Review

The Development of Visible-Light Photoredox Catalysis in Flow

Zachary J. Garlets, John D. Nguyen, and Corey R. J. Stephenson*[a]

Abstract: Visible-light photoredox catalysis has recently emerged as a viable alternative for radical reactions otherwise carried out with tin and boron reagents. It has been recognized that by merging photoredox catalysis with flow chemistry, slow reaction times, lower yields, and safety concerns may be obviated. While flow reactors have been successfully applied to reactions carried out with UV light, only recent developments have demonstrated the same potential of flow reactors for the improvement of visible-light-mediated reactions. This review examines the initial and continuing development of visible-light-mediated photoredox flow chemistry by exemplifying the benefits of flow chemistry compared with conventional batch techniques.

Keywords: Photochemistry · Radicals · Radical reactions · Redox chemistry

1 Introduction

The applications of flow-through processes for synthesis and methodology development have identified continuous flow reactors as useful emerging technologies for modern synthetic chemistry.[1] In particular, the combination of flow-through processes with photochemical methods has demonstrated striking improvements in the efficiency and scalability of photochemical reactions due to the increased ability to control reaction variables that are difficult to control in batch reactions.[2]

Although photochemical processes have been known for nearly two centuries,[3] the ability to carry out these processes in an efficient manner has been hindered by the requirement for small-volume well reactors containing mercury vapor discharge lamps. These batch reactors are difficult to apply to large-scale reactions because irradiation can only penetrate a short distance into the reaction vessel. These scale-up issues have motivated photochemists to develop falling-film reactors, which somewhat alleviate the issue of scale up, but these reactors still suffer from the need to continuously recycle the reaction mixture to achieve high conversions.[4] The design and construction of single-pass, continuous-flow photochemical reactors developed by several groups has allowed for scale-independent photochemical reactors capable of efficiently converting gram and kilogram quantities of material.[5]

Overall, the advantages that flow-through processes have over batch processes are the same for both photochemical and non-photochemical reactions. For example, flow-through processes are typically more predictable upon scale up, have fewer safety hazards, and are generally more efficient in terms of both yields and reaction time.[2a] In addition, flow-through systems are particularly advantageous for photochemical processes because the high surface-area-to-volume ratios allow for more thorough irradiation of the reaction mixture. Recently, visible-light photocatalysis has successfully been adapted to flow reactor designs utilized by UV flow photoreactors.[5] In fact, many of the visible-light-induced transformations that have been applied to continuous flow were initially developed as UV-induced batch reactions. Herein, we describe recent applications of continuous-flow chemistry to visible-light photoredox catalysis[6] with an emphasis on advantages over batch reactions as well as an outlook on the influence of flow chemistry for the future development of photochemistry.

The facility with which each photoreactor can be tailored to the specific reaction under investigation is an outstanding feature of a flow setup. The visible-light photoredox flow reactors described below range in complexity, but can be generalized by the same basic description. The reactants are pumped by an HPLC pump, peristaltic pump, or syringe pump through the photoreactor with flow rates ranging from μmol/min to mL/min based on the required residence time (t_R), which is defined as the average time that the reactants are subjected to irradiation within the photoreactor for full conversion. The reac-

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tion material may be siphoned from a round-bottomed flask or injected directly. In addition, all of the reaction components may be pre-mixed and then subjected to flow, or otherwise mixed within the flow system. Fluorinated ethylene propylene (FEP) or perfluoroalkoxy polymer resin (PFA) tubing are typically used because they are flexible, chemically resistant, and transmit light. The inner diameter of the tubing is typically less than 1 mm to allow for optimal absorbance at typical catalyst concen-

trations (1.0 mM). The visible-light flow reaction may also require engineered cooling to maintain the ambient temperature of the reactor. Reaction cooling can be achieved either by the passage of air through the reaction vessel or by utilizing a cooling condenser to maintain desired reaction temperatures. After irradiation is complete, the reaction mixture may be subjected to workup or re-applied to flow conditions.

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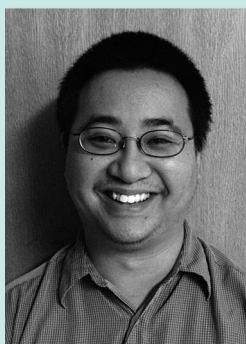
Corey R. J. Stephenson received a B.Sc. Honours degree in 1998 from the University of Waterloo, and a PhD in 2005 from the University of Pittsburgh working under the direction of Professor Peter Wipf. After carrying out postdoctoral research in the laboratory of Professor Erick M. Carreira at the ETH Zürich, Switzerland, he joined the Department of Chemistry at Boston University as an Assistant Professor in September 2007. He was granted tenure and promoted to Associate Professor in February, 2013. Since July 2013, he has been an Associate Professor at the University of Michigan, Ann Arbor, where his research group focuses on catalysis, natural product synthesis, and continuous-flow chemistry.

2 Initial Developments of Visible-Light-Mediated Photoredox Flow Chemistry

The initial investigations of visible-light photoredox catalysis utilizing flow chemistry were conducted independently by Seeberger, Gagné, Stephenson and Jamison.[5c–e] While the benefits of flow chemistry were applied previously to UV-light-mediated organic transformations,[7] applications of flow chemistry to visible-light-mediated photoredox transformations were overlooked. Recognizing the rapid development of visible-light-mediated photoredox chemistry, these groups sought to demonstrate the utility of flow reactors for improving slow reaction times and poor scale up when using conventional batch techniques.

