SEMINAR

連続マイクロフロー型光化学反応とその創薬・医薬品開発／製造への応用

James Cook University, School of Pharmacy and Molecular Sciences, Townsville QLD 4811（Australia）

Michael Oelgemöller

Corresponding author:
E-mail: michael.oelgemoeller@jcu.edu.au

Kobe University, Graduate School of Engineering, 1-1, Rokkoudai-cho, Nada-ku, Kobe 657-8501（Japan）

Akiko Murata

Continuous microflow photochemistry and its application in pharmaceutical drug discovery, development and production

Microflow photochemistry has recently emerged as a new methodology that successfully combines flow operation, micro-space and activation by light（'lab & light on a chip'）. Numerous micro-photoreactors for micro-scale synthesis to technical-scale production have been already developed. The main advantages of microflow photoreactors are their beneficial light transmissions, controlled exposure times, accurate temperature control and removal of photoproducts from the irradiated area. These operation features commonly result in higher yields, enhanced selectivity, improved energy efficiencies and reductions of solvent volumes and subsequently waste. This review highlights selected examples of microflow photochemical reactors and transformations of pharmaceutical interest. It unambiguously shows the potential of this enabling technology over conventional（batch）processes.

マイクロフロー型光化学反応は、流体操作・マイクロ空間・光活性化を効果的に組み合わせて利用した新しい方法論（'lab & light on a chip'）で、近年に出現した研究分野である。マイクロスケールの合成用途から製造技術スケールの生産用途まで、これまで既に多数の光マイクロリアクターが開発されている。本方法論の主な特長は、光透過率が高いことから照射効率が高いこと、照射時間の制御による露光量制御や反応温度の精密制御が可能になること、光反応場と別の位置の流路により生成物が回収できることが挙げられる。これらの特長により、光マイクロリアクターを用いた反応は一般的に高収率で選択性も高く、エネルギー効率に優れ、溶媒使用量や廃棄物を低減できる。本稿ではマイクロフロー型光化学リアクターを用いた医薬品・医薬中間体の合成に焦点を当て、いくつかの実例を挙げてレビューする。本方法論による新規プロセスの実現技術は、従来のプロセス技術（バッチ技術）を凌駕する可能性を有することが明らかになった。

Introduction

Light is considered a 'clean and green reagent' that allows for the easy construction of high energy molecules with a 'flick of a switch'.[1] Photoinduced reactions are thus often used as key-steps in the synthesis of natural products.[2] Over the last decades, numerous additional examples of highly efficient, chemo-, regio-, diastereo- and enantioselective transformations have been described.[3] Visible light photoredox（orano）catalysis has furthermore extended the synthesis versatility of photochemistry.[4] In light of these advantages, it is surprising that photochemical reactions are not widespread

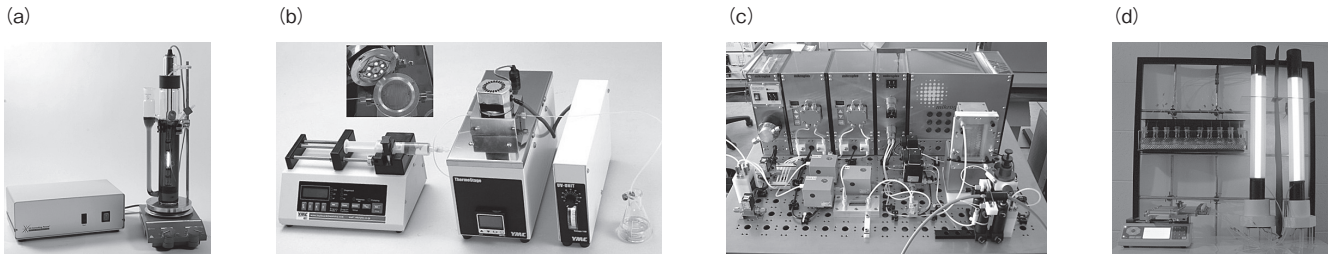
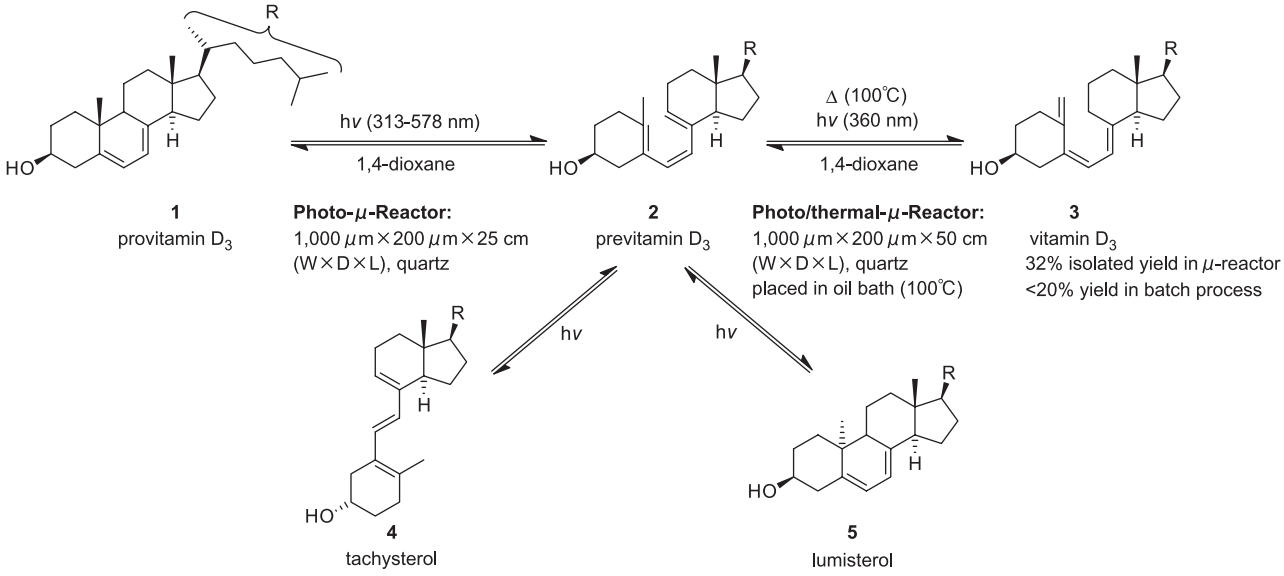


