Photo-oxidation in Three-phase Flow with Continuous Photosensitizer Recycling

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ABSTRACT

Microreactors have emerged as a promising platform for conducting photo-oxidations, offering green routes to facilitate significant chemical transformations. In this study, the sustainability of photo-oxidations is improved by a three-phase gas/liquid/liquid flow reaction in a photo microreactor with continuous recycling, which is applied to a model reaction. Recycling is enabled by the photosensitizer and the substrate, which are in immiscible phases. The effect of various operational parameters on the reaction and the contact pattern among phases is explored, and the interplay between the flow pattern and photo-oxidation is discussed. The highest conversion is detected for flow conditions that display significantly lower diffusion distance between the flow pattern and mass transfer. Furthermore, phase separation was automated using a liquid-liquid separator where the photosensitizer and organic substrate were recycled continuously to achieve full conversion. The proposed approach eliminates the downstream purification step and provides a sustainable pathway toward photo-oxidations in microreactors.

KEYWORDS: microreactors, photo-oxidation, singlet oxygen, three-phase flow, continuous recycling

INTRODUCTION

Singlet oxygen (¹O₂) is the lowest energy excited electronic state of molecular oxygen,^{1,2}, and due to its high reactivity, it has been the subject of various applications, including photodynamic therapy,^{3,4} synthesis of fine chemicals,⁵ and wastewater treatment.⁶ Among different approaches to producing ¹O₂, photosensitization, mainly conducted with dye-type photosensitizers, is controllable and straightforward.^{7,8} In the photosensitized production of ¹O₂, there is a direct energy transfer between the photosensitizer and molecular oxygen, leading to the formation of ¹O₂.⁹ In the presence of ¹O₂, alkenes and aromatic compounds react to generate endoperoxides, 1,2-dioxetanes, and hydroperoxides.¹⁰ Photo-oxidation involving singlet oxygen can be considered a green chemistry process as it needs only the organic substrate, light, photosensitizer, and molecular oxygen, which is known as a green and low-cost oxidant.¹¹

The formation and use of singlet oxygen are increasingly investigated in photochemical flow reactors.^{3,12–14} Microreactors having high surface-to-volume ratios and accompanied short optical pathlengths provide a suitable environment for photosensitized oxidations due to enhanced mass transfer properties and precise control over reaction time that minimizes side reactions.^{15–17} Moreover, performing the photooxidations in multiphase flow brings improved mass transfer compared to single-phase flow.¹⁸ Jacobs et al. compared the efficiency of photo-oxidation of 9,10diphenylanthracene in single and two-phase (gas/liquid) Taylor flow and reported that higher conversion is obtained for two-phase conditions.¹⁸ This performance was attributed to the increased level of mixing due to introducing the gas phase to the flow, the elimination of mass transfer limitations, and the highly reactive liquid film occurring on the wall due to the Taylor flow. Two comparatively large-scale applications of photooxidation based on singlet oxygen are in the synthesis of artemisinin and rose oxide.^{19–21} In a research study by Gupton et al., a two-phase gas/liquid flow in a photo-microreactor equipped with an immobilized Rose Bengal column was used to produce the anti-malarial drug artemisinin via a singlet oxygen-including route.²² In a different study, the production of the fragrance rose oxide by photo-oxidation of citronellol was studied in gas-liquid flow in a photo-microreactor where the photosensitizer and the substrate were both in the

same phase.¹⁹ Even though studies for synthesizing these chemicals provide essential information, recycling the photosensitizers is mainly overlooked, which constitutes an economic and environmental barrier to their wider application on a larger scale.

From an economical and environmental point of view, recycling the photosensitizer would improve the sustainability of the photo-oxidations carried out in microreactors. The photosensitizer can be separated and reused in flow by immobilizing on polymers²²⁻²⁵ or silica.^{3,26,27} Common challenges caused by immobilization are decreasing activity, despite the lower photobleaching degree compared to a free photosensitizer,³ leaching,²⁸ and clogging of microchannels when the supported photosensitizer is in suspension.²⁹ Another way to separate the photosensitizer in flow is by introducing it in a different phase than the substrate. This method's main advantage is simplifying the sensitizer recycling by phase separation without deactivation.³⁰ Additionally, since the recovered sensitizer is not deactivated, it does not require further energy-intensive downstream treatment steps before reuse. Large amounts of products could be achieved efficiently by continuously recycling the sensitizer, increasing the overall sustainability of the catalytic process. Fabry et al. performed photocatalytic isomerization of olefins in a glass microreactor using a photosensitizer in a liquid/liquid flow.³¹ In this study, a continuous recirculation of the photosensitizer, which is immobilized in an ionic liquid, was conducted by simply separating the two liquids, the ionic liquid and toluene phases.³¹ Three-phase gas/liquid/liquid (G/L/L) flow in microreactors for metal-catalyzed gas-liquid hydrogenation with online recycling was studied by Yap et al.³² Catalyst metal was introduced to the liquid, and a G/L/L flow was established to remove the catalyst via phase separation of two liquids.³² Yu et al. showed that for a gas/liquid/solid flow photo-oxidation in a microreactor, where the photo-oxidation of methylene blue dye was performed in the presence of oxygen gas, and a TiO₂-coated microchannel, mass transfer efficiency was improved due to the presence of gas bubbles. Furthermore, the reaction efficiency was fine-tuned by controlling the operating parameters such as flow rate ratios of each phase.33

Even though G/L/L three-phase systems have proven to be very efficient for recycling³⁴ and have been applied in chemical transformations, including selective

hydrogenation of unsaturated aldehydes³⁰ and crystallization of proteins³⁵ in microreactors, the potential of G/L/L systems in microreactors still needs to be explored in detail. The current literature lacks knowledge of G/L/L systems in photo-oxidation reactions, most likely due to inherent characteristics of the G/L/L flow, where contacting the reactants is challenging as reactants in gas and liquid phases are separated by a continuous phase and two interfaces between gas-liquid and liquid-liquid. Even though G/L/L reactions are applied on an industrial scale for some applications, including hydroformylation, hydrogenation, and carbonylation,^{34,36} it was reported that the insufficient mass and heat transfer and poor control of the contact pattern limit the efficiency, reliability, and also reproducibility of the system.³⁷ The required contacting mechanism of the phases is specific to the reaction type, and each reaction needs particular requisites of the contact patterns to achieve high performance. More research is required to harness the advantages of three-phase G/L/L flow in photo-reactions. Depending on the application of the G/L/L reaction, the continuous phase may either carry the photosensitizer or serve as a medium within phases enabling the transport of reactive species.³⁸ It is well known that the rate of multiphase reactions is determined by the mass transfer of reactants between phases,³⁹ and mass transfer limitations are even more profound when conducting fast oxidation processes such as singlet oxygen-mediated photo-oxidations.¹⁵

This study combines three-phase flow with adjustable contact patterns in microreactors with continuous recycling to develop a purification-free photo-oxidation process. The singlet oxygen-mediated oxidation of the substrate, 1,3diphenylisobenzofuran (DPBF), in the presence of Rose Bengal (RB) as a photosensitizer, is used as a model reaction. This choice is motivated by the singlet oxygen generated from this specific reaction has high reactivity, which is advantageous for its adoption for photochemical transformations.¹ This model reaction explores significant parameters that have the most influence on photo-oxidation performance. The three-phase flow consists of a G/L/L flow: DPBF is solubilized in the organic phase (toluene), RB in the aqueous phase, and pure oxygen gas is used as a source of molecular oxygen. Firstly, we focused on the influence of the operational parameters on DPBF conversion to determine the interplay between hydrodynamics, mass, and photon

transport. Next, the most performant flow patterns are implemented into a continuous recycling system, recirculating the RB and DPBF until full conversion. To our knowledge, a three-phase G/L/L photo-oxidation reaction in a microreactor with an adjustable contact pattern between phases and continuous recycling of the photosensitizer and the substrate has not yet been reported.

