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Flow Photochemistry – a Green Technology with a Bright Future

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1.1 Introduction to Synthetic Organic Photochemistry

According to the International Union of Pure and Applied Chemistry (IUPAC), photochemistry is "the branch of chemistry concerned with the chemical effects of ultraviolet, visible, or infrared radiation" [1]. Owing to the multidisciplinary nature of light, photochemistry thus finds widespread applications in the fields of analytical, environmental, food, inorganic, material, medicinal, organic, pharmaceutical, polymer, and physical chemistry [2, 3]. In terms of organic synthesis, light energy is utilized to activate molecules within their chromophoric groups. For multichromophoric substrates, this activation can be selectively achieved [4]. The amount of energy required for activation corresponds to the wavelength of the light as expressed in the Planck relation (Equation 1.1) [5]:

$$E = h \times \nu = h \times c/\lambda = h \times c \times \tilde{\upsilon} \tag{1.1}$$

where E is the energy of light; h, the Planck constant; ν, the frequency; c, the velocity of light; λ, the wavelength; and $\tilde{\upsilon}$, the wavenumber.

The excited state reached can undergo a multitude of energy- as well as electron-transfer processes, which are commonly shown in a Jablonski diagram [6]. Deactivation processes are common and include fluorescence, phosphorescence, or internal conversion. Alternatively, the excited state energy can be utilized for chemical changes. Owing to the different structural and physicochemical properties of excited states, photochemical reactions can differ significantly from thermal reactions. There are three main photochemical processes (Scheme 1.1) [1]: direct excitation, photosensitization, and photoinduced electron transfer reactions. In the first case, light is absorbed by the substrate and its subsequent excited state can undergo a chemical transformation either on its own or by reaction with another (ground-state) molecule. In the second case, light energy is used to activate a photosensitizer (or photocatalyst) into its excited state. This excess of energy is consequently transferred to another substrate by collision. The latter reagent enters its corresponding excited state and can undergo further chemical changes. In the third reaction mode, an electron is transferred between the excited state of one compound and the ground state of another substrate. The corresponding radical-ion pair can

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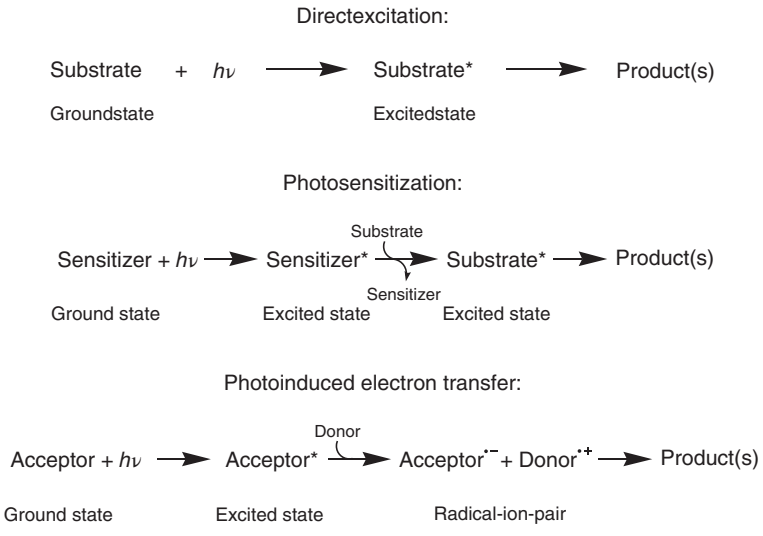


Scheme 1.1 Simplified main photoreaction modes.

undergo further transformation. In reality, photochemical pathways are often much more complex.

The extra energy provided via the excited state often enables chemical transformations that are thermally not feasible. Photochemistry is thus commonly applied to the synthesis of high-energy compounds such as strained rings [7, 8] or complex target molecules such as natural products [9–12]. More generally, photochemical transformations include additions, cleavages, isomerizations, rearrangements, and redox reactions. Many of these conversions proceed with high chemical yields and selectivities [13–16]. In contrast to these "productive chemical pathways," physical deactivation processes do not yield any "chemical products"; however, they are used extensively in analytical, environmental, forensic, medical, sensory, or spectroscopic sciences.

An important performance parameter in photochemistry is the quantum yield (Φ_λ), which describes the efficiency of a photochemical pathway at a given wavelength (Equation 1.2) [17]. This value is unity ($\Phi_\lambda = 1$) when each photon absorbed by the substrate yields to the formation of a product molecule. Much smaller quantum yields ($\Phi_\lambda \ll 1$) are typically observed owing to competing deactivation or quenching processes. This low efficiency thus necessitates exhaustive irradiation times although the final chemical yield may still be large. When light is only required for the initiation step as in chain reactions, quantum yields can become very large instead ($\Phi_\lambda \gg 1$). The quantum yield is typically determined experimentally using actinometry [18].

$$\Phi_\lambda = \frac{\text{amount of product formed}}{\text{amount of photons absorbed}} \tag{1.2}$$

Light absorption within a solution used in photochemical synthesis depends on the concentration of the chromophore and the thickness of the solution. This

dependency is expressed in the Beer–Lambert–Bouguer law (Equation 1.3) [19, 20]. Effective light penetration is thus limited to a narrow layer within the reaction mixture. To minimize this limitation, photochemical conversions are typically performed in high dilutions and in thin reaction vessels. In practice, this approach naturally results in large volumes of solvents.

