

Micro-photochemistry: photochemistry in microstructured reactors. The new photochemistry of the future?^{†‡}

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The use of a confined space in which to carry out reactions has proven popular in recent years, as demonstrated by the large volume of work published on 'molecular microreactors' such as zeolites, micelles and nanoparticles. This article looks at reactions in microstructured reactors, also known as microchannelled reactors or microreactors. In general, these consist of a 'chip' with narrow channels etched into it. Microstructured reactors have been the subject of several review articles to date, focusing on preparation, types of reactions that may be carried out and on the potential for 'green' applications. However, the use of microstructured reactor technology in photochemistry has, until now, not been subject to review. This perspective aims to outline the work done to date in this area and in particular to demonstrate the advantages and future perspectives of this technology in photochemical processes. Photochemistry in microstructured reactors is an emerging area of interest and to date has demonstrated significant potential as a viable alternative to traditional photochemical synthesis.

Introduction

With the recent interest in miniaturisation, it is no surprise that chemical researchers have shown an interest in microtechnology. This is reflected in the many volumes of work published on micro- and nanotechnologies in chemical synthesis since the beginning of the 21st century. As a consequence, the term '(molecular) microreactor' has become commonplace in chemical communities. This term refers to a confined space in which a chemical reaction

can occur and has been used in reference to micelles, zeolites, supramolecular systems and nanoparticles.¹⁻⁷ However, it also refers to microstructured reactors, otherwise known as microchannelled reactors. In general, microstructured reactors consist of a solid support with channels of only several micrometres in width and depth (10–1000 μm). The overall size of the 'chip' is usually only several centimetres in length, width and depth. Over the past decade, microstructured reactors have become increasingly more widespread in research, in particular in analytical applications. The 'lab on a chip' concept has led to a great deal of interest in miniaturisation of technology.⁸⁻¹² In particular total miniaturisation is of interest, where the pumping system and detector are part of a micro modular system. Microstructured reactors have also demonstrated significant promise in the area of synthetic organic chemistry, including photochemical transformations, as detailed in many review articles to date.¹³⁻²⁷ However, the application of microstructured reactors in organic photochemistry has not

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[†] This subtitle refers to Giacomo Ciamician's visionary lecture *The Photochemistry of the Future*, presented before the International Congress of Applied Chemistry in New York in 1912.⁴⁸

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Michael Oelgemöller and Emma Coyle

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Emma Coyle was born in 1983 and grew up in Roscommon, Ireland. She was awarded the status of best student of her course for the year 2006, when she received her degree in Chemical and Pharmaceutical Science from Dublin City University. She is currently a PhD student in the School of Chemical Sciences and the National Centre for Sensor Research at Dublin City University. Her work focuses on the study of green chemistry, with a particular interest in solar synthesis of fine chemicals.

been subject to review in its own right. Solely the photochemical activities of Matsushita *et al.* have recently been summarised.¹⁶

Commercially available microstructured reactors have been commonly adopted for photochemical applications, particularly the serpentine channel and the falling film type reactor. The main feature of the serpentine reactor is its long path length, which may range from several centimetres to a metre or more. The dwell device produced by mikrogas (Fig. 1), for example, has a total path length of 1.15 m (20 turns) on a 118 mm × 73 mm aperture. This reactor consisted of a (bottom) serpentine channel with a second (top), heat-exchanging channel through which water is passed in order to control the reactor temperature. The longer path length can be used to increase residence time, and is therefore suited to reactions in which a longer reaction time is needed. In the serpentine reactor the reagents may be pre-mixed, or mixed on-chip *via* a 'T' (or 'Y') structure, *i.e.* two separate inlets that lead into a single channel.

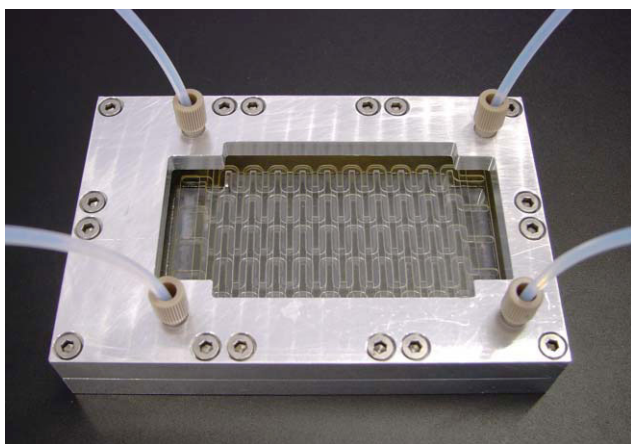


Fig. 1 Dwell device (mikrogas).²⁸ The parallel heat-exchange channels can be clearly seen.

Another commercially available design is the falling film reactor (Fig. 2), which utilises a multitude of thin falling films that move by gravity force in parallel microstructured channels. These devices are specifically designed for gas-liquid reactions, *e.g.* oxidations and hydrogenations, where the gas flows against a film of liquid. The high specific interface area (up to 20 000 m²/m³) enables



Fig. 2 Cylindrical falling film micro reactor (FFMR-cyl) for 10-fold scale-up and its standard version FFMR (with courtesy of IMM).²⁹

sufficient saturation of the film with reactant gas. This reactor type is thus more efficient than closed channel devices, which require presaturation of the reaction mixture with reagent gas. Scale-up can be achieved using cylindrical reactor models.

Beside commercially available types of micro reactors, many researchers continue to custom build their own reactors. This enables flexibility with respect to solid substrate and glass used, as well as optimisation of path length and depth. An example of a microchip reactor in combination with a UV-LED-array is shown in Fig. 3.

