

Flow photochemistry

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Review

Flow Photochemistry: Shine Some Light on Those Tubes!

Carlo Sambigiò¹ and Timothy Noël^{1,@,*}

Continuous-flow chemistry has recently attracted significant interest from chemists in both academia and industry working in different disciplines and from different backgrounds. Flow methods are now being used in reaction discovery/methodology, in scale-up and production, and for rapid screening and optimization. Photochemical processes are currently an important research field in the scientific community and the recent exploitation of flow methods for these methodologies has made clear the advantages of flow chemistry and its importance in modern chemistry and technology worldwide. This review highlights the most important features of continuous-flow technology applied to photochemical processes and provides a general perspective on this rapidly evolving research field.

Microflow Technology and Photochemistry: A Perfect Match

The use of light to promote chemical reactions has been exploited since the 18th century, but only recently a resurgence has been observed in synthetic organic chemistry, in particular due to the development of visible-light photoredox catalysis [1–5]. All transformations involving light (e.g., Figure 1A–D) must consider, besides classical chemical parameters (i.e., reaction conditions), the photophysical aspects of the sensitizer (see Glossary)/photocatalyst (when used), and the reactor design. The latter, although often neglected by chemists, is a critical aspect for the outcome of the studied chemical transformation. This includes, for example, the size, shape, and material of the reaction vessel, the characteristics and positioning of the light source(s), and heat-transfer properties, particularly when high-intensity lamps are used [6,7]. The engineering and technological aspects of photochemical processes are often at the basis of the irreproducibility and non-scalability of such transformations.

According to the Beer–Lambert law, light transmittance decreases exponentially with the distance from the light source (Figure 1F). For a standard batch reactor (diameter at least in the centimeter range), light intensity decreases considerably from the flask walls to the middle of the reaction mixture, resulting in slow reactions and nonhomogeneous irradiation of the reaction mixture. Performing photochemical reactions in microchannels (ID < 1 mm) allows a higher and more homogeneous photon flux, resulting in shorter reaction times and consequently less side-product formation due to over-irradiation, often observed in batch [8,9]. Another advantage of microflow chemistry, correlated with the large surface:volume ratio, is improved heat and mass transfer, with the possibility to perform mass-transfer-limited multiphasic reactions efficiently [10]. Reactive chemicals and intermediates can be handled more safely in flow than in batch, as no accumulation of dangerous components occurs within the confined reactor volume due to the continuous nature of the process. Together, these result in often faster, safer, and higher-yielding reactions, with the possibility to perform reactions under conditions impossible in batch (high P/T; so-called novel process windows [11]), and make microflow systems a valid alternative to traditional batch chemistry for many purposes. Moreover, the ease of automation and coupling with inline analysis, separation, and purification methods allows the development of continuous multi-step synthesis and automated production platforms. These advantages are nicely showcased in the growing use of flow in the pharmaceutical industry [12–16].

The typical flow setup for photochemical processes comprises transparent tubing made of perfluorinated materials (e.g., PFA, ETFE) efficiently coiled around a light source [17], or surrounded by it, for uniform irradiation (Figure 1E). A more expensive alternative is the use of flat, transparent microreactors with engraved microchannels irradiated from both sides of the plate.

Highlights

(Solar) Photochemistry in flow benefits from better, more uniform irradiation than in batch, resulting in shorter, more selective reactions and efficient scale-up.

Photochemical multiphasic reactions fully exploit the photon- and mass-transfer enhancement properties offered by flow chemistry.

Flow photochemistry is gaining popularity in the pharmaceutical industry due to the many advantages demonstrated in the chemistry itself and the large potential for automation.

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In this review, we present recent advances in specific areas of flow photochemistry for which the use of flow has large advantages compared with traditional batch chemistry.

Before the Flow: Traditional versus Photochemical Methods

Photochemistry has emerged in many cases as an alternative or complementary way to promote chemical reactions. For example, a recent review by Stephenson nicely discusses the complementarity between traditional (thermal) chemistry and photoredox processes in the fields of cross-coupling reactions and alkene functionalization [1]. For instance, in the first case, more stubborn substrates in thermal reactions (e.g., alkyl halides) can be efficiently employed under photoredox conditions, or limitations in oxidative additions or transmetalation steps can be overcome. These reactions are of industrial importance and are being increasingly studied in flow, as shown in this review (e.g., Figures 3E, 4C, and 5E). For alkene functionalization, different mechanisms become available in photoredox, allowing complementarity and broadening of the substrate scope.

Photochemistry is also a milder way to generate reactive intermediates otherwise obtained under thermal conditions or with specific chemicals. An example of this is the generation and reaction of singlet oxygen, a commonly encountered benchmark reaction in flow photochemistry (Figures 2A–D, 3E, and 4C) and critical in wastewater treatment. In this case, photochemistry is the traditional way to generate singlet oxygen, but other methods are available starting from alkaline metal oxides and hydrogen peroxide (dark singlet oxygen); 2 mol of peroxide generate 1 mol of singlet oxygen, reducing the atom economy of the reaction and producing water, a known quencher of singlet oxygen. Furthermore, the reaction occurs under alkaline conditions, which might interfere with the reagents, and requires often-toxic metal oxides as catalysts [18]. In comparison, the photochemical generation of this intermediate requires only catalytic amounts of a photocatalyst and oxygen.

Radical trifluoromethylation reactions are another important class of reactions investigated in flow photochemistry (Figures 2A and 5B). The trifluoromethyl radical can alternatively be generated by a variety of reagents by the action of stoichiometric oxidants or reductants. Examples are hydroperoxides (superstoichiometric amounts), often in the presence of ca. 10% of Fe or Cu catalyst for their activation. Alternatively, stoichiometric TEMPO derivatives have also been used in uncatalyzed reactions. While some of these protocols can be performed at room temperature, often the expensive and atom-uneconomic Togni or Umemoto reagents are used, and the use of ca. 10% of metal catalysts make several of these reactions considerably more wasteful than a photoredox process [19].