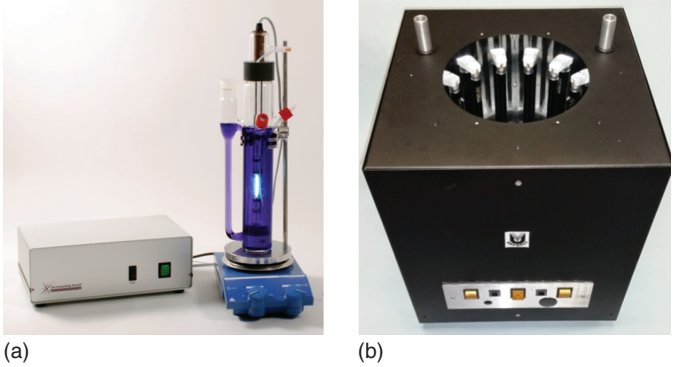
$$A = -\log T = -\log(I/I_0) = \varepsilon \times l \times c \tag{1.3}$$

where A is the absorbance of a solution at a given wavelength; T, the transmittance; I, the intensity of light exiting a medium; I_0, the intensity of light entering a medium; ε, the molar absorption coefficient; l, the thickness of solution traversed by light (path length); and c, the molar concentration of absorbing species.

1.2 Conventional Batch Photochemistry

1.2.1 Batch Photochemical Technology

Two general types of reactor systems are commonly used for preparative photochemistry on laboratory scales (Figure 1.1): immersion-well and chamber reactors [21, 22]. The two systems typically utilize different light sources [23]. The former incorporates a single low-, medium-, or high-pressure mercury lamp within a double-walled immersion well at its center. The reaction medium surrounds the lamp in a separate reaction vessel. This inside-out irradiation arrangement allows for an effective utilization of light. The entire setup can be operated safely in an enclosing cabinet. Merry-go-round setups with rotating test tubes around an immersion well have also been developed and allow for space-efficient parallel photoreactions. In contrast, chamber reactors combine an external array of fluorescent tubes with internal reaction vessels such as test tubes or Schlenk flasks. This outside-in configuration allows for multiple reaction containers to be used. Cooling is provided by internal fans or by



(a) (b)

Figure 1.1 (a) Immersion-well reactor system equipped with a 150 W medium-pressure mercury lamp. (Reproduced with permission of Peschl Ultraviolet GmbH, Germany.) (b) Chamber reactor equipped with 16 × 8 W UVA fluorescent tubes. (Reproduced with permission of Southern New England Ultraviolet Company, USA.)

inserting cooling fingers into the reaction vessels. Specialized merry-go-round accessories can be placed inside the reactor chamber as well. In typical research laboratory practice, the total reaction volume is limited to below 1 l in both devices. Both reactor types are well established and in widespread use.

More advanced photoreactor systems are falling-film [24], "liquid-bell" [25], or spinning-disk reactors [26, 27]. Multilamp immersion well or specialized thin-film reactors are used on industrial scales [28].

1.2.2 Photochemistry and Green Chemistry

Owing to their specialized operating features and protocols, preparative photochemistry is commonly viewed as a "green" methodology par excellence [29–32]. Typical arguments to support this claim are as follows:

- Light (or a photon) on its own is a "clean and traceless reagent".
- The energy input is directly controlled with the wavelength.
- Most photochemical reactions can be terminated instantly by simply turning off the light source.
- Photochemistry offers direct, sensitized (catalyzed), or redox pathway options.
- Activation can be often achieved at room (or low) temperature.
- Light energy is absorbed selectively by the chromophoric group of a molecule and does typically not affect solvent, other reagents, or product(s).
- Protecting groups and subsequently additional synthesis steps can be avoided.

Despite these advantages, there are a number of "non-green" process parameters that hamper the widespread use of photochemistry. Some are caused by the utilization of light itself, while others are linked to the photophysical properties of the reagents. Some of the more serious disadvantages are as follows:

- High-energy and intense light sources are hazardous to humans and require strict risk assessments and operation protocols.
- Reactor materials, pipes, and gaskets experience extreme light (and heat) stresses and need to be replaced frequently.
- The conversion of electrical (or fossil) energy into light comes with significant power losses.
- Most light sources generate significant amounts of heat, thus necessitating efficient and energy intensive process cooling.
- Optical filters are commonly applied to minimize degradation of reagents and products by polychromatic or broadly emitting lamps, thus further reducing the energy efficiency of the overall process.
- The limited lifetime of most lamps (~2000 h) imposes significant service and replacement costs.
- The low quantum yields (Φ_λ) of most photochemical transformations demand prolonged and continuous irradiations.
- Photochemical reactions require inert and transparent solvents and are thus commonly conducted in hazardous benzene, acetonitrile, carbon tetrachloride, or methanol.
- Light is typically absorbed within a narrow layer of the reaction mixture and solvents demanding high dilutions are thus required to limit this effect.

Some of these drawbacks can be avoided or minimized by technical developments or reaction designs [30, 33]. New energy-efficient light sources such as monochromatic lasers [34], near-monochromatic excimer lamps [35–37], or narrowly emitting light-emitting diodes (LEDs) [38, 39] and organic light-emitting diodes (OLEDs) [40] are now becoming available, thus avoiding the need for optical filters and reducing electricity costs. Photochemical conversions have also been successfully conducted in alternative and more sustainable reaction media such as water [41–43], micelles [44], ionic liquids [45], or supercritical CO_2 [46]. The introduction of suitable leaving groups such as gaseous CO_2 [47, 48] and N_2 [49] or oxophilic TMS [50] has likewise increased photonic efficiencies and hence shortened reaction times. To address the naturally high energy demand required to power the artificial light sources, selected examples of solar chemical production with sunlight have also been realized [51–55].