Figure 1. (a) Immersion well batch reactor (UV-LRS-1; with courtesy of UV-Consulting Peschl), (b) KeyChem-Lumino system (with courtesy of YMC), (c) automated microphotoreaction system (with courtesy of mikroglas chemtech) and (d) multi-microcapillary flow reactor (MμCFR).

in industry and limited to selected commodity chemicals.[5] Recently, microflow chemistry has been developed as a new continuous production tool that has been rapidly integrated in the pharmaceutical industry.[6,7] Microflow conditions have been subsequently utilized for photochemical reactions and this has enabled a renaissance of this neglected technology. Consequently, microflow photochemistry ('lab & light on a chip') has emerged as a promising new photochemical synthesis tool.[8]

From Conventional to Microphotoreactor Technology

Laboratory-scale reactions (typically ≤1 L) are commonly performed in batch using immersion well type reactors (**Fig. 1a**). These reactors comprise of an outer reaction vessel, an inner immersion well and a mercury pressure lamp at its core. Open chamber reactors with an outer ring of fluorescent tubes have likewise been developed and are commonly used in research laboratories for small scale synthesis (typically ≤100mL). Merry-go-round accessories with multiple irradiation tubes are available for both reactor types and enable limited parallel synthesis. Conventional batch systems have a number of disadvantages that have limited their applications, especially on large industrial scales. Due to the rapid absorption of light by the chromophoric reagent within the reaction mixture (as expressed in the Beer-Lambert law), photochemical reactions require high dilutions and narrow reaction vessels. The batch operation also causes further degradation of light-sensitive photoproducts. Polymeric and iron deposits from cooling water on glass parts around the light source are thus commonly observed and demand constant cleaning and maintenance. The intense heat generation of immersion well lamps furthermore necessitates excessive cooling. Due to the micro-dimensions (by definition ≤1 mm) of their reaction channels and the flow-through operation, microreactors avoid most of these drawbacks. Although custom-build devices are most commonly utilized in microflow photochemical synthesis, complete microreactor systems have been developed and are commercially available. The KeyChem-Lumino reactor (**Fig. 1b**), for example, utilizes an array of UV-LEDs as miniaturized light sources (shown as insert). The reaction mixture is pushed through the microchannel with a syringe pump attachment. For temperature control, the reactor is mounted onto a compact cooling unit. An example of an automated microreactor unit designed by mikroglas chemtech is shown in **Fig. 1c**. The plant has separate inlets for reagents and inert gas, which are mixed in a premixer and pumped into the reaction loop (dwell device with 308 nm excimer cube). The progress of the reaction is monitored continuously by an in-line IR-sensor. At maximum conversion, the product mixture is eluted automatically from the reaction loop and collected at the outlet. An external cooling circuit offers optional temperature control. In contrast to these embedded microreactors with fixed dimensions and volumes, microcapillary reactors allow for a more flexible design.[9] This trend has lead to the development of a multi-microcapillary flow reactor (MμCFR) for parallel microflow photochemistry operations.[10] The reactor has been applied successfully to typical R&D scenarios, i.e. process optimization, process validation, scale-up and paral-



Scheme 1. Cascade photo/thermal synthesis of vitamin D_3 (**3**) from provitamin D_3 (**1**).

lel library synthesis.

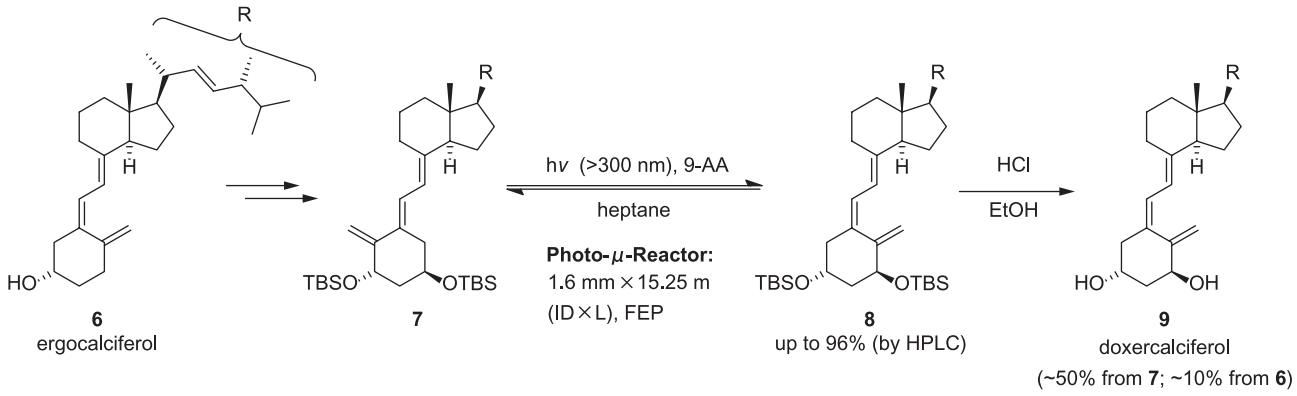
Microflow Photochemical Reactions of Pharmaceutical Interest

Summarizing review articles on photochemical transformations under microflow conditions have been published independently by Oelgemöller and Matsushita.[8] The following chapter highlights recent examples of interest to the pharmaceutical industry. It should be noted that some reactor systems from the chosen examples have inner dimensions of >1mm and are thus not strictly microreactors.