Multiphasic Systems in Continuous-Flow Photochemistry

Gas reagents are often cheaper, more sustainable, and more atom-economic than their liquid or solid alternatives and therefore represent the best option from a green-chemistry perspective. Gases are, however, difficult to handle in batch. Filling the headspace of a batch reactor with a gas in unpressurized systems results in serious mass-transfer limitations, while pressurized systems present serious safety concerns in case of toxic or reactive gases, and/or require the use of steel flasks (e.g., autoclaves) that prevent the use of light for photochemical reactions. Microflow chemistry represents a better alternative to these methods, as it avoids headspace and high amounts of gas in each section of the reactor. Moreover, microflow reactors can be easily pressurized in a safe manner, providing good mass transfer and large, well-defined interfacial areas without compromising safety or irradiation [20–22]. Several methods for gas–liquid reactions in flow have been developed [23], generally suitable for photochemical conditions. It is worth noting that the transparent material of the reactor limits the usable pressure range, although relatively large pressures are easily tolerated in transparent microflow tubing.

Solid–liquid reactions are, on the contrary, a constant challenge in flow chemistry, as feeding and pumping solid material in a continuous manner is not straightforward. Even initially homogeneous reactions where solid intermediates or products are formed are difficult due to clogging of the microchannels [24–26]. While some tricks exist to deal with clogging (e.g., sonication [27]), this is constant source of trouble for flow chemists. However, such processes are important in modern chemistry,

Glossary

Artemisinin: an important drug for malaria treatment.

Beer–Lambert law: this law correlates the attenuation of light with the characteristics and concentration of a specific absorbing material and the distance from the light source (optical path). It states that the fraction of light transmitted (transmittance) through the material decreases with increasing concentration and optical path.

Concentrating (parabolic) collectors: devices that make use of mirrors or lenses to focus and concentrate solar irradiation from a large area to a single focal point or limited area.

Continuous stirred-tank reactor (CSTR): a common type of continuous reactor used in industry. It comprises a large-volume vessel equipped with a stirrer, where the reagents are continuously pumped in and the products continuously removed.

Design of experiments (DoE): a statistical approach to model and predict the effect of reaction parameters on the output of the reaction. Starting from little initial data, it leads to full optimization with a limited number of experiments.

Laser: a device that emits a coherent beam of light (i.e., all of the electromagnetic waves have the same phase and frequency), typically monochromatic and of high intensity.

Novel process windows: an approach to boost chemical reactions in flow by using harsh reaction conditions that would normally be impossible in batch. Examples are high temperatures (above boiling point) and pressures, high concentrations (or solvent free), and explosive conditions.

Photon flux: defined as the number of photons per second per unit area.

Sensitizer: a molecule that absorbs energy in form of light and then transfers it to a reagent, thus initiating a reaction.

Singlet oxygen: an excited state of molecular oxygen generated by light irradiation and more reactive with organic compounds than triplet oxygen (ground state).

particularly heterogeneous catalysis due to its sustainable aspects (e.g., catalyst recycling, ease of separation). Because of this, significant effort has been expended towards transferring these reactions into flow, and a few methods have been developed to facilitate this task.

Segmented flow (Taylor flow or slug flow) is the simplest method to perform gas–liquid transformations, does not require any special flow equipment, and is therefore the most widely used approach. From a pure gas and pure liquid feed, a simple T/Y-shaped mixer is required to generate a liquid flow intercalated by gas bubbles, with a large contact surface between the two phases (Figure 2A). The internal recirculation movement of the gas and liquid segments ensures efficient mixing and diffusion of the gas inside the liquid. Many types of photochemical reactions have been performed employing this strategy, including trifluoromethylations with CF_3I [28,29], C–H oxidations with O_2 [30], and carboxylations with CO_2 [31,32]. Another interesting example of gas–liquid reaction under segmented

Stern–Volmer analysis: while fluorescence-quenching tests are used to determine whether a substrate or reagent is able to quench a photoredox catalysts (i.e., able to be oxidized or reduced), Stern–Volmer measurements provide quantitative information about the quenching.