These improvements, however, failed to induce any interest in photochemistry as an industrially relevant manufacturing method. With a few exceptions, industrial-scale photoreactions are limited to low-volume (but high-value) fine chemicals such as fragrances, flavors or vitamins, or bulk (but low-value) chemicals such as haloalkanes, oximes, sulfonyl chlorides, and sulfonic acids [56–58].

1.3 Continuous-Flow Chemistry

1.3.1 Introduction to Continuous-Flow Chemistry

In flow chemistry, a chemical reaction is conducted in a continuously flowing stream. Solutions of reagents are pumped from various reservoirs into a reaction channel, where the chemical transformation subsequently takes place [59, 60]. For typical laboratory applications, micro- to mesoreactors are most frequently employed. While their channel widths and depths are typically small (<1 mm for micro- and 1–6 mm for mesoreactors) they can be very long. These inner dimensions result in some significant advantages over batch processes, among which are the following:

- Rapid achievement of mixing within very short times [61].
- Intensification of heat transfer for cooling or heating owing to the large area-to-volume ratio inside the reactors.
- Enabling chemistries that cannot be realized under batch conditions [62].
- Increase in operation safety due to favorable temperature control and the absence of evaporated gas [63].
- Adjustable reaction volumes for flexible on-demand manufacturing [64].
- Easier automation option with possible in-line monitoring and analysis for unattended operation on site [65].
- Coupling of continuous processes for multistep reactions without the need for isolation and purification of intermediates [66, 67].
- Easy control of the reaction time via the flow rate or pumping speed.
- Integration of solid-phase reagents such as catalysts or scavengers [68, 69].
- “Greener” operations due to higher yields, selectivities, and smaller scales [70, 71].

- Easy scale-up by simply changing the reactor volume or by parallel operation of multiple reactor modules.

As a result, continuous-flow devices have found widespread use in chemical synthesis. Fully automated, mobile container modules for end-to-end manufacturing of pharmaceuticals have also been developed [72].

1.3.2 Continuous-Flow Photochemistry

The design and operation features of flow reactors make them especially attractive for photochemical applications. Furthermore, many early flow devices were manufactured from transparent materials such as glass or organic polymers and thus, could be simply combined with suitable light sources. Other specific benefits of flow photochemistry include the following:

- An efficient penetration of light throughout the reaction mixture inside the narrow channels, even for high chromophore concentrations.
- The continuous removal of (photoactive) products from the irradiated area and thus minimization of secondary follow-up photoreactions.
- The ability to match the irradiated area of the flow channel with the emissive area of the lamp, thus reducing "light losses".
- The possible implementation of miniaturized and/or low-energy light sources such as LEDs, OLEDs, or fluorescent tubes.

As a result of these advantages, photochemical transformations conducted under continuous-flow conditions commonly show shorter reaction times, higher yields, increased selectivities, better product qualities, improved productivities, and/or superior photonic and energy efficiencies than conventional batch methods. Compact flow photoreactors also have a smaller laboratory "footprint" than the cumbersome immersion well or chamber reactors. Lamps can likewise be incorporated into the reactor body, which minimizes the potential exposure of operators to bright or harmful light. Continuous-flow photochemistry thus successfully combines the advantages of flow technology and organic photochemistry (Figure 1.2). This has sparked a renaissance in photochemistry as a synthesis method, especially for industrial R&D applications [73–79]. It should be noted, however, that flow photochemical techniques have been used in analytical chemistry for decades, although in a destructive way, to increase the detectability of certain analytes (post-column photochemical reaction systems) [80, 81]. Large macroscale continuous-flow operations are also common in photochemical water treatment [82, 83].

1.3.3 Continuous-Flow Photochemical Technology

Early flow photochemical experiments were typically conducted using improvised reactor components. Existing pumping systems and reactor bodies were simply combined with available light sources. The resulting devices often had a poor match of reactor aperture and emissive area of the lamp. Despite their limitations, they demonstrated the superiority of flow photoreactors over conventional batch reactors. Today, many studies continue to use custom-built

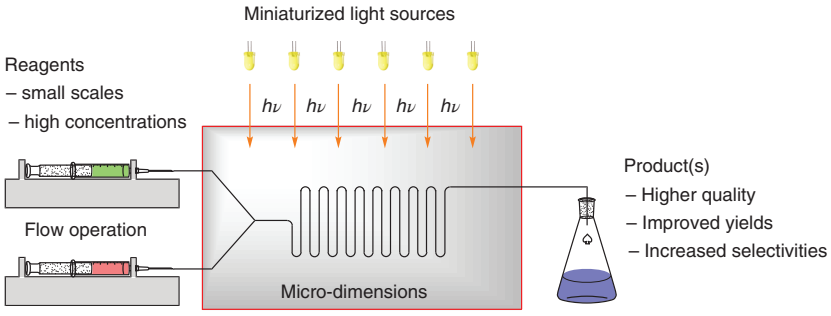
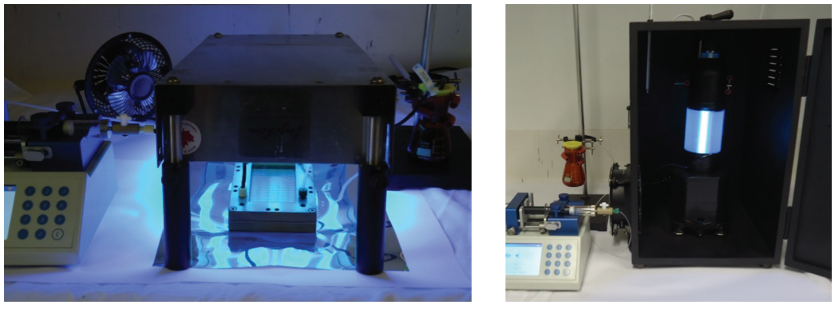


Figure 1.2 Schematic concept of continuous-flow photochemistry.