To test the potential application of flow chemistry to photoredox catalysis, Seeberger and co-workers constructed a reactor suitable for visible-light-mediated reactions. The reactor was composed of FEP tubing wrapped around two metal supporting rods. On each side of the tubing setup, a 17 W, cold, white light-emitting diode (LED) was positioned. The reactor required no external cooling because the LEDs contained heat sinks to maintain the temperature. Two HPLC pumps were used to pump the components of the reaction, which would eventually meet at an ethylene-*co*-tetrafluoroethylene T-mixer before exposure to the LED lamps. One HPLC pump dispensed a mixture of tris(bipyridine)ruthenium(II) chloride (Ru(bpy)$_3$Cl$_2$) in DMF, while the other HPLC pump added the remaining reactants, which were dependent upon the specific photoredox transformation being examined. All of the reactants were loaded into the system through a 2 mL injection loop. After passing through the photoreactor, the product mixture was dispensed into a flask charged for workup.

The continuous flow photoreactor was applied to four established photoredox reactions catalyzed by Ru-(bpy)$_3$Cl$_2$ (Scheme 1). Seeberger and co-workers performed each reaction in batch and in flow to compare the efficiency of each process. The first reaction examined was the reduction of azides to amines first developed by Liu and co-workers (Scheme 1A).[8] The yield for the reduction of **1** to **2** was improved from 70 to 89%, while the reaction time was reduced 12-fold when comparing batch to flow. The flow conditions were next applied to the reductive ring opening of epoxychalcone **3**
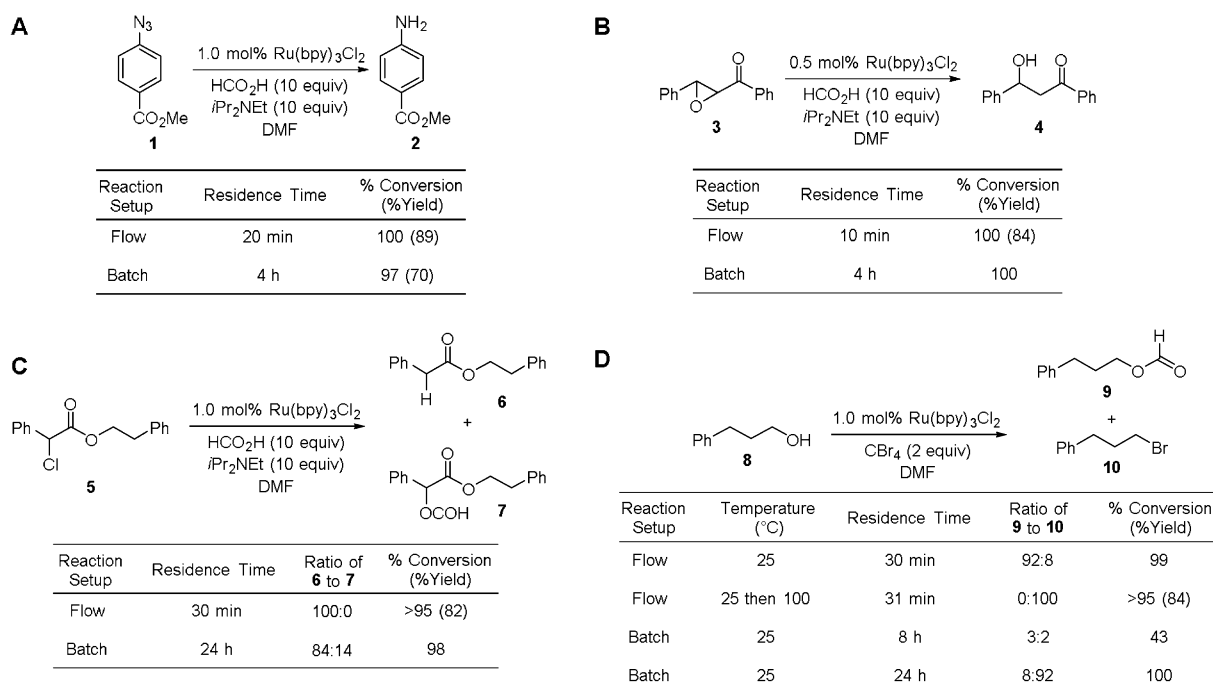
Scheme 1. Visible-light photoredox reactions in flow.

(Scheme 1B).[9] The reaction time was dramatically improved from 4 h to 10 min while maintaining high yield. Seeberger and co-workers also applied flow conditions to the reductive dehalogenation developed by Stephenson and co-workers (Scheme 1C).[10] The flow conditions eliminated the byproduct generated by capture of the formate as well as reduced the reaction time while maintaining good yields. Interestingly, Seeberger and co-workers were able to replace Hantzsch ester in these reactions with excess formic acid and iPr$_2$NEt.

