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Continuous Flow Singlet Oxygen Photooxygenation Reactions: Recent Advances and Applications

Bruno Cerra, Federico Paccoia, and Antimo Gioiello*

Abstract: Photooxygenation reactions are sustainable alternatives to standard oxidation methods for the synthesis of crucial building blocks, natural products and drugs. This review is intended to provide readers with the latest advances on the development of singlet oxygen ($^1O_2$) mediated photooxygenations using continuous flow technology.

Keywords: Flow chemistry · Photooxygenation · Reactor technology

Bruno Cerra graduated in Pharmaceutical Chemistry and Technology (2011) and obtained his PhD in Medicinal Chemistry (2015) from the University of Perugia, with a thesis focused on multicomponent flow-based and microbial-assisted reactions for the preparation of compound libraries and chiral building blocks. He was a visiting PhD student at the Institute of Applied and Synthetic Chemistry (Technische Universität, Vienna, Austria), post-doctoral scientist at the University of Perugia and Tes Pharma (Perugia, Italy), and head of chemical research at Steroid (Milan, Italy). In 2022, he got a tenure track position at the University of Perugia.

Federico Paccoia graduated in Pharmaceutical Chemistry and Technology at the University of Perugia (2022). He then spent six months as a synthetic chemist at Molecular Discovery (UK) working on PROTACs. In 2022, Federico Paccoia started his PhD studies in Pharmaceutical Sciences under the supervision of Prof. Antimo Gioiello on a project aimed at the design and chemical optimization of lead compounds to treat Strongyloidiasis and other neglected diseases.

Antimo Gioiello is a professor of Medicinal Chemistry at the University of Perugia (Italy). After graduation in Organic Chemistry (2001), he obtained his PhD in Medicinal Chemistry (2005). He leads several academic and industrial collaborations, and his work experience spans various stages of drug discovery. The main research interests of his group include steroid chemistry, the discovery and development of preclinical candidates for steroid-responsive therapeutic targets, and the implementation of enabling synthesis and technologies for lead discovery and process optimization. Antimo Gioiello is cofounder of Tes Pharma (Perugia, Italy) and a member of the scientific board of the Umbrian Center for Research and Innovation (CURI).

*Correspondence: Prof. A. Gioiello, E-mail: antimo.gioiello@unipg.it, Department Pharmaceutical Sciences, University of Perugia, 06123 Perugia (Italy)

1. Introduction

According to IUPAC, oxygenation reactions consist of the incorporation of molecular oxygen into a molecular entity. They are considered fundamental chemical transformations that have found widespread applications in both academia and industry for the synthesis of pharmaceuticals, fine chemicals, and crucial synthetic intermediates.[1] Traditional oxygenation methods involve the use of stoichiometric oxidants such as peroxides, quinones, hypochlorites, and inorganic reagents (*e.g.* permanganate and dichromate), whose usage should be limited because of environmental issues associated with the formation of salt-containing effluent and by-products. In the wake of increasingly stringent sustainability criteria, recently the attention has been directed towards the use of molecular oxygen as an abundant, natural, and safe alternative oxidant for chemical processes.[2,3]

In its basal state, molecular oxygen ($^3O_2$) features an open-shell electronic configuration with two electrons of equal spin occupying different molecular orbitals.[4] This state is capable of accepting one single electron at a time during a redox (radical-type) reaction, resulting in a low reactivity with most organic compounds. Molecular oxygen has two excited states of singlet multiplicity with the lower energy one, namely singlet oxygen ($^1O_2$), being characterized by two electrons occupying the same orbital with opposite spins, thus increasing its oxidative capacity compared to $^3O_2$. Singlet oxygen can be generated by dye-sensitized photoexcitation of $^3O_2$,[4] and has been proven to be a very attractive reactive oxygen species that can undergo various chemical transformations (Fig. 1).[5,6]

This review article is focused on photochemical reactions involving the use of singlet oxygen and continuous flow technology. The main emphasis will be placed on the major achievements in the last 10 years (2015–2024) illustrating aspects related with the reaction efficiency and scope, flow set-up, and technological advances of photochemical devices. Examples are categorized by substrate type, including furans, monoterpenes, and precursors of bioactive compounds.

2. Photooxygenation Reaction Using Flow Reactor Technology

Photochemical reactions have received an increasing amount of attention due to their generally mild reaction conditions and low energy consumption. They have displayed high potential for the sustainable generation of privileged scaffolds and fine chemicals.[7,8] However, the implementation of photochemical singlet oxygenations is limited using conventional batch conditions, es-

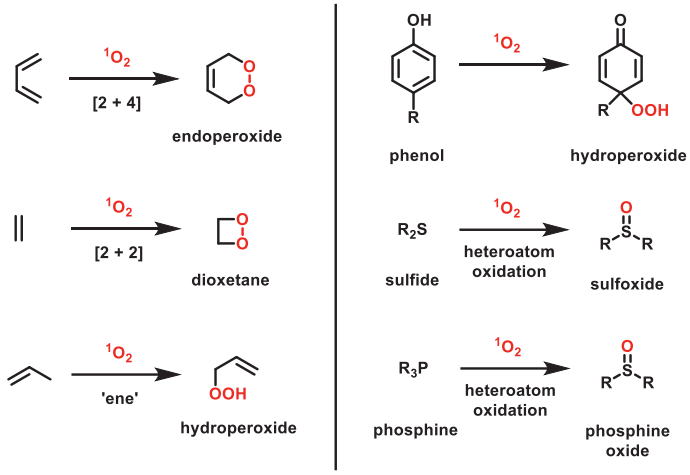

Fig. 1. Representative singlet oxygen-mediated photooxidation reactions.

pecially at large scale. As light intensity is distance-dependent, irradiation using large batch reactors is not uniform, leading to longer reaction times and poor selectivity, which often results in by-product formation. Moreover, the use of oxygen-rich conditions combined with the use of flammable organic solvents poses significant safety hazards. Technical challenges associated with efficient and homogeneous irradiation and the extremely short lifetime of $^1O_2$[9] has further impeded transfer of this methodology to the chemical industry.