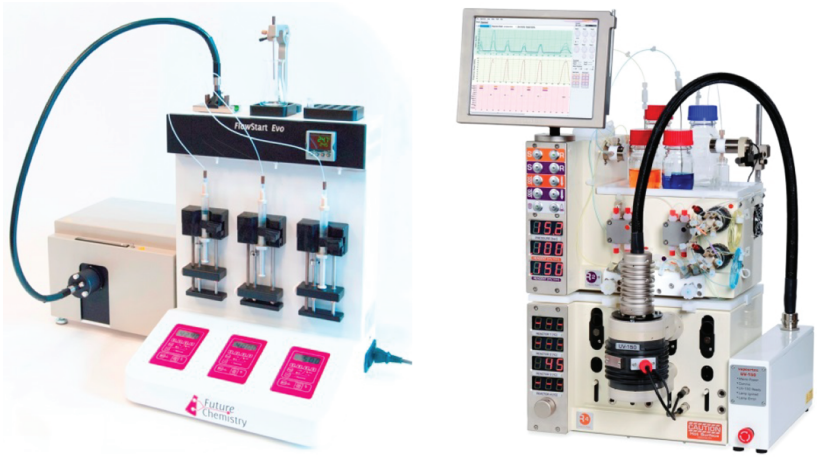
(a) (b)

Figure 1.3 (a) Dwell device (Mikroglas Chemtech GmbH, Germany) under a 5 × 8 W UVB panel. (EXPO, Luzchem Research Inc., Canada.) (b) Improvised FEP-capillary reactor equipped with a single 8 W UVA fluorescent tube. (James Cook University, Australia.)

"in-house" designs. Representative examples of the two main reactor types are shown in Figure 1.3:

- Embedded modules based on microchip or block reactors with fixed inner dimensions. They are commonly combined with external light-sources such as UV panels or LED arrays.
- Flexible fluorinated ethylene propylene (FEP) or polytetrafluoroethylene (PTFE) capillary-based reactors. The capillary is typically wrapped around a glass cylinder and irradiated by a lamp at its center.

Owing to the growing interest in flow photochemistry in both academia and industry, dedicated reactor systems have now been commercialized for microscale synthesis as well as mesoscale production. Figure 1.4 shows two examples of commercially available microflow devices. The Photochemistry Module Deep UV by FutureChemistry contains a UV lamp and a special light guide that directs the light to the microchip reactor on top of a cooling system [84]. Slide-in filters allow operation in four wavelength ranges. A larger reactor system for multigram per hour preparative photochemistry has been recently developed by Vapourtec [85]. The reactor has a dimmable medium-pressure mercury lamp (75–150 W) inside an exchangeable FEP reactor coil. Several



(a) (b)

Figure 1.4 (a) Photochemistry Module Deep UV. (Reproduced with permission of FutureChemistry Holding BV, The Netherlands.) (b) Vapourtec UV-150 photochemical reactor. (Reproduced with permission of Vapourtec Ltd, UK.)

optical filters can be positioned between the lamp and the capillary coil in order to remove undesired wavelengths.

Additional flow photoreactor packages that utilize LEDs as light sources have been commercialized by Corning S.A.S. (Advanced-Flow™ G1 Photo Reactor) [86] and YMC Co. Ltd (KeyChem-Lumino system) [87].

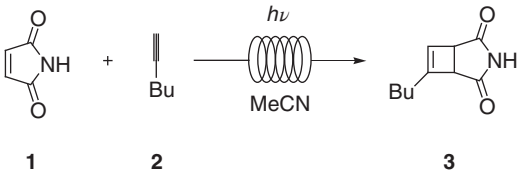
1.4 Selected Examples of Photochemical Reactions under Flow Conditions

A number of review articles summarizing preparative photochemistry in flow reactors have already been published, clearly demonstrating the impact of this emerging methodology [73–79]. The following sections present some important examples.

1.4.1 Homogeneous Photoreactions

The potential of flow photochemistry for large-scale productions was first demonstrated by Hook *et al.* for a series of inter- and intramolecular photocycloaddition reactions [88]. The group constructed several types of FEP-capillary reactors using standard or modified photochemical and analytical equipment. Conventional medium-pressure mercury lamps served as light sources. The main aim of this study was to demonstrate the superiority of a continuous flow system over a batch reactor with respect to product quality, productivity (over a 24 h period), and uninterrupted functionality.

