

Design of a Kilogram Scale, Plug Flow Photoreactor Enabled by High Power LEDs

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ABSTRACT: A simple and inexpensive photoreactor with a throughput of kilograms of material per day has been developed. This achievement was enabled by using high-power Light Emitting Diodes (LEDs) to provide high light density, leading to minimization of the footprint of the reactor. A study of the impact of tube diameter enabled maximization of the photon absorbance without increasing photocatalyst loading. Further optimization of reaction conditions using a design of experiments (DoE) elucidated reaction sensitivities that allowed the reaction rate, yield, and productivity to be maximized upon scale-up. The reactor has been operated continuously for 6 h leading to reaction performance that provided 12 kg of material per day at 90% conversion.

KEYWORDS: photoreactors, flow chemistry, photochemistry, photoredox, light-emitting diodes

T he past decade has seen the emergence of a new golden age of photochemical transformations.¹ This renewed interest in photochemistry² and rapid expansion of the field can be, in part, ascribed to the development of novel ruthenium, iridium,³ and organic photocatalysts.⁴ These catalysts are both highly absorbing and capable of exhibiting reductive and oxidative functions. The redox properties of these catalysts have allowed for the generation of highly reactive intermediates selectively under mild reaction conditions, allowing for cycloadditions,⁵ alkene difunctionalizations,⁶ and cross-couplings^{7–9} to proceed with exquisite selectivity. Although these photochemical methods have been widely adopted by the medicinal chemistry community¹⁰ and academia,¹¹ photochemical methods are used sparingly in pharmaceutical manufacturing.¹²

Another reason for the rapid expansion of these synthetic methods resides in the parallel development of light emitting diodes (LEDs) which are readily available, robust, and inexpensive. This revolutionary technology has impacted the lighting industry and was recognized with the Nobel prize in physics in 2014.¹³ Unique to these light sources is the remarkably long lifetimes and their ability to produce nearly monochromatic light in the visible and UVA regions in a highly energy-efficient manner.^{14,15}

With the notable advantages that photochemistry offers generating highly reactive intermediates selectively under mild reaction conditions, it is essential to develop workflows and reactors that will harness the intrinsic power of these methods on scale. Over the past 15 years, many reactor designs have been developed to provide access to larger scale photochemical transformations.^{16–21} Most of these reactors rely on continuous flow processing.^{22–26} This approach is typically favored to overcome one of the biggest challenges of photochemistry: light penetration. As described by the Beer– Lambert law, light penetration across a defined path length is governed by the extinction coefficient of the light absorbing species, typically the photocatalyst, and its corresponding concentration. The advantage of performing a photochemical reaction in a flow reactor²⁷ arises from the ability to match the tubing diameter with the optical path length, the high specific surface area, and the tight control of the residence time distribution, thus minimizing inadequate irradiation of the reaction stream. These advantages were recently harnessed by Harper and co-workers in the design of a laser-irradiated continuous stirred tank reactor (CSTR) with precise control of photon flux and absorbance to enable 1.2 kg/day productivity for a metallaphotoredox C–N cross-coupling reaction.²⁸

Continuous flow processes rely on three approaches to increase production: scale-out, scale-up, and numberingup.^{29,30} While scale-out (running a reactor for extended periods of time) provides the most straightforward solution, the low throughput per day of laboratory scale reactors precludes their use in chemical manufacturing where hundreds of kilograms are required within a day. To overcome the shortcomings of the scale-out approach, many have suggested numbering-up (running many reactors in parallel) to solve the low throughput. While this approach helps to overcome some of the challenges of scaling-out, the increase in the footprint for the required number of reactors and their associated parts becomes limiting. Additionally, significant controls must be designed and implemented to monitor these reactors in a manufacturing setting to ensure batch quality. For instance, a single part failure in any of these reactors could lead to failing specifications for material quality. As highlighted earlier, scaleup (increasing the reactor size) can be challenging due to the inherent limits of light penetration. Under certain circum-

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stances, a light-limited process could turn into a mass transferlimited process, where the rate of reaction is limited by the ability to move substrates from the dark zone to the irradiated zone within the reactor.

