Visible-Light Photoredox Catalysis in Flow**

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Photoredox catalysts have recently been used as powerful tools for synthetic chemists to exploit the energy gained by the absorption of low-energy light within the visible spectrum to initiate a variety of organic transformations.[1] The development of methods based on the single-electron transfer properties of photoredox catalysts, particularly in the last several years, has represented a shift in models with respect to the way synthetic chemists consider both photochemistry and redox manipulations of organic molecules.[2–4] In addition, the advent of new technologies has enabled chemists to conduct reactions with greater efficiency than ever before. Among these new technologies is the development and wide implementation of flow reactors.[5, 6] Conducting transformations in flow has many advantages compared to the more traditional batch reactions, in particular: a more predictable reaction scale-up, decreased safety hazards, and improved reproducibility. In addition, for photochemical transformations, the high surface-area-to-volume ratios typical of flow reactors allow for more efficient irradiation of a reaction mixture.[7] Due to this feature, we reasoned that a mesofluidic photochemical flow reactor would be amenable to our group's ongoing study of visible-light-induced organic transformations mediated by photoredox catalysts (Figure 1).[8]

Our group has studied the use of both the oxidative and reductive quenching cycles of photoredox catalysts to initiate synthetically useful manipulations of organic molecules such as intra- and intermolecular radical reactions,[8] formal C−H oxidation reactions,[9] and the halogenation of alcohols.[10] During these studies, it was commonly observed that large-scale reactions were often slower than those conducted on smaller scale.[11] As a consequence of the Beer–Lambert law, the penetration of visible light through a reaction medium decreases exponentially with increasing path length. We hypothesized that this may be one reason for the observed loss of reaction efficiency. To potentially circumvent this
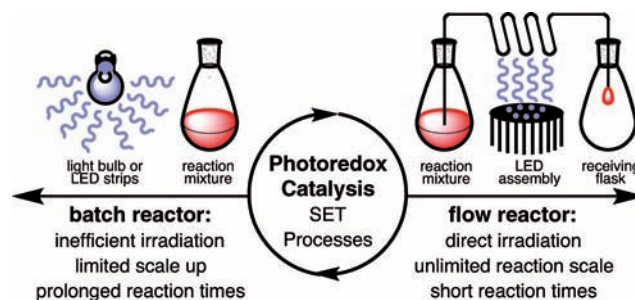

Figure 1. Photoredox catalysis in flow. Enabling increased efficiency by reactor technology (SET = single-electron transfer).

problem we sought to design a reactor having a considerably smaller path length through which the light must travel. In addition, a reactor having a greater surface-area-to-volume ratio would result in an increased photon flux density, potentially accelerating the reaction.[12] Commercially available PFA (perfluoro alkoxy alkane) tubing having an internal diameter of 0.762 mm was identified as a viable choice because of its chemical resistance and optical transparency. Furthermore, a photoreactor of this size will allow for optimal absorbance at typical catalyst concentrations (around 1.0 mM). For instance, the molar extinction coefficient of $Ru(bpy)_3Cl_2$ (bpy = 2,2′-bipyridine) has been measured to be $13\,000\,M^{-1}\,cm^{-1}$,[13] as such the thickest portion of the tubing allows for the absorption of 90% of the incident radiation. Likewise, when carried out in batch reactors, 99% of the incident radiation is absorbed by the reaction medium residing within 1.5 mm of the reactor surface while the remaining internal volume receives little productive radiation.[14]

In designing our reactor, we sought to make it as simple as possible without using specialized equipment in the hopes that a similar design could be readily implemented in other laboratories. Our optimized reactor involved wrapping 105 cm (corresponding to a 479 µL reactor volume) of PFA tubing in figure-eights around a pair of glass test tubes. We then used a peristaltic pump to pump the reaction mixture through the tubing with irradiation from a commercially available assembly of seven blue light emitting diodes (LEDs).[15] Finally a silver-mirrored Erlenmeyer flask was positioned above the reactor to reflect any incident light back onto the tubing.[16]

Our initial experiments focused on the oxidative generation of iminium ions from *N*-aryl tetrahydroisoquinolines, using reaction conditions similar to those we recently reported.[9c] Employing $BrCCl_3$ as the terminal oxidant, we observed rapid formation of the iminium ion, **2**, from the corresponding tetrahydroisoquinoline, **1**. Optimization studies showed that subjecting a solution of **1**, $BrCCl_3$, and $Ru(bpy)_3Cl_2$ (0.5 mol%) in dimethylformamide (DMF) to

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irradiation in our newly designed flow photoreactor, required only a very short residence time (t_R) for complete consumption of **1**. In particular, pumping this mixture through the photoreactor at a rate corresponding to a t_R of 0.5 min and collecting the mixture in a flask containing 5.0 equivalents of a diverse set of nucleophiles allowed for the efficient and rapid generation of a variety of α-functionalized amines, in yields comparable to those observed in the batch reactions (Scheme 1). As expected with the flow reactor, the scale-up of the reaction was trivial and allowed for the oxidative *aza-*