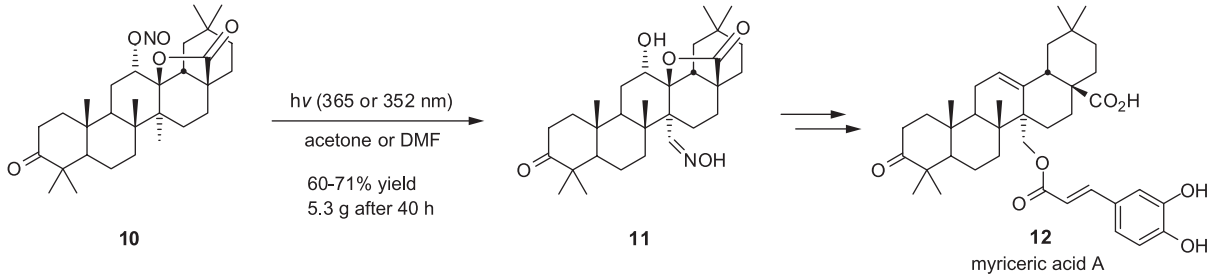
Photorearrangements and Photoisomerizations

The synthesis of vitamins represents an important industrial application of organic photochemistry.5 Consequently, Takahashi and coworkers have studied the conversion of provitamin D_3 (**1**) to vitamin D_3 (**3**) in custom-made quartz microreactors.[11a] Initial photochemical ring opening to previtamin D_3 (**3**), followed by a subsequent thermal hydrogen shift yields the desired product **3** (Scheme 1). Highest conversions and selectivity were obtained in 1,4-dioxane as the solvent. Using 20-30mM solutions of **1**, the cascade reaction was performed in series using two microreactors. Irradiations were realized in the first photo-microreactor using a high-pressure mercury lamp (400W) equipped with a Vycor filter (λ = 313-578nm). The second reactor was irradiated with the same light source through a glass UV filter (λ = 360nm) and was placed in an oil bath at 100℃. The combination of photochemical and thermal conditions for the second reactor proved beneficial in terms of selectivity since it enabled the photoisomerization of tachysterol (**4**) to previtamin D_3 (**2**) and reduced photocyclization to lumisterol (**5**). Consequently, a total residence time of 30 min for the tandem reactor furnished vitamin D_3 (**3**) in an improved yield of 60% (by HPLC) or 32% (after isolation), significantly higher than the <20% known from the industrial batch process. In an extension of this work, Fuse et al. realized the two-step synthesis of activated vitamin D_3 and its analogues utilizing the same reactor setup.[11b] In all cases, the continuous microflow process avoided intermediate isolation and high dilution conditions.

A similar process for the production of doxercalciferol (1α-hydroxyvitamin D_2; **9**) has been reported by Anderson and coworkers.[12] Starting from ergocalciferol (**6**), the bis-tert-butyldimethylsilyl (bis-TBS) ether **7**



Scheme 2. Synthesis of doxercalciferol (9) from ergocalciferol (6).



Scheme 3. The Barton reaction as a key-step in the synthesis of myriceric acid A (12).

was synthesized and its photoisomerization to the doxercalciferol precursor **8** was subsequently investigated using 9-acettylanthracene (9-AA) as a sensitizer (Scheme 2). The continuous flow reactor consisted of fluorinated ethylene propylene (FEP) tubing wrapped tightly around an immersion well equipped with a Pyrex sleeve and a 450 W mercury pressure lamp. A previously degassed solution of **7** and 9-AA in heptane was pumped through the reactor using a metering pump. The sensitizer was removed conveniently by in-line filtration over a short carbon/Celite (1:2 w/w) column. Careful modification of flow-rate, temperature, 9-AA load and starting concentration of **7** gave high conversions to **8** of up to 96% (by HPLC). Ethanol and ethyl acetate could likewise be used as alternative solvents. Subsequent deprotection furnished the desired doxercalciferol **9** in a yield of about 50% (from **6**) and in high purity. Overall, **9** was obtained in about 10% from ergocalciferol (**6**) without the need for chromatographic purification.

The Barton reaction has been used as a key-step in the synthesis of the steroid myriceric acid (**12**), a potent endothelin A receptor antagonist. Ryu and coworkers have intensively investigated the conversion of the intermediary nitrite **10** to the corresponding oxime **11** using various microreactor setups (Scheme 3).[13] A glass-covered, stainless steel microreactor (Type I) equipped with a 300 W high-pressure mercury lamp was initially utilized for a detailed reaction optimization study. Using an acetone solution of **10** and catalytic amounts of pyridine, a soda lime cover at a distance of 7.5 cm resulted in the highest selectivity. Its cut-off wavelength at >320 nm avoided secondary photodecomposition and the desired oxime **11** was obtained in a yield of 59%. Higher yields were realized with a 15W black light (UVA) lamp or a UV-LED panel (48 × 35 mW). Choosing a Pyrex glass top and a residence time of 12 min, **11** was formed in

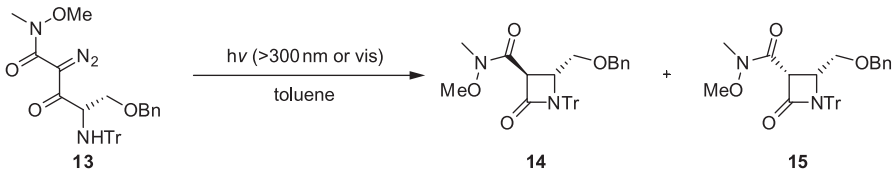


Photo-μ-Reactor I (UV):
1.6 mm (ID)
15 coils, FEP, -5℃

Photo-μ-Reactor II (vis):
1.6 mm × 2.75 m
(ID × L), FEP

81% (~3:1; 3.5 h; 1.0 g) in μ-Reactor I
90% (~2.5: 1; 7 h; 0.6 g) in Batch (UV)
91% (~3.3: 1; 48 h; 1.0 g) in μ-Reactor II
95% (~3.8: 1; 18 h; 0.1 g) in Batch (vis)

Scheme 4. Intramolecular Wolff-rearrangement of β-ketoamide **13** to the diastereoisomeric β-lactams **14** and **15**.