The first reactor incorporated small-bore FEP tubing (ID: 0.7 mm; *L*: 150 m; *V*: 60 ml) in four layers wrapped around a quartz immersion well equipped with a 400 W mercury lamp and filtered through a Pyrex insert (Model A). Complete



1 **2** **3**

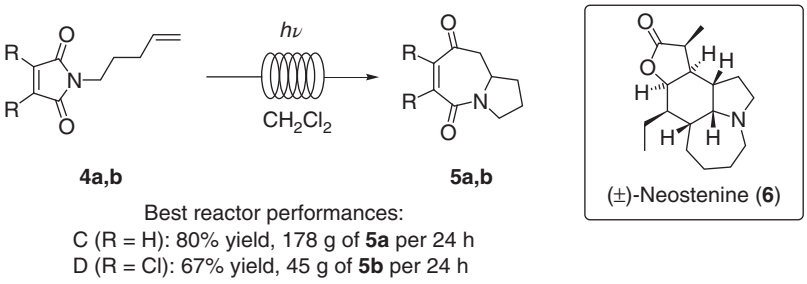
Best reactor performances:
A: 13% conversion, 175 g of **3** per 24 h
B: 100% conversion, 96 g of **3** per 24 h
C: 83% conversion, 685 g of **3** per 24 h

Scheme 1.2 [2+2]-Photocycloaddition of **1** and **2** to yield **3** as a model reaction for productivity performances.

conversion of a 0.1 M solution of maleimide (**1**), reacting with hex-1-yne (**2**) to form the cyclobutane (**3**), in MeCN was achieved by this reactor at a flow rate of 2 ml/min (Scheme 1.2), corresponding to a productivity of 50 g per day. At the higher concentration of **1** of 0.5 M and an elevated flow rate of 8 ml/min, the conversion rate dropped to 17%, but the device could theoretically generate 175 g of **3** in 24 h. The second reactor made use of the same diameter FEP tubing (ID: 0.7 mm; *L*: 176 m; *V*: 67 ml) wrapped around a customized Pyrex immersion well that allowed closer proximity of the tubing to the light source, and consisted of five layers around a 400 W mercury lamp (Model B). As with their first reactor, a 0.1 M of **1** at a flow rate of 4 ml/min achieved complete conversion, which translated to a productivity of 96 g in 24 h. Being interested in multigram outputs, the authors constructed a third reactor of wider-bore FEP tubing (ID: 2.77 mm; *L*: 49 m; *V*: 280 ml) in three layers, which was wrapped around a novel custom Vycor immersion well, allowing better UV light transmission (Model C). As more reagent solution could be accommodated by the wider tubing, utilization of a 600 W mercury lamp afforded a conversion of 83% of **1** (0.4 M) to **3** at a flow rate of 8 ml/min. From this, the authors estimated the maximum amount of product produced as 685 g over a 24 h period. The same reactor equipped with three layers of tubing was subsequently used successfully to demonstrate continuous operation for 24 h.

The [5+2]-photocyloaddition to form the rearranged bicyclic azepine **5a** was subsequently investigated in reactor Model C, but using a 400 W lamp as a light source (Scheme 1.3). Irradiation of a 0.1 M solution of **4a** in CH_2Cl_2 at a flow rate of 8 ml/min resulted in an isolated yield of **5a** of 80%. This translated to a theoretical productivity of 128 g in 24 h. Owing to the photolabile nature of the corresponding dechlorinated product **5b,** the flow reactor and the reaction conditions had to be further modified. A single layer of FEP tubing (*V*: 60 ml) was wrapped around a Pyrex immersion well (Model D). A diluted (0.01 M) solution was subsequently pumped through the reactor at a flow rate of 10 ml/min. From this, the desired product **5b** was isolated in a yield of 67%, corresponding to a productivity of 45 g/24 h.

The shortened version of the capillary reactor was later applied successfully to the protecting group free synthesis of (±)-neostenine (**6**) using the [5+2]-photocyclization as a key step [89].

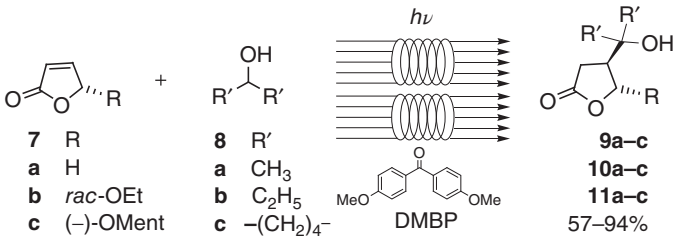


Scheme 1.3 [5+2]-Photocyclization of **4a,b** to **5a,b** and estimated productivities.

Figure 1.5 Multi-microcapillary flow reactor (MμCFR; Dublin City University, Ireland). The left fluorescent tube is turned on.

The flexibility of FEP capillaries makes them interesting for parallel operations. This was demonstrated by Yavorskyy *et al.* through the construction of a multi-microcapillary flow reactor (MμCFR) with 10 individual capillaries (Figure 1.5) [90]. Two bundles of five FEP capillaries (ID: 0.8 mm; *L*: 11.5 m; *V*: 5 ml) each were wrapped around two separate Pyrex glass columns each equipped with a single 18 W UVA fluorescent tube. Reaction mixtures were supplied using a programmable 10-head syringe pump system and the products were collected in 10 separate flasks protected from light. The reactor was subsequently used for typical R&D applications in chemical and pharmaceutical research such as reaction optimization, process validation, scale-up, and parallel library synthesis [91–93].