Seeberger and co-workers also examined the conversion of alcohols into halides (Scheme 1D). This reaction is of special interest because it exemplifies how the reactor apparatus can be easily adapted to suit the needs of the reaction. As demonstrated by Stephenson and co-workers,[11] this reaction proceeds via a Vilsmeier–Haack intermediate, which, upon addition of the alcohol, forms intermediate **12** (Figure 1). This iminium cation can be hydrolyzed to the formate ester or displaced by a bromide anion in an S_N2 fashion to afford the halogenated prod-

uct. Seeberger and co-workers were able to demonstrate that altering the reaction apparatus could change the product distribution to favor the production of **10**. Since the halogenated product is likely to be produced by an S_N2 mechanism (Figure 1), the authors reasoned that substitution of the halogen could be facilitated by increasing the temperature. Therefore, a length of polytetrafluoroethylene (PTFE) tubing was attached to the photoreactor to subject the reaction mixture to heating after light irradiation. The composite flow reactor subjected the reaction mixture to irradiation for 23.5 min followed by heating at 100 °C for 7.5 min for a combined residence time of 31 min. When comparing the flow reaction with and without additional heating residence for the reaction of **8**, the ratio of formate ester **9** to brominated product **10** was improved from 92:8 to 0:100. With these four examples, Seeberger and co-workers demonstrated the benefits of combining visible-light photoredox catalysis with flow chemistry.

The group of Stephenson has investigated photoredox catalysis for many organic transformations previously dominated by toxic tin or boron reagents. Several attributes of flow chemistry were attractive for improving the efficiency and yield of many of the transformations already investigated by the group.[12] Thus, Stephenson and co-workers set out to design a practical flow reactor that could mediate improved photoredox transformations. The initial reactor was composed of 105 cm of PFA tubing wrapped around two test tubes in figures of eight. This equates to a total reactor volume of 479 µL. The reactant mixture was pumped by a peristaltic pump from a reactant
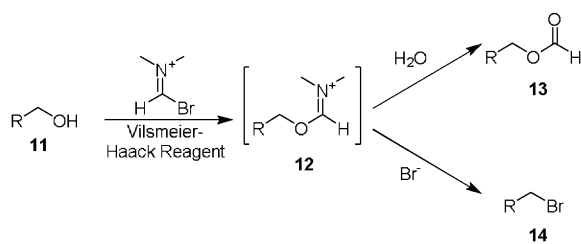

Figure 1. Proposed mechanism of bromination.

flask through the photoreactor and then dispensed into a receiving flask. Blue LEDs (5.8 W) were positioned below the PFA tubing, and incident light was reflected back towards the resident volume by a silver mirrored flask. With the construction of a simple flow system (Figure 2), Stephenson and co-workers set out to examine the extent to which this flow reactor could improve the efficiency of visible-light photoredox chemistry already established in the group.
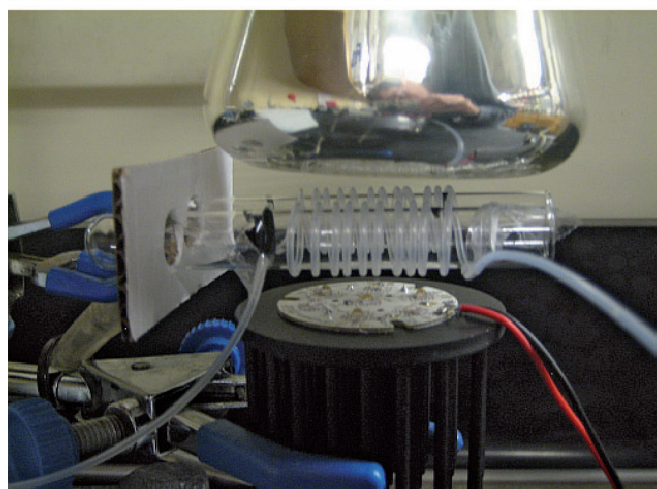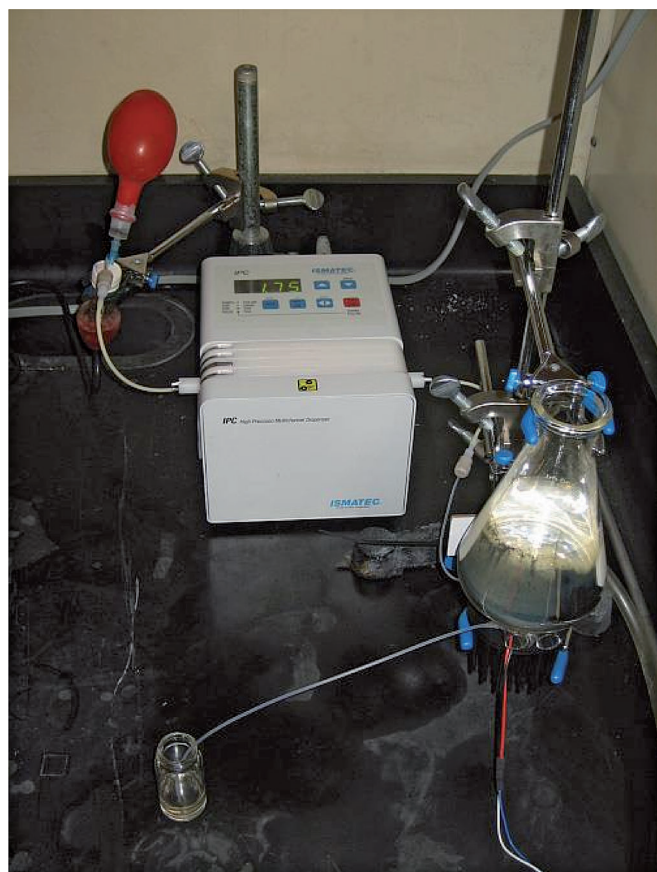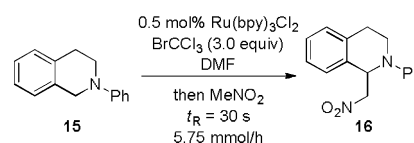

Figure 2. Stephenson's flow reactor setup.

