3

Microphotochemistry: Photochemical Synthesis in Microstructured Flow Reactors

3.1 Introduction

Over the last decades, microtechnology has received a great deal of attention. Its application rapidly grows in many areas, as evident, for example, in electronics and engineering. The development of microstructured devices for chemical reactions was observed only within the last 10 years.1–12 Miniaturization of chemical reactors offers many practical advantages of relevance to the pharmaceutical and fine chemicals industry.13,14 Also, the possibility of preparing chemicals in the required volume at the point of use neglects the need to store and transport hazardous materials. The small scales of microreactions make them additionally advantageous for green chemistry.15–19 Since light is regarded as a “clean reagent,” organic photochemistry can likewise serve as a green synthetic method.20–23 The potential of organic photochemistry as a powerful synthesis method is furthermore well documented, and a number of elegant chemo- and enantioselective transformations with high chemical and quantum yields have been realized.24–26 The combination of microtechnology and photochemistry, that is, microphotochemistry, thus represents a promising and appealing new concept (Figure 3.1).27–29

3.2 From Conventional (Batch) to Micro (Flow) Photoreactors

Immersion well reactors or chamber reactors (Figure 3.2) are most commonly used in conventional laboratory-scale photochemistry.10 The total volume of such laboratory batch systems is typically limited to 1 L. As common light sources, single low-, medium-, or high-pressure mercury lamps are used in immersion well reactors, while an array of fluorescent lamps is used for chamber reactors.

The application of batch systems for photochemical reactions has a number of disadvantages. Depending on the spectroscopic properties of the chromophoric reagent, complete light absorption is
typically observed within a narrow layer of the reaction solution (as expressed in the Beer–Lambert law). High dilutions are thus commonly applied to reduce this effect. In addition, photochemical processes occur most effectively closest to the light source, which limits the total irradiation volume of the reaction. Common lamps typically show emission of numerous wavelengths or of broad emission (±50 nm) at the chosen wavelength. Therefore, optical filters must be frequently applied, which reduce the energy efficiency of the lamps. Electric losses due to the generation of heat further lower the energy efficiency and require the usage of intensive water or air cooling during operations. The limited lifetime of lamps (~2000 h) additionally causes significant installation, maintenance, and operation costs. Batch processes with fixed volumes cannot be easily automated and follow-up reactions or decompositions are frequently observed. The formation of polymeric films and iron deposits on immersion wells is also common. Some novel reactor types, for example, falling-film or spinning-disc reactors, can reduce these effects but have not been adopted widespread.

Many of these disadvantages can be overcome by carrying out photochemical transformations in microreactors or microchips (Figure 3.3), on demand equipped with miniaturized light sources. Many microreactor devices, including complete systems as the KeyChem-Lumino reactor, are now commercially available, although many researchers continue to custom build their own devices.

Microstructured reactors are (generally, but not absolutely) reactors with three-dimensional structures, the inner parameters of which are under 1 mm in size. There are two main types of “closed” microreactors, namely serpentine reactors and falling-film reactors. These reactors consist of a solid support with one or more microchannels. “Open” reactors without solid base use flexible microcapillaries instead.

The main feature of “closed” serpentine reactors is the long channel length, which can range from several centimetres to over a meter. Longer channels can be used to increase residence times, thus
making them advantageous when prolonged irradiation is needed. On-chip mixing of reagents can be achieved using separate inlets. Multilane microreactors have also been developed and can be used for scale-up.

Falling-film reactors were specifically designed for gas–liquid reactions.\(^{35}\) The central element of its design is the reaction plate on which parallel microchannels are arranged. In these channels, the liquid phase generates thin falling films that move by gravity force. The large interfacial area of up to 20,000 m\(^2\)/m\(^3\) guarantees efficient saturation of the film with reactant gas that is flowing over the liquid phase. In contrast, closed channel devices require presaturation of the reaction mixture with reagent gas. Scale-up can be realized using cylindrical falling-film reactor models or larger channel plates.

The advantages of photochemical synthesis in microdimensioned reaction vessels were first discussed by Porter and Volman, although for batch systems.\(^ {36}\) Microstructured flow systems have additional characteristics, which make them beneficial for photochemical processes. The thin layers of the microchannels (100–1000 \(\mu\)m) ensure extensive penetration of light throughout the reaction mixture, even for relatively concentrated solutions. Microstructured devices also have a large surface-area-to-volume ratio that provides fast heat and mass transfer. The typically continuous flow mode circumvents undesired side reactions or decompositions caused by follow-up reactions. The starting reagents may be mixed directly online in a mixing channel preceding the actual reaction channel. The reagents can also be introduced to the reaction region in a specific sequence, thus removing the necessity for premixing. The irradiation time in a microreactor is easily changed, as it is directly proportional to the flow rate of the system. By changing the flow rate, product formation can be precisely controlled.

The small experimental scale of microreactions reduces the total amount of waste and only requires small amounts of solvents and chemicals. The microreactor design also allows online UV\(^ {37}\) or IR monitoring\(^ {38}\) of the reaction. The small reactor size enables employing miniaturized or compact energysaving light sources such as light-emitting diodes (LEDs).\(^ {39,40}\) The processes in microreactors and the microreactor itself are safer in operation and can be automated. Likewise, the reactions proceeding in a small volume can be controlled much more easily with respect to pressure, temperature, and residence time.\(^ {41}\) Thus, the risk of highly exothermic or explosive reactions can be reduced drastically. Microreactors can be operated in series or in parallel clusters for scale-up or optimization studies. Parallel networks of microreactors offer an efficient route to generate product volume on demand at the point of use.

### 3.3 Photochemical Reactions in Microreactors

A number of examples concerning photochemical performances in microreactors already exist in the literature.\(^ {27,28}\) Based on the conditions required, these reactions can be divided into three basic categories: homogeneous reactions (the reagents are all in the same phase, i.e., in solution), heterogeneous reactions (reactions between liquid and gaseous reagents), and catalytic reactions (reactions that involve heterogenic catalysis).
3.3.1 Homogeneous Reactions

3.3.1.1 Photopinacolization

The photopinacolization is one of the earliest photochemical reactions that was investigated in microstructured reactors with online UV detection. Jensen and coworkers studied the transformation of benzophenone 1 using isopropanol as solvent in two house-made microreactors (Scheme 3.1).\(^{37}\) One reactor was fabricated by bonding a patterned silicon wafer to a Pyrex plate. The second reactor had a sandwich structure of a silicon wafer between two quartz wafers and allowed irradiation with lower wavelengths. In this investigation, a miniaturized fluorescent UV lamp was used as a light source.

