Supporting Information

A Continuous Stirred-Tank Reactor (CSTR) Cascade for Handling Solid-Containing Photochemical Reactions

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Set-up of the photo-CSTR platform

As shown in Figure S1, the set-up combines the slurry pump, the CSTR cascade, blue LED light sources, focusing lenses and the pressurized fraction collector. The stir bars in the CSTR cascade are controlled by a magnetic stirrer, placed behind the CSTR. Due to the strong heat formation of the LED light sources, air cooling was necessary to maintain a temperature of 35° C of the reactor. The reaction temperature was measured with a thermocouple wire which was squeezed in between the two aluminum covers of the CSTR. The tubes used were made of PFA with an inner diameter of 0.76 mm. The pressurized fraction collector was connected to an argon cylinder in order to maintain a positive pressure of 0.7 atm. Mixing in the CSTR cascade was achieved by the magnetic stirrer (placed vertically behind the CSTR) which moves the magnetic stir bars located in the CSTR chambers (see Figure S1 and Figure S2a).



Figure S1. Image of the continuous stirred-tank reactor (CSTR) platform for handling solidcontaining photochemical reactions

Figure S2 shows a schematic of the CSTR cascade (a) and the open CSTR cascade without glass window, stir bars and aluminum covers (b).



Figure S2. (a) Flowchart of the CSTR cascade. All ports are shown – the blue arrows indicate the ports which were being used for the experiment while the black this arrow indicate optional ports. In the CSTR chambers the magnetic stir bars are located which are powered by the magnetic stirrer placed behind the CSTR cascade (b) Dimensions of the manufactured CSTR cascade. The dashed line represents the drill in the PTFE reactor block (CSTR 1 ID= 2.5 mm, CSTR 2 ID= 0.7 mm) which connects the single CSTR chambers

The tubes connecting the slurry pump - CSTR as well as the CSTR - pressurized fraction collector are equipped with vibration motors (attached with a tape around the tubing) (Model No. 306-10H, Precision Microdrives) in order to enhance solids transport (Figure S3).



Figure S3. Oscillation motor, Model No. 306-10H, Precision Microdrives¹

We used an aspheric condenser lens (Ø75 mm, f=60 mm, NA=0.61, ARC: 350-700 nm, article number: ACL7560U-A) by Thorlabs to focus the blue LED light and increase the photon flux within the CSTR (Figure S4).



Figure S4. (a-b) Condenser lenses used to focus the LED light (c) Schematic of the optical setup consisting of the three LED light sources, the condenser lenses and the CSTR cascade.

The pressurized fraction collector consists of a glass body with a polymer cap, containing builtin tubes for argon (ID 2.5 mm) and the slurry outflow of the CSTR (ID 0.7 mm) (Figure S5). The fraction collector can fit five 20 mL vials and two 7 mL vials. One vial is equipped with a magnet allowing rotation of the vial turnstile with another magnet placed on the outside of the fraction collector.



Figure S5. Pressurized fraction collector for 10 PSI argon overpressure. The suspension stream can be collected in 7 vials which can be rotated via a magnet. One magnet is attached to a vial inside the glass, the other magnet is placed on the outside of the glass

Characterization of the slurry pump

Figure S6 depicts the components of the slurry pump. In order to gain knowledge about the stability of the mass outflow of the slurry pump, we performed an experiment using a suspension of Na_2CO_3 in DMF (8.3 % w/t) as a model system. Samples of the biphasic outflow were taken during 100 minutes. The mass of the samples was determined and compared to the theoretical mass of the suspension (Figure S7).



Bottom cap

Figure S6. Components of the slurry pump.





Chemical Actinometry

For the [4+2] cycloaddition of DPA with singlet oxygen a solution of 0.1 mM DPA and 0.2 mM Ru(bpy)₃Cl₂ in acetonitrile were utilized (Figure S8). 200 mL of the solution was prepared in a dark room and bubbled with pressurized air for 30 min. Then, the mixture, along with a HPLC pump was placed in a dark box and the reaction mixture was pumped into the system. Non-transparent PEEK tubes were used for all connections in order to prevent irradiation before or after the reactor. Both reactors, the CSTR as well as a PFR were characterized and

compared (Figure S9a-d). While the set-up for all experiments was kept the same, the position/modification of the lights influences the irradiation of the reactor. ^{2, 3} The reported electrical input power (10%, 25% and 50%) of the LED was controlled using an A-Series Spectral Controller by Kessil Lightening. It is noteworthy to mention that the actual output power and the controllable input power of the LED are not equal.