In on our most recent work,³¹ we have developed a large volume photoreactor that enabled a C-N cross-coupling at a throughput of up to 10 kg/day at 82% conversion. While this reactor was highly productive, it occupied a large footprint and had low light density due to the light source. Specifically, the original unit was approximately 1.2 m³, rendering it difficult to use in a numbering-up strategy and leaving little room to increase the size of the reactor. Even if a different light source were to be used to operate this reactor, the long length of the reactor tubing (0.4 km), in conjuction with the narrow diameter (3.175 mm I.D.), limits its operation to flow rates below 0.6 L/min to avoid excessively high pressure drops.³ Furthermore, using this narrow tubing limits photon absorption without the use of an unnecessarily high loading of photocatalyst. To overcome these challenges, we initiated the remodeling of the reactor with these main goals:

- (1) Minimize the footprint and volume of the reactor;
- (2) Increase the light density;
- (3) Explore wider diameter tubing to improve the absorbance of light, eliminate pressure drop issues, and overcome potential precipitation issues;
- (4) Develop a clear workflow to optimize photochemical transformations.

To leverage prior experience, the photoredox C–N coupling between pyrrolidine and 4-bromobenzotrifluoride was chosen as our model system (eq 1).^{9,33,34} This class of reaction has seen significant interest in medicinal chemistry and requires technical solutions for its application in a manufacturing setting. Additionally, this reaction represents a broader class of reactions that rely on the synchronicity of an interdependent dual catalyst pathway that is envisioned to be mechanistically complex and challenging to study.³⁵

We initiated our reactor optimization by exploring a series of light sources and rapidly identified a 100 W chip-based LED that emits light at 440 nm as a preferred option.³⁶ Their small size (4.84 cm²), combined with their high-power density output of 6.29 W/cm^{2,37} rendered them ideal to serve as the light source for a small reactor. The initial work pursued was testing the capability of these LEDs to promote the desired chemical transformation in a batch reactor. A 250 mL flask, equipped with an overhead stirrer, was surrounded by up to three light sources (Figure 1). Given the photocatalyst concentration and large path length, the reactions were performed under conditions of full photon absorption.38 Irradiating the reaction mixture at 440 nm³⁹ using these LEDs afforded excellent conversion to the desired C-N coupled product without formation of any impurities. Next, we studied the impact of increasing the number of photons on the reaction kinetics. Unsurprisingly, by increasing the light output power, from 30 to 82.5 W, we saw an increase in reaction rate. Supporting the hypothesis that this reaction is photon-limited, the curves formed a perfect overlay when the conversion was

represented as a function of emitted photon equivalents.⁴⁰ The direct correlation of conversion with photon equivalents allowed for the use of photon equivalents as a scaling factor for the reactor; i.e. the flux of light could be used to calculate a "molar flow rate" of photons analogous to any reaction stream in a flow reactor.

By incorporating our initial goal to minimize the reactor footprint, a flow reactor was assembled using the same 100 W LED chips. We elected to build a reactor that would fit in a 5.5 gallon aquarium, as this constraint would allow operation of the photoreactor in a conventional fume hood. Additionally, the aquarium serves as a reservoir enabling control of the reaction temperature. While the temperature of a single LED chip was well-controlled when mounted to an aluminum heat sink equipped with a fan, the space limitations around the vessel precluded the use of this cooling strategy.⁴¹ To maximize cooling capability, lights were mounted on an aluminum heat sink equipped with a copper coil for water cooling. Using plates that matched the width and length of the aquarium, 15 LEDs were affixed, resulting in a power output of 390 W or 0.93 W/cm² per plate (Figure 2).

Next, we assembled a frame that could support the tubular reactor. To prevent kinking of the tubing, 3D printed guides were affixed to the frame to facilitate the coiling of tubing.⁴² An important feature of this reactor is that the components are readily available and inexpensive, rendering it feasible for numbering-up and promoting its broader accessibility in the photochemistry community.

The flow reactor was initially tested using a single LED panel. The impact of tubing diameter was examined by comparing three different internal diameters (IDs) (3.18 mm, 4.76 mm, and 7.94 mm).⁴³ To compare irradiation versus tubing diameter, each section of tubing covered the same surface area on the inner aquarium walls. This arrangement ensured that the reaction streams were exposed to the same quantity of emitted photons. Specifically, the reaction mixture was pumped at the same flow rate (212 mL/min) independent of tubing diameter, thus maintaining the same ratio between the molar flow rate of 4-bromobenzotrifluoride (53.0 mmol/ min) and the molar flow rate of emitted photons (79.4 mmol/ min). The results showed that increasing the width of the tubing under investigation led to higher conversion by minimizing the transmittance of light (see Table 1) and allowing for the absorbance of a larger number of the emitted photons. It is worth noting that emitted photons equivalents can only be used as a reasonable estimate of absorbed photon equivalents when experiments are run under conditions of full absorption and not at high transmittance. Additionally, taking into account that the total footprint of the system is identical regardless of the reactor volume,⁴⁴ productivity was chosen to evaluate the efficiency of the photoreactor. As shown in Table 1, the highest productivity was observed when wider diameter tubing was used.

