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RESEARCH ARTICLE

Photon Equivalents as a Parameter for Scaling Photoredox Reactions in Flow: Translation of Photocatalytic C-N Cross-Coupling from Lab Scale to Multikilogram Scale

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Abstract: With the development of new photocatalytic methods over recent decades, the translation of these chemical reactions to industrial production scales using continuous flow reactors has become a topic of increasing interest. In this context, we describe our studies toward elucidating an empirically-derived parameter for scaling photocatalytic reactions in flow. By evaluating the performance of a photocatalytic C-N cross-coupling across multiple reactor sizes and geometries, it was demonstrated that expressing product yield as a function of the absorbed photon equivalents provided a predictive, empirical scaling parameter. Through the use of this scaling factor and characterization of the photonic flux within each reactor, the cross-coupling was scaled successfully from milligram-scale in batch to a multi-kilogram reaction in flow.

Introduction

Over the past several decades, the field of synthetic photochemistry has experienced a significant resurgence. This trend has been driven, in large part, by the development of new methods in which visible light is harnessed by using photocatalysts such as metal polypyridyl complexes, acridinium and pyrylium salts, cyanoarenes, xanthenes, and benzophenones.[1] Many of these approaches allow for the implementation of classical radical chemistry under milder conditions with greater functional group compatibility. Other techniques, however, have merged photocatalysis with a second catalytic platform, such as transition metal catalysis[2], organocatalysis[3], and biocatalysis[4], enabling the construction of bonds through unconventional coupling partners.

With the advent of these methods that allow for new bond disconnections, synthetic photoredox catalysis has become of interest for low-volume, fine chemical industries, such as the pharmaceutical industry.[5] Recent publications demonstrate an increased interest in the area of photocatalysis among the research divisions of pharmaceutical companies.[6] While these contemporary works have been exploratory in nature and performed solely on the laboratory scale, more traditional photochemical transformations have been performed routinely on industrial scales within the commodity chemical industry for decades.[7]

Many of the photochemical transformations routinely employed on scale can be categorized as either unimolecular or

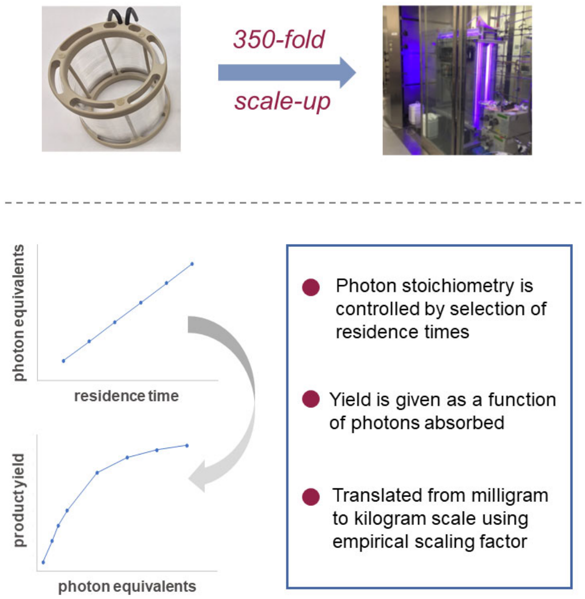

Figure 1. Photon equivalents as an empirical scaling factor in flow

radical chain reactions, factors that are associated with highly productive and efficient photochemical transformations. However, many of the newer methods are bimolecular in nature and are not highly efficient radical chain processes. Based on this trend, we were interested in the translation of a dual catalytic, bimolecular photoredox transformation from small-scale batch conditions to a preparatory scale continuous flow reactor. Specifically, we wished to explore the parameters that might impact the scalability of the chemistry.

