz, 2H), 7.67 – 7.54 (m, 4H), 5.65 (s, 1H), 5.13 (ddd, J = 10.4, 6.8, 3.9 Hz, 1H), 3.50 (t, J = 9.6 Hz, 1H), 2.34 (dt, J = 12.2, 7.0 Hz, 1H), 2.02 – 1.90 (m, 1H), 1.48 (s, 9H). 13C NMR (101 MHz, DMSO-d₆) δ 153.7, 127.5, 126.7, 126.6, 125.8, 125.7, 123.4, 120.7, 80.5, 28.5. HR-MS (ESI) m/z, calculated for [M+Na]+: 400.1529; found: 400.1526.

10.1.1 UV-Vis spectroscopy of PQ-PY photoclick reaction in flow



Figure S27: Kinetic profile of the photoclick reaction for the production of PQ-PY followed via UV-Vis spectroscopy.



10.1.2 HPLC monitoring of PQ-PY photoclick reaction in flow



Peak Table Compound Group Calibration Curv

- controore	Compound Gro		uive						
Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	
1	17,678	86369	9421	M	0,000				
2	18,749	334321	35634	M	0,000				
3	22,448	235433	29366	M	0,000				
4	27,185	1211620	139645	M	0,000				
Total		1867743	214066		0,000				



Peak Table	Compound Gro	up Calibration Cu	rve				
Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#
1	17,682	39324	4433	М	0,000		
2	18,753	306859	33834	M	0,000		
3	22,445	268223	32895	M	0,000		
4	27,185	1333952	154093	M	0,000		
Total		1948359	225255		0,000		



Figure S28: HPLC analysis results for the determination of the yield of the PQ-PY production in flow over time.

Name

10.2 5-Hydroxy-2(5H)-furanone (hydroxybutenolide)



Figure S29: Conversion of renewable feedstock and biomass derived furfural to commodity chemicals such as hydroxy-butenolide for applications in coatings, resins, and paints.

A solution of freshly distilled (65 °C, 4 mbar) furfural (1 eq., 0.50 g, 5.2 mmol) and methylene blue (0.023 g, 0.072 mmol, 1.38 mol%) in 50 mL of methanol (30 min. oxygenated) was prepared in a 250 mL Erlenmeyer flask, with an oxygen balloon (1 atm) to ensure O_2 atmosphere. The solution was stirred at 600 rpm and pumped by a diaphragm liquid dosing pump (SIMDOS® 02 FEM 1.02 RC-P) at a flow rate of 2 mL/min from the reactant flask into the thin film flow reactor (residence time $t_R = 3.2$ min). The flow setup was irradiated with white light (LED, 500 mW, 152 mW / cm² @ 445 nm). With another pump (SIMDOS® 02 FEM 1.02 RC-P) the reaction mixture from the receiving product flask was transferred back into the reactant flask to ensure recirculation to achieve full conversion. The reacted mixture was collected for 24 h and monitored through ¹H-NMR spectroscopy (1 h, 2 h, 3 h, 4 h, 6 h, 20 h, 24 h). Under the optimized conditions described above, furfural is quantitatively converted into hydroxybutenolide. The collected solution contains hydroxybutenolide (0.1 mol L⁻¹), methyl formate (max. 1 eq., produced during reaction) and methylene blue (1.44 mmol L⁻¹) in methanol.^{16,20} This solution can be used directly for further transformations compatible with these components. For other purposes, methanol and methyl formate can be removed by rotary evaporation.²¹

As previously described^{16,21,22} the product can be purified as follows:

It is important to note that condensation of hydroxybutenolide with methanol (forming methoxy butenolide) will slowly occur at room temperature if the collected reaction mixture is left unattended. Cooling of the collection flask (*e.g.* with an ice bath) will effectively prevent this condensation from happening. Similarly, rotary evaporation should be performed under 25°C. Following these guidelines, hydroxybutenolide stained with methylene blue can be obtained quantitatively as a blue oil in > 97% purity. Note that methylene blue is present in such small amounts (0.5 mol%) that it is not detectable by ¹H-NMR.

Most of the methylene blue can be precipitated by slowly diluting the well-stirred crude blue oil at room temperature with diethyl ether (10 mL per gram of crude). Filtration of the supernatant solution on neutral aluminum oxide (1 g per gram of crude), rinsing with more diethyl ether (5 mL per gram of crude) affords a lightly colored filtrate, which is then concentrated, re-dissolved in chloroform (1 mL per gram of residue) and cooled to -18° C (*e.g.* in a freezer). Addition of a seed of solid hydroxybutenolide triggers crystallization, which is allowed to proceed at -18° C for a few hours (typically overnight). The crystallized material is then filtered, rinsing with a minimal amount of ice-cold chloroform (1 mL per gram of residue) or pentane (excess). Hydroxybutenolide is then obtained as a white solid of high purity, albeit with a loss of yield (typically 60% isolated).

Alternatively, removing the methylene blue can be done by silica gel column chromatography (gradient: AcOEt/pentane 10% to 60% over 25 column volumes).

5-hydroxy-2(5H)-furanone

¹H-NMR (400 MHz, CDCl₃) δ 7.22 (dd, J = 5.6, 1.2 Hz, 1H), 6.14 (dd, J = 7.2, 1.4 Hz, 2H).

Methyl formate

¹H-NMR (400 MHz, CDCl₃) δ 8.02 (q, J = 0.8 Hz, 1H), 3.71 (d, J = 0.8 Hz, 2H).



Figure S30: ¹H-NMR spectrum of 5-hydroxy-2(5H)-furanone and methyl formate after flow production in thin film flow reactor (closed system), crude in methanol measured in CDCl₃.



Figure S31: Kinetics followed *via* ¹H-NMR spectroscopy. Conversion of furfural (yellow) to 5-hydroxy-2(5H)furanone (green) and methyl formate (grey) over time through flow production in thin film flow reactor (closed system), crude in methanol measured in CDCl₃. The other peaks appearing and disappearing (7.35 ppm, 6.35 ppm, and 5.35 ppm), are most probably related to the intermediate endoperoxide after Diels-Alder reaction with ¹O₂.

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