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## LED-driven spiral-shaped microreactor as a tool to investigate sensitized photooxygenations

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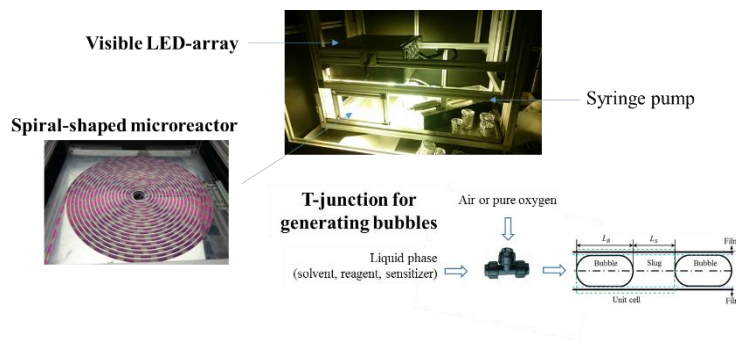
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Organic photochemistry is a key synthesis pathway in sustainable chemistry<sup>1,2</sup>, for example in the search for new compounds, for applications in medicine or agriculture, as well as in many other fields (e.g. material and environmental sciences). A variety of the fundamental principles of Green Chemistry<sup>3</sup> are addressed by photochemistry: (i) multi step syntheses of complex molecules are shortened and simplified (often, a high molecular complexity is generated in one step from simple precursors); (ii) a large panel of novel compound families (e.g. strained rings) becomes accessible or more easily accessible; and (iii) in many reactions, the photon acts as a “traceless reagent” and no chemical catalysts (acid, base, metal, etc.) or activating groups are needed. Among the large portfolio of photochemical transformations, sensitized photooxygenations involving singlet oxygen are particularly attractive (e.g. photooxygenations of terpenes or the synthesis of the antimalarial drug artemisinin)<sup>4</sup>. Paradoxically, they have not found widespread implementations in the chemical industry, mainly due to the currently available technology based on outdated batch reactors (large dilution with poor light penetration) equipped with energy-demanding mercury lamps (intensive cooling, limited lifetime). Continuous-flow microstructured technologies have emerged as alternatives to batch processing and their suitability for photochemical reactions has been recently demonstrated<sup>5</sup>. The combination of these devices with LED light sources additionally offers promising solutions for improving light penetration and

controlling of light, thus enabling energy-savings while at the same time increasing yields and selectivity<sup>6</sup>.

In keeping with this context, we have designed and built a LED-driven spiral-shaped continuous-flow microreactor in Toulouse (France) specifically devoted to flow photochemical investigations. Its design aims at (i) studying how and why the operating conditions (irradiation, hydrodynamics conditions, initial concentration of reagents etc.) can affect a reaction's yield and selectivity; (ii) acquiring data to establish a kinetic model based on mechanistic considerations; (iii) providing a tool for defining a methodology for smart scale-up. This device has been successfully used to investigate a monophasic photochemical reaction (photochromic system) requiring UV radiations<sup>7</sup>. In an extension to this earlier work, the design of the continuous-flow microreactor has been extended to enable the study of heterogeneous sensitised photooxygenations.

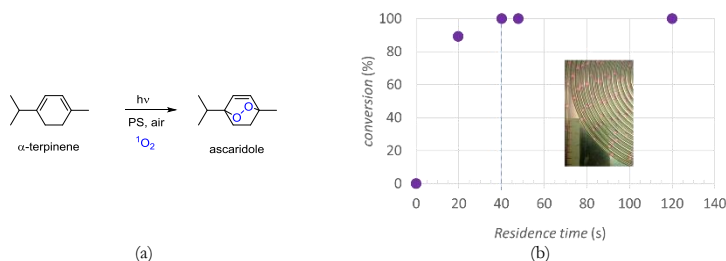


**Figure 1.** LED-driven spiral-shaped continuous-flow microreactor for investigating sensitized photooxygenations.

The spiral-shaped microreactor consists of a tube (FEP material) inserted inside a channel carved into a flat aluminium plate and wound into a spiral geometry (Fig. 1). The use of tubing offers several advantages: low cost, easy replacement ('disposable' microreactor), controlled irradiation time (equal to the residence time), transparency to UV and visible light and flexibility in volume. Different diameters of tubing can be used,