EXPERIMENTAL SECTION

Experimental Procedure for DPBF Photo-oxidation in Three-phase Flow. To obtain DPBF and RB solutions with different concentrations, DPBF is dissolved in toluene, and RB is dissolved in MilliQ water. These solutions and O₂ gas are then introduced to the reactor. A schematic of the experimental setup used in this study is shown in Figure 1. The microreactor (Chemtrix Inc.) is a plate microreactor. It has a serpentine crosssectional channel (d=1 mm) with six straight sections and an overall length of 70 cm that is etched in a borosilicate glass plate with a volume of 0.549 mL. The mass flow controller (MFC, Bronkhorst) controls the O₂ gas (purity level > 99.9, Alphagaz[™]) flow rate, and O₂ gas is introduced to the microreactor, where it meets the two organic and aqueous liquid phases via a cross-junction, located inside the microreactor. A pressure sensor is placed before the back pressure regulator (BPR-10, Zaiput), and a screwdriver and a syringe filled with air connected to the BPR are used to regulate the gas pressure to ensure a stable oxygen flow. Placing the BPR in the gas line just before the cross-junction at the inlet of the reactor, where three phases meet, prevents fluctuations resulting from the bubble formation and ensures a stable three-phase flow. Next, the RB solution (aqueous phase) is introduced to the reactor from the second inlet by using a syringe pump. Lastly, the DPBF solution is fed into the microreactor through the third inlet (Figure 1). At the reactor outlet, three phases pass through a flow cell connected to a lamp and a spectrometer by optical fibers for real-time absorbance measurements of fluids. Next, the three-phase flow is collected in a waste flask. To enable the photon flux required for the photochemical reaction, the microreactor is irradiated by a set of green LEDs (λ_{max} = 526 nm) mounted on a board. The LEDs are placed to match the microreactor channels, and the distance between green LEDs and the microreactor was kept constant at 2 cm.





Online Monitoring of the Reaction. The outlet of the reactor is connected to a cross-cell (Avantes) for online absorption measurement. A compact spectrometer (Ultra low straylight fiber optic UV/VIS/NIR spectrometer 200-1100 nm, Avantes) and a balanced deuterium-halogen light source (215-2500 nm, Avantes) are connected to the flow cell via optical fibers (400 µm UV/VIS fiber, Avantes). The spectrometer is connected to a computer that continuously monitors the absorbance values at 419 nm (for DPBF) and at 550 nm (for RB) to visualize when the reactor reaches steady state, which is later stored to RAM by using the software Avasoft 8, to calculate DPBF conversion. A fast alternation between gas and liquid phases is observed in a three-phase flow. Therefore, a short integration time of 0.04 ms is applied to obtain sufficient data points for the liquid phases, and each absorbance measurement (220-1000 nm) consists of 200 spectra; each spectrum is the average of 50 scans. These spectra, consecutively acquired every 8 ms, were stored in the spectrometer RAM and read by the Avasoft software on the computer. Before each absorbance measurement, reference and dark measurements were performed by passing pure toluene through the flow cell. The average of six

absorption measurements was used to calculate the concentrations of DPBF and RB, and the data processing is explained in detail in Section 1 in the Supporting Information (SI).

Determination of G/L/L Flow Characteristics Using Image Processing. The characteristics of the three-phase flow were analyzed by acquiring images of the entire microreactor channels. This method developed by our group has successfully been applied for two-phase flow characterization in the same reactor.^{14,40} Images were obtained using a full-frame CMOS sensor camera (Nikon, D810) and a 24-70 mm lens (Nikon, AF-S NIKKOR) with a focal length of 35 mm and a f-number of 2.8. A shutter speed of 1/3200 s and a resolution of 7360×4912 pixels were used for this purpose. Green-light LED array used during the photochemical reaction is used as a light source during the image analysis. A light-diffusing smoked glass was placed on the reactor glass plate towards the LED array to ensure uniform light illumination throughout the reactor channels. For each flow condition, three images were acquired and processed in MATLABTM to determine the length of each phase in the straight channels of the reactor. Results obtained from MATLAB[™] were averaged to determine the length of each phase (L_b, L_{DPBF}, L_{RB}) . The procedure is described in Section S2 of the SI. The bubble velocity was measured by recording videos using the same camera at 59.9 fps and with a resolution of 1920×1080 pixels. For different flow conditions, 1-minute-long videos were recorded, and the velocity was calculated by using the time required for the bubble to travel along each channel of the reactor. Three different bubbles were considered while calculating the average bubble velocity, u_b . Bubble velocities determined for different flow rate conditions are shown in Figure S12.

Flow rate ratios of G/L/L phases in three-phase flow affect the flow pattern where the length and shape of each phase in the unit cell differ. A unit cell in this study is defined as the distance between the rear of a gas bubble to the rear of the next gas bubble, and this definition is shown in Figure 2. Bubble length (L_b) is defined as the distance from the rear to the nose of the same bubble. Similarly, the length of the RB slug (L_{RB}) refers to the distance from the rear to the nose of the same slug. The length of the DPBF slug (L_{DPBF}) refers to the remaining section in a single unit cell.



Figure 2. Schematic representation of G/L/L Taylor flow unit cell in a microreactor.

As shown in Figure 2, the DPBF solution is the wetting phase in the microreactor, whereas O_2 and RB solution are the dispersed phases. The continuous phase, DPBF dissolved in toluene, is the substrate in this system, and during the flow, a film is formed around dispersed phases. Consequently, dispersed phases pass through a cross-section smaller than the microreactor channel's cross-section. For simplification, bubble film thickness (δ_{fb}) and RB slug film thickness (δ_{fRB}) are assumed equal and represented with overall film thickness, δ_{F} . Details of the image analysis and film thickness calculations are given in Section S2 in SI.

RESULTS AND DISCUSSION

Photosensitized Oxidation of DPBF in Three-phase Flow. DPBF is a common substrate used as singlet oxygen (¹O₂) trapping agent^{41,42} and probe for superoxide anion radical (O₂⁻⁻).⁴³ It is insoluble in water but is known to be soluble in water/alcohol solutions¹ and in organic solvents, including toluene, acetonitrile, cyclohexane, DMF, and DMSO.⁴³ Irrespective of the solvent used, DPBF is known to absorb the light around 410 nm, and bright, blue-like fluorescence is emitted afterward.⁴³ The π-system of isobenzofuran breaks down due to a reaction between DPBF and ¹O₂ to form o-dibenzoylbenzene (DBB), and the product cannot absorb or emit visible light (Scheme 1).⁴³ This property of DPBF is used to quantify the ¹O₂ production and detection of O₂⁻⁻.^{1,43} In this study, RB is used as a photosensitizer as its absorption spectrum overlaps with the emission spectrum of green LEDs, which are used as an irradiation source in this study, with a maximum at

526 nm (Figure 3). Additionally, RB is known to produce singlet oxygen in high yields; it was reported that the quantum yield (Φ_{Δ}) for singlet oxygen production in water is 0.75-0.76.^{1,9,44}



Scheme 1. The reaction of 1,3-diphenylisobenzofuran (DPBF) with ¹O₂.⁴³





The three-phase flow in this study consists of a continuous organic phase (DPBF dissolved in an organic solvent) with dispersed gas (O₂) and dispersed aqueous phases (dissolved photosensitizer RB).

The flow pattern used for the RB-sensitized photo-oxidation of DPBF directly influences hydrodynamics and photochemical reaction, as the amount of light absorbed

by the medium is sensitive toward the changes in the flow. The effect of flow rate ratios between phases, total flow rate, photon flux, and RB concentration on photo-oxidation performance is explored in this section.

