Applications of continuous-flow photochemistry in organic synthesis, material science, and water treatment

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Applications of continuous-flow photochemistry in organic synthesis, material science and water treatment

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ABSTRACT: Continuous-flow photochemistry in microreactors receives a lot of attention from researchers in academia and industry as this technology provides reduced reaction times, higher selectivities, straightforward scalability and the possibility to safely use hazardous intermediates and gaseous reactants. In this review, an up-to-date overview is given of photochemical transformations in continuous-flow reactors, including applications in organic synthesis, material science and water treatment. In addition, the advantages of continuous-flow photochemistry are pointed out and a thorough comparison with batch processing is presented.
1 Introduction

Sunlight strikes our planet every day with more energy than we consume in a whole year. Therefore, many researchers have explored ways to efficiently harvest and use light energy for the activation of organic molecules. Light activation of molecules provides access to reaction pathways which are otherwise impossible to reach with classical thermochemical activation. Another fascinating aspect of photochemistry is the use of photons as "traceless and green reagents", hence rendering photochemical processes green and sustainable.

In the last decade, visible light photoredox catalysis emerged as a new and powerful mode to activate small molecules. This new field exploits transition metal complexes or organic dyes to harvest visible light photons and convert this energy to an electrochemical potential, thus facilitating subsequent single electron transfers with organic substrates. Owing to the generally mild reaction conditions, the use of visible light as a perennial energy source and its broad applicability, visible light photoredox catalysis has gained tremendous momentum over the past five years and has triggered a renewed interest towards photochemistry in general.

However, this renewed interest in photochemistry also brought some old and unsolved problems to the surface. Most of these issues are associated with the complexity of photochemical processes. Scalability is hampered due to the attenuation effect of photon transport (Bouguer-Lambert-Beer law), which prevents the use of a dimension-enlarging strategy for scale-up. If larger reactors are used, over-irradiation of the reaction mixture can become an important issue as the reaction times are substantially increased. This often results in the formation of byproducts, complicating the purification process significantly.

The use of continuous-flow microreactors for photochemical applications has received a lot of attention as it allows to overcome the issues associated with batch photochemistry. The narrow channel of a typical microreactor provides opportunities to ensure a uniform irradiation of the entire reaction mixture. Consequently, photochemical reactions can be accelerated substantially (from hours/days in batch to seconds/minutes in flow) and lower photocatalyst loadings are often feasible. This reduction in reaction time minimizes potential byproduct formation and increases the productivity of the photochemical process. Furthermore, scale-up of photochemical reactions is facilitated in continuous-flow reactors. This can be achieved by continuous introduction of reactants into the flow reactor and by placing several devices in parallel (numbering-up). Other advantages of microreactors are the improved mass- and heat-transfer characteristics, enhanced safety, ease of processing multiphase reaction mixtures and potential to include inline analytical technologies, allowing to develop fully automated and/or self-optimizing processes.

This review will highlight the use of continuous-flow photoreactors for applications in organic synthesis, material science and water treatment. Some fundamentals of continuous-flow photochemistry are given in the introduction section, which will help the reader to understand
the basic principles behind this technology. Moreover, this section will allow researchers new to the field to get the maximum out of their flow devices. Next, an overview is given of different materials, solvents and light sources that can be used to carry out photochemical reactions in flow. Throughout this manuscript, we have sought to highlight and explain the differences between batch and flow reactors. Although the main focus of this review is the use of microreactor technology for photochemistry, we have also included mesoscale reactors where appropriate.

2 Fundamental of flow photochemistry

2.1 Nine good reasons why to go with photoflow

2.1.1 Reason 1: Improved irradiation of the reaction mixture

Photochemical reactions are driven by the absorption of photons. Consequently, a homogeneous energy distribution inside a photoreactor is crucial to obtain high yields and high selectivities. According to the well-known Bouguer-Lambert-Beer equation (Eq. 1), the radiation distribution will not be uniform in a reactor due to absorption effects.

\[ A = \log_{10} \frac{I_0}{I} = \log_{10} \frac{I_0}{I} = \varepsilon c l \]  

This equation shows a clear correlation between the absorption and the molar extinction coefficient \( \varepsilon \) of the light absorbing molecules, their concentration \( c \) and the path length of light propagation \( l \). By plotting this relationship between absorption and reactor radius, the importance of reactor size can be conclusively shown (Figure 1). With strong absorbers, such as common photocatalysts and organic dyes, the light intensity is rapidly decreasing towards the center of the reactor. In order to keep the radiation distribution uniform and thus maximize the efficiency of the photochemical process, microreactor technology can be used.

![Figure 1](image)

**Figure 1** Transmission of light as a function of distance in a photocatalytic reaction using Ru(bpy)\(_3\)Cl\(_2\) \((c = 0.5, 1 \) and \( 2 \) mM, \( \varepsilon = 13,000 \) cm\(^{-1}\) M\(^-1\)) utilizing the Bouguer-Lambert-Beer correlation (Eq. 1).

The absorption of photons is crucial to carry out photochemical reactions. However, not every photon will give rise to the conversion of one molecule of starting material; excited states can return to their ground state by radiative or non-radiative processes (e.g. heating). The quantum yield is an important parameter to describe the efficiency of the photochemical reaction:

\[ \phi = \frac{\text{number of molecules of product formed}}{\text{number of photons absorbed by reactive medium}} \]  

The quantum yield is typically between 0 and 1 for non-chain mechanisms.\(^43\) Quantum yields above 1 indicate that a chain reaction occurs, e.g. in photoredox catalysis\(^44\) or polymerization reactions.\(^47\) In such chain reactions,
photon absorption leads to the generation of e.g. a radical (i.e. photo initiation) which is subsequently propagated until termination occurs. The quantum yield can be determined by carrying out photon flux measurements and subsequently performing the reaction in the same setup. The photon flux is defined as the number of photons observed per unit time. It is important to understand that not every photon emitted by the light source will end up in the photoreactor. By using refractors or miniaturized light sources, the photon flux through the reactor can be improved. Loubière and co-workers have compared the photon flux for a microreactor and batch reactors. The batch reactor received a photon flux of $7.4 \times 10^{-6}$ einstein/s, while the microreactor had a photon flux of $4.1 \times 10^{-6}$ einstein/s. However, this value needs divided by the reactor volume to obtain the absorbed photon flux density. For the microreactor, $5.02 \text{ einstein/(m}^3\text{s})$ was observed, while the batch reactor only had $0.033 \text{ einstein/(m}^3\text{s})$. This 150-fold higher absorbed photon flux density explains clearly why photochemical reactions can be substantially accelerated in microreactors. The photon flux strongly affects the intrinsic reaction rate of photochemical processes; the higher the photon flux, the faster the reaction will be completed.

Another important definition for photochemical processes is the so-called photonic efficiency ($\xi$), which is defined as follows:

$$\xi = \frac{\text{reaction rate}}{\text{photon flux}}$$

The photonic efficiency in batch reactors is typically around $0.0086-0.0042$. In microreactors, this value can be substantially improved by using microscale light sources (e.g. LEDs) or refractors. Noël and co-workers reported values up to 0.66 for a photomicroreactor using LED irradiation.

### 2.1.2 Reason 2: Reliable scale-up

Increasing the productivity of photochemical reactions to industrial scale has proven to be a formidable challenge for chemists and chemical engineers in the past. Due to the Bouguer-Lambert-Beer limitation of photon transport, scalability has been problematic even on a laboratory scale. In fact, advantages of photochemical syntheses observed on a small scale cannot be fully exploited on a larger scale when using a classical dimension-enlarging strategy. Consequently, the wide implementation of photochemical transformations in the pharmaceutical and fine-chemical industry has been severely hampered.

Due to the attenuation effect of photon transport, the diameter of the photoreactor has to be kept as small as possible to avoid non-uniform energy profiles. Microreactor technology has been embraced by the scientific community as the ideal reactor to scale photochemistry. Essentially two strategies can be distinguished to scale-up photochemistry with photomicroreactors: 1) longer operation times and increasing the throughput by increasing the flow rates and 2) numbering-up.

The first strategy is the most popular one on a laboratory scale as it is simple and straightforward to do. Reaction conditions are often optimized using only small amounts of starting materials in a microreactor. The same device
can be subsequently used, without tedious reoptimization of the reaction conditions, to produce the desired amount of material by continuous introduction of starting materials. Higher throughputs can be achieved by increasing the flow rates while keeping the residence time constant. One should note that in flow reactors this will lead to a change in the hydrodynamics and the heat transfer. However, this is not a drawback as higher flow rates usually provide higher mass- and heat-transfer characteristics, which allows to reduce the reaction times. A drawback of this approach is that the pressure drop, and thus energy dissipation, over the reactor will increase. Importantly, photochemical transformations are already substantially accelerated in microreactors; reaction times are usually reduced from hours in batch to the minutes/seconds range in flow. This benefit also provides a substantial increase in productivity compared to batch technology. With this strategy, typically several milligrams to hundreds of grams can be prepared in a reasonable time frame. This is often enough to prepare sufficient amount of material for the initial stages of a drug discovery process or to screen the properties of new materials.

More material can be prepared by placing several microreactors in parallel. This strategy is called numbering-up and one can distinguish basically two different approaches, i.e. internal and external numbering-up (Figure 2). External numbering-up is achieved by placing several microreactors along with their pumping system and process control in parallel. So, the entire microreactor setup is copied several times until the desired amount of product can be reached. This is a reliable way of scaling up since individual reactor failure will not influence the throughput of the other reactors. However, this is a very costly strategy as typically the most expensive parts of any microreactor setup are the pumps and the process control. Examples of external numbering-up can be found in literature and in the industry. Researchers from Heraeus Noblelight GmbH developed an external numbering-up setup with 12 parallel photomicroreactors which allowed to produce 2 kg of 10-hydroxycamptothecine per day (Figure 2).

In contrast, internal numbering is more economically feasible as only the reactor itself is numbered-up while the process control and pumping system is shared. The essential part in the design of efficient internal numbering up is the distributor section, which equalizes and regulates the reaction streams over the different microreactors. Small differences in pressure drop will lead to significant maldistribution and thus in non-equal reaction conditions in the different reactors. Noël and co-workers have developed a convenient numbering-up strategy for gas-liquid photocatalytic reactions (Figure 2c). The modular design allows to scale the photocatalytic aerobic oxidation of thiols to disulfides within $n$ photomicroreactors ($n = 0, 1, 2, 3$ was reported). Excellent flow distribution was observed in the presence of a photochemical reaction, showing a standard deviation $< 10\%$ for the mass flow rates. The variation in yield between individual reactors was about $5\%$. Other examples of internal numbering-up for photochemical applications
are the falling film microreactor (Figure 2a), microcapillary films and a Corning Advanced-Flow G1 Photo Reactor.

Figure 2 Examples of numbering-up for the scale-up of photochemical transformations: (a) Internal numbering-up in a falling film microreactor. Reprinted with permission from ref. Copyright 2005 Wiley and Sons. (b) External numbering-up of a photochemical production unit by Heraeus Noblelight GmbH. (c) Internal numbering-up of photomicroreactor for gas-liquid visible light photocatalysis.

2.1.3 Reason 3: Improved reaction selectivity and increased reproducibility

One of the key aspects in any chemical reaction is the product selectivity. It is generally accepted that microreactors provide opportunities to increase the reaction selectivity substantially. This is often attributed to the enhanced mass-, heat- and photon-transport phenomena observed in microchannels, which offers a high reproducibility of the reaction conditions. Such benefits can be related to the increased surface-to-volume ratio in microchannels.

A typical flow setup can be schematically represented as depicted in Figure 3 and consists of a mixing zone, a reaction zone and a quenching zone. In batch, reaction time is defined by how long the reactants are residing in the vessel. In contrast, in flow reactors, reaction time (also called residence time) is defined by the average time that the reactants spend in the reactor. Consequently, reaction/residence time is related to the flow rate. Due to the presence of a quencher, reaction times can be precisely controlled and thus follow-up reactions (e.g. degradation of the compound) can be avoided by minimizing the time spent in the reaction zone. This was demonstrated in the photocatalytic aerobic oxidation of 2-furylmethanethiol. Prolonged light exposure resulted in batch in the formation of overoxidized byproducts before full conversion could be reached. Because of the homogeneous irradiation and precise control over reaction times in flow, the reaction could be completed in only 20 minutes in very high selectivity.
Scheme 1 Schematic representation of a photochemical microreactor setup including (i) a mixing zone, (ii) a reaction zone, and (iii) a quenching zone.

2.1.4 Reason 4: Fast mixing

One of the key features of microreactors is their size. In this review, we define microreactors as continuous-flow reactors that have an inner diameter ≤ 1 mm. Flow reactors with a diameter larger than 1 mm are called milli- or meso-reactors. Actually, the size of the reactor is very important to explain the observed mixing phenomena in continuous-flow photochemistry. 69-70

In microscale photomicroreactors, the observed flow pattern is laminar flow (Scheme 2). In this flow regime, fluid is flowing in parallel layers and mixing is governed by diffusion across parallel lamellae. It is easy to understand that the smaller the diameter of the reactor, the faster a uniform concentration of reactants across the channel will be obtained. This insight led to the development of micromixers in which the diffusion distance is minimized to obtain mixing times in the milliseconds range. 71-73

Scheme 2 Laminar flow regime encountered in microchannels. Note that the velocity profile in the fully developed region (after t<sub>n</sub>) is parabolic. The velocity at the wall is much lower than the velocity in the center of the capillary.

Mixing is especially important to prevent the formation of byproducts which originate because of local concentration gradients. This is called disguised chemical selectivity and occurs when the mixing time is much larger than the reaction time. 74 On a macroscale, such selectivity issues are overcome by lowering the reaction temperature as this will slow down the reaction kinetics significantly. However, in microscale reactors, the mixing efficiency can be substantially increased due to the small size of the reactor. This provides opportunities to carry out reactions at higher temperatures than in conventional batch equipment.

2.1.5 Reason 5: Fast heat exchange

Fast heat transfer to the environment is important to keep the reaction temperature inside the reactor stable and to avoid byproduct formation via thermal pathways. For photochemical processes, increases in reaction tem-
perature can occur due to heating from the light source and exothermic reactions, e.g. singlet oxygen reactions.\textsuperscript{75} Due to the high surface-to-volume ratio, microreactors provide in general an efficient heat dissipation. Consequently, hot spot formation can be largely avoided and microreactors are often considered as isothermal reactors. In addition, material properties and surface characteristics play a pivotal role in the heat management of microreactors. The higher the heat conductivity of the reactor material, the faster heat can be transferred to the coolant (Table 1). Silicon microreactors provide excellent thermal conductivities and are easy to make.\textsuperscript{76} Another important material used for the fabrication of photomicroreactors are polymer-based capillaries. They are commercially available, inexpensive, chemically stable and provide optimal transparency properties, however, they have a low thermal conductivity.

<table>
<thead>
<tr>
<th>Material</th>
<th>Thermal conductivity [W m$^{-1}$ K$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFA</td>
<td>0.105</td>
</tr>
<tr>
<td>FEP</td>
<td>0.10-0.24</td>
</tr>
<tr>
<td>Glass (e.g. Quartz)</td>
<td>1</td>
</tr>
<tr>
<td>Silicon</td>
<td>149</td>
</tr>
</tbody>
</table>

**Table 1 Thermal properties of common materials used for the fabrication of photomicroreactors.**

### 2.1.6 Reason 6: Multiphase chemistry

Multiphase reactions are very common in the chemical industry, e.g. oxidations, hydrogenations, halogenations and phase-transfer catalysis reactions. They involve the combination of two or more immiscible phases (e.g. liquid-liquid or gas-liquid reactions). When mass transfer from one phase to the other is the rate-determining step, it is crucial to maximize the interfacial area. In batch, the interfacial area is low and poorly defined, which leads to prolonged reaction times. Due to the small characteristic dimensions of microreactors, large and well-defined interfacial areas are observed, which can reach up to 9000 m$^2$.m$^{-3}$. These large interfacial areas lead to efficient mass transfer between the two phases. More specifically, the mass transfer between two phases can be described with the overall volumetric mass transfer coefficient ($k_{l(a)}$), which is for microreactors one to two orders of magnitude higher than for classical multiphase reactors.

Several microreactor designs have been developed to carry out multiphase reaction conditions (Scheme 3).\textsuperscript{77,78} A first design involves single channel microreactors, e.g. transparent polymer-based capillaries, which are commonly used in photochemical applications. Two flow regimes are typically used in single channel microreactors, i.e. segmented flow (also known as Taylor flow or slug flow) and annular flow (sometimes referred to as pipe flow). Segmented flow is characterized by liquid slugs and elongated bubbles of an immiscible phase (e.g. gas or liquid). In both, toroidal vortices are established which cause a powerful mixing effect and intensify the mass transfer from one phase to the other. The bubble is separated from the reactor walls by a thin liquid film. In photochemical applications, this thin film will receive the highest intensity of photons and it can be anticipated that reaction rates are locally very high. The internal circulation patterns will result in a thin-film renewal exposing different fluid to high photon fluxes. Annular flow is obtained when one phase flows at a higher velocity in the center of the capillary, while the wetting phase forms a
thin layer at the channel wall. This thin film will be in close contact with the phase flowing in the center of the reactor and will receive the highest photon flux. A second design concerns the falling film microreactor in which the liquid phase is directed over the channels by using gravitational forces. The gas phase can be subsequently directed co- or counter-currently in front of the liquid phase. A third design is the membrane reactor in which the two phases are separated by a permeable membrane. Through the membrane, reactants can diffuse from one phase to the other. A notable and popular example of membrane reactors are the so-called tube-in-tube reactors. 

Multiphase flows are also important for the preparation of polymeric particles (Scheme 4). In laminar flow regimes, axial dispersion leads to a broad residence time distribution. In other words, not every particle stays the same time in the reactor which results in a relatively large particle size distribution. Particles at the channel walls are a bit larger due to the lower velocity, while those in the center will be smaller. A lower polydispersity can be obtained by adding an immiscible phase to generate a segmented flow regime. Each segment can be considered as an individual reactor in which all particles spend exactly the same time. Due to the internal circulation, excellent micromixing and low dispersion is obtained and homogeneous reaction conditions are observed in the segment which leads to a small size distribution.

![Scheme 3 Overview of the most common microreactor types used for multiphase flows.](image)

### 2.1.7 Reason 7: Multistep reaction sequences

The synthesis of complex organic molecules typically involves several synthetic steps along with intermediate
purifications. This traditional way of performing organic
reactions is very time consuming and, in times of increasing labor costs, very expensive to carry out. Throughout the years, chemists and chemical engineers have sought ways to simplify the synthetic process. One attractive technology to facilitate multistep reaction sequences is microreactor technology (Scheme 5). It allows to combine several reaction and purification steps in one continuous streamlined flow process. Such flow networks require less manual handling for the practitioner and results in substantial time and economic gains. Furthermore, inline spectroscopic tools, self-optimization protocols and automation allow to further reduce human interaction.

The use of multistep flow sequences is especially interesting when hazardous intermediates have to be prepared, such as singlet oxygen, diazonium salts, azides. Such intermediates can be generated in flow in small quantities and are immediately reacted away. Consequently, the total inventory of hazardous chemicals is kept low and safety risks associated with these chemicals can be minimized.
Multistep reaction sequence in batch and flow.

### 2.1.8 Reason 8: Immobilized catalysts

Immobilization of photocatalysts is an interesting way of recuperating and recycling the catalyst and thus increasing the economic viability of the photocatalytic process. Heterogeneous photocatalysts, such as semiconductors (e.g., TiO$_2$ and ZnO), are extensively used in photochemical applications due to their abundance, low cost, and robustness. These catalysts can be introduced in the reactor as a slurry. However, such an approach can lead rapidly to reactor clogging when using microstructured photoreactors and a downstream separation step is required to remove the catalyst from the products. An alternative approach is the immobilization of this catalyst on the reactor walls or in a packed bed (Figure 3). The use of packed-bed reactor is often not desired as light will not be able to penetrate to the center of the catalyst bed. Alternatively, wall-coated photomicroreactors have been reported in literature. In these examples, a thin layer of photocatalyst is immobilized on the reactor walls and the catalyst can be irradiated from the front or the backside of the catalyst. Due to the short diffusion distances and the large surface-to-volume ratios in the microchannels, enhanced performances are usually observed. The illuminated catalyst surface area per unit of liquid in the reactor ($\kappa$) is high for microreactors ($\kappa = 11,667 \text{ m}^2\cdot\text{m}^{-3}$), compared to slurry photoreactors ($\kappa = 2,631 \text{ m}^2\cdot\text{m}^{-3}$) or external type annular photoreactors ($\kappa = 27 \text{ m}^2\cdot\text{m}^{-3}$). Photocatalysts can also be immobilized on a membrane.

**Figure 3** TiO$_2$ – based photocatalytic microreactors: (a) Micro packed-bed photomicroreactor with TiO$_2$ nano-
2.1.9 Reason 9: Increased safety of operation

Increasing the operational safety of hazardous reactions is one of the main arguments for the chemical industry to switch to a continuous-flow protocol. Microreactors have small dimensions which reduces the total inventory of hazardous chemicals and thus avoids any safety risks associated with its handling. Furthermore, the impact of an explosion is directly related to the total amount of explosive materials present in the reactor to the power of $1/3$. Despite the advantages of microreactors, one must still be careful as explosions can propagate into the neighboring storage vessels which might contain larger amounts of explosive material.\textsuperscript{95} This also demonstrates the need of suitable quenchers at the reactor outlet, which can prevent explosion propagation.

Due to the increased safety, reaction conditions which are impossible to carry out in batch are now accessible in flow microreactors. This is especially true for photochemical reactions involving singlet oxygen. It is known that pure oxygen results into higher reaction rates and, in flow, such processing conditions become accessible. Several examples of singlet oxygen generation are discussed in this review.

2.2 Materials used for photomicroreactor fabrication

Microflow reactors can be constructed from a wide variety of materials. However, for photochemical reactions, it is imperative that at least one of the reactor walls is transparent, so that the desired wavelength can reach the reaction medium. Glass microreactors have been demon-
strated to be excellent for such purposes. In addition, they also act as a wavelength filter. A list of different, commonly applied, glass-based materials are given in Table 2. Notably, these glass microreactors are quite difficult to construct and require chemical etching techniques and clean room facilities, which are not always present in a standard laboratory environment.\textsuperscript{96} Another drawback of glass microreactors is the incompatibility with strong basic reaction conditions and extreme reaction temperatures.\textsuperscript{97-98}

Figure 4 Different materials used for microphotoreactor. (a) Fluoropolymer film wrapped around a cylindrical LED lamp. Reprinted with permission from ref. 99. Copyright 2014 The Royal Society of Chemistry. (b) glass microchip irradiated with 5 UV-B lamps. Reprinted with permission from ref. 55. Copyright 2008 The Royal Society of Chemistry. (c) A FEP-capillary coiled around a mercury lamp. Copyright 2012 Knowles et al.

Nowadays, photomicroreactors are increasingly constructed from polymer-based materials, such as polymethylmethacrylate (PMMA), polydimethylsiloxane (PDMS), perfluoroalkoxyalkane (PFA) or polytetrafluoroethylene (PTFE), and many more.\textsuperscript{100} These polymer-based materials have excellent light transmission, are easy to handle and are commercially available at affordable prices. However, PMMA and PDMS are susceptible to swelling when subjected to organic solvents for a prolonged time, rendering them unpractical for some photochemical transformations. One way to increase the solvent resistance of such polymers is applying a protective coating. Several methods have been suggested in the literature, such as transparent glass coatings via sol-gel methods.\textsuperscript{101-102} In contrast, fluorinated polymers (e.g. PTFE, PFA and FEP) provide a high chemical stability and good optical properties towards both UV and visible light. Moreover, they can withstand relative high temperatures and show excellent physical properties. These materials are commercially available as capillary tubing in a wide variety of different lengths and diameters. Given the ease of handling of these capillaries and low cost, such materials have become increasingly popular in the photochemical community. However, it should be noted that for UV applications these polymers tend to degrade after prolonged irradiation times.\textsuperscript{103} In addition, high purity polymers should be used, as leaching of the plasticizers from the polymer (e.g. PFA) can occur, with a negative impact on the photocatalytic process.\textsuperscript{103}
Table 2 Overview of different materials used to construct photo microreactors.  a Wavelength cut-off at 50% transmittance.  b UV wavelength: 250-400 nm.  c visible light: 400-700 nm.

<table>
<thead>
<tr>
<th>Reactor Material</th>
<th>Wavelength cut-off</th>
<th>Pro / Consbc</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartz glass</td>
<td>170 nm</td>
<td>Incompatible with anisotropic etching</td>
<td>96</td>
</tr>
<tr>
<td>Vycor glass</td>
<td>220 nm</td>
<td>Incompatible with strong alkaline reaction mixtures</td>
<td></td>
</tr>
<tr>
<td>Corex glass</td>
<td>260 nm</td>
<td>UV wavelength cut-off</td>
<td></td>
</tr>
<tr>
<td>Pyrex glass</td>
<td>275 nm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymethylmethacrylate (PMMA)</td>
<td>248 nm</td>
<td>Incompatible with some organic solvents (swelling)</td>
<td>104-106</td>
</tr>
<tr>
<td>Polydimethylsiloxane (PDMS)</td>
<td>±255 nm</td>
<td>UV wavelength cut-off</td>
<td></td>
</tr>
<tr>
<td>High visible light transmittance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polytetrafluoroethylene (PTFE)</td>
<td>±200 nm</td>
<td>High chemical resistance, pressure and temperature resilience</td>
<td>107</td>
</tr>
<tr>
<td>Perfluoroalkoxyalkane (PFA)</td>
<td>±180 nm</td>
<td>UV wavelength cut-off</td>
<td></td>
</tr>
<tr>
<td>Perfluroethylenepropylene (FEP)</td>
<td>±180 nm</td>
<td>High visible light transmittance</td>
<td></td>
</tr>
</tbody>
</table>

2.3 Solvent Choice

The selection of a proper solvent is a crucial step in the development of any chemical reaction. However, in continuous-flow reactions, this is even more important as the solvent needs to be able to solubilize all the chemicals and products to prevent reactor clogging and undesired light scattering. Solvents should also be selected based on their optical properties (e.g. wavelength cut-off, see Table 3). Preferentially, solvents are transparent to the wavelengths required to facilitate the photochemical reaction. Notably, solvents can have a strong influence on the lifetime of the excited state. In some cases, the solvent might even have a sensitizing function, e.g. acetone.