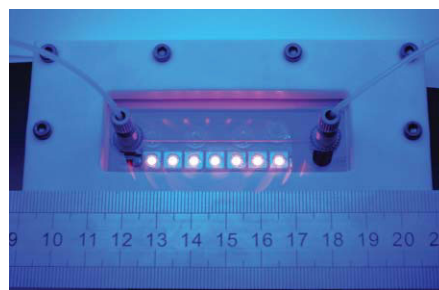


Fig. 3 Quartz microchip design with 365 nm/500 mV UV-LED-array, Matsushita *et al.*³⁹

Engineering of microreactors is a significant research area, with many groups working to optimise reactor design using photochemical processes as model reactions. The engineering of a microstructured reactor may be done using a variety of techniques.³⁰ The solid support used may be glass, silicon, metal, ceramic or polymeric in nature. The choice of solid may depend on the reaction to be carried out, for example some polymers are not stable to all solvents. For photochemical reactions use of glass as the solid substrate is ideal, as this provides a transparent 'window' through which the reaction mixture may be irradiated. The channels are generated using photolithography, hot embossing, microlamination and other microfabrication techniques.

The photochemical reactions carried out to date may be categorised as homogeneous reactions (such as photocyanation,³¹ [2 + 2]-cycloadditions,^{32,33} the Barton reaction,³⁴ photochemical pinacolisation³⁵), heterogeneous reactions between liquid and gaseous reagents (*e.g.* additions of singlet oxygen^{36–38}) or catalytic processes using semiconductors (such as catalytic reactions using titanium dioxide^{39–42}).

Photochemistry—past and present

Photochemical reactions have occurred in nature since before life began on Earth, but interest in laboratory applications of photochemistry did not commence in earnest until the eighteenth century. One of the first photochemical reactions noted in a laboratory was Scheele's observation of the blackening of silver halide salts in sunlight (in 1775). A small amount of interest in photochemistry continued through the eighteenth century and nineteenth century.⁴³

Understanding of photochemistry improved through the development of the laws of photochemistry—the Grotthaus–Draper law (1842) and the Stark–Einstein law (1913). The scope of organic photochemistry was greatly expanded during the twentieth century,⁴⁴ through the works of Giacomo Ciamician in Italy

(1857–1922),⁴⁵ Alexander Schönberg in Egypt (1892–1985)⁴⁶ and Günther Otto Schenck in Germany (1913–2003)⁴⁷ as well as many others. At the International Congress of Applied Chemistry in New York in 1912, Ciamician presented his remarkable vision of “The Photochemistry of the Future”.⁴⁸ In this speech he outlined his belief that photochemistry, which was an entirely solar discipline at that time, could be a key component of industry in the future: “*On the arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over the plains, and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them even more abundant fruit than nature, for nature is not in a hurry and mankind is.*”

However, early research in organic photochemistry was hindered by the lack of suitable light sources and synthetic photochemical reactions were carried out outdoors in sunlight. As a result, interest in synthetic photochemistry failed to endure and studies in the subject remained rare for many years. With the advent of better technology,⁴⁹ organic photochemistry underwent a revival. Developments in reactor design and use of more specific light sources led to an increase in research in the area in the latter part of the 20th century. A recent review by Hoffmann outlines current progress in synthetic organic photochemistry,⁵⁰ focussing on research since the beginning of the 21st century. This review demonstrates that organic photochemistry is an evolving and lively topic, with much research into new reactions and technology over the past decade.

However, Ciamician’s dream has not been realised to date. Although photochemistry has produced significant research interest in academia,⁵⁰ it is rare for photochemical processes to be realised on an industrial scale. There are several contributing factors for this neglect:⁴⁹

- Specialised reaction vessels are required in which a light source may be incorporated. The most commonly used type of photoreactor is an immersion well, in which the light source is placed in the centre of the reaction mixture. However, during scale-up, it is very difficult to reproduce the same ratio of area irradiated to volume of reactant.

- Light sources pose a difficulty on an industrial scale. Lamps used in photochemistry include medium and high pressure mercury lamps, xenon lamps and halogen lamps, all of which are costly to run. These have a limited lifetime and additionally tend to generate a large amount of heat and therefore require additional cooling systems.

- Photochemical reactions are typically carried out under batch reaction conditions. This method tends to be relatively inefficient compared to a continuous-flow process. Photochemical reactions operated in continuous-flow have been investigated and have proven to be far more effective at large-scale photochemical synthesis than the corresponding batch approach.⁵¹ However, batch reactions continue to be the most common approach to photochemistry.

Some examples of large-scale photochemical synthesis in industry do exist.^{49,52–55} Despite these examples, however, the acceptance of synthetic photochemistry in industrial research laboratories, e.g. for the development of new lead compounds, remains low. A recent account by Bochet⁵⁶ addresses the perceived disadvantages

of photochemical synthesis and endeavours to show that these difficulties are easily overcome.