To test the flow photoreactor, the oxidative generation of iminium ions from *N*-aryl tetrahydroisoquinolines (THIQ) was initially investigated (Scheme 2). Using reac-


Scheme 2. THIQ iminium trapping in batch and flow.

tion conditions previously developed,[12d,e] the iminium ion was formed with a very short residence time of 30 s in the photoreactor. Subsequent trapping with nitromethane in the receiving flask resulted in a conversion rate of 5.75 mmol/h.

This was a vast improvement upon the batch reaction, which reportedly formed **16** at a conversion rate of 0.081 mmol/h. This faster rate is even observed despite lowering of the catalyst loading from 1.0 mol% in batch to 0.5 mol% in flow. This specific example highlights the ability of flow chemistry to generate a reactive intermediate in situ, which can be intercepted once the reaction has departed the flow reactor.

Having confirmed the improved efficiency of flow reactors for visible-light photoredox catalysis, other known reactions were evaluated with the new flow reactor. Flow conditions were able to improve the efficiency of radical reductive cyclization reactions, intermolecular radical functionalization of heterocycles, and intermolecular atom-transfer radical addition reactions, as shown in Scheme 3.
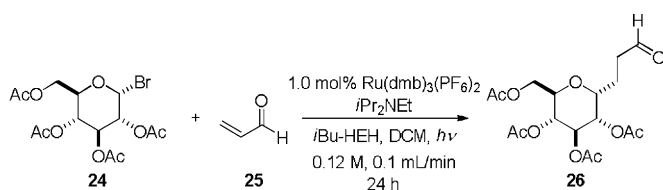
The photoredox flow reactor exhibited diverse applicability to many transformations previously explored in the
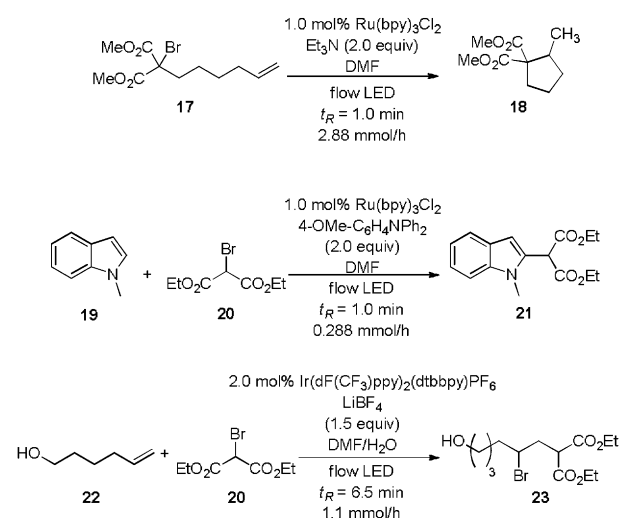
Scheme 3. Other visible-light-mediated reactions in flow. dF-(CF$_3$)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl.

group (Scheme 3).[12] The photoredox-mediated radical cyclization of **17** occurred at 0.0092 mmol/h in batch, but was improved to 2.88 mmol/h when the reaction was performed in flow. Likewise, the intermolecular radical addition of **20** to **19** proceeded at 0.042 mmol/h in batch, but the reaction rate was increased to 0.288 mmol/h in flow. The reaction rate for atom-transfer radical addition to **22** increased from 0.63 mmol/h in batch to 1.1 mmol/h in flow. All of the reactions saw improved reaction times when performed in a flow setting, demonstrating that flow chemistry could enhance the efficiency of photoredox catalysis.

Gagné and co-workers also applied photoredox flow chemistry to the conjugate addition of glycosyl radicals to acrolein (Scheme 4).[5e] Their initial studies revealed that

Figure 3. Gagné's flow reactor setup (reprinted with permission from Ref. [5e]).

its two outstanding features of flow chemistry. First, the reactor can be adapted and modified easily. Here, two modules were connected in series to increase the residence time. Concurrently, this setup was able to demonstrate that large quantities of material on a gram scale could be efficiently generated.

Scheme 4. Conjugate addition of glycosyl radicals to acrolein. dmb = 4,4′-dimethyl-2,2′-bipyridine, *i*Bu-HEH = diisobutyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

glycosyl radical addition to acrolein under photoredox conditions suffered from poor turnover frequency (TOF) when performed in a 25 mL Schlenk flask (3.5 h⁻¹). Interestingly, when the reaction was performed in a 5 mm NMR tube, the TOF improved 20-fold (70 turnovers/h). They proposed that a thinner reaction vessel diameter resulted in faster reaction rates. In particular, light is unable to penetrate the reaction mixture beyond the outer surface of the reaction volume.