For photochemical reactions, arriving at the appropriate reactor design and the set of optimal reaction conditions represent a challenge as reaction rate and photon transport are convoluted. The photon penetration depth into the reaction mixture is dependent on its optical properties as described by the Beer-Lambert-Bouguer Law. To achieve efficient and complete irradiation of the reaction stream, it is often advantageous to design the reactor with a high surface area to volume ratio using a length scale comparable to photon penetration depth. Without a sufficiently high surface area, portions of the solution within the reactor may remain unirradiated. This scenario may give rise to an added complication, in which the reaction exhibits sensitivity to mixing effects. For these reasons, continuous flow approaches have been employed frequently in the scaling of photochemical reactions, although only a handful of reports have detailed the strategy used to scale these reactions.[8,9]

Results and Discussion

As part of our strategy for scaling up photochemical reactions in flow, we hypothesized that a simple scaling factor incorporating the number of photons absorbed by the reaction solution could be applied to facilitate scale-up when photons are involved in the rate-limiting reaction step. This scenario occurs when a photochemical event is the rate-limiting step, which we expect to be common in many photochemical transformations of pharmaceutical relevance. To investigate this scale-up strategy, we studied a dual-catalytic C-N cross-coupling reaction that was initially disclosed by the labs of MacMillan and Buchwald in collaboration with Merck Research Laboratories.[10] As the previously disclosed conditions resulted in the precipitation of salts, DMSO was employed as the solvent to obtain a monophasic solution amenable to flow. Additionally, more readily available $Ru(bpy)_3(PF_6)_2$ and $NiBr_2{*}3H_2O$ were selected as the photocatalyst and nickel precatalyst, respectively. With these conditions in hand, a batch reaction profile was established using a 405 nm laser (260 mW output) as the light source. With the laser positioned directly above the reaction vial, all photons were captured by the reaction solution upon visual inspection, and a yield of 88% was obtained after 120 min of irradiation (**Figure 2A**).

We translated these conditions into a plug flow reactor using the commercially available 10 mL Vapourtec UV-150 photoreactor (Vapourtec Ltd., U.K.) that was outfitted with a 405 nm light-emitting diode (LED) array (9 W output). With a residence time of 15 minutes, it was possible to achieve yields greater than 90% (**Figure 2A**). The comparison of the batch and flow reactions revealed a great discrepancy between reaction times due to different reactor volumes, geometries, and light sources. However, upon relating product yield to the number of photons emitted by the lamp at each time point, a correlation between the two sets of data became apparent (**Figure 2B**). This observation, although based on an estimation of photons emitted by the lamp and an assumption of a well-designed reactor, led us to hypothesize whether the reaction performance across vastly different reactor setups may be predicted by a value relating product yield to the total light absorbed by the reaction. This value, which we have termed "photon equivalents", is the ratio of absorbed photons to aryl bromide substrate for a given time of irradiation.