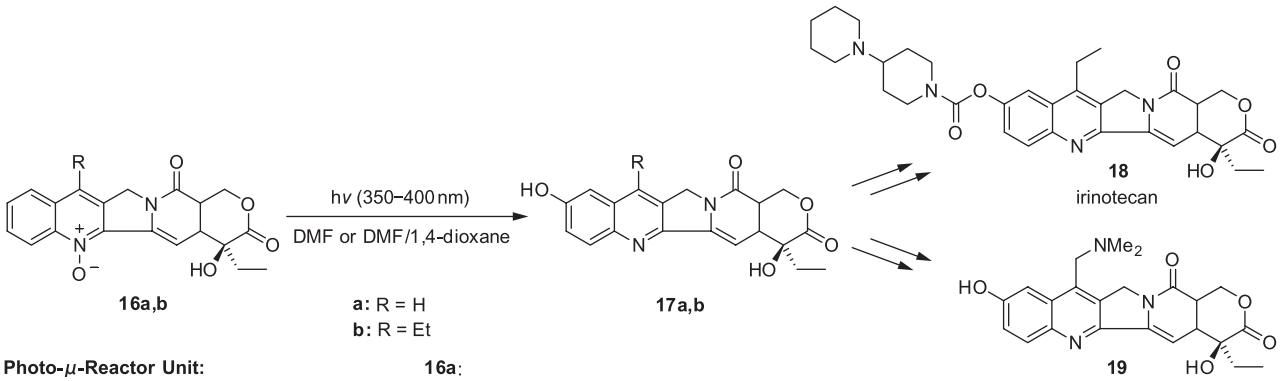


Photo-μ-Reactor Unit:
Heraeus Nobelight, thin flim reactor (quartz)
40-100 μm (film thickness),12 reactors

16a:
0.6 weight-%, 95% conversion and 90% yield in μ-reactor, 2kg/day
0.1 weight-%, 90% conversion and 50% yield in batch

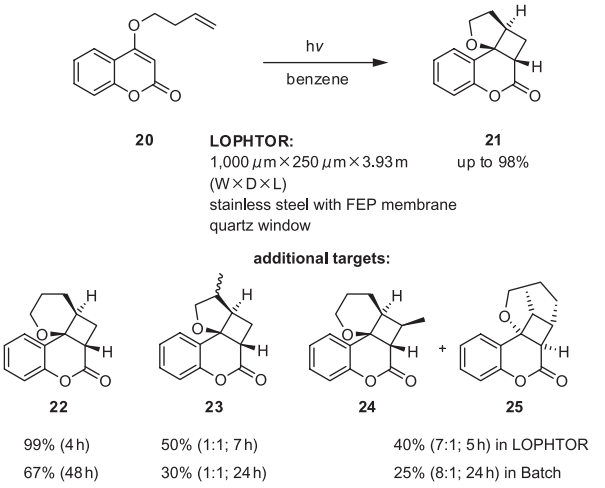
Scheme 5. The photorearrangement of N-oxides **16** to **17** in the production of the anti-cancer compounds irinotecan (**18**) and topotecan (**19**).

high yields of 71% and 70% (by HPLC), respectively. A scale-up was subsequently investigated in DMF using two in-series stainless steel reactors (Type Ⅱ) and an array of 8×20W black light lamps. With a set residence time of 32 min, continuous operation for 20 h gave 3.1 g of pure **11** (60% yield). The fully automated synthesis of **11** was furthermore achieved in a single multi-lane stainless steel reactor (Type Ⅲ) equipped with a Pyrex top and six evenly positioned 15W black light bulbs. With a fixed residence time of 20 min and after constant operation for 40 h, 5.3 g of **11** (61% yield) were isolated.

An interesting example of a photoinduced, intramolecular Wolff rearrangement for the construction of β-lactams has been reported by Mimieux Vaske et al. (**Scheme 4**).[14] Two different capillary reactors were constructed for this study and were operated in circulation mode until complete conversion was achieved. Initially, a capillary reactor equipped with a standard UV lamp as a central light source was employed and the reactor was cooled in an ice/NaCl bath (Type Ⅰ). A constantly degassed solution of the β-ketoamide **13** was pumped through the photoreactor in a loop for 3.5 h and the stereoisomeric β-lactams **14** and **15** were isolated in a combined yield of 81% and a ratio of approximately 3:1. The batch process on a slightly smaller scale gave a somewhat higher yield of 90% but required prolonged irradiation of 7 h and furnished a lower selectivity of ~2.5:1 (**14:15**). To allow irradiations at ambient temperature, a less heat-intensive 100W fluorescent bulb was alternatively investigated (Type II). Under continuous flow conditions on a 1.0 g (**13**) scale, the photorearrangement gave a combined yield of 91% and a selectivity of ~3.3:1 in favour of **14** after 48 h. In contrast, the reaction in batch mode on a much smaller scale of 0.1 g (**13**) required 18 h but showed a marginally improved yield and selectivity of 95% and ~3.8:1 (**14:15**), respectively.

The first industrial-scale production process under microflow photochemical conditions has been realized by Heraeus Noblelight (**Scheme 5**).[15] The photorear-

Figure 2. Photochemical production plant (with courtesy of Heraeus Noblelight) for the synthesis of the anti-cancer compounds irinotecan (**18**) and topotecan (**19**).

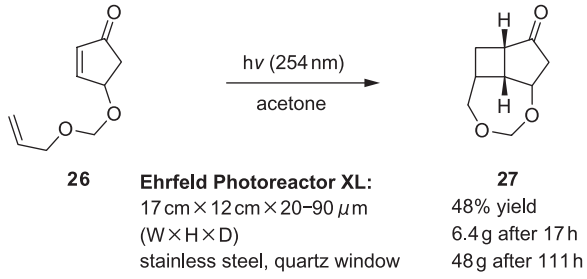


Scheme 6. Intramolecular [2+2]-cycloaddition of coumarin derivative **20** and additional target molecules **22**–**25** as studied by Abbott Laboratories.

rangement of the N-oxides **16** to the corresponding 10-hydroxycamptothecins **17** represents a key-transformation in the synthesis of anti-cancer drugs irinotecan (**18**) and topotecan (**19**). Their annual demand (<1 $t \cdot a^{-1}$) is achieved using a microflow photochemistry plant with 12 individual units (**Figure 2**). The entire plant enables the production of 2 kg of 10-hydroxycamptothecin (**17**) per day. Each microreactor unit consists of two quartz plates which are separated by a thin gasket. The reaction mixture of **16** in DMF or DMF/1,4-dioxane is pumped into the reactor block from the bottom. A thin liquid film (40–100 μm) is formed, which is irradiated from both sides using 2×250 W high pressure mercury lamps equipped with spectral filters (350–400 nm). With an initial concentration of 0.6 weight-% of **16a**, a conversion to **17a** of 95% was achieved. The isolated yield of **17a** was likewise high with 90%. In contrast, the analogue reaction under batch conditions produced a much lower conversion of 85% and required a dilution to 0.1 weight-% of **16a**. The isolated yield of **17a** was significantly lower with just 50% due to subsequent photodecomposition.