Figure S8. Oxidation of 9,10-diphenylantracene (DPA) 1 to the corresponding endoperoxide 2 as a chemical actinometery.

The PFR consists of transparent FEP tubing (ID = 0.76 mm, length = 51 cm) positioned on an aluminum block (83x75 mm). During the actinometric experiment the tubing reaching out of the reactor was covered with aluminum foil in order to prevent further reaction in the tubing parts extending the 51 cm. The total reactor volume is 233 μ L and the surface (of the PFR) perpendicular to the light source is 3.89 cm².

Figure S9gh depict a simplified model for the irradiation efficiency in the PFR vs the CSTR. According to the Lambert-Beer law⁴, light penetrated diminishes with increasing reactor depth. Here, we used the extinction coefficient⁵ of Ru(bpy)₃Cl₂ $\varepsilon = 14600 \text{ M}^{-1} \text{ cm}^{-1}$ at wavelength $\lambda = 452 \text{ nm}$ for simplicity in the following calculation (In reality, the blue LED has an emission spectrum from 420 nm to 460 nm). Based on Beer–Lambert law (Equation S1, where A is the absorbance, ε is the molecular absorption coefficient, c is the molar concentration, and l is the optical path length), we can obtain the light intensity plot at different depth of reactor with the 0.2 mM Ru(bpy)₃Cl₂ solution (Figure S9gh).

$$A = \varepsilon \times c \times l$$
 Equation S1

Chemical actinometry is measuring the average light intensity (photon flux) across the reactor. With all other parameters (i.e. reactor illumination area, photocatalyst concentration, and light source) kept the same and only varying the depth of the reactor (PFR vs. CSTR), the photon flux per reactor volume should be proportional to the integral of the light intensity divided by reactor depth (Equation S2, where k is constant).

photon flux per reactor volume
$$\sim \frac{A}{L} = k \times \frac{A}{L}$$
 Equation S2

The integral of the light intensity is highlighted area in Figure S9gh for PFR and CSTR. Thus, we can obtain the calculated ratio of photon flux per reactor volume PFR:CSTR 5:1, similar to the experimental value (PFR:CSTR = 3.5:1), which explains the big difference between surface area ratio (13:1) and photon flux ratio (3.5:1) for PFR and CSTR. We expect that deviation of the calculated photon flux ratio from the experimental ratio may be caused by factors such as: broad light source wavelength, tubular shape of the PFR, light adsorption by glass window or tube material, and reflection and diffraction of light.

The conversion was monitored via in-line UV-Vis spectrometer (light source: Ocean Optics, Inc., DH- 2000-BAL; spectrometer: Ocean Optics, Inc., HR2000+). The absorbance of 0% conversion was measured by covering the reactor, while the full conversion value was obtained by irradiating a closed glass vial of the reaction mixture for one hour. The conversion of the DPA was calculated based on the absorption peak at 373 nm according to the following equation S3.⁶

Conversion (%) =
$$\left(1 - \frac{Abs(x) - Abs(full)}{Abs(0) - Abs(full)}\right) x \, 100$$
 Equation S3



Figure S9. (a) Schematic of the chemical actinometry in the CSTR (b) Image and specifics of the CSTR (c) Schematic of the chemical actinometry in the PFR (d) Image and specifics of the PFR (e,f) Comparison of the light path in PFR vs CSTR (g) Light attenuation in PFR according to Equation S1 (h) Light attenuation in CSTR according to Equation S1

	Outlet Concentration of DPA (µmol/L)			
Residence time [min]	10% power	25% power	50% power	
0.5	54.89	44.26	28.34	
0.6	48.26	39.10	23.70	
0.75	43.41	32.97	19.03	
1	37.77	23.97	11.71	

The following tables (Table S1-S3) summarize the presented data of Figure 6. Table S1 Data of Figure 6b

Table S2 Data of Figure 6c

LED input power	Absorbed photon flux (mol s ⁻¹ m ⁻³)	
10%	0.07913	
25%	0.09778	
50%	0.12573	

Table S3 Data of Figure 6d

	Surface to volume ratio (cm ⁻¹)	Absorbed photon flux (mol s ⁻¹ m ⁻³)
PFR	16.7	0.07913
CSTR	1.27	0.27488

Residence time distribution (RTD) experiments

Liquid-Liquid-RTD

Single phase residence time distribution measurements were performed as shown in the flowchart in Figure S10a. Methylene blue was used as a liquid tracer (in water) and injected via six-way valve in a carrier stream in water. UV/Vis spectrometer were placed before and after the CSTR. Figure S10b shows the RTD profile of CSTR 2 in comparison with the ideal CSTR in series model.