Table 3 Most common solvents utilized for photochemical applications.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Cut-off Wavelength (λ / nm)</th>
<th>Relative dielectric constant (εᵣ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>water</td>
<td>185</td>
<td>78.3</td>
</tr>
<tr>
<td>acetonitrile</td>
<td>190</td>
<td>35.94</td>
</tr>
</tbody>
</table>

n-hexane 195 1.88
ethanol 204 24.5
methanol 205 32.66
cyclohexane 215 2.02
diethyl ether 215 4.20
1,4-dioxane 230 2.21
methylene chloride 230 8.93
chloroform 245 4.81
tetrahydrofuran 245 7.58
acetic acid 250 6.17
ethyl acetate 255 6.02
carbon tetrachloride 265 2.23
dimethylsulfoxide 277 46.45
benzene 280 2.27
toluene 285 2.38
pyridine 305 12.91
acetone 330 20.56

2.4 Light sources

The selection of a proper light source for photochemical applications depends mainly on the overlap between the emission spectrum of the light source and the absorption characteristics of the photoactive reactants or catalysts.
Other important selection criteria are cost, energy efficiency, lifetime of the light source and match between the light source dimensions and the photoreactor.

Figure 5 Different light sources applied to continuous-flow photochemistry. (a) Blue LED array wrapped inside a disposable plastic syringe to irradiate a coiled capillary microreactor.\(\text{10}\) (b) Photomicroreactor with quartz top plate irradiated with UV LEDs (360 nm). Reprinted with permission from ref. \(\text{11}\). Copyright 2011 Akademiai Kiado. (c) Same reactor as (b) irradiated with a black light (360 nm). Reprinted with permission from ref. \(\text{11}\). Copyright 2011 Akademiai Kiado. (d) Highpower cold white LED lamps irradiated a FEP capillary microreactor. Reprinted with permission from ref. \(\text{12}\). Copyright 2012 The Royal Society of Chemistry.

Perhaps the most common artificial light sources are mercury-based light sources for UV applications and compact fluorescent light bulbs (CFL) for visible light-induced transformations. These light sources have a long life span, have a relative efficient light emittance (lumen per watts) and can emit a broad range of wavelengths (Scheme 6). Medium and low pressure mercury lights are often utilized for mid and low UV-wavelengths (UV-A and UV-B, 350–250 nm), while high-pressure mercury light sources emit wavelengths up to 600 nm. In contrast to medium pressure mercury sources, fluorescent black lights are more practical in use and have an UV emission between 310 and 450 nm. The lamp emission can be tuned by application of a phosphor coating which absorbs monochromatic Hg irradiation and reemits less energetic irradiation. Compact fluorescent light bulbs are also prominently applied in numerous visible light photochemical transformations. Despite the practicality of these light bulbs, they are not always easy to use in microflow applications as the dimensions do not match with those of the microchannels.\(\text{10, 100}\) Consequently, the energy efficiency of the setup is low since a lot of light is not directed towards the reaction channels (Figure 5). In this regard, the application and integration of Light Emitting Diodes (LEDs) in microfluidic applications has become very popular. LEDs are much more flexible because of their relative small footprint and very narrow emission bands (± 20 nm). The emitted wavelength can be tailored and matched with the photochemical application (Scheme 6).\(\text{10, 93, 113–115}\) Furthermore, LEDs are energy efficient, inexpensive and their temperature can be controlled with cheap and low energy cooling systems (e.g. fans for air cooling).
Overview of common light sources used for photochemical applications and their emission spectra. A legend is provided with icons for the different light sources which are used in this manuscript.

The utilization of solar energy to drive chemical transformations would be a huge breakthrough for the chemical industry in terms of sustainability and cost efficiency. However, sunlight is generally diffuse due to scattering and reflections by trees or built environment. Furthermore, shading due to clouds and day-night cycles reduces the performance of the photochemical process significantly. Specialized equipment, such as continuous-flow reactors in combination with reflectors, has been developed and can be used in countries that have a high amount of solar irradiation (Figure 6). Another important issue is the poor match between the emission spectrum of the sun and the absorption characteristics of the photocatalyst. Incompatible light energy can enable undesired reaction pathways, giving rise to substantial byproduct formation. However, the application of solar energy for large scale water purification and processing is more established, specifically in combination with heterogeneous detoxification and disinfection at water treatment plants.\textsuperscript{16-17}

Figure 6 PROPHIS (Parabolic Trough Facility for Organic Photochemical Synthesis) in Cologne. Reprinted with permission from ref. \textsuperscript{18}. Copyright 2001 The Royal Society of Chemistry
3 Continuous-flow photochemistry in organic synthesis

3.1 Short historical perspective of continuous-flow photochemistry

The first experimental account of a chemical modification induced by light dates back to 1834, when Hermann Trommsdorff described the effects of sunlight exposure on α-santonin crystals, a sesquiterpene lactone used as febrifuge and isolated from Artemisia plants. Remarkably, through the use of a prism, he understood the dependence of the wavelength on the crystal decomposition (“Das Santonin, wird sowohl durch den unzerlegten, als durch den blauen und violetten Strahl gefärbt... der gelbe, grüne und rothe bringen nicht die mindeste Veränderung hervor”, santonin is turned yellow not only by the undivided, but also by the blue and violet rays... whereas... the yellow, green and red ones cause not even the slightest changes). The photodegradation of santonin was further investigated by another pioneer of photochemistry, Stanislao Cannizzaro. Starting from his seminal work, his disciples Paternó, Ciamician and Silber took the first steps towards modern photochemistry. Paternó first discovered in 1909 the eponym [2+2] photocycloaddition between alkenes and carbonyls, further expanded by Büchi. Around the same period, Giacomo Ciamician and Paolo Silber laid the foundation of modern photochemistry through a systematic investigation of photochemical reactions (photoreductions, photocycloadditions, α- and β-cleavage of ketones). The importance of Ciamician’s work lies also in the awareness that photochemistry could be a more sustainable alternative to thermally-induced transformations, which depend on non-renewable fossil sources. In this visionary paper, he also made the following statement:

“On the arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over the plains and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them bear even more abundant fruit than nature, for nature is not in a hurry and mankind is. And if in a distant future the supply of coal becomes completely exhausted, civilization will not be checked by that, for life and civilization will continue as long as the sun shines!”. The highlighted part can be regarded as one of the first statements of continuous-flow reactors for photochemical applications.

In the days of Ciamician, photochemistry was almost exclusively done with sun irradiation as light source. Therefore, it can be described in modern terms as “green” and “sustainable”. Carl Theodore Liebermann, in 1895, first experimented with arc lamps as alternative light sources.

Deriving from these earliest approaches, photochemistry continuously evolved. In the late 20th century, fundamental applications emerged: among them the
synthesis of cubane, lycopodine, estrone and ginkgolide B.

It did not take long before the usefulness of photochemistry was implemented in the chemical industry. For example, the industrial synthesis of vitamin D$_3$ proceeds through a photochemical step. More specifically, the 9,10 double bond in provitamin D is cleaved via UV irradiation to yield the E and Z isomers of previtamin D. Moreover, since the installation of the first photochemical production unit in 1963, the synthesis of ε-caprolactam through the photonitrosation of cyclohexane (Toray process) has been an important step towards Nylon 6. The nitrosation of the alkane is based on the photoinduced cleavage of NOCl in the presence of HCl. This photochemical strategy was later replaced by the catalytic air oxidation of cyclohexane. However, it is estimated that a small portion (10%) of the yearly Nylon 6 world production still relies on photonitrosation.

The first examples on the application of microflow technology to photochemical synthesis date back to the beginning of the 2000s. However, the concept of flow reactors and its use in synthetic chemistry were not new to the chemical community. In fact, already in the 1960’s, larger tubular reactors were employed for photochemical transformations and their optimization from an engineering point of view was also investigated.

By the late 1980’s, PTFE tubing photoreactors started to be employed as integrated post-column analytical systems for HPLC. With an online photochemical derivatization, the products eluting from the HPLC column could be more easily identified. Both commercially available photoreactor and home-made ones were developed for this purpose. Typically, a PTFE tubing reactor (ID 300 μm) assembled in a crocheted geometry was placed between the analytical column and the detector (e.g. DAD). The reactor was illuminated with one or multiple 8 W low pressure mercury UV-lamp, causing the products to be photoderivatized. Owing to the changes in the spectral properties of the eluted compounds, hard-to-detect species could be unequivocally identified.

The advent of miniaturization techniques, represented the real paradigm shift in flow photochemistry. Indeed, the effective exploitation of the microscale, allowing for homogeneous and efficient light irradiation (e.g. LED lights), enabled unprecedented approaches. As such, a new unmatched level of process intensification for photochemical reactions was possible. Every year, the number of papers on photochemical reactions in continuous-flow are steadily increasing, as shown in Figure 7.

![Figure 7 Number of citation per year on Web of Science to papers responding to the query "photo-chemistry"](image-url)
3.2 Photochemistry

3.2.1 Photocycloadditions

Photocycloadditions have been extensively carried out in continuous-flow photomicroreactors. The popularity of photocycloadditions lies in the possibility to rapidly prepare highly complex organic molecules, such as substituted cyclobutanes. Moreover, short reaction times and equimolarity of the reaction partners are advantages observed when they are performed in flow. Loubière et al. reported a simplified model for the rigorous comparison between a photomicroreactor and a conventional photo batch reactor. The model combines reaction kinetics, mass and radiative transfer equations for an intramolecular \([2+2]\) photocycloaddition. The results demonstrate that higher conversions and a higher energy efficiency are typically observed in a photomicroreactor.

One of the first photocycloadditions in flow has been reported in 2004 by Ryu et al., who demonstrated the \([2+2]\) cycloaddition of cyclohexenones with vinyl acetates (Scheme 7).

![Scheme 7: Photocycloaddition of cyclohexenone with vinylacetate.](image_url)
The photomicroreactor contained a channel with a rectangular section of 0.5 x 1 mm and was irradiated with a 300 W high pressure mercury lamp. In comparison with batch, a significant decrease in reaction time was observed (71% yield in 2 hours in flow, 22% in 4 hours in batch). The same reaction was further investigated with respect to the nature of the light source. Different energy-saving light sources were tested, and the results underscore how uncompetitive mercury-vapor UV-lamps are in comparison with black light and UV LEDs in terms of yields, irradiation times and energy consumption (0.12 yield/Wh for the mercury lamps, vs 2.70 yield/Wh for the black light and 214 yield/Wh for the UV-LEDs) (Scheme 7, table). In the model reaction between cyclohexenone and vinyl acetate, a product yield of 71% and 82% was obtained in two hours with mercury lamp and black light respectively, while the use of UV-LED resulted in a 91% yield in just 15 minutes. Another early example of photocycloadditions in flow has been published in 2005 by Booker-Milburn and co-workers. In the total synthesis of Stemona alkaloids, a key [5+2] intramolecular photocycloaddition was needed, whose scale-up had proven especially difficult in batch (Scheme 8). The product underwent photodegradation after prolonged exposure, while the substrate concentration had to be kept low (0.02 M) to prevent dimerization. Short reaction times (30 min) were required to increase the product selectivity, however, this prevented the full conversion of the substrate. The low substrate concentration further aggravates the scale-up potential of this reaction in batch. It was rationalized that these limitations could be surmounted by using a continuous-flow reactor. The reactor consists of a simple design in which FEP capillary tubing (ID 700 μm) was coiled around the UV lamp. The simplicity of realization combined with the reuse of the readily available glassware for batch immersion wells made this reactor setup popular among the flow photochemistry community. In this review, we will refer to modified versions of this reactor design as a FEP coiled reactor. The positive results obtained with the
capillary microreactor and the need for a higher productivity led to the fabrication of a reactor with a meso-sized capillary (ID 2.7 mm), whose lower pressure drop allowed higher flowrates (up to 10 mL/min). Because of the substrate absorbance at 280-300 nm, further improvements were obtained by using Vycor instead of Pyrex as material for the immersion well. In particular, the substrate concentration could be increased from 0.1 to 0.4 M, resulting in a projected yield over 24 hours of 685 g, compared to 50 g/day with the first reactor. A similar Vycor coiled FEP mesoreactor was used by Aggarwal et al. for the scale up of the photochemical step in the synthesis of a bicyclic chiral sulfide. Another highly UV-transparent glass material (Schott 8337, λ cutoff = 200 nm) was used for microreactor fabrication by the Jensen group.

In a coiled capillary photomicroreactor, Conradi and Junkers observed a four-fold increase in yield (from 6 to 23%) by switching the solvent from ethyl acetate to acetonitrile for the [2+2] photocycloaddition of maleimide with octene. This result was rationalized by the more favorable UV cut-off of acetonitrile (Scheme 9).

A further improvement (from 23 to 99% yield) was obtained by upgrading the light source from a 16 W to a 400 W UV-lamp. Notably, with the optimized conditions, up to 265 g of product per day could be produced in an atom-efficient way (ene:alkene ratio 1:1). Particularly striking is the comparison with batch, where a ten-fold excess of ene is required to achieve similar conversions. Moreover, traditional immersion well or multilamp batch reactors, required several hours (respectively 12 and 8 hours) for reaction completion, while the microflow reactor reached full conversion in less than 10 minutes.

Scheme 9 [2+2] Photocycloadditions in flow.
A similar ene-enone reaction in microflow was reported by Oelgemöller and co-workers.\textsuperscript{160} The [2+2] photocyclization of 2-furanone with either cyclopentene or 2,3-dimethylbut-2-ene was studied, both in batch and in a microflow reactor. The flow setup was made by wrapping 10 m FEP capillary tubing (ID 800 μm) around a Pyrex glass cylinder. The reactor was subsequently placed in a Rayonet chamber hosting 8 UV-C lamps. For the batch experiments, the same chamber was used with quartz test tubes. The microreactor showed a five-fold decrease in reaction time compared to batch, owing to its higher light and photonic efficiencies (Scheme 9B).

The development of another gas-liquid flow photoreactor was reported by Horie et al.\textsuperscript{161} Interestingly, the reactor was specially designed to handle solid-forming reactions (Scheme 9C). The photodimerization of maleic anhydride to yield cyclobutane tetracarboxylic dianhydride, a highly insoluble compound, was tested. The reactor featured a FEP capillary (ID 1.2 mm) coiled around a quartz beaker containing a mercury UV-lamp. The beaker was then positioned in an ultrasonic bath. Ultrasonic waves were used to prevent deposition of the solid product on the reactor wall and to break-up particle agglomerations.\textsuperscript{104, 106, 163-164} A N\textsubscript{2} stream was added to form a segmented flow regime. Consequently, the suspended solid particles were kept into solution through the intensified mixing in such flow regime and were eventually pushed out of the microchannel.

Diastereoselective photocycloadditions were also performed in microfluidic devices.\textsuperscript{165-170} Enhanced enantioselectivity compared to batch reactors was observed in most cases, thanks to the improved control over reaction temperature.\textsuperscript{171-172} Mizuno et al. reported the intramolecular [2+2] photocycloaddition of 1-cyanonaphtalene derivatives in a PDMS reactor (Scheme 10).\textsuperscript{173} Reactions with 2-butenyloxymethyl substituted cyanonaphthalene resulted mainly in the photocycloadduct at the 1,2 position on the naphthalene. The formation of the photocycloadduct at the 3,4 position could be minimized in flow (yield 1,2-/3,4-adduct: 56%/17% in 180 min in batch, 55%/7% in 3.4 min in flow). A marginal enantiomeric excess (e.e.) of 2.0 % was obtained in the presence of Eu(hfc)\textsubscript{3}. In the absence of any chiral auxiliary, higher conversions were obtained in a commercially available Pyrex microreactor.\textsuperscript{93}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{diagram.png}
\caption{Diastereoselective [2+2] photocycloaddition of 1-cyanonaphtalene.}
\end{figure}

Kakiuchi and co-workers investigated the [2+2] Paternò-Büchi reaction between 2,3-dimethyl-2-butene and a benzoylformic acid esterified with a chiral auxiliary (Scheme 11-A).\textsuperscript{174} A FEP coiled reactor (ID 1.0 mm) irradiated with a 500 W high-pressure mercury lamp
was compared with batch, resulting in shorter reaction times (420 vs. 60 seconds) but similar d.e. (about 50%) despite cooling at 10 °C. A further increase in efficiency was observed when a slug flow regime was adopted by adding an immiscible phase, e.g. gaseous nitrogen or water (in both cases full conversion was achieved in only 30 seconds). This improved result can be ascribed to (i) the light dispersion effect of the slug bubbles, (ii) the improved mixing efficiency and (iii) the presence of a highly irradiated thin layer of reaction mixture formed between the channel wall and the slug.

A FEP microcylinder reactor (ID 1.0 mm, 1.18 mL) was coiled around a quartz immersion well containing a 500 W high pressure UV-lamp and the reactor was placed in a cooling bath. A large excess of ethylene gas was dosed into the reaction mixture by means of a mass flow controller generating a slug flow regime. Consequently, a thin liquid layer of reaction mixture was generated between the reactor wall and the ethylene gas bubbles. In this confined space, no gas-liquid mass transfer limitations are observed and the light intensity is maximized. The microreactor assembly displayed a substantial improved performance in terms of yield and diastereoselectivity when compared to a conventional Pyrex test-tube (full conversion in 1 min with 52% d.e. in flow vs 15 min in batch with 47% d.e.). The higher diastereoisomeric excess (d.e.) observed in flow was ascribed to the superior heat transfer observed in microchannels. More specifically, the precise control over the reaction temperature, favored the thermodynamically more stable s-trans conformation. The same reaction with a non-gaseous alkene (cyclopentene) was also investigated in two different microfluidic reactors yielding similar enhancement over the diastereoselectivity. The enhanced diastereoselectivity observed in microreactors can be further improved using supercritical carbon dioxide (scCO₂) as a solvent. The [2+2] photocycloaddition of a cyclohexenone bearing a menthol chiral auxiliary with cyclopentene was studied in a microreactor made of Pyrex glass (ID 600 μm) and was irradiated with UV-LEDs. The reaction selectivity in scCO₂ was higher than in conventional organic solvents (60% d.e. in scCO₂ vs. 36% in toluene), thus

Scheme 11  Diastereoselective [2+2] photocycloaddition with chiral auxiliary.

Terao et al. also investigated photocycloadditions with gaseous ethylene, exploiting the convenient handling of multiphase reaction systems in microflow. In particular, the diastereoselective cycloaddition of a chiral auxiliary-bearing cyclohexenone with gaseous ethylene was studied (Scheme 11-B). A FEP microcapillary reactor (ID 1.0 mm, 1.18 mL) was coiled around a quartz immersion well containing a 500 W high pressure UV-lamp and the reactor was placed in a
suggesting a clustering effect of scCO₂ at critical density.

Beeler et al. reported the continuous-flow [2+2] photocycloaddition of cinnamates in a cone-shaped reactor (Figure 8), which was irradiated with a Xenon(Hg) UV source. The dimerization of methylcinnamate yielded solely the head-to-head β-truxinate and δ-truxinate in a 1:1 mixture with higher yields and conversions than the corresponding batch protocol. Interestingly, the addition of a thiourea catalyst (8 mol%) increased the diastereoselectivity (3:1 δ/β) (Scheme 12). ¹H-NMR studies showed peak-sharpening of the amidic hydrogens of the thiourea catalyst indicating hydrogen bonding with the carbonyl moiety. Moreover, a possible triplet sensitization by the thiourea was suggested, implicating a dual role of the catalyst.

Scheme 12 [2+2] photocycloaddition of cinnamates in flow.

Figure 8 The cone-shaped reactor reported by Beeler et al. Reprinted with permission from ref. Copyright 2015 John Wiley & Sons

Pauson–Khand reactions are often applied to prepare cyclopentenone scaffolds by co-cyclization of alkynes, alkenes and CO. The decarbonylation step from an alkyne-cobalt complex can be promoted thermally, but an improved functional group tolerance can be obtained with other activation methods such as microwave, ultrasound and especially light irradiation.
Asano and Yoshida reported a microflow protocol for the photoinitiated Pauson–Khand reaction. In particular, a microchip with a serpentine channel (200 x 1000 μm section) was irradiated with a medium pressure mercury lamp. After a residence time of 55 seconds, most of the dicobalt complexes were fully converted into the corresponding cyclopentenones with moderate to high yields (Scheme 13).

Scheme 13 Pauson–Khand reaction in flow.

An unexpected UV-induced photocyclization was reported by Booker-Milburn and co-workers. The authors serendipitously observed the formation of a tricyclic, fused aziridine ring system (Scheme 14). The postulated mechanism proceeds through a [2+2] photocycloaddition followed by a UV-initiated bond cleavage. The obtained biradical intermediate ultimately evolves in the final aziridine ring through a C–C bond formation. The photoreactor consisted of a FEP capillary (ID 2.7 mm, 90 mL) wrapped around a quartz tube containing a 36 W germicidal UV-C lamp ($\lambda_{\text{max}} = 254 \text{ nm}$) and the solution was pumped with a valveless piston pump at controlled flow rates.

Scheme 14 UV-induced photocyclization yielding a tricyclic fused aziridine ring system.
3.2.2 Photoisomerizations

The excited states, reached through light absorption, may induce reversible or irreversible isomerizations of organic substrates. Consequently, relatively simple starting materials can be converted in complex structures (e.g. cyclobutenone rings), which are often elusive to prepare via other thermal or chemical pathways. Reversible photoisomerization reactions are also key in the design of chemical switches and molecular motors.\textsuperscript{99-106}

The continuous-flow photochemical rearrangement of nitrones was exploited by Jamison and co-workers to synthesize amide bonds.\textsuperscript{197} An immersion-well 450 W UV-B lamp was used to irradiate a quartz capillary microreactor (ID 760 μm, 625 μL), which was connected to a back pressure regulator (20 psi). In this reactor, alkyl-aryl nitrones could be converted to the desired amide in 60-90% yield within 5-20 minutes in the presence of catalytic amounts of trifluoroacetic acid (TFA, 0.25 eq.). The methodology was subsequently used for the synthesis of di- and tetrapeptides (Scheme 15).\textsuperscript{197} Lower yields (around 50%) compared to the alkyl-aryl nitrones were obtained, but no epimerization of the stereocenters was observed.

Photochemical rearrangement of N-oxides were also performed in flow.\textsuperscript{198} Bauer, Bach and co-workers used a meso Duran tube reactor to suppress the undesired [2+2] photodimerization of a 4-substituted quinolone product obtained by a photoinduced N-oxide rearrangement.\textsuperscript{99-100}

Scheme 15 Photochemical rearrangement of nitrones yielding amides.
The formation of ketenes from α-diazo ketones is known as the Wolff rearrangement. An efficient way to induce this transformation is by photolysis. Due to the reactivity and synthetic versatility of ketenes, several photoinduced transformations based on this reaction have been reported also in flow.

Basso et al. developed a ketene three-component reaction (K-3CR), including a diazo ketone, a carboxylic acid and an isocyanide (Scheme 16). Specifically, an α-diazo ketone generates a reactive ketene intermediate through a UV-induced Wolff rearrangement. This intermediate further reacts with the isocyanide and the carboxylic acid to yield the final olefin. The use of a FEP water-cooled microreactor (ID 800 μm), irradiated with 16x8 W black light, allowed to obtain the desired olefin with similar yield and Z/E selectivity than in batch, but with higher efficiency and sustainability (in term of both STY and PMI).

Scheme 16 Ketene three-component reaction in flow.

An intramolecular variant of the Wolff rearrangement has been reported by Konopelski et al. Enantiomerically pure trans-β-lactams can be prepared in continuous-flow starting from α-amino acid-derived β-ketoamides (Scheme 17). In particular, a Weinreb α-diazo-β-ketoamide derived from L-serine was irradiated in batch and in flow with a medium-pressure mercury lamp. The coiled-FEP capillary reactor needed rigorous cooling due to the thermal instability of the diazo intermediate. Compared to batch, the flow synthesis showed a reduced reaction time and ease of scale up, and was therefore preferred despite the slightly diminished yields (81% instead of 90%). Owing to the concerns associated with the use of a UV lamp, a compact fluorescent light (CFL) was also evaluated, resulting in improved yields (95% batch and 91% flow), greater safety and lower costs despite the lower throughput.

Scheme 17 Intramolecular Wolff rearrangement yielding enantiomerically pure β-lactams in flow.
Figure 9 FEP coiled reactor used for the photochemical benzannulation based on the reaction of ynamides and diazoketones. Reprinted with permission from ref. 207. Copyright 2013 American Chemical Society

The synthetic value of the Wolff rearrangement is well exemplified by its key role in triggering a pericyclic cascade reaction as shown by Danheiser et al.207 A wide range of benzofused nitrogen heterocyclic compounds was obtained from the reaction of α,β-unsaturated α-diazo ketones with ynamines. The mechanism involves an initial Wolff rearrangement of the diazo ketone to the corresponding vinylketene. This vinyl ketene is subsequently engaged in a regioselective [2+2] photocycloaddition with a ynamide partner, yielding a substituted vinylcyclobutenone. After light-induced electrocyclic cleavage of the cyclobutenone and subsequent ring-closure, the final polysubstituted aniline product is obtained (Scheme 18).