The implementation of continuous flow chemistry allows to overcome most of the issues associated with batch photooxygenation. The narrow channel of flow reactors ensures a uniform irradiation of the solvent-oxygen mixtures, accelerating the reaction and reducing the formation of by-products. The conduction of photooxygenation reactions under flow conditions not only improves light penetration, but also enhances gas-liquid mass transfer and safety standards.[9–12] Gas delivery can also be precisely controlled at high pressures, facilitating the dissolution of low soluble gases, such as oxygen. Moreover, the scale-up is potentially easier by numbering-up reactors or through prolonged processing.[13] Other benefits include the spatial separation of reagent addition and mixing, high reagent dispersion, low hazard potential and multidimensional parameter control.

Over the past years, various apparatus, reactor types and set-ups have been described using novel engineering concepts, ranging from micro to more advanced technologies for scale-up.[14,15] These include the combination of flow systems with LED light sources, offering novel solutions for improving safety and controlling the emitted light spectrum, enabling energy-savings while increasing efficiency (yields) and selectivity. Home-made built reactors, spinning disks, ultrasonic and coaxial devices, 'Do It Yourself'-assembled set-ups, 3D-printing technology, and cheap LED toolkits have made flow photochemistry more intuitive, accessible and affordable for both laboratory practice and R&D programs.[16–22]

3. Novel Methodologies for Flow Photooxygenation Reactions

Over the years, the field of flow photochemical oxygenations has significantly evolved, often requiring the assembly of a novel, specific set-up, and the optimization of reaction conditions, as they are not usually simply transferable from one transformation to another.

In 2017, Vassilikogiannakis and his group described a novel methodology for the oxygenation of furans (**1a-g**) to hydroxycyclopent-2-enones (**2a-g** and **3a-g**) (Fig. 2).[23] Conventional methods were based on the use of harsh reagents and showed a poor functional group tolerance, thus limiting their adoption in research laboratories. In a previous piece of work, Kappe and coworkers reported the selective, high yielding, singlet oxygen-mediated oxidation of 5-hydroxymethylfurfural (5-HMF) and its derivatives using light, oxygen and catalytic amounts of rose bengal (RB) as a photosensitizer.[24] The set-up consisted of a perfluoroalkoxy (PFA) coil wrapped around a glass cylinder in which a cooled fluorescent light source was placed. In this case, using a flow nebulizer system named NebPhotOX (Nebulized Photo OXidation) (Fig. 2),[23] a MeOH solution of substrates and RB was nebulized by oxygen or air, prior to being directed into a cylindrical pyrex chamber and irradiated with visible light LED strips. The aerosol was then condensed and collected into cooled vessels. A series of furans were tested and they gave excellent conversions (>90%) to the corresponding hydroperoxides, which were then readily reduced in the collection flask with Me_2S in the presence of Et_3N (0.3 equiv.) to give 4-hydroxycyclopenten-2-enones **2a-g**. Interestingly, when the reduction was conducted with a slight increase in the amount of Et_3N (0.5 equiv.) and an extended reaction time (up to 12 h), the corresponding rearranged products **3a-g** were isolated in 40–75% yield.

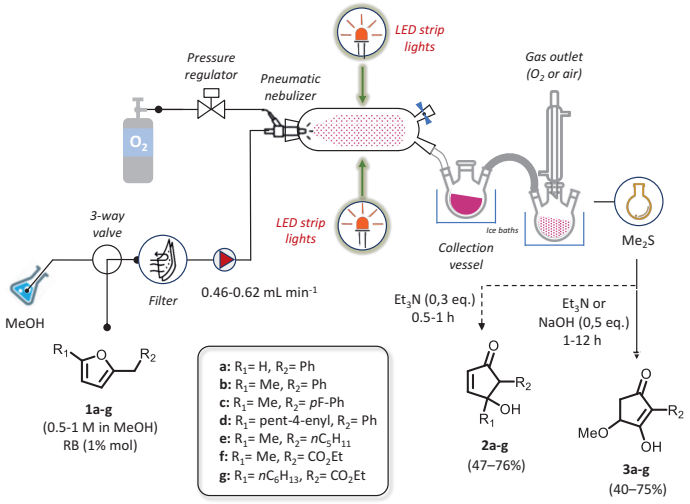

Fig. 2. Schematic representation of the NebPhotOX flow system and reaction scope.

A common problem with photooxygenation is the photobleaching/degradation of the photosensitizer under prolonged irradiation.[25] To overcome this issue, Monbaliu, Heinrichs and colleagues proposed the loading of the photosensitizer on mesoporous silica nanoparticles (MSNs).[26] In particular, RB was incorporated into MSNs (RB@MSNs) by conjugation of amino-functionalized MSNs ((3-aminopropyl)triethoxysilane linker) and activated RB (HATU coupling). The flow system included a pump for the injection of the substrate and the colloidal suspension of RB@MSNs (Fig. 3), which were mixed through a T-static mixer with a pure stream of O_2 delivered at 2 mL min^{-1}.