For greater conversions to benzopinacol 2, longer residence times or lower flow rates were required. No detectable product formation was obtained for flow rates greater than 10 μL min\(^{-1}\). With reduced flow rates, the conversion improved. An adequate flow rate was established to be 4 μL min\(^{-1}\) and showed conversions of up to 60%. At flow rates lower than 3 μL min\(^{-1}\) product 2 tended to crystallize in the microchannel, thus clogging the device. The progress of the reaction was monitored off-chip using HPLC analysis and online using UV spectroscopy. The concentration of benzophenone was 0.5 M, which is relatively high for photochemical reactions. The use of these concentrated solutions effectively demonstrated the general advantage of microstructured reactors, as the shallow channel depth of 500 μm enabled complete irradiation of the reaction mixture.

3.3.1.2 Barton Reaction

The preparation of the steroidal product 4 from substrate 3 via the Barton reaction (Scheme 3.2) was selected as a model reaction for microreactor testing.\(^{42,43}\) This reaction is of importance because product 4 is a key intermediate for the synthesis of myriceric acid A (an endothelin receptor antagonist). The experiments were carried out in a glass-covered stainless steel microreactor Type A or Type B (manufactured by Dainippon Screen Mfg). Microreactor Type A had a one-lane channel of 1000 μm width, 107 μm depth, 2.2 m length, and a hold-up volume of 0.2 mL. It was used for the initial process optimization. Microreactor Type B had 16 lanes with a channel 1000 μm wide, 500 μm deep, 0.5 m long, and a hold-up volume of 4 mL. This reactor type was used for multigram-scale production.

The initial work was concentrated on increasing reaction output through an optimized and energy-saving experimental setup. Therefore, the application of three different types of transparent glass covers (quartz, soda lime glass, and Pyrex) and two light sources (300 W high-pressure Hg lamp and 15 W...
black light) were investigated. It was determined that Pyrex was most suited to the desired 15 W black light source. Due to the thermal instability of product 4 at temperatures greater than 50°C, the authors also examined the temperature dependence and the distance between the microreactor and the light source. Under optimized conditions, a residence time of 12 min furnished the desired product 4 in a yield of 71%. In an extension of this study, the same authors examined a UV-LED panel (48 pieces × 35 mW) as a light source suitable in combination with microreactor Type A. After a residence time of 12 min, the desired product 4 was isolated in a yield of 70%. This result clearly demonstrated that UV-LEDs, despite their low intensity (compared to high-pressure mercury lamp), have sufficient strength to initiate photochemical processes. The authors also reported a gram-scale synthesis of the target compound using two microstructured reactors Type B connected in series and coupled with 8 × 20 W black lights. After constant operation for 20 h, the amount of product 4 isolated was 3.1 g (60% yield). Encouraged by the successful gram-scale synthesis, Sugimoto and coworkers focused their forthcoming work on the development of practical and automated multigram-scale synthesis. For this research, they used an automated photomicroreactor system, DS-AMS-1 (manufactured by Dainippon Screen Mfg). This system provided operation monitoring via PC software and moreover had important safety functions. It employed one set of a Type B microreactor and six small (15 W) black light lamps. After continuous operation for 40 h, product 4 was obtained in an amount of 5.3 g (61% isolated yield). This clearly demonstrated the potential for numbering up of microstructured reactors and process optimization for the larger scale production of chemicals.

3.3.1.3 Photocycloaddition Reactions
3.3.1.3.1 Photochemical [2 + 2] Cycloaddition of Cyclohex-2-Enone with Vinyl Acetate

The photochemical [2 + 2] cycloaddition reaction is one of the most powerful and versatile methods for the formation of four-membered rings and has been extensively applied in organic synthesis. Fukuyama and coworkers selected the photochemical [2 + 2] cycloaddition of cyclohex-2-enone 5a with vinyl acetate 6a as a model reaction (Scheme 3.3) for testing in a commercially available microreactor dwell device (FOTURAN® glass, manufactured by mikroglas). This reactor has a channel of 500 μm depth, 1000 μm width, and 1.4 m length.

A regular 300 W high-pressure mercury lamp was used as a light source in this study. After 2 h of irradiation (flow rate of 0.5 mL h⁻¹) a GC yield of 88% for the desired product 7a was obtained. Under the same conditions, the batch reactor (10 mL Pyrex flask) furnished only 8% of 7a. The same reaction was repeated with two microreactors in series at a flow rate of 1 mL h⁻¹, which resulted in a similar isolated yield of 85%. Thus, microstructured reactors can shorten irradiation times and increase yield at the same time.

In an extension of the work, the suitability of the photochemical [2 + 2] cycloaddition for microflow conditions was further verified and two additional cyclohexenones, 5b and 5c, and two additional alkenes, 6b and 6c, were examined (Scheme 3.4).

In all cases examined, the corresponding cycloaddition products 7b–e were obtained in yields of 47%–70% as regioisomeric mixtures.

\[
\text{5a} + \text{6a} \rightarrow \text{7a} \quad h \nu (365 \text{nm}) \quad 2 \text{h}
\]

**SCHEME 3.3** Photochemical [2 + 2] cycloaddition of cyclohex-2-enone with vinyl acetate.
3.3.1.3.2 Diastereoselective [2 + 2] Photocycloaddition of a Chiral Cyclic Enone with Cyclopentene

Asymmetric photoreactions are of special importance due to the formation of potentially biologically active natural products and unique structural compounds.45,46 Hence Ryu and colleagues explored the utility of a microflow system in photoinduced asymmetric reactions and compared the results with those obtained using a larger volume batch reactor.47 The model reaction examined was the reaction of the cyclohexenonecarboxylate derivative 8, which incorporated a (−)-8-(phenyl)menthyl group as a chiral auxiliary, with cyclopentene 9 (Scheme 3.5).

A microreactor with a single channel of 1000 μm × 100 μm × 2.2 m (width × depth × length) and a hold-up volume of 0.2 mL (Dainippon Screen Mfg) was employed. A simple Pyrex test tube with an inner diameter (ID) of 13 mm was used for the batch comparison test. Both systems were irradiated simultaneously by a common high-pressure Hg lamp. The photoreaction in the microflow system reached completion in 0.5 h, which was two times faster than in the batch system (1 h). However, the ratios of stereoisomers 10 and 11 were almost identical in both systems. Additionally, the authors investigated the

![Scheme 3.4](image)

**SCHEME 3.4** Photochemical [2 + 2] cycloaddition of cyclohexenones with alkenes.

![Scheme 3.5](image)

**SCHEME 3.5** Diastereoselective [2 + 2] cycloaddition of a chiral cyclic enone and cyclopentene.
effect of temperature on the diastereoselectivity. The highest diastereoisomeric excess values of 10 (82%) and 11 (54%) were observed in the microflow reaction at −40°C. This was explained by a more accurate temperature control in the microflow system associated with a very large surface-area-to-volume ratio of the reaction chamber. In summary, this study has shown that a flow microreactor can be used for asymmetric photoreactions.