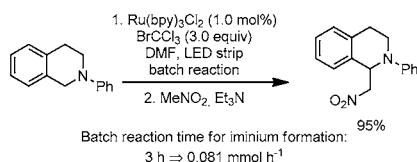oxidative formation of iminium ions:
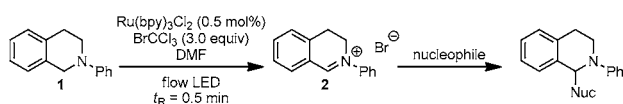
trapping with diverse nucleophiles:
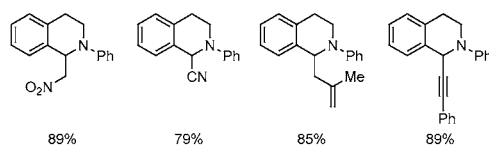
t_R for iminium formation in flow:
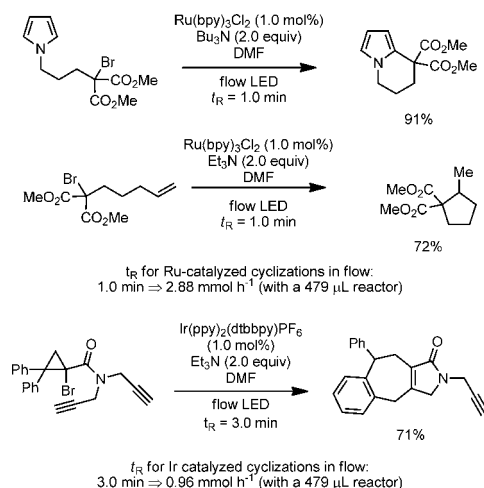0.5 min ⇒ 5.75 mmol h^{-1} (with a 479 μL reactor)

comparison with batch reaction:[9c]

Batch reaction time for iminium formation:
3 h ⇒ 0.081 mmol h^{-1}

Scheme 1. Oxidation of tetrahydroisoquinolines in flow.

Henry reaction of **1** with MeNO$_2$ to be conducted on a 1.0 g scale with none of the issues observed for scaling up batch reactions. Furthermore, when conducted in batch, a reaction time of 3 h was required for complete oxidation of **1** on a 0.24 mmol scale. This corresponds to a material throughput of 0.081 mmol h^{-1}. However, using the flow apparatus (with a reactor volume of 479 μL) enables a much higher rate of substrate conversion, 5.75 mmol h^{-1}. In addition, this rate can be increased by using a photoreactor having a greater internal volume which would require only the use of a longer section of tubing.

Having validated our hypothesis of increased reaction efficiency of photoredox-mediated transformations performed in a photochemical flow setup, we examined a number of other reactions developed by our group. Firstly, a number of intramolecular radical cyclization reactions were evaluated, including: intramolecular heterocycle functionalization,[8b] hexenyl radical cyclization,[8c] and a tandem radical cyclization/Cope rearrangement sequence (Scheme 2).[8g] We were delighted to find that both radical cyclizations onto heteroaromatics and terminal olefins catalyzed by Ru-(bpy)$_3$Cl$_2$ proceeded efficiently with short residence times, 1.0 min, affording the products in yields comparable to those observed in batch reactions. Notably, the intermolecular
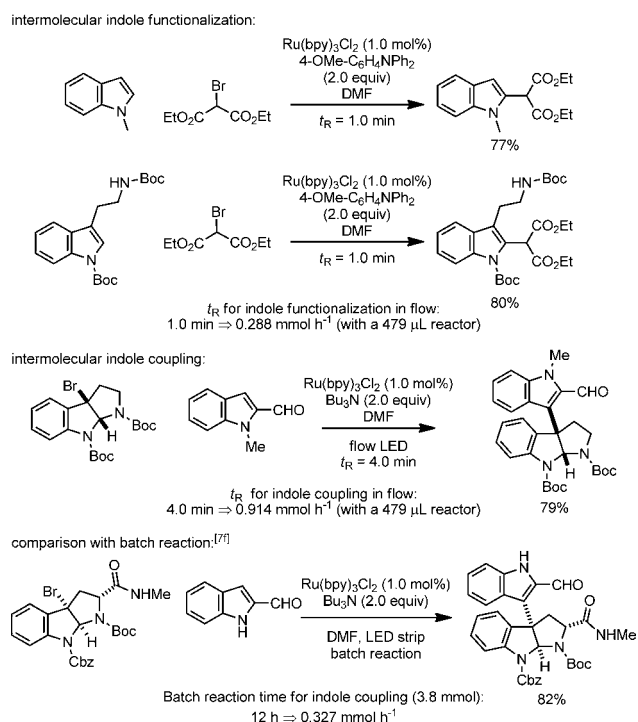

t_R for Ru-catalyzed cyclizations in flow:
1.0 min ⇒ 2.88 mmol h^{-1} (with a 479 μL reactor)

t_R for Ir catalyzed cyclizations in flow:
3.0 min ⇒ 0.96 mmol h^{-1} (with a 479 μL reactor)