typically ranging from around a hundred  $\mu\text{m}$  to several mm and the length of the tubing can also be modulated from a few cm and up to 10 m. Thanks to its spiral geometry, the developed device is also flat and compact ( $160 \times 160 \text{ mm}^2$ ), allowing for homogeneous irradiation over the whole tubing surface. This microreactor is now illuminated by a purpose-built visible-LED array (Fig. 1), made by the Led Engineering Development® company (Montauban, France), instead of the original UV-LED array<sup>8</sup>. Compared to standard white LEDs, this advanced array consists of almost 1800 individual LEDs of ten different types, enabling an almost flat spectrum over the entire visible domain. The novel light-source additionally offers the possibility to select a specific spectral domain (e.g. 400-500 nm, 450-600 nm, 550-700 nm etc.) by means of an equalizer and an interface with Labview® software. Whatever the spectral domain selected, the photon flux emitted by the LED array can be modulated from a few  $\text{mW.cm}^{-2}$  to  $50 \text{ mW.cm}^{-2}$ . The distance between the LED array and the spiral-shaped microreactor plate is chosen carefully to ensure an uniform illumination of the microreactor surface. For implementing sensitized photooxygenations, the microreactor is fed through two inlets: the reaction solution containing the solvent, the starting material and the sensitizer (injected by a high-pressure syringe pump) and the gas phase containing oxygen (either pure oxygen or air). The latter is injected inside the microreactor tubing in a T-junction and regulated with a mass flow controller (Fig. 1). Following this approach, a segmented gas-liquid flow (called Taylor flow) is generated, which is characterised by a series of regular elongated bubbles separated by liquid slugs. In this flow pattern, the liquid surrounding the gas bubbles has two distinct regions: a recirculating region in the liquid slug between two consecutive bubbles and a liquid film region close to the wall. When compared to conventional gas-liquid reactors, such as bubble columns, higher interfacial areas (more than  $1000 \text{ m}^2.\text{m}^{-3}$ ) and intensified gas-liquid mass transfer (multiplied by 100-1000)<sup>8</sup> are obtained, while at the same time generating regular and segmented gas-liquid flow. The spatial distribution of both phases (i.e. bubble length and liquid slug length) can be simply modified by changing the liquid flow rate and/or the gas flow rate.

To illustrate the potentiality of this LED-driven microreactor, the sensitized photooxygenation of alpha-terpinene was chosen as a benchmark reaction<sup>9</sup> (Fig. 2a). The major product, ascaridole, is generated via [4+2] cycloaddition of singlet oxygen with the diene, with para-cymene being a minor by-product. The reaction is carried out in ethanol as a green solvent. Rose Bengal is used as sensitizer because of its industrial importance and solubility in alcoholic solution, while air is used as reagent gas. Gas chromatography is routinely implemented to determine the amounts of ascaridole, alpha-terpinene and by-products, while NMR spectroscopy is used to identify the components in the reaction media. The diameter of the chosen tubing was equal to 1 mm and its exposed length was 5 m. Different initial concentrations of alpha-terpinene and Rose Bengal and various gas and liquid flow rates were subsequently studied, as well as different photon fluxes emitted by the LED-array (power, spectral domain). Exemplary results are shown in Fig. 2b. Full conversion is reached within a residence time of 40 seconds and the desired ascaridole is obtained as the sole product. Another key parameter to take into account is the bubble lengths, as it controls the stoichiometric conditions imposed (molar flux of oxygen vs. molar flux of alpha-terpinene) and enables mixing between the reactants and the transfer of oxygen from the gas bubbles to the liquid phase.



**Figure 2.** (a) Sensitized photooxygenation of alpha-terpinene as a benchmark reaction, (b) Conversion versus residence time profile.

All these findings illustrate that the developed LED-driven continuous-flow microreactor is a well-adapted tool for producing milligram quantities of a product of interest in minutes and that it can be used for

quick data acquisition. A large range of operating parameters can likewise be screened under controlled conditions and by decoupling the effects of different parameters. This is a key feature to optimize the operating conditions and more generally to define the best strategy for smart scale-up.

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