

## Translation of Batch to Continuous Flow in Photoredox Reactions

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Optimization of photoredox reactions by high-throughput experimentation with the batch method can be directly translated to continuous-flow reactions.

The vast majority of chemical syntheses are carried out by either batch or flow methods (Figure 1). Batch methods are commonly used for fine chemical synthesis in fields such as active pharmaceutical ingredients (APIs), agrochemicals, and fragrances; in this approach, all reagents are charged into a reaction vessel where they react. In the flow method, materials are continuously introduced from one end into a hollow loop or column as reactors, and products are continuously eluted from the other end. The continuous-flow method has several advantages over the batch method in terms of efficiency, safety, and scalability, and is suitable for on-demand synthesis.<sup>1</sup> Another advantage can be seen in photoredox catalysis, in which photon-harvesting molecules convert light energy into chemical energy. Photoredox catalysis is currently being studied very extensively because it is environmentally friendly and can be used to achieve unique reactions via high-energy intermediates.<sup>2</sup> However, most of these processes have been developed as batch methods, which pose a problem for scale-up. This is because, as known by the Beer–Lambert law, when the volume of the reaction vessel is increased, insufficient light intensity may reach the interior of the reaction mass. Flow reactions, which utilize a narrow tubular space, can be used to overcome this problem.<sup>3</sup> Despite the many advantages, research on the synthesis of fine chemicals by flow reactions has lagged far behind that of batch reactions, and a method to develop flow reactions more rapidly is desired. In this issue of *ACS Central Science*, MacMillan et al. describe an approach in which microscale

	Batch systems	Continuous-Flow systems
Efficiency	✗	✓ Safe, Scalable, On-demand
Scalability in photoredox reactions	✗	✓ Good light penetration
Cost for optimization	✓	✗ Large amount of materials, Reactor dependence
<b>Authors' work:</b>		
	direct translation	

Figure 1. Batch reactions vs flow reactions.

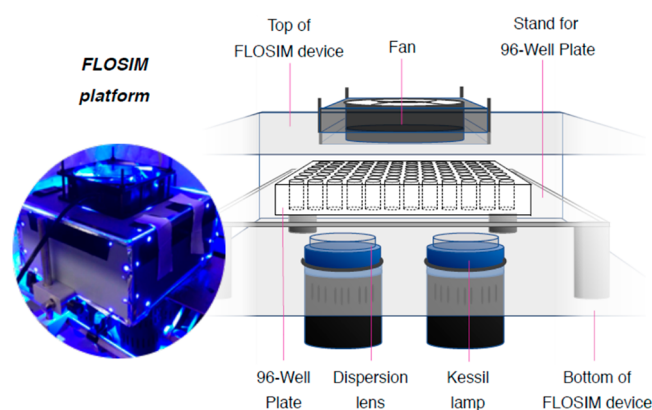
high-throughput experimentation (HTE) is used to identify optimal reaction conditions that can be directly translated to flow systems.<sup>4</sup>

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There are several issues that make rapid optimization of flow reactions difficult: (1) each reaction requires a pump and a reactor, and thus experiments are not possible to perform in parallel with a single flow system; (2) the size of the flow reactors often influences the optimal reaction conditions; (3) compared with microscale batch reactions, flow reactions require much larger amounts of reagents; and (4) generation of precipitation causes clogging. To overcome these problems in optimizing flow reactions, MacMillan et al. developed the flow simulation (FLOSIM) HTE setup, which matches the path length of irradiation under flow conditions. The platform consists of a multienvironment 96-well glass plate device, two Kessil LEDs (PR160), two ThorLabs concave lenses, and a fan (Figure 2). After examining the

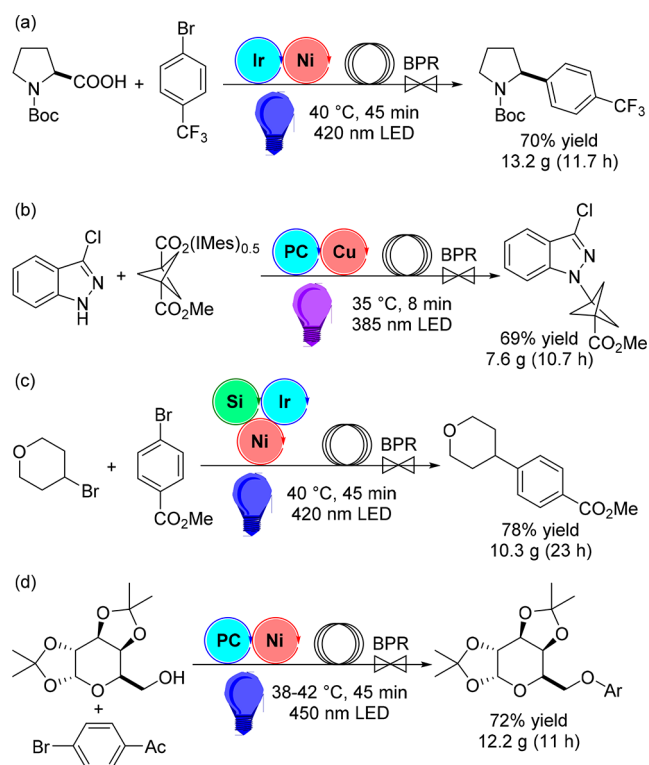


**Figure 2.** FLOSIM device reproduced with permission from ref 4. Copyright 2021 The Authors. Published by the American Chemical Society.