Photocycloadditions

Vasudevan and co-workers from Abbott Laboratories have recently designed a flow-based photochemical reactor (LOPHTOR) and have applied it to intramolecular [2+2]-cycloadditions of coumarin derivatives like **20** (**Scheme 6**).[16] The cyclobutane photoproduct **21** served as novel building blocks in their lead development program. The reactor contained a stainless steel reaction channel plate that was sealed off with a pressurized FEP membrane. Irradiation was achieved through a quartz window using a 450 W medium pressure mercury lamp. An auto-sampler system connected to the inlet of the LOPHTOR device enabled rapid optimization of the reaction conditions. With a 0.085 M solution of **20** in benzene, the optimal residence time of 2 h was determined and the corresponding cyclobutane **21** was isolated in an excellent yield of 98%. Under the same reaction conditions, a 10-times scale-up was achieved with no drop in yield. When the transformation was performed under batch conditions, the desired compound **21** was isolated in a much reduced yield of 30% despite prolonged irradiation for 24 h. Scale-up potential was also demonstrated through a concentration study. Choosing a standard residence time of 2 h, the conversion rate remained high with >95% across a broad concentration range of **20** of 0.085–0.425 M. The batch vs. microreactor comparison was furthermore extended to other coumarin derivatives. In all cases, the LOPHTOR reactor achieved higher yields and conversions rates for the corresponding cyclobutanes **22**–**25** after much shorter irradiation times. Regio- and diastereoselectivity, how-



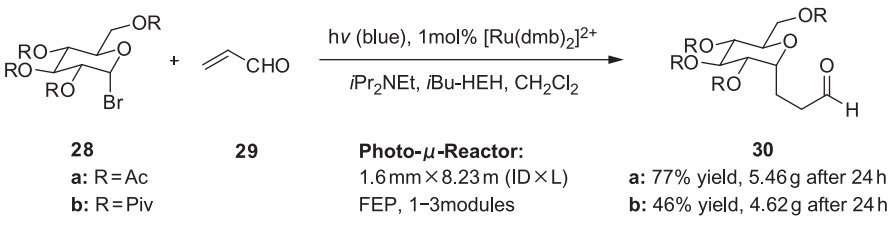
Scheme 7. Intramolecular [2+2]-cycloadditions of cyclopentenone derivative **26** as studied by Hoffmann-LaRoche.

ever, were comparable in both setups.

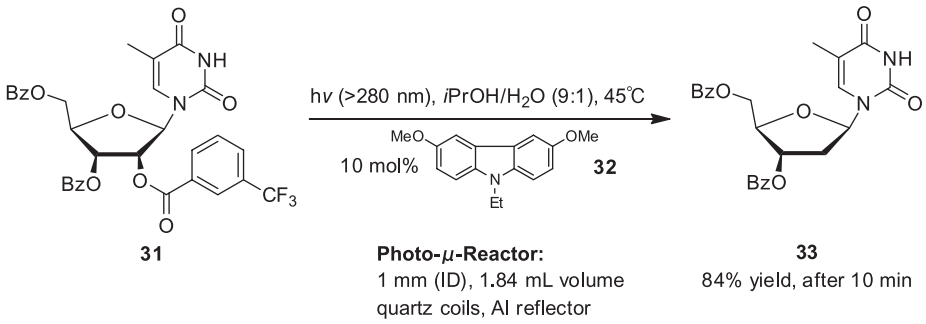
In a related study, Nettekoven and coworkers from Hoffmann-LaRoche examined the multi-gram synthesis of the novel cyclobutane building block **27** in a commercially available microreactor (**Scheme 7**).[17] The selected Ehrfeld Photoreactor XL is fabricated from stainless steel and has a Quartz window separated by a narrow dartek® gasket. When an acetone solution of the cyclopenenone derivative **26** was pumped into the reactor room from the bottom, a thin liquid film of 20–90 μm was created. Irradiations were performed using a unit of 4×8W UVC fluorescent tubes (λ=254 nm). The transformation of **26** was systematically optimized in terms of flow rate, layer-thickness and reagent concentration. Using an optimal flow rate of 3 mL/min (film: 90 μm) and an initial concentration of **26** of 0.5% in acetone, the reactor system delivered 6.4 g (48%) of the desired tricyclic product **27** after 17 h of continuous operation. A further scale-up was realized successfully and 48 g (48%) of **27** were obtained after 111 h.