Influence of Flow Rate Ratios. For G/L/L flow, eight different flow rate ratios between phases were applied to determine their influence on the photo-oxidation performance. For all flow conditions, the microreactor was operated in a stable Taylor flow regime. Samples were named after their corresponding oxygen, DPBF, and RB flow rates, respectively. For instance, the flow condition named G/L/L:35/15/50 shows O₂ gas bubbles with 0.35 mL min⁻¹, DPBF slugs with 0.15 mL min⁻¹, and RB slugs with 0.50 mL min⁻¹. To designate the effect of these flow rate ratios on the mass transfer, photo-oxidation of DPBF in a microreactor was conducted, and conversion of DPBF was calculated. During these measurements, the total flow rate (Q_{total}) was kept constant at 1 mL min⁻¹, and the initial DPBF concentration ([DPBF]) and initial RB concentration ([RB]) were kept constant at 0.6 and 0.1 mM, respectively. LEDs were operated at a forward current (I_F) of 8 mA/LED. Concentration change was followed by online UV-Vis spectroscopy as described in Section S1 in the SI. Conversion values are given in Table 1, together with the standard deviation calculated based on six repetitions for each measurement.

Elow condition	Flow	rate (mL	Conversion (9/)	
Flow condition	O ₂	DPBF	RB	Conversion (%)
G/L/L:35/15/50	0.35	0.15	0.50	31.48 ± 2.88
G/L/L:35/25/40	0.35	0.25	0.40	25.51 ± 1.91
G/L/L:35/40/25	0.35	0.40	0.25	21.63 ± 1.63
G/L/L:35/50/15	0.35	0.50	0.15	17.39 ± 1.57
G/L/L:40/25/35	0.40	0.25	0.35	29.14 ± 1.53
G/L/L:40/35/25	0.40	0.35	0.25	21.22 ± 2.58
G/L/L:50/15/35	0.50	0.15	0.35	35.18 ± 1.83
G/L/L:50/35/15	0.50	0.35	0.15	20.25 ± 1.29

Table 1. DPBF Conversion for Different Flow Rate Ratios (Q_{total} =1 mL min⁻¹, [DPBF]=0.6 mM, [RB]=0.1 mM, and I_F =8 mA/LED).

Table 1 implies that flow conditions G/L/L:35/15/50 and G/L/L:50/15/35 exhibit significantly higher conversion than those under the same operating conditions. To reveal the reason behind the effect of the flow pattern on DPBF conversion, image analyses for these flow conditions were conducted, and the procedure is described in detail in Section S2 in the SI. Table 2 displays the length of each phase in the three-phase flow identified by image processing.

Flow condition	Flow rate (mL min ⁻¹)		Length (mm)						
	O ₂	DPBF	RB	O ₂	DPBF	RB	Unit cell		
G/L/L:35/15/50	0.35	0.15	0.50	1.93 ± 0.29	0.49 ± 0.05	3.85 ± 0.45	6.77 ± 0.48		
G/L/L:35/25/40	0.35	0.25	0.40	1.79 ± 0.23	0.87 ± 0.09	3.00 ± 0.32	6.06 ± 0.41		
G/L/L:35/40/25	0.35	0.40	0.25	1.88 ± 0.24	1.24 ± 0.15	1.64 ± 0.19	5.05 ± 0.11		
G/L/L:35/50/15	0.35	0.50	0.15	1.74 ± 0.21	1.68 ± 0.15	1.43 ± 0.15	5.94 ± 0.14		
G/L/L:40/25/35	0.40	0.25	0.35	2.16 ± 0.24	0.74 ± 0.08	2.20 ± 0.24	5.23 ± 0.32		
G/L/L:40/35/25	0.40	0.35	0.25	2.08 ± 0.23	1.38 ± 0.14	1.87 ± 0.18	5.41 ± 0.39		
G/L/L:50/15/35	0.50	0.15	0.35	2.46 ± 0.29	0.57 ± 0.06	2.52 ± 0.26	5.64 ± 0.23		
G/L/L:50/35/15	0.50	0.35	0.15	3.18 ± 0.36	1.61 ± 0.15	1.30 ± 0.13	6.41 ± 0.19		

Table 2. Length of Oxygen Bubbles, DPBF Slugs, and RB Slugs for Different Flow Rate Ratios (Q_{total} =1 mL min⁻¹).

For six out of the eight different flow conditions shown in Table 2, the prevalent unit cell configuration consists of an RB slug and the O_2 bubble with a DPBF substrate layer in between, as depicted in Figure 4-a (see experimental section and Figure S10 in SI for more information). However, the unit cell configuration was different for flow conditions G/L/L:35/15/50 and G/L/L:50/15/35. The low flow rate of DPBF (0.15 mL min⁻¹) in these specific flow conditions eliminates the substrate layer between the RB slug and the O_2 bubble, resulting in a unit cell configuration displayed for G/L/L: 35/15/50 in Figure 4-b.



Figure 4. Acquired images of different G/L/L Taylor flow unit cell configurations in the microreactor a) for the flow condition G/L/L: 35/25/40 and b) G/L/L: 35/15/50.

As seen from Figure 4-b, the RB slug is in close proximity to the gas bubble, which is known as the 'bubble-slug cluster' in the literature.³⁷ In this configuration, the distance between the RB slug and the O₂ bubble is smaller, and this decrease in diffusion distances between the two phases affects mass transfer between phases. The positive effect of lower diffusion distances between the RB slug and O₂ bubble to the photooxidation process is also supported by experiments conducted using pure nitrogen. For the flow conditions displaying bubble-slug clusters (G/L/L: 35/15/50 and G/L/L: 50/15/35), N₂ gas was used instead of O₂ to determine the influence of the diffusion distance on photo-oxidation performance. As discussed above in Table 1, the conversion of DPBF for the flow condition G/L/L: 35/15/50 is 31.48±2.88%, and for G/L/L:50/15/35, the conversion is 35.18±1.83%. These conversion values decreased to 11.46±3.89% and 8.18±4.02% for G/L/L: 35/15/50 and G/L/L: 50/15/35, respectively, when the same reaction was performed in the presence of N₂. The equilibrium dissolved oxygen concentration before entering the reactor in the organic phase is 1.85 mM,⁴⁵ and 0.26 mM in water.⁴⁶ This implies that the amount of oxygen in the organic phase is higher than it is needed to fully convert DPBF. However, the continuous supply of oxygen was found to favor the photooxidation of DPBF. For the flow condition G/L/L: 35/50/15, which does not display a bubble-slug cluster, the conversion decreased from 17.39% to 8.38% when the reaction was performed with N₂ instead of O₂. The decrease in conversion with N₂ as a gas phase is, therefore, less prominent for the flow condition without bubble-slug clusters, implying the significance of hydrodynamics on the three-phase photo-oxidation performance. These findings support the significance of the diffusion distance between the O₂ phase and RB slug to enhance oxygen diffusion, proving that the O₂ phase has a crucial role in this G/L/L system.

Bubble-slug or slug-bubble clusters have been previously reported,^{37,47,48} mentioning that various factors such as flow ratios, channel materials, surfactant concentrations, and the formation mechanisms of bubbles and droplets can affect the distance between bubbles and slugs.³⁷ As also seen in Table 2, by increasing the flow rate of each phase, the length of the corresponding slug or bubble is also increased, as expected. The gas fraction, β_G , is defined in Equation 1, where Q_G denotes to volumetric gas flow rate, whereas Q_L is the volumetric liquid flow rate of the RB and DPBF solutions.

 β_G was kept higher than 0.35 as lowering it disturbs the flow stability and repeatability of the measurements.

$$\beta_G = \frac{Q_G}{Q_G + Q_L} \tag{1}$$

As mentioned earlier, the contact among phases is very important to limit the mass transfer resistance observed in a three-phase flow. Therefore, the diffusion distance between these two phases should be as low as possible to promote the contacting area of the phases and hinder the effect of mass transfer limitations between the photosensitizer and molecular oxygen. Therefore, for the studied photosensitized singlet oxygen oxidation reaction in three-phase G/L/L flow in the microreactor, it is of interest to establish a unit cell configuration where the RB slug and the O₂ bubble are in close proximity (Figure 4-b), which is the prevalent case for the flow conditions G/L/L:35/15/50 and G/L/L:50/15/35, and resulted in a higher DPBF conversion.