The reaction cascade was performed in both a conventional immersion well reactor and a continuous-flow FEP coiled reactor (ID 760 μm, 1.2 mL, Figure 9). In flow, no significant improvement in yield was observed. However, a more straightforward scale up and reduced reaction time (from 3-8 hours to 21 minutes) became possible.

Scheme 18 Pericyclic cascade yielding benzofused anilines.

A Wolff rearrangement is also the concluding step in the Arndt-Eistert homologation sequence, yielding enantiopure β-amino acids starting from the corresponding α-amino acids.208 Kappe and co-workers developed a fully continuous four-step process to prepare β-amino acids (Scheme 19).209 α-diazoketones, obtained via the in situ generation of diazomethane, were introduced in a PFA coiled (ID 760 μm, 3 mL) reactor and irradiated with a UV-CFL light source (256 nm). A model reaction was used to optimize the photochemical step, and it was found that an irradiation time of 10 minutes afforded the desired products in 57% isolated yield. The complete homologation se-
quence was applied to several Boc and Cbz-protected amino acids, resulting in the corresponding β-amino acid derivatives in moderate to good yields (23-54%). Similarly, Fuse and co-workers performed a continuous-flow Arndt-Eistert synthesis for the preparation of α-aryl carboxylic acids.210

![Scheme 19](image)

**Scheme 19 Continuous-flow synthesis of β-amino acids via Arndt-Eistert homologation, featuring a light-induced Wolff rearrangement.**

The synthesis of N-arylacetyl oxazolidinone, a precursor for the preparation of the non-natural amino acid 3,5-dihydroxyphenylglycine (Dpg), also involved a Wolff rearrangement.210 After a preliminary screening in a 50 μL reactor, the optimized reaction conditions were translated to a flow protocol using a FEP coiled reactor (ID 1.0 mm, 500 μL). The flow procedure enabled efficient scale up (gram scale) employing a portable 4 W UV lamp as light source (5 min irradiation time, 82% yield).

The rearrangement of 4-hydroxycyclobutenones to yield 5H-furanones was studied in a photochemical reactor by Harrowven et al. (Scheme 20).212 In a PFA-coiled capillary reactor (ID 1.0 mm, 19 mL), different low-energy 9 W light sources were evaluated. Using a UV-B lamp with a broad emission, 54% yield of the desired product was obtained in 120 min residence time. However, significant byproduct formation was observed. Switching the solvent to acetonitrile and using an UV-B lamp (310-320 nm), resulted in improved yields up to 97% in 90 minutes residence time. The improved results can be attributed to the avoidance of light absorption by the product, which initiates product decomposition. Interestingly, the use of an UV-A lamp (350-395 nm) resulted in a reduced reaction rate, while the use of an UV-C lamp (254 nm) afforded full conversion albeit with the formation of byproducts. Furthermore, the hypothesized torquoselectivity of the ring opening of cyclobutenone was confirmed through DFT calculations. In fact, the calculations showed that the photoinduced electrocyclic opening of cyclobutene yields both the E and Z vinylketene. The E isomer reacts further to the corresponding furan, while the Z isomer reacts back to the starting material. However, in presence of an internal nucleophile, the Z isomer can further react to quinolizinones (Scheme 20).
Another photochemical transformation successfully accelerated in flow is the nitrite photolysis, also known as the Barton reaction. Ryu et al. reported a gram-scale application for the production of a key intermediate en route to myriceric acid A, an endothelin receptor antagonist (Scheme 21). After a preliminary optimization of the reactor material, light source and residence time, the best conditions were found to be a 12 minute irradiation of the reaction mixture with a 15 W black light in a Pyrex-covered reactor. The small scale 0.2 mL reactor was then replaced by two 4 mL reactors with 8 black lights (20 W each) allowing a throughput of 3.1 g in 20 hours. In a follow-up paper, the use of UV-LEDs (365 nm) was also investigated and an automated photomicroreactor system, employing an array of 48 LEDs, yielded 5.3 g of product in 40 hours.

Scheme 21 Barton reaction in flow on a steroidal substrate en route to myriceric acid A.

The photolysis of phenyl azides can be exploited to generate reactive nitrenes. These compounds can subsequently rearrange in the presence of water to yield 3H-azepinones. The mechanistic details of the phenyl azide photolysis were subject of intense research in the last decades and are now understood in detail. However, due to the technical difficulties in scaling photochemical reactions, this transformation was not widely applied. Seeberger and co-workers reported a continuous-flow UV-induced photolysis of aryl azides yielding azepinones (Scheme 22). The adoption of microreactor technology allowed to scale the reaction while keeping the yields in the same range as small scale batch reactions. The reactor was made of FEP capillary (760 μm, 14 mL) coiled around a 450 W medium pressure mercury lamp and surround-
ed by a cooling jacket. A 6.9 bar back pressure regulator was used to prevent the formation of gaseous nitrogen slugs and to accurately control the residence time. With this setup, a variety of 3H-azepinones were prepared in moderate to good yields (35–75%) and allowed to synthesize a pharmaceutically relevant benzodiazepine scaffold. Azide photolysis in flow was also applied to the synthesis of dihydropyrroles starting from aromatic vinyl azides and activated alkenes.  

Therefore, a photochemical flow set-up consisting of three cylinder reactors connected in series (ID 1.0 mm, 37.5 mL), each wrapped around a 8 W black-light blue UV-A lamp, was employed. Within 90 minutes residence time, an array of sulfides and sulfoxides was successfully aminated in good to excellent yields (71–98 %) (Scheme 23). Notably, the amination of sulfoxides derivatives was found to be stereoselective, with retention of the initial enantiomeric ratio.

![Scheme 22 Photolysis of aryl-azides yielding 3H-azepinones](image)

A photochemical strategy for the amination of sulfides and sulfoxides was reported by Lebel and co-workers. The reaction proceeds through the decomposition of trichloroethoxysulfonyl azide (TcesN₃), catalyzed by iron(III) acetylacetonate (Fe(acac)₃), to yield a reactive nitrene intermediate that further reacts with sulfides or sulfoxides. Optimization studies showed the ability of Fe(acac)₃ to absorb UV-A light.

![Scheme 23 Azide mediated amination of sulfide and sulfoxide](image)

Microreector technology is particularly useful to reduce the safety hazards associated with the handling of highly toxic and explosion-prone materials such as halogen azides. The in situ generation and photodecomposition of bromine azide has been recently performed in a continuous flow setup by Kappe and co-workers (Scheme 24). BrN₃ was generated in situ by mixing NaN₃ and NaBr in the presence of oxone as oxidizing agent. BrN₃ was subsequently extracted into the organic phase where it reacted with an olefin.
substrate. The influence of UV irradiation (CFL 365 nm, 105 W) on the reaction was investigated in a FEP coiled reactor (ID 760 μm, 18mL). The accelerated photodecomposition of the halogen azide enabled the reaction with less reactive olefins (e.g. ethyl cinnamate, 99% conversion with light, 43% without). The selectivity was also increased under photochemical conditions with less ionic Markovnikov-like mechanism byproduct.

Recently, a photo-Favorskii rearrangement in flow was reported by Baxendale et al. to prepare ibuprofen in flow.\textsuperscript{220} In contrast to previously reported flow syntheses of this anti-inflammatory drug,\textsuperscript{221-222} the arylpropionic scaffold was not obtained through a Friedel-Crafts acylation with propionic acid followed by a 1,2-aryl migration. Instead, chloropropionyl chloride was used as an acylation partner. The conversion of the obtained α-chloropropiophenone towards ibuprofen was achieved in a photoflow process, resulting in an 84% yield for the product and a 13% Norrish type I derived byproduct (Scheme 25).

Scheme 24 Photodecomposition of bromine azide in a continuous-flow microreactor.

A photo-Claisen-type ortho-rearrangement of an aryl naphthylmethyl ether was also achieved in flow. The reaction was performed in a Pyrex microchip (200 x 90 μm channels, 1.08 mL), irradiated with a 300 W high pressure mercury lamp.\textsuperscript{223} Compared to batch, higher conversions and a better product-to-byproducts ratio was observed.

Performing a photochemical reaction in flow allows to easily tailor several reaction parameters, such as reac-
tor temperature, flow rate and concentration. Researchers from Genzyme, took advantage of this possibility and applied a design of experiment (DoE) technique to optimize the flow photoisomerization of an intermediate in the doxercalciferol (vitamin D2) synthesis. Under optimized conditions, a 4 wt% loading of photosensitizer (9-acetylanthracene) was used at 10 °C resulting in a product yield of 96%.

### 3.2.3 Cyclizations

Photocyclization reactions frequently result in the formation of highly complex photoactive π-conjugated systems. Consequently, the reduced reaction time provided by microreactor technology offers a mean to prevent the photodegradation of these compounds, which is often observed in batch.

An intriguing example of continuous-flow photocyclizations was reported by Seeberger and co-workers, who described the synthesis of several pyridocarbazoles. These compounds all featured a common scaffold which, through complexation with transition metals, affords high affinity kinase inhibitors (Scheme 26).
The key synthetic step involved a Mallory photocyclization. In batch, this transformation is plagued by the formation of a significant amount of byproduct, which greatly complicates the compound purification. On the contrary, the flow synthesis proceeded cleanly towards the desired product (see NMR spectra in Figure 10) in only 15 minutes, while the corresponding batch experiment required 4.75 hours.

Figure 10 Comparison of the NMR spectra of starting material and products of the Mallory reaction. The product obtained in batch is contaminated with the formation of a byproduct (see arrows) absent in flow. Reprinted with permission from ref. 225. Copyright 2013 Royal Society of Chemistry

Rueping and co-workers introduced another continuous-flow Mallory reaction, i.e. the oxidative photocyclization of stilbene derivatives.226-227 The initial optimization was performed in a FEP capillary (5 ml), which was irradiated with a 150 W high-pressure mercury lamp. The photocyclization of (E)-stilbene to yield phenanthrene proceeded smoothly (95% yield) within 83 minutes. The mechanism proceeds through a photoisomerization of (E)-stilbene to (Z)-stilbene which subsequently undergoes an oxidative photocyclization in the presence of iodine.

Scheme 27 Photoisomerization followed by photocyclization of stilbenes.

It is important to note that oxygen cannot be used as the final oxidant as this would form singlet oxygen, resulting in oxidation byproducts. In a larger setup (24 ml volume), the scope and scale-up potential of this reaction was evaluated (Scheme 27). Several trisubstituted olefins were converted into functionalized phenanthrenes in moderate to good yields (34 to 89%). Moreover, a two-step synthesis of helicene derivatives was developed by combining a standard Wittig reaction with a subsequent photochemical cyclization. Similarly, Okamoto and co-workers, accomplished a continuous-flow synthesis of several polycyclic aromatic hydrocarbons on gram scale.228

Czarnocki and co-workers recently reported the use of a continuous-flow photocyclization for the formal synthesis of (−)-podophyllotoxin, a lignan known for its antineoplastic properties.229 Starting from 3,4-
bisbenzylidene succinate cyclic amide ester, the core framework of podophyllotoxin could be obtained via a UV-induced cyclization (Scheme 28). The reactor featured a quartz tube (3 m) coiled to form a rectangular section and was irradiated with a UV mercury lamp. The desired compound could be obtained in 61% yield.

Scheme 28 UV-induced continuous flow cyclization for the synthesis of (-)-podophyllotoxin.

A tandem photocyclization-reduction of 2-aminochalcones yielding enantiomerically pure tetrahydroquinolines was reported by Sugiono and Rueping (Scheme 29). Three commercially available glass reactors were connected in parallel and positioned in a water bath to keep the reaction temperature at 55 °C. The channels were subjected to irradiation emitted by a 150 W high pressure mercury lamp. The reaction proceeds through the photocyclization of the 2-aminochalcones to the corresponding quinoline. In the presence of a chiral Brønsted acid and a Hantzsch dihydropyridine, acting as hydride source, the final tetrahydroquinolines were achieved in good yields and enantioselectivities (63-88%, e.e. up to 96%).

Scheme 29 Synthesis of enantiomerically pure tetrahydroquinolines via a photocyclization-reduction cascade.

The beneficial use of laser radiation in photochemical reactions was demonstrated by Bräse and co-workers. They reported the photochemical decomposition of arylazides into carbazoles (Scheme 30). Special miniaturized polyether ether ketone (PEEK) and polytet-
rafluoroethylene (PTFE) tubing were covered with quartz plates, which was housed in a stainless frame (Figure 11). Multiple capillaries of different volumes were hosted in the miniaturized reactor, allowing to perform a series of parallel reactions. Frequency-tripled Nd:YAG laser radiation of 355 nm with a single-pulse power of 0.16 to 3 W was selected, resulting in an impressive reduction of the reaction time (30 seconds in flow, 18 hours in batch). Furthermore, the high energy and the focused beam, typical for a laser, contributed in diminishing any byproduct formation, i.e. diazocompounds. Because of the increasing availability of affordable laser systems, which provide a precise control over the wavelength and size of the light beam, it is likely that the use of laser light sources in combination with microreactor technology will further spread in the coming years. Another example of laser irradiation in microflow has been reported by Ouchi et al.\textsuperscript{232} The irradiation of flavone with a XeCl excimer laser (248 nm) in the presence of NaBH₄ was performed in a quartz microreactor (irradiated volume: 0.1 x 0.4 x 16.5 mm, 660 μL). This resulted in an accelerated reaction and increased selectivity towards flavanone and flavanol.

\textbf{Scheme 30} Laser-assisted arylazides photolysis into carbazoles.

Figure 11 Miniaturized reactor used for the laser irradiation of 2-azidobiphenyl in flow. From left to right, the increasing depth of the different reactors, is noticeable. Reprinted with modifications from ref. 231. Copyright 2012 Bräse and co-workers.

\subsection{3.2.4 Singlet oxygen mediated oxidations}

Molecular oxygen is an attractive oxidant due to its atom efficiency, reduced cost and sustainable nature.\textsuperscript{75, 233} Singlet oxygen can be produced starting from triplet oxygen, that is oxygen in its ground state, by light irradiation in the presence of a suitable photosensitizer.\textsuperscript{234-236} Some frequently used photosensitizers with their maximum absorption wavelength are enlisted in Scheme 31. Organic dyes, such as methylene blue, Rose Bengal and tetraphenylporphyrin (TPP), are among the most commonly used sensitizers. Metal-based photosensitizers can also be em-
ployed. However, virtually any photoactive molecule generating an excited state with a sufficiently long life span can be quenched by O₂ to produce singlet oxygen. Photosensitizers absorb light in a specific wavelength region depending on their structure. In the presence of oxygen, energy transfer from the excited state of the photosensitizer can occur, yielding singlet oxygen. Compared to triplet oxygen, singlet oxygen shows higher electrophilicity, which allows to oxidize substrates which are otherwise unreactive to oxygen.\textsuperscript{237-241} The lifetime of singlet oxygen is highly dependent on the solvent in which the reactions are carried out: typically, chlorinated solvents afford a longer lifetime than polar protic solvents.\textsuperscript{242} Due to its high reactivity, singlet oxygen-mediated oxidations are often plagued by undesired byproduct formation due to overoxidation or other non-selective oxidation processes. However, by preventing product degradation through precise control over irradiation time, flow photochemistry provides a key advantage.

![Common photosensitizers for singlet oxygen generation](image)

Scheme 31 Common photosensitizer for the generation of singlet oxygen and relative wavelength of absorption.
One of the first examples of continuous-flow generation and safe use of singlet oxygen was reported in 2002 by de Mello and co-workers.243 The formation of ascaridole endoperoxide starting from \( \alpha \)-terpinene was used as model reaction (Scheme 32).244 The glass microreactor was made using direct-write laser lithography. The etched channels (50 x 150 \( \mu \)m) resulted in a total reactor volume of 375 \( \mu \)L. A conversion of > 80\% was obtained in less than 5 seconds using a 20 W tungsten lamp.

More recently, the same group reported the use of a microcapillary film reactor composed of 10 parallel FEP channels (ID 100 \( \mu \)m) embedded in a plastic ribbon.64 To perform the ascaridole reaction, oxygen was supplied to the reactor by exploiting the gas permeability of the FEP tubing. Different wall thicknesses and external oxygen pressure were studied to assess the through-wall mass transport of oxygen. A yield of 90\% of ascaridole was observed using a 14 minutes residence time in a capillary with a wall thickness of 61.5 \( \mu \)m and an oxygen pressure of 65 psi.

Scheme 32 Synthesis of ascaridole through [4+2] photooxygenation of \( \alpha \)-terpinene in a glass microchip.

Park and co-workers investigated the continuous-flow photooxygenation of monoterpenes.245-246 A monochannel microreactor was employed for the optimization of the reaction conditions, while a tube-in-tube reactor allowed for a higher throughput and thus for scale-up of the reaction conditions (Figure 12). Generation of singlet oxygen was obtained through irradiation with 16 W LEDs. Both reactors performed better than corresponding batch experiments, providing higher conversions (e.g. for citronellol photooxygenation, full conversion was obtained in 2 minutes in both the microreactors, while reaction took 3 hours in batch). The use of solar energy was also investigated in the monochannel microreactor, however lower yields (48\% solar vs. 99.9\% LED irradiation) were observed despite the implementation of a convex lens to focus the sunlight towards the reaction channels.

Figure 12 Tube in tube reactor for the photooxygenation of monoterpenes. Reprinted with permission from ref. 246. Copyright 2015 The Royal Society of Chemistry

The continuous-flow TPP-sensitized singlet oxygen-mediated oxidation of \( \alpha \)-pinene to pinocarvone was extensively studied by Lapkin and co-workers with respect to different lamp-reactor designs and flow regimes (Scheme 33).247 Microreactors afforded up to 10 times higher space-time yields compared to traditional immersion-well reactors, with photonic efficiencies mostly similar or higher as a result of the better light
use in the reactor. Among the tested conditions, the best results in terms of photonic efficiency were obtained when the reaction was performed in a homogeneous flow. However, the conversion was limited by the oxygen solubility in the solvent. Higher space-time yields could be obtained when using a segmented oxygen-liquid regime. Interestingly, a cost objective function was included in the reactor model and the operating cost ($/mol of pinocarvone produced) had its minimum when using microchannels in the 100-1000 μm range (Figure 13).

For the same benchmark reaction, Carofiglio et al. used a silica-immobilized fullerene as a photosensitizer, therefore providing an example of heterogeneous photooxidation. The microreactor (ID 500 μm, 152 μL) was fabricated by a thiol-ene rapid prototyping technique and encased between two glass plates. White LEDs were used a light source. Despite the full conversion of the starting material, the reported yields were low to moderate (e.g. 53% yield at 97% conversion), which was attributed to the poor oxygen solubility in the reaction mixture.

Similarly, Boyle and co-workers accomplished the fabrication of a 16-channel glass chip with an immobilized porphyrin as a photosensitizer (Figure 14). Through silanization of the glass surface of the chip with (3-aminopropyl)triethoxysilane (APTES), the introduction of an amine linker was achieved. Next, the isothiocyanate group on the porphyrin was reacted with this amine linker to yield a thiourea moiety, thus covalently binding the photosensitizer to the chip. The efficiency of the microreactor was then tested for the photooxidation of cholesterol, α-terpinene and citronellol.

Figure 13 Operating cost in $/mol as function of microchannel depth (x axis). Reprinted with permission from ref. Copyright 2014 American Chemical Society

Figure 14: 16 parallel channel glass reactor used for the photooxygenation of cholesterol. Reprinted with
Supported photosensitizers for the generation of singlet oxygen in supercritical CO$_2$ (scCO$_2$) were developed by Poliakoff and co-workers.\textsuperscript{250-251} The high pressure needed to perform reactions in scCO$_2$ requires specialized equipment.\textsuperscript{252} However, due to the absence of mass transfer limitations (high diffusivities and complete miscibility of gaseous O$_2$ in scCO$_2$) and the extended lifetime of 1$^\text{O}_2$, scCO$_2$ processes are in general sustainable and attractive.\textsuperscript{253} Poliakoff et al. prepared supported porphyrin photosensitizers on PVC beads and successfully applied these to the photooxygenation of $\alpha$-terpinene and citronellol (Scheme 34).\textsuperscript{250}

The photochemical oxidation of (S)-(−)-β-citronellol to its corresponding hydroperoxides isomers is one of the key steps required for the synthesis of (−)-rose oxide, which is of interest to the fragrance industry (Scheme 34). This singlet oxygen-mediated reaction has been used as another popular model reaction for the optimization and validation of different photomicroreactors. Using this benchmark reaction, Meyer et al. compared a Schlenk-tube batch reactor (40 ml total volume, of which only 7.46 ml was effectively irradiated) and a glass microreactor (ID 1.0 mm, 0.47 ml).\textsuperscript{254} In both cases, the reaction mixture was saturated with compressed air as the oxygen source. Blue LEDs were chosen as a suitable light source. In the industrial process of rose oxide, Rose Bengal is commonly used as photosynthesizer. However, the authors selected Ru(6bpy)$_2$Cl$_2$ (6bpy=tert-butyl bipyridine) as a sensitizer as it displays a higher quantum yield for singlet oxygen production. Space-time yield comparisons showed a slight advantage for the microreactor. Furthermore, the microreactor was tested to compare the performance of Ru(6bpy)$_2$Cl$_2$ with Rose Bengal, and the light source was switched to a 450 W Xe-lamp to match the absorption of both sensitizers. Despite the higher quantum yield and stability postulated for Ru(6bpy)$_2$Cl$_2$, Rose Bengal showed a higher conversion rate (55% conversion with Ru-based catalyst vs. 75% with Rose Bengal after 400 minutes of irradiation).

Kim and co-workers reported the oxidation of β-citronellol to validate their dual- and triple-channel microreactor concept (Scheme 34).\textsuperscript{255-256} This multiple channel design was developed to improve the reaction rate of biphasic gas-liquid reactions by dramatically increasing the interfacial area between the gaseous phase and the liquid reaction stream. In the dual-channel microreactor (ID 220 μm, 38.9 μL), oxygen diffuses into the liquid phase from the bottom channel through a gas-permeable PDMS membrane. The liquid solution-containing channel had to be coated with a layer of polyvinylsilazane (PVSZ) to prevent swelling of the PDMS layer. Interestingly, the PVSZ coating could be avoided in the triple-channel microreactor (250 x 40 μm, 3.3 μL), where the channel containing the reaction mixture is surrounded by two oxygen channels (Figure 15). This triple-channel microreactor design proved to be easier to fabricate, and featured an overall increased interfacial area. When compared to batch, both microreactor designs showed a significant improvement in
reaction rate for the oxidation of citronellol using methylene blue as a photosensitizer. Full conversion was obtained within 2 and 3 minutes for the triple- and dual-channel microreactor respectively, while the batch reactor required 3 hours. The methylene blue-mediated photooxygenation of (i) allylic alcohols to allyl hydroperoxide alcohols and (ii) α-terpinene to ascaridole were also successfully performed in these reactors.
Scheme 34 Different microflow conditions for the photooxygenation of citronellol and role of this photochemical step in the synthesis of the fragrance rose oxide.

Figure 15 A: Graphical representation of dual and triple-channel microreactor for photooxidation of allylic alcohol. B: Photograph of the chip. Reaction channel (red) and outer channels (blue) are filled with dye solution for demonstration purposes. Copyright 2011 Kim and co-workers.
Lévesque and Seeberger used a 78 μl silicon-glass microreactor to generate singlet oxygen in the presence of Rose Bengal and green LEDs.\textsuperscript{257} As a model reaction, the photooxidation of citronellol was selected. The silicon device was ideal to rapidly screen various reaction parameters while keeping the total consumption of reagents small. However, to increase the productivity, a FEP coiled reactor (ID 760 μm) was used instead and was irradiated with a 450 W mercury lamp. Rose Bengal was also replaced by tetraphenylporphyrin as photosensitizer due to an increased photostability. With this reactor, full conversion was observed with only 1.6 equivalents of oxygen, which significantly reduced the risks associated with unreacted oxygen. A further increase in throughput was achieved by increasing the reactor volume (from 5 to 14 mL) using an HPLC pump, a mass flow controller and a back pressure regulator. A variety of substrates were successfully oxidized in good yields and high productivity (Scheme 35).\textsuperscript{257}

From left to right, oxidation of 2-methylfuran, α-pinene and a sulfide.

Scheme 35 Singlet oxygen mediated reactions performed in a continuous-flow FEP coiled reactor.
Seeberger et al. reported an innovative and practical synthesis of the anti-malaria drug artemisinin starting from dihydroartemisinic acid and employing a key singlet oxygen reaction in flow. The reaction sequence from dihydroartemisinic acid, a waste product, to artemisinin involved a singlet oxygen ene reaction resulting in an allylic hydroperoxide (Scheme 36).

This hydroperoxide was converted through an acid mediated Hock cleavage and a subsequent oxidation delivered the target artemisinin. The three reactions were individually optimized and ultimately integrated in a fully continuous process. This process was further scaled for industrial application in a follow-up paper.