The sensitized addition of alcohols (**8a–c**) to various furanone derivatives (**7a–c**) was chosen as a model reaction to determine the performance of the MμCFR reactor (Scheme 1.4) [94]. Using the **7a**/**8a** combination, various process parameters were screened in separate runs in order to rapidly establish optimal reaction conditions. From a library of different aromatic ketones [95], 4,4′-dimethoxybenzophenone (DMBP) was identified in the first run with a

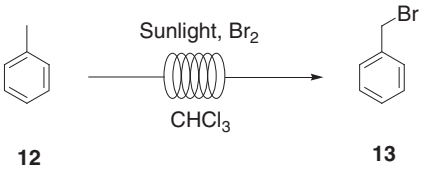


Scheme 1.4 Parallel sensitized addition reactions of alcohols (**8a–c**) to furanone derivatives (**7a–c**).

residence time of 5 min as the best sensitizing material. Several other ketones were identified from the same run as active photosensitizers. In a subsequent run, the concentration of DMBP was varied and a maximum conversion of 90% was reached with a loading of 10 mM. Higher concentrations caused precipitation of DMBP and consequently a drop in conversion rates owing to light scattering. To prevent any clogging of the capillary and hence the danger of tube rupture [96], a somewhat lower DMBP concentration of 6.7 mM was chosen for all subsequent experiments. In the third run, the concentration of furanone (**7a**) was screened over a broad range under otherwise fixed conditions. With increasing concentration, conversion rates dropped from 80% at the lowest concentration of 33.3 mM to just 2% for the highest concentration of 200 mM. The optimized reaction parameters were subsequently used for a validation and scale-up study. Selecting a fixed residence time of 5 min, an average conversion of $70.8 \pm 4.2\%$ was determined, thus demonstrating good reproducibility within the error range of ^{1}H-NMR spectroscopy. In a following experiment, the residence time was extended to 10 min to reach complete conversions and the combined product compound **9a** was obtained in a yield of 94%, with a reasonable quantity of approximately 500 mg. More advanced continuous pumping systems than the chosen syringe pump can deliver larger quantities of product over longer periods of operation. The true potential of parallel flow photochemistry was demonstrated through the synthesis of a small 3×3 product library. The corresponding addition products **9a–c, 10a–c,** and **11a–c** were obtained from two successive runs in good to excellent yields of 57–94%.

Fully- and semiautomated flow devices for reaction optimization and screening have likewise been developed but require in-series operation [97–99].

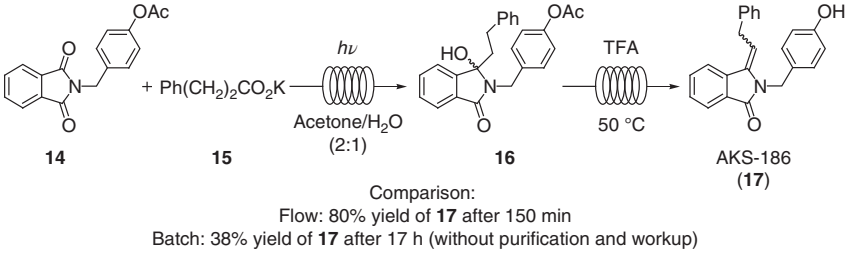
A major cost driver for the chemical industry is the energy demand of its production processes [100–102]. Artificial light sources have likewise been identified as the main source of energy consumption on laboratory scales [103, 104]. Kim *et al.* have thus conducted a series of photobrominations in concentrated sunlight (Scheme 1.5) [105]. A Fresnel lens was used to focus natural sunlight onto a spiral FEP capillary tube (ID: 1 mm; *L*: 5 m; *V*: 4 ml), which was placed inside a shallow Dewar flask as a reflector. This simple design achieved a concentration factor of 4 suns in practice. The reagent solutions of toluene (**12**) and bromine in chloroform were introduced into a T-mixer by separate syringe pumps. Choosing a residence time of 90 s, a high selectivity toward monobromination was obtained and the desired benzyl bromide (**13**) was



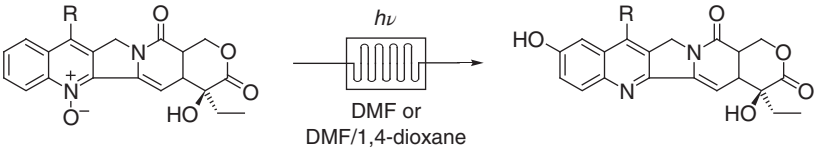
Scheme 1.5 Photobromination of toluene (**12**) under continuous flow conditions in concentrated sunlight.

generated in a good yield of 82%. Multigram quantities of **13** became available by performing 16 consecutive injections. Following this strategy, the improvised setup achieved an estimated productivity of 44.1 g/day.

An innovative feature of flow chemistry is the possible combination of several reaction steps in series without isolation and purification of intermediates. This has been demonstrated by Josland and co-workers for the tandem photochemical–thermal synthesis of the biologically active 3-alkylmethylene-1*H*-isoindolin-1-one AKS-186 (**17**) shown in Scheme 1.6 [85, 106]. The advanced easy-Photochem reactor (Figure 1.4b) by Vapourtec Ltd, UK, was utilized for this approach as it conveniently combines a powerful photochemical module (FEP capillary; ID: 1.3 mm; *V*: 10 ml) with a secondary thermal reactor loop (perfluoroalkoxy alkane, PFA, capillary; ID: 1.3 mm; *V*: 10 ml). The photodecarboxylative addition involving phthalimide **14** (10 mM) and excess amounts of potassium phenylpropanoate (**15**) was initially studied using the UV-150 module alone. Using a lamp power of 82 W and a flow rate of 1.25 ml/min (residence time of 8 min), complete conversion was achieved and the desired hydroxyphthalimidine **16** was isolated in an excellent yield of 95%. The subsequent thermal reaction step was realized by injecting neat trifluoroacetic acid (TFA) into the effluent stream of the photoreactor module and by maintaining the thermal reactor coil at 50 °C. Adopting the initial flow conditions resulted in a conversion of **16** of approximately 50% and furnished a complex mixture of various dehydration and deprotection products, including the desired **17**. The reaction conditions were thus modified to allow for sufficient reaction time in the thermal loop. With an initial concentration of 0.5 mM of **14** and a reduced flow rate of 0.1 ml/min