To this end, many researchers are seeking to develop new photochemical techniques, leading to an emerging field of new technologies. While this review focuses on microstructured reactors, other concepts and reactor designs have emerged,^{21,57} for example *spinning disc reactors*,^{58,59} *continuous flow reactors* (for macro-⁵¹ and micro-scale^{60,61} synthesis), *excimer radiation systems*,^{62–64} *thin film reactors*,⁶⁵ *solar parabolic trough reactors* (e.g. the PROPHIS-plant^{66–69}) or *microbatch reactors*.^{70,71} Reactions carried out in various ‘microspaces’ have also been reported.^{1,7} These include micelles,² zeolites,³ supramolecular systems,⁴ nanoparticles⁶ and porous ceramics.^{72,73} However, of all the emerging technologies, microstructured reactors show the most potential for widespread use in preparative organic chemistry including photochemistry.^{13–27} The advent of microstructured reactor technology may furthermore provide a means to carry out large scale photochemical reactions. Giacomo Ciamician’s vision for the future may yet be realised, but in the form of a microchip, rather than the dramatic scene he envisaged. By scaling down photochemical reactions using microstructured reactors it may be possible to have key photochemical steps carried out in research laboratories. In addition, ‘numbering up’, i.e. using several microreactors in parallel, rather than scaling up may enable the industrial production of large amounts of photochemical products. There are several additional advantages of microstructured reactors, which make them ideal for photochemical processes:²⁴

- They provide a means of ensuring uniform irradiation to the entire reaction solution. As the depth of a microreactor is small (100–1000 μm), maximum penetration of light and thus irradiation of the reaction mixture can be achieved readily, even for relatively concentrated solutions.

- Microphotochemistry is commonly performed under continuous-flow rather than batch conditions. Consequently, irradiation time for photochemical processes in a microreactor is easily altered, as this is directly proportional to the flow rate of the system. This feature allows rapid optimisation of micro-photochemical reactions.

- Microstructured reactors possess high heat transfer coefficients. As a result, microstructured reactors are cooled very efficiently.

- Miniaturised light sources may be employed, for example light-emitting diodes (LEDs).^{60,70,74–77} These provide a clear alternative to conventional light sources, as they are available in a range of wavelengths, small in size and energy efficient. In addition, they produce less or no heat, thus reducing the need for coolant.

- Microchip designs allow on-line monitoring of the reaction, e.g. by UV-spectroscopic analysis of the effluent.³⁵

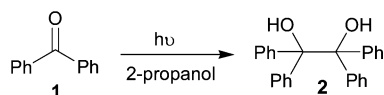
Already many examples exist in the literature documenting the advantages of microstructured reactor technology in photochemical synthesis. The reactions carried out to date may be divided in three categories, based not on reaction type, but rather on conditions required.

Homogeneous reactions

In these reactions the reagents are all in the same phase, i.e. all in solution. Therefore there are few additional requirements for the microstructured reactor beyond the ability to pump the reagents

in solution through the reactor. A preprepared mixture may be introduced through a single inlet or mixing of reagents may occur on-chip by applying a T-inlet.

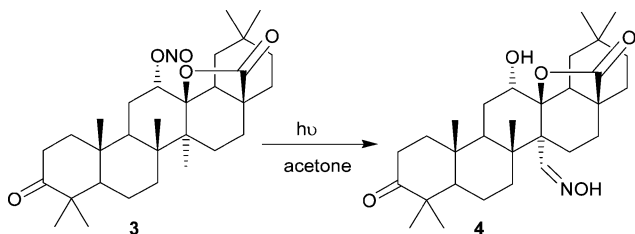
One of the earliest reported photochemical reactions in a microstructured reactor was the photo-pinacolisation of benzophenone **1** in isopropanol (Scheme 1).³⁵ Microstructured reactors were prepared in-house, one with a Pyrex cover-plate and one consisting of a silicon wafer sandwiched between 2 quartz wafers. This type of microstructured reactor is of significance as lower wavelengths of light may be used for irradiation than allowed by Pyrex.⁴⁹ The light source used was a mini UV lamp, which provided light of 365 nm. The typical concentration of the benzophenone solution was 0.5 M. The use of a concentrated solution effectively demonstrated the advantage of a microstructured reactor, as the shallow channel depth ensured complete irradiation of the reaction mixture which would not have been possible under conventional photochemical set ups. The progress of the transformation was monitored *off-chip* using HPLC and *on-line* using UV-spectroscopy.



Scheme 1 Photo-pinacolisation of benzophenone.

The authors reported that this reaction required flow rates of less than $10 \mu\text{L min}^{-1}$ to ensure adequate residence time on the chip. Although a larger residence time results in greater conversion, rates above $3 \mu\text{L min}^{-1}$ were used to avoid precipitation of product **2** in the microstructured reactor. Above this threshold, crystallisation of the product was observed in the effluent storage device instead. At a flow rate of $4 \mu\text{L min}^{-1}$ conversions of up to 60% were achieved.

Sugimoto and co-workers have reported the application of microstructured reactors in the preparation of the key steroidal substrate **4** *via* Barton reaction (Scheme 2).³⁴ The microstructured reactors used (manufactured by Dainippon Screen⁷⁸) were made from stainless steel with channels $1000 \mu\text{m}$ wide, $107 \mu\text{m}$ deep and total path length of 2.2 m.

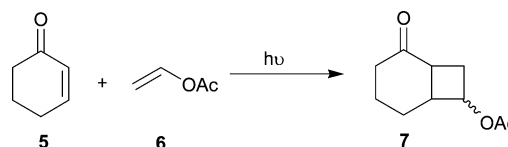


Scheme 2 Barton reaction.