Photoadditions and Photocleavages

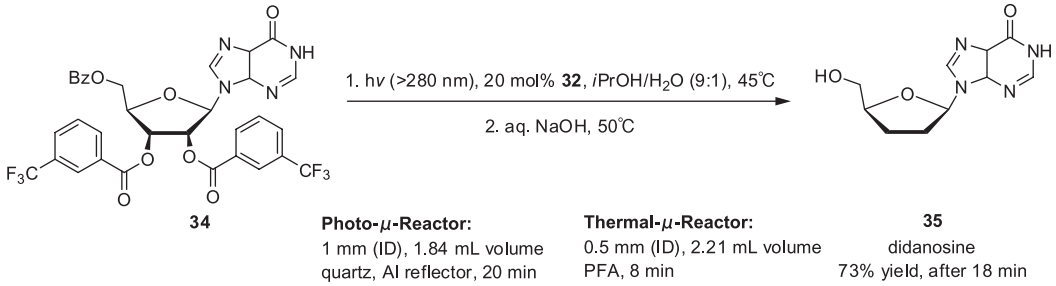
An interesting example of a photoredox reaction has been investigated by Andrews and co-workers (**Scheme 8**).[18] Under batch conditions, the addition of glucosyl bromide **28a** to acrolein (**29**) depended critically on the size of the reaction vessel. When using an NMR tube with a diameter of 5 mm, a 73% conversion to **30a** was reached within 1 h, thus corresponding to a turnover frequency (TOF) of 70 h^{-1}. In a 25 mL Schlenk flask, however, the same transformation required 24 h to achieve a conversion of 85%, therefore resulting in a significantly reduced TOF of just 3.5 h^{-1}. This finding was attributed to the strong absorption of the photoredox catalyst [Ru(dmb)$_3$]$^{2+}$ (ε=17,000 $m^{-1}cm^{-1}$; dmb=4,4'-dimethyl-2,2'-bipyridine) which resulted in poor light transmission and complete absorption of light within a narrow layer of the reaction mixture. The transformation was thus transferred to continuous flow conditions using FEP tubing, which was wrapped around a standard Liebig condenser. Inside the condenser were placed three stripes of 1W blue LEDs that were cooled by passing water through the condenser jacket. Up to 3 of these reactor modules were connected in series to achieve multi-gram scale synthesis of the C-glycoside intermediate **30a**, which subsequently served as a precursor to a series of C-linked glycoconujugates. The effects of tubing diameter and catalyst loading on the TOF were furthermore studied and values between 17–120 h^{-1} were determined. Multi-gram scale preparations of **30a** were achieved with two reactor modules using a 121 mM solution of **28a**, 4 equivalents of **29** and continuous operation at a flow rate of 0.1 mL/min for 24 h. Following this approach, 5.46 g (77%) of **30a** could be isolated. The pivaloate-derived starting material **28b** required extended irradiation times and near complete conversion of >97% was



Scheme 8. Photoredox additions of glucosyl bromides **28** to acrolein (*i*Bu-HEH=diisobutyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate).



Scheme 9. Synthesis of 2'-deoxynucleoside **33** via photosensitized deoxygenation of **31**.

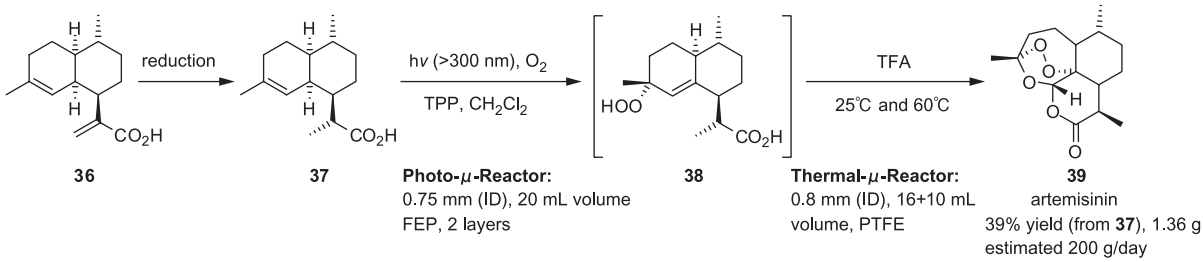


Scheme 10. Continuous microflow synthesis of the anti-HIV drug didanosin **35** from **34** via tandem photodeoxygenation/deprotection.

reached after 24h with three modules. From this experiment, 4.62g (46%) of the corresponding aldehyde **30b** were isolated. The results unambiguously confirm that microscopic dimensions can successfully compensate for unfavorable absorption properties.

Photosensitized deoxygenation reactions to prepare 2'-deoxy- and 2',3'-dideoxynucleosides have been described by Shen and co-workers (**Scheme 9**).[19] Under batch conditions, the transformation requires prolonged irradiation times of 2h and frequently results in over-deoxygenation and thus reduced yields. The authors designed and applied a specialized photochemical microflow reactor using customized quartz tubing in combination with 450W medium pressure mercury lamp in an quartz immersion well, a Pyrex filter and an aluminium mirror. This photoreactor was submerged in a cooling water bath to maintain temperatures of 0-50℃. The flow operation mode led to a considerable decrease in irradiation time (<20 min), coupled with an increase in selectivity and isolated yield. Stepwise process optimization identified 10mol% of 3,6-dimethoxy-9-ethylcarbazole **32** as the most effective photosensitizer and 45℃ as the best reaction temperature. Under these conditions and using a degassed, 0.01 M solution of **31** in aqueous (10 vol%) isopropanol, the transformation of the m-CF_3-benzoate **31** in the presence of **32** furnished the desired thymidine **33** in an isolated yield of 84% after only 10min of irradiation. The flow reaction conditions were subsequently applied to other ribonucleosides, which all produced high yields of 61-85% after short residence times of <10 min. Double deoxygenations to 2',3'-dideoxynucleosides were furthermore demonstrated successfully but required a higher photosensitizer loading of 20mol% and extended irradiation times of 20min.

The photodeoxygenation protocol was furthermore coupled with deprotection to realize an integrated continuous one-flow, two-step process for the synthesis of unprotected deoxynucleosides. An aqueous solution of NaOH was injected via a T-mixer into the effluent stream of the photoreaction and the reaction mixture was pumped through a perfluoroalkoxy (PFA) tubing at 50℃. Complete deprotection proceeded smoothly within 10min and furnished the corresponding fully unprotected 2'-deoxynucleosides in high combined yields of up to 85%. The total reaction time for the tandem process was kept below 20min. An elegant application of this microre-



Scheme 11. Continuous synthesis of the anti-malaria drug artemisinin (**39**) from **37** via a tandem photochemical/thermal process under microflow conditions.

action coupling was the synthesis of the anti-HIV drug didanosine **35** from **34** in a yield of 73% (Scheme 10).