Liu et al. attributed the higher conversions in resazurin oxidation in a microreactor in the presence of bubble-slug clusters to the increased level of mixing between the continuous slug and the liquid film.⁴⁹ It was also reported that as a result of the forward movement of the gas bubble during the flow, the liquid film moves backward, resulting in increased mixing between the liquid film and the continuous phase (DPBF in this study), causing a refreshing of the film.^{49,50} The film thickness calculations are provided in Section S2 of the SI, and no significant difference is observed among different flow conditions for these calculations. In light of these findings, it was observed that the flow pattern involving bubble-slug clusters is characterized by the lowest DPBF liquid fraction and, therefore, the shortest toluene slug. These conditions allow increased proximity between DPBF, RB, and oxygen gas.

In the presence of RB as a photosensitizer and O_2 , photo-oxidation of DPBF can be summarized in two main steps. Firstly, highly reactive 1O_2 is produced by the O_2 molecule in the presence of RB. Secondly, 1O_2 reacts with the substrate DPBF leading to its oxidation in the continuous phase. Therefore, the efficiency of photo-oxidation of DPBF is affected by the length of each phase, and their ratio with respect to each other, as this is directly related to the fraction occupied by the corresponding phase in the microreactor.

Figure 5 displays the dependency of the DPBF conversion on the length ratio of the RB slug and DPBF slug in a unit cell (RB/DPBF) and the length ratio of the DPBF slug and length of a unit cell (DPBF/Unit cell).



Figure 5. The influence of **a**) RB/DPBF length ratio and **b**) DPBF/Unit cell length ratio on DPBF conversion in the microreactor (Q_{total} =1 mL min⁻¹, [DPBF]=0.6 mM and [RB]=0.1 mM, *I_F*=8 mA/LED).

Figure 5-a implies that the RB/DPBF has a positive effect on conversion. As a higher fraction of the microreactor is occupied by RB solution, more photons are absorbed, and more ${}^{1}O_{2}$ is generated, causing an increase in the DPBF conversion. Similarly, Figure 5-b shows that conversion increases as the contribution of DPBF in a single unit cell decreases. The photo-oxidation of DPBF is directly related to the presence of ${}^{1}O_{2}$. For this reason, a high fraction of RB and O_{2} and a low fraction of DPBF in the three-phase flow facilitates reaction performance.

Influence of Total Flow Rate. Investigating the effect of total flow rate, Q_{total} , on conversion in microreactors is essential to determine the suitable flow rates for reaction completion. This analysis was conducted for the flow conditions G/L/L:35/15/50 and G/L/L:50/15/35, which displayed the highest DPBF conversions and the lowest diffusion distances between RB slugs and O₂ bubbles.

The Q_{total} of the three-phase flow was changed between 0.6 and 1.4 mL min ⁻¹, and five different Q_{total} values were considered. Figure 6 shows the results of this analysis,

where for both flow conditions (G/L/L:35/15/50 and G/L/L:50/15/35), a decreasing trend is observed for DPBF conversion as a function of the Q_{total} , which is in line with the results reported by Liu et al. for a three-phase flow in a microreactor where higher concentration changes were obtained at higher residence times for the resazurin oxidation.⁴⁹

For two-phase flow in microreactors, it was reported that the superficial velocity is increased due to higher Q_{total} , causing better mixing and recirculation together with a higher renewal of the surrounding liquid film. However, this situation does not necessarily indicate higher conversions, as the improved mixing could be offset by the shorter time spent in the microreactor due to the higher flow rates.⁵¹ Levesque et al. reported that for the photo-oxidation of citronellol in the two-phase flow, higher Q_{total} results in higher conversions due to improved mass transfer characteristics, as expected from Fick's law.¹³ The study of Wang et al. showed that for a single-phase flow in a microreactor, as the Q_{total} increases, conversion first increases and then decreases due to the shortening of the residence time.⁵² For the experimental system used in this study, as the microreactor is operated in the Taylor flow regime, plug flow is assumed,¹⁵ the residence time *t* can be calculated according to Equation 2, where Q_{total} is the total flow rate of gas and liquid phases in the three-phase flow, and $V_{reactor}$ is the microreactor volume.

$$t = \frac{V_{reactor}}{Q_{total}} \tag{2}$$

For the photo-oxidation of DPBF, the produced amount of singlet oxygen in the microreactor depends on the time of exposure of the RB phase to irradiation. As also evident from Figure 6, by assuming that the irradiation time is equal to the residence time, with the increase in the Q_{total} , three phases in the flow are exposed to light irradiation for a shorter period of time. This situation points out that under the studied conditions, the three-phase flow might be mainly limited by photon transport and not by mass transfer.



Figure 6. The influence of Q_{total} on DPBF conversion for flow conditions **a)** G/L/L:35/15/50 and **b)** G/L/L:50/15/35 ([DPBF]=0.6 mM and [RB]=0.1 mM, I_F = 8mA/LED).

As mentioned in the previous section (Figure 5), the contribution of each phase during the flow has an effect on the DPBF conversion. Hence, to identify the alterations in the length of each phase as a function of the total flow rate, an image analysis was performed, and the results showing the length of each phase in the unit cell configuration are shown in Figure S11. This analysis showed that changing Q_{total} while keeping the flow rate ratios constant for both flow conditions does not significantly affect the length of phases. This finding is in line with the previous results of Roibu et al., where the length of bubbles and slugs in two-phase flow in a microreactor as a function of Q_{total} was invariant.⁴⁰ The stability of the length of phases as a function of the total flow rate implies that the reaction efficiency depends on the residence time and is not affected by the changes in the length of phases.

Influence of the Light Intensity. The light emitted by the light source is absorbed by the photosensitizer in the microreactor; therefore, the light intensity plays a significant role in photochemical reactions. The emitted photon flux depends on the LEDs' forward current (I_F), and the current was monitored using a digital multimeter. The LEDs were predominantly operated at a forward current of 8 mA. Additionally, six different light intensities were applied to identify the effect of light intensity on DPBF conversion for flow

conditions G/L/L:35/15/50 and G/L/L:50/15/35. As seen in Figure 7, the increase in light intensity positively affects conversion, pointing out that the photosensitizer absorbs the additional incident light, and the mass transfer between phases is efficient. A linear increase of the conversion as a function of light intensity was observed until 8 mA. This observation is related to the dependence of I_F as a function of the forward voltage, which was reported for the same LED source in a previous study by Roibu et al.⁵³ The results of this earlier study showed that there is a linear relationship between forward current and irradiance of LEDs until \cong 8 mA, whereas for higher currents, the linearity is disturbed.⁵³ For this reason, for light intensities higher than 8 mA, a further increase caused fluctuations in conversion.



Figure 7. The influence of applied current on conversion for flow conditions **a**) G/L/L:35/15/50 and **b**) G/L/L:50/15/35 ($Q_{total}=1$ mL min⁻¹, [DPBF]=0.6 mM and [RB]=0.1 mM).

As can be seen in Figure 7-a, for the flow condition G/L/L:35/15/50, a conversion of ~9% for an applied current of I_F = 1.77 mA is observed. For the same DPBF and RB concentrations, a conventional two-phase flow (G/L:35/65, G: oxygen, L: DPBF and RB dissolved in ethanol) results in full conversion. This finding is expected as the apparent absorbed photon flux per reactant volume decreases (see Section S4, Table S6) when the contact between oxygen and photosensitizer phase is significantly diminished and the

reactant and the photosensitizer are separated in different phases, which might limit the mass transfer between the photosensitizer and the oxygen and, the mass transfer between singlet oxygen and the reactant. While the generated singlet oxygen in ethanol readily reacts with DPBF present in the same phase, when the reactant and photosensitizer are separated in different phases, only a part of the singlet oxygen generated in the water phase, probably located at the water-organic interface, would react with the DPBF. However, as mentioned earlier, it is important to note that recycling the substrate and the photosensitizer is mostly overlooked in two-phase flow photo-oxidation studies. On the contrary, the three-phase flow enables more control and manipulation ability on the flow characteristics that enhance the reliability of the process,⁵⁴ with an added advantage of continuous automated separation and the easier recycling of the separated phases.