Therefore, Gagné and co-workers hypothesized that flow chemistry could improve the efficiency of the conjugate addition of glycosyl radicals to acrolein. The reactor setup utilized a Liebig condenser as the manifold. Transparent FEP tubing was wrapped around the condenser, serving as the conduit for the reaction mixture. Three 12″ blue LEDs were placed within the condenser. The flow rate was controlled by a preparative HPLC pump, which passed the reaction mixture through the reactor and into a flask. The reaction temperature was maintained by running water through the condenser, creating a heat barrier between the LEDs and the FEP tubing (Figure 3).

With this setup in hand, Gagné was able to generate high yields of the desired product by subjecting a mixture of **24**, **25**, *i*Pr₂NEt, Ru(dmb)₃(PF₆)₂ and *i*Bu-HEH in DCM to continuous photoredox flow conditions (Scheme 4). Using two modules connected in series, a continuous flow reaction was performed over 24 h, which provided 4.5 g of **26** in 70 % yield. This flow setup exhib-
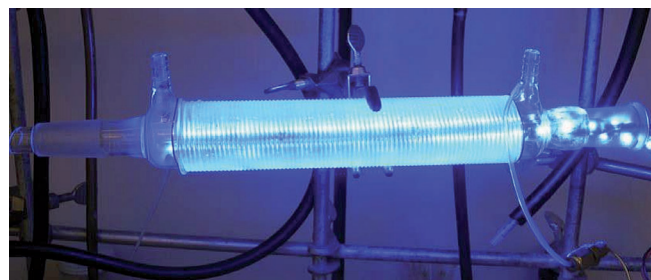
3 Continuing Development of Visible-Light Photoredox Flow Chemistry

Zeitler and Neumann compared batch reactors, microflow reactors, and tube reactors for the synergistic asymmetric photoredox α-alkylation of aldehydes using the organic dye eosin Y (Scheme 5).[13] This flow study explores earlier work performed in the Zeitler laboratory[14] for designing a metal-free asymmetric alkylation based on the seminal work of MacMillan and co-workers.[15] The overall study demonstrates the remarkable advantage of flow chemistry for scaling up reactions, while decreasing the reaction time. A microflow reactor is characterized by small reaction volumes and slower flow rates, while a tube reactor is more akin to what has been described thus far. The microflow reactor used in this study was
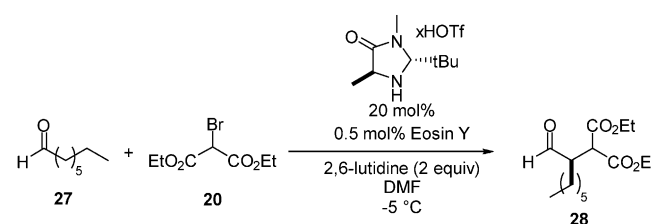
Reaction Setup	Residence Time	mmol/h	%ee	% Yield
Batch	18 h	0.018	88	85
Microflow	45 min	0.037	87	86
Tube Reactor	160 min	1.92	82	92

Scheme 5. Zeitler's comparative study of the synergistic effect of organocatalytic α-alkylations.

made of borosilicate glass and had an effective internal volume of 100 µL (with a channel width of 0.6 mm and a channel depth of 0.5 mm). The microflow reactor was irradiated with blue or green LEDs, and the temperature of the reaction vessel was controlled by an aluminum cooling block connected to a chiller. The tube reactor was fashioned after the design of Booker-Milburn.[5a] It was composed of 0.8 mm internal diameter FEP tubing wrapped around a 60 mm glass beaker, which had a 23 W household fluorescent light bulb inside. The temperature of the tube reactor was maintained by submerging the whole reactor in a cooling bath.
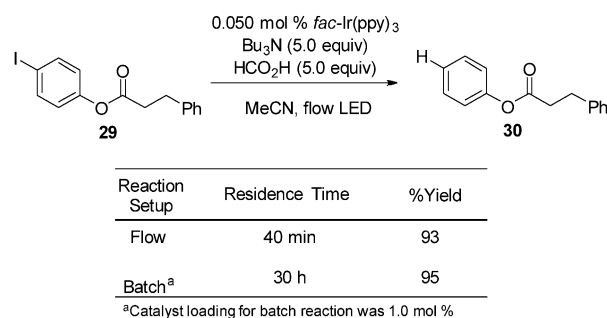
Throughout this study, Zeitler and co-workers examined the benefits of photoredox microflow chemistry for reductive dehalogenations, aza-Henry reactions, and organocatalytic α-alkylations of aldehydes. However, Zeitler readily admits that microflow chemistry is primarily useful for optimization studies, whereas continuous flow chemistry in a tube reactor is more appropriate for higher throughput reactions. Zeitler and co-workers investigated the productivity and scalability of synergistic organocatalytic photoredox α-alkylations in flow by comparing this transformation in batch, microflow, and in a tube reactor.

The initial optimized microflow conditions did not transfer well to the first-generation tube reactor due to clogging from the precipitation of 2,6-lutidine hydrobromide. The second-generation tube reactor increased the irradiated tube length from 8.5 to 21 m by wrapping the tubing in two layers around the light source. This resulted in an internal volume of 10.5 mL. Decreasing the concentration from 0.5 to 0.4 M prevented clogging in the extended length flow reactor and allowed full conversion. Cooling of the reaction vessel was also imperative for obtaining good enantiomeric excess.