Photooxygenations

The synthesis of the important anti-malaria compound artemisinin (**39**) via a combined photochemical-thermal microflow process has been recently established by Lévesque and Seeberger (Scheme 11).[20] The starting material, dihydroartemisinic acid (**37**) is readily available in large quantities from artemisinic acid (**36**) via reduction. Into a 0.2 M solution of **37** in dichloromethane containing a small amount of tetraphenylporphyrin (TPP; 1 mM) as a photosensitizer is carefully injected a slow stream of oxygen. A slug flow pattern is created and this mixture is introduced into a FEP capillary reactor where it is irradiated with UV light from a 450W medium pressure mercury lamp. Photooxygenation generates the hydroperoxide intermediate **38**, which is mixed with trifluoroacetic acid (TFA) at the outlet of the photochemistry module. This mixture enters a second, thermal (60℃) reactor module made of polytetrafluoroethylene (PTFE) tubing, in which **38** is converted into artemisinin (**39**) via a multi-step reaction cascade. The residence times were estimated to 2 min for the photochemical and 2.5 min for the thermal reactor, respectively. The entire process operates very efficiently without the need of purification or isolation of intermediates. Following this approach, artemisinin (**39**) is isolated from **37** (5 mmol scale) in a yield of 39% over two steps. The simple tandem reactor system had a capability of producing 200g of **39** per day. Thus, the authors estimated that about 1,500 reactor systems would satisfy the annual artemisinin (**39**) demand of >200 million doses.

Conclusion

The examples presented in this article unambiguously demonstrate the superiority of microflow photochemistry over conventional batch processes. By reducing the dimensions of the reactor and operation in flow mode, efficiencies (conversions/yields/energy usage) and selectivity can be drastically improved. It is hoped that this novel synthesis tool will find widespread applications in pharmaceutical R&D and production processes. The operating Heraeus Noblelight process[15] and the examples by Abbott Laboratories[16] and Hoffmann-La Roche[17] clearly support this evaluation. Microflow photochemistry may thus emerge as the 'new photochemistry of the future'.[21]

Acknowledgements

Funding by the Environmental Protection Agency (EPA, 2008-ET-MS-2-S2), the Department of Environment, Heritage and Local Government (DEHLG, 2008-S-ET-2) and James Cook University (JCU-CRIG 2011) is greatly acknowledged.

References

1. (a) Hoffmann, N. Homogeneous Photocatalytic Reactions with Organometallic and Coordination Compounds—Perspectives for Sustainable Chemistry. *ChemSusChem* **5**, 352-371 (2012). (b) Oelgemöller, M., Jung, C. & Mattay, J. Green photochemistry: Production of fine chemicals with sunlight. *Pure Appl. Chem.* **79**, 1939-1947 (2007). (c) Albini, A., Fagnoni, M. &

Mella, M. Environment-friendly organic synthesis. The photochemical approach. *Pure Appl. Chem.* **72**, 1321–1326 (2000).
2. (a) Bach, T. & Hehn, J. P. Photochemical Reactions as Key Steps in Natural Product Synthesis. *Angew. Chem. Int. Ed.* **50**, 1000–1045 (2011). (b) Iriondo-Alberdi, J. & Greaney, M. F. Photocycloaddition in Natural Product Synthesis. *Eur. J. Org. Chem.* 4801–4815 (2007).
3. (a) Hoffmann, N. Photochemical reactions as key steps in organic synthesis. *Chem. Rev.* **108**, 1052–1103 (2008). (b) Demuth, M. & Mikhail, G. New developments in the field of photochemical syntheses, *Synthesis* 145–162 (1989).
4. (a) Ravelli, D. & Fagnoni, M. Dyes as Visible Light Photoredox Organocatalysts. *ChemCatChem* **4**, 169–171 (2012). (b) Narayanam, J. M. R. & Stephenson C. R. J. Visible light photoredox catalysis: applications in organic synthesis. *Chem. Soc. Rev.* **40**, 102–113 (2011).
5. (a) Braun, A. M., Maurette, M. & Oliveros, E. *Photochemical Technology*, Wiley, Chichester, 1991. (b) Gollnick, K. Photooxygenation and its application in chemistry. *Chim. Ind.* **63**, 156–166 (1982). (c) Fischer, M. Industrial applications of photochemical synthesis. *Angew. Chem. Int. Ed.* **17**, 16–26 (1978).
6. (a) Wegner, J., Ceylan, S. & Kirschning A. Flow Chemistry—A Key Enabling Technology for (Multistep) Organic Synthesis. *Adv. Synth. Catal.* **354**, 17–57 (2012). (b) Wiles, C. & Watts, P. Continuous flow reactors: a perspective. *Green Chem.* **14**, 38–54 (2012). (c) Yoshida, J.-i., Kim, H. & Nagaki, A. Green and Sustainable Chemical Synthesis Using Flow Microreactors. *ChemSusChem* **4**, 331–340 (2011).
7. (a) Baraldi, P. T. & Hessel, V. Microreactor and flow chemistry for industrial applications in drug discovery and development. *Green Process Synth.* **1**, 149–167 (2012). (b) Malet-Sanz, L. & Susanne, F. Continuous Flow Synthesis. A Pharma Perspective. *J. Med. Chem.* **55**, 4062–4098 (2012). (c) Anderson, N. G. Using Continuous Processes to Increase Production. *Org. Process Res. Dev.* **16**, 852–869 (2012). (d) Chin, P., Barney, W. S. & Pindzola, B. A. Microstructured reactors as tools for the intensification of pharmaceutical reactions and processes. *Curr. Opin. Drug Dis. Dev.* **12**, 848–861 (2009).
8. (a) Oelgemöller, M. Highlights of Photochemical Reactions in Microflow Reactors. *Chem. Eng. Technol.* **35**, 1144–1152 (2012). (b) Oelgemöller, M. & Shvydkiv O. Recent Advances in Microflow Photochemistry. *Molecules* **16**, 7522–7550 (2011). (c) Coyle E. E. & Oelgemöller, M. Micro-photochemistry: photochemistry in microstructured reactors. The new photochemistry of the future? *Photochem. Photobiol. Sci.* **7**, 1313–1322 (2008). (d) Matsushita, Y., Ichimura, T., Ohba, N., Kumada, S., Sakada, K., Suzuki, T., Tanibata, H. & Murata, T. Recent progress on photoreactions in microreactors. *Pure Appl. Chem.* **79**, 1959–1968 (2007).
9. (a) Yavorskyy, A., Shvydkiv, O., Nolan, K., Hoffmann, N. & Oelgemöller, M. Photosensitized addition of isopropanol to furanones in a continuous-flow dual capillary microreactor. *Tetrahedron Lett.* **52**, 278–280 (2011). (b) Lévesque, F. & Seeberger, P. H. Highly Efficient Continuous Flow Reactions Using Singlet Oxygen as a "Green" Reagent. *Org. Lett.* **13**, 5008–5011 (2011). (c) Gutierrez, A. C. & Jamison, T. F. Continuous Photochemical Generation of Catalytically Active $[CpRu]^+$ Complexes from CpRu (η^6-C_6H_6)PF_6. *Org. Lett.* **13**, 6414–6417 (2011). (d) Hook, B. D. A., Dohle, W., Hirst, P. R., Pickworth, M., Berry, M. B. & Booker-Milburn, K. A practical flow reactor for continuous organic photochemistry. *J. Org. Chem.* **70**, 7558–7564 (2005).
10. Yavorskyy, A., Shvydkiv, O., Hoffmann, N., Nolan, K. & Oelgemöller, M. Parallel Microflow-Photochemistry: Process Optimization, Scale-up and Library Synthesis. *Org. Lett.* **14**, 4342–4345 (2012).
11. (a) Fuse, S., Tanabe, N., Yoshida, M., Yoshida, H., Doi, T. & Takahashi, T. Continuous-flow synthesis of vitamin D_3. *Chem. Commun.* **46**, 8722–8724 (2010). (b) Fuse, S., Mifune, Y., Tanabe, N. & Takahashi, T. Continuous-flow synthesis of activated vitamin D_3 and its analogues. *Org. Biomol. Chem.* **10**, 5205–5211 (2012).
12. Anderson, B. G., Bauta, W. E. & Cantrell, W. R. Development of an Improved Process for Doxercalciferol via a Continuous Photochemical Reaction. *Org. Process Res. Dev.* **16**, 967–975 (2012).
13. Sugimoto, A., Sumino, Y., Takagi, M., Fukuyama, T. & Ryu, H. The Barton reaction using a microreactor and black light. Continuous-flow synthesis of a key steroid intermediate for an endothelin receptor antagonist. *Tetrahedron Lett.* **47**, 6197–6200 (2006). (b) Sugimoto, A., Fukuyama, T., Sumino, Y., Takagi, M. & Ryu, I. Microflow photo-radical reaction using a compact light source: Application to the Barton reaction leading to a key intermediate for myriceric acid A. *Tetrahedron* **65**, 1593–1598 (2009).
14. Mimieux Vaske, Y. S., Mahoney, M. E., Konopelski, J. P., Rogow, D. L. & McDonald W. J. Enantiomerically Pure trans-β-Lactams from α-Amino Acids via Compact Fluorescent Light (CFL) Continuous-Flow Photolysis. *J. Am. Chem. Soc.* **132**, 11379–11385 (2010).
15. Werner, S., Seliger, R., Rauter, H. & Wissmann, F. Quarzglas-Mikrophotoreaktor und Synthese von 10-Hydroxycamptothecin und 7-Alkyl-10-hydroxycamptothecin. *EP–2065387A2* (2009) [*Chem. Abstr. 150*,

