# **ORGANIC PROCESS RESEARCH & DEVELOPMENT** DPRS

# Toward the Waste-Free Synthesis of Fine Chemicals with Visible Light

Rosaria Ciriminna,<sup>†</sup> Riccardo Delisi,<sup>†</sup> Yi-Jun Xu,<sup>\*,‡</sup> and Mario Pagliaro<sup>\*,†</sup>

<sup>†</sup>Istituto per lo Studio dei Materiali Nanostrutturati, CNR, via U. La Malfa 153, 90146 Palermo, Italy

 $^{\ddagger}$ State Key Laboratory of Photocatalysis on Energy and Environment, College of Chemistry, New Campus, Fuzhou University, Fuzhou 350108, People's Republic of China

ABSTRACT: Progress in photochemistry and concomitant significant advances in flow chemistry, nanochemistry, and solid state lighting from the past decade hold the potential to make visible-light photocatalysis part of the synthetic tools used by the fine chemical and pharmaceutical industries for the production of active ingredients. This study identifies key advances and remaining gaps toward the widespread adoption of heterogeneously catalyzed processes using visible photons for manufacturing functional molecules on a large scale.

# 1. INTRODUCTION

The industrial practice of synthetic organic chemistry nowadays relies on homogeneous and, to a lesser extent, on heterogeneous catalysis.1 A further important progress would be the introduction of technically feasible photocatalytic syntheses, especially of visible light photocatalysis in which visible photons act as intrinsically clean reactants for chemical syntheses under mild conditions.<sup>2</sup>

Despite intense research efforts and significant results at least partly achieved,<sup>3</sup> a frequent question faced by researchers in visible light photocatalysis addresses the technical and economic feasibility of synthetic photocatalysis.

Admittedly, after more than one century after the "Photochemistry of the Future" prophecies of Ciamician devising a world in which "solar reactors were to produce chemicals and fuels",<sup>4</sup> very few industrial syntheses are actually based on visible light photocatalysis including the low-cost synthesis of rose oxide<sup>5</sup> and the promising industrial debut in 1943 with the production of the anthelmintic drug ascaridole via solar irradiation of  $\alpha$ -terpinene.<sup>6</sup>

In general, photochemical processes were not used by industry for large-scale chemical productions because for decades they were not economically and technically competitive with conventional thermal conversions carried out in batch, requiring large photon fluxes transmitted into large volume vessels needing rapid cooling.

Yet, we argue in this work, this situation is likely to change in the near future as the photocatalytic synthesis of valued functional molecules could become competitive with conventional catalytic processes due the significant advantages offered by continuous flow photochemistry. The largely reduced dimension of continuous flow photochemical reactors ensures (i) a high photon flux within the reaction volume and little or no flux in nonirradiated volumes, (ii) reduces the hazard of maintaining a large volume of solvent in close proximity to the lamp, and (iii) resolves the penetration depth issue limiting photochemical conversions in batch as the thickness of the irradiated fluid is often <1.5 mm.

Likewise to continuous chemical conversions in general, furthermore, the photochemical reaction can be scaled simply by running the process for longer times thereby resolving the scalability issue typical of photochemical reactions in batch.<sup>8</sup> Following detailed reviews on photocatalysis for synthetic purpose,<sup>9</sup> including accounts<sup>10</sup> on visible-light photocatalytic redox reactions, this article focuses on the challenges needed to go from basic science to possible industry implementation of visible light photocatalysis suggesting avenues for the introduction of technically feasible and economically viable photosyntheses of fine chemicals, especially carrying out the photoreactions under flow.

# 2. OVERCOMING THE OBSTACLES TO SYNTHETIC PHOTOCHEMISTRY

The comments of an organic process industrial chemist writing in 2010 point to the typical problems then encountered with conventional photochemical syntheses on industrial scale:

"I've seen some attempts to scale up photochemical reactions in 10 L flask, with the light source immersed (lamps enclosed in borosilicate glass pockets), ending in total messes, with the product sticked to the lamp surface, no matter how heavy was the stirring".<sup>11</sup>

Actually, an important advance had occurred in 2005 when Booker-Milburn, Berry, and co-workers devised a simple methodology to carry out photochemistry under flow using a compact flow reactor comprised of an expensive, but UVtransparent and solvent resistant fluoropolymer (FEP, fluorinated ethylene propylene copolymer) tubing wrapped around a UV lamp (Figure 1).<sup>12</sup>

An HPLC pump is used to flow the substrate solution through the illuminated FEP tubing. This simple, yet powerful idea opened the route to reliably perform continuous organic

Special Issue: Continuous Processing, Microreactors and Flow Chemistry

Received: December 30, 2015 Published: January 28, 2016





**Figure 1.** Schematic of a typical macroflow photochemical reactor (above) and images of the FEP photochemical flow reactor developed by Booker-Milburn and Berry. Adapted from ref 12. Copyright 2005, American Chemical Society.

photochemistry on much larger scale than in conventional photochemistry. The new configuration, indeed, allows much better irradiation (more uniform, ultrashort path length, and easily controlled irradiation time) solving the key issue that for decades limited conventional photochemistry under batch to <1 g reactions.