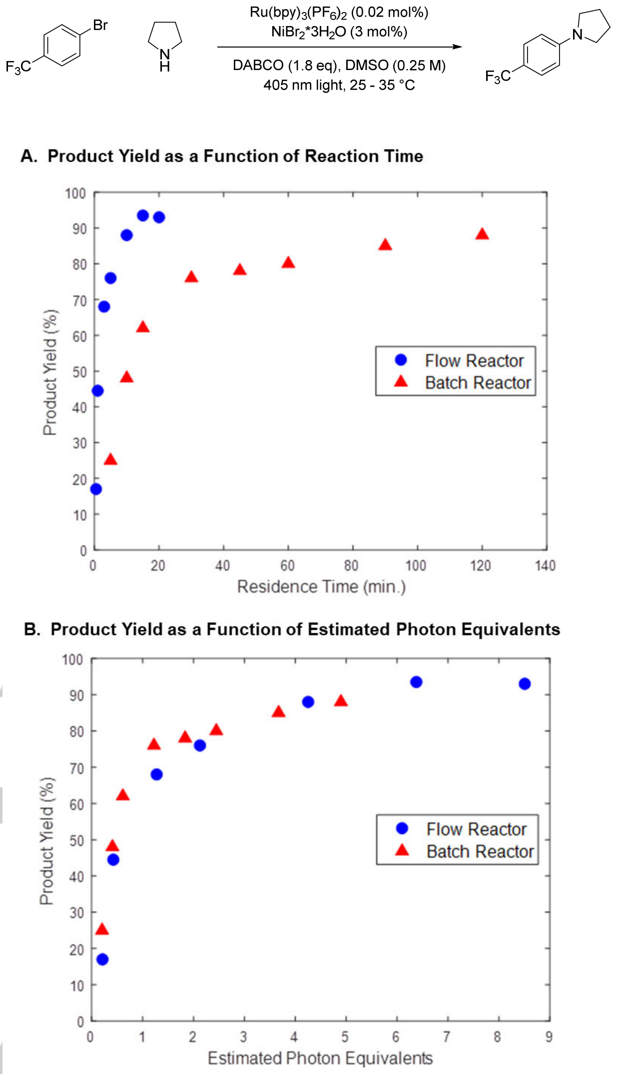

Figure 2. Translation of photoredox C-N cross-coupling protocol from batch to flow. [a] Comparison of batch and flow conditions as a function of reaction times. [b] Comparison of batch and flow results as a function of equivalents of photons, as estimated from lamp radiative power. Bpy, 2,2'-bipyridine; DABCO, 1,4-diazabicyclo[2.2.2]octane; DMSO, dimethylsulfoxide.

To further investigate our hypothesis regarding photon equivalents as a scaling factor, it was necessary to refine our data set to take into consideration only those photons that are absorbed by the reaction stream. To accomplish this, we outlined an approach to calculate equivalents of absorbed photons from time course data, photon flux measurements of each reactor, and absorbance values for the reaction stream.[11] Ahead of this, however, it was critical to ensure that the scaling parameter both

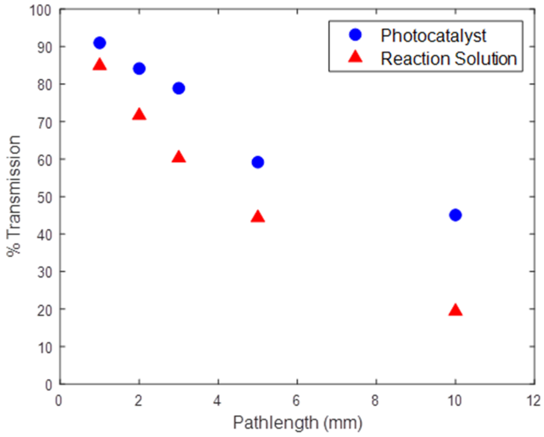

Figure 3. Transmittance of the photocatalyst and the reaction solution at various pathlengths

accounts for the observed reaction performance in the lab and is maintained upon scale up, as multiple reaction elements may be at play in a photochemical process, including photon absorbance, transport phenomena, and reaction kinetics.

To remove the mixing rate as a significant process factor, it was essential to confirm that the flow reaction would operate free of dark spots. Thus, we measured the percent transmittance for the starting reaction solution at various pathlengths to ensure that the solution would be fully irradiated in the larger scale reactors that feature pathlengths between 1/16” I.D. (1 mm) and 1/8” I.D. (3 mm) (**Figure 3**). From these absorbance measurements, it was established that we could operate at pathlengths of 1 mm to 10 mm without concern of becoming photon-limited.

Following the initial proof-of-concept in the 10 mL flow platform, we evaluated the performance of this reaction in a bespoke photoreactor outfitted with 405 nm LED arrays, similar to that previously described in the literature.[12] These reactors featured arrays of 405 nm LEDs surrounding both the inner and outer walls of the radial tubular reactor (**Figure 4A, B**). This LED housing could be outfitted with reactors of various sizes that were constructed from PFA tubing. A time course study of the reaction performance in a 60 mL volume reactor (PFA tubing, 1/16” I.D., 1/8” O.D.) showed that a residence time of twenty minutes was sufficient to achieve good levels of conversion (**Figure 4C**), consistent with that seen in the 10 mL plug flow reactor. In a similar manner, reaction performance was assessed in a 150 mL plug flow reactor (PFA tubing, 1/8” I.D., 3/16” O.D.) (**Figure 4D**). Upon performing the photoredox C-N cross-coupling reaction in this plug flow reactor, a longer residence time of 40 minutes was needed to reach conversion levels greater than 90%, while conversions greater than 80% yield were achieved after approximately twenty minutes.