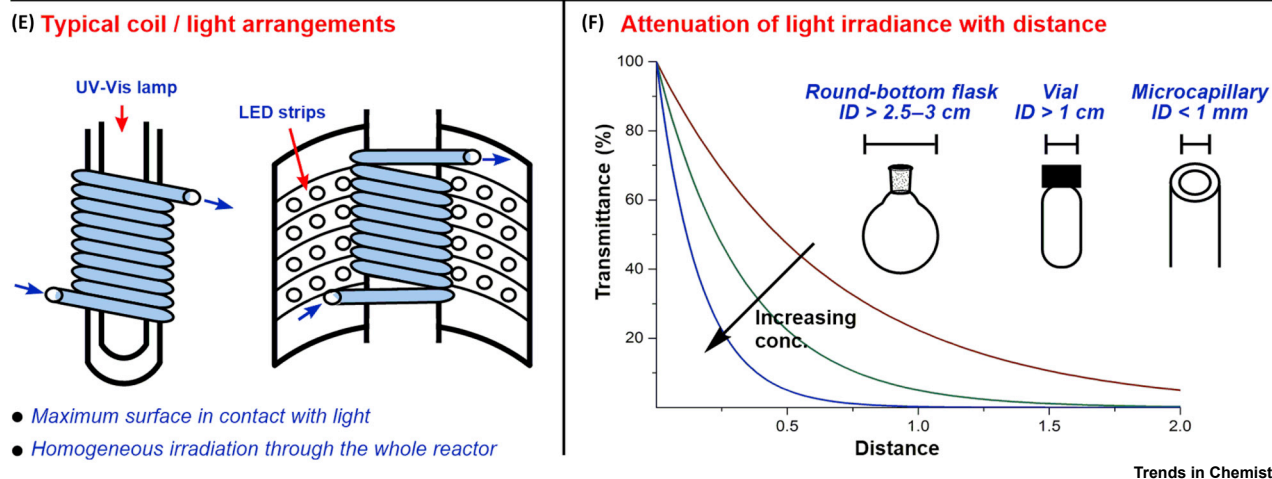
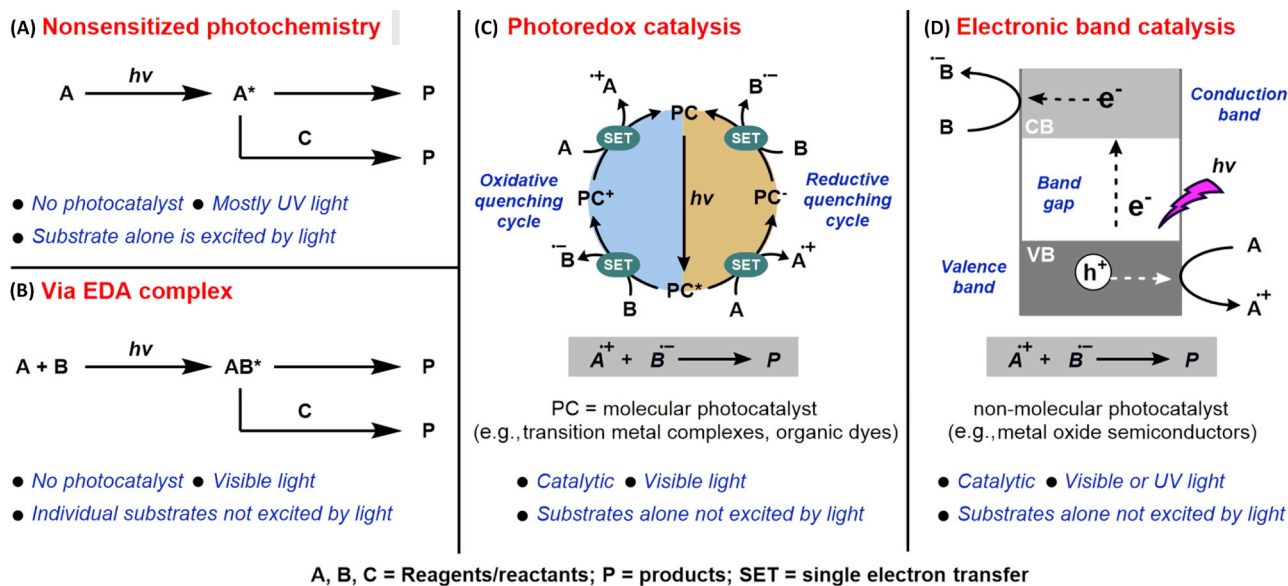
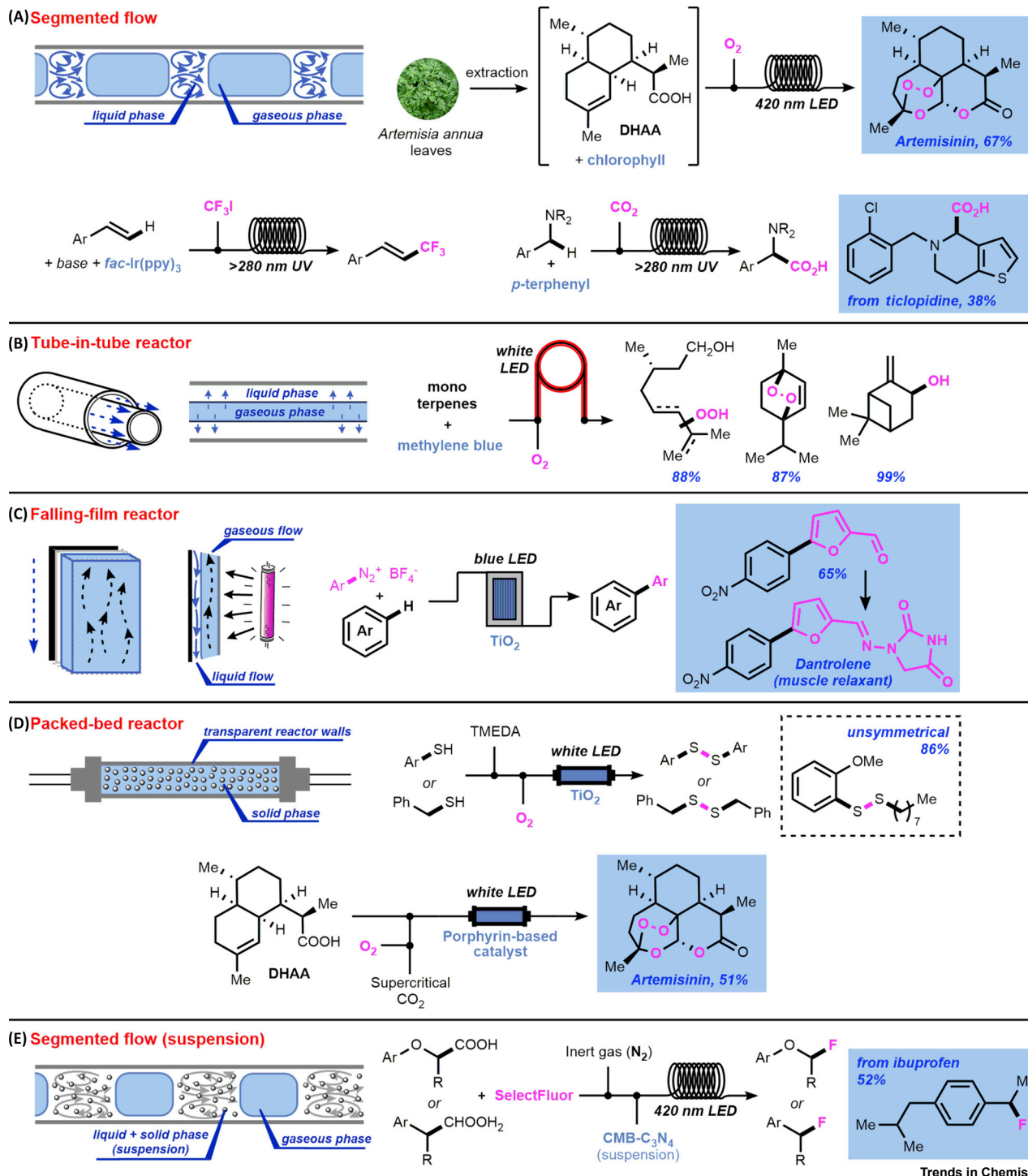


Figure 1. Flow Photochemistry: A Perfect Match.