Lastly, a design of experiments (DoE) was performed to optimize the reaction conditions and reactor setup to maximize the reaction rate, the conversion, and the productivity (defined as kilograms of product produced per day) of the reaction (Table 2). To ascertain the effect of process conditions on the dynamics of the reaction rate and to optimize the reaction conditions, time profiles were collected in each experiment of the DoE.⁴⁶ These time profiles indicated that the key parameters affecting the initial reaction rate, conversion, and productivity were (1) high NiBr₂ loading, (2) a positive

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Figure 1. (A) Reactor setup. See <u>Supporting Information</u> for details. (B) Time course plot of the C–N coupling reaction in function of time. (C) Time course plot of the C–N coupling reaction as a function of equivalents of emitted photons.



Figure 2. LEDs affixed to the aluminum heat sink to create a highdensity LED plate $(30.5 \times 17.7 \text{ cm} \times 1.5 \text{ cm})$.

Table 1. Influence of Tubing Diameter on PhotonTransmittance and Conversion

diameter (ID in mm)	reactor volume (mL)	flow rate of solution (mL/ min)	conversion	transmittance	productivity (mmol/ min)
7.94	725	212	67.8%	27.3%	35.9
4.76	375	212	55.2%	45.8%	29.3
3.18	195	212	36.2%	59.3%	19.2

^aReaction conditions: 4-bromobenzotrifluoride (0.25 M), pyrrolidine (1.5 equiv), DABCO (1.8 equiv), NiBr₂·3H₂O (3.0 mol %), and Ru(BPY)₃(PF₆)₂ (0.02 mol %) in DMSO.

interaction between NiBr₂ loading and optical path length to ensure high reactivity along with full photon absorption, and (3) high 4-bromobenzotrifluoride concentration. Additionally, the concentration of the expensive photocatalyst could remain low because we observed full absorption of the light at this path length and concentration. The optimized reaction conditions are listed in Table 2.

Table 2. Comparison between Published³¹ and OptimizedReaction Conditions

Factor	Previous	Optimized
Path length and Tube ID (mm)	3.18	7.9
4-bromobenzotrifluoride (M)	0.25	0.40
$NiBr_2(H_2O)_3 \pmod{\%}$	3	5
$Ru(bpy)_3(PF_6)_2 \pmod{\%}$	0.02	0.02
Initial rate (mol $L^{-1} s^{-1}$)	7.9×10^{-4}	2.0×10^{-3}
End ^a conversion (%)	85	99
Productivity at 85% conv. (mmol/h)	1.9	15.6
	20	

^aEnd refers to asymptotic values after 20 min reaction time.

SCALE UP

Having optimized the reaction conditions and the tubing diameter to maximize absorbance, the effect of residence time on the conversion and the productivity was probed (Figure 3). This survey revealed that a residence time of 10 min was required to achieve full conversion. Based on the flow rate and



Figure 3. Conversion and productivity of the C–N coupling reaction as a function of residence time.

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Figure 4. Photoreactor setup in preparative laboratory facilities.

the concentration of our starting material, we calculated that these conditions would allow for a productivity of approximately 10 kg/day. Upon shortening the residence time, the productivity increased as a function of higher molar flow rate while the conversion to product decreases. At roughly 50% conversion, the productivity was predicted to generate up to 50 kg/day of the C–N coupled product. These conditions could be preferable when employing inexpensive starting materials and generating easily isolable products.⁴⁷ The next step was to demonstrate the use of our reactor for extended periods of time at two complementary sets of conditions that have been established to proceed in high conversion and high productivity, respectively.