Influence of RB Concentration. The incoming LED radiation is absorbed by RB, therefore, investigating the effect of RB concentration on DPBF conversion is crucial. The results of this analysis are presented in Figure 8 for G/L/L:35/15/50 and G/L/L:50/15/35. For both of these flow conditions, an increase in RB concentration had a positive effect on the conversion up to around 35%, and further concentration increase did not affect conversion. A stabilizing trend in conversion is detected when the RB concentration is greater than 0.1 mM.

The apparent fraction of the absorbed photon flux, which is based on the experimental variation of DPBF concentration for flow conditions G/L/L:35/15/50 and G/L/L:50/15/35, is calculated and shown in Tables S4-S5. The estimated fraction of the absorbed photon flux, calculated based on the photon flux received in the microreactor and the Lambert-Beer law, is provided in Table S7. The difference between the apparent and estimated fraction of the absorbed photon flux implies that a small fraction of the generated singlet oxygen reacts with DPBF, most probably the singlet oxygen produced at the interface between the aqueous and the organic phase. The stabilization of conversion for G/L/L:35/15/50 and G/L/L:50/15/35 at ~35% above RB concentrations of 0.1 mM correlates with the increasing light attenuation, as 61.04% of the incident light is absorbed at 0.1 mM (Table S7). Additional possible reasons are the presence of mass transfer limitations observed in gas-liquid flow for RB concentrations above 0.2 mM,¹⁴ the

quenching of singlet oxygen by excess RB molecules¹⁰ and the formation of RB aggregates in water.⁵⁵



Figure 8. The influence of RB concentration on conversion for flow conditions **a**) G/L/L:35/15/50 and **b**) G/L/L:50/15/35 ($Q_{total}=1$ mL min⁻¹, [DPBF]=0.6 mM, $I_F=8$ mA/LED).

The experiments were also conducted without RB under the same conditions, and results are displayed in Table S3. These results indicate no conversion in the absence of RB, which highlights the necessity of the RB photosensitizer for the photo-oxidation to produce singlet oxygen.

Calculating the photonic efficiency (*PE*), external photonic efficiency (ξ_{ext}), and quantum efficiency (Q_E) enables to make the comparison between different reactor configurations, as these parameters are performance indicators that are normalized to photons.⁵⁶ These parameters are shown in Table S11 (Section S4). The observed *PE* values in the range of 0.007-0.043 indicate that only a small fraction of photons are participating in the reaction. A direct comparison of the calculated photonic efficiencies with literature values is not possible, as singlet oxygen-mediated photo-oxidation of DPBF, to the best of our knowledge, has not been studied with a green LED in a microreactor. However, Meyer et al. reported a ξ_{ext} of 0.048 for the singlet oxygen-aided oxidation of citronellol in a microreactor that is irradiated by a LED light of a maximum

emission wavelength of 468 nm and of which incident photon flux was measured by radiometry.⁵⁷

Recycling of Substrate and Photosensitizer. Continuous recycling of the photosensitizer and the substrate in microreactors for intensified multiphase G/L/L reactions opens up new avenues for their application in various fields. By recycling the photosensitizer, photo-oxidations could become attractive in a multi-step synthesis.⁵⁸ Increasing the conversion by increasing the light intensity is not a viable option, as increasing the light intensity results in various disadvantages, e.g., increased operating costs and cooling capacity to remove the heat caused by the large light intensity. Therefore, recirculation of DPBF to reach full conversion can be implemented as a strategy to avoid photosensitizer degradation under powerful light sources. The efficiency of a multi-step process, including photo-oxidation, might increase by separation, followed by recycling. Here, a recycling strategy for both the photosensitizer RB and the substrate DPBF is suggested to improve the photo-oxidation efficiency in the microreactor. Figure 9 illustrates the setup used for the recycling experiments. The setup used for continuous recycling is almost identical to that without continuous recycling (see Figure 1 in the experimental section for more information), the only exception being the replacement of syringe pumps with high-performance liquid chromatography (HPLC) pumps in the recycling case. As seen in Figure 9, liquid feeds were withdrawn from the reservoirs and pumped through the reactor inlet through HPLC pumps. A MFC was used to control the O₂ gas flow rate. The reactor outlet is connected to a flow cell to measure the concentration change throughout the reaction, and then the flow is brought to a liquidliquid separator (Zaiput, SEP-10). The liquid-liquid separator is equipped with hydrophobic polytetrafluoroethylene (PTFE) membrane with a 3 µm pore size (Merck Millipore). The hydrophobic membrane allows permeation of the continuous organic phase (DPBF in toluene), whereas the dispersed phase (RB in water) and the O₂ gas cannot permeate through the membrane. The O_2 gas moves with the aqueous permeate, which is collected in a separate reservoir and escapes to the environment at the end of each cycle, so that only the aqueous solution is recycled continuously. The separated continuous (DPBF in toluene) and dispersed phases (RB in water) are then fed to their corresponding reservoirs to continue the recirculation. Recycling was conducted until a

full conversion of DPBF was reached, which is continuously monitored via the UV-Vis spectrometer and Avasoft software.

Recycling experiments were conducted for G/L/L:35/15/50 and G/L/L:50/15/35 flow conditions, previously showing superior photo-oxidation performance. The Q_{total} was kept constant at 1 mL min⁻¹, and the initial volume of RB and DPBF solutions in feed reservoirs were 15 and 4 mL, respectively.



Figure 9. Schematic of the experimental setup used for the recycling experiments for G/L/L:35/15/50 and G/L/L:50/15/35.

It should be noted that if the concentration of an organic solvent is within the flammability limits, there might be an ignition in the presence of oxygen. Operating the system below the limiting oxygen concentration (LOC) is important to avoid this.⁵⁹ By keeping the oxygen concentration below the reported LOC value (vol%), the combustion, irrespective of the organic solvent concentration, could be prevented.⁶⁰ The flammability limit of toluene in the presence of oxygen is 11.6 vol% at room temperature and ambient pressure.⁶¹ The experiments of the current study are conducted in a fume hood with a ventilation rate of 675 m³ h⁻¹. Therefore, under these operation conditions, there is no risk of ignition.

For both G/L/L:35/15/50 and G/L/L:50/15/35 conditions, 180 minutes are needed to reach full conversion. As the Q_{total} during these recycling experiments was kept constant at 1 mL min⁻¹ and the volumetric flow rate of the DPBF phase was the same (0.15 mL min⁻¹) for both flow conditions, as expected, full conversion was obtained at equal times. To determine the number of cycles required for the substrate (DPBF in toluene) to reach full conversion, the mean residence time (RT) of this phase in the closed recirculation system under the same conditions applied during continuous recycling experiments was conducted. The details of the measurement are described in Section S5 in the SI. As a result of this analysis, the mean RT of the DPBF phase was found to be 15 minutes for both G/L/L:35/15/50 and G/L/L:50/15/35. Conversion as a function of a number of cycles is presented for these flow conditions in Figure 10, showing that twelve cycles are needed for the DPBF solution to be fully converted under studied conditions.

The concentration of the RB-water solution was measured to be the same before and after the experiment (See Section S6 in SI, Figure S15), showing that the RB solution has a sustained activity during the continuous recycling, which is the main benefit of conducting multiphase photochemical reactions in continuous flow reactors. This is in agreement with the existing literature, where a separation of a catalyst in a second immiscible liquid phase was shown to be an effective strategy to enhance recycling performance and retain its catalytic activity with low leaching from the catalyst.^{34,62} These results imply that continuous recycling of the phases allows for a robust operation over extended cycles without extra downstream purification steps and increases the overall sustainability of the process.



Figure 10. Recycling results for **a)** G/L/L:35/15/50 and **b)** G/L/L:50/15/35 (Q_{total}=1 mL min⁻¹, [DPBF]=0.6 mM and [RB]=0.1 mM, *I_F*=8 mA/LED).