In the very first publication mentioned above,<sup>12</sup> for example, the new flow reactor, was capable of producing >500 g of cyclobutene photocycloaddition [2 + 2] product in 24 h of continuous processing period.

The fundamental limitation of organic photochemistry in batch reactors typically surrounding an immersed UV mercury lamp resides in the Beer–Lambert logarithmic law (eq 1, in which  $\varepsilon$  is the extinction coefficient, l is the length of solution the light passes through, and c is the molar concentration) governing light penetration (the ratio of transmitted light I to incident light  $I_0$ ) in solution:

$$\log(I_0/I) = \varepsilon lc \tag{1}$$

This is the main physical obstacle from which Brooker-Milburn and co-workers started when developing the new photochemical reactor emphasizing<sup>13</sup> that, for example, very little light is available beyond a 1 mm path length off the lamp irradiating a 0.05 M solution of a compound with modest (200 mol<sup>-1</sup> cm<sup>-1</sup>) extinction coefficient, as 90% of the incident light is then absorbed from the solution just around the lamp.

The practical consequence is frequent over irradiation and prolonged reaction times that, coupled to poor heat/mass transfer rates in large-volume reactors, usually led to mediocre efficiency, making photochemistry in batch a barely utilized synthetic technique in synthetic organic chemistry.

The use of the continuous transparent microeactor solves this bottleneck due to much shorter path lengths that can be irradiated effectively and uniformly. At the same time, the continuous flow reactor, being scale-independent, avoids the need for expensive (and hazardous) bigger lamps when scaling up the photochemical reaction.

Rapid advances from several academic and industrial research groups quickly followed the first report. Seeberger and coworkers, for instance, introduced the synthesis of artemisinin under flow using photochemically generated singlet oxygen;<sup>14</sup> and subsequently advanced a number of photochemical (direct excitation of chromophores within the starting molecules) and photocatalytic reactions under both UV and visible light radiation.<sup>15</sup>

Zeitler and co-workers developed a modified version of the Booker-Milburn system with an enlarged irradiation zone which allowed for full conversion at high flow rates and low temperature of several substrates in visible light photo reduction or oxidation catalytic reactions using different photocatalysts under microflow conditions.<sup>16</sup>

A large pharmaceutical company in the US developed a similar flow-through photochemical reactor (*Lophtor*) with enhanced control of irradiation time, temperature, and wavelength with minimal manual intervention, ideally suited for identifying the optimal conditions and then for the synthesis of hundred of mg of complex molecules in an unattended manner, and thus for drug discovery.<sup>17</sup>

Several other research groups across the world reported other visible-light-mediated photoredox processes under flow offering clear benefits when compared with conventional batch techniques.<sup>18</sup>

In this respect, Brooker-Milburn's team in 2014 published the results of a comprehensive comparative study using a broad range of synthetic photochemical transformations in both flow and batch reactor modes (Figure 2).<sup>19</sup>

Even though yields and productivities were essentially identical in all cases, the flow reactors were found to be ideally suited for producing products on scales of greater than 10 g in a single run, and for processing larger volumes safely and efficiently, including the scale-up of the ring-opening reaction



**Figure 2.** Batch and flow reactors used in the comparison of (a) a 400 W medium-pressure Hg lamp batch reactor and power supply with equivalent three-layer FEP flow reactor and peristaltic pump and (b) a triad of one-layer FEP reactors customized for use with 40 cm 36 W low-pressure Hg lamps. Reproduced with permission from ref 19. Copyright 2014, Wiley-VCH.

of [1.1.1] propellane, an explosive compound, with butane-2,3dione (Scheme 1).