The gas-liquid feed was then irradiated with 12 green LEDs mounted on 4 heat exchangers surrounding the PFA capillary microreactor coil. A back-pressure regulator (BPR) set at 8.5 bar was inserted downstream. Results demonstrated that covalent anchorage of RB on silica nanoparticles reduced its sensitivity to photobleaching, maintained a high rate of photooxidation, and improved the processability, facilitating downstream operations and RB@MSN recovery. Various substrates were reacted providing oxygenated products in moderate to excellent yields with residence times of 51–300 seconds (Fig. 3).

More recently, a solvent-free $^1O_2$ photooxygenation of olefins under flow conditions was developed in the presence of low cat-

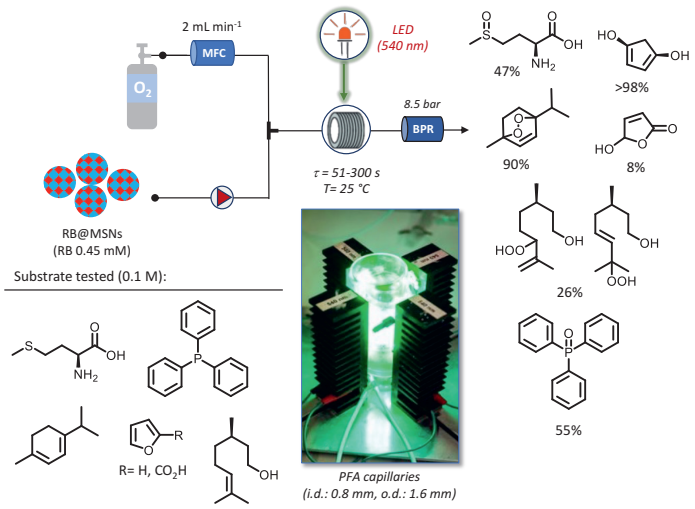

Fig. 3. Microfluidic set-up for heterogeneous photooxygenations using RB incorporated into mesoporous silica nanoparticles (RB@MSNs). MFC = Mass flow controller.

alytic loading of different organic dyes such as RB, methylene blue (MB), and tetraphenylporphyrin (TPP) (Fig. 4).[27] The sensitizer, dissolved in the liquid substrate, was mixed with pressurized O_2 forming a biphasic slug flow within the transparent tubular flow reactor. A nearly complete gas consumption was accomplished by the mutual adjustment of the liquid and gas flow rate and pressure. The methodology minimized competing $^1O_2$ deactivation and simplified reaction workup, affording the desired oxygenated products in good to high yields (Fig. 4).

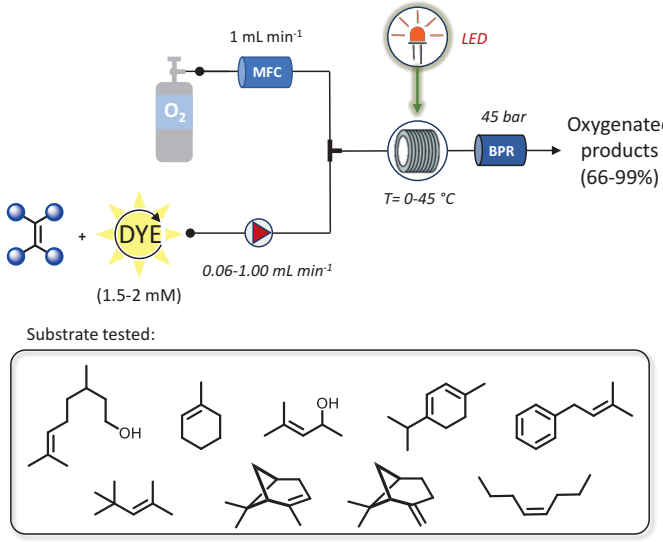

Fig. 4. Solvent-free photooxygenation of alkenes.

Last year, Park and colleagues developed a photooxygenation-epoxidation cascade sequence converting alkenes to epoxy alcohols in a continuous flow modality (Fig. 5).[28] In batch, using MB as the photosensitizer and $Ti(OiPr)_4$ as the catalyst, the reaction gave suboptimal yields, probably because of the presence of MB in the second epoxidation step. In contrast, flow chemistry offered the possibility to introduce the photosensitizer and the Ti catalyst simultaneously, to expand the light-exposed area, and to easily remove the MB from the reaction mixture. Alkenes were efficiently converted into epoxy alcohols with yields of up to 93%. Furthermore, the process proved to be simpler and faster (5 min *vs* 12 h) using a cartridge filter that improved filtration efficiency even during extended operations. These advantages make this flow cascade sequence suitable for both laboratory and large-scale preparation.