The study compared the effectiveness of three different types of transparent cover—quartz, soda lime glass and Pyrex—and determined that Pyrex was most suited to the light source, a 15 W black light. In addition, the authors mention studies of temperature dependence (extensive degradation of the product at temperatures greater than $50 \text{ }^\circ\text{C}$) and distance between microreactor and the light source, which was optimised at 7.5 cm. Following optimisation, a residence time of 12 minutes produced the desired product **4** in 71% yield. Also reported is a gram-scale synthesis of the target compound, using two microstructured reactors ($1000 \mu\text{m}$ wide, $500 \mu\text{m}$ deep and 1 m total length,

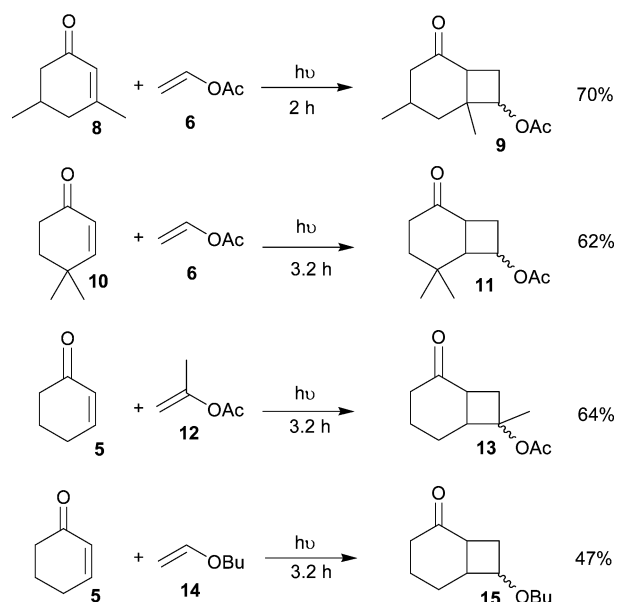
manufactured by Dainippon Screen⁷⁸) connected in series and $8 \times 20 \text{ W}$ black lights. After continuous operation for 20 h the desired product was isolated in 60% yield. This clearly demonstrates the potential for numbering up of microstructured reactors for the large scale production of chemicals.

An investigation into the use of microstructured reactor technology for photochemical [2 + 2]-cycloadditions was carried out by Fukuyama *et al.* (Scheme 3).³³ This study demonstrates the application of a commercially available microreactor (mikroglas dwell device with FOTURAN[®] glass, Fig. 1) for a range of substrates. A common high pressure mercury lamp (300 W) was used as a light source. The model reaction examined was the reaction of cyclohex-2-enone **5** with vinyl acetate **6** (Scheme 3).



Scheme 3 [2 + 2]-Cycloaddition of cyclohex-2-enone with vinyl acetate.

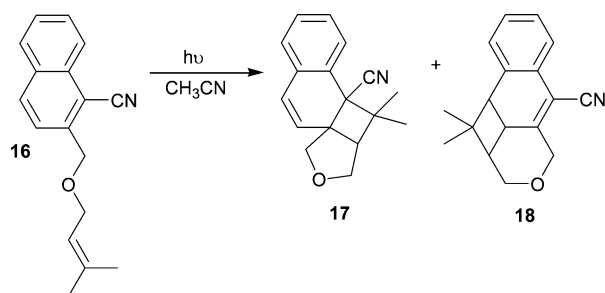
At a flow rate of 0.5 mL h^{-1} , which corresponds to a residence time of 2 h, a yield of **7** of 88% was achieved. This was compared to a batch reactor (10 mL) irradiated using the same light source for 2 h, which yielded only 8% of **7**. This demonstrates that the use of microstructured reactor technology can both shorten irradiation times and increase yield. The reaction was repeated with 2 reactors in series at a flow rate of 1 mL h^{-1} , which resulted in a similar yield of 85%. A study of other cyclohexenones, **8** and **10**, and alkenes, **12** and **14**, was carried out and the corresponding photoaddition products (a mixture of regioisomers) were obtained in yields of 47–70%. These findings effectively showed the ability to transfer this technology to related reactions (Scheme 4).



Scheme 4 Series of photochemical [2 + 2]-cycloadditions.

Microstructured reactors have been shown to increase regioselectivity of some reactions. A communication by Maeda *et al.* reports a comparison of regioselectivity of the intramolecular

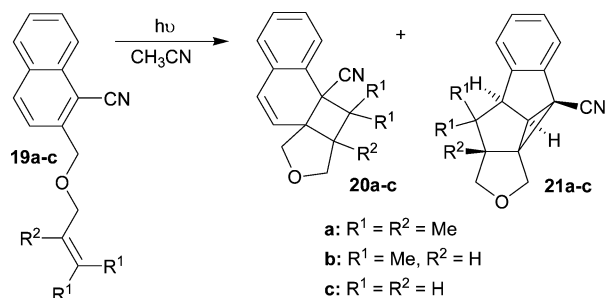
[2 + 2]-photocycloaddition of 1-cyano-2-((3-methyl-2-butenyloxy)methyl)naphthalene **16** in acetonitrile under batch conditions and following the microstructured reactor approach (Scheme 5).³²



Scheme 5 Intramolecular [2 + 2]-photocycloaddition of 1-cyano-2-((3-methyl-2-butenyloxy)methyl)naphthalene.

The reaction was carried out in custom-built reactors made from poly(dimethylsiloxane) with inserted capillary tubes as the channels (diameter 100 μm , total length 45 mm or 202 mm). Flow rates of 0.03–0.05 mL h^{-1} were used. The reaction was optimised to use a path length of 202 mm and flow rate of 0.05 mL h^{-1} . Under these conditions the regioselectivity of the reaction was improved compared to batch conditions (55:7 for microreactor compared to 56:17 for batch). This is explained by the rapid flow rate, the cycloadduct **17** initially formed is rapidly expelled from the system, thus reducing photocycloreversion back to the starting material **16**. Longer irradiation times (greater residence times) gives increased yield of **18** as reversion to starting material does not occur for this product. The effect on enantiomeric excess was also examined when the products were eluted using $\text{Eu}(\text{hfc})_3$ and was shown to have a small but significant effect (2% ee).