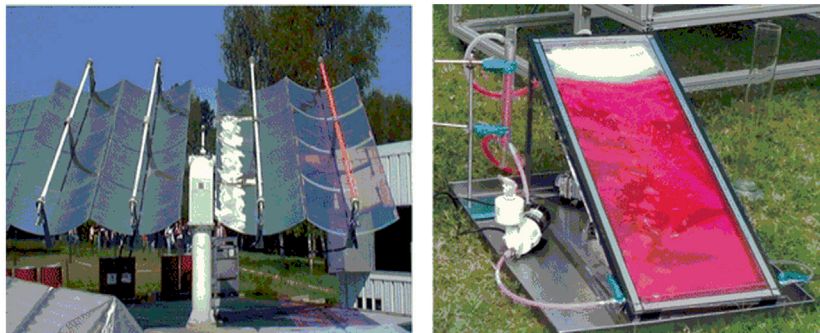
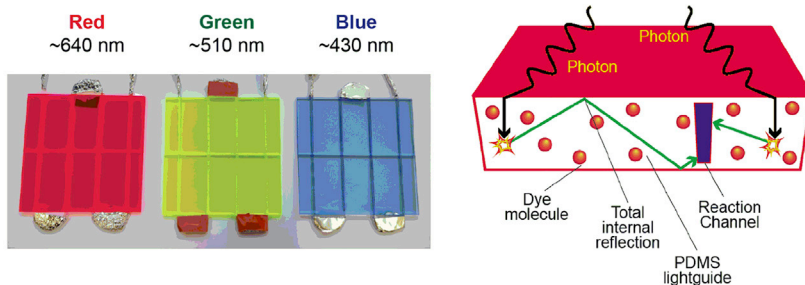
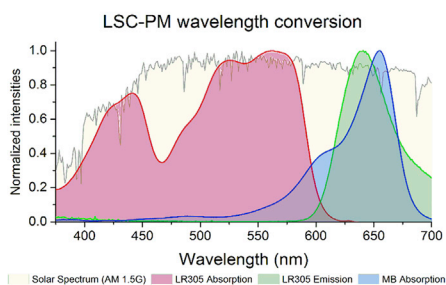
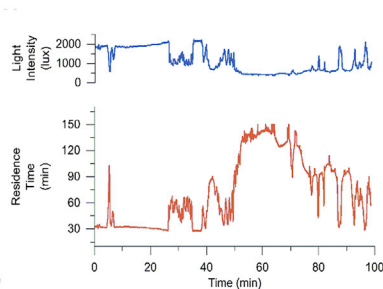
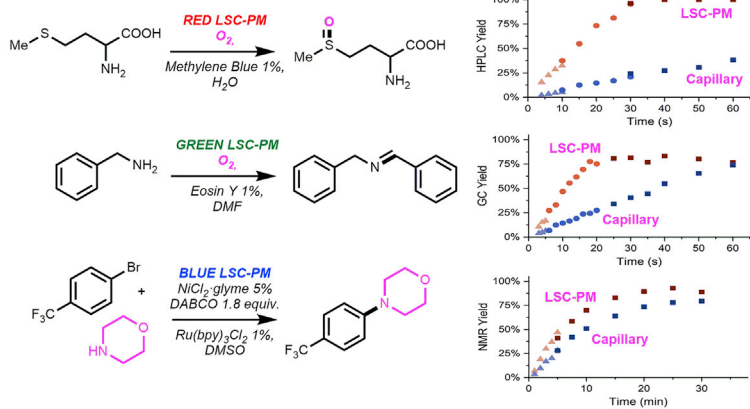
(A) Nonsensitized photochemical transformations; (B) photochemistry via electron donor–acceptor (EDA) complex; (C) concept of photoredox catalysis; (D) photocatalysis by semiconductors and analogs; (E) typical setups for flow photochemistry; (F) attenuation of light irradiance with distance from light source.



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Figure 2. Multiphase Systems in Flow Photochemistry.

(A) Gas-liquid segmented flow [28,31,33]; (B) tube-in-tube reactor for gas-liquid reactions [38]; (C) falling-film (micro)reactor [41]; (D) packed-bed reactor [47,48]; and (E) segmented flow for solid-liquid reactions [53].

(A) Parabolic concentrators and flat bed reactor**(B) Red, green and blue LSC-PMs and working principle****(C) Down-conversion in red LSC-PM****(D) Residence time adjustment vs light intensity****(E) LSC-PMs vs capillary for solar photochemistry**

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flow conditions is the synthesis of the antimalarial drug **artemisinin** via photogenerated singlet oxygen oxidation directly from extracts of the plant *Artemisia annua*, containing both the precursor of this drug [dihydroartemisinic acid (DHAA)] and the chlorophyll photocatalyst, demonstrated by Gilmore [33].

An alternative to segmented flow is the tube-in-tube reactor (developed by Ley [34]) comprising two concentric tubes filled respectively with liquid solution and gas and separated by a gas-permeable membrane. The gas permeates the membrane and diffuses homogeneously into the liquid (Figure 2B). This reactor has been used primarily for thermal reactions, or as a method to presaturate a solution with gas prior to a photochemical reaction [35–37]. However, as the tubes can be made of transparent materials, this method is also directly suitable for photochemical applications, as demonstrated by Park and colleagues for the photooxygenation of monoterpenes via singlet oxygen [38].