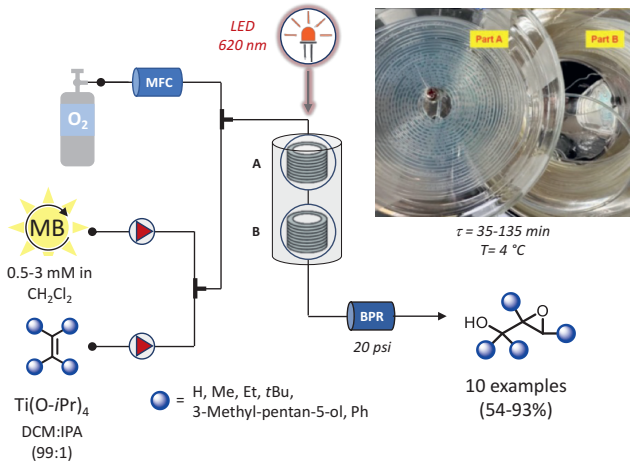

Fig. 5. Three-step one-flow synthesis of epoxy alcohols from alkenes.

3.1 *Flow Photochemical Oxygenation of Monoterpenes*

Monoterpenes are natural compounds present in several essential oils and well-known products as food additives and fragrances.[29] Monoterpenes, such as α-pinene (**4**), β-pinene (**5**), δ-limonene (**6**) (Fig. 6), have been used as starting materials for the preparation *via* photooxygenation reactions of pharmaceutical products endowed with anti-inflammatory, anti-malarial, anti-cancer and anthelmintic activities.[30] However, photooxygenation reactions of monoterpenes using conventional (batch) methods are generally characterized by long reaction times due to the ineffective irradiation, the slow generation and short lifetime of singlet oxygen. In this regard, the application of flow devices coupled with the availability of novel photosensitizers and more efficient light sources has provided a valuable solution to speed-up the photooxygenation rate while improving the reaction selectivity.

In 2015, Park *et al*. reported the continuous flow photooxygenation of a set of monoterpenes (Fig. 6).[31] In particular, the solution of the monoterpene **4–6** and the photosensitizer MB were mixed in a T-junction with a stream of oxygen, and the thus formed liquid-gas slug flow was irradiated with a 16 W LED lamp in a monochannel reactor maintained at 5 °C (Fig. 6A). Interestingly, compared to conventional batch procedures, the use of this system resulted in shorter reaction times (15–60 min *vs* 18–24 h) and improved selectivity. The authors also reported the use of a tube-in-tube reactor for process intensification, obtaining similar yield and selectivity along with a substantial increase of the daily output parameter (DOP, from 17- to 68-fold in comparison with conventional batch synthesis) (Fig. 6B).

An alternative method was later proposed by the Oelgemöller group that developed a falling film microreactor technology to increase the gas-liquid interfacial area and, consequently, the reaction performance (Fig. 7).[32] The reactor was made from a heat exchange unit, a borosilicate or quartz window irradiated with an external light source, and a reaction plate composed of 32 microchannels where the reaction mixture flowed as a thin film. After optimization, ascaridole (**11**) was obtained in 89% yield and with a productivity of 3.2 mol L^{-1} h^{-1} from a 50 mM stock solution of α-terpinene (**10**).

A further improvement of the process was achieved with a study aimed at investigating the reaction mechanism (*e.g.* sensi-

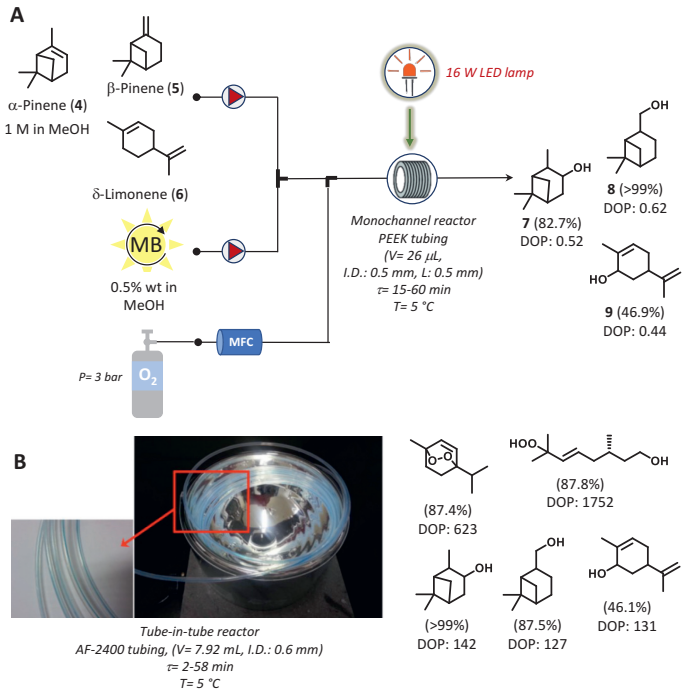

Fig. 6. Products generated by continuous flow photooxygenation of monoterpenes using a monochannel reactor (A) or a tube-in-tube reactor (B).

tizer bleaching) along with kinetic and operational parameters. Using the same set-up as illustrated in Fig. 7, in this case the authors opted for a commercially available flow (capillary) reactor module irradiated with an LED array composed of 4 LEDs emitting at 530 nm and 2 LEDs emitting at 580 nm.[33] Experimental screening carried out under continuous flow modality led the authors to identify an operating domain that reached a quantitative and selective conversion of α-terpinene (**10**) into ascaridole (**11**) in only 50 seconds, while minimizing the photobleaching of RB. Notably, a simplified mathematical model was proposed to predict the conversion at the reactor's outlet when pure oxygen was used.