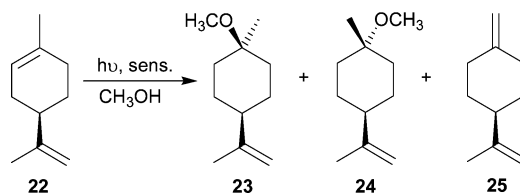
In an extension of this work, Mizuno investigated other intramolecular photocycloaddition of 2-(2-alkenyloxymethyl)naphthalene-1-carbonitriles **19a–c** (Scheme 6).⁷⁹ This study includes a comparison to a batch reaction (Pyrex tube, diameter 8 mm) and investigation of effects of substituents, solvent, residence time and flow rate and the dimensions of the microchannel. The first (Type A) microreactor was commercially available (ICCDI05, Institute of Microchemical Technology⁸⁰), with a width of 100 μm , depth 40 μm and length 120 mm. A second (Type B) microreactor was made in-house, using Pyrex plates, with channel width 2.5 mm, depth 50 μm and length 60 mm. The light source used was a xenon lamp (500 W).



Scheme 6 Intramolecular photocycloaddition of 2-(2-alkenyloxymethyl)naphthalene-1-carbonitriles.

The findings of this study show, once again, that microreactors enable increased regioselectivity, as the initial photoproducts **20a–c** may be selectively formed and the undesirable photocycloreversion reaction may be avoided. The rapid flow rate ensures that the initial product is removed from the irradiation chamber before the secondary reaction, yielding **21a–c**, may occur. In addition, this study demonstrated the efficiency of reactions in microstructured reactors, with conversions of 69–75% achieved after one minute in the microreactor, compared to 74% after 3 h in a batch reactor. It was also shown that use of a wider channel while maintaining a shallow channel depth could significantly increase output.

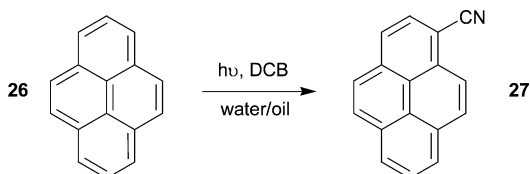
As discussed in the previous example, use of microstructured reactors has been shown to reduce the occurrence of unwanted side reactions. Rapid flow rates decrease the residence time of the substrates and can ensure that the products are rapidly removed from the reactor. Sakeda *et al.* have demonstrated this principle using the asymmetric photosensitised addition of methanol to (*R*)-(+)-(*Z*)-limonene **22** as a model reaction (Scheme 7).⁸¹



Scheme 7 Asymmetric photosensitised addition of methanol to (*R*)-(+)-(*Z*)-limonene.

Three microstructured reactors of different dimensions were made from quartz. A low-pressure mercury lamp (40 W) was used as light source. A study of the effect of channel size on photon efficiency was carried out. Photon efficiency was shown to increase with decreasing channel size and was significantly greater for microstructured reactors than batch conditions. High spatial illumination homogeneity, excellent light penetration and short exposure times were used as an explanation. In addition, the diastereomeric excess (de) of the photoproduct was found to be slightly larger than that obtained under batch conditions. This was explained by suppression of side reactions in the microstructured reactors.

An unusual example of use of microreactors in photochemical synthesis is the photocyanation of pyrene **26** (Scheme 8) across an oil/water interface as reported by Ueno and co-workers.³¹ The chips used were fabricated in-house by imprinting method using commercially available polystyrol substrate, with width of 100 μm , depth 20 μm and length 350 mm. The reactors used had either 2 inlets or 3 inlets at the start of the serpentine reaction channels. This facilitated the introduction of the oil and water phases separately, with equal flow rates, thus ensuring formation of a stable water/oil or water/oil/water interface, respectively. Once stable interfaces were established the reactors were irradiated



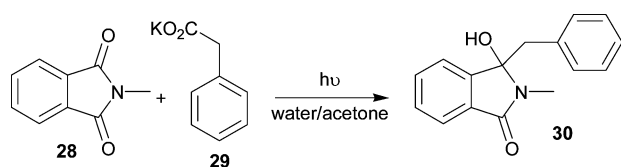
Scheme 8 Photocyanation of pyrene.

using a high-pressure mercury lamp (300 W) with a copper sulfate solution filter (>330 nm).

An aqueous solution of sodium cyanide and a solution of pyrene and 1,4-dicyanobenzene (DCB, electron acceptor) in propylene carbonate were used. During irradiation, photo-induced electron transfer (PET) occurs between pyrene and DCB and the resulting radical undergoes nucleophilic attack by CN^- at the oil/water interface. The product, 1-cyanopyrene **27**, remains in the oil phase.

The results from this investigation show that after a residence time of 210 s the photoproduct was obtained in 28% yield for the oil/water system and in 73% yield for the water/oil/water system. Decreasing flow rate would increase residence time, and hence yield, but at rates below $0.2 \mu\text{L min}^{-1}$ a stable oil/water interface could not be obtained. It is anticipated that optimisation of channel length can increase this yield, as 100% conversion had not occurred.