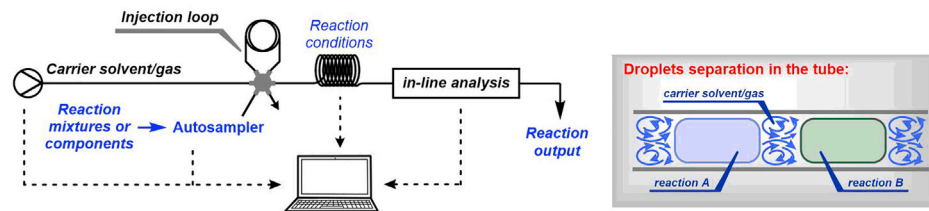
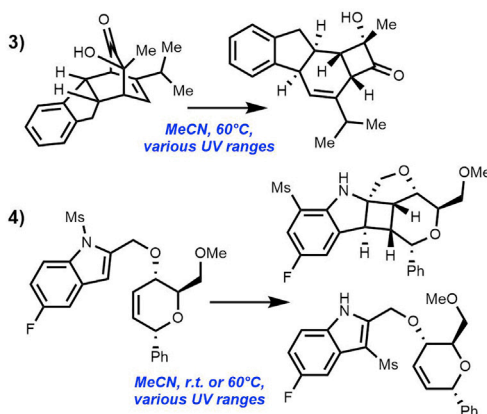
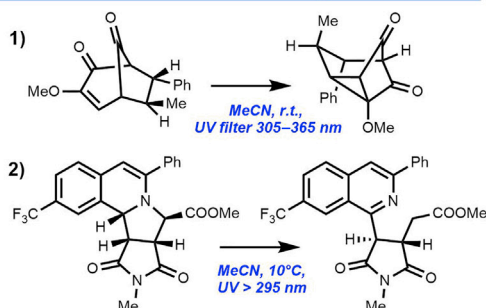
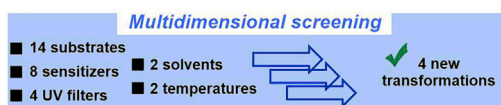
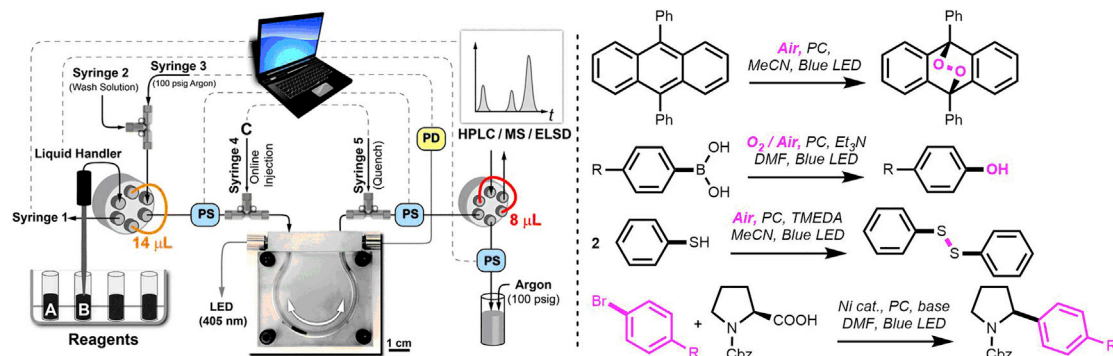
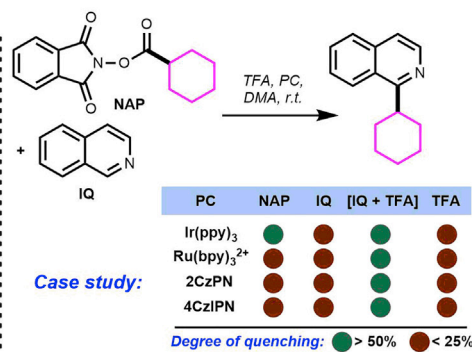
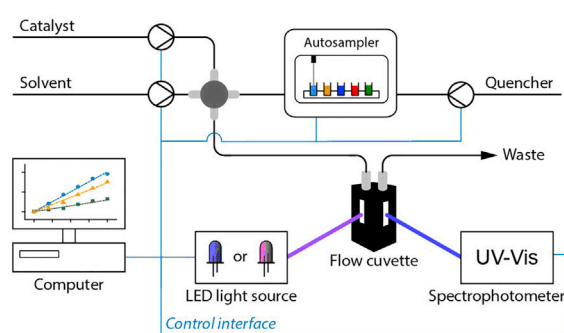
Falling-film microreactors are miniaturized reactors that can be adapted to a variety of gas–liquid transformations. In a typical setup, a liquid phase is injected into the microreactor from the top, forming a thin layer of liquid (film), while a gas is injected in counterflow from the bottom, ensuring increased contact time (Figure 2C). A transparent window allows irradiation for photochemical transformations. Applications of falling-film reactors in synthesis and catalysis are relatively rare, but a few recent studies on their use in photooxygenation reactions have been reported by Oelgemöller and Rehm [39,40]. These reactors are, interestingly, also suitable for heterogeneous catalysis. An interesting example was reported by Rehm and Rueping, who studied a TiO₂-catalyzed photochemical coupling between diazoarenes and heterocycles operating under blue-light irradiation [41]. The reactor walls were coated with the solid catalyst, with an inert (rather than reactive) gas flowing counter current. The TiO₂ catalyst, normally nonabsorbing in the visible region, was activated for blue-light absorption via ligation with the diazocompound, as shown previously [42].

The coating of microreactors, as above, or tubular reactors [43,44] is a common strategy to promote heterogeneous reactions without feeding the solid continuously into the reactor. However, this requires considerable preparation and analysis time to immobilize the catalyst. Another method that can be used for both solid reactants and catalysts is the use of packed-beds. For photochemical applications, the reactor must be made of transparent material, and care should be taken to minimize the pressure drop over the bed. Whereas packed-beds or similar have been employed in wastewater treatment [45,46], few synthetic photochemical applications have appeared. Interesting examples are the synthesis of artemisinin from DHAA with supercritical CO₂ and O₂ feeds using a packed-bed of a porphyrin catalyst, reported by George, Poliakoff, and Rossen [47], and the TiO₂-catalyzed synthesis of disulfides under aerobic conditions, reported by Noël [48]. The TiO₂ was here activated for visible-light absorption via ligation with TMEDA.

The feeding of solid material into a flow reactor can be performed via the ‘slurry-Taylor’ process, which involves pumping a suspension through the reactor, alternating it with an inert solvent or gas; a segmented flow is then obtained that prevents solid particles from depositing in the reactor, instead being pushed forwards through the tubing [49–51]. The mixing within the suspension segments promotes the reaction, similarly to the gas–liquid version. Besides applications in singlet oxygen chemistry [52], Gilmore and Seeberger recently exploited this method for a (decarboxylative) fluorination catalyzed by a carbon nitride catalyst [53]. The combination of continuous stirring and

Figure 3. Solar Photochemistry.

(A) Examples of parabolic concentrators (left) and a flat-bed reactor (right). Adapted, with permission, from [56]. (B) Luminescent solar concentrator-PhotoMicroreactor (LSC-PM) and basic working principle. Adapted, with permission, from [61,63]. (C) Down-conversion of solar light to 640-nm red light in red LSC-PM. Adapted, with permission, from [61]. (D) Automated residence time adjustment according to light intensity in LSC-PM. Adapted, with permission, from [63]. (E) Reactions in solar simulator: comparison of LSC-PM and standard microchannel reactor under identical conditions. Adapted, with permission, from [63].