CONCLUSIONS

The results of this study reveal the assets of the three-phase flow in microreactors and stand as an example to constitute a more sustainable and efficient approach towards photo-oxidation. This is due to the elimination of downstream purification steps and continuous recycling of the photosensitizer, which were simultaneously achieved by employing a three-phase G/L/L flow. To evaluate the efficiency of this approach, the photo-oxidation of DPBF in the presence of RB as a photosensitizer is used as a model reaction, and the formation and use of singlet oxygen in a microreactor are discussed in detail. Thanks to the intrinsic characteristics of the three-phase G/L/L Taylor flow, by contacting gas and two immiscible liquids, a suitable environment for facile phase separation is established, and the downstream phase separation is automated using a liquid-liquid separator. Additionally, reaction efficiency is improved, and better control of the flow pattern by manipulating the contribution of each phase was obtained as a result of consistent and controllable mixing properties throughout the reactor channels.

Image analyses provided an informative insight into the hydrodynamics of the G/L/L flow. Amongst two distinct unit cell configurations, the lower distance between the RB slug and O₂ bubble provided a significantly better environment for the singlet oxygen photo-oxidation due to decreased diffusion distances. This finding will help researchers

working in the area of three-phase flow to choose the most efficient flow configuration by considering the corresponding reaction mechanism. The large contribution of the RB phase in the unit cell was found to enhance reaction performance. This is attributed to the increased probability for the dissolved oxygen molecules to reach the RB phase and form singlet oxygen. On the other hand, the ratio of the length of the DPBF phase to the unit cell was found to hinder the reaction performance, showing a trade-off between the throughput and reaction efficiency.

In this respect, continuous recycling was achieved to increase the reactor throughput, recover the photosensitizer, and separate the product phase. Recycling experiments were conducted for two optimum flow conditions, where the unit cell configuration provided higher reaction efficiency. Results of these measurements showed that a full conversion is reached within three hours, which corresponds to twelve cycles, in the photo microreactor system. Compartmentalization of the photosensitizer phase through a second immiscible liquid opens up new opportunities for robust and easy photosensitizer recovery and reuse. Additionally, the reactant phase was recirculated until reaching full conversion, which allows for phase separation and conversion increase.

The approach adopted in this study offers a sustainable route by continuously separating the photosensitizer and the reaction stream until full conversion is achieved without an additional purification step. Therefore, it introduces an environmentally friendly route toward multiphase photo-oxidations in microreactors. Additionally, continuous recycling offers a new and sustainable strategy, allowing this approach to be extensively applied to other photochemical transformations in microreactors. Finally, the methodology employed here provides an informative insight regarding singlet oxygen-involved reactions in synthetic chemistry by elucidating the crucial impact of various operational parameters on the overall process efficiency. Thus, further research could be conducted to identify the implementation capacity of this approach for singlet oxygen-mediated synthesis of fine chemicals in three-phase flow systems in photo microreactors.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at `` ``.

Measuring DPBF and RB concentrations by UV-Vis spectroscopy (Section S1); DPBF solutions in toluene, RB solutions in water, DPBF and RB concentrations in the reaction mixture, Flow characteristics using image processing in MATLAB[™] (Section S2); Bubble velocity, Experiments for different flow conditions without Rose Bengal (Section S3); Determination of light absorption (Section S4); Calculation of the mean residence time (Section S5); RB solution after recycling experiment (Section S6); Environmental metrics (Section S7).

Data Availability

The MATLAB[™] code used for image processing will be made available upon request.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

REFERENCES

- Entradas, T.; Waldron, S.; Volk, M. The Detection Sensitivity of Commonly Used Singlet Oxygen Probes in Aqueous Environments. *J. Photochem. Photobiol. B Biol.* 2020, 204, 111787. https://doi.org/10.1016/j.jphotobiol.2020.111787.
- (2) Ogilby, P. R. Singlet Oxygen: There Is Indeed Something New under the Sun. Chem. Soc. Rev. 2010, 39, 3181–3209. https://doi.org/10.1039/b926014p.
- (3) Mendoza, C.; Emmanuel, N.; Páez, C. A.; Dreesen, L.; Monbaliu, J. C. M.; Heinrichs, B. Improving Continuous Flow Singlet Oxygen Photooxygenation Reactions with Functionalized Mesoporous Silica Nanoparticles. *ChemPhotoChem* **2018**, 2 (10), 890–897. https://doi.org/10.1002/cptc.201800148.
- (4) Fatima, K.; Masood, N.; Luqman, S. Quenching of Singlet Oxygen by Natural and Synthetic Antioxidants and Assessment of Electronic UV/Visible Absorption Spectra for Alleviating or Enhancing the Efficacy of Photodynamic Therapy. *Biomed. Res. Ther.* 2016, 3 (2), 514–527. https://doi.org/10.7603/s40730-016-0008-6.
- (5) Esser, P.; Pohlmann, B.; Scharf, H.-D. Photochemical Synthesis of Fine Chemicals with Sunlight. *Angew. Chemie - Int. Ed.* **1994**, *33*, 2009–2023. https://doi.org/10.1002/chin.199513336.
- (6) Pibiri, I.; Buscemi, S.; Palumbo Piccionello, A.; Pace, A. Photochemically Produced Singlet Oxygen: Applications and Perspectives. *ChemPhotoChem* **2018**, *2* (7),

535–547. https://doi.org/10.1002/cptc.201800076.

- Mendoza, C.; Emmanuel, N.; Páez, C. A.; Dreesen, L.; Monbaliu, J. C. M.; Heinrichs, B. Transitioning from Conventional Batch to Microfluidic Processes for the Efficient Singlet Oxygen Photooxygenation of Methionine. *J. Photochem. Photobiol.* A Chem. 2018, 356, 193–200. https://doi.org/10.1016/j.jphotochem.2017.12.028.
- (8) Figueiredo, T. L. C.; Johnstone, R. A. W.; SantAna Sørensen, A. M. P.; Burget, D.; Jacques, P. Determination of Fluorescence Yields, Singlet Lifetimes and Singlet Oxygen Yields of Water-Insoluble Porphyrins and Metalloporphyrins in Organic Solvents and in Aqueous Media. *Photochem. Photobiol.* **1999**, *69* (5), 517–528. https://doi.org/10.1111/j.1751-1097.1999.tb03322.x.
- (9) DeRosa, M. C.; Crutchley, R. J. Photosensitized Singlet Oxygen and Its Applications. *Coord. Chem. Rev.* **2002**, 233–234, 351–371. https://doi.org/10.1016/S0010-8545(02)00034-6.
- (10) Wilkinson, F.; Brummer, J. G. Rate Constants for the Decay and Reactions of the Lowest Electronically Excited Singlet State of Molecular Oxygen in Solution. *J. Phys. Chem. Ref. Data* **1981**, *10* (4), 809–999. https://doi.org/10.1063/1.555655.
- (11) Flors, C.; Griesbeck, A. G.; Vassilikogiannakis, G. Singlet Oxygen: Chemistry, Applications and Challenges Ahead. *ChemPhotoChem* **2018**, 2 (7), 510–511. https://doi.org/10.1002/cptc.201800120.
- (12) Pasha, M.; Liu, S.; Shang, M.; Qiu, M.; Su, Y. A Synergistic Study on the Synthesis of Juglone via Photooxidation in a UV–Vis LED Based Photomicroreactor. *Chem. Eng. J.* **2022**, 445 (136663). https://doi.org/10.1016/j.cej.2022.136663.
- (13) Lévesque, F.; Seeberger, P. H. Highly Efficient Continuous Flow Reactions Using Singlet Oxygen as a "Green" Reagent. Org. Lett. 2011, 13 (19), 5008–5011. https://doi.org/10.1021/ol2017643.
- (14) Roibu, A.; Mc Carogher, K.; Bharadwaj, R.; Eyckens, R.; Kuhn, S. Modelling Approaches to Predict Light Absorption in Gas-Liquid Flow Photosensitized

Oxidations. *Chem. Eng. J.* **2023**, 452 (P2), 139272. https://doi.org/10.1016/j.cej.2022.139272.