The same authors exploited the potential of integrating a LED-driven spiral-shaped microreactor with RB-anchored polymer colloids using EtOH and air as an oxygen source (Fig. 8).[34] The photoactive polymer colloids were prepared by miniemulsion

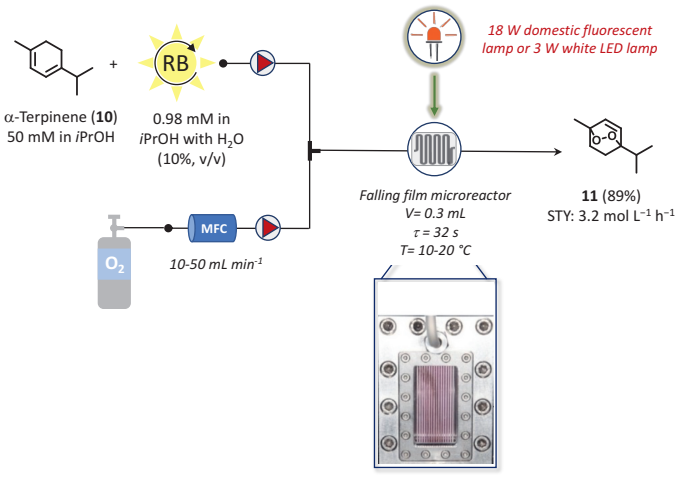

Fig. 7. Photooxygenation of α-terpinene (**10**) to ascaridole (**11**) using a falling film microreactor technology.

copolymerization of vinyl acetate, *N*-vinylcaprolactam, divinyl adipate crosslinker, and vinylbenzyl RB (VBRB) monomer. The microreactor consisted of a fluorinated ethylene propylene tube wound into an Archimedean spiral and fixed in a channel imprinted on a plate. The performance in terms of conversion, selectivity, photobleaching and reusability of the heterogeneous sensitizer was investigated to identify optimal conditions. As a result, a nearly quantitative conversion (>99%) was obtained in 4 min with less than 1% of photobleaching.

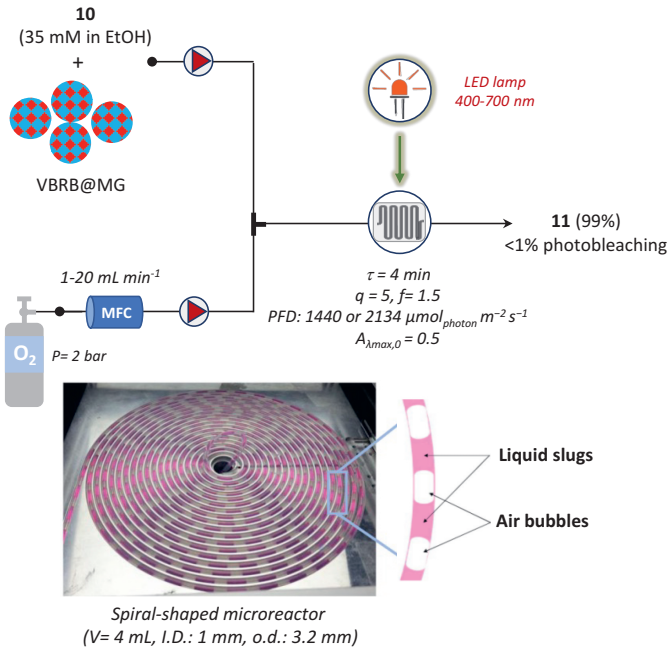

Fig. 8. Photooxygenation of α-terpinene (**10**) using a LED-driven spiral-shaped microreactor technology and RB-anchored polymer colloids.

More recently, the continuous flow photooxygenation of (+) and (–)-α-pinene (**12**) into the corresponding pinocarvones (**13**) was reported (Fig. 9).[35] A home-made photoreactor was realized using a series of white LED lamps and a glass tube wrapped with PFA polymer tubing. After mixing in a 250 μL microchip reactor, the reaction mixture composed of the starting material, oxygen, tetraphenylporphyrin (TPP), dimethylaminopyridine (DMAP), pyridine and acetic anhydride was reacted into the photoreactor, collected and purified. Under the best conditions, (–)- and (+)-pinocarvones (**13**) were isolated in 73–76% yield at the multi-gram scale, with spaime yield (STY) up to 5.65 mol g L^{-1} per day. Furthermore, the robustness of the protocol was confirmed by performing a 24 h long-run experiment, and the versatility was assessed with the preparation of *t*-pinocarveols **14** (Fig. 9).

The rotor-stator spinning disc reactor (pRS-SDR) is a powerful device that is able to significantly improve gas-liquid mixing, bubble dispersion, and interphase mass transfer. It has been applied for scaling gas-liquid and gas-liquid-solid photochemical reactions, such as the oxidation of α-terpinene (**10**) to ascaridole (**11**). Although excellent productivity has been achieved, light source limitations affected the overall performance of the pRS-SDR.[36,37] To overcome this issue, very recently Noël and coworkers reported the successful integration of a pRS-SDR reactor with a high-intensity light source.[38] The study explored the photooxygenation of **10** (cycloaddition) and (–)-citronellol (**15**) (Schenck-ene reaction) by investigating the effect of different experimental parameters including light intensity, optical power, rotational speed, flow rate and substrate concentration. Under optimal conditions, the oxidation of α-terpinene (**10**) reached an