3.3.1.3.3 Intramolecular [2 + 2] Photocycloaddition of a 1-Cyanonaphthalene Derivative

Continuous flow microreactors have also been used in regioselectivity studies. The intramolecular [2π + 2π] photocycloaddition of 1-cyano-2-((3-methyl-2-butenyloxy)methyl) naphthalene 12 in acetonitrile has been reported by Maeda et al. (Scheme 3.6). The authors in particular compared the regioselectivity and efficiency for batch and microstructured reactor conditions. The transformation was performed in custom-built reactors made from poly(dimethylsiloxane) with channels 300 μm wide, 50 μm deep, and 45 or 202 mm long. The reaction mixture was pumped through the microchannel at two flow rates of 0.03 and 0.05 mL h⁻¹ and was irradiated by a xenon lamp coupled with a UV-29 filter. The channel pathlength of 202 mm afforded prolonged reaction time and was found as optimal. After an irradiation time of 3.4 min, the intramolecular photocycloadduct at the 1,2-position of the naphthalene ring 13 and the photocycloadduct at the 3,4-position 14 were detected in a ratio of 55:7 in the microreactor, respectively. In contrast, only 5% of photocycloadduct 13 and traces of photocycloadduct 14 were noticed under batch conditions after the same reaction time. This reaction was also investigated in the batch system with a longer residence time of 180 min and photocycloadducts 13 and 14 were detected in a ratio of 56:17, respectively, but the regioselectivity was still not as good as in the microreactor. The improved regioselectivity in the microreactor was explained by the flow mode. The initially formed cycloadduct 13 is continuously removed from the system, therefore reducing photocycloreversion to 12. Extended irradiation times gave higher yields of 14 since reversion to the starting material does not take place for this compound. The enantioselectivity was also investigated using Eu(hfc), and a small but significant enantiomeric excess of 2% (e.e.) was determined.

3.3.1.3.4 Intramolecular [2 + 2] and [2 + 3] Photocycloadditions of 2-(2-Alkenyloxymethyl)-Naphthalene-1-Carbonitriles

Mizuno and coworkers examined other intramolecular photocycloadditions of 2-(2-alkenyloxymethyl)-naphthalene-1-carbonitriles 15a–c (Scheme 3.7). This investigation included a comparison to a batch reaction (Pyrex tube with a diameter of 8 mm) and a study on the effects of substituents, solvent, residence time, flow rate, and the microchannel dimensions.

Two microreactor types were utilized. The first (Type A) microreactor was commercially available (ICCD105, Institute of Microchemical Technology), and was made from Pyrex glass with a channel of 100 μm width, 40 μm depth, and 120 mm length. A second (Type B) microreactor was made in-house from Pyrex plates and had a channel width of 2.5 mm, a depth of 50 μm, and a length of 60 mm. A 500 W xenon lamp was used as a light source.

\[
\text{CN} \quad \text{CN} \\
\text{MeCN} \quad hν (>290 \text{ nm}) \quad \text{CN} + \text{CN} \\
\begin{array}{c}
\text{12} \\
\text{13:14 ratio:} \\
55:7 \text{ after 3.4 min in } \mu-\text{reactor} \\
56:17 \text{ after 3 h in batch}
\end{array}
\]

The irradiations performed in the microreactors allowed for increased regioselectivity and the initial photoproducts 16a–c were selectively formed, while undesirable photocycloreversions yielding 17a–c were suppressed. Additionally, higher conversions of 69%–75% were achieved in the microreactors after just 1 min, while the batch reactor showed a lower conversion of 74% after 3 h of irradiation. The increase in efficiency was explained by the better light penetration through the reaction medium in the microreactors compared to the batch system. It was also demonstrated that wider channels can significantly increase output while maintaining a shallow channel depth.

3.3.1.3.5 Intramolecular [2 + 2] Photocycloaddition of a Coumarin Derivative

Abbott Laboratories have recently designed a convenient flow-based photochemical microreactor named LOPHTOR. The unique aspect of this new tool was its integration with an autosampler that enabled a set of conditions to be programmed and executed without human intervention. The reaction microchannels of 1000 μm width, 250 μm depth, and 3.93 m length were fabricated from stainless steel that contained integrated cooling channels on the back side. The total volume of the serpentine flow cell channels was 0.98 mL and it was sealed during operation by a fluorinated ethylene propylene (FEP) membrane using nitrogen. This membrane also created a transparent cover of the channel. A medium pressure mercury arc lamp (450 W) with concentrator and cold integral mirror was used for irradiation. On demand, selective wavelength filtering could be provided by a set of uranium-doped quartz plates.

The utility of LOPHTOR for photochemical synthesis was evaluated by the authors using the known intramolecular [2 + 2] cycloaddition of coumarin derivative 18 (Scheme 3.8) as model reaction. For comparison purposes, the same transformation was attempted in a batch mode, that is, in the roundbottom flask fitted with a magnetic stirring bar and condenser.

Initially, Vasudevan and coworkers investigated the dependency between product yields and residence time. Complete conversion of starting material 18 was achieved after 2 h in the microreactor and product 19 was isolated in a yield of 98%. In contrast, a much lower product yield of 30% was obtained.
in the batch system even after prolonged irradiation for 24 h. The substrate portfolio was subsequently expanded and the reaction procedure was applied to other coumarin derivatives. In all cases examined, a similar tendency was established. The product yields were significantly lower using the conventional batch photochemical setup, despite longer reaction times, and were characterized by extensive formation of side products.

The effect of the reactant concentration on the conversion of 18 to 19 was also evaluated. Five different concentrations of 18 in the range from 0.085 to 0.425 M were tested and no decrease in conversion rate was observed. This provides a convenient manner for scale-up of this process to generate hundreds of milligrams of material that will ideally suit early drug discovery applications.

### 3.3.1.3.6 Photochemical [2 + 2] Cycloaddition of Maleimide with 1-Hexyne and Intramolecular [5 + 2] Photocycloaddition of 3,4-Dimethyl-1-Pent-4-Enylpyrrole-2,5-Dione

The application of continuous flow technology to perform organic photochemistry on large scale was investigated by Booker-Milburn et al. The main focus of this research was to show the superiority of a continuous flow system over a batch reactor with respect to the product quality, 24 h isolated yield, and nonstop functionality. This is one of the first research studies on photochemistry where simple UV-transparent FEP tubing was used as the reaction vessel. The authors described this system as a flow reactor rather than a microreactor. However, during the reactor design optimization FEP tubing with an inner diameter of 700 μm and an outer diameter (OD) of 1100 μm was used, which defines the reactor as a microchannel. Four different flow reactors were constructed with hold-up volumes from 60 up to 280 mL, which were entirely determined by the tubing length and dimensions. In two of these designs, FEP tubing with the aforementioned diameter was employed. Being interested in multigram output, Booker-Milburn and coworkers considered wider tubing with the dimensions 2700 μm ID × 3100 μm OD as optimal. One to five layers of this tubing were wrapped around a standard Pyrex or Vycor filter. An immersion well equipped with a 400 or a 600 W medium pressure Hg lamp as light sources was used as a base for this construction.