In particular, TPP was substituted with 9,10-dicyanoanthracene (DCA) as a singlet oxygen sensitizer, as it provided a higher quantum efficiency and acid photostability. In addition, performing the ene reaction at -20 °C improved the selectivity towards the formation of the desired product. The industrial suitability of this process, was demonstrated in 2014, when Sanofi started to exploit this novel semisynthetic route to artemisinin. In the production site of Garessio (Italy), the current production of artemisinin reaches 50-60 metric tons per year, nearly a third of the annual global need.

The synthesis of rhodomyrtosone A involves a [4+2]-cycloaddition with singlet oxygen and was carried out in flow to provide a scalable production of this intermediate. A methanolic solution of the starting material, saturated with oxygen, was pumped in a PFA capillary (ID 1.5 mm, 3.1 mL), which was coiled around a UV lamp and cooled to -10 °C. The corresponding endoperoxide was obtained as a 1:1 mixture of diastereomers in 50% yield (Scheme 37).
Scheme 37 Total synthesis of rhodomyrtosone A. The highlighted step is performed in flow.

Microflow conditions:
- PFA-tubing (1.5 mm ID, 3.1 mL)
- Hanovia UV lamp, T: -10 °C
- Solvent: MeOH (0.01 M), O₂ (sat.)
In batch, the oxidation of indane to yield 1-indanone resulted in the production of several byproducts, such as 1,3-indanedione or ring-opened compounds, and reached a maximum conversion of only 60% (Scheme 38). The same reaction was performed in a commercial glass microreactor (500 x 300 μm, 360 μL) using oxygen in a slug flow regime. Interestingly, the formation of byproducts was suppressed in flow and the desired compound could be obtained in 83% yield. 263

Scheme 38 Photooxidation of indane with oxygen slug flow in a glass microreactor.

Kappe and co-workers presented the use of singlet oxygen for the oxidation of 5-hydroxymethylfurfural (5-HMF), a common intermediate for the synthesis of biofuels and polyester precursors. 264-266 Oxidation of 5-HMF results in the formation of 5-hydroxy-5-(hydroxymethyl)-furan-2(5H)-one (H₂MF), a highly functionalized building block with similar applications as 5-HMF. The reactor consists of a 10 ml PFA capillary (ID 1.0 mm) which is subjected to 60 W compact fluorescent light (CFL) irradiation. The liquid stream, containing a solution of starting material in i-PrOH/H₂O (1:1) and Rose Bengal (1 mol%), was merged with molecular oxygen. At an operational pressure of 17 bar, a homogeneous flow regime was observed and full conversion was reached with a 93% isolated yield for the desired product (Scheme 39). The reaction conditions were then applied to a small array of 5-HMF derivatives.

Selected examples:

Scheme 39 Flow photooxygenation of 5-hydroxymethyl-furfural, platform molecule for biofuels and polyester precursors.

Singlet oxygen photochemistry was also used for the oxidative cyanation of primary and secondary amines as demonstrated by Seeberger and co-workers (Scheme 40). 267 A FEP coiled reactor (ID 760 μm, 7.5 mL) was irradiated with low-energy LEDs (420 nm). The first step involved an oxidative transformation yielding the corresponding imine in high selectivity. Subsequently, these imine intermediates were cyanated in the presence of trimethylsilyl cyanide (TMSCN) to afford the desired α-aminonitrile. Tetraphenylporphyrin was selected as photosensitizer and tetra-n-butylammonium fluoride (TBAF) was added in catalytic amounts to activate TMSCN, allowing to decrease the amount of TMSCN from 5 to 2.5 eq. With a controlled reaction temperature of -50 °C, a small array of activated and unactivated amines were subjected to the oxidative cyanation protocol to synthesize α-aminonitriles in good to excellent yields (71-99%). More recently,
Seeberger et al. reported a detailed mechanistic study correlating the regioselectivity, obtained in the oxidation of primary and secondary amines, with the bond dissociation energy of the competing C-H bonds adjacent to the nitrogen atom.\(^{268}\)

![Scheme 40](image)

**Scheme 40** Continuous-flow oxidative photocyanation of amines and subsequent use of the cyanated derivatives for fluorinated amino acids synthesis.

In another report, the photooxidative cyanation procedure was coupled in a semi-continuous-flow process to the acid-mediated hydrolysis of the nitrile group, to yield an array of \(\alpha\)-amino acids (Scheme 40).\(^{269}\) Primary benzyl and homobenzyl amines containing different fluorine substituents were converted, providing access to fluorinated amino acids. However, no control over the chirality of the amino acidic stereocenter was possible, resulting in the formation of a racemic mixture.

The photochemical generation of singlet oxygen was reported in a falling-film reactor by Jähnisch and Dingerdissen.\(^6\) The microreactor features a reaction plate with 32 parallel channels (ID 600 \(\mu\)m) covered with a quartz window (Figure 16). This design uses gravity to produce a thin layer of liquid which is co-currently brought into contact with the oxygen gas phase. The photooxygenation of cyclopentadiene, yielding an endoperoxide intermediate and a cyclopentene diol as final product, was performed in the reactor in the presence of Rose Bengal as photosensitizer. The use of the falling film microreactor allowed for an easier and safer handling of the explosive endoperoxide intermediate, and afforded the desired product in preparative scale (0.95 g, 20% yield). The same reactor had been previously reported for the photochlorination of toluene-2,4-diisocyanate, showing better selectivity and space-time yield compared to a conventional batch reactor.\(^{270}\)

![Figure 16](image)

**Figure 16** Falling film microreactor for the photooxygenation of cyclopentadiene. Reprinted with permission from ref. \(^6\). Copyright 2005 John Wiley & sons.
3.2.5 Photocleavage and photodeprotection

Protecting groups (PGs) are of paramount importance in the synthetic chemists toolbox to enable multistep organic synthesis. Photolabile PGs exhibit appealing cleavage conditions (mild and neutral) and orthogonality to traditional PG. Beeler and co-workers reported the continuous-flow deprotection of several amine substrates through the removal of the photolabile 2-methoxy-9-methylxanthene (Scheme 41). In a FEP-coiled reactor (ID 800 μm, 350 μL) equipped with a mercury lamp (λ > 305 nm), deprotection of all the substrates (including a Boc-protected piperazine, amino alcohol and phenylalanine methyl ester) was achieved in good yields (61-83%) within 10 minutes residence time. Stability of the protecting group in acid and basic conditions and at high temperatures was proven. Furthermore, the applicability of this protection strategy was demonstrated in a three-step flow synthesis, where the orthogonality with a Boc protecting group and the compatibility with amidation and acylation steps was demonstrated.

Scheme 41 Photodeprotection of the photolabile xanthene-derived amine protecting group in continuous-flow.

The troublesome cleavage of the 2-nitrobenzyl PG is the main reason why its wider adoption has been hampered. Wendell and Boyd described a flow protocol highly simplifying the deprotection of this photo-PG. A commercial UV flow reactor (10 mL, 105 W medium pressure mercury lamp) was used. With the continuous-flow removal methodology, the deprotection of the amine function of electron poor indoles, indazoles and few pyrazoles could be achieved. Compared to batch, higher deprotection yields (e.g. 84% in flow vs. 40% in batch) were obtained and the reaction time could be significantly reduced (from several hours in batch to 10 minutes in flow).

Photolabile groups were also exploited as useful linkers for solid phase synthesis. Seeberger and co-workers reported the use of a nitrobenzyl ether-based linker to conveniently connect a standard Merrifield resin to a monosaccharide (Scheme 42). The linker proved to be compatible with the strong basic and acidic reaction conditions required for the solid phase synthesis of a hexasaccharide glycosaminoglycan (GAG) and of a 30-mer mannoside derivative through automated synthesis. In both cases, the photocleavage of the desired product from the resin was performed through a FEP-coiled microreactor (ID 760 μm, 12 mL) irradiated with a 450 W mercury lamp equipped with a UV Pyrex filter. The resin-bound oligosaccharides were flushed through the microreactor with a syringe pump. After reaction,
the solid support was easily filtered off providing an efficient way of purifying the target compound.

Scheme 42 Continuous-flow photocleavage of a nitrobenzyl ether linker in sugar solid phase synthesis.

In a later report, Seeberger et al. thoroughly investigated the cleavage efficiency of this photolabile linker in batch and in flow. A double-jacketed batch reactor irradiated with a UV lamp and a Pyrex filter was used as a reference. The coiled FEP-tubing microflow setup was entirely built in a sealed aluminium box. A 450 W lamp with a Pyrex filter was employed and inserted into a double-jacketed immersion well. The FEP tubing (ID 760 μm or 1.5 mm, 12 or 15 mL respectively) was coiled around the jacket. A PS resin loaded with the photolabile linker and a fluorescein thiourea (FTU) was prepared to assess the stability and the impact of the cleavage step (Scheme 43). Evaluation of the efficiency was performed by comparing the beads fluorescence before and after cleavage via laser confocal microscopy. In batch photocleavage experiments, irradiation for 30 minutes without shaking resulted in a highly heterogeneous population of the resin, with some beads completely cleaved, while others still carrying the fluorescent moiety. When the batch reactor was shaken, almost all beads displayed partial cleavage but the overall cleavage efficiency was still poor. Improved results were obtained in flow, where the use of a wide 1.5 mm ID tubing provided a vigorous turbulent mixing, ultimately resulting in a uniform and efficient photocleavage. It was postulated that the mixing observed in the larger diameter FEP tubing allowed every bead to be efficiently irradiated. A less efficient mixing was observed in an 760 μm ID tubing. Herein, the formation of multilayer slugs prevented optimal irradiation of the system.

Scheme 43 Preparation of polystyrene (PS) resin loaded with the photocleavable linker and FTU. Subsequent cleavage in continuous-flow afforded a more efficient and homogeneous deprotection compared to batch.

3.2.6 Light-induced halogenation / dehalogenation reactions

Časar and co-workers improved the benzylic bromination of a 5-methyl-substituted pyrimidine. This compound constitutes a crucial intermediate in the synthet-
ic route towards rosuvastatin, a top selling drug for the treatment of hypercholesterolemia (Scheme 44). The batch procedure showed complete conversion, however, the formation of regioisomers and polybrominated byproducts could not be prevented. Furthermore, the removal of such byproducts proved problematic, which represented a risk hampering the further steps to the final product. To better control the rate of bromination, and prevent the formation of the polybrominated byproducts, a photoflow procedure was envisioned. A FEP capillary (ID 760 μm, 18 mL) was coiled around a quartz cooling jacket and irradiated with a 150 W medium-pressure mercury lamp. With a residence time of 5 minutes, the reaction could be completed and afforded an astonishing 58.3 mmol/h of product, nearly 4 times higher than could be obtained in batch. Moreover, no overbromination of the 5-benzylic position and a lower overall level of impurities were observed.

Scheme 44 Benzyl flow bromination of an intermediate for the production of rosuvastatin.

Benzylic bromination was described in a milli photoreactor by Kappe and co-workers. Unlike other examples reporting the use of N-bromosuccinimide (NBS) as Br source, molecular bromine was used instead, providing a more atom efficient methodology. Several alkanes and alkylarenes were successfully halogenated using a slug-flow regime in a commercial chip microreactor (0.5 x 1.0 mm section, 950 μL) (Scheme 46). For alkanes, a solution of bromine in the substrate was mixed with water. For alkylarenes, the substrate and bromine were dissolved in trifluorotoluene and mixed with water. A 15 W black light was used for photoexcitation. High yields
and selectivity were observed (58 to 99% yield and 84-99% selectivity), with no dibromo byproducts formed. Substrates containing photoreactive moieties, such as azides, were found to be compatible with the methodology as no decomposition of the starting material was observed.

Quartz capillary tubing (1.5 mm ID, 12.5 mL) was used for the photochemical defluorination of 3,5-diaminotrifluoromethyl-benzene (Scheme 47), a derivative of the water pollutant 3,5-dinitrotrifluoromethylbenzene. A total of twelve 15 W UV-B tubes (310 nm) were placed around and inside the reactor coil. Within 5 minutes residence time, full conversion of the starting material was observed in water. However, the desired 3,5-diaminobenzoic acid partly dimerized through an amide bond formation resulting in poor selectivity. Up to now, no further synthetic applications were reported for this transformation.

Scheme 46 Bromination of alkanes and alkylarenes with molecular-bromine.

Scheme 47 Defluorination of 3,5-diaminotrifluoromethyl-benzene with UV-B light in flow.
### 3.2.7 Photochemical decarboxylations

The controlled extrusion of CO$_2$ from organic molecules, so-called decarboxylation reaction, is a valuable transformation in organic chemistry. The popularity of this transformation can be explained by the abundance of carboxylic groups in biomass sources.$^{383}$

Microflow photochemistry has also been used to facilitate photodecarboxylation chemistry. In particular, a mixture of acetone and pH 7 buffer was used as solvent for the benzylation of unprotected phthalimides in a glass microreactor (ID 1.5 mm) (Scheme 48).$^{284}$

![Scheme 48 Photodecarboxylative benzylation of phthalimides in flow.](image)

Scheme 48 Photodecarboxylative benzylation of phthalimides in flow.

Acetone served both as triplet sensitizer and as cosolvent, while a pH 7 buffer was needed to selectively deprotonate the phenylacetates ($pK_a = 5$-$6$) and to keep the phthalimide protonated ($pK_a = 8.3$). After irradiation, acetone was evaporated and, in most cases, the precipitated photoproduct could be isolated by simple filtration. A commercially available glass microreactor was irradiated with 5 UV-B lamps resulting in a shorter reaction time and higher yields compared to batch (e.g. 98% yield after 2 hours vs. 80% in 3 hours). Similarly, the photodecarboxylation of phthaloyl glycine and other N-protected phthalimides was also performed in an acetone/water mixture.$^{109}$ In this case, an accurate comparison of the flow photoreactor with the batch reaction was made. The calculated space-time yields clearly favored the microreactor compared to the batch setup (see Figure 17), especially when an identical number of UV lamps was used (i.e. 5). This reaction was further implemented in preparative scale-up with a falling film reactor using a XeCl excimer laser.$^{285}$ Interestingly, when 4-4’-dimethoxybenzophenone (DMBP) was used instead of acetone as sensitizer, the photodecarboxylation of phthalimides derivatives showed no differences in conversion from batch to flow.$^{286}$

![Figure 17 space-time yields comparison of microreactor and batch irradiation for the acetone-sensitized photodecarboxylation of phthalimides. Reprinted with permission from ref. 109. Copyright 2010 American Chemical Society.](image)

Figure 17 space-time yields comparison of microreactor and batch irradiation for the acetone-sensitized photodecarboxylation of phthalimides. Reprinted with permission from ref. $^{109}$. Copyright 2010 American Chemical Society.

A similar photodecarboxylative methodology was used for the addition of α-thioalkyl-substituted carboxylates to alkyl phenylglyoxylates (Scheme 49).$^{287}$ Reactions were performed in a commercially available microreactor featuring a bottom serpentine channel (0.5 x 2 mm section, 1.15 mL), through which the reaction mixture was flown, and a top channel where water was circulated in order to control the reaction temperature. 5 UV-A lamps (350 nm) were used to irradiate a mixture of α-thioalkyl-substituted carboxylate and alkyl phenylgly-
oxylate in aqueous acetonitrile. In all tested cases, the formation of the desired alkylated product was accompanied with the dimerization byproduct. However, the decarboxylative protocol with a sulfur-containing carboxylate showed higher chemoselectivity (77:23, product vs. byproduct) than the simple thioether strategy (20:80) (Scheme 49). Hence, it was postulated that the carboxylate group in α-position of the thioether enhances and directs the alkylation of the phenylglyoxylates by facilitating a photoinduced electron transfer.

Scheme 49 Photodecarboxylative addition of α-thioalkyl-substituted carboxylates to alkyl phenylglyoxylates in flow.

3.2.8 Miscellaneous

The sensitized addition of isopropyl alcohol to 2-furanone has been extensively used as a model reaction by Oelgemöller and co-workers.\textsuperscript{60, 188–200} DMBP was used as triplet sensitizer to generate a ketyl radical by hydrogen abstraction. Subsequently, the ketyl radical adds to the conjugated double bond of the furanone. The stabilized oxoallyl radical can engage in a second hydrogen abstraction event, closing the cycle and leading to the final product (Scheme 50). Initially, an LED-driven microchip reactor (150 x 150 μm, 13 μL) employing UV-LEDs (365 nm) was introduced.\textsuperscript{188} The microreactor proved to be superior in terms of reaction time compared to the batch irradiation of a Pyrex glass tube in a Rayonet chamber reactor (flow: full conversion in 2.5 min; batch: 90% conversion in 5 min).

Scheme 50 Sensitized addition of isopropyl alcohol to 2-furanone in a microchip reactor.

The synthesis of terabic acid from maleic acid was used as model reaction by Oelgemöller and co-workers to compare three different reactor systems (Scheme 51): a batch tube irradiated in a Rayonet chamber, a glass microreactor and a FEP capillary (ID 760 μm, 5 mL) coiled around a UV-B lamp.\textsuperscript{290} Based on conversion, the microcapillary photoreactor showed the best performance (99% conversion in 15 min vs. 68% in 20 min for the microreactor device and 71% in 15 min for batch). When energy efficiencies were taken into account, the batch setup results were similar to the glass chip, while the microcapillary unit was nearly three-times more efficient. The stereoselectivity aspects of the photosensitized addition of methanol to limonene were also studied in microreactors by Inoue and co-workers.\textsuperscript{291}

Scheme 51 Synthesis of terabic acid from maleic acid in a glass microreactor.
Switching from a traditional immersion well reactor to a flow microreactor has the immediate advantage of an easier scale up of the reaction protocol. This feature was exploited by Jamison and co-workers for the flow synthesis of a cyclopentadienyrruthenium complex. An additional gain of the flow protocol is the possibility to directly use the photoprocess in a subsequent transformation, thus effectively utilizing the continuous nature of consecutive flow processes. This second aspect is exemplified by a follow-up paper from the same group employing the in-situ photogenerated ruthenium catalyst for an ene-yne coupling. In particular, the final photochemical step in the synthesis of CpRu(MeCN)3PF6 was adapted to flow using a high purity PFA-coiled reactor (ID 760 μm, 250 μL) irradiated with a 450 W medium-pressure mercury lamp. High-purity PFA was required due to the leaching of a polymer plasticizer which hampered the reaction. The substrate concentration could be increased three-fold in flow compared to batch without loss in conversion, resulting in a final throughput of 1.56 g per hour in a preparative-scale photoreactor (5 mL). A modified version of this flow synthesis was then applied to the in situ generation of a catalytically active ruthenium species, which was directly intercepted by an ene-yne substrate (Scheme 52). In the reaction optimization, the capillary material was changed to quartz due to darkening/degradation of the HPFA capillary after repeated use. Finally, a Pyrex filter was added to prevent any E/Z isomerization. Interestingly, the homogeneous Ru catalyst could be recovered quantitatively from the reaction mixture by precipitation in a hexane/ether 1:1 mixture. Its further use in other reactions did not cause any observable decrease in catalytic activity. An effective recycling strategy for rare earth metal-based catalysts (as ruthenium and the platinum group in general) is of increasing importance, due to their forthcoming exhaustion.

Scheme 52 Photochemical generation of [CpRu]+ as active catalytic species for ene-yne coupling in continuous-flow.
Another successful integration of a photochemical step in a multistep process was the continuous-flow synthesis of 2'-deoxynucleosides.\textsuperscript{293-294} Quartz tubing (ID 1.0 mm, 1.84 mL) was coiled around a 450 W medium pressure mercury lamp. A layer of aluminum foil was placed around the reactor to reflect the UV photons back towards the tubing. It was shown that indeed an increased photon flux was obtained which led to a higher conversion. This procedure was subsequently applied in a 3-step continuous-flow protocol starting with the (i) glycosylation of the protected ribose, followed by the (ii) photochemical deoxygenation and (iii) deprotection of the hydroxyl in the 3' and 4' position (Scheme 53).

Microreactor technology has also been recently applied to the radical C-H arylation of heteroarenes. In particular, Kappe and co-workers investigated the reactivity of \textit{in situ} generated diazonium salts in presence of a photocatalyst (Scheme 54).\textsuperscript{295} Surprisingly, it was found that neither photocatalyst nor light were required for the reaction process. Nevertheless, the reaction was significantly accelerated in the presence of light irradiation and under continuous-flow conditions (from 24 hours in the dark to 5 hours in batch and 45 minutes in flow). A FEP coiled reactor (ID 1.0 mm, 10 mL) was irradiated with a medium pressure mercury lamp. Interestingly, the enhanced light irradiation in microflow resulted in a higher selectivity, presumably preventing a competing thermal process. The proposed mechanism, which accounts for these experimental observations, involves the formation of diazo anhydrides from self-condensation of the corresponding nitrosoamine.

![Scheme 53 Continuous-flow synthesis of 2'-deoxynucleosides.](image)

Scheme 53 Continuous-flow synthesis of 2'-deoxynucleosides.

The synthesis of vitamin D\textsubscript{3} is one of the few industrial photochemical processes. Takahashi and co-workers recently reported an elegant synthesis of vitamin D\textsubscript{3} starting from provitamin D\textsubscript{3} in a continuous-flow photomicroreactor (Scheme 55).\textsuperscript{296} This two-step transformation begins with the UV-B induced isomerization of provitamin D\textsubscript{3}, yielding previtamin D\textsubscript{3} and isomers in equilibrium.\textsuperscript{297} Consequently, previtamin D\textsubscript{3} is thermally converted into the final product, vitamin D\textsubscript{3}. The authors anticipated that irradiating the reaction mixture during the thermal isomerization could improve
the yield, since the photoisomerization of the byproducts would shift to produce more previtamin D₃. A continuous-flow setup consisting of two quartz micro-reactors (0.2 x 1 mm, respectively 50 and 100 μL) was designed so that the first would receive direct irradiation from a Vycor-filtered 400 W high-pressure mercury lamp. The second reactor was placed in a 100 °C oil bath and irradiated by the same light source through a glass filter (λ > 360 nm). This two-stage continuous-flow synthesis resulted in an isolated yield of 32%, and was further applied to the synthesis of vitamin D₃ analogues.²⁹⁸-²⁹⁹

![Scheme 55](image)

**Scheme 55** Continuous-flow conversion of provitamin D₃ into vitamin D₃.

### 3.3 Photocatalysis

In the last decade, photocatalysis positioned itself as an important photochemical strategy, allowing for unprecedented and challenging transformations. Because of its distinctive traits, photocatalysis will be treated in a dedicated section. For photocatalytic applications in wastewater treatment, e.g. photo-Fenton and TiO₂ catalytic reactions, we refer to section 5.1.

![Scheme 56](image)

**Scheme 56** Example of possible mechanisms for a photocatalytic cycle. Adapted from ref. ⁴⁴.

The mechanism of photocatalytic redox reactions is often controversial. In particular, two school of thoughts debate on whether chain processes might be involved in photoredox transformations.⁴³-³⁰° On one hand, closed catalytic cycles are considered as the mechanistic path to the final neutral product. On the other hand, recent in depth studies demonstrated that radical chain propagation cycles might play a major role in the mechanism of certain photocatalytic reactions (Scheme 56).⁴⁴ Quantum yield measurements were used to prove the presence of radical propagating chains.⁴⁵ An experimental quantum yield higher than 1 means that, on average, each excited state of the photocatalyst produces more than one molecule of product. Therefore, quantum yields < 1 are compatible with a closed catalytic cycle, while quantum yields >> 1 indicate a
radical chain propagating mechanism. In a recent report, Cismesia and Yoon proved the chain propagating nature of three previously reported reactions, through quantum yield and luminescence quenching measurements. In particular, a $4+2$ oxidative quenching, a $2+2$ reductive quenching and a neutral radical initiated reaction were investigated: in all three cases, values well above 1 were found for the quantum yields. However, as underlined by the authors, the mechanism of the photoredox transformation is always reaction specific. Therefore, accurate (control) experiments are crucial to propose a reliable photoredox mechanism.

Transition metal photocatalysts
The use of transition metal complexes in photoredox-catalysis flourished in the last decade. The ability of these complexes to engage in single electron transfer (SET) processes originates from the formation of highly reactive excited states upon visible light irradiation. Ruthenium and iridium complexes (especially tris($2,2'$-bipyridine) ruthenium (II) and fac-Ir(ppy)$_3$ where ppy=2-phenylpyridine)) are the most common used metal-based photocatalysts for photoredox-catalysis, although reports employing other metals (e.g. cobalt, copper etc.) exist as well.

The lifetime of the excited state of metal-based photocatalyst is crucial for their ability to participate in electron-transfer reactions. This lifetime depends highly on the reaction medium (e.g. solvent) and on the nature of the ligand associated with the metal. Visible-light photocatalysis can use simple and inexpensive light sources, such as CFL and LEDs. Since the majority of organic molecules does not absorb in the visible right range, side reactions can be minimized. Finally, despite their high cost, metal-based photocatalysts exhibit high efficiency even at low catalyst loading ($\leq 1$ mol %).

3.3.1 Ruthenium complexes
Gagné and co-workers reported the synthesis of C-glycoamino acids and C-glycolipid derivatives. The production of the key intermediate α-C-glycoside was needed on a gram scale (Scheme 57). The photocatalytic route to this product, involving the reductive quenching of Ru(bpy)$_3^{2+}$, was found to depend heavily on the reaction vessel diameter (i.e. 1 h reaction time in an NMR tube compared to 24 h in a 25 mL flask). The high molar extinction coefficient of the photocatalyst was identified as the main cause, limiting the light penetration to the first millimeter of reaction mixture. Switching to flow was envisioned as the solution to obtain both efficient irradiation and high productivity. A FEP coiled reactor (ID 1.6 mm, 15.9 mL) irradiated with blue LEDs was used, resulting in the production of 5.5 grams of product per day (85% yield).