To test our hypothesis regarding photon equivalents as a scaling factor, it was paramount to measure the photon flux in the reaction stream. Measuring the radiance directly from the light source results in an over-estimation of the photon flux as numerous reactor design variables, such as reactor wall thickness, reactor wall curvature, and LED positioning relative to the reaction stream, cause a fraction of the emitted photons to never contact the reaction stream. Therefore, chemical actinometry using potassium ferrioxalate was used to measure the incident photon rate inside of the reactor.[13] In this system, the photon flux is calculated by monitoring the conversion of Fe(III) to Fe(II) under initial reaction rate conditions. Here, a stopped flow approach is used to monitor actinometer conversion at short reaction times (see Supplemental Information). In this manner, the photon flux through the 10 mL Vapourtec reactor was measured to be 8 W (0.2 mmol photons/min).[14] This number represents the total number of photons irradiating inside the reactor, not the number of photons absorbed by the reaction solution. To arrive at the number of absorbed photons per unit time, the optical absorbance of the reaction solution must be considered. Based on measured absorbance data and the reactor diameter, it was calculated that 1.8 mmol photons/min were absorbed by the reaction solution (for a discussion and examples of the analysis applied, see Supplemental Information). This number was then further converted into equivalents of absorbed photons by dividing the number of absorbed photons at a particular time by the initial concentration of aryl halide. We subsequently carried out analogous studies on both the 60 mL reactor (PFA tubing, 1/16” I.D., 1/8” O.D.) and the 150 mL reactor (PFA tubing, 1/8” I.D., 3/16” O.D.) and the photon fluxes were measured to be 18 W and 15 W, respectively. Converting these photon fluxes into photons absorbed (3.5 mmol photons/min and 3.1 mmol photons/min, respectively), a plot depicting conversion to product as a function of absorbed photon equivalents gave the curves shown in **Figure 5**, which closely overlay with one another, further supporting that absorbed photon equivalents can be employed as a useful and relatively precise scaling factor.

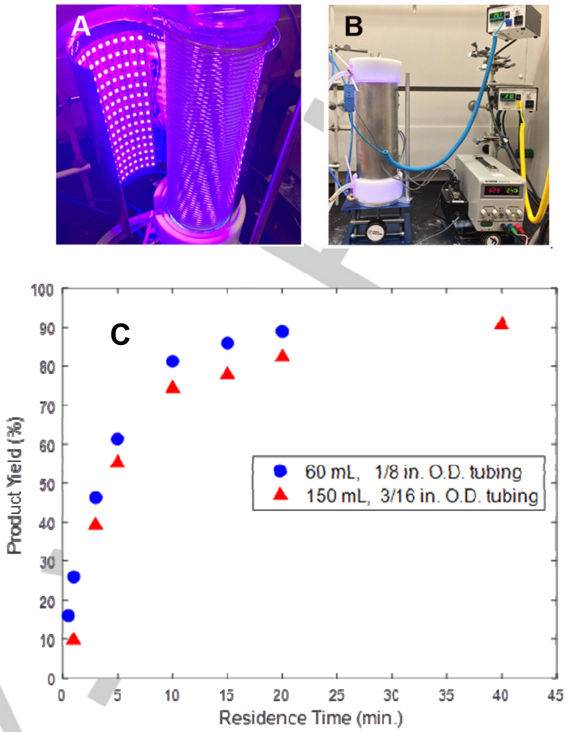

Figure 4. Scaling of reaction conditions to larger scale laboratory reactors. [A] Housing featuring arrays of 405 nm LEDs; [B] Reactor setup fully assembled; [C] Reaction course data in the 60 mL and 150 mL reactors.