(A) Screening platforms via segmented flow**(B) Reaction discovery via multidimensional screening****(C) Photoredox optimization for via segmented oscillatory flow****(D) Automated quenching screening and Stern-Volmer analysis**

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the use of dense ionic-liquid solvent were critical to maintaining the solid catalyst in suspension prior to injection into the reactor.

Heterogenization of homogeneous catalysts to prevent degradation and facilitate separation is also a viable alternative. Dreesen, Monbaliu, and Heinrichs demonstrated this concept by anchoring a photocatalyst to silica nanoparticles for photooxygenation reactions [52]. A very fine colloidal suspension was obtained and easily pumped through the reactor without recourse to a slurry-Taylor.

Solar Photochemistry

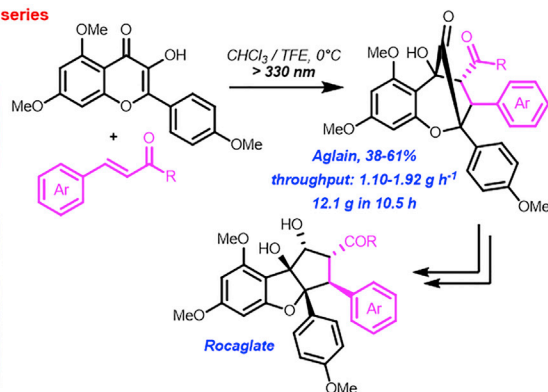
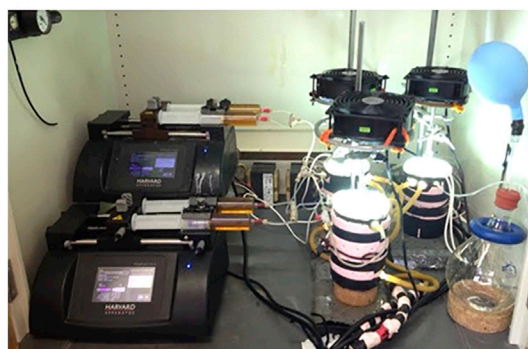
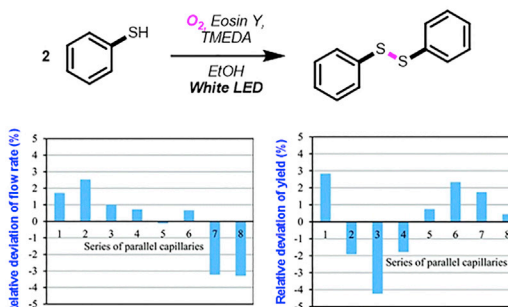
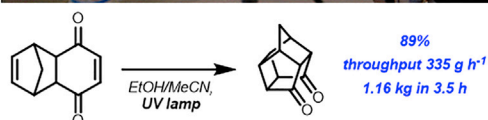
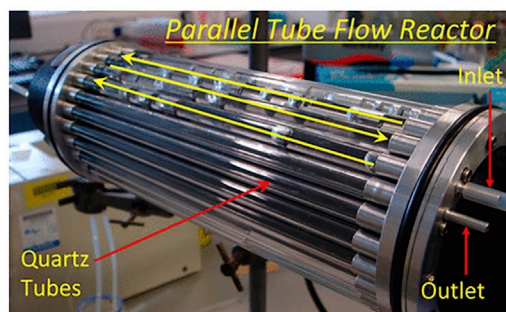
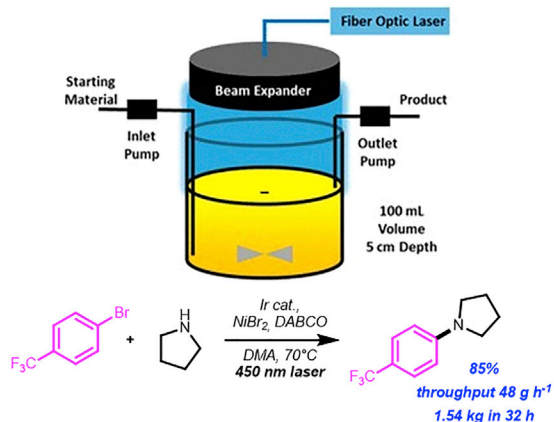
Light is typically referred to as a green, traceless reagent in photochemical reactions. Although this is theoretically true, artificial light sources (requiring electricity primarily produced from fossil fuels) – often energy-inefficient low- or high-intensity lamps – are typically used to supply the required photons. The shift to a more sustainable and really ‘traceless’ photochemistry can be accomplished by using sunlight as a natural light source. As it contains UV, visible, and IR light, sunlight is theoretically a suitable light source for a variety of transformations. The rediscovery of sunlight has recently led to diverse research investigations and many photochemical transformations have been performed under the sun [54–56]. However, the polychromatic nature of sunlight is also a downside, as it may result in nonselective transformations. Another important limitation is the nonhomogeneous solar irradiation with time (e.g., seasonal/weather change, day/night alternance) and space (e.g., geographic region), which prevents reliability, reproducibility, and ultimately its application to the manufacturing of chemicals on an industrial level.

When dealing with solar photochemistry, the most important aspects of the process are constituted by reactor design and photon-harvesting techniques, critical for process performance. Although solar photochemical reactions can be performed in batch using standard laboratory glassware [57], flatbed reactors or tubular reactors featuring **concentrating** (or nonconcentrating) **parabolic collectors** (Figure 3A) are commonly used, especially for the treatment of wastewater, which is currently still the main application of solar photochemistry [58,59]. These devices are typically used under flow conditions and the reaction mixture is recirculated to ensure high conversions.