Scheme 57 Gram-scale continuous-flow synthesis an α-C-glycoside via a reductive quenching Ru cycle (HAT = Hydrogen Atom Transfer).
Stephenson and co-workers demonstrated several visible-light transformations catalyzed by Ru and Ir complexes, thus enabling a completely new variety of unprecedented reactions. Transferring these reactions to a microflow photoreactor came as a natural strategy to reduce reaction times and improve irradiation efficiency. An operationally simple reactor was constructed from 105 cm of PFA tubing (ID 760 μm, 479 μL) coiled around some standard glass tubes in an eight-shaped fashion. Seven blue LED lights were used for illumination, and a silver coated beaker was positioned above the reactor as a reflecting mirror. Radical cyclization of heteroaromatic and terminal olefins catalyzed by Ru(bpy)$_{3}^{2+}$ reached completion within only 1 minute residence time in good to excellent yields (71–91% vs. incomplete conversion in 2 days in batch)(Scheme 58A and B). In the same way, intramolecular malonation of indoles catalyzed by Ru(bpy)$_{3}^{2+}$ using triarylamine as reductive quencher afforded the target compound with 77% yield in 1 minute reaction time (Scheme 58B).

Furthermore, intramolecular atom transfer radical additions (ATRAs) with terminal alkenes and alkylbromides rapidly afforded the desired product (Scheme 58C). The oxidative quenching cycle was catalyzed by an Ir(dF(CF$_{3}$)ppy)$_{2}$dtbbpyPF$_{6}$ (dF(CF$_{3}$)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbbpy = 4,4’-di-tert-butyl-2,2’-bipyridine) catalyst and required between 6.5 to 9 minutes residence time for completion. The oxidative formation of iminium ions, starting from N-arylated tetrahydroisoquinolines, was also implemented in the same photoreactor. The reaction conditions in DMF required BrCCl$_{3}$ as terminal oxidant and Ru(bpy)$_{3}^{2+}$ as photocatalyst. The formation of an iminium ion and its subsequent trapping by a nucleophile (such as nitromethane) resulted in the formation of a variety of α-functionalized tetrahydroisoquinolines within 30 seconds residence time (Scheme 59).

Scheme 58 Continuous-flow radical cyclization of heteroaromatic olefins (A), intermolecular indole functionalization (B) and intermolecular atom transfer radical addition (ATRA) catalyzed by Ru(bpy)$_{3}^{2+}$.

Scheme 59 Photoredox-catalyzed intramolecular atom transfer radical additions in continuous flow.
Interestingly, a similar aza-Henry reaction was described concurrently by Neumann and Zeitler in a commercial glass chip photoreactor (500 x 600 μm, 100 μL total volume). Not only tetrahydroisoquinoline was used as substrate, but also N-phenyl pyrrolidine and dimethylaniline, generating far less stabilized iminium ions. All substrates could be converted to the final nitromethane addition product within 30 and 130 min residence time in good to excellent yields (59-93%).

Another continuous-flow Ru-catalyzed tetrahydroisoquinoline-based reaction has been recently reported by Maurya and co-workers. Structurally diverse imidazoles were obtained starting from a vinyl azide and secondary amines (Scheme 60). The flow reactor consisted PFA tubing (ID 760 μm, 4.5 mL) wrapped around a LED lightsource. The flow protocol allowed for improved yields (65 vs. 55%) and shorter reaction times (44 min vs. 12 h) compared to batch.

Scheme 60 Ru-catalyzed imidazole synthesis in continuous-flow.

The synthesis of symmetric anhydrides via photoredox catalysis was demonstrated by Stephenson and co-workers (Scheme 61). The oxidative quenching of Ru(bpy)$_3^{2+}$ by CBr$_4$ in DMF allowed the in situ formation of the corresponding iminium ion (Vilsmeier-Haack reagent) which further reacted with a carboxylic acid to form the anhydride. An array of substituted aryl- and alkyl-carboxylic acids were successfully converted to the corresponding anhydrides (61-99% yield) with the exception of α-amino acids (5% yield). When the reaction of 4-tert-butylbenzoic acid was integrated in a continuous-flow photoreactor, 97% of the desired anhydride was obtained in 6.4 minutes residence time (vs. 85% yield in 18 h in batch).

Scheme 61 Continuous-flow synthesis of symmetric anhydrides using visible light-mediated photoredox catalysis.

Bou-Hamdan and Seeberger reported the application of some previously published Ru(bpy)$_3^{2+}$-catalyzed reactions in a continuous-flow microreactor. The microfluidic set-up consisted of a FEP capillary (760 μm, 4.7 ml, 100 psi BPR) wrapped around two vertical rods and placed between two 17 W white LED lamps. Among the tested transformations, the reduction of α-chlorophenylacetates, inspired by the photocatalytic C—Br reduction reported by the Stephenson group, was achieved (Scheme 62). Within 30 minutes residence time, 82% of the reduced product was obtained in the presence of Ru(bpy)$_3^{2+}$ and with total absence of the formate ester byproduct, observed in batch. The
same reactions in batch required 24 hours for similar conversions with a 14% yield of side product.

Noël and Wang developed a photoredox-mediated Stadler-Ziegler reaction for the preparation of aryl-alkyl and diaryl sulfides (Scheme 63). A variety of aryl amines were converted in situ to the corresponding diazonium salts in the presence of tert-butyl nitrite and catalytic amounts of p-toluenesulfonic acid (PTSA). Subsequently, the phenyl radical generated by oxidative quenching of Ru(bpy)$_3^{2+*}$ is coupled to aliphatic or aromatic thiols. Reactions were performed in a PFA capillary reactor (ID 540 μm, 460 μL) coiled around a 50 mL syringe and positioned inside an aluminum-coated beaker containing an array of 3.12 W blue LEDs. Control over the reaction temperature was obtained through air-cooling of the reactor. Good to excellent yields and an impressive acceleration of the transformation were obtained in flow (79-84% in 15 seconds vs. 5 h in batch). In the process, nitrogen evolution from the diazonium salt resulted in the formation of a slug flow. Furthermore, the small volume provided a safe environment, reducing the hazards correlated with the handling of potentially explosive diazonium salts and diazosulfide intermediates.

![Scheme 62 Photocatalytic dehalogenation of α-chlorophenylacetates in continuous flow.](image)

**Scheme 62** Photocatalytic dehalogenation of α-chlorophenylacetates in continuous flow.

![Scheme 63 Continuous-flow Stadler-Ziegler synthesis of arylsulfides facilitated by photoredox catalysis.](image)

**Scheme 63** Continuous-flow Stadler-Ziegler synthesis of arylsulfides facilitated by photoredox catalysis.
The uniform irradiation and the safe handling of fluorinating reagents makes continuous-flow particularly appropriate for the synthesis of fluorine-containing groups. Trifluoromethylation and perfluoroalkylation of five-membered heterocycles was achieved by Noël and co-workers (Scheme 64). By implementing a similar reactor reported for the synthesis of diaryl sulfides, the perfluoroalkylation of pyrrole and indole derivatives was accomplished via a Ru(bpy)$_3^{2+}$ mediated reductive quenching cycle in the presence of TMEDA ($N,N',N,N'$-tetramethyl-1,2-diaminoethylene) as electron donor. The reaction reached completion within 10-20 minutes residence time in good to excellent yields (53-99%). Furthermore, trifluoromethylation of the same substrates and of a broad variety of other five-membered heteroarenes was obtained in a segmented gas-liquid reaction. Gaseous CF$_3$I was used as a cheap trifluoromethylating agent and dosed via a mass flow controller. The liquid phase and gaseous phase were combined in a T-shaped micromixer prior to entering the irradiated zone of the reactor. All substrates were converted to the corresponding trifluoromethylated derivatives in good to excellent yields (55-95%) within few minutes (8-16 minutes vs. 12-72 hours in batch).

![Scheme 64 Trifluoromethylation and perfluoroalkylation of heterocycles by photoredox catalysis in flow.](image-url)
Similarly, the CF$_3$ radical generated via reductive quenching of Ru(bpy)$_3^{2+}$, was coupled to a series of aryl, heteroaryl and alkyl thiols, affording a visible light-mediated strategy for the formation of S-CF$_3$ bonds (Scheme 65). The method revealed its compatibility towards a wide variety of functional groups, such as free carboxylic acids, alcohols and amines. Aliphatic thiols could be efficiently converted in the presence of triphenylphosphine and water as reducing agents, minimizing the formation of the disulfide side product. All substrates were converted within one minute residence time in excellent yields (47-96%). The segmented-flow observed in the presence of gaseous CF$_3$I afforded excellent mixing and facilitated the gas-liquid mass transfer of the gaseous reagent, therefore further accelerating the reaction. Interestingly, in flow, near equimolar reaction conditions (thiol: CF$_3$I 1:1.1) could be used while batch required a large excess to reach full conversion (thiol:CF$_3$I 1:4). This can be attributed to the improved contact between gas and liquid phase in flow. In batch, the gas is present in the head space and diffuses marginally back into solution.

Another strategy for the radical trifluoromethylation of arenes and heteroarenes was recently published by Stephenson and co-workers. The use of inexpensive and readily available trifluoroacetic anhydride (TFAA) was made possible by appending a sacrificial redox auxiliary (N-oxide) to lower the high reduction potential of the trifluoroacetic anion. The TFAA adduct, resulting from the addition of N-oxide, can oxidatively quench the excited state of Ru(bpy)$_3^{2+}$, ultimately resulting in CO$_2$, evolution, formation of CF$_3$ and pyridine (Scheme 66). The methodology demonstrated high tolerance to various functional groups and did not show any air or moisture sensitivity. The trifluoromethylation of 20 g of N-Boc-pyrrole was also performed in a commercially available photochemical reactor. PFA tubing (ID 1.3 mm, 10 mL volume) was irradiated with 450 nm light (24 W). With a residence time of 10 minutes, the formation of 71% of product (both mono- and difluoromethylated in position 2 and 5) was observed.

Scheme 66 Radical trifluoromethylation of arenes and heteroarenes using trifluoroacetic anhydride.

Several photocatalytic reactions involve the functionalization of a single unreactive C—H bond, but in a recent paper from Maurya and co-workers, multiple C—C
bond forming events were obtained in a reaction cascade induced by an initial photocatalytic step.\textsuperscript{38} In the proposed mechanism, the Ru-induced formation of the iminium ion of the tetrahydro-\textbeta-carboline tricycle couples with a dipolarophile, yielding the cycloaddition product that oxidatively rearomatizes to the final compound (Scheme 67). Several derivatives of the naturally occurring \textbeta-carboline scaffold were obtained in batch, and one test reaction was transferred to flow. The white LED irradiated PFA coiled reactor (ID 540 \textmu m, 980 \textmu L), afforded slightly better yields (75\% vs. 69\%) and significantly reduced reaction time (8 minutes in flow, 12 hours in batch) compared to batch.

![Scheme 67 Flow synthesis of \textbeta-carboline derivatives via photoredox catalysis.](image)

Schroll and König investigated the Ru(bpy)\textsubscript{3} catalyzed SET to 2,2,6,6-tetramethylpiperidine nitroxide (TEMPO). The resulting one-electron oxidized product, TEMPO\textsuperscript{+} was reacted with stable enolates yielding the corresponding \alpha-oxyaminated derivative. When a commercial glass chip reactor (ID 1.0 mm, 1.7 mL) irra-
diated with blue LEDs was used, the reaction time was shortened from 3 hours to 10 minutes.\textsuperscript{39}

Kim and co-workers recently fabricated a novel monolithic and flexible fluoropolymer microreactor made of perfluoropolyether (PFPE) through soft litography.\textsuperscript{320} This material resembles PDMS in terms of low surface energy and toxicity, with high elasticity and gas permeability. However, PFPE is also chemical resistant, suitable for strongly acidic or basic reaction mediums and for high temperatures. Among the reactions tested, a photochemical [2+2] enone intramolecular cyclization\textsuperscript{16} catalyzed by Ru(bpy)\textsubscript{3}Cl\textsubscript{2} was performed (Scheme 68). The reactor (300 x 50 \textmu m) was illuminated with a 30 W white LED lamp, placed 5 cm away from the reactor. Compared to a batch reactor illuminated in the same way, the same yield could be obtained in shorter reaction time (80\% in flow within 1 min residence time vs 30 min in batch).

![Scheme 68 Intramolecular [2+2] enone cyclization in a fluoropolymer reactor.](image)

### 3.3.2 Iridium complexes

Stephenson and co-workers reported a novel visible-light induced radical reductive deiodination, which was applied to a variety of alkyl, alkenyl and aryl iodides (Scheme 69).\textsuperscript{211} Upon formation of the carbon radical, the substrate showed efficient intramolecular cyclization affording a convenient strategy for the formation of
several heteroatom-containing ring structures. Optimized conditions for the alkyl and aryl substrates involved the use of fac-Ir(ppy)$_3$ as catalyst in presence of either Hantzsch ester/tributylamine or formic acid/tributylamine serving as an electron donor/H donor system. The proposed mechanism proceeds through the oxidative quenching of the excited Ir catalyst by the iodide substrate. The reductive cleavage delivers a carbon radical able to cyclize/subtract an H atom from tributylamine, the Hantzsch ester or the formate. The reaction was then transferred to a microflow reactor (PFA tubing, 760 μm, 1.33 ml, 5.88 W blue LEDs) providing a reduction of the reaction time (40 min vs. 30 h in batch). Similar yields were obtained with only half the catalyst loading (93% yield with 0.05% catalyst vs. 95% with 1% catalyst in batch).

Scheme 69 Ir-catalyzed radical reductive deiodination of alkyl, alkenyl, and aryl substrates in flow.

The same authors later implemented this reactor in a two-step deoxygenation protocol of primary and secondary alcohols (Scheme 70). First, alkyl alcohols were converted in batch into aryl iodides following the Garegg-Samuelsson reaction. In the second step, a radical reductive deiodination afforded the hydrogenated products. The reaction proceeded within 18 minutes residence time and with only 0.25 mol% of Ir catalyst, giving an array of desired products in good to high yields (67-87%). Flow provided a 120 fold improvement over the batch conditions (75% conversion in 144 h). The overall protocol exhibited a good functional group tolerance, with one case showing the selective reduction of a primary alcohol in the presence of a secondary alcohol.

Scheme 70 Deoxygenation of primary and secondary alcohols using Ir-mediated photocatalysis.

Stephenson and co-workers exploited an identical flow setup to perform a two-step visible-light Ir-catalyzed strategy for lignin degradation. The reaction was hampered in batch by the presence of the dark colored impurities which are characteristic for lignosulfonates. Rueping and co-workers demonstrated the visible-light catalyzed (E)- to (Z)-isomerization of stilbenes in a continuous-flow photoreactor including a catalyst recycling strategy. Unlike the well-known UV-induced isomerization of stilbene derivatives, this methodology prevented the formation of any byproducts. The proposed mechanism relies on the excitation of an iridium catalyst (namely [Ir(ppy)$_2$(bpy)](PF$_6$)) which can subsequently excite the (E)-stilbene isomer through an energy transfer that ultimately causes the isomerization to (Z)-stilbene (Scheme 71). Due to a difference in energy between the triplet state of the two isomers, only the (E)-isomer can be engaged in energy transfer processes.
with the photocatalyst, providing a high selectivity (around 99:1 Z/E ratio for most substrates). By exploiting favorable extraction kinetics of the catalyst by an ionic liquid ([bmim][BF$_4$], bmim = 1-butyl-3-methylimidazolium), continuous recycling of the catalyst proved possible. A solution of the stilbene in n-pentane and a solution of [Ir(ppy)$_2$(bpy)](PF$_6$) immobilized with the ionic liquid in DMF were pumped through a glass millireactor and irradiated with high power blue LEDs. Upon exiting the microreactor, the n-pentane phase readily separated from the catalyst containing ionic liquid phase.

**Scheme 71** Continuous recycling of Ir catalyst in ionic liquids applied to the E/Z isomerization of stilbenes.

Another strategy for the continuous recycling of an Ir catalyst was recently published by Reiser and co-workers.$^{326}$ Firstly, the synthesis of the polyisobutylene-tagged Ir(ppy)$_2$(PIB-ppy) was achieved. (Scheme 72).

The polyisobutylene (PIB) tether allows for the recovery of the catalyst through liquid/liquid extraction with heptane in a thermomorphic solvent system.$^{327}$ In such a system, solvents of different polarity exhibit no reciprocal solubility at room temperature, while they become miscible when a certain temperature is reached. After cooling, the two phases are separated again, making the process completely reversible. A photocatalytic test reaction (i.e. the E to Z isomerization of styrenes via uphill catalysis$^{328}$) was performed in a commercially available glass reactor in an acetonitrile/heptane thermomorphic solvent system. To obtain miscibility of the system, the reaction was carried out at 90 °C and irradiated with 8 blue LEDs. A 60 psi BPR was added to the set-up to prevent boiling of the solvent mixture. Upon exiting the reactor, the solvent mixture was led into a cooling unit where separation of the two phases occurs. The catalyst-containing heptane phase was guided back to the inlet of the reactor and re-used up to 30 times. The product dissolved in the acetonitrile phase was collected and isolated (Figure 18).

**Figure 18** Schematic representation of the continuously operating, catalyst recycling setup. Reprinted from ref. 326. Copyright 2016 The Royal Society of Chemistry.

To verify whether thermochemical effects occurred, the same reaction was also performed at room temperature by keeping the system biphasic. The use of the microchip afforded a sufficiently high surface area for the

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*PIB = polyisobutylene*.
reaction to take place at the interface of the two solvents without efficiency loss. However, slightly reduced reaction times (82:18 Z/E ratio with a flow rate of 20 μmol/min at 90 °C and 82:18 Z/E ratio with a flow rate of 10 μmol/min at 19 °C) were observed.

Jamison and co-workers developed a visible light-induced decarboxylative radical cyclization for the preparation of pyrrolo[1,2-a]quinolines. Starting from ortho-heterocycle-substituted arylisocyanides and using hypervalent phenylidene dicarboxylates as source of alkyl radicals, the desired pyrrolo[1,2-a]quinoline product was obtained with fac-Ir(ppy)$_3$ as optimal photocatalyst (Scheme 73). The method showed high functional group tolerance and the substrate scope was broadened by replacing the pyrrole ring with other nitrogen-containing heterocycles (e.g. indole, imidazole and benzimidazole). The photocyclization procedure was further integrated in a convenient three-step continuous-flow synthesis. The multistep protocol involves the preparation of the desired phenyliodine (III) dicarboxylate, which reacted in the presence of pyrrole and photocatalyst/light to yield pyrrolo[1,2-a]quinoline. The process was performed in three different PFA capillary reactors (ID 760 μm, volumes of 90, 228 and 1140 μL respectively, 20 psi BPR) connected in series (See microfluidic setup in Scheme 73). The photo-cyclization step involved solely the third reactor which was irradiated with a 26 W CFL and placed in a water cooling bath to maintain the reaction temperature at 25 °C. The overall synthesis was completed in 14.6 minutes residence time, with 9.5 minutes required for the photo-cyclization product (vs. 5 hours in batch). The desired compound could be obtained in an overall yield of 47% (corresponding to 78% yield per step).

Scheme 73 Synthesis of functionalized polycyclic quinoxaline derivatives via photoredox catalysis.

The application of continuous-flow photoredox catalysis to the synthesis of complex natural products was demonstrated by Beatty and Stephenson with the photocatalytic fragmentation of the alkaloid (+)-catharanthine. This fragmented intermediate can be further employed in the synthesis of (-)-pseudotabersonine, (-)-pseudovincadifformine and (+)-coronaridine. It was postulated that (+)-catharanthine oxidizes as a result of a SET from the excited state of the Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ catalyst. In the presence of trimethylsilyl cyanide (TMSCN), the radical form of (+)-catharanthine can be stereoselectively trapped. A final reduction and deprotonation step affords the key intermediate (Scheme 74). The flow apparatus consists of a PFA capillary (ID 760 μm, 1.34 mL)
irradiated with 5.88 W blue LEDs. A solution of (+)-catharanthine, Ir catalyst, TMSCN in MeOH was pumped into the photomicroreactor affording the desired intermediate within 2 minutes residence time in 96% yield. Notably, the use of microreactor technology not only afforded shorter reaction times and easy scalability, but also provided a safer strategy for the handling and controlled release of HCN formed in the reaction.

Hoffmann, Rueping and co-workers achieved the trifluoromethylation of electron-deficient olefins using sodium triflinate as CF$_3$ source and Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ as photocatalyst (Scheme 75). The same reaction could also be performed with near-UV light (350 nm) and a benzophenone photogano catalyst. Also in this case, it was possible to accelerate the reaction kinetics (from 6 h to 30 min) by performing the reaction in continuous flow. The flow setup consisted of 10 meters of FEP tubing (ID 760 μm, 5.0 mL) wrapped around 8 glass rods and irradiated with 16 black light lamps (8 W each, 350 nm) inside the chamber of a Rayonet reactor.

Scheme 74 Synthesis of natural products via photoredox catalysis in flow.

Scheme 75 Trifluoromethylation of electron-deficient olefins with sodium triflinate.

The same heteroleptic iridium photocatalyst was employed by Knowles and co-workers for the indoline oxidation of an intermediate en route to elbasvir, an anti-hepatitis C drug (Scheme 76). Standard oxidation conditions were associated with the epimerization of an hemiaminal stereocenter, with the only exception of permanganate, whose industrial use was environmentally problematic. A multi-parallel experimentation campaign of several photocatalysts coupled with different stoichiometric oxidants lead to the identification of Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ and tert-butylperaceta (tBPA) as competent oxidant system without significant
loss of enantiopurity (e.e. up to 99.9%). The absence of epimerization was rationalized through extensive mechanistic studies. The industrial suitability of the process was proven on a 100 g scale flow synthesis. In particular, 19 m of PFA tubing (ID 3.175 mm, 150 mL) was coiled around a glass condenser, used to control the reaction temperature (-5 °C), and irradiated with 720 UV-LEDs (440 nm). A flow rate of 2.5 mL/min, corresponding to a residence time of one hour, resulted in an 85% isolated yield and 99.8% e.e.

Scheme 76 Ir-catalyzed indoline oxidation.

The spin-selective generation of triple nitrenes from azidoformates was reported by Yoon and co-workers and applied to the photocatalytic aziridination of aliphatic and styrenic alkenes. [Ir(ppy)_2(dttbpy)]PF_6 was chosen as photocatalyst, and 2,2,2-trichloroethyl azidoformate (TrocN_3) proved to be the most effective reagent. With the optimized conditions, a variety of alkenes underwent the desired transformation in good yields (61-91%) within 4 hours. However, batch experiments showed that the reaction rate was inversely proportional to the reaction scale (77% in 4 h on 0.1 mmol scale vs. 75% in 20 h on 0.4 mmol scale) suggesting that the transformation was photon-limited. A higher irradiation efficiency and scalability of the reaction was demonstrated in a FEP-coiled reactor (ID 760 μl, 1.9 mL) exposed to with 15 W blue LED lamp irradiation (Scheme 77). Shorter residence time was required for the aziridination of cyclohexene (72% in 2.3 h vs 77% 4 h in batch) and a preparative scale reaction afforded 785 mg (70%) of pure product within 16 hours.

Scheme 77 Photocatalytic aziridination of cyclohexene.

3.3.3 Copper complexes

Collins and co-workers reported the use of a copper-based sensitizer, namely [Cu(XantPhos)(dmp)]BF_4 (XantPhos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, dmp = 2,9-dimethyl-1,10-phenanthroline), for the successful synthesis of [5]helicenes and N-substituted carbazoles (Scheme 78). The copper catalyst could be synthesized in situ (from Cu(MeCN)BF_4,XantPhos and neocuproine), mixed with a solution of the reactants and then recirculated multiple times in a commercially available photoreactor. This reactor consists of FEP tubing (ID 1.0 mm) wrapped around two CFL light sources (30 W each) and was used to demonstrate the synthesis of [5]helicenes starting from a stilbene precursor. Compared to previously reported UV-catalyzed synthesis of helicenes, this strategy allowed the use of visible light and afforded the desired product without the generation of over-
oxidized and regioisomerized byproducts. The flow set-
up compared positively to the batch reactor, yielding a
gram-scale synthesis with a notable reduction in reac-
tion time (40% in 10 h in flow vs. 42% in 120 h in batch).

Scheme 78 Cu-based sensitized synthesis of

The same group reported a different microflow photo-
reactor for the effective synthesis of carbazole deriva-
tives enabled by a [Cu(XantPhos)(dmp)]BF\(_4\) photocata-
lyst (Scheme 79). The reactor featured three 10 ml
units connected in series, each one irradiated with a 23
W CFL. Starting from triarylamines or tertiary diaryl
amines, a wide variety of N-substituted carbazoles were
successfully isolated in good to excellent yields (50-
95%) within a residence time of 10 hours, which was
considerably shorter than the corresponding batch
reaction (14 days).

Finally, a similar UV-induced strategy was applied to
enable the synthesis of the carbazole-containing anti-
inflammatory drug caprofene (80% yield in 3 hours).

3.3.4 Cobalt complexes

Carreira and co-workers demonstrated the synthesis of
allylic trifluoromethanes starting from styrene deriv-
aves. 2,2,2-trifluoroethyl iodide was used as the cou-
pling partner and a triphenyltin-Co complex functioned
as the photocatalyst (Scheme 80). The reaction was first
optimized in batch, but due to the long reaction times
(24 h) it was later implemented in a commercially avail-
able millichip glass reactor. The reactor (8 mL internal
volume) was placed in between two water-cooled layers
and irradiated with an array of 48 blue LEDs (total
power 240 W). Conversions up to 65% were observed
within 30 minutes residence time. Next, the authors
assessed their previously reported intramolecular co-
balt-catalyzed alkyl-Heck cyclizations in flow. For this
reaction, similar conversions to those observed in batch
were obtained within only 30 minutes residence time
(vs. 24-48 hours in batch).