Figure S10. (a) Schematic of the liquid RTD experiment (b) RTD of CSTR 2 under three different flowrates (0.1, 0.5, 2 mL/min) and comparison with ideal CSTR in series model

The raw data of the measured RTD profiles as well as the regression of the outflow with the EMG model for CSTR 1 and CSTR 2 are shown in Figure S11 - Figure S16.



Figure S11. RTD profile and EMG regression in CSTR 1 at 2 mL/min



Figure S12. RTD profile and EMG regression in CSTR 1 at 0.5 mL/min



Figure S13. RTD profile and EMG regression in CSTR 1 at 0.1 mL/min



Figure S14. RTD profile and EMG regression in CSTR 2 at 2ml/min



Figure S15. RTD profile and EMG regression in CSTR 2 at 0.5 mL/min.



Figure S16. RTD profile and EMG regression in CSTR 2 at 0.1 mL/min

Solid-liquid RTD

Solids RTD measurements were performed in two different set-ups. Initially, the outlet profiles were measured as shown in the flowchart (Figure S17, Figure S18). Further, the set-up was modified (removal of the CSTR) and the inlet RTD profiles were measured (Figure S19).



Figure S17. Flowchart of solids RTD - Outlet RTD measurements



Figure S18. Image of the set-up for solids RTD measurement.



Figure S19. Flowchart of solids RTD - Inlet measurements

Figure S20 and Figure S21 show the measured RTD profiles along with the regression using the EMG model.



Figure S20. RTD profile and EMG regression in CSTR 2 at 0.5 mL/min using the 75 μ m tracer



Figure S21. RTD profile and EMG regression in CSTR 2 at 0.5 mL/min using the 10 μ m tracer

Particle analysis

Particle size distribution was measured on a Laser diffraction particle size analyzer, a Mastersizer 3000 (Malvern) with Hydro SV accessory.

Specifics:

- Laser: 4mW He-Ne, 632.8nm
- Analysis: Mie scattering
- Distribution: volume distribution
- Angular range: 0.015 144 degrees
- Particle refractive index: 1.59
- Dispersant refractive index: 1.33
- Dilution factor: ~700-1000 x

SEM images were taken on a Phenom G1 (FEI).

Specifics:

- Image mode: Backscatter
- Accelerating voltage: 5kV
- Sample prep: sputter coating, gold/palladium 60/40

Particle analysis of K₃[Fe(CN)₆] (<10µm)

The commercially available particles of $K_3[Fe(CN)_6]$ (10µm, according to Sigma Aldrich) were analyzed in terms of particle size distribution (Figure S22) and SEM images were taken (Figure S23).



Figure S22. Particle size distribution of the commercially available K_3 [Fe(CN)₆] particles (10 μ m, according to Sigma Aldrich)



Figure S23. SEM images of the K₃[Fe(CN)₆] particles (10µm, according to Sigma Aldrich) particles

Particle analysis of K₃[Fe(CN)₆] (<75µm)

The particles of $K_3[Fe(CN)_6]$, obtained via grinding and sieving of large pieces, were analyzed in terms of particle size distribution (Figure S24) and SEM images were taken (Figure S25).



Figure S24. Particle size distribution of the prepared K_3 [Fe(CN)₆] (75µm) particles



Figure S25. SEM images of the prepared K_3 [Fe(CN)₆] (75µm) particles

Particle analysis of NaBr (Outflow of the CSTR)

The solids in the outflow of the CSTR contain mainly the precipitated NaBr along with the excess base Na₂CO₃. Particle size distribution measurements (Figure S26) as well as SEM image analysis was performed (Figure S27).