Luminescent solar concentrators (LSCs) are a relatively new type of solar concentrators. LSCs comprise a transparent polymer plate doped with fluorescent dyes (luminophores) that, after absorbing radiation of certain wavelengths, release part of the energy in form of lower-energy radiation (down-conversion) while the rest is transmitted through the plate. The luminescent photons travel through the LSC to its edges, where the resulting concentrated light is typically collected for photovoltaic applications [60]. However, if the emitted light matches the absorption characteristics of a photocatalyst, this material can be used to promote photocatalytic reactions by flowing a reaction mixture through microchannels embedded in the LSC. The concept of a LSC-PhotoMicroreactor (LSC-PM) (Figure 3B) was demonstrated by Noël and Debije in 2017 using a microchannel-engraved plate doped with a red-light-emitting dye (LR305) for reactions using either artificial or solar light. The emitted light matched the absorption of the photocatalyst methylene blue (MB) (Figure 3C), which was used to catalyze photo-oxidation reactions [61]. To address the issue of variable radiance due to passing clouds, a light sensor was connected to the edge of the LSC plate to measure in real time the amount of light falling onto the reactor. By converting this signal to a certain flow rate, the authors were able to continuously adjust the residence time so that the conversion could be maintained at a constant value during the whole experiment (Figure 3D) [62]. An improved LSC-PM design with better mechanical, chemical, and photophysical properties was later reported. By incorporating

Figure 4. Automated Screening Platforms for Flow Photochemistry.

(A) Basic working principle and setup for screening platforms via segmented flow. (B) Beeler’s reaction discovery platform via multidimensional screening. Adapted, with permission, from [78]. (C) Jensen’s oscillatory system for photoredox reaction study and examples of reactions investigated. Adapted, with permission, from [79–81]. (D) Noël’s automated procedure for photoredox quenching screening and Stern–Volmer analysis. Adapted, with permission, from [82].

(A) Scaled-up synthesis of aglain with three reactors connected in series**(B) Kilo-scale trifluoromethylation of arenes****(C) Numbering-up strategy for segmented flow photochemistry****(D) Firefly reactor****(E) Laser photoredox in CSTR**

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red-, green-, and blue-emitting dyes, its use was expanded to various visible-light-driven photochemical transformations, ranging from singlet oxygen oxidation to dual photocatalytic reactions and trifluoromethylation chemistry [63]. A comparison with non-doped reactors under otherwise identical conditions nicely demonstrated the enhancement of the reaction performance of the LSC-PMs (Figure 3E).

Considering its renewable nature, the exploitation of solar light for chemical synthesis should (will) increase at some point in the future. For this to happen, however, effort should be directed towards finding solutions to the limitations of solar light (polychromatic nature, variability with weather, and day–night alternance). While filters can be used to cut off certain wavelengths, the polychromatic nature of solar light should rather be used advantageously. One way would be to employ down-conversion, as illustrated for the LSC-PM, or even up-conversion strategies, to exploit the large amount of IR radiation coming from the sun [54]. Besides the intrinsic difficulties of these technologies, the development of specific reactors to selectively harvest IR light while transmitting other, undesired wavelengths from the solar irradiation will also be an important part of the necessary research efforts.

In terms of variable irradiation, the control of flow rate to allow constant conversion over time was discussed above. Unfortunately, this method might not be suitable for large-scale processes (ideally production) because flow-rate variation at this scale will result in the variation of mass- and heat-transfer properties that are critical in a continuous process, and in variable productivity. An alternative might be the combination of solar light and artificial irradiation. This strategy has already been applied to photochemical air-purification processes to overcome day–night alternance, yielding promising results [64,65]. The artificial light source can, for better exploitation of solar energy, be powered via photovoltaic systems, an already existing technology that may be beneficial in this field.

Automated Screening Platforms for Flow Photochemistry

The ease of connection to inline analytical techniques [66] and the possibility to remotely control the individual components of a typical flow system (e.g., temperature/pressure controllers, pumps, injection valves, mass flow controllers) [67] makes flow chemistry amenable to automation. Many automated strategies for screening and optimization in flow, for both discrete (solvents, catalysts, ligands) and continuous (temperature, loading, time) reaction variables, can now be found in the literature. Similar automated systems can be employed for reaction discovery (by combining stocks of different reactants) and for the rapid synthesis of compound libraries, amply demonstrating the rapidity and versatility of flow systems for such purposes [68–71]. Inline analytics allow immediate evaluation of the reaction's outcome and combination with smart algorithms [machine learning, artificial intelligence, and **design of experiments (DoE)**] enables self-optimization protocols [72,73], reducing the number of experiments necessary to optimize complex systems. Many of these systems are based on segmented flow strategies, where droplets (segments) of the reaction mixture (each with its own unique reaction conditions) are pushed through the reactor, alternated by inert gases or solvents to avoid cross-contamination (Figure 4A) [69,74–76].

Although these methods are currently widely employed, few examples of automated screening/optimization platforms have appeared specifically for photochemical applications. An early example was developed by Beeler and Jensen for UV-promoted reactions in a glass microreactor [77] and subsequently applied to a partially automated multidimensional screening for reaction discovery [78]. From a combination of 14 substrates, eight photosensitizers, four UV filters, two solvents, and two temperatures, four new reactions were discovered, including rearrangements, ring openings, and cycloadditions (Figure 4B).

Figure 5. Scale-Up Strategies and Designs.

(A) Scale-up of aglain synthesis with three reactors in series. Adapted, with permission, from [87]. (B) Kilogram-scale trifluoromethylation of arenes. Adapted, with permission, from [90]. (C) External numbering-up of a segmented flow photoreaction. Adapted, with permission, from [92]. (D) Firefly reactor. Adapted, with permission, from [84]. (E) AbbVie's kilogram-scale continuous stirred-tank reactor (CSTR)–laser setup. Adapted, with permission, from [96].

More recently, Jensen reported a fully automated segmented oscillatory flow reactor for the study of different processes, screening a number of continuous and discrete variables within the same platform [79]. Here, each reaction droplet, instead of being pushed through the reactor, is oscillated back and forth in a short microchannel for the desired residence time, providing good mixing and reducing the reactor size. An efficient cooling system was also included to accurately control the temperature. This system was later combined with a high-power light-emitting diode (LED) source for the investigation of photoredox processes [80,81]. Parameters such as residence time, temperature, LED power, catalysts, and bases could be quickly screened for optimization purposes and library synthesis. The combination with automated LC-MS analysis and a self-optimizing algorithm, plus the possibility to scale-up reactions with the same platform, makes this a powerful and versatile system for many purposes.