Recent investigations in the synthesis of bioactive compounds through photodecarboxylative addition of carboxylates to phthalimides⁸² in our laboratory have shown that these are feasible in microreactors.⁸³ The microreactor used is a dwell device (mikroglas, Fig. 1) with a reaction channel of 500 μm in depth, 2000 μm in width and length 1.15 m. The reaction of N-methylphthalimide (NMP) **28** with potassium phenylacetate **29** was used as a model reaction (Scheme 9).



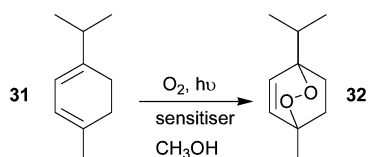
Scheme 9 Reaction of N-methylphthalimide with potassium phenylacetate.

Using UV irradiation (300 nm), the effect of flow rate on yield of the addition product was investigated. At a flow rate of 0.8 mL min^{-1} (residence time 21 mins), conversion of 97% to the benzylated product **30** was achieved.

Heterogeneous reactions

In heterogeneous liquid–gas reactions, it is necessary to provide a supply of gas to the microstructured reactor. The falling-film type reactor is commercially available for this purpose, while other reactors have been adapted for use also.

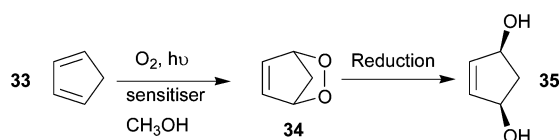
The use of microstructured reactors for reactions requiring singlet oxygen has been the subject of several investigations. For example, the synthesis of ascaridole **32** from α -terpinene **31** via dye-sensitised photooxygenation (Scheme 10) has been used as a model reaction for generation and use of singlet oxygen in a microstructured reactor.³⁸



Scheme 10 Dye-sensitised photooxygenation of α -terpinene.

The reactor was prepared in-house using a glass substrate and consisted of two inlets, for reaction solution and oxygen, a serpentine irradiation sector (of total length 50 mm) and an outlet channel. The channels had an average depth of 50 μm and an average width of 150 μm . A mixture of methanol and rose bengal (sensitiser) was introduced *via* a divergent inlet channel and mixed with oxygen on-chip. Singlet oxygen was generated within the serpentine channel of the microstructured reactor when irradiated with a tungsten lamp (20 W, 6 V). The volume of aerated solvent in the system at any time was in the region of picolitres. This represents far less of a danger than the larger quantities of aerated solvent required in the laboratory procedure. The yield of ascaridole after workup was greater than 80%, as determined by GC analysis. This work demonstrates clearly that microstructured reactors provide a novel platform for photooxygenation reactions.

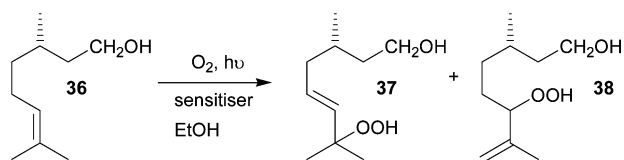
This was further demonstrated by Jähnisch and Dingerdissen, who reported the photooxygenation of cyclopentadiene **33**, followed by reduction to 2-cyclopenten-1,4-diol **35**, (Scheme 11) in a falling film microstructured reactor (FFMR by IMM, Fig. 2).^{37,84}



Scheme 11 Dye-sensitised photooxygenation of cyclopentadiene and reductive ring-opening.

This reaction proceeds *via* a potentially explosive endoperoxide **34**, which is a concern for large scale conventional synthesis. However, in the microstructured reactor, the concentration of the intermediate remains low at all times. The reactor was furthermore cooled to 10–15 $^\circ\text{C}$. The endoperoxide is reduced immediately after leaving the reactor by passing the effluent into a solution of thiourea in methanol at 10 $^\circ\text{C}$. This ensures that the quantity of the endoperoxide intermediate present is always kept at a safe level. At an influent flow-rate of 1 mL min^{-1} (and an O_2 flow of 15 L h^{-1}), the authors reported a yield of 20% of **35** for the non-optimised procedure.

In a recent study, microstructured reactors have been shown to be applicable in the Schenck-ene reaction of (–)-citronellol **36** (Scheme 12),³⁶ a key step in the synthesis of rose oxide.⁵⁵



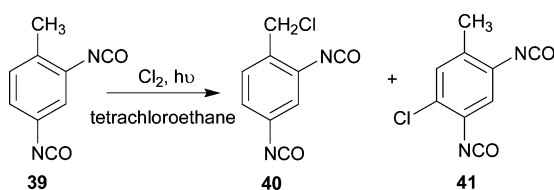
Scheme 12 Dye-sensitised photooxygenation of (–)-citronellol.

This study compared the efficiency of a commercially available microstructured reactor (HT-residence glass, Little Things Factory⁸⁵) to a batch reactor in terms of space-time yield and photonic efficiency. The microreactor consisted of a serpentine channel of width 1 mm. The sensitizer used was a ruthenium polypyridyl complex, $\text{Ru}(\text{bpy})_3\text{Cl}_2$ (tris(4,4'-*tert*-butyl-2,2'-dipyridyl) ruthenium(II)-dichloride) and the light source an LED array (4×10 LEDs, nearly monochromatic at 468 nm). The reaction mixture was purged with compressed air and was

continuously pumped through the microreactor in a loop for about 60–70 h. The progress of the reaction was monitored by HPLC.

The results of this investigation demonstrated that the microstructured reactor method has a greater photonic efficiency and space-time yield than the batch reactor method. In addition, this study demonstrated the use of miniaturised light sources, *i.e.* LED arrays, for photochemical reactions.