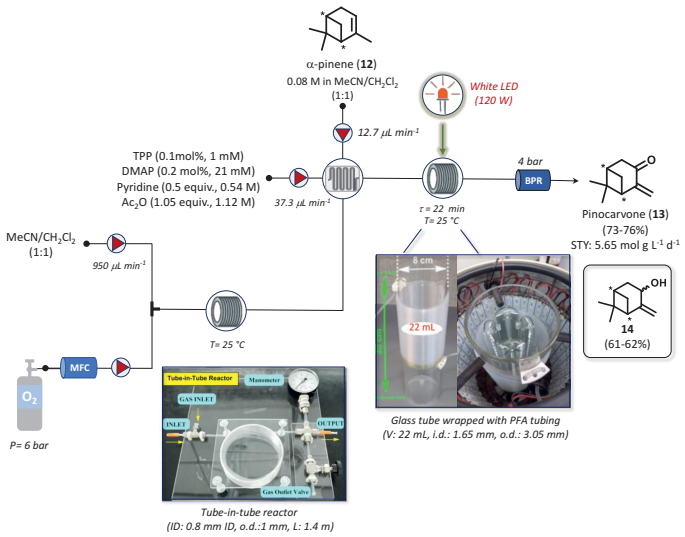

Fig. 9. Continuous photooxygenation of (+) and (–)-α-pinenes **12** to the corresponding pinocarvones **13** or *trans*-pinocarveols **14**.

almost full conversion working at the maximum values of light intensity, allowing an impressive productivity of 16.3 kg per day to be achieved (Fig. 10). Meanwhile, the robustness of the protocol was confirmed by performing a 24 h long run experiment, while the versatility was proved with the preparation of the allylic alcohol derivative **16** from (–)-citronellol (**15**) (Fig. 10).[38]

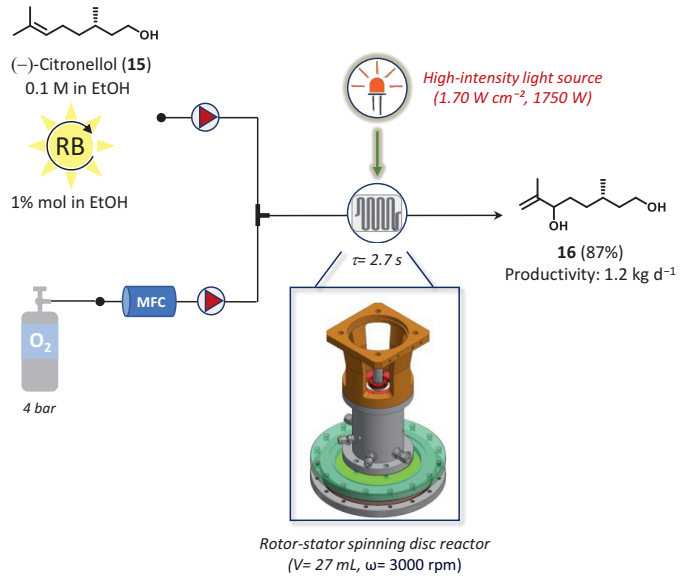

Fig. 10. Flow set-up for the photooxygenation of α-terpinene (**10**) and (-)-citronellol (**15**) using a rotor-stator spinning disc reactor (pRS-SDR) combined with a Signify high-intensity light source.

3.2 *Synthesis of Pharmaceutical Products*

Photooxygenation reactions are a powerful tool to unlock peculiar reaction routes not accessible through conventional ground-state reactivity, providing alternative, sustainable approaches to biologically active compounds.[39] In addition, they have been exploited to produce intermediates for chemical libraries of building blocks as well as to enhance chemical diversity in drug discovery.

In 2018, Mendoza *et al.* described the photochemical oxidation of the natural amino acid L-methionine (**17**) under conventional batch conditions and its subsequent transition to a continuous flow microreactor (Fig. 11).[40]

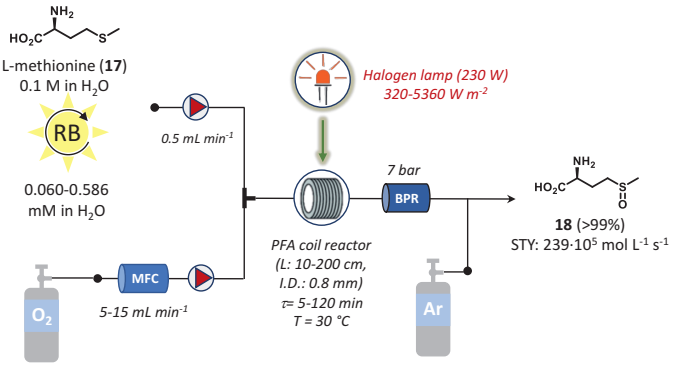

Fig. 11. Continuous photooxygenation of L-methionine (**17**).

After the kinetic study and experimental parameter investigation, the light penetration efficiency and the mass transfer emerged as critical parameters for the reaction performance. The flow photomicroreactor comprised PFA capillaries wrapped in coils around a photochemical quartz double-walled well connected to a thermostat, and a halogen lamp for the irradiation. The adoption of the microreactor technology and set-up illustrated in Fig. 11 guaranteed an improved gas-liquid transfer efficiency with a subsequent increase of the oxygen availability, as well as a higher light penetration. These benefits resulted in a short reaction time (5 *vs* 120 min) and a 3-fold increase of STY compared to batch photooxygenation.