Zeitler was able to conclude that the tube reactor clearly offered the best option for scaling up of photocatalytic reactions. The tube reactor was able to produce 1.92 mmol/h of product, while the microflow reactor could only produce 0.037 mmol/h of product and batch could only produce 0.018 mmol/h. Since the enantiomeric excess was comparable for all three systems, flow in a tube reactor was demonstrated to be the most efficient.

Stephenson's group has continued to utilize flow chemistry in the development of photoredox catalysis. Another example from the Stephenson group incorporates flow chemistry into a strategy for reductive deiodination.[16] Here, the advantages of flow chemistry for reducing reaction times are exemplified. Using a combination of *fac*-Ir(ppy)$_3$, tributylamine, and either Hantzsch ester or formic acid in acetonitrile, alkyl, alkenyl, and aryl iodides were dehalogenated upon irradiation in batch. Some substrates required a reaction time of 60 h when performed under batch conditions, suggesting the need for improved efficiency. Therefore, Stephenson and co-workers once again utilized photoredox flow chemistry to increase reaction rates.

As shown in Scheme 6, when **29** is reduced in batch, 30 h are required to obtain 95 % yield with an overall efficiency of 0.020 mmol/h. Using a 1.33 mL flow reactor with residence time, t_R, equal to 40 min, a comparable

Reaction Setup	Residence Time	%Yield
Flow	40 min	93
Batch[a]	30 h	95

[a]Catalyst loading for batch reaction was 1.0 mol %

Scheme 6. Reductive deiodination in flow.

93 % yield is obtained, while improving the molar efficiency to 0.900 mmol/h. This improved efficiency occurs despite lowering the catalyst loading to 0.050 mol%.

Another application from the Stephenson group incorporated the benefits of photoredox flow chemistry by utilizing a two-step batch to flow strategy for deoxygenation.[17] This work initially envisioned the fusion of two photoredox strategies: conversion of alcohols into bromides or iodides[11] and hydrodeiodination of alkyl, aryl, or alkenyl iodides.[16] Unfortunately, a one-pot protocol for overall deoxygenation was unattainable due to the incompatibility of the reaction conditions for each photoredox strategy. The iodination of alcohols using photoredox required the use of DMF, while dehalogenation encountered a slow rate in DMF.

Due to the incompatibility of the reaction conditions, the group turned to the Garegg–Samuelsson[18] reaction to first convert the alcohol to an iodide in batch. This mixture could be subjected to photoredox conditions to allow hydrodeiodination to afford the overall deoxygenated product, as shown in Figure 4. First, the two-step batch reaction was attempted, but only 50 % conversion was obtained after 72 h of irradiation. Therefore, flow chemistry
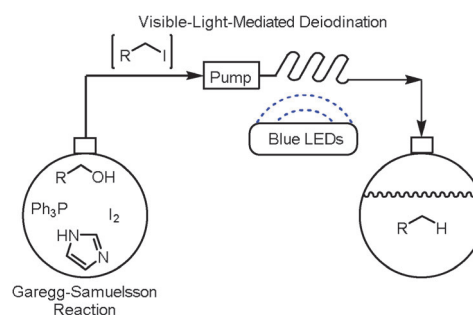

Figure 4. Batch to flow photoredox-mediated deoxygenation.

was investigated to improve the conversion of the photocatalytic step of the reaction.

The group used the same reactor previously developed, but changes were required for the flow reaction to occur. In this case, Hantzsch ester and tributylamine were exchanged for *N,N*-diisopropylamine because the Hantzsch ester had a lower solubility under flow conditions. Methanol was also included to increase the solubility and generate a homogeneous reaction mixture. This transformation also allowed a reduction in catalyst loading from 1.0 to 0.25%. With the reaction conditions in hand, a flow rate of 75 µL/min was found to be optimal for a 1.34 mL reactor, which resulted in an 18 min residence time. The deoxygenation of **31** was dramatically improved in flow, providing an 88% yield with an overall rate of 0.64 mmol/h, while the batch reaction only afforded 75% conversion with an overall rate of 0.0052 mmol/h (Scheme 7).
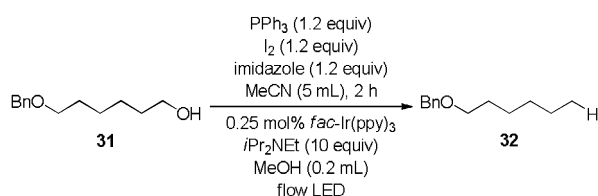
Scheme 7. Photoredox flow chemistry for deoxygenation.

Visible-light flow chemistry was utilized by Collins and co-workers to perform the photocyclization of **33** to form [5]-helicene (Scheme 8).[19] Traditionally, this reaction was
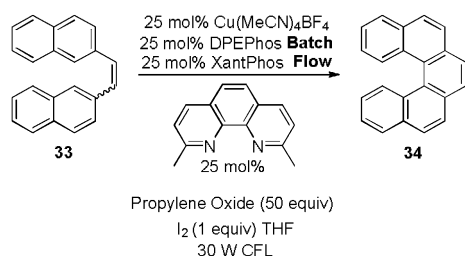

Scheme 8. Visible-light photocyclization to form [5]-helicene.

mediated by UV light, but a lack of regiocontrol resulted in high yields of undesired cyclizations. They reasoned that the use of a visible-light-mediated reaction could facilitate cyclization with the addition of a photosensitizer. Although ruthenium- and iridium-based photocatalysts failed to achieve the desired product, a copper-based photosensitizer exhibited some success when ligated by DPEPhos. Under optimized conditions in a batch reactor, [5]-helicene was formed in 42% yield over the course of 5 days when performed on a gram scale.