Heterogeneous reactions in microstructured reactors are not limited to reactions of singlet oxygen. The photochlorination of toluene-2,4-diisocyanate (TDI, Scheme 13) **39** has been demonstrated in a falling film reactor (FFMR by IMM, Fig. 2), with 32 parallel channels of width 600 μm , depth 300 μm and length 66 mm and a Quartz cover.⁸⁶ The light source was a xenon lamp (1000 W, unfiltered). The reactor was maintained at a temperature of 130 °C to decrease side reaction to form a ring chlorinated product **41**.



Scheme 13 Photochlorination of toluene-2,4-diisocyanate.

The microreactor results were compared to those obtained in a batch reaction and demonstrated that use of the microstructured reactor led to increased product selectivity. This is due to the high surface to volume ratio and hence a lower local concentration of chlorine radicals in the microstructured reactor. In addition, the space-time yields were orders of magnitude higher compared to the conventional reactor.

To investigate the effect of the reactor material on the reaction, two reaction plates were used, one nickel and one iron. This study showed that the selectivity of the desired product **40** was affected significantly by the microreactor material (50% for iron, 67% for nickel), which is attributed to the formation of FeCl₃, which acts as a Lewis acid. This led to enhanced production of resin-like condensation products.

An investigation of effect of flow rate and residence time revealed that shorter residence times gave higher selectivity, by avoiding follow up reactions. However, increased residence times give a thinner film and consequently greater conversion rates.

These examples of liquid–gas reactions have clearly shown that microstructured reactors offer a viable route to many fine chemicals, with potential to reduce safety risks in the laboratory. However, optimisation of the technology to maximise effectiveness of mixing is essential.

Catalytic reactions

Microstructured reactors show potential for use in catalytic reactions. One of their key features is a large surface to volume ratio, therefore if a catalyst were immobilised on the walls of the channels it could be possible to maximise interaction of catalyst and reagents. Microstructured catalytic photoreactors show potential for use in the treatment of waste water and exhaust air, as well as some synthetic processes. Several examples have been

documented in the literature to date, in particular focussing on the use of titanium dioxide as a catalyst.⁸⁷

The photodegradation of chlorophenol in the presence of a titanium dioxide catalyst was one of the first microstructured reactor based catalytic reactions to be investigated.^{75,88} A microstructured reactor was prepared with TiO₂ as a photocatalyst on the walls of the channels (cross-section 300 μm \times 200 μm). This was irradiated using an array of eleven UV-A LEDs, with a peak emission of 385 nm.

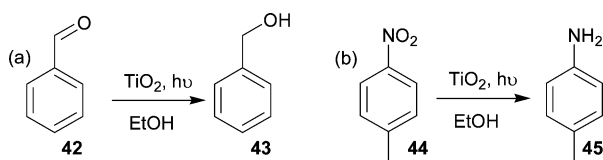
The degradation study was carried out using different initial concentrations of chlorophenol and different flow rates. It was shown that greater degradation was achieved for lower concentrations and lower flow rates. The specific surface area irradiated in the microstructured reactor was 4–400 times greater than that of other reactor types, *e.g.* slurry or immersion type reactors. This study also demonstrated miniaturisation of the light source, thus showing potential of this technology for total-miniaturisation. However, a downside of this reactor type is its minute capacity. To prove beneficial on a larger scale numbering-up is necessary.

Another decomposition study looked at the coating of capillary tubes for use as microchannel reactors.⁸⁹ In this case the microchannel is not embedded in a solid substrate, the capillary acts as a single microchannel. The photocatalytic degradation of methylene blue was used as a model reaction to investigate the use of catalytic coatings (TiO₂ coating, with and without silica) in microspace in comparison to a batch reaction. The reactions were irradiated at a wavelength of 254 nm. Results of this study show that without titania the conversion is very slow, and rate increases with the use of TiO₂, with most rapid degradation occurring using SiO₂/TiO₂ coating. The reaction rate was affected by diameter of the capillary, *i.e.* depth of the solution, with completion of the reaction after just 40 s in a channel with 200 μm diameter, compared to 2 min for a diameter of 530 μm . In the case of the batch reaction the reaction reached completion after one hour.

Further photodegradation studies in microstructured reactors were carried out by Kitamura *et al*, in which a silica supported porphyrin derivative was used to catalyse degradation of phenol by singlet oxygen.⁹⁰ Polystyrene was used as a substrate and the silica beads covalently modified with metal-free monopyridyltriphenylporphyrin were incorporated. These were not fused to the channel walls, therefore the reactor was constructed with a ‘dam’ (130 μm height) to prevent elution of the beads during the reaction. Irradiation was performed with a 300 W high-pressure Hg lamp and the emitted light was passed through a CuSO₄ filter solution (>330 nm).

The investigation looked at the effect of flow rate and channel depth on decomposition yield. In accordance with expectations, decreased flow rates led to increased decompositions (65% at 3 $\mu\text{L min}^{-1}$ and 93% for 0.5 $\mu\text{L min}^{-1}$). Decreasing channel depth from 130 μm to 30 μm also led to an increase in yield (35% to 65%, respectively), which is believed to be due to greater interaction between sensitiser and dissolved oxygen. When compared to a batch reaction, with similar concentrations of sensitiser, the microreactor was shown to be more effective, with decomposition yields of 93% after 42 s, compared to 70% after two hours for the batch experiment.