A series of 7-iminothieno[3,2-*c*]pyridine-4,6(5H,7H)-dione derivatives was prepared by photooxygenation reactions to access nanomolar inhibitors of the protein tyrosine phosphatase PTP4A3 (Fig. 12).[41] The reaction was firstly optimized by evaluating the effect of the solvent, substrate concentration, type of sensitizer, light source and residence time. The system comprised a variable peristaltic pump, a standard FEB tubing mesoreactor, and a white compact fluorescent lamp (CFL) or a white LED lamp as the light source. Interestingly, no sensitizer was required as the thienopyridone scaffold acted as its own photosensitizer with a strong green fluorescence. Moreover, the oxygen molar fraction in the solvent of choice exposed to ambient air was sufficient to trigger the reaction. Optimal conditions were applied for the preparation of different iminopyridinedione analogues, showing a good substrate scope and functional group tolerance. Worthy of note, a marked reduction of the reaction time with respect to standard batch conditions (42 min *vs* several days) was achieved providing in most of the cases a direct access to the corresponding N-H imines (8–42% yield) over the ketone side-product. Interestingly, 16 out of 19 synthesized analogues exhibited *in vitro* inhibitory activity toward PTP4A3 in the nanomolar range of potency (Fig. 12).[42] A 3D-printed polypropylene photoflow reactor irradiated with 100 W blue LED was later developed by the same group and successfully applied to the same reaction, shortening the reaction times to 2 min.[43]

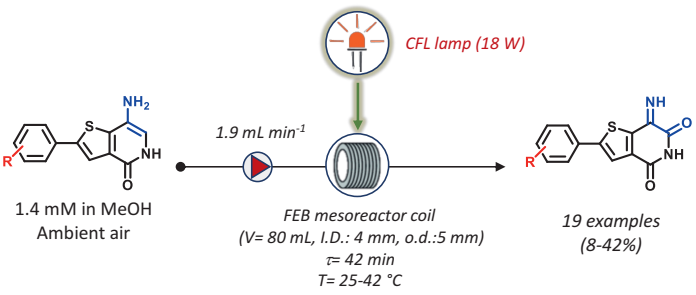

Fig. 12. Flow photooxygenation of aminothieno-pyridinones for the preparation of iminopyridinedione PTP4A3 phosphatase inhibitors.

Singlet oxygen-promoted photooxygenation of dihydroartemisinic acid (DHAA) has been exploited as a sustainable approach for the preparation of the tertiary hydroperoxide intermediate (**20**) that, after Hock-cleavage and oxidative cyclisation, affords the anti-malarial drug artemisinin (**21**) (Fig. 13). The photooxygenation of DHAA (**19**) upon appropriate light irradiation and in the presence of a dye has been widely applied, also through the use of continuous flow chemistry.[44–47] In 2021, Tamtaji and Kazemeini reported the process optimization by design of experiments (DoE) of DHAA (**19**) photooxygenation using a heterogeneous photosensitizer (Fig. 13).[48] The flow equipment consisted of a home-made glass microreactor assembled with a plexiglass holder, and consisting of two inlet ports, one outlet port and a photo-active zone irradiated with a 20 W white LED lamp. Moreover, the system comprised a peristaltic pump for oxygen feeding, and a glass syringe pump for feeding the solution of the substrate and the sensitizer. As a heterogeneous photosensitizer, the authors prepared and characterized MB immobilized on PS microspheres. Thus, a central composite design (CCD) was adopted to determine the effect of DHAA (**19**) as a function of substrate/oxygen flow rate ratio, substrate, and photosensitizer concentration, while keeping the oxygen flow rate constant. The conduction of 15 experiments and the data generated resulted in a quadratic polynomial equation, which enabled the identification of the optimal reaction conditions (Fig. 13).

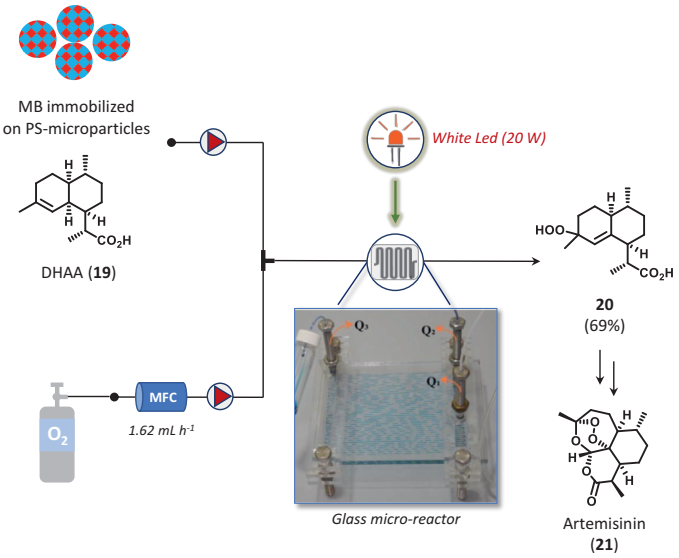

Fig. 13. Central composite design optimization for the photooxygenation of DHAA (**19**) in a flow microreactor using MB-immobilized polystyrene microparticles as the photosensitizer.