These reactors were assessed using the [2 + 2] photocycloaddition of maleimide 20 with 1-hexyne 21 to the cyclobutene product 22 and the intramolecular [5 + 2] photocycloaddition of 3,4-dimethyl-1-pent-4-enylpyrrole-2,5-dione 23a to the bicyclic azepine 24a as model systems (Scheme 3.9). Using an
optimized system with three layers of FEP tubing and a Vycor filter, these reactions were performed with outstanding results compared to common batch reactors. A 0.4 M solution of the maleimide 20 underwent 83% conversion at 0.8 mL min\(^{-1}\) flow rate representing a projected yield of the desired cyclobutene 22 of over 685 g/day. At the same flow rate a 0.1 M solution of compound 23a was irradiated and the bicyclic azepine 24a was isolated in a yield of 80%. This remarkable result represents a 24 h yield of 178 g of 24a.

Using flow reactors, the residence time could be tuned by adjusting the volume of the reactor and the flow rate. Following this strategy, problematic photochemical reactions could be performed continuously, achieving the highest possible yield of product and limiting by-product formation. To demonstrate this principle, the authors selected the intramolecular [5 + 2] photocycloaddition reaction of 3,4-dichloro-1-pent-4-enyl-pyrrole-2,5-dione 23b to the bicyclic azepine 24b and tested it in flow and batch setups. As expected, the desired azepine 24b was obtained in significantly higher yield in the flow reactor (45 g) compared to the batch system (0.5–1 g). The reactor was also applied to the protecting-group-free synthesis of (±)-neostenine using the [5 + 2] photocycloadditions as a key step.\(^{52}\)

### 3.3.1.4 Photodimerization of Maleic Anhydride

An important example of a problematic photochemical reaction is the photodimerization of maleic anhydride 25 (Scheme 3.10). It is known that this reaction yields the insoluble cyclobutane tetracarboxylic dianhydride (CBTA) 26, which is used as raw material for polyimide and for alignment films for liquid crystal displays. This reaction was selected by Yoshida and coworkers as a model reaction for a novel liquid/gas slug flow microreactor.\(^{53}\)

The microreactor approach demonstrated that the clogging problem within the reactor can be overcome by a combination of slug flow and ultrasonication. Inert N\(_2\) gas introduced into the solution flow as a spacer swept through the reactor tube and transported precipitated products in the liquid segments. At the same time, ultrasound vibrations inhibited the adhesion and sedimentation of precipitate within the reactor tube. FEP tubes of various sizes were used as the reaction vessel and the impact of the tube dimensions on product conversion was examined. Additionally, the effects of maleic anhydride concentration and residence time were also investigated. A standard 400 W high-pressure Hg lamp was employed as a light source. The experimental results showed that a 10% solution of maleic anhydride 25 underwent a satisfactory conversion of 70% after a residence time of 22 min in a FEP tube of 1.4 mm OD and 0.8 mm ID, respectively. The quality of the desired product 26 in the microreactor was of higher purity when compared to that from the batch system (cylindrical glass vessel with an ID of 75 mm and a height of 300 mm). Moreover, the unique design of the slug flow microreactor made it adaptable for continuous circulation and recycle operation. This allowed for an improvement of conversions and reduction in maleic anhydride waste. The slug flow microreactor was operated continuously for over 16 h without clogging.

### 3.3.1.5 Diastereodifferentiating Addition of Methanol to (R)-(+)-(Z)-Limonene

Another example of asymmetric synthesis performed in microreactors was the toluene-sensitized photoaddition of methanol to (R)-(+)-(Z)-limonene 27 (Scheme 3.11) as reported by Sakeda et al.\(^{54}\) This transformation occurs with the formation of three addition products: cis- and trans-4-isopropenyl-1-methoxy-1-methylcyclohexane (cis 28 and trans 29 isomers) and exocyclic isomer 30. Compared to

Scheme 3.10 Photodimerization of maleic anhydride.
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A microbatch cell, the authors found faster reactions and higher diastereomeric excess (d.e.) values in microchanneled reactors. Three kinds of quartz microreactors (Shimadzu Co.) with channel sizes of 500 \( \mu \text{m} \times 300 \mu \text{m} \times 60 \text{mm} \), 400 \( \mu \text{m} \times 40 \mu \text{m} \times 100 \text{mm} \), and 200 \( \mu \text{m} \times 20 \mu \text{m} \times 100 \text{mm} \) (width \( \times \) depth \( \times \) length) and a quartz batch cell with a total volume of 1 mL (light passlength of 3 mm) were utilized for this study. Irradiations were conducted using a low-pressure mercury lamp (40 W, 254 nm). The irradiation time within the microchannels was controlled by the injection rate of the syringe pump. The yield of cis and trans isomers increased linearly during the examined irradiation period of 135 s within the microreactors. In contrast, the yield in the batch cell increased linearly only up to 20 min and reached a plateau. Furthermore, the diastereomeric excess value was 30.6\% (36 s of irradiation) in the microreactor while it was 28.7\% (15 min of irradiation) in the batch cell. The origin of the difference observed for the d.e. value in the MR versus the batch cell was clarified by the estimated reaction constants for cis and trans isomer formation. These constants were significantly higher for the microchannels than for the batch chamber. In addition, a comparison study on the effect of the channel size on the photon efficiency was performed. Photon efficiency increased with decreasing channel size and was greater for the microreactors (0.11–0.29) than the batch system (0.06). The superior performance of the microreactor was explained by a better light penetration, the higher spatial illumination homogeneity, short exposure times, and a fast and continuous product removal from the irradiated area, which suppressed side reactions.

3.3.1.6 Continuous-Flow Synthesis of Vitamin D₃

The first example of a combined photochemical and thermal reaction in a microreactor was described recently by Takahashi et al. The two-step conversion of provitamin D₃ 31 to vitamin D₃ 33 via previtamin D₃ 32 was selected as a model transformation in this study (Scheme 3.12).