Encouraged by these results, the use of absorbed photon equivalents as a scaling factor was explored at the multi-kilogram scale. To investigate this, a 3.5 L plug flow reactor for preparatory scale was constructed from PFA tubing (1/8” I.D., 3/16” O.D.), wound in an elliptical shape around a steel frame, and

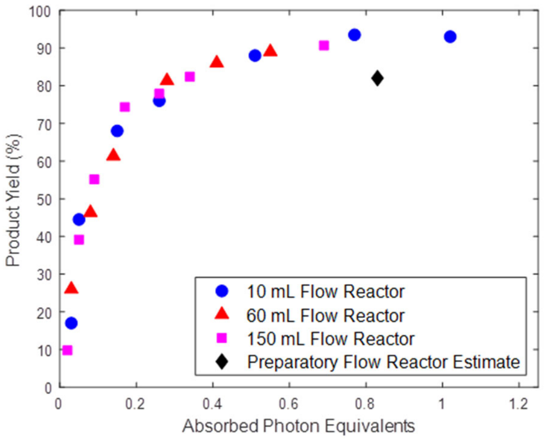

Figure 5. Overlay of reaction curves for several scales of plug flow reactors showing good agreement of data upon expressing product yield as a function of equivalents of absorbed photons.

submerged into a transparent cooling tank (for details regarding the reactor, see Supplemental Information). To irradiate the solution, the acrylic tank was flanked by panels of LEDs, with a total input power of 2300 W (644 W output) for the entire reactor. To measure the photon flux within this prep lab scale reactor, actinometry studies on a miniature version of the reactor were performed, as carrying out actinometry studies on the full-size reactor was deemed prohibitively challenging due to equipment synchronization, material requirements, and pressure drop. Based on the actinometry studies on the aforementioned small-scale model reactor, the photon flux through the 3.5 L reactor was extrapolated to be 850 W, giving a value of 0.04 equivalents of absorbed photons/min. The photon flux measured is at least a 32% overestimation of the total radiative power (644 W) as reported by the manufacturer. Despite this disrepancy, we chose to continue to apply these measured photon equivalents as a scaling factor, as had been done on the other scales.

Based on these measurements, and time course data obtained on the 10 mL, 60 mL, and 150 mL reactors, we predicted that conversion of approximately 90% could be achieved after 0.8 equivalents of photons had been absorbed, which equates to a residence time of approximately 20 minutes. This was a conservative prediction to account for potential error propagation in scaling the small scale model actinometry results to the preparatory flow reactor. We then carried out the scale up of the cross-coupling on the 3.5 L reactor using a residence time of twenty minutes, as had been predicted by the non-dimensional analysis of the actinometry results. Analysis of the reaction stream over ten reactor volumes showed that the reaction was stable, with consistent yields of product being observed throughout the course of the experiment upon reaching steady state. Overall, 1.4 kg of product was produced, in 82% yield, with a productivity value of 10 kg/d, largely consistent with the prediction of 90% made through use of photon equivalents as a scaling parameter.

Conclusion

In conclusion, we have demonstrated the ability for photochemical reactions to be scaled from small-scale batch reactors to multi-kilogram continuous flow reactors through the employment of photon equivalents as a scaling factor. These results suggest that a simple approach, which relies on empirically obtained reaction time course data, absorbance measurements, and actinometry, is sufficient to predict with accuracy the reaction times needed to achieve the desired level of conversion in a reactor of differing size and geometry. We envision this strategy greatly simplifying the initial, routine translation of photochemical reactions from batch to flow across different reactor geometries and scales.

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The authors declare no conflict of interest.

Keywords: flow chemistry • photocatalysis • photochemistry

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[14] For a detailed discussion of the actinometry studies, see Supplemental Information.

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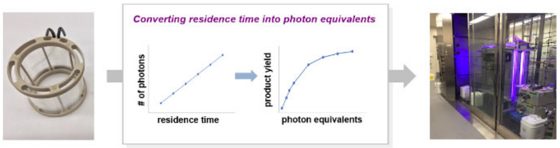

A predictive scaling parameter for photochemical reactions, termed absorbed photon equivalents, was established by a study of how a photoredox cross-coupling reaction performed across multiple reactor sizes and types. Through the measurement of photon flux in each reactor and simple absorbance measurements of the reaction solution, we were able to arrive at this scaling factor and subsequently employ it to the successful scale-up of this model reaction from milligram scale in batch to multi-kilogram scale in flow.