In another study, the reaction was investigated by means of a quantitative kinetic analysis.[49] Substrate and gas mixing resulted in a liquid-gas slug flow, before entering the photoreactor composed of wrapped transparent tubing immersed in a cooling bath and irradiated by blue LEDs (Fig. 14). Gas and liquid were then separated in-line by a membrane separator. The experimental data generated by varying key operative parameters (photosensitizer concentration, photon flux, substrate flow rate and gas phase composition) allowed the generation of a quantitative kinetic model that was parameterized by steady-state experiments. In particular, the identification of kinetic parameters was based on an iterative strategy by applying a model-based experimental design. After validation, the model was interrogated to identify the operating window for improving the photooxygenation of DHAA while avoiding mass transfer limitations (Fig. 14).

Very recently, the photooxygenation of olefins has been investigated under continuous flow conditions for the preparation

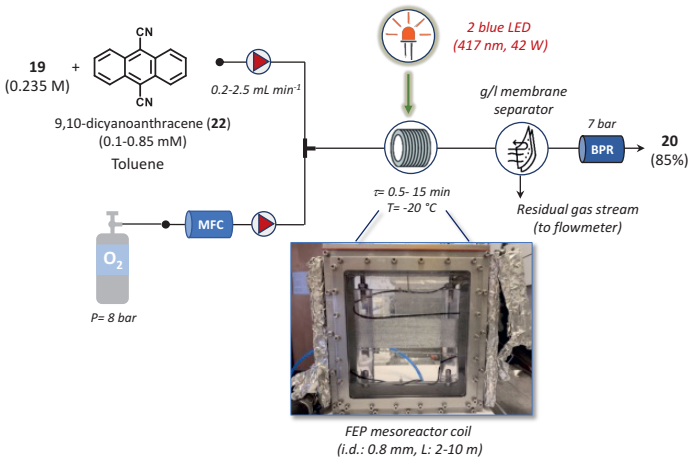

Fig. 14. Photooxygenation of dihydroartemisinic acid (**19**) in a flow mesoreactor.

of 1,2-dioxetanes, which serve as chemical probes for bioanalytical and cell imaging applications.[50] The setup employed MB (1–6 mol%) as a photosensitizer and red LED irradiation (610 nm) to generate singlet oxygen in CH_2Cl_2 under slug flow conditions with controlled O_2 input (Fig. 15). Optimization on a model acridine-containing olefin in a photochemical flow system revealed that lowering the temperature (down to –5 °C), increasing the oxygen flow rate, and reducing the residence time to 50 seconds were critical to maximizing the formation of the desired 1,2-dioxetane while minimizing its decomposition. The optimized conditions, which already outperformed conventional batch protocols (94% *vs* 34% yield) also proved superior in terms of scalability and reproducibility. These conditions were then adapted to a commercial mesofluidic photoreactor. Notably, decreasing MB loading from 6 mol% to 3 mol%, reducing O_2 input to 1.25 mL min^{-1}, and adjusting the light intensity from 100% to 10% afforded excellent conversion and selectivity, affording the corresponding dioxetane product in 97% yield with a productivity of 600 mg h^{-1} at 2 min-residence time. A broad substrate scope was then investigated, including adamantylidene derivatives, endocyclic alkenes, and aryl-substituted olefins (Fig. 15), In particular, under Schenck ene conditions the method provided synthetically useful allyl hydroperoxides.[15] To rationalize and predict olefin reactivity, a chemometric model was constructed using DFT-derived electronic descriptors and analyzed by principal component analysis (PCA) and linear discriminant analysis (LDA). The model exhibited robust predictive power and performance in classifying reactive versus unreactive substrates, achieving 91% accuracy in leave-one-out cross-validation. When tested on an external set of 40 acridine-based olefins, it correctly predicted reactivity in 85% of cases, highlighting its potential as a valuable tool for guiding the design of photooxygenation reactions under flow conditions.[50]

4. Conclusions

Batch photooxidations have been used for years despite several limitations, including the scale-up, long reaction times, sensitizer photobleaching, and mass transfer limitations between oxygen and the substrate. Major progress has been made with the advent of continuous flow technology that has rendered photosensitized oxidations a more sustainable and practical approach. In this review, we have showcased the potential of singlet oxygen photooxygenation reactions conducted using flow chemistry. In particular, we have highlighted the advances made in the development of photochemical flow devices and set-ups designed to improve reaction performance and sustainability, therefore streamlining the preparation of fine chemicals, synthetic precursors, and bioactive products.

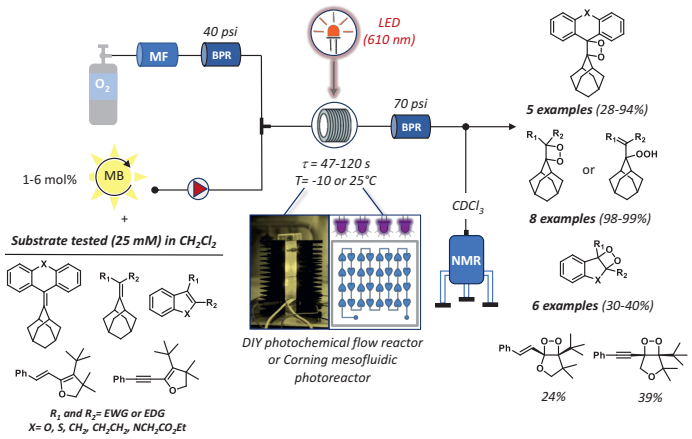

Fig. 15. Flow photooxygenation methods for the preparation of 1,2-dioxetane derivatives and allyl hydroperoxides.

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