Figure S26. Particle size distribution of the outflow of the CSTR, containing precipitated NaBr and the excess base Na₂CO₃



Figure S27. SEM image of the outflow of the CSTR, containing precipitated NaBr and the excess base Na₂CO₃

CSTR simulating batch experiments

In order to allow quick solvent screening with minimal reagent consumption we designed batch experiments (Figure S28a,b). A stock suspension was prepared of methyl-4-bromobenzoate (1

40 4-bromotetrahydropyran equiv., mmol/L), (1.5)equiv., 60 mmol/L), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2 mol%), $NiCl_2(dtbbpy)$ (1 mol%), $(Me_3Si)_3SiH$ (1.3 equiv.), Na₂CO₃ (2 equiv.) naphthalene (10 mol%, internal HPLC standard) and 1,3,5trimethoxybenzene (10 mol%, internal NMR standard) in the desired dry and degassed solvent (DME or DME:DMA 1:1). The starting material suspension was degassed again with argon. 2 mL of the well suspended mixture were added to a dry vial, (1) analyzed via HPLC (2) and irradiated for 30 minutes (3). Then the products were analyzed via HPLC (4), 2 mL of stock suspension was added under argon overpressure (5) and the mixture was analyzed again via HPLC (6). The mixture was irradiated for 30 minutes (7) and analyzed again via HPLC (8). Yield and conversion were determined via HPLC using naphthalene and 1,3,5trimethoxybenzene as internal standards. Figure S28c,d shows the results of the analysis of the HPLC samples in terms of yield and conversion at the analytical steps 2,4,6,8 from the flowchart (Figure S29b).



Figure S28. (a) Cross coupling of 4-bromotetrahydropyran **3** and methyl-4-bromobenzoate **4** (b) Flowchart of the steps during the solvent screening batch experiments starting from (1) till (8) (c) Yield and Conversion at steps 2,4,6,8 using only DME (d) Yield and conversion at steps 2,4,6,8 using a solvent combination of DMA:DME 1:1

NaBr spiking experiments

In order to investigate whether NaBr causes inhibition of the reaction we designed the batch experiments. A stock suspension was prepared of methyl-4-bromobenzoate (1 equiv., 40 mmol/L), 4-bromotetrahydropyran (1.5 equiv., 60 mmol/L), Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2 mol%), NiCl₂(dtbbpy) (1 mol%), (Me₃Si)₃SiH (1.3 equiv.), Na₂CO₃ (2 equiv.) and naphthalene (10 mol%, internal HPLC standard) in dry and degassed DME. The starting material suspension was degassed again with argon. 1 mL of the well suspended mixture was added per vial (5 vials). The vials were irradiated (440 nm, blue LED) and analyzed in terms of yield after five minutes of reaction time. Then four (out of the five) vials were treated with 20 mol%, 80 mol%, and 100 mol% of NaBr (See Table S4). No NaBr was added to the first vial (control experiment). Further, yield was analyzed after 15, 35 and 95 minutes. Yield was determined using naphthalene as an internal standard for HPLC. As shown in Table S4 addition of NaBr did not lead to inhibition of the reaction.

		Yield (HPLC)			
Vial	NaBr	5 min	15 min	35 min	95 min
1	0 mol%	6%	15%	35%	88%
2	20 mol%	7%	10%	28%	83%
3	80 mol%	5%	17%	33%	79%
4	100 mol%	7%	11%	30%	86%

Table S4 NaBr spiking experiments

General procedure for the preliminary batch experiments



For the batch experiments, the following procedure was adapted from the literature.⁷ Alkylbromide (194 mg, 0.698 mmol, 1.5 equiv.), methyl 4-bromobenzoate (100 mg, 0.465 mmol, 1 equiv.), Na₂CO₃ (99 mg, 0.93 mmol, 2 equiv). Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (10.43 mg, 0.0093 mmol, 0.02 equiv.), NiCl₂(dtbbpy) (1.85 mg, 0.00465 mmol, 0.01 equiv.), (Me₃Si)₃SiH (186 μ L, 0.6045 mmol, 1.3 equiv.), naphthalene (10 mol%, internal HPLC standard) and 1,3,5-trimethoxybenzene (10 mol%, internal NMR standard) were added to a dry vial, equipped with a stir bar. The vial was sealed and placed under argon. Then DME (2 mL, already degassed by sparging with argon) was added. The mixture was sonicated and then irradiated (blue LED 440 nm) at 35-37°C for 15 hours. For work-up, the suspension was washed with water, reextracted with ethyl acetate, dried over MgSO₄ and evaporated under vacuo. Yield and conversion were determined via HPLC (with naphthalene as an internal standard) and confirmed with quantitative NMR using 1,3,5-trimethoxybenzene as an internal standard.