Scheme 1. Photochemical Ring Opening and Reaction of Propellane with Butane-2,3-dione in Flow [Reproduced with permission from ref 19. Copyright 2014, Wiley-VCH]



For example, in place of the FEP tubing, less expensive PTFE tubing can be effectively used, as shown by the photocatalytic synthesis of antibiotic lactone  $\gamma$ -keto esters on a gram scale (5.5 g/day) mediated (in one of two consecutive reactions, one of which is photochemical, conducted under flow; Figure 3) by



**Figure 3.** In the flow photocatalytic reactor used for the preparation of  $\gamma$ -keto esters, tubing is comprised of less expensive PTFE. [Reproduced with permission from ref 20. Copyright 2014, Wiley-VCH].

the robust, highly active and easily removed *n*-tetrabutylammonium decatungstate  $(nBu_4N)_4[W_{10}O_{32}])$  photocatalyst for the addition of aldehydes to electron-poor olefins, involving the conjugate radical addition of a photogenerated acyl radical (from aldehyde I) to a  $\alpha_{,\beta}$ -unsaturated ester II (Scheme 2).<sup>20</sup>

In brief, the advantages of photochemical reactions under flow in microreactors are so evident that they were readily investigated by the chemical community and in early 2014,

Scheme 2. Synthesis of  $\gamma$ -keto Esters III Based on the Decatungstate-Photocatalyzed Addition of Aldehydes I to Electron-Poor Olefins II [Adapted with permission from ref 20. Copyright 2014, Wiley-VCH]



Rehm was able to publish the first overview dealing with photochemistry under  ${\rm flow.}^{21}$ 

Several reactions including efficient in situ generation of singlet oxygen for photooxygenation of 1,5-dihydroxynaphthalene to Juglone after just 160 s of exposure to visible light,<sup>22</sup> organocatalysis combined with photoredox catalysis for asymmetric synthesis of small molecules under batch,<sup>23</sup> incorporation of fluorinated alkyl groups into a broad scope of molecules,<sup>24</sup> and safe generation of hazardous compounds for direct use in important C–S bond forming reactions,<sup>25</sup> were reviewed therein.

The field is developing so rapidly to already deserve a new review. Suffice it to mention recent work from Beeler and co-workers on [2 + 2] photocycloaddition of a range of cinnamate substrates under flow to predictably form cyclobutane diastereomers.<sup>26</sup>

What is relevant here is that Rehm was concluding his report emphasizing that many of the reactor concepts developed until then were "custom-built without a clear tendency on standardized components for industry"; calling for the immobilization of tailor-made photocatalysts "on appropriate supports like polymers or metal oxides" to allow their use as heterogenized photocatalysts in continuous-flow processes without time-consuming catalyst separation as reported, for example, by Rocha Gonsalves and co-workers in 2007 with porphyrins covalently linked to sulfonated polystyrene resins, later used to to generate singlet oxygen and synthesize Juglone and ascaridole in batch.<sup>27</sup>

A few months later, in 2014, a Europe's company (Vaportec) was the first to launch on the market a new continuous processing photoreactor (UV-150) using a compact high intensity, dimmable metal halide 150 W lamp, a cooling system, temperature control, wavelength filtering and reflective surfaces designed to ensure that the photons emitted by the lamp are efficiently absorbed by the reagents. The new integrated system goes beyond the lack of control and scalability inherent within traditional batch systems.

In the subsequent months, several reports appeared in the chemical literature illustrating the synthetic potential of the new reactor, including the photochemical production of multigram quantities (within a working day) of the anti-inflammatory drug isobutylphenyl propionic acid (ibuprofen, annual production >9,800 tonnes) via photo-Favorskii rearrangement of  $\alpha$ -chloropropiophenone.<sup>28</sup>

#### 3. FROM TRADITIONAL TO SOLID STATE LIGHTING

Another major progress of relevance to this study, almost concomitant to the first developments of photocatalysis under flow, has been the introduction of the almost punctiform and energy efficient light emitting diode (LED) lamps in place of discharge lamps (especially mercury vapor lamps) used as traditional photon sources.<sup>29</sup>

The uniquely new properties of these solid state lighting sources, indeed, opens new possibilities in photocatalysis and photochemistry, not only thanks to largely reduced power consumption and to the lack of infrared and ultraviolet heating radiation, but also to the unprecedented freedom in the design and miniaturization of the photoreactor, which allows better photoenergy utilization.