Collins and co-workers opted to use a flow reactor in an attempt to shorten the reaction time. A commercially

available flow reactor was used to pump the reaction mixture through FEP tubing that was wrapped around two compact fluorescent light bulbs (CFLs), which heated the reaction slightly. The flow reaction was comprised of 30 min runs at a flow rate of 1 mL/min. A total of 20 runs were carried out for a gram scale reaction, resulting in 40% yield of [5]-helicene in 10 h. Although this example cannot be categorized as a single-pass, continuous-flow reactor, it exhibits the drastic effect that photoredox flow conditions have on reaction rate. In addition, Collins and co-workers demonstrated that other metal photocatalysts could be effectively utilized in photoredox flow chemistry.

Noël and co-workers reported the utility of photocatalytic flow reactions for the development of a one-pot Stadler–Ziegler synthesis of aryl sulfides (Scheme 9).[20] A
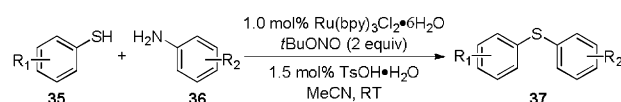
Scheme 9. Photoredox coupling of thiophenols and aryl amines.

one-pot procedure for aryl sulfide formation was needed because the synthesis of aryl sulfides was a multistep process that required handling of diazonium salts. To make an aryl sulfide, an aryl amine is converted into a diazonium salt by nitrosation. The coupling partner is prepared by treating a thiophenol with base to form sodium thiophenolate. Finally, these two salts are combined to generate the aryl sulfide. This multistep approach is time consuming, inefficient, and potentially dangerous, and therefore, Noël and co-workers attempted to provide an alternate approach for aryl sulfide coupling by developing a photoredox flow system (Figure 5). Although traditional Stadler–Ziegler couplings utilize sodium nitrite, Noël and co-workers employed alkyl nitrites to generate the required nitrosyl cation with a catalytic amount of acid. The departure of nitrogen gas from the in situ generated diazonium is enabled by the oxidative quenching cycle of the photoredox catalyst, forming an aryl radical. This radical is captured by the thiophenolate, which is oxidized by the photocatalyst, turning over the catalytic cycle.

When thiophenol was coupled with 4-methoxyaniline using Noël's method, 85% yield was obtained in 5 h. This resulted in 0.17 mmol/h of product formation. Noël and co-workers turned to flow chemistry to further enhance the efficiency of the reaction and further minimize the danger associated with the in situ generated diazonium cation or diazo aryl sulfide. The safety hazards associated with the reaction are lessened because the diazonium is generated in much smaller quantities.

The reaction setup is composed of a syringe pump, which simultaneously pumps two different mixtures through PFA capillary tubing. The first mixture contains
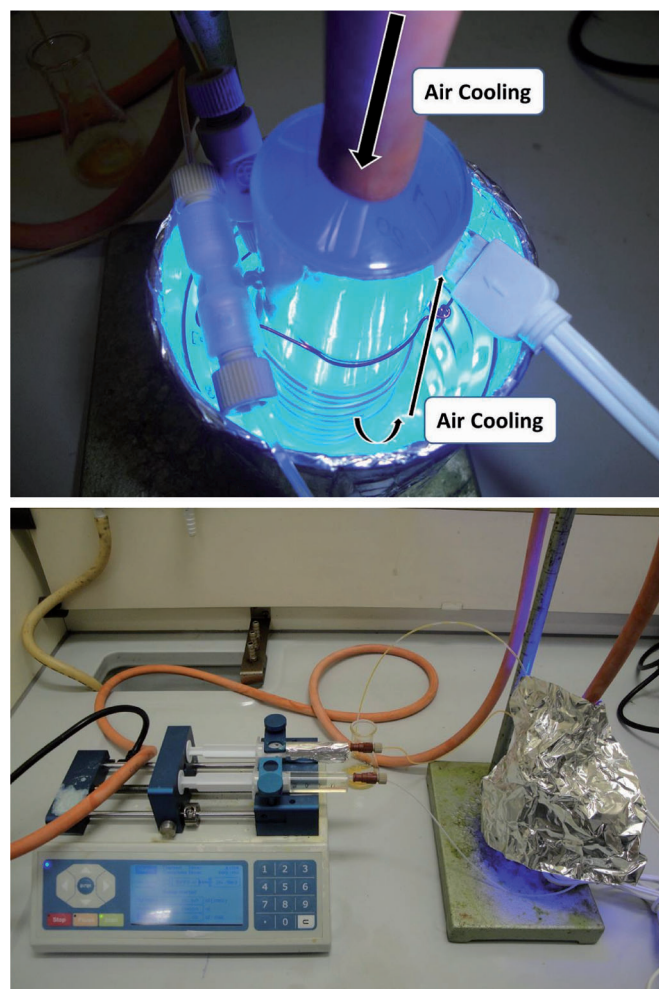
Figure 5. Photoredox flow setup for the synthesis of aryl sulfides (reprinted with permission from Ref. [20]).