Scheme 2. Intramolecular radical reactions in flow.

pyrrole functionalization, when preformed on large scale in batch ($>$2.0 g, 6.2 mmol), failed to afford complete conversion of the starting material even after prolonged reaction time ($>$2 days). However, the use of the flow reactor could allow for the transformation of large quantities of substrate without the need to perform multiple smaller scale reactions to achieve the desired conversion.
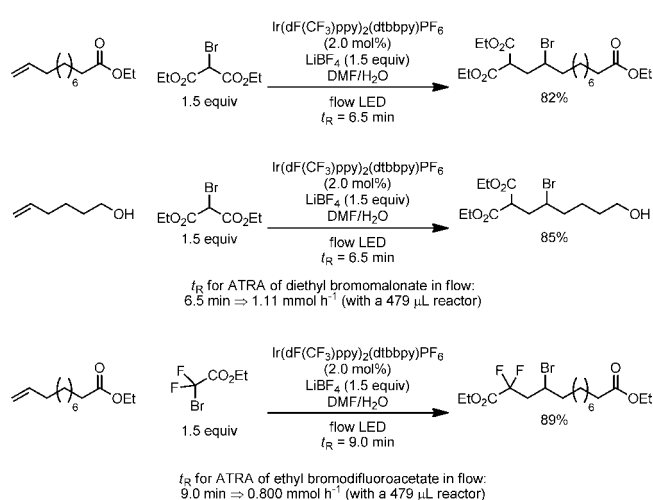
Likewise, the Ir(ppy)$_2$(dtbbpy)PF$_6$ (ppy = 2-phenylpyridine and dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) catalyzed radical cyclization/rearrangement afforded the product in good yield, but required a slightly longer residence time, t_R = 3.0 min. Again, performing these reactions in flow afforded a much higher rate of material throughput when compared to the transformation conducted in batch. Notably, for the cyclization/rearrangement cascade catalyzed by Ir(ppy)$_2$-(dtbbpy)PF$_6$, the batch reaction only afforded a substrate conversion rate of 0.048 mmol h^{-1} (t_R = 4.0 min corresponds to a material throughput of 0.96 mmol h^{-1} with our photoreactor).

Intermolecular radical reactions are also feasible in this flow setup (Scheme 3). Intermolecular malonation of indoles, using the triarylamine reductive quencher, 4-MeO-C$_6$H$_4$-NPh$_2$, proceeded smoothly with a t_R = 1.0 min.[8d] Furthermore, the bromopyrroloindoline coupling with 1-methyl-indole-2-carboxaldehyde, similar to the key transformation used in the recent synthesis of gliocladin C from our group, proceeded efficiently with a residence time of 4.0 min.[8f] This result is particularly promising since the scale-up of this reaction required prolonged reaction times, up to several days for a 10 g scale reaction.[17]

Finally, we applied this new reaction technology to our reported protocol for the intermolecular atom transfer radical addition (ATRA) using the oxidative quenching pathway of the photocatalyst, Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ (Scheme 4; dF(CF$_3$)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine).[8e] While requiring slightly longer residence times than those observed for the transformations using the reductive quenching cycle of Ru- and Ir-based catalysts, this transformation proceeded efficiently and cleanly to give the corresponding ATRA products in good yields. Again,

intermolecular indole functionalization:

t_R for indole functionalization in flow:
1.0 min ⇒ 0.288 mmol h^{-1} (with a 479 µL reactor)

intermolecular indole coupling:

t_R for indole coupling in flow:
4.0 min ⇒ 0.914 mmol h^{-1} (with a 479 µL reactor)

comparison with batch reaction:[7f]

Batch reaction time for indole coupling (3.8 mmol):
12 h ⇒ 0.327 mmol h^{-1}

Scheme 3. Intermolecular radical reactions in flow.

t_R for ATRA of diethyl bromomalonate in flow:
6.5 min ⇒ 1.11 mmol h^{-1} (with a 479 µL reactor)

t_R for ATRA of ethyl bromodifluoroacetate in flow:
9.0 min ⇒ 0.800 mmol h^{-1} (with a 479 µL reactor)

Scheme 4. Intermolecular ATRA reactions in flow.

a greater rate of material throughput was observed using the flow reactor. On average, the ATRA of diethyl bromomalonate in batch allowed for the conversion of 0.200 mmol of alkene per hour.

In summary, we have designed a readily prepared and easily implemented photochemical flow reactor which enables the marked acceleration of a variety of transformations mediated by photoredox catalysis. The entire setup has a sufficiently small footprint to easily fit in a standard fume hood and can be assembled quickly and inexpensively. In all cases the reactor employed in this work has shown an increased efficiency in terms of material throughput for all the transformations studied. Even higher rates of substrate

conversion (in terms of mmol of material per hour) are possible simply by employing a photoreactor with a greater internal volume. Further studies into applying this technology to a greater range of photoredox methods is underway.

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[16] For more information on the reactor design please see the Supporting Information.

[17] L. Furst, C. R. J. Stephenson, unpublished results.