For example, Lapkin and co-workers have lately shown that in in the oxygenation of  $\alpha$ -pinene to pinocarvone with photochemically generated singlet oxygen (<sup>1</sup>O<sub>2</sub>) carried out under flow (Scheme 3), higher quantum yields are obtained Scheme 3. Oxygenation of  $\alpha$ -Pinene to Pinocarvone with Photochemically Generated Singlet Oxygen [Copyright 2014, American Chemical Society]



with the microreactor-LED assemblies (Figure 4), compared to all other systems studied (actinic fluorescent and Xe arc lamps



**Figure 4.** A microreactor with segmented gas-liquid flow irradiated by a LED array or metal halide lamp. [Copyright 2014, American Chemical Society].

in different lamp-reactor geometries: immersed well, annular recirculating reactor, and microreactor unit) due to better energy utilization.<sup>30</sup>

Besides better power utilization (higher lm/W ratio), the narrow radiation pattern of the single LED sources *and* the circular lamp-reactor geometry (several times more efficient) explain the optimal performance of LED array based flow microreactors. No such microreactor configuration was accessible prior to the introduction of small and easily integrated LED sources of blue and white light.<sup>31</sup>

The large optimization potential opened by the possibility to eventually tune the photon fluxes within microreactors has been lately identified by Ziegenbalg and co-workers highlighting the crucial importance of an optimized design of the micro photoreactor.<sup>32</sup>

Using the synthesis of ascaridole from  $\alpha$ -terpinene and  ${}^{1}O_{2}$  as a test reaction, the team developed and applied a general model for determining bottlenecks of a photoreactor setup focusing on the photon fluxes. The resulting model revealed potential for optimization by showing the sensitivity of the reactor setup to different possible process conditions and configuration of the OLED (organic light-emitting diode) panels used.

In detail, the team found that the external photonic efficiency is the key factor. Replacing first-generation OLED panels with second-generation light sources, improves the productivity by a factor of almost four; while the energy consumption remains nearly unvaried ( $\eta_{lum} = 12.8\%$ ), which corresponds to similar increase of the overall energy efficiency (Table 1). The magnitude of the emitted photon flux is *not* directly correlated to the improvement in conversion, but rather the amount of photons emitted by the LED lamp is regulated to match the transformation along with the residence time in the presence of said photons.

These results are general and of particular industrial relevance as the continuous synthesis of a wide variety of valued substances clearly appears on the horizon, including the

Table 1. Conversion  $X_{\text{terp}}$  for Different Process Conditions with First-Generation (CDW-031) or Second-Generation (CDW-030) OLED Panels<sup>*a*</sup>

		$X_{ m terp}$		
$V (mL min^{-1})$	rO <sub>2/terp</sub>	CDW-031	CDW-030	$X_{\rm imp}$ (%)
0.5	0.5	19.1	32.2	168
0.5	10.25	89.3	97.4	109
0.5	20.0	92.5	97.5	105
3.25	0.5	15.4	22.3	145
3.25	10.25	44.4	96.2	217
3.25	20.0	41.5	97.4	235
6.0	0.5	3.3	14.9	453
6.0	10.25	20.4	65.9	324
6.0	20.0	33.9	95.5	282

<sup>*a*</sup>The  $X_{imp}$  number illustrates to which extent the higher photon flux enhances the conversion. [Copyright 2014, American Chemical Society].

scaled-up synthesis of biologically active compounds by simply coupling a photoreactor and thermal reactor modules.<sup>33</sup>

#### 4. TOWARD HETEROGENEOUS PHOTOCATALYSIS UNDER FLOW

Most photocatalytic processes developed until the early 2000s relied on UV irradiation with mercury lamps in batch reactors using wide band gap crystalline  $TiO_2$  as a photocatalytic semiconductor.<sup>34</sup> Since then, accelerated innovation in nanochemistry aimed to develop selective synthetic processes using visible light have led to the introduction of new semiconductor light absorber nanostructures of the right band gap, including low-cost Bi<sub>2</sub>WO<sub>6</sub>,<sup>35</sup> plasmonic-metal nanoparticles,<sup>36</sup> and graphene/semiconductor composites,<sup>37</sup> capable to maximize visible light absorption and minimize losses due to electron–hole recombination.

A further advance, which maximizes the physical and chemical stability of the catalyst involves the encapsulation of the photocatalyst in a transparent porous matrix, such as in the case of CdSe in mesoporous alumina, which protects and stabilizes the otherwise unstable semiconductor leading to the sustained production of hydrogen upon solar irradiation in highly acidic media (Figure 5);<sup>38</sup> or in the case of sol–gel



**Figure 5.** Hydrogen evolution under visible light illumination ( $\lambda > 410$  nm) due to alumina-embedded CdSe structures added to 0.1 M KI solution at pH 2 as a function of time. No significant decrease in activity takes place for more than 20 h of irradiation time. [Copyright 2013, American Chemical Society].