Methyl 4-(tetrahydro-2H-pyran-4-yl)benzoate (5)



Following above general procedure for the preliminary batch experiments, using 0.698 mmol 4-bromotetrahydropyran. Analysis via HPLC (internal calibration) gave 80% yield, 100% conversion. The NMR data matched the data obtained from the flow chemical experiments (see below).

tert-Butyl 4-(4-(methoxycarbonyl)benzyl)piperidine-1-carboxylate (9)



Following above general procedure for the preliminary batch experiments, using 0.698 mmol tert-butyl 4-(bromomethyl)piperidine-1-carboxylate. Analysis via HPLC (internal calibration) gave 60% yield, 100% conversion. The NMR data matched the data obtained from the flow chemical experiments (see below).

General flow procedure



Methyl 4-bromobenzoate (1 equiv., 40 mmol/L), alkylbromide (1.5 equiv., 60 mmol/L), Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2 mol%), NiCl₂(dtbbpy) (1 mol%), (Me₃Si)₃SiH (1.3 equiv.), Na₂CO₃ (2 equiv.), naphthalene (10 mol%, internal HPLC standard) and 1,3,5-Trimethoxybenzene (10 mol%, internal NMR standard) were added to the slurry pump and suspended in DME. The starting material suspension was degassed by sparging with argon directly in the slurry pump using a long needle. During this procedure the slurry pump was positioned upside down (outlet on top instead on the bottom). The slurry pump was positioned on a stir plate approx. 30 cm above the CSTR and connected to a positive displacement pump, necessary for feeding the hydraulic liquid. The CSTR was purged with dry argon, then filled with degassed DME and connected to the slurry pump. Next, the fraction collector was purged with argon, connected to the CSTR and then set to 10 PSI argon overpressure. The flow rate for the positive displacement pump was set to 176 µL/min (30 min residence time in the CSTR), stirring in the CSTR was started, irradiation via blue LEDs was started, air cooling was started and the vibration motors at the slurry pump and at the outlet of the CSTR were started. Samples were taken in the fraction collector by rotating the collector with the magnetic mechanism. For work-up, the suspension was washed with water, reextracted with ethyl acetate, dried over MgSO4 and evaporated under vacuo. Yield and conversion were determined via HPLC and confirmed with quantitative ¹H NMR using naphthalene and 1,3,5trimethoxybenzene as internal standards. Purification was done by preparative HPLC.

Methyl 4-(tetrahydro-2H-pyran-4-yl)benzoate (5)



Following above general flow procedure, on 60 mmol/L using 4-bromotetrahydropyran. The HPLC (internal calibration) analysis gave 77% yield, 100% conversion and a productivity of 77 mg/h. Purification by preparative HPLC (MeCN/H₂O with 0.1% formic acid) afforded product **5** as colorless oil.

¹H NMR (400 MHz, Chloroform-d) δ 8.03 – 7.96 (m, 2H), 7.34 – 7.28 (m, 2H), 4.14 – 4.06 (m, 2H), 3.91 (s, 3H), 3.54 (td, J = 11.5, 2.6 Hz, 2H), 2.83 (tt, J = 11.5, 4.4 Hz, 1H), 1.92 – 1.77 (m, 4H).

¹H NMR matches previously reported data ⁷

tert-Butyl 4-(4-(methoxycarbonyl)benzyl)piperidine-1-carboxylate (9)



Following above general flow procedure, 60 mmol/L using tert-butyl 4-(bromomethyl)piperidine-1-carboxylate. The HPLC (internal calibration) analysis gave 58% yield, 99% conversion and a productivity of 80 mg/h. Purification by preparative HPLC (MeCN/ H_2O with 0.1% formic acid) afforded product **9** as colorless oil.

¹H NMR (400 MHz, Chloroform-d) δ 8.00 - 7.89 (m, 2H), 7.25 - 7.15 (m, 2H), 4.08 (d, J = 13.4 Hz, 2H), 3.91 (s, 3H), 2.71 - 2.54 (m, 4H), 1.70 (th, J = 11.0, 3.6 Hz, 1H), 1.63 - 1.52 (m, 2H), 1.45 (s, 9H), 1.24 - 1.08 (m, 2H).

¹H NMR matches previously reported data⁸

¹³C NMR (101 MHz, CDCl₃) δ 167.10, 154.84, 145.79, 129.62, 129.14, 128.03, 79.33, 52.02, 43.90, 43.14, 38.02, 31.95, 28.47.

HRMS (ESI): m/z [M+Na]+ calculated for C19H27NO4Na 356.1837, found: 356.1843







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