- (15) Gemoets, H. P. L.; Su, Y.; Shang, M.; Hessel, V.; Luque, R.; Noël, T. Liquid Phase Oxidation Chemistry in Continuous-Flow Microreactors. *Chem. Soc. Rev.* 2016, 45 (1), 83–117. https://doi.org/10.1039/c5cs00447k.
- (16) Lévesque, F.; Seeberger, P. H. Continuous-Flow Synthesis of the Anti-Malaria Drug Artemisinin. Angew. Chemie - Int. Ed. 2012, 51 (7), 1706–1709. https://doi.org/10.1002/anie.201107446.
- (17) Nakano, M.; Nishiyama, Y.; Tanimoto, H.; Morimoto, T.; Kakiuchi, K. Remarkable Improvement of Organic Photoreaction Efficiency in the Flow Microreactor by the Slug Flow Condition Using Water. *Org. Process Res. Dev.* **2016**, *20* (9), 1626– 1632. https://doi.org/10.1021/acs.oprd.6b00181.
- (18) Jacobs, M.; Meir, G.; Hakki, A.; Thomassen, L. C. J.; Kuhn, S.; Leblebici, M. E. Scaling up Multiphase Photochemical Reactions Using Translucent Monoliths. *Chem. Eng. Process. - Process Intensif.* **2022**, *181* (May), 109138. https://doi.org/10.1016/j.cep.2022.109138.
- (19) Hamami, Z. E.; Vanoye, L.; Fongarland, P.; de Bellefon, C.; Favre-Réguillon, A. Improved Reactor Productivity for the Safe Photo-Oxidation of Citronellol Under Visible Light LED Irradiation. *ChemPhotoChem* **2019**, *3* (3), 122–128. https://doi.org/10.1002/cptc.201800201.
- (20) Turconi, J.; Griolet, F.; Guevel, R.; Oddon, G.; Villa, R.; Geatti, A.; Hvala, M.; Rossen, K.; Göller, R.; Burgard, A. Semisynthetic Artemisinin, the Chemical Path to Industrial Production. *Org. Process Res. Dev.* 2014, *18* (3), 417–422. https://doi.org/10.1021/op4003196.
- (21) Véronique Nardello-Rataj, Paul L. Alsters, and J.-M. A. Industrial Prospects for the Chemical and Photochemical Singlet Oxygenation of Organic Compounds. In Liquid Phase Aerobic Oxidation Catalysis: Industrial Applications and Academic Perspectives; Wiley-VCH Verlag GmbH & Co. KGaA, 2016; pp 369–395.

- Kong, C. J.; Fisher, D.; Desai, B. K.; Yang, Y.; Ahmad, S.; Belecki, K.; Gupton, B.
 F. High Throughput Photo-Oxidations in a Packed Bed Reactor System. *Bioorganic Med. Chem.* 2017, 25 (23), 6203–6208. https://doi.org/10.1016/j.bmc.2017.07.004.
- (23) Hansen, A.; Renner, M.; Griesbeck, A. G.; Büsgen, T. From 3D to 4D Printing: A Reactor for Photochemical Experiments Using Hybrid Polyurethane Acrylates for Vat-Based Polymerization and Surface Functionalization. *Chem. Commun.* **2020**, 56 (96), 15161–15164. https://doi.org/10.1039/d0cc06512a.
- (24) Radjagobalou, R.; Blanco, J. F.; Petrizza, L.; Le Bechec, M.; Dechy-Cabaret, O.; Lacombe, S.; Save, M.; Loubiere, K. Efficient Photooxygenation Process of Biosourced α -Terpinene Combining Controlled LED-Driven Flow by Photochemistry and Rose Bengal-Anchored Polymer Colloids. ACS Sustain. Chem. 2020, 8 (50), 18568–18576. Eng. https://doi.org/10.1021/acssuschemeng.0c06627.
- (25) Tamtaji, M.; Kazemeini, M.; Tyagi, A.; Roxas, A. P. Continuous Sinic Acid in a Reusable Microreactor with Physically Immobilized Photocatalysts. *Mater. Res. Bull.* 2022, 145 (August 2021), 111540. https://doi.org/10.1016/j.materresbull.2021.111540.
- (26) Lancel, M.; Gomez, C.; Port, M.; Amara, Z. Performances of Homogeneous and Heterogenized Methylene Blue on Silica Under Red Light in Batch and Continuous Flow Photochemical Reactors. *Front. Chem. Eng.* **2021**, 3 (November), 1–8. https://doi.org/10.3389/fceng.2021.752364.
- Blanchard, V.; Asbai, Z.; Cottet, K.; Boissonnat, G.; Port, M.; Amara, Z. Continuous Flow Photo-Oxidations Using Supported Photocatalysts on Silica. *Org. Process Res. Dev.* 2020, 24 (5), 822–826. https://doi.org/10.1021/acs.oprd.9b00420.
- (28) Valverde, D.; Porcar, R.; Lozano, P.; García-Verdugo, E.; Luis, S. V. Multifunctional Polymers Based on Ionic Liquid and Rose Bengal Fragments for the Conversion of CO2 to Carbonates. ACS Sustain. Chem. Eng. 2021, 9 (5), 2309–2318. https://doi.org/10.1021/acssuschemeng.0c08388.

- Buglioni, L.; Raymenants, F.; Slattery, A.; Zondag, S. D. A.; Noël, T. Technological Innovations in Photochemistry for Organic Synthesis: Flow Chemistry, High-Throughput Experimentation, Scale-up, and Photoelectrochemistry. *Chem. Rev.* 2022, 122 (2), 2752–2906. https://doi.org/10.1021/acs.chemrev.1c00332.
- (30) Önal, Y.; Lucas, M.; Claus, P. Application of a Capillary Microreactor for Selective Hydrogenation of α,β-Unsaturated Aldehydes in Aqueous Multiphase Catalysis. *Chem. Eng. Technol.* 2005, 28 (9), 972–978. https://doi.org/10.1002/ceat.200500147.
- (31) Fabry, D. C.; Ronge, M. A.; Rueping, M. Immobilization and Continuous Recycling of Photoredox Catalysts in Ionic Liquids for Applications in Batch Reactions and Flow Systems: Catalytic Alkene Isomerization by Using Visible Light. *Chem. - A Eur. J.* **2015**, *21* (14), 5350–5354. https://doi.org/10.1002/chem.201406653.
- (32) Yap, S. K.; Wong, W. K.; Ng, N. X. Y.; Khan, S. A. Three-Phase Microfluidic Reactor Networks – Design, Modeling and Application to Scaled-out Nanoparticle-Catalyzed Hydrogenations with Online Catalyst Recovery and Recycle. *Chem. Eng. Sci.* 2017, 169, 117–127. https://doi.org/10.1016/j.ces.2016.12.005.
- (33) Yu, G.; Wang, N. Gas-Liquid-Solid Interface Enhanced Photocatalytic Reaction in a Microfluidic Reactor for Water Treatment. *Appl. Catal. A Gen.* **2020**, *591* (August 2019), 117410. https://doi.org/10.1016/j.apcata.2020.117410.
- (34) Schrimpf, M.; Esteban, J.; Rösler, T.; Vorholt, A. J.; Leitner, W. Intensified Reactors for Gas-Liquid-Liquid Multiphase Catalysis: From Chemistry to Engineering. *Chemical Engineering Journal*. Elsevier B.V. September 15, 2019, pp 917–939. https://doi.org/10.1016/j.cej.2019.03.133.
- (35) Zheng, B.; Ismagilov, R. F. A Microfluidic Approach for Screening Submicroliter Volumes against Multiple Reagents by Using Preformed Arrays of Nanoliter Plugs in a Three-Phase Liquid/Liquid/Gas Flow. *Angew. Chemie - Int. Ed.* 2005, 44 (17), 2520–2523. https://doi.org/10.1002/anie.200462857.
- (36) Purwanto, P.; Delmas, H. Gas-Liquid-Liquid Reaction Engineering:

Hydroformylation of 1-Octene Using a Water Soluble Rhodium Complex Catalyst. *Catal. Today* **1995**, *24* (1–2), 135–140. https://doi.org/10.1016/0920-5861(95)00013-6.