3.3.5 Decatungstates

Among polyoxometalates (POMs, i.e. transition metal
oxygen–anion clusters), decatungstates occupy an im-
portant position in photocatalysis. Particularly, the
tetrabutylammonium salt of decatungstate (TBADT) is often used due to its absorption in the 350-400 nm range. The excited state of decatungstate anion is particularly apt in hydrogen abstraction reactions from unactivated alkanes. The selectivity of the reaction depends on the accessibility of carbons, which can be attributed to the size and charge of the photocatalyst. Recently, the Britton group reported the use of this photocatalyst in continuous-flow microreactors. In particular, a TBADT-catalyzed benzylic C-H fluorination with N-fluorobenzenesulfonimide (NFSI) was reported. The only limit of the reported protocol lies in the slow reaction time (typically 16 hours) due to inefficient irradiation. As a model reaction, the fluorination of ibuprofen methyl ester was tested in flow. The use of a flow reactor made of FEP tubing (3 m, 1.4 mL) coiled around a black light tube (365 nm) resulted in a reduced reaction time, from 24 to 5 hours. Later, Britton et al. published, in collaboration with researchers from Merck, the C—H fluorination of leucine methyl ester in flow with sodium decatungstate. The synthesis of γ-fluoroleucine is of great interest, since this non-natural amino acid is a crucial intermediate in the synthesis of odanacatib. Odanacatib is a potent and selective cathepsin K inhibitor, recently submitted to the FDA (Food and Drug Administration) for final approval. To underline the importance of this product, researchers from Merck reported no less than six different synthetic routes to this intermediate in the last ten years. The investigation started with the desamino derivative of leucine, whose TBADT-catalyzed NFSI-mediated γ-fluorination had already been reported. Switching to leucine, the protection of the amine as a salt was need-
Fagnoni and co-workers also used a TBADT-mediated photocatalytic reaction for the synthesis of substituted γ-lactones.\textsuperscript{347} The hydrogen atom transfer capabilities of the photocatalyst were exploited to convert aliphatic aldehydes into the corresponding acyl radical. This radical then adds to an electron-poor double bond, and the radical adduct is reduced by the catalyst via a back hydrogen-atom transfer, yielding a γ-keto ester. To afford the final compound, the ketone was reduced with NaBH\textsubscript{4} and engaged in an acid-promoted cyclization (Scheme 82). This reaction sequence was performed both in batch and in flow. For the flow protocol, a PTFE coiled reactor (ID 1.3 mm, 12 mL) was irradiated with a medium pressure Hg lamp (125 W). Despite similar yields (66% in batch vs. 67% in flow), the flow process was three time faster (2 h vs. 6h).

![Scheme 82](image)

Scheme 82 Synthesis of γ-lactones via tetrabutylammonium decatungstate-mediated photocatalysis in continuous flow.

In a follow-up paper, Fagnoni \textit{et al.} further investigated the reaction with different carbon-centered radicals precursors and olefin partners, resulting in TBADT-catalyzed acylation and alkylation reactions.\textsuperscript{348} The photoreactor was upgraded to a preparative scale analogue with FEP tubing (ID 2.1 mm, 50 mL) irradiated with a 500 W medium pressure Hg lamp. A wide range of aldehydes, amides and ethers were used as substrates for H-abstraction, and coupled with several electron-poor olefins (Scheme 83). The results obtained in flow were then compared by means of green metrics to the batch and batch solar counterparts. Thanks to the improved light irradiation in flow, a higher substrate concentration could be used, resulting in a higher productivity (STY) and sustainability (process mass intensity, PMI).

![Scheme 83](image)

Scheme 83 Tetrabutylammonium decatungstate-mediated photocatalyzed acylation and alkylation in flow.
Heterogeneous photocatalysts

3.3.6 TiO₂

TiO₂ is the most widely used semiconductor photocatalyst for photochemical transformations. However, its application remains mainly limited to the field of water and air purification (see section 5.1.1). TiO₂ is sensitive to UV-radiation, however, progress has been made in making TiO₂ responsive to visible light, through so-called doping. For a more detailed explanation of the physical properties of this semiconductor and the mechanism involved in its activity we refer to Section 5.1.1.

As a photocatalyst, TiO₂ is exclusively used with a particle size in the nano range. Therefore, photocatalytic reactions reporting its use are heterogeneous. Kappe and co-workers developed a continuous-flow synthesis of TiO₂ nanocrystals capped with oleic acid. Such nanoparticles could be efficiently dispersed in toluene, creating concentrated colloidal dispersions. Their photocatalytic activity was tested for the tandem addition-cyclization reaction of N-methylmaleimide and N,N-dimethylaniline in continuous flow (Scheme 84). A spiral of PFA capillary (ID 760 μm, 650 μL) was irradiated with UV-LEDs at 365 nm. A solution containing both substrates and the TiO₂ colloidal dispersion was recirculated in the microreactor. The desired tetrahydroquinoline was obtained in 91% yield after 5 h of reaction time.

Scheme 84 Photocatalytic addition of N,N-dimethylaniline to N-methylmaleimide.

To overcome the issues associated with the handling of solid particles in microreactors (i.e. clogging/fouling), a solution was found in the immobilization of the TiO₂ nanoparticles on the channel of the microreactor, or on a specific surface (i.e. membranes, filters). Thanks to the use of microchannels, a large interfacial area can be kept, which compares to the surface area observed for the nanoparticles in suspension. Examples highlighting the use of immobilized TiO₂ include the synthesis of L-pipecolinic acid starting from L-Lysine (Scheme 85). The reaction was performed in a Pyrex glass chip (770 μm x 3.5 μm) containing a Pt/TiO₂ thin film (0.2 wt% of Pt). Irradiation of UV light afforded 87% conversion of the starting material in less than one minute, with a 70 times higher conversion rate compared to batch. However, no improvement was observed in the e.e., which was similar to batch (around 50% in both cases).

Scheme 85 Photocatalytic synthesis of pipecolinic acid in a microreactor.
### 3.3.7 Mesoporous graphitic carbon nitride

Mesoporous graphitic carbon nitride (mpg-C$_3$N$_4$) has recently been reported as an efficient heterogeneous photocatalyst. The activity of heterogeneous catalysts is dependent on the area exposed to the light. Light penetration in batch reactors is limited to the outer layer of the reaction vessel, while theoretically, in flow, a more efficient irradiation could be achieved. However, as previously stated for titanium oxide, the use of heterogeneous photocatalysts in continuous-flow is not trivial.

Recently, Blechert and co-workers, reported a continuous-flow radical cyclization catalyzed by graphitic carbon nitride. Since mpg-C$_3$N$_4$ has redox properties comparable to ruthenium catalysts, the cyclization of bromomalonates was chosen as a model reaction (Scheme 86). Similar to the Ru photocatalysts, blue LEDs can be used as an inexpensive and energy-efficient light source. A packed-bed reactor was constructed loading a mixture of 2.5 wt% of photocatalyst with silica and glass beads in a FEP capillary (ID 2 mm, 620 μL). Notably, the activity of the ground catalyst was found to be higher than the non-ground one, indicating that a particle size reduction caused by grinding led to an increase of active surface. Interestingly, the presence of triethylamine as a sacrificial electron donor was not needed, suggesting the presence of a different reaction mechanism compared to the homogeneous reaction system. Indeed, changing the reaction solvent from THF to deuterated THF resulted in a slower reaction (from 99% to 15% conversion in 4 hours), indicating an active role of the solvent in the reaction. Moreover, a correlation was found between the rate of hydrogen abstraction by the alkyl radical and the C–H bond dissociation energy (BDE) values of the H-donor solvent. Using optimized reaction conditions, an array of bromomalonates were cyclized in good to excellent yields (74-99%), with the catalyst showing only a marginal reduction in efficiency even after 60-70 reaction cycles. Overall, the use of a heterogeneous catalyst, together with the absence of any additive, made this reaction sustainable.

![Scheme 86 Continuous flow radical cyclization photocatalyzed by graphitic carbon nitride.](image)

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### 3.3.8 Eosin Y

The use of the organic dye eosin Y as a photocatalyst has recently emerged as a low-cost, metal-free alternative to transition metal complexes for visible light transformations. Noël and co-workers used Eosin Y...
to enable the aerobic oxidation of thiols to disulfides (Scheme 87). It was found that ruthenium and iridium complexes were not suitable for this transformation. Eosin Y provided a much reduced reaction time for the conversion of \( \rho \)-methoxythiophenol to the corresponding disulfide (full conversion in 16 hours, compared with 50% of Ru and 10% of Ir catalyst). The optimized reaction conditions (1 mol% catalyst loading, 1 equivalent of TMEDA and ethanol as green solvent) were next applied to flow, using pure oxygen in a Taylor flow regime. This flow regime allowed to overcome any mass transfer limitations, which were present in the batch protocol. An in-house developed photoreactor was used, which was obtained by coiling PFA capillary (ID 760 μm, 950 μL) around a disposable syringe wrapped with aluminium-foil, and was irradiated with a white LED strip. A variety of disulfides were synthesized in excellent yields (87-99%) in only 20 minutes residence time. Moreover, the precursor of the nonapeptidic hormone oxytocin, was converted in water to its active form through formation of an intramolecular disulfide bridge with an irradiation time of 200 seconds.

Scheme 87 Eosin Y catalyzed aerobic oxidation of thiols to disulfides in flow.

Noël et al. found that eosin Y was the best tradeoff between conversion and scope in a screening of different organic dyes for the perfluoroalkylation of heteroarenes. The perfluoroalkylation of N-methylpyrrole with heptafluoro-1-iodopropane was first investigated, both in batch and in flow (Scheme 88). The same in-house reactor previously described was used, this time with a reactor volume of 480 μL. After an initial base screening, TMEDA was chosen as sacrificial electron donor, and the catalyst loading was increased to 5% to reach full conversion. Other perfluoroalkyl halides were used to afford the corresponding perfluoroalkylated pyrrole and indole derivatives in good yields.

Scheme 88 Metal-free trifluoromethylation of 5-membered heterocyclic structures in flow.

Kappe and co-workers reported an eosin Y-mediated \( \alpha \)-trifluoromethylation of ketones via a continuous-flow two-step process (Scheme 89). The ketone was first converted to the corresponding silyl enol ether and subsequently exposed to light irradiation in presence of the photocatalyst and a suitable trifluoromethylating agent (triflyl chloride, \( \text{CF}_3\text{SO}_2\text{Cl} \)). Using acetophenone as model substrate, the nature of different photocatalysts was evaluated in batch. Also in this case, Eosin Y proved to be a better photocatalyst than Ru(bpy)_3Cl_2, both in terms of conversion and selectivity (respectively
85 and 95% for eosin Y vs. 20 and <10% for the Ru complex. A continuous-flow process was designed for this protocol, including a first reactor (2.0 mL) for the conversion of the ketone into the silyl enol and a second photoreactor (FEP, ID 3.2 mm, 28 mL, 30 W CFL) for the trifluoromethylation step. Using this flow process, a wide range of phenones and heteroaromatic ketones were trifluoromethylated in good to high yields (56-87%).

![Scheme 89 Eosin Y photocatalyzed continuous-flow trifluoromethylation of ketones.](image)

A careful batch-to-flow comparison of an eosin Y catalyzed reaction was carried out by Neumann and Zeitler. The reductive dehalogenation of α-bromoacetophenone catalyzed by eosin Y in the presence of DIPEA and Hantzsch ester, already reported in batch, was reinvestigated in flow. A commercial glass chip photoreactor (500 x 600 μm, 100 μL) was used and subjected to green LED irradiation to match eosin Y absorption maximum (λ_{max} = 530 nm). The product was obtained in 40 seconds to 20 minutes in flow, while batch required 12 to 18 hours to reach a similar conversion. Moreover, the authors reported an enantioselective reaction in flow, which was first reported by Nicewicz and MacMillan. Using 0.5% of eosin Y and 20 mol% of imidazolidinone catalyst in flow resulted in a similar yield and enantiomeric excess than observed in batch. However, the reaction time was significantly reduced (45 minutes vs. 18 hours).
3.3.9 Rose bengal

The role of rose bengal as photosensitizer for singlet-oxygen mediated reactions has already been described in a dedicated section (3.2.4). Recently, rose bengal has also been proposed as an organophotocatalyst in other photocatalytic synthetic transformations. For example, Rueping et al. used Rose bengal for the continuous-flow generation of α-aminoalkyl radical derived from N,N-dimethylaniline and N-aryl tetrahydroisoquinoline.\(^{369}\) Known reactions from literature were converted to continuous-flow using a FEP coiled reactor (ID 760 μm, 9.3 mL) irradiated with a green LED strip. N-aryl tetrahydroisoquinoline was reacted with nitroalkanes, cyanotrimethylsilane, dialkyl malonates and dialkyl phosphites yielding the corresponding products in moderate to excellent yields (49-92%) (Scheme 90) and with shorter reaction time (3-5 h) compared to the original reports. A similar acceleration of the reaction kinetics was also observed in the oxidative Ugi multicomponent reaction.\(^{369}\) Rose bengal also proved to be superior to [Ru(bpy)]\(^{3+}\) as photocatalyst for the flow hydroxylation of phenyl boronic acid to phenols.\(^{370}\)

![Scheme 90](image)

Scheme 90 Nucleophilic trapping of α-N-aryl tetrahydroisoquinolines in flow.

3.3.10 Xanthones

Kappe and co-workers reported a benzylic fluorination in flow using Selectfluor as F-source and xanthone as organic photocatalyst (Scheme 91).\(^{371}\) A photoreactor made of FEP tubing (ID 1.6 mm, 28 mL) was coiled around a glass cylinder and irradiated with a 105 W black light CFL. With the optimized conditions (1.2 eq. selectfluor, 5 mol% cat., MeCN 0.1 M) in hand, a wide variety of fluorinated derivatives was obtained in good to excellent yields (60-89%) with a residence time of 28 minutes. The advantages offered by the flow protocol became clear in the fluorination of the common fragrance celestolide, which was unstable in acetonitrile. However, by reducing the residence time to 9 minutes and including an inline dilution of the reaction stream with dichloromethane, the corresponding product could be obtained in high yield (88%). This result highlights the potential of flow chemistry to provide a fine control over irradiation/reaction time.

![Scheme 91](image)

Scheme 91 Continuous flow benzylic fluorination using xanthone as photo-organocatalyst.

Xanthone and thioxanthone have also been used as a triplet sensitizer for the visible-light photocatalytic \([2 + 2]\) cycloaddition of atropoisomeric maleimides with an alkenyl tether (Scheme 92).\(^{371}\) High enantioselectivities (e.e. > 99%) were observed both in batch and in a FEP
coiled reactor (ID 1.6 mm, 28 mL). Relative to the batch process, the flow setup provided an increased efficiency and scalability (full conversion in 60 min in flow vs. 18% conversion in batch with the same conditions).

Scheme 92 photocycloaddition of atropoisomeric maleimides.

4 Continuous-flow photochemistry in material science

4.1 Polymer synthesis

Scheme 93 Polymer synthesis in microflow: (1) Photopolymerization (2) Co-polymerization (3) Photo-functionalization of polymers.

The synthesis of high performance polymeric materials can be substantially facilitated by the use of microreactor technology. Recently, the number of examples showing efficient polymer synthesis in flow have increased exponentially. Among these studies, a significant fraction utilizes light energy to initiate polymerizations or to allow late-stage modification of the polymer. The small length scales encountered in microreactor technology provide several benefits for polymerizations processes. First, the typical high surface-to-volume ratio observed in microreactors allows a more effective control over highly exothermic polymerization reactions (high heat transfer characteristics). Consequently, microreactors can be seen as near isothermal reactors and provide equal processing conditions throughout the entire reactor. Second, fast mixing allows to control polymerizations with very fast kinetics, such as free radical polymerizations (high mass transfer). Third, microreactors provide a safe and reliable environment for the handling of toxic and potentially explosive materials while being apt for harsh experimental conditions (e.g. high temperature and pressure). Fourth and specifically for photopolymerizations, an important benefit is presented by the homogenous light irradiation of the entire reaction mixture. Last, the often problematic scale-up of photopolymerizations can also be addressed by using continuous-flow reactors. All these benefits make microreactors ideally suited to prepare high performance polymers with a narrow polydispersity index (PDI) and well-defined properties.

4.1.1 Continuous-flow synthesis of polymers

The flow photopolymerization of n-butyl acrylate was one of the first examples reported. A glass serpentine reactor with an internal diameter of 1.5 mm and a wall thickness of 6 mm was subjected to UV irradiation. The
effect of photoinitiator concentration, light intensity and exposure time were studied with respect to monomer conversion, polymer PDI and molecular weight distribution and the results were compared to thermal polymerizations, both in microreactor and in batch. The reaction kinetics were substantially faster for the photoinitiated system in the microreactor (38 s vs. 180 s to achieve ≈ 80 % conversion). Moreover, lower PDI was observed in the microreactor compared to batch (2.03 vs. 9.61). A follow-up paper investigated the effect of the channel diameter (from 1.5 to 0.5 mm) and demonstrated that a more uniform irradiation was obtained in the narrow diameter reactor. This resulted in a higher conversion (= 15% more in flow within 9.5 s) and lower polymer branching (0.42 % molar branching at 30 °C by keeping the temperature constant, 1.334 % molar branching without control over the temperature). Efficient light distribution within the reactor vessel becomes increasingly important when scattering effects are more pronounced. Scattering phenomena are observed in opaque systems, like emulsions or mini-emulsions, which are commonly encountered in the synthesis of hybrid polymer latexes.

While translating their recently reported visible light-mediated photocatalytic radical polymerization of methacrylates to flow, Poelma, Hawker and co-workers undertook an extensive screening of tubing materials (Scheme 94). For their air-sensitive reaction, it was found that the oxygen permeability of the channel was more important than its light transparency. In particular, a reactor made of Halar tubing (ID 500 μm, total length 550 cm) performed slightly better than Tefzel, FEP and PFA (Halar has a 35 time lower oxygen permeability). Yet, the increase in reaction rate was only 30%, while the polymer PDI was in the same range as the corresponding batch protocol.

![Scheme 94 Influence of tubing material on conversion and polydispersity index in the visible light-mediated photocatalytic radical polymerization of methacrylates.](attachment://Scheme_94.png)
The same tubing material has been used successfully by Chen and Johnson. Halar tubing (ID 760 μm) was coiled around a glass bottle and irradiated by UV lamps. This setup enabled the photocontrolled radical polymerization (photoCRP) of trithiocarbonates in flow (Scheme 95).

Scheme 95 Continuous-flow photocontrolled living radical polymerization of trithiocarbonates.

Compared to batch, this setup exhibited a four-fold increase in reaction rate and allowed to achieve molecular weights above 100 kDa and narrow PDIs (1.09-1.19). Interestingly, those excellent results could be achieved as well with challenging triblock copolymers. The scale-up potential of continuous-flow microreactors was proven by synthesizing 2.95 grams of poly(DMA) (DMA = N,N-dimethylacrylamide) in 400 minutes.

Gardiner and co-workers reported a photo-initiated RAFT polymerization of methacrylates and acrylamides in a continuous-flow reactor. PFA was preferred as material for the tubing due to its high transparency (better than Tefzel and Halar) and increased durability (compared to FEP). The oxygen permeability of the capillary was circumvented by continuous flushing of the reactor coil with a pre-cooled nitrogen stream, serving both as cooling agent and inert gas. A commercial photoreactor (ID 1.3 mm, 10 mL) was irradiated with a medium pressure mercury lamp (150 W). Depending on the molar ratio of RAFT agent and photoinitiator, full and fast conversion with high polydispersity (5 min at 30 °C, PDI > 1.5) or good conversion with control over molecular weight and polydispersity (PDI < 1.3) were achieved.

The copper-mediated photocontrolled radical polymerization of methyl acrylate has been performed in milli- and microreactors by Junkers and co-workers. For the milli setup, 25 m of PFA tubing (ID 750 μm, 11 mL) was coiled around a 400 W medium pressure UV-lamp, while the glass chip microreactor (19.5 μL) was placed under a UV flood lamp. Low dispersity indexes and high conversions were obtained in both reactors (e.g. PDI = 1.16 for a diblock copolymer in the microreactor) within very short residence times (maximum 20 minutes). A later paper from the same group reports the flow conditions for the synthesis of methyl acrylate/methyl methacrylate (MMA) block copolymers. The reactor consists of 25 m PFA tubing wrapped around a quartz glass tube (ID 750 μm) in which a 15 W 365 nm UV lamp was placed. Similar PDIs were obtained (1.15-1.37 in batch, 1.15-1.40 in flow) but the reaction time was significantly shortened in flow (3-7 h in batch, 5-60 min in flow owing to the higher irradiation efficiency).
The improved thermal control of microreactors can also impact the quality of the polymer. In a recently reported photoinduced Co-mediated radical polymerization, Junkers, Detrembleur and co-workers, observed that the reaction could be carried in flow (19.5 µL glass chip) at elevated temperatures without the formation of crosslinked side-products, which are typically observed in batch experiments. Furthermore, a 4-fold acceleration in reaction rate was observed compared to batch.

### 4.1.2 Late-stage modification of polymers

Late-stage chemical modification of polymers is often regarded as challenging because of the difficulty in obtaining a site-selective functionalization while keeping the main polymer chain intact. This strategy is of high interest as it allows to rapidly tune material properties by preparing a large panel of slightly modified polymers derived from a common lead polymer.

Seeberger and co-workers reported the innovative use of a photochemical [2+2] cycloaddition to afford glycoconjugated polymers (Scheme 96). These designed polymers are obtained by an UV-induced reaction between a polylysine polymer bearing a maleimide motif and a nonapodal or tripodal sugar-based dendrimer, which is decorated with an alkyne moiety. The reaction was carried out in water at room temperature in a continuous-flow microreactor (FEP tubing, ID 760 µm, 450 W medium pressure mercury lamp). A set of glycodendronized polylysines were obtained within 40 min residence time in good to excellent yields. The flow protocol provided a fast and easily scalable synthetic route. These photofunctionalized polymers were subsequently assessed for their ability to act as probes for the detection of mannose-binding invasive strains of *E. Coli*, displaying optimal binding selectivity and sensitivity towards the tested pathogens. The same group later reported the synthesis of sequence-defined carbohydrate-functionalized poly-oligo(amidoamine) polymers via a photochemical thiol-ene coupling in continuous-flow.
Scheme 96 Continuous-flow functionalization of polymers with glyco-dendronized polylysine via a [2+2] photocycloaddition. The biocompatible products are used for the detection of bacteria.
As demonstrated above, continuous-flow \([2+2]\) cycloadditions can be regarded as smart tools for various site-selective modifications of polymeric structures in a time-efficient fashion. Furthermore, flow procedures provide means to rapidly fine-tune the reaction conditions.\(^{396}\) For instance, Conradi and Junkers reported a photoinduced \([2+2]\) cycloaddition to provide a controllable switch to functionalize maleimide-containing polymers with a small array of different alkenes (Scheme 97).\(^{397}\) The reactor was made from transparent PFA tubing (ID 760 \(\mu\)m, 11 mL) wrapped around a quartz cooling mantle (4°C). The reactor was exposed to UV irradiation from a 400 W medium pressure UV lamp. The reported examples showed reduced reaction times (several minutes) in flow under optimized reaction conditions. Thioxanthone (TXS) was used as an organic photosensitizer and further allowed to reduce the amount of byproduct formation by avoiding photodegradation. Interestingly, the advantages of using TXS for the \([2+2]\) cycloaddition are not observed in batch.

Scheme 97 UV-induced cycloaddition for polymer modification. The terminal maleimide group is reacted quantitatively with a small array of alkenes in \(1\) minute in a flow photomicroreactor.

4.2 Polymer particle synthesis

Polymer particles with a narrow polydispersity have a broad application potential, e.g. chromatography, encapsulation of drugs, resins, optical data storage, etc. Microreactor technology has made great contributions in the fabrication of such monodispersed polymer particles, as this technique provides a great control over particle size, shape and composition.\(^{398-404}\) However, it must be noted that essentially all examples on the light-assisted continuous-flow synthesis of particles use UV-light exclusively for the final curing or solidification of the particles,\(^{405}\) with their actual preparation based mainly on micro-emulsification.\(^{406-407}\)

Whitesides, Stone and co-workers have developed different microfluidic flow-focusing devices (MFFDs), which allow to prepare polymer particles in various shapes and sizes by a stringent control of the hydrodynamics.\(^{408-409}\) MFFD are typically obtained in poly(dimethylsiloxane) (PDMS) or in polyurethane (PU) through standard soft lithography techniques.\(^{405-406}\) These devices use a flow-focusing geometry integrated in a planar microchannel design, as depicted in Figure 19. Two immiscible liquids are forced through a small orifice, with one liquid representing the dispersed phase, flowing in the central channel, and another immiscible liquid, representing the continuous phase, flowing through the outer channels. The pressure and the viscous stress caused by the continuous phase on the dispersed phase forces the latter into forming a narrow thread that breaks up into small droplets when
passing through the orifice. The dispersed droplets, flowing in the continuous phase, present monodisperse or polydisperse patterns, and their size can be easily fine-tuned by regulating flow rates through the orifice as well as by other important variables (channel diameter, interfacial tension, etc.). Notably, the produced droplets are significantly smaller than the orifice, with a particle size ranging in the order of hundreds of nanometers to micrometers. Once the droplets are released, they are collected and solidified via photochemical or thermal methods.