376721 (2009)].
16. Vasudevan, A., Villamil, C., Trumbull, J., Olson, J., Sutherland, D., Pan, J. & Djuric, S. LOPHTOR: A convenient flow-based photochemical reactor. *Tetrahedron Lett.* **51**, 4007–4009 (2010).
17. Nettekoven, M., Püllmann, B., Martin, R. E. & Wechsler, D. Evaluation of a flow-photochemistry platform for the synthesis of compact modules. *Tetrahedron Lett.* **52**, 1363–1366 (2012).
18. Andrews, R. S., Becker, J. J. & Gagné, M. R. A Photoflow Reactor for the Continuous Photoredox-Mediated Synthesis of C-Glycoamino Acids and C-Glycolipids. *Angew. Chem. Int. Ed.* **51**, 4140–4143 (2012).
19. Shen, B., Bedore, M. W., Sniady, A. & Jamison, T. F. Continuous flow photocatalysis enhanced using an aluminum mirror: rapid and selective synthesis of 2'-deoxy and 2',3'-dideoxynucleosides. *Chem. Commun.*, **48**, 7444–7446 (2012).
20. Lévesque, F. & Seeberger, P. H. Continuous-Flow Synthesis of the Anti-Malaria Drug Artemisinin. *Angew. Chem. Int. Ed.* **51**, 1706–1709 (2012).
21. This statement refers to Giacomo Ciamician's visionary lecture, presented before the International Congress of Applied Chemistry in New York in 1912: Ciamician, G. The photochemistry of the future. *Science* **36**, 385–394 (1912).

Profile

Michael Oelgemöller:
Michael Oelgemöller received his Diploma from the University of Münster in 1995 and his PhD from the University of Cologne in 1999. He was a researcher at the Inoue Photochirogenesis project in Osaka (1999–2001) and at Bayer CropScience Japan in Yuki (2001–2004). From 2004–2008 he held a position as a lecturer in Organic and Medicinal Chemistry at Dublin City University, Ireland. In February 2009 he joined James Cook University in Australia as an Associate Professor in Organic Chemistry. His research activities include synthetic organic photochemistry, solar photochemistry, the development of new photochemical synthesis tools and photochemical water treatment. He received the Kurt-Alder award of the University of Cologne in 2000 and has been a visiting professor at Osaka University (2006), the University of Pau (2009 and 2012), Osaka Prefecture University (2011) and the Nara Institute of Science and Technology (2012). He is a leading expert in green (solar) photochemistry and microflow photochemistry.

Akiko Murata:
From 1997–2009 Akiko Murata worked in the Research and Development division of Dainippon Screen Mfg. Co., Ltd. As an assistant manager within the process technology division, she was in charge of material development and the development of microreactors. During 2004-2006 she was furthermore a research student at Osaka Prefecture University. In 2009, she worked for Nano cube Japan Co., Ltd. In 2010, she became a research assistant and PhD course student in Functional Molecular Chemistry at the Graduate School of Engineering of Kobe University.