- (37) Liu, Y.; Chen, G.; Yue, J. Manipulation of Gas-Liquid-Liquid Systems in Continuous Flow Microreactors for Efficient Reaction Processes. J. Flow Chem. 2020, 10 (1), 103–121. https://doi.org/10.1007/s41981-019-00062-9.
- Widianto, A. Y.; Aubin, J.; Xuereb, C.; Poux, M. Gas-Liquid-Liquid Reactions: Contacting Mechanisms and Effective Process Technologies. *Catal. Today* 2020, 346 (February 2019), 46–57. https://doi.org/10.1016/j.cattod.2019.02.064.
- (39) Su, Y.; Straathof, N. J. W.; Hessel, V.; Noël, T. Photochemical Transformations Accelerated in Continuous-Flow Reactors: Basic Concepts and Applications. *Chem. - A Eur. J.* **2014**, *20* (34), 10562–10589. https://doi.org/10.1002/chem.201400283.
- (40) Roibu, A.; Van Gerven, T.; Kuhn, S. Photon Transport and Hydrodynamics in Gas-Liquid Flows Part 1: Characterization of Taylor Flow in a Photo Microreactor. *ChemPhotoChem* **2020**, *4* (10), 5181–5192. https://doi.org/10.1002/cptc.202000065.
- Mendenhall, G. D.; Howard, A.; Mendenhall, G. D. Autoxidation and Photooxidation of 1,3-Diphenylisobenzofuran: A Kinetic and Product Study. *Can. J. Chem.* **1975**, No. 14661, 1971–1973.
- Wang, P.; Qin, F.; Zhang, Z.; Cao, W. Quantitative Monitoring of the Level of Singlet Oxygen Using Luminescence Spectra of Phosphorescent Photosensitizer. *Opt. Express* 2015, 23 (18), 22991–23003. https://doi.org/10.1364/OE.23.022991.
- (43) Zhang, X. F.; Li, X. The Photostability and Fluorescence Properties of Diphenylisobenzofuran. J. Lumin. 2011, 131 (11), 2263–2266. https://doi.org/10.1016/j.jlumin.2011.05.048.
- (44) Wilkinson, F.; Helman, W. P.; Ross, A. B. Quantum Yields for the Photosensitized Formation of the Lowest Electronically Excited Singlet State of Molecular Oxygen

in Solution. *J. Phys. Chem. Ref. Data* **1993**, 22 (1), 113–262. https://doi.org/10.1063/1.555934.

- (45) Sato, T.; Hamada, Y.; Sumikawa, M.; Araki, S.; Yamamoto, H. Solubility of Oxygen in Organic Solvents and Calculation of the Hansen Solubility Parameters of Oxygen. *Ind. Eng. Chem. Res.* **2014**, 53 (49), 19331–19337. https://doi.org/10.1021/ie502386t.
- (46) Yamamoto, H. Solubilities of Argon Oxygen and Nitrogen in 12-Propanediol-Water Mixrd Solvent.Pdf.
- (47) Rajesh, V. M.; Buwa, V. V. Experimental Characterization of Gas-Liquid-Liquid Flows in T-Junction Microchannels. *Chem. Eng. J.* 2012, 207–208, 832–844. https://doi.org/10.1016/j.cej.2012.07.082.
- (48) Ładosz, A.; Rigger, E.; Rudolf von Rohr, P. Pressure Drop of Three-Phase Liquid– Liquid–Gas Slug Flow in Round Microchannels. *Microfluid. Nanofluidics* 2016, 20
 (3), 1–14. https://doi.org/10.1007/s10404-016-1712-7.
- (49) Liu, Y.; Yue, J.; Xu, C.; Zhao, S.; Yao, C.; Chen, G. Hydrodynamics and Local Mass Transfer Characterization under Gas–Liquid–Liquid Slug Flow in a Rectangular Microchannel. *AIChE J.* **2020**, *66* (2), 1–13. https://doi.org/10.1002/aic.16805.
- (50) Čech, J.; Přibyl, M.; Šnita, D. Three-Phase Slug Flow in Microchips Can Provide Beneficial Reaction Conditions for Enzyme Liquid-Liquid Reactions Three-Phase Slug Flow in Microchips Can Provide Beneficial Reaction Conditions for Enzyme Liquid-Liquid Reactions. *Biomicrofluidics* **2013**, 7 (054103). https://doi.org/10.1063/1.4821168.
- (51) Zaloha, P.; Kristal, J.; Jiricny, V.; Norbert, V.; Xuereb, C.; Aubin, J. Characteristics of Liquid Slugs in Gas – Liquid Taylor Flow in Microchannels. **2012**, *68*, 640–649. https://doi.org/10.1016/j.ces.2011.10.036.
- (52) Wang, Y.; Ni, L.; Wang, J.; Xu, F.; Jiang, J. Experimental and Numerical Study of the Synthesis of Isopropyl Propionate in Microreactor. *Chem. Eng. Process. -Process Intensif.* **2022**, *170* (September 2021).

- (53) Roibu, A.; Bharadwaj Morthala, R.; Leblebici, M. E.; Koziej, D.; Van Gerven, T.; Kuhn, S. Design and Characterization of Visible-Light LED Sources for Microstructured Photoreactors. *React. Chem. Eng.* **2018**, *3* (6), 849–865. https://doi.org/10.1039/c8re00165k.
- (54) Yue, J.; Rebrov, E. V.; Schouten, J. C. Gas-Liquid-Liquid Three-Phase Flow Pattern and Pressure Drop in a Microfluidic Chip: Similarities with Gas-Liquid/Liquid-Liquid Flows. *Lab Chip* **2014**, *14* (9), 1632–1649. https://doi.org/10.1039/c3lc51307f.
- (55) Xu, D.; Neckers, D. C. Aggregation of Rose Bengal Molecules in Solution. J. Photochem. Photobiol. A Chem. 1987, 40 (2–3), 361–370. https://doi.org/10.1016/1010-6030(87)85013-X.
- (56) Ziegenbalg, D.; Pannwitz, A.; Rau, S.; Dietzek-Ivanšić, B.; Streb, C. Comparative Evaluation of Light-Driven Catalysis: A Framework for Standardized Reporting of Data**. *Angew. Chemie Int. Ed.* 2022, 61 (28). https://doi.org/10.1002/anie.202114106.
- (57) Meyer, S.; Tietze, D.; Rau, S.; Schäfer, B.; Kreisel, G. Photosensitized Oxidation of Citronellol in Microreactors. *J. Photochem. Photobiol. A Chem.* 2007, 186 (2–3), 248–253. https://doi.org/10.1016/j.jphotochem.2006.08.014.
- (58) Amara, Z.; Bellamy, J. F. B.; Horvath, R.; Miller, S. J.; Beeby, A.; Burgard, A.; Rossen, K.; Poliakoff, M.; George, M. W. Applying Green Chemistry to the Photochemical Route to Artemisinin. *Nat. Chem.* **2015**, 7 (6), 489–495. https://doi.org/10.1038/nchem.2261.
- (59) Perry's Chemical Engineers' Handbook; McGraw-Hill: New York, 2008.
- (60) Gavriilidis, A.; Constantinou, A.; Hellgardt, K.; Hii, K. K. M.; Hutchings, G. J.; Brett, G. L.; Kuhn, S.; Marsden, S. P. Aerobic Oxidations in Flow: Opportunities for the Fine Chemicals and Pharmaceuticals Industries. *React. Chem. Eng.* 2016, *1* (6), 595–612. https://doi.org/10.1039/c6re00155f.
- (61) Brooks, M. R.; Crowl, D. A. Flammability Envelopes for Methanol, Ethanol, Acetonitrile and Toluene. *J. Loss Prev. Process Ind.* **2007**, *20* (2), 144–150.

https://doi.org/10.1016/j.jlp.2007.01.001.

(62) Behr, A.; Henze, G.; Schomäcker, R. Thermoregulated Liquid/Liquid Catalyst Separation and Recycling. *Adv. Synth. Catal.* **2006**, *348* (12–13), 1485–1495. https://doi.org/10.1002/adsc.200606094.