position and number of LEDs and fans, the homogeneity of the system was confirmed. The general workflow for the translation of a photoredox reaction from batch to flow is that (1) HTE screening is performed on a 96-well glass plate, where it is exposed to light irradiation for a short period of time equivalent to the desired residence time in the flow system; (2) the crude reaction mixtures are analyzed by ultraperformance liquid chromatography (UPLC, 4 min per sample); and (3) the optimal conditions determined by the platform can be directly reproduced in a commercial flow system.

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The platform enables several hundreds to 1000 “flow-type” reactions to be performed in short order to examine the effect of residence time, solvent, concentration, organic



**Figure 3.** Achieved reactions under multigram flow conditions.

base, photocatalyst, catalyst loading, and the transition-metal complex. The authors achieved several reactions, optimized by the HTE systems, in multigram flow conditions, such as decarboxylative C–C coupling (Figure 3a),<sup>5</sup> decarboxylative C–N coupling (Figure 3b),<sup>6</sup> cross-electrophile coupling (Figure 3c),<sup>7</sup> and C–O coupling (Figure 3d) reactions.<sup>8</sup> In all cases, the low, moderate, and high yield results under HTE conditions could be reproduced under flow conditions and multigram synthesis in flow. One of limitations is that conditions that generate precipitation during the reaction cannot be applied to flow because it causes clogging of the tube reactor. In cross-electrophile coupling, the initial optimized conditions using 2,6-lutidine failed to translate to the flow reaction because the poorly soluble lutidine salt formed. In this case, the authors performed approximately 1000 experiments to identify homogeneous conditions. Finally, decreasing the amount of base and switching to *N,N*-dimethylacetamide as a more polar solvent enabled the precipitation issue to be overcome, and the high efficiency of the new conditions could be translated to the flow reaction. MacMillan et al. also demonstrated that HTE FLOSIM optimization was applicable to various commercial flow reactors.

High-throughput screening of flow reactions, especially at the laboratory level, is difficult because of the cost and size of the equipment. The platform described herein solves these problems with an approach in which batch reactions can reproduce the results of flow reactions. Although flow

reactions are very compatible with automated control by machines combined with autosamplers, the authors' method is efficient and can be applied not only to photoredox reactions but also to various homogeneous reactions. However, the current approach is not considered to be easily translatable to flow reactions in which the liquid is pumped into a column packed with a heterogeneous catalyst. If organic reactions can be developed and optimized rapidly using flow methods, it could be a revolution in fine chemical synthesis.

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##### Notes

The authors declare no competing financial interest.

#### REFERENCES

- (1) Kobayashi, S. Flow "Fine" Synthesis: High Yielding and Selective Organic Synthesis by Flow Methods. *Chem. - Asian J.* **2016**, *11*, 425.
- (2) Cheng, W.-M.; Shang, R. Transition Metal-Catalyzed Organic Reactions under Visible Light: Recent Developments and Future Perspectives. *ACS Catal.* **2020**, *10*, 9170.
- (3) Rehm, T. H. Reactor Technology Concepts for Flow Photochemistry. *ChemPhotoChem.* **2020**, *4*, 235.
- (4) González-Esguevillas, M.; Fernández, D. F.; Rincón, J. A.; Barberis, M.; Frutos, O. d.; Mateos, C.; García-Cerrada, S.; Agejas, J.; MacMillan, D. W. C., Rapid optimization of photoredox reactions for continuous flow systems using microscale batch technology. *ACS Central Science* **2021**, DOI: [10.1021/acscentsci.1c00303](https://doi.org/10.1021/acscentsci.1c00303).
- (5) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. Merging photoredox with nickel catalysis: Coupling of  $\alpha$ -carboxyl  $sp^3$ -carbons with aryl halides. *Science* **2014**, *345*, 437.
- (6) Liang, Y.; Zhang, X.; MacMillan, D. W. C. Decarboxylative  $sp^3$  C–N coupling via dual copper and photoredox catalysis. *Nature* **2018**, *559*, 83.
- (7) Zhang, P.; Le, C. C.; MacMillan, D. W. C. Silyl Radical Activation of Alkyl Halides in Metallaphotoredox Catalysis: A Unique Pathway for Cross-Electrophile Coupling. *J. Am. Chem. Soc.* **2016**, *138*, 8084.
- (8) Terrett, J. A.; Cuthbertson, J. D.; Shurtleff, V. W.; MacMillan, D. W. C. Switching on elusive organometallic mechanisms with photoredox catalysis. *Nature* **2015**, *524*, 330.