The first step of this transformation is a photochemical one and was carried out in a custom-made quartz microreactor with a channel 200 \( \mu \text{m} \) deep, 1 mm wide, 250 mm long, and with a volume of 50 \( \mu \text{L} \). For the second step, a microreactor that enabled simultaneous photo- and thermal reactions was utilized. Its microchannel was 200 \( \mu \text{m} \) deep, 1 mm wide, and 500 mm long and had an internal volume of 100 \( \mu \text{L} \).

SCHEME 3.11 Diastereodifferentiating photosensitized addition of methanol to (R)-(+-)(Z)-limonene.

SCHEME 3.12 Two-step conversion of provitamin D₃ to vitamin D₃.
Those two microreactors were connected via polyetheretherketone (PEEK) tubing and employed a single 400 W high-pressure mercury lamp. The first reactor was irradiated through a Vycor filter (313–578 nm). The second reactor was irradiated through a combination of a Vicor and glass UV filters (360 nm) and was placed in a hot oil bath (100°C). Using this setup, an optimization study on the reaction conditions, in particular the solvent, concentration, and flow rate, was carried out. A fairly concentrated 30 mM solution of provitamin D₃ in 1,4-dioxane was introduced at a flow rate of 5 μL min⁻¹ with a syringe pump. After chromatographic purification, the desired vitamin D₃ 33 was obtained in a yield of 32% (HPLC-UV yield: 60%), which was significantly higher compared to the existing industrial process, where the yield of vitamin D₃ is below 20%.[30] The parallel application of photo- and thermal conditions within the second step of the vitamin D₃ synthesis shifted the equilibrium of the competing photoisomerization of the side product tachysterol (not shown) toward previtamin D₃ 32. Moreover the generation of second undesired product lumisterol (not shown) was suppressed to less than 10%. Consequently, the microflow synthesis of vitamin D₃ did not require any purification of intermediates or high-dilution conditions, thereby reducing the amounts of waste.

### 3.3.1.7 Photodecarboxylative Benzylations of Phthalimide

Recently, Oelgemöller et al. have studied photodecarboxylative benzylations of phthalimide under batch and microflow conditions.[56] The benzylated hydroxyphthalimides 36a and 36b were synthesized from the corresponding phenylacetates 35a or 35b and phthalimide 34 (Scheme 3.13), respectively.

Conventional batch transformations were performed in a Pyrex Schlenk tube (volume 100 mL) that was irradiated in a Rayonet chamber reactor equipped with 16 UVB fluorescent lamps (8 W each, λ = 300 ± 25 nm). The dwell reactor (mikroglas) was made from Foturan™ glass and consisted of a (bottom) serpentine reaction channel (0.5 mm depth, 2 mm width, and 1.15 m length) and a top heat-exchanging channel. The microreactor was placed under a UV panel (Luzchem) fitted with five UVB lamps. Only two reactions were tested under micro conditions and improved yields of 97% (36a) and 98% (36b) were achieved after 2 h. Despite its larger lamp power, the batch reactor gave somewhat lower yields of 92% (36a) and 80% (36b) after an extended irradiation period of 3 h. The cosolvent acetone (50 Vol-%) functioned as a sensitizer and the improved performance in the microreactor was thus explained by a better light penetration through the solution. The same authors extended their study to other intra- and intermolecular photodecarboxylation reactions involving phthalimides and alkyl phenylglyoxolates.[57,58]

### 3.3.1.8 Photoaddition of Isopropanol to Furanones

Oelgemöller and coworkers have also investigated the 4,4′-dimethoxybenzophenone (DMBP)-sensitized addition of isopropanol 38 to furanones 37a–c (Scheme 3.14).[59–61] The reaction was chosen as a model for a microreactor comparison study. Three types of microstructured reactor setups were examined; the dwell device (described in Section 3.3.1.7) under a UVA-panel (5 × 8 W), a microchip (Micronit

![Scheme 3.13](image)

**SCHEME 3.13** Photodecarboxylative addition of phenylacetates to phthalimide.
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Microfluidics) incorporating a panel of 365 nm high-power UV-LEDs (6 × 75 mW), and an in-house microreactor that consisted of two parallel PTFE capillaries wrapped around a Pyrex tube containing a single UVA-lamp (1 × 8 W) in its center. Conversion rates of 37a–c were determined by NMR spectroscopy. The results from the microflow systems were compared to those in a conventional test tube irradiated in a batch chamber reactor (Rayonet, 16 × 8 W).

The batch system, the dwell device, and the microcapillary reactor gave high to almost complete conversions to 39a–c after just 5 min of irradiation. Despite its weaker light sources, the microchip reached high conversions already after 2.5 min. Based on the conversion rates, reactor geometries and energy efficiency calculations the microreactor systems gave superior results compared to the batch process. Of the three microreactor designs examined, the LED-driven microchip gave the best overall results. This was explained by the highest light transmission through the very shallow reaction channel of the microchip (150 μm depth), compared with the wider channel of the dwell device (500 μm depth) and the inner diameters of the microcapillary (558 μm) and the test tube (9 mm), respectively. However, the capillary reactor was seen as the best setup in terms of handling and improvement potential.

3.3.1.9 Photocyanation of Pyrene

The photocyanation of pyrene 40 (Scheme 3.15) across an oil/water interface has been described by Ueno and coworkers.62 This transformation was performed in microchips made in-house from polystyrol substrate, with channel width of 100 μm, depth of 20 μm, and length of 350 mm. The reactors had either two or three inlets to the serpentine reaction channels. This allowed for a separate introduction of the oil and water phases, with equal flow rates, thus ensuring formation of stable water/oil or water/oil/water interfaces, respectively. The microchips were irradiated with light from a high-pressure mercury lamp (300 W) through a copper sulfate solution filter (>330 nm).

An aqueous solution of sodium cyanide (1 M) and a solution of pyrene 40 (20 mM) and 1,4-dicyanobenzene (DCB, 40 mM) in propylene carbonate were pumped through the reactors. The product, 1-cyanopyrene 41, remained in the oil layer. After a residence time of 210 s, the photoproduct 41 was obtained in yields of 28% for the oil/water system and 73% for the water/oil/water system, respectively. Below a flow rate of 0.2 μL min⁻¹ no stable oil/water interface could be obtained, which prevented further improvement of conversion rates and consequently yields.

![Scheme 3.14](image1.png)

**SCHEME 3.14** Sensitized isopropanol addition to furanones.

![Scheme 3.15](image2.png)

**SCHEME 3.15** Photocyanation of pyrene.
3.3.2 Heterogeneous Reactions

The heterogeneous reactions are characterized by interactions between liquid and gaseous reagents. It is thus necessary to continuously provide a supply of reagent gas to the reaction media. The falling-film-type reactor was especially designed for the purpose, but other reactor systems have been utilized as well.