A conceptually different application of automated flow-based platforms was reported by Noël and colleagues, who developed a protocol for automated fluorescence quenching screenings and **Stern–Volmer analysis** for photoredox processes [82]. These tests are often used in preliminary experiments in reaction discovery to identify potential substrates and reagents and to elucidate mechanistic aspects of photoredox processes. While continuously measuring the fluorescence of a photocatalyst solution via a flow cuvette, the different quenchers are injected into the flow at set intervals and the variation of fluorescence is measured, thus revealing the possible quenchers. For the Stern–Volmer analysis, the concentration of the quencher is changed by adjusting the flow rates and the fluorescence quenching is measured and automatically plotted by an in-house-developed algorithm.

Scale-Up Strategies and Designs

Due to the attenuation of light intensity with distance, scaling-up photochemical reactions by simply enlarging the reaction vessel, as for typical thermal reactions in the laboratory, is not an efficient method; the advantages of flow chemistry are here more evident than ever. Three main ways to scale-up flow reactions are used: (i) increasing the operation time of the reactor; (ii) increasing the throughput by increasing the flow rate and the length of the reactor; and (iii) using multiple reactors in parallel, often referred to as numbering-up [83]. It is worth mentioning that, for large-scale processes, heat management becomes critical, as considerable heat is generated by the light source (either longer operational time or increased number of light sources).

The first method is the most straightforward to use at a laboratory scale, does not require reoptimization of previously found reaction conditions, and does not result in changes of the flow properties. A limitation of this method is observed when tubing made of perfluorinated polymers is used under UV irradiation. This type of tubing is commonly used due to its flexibility and transparency, but prolonged exposure to UV might result in fouling (in turn lowering the transparency) [84–86] and/or mechanical damage [84], ultimately resulting in reaction inhibition or reactor replacement.

The second method is similar to the previous one. However, while in the first case the same flow rate, reactor length, and residence time are used, in the second case the flow rate and reactor length are directly multiplied to enable a higher throughput. The change in flow rate results in differences in the flow characteristics and the increased length results in greater pressure drops over the length of the reactor. The throughput of the reaction is therefore not always directly scaled-up (i.e., double reactor length does not give double product amount) and the yield might also change. Although further optimization might be required, this strategy is simple to apply and good results are typically obtained. A nice example has been reported by Beeler for the large-scale synthesis of analogs of the natural products aglain and rocaglate, obtained with 1.16-g h^{-1} throughput (Figure 5A) [87]. This technique is particularly useful in the case of commercial reactors with well-defined reactor lengths, which can be combined in series with minimum alteration to the system [88,89].

An example of a visible-light-promoted reaction scaled-up from batch is the trifluoromethylation of arenes using trifluoroacetic anhydride and pyridine-*N*-oxides as reagents, reported by Stephenson. In this case, 150 ml PFA tubing was coiled around a beaker where high-intensity LED lamps were

placed and the reaction mixture was pumped continuously for 48 h, resulting in 0.95 kg of trifluoromethylated product (productivity: 20 g h⁻¹; Figure 5B) [90].

Parallelizing strategies avoid long operational times and represent an interesting alternative for scale-up. Contrary to external numbering-up, which simply involves the simultaneous use of multiple complete reactor systems, internal numbering-up requires only a single feed that is then distributed through multiple reactor channels. This is a cheaper and space-saving solution but presents the significant challenge of uniformly distributing the flow in the various channels, a key factor for obtaining reproducible results. Further difficulties arise in case of gas–liquid reactions with segmented flow [91]. An interesting example has been reported by Noël and Su for the aerobic dimerization of thiophenol in an eight-microcapillary reactor (Figure 5C). Critical for good flow distribution was the generation of the segmented flow before the splitting. This provided a uniform distribution and little variation in the reaction yield over the eight microcapillaries [92,93]. A similar approach has been reported for the scale up of a LSC-PM for solar chemistry [94] and for a homogeneous UV-promoted [4+2] cycloaddition [95].

Other reactor designs specific for large-scale photoreactions have been reported in recent years. To solve the limitations associated with UV irradiation on fluorinated polymers, Booker-Milburn and co-workers designed a quartz-based compact flow reactor (the Firefly) able to process liters of solution and run continuously for long times, giving productivities of 21–335 g h⁻¹ for various UV-promoted cyclization reactions (Figure 5D) [84]. Another interesting continuous photoreactor design was reported by AbbVie scientists for a dual-catalytic Csp²-Csp³ decarboxylative coupling. In their hands, lasers proved advantageous compared with other light sources and convenient in terms of reactor design. A continuous stirred-tank reactor (CSTR) illuminated from above by an expanded high-intensity blue laser beam proved suitable for kilogram-scale reactions, with a productivity of 1.54 kg in 32 h (48 g h⁻¹; Figure 5E) [96].

Concluding Remarks

Flow chemistry is gaining popularity in both academic and industrial settings due to the many advantages in comparison with batch reactions for various transformations. As for multiphase and hazardous reactions, photochemical processes are (due to the Beer–Lambert limitation) another obvious candidate for transfer to continuous flow. Limitations in this field (see Outstanding Questions) are either intrinsic to flow technology (e.g., handling of solids) and photochemistry (e.g., variable solar irradiation) or derive from the combination of the two (e.g., reactor fouling/damage on prolonged UV irradiation). However, advances in chemistry, engineering, and material science hold great promise for the future of the field and possibly for its routine application in chemical production at industrial level. Finally, we would like to stress that flow chemistry is now a well-advanced and widespread discipline, and higher education institutions around the world should integrate it into their chemistry courses to promote the advancement of this multidisciplinary and rich field [97].

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Outstanding Questions

When will solar irradiation become a common light source to perform photochemical reactions?

When will the handling of solids become routine in microflow chemistry? A general approach to introduce heterogeneous reagents and catalysts and to deal with solid-forming reactions is urgently needed.

When will we see the first photocatalytic applications on scale in the pharmaceutical industry? Currently, test pilots are being built for photocatalysis, but a large-scale production facility is still missing.

When will flow chemistry become a mainstay in the educational program of any chemistry major? Currently, students are almost exclusively trained using batch labware (i.e., flasks and test tubes).

Many flow studies involve rather simple reactions and substrates, but complex, highly functionalized molecules of interest to the pharmaceutical industry are rarely investigated in flow. When will the field of total synthesis use flow chemistry more routinely? Our feeling is that education plays a key role here.

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