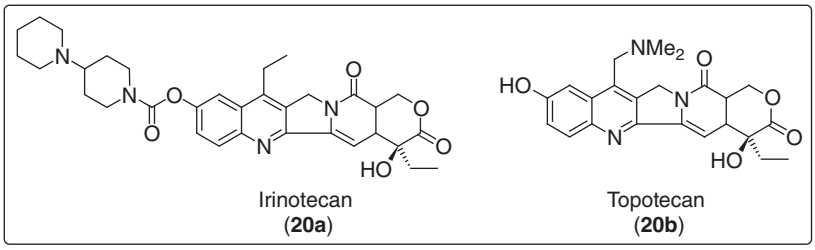


Scheme 1.6 Tandem photochemical–thermal synthesis of AKS-186 (**17**) under continuous flow conditions.



18a,b **a:** R = H **b:** R = Et **19a,b**

Comparison for **18a** (R=H):
Flow: 0.6 wt% of **18a**, 95% conversion and 90% yield of **19a**
Batch: 0.1 wt% of **18a**, 90% conversion and 50% yield of **19a**



Scheme 1.7 Synthesis of camptothecin derivatives **19a,b** through photorearrangement and structures of irinotecan (**20a**) and topotecan (**20b**).

(residence time of 100 min) and an injection of TFA at a flow rate of 0.2 ml/min (residence time of 50 min), complete conversion was achieved and the fully dehydrated and deprotected product **17** was isolated in an overall yield of 80%. In comparison, the reported stepwise batch process produced an overall yield of just 38%, which was mainly caused by the poor conversion of 52% for the photochemical step [107]. The combined continuous-flow multistep approach conveniently delivers the desired product in better yields without the need of solvent-demanding and thus waste-producing purification and isolation steps.

Although most flow photochemical studies are performed in academia or industrial research divisions, an example of a small-scale manufacturing plant has been realized by Heraeus Noblelight [108]. This industrial process generates 10-hydroxycamptothecin derivatives **19a,b** through a photoinduced rearrangement of the corresponding *N*-oxides **18a,b** (Scheme 1.7). This transformation represents a key step in the synthesis of the low-volume anticancer drugs irinotecan (**20a**) and topotecan (**20b**). The microflow plant (Figure 1.6) comprises 12 individual reactor units and is capable of meeting the annual demand of the target compounds (<1 t/a) with a daily output of 2 kg/day. Each microreactor is composed of two parallel quartz glass plates separated by a thin gasket. The reaction mixture of **18a,b** in DMF or DMF/1,4-dioxane is pumped into this reactor block from the bottom and forms a thin film (40–100 μm), which is irradiated by two 250 W high-pressure mercury lamps equipped with spectral filters (350–400 nm). Under these flow conditions, a 0.6 wt% solution of **18a** was capable of achieving a conversion of 95% and an overall yield of **19a**

Figure 1.6 Flow photochemical production plant. (Oelgemöller 2012 [76]. Reproduced with permission of Wiley.)

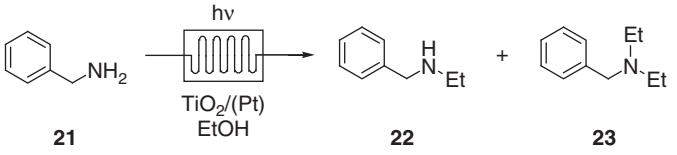
of 90%. A comparable batch process required a more dilute (0.1 wt%) solution and could only achieve 85% conversion with a 50% overall yield to **19a.** Flow operation thus allows for higher concentrations of starting material to be used and significantly reduces photodegradation of the photoproduct.

1.4.2 Heterogeneous Photoreactions

Heterogeneous TiO_2 photocatalysis has demonstrated promising potential in preparative photochemistry [109, 110]. The solid photocatalyst applied can be easily recovered and recycled, which make this methodology attractive for green chemistry. Under flow conditions, the photocatalytic material is commonly attached to the walls of the reaction channels to avoid clogging of the reactor [111].

An interesting example is the photocatalytic *N*-alkylation of benzylamine (**21**), as described by Matsushita *et al.* (Scheme 1.8) [112]. The sides and beds of the reaction channel of a custom-made quartz microreactors (*W*: 0.5 mm; *D*: 0.5 mm; *L*: 40 mm) were coated with two TiO_2 photocatalysts, Pt-loaded and Pt-free, respectively. A fitting 7×1.4 mW ultraviolet light-emitting diode (UV-LED) array (365 nm) served as a miniaturized light source. A standard 1 mM solution of **21** in ethanol was injected into the microchip and after a residence time of just 150 s, a selective and high conversion of 85% to **22** was determined. Methanol and isopropanol were likewise tested but gave significantly lower yields.