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encapsulated flower-like  $Bi_2WO_6$  (SiliaSun) affording valued dihydroxyacetone from glycerol in the presence of oxygen under ambient conditions and visible light irradiation.<sup>39</sup>

The next advance, we argue in this study, will involve the possibility to carry out synthetic photocatalysis inside similar transparent porous matrixes under flow. Indeed, in 2014 Blechert and co-workers reported that the cyclization of 2-bromo-1,3-dicarbonyl compounds mediated by transparent, mesoporous graphitic carbon nitride (g-C<sub>3</sub>N<sub>4</sub>) conducted in a continuous flow photoreactor affords complete conversion of 0.04 mmol of substrate into functionalized cyclopentane in 40 min only.<sup>40</sup>

Previously, Wang and Blechert had reported that  $g-C_3N_4$  selectively mediates the oxidation of alcohols to carbonyls<sup>41</sup> and of amines to imines.<sup>42</sup> The reactions were carried out at 100 °C on 1 mmol scale in the presence of atmospheric oxygen, under exposure to visible light. Perhaps not surprisingly with both reactions carried out in batch, the  $g-C_3N_4$  catalyst lost one-third of its original activity after the fourth run.

On the other hand, the continuous photocatalytic cyclization reaction carried out at room temperature under flow resulted in exceptional catalyst stability (a modest activity loss observed even after 60-70 reaction cycles). Hence, the authors concluded, similar heterogeneously catalyzed photocatalytic conversions under flow "might find widespread use in chemical synthesis".<sup>40</sup>

# 5. OUTLOOK AND CONCLUSIONS

Photochemistry and photocatalysis for the synthesis of fine chemicals is a under-utilized yet rapidly emerging synthetic technique in the context of rapid advances in nanocatalysis, flow chemistry science, and engineering, as well as in solid state lighting. In the last two years, flow photochemistry systems have been marketed aiming to make the technique easily and safely available for practitioners of organic synthesis.

Seen from a perspective viewpoint, one may notice that this change is occurring while the practice of synthetic organic chemistry in the fine chemical industry is changing again,<sup>43</sup> after the first shift from stoichiometric processes to homogeneously and, more recently, to heterogeneously catalyzed conversions in batch<sup>44</sup> and then in flow.<sup>45</sup>

This progress will be followed by a second major progress in which a wide range of compounds including active pharmaceutical ingredients will be obtained in high yield and purity under continuous flow in modular photochemical microreactors, with a few fine chemical and pharmaceutical companies already using catalysis under flow for certain productions.<sup>46</sup>

Yet, a recent industrial outlook from pharmaceutical technology practitioners reveals that, as of late 2015, the concomitant lack of comprehensive regulatory guidelines *and* of chemists with expertise in flow chemistry,<sup>47</sup> continued to hinder widespread industrial adoption of continuous API synthesis.

"The main barrier to using photochemistry", commented Booker-Milburn five years after the introduction of the FEP reactor, is "the fear of photochemistry itself".<sup>48</sup>

The practice of photocatalysis under flow in the abovementioned safe microreactors will actually provide chemists with an eminent green chemistry technology through which to dispel chemistry-related fears in society.<sup>49</sup>

Eventually, beyond those commercialized by the pioneering companies mentioned above, a number of new integrated devices for the heterogeneously catalyzed synthesis of functionalized molecules comprised of transparent tube reactors surrounded by LED arrays emitting narrow beams of visible light will become commercially available, along with newly developed nanostructured visible-light photocatalysts.

To fill the gap of young chemists with expertise in flow chemistry requires to renew the chemistry curricula of universities across the world to include flow chemistry<sup>50</sup> in the general curriculum of chemistry graduates. At the same time, the development of new visible light photocatalysts suitable for prolonged use in said modular flow reactors requires dedicated education in nanochemistry<sup>51</sup> to shape the future scholars that will actually develop such catalysts.

Eventually, we believe that the industrial shift already initiated, along with the above joint eductional and research efforts, will make synthetic photocatalysis under flow over solid catalytsts a central technology of tomorrow's fine chemical, specialty and pharmaceutical industries.

#### AUTHOR INFORMATION

#### **Corresponding Authors**

\*E-mail: yjxu@fzu.edu.cn.

\*E-mail: mario.pagliaro@cnr.it.

# Notes

The authors declare no competing financial interest.

#### ACKNOWLEDGMENTS

This article is dedicated to Professor Valentine Ananikov, Moscow State University and Russian Academy of Sciences, for his eminent contributes to the progress of synthetic organic chemistry, on the occasion of his plenary lecture at FineCat 2016. We thank Dr Omar Jina (Syrris) and Dr Valerica Pandarus (SiliCycle) for useful discussion on flow chemistry.

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### NOTE ADDED AFTER ASAP PUBLICATION

This review was published ASAP on February 4, 2016. Scheme 1 has been updated and the corrected version was reposted on February 19, 2016.