Figure 19 (a) Representation of a MFFD associated with light- (b) or thermally-induced (c) curing of the droplets. Different droplets shapes can be prepared in the microfluidic channel. When the droplet volume is higher than the channel section, the spherical droplet (d) is forced into a discoidal (e) or rod (f) shape. Reprinted with permission from ref. 405. Copyright 2005 John Wiley & Sons.

Initially, all reported synthetic strategies for polymer particles employed a two-stage process, including an in-flow emulsification step followed by a subsequent batch treatment for particle solidification. Around 2004-2005, more reports appeared in which both steps were carried out in continuous-flow. Nevertheless, still a lot of examples describing off-chip photopolymerization are reported in current literature, however, a full description of all these methods is beyond the scope of this review.

MFFDs employing a downstream photopolymerization step have been extensively reported in the literature and have been applied for the fabrication of several microparticles, including liquid-containing capsules. By means of a constriction module (i.e. a channel morphology change), placed after the emulsion formation and before the UV-induced hardening step, it is also possible to shape the particles into cylinders or disks (Figure 19). In-situ UV polymerization has also been used to encapsulate and protect crystalline colloidal arrays from ionic impurities.

Kumacheva and co-workers reported a microfluidic synthesis of Janus and three-phase particles. This was achieved by an emulsification of immiscible monomer liquid streams followed by a photopolymerization of the monomer droplets to a solid state. The desired droplets were formed through the use of a MFFD and were irradiated by a 400 W UV-light source to induce photopolymerization (Figure 20). The Janus and ternary particles could be obtained in a size range from 40 to 100 μm, with high control over their structure and particle size distribution, which was provided by careful changes in flow rates.
Other reports showed diverse synthetic strategies for the photoassisted formation of Janus particles in microfluidic devices. Through a MFFD, monodispersed colloid-filled hydrogel Janus granules were obtained using a simple Y-junction operated at low flow rate to minimize the mixing between the co-flowing streams. Consequently, convective mass transport across the interface can be avoided and even Janus particles from miscible solutions can be made. Later on, a more broadly applicable fabrication of Janus particles from highly diverse immiscible fluids was reported, with an emphasis on the formation of particles featuring both a hydrophilic and lipophilic part, dispersed in different carrier mediums.

An operationally simple microfluidic device for the synthesis of polymeric beads was reported by Serra and co-workers. The device essentially consists of a T-junction in which a needle delivers the dispersed phase into the continuous phase. Polymerization occurs downstream under UV-irradiation.

Droplets are introduced in a transparent PTFE tubing exposed to UV-light. This design allows to focus the particle formation towards the channel center and prevents the adhesion of the particles to the channel wall. Consequently, microreactor clogging can be avoided. An additional advantage is that the PMMA beads could be produced without using any surfactant. Finally, the polymer particles are collected in a convergent pipe ending in a clogged needle to stack them and create a necklace-like structure. This device was successfully applied by the same group to the continuous-flow encapsulation of ketoprofen. The beads proved to be suitable for use in drug delivery systems.
To increase the UV exposure time while keeping a high flowrate in the droplet formation zone, Zourobo et al. etched a spiral microflow reactor with an increased channel size in the polymerization part (from 200 x 200 μL to 500 x 300 μL). This reactor was subsequently applied in the synthesis of polymer beads, which were molecularly imprinted with propranolol.

Another easy and reliable strategy to obtain monodisperse monomer droplets in microfluidic devices is the perpendicular insertion of a needle into the continuous phase tubing (Figure 22).

Figure 22 A schematic drawing of the microfluidic device used by Du Prez and co-workers. A needle delivering the reagent phase was inserted perpendicularly into the continuous phase, thus creating monodisperse monomer droplets. Polymerization under UV-irradiation afforded the functionalized polymer beads. Reprinted with permission from ref. 422. Copyright 2010, The Royal Society of Chemistry.

This approach was applied by Du Prez and co-workers to prepare functionalized macroporous polymer beads, useful as supports for solid phase peptide synthesis (SPPS). Similarly, high internal phase emulsion (HIPE) acrylates droplets were photopolymerized in flow. This allowed to prepare highly porous capsules, which were further functionalized with azide functional groups for Copper(I)-catalyzed Azide-Alkyne Cycloaddition (CuAAC).

To increase the throughput of microfluidic devices and to match the productivity demands of industrial applications, Nisisako and Torii reported a numbering-up design fitting 256 droplet-formation units on a 4.2 x 4.2 cm squared chip with only two inlets (continuous and dispersed phase) and a single outlet. Production of both homogeneous and biphasic Janus particles with a coefficient of variation (CV) as low as 1.3% was feasible and a throughput up to several kilograms per day was obtained. Compared to other numbering-up strategies, this approach made a more efficient use of the UV light source for the photopolymerization process.

Figure 23 Scale-up of a microfluidic flow-focusing device (128 channels). Reprinted with permission
Wen and co-workers reported the manufacturing of porous polymer particles through a binary UV-induced reaction. H$_2$O$_2$ droplets were first encapsulated into a liquid photoinitable polymer precursor mixture of tripropylene glycol diacrylate (TPGDA) using liquid paraffin as the continuous phase. Polymer microspheres containing various amounts of H$_2$O$_2$ were obtained by controlling the flow rates of the continuous medium and by the addition of polyvinyl alcohol (PVA) as surfactant. After the initial formation, the microspheres were delivered to a larger diameter tubing where the photopolymerization of the polymer precursor and the H$_2$O$_2$ decomposition, with release of O$_2$, were carried out simultaneously. This strategy provided highly porous poly-TPGDA microspheres, with a maximum void of 70%.

An interesting application constitutes the manufacturing of hydrogel particles containing an enzyme. Here-to, a hydrogel solution, containing the biocatalyst, is introduced in the microfluidic device and is surrounded by an immiscible mineral oil isolating it form the reactor wall. The obtained hydrogel droplets can be subsequently polymerized under UV light irradiation. This strategy enables simultaneous microbead formation and enzyme immobilization. Notably, no noticeable deactivation of the biocatalyst was reported. Several attempts for the continuous-flow encapsulation of cells in polymer microgels were also described. However, photopolymerization is often avoided in these applications because of the negative influence of UV irradiation on the cells. One example reported the synthesis of acrylate-based microcapsules containing yeast cells. By virtue of almost instantaneous photopolymerization, solidification of the capsules was achieved rapidly without any consequences for the cell functionalities.

Hollow particles and microcapsules were also obtained via photopolymerization strategies in microfluidic devices. Tunable hollow microcapsules featuring a polymeric shell and a hydrophilic core are of great interest for drug delivery systems. These capsules provide a triggered release of the Active Pharmaceutical Ingredient (API), which can be obtained through a post-administrational control of the polymeric layer. Lee and co-workers reported the continuous-flow synthesis of monodispersed poly(n-isopropylacrylamide) (PNIPAM) microcapsules through a photopolymerization reaction occurring at the interface of two immiscible phases. A water dispersed phase containing NIPAM and a cross-linker, and a hexadecane continuous phase containing a photoinitiator were pumped in the microfluidic device and resulted in the formation of microdroplets. Next, the monomer and the cross-linker migrated to the surface of the droplet, while the photoinitiator diffused from the continuous phase to the particle surface. Upon UV irradiation, a photopolymerization process occurs at the particle shell, delivering aqueous core-polymer shell hollow microcapsules (Figure 24).
Figure 24 Schematic diagram of the MFFD employed to synthesize monodisperse hollow particles and microcapsules. (a) Droplets formed in the aqueous dispersed phase, (b) enlarged representation of the NIPAM and cross-linker (BIS) containing droplets in the hexadecane phase, (c) UV-induced interfacial photopolymerization, (d) final microcapsule. Reprinted with permission from ref. 430. Copyright 2008 The Royal Society of Chemistry

Using a similar strategy, Chu and co-workers obtained poly(hydroxyethyl methacrylate-methyl methacrylate) (poly(HEMA-MMA)) hollow and porous microspheres through the use of a glass MFFD for the preparation of monodispersed oil-in-water microcapsules. The interfacial-initiated photopolymerization was used to obtain a hollow particle solidification, while polymerization on the inside of the particle in presence of an appropriate porogen agent was used to encapsulate porous microspheres.

Asua and co-workers reported a mini-emulsion photopolymerization in flow to prepare waterborne polyurethane/acrylic hybrids. A photopolymerization in an aqueous dispersed medium could be carried out with a 20% solid content emulsion in water without reactor clogging. An isocyanate terminated polyurethane (PU) was mixed with a liquid stream containing acrylate monomers, 0.4% of 2-hydroxyethy methacrylate (HEMA), and variable amounts of photoinitiator. The miniemulsion was introduced into a reactor made of 15 quartz tubes of 40 cm length with an inner diameter of 1 mm. The reactor was subjected to UV light to promote the acrylate photopolymerization. During this process, the isocyanate moiety of the PU reacts with the free hydroxyl of the HEMA monomer in the acrylate polymer yielding a sol-gel hybrid latex. In the absence of polyurethanes, only the acrylate sol suspension was observed. Monomer conversion was increased with prolonged residence times and increasing photoinitiator concentrations. By tuning the process parameters, a broad range of gel contents (from 0.4 to 0.7) and sol molecular weights (from 30 to 160 kDa) were obtained. On the other hand, when using the same formulation (in the absence of any photoinitiator) at 70 °C in a re-do mini-emulsion polymerization, only a latex could be obtained with a gel content of 0.62 and molecular weight of the sol of 214 kDa. This setup could not be applied directly to the synthesis of adhesives due to the relatively low solids content (20 wt%). Higher solid loadings resulted in reactor clogging due to the adhesion of the polymer to the channel wall. A detailed study of the clogging mechanism provided insights to design a new reactor made of two distinct sections. The first section was optimized to obtain a monomer conversion of about 45% and was made of low surface energy material (i.e. silicone) to avoid interaction of the channel wall with the polymeric droplets. The second section was made from quartz material which provided a high UV transparency for the photopolymerization.
With the improved reactor design, mini-emulsion photopolymerization with a solid content up to 46 wt% was possible, allowing the continuous-flow synthesis of pressure sensitive adhesives.\textsuperscript{435} Despite the time-consuming optimization of the reactor to avoid clogging,\textsuperscript{436} the tunable characteristics of the system finally afforded hybrid polymer with diverse polymerization rate and microstructure. The irradiation parameters were then related with the performances of the adhesives. In Figure 25, a probe-tack test, indicative for the stress resistance of pressure sensitive adhesives, shows how the different intensity of irradiation influences the performance of the hybrid polymer.

![Figure 25 Effect of irradiation power on pressure sensitive adhesive performance in a probe-tack test. Reprinted with permission from ref. 435. Copyright 2014 Elsevier](image)

MFFD were also successfully applied to the synthesis of tripropylene glycol diacrylate and acrylic acid copolymeric particles.\textsuperscript{437} The heat generated by the exothermic acrylate photopolymerization has been exploited by Li et al. to trigger a second reaction, i.e. the polycondensation of a urethane oligomer yielding polymeric particles with an interpenetrating polymer network structure.\textsuperscript{438}

The synthesis of magnetic microparticles by MFFD has proven challenging due to the high UV absorption of inorganic materials preventing an efficient photopolymerization of the droplets. To address this issue, Hwang et al. embedded a piece of aluminum foil in the microfluidic chip as back reflector for the UV-exposed region.\textsuperscript{439} This offers a multidirectional light exposure and an increased UV energy flux to the droplets, thus preventing shape deformation. In this way, magnetic hydrogel microparticles exhibiting a superparamagnetic behavior were obtained in sphere, disk and plug shape.

![Figure 26 Microfluidic flow-focusing device applied to the synthesis of magnetic microparticles. Reprinted with permission from ref. 439. Copyright 2008 The Royal Society of Chemistry](image)

Doyle and co-workers reported the first example of continuous-flow lithography.\textsuperscript{440} This technique relies on the combined use of microfluidic technology and microscope projection photolithography to afford the continuous-flow synthesis of complex shaped and Janus-like polymer particles. The simple yet effective setup, features a PDMS device through which an acry-
late oligomer stream containing a photoinitiator is flown. A transparent mask, containing the planar geometry of the desired particle, is inserted in the field-stop plane of an inverted optical microscope. Through the microscope objective, the size of the printed geometry on the transparent mask is reduced by 7.8 up to 39 times. A pulsing UV beam exiting the microscope is focused on the PDMS device, causing the ultra-rapid (< 0.1 seconds) continuous photopolymerization of the polymeric monomer. This results in the formations of particles with a mask-defined shape (Figure 27).

**Figure 27** Schematic representation of the continuous-flow lithography setup. The transparency mask between UV light source and objective determines the shape of the polymerized objects. Reprinted with permission from ref. 440. Copyright 2006 Nature Publishing Group.

Furthermore, the presence of molecular oxygen, which diffuses from air through the gas-permeable PDMS reactor walls, enables the formation of a non-polymerized monomer layer at the surface of the microchannel. This layer acts as a lubricant and facilitates the freshly formed particle to flow out of the reactor. It was postulated that the role of oxygen in preventing polymerization close to the PDMS walls derives from its interaction with the photogenerated free radicals, forming chain terminating peroxide species. Through this successful strategy, a broad array of different particles was synthesized, as represented in Figure 28. The particle planar geometry corresponds to the dimensions obtained after reduction of the image by the microscope objective, while its height corresponds to the difference between the channel height and the lubrication oxygen layers. With the same device, Janus particles could be prepared, adding the unprecedented possibility to control the proportion of the two constituting chemical entities. This was achieved by adjusting the position of the light beam in the channel and the thickness of the flowing streams.

**Figure 28** Array of shapes obtained through continuous-flow lithography. A-C: Flat structures (20-µm-high channel). D: Cuboid (9.6-µm-high channel). E-F: High-aspect-ratio structures (38-µm-high channel). G-I: Curved particles (20-µm-high channel). Reprinted with permission from ref. 440. Copyright 2006 Nature Publishing Group.

The limitations of continuous-flow photolithography lie in the optical resolution and depth of field of the inverted microscope, with the former influencing the size of the smallest attainable particle, and the latter caus-
ing the edges to bevel. To circumvent these technical obstacles, stop-flow lithography and analogous strategies were successfully introduced. Due to their non-continuous nature, they will not be treated in this context. The continuous-flow lithography technique has also been applied to the synthesis of self-assembled amphiphilic polymeric microparticles and multifunctional encoded particles for high-throughput assays.

4.3 Nanoparticles

4.3.1 Polymer-based nanoparticles

Seminal work on polymeric nanoparticle synthesis in a photochemical reactor was reported in 2014 by Chemtob and co-workers. Microemulsions, containing monofunctional acrylates or difunctional thiol-ene monomers in presence of a photoinitiator, were prepared in water through high shear homogenization. The prepared microemulsions were flown through a microreactor with a volume of 1.7 mL and an inner diameter of 1 mm. The reaction stream was irradiated with two 36 W UV lamps. The difunctional thiol-ene monomers afforded the formation of a linear poly(thioether) latex and performed better than the acrylates in terms of yields, with full conversion observed within 10 min (latex size 155 nm). Acrylates and methacrylates showed only partial conversion at room temperature, but their reactivity was improved either by decreasing the initial particle size of the microemulsion or by increasing the reaction temperature. This provided polyacrylate latexes with a particle size ranging from 75 and 125 nm.

4.3.2 Metal-based nanoparticles

Particularly challenging and interesting for their application in different fields (e.g. catalysis, biomedicine, surface-enhanced Raman scattering) is the synthesis of noble metal nanoparticles with a high degree of homogeneity in size and shape. Only a limited amount of reports account for continuous-flow photochemical synthesis of metal nanoparticles. Carofiglio and co-workers reported two different microfluidic setups for the photochemical nucleation (under a UV mercury lamp) and the light-induced shape-selective growth of silver nanoparticles (under monochromatic LED irradiation). By selecting the proper irradiation wavelength, silver nanoparticles (AgNPs) could be converted into larger spherical, decahedral or triangular nanoparticles (Figure 29).

Figure 29 UV-Vis spectra of the silver nanoparticles colloids obtained after irradiation at different wavelength. Solid black line: pristine sample; circles: after irradiation at 627 nm; dash-dotted line: after irradiation at 455 nm; dotted line: after irradiation at 627 nm.

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Micro-segmented flow regimes are an interesting flow pattern to prepare narrow-sized nanoparticles. In a micro-segmented flow an immiscible phase, often referred to as carrier medium, is used to break the continuous phase in discrete and reproducible slugs or
droplets (Figure 30). In such a droplet, toroidal vortices are established which enable a fast and intensified mixing. Segmented flow regimes in microreactors are considered to be ideal plug flow reactors in which all the fluid elements have the same residence time distribution. This is especially important for the preparation of nanoparticles, as differences in residence time will lead to a broader size distribution. Furthermore, the homogeneous and fast convective mixing in segmented flow prevents the formation of localized concentration gradients. In the case of a droplet segmented-flow, an additional advantage is given by preventing the reacting phase from being in contact with the microreactor wall. Such particle-wall interactions often lead to nanoparticle aggregation and thus reactor fouling.

Recently, the first photochemical synthesis of gold nanoparticles in a continuous-flow process was reported by Hafermann and Köhler. A solution of tetrachloroaurate and a solution of the photoinitiator and polyvinylpyrrolidone were mixed in a segmented flow by using a crossed mixer. The originated segments exhibited an ID of 500 μm and were irradiated under UV light. It was found that particles which were subjected to prolonged UV exposure, were significantly smaller than those obtained with shorter UV exposure times (2.5 vs 4 nm respectively). This can be rationalized by considering the radical concentration in the channel. Longer exposure times result in the formation of larger initiator concentrations for the same quantity of metal, causing a higher amount of gold particles to start nucleating independently. The same group later reported the continuous-flow synthesis of other noble metal nanoparticles, such as platinum, palladium, rhodium and iridium particles, in the range of a few nanometers (2.5 nm) by using the same microfluidic device.

A borderline case between inorganic and polymer-based particle synthesis is represented by the work of Serra, Köhler and co-workers. The authors reported a continuous-flow preparation of homogeneous polymeric microbeads filled with ZnO and Au nanoparticles. Similarly, Kim, Lee and co-workers reported the preparation of monodispersed inorganic-organic hybrid Janus particles, featuring a perfluoropolyether-based hydrophobic lobe and a more hydrophilic carbosilane-based hemisphere.
5. Continuous-flow photochemistry for water treatment

5.1 Water purification

Due to the rapid depletion of clean water sources on the planet, together with the unsustainable rate of population growth, the need to develop technologies for the recycling of wastewater is as relevant as ever. Additionally, the strict policies regulating the standards of wastewater pollution for industrial applications impose the need for effective decontamination treatments. Current purification methods, based primarily on physical separation of contaminants and biological oxidation, fail to provide an efficient solution for the decontamination of toxic, non-biodegradable organic compounds. In this context, Advanced Oxidation Processes (AOPs), employing highly reactive oxygen species, prove to be one of the most efficient processes for water purification. Among these, photocatalytic reactors represent a promising solution to facilitate highly efficient and sustainable water treatments.

In photocatalytic reactors, highly reactive oxygen species are generated through heterogeneous or homogeneous photocatalysis by means of UV and/or visible light irradiation. In both cases, the *in situ* photogenerated reactive oxygen species (ROS) afford disinfection of water pathogens through peroxidation of the phospholipids in the lipid membrane. This results in the progressive loss of cell functions and, eventually, leads to cell death. Organic water contaminants can be mineralized by the *in situ* photogenerated ROS through partial or complete oxidation, ultimately yielding CO₂, H₂O and environmentally friendly byproducts.

With a few exceptions, heterogeneous photocatalysis for water treatment coincides with TiO₂ photocatalysis, while homogeneous photocatalysis is mainly represented by iron-catalyzed photo-Fenton reactions.

To date, the main application for TiO₂ and photo-Fenton reactions are large scale solar photocatalytic treatment plants. Several examples show the efficiency of solar plants in the removal of different contaminants from wastewater including reports of demineralization of recalcitrant contaminants. Solar photocatalytic plants are generally operated in recirculating batch mode, therefore their description is beyond the scope of this review. For an extensive review on the design and optimization of solar plants for water treatment, we refer to the work from Malato et al.

![Figure 31 Solar detoxification plant “SOLARDETOX”. Left: TiO₂ separation system; right: solar parabolic collectors. Reprinted with permission from ref. 467. Copyright 2009 Elsevier.](image)

In the next sections, both TiO₂ and iron catalyzed photo-Fenton reactions will be discussed, mainly focusing on examples of microreactors for water treatment.

### 5.1.1 Decontamination with TiO₂

Heterogeneous photocatalysis for water treatment is primarily based on the use of semiconductor catalysts,
with TiO$_2$ being by far the most commonly used.\textsuperscript{469} Unlike other known semiconductors (e.g. ZnO, CdS and GaP), nanoscale TiO$_2$ features a high reactivity upon irradiation between 300 and 390 nm and a high stability during consecutive catalytic cycles.\textsuperscript{467} Additionally, operational advantages regarding the use of TiO$_2$ lie in the room temperature and atmospheric pressure conditions. The solid photocatalytic particles used for water purification are in the nanoscale range (typically $\approx$ 25 nm). This small size affords a large surface area and optimal interaction with the pollutants; moreover, TiO$_2$ nanoparticles have enhanced capacity to scatter UV light, when compared to the bulk material.\textsuperscript{470} This can easily be explained by taking into account that light scattering is governed by Rayleigh’s theory\textsuperscript{471} for fine particles, while the bulk metal oxide abides to Mie’s theory.\textsuperscript{472} As a consequence, bulk TiO$_2$ is a white opaque material able to scatter visible light, while TiO$_2$ nanoparticles are transparent to visible light but scatter UV light efficiently.

In photocatalytic reactors, TiO$_2$ nanoparticles are either dispersed in the liquid phase (i.e. slurry reactors) or immobilized on a solid support (i.e. packed-bed or wall-coated reactors). For the comparison of the different reactors and their operational conditions, the golden standard is represented by the Degussa P-25 TiO$_2$ catalyst\textsuperscript{473} containing 75% of TiO$_2$ anatase and 25% rutile.\textsuperscript{474}

**Mechanism of TiO$_2$ decontamination**

Examples of the photocatalytic properties of TiO$_2$ have been extensively reported in literature, demonstrating its ability to allow both reductive and oxidative reaction pathways.\textsuperscript{475} This reactivity is due to the peculiar characteristics of the lone electron pair in the external orbital. This lone electron pair can be photoexcited when the TiO$_2$ surface is irradiated with light of higher energy than the band gap between the valence and conduction band of the catalyst. This band gap corresponds to photons that have an energy between 3.0-3.2 eV (depending on the polymorphous form considered). Consequently, UV light with $\lambda < 400$ nm is needed for the excitation. The direct effect of the photoexcitation is the formation of an electron-hole pair (e$^-$$h^+$), enabling a series of chain oxidative-reductive reactions on the surface of the catalyst.

\begin{equation}
\text{TiO}_2 \xrightarrow{\text{hv}} e^- + h^+
\end{equation}

The interaction of the electron-hole pair with water generates superoxide and hydroxyl radicals, as shown in the following equations.

\begin{equation}
O_2 + e^- \rightarrow O_2^-
\end{equation}

\begin{equation}
OH^- + h^+ \rightarrow OH
\end{equation}

It is widely accepted that the presence of radical scavengers is crucial for an efficient photocatalytic process.\textsuperscript{487} These scavengers prevent the recombination of the photoexcited electrons with the valence band. Moreover, the presence of dissolved oxygen was found to be essential in averting the fast recombination of the electron-hole pair, by promoting the formation of a superoxide radical ($O_2^-$). This superoxide can subsequently be protonated to a hydroperoxyl radical (HO$_2^+$) and, eventually, to H$_2$O$_2$. The presence of water molecules is also a prerequisite for the formation of highly reactive hydroxyl radicals.\textsuperscript{476}
Reactor engineering aspects for continuous-flow decontamination with TiO\textsubscript{2}

Crucial for the successful engineering of photocatalytic reactors is the fundamental understanding of the individual mechanistic steps occurring at the surface of the TiO\textsubscript{2} solid particle. The first step to be considered is the mass transfer of the organic contaminants from the water phase to the TiO\textsubscript{2} surface (Scheme 98, step 1). Mass transfer limitations are especially relevant in reactors featuring TiO\textsubscript{2} particles immobilized on an inert support. In fact, the immobilization of the catalyst creates a lower surface area, reduces the number of active catalyst sites and hinders the light penetration through the catalyst layer, compared to slurry TiO\textsubscript{2} particles. However, due to the large surface-to-volume ratio characteristic for microflow technology, mass transfer limitations can be largely avoided.

![Scheme 98 Mechanism of photodecontamination with TiO\textsubscript{2}](image)

The second important step is the adsorption of the pollutants onto the activated surface of the TiO\textsubscript{2} nanoparticles (Scheme 98, step 2). A published report proved the direct correlation between the rate of photocatalytic decontamination and the percentage of molecules adsorbed on the photocatalyst.\textsuperscript{477} This finding underscores the significance of the adsorption step for the reaction efficiency. Similarly, the vicinity of pathogens to the activated surface of TiO\textsubscript{2} particles is also crucial for photodisinfection.

Once the pollutants are adsorbed on the TiO\textsubscript{2} surface, the photocatalytic reaction can occur (Scheme 98, step 3) followed by desorption of the intermediate product and a net diffusion from the surface to the bulk liquid phase (Scheme 98, step 4 and 5).