thiol, aniline, acid, and photocatalyst, while the second mixture contains only the alkyl nitrite. The alkyl nitrite is delivered separately from the other reaction components to avoid excessive generation of the diazonium cation. The two mixtures merge at a Tefzel mixing tee before entering the microreactor. The microreactor is a simple setup composed of common laboratory items. The PFA tubing is wrapped around a 50 mL syringe, which is coated on the inside with aluminum foil. The total residence volume of the microreactor is 464 μL. The syringe sits in an aluminum foil covered beaker with blue LEDs coiled on the inside wall. The PFA tubing eventually leaves the microreactor and deposits the product mixture into a vial. The heat generated by the LEDs was mitigated by the passage of air through the top of the syringe manifold, alleviating heat buildup that might cause detonation of the diazonium salt.

With the flow microreactor constructed to minimize the hazard of diazonium salts and maximize the reactivity of photoredox catalysis, Noël and co-workers were able to compare the one-pot batch reaction to the continuous-

flow reaction for coupling thiophenol with 4-methoxyaniline. Full conversion was obtained in a very short 15 s residence time, which was a dramatic improvement upon the 5 h batch reaction. The flow reaction was able to improve the batch reaction by 78-fold, which ultimately afforded 13.2 mmol/h of product compared with 0.17 mmol/h of product for the batch reaction.

The Rueping group has extended the applications of photoredox chemistry in flow by developing two different strategies that benefit from the use of common organic dyes, such as eosin Y, rose bengal, or rhodamine B.[21] The first transformation accomplishes cross dehydrogenative coupling of THIQ derivatives and various nucleophiles. Initially, organodyes were unable to carry out the transformation in batch, and the reactions suffered from either long reaction times or insufficient product formation. Therefore, flow chemistry seemed like a plausible solution to accomplish this C–C bond-forming transformation. The flow reactor consisted of 4.6 m of FEP tubing (internal diameter of 0.8 mm) coiled around a glass tube. This amounted to a reaction volume of 9.3 mL. Green LEDs (20 W) were placed inside the glass tube. The flow was controlled by an HPLC pump. Finally, air was passed between the LEDs and the glass to alleviate any heat buildup.

While optimizing the reaction conditions, several important parameters became apparent. First, a cooling condenser led to a drop in conversion, which may have occurred from lower irradiation of the tubing. Second, slowing the flow rate improved the yield, but at the cost of increasing the reaction time. Lastly, they observed that too much catalyst impeded the reaction.

With optimized conditions, several transformations were accomplished. The reaction tolerated many nucleophiles, including nitromethane, cyanotrimethyl silane, dialkyl malonates, and phosphonates. Also, the reaction was accomplished despite electron-withdrawing or -donating substitutions on the aryl ring.[21]
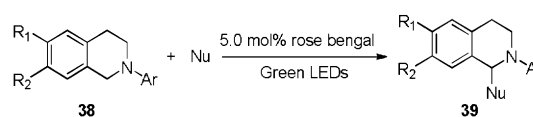
Scheme 10. Flow photoredox catalyzed by rose bengal.

Rueping and co-workers also utilized rose bengal to carry out an Ugi-like multicomponent photoredox reaction in flow.[21] In this reaction, *N,N*-dimethylaniline was transformed into an iminium ion, which was subsequently captured by an isocyanide (Scheme 11). The addition of water then allowed the formation of the amide. The optimized flow conditions required a flow rate of 3.0 mL/min and a cycling method that reintroduced the reaction mixture to photoredox flow conditions by dispensing the reaction mixture into the starting flask once it was exposed

Review
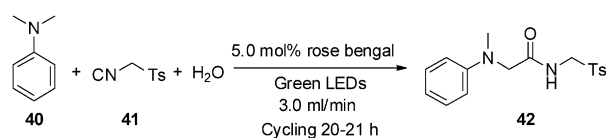
Scheme 11. Multicomponent reaction in photoredox flow.

to the green LEDs. This method generally resulted in an overall reaction time of 20–21 h.

The reaction tolerated a variety of *N,N*-dimethylanilines as well as isocyanides. The reaction shown in Scheme 11 between *N,N*-dimethylaniline and *p*-toluenesulfonyl methyl isocyanide exemplifies the ability of flow chemistry to reduce the reaction time. In this case, the reaction time was reduced threefold when compared with batch conditions.

4 Summary

Photoredox flow chemistry has emerged as a suitable enabling technology for the improvement of the rapidly developing field of photoredox catalysis. A flow reactor is preferable to conventional batch techniques because it benefits from shorter reaction times, improved yields, and improved scalability. Performing a reaction under flow conditions maximizes light penetration of the reactants, which allows efficient catalysis to occur. In addition, flow reactors can be easily constructed and modified to suit the needs of specific photoredox reactions.

As the field of photoredox chemistry continues to develop, chemists will continue to appreciate the benefits of flow chemistry. Transformations that have difficulty proceeding or seemingly do not proceed using batch conditions may be realized by the application of flow chemistry. The batch to flow deoxygenation method represents one example where a multistep process was streamlined using flow conditions. Although few multistep, continuous-flow photoredox processes have been developed thus far, these systems will be actively pursued as chemists seek means of streamlining photoredox reactions.

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