To reflect application to a larger scale, the reactor was transferred and modified for use in our preparatory lab facility to accommodate the larger volumes of input and output streams intended (Figure 4). Also, to further maximize the absorption of the photons emitted by the LED panels, the volume of the reaction was extended to 890 mL. The reactor was connected to a 100-L vessel containing the reaction solution, and the flow rate was controlled by a peristaltic pump. The temperature of the reaction was controlled by recirculation through a heat exchanger submerged in a tank of ice water. To minimize light exposure beyond the reactor, it was surrounded by an amber poly(methyl methacrylate) box.⁴⁸

The reaction was demonstrated on kilogram scale at high conversion and high productivity to probe the reactor and reaction stability. Samples obtained every 15 min during the experiments showed consistent levels of conversion throughout both runs (Figure 5a). Additionally, the reaction temperature and the temperature of all the reactor components were demonstrated to be stable (Figure 5b). The reaction was run under high conversion conditions for 130 min, after which 90.3% conversion of starting material was measured and an assay yield of 1.14 kg of product was obtained (Table 3). By extrapolating these results to 24 h, these conditions would provide 12.6 kg of material in a day. The flow rate was then increased to examine the reaction at high productivity (near 50% conversion) for over 30 min.⁴⁹ An assay of the product stream under these conditions showed 42.0% conversion and 41.5% assay yield, thus achieving a productivity of 43.4 kg per day. These productivities achieve the values that would be required for use in a commercial facility,⁵⁰ and numbering up would allow for even greater throughputs of material in a single day.

CONCLUSION

In conclusion, we have built a photoreactor capable of generating kilograms of material in a single day from cheap



Figure 5. (A) Conversion at steady state determined by ¹H NMR spectroscopy. (B) Temperature profiles of reaction and reactor components throughout the high conversion (left) and high productivity (right) runs.

 Table 3. Summary of Results for Kilogram Scale

 Demonstration of the Photoreactor

Entry	Flow Rate (mL/min)	Conversion/ Assay Yield (%)	Time (min)	Assay Mass of 3 (kg)	Theoretical Productivity (kg/day)
1	105	90.3/90.0	130	1.14	12.6
2	925	42/41.5	37.2	1.12	43.4

and readily available parts. Its small footprint and affordability make this an attractive reactor for the synthetic community and should allow for broad application in academia and industry. In support of this claim, we have demonstrated the successful scale up of a metallaphotoredox C–N cross coupling reaction using a reactor composed of 30 100-W LED chips that can achieve a productivity sufficient to produce a low volume drug and is small enough to be operated in a standard laboratory hood. The studies culminated in a 6 h demonstration that showed a reaction throughput of up to 12.6 kg per day at 90% conversion or up to 43.4 kg per day when operated for high productivity. Further studies are

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ongoing in our laboratory to apply the knowledge gained through these studies to the multikilogram scale synthesis of pharmaceutically relevant compounds and will be disclosed in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00373.

Remaining experimental procedures and a discussion of the equipment used (PDF)

STL files for the tubing holders (ZIP)

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

LED, light-emitting diode; NMR, nuclear magnetic resonance; UV, ultraviolet

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(37) Please refer to Supporting Information Section 6 for details on power density measurements.

(38) For transmission through the batch reactor, please refer to the Supporting Information.

(39) Please refer to Supporting Information Section 3 for absorption spectra as a function of reaction conversion and the selection of 440 nm as the optimal wavelength for the reaction.

(40) For calculation of photon emission, refer to Supporting Information.

(41) Additionally, the fans require a significant amount of wiring that led to concerns for their use in a chemical fume hood.

(42) For STL files of each holder, see Supporting Information.

(43) Tubing with larger diameter were excluded of this study due to their prohibitively large bent radius, that would preclude the assembly of a small foot print reactor.

(44) Footprint refers to the total volume of the system, including the cooling reservoir (fish tank) and light panels. In every case, the reactor tubing could easily fit in the 5.5 gallon fish tank.

(45) These experiments were performed with 12 of the 15 lights powered on.

(46) DoE details and results can be found in Supporting Information Section 6.

(47) Further decreases to the flow rate are predicted to further increase the productivity (kg/day) for the reaction; however, we cannot justify referring to systems with such low conversions as productive, regardless of their raw throughput.

(48) For a detailed description of the reactor set up, see the Supporting Information.

(49) At this flow rate, the temperature of the cooling bath was adjusted to ca. 35 $^\circ C$ in order to maintain the reaction temperature near 50 $^\circ C.$

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(50) Operation of a photoreactor in a plant setting, where flammable gases, vapors, or liquids can exist, would require the implementation of few key safety parameters. Incasing the LED panels in the purge chamber would be the minimal requirement to meet hazardous location classification standards.