Evidently, the overall reaction rate will depend mainly on the slowest of these steps, i.e. the rate determining step. In case of no mass transfer limitations, the concentration of the pollutants in the proximity of the activated catalyst can be considered equal to the concentration in the bulk solution. In such cases, the reaction rate will depend on the intrinsic reaction rate and the photon transport efficiency. However, when mass transfer limitations do occur, preventive measures can be taken by carrying out the reaction in a microreactor.

Further intensification of the transport phenomena can be achieved by increasing the flow rate or by reducing the channel diameter.

Up to date, the major drawback for the industrial scale application of TiO\textsubscript{2}-based AOPs lies in the post-operational separation of the photocatalyst from the slurry.\textsuperscript{459} Importantly, particle agglomeration of TiO\textsubscript{2}, a direct consequence of its fine size particle and large surface energy, hampers the post-separation, prevents the particle size preservation, and shortens the lifespan of the catalyst. To circumvent the post-separation issue, two main strategies are currently in use: (i) coupling the photocatalytic reactor with systems capable of
physically removing the TiO$_2$ particles, either by membrane filtration,$^{478}$ sedimentation,$^{479}$ or cross-flow filtration$^{480}$ or (ii) immobilizing the photocatalyst on a solid inert support.

Despite the aforementioned limitations of photoreactors with immobilized TiO$_2$ particles, great interest remains for their possible application in large scale plants, where the total removal of the metal oxide from purified water needs to be guaranteed.

Several materials have been developed to enable the immobilization of TiO$_2$ nanoparticles, including mesoporous clays,$^{481-482}$ nanofibers$^{483}$ and nanowires.$^{484}$ Microfiltrating photocatalytic membranes of different materials have also been reported,$^{485-490}$ with some examples displaying TiO$_2$ particles embedded in the membrane structure.$^{490-493}$ In these systems, the photocatalytic degradation of the contaminants occurs at the surface of the membrane with no need of post-operational removal of the catalyst. Despite the convenient design, these membranes are often subject to deterioration and loss of the TiO$_2$ layer. Other improvements in the catalyst design have been achieved by the so-called catalyst doping: metallic (Pt, Pd etc.) or non-metallic (N, F, S etc.) elements can be incorporated on the nanoparticle surface. Semiconductor doping allows to narrow the energy band gap between the valence and conduction band of the metal oxide catalyst, therefore broadening its applicability to visible light excitation.

Because of the high costs associated with the use of noble metals, the attention is now shifted to non-metallic dopes, which are suitable for industrial scale applications.$^{49}$

The next paragraph will focus on examples of TiO$_2$ immobilized microreactors, considering important aspects in their design, applicability and scale up potential. For an extensive overview on the use of batch reactor technology for water treatment, featuring both immobilized and dispersed TiO$_2$ particles, we refer to specialized reviews.$^{484,494-498}$

**Microflow reactors**

The importance of an increased surface-to-volume ratio in microflow reactors for water treatment is well exemplified by the UV-mediated N-alkylation of amines reported by Matsushita et al (Scheme 99).$^{114}$ The mechanism of this transformation involves the dehydrogenation of the alcoholic solvent to form the corresponding aldehyde and H$_2$, followed by a condensation with an amine-bearing substrate. Finally, the resulting imine is reduced by H$_2$ to yield the desired N-alkyl derivative. In batch, the alkylation of benzylamine with ethanol occurred in 4 hours with a yield of 84% using Pt-loaded TiO$_2$ and a 400 W high-pressure mercury lamp. In a TiO$_2$-coated microreactor (Figure 32) with UV-LEDs as light source, the same reaction was observed with similar yield in only 6-150 seconds residence time.$^{499-500}$ Both the Pt-free catalysis and the acceleration effect were attributed to the increased illuminated surface-to-volume ratio obtained with microreactor technology.
Figure 32 Schematic view of the photocatalytic microreactor for UV-mediated N-alkylation of amines. Reprinted with permission from ref. 499. Copyright 2007 Elsevier.

Scheme 99 UV-mediated N-alkylation of amines serendipitously discovered during wastewater treatment degradation studies in a TiO₂-immobilized microreactor.

In microreactor devices, a substantial increase in specific photocatalytic surface area is observed due to the high surface-to-volume ratio. Consequently, the rate determining step for photocatalytic degradation becomes the oxygen concentration in water. For example, in the branched microreactor proposed by Lindstrom et al. the conversion rate for the degradation of methylene blue increased by a factor five by adding gaseous oxygen to the dye solution.501

The use of microreactor technology for photocatalytic wastewater treatment with TiO₂ also allows an improved mass transfer to the heterogeneous photocatalyst.499 The absence of any mass transfer limitations was confirmed in a microreactor employing TiO₂ as photocatalyst. In this example, the reaction rate was only limited by the low photonic efficiency of the immobilized TiO₂.93

In a recent comparison of different reactor designs for TiO₂-based photocatalytic wastewater treatment, a new metric was introduced. The so-called photocatalytic space-time yield (PSTY), accounts for the reactor space-time yield normalized to the power of the light source.502

$$PSTY = \frac{STY}{LP}$$

(7)

Where STY is the space-time yield and LP the lamp power. In particular STY, for the comparison of the continuous-flow examples, is calculated using a plug flow reactor model.

$$STY = \frac{1m^3}{\tau}$$

(8)

The lamp power (LP) is normalized to the reactor volume (V) expressed in cubic meters.

$$LP = P \times \frac{1m^3}{V}$$

(9)

By means of this parameter the authors were able to directly compare slurry and immobilized catalyst reactors. The overall comparison showed that slurry reactors performed better than the TiO₂-immobilized ones. Nevertheless, this difference in performance might be attributed to the higher illumination efficiency obtained in larger reactors. Even so, the microreactor proposed by Visan et al. was found to be the best among the immobilized catalyst reactors.503 The reactor design is based on a chip obtained by bonding a TiO₂ coated substrate with a PDMS slab featuring a ≈ 6 cm long channel with a cross-section of 500 x 50 μm (Figure 33). As outlined by Van Gerven and co-workers, the performance of such a reactor is even more relevant.
when taking into account that the light source (a 120W arc-lamp) could be replaced by a more energy-efficient UV-LED array. While there was no apparent impact on the process performance, the use of UV-LEDs provided massive energy savings. The use of UV-LEDs to promote TiO$_2$-mediated photodegradation of pollutants was first introduced by Ye and co-workers back in 2005. \(^{113}\)

![Image](image.png)

Figure 33 Production of microreactors for water treatment with soft lithography and bonding on TiO$_2$-coated substrate. Reprinted with permission from ref. \(^{903}\). Copyright 2013 Elsevier.

An overview of different nanoparticle-based photomicroreactors reported in the literature is summarized in Table 4. One of the most studied model pollutants is methylene blue. Nevertheless, its use has been criticized because of its photosensitive nature, its complicated degradation pathways and its possible adsorption to hydrophobic materials (e.g. silica-gel used as support for TiO$_2$). \(^{504-505}\)

<table>
<thead>
<tr>
<th>Type of microreactor</th>
<th>Light-source</th>
<th>Model pollutant</th>
<th>Channel size</th>
<th>PSTY$^6$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary – single</td>
<td>UV lamp (254 nm)</td>
<td>Methylene blue</td>
<td>530 $\mu$m$^{106-107}$</td>
<td>5.24 x 10$^{-5}$</td>
</tr>
<tr>
<td></td>
<td>UV LED (365 nm)</td>
<td>Rhodamine 6G</td>
<td>530 $\mu$m$^{108}$</td>
<td>1.86 x 10$^{-5}$</td>
</tr>
<tr>
<td></td>
<td>UV LED (365 nm)</td>
<td>p-chlorophenol</td>
<td>500 $\mu$m$^{109}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UV LED (365 nm)</td>
<td>Phenol</td>
<td>200-1000 $\mu$m$^{110}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UV-LED (365 nm)</td>
<td>New coccine etc.</td>
<td>530 $\mu$m$^{114}$</td>
<td></td>
</tr>
<tr>
<td>Capillary – array</td>
<td>UV lamp (254 nm)</td>
<td>Methyl orange</td>
<td>320 μm&lt;sup&gt;93a&lt;/sup&gt;</td>
<td>1.15 x 10&lt;sup&gt;-6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chip – single channel</td>
<td>UV-LED (365/385 nm)</td>
<td>Bisphenol A etc.</td>
<td>500 x 100 μm&lt;sup&gt;94&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UV-LED (365 nm)</td>
<td>Cu-EDTA</td>
<td>100 x 19 μm&lt;sup&gt;95a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UV lamp (352-368 nm)</td>
<td>p-chlorophenol</td>
<td>1000 x 100 μm&lt;sup&gt;95b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UV lamp (365 nm)</td>
<td>Salicylic acid</td>
<td>1.0 x 0.5 mm&lt;sup&gt;95c&lt;/sup&gt;</td>
<td>2.59 x 10&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.5 x 0.5 mm&lt;sup&gt;95c&lt;/sup&gt;</td>
<td>3.45 x 10&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.0 x 0.5 mm&lt;sup&gt;95c&lt;/sup&gt;</td>
<td>5.19 x 10&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chip – array of channels</td>
<td>UV LED (385 nm)</td>
<td>p-chlorophenol</td>
<td>300 x 200 μm&lt;sup&gt;95c&lt;/sup&gt;</td>
<td>7.24 x 10&lt;sup&gt;-4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chip – serpentine</td>
<td>UV lamp (365 nm)</td>
<td>Methylene blue</td>
<td>1 x 0.5 mm&lt;sup&gt;94&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UV light</td>
<td>Cortisone-21-acetate</td>
<td>500 x 50 μm&lt;sup&gt;95c&lt;/sup&gt;</td>
<td>1.08 x 10&lt;sup&gt;-2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>UV light</td>
<td>Methylene blue</td>
<td>500 x 100 μm&lt;sup&gt;95c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UV light</td>
<td>Dichloroacetic acid</td>
<td>500 x 500 μm&lt;sup&gt;95c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UV-LED</td>
<td>Methylene blue</td>
<td>100 x 40 μm&lt;sup&gt;95d-95f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UV-LED (365 nm)</td>
<td>Several dyes</td>
<td>400 x 50 μm&lt;sup&gt;95d&lt;/sup&gt;</td>
<td>9.10 x 10&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chip – branched</td>
<td>UV light</td>
<td>Methylene blue</td>
<td>150 x 50 μm&lt;sup&gt;95f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Planar microreactor</td>
<td>Blue LED&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Methylene blue</td>
<td>10 x 10 x 0.1 mm&lt;sup&gt;95e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solar light</td>
<td>Methylene blue</td>
<td>50 x 18 x 0.1 mm&lt;sup&gt;95g&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UV lamp (310-400 nm)</td>
<td>Methylene blue</td>
<td>20 x 10 x 0.25&lt;sup&gt;95h&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UV lamp</td>
<td>Methylene blue</td>
<td>50 x 18 x 0.1 mm&lt;sup&gt;95i&lt;/sup&gt;</td>
<td>9.85 x 10&lt;sup&gt;-2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> BiVO<sub>4</sub> as photocatalyst

<sup>b</sup> PSTY values as reported by Leblebici et al.<sup>95j</sup> or calculated assuming no mass-transfer limitation. Missing values could not be derived due to missing experimental details (e.g. UV lamp power).
5.1.2 Photo-Fenton and Photo-Fenton-like oxidations

Photo-Fenton reactions represent an alternative strategy for the production of hydroxyl radicals, starting from $\text{H}_2\text{O}_2$.\textsuperscript{522} The degradation of $\text{H}_2\text{O}_2$ in the presence of $\text{Fe}^{2+}$ was first reported by H.J.H. Fenton in 1894.\textsuperscript{523} Later, it was discovered that UV and visible light up to 600 nm could be used to accelerate the Fenton reactions significantly.\textsuperscript{524} Applications of the photo-Fenton process for the treatment of wastewater date back to the late 90’s and early 2000’s with the work from the groups of Pignatello, Kiwi, Pulgarín, Bauer and others.\textsuperscript{525-529} Ever since, the so-called photo-Fenton reactions evolved as one of the most efficient AOPs to afford degradation of water pollutants. This reaction appears to be especially useful for large scale solar plants for water purification.\textsuperscript{467}

The reason behind the acceleration of Fenton reactions in the presence of light lies in the photochemical regeneration of $\text{Fe}^{2+}$ from $\text{Fe}^{3+}$ with the concomitant formation of yet another hydroxyl radical. The mechanism of the Fenton reaction and the photochemical regeneration of $\text{Fe}^{3+}$ are shown in the following equations:

\begin{align*}
\text{Fe}^{2+}_{(aq)} + \text{H}_2\text{O}_2 &\rightarrow \text{Fe}^{3+}_{(aq)} + \text{OH}^- + \text{OH} \cdot \quad (10) \\
\text{Fe}^{3+}_{(aq)} + \text{H}_2\text{O} &\rightarrow \text{Fe}^{2+}_{(aq)} + \text{OH} \cdot + \text{H}^+ \quad (11)
\end{align*}

Compared to semiconductor photocatalysis, the photo-Fenton reaction is feasible with visible light due to the fact that iron-hydroxy and iron-organic complexes present in the water adsorb in the visible light range. Recent studies suggest the possibility to use alternating light/dark cycles during the photodegradation process.\textsuperscript{520-522} It was found that precursors susceptible to photodegradation can accumulate during the dark period and promptly decompose when exposed to light.

Such an alternating illumination could improve the cost efficiency of the whole water treatment by reducing the energy cost for the illumination and by simplifying the design of the reactor in case of solar plants.

A major drawback for the applicability of photo-Fenton reactions is the need to control the wastewater pH throughout the degradation process. The optimal pH for operation was calculated to be 2.8.\textsuperscript{524, 532} Under these conditions, the precipitation of iron salts is avoided and the concentration of mono- and dihydroxylated iron(III) complexes is maximized.\textsuperscript{533} These complexes absorb UV light better than non-hydroxylated iron complexes. Nevertheless, because of the ability of iron to form complexes with different Lewis bases and due to the presence of organic acids in the wastewater, the necessity to operate at a pH of 2.8 is no longer required.\textsuperscript{534-536} In fact, when the ferric ion is complexed, its photoreduction to $\text{Fe}^{2+}$ can occur with visible light. Furthermore, organic acids, present in wastewater, can have a positive influence on the control of the pH. For all this reasons, a pH value of 4-5 is generally considered sufficient to prevent any iron complex precipitation.\textsuperscript{530}

To date, Fenton and photo-Fenton reactions remain one of the most investigated AOPs for wastewater treatment. Several examples of lab scale and pilot-scale solar or UV reactors have been reported, describing the demineralization of organic pollutants such as dyes,\textsuperscript{537-538} drugs\textsuperscript{464, 518, 539} and byproducts from the plastic industry.\textsuperscript{466} Furthermore, enhanced photo-Fenton reactions
can be obtained through coupling with other methods for water purification, such as ozone,\textsuperscript{540} ultrasounds\textsuperscript{541} and TiO\textsubscript{2} \textsuperscript{542-544}. Plenty of examples show the favorable consecutive combination of photo-Fenton and biological treatments.\textsuperscript{545} The use of photo-Fenton reactions as a pretreatment has been shown to increase the biodegradability of wastewater by forming intermediates, which are easily decomposed by microorganisms.\textsuperscript{546} Notably, only a few examples show the sole use of photo-Fenton reactions for water disinfection. One study reported the use of photo-Fenton for the successful disinfection of \textit{E. Coli} from lake water at a neutral pH and low iron and H\textsubscript{2}O\textsubscript{2} concentrations (ppm).\textsuperscript{530} Despite the fact that photo-Fenton reactions generally belong to homogeneous catalysis, few cases have been reported in literature in which different iron minerals are immobilized on inert supports\textsuperscript{547-549} or incorporated in novel iron-based materials.\textsuperscript{550-552} The advantages of heterogeneous photo-Fenton reactions are the easy post-operational separation of iron and the avoidance of pH control, with reactions possible up to a pH of around 7. On the down side, mass transfer limitations and less efficient light irradiation are the unavoidable drawbacks associated with the use of a heterogeneous catalyst\textsuperscript{464}, as highlighted in section 3.3.6 for TiO\textsubscript{2}.

The number of reports on the use of continuous-flow reactors for photo-Fenton waste water treatment is limited. The only example is a Y-shaped 0.9 x 1 mm channel in PMMA which is covered with a quartz plate.\textsuperscript{553} This device was used to study the degradation of an azo dye. Several important process parameters were evaluated, such as pH, H\textsubscript{2}O\textsubscript{2} dye and Fe\textsuperscript{2+} concentrations, and flowrate. The best performance resulted in an 86\% discoloration of the model pollutant with a residence time of about one second. This result outperforms those results obtained with conventional batch technology, which typically requires longer reaction times due to a lower mixing efficiency.\textsuperscript{553-554}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Y-shaped Photo-Fenton reactor for azo dye degradation. Reprinted with permission from ref. \textsuperscript{552}. Copyright 2013 Balaban Desalination Publications.}
\end{figure}
6. Conclusions

Photochemistry has recently witnessed a remarkable increase of attention from researchers in academia and industry. In our opinion, there are two important reasons for that. The first reason is the emergence of visible light photoredox catalysis for organic synthetic chemistry. The use of this novel catalysis mode provided access to unprecedented reaction pathways, which could be carried out in a highly selective and mild fashion (room temperature, visible light, avoidance of toxic chemicals). The second reason is the use of continuous-flow reactors which gives a great degree of operational flexibility in the handling of such photochemical reactions.

As exemplified throughout this review, the implementation of continuous-flow photoreactors is crucial to facilitate photochemical transformations in organic synthetic chemistry, material science and even water treatment. The most important features of this technology is the reduced reaction times, the straightforward scalability and the possibility to safely use highly reactive and hazardous chemicals. Some recent examples have begun to venture into more complex applications, such as the continuous-flow synthesis of complex biologically active molecules. Notably, continuous-flow photoreactors have also been implemented in pharmaceutical companies to produce APIs on a ton scale.

While significant progress has clearly been made, moving forward is not without a challenge. Visible light photoredox catalysis has only recently emerged as a potential alternative compared to traditional organic chemistry. Therefore, it is evident that it will further impact synthetic chemistry in the coming years. An intriguing application would be the use of this catalysis mode to prepare polymer beads which encapsulate cells or other UV-sensitive biologically active compounds. Furthermore, the use of hazardous chemicals or other difficult-to-handle reagents (e.g. gases) has been avoided in the last couple of decades due to their unsustainable nature. However, as shown in this review, such compounds can now be safely processed in microreactors and thus novel applications and opportunities can be envisioned. Automated and self-optimizing flow processes have been developed in the past and reduce the manual labor to an absolute minimum. It would be very exciting to see when the first ChemDraw structure can be inserted in a computer, after which the computer prepares the compound for us. Currently, these are still wild and almost science fiction ideas but these remarkable times show us already that we are able to overcome challenging problems which were decades ago impossible to do.

In order to overcome the remaining hurdles in chemistry, a multidisciplinary approach will probably be the best strategy to use. This includes intense collaborations between academia and industry. In times of dropping funding opportunities, support from the industry becomes even more vital to address the challenges of the future. This represents not only financial support but also implementation of these novel technologies in existing plants, which will facilitate its widespread use, reduce the overall cost of the technology and will stimulate new research efforts in real life examples.
# 7. List of acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HMF</td>
<td>5-Hydroxymethylfurfural</td>
</tr>
<tr>
<td>AgNP</td>
<td>Silver nanoparticle</td>
</tr>
<tr>
<td>AOP</td>
<td>Advanced Oxidation Process</td>
</tr>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>APTES</td>
<td>(3-Aminopropyl)triethoxysilane</td>
</tr>
<tr>
<td>ATRA</td>
<td>Atom Transfer Radical Addition</td>
</tr>
<tr>
<td>BDE</td>
<td>Bond Dissociation Energy</td>
</tr>
<tr>
<td>bmim</td>
<td>1-Butyl-3-Methylimidazolium</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxy carbonyl</td>
</tr>
<tr>
<td>BPR</td>
<td>Back Pressure Regulator</td>
</tr>
<tr>
<td>bpy</td>
<td>2,2'-bipyridine</td>
</tr>
<tr>
<td>Cbz</td>
<td>Carboxybenzyl</td>
</tr>
<tr>
<td>CF&lt;sub&gt;3&lt;/sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>Triflyl Chloride</td>
</tr>
<tr>
<td>CFL</td>
<td>Compact Fluorescent Lamp</td>
</tr>
<tr>
<td>CuAAC</td>
<td>Copper(I)-Catalyzed Azide-Alkyne Cycloaddition</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
</tr>
<tr>
<td>DCA</td>
<td>9,10-dicyanoanthracene</td>
</tr>
<tr>
<td>DCE</td>
<td>Dichloroethane</td>
</tr>
<tr>
<td>d.e.</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMA</td>
<td>N,N-Dimethylacrylamide</td>
</tr>
<tr>
<td>DMBP</td>
<td>4,4'-Dimethoxybenzophenone</td>
</tr>
<tr>
<td>dmp</td>
<td>2,9-Dimethyl-1,10-Phenanthroline</td>
</tr>
<tr>
<td>Dpg</td>
<td>3,5-dihydroxyphenylglycine</td>
</tr>
<tr>
<td>e.e.</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FEP</td>
<td>Fluorinated ethylene propylene</td>
</tr>
<tr>
<td>FTU</td>
<td>Fluorescein Thiourea</td>
</tr>
<tr>
<td>GAG</td>
<td>Glycosaminoglycan</td>
</tr>
<tr>
<td>HMF</td>
<td>5-Hydroxy-5-(Hydroxymethyl)-Furan-2(5 H)-one</td>
</tr>
<tr>
<td>HEMA</td>
<td>2-Hydroxyethyl Methacrylate</td>
</tr>
<tr>
<td>HIPE</td>
<td>High Internal Phase Emulsion</td>
</tr>
<tr>
<td>ID</td>
<td>Internal diameter</td>
</tr>
<tr>
<td>MFFD</td>
<td>Microfluidic Flow-Focusing Device</td>
</tr>
<tr>
<td>MMA</td>
<td>Methyl Methacrylate</td>
</tr>
<tr>
<td>mpg-C&lt;sub&gt;3&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Mesoporous Graphitic Carbon Nitride</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NFSI</td>
<td>N-Fluorobenzenesulfonimide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>PDI</td>
<td>Polydispersity Index</td>
</tr>
<tr>
<td>PDMS</td>
<td>Polydimethylsiloxane</td>
</tr>
<tr>
<td>PG</td>
<td>Protecting Group</td>
</tr>
<tr>
<td>photo-CRP</td>
<td>Photo-Controlled Radical Polymerization</td>
</tr>
<tr>
<td>PIB</td>
<td>Polyisobutylene</td>
</tr>
<tr>
<td>PFA</td>
<td>Perfluoroalkoxy alkane</td>
</tr>
<tr>
<td>PMI</td>
<td>Process Mass Intensity</td>
</tr>
<tr>
<td>PMMA</td>
<td>Poly(Methyl Methacrylate)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>PNIPAM</td>
<td>Poly(N-Isopropylacrylamide)</td>
</tr>
<tr>
<td>poly(HEMA-MMA)</td>
<td>Poly(Hydroxyethyl Methacrylate-Methyl Methacrylate)</td>
</tr>
<tr>
<td>POM</td>
<td>Polyoxometalate</td>
</tr>
<tr>
<td>ppy</td>
<td>2-Phenylpyridinato-C$_2$N</td>
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<tr>
<td>PSTY</td>
<td>Photocatalytic Space-Time Yield</td>
</tr>
<tr>
<td>PTSA</td>
<td>p-Toluensulfonic Acid</td>
</tr>
<tr>
<td>PU</td>
<td>Polyurethane</td>
</tr>
<tr>
<td>PVA</td>
<td>Polyvinyl Alcohol</td>
</tr>
<tr>
<td>PVSZ</td>
<td>Polyvinylsilazane</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive Oxygen Species</td>
</tr>
<tr>
<td>scCO$_2$</td>
<td>Super critical CO$_2$</td>
</tr>
<tr>
<td>SET</td>
<td>Single Electron Transfer</td>
</tr>
<tr>
<td>SPPS</td>
<td>Solid Phase Peptide Synthesis</td>
</tr>
<tr>
<td>STY</td>
<td>Space-Time Yield</td>
</tr>
<tr>
<td>TBADT</td>
<td>Tetrabutylammonium Decatungstate</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra-N-Butylammonium Fluoride</td>
</tr>
<tr>
<td>t-bpy</td>
<td>tert-Butyl Bipyridine</td>
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<tr>
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<td>2,2,6,6-Tetramethylpiperidine Nitroxide</td>
</tr>
<tr>
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<td>Trifluoroacetic Acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>Trifluoroacetic Anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
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<td>TMEDA</td>
<td>N,N,N',N'-Tetramethyl-1,2-diaminoethylene</td>
</tr>
<tr>
<td>TMSCN</td>
<td>Trimethylsilyl cyanide</td>
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<td>TPGDA</td>
<td>Tripropylene glycol diacrylate</td>
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<tr>
<td>TPP</td>
<td>Tetraphenylporphyrin</td>
</tr>
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<td>Thioxanthone</td>
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<tr>
<td>UV</td>
<td>Ultraviolet light</td>
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<tr>
<td>VIS</td>
<td>Visible light</td>
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<tr>
<td>XantPhos</td>
<td>4,5-Bis(Diphenylphosphino)-9,9-Dimethylxanthene</td>
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</tbody>
</table>
ACKNOWLEDGMENT

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