The "enabling" potential of flow photochemistry was subsequently demonstrated. In contrast to batch operation conditions, the alkylation proceeded with high efficiency even without the platinum cocatalyst. In addition, all experiments



Comparison:
Flow: 85% yield of **22** after 150 s
Batch: 84.4% yield of **22** after 4 h (2.4% of **23**)

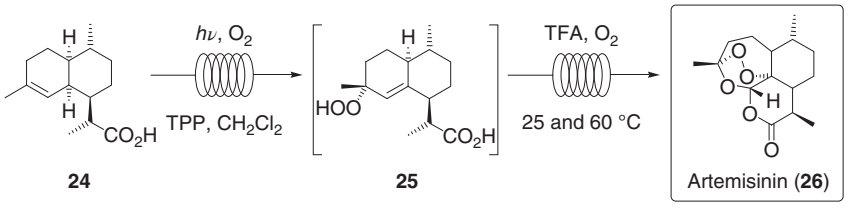
Scheme 1.8 Photocatalytic alkylation of benzylamine (**21**) under continuous flow conditions.

under flow conditions proceeded selectively and, in contrast to analog batch reactions, no bisalkylation to **23** was found. Flow operation thus avoids the need of expensive photocatalysts and resource-demanding purification methods.

In a continuation of this work, the same authors employed other amines in an improved flow reactor system and reported similar outcomes [113].

Of the gas–liquid heterogeneous reactions, photooxygenations are particularly important in the fine chemical industry [56, 57]. These transformations utilize oxygen or air as a reagent gas and catalytic amounts of an organic dye. The dye produces the highly reactive singlet oxygen ($^1O_2$), which reacts with unsaturated substrates to a variety of oxygenated products such as endoperoxides, allylic hydroperoxides, or dioxetanes [114–117]. The high oxygen content of these products makes them potentially explosive, especially on large scales [118]. These materials are thus typically not isolated and are further reduced to more stable derivatives. The continuous nature and the naturally small scales make flow reactors especially attractive for these transformations. The accumulation of potentially explosive compounds is minimized and oxygenated intermediates can be quickly converted continuously by consecutive flow steps or chemical quenching within the collection reservoir.

A remarkable achievement in industrial photochemistry was the recent technical-scale synthesis of the frontline antimalarial agent artemisinin (**26**) [119]. This semisynthetic route from dihydroartemisinic acid (**24**) was subsequently investigated under continuous flow conditions by Lévesque and Seeberger (Scheme 1.9) [120]. Oxygen gas was injected into a 0.2 M solution



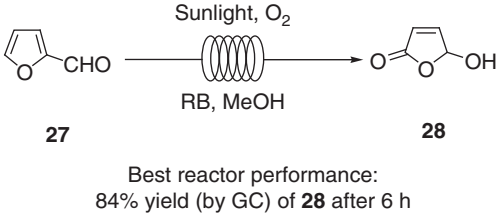
Reactor performance:
39% yield (from **24**), 1.36 g of **26**
estimated 200 g of **26** per 24 h

Scheme 1.9 Continuous-flow synthesis of artemisinin (**26**) from **24** via a tandem photochemical–thermal process.

of **24** in dichloromethane containing a small amount of tetraphenylporphyrin (TPP; 1 mM) as a photosensitizer. The resulting slug flow was pumped into an FEP capillary (ID: 0.75 mm; *V*: 20 ml) and irradiated with a conventional 450 W medium pressure mercury lamp for an estimated residence time of 2 min. Photosensitized oxygenation produced the hydroperoxide intermediate **25**. TFA was injected into the effluent stream of the photochemical module and the reaction mixture entered a thermal capillary reactor made of PTFE tubing (ID: 0.8 ml; *V*: 16 + 10 ml) with an estimated residence time of 2.5 min. The loop was kept at 25 and 60 °C in separate sections and the intermediate **25** was converted into the desired artemisinin (**26**) via a complex reaction cascade. The coupled process operated highly efficiently without the need of purification or isolation of the potentially hazardous hydroperoxide **25** and artemisinin (**26**) was subsequently isolated in an overall yield of 39%. The compact tandem reactor platform had an estimated productivity of 200 g of **26** per day and about 1500 of these reactor systems would satisfy the annual artemisinin (**26**) demand of approximately 200 million dosages.

In a subsequent study, the same group successfully produced artemisinin in an improved overall yield of 46% (16.08 g) using 9,10-dicyanoanthracene (DCA) as a photosensitizer, toluene as a solvent, a 12 W LED-module (420 nm emission wavelength), and a simple FEP capillary reactor (four layers wrapped around a transparent polycarbonate plate; ID: 0.76 mm; *V*: 7.5 ml) [121].

Another example of the use of solar light for the photooxygenation of furfural (**27**) in flow has been recently described by Nsubuga *et al.* (Scheme 1.10) [122]. A simple quartz capillary reactor (ID: 0.3 cm; *L*: 15 cm; *V*: about 1.1 ml) was placed on a mirror. The reaction medium was pumped from a reservoir in a circulating loop and conversion rates and yields were determined by GC–MS analysis. The authors investigated the influence of the solvent, amount of rose bengal (RB) photosensitizer, circulation time, light, and weather conditions. The highest yield of **28** of 84% was obtained after operation for 6 h in direct sunlight.



Scheme 1.10 Photooxygenation of furfural (**27**) to hydroxyfuranone (**28**) in sunlight.

1.5 Summary, Conclusion, and Outlook

The examples presented in this chapter unambiguously demonstrate that continuous-flow operation is a powerful approach in preparative photochemistry. In many cases, products are produced in higher yields and with better qualities and selectivities, thus minimizing resource-demanding separation and

purification steps. Compared to conventional batch procedures, flow operation also allows higher initial concentrations of reagents, thus reducing the amount of solvents and hence waste. Natural sunlight can furthermore be utilized as a sustainable energy source that circumvents energy-demanding artificial lamps. It is hoped that continuous-flow photochemistry will find widespread applications in chemical R&D processes as well as manufacturing. [123, 124] The technical Heraeus process for the small-scale production of anticancer compounds "lights the way into a bright future".

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