Also of interest is the use of photocatalytic microstructured reactors in synthesis, rather than degradation. A communication on the reduction of benzaldehyde **42** and nitrotoluene **44** (Scheme 14)



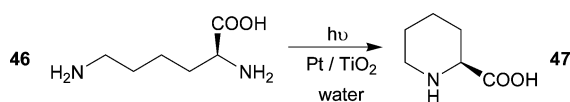
Scheme 14 Photocatalytic reduction of (a) benzaldehyde and (b) nitrotoluene.

using titanium dioxide was reported in 2006.⁴² This report also focuses on full miniaturisation, and UV-LEDs with an emission of 365 nm were chosen. Quartz microreactors were fabricated with a catalytic coating on the bottom and sides of the channels (width 500 μm , depth 100 μm and length 40 mm).

Alcoholic solutions of benzaldehyde were used and ethanol was found to be the most efficient solvent, with a yield of **43** of 11% after 60 s. Photoreduction of nitrotoluene was found to be more rapid, with yields of 46% for **45** after 60 s. Although these reactions are not optimised, they show that microstructured reactor technology provides an effective route to reduction of these compounds.

Further photocatalytic degradations have been recently summarised by Matsushita *et al.*³⁹ In this comparison study, model pollutants such as chlorophenols, bisphenols and dimethylformamide were treated in the presence of titanium dioxide and UV light (LED and tuneable OPO laser). Light source optimisation, using a microreactor with a depth of 100 μm and degradation of DMF as a model reaction (Fig. 3), revealed that LEDs demonstrated a significant photonic efficiency compared to an OPO laser or xenon laser.

Another example of a synthetically useful transformation has been reported by Takei *et al.*⁹¹ The authors examined the photocatalytic synthesis of L-pipecolic acid **47** from L-lysine **46** (Scheme 15) in a self-fabricated reactor.

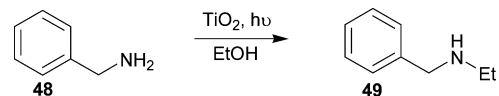


Scheme 15 Photocatalytic synthesis of L-pipecolic acid.

A Pyrex microstructured reactor with channels 770 μm wide and 3.5 μm deep was fused to a substrate with a 300 nm thick coating of TiO_2 . Platinum was used as a reducing agent at 0.2 wt% in the film. The reaction set-up was irradiated using a high-pressure mercury lamp with a UV transmitting filter. The reaction was compared to a batch set-up using a cuvette and TiO_2 particles in suspension. Conversion of L-lysine to L-pipecolic acid **47** in the microstructured reactor was 87% after a residence time of 0.86 min. This conversion rate was 70 times greater than that of the batch reaction.

Examination of selectivity and enantiomeric excess (ee) showed that these were independent of reaction time. However, looking at productivity in terms of moles produced per minute the batch reactor was superior. This is due to the larger capacity (4 mL) but this disadvantage may be overcome through numbering up of microreactors in the future. A significant advantage of the catalytic microstructured reactor is the elimination of a separation step, as the photocatalyst remains in the microstructured reactor while the product is eluted.

Another study on synthetic reactions in microstructured reactors is the N-alkylation of benzylamine **48** (Scheme 16).^{39,40} Quartz microreactors (width 500 μm , 40 mm length, various depths) were used, with the bottom and sides coated with titania (Pt-loaded and Pt-free). UV-LED arrays were employed as light sources (365 nm). The reaction products were analysed by GC or HPLC methods.



Scheme 16 N-ethylation of benzylamine.

It was shown that benzylamine could be converted to the alkylated product **49** in yields of up to 43% in just 90 s. Optimisation of the reaction solvent was carried out, resulting in use of ethanol in further studies. Other amines were investigated as well and aniline and butylamine were N-alkylated in yields of 11% and 36%, respectively. An investigation of the effect of decreasing depth was performed, using reactors with depths of 300 μm , 500 μm and 1000 μm . It was shown that the efficiency of N-alkylation was enhanced by decreasing depth, this is attributed to the increased surface to volume ratio. Interestingly, this reaction was shown to proceed in the presence of titanium dioxide photocatalyst, even without platinum. Yields of 98% were achieved after 90 s. In contrast, this reaction does not occur in batch conditions without the presence of platinum. In addition, no bis-alkylated product was obtained when platinum was present, as is usually the case in batch conditions. The absence of bis-alkylation was achieved by the continuous-flow mode, which prevents the undesired follow-up reaction.

In a recent extension of this work, the authors further investigated the N-alkylation of aniline and piperidine.⁴¹ Again, the transformation proceeded quite rapidly in the microstructured reactors with immobilised TiO_2 (with and without Pt-loading). Prolonged irradiation in the microreactor resulted in efficient bis-alkylation as demonstrated for benzylamine.

Finally, the decomposition of Fe(III) oxalate has been studied by Kirner and co-workers to test a novel static micromixer.⁹²

Conclusions

The literature to date clearly demonstrates the versatility and potential of microstructured reactors in organic photochemistry, as reactors may be used for a range of reaction types. Advantages discussed include elimination of side reactions, enhanced selectivities, increased photonic efficiency and reduction of hazards. In catalytic applications a large area-volume ratio is possible, resulting in improved catalytic effect.

Some difficulties have been encountered, particularly in the minute volumes handled. To overcome this challenge, the concept of 'numbering up' has been proposed. By operating many reactors in parallel or in series the output volume may be significantly increased.

Although a range of photochemical reactions have been carried out in microreactors to date, a lot of work remains in this area. However, optimisation of reactor dimensions, flow rates and other conditions affecting reactions should lead to further successes in the future. Hence, Giacomo Ciamician's vision of

the *Photochemistry of the Future* may actually be realised in 'miniaturised' formats.⁴⁸

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