3.3.2.1 Photooxygenation Reactions

3.3.2.1.1 Photochemical Generation and Addition of Singlet Oxygen to \( \alpha \)-Terpinene

The first study concerning the safe synthesis of the potentially explosive endoperoxide in a microreactor was reported by Wootton et al.\(^6\) The photochemical synthesis of ascaridole 43 proceeds via addition of singlet oxygen to \( \alpha \)-terpinene 42 in the presence of an organic dye as sensitizer (Scheme 3.16). This reaction requires sufficient oxygen saturation and therefore large quantities of oxygenated organic liquids with explosive nature are often formed in conventional conditions.

The reactor was built in-house from a glass substrate and consisted of two inlets at the start of the serpentine irradiation area (total length 50 mm, average depth of 50 μm, and average width of 150 μm) and an outlet channel. A methanol solution of \( \alpha \)-terpinene and Rose Bengal was introduced via a divergent inlet channel with a flow rate of 1 μL min\(^{-1}\) and mixed with oxygen on-chip (flow rate of oxygen of 15 μL min\(^{-1}\)). This design made presaturation of the \( \alpha \)-terpinene solution with oxygen unnecessary. Irradiation was performed using an unfiltered tungsten lamp (20 W, 6 V). The small volume of aerated solvent in the system together with nitrogen degassing of the product mixture at the outlet avoided accumulation of oxygenated solvents. The conversion of ascaridole 43 after workup was determined by GC and was 85% at a residence time of only 5 s.

3.3.2.1.2 Photochemical Generation and Addition of Singlet Oxygen to Cyclopentadiene

A further example for the safe conduction of a potentially explosive reaction in a microstructured reactor has been described by Jähnisch and Dingerdissen.\(^6\) These authors showed that the falling-film microreactor (FFMR by IMM) is also suitable for the continuous photochemical generation of singlet oxygen in the presence of dissolved Rose Bengal. The photooxygenation of cyclopentadiene 44 by singlet oxygen, followed by the reduction to 2-cyclopenten-1,4-diol 46, has been chosen as a model reaction (Scheme 3.17). The initially generated endoperoxide 45 is potentially explosive, which represents a safety concern for the large-scale conventional synthesis.

\[ \text{SCHEME 3.16} \quad \text{Photoaddition of singlet oxygen to } \alpha \text{-terpinene.} \]

\[ \text{SCHEME 3.17} \quad \text{Photoaddition of singlet oxygen to cyclopentadiene and subsequent reduction.} \]
The photooxygenation step of this transformation took place in the reaction plate of the falling-film microreactor, which had 32 parallel microchannels of 66 mm length, 600 μm width, and 300 μm depth. A methanol solution of cyclopentadiene was pumped through the microreactor at a flow rate of 1 mL/min, thus creating a very thin layer of liquid. The reactor was additionally cooled to 10°C–15°C. The effluent containing the endoperoxide was passed into a solution of thiourea in methanol at 10°C. The aforementioned techniques and short holdup insured that the quantity of the endoperoxide and the oxygenated solution was always kept at a safe level. As light source, a xenon lamp (1000 W) was used. The oxygen was fed to the reactor counter-currently to the liquid with a flow rate of 15 L h⁻¹. Under nonoptimized conditions, the desired product 2-cyclopenten-1,4-diol was obtained in a yield of 20% (0.95 g). This study proved that a falling-film microreactor is suitable for photooxygenation reactions on a preparative scale.

### 3.3.2.1.3 Photosensitized Oxidation of Citronellol

The photochemical oxidation of (S)-(−)-β-citronellol 47 is used in the fragrance industry to produce (−)-rose oxide. The Schenck-ene reaction of 47 with singlet oxygen yields a mixture of the peroxides 48 and 49 (Scheme 3.18). This transformation was selected by Meyer and coworkers as a model reaction for a reactor comparison study based on space–time yields (STY) and photonic efficiencies.

The microscale oxidation of 47 was carried out in a commercially available microstructured reactor (Little Things Factory GmbH) that was made of HT-residence glass and consisted of a single half-round serpentine channel with a width of 1 mm, depth of 0.5 mm, and a total volume of 270 μL. The reaction mixture was saturated with compressed air in a double-wall storage container outside the microreactor and was continuously pumped through the microreactor in a loop. The illumination took place for about 60–70 h using an LED array (4 × 10 LEDs, λ_max = 468 nm) with light intensities from 1 to 7.98 mW/cm². The batch experiments were performed in the modified Schlenk-tube reactor with an illuminated volume of 7.46 mL (total volume 40 mL). A LED-stick (2 × 15 LEDs, λ_max = 468 nm) with a light intensity of 6.5 mW/cm² was placed at the center of this reactor. Prior to irradiation for 5–8 h, the ethanol solution of (−)-β-citronellol was purged with compressed air for 20 min. The progress of the reaction was monitored by HPLC. The photonic efficiency for the LTF-microreactor was 0.048, which was two times higher than for the Schlenk reactor. Likewise, the STY was about one order of magnitude higher in a microreactor than in a Schlenk reactor. In contrast to the industrial process, a ruthenium complex (tris(4,4'-tert-butyl-2,2'-dipyridyl)-ruthenium(II)-dichloride) was used as photosensitizer. While the ruthenium complex has a higher photostability and quantum yields of singlet oxygen formation compared to Rose Bengal, a sensitizer comparison study with a 450 W xenon lamp (λ = 50–1600 nm) showed that Rose Bengal is about twice as efficient as the ruthenium complex.

### 3.3.2.2 Photochlorination Reaction

The portfolio of heterogeneous reactions is not limited to photooxygenations. The selective photochlorination of toluene-2,4-diisocyanate 50 (TDI, Scheme 3.19) was examined by Jähnisch et al. in a falling-film reactor (IMM). The main product of this transformation, 1-chloromethyl-2,4-diisocyanatobenzene 51 (1Cl-TDI), is used industrially as an intermediate in the synthesis of polyurethanes.
The experiments were carried out using a reaction plate with 32 parallel channels of 600 μm width, 300 μm depth, and 66 mm length each. A relatively concentrated solution of toluene-2,4-diisocyanate 50 (100 mmol in 30 mL of tetrachloroethane) was introduced to the reactor at flow rates ranging from 0.12 (residence time of 14 s) to 0.57 mL/min (residence time of 5 s) and was irradiated by the xenon lamp (1000 W, unfiltered) through the quartz window of the reactor. The backside of the reaction plate was kept at a temperature of 130°C to reduce the undesired side reaction to the ring chlorinated product toluene-5-chloro-2,4-diisocyanate (5Cl-TDI) 52. The conversion of TDI 50 drastically increased from 30% to 81% when increasing the residence time from 5 to 14 s, while the selectivity of the target product 1Cl-TDI 51 decreased somewhat from 80% to 67%. The yield of 1Cl-TDI 51 improved from 24% after 5 s to 54% after 14 s. The effect of the reactor material was investigated by using different reaction plates, one nickel and one iron. The selectivity of the desired product 51 was affected notably by the plate material (50% for iron, 67% for nickel) and this was explained by the formation of FeCl₃, which functions as a Lewis acid.

For comparison, batch reactions were carried out in the glass flask using a high-pressure mercury lamp as a light source. At similar conversion rates of toluene-2,4-diisocyanate 50 (55% in FFMR, 65% in batch), the selectivity for the target product 1Cl-TDI 51 was significantly higher in the batch reactor (54%) compared to the FFMR (5%). The space–time yield achieved in the microstructured reactor (401 mol L⁻¹ h⁻¹) for the formation of product 51 was orders of magnitude higher compared to the conventional reactor (1.3 mol L⁻¹ h⁻¹). The advanced performance of photochlorination reaction in falling-film microreactor was explained by the better penetration of photons and the higher mass-transfer rates in the thinner liquid films. Also the chlorine radicals are located over the total film volume and high local concentration, which leads to recombination, are avoided. In a conventional reactor, the radical concentration near the light source is high, while at the center of the reactor it is very low. As a result, the selectivity of the desired side-chain chlorinated derivatives decreases and prefers to take place at the aromatic core instead.

Recently, Ryu and coworkers have studied the photochlorination of cycloalkanes using various microflow reactors. Monochlorination of cyclohexane to chlorocyclohexane was achieved using natural light and molecular chlorine. Likewise, the reactions of various cycloalkanes with sulfuryl chloride were successfully realized with high monochlorination selectivity using a 15 W black light.

### 3.3.3 Catalytic Reactions

Due to their large surface-to-volume ratios, microreactors are especially interesting for use in catalytic reactions. Immobilization of a catalyst on the channel walls consequently increases the specific illuminated surface area of the photocatalyst and subsequently maximizes interactions of catalyst material with light and reagents. The product is simply separated from the catalyst by the flow and this feature can also improve the selectivity of the process. One of the most widely used heterogeneous photocatalyst is titanium dioxide (TiO₂). Catalytic microphotoreactors have been particularly studied for the treatment of waste water and exhaust air, while synthetic applications are rather rare.
3.3.3.1 Photocatalytic Synthesis of \( \text{L}-\text{Pipecolinic Acid} \)

The first application of a photocatalytic microsystem in organic synthesis has been reported by Takei et al.\(^8\) The authors studied the photocatalytic synthesis of \( \text{L}-\text{pipecolinic acid} \) (L-PCA) from \( \text{L}-\text{lysine} \) (Scheme 3.20) in a home-made microchip. The titania-modified microchannel chip (TMC) used in this study was composed of two Pyrex glass substrates. One substrate with branched channels of 700\( \mu \)m wide and 3.5\( \mu \)m deep was fused to another substrate with a 300 nm thick coating of TiO\(_2\). The TiO\(_2\) coating served as catalyst and was made of particles with a diameter of 100 nm. The film contained platinum as reducing agent at 0.2 wt%. A high-pressure mercury lamp with a UV transmitting filter was used for irradiations.

A 2 mM aqueous solution of \( \text{L}-\text{lysine} \) was pumped through the microchip at different flow rates. The crude product mixture was collected from the reactor outlet and was analyzed by HPLC. The results were compared to a batch system comprising a bulk cuvette and TiO\(_2\) particles (diameter 25 nm) in suspension. It is notable that the ratio of illuminated surface area to the solution volume was comparable in both setups (0.29 m\(^2\)/mL for the TMC and 0.25 m\(^2\)/mL for suspended particles). The conversion of \( \text{L}-\text{lysine} \) to \( \text{L}-\text{pipecolinic acid} \) in the microchip reached 87% after a residence time of less than 1 min (0.86 min). In the batch experiment the same conversion rate of 86% was achieved only after 1 h. Analysis of selectivity and enantiomeric excess (e.e.) revealed that these parameters were independent of reaction time and were similar in the micro- and bulk setup (selectivity was 22% and e.e. was 50% and 47%).

In contrast, the productivity for \( \text{L}-\text{PCA} \), that is, the amount produced per minute, was much lower in the microchip (2.8 \times 10^{-10} \text{mol/min}) compared to the bulk system (1.9 \times 10^{-8} \text{mol/min}). This was due to the larger volume of the batch cuvette (4 mL), but this disadvantage may be overcome through number-up of microreactors in the future. A significant advantage of the catalytic microstructured reactor is the exclusion of the separation step, as the immobilized photocatalyst remains in the microchannel while the product is eluted.

3.3.3.2 Photocatalytic N-Alkylation of Amines

Synthetic photocatalysis in microstructured reactors has been intensively studied by Matsushita and Ichimura et al.\(^7\) In their work they used not only miniaturized reactors but also miniaturized light source such as UV-LED arrays. A remarkable example was the TiO\(_2\)-catalyzed N-ethylation of benzylamine (Scheme 3.21).

This reaction was studied in three house-made quartz microreactors with specific illuminated surface areas per unit of volume of 7.3 \times 10^3 \text{m}^2/\text{m}^3, 6.0 \times 10^3 \text{m}^2/\text{m}^3, and 4.0 \times 10^3 \text{m}^2/\text{m}^3, respectively. These large areas

\[ \text{H}_2\text{N} \quad \text{COOH} \]
\[ \text{H}_2\text{N} \quad \text{NH}_2 \]

Scheme 3.20 Photocatalytic synthesis of \( \text{L}-\text{pipecolinic acid} \).
were realized in reactor channels with a width of 500 μm, length of 40 mm, and depth of 300, 500, or 1000 μm, respectively. The sides and bottom of the channels were coated with TiO$_2$ catalyst (Pt-loaded and Pt-free). A 1 mM alcohol solution of benzylamine 55 was fed into the microreactors at a flow rate between 2 and 40 μL/min and was irradiated with an UV-LED array ($\lambda_{\text{max}}$ = 365 nm) with a total optical power output of 9.8 mW. The product solutions were analyzed by GC or HPLC methods. Benzylamine 55 could be converted in high selectivity to the N-alkylated product 56 in yields of 43% after just 90 s or 85% after 150 s, respectively.

Ethanol was found to be the most suitable solvent for this transformation due to the kinetic stability of its ethoxy radical intermediate. Consequently, ethanol was applied for alkylation reactions of other amines. Aniline and butylamine were tested and gave the corresponding N-ethylated products in yields of 11% and 36%, respectively, after a residence time of 180 s.

The effect of the depth of the microchannel was also examined and showed that the efficiency of N-alkylation was enhanced with decreasing channel depth. This observation was attributed to the increased illuminated surface-to-volume ratio.

Remarkably, this reaction proceeded in the presence of titanium dioxide photocatalyst, even without cocatalyst platinum and yields of up to 98% of N-alkylated product 56 were achieved after 90 s. In contrast to other studies, N-alkylation did not occur under batch conditions without the presence of platinum. Selectivity was high in the microreactors and no N,N-dialkylated product 57 was obtained in the presence or absence of platinum. This was achieved by the continuous-flow mode and monochromatic irradiation, which prevented the undesired follow-up reaction. In contrast, bis-alkylation is frequently observed under batch conditions.

The authors further expanded their study on the N-alkylation of amines by optimizing the irradiation and flow conditions. A novel photocatalytic microreaction system with a microchannel 500 μm wide, 25 μm deep, and 50 mm long was developed. The high surface area of TiO$_2$/Pt photocatalyst (4.0 × 10$^3$ m$^2$/m$^3$) achieved was irradiated with a more powerful LED array (total optical power output 490 mW). In this microsystem, the alkylation of amines (benzylamine, aniline, and piperidine) proceeded faster compared to the previously described model. For example, N-ethylbenzylamine 56 was obtained in a yield of 62% after 6 s, however, the bis-alkylated product N,N-diethylbenzylamine 57 was also detected in 3.8% yield. The same trend was noticed for aniline. At a shorter residence time (5 s), the formation of the main product 56 increased with increasing light intensity, whereas at a prolonged residence time (60 s), the formation of the tertiary amine 57 enhanced with increasing light intensity. These results clearly demonstrate that the outcome of the reaction (mono- vs. bis-alkylation) can be controlled by precise control of the irradiation and flow conditions.

### 3.3.3.3 Photocatalytic Reduction in Microreactors

Another example of a synthetically useful transformation has been also reported by Matsushita et al. The authors examined the photocatalytic reduction of benzaldehyde 58 and nitrotoluene 60 (Scheme 3.22) in microreactors.

![Scheme 3.22](attachment:image.png)

**SCHEME 3.22** Photocatalytic reduction of (a) benzaldehyde and (b) nitrotoluene.
For this study, photocatalytic quartz microreactors with immobilized photocatalyst were fabricated. These reactors contained a microchannel of 500 μm width, 100 μm depth, and 40 mm length with a total specific illuminated surface area per unit of liquid of approximately $1.4 \times 10^4 m^2/m^3$. The bottom and side walls of the microchannel were coated with a TiO$_2$ layer. An array of 365 nm UV-LEDs with an optical power output of 1.4 mW was employed as a light source.

Alcoholic solutions of benzaldehyde saturated with nitrogen were used. Ethanol was found to be the most efficient solvent and gave a yield of benzyl alcohol of 11% after 60 s. Photoreduction of $p$-nitrotoluene gave $p$-toluidine in yields of 46% after 60 s. Although the reactions were not further optimized, they demonstrated that microstructured reactor can be utilized for the efficient reduction of organic compounds.

### 3.3.4 Microphotochemistry in Industry

The reactions described earlier have been performed on laboratory scales. However, isolated examples of gram-scale synthesis have been achieved. In contrast, photochemical processes realized on industrial scale are still rare. There are several contributing factors for this neglect. Microreactors are generally made from expensive materials, such as stainless steel or quartz glass. The fabrication of reactor microchannels is also costly and complicated. Despite the increased utilization of energy-efficient LEDs as light sources for photochemical reactions, medium- and high-pressure mercury lamps are still predominantly used in industry. These conventional lamps are costly to run, have a limited lifetime, and additionally tend to generate a large amount of heat and therefore require additional cooling systems. In contrast, product synthesis in kilograms quantity using microreactor clusters requires complex automation and control devices.

Nevertheless, the proven advantages of photochemical synthesis in microreactors make it an interesting synthesis tool for low-volume processes.

#### 3.3.4.1 Synthesis of 10-Hydroxycamptothecin and 7-Alkyl-10-Hydroxycamptothecin

The first industrial production of camptothecin derivatives using a microphotoreactor plant was realized by Heraeus. The synthesis of 10-hydroxycamptothecin and 7-ethyl-10-hydroxycamptothecin from camptothecin-N-oxide or 7-ethyl camptothecin-N-oxide (Scheme 3.23) was performed in this plant. Compounds and are precursors in the synthesis of the anticancer drugs irinotecan and topotecan.

The developed plant consisted of twelve microreactors operated in parallel and irradiated by individual light sources (Figure 3.4). The microreactors themselves are characterized by their simple design. They comprise of two parallel quartz glass separated by a spacer, which creates a gap from 40 to 100 μm. The design produces a very thin film of the reaction solution. As light source, mercury high-pressure emitters (Heraeus Noblelight) with a UV emission wavelength range from 350 to 400 nm and an optical power output of 250 W were used. These lamps also comprised spectral filters with a specific band pass and coating on both sides.

The productivity of the microreactor plant was evaluated using the amount of 10-hydroxycamptothecin produced within 24 h. At conversion rate of 95% of , the desired product is produced in

![Scheme 3.23 Synthesis of camptothecin derivatives.](image-url)
an amount of 2 kg/day (yield 90%). In contrast, the batch system reached a maximum conversion of only 85% and a much lower product yield of 50%. Moreover, the concentration of the camptothecin–N-oxide solution used in the microsystem (0.6 wt%) was six times higher than in the batch system (0.1 wt%).

This remarkable process represents the first example of a photochemical production in a microreactor array.

3.4 Concluding Remarks

The examples presented in this chapter clearly demonstrate the versatility and potential of microphotochemistry as a synthesis tool. Microstructured reactors have been successfully used for a broad range of photochemical reaction types. The technology takes full advantage of the small dimensions and flow condition of microtechnology. This results in the reduction or complete elimination of side reactions, enhanced selectivity, increased photonic efficiency, and reduction of hazards and wastes. The large area-to-volume ratio within the microchannels is especially advantageous for photocatalytic applications. It is hoped that microphotochemistry will emerge as an important future R&D tool, for example in modern lead development processes, and ultimately as a production technology. The Heraeus process clearly demonstrates this potential. Consequently, microphotochemistry may emerge as “the new photochemistry of the future.” This statement refers to Giacomo Ciamician’s visionary lecture, presented before the International Congress of Applied Chemistry in New York in 1912.86

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References

14. A. de Mello and R. Wootton, But what is it good for? Applications of microreactor technology for the fine chemical industry, *Lab Chip*, 2002, 2, 7N–13N.
23. A. Albini and M. Fagnoni, Green chemistry and photochemistry were born at the same time, *Green Chem.*, 2004, 6, 1–6.


Microphotochemistry: Photochemical Synthesis